Robert Carachi
Jay L. Grosfeld
Editors

The Surgery of Childhood Tumors

Third Edition

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A Brief History of Pediatric Oncology

1

Robert Carachi and Jay L. Grosfeld

Dr Odile Schweisguth was born during the turbulent period of the first world war in Vosges (France) in 1913. Her first contact with medicine was at the Red Cross Nursing School and with the mentoring and support of one of her teachers there, was admitted to the medical school in Nancy in 1932, graduating in Paris in 1936. Her early training was carried out in "Hopital des Enfants Malades" in Paris. She became the first pediatric oncologist when she was appointed to the Consultant post in 1948 at the Institute Gustave Roussy to establish a new paediatric section at this renowned Cancer centre in France. She set up over her working life until she retired in 1978, a separate paediatric oncology ward fully staffed caring for children with cancer and to look after the dying children. The volume of patients increased to 350 per year once it was fully established. Her visit in 1959 for 2 months to the Sidney Farber at the Boston Children's Hospital established a lifelong friendship and a strong voice for children's cancer. Her interest was on long term morbidity because the main treatment modality available at that time was radiation and radiotherapists had no means of scaling down the treatment for children. She was a strong advocate for the rights of childhood cancer survivors. An initial meeting on childhood cancers in 1959 was organised and Odile Schweisguth was its director. This led to comprehensive pediatric oncology care worldwide with the formation of the new society called Societe International d'Oncologie Pediatrique, at a meeting in Madrid in 1969. She was elected as the first Present of SIOP, with a membership worldwide of over a thousand members. Odile died at the age of 89 in March 2002.

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About SIOP

History

On 3 July 1967, a small group of paediatricians, surgeons, pathologists and others met in the Paediatric Department "Service Milhit" of the Institut Gustav in Villejuif/Paris, France. Everyone there knew SIOPs now honorary member Dr Odile Schweisguth, and shared a keen interest in paediatric oncology.

A decision was taken at this meeting, to form the Club d'Oncologie Pediatriquie (Paediatric Oncology Club). During the second meeting of the Club, held at IGR in 1668, participants agreed to convene the following year in Madrid, hosted by the late Dr J Monereo, Paediatric Surgeon. It was during this memorable assembly that it became obvious that there was a clear and widespread interest in paediatric oncology and the Club was transformed to the Societe International d'Oncologie Pediatrique (SIOP) on 6 November 1969.

The Founding Members of the Society who were present at the founding meeting of the Society in Madrid and voted for the constitution, were Doctors Bouchon, Boureau, Brunat, Carton, Delemarre, Gerard-Marchant, Gompel, Gubler, Hitzig, Hurtado, Kaser, Lemerle, Massimo, Maurus, Monero, Neidhardt, Noel, Pages, Payan, Pellerin, Pluss, Orsini, Raybaud, Schlienger, Schweisguth, Sullivan, Voute and Wagner. SIOP was initially a bilingual Society; French and English were both used at meetings. According to the statutes, it is still bilingual; however English has taken over as the conference language, but a French flavour remains!

Furthermore, SIOP has fulfilled its original intention of becoming a truly international society and not restricting its influence and membership to one continent or part of a continent. Over the years, most of the annual meetings have been

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held in Europe, the saying "doing Europe with SIOP", but this policy has been changed and at the moment, the majority of our members are from Europe and North America.

In the early years, the Society was mostly clinically orientated, promoting involvement in clinical studies and trials, such as medulloblastoma, neuroblastoma and rhabdomyosarcoma, for example. Eminent surgeons, pathologists, paediatricians and radiotherapists met together. In recent years, more basic scientific aspects of paediatric oncology have featured at the annual meetings.

SIOP continues to work in the interest of our patients, children with cancer, who wish to be cured to lead normal lives alongside other healthy children.

SIOP was legally established in 1969. Under the name of International Society of Paediatric Oncology there exists an association governed by the present statutes and by the provisions of articles 60 ff. of the Swiss Civil Code. Its registered office is in Zurich, Switzerland.

The first annual general meeting was held in Madrid (Spain) in 1969 and was devoted to neuroblastoma, nephroblastoma, lymphoscarcoma and immunology. Beginning with a few enthusiastic members to more than 1400 active Ordinary Members, SIOP remains a friendly Society in which all the challenges of treating patients with malignancies are discussed in depth. The central secretariat of SIOP is established in The Netherlands where one can receive detailed information on the Society. Address of the Secretariat is:

SIOP Secretariat c/o Kenes Associations Worldwide
1 – 3 Rue de Chantepoulet
1211 Geneva, Switzerland
Email: irah@kenes.com

Societe Internationale D'Oncologie Pediatrique- International Society of Paediatric Oncology

Constitution

1. The official name of this organisation shall be the Societe Internationale d'Oncologie Pediatrique with the acronym SIOP. It is also to be known by the English translation; namely the International Society of Paediatric Oncology. The name of the organisation and its acronym SIOP may only be used by a member for professional identification or in a curriculum vitae. A member shall not use the name or acronym for any commercial purpose or to advertise his services without the express approval of the Board. A violation of this prohibition may subject the member to censure, suspension or expulsion from the Society by the Board.

   The Society was founded in 1969. Under the name of "International Society of Paediatric Oncology" there exists an association governed by the present statutes and by the provisions of articles 60 ff. of the Swiss Civil Code.
2. SIOP has its domicile where its administration is domiciled.
3. The financial year starts with the annual Congress of the Society in October each year or as may be decided by the Board.

Article II: Vision and Mission of SIOP and charitable status of the Society

SIOP is a non-profit organisation and acts in a selfless manner. Members do not receive funds or additional benefits. SIOP aims for a charitable tax exempt status.

1. Vision
   No child should die of cancer
2. Mission
   The mission of the international Society of Paediatric Oncology (SIOP) is :
   (a) To ensure that each child and young adult with cancer has access to state of the art treatment and care
   (b) To ensure that all involved in childhood cancer worldwide have access to the latest progress through meetings, networking and continuing professional development
   (c) To support those caring for children and young adults with cancer to provide the best curative and palliative therapies.
   (d) To advocate for appropriate longterm follow up for children and young adults after treatment for cancer.

The International Society of Paediatric Surgical Oncology (IPSO)

IPSO is an international society of surgeons who specialise in the surgical care of children with cancer.
IPSO's aims are:

- To set up a global standard for surgical care of children with cancer
- To provide a forum and enhance communication between surgeons who specialise in children's cancer
- To promote and support clinical trials aimed at improving the outcome in the treatment of children's cancer
- To encourage co-operation with other organisations concerned with children's cancer

IPSO is a truly global organisation with an expanding membership from all parts of the world. At the last count, 48 coun-

tries were represented. Membership is open to all surgeons who have a demonstrable commitment to paediatric surgical oncology, and we are always keen to attract new members.

IPSO meets once a year in conjunction with our sister organisation SIOP (The International Society of Paediatric Oncology) and has regular joint meetings with other international organisations who represent specialist children's surgery.

IPSO strongly supports the continuing professional development of surgeons who care for children who have cancer, and to this end IPSO runs an annual course in paediatric surgical oncology, in collaboration with EUPSA (the European Paediatric Surgeons Association).

Historical Background

IPSO

Aims

To:

Further knowledge, promote research and set standards in paediatric surgical oncology :

Facilitate communication between various surgical disciplines (orthopaedics, neurology, plastic surgery etc) and also other medical specialties involved in the treatment of paediatric cancer. Maintain a forum for discussion and/or advice on problems relevant to paediatric surgical oncology.

Exchange and diffuse information on paediatric cancer in general which may impact surgical practice. Be involved in the formulation and implementation of requirements for postgraduate training and education as well as specialist recognition on an international level.

Development

1989: First full surgical symposium back to back with SIOP meeting Prague.

Main topic Surgical Oncology (local organisers J Snadjauf J, Koutecky)

1990: Second surgical symposium back to back with SIOP meeting Rome, 1990. (Local organisers C Boglino, R Cozzi, M Castello)

1991: Letter of intent to form an independent society sent to all participants of above symposia and other pediatric surgeons known or shown to have special interest in surgical oncology. Number 179. (D Hays)

1991: Draft constitution prepared by A Gentil-Martins

1992: Positive response received from 1010 replies (List of names and countries available)

IPSO Officially founded as independent society in 1991 at Rhodes SIOP meeting (Again including a separate surgical symposium Local Organiser – D Keramidas).

Constitution and executive council approved at first general assembly

Membership: All surgeons attending any of the three above symposia considered as members (numbers) see attached list.

Executive 1991

Founding President – J Plaschkes

Secretary/treasurer – R Spicer

F Cattalliotti

A Gentil-Martins

P Exelby (SIOP scientific committee representative)

A Brief History of Modern Pediatric Oncology in the United States

Following WWII, as many medical specialists returned to civilian practice, an increased interest in improving the dismal outcome for children with leukemia and other malignant conditions was observed. Early use of then sparsely available chemotherapy in leukemic children was spearheaded by the work by Sidney Farber in Boston in 1948. Implementation of postoperative radiotherapy for children with Wilms tumor was reported by Gross and Neuhauser in 1949. However, the relatively low incidence of childhood cancer cases managed at any single center made it difficult to determine the most appropriate treatment and stimulated interest in developing collaborative efforts to accrue an adequate number of patients for clinical studies. It soon became obvious that in order to carry out randomized prospective and controlled clinical trials would require cooperative group studies implementing multidisciplinary care including, surgery, radiotherapy and chemotherapy.

In 1955, the Acute Leukemia Cooperative Chemotherapy Study Group A was formed. This was mainly an adult study group that also cared for some children with leukemia. The group's activities expanded somewhat to include patients with solid tumors including cases of Wilms tumor and neuroblastoma. In 1967, childhood cases split off with formation of the Children's Cancer Study Group A (CCSG-A). Subsequently, the name was shortened to the Children's Cancer Group (CCG). In 1968, the National Wilms tumor Study Group (NWTSG) was formed led by Dr. Giulio D'Angio (a radiotherapist). The other founding members included Drs. Daniel Green, Audrey Evans (Hematologist-Oncologists), J. Bruce Beckwith (pathologist), and Norman Breslow (statistician). Drs. Harry Bishop (pediatric surgeon) and Willard Goodwin (urologist) joined the initial group. Since then this highly successful group has carried out a total of five different major Wilms tumor studies leading to an overall survival rate of near 90 %. Full details concerning Wilms tumor are covered in detail in Chap. 12.

During the same period, in 1956 the Southwest Cancer Chemotherapy Study Group (SWOG) was organized with a small pediatric component based at the MD Anderson Cancer Hospital in Houston, TX. In 1973 SWOG merged with the Cancer and Acute Leukemia Group B (CALG-B) which included both adult and pediatric oncologists. In 1979 the pediatric oncologists split off and developed the Pediatric Oncology Group (POG) led by Dr. Teresa Vietti of St Louis, MO.

In 1970 the Intergroup Rhabdomyosarcoma Study Goup (IRSG) was formed with members from both CCG and POG. Dr. Harold Mauer (Hematology-Oncology) was the lead physician supported by Drs. William Newton (pathology), Ruth Heyn, Milton Donaldson (Hematology-Oncology), Daniel Hays and Walter Lawrence (Surgeons) and Melvin Tefft (radiotherapy).

In 2000, The NWTSG, IRSG, CCG and POG merged into a single group named the Children's Oncology Group (COG).

Children's Oncology Group (COG)

The Children's Oncology Group founded in 2000, is the largest Cooperative Cancer group in the world including the United States, Canada, and a number of international sites (Australia, New Zealand, and areas of Europe). COG sites care for more than 90 % of the 13,500 pediatric cancer patients seen in the US annually.

COG is primarily funded by grants from the US National Cancer Institute (NCI) and other granting agencies as well as philanthropic sources through gifts to the COG Foundation.

There are two types of COG centers:

1. COG Phase I consortium consisting of 21 premier pediatric oncology program centers that carry out early clinical cancer trials, and
2. the Community Cancer Oncology Program (CCOP) centers that manage patients in assigned clinical protocols

Two hundred member institutions in COG carry out nearly 100 clinical trials at any given time. The group manages pediatric patients with hematologic malignancies (leukemias and lymphomas), solid tumors (including bone tumors), central nervous system tumors and rare cancers. Approximately 8000 cancer experts work and perform research at COG facilities. In addition to disease specific clinical research, COG members conduct studies in cancer drug development, supportive care, epidemiology, stem cell transplantation, behavioral sciences and survivorship. The group maintains a vigorous long-term follow up outcomes and guidance program that monitors late effects of treatment.

Scientific research collaboration occurs at a world-wide level in areas such as molecular genetics, molecular biology, immunology, proteomics, targeted therapies, antiangiogenesis, cellular proliferation, apoptosis and tumor vaccine development.

Children's Oncologic Surgeons represent one of the key multidisciplinary groups that compose the COG. There is a COG Executive Committee and the Chair of the Surgery Discipline Committee is the surgical representative to that Committee. When COG was initially formed in 2000, Dr. Gregory Reaman (National Children's Hospital, Washington, DC) was the overall COG Chairman and Dr.

Robert Shamberger of Boston, MA (Boston Children's Hospital) was the first Chair of the Surgery Discipline committee. Dr. Peter Adamson of Philadelphia, PA (CHOP) is the current COG Chairman and the Chair of the COG Surgery Discipline Committee is Dr Michael LaQuaglia of (Memorial Sloan-Kettering Cancer Center), New York, NY. Within the Surgical Committee there is a surgical leadership Group whose members are often appointed to the various solid tumor Committees and other relevant Committees in COG by the Chair. Some examples include:

Neuroblastoma: Dr Jed Nuchtern (Houston, TX) Vice-Chair, and others that are members of the senior surgery investigator group including Drs. Michael LaQuaglia, Andrew Davidoff, Daniel vonAllmen and Stanton Adkins.

Rhabdomyosarcoma: Dr. David Rodeberg (Vice-Chair), Dr. Andrea Hayes-Jordan-other soft tissue sarcomas.

Wilms Tumor: Dr. Peter Ehrlich (Vice-Chair), with Drs. Robert Shamberger, Thomas Hamilton and Michael Richey – senior surgery investigators.

Rare tumors:

- **Hepatoblastoma**: Dr. Rebecka Meyers lead investigator, Drs Max Langham and Gregory Tijan – senior investigators
- **Germ Cell Tumors**: Drs. Frederick J. Rescorla and Deborah F. Billmire Co-Principle investigators
- **Adrenocortical tumors**: Drs. Michael LaQuaglia and Christopher Weldon-Co-Principle investigators

Informatics: Dr. John Doski

Many of the aforementioned individuals are contributors to this 3rd edition of *Surgery of Childhood tumors*.

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Epidemiology of Childhood Tumours

2

Charles A. Stiller

Classification

Traditionally, descriptive data on cancers occurring in people of all ages combined have been presented with the diagnoses categorised according to the International Classification of Diseases (ICD), in which cancers other than leukaemias, lymphomas, Kaposi sarcoma, cutaneous melanoma and mesothelioma are classified purely on the basis of primary site. The malignant solid tumours of children are histologically very diverse and a substantial proportion consists of characteristic entities that are rarely seen in adults. Therefore, it is appropriate to group childhood cancers in a way which more fully takes morphology into account, and standard classifications have been devised with the categories defined according to the codes for topography and morphology in the International Classification of Diseases for Oncology (ICD-O) [1–3]. The current scheme is the International Classification of Childhood Cancer, Third Edition (ICCC-3), based on the third edition of ICD-O [3]. ICCC-3 contains 12 main diagnostic groups:

I. Leukaemias, myeloproliferative diseases, and myelodysplastic diseases
II. Lymphomas and reticuloendothelial neoplasms
III. CNS and miscellaneous intracranial and intraspinal neoplasms
IV. Neuroblastoma and other peripheral nervous cell tumours
V. Retinoblastoma
VI. Renal tumours
VII. Hepatic tumours
VIII. Malignant bone tumours
IX. Soft tissue and other extraosseous sarcomas
X. Germ cell tumours, trophoblastic tumours, and neoplasms of gonads
XI. Other malignant epithelial neoplasms and malignant melanomas
XII. Other and unspecified malignant neoplasms

All of the groups except retinoblastoma are split into subgroups, and the most heterogeneous subgroups are in turn split into divisions. Most groups contain only malignant neoplasms, but groups III and X also include non-malignant intracranial and intraspinal tumours since they are usually recorded by cancer registries.

Successive classifications have been designed to have as much continuity as possible with their predecessors, while recognising advances in understanding of tumour pathology and biology. Although the nomenclature of many groups and subgroups has changed since the previous version of the classification, their contents are largely the same.

Incidence

The annual incidence of cancer in children under 15 years of age is usually between 100 and 160 per million. There is a risk of 1 in 650 to 1 in 400 that a child will be affected during the first 15 years following birth. Table 2.1 shows annual incidence rates per million children in the UK for 1998–2007 based on data from the population-based National Registry of Childhood Tumours. The total incidence, just under 150 per million, and the relative frequencies of the different groups and subgroups were typical of those in industrialised countries. In the table, the ICCC-3 subgroups for Burkitt lymphoma and other non-Hodgkin lymphoma (NHL) have been combined because they are usually considered together clinically, and data for some other subgroups and divisions are not shown separately because of small numbers.

Leukaemia formed the most frequent diagnostic group, about one third of the total incidence. The lymphoid subgroup, which in childhood consists almost entirely of precursor cell

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Table 2.1 Registration rates for cancers diagnosed at age 0–14 years in the UK, 1998–2007

		Annual rates per million children for age group (years)				Age standardised rates per million (World standard population)		
ICCC-3 categories	Total registrations	0	1–4	5–9	10–14	Boys	Girls	Children
I-XII. All Cancers	15,729	209.5	198.2	112.5	119.9	158.3	138.6	148.7
I. Leukaemias	4971	45.5	81.6	36.8	26.7	52.4	44.2	48.4
(a) Lymphoid leukaemias	3884	19.7	69.2	30.1	18.4	41.6	34.3	38.0
(b) Acute myeloid leukaemias	742	17.5	8.3	4.7	5.6	7.4	6.8	7.1
(c) Chronic myeloproliferative diseases	114	1.3	0.5	0.7	1.7	1.0	1.0	1.0
(d) Myelodysplastic syndrome and other myeloproliferative	188	5.7	2.9	1.0	0.8	2.1	1.6	1.9
(e) Other and unspecified	43	1.3	0.6	0.3	0.2	0.3	0.5	0.4
II. Lymphomas etc	1621	1.6	8.1	13.5	23.2	18.2	9.0	13.7
(a) Hodgkin lymphoma	733	–	1.6	4.4	13.7	7.3	4.5	5.9
(b, c) Non-Hodgkin lymphomas	862	1.0	6.2	8.9	9.3	10.5	4.4	7.6
(d, e) Other and unspecified	26	0.6	0.3	0.2	0.2	0.4	0.1	0.2
III. CNS, intracranial, intraspinal	3992	37.4	42.5	36.5	31.4	38.8	35.0	36.9
(a) Ependymomas and choroid plexus tumours	399	9.1	6.3	2.4	1.9	4.6	3.3	4.0
1. Ependymomas	292	2.6	4.8	2.0	1.7	3.3	2.4	2.8
2. Choroid plexus tumours	107	6.6	1.5	0.3	0.2	1.3	0.9	1.1
(b) Astrocytomas	1700	9.4	17.7	18.0	13.9	15.1	16.1	15.6
(c) Intracranial and intraspinal embryonal tumours	743	9.3	9.4	6.9	4.3	8.5	5.6	7.1
1. Medulloblastomas	546	3.3	6.4	5.9	3.4	6.5	3.6	5.1
2. Primitive neuroectodermal tumour	129	3.4	1.8	0.8	0.7	1.2	1.3	1.3
3. Atypical teratoid/rhabdoid tumour	65	2.6	1.2	0.1	0.2	0.8	0.6	0.7
(d) Other gliomas	400	1.1	4.1	4.5	2.9	3.8	3.5	3.7
(e) Other specified	543	3.3	3.5	4.6	6.6	4.9	4.6	4.7
1. Pituitary adenoma and carcinoma	52	–	0.1	0.2	1.1	0.4	0.5	0.4
2. Craniopharyngioma	189	0.3	1.0	2.3	2.0	1.7	1.5	1.6
3. Pineal parenchymal tumours	53	0.9	0.7	0.3	0.4	0.5	0.5	0.5
4. Neuronal, neuronal-glial	204	2.1	1.5	1.6	2.3	1.9	1.7	1.8
5. Meningiomas	45	–	0.3	0.3	0.7	0.3	0.4	0.4
(f) Unspecified	207	5.1	1.5	1.7	1.8	2.0	1.9	1.9
IV. Neuroblastoma etc	946	44.2	17.7	3.0	0.8	10.3	9.9	10.1
(a) Neuroblastoma and ganglioneuroblastoma	930	44.2	17.6	2.9	0.6	10.1	9.8	10.0
(b) Other peripheral nervous cell	16	–	0.2	0.1	0.2	0.2	0.1	0.1
V. Retinoblastoma	417	24.8	7.9	0.5	0.1	4.3	4.8	4.6
VI. Renal tumours	862	16.3	19.3	4.3	1.3	8.3	9.8	9.0
(a) Nephroblastoma and other non-epithelial	844	16.3	19.3	4.3	0.9	8.2	9.6	8.9
1. Nephroblastoma (Wilms tumour)	771	12.3	18.1	4.1	0.8	7.2	9.0	8.1
2. Rhabdoid	31	3.0	0.3	0.0	–	0.3	0.3	0.3
3. Sarcomas	34	0.9	0.9	0.1	0.0	0.5	0.2	0.4
4. Peripheral neuroectodermal tumour	8	0.1	0.0	0.0	0.1	0.1	0.1	0.1
(b) Renal carcinoma	16	–	0.0	0.0	0.4	0.1	0.1	0.1
(c) Unspecified	2	–	–	0.1	–	0.0	0.0	0.0
VII. Hepatic tumours	182	8.4	3.1	0.4	0.6	2.0	1.8	1.9
(a) Hepatoblastoma	146	7.8	2.9	0.2	0.1	1.7	1.4	1.6
(b) Hepatic carcinoma	32	0.1	0.2	0.2	0.5	0.3	0.3	0.3
(c) Unspecified	4	0.4	–	–	0.0	0.0	0.0	0.0

Table 2.1 (continued)

		Annual rates per million children for age group (years)				Age standardised rates per million (World standard population)		
ICCC-3 categories	Total registrations	0	1–4	5–9	10–14	Boys	Girls	Children
VIII. Malignant bone tumours	620	0.3	1.1	4.8	10.8	5.2	4.9	5.0
(a) Osteosarcoma	322	–	0.3	2.2	6.0	2.6	2.5	2.6
(c) Ewing sarcoma family	262	0.1	0.7	2.2	4.2	2.2	2.1	2.2
(b, d, e) Other and unspecified	36	0.1	0.1	0.3	0.5	0.3	0.3	0.3
IX. Soft tissue and extraosseous sarcomas	993	12.0	10.4	7.4	9.0	10.1	8.1	9.2
(a) Rhabdomyosarcoma	499	5.3	7.4	4.5	2.4	5.5	4.1	4.8
(b) Fibrosarcoma etc	72	1.9	0.3	0.2	1.1	0.7	0.6	0.6
(c) Kaposi sarcoma	4	–	0.0	0.0	0.1	0.0	0.0	0.0
(d) Other specified	356	3.4	2.1	2.3	4.9	3.3	2.9	3.1
1, 2. Ewing sarcoma family	147	0.9	1.1	1.1	1.8	1.1	1.5	1.3
3. Extrarenal rhabdoid tumour	20	1.4	0.2	0.1	0.1	0.3	0.2	0.2
4. Fibrohistiocyytic tumours	46	0.4	0.1	0.4	0.7	0.5	0.3	0.4
5. Synovial sarcoma	71	–	0.3	0.4	1.3	0.7	0.4	0.6
(e) Unspecified	62	1.4	0.6	0.4	0.6	0.6	0.5	0.6
X. Germ cell, trophoblastic and gonadal	518	16.4	3.7	2.1	5.8	4.3	5.3	4.8
(a) Intracranial and intraspinal germ cell	176	1.7	0.6	1.1	2.7	1.9	1.0	1.5
(b) Other malignant extragonadal	144	11.7	1.6	0.2	0.3	1.0	2.1	1.5
(c) Malignant gonadal germ cell	189	3.0	1.5	0.6	2.7	1.4	2.0	1.7
(d, e) Other and unspecified gonadal	9	–	–	0.1	0.1	0.0	0.1	0.1
XI. Other malignant epithelial and melanoma	517	1.4	1.9	2.9	9.1	3.6	5.0	4.3
(a) Adrenocortical carcinoma	28	0.6	0.6	0.1	0.1	0.2	0.4	0.3
(b) Thyroid carcinoma	118	–	0.4	0.7	2.1	0.7	1.3	1.0
(c) Nasopharyngeal carcinoma	28	–	–	0.0	0.7	0.3	0.1	0.2
(d) Malignant melanoma	129	0.9	0.5	0.7	2.2	0.8	1.3	1.1
(e) Skin carcinoma	108	–	0.2	0.7	2.0	0.8	0.9	0.9
(f) Other and unspecified carcinomas	106	–	0.1	0.7	2.0	0.7	1.0	0.8
XII. Other and unspecified	90	1.3	0.9	0.3	1.1	0.8	0.8	0.8
(a) Other specified	20	0.6	0.3	0.0	0.2	0.2	0.2	0.2
(b) Unspecified	70	0.7	0.6	0.3	1.0	0.6	0.6	0.6

Source: National Registry of Childhood Tumours

acute lymphoblastic leukaemia (ALL), accounted for 78 % of leukaemias and one quarter of all childhood cancers; nearly all the remaining leukaemias were acute myeloid (AML). The most numerous solid neoplasms were CNS and other intracranial and intraspinal tumours, accounting for one quarter of total cancer incidence. The next most frequent diagnostic groups were, in descending order of incidence, lymphomas, soft tissue sarcomas, neuroblastoma and other peripheral nervous cell tumours and renal tumours, each accounting for 5.5–10 % of the total. The remaining groups together accounted for 15 %. Overall, incidence in the first 5 years of life was about 1.7 times that at 5–14 years of age. Boys were affected 1.1 times as often as girls. There were, however, pronounced differences in age distribution and sex ratio between different types of childhood cancer. The principal embryonal tumours, namely those of the CNS (including medulloblastoma and other primitive neuroectodermal tumours), neuroblastoma, retinoblastoma, nephroblastoma (Wilms tumour) and hepatoblastoma, all had their highest incidence in early childhood, and about 40 % of the cumulative incidence of retinoblastoma and hepatoblastoma were observed in the first year of life. Contrastingly, incidence of some diagnostic categories increased with age, and more than two thirds of the cumulative childhood incidence of Hodgkin lymphoma and osteosarcoma occurred at age 10–14 years. Incidence was higher among boys than girls in most diagnostic categories and NHL had a male:female ratio of more than 2:1, but for a few cancers, notably germ cell tumours of certain sites, thyroid carcinoma and malignant melanoma, there was a marked excess of girls.

Table 2.2 shows the distribution by morphology of childhood cancers in selected anatomical sites, based on the same data as Table 2.1. The proportions of lymphomas in some sites are probably underestimates, as some cases coded to less specific or multiple sites may in fact have arisen in one of the sites listed. While most cancers of most sites in adults are carcinomas, the pattern in childhood is strikingly different. Tumours of the head and neck included substantial numbers of lymphomas and sarcomas. Lymphomas predominated among cancers of the gastro-intestinal tract. Most cancers of the liver, kidney and eye were characteristic childhood embryonal tumours. Cancers of the ovary were nearly all germ cell tumours. The majority of testicular cancers were germ cell tumours, but there were also substantial numbers of paratesticular rhabdomyosarcomas. Rhabdomyosarcoma was the most common type of childhood cancer in other genito-urinary sites of both sexes.

Table 2.2 Histological types of cancers of selected primary sites diagnosed at age 0–14 years in the UK, 1998–2007

Primary site (ICD-O-3)	Type	Number of registrations
Major salivary glands (C07-08)	Total	52
	Lymphoma	8 (15 %)
	Rhabdomyosarcoma	4 (8 %)
	Carcinoma	40 (77 %)
Other mouth (C00-06)	Total	34
	Lymphoma	2 (6 %)
	Rhabdomyosarcoma	9 (26 %)
	Other sarcoma	5 (15 %)
	Germ-cell tumour	1 (3 %)
	Carcinoma	14 (41 %)
	Unspecified	3 (9 %)
Tonsil (C09)	Total	45
	Lymphoma	45 (100 %)
Nasopharynx (C11)	Total	72
	Lymphoma	13 (18 %)
	Rhabdomyosarcoma	30 (42 %)
	Other sarcoma	1 (1 %)
	Carcinoma	28 (39 %)
Other upper aerodigestive (C10,12-14,30-32)	Total	71
	Lymphoma	15 (21 %)
	Neuroblastoma	1 (1 %)
	Esthesioneuroblastoma	8 (11 %)
	Rhabdomyosarcoma	33 (46 %)
	Other sarcoma	5 (7 %)
	Germ cell	2 (3 %)
	Carcinoma	3 (4 %)
	Unspecified	4 (6 %)
Stomach (C16)	Total	6
	Lymphoma	2 (33 %)
	Germ cell	3 (50 %)
	Carcinoma	1 (17 %)
Small intestine (C17)	Total	44
	Lymphoma	39 (89 %)
	Carcinoma	4 (9 %)
	GIST	1 (2 %)
Colon, rectum (C18-19)	Total	51
	Lymphoma	30 (59 %)
	Carcinoma	19 (37 %)
	Unspecified	2 (4 %)
Liver (C22)	Total	224
	Lymphoma	10 (4 %)
	Hepatoblastoma	146 (65 %)
	Carcinoma	32 (14 %)
	Sarcoma	30 (13 %)
	Germ cell	2 (1 %)
	Unspecified	4 (2 %)
Pancreas (C25)	Total	5
	Lymphoma	2 (40 %)
	Sarcoma	1 (20 %)
	Pancreatoblastoma	2 (40 %)
Lung (C34)	Total	36
	Lymphoma	6 (17 %)
	Sarcoma	6 (17 %)
	Carcinoid/bronchial adenoma	6 (17 %)
	Other carcinoma	5 (14 %)
	Pleuropulmonary blastoma	11 (31 %)
	Mesothelioma	1 (3 %)
	Unspecified	1 (3 %)
Ovary (C56)	Total	135
	Lymphoma	4 (3 %)
	Neuroblastoma	1 (1 %)
	Sarcoma	2 (1 %)
	Germ cell	120 (89 %)
	Carcinoma	4 (3 %)
	Sertoli-Leydig	2 (1 %)
	Mesothelioma	1 (1 %)
	Unspecified	1 (1 %)
Other female reproductive (C52-55,57)	Total	27
	Rhabdomyosarcoma	13 (48 %)
	Other sarcoma	1 (4 %)
	Germ cell	11 (41 %)
	Carcinoma	2 (7 %)
Prostate (C61)	Total	8
	Rhabdomyosarcoma	8 (100 %)
Male genital (C62-63)	Total	124
	Lymphoma	1 (1 %)
	Rhabdomyosarcoma	51 (41 %)
	Germ cell	70 (56 %)
	Sertoli cell	1 (1 %)
	Unspecified	1 (1 %)

Table 2.2 (continued)

Primary site (ICD-O-3)	Type	Number of registrations
Kidney (C64)	Total	895
	Lymphoma	12 (1 %)
	Neuroblastoma	17 (2 %)
	Nephroblastoma (Wilms)	767 (86 %)
	Rhabdoid	31 (3 %)
	Clear cell sarcoma	34 (4 %)
	pPNET	8 (1 %)
	Other sarcoma	7 (1 %)
	Germ cell	1 (<0.5 %)
	Carcinoma	16 (2 %)
	Unspecified	2 (<0.5 %)
Bladder (C67)	Total	43
	Lymphoma	1 (2 %)
	Rhabdomyosarcoma	32 (74 %)
	Other sarcoma	6 (14 %)
	Carcinoma	3 (7 %)
	Paraganglioma	1 (2 %)
Orbit (C69.6)	Total	65
	Chloroma	3 (5 %)
	Lymphoma	5 (8 %)
	Rhabdomyosarcoma	56 (86 %)
	Other sarcoma	1 (2 %)
Other eye (C69.0-69.5,69.7-69.9)	Total	432
	Lymphoma	1 (<0.5 %)
	Medulloepithelioma	1 (<0.5 %)
	Retinoblastoma	417 (97 %)
	Melanoma	8 (2 %)
	Sarcoma	4 (1 %)
	Unspecified	1 (<0.5 %)
Thyroid (C73)	Total	124
	Lymphoma	3 (2 %)
	Differentiated carcinoma	91 (73 %)
	Medullary carcinoma	27 (22 %)
	Unspecified	3 (2 %)

Source: National Registry of Childhood Tumours

In addition to the diseases included in ICCC-3, children can also develop many types of non-malignant neoplasm. They are not generally notified to cancer registries, hence estimates of their incidence are difficult to obtain. A few categories, however, have been routinely ascertained by some specialist population-based registries, or have been the subject of special studies. The incidence of Langerhans cell histiocytosis (LCH) has recently been reported as around 6 per million in Germany [4] and Switzerland [5] and 4 per million in the UK and Ireland [6]. Mesoblastic nephroma accounted for 3 % of all renal tumours in North-west England [7], 4 % in Germany [4] and 6 % in the West Midlands of England [8], indicating an annual incidence of about 0.4 per million. In North-west England 61 % of all extracranial germ cell tumours were non-malignant [9]; they represented 48 % of germ cell tumours in the testes, 60 % in the ovaries and 69 % in other sites. In the West Midlands of England, all 49 extracranial germ cell tumours diagnosed in the first 3 months of life were benign teratomas, though four did recur as malignant tumours [10]; benign teratomas represented 29 % of all registered neoplasms in this age group, making them more numerous than neuroblastomas. Adrenocortical adenoma accounted for 29 % of adrenocortical tumours in North-west England [11], implying an annual incidence of about 0.1 per million. It is not always possible to distinguish morphologically between benign and malignant adrenocortical tumours, however, and they should perhaps be regarded as lying on a continuum of clinical behaviour [12]. Carcinoid tumours of the appendix had an annual incidence of 1.1 per million children in the West Midlands of England [13].

There are pronounced variations in the occurrence of different types of childhood cancer between ethnic groups and world regions. ALL is less common among less affluent populations, including not only those of developing countries but also African-Americans in the USA. The deficit is largely due to the attenuation or even the absence of the early childhood peak that has been characteristic of western industrialised countries since the mid-twentieth century. Lymphomas, on the other hand, tend to be more frequent in less developed countries, the most extreme example being the very high incidence of Burkitt lymphoma in a broad band across equatorial Africa and also in Papua New Guinea.

Increases in the incidence of various childhood cancers have been recorded in many countries during past decades [14–17]. Mostly the changes have been quite small, often no more than 1 % per year [14]. There have, however, been a few examples of much larger increases. Where population screening for neuroblastoma in infancy was offered either as a service or in the context of a scientific study, there was a dramatic increase in incidence resulting from detection of additional cases that would otherwise never have presented clinically [18–20]. The very large increase in childhood Kaposi sarcoma in some sub-Saharan African countries is linked to the AIDS epidemic, through immunosuppression consequent on HIV infection allowing HHV-8 viral load to increase uncontrollably [21]. The equally spectacular rise in thyroid cancer among children in regions most severely contaminated with radioactive fallout from Chernobyl was certainly due in part to radiation exposure, though intensive screening also contributed [22]. Incidence has fallen to lower levels among children who were born after the Chernobyl accident [23].

Increases in the incidence of CNS tumours, especially low-grade gliomas, are consistent with improved detection following the introduction of computed tomography (CT) and magnetic resonance imaging [17, 24]. It is difficult to apportion the relative contributions of improved detection

and diagnosis, improved registration and genuine increases in risk to the rather small increases in incidence of most other childhood cancers [16, 17].

Aetiology

Despite intensive research over several decades, very little is known about the causes of most childhood cancers. Some of the most well established risk factors are genetic in nature. An increasingly long list of hereditary syndromes, mostly associated with identified single gene defects, carry a raised risk of specific childhood cancers [25–27]. Germline mutations or deletions of RB1 give rise to heritable retinoblastoma. Children with neurofibromatosis 1 have an increased risk of gliomas, soft-tissue sarcomas and juvenile myelomonocytic leukaemia. Germline mutations of TP53 carry a raised risk of various cancers including soft tissue sarcoma, osteosarcoma, adrenocortical carcinoma, brain tumours and leukaemia, as well as pre-menopausal breast cancer; Li-Fraumeni syndrome is the resulting aggregation of specific combinations of these cancers within a family. An especially wide range of genetic disorders, both heritable and sporadic, is associated with Wilms tumour, including Beckwith-Wiedemann, Denys-Drash, WAGR, and Simpson-Golabi-Behmel syndromes [28]. Constitutional chromosomal abnormalities are implicated in about 1 % of all childhood cancers [29]. The most important is Down syndrome, which carries a greatly raised risk of leukaemia and almost certainly an increased risk of germ cell tumours, though the total excess of cancer is reduced by an apparent protective effect against several other types of solid tumours [30]. Risks associated with other, usually isolated, congenital abnormalities will be discussed towards the end of this section.

In 1991 it was estimated that genetic conditions were responsible for about 3 % of all childhood cancer [31]. That figure will now be higher, not least because the 1991 estimate did not include Li-Fraumeni syndrome, but the proportion attributable to known genetic disorders is probably still under 5 % in most populations. The main exception must be North African populations with high frequencies of the recessive DNA repair disorder xeroderma pigmentosum (XP), which carries a 1000 fold increased risk of skin cancer among children and adolescents [32]. In a series of 900 childhood cancers other than leukaemia from the National Cancer Institute in Tunisia, 8 % were skin carcinomas associated with XP [33].

The largest study of parental age as a risk factor for childhood cancer found positive linear trends in risk with maternal age for several diagnostic groups but there was little evidence of any effect of paternal age after adjustment for maternal age [34]. It was not possible to determine the mechanisms whereby cancer risk increased with mother's age, but it seemed likely to involve germline mutations.

An enormous number of exogenous or environmental exposures have been investigated as possible risk factors for childhood cancer [35, 36]. The only ones to which more than a handful of cases can be attributed worldwide are ionising radiation and certain infectious agents.

The relationship between *in utero* radiation exposure from obstetric x-rays and subsequent cancer in the child was established almost half a century ago [37]. At that time as many as 1 in 20 cases of childhood cancer may have been attributable to obstetric irradiation but the proportion nowadays must be much lower since ultrasound has largely supplanted x-rays. The use of x-rays to treat certain benign conditions produced an increased risk of cancer but this practice is also obsolete and therefore responsible for virtually no new cases of childhood cancer. A large national study of cancer following CT scans before the age of 22 years found that a cumulative dose of 50 mGy might almost triple the risk of leukaemia and cumulative dose of 60 mGy might triple the risk of a CNS tumour [38]. Radiotherapy treatment for childhood cancer is itself carcinogenic but the numbers of subsequent malignancies occurring within childhood are relatively small. Large numbers of thyroid carcinomas occurred among children in the areas of Ukraine, Belarus and Russia most heavily exposed to radioactive iodine as a result of the Chernobyl nuclear power station explosion in 1986 but there is little evidence of increased risk in less severely contaminated regions [39]. It has been estimated that around 15 % of childhood leukaemia in Britain may be attributable to natural background ionising radiation [40].

Ultraviolet (UV) radiation from the sun causes malignant melanoma and skin carcinomas, mainly in adults. The excess of skin cancers in children with XP results from UV exposure of a highly susceptible group. The possibility of carcinogenic effects of electromagnetic fields arising from electric power cables has caused public concern for more than two decades. A moderately raised risk of leukaemia has consistently been found for the highest exposure levels experienced by fewer than 1 in 20 children in industrialised countries but the reasons for this are unclear [41–45]. There is little evidence for an association between magnetic field exposure and childhood brain tumours [44, 46, 47].

Several specific infections are known to increase the risk of cancer. Among children worldwide, the types of cancer with the largest numbers of cases attributable to infectious agents are Burkitt lymphoma, Hodgkin lymphoma and nasopharyngeal carcinoma (all associated with Epstein-Barr virus, with malaria as a cofactor for Burkitt lymphoma in the region of highest incidence), hepatocellular carcinoma (hepatitis B) and Kaposi sarcoma (HHV-8) [48]. The introduction of universal vaccination against hepatitis B has been followed by reductions of around 70 % in the occurrence of childhood hepatocellular carcinoma in Taiwan and South Korea [49, 50].

Many epidemiological studies support the suggestion that infection is involved in the aetiology of some childhood leukaemias [51]. Most of these studies are relevant to either or both of two hypotheses. Kinlen's hypothesis that leukaemia is a rare response to a specific, but unidentified infection is supported by the finding of increased incidence in many situations of population mixing which could have led to impaired herd immunity [52]. Greaves's hypothesis that common ALL can arise as an abnormal response to infectious challenge, especially in children with weaker immunity, is supported by studies showing a protective effect of breast feeding and early daycare attendance [53–55].

Some medical treatments are undoubtedly carcinogenic. The excess risk from radiotherapy has already been mentioned. Some chemotherapeutic drugs used to treat cancer produce an increased risk of subsequent cancers but relatively few of these occur in childhood. Children who receive a solid organ transplant are especially vulnerable to neoplasms, of which post-transplant lymphoproliferative disorder and skin carcinomas are the most frequent [56]. Daughters of women who took diethylstilboestrol (DES) in pregnancy had an increased risk of clear cell carcinoma of the vagina or cervix [57] but most of these tumours occurred in early adulthood and DES ceased to be used more than 30 years ago. Many studies have found associations between exposure to other medical treatments *in utero* or postnatally and various childhood cancers but there has been little consistency between reports.

With the increasing use of assisted reproductive technology (ART), there has been a succession of anecdotal reports of cancer in children born following ART. Combined data from studies up to 2005 of children born after ART failed to reveal any significant increase in the risk of cancer [58, 59], but the expected numbers of cancers were relatively small and follow-up was short for children born after some types of ART. A more recent study in Sweden found a significantly increased odds ratio of 1.34 for cancer (excluding LCH) in children born after in vitro fertilization, but there were fewer than 50 cases of cancer of all types combined [60]. In the same study there were 6 cases of LCH compared with 1.0 expected [60]. No other study has reported an association of LCH with ART.

A wide range of other exogenous exposures to the child, to the mother antenatally or to the father preconceptionally, have been suggested as contributing to the aetiology of childhood cancer. Mostly the evidence comes from a small number of studies or is inconsistent between studies [61, 62].

Malformations and other physical characteristics associated with certain childhood cancers could be markers for underlying genetic or environmental causes. In large population-based studies, 3–4 % of children with malignant solid tumours also had a congenital anomaly, in many cases not as part of any recognised syndrome [63, 64]. The overall relative risk is about 3 for all anomalies [65] , and about 1.5 for non-chromosomal anomalies [64]. Such occurrences could result from an unknown genetic defect or, as seems more likely, for example, in the association of hernia with Ewing sarcoma, have a common environmental cause [66].

High birth weight has been associated with raised risk of several types of childhood cancer, notably leukaemia [67, 68], CNS tumours [69], and neuroblastoma [70], perhaps resulting from increased growth rate *in utero*. By contrast, infants with very low birth weight have a greatly increased risk of hepatoblastoma which may be attributable to exposures in neonatal intensive care units but there is as yet no conclusive evidence [71]. Children who are twins have consistently been found to have a risk of cancer around 80 % of that in singleton children [72, 73]. The reasons for this are unknown but possible explanations include lower birth weight, earlier restriction of growth in twin pregnancies, and higher *in utero* death rates of embryos in which tumorogenesis is initiated shortly after conception [73]. Patients with osteosarcoma are significantly taller than the general population, indicating a role of accelerated long bone growth around puberty [74].

Survival

Table 2.3 shows actuarial 5-year survival rates for children in Great Britain with cancer diagnosed during 2003–2007 [75]. More than three quarters of children survived for 5 years, and the survival rate comfortably exceeded 80 % for several important diagnostic groups. Five-year survival rates above 75 % are seen in many other industrialised countries [76, 77]. Survival tends to be lower in less affluent countries of Eastern Europe [77], and lower still in developing countries [78]. The prognosis for many childhood cancers has improved dramatically over past decades. In Great Britain, 5-year survival of children diagnosed in 1971–1975 was 39 %, compared with 77 % for those diagnosed a quarter century later [75]. This means that the risk of death within 5 years from diagnosis was reduced by 63 %. Figures 2.1, 2.2 and 2.3 show that survival for all major diagnostic groups increased in Britain between 1983 and 1987 and 2003–2007, though the timing of the largest increases varied between diagnostic groups. Broadly similar trends have been observed in other industrialised countries [79–83].

The results quoted here are derived from cancer registry data and estimate survival rates at the population level. Survival data can also be found in countless publications from clinical trials and single or multi-institutional case series. Very often the results appear better than those from population based data, but they could well be unrepresentative of all cases in the population because of selective exclusion of those with a poor prognosis or not offered

Table 2.3 Five year survival of children in Great Britain with cancer diagnosed during 2003–2007

	Five-year survival (%)
All cancers	79
Leukaemia	86
ALL	90
AML	68
Lymphomas	89
Hodgkin	94
Non-Hodgkin (incl. Burkitt)	85
CNS tumours	71
Ependymoma	70
Astrocytoma	81
Embryonal	53
Other glioma	43
Craniopharyngioma	95
Neuroblastoma	63
Retinoblastoma	99
Renal tumours	84
Nephroblastoma (Wilms tumour)	90
Hepatic tumours	71
Hepatoblastoma	78
Bone tumours	64
Osteosarcoma	63
Ewing sarcoma family	63
Soft tissue sarcoma	68
Rhabdomyosarcoma	65
Germ cell and gonadal	92
CNS germ cell	89
Other extragonadal germ cell	87
Gonadal germ cell	99
Thyroid carcinoma	100
Malignant melanoma	91

Source: National Registry of Childhood Tumours [75]

most effective treatment. Increases in survival have, nevertheless, occurred concurrently with the development of paediatric oncology clinical trials groups and increased referral to specialist treatment centres in many countries. Several studies have found that survival was higher for children who were treated at large or specialist centres or entered in clinical trials [84, 85]. A recent national study in Britain found that for a wide range of childhood cancers changes in population-based survival between the eras of successive clinical trials paralleled those reported by the relevant trials [86].

Improved survival has resulted in increasing numbers of long-term survivors of childhood cancer. The cumulative risk of a second primary malignancy is about 3.6 % within 25 years of diagnosis [87] and about 5 % by the age of 40 years [88]. Many other aspects of the health of long-term survivors and their offspring are the subject of several large epidemiological studies [89–98].

Mortality

Population mortality rates from childhood cancer in western countries have fallen dramatically since the mid twentieth century, in line with the moderate increase in incidence and very marked improvements in outcome. Table 2.4 shows estimated age standardised mortality rates for childhood cancer by world region in 2008 [99]. In wealthy industrialised countries, mortality was typically around 20–30 per million. It was considerably higher in Eastern Europe, reflecting the lower survival rates still obtained in that region. Results for other world regions are harder to interpret because of incompleteness and inaccuracy in the data for many countries [100].

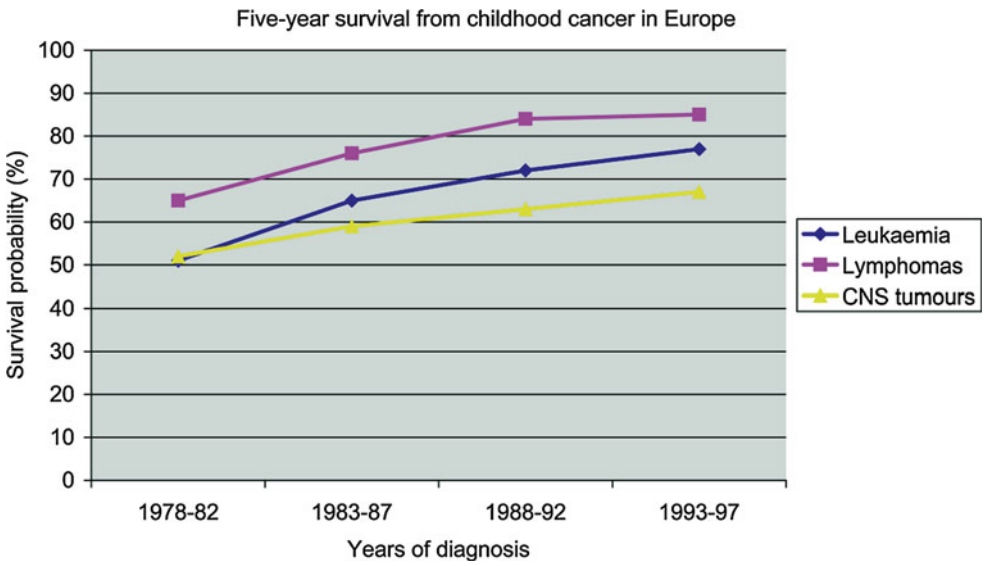

Fig. 2.1 Five year survival of children in Great Britain with leukaemias, lymphomas and CNS tumours diagnosed 1983–2007 (Source: National Registry of Childhood Tumours)

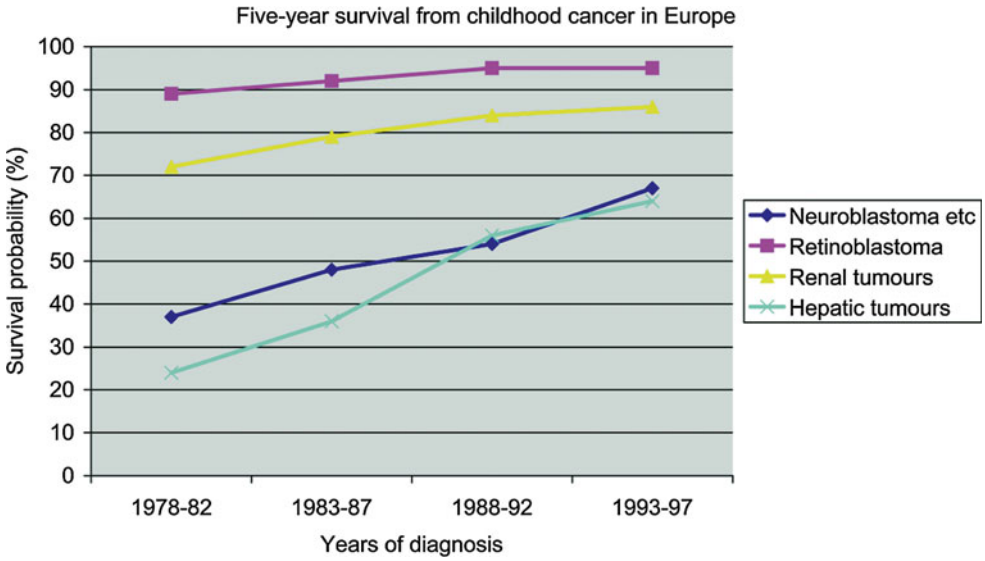

Fig. 2.2 Five year survival of children in Great Britain with neuroblastoma and other peripheral nervous cell tumours, retinoblastoma, renal tumours and hepatic tumours diagnosed 1983–2007 (Source: National Registry of Childhood Tumours)

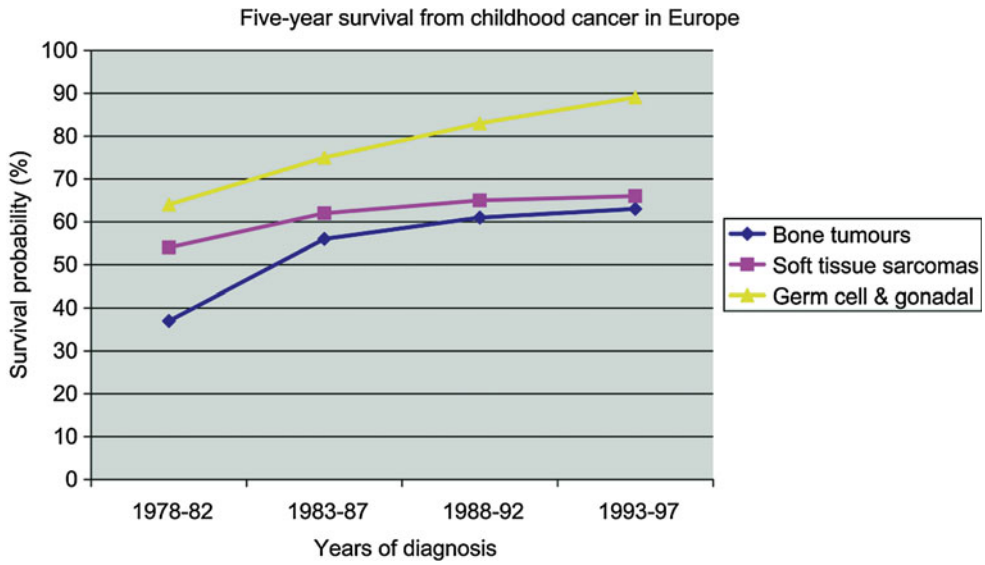

Fig. 2.3 Five year survival of children in Great Britain with bone tumours, soft tissue sarcomas and germ cell and gonadal tumours diagnosed 1983–2007 (Source: National Registry of Childhood Tumours)

Overall, and for cancers other than those of the brain and nervous system, mortality rates tended to be highest in developing countries, reflecting their generally lower survival rates. Mortality from cancers of the brain and nervous system showed a different pattern with low rates in developing countries outside the Americas and Western Asia; since survival is lower in these countries, the lower mortality must be a result of under-recording and lower incidence.

Table 2.4 Estimated age-standardised mortality rates per million for cancer at age 0–14 years, 2008, by world region

	Total	Leukaemia	Lymphoma	Brain/nervous system	Renal
Northern Africa	78	19	17	9	9
Sub-Saharan Africa	68	8	21	2	8
USA/Canada	24	7	1	7	1
Central America	63	32	5	9	1
South America	46	19	3	9	2
Western Asia	77	29	16	10	5
India	37	13	4	5	1
Other South and Central Asia	59	20	9	6	3
China	46	25	2	10	1
Japan	19	7	1	5	<1
South-Eastern Asia	70	34	6	8	3
Nordic Countries	28	10	1	9	1
British Isles	27	7	1	9	1
Former USSR in Europe	41	12	2	12	2
Other Eastern Europe	36	12	3	12	1
Western Europe	21	6	1	9	1
Southern Europe	30	10	1	9	1
Australia/New Zealand	25	8	<1	10	1

Source: GLOBOCAN 2008 [99]

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Tumor Biology and Environmental Carcinogenesis

3

Andrew M. Davidoff

Introduction

During normal development and self-renewal, cells evolve to perform highly specialized functions to meet the physiologic needs of the organism. These processes involve tightly regulated activities that include continued cell proliferation, differentiation into specialized cell types, and programmed cell death (apoptosis). An intricate system of checks and balances ensures proper control over these physiologic processes. The genetic composition (genotype) of a cell forms the basis for that control, but the environment also plays a crucial role in influencing cell fate. Cells use complex signal transduction pathways to sense and respond to neighboring cells and their extracellular milieu. In addition, environmental factors may have a direct impact on cell phenotype and fate by causing DNA damage that permanently alters the host genome.

Cancer is a genetic disease whose progression is driven by a series of accumulating genetic changes influenced by hereditary factors and the somatic environment. These genetic changes result in individual cells acquiring a phenotype that provides those cells with a survival advantage over surrounding normal cells. Our understanding of the processes that occur in malignant cell transformation is increasing, with many discoveries in cancer cell biology having been made using childhood tumors as models.

Cell Fate

Stem Cells

The development and maintenance of the tissues that comprise an organism are driven by stem cells. These are cells with the potential for both self-renewal and terminal differentiation into one or more cell types. They, therefore, play a critical role in normal tissue turnover and repair. The fate of most of these stem cells is generally one of terminal differentiation and either quiescence or apoptosis. However, a small percentage of stem cells maintain their pleuripotent capacity. It is becoming increasingly recognized that these same stem cells that are essential for maintaining an organism are also central to the development of malignancy and therapy resistance [133]. Cancer stem cells, like normal stem cells, possess remarkable proliferative and self-renewal capacities, while the larger portion of partially differentiated tumor cells possess quite limited reproductive potential.

Programmed Cell Death

Multicellular organisms have developed a highly organized and carefully regulated mechanism of cell death in order to maintain cellular homeostasis. Normal development and morphogenesis are often associated with the production of excess cells, which are removed by the genetically programmed process called apoptosis. Apoptosis is a highly regulated event which can be effected by either death receptor-mediated or mitochondrial pathways by activating specific signaling molecules. Both pathways converge onto a group of effector caspases, leading to morphologic and biochemical changes characteristic of apoptosis. Cells undergoing apoptosis have distinct morphologic features (plasma membrane blebbing, reduced volume, nuclear condensation), and their DNA is subjected to endonucleolytic cleavage.

Receptor-mediated apoptosis is initiated by the interaction of "death ligands" such as tumor necrosis factor α (TNFα), Fas, and TNF-related apoptosis-inducing ligand (TRAIL) with their respective receptors. This interaction is followed by aggregation of the receptors and recruitment of adaptor proteins to the plasma membrane, which activate caspases [92]. Caspases are a large family of proteases that function in both the initiation of apoptosis in response to proapoptotic signals and in the subsequent effector pathway

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Table 3.1 Proto-oncogenes and tumor suppressor genes in pediatric malignancies

Oncogene family	*Proto-oncogene*	*Chromosome location*	*Tumors*
Growth factors and receptors			
	erb B2	17q21	Glioblastoma
	trk	9q22	Neuroblastoma
Receptor tyrosine kinase			
	alk	2p23	Neuroblastoma
	ret	10q11.2	Medullary thyroid carcinoma, Multiple endocrine neoplasia 2A/B, pheochromocytoma
Signal transducers			
	H-ras	11p15.1	Neuroblastoma
Transcription factors			
	c-myc	18q24	Burkitt lymphoma
	N-myc	2p24	Neuroblastoma
Syndrome	*Tumor suppressor gene*	*Chromosome location*	*Tumors*
Familial polyposis coli	APC	5q21	Intestinal polyposis, colorectal cancer
Familial retinoblastoma	RB	13q24	Retinoblastoma, osteosarcoma
WAGR[a]	WT1	11p13	Wilms tumor
Denys-Drash[b]	WT1	11p13	Wilms tumor
Beckwith-Weidemann[c]	WT2 (?)	11p15	Wilms tumor, hepatoblastoma, adrenal tumors
Li-Fraumeni	p53	17q13	Multiple
Neurofibromatosis type 1	NF1	17q11.2	Sarcomas, breast cancer
Neurofibromatosis type 2	NF2	22q12	Neurofibroma, neurofibrosarcoma, brain tumor
Von Hippel-Lindau	VHL	3p25-26	Renal cell cancer, pheochromocytoma, retinal angioma, hemangioblastoma

Reprinted with permission from Davidoff and Krasin [31]
[a]WAGR: Wilms tumor, aniridia, genitourinary abnormalities, and mental retardation
[b]Denys-Drash: Wilms tumor, pseudohermaphroditism, mesangeal sclerosis, renal failure
[c]Beckwith-Weidemann: multiple tumors, hemihypertrophy, macroglossia, hyperinsulinism

that disassembles the cell. Thus, apoptosis limits cellular expansion and counters cell proliferation. Because cell survival signals may also be activated through parallel pathways, the fate of a cell is determined by the balance between death signals and survival signals [65]. Other signals arising from cellular stress (e.g., DNA damage, hypoxia, oncogene activation) may also effect cell cycle arrest or apoptosis.

An alternative to cell death mediated by receptor-ligand binding is cellular senescence, which is initiated when chromosomes reach a critical shortened length. Eukaryotic chromosomes have DNA strands of unequal length, and their ends—telomeres—are characterized by species-specific nucleotide repeat sequences. Telomeres stabilize the ends of chromosomes, which are otherwise sites of significant instability [121]. Over time and with each successive cycle of replication, chromosomes are shortened by failure to complete replication of their telomeres. Thus, telomere shortening acts as a biologic clock, limiting the lifespan of a cell. Germ cells, however, avoid telomere shortening by using telomerase, an enzyme capable of adding telomeric sequences to the ends of chromosomes. This enzyme is normally inactivated early in the growth and development of an organism. Persistent activation or the reactivation of telomerase in somatic cells appears to contribute to the immortality of transformed cells.

Malignant Transformation

Alteration or inactivation of any of the components of normal cell regulatory pathways may lead to the dysregulated growth that characterizes neoplastic cells. Malignant transformation may be characterized by cellular dedifferentiation or failure to differentiate, cellular invasiveness and metastatic capacity, and/or decreased drug sensitivity. Tumorigenesis reflects the accumulation of excess cells that results from increased cell proliferation and decreased apoptosis or senescence. Cancer cells do not replicate more rapidly than normal cells, but they show diminished responsiveness to regulatory signals. Positive growth signals are generated by proto-oncogenes, so named because their dysregulated expression or activity can promote malignant transformation. These proto-oncogenes may encode growth factors or their receptors, intracellular signaling molecules, and nuclear transcription factors (Table 3.1). Conversely, tumor suppressor genes, as their name implies, control or restrict cell growth and proliferation. Their inactivation, through various mechanisms, permits the dysregulated growth of cancer cells. Also important are the genes that regulate cell death. Their inactivation leads to resistance to apoptosis and allows accumulation of additional genetic aberrations.

Cancer cells carry DNA that has point mutations, viral insertions, or chromosomal or gene amplifications, deletions, or rearrangements. Each of these aberrations can alter the context and process of normal cellular growth and differentiation. Although genomic instability is an inherent property of the evolutionary process and normal development, it is through genomic instability that the malignant transformation of a cell may arise. This inherent instability may be altered by inheritance or exposure to destabilizing factors in the environment. Point mutations may terminate protein translation, alter protein function, or change the regulatory target sequences that control gene expression. Chromosomal alterations create new genetic contexts within the genome and lead to the formation of novel proteins or to the dysregulation of genes displaced by aberrant events.

Genetic abnormalities associated with cancer may be detected in every cell in the body or only in the tumor cells. Constitutional or germline abnormalities are either inherited or occur de novo in the germ cells (sperm or oocyte). Interestingly, despite the presence of a genetic abnormality that might affect growth regulatory pathways in all cells, specific genetic abnormalities generally predispose only to certain tumor types. This selectivity highlights the observation that gene function contributes to growth or development only within a particular milieu or physiologic context.

Specific tumors occur earlier and are more often bilateral (in paired organs) when they result from germline mutations than when they result from sporadic or somatic alterations. Such is often the case in two pediatric malignancies, Wilms tumor and retinoblastoma. These observations led Alfred Knudson to propose a "two-hit" model of carcinogenesis in which the first genetic defect, already present in the germ line, must be complemented by an additional spontaneous mutation before a tumor can arise [62]. In sporadic cancer, cellular transformation occurs only when two (or more) spontaneous mutations take place in the same cell. The critical features of the Knudson model – the small number of mutations required for malignant transformation, the possible inheritance of a first mutation and the gradual disappearance of transformable target cells with increasing age, provide a conceptual framework for mutational theories of the genetics of most childhood tumors. In this scheme familial tumors will present earlier than sporadic tumors of the same histologic type; inheritance of a tumorigenic mutation will also predispose to multiple tumor occurrences.

Much more common, however, are somatically acquired chromosomal aberrations, which are confined to the malignant cells. These aberrations affect growth factors and their receptors, signal transducers, and transcription factors. The general types of chromosomal alterations associated with malignant transformation are shown in Fig. 3.1. Although a low level of chromosomal instability exists in a normal population of cells, neoplastic transformation occurs only if these alterations affect a growth-regulating pathway and confer a growth advantage.

DNA Content

Normal human cells contain two copies of each of 23 chromosomes; therefore, a normal "diploid" cell has 46 chromosomes. Although cellular DNA content, or ploidy, is accurately determined by karyotypic analysis, it can be estimated by the much simpler method of flow cytometry. The DNA index (DI) is defined as the ratio of the number of chromosome copies per cell to that of a normal cell (i.e., 46). Diploid cells have a DI of 1.0, whereas near-triploid cells have a DNA index ranging from 1.26 to 1.76. The majority (55 %) of primary neuroblastoma cells are triploid or near triploid, having between 58 and 80 chromosomes, whereas the remainder are near diploid (35–57 chromosomes) or near tetraploid (81–103 chromosomes) [57]. Neuroblastomas consisting of near-diploid or near-tetraploid cells usually have structural genetic abnormalities (e.g., chromosome 1p deletion and amplification of the *MYCN* oncogene), whereas those consisting of near-triploid cells are characterized by three almost complete haploid sets of chromosomes with few structural abnormalities [12]. The DI can have prognostic significance; patients with near-triploid tumors typically have favorable clinical and biologic prognostic factors, and excellent survival rates, compared with those who have near-diploid or near-tetraploid tumors [75].

Chromosomal Translocations

Many pediatric cancers, particularly soft-tissue neoplasms and hematologic malignancies, have recurrent, nonrandom abnormalities in chromosomal structure, typically chromosomal translocations (Table 3.2). The most common result of a nonrandom translocation is the fusion of two distinct genes from different chromosomes. The genes are typically fused within the reading frame and express a functional, chimeric protein product that has transcription factor or protein kinase activity. These fusion proteins contribute to tumorigenesis by activating genes or proteins involved in cell proliferation. For example, in Ewing sarcoma the consequence of the t(11;22)(q24;q12) translocation is the fusion of *EWS*, a transcription factor gene on chromosome 22, and *FLI-1*, a gene encoding a member of the ETS family of transcription factors on chromosome 11 [81]. The resultant chimeric protein, which contains the DNA-binding region of FLI-1 and the transcription activation region of EWS, has greater transcriptional activity than does EWS alone [82]. The EWS:FLI-1 fusion transcript is detectable in approximately 90 % of Ewing sarcomas. At least four other EWS fusions have been identified in Ewing sarcoma; fusion of EWS with ERG (another ETS family member) accounts for an additional 5 % of cases [124]. Alveolar rhabdomyosarcomas have characteristic translocations between the long arm of chromosome 2 (75 % of cases)

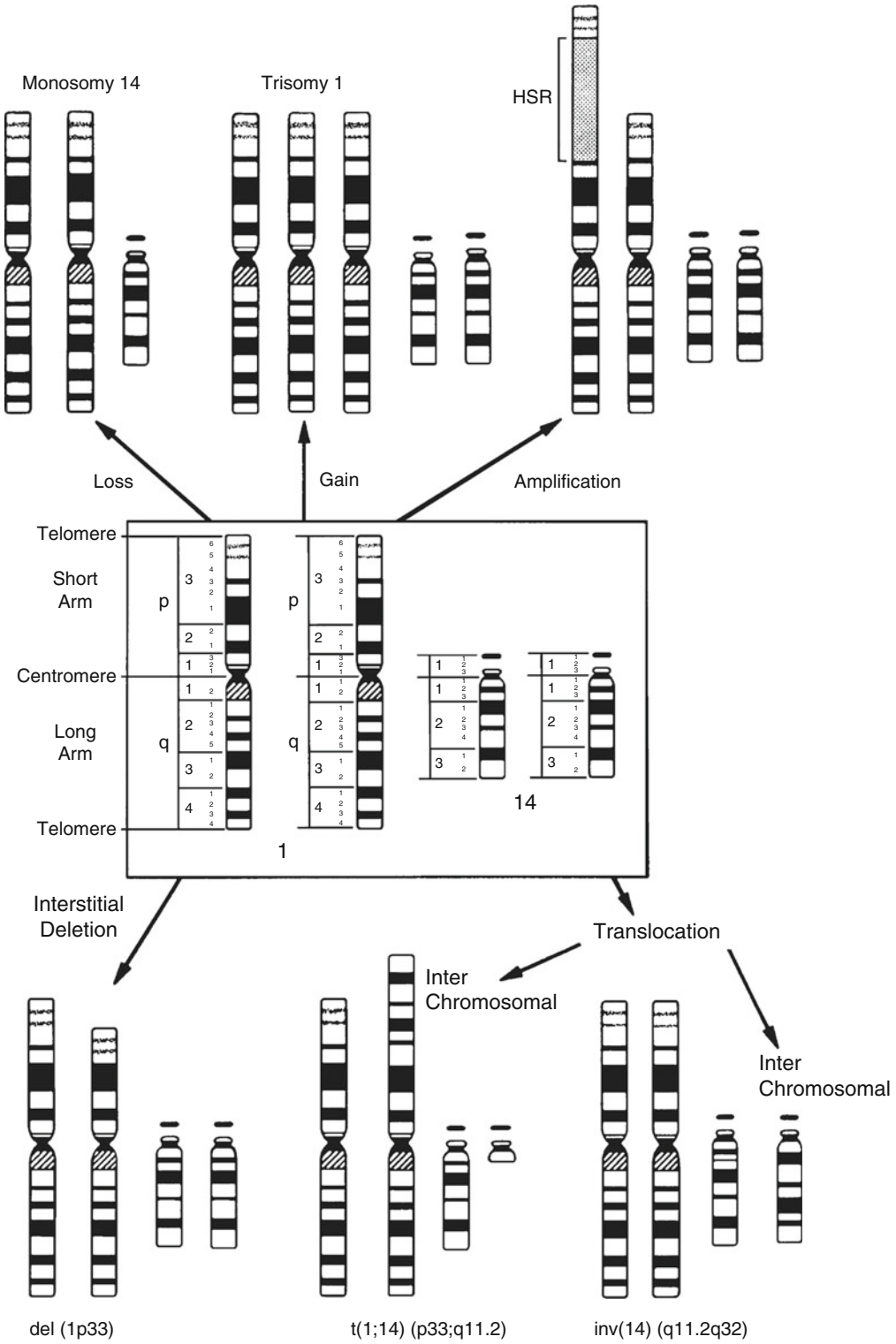

Fig. 3.1 The spectrum of gross chromosomal aberrations using chromosomes 1 and 14 as examples (Reprinted with permission from Look and Kirsch [76])

or the short arm of chromosome 1 (10 % of cases) and the long arm of chromosome 13. These translocations result in the fusion of *PAX3* (at 2q35) or *PAX7* (at 1p36) with *FOXO1*, a gene encoding a member of the forkhead family of transcription factors [47]. The *EWS*:*FLI-1* and *PAX7*:*FOXO1* fusions appear to confer a better prognosis for patients with

Table 3.2 Common, recurrent translocations in soft tissue tumors

Tumor	Genetic abnormality	Fusion transcript
Ewing sarcoma/Primitive neuroectodermal tumor	t(11;22)(q24;q12) t(21;22)(q22;q12) t(7;22)(p22;q12) t(17;22)(q12;q12) t(2;22)(q33;q12)	*FLI1-EWS* *ERG-EWS* *ETV1-EWS* *E1AF-EWS* *FEV-EWS*
Desmoplastic small round cell tumor	t(11;22)(p13;q12) t(11;22)(q24;q12)	*WT1-EWS* *FLI1-EWS*
Synovial sarcoma	t(X;18)(p11.23;q11) t(X;18)(p11.21;q11)	*SSX1-SYT* *SSX2-SYT*
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14) t(1;13)(p36;q14)	*PAX3-FOXO1* *PAX7-FOXO1*
Malignant melanoma of soft part (clear cell sarcoma)	t(12;22)(q13;q12)	*ATF1-EWS*
Myxoid liposarcoma	t(12;16)(q13;p11) t(12;22)(q13;q12)	*CHOP-TLS*(*FUS*) *CHOP-EWS*
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12)	*CHN-EWS*
Dermatofibrosarcoma protuberans and Giant cell fibroblastoma	t(17;22)(q22;q13)	*COL1A1-PDGFB*
Congenital fibrosarcoma and Mesoblastic nephroma	t(12;15)(p13;q25)	*ETV6-NTRK3*
Lipoblastoma	t(3;8)(q12;q11.2) t(7;8)(q31;q13)	? ?

Reprinted with permission from Davidoff and Hill [30]

Ewing sarcoma and alveolar rhabdomyosarcoma, respectively [6, 32]. Translocations that generate chimeric proteins with increased transcriptional activity also characterize desmoplastic small round cell tumor [69], myxoid liposarcoma [108], extraskeletal myxoid chrondrosarcoma [23], malignant melanoma of soft parts [140], synovial sarcoma [24], congenital fibrosarcoma [130], cellular mesoblastic nephroma [111], and dermatofibrosarcoma protuberans [94].

Proto-oncogene Activation

Proto-oncogenes are commonly activated in transformed cells by gene amplification or point mutation. Gene amplification (i.e., selective replication of DNA sequences) enables a tumor cell to increase expression of crucial genes whose products are ordinarily tightly controlled. The amplified DNA sequences, or amplicons, may be maintained episomally (i.e., extrachromosomally) as double minutes—paired chromatin bodies lacking a centromere—or as intrachromosomal, homogeneously staining regions. In about one third of neuroblastomas, for example, the transcription factor and proto-oncogene *MYCN* is amplified. *MYCN* encodes a 64-kDa nuclear phosphoprotein (MycN) that forms a transcriptional complex by associating with other nuclear proteins expressed in the developing nervous system and other tissues [63]. Increased expression of MycN increases the rates of DNA synthesis and cell proliferation and shortens the G1 phase of the cell cycle [77]. The *MYCN* copy number in neuroblastoma cells can be amplified 5- and 500-fold and is usually consistent among primary and metastatic sites and at different times during tumor evolution and treatment [11]. This consistency suggests that *MYCN* amplification is an early event in the pathogenesis of neuroblastoma. Because *MYCN* gene amplification is usually associated with advanced stages of disease, rapid tumor progression, and poor outcome, it is a powerful prognostic indicator for neuroblastoma [13, 119]. The cell surface receptor gene *ERBB2* is another proto-oncogene commonly overexpressed due to gene amplification, an event that occurs in breast cancer, osteosarcoma, and Wilms tumor [104].

An example of proto-oncogene activation by point mutation involves the tyrosine kinase receptor, anaplastic lymphoma kinase (ALK), on the short arm of chromosome 2 (2p23). Receptor tyrosine kinases (RTK) are high-affinity cell surface receptors for many growth factors, cytokines and hormones. When activated through ligand binding, these proteins mediate phosphorylation of tyrosine resides on target molecules or substrates, resulting in intracellular signaling and, ultimately, the regulation of normal cellular processes. Mutation of RTK's can lead to constitutive activation of the signaling pathway in the absence of ligand. Recently, activating mutations of *ALK* have been shown to be the germline abnormality associated with hereditary neuroblastoma [89]. These mutations can also be somatically acquired, as can amplification of the gene, although the prevalence of ALK activation in sporadic neuroblastoma is not known [19]. Activated ALK has proven to be a targetable abnormality in neuroblastoma, with drugs such as crizotinib, an anti-ALK antibody, showing efficacy [21].

Another example is the *RET* proto-oncogene, which encodes a RTK for members of the glial cell line-dervied neurotrophic factor family of extracellular signaling molecules. Mutation of the *RET* proto-oncogene, resulting in gain of

function, is associated with medullary thyroid carcinoma, pheochromocytoma and multiple endocrine neoplasias types 2A and 2B [91]. Interestingly, the various specific mutations have a different influence on the tumor phenotype [90].

Inactivation of Tumor Suppressor Genes

Tumor suppressor genes, or antioncogenes, provide negative control of cell proliferation. Loss of function of the proteins encoded by these genes, through deletion or mutational inactivation of the gene, liberates the cell from growth constraints and contributes to malignant transformation. The cumulative effect of genetic lesions that activate proto-oncogenes or inactivate tumor suppressor genes is a breakdown in the balance between cell proliferation and cell loss due to differentiation or apoptosis. Such imbalance results in clonal overgrowth of a specific cell lineage. The first tumor suppressor gene to be recognized was the retinoblastoma susceptibility gene, *RB*. This gene encodes a nuclear phosphoprotein that acts as a "gatekeeper" of the cell cycle. RB normally permits cell cycle progression through the G1 phase when it is phosphorylated but prevents cell division when it is unphosphorylated. Inactivating deletions or point mutations of *RB* cause the protein to lose its regulatory capacity.

The nuclear phosphoprotein, p53, has also become recognized as an important tumor suppressor gene, perhaps the most commonly altered gene in all human cancers. Inactivating mutations of p53 also cause the protein to lose its ability to regulate the cell cycle. The *p53* gene is frequently inactivated in solid tumors of childhood, including osteosarcoma, rhabdomyosarcoma, brain tumors, anaplastic Wilms tumor, and a subset of chemotherapy-resistant neuroblastoma [5, 59, 66]. In addition, heritable cancer-associated changes in the *p53* tumor suppressor gene occur in families with Li-Fraumeni syndrome, an autosomal dominant predisposition for rhabdomyosarcoma, other soft tissue and bone sarcomas, premenopausal breast cancer, brain tumors, and adrenocortical carcinomas [78].

Recently, inactivating mutations of *ATRX*, a transcriptional regulator that is part of a multiprotein complex that plays a role in regulating chromatin remodeling, nucleosome assembly, and telomere maintenance, have been found in neuroblastoma, particularly high stage tumors in older patients [22]. *ATRX* mutations appear to be loss-of-function mutations associated with an absence of the ATRX protein in the nucleus, and with long telomeres. How these alterations lead to lengthened telomeres is uncertain, however. These results may provide a molecular marker and potential therapeutic target for neuroblastoma among adolescents and young adults. It may also delineate the subset of children with neuroblastoma who have a chronic but progressive clinical course when receiving standard therapeutic approaches who may require a different treatment strategy.

Other tumor suppressor genes inactivated in pediatric malignancies include Wilms tumor 1 (*WT1*), neurofibromatosis 1 (*NF1*), and von Hippel-Lindau (*VHL*). In addition, other tumor suppressor genes are presumed to exist but have not been definitively identified. For example, early karyotype analyses of neuroblastoma-derived cell lines found frequent deletion of the short arm of chromosome 1 [14]. Deletion of genetic material in tumors suggests the presence (and subsequent loss) of a tumor suppressor gene, but no individual tumor suppressor gene has been identified on chromosome 1p. Functional confirmation of the presence of a 1p tumor suppressor gene comes from the demonstration that transfection of chromosome 1p into a neuroblastoma cell line results in morphologic changes of differentiation and ultimately cell senescence [4]. Approximately 20–35 % of primary neuroblastomas exhibit 1p deletion, as determined by fluorescent in situ hybridization (FISH), and the smallest common region of loss is located within region 1p36 [45]. Deletion of 1p is also common in Wilms tumor [48]. Other chromosomal regions, whose loss in tumor cells suggests the loss of a tumor suppressor gene, include 11q in neuroblastoma [3] and 16q in Wilms tumor [49].

Genetic Variants

Cancer epidemiology genome-wide association studies (GWAS) examine the association of common genetic variants, most often single nucleotide polymorphisms (SNPs) or copy number variations (CNV), with the presence of a particular cancer. The causal relationship between the DNA variant associated with the cancer is not always certain but an excessive inheritance of "risk" variants has been postulated to increase susceptibility to the disease. Several GWAS studies have been performed in patients with neuroblastoma and Wilms tumors and have identified a number of such genetic risk variants [80, 129]. These observations suggest that developmental childhood cancers are likely influenced by common DNA variations, leading to the development of a putative genetic model (Fig. 3.2) [80]. Recent data suggest that the higher prevalence of high-risk disease in Black and Native American patients with neuroblastoma may be associated with certain genetic variants found more commonly in these ethnic groups [52].

Finally, GWAS studies have revealed genome variations that affect not only susceptibility to specific cancers but that may also influence the pharmacokinetic and pharmacodynamic characteristics of administered chemotherapeutics. Several genetic factors with relatively small effects may combine in the determination of a pharmacogenomic phenotype [102]. Because the therapeutic index of many drugs, especially in children, is very narrow with substantial risk for toxicity at doses required for therapeutic effects, identifying and understanding the impact of these variants is critical for optimizing treatment.

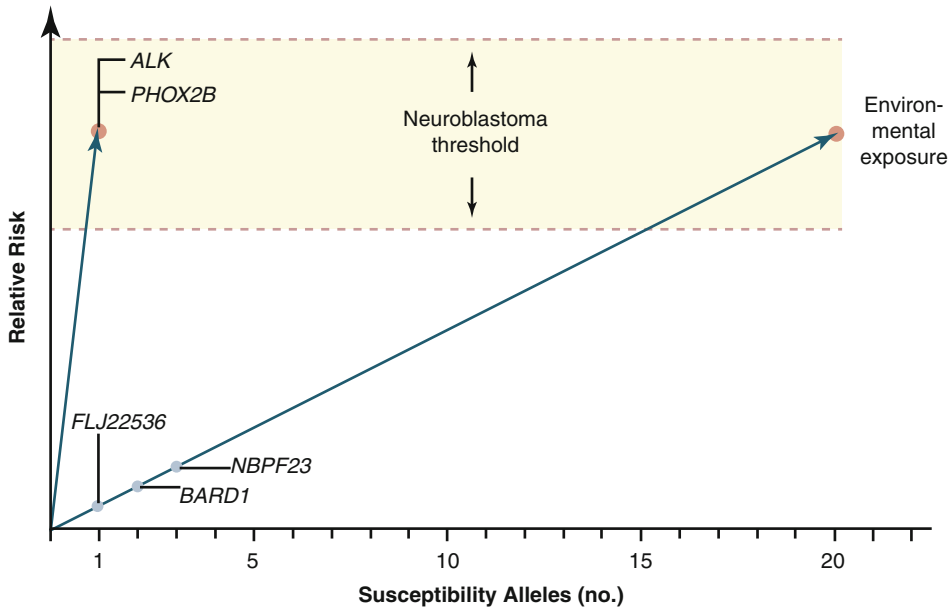

Fig. 3.2 A threshold for the development of neuroblastoma may exist which can be reached through a combination of inherited genetic factors together with the effects of environmental exposures. Certain mutations (e.g., to *ALK* or *PHOX2B*) may themselves allow a cell to reach this threshold. Alternatively, common (but less impactful) DNA variations in a larger number of genes such as *FLJ22536*, *BARD1*, and *NBPF23*, may combine to allow a cell to reach this threshold (Reprinted with permission from Maris [80])

Epigenetics

As stated previously, the hallmark of cancer is dysregulated gene expression. However, not only do genetic factors influence gene expression but epigenetic factors do as well, with these factors being at least important as genetic changes in their contribution to the pathogenesis of cancer. Epigenetic alterations are defined as those heritable changes in gene expression that do not result from direct changes in DNA sequence. Mechanisms of epigenetic regulation most commonly include DNA methylation and modification of histones, although the contribution of microRNAs (miRNA), a class of noncoding RNAs, is becoming increasingly recognized. Whole-genome sequencing of tumors, made possible recently by significant advances in technology, has been performed to investigate the genetic landscape of a variety of pediatric tumors [36]. Initially it was felt that early alterations of genes such as *RB* and *MYCN* may underlie the rapid acquisition of cooperating mutations in key cancer pathways through chromosome instability. However, few recurring amino acid changes have been detected in retinoblastoma and neuroblastoma specimens [22, 88, 138], suggesting that the tumor genomes are more stable than previously believed. However, unlike the genetic landscape, the epigenetic profiles showed profound changes suggesting that epigenetic changes may have a more dominant role in pediatric tumorigenesis.

DNA methylation is a reversible process that involves methylation of the fifth position of cytosine within CpG dinucleotides present in DNA. These dinculeotides are usually in the promoter regions of genes; methylation of these sites typically causes gene silencing, thereby preventing expression of the encoded proteins. This process is part of the normal mechanism for imprinting, X-chromosome inactivation and generally keeping large areas of genomic DNA silent, but may also contribute to the pathogenesis of cancer by silencing tumor suppressor genes. However, both abnormal hypo- and hypermethylation states exist in human tumors, resulting in both dysregulated expression and silencing, respectively, of affected genes. These modifications of the nucleotide backbone of human DNA are becoming increasingly recognized in human cancer both for their frequency and importance. For example, promoter methylation resulting in silencing of caspase 8, a protein involved in apoptosis, likely contributes to the pathogenesis of *MYCN-amplified* neuroblastoma [127], as well as Ewing sarcoma [46].

Histones are the proteins that give structure to DNA, and together with the DNA form the major components of chromatin. The functions of histones are to package DNA into a smaller volume to fit in the cell, to strengthen the DNA to allow replication, and to serve as a mechanism to control gene expression. Alterations in histones can mediate changes in chromatin structure. The compacted form of DNA, termed heterochromatin, is largely inaccessible to transcription factors and, therefore, genes in the affected regions are silent. Other modifications of histones can cause DNA to take a more open or extended configuration (euchromatin), allowing for gene transcription. The N-terminal tails of histones can be modified by a number of different processes including methylation and acetylation, mediated by histone acetyl transferases (HAT) and deacetylases (HDAC), and histone methyltransferases (HMT). Each of these processes alters histone function, which, in turn alters the structure of chromatin and, therefore, the accessibility of DNA to transcription factors. Methylation of the DNA itself can also effect changes in chromatin structure.

MicroRNAs are a group of small, regulatory noncoding RNAs that appear to function in gene regulation. These miRNAs are single–stranded RNA fragments of 21–23 nucleotides that are complementary to encoding mRNAs [113]. Their function is to down-regulate expression of target mRNAs; it is estimated that miRNAs regulate the expression of about 30 % of all human genes [73]. These miRNAs regulate gene expression primarily by incorporating into silencing machinery called RNA-induced silencing complexes (RISC). MiRNAs are involved in a number of fundamental biologic processes, including development, differentiation, cell cycle regulation and senescence. However, broad analyses of miRNA expression levels has demonstrated that many miRNAs are dysregulated in a variety of different cancer types, including neuroblastoma and other pediatric tumors [131], frequently losing their function as gene silencers/tumor suppressors. The activity of miRNAs, like gene expression, is also under epigenetic regulation.

Metastasis

Metastasis is the spread of cancer cells from a primary tumor to distant sites and is the hallmark of malignancy. The development of tumor metastases is the main cause of treatment failure and a significant contributing factor to morbidity and mortality resulting from cancer. Although the dissemination of tumor cells through the circulation is probably a frequent occurrence, the establishment of metastatic disease is a very inefficient process. It requires several events, including entry of the neoplastic cells into the blood or lymphatic system; survival in the circulation, avoidance of immune surveillance, invasion of foreign (heterotopic) tissues, and the establishment of a blood supply to permit expansion of the tumor at the distant site. Simple, dysregulated cell growth is not sufficient for tumor invasion and metastasis. Many tumors progress through distinct stages that can be identified by histopathologic examination, including hyperplasia, dysplasia, carcinoma in situ, invasive cancer, and disseminated cancer. Genetic analysis of these different stages of tumor progression suggests that uncontrolled growth results from progressive alteration in cellular oncogenes and inactivation of tumor suppressor genes but these genetic changes driving tumorigenicity are clearly distinct from those that determine the metastatic phenotype.

Histologically, invasive carcinoma is characterized by lack of a basement membrane around an expanding mass of tumor cells. Matrix proteolysis appears to be a key part of the mechanism of invasion by tumor cells, which must be able to move through connective tissue barriers, such as the basement membrane, to spread from their site of origin. The proteases involved in this process include matrix metalloproteinases and their inhibitors, tissue inhibitors of matrix metalloproteinases. The local environment of the target organ may profoundly influence the growth potential of extravasated tumor cells [39]. The various cell-surface receptors that mediate interactions between tumor cells and between tumor cells and the extracellular matrix include cadherins, integrins (transmembrane proteins formed by the noncovalent association of α and β subunits), and CD44, a transmembrane glycoprotein involved in cell adhesion to hyaluronan [128]. Tumor cells must decrease their adhesiveness to escape from the primary tumor, but at later stages in metastasis, the same tumor cells need to increase their adhesiveness during arrest and intravasation to distant sites.

Angiogenesis

Angiogenesis is the biologic process of new blood vessel formation. This complex, invasive process involves multiple steps including proteolytic degradation of the extracellular matrix surrounding existing blood vessels, chemotactic migration and proliferation of endothelial cells, the organization of these endothelial cells into tubules, the establishment of a lumen that serves as a conduit between the circulation and an expanding mass of tumor cells, and functional maturation of the newly formed blood vessel [44, 110]. Angiogenesis involves the coordinated activity of a wide variety of molecules including growth factors, extracellular matrix proteins, adhesion receptors, and proteolytic enzymes. Under physiologic conditions the vascular endothelium is quiescent and has a very low rate of cell division, such that only 0.01 % of endothelial cells are dividing [44, 53, 110]. However, in response to hormonal cues or hypoxic or ischemic conditions, the endothelial cells can be activated to migrate, proliferate rapidly, and create lumens.

Angiogenesis occurs as part of such normal physiologic activities as wound healing, inflammation, the female reproductive cycle, and embryonic development. In these processes, angiogenesis is tightly and predictably regulated. However, angiogenesis can also be involved in the progression of several pathologic processes in which there is a loss of regulatory control that results in persistent growth of new blood vessels. Such unabated neovascularization occurs in rheumatoid arthritis, inflammatory bowel disease, hemangiomas of childhood, ocular neovascularization, and the growth and spread of tumors [43].

Compelling data implicate the requirement for tumor-associated neovascularization in tumor growth, invasion, and metastasis [9, 41, 42, 105]. A tumor in the prevascular phase (i.e., before new blood vessels have developed) can grow to only a limited size, approximately 2–3 mm^3. At this point the rapid cell proliferation is balanced by equally rapid cell death by apoptosis, resulting in a nonexpanding tumor mass. The switch to an angiogenic phenotype with tumor

neovascularization results in a decrease in the rate of apoptosis, thereby shifting the balance to cell proliferation and tumor growth [55, 74]. This decrease in apoptosis occurs, in part, because the increased perfusion resulting from neovascularization permits improved nutrient and metabolite exchange. In addition, the proliferating endothelium may supply, in a paracrine manner, a variety of factors that promote tumor growth, such as insulin-like growth factors I and II (IGF-I, IGF-II) [51].

In experimental models, increased tumor vascularization correlates with increased tumor growth, whereas restriction of neovascularization limits tumor growth. Clinically, the onset of neovascularization in many human tumors is temporally associated with increased tumor growth [126], and high levels of angiogenic factors are commonly detected in blood and urine from patients with advanced malignancies [93]. In addition, the number and density of new microvessels within primary tumors have been shown to correlate with the likelihood of metastasis as well as the overall prognosis for patients with a wide variety of neoplasms, including pediatric tumors such as neuroblastoma and Wilms tumor [1, 83].

It has become increasingly evident that the regulation of tumor angiogenesis is complex: new blood vessel formation occurs as the result of competing pro- and antiangiogenic signals originating in multiple tissues [20]. Specific genetic events in certain cancers, such as altered expression of the p53 tumor suppressor gene [28, 139] or the human EGFR gene [71, 103, 136], not only affect the cell cycle but also play a role in angiogenesis by modulating key signals (e.g., upregulating the expression of vascular endothelial growth factor [VEGF], or downregulating the expression of the endogenous angiogenesis inhibitor thrombospondin 1).

Metastasis also appears to be dependent on angiogenesis [40, 74]. This dependence is probably due to several factors. First, new blood vessels in the primary tumor provide increased opportunities for the shedding of tumor cells into the circulation. Also, disruption of the basement membrane by proteases released by the proliferating endothelial cells may contribute to the metastatic potential of a tumor [15, 112]. Finally, successful growth of metastatic cells in foreign target organs depends on the stimulation and formation of new blood vessels, perhaps even when cells metastasize to the bone marrow.

Environmental Carcinogenesis

As stated previously, tumorigenesis is a complex process in which the progressive acquisition of combinations of critical genetic and epigenetic alterations shifts normal cells into uncontrolled growth and clonal expansion. These alterations in the genome can either be inherited or acquired, the later being as a result of the influence of factors intrinsic to a dividing cell or of the environment on the host genome. The most significant host factor relates to the normal, albeit, low rate of inaccurate DNA replication that goes uncorrected by normal host mechanisms. Living organisms have been selected for their ability to accurately replicate their genomes, although not with absolute precision. This ensures stability while permitting the dynamic of genetic change essential to environmental adaptation and consequent evolution. Variability in the local environment may make such mistakes more or less likely. This rate of accumulating alterations in the genome can also be significantly increased when there are defects in the normal genetic corrective mechanisms, or when there is increased host cell genomic instability. Critical for tumorigenesis, however, in addition to the initial occurrence of DNA damage, is the persistence of the DNA alterations and their eventual transmission to clonal descendants of the originally affected cell. Two conditions need to be fulfilled for persistence and inheritance of DNA damage. (1) The DNA repair systems of the cell fail to remove or correct the damage and (2) the residual lesion should not only be compatible with continued cell viability and proliferative capacity but also should confer a survival advantage.

The first line of cellular defense against DNA damage is the recognition of the damage and the implementation of a variety of molecular mechanisms which have evolved to effect repair. An important class of genetic lesions are mismatches which result in non-complementary DNA sequence over a short region. Unrepaired mismatches generate point mutations at the next round of cell division and the synthesis of mutant or truncated proteins. Removal of these mismatches and restoration of normal complementary base-pairing is the responsibility of mismatch repair enzymes. Other DNA lesions require different sorts of repair. DNA strands can be broken, generating a spectrum of lesions from point mutations to large scale chromosomal aberrations. Several mechanisms exist for strand break repair including the process of homologous recombination. The DNA repair processes are intimately linked to cell cycle control in proliferating cells, with several check points existing at which DNA-damaged cells are blocked until the repair processes have been completed. One example is the p53 tumor suppressor gene and its role in cell cycle arrest. DNA damage by a variety of extrinsic agents leads to cellular accumulation of the p53 protein, largely by stabilization of the protein, and the resultant blocking of the damaged cell at the G1 checkpoint. Successful repair of DNA damage leads to a reduction in p53 levels and release from the G1 block. However, incomplete or unsuccessful repair continues to generate the p53 blocking signal. Long-term-G1 blocking then invokes a cell death pathway, usually apoptosis, to eliminate unrepairable mutant cells. Thus p53 plays a critical role as the "guardian of the genome" to prevent the onset of genetic instability [70].

Epidemiology

The opportunity to practice prevention of cancer depends on the existence of potentially avoidable factors and their recognition so that appropriate action can be taken. The impact or causal role of environmental factors on the development of human malignancies was first recognized by noting unexpectedly high cancer incidences in certain occupational groups. Fabia and Thuy first suggested that a father's occupation might increase the risk of a child developing cancer [37]. The ability of certain chemicals was then documented in various animal models of carcinogenesis. In addition, population based studies confirmed histology and anatomic site-specific cancer rates among geographically distinct populations. Changes in cancer frequency among migrating ethnic groups, high cancer rates associated with specific occupations and most notably the risk of cancer associated with such activities as smoking and tobacco use have confirmed that environmental and lifestyle exposures contribute to human cancer risk. In addition, it has become recognized that certain people carry hereditary susceptibility genes that increase risk for developing cancer with particular environmental exposures. Environmental agents may cause mutations which are distinct or different from the predominant mutational type resulting from intrinsic mutagenesis or from the action of other environmental agents. This gives rise to the possibility of "molecular fingerprinting" by which environmental agents might be identified by the characteristic mutational type they have caused in the oncogenes or tumor suppressor genes of a tumor suspected of having environmental causation. An example is the characteristic mutations in the p53 gene associated with aflatoxin-mediated hepatocellular carcinoma [56].

The critical corollary to the identification of these factors is that exposure or lifestyle modification may be able to decrease the incidence of cancer development. Epidemiology, broadly defined, is the study of disease occurrence in different population groups in order to help identify causative risk factors and to plan appropriate preventive strategies. Epidemiology may also provide clues to etiology and pathogenesis.

Strong evidence exists that a substantial proportion of adult cancers are environmentally influenced, with tobacco, alcohol and diet being among the most important factors [2]. It is much less obvious that environmental factors play an important role in the development of childhood cancer. This is likely due to the fundamental differences between oncogenesis in children and adults that influence the impact of environmental exposures on carcinogenesis. Most adult tumors are of epithelial origin, such as in the gastrointestinal or respiratory tracts, surfaces that are directly exposed to carcinogens, whereas most pediatric tumors are of mesenchymal origin in tissues or sites with minimal contact with the environment. In addition, during embryogenesis fetal tissues are normally undergoing rapid cell division with high rates of proliferation, much like cancer cells, and then ultimately undergo differentiation or apoptosis. Additionally, adult cancers, despite variations between pathologic types, usually conform to a pattern in which the incidence increases with age, reflecting an accumulation of multiple mutations with time. Childhood cancers, in distinction to those in adults, typically have an incidence that initially increases with age, reaches a peak and then falls (Fig. 3.3), suggesting that other epigenetic factors, other than simply an accumulation of genetic mutations contribute to the development of malignancies in children. Finally, the cumulative effects of carcinogens such as irradiation and other environmental exposures often are not apparent for many years and, therefore, are less likely to have a direct impact on the development of pediatric malignancies. Thus, few environmental factors have been identified as being associated with pediatric oncogenesis. Nevertheless some environmental factors have been associated with the evolution of pediatric tumors and are discussed below.

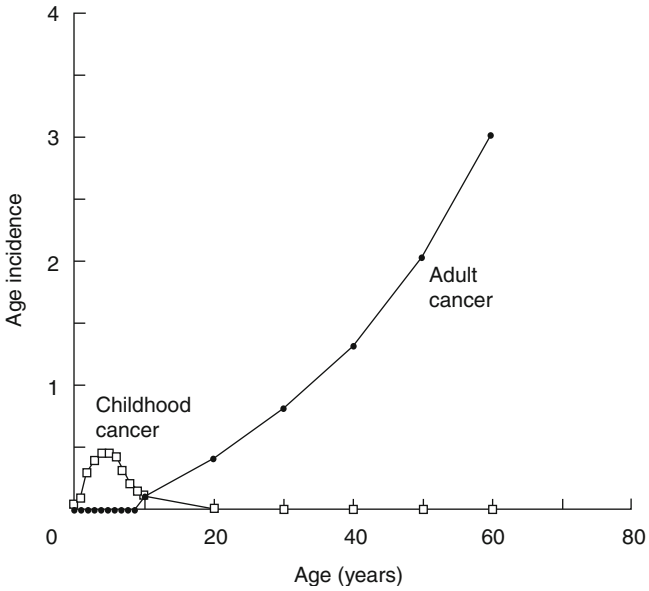

Fig. 3.3 Schematic illustration of the differing age-incidence patterns of adult and childhood cancer (not to scale)

Potential Causative Agents

Radiation

Ionizing radiation is tumorigenic and is capable of causing or contributing to the development of a wide variety of malignancies. It causes a variety of heritable DNA lesions, from point mutations to chromosomal deletions or

rearrangements, induces transformation to a malignant state in cells in culture and causes a range of types of cancer in experimental animals in a dose-dependent fashion. The developing fetus is particularly sensitive to the effects of ionizing irradiation, which increases the risk of childhood cancer by approximately 6 %/Gy exposure [34]. For postnatal irradiation the risk is about half of that for the fetus [109]. The radiation being delivered to children as part of diagnostic imaging studies, particularly CT scans, is currently being closely scrutinized as its potential role in the subsequent development of cancer is becoming increasingly appreciated [35]. It should be noted, however, that most of the cancers to which childhood irradiation makes a contribution will appear in adulthood, as radiation-induced cancer generally has a very long latency period [86]. Non-ionizing radiation such as ultraviolet light and electromagnetic fields may also contribute to the development of cancer, although, again, the association of skin cancer with UV exposure, for example, is well known but typically results in a heightened incidence in adult years. The epidemiologic evidence that electromagnetic radiation leads to cancer is conflicting [68], and the data regarding the effects of high-voltage transmission lines, electrical appliances and video display screens do not seem to support a causal role for these factors.

Chemical Agents

There are many chemical agents which have DNA-damaging capacity and therefore tumorigenic potential, but few for which there is any clear evidence of significant involvement in the causation of childhood cancer. Several chemical factors have been suggested as relevant to childhood cancer, including pesticides, vitamin K administration, passive cigarette smoke and maternal use of "recreational" drugs. An uncommon but very striking factor is the well-known risk associated with use of the hormone diethylstilbestrol which used to be administered in pregnancy in some cases where miscarriage was anticipated. This resulted in a 0.1 % risk of the development of clear cell adenocarcinomas of the cervix or vagina in female offspring [87]. There have been some reports of other childhood cancers, particularly neuroblastoma, associated with induced ovulation, although the evidence is not overwhelming [79].

Viruses

The role played by several viruses in human malignancies has been well established, most notably Epstein-Barr virus (EBV) and its association with Burkitt lymphoma, whereby immortalization of B cells by EBV has been suggested to be the initial event in multistep carcinogenesis [61]. EBV also appears to have a causal role in the development of nasopharyngeal carcinoma and some cases of Hodgkin lymphoma [50]. Cancer also occurs with increased frequency in children with human immunodeficiency virus (HIV) infection. The most common types are lymphomas and leukemias, although solid tumors including leiomyosarcoma and Kaposi sarcoma also occur with an increased incidence [106, 123]. However, neither the specific clinical, immunological, and viral risk factors for malignancy in these patients, nor the pathogenesis of HIV-related pediatric malignancies have been clearly elucidated.

Parental Occupation and Exposure to Noxious Agents

Parental occupation and exposures have been linked to an increased risk of a variety of childhood cancers [26, 116]. Transgenerational effects may be due to direct germ cell mutation, transport of carcinogens in the semen or epigenetic alterations of gene expression [100]. Paternal exposure to solvents such as benzene, xylene, toluene and carbon tetrachloride have been implicated in the pathogenesis of hematologic malignancies and brain tumors as have paints and pesticides [95]. Increased risk of childhood cancers such as leukemia, Ewing sarcoma, Germ cell tumor and Wilms tumor have been associated with certain paternal occupations including auto mechanic, welder, and to exposure at work to motor vehicle exhaust fumes, pesticides, petroleum and ether [54, 120, 122]. Although increased risk of some childhood cancers in association with potential carcinogen exposure is suggested by multiple studies, methodological limitations common to many studies restrict conclusions; these include exposure classification, small sample size and potential biases in control selection.

Iatrogenic Factors

Because the survival rates for childhood cancers have improved to more than 80 %, the proportion of childhood cancer survivors within the general population increases every year. Survivors are at risk for multiple late sequelae of therapy, including the development of a secondary malignancy. A significant factor contributing to this risk, in addition to the genetic predisposition of the patient, is the type of therapy received [7]. For example, an increased risk of subsequent leukemia is well-documented after exposure to epipodophyllotoxins and alkylating agents [107]. Similarly, the risk of carcinomas of the breast and thyroid, particularly after treatment for childhood Hodgkin lymphoma, has been extensively reported, and is related, in part to exposure to ionizing radiation as part of the treatment of the initial cancer [8]. Other examples include therapy-related brain tumors after cranial irradiation, osteosarcoma after irradiation for retinoblastoma and tumors, such as thyroid cancer, arising as a complication of low-dose irradiation given in the past as treatment for tinea capitis and acne. These secondary malignancies often occur in adulthood but may occur late in the teenage years.

Tumor Types

Neuroblastoma

Several case-control studies have examined the relationship between maternal and paternal occupation and exposure, and the risk of neuroblastoma in offspring [18, 84, 125, 134]. Two studies found an association with fathers employed in electronics-related occupations including electricians and welders (odds ratio = 11.7, 95 % confidence interval 1.4–98.5) [125]. Another study found increased risks in electrical, farming and gardening, and painting occupations [98]. A variety of other paternal occupations and industries have been shown to have an increased risk of having a child with neuroblastoma [18, 134]. Paternal exposures to hydrocarbons such as diesel fuel, lacquer thinner and turpentine were associated with an increased incidence of neuroblastoma as were exposures to wood dust and solders [33]. Pesticide use in both home and garden were modestly associated with neuroblastoma [29]. Certain maternal occupations have also been found to have an association with an increased risk [18, 125, 134].

Several epidemiologic and case series have suggested a relationship between the use of certain medications just prior to and during pregnancy and neuroblastoma, specifically hormone use and fertility drugs [64, 85, 118]. although others studies have not confirmed such an association [27]. One study by Schuz et al. observed a positive association with the use of oral contraceptives or other sex hormones during pregnancy (particularly with male offspring), a shorter gestational duration, lower birth weight, and maternal alcohol consumption during pregnancy [117]. Other drugs have been implicated although the data have not always been consistent among different studies. Similarly the results for smoking, alcohol use and the use of hair dye in some studies are suggestive but not conclusive [60, 64, 118]. while other studies find no association [137]. Maternal use of any illicit or recreational drug around pregnancy has been associated with an increased risk of neuroblastoma in offspring (odds ratio = 1.82, 95 % confidence interval 1.13–3.00), particularly the use of marijuana in the first trimester of pregnancy [10]. Other studies have suggested an association between maternal hair dye use and elevated risk of childhood cancer including neuroblastoma (OR = 1.6, 95 %CI = 1.2–2.0). Vitamin use during pregnancy might reduce the incidence of neuroblastoma, consistent with findings for other childhood cancers [99]. Also, children with neuroblastoma were less likely to have breast-fed than control children (CR = 0.6, 95 % CI = 0.5–0.9) with the decreased association between breast-feeding and neuroblastoma increasing with increasing duration of breast-feeding.

Wilms Tumor

The first suggestion that paternal occupational exposures might be of importance in the etiology of Wilms tumors came from Kantor et al. [58] From a comparison of birth certificates for 149 Connecticut tumor registry cases with 149 matched controls, they estimated relative risks of 2.4 for hydrocarbon-related occupations and 3.7 for those with a potential for lead exposure. This was later supported by Wilkins and Sinks although their results did not reach statistical significance for the association [135]. Others have attempted to confirm this finding [17, 67, 114]. Although suggestive associations have been found in some studies for machinists, mechanics and welders the numbers are small and the patterns are inconsistent. Olshan et al. found no consistent pattern of increased risk for paternal exposure to hydrocarbons and lead but did find that certain paternal occupations did have an elevated odds ratio of Wilms tumor including vehicle mechanics, auto body repairmen and welders [96]. Offspring of fathers who were auto mechanics had a 4- to 7-fold increased risk of Wilms tumor. Other early studies have suggested possible associations with maternal smoking, coffee/tea drinking and exposure to synthetic progestins during pregnancy and the use of hair coloring products [17, 72, 95]. However, these studies are subject to several methodologic limitations including misclassification of exposure, selection bias, and small sample size and later studies have, in general, failed to confirm most of the previously reported maternal risk factors for Wilms tumor [97]. Breast feeding was associated with a reduced risk of Wilms tumor (odds ratio = 0.7, 95 % confidence interval = 0.5–0.9).

Liver Tumors

Environmental factors have also been implicated in hepatoblastoma. An association with certain occupational exposures in fathers of children with hepatoblastoma, including excess exposures to metals such as in welding and soldering fumes (odds ratio 8.0), petroleum products, and paints (odds ratio 3.7), has been observed [16]. Prenatal exposure to acetaminophen in combination with petroleum products has also been noted in association with hepatoblastoma [115]. There is a striking association of hepatoblastoma with prematurity, with the relative risk increasing with decreasing birth weight [38]. However, the etiology behind this association is currently unknown. An increased incidence of liver tumors is also seen in association with fetal alcohol syndrome, exposure to hepatitis B and aflatoxin, and prolonged parenteral nutrition in infancy [101]. The most striking association, however, is in children with metabolic diseases such as tyrosinemia. In children with these disorders, the tissues are exposed to high, continuous levels of endogenous carcinogens, and are at such high risk for the development of malignancies such as hepatocellular carcinoma early in life, that early organ transplantation is recommended [25, 132].

Summary

The potential role of environmental exposures in the etiology of childhood cancer remains uncertain. The relatively few epidemiologic studies that have been conducted have been limited by a number of confounding factors, including sample size, exposure misclassification and selection bias. Nevertheless, sufficient suggestive data exist to warrant further evaluation into the role of environmental exposures in pediatric oncogenesis. The goal being, of course, to identify factors that can be eliminated or avoided in order to decrease the risk for developing a malignancy.

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Screening for Genetic Susceptibility to Paediatric Tumours

4

Victoria A. Murday

Introduction

About 5 % of all malignant tumours arise in individuals who have an underlying genetic predisposition due to a single high risk gene. The proportion in children is probably higher but is currently unknown but is estimated as 10–20 % or more, and a much larger proportion may be in part due to lower risk susceptibility genes.

Children and adolescents with a tumour susceptibility may only be recognised to have an underlying predisposition when they present with a tumour but sometimes may be identified as at risk through their family history or because they have an identifiable phenotype, known to be associated with an increased chance of developing a tumour. If this is the case presymptomatic clinical and/or genetic screening may be appropriate. This should only be done within the context of adequate genetic counselling.

In general predictive genetic testing for adult onset disorders in children is discouraged until the person is able to themselves consent, however for conditions with a paediatric onset testing is available following careful discussions with the parents. Families may prefer not to have a genetic test but pursue clinical screening as an alternative without genetic testing first.

Identifying those at risk may also help with prompt diagnosis and treatment should a tumour develop, including reducing the time and number of diagnostic investigations, even if presymptomatic screening is inappropriate.

It may also be important in treatment planning, as the tumours may respond differently to treatment when due to a germ line mutation, some being superior to others [48]. Some disorders may respond adversely to certain therapies, where an underlying condition may make the treatment toxic or induce further tumours or increased late adverse effects, for instance radiotherapy would be contraindicated in Li Fraumeni or certain DNA repair disorders [49, 64].

Children and adolescents with an underlying susceptibility may be at risk of developing further tumours and other family members may also be at risk. Screening may allow early treatment or prevention for other family members. There may also be other important health risks attached to the condition that need to be considered in the individual or family.

Presymptomatic clinical screening is always a two edged sword. On the one hand the aim is to detect tumours at an earlier stage, to potentially simplify surgical treatment and hopefully reduce the need for radiotherapy and chemotherapy. It may be reassuring for the family to know those at risk are being screened, but stress levels will be raised prior to each screen and to be effective the screening may need to be done very frequently, never allowing time for the parents to relax. False positives may lead to unnecessary surgery and worry, and indeed false negatives may lead to inappropriate reassurance. In addition the evidence that treatment is improved may be lacking or equivocal. For these reasons it is important to limit clinical screening to those disorders in which screening is known to be effective in improving outcome or where the risk is sufficient to justify the morbidity related to screening itself.

Of particular importance are disorders in which there is a premalignant lesion or a high enough risk to justify prophylactic surgery. Examples of this would be the removal of benign adenomas or other polyps in disorders predisposing to bowel malignancies or prophylactic thyroidectomy in those who have inherited the gene for multiple endocrine neoplasia Type 2 would be another.

However just because clinical screening and prophylactic surgery may not be applicable to children it may be that screening or prophylaxis for other cancers in adulthood may be important. For instance identifying that a child has a *p53* mutation may lead to the individual or their mother being identified at risk of breast cancer, who may consider prophylactic mastectomy for what may be an 80 % risk before the age of 50 [41].

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Table 4.1

1. Family history
2. Adult tumour occurring in childhood or adolescence
3. The tumour is frequently due to an underlying susceptibility
4. Associated anomalies of development and growth
5. Abnormal reaction to treatment
6. Unusual histology/multifocal/bilateral pathology

Recognising an Underlying Genetic Susceptibility

Recognising that a child or adolescent with a tumour has a genetic susceptibility depends upon recognising that something unusual or unexpected has happened, something which is unlikely to have occurred by chance. It may be the early onset of a tumour, multiple primaries or unusual pathology. It may be the presence of developmental anomalies, as we now know that many of the genes involved in the development of paediatric tumours are developmental genes which can give rise to malformations or disordered growth. An abnormal sensitivity to treatment may suggest an underlying DNA repair disorder. Alternatively it may be a family history of malignancies and tumours in the family, unlikely to have clustered together by chance. Occasionally the child will come from a family with a known predisposition and in this situation the child should be followed and screened as appropriate for the particular disorder (Table 4.1).

Family History

Paediatric tumours are individually so rare that the recurrence of the same paediatric tumour within a family is likely to be due to an underlying susceptibility even if they are not first degree relatives. A recurrence in up to third degree relatives should at least raise suspicions as many of these disorders are not fully penetrant. The underlying genes for these families are gradually being identified and by the time this is published more will have been found. Examples would be *WT1* in families with a Wilms recurrence or *ALK* mutations where neuroblastoma recurs in a family [43]. Genetic referral /testing should therefore be pursued in these families. In addition in some families it may not be the same paediatric tumour that recurs so it is useful to recognise the pattern of tumours of these conditions. e.g., DICER 1 families [59], however since every paediatric tumour is rare even different tumours occurring in close relatives would be an indication for genetic referral.

Some adult cancer susceptibilities have paediatric involvement. In some such as Li Fraumeni this may not be an unusual occurrence, in others it may be a rare. Taking a family history of adult tumours is therefore mandatory including third degree relatives (grandparents, aunts, uncles and cousins). This may be the only clue that a child has developed a tumour because of susceptibility. A good example of this would be a sarcoma in a child from a Li Fraumeni syndrome family, since a sarcoma without a family history of tumours is unlikely to be due to a germ line mutation but in the context of other tumours in the family may be highly significant.

More than one tumour occurring in a single individual also significantly increases the chance of there being an underlying susceptibility whether these are synchronous or metachronous.

Adult Tumours in Childhood

In most of the disorders which cause susceptibility to the common cancers of adulthood, such as adenocarcinomas of the bowel or breast, tumours occur at an earlier age than in the general population. The age range can therefore stretch down into the paediatric and adolescent age range. This results in most of these tumours which occur in this younger age range being due to one of these susceptibilities. For instance colorectal cancer is rare in childhood and adolescence. When it occurs it is usually due to familial adenomatous polyposis (FAP), juvenile polyposis (JP) or hereditary nonpolyposis colorectal cancer (HNPCC). The age range for the autosomal recessive MYH polyposis tends to be later but can occasionally occur into the adolescent age range [18].

It's important to remember that there may not be a family history, either because there has been a new dominant mutation in the child or the parents are still young and one of them may have a susceptibility gene but not yet presented with a tumour.

Some of these adult onset disorders have an additional low risk of embryonal tumours, for instance medulloblastoma or hepatoblastoma can occur in FAP and medulloblastoma in Gorlin Syndrome. The risk of hepatoblastoma is low in FAP <1 %, however because of the importance of not missing a case of FAP, genetic testing for the *APC* gene is indicated. Other solid tumours can also occasionally also occur, sarcomas (particularly osteosarcoma), leukaemia and gliomas can all occur at a low frequency in HNPCC.

Homozygotes for a number of these dominant cancer syndromes also occur and can give rise to autosomal recessive cancer susceptibility in childhood. Since many of these genes are in DNA repair pathways there may be features in common with other DNA repair defects. Examples are Turcots syndrome, homozygotes for HNPCC, and Fanconi syndrome D1, homozygotes for BRCA2. There may be a family history of adult malignancies in these families on both sides and a history of consanguinity is not uncommon so it is important to remember to ask about this when taking the family history [52].

Familial Adenomatous Polyposis

In the classical form for FAP half of affected individuals will have colorectal adenomas by 15 years of age. Screening by flexible sigmoidoscopy is therefore recommended annually from the age of 10 years in the offspring of affected individuals or those shown to have inherited the gene. The adenomas tend to arise distally at first. As a rule upper GI polyps do not occur until adulthood so upper GI screening is not necessary until later on.

The risk of developing colorectal cancer before 20 years is low but does occur so prophylactic colectomy is indicated if the polyps are not controllable by polypectomy.

If colorectal cancer does occur in childhood or adolescence even in the absence of a family history FAP is the most likely diagnosis. There are a number of additional phenotypic features that can aid diagnosis. Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is present in a significant proportion, supernummery teeth may occur, epidermoid cysts, osteomas and desmoids are also features.

Two other malignant tumours may occur in FAP in children, papillary carcinoma of the thyroid with an unusual cribriform pathology and hepatoblastoma [22].

Genetic Testing

Genetic testing for FAP should be carried out in children with any of the following tumours: colorectal cancer, multiple colorectal adenomas, cribriform papillary carcinoma of the thyroid, hepatoblastoma, and also in children with CHRPE or prepubertal epidermoid cysts, since missing the diagnoses would be a serious concern.

If no mutations are detected colorectal screening should still be carried out if more than one of these extra colonic features is present, or for children with papillary carcinoma of the thyroid with the typical histology [22].

Juvenile Polyposis

Juvenile polyposis is caused by mutations in a number of different genes. The cumulative lifetime risk of colorectal cancer is lower than in FAP but is still 50 %. The cancers can however occur throughout life, and the condition can present at any age.

The disorder can occur as an autosomal dominant disorder with no other associated features due to BMPR1A but other families have associated hereditary haemorrhagic telangiectsia (HHT) with mutations in SMAD4.

Associated malformations include patent vitello-intestinal duct, gut malrotation, AV malformations, cleft palate, mental retardation, capillary haemangiomas and hydrocephalus [14].

Genetic Testing

Testing for the two genes should be carried out to exclude the additional risk of AV malformations in HHT associated with SMAD4 mutations and allow genetic testing for other relatives.

Screening

Children with mutations in *BMPR1A, SMAD4* and at risk from gene negative families require 1–3 yearly from colonoscopy from the first year and 1–5 yearly gastroduodenoscopy depending on the extent of disease found [19].

Individuals with *SMAD4* in addition require spiral CT of the chest and brain MRA to identify any AV malformations, so as to identify those at risk of stroke.

Peutz Jeghers (PJS)

The phenotypic hallmark of this disorder is mucocutaneous lentigines which occur round the mouth, anus and conjunctival edge. They are usually not present at birth but gradually appear during childhood and then often fade or disappear in adulthood. Café au lait patches can also occur on the extremities and there can be lentigines over the dorsum of the finger joints. There is a significant risk of malignancy life long [62].

Genetic testing for STK11 should be carried out in children with the typical pigmentation or presenting with a PJ polyp even if solitary. PJS can be associated with developing other rare tumours in the young including Sertoli cell tumours of the testis [26], which are usually benign, sex cord cell tumours of the ovary and adenoma malignum of the cervix. Mutation analysis for STK11 should be carried if any of these occur and if no mutations are found gut screening should still be considered.

Screening

From birth children should have annual full blood count and clinical review asking about abdominal pain and bleeding. When endoscopy should start is a matter of debate in a symptom free child. However intersussception can occur at any age, but is commoner in adolescents than younger children.

Top and tail endoscopy 3 yearly and capsule endoscopy 3 yearly is recommended [2].

The Tumour Is Frequently due to a Germ Line Susceptibility (Table 4.2)

Some tumours frequently arise due to germ line mutations. Examples of this would be retinoblastoma, phaeochromocytoma, malignant rhabdoid tumours and pleuropulmonary blastoma. These can occur in individuals who are phenotypically otherwise completely unremarkable and with no family history.

Most of these tumour susceptibilities can show reduced penetrance and so it is important to know if there is a germ line alteration. Brothers and sisters may be at risk if a parent has the mutation but not expressed the disorder. Also there may be a risk of second tumours in the affected child, and this may affect the choice of treatment and subsequent clinical screening.

Table 4.2

Tumours frequently due to germline alterations
Retinoblastoma (40 %)
Atypical rhabdoid (35 %)
Pleuropulmonary blastoma (78 %)
Cystic nephroma (66 %)
Wilms tumour (9–17 %)
Ovarian Sertoli-Leydig tumour (50 %)
Pheochromocytoma (100 %)
Adrenocortical tumours
Medullary thyroid carcinoma (100 %)
Tumours with usual adult onset (most)
Genetic testing is indicated

It is important to offer families the opportunity for genetic testing to establish risks to the individual and their relatives. In some circumstances parents may consider prenatal diagnosis in future pregnancies, or may themselves be at risk of developing adult malignancies. Referral for formal genetic counselling is therefore recommended. In addition it is helpful to collect samples for genetic analysis prior to starting treatment. Samples can be stored and discussion about testing delayed until an appropriate time, this may be months or even years after the diagnosis.

Familial Retinoblastoma

Retinoblastoma is a rare paediatric tumour of the eye usually occurring under the age of 5 years, about 40 % overall are due to a germ line mutation in *Rb*. The susceptibility is inherited as an autosomal dominant with high penetrance. Bilateral cases are always due to a germ line mutation, and unilateral retinoblastoma is genetic in about 10 % of cases. In the 1960s a number of cases were reported with a deletion at 13q14. Linkage was then carried out in families with markers from this chromosomal location which confirmed that the susceptibility gene in the families was at 13q14. In 1971 Knudson wrote suggesting a two hit hypothesis, he compared the age of onset in unilateral cases with those with bilateral disease and suggested that the sporadic form of disease required two 'hits' and inherited disease only one. Later loss of heterozygosity studies confirmed that the second hit was an alteration or deletion of the other copy of the gene on the homologous chromosome (See Chap. 3). This was therefore the first tumour suppressor gene to be identified.

Children who develop a retinoblastoma should have a genetic test to establish if there is a germ line mutation so that other relatives can benefit from genetic testing and clinical screening or be discharged from screening if at a low risk. In addition there is a risk of second tumours in those with germ line mutations, particularly if they have received radiotherapy which is therefore contraindicated, another important reason to know before treatment. These second tumours are most commonly sarcomas.

All retinoblastoma patients should have mutation analysis for *Rb.*

Screening

Retinal examination should be carried out under anaesthetic from birth every month for 3 months, then 3 monthly until 2 years of age, then 4 monthly until 3 years. Examinations can then be without anaesthetic 6 monthly until 5 years then annual until 11. Clinical review annually for sarcoma should be lifelong.

WAGR, Denys-Drash and Frasier Syndrome

In 9–17 % of Wilms tumour patients there is an underlying genetic predisposition [57]. Most have other developmental disorders or features. Some of these have an overgrowth syndrome (see below) some have a chromosomal deletion such as WAGR, others have mutations in the gene WTI, either as part of a syndrome (Denys-Drash or Frasier) or as an isolated susceptibility without other phenotypic features [55].

WAGR results from a deletion at 11p13 that includes WT1 and Pax6, a gene which causes aniridia. There is often a genital malformation and developmental delay. The risk of Wilms is around 50 %. Denys Drash is a triad of Wilms tumour, nephropathy due to mesangial sclerosis and genitourinary abnormalities which can be severe with possible sex reversal in males of the external genitalia. The risk of Wilms in this condition is probably higher than 50 %. In Frasier syndrome there is nephropathy, gonadal dysgenesis, a risk of gonadoblastoma and sex reversal in males [29]. The risk of Wilms is <10 %. Both of these latter disorders are due to mutations in WT1.

Every child with Wilms tumour with an additional developmental disorder should prompt genetic review. In addition since Wilms tumour can also arise in families as a dominant susceptibility with mutations in WT1 a careful family history should be taken. These germ line mutations account for a significant number of familial cases with no other associated features, WT1 mutation analysis should be done if there is a family history. In addition 20 % of affected individuals in these families have bilateral tumours as compared to 3 % of sporadic cases. Bilateral cases should also therefore be offered genetic testing for WT1 even in the absence of any other phenotypic expression or family history as well as those with a family history.

Children with isolated aniridia should have a comparative genome hybridisation array to ensure that they do not have a deletion that includes the *WT1* gene.

Clinical Screening for Wilms Tumour

Children with a greater than 5 % risk should be screened by abdominal ultrasound 3–4 monthly and urinalysis

until 5 years of age. This should be continued until 7 years of age in children with Beckwith-Wiedemann, Simpson Golabi Behmel and some dominant Wilms families [56].

SMARCB1 and Rhabdoid Tumours

About 35 % of rhabdoid tumours are due to mutations in INI1, also known as SMARCB1, the gene for multiple swannomatosis [21]. The children with germ line mutations tend to develop their rhabdoid tumours very young, however 20 % of children over 2 years may still have mutations. Choroid plexus carcinoma, medulloblastoma, malignant peripheral nerve sheath tumours and central PNETs can also occur [6, 21, 58].

Genetic testing is indicated because of the risk of further tumours and variability in penetrance which may mean other relatives may be at risk.

Screening for SMARCB1 Families

Cranial ultrasound has been suggested every month from birth until the closure of the fontanelle and then MRI until 4 years of age every 6 months with abdominal ultrasound every 2–3 months until 4 years of age [68].

DICER1 Syndrome and Pleuropulmonary Blastoma

Pleuropulmonary blastoma is due to mutations in DICER1 in three quarters of cases.

A number of different tumours occur as a result of an underlying mutation in DICER1, an RNase endonuclease important in gene expression. Affected individuals commonly develop pleuropulmonary blastoma and ovarian Sertoli-Leydig tumours, usually in the second and third decade. Other tumours reported are cystic nephroma and Wilms tumours. Non toxic goiter and cysts of the thyroid occur. Medulloblastoma has also been reported [59].

Clinical review is recommended at present with advice and education for the family to report concerning symptoms. MRI and other imaging may be appropriate when more information is available on penetrance and risk. However this would require an anaesthetic in young children because of the early age of onset of the PPBs and early indications suggest that the risk to gene carriers of developing tumours may be low [59].

Multiple Endocrine Neoplasia (MEN) Type 2 and Medullary Thyroid Cancer (MTC)

MTC in children occurs almost exclusively as part of multiple endocrine neoplasia (MEN) type 2A and B. Both types are due to alterations in the tyrosine kinase receptor RET. *RET* mutations are now grouped into three risk groups. High risk, where the activating mutation is in a critical position in the substrate binding pocket of the intracellular TK domain, these mutations are responsible for MEN2B. Then there are medium risk alterations which lead to ligand independent dimerisation. These mutations lead to MEN 2A. The lowest risk mutations are in the intracellular tyrosine kinase domain; these generally give rise to adult onset disease familial medullary carcinoma.

It is important to diagnose MEN 2 in cases of medullary thyroid carcinoma since there may be a coexisting phaeochromocytoma which should be excluded and treated prior and to any surgical intervention, by the measurement of 24 h urinary and plasma fractionated catecholamines and metanephrines.

Preoperative investigations for hyperparathyroidism should also be done in MEN2A so enlarged glands can be removed at the time of thyroid exploration.

The identification of a *RET* mutation will permit screening of family members and thereby permit prophylactic thyroidectomy and clinical screening for the other associated tumours [7].

Endocrine Tumours

All endocrine tumours in children have a high chance of being due to an underlying genetic susceptibility, and this should always be considered when one is diagnosed in children or adolescents [63].

MEN 2B

Prophylactic surgery is indicated in this disorder in the first year of life. Ninety-five percent of cases are due to a single mutation at codon 918, making genetic diagnosis of the disorder relatively straightforward. However there is rarely a family history due to the severity of the condition. The disorder is very aggressive, virtually 100 % penetrant, with a mean age of symptomatic diagnosis of MTC at 20 years and death at 21 years.

MEN 2B is associated with a number of additional recognisable phenotypic features. Multiple mucosal neuromas will develop and bee sting lips. There may be enlarged corneal nerves, café au lait patches and facial lentigines. Marfanoid habitus is apparent in 75 %; however they can be short or have normal stature. These features will develop gradually during childhood, too late for prophylactic surgery. However intestinal ganglioneuromatosis is present in 40 % of infants with MEN2B and **all** children or infants presenting this disorder should be genetically tested for MEN2B, as missing the diagnosis is catastrophic [60].

MEN2A

MEN2A is not commonly associated with any additional diagnostic phenotypic features in childhood. However some children with this disorder may have Hirschsprung's Disease which can help with early diagnosis [12].

Unlike MEN2B there is often a family history. To prevent the development of MTC prophylactic surgery is indicated.

The families should be under regular surveillance in a specialized endocrine genetic clinic to ensure timely intervention and genetic testing and surgery for children. About 85 % have a mutation at codon 634 at the more severe end of the spectrum and require prophylactic surgery early by 5 years of age. These individuals have a higher risk of phaeochromocytoma (often bilateral) and hyperparathyroidism than the other MEN2A mutations. Prophylactic surgery can be delayed until 10 years with less severe mutations but it would be important to screen clinically these children if surgery is to be delayed. Mutations at codons 609, 611, 618, 620, 630, 634 account for 98 % of families.

Genetic Testing in MEN2

Children presenting with MTC should have *RET* mutation analysis.

Children with ganglioneuromatosis should have codon 918 and 883 of *RET* analysed.

In children presenting with Hirschsprung's disease mutation analysis of exon 10 should be considered as codon 609, 618 or 620 occur in Hirschsprung's disease with MEN 2A.

Biochemical Screening of Patients with MTC or MEN 2 Syndromes

In MEN2A families in which genetic testing has not been done, is unavailable or the family have declined, at risk individuals require biochemical testing with basal calcitonin and a pentagastrin test, repeated every 1–2-yearly. N.B. there is a 5 % false positive and false negative rate for this test.

Serum calcitonin should be checked at 2–3 post-operative months and at subsequent visits 6 monthly, even in patients who have undergone prophylactic surgery.

Annual 24 h urinary collection for metanephrines and catecholamines should be measured annually to exclude a phaeochromocytoma.

Annual measurement of calcium and PTH should be undertaken in MEN 2A families.

Von Hippel Lindau Disease (VHL)

VHL is characterised by the combination of retinal angioma (60 %), cerebellar (60 %) and spinal haemangioblastoma (14 %), renal cell carcinoma (30 %) and phaeochromocytoma (7–19 %). About 5 % develop pancreatic islet cell tumours.

The risk of phaeochromocytoma varies from family to family depending on the mutation. Some families present as phaeochromocytoma families with a lower risk of the other features. These most commonly have missense amino acid substitutions which do not radically alter the protein structure.

Von Hippel Lindau Disease (VHL) accounts for 75 % of sporadic phaeochromocytoma in children and adolescents <20 year. VHL phaeochromocytoma are multifocal in 40 % of cases and so pathology may also be helpful.

Familial Paraganglioma

Familial paraganglioma is an autosomal dominant susceptibility to phaeochromocytoma, carotid body tumours (often bilateral), globus jugulare and paraganglioma. It is due to mutations in the succinate dehydrogenase genes (Mitochondrial complex II mutation SDH subunits A, B, C and D) and more rarely TMEM127 and MAX. Phaeochromocytoma tends to occur before paraganglioma and carotid body tumours which are mainly of adult onset. In SDHD families the tumours will only occur if inherited from the father, however there are rare exceptions to this.

Familial paraganglioma is the commonest cause of phaeochromocytoma in children after VHL. SDH tumours are rarely multifocal. If the tumour is malignant then SDHB is most likely to be the underlying gene. Thirty to eighty percent are reportedly malignant, whereas only 10 % of phaeochromocytoma in MEN 2 and 5 % in VHL will be malignant [8].

In SDHD families truncated or nonsense mutations have a higher risk of phaeochromocytoma (P81L mainly) than missense mutations [53].

Parathyroid Tumours

Parathyroid tumours occur in MEN1, 2A, and 4 and in the dominant disorder hyperparathyroidism with jaw tumours (HPTJW). Hyperparathyroidism is the most frequent and usually the presenting problem in MEN1 whilst in MEN2A medullary thyroid carcinoma usually precedes the development parathyroid problems. Hyperparathyroidism occurs in 25 % patients with MEN 2A. Supernumerary and/or ectopic parathyroid tissue occurs more frequently in familial disease. Parathyroid carcinoma may occur in association with both MEN 1 and HPTJW but is rare in MEN1 and more common in HPTJW.

Genetic Testing

Since 75 % of phaeochromocytoma under the age of 20 years have VHL mutations should be sought in the *VHL* gene first, unless there is a family history or clinical features that would suggest another diagnosis [44]. If there is no family history it will depend on whether the tumour is adrenal or extra adrenal, bilateral or malignant. SDH tumours are rarely multifocal but often extra adrenal [20]. If the phaeochromocytoma is malignant then SDHB should be tested before any other genes. Genetic testing is mandatory, since the type of clinical follow up will depend on the diagnosis. Soon all the genes will be tested simultaneously by a next generation sequencing panel.

Any child presenting with a haemangioblastoma of the CNS or a renal cell carcinoma should also have a mutation analysis for *VHL* because of the lifelong risk and screening implications.

Clinical Screening

Annual clinical examination and urine spot from 5 years of age followed by annual 24 h urine and plasma for catecholamines from 10 years with annual renal ultrasound and 3 yearly full body MRI from the age of 15 years.

In addition children from VHL families or diagnosed with VHL should have annual retinal fluorescein angiography [50].

Phaeochromocytoma

Phaeochromocytoma occurs as part of MEN2, VHL, NF1 and familial paraganglioma syndromes. They are often multiple or bilateral, but malignancy is rare in childhood (<6 %), especially when part of MEN 2 syndromes. Where there is clinical suspicion of a phaeochromocytoma, a detailed family history and clinical examination for any physical characteristics of these familial syndromes should be undertaken, looking for NF1 and MEN2B. Examination of the skin of the parents may also be appropriate.

MEN1

MEN1 is an autosomal dominant disorder with mutations in the *MENIN* gene. Disease expression before 10 years of age is rare. Hyperparathyroidism is the commonest (>90 %), and usually earliest, manifestation of the disease [69]. Pituitary, adrenocortical, and islet cell tumours and carcinoids are associated, facial angiofibromas, collagenomas and lipomatous tumours may also be part of an MEN1. Pancreatic neuroendocrine tumours are uncommon in MEN1 in childhood.

The diagnosis of MEN1 should be suspected in any child or adolescent with hyperparathyroidism and mutation analysis of *MENIN* gene should be carried out. A mutation will be detected in more than 80 % of clinically diagnosed MEN1. Failure to detect a mutation in the *MENIN* gene does not however exclude a diagnosis of MEN1.

Hyperparathyroidism and Jaw Tumours

This is a rare dominantly inherited tumour susceptibility to parathyroid tumours caused by mutations in *parafibromin*. It can present with hyperparathyroidism in adolescents and is associated with an increased risk of malignancy. Approximately one third of patients also develop ossifying fibromas, primarily of the mandible and maxilla. Kidney cysts and hamartomas can also occur.

Autosomal Dominant Hyperparathyroidism

Autosomal dominant hyperparathyroidism families without other features suggestive of MEN have been found to have germ line mutations in both the *MENIN* gene whilst other families have *parafibromin* mutations.

Genetic Testing

Mutation analysis for *MENIN, RET* and *parafibromin*, depending on the family history. Children and adolescents with hyperparathyroidism and no detected mutation in *MENIN*, should have mutation analysis of *parafibromin*.

Children and adolescents with parathyroid carcinoma or atypical parathyroid adenoma, and without family history of MEN 1, should have mutation analysis of *parafibromin* prior to *MENIN* [65].

Clinical Screening for Hyperparathyroidism

Serum calcium and PTH should be screened from 10 years of age every 1–2 years.

PTH and serum calcium screen should be tested once in the parents of children with hyperparathyroidism in the absence of a family history and a negative genetic test in the affected child.

Adrenocortical Tumours (ACT)

Adrenocortical tumours (ACT) are rare in childhood often occurring in genetically susceptible individuals, and may present atypically or with complex adrenal steroid hyper secretion. The diagnosis should always be considered in the child with refractory hypertension. Adrenocortical tumours occur in several cancer susceptibilities and between 50 and 80 % of ACT's in childhood have an inherited basis.

They may occur as part of Li Fraumeni syndrome, Carney complex and rarely as part of MEN1 [39]. These disorders may be diagnosable from the family history. ACT with a low chance of malignancy can occur in patients with isolated hemi-hypertrophy and/or the Beckwith-Wiedemann syndrome (see below).

Clinical examination and where appropriate biochemical screening for associated conditions should be carried out.

Pituitary Tumours

In children, pituitary tumours (usually prolactinomas 63 %) may be the first manifestation of MEN1 and they can occasionally arise before the age of 10 years [65].

Familial pituitary tumours also occur due to germ line mutations in *AIP*, these are usually GH secreting. *AIP* mutations account for approximately 20 % of pituitary tumour families and accounts for a significant proportion in the paediatric and adolescent age range [25].

Since *AIP* is a more common genetic cause for a sporadic pituitary tumour the gene should be tested prior to *MENIN* [24, 46].

Pituitary tumours can also be part McCune Albright and Carney complex which should be diagnosable from the other associated features [24].

Screening in Pituitary Families and MEN1

Annual clinical review is recommended for symptoms of hyperprolactinaemia (causing secondary amenorrhoea, galactorrhoea), Cushing's disease from ACTH hyper secretion and Growth hormone excess, gigantism with possible secondary glucose intolerance being more likely than acromegalic features.

Biochemical Screening in MEN1

Serum calcium and PTH and prolactin should be measured every 1–2 years from 10 years of age.

Fasting glucose and gut hormone profiles, and measurement of chromogranin A and pancreatic polypeptide from the age of 16 years [7].

Li Fraumeni

Li Fraumeni is a dominant disorder caused by germline mutations in TP53. It is associated with susceptibility to sarcoma, breast cancer, brain tumour, leukaemia, adrenocortical tumours [3, 41, 70]. Approximately half of children with ACT have Li Fraumeni syndrome. ACT in childhood may be the first manifestation of Li Fraumeni syndrome within a family and can be important in making the diagnosis [11].

X-Ray irradiation should be kept to a minimum given the high prevalence of *p53* germ line mutations and the risk of second tumours. Families should therefore be offered testing for *p53*. However this should only be offered in the context of adequate genetic counselling because of the serious implications to the family.

Genetic referral and investigation must be offered and long-term follow-up for second tumours recommended. Radiotherapy is not advised given the high chance of a genetic cancer predisposition. Secondary tumours have been reported within the radiation field.

Sarcomas in children although they occur relatively frequently in families the chance of finding a mutation in a sporadic case is low without a family history of other tumours and is not at present an indication for genetic testing [42].

Screening for Li Fraumeni

The current recommendation is for annual clinical review with abdominal ultrasound and biochemical screening for adrenocortical carcinoma. However screening protocols during childhood have been suggested including annual whole body and brain MRI for brain tumours and sarcomas, this would require anaesthetic in a young child and are currently not universally recommended. The success of screening is unknown although early results are encouraging [71].

The Carney Complex

Carney complex is an autosomal dominant susceptibility to cardiac myxomas, cutaneous myxomas, psammomatous melanotic schwannomas, and pituitary and Sertoli cell tumours [26]. Lentigines somewhat recognisant of PJS occur, and the condition is also sometimes confused with NF1. One third of patients with Cushing's syndrome have pigmented multinodular adrenocortical disease (PPNAD) of which Carney Complex is a relatively common cause [15, 16].

Annual clinical review with biochemical screening for adrenocortical tumours and pituitary adenomas is recommended. Males should be educated to examine their testes regularly. Annual cardiac ECHO looking for cardiac myxoma is recommended.

McCune-Albright – Polyostotic Fibrodysplasia

McCune-Albright is a mosaic syndrome due to *GSA* mutations and associated with Cushing's syndrome due to adrenal nodular disease. Cafe au lait patches with the characteristic 'coast of Maine' outline are a feature of this disorder as is polyostotic fibrous dysplasia, precocious puberty and other endocrine disorders.

Annual review in an endocrine clinic is recommended.

Genetic Testing

Clinical examination may guide which gene to test. If there are no clinical clues then *P53* mutation analysis should be offered to all childhood patients with sporadic ACT. Testing for *MENIN* should also be considered.

Carney Complex show genetic heterogeneity with linkage to 2p16 and 17q2, the gene on 17q is PRKAR1A and identified in about half the families. The other gene is yet to be identified [35].

Differentiated Thyroid Cancer (DTC)

Children usually present with a solitary or dominant thyroid nodule but malignancy can be present in what appears clinically to be a diffuse or simple multinodular goitre.

Differentiated thyroid cancer can occur in FAP, Cowden's disease, the Carney complex and dominant papillary carcinoma families.

Only 5–10 % of all thyroid cancers occur in childhood, predominantly in female adolescents. More than 90 % of childhood thyroid cancers are differentiated, most are papillary carcinoma (80–90 %) and only 5–15 % are follicular cancers.

Papillary carcinoma with a cribriform histology is highly suggestive of FAP. Annual sigmoidoscopy should be initiated from 10 years of age.

Follicular carcinoma in a patient with multinodular goitre and/or follicular adenomas should raise the possibility of Cowden's disease. PTEN mutation analysis should be considered.

Tumours Associated with Abnormal Growth or Developmental Anomalies

Growth Disorder (Table 4.3)

An abnormal growth pattern may be an indication of underlying genetic disorder, a number of overgrowth syndromes are associated with increases in risk and conversely children with DNA repair disorders often have short stature and may have microcephaly.

In addition abnormal growth associated with learning difficulties and/or structural anomalies may suggest a chromosomal disorder or single gene syndrome associated with a tumour risk.

Overgrowth and Macrocephaly

Overgrowth syndromes have a number of features in common; they are often associated with macrocephaly and an advanced bone age. It is always important when assessing growth to take into account the head circumferences, height and weight of the parents and to take a history of diabetes or gestational diabetes in the mother. The overgrowth may be symmetrical or asymmetric, it may be apparent only as isolated macrocephaly, or affect only one side of the body or even only one limb. Most overgrowth disorders are inherited as an autosomal dominant but usually present as new dominant mutations or may be mosaic with no family history, there are some rare recessive families. Localised overgrowth may be due to a mosaic genetic disorder or be sporadic conditions but still have an increased risk of developing a malignancy.

The risk of solid tumours varies enormously from one disorder to another and it is therefore important to establish the diagnosis of the overgrowth disorder accurately before instigating screening [27].

The tumour risk is highest in Beckwith-Wiedemann, Simpson Golabi Behmel and Pearlman and these are the three conditions in which screening is frequently recommended [51].

Table 4.3

Growth disorders
Overgrowth syndromes
Single gene
Chromosomal
Localised growth anomaly
Hemihypertrophy
Isolated macrocephaly
Growth failure
Chromosomal
DNA repair disorders

Beckwith-Wiedemann

There is global overgrowth evident at birth with a high birth weight, this may be asymmetric with hemi hypertrophy. Macroglossia is usually evident. Abdominal muscle diastasis or exompholos can occur. Many newborn with BWS develop hypoglycaemia.

BWS arises as a result of imprinting disorder at 11p15. There are two imprinting centres in the region and imprinting anomalies occur at one or both centres, so multiple different genetic mechanisms can give rise to the disorder [40].

There is an increased risk of embryonal tumours particularly Wilms. The overall risk of developing Wilms tumour is between 5 and 10 % but it depends on the mechanism by which the disorder arises. Clinically if there is hemi hypertrophy the risk of an embryonal tumour is around 20 %. The condition and tumour risk can be dissected at the molecular level. The methylation pattern at the KvDMR1 region and the gene H19 determines the risk stratification. Following the clinical diagnosis it is therefore helpful to arrange molecular testing in order to establish risk and the potential tumour spectrum. Clinical screening is indicated in some types of BWS but not in others. Imaging and biochemical screening is indicated in those cases with uniparental disomy, which account for 20 % of cases and will be hypomethylated at H19 and KvDMR1, and imprinting centre 1 defects, which account for another 5 %, and will have normal methylation at KvDMR1 and be hypermethlated at H19. Clinical review without other investigations is adequate in the other 75 % of BWS cases [51].

Hemi Hypertrophy

The phenotype of BWS is not always obvious, with sometimes only the hemi hypertrophy being apparent. In isolated hemi hypertrophy the overall risk of Wilms is less than 4 % [13]. Many of those, about a third, who do develop tumours are unrecognised BWS with molecular abnormalities at 15p15. Whether screening is indicated in isolated hemi hypertrophy without a BWS is debateable. Currently this is recommended, but as the benefits of the screening are difficult to establish, even in those with a high risk, it could be argued that if BWS is excluded that the risks do not justify screening [51, 72].

Simpson Golabi Behmel

This condition can look very much like BWS as there are overlapping features including the overgrowth and ear creases. However it can usually be distinguished by the additional dysmorphic features. Accessory nipples are a good clinical sign as are genital anomalies, structural heart problems and clefting. It is usually associated with learning difficulties in males. The inheritance pattern is X linked recessive so the FH may be helpful. Carrier females are often

big as well. There is a 10 % risk of embryonal tumours in males, the majority of which are Wilms. The condition arises as a result of mutations in GPC3. Since this is an X linked disorder it is important to identify this condition as others in the family may be at risk.

Since the risk is 10 % screening is appropriate.

Perlman and 2q37.1 Deletions

Perlman syndrome is a severe rare autosomal disorder with a very high risk of developing Wilms tumour. There is a high mortality in infancy; the condition is associated with renal dysplasia and cryptorchidism. Prenatal overgrowth with visceromegaly occurs. The disorder is associated with developmental delay and facial dysmorphism, the facial features being very coarse.

The gene for the disorder is DIS3L2 which resides at 2q37.1 Children with hemizygous deletions in this region do not have Pearlman syndrome but do have a small but significant risk of Wilms at 3 %. This may be due to loss of heterozygosity in renal tissue leading to the development of the tumour, recessive at the cellular level [1].

Recommended Clinical Screening (Table 4.4)

Clinical screening is suggested for high risk BWS patients, SGB and Perlman. It is recommended that screening should include clinical assessment, abdominal ultrasound, serum VMA, HVA and catecholamines and urinalysis. Under the age of 4 this should be 3 monthly reducing to 4 monthly between 4 and 7 years and then twice a year until the age of 10 years. Ninety-four percent of tumours will occur before the age of 10 years [27].

Soto Syndrome and Weaver Syndrome

Macrocephaly is striking in Soto and Weaver and both are associated with dysmorphic facial features. The head circumference (HC) is generally over 97th. In childhood the height and weight are also above the 97th but tend to return to normal in adulthood in patients with Soto syndrome.

Table 4.4

Screening in overgrowth
Recommended for high risk BWS, Perlman, and SGB as risk over 10 %, 94 % cases <10 years
Clinical assessment
Abdominal ultrasound
Serum VMA, HVA, catecholamines
Urinalysis
Screening frequency
<4 years every 3 months
4–7 years every 4 months
7–10 years every 6 months

These two overgrowth syndromes can be difficult on occasions to differentiate. Mutations in NSD1, a histone methyltransferase, causes Soto syndrome and some cases of Weaver are said to have mutations in NSD1, however they may be cases of Soto that have been incorrectly diagnosed. In cases with Soto syndrome confirmed by NSD1 mutation analysis the incidence of tumours is low, probably only 2 % and seem to be mainly of neural crest origin, neuroblastoma, ganglioneuroma and ganglioglioma. Sacrococcygeal tumours have also been reported. Some of the tumours may just be benign overgrowth of differentiated cells. There have been no cases of embryonal tumours in Soto cases due to NSD 1 mutations, they do however have increased incidence ALL, T cell lymphoma and small cell lung cancer. Most are new dominant mutations and have variable learning difficulties.

Children with Soto have triangular facies with a broad prominent forehead and high check colour. Sometimes they have a wide alveolar ridge. The palpebral fissures tend to be down slanting. The face in Weaver tends to be more square shaped and the chin is small with a prominent transverse crease, in young children is tends to have a 'stuck on afterwards' appearance. There are several genes for Weaver syndrome. The carpal bone age is greatly advanced compared to metacarpal and phalangeal bone age. Recently mutations in EZH2 have been identified in cases of Weaver syndrome [66]. Neuroblastoma has been reported in Weaver but the risk is unknown in cases with EZH2 mutations.

Since the incidence of solid tumours is low presymptomatic clinical screening is not routinely offered for Soto and Weaver syndrome.

Cowden Syndrome and PTEN

Cowden syndrome and Bannayan Zonnana are caused by mutations in the gene PTEN. Some cases are more like Proteus syndrome. In adulthood they develop tricholemmomas, oral papillomas and acral keratosis, and in childhood and adolescence they may have lipomas, vascular malformations, and lymphangiomas [5]. Children with PTEN mutations may have global overgrowth or isolated macrocephaly. Some have macrocephaly and may be otherwise small. Learning difficulties may be variably associated. They have an increased risk of benign and malignant disease of thyroid, breast and uterus. Tumours can occur in the adolescent age range. Large fibroadenomas of the breast can occur in adolescents. Goitre is common and the pathology of the thyroid is characteristic with follicular carcinoma developing on a background of a multinodular goitre [5].

The condition can be confused with MEN2B. There may be c-cell hyperplasia and neuro cutaneous neuromas can occur, ganglioneuromatosis of the gut and corneal nerve hyperplasia also occur in both conditions, they should be distinguishable by the presence of macrocephaly [54].

The gene for PTEN is adjacent to one of the genes for juvenile polyposis SMAD4 and occasionally patients who have both genes deleted have been reported.

Genetic testing is indicated since this will alter screening in adulthood. However no screening other than clinical review annually is recommended as the risks in childhood and adolescence is relatively low. If the disorder is associated with a deletion of SMAD4 then bowel screening would be indicated as well as a one off screen for AV malformations in the chest and head. Annual clinical review in childhood is adequate with further screening for tumours in adulthood [5].

Gorlin Syndrome, SUFU Mutations and Medulloblastoma

Gorlin syndrome is another overgrowth syndrome associated with macrocephaly. There is hypertelorism, frontal bossing, cleft lip and palate can occur. There may be a variety of skeletal anomalies including short forth metacarpals, bifid ribs, jaw cysts, polydactyly and calcification of the falx. Mild developmental delay may also be a feature. Basal cell carcinomas are common and may be multiple with an early age of onset. Medulloblastoma and meningiomas can both occur. Females often develop calcified fibromas of the ovary. It is important to consider the diagnosis in children with medulloblastoma because of the risk of multiple BCCs that will arise in any radiation field. All children with medulloblastoma should have a clinical examination for macrocephaly or any of the other associated features of Gorlin. Mutations are in the gene for Patched-1 a receptor in the sonic hedgehog signalling pathway. Germ line mutations in another gene in this pathway SUFU has also been found in children with medulloblastoma of the desmoplastic type [9, 10, 67]. About 9 % of medulloblastomas are due to mutations in Patched-1, 9 % have SUFU [45]. Since these genes may be responsible for 20 % of cases of medulloblastomas genetic testing is indicated, particularly is the tumours are desmoplastic/nodular.

Regular Dermatolological Surveillance from BCCs is Mandatory in Gorlin

Abnormalities of Ras Signalling and Paediatric Tumours

Over the last few years a number of genetic conditions, with phenotypic overlap have been found with causative genes coding for components of the same Ras MAPKinase signalling pathway: Noonan syndrome, Cardiofaciocutaneous syndrome (CFC) and Costello syndrome. Many of these conditions are associated with an increased risk of malignancy in children [36].

These disorders are characterised by distinct facial features, variable developmental delay, congenital heart disease and short stature. Noonan syndrome is characterised by webbing of the neck, down slanting palpebral fissure, hypertelorism and posteriorly rotated ears. There may be widely spaced nipples and pectus of the chest. Cryptorchidism is common. Pulmonary stenosis and hypertrophic cardiomyopathy are frequent. Mutations in PTPN11 are a common finding. Noonan syndrome can be caused by mutations in most of the genes in this pathway.

Noonan syndrome is associated with a significant risk of malignancy, these are usually haematological. Juvenile myelomonocytic leukaemia (which can spontaneously regress in patients with PTPN11), ALL and AML are most common.

However the cumulative risk is only 4 % by age 20 and so screening is usually not recommended; again clinical review remains important to detect problems early.

The dysmorphic features in CFC is similar to Noonan but with additional ectodermal features. *BRAF* and *KRAS* are the usual genes involved. CFC is not usually associated with an increased risk of solid tumours, although leukaemia has been reported.

Costello Syndrome

Costello syndrome due to mutations in *HRAS*, is associated apparent overgrowth at birth followed by failure to thrive and relative macrocephaly. The facial features are coarse. The small joints are very hyper extensible and the skin feels soft and doughy. Hypertrophic cardiomyopathy and arrhythmias can occur [32].

Costello is more frequently associated with a risk of solid tumours, rhabdomyosarcoma but also neuroblastoma and bladder cancer, the latter may occur in adolescence. At least 15 % of children with Costello syndrome will develop a tumour by age 20 years and clinical screening is therefore justified. Unfortunately this is complicated by the finding that children with Costello have a high urinary catecholamine, even in the absence of a tumour so urinary screening is not possible [28]. Abdominal and pelvic ultrasound has been suggested as well as urinalysis for haematuria. However the benefits in this rare disorder are still to be confirmed. Regular clinical review however is mandatory.

Genetic testing for the genes in this pathway is now available by next generation sequencing. This is important in establishing tumour risk as the risk varies depending on which gene is involved, although this is not yet fully delineated.

Neurofibromatosis Type 1

Neurofibromin the gene responsible for neurofibromatosis type 1 is also part of this pathway. Many studies have overestimated the risk of malignancy due to ascertainment bias. A population study carried out in Wales has estimated a relative lifetime risk of malignancy of 2.5 [34].

The condition is most easily diagnosed by clinical examination. More than 5 Café au lait patches >0.5 cm (or >1.5 cm in adults) in diameter are suggestive of the diagnosis and the presence of cutaneous neurofibromas. In addition Lisch nodules of the iris or axillary freckling are pathopneumonic. However clinical features may not be present in a young child and are more likely to be seen in the second decade. Macrocephaly and Lisch nodules may be present from early on. Often one of the parents will be affected and should be asked about features and examined for NF1 if the diagnosis is suspected [23].

There is some suggestion that deletions of Neurofibromin are associated with a higher risk of tumour development.

Optic glioma (pyelocytic astrocytoma) occur in 15 % of patients but only 5 % become symptomatic, growth tends to plateau and in the absence of visual symptoms is not an indication for treatment. Rhabdomyosarcomas, mostly arising in the pelvis occur in 1.5 % of children usually <5 years. Haematological malignancies are rare but chronic myelomonocytic leukaemia occurs in childhood. ALL and Non Hodgkin's lymphoma can also occur. Endocrine tumours can occur, but rarely in children, particularly phaeochromocytomas and carcinoids. In addition there is a 1 % lifetime risk of each of malignant peripheral nerve sheath tumours and astrocytomas.

Since the incidence of tumours is low routine screening is not recommended in the UK except by clinical review annually. This should include visual fields [4].

Growth Failure (Table 4.5)

DNA repair disorders

These were amongst some of the first genetic disorders identified as having a risk of malignancy. This group of disorders have a number of features in common that help with diagnosis either at or prior to presentation of the malignancy. Restricted growth and microcephaly, neurological problems and developmental delay are common [38]. Freckling, sun sensitivity and café au lait patches also frequently occur. There may be recurrent infections due to immunodeficiency, and premature ageing may be present. This group of disorders are not uncommonly responsible for extreme reactions to treatment [49].

Table 4.5

When to suspect a Chromosomal disorders
MR
Dysmorphic features
Structural anomalies
Growth disorder
Usually small but can be overgrowth
Investigate by array

There are four main types of DNA repair. Base Excision repair, nucleotide excision repair double stand break repair, and mismatch repair. Each is responsible for repairing different sorts of damage. There is cancer susceptibilities associated with each type of repair. In addition there are some DNA repair disorders that affect more than one type of repair because the underlying defective mechanism is used in more than one type. An example would be disorders associated with RecQ helicase deficiency such as Blooms syndrome.

Base excision repair

MYH Polyposis

MYH polyposis is a disorder of base excision repair. It is inherited as an autosomal recessive but clinically is very like familial adenomatous polyposis. It is characterised as a susceptibility to developing colorectal adenomas and cancer. However the adenomas are less frequent than in familial polyposis and can vary from one or two up to a maximum of about 100. Gastro duodenal polyps can also occur and rarely duodenal cancer. Pilomatrixomas can also occur.

This disorder should be considered in cases of polyposis which are negative on genetic testing. However it usually has an adult onset but cases have occurred in children and adolescents. There are common alleles present which can be easily screened for genetically.

Colorectal screening is recommended from 18 years of age by annual colonoscopy.

Nucleotide Excision Repair (NER)

Nucleotide excision repair is important in the repair of thymine dimers caused by UV radiation and some of the results of oxidative damage.

Xeroderma Pigmentosa

Xeroderma pigmentosa (XP) is an AR disorder of NER. There is extreme sun sensitivity and photophobias, about 20 % have additional neurological problems. Developmental delay, growth failure and microcephaly can occur. Affected individuals develop all types of skin cancers. Prevention is very important in this disorder by sun and x ray avoidance and therefore initially testing fibroblasts for DNA repair disorders such as unscheduled DNA synthesis, followed by gene testing is important to confirm the diagnosis. Children who have unusual sun sensitivity should be tested for the disorder. This disorder can be very severe and parents may elect to have prenatal diagnosis in subsequent pregnancies. There are 8 genes involved in NER and global genome repair.

Double Strand Break Repair

Most of the known autosomal recessive DNA repair disorder conditions involve double strand break repair including Ataxia Telangiectasia and Fanconi anaemia.

The usual presentation of Ataxia Telangiectasia (AT) is neurological with cerebellar ataxia, choreoathetosis, dysarthria and abnormalities of ocular movement. Most affected individuals will be in a wheelchair by their teens. Oculocutaneous telangiectsia, pigmentary abnormalities and acanthosis nigracans are skin manifestation. Immunodeficiency with disordered B-cell and T-helper cell function, thymic hypoplasia and low IgA (70 %) and IgE (80 %) occurs.

Cytogenetically there are spontaneous chromatid gaps, breaks and interchanges which are increased by X-radiation. Blood lymphocytes develop abnormal clones with stable cytogenetic rearrangements.

There is a 10–20 % risk malignancy mainly lymphoma (60 %) and leukemia (27 %).

Clinical review and education of the parents is the only screening recommended.

Fanconi's Anaemia (FA)

Fanconi's anaemia is recessive. Short stature and a variety of congenital anomalies (60 %) can occur; thumb and other radial ray are common. There can also be anomalies in almost any system, urinary tract, gastrointestinal tract including anal atresia and developmental delay can be present. Café au lait patches and other pigmentary anomalies are common. Bone marrow failure usually occurs in the first decade, usually first thrombocytopenia or leucopoenia. There is hypersensitivity to DNA cross linking agents so it is important to establish the diagnosis before beginning treatment for malignancies [49].

There is a high risk AML, squamous carcinomas are also increased. There are at least 15 genes for FA. The disorder is confirmed by chromosome breakage studies [47] followed by gene testing to establish the subgroup.

Complementation group D1 are homozygotes for BRCA2 and there is a 20 % risk of Wilms tumour and screening for Wilms is therefore recommended in this subgroup. However this is usually the first presentation of the disorder in the family so the opportunity rarely arises. Finding the mutations will however allow genetic testing of other members of the family and facilitate clinical screening for both homozygotes and heterozygotes for BRCA2 [52].

Clinical screening is by clinical review except in D1 where screening for Wilms is indicated [52, 56].

Lynch Syndrome, Turcot and Mismatch Repair

Mutations in the mismatch repair genes, MSH2, hLMH1, MSH6, and PMS2 cause hereditary non polyposis colorectal cancer (HNPCC) now more commonly known as Lynch syndrome. Homozygotes for mutations in the HNPCC genes hMLH1 and PMS2 cause Turcots syndrome. This disorder is often confused with NF1 because of the presence of café au lait patches and brain tumours including PNET tumours [37]. However they are also at risk of colorectal neoplasia at a very young age and leukemia. Occasionally there is syndactyly. It is important not to miss the diagnosis because of the risk of recurrence in sibs and risk of adult onset tumours in the parents and other relatives.

Clinical Screening

Adenomas and gastrointestinal malignancy can occur at a young age in Turcots syndrome. Colonoscopy from 6 years is indicated and capsule endoscopy from 8 years of age [33]. Annual clinical review with full blood count should also be recommended [17].

Disorders Associated with RecQ Helicase Deficiencies

In disorders associated with RecQ helicase deficiencies both BER and DSB and mismatch repair are affected. The disorders include Werner, Bloom and Rothman Thompson syndromes.

In Blooms syndrome there is a sun sensitive rash, dwarfism and immune deficiency. There is an increase in risk of all types of cancers. Death from malignancy is usual before third decade. Chromosome gaps, breaks and rearrangements are seen on cytogenetic and SCE is increased.

In Werner's syndrome there is premature ageing, an increased incidence of sarcomas with an average age at death 4 years. They have premature cardiovascular disease. Chromosome losses and deletions occur.

In Rothmans-Thompson they have bilateral juvenile cataracts, sun sensitive rash with poikiloderma congenitale. As in FA radial ray defects are common. They have sparse hair.

Screening is by regular clinical review.

Mosaic Variegate Aneuploidy

Mosaic variegate aneuploidy is an autosomal recessive disorder due to mutations in BUB1B which codes for a protein important in the mitotic spindle checkpoint and CEP57, a centrosomal protein [30, 61]. Affected individuals have constitutional mosaicism for chromosomal aneuploidies. A quarter of affected children develop Wilms tumour, rhabdomyosarcomas and hematological malignancies.

Screening by clinical review and for Wilms is therefore suggested.

Chromosomal Disorders (Table 4.6)

Chromosomal disorders are often associated with disordered growth. This is usually growth failure but can be overgrowth.

Table 4.6

Growth failure
Suspecting a DNA repair defect
Café au lait patches
Sun sensitivity
Freckles
Short stature/failure to thrive
Neurological problems+/– microcephaly
Premature ageing
Immunological problems
Abnormal reaction to radiotherapy/chemotherapy

Table 4.7

Genetic referral
If tumour frequently genetic
If histology unusual/bilateral or multifocal
If there are other associated features
Congenital anomaly
Growth disorder
MR
Pigmentary anomalies
Abnormal reaction to treatment

There may be a more complex phenotype with learning difficulties, dysmorphic features, structural anomalies or other clinical disorder that may indicate a possible chromosomal or single gene disorder.

Some chromosomal disorders may be recognised as being associated with a risk of malignancy and children with these diagnoses should benefit from appropriate screening, aniridia Wilms (WAGR) syndrome would be an example or deletions of 13q14 deleting the Rb gene. These disorders are associated with an increased risk because they involve the deletion of a known tumour suppressor gene such as the deletion of the WT1 gene in WAGR. The finding of an anomaly known to be associated with one of these deletion syndromes should therefore lead to a genetic test to identify if the tumour gene is also deleted. For instance children with aniridia should have testing to see if the deletion extends into the WT1 gene, this would be now done by chromosome array. A deletion can occur anywhere and include one of the known tumour suppressor genes. If a child is identified with a chromosomal deletion, perhaps done for developmental delay it is important to follow this up with an array to identify genes that are deleted. If this includes a tumour suppressor then clinical screening should be instigated if appropriate.

Genetic Testing (Table 4.7)
Karyotype and array comparative genome hybridisation.

Summary

In summary a genetic susceptibility should be suspected when anything unusual happens whether this is an early age of onset, especially an adult tumour in childhood, disordered growth, developmental and structural anomalies, a family history, multiple primaries or unusual pathology including multifocal tumours.

Any of these finding should prompt genetic referral or testing after suitable counselling [31].

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Genetic Counseling for Childhood Tumors and Inherited Cancer-Predisposing Syndromes

5

Edward S. Tobias

General Principles of Cancer Genetics

Chromosomal changes are common in all types of malignancy and are helpful for identification of the underlying pathogenesis and for prognostic assessment. These chromosomal changes usually occur after birth and are thus acquired rather than inherited. The cells at birth usually have normal chromosome constitutions (46,XY or 46,XX) and a variety of acquired changes are seen (Figs. 5.1, 5.2, 5.3, 5.4 and 5.5) including loss or gain of chromosomes (in part or whole) and chromosome rearrangements. Loss of chromosomal material means that genes on the partner chromosome are unmatched and such loss of heterozygosity has been an important clue to the location of tumor suppressor genes. For example, cytogenetic analysis in neuroblastomas commonly reveals loss of the distal short arm of chromosome 1 and this area is believed to hold as yet uncloned tumor suppressor gene(s) for this tumor type. Table 5.1 lists examples of regions which show loss of heterozygosity (by cytogenetic or molecular analysis) with the associated childhood tumor types and names of the tumor suppressor genes where these have been cloned. These genes in Table 5.1 are all on the autosomes (chromosomes 1–22 inclusive) and as these autosomes are paired there are normally two copies of each tumor suppressor gene in each cell. Both copies need to be inactivated for a tumor to occur or progress. In sporadic tumors two separate mutations are required to inactivate each normal gene. These mutations may be unexplained or induced by mutagenic agents. In contrast in many familial forms of pediatric cancer only one of the tumor suppressor genes is active at birth as the partner gene is inherited in an inactive form from a parent. The parent thus carries one normal and one underactive copy of this tumor suppressor gene and on average one half of the children will inherit the underactive gene and be predisposed to cancer (i.e., inherited as an autosomal dominant trait). As only a single mutation step is required to inactivate the remaining gene, tumors tend to occur at an earlier age in the familial forms than their sporadic counterparts and are more commonly multifocal or bilateral in paired organs. In some tumors the somatic inactivation of a single remaining copy of a tumor suppressor gene occurs by an epigenetic event (rather than by a mutation) whereby methylation of cytosine bases in the promoter region of the gene causes transcriptional repression or silencing.

Occasionally, childhood tumors result from the inheritance of *two* mutated alleles (gene copies) of a gene. The condition may be autosomal recessive, as in Perlman's syndrome or Rothmund-Thomson syndrome. Alternatively, two inactivated alleles (instead of the more commonly found single mutated allele) of a gene associated with an autosomal dominantly inherited cancer syndrome may be inherited (e.g., *BRCA2* homozygotes causing Fanconi syndrome and *PMS2* causing SPNET).

Chromosome rearrangements can also provide important clues to the other main class of genes which are involved in tumor occurrence and progression: the oncogenes (Table 5.2). For example (Fig. 5.1), Ewing's sarcoma is commonly associated with a specific translocation between chromosomes 11 and 22 (with breakpoints on the long arm of 11 at band q24 and the long arm of 22 at band q12). This translocation results in a novel fused gene (*EWS* with either *ETS* or *FUS*) whose product is believed to cause the tumor [1, 2]. This and other oncogenes usually produce their effect via an altered gene product rather than loss of activity as for the tumor suppressor genes. Oncogenes may also be involved in tumor progression by amplification (a selective increase in the number of copies of a specific gene) to produce an increased level of the normal protein product. For example, amplification of *MYCN* on chromosome 2 occurs in some neuroblastomas and is associated with a worse prognosis (Fig. 5.3a, b).

The effects of these chromosomal changes can also be influenced by the parental origin of the chromosome. For

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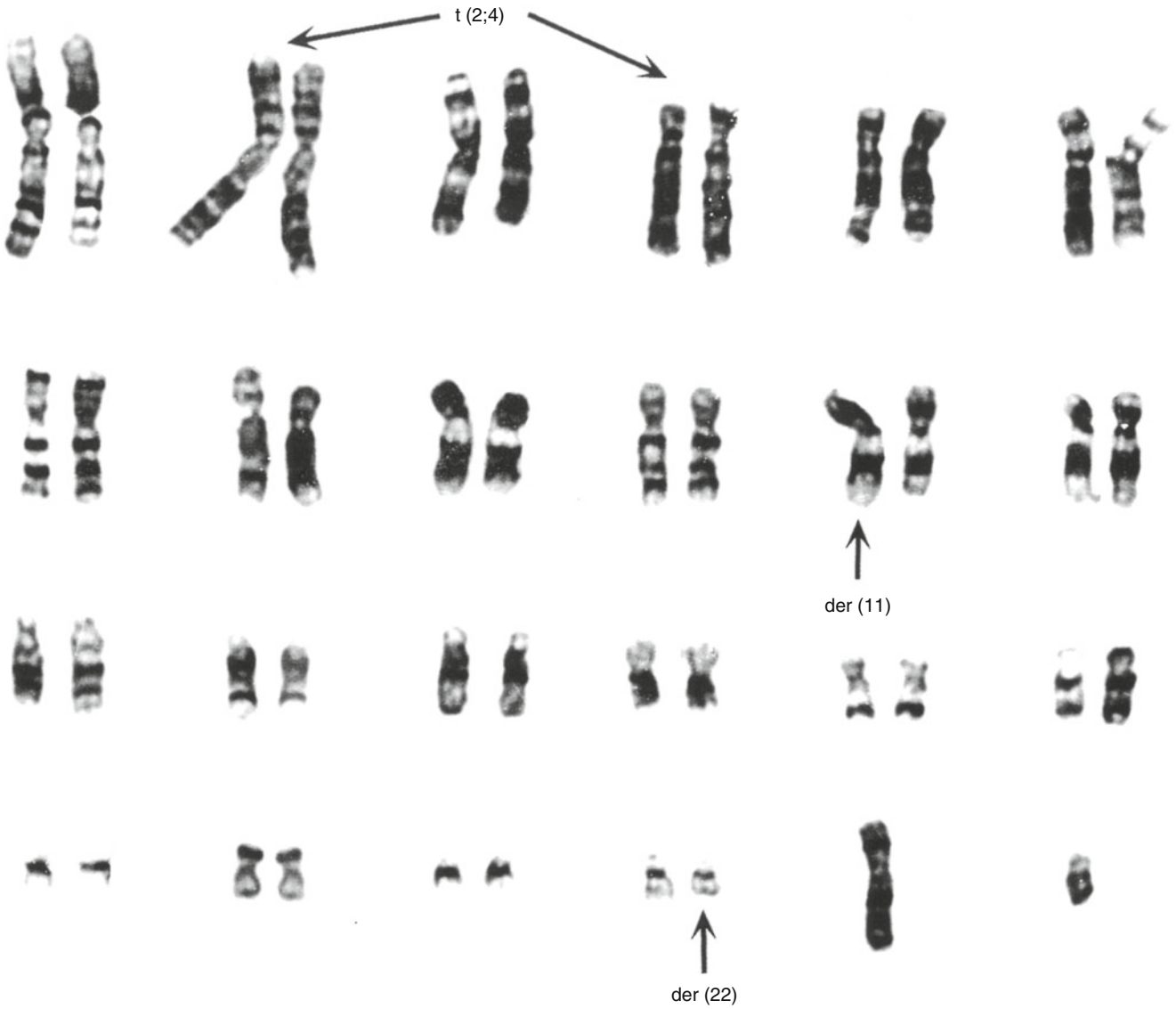

Fig. 5.1 G-banded karyotype of a cell from a patient with Ewing's sarcoma showing the characteristic translocation between chromosomes 11 and 22 [t(11;22)(q24;q12)]. This translocation is found in 90 % of cases of Ewing's sarcoma. The cells from this patient also carried an apparently balanced translocation between chromosomes 2 and 4 [t(2;4)(p23;p14)]

Fig. 5.3 (**a**) Metaphase cell from a patient with neuro-blastoma showing a homogeneously staining region (*hsr*) on chromosome 4. Hybridization with a probe for *MYCN* shows the hsr to be comprised of amplified sequences of the *MYCN* gene. (**b**) Fluorescence in situ hybridization of *MYCN* in a case of neuroblastoma exhibiting double minute chromosomes. This figure contains both a metaphase spread and an interphase nucleus; however, both show the presence of multiple copies of the double minutes

Fig. 5.2 G-banded karyotype from a patient with Wilms' tumor showing an isochromosome for the long arm of chromosome 7. This results in monosomy for the short arm of chromosome 7 and trisomy for the long arm

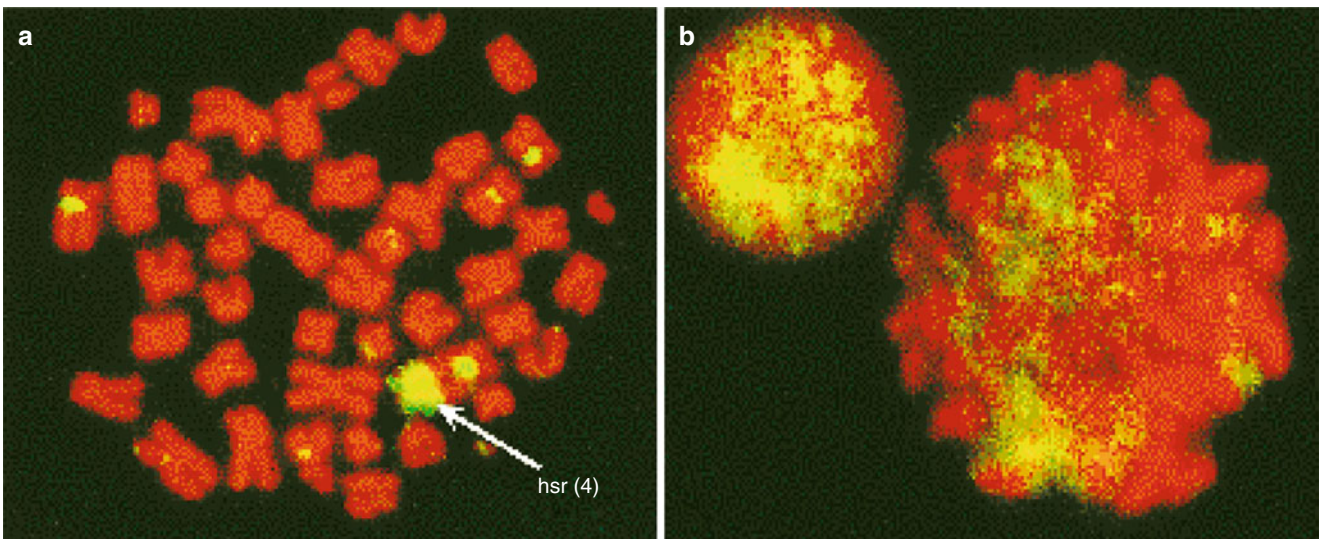

Fig. 5.4 G-banded karyotype from a patient with a giant cell tumor showing an interstitial deletion of chromosome 5 [del (5) (q15q33)] and also a telomeric association between chromosomes 12 and 18 [tas(12; 18)p13;q23)]

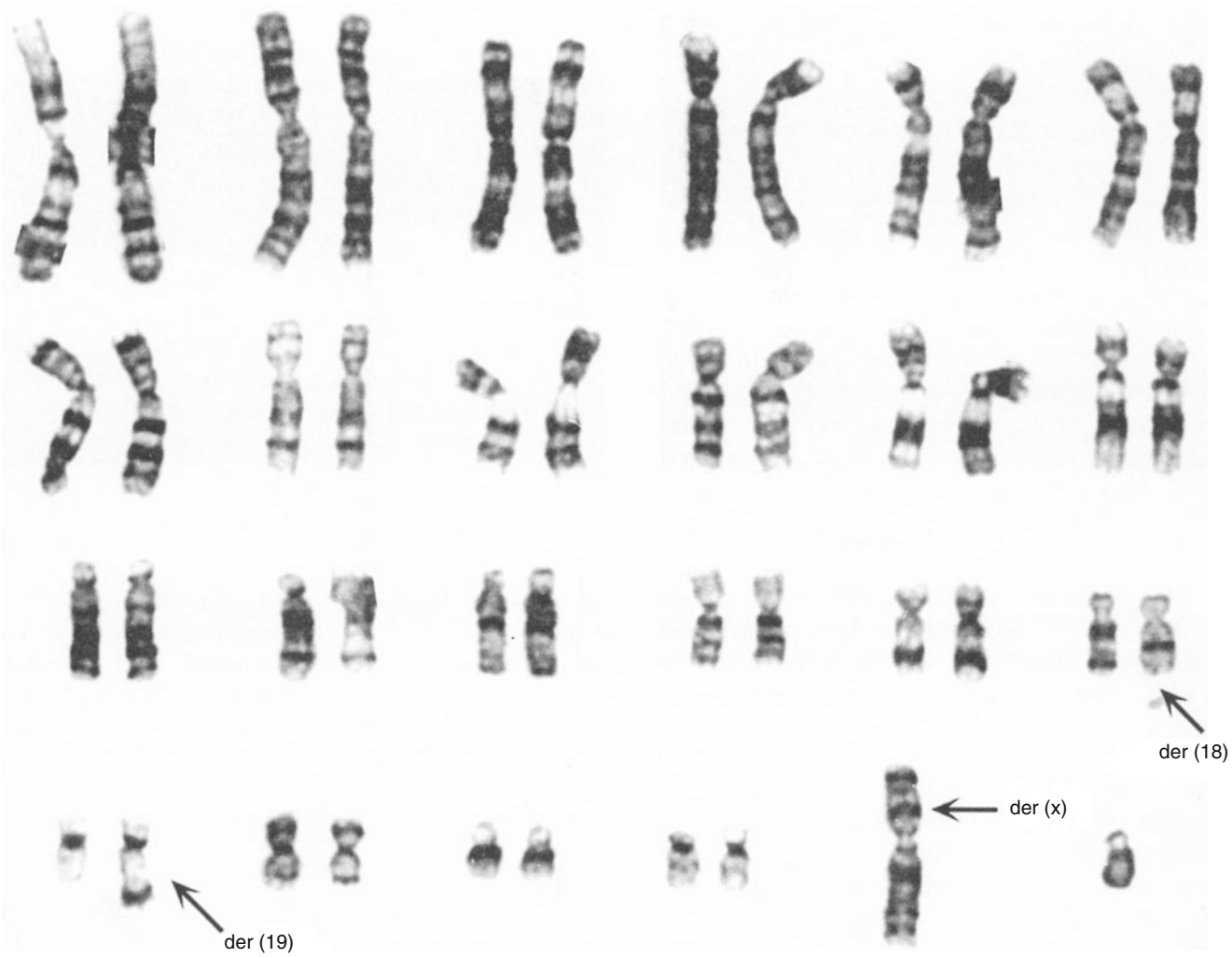

Fig. 5.5 G-banded karyotype from patient with synovial sarcoma showing the characteristic translocation between chromosomes 18 and X [t(X;18)(p11;q11)]. This karyotype also has a derivative chromosome 19 from a translocation between chromosomes 17 and 19 [der (19) t(17;19)(q21;q13)]

Table 5.1 Examples of tumor suppressor genes known to be involved in childhood tumors

Chromosomal location gene(s)	Tumor type(s)	Cloned tumor suppressor
1p	MutYH- or MYH-associated polyposis	*MutYH or MYH*
2q	Nephroblastoma	*DIS3L2*
3p	Retinal angiomas, phaeochromocytomas	*VHL*
5q	Familial polyposis	*APC*
7p	SPNET	*PMS2*
8q	Exostoses	*EXT1*
9q	BCC, medulloblastoma, Gorlin syndrome	*PTCH*
11p	Nephroblastoma	*WT1*, *WT2*, *CDKN1C*
11p	Exostoses	*EXT2*
13q	Retinoblastoma, osteosarcoma	*RB1*
17p	Adrenocortical carcinoma, Li-Fraumeni syndrome	*TP53*
17q	Neurofibroma, CNS tumors	*NF1*

Human gene symbols are shown in italic capitals. Additional details of the genes, encoded proteins and the related clinical conditions are available from the online databases that are categorized and listed at www.essentialmedgen.com
p short arm, *q* long arm of a chromosome, *BCC* basal cell carcinoma, *SPNET* supratentorial primitive neuroectodermal tumor

Table 5.2 Examples of proto-oncogenes implicated in human malignancy

Proto-oncogene	Molecular abnormality	Disorder
RET	Point mutation	Medullary thyroid cancer and MEN2
MYC	Translocation 8q24	Burkitt's lymphoma
ABL1	Translocation 9q34	Chronic myeloid leukemia
MOS	Translocation 8q22	Acute myeloid leukemia
MYC	Amplification	Carcinoma of breast, lung, cervix, esophagus
MYCN	Amplification	Neuroblastoma, small cell carcinoma of lung
KRAS2	Point mutation	Carcinoma of colon, lung, and pancreas; melanoma
HRAS	Point mutation	Carcinomas of genitourinary tract, thyroid

Human gene symbols are shown in italic capitals. Additional details of the genes, encoded proteins and the related clinical conditions are available from the online databases that are categorized and listed at www.essentialmedgen.com
p short arm, *q* long arm of a chromosome, *MEN2* multiple endocrine neoplasia type 2

example, in patients with neuroblastoma but without *MYCN* amplification the associated 1p deletion is almost always maternal in origin [3]. In contrast, familial mutations in the succinate dehydrogenase D, *SDHD*, gene appear to predispose to phaeochromocytomas and paragangliomas generally only when inherited from the father [4]. These observations reflect genomic imprinting – a process in which defined parts of particular chromosomes are only active if inherited from the mother or father but not both.

Thus the occurrence and progression of tumors is influenced by a variety of genetic changes. Retinoblastoma appears to be an exceptional tumor in that it occurs with inactivation of the tumor suppressor gene *RB1* alone whereas most tumors involve multiple genetic changes. This accumulation of changes varies between tumor types and the exact pattern varies even for a particular tumor type. In general, early changes are viewed as key steps in the pathogenesis and in some instances the cumulative pattern or particular changes can be useful in assessment of prognosis.

Genetic Counseling Aspects of Childhood Cancer

Epithelial cancers in infancy and childhood (i.e., lung, breast and gastrointestinal cancer) are extremely rare. Tumors in childhood are generally of mesodermal origin and may be subdivided into leukemias (35 %), brain tumors (20 %) and solid tumors (45 %). The solid tumors and brain tumors are of most relevance to the pediatric surgeon and hence this chapter will focus on the genetic aspects of the more common types of these tumors and their associated inherited syndromes.

General Principles of Genetic Counseling

Genetic counseling is the communication of information and advice about inherited conditions [5, 6]. A standard medical history and examination is required for the affected person and in addition the family pedigree needs to be constructed.

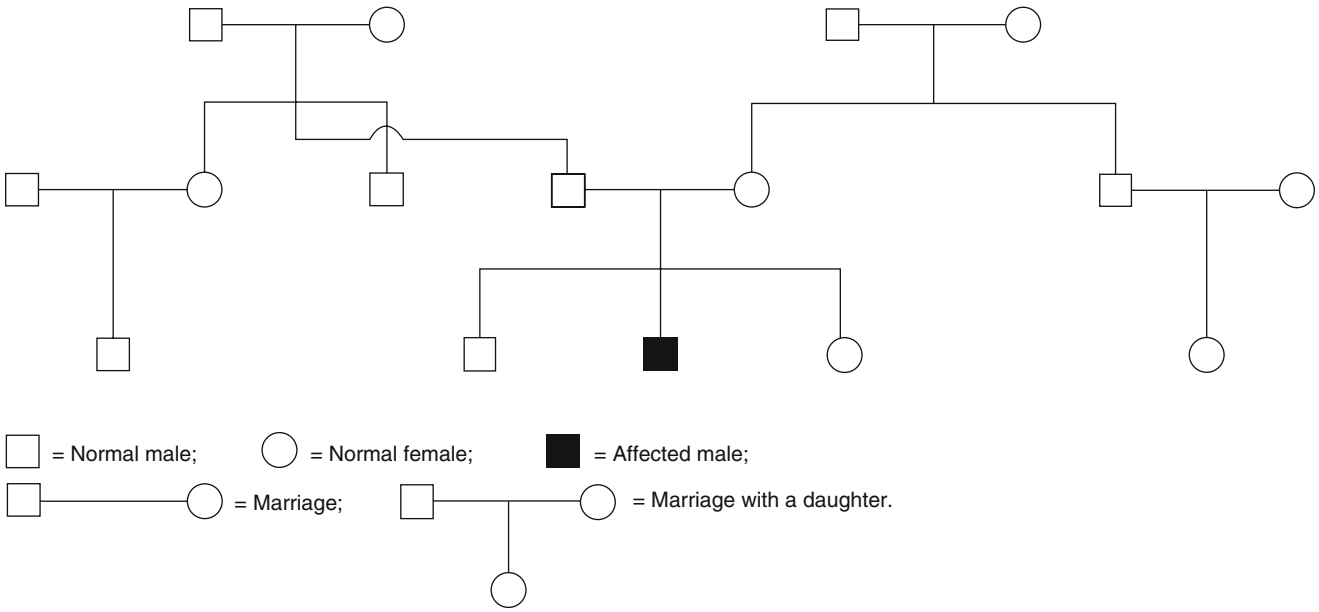

Fig. 5.6 Pedigree of a family with a child who has Wilms' tumor

Figure 5.6 illustrates the pedigree from a family with a child with Wilms' tumor. Squares symbolize males, and circles females. All members of the same generation are placed on the same horizontal level and brothers and sisters are ordered with the eldest to the left. In this family the affected boy (shown shaded) has a normal older brother and a younger sister and no other relatives are or were affected. If other relatives had related tumors then it would be necessary to either see them in the clinic or confirm the details from their records. For certain tumor syndromes it might also be necessary to examine apparently normal parents and other relatives for minor features of the condition. Alternatively, if a specific mutation is identified in the proband, genetic testing for this mutation can subsequently be offered to the relatives where appropriate. It should be noted that if neither parent of a proband with an autosomal dominantly inherited syndrome has the condition or the causative mutation, the risk to siblings of the proband may be very low but not zero. The residual recurrence risk is due to the possibility of gonadal mosaicism whereby a proportion of gonadal cells in a parent may contain the mutation without it being present constitutionally in that individual.

The key is to establish the precise diagnosis before attempting to provide genetic counseling. This may involve further tests or literature searches or opinions from colleagues in the regional clinical or cancer genetics services. Once the diagnosis is secure adequate time in an appropriate setting needs to be allowed for discussion of the facts. Ideally both parents should be seen and few couples can be adequately counseled in under 30 min. A crowded clinic or the corner of a hospital ward are inappropriate and the information is unlikely to be retained if given too soon after the initial shock of a serious diagnosis. Counseling needs to include all aspects of the condition and the depth of explanation should be matched to the educational background of the couple. Pictures of chromosomes can be helpful in explaining modes of inheritance and we routinely send the parents a summary letter of the salient points after the session. Most couples can be counseled in a single session with the option to return if new questions arise or for recall if relevant new research advances occur. Parents may feel responsible for their child having the condition. These fears need to be aired and allayed. In inherited tumors and syndromes there is an additional need to minimize feelings of guilt and stigmatization.

Genetic Counseling for Specific Tumor Types

In this section general counseling (and, where available, molecular) information is provided for the more common tumor types of relevance to the pediatric surgeon and further information is available in the chapter in this textbook by Dr Murday, and also in textbooks of general cancer genetics [7]. In addition, the chapter on cancer genetics by Tobias et al. in *Essential Medical Genetics* (6th edition) [5] provides general background principles and further information relating to familial adult cancers. Detailed descriptions of cancer genes, their encoded proteins and the intracellular molecular pathways in which they are involved are provided in the chapter entitled "The Molecular Biology of Cancer" by *Tobias in Emery & Rimoin's Principles & Practice of Medical Genetics* [8].

Links to many invaluable online worldwide sources of additional information on genetic conditions and the genes involved are categorized and freely provided at www.essentialmedgen.com.

Ependymoma

Most ependymomas are sporadic with a low recurrence risk but one exceptional family has been described where sisters and a maternal male cousin were affected [9]. Another has been reported in which two siblings had cervical spinal cord ependymoma and another had schwannoma, with evidence for the possible involvement of a tumor suppressor gene on chromosome 22 in familial ependymoma [10]. Ependymomas can occur as part of the spectrum of neurofibromatosis type 2.

Ewing's Sarcoma

Ewing's sarcoma is usually a sporadic event and has not so far been reported in a parent and child. Furthermore, the tumor does not appear to occur as part of specific familial cancer syndromes.

Gliomas

Genetic conditions associated with a predisposition to glioma include Gorlin's syndrome, Li-Fraumeni syndrome, Maffucci's syndrome, neurofibromatosis type 1, neurofibromatosis type 2, tuberous sclerosis and Turcot's syndrome. Familial glioma not associated with these conditions occurs but is rare [11].

Gonadoblastoma

The majority of gonadoblastomas develop in 46,XY individuals with gonadal dysgenesis. Gonadal dysgenesis has a variety of causes and recurrence risk will depend upon the precise diagnosis.

Hepatoblastoma

Congenital abnormalities are common in children with hepatoblastoma and have been reported in up to a third of cases. The abnormalities include hemihypertrophy, polycystic kidney disease and abnormalities of the urogenital system. Hepatoblastoma is a recognized complication of several overgrowth syndromes including congenital hemihypertrophy, Beckwith–Wiedemann syndrome, Sotos syndrome and Bannayan–Riley–Ruvalcaba syndrome. Hepatoblastoma may also rarely occur in children with familial adenomatous polyposis coli [12]. Congenital hypertrophy of the retinal pigment epithelium has been observed with the latter association. In the absence of these associated syndromes and of any relevant family history, a low recurrence risk may be appropriate as familial cases appear to be rare [13, 14]. For further information concerning hepatoblastoma, see Chap. 16.

Lymphoma

A variety of genetic immunodeficiency disorders predispose to malignant lymphoma. They include ataxia–telangiectasia, Chédiak–Higashi syndrome, common variable immunodeficiency, hyper IgM syndrome, severe combined immunodeficiency, Wiskott–Aldrich syndrome and X-linked lymphoproliferative syndrome (Duncan disease). Non-Hodgkin's lymphoma is about six times as frequent as Hodgkin's disease in these patients with primary immunodeficiencies. In the absence of an underlying primary immunodeficiency there is a sevenfold increased risk for siblings of a young (<45 years) patient with Hodgkin's disease. The low incidence means, however, that the actual risk to siblings is still low [15]. Part of this familial risk might relate to shared environment but part appears to relate to the HLA locus which might operate by predisposing to a particular infection or by producing an aberrant response to a particular infectious agent. In addition, a non-HLA genetic factor (a susceptibility gene on chromosome 4 in particular) is now also believed to play a causative role [16]. Further extending the range of discovered predisposing genetic factors, evidence was published in Nature in 2012, implicating, in lymphoma etiology, a newly discovered tumor suppressor gene network linked to hypusine, an unusual amino acid and which regulates apoptosis [17]. For more in depth information concerning lymphoma see Chap. 21.

Medulloblastoma and Primitive Neuroectodermal Tumor (PNET)

Familial medulloblastomas are uncommon but have been reported in twins and siblings [18]. Genetic disorders associated with medulloblastoma include ataxia–telangiectasia, blue rubber bleb nevus syndrome, familial adenomatous polyposis, Gorlin's syndrome and von Hippel–Lindau syndrome. In addition, medulloblastoma can occur as a result of an inherited mutation in either *BRCA2* (which more commonly predisposes to breast and ovarian cancer) or *SUFU* (a gene that has been reported to cause familial meningioma and a Gorlin's-like syndrome) [20]. A childhood medulloblastoma (or primitive neuroectodermal tumor) of the desmoplastic subtype at the age of less than 2–3 years is highly suggestive of Gorlin's syndrome or an inherited *SUFU* mutation [19, 21]. Childhood PNETs can also occur in patients with inherited *TP53* mutations (Li Fraumeni syndrome) [22].

Histologically similar to the medulloblastoma is another embryonal CNS tumor, supratentorial primitive neuroectodermal tumor (SPNET). This tumor is however more aggressive, has a poorer prognosis and is most likely derived from primitive neuroepithelial cells. It is now recognized that SPNET can occur together with café- au-lait skin pigmentation (similar to that occurring in neurofibromatosis type 1) in patients who have inherited mutations in both copies of the *PMS2* DNA mismatch repair gene [22]. Such patients are

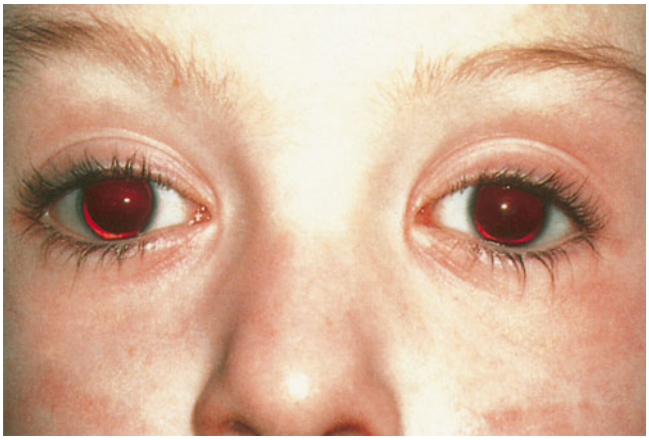

Fig. 5.7 A child with bilateral aniridia

also now believed to possess an increased risk of leukemias, lymphomas, astrocytomas, glioblastomas and, in early adult life, colorectal neoplasia [23]. Homozygous *PMS2* syndrome is an important cause of pediatric malignancy among a population in the UK that originated from south Asia and its risk of recurrence in siblings is 25 % [23].

Nephroblastoma (Wilms' Tumor)

Most cases of nephroblastoma are sporadic with a low recurrence risk but multiple families with familial Wilms' tumor have been described. An underlying genetic predisposition is present in 9–17 % of cases of Wilms' tumour, with the predisposition including familial Wilms' tumor in addition to several syndromes of which Wilms' tumour is just one component. Familial Wilms' tumor, which accounts for less than 5 % of affected patients, is inherited as an autosomal dominant trait (OMIM 194070) with incomplete penetrance (i.e., not all gene carriers develop the tumor). Bilateral tumors are more likely to be familial. Wilms' tumor can be caused by mutations in the *WT1* gene at chromosome 11p13, although mutations in other genes can also predispose to the condition. In addition, Wilms' tumor occurs as a recognized complication of Beckwith–Wiedemann syndrome, Denys-Drash syndrome, Fraser syndrome, hemihypertrophy, Perlman's syndrome, sporadic aniridia and WAGR syndrome (*W*ilms' tumor, *a*niridia, *g*enitourinary abnormalities or *g*onadoblastoma and mental *r*etardation) (Fig. 5.7). Wilms' tumor is described in depth in Chap. 12.

Neuroblastoma

Most cases of neuroblastoma are sporadic and familial cases (in which predisposition to neuroblastoma is inherited as an autosomal dominant trait, OMIM 256700) account for less than 1 % of the total. The mean age at diagnosis in familial cases is 9 months compared with 30 months in non-familial cases and familial tumors are frequently multiple [24]. Neuroblastoma is occasionally a feature of neurofibromatosis type 1, Hirschsprung disease, Beckwith–Wiedemann syndrome, congenital hemihypertrophy and Costello syndrome. More information concerning neuroblastoma is provided in Chap. 14.

Osteogenic Sarcoma

Most osteosarcomas are sporadic but affected sibs have been described. Osteosarcoma may occur in patients with inherited retinoblastoma, Li Fraumeni syndrome, multiple exostoses and Rothmund–Thomson syndrome.

Retinoblastoma

Retinoblastoma may be sporadic (at least 60 % of cases) or inherited as an autosomal dominant trait caused by mutations in the *RB1* tumor suppressor gene on chromosome 13 (OMIM 180200). Sporadic cases are usually unilateral and have a later age of onset than the inherited form. Where a family history of retinoblastoma is absent, around 15 % of patients with unilateral unifocal retinoblastoma have an inherited mutation. An inherited mutation is very likely to be present if the tumor is bilateral or if there is a family history of retinoblastoma. In the inherited form, with a protein-inactivating mutation, the penetrance is high with a risk of developing retinoblastoma of at least 90 %, and bilateral tumors occur in 30 %. Mutation carriers are also at an increased risk for later osteogenic sarcoma. The tumor risk may be lower, however, in the minority of families in which the mutation does not truncate the protein (i.e., is not a frameshift or nonsense mutation). The *RB1*-encoded protein is involved in the regulation of the cell-cycle in response to DNA damage, causing (G1/S checkpoint) cell cycle arrest in order to allow the cell time to repair the DNA damage prior to DNA replication. Retinoblastoma is described in depth in Chap. 25.

Rhabdomyosarcoma

Associated syndromes include Beck with–Wiedemann syndrome, Li-Fraumeni syndrome, neurofibromatosis type 1, Costello syndrome and WAGR syndrome. Most rhabdomyosarcomas, however, are sporadic with a low recurrence risk for other relatives.

Teratoma

Most teratomas develop in the sacrococcygeal area and these tend to be benign. There may be associated malformations of the sacrum, vertebrae and gastrointestinal or urogenital tracts. Most are sporadic with a low recurrence risk but familial teratoma with an autosomal dominant mode of inheritance has been described. The hallmark of this condition is the presence of partial sacral agenesis with intact first sacral vertebrae. Other common features are a presacral mass and an anorectal malformation (forming, with the sacral bone defect, the Currarino triad) and urogenital malformations (Fig. 5.8a, b) [25]. Gene tracking in affected families

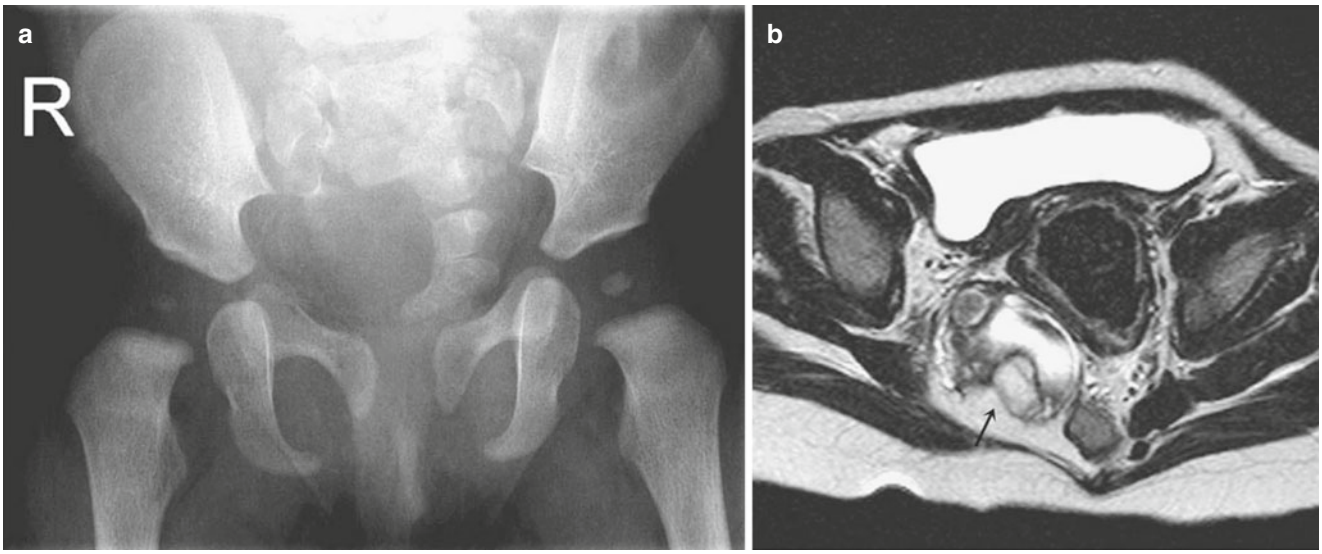

Fig. 5.8 (**a**) Pelvic anteroposterior radiograph showing a left hemisacrum with a sickle-shaped defect distal to S2 vertebrae (From Low et al. [71]). (**b**) Axial T2-weighted turbo spin-echo sequence showing the pre-sacral mass (*arrow*). The mass is of mixed composition with elements of fluid and fat signal (From Low et al. [71])

supported a localization of this gene to the long arm of chromosome 7 [26] and mutations have now been found in the *HLXB9* gene in most familial cases of Currarino triad and in some apparently sporadic cases [27].

After the first few years of life, most teratomas are gonadal. Ovarian teratomas (dermoid cysts) originate through failure of extrusion of the second polar body or refusion of it with the ovum (i.e., self-fertilization). They are usually sporadic with low recurrence risks but occasional families have been described where the condition appears to be inherited [28]. In comparison with sporadic dermoid cysts the familial cases tended to be of earlier onset and were often (10–25 %) bilateral. For further information concerning teratoma see Chap. 19).

Inherited Cancer-Predisposing Syndromes

Over 200 syndromes have been described in which cancer occurs as a recognized complication. Many of these syndromes are inherited and detailed continuously updated information is available for each in On-line Mendelian Inheritance in Man (OMIM). The web site for OMIM is www.ncbi.nlm.nih.gov/omim. In OMIM each condition has a unique number and these are provided for each entry in this section. Some of these conditions can be caused by mutations in more than one gene and these have two or more OMIM numbers. This chapter focuses on the main features of the more common syndromes which are associated with childhood tumors. For more detailed information including further references, and for rarer syndromes or syndromes mainly associated with adult tumors see OMIM.

PTEN Hamartoma Tumor Syndrome (Including Bannayan–Riley–Ruvalcaba and Cowden Syndromes, OMIM 153480)

Bannayan-Riley-Ruvalcaba syndrome is inherited as an autosomal dominant trait and is characterized by macrocephaly, pseudopapilledema, hamartomatous intestinal polyps, café-au-lait spots on the penis, a lipid storage myopathy, Hashimoto's thyroiditis and lipomas [29]. The lipomas and hemangiomas may be aggressive in growth and the intestinal hamartomas may have the potential to become malignant. Mutations in the *PTEN* gene are found in the blood of 50–60 % of patients with this syndrome and in 80 % of patients with the related Cowden syndrome (with particularly high associated adult cancer risks for breast, follicular thyroid and endometrial cancers) [30]. Unfortunately, significant intrafamilial variability has been observed, without a strong genotype-phenotype correlation. Therefore, both conditions are now regarded as existing within a spectrum of PTEN hamartoma tumor syndrome (PTHS), a term used to describe any carrier of an inherited *PTEN* mutation [31]. The greatest lifetime cancer risks were recently calculated for breast (85 %), thyroid (35 %), endometrial (28 %) renal cell (34 %) and even colon (9 %) and melanoma (6 %), necessitating appropriate physical screening as recommended [31].

The PTEN protein has an unusual lipid- and protein-phosphatase domain and normally functions as a tumor suppressor by inhibiting both the PI3K/AKT/mTOR and RAF/MEK/MAPK pathways. The consequent up-regulation of these two pathways in affected patients, causes increased cell survival and cell proliferation, respectively [31].

Trials are currently underway to assess the potential benefits of an mTOR inhibitor in prevention or treatment of PHTS-related tumors.

Beckwith–Wiedemann Syndrome (EMG Syndrome, OMIM 130650)

The cardinal features in the neonate are exomphalos, macroglossia and gigantism and the alternative name is an acronym of these features (EMG). Other features include earlobe grooves or posterior helical ear pits, visceromegaly (liver, kidney and spleen), cryptorchidism and neonatal hypoglycemia.

The majority of cases appear to be sporadic with a low recurrence risk but autosomal dominant inheritance with very variable expression is evident in 10–15 % of cases. The principal cause of Beckwith–Wiedemann syndrome (BWS) is the deregulation of imprinted growth-regulatory genes within either (or both) of two distinct domains (domain 1 and domain 2) within a region on the short arm of chromosome 11 at 11p15. Loss of activity of cyclin-dependent kinase inhibitor 1c (*CDKN1C*) appears to underlie the condition in at least some familial cases [33]. This gene is located in domain 2 at 11p15 and normally only the maternally inherited copy is active. This copy can be inactivated by a variety of point mutations (found in 40 % of familial cases, with a resulting 50 % recurrence risk) or by chromosomal changes which lead to a paternally derived duplication of chromosome 11p, or uniparental disomy for chromosome 11 (where both copies of chromosome 11 are derived from the father). In one of the families described by Hatada et al. [33] the mother of an affected child carried the same mutation in *CDKN1C* as her child but was clinically unaffected, as this mutation had been inherited from her father and was thus imprinted. This mother had a 1 in 2 recurrence risk for each subsequent pregnancy.

In contrast to the less common familial cases, recent molecular analyses have found that in the majority of affected patients, the cause is an epigenetic alteration at imprinting centre 2 (IC2) within domain 2 at 11p15, without an underlying genomic alteration [34]. This specific alteration is reported to have a low recurrence risk [34].

Patients with BWS have an increased risk of Wilms' tumor, neuroblastoma, adrenal carcinoma, rhabdomyosarcoma and hepatoblastoma and this risk is enhanced in the patients who have hemihypertrophy. Overall, 12.5 % of children with BWS have hemihypertrophy and this figure rises to 49 % in those with tumors. The increased risk of tumors relates largely to the first 8 years of life and the estimated combined risk approximates to 7.5 %. The risks for embryonal tumor development may, however, be lower in those particular patients who possess only an isolated epigenetic IC2 alteration, without an underlying genomic alteration [34].

Blue Rubber Bleb Nevus Syndrome (Bean Syndrome, OMIM 112200)

This condition may be sporadic or be inherited as an autosomal dominant trait. Multiple hemangiomas occur especially on the trunk and upper limbs and mucous membranes. Intestinal and pulmonary angiomas may occur and may bleed. Patients appear to be at increased risk of cerebellar medulloblastoma.

Costello Syndrome

This syndrome, like Noonan syndrome and cardiofaciocutaneous (CFC) syndrome, with which it overlaps phenotypically, is caused by mutations in the genes encoding the Ras/Raf/MAPK signaling pathway. This pathway normally causes activation of gene expression in the nucleus in response to receptor tyrosine kinase activation at the cell membrane. Costello syndrome is caused by mutations in the *HRAS* gene and includes relative microcephaly, coarse facial features, hyperextensible small joints and soft doughy skin. Of the syndromes associated with dysregulation of the Ras/Raf/MAPK signaling pathway, Costello syndrome is notable for its tumor predisposition. These include elevated risks of developing rhabdomyosarcoma, neuroblastoma in early childhood and transitional cell bladder carcinoma in adolescence and young adulthood.

Denys–Drash Syndrome (Wilms' Tumor and Pseudohermaphroditism, OMIM 194080)

This rare disorder is due to a variety of point mutations in the Wilms' tumor gene (*WT1*) and is characterized by male pseudohermaphroditism, Wilms' tumor and a progressive renal failure due to mesangial sclerosis [35]. Over 90 % of patients with Denys-Drash syndrome possess constitutional heterozygous mutations in the *WT1* gene [36]. Wilms' tumor in patients with the syndrome presents early (mean 18 months) and is usually bilateral. Gonadoblastoma or diaphragmatic hernia may also occur. Children who survive will be at high risk of having affected offspring (on average 1 in 2 will be affected) but for normal parents and other relatives of an affected child the recurrence risk will be very low.

Familial Adenomatous Polyposis Coli (FAP, OMIM 175100)

This condition is inherited as an autosomal dominant trait and is caused by a variety of mutations in the *APC* tumor suppressor gene on chromosome 5q. The APC protein normally acts as a component of a protein complex that negatively regulates the

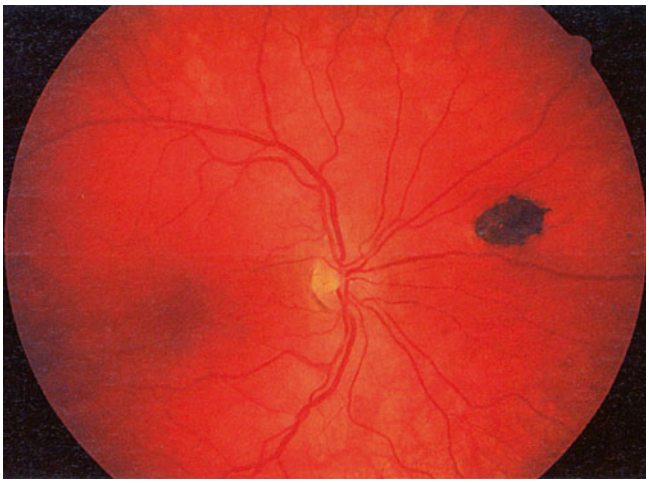

Fig. 5.9 Congenital hypertrophy of the retinal pigment epithelium (*CHRPE*) in familial adenomatous polyposis

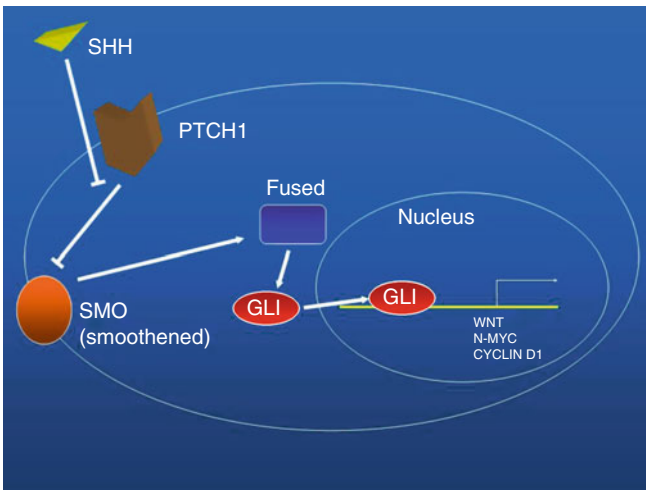

Fig. 5.10 The GLI pathway. Under normal circumstances, binding of the SHH ligand to the PTCH1 receptor causes inhibition of the negative regulation of SMO protein, leading to the activation of Fused and subsequently also the activation of GLI. In turn, this leads to increased expression of genes that drive cell proliferation, such as those encoding WNT, N-MYC and CYCLIN D1 proteins. In Gorlin syndrome, gene mutation (particularly of *PTCH1*) causes dysregulation of this pathway leading to the tumorigenic continuous overexpression of these important genes

abundance of beta-catenin. Inactivation of the APC protein thus leads to overaccumulation of beta-catenin, which is then able to enter the nucleus and cause the over-transcription of many genes, including proto-oncogenes. The most consistent feature is childhood onset of multiple intestinal polyps which have a high risk of malignant degeneration in adulthood. Other less consistent features are retinal pigmented spots (congenital hypertrophy of the retinal pigment epithelium) (Fig. 5.9), facial bone osteomas, desmoid tumors and epidermoid or sebaceous cysts. In addition to gastrointestinal malignancy, patients are at increased risk of gliomas. The mutations are catalogued in the online InSIGHT database at http://insight-group.org/variants/database/ [37].

Gorlin's Syndrome (Nevoid Basal Cell Carcinoma Syndrome, OMIM 109400)

This condition is inherited as an autosomal dominant trait and can be caused by a variety of mutations in the *PTCH1* gene on chromosome 9q [38]. The PTCH1 protein, a transmembrane receptor for SHH (sonic hedgehog) ligand, is normally a negative regulator of the Smo/Fused/Gli transcriptional activation pathway. Inactivation of PTCH1 thus leads to overexpression of a set of proto-oncogenes that include *NMYC* and the gene encoding cyclin D1 (see Fig. 5.10). About 20–30 % of patients possess *de novo* mutations rather than having inherited a mutation from a parent. The main features are multiple basal cell carcinomas of the skin and palmar and plantar pits. By 30 years of age 90 % of patients will have skin lesions but only 15 % manifest before puberty. Non-dermatological features include hypertelorism with a broad nasal bridge, frontal and parietal bossing, a prominent chin, jaw odontogenic keratocysts, cleft lip and palate, fusion defects of the cervical spine, rib abnormalities and calcification of the falx cerebri [39]. There is an increase in the incidence of non-dermatological tumors including squamous cell carcinoma and fibrosarcoma in jaw cysts, nasopharyngeal carcinoma, medulloblastoma, meningioma, craniopharyngioma, cardiac fibroma and ovarian fibroma. In fact, about 5 % of individuals with Gorlin's syndrome develop the childhood brain malignancy medulloblastoma (or primitive neuroectodermal tumor [PNET]). This tends to be of desmoplastic histology [21] and to have a favorable prognosis. The peak incidence of medulloblastoma in Gorlin's syndrome is about 2 years of age compared to 7 years in its sporadic form [21].

Li–Fraumeni Syndrome (OMIM 151623)

This condition is inherited as an autosomal dominant trait and is characterized by a predisposition to breast cancer, brain tumors, sarcomas, leukemia and adrenocortical carcinoma in children and young adults. Additional tumors which appear to occur with increased frequency include pancreatic, prostatic, lung and laryngeal carcinomata and malignant melanoma. Of affected patients, almost 50 % develop cancer by 30 years of age and 90 % by 70 years of age. Multiple primaries may occur and recurrent cancers often arise in the radiotherapy field suggesting a susceptibility to radiation carcinogenesis. In the majority of families the cause is an inherited inactivating mutation in one copy of *TP53* on chromosome 17p [40]. This gene encodes a protein that plays a pivotal role in both DNA repair and programmed cell death (apoptosis) (see Fig. 5.11). A deletion in the *TP53* gene is responsible for around 10 % of these mutations [41]. Unusually for a tumor suppressor gene,

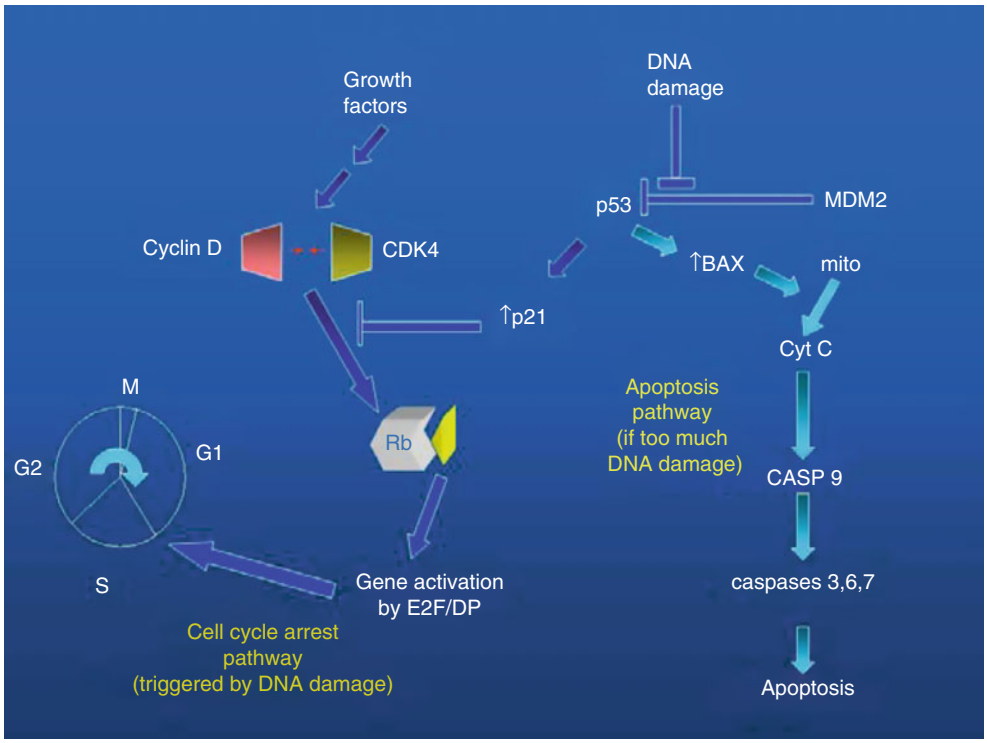

Fig. 5.11 The crucial role of the p53 protein (encoded by the *TP53* gene) in the cellular responses to DNA damage. DNA damage usually results in increased levels of p53 protein (by inhibiting its MDM2-mediated breakdown). The increased levels of p53 then cause an increase in p21 and a consequent block of the CDK4-mediated release of E2F from Rb (that is required for S phase entry in the cell cycle). Increased p53, therefore, results in cell-cycle arrest. If the DNA damage is too extensive for it to be repaired by the cell, then p53 can trigger programmed cell death (apoptosis) via the activation of: BAX, mitochondrial cytochrome C release and caspases, 9, 3, 6, and 7 (Please also see *Essentials of Medical Genetics* 6th edition, for additional pathway information

a single mutated copy of the *TP53* gene can occasionally give rise to cancer development without the inactivation of the other allele. This phenomenon is most likely to be due to a "dominant negative" effect of some mutations whereby the mutation prevents the normal efficient assembly of the protein into functional tetramers [41]. It relates especially to those mutations located within the central core (DNA-binding) domain of the gene [42]. Interestingly, missense (amino acid substitution) mutations located within this domain are reported to be associated with a higher risk of breast and brain cancer while those located outside the DNA-binding domain are more commonly associated with adrenocortical carcinoma [41]. In Li-Fraumeni syndrome families possessing normal *TP53* genes, heterozygous germline mutations have, rarely, been found in another gene, the *CHK2* gene [43] but this and several other candidate genes (including *MDM2*, *PTEN*, *CDKN2A*, *BCL10*, *CHK1*, *TP63* and *BAX*) have now been excluded as important causes of the syndrome [41–43]. At present, it remains unclear whether mutations in any other genes predispose to Li-Fraumeni syndrome.

McCune–Albright Syndrome (Polyostotic Fibrous Dysplasia, OMIM 174800)

This sporadic syndrome is usually caused by mosaicism for an activating mutation in the *GNAS1* gene, which encodes the alpha subunit of the stimulatory signal transduction protein, Gs. The syndrome is characterized by polyostotic fibrous dysplasia, café-au-lait pigmented skin patches, and endocrinological abnormalities including precocious puberty, thyrotoxicosis, pituitary gigantism and Cushing's syndrome. Osteosarcomatous transformation in areas of fibrous dysplasia has been described as a complication of this condition [44]. The timing of occurrence of the somatic mutation during embryonic development appears to determine the extent of disease, with earlier occurrence resulting in McCune-Albright syndrome and later occurrence resulting in more focal disease such as just a thyroid or pituitary adenoma. Transmission of mutations from parent to child has almost never been observed and the inheritance of such mutations is presumed to be incompatible with embryonic survival [45].

Maffucci's Syndrome (Osteochondromatosis, Multiple Enchondromatosis, Ollier Disease, OMIM 166000)

This is usually a sporadic condition in which osteochondromatosis (mostly enchondromas) and hemangiomas occur. The enchondromas may result in pathological fractures or deformity. Patients are predisposed to malignancy including chondrosarcoma most commonly, but also fibrosarcoma, angiosarcoma, osteosarcoma, teratomas, ovarian granulosa cell tumors and gliomas [46]. The condition in some cases may result from mutations in the the PTH/PTHRP type I receptor (*PTHR1*) gene [47] but such cases are likely to rep-

resent a minority, with other unidentified causative genes being responsible for the majority [48].

Multiple Exostoses (Diaphyseal Aclasis, Multiple Osteochondromatosis, OMIM 133700, 133701, 600209)

This condition is inherited as an autosomal dominant trait and is caused by a variety of mutations in one of three genes: *EXT1*, a tumor suppressor gene on the long arm of chromosome 8, *EXT2*, a tumor suppressor gene on the short arm of chromosome 11 and a third as yet uncloned gene on chromosome 19 [49]. Both *EXT1* and *EXT2* encode glycotransferase enzymes of the endoplasmic reticulum that synthesise heparansulfate and proteoglycans [50]. In hereditary cases, mutations are detected in *EXT1* and *EXT2* in 56–78 % and 21–44 % of families, respectively [50]. Clinically the families with mutations in the different genes appear to be indistinguishable. Affected patients develop cartilaginous excrescences near the ends of the diaphyses of the bones of the extremities which later undergo ossification. They may result in local deformity or nerve compression and patients may show disproportionate short stature in severe cases. Sarcomatous degeneration of an exostosis occurs in 0.5–2 % of patients and should be suspected when growth of an exostosis occurs after puberty. Each affected person has a high risk of passing the condition to his or her offspring (on average 1 in 2 will be affected). Gene carriers invariably show exostoses by puberty but these may not be prominent, especially in females, and it is important to radiograph the long bones before concluding that an apparently unaffected person at risk has received the normal gene and hence has a negligible risk for their family [51]. Multiple exostoses may also form part of the Langer-Giedion syndrome (microdeletion of chromosome 8q resulting in the loss of at least the *EXT1* and *TRPS1* genes) which also includes learning difficulties and features of trichorhinophalangeal dysplasia [52].

MYH-Associated Polyposis (OMIM 608456)

A colorectal adenoma and carcinoma predisposition syndrome with phenotypes very similar to FAP (but usually with a generally later age of onset and slightly less profuse polyposis) was described more recently than FAP. This MutYH-associated polyposis (MAP) is an autosomal recessive condition that results from the inheritance of a mutation in each copy of a base excision repair (BER) gene *MutYH* (human MutY homologue, also known as *MYH*) in the absence of inherited mutations in the *APC* gene [53–55]. The mean age at diagnosis of 25 reported unrelated MYH polyposis cases was 46 years (median 48 years, range 13–65 years) [54]. Mutations of the MutYH gene are catalogued (as for mutations of other hereditary colorectal cancer predisposition genes) in the online InSIGHT database at http://insight-group.org/variants/database/ [37].

Neurofibromatosis Type 1 (OMIM 162200)

Neurofibromatosis type 1 is inherited as an autosomal dominant trait and is caused by a variety of mutations in the *NF1* tumor suppressor gene on chromosome 17q. In around 25–50 % of cases, the mutations occur *de novo* with the parents being unaffected. Many mutations have been described of which around 80 % are predicted to disrupt the encoded protein, neurofibromin, loss of which is predicted to cause overactivity of the RAS cell signaling pathway [56]. Affected children are usually recognized by the presence of multiple café-au-lait patches and later skin neurofibromata. The presence of iris hamartomas (Lisch nodules) on slit lamp examination may be helpful for confirmation of the diagnosis. Associated tumors include optic pathway gliomas (present in 15 % on CT scan but only one-third of these are symptomatic), other brain tumors (1–2 %), malignant degeneration of a neurofibroma (1.5 %), phaeochromocytomas and rhabdomyosarcomas. In general, around two thirds of patients are only relatively mildly affected. There is no clear genotype-phenotype correlation at present, other than the association of *NF1* gene deletions (rather than point mutations) with dysmorphic features, increased numbers of neurofibromas and significant developmental delay (in addition to the typical NF1 manifestations) [57]. In addition, patients with large *NF1* gene deletions may be more predisposed to malignant peripheral nerve sheath tumors (MPNSTs) [58].

Neurofibromatosis Type 2 (OMIM 101000)

Neurofibromatosis type 2, which is generally more serious but approximately 10 times rarer than type 1, is caused by a variety of mutations in the *NF2* tumor suppressor gene on 22q. The *NF2*-encoded protein, normally physically links cell membrane proteins to structural intracellular proteins of the cytoskeleton. It also functions in cell adhesion and in the coordination of growth factor receptor signalling. Bilateral acoustic schwannomas are the most common tumor type but patients may also have spinal schwannoma or meningiomas, falx meningioma, parenchymal astrocytoma or ependymoma, or skin plaques (neurilemmomas). The condition is inherited as an autosomal dominant trait with full penetrance by 60 years of age. Helpful consensus guidelines have been published for the management of patients with neurofibromatosis type 2 and their families [59]. Clinical screening of at-risk individuals can begin from birth and genetic counseling and

testing of affected individuals and their at-risk relatives should be offered because presymptomatic diagnosis improves the clinical management of the disease [59].

Perlman's Syndrome (Renal Hamartomas, Nephroblastomatosis and Fetal Gigantism, OMIM 267000)

This rare disorder, caused by mutations in the *DIS3L2* gene, is inherited as an autosomal recessive trait and is characterized by macrosomia, visceromegaly, hypertrophy of the islets of Langerhans, renal hamartomas with or without nephroblastomatosis, learning disability, dysmorphic features (enophthalmos, broad depressed nasal bridge and everted upper lip) and cryptorchidism in males. There is a high risk of Wilms' tumor which is frequently bilateral [60]. The *DIS3L2* gene encodes a component of the RNA exosome, an intracellular complex that normally functions in the degradation of RNA molecules.

Rothmund–Thomson Syndrome (Poikiloderma Atrophicans and Cataract, OMIM 268400)

This condition is inherited as an autosomal recessive trait and, in most cases, appears to be caused by mutations in the gene *RECQL4*, which encodes a DNA helicase that is required for chromosome stability [61, 62]. The syndrome is characterized by skin atrophy, pigmentation and telangiectasia accompanied by juvenile cataract, saddle nose, congenital bone defects, disturbances of hair growth, short stature and hypogonadism. Patients appear to be at increased risk of osteosarcoma [63].

SOTOS Syndrome (Cerebral Gigantism, OMIM 117550)

This condition is characterized by excessively rapid growth, acromegalic features and a non-progressive cerebral disorder with mental handicap. It may be sporadic or inherited as an autosomal dominant trait. About 80–90 % of individuals with Sotos syndrome have a demonstrable mutation or deletion of the *NSD1* gene, while a minority of patients may instead have a mutation within the *NFIX* gene [64]. Around 95 % of cases represent new mutations but the risk of transmission to each child of an affected patient is 50 %. Tumors occur in fewer than 5 % of people with Sotos syndrome but include hepatoblastoma, neuroblastoma, sacrococcygeal teratoma, presacral ganglioma, and acute lymphoblastic leukemia (ALL) [65, 66]. The *NSD1* gene is one of a growing number of human syndrome-associated genes that encode proteins that normally function as epigenetic regulators. The *NSD1*-encoded protein is a histone methyltransferase that acts upon lysine amino acids within histone 3 and histone 4, allowing it to act as either a transcriptional co-activator or as a co-repressor, depending on the cell type [67].

Tuberous Sclerosis (OMIM 191100, 191092)

This condition is inherited as an autosomal dominant trait and is caused by a variety of mutations in one of two genes: *TSC1* and *TSC2*, tumor suppressor genes on the long arm of chromosome 9 and the short arm of chromosome 16, respectively. Affected patients develop a facial fibroangiomatous rash (adenoma sebaceum), white skin patches, skin fibromatous plaques (shagreen patches), enamel pits, whitish retinal phakomata, intracranial calcification, epilepsy and mental handicap. Tumors include renal angiomyolipomata, renal cell carcinoma (occasionally), cardiac rhabdomyomata and malignant gliomas, usually giant cell astrocytomas (in 6 %). Clinically, it now appears that mutations in *TSC1* are generally associated with a less severe phenotype than those in *TSC2* [68, 69]. Approximately 60 % of cases represent new mutations. In these cases the recurrence risk in a future child (of the normal parents) will be small, but with a residual risk of around 2–3 % due to the possibility of gonadal mosaicism in one parent.

The recognition of the upregulation of mTOR (or mTORC1 complex) protein activity in TSC-related tumours has led to successful trials of mTOR inhibitors such as everolimus in patients with tuberous sclerosis who develop subependymal giant cell astrocytoma (SEGA). For instance, SEGA volume was reported to be reduced by at least 30 % from baseline in 65–79 % of patients in a treatment group of affected patients, whose median age was 11 years [70].

WAGR Syndrome (Wilms' Tumor, Aniridia, Genitourinary Anomalies, Mental Retardation Syndrome, OMIM 194072)

This syndrome's name is an acronym of the features of Wilms' tumor, aniridia, genitourinary malformations and mental retardation. It is caused by a microdeletion of chromosome 11p which encompasses *WT1* (resulting in a high risk of Wilms' tumor) and adjacent genes such as *PAX6* (the loss of which causes aniridia). An affected parent will have a 1 in 2 risk for affected offspring but normal parents with a *de novo* microdeletion in their child will have a low recurrence risk.

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Tumour Markers

6

Philip J. Hammond and D. Fraser Davidson

Introduction

Tumour markers are biological compounds found in association with a malignancy and their clinical applications have been refined over recent decades. They are usually detected in the serum or urine of children with cancer but may also be found in other body fluids such as ascites, pleural effusion or cerebrospinal fluid [1–3]. These compounds may be produced by tumour tissue itself or represent host tissue-derived metabolic or immunological products released in response to neoplasia [4]. Such markers consist of oncofetal proteins (AFP, CEA), enzymes (NSE, alkaline phosphatase), hormones (hCG, catecholamines and their metabolites), carbohydrate antigens (CA125, CA19.9), and others (such as neopterin, neurotensin and transcobalamin I).

In clinical practice tumour markers may be used in the differential diagnosis of paediatric tumours, in detecting residual disease following apparent complete resection (thereby informing the staging of disease), as a method of evaluating response to treatment, or to detect recurrent disease before it is apparent clinically or by diagnostic imaging [5]. Some tumour markers lack specificity but the level may reflect the extent or stage of the disease thereby giving an indication of tumour activity or prognosis – termed 'prognostic factors' [6]. Recently they have also been used as targets for therapeutic intervention in clinical trials [7].

The ideal tumour marker would be produced exclusively by malignant tissue (or even by tissue predisposed to progressing to malignancy). Such a marker would be highly sensitive to detect early-stage disease with few false-negatives and sufficiently specific to safeguard against false-positives. Unfortunately this ideal tumour marker does not exist and hence reliance on tumour markers in clinical practice must be tempered by an awareness of their sensitivity and specificity. For instance, screening whole populations of well infants for occult (hidden) neuroblastoma using urinary catecholamine metabolites has caused much controversy and presented clinicians with difficult treatment decisions (*vide infra*). Although tumour markers are typically imperfect as screening tests, their serial assessment is most often used to monitor response to treatment and detect recurrence. In this chapter the tumour markers which are practically useful in the management of childhood solid tumours will be discussed.

Germ Cell Tumour Markers

Alpha-Fetoprotein

Alpha-feto protein (AFP) is a major plasma protein of the fetus which is synthesized in the yolk sac and the liver at an early stage of development (with a trace amount also being synthesised by the fetal gastrointestinal tract). It has a molecular weight of 70 kDa and consists of a single polypeptide chain. Its structural similarity to albumin suggests a similar function as a carrier in plasma and in the maintenance of osmotic pressure. Its production starts at about the 6th week of gestation and trails off after birth. The serum AFP concentration decreases exponentially from approximately 50,000 ng/ml at birth to a level of less than 20 ng/ml by 8 months of age [8]. Preterm infants have ten times higher levels of AFP than term infants do at birth. The biological half-life of AFP has been estimated to be about 5 days by serial measurements in children following complete resection of AFP-producing tumours. Non-neoplastic conditions during infancy or later in life may result in elevated AFP concentrations. In the first 6 months elevated levels may be found in children with neonatal hepatitis, biliary atresia or congestive

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hepatomegaly. AFP is not an acute-phase reactant and hence elevated values following hepatic trauma or toxic injury have not been observed. As with any immunoassay, clinical correlation is vital to guard against over-reliance on laboratory values in view of possible interference. For instance, erroneously high or low values may result from interference from endogenous antibodies or alternatively the hook effect may give rise to erroneously low values [9, 10].

Human Chorionic Gonadotrophin

Human chorionic gonadotrophin (hCG) is a glycoprotein hormone which is composed of two subunits, α and β. While the α subunit of hCG is structurally similar to the α subunit of LH, FSH, and TSH, the β subunit of hCG (β-hCG) is different from the β subunit of these pituitary hormones. Recognition of the antigenically distinct β subunit has enabled the development of a specific immunoassay without interference from the other hormones or the α subunit. The serum half life of β-hcg is approximately 24 h indicating that blood levels should rapidly return to normal after complete resection of an hCG-producing tumour.

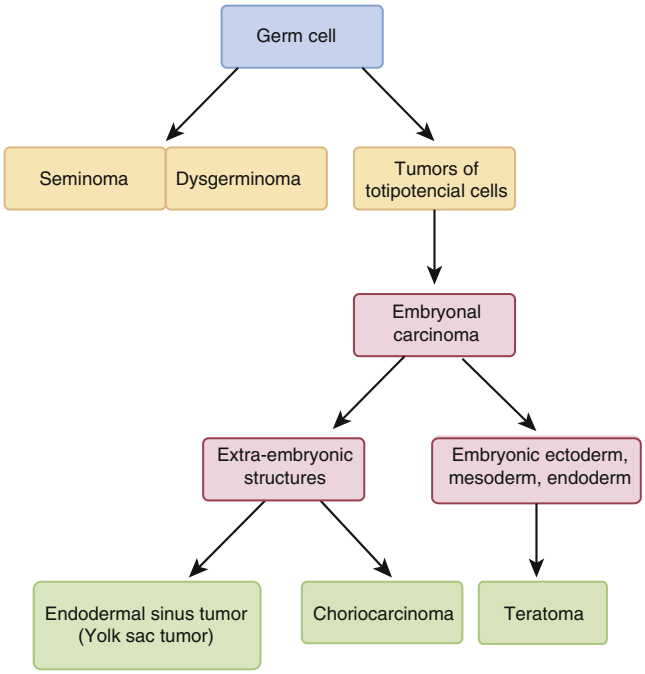

Fig. 6.1 Teilum's concepts of the origin and classification of Germ Cell Tumours

Clinical Applications of AFP and β-hCG

Germ cell tumors (GCT) have diverse clinical, pathological and prognostic features because they arise from totipotential and pluripotential cells in children and may be gonadal or extra-gonadal. In children two-thirds of GCTs are located in extra-gonadal sites, the majority being in the sacrococcygeal region in infants, anterior mediastinum, and midline central nervous system sites. They comprise mature and immature teratomas, yolk sac tumors (endodermal sinus tumours), embryonal carcinoma, germinoma (dysgerminoma/seminoma), choriocarcinoma and gonadoblastoma. Classifications of GCTs are essentially modifications of Teilum's concepts [4, 11] (see Fig. 6.1). Mixed GCT types are often found within a single neoplasm, thereby making the detailed histological examination so important.

Germinoma is a general term for a malignant germ cell tumour and has largely replaced the terms 'seminoma' and 'dysgerminoma' which referred to germinomas arising in the testis and ovary, respectively. They represent 15 % of all paediatric germ cell tumours and are most commonly found in the ovary in girls or the pineal gland in adolescent boys. Testicular germinoma (seminoma) is rare in children. Markers for AFP and β-hCG are negative in 'pure germinoma' but may be elevated if other GCT types are also present within the germinoma.

The term 'embryonal carcinoma' refers to a highly malignant neoplasm composed of undifferentiated, totipotential embryonal cells with the potential to differentiate into extra-embryonal neoplasms (endodermal sinus tumours and choriocarcinomas) and tumour derived from all three germ layers (teratomas). Embryonal carcinoma is rare in children, but is a major component of the malignant germ cell tumor of the testis and mediastinum in adolescents and raised serum AFP levels have been demonstrated in up to 70 % of these patients. Such tumours may also contain areas of other GCT.

Endodermal sinus tumours (Yolk sac tumours) are the most common malignant GCT in children, most frequently involving gonadal or sacrococcygeal sites. It is the commonest testicular tumour in boys less than 3 years of age. Less common primary sites in children include the anterior mediastinum, pineal region of the CNS, vagina, and liver. Serum AFP is elevated in about 75 % of patients with pure endodermal sinus tumours [4].

Choriocarcinoma is a highly malignant GCT characterized by syncytiotrophoblastic differentiation and strong immunopositivity for β-hCG. It may occur in gestational or non-gestational forms, and the possibility of pregnancy mimicking an abdominal tumour in an adolescent girl should be considered before potentially hazardous investigations with ionizing radiation are performed. Rarely, choriocarcinoma may present in infancy as a disseminated complication of maternal-placental choriocarcinoma [12]. Most paediatric choriocarcinomas are non-gestational and arise in the gonads, mediastinum, retroperitoneum or brain. Almost all extra-gonadal choriocarcinomas occur in males.

Approximately 5 % of GCTs are found within the CNS, with the majority being located in the midline in the pineal region. Such tumours tend to present with raised intracranial pressure, nystagmus, or isosexual precocious puberty. Occasionally the risk of open or stereotactic biopsy of such deep midline brain lesions makes the procedure unacceptable and hence the monitoring of tumour markers may provide a method of monitoring tumour response to chemotherapy or irradiation. When a tumour of germ cell origin is amongst the differential diagnosis, serum AFP and β-hcg levels should be included in the measurement of tumour markers.

Immuno-histochemical staining demonstrates tumour cells which are positive for AFP. Although the exact nature of the intra-cellular periodic acid-schiff (PAS)-positive hyaline globules, which are characteristic of yolk sac tumours, is unknown, the globules are frequently positive for AFP. After surgical excision of a yolk sac tumour, serum AFP levels decrease to normal with a half life of approximately 5 days. Recent recommendations have suggested the reporting of serial values in graphic form to allow the clinician to visualise changes with time and intervention [2]. Sudden elevation of serum AFP levels may indicate the presence of metastatic or recurrent disease [13]. Serum AFP levels may be increased when there are foci of yolk sac tumours within the teratoma. Patients diagnosed with immature teratomas and high AFP at the time of diagnosis have a higher risk of malignant recurrence. Malogolowkin et al. therefore recommend that immature teratomas with high serum AFP should be treated in a similar way to malignant germ cell tumours [14]. Bilik et al. reported that yolk sac tumours recurred in 8 % of patients whose sacrococcygeal teratoma had initially been treated in the neonatal period and that all recurrences were accompanied by an increase in serum AFP [15]. To help differentiate AFP produced in yolk sac tumors from physiologically elevated AFP in early infancy some investigators have attempted to analyse the AFP subfraction profile or fucosylation and glycoaminylation indices of AFP [16, 17].

When elevated, these biomarkers are mainly used to monitor response to therapy and particularly in early detection of recurrence. Some investigators have even reported excellent outcome with serum markers being used to inform the duration of cisplatin-based chemotherapy [18]. Although most children with GCTs have elevated AFP and/or β-hCG, there is a group in whom these markers are negative. Tumour recurrence without elevation in serum AFP or β-hCG has also been documented in children who had raised biomarkers at initial presentation.

Other Markers for Germ Cell Tumours

The cancer antigen CA 125 is a glycoprotein which is expressed in celomic epthelium during embryonic development. In adults the normal values for CA 125 in serum is less than 35 U/ml and the levels are increased in about 80 % of patients with epithelial ovarian cancer as well as in some patients with carcinoma of the endometrium, pelvic inflammatory disease and endometriosis. The serum CA 125 is useful in monitoring the clinical course of patients and at the same time it is a potent prognostic factor in ovarian cancer [5]. On the other hand, little is known about the oncologic significance of the marker in children. An increase in serum CA 125 is observed in patients with yolk sac tumour and embryonal carcinoma [19]. The levels decline after the initiation of therapy but re-elevation of the levels was not associated with recurrence [19]. Although the majority of ovarian tumours in childhood and adolescence are germ cell tumours, those of epithelial origin still represent approximately a third of cases in adolescents in whom CA125 may be helpful as a marker for pre-clinical recurrence. Although the significance of CA 125 in childhood germ cell tumours is not yet fully understood, the measurement of serum levels may sometimes be useful in monitoring the disease process.

Hepatic Tumour Markers

Alpha-Fetoprotein and Human Chorionic Gonadotrophin

Over half of hepatic tumours in children are malignant, and of these over 90 % are hepatoblastomas or hepatocellular carcinoma; both secrete AFP which is useful for diagnosis and following the patient's clinical course [20]. Hepatoblastomas arise from hepatic blastema and may also contain epithelial and mesenchymal elements. Ninety per cent of hepatoblastomas are diagnosed within the first 3 years of life, and the AFP concentration is elevated, often to massive levels, for the patients age in more than 95–98 % of cases [3, 9]. Although the AFP concentration is relatively higher in hepatoblastomas with embryonal histology than in tumours with fetal histology, there is no prognostic significance. Liver tumours such as hepatoblastoma may also secrete hCG in the serum in 2–3 % of cases which may result in virilization or isosexual precocious puberty [21]. It should be emphasized that the serum β-hcg level does not necessarily correspond to the clinical course in some patients [22] (Fig. 6.2).

Hepatocellular carcinoma is more common in later childhood and is less frequently associated with cirrhosis in this age group compared to adults but retains its association with hepatitis B infection. AFP is elevated in up to 50–80 % of hepatocellular carcinomas [5]. In adults, 77 % of patients with hepatocellular carcinoma have serum AFP levels of >20 ng/ml and the levels exceeded 200 ng/ml in 80 % of

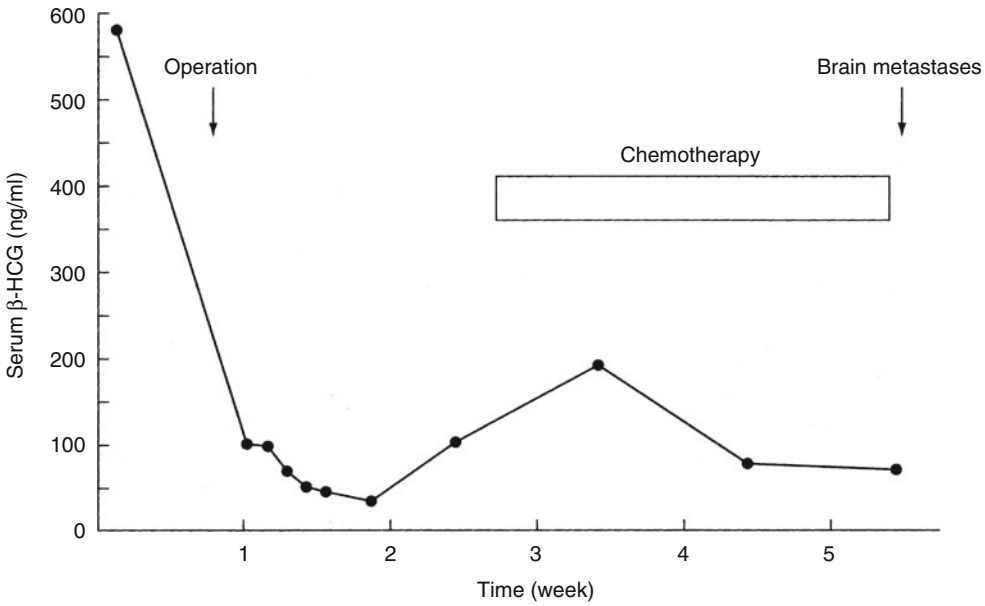

Fig. 6.2 Serum B-hCG as a tumour marker may be used for diagnosis as well as disease monitoring in a patient with Hepatoblastoma

patients with HbsAG-positive hepatocellular carcinoma, whereas AFP levels were within normal range (<20 ng/ml) in more than 99 % of patients with acute and chronic hepatitis B, cirrhosis and other malignant tumours [20].

Rarely elevated AFP levels have been observed in other tumours of the gastrointestinal tract in adults (such as pancreatic tumours). Although there is a low false-positive rate, mild elevations in AFP may be observed in some non-malignant conditions including biliary atresia, neonatal or viral hepatitis, liver cirrhosis, hereditary tyrosinaemia (type 1), systemic lupus, or pregnancy. Some investigators have tried to differentiate AFP derived from hepatic malignancy from that derived from yolk sac tumours and benign hepatic disease. In brief, AFP derived from hepatobastoma or hepatocellular carcinoma includes a subfraction which binds to lens culinaris hemagglutinin (LCH), but AFP from a benign hepatic disease does not react with LCH. The presence of a greater fraction (>25 %) of AFP which is non-reactive to concanavalin A helps differentiate AFP derived from a yolk sac tumour from that of hepatic origin [17].

Serum AFP levels decline exponentially after complete tumor resection and remain within normal limits (<10 ng/ml) unless recurrence occurs. Failure of high AFP levels to return to normal after surgery indicates incomplete resection of the tumour or the presence of metastases. AFP may be secreted from the regenerating liver after surgical resection, but this does not interfere with its expected decline. The increase in AFP levels in patients with apparent clinical remission may occur when there is liver dysfunction due to chemotherapy or viral infection. Alternatively, chemotherapy may result in the release of AFP from tumour cells undergoing necrosis. In that case the AFP subfraction profile obtained by lectin-affinity immunoelectrophoresis (particularly AFP L-3 isoform) may allow differentiation of the source of AFP [16]. Although caution is necessary, the measurement of AFP is practically useful in monitoring the disease course as well as in making a diagnosis (Fig. 6.3).

Other Markers for Hepatic Tumours

The serum unsaturated vitamin B12-binding protein (transcobalamin I) is significantly elevated in fibrolamellar variant of hepatocellular carcinoma and rises with disease progression. Fibrolamellar carcinoma occurs in the non-cirrhotic livers of older children and young adults [4]. Because the serum AFP level is not increased in the majority of these patients, the serial measurement of serum transcobalamin is considered important in this tumour and has been shown to rise with recurrent disease before clinical or radiological concern [23]. Neurotensin, a polypeptide hormone found in the CNS and gastrointestinal tract, has also been shown to be elevated specifically in patients with AFP-negative fibrolamellar hepatocellular carcinoma [24].

In other primary hepatic tumors (such as rhabdomyosarcomas or fibrosarcomas) or secondary involvement by metastatic or haemopoietic malignancy the serum AFP levels are not elevated (although the non-specific serum tumour marker LDH may be raised). In hepatoblastoma it has been suggested that interleukin-6 is produced in stromal cells in response to tumour-released cytokines and that this may be responsible for the thrombocytosis which is sometimes observed. Hypercholesterolaemia is also occasionally seen. Due to poor sensitivity and specificity, however, neither has been established as a useful tumour marker in hepatoblastoma.

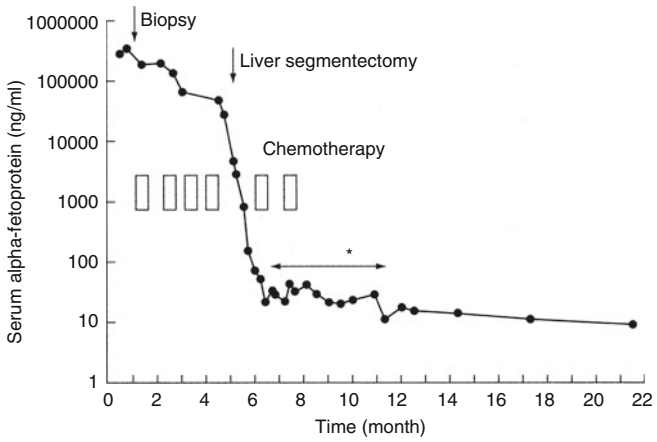

Fig. 6.3 Serum alpha-fetoprotein (AFP) levels in a patient with hepatoblastoma. The AFP levels declinedexponentially after tumor resection but remained slightly higher than the normal limits, around 30–50 ng/ml (*), for several months. AFP secretion from the regenerating liver or chemotherapy induced liver dysfunction was a possible reason for the higher levels

Tumour Markers for Neuroblastoma and Related Tumours

Neuroblastoma is the most common solid abdominal tumour of childhood comprising approximately 10 % of all childhood cancers [4, 5]. It is one of the 'small round blue cell' tumours of childhood and demonstrates diverse clinical and biological traits with tumour markers being used to define disease activity and monitor the response to therapy. These markers include catecholamines and their metabolites, lactate dehydrogenase (LDH), ferritin and neuron-specific enolase (NSE). Of these the catecholamines are confirmatory indices, while serum NSE is useful in monitoring the disease activity and both LDH and ferritin are prognostic markers.

Catecholamines and Metabolites

Neuroblastomas originate from sympathetic neuroblast cells, which are derived from the embryonal neural crest. These neuroblasts normally mature and differentiate into cells of the sympathetic ganglia and adrenal medulla. Differentiation ranges from benign ganglioneuromas to undifferentiated neuroblastomas, with spontaneous regression being between 10 and 100 fold greater than that for any other human cancer [25]. Neoplastic transformation is characterised by defective storage of dopamine for further metabolism to norepinephrine. Unlike normal neural crest cells, neuroblasts lack the catecholamine storage vesicles, and on their release into the circulation these catecholamines are rapidly degraded into vanillylmandelic acid (VMA) and homovanillic acid (HVA). Neuroblastoma cells also lack the enzyme phenylethanolamine N-methyltransferase (PNMT), which converts norepinephrine (NE) into epinephrine (E). As a consequence, the major urinary metabolites excreted are HVA, with some VMA. It has been noted that the additional combination of methylated catecholamines like urinary normetadrenaline (also known as normetanephrine [NMN]) with either VMA or HVA significantly enhanced the diagnostic power of testing, and inclusion of 3-methoxytyramine [3MT] (a metabolic intermediate of dopamine catabolism) in the tests profile could increase diagnostic sensitivity up to 100 % [26]. The biosynthesis and catabolism of circulating catecholamines is depicted in Fig. 6.4; it can be seen that NE and E are primarily metabolized into VMA while Dopamine is metabolized into HVA. More undifferentiated tumours tend to excrete higher levels of HVA whilst more mature tumours excrete more VMA. A high VMA/HVA ratio therefore has been shown to confer a more favourable prognosis [27]. Therefore the analysis of metabolites is clinically more useful as a tumour marker than the catecholamines themselves [28]. In a review of urinary excretion of these analytes using high-performance liquid chromatographic (HPLC) methods in 35 children with advanced neuroblastoma, HVA was elevated in 34 patients, and dopamine and VMA elevated in 29 patients [29]. Urinary catecholamine metabolites are elevated in 90–95 % of patients with neuroblastoma using HPLC assays. Of all the metabolites, VMA and HVA are the ones that are most commonly used and have a sensitivity which exceeds 90 % in combination, though their individual sensitivities are below 80 % each. Other metabolites with good sensitivity and specificity are NMN and dopamine. Recent studies have suggested reporting a combination of NMN with HVA or VMA with up to 100 % sensitivity and specificity [28]. Dopamine is less sensitive and specific in infants but its importance increases with the age of the child. Serum VMA and HVA have also been studied in patients with neuroblastoma but the levels are less consistently elevated than the urinary levels.

False-positive elevations of catecholamine metabolites without additional evidence of malignancy are rare. Traditionally 24-h urine collections have been used to take account of the diurnal variation of catecholamine metabolite secretion. Untimed random collections of urine are easier to obtain in children and with measurements expressed as milligrams per gram of creatinine they take into account the urine production rate and have been shown to be at least as good as previously published data [26]. Occasionally, elevated levels may be observed in children with Duchenne muscular dystrophy, perhaps reflecting reduced muscle mass and creatinine excretion. Because certain foods (such as fruits and nuts) contain significant concentrations of catecholamines some clinicians advise dietary restrictions whilst assessing urinary biogenic amine excretion [30]. Similarly,

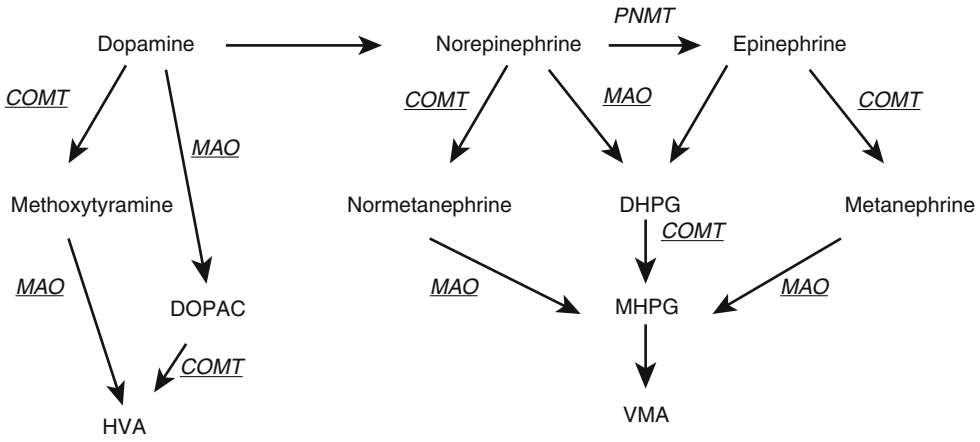

Fig. 6.4 Metabolic pathways of the catecholamines in normal sympathetic nervous tissue and the adrenal gland. *TH* Tyrosine hydroxylase, *DDC* DOPA decarboxylase, *DBH* dopamine-β-hydroxylase, *PNMT* phenylethanolamine-N-methyltransferase, *DOPA* 3;4 – dihydroxyphenylalanine, *VMA* vanillylmandelic acid, *HVA* homovanillic acid, *VLA* vanillactic acid

certain medications may artificially increase or decrease catecholamine metabolite excretion; for instance, false-positive results may occur in children on paracetamol, theophylline, L-dopa (as treatment for paediatric movement disorders), chlorpromazine or sympathomimetics [31].

Assays of catecholamines and their metabolites have been found to be less useful for detecting recurrence during follow-up of patients who have been treated for neuroblastomas previously. In cases with diagnosed recurrence, the levels of these metabolites was found to be raised in only 55 % of the patients; this contrasts with more than 90 % sensitivity at the time of presentation [32]. Thus relapse or progression is less reliably detected or excluded by monitoring tumour markers alone.

Phaeochromocytoma and Paraganglioma

Phaeochromocytomas arise from the adrenal medulla whilst paragangliomas have an extra-adrenal (commonly paravertebral) origin. Both tumours are derived from neural crest catecholamine-secreting cells. Although approximately 12 % are malignant this is poorly determined by histological examination of tumour and is usually determined with reference to clinical behaviour [33]. Over half the children present with paroxysmal headaches, palpitations, sweating or sustained hypertension. Diagnosis relies on elevated urinary catecholamines and their metabolites followed by localization of the tumour. Although the VMA may be elevated, the HVA and dopamine results tend to be within normal limits, displaying a different pattern from that associated with childhood neuroblastoma [26]. In view of their enhanced sensitivity, recent recommendations for the diagnosis of chromaffin tumours in childhood advocate the use of urinary metadrenalines [34]. It may be that the urine tests of particular value in detecting the presence of phaeochromocytoma are the free metadrenalines (particularly free normetadrenaline [fNMA]) [35]. This reflects the findings reported in phaeochromocytoma occurring in adults in whom urinary excretion of the free metadrenalines (fNMA & fMA) exhibited superior test sensitivity to that of either urinary VMA, urinary catecholamines or plasma catecholamines [26]. Metadrenalines (NMA & MA) are metabolites of noradrenaline and adrenaline with the majority (>90 %) being excreted in the urine as sulphate conjugates (probably following conjugation in the gastro-intestinal tract). Contrary to this physiological state, chromaffin tumours tend to produce 'free' (unconjugated) noradrenaline or adrenaline as there is no apparatus for sulphate conjugation and hence their metabolites are excreted in the methylated unconjugated form (fNMA & fMA). In view of these 'free' metadrenalines being tumour products the sensitivity of the test is amplified if only the 'free' fraction is measured.

Surgical resection remains the treatment of choice for phaeochromocytoma and paraganglioma and MIBG therapy may be beneficial for patients with features suggestive of incomplete resection or malignancy [36]. Childhood tumours are more likely to be extra-adrenal and have predisposing genetic mutations compared to the adult population. Genetic tests demonstrate one of four identifiable mutations in about 70–94 % of 'early onset' cases of phaeochromocytoma – von Hippel-Lindau syndrome, succinate dehydrogenase, multiple endocrine neoplasia (MEN), and neurofibromatosis (NF1) [37, 38]. Children with phaeochromocytoma should be entered into a surveillance screening programme for early detection of related tumours and in order to avoid neurological sequelae of hypertension and possibly malignant transformation of metachronous or recurrent tumours. Regular urine tests will be better tolerated by individuals undergoing a long-term surveillance programme than regular cross-sectional (or functional) imaging or blood tests and make compliance with follow-up more likely.

Carcinoid Tumour

Carcinoid tumours arise from enterochromaffin cells which also originate in the neural crest. These rare tumours may be benign or malignant, with benign tumours being found most frequently in the appendix. They produce excessive

5-hydroxytryptamine (serotonin) and histamine which may result in 'carcinoid syndrome' which is characterized by flushing, tachycardia, frequent watery stools and wheeze. Serotonin is metabolized to 5-hydroxyindolacetic acid (5-HIAA) which is excreted in the urine and may be measured in a 24-h urine sample for diagnosis. Urinary serotonin and 5-HIAA may be useful in monitoring disease progress in certain patients [4].

Other Tumour Markers for Neuroblastoma

Several tumour-derived molecules or tumour-associated metabolic or immunological products from host tissue have been reported. Although they are the focus for study by many investigators, in comparison to the tumour markers discussed previously, they have limited clinical application at present in paediatric oncology.

Neuron-Specific Enolase (NSE) is a specific isoenzyme of the glycolytic enzyme enolase, and is localised within neurons of the central and peripheral nervous tissue. Enolase in mammalian brain is composed of two immunologically distinct subunits, α and γ, and both αγ and γγ dimers of enolase are specific for the nervous system [39]. NSE is also present in a wide variety of peripheral and central neuroendocrine cells derived from the neural crest (termed amine precursor uptake and decarboxylation [APUD] cells). The diversity of mature tissues expressing NSE has been the major factor limiting its use in diagnosing malignancies from specific tissues. Serum levels of NSE are elevated in patients with neuroblastoma and those with small cell lung cancer [40]. Elevated serum NSE has also been demonstrated in patients with other childhood tumours including Wilm's tumour, lymphomas, leukemias, hepatoblastoma, PNET and dysgerminoma [41]. It is therefore clear that the serum level of NSE has poor specificity although is a good indicator of the disease course in children with neuroblastoma. Attempts have been made to enhance the specificity of the NSE for the diagnosis of neuroblastoma with the calculation of the ratio of NSE to non-neuronal enolase [42].

The normal range for serum NSE is up to about 14.6 ng/ml. The main clinical application is currently as a prognostic factor in patients with a confirmed diagnosis of neuroblastoma. Zeltzer et al. demonstrated median serum NSE values in patients with stages I, II, III, IV and IV-S disease were 13, 23, 40, 214 and 40 ng/ml, respectively [43]. Of note, the infants with stage IV-S disease had lower NSE levels reflecting a good prognosis despite their extensive tumour burden. Serum levels higher than 100 ng/ml were thus associated with advanced stage disease and a poor outcome.

Lactate dehydrogenase (LDH) is an enzyme that catalyses the reversible conversion of pyruvate to lactate, and is widely distributed in human tissues. Total serum LDH activity decreases with age and hence this must be taken in account when comparing values to the normal range. An elevated serum LDH concentration is observed in 70–80 % of children with malignant tumours, such as leukemias, lymphomas, Wilms' tumour, hepatoblastoma and neuroblastoma and is useful in differentiating malignant tumours from benign lesions [44]. Attempts have been made to enhance specificity of human LDH with the study five isoenzymes. Each isoenzyme is a tetramer of two subunits, H and M. An increase in LDH2 and LDH3 is the most frequently encountered malignant pattern and is observed in neuroblastoma [45]. An increase in LDH1 is reported in germ cell tumours including yolk sac tumour, dysgerminoma and seminoma [46]. In neuroblastoma, serum LDH is increased in patients with advanced disease, and serial measurement of LDH is a useful monitor of tumour activity. There is a correlation between the absolute LDH level and the patient's prognosis, which has been demonstrated in previous studies [47]. Although LDH lacks tumour specificity, it retains clinical utility as a prognostic factor and marker of tumour activity.

Ferritin is an iron storage protein composed of a total of 24 subunits of two different sizes. Different combinations of these two subunits yield a variety of isoferritins. In neuroblastoma, elevated serum ferritin has been found to closely correlate with the presence of active disease with the level normalizing following remission. The ferritin level at diagnosis is a prognostic indicator, with high serum ferritin a feature of advanced disease and poor outcome [48]. Serum ferritin concentrations are also elevated in several malignant and non-malignant conditions including leukemia, Hodgkin's lymphoma, hepatocellular carcinoma and inflammation or infection [49].

Children with neuroblastic tumours which secrete vasoactive intestinal polypeptide (VIP) often present with severe diarrhoea, hypokalemia, dehydration and malnutrition. In such patients removal of the tumour results in normalization of plasma VIP and resolution of diarrhoea [50]. Immunohistochemical staining has demonstrated that VIP is localised exclusively within normal sympathetic ganglia and differentiating cells of ganglioneuroblastomas and ganglioneuromas, but not found in undifferentiated neuroblastoma. Children who present with tumours that secrete VIP have an improved prognosis. Scheiben et al. reported that 6 of 22 patients (27 %) with neuroblastic tumours had a high plasma concentration of VIP ranging from 28 to 95 pmol/l (normal limit, 19.0 pmol/l) and that only one (whose plasma level of VIP was 95 pmol/l) had diarrhoea [51].

Gangliosides are sialic acid-containing glycosphingolipids occurring primarily on the membrane of the cell. A monoclonal antibody (MAB 126) produced against cultured human neuroblastoma cells (LAN-1) was found to react specifically to a disialoganglioside (Gd2) antigen expressed on

cell lines derived from melanoma and neuroblastoma. Increased levels of Gd2 antigen were demonstrated in sera of patients with neuroblastoma and in primary neuroblastoma tissues. Gd2 expression may be inversely related to the degree of differentiation of the tumour because Gd2 was seldom detected in ganglioneuroblastoma and ganglioneuroma. However the usefulness of ganglioside as a tumour marker has not been fully evaluated [52].

Chromogranin A is an acidic protein co-stored and co-released with catecholamines from storage vesicles. Hsiao et al. measured serum chromogranin A at diagnosis in patients with neuroblastoma. Serum chromogranin A (normal value, ≤ 52 ng/ml) was a useful marker with a sensitivity of 91 % and specificity of 100 %, and correlated with the disease stage. The survival rate for patients with low serum chromogranin A levels (less than 190 ng/ml) was 69 % but it was only 30 % for those with higher levels. This suggests that the serum chromogranin A level at diagnosis may be a useful predictor of survival [53].

Creatinine kinase catalyses the transfer of a high energy phosphate bond from adenosine triphosphate to adenosine diphosphate and has three isozymes. Ishigoro et al. measured the CK-BB isozyme level in patients with neuroblastoma and observed that 60 % of patients had CK-BB levels higher than 11 ng/ml. There was a correlation between serum CK-BB levels and patients prognosis, and especially those whose serum level was greater than 15 ng/ml had a poor prognosis [54].

Neuropeptide Y (NPY) is a 33 aminoacid peptide found in the adrenal medulla, sympathetic nervous system and central nervous system. Tumour cells which are immunoreactive for NPY have been demonstrated in pheochromocytomas and ganglioneuroblastomas, and NPY concentrations in these tumours were higher than in other endocrine tumours. Rascher et al. reported that plasma NPY levels were elevated in more than 90 % of patients with neuroblastoma and the serial estimation was a sensitive marker of relapse [55]. These tumour markers have not received the same wide clinical acceptance as catecholamine metabolites.

Genetic and Biological Markers for Neuroblastoma

A large number of molecular or genetic markers are also known to be associated with neuroblastoma prognosis although most are determined by analysis of tumour biopsy tissue itself rather than assayed in tissue fluids (and are therefore not specifically 'tumour markers'). These include N-myc amplification, gain of chromosome17q, deletion of 1p, DNA-ploidy and index, multidrug resistance associated protein (MRP), CD44 expression and TRKA expression. These biological markers are covered in more detail in the neuroblastoma and tumour genetics chapters.

Screening for Neuroblastoma with Urinary VMA and HVA

In 1973, Sawada et al. [56] first developed mass screening in Kyoto City assaying VMA. In 1985 the Japanese welfare ministry began a national screening programme for neuroblastoma with urinary VMA and HVA [57]. When a baby reached 6 months of age, urine was collected by a filter paper and sent to the local laboratory, where urine samples were assayed for the levels of VMA, HVA and creatinine by HPLC. If VMA and/or HVA levels are higher than the normal range, the child was assessed in a secondary hospital and if a neuroblastoma was detected it was referred to a regional oncological service.

Numerous studies have looked at the biology of screening-detected neuroblastomas and have revealed that most tumours are biologically favourable. Hachitanda et al. examined biological factors in a series of 100 neuroblastomas detected by screening [58]. According to the study, 93 % had favourable histology and 7 % had unfavourable histology showing stroma-poor, undifferentiated histology with a high mitosis-karyorrhexis index. It is generally agreed that 10–20 % of neuroblastomas detected by screening have unfavourable biological factors, such as unfavourable histology, DNA diploidy or tetraploidy and low H-ras p21 expression, but N-myc amplified (>10 copies) tumours are extremely rare. Despite the unfavourable factors tumour progression is hardly seen and the clinical outcome of these patients tends to be favourable [59].

In contrast, infants with false-negative screening who later present with neuroblastoma, usually children older than 1 year of age have advanced stage tumours. Half of them are N-myc amplified tumour and the results of treatment are generally dismal. The pattern of catecholamine metabolism is more often dopaminergic and more HVA than VMA is secreted. Because of these biological studies it appears that the screening is ineffective in detecting unfavourable tumours [59]. It is however, still unknown whether a low risk tumour develops into a high risk tumour if left undetected until it presents clinically.

Treatment of Neuroblastomas Detected on Screening

As the screening-detected tumours are biologically favourable and patients with such tumours survive without recurrence, it is recommended that the treatment should be the minimum even in patients in advanced stages. Aggressive surgery and the administration of high-dose chemotherapy is unnecessary in most cases and should be avoided in asymptomatic patients who have a tumour detected by screening. It has been observed that tumours detected on screening regress spontaneously without treatment [57].

Effects of Neuroblastoma Mass Screening

After implementation of screening programmes both in Japan and in Canada, it appears that neuroblastomas detected by screening as well as those detected clinically before the age of 1 year were predominantly of a favourable histology and carried a good prognosis. Tumours missed by screening and detected clinically after 1 year of age were predominantly of unfavourable histology [59].

Mass-screening programs carried out in Japan, Germany and Canada for early detection of neuroblastomas have not been found to be helpful. The tumours detected in this way were found to be biologically favorable with a high tendency for spontaneous regression. Thus though the program had led to an increase in the number of cases diagnosed it had not led to a decrease in the mortality attributed to neuroblastomas [60]. The consensus from the results of these programs is that there are two different subsets of neuroblastoma, and the more favorable type presents earlier and is the one that is detected by screening. The poorer prognosis group is not detected by screening; hence the mortality attributable to neuroblastoma has not decreased [4, 59]. In recent years a group from Japan have suggested that the effectiveness may be enhanced by screening children at 18 months of age [61].

Another issue related to screening is the possibility of unnecessary treatment of biologically favorable tumours destined for regression. In this regard, Yamamoto et al. have defined criteria for observation of tumours detected on routine screening – small masses on radiography, no invasion of spinal cord or vascular structures, relatively moderate catecholamine excretion and parental consent [62].

Tumour Markers for Wilms Tumour

Wilms' tumour is the most common renal tumour in paediatrics. Multidisciplinary treatment of Wilms' tumour has led to a high success rate, with over 90 % of patients achieving long-term survival [6]. However, late effects of treatment and management of relapse remain significant clinical problems. If accurate prognostic methods were available, effective therapies could be tailored to optimise care. Molecular prognostic markers for Wilms' tumour are seldom used in clinical practice although previous studies have linked allele loss on 1p or 16q, genomic gain of 1q, and overexpression from 1q with an increased risk of relapse [63].

Although several tumour markers for Wilms' have been investigated none have translated into routine clinical practice.

The plasma renin and prorenin concentrations in patients with nephroblastoma have been found to be raised compared with a control group of patients [64, 65].

Urinary hyaluronic acid in patients with nephroblastoma have been found to be elevated preoperatively in more than 70 % of cases and declined following resection [66].

Tumor Markers for Other Tumors

Serum carcinoembryonic antigen (CEA) is an oncofetal glycoprotein normally expressed by mucosal cells and was initially described in fetal intestine and liver. It is elevated in 70 % of adult patients with colorectal adenocarcinoma. Elevated serum CEA values have been reported in children with colorectal cancer as well as children with a variety of malignant and non-neoplastic conditions including Wilm's tumour, hepatoblastoma, germ cell tumour and hepatitis. Unfortunately it has not proven to be sensitive nor specific in the paediatric population [67].

Elevated serum soluble interleukin-2 receptor levels have been noted in several lymphoproliferative disorders including Hodgkin's and non-Hodgkin's lymphoma and T-cell leukaemia although this marker has not been extensively studied [4]. Elevated levels have been correlated with advanced disease and unfavourable prognosis.

Neopterin is a metabolite derived from macrophages and has been shown to be elevated in adult patients with non-Hodgkin's lymphoma in whom higher levels conferred an unfavourable prognosis. Raised levels seem to signify activation of the host immune system rather than representing a product of malignant cells. As expected, it has also been noted to be elevated in patients with viral infections and other malignancies which currently limits its clinical application.

Carbohydrate 19.9 (CA 19.9) is a carbohydrate cell surface antigen usually associated with colorectal, gastric, pancreatic and biliary tract cancers. It has also been detected in the serum of patients with inflammatory bowel disease, cirrhosis, cholangitis and pancreatitis which has hampered its clinical utility in paediatric oncology [67].

Serum Alkaline phosphatase (ALP) is derived from the cell membrane of osteoblasts and hence it was thought that this may be of value as a marker of osteosarcoma. The interpretation of ALP in children should be with caution in view of the variability with age and the prevalence of transient hyperphosphatasemia [68, 69]. Unfortunately elevated levels are also frequently observed in patients with healing fractures or liver disease and hence it has limited clinical application.

Although endocrine tumours are rare in childhood, and most are non-functioning, certain cancers are associated with elevated hormone levels (see Table 6.1). These may be secreted from benign or malignant tumours within an endocrine gland or may represent ectopic hormone production. Frequently it is the end-organ manifestations of inappropriate hormone secre-

Table 6.1 Examples of hormones used as tumour markers in paediatrics

Hormone tumour marker	Tumour type	Syndrome
PTH (parathyroid hormone)	Parathyroid hyperplasia/adenoma/carcinoma (rarely ectopic production from renal carcinoma/hepatoma)	MEN I & IIa
Insulin	Insulinoma/Carcinoid	Hypoglycaemia
Gastrin	Gastrinoma	Zollinger-Ellison syndrome
Glucagon	Glucagonoma/Carcinoid	Hyperglycaemia
VIP (vasoactive intestinal peptide)	VIPoma	Watery diarrhoea, hypokalaemia
T3/T4 (thyroxine)	Thyroid adenoma/carcinoma	Hyperthyroidism
Thyrocalcitonin	Medullary thyroid carcinoma (C-cell)	MEN IIa & IIb
Renin	Wilms tumour	Hypertension
Androgens	Leydig cell tumour (testis) Sertoli-Leydig cell (ovary) (rarely adrenal adenoma/carcinoma)	Isosexual precocity (male) Virilism (female)
Oestrogens	Granulosa cell tumour (ovary) Sertoli cell tumour (testis) (rarely adrenal adenoma/carcinoma)	Isosexual precocity (female) Feminization (male)
Cortisol/Aldosterone	Adrenal hyperplasia/adenoma/carcinoma/rests	Cushing's/Conn's syndrome
Prolactin/ACTH/Growth Hormone/TSH/LH/FSH	Secretory adenomas (rarely ectopic production from neuroblastoma, phaeochromocytoma, hepatoblastoma)	Galactorrhoea Cushing's Gigantism Hyperthyroidism Precocious puberty

tion which is the presenting complaint in some tumours. These hormones may aid in localizing the site of tumour or serial estimations offer a way of monitoring response to treatment and of detecting pre-clinical recurrence [4].

Tumour Markers – The Future

Scientists continue to study tumour markers and their possible role in the early detection and diagnosis of cancer [2, 3]. A new era of molecular and genetic prognostic factors has arrived and it may be that such methods will improve sensitivity and specificity and replace some less precise serum markers. Scientists are also evaluating patterns of gene expression for their ability to predict a patient's prognosis or response to therapy. This is hoped to allow application of a multi-disciplinary management plan tailored to the precise genetic and molecular requirements of the tumour and 'host' to optimise patient outcome.

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Tumor Imaging

7

Melanie Hiorns and Owen Arthurs

Malignant disease in children (including haematological disease, such as leukemia and lymphoma) accounts for approximately 1 % of all registered malignancies. Whilst each year approximately 12,500 children and adolescents are diagnosed with cancer in the United States, nearly 80 % of children diagnosed with cancer become long-term survivors, and the majority of them are considered cured. Nevertheless, in the USA cancer remains the leading cause of death from disease among children.

Leukemias, tumors of the brain and nervous system, the lymphatic system, kidneys, bones and muscles are the most common childhood cancers. The solid tumors account for approximately half of all these tumors, and it is this group which will be considered in this chapter. Imaging has several important roles in the management of childhood cancer: diagnosis; staging of disease, including assessing the local extent, possible resectability of the tumor and identifying metastases; providing image guidance for biopsy; monitoring treatment and complications: and surveillance imaging for the purpose of detecting recurrent disease.

There have been continued advances in imaging technology over the last few years, and evaluation of these new techniques with an understanding of their use, advantages and limitations is necessary.

General Principles

Most children dislike hospitals, and busy radiology departments with large pieces of equipment may be especially frightening. It is therefore important for staff to take extra care with the child and family, recognizing their particular needs. Taking time, allowing parents to stay with their child, allowing children to wear their own clothes when possible, toys, videos and careful explanations will all help to enlist the child's co-operation and result in good quality images. Most pediatric radiology departments have access to specially trained play therapists who can talk a child through a proposed test as a play exercise before the real test takes place. They may also have access to distraction aids such a small portable DVD players in which the child can become absorbed and distracted. Sedative drugs and general anesthesia may be necessary for the infant and young child when longer periods of immobility are necessary. Local anesthetic cream on at least two sites of possible venepuncture will reduce the child's fear and distress at the time of injection of contrast medium or an isotope. Warming the jelly for ultrasound studies is useful. It is likely that the child will have little understanding of what is taking place, but the parents and family will be anxious and distressed. The referring clinician and radiology staff must endeavour to explain carefully what is going to happen in order to reduce the parents' and child's fears and anxiety. Involving the parents with the examination, such as helping with gently restraining the child, can make both parent and child feel less alienated and more in control.

Ionizing radiation is an important consideration in of imaging, even in the child who has cancer. With increasing cure rates and the potential risk of a second malignancy (either iatrogenic or de novo), radiation exposure should be minimized and other techniques, such as ultrasound and magnetic resonance imaging (MRI) should be used whenever possible, particularly in children who are going to receive multiple imaging episodes as part of their follow-up over many years.

In most countries children with cancer are treated in specialist centres according to recognized protocols. In Europe and North America protocols for the diagnostic and follow-up imaging of most tumors exist within organizations such as the International Society of Pediatric Oncology (SIOP), the United Kingdom Children's Cancer Study Group (UKCCSG), and the Children's Oncology Group (COG; formed in 2000 by the

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amalgamation of four previous groups: the Children's Cancer Group, the Pediatric Oncology Group, the National Wilms' Tumor Study Group and the Intergroup Rhabdomyosarcoma Study Group), and should be followed in order to provide consistent results which enable treatment, staging and prognosis to be evaluated. Many clinicians consider it optimal that children are entered into a relevant clinical trial, both for their own benefit and for future patients and the various organizations listed above have the most up to date information regarding particular trials for any particular tumor type.

Plain Radiography

It is likely that the initial radiograph diagnosis of the child with a tumor will take place at the local hospital with a plain radiograph and ultrasound. Computed tomography (CT) may variably be performed at the local hospital but most cross-sectional imaging such as CT and magnetic resonance imaging (MRI), and nuclear medicine, should in most instances take place at specialist centres where appropriate expertise and facilities are available.

A plain radiograph may be the first radiological investigation and if interpreted carefully may be helpful in making the diagnosis.

A plain abdominal radiograph in a child with a large abdominal mass may demonstrate calcification, erosion of the pedicles of the spine, and displacement of the paravertebral line, all of which are features of neuroblastoma. The lung bases may be included on the film and demonstrate pulmonary metastases seen in Wilms' tumor, hepatoblastoma or rhabdomyosarcoma. Plain chest radiographs are essential in the detection of pulmonary metastases in the follow-up of Wilms' tumor, hepatoblastoma and all sarcomas (Fig. 7.1). Associated features such as pathological fractures or bone infiltration in disseminated neuroblastoma and rarely osteoporosis in hepatoblastoma may be seen. Plain radiographs still have an important role in the diagnosis of primary bone tumors and may provide the diagnosis more easily than other modalities. Characteristic radiographic appearances are described in both benign and malignant bone tumors such as osteochondromas, osteoid osteomas, osteogenic sarcomas and Ewing's tumor.

Ultrasound

Ultrasound examination lends itself particularly well to the investigation of children with cancer. The technique does not use ionizing radiation, very rarely requires sedation and provides excellent images in most children. It is highly operator-dependent, which can be particularly relevant when scanning uncooperative infants. It should be the first investigation in the evaluation of all abdominal masses.

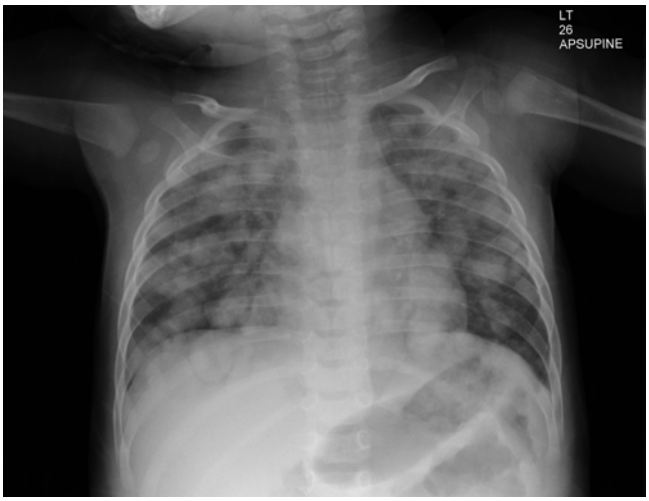


Fig. 7.1 Chest radiograph demonstrating multiple pulmonary nodules of different sizes in an 18 month old child with metastatic PNET (peripheral neuroectodermal tumor). See also Fig. 7.13

Ultrasound will distinguish between congenital cystic lesions of the kidney, gut or mesentery, and solid tumors. Pelvic tumors are seen clearly with ultrasound, particularly intravesical tumors. Extravesical tumors can be distinguished from ovarian cysts, and hematocolpos, and are usually clearly demonstrated although pelvic wall involvement and extension into the sacrum is likely to be underestimated. Ultrasound has a role in chest pathology, which is limited to determining whether the opaque hemithorax is primarily solid or fluid. Musculoskeletal ultrasound is used to determine whether a soft tissue mass is discrete, cystic or vascular.

Computerized Tomography

Computerized tomography produces excellent images of the head, neck, thorax, abdomen and pelvis. It is limited in the peripheral musculoskeletal system where MR is the imaging of choice for the soft tissues, although CT still gives exquisite bony detail which can be used for 3D reconstructions for surgical planning especially in orthopedics and reconstruction surgery. Although CT is well established it utilizes ionizing radiation and therefore modern imaging of most tumors in the pediatric population should preferentially be by MRI where this is feasible. Furthermore, MRI has advanced so rapidly in recent years that it is now considered the superior modality (outside the lungs) irrespective of the radiation issues surrounding CT. However CT is generally more readily available, cheaper and easier for the patient than MRI and new scanners are now so fast that patients who previously required a general anesthetic or sedation for CT may now be able to have the scan unsedated. It provides excellent images

of lung parenchyma, mediastinum, head and neck, abdomen and pelvis. Intravenous injection of intravenous contrast medium is essential to delineate mediastinal masses, hepatic tumors, renal masses and head and neck tumors and can allow CT angiography giving vessel detail to challenge conventional angiography. Spiral CT rotates the X-ray beam and the diametrically opposing detectors around the patient. Modern scanners have multiple detectors (typically 64 or 128 or more) with the capability of very thin slice thicknesses (as low as 0.5 mm, then reconstructed to 0.3 mm) allowing very rapid scanning of large body areas which can be completed in 5–10 s which, with extensive image post processing and manipulation, can finally produce reconstructed images in any plane and in 3D.

Magnetic Resonance Imaging

MRI provides exquisite anatomical detail of many pediatric tumors. It has advantages over CT and ultrasound scanning including greater inherent soft tissue contrast, multiplanar imaging, non-invasive angiography, and the lack of exposure to ionizing radiation. In the past, there have been some practical disadvantages of MRI which included the reduced availability of MR scanners, the noise and length of time of sequences, as well as the relatively frightening appearances of scanners which resulted in a need for sedation or general anesthesia in many children. However continuing development of faster sequences and improving scanner design is transforming the feasibility of MRI in pediatric age group and MRI should be considered the imaging modality of choice for tumors of the musculoskeletal system, central nervous system (including the spine), head and neck, abdomen, pelvis and mediastinum. Modern sequences and the use contrast agents can also give detailed information about the vascularity and enhancement characteristics of tumors, as well as non-malignant lesions such as vascular malformations. Magnetic resonance angiography (MRA) is particularly useful in evaluating tumor proximity or involvement of major vessels. Whole body MR may also compete with PET imaging to stage abdominal tumors. Specific advantages of MR include determination of resectability of hepatic tumors using combined MR and MRA, staging of neuroblastoma in the bone marrow, lymph nodes, liver and spinal canal; response of bilateral Wilms' tumor and nephroblastomatosis: detection of pelvic tumor with sagittal sectioning, and peritoneal tumors with contrast enhancement [18]. In particular, where repeated imaging is likely to be required in the diagnosis, surveillance, follow-up and complications over long periods of time, MRI should be considered in the first instance.

Fast spin-echo short inversion time inversion-recovery (STIR) whole-body magnetic resonance (MR) imaging is an evolving technique that allows imaging of the entire body in a reasonable time. Its wide availability and lack of radiation exposure makes this method appealing for the evaluation of children. Bone marrow lesions, including marrow infiltration from lymphoma, metastases, and tumor-related edema, appear with high signal intensity, and are more easily detected, on STIR images than with scintigraphy. Focal parenchymal lesions can be distinguished by their slightly different signal intensity, but pathologic lymph nodes cannot at present differentiated from normal nodes on the basis of signal intensity. The STIR technique is highly sensitive for detection of pathologic lesions, but it is not specific for malignancy; thus, the method cannot be used to differentiate benign conditions from malignant neoplastic lesions with certainty at present [27]. It is however already useful for identifying lesions that otherwise would have been overlooked and these can then be imaged directly with other modalities if necessary. MRI is now beginning to give more useful functional information about the cellularity of some types of tumor using ADC (diffusion) maps, further enhancing its diagnostic advantage [21].

Any patient having an MRI scan must be free of all ferromagnetic materials and should not have a pacemaker as these can be deprogrammed by the radiofrequency field. Many devices such as cochlear implants are now MR compatible within the manufacturer's guidelines. Some non-ferromagnetic materials such as titanium may be present in the patient and whilst these are not a contraindication, they will still produce significant artefacts on the images. Similarly, all equipment such as anesthetic and resuscitation facilities must be MR compatible.

There are several advantages and disadvantages that much be appreciated in comparing one cross-sectional modality against another, emphasised in Table 7.1 [16]. It is well recognised that MRI has superior soft tissue contrast resolution (the ability to distinguish between two tissue types), which is often the most crucial diagnostic aspect of tumor imaging, but there are several points which make CT the pragmatic choice in many centres, including availability, expertise, cost and speed of imaging.

Nuclear Isotopes

Nuclear scintigraphy is useful in diagnosis, staging and assessment of tumor response and evaluation of treatment in various pediatric tumors. The technological aspects of radioisotope scanning are particularly important when imaging children.

Careful calculation of dosage of radiopharmaceuticals in proportion to weight is required. Special immobilization of the patient can be achieved by wrapping the patient securely, with sedation and or general anesthesia. Image magnification

Table 7.1 Comparison of benefits between CT and MRI

CT	MRI
Uses high dose ionizing radiation	No ionizing radiation
Excellent spatial resolution	Excellent contrast resolution
Actual scanning time measured in seconds (typically less than 5 s)	Actual scanning time measured in minutes (typically 45 min in total)
Rarely requires general anaesthetic in children	May require sedation or general anaesthetic, depending on age
Can give absolute values of different tissue types (Hounsfield Units)	Only relative differences between tissue types
Excellent at showing calcification	Poor at showing calcification (signal void)
Poor at showing oedema or pathological changes in specific tissue types	Excellent at showing oedema and pathological changes in specific tissue types
Typically requires intravenous medium to enhance differences between soft tissue types	Natural differences between tissue types demonstrated; may require intravenous contrast medium in addition
Risk of contrast anaphylaxis	Risk of NSF (rare but patients with renal failure at increased risk)
Widely available	Less widely available, especially for children
Cheaper	More expensive
Usually available as an emergency imaging technique	Not routinely available as an emergency technique
No significant contraindications	Contraindicated in patients with any implanted metallic devices or foreign bodies
Less prone to movement artefacts as imaging is very fast	Prone to motion artefacts depending on sequence type

Adapted from Hiorns [16]

and the capability to perform single photon emission computed tomography (SPECT) are essential to performing state of the art pediatric nuclear medicine. Multiple head detector gamma camera systems are available and have the advantages of increased resolution and sensitivity, and decreased time of examination in a child.

Nuclear imaging techniques such as bone scans, meta-iodo-benzyl guanidine (MIBG) scans and (111) In-diethylenetriaminepentaacetic acid-octreotide scans have greatly increased the sensitivity and specificity of both diagnostic and follow-up protocols for pediatric solid tumors. Molecular targets that are specific for certain pediatric tumors are now being developed. Targets include cell membrane receptors targeted by specific ligands (such as octreotide), subcellular organelles targeted by false transmitters (such as MIBG), and cellular proteins targeted by antibodies [37].

Non-specific radiopharmaceuticals such as technetium 99m-labeled methylene diphosphonate (Tc99m-MDP) are routinely used in the detection of bone metastases in all children with neuroblastoma, osteogenic sarcoma, Ewing's sarcoma and bone metastasizing Wilms' tumor. Although MDP scintigraphy will not necessarily distinguish benign from malignant disease, it is still the appropriate and most sensitive method to survey the skeleton for metastatic disease. However in the future it may be that this technique is largely surpassed by whole body MRI sequences specifically designed to detect metastases (STIR sequences) as described above.

Tumor-specific radiopharmaceuticals including meta-iodo-benzyl guanidine (MIBG) and gallium-67 (^{67}GA) are used in the management of children with cancer. Of interest is the fact that Tc 99m-MIBG may be taken up by both bone metastases and primary tumor in the instance of neuroblastoma, although not all neuroblastoma is MIBG-avid (Fig. 7.2) [5]. Others, including thallium-201 (^{201}TI), sestamibi, and 2-[fluorine – 18]-fluoro-2-deoxy-D-glucose (FDG) PET scanning are being investigated extensively (see below) [9].

Positron Emission Tomography (PET)

Positron emission tomography (PET) involves the acquisition of physiologic images based on the detection of radiation from the emission of positrons. Positrons are emitted from a radioactive substance (2-[fluorine – 18]-fluoro-2-deoxy-d-glucose (FDG) administered to the patient. Different uptake intensities on a PET image represent different levels of tissue glucose metabolism. Healthy tissue will accumulate some of the tagged glucose, which will show up on the PET images. However, cancers, which use up more glucose than normal tissue, will accumulate more of the substance and appear brighter than normal tissue on the PET images.

18F-FDG-PET scans are useful both in the detection of cancer and in examining the effects of cancer treatment by characterizing biochemical changes in the cancer. A functional PET study may be combined simultaneously, or sequentially, with an anatomical CT or MRI study to exactly localise areas of abnormal tissue, to plan both biopsy and definitive surgery, as well as identify sites of recurrence.

PET is now playing an important role in many paediatric tumors, particularly lymphoma. There is growing evidence that PET in conjunction with low dose CT is the most sensi-

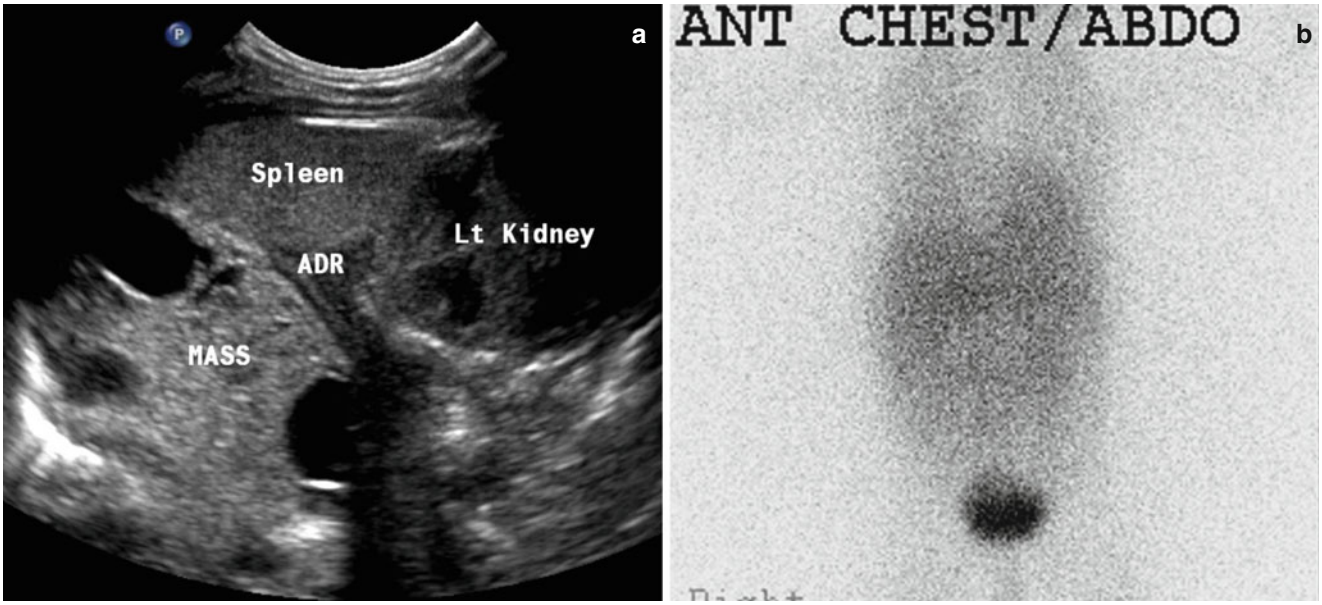


Fig. 7.2 Neuroblastoma in the left suprarenal region. (**a**) Ultrasound shows the relationship of the left kidney, spleen and the normal left adrenal to the left sided suprarenal mass. (**b**) MIBG performed at the same time shows no uptake by the tumor

tive and specific imaging technique currently available for patients with lymphoma, although its impact on clinical outcome in most clinical situations remains to be confirmed. This has led to the commercial availability of combined PET-CT scanners, as well as PET-MRI scanners. These allow co-registration of images by computer in order to give as precise anatomical and functional detail as possible (Fig. 7.3). (18)F-FDG PET is used widely in adult imaging particularly in thyroid, head and neck, lymphoma, lymphoma and breast and colorectal cancer [11], and is now being evaluated for use in primary bone tumors in children.

Neck Masses

Tumor-like masses in the neck are unusual in children and are most commonly benign. Most common are congenital cystic lesions (thyroglossal duct cysts, branchial cysts, dermoid cysts, lymphangiomas, cystic hygromas. Common neoplastic lesions are hemangiomas and lymphomas. The most common malignant tumors in the head and neck region are lymphomas (Fig. 7.4) and rhabdomyosarcomas, but thyroid tumors are also well recognized (Fig. 7.5). Lymph node enlargements, reactive or/and infectious, account also for a significant amount of cervical masses [22]. Imaging initially by ultrasound can provide both anatomical and vascular information. If a tumor is identified MR would be the next imaging modality of choice. As many of these masses contain cystic elements, MR can generally give better tissue differentiation than CT.

Abdominal Masses

Children may present with abdominal enlargement resulting from a large abdominal or pelvic tumor. Nephroblastoma, neuroblastoma, rhabdomyosarcoma, teratoma and hepatoblastoma frequently present with a large abdominal mass (Fig. 7.6). Acute urinary retention may occur in instances of pelvic tumor. Initial imaging with ultrasound is essential and will typically confirm the presence of a solid echogenic mass and exclude both cystic and congenital renal lesions. The organ of origin of the mass, whether it be renal, suprarenal, hepatic or pelvic is often identified, resulting in a provisional diagnosis. Further cross-sectional imaging with MRI or CT is then performed to stage the local extent of disease, plan potential surgery and identify distant metastases. It may be beneficial if this is performed in the centre that will be treating the patient, as protocols for imaging vary and any individual institution may have a preferred way of imaging the child, or may be entering relevant children into clinical trials which demand a certain imaging protocol. The prime objective is to image the child optimally on the first occasion and avoid repeat imaging once a tertiary referral has been made. Imaging is often performed locally in cases where the diagnosis of malignancy is in doubt, such as some cases of inflammatory disease, e.g. renal abscess, hepatic abscess, xanthogranulomatous pyelonephritis or if the child is so compromised clinically by the size or effects of the mass that further imaging must happen immediately. Conventionally, an ultrasound followed by MRI or CT are performed in all units dealing with these cases. Either CT

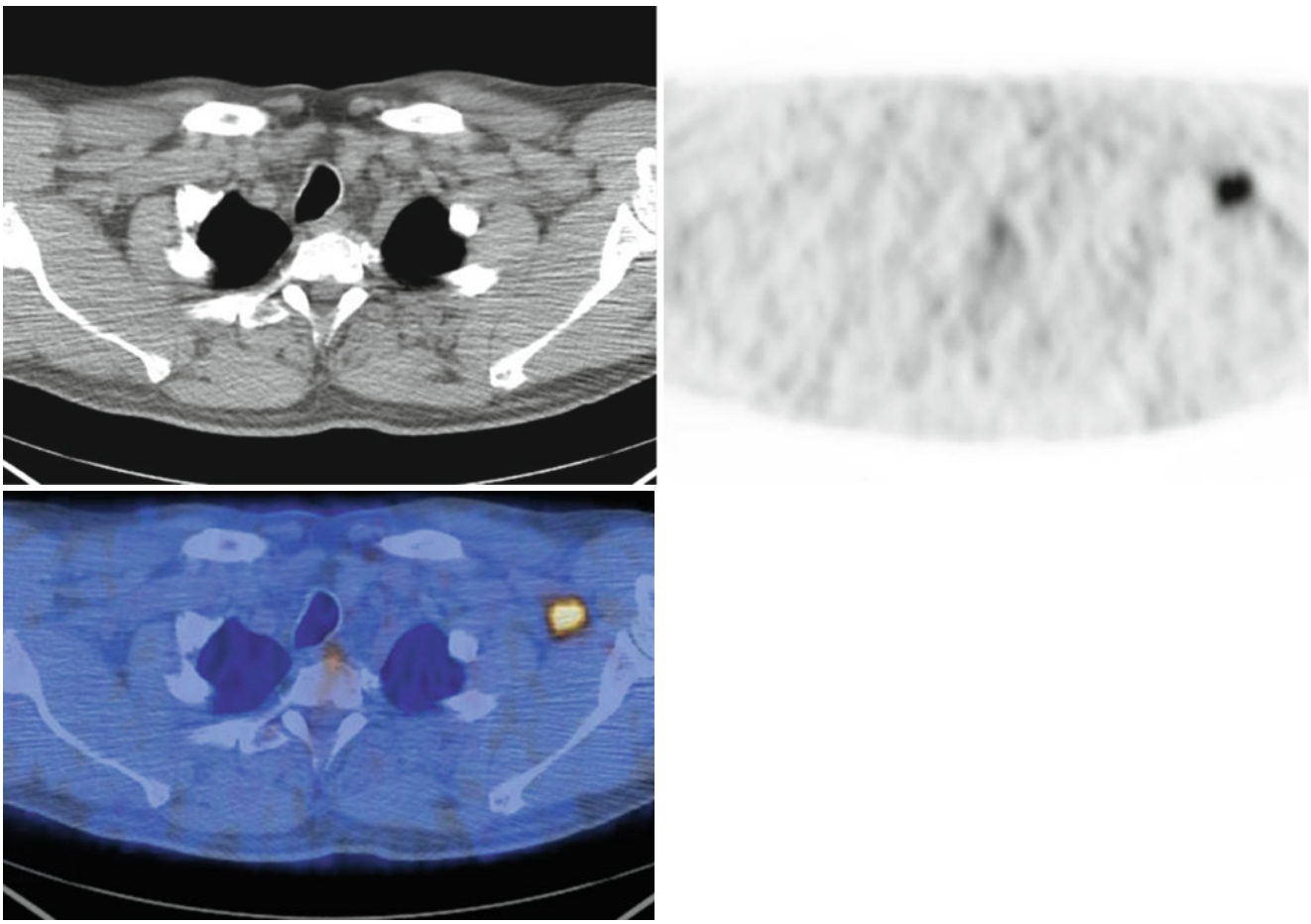


Fig. 7.3 PET scan highlighting a left axillary lymph node that was missed on the conventional CT (*above*) in a patient with lymphoma (Courtesy of Dr Tom Lynch)

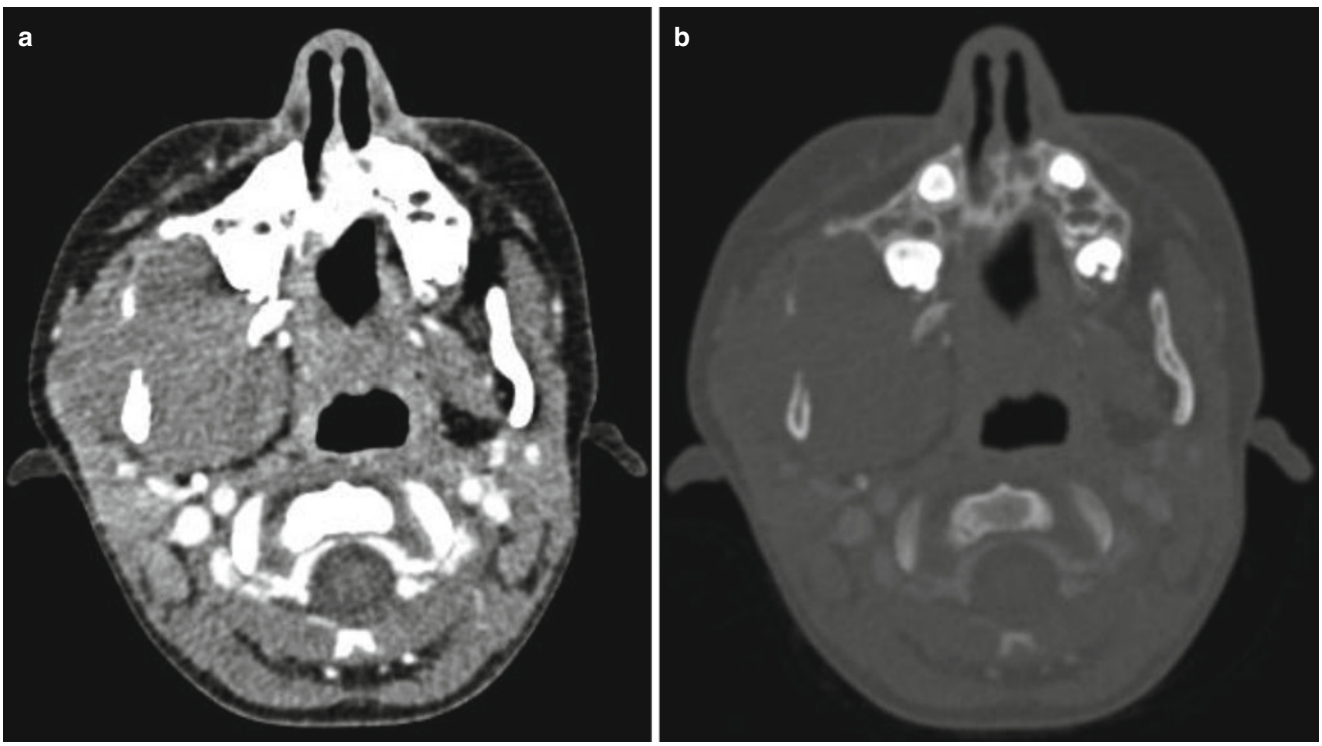


Fig. 7.4 Burkitt's lymphoma. Facial CT showing a large soft tissue mass arising from the ramus of the right mandible (**a**), causing bone destruction, best seen on bone window settings (**b**). The appearances are typical for Burkitt's lymphoma

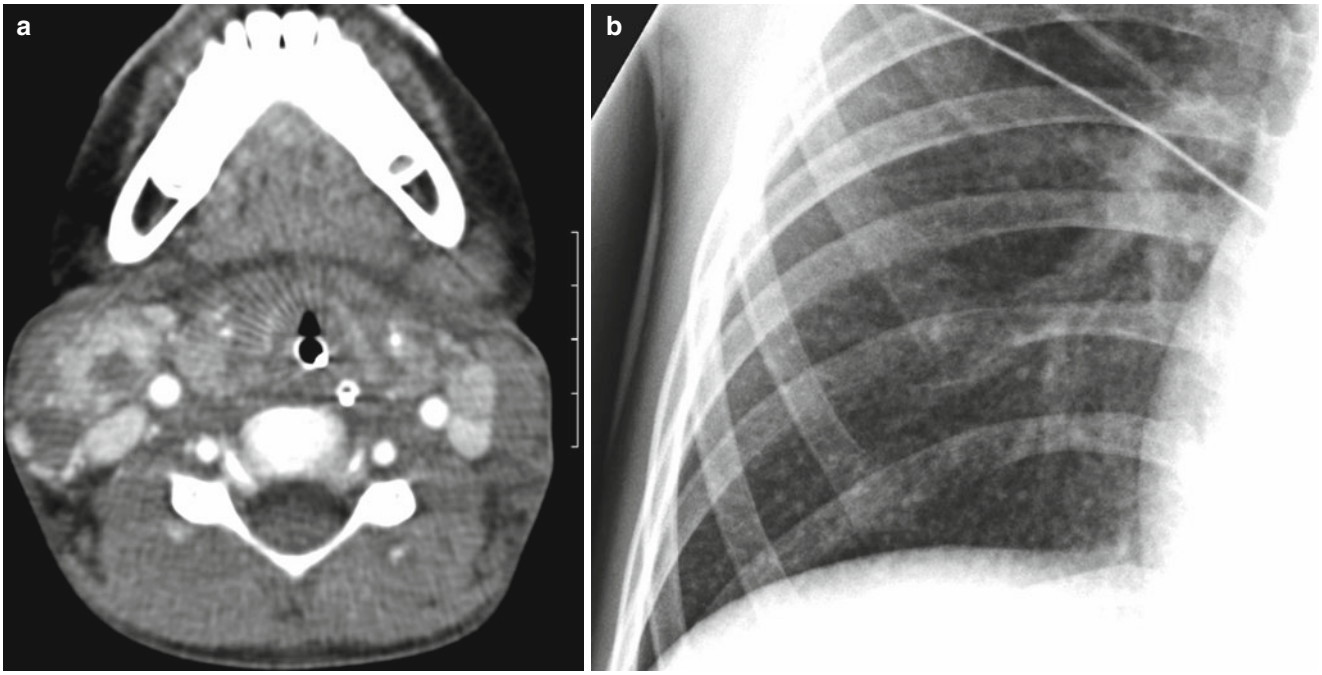


Fig. 7.5 Papillary thyroid carcinoma. (**a**) CT showing swelling is present on both sides of the neck due to lymph node enlargement. (**b**) Chest X-ray with multiple miliary metastases seen in the lungs typical of papillary thyroid cancer. This tumor carries a relatively good prognosis despite the metastases

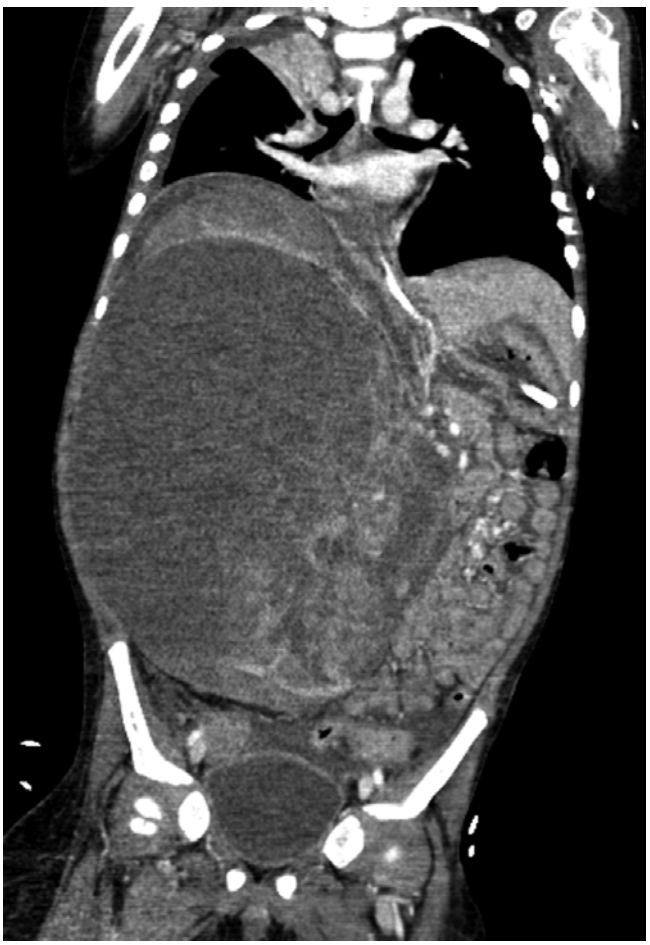


Fig. 7.6 Wilms' tumor. CT scan (coronal reconstruction) showing the typical presentation of very large abdominal mass, which is causing significant 'mass effect' and compressing other abdominal contents

or ultrasound are suitable for image guided core-needle biopsy of the mass, which in most cases (approximately 95 %) yields sufficient tissue for both histological diagnostic, and prognostic and cytogenetic markers [17, 47].

Thoracic Masses

Thoracic tumors of childhood arise either in the mediastinum, or from the chest wall and rarely from the lung parenchyma.

The mediastinum is the site of the normal thymus which is a relatively large organ in childhood occupying the anterior and superior mediastinum extending down onto the diaphragm and up into the neck. It is therefore important to recognize the appearance of the normal thymus to avoid confusion with a tumor. On plain chest radiograph the thymus is a bilateral superior mediastinal mass which on the right side may demonstrate a characteristic sail-like opacity with a well-defined inferior and lateral margin. On the left side a wavy lateral margin is produced by normal compression of the adjacent anterior rib. Rarely, thymic tissue occurs in the posterior mediastinum either as direct extension from the anterior mediastinum or as ectopic tissue. If there is some doubt as to whether a mediastinal mass in an infant is normal thymus, ultrasound is a simple non-invasive technique that will demonstrate the characteristic homogeneous, 'liver-like' echogenicity of this structure. Tumors of the mediastinum do not demonstrate this homogeneous echogenicity (Fig. 7.7).

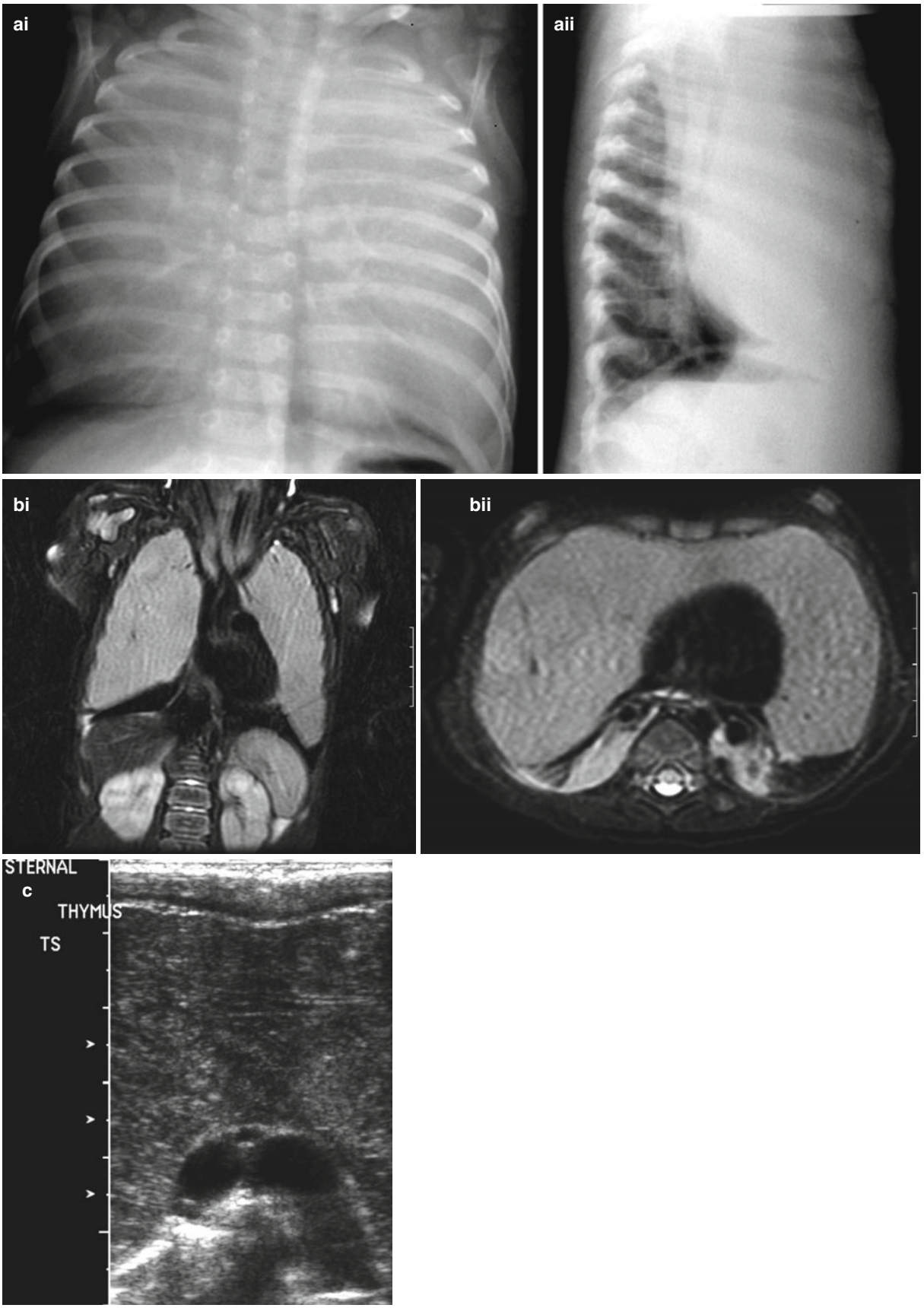


Fig. 7.7 Massive thymus in a neonate. (**a**) AP (i) and lateral (ii) chest radiographs show that the thymus occupies nearly all of the thoracic cavity. (**b**) The thymus is confirmed on MR (i) coronal and (ii) axial which shows the degree of compression of the lungs which are compressed posteriorly. (**c**) However ultrasound confirms that the thymus only contains normal appearing thymic tissue despite it enormous size

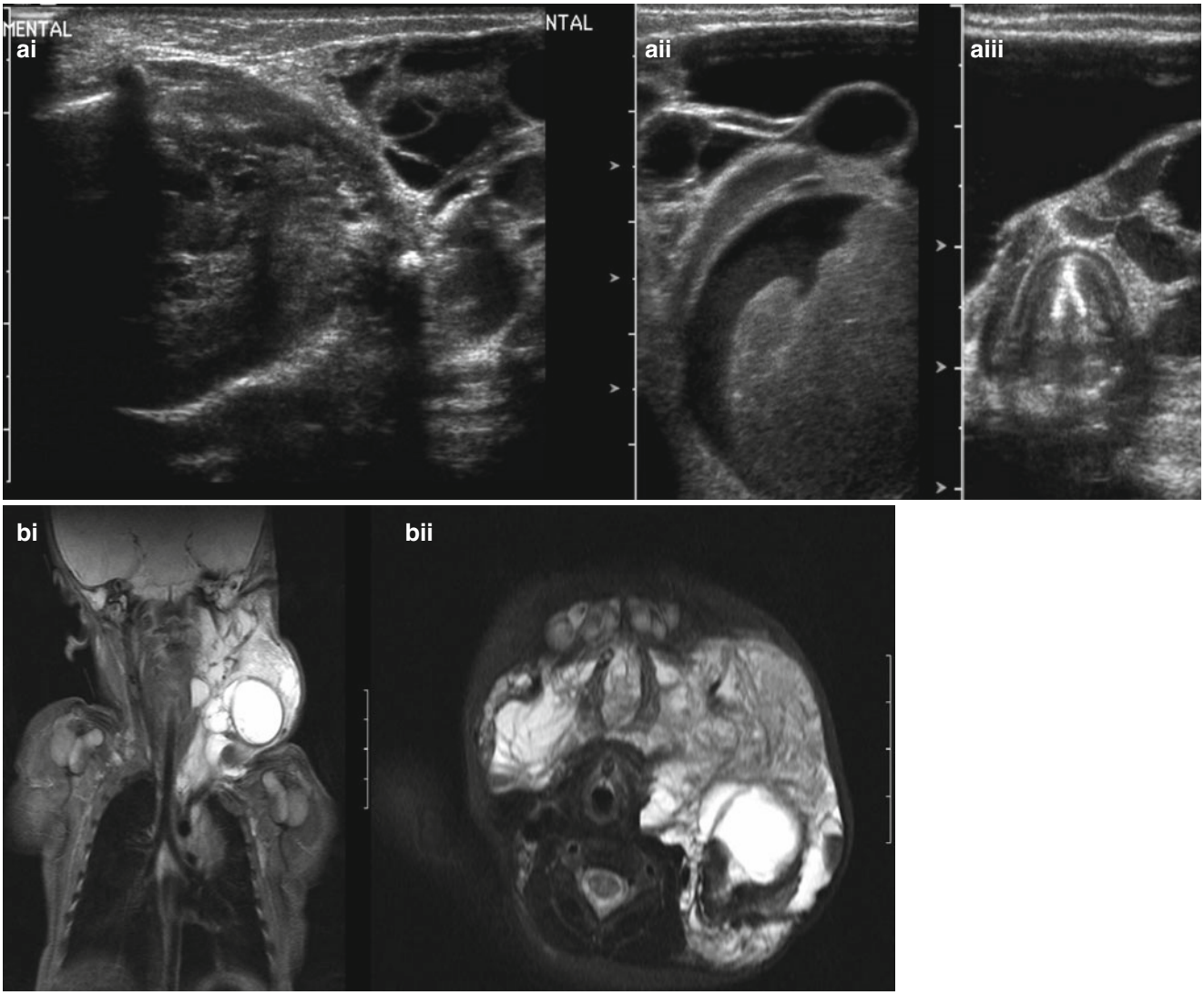


Fig. 7.8 Cystic hygroma in the neck. (**a**) Ultrasound showing a bulky tumor of heterogenous echo texture with (i) solid components and (ii) cystic structures and (iii) extending across the midline (the vocal cords can be seen as an inverted echogenic 'V'). (**b**) MR with STIR sequences in (i) coronal and (ii) axial planes shows excellent delineation of the mass and the variety of tissue components

The normal thymus imaged by CT is characteristically quadrilateral in shape in the neonate and infant and becomes more classically arrow-head in shape in older children. It is homogeneous in attenuation with a smooth edge and does not compress, distort or invade underlying structures such as the trachea and major blood vessels. MRI is also useful in distinguishing the normal thymus from an abnormal mediastinal mass [53].

An important cause of an anterior mediastinal mass in neonates is the cystic hygroma (Fig. 7.8), which usually arises in the neck and extends into the chest. Clinically these are soft and hypoechoic on ultrasound. Imaging of the mediastinum with CT demonstrates a mediastinal mass of low, homogeneous attenuation which often encases and appears to displace and compress underlying large blood vessels and may displace the trachea. On MRI it is of homogeneous signal intensity, low on T1 weighted sequences and high on T2 weighted sequences. Prior to embarking on a diagnosis of malignancy in an infant it is important that these conditions are considered.

Mediastinal masses are classified according to their site of origin into anterior, middle and posterior mediastinal masses. Lymphomas, teratomas and cystic hygromas are found in the anterior mediastinum, congenital duplication cysts and lymphadenopathy in the middle mediastinum and neurogenic tumors, such as ganglioneuroma and neuroblastoma in the posterior mediastinum.

Masses arising from the chest wall include primitive neuroectodermal tumors, (PNET) and often arise from the ribs.

Mediastinal and Chest Wall Tumors

Lymphoma

Lymphoma occurs with an incidence of about nine cases per annum per million children under the age of 15 years accounting for 6 % of all childhood cancers. Hodgkin's lymphoma is slightly more common overall than non-Hodgkin's lymphoma but under the age of 10 years and in very young children non-Hodgkin's lymphoma is much more common. Both Hodgkin's and non-Hodgkin's lymphoma involve the thorax and lymphoma is the most common intra-thoracic neoplasm in the pediatric age group [57] and as such is an important causes of a mediastinal mass. Imaging is important for both diagnosis and management particularly for Hodgkin's lymphoma because therapy and prognosis are very dependent on the location and extent of disease. Diagnostic strategies and treatment approaches for these tumors are largely determined by protocols established by one of the large, multi-institutional cooperative groups and are frequently revised [46, 57].

Clinical presentation may be non-specific or acute with symptoms and signs of tracheal and superior vena cava obstruction from tumor (Fig. 7.9).

A chest radiograph should be performed on all patients and typically demonstrates a mediastinal mass (Fig. 7.10) sometimes with a pleural effusion; a lateral film will confirm the location of the mass in the anterior mediastinum and is useful in the assessment of the airway which is compressed and displaced posteriorly. An ultrasound scan can be performed to confirm the presence of a pleural effusion and may demonstrate pleural deposits but is limited and further defini-

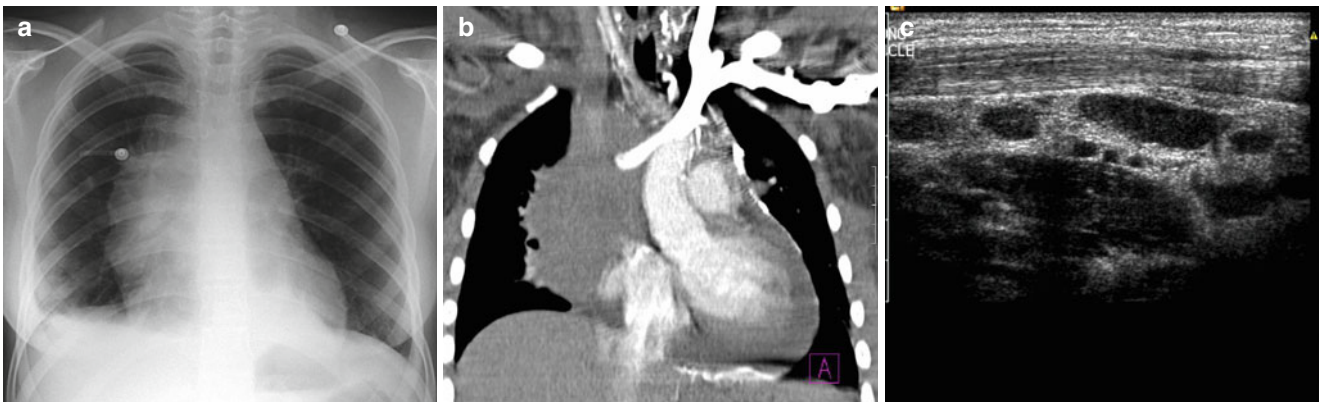


Fig. 7.9 Large B-cell lymphoma of the anterior mediastinum. (**a**) Chest radiograph showing the mass bulging out from the right of the mediastinum and an associated right sided pleural effusion. (**b**) CT (coronal reconstruction) showing the right sided mediastinal mass which is obliterating the superior vena cava just as the left brachiocephalic vein enters, note the collateral drainage in the neck and over the pericardium. (**c**) Ultrasound showing multiple lymph nodes also present in the neck

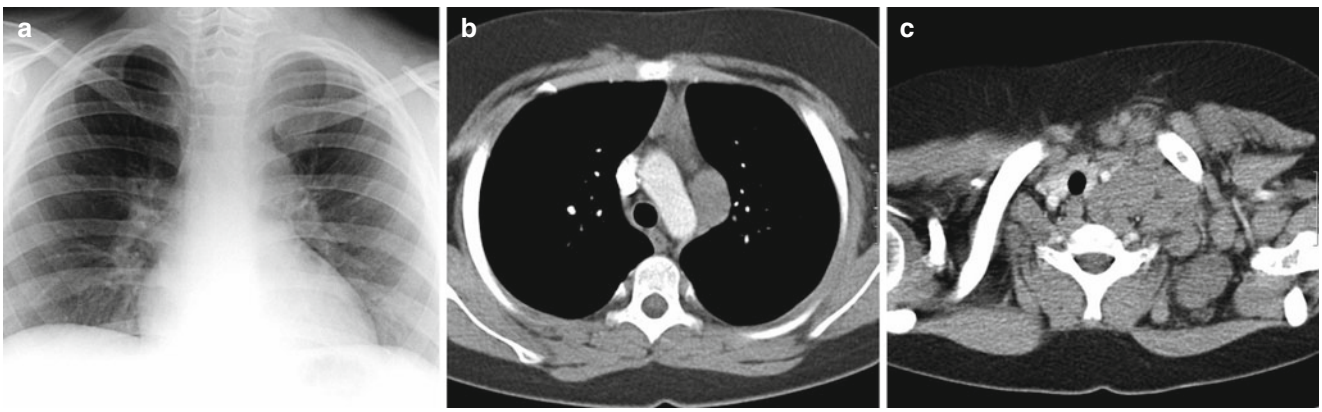


Fig. 7.10 Nodular sclerosing Hodgkin's disease. (**a**) Chest radiograph showing increased soft tissue in the left mediastinum in the region of the aortic knuckle. (**b**) CT confirms tumor lateral to the aortic arch where normally there should be no tissue. (**c**) CT in the neck shows extensive nodal disease, especially on the left side

tive imaging should be carried out with CT or MRI. A large mediastinal mass, with or without hilar lymphadenopathy and/or involvement of the thymus is usually demonstrated. The airway can be further visualized and compression assessed in more detail: this is of particular importance as problems may arise during anesthesia for biopsy and if symptoms are severe a first cycle of chemotherapy may have to be given to shrink the mass before anesthetic and biopsy. Lung involvement also occurs. It is more common in Hodgkin's lymphoma, and is seen as infiltrates, an area of consolidation or nodules. A pericardial effusion may be present and is evidence of pericardial involvement.

In Hodgkin's lymphoma the presence or absence of disease at other sites must be determined; this is less important in non-Hodgkin's lymphoma which is considered to be a disseminated disease [46]. Further imaging with MRI (or CT, if MRI is unavailable) of the abdomen and pelvis is necessary to look for enlarged lymph nodes and involvement of the liver and spleen. Unfortunately CT is poor at detecting splenic involvement and the presence of splenomegaly on CT does not correlate well with the presence of disease. Ultrasound scanning may also underestimate splenic involvement and gas in the bowel can interfere with visualization of lymph nodes in ultrasound. MRI may be the best modality for demonstrating the difference between normal splenic tissue and tumor. At the end of chemotherapy and radiotherapy most patients show no evidence of any residual tumor and surgery is not required.

However, in some cases, particularly Hodgkin's lymphoma a residual mass remains in the mediastinum at the site of the original tumor. This may be due to residual active tumor, or a fibrotic mass or sometimes cysts in the thymus following treatment. While re-excision or biopsy may be required to distinguish between these, it is desirable to avoid this if possible and the yield may be low. Imaging with T2 weighted, and T1 post contrast sequences on MR has been suggested as a means of differentiating active tumor from fibrotic tissue, with tumor showing high signal intensity and fibrosis low signal intensity. However, results are inconclusive and may confuse areas of inflammation with tumor and MR likely to be superseded by PET for this particular indication.

The introduction of functional imaging modalities, such as positron emission tomography (PET) scanning, provide the means to correlate tumor activity with anatomic features generated by CT and modify treatment based on tumor response. For centres with access to this modality, PET imaging now plays an important role in staging, evaluating tumor response, planning radiation treatment fields, and monitoring after completion of therapy for pediatric Hodgkin's lymphoma (Fig. 7.11) [24]. This trend will likely increase in the future as a result of PET's superior sensitivity in correlating sites of tumor activity compared to other available functional imaging modalities. Ongoing prospective studies of PET in pediatric patients will increase understanding about the optimal use of this modality in children with cancer and define the characteristics of FDG-avid non-malignant conditions that may be problematic in the interpretation of tumor activity [20]. The fusion of positron emission tomography (PET) with CT provides the most accurate imaging method for disease characterization and treatment response [25].

Experience with 18F FDG PET-CT is growing, and is particularly sensitive at detecting residual or recurrent disease in known malignancies, such as lymphoma and sarcoma. Caution is still advised as numerous non oncological processes can mimic recurrent or residual tumor including infection/inflammatory conditions [2, 48].

Teratoma

Mediastinal teratomas occur in the anterior mediastinum and are usually very large at presentation (Fig. 7.12). Imaging with a chest radiograph will demonstrate the mass which may contain calcification. On further imaging with CT a large irregular and non-homogeneous mass is seen, often but not necessarily with calcification, and with areas of low attenuation which may be fat or necrosis and cysts. MRI can also be used to image the mass and will show the different tissue types in great detail and will show the extent of the mass. Initial treatment is by surgical excision and histological examination will determine whether the lesion is benign or malignant. If the tumor is malignant a CT scan of the chest is required to search for lung nodules.

Neuroblastoma

Neurogenic tumors, both benign and malignant, occur in the posterior mediastinum. They may be discovered on a chest radiograph as an incidental mass or present with neurological symptoms due to extension of tumor into the spinal canal. Imaging of the primary tumor is with CT or MR although the latter is better at showing the true extent of the mass and its relationship to the ribs, intervertebral foramina and the spinal canal. More extensive discussion of the imaging of neuroblastoma is covered later in this chapter.

Primitive Neuroectodermal Tumor (PNET)

PNETs occur most frequently in the central nervous system but also occur in the bones and soft tissues (Fig. 7.13). Histologically they resemble neuroblastoma and Ewing's tumor. 'Askins' tumors are PNETs arising from the chest wall [1].

Initial imaging with a chest radiograph will show a large mass often associated with a pleural effusion, rib destruction and hilar and mediastinal lymphadenopathy. Further imag-

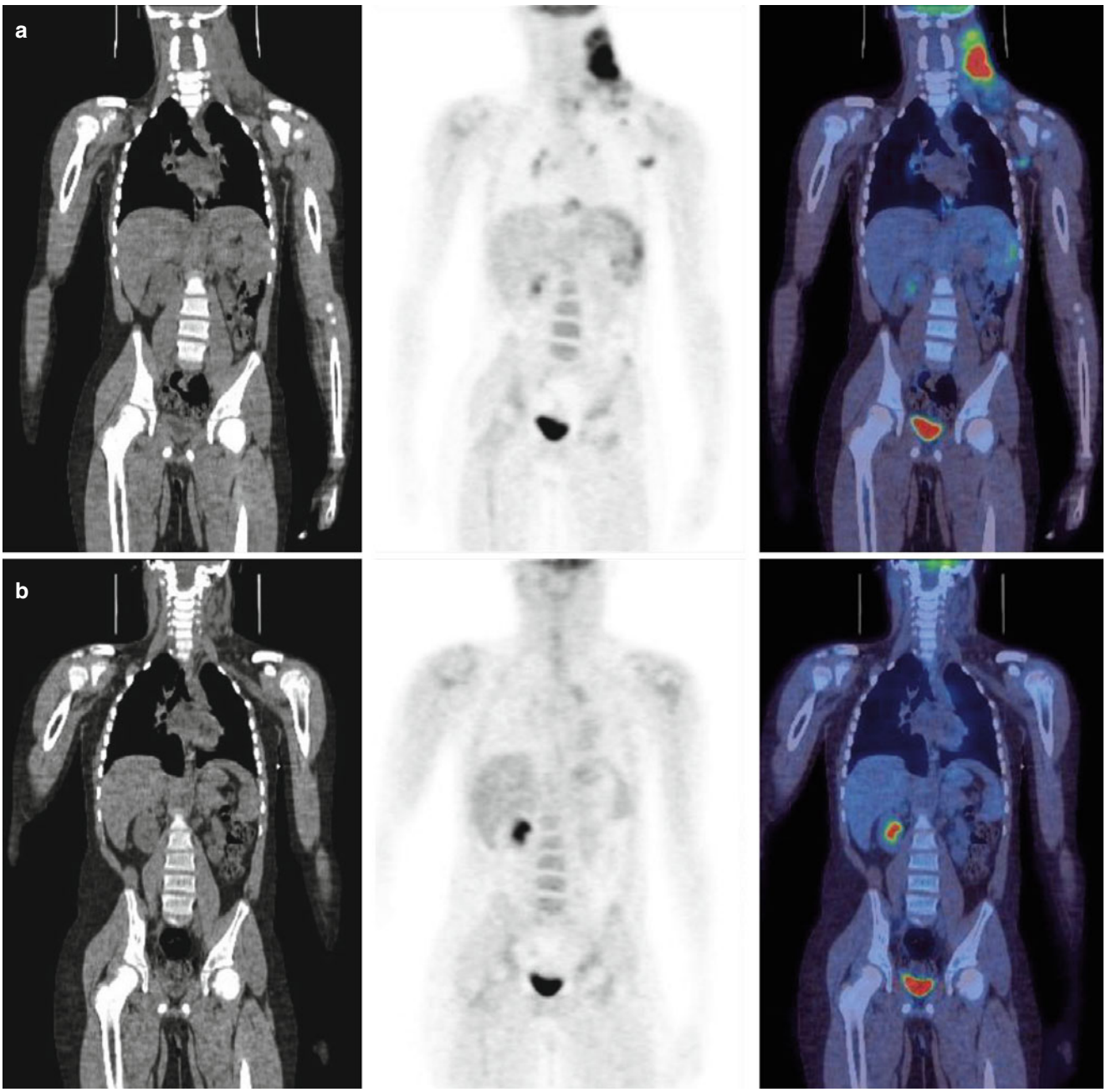


Fig. 7.11 Mediastinal disease in lymphoma. An FDG-PET image is acquired simultaneously with a low-dose CT, which are then fused together. In this example, disease in the neck and mediastinum show a good response to treatment: images acquired before (**a**) and after (**b**) following induction chemotherapy (Images courtesy of Dr Sally Barrington, St Thomas' Hospital, London, UK)

ing with MR or CT is required to demonstrate the true extent of the tumor which may extend into the spinal canal, be closely applied to the heart, major blood vessels, the main bronchi and be unresectable. Excellent images of these structures and their relationship to the tumor are provided by MR in the coronal plane. Metastatic disease occurs in the lungs and more rarely bones; therefore a CT scan of the lungs and an isotope bone scan is necessary.

Osteogenic Sarcoma and Ewing's Tumors

Childhood osteogenic sarcoma and Ewing's sarcoma are by far the most common primary bone tumors, together accounting for over 80 % of lesions.

Imaging studies are extremely important in identifying the primary site of tumors providing the differential diagnosis, staging the tumor and monitoring the response to therapy. As

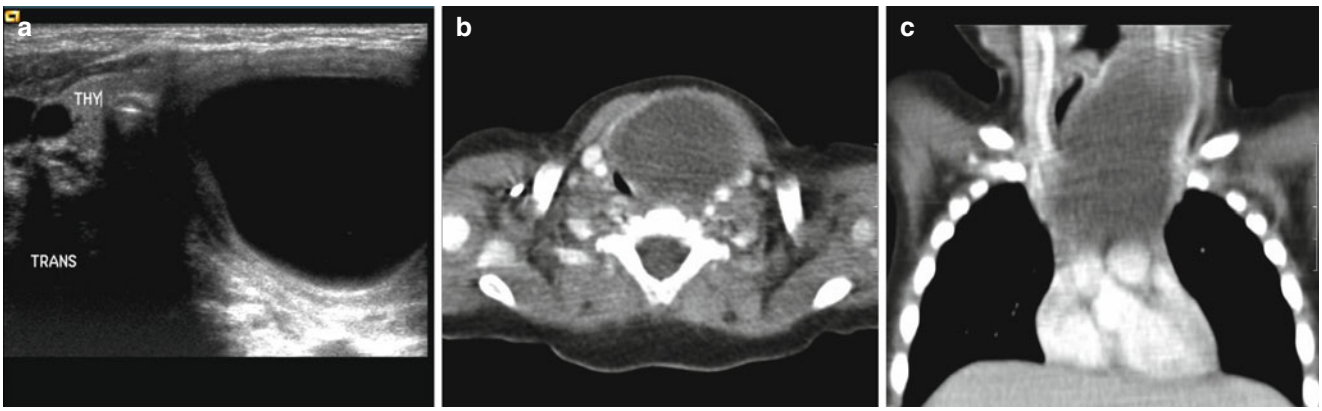


Fig. 7.12 Mature teratoma of the upper anterior mediastinum extending into the neck. (**a**) Ultrasound of the neck showing a predominantly cystic lesion just lateral to the thyroid. (**b**) CT with contrast in the transverse plan showing displacement of the vessels of the neck and the low attenuation mass. (**c**) Coronal reconstruction of the CT shows the mass to be extending up out of the anterior mediastinum and displacing the vessels

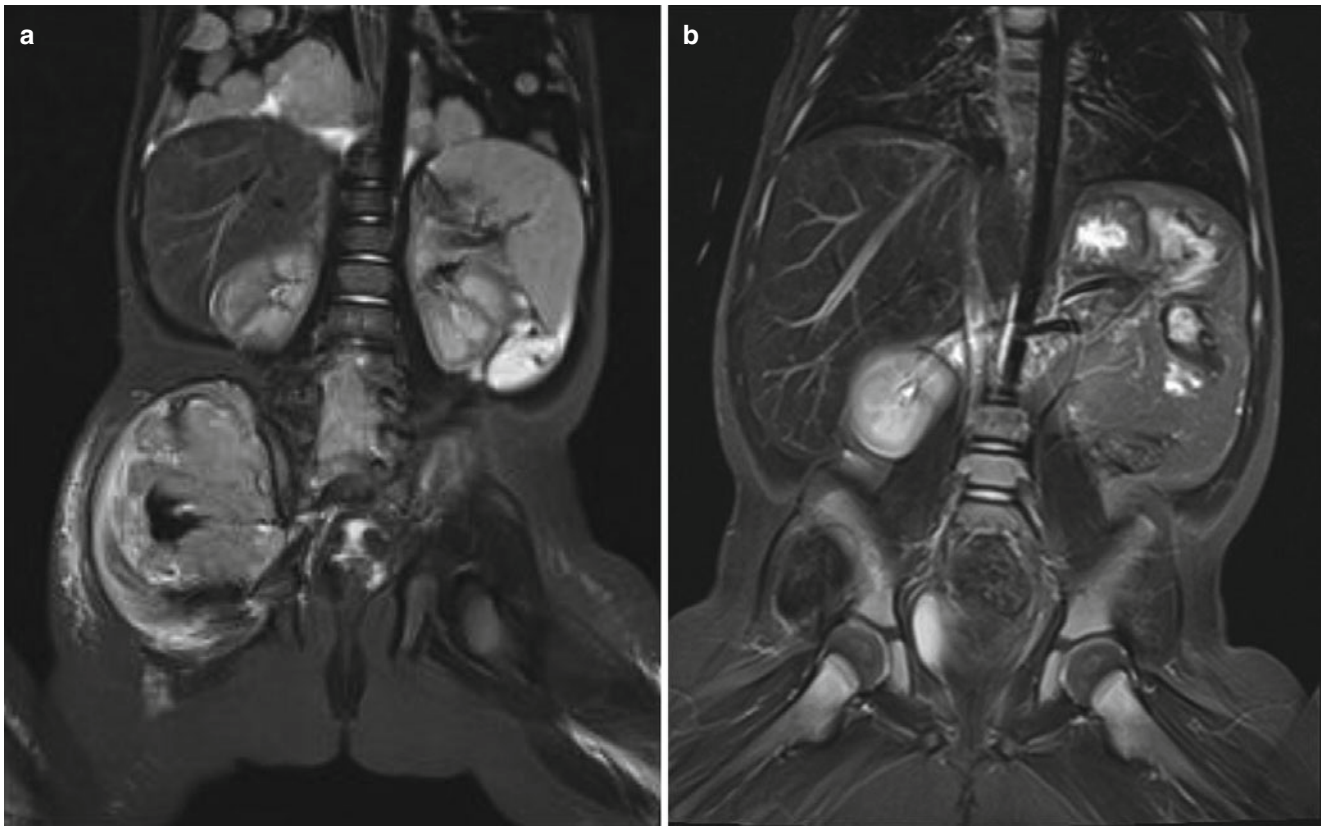


Fig. 7.13 (**a**) Peripheral neuroectodermal tumor (PNET) of the right iliac bone, causing a right buttock mass. Multiple pulmonary metastases are seen, even on the coronal STIR MRI images (the chest radiograph of this patient is given in Fig. 7.1). (**b**) Following treatment, the mass shows a good response and the lung metastases have resolved

the radiological approach to both tumors is essentially similar they will be dealt with together.

Most patients will present with symptoms of local pain, a history of trauma or soft tissue swelling. A plain radiograph of the lesion is extremely important and should be performed in all cases. The characteristic appearances of a malignant tumor are of a poorly defined lesion, bone destruction associated with a periosteal reaction, and a soft tissue mass. Benign bone tumors demonstrate a well defined margin or narrow zone of transition. Imaging may distin-

guish between an osteogenic sarcoma and Ewing's sarcoma because although both will have a periosteal reaction and bone destruction, an osteogenic sarcoma is much more likely to have a metaphyseal location with a significant periosteal reaction and new bone formation and cortical destruction is present in almost all cases. Ewing's sarcoma may occur in both long and flat bones. In the long bones the location is commonly in the diaphysis and classically the appearance is of a symmetrical lesion with permeative bone destruction, a laminated periosteal reaction and a soft tissue mass. In the flat bones such as the scapula and the pelvis the lesion is usually large with extensive bone destruction and a large soft tissue mass. Although cross-sectional imaging is crucial in demonstrating the extent of tumor and staging establishing the diagnosis requires biopsy and histopathological examination.

Treatment is with chemotherapy and surgical resection with limb salvage if possible, or radiotherapy in cases of Ewing's sarcoma usually where resection is not possible. It is therefore very important to accurately delineate the local extent of the tumor and its relationship to the adjacent soft tissues, including normal muscles, blood vessels and nerves. MR is now the gold standard modality for assessing the true intraosseous and soft tissue extent of a lesion and should be performed early in the work-up of all bone tumors and be the main tool during treatment, at the end of chemotherapy prior to any surgical intervention and in long term follow up [26]. Whilst it is true that CT may give a better impression of the bony destruction it generally underestimates the extent of marrow involvement and the main purpose of CT in current imaging strategies is for planning orthopedic surgery and/or reconstruction. Compared with CT scanning, MRI is superior in delineating both the soft tissue and bone marrow extent of the tumor. Specific MRI protocols may differ in various tumor centres with preferences for T1 weighted sequences for marrow disease and T2 weighted sequences or T1 weighted sequences with intravenous contrast for soft tissue extent. In particular there is some debate as to which is the most accurate way of determining the tumor margin and distinguishing it from adjacent edema. During treatment MR appearances can be difficult to interpret because tumor necrosis may cause changes in the tumor signal with tissue shrinkage noted early in the treatment, thus giving the erroneous impression of tumor growth.

The most common sites of metastatic disease are the lungs and skeleton and CT scanning of the lungs and radioisotope scintigraphy with Tc99m-MDP is essential in all patients. In osteosarcoma. Lung metastases may be calcified. Metastases can occur in other sites, the lymph nodes most commonly but also the myocardium, pleura, inferior vena cava, kidneys, liver and brain. If a potential tumor is to be biopsied this should only be after discussion with the surgeon as it is critical that the biopsy be at a site that will subsequently be excised when the definitive surgery in performed to avoid seeding of tumor and subsequent recurrence.

Other rare causes of thoracic masses include inflammatory lesions such as Castleman's syndrome and inflammatory pseudotumors, and other malignant tumors such as, rhabdomyosarcoma and malignant thymoma. The lungs and the mediastinum are also sites of metastatic spread of tumors arising elsewhere.

Initial imaging of any thoracic lesion includes plain chest radiographs, followed by cross-sectional imaging with CT and/or MR. While CT, with intravenous contrast enhancement provides excellent images of the mediastinum and chest wall, MR with the improved inherent soft tissue contrast and multiplanar imaging frequently provides more information about tumor extent and relationship to vital structures [26, 10].

Musculoskeletal Masses

Primary tumors of the musculoskeletal system in childhood include osteogenic sarcoma, Ewing's tumor, and rhabdomyosarcoma and other soft tissue sarcomas [51]. Primary lymphoma of bone occurs but only rarely in children. Benign bone tumors such as osteoid osteoma, osteoblastoma, aneurysmal bone cyst and giant cell tumor are also less common.

Initial presentation is with pain, swelling and limitation of movement. There is frequently a history of previous trauma. Tumors are usually diagnosed on plain radiographs if they arise from the skeleton and further imaging with MR and nuclear scintographic scans which demonstrate both the local tumor extent and associated skip lesions. Primary soft tissue tumors may or may not show underlying bone erosion and MR scanning is necessary to delineate them. As MRI is highly sensitive to both neoplastic and inflammatory changes in the soft tissues it therefore may not differentiate between malignant and benign or inflammatory lesions, such as infection, post-traumatic myositis ossificans, fibromatosis, hemangioma and lymphangiomatosis. Definite diagnosis usually requires an open biopsy although there are a small number of soft tissue tumors with MR imaging appearances characteristic enough to allow a specific diagnosis, obviating the need for biopsy [50]. If a potential tumor is to be biopsied this should only be after discussion with the surgeon as it is critical that the biopsy be at a site that will subsequently be excised when the definitive surgery in performed to avoid seeding of tumor and subsequent recurrence. Central tumors may present with less obvious clinical symptoms such as back pain or painful scoliosis both of which are uncommon in children and may be due to a primary tumor of the vertebral body. Pelvic pain is usually related to Ewing's sarcoma.

Other soft tissue masses in clue all the vascular malformations (arteriovenous malformation, hemangiomas, lymphangiomas (Fig. 7.14), hemangiolymphangiomas and venous malformations) [8]. Proteus syndrome presents with multiple hamartomatous soft tissue masses of varying size (Fig. 7.15). Lipoblastomatosis and other fatty tumors will also present with a mass lesion. All of these masses are best examined by a combination of ultrasound and MR.

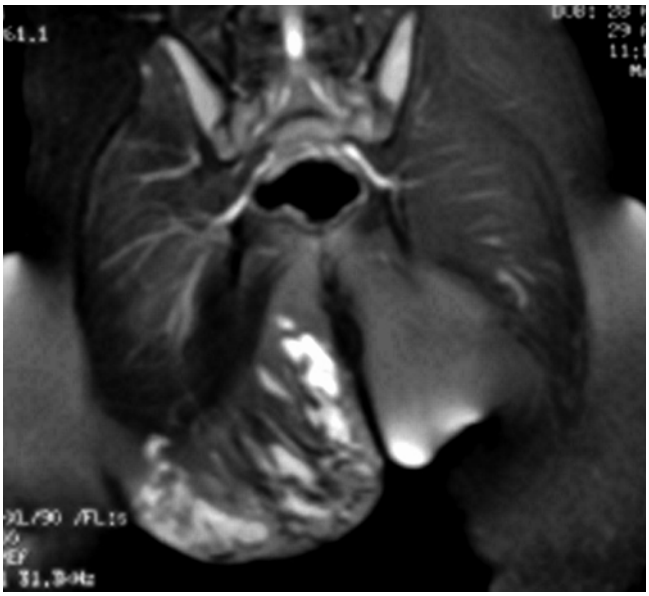


Fig. 7.14 Lymphangioma of the right buttock. MR coronal T2 image showing a heterogenous lesion of high signal in the right buttock

Renal Tumors

Differential Diagnosis of Pediatric Renal Masses

With the identification of a renal mass Wilms' tumor will inevitably be considered but a variety of pediatric renal masses must be differentiated from Wilms' tumor on the basis of their combined clinical and imaging features. Wilms' tumor is distinguished by vascular invasion and displacement of adjacent structures and is bilateral in approximately 10 % of cases. Nephroblastomatosis occurs most often in neonates and is characterized by multiple bilateral subcapsular nodules, often synchronous with a Wilms' tumor. Renal cell carcinoma is unusual in children except in association with von Hippel-Lindau syndrome and typically occurs in the second decade. Mesoblastic nephroma should be primary consideration in a neonate with a solid renal mass. Multilocular cystic nephroma is suggested by a large mass with multiple cysts and little solid tissue. Clear cell sarcoma is distinguished by frequent lung and skeletal metastases, and rhabdoid tumor (Fig. 7.16) is distinguished by its association with brain neoplasms.

Angiomyolipoma frequently contains fat and is associated with tuberous sclerosis. Renal medullary carcinoma occurs in patients with sickle cell trait or hemoglobin SC disease and manifests as an infiltrative mass with metastases. Ossifying renal tumor of infancy is differentiated from mesoblastic nephroma by the presence of ossified elements. Metanephric adenoma lacks specific features but is always well defined.

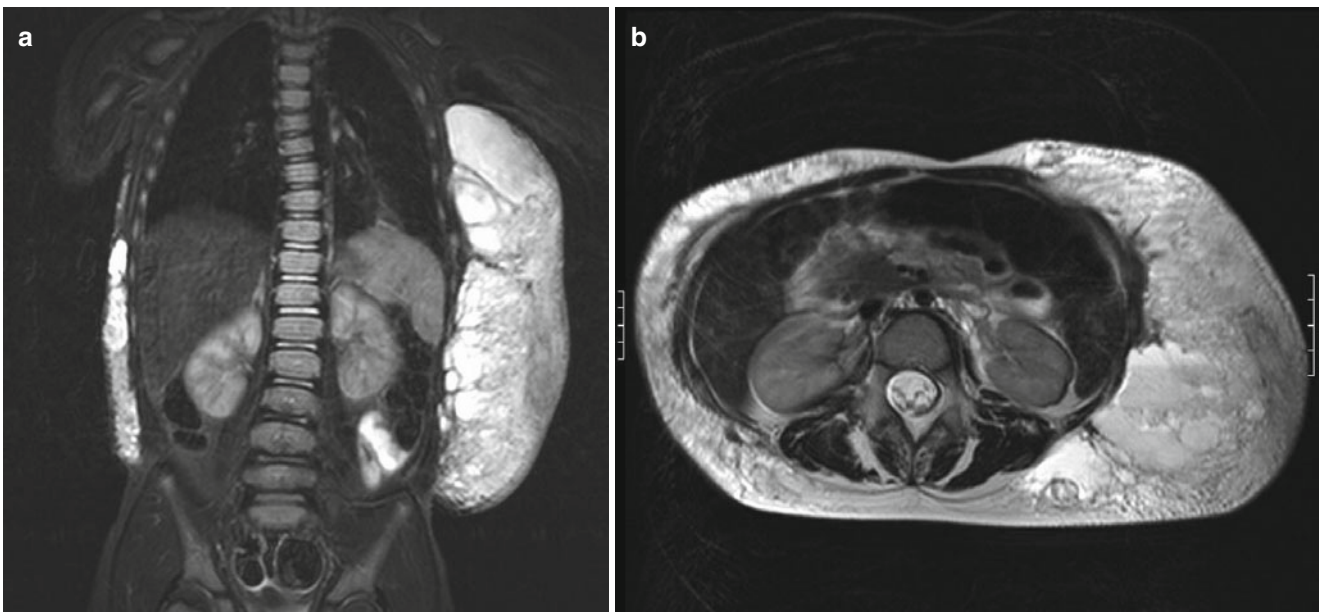


Fig. 7.15 Proteus syndrome. (**a**) MR (coronal STIR) showing a large, partly pedunculated, soft tissue mass arising form the left lateral chest wall with a smaller component extending to the right side. (**b**) MR (axial T2-W) demonstrating the full extent of the mass as it wraps around the abdominal wall

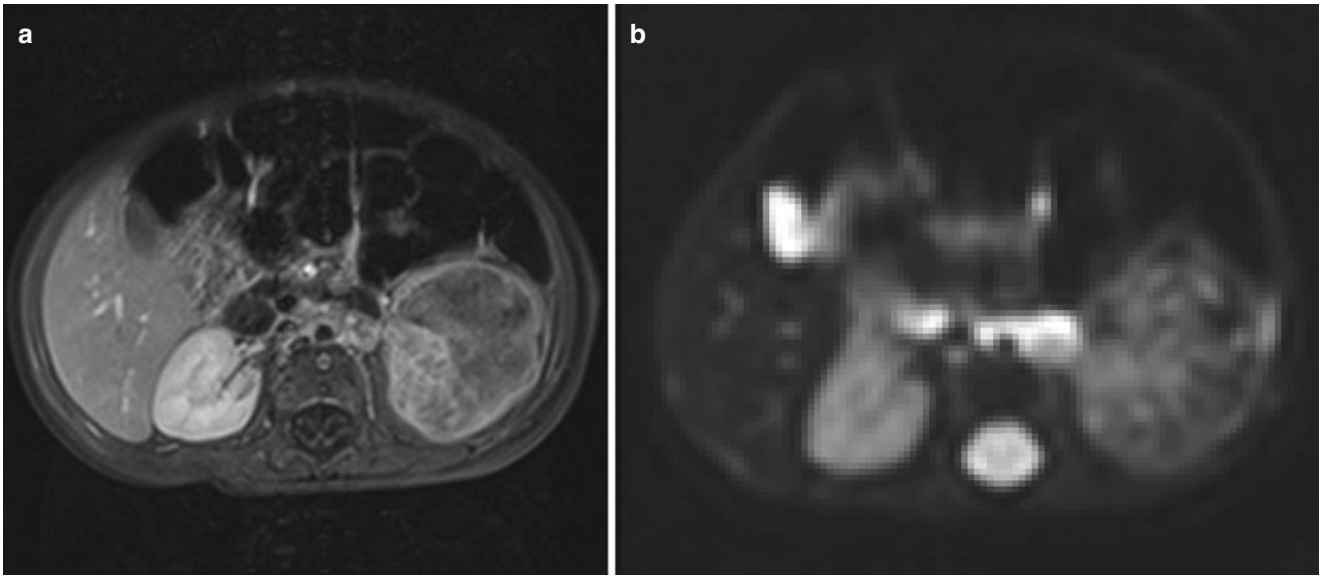


Fig. 7.16 Rhabdoid tumor of the kidney. (**a**) A large left sided rhabdoid tumor on contrast enhanced MRI, with normal enhancement in the contralateral kidney. (**b**) The ADC map of the same tumor shows relatively restricted diffusion, indicating high cellularity

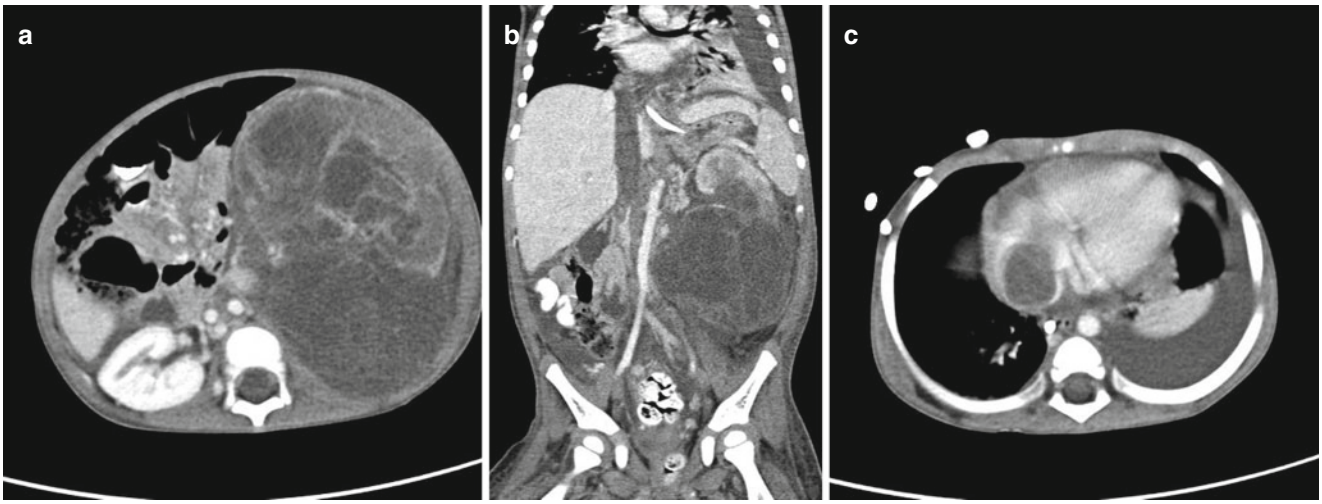


Fig. 7.17 Wilms tumour on contrast enhanced CT. (**a**) Large left sided Wilms tumor, (**b**) coronal reformat showing tumour thrombus distending the IVC and extending to the chest, (**c**) and tumour thrombus extending into the right atrium (a left sided pleural effusion is also present)

Renal lymphoma is characterized by multiple homogeneous masses, often with associated adenopathy [29].

Nephroblastoma (Wilms' Tumor)

Wilms' tumor is the most common malignant renal tumor of children accounting for 5–6 % of childhood cancers in the United States. The survival rate of children with Wilms' tumor has improved dramatically, partly due to large multicentre studies conducted by the National Wilms' Tumor Study Group (NWTSG) and the International Society of Pediatric Oncology [4]. As a result much of the imaging in Wilms' tumor is now protocol driven and many children form part of large ongoing trials. The initial detection of a renal mass will most commonly be by ultrasound but imaging will usually include MR or CT. Although there is increasing use of MR, CT is still favoured by some surgeons for surgical planning.

Ultrasound characteristically demonstrates a large mass arising from the kidney with or without echo-poor lakes. Both CT and MRI demonstrate an intrinsic renal mass with medial distortion of the collecting system which does not enhance, or only minimally, with intravenous contrast medium [6]. Associated pararenal and para-aortic lymphadenopathy may be demonstrated but may be reactive rather than because of malignant involvement which must be proven by biopsy. Caval thrombosis occurs, and can

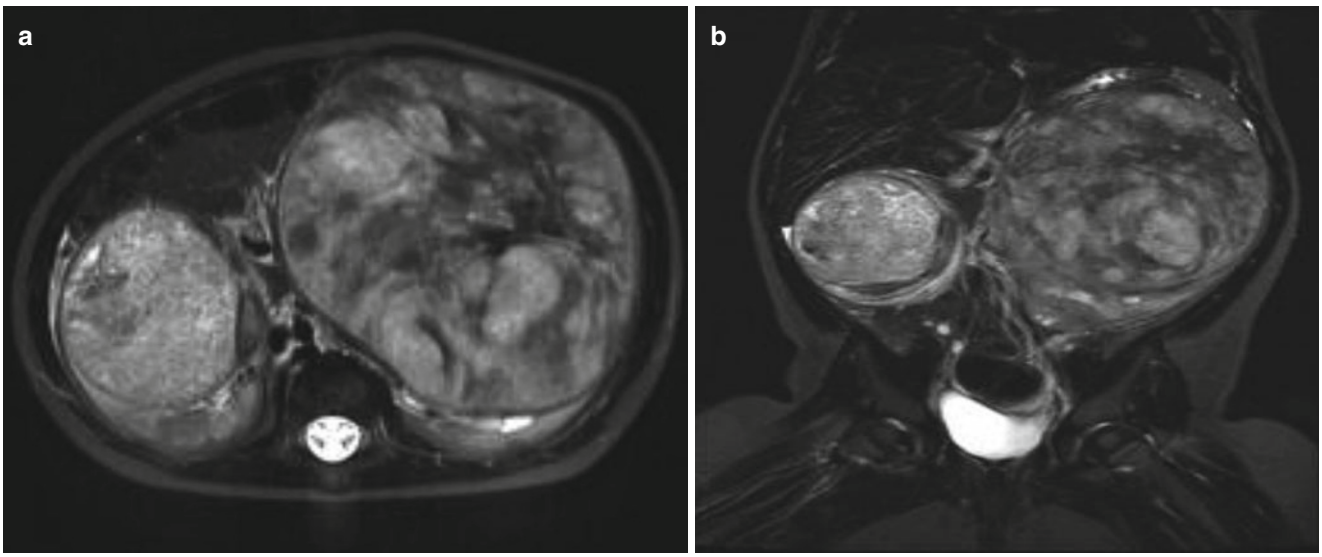


Fig. 7.18 Bilateral Wilms' tumors. Large right sided Wilms' tumor and smaller left sided Wilms' tumor on axial (**a**) and coronal (**b**) STIR imaging

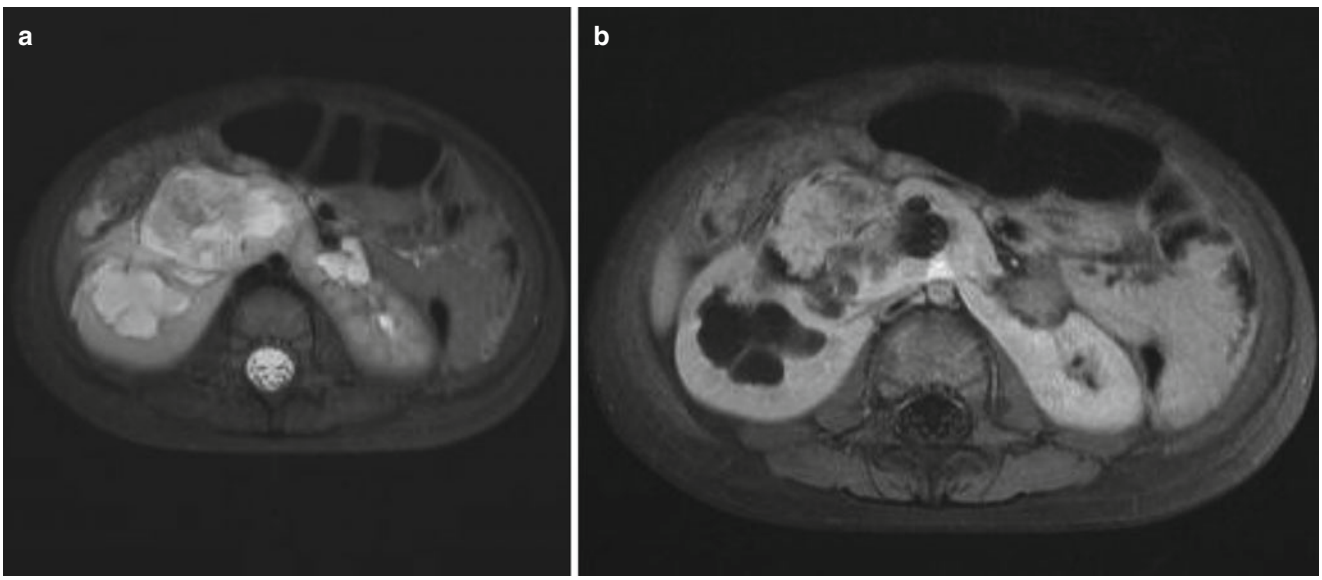


Fig. 7.19 Wilms' tumor in a horseshoe kidney. (**a**) Axial STIR and (**b**) axial contrast-enhanced T1W MRI sequences demonstrating a right sided Wilms' tumor arising from a horseshoe kidney

extend up into the right atrium, and can be demonstrated with ultrasound (including transesophageal ultrasound), CT or MRI. IVC thrombus may be difficult to evaluate in the presence of a large right-sided renal mass and should be sought for and excluded with care (Fig. 7.17) [41]. Thrombus confined to the renal vein is difficult to demonstrate reliably but fortunately, does not present a major surgical hazard. Direct extension of a right-sided Wilms' tumor into the liver occurs and can be assessed with ultrasound, CT or MRI.

Bilateral Wilms' tumors occur in 5–10 % of cases (Fig. 7.18) and present at a younger age than unilateral tumors [34]. The ability of imaging to demonstrate small contralateral lesions is now such that direct manual examination of the contralateral kidney at surgery is unnecessary. CT or MRI are reliable and more accurate than ultrasound. Bilateral lesions associated with nephroblastomatosis may not be malignant, and there is some evidence that imaging is useful in determining the need for excision of these lesions, particularly after chemotherapy [13]. Wilms' tumor occurring in a horseshoe kidney is also well recognized [32] (Fig. 7.19) and the presence of a horseshoe kidney confers a slightly increased risk. Imaging will be especially challenging to delineate the

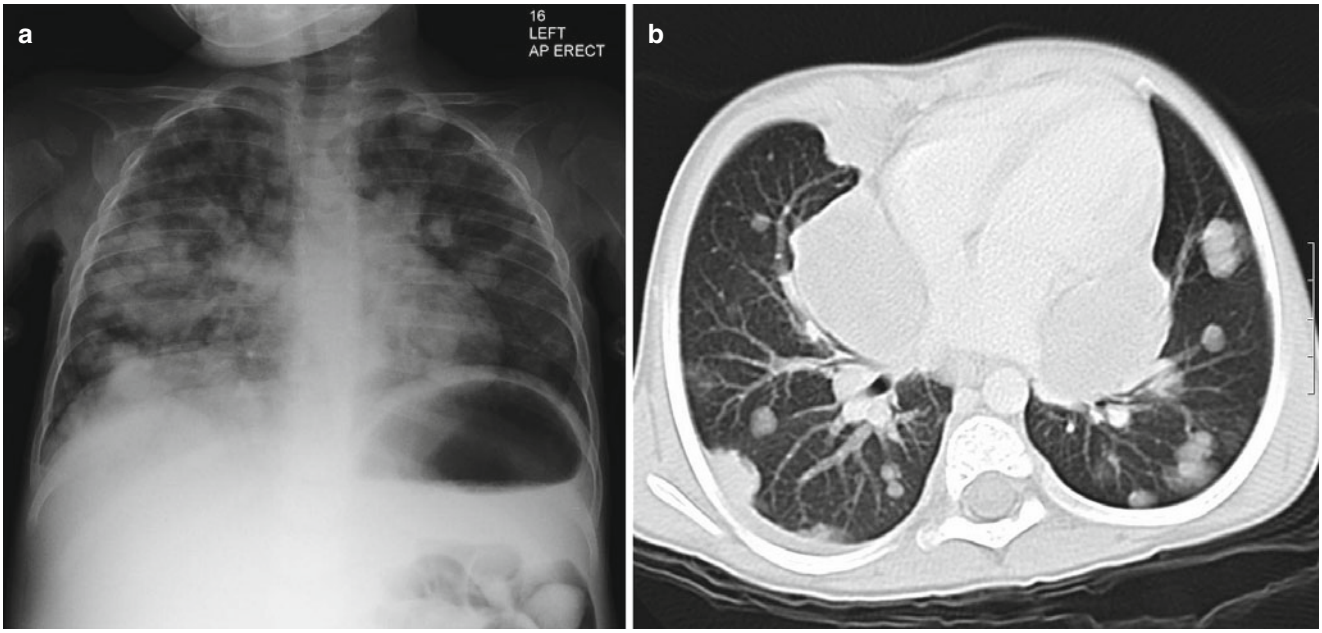


Fig. 7.20 Lung metastases in Wilms' tumor. (**a**) Chest X-ray showing extensive lung metastases. (**b**) Lung metastases are best demonstrated on chest CT with dedicated lung window settings

extent of the tumor(s) and the vascular supply both to tumor and the kidney overall. In these complicated cases a combination of MR and either CT angiography or conventional angiography will be necessary.

Lung metastases from Wilms' tumor may be detected on plain chest radiograph, but CT scanning with its improved resolution is the most sensitive technique to detect the presence of pulmonary metastases (Fig. 7.20). Most cancer trials use conventional radiographs for detection of possible recurrence, and the added value of potential earlier detection of recurrence using CT is currently undefined [33].

The local recurrence rate of Wilms' tumor is low, and following surgery and chemotherapy follow-up with abdominal ultrasound and chest radiographs is sufficient. If there is a high risk of recurrence or findings on routine imaging are suspicious, then further investigation with CT and/or MRI is recommended. More sophisticated imaging such as diffusion weighted MRI may be of use in evaluation of tumor response in the future (Fig. 7.21).

Unusual histological variants of Wilms' tumor (considered to be different entities by some investigators) include the sarcomatous type which frequently metastasizes to the skeleton and therefore requires isotope bone scanning and the rhabdoid type which metastasizes to the central nervous system and requires CT or MRI of the brain [54].

Patients who are at increased risk of developing a Wilms' tumor require screening. Genitourinary anomalies Denys–Drash syndrome, sporadic aniridia, Beckwith–Wiedemann syndrome (BWS), Perlman's syndrome, and hemihypertrophy are anomalies with an increased incidence of Wilms' tumor [31, 40]. Genitourinary anomalies are common but the incidence of Wilms' tumor in these patients is low. Similarly, true hemi-hypertrophy is rare and only 3 % of these children develop Wilms' tumors. Regular screening in these children may not be cost-effective. However, patients with sporadic aniridia have a 33 % risk of developing Wilms' tumor and those with Beckwith–Wiedemann syndrome a 10 % risk of developing a tumor and therefore some centres advocate regular screening with ultrasound until the child is 5–10 years of age. NWTSG recommends surgical staging in each case; and thus the role of imaging is to assist surgical planning, and to identify stage IV disease.

Wilms' tumor is the most common cancer in children with BWS, occurring in about 5–7 % of all children with BWS. Most children develop Wilms tumor prior to their fourth birthday; however children with BWS can develop Wilms tumor up to 7 or 8 years of age. By 8 years of age 95 % of all Wilms tumor have occurred. Screening by ultrasound at intervals of 3 months until the child's seventh birthday is current practice for BWS in many leading centres and is likely to become the established guideline.

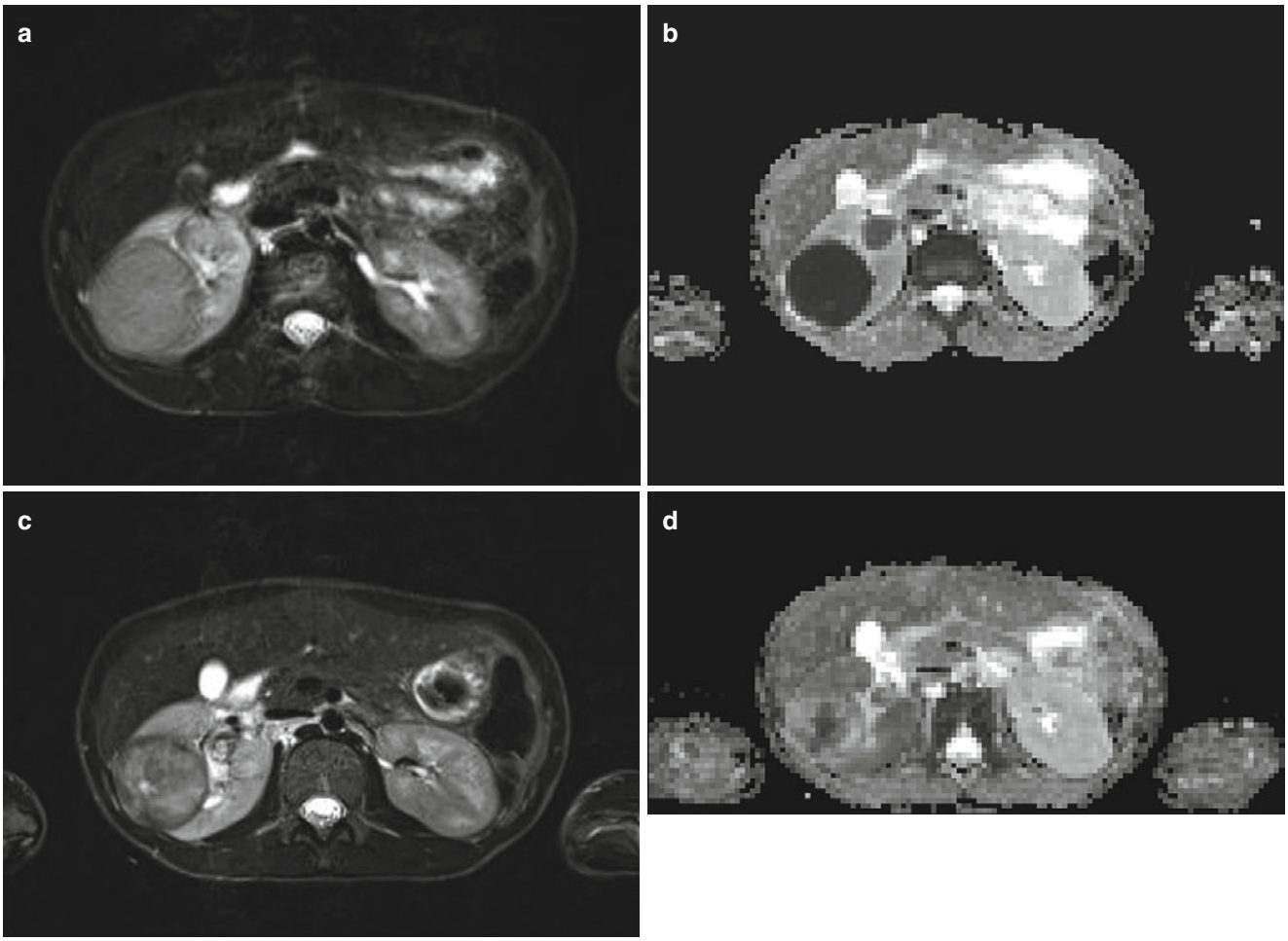


Fig. 7.21 The use of ADC maps for tumor evaluation: Right sided Wilms tumor at presentation shows a solid mass. (**a**) On axial T2W STIR imaging. (**b**) With areas of restricted diffusion (appearing dark grey) on ADC, indicating high cellularity. (**c**) Following chemotherapy on pre-operative imaging, although the size of the tumor is unchanged on similar STIR imaging, the signal characteristics have changed, (**d**) and the ADC map now shows no restricted diffusion in the tumor implying tumor necrosis. Some ADC changes in the surrounding native right kidney are likely to be due to reactive change secondary to urinary obstruction

Staging in Wilms' tumor is further detailed in Chap. 9.

There is a divergence in the staging and treatment strategy of Wilms' tumor between North America and Europe. Current practice in North America is that the tumor is first surgically removed and histology of the resection specimen is obtained, followed by chemotherapy. If the tumor is inoperable it is biopsied at the time of surgery and up-staged to Stage 3. In Europe it is current practice to biopsy the tumor to establish the tumor type and then to give appropriate chemotherapy before surgery at a later stage. Staging is then at surgery unless imaging shows distant metastases, which is Stage IV disease. It is not surprising that the percentage of patients with stage I and II will be higher when pre-operative chemotherapy is used, but there is no evidence to suggest that either approach has a better long term prognosis, which is usually excellent.

Nephroblastomatosis

Nephroblastomatosis represents persisting nephrogenic rests of fetal renal tissue. Nephrogenic rests are found in approximately 1 % of infant kidneys at autopsy, and although the malignant potential of any individual lesion is unknown, they are associated with an increased risk of Wilms' tumor, presumed secondary to neoplastic change. Nephrogenic rests are associated with many syndromes including Beckwith-Wiedemann syndrome, hemihypertrophy, and sporadic aniridia. Children with identifiable syndromes, once diagnosed, should be screened (usually by ultrasound) for the development of Wilms' tumor. Nephrogenic rests are also linked with other lesions such as multilocular cystic nephroma and multicystic dysplasia, usually without malignant complications [28, 45].

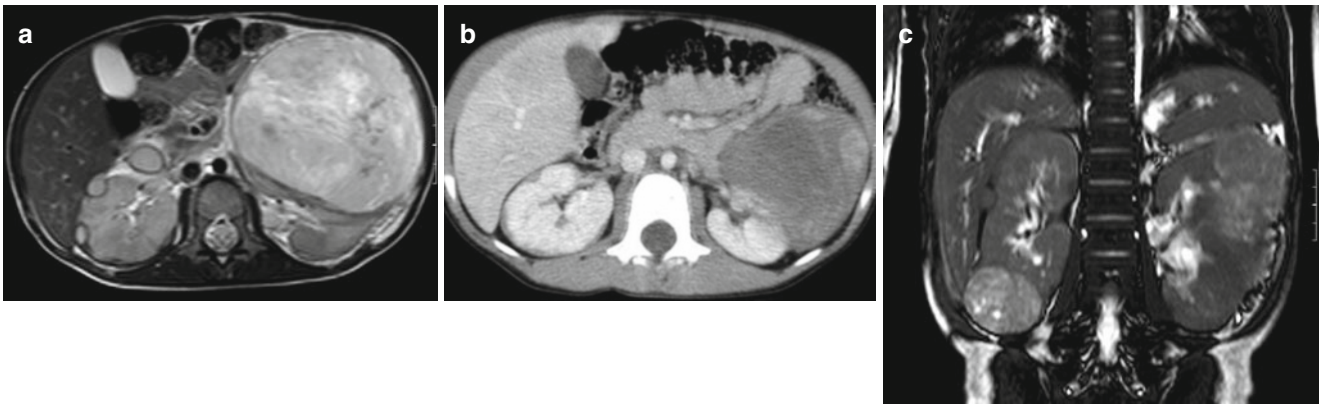


Fig. 7.22 Bilateral Wilms' tumor with nephroblastomatosis. (**a**) T2 MR sequence showing the large Wilms' tumor in the left kidney and nodules of nephroblastomatosis in the periphery of the right kidney. (**b**) CT with contrast showing the left sided Wilms' tumor and additionally both the nodular and plaque like nephroblatomatosis of the right kidney. (**c**) Coronal MR (BFFE sequence) showing the difference in signal between the Wilms' tumor in the lower pole of the right kidney and the nodule of nephroblastomatosis on the lateral margin of the right kidney. Part of the left sided tumor can also be seen

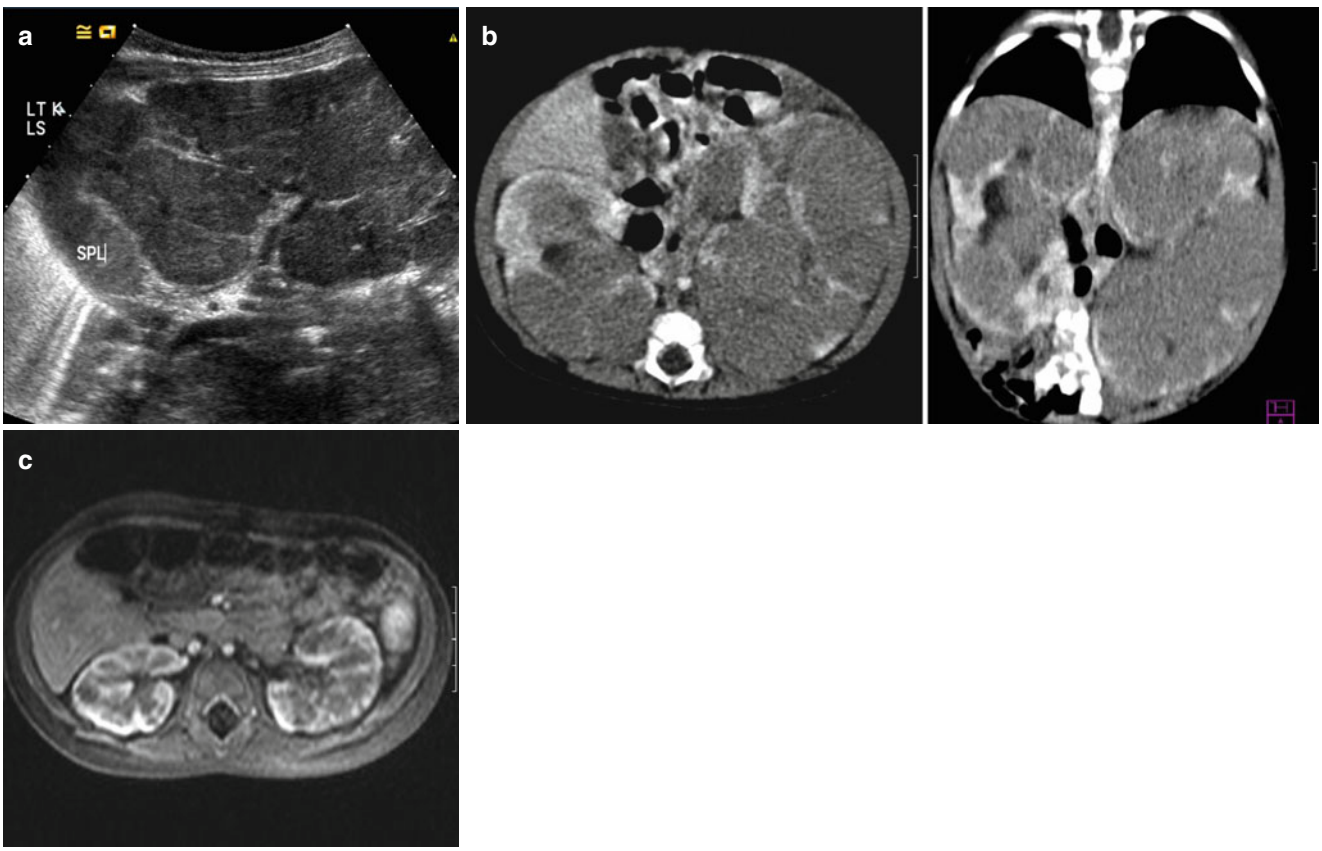


Fig. 7.23 Nephroblastomatosis. (**a**) Ultrasound showing a diffusely enlarged and infiltrated left kidney, displacing the spleen superiorly. (**b**) Contrast enhanced CT showing that both kidneys are diffusely affected and occupy much of the abdomen (i) axial and (ii) coronal planes. (**c**) MRI with contrast enhancement showing the dramatic reduction in size following treatment

Nephroblastomatosis commonly presents as multinodular, peripheral, cortical lesions (Fig. 7.22); the diffuse form of distribution being less common (Fig. 7.23). Foci are usually homogeneous and of low echogenicity, density or signal intensity. Ultrasound is usually the first line examination, revealing hypoechoic lesions but lesions smaller than 1 cm are difficult to depict using ultrasound alone. Where there is a strong clinical suspicion, MRI gives better tissue contrast and yields low signal intensity homogeneous lesions. The most reliable criterion to dif-

ferentiate nephroblastomatosis from Wilms' tumor is their homogeneity. Due to the significant radiation dose of serial CT, MR imaging should be the method of choice wherever it is available. The cost-effectiveness and availability of US makes it ideal for serial follow-up of known lesions.

Mesoblastic Nephroma

This renal tumor (Fig. 7.24) is the most common localized renal tumor in the infant under 12 months of age. It is histologically benign, although rare cases with metastases have been described and treatment is with surgical resection alone. Imaging is the same as for Wilms' tumor. Routine postoperative imaging is unnecessary.

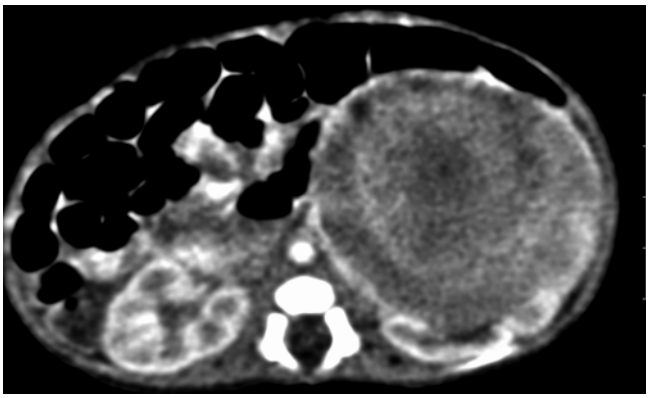


Fig. 7.24 Mesoblastic nephroma. A large left renal tumor is demonstrated on CT scan of kidneys in this 10-month-old infant. Nephrectomy confirmed mesoblastic nephroma

Others

Other rare causes of renal tumors include renal cell carcinoma, malignant mesenchymal sarcoma, (a malignant form of mesoblastic nephroma), renal lymphoma, angiomyolipoma and multilocular cystic nephroma. Renal cell carcinoma often presents with intratumoral calcification and haemorrhage. The imaging strategy is essentially the same as for Wilms' tumor, useful diagnostic features include; bilateral involvement with node or other organ involvement in lymphoma, the highly vascular, cystic and fat components in angiomyolipoma and the predominantly cystic nature of the multilocular cystic nephroma.

Intrarenal neuroblastoma has been described and can be confirmed with urine catecholamine measurements. Infective lesions occasionally present as a renal mass and must be excluded on imaging. Acute infection, with or without abscess formation, may present as a lump on ultrasound which does not enhance following intravenous contrast medium on CT, with a wedge-like, or cystic appearance. Chronic infective lesions such as xanthogranulomatous pyelonephritis are rare in childhood and characteristically give bizarre reniform masses with calculi and perinephric fluid collections. Perinephric inflammatory changes are an important imaging indicator of infection rather than neoplasia.

Neuroblastoma

Neuroblastoma is the most common extracranial pediatric solid tumor and may occur at a number of sites, with most (60 %) arising in the abdomen (Fig. 7.25), 20 % in the chest (Fig. 7.26), predominantly the posterior mediastinum, and

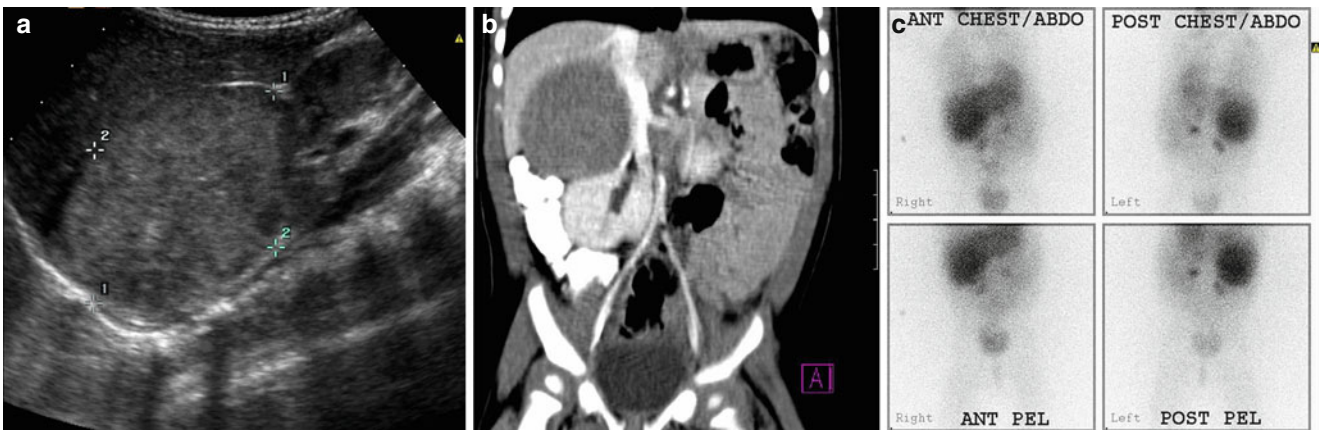


Fig. 7.25 Neuroblastoma. (**a**) Classic appearance on ultrasound with a tumor arising from the right suprarenal area, pushing up on the under surface of the liver and displacing the right kidney inferiorly. (**b**) CT with contrast reconstructed in the coronal plane confirming the right supra renal mass and demonstrating the inferior displacement of the right kidney. (**c**) MIBG showing avid uptake in the tumor and normal uptake in the liver (with some normal excretion in the collecting systems of both kidneys)

then more rarely in the neck and pelvis (Fig. 7.27). This embryonal neoplasm often encases vascular structures (Fig. 7.28) and, unlike most solid cancers, usually presents with substantial metastatic disease (bone, bone marrow, lymph nodes, liver: spread to lung or brain is rare) and as a result requires a multitude of imaging studies to fully assess the extent of disease at presentation (Fig. 7.29). Hence the role of radiological imaging is to assist in making the diagnosis, to demonstrate the extent of the disease, and to demonstrate or exclude the presence of metastases [15, 35]

If the tumor presents in the abdomen, ultrasound, CT and MR scans will all demonstrate a large, irregular and poorly defined solid mass arising from the suprarenal area or the paravertebral region [35]. However there is a growing body of literature supporting the use of MRI as the technique of choice for the evaluation of local and regional disease in children with suspected neuroblastoma. The mass frequently crosses the midline and may extend into the spinal canal, and both displace and encase the aorta and inferior vena cava. The ipsilateral kidney is displaced laterally and inferiorly.

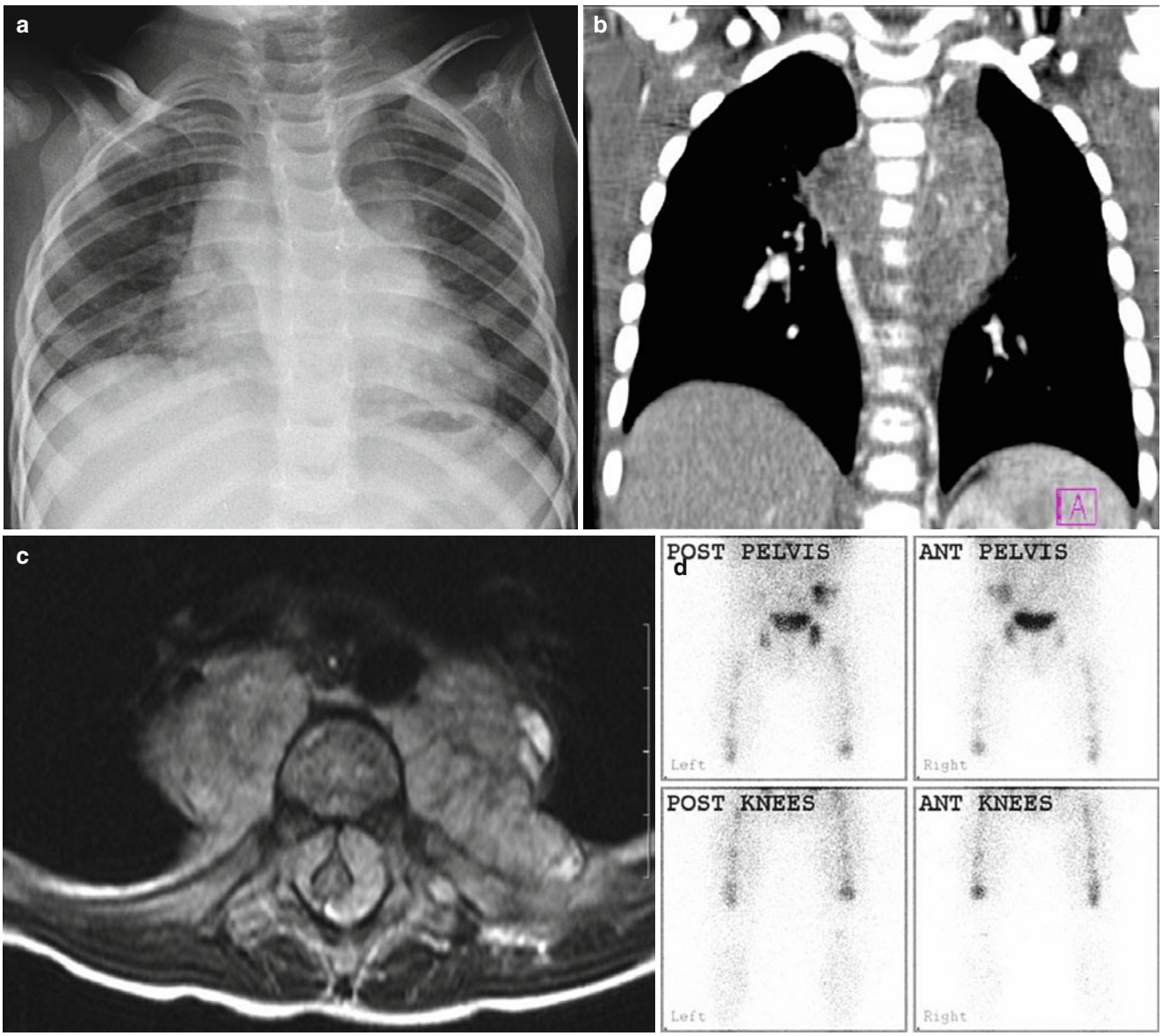


Fig. 7.26 Thoracic neuroblastoma with spinal invasion and mandibular metastasis. (**a**) Chest radiograph showing diffuse widening of the mediastinum and increased soft tissue density in the midline. (**b**) CT with contrast in a coronal reconstruction with tumor seen both sides of the thoracic spine. (**c**) MR of the spine showing tumor invasion into the spinal canal bilaterally forming a horseshoe of tissue around the spinal cord which is compressed in the centre. (**d**) MIBG with extensive areas of increased uptake consistent with metastases. (**e**) Ultrasound of the mandible with an expanding soft tissue mass erupting from the bone, the 'sunray' linear echoes represent an intense periosteal reaction. (**f**) CT confirms a destructive lesion in the left mandible with an associated soft tissue mass representing a neuroblastoma deposit

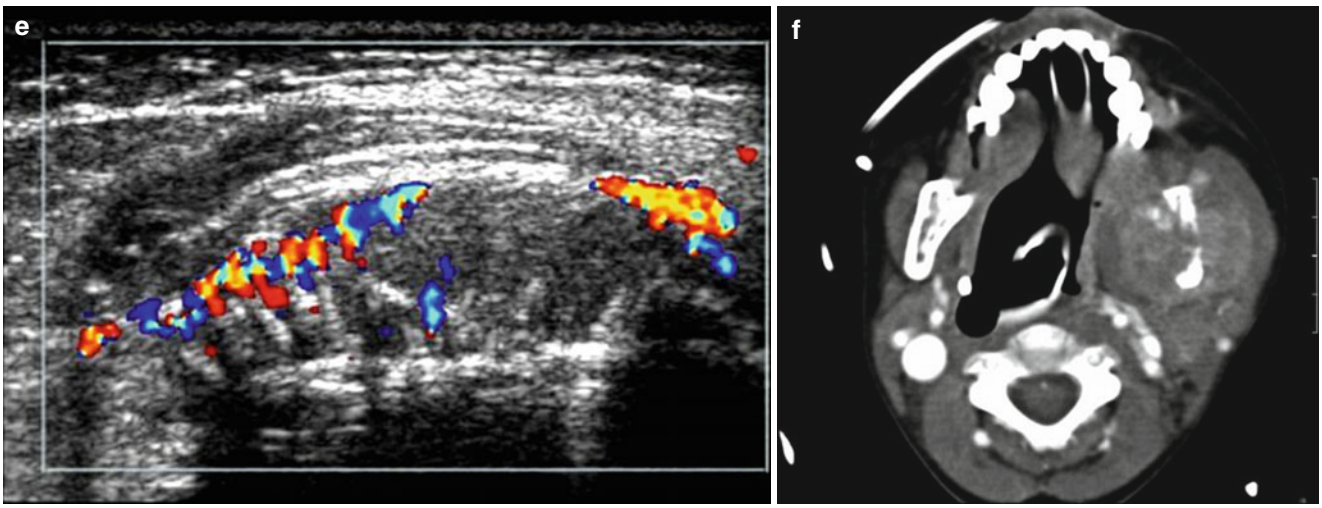


Fig. 7.26 (continued)

Rarely, the tumor may extend into the kidney or encase the renal hilum, so that when tumor resection is attempted a nephrectomy may be required. Smaller tumors (stage I and II) are often more clearly defined and do not extend beyond the vertebral bodies. Calcification is often present within the mass and may be more obvious after treatment with chemotherapy. This is a good example of a tumor in which repeated imaging over the lifetime of the child is likely to be performed, and thus the choice of MRI over CT in the first instance and for subsequent imaging is a pragmatic, well informed approach.

Neuroblastoma arising in the thorax will be seen on the chest radiograph as a posterior mediastinal mass. Displacement and erosion of the posterior ribs and vertebral bodies may be observed with extension into the spinal canal. Both CT and MR are able to demonstrate the tumor, although MR is the imaging method of choice to demonstrate disease in the spinal canal (Fig. 7.30).

Metastases occur most frequently in the bone and bone marrow. These are detected with ^{99m}Tc-MDP isotope bone scanning and (iodine) ^{123}I-MIBG scanning; MDP bone scanning is a highly sensitive but non-specific means of detection of bone metastases; MIBG scanning is specific as the isotope is taken up by neurosecretory granules in the neuroblastoma cells. Although this would appear to be the isotope of choice in this tumor, some tumors do not take up MIBG and the role of the two investigations remains complementary in many institutions [49] There is further evidence that 18F-FDG PET may give better sensitivity in paediatric neuroblastoma [30] (Fig. 7.31).

Until recently, the staging of Neuroblastoma related to surgical findings, based on whether the tumor was localised at surgery with complete excision (stage 1), partial excision (stage 2), unresectable or lymph node spread (stage 3) or metastatic (stage 4); International Neuroblastoma Staging System (INSS). Imaging therefore only really helped differentiate between stages 3 and 4. A special stage 4S was also described for local disease in infants under 1 year of age with dissemination limited to skin, liver and/or bone marrow, because they had a particularly good prognosis.

However, the International Neuroblastoma Risk Group Project (INRG) now propose a new system designed for staging based on imaging findings, prior to any treatment, including surgery [7]. This includes only two stages of localised disease, dependent on whether image-defined risk factors (IDRFs) are present or absent. IDRFs at the time of diagnosis include perivascular involvement with arterial encasement, infiltration of adjacent organs or paraspinal involvement. Multifocal primary tumors, pleural effusion and ascites are not considered IDRFs. The idea of using this staging system is to reach an international standard of imaging reporting, which will make international trials of new treatment easier. The new INRG risk assignment will classify neuroblastoma at diagnosis based on a new International Neuroblastoma Risk Group Staging System (INRGSS) [7]:

- Stage L1: Localized disease that do not involve vital structures (i.e. without IDRFs).
- Stage L2: Localized disease with IDRFs.
- Stage M: Metastatic disease.
- Stage MS: Metastatic disease "special" where MS is equivalent to stage 4S in infants <18 months of age.

Further stratification can be made according to age, tumor grade, n-myc amplification (greater than ten copies of a DNA segment termed the Myc oncogene) and other genetic markers, to place patients into four pre-treatment risk groups: very

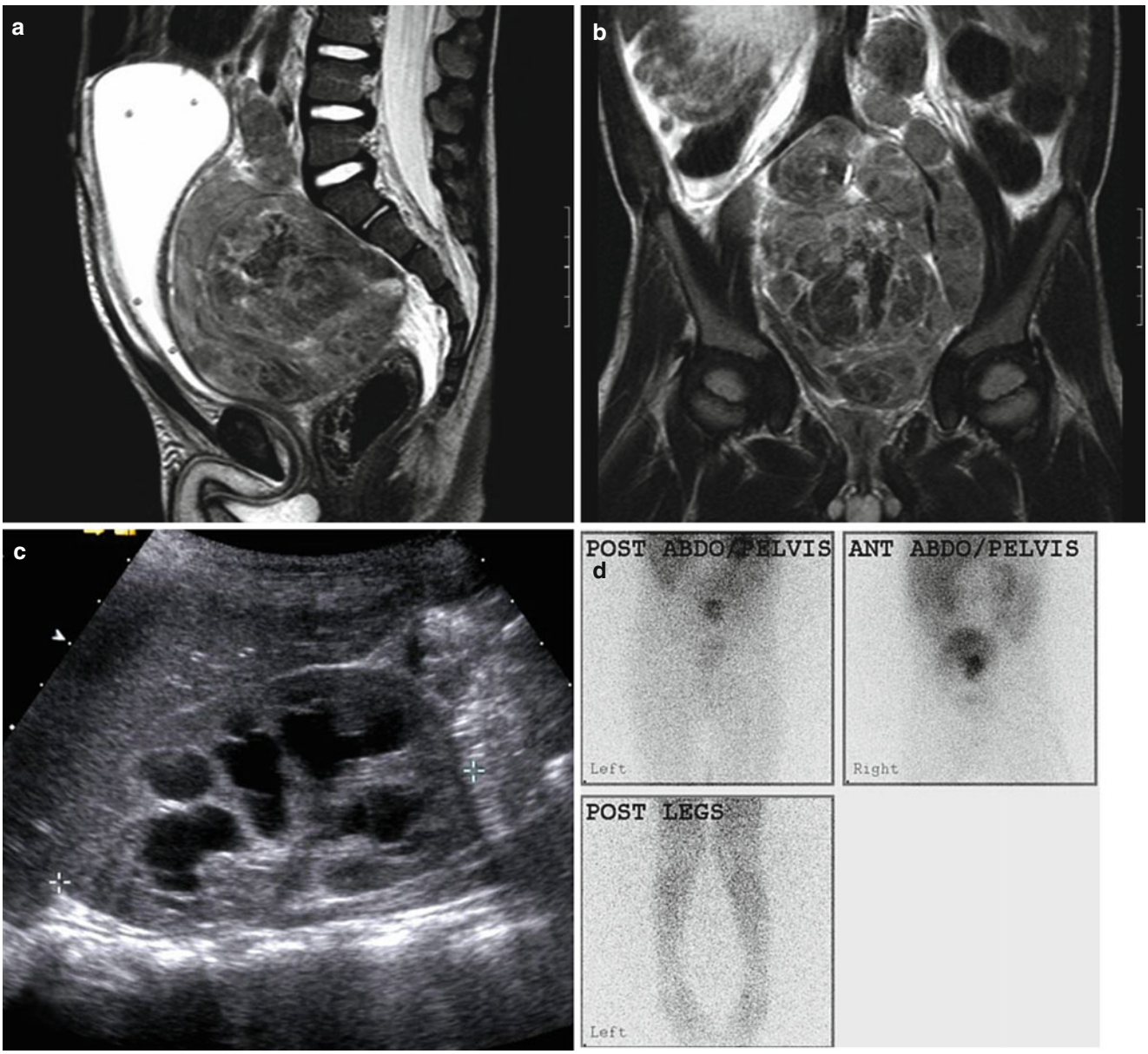


Fig. 7.27 Pelvic neuroblastoma. (**a**) Sagittal T2-W MR showing a large neuroblastoma arising from the pelvis. The tumor is compressing the bladder anteriorly and the bowel posteriorly. (**b**) Coronal MR showing how the tumor is extending superiorly out of the pelvis and the associated local nodal spread. (**c**) Ultrasound showing the associated hydronephrosis which was bilateral secondary to the ureters being obstructed by the bulk of the tumor. (**d**) MIBG confirming this pelvic neuroblastoma is MIBG avid. The increased activity superimposed over the tumor on the anterior view represents isotope being normally excreted into the bladder and should not be misinterpreted as tumor extension

low, low, intermediate, or high risk. In all neuroblastoma groups the core imaging includes: AP chest X-ray, abdominal ultrasound, MRI (or CT if unavailable) of the primary tumor, isotope scanning with I^{123} or preferably I^{131} MIBG, and ^{99m}TcMDP scintigraphy if MIBG is negative. In the high risk groups follow up will include repeat MIBG scans to detect recurrence that is undetectable by other imaging modalities.

Adrenocortical Tumors

Clinical manifestations of endocrine abnormalities are common in adrenal cortical tumors and patients present with Cushing's syndrome, virilization and others. The distinction between benign and malignant tumors is based primarily on size and the presence of associated lymphadenopathy and metastases. Radiologically tumors

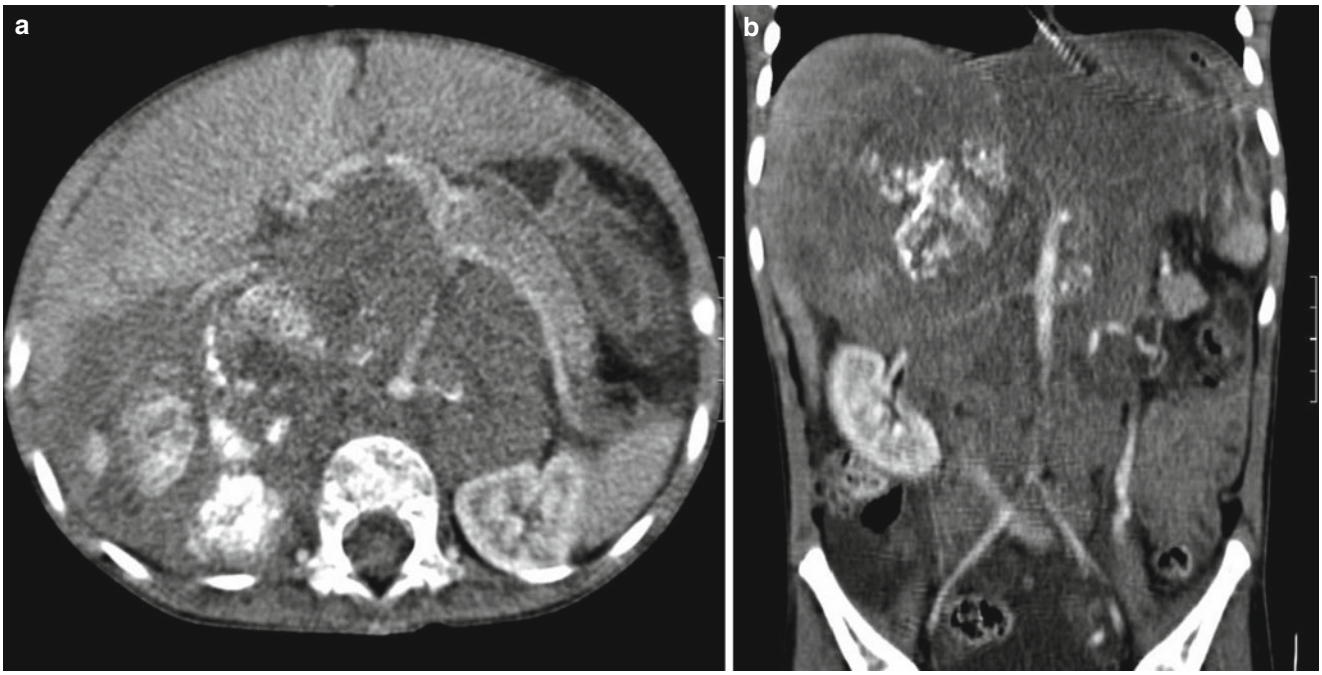


Fig. 7.28 CT in an infant with neuroblastoma. (**a**) The tumor extends throughout the retroperitoneum and characteristically engulfs vessels and pushes them anteriorly. (**b**) Coronal reformats showing the tumor has probably arisen from the right suprarenal area and contains typical scattered calcification. The renal arteries are stretched by the mass effect of the tumor

are usually well defined and if measuring less than 4–6 cm in diameter are benign, unless there is other evidence such as metastases or lymphadenopathy. Characteristically the tumors are identified by CT scanning, do not enhance following contrast medium injection, and are well defined.

Hemangioma

These usually present in young infants, often in the neonatal period, and may be solitary or diffuse, and are also known as hemangioendothelioma. Clinical presentation is with an abdominal mass which may be complicated by cardiac failure, a consumptive coagulopathy (Kasabach–Merritt syndrome) with thrombocytopenia and hemoperitoneum. The natural history is spontaneous regression, provided the child does not succumb to the complications of the disease. Ultrasound with Doppler color flow will demonstrate the mass and hypervascularity with dilated hepatic veins and an enlarged hepatic artery. Use of CT demonstrates single or multiple lesions which enhance intensely and peripherally with intravenous contrast medium. This is unlike hepatoblastoma and hepatocellular carcinoma which do not enhance. However, gadolinium enhanced MR will also show these lesions with great sensitivity and specificity and is now the imaging modality of choice.

Abdominal B Cell Lymphoma

Lymphoma with involvement of the bowel and mesentery is almost always caused by non-Hodgkin's lymphoma (B cell origin).

Clinical presentation is varied including diarrhea, weight loss and intussusception. Plain abdominal radiographs are non-specific and most commonly show dilated loops of intestine or bowel obstruction. Abdominal CT is probably more accurate than ultrasound in achieving a diagnosis but both studies will show nodular mass lesions, lumen narrowing, focal aneurysmal bowel dilatation and ascites. On ultrasound the mass lesions may be homogeneously hypoechoic. The CT scanning should be carried out after administration of oral contrast medium and a characteristic appearance of contrast-filled loops of bowel, trapped and encased by large soft tissue masses is seen. Involvement of the peritoneum and omentum occurs and CT will show omental cakes lying between the bowel and the anterior abdominal wall, with loss of normal fat planes [3]. If the child presents with non-specific gastrointestinal symptoms a barium follow-through may be performed. This will demonstrate bowel dilatation and narrowing with mucosal irregularity, bowel wall thickening and separation of bowel loops (Fig. 7.32).

Lymphoma may also occur within the liver and spleen and as a nodular infiltrate in the pancreas and both kidneys. Paraaortic lymphadenopathy may also be demonstrated on CT.

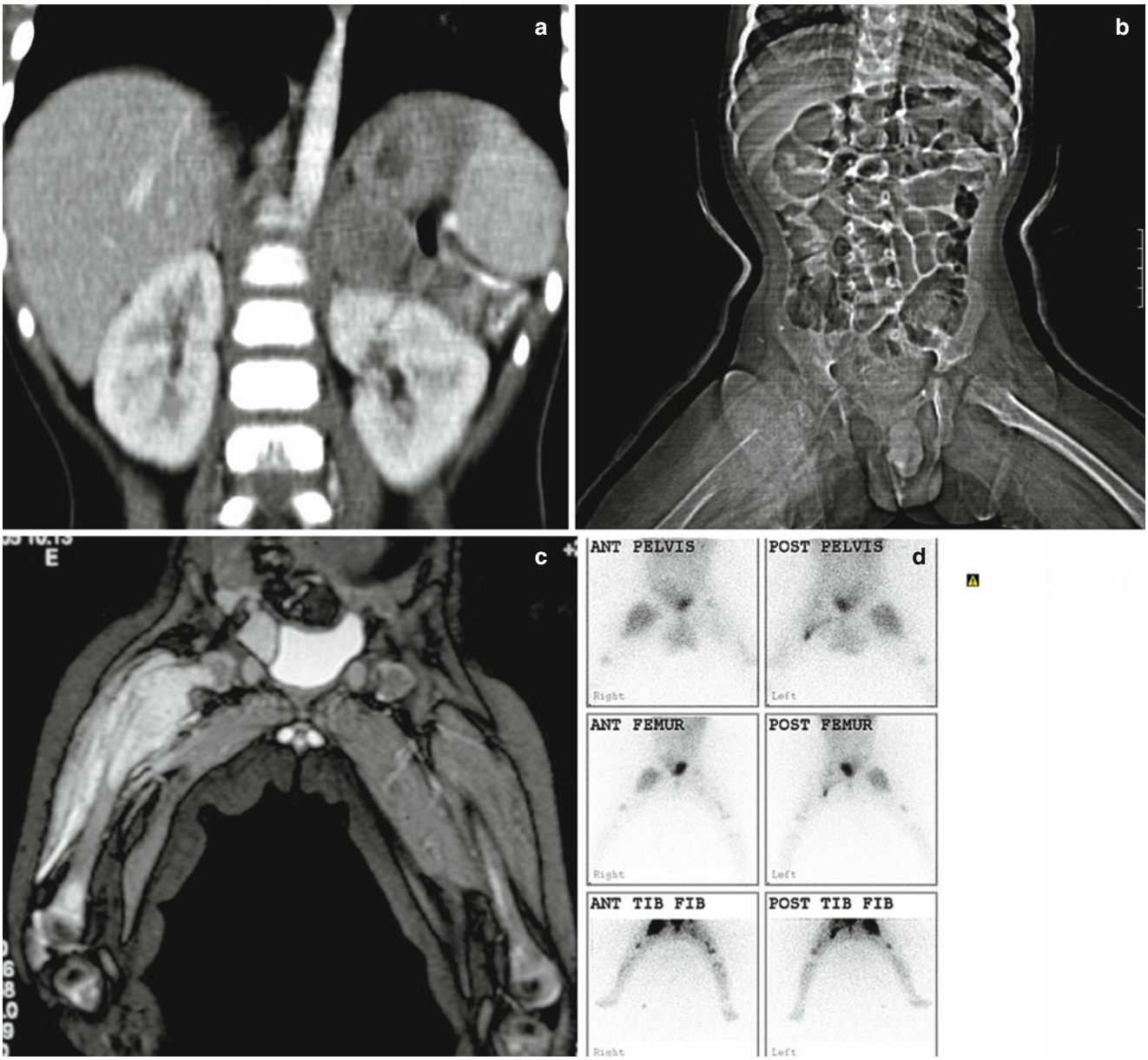


Fig. 7.29 Metastatic neuroblastoma in a child presenting with a femoral fracture. (**a**) CT shows a left suprarenal neuroblastoma displacing the left kidney. (**b**) The topogram for the CT shows the destroyed upper right femur secondary to metastatic disease and which was associated with a soft tissue mass. (**c**) MR shows the full extent of the upper right femoral metastatic disease. (**d**) MIBG shows further deposits scattered through both femora

Fig. 7.31 Neuroblastoma with PET correlation. (**a**) Axial MRI showing a large heterogeneous, predominantly right-sided, neuroblastoma. (**b**) Coronal MR shows the full extent of the nodal enlargement which is extending superiorly into the chest through the diaphragm, (**c**) I-123 MIBG single-photon emission computed tomography (SPECT) can be used to acquire a 3D dataset, simultaneously with a low dose CT, which can then be used to overlay the data onto the MRI (**d**) confirming areas of active disease (Images courtesy of Dr Lorenzo Biassoni, Great Ormond Street Hospital, London)

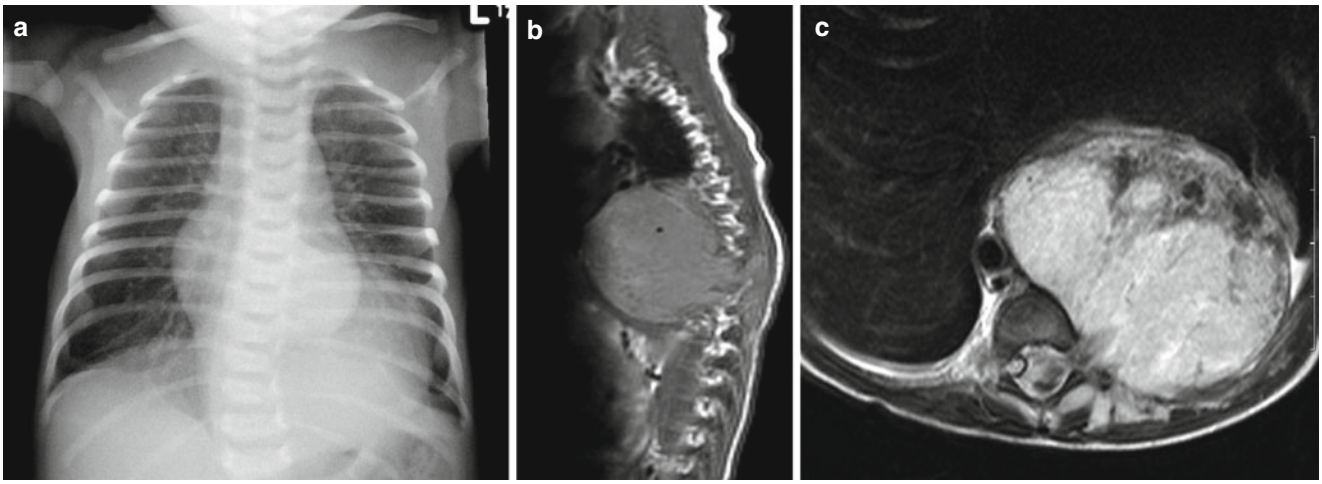
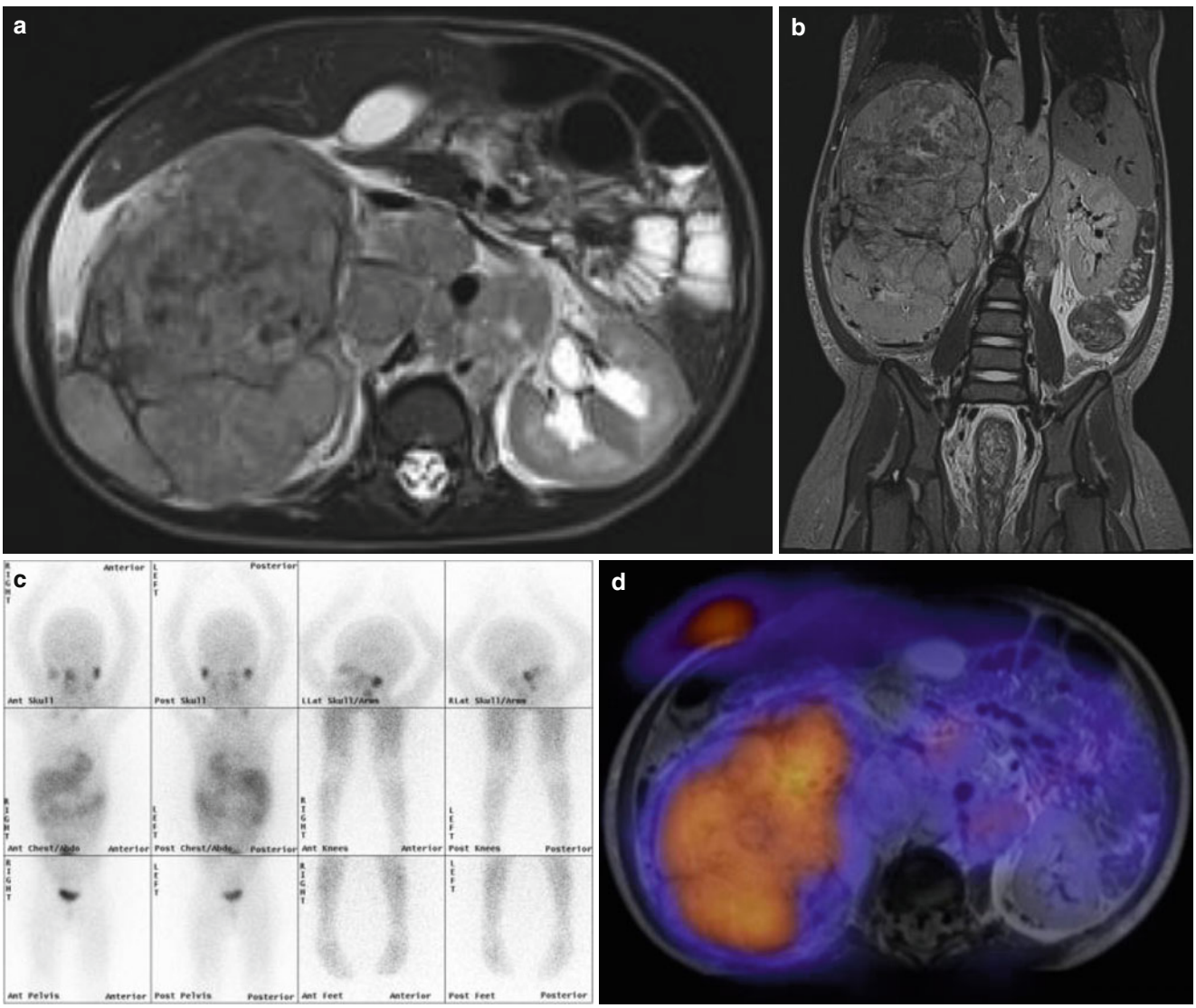


Fig. 7.30 Thoracic neuroblastoma with intraspinal extension. (**a**) Chest radiograph showing a large low left sided thoracic mass with splaying of the left sided ribs and causing a thoracic scoliosis. (**b**) Sagittal MR showing tumor extending through the thoracic intervertebral foramina at several levels. (**c**) Axial MR after gadolinium showing the left sided tumor extending into the spinal canal and markedly compressing and displacing the spinal cord to the far right side of the spinal canal



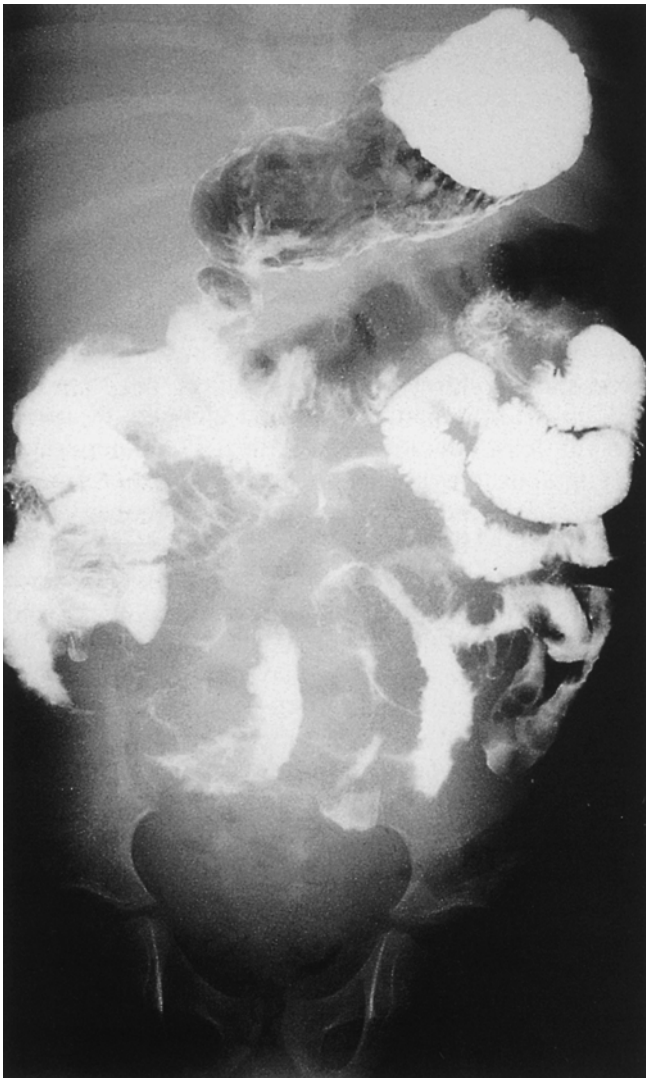


Fig. 7.32 Gastrointestinal lymphoma in a 4-year-old boy with marked weight loss, abdominal pain and anemia. Barium follow-through examination shows narrowing of distal ileum with bowel wall thickening and separation of bowel loops

Rhabdomyosarcoma

Rhabdomyosarcoma is the most common soft-tissue malignancy in childhood [14], accounting for over 50 % of all pediatric soft tissue sarcomas and representing 4–8 % of malignant solid tumors in children, ranking behind CNS tumors, lymphoma, neuroblastoma and Wilms' tumor. Rhabdomyosarcoma can be found in virtually any organ or tissue in the body including the musculoskeletal system. Diagnostic imaging is important and imaging protocols depend upon the anatomical location of the primary tumor. The three most common locations in descending order of frequency are the head and neck (Fig. 7.33), the genitourinary system (Fig. 7.34) and the extremities [36, 39]. Rhabdomyosarcoma also occurs in the biliary tree, the chest and retroperitoneum, and rarely the heart itself (Fig. 7.35).

Plain radiographs are of limited value in imaging the primary tumor unless there is destruction and erosion of the adjacent bone which can occur with both extremity and head and neck tumors. Cross-sectional imaging with MR and/or CT is always required. Ideally first loco regional evaluation should be made with MRI but CT is acceptable if MRI is not available. MRI is preferable for most locations, other than the chest, including head and neck tumors with possible skull base invasion. MRI is mandatory in a primary genitourinary or paraspinal tumor. CT is occasionally useful for assessing subtle bone destruction but MRI is sufficient for most head and neck lesions. Ultrasound is especially useful as an adjunct for genitourinary and biliary tumors.

On CT, rhabdomyosarcoma has a soft tissue attenuation and can be difficult to distinguish from adjacent soft tissues, particularly in the extremities and head and neck, unless intravenous contrast medium is given, and even with contrast CT remains inferior to MRI. Calcification is rare and should suggest an alternative diagnosis. Enhancement is variable and non-homogeneous and the margins of the tumor are irregular and poorly defined. Use of MRI is significantly better than CT in demonstrating the soft tissue mass and while lesions are of soft tissue signal intensity on T1 weighted sequences they are of high signal intensity on T2 weighted sequences and can therefore be more easily distinguished from adjacent muscle and soft tissue. The tumors can both encase and displace blood vessels and extend into the spinal canal and intracranial fossa either by destruction of the skull base and bone or through the intervertebral and cranial foramina. For showing subtle bone destruction CT is better than MRI – therefore both CT and MRI are important in these cases [42].

CT of the thorax is mandatory in all patients with rhabdomyosarcoma to assess the presence of lung metastases and under current protocols most centres also require PA and lateral chest radiographs. Defining pulmonary spread of tumor is critical to staging although differentiation between metastatic and benign nodules (such as granulomatous disease, hamartomas, intrapulmonary lymph nodes etc) can be impossible. One pulmonary/pleural nodule of 1 cm or lesions >5 mm in more than one site should be considered evidence of metastases provided there is no other clinical explanation for the lesion. A radionuclide bone scan (with plain X-rays and/or MRI of any isolated abnormal site) is mandatory in all patients at diagnosis. Lower limb tumors must have evaluation of pelvic lymph nodes by CT/MRI even if femoral nodes are clinically/radiologically (including ultrasound) normal. Upper and lower limb tumors would normally have surgical evaluation of axillary or inguinal nodes, respectively, even if nodes are clinically/radiologically normal.

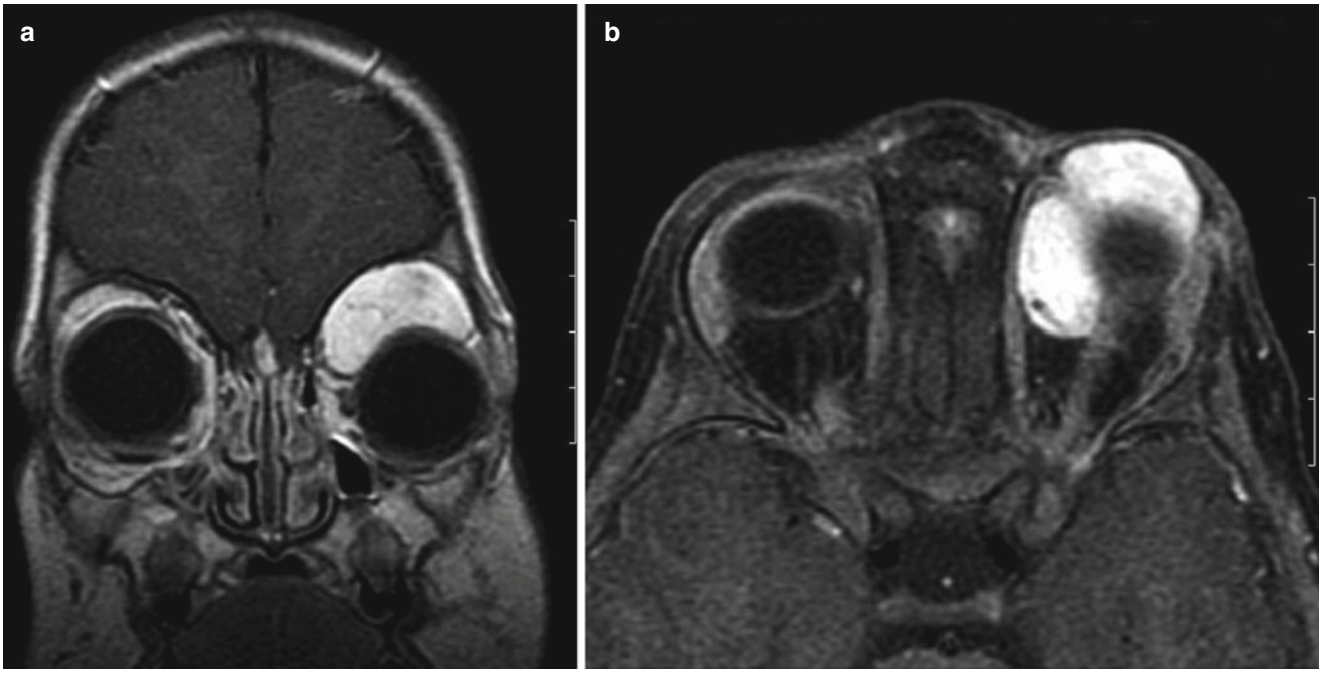


Fig. 7.33 Orbital rhabdomyosarcoma. (**a**) Coronal MR showing a mass in the superior orbit. (**b**) Axial MR shows the relationship to the optic nerve which is displaced superiorly

Liver Tumors

Liver tumors are relatively rare in childhood, representing 1–2 % of all tumors. Two thirds of these tumors are malignant [44]. The clinical presentation is usually abdominal enlargement due to an abdominal mass, with associated pain, fever, pallor, anemia and rarely, jaundice or heart failure may occur. Imaging may be critical in distinguishing between benign and malignant tumors [44]. The differential diagnosis of a malignant liver mass in children includes hepatoblastoma, undifferentiated (embryonal) sarcoma and rarely hepatocellular cancer, and of a benign mass hemangioma, infantile haemangioendothelioma (Fig. 7.36), mesenchymal hamartoma (a benign cystic lesion), focal nodular hyperplasia, adenomas and germ cell tumors (benign or malignant).

Hepatoblastoma

This is the most common primary hepatic malignancy of childhood, although it is quite rare, accounting for only 0.9 % of all pediatric cancers. It usually occurs in children younger than 3 years of age, and is usually asymptomatic at diagnosis. The prognosis is poorest in the neonate. It has been associated with Beckwith-Wiedemann syndromes and hemihypertrophy, APC mutations (which occur in familial adenomatosis polyposis) and low birth weight.

Hepatoblastomas are usually unifocal, most frequently located in the right lobe of the liver (approximately 50 %) but may be in the left lobe or be centrally located, and may be unifocal or multifocal. Ultrasound imaging is the initial investigation of choice and will demonstrate a solid mass of variable echogenicity, sometimes with calcification. Ultrasound is useful for determining vascular involvement, particularly thrombus in the inferior vena cava or portal vein. Both CT and MRI will demonstrate the anatomy and the extent of the tumor in more detail (Fig. 7.37). In order to plan for surgical excision it is necessary to delineate the hepatic veins and the segmental anatomy; while this can be shown on CT, MRI is considered to be more accurate (Fig. 7.38). The exact delineation of the extent of the tumor and the number and location of liver segments involved is crucial for surgical planning and management (Fig. 7.39) and especially in children who are treated according to the protocols of the International Childhood Liver Tumor Strategy Group (SIOPEL) [43]. Extrahepatic disease may also be demonstrated on CT or MRI.

CT of the chest is also necessary to determine the presence of pulmonary metastases. Following treatment with preoperative chemotherapy, imaging is essential to assess tumor resectability. In addition to the imaging already described most units have replaced conventional angiography with MRA. Angiography is occasionally helpful for planning complicated surgery, or for hepatic artery chemoembolisation.

Follow up of hepatoblastoma is by MRI but interpretation can be difficult. It is possible that FDG-PET (and/or PET CT) may have an important role to play in the assessment of

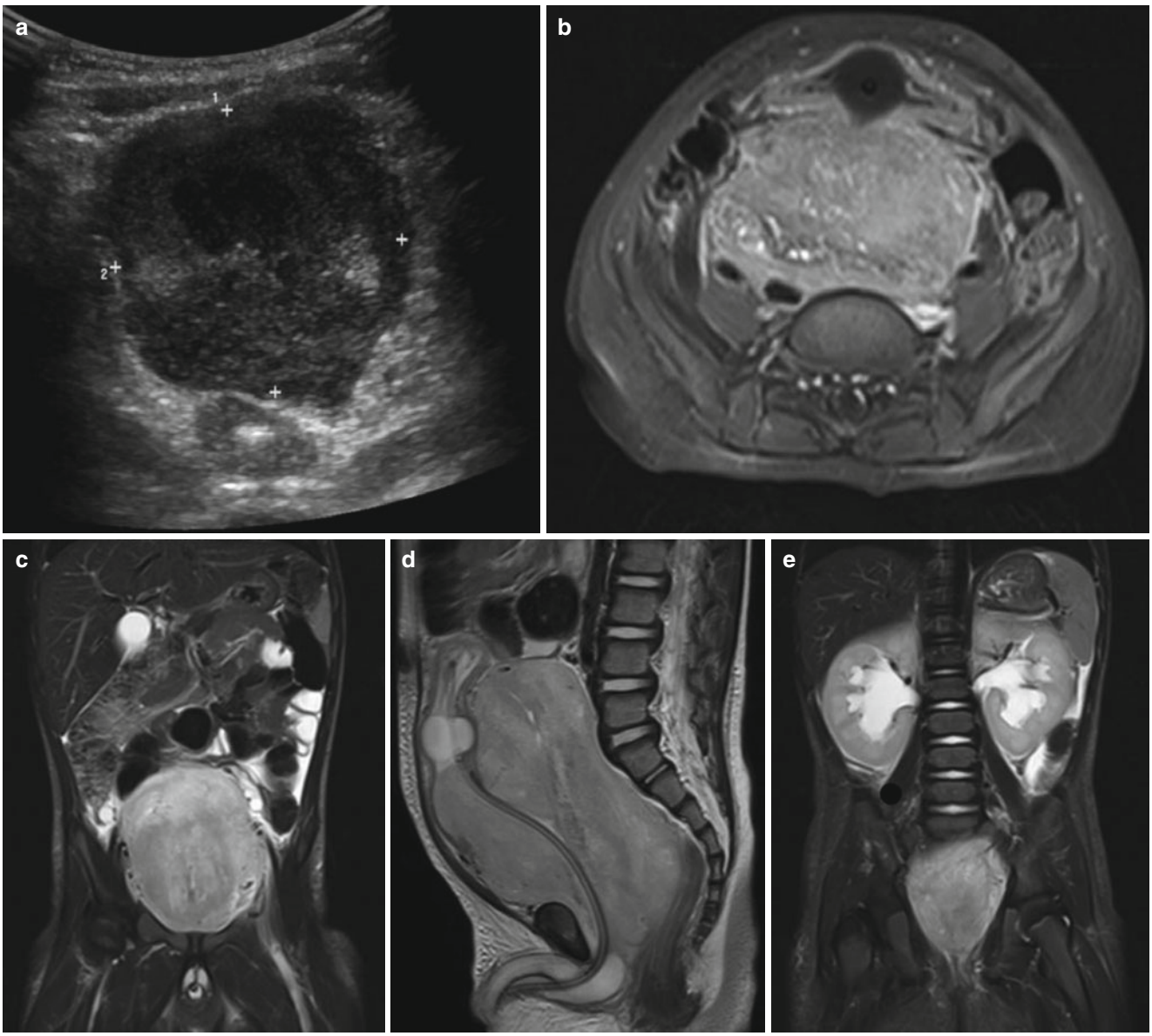


Fig. 7.34 Prostatic rhabdomyosarcoma. Ultrasound (**a**) shows the deep pelvic mass with the rectum compressed posteriorly. Axial (**b**) and coronal (**c**) MRI sequences show the large mass completely filling the pelvis. On the sagittal view (**d**), the mass extends deep into the perineum, and is likely to arise from the prostate, and the urinary bladder is displaced anteriorly and superiorly (with a urethral catheter in situ) and the rectum is compressed posteriorly. Bilateral hydronephrosis (**e**) Is caused by the mass effect of the tumour compressing the distal ureters in the deep pelvis

recurrence in the near future [12, 38]. Scintigraphy with ^{99m}Tc-labelled monoclonal anti-AFP ahs been proposed as a method of staging children with hepatoblastoma but the clinical usefulness of this technique is not yet known [23].

Staging of Hepatoblastoma is given in Chap. 9

Hepatocellular Carcinoma

Hepatocellular carcinoma is less common than hepatoblastoma and usually occurs in the second decade and in children with chronic liver disease, such as cirrhosis secondary to diseases like biliary atresia, Byler's disease and tyrosinemia. It is more often multifocal and invasive when compared with hepatoblastoma with evidence of tumor thrombi in main hepatic veins and portal veins. Imaging and preoperative work-up is the same as quoted for hepatoblastoma with more emphasis on the portal and venous systems which often require careful ultrasound examination and Doppler scanning.

Metastatic spread is to the lungs primarily but other sites are involved depending on the primary site. Scanning of the lung by CT is essential; bone marrow metastases are usually detected by bone marrow aspirates or trephines and liver or lymph node spread is imaged with CT or MR.

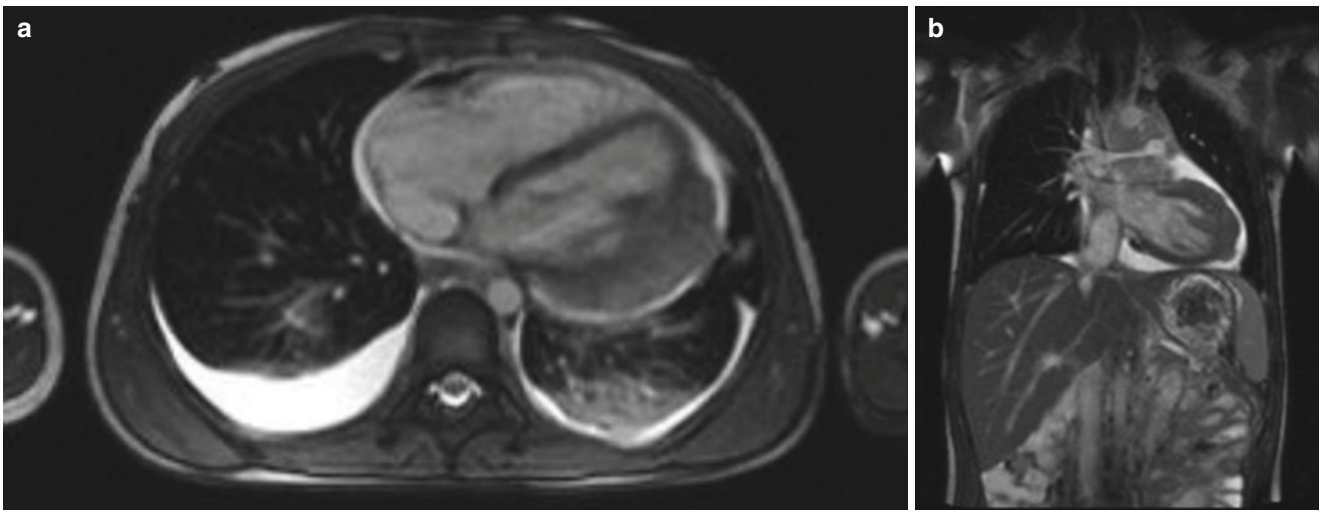


Fig. 7.35 Cardiac Rhabdomyosarcoma. Axial (**a**) and coronal (**b**) single-shot balanced gradient echo MRI sequence through the thorax demonstrate a large exophytic mass arising from the free wall of the left lateral ventricle. There are pericardial and bilateral pleural effusions

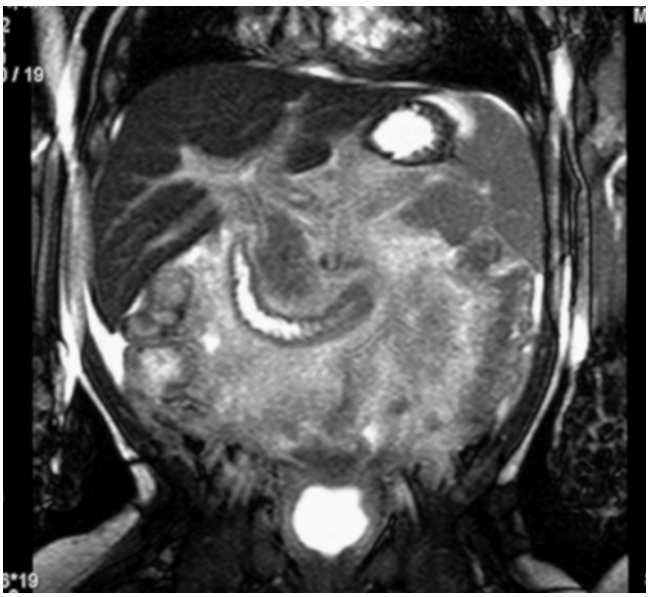


Fig. 7.36 Haemangioendothelioma of the liver. MR in a coronal plane shows the very extensive tumor arising from the liver and extending out to occupy much of the abdomen. A central loop of bowel has been engulfed by the mass

Response to therapy is assessed with repeat cross-sectional imaging and reduction in tumor size; timing is controversial with some debate about the most optimal time as some rhabdomyosarcomas are relatively slow to shrink initially but demonstrate a good response eventually. At the end of chemotherapy small residual masses at the primary site may remain surgically inaccessible e.g. in the orbit or bladder. Imaging and histology may find it difficult to establish definite evidence of residual viable tumor and in some instances conservative surgery with vigilant postoperative follow-up is useful. This requires full imaging of the primary site with MR and/or CT.

Hepatobiliary Rhabdomyosarcoma is rare and characterised by usually embryonal-type rhabdomyosarcoma along the biliary tract. The tumor has a botryoid appearance (grape-like masses) and causes biliary duct dilatation resulting in a characteristic clinical presentation of jaundice and an abdominal mass. If the tumor arises in the distal biliary ducts, it is indistinguishable from other primary tumors of the liver. Imaging is with a combination of ultrasound, CT and MR. As surgical resection is rarely possible, the prognosis is poor. Surgical relief of the biliary obstruction may be necessary and percutaneous or peroperative cholangiography will demonstrate the intraluminal and botryoid tumor.

Pelvic Tumors

Rhabdomyosarcoma

Genitourinary tumors occur at the base of the bladder and prostatic region, the vagina, the testes, penis and perineum. Ultrasound is a very useful modality in bladder tumors and should be performed while the patient has a full bladder. Tumors may arise within the bladder, at the base or at the dome and characteristically have a lobulated, polypoid appearance and are described as botryoid tumors (Fig. 7.40). This appearance is also true of vaginal lesions. Tumors arising from the prostatic region displace the bladder anteriorly and superiorly and have a more defined uniform structure. Compression of the ureters and bilateral hydronephrosis may occur. Both CT and MRI can be used to further delineate the extent of the tumor, including spread beyond the bladder into

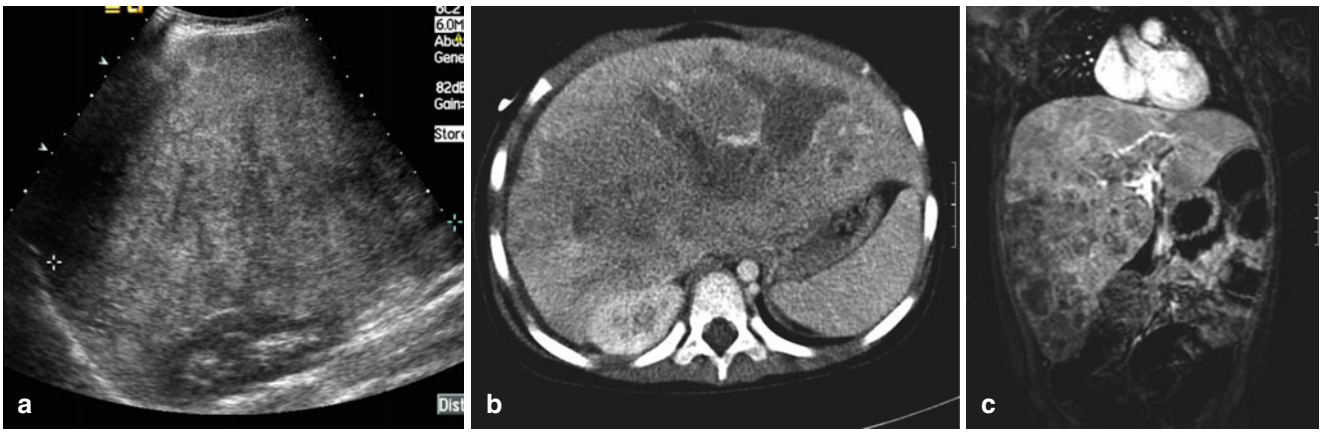


Fig. 7.37 Hepatoblastoma. (**a**) Ultrasound shows extensive involvement of the liver which is enlarged. (**b**) CT shows a diffuse infiltrative pattern. (**c**) Coronal MR (T1 weighted post contrast) showing the extent of liver enlargement. Much of the left lobe is unaffected

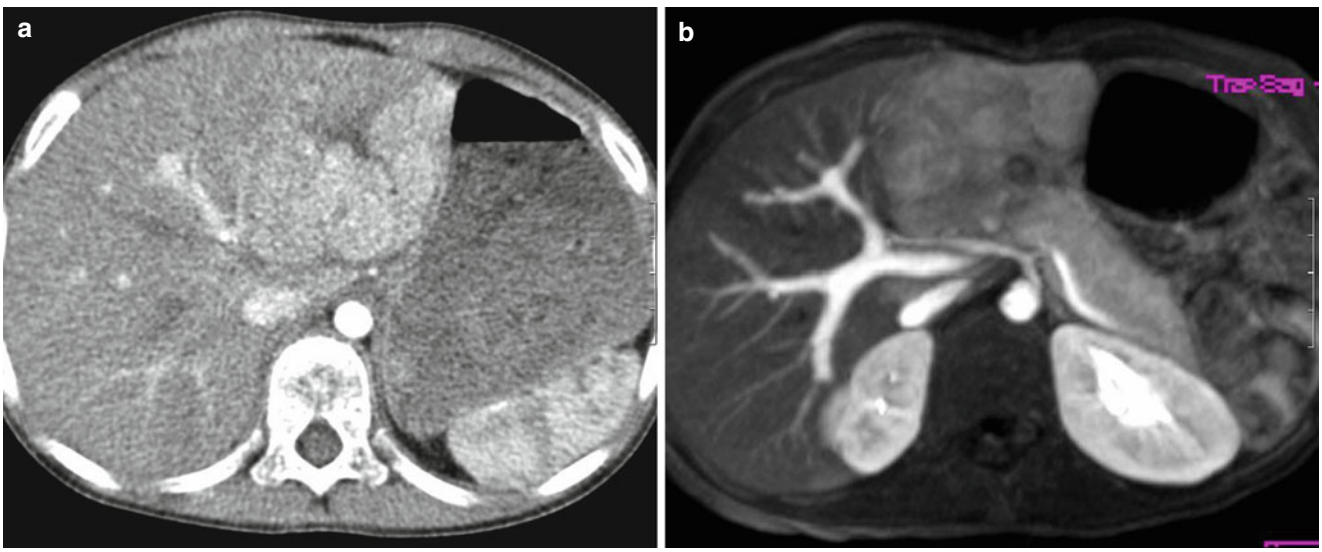


Fig. 7.38 Hepatoblastoma. (**a**) CT of hepatoblastoma showing the tumor but not clarifying its relationship to the hepatic vessels which is essential for staging. (**b**) MR in the same patient with a maximum intensity projection (MIP). This reconstruction technique allows the 'sandwiching' together of several slices to give a better overall impression of the anatomy. The relationship of the tumor to the hepatic artery and portal vessels can now be clearly delineated

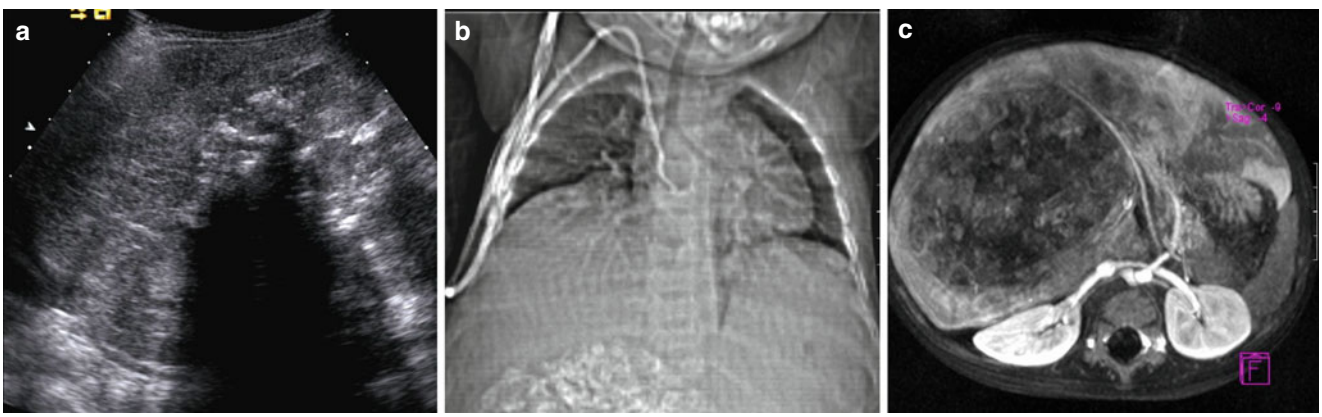


Fig. 7.39 Hepatoblastoma. (**a**) Ultrasound shows a large mass with echogenic foci representing calcification which is typical of hepatoblastoma. (**b**) Topogram from the CT shows the liver mass to be elevating the right diaphragm and also demonstrates the calcification in the tumor. (**c**) MR with a MIP reconstruction gives maximal detail about the relationship of the tumor to surrounding vessels

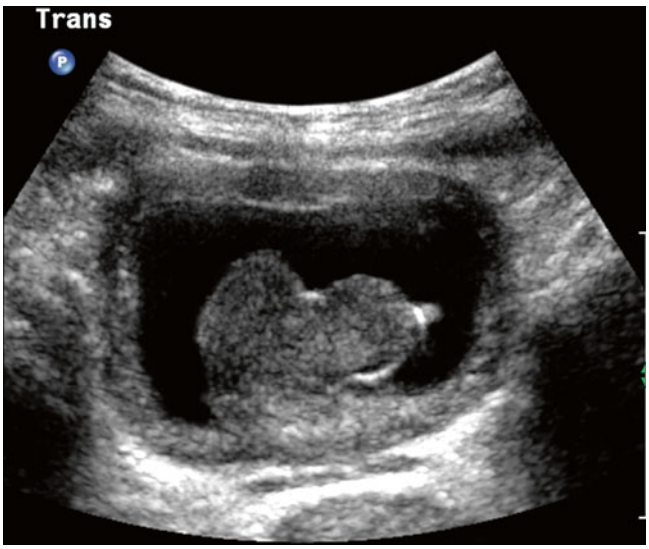


Fig. 7.40 Bladder rhabdomyosarcoma. Ultrasound showing the tumor arising from the bladder base and having a significant exophytic component

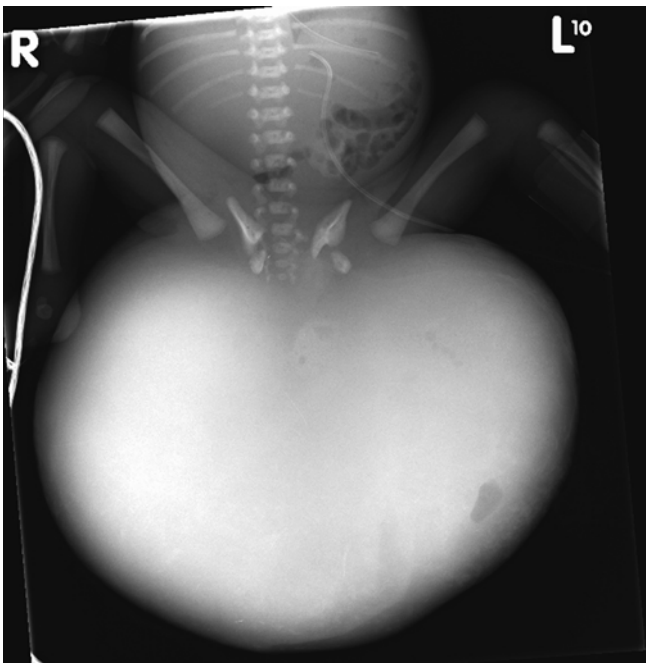


Fig. 7.41 Pelvic radiograph of a neonate showing a huge exophytic sacrococcygeal teratoma splaying the pubic symphysis and the legs

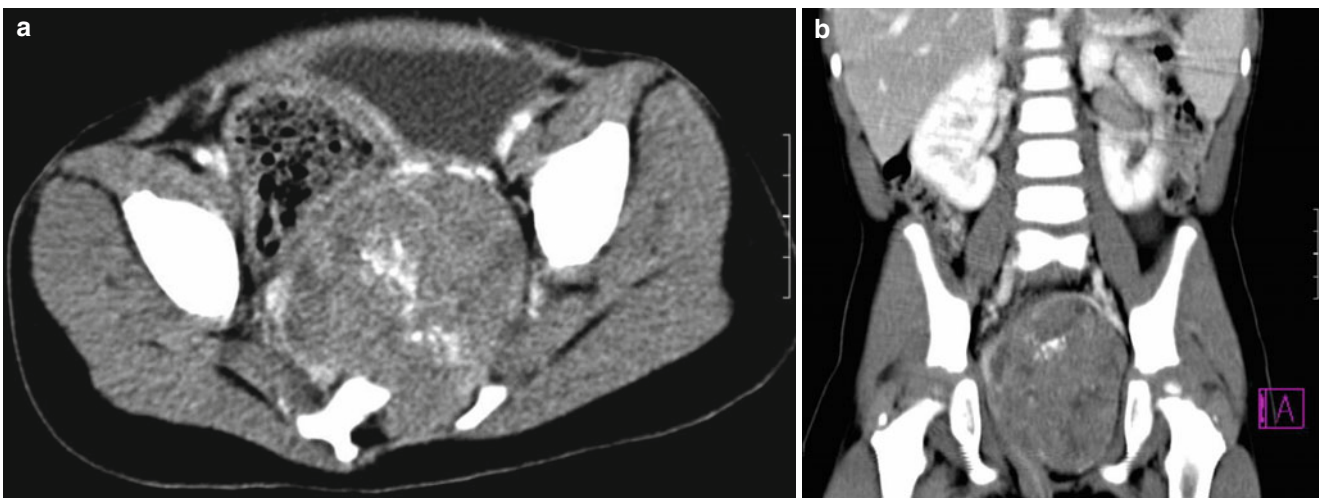


Fig. 7.42 Sacrococcygeal teratoma in a neonate. (**a**) CT through the low pelvis showing the large mass containing calcification and disrupting the sacrum. Note both the rectum and the bladder are pushed anteriorly identifying this as a presacral mass. (**b**) Coronal reconstruction in the same patient demonstrating the diastasis of the pubic symphysis

the perivesical fat, lymph nodes, soft tissues and rectum [52]. MRI is by far superior modality as multiplanar imaging is an advantage when assessing pelvic lesions and in particular is helpful in demonstrating the relationship of the tumor to other organs and the sacral foramina and spinal canal. MRI of genitourinary tumors is mandatory. Paratesticular tumors must have evaluation of regional (para aortic) lymph node by CT/MRI and ultrasound. CT of the thorax is also a prerequisite in genitourinary rhabdomyosarcomas (see above).

Teratoma

Sacrococcygeal tumors occur in the neonate and are readily identified at birth as tumors that are exophytic, usually with a significant external component (Fig. 7.41). Most are benign and imaging is required to enable surgical planning. Whilst the lesion will be apparent on ultrasound, CT will more clearly demonstrate cysts, fat and calcification as well as the rare cases with erosion of the sacrum (Fig. 7.42). For suspected

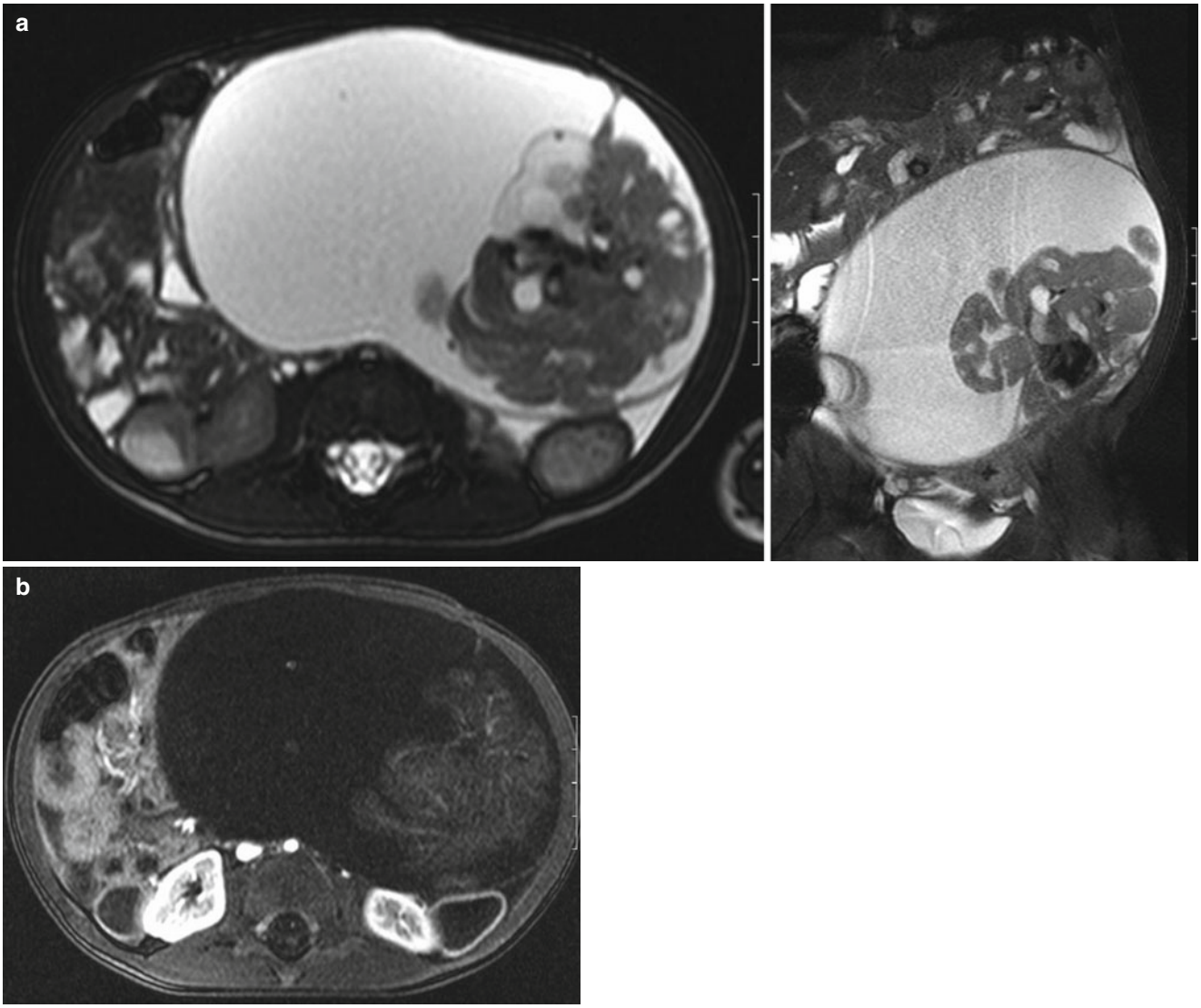


Fig. 7.43 Teratodermoid of the mid abdomen. (**a**) T2-W MR (i) axial and (ii) coronal) through the mid abdomen shows a large predominantly cystic mass, that contains tissues of mixed types. (**b**) There is very little enhancement after gadolinium on this T1-W sequence

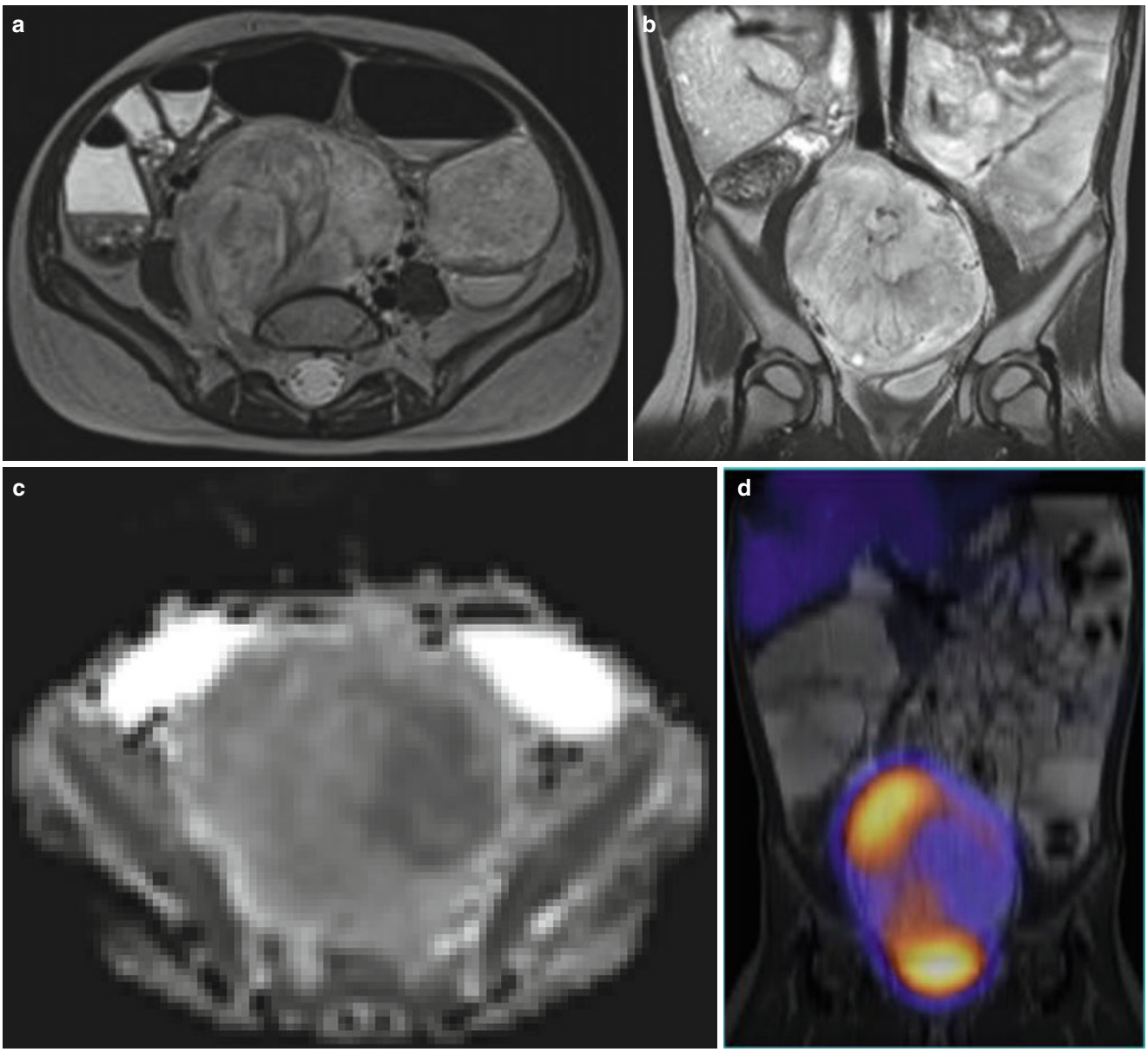


Fig. 7.44 Ganglioneuroblastoma. A large pelvic tumor on axial (**a**) and coronal (**b**) MRI is heterogeneous, enhances and extends into the L5 neural foramen (**a**). The ADC map was very heterogeneous (**c**), and thus although an initial biopsy of the centre of the mass revealed ganglioneuroma (benign), there was concern that the tumor did not respond to chemotherapy. MIBG showed high uptake in the periphery of the mass and the SPECT images fused with a low-dose CT (**d**) confirmed the areas of active tumor. Biopsy of the periphery showed undifferentiated elements indicating ganglioneuroblastoma, adversely affecting prognosis (MIBG images courtesy of Dr Lorenzo Biassoni, Great Ormond Street Hospital, London)

metastases or entire spinal extension MRI in the sagittal plane provides useful anatomical information and is recommended. Teratomas may also occur in the abdomen (Fig. 7.43).

Testicular teratomas also occur in the young infant whereas ovarian and some testicular tumors occur at puberty. Pelvic ultrasound with a full bladder will demonstrate an ovarian mass and CT will often confirm the diagnosis in a mass with cysts, calcification and fat.

Metastatic disease is rare as many pelvic teratomas are benign. However, they occur in both local lymph nodes and the lungs. Therefore an abdominal CT or MRI is recommended in patients with testicular teratomas to look for spread to regional lymph nodes although there is some doubt in the accuracy and significance of the results [19]. Other benign pelvic tumors include ganglioblastoma, although it may be difficult to distinguish this from the more malignant ganglioneuroblastoma (Fig. 7.44).

Second Malignant Neoplasms

Therapeutic advances in the treatment of pediatric cancers have improved the prognosis but have also increased the risk of developing rare second malignant neoplasms (SMNs). Primary neoplasms that are often associated with SMNs include lymphoma, retinoblastoma, medulloblastoma, neuroblastoma and leukemia [55]. The most common SMNs are CNS tumors, sarcomas, thyroid and parotid gland tumors, and leukaemia, especially acute myeloid leukemia. Genetic predisposition, chemotherapy and particularly radiotherapy are all implicated as pathogenic factors in SMN. It is therefore especially important in the life long follow up of these patients that any imaging should avoid ionizing radiation where at all possible. MRI is the optimal investigation as it can cover small or large body areas and provides excellent anatomic detail, particularly in the head and neck [56]. In the abdomen follow up can be by a combination of ultrasound and MRI.

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Tumor Pathology: General Principles

8

Allan G. Howatson and Srinivas Annavarapu

Introduction

The pediatric tumors are unique in that they recapitulate many of the features shared by normal development – rapid increase in size, increased proliferation rate and brisk mitotic activity. Thus, a multidisciplinary approach is required for the diagnosis and management of these tumors. The success of this approach demands close co-operation between specialists from several disciplines and this is best facilitated by good communication and the development of a clear mutual understanding of the nature of the work of these disciplines. This has resulted in dramatic improvements in outcome for children with cancer.

The purpose of this chapter is to establish the role of the pathologist in this multidisciplinary process, to explain the procedures involved, and to indicate the ways in which the surgeon can facilitate this effort. More detailed consideration of the pathology of individual neoplasms can be found in the relevant chapters of this book.

The role of the pathologist goes beyond providing histological diagnosis and includes provision of prognostic information, facilitation of ancillary studies, audit and research. It is important for the surgeons and oncologists to appreciate that the pathological diagnosis is a clinical opinion based on the interpretation of histological findings in the light of clinical details provided, and that it is not just a 'result'. Just like any informed opinion, its formulation is the product of integration of clinical information, imaging studies and other laboratory investigations, as well as gross and microscopic study. It should be obvious that this may take time and that denial of access to such vital information can only delay the process at best or lead to a diagnosis that may result in inappropriate therapy at worst.

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The Diagnostic Specimen

It should be emphasized that all tumor tissue or suspected tumor tissue, with the sole exception of cytology specimens, should be submitted to the pathology laboratory promptly, unfixed, and in a dry, sterile container. The pathology laboratory should always be alerted in advance, so that they are ready to receive the specimen and process it in an appropriate and timely manner.

There are potentially five types of specimens that might be submitted to the pathologist:

1. Cytology specimen
2. Needle biopsy
3. Incisional biopsy
4. Excisional biopsy
5. Resected specimen

The latter may be either pre- or post treatment and may or may not be an attempt at complete surgical extirpation of the tumor – in which case assessment of margins is important.

The Request Form

In each instance it is essential that a standard request form, paper or electronic, is correctly completed and submitted with a properly labeled and identified specimen. The importance of a correctly completed request cannot be overemphasized. Full patient identification details are necessary if errors of attribution of specimens are to be avoided.

The accurate spelling of a name and also of unique patient identifiers such as date of birth and hospital number are essential. The significance of the site of biopsy is self-evident. Frequently the clinical history is omitted or is inad-

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equate. This omission should be unacceptable in modern practice. The pathologist, as a medical consultant, requires clinical information to assist in the integration of evidence derived from gross and histological examination of a specimen if an accurate and clinically meaningful opinion and diagnosis is to be proffered. It is also very useful for the surgeon to have a dialogue with the pathologist beforehand to indicate any specific features of the case that he particularly needs to be resolved. A good and clear communication with the pathologist in advance of taking the specimen is good practice and in the best centers is routine.

Cytology

In general, cytological techniques have not been much employed in the diagnosis of pediatric neoplasia. This probably reflects the relative rarity of pediatric tumors and may be a hangover from the concept of the "small blue cell tumor of childhood" in which various neoplasms of differing biological potential can appear somewhat similar histologically. In addition, most pediatric lesions are not directly amenable to the surface scraping and fluid aspiration methodologies of classical cytology (Fig. 8.1). However, with the advent of fine needle aspiration cytology (FNAC) that can be guided by radiology, this situation has changed rapidly [1].

The imaging [ultrasound or computed tomography (CT)] guided FNAC allows samples to be obtained from otherwise inaccessible areas and allows for greater use of cytology. The most useful cytological investigation with regard to pediatric neoplasia is FNAC in which both superficial and deeply sited lesions become accessible either by palpation and direct puncture or by means of imaging-guided FNAC [2–5]. The use of cytology for primary diagnosis however is limited by the preference of an institution, the technical skills available for obtaining such samples and most importantly, the confidence and experience of the pathologist.

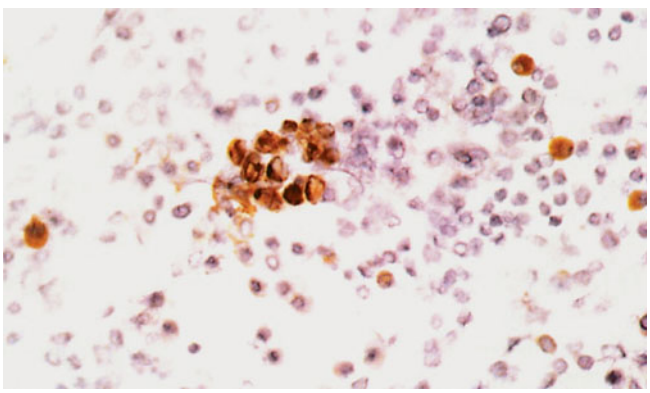

Fig. 8.1 Smear of rhabdomyosarcoma cells stained for desmin, found in ascitic fluid

The question as to who should perform the aspiration is dependent on local circumstances. In the case of palpation and direct puncture, what is more important is that the operator is experienced in the technique of sampling and this can either be a surgeon or a pathologist. Several passages through the lesion with aspiration are required to ensure an adequate sample, and the use of a needle of appropriate gauge (23 or 25) and an aspiration gun to allow single-handed manipulation of needle and syringe are obviously important (Figs. 8.2a, b). In the case of deep-seated lesions, which require imaging guidance, these can be performed by radiologists or other clinicians with expertise in interventional techniques (Fig. 8.3).

A significant feature of a fine needle aspiration is the potential for obtaining "microbiopsies" with preserved histological microanatomy which pathologists frequently find useful in the diagnosis of many pediatric tumors. It is also possible to make cell pellets from an aspiration specimen if pathologists are less experienced in dealing with cytological preparations [6]. These pellets can be then processed and sectioned as histological blocks in the more usual way.

Central to the success of fine needle aspiration is the adequacy of the aspirate and the subsequent production of good smears and cytocentrifuge preparations. It is therefore necessary that the surgeons inform the laboratory well in advance in order for a cytotechnician to be on hand to facilitate the preparation of air-dried and alcohol-fixed smears. A poorly prepared slide can negate the entire procedure and it is frequently difficult to get an adequate smear, particularly if one is not experienced in the preparation of these slides.

Great care is needed if a potentially confusing artifact is to be avoided in the case of alcohol-fixed preparations. Any degree of air-drying in a poorly fixed smear preparation causes artifactual nuclear enlargement and irregularity of chromatin distribution – features seen in malignant cells. It is preferred to have both alcohol-fixed slides stained by the Papanicolaou method and air-dried slides stained by the May-Grun- wald-Giemsa or Diff-Quick methods. These can be either on smears or cytocentrifugation preparations. Cytocentrifugation has the advantage, in fluids and hypocellular samples, of concentrating the cellular component to be studied.

In addition to the standard cellular morphology that can be expected in aspirates of pediatric tumors, it is also possible to apply ancillary techniques to these specimens [7]. Therefore, prior to the aspiration procedure, consideration should be given to the possibility that the diagnosis of a case may benefit from investigations other than morphology. Of particular value are cytogenetics and molecular genetics, immunocytochemistry and electron microscopy. Portions of the aspirate can be allocated to these purposes in order of priority as determined by the clinical presentation of the individual case and presumptive clinical diagnosis.

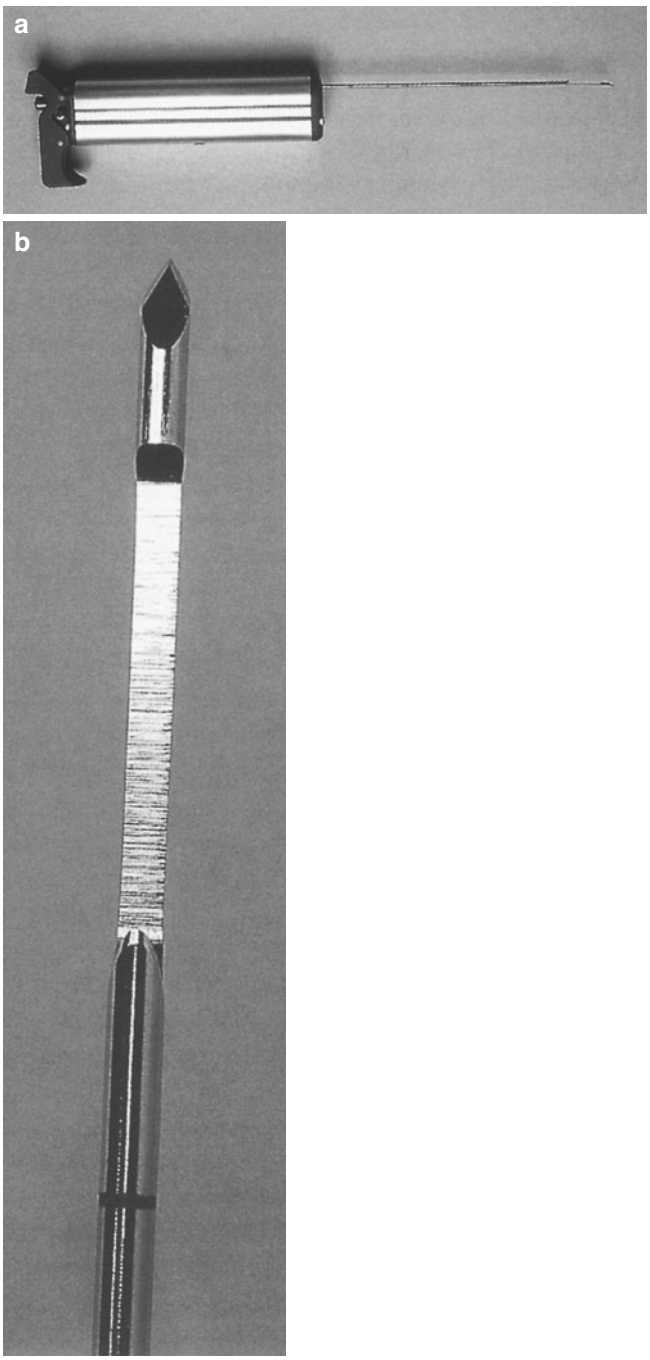

Fig. 8.2 (**a**) Biopsy using an automatic cutting device with a 2.2- cm long needle throw (Pro-Mag 2.2 Manan Medical Products, Inc. Northbrook, USA) and a 14-gauge cutting needle (Manan Medical Products Inc). The biopsy is taken during suspended inspiration. (**b**) Close up of needle tip

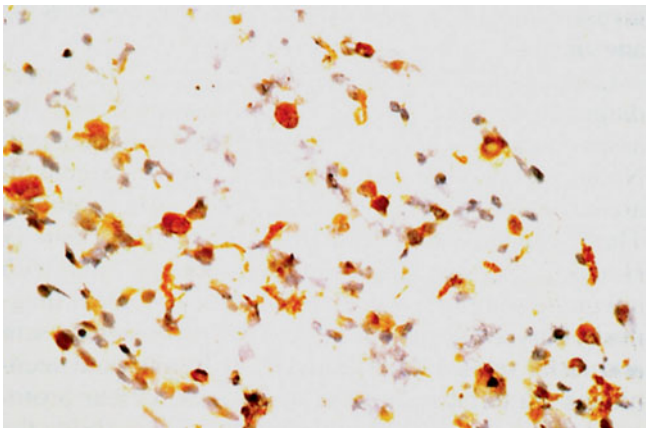

Fig. 8.3 Fine needle aspiration of an embryonal rhabdomyosarcoma stained for desmin

It should be understood that the cytological diagnosis of pediatric neoplasms is a difficult area and expertise is developed over a period of time. It is not possible for a pathologist without experience of this technique to receive a specimen and be expected to make an erudite diagnosis at once. The learning curve is long, and with the paucity of material resulting from small numbers of cases it can be an area fraught with difficulty. It is often sound practice for the pathologist to aspirate resected specimens in the laboratory in order to practice looking at more material than otherwise would be submitted for primary diagnosis.

The complications of fine needle aspiration are minimal. Local bleeding is usually of minor significance even with substantial vascular lesions and needle aspiration of lesions in the lung very seldom lead to pneumothorax.

Cytology has another significant use in pediatric neoplasia and that is to identify infections related to immunocompromise resulting from therapy. Cytological preparations of skin scrapings can identify viral infections such as herpes simplex and infections of the respiratory tract, e.g., Pneumocystis carnii, fungal infections, and viral infections such as Cytomegalovirus (CMV), are also amenable to diagnosis in bronchial lavage specimens by cytological techniques.

It is clear that cytological diagnosis will become an increasingly important part of the pediatric pathologist's workload because it is a relatively noninvasive technique and reduces the use and risk of anesthesia.

Cases which will benefit most from cytological diagnosis involve "neck lumps" and in particular the assessment of cases of lymph node enlargement. Nodal pathologies with persisting node enlargement are a frequent cause of referral to pediatric surgeons. These can be either reactive or neoplastic (usually Hodgkin's or non-Hodgkin's lymphoma) and with adequate sampling are amenable to cytological diagnosis thus avoiding open biopsy with resulting scar and risks related to anesthesia. If cytological techniques are to be applied in such cases, a clear protocol for the pre-biopsy assessment of the child, the obtaining of an adequate sample by a competent experienced operator, the performance of ancillary studies (particularly microbiology) and a plan for follow-up and open biopsy in cases of persistence of the

mass must be in place and followed in all instances if false negative diagnoses are not to be detrimental to the patient. Kardos et al. [8] laid out such a protocol that fulfills these requirements and provides a model of sound practice – it is highly recommended.

It must be emphasized that cytology alone cannot provide all the answers required of a tissue diagnosis and the need for larger biopsy samples will remain with us for the foreseeable future especially when fresh tissue is required for special biological and cytogenetic investigations that may influence therapy.

The Diagnostic Needle Core Biopsy

The core of tissue derived from a needle biopsy either by use of a Tru-cut needle [9] or the more recently available biopsy gun can provide adequate tissue to allow accurate diagnosis of the majority of pediatric neoplasms [10]. More than one core, and preferably at least three, should be taken to allow for tumor heterogeneity and to permit ancillary investigations. With the modern instruments, trauma of the tissue core is usually minimal and although the sample is small, typically 10 × 1 × 1 mm, it is usually possible to obtain material for ancillary studies and for immunohistochemistry. The paucity of material does, however, frequently make it difficult for the pathologist to provide other information, for instance in relation to the presence or absence of anaplasia in nephroblastoma, tumor grading in soft tissue sarcoma or the mitosis/karyorrhexis index (MKI) and other prognostic features in neuroblastoma.

In general, directed biopsies using ultrasound and CT guidance give better samples than a blind biopsy performed either percutaneously or under direct vision at surgery. Drying artifact during transit of fresh samples to the laboratory is a potential problem and rapid transfer in a closed container is essential.

Incisional Biopsy

Incisional biopsies under direct vision provide very adequate tissue samples, which permit all necessary ancillary studies to be performed in the majority of cases. The surgeon will of course have placed his incision to avoid any potential compromise of subsequent resection and to minimize contamination of surrounding structures and tissue compartments. The surgeon should avoid crushing the tissue with forceps during removal. In the archetypical small blue cell tumors of childhood the cells are fragile and injudicious application of force renders the tumor cells into an amorphous smear of nuclear material impervious to diagnosis (Figs. 8.4a, b). The surgeon should also avoid placing the tissue on any surface which might dry out the tissue during transit to the laboratory.

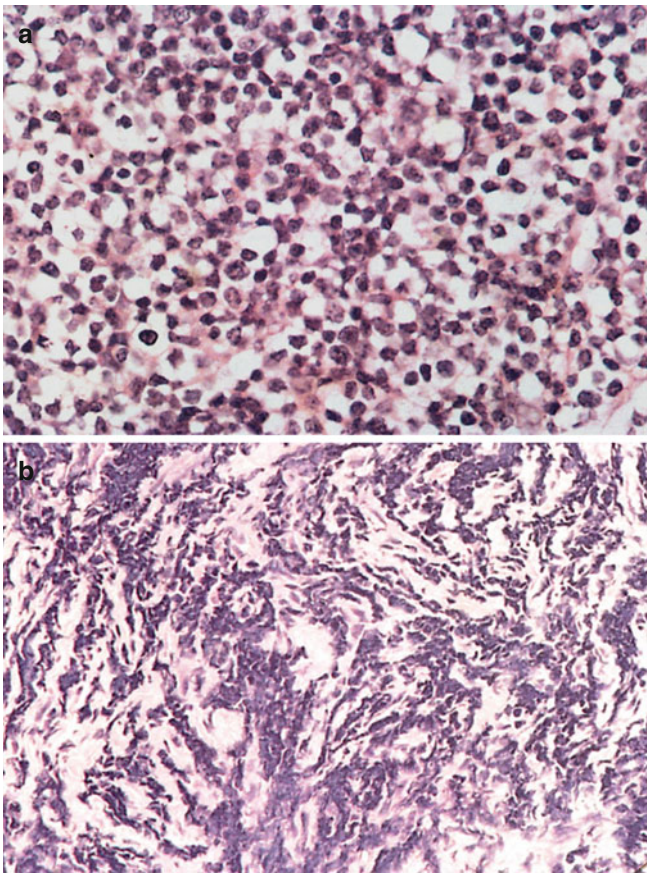

Fig. 8.4 (**a**) Intact biopsy of Ewing's sarcoma. (**b**) Surgical crush artifact of a biopsy of a Ewing's sarcoma

Covering the sample in gauze delays drying artifacts. The skin incision must be placed such that further surgery will include this area, as the biopsy will inevitably have seeded cells into the wound.

Excisional Biopsy

Excisional biopsy entails the apparent complete removal of a small lesion, perhaps up to 5 cm in its greatest dimension. Very frequently this involves the "shelling-out" of a lesion such as lymph node or soft tissue tumors of the limbs. It is usual in the latter situation for tumor to be left behind as the plane of dissection is frequently through the tumor pseudocapsule and not through noninvolved healthy tissue [11]. Once again, this technique provides very adequate material for ancillary studies such as cytogenetics, molecular genetics, and other research activities. The surgeon should consider marking the margins of specific interest if he or she believes that the excisional biopsy represents a clearance of the tumor, and the tumor should not be incised prior to transfer to the pathology department as excision margins will be compromised or contaminated by tumor, giving rise to a risk

of a false diagnosis of incomplete excision resulting in inappropriate further surgery or adjuvant therapy. Again, covering the sample in wet gauze delays drying artifacts.

Surgical Resection

A definitive surgical resection can either be performed as a primary surgical procedure or following pre-operative chemotherapy or radiotherapy. The advent of preoperative therapy allows tumor shrinkage and reduction in vascularity. Many tumors, which were deemed not amenable to resection prior to therapy, may become resectable after chemotherapy (Fig. 8.5) [12, 13].

The margins of the resected specimens should be marked in all cases. It is important that the surgeon should not incise these specimens prior to receipt in the pathology department since this may lead to capsular retraction and render the margins contaminated, making it impossible for the pathologist to be sure that the tumor is completely excised with a margin of clear noninvolved tissue. Any lymph nodes or other tissues removed at the time of primary or post therapy resection should be specifically labeled with their site clearly indicated in the request form and on the specimen containers. It is insufficient to say "lymph node" and not to specify the site from which it is taken because the site of lymph node involvement may determine the stage of the disease and fields for any subsequent radiotherapy.

Specimen Handling in the Pathology Department

Assessment of a specimen submitted for diagnosis involves both gross and microscopic examinations. Even the smallest of biopsy specimens can yield useful information on gross examination [14]. The presence of necrosis, hemorrhage, or a variegated appearance may indicate a heterogeneous histological structure. In the case of larger specimens, the gross examination takes on more importance, particularly with regard to the surgical margins of excision and the vascular and neural margins if appropriate.

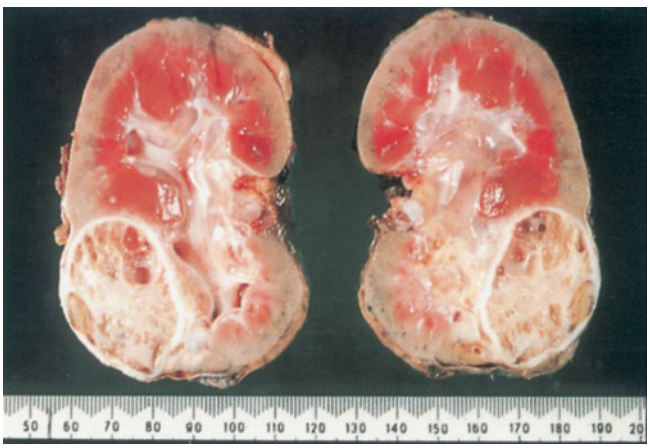

Fig. 8.5 Nephroblastoma after chemotherapy

All tumor specimens, biopsies and resections, should be submitted to the laboratory fresh, i.e., not in fixative. There should be no delay in the receipt of this material in the laboratory and prior notification is essential if appropriate preparations for taking ancillary study samples are to be made in the laboratory. The range of investigations and sampling will obviously be dependent on the size of the sample submitted for diagnosis. In the case of a cytology fine needle aspirate, it is often possible to have some cells submitted for cytogenetic analysis and some for electron microscopy, but often the entire specimen is used for primary cytologic diagnosis. Needle biopsies represent a larger sample, but the volume of material is still extremely small and it may be that only a small piece for cytogenetics can be spared, with the remainder being submitted for histological examination. Incisional biopsies, excisional biopsies, and resected specimens should all provide sufficient material for histological diagnosis, cytogenetics, electron microscopy, and storage of tissue for subsequent molecular studies if required (tumor banking). In addition, it is also often appropriate to submit material for microbiological investigation, particularly in instances of lymphadenopathy. Additional samples may also be taken for ongoing clinical trials if relevant (Fig. 8.6).

The use of intraoperative frozen section for histological diagnosis in pediatric neoplasia should be confined to very specific indications. The desire of the surgeon to be able to tell the parents of the nature of the diagnosis and likely prognosis at the end of the operation is not a sufficient reason for a frozen section to be performed. The only uses for a frozen section during operation are to confirm the presence of tumor, to ascertain that adequate diagnostic material of the native lesion is present in the sample excised, and to assess the need to take wider margins if required. It is often difficult, as a result of artifact related to the frozen section process, to come to a specific histological diagnosis in some of the small, round cell type and spindle cell type pediatric neoplasms. It is wholly inappropriate to use the frozen section diagnosis as a definitive statement for discussions with parents. Such discussions should await the formulation of a definitive paraffin histology-based diagnostic opinion and report.

In the case of excisional biopsy and resection specimens in which complete surgical extirpation of the tumor is intended, evaluation of the surgical margins is important with regard to decisions for further local and systemic therapy. A technique that is widely employed to determine true surgical margins is to paint the entire specimen with Indian

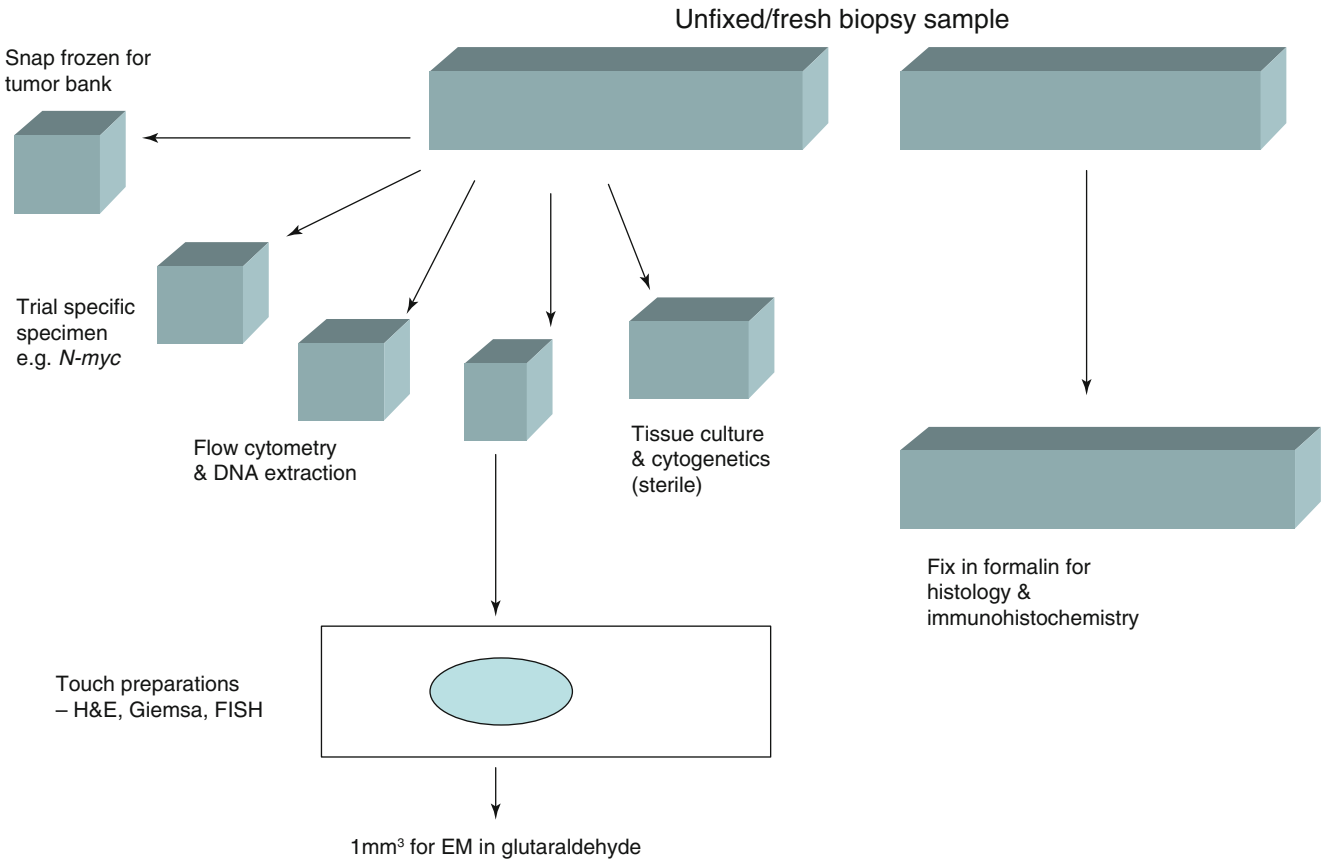

Fig. 8.6 A guide to handling a pediatric tumor biopsy specimen

ink ("inking") or other suitable dyes prior to the incision of a specimen. The dye must be dried onto the surface of the specimen before the specimen is placed in fixative, but if the margin is in question it is a valuable technique. It is axiomatic that the surgeon should not compromise the margins of excision by incising the specimen prior to submission to the pathologist.

Gross examination is vitally important in order that one can be sure that the blocks being sampled from the specimen relate to true surgical margins and not to areas of artifact. It is therefore important that the specimen should be thoroughly examined macroscopically, weighed where appropriate, measured, and photographed, preferably prior to fixation. Where fresh tumor samples must be taken for ancillary studies prior to fixation it is best to incise the specimen through an area in which there is no doubt that excision is complete, i.e., one with a thick intact capsule or covering layer of normal tissue.

Ancillary Studies

Ancillary studies are essential, not optional, in all cases of pediatric neoplasia in which material is submitted for diagnosis. The majority of new SIOP trial protocols include mandatory sampling for biological studies. It is routine practice in our laboratory to take samples in culture medium for cytogenetics as the minimum additional investigation in every case. With more substantial specimens, i.e., open biopsies or resections, a more detailed protocol is applied (Table 8.1). In taking these samples, every effort should be made to use "sterile technique" and sterile disposable instruments, etc. This is particularly important for those samples to be cultured for cytogenetic studies. In the USA, the Children's Cancer Group (CCG) provide kits for specimen procurement in cases of pediatric neoplasia thus facilitating diagnostic studies and ongoing biological research into these complex and fascinating conditions.

Both normal and tumor tissues should be sampled and stored whenever possible. The samples should be taken as promptly as possible after removal of the specimen from the patient. This must be done by the person reporting the specimen, i.e., the pathologist. Therefore, a short delay in transit to the laboratory is acceptable. Our procedure is to leave the photography until after samples have been taken. With a large specimen it is possible to section it and, if homogeneous, take the samples from one half leaving the other for photography. It is always possible to take the samples without compromising assessment of margins. If studies of

Table 8.1 Pediatric neoplasia: ancillary studies (excluding "routine" paraffin section immunohistochemistry)

Cytogenetics	Tumor and normal tissue in cytogenetics medium
Molecular genetics	Tumor and normal tissue snap frozen in liquid nitrogen and stored in liquid nitrogen (gaseous phase) or at –80 °C. Sample held on water ice for mRNA studies to be dealt with without delay
Immunohistochemistry/Fluorescent in situ hybridization (FISH)	Snap frozen in OCT medium, store at –80 °C
Touch imprints (>10) for FISH	Air dry
Electron microscopy	Paper-thin section or 1 mm cubes in 4 % gluteraldehyde
Tissue storage (long term)	Tumor and normal tissue for research, flow cytometry, etc., s stored in liquid nitrogen (gaseous phase) or at –80 °C

mRNA are contemplated, then the tissue sample should be stored in sterile conditions on water ice prior to uplift. The delay in taking the sample should be as short as practicable as mRNA is susceptible to relatively rapid deterioration.

In the case of heterogeneous lesions, the sampling should incorporate multiple areas. Foci of obvious necrosis can be avoided but hemorrhagic areas are often the most viable, and firm fleshy areas may be more fibrous and contain fewer tumor cells. The concept of heterogeneity does not apply to macroscopic appearances only. Within a large tumor mass there is the possibility of clonal heterogeneity and this may be significant if assessment of prognostic features is to have a bearing on the intensity of therapy. Examples would be the identification of N-myc amplification in composite nodular ganglioneuroblastoma or 1p deletion in neuroblastoma [15] – bad prognostic features that can be variably present in different parts/cellular nodules of a tumor, and if only one area is examined a false negative result may be obtained. It is therefore good practice to take tissue from several areas of all substantial tumor specimens in order to minimize this potential problem.

The number of blocks that should be taken for histological examination from a large specimen varies according to the individual case. A useful rule of thumb is to take a minimum of one block for each centimeter of the largest dimension of the lesion, but this should not be regarded as an absolute and in most instances many more blocks are indicated. Points of interest and resection edges of nerves, vessels, and soft tissue margins of questionable clearance which have been indicated by the surgeon by means of marker sutures or in the request form should receive particular attention and will require a larger number of blocks to be taken. Tissue blocks should be taken from normal tissue as well as the lesion. Sectioning of a block of appropriate size is much easier after fixation. The site of origin of individual blocks should be recorded on an appropriate diagram or photograph of the specimen at the time of sampling (Fig. 8.7). This allows the pathologist to return to a specific area of the specimen if initial histological examination identifies additional features requiring further detailed assessment, e.g., focal or diffuse anaplasia in nephroblastoma [16]. It is good practice to take "mirror image" blocks from the tumor with one block frozen down in liquid nitrogen for research purposes while the other is processed for histology. This allows molecular studies, preparations of microarrays, and morphological studies to be conducted on the same potentially clonal areas of an individual tumor.

Fixation and Processing

A number of standard fixatives are available to the pathologist, but the most flexible given the need for speed of fixation, lack of toxicity, etc., is 10 % buffered formalin solution. It is possible to perform electron microscopy on tissues, which have been in 10 % formalin fixative even although ultrastructure is degraded. This fixative is also ideal for most immunohistochemical studies.

In North America, the fixative B5 (sublimate sodium acetate formalin) is widely used for lymph node and renal biopsies. Other commonly used fixatives include Bouin's, Zenker's, and Carnoy's. All have advantages for specific indications but for general use these are outweighed by problems of cost, preparation, and disposal.

Heat fixation by microwave using a standard domestic microwave oven is effective for specimens of substantial size, but we have found a significant frequency of unacceptable cellular artifact and do not use this method as routine.

The volume of fixative is critical. A ratio of 10:1 fixative to specimen is an acceptable minimum. It is important that the specimen should be entirely immersed in the fixative solution. The purpose of these fixatives is to complex the proteins in the tissue, stabilizing tissue and thus stopping the autolytic processes that would degrade tissue structure and ultrastructure.

The penetration of fixative into tissue blocks is one of the most significant rate-limiting factors in determining how long it takes to have material available for the pathologist to study under the microscope. In general terms formalin will penetrate at a rate of 1 mm/h and will go on for a considerable period slowly penetrating into the middle of large tissue specimens. Other fixatives penetrate much more slowly or only penetrate the surface of the tissue sample to any great degree.

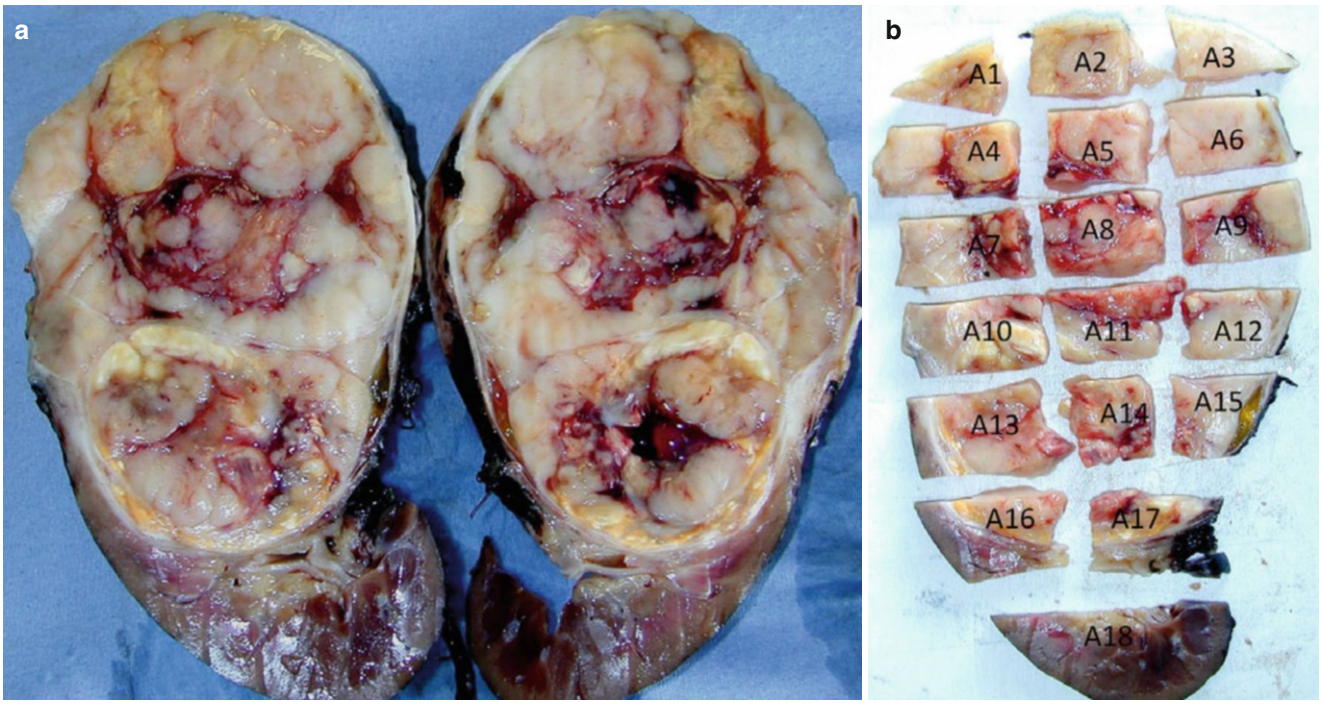

Fig. 8.7 Nephroblastoma after chemotherapy. A photographic block-sheet of the specimen at the time of sampling allows the pathologist to re-visit area of interest

The penetration of formalin is temperature- dependant and while it is entirely satisfactory at as low as 4 °C, it is probably accelerated at higher temperatures and this is one means by which the fixation time can be reduced if there is an urgent requirement for a tissue diagnosis. Standard vacuum embedding processing machines also accelerate both fixation and processing and save time. One can process needle core biopsy samples over a period of only 4 h and have a paraffin section cut and stained for viewing within 5 h of the biopsy having been taken. However, this means that we must accept some degradation in morphology and perhaps also compromise immunohistochemical studies as the fixation may not be as good as it would be with a longer fixation, and processing period and protein linkages which expose or mask antigens are not optimal. More usually, tissue samples are fixed for approximately 24 h before being processed on a cycle that takes between 16 and 18 h to remove tissue water and fat and to replace these with paraffin, providing a paraffin block for sectioning. Dehydration is achieved by use of alcohols; fat is removed by alcohol and xylene (Table 8.2). For bone lesions, decalcification may be necessary and will delay block sampling and subsequent histological examination by several days.

The new generation of tissue processors utilize microwaves to accelerate fixation and this together with use of alternative solvents allows needle biopsies to be processed within 1 h, or a block of a tumor resection (5 mm thickness) to be processed in 3 h. Decalcification of a bone tumor sample can be completed in 12 h.

Table 8.2 Typical tissue processing cycles (vacuum embedding)

Overnight (standard blocks)			Rapid (small biopsies)		
1	120	45	1 Formalin	Passed	
2	30	No heating	2 Water	Passed	
3	60	No heating	3 70 % Spirit	Passed	
4	60	No heating	4 Methylated spirit	25	45
5	60	No heating	5 Methylated spirit	25	45
6	60	No heating	6 Methylated spirit	25	45
7	60	45	7 Methylated spirit	30	45
8	90	45	8 Absolute alcohol	30	45
9	90	No heating	9 Xylene	30	45
10 Xylene	90	No heating	10 Xylene	30	45
11 Wax	45	60	11 Wax	15	60
12 Wax	45	60	12 Wax	15	45
13 Wax	45	60	13 Wax	15	45
14 Wax	45	60	14 Wax	30	45

The Preparation of Histological Material

The histological examination of surgical material is an essential part of the diagnostic process. This requires the cutting of sections from the paraffin block, usually at a thickness of 4–5 μm and these sections are then stained with a variety of dyes, which can demonstrate the various component parts of the tissue sample in question. The standard histological stain for daily use is the hemotoxylin and eosin (H & E) stain, which provides a very good demarcation between nuclei, stained

blue with hematoxylin, and the cytoplasm, stained varying degrees of pink with eosin.

The diagnostic utility of other special stains has been to a considerable extent superseded by the development of immunohistochemistry. However, a limited number of these stains remain useful in specific tumors (Fig. 8.8, Table 8.3).

Formalin-fixed paraffin-embedded tissue sections are also utilized for immunohistochemical studies. Cytology touch preparations and frozen sections are better for in situ hybridization studies and are also essential for immunofluorescence studies when appropriate.

The Diagnostic Process

The development of a final diagnostic opinion is the result of consideration and integration of several sources of information, i.e., clinical presentation, anatomic localization (clinical and imaging), laboratory investigations (e.g., biochemistry) and operative appearances. With this information on hand, the macroscopic examination and sampling of a specimen leads to the final step of histological examination.

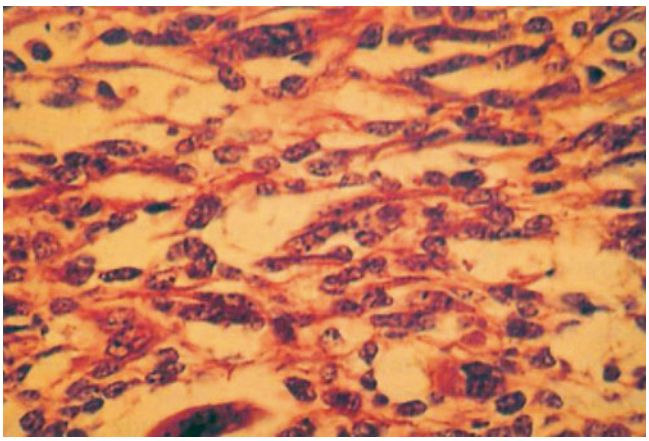

Fig. 8.8 PTAH staining showing cross-striations in a rhabdomyosarcoma

Table 8.3 Special stains in pediatric neoplasia Stain

Stain	
Periodic acid-Schiff (PAS) ± diastase	Glycogen in Ewing's sarcoma
Reticulin	Reticulin fibers (types III and IV collagen) in soft tissue tumors
Phosphotungstic acid-hematoxylin (PTAH)	Cross-striation in rhabdomyoblasts (little used)
Masson-Fontana-melanoma Grimelius	Melanin pigment in clear cell sarcoma and Argyrophilic reaction in paraganglionoma
Perls Prussian Blue pigment von Kossa	Ferric iron Calcium
Alkaline phosphatase	Positive in osteoblasts in osteosarcoma

While it is true that a diagnosis can be inferred from any or all of the steps outlined above, there is no doubt that only histology can provide a definitive diagnostic opinion and this examination will also deliver prognostic information relevant to the individual case.

In making a histological diagnosis the pathologist assesses the presence of features of malignancy and seeks evidence of differentiation, i.e., the development of features indicative of the cell lineage of origin which can be recognized by H & E staining, special stains, and immunohistochemical studies.

The histological diagnosis of malignancy is based on assessment of a lesion with regard to the age of the patient, the site or organ of origin, the nature of the lesion in relation to surrounding structures, the presence of necrosis, degree of organization/differentiation, and cellular morphology. For example, a highly cellular mass in the middle of the kidney is likely to be a neoplasm. Necrosis of a spindle cell proliferative lesion of soft tissue is a strong indicator that one is dealing with a sarcoma. In all instances infiltrative invasive lesional margins as opposed to encapsulated/pseudo-encapsulated expansile margins suggests malignancy. These features and the presence or absence of differentiation do not absolutely predict behavior and the cellular morphology is important. Nuclear enlargement with increased hematoxylin staining density (hyperchromatism) and variation in nuclear and cellular size and shape (pleomorphism) are typical features of neoplasms. An increased mitotic rate with atypical and abnormal mitotic figures is frequently but not invariably seen. Thus, it is the assessment of the lesion both in isolation and in the context of its surroundings that leads to a diagnosis. Frequently, however, the tumor may present as a lesion of small blue cells or an apparently undifferentiated sarcoma. In these instances the search for evidence of differentiation indicating the cell lineage of the tumor requires studies of molecular or ultrastructural differentiation by immunohistochemistry and electron microscopy.

Patterns of regression in childhood tumors can be spontaneous or treatment-induced and may present as either maturation or true regressive changes, e.g., necrosis, fibrosis, cystic degeneration, myxoid degeneration, or calcification [17–19].

Spontaneous regressive features, i.e., not related to therapy, can indicate some prognostic potential. Necrosis is generally regarded as a feature of aggressive, fast-growing malignant tumors but may also indicate the potential for a good response to chemotherapy because of the high cell turnover rate, although this is not true for rhabdoid tumors. The presence of a significant lymphoid cell infiltrate is sometimes an indication of a better prognosis lesion, e.g., inflammatory fibrosarcoma, or a pseudotumor. Myxoid change tends to be a feature of benign or slow-growing tumors of low malignant potential. Myxoid change in botyroid rhabdomyosarcoma is associated with better prognosis.

Maturation of untreated tumors is characterized by increasing differentiation towards mature tissue phenotype. The classical example is neuroblastoma where spontaneous maturation to ganglioneuroblastoma or ganglioneuroma is well recognized. In the case of ovarian teratomas the presence of gliomatosis peritonei is a marker of a good prognosis. Lipoblastomas mature with age into lipomas.

Similar patterns of regression and maturation are seen as an effect of therapy and can pose problems for the pathologist if they are so marked as to preclude most of the prognostic assessment of a tumor (Fig. 8.9). Chemotherapy frequently downstages a tumor – an effect most often seen in nephroblastoma. Post-chemotherapy cystic change in nephroblastoma is common and care must be taken not to mistake this feature and make a diagnosis of cystic partially differentiated nephroblastoma. In osteosarcoma the post- chemotherapy assessment of tumor response is a very accurate predictor of prognosis. If 10 % or more of the tumor cells remain viable after a course of intensive therapy then the prognosis is poor.

It should be remembered that tumors are composed of clones of cells, which as a result of mutation during tumorigenesis may have different patterns and degrees of response to therapy. This may result in a very heterogeneous response with fibrosis of tumor adjacent to viable lesional tissue. Occasionally the therapy seems to select out a particularly "resistant" aggressive clone and the pattern of dedifferentiation is seen. The prognostic implications of maturation under the influence of therapy are not yet clear and similarly metaplasia is not thought to have prognostic significance.

Immunohistochemistry

Immunohistochemistry is a vital tool in diagnostic histopathology and is one of the most useful ancillary investigation in the diagnoses of pediatric tumors. In recent years there has been a massive expansion in the use of antibodies in tissue diagnosis. The principal influence has been in adding a degree of objectivity into the essentially subjective area of histological diagnosis by confirming lineage differentiation in embryonal and undifferentiated neoplasms (Fig. 8.10a–g).

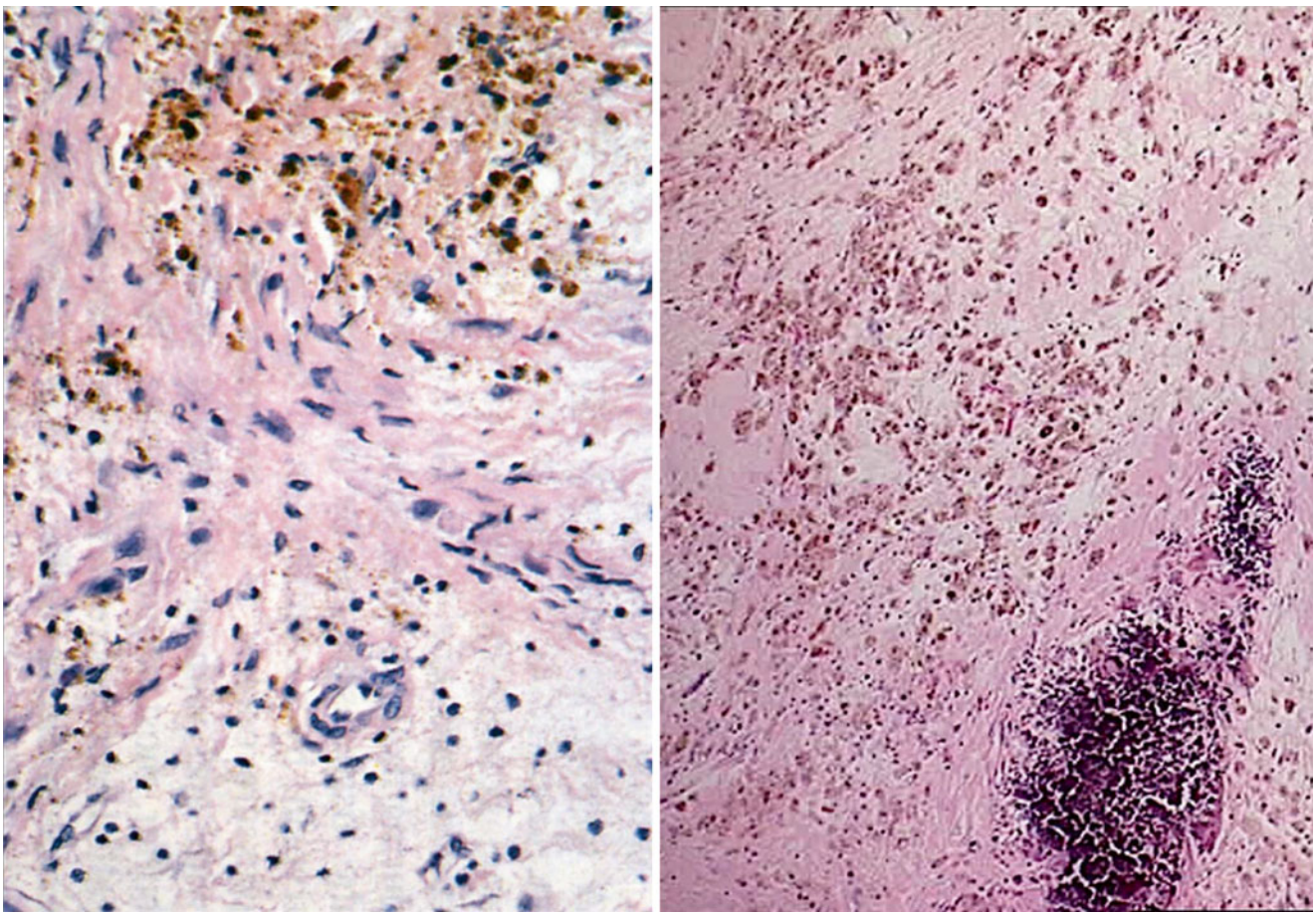

Fig. 8.9 Histology of an embryonal rhabdomyosarcoma showing postchemotherapy changes. Foamy macrophages, hemosiderin-laden macrophages, calcification and fibrosis

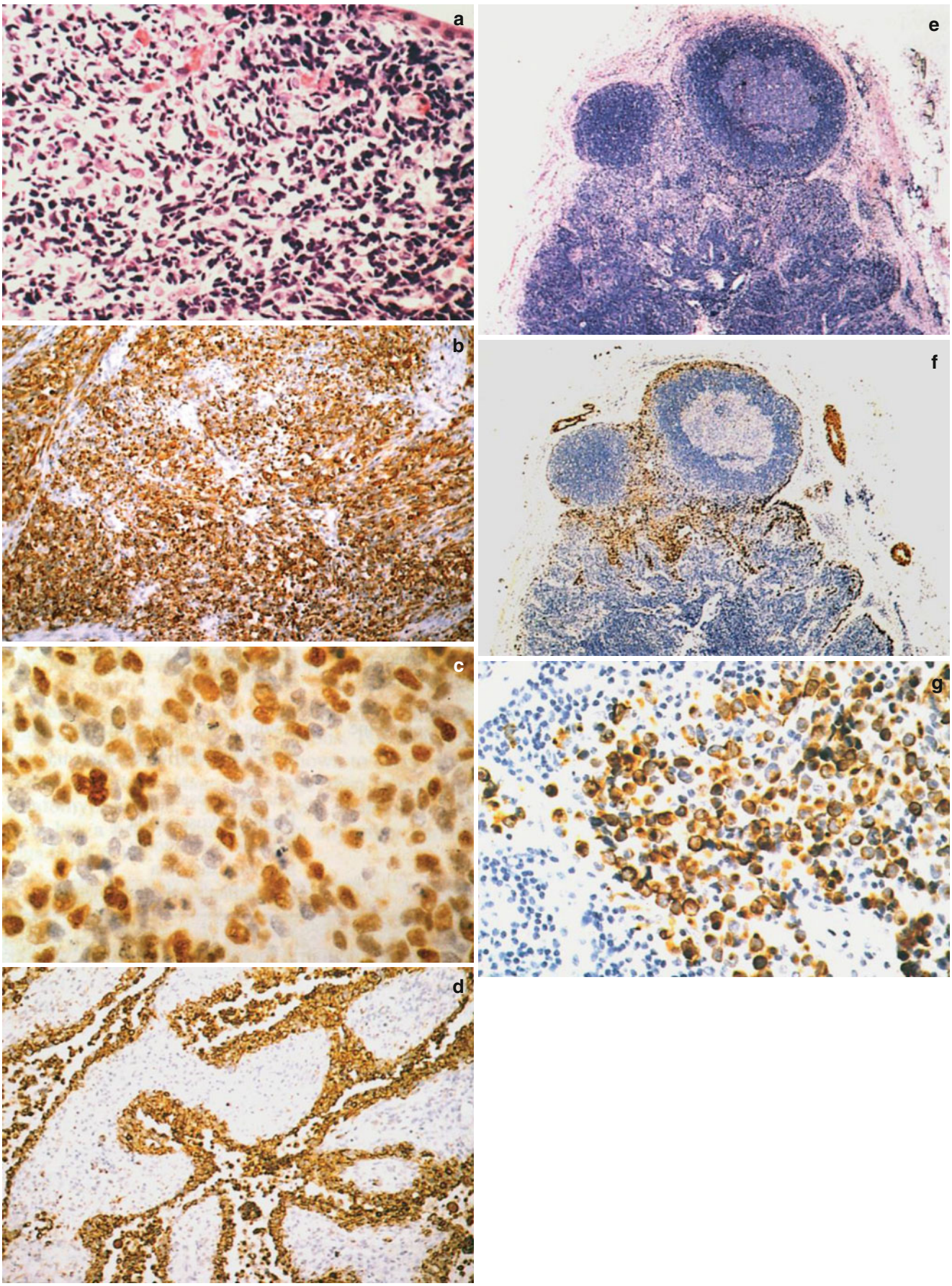

Fig. 8.10 (**a**) Embryonal rhabdomyosarcoma (H & E stain). (**b**) Desmin stain of rhabdomyosarcoma. (**c**) Myo D 1 stain of rhabdomyosarcoma. (**d**) Alveolar rhabdomyosarcoma desmin stain. (**e**) Lymph node (H & E). (**f**) Lymph node with desmin stain. (**g**) Magnification of (**f**)

Immunohistochemistry is based on the premise that a particular component of a tissue, acting as an antigen, can be identified by a specific antibody carrying a label that can be rendered visible. A number of techniques are routinely used, but the underlying philosophy is the same for all. The variation in technique relates to attempts to maximize the intensity of the label signal indicating the presence of a specific antigen of interest.

Two types of antibodies are used. The first are polyclonal and tend to be less specific and sensitive while the second, which are now more commonly used, are monoclonal antibodies which allow for the use of very sensitive and highly specific detection techniques. The most commonly used methods of demonstrating the presence of antibody binding to tissue antigen are the peroxidase-antiperoxidase immune complex method and the avidin-biotin immunoenzymatic method. More detailed consideration of the principles and techniques can be found in a variety of specialist texts [20, 21].

The antibodies are named either by reference to the antigen (protein product/structure) to which they bind or in the case of leukocytes and related antigens, by the cluster differentiation antigen designation (CD) which have been determined at a series of international workshops.

Sensitivity and specificity are of vital importance. A number of techniques have been employed to increase sensitivity and, in general, these attempt to unmask antigens which are hidden during tissue processing presumably by the complexing of proteins during fixation. This can be achieved by digestion of the tissue sections by proteolytic enzymes, e.g., trypsin, by a combination of heat and pressure in a pressure cooker, or by treatment with microwaves with and without the use of additional chemical buffer, most commonly citrate. This process of so-called antigen retrieval using microwaving of sections in citrate or other buffers is now widely used and is extremely successful in allowing low antigen concentrations to be exposed for antibody binding thus increasing the frequency and intensity of positive reactions. Care must be exercised in the use of antigen retrieval as it is possible to produce very convincing and wholly inappropriate false-positive reactions with several antibodies. Meticulous attention to the practical and technical aspects is essential and each laboratory has to establish its own specific methodological conditions, within general principles, for each antibody whichever technique is employed.

Antibodies are used in panels, i.e., several different antisera are individually applied to separate, usually consecutive, sections of a block or blocks of tumor in order to demonstrate evidence of lineage differentiation.

It is vital to avoid false-positive and false-negative staining and to that end standard positive controls and negative controls are always included in staining batches. Pediatric neoplasms commonly exhibit pluripotent differentiation [22] and this potential pitfall is partly negated by the use of multiple antibodies. Example panels of some antibodies commonly used in the diagnosis of pediatric tumors are provided in Table 8.4. The use of more than one antibody specific for

Table 8.4 Examples of antibodies useful in pediatric tumor diagnosis

Leukocyte common antigen (CD45)	B & T Lymphocytes	Lymphomas
CD20 (L26)	B lymphocytes	Lymphomas
CD45RO(UCHL-1)	T lymphocytes	Lymphomas
CD30 (Ber H-2)	Activated lymphocytes/macrophages/ Reed-Sternberg cells	Hodgkin's disease/Anaplastic large cell lymphoma
CD15 (LeuM1)	Reed-Sternberg cells	Hodgkin's disease CD68
(KP1)	Macrophages	Histiocytic neoplasms
Kappa/Lambda	Ig light chains	Lymphoid clonal proliferation
Neuron-specific enolase (NSE)	Neuroectoderm	Neuroblastoma
S100	Glial/Schwann cells/others	Neurofibroma, etc., Langerhan's cells
β2-microglobulin	β2-microglobulin	PNET
Synaptophysin	Neuroectoderm/neuroendocrine	Ewing's/PNET
MIC-2 (CD99)	MIC-2 gene product (glycoprotein P30/32)	Ewing's/PNET
Vimentin	Intermediate filaments/mesenchyme	Ewing's/soft tissue sarcoma
Actin (common, smooth muscle, sarcomeric)	Muscle filaments	Rhabdomyosarcoma
Desmin		Muscle (smooth/striated)
Rhabdomyosarcoma Myoglobin		Striated muscle
Rhabdomyosarcoma Myo D-1		Skeletal muscle
Rhabdomyosarcoma Cytokeratins (AE1-AE3, CAM 5.2, etc.)		Epithelial
Synovial sarcoma		
CD1a histiocytosis	Langerhan's cells	Langerhan's cell

a particular cell lineage is recommended when diagnostic confirmation is sought.

A common problem in immunohistochemistry is the need to recognize and avoid blind overreliance on the presence of a "positive" reaction. There is much cross-reaction and variable expression of antigens in pediatric tumors. For example, in primitive rhabdomyosarcomas it is not uncommon to see positive staining for neuron-specific enolase, which is generally regarded as a marker useful in the diagnosis of neuroblastoma. Similarly, the MIC2 (CD99) Ewing's/primitive neuroectodermal tumor (PNET) marker can be expressed in other pediatric tumors, in particular lymphoma and rhabdomyosarcoma. It is therefore not sufficient merely to expose the section to the antibody, blindly identify a positive labeling signal, and attribute a diagnosis. The positive staining must be in the correct tissue fraction and must correlate with the morphology of the lesion and the clinical presentation of the case. Evaluation of these studies requires an experienced medical practitioner to correlate the data. Blind adherence to immunohistochemical staining may lead to erroneous diagnosis.

Electron Microscopy

The advent of immunohistochemical techniques has been associated with a dramatic reduction in the utilization of electron microscopy in the diagnosis of pediatric neoplasia. There are instances, however, where ultrastructure can indicate lineage specificity of otherwise undifferentiated tumors and clarify its true nature (i.e., neuroendocrine "granules" in neuroblastoma, cytoplasmic glycogen in Ewing's sarcoma, cytoplasmic filaments with Z bands in rhabdomyosarcoma). Electron microscopy is particularly important in the diagnosis of Langerhan's cell histiocytosis where the identification of Birbeck granules is diagnostic (Fig. 8.11).

Tissue submitted for electron microscopy studies must be placed in special fixatives, e.g., gluteraldehyde 4 %. The processing of tissue for electron microscopy requires only very small tissue samples because gluteraldehyde penetrates so poorly. It is labor-intensive and expensive. In tumor diagnosis, we reserve electron microscopy for very specific indications and do not perform these studies as routine in all pediatric neoplasms, although we take appropriate samples in gluteraldehyde fixative from all tumors if sufficient tissues are submitted and additional studies are required.

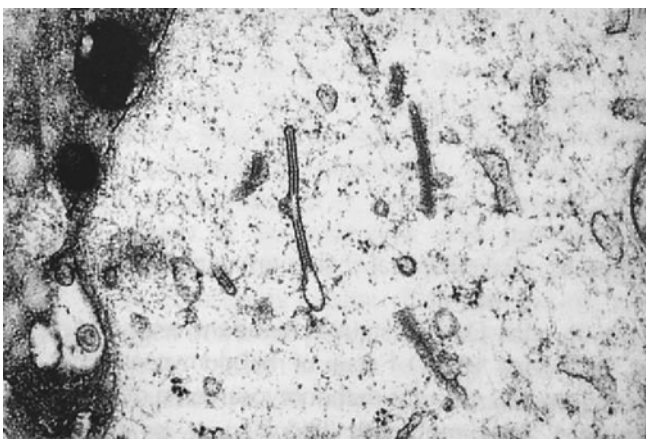

Fig. 8.11 Electron micrographs showing diagnostic Birbeck granules in Langerhan's cells

Cytogenetics

Several pediatric tumors are characterized by specific chromosomal translocations which, in those cases which are diagnostically difficult on light microscopy, can help clarify the diagnosis. Examples include t(2:13) (q35: q14) in alveolar rhabdomyosarcoma [23], t(11:22) (q24:q12) in Ewing's sarcoma, and peripheral PNETs [24], t(x:18) (p11.2:q11.2) in synovial sarcoma [25]. Many other tumors also express consistent chromosomal abnormalities and more examples are being identified almost with every passing week.

Previously these were identified by classical G- banding studies of metaphase spreads of cultured tumor cells, but more recently the use of specific probes and the fluorescent in situ hybridization (FISH) technique has been employed in the rapid identification of chromosomal abnormality such as translocations. FISH can be done on cytological samples and frozen sections thus avoiding the need for expensive and time-consuming tumor cell culture. Interphase FISH studies can also be performed on formalin fixed paraffin embedded sections, including sections from archived tumor cases. The procedure is more technically demanding than that with non-formalin fixed material and requires careful attention to protein digestion and chemical pretreatments to increase cellular permeability and facilitate entry and binding of the DNA probes.

A more detailed review of these cytogenetic lesions and the methodologies employed in their investigation is provided in subsequent chapters of this book.

Molecular Genetics

As diagnostic samples become ever smaller, the provision of adequate tissue for classical cytogenetic analysis becomes problematic. This challenge has been met by the now routine application of polymerase chain reaction (PCR) techniques to amplify tumor DNA or RNA (reverse-transcriptase polymerase chain reaction, RT- PCR) in small tumor samples, thus allowing identification of tumor specific translocations and their fusion transcripts [26–28]. Once again, both standard PCR (DNA) or RT-PCR (RNA) is easier on unfixed samples, fresh or snap frozen in liquid nitrogen, but results can also be achieved on archived tumor paraffin blocks.

The Prognostic Process

Increasingly, in cases of pediatric neoplasia, it is necessary for the pathologist to provide prognostic information as well as a histological diagnosis. This is done by further detailed evaluation of the histology and, in the case of some tumors, by molecular and cytogenetic studies of tumor tissue samples.

Standard Histological Criteria

In many types of tumor the histological subtype alone carries prognostic implications. For example, alveolar rhabdomyosarcoma is known to carry more serious prognosis stage for stage than embryonal rhabdomyo-sarcoma. Spindle cell rhabdomyosarcoma has a better prognosis than any other variant (Figs. 8.12 and 8.13).

It is important to search for prognostic features in individual tumor types, e.g., anaplasia/unfavorable histology in nephroblastoma, the MKI and extent of cellular and stromal differentiation in neuroblastoma [29, 30], because features such as these can influence therapy in individual tumors of a given stage. These and other examples will be discussed in more detail in the chapters relating to individual tumor types.

The more general principles regarding prognostication relate to assessment of tumor stage and, particularly in soft tissue sarcomas, the histological grade. Staging is based on the gross anatomical distribution of disease modified by histological assessment of local excision margins and confirmation/identification of nodal and distal metastases. Specific staging systems apply to several of the organ-specific pediatric tumors, e.g., nephroblastoma, and the National Wilms' Tumor Study (NWTS) definitions of stage are described elsewhere in this book.

An alternative staging system applicable to tumors of all sites is the TNM system: "T" related to the size of the primary tumor, "N" to the presence or absence of nodal metastases, and "M" to the presence or absence of distant metastases [31]. The grading system of Coindre et al. [32] as used by review pathologists in United Kingdom Children Cancer Study Group trials is shown in Table 8.5 for illustration. The reader is directed to references to the grading systems of Markhede, Myhre Jensen, Costa, and Trojani at the end of this chapter for further information [33–36].

Cytogenetics and Molecular Genetics

Vital prognostic information that has a significant bearing on intensity and duration of therapy in certain pediatric neoplasms is obtained from genetic analyses. For example, in rhabdomyosarcoma the confirmation of the alveolar subtype by demonstration of t(2:13) in a lesion previously considered embryonal on light microscopy will result in a more intensive therapeutic regimen. In neuroblastoma the identification of 1p deletion and N-myc amplification [37] are proven indicators of more aggressive tumors with a worse prognosis which require intensive therapy compared with neuroblastomas without these features. High trk-A proto-oncogene expression is associated with a better prognosis and is inversely related to N-myc amplification [38].

An important advance in prognostication has resulted from the capacity of molecular genetic techniques, particularly RT-PCR, to identify previously undetectable tumor cells in peripheral blood or bone marrow samples [39].

Tumors will spread via the blood stream as they metastasize. There is now clear evidence that the presence of this otherwise occult tumor spread is associated with increased incidence of established metastases, reduced disease-free interval, and reduced survival [40]. In those tumors characterized by specific chromosomal translocations and resultant gene fusion transcripts (Table 8.6) the use of RT-PCR can

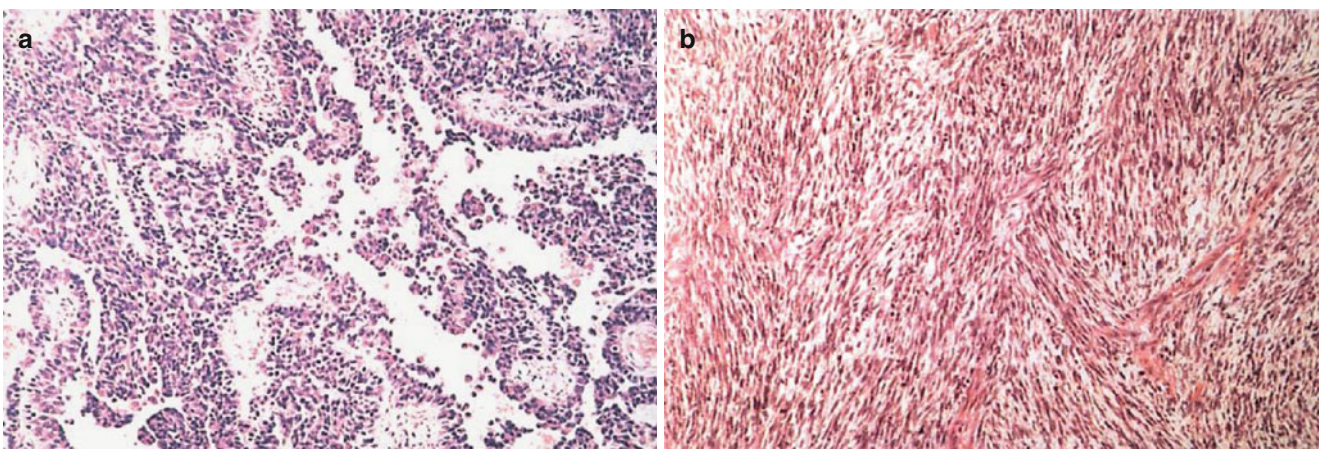

Fig. 8.12 (**a**) Alveolar rhabdomyosarcoma; (**b**) spindle cell variant

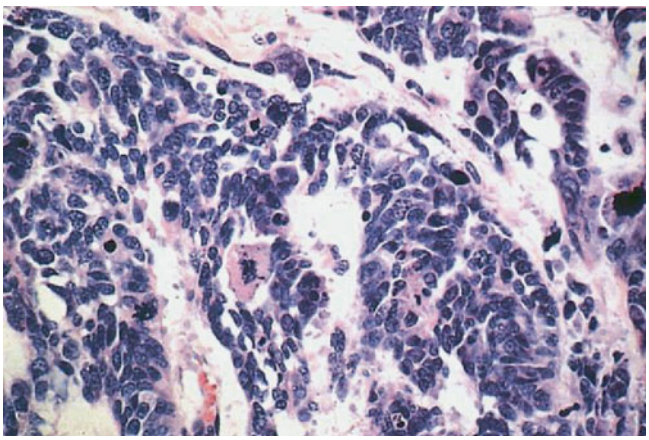

Fig. 8.13 Unfavorable nephroblastoma

Table 8.5 Histological grading in soft tissue sarcoma [32]

Feature		Score
Mitoses	0–9 (per 10 high power fields	1
	10–19 (per 10 high power fields)	2
	>20 (per 10 high power fields)	3
Necrosis	None	1
	<50 % of the tumor	2
	>50 % of the tumor	3
Differentiation	Very highly differentiated	2
	Moderately differentiated but cell type easily recognizable Poorly differentiated or cell type uncertain	3

Grade is determined by aggregate score for all these features, i.e., Grade I, Score 3–4; Grade II, Score 5–6; Grade III, Score 7–9

Table 8.6 Some pediatric tumors with specific, diagnostic chromosomal translocations

Ewing's sarcoma group	t(11;22)(q24:q12) t(21;22)(q22;q12) t(7;22)(p22;q12) t(17;22)q12;q12 t(2;22)q33;q12	EWS-FLI1 EWS-ERG EWS-ETV1 EWS-E1AF EWS-FEV
Desmoplastic small round cell tumor	t(11;22)q13;q12	EWS-WT1
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14) t(2;13)(q335;q14)	PAX3-FKHR PAX7-FKHR
Synovial sarcoma	t(x;18)(p11.2;q11.2)	SYT-SSX1 SYT-SSX2 SYT-SSX4
Congenital fibrosarcoma	t(12;15)(p13;q25)	ETV6-NTRK3

detect this tumor spread in blood and marrow thus providing objective evidence for upstaging or intensification of chemotherapy. Some SIOP tumor protocols now include this investigation as part of patient surveillance.

A more detailed review of this area is given in subsequent chapters of this book.

Additional Techniques

There are a number of techniques, which are nonstandard, but which can provide further valuable diagnostic and prognostic information in pediatric neoplasms.

Flow Cytometry

Flow cytometry is a technique which allows cell suspensions to be analyzed for the presence or absence of a number of features including cell size, DNA content (ploidy), and the presence or absence of cell surface or cytoplasmic antigens [41].

The general principle is that the sample is a suspension of cells stained with dyes or labeled by antibodies to specific cellular antigens, which are passed through a beam of laser light. The cells and their constituent parts reflect back the light, which is picked up by detectors, which count the number of "events" and analyze the different constituent populations of the cell suspension. The data obtained is presented in a digitized form, usually as a scatter curve or as a histogram.

In the case of neoplasia, the features which are most usefully measured using flow cytometry are ploidy and cell surface marker phenotype. Neoplasms can be either diploid (with normal DNA content) or aneuploid (abnormal DNA content). Aneuploidy usually correlates with tumor aggressiveness and a worse prognosis; however, in neuroblastoma hyperdiploid tumors have a better prognosis [42].

The other major use for flow cytometry is in the study of lymphoid tissue enlargement where one cannot be sure if the process is a bizarre reaction or a lymphoma. If the cells are exposed to antisera which bind to cell surface markers it is possible to define the presence of small clones of atypical cells, frequently aneuploid or abnormally large, within a more heterogeneous cell population within the lymph node and also determine the specific lineage, e.g., T or B lymphocyte in non-Hodgkin's lymphoma or CD30 positive Reed-Sternberg cells in Hodgkin's disease. We have used this technique with some success in patients with lymphadenopathy who present with bizarre lymphoproliferative pathology in various inherited immune deficiency disorders.

Flow cytometry with analysis of DNA content/ ploidy can also be performed in paraffin-embedded tissues in which the nuclei are released from the paraffin and rendered in suspension. The DNA is then stained, the nuclei can be counted and the nucleic acid content and therefore ploidy determined.

Indices of Cell Proliferation in Tumors

Growth fraction and other indicators of cell proliferation in tumor samples correlate with prognosis. The S-phase fraction, i.e., number of cells that have committed to mitosis,

indicate the number of dividing cells. Modern techniques of assessment of cell proliferation are based on immunohistochemical principles using antibodies to proteins involved in the mitotic phase of the cell cycle, or in the phase of cell cycle prior to mitoses, or on the identification of features, which correlate with proliferation.

Ki-67 is a nuclear protein expressed in cells in the proliferative phases of the cell, G1, G2, M, and S. It is the most widely used index for the immunohistochemical assessment of growth faction in paraffin sections and appears to correlate with increased tumor aggressiveness [43]. PCNA is another of these proteins but it is less specific, being present in a proportion of cells in the resting phase of the cell. AgNOR proteins were previously used as potential indicators of tumor aggressiveness and proliferation based on their ability to bind with silver stains but now they have little role in paediatric tumors as there are other more robust and reliable prognostic indicators as described previously [44]. Flow cytometry can also measure indices of cell proliferation using real-time PCR very quickly and reliably and are used in hematological malignancies [41].

p53

The p53 tumor suppressor gene product is involved in many cellular pathways including cell cycle control, DNA repair, and programmed cell death (apoptosis) [45, 46]. In human cancers p53 is the most frequently detected mutated gene, and loss of gene product function by mutation or allelic loss is regarded as a central part of the process of tumorigenesis. The Li-Fraumeni familial cancer syndrome is the result of autosomal dominant transmission of germ line abnormalities of the p53 gene [47, 48] and this syndrome is now recognized as having implications for pediatric neoplasia, particularly rhabdomyosarcoma and adrenocortical carcinoma, as well as several different carcinomas and sarcomas in adults.

Given the key role of p53 in cell cycle regulation, p53 immunohistochemistry is used in pediatric adrenocortical tumors [49]. Abnormal p53 protein accumulates in cells bearing p53 gene mutations. Increased p53 immunostaining correlates with more aggressive behavior and poor prognosis [50].

Future Perspectives

The key challenges for pathology in the near future will lie in the need to support more complex and detailed ancillary investigations of pediatric tumors principally for prognostic purposes, which will increasingly select and direct the therapeutic options in any given case. This challenge will be faced in light of increasingly small diagnostic samples and pre-surgical therapy. Cytological diagnosis, particularly the use of fine needle aspiration, will increasingly become the primary diagnostic methodology providing samples for histological diagnosis and genetic studies.

Tumor profiles generated by micro-array based gene expression will enable more accurate tumor diagnosis, classification and prognostication especially in undifferentiated tumors [51–54]. New targets for therapy will be unmasked providing new tools to predict disease recurrence and response to therapy. In a given tumor, genotypes of the different clones that impart tumor heterogeneity, can be analyzed by Laser capture micro-dissection (LCM) where defined population of target cells can be dissected out from tissue sections by a laser gun under direct microscopic visualization. This can then be compared to normal tissues using advanced molecular techniques to generate specific molecular signatures enabling ‘personalized therapy’ for patients [55].

Another major breakthrough in the field of histopathology is the advent of digital pathology. Digital imaging and information communication technology (ICT) can now provide ‘virtual’ interfaces where the entire glass slide can be scanned into an high resolution digital image that can be transmitted immediately and can be viewed remotely. Telepathology using motorized robotic stage even allows the remote user to access and control the digitalized slide in real-time, which can be viewed simultaneously by many pathologists [56]. Thus, expert consultation can be available more readily in difficult cases. As molecular diagnosis finds greater acceptability and applicability in diagnosis and prognostication of pediatric tumors, wider incorporation of advanced molecular techniques will become an integral part of tumor analysis. It is imperative for the pathologist to embrace these novel molecular techniques and diagnose tumors using their knowledge of tumor morphology.

Surgeons will have to appreciate the pressures placed on the pathologist in these circumstances and develop appropriate protocols with their colleagues to ensure that the essential diagnostic and prognostic processes are not compromised to the detriment of the clinical care of patients. Surgeons and pathologists have a responsibility to ensure the supply and retention of tumor and normal tissue samples for research purposes if progress in diagnosis, prognostication, and treatment is to be maintained.

The role of diagnostic histopathology in the management of pediatric neoplasia is greater today than ever. The remarkable and rapidly accruing in-sights into the molecular biology and cytogenetics of tumors and tumorigenesis has dramatically increased the role of pathology where the pathologist is expected to do more with tumor samples submitted for examination. In the face of rapid advances in the field of pediatric oncology, there is an ever increasing need for all specialists to work together in an organized and

coherent multi-disciplinary team approach. Pathologists, as part of this team, have a vital contribution to make, which is at the fulcrum of clinical management.

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Chemotherapy and Novel Cancer Targeted Therapies

9

Milind D. Ronghe and Dermot Murphy

Introduction

Children's cancers are rare and account for 1 % of all malignancies. Within Europe this represents some 12,000 new cases each year, with approximately 1,600 per year in the United Kingdom. In the UK, 1 in every 600 children under 15 years of age develop cancer. Although rare, childhood cancer is the second commonest cause of death in children between 1 and 14 years of age. These cancers are quite different from cancers affecting adults. Most adult tumours are carcinomas and are usually classified by their site of origin, whereas paediatric tumours occur in different parts of the body, look different under the microscope and are classified by histological subtypes. Tumour types that are common to both adults and children, such as lymphomas and leukaemia, differ in their biology, behaviour and prognosis and hence demand different treatment. They also respond differently to treatment. Some embryonal tumours presenting in infancy undergo spontaneous remission or maturation (e.g., Stage IVS neuroblastoma).

Survival rates for childhood cancer have improved dramatically over the last 20 years, such that approximately 70 % of children can expect to become long-term survivors [1, 2]. This is reflected by the fact that today, 1 in 750 of the young adult population is now a survivor of childhood cancer. Treatments used to achieve this success are surgery, chemotherapy and/or radiotherapy. Factors contributing to these improved survival rates are: the development of dedicated paediatric oncology centres, advances in surgical techniques, novel chemotherapy agents and regimens, targeted radiotherapy and improvements in supportive care (early treatment of febrile neutropenia, better intensive care, improved transfusion services).

Surgery was the mainstay of treatment of solid tumours in children before the advent of effective chemotherapy. Cure could be obtained by surgery alone in the proportion of children with localised disease, and good palliation obtained in many others, and the surgeon was often the key clinician in the management of paediatric solid tumours. However, very few tumours present as a purely localised surgical problem. The surgeon becomes part of a larger team, needing to integrate surgical procedures with chemotherapy and/or radiotherapy. Although improvements in radiotherapy and surgery have reduced the late sequelae of curative therapy, chemotherapy now remains the mainstay of treatment for most childhood cancers. This chapter aims to discuss the factors which affect the way the paediatric surgeon interacts with a multidisciplinary team of experts, including the paediatric oncologist, radiologist, pathologist and radiotherapist. The best outcome will be achieved by collaboration of interested specialists clearly understanding the efficacies and limitations of various forms of treatment.

Although complete tumour resection is of paramount importance for cure, most paediatric cancers are advanced at presentation (e.g., 55–60 % sarcomas are High Risk at diagnosis, 25 % of Bone tumours are metastatic at diagnosis, 90 % of Neuroblastomas occurring after infancy are stage IV) and require systemic treatment. The prognosis for malignant solid tumours has improved since the introduction of effective chemotherapy capable of reducing the tumour volume and making previously unresectable tumours resectable. The operation also becomes safer and easier after preoperative chemotherapy. Furthermore, there is no delay in treating metastatic disease, which is detectable at diagnosis in a significant proportion of patients.

Some diseases, such as osteosarcoma, cannot be cured except with surgery to remove the local tumour, whereas in others such as lymphoma, biopsy followed by chemotherapy is all that is needed. In others, such as Ewing's sarcoma and rhabdomyosarcoma, the best treatment results may be

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obtained with systemic chemotherapy and a combination of surgery and/or radiotherapy for local control. In Europe, since the early 1990s, the concept of pre-operative chemotherapy and delayed surgery for solid tumours of childhood became standard clinical practice due to successful Wilms' tumour trials of the SIOP (International Society of Paediatric Oncology) Group [3–5].

Children presenting with malignant diseases other than leukaemia often present with palpable masses and are usually seen first by a surgeon. Except in emergencies, a thorough consideration of the possible differential diagnosis should be made before any surgical procedures are undertaken. This should ideally be done in discussion with the paediatric oncology team. Any necessary pre-surgical staging or investigations can then be planned, depending on the nature of the suspected lesion and the facilities available. Biopsy should ideally be performed in the regional specialist centres, where the necessary support services are available (e.g., molecular biology services) and once radiological examination of the lesion is complete. If appropriate, a number of interventions (such as bone marrow aspiration/trephine for staging) can be carried out while the child is anaesthetised for biopsy/surgery.

In nearly all cases of malignancy, diagnosis must be confirmed by biopsy of the primary tumour. Traditionally, tumour material would be obtained by incisional or excisional biopsy at open operation, but advances in imaging techniques have led to much greater use of trucut biopsies obtained with ultrasound or computerised termography (CT) guidance. In a tumour with obvious heterogeneity on initial imaging, open biopsy may still be preferable, to ensure that a representative sample is obtained. Biopsy sites must be within potential radiation fields, as malignant cells may seed along the biopsy track. In rare instances, a combination of radiological and biochemical or molecular biological findings may enable a definitive diagnosis to be made without biopsy, e.g., a tumour in the characteristic site, such as the anterior mediastinum or pineal region, with high alphafetoprotein (AFP) levels in the blood can be confidently diagnosed as a germ cell tumour and a heterogeneous abdominal mass with calcification, raised urinary catecholamines and infiltration of the bone marrow, is a neuroblastoma. However, failure to obtain tissue makes it impossible to acquire important information regarding the biological and genetic characteristics of the tumour that often determine the risk factors affecting therapeutic decisions. Although the overall cure rate for childhood tumours is now around 70 %, it is only by increased understanding at the biological level that further progress will be made, particularly in an appropriate risk stratification of current intensive treatments and in the development of novel therapies. With increased survival rates for childhood cancer, philosophy of treatment has changed over the years from 'Cure at any cost' to 'Cure at least possible cost'.

Staging

Once the diagnosis has been confirmed, the extent of the tumour (size, position, relationship to surrounding structures, appearance of lymph nodes) must be established. Unfortunately, there is no single uniform staging approach for childhood malignancies and the surgeon will need to be aware of the requirements for staging of each tumour type according to the current protocols (see Table 9.1).

- The staging of disease directs the treatment given and should help to avoid excessive therapy: in easily curable conditions excessive therapy is known to put the child at increased risk of adverse late effects of treatment.
- The stage of the disease also tends to reflect the prognosis and, consequently, aids counselling of the family.
- Staging systems generally progress from localised disease (stage I) to widespread disease (stage IV) and are based on the results obtained from clinical examination, radiology and pathology.

More extensive tissue sampling and biopsy is usually only needed at the time of definitive operation. This information will determine what type of further treatment is required post-operatively. For example, in the current SIOP Wilms' tumour trial, pathologists make precise evaluation of the stage of the disease post nephrectomy. Children are then risk stratefied and treated according to different therapy, depending on tumour histological subtype and stage of disease.

Increasingly, the chemotherapy response of the primary tumour in the post-surgical specimen is used in deciding post-operative treatment for a number of malignant solid tumour (e.g., in osteosarcoma and Ewing's Sarcoma <90 % necrosis of the tumour is considered a poor response and these patients are now randomised to receive more intensive treatment to improve the chances of long-term survival.

Intra-operative photography or clear diagrams can be very helpful to the radiotherapist and, even in the era of three-dimensional imaging, a description of the tumour in relation to fixed anatomical points is also useful. The use of titanium clips is valuable to delineate tumour margins and does not affect subsequent imaging.

Although chemotherapy is needed for nearly all tumours in childhood and is often given before definitive surgery, primary surgical excision is still indicated for a number of malignancies. These include stage I testicular tumours, where no further treatment is needed if an associated raised AFP titre falls to normal with and expected half-life of 2.7 days post-operatively, stage I or II neuroblastoma (abdominal or thoracic), some adult-type soft tissue sarcomas, most brain tumours such as astrocytomas and medulloblastomas.

Table 9.1 Staging procedures for paediatric tumours

Germ cell	Wilms'	Neuroblastoma	Lymphoma	Rhabdomyosarcoma	Hepatoblastoma	Osteosarcoma	Ewing's
AFP level	USS Abdo CT/MRI Abdo	Urinary Catecholamines	Bone marrow Aspirate and trephine	CT/MRI scan local Tumour	CT/MRI Liver and abdo	MRI (of primary) before biopsy	CT or MRI (of primary) before biopsy
HCG	Chest x-ray CT Chest	Bone marrow aspirate/ trephines	CSF exam	CT chest MRI abdo/pelvis	MR angiography CT chest	CT chest	CT chest
MRI/CT Abdo/ chest		Bone/MIBG scan CT chest/ MRI abdo Estimation of N-*myc* copy +1p deletion (from fresh tumour)	CT chest MRI of abdo/ pelvis Bone scan	CT/MRI brain scan (for head/ neck (for head/neck disease) Bone scan Bone marrow aspirate/ trephine	Bone marrow aspirate/trephine	Bone scan	Bone scan Bone marrow aspirate/ trephine Fresh tumour for chromosome analysis

In some cases a presumptive diagnosis may be confirmed by tests other than biopsy of the primary tumour. Fresh material is often required from the biopsy to determine which protocol is used for treatment. *AFP* Alpha Feto Protein, *HCG* Human Chorionic Gonadotrophin, *CSF* Cerebrospinal fluid

Staging for paediatric CNS tumours involves pre-operative MRI of brain and spine, post-operative scan (usually within 48–72 h after resection) to assess the degree of residual disease, plus CSF sampling for malignant cells

Debulking of tumours are rarely indicated as primary surgical procedures, except for some brain tumours. In particular, they confirm no advantage in the treatment of lymphoma, which may present with widespread intra-abdominal disease, although surgery may be necessary if chemotherapy results in a complication such as perforation or bleeding, or if the patient presents with intestinal obstruction. It is important that the surgeon is then as conservative as possible in his approach, since the chance of complete remission of disease following chemotherapy is high and surgery, performed at any stage in the disease does not lead to improved cure rates.

Emergency operations are unavoidable for intussusceptions, torsion of the tumour, perforation and some rapid enlargement due to intra-tumoural bleeding, cystic degeneration or necrosis.

Insertion of central venous catheter is probably the single most frequent operation that paediatric surgeons perform while caring for a child with malignancy. Centrally placed, long-term venous catheters are used for the administration of chemotherapy, antibiotics and for blood sampling. Central venous catheters make the care of the child easier, both for the child and for the medical team. Currently there are two main types of catheters used in clinical practice – tunnelled, external catheters (Hickman line, Broviac line, Groshong catheters) and totally implanted access devices such as a portocath. External, tunnel catheters are generally easier to access, are less expensive than portocaths, offer less risk of extravasation into subcutaneous tissue, allow more rapid infusions and can be removed easily at the end of treatment. However, the portocath offers an improved cosmetic result, less restriction in normal activities, less maintenance care and they are well protected, thus decreasing the chance of damage and are associated with a lower risk of infection. Numerous methods of catheter care, flushing, are practised in various paediatric oncology centres and none have proved superior when the literature is taken as a whole.

In addition to the insertion of central venous lines, diagnostic biopsies and resection of individual tumours, the surgeon has a role in facilitating treatment given by other members of the oncology team, i.e., insertion of a mesh to displace the bowel out of the future field of radiation or insertion of pain control devices and surgical exposure for brachietherapy.

Furthermore, a surgeon also has a role in providing enteral access in patients receiving intensive chemotherapy. Children with cancer often have associated cachexia, with significant weight loss and malnutrition. The intensity and type of primary therapy (chemotherapy, surgery and/or radiotherapy) is associated with decline in the nutritional status. Furthermore, patients receiving intensive chemotherapy have prolonged illnesses – mucositis, diarrhoea, sub-optimal dietary intake and decreased appetite – all are side effects of chemotherapy that contribute to further weight loss. Numerous studies have demonstrated that a nutritionally-repleted patient tolerates therapy better and with fewer complications [6–8]. In addition to providing nutritional requirements, gastrostomy tubes can perform other functions. Clinical experience has demonstrated that gastrostomy tubes are an effective way to delivery medications and to provide hydration to children experiencing excessive emesis. The quality of life of both the child and family also appears to improve, as eating is a frequent source of conflict between the child and parents. Providing nutrition through a gastrostomy tube alleviates the frustration associated with forced feeding of the child via the mouth. Maintenance of normal patient nutrition throughout cancer treatment allows normal growth and improves quality of life.

In many cases of solid tumours, surgical excision of primary tumour is the preferred local treatment since radiotherapy has a much greater risk of long-term sequelae. The general principles of underlined choice of local treatment are that surgical excision is the treatment of choice where: (1) complete excision is possible and results in improved survival and cure; (2) it will give functional and cosmetic results better than those obtained by other treatment.

Surgeons may also be consulted to deal with complications related to other forms of treatment: extravasation of chemotherapy agents causing tissue necrosis, typhilits (neutropenic enterocolitis), intestinal perforation, strictures or avascular necrosis or other damage due to late effects of radiotherapy.

Surgical decisions, as well as those concerning chemotherapy, radiotherapy and overall treatment strategies are best made after joint discussion, which is facilitated by a formal system of consultations such as regular multi-disciplinary oncology team meetings (Tumour Board), as well as maintaining communication between the key team members during the treatment.

In the United Kingdom, more than 80 % of children with malignant disease are registered with the United Kingdom Children's Cancer Leukaemia Group (UKCCLG) (Table 9.2) [9] and are treated according to agreed tumour protocols. Although there are approximately 1,600 cases of childhood cancer diagnosed in the UK annually, when broken down into individual tumour types, the numbers even for the commonest childhood tumours, are often too small to ensure that clinical trials can be completed satisfactorily at a national level. It is for this reason that the majority of the Phase III clinical trials in childhood cancer are now increasingly conducted at an international or collaborative basis (see Table 9.3). The power of such collaboration is the ability to conduct large trials with rapid accrual, which would allow the investigation of new agents to be undertaken quickly and effectively and thus be able to answer more rapidly some still unanswered questions regarding the treatment of children with malignant tumours. Active participation of all the interested clinicians

Table 9.2 Percentages of children with cancer or non-malignant CNS tumour initially referred to UKCCLG, classified by age at diagnosis, Great Britain 1978–2006

Age at diagnosis	1978–1982	1983–1987	1988–1992	1993–1997	1998–2002	2003–2006
0–9	62	74	81	90	92	92
10–12	55	63	67	81	86	84
13–14	36	46	51	71	76	80
Total	57	69	76	86	89	90

Table 9.3 Commonly used protocols for solid tumours

Tumour	Current protocol	Drugs	Acronyms
Neuroblastoma (stage IV)	HR-NBL-1/ESIOP (Induction)	Vincristine	
		Cyclophosphamide	RAPID
		Etoposide	COJEC
		Cisplatin	
		Carboplatin	
	(Myeloablative Treatment)	Busulphan	
		Melphalan	Bu-Mel
Unresectable/refractory Neuroblastoma	TVD Protocol	Topotecan Vincristine Doxorubicin	TVD
Wilms'	SIOP WT 2002	Vincristine/Actinomycin Doxorubicin	AV AVD
	(High risk)	Etoposide Carboplatin Cyclophosphamide	
Sarcoma	EpSSG RMS-2005 for Rhabdomyosarcoma	Ifosfamide Vincristine Actinomycin Doxorubicin	IVADO
	EpSSG – Non-Rhabdomyosarcoma	Ifosfamide Doxorubicin	
Ewing's	EURO-EWING'S (Induction)	Vincristine	VIDE
		Ifosfamide	
		Doxorubicin	
		Etoposide	
	(Consolidation)	Cyclophosphamide	{VAC {VAI
Hepatoblastoma	SIOPEL-6 (Standard Risk)	Cisplatin	
	Super PLADO (Intermediate Risk)	Cisplatin/Carboplatin Doxorubicin	PLADO
	SIOPEL-4 (High risk)	Cisplatin Doxorubicin Carboplatin	
Germ cell GC3	GC-3	Etoposide Carboplatin Bleomycin	JEB
Osteosarcoma	EURAMOS	Methotrexate Adriamycin CisPlatinum	MAP
Hodgkin's	Hodgkin 2000	Vincristine	
		Prednisolone	OEPA
		Etoposide	
		Adriamycin	
		Cyclophosphamide	
		Procarbazine	

(continued)

Table 9.3 (continued)

Tumour	Current protocol	Drugs	Acronyms
Non Hodgkin's lymphoma	EURO-LB 02	Prednisolone	COP COPADM CYM
		Vincristine	
		Daunorubicin	
		Asparaginase	
		Cyclophosphamide	
		Methotrexate	
Medulloblastoma	SIOP PNET4 (Avg Risk)	Vincristine Cisplatin CCNU (Lomustine)	Packer
High grade anaplastic Astrocytoma		Temozolamide	
Low grade glioma	LGG-2	Vincristine Carboplatin Etoposide	VCE

treating childhood cancer in a group such as the UKCCLG or SIOP is therefore essential to keep up to date with the various protocols/clinical trials, which in turn will continue to improve the outcome of childhood cancer.

Chemotherapy

The effective use of cancer chemotherapy requires a thorough understanding of principles of neoblastic cell growth kinetics, basic pharmacologic mechanisms of drug action and pharmaco-kinetic and pharmaco-dynamic variability. Development of selective, highly effective therapy for cancer has been hindered by lack of understanding of the molecular mechanisms, malignant transformation and denovo or acquired drug resistance. In spite of scientific advances in the field of molecular oncology, information remains incomplete, therefore therapy continues to be largely empiric.

The Cell Cycle and Tumour Growth Kinetics

The growth pattern of individual neoplastic cells may greatly affect the overall biological behaviour of human tumours and their responses to specific types of cancer therapy. Tumour cells can be subdivided into three general populations: (1) cells that are not dividing and are terminally differentiated; (2) cells that continue to proliferate; and (3) nondividing cells that are currently quiescent but may be recruited into the cell cycle. The kinetic behaviour of dividing cells is best described by the concept of the cell cycle.

The cell cycle is composed of four distinct phases during which the cell prepares for and undergoes mitosis. The G_1 phase consists of cells that have recently completed division and are committed to continued proliferation. After a variable period of time, these cells begin to synthesise DNA, marking the beginning of the S phase. After DNA synthesis is complete, the end of the S phase is followed by the premitotic rest interval called the G_2 phase. Finally, chromosome condensation occurs and the cells divide during the mitotic M phase. Resting diploid cells that are not actively dividing are described as being in the G_0 phase. The transition between cell cycle phases is strictly regulated by specific signalling proteins; however, these cell cycle checkpoints may become aberrant in some tumour types.

The most common anti-cancer drugs are cytotoxic agents which are cell poisons that act indiscriminately on most cells, either causing direct damage to DNA or inhibiting cell replication. The mechanism of action of most current anti-cancer drugs are non-selective and target vital micromolecules (e.g., nucleic acid) or metabolic pathways that are critical to malignant and normal cells. The molecular basis of cytotoxic-induced cell death is the subject of considerable interest, and it is becoming clear that one of the important common pathway is that of programmed cell death or apoptosis [10].

Cancer chemotherapy relies on exploiting the therapeutic index – the ratio of cell killing in the malignant cell population compared with killing of normal cells. Mechanisms for recovery from damage are generally more efficient in normal cells than in their malignant counterparts and, if time is allowed between courses of treatment for this recovery to occur, malignant cells can be differentially killed by repeated courses of chemotherapy.

In the clinical development of anti-cancer drugs, the initial dose finding trials (phase I), and subsequent studies to define the spectrum of activity of a new agent (phase II) employ an empirical methodology. Phase I trials can be seen as toxicity-screening studies where a new drug is administered for the first time to humans in order to determine the maximum tolerated dose. There are usually two aims of the phase I trial – to establish the optimal dose to be used in the phase II trial for

drug efficacy, and to determine the type and degree of toxicity (adverse effects) associated with the drug. In phase II trials, the response is evaluated in patients with different forms of cancer to determine which tumours the drug may have activity against. The end points of such trials are the response rate and toxicity. After a drug is found to have some activity in phase II trials, the next step is to determine its relative efficacy in a larger phase III trial, where the drug is compared – either alone or in combination – with other drugs, i.e., to a control group, usually the best available treatment, or a historical control. Most UKCCLG trials are phase III, comparing patients on a new treatment versus standard treatment, to try and establish whether new treatment is better than standard treatment. The dose and schedule of the anti-cancer drugs are empirically based. All patients receive the same fixed dose of drugs, adjusted for body weight or surface area, with subsequent dose or schedule modifications based only on ensuing toxicities, rather than on achieving a therapeutic plasma drug concentration. Commonly used cytotoxic agents and their metabolism use and side effects are listed in Table 9.4. Despite various limitations, several principles of cancer chemotherapy have evolved from clinical experience, including the use of multi-drug combination chemotherapy regimens, the administration of chemotherapy before the development of clinically evident metastatic disease (adjuvant chemotherapy) and administration of drugs in maximally tolerated doses (dose intensity).

Combination Chemotherapy

Multi-agent therapy has three important theoretical advantages over single-agent therapy. Firstly, it maximises the cell kill, while minimising host toxicities by using agents with non overlapping dose-limiting toxicities. Secondly, it may increase the range of drug activity against tumour cells with endogenous resistance to specific types of therapy. Finally, it may also prevent or slow the development of newly resistant tumour cells. Specific principles for selecting agents for use in combination chemotherapy regimens are listed in Table 9.5 [11].

Adjuvant Chemotherapy

The aim of adjuvant chemotherapy is to prevent metastatic recurrence by eliminating micro-metastatic tumour deposits in the lungs, bone, bone marrow or other sites at the time of diagnosis. Adjuvant chemotherapy has been demonstrated to be efficacious for most of the common paediatric cancers, including Wilms' tumour, Ewing's sarcoma, osteosarcoma and rhabdomyosarcoma. Adjuvant chemotherapy should be given as soon as possible after definitive local therapy. A delay to allow for recovery from surgery or radiation therapy may compromise the chance of curing the patient.

Increasingly, chemotherapy is now used in a neo-adjuvant setting (before the definitive treatment) in paediatric solid tumours as chemotherapy shrinks the tumour and the operation becomes safer and easier. Neo-adjuvant chemotherapy also provides earlier set treatment for micro-metastases.

Dose Intensity

Most anti-cancer drugs have a steep dose response curve, and a small increment in the dose can significantly enhance the therapeutic effect of the drug. The maximum tolerated dose of the drug combination should be given as frequently as possible to achieve optimal cell kill at a time when the size of the drug-resistant population is limited. Methods for maximising dose intensity include: greater physician and patient willingness to tolerate drug toxicities, more aggressive supportive care, selective rescue of the patient from toxicity such as with peripheral stem cell transplantation or the administration of colony-stimulating factors such as G-CSF, use of regional chemotherapy (intra-arterial, intrathecal delivery) to achieve high drug concentrations at local tumour sites and the development of new treatment schedules such as long-term continuous infusions that may allow more drugs to be administered over a given period.

Whatever the final pathway of cell death, there remains a correlation between sensitivity to anti-cancer drugs and the stage of the cell cycle at the time of drug exposure. During the S-phase most agents are effective, in contrast to the G0-resting phase, during which most tumour cells will be chemo-resistant. Anti-cancer drugs can be classified on the basis of the cell cycle phase during which they are more effective. For example, Nitrogen mustard, alkylating agents and gamma radiation are non-cycle-specific, being effective at most phases of the cell cycle and in some cases including the G0 population. Phase specific agents include Vinblastine and Vincristine, which are active during the mitotic phase; Etoposide and Tenoposide effective during the G2 pre-mitotic phase; and Methotrexate, 6-Mercaptopurine and Cytosine Arabinoside effective during the S-phase. Agents that are cycle but not phase specific include 5-Fluorouracil, Actinomycin D and Doxorubicin (Table 9.6, Fig. 9.1).

All cytotoxic drugs produce DNA damage but by different mechanisms. Alkylating agents induce arrest of DNA transcription regulation. Antimetabolites produce DNA injury by inhibiting thymidine synthetase, or blocking purine synthesis or DNA repair. Anthracyclines produce intercalation (cross-linking) between strands of DNA, may generate free radicals or interact with DNA-modifying enzymes. The final common pathway of cytotoxic induced cell death is apoptosis but, by exploiting these different mechanisms of

Table 9.4 Classification of the commonly used cytotoxic agents

Agent type	Substance name	Major clinical use	Metabolism	Excretion	Toxicities
1. Antimetabolites	Methotrexate	Leukaemia, lymphoma, CNS, osteosarcoma	Hepatic	Renal, 50–90 % excreted unchanged; biliary	BM, M, kidney, lung liver, CNS
	5-Fluorouracil	Colorectal, liver	Hepatic	Renal	BM, M, diarrhoea
	6-Mercaptopurine (6-MP)	Leukaemia, lymphoma	Hepatic; allopurinol inhibits metabolism	Renal	BM, liver
	6-Thiogranine (6-TG)	Leukaemia, lymphoma	Hepatic	Renal	BM
	Cytarabine	Leukaemia, lymphoma, CNS	Hepatic	Renal	BM, M, cholestasis, N+V, diarrhoea, CNS, lung, conjunctivitis
2. Alkylating agents	Nitrogen mustard	Hodgkin's disease	Hepatic	Biliary	BM, N+V, alopecia, sterility
	Cyclophosphamide	Leukaemia, lymphoma, neuroblastoma, rhabdomyosarcoma, Ewing's sarcoma, germ cell tumours	Hepatic	Renal	BM, cystitis, alopecia, lung, heart, sterility
	Ifosfamide		Hepatic	Renal	BM, alopecia, cystitis encephalopathy, kidney, sterility, heart
	Melphalan	Neuroblastoma, sarcomas, leukaemia, Hodgkin's disease	Hepatic	Renal	BM, M, alopecia, heart, sterility
	Busulphan	Leukaemia	Hepatic	Renal	VOD; lung fibrosis; sterility; Addisonian-like state
	BCNU (Carmustine)	Brain tumours, lymphomas	Hepatic	Renal	Late bone marrow toxicity (up to 6/52), sterility, lung, heart
	CCNU (Lomustine)				
3. Platinum compounds	Cisplatin	Germ cell tumours, neuroblastoma, sarcomas, CNS, liver		Renal	N+V, renal, hearing loss
	Carboplatin				
4. Vinca alkaloids	Vincristine	Leukaemia, lymphoma, Wilms' tumour, neuroblastoma, rhabdomyosarcoma, Ewing's sarcoma	Hepatic	Biliary	Neurotoxicity, jaw pain, constipation, inappropriate ADH secretion
	Vinblastine	Lymphoma	Hepatic	Biliary	Jaw pain, mucositis
	Vindesine	Sarcomas	Hepatic	Biliary	BM
5. Epipodophylotoxins	Etoposide (VP-16)	Leukaemia, lymphoma, neuroblastoma, germ cell tumours		Renal	BM, N+V, neurotoxicity, leukaemia, alopecia
	Teniposide (VM026)				

6. Antitumour antibiotics	Doxorubicin	Leukaemia, lymphoma, neuroblastoma, rhabdomyosarcoma, Ewing's sarcoma, Wilms' tumour	Hepatic	Biliary, renal	BM, N+V, heart, mucositis, alopecia, radiation recall
	Daunorubicin	Leukaemia	Hepatic	Biliary, renal	BM, N+V, heart, alopecia, radiation recall
	Epirubicin	Lymphoma, sarcoma	Hepatic	Biliary, renal	BM, alopecia, heart
	Mitozantrone	Lymphoma, leukaemia	Hepatic		BM, cholestasis
	Actinomycin D	Wilms' tumour, Ewing's sarcoma, rhabdomyosarcoma	–	Renal	BM, N+V, skin (with radiation), liver, alopecia
	Bleomycin	Germ cell tumours, lymphoma	Hepatic	Renal	Lung fibrosis, fever, pigmentation, Raynaud's Phenomenon
7. Miscellaneous	Dacarbazine	Sarcoma, Hodgkin's disease	Hepatic	Renal	"Flu" symptoms, liver
	Procarbazine	Hodgkin's disease	Hepatic	Renal	Liver, "flu" symptoms
	L-Asparaginase	Leukaemia	–	Reticuloendothelial system	Hypersensitivity, liver, CNS
	Prednisolone	Leukaemia, lymphoma	Hepatic	Renal	Hypertension, blood sugar diabetes, cataracts, Cushing's, osteoporosis, immunosuppression

BM bone marrow, *M* mucositis, *N+V* nausea and vomiting

Table 9.5 Principles for selecting agents for use in combination chemotherapy regimens

Drugs known to be active as single agents should be selected for use in combinations; preferentially drugs that induce complete remission should be included.
Drugs with different mechanisms of action and with additive or synergistic cytotoxic effects on the tumour should be combined.
Drugs with different dose-limiting toxicities should be combined so that full or nearly full therapeutic doses can be utilised.
Drugs should be used at their optimal dose and schedule.
Drugs should be given at consistent intervals, and the treatment-free time period should be as short as possible to allow for recovery for the most sensitive normal tissues.
Drugs with different patterns of resistance should be used to minimise cross-resistance.

Table 9.6 Cell-cycle-phase-specific drugs

S phase-dependent	**M phase-dependent**
Antimetabolites	Vinca alkaloids[a]
Cytarabine	Vinblastine
Doxorubicin	Vincristine
Fludarabine	Vinorelbine
Gemcitabine	Podophyllotoxins
Hydroxyurea	Etoposide
Mercaptopurine	Teniposide
Methotrexate	Taxanes
Prednisolone	Docetaxel
Procarbazine	Paclitaxel
Thioguanine	**G_2 phase-dependent**
	Bleomycin
	Irinotecan
	Mitoxantrone
	Topotecan
	G_1 phase-dependent
	Asparaginase
	Corticosteroids

[a]Have treatest effects in S phase and possibly late G_2 phase; cell blockade or death, however, occurs in early mitosis

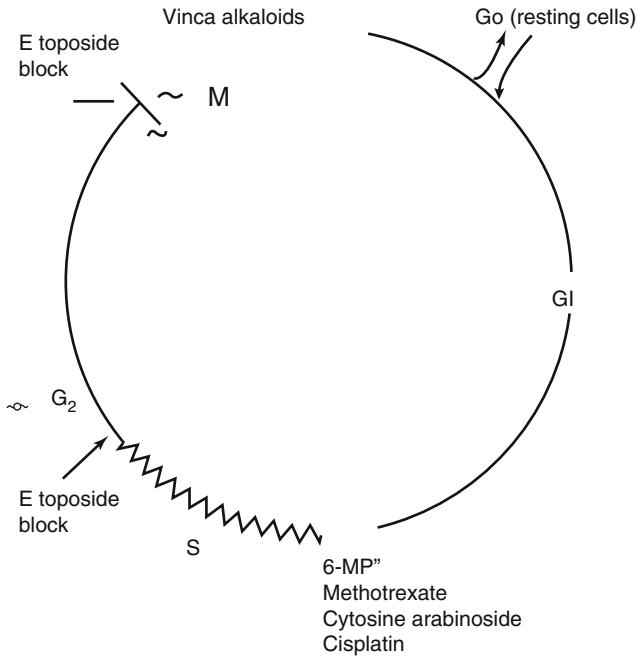

Fig. 9.1 Cell cycle and phase-specific drugs

damage, greater tumour cell kill can be achieved. One of the main reasons why chemotherapy may fail to kill all tumour cells is that clones of 'resistant' cells may develop. Tumour resistance is related to a genetic event in the cell – a mutation, gene amplification, deletion or chromosome translocation which may affect drug transport, intracellular drug activation or efflux from the cell.

Three genes have so far been implicated in multiple drug resistance (MDR) – IP glycoprotein, which acts as a transmembrane pump to reduce the intracellular drug concentration, multiple drug resistance-associated protein gene (MRP) which is related to non p-glycoprotein mediated resistance, and DNA topoisomerase II mutations which affect DNA conformation [12, 13].

Irrespective of the precise mechanism of drug resistance, it has been suggested by Goldie – Coldman hypothesis [14] that there is a high likelihood of drug resistant mutants at the time of initial diagnosis and that two important considerations must therefore be taken into account in protocol design. Firstly, the earliest use of non-cross resistant drugs (combination chemotherapy), and secondly the maximum tolerated dose of the drug combinations should be given as frequently as possible to achieve optimum cell kill, at a time when the size of the drug resistant population and number of mechanisms are limited.

High-dose chemotherapy offers a strategy for overcoming multiple drug resistance and is feasible as long as bone marrow suppression, which can be overcome by bone marrow or peripheral stem cell rescue, is the only dose limiting toxicity.

In adults, local perfusion of cytotoxic agents has been attempted in a number of situations. Isolated limb perfusion has achieved some success as a treatment for melanoma, but this tumour is extremely uncommon in children. Hepatic artery infusion has been used to treat liver metastases, particularly from colonic cancers in adults. Again the usefulness of this approach is limited in children where systemic therapy is needed for most tumours because of the pattern of tumour spread. It may have some place in the treatment of

hepatoblastoma. Randomised trials comparing regional perfusion with systemic therapy have not shown a specific advantage for localized therapy.

For solid tumours, chemotherapy has two main goals – to eliminate overt metastases or microscopic spread, and to destroy or reduce the primary tumour mass so that, with or without further local treatment, complete response (CR) can be obtained. Without complete response, cure will never be possible. For the purposes of comparison in trials, different categories of Response criteria are used to assess the effectiveness of systemic treatment (Table 9.7).

Management of Side Effects of Chemotherapy

Acute Complications

Early complications include metabolic disorders (tumour lysis syndrome), bone marrow suppression, immunosuppression, nausea and vomiting.

Tumour Lysis Syndrome

Patients with large tumour burden may have substantial breakdown of tumour cells following the start of treatment and renal function may be impaired from uric acid nephropathy. This problem is seen most often in haematological malignancies, but can occur in solid tumours (Burkitt's lymphoma, germ cell tumours, metastatic neuroblastoma). Before initiating treatment for these malignancies, renal function should be measured, adequate hydration should be ensured and Allopurinol (xanthine-oxidase inhibitor) should be given. In patients with very high risk of tumour lysis (bulky disease, high white cell count in acute leukaemia, high lactate dehydrogenase (LDH) and uric acid, those presenting with oliguria) Rasburicase (urate oxidase inhibitor) should be used to avoid tumour lysis syndrome. In the tumour lysis syndrome the phosphates and potassium are released into the circulation from cells that are lysed by chemotherapy, leading to hyperkalaemia, hyperphosphataemia, hypocalcaemia. It is prudent to inform the renal team as the treatment is initiated in these high risk cases. It is also important to remember that there other causes of renal failure (obstruction of urinary tract, sepsis, fluid shifts) apart from tumour lysis in these patients.

Table 9.7 For the purposes of comparison in trials, different categories of Response criteria are used to assess the effectiveness of systemic treatment. In general these are as follows

Response criteria for solid tumours:
Complete Response (CR): Complete disappearance of all visible disease.
Very Good Partial Response (VGPR): Tumour volume reduction ≥90 % but <100 %
Partial Response (PR ≥ 2/3): Tumour volume reduction ≥66 % but <89 %.
Minor Partial Response (PR < 2/3): Tumour volume >33 % but <66 %
Stable Disease (SD): No criteria for PR or PD (<33 % tumour volume reduction)
Progressive Disease (PD): Any increase of more than 40 % in volume (or >25 % in area) of any measurable lesion, or appearance of new lesions.
Response criteria for CNS tumours:
Complete Response (CR): Disappearance of all enhancing tumour
Partial Response (PR): ≥50 % reduction in size of enhancing tumour
Progressive Disease (PD): ≥25 % increase in size of enhancing tumour
Stable Disease (SD): All other situations

Bone Marrow Suppression

Tumours that invade the bone marrow can cause pancytopenia. The majority of chemotherapy drugs produce myelosuppression. Anaemia can be corrected by transfusions of packed red cells and thrombocytopenia by platelet transfusions. Neutropenia (ANC $<0.5 \times 10^9$/l) poses a significant risk of life-threatening infection. Febrile neutropenia patients should be hospitalised and treated as an emergency with empirical broad spectrum intravenous antibiotics pending the results of appropriate cultures. Treatment should be continued until the fever resolves or neutrophil count rises. If there is no response to antibiotics, antifungal or antiviral drugs may be required. Fever may be related to sepsis from indwelling central venous line requiring its removal. Bone marrow recovery may be facilitated by the use of G-CSF (granulocyte colony stimulating factor).

Infection

Opportunistic infections with pneumocystis carinii can produce fatal interstitial pneumonitis and prophylaxis with Trimethoprim/Sulfa-methoxazole is recommended where severe immunosuppression is anticipated from chemotherapy.

Children receiving chemotherapy and exposed to chicken pox contact require zoster immunoglobulin and if clinical disease develops, they require hospitalisation and treatment with intravenous high dose Aciclovir.

Nausea and Vomiting

This is often the most troubling side-effect from the patient's point of view and should be treated effectively from the first course of chemotherapy. Protocols containing Cisplatin, Actinomycin-D and Cyclophosphamide or Ifosfamide are associated with the highest incidence of vomiting, but sickness is also a problem with Procarbazine, Adriamycin® (Doxorubicin), Daunorubicin and Carboplatin. The new

5-hydroxytryptamine (5-HT_3) antagonists such as Ondansetron and Granisetron act centrally in the chemo-receptor trigger zone in the brain and are effective in preventing vomiting with most agents. These drugs are given intravenously at the time of chemotherapy and orally for 5 days until the gastrointestinal side-effects resolve. Dexamethasone is often added, also for 5 days, and is effective, though its mechanism of action is uncertain. Additional sedation, and relative amnesia, can be obtained by including Benzodiazepine such as Lorazepam in the anti-emetic regimen. If emesis is less severe, Domperidone, Prochlorperazine, Chlorpromazine or Metoclopramide have been used but are less effective and may have troublesome side-effects.

Malnutrition/Mucositis

This is a particular risk in patients receiving intensive chemotherapy, radiotherapy to the abdomen or head and neck. As these treatments cause mucositis, careful oral hygiene is important during this phase. If oral or enteral intake is inadequate then patients may require intravenous fluid and electrolyte supplementation or total parenteral nutrition. Intravenous opiate analgesia may also be required at this time.

Late Effects

Successful treatment of childhood cancer with multi-agent chemotherapy in combination with surgery or radiotherapy causes significant morbidity in later life [15]. Successful surgical resection may require the loss of important functional structures. Radiotherapy can produce irreversible organ damage with symptoms and functional limitations depending on the organ involved and the severity of damage. Endocrine consultation regarding growth, sex maturation and thyroid function is necessary for any child who has received cranial or total body irradiation, or who has chemotherapy-induced ovarian or testicular damage.

Chemotherapy also carries the risk of severe organ damage. Of particular concerns are leucoencephalopathy after high dose Methotrexate therapy, myocardial damage from anthracyclines, pulmonary fibrosis after Bleomycin, sterility in patients treated with alkylating agents, hearing loss after Cisplatin chemotherapy and renal tubular damage from Ifosfamide. Patients must be closely monitored by obtaining baseline and sequential measurements during their treatment, wherever possible.

Psychosocial evaluation and educational support is often needed especially following treatment of brain tumours in children. Periods of physiological stress, for example pregnancy, may lead to overt expression of subclinical damage (e.g. heart failure after Adriamycin (doxorubicin) or foetal loss after uterine muscle irradiation). Long-term follow-up of all children treated for cancer is essential if we are to improve the cure rates and minimize harmful effects of treatment including the increased risk of second malignancy.

New Drugs for Children and Adolescents with Cancer

The overall cure rate for children diagnosed with cancer now approaches 80 % [16]. Although this means 1/5th of children will die of their disease and 40 % [17] of survivors are burdened by the late effects of therapy, this still represents one of the most remarkable improvements in outcome in modern medical history. Thirty years ago cure rates were <20 % and it is only 50 years ago that the outcome for children with cancer was so appalling that there were strong debates about the ethics of giving children chemotherapy at all.

As alluded to earlier in this chapter, part of this turnaround can be attributed to improvements in surgery, radiotherapy, and supportive care. As a consequence, it is now rare for children to die during their anticancer therapy. Much of the turnaround, however, has been as a direct consequence of a better use of standard chemotherapeutic drugs. It is unlikely that further improvements in cure rates will be achieved by modification of existing modalities of treatment. Novel compounds as well as novel approaches to treatment will be required to help children who are currently incurable.

The explosion of molecular biological knowledge and techniques coupled with a better understanding of host/tumor interactions has spurred on whole new areas of drug development. However, host/tumor inter-actions have long been recognized: In the 1800s, Coley, demonstrated tumor regression following infection in some of his patients [18]. Donor Lymphocyte Infusions (DLI) following allogenic transplantation is now standard hematological practice (see below) The drive for all new therapeutic interventions is to devise compounds that maximally target the tumor and minimize or avoid systemic side effects. New risk based algorithms will be needed to better define an individual's response to therapy and maximize each child's chance of cure.

The era of personalized medicine has been ushered in by a revolution in the understanding of tumour and host biology. Hanahan and Weinberg's model of cancer at a cellular level [19] provides a framework that neatly encapsulates how new drug development has evolved. Each of their 6 hallmarks have been targeted by novel compounds (See Fig. 9.2).

They have recently further clarified this model adding two further emerging hallmarks and two enabling characteristics of tumours which will allow for further sophistication in drug selection and trial design.[20] (See Fig. 9.3).

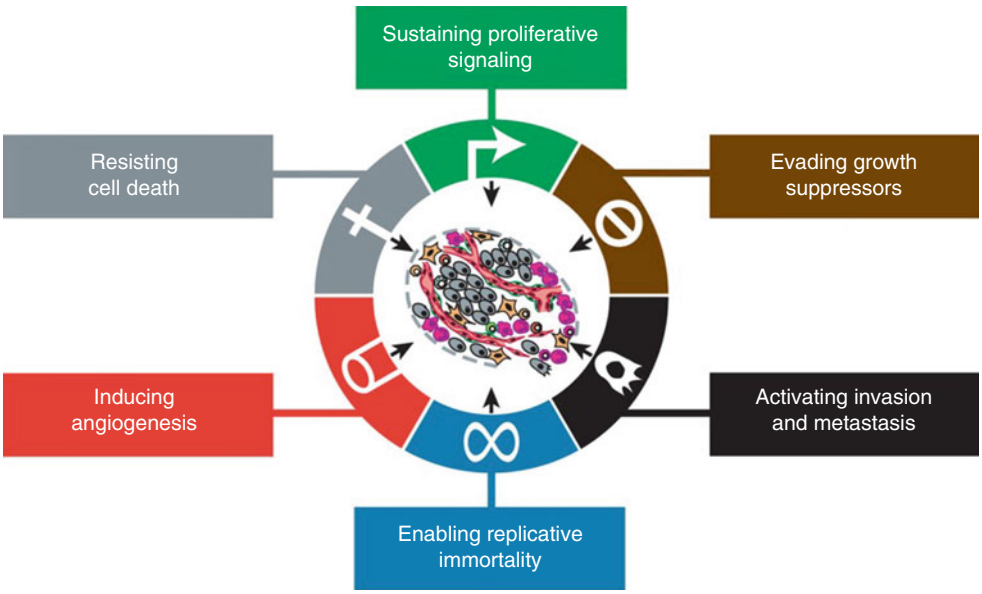

Fig. 9.2 Hanahan and Weinberg's model of cancer at a cellular level provides a framework that neatly encapsulates how new drug development has evolved. Each of their six hallmarks have been targeted by novel compounds [19]

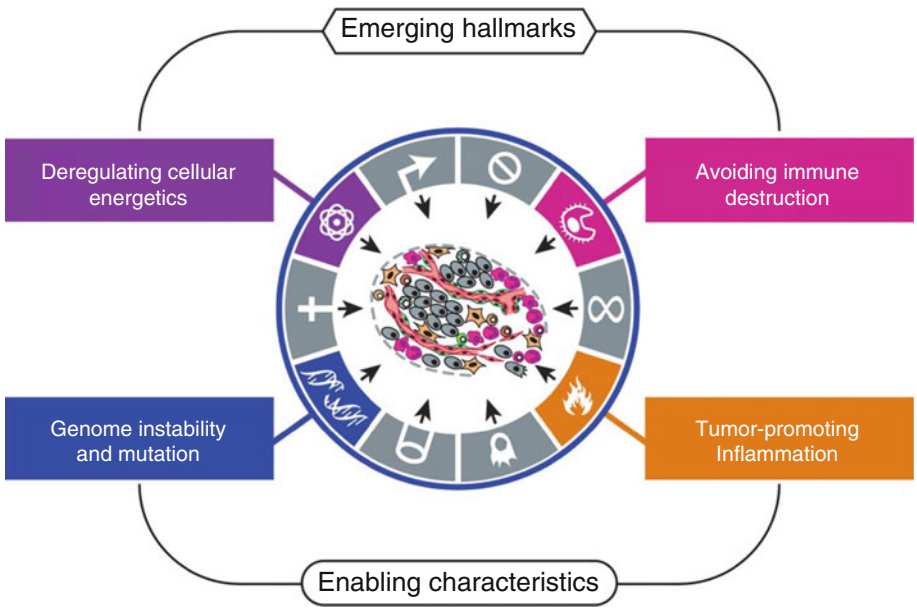

Fig. 9.3 Hanahan and Weinberg's model further clarified by adding two further emerging hallmarks and two enabling characteristics of tumours which will allow for further sophistication in drug selection and trial design [20]

Targeted Therapy

Improved understanding of cellular biology, including surface markers and intra cellular pathways has led to an explosion in targeted agents. There are over 800 compounds currently in development. Some target specific paediatric diseases but many more share common targets with adult tumours (See table 9.8) [21].

Those drugs sharing a common target which may be beneficial to children should be identified and fast tracked for development.

Examples of successful targeting are illustrated by the Tyrosine Kinase Inhibitors: tyrosine kinases act on act on pathways and biological systems that are responsible for many aspects of cell survival. These pathways are important in cellular proliferation, differentiation, motility, and apoptosis. There are two main classes of tyrosine kinases: transmembrane proteins and those found within the cell (see Fig. 9.4). Both have enzymatic properties under strict regulation so that cells that are not rapidly dividing have very low levels of tyrosyl phosphorolated protein [22]. The first successful clinical use of a tyrosine kinase inhibitor was imatinib in chronic myeloid leukemia (CML) [23]. This dramatic response accelerated research into tyrosine kinase inhibitors for solid tumors. The most successful use so far has been in adults with gastrointestinal stromal tumors (GISTs) where Imatinib has been

Table 9.8

	Target	Adult disease	Pediatric disease
Same target and disease			
Vemurafenib,3 dabrafenib25	V600E BRAF	Melanoma	Melanoma
Ganitumab,26 figitumumab,27 R150728	IGF-1R	Ewing's sarcoma	Ewing's sarcoma
Not yet developed	PARP	Ewing's sarcoma29	Ewing's sarcoma29
Imatinib,5,30dasatinib,31 nilotinib32	BCR-ABL	Chronic myeloid leukaemia/ Philadelphia-chromosome-positive acute lymphoblastic leukaemia	Chronic myeloid leukaemia/ Philadelphia-chromosome-positive acute lymphoblastic leukamia
Brentuximab vedotin33	CD30	Hodgkin's lymphoma, anaplastic large-cell lymphoma	Hodgkin's lymphoma, anaplastic large-cell lymphoma
Crizotinib12	ALK	Anaplastic large-cell lymphoma	Anaplastic large-cell lymphoma
Rituximab34	CD20	Non-Hodgkin lymphoma	Non-Hodgkin lymphoma
Midostaurin35	FLT3	Acute myeloid leukaemia	Acute myeloid leukaemia
Blinatumomab36	CD19	Acute lymphoblastic leukaemia	Acute lymphoblastic leukaemia
Same target but different disease			
Crizotinib	ALK	Non-small-cell lung cancer4	Neuroblastoma12,37
Vemurafenib, dabrafenib	V600E BRAF	Melanoma3,25	Glial tumours,38 histiocytosis39
Dalotuzumab, ganitumab, figitumumab, R1507	IGF-1R	Breast, prostate, lung40	Wilms' tumour, neuroblastoma22,41
Everolimus	mTOR	Kidney,42 breast,43 pancreatic neuroendocrine tumours44	Subependymal giant-cell astrocytoma associated with tuberous sclerosis21
Vismodegib	Hedgehog pathway	Basal-cell carcinoma45	Medulloblastoma6,46
Sorafenib	FLT3	Renal-cell carcinoma,47 hepatocellular carcinoma48	Acute myeloid leukaemia49
Specific paediatric target and disease			
ch14.18,50 ch14.18/CHO51	GD2	–	Neuroblastoma
Not yet developed	N-MYC52	–	Neuroblastoma
Not yet developed	PAX3/7-FOXO153	–	Rhabdomyosarcoma
Not yet developed	EWS-FLI54	–	Ewing's sarcoma

used to target mutations in c-KIT. Preclinical data show expression of c-KIT and platelet-derived growth factors (PDGF) in other solid tumors. Many of these affect children and include glioblastoma, sarcomas, and chondromas.

Other targets that may be inhibited by small molecules include endothelial and vascular endothelial growth factors (EGF/VEGF) (See Fig. 9.3) and once again evidence of expression has been found in cell lines in many pediatric tumors. Drugs targeting these pathways are currently undergoing Phase I and II trials in the pediatric setting.

Similarly Vismodegib, a sonic hedgehog pathway inhibitor has improved outcomes for adult patients with basal cell carcinomas [24]. Crizotonib, which targets the ALK pathway is effective in non-small-cell lung cancer [25]. In some ways the commonality of pathways such as IGF-1R [26], mTOR [27] and PARP [28] overcomes the hurdle imposed by the epidemiological differences between paediatric and adult, teenage and young adult and adult tumor types (Fig. 9.5) [16].

However different alterations in the same gene have been noted in different diseases, for example ALK is translocated in anaplastic large cell lymphoma, lung cancer and inflammatory myofibroblastic tumours but amplified or mutated in neuroblastoma. This may result in differing outcomes in different diseases despite targeting the same pathway. Children could be exposed to inevitable side effects with no benefit, or even worse, the disease could be driven at a molecular level rather than being inhibited. Functional validation and evidence of anti tumour activity in pre clinical models is vital before "first time in child" clinical trials.

Cell surface markers can also act as targets for drug therapy, however the 30 years since Kohler and Millstone's landmark publication [29] describing, for the first time, a generation of humanized monoclonal antibodies from mice has been frustrating. This tantalizing paper opened the promise of "magic bullet" therapy. Unfortunately, this initial enthusiasm gave way to the harsh reality of drug development. For this type of biological agent to be effective many hurdles have to be overcome. Tumor antigens need to be expressed on cell surfaces, there needs to be a high binding affinity between these markers and the compound and the antigens themselves should be specific-specific. Significant problems with allergy and toxicity also have to be overcome. However, much has been learned during this time and that knowledge in itself has spurred further drug development.

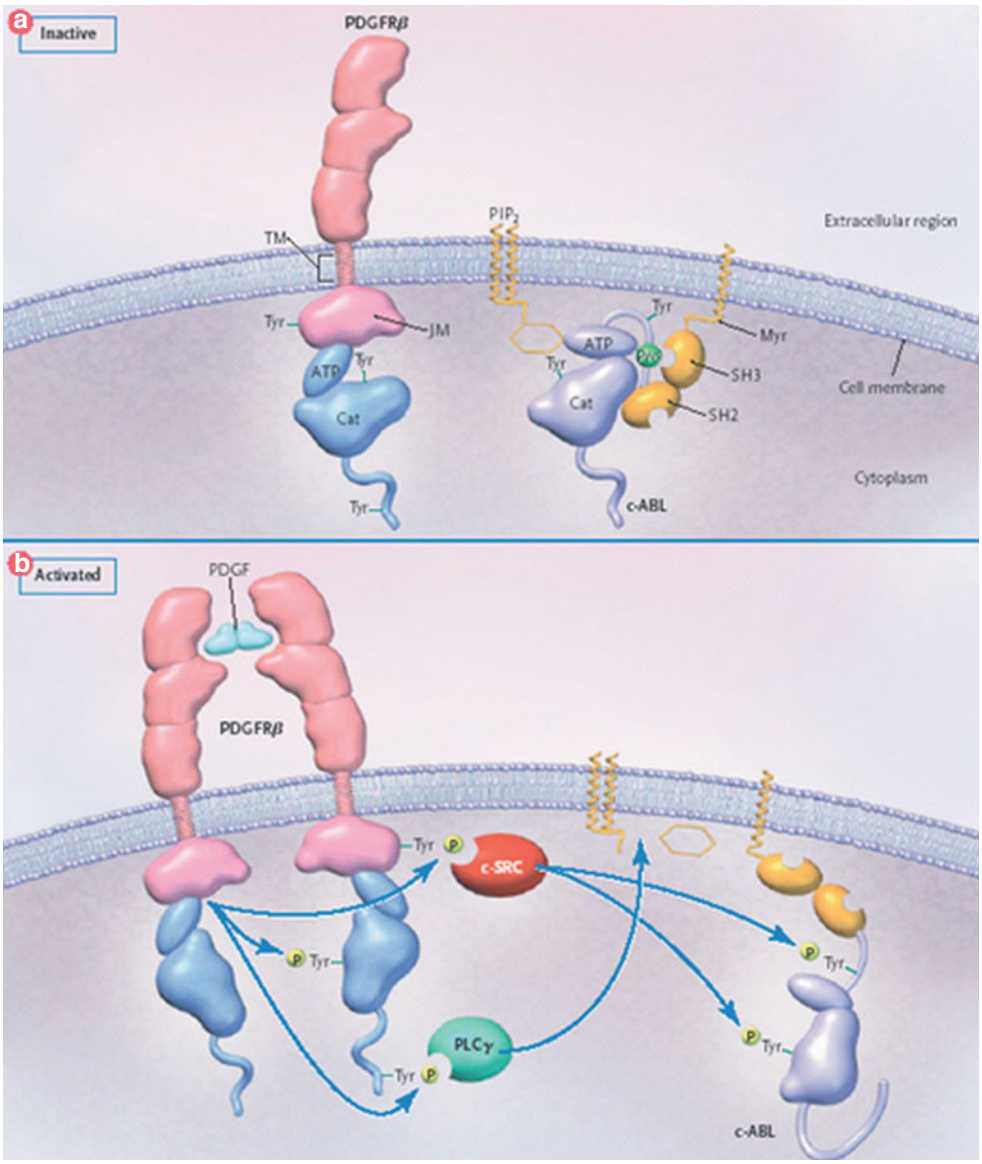

Fig. 9.4 Mechanisms of activation of normal TKs. A typical receptor TK [platelet-derived growth factor receptor β (PDGFR β)] and nonreceptor TK (c-ABL) are depicted, with the ATP- binding (ATP) and catalyic (*Cat*) lobes of the kinase domains and the transmembrane (*TM*) region of PDGFRβ indicated. Panel (**a**) shows both kinases in their inactive states. Inactive PDGFRβ is monomeric and unphosphorylated, and the catalytic domain is inhibited by protrusion of a regulatory tyrosine (*Tyr*) in the activation loop into the substrate cleft and by an intramolecular interaction with the juxtamembrane (*JM*) domain. Inactive c-ABL is associated with the membrane through a covalent N-terminal myristate group (*Myr*) and is inhibited through intramolecular interaction of the Src homology-3 (*SH3*) domain with an adjacent proline (*Pro*) residue and by direct interaction of the catalytic domain with an inhibitory membrane lipid, phosphatidylinositol-4,5-bisphosphate (*PIP2*). In Panel (**b**), PDGFRβ is activated upon binding of the ligand (dimeric platelet-derived growth factor (*PDGF*), which induces oligomerization of the receptor and intermolecular phosphorylation (*P*, in *yellow*) of the activation on-loop tyrosine. This leads to a conformational change in the catalytic domain and increased enzymatic activity, while phosphorylation of other tyrosines within the intracellular domain of the receptor creates binding sites for SH2 domain-containing signaling proteins, including c-SRC (*red oval*) and phospholipase Cγ (PLCγ) (*green oval*). c- ABL is activated through the phosphorylation of two regulatory tyrosines, one in the activation loop and the other near the SH3 binding site, which can be phosphorylated by another TK, such as c-SRC. In addition, activated PLCγ can hydrolyze and destroy the lipid inhibitor PIP2 (Further detail is provided in the review by Krause and Van Etten [38])

It is also important to understand whether the target for monoclonal antibody therapy is present on the tumor mass alone or on the tumor stem cells (e.g., CD33 is present on committed AML blasts but absent from the leukemic stem cell). If the target is only expressed on mature tumor cells the monoclonal therapy should be seen as cytoreductive therapy. However, if the tumour stem cell expresses the antigen, monoclonal antibody therapy can be used in the setting of minimal residual disease where a successful result is more likely.

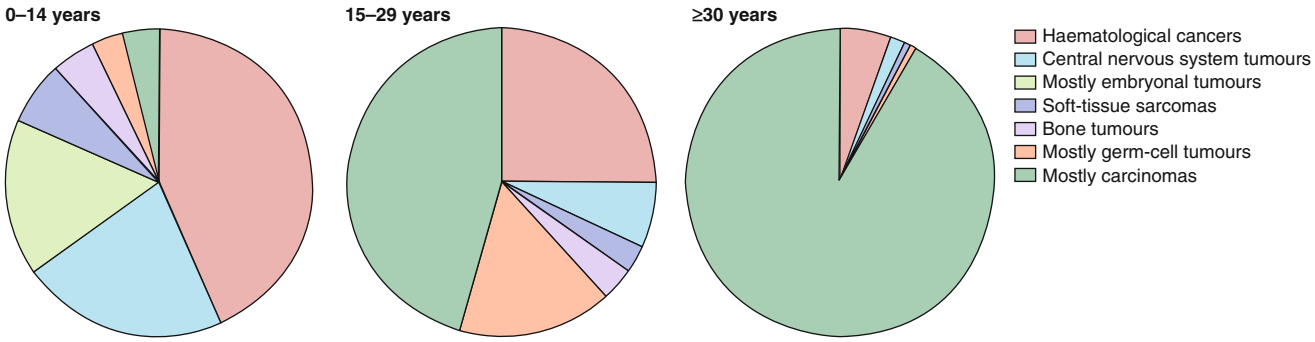

Fig. 9.5 In some ways the commonality of pathways such as IGF-1R7, mTOR8 and PARP 9 overcomes the hurdle imposed by the epidemiological differences between paediatric and adult, teenage and young adult and adult tumor types

The era of monoclonal therapy has firmly arrived: Rituximab, a monoclonal antibody targeting cells expressing CD20 antigens, is licensed for use against follicular lymphoma and diffuse large B-cell non- Hodgkin's lymphoma (NHL) [30]. Cetuximab is active against tumors expressing epidermal growth factor (EGFR). It has been used in adult practice against metastatic colon cancer and advanced squamous cell cancers in the head and neck [31].

The most impressive use of monoclonal antibody therapy in childhood solid tumours has been seen in neuroblastoma treatment. The chimeric anti GD2-antibody ch14.18 was used in combination with IL2 and GM-CSF and seen to improve 2 year overall and event free survival in children in a state of minimal residual disease, treated with a variety of induction regimens and following autologous stem cell transplant [32]. Further encouraging 10 year survival figures for German children exposed to the antibody alone raise the possibility of prevention of late relapse [33]. However fundamental questions about the role of each of the immunomodulatory agents and how they should be used in combination still remain.

Other Immunomodulators

Other biological agents act by immunostimulation or by driving differentiation: Muramyl tripeptide phosphatidylethanolamine (MTP-PE) induces phagocytosis and costimulation of cytokines. Some useful effect has been seen in osteosarcoma [34] and it is likely to form part of the next international Phase III trial in that disease.

All-Transretinoic acid (ATRA) drives differentiation of the promyelocytes in the APML variant of Acute Myeloid Leukemia. Cis-retinoic acid drives differentiation of primitive neuroblasts to mature ganglioneuronal cells. Both of these retinoids are now incorporated in the standard treatment of these diseases in children.

Cancer Vaccination and T-cell Therapy

Vaccination works by stimulating host T-cells to fight off disease. Anticancer vaccines have been worked on for many years and recent increased understanding of cellular biology has meant there have been crucial developments in producing useful anticancer vaccines. Vaccination strategy is not only dependent on optimizing antigen presentation but also the interaction of that presenting cell with disease-modulating T-cells. The most exciting results have been seen using patient-specific vaccines derived from autologous tumor cell lines. Melanoma, which increasingly affects teenagers and young adults, has shown the most susceptibility to a vaccination approach. A recent report of patient-specific dendritic cell vaccines in a cohort of heavily pretreated patients with metastatic disease, will hopefully prove to be a large step forward in the long search for a successful anticancer vaccine [35]. The United Kingdom has recently opened a phase I trial of dendritic vaccine therapy for children with relapsed or progressive high grade gliomas.

The infusion of donor lymphocytes following bone marrow transplant in patients with relapsed leukemia has become standard practice in pediatric patients. These T-cells are not specific-specific and are associated with the development of significant graft-versus-host-disease (GVHD). Indeed, it is believed that the mechanism for GVHD is closely related to the mechanism for the graft-versus-leukemia-effect (GVL) and clinicians view mild GVHD post DLI as a marker of effect. However, specific-specific T-cell populations have the advantage of destroying the disease with less systemic side effects. Manipulated cytotoxic T-cells have been successful in eradicating viral-induced cancers: EBV-driven lymphoproliferative disease, Hodgkin's disease, and nasopharyngeal carcinomas have all responded to EBV-specific cytotoxic T-cell therapy [36]. Despite the excitement generated by novel therapies, there are of course challenges to their use. Although their toxicity should be less than a conventional chemotherapeutic agent, this does not mean they are without significant

side effects. Allergic reactions and cytokine release syndromes are common following monoclonal therapy. Cytokine storms have resulted in life-threatening events [37].

Immune disregulation, cardiotoxicity, and skin problems have all been noted as side effects of targeted small molecules. Resistance to therapy is increasingly recognized and mono-therapy with targeted agents is as unlikely to be successful as it is with conventional agents.

Future Challenges

We are unlikely to see the large step change in cure rates that has characterized the last 30 years of anticancer therapy in children. As important as an increased understanding of molecular biology will be a regulatory and fiscal environment that encourages new drug development in rare tumors. There will also need to be improvements in trial design and analysis to be able to identify real but small improvements in outcome. There will need to be co-operation and partnerships between clinicians, scientists, statisticians regulators and the pharmaceutical industry. Long-term follow up will be crucial in identifying any, as yet, unrecognized late effects.

So what does the future hold? Genetic analysis at birth may be able to predict life time risks and allow tailored lifestyle advice. Chemo-prevention and prophylactic surgery are already established adult practice. Real time micro array is now being used to augment pathology in a large breast cancer trial. Disease biomarkers will need to be better understood and validated. It is likely that gross disease will continue to be debulked by traditional treatment modalities. This may be followed by establishing a patient-specific, tumor profile with microarray technology, host genetics may give a clear picture of innate drug handling, allowing a truly bespoke, targeted attack of disease residuum with a combination of small molecules, immunomodulation, or vaccination.

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Radiotherapy

10

Fiona Cowie

Introduction

With improvements in staging, surgery, and systemic therapies, the role of radiation treatment in children has changed dramatically over the past few decades. Improved cure rates as demonstrated in sequential clinical trials have shifted the focus from cure alone to cure with best long-term function and quality of life. This has particular implications for radiotherapy where the long-term consequences are well recognized. Over the same period pediatric radiotherapy has become more refined as a result of improvements in techniques for both planning and delivery of treatment. Whenever radiation therapy is being considered for a child the indications should be very carefully thought through and the role of radiotherapy in that child's management continually appraised.

Radiation can now be (almost) completely omitted from the treatment of some disease types, for example non-Hodgkin's lymphoma where it's only role is in palliation, relapsed or CNS disease.

What Is Radiotherapy

Radiotherapy (RT) is the treatment of disease (almost exclusively malignant tumors) with electromagnetic or particle radiation. This may be delivered as beams from outside the body (like an x-ray) often called XRT, or by using radioactive material, which is inserted (e.g., radioactive source), ingested (Iodine) or injected (mIBG). Most radiation treatment is external beam radiation and is delivered using a machine called a linear accelerator, which delivers photon radiation; some machines can also produce electrons. Rarely now cobalt sources are used, although historically they were very important. Some departments may have a proton beam treatment unit, although there is no suitable facility in the UK.

The energy from radiation is ionizing. This means that it disrupts the atomic structure of material it passes through, in this case human tissue. Ionization produces chemical and biological changes in tissues. These changes may be to any molecular cell component; however, the most important is damage to DNA, especially bonds between molecules.

This DNA damage may not be expressed biologically for years. Some cells will die quickly (apoptosis); however, others will do so at a later date when a damaged region of DNA is "used." Some cells function too poorly to divide but may die earlier than expected.

Normal tissue is affected in the same way as malignant tissue, but normal cells initially have more intact DNA and their DNA repair is better (especially in tissues with rapid turnover, for example, mucosa).

Radiobiology

Radiobiology is the study of the effects of radiation on tissues and how particular cells or tissue types are affected by the type of radiation, total dose given, dose per fraction, interval between fractions, and overall duration of treatment [4]. This has allowed the development of radiotherapy schedules; initially these were empirical but have now evolved with a strong scientific basis. Much of this data is from cell line work and may be expressed as SF2; this is the surviving fraction (of cells) after 2 Gy. Using this type of experimental data a comparison can be made between tumor types or treatment conditions.

Type of Radiation

The energy of a radiotherapy beam and what it is made up of (photons, electrons, or protons) will affect the way in which this energy is deposited in tissue and thus affect the tissue

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response to it. For example, low energy photons (orthovoltage or kilovoltage) are preferentially absorbed in bone and do not exhibit the skin-sparing phenomenon seen with megavoltage photon irradiation. For this reason orthovoltage radiotherapy can be particularly useful for treating skin or bone lesions. In children, however, it may cause greater disruption of bone growth in the longer term than higher energy treatment.

Total Dose

The total dose needed for different tumor types varies; some are more sensitive (e.g., lymphoma, leukemia), others are relatively resistant (e.g., osteosarcoma), many, however, are between these extremes. For example, we know that the dose needed to treat Ewing's sarcoma is greater than that needed for Wilms' tumor. This knowledge guides the recommended total dose delivered. The dose required doesn't vary with the age of the child – though the biology of a particular tumor may vary between a very young child compared with an older child (e.g., neuroblastoma). Radiation dose is commonly expressed as Gray (Gy) or centigray (cGy), where 100 cGy = 1 Gy.

Dose Per Fraction

If the total dose were delivered in a single treatment the antitumor effect would be excellent; however, the effect on normal supporting tissues would unfortunately be devastating. For the majority of situations where a large area or volume of the patient has to be treated this is unacceptable. There are two main exceptions to this, palliative treatment (where the total dose is lower), and small brain lesions. The latter can be treated with stereotactic radiosurgery (single treatment to a small area with a high dose using multiple fields) though this is not employed as often in children as in adults.

The total dose is therefore divided into a number of small doses or fractions, which are delivered on a daily (or more rarely twice a day) basis. This allows the normal tissues (and the tumor cells) a chance to repair some of the DNA damage. The reason radiotherapy works to kill tumor cells is that they do not repair DNA damage as efficiently as normal cells.

As the dose per fraction gets smaller, there is greater relative sparing of normal tissues, but a higher risk that tumor cells are also spared permanent damage.

This illustrates the reason why gaps or breaks in treatment are detrimental to clinical outcome; a break in treatment will allow time for more DNA repair. Clinical data bears this out, e.g., medulloblastoma, survival is linked to overall time of radiation treatment.

Interval Between Fractions

Traditionally a dose of radiotherapy is given daily with a 24 h interval between treatments. Shortening the interval between fractions, for example to 6–8 h, should result in a greater biological effect on both normal and tumor cells. If the interval is long enough for the normal tissue to recover, but not long enough for tumor tissue recovery, there will be a greater amount of damage to tumor cells. This type of radiotherapy delivery is called hyperfractionation. It poses logistic problems, as the working day is typically 8 h long. Treatment therefore has to be given first thing in the morning and last thing at night. It is difficult to deliver this type of treatment to an anesthetized child. As there are theoretical advantages in this approach it has been used in both Ewing's sarcoma and medulloblastoma, but does not yet represent a standard treatment approach.

Overall Time

Most radiotherapy departments' work only 5 days a week and some are unable to treat on bank holidays. These gaps in treatment are inevitable; however, it is important to make every attempt to avoid any other gaps in treatment, for example due to transport problems, the patient being too ill to receive treatment, or machine breakdown. When such gaps do occur an adjustment to the remaining treatment may need to be made, although this is not always possible. The result may be a poorer chance of disease control or a greater chance of long-term toxicity.

Typical Pediatric Treatment Schedules

Most children will be treated with fraction sizes of 1.8 Gy (range 1.5–2 Gy) per day, 5 days per week for 2–6 weeks, depending upon the indications for radiotherapy and the disease type.

Challenges of Pediatric Radiotherapy

When radiation treatment is delivered to a child there are a number of aspects that differ from an adult's treatment. These need to be taken into account by the radiotherapy team and department and may necessitate a change in practice compared with "normal" departmental policy [5].

Ensuring the cooperation and compliance of the child is vital if accurate high quality treatment is to be given. This is generally much easier in adult patients who can understand what they are being asked to do and follow instructions, even if they are uncomfortable or scared.

Most pediatric treatment regimens are complex and require different treatments to be dovetailed together. This may cause difficulties in booking radiotherapy as occasionally little warning can be given or dates need to be changed at short notice.

Children are particularly prone to long-term consequences of radiotherapy; growing tissues will ultimately display changes that will never be observed in a fully grown person. Many parts are immature and have to both develop and grow; both of these processes are liable to be affected by irradiation. A particular point of concern is the developing CNS, which is very sensitive to the detrimental effect of radiotherapy. Children under 3 years of age are at particular risk of neurocognitive changes; however, older children may also be affected.

These detrimental effects may be minimized by following the principles of radiotherapy to children, which encourage:

1. Using the lowest effective total dose
2. Using the smallest possible treatment volume
3. Using a low dose rate or dose per fraction
4. Treating over an appropriate overall time

Lowest Effective Total Dose

Dose response curves in radiotherapy are a sigmoid shape (see Fig. 10.1). A small decrease in dose may result in a big reduction in the antitumor effect. Th e risk of side effects can also be expressed with a curve of this shape. Although the total dose used has to be effective at dealing with the tumor, if it can be reduced a little this may significantly decrease the long-term toxicity.

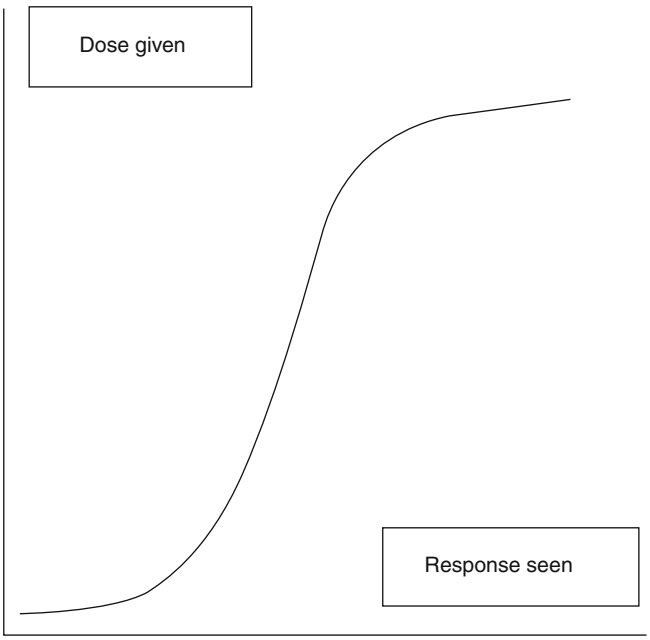

Fig. 10.1 Typical sigmoid dose-response curve

The small bowel, for example, presents a problem; toxicity is expressed rapidly and bowel is often unavoidably treated. Here, however, a small reduction in dose can result in a significant reduction in toxicity.

Smallest Possible Treatment Volume

Careful use of shielding and consideration of field arrangement will help to avoid structures at greatest risk of side effects. In this way the lens of the eye may be spared, or the jaw and developing teeth. The dose received by any area or organ at risk can be estimated during planning and in some cases measured during treatment.

Due to the known effects of radiotherapy on growing and developing tissues, symmetrical irradiation of the neck and spine is generally encouraged. For example, stage 1A Hodgkin's of the neck can be treated with radiotherapy alone, but conventionally the whole neck is irradiated even if the disease is unilateral.

In order to avoid an "organ at risk" (OAR), the beam arrangement or shape of the field may be manipulated, providing the target area is still treated appropriately. There may need to be a clinical decision about which toxicity is "preferable," or whether the target can be compromised. An example of this would be avoiding the femoral epiphyses at the expense of a higher rectal dose in a pelvic treatment.

Low Dose Rate or Dose Per Fraction

As previously discussed, small fraction sizes allow greater normal tissue repair, although if the dose per fraction is too low the desired effect on tumor cells will be reduced. Taken to its extreme, continuous irradiation at a low dose rate allows both recovery of normal tissues and tumor cell death. This is employed in low dose rate brachytherapy.

An Appropriate Overall Time

If treatment is extended over a prolonged time period (e.g., due to patient illness or machine breakdown) the antitumor effect is reduced.

Some protocols are looking at shortening the overall time a treatment is delivered over (e.g., hyperfractionated accelerated radiotherapy HART in medulloblastoma) to increase the antitumor effect.

Procedures

Decision to Irradiate

This is often made after discussion at a Multi Disciplinary Team (MDT) meeting where response on radiological, pathological, or clinical grounds is examined. Many therapeutic protocols specify that radiotherapy needs to be considered at a particular point in the child's overall management. In other cases radiotherapy may be one of the options when management strategy is being formulated [5].

No one takes this decision lightly. There are times when radiotherapy is technically easy but may not be in the child's best interests. On other occasions, radiotherapy may be the most appropriate choice but be technically very challenging.

Booking

All departments will have a system for arranging or booking radiotherapy planning and treatment. This will not only require patients demographic details (name, date of birth, address, etc.) but also the tumor type, site to be treated, need for anesthetic, and much more. A booking request can generally only be completed after a clinical oncologist (radiotherapist) has seen the patient. Departmental policy regarding prioritization varies. There is usually a classification into routine, urgent, and emergency treatments, based upon clinical need and tumor biology. Booking radiotherapy generally authorizes exposure to ionizing radiation (in the form of scans and x-rays), though formal written consent will be required for treatment.

Information Giving and Preparation

Before the child and parents or caregivers visit the department to begin the planning process they need to understand what will happen and what is expected of the child. Many departments will have information sheets or leaflets; some will have videos or websites. An initial visit to the department can be invaluable for children of all ages. This allows them to look around, see into the different areas and rooms they will need to enter, perhaps handle an immobilization device or to move the couch and obviously to ask questions.

Most departments will have an identified person who can act as a link for the family. This may be a radiographer, nurse, play specialist, or doctor.

It is increasingly recognized that pretreatment preparation is vital and may enable children who would otherwise need a general anesthetic (GA) to receive radiotherapy to manage without. Time spent at this stage can result in huge benefits later.

Anesthetic

There will always be some children who are not able to receive radiotherapy without sedation or GA. As children receiving treatment will be alone in the treatment room they need to be remotely supervised, completely still, and may need to wear a restraining/immobilization mask or device. General anesthetic with appropriate telemetry and support/recovery is usually preferred over sedation. For this to be a viable option all rooms used (mould room, simulator, treatment room with back-up room) must be fitted out appropriately. For instance, adequate lighting, anesthetic machine availability, available oxygen and suction, an induction and recovery area. Marks on the shell are used to accurately set up the treatment fields. Telemetry is in place and remotely viewed on a linked screen outside the room.

Venous access is desirable for anesthetic delivery and central venous access in the form of a tunneled line can be justified for daily anesthetics over a week or more. The alternative of using peripheral access will be preferred in some departments.

Pediatric anesthetists obviously play a central role in this part of the service. They must be adequately supported during the procedure and able to ensure the child recovers safely and appropriately each day. As many radiotherapy facilities are remote from a pediatric hospital there are obviously logistic difficulties that must be overcome.

Immobilization

Radiation treatment is planned with very little margin allowed for movement of the patient. It is known that if the patient stays "still" a margin of up to 10 mm needs to be added to the target volume depending upon the site treated. This can be challenging in adults but is more so in children, their smaller overall size means adding this extra margin will irradiate a proportionally larger amount of them.

In all patients, however, accurate and reproducible set up in a comfortable and stable position offers the best chance to get things right. A variety of aids are used here: knee bolsters, vacuum bags, body casts, foam wedges, and beam directing shells all have a place. Vacuum bags are plastic bags full of polystyrene beads that mould to the shape of the patient when the air is sucked out. They retain their shape over the course of treatment (a plug is put in) and can then be reused.

Plastic (or other rigid material) can be used to make a body cast in a similar way. These support part of body in the desired position and can be marked to aid set up.

Plastic beam directing shells (BDS) or masks are used for all head and neck treatments (Fig. 10.2). Here accuracy is more vital and small movements detrimental. Marks drawn on the shell mean that no marks need to be drawn on the patient.

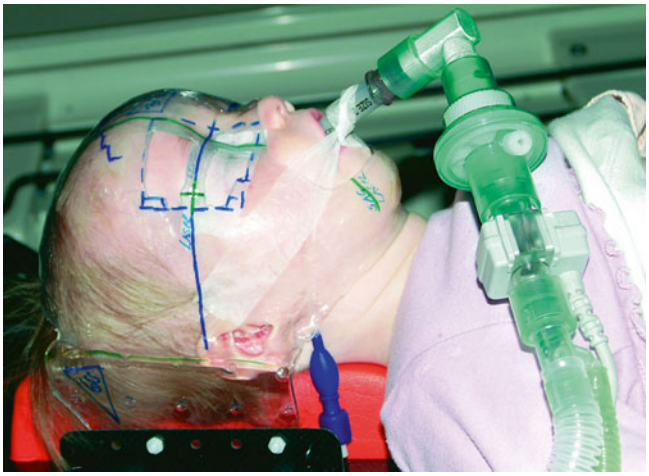

Fig. 10.2 Anaesthetised child with immobilisation shell marks to guide radiotherapy delivery

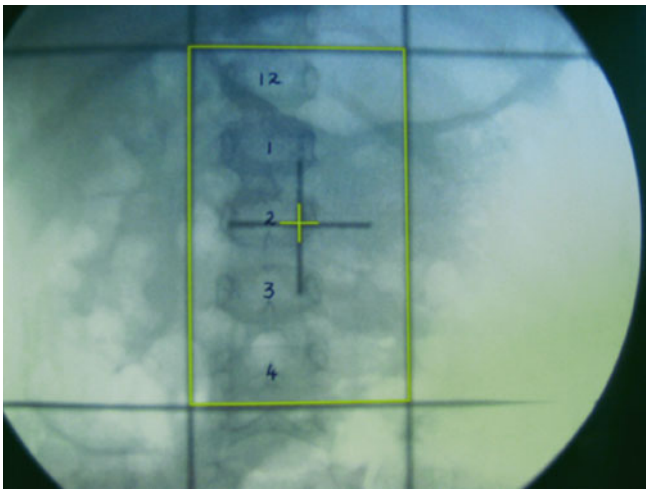

Fig. 10.3 Image showing treatment field edges and field centre. Demonstrates coverage of the full width of vertebral bodies

Planning

All planning and treatment is done with the child in the chosen position and immobilization device. All couch tops are identical in terms of geometry with respect to simulator and treatment beams. Simple planning can be done in a simulator using radiography to define the field to be treated, or by looking at the patient [1].

More complex plans require a CT scan first. Marks are drawn on the patient or radio-opaque markers stuck onto the skin. These will be used to make shifts in position (side to side or up and down) once the plan has been created. These all have to stay on until the patient comes for the next visit (often a week later).

CT scans are used to delineate the treatment volume on a computer-based system. The physics-planning department then creates a plan. This can be viewed on a computer system to look at dose distribution, hot spots, normal tissue doses, etc. before the patient attends for a treatment verification visit.

Verification is carried out before the patient starts treatment; often this is done using beams eye x-ray pictures, which can be checked against the physics plan. An example of this is seen in Fig. 10.3; this shows the field that will be treated for para-aortic nodal irradiation in Wilms' tumor; note the whole vertebral bodies are included to ensure uniform growth. Any changes to be made can be done at this stage. Permanent marks are needed to guide treatment set up on a daily basis. Tattoos are commonly used; these are pinprick marks made at one or more sites. While there is no difficulty performing a tattoo on an anesthetized or older compliant child, younger children may present a problem. Unfortunately, it is not possible to use topical local anesthetic as the precise position of the marks is critical and the location is not certain until the simulation visit is nearly completed. Play specialist input may be helpful for fearful children and many need some preparation.

Consent

Written informed consent prior to any radiation exposure is vital. It is required for all treatments, palliative and radical. The child will have been involved in discussions regarding treatment aims, side effects, and alternatives in an age-appropriate fashion. For those girls who could potentially become pregnant (over the age of 12 years in the UK) a signed declaration that they are not pregnant is required. No pregnancy test is undertaken unless there is uncertainty, in which case a spot urine test is performed.

Treatment

While the planning sessions may take 20–40 min, a treatment session is generally quicker. The total length of time a child is in the treatment room may be 10–30 min, depending upon their cooperation, how quickly the correct treatment position can be obtained, and the number of fields to be treated.

While the treatment beam is on, no one else is allowed in the treatment room. Unlike the simulator or CT simulator, the linear accelerator beam energy means that there is no window into the room. Patient observation is by closed circuit television (CCTV). There may be no physical door, just a long, curved corridor, so a shouted conversation is possible, or an intercom may be used.

Music or a story can be played on a CD player or the radio can be on. In some cases prior preparation is invalu-

able, for instance, asking the parents to practice with the child lying on a table at home, while listening to their chosen music with the parents waiting outside the door. The child can judge how far into the music or story they need to lie for.

It does not hurt to receive radiotherapy. Most patients are not aware of anything during exposure. Side effects may occur hours or days later.

Palliative Treatment

Palliative radiotherapy needs to be quick, simple, and effective. There is much less need to be concerned about the long-term side effects, providing short-term toxicity can be minimized and remain acceptable. Palliative treatments may be given in a single dose or a daily dose over a shorter period of time (a week for example). It is generally possible to get palliative treatment started within a few days of making the decision to irradiate.

In some cases where cure is unlikely aggressive palliative radiotherapy is called for, in the same way that intensive chemotherapy regimens may be used in this situation. For instance, irradiating as many of the disease sites as possible after completion of chemotherapy is suggested for metastatic Ewing's sarcoma, even though this may call for several areas to be treated. Decisions about how this type of recommendation is interpreted need to be made carefully.

Surgical Procedures to Reduce Toxicity of Radiotherapy

In some cases it is possible to insert a sling or mesh to lift small bowel away from the area to be irradiated; tissue expanders can be used in a similar way to push small bowel or other organs away from the irradiated area. Figure 10.4 shows a patient with a tissue expander in his pelvis. The red line shows the target volume and the treatment beams are indicated. The tissue expander helped to keep small bowel out of the treated area. Tissue expanders can be removed after treatment has been completed; a mesh may be absorbable. This approach is only valuable if it is possible to move structures such as the bowel away from the area to be treated. Early and comprehensive discussions between the surgeon, radiotherapist, and radiologist are needed if this is being considered.

Gonads can occasionally be moved to a safer area. If this is being considered it is important to discuss the proposed new location with the radiation therapist prior to surgery. It may be helpful to mark their new position with a clip for localization purposes on the planning images. In this way a dose estimate can be calculated prior to irradiation.

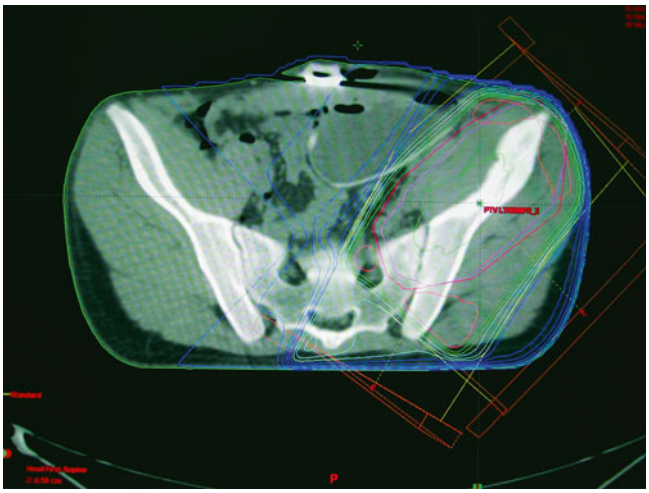

Fig. 10.4 Pelvic CT scan showing spacer, target volume, beam arrangement and isodoses

If any clips are placed at the time of surgery these will be seen at radiotherapy planning. If the operation record states where these are in relation to the tumor bed or at-risk area it can allow the radiation target to be placed with greater certainly. If, however, the clips were placed for hemostasis this should be annotated, as they would not need to be included in the target. Titanium clips are preferred.

Patients with a cystic component to a brain tumor will benefit from aspiration of the cyst to reduce its volume, even if debulking of the tumor is not feasible. The benefit may be seen in terms of clinical improvement; however, from a radiation treatment point of view a large cyst will require larger radiation treatment fields than a small cyst. Care must be taken in this situation to monitor the cyst for reaccumulation as this might push the edge of the cyst or tumor outside the volume being treated.

Surgeons have a common role in placing tunneled central lines or ports and occasionally enterostomy tubes. When required these allow the treatment to be given with a minimum of delay or upset to the child.

Timing of Radiotherapy with Respect to Surgery

Many pediatric oncology treatment protocols specify the sequencing of different treatment modalities, in particular if surgery should precede radiotherapy. There are some situations where preoperative radiotherapy can be considered and may have advantages. This predominantly occurs in the

management of those soft tissue sarcomas where both radiotherapy and surgery are required. In adult sarcoma practice there does not appear to be any difference in survival for patients treated with preoperative compared with postoperative radiation for limb tumors. There is, however, a greater risk of serious postoperative wound complications in the group treated with preoperative radiotherapy. This result may not be directly applicable to pediatric practice as postoperative wound complications are much less common than in adults.

Adverse Effects and Management

Side effects are well recognized and depend a great deal on the area being treated. They are usually divided into acute effects (those seen during the period of irradiation or shortly after) and late effects (these may take months or years to become apparent) [5].

Acute Effects

These are not significantly worse in children than in adults – though they may cause greater distress and require careful management.

Most of these only affect the regions through which the irradiation passes. General side effects, however, occur, such as lethargy or tiredness regardless of the region treated. These are seldom severe in children and many experience no change in their activity levels. Nausea and vomiting may occur if the bowel, stomach, or liver are treated and can also be a problem with some CNS treatments. A standard antiemetic approach with an HT3 antagonist such as ondansetron or granisetron without steroids is usually sufficient. In some cases anorexia due to treatment may necessitate enteral feeding (e.g. craniospinal irradiation).

Skin and mucosal reactions develop during the course of treatment and generally settle rapidly without sequelae, the exception being some severe reactions, which may heal with scarring. It is rare for skin reactions to become severe in children; the doses used are lower than for many adult treatments and recovery more rapid. There are of course exceptions to this, which are usually predictable and dose related. The mucosa affected includes the lining of GI tract, GU tract, and respiratory system. Mucositis may be severe, particularly in those children who are receiving concomitant chemotherapy; occasionally parenteral opiate analgesia and feeding are needed.

Hair loss when a hair bearing area is irradiated develops after 10–14 days. Many children will already have alopecia due to chemotherapy. In rare cases radiotherapy causes permanent hair loss or thinning; this depends upon the total dose, comorbid factors, concomitant chemo, and dose received by hair follicles. Some treatments predictably cause a recognizable pattern of permanent thinning (e.g. posterior fossa boost for medulloblastoma treatment).

Those patients who have received prior or concomitant chemotherapy with drugs that may exacerbate the side effects of radiotherapy should be monitored with extra vigilance. They may develop radiation reactions of greater severity than expected.

Very few patients have a genetic radiation hypersensitivity syndrome (e.g., Ataxia Telangiectasia). Radiation should be avoided in these patients as acute side effects can be devastating or life threatening.

Late Effects

These occur after a time lag of several years or decades. DNA damage during radiotherapy may not be manifested until many years later. Many long-term side effects are a result of damage to endothelial cells lining small blood vessels. This leads to proliferation of small vessels, fibrosis, necrosis, or end organ failure.

The range of problems a child might be at risk of can be predicted from the treatment plan. However, while some of the problems are inevitable, their extent or severity may vary (for example, organ function, growth, or neurocognitive impairment). Other problems are not inevitable, but potentially very serious if they occur (for example, second malignancy).

Impairment to organ function after irradiation depends upon the type of organ involved. In some cases a small part of the organ (e.g., liver or kidney) can be irradiated to a high dose providing enough is left untreated. This is particularly important in those patients with only one kidney after a nephrectomy for Wilms' tumor or neuroblastoma. In other cases (such as spinal cord) no part of the structure can receive a high dose without significant risk of serious sequelae. Figure 10.5 shows a CT planning scan of a child with neuroblastoma; both kidneys are functioning and preserved after surgery. Unfortunately, the tumor bed and resected nodal area need to be irradiated. The red outline shows the tumor bed; the nodal area is not seen on this view as it is situated more anteriorly. The yellow rectangle shows the treatment field that has been further shaped by a multileaf collimator (MLC) indicated by the orange line. In this case treating part of both kidneys is unavoidable, but manageable as the total dose needed is low and enough of each kidney is left unirradiated.

Doses of 25–30 Gy result in failure of soft tissue development (rather than true atrophy). Thirty Gy will inhibit future bone growth, although within a bone there will be cells

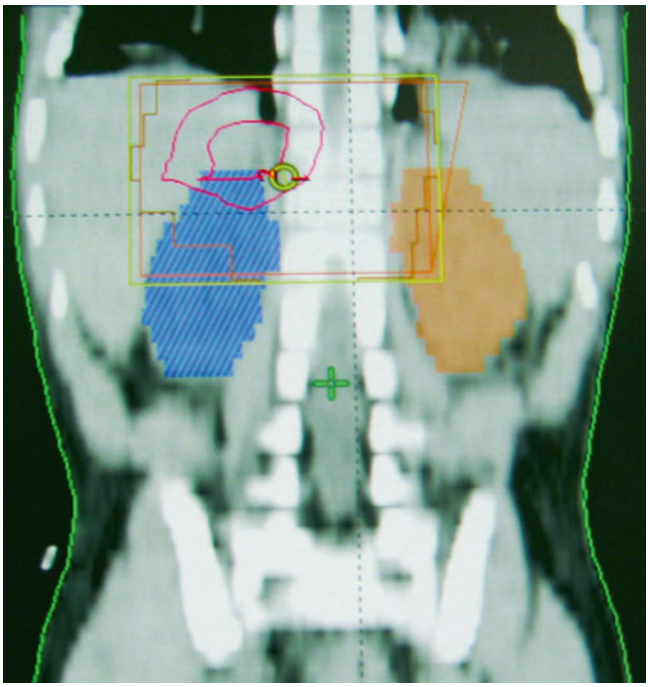

Fig. 10.5 Saggital reformatted planning CT scan showing position of kidneys, target area (*red*) and edges of the anterior treatment field (*yellow*)

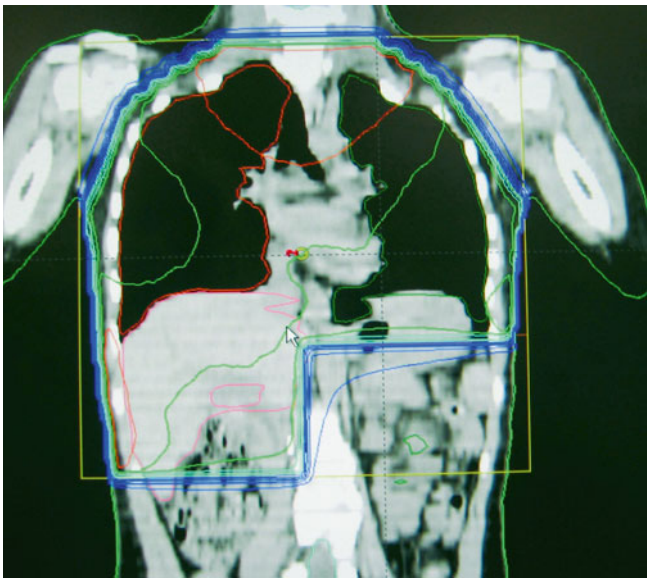

Fig. 10.6 Saggital reformatted planning CT scan showing fields for a patient with Wilms tumour requiring radiotherapy to both lungs and right flank

already committed to "growing" which may produce a further 1–1.5 cm of postirradiation bone lengthening. Less than 30 Gy to bone will also affect growth, but not so severely and as little as 10 Gy can still impair bone and soft tissue growth; this may result in visible cosmetic asymmetry, absence of breast development, scoliosis, or functional problems (e.g. length discrepancy).

As the developing CNS is very sensitive to irradiation, particularly in younger children, developmental delay and neuropsychological impairment are a significant concern. Irradiation is avoided wherever possible. When it is required to effect a cure, careful monitoring and appropriate counseling and advice are imperative.

Second tumors are a devastating consequence of therapy. When they occur, there is generally a lag time of several years and they occur in the region exposed to irradiation [7]. These patients may be susceptible to developing more than one malignancy for a number of additional reasons: genetic factors, use of alkylating and other agents in chemotherapy, and if cured the prospect of a long life ahead.

Figure 10.6 illustrates the fields required for whole lung and renal bed irradiation in a patient with Wilms' tumor and pulmonary metastases. It can be seen from these treatment fields that the large treated area leads to the possibility of serious late effects – especially if the child is very young at the time of treatment. In a girl, both breast buds will be included in these fields; this may result in breast hypoplasia or poor development during puberty and in some cases requires breast augmentation in later life.

Other Techniques

Brachytherapy

This term encompasses treatment that is given by a source emitting radiation; this is inserted into the body or less frequently placed on the outside [2, 6]. These sources are made into a solid object such as wire (iridium), seed (gold), or a flat plaque (ruthenium).

There are a number of different ways this type of treatment can be administered; insertion or application under anesthesia is generally required. Whenever an active source is used, full radiation protection procedures are employed.

The advantage of this approach is that a high dose can be delivered to a small, defined volume. This is particularly advantageous in children, as surrounding organs at risk will receive a lower dose than with conventional external beam radiotherapy. However, there are a number of problems and brachytherapy is not suitable in many situations requiring radiotherapy. The major difficulties are compliance (treatment may require several days in a protected room, with limited close family contact and uncomfortable tubes or sutures), clinical experience, low level of supporting published evidence and concern about long-term effects (these will still occur). Close collabora-

tion between all involved specialties is obviously required, as is specialist accommodation and experience in dealing with this type of treatment. As a result there are only a few very specialized centers where this treatment is offered.

Stereotactic Radiosurgery (SRS)

This refers to the very accurate delivery of a single high dose of radiotherapy using multiple thin beams [2]. At present it is only possible to do this if the area to be treated is in a site which can be immobilized very precisely in order that the target can be accurately localized (eg within brain). It also needs to be small enough (a few centimeters), and not too close to a critical structure (brainstem or optic nerves, for example). This type of treatment causes radionecrosis and there are biological uncertainties about the effect of such a treatment on adjacent normal structures. There are a limited number of suitable situations in pediatric practice, but some small brain lesions may be suitable.

Stereotactic Radiotherapy

This is similar to the SRS (above), however rather than a single treatment on 1 day, multiple treatments are given over a number of weeks. The criteria are similar to SRS except it is employed for potentially curable situations.

Proton Beam Irradiation

Protons are another type of energy (charged particles) that can be artificially produced (by a cyclotron) and used therapeutically [2]. They are available in a few centers and have very different physical characteristics to photons. Their principle advantage is that the energy deposition within tissue falls off abruptly at a defined depth within tissue. This may greatly reduce the volume of tissue exposed to the damage caused by radiation and hence the acute and long-term side effects. Not all situations requiring radiotherapy would be suitable for proton beam irradiation, and in some cases it would offer limited advantages over conventional therapy. However, there are an increasing number of situations where its advantages are being recognized as a way of reducing exposure of normal tissue or increasing dose to a focused target area. Whilst proton beam facilities are available in many countries, there are currently none in the UK for any treatment except intra ocular disease (uveal melanoma).

Proton therapy is currently funded by the UK for certain indications. These patients are treated in the USA or mainland Europe.

Intensity Modulated Radiotherapy (IMRT)

This term refers to a way of delivering conventionally fractionated radiotherapy that may have significant advantages over treatments using fixed beam shaping [2]. It aims to create a uniform dose distribution in the target area by delivering a nonuniform dose to the treatment fields. It requires the shape of the treatment field to constantly change during a treatment and typically the number of treatment fields is greater than the usual 2–4. The advantage in shaping the high dose treatment region around the target while sparing adjacent normal structures may allow the dose to tumor to be increased; this is particularly important in those situations where the tumor is relatively resistant. Equally important is the ability to spare a critical structure that is sensitive to radiation (for example, the spinal cord). There is, however, concern about the great integral dose of radiation received by the whole body from this type of approach which may ultimately be expressed as a higher number of patients developing second tumors in the decades to come [3].

There are many variations of IMRT. These depend upon both the hardware (treatment machine) and software (planning systems) that a particular center is using.

Examples include: VMAT = Volumetric Modulated Arc Therapy
Tomotherapy = Helical IMRT
IGRT = Image guided Radiotherapy, of which Rapid Arc is one example
IMPT = Intensity Modulated Proton Therapy

These are in constant development with new acronyms appearing frequently. The advantages or disadvantages of one over another may be relatively small. Longer follow up is needed to examine outcomes.

Whilst IMRT is increasingly available it is still not routine practice everywhere, and in some situations will not offer advantages over conventional treatment. Its place in pediatric radiotherapy is increasing but continues to be evaluated.

Therapeutic Radioisotopes

This refers to the administration of a radiolabeled target molecule that is specific to certain cells. These cells will be irradiated and therefore damaged. These compounds may be injected or ingested, and may be given alone or in combination with conventional chemotherapy.

The commonest of these is mIBG therapy for neuroblastoma. This is a useful palliative treatment and currently under investigation as part of a curative approach for advanced disease. It requires appropriate care and isolation of the child after treatment to comply with radiation

protection legislation. Typically a child needs to be isolated with limited close contact for several days. Thyroid blockade with iodine is needed. It is, however, a tolerable and often very effective treatment.

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Perinatal Tumors

11

Richard G. Azizkhan and Daniel von Allmen

Introduction

Most solid tumors observed in early infancy are benign. Malignant tumors diagnosed during the neonatal period are rare. They account for only 2 % of all childhood cancers and have a reported incidence of 1: 27,000 live births in the United States [1]. Management of affected infants is extremely challenging. Because factors such as drug absorption, metabolism, distribution, and elimination are affected by age and physiologic maturity, complications associated with the immature physiology of the neonate are common. Age-dependent maturation of the renal, hepatic, hematopoietic, and neurodevelopmental systems make the neonate particularly vulnerable to the deleterious effects of aggressive multimodal therapy involving extirpative surgery, chemotherapy, and radiotherapy [2, 3]. Over the past three decades, the long-term effects of administering anti-cancer therapies to neonates have become increasingly evident [2–9]. An additional complicating factor is that many neonatal malignancies significantly differ from similar tumors in older children with respect to their biological behavior [10–12]. Certain benign tumors (e.g., sacrococcygeal teratoma) may have malignant potential and undergo malignant change if untreated. Other tumors that are histologically malignant (e.g., fibrosarcoma) may exhibit benign behavior. Some benign tumors may be life threatening because of their size, anatomic location, and impact on infant physiology. Congenital neuroblastoma may have an unpredictable course, with many tumors involuting spontaneously and others progressing to a fatal outcome. Due to the rarity of malignant neoplasms in neonates, existing treatment protocols are based on studies that predominantly comprise older children. As such, these protocols do not consider the unique aspects of treating perinatal tumors.

These combined factors make tumors in the neonatal period a unique clinical domain and a domain in which most clinicians have little experience. The aim of this chapter is thus be to provide a broad introduction to the most frequently seen, though rare, perinatal neoplasms.

Overview

Epidemiology and Clinical Presentation

Nearly 50 % of tumors occurring in neonates are observed at birth; another 20–29 % become evident within the first week of life [13, 14]. Although there is variation in the reported frequency of specific tumor diagnoses across neonatal series [15–20], teratomas and neuroblastoma account for approximately two thirds of reported neoplasms. Liver and renal tumors are considerably rarer. The most common finding on physical examination is a palpable mass. Nonspecific symptoms such as irritability, lethargy, failure to thrive, and feeding difficulties may indicate the presence of an occult neoplasm. Petechial hemorrhages and other hematologic abnormalities may indicate extensive bone marrow replacement by tumor cells such as neuroblastoma or leukemia (Fig. 11.1).

The association between congenital abnormalities and tumors is well documented, with concurrence reported in as many as 15 % of neonatal tumors [17, 21, 22]. Many such associations are related to chromosomal defects, particularly trisomies 13, 18, and 21. An increased incidence of leukemia and retroperitoneal teratoma has been reported in neonates with Down syndrome [22] and teratomas are associated with regional and distal congenital anomalies such as cloaca, limb hypoplasia, and spina bifida [20].

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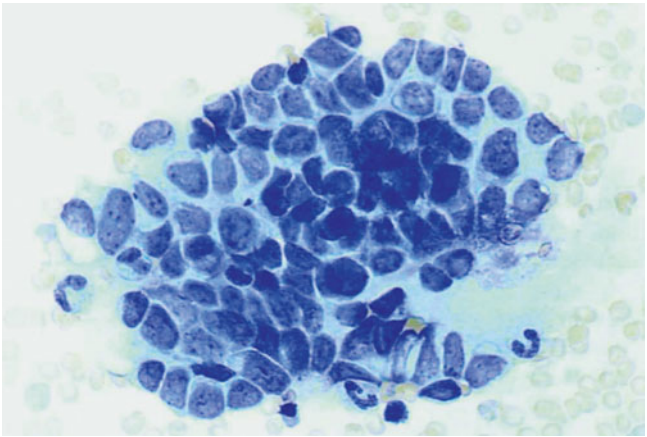

Fig. 11.1 Neuroblastoma cells in bone marrow

Oncogenesis and Genetic Risk Factors

Many neonatal malignancies are inherited or occur spontaneously as the result of a de novo mutational event. The etiology of these tumors is likely multifactorial, including both genetic and environmental factors. Both genetically determined syndromes and constitutional chromosomal defects may result in an increased risk of malignancy. This includes single-gene malignancy-related syndromes and the familial associations of tumors [20]. Particular constitutional chromosome anomalies specifically favor neoplasms occurring in the fetal and neonatal period. These anomalies have been identified in retinoblastoma (13q) and nephroblastoma (11p) [23]. In patients with Denys-Drash syndrome, there is an association with genetic mutations located at 11p13 and WT1. These patients commonly have Wilms tumor. The specific site of the point mutation identified in most cases is located on the WT1 exon 9 [24]. Other examples of constitutional chromosomal anomalies associated with neoplasms include an increased risk of leukemia in patients with Down syndrome [25, 26] and a high frequency of poor-prognosis neonatal leukemia involving the 11q23 locus of the MLL gene. This specific genetic defect is rare in older children [27]. Genes that confer a higher risk of neoplasia by enhancing susceptibility to oncogenic factors are likely to exist and also appear to play a role in certain inherited syndromes. For example, there is an increased risk of hepatoblastoma and rhabdomyosarcoma in patients with Li-Fraumeni syndrome (p53 mutation) [20].

Environmental factors may also play a role in neonatal oncogenesis. A clear dose-related increase in tumor tendency following prenatal or neonatal radiation exposure has been reported [28]. Other possible associations include drugs taken during pregnancy, maternal infections and tumors, and environmental exposure to carcinogens. However, epidemiological data specifically examining these associations is limited, and it is difficult to draw unequivocal conclusions.

Diagnostic Investigations

Dramatic improvements in both prenatal and postnatal ultrasonography (US) and magnetic resonance imaging (MRI) have had a marked impact on perinatal diagnosis, management, and outcome [29–31]. Knowledge of the presence of a fetal tumor allows for timely counseling and close monitoring throughout pregnancy. Prenatal US has been particularly useful in identifying large sacrococcygeal or cervical teratomas that may complicate vaginal delivery or be responsible for intrauterine fetal demise or postnatal complications. US can also detect adrenal or thoracic masses in the fetus, providing useful information regarding both the nature of the mass and, in most cases, its origin. Fetal MRI can better characterize and delineate specific anatomic details and the extent of tumor involvement. These complementary imaging techniques, together with prenatal assessments, enable planning for the mode, timing, and location of delivery as well as postnatal management strategy. Fetal surgery and the ex utero intrapartum treatment (EXIT) procedure are useful in managing non-immune hydrops and congestive heart failure caused by neoplasms. In addition, EXIT to ECMO is appropriate for some patients, allowing a smoother transition from the in-utero state and time to allow postnatal lung development and stabilization of the hydropic infant [32]. Prompt tumor resection is then required. The EXIT procedure is also used to salvage infants with high-grade airway obstruction caused by tumors [33].

Contrast-enhanced computed tomography (CT) provides excellent postnatal images of most neoplasms, though it has limitations in evaluating intraspinal involvement and also has the disadvantage of emitting ionizing radiation. MRI, however, is particularly useful for evaluating tumors that involve the central nervous system or spinal canal. It is also extremely useful in the preoperative delineation of the vascular anatomy of the tumor and adjacent organs. Although limited information is available on the use of positron emission tomography (PET) in neonates, evidence suggests that it is helpful in determining cerebral glucose metabolism and, more importantly, it is useful in the management of selected pediatric patients with malignancy [34, 35]. PET used in conjunction with CT has recently been shown to have a limited role in early diagnosis; however, it plays an important role in initial staging, treatment response evaluation, and detection of metastatic disease in pediatric cancers [36].

Cytogenetics plays an important role in the diagnosis, risk stratification, and monitoring of patients with neonatal tumors. Most cancer cells are thought to have a high incidence of chromosomal changes and genetic mutations that frequently are identifiable and, in some cases, are prognostically significant. For example, N-myc amplification is a specific molecular marker that characterizes a subset of aggressive neuroblastomas that usually has a poor prognosis [37].

Therapeutic Interventions

Surgical Management

Although fetal surgery is occasionally considered for potentially lethal tumors causing non-immune hydrops, the vast majority of perinatal tumors are surgically managed postnatally. Surgical extirpation remains the definitive treatment modality in most neonates with solid tumors. The timing of surgery and the surgical strategies employed must take into account the physiologic and metabolic needs of the neonate. Avoidance of hypoglycemia and hypothermia, especially if significant fluid or blood replacement is required or prolonged exposure occurs are important considerations.

The impact of surgery on the subsequent growth and development of the neonate can be profound, especially when major tumor extirpations are extensive or resection of unaffected tissues integral for normal structure and function has occurred. In some patients, appropriate surgical management may result in impairment of gastrointestinal or bladder function, ambulation, or future sexual function, thereby creating life-long physical and emotional burdens for patients. Interrupting or traversing normal growth centers in order to resect tumors can have a profound effect on structural symmetry and function. For example, intrathecal tumor removal extending over several vertebral segments often results in some degree of post-laminectomy scoliosis later in childhood. Preserving function and structure without compromising survival is thus the paramount principle guiding contemporary surgical and multimodal treatment strategies. For many patients in whom a tumor is initially unresectable (e.g., those with stage 3 neuroblastoma) or involves important structures that should be preserved, the administration of several courses of preoperative chemotherapy has been extremely beneficial. This approach has allowed delayed complete primary resection with preservation of vital structures, thus improving surgical outcomes and quality of life.

Radiotherapy

Because many malignant tumors in childhood are radiosensitive, radiotherapy plays an important role in the management of advanced-stage tumors. In light of the scarcity of neonatal data, however, treatment parameters such as dosing schedules have been extrapolated largely from investigations of older children. Because the neonate experiences rapid growth of organs and structures, radiotherapy has a profound impact on subsequent development. The sensitivity and detrimental effects of radiation therapy on the central nervous system, skeletal growth, and visceral organs appear to be inversely related to the child's age and directly related to the radiation dose [6].

In a seminal study of children younger than age 2, Meadows et al. [6] found that growth disturbances and musculoskeletal abnormalities were the most common late effects of radiation therapy. Approximately 85 % of patients had some degree of bone or soft tissue abnormality; this problem was most severe in children who had received thoracic or spinal irradiation. Other authors have documented a wide spectrum of significant late radiation effects, including scoliosis and severe bony deformities (70 %) and delayed physical development [14, 38]. Children receiving radiation to the cerebrospinal axis for leukemia or brain tumors reportedly experience major delays in cognitive development, and infants treated with cranial irradiation have a high incidence of learning disabilities and mental retardation [39, 40]. The severity of these disabilities is strongly correlated with radiation dose. As in older children, other significant late effects of radiation therapy in neonates include breast agenesis, aortic arch dysgenesis, second malignancies (particularly leukemias and breast and thyroid cancer), and chronic renal and hepatic insufficiency [40–44].

Chemotherapy

The lack of substantial pharmacologic data on newborns significantly complicates the administration of chemotherapeutic agents. Knowledge of drug interactions, metabolism and clearance, and toxicity are all areas of notable deficiency. As such, they remain the focus of intense ongoing discussion and contemporary investigation. In an overview of a workshop (2003) concerning cancer pharmacology in infants and young children, a significantly greater incidence of neurotoxicity for vincristine, hepatic toxicity for actinomycin D, and ototoxicity for cisplatin [45] was observed in infants and young children. For virtually all of these older agents and the newer camptothecin agents, the limited available data indicate that weight-based dosing in young children normalizes the drug clearance profiles and may improve the toxicity profiles, bringing them in line with that of older children [45].

During the course of the second National Wilms Tumor Study, the prescribed doses of actinomycin D, vincristine, and doxorubicin were reduced by 50 % due to observed excessive myelosuppression in infants younger than 1 year of age. Interestingly, reduction of dose did not compromise therapeutic effectiveness [46]. A similar dose reduction approach was followed in the Intergroup Rhabdomyosarcoma Study protocols [47]. Excessive drug-related toxicity has not been observed in infants with leukemia. Moreover, reduced dosage protocols have had a detrimental effect on clinical response and outcome [48].

Teratomas

Teratomas are embryonal neoplasms that contain tissues from at least two of the three germ layers (ectoderm, endoderm, and mesoderm). Although the etiology of these neoplasms is uncertain, three theories have been postulated, including the totipotent primordial germ cell theory, the primitive node theory, and the incomplete twinning theory [49]. Teratomas arise in both gonadal and extragonadal sites, with location thought to correspond to the embryonic resting sites of primordial totipotential germ cells. Tumor location correlates with the age of the patient. Teratomas occurring in infancy and early childhood are generally extragonadal, whereas those presenting in older children more commonly occur in the ovary or testis [50]. More than 50 % of teratomas are evident at birth and are most commonly seen in the sacrococcygeal area. Although more than one third of teratomas of the testis are recognized in the first year of life, these lesions are rarely diagnosed in the neonatal period. The sacrococcyx is also the most common extragonadal location irrespective of age (45–65 %) [51]. Cervicofacial and central nervous system tumors and tumors of the retroperitoneum are seen less frequently. Teratomas presenting in the mediastinum, heart, and liver are much less commonly seen. Excluding testicular teratomas, 75–80 % of teratomas occur in females. Approximately 20 % of tumors contain malignant components, the most common being endodermal sinus tumor [51]. Routine prenatal US at 18–20 weeks' gestation identifies most teratomas present in neonates, irrespective of the anatomic location of the lesion.

A wide range of congenital anomalies is seen in association with teratomas, and the type of anomaly frequently depends on the tumor site and size. Single or combined malformations of the genitourinary tract, rectum, anus, vertebrae, and caudal spinal cord are sometimes found in patients with extensive sacrococcygeal teratomas [52–54]. Disfiguring cleft palate defects are found in newborns with massive cranial and nasopharyngeal teratomas [55]. Klinefelter's syndrome is strongly associated with mediastinal teratoma. Teratomas may also form part of the Currarino triad (anorectal malformation, sacral anomaly, and a presacral mass) [56].

Teratomas can present as solid, cystic, or mixed solid and cystic lesions. Most teratomas that are present at birth consist of ectodermal and mesodermal components. Epidermal and dermal structures such as hair, sebaceous glands, sweat glands, and teeth are frequently present. Virtually all teratomas have mesodermal components, including fat, cartilage, bone and muscle. Endodermal components commonly seen include intestinal epithelium and cystic structures lined by squamous, cuboidal, or flattened epithelium [57]. Pancreatic, adrenal, and thyroid tissue, as well as mature and immature neuroepithelial and glial tissue is also frequently seen (Fig. 11.2).

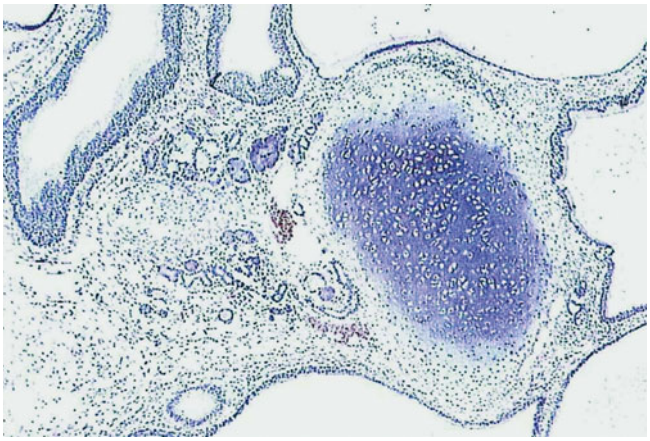

Fig. 11.2 Microphotograph of a benign teratoma showing differentiated cartilage, respiratory epithelium, mucinous epithelium, and salivary gland acini

Tumors are histologically classified as either mature or immature, with most pediatric teratomas classified as mature. These tumors exhibit an absence of coexisting malignant cells and little or no tendency to malignant degeneration. They nevertheless may be fatal if the airway is compromised or if vital structures such as the brain or heart are involved. Moreover, depending on location and size, even benign tumors may be inoperable and incompatible with extrauterine life.

Although useful tumor grading systems have been developed [58, 59], these systems are of limited use in regard to the fetus or newborn in that embryonic or immature elements may be appropriate for the stage of development [60, 61]. Regardless of tumor grade in these patients, immature teratomas are associated with a favorable prognosis, and only in rare cases does immature neuroglial tissue metastasize to adjacent lymph nodes, lungs, and other distant organs from an immature primary site [62, 63].

The most important predictor of recurrence in pediatric immature teratomas appears to be the presence of microscopic foci of yolk sac tumor [64]. Because they are small, these tumors may be missed by the pathologic sampling process. Such oversights may account for metachronous metastases after resection of the immature teratoma metastasis.

In general, the prognosis of neonates depends upon the resectability of the tumor and the presence of metastases or metastatic potential. Alpha-fetoprotein (AFP) is the principle tumor marker and is especially helpful in assessing the presence of residual or recurrent disease [65]. This assessment should, however, consider that neonates normally have a high AFP at birth, which rapidly dissipates due to its short half-life. In some patients, elevation of beta-human chorionic gonadotropin (β-hCG) indicates the presence of a component of choriocarcinoma [66].

Teratomas detected prenatally reportedly have a mortality rate three times higher than those diagnosed postnatally [49]; this higher rate is related to tumor location (head and neck involvement) and the presence or absence of hydrops. Regardless of tumor location, a fetus with hydrops has a poor prognosis.

Sacrococcygeal Teratoma

Clinical Presentation and Diagnosis

Sacrococcygeal teratoma (SCT) is the predominant teratoma as well as the most common extracranial neoplasms in newborns. The tumor has an estimated incidence of 1:20,000 to 1:40,000 live births and a female predominance ranging from 2:1 to 4:1 [67–69]. Ten percent to 20 % of patients with SCT have coexisting congenital anomalies such as tracheoesophageal fistula, imperforate anus, anorectal stenosis, spina bifida, genitourinary malformations, meningomyelocele, and anencephaly [70–72]. Also, many patients have significant structural abnormalities of juxtaposed organs resulting from displacement by a large teratoma.

The classification system currently used by the American Academy of Pediatrics Surgery Section (AAPSS) was developed by Altman et al. [73] in the early 1970s. This system divides SCTs into four distinct anatomic types that differ in the degree of intra- and extrapelvic extension (Fig. 11.3). Type I (46.7 %) is predominantly external with minimal presacral extension. Type II (34.7 %) arises externally and has a significant intrapelvic component. Type III (8.8 %) is primarily pelvic and abdominal but is apparent externally. Type IV (9.8 %) is presacral and has no external manifestation. These authors found that the incidence of malignant components not only correlated with anatomic type (8 % in type I vs. 38 % in type IV) but also with age at diagnosis and gender; however, the size of the tumor was unrelated. The rate of malignancy of tumors in older infants (>6 months) and children is significantly higher than that of the visible exophytic tumors seen in neonates. Malignant change is more frequent in males, particularly those with solid versus complex or cystic tumors [74, 75]. The most common malignant elements identified within sacrococcygeal lesions are yolk sac tumor and embryonal carcinoma (Fig. 11.4) [76].

In countries where antenatal US screening is carried out, most large SCTs are diagnosed before birth. Uterine size larger than expected for a gestational date (polyhydramnios or tumor enlargement) is the most common obstetrical indication for initiating maternal-fetal US examination. US may reveal an external mass arising from the sacral area of the fetus (Fig. 11.5). The mass is composed of solid and cystic areas, with foci of calcification sometimes apparent. Most prenatally diagnosed SCTs are extremely vascular and can be seen on color-flow Doppler studies.

Fetal MRI has become an especially useful adjunctive imaging modality, as it provides important anatomic detail that may not be apparent on US alone. It may help define the pelvic component of SCT and its impact on other pelvic structures [77]. For neonates in whom fetal surgery is being considered, fetal MRI provides a broader field of view than US and may be helpful in operative planning. Additionally, in cases of cystic SCT, it may be helpful in excluding myelomeningocele from the differential diagnosis [78, 79].

Lumbosacral myelomeningocele is the most likely diagnosis to be confused with SCT. Lumbosacral myelomeningocele and cystic SCT may show similar findings on US. Since both are associated with elevated maternal levels of AFP, these levels are not helpful in distinguishing between the two entities. Other critical information gained from US includes the possible presence of abdominal or pelvic extension, evidence for bowel or urinary tract obstruction, assessment of the integrity of the fetal spine, and documentation of fetal lower extremity function [80]. Imaging of the fetal brain is helpful in establishing the diagnosis in that most fetuses with lumbosacral myelomeningocele have cranial signs such as Arnold-Chiari malformation [81]. When there is doubt, performing a fetal MRI can be extremely valuable in clarifying fetal anatomy and in making a definitive diagnosis (Fig. 11.6). Other soft tissue tumors that may mimic SCT include neuroblastoma, hemangioma, leiomyoma, and lipoma [81].

Tumors can grow at an unpredictable rate to tremendous dimensions and may extend retroperitoneally displacing pelvic or abdominal structures (Fig. 11.7). Large tumors can cause placentomegaly, nonimmune fetal hydrops, and the mirror syndrome [82, 83]. These conditions are thought to result from a hyperdynamic state induced by low-resistance vessels in the teratoma. Without fetal intervention, high-output cardiac failure and hydrops resulting in fetal demise is almost certain. Thus, in a select subset of fetuses that meet specific criteria, restoring more normal fetal physiology may be achieved by surgical debulking of the SCT in utero [84].

Neonatal death may occur due to obstetric complications from tumor rupture, preterm labor, or dystocia [85–87]. Impending preterm labor from polyhydramnios or uterine distension from tumor mass may therefore require treatment by amnioreduction or cyst aspiration. Dystocia and tumor rupture can be avoided by planned cesarean section delivery for infants with tumors larger than 5 cm [82].

Antenatal diagnosis carries a significantly less favorable outcome than diagnosis at birth, and prognostic factors outlined in the current SCT classification system are not applicable to fetal cases. Although the mortality rate for SCT diagnosed in neonates is 5 % at most, that for fetal SCT is close to 50 % [82, 85, 86]. Results of most clinical series indicate that hydrops and/or polyhydramnios and placentomegaly portend a fatal outcome. The indication for

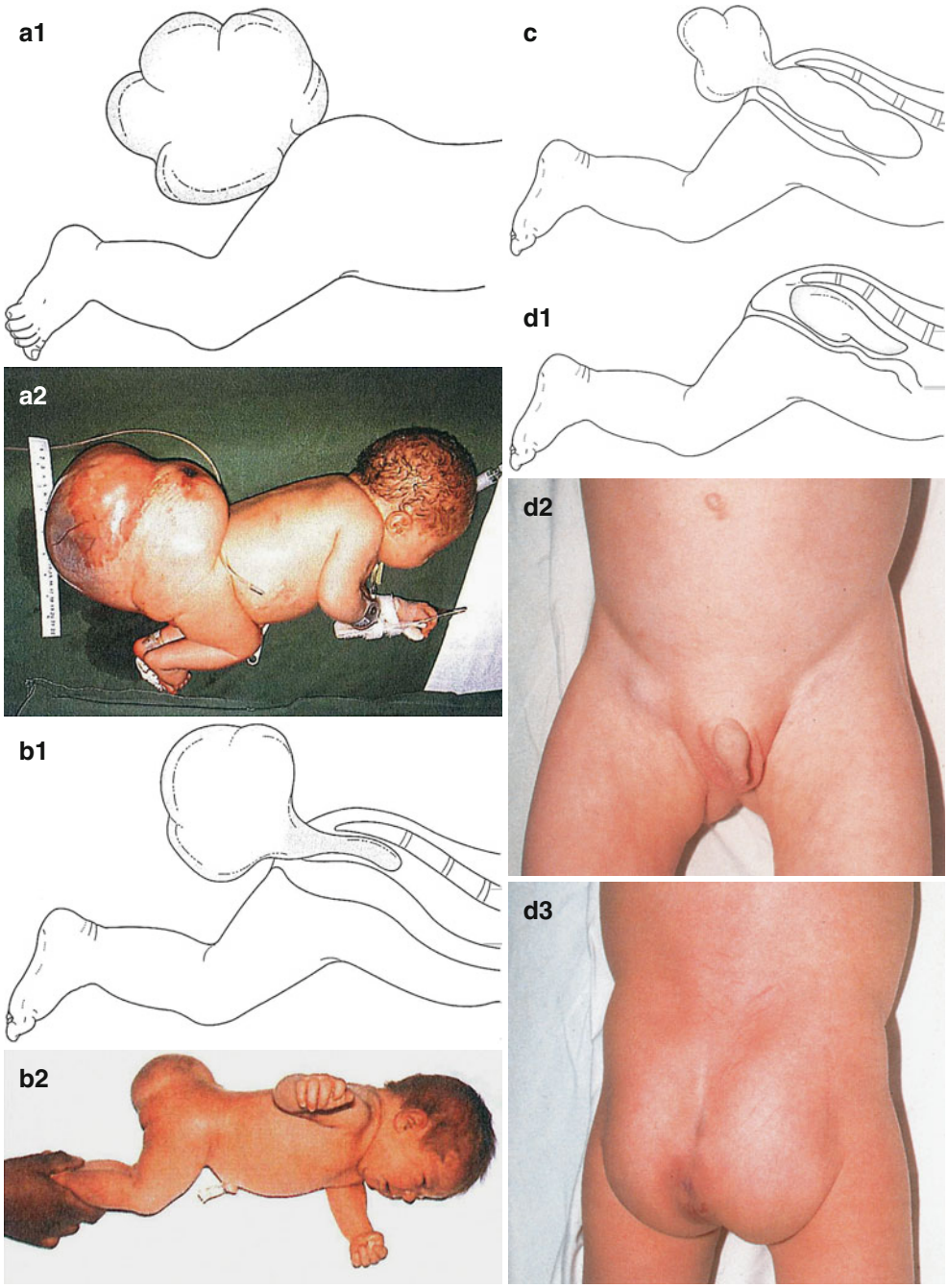

Fig. 11.3 Clinical staging of sacrococcygeal teratoma: (**a1**, **a2**) Stage I illustration and clinical photograph (**b1**, **b2**) Stage II illustration and clinical photograph (**c**) Stage III Illustration only (**d1**) Stage IV Illustration (**d2**) Intrapelvic tumor (**d3**) Secondary metastases in groin lymph nodes

maternal-fetal US has also been shown to be a predictive factor [85]. If SCT is an incidental finding on routine prenatal US, the prognosis is favorable at any gestational age. Many of these lesions are predominantly cystic and relatively avascular and can be managed postnatally with surgical resection. If US is initiated due to maternal indications, the outcome is much less favorable. Additionally, prematurity from polyhydramnios or cesarean section performed before 30–32 weeks' gestation results in increased mortality [50]. In light of these factors, antenatal diagnosis requires referral to a high-risk obstetric center, with immediately available neonatal intensive care and qualified pediatric surgical and anesthesia expertise.

Postnatal diagnosis is determined by clinical findings on physical examination, serum levels of AFP and ß-HCG, and a number of radiographic imaging studies. Ninety percent of SCTs are noted at delivery, with a protruding caudal mass extending from the coccygeal region. These tumors are easily recognized and a diagnosis can generally be made by physical examination alone. Intrapelvic components can be diagnosed by a rectal digital examination. SCTs seen at birth are predominantly benign, and many are functionally asymptomatic.

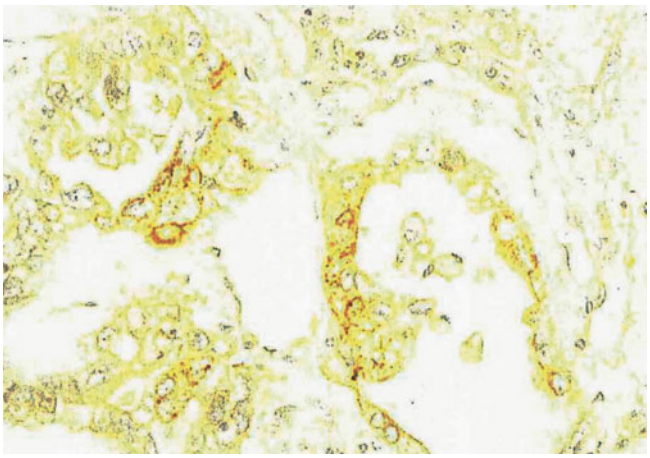

Fig. 11.4 Histology of an endodermal sinus tumor with alpha-fetoprotein stain

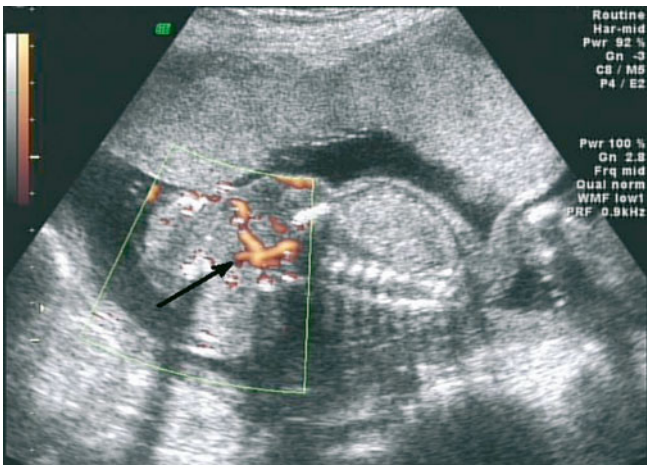

Fig. 11.5 Antenatal maternal-fetal Doppler ultrasound of a 21-week gestation fetus with a sacrococcygeal tumor showing solid and cystic components. *Black arrow* marks vessel with high blood flow within the tumor on the Doppler image (Courtesy of Timothy Crombleholme, MD)

Intrapelvic variants may have a delayed postnatal presentation [67, 73, 82]. They are typically noted in infants and children from ages 4–6 months to 4 years. In contrast to the SCTs seen in neonates, these tumors are located in the pelvis and have no external component. More than one third are associated with malignancy. Clinical presentation may include constipation, anal stenosis, or symptoms related to the tumor compressing the bladder or rectum and a palpable mass. Presacral tumors are associated with sacral defects and anorectal malformations (Currarino triad) [51].

Radiographs of the pelvis identify any sacral defects or tumor calcifications. CT with intravenous and rectal contrast material defines the intrapelvic extent of the tumor, identifies any nodal or distant metastases, and demonstrates possible urinary tract displacement or obstruction. CT imaging also

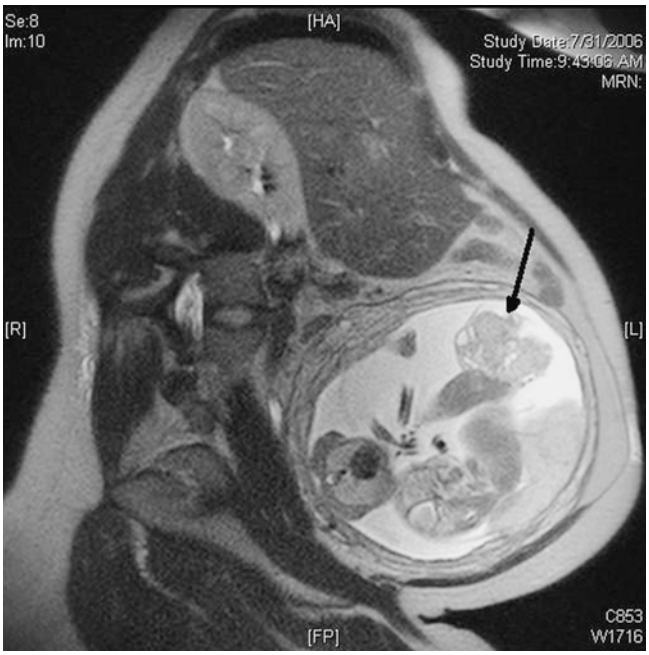

Fig. 11.6 MRI of twin gestation at 21 weeks with one twin having a large sacrococcygeal teratoma (*black arrow*) associated with hydrops and high output failure (Courtesy of Timothy Crombleholme, MD)

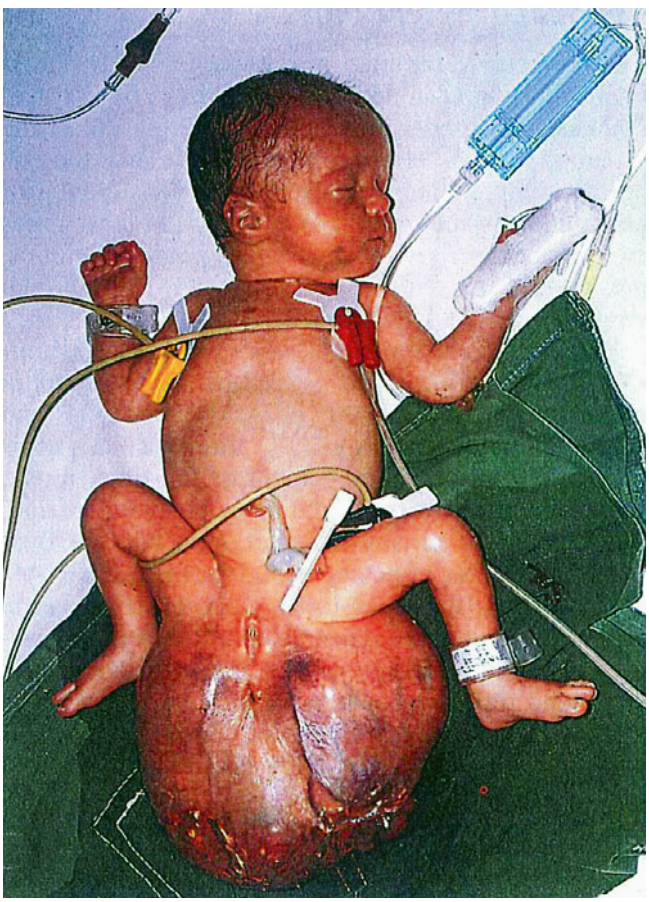

Fig. 11.7 Neonate with a large sacrococcygeal teratoma

identifies liver metastasis and periaortic lymph node enlargement. MRI is useful when spinal involvement is suspected or if the diagnosis is in doubt. A chest radiograph is useful in revealing obvious pulmonary metastases. Because chest CT is more reliable in picking up smaller metastatic lesions, it should be performed when there is a high index of suspicion.

Management Approaches

Advancements in antenatal diagnosis have given rise to the development of two primary fetal interventions in patients with teratomas—early delivery and open fetal surgery. Because these interventions are invasive to the fetus and may also cause maternal morbidity, they are, however, reserved for select cases in which the fetus develops progressive hydrops and shows evidence of high-output cardiac failure.

Operative Treatment

Fetal Surgery

SCTs are highly vascular tumors; a fetus with large lesions may thus develop high cardiac output failure, anemia, and ultimately, hydrops, with a mortality rate approximating 100 %. Signs of cardiac compromise are therefore an indication for surgery prior to 27–32 weeks' gestation [88]. Since the first reported fetal resection of SCT in 1997 [89], this approach has resulted in a number of long-term survivors. Because in utero SCT resection commonly precipitates preterm labor, meticulous monitoring and tocolytic therapy during the immediate postoperative period is essential. Hospitalized patients undergo daily US and fetal echocardiography as indicated. Although signs of hydrops generally begin to resolve within several days of tumor resection, complete resolution may take weeks [30]. Since the intrauterine procedure is not designed to completely remove the teratoma, patients often require a second operation postnatally to remove the coccyx and any residual tumor mass. At surgery, the exophytic tumor is dissected free of the anus and rectum. The tumor is then removed by dividing it near the coccyx with a thick tissue-stapling device [30].

A rapidly enlarging macrocystic SCT results in polyhydramnios and placentomegaly, with associated mirror syndrome. Because this syndrome resembles severe preeclampsia and is life threatening to the mother, immediate delivery of the fetus or infant is essential.

Early Delivery

Serious or life-threatening complications are difficult to predict and often occur precipitously, making the third trimester of pregnancy extremely dangerous for a fetus with high-risk SCT. Unfortunately, the commonly accepted paradigm of watchful waiting frequently results in fetal death.

Based on published findings [88] as well as our own institutional experience, we have modified our treatment paradigm. This revised approach recognizes that rapid phases of tumor growth, early signs of internal hemorrhage, ominous changes in Doppler arterial wave forms, progression of placentomegaly or polyhydramnios, and early indications of maternal mirror syndrome are factors that should prompt consideration of early delivery. In the absence of hydrops, this approach is associated with good outcomes in appropriately selected fetuses with high-risk SCT [88].

Postnatal Intervention

The mainstay of treatment is complete surgical resection, with the exception of emergencies related to tumor rupture or hemorrhage that adversely affect the neonate's hemodynamic status. The operative procedure can be undertaken on an elective basis early in the newborn period. The anatomic location of the tumor determines the operative approach. Tumors with extensive intrapelvic extension or a dominant abdominal component (type III or IV) are initially approached through the abdomen. A posterior sacral approach is sufficient for most type I tumors and type II tumors.

Operative goals include: (a) complete and prompt tumor excision. A significant delay may result in serious complications, including pressure necrosis, tumor hemorrhage, and malignant degeneration; (b) resection of the coccyx to prevent tumor recurrence; (c) reconstruction of the muscles of anorectal continence; and (d) restoration of a normal perineal and gluteal appearance [90, 91].

Initial control of the middle sacral and hypogastric arteries may be required to safely remove tumors in these fragile infants. The procedure is performed in a temperature-controlled environment, and infants are protected from heat loss with appropriate measures. The urinary bladder is catheterized and the operation is generally performed with the patient in a prone jackknife position, cushioned in a sterile foam ring. After skin preparation and sterile draping, a frown-shaped or inverted chevron incision is made superiorly to the tumor (Fig. 11.8a). This incision provides excellent exposure and keeps later wound closure some distance from the anal orifice. To delineate the rectum, the surgeon's finger and/or a Hegar dilator also may be inserted 3 cm into the anal canal. After raising skin flaps off the tumor, the attenuated retrorectal muscles are carefully identified and preserved. The mass is mobilized close to its capsule, and hemostasis is achieved with electrocautery or ligatures. To retard heat loss, warm gauze pads are placed over the exposed dissection and the tumor mass. The main blood supply to the tumor usually arises from a primitive middle sacral artery or from branches of the hypogastric artery. After division of the coccyx from the sacrum, the vessels can be observed exiting the presacral space ventral to the coccyx. For patients with extremely large or vascular lesions in which excessive fluid shifts or hemorrhage may result in operative mortality, surgeons occasionally use extracorporeal membrane oxygenation (ECMO) in conjunction with hypothermia and

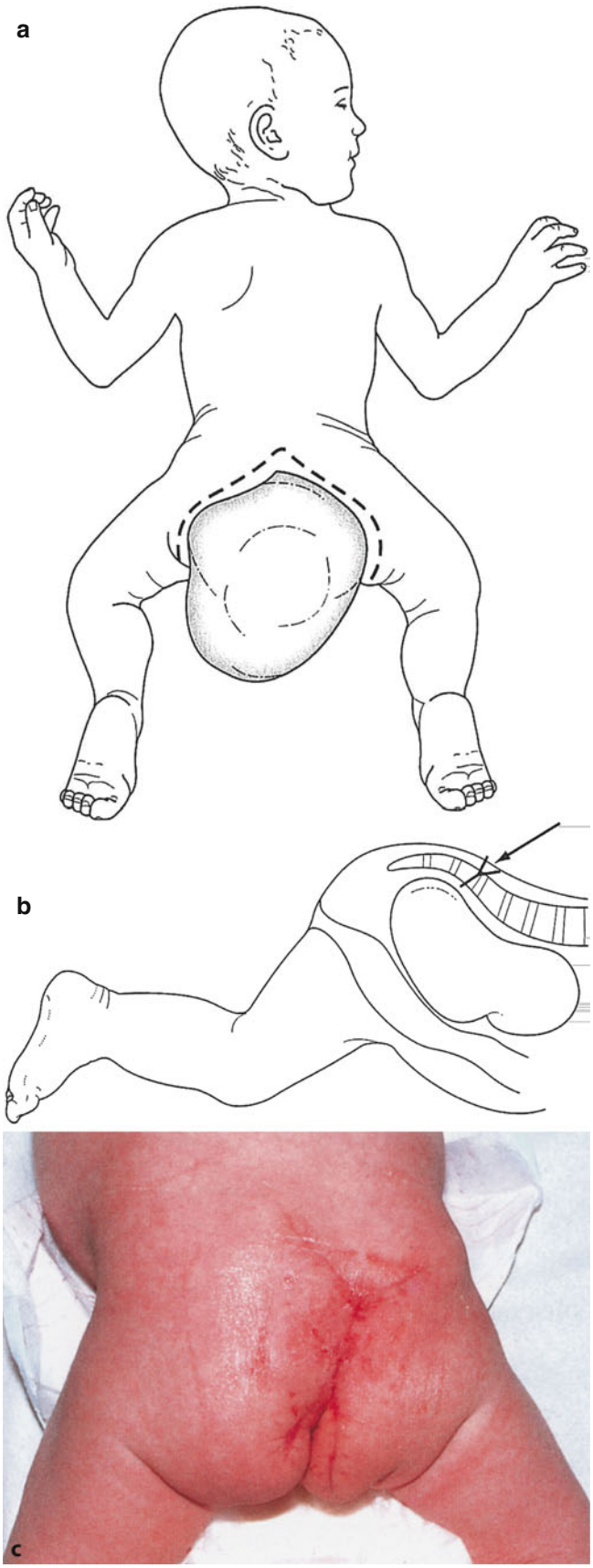

Fig. 11.8 Operative details (**a**) Position of the patient for surgery. The chevron incision is used. (**b**) Cross-section of tumor and excision of coccygeal segment to ensure complete incision (**c**) Postoperative cosmetic result

hypoperfusion to facilitate better control of bleeding during resection [32].

As failure to remove the coccyx is associated with a recurrence rate as high as 37 % [92], the coccyx is excised in continuity with the tumor (Fig. 11.8b). The tumor is dissected free from the rectal wall and the anorectal muscles are reconstructed. The levator muscles are attached superiorly, providing support to the rectum and positioning the anus in the normal location. A closed-suction drain may be placed below the subcutaneous flaps. The wound is then closed in layers with interrupted absorbable sutures. A urinary catheter is left in position for several days. To maintain cleanliness of the wound, the patient is kept prone for several days after surgery.

Premature newborns with large teratomas are challenging to manage. Due to lung immaturity, increased tumor vascularity, and poor tolerance of blood loss, surgical risks are high [93]. In these patients, devascularization and staged resection may be considered to avoid excessive blood loss. The fetus with a large SCT presents an even greater management challenge. As mentioned earlier, fetal hydrops and placentomegaly are associated with fetal demise.

The most serious complication of excision is intraoperative hemorrhage, and the major cause of mortality is hemorrhagic shock. One successful preoperative strategy for stabilizing patients with vascular tumors in which there is significant bleeding is to tightly wrap the teratoma with an elastic bandage. As a salvage approach for acute life-threatening hemorrhage, performing an emergent laparotomy and temporarily cross-clamping the distal abdominal aorta has been reported [94].

As with any surgical procedure, wound complications can occur. Resection of teratomas with significant intrapelvic and intraperitoneal extension may be associated with temporary or persistent urinary retention in the postoperative period, but these symptoms generally resolve. Although patients with small tumors usually have normal anorectal function, up to 40 % of premature infants with large SCTs and in whom the levator and gluteal muscles are severely attenuated, have fecal incontinence. Long-term bowel management strategies allow most patients to achieve socially manageable bowel function.

Adjuvant Chemotherapy

Detection of malignant elements necessitates adjuvant multiagent chemotherapy. The most active antineoplastic drugs include cisplatin, etoposide, and bleomycin. Reports indicate impressive survival after administration of intensive chemotherapy both in children with locally advanced disease and in those with metastatic disease [95–97]. Even with malignant transformation of SCT, reported survival is 88 % with local disease and 75 % with distant metastases [98]. Moreover, it appears that stage, extent of metastasis, and extension into bone have no prognostic significance when children are treated with platinum-based regimens [99].

For patients in whom the primary malignant tumor is unresectable, a course of multiagent chemotherapy is administered to facilitate subsequent resection. If a good tumor response is indicated by a diminishing serum AFP level, CT imaging, and a chest radiograph, resection is undertaken after several cycles of chemotherapy.

In patients with localized malignant recurrence, complete resection remains the cornerstone of salvage treatment. This is carried out in conjunction with adjuvant chemotherapy.

Chemotherapy also has been effective in the treatment of metastatic foci in the lungs and liver. However, to ensure removal of any malignant elements, residual lesions must be excised. Although radiation therapy is uncommon and used selectively, it may have a role in controlling unresectable disease.

Long-Term Outcomes

Patients diagnosed with SCT before 30 weeks' gestation tend to have poorer outcomes and a higher likelihood of developing complications such as hydrops, placentomegaly, dystocia, and fetal demise [86]. For most patients diagnosed postnatally, the prognosis is favorable in regard to both survival and quality of life. Factors such as tumor maturity and morphology and degree of hemorrhage may also affect morbidity and outcome. When the diagnosis is made prior to 2 months of age or excision is performed prior to 4 months of age, the malignancy rate is 5–10 % [100, 101]. Additionally, cystic tumors, which are generally mature, carry a better prognosis. Complications related to hemorrhage, vascular steal, and malignancy are seen more frequently in patients with solid tumors.

The long-term survival of newborns who have undergone complete resection is generally excellent regardless of tumor histology [102]. Nevertheless, because all SCTs have a risk of local and/or distant recurrence, close follow-up at 3-month intervals for a 3- to 4-year period is essential. An 11 % tumor recurrence with mature teratoma and a 4 % recurrence with immature teratoma have been reported [71]. Although 43–50 % of these occurrences are malignant, the chemosensitivity of yolk sac (endodermal sinus) tumor results in a high survival rate. Serum AFP levels are monitored and physical examinations are performed. Special attention is given to rectal examination in that it may detect a presacral recurrence. When serum AFP levels do not fall appropriately, abdominal US is performed. When there is an index of suspicion, an abdominopelvic CT or MR imaging and a lung CT are performed. Recurrent tumor may be benign, but should be re-excised to minimize the long-term risk of malignant transformation.

Head and Neck Teratomas

Head and neck teratomas account for 5 % of all neonatal teratomas. These neoplasms have no sex or race predilection. They can occur in the brain, orbit, oropharynx, and neck.

Intracranial Teratomas

Intracranial teratomas account for approximately 50 % of all brain tumors in early infancy [67]. These tumors occur most commonly in the pineal region but also are found in the hypothalamus, ventricles, and suprasellar and cerebellar regions. Unlike intracranial teratomas in older children, most intracranial teratomas in neonates are benign. The most common presenting symptoms and findings are related to the presence of obstructive hydrocephalus. On imaging studies, these lesions may be suspected by visualizing midline or paraxial intracranial calcifications.

Although complete resection is the treatment of choice, many neonatal intracranial teratomas are not resectable. Palliative shunting to alleviate intracranial pressure and hydrocephalus has little long-term benefit. Moreover, in some infants, shunting has been associated with extracranial spread of tumor. The role and effectiveness of chemotherapy for this subgroup of patients are currently areas of investigation.

Long-term survival is predicated on complete tumor removal. Outcomes are significantly worse for patients with extensive intracranial involvement that is not amenable to complete resection; reported survival rates for these patients range from 15 to 20 % [103].

Cervical Teratomas

Cervical teratomas are extremely rare neoplasms, occurring with an estimated incidence of 1:40,000 to 1:80,000 live births. These lesions account for 2 % of all neonatal tumors and 3–6 % of teratomas [104, 105]. Both sexes are equally affected. Although most cervical teratomas are histologically benign, they frequently cause significant airway and esophageal obstruction in the perinatal period and are thus potentially fatal. Primary tumor sites include the tongue, nasopharynx, palate, sinus, mandible, tonsil, anterior neck, and thyroid gland.

Prenatal US is a reliable and essential diagnostic tool for detecting these lesions in utero, allowing for careful arrangement of the time, mode, and place of delivery (Fig. 11.9a). When large cervical teratomas are prenatally detected, findings generally reveal multiloculated irregular masses with both solid and cystic components [106]. Of cases detected prenatally, cystic lymphatic malformations are the most likely entity to be mistaken for cervical teratoma. Similarities in size, sonographic findings, clinical characteristics, location, and gestational age at presentation can make this distinction difficult [107]. Other lesions to be considered in the differential diagnosis include large branchial cleft cyst and congenital thyroid goiter. To delineate anatomy more clearly, fetal MRI is the diagnostic imaging study of choice. MRI provides a larger field of view than fetal US and more clearly defines tissue planes, permitting a clear distinction between teratoma and vascular malformations. Because fewer than

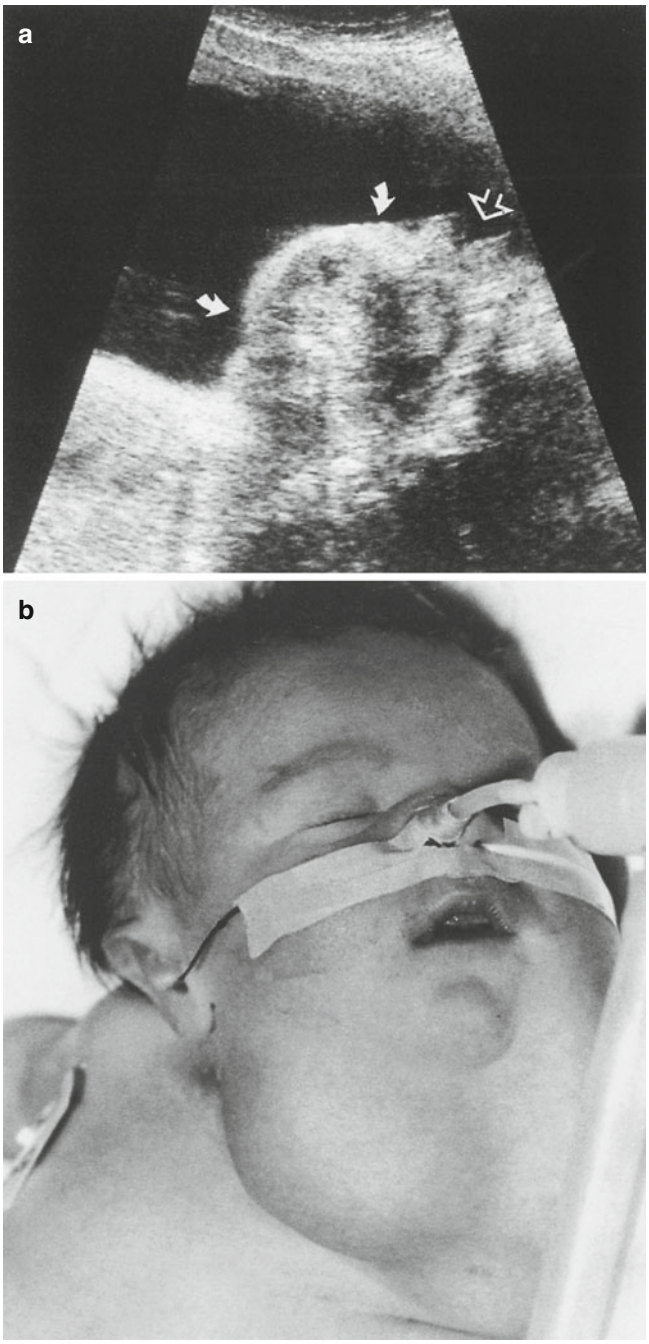

Fig. 11.9 (**a**) Antenatal ultrasound of a cervical teratoma (**b**) Infant with a cervical teratoma causing respiratory distress

30 % of cervical teratomas are associated with elevated AFP levels, this assay is not particularly helpful in the differential diagnosis of fetal cervical masses [81]. Approximately one third of prenatally diagnosed cases are complicated by maternal polyhydramnios, which is thought to be due to esophageal obstruction and/or interference with fetal swallowing. There is a high incidence of preterm labor and delivery that may be secondary to increased uterine size resulting from polyhydramnios and/or tumor.

Cervical teratomas are generally large and bulky, often measuring 5–12 cm in diameter (Fig. 11.9b). Tumor masses greater than the size of the fetal head have been reported [107–109], as has involvement of the oral floor, protrusion into the oral cavity (epignathus), and extension into the superior mediastinum [108]. Massive lesions may cause dystocia, requiring a cesarean section to deliver the baby. Various anomalies occurring in association with cervical teratomas have been reported. These include craniofacial and central nervous system anomalies, hypoplastic left ventricle, trisomy 13, and a case each of chondrodystrophia fetalis and imperforate anus [104]. Mandibular hypoplasia also has been seen as a direct result of mass effect on the developing mandible [81].

Up to 50 % of cervicofacial teratomas have calcifications present and these are often seen more easily on postnatal plain radiographs. When calcifications are present in a partially cystic and solid neck mass, they are virtually diagnostic of cervical teratoma [106]. A postnatal CT scan or MRI is essential in delineating the anatomic extent and precise involvement of the neoplasm.

As shown in a number of series [104, 108–112], airway obstruction at birth is life threatening and associated with a high mortality rate. In patients with massive fetal neck masses, this is generally associated with a delay in obtaining an airway and ineffective ventilation. Delay in acquiring an adequate airway can result in hypoxia and acidosis and if longer than 5 min, can result in anoxic injury. In light of these concerns, most cervicofacial teratomas are definitively treated immediately after delivery, which preferably should take place at a tertiary care center with an expert perinatal team that includes a pediatric surgeon. Optimally, if a cesarean section is performed, maternal-fetal placental circulation should be maintained while an airway is secured. This is accomplished by employing an EXIT procedure; this allows time to perform procedures such as direct laryngoscopy, bronchoscopy, tracheostomy, surfactant administration, and cyst decompression, which may be required to secure the airway [81]. Because precipitous airway obstruction may occur due to hemorrhage into the tumor, orotracheal intubation is indicated in all patients, regardless of the presence or absence of symptoms.

In some reported series [112–114], infants have either had acute airway obstruction or lost a previously secure orotracheal airway within a few hours or days after delivery. Because early resection after stabilization is the most effective method of achieving total airway control, it is the treatment of choice. Delaying surgery can have other serious ramifications, including retention of secretions, atelectasis, and/or pneumonia due to interference with swallowing [54, 107]. Resection also removes the risk of malignant degeneration, which occurs at much higher frequencies (>90 %) in cases of cervical teratomas that are not diagnosed or treated until late adolescence or adulthood [115].

To minimize operative morbidity, dissection of the teratoma should begin in areas distant to important regional nerves. Cervical teratomas often have a pseudocapsule, which facilitates gentle elevation of the tumor out of the neck. If the tumor arises from the thyroid gland, the involved thyroid lobe is excised in continuity with the teratoma. As glial metastases may be present, any enlarged lymph nodes should be excised with the tumor. After excision, a drain is left in place for 24–48 h. Because tumors are often large, envelopment of vital anatomic structures in the neck is common. In some cases, complete tumor excision with acceptable functional and cosmetic results can be achieved only by staged procedures.

In contrast to the high incidence of malignancy (>60 %) in adults, malignant cervicofacial teratomas with metastases are comparatively uncommon in neonates, with a reported incidence of 20 % [104]. Despite the existence of poorly differentiated or undifferentiated tissue in the primary tumor, many infants remain free from recurrence following complete resection of a cervical teratoma. Such cases suggest that malignant biologic behavior is uncommon in this population [106, 107]. Reported findings show a number of consistent histologic patterns [104]. Neuroectodermal elements and immature neural tissue are the most commonly observed tissues in metastatic foci. In approximately one third of cases, the metastases are more differentiated but confined to regional nodes. Patients with isolated regional node metastases who are treated with excision of the primary tumor generally survive free of disease [51]. This supports the concept that the presence of metastases containing only differentiated tumor usually correlates with a good prognosis.

There are currently no chemotherapy guidelines for neonates with malignant cervical teratomas. Based on results of their series, however, Azizkhan et al. [104] recommend that this modality be reserved for infants with disseminated disease (undifferentiated lesions) and those who have invasive tumors and residual disease after resection.

Although cervical teratoma is generally a benign tumor, the possibility of malignant transformation mandates close surveillance for tumor recurrence. Serum AFP levels should be monitored at 3-month intervals in infancy and annually thereafter, with a rising level alerting the clinician as to the possibility of tumor recurrence. As previously discussed, AFP levels must be interpreted with caution and viewed within the framework of their natural half-life. Imaging studies twice a year for the first 3 years of life are also recommended. Since the thyroid and parathyroid glands may be removed or affected by tumor excision, the risk of temporary or permanent hypothyroidism must be considered. If these complications are encountered, they must be monitored and managed appropriately.

Retroperitoneal Teratomas

The retroperitoneum is the third most common extragonadal site, accounting for 2–5 % of all pediatric teratomas [116, 117]. Most lesions are observed in early infancy and 50 % are identified in the first year of life [67, 103]. Females are more commonly affected (2:1) than males. Infants generally present with a palpable abdominal mass. CT or MR imaging of the abdomen helps differentiate this neoplasm from the more commonly occurring neuroblastoma or Wilms tumor. Laparotomy or a minimally invasive laparoscopic approach is used for complete tumor resection; however, larger lesions are more likely to require an open procedure. Although an overall malignancy rate of 7 % has been documented in children with teratomas, approximately 24 % of retroperitoneal teratomas diagnosed during the first postnatal month have been found to be malignant, based on histology or clinical course [118]. Additionally, 30–40 % of tumors have histologically immature elements. Malignant recurrence has been reported in patients with benign retroperitoneal teratomas containing immature components. As such, malignant lesions and lesions containing high-grade immature elements should be treated with adjuvant cisplatin-based chemotherapy following resection [117].

Mediastinal Teratomas

The mediastinum is the second most common extragonadal site for teratomas in children; however, mediastinal teratoma is rarely diagnosed in the neonate. Although these lesions occasionally originate within the heart, the pericardium, or the posterior mediastinum, they most frequently arise in the anterior mediastinum. As with previously discussed teratomas, diagnosis with prenatal US has been reported; nevertheless, most mediastinal lesions are diagnosed postnatally by the presence of a mediastinal mass with calcifications on a plain radiograph. Infants may present with chronic cough, wheezing, or severe respiratory distress caused by airway compression. Surgical approaches vary, depending on the site and size of the lesion [119, 120]. Small lesions are amenable to video-assisted thoracic surgery (VATS), whereas lesions within the pericardium require sternotomy or resection. Rarely, cardiopulmonary bypass is required for successful excision.

Most lesions in infants are benign; however, about 20 % of resected tumors show immature elements on histologic examination [121]. Nonetheless, neonates with benign mature or immature mediastinal teratomas have identical outcomes following complete resection.

Neuroblastoma

Neuroblastoma arises from neural crest cells and can present anywhere along the sympathetic chain, including the adrenal medulla and sympathetic ganglia. It is the second most common tumor diagnosed in the neonatal period, with a reported incidence of 5–8 per million live births [122, 123]. It is also the most common neonatal malignancy, accounting for nearly one third of all malignancies diagnosed in newborns [122, 123]. Autopsy series of infants who have died from unrelated causes indicate an occurrence rate (in situ neuroblastomas) far exceeding the reported incidence of neuroblastoma [124, 125]. Most of these tumors are occult and known to regress spontaneously.

Up to 80 % of neuroblastomas have recognizable and abnormal chromosomal patterns. In most cases, the defect is found on chromosomes 1 and 17 [18]; however, other abnormalities have been identified at 4p, 6q, 9q, 10q, 11q, 12q, 13q, 14q, 16q, 22p, and 22q [126]. The most important of these abnormalities are N-myc amplifications, deletions of chromosome 1p, and aneuploidy [18, 127–129]. Amplification of the N-myc oncogene is associated with a more aggressive tumor type that often presents with advanced stage disease. As such, it is considered a critical prognostic factor [18, 127–129].

Clinical Presentation

The most common presentation of neonatal neuroblastoma is an abdominal mass arising from the adrenal gland. Primary lesions also can occur in the neck, mediastinum, retroperitoneum, and pelvis. Symptoms vary, depending on the anatomic location of the tumor, its physiology, and its mass effect. Nearly half of tumors have metastases at diagnosis, most commonly to the liver [130]. Hepatomegaly or massive abdominal distention associated with respiratory compromise may be the initial findings in patients with disseminated disease. These patients also may have skin nodules and bone marrow involvement (stage 4S).

Most neuroblastomas diagnosed during the neonatal period present as solid lesions, although cystic lesions have been described; such lesions may arise from an adrenal cyst or develop as a result of hemorrhage or degeneration within a solid neuroblastoma [131].

Diagnostic Evaluation

Antenatal

The routine use of antenatal US has increasingly identified the presence of adrenal tumors and other intraabdominal masses [132–135]. Fetal MRI may help distinguish neuroblastomas from other mass lesions. Unlike neuroblastomas diagnosed during the neonatal period, prenatally diagnosed lesions often have a cystic component [133]. More than 90 % of these cystic tumors arise in the adrenal grand, suggesting a link between perinatal tumors and the nodular collections of neuroblasts that are part of normal adrenal development [136]. Moreover, there is evidence that cystic tumors are caused by a disturbance in the natural course of neuroblastic nodule regression [136]. Most antenatally diagnosed cystic tumors are stage 1, 2, or 4S and usually have favorable biological characteristics. Evidence indicates that these lesions have a tendency to regress spontaneously [137].

Although increased urinary excretion of catecholamine metabolites is found in most children with neuroblastoma, a significant percentage of infants in whom there is a fetal diagnosis of intraabdominal neuroblastoma have negative markers, reflecting the presence of a nonfunctioning tumor [138, 139]. Catecholamine-secreting fetal tumors are sometimes recognized however, by the onset of maternal hypertension or pre-eclampsia appearing in the last trimester of pregnancy [140]. These offspring usually have either stage 4 or 4S disease or multiple metastases to the placenta [132].

Postnatal

Imaging studies may help to differentiate neuroblastomas from adrenal hemorrhage, renal masses, and intraabdominal extralobar sequestration. As most neuroblastomas secrete varying quantities of catecholamine metabolites such as vanillylmandelic acid (VMA) and homovanillic acid (HVA), these should be checked by random urine studies [141, 142]. Tissue diagnosis can be made by open biopsy; however, open biopsy should be avoided in neonates with massive liver involvement and in those who are high surgical risks due to impaired ventilation or concern about wound closure. In such patients, elevated urinary catecholamine levels and demonstrated bone marrow involvement are sufficient to confirm the diagnosis. Tissue samples also should be analyzed for amplification of the N-myc oncogene, chromosome IP, other tumor markers (e.g. TrK-A) and for ploidy, which significantly affect prognosis [127–129].

Because most neonatal neuroblastomas are low stage and may regress spontaneously, the Children's Oncology Group (COG) has undertaken a prospective randomized study to determine outcomes associated with observation alone for adrenal lesions identified in neonates. Results indicate that lesions which do not show radiographic signs of progression can be managed with observation alone (i.e. without tissue diagnosis), with the expectation that spontaneous regression will occur (Unpublished results of COG study).

Staging requires CT or MRI scans of the primary lesion and suspected metastatic sites. A technetium or MIGB bone scan should be obtained to identify possible cortical bone

metastases. PET scans may also be useful in evaluating metastatic disease [143, 144].

Patients are currently stratified into prognostic risk groups based on an assessment of biologic factors and tumor staging according to the International Neuroblastoma Staging System (INSS) and the International Neuroblastoma Risk Group Staging System (INRGSS) [145, 146].

Stage 4S Disease

Infants younger than 12–18 months of age often present with a pattern of metastatic disease (stage 4S) that is unique to this age group. Stage 4S infants have a small or undetectable primary neuroblastoma with metastases to the liver, skin, and bone marrow [147, 148]. The adrenal is the most common primary site. Skin lesions typically present as multiple bluish subcutaneous nodules. Stage 4S tumors exhibit particularly interesting biologic behavior. Most (75 %) of these tumors regress spontaneously during infancy [149, 150]. Frequently, however, newborns with massive hepatic involvement are subject to a wide spectrum of significant respiratory and cardiovascular problems that may be fatal.

Treatment and Prognosis

Treatment strategies are based on stage and biologic features. As most oncologic studies do not segregate neonates from the broader grouping of infants younger than age 1 year, information pertaining to both treatment and prognosis in this specific age group is scant. Overall survival rates of infants younger than age 1 year, however, are known to be significantly greater than those of older children. Neonates with high-risk disease do not have this survival advantage.

Stages 1 and 2

Most neonates with stage 1 or 2 disease have a favorable prognosis. Surgery alone is generally sufficient to control disease, and survival is nearly 100 % [130]. In patients with stage 2 disease without N-myc amplification, residual microscopic disease usually regresses without additional intervention.

Stages 3 and 4

The incidence of stage 3 and 4 tumors in neonates and infants younger than 1 year is lower than that in older children [147]. Infants with stage 3 disease generally undergo several cycles of combination chemotherapy followed by delayed primary resection. Those without N-myc amplification have an excellent prognosis and enjoy a 90 % event-free survival [151]. Infants with stage 4 disease without N-myc amplification do not fare as well. Although studies show variable survival rates, these rates exceed 50 % [152–154].

Infants with stage 3 or 4 disease and N-*myc* amplification are considered to be a particularly high-risk group, requiring more intensive high-dose chemotherapy and radiation therapy and possible stem cell rescue. Despite this approach, those with more than 10 copies of the N-myc oncogene may have rapidly progressive disease; only 30–40 % of these patients survive.

Stage 4S

The survival rate of infants with stage 4S disease is greater than 80 %, often without treatment [155, 156]. Most patients have favorable genetic and biologic factors, including high protooncogene Trk-A expression, absence of N-myc amplification, favorable histology, and no evidence of allelic loss of chromosome 1p [155].

Despite the high rate of spontaneous tumor regression, progressive hepatomegaly may lead to respiratory embarrassment or inferior vena caval compression. In these patients, low-dose radiation to the liver (1–1.5 Gy per day over several days, with a total dose of 6–12 Gy) and low-dose chemotherapy are used to accelerate tumor regression. As a measure of last resort, some surgeons have released the intraabdominal compartment syndrome by creating a ventral hernia, using a large silastic patch to cover the surgical defect.

Most deaths in stage 4S occur in infants younger than 2 months of age with severe symptoms due to hepatomegaly. As compared to older infants, this younger group exhibits less tolerance to therapy [148, 156].

Soft Tissue Sarcomas

More than 75 % of soft tissue masses in children younger than age 1 year are benign lesions of vascular or fibromuscular origin. Soft tissue sarcomas diagnosed during the neonatal period are extremely rare, accounting for approximately 10 % of all neonatal malignant tumors and only 2 % of all childhood sarcomas [157] (Fig. 11.10). Some soft tissue sarcomas in neonates have a better prognosis than in older children, and the distinction between benign and malignant tumors is less clear in the neonate [158]. These tumors fall into two diagnostic groups, including rhabdomyosarcoma (RMS) and an exceedingly rare and diverse group of tumors collectively referred to as non-rhabdomyosarcoma soft tissue sarcomas (NRSTS).

Soft tissue sarcomas usually present as a mass on physical examination. Imaging studies such as US or MRI are used to assess evidence of local or distant spread; however CT scanning should be avoided because of the high radiation dose. In some patients, diagnostic bone marrow aspiration also may be used to rule out bone marrow involvement. In large tumors, incisional biopsy may be required to confirm the diagnosis. It is necessary to provide at least a cubic cm of fresh and unfixed tissue to the pathologist, allowing for

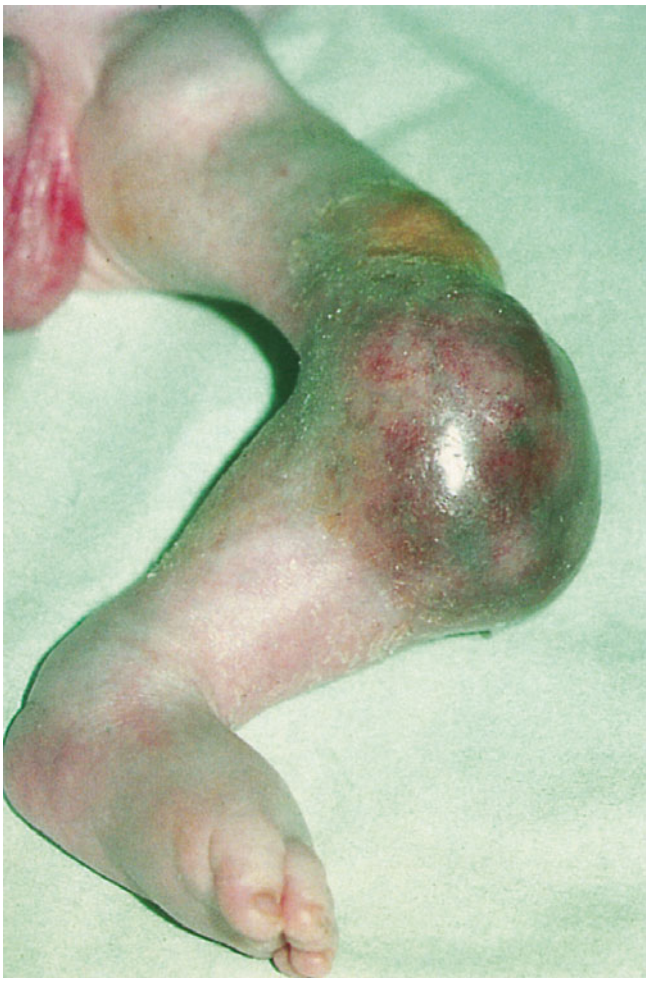

Fig. 11.10 Clinical photograph of a neonate with a sarcoma of the knee with metastatic spread to groin and lymph nodes

cytogenetic studies, electromicroscopy, and conventional immunohistochemistry [158].

Soft tissue sarcomas differ in their natural history and their response to chemotherapy. As in older children, RMS in neonates is responsive to chemotherapy. Some NRSTS in neonates, however, are chemosensitive whereas others are not [159]. In view of the known long-term effects of radiotherapy, this should be used only as a treatment of last resort. Surgery plays a major role both in establishing the diagnosis and in tumor management, especially in neonates. Optimally, localized soft-tissues masses are treated by wide excision with a clear margin, if this can be achieved without compromising function, growth, or appearance [160].

Rhabdomyosarcoma

Although RMS is the most common soft tissue sarcoma in older children, it accounts for only a third of soft tissue sarcomas in the first month of life. Because less than 5 % of all RMS presents in patients younger than age 1, data pertaining to neonatal RMA is extremely limited. In an Intergroup Rhabdomyosarcoma Study reported in 1994, there were only 14 neonates in a study group of 3217 patients, an incidence of 0.4 % [47].

Two histologic types of rhabdomyosarcoma have been described: alveolar (ARMS) and non-alveolar RMS. These tumors differ in their clinical behaviors and are associated with distinct chromosomal translocations. The predominant histologic non-alveolar RMS subtype presenting in neonates is embryonal (ERMS). These lesions are associated with allelic loss of the 11p15 region [161].

Approximately half of neonatal RMS arises in the bladder, vagina, and testicular and sacrococcygeal regions [162]. A common characteristic of neonatal RMS is its aggressive biologic behavior, with 50 % of patients having widespread disease at the time of diagnosis [157]. Metastatic disease can appear in the lungs, lymph nodes, liver, bone marrow, bone, and brain.

The treatment of neonatal RMS includes both surgery and chemotherapy; however, some tumors are not resectable prior to preoperative chemotherapy. Chemotherapy regimens vary, depending on the specific site and stage of the tumor. Although combination chemotherapy with vincristine, actinomycin D, and cyclophosphamide (VAC) has historically been considered the most effective chemotherapy regimen, this regimen has been modified to reduce long-term toxicity. Currently, neonates with low-risk RMS are treated only with vincristine and actinomycin D (VA), thus reducing the risk of myelosuppression, infertility, and second malignancies [158, 163]. Neonates with high-risk RMS undergo a more intensive regimen, with the addition of ifosfamide or anthracyclines. Complete resection of nonmetastatic primary tumors is recommended if it can be accomplished with acceptable morbidity and without impacting function.

Brachytherapy and conventional radiotherapy are reserved for infants with gross or microscopic residual disease. Prognosis depends on stage at presentation, histologic characteristics of the lesion, and the location of the primary tumor. Infants with embryonal histology and complete surgical resection do well, with cure rates higher than 90 % [164]. Those with primary tumors in the head and neck (except parameningeal) and genitourinary region enjoy this same favorable prognosis [164]. Infants with metastatic disease at diagnosis do not fare well, with a 5-year survival rate of less than 30 % [157, 165].

Non-rhabdomyosarcoma Soft Tissue Sarcomas

NRSTS are exceedingly rare, with published experiences consisting only of small series or case reports. These tumors comprise a wide spectrum of pathologies, including undifferentiated sarcomas, synovial sarcomas, liposarcomas, peripheral primitive neuroectodermal tumor (PNET), and

infantile fibrosarcoma (IFS). A study conducted by the Children's Cancer Study Group (n=9) [157] found that 5 of 9 newborns with a range of NRSTS survived (mean followup 9 years). Primary tumor sites were the head and neck, extremities, and trunk. Tumor management was based on tumor location, biology, and resectability. Survivors had localized disease at the time of surgery. Four had complete surgical resections, and one had microscopic disease at the surgical site; this patient was treated with chemotherapy. All patients with unresectable regional or metastatic disease died despite adjuvant chemotherapy.

Infantile Fibrosarcoma

Infantile fibrosarcoma (IFS) is the most common soft tissue sarcoma in children younger than age 1. Its incidence is higher in the first 6 months of life, and approximately one third of tumors diagnosed before age 5 are diagnosed shortly after birth [166]. IFS often presents as visible enlarging soft tissue masses. These masses typically affect the extremities (66 %); however, they are also seen in the abdomen (21 %) and thorax (3 %) [167] and have been documented in atypical locations, such as the intestine, lung, kidney, and colon [168]. Although these tumors are histologically similar to fibrosarcoma occurring in adults, they differ significantly in their behavior, as they have a low metastatic rate and a 5-year disease-free survival greater than 90 % [169, 170]. IFS is characterized by the chromosomal translocation (t 12;15) involving the ETV6 and NTRK3 genes, which is not found in fibrosarcomas that occur later in childhood and which has a much worse prognosis [171, 172]. Spontaneous resolution of congenital fibrosarcomas has been documented [160].

Primary excision is the first line of treatment. Large bulky neoplasms that are not amenable to limb-sparing surgical procedures can be managed with a perioperative chemotherapy (VA) [167].This approach allows for delayed and less extensive resection that might otherwise result in significant mutilation or morbidity. In some cases, chemotherapy may even lead to complete remission, thus eliminating the need for excision. Although metastases are uncommon, local tumor control may be exceedingly difficult, with tumor recurrence reported as high as 40 % [157, 166, 173]. In general, prognosis is not adversely affected by local tumor recurrence or metastatic spread, although exceptions have been reported [174].

Renal Tumors

Congenital renal neoplasms are extremely rare in neonates, accounting for only 8 % of neonatal tumors [15, 16]. The most common tumor of the kidney in the neonate is congenital mesoblastic nephroma (CMN), which accounts for approximately 75 % of renal neoplasms in this age group [175]. This is followed by Wilms tumor, which has an incidence in neonates lower than 0.2 % [175, 176].

Congenital Mesoblastic Nephroma

Although congenital renal neoplasms are rare, CMN is among the most common to present during the first few months of life, accounting for 50 % of all renal masses in the neonate [177]. CMN is a benign mesenchymal renal tumor that is histologically characterized by the proliferation of spindle-shaped cells arranged in fascicles that separate normal renal parenchymal tissue. Two variants of CMN have been identified: classical and cellular (42–63 %) [178]. Both types can coexist in distinct areas of a given tumor. CMN typically presents as a palpable, non-tender abdominal mass (Fig. 11.11a, b); however, hematuria, hypertension, and vomiting can also occur. Although numerous authors have described the detection of CMN with prenatal US during the third trimester, there are no specific prenatal sonographic characteristics that reliably distinguish between CMN and Wilms tumor [179]. In most published series polyhydramnios has been detected.

Fetal MRI is helpful in establishing an accurate prenatal diagnosis, offering better tissue contrast and definition of the relationship of the tumor to adjacent structures [180]. Postnatal imaging modalities such as MRI can be useful in making a more precise diagnosis but also are limited in distinguishing between the two tumors. Histology thus remains essential for establishing a definitive diagnosis [181]. Although most affected children have no associated abnormality, associations have been described for both histologic variants [182].

As most cases of CMN are confined to the renal capsule, nephroureterectomy is usually curative. In some patients, however, the growth pattern is one of local invasion and extension through the renal capsule. During the course of resection, these tumors may be particularly friable and prone to intraoperative bleeding and rupture [15, 183]. Despite these possible complications, a survival rate exceeding 90 % has been reported [15]. Metastases, which rarely occur, are managed with combination chemotherapy comprising vincristine, doxorubicin, and cyclophosphamide or iphosphamide [184, 185].

Wilms Tumor

Although rare, Wilms tumor is the most common renal malignancy in neonates. This tumor is thought to arise from nephrogenic rests that persist beyond 36 weeks of gestation

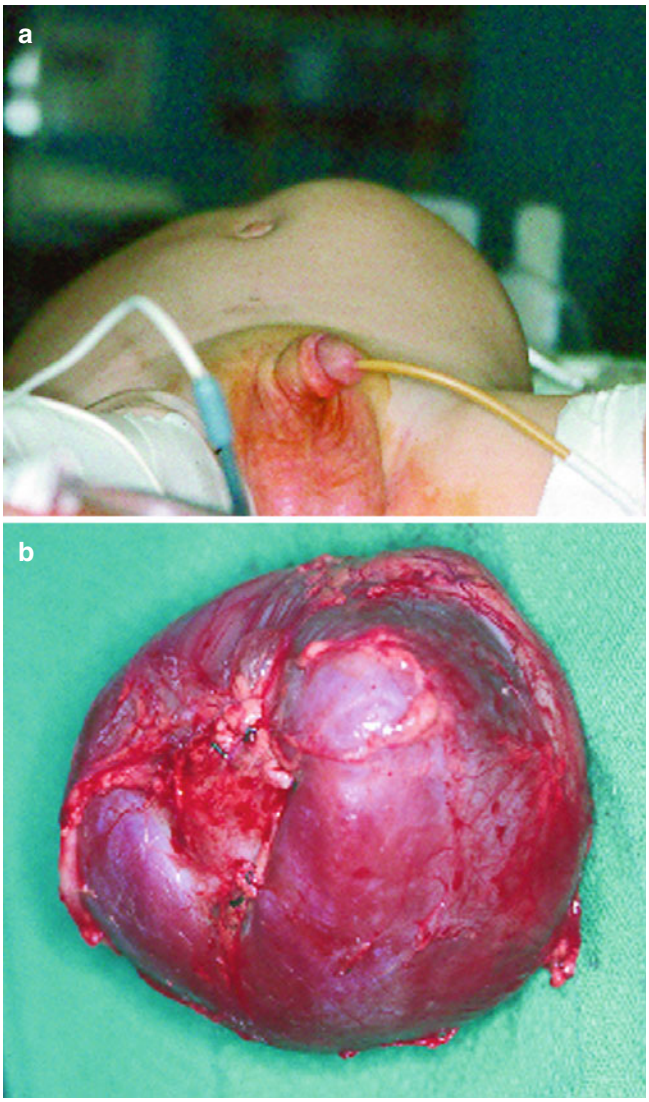

Fig. 11.11 (**a**) A 3-week-old infant with a congenital mesoblastic nephroma (**b**) Operative specimen

[186]. Unlike CMN, Wilms tumor has a robust association with numerous genetic conditions. Both WAGR syndrome (Wilms, aniridia, genitourinary tract abnormalities, mental retardation) and Beckwith-Wiedemann syndrome (gigantism, omphalocele, macroglossia, hemihypertrophy) are associated with an increased risk of developing WT. These syndromes are associated with a loss of function of the WT1 gene at chromosome band 11p13 (WAGR) or WT2 at chromosome band 11p15 (BWS) [187, 188]. Fetal Wilms tumor may present as part of Perlman syndrome, which is characterized by familial nephroblastomatosis, fetal ascites, polyhydramnios, hepatomegaly, macrosomia, and Wilms tumor [189, 190]. Other associated anomalies include aniridia, hemihypertrophy, cryptorchidism, and hypospadias. Among patients with Wilms tumor who have no identifiable syndrome, approximately 40 % have abnormalities in expression of WT1 and WT2 [191]. This tumor affects both sexes equally [192].

Relatively few cases have been diagnosed antenatally, and as mentioned above, antenatal sonographic features of this tumor may be indistinguishable from those of CMN. Both CMN and Wilms tumor present as complex masses that may originate from and replace the entire kidney. Tumors are mainly solid, however, cystic regions may exist within the tumor. Wilms tumor may have a well-defined pseudocapsule. Fetal MRI provides clear anatomic definition of the extent of the tumor and its impact on adjacent structures. Postnatal MRI provides optimal preoperative imaging, however, histopathology is essential to confirm the diagnosis.

As with CMN, Wilms tumor in neonates usually presents as a non-tender abdominal mass. Important to note, 50 % of cases have hypertension, an important indication of the need for further evaluation [193]. Hematuria and hypercalcemia have also been reported [194], though they are not specific for this particular tumor. Most tumors are low stage and have favorable histology, however, metastatic disease can occur [176, 195]. The most common site of metastasis is the lungs.

For infants with unilateral Wilms tumor, the mainstay of treatment is nephroureterectomy for all tumors. In North America, stage II and higher tumors are treated with nephroureterectomy followed by combination chemotherapy with vincristine, dactinomycin, and doxorubicin (COG protocol). The SIOP (Societé Internationale D'oncologie Pediatrique) protocol for higher risk tumors is somewhat different, as it calls for upfront chemotherapy followed by nephroureterectomy [196].

Liver Tumors

Primary tumors of the liver are extremely rare, accounting for only 2 % of all pediatric tumors and 5 % of neoplasms occurring in the fetus and neonate [197]. They include a wide spectrum of benign and malignant lesions that occur with a distribution that is different from that in older children [198]. Most benign neonatal liver tumors are of vascular origin. Hemangiomas are the most common primary liver neoplasm, followed by mesenchymal hamartoma and hepatoblastoma.

Infantile Hepatic Hemangiomas

Hepatic hemangiomas follow a natural history similar to that of cutaneous lesions, and as with cutaneous lesions, they occur more commonly in females. Most hepatic hemangiomas are asymptomatic and incidentally discovered during imaging of the abdomen. Diffuse involvement of the liver is more often associated with severe complications during the

proliferative phase, such as high output cardiac failure, hepatic dysfunction, abdominal compartment syndrome, and hypothyroidism. Significant symptoms or complications generally become evident during the first 3–4 months of life. Cutaneous hemangiomas are frequently the first indication of potential visceral involvement; however, hepatic and other visceral hemangiomas also can occur without cutaneous involvement [199].

Hepatic hemangiomas present variably, from tiny asymptomatic tumors that are detected incidentally to large (>5 cm in diameter) single or multiple tumors that may or may not be associated with high output cardiac states. Infants are frequently seen with a triad of hepatomegaly, anemia, and high-output cardiac failure [200]. A systolic bruit may occasionally be heard over the enlarged liver. In rare cases, progressive and massive liver enlargement may cause abdominal compartment syndrome, resulting in life-threatening visceral ischemia and ventilatory failure [201].

US of the liver in infants with multiple (>5) or solitary lesions is useful both for initial screening [202] and for followup on lesions that are well characterized. US demonstrates either a single lesion or multiple lesions with draining veins and often a dilated proximal abdominal aorta. There may also be signs of significant intrahepatic shunting. Antenatal US may detect large hepatic lesions [203].

MRI is the imaging technique of choice for completely defining the extent and location of hepatic hemangiomas and their relationship to vascular structures. Although imaging features vary, most lesions appear as focal or multifocal T2-hyperintense spheres with centripetal contrast enhancement and dilated feeding and draining vessels (Fig. 11.12a). Three atypical patterns have also been found, including focal mass lesions with a large central varix with or without direct shunts, focal mass lesions with central necrosis or thrombosis, and massive hemangiomatous involvement of the liver with abdominal vascular compression [204]. The latter pattern of massive replacement of liver is associated with abdominal compartment syndrome, hypothyroidism, and a high mortality rate. Hypothyroidism is attributed to high levels of type 3 iodothyronine deiodinase activity produced by hemangiomas; this activity inactivates circulating thyroid hormone [205]. Patients with diffuse liver hemangiomatosis should therefore undergo screening for hypothyroidism. Because an abnormal thyroid-stimulating hormone level may not develop until a hemangioma proliferates, repeat testing is indicated when lesions undergo considerable growth. For patients with diffuse hemangiomatosis, high-output cardiac failure, and compartment syndrome, the mortality rate exceeds 50 %.

If embolic therapy is required, angiography should first be performed to clearly outline the vascular anatomy and aberrant shunting through the liver. Angiographic features of hepatic hemangiomas are variable, ranging from discrete

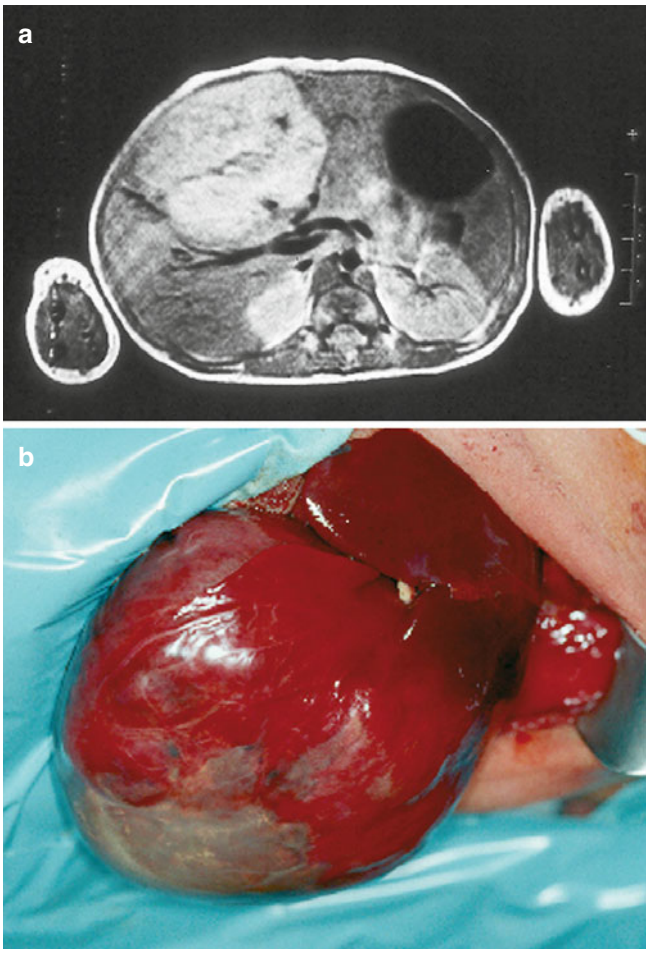

Fig. 11.12 (**a**) MRI of the liver demonstrating a large intrahepatic hemangioma (**b**) Operative photograph showing a large hemangioma of the liver in a 1-month-old infant

hypervascular tumors to diffuse tumors with macroscopic arteriovenous, arterioportal, and portosystemic shunting [200, 206]. Because hepatic hemangioma and arteriovenous malformations are rheologically fast flow, they may be mistaken for one another; however, true arteriovenous malformations are extremely rare. Large solitary lesions diagnosed antenatally or soon after birth are likely to be congenital hemangiomas that are characterized by central necrosis of the lesion, capillary proliferation in the periphery of the lesion, and indistinct lesion margins due to abnormally large vessels extending into the adjacent liver tissue (Fig. 11.12b).

When imaging features are atypical and the diagnosis is unclear, incisional or excisional biopsies are extremely helpful in determining the pathology of a lesion and the most appropriate course of treatment. Differential diagnosis includes neuroblastoma, hepatoblastoma, and mesenchymal hamartomas, as well as a number of other neoplasms. Most infantile hepatic hemangiomas, including those detected incidentally on imaging studies, remain asymptomatic throughout their natural clinical course. Patients with focal

lesions without high flow seen on Doppler US generally do not require treatment [204]. Patients with small, asymptomatic lesions should be followed with sequential physical examinations and US studies. Treatment should be reserved for infants with enlarged lesions that cause significant symptoms or complications.

Propranolol, a nonselective beta-blocker used for the management of infants with cardiovascular conditions, has become the preferred treatment for hepatic hemangiomas as well as other function or life-threatening hemangiomas [207]. Although the mechanism of action of propranolol remains speculative, it is thought to involve the downregulation of vascular endothelial growth factor (VEGF) and beta fibroblast growth factor (bFGF) gene expression and to trigger apoptosis of capillary endothelial cells. By using propranolol as our first-line therapy, we have achieved a response rate of greater than 90 %. Patients typically receive 3–4 mg/kg/day for up to 1 year, which generally corresponds to the proliferative phase. They are then weaned off the propranolol. Corticosteroids may be used adjunctively and in some patients the combined approaches have a synergistic effect. Patients who are critically ill are initially treated with both propranolol and corticosteroids. Once they are stabilized, propranolol alone is administered. Caregivers should be aware of possible adverse effects of propranolol, which include hypoglycemia, hypotension, and brachycardia. These may manifest in lethargy, labored breathing, and diaphoresis.

For lesions that are unresponsive to propranolol and steroids, vincristine is the current drug of choice. Because it is a vesicant, it is best delivered through central venous access. An initial weekly dose of 0.05–1 mg per m^2 is administered by intravenous injection. This dose is then tapered, increasing the interval between injections depending on the clinical response. Treatment is administered for 4–6 months.

The angiogenesis inhibitor interferon-α is also occasionally used for lesions that are refractory to corticosteroid therapy. It is typically administered as a daily subcutaneous injection at a dosage range of 1–3 million units/m^2. Because of its known neurotoxicity, particularly its association with spastic diplegia [208, 209], the use of interferon-α in children younger than age 1 year is generally avoided.

In patients with persistent high-output cardiac failure, angiography and embolization may be performed, with the latter being useful only if there are direct macrovascular shunts through the lesion. Because angiography and embolization are associated with risk of injury to the femoral access vessel or inadvertently embolized visceral vessels, it should be performed only by an interventional radiologist with skill and experience with these techniques in infants.

Other treatment options reserved for refractory lesions include surgical resection of large solitary lesions, hepatic artery ligation, and liver transplantation. Prior to contemporary pharmacologic therapy, resection of solitary lesions and embolization were frequently the only viable treatment options. Because they are associated with extremely high mortality, however, they are now infrequently performed. Although rarely done, hepatic artery ligation is associated with a survival rate of 80 % [210]. Liver transplantation is rarely performed and is reserved for patients in whom there is diffuse hepatic involvement and an imminent risk of death [211].

Mesenchymal Hamartomas

Hepatic mesenchymal hamartomas are benign tumors that typically present as a large, palpable, nontender cystic liver mass. They are more common (75 %) in the right lobe and have a slight male predominance. Lesions are generally diagnosed during the first 2 years of life, however, they are not uncommonly reported in the newborn [198]. The mass is usually encapsulated, although occasionally it can infiltrate into the hepatic parenchyma and cause respiratory distress or heart failure from arteriovenous shunting. Histologically, mesenchymal hamartomas are lined by bile duct epithelium. The phenotypic appearance of lesions may be either multicystic or with a dominant cyst. The cysts do not contain normal bile nor do they communicate with the biliary tree. The tumor stroma has a myxoid or fibrous appearance with combined vascular and biliary elements [212].

Aneuploidy has been documented by flow cytometry and balanced translocations between chromosome 11 and 19 t (11;19) (q13;q13.4) have been found by cytogenetic analysis; the latter finding is consistent with the possibility of a clonal genetic defect. Aneuploidy and karyotype changes are more commonly associated with malignant lesions and when found in mesenchymal hamartomas may indicate an inherent genetic instability [212].

Although lesions have been detected as early as the 19th week of gestation, they are more commonly found during the third trimester. They are sometimes pedunculated and their hepatic origin may be difficult to ascertain. Maternal AFP and β-hCG are sometimes elevated. Large tumors present a threat to the fetus, as they may lead to the onset of polyhydramnios and hydrops secondary to compression of the inferior vena cava and the umbilical vein. They may also cause rapid loss of fluid into the cysts. The volatile fluid shifts in these lesions may bring about premature labor.

Most lesions presenting postnatally are asymptomatic and appear as palpable abdominal masses in otherwise normal infants. Biochemical markers of liver function are generally normal. Although AFP may be elevated, it should return to normal following surgical resection.

The initial diagnostic modality of choice is US. This is followed by MRI or CT scans, which provide more

information regarding anatomic details that are beneficial for surgical planning.

Although spontaneous tumor regression can occur, cases of massive local recurrence and later transformation to undifferentiated sarcoma have been reported [213, 214]. Thus, when feasible, complete surgical resection is the treatment of choice.

Hepatoblastoma

Hepatoblastoma is a rare embryonal neoplasm composed of malignant epithelial tissue with variable differentiation, most often with embryonal or fetal components [198]. It is the most frequently occurring liver tumor during the first year of life; however less than 10 % of these tumors occur in neonates [215].

A broad spectrum of congenital anomalies and malformation syndromes has been reported in association with hepatoblastoma. There is an increased incidence among patients with Beckwith-Weidemann syndrome, Li-Fraumeni syndrome, hemihypertrophy, and familial adenomatous polyposis [216–220]. There also is an increased incidence of hepatoblastoma in males (2:1) and premature infants [221, 222]; in the latter group, the risk increases as birth weight decreases [223].

Hepatoblastomas are occasionally detected prenatally by abdominal US and can cause polyhydramnios and stillbirth. Tumor rupture and massive hemorrhage have been described following delivery [224, 225].

Postnatally, hepatoblastoma presents with abdominal enlargement and hepatomegaly. AFP levels are elevated in most patients and are especially useful in monitoring disease status following treatment. The lungs are the primary site of metastasis, though bone and brain involvement can occur. US is useful in distinguishing solid from cystic masses. Hepatoblastoma generally appears as a large hyperechoic mass. Color Doppler imaging is also helpful in evaluating the involvement of the portal vein, hepatic veins, and the inferior vena cava. A CT or MRI liver scan is helpful in delineating the extent of the lesion and assessing its resectability. MRI scans in particular can clearly delineate the vascular anatomy of the liver in relationship to the tumor.

Complete surgical resection and subsequent chemotherapy with cytotoxic agents (e.g., cisplatin and doxorubicin) is the treatment of choice [226, 227]. For neonates with lesions that initially are not resectable, preoperative chemotherapy can be beneficial. For patients with unresectable tumors confined to the liver, hepatic transplantation is an option [211]. Prognosis is largely dependent on resectability. Approximately two thirds of patients with tumors that are initially unresectable can be rendered disease-free with several cycles of chemotherapy followed by surgical resection and subsequent postoperative chemotherapy [228, 229]. Despite preoperative chemotherapy, it is clear that hepatoblastoma is likely to be fatal without complete resection of the tumor [230].

Retinoblastoma

Retinoblastoma is a rare malignant tumor that arises from the embryonic neural retina and is estimated to occur in 1 in 15,000 to 1 in 34,000 live births [231]. Although it is believed to be congenital, it may not be observed at birth. Eighty percent of cases are diagnosed before the age of 3–4 years (mean, age 2). Bilateral tumors are estimated to occur in 20–30 % of affected children [232]. In this subgroup, the diagnosis typically becomes clinically apparent earlier (mean, age 12 months) [233].

Retinoblastoma develops in cells that that have mutations in both copies of *RBI,* the retinoblastoma locus, located on chromosome 13q14. The tumor is detected by absence of the normal red reflex when the infant's eyes are examined with an ophthalmoscope. All newborns should thus be screened for this reflex and any infant with a family history of retinoblastoma should undergo a comprehensive ophthalmologic examination. These patients are particularly at risk for bilateral involvement.

When detected early, cure rates exceed 90 % [234, 235]. When disease is intraocular, laser therapy or cryotherapy is used either with or without adjuvant chemotherapy, depending on the size of the lesion. In selective cases, radiotherapy is also used to salvage vision. Extensive intraocular disease can be managed with enucleation [236]. Metastatic disease requires aggressive chemotherapy [237, 238].

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Renal Tumors

12

Thomas E. Hamilton and Robert C. Shamberger

A broad spectrum of tumors arise in the kidney in infants and children ranging from benign to some of the most malignant tumors seen in children. Wilms tumor is the most common renal tumor in childhood and is the second most common abdominal tumor presenting in infants and children after neuroblastoma. Today the vast majority of children with Wilms tumor can be cured by multidisciplinary therapy. Their treatment is in fact the paradigm for management of most childhood tumors and is based upon evidence obtained from three cooperative group organizations, the National Wilms Tumor Study Group (NWTSG) now merged with the Children's Oncology Group (COG), the United Kingdom Children's Cancer Study Group (UKCCSG), and the Sociètè Internationale d' Oncologie Pèdiatrique (SIOP). These organizations have performed multiple randomized therapeutic trials which have established the basis for current therapy. Current pathologic classification and staging were established by central pathologic review of the specimens from patients enrolled in these studies. Translational research accrued from these studies has allowed for risk-based stratification and directly impacts patient care. It could never have been established without multiinstitutional participation due to the relative rarity of pediatric renal tumors. In this chapter the early history of treatment of pediatric renal tumors will be presented followed by a discussion of their etiologic factors, pathologic subtypes and premalignant syndromes. Current treatment algorithms for Wilms tumors and other tumors of the kidney will be reviewed.

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History

The first descriptions of Wilms tumor have been variably attributed to either Rance in 1814 or Wilms in 1899 [136, 192]. Ironically, however, the first known specimen of this tumor was collected by the British surgeon John Hunter between 1763 and 1793 when he was assembling specimens for his museum [9]. This case of a bilateral tumor in a young infant remains in the Hunterian Museum of the Royal College of Surgeons in London to this day (Fig. 12.1). Wilms' name became indelibly linked to the mixed renal embryonal tumor following publication of his comprehensive monograph on mixed tissue tumors of the kidney in 1899 where he described seven children suffering from nephroblastomas. Early surgery for this tumor was fraught with challenges. The first successful resection is attributed to Thomas Richard Jessop at the General Infirmary in Leeds in 1877 [191]. Czerny reported an early series of 150 patients resected before 1891 [191]. The operative mortality of this series was about 75 % and only five children survived for greater than 5 years.

William E. Ladd and Robert E. Gross [72, 101] established the principles of surgical therapy for Wilms tumor including transperitoneal exposure and preliminary ligation of the renal pedicle. They stressed the need to remove the perirenal fat to include lymphatic extensions of the tumor and to avoid rupture of the renal capsule, principles we continue to follow to this day. Adoption of their techniques significantly lowered the operative mortality of nephrectomy in children. Gross and Neuhauser later proposed the routine addition of abdominal radiation to the therapy of Wilms tumors and reported an estimated 47 % frequency of cure [72]. Under Gross's tutelege, pediatric surgeons in North American generally performed primary resection of Wilms tumors while in Europe the Paris school lead by Schweisguth and Bamberger reported early success with preoperative irradiation establishing a precedent for preoperative therapy [159].

From 1931 to 1939, survival following surgical resection alone involving ligation of the renal pedicle before removal

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was 32 % at Children's Hospital in Boston [47]. After 1940, most of the patients received postoperative radiation to the renal fossa, achieving lower local recurrence rates, but radiation did not significantly impact the frequency of pulmonary metastases or improve the long-term survival. Actinomycin D was the first active agent identified for the treatment of Wilms tumor. An 89 % 2-year disease-free survival was achieved from 1957 to 1964 in 53 patients without demonstrable metastasis treated with combined therapy of surgery, local radiation, and actinomycin-D [48]. This would be a very acceptable survival even today. Eighteen of 31 children with metastasis (58 %) were alive and free of disease greater than 2 years later. Subsequently, vincristine sulfate was identified as an active agent in Wilms tumor and was added to its standard therapy [174]. In the ensuing decades other agents were added to the management of the unfavorable histology subtypes and recurrent tumors.

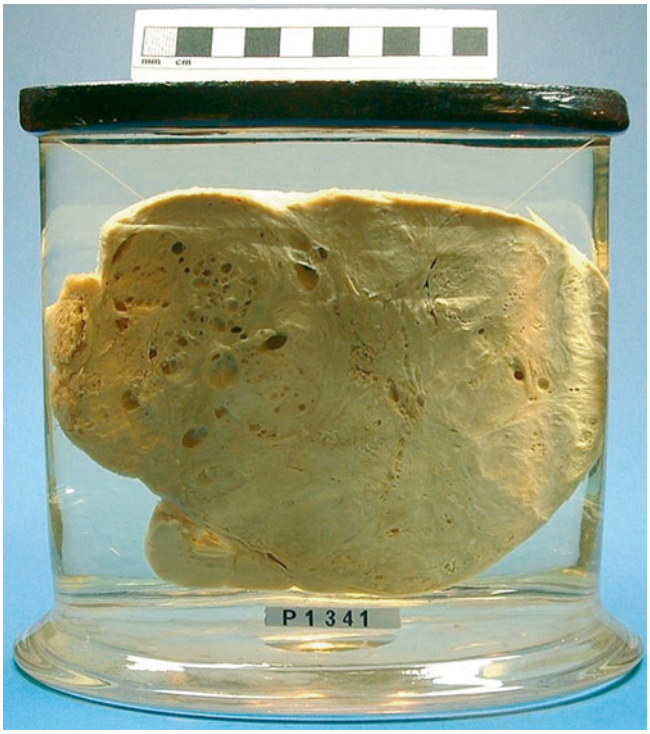

Fig. 12.1 First documented specimen of a nephroblastoma collected by John Hunter for inclusion in the "Hunterian Museum" of the Royal College of Surgeons of England. This specimen is one of two from a child with bilateral renal tumors (Photo courtesy of the Hunterian Museum at the Royal College of Surgeons)

Wilms tumor was the first malignancy in which the importance of adjuvant treatment of the tumor was recognized and Sidney Farber espoused its use decades before it would be applied to other pediatric and adult solid tumors [47]. Adjuvant therapy "was based upon the supposition that in the children with Wilms tumor who died, the tumor must have metastasized already at the time of discovery of the primary tumor" although no evidence of spread was available.

Wilms Tumor Incidence and Etiology

Wilms tumor is the most frequent tumor of the kidney in infants and children. Its incidence is 7.6 cases for every million children less than 15 years of age or one case per 10,000 infants [17]. Its frequency varies by race; rarer in East Asian populations than in Caucasians, but more frequent in Africa and in African American children [172]. The frequency of Wilms tumor far outstrips the occurrence of renal cell carcinoma in children until the age range of 15–19 years when renal cell carcinoma becomes more frequent [17] (Fig. 12.2).

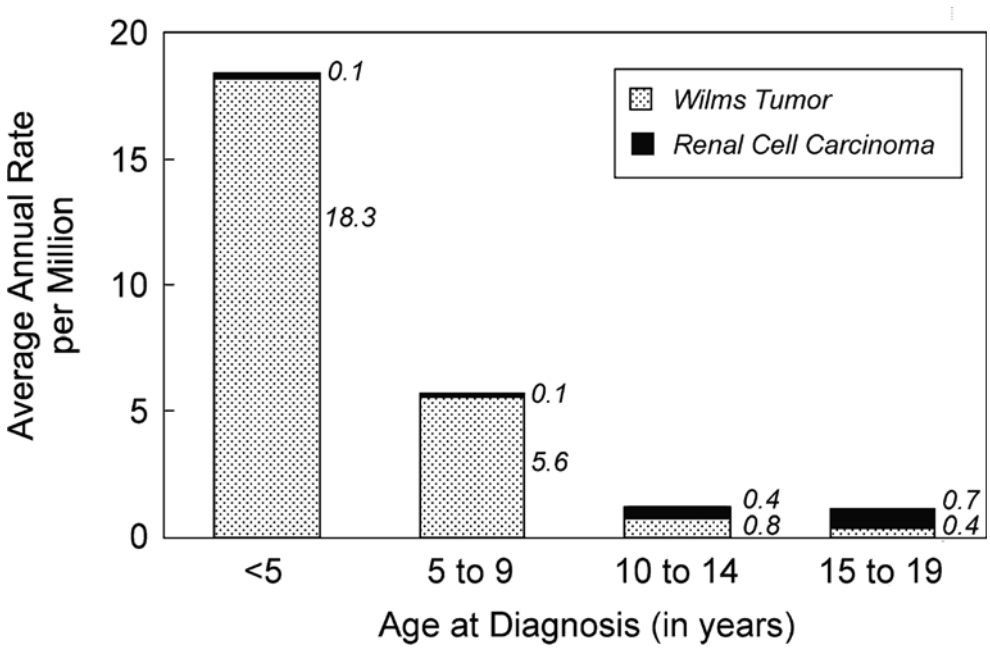

Fig. 12.2 Age-specific occurrence of Wilms tumor and renal cell carcinoma is depicted in this chart derived from SEER data for 1975 to 1995. The marked dominance of Wilms tumor in children up to 9 years of age is well demonstrated. Only in children over 15 years of age does renal cell carcinoma become more prevalent than Wilms tumor

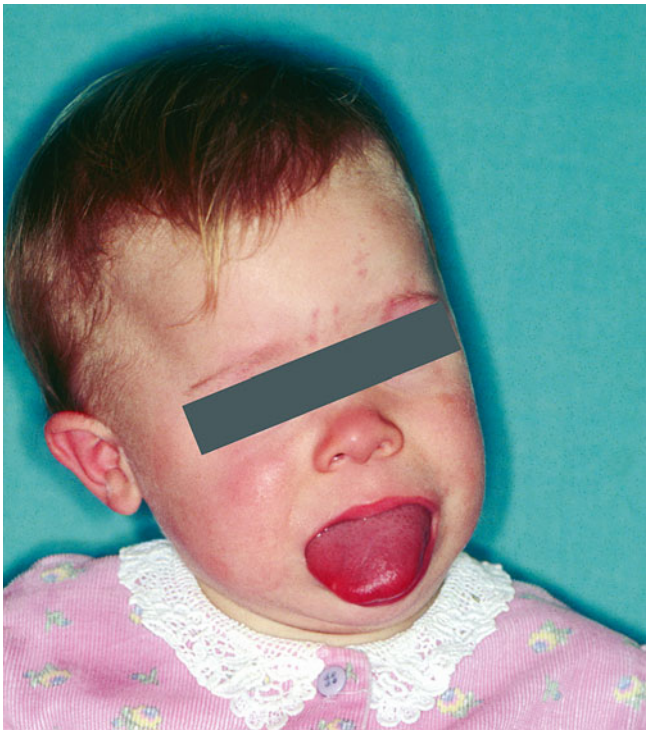

Fig. 12.3 Child with Beckwith-Wiedemann syndrome demonstrating the macroglossia characteristic of this syndrome as well as the mild mid face deficiency which produces a sleepy appearance in children with this syndrome

Wilms tumor is associated with several congenital syndromes in just under 10 % of cases including sporadic aniridia, isolated hemihypertrophy, the Denys-Drash syndrome (nephropathy, renal failure, male pseudohermaphroditism, and Wilms tumor), genital anomalies, Beckwith-Wiedemann syndrome (visceromegaly, macroglossia, omphalocele, and hyperinsulinemic hypoglycemia in infancy) (Fig. 12.3) and the WAGR complex (Wilms tumor with aniridia, genitourinary malformations, and mental retardation) which suggested a genetic predisposition to this tumor [91]. Wilms tumor is also reported in individuals with Simpson-Golabi-Behmel syndrome, another overgrowth syndrome similar in many respects to Beckwith-Wiedemann [89]. These congenital disorders have now been linked to abnormalities at specific genetic loci implicated in Wilms tumorigenesis.

Genetic Origins

The identification of a large chromosomal deletion of band p13 of the eleventh chromosome in children with the WAGR syndrome led to a search at this site for a gene producing the Wilms tumor [51, 140]. This deletion includes the aniridia gene (*PAX6)* and a putative Wilms tumor suppressor gene *(WT1)*. It should be recognized that children can lack the *PAX6* gene but not the *WT1* gene and are then not at increased risk for the development of Wilms tumors. In fact, from the Danish aniridia registry 44 of 144 cases of aniridia were sporadic. Of the sporadic cases 5 included a deletion of the *WT1* gene and of those only 2 developed a Wilms tumor [71]. None of the familial cases lacked the *WT1* site. The risk of Wilms tumor occurring in all patients with aniridia is low, but it is estimated that in the children with sporadic aniridia the risk of developing a Wilms tumor was 67 times higher than a normal population, but it is entirely attributable to the small proportion of children who lack the *WT1* gene. It is estimated that between 45 and 57 % of children with the WAGR syndrome will develop a Wilms tumor [50, 122].

The protein product of the *WT1* gene is a developmentally regulated transcriptional factor of the zinc finger family which regulates the expression of other genes including growth-inducing genes such as those encoding early growth response, insulin-like growth factor II, and platelet-derived growth factor A chain [137, 138]. Suppression of these growth associated genes may explain the tumor suppressor role of *WT1*. Recently, the *WT1* gene product has been found to physically bind to the p53 protein [112]. Children with the WAGR syndrome have constitutional deletions of band 11p13 while virtually all patients with Denys-Drash syndrome carry point mutations of *WT1* in the germline [140]. These result in a dominant negative oncogene and more severe somatic abnormalities than in the WAGR syndrome attributed to the inhibition by the mutated protein on the action of the normal "wild-type" protein produced by the normal chromosome [110]. The second *WT1* allele is lost in the Wilms tumor cells in patients with WAGR and similarly the tumor in children with Denys-Drash syndrome have loss of the remaining "wild-type" allele [105]. The most common phenotypic abnormality in the WAGR syndrome besides aniridia is cryptorchidism found in 60 % of male patients while abnormalities of the internal reproductive organs including streak ovaries and bicornuate uterus are seen in 17 % of females followed by ambiguous genitalia in boys and girls [50]. Mental retardation was seen in 70 % of children and renal failure in 29 % which was produced by both nephrectomy and glomerulonephritis predominantly focal segmental glomerulosclerosis (FSGS). Studies have demonstrated that children with WAGR syndrome more frequently have bilateral tumors (17 % vs 6 %) and are younger at diagnosis (22 vs. 39 months) than children without WAGR [26].

The Beckwith-Wiedemann syndrome has been associated with a 5–10 % incidence of Wilms tumor and other embryonal tumors. Abnormalities at the 11p15 locus, particularly loss of heterozygosity, have been associated with Beckwith-Wiedemann patients [97, 132, 139]. The locus for a putative second Wilms tumor gene (*WT2*) has not been defined nor is

it known whether the Beckwith-Wiedemann locus and *WT2* are the same or contiguous loci [171]. At the *WT2* site, there are several imprinted genes which are expressed preferentially from one of the parental alleles [171]. In some cases, a constitutional duplication of the paternal 11p15 chromosomal fragment has been identified (trisomy at 11p15) [186]. In other cases, both copies are from the father with none from the mother (uniparental isodisomy) [76, 82]. These findings led to speculation that the Beckwith-Wiedemann gene is expressed only by the paternal allele and these genetic abnormalities which lead to the presence of two paternal alleles would double the expression of this gene and may result in the overgrowth.

Two *WT2* candidate genes are the insulin-like growth factor 2 gene and the *H19* gene. The insulin-like growth factor 2 (*IGF2*) gene is present at the 11p15 locus. It is an embryonal growth-inducing gene with expression restricted to the paternal allele [42]. However, there is no direct evidence to link the *IGF2* gene to the causation of the Beckwith-Wiedemann syndrome [35]. Loss of expression of *H19*, a tumor-suppressor gene of uncertain function, has also been reported in Wilms tumors [170]. The *H19* gene is expressed preferentially from the maternal allele. With loss of heterozygosity, the cell may loose the maternal (active) copy and hence its tumor suppressor function.

It is of note that children whose manifestations of the Beckwith-Wiedemann syndrome include hemihypertrophy appear to have a greater risk for the occurrence of malignancy than those who do not. In a series reported by Wiedemann, cancer was reported in 7.5 % of all children with the syndrome, but in more than 40 % of children with both the syndrome and hemihypertrophy [189].

The Simpson-Golabi-Behmel syndrome is an overgrowth syndrome phenotypically similar to Beckwith-Wiedemann syndrome with macroglossia, coarse facial features and visceromegally The less frequent manifestations of diaphragmatic and heart defects and polydactyly are unique to Simpson-Golabi-Behmel syndrome. It is a sex-linked syndrome localized to Xq25-27 and the protein product Glypican 3 may interact with the *IGF-II* receptor [88, 192]. Expression of this protein is seen primarily in mesodermal fetal tissues including lung, liver and kidney [54].

Familial cases of Wilms tumor account for only 1–2 % of cases and have not been associated with the above syndromes. Analysis of two kindreds revealed a link with chromosome band 17q12-21, and the putative tumor gene at this locus has been named *FWT1* [135]. In addition, loss of heterozygosity was see at 19q in tumors from individuals from two families whose predisposition is not due to the previously defined 19q locus suggesting that alterations at two distinct loci are critical rate-limiting steps in the etiology of these familial Wilms tumors involving both germ-line predisposing mutations and somatic alteration at a second focus. Subsequent studies demonstrated in five kindreds an inherited Wilms tumor predisposition gene at 19q13.3-q13.4 called *FWT2* [116].

WT1 and *WT2* do not appear to have any prognostic significance for children with Wilms tumor in marked contrast with the *MYCN* gene in neuroblastoma. They also appear in a small percentage of children with Wilms tumor who have the associated syndromes. Recent studies have suggested that loss of heterozygosity on chromosome 16q in Wilms tumors (observed in 15–20 % of cases) was associated with a 3.3 times greater incidence of relapse and a 12 times greater incidence of mortality as compared to children without these chromosomal changes [75]. This region of loss has now been localized to an area of 6.7 megabases which contain three recognized tumor suppressor genes and one of them *E-cadherin* has been shown to have reduced expression in Wilms tumors with LOH at 16q [155]. A similar trend was seen for children with loss of heterozygosity for 1p which occurs in approximately 10 % of Wilms tumors, but these trends were not statistically significant. Identification of increased expression of the *p53* has also been associated with advanced stage at presentation and increased frequency of recurrence [155]. One of the primary goals of the fifth NWTS study was to assess whether identified chromosomal abnormalities were of prognostic significance in Wilms tumor and might provide guidance for future therapeutic recommendations. NWTS-5 was the first protocol completed not to involve randomization, and prospectively confirmed that LOH at both 1p and 16q was an adverse prognostic factor for all stages of Wilms tumor. This study served as the gateway for the use of genetic alterations of tumor to guide risk-based therapy by NWTSG [73].

Vicki Huff published a detailed review on the genetic alterations in Wilms tumors.[1] Genes mutated in Wilms tumor include *TP53*, a classic tumor suppressor gene, *CTNNB1* (encoding B-catenin) a classic oncogene; *WTX*, a tumor suppressor gene based on increasing data and Wilms tumor 1 (*WT1*). *WT1* has an important role in regulating normal differentiation in various organs. Loss or overexpression results in differing phenotypic consequences depending on the status of cellular differentiation as does its oncogenic or tumor suppressor effect. Understanding how cells respond to the loss or alteration of *WT1* in various stages of differentiation and in the presence of other gene mutations in variable microenvironments are the target for future study to best understand the malignancy [80, 87].

Two recent international studies have provided additional insights to understanding the genetic alterations in Wilms tumor. Turnbull and co-authors reported in Nature Genetics a genome wide association study identifying susceptibility loci for Wilms tumor using 757 individuals with Wilms

[1] Huff [87].

tumor and 1,879 controls. Clear significant associations at 2p24 (rs3755132, P = 1.03 × 10(−14); rs807624, P = 1.32 × 10(−14)) and 11q14 (rs790356, P = 4.25 × 10(−15)). Both regions contain genes that are plausibly related to Wilms tumorigenesis. Candidate association signals at 5q14, 22q12 and Xp22 were also identified. Scott and co-authors report the ability to stratify genetic and epigenetic changes in Wilms tumors into three distinct groups. Somatic defects at five loci, *WT1*, *CTNNB1*, *WTX*, *TP53* and the imprinted 11p15 region, are implicated in Wilms tumor, the most common childhood kidney cancer. In their study all five loci in 120 Wilms tumors were analyzed. They identified epigenetic 11p15 abnormalities in 69 % of tumors, 37 % were *H19* epimutations and 32 % were paternal uniparental disomy (pUPD). Identified mutations of *WTX* in 32 %, *CTNNB1* in 15 %, *WT1* in 12 % and *TP53* in 5 % of tumors. Several significant associations: between 11p15 and *WTX* (P = 0.007), between *WT1* and *CTNNB1* (P less than 0.001), between *WT1* and *pUPD* 11p15 (P = 0.01), and a strong negative association between *WT1* and *H19* epimutation (P less than 0.001) were also identified. They used this data to stratify Wilms tumor into three molecular groups, based on the status at 11p15 and *WT1*. Group 1 tumors (63 %) were defined as 11p15-mutant and *WT1*-normal; a third also had *WTX* mutations. Group 2 tumors (13 %) were WT1-mutant. They either had 11p15 pUPD or were 11p15-normal. Almost all had *CTNNB1* mutations but none had *H19* epimutation. Group 3 tumors (25 %) were defined as 11p15-normal and *WT1*-normal and were typically normal at all five loci (P less than 0.001). They also identified a novel clinical association between *H19* epimutation and bilateral disease (P less than 0.001). The data provide new insights into the pattern, order, interactions and clinical associations of molecular events in Wilms tumor [160, 180].

Routine radiographic screening of children with syndromes associated with Wilms tumor has been recommended. Ultrasonograms are generally obtained every 3 months until the children are 5 years of age. No prospective studies, however, have been performed to evaluate the cost effectiveness or efficacy of following this recommendation [32, 63]. Retrospective reviews of routine ultrasonographic screening report conflicting results on its proported benefits as assessed by the stage distribution at presentation or the outcome of the children with prospective screening [31, 37].

Pathologic Precursors: Nephrogenic Rests, Nephroblastomatosis, and Multicystic Dysplastic Kidneys

The presence of nephrogenic rests (NR: persistent metanephric blastemal tissue in the kidney after the 36th week of gestation) has been associated with the occurrence of Wilms tumor. The rests may occur in a perilobular (PLNR) or intralobular (ILNR) location and may be single or multiple. In children with aniridia or the Denys-Drash syndrome, the lesions are primarily ILNR, while children with hemihypertrophy or the Beckwith-Wiedemann syndrome have predominantly PLNR [13]. The presence of multiple or diffuse nephrogenic rests is termed nephroblastomatosis.

The frequency of nephrogenic rests was established in an autopsy series of infants under 3 months of age. Nine of 1,035 infants (0.87 %) had PLNRs, and ILNRs occurred in only 2 of 2,000 cases (0.1 %) [15]. Most nephrogenic rests when identified are sclerosing, an apparently indolent or involutional phase. The vast majority will spontaneously resolve without the appearance of a tumor as the incidence of nephrogenic rests is about 100 times greater than that of Wilms tumor (1/10,000 infants).

Nephrogenic rests are classified histologically as incipient or dormant nephrogenic rests, regressing or sclerosing nephrogenic rests, and hyperplastic nephrogenic rests [11]. Incipient or dormant rests are composed predominantly of blastemal or primitive epithelial cells resembling those in embryonic kidney and Wilms tumor, but are microscopic with sharp margins from adjacent renal parenchyma. In infants and young children the term incipient is used while dormant is used in older children. Regressing or sclerosing rests demonstrate maturation of the cellular elements and progress to obsolescent rests which are composed primarily of hyalinized stromal elements. Hyperplastic nephrogenic rests are problematic in that they are often difficult to distinguish histologically or radiographically from small Wilms tumors. They contain diffuse or synchronous proliferation of components throughout the rest. This uniform growth leads to preservation of the original shape of the rest in contrast with neoplastic proliferation of a single cell, which produces a more spherical expanding nodule within the rest. It is almost impossible for even the most sophisticated pediatric pathologist to distinguish a hyperplastic nephrogenic rest from a Wilms tumor based on an incisional or needle biopsy which does not include the margin between the rest and the remaining kidney. "Preservation of the shape of the original rest is the most obvious clue that one is dealing with a hyperplastic, rather than a neoplastic change" [11]. Most hyperplastic nodules lack a pseudocapsule at their periphery, while most Wilms tumors have one. This is often the most helpful histologic finding in distinguishing these two lesions. Hence, biopsies which do not contain the lesion and its margin will rarely adequately differentiate between these two entities.

Nephrogenic rests are frequently found in association with Wilms tumors despite their relatively rare occurrence. In a review of cases of Wilms tumors reported in the National Wilms Tumor Study-4 (NWTS-4), 41 % of the unilateral Wilms tumors were associated with nephrogenic rests [13]. While in children with synchronous bilateral Wilms tumor,

the incidence of nephrogenic rests was 99 %. These were primarily PLNRs-possibly due to the fact that these lesions are much more prevalent than the ILNRs. Similarly, an increased incidence of nephrogenic rests is seen in children with the syndromes associated with Wilms tumor which were discussed above (Table 12.1) [11].

Gylys-Morin and colleagues have demonstrated that magnetic resonance imaging (MRI) scans can be particularly helpful in following children with nephroblastomatosis and it was later confirmed by Rohrschneider and coauthors that MRI or contrast-enhanced CT were preferable to ultrasound in this setting [77, 153]. Alterations in imaging characteristics of the lesions may suggest a transition from nephrogenic rests to Wilms tumor as does growth of isolated lesions.

Diffuse hyperplastic perilobar nephroblastomatosis (DHPLN) is a distinct entity which must be distinguished clinically from Wilms tumor. Infants with DHPLN often present with large unilateral or bilateral flank masses (Fig. 12.4a, b). A characteristic radiographic finding is massively enlarged kidneys that maintain their normal configuration and lack evidence of necrosis. As with the isolated nephrogenic rests, proliferation of the thin rind of nephrogenic rests on the periphery of the kidney preserve its normal configuration, but produce marked enlargement of its size. This is in contrast with Wilms tumor where the normal renal configuration and collecting system are generally distorted. Nephrectomy is *not* required in cases of DHPLN. Chemotherapy, however, has been employed to control the proliferative element of the nephrogenic rests and to accelerate the decrease in size of the kidney and secondary respiratory compromise. It has not, however, been established that treatment with chemotherapy will decrease the subsequent occurrence of Wilms tumors. A recent review of 52 cases of DHPLN revealed a mean age of diagnosis of 16 months. Involvement was bilateral in 49 children. Thirty-three patients had biopsy and adjuvant therapy. Eighteen (55 %) developed Wilms tumors at a mean of 35 months. Sixteen patients had initial nephrectomy and adjuvant therapy and three (19 %) developed a Wilms tumors at a mean of 36 months from diagnosis. All three patients who did not receive adjuvant therapy developed Wilms tumors by 10 months after diagnosis. In total, 24 of 52 children developed Wilms tumors; single in 13 and multiple in 11 children. Eight of the 24 children had anaplastic tumors, an extremely high proportion [130].

An increased risk of Wilms tumors arising in multicystic dysplastic kidneys has been suggested and in the past many of these lesions were resected to prevent the occurrence of Wilms tumor. Narchi summarized 1,041 infants and children with multicystic dysplastic kidneys reported in the world's literature in 26 series and found no cases of Wilms tumors and concluded that nephrectomy was not required [124]. The frequency of nephrogenic rests in multicystic dysplastic kidneys has been estimated to be 4 %, approximately five times the prevalence in a random autopsy population of infants under 3 months of age [12]. If one were to estimate the frequency of Wilms tumor in these kidneys, the standard risk of 1 in 10,000 infants might be said to be increased to 1 in 2,000. Review of the NWTS

Table 12.1 Association of nephrogenic rests with Wilms tumor and associated syndromes

Population	PLNR (%)	ILNR (%)
Unilateral Wilms tumor	25	15
Bilateral Wilms tumor (synchronous)	74–79	34–41
Bilateral Wilms tumor (metachronous)	42	63–75
Beckwith-Wiedemann/hemihypertrophy and Wilms tumor	70–77	47–57
Aniridia and Wilms tumor	12–20	84–100
Denys-Drash and Wilms tumor	11	78

Adapted from Beckwith [11]
PLNR perilobar nephrogenic rests, *ILNR* intralobar nephrogenic rests

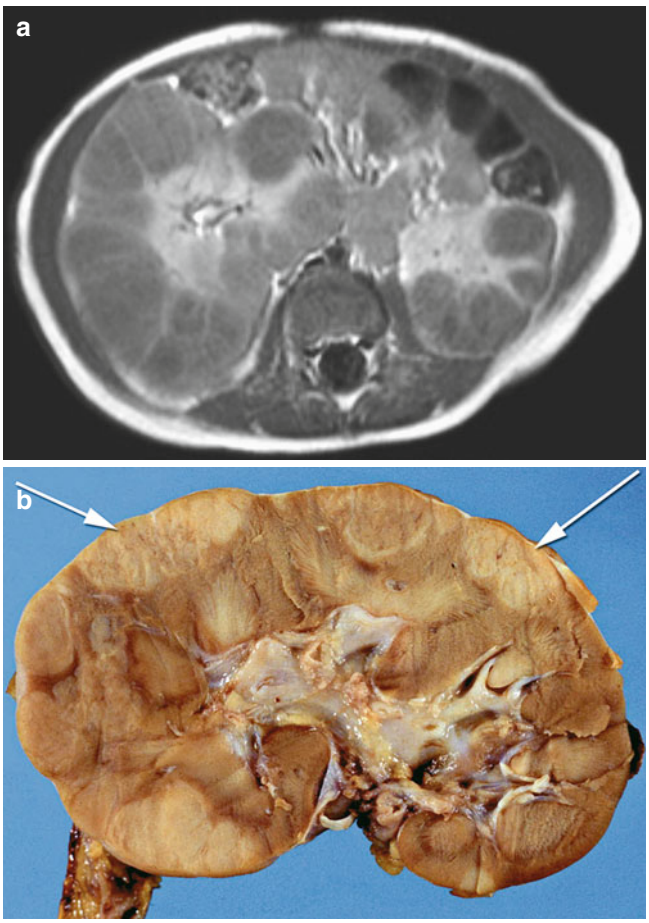

Fig. 12.4 (**a**) MRI of a 15 month old male presenting with palpable bilateral flank masses revealed diffuse subcapsular lesions without necrosis most consistent with diffuse perilobar nephroblastomatosis. (**b**) Kidney removed from a similar child demonstrates diffuse lesions (*arrows*) in the perilobar region which histologically were nephrogenic rests

pathology files, however, identified only three cases of dysplastic kidneys in over 7,000 children with Wilms tumor over a 26 year interval, and only one case in more than 1,500 referral cases sent to Dr. Beckwith from around the world. Although it is impossible to estimate the number of children at risk from Wilms tumors in remaining dysplastic kidneys, it must be concluded that the risk of development of Wilms tumor in kidneys with multicystic dysplasia or congenital obstruction must be extremely low and does not justify nephrectomy to avoid the development of Wilms tumors.

Pathology of Renal Tumors

The collection of large numbers of renal tumor specimens by the cooperative group trials has facilitated the development of accurate pathologic classifications in a much shorter period of time than would have been feasible without these trials. Early reports of Wilms tumors and the initial cooperative group trials included essentially all renal sarcomas under this rubric. With time and experience, however, several subgroups of tumors have now been identified, which are at particularly high risk of recurrence and adverse outcome [8, 14]. In NWTS-1 anaplastic and sarcomatous variants comprised only 11.5 % of the tumors, yet they accounted for 51.9 % of the deaths due to tumor. Unfavorable histology proved to be the most important factor in outcome in NWTS-1 and that finding continues through the current trials. Wilms tumors are currently divided into those with "favorable" histology and those with "unfavorable" histology (Table 12.2). The later group includes tumors with focal or diffuse anaplasia [45, 64]. Clear cell sarcoma of the kidney and malignant rhabdoid tumors of the kidney were initially grouped with the unfavorable histology Wilms tumors, although their adverse outcome was well recognized in NWTS-1 [14]. They are now considered as distinct entities from Wilms tumor based on their pathologic appearance and response to quite different therapies [114, 187].

Table 12.2 Pathologic classification of renal tumors

Histology
Favorable histology Wilms tumor
Unfavorable histology Wilms tumor
Diffuse anaplasia
Focal anaplasia
Clear cell sarcoma
Malignant rhabdoid tumor of the kidney
Renal cell sarcoma
Renal adenocarcinoma
Renal neurogenic tumors
Renal teratoma

The staging system used by the NWTSG/COG is a pretreatment surgical staging system (Table 12.3). It must be carefully distinguished when comparing treatment results with children treated on the SIOP protocols where the staging information is obtained *after* preliminary treatment of

Table 12.3 Staging utilized by Children's Oncology Group

Stage I Tumor limited to kidney, completely resected. The renal capsule is intact. The tumor was not ruptured or biopsied prior to removal. The vessels of the renal sinus are not involved
There is no evidence of tumor at or beyond the margins of resection
NOTES:
For a tumor to qualify for certain therapeutic protocols as Stage I, regional lymph nodes must be examined microscopically
By definition, extrarenal tumors cannot be Stage I
Stage II The tumor is completely resected and there is no evidence of tumor at or beyond the margins of resection. The tumor extends beyond kidney, as is evidenced by any one of the following criteria:
There is regional extension of the tumor (i.e. penetration of the renal capsule, or extensive invasion of the soft tissue of the renal sinus, as discussed below)
Blood vessels within the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, contain tumor
NOTE: Rupture of spillage confined to the flank, including biopsy of the tumor, is no longer included in Stage II and is now included in Stage III
Stage III Residual nonhematogenous tumor present following surgery, and confined to abdomen
Any one of the following may occur:
Lymph nodes within the abdomen or pelvis are involved by tumor. (Lymph node involvement in the thorax, or other extra-abdominal sites is a criterion for Stage IV)
The tumor has penetrated through the peritoneal surface
Tumor implants are found on the peritoneal surface
Gross or microscopic tumor remains postoperatively (e.g., tumor cells are found at the margin of surgical resection on microscopic examination),
The tumor is not completely resectable because of local infiltration into vital structures,
Tumor spillage occurring either before or during surgery,
The tumor is treated with preoperative chemotherapy (with or without a biopsy regardless of type- tru-cut, open or fine needle aspiration) before removal,
Tumor is removed in greater than one piece (e.g. tumor cells are found in a separately excised adrenal gland; a tumor thrombus within the renal vein is removed separately from the nephrectomy specimen). Extension of the primary tumor within vena cava into thoracic vena cava and heart is considered Stage III, rather than
Stage IV even though outside the abdomen
Stage IV Hematogenous metastases (lung, liver, bone, brain, etc.), or lymph node metastases outside the abdomino-pelvic region are present. (The presence of tumor within the adrenal gland is not interpreted as metastasis and staging depends on all other staging parameters present)
Stage V Bilateral renal involvement by tumor is present at diagnosis. An attempt should be made to stage each side according to the above criteria on the basis of the extent of disease

Table 12.4 Staging system utilized by the Societe Internationale d'Oncologie Pediatrique (Based on findings after preoperative therapy)

Stage	Description
Stage I	Tumor limited to the kidney, complete excision
Stage II	Tumor extending outside the kidney, complete excision
	Invasion beyond the capsule, perirenal/perihilar
	Invasion of the regional lymph nodes[a] (Stage IIN1)
	Invasion of extra-renal vessels
	Invasion of ureter
Stage III	Invasion beyond the capsule with incomplete excision
	Preoperative or perioperative biopsy
	Preoperative/perioperative rupture
	Peritoneal metastases
	Invasion of para-aortic lymph nodes[b]
	Incomplete excision
Stage IV	Distant metastases
Stave V	Bilateral renal tumors

[a]Hilar nodes and/or periaortic nodes at the origin of the renal artery

[b]Para-aortic nodes below the renal artery

the tumors (Table 12.4). The intensity of adjuvant treatment in the COG protocols is determined by such factors as regional lymph node involvement and penetration of the renal capsule by tumor which cannot be accurately determined by radiographic studies or by examining tumors after preoperative treatment. The staging criteria have been adjusted during the course of the NWTSG/COG studies as the prognostic significance of criteria were established [48].

SIOP has developed a classification of renal tumors based on the post chemotherapy histology present at resection. This was also revised based on review of outcomes of children compared with the histologic appearance [184]. Tumors are now classified as completely necrotic (low risk tumor), and tumors with diffuse anaplasia or blastemal predominance (high risk tumor) and others (intermediate risk tumors). The prognostic implications of this classification will be assessed on the current study as will the potential for decreasing the extent of therapy of the more favorable groups.

Wilms tumor is characterized as a triphasic embryonal neoplasm with blastemal, stromal and epithelial components [8] (Fig. 12.5). Each of these components can express several patterns of differentiation which define the histologic subgroups of Wilms tumors. One particular subtype, the fetal rhabdomyomatous nephroblastoma, has been associated with poor response to chemotherapy, but a generally favorable prognosis [111]. In contrast, the diffuse blastemal subtype is associated with presentation at an advanced stage, but also with rapid response to chemotherapy. The anaplastic tumors are characterized by large, pleomorphic and hyperchromatic nuclei with abnormal multipolar mitotic figures (Fig. 12.6a, b). Anaplasia can occur in the epithelial, stromal,

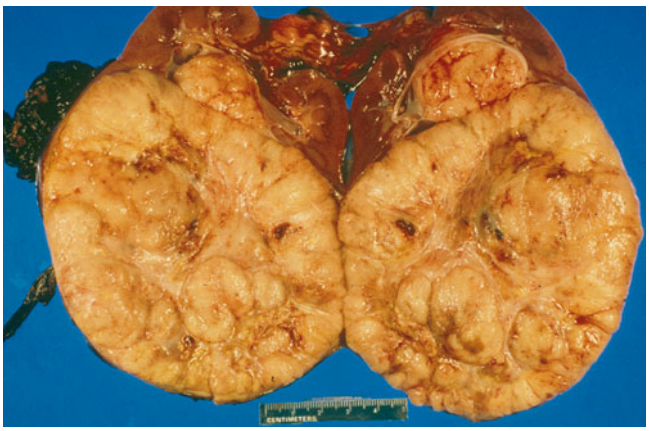

Fig. 12.5 Kidney with favorable histology Wilms tumor reveals lesion arising from the renal parenchyma with normal renal tissue extending over the surface of the tumor. This finding radiographically helps establish the origin of the tumor from within the kidney as compared with neuroblastoma which can indent the renal tissue, but is rarely surrounded by it

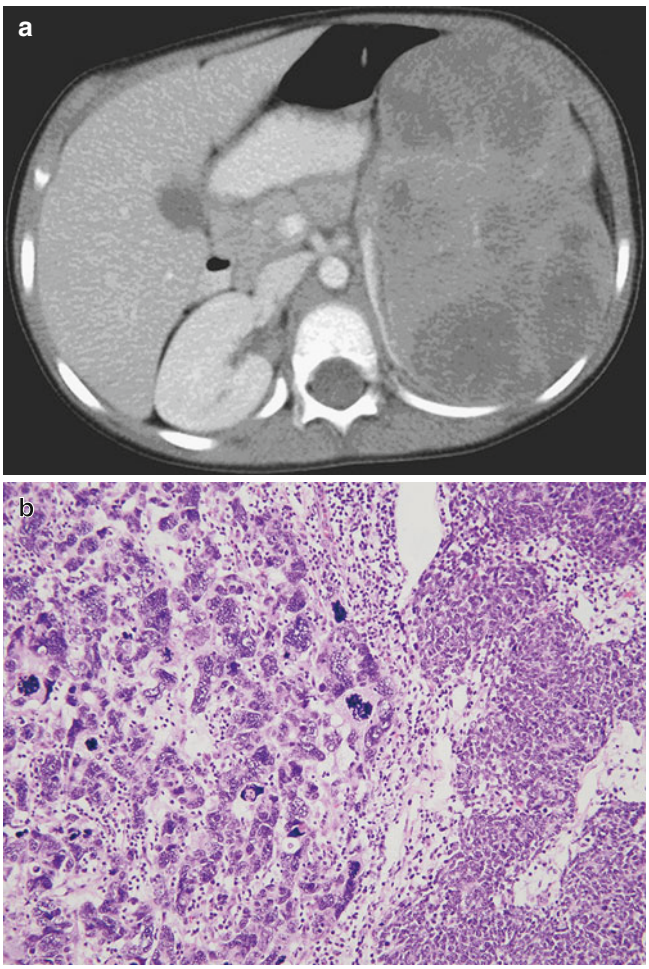

Fig. 12.6 (**a**) CT scan of a 2.5 year old girl who presented with a large asymptomatic left abdominal mass. Child underwent primary resection which revealed a stage II tumor. (**b**) Histology of the tumor demonstrated areas of anaplasia on the left with remarkable nuclear atypia adjacent to areas of bland favorable histology tumor on the right

or blastemal populations or any combination of these three. Anaplasia occurs primarily in children over 2 years of age. In NWTS-1 66.7 % of the patients with anaplasia relapsed and 58.3 % succumbed to their tumor [14]. Even in this early report, the distinct implications of the "diffuse" versus the "focal" pattern were appreciated with a higher frequency of relapse and death in the "diffuse" subgroup. This was confirmed in review of the NWTS-2 and NWTS-3 data. While children with stage I anaplastic tumors generally did well, children with stage II to IV tumors did poorly. The severity of dysplasia was not a predictive factor. However, anaplasia in extrarenal tumor sites and a predominantly blastemal tumor pattern were both adverse prognostic factors [195]. The definitions of diffuse and focal anaplasia are now well established [49] (Fig. 12.7a, b).

Approximately 1 % of children presenting with a unilateral tumor will develop contralateral disease. Fifty-eight of 4,669 children registered in the first four NWTSG studies developed metachronous disease [33]. Analysis of this cohort by a matched case control study demonstrated that the children with nephrogenic rests had a significantly increased risk of metachronous disease, particularly those with PLNRs. This finding was especially true for young children where a Wilms tumor occurred in 20 of 206 children under 12 months old in comparison to zero of 304 children over 12 months old. These young infants under 12 months of age with Wilms tumor who also have nephrogenic rests require several years of regular surveillance for the development of contralateral disease. This increased risk for metachronous tumors in children with Wilms tumor and nephrogenic rests has been confirmed by others [16].

Clear cell sarcoma of the kidney (CCSK) is a highly malignant tumor with an unusual proclivity to produce bony metastasis. It generally presents as a large unifocal and unilateral tumor with homogeneous mucoid, tan or gray-tan cut surface, but may have foci of necrosis or prominent cyst formation [4, 8] (Fig. 12.8a, b). CCSK invades surrounding renal parenchyma rather than compressing the margin into a pseudocapsule as occurs with a Wilms tumor. Its classic appearance is that of a deceptively bland tumor with uniform oval nuclei with a delicate chromatin pattern and a prominent nuclear membrane and sparse poorly stained vacuolated "water-clear" cytoplasm with indistinct cell membranes. While the cells often appear in cords or nests divided by an arborizing network of vessels and supporting spindle cell septa, nine major histologic patterns have been identified [5]. The cell of origin of CCSK is not known. In addition to osseous metastasis, clear cell sarcoma also has a significant incidence of brain metastasis. Late recurrence is seen with this tumor with 30 % of the relapses occurring greater than 2 years after diagnosis [99]. For this reason, clinical trials must consider results after an adequate interval of follow-up.

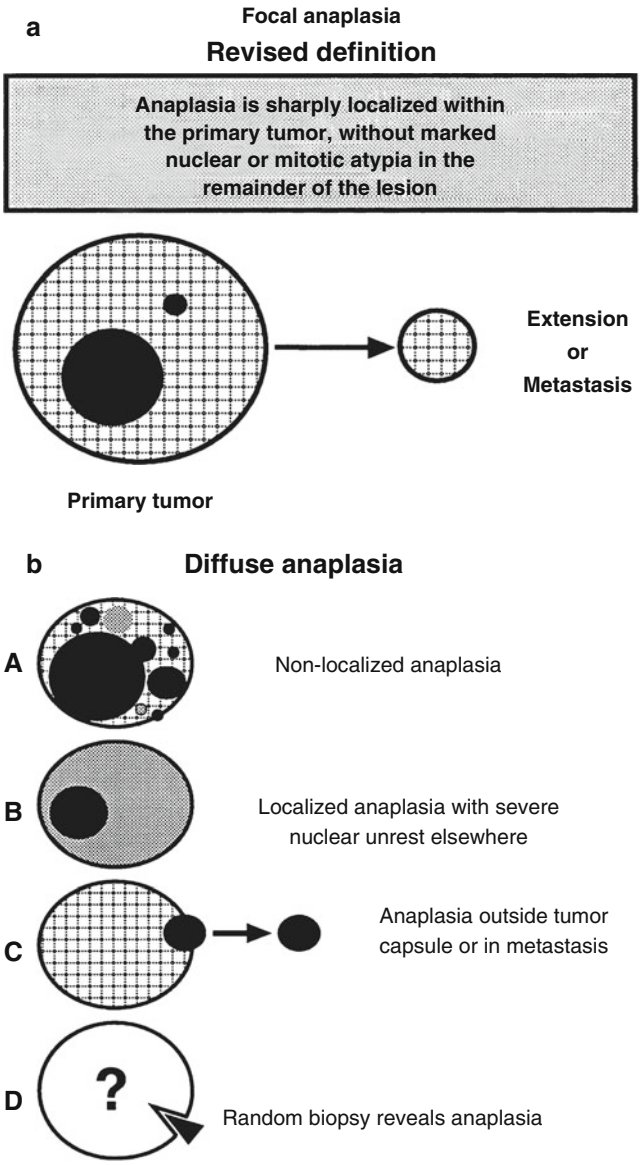

Fig. 12.7 (**a**) Schematic diagrams of the current definitions of focal and (**b**) the four criteria for diffuse anaplasia are shown (Reprinted from Faria et al. [49], with permission from Lippincott Williams & Wilkins)

Outcomes for NWTS studies 1–5 and the revised criteria for stage 1 clear cell sarcoma (lymph nodes must be sampled and negative, entire tumor resected without violation) have recently been reported. Multimodality therapy was utilized for all stages with various chemotherapy regimens. Outcomes for the revised stage 1 patients were excellent irrespective of irradiation dose or chemotherapy regimen. The COG will now prospectively evaluate outcomes for children treated with primary surgery and regimen I (vincristine, doxorubicin, cyclophosphamide and etoposide) alone without RT. Only select stage 1 CCSK patients who have adequate surgical staging with lymph node sampling and central review will be eligible for omission of RT [95].

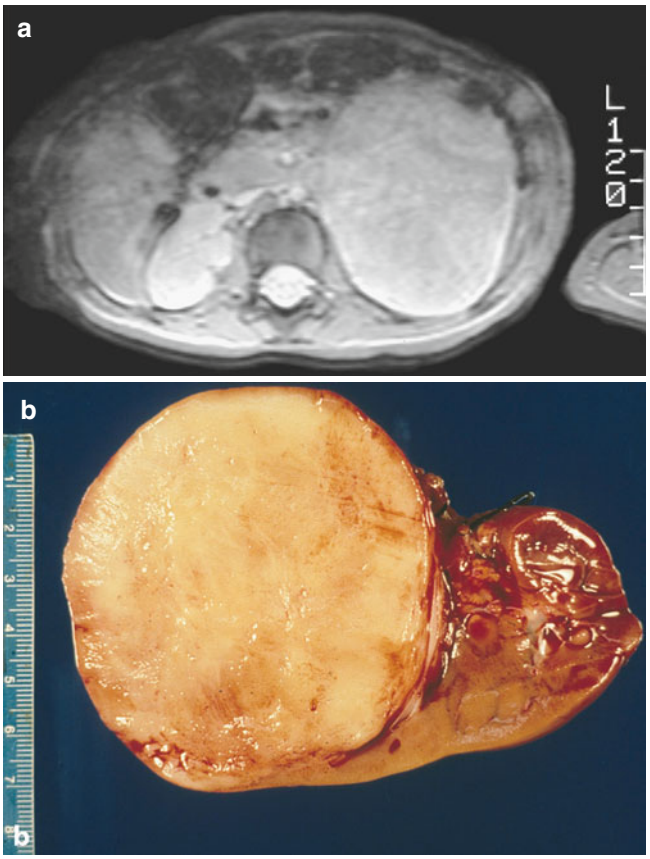

Fig. 12.8 (**a**) MRI scan of a 21 month old female who presented with a palpable left flank mass. (**b**) Cut surface of the tumor reveals homogeneous texture of the tumor consistent with clear cell sarcoma of the kidney

Malignant rhabdoid tumors of the kidney occur in young infants with a median age of 11 months and 85 % of the cases occur within the first 2 years of life [187]. A characteristic involvement of the perihilar renal parenchyma is seen. Rhabdoid tumors are characterized histologically by monomorphous, discohesive, rounded to polygonal cells with acidophilic cytoplasm and eccentric nuclei containing prominent large "owl eye" nucleoli reminiscent of skeletal muscle, but lacking its cytoplasmic striations, ultrastructural features, and immunochemical markers [8]. A large PAS positive hyaline, cytoplasmic inclusion occurs in a variable population of tumor cells and is a hallmark of this tumor [78]. Ultrastructural examination reveals parallel cytoplasmic filamentous inclusions packed in concentric whorled arrays, a distinctive feature of this tumor which suggests a neuroectodermal origin. The tumor tends to infiltrate surrounding renal parenchyma rather than compress it. Rhabdoid tumors are notable for the occurrence of second primary neuroglial tumors in the midline of the brain resembling medulloblastoma [24]. A consistent deletion of 22q11-12 was described in both renal and extrarenal rhabdoid tumors [129, 158]. These deletions have now been demonstrated to delineate an area of overlap at the site of the *hSNF5/INI1* gene and tumors have bi-allelic alternations or deletions of this gene [18, 182].

The occurrence of primitive neuroectodermal tumor (PNET) of the kidney is well documented [152]. It is clearly distinct from Wilms tumor and the other variants previously discussed, and demonstrates spread to lymph nodes, lung, bone, liver and bone marrow as is seen in PNET at other anatomic locations [127].

A single institution series of eight patients over 15 years with primary renal neuroblastoma has recently been reported. The tumors were characterized by age 17 months, large size, hypertension, lack of MYCN amplification and lack of bone marrow involvement. The authors emphasize the incidence may be higher then previously thought and early recognition is important as prognosis and management is very different from Wilms tumor [46].

Clinical Presentation

The classic presentation of Wilms tumor is the identification of an asymptomatic flank mass in an otherwise healthy toddler. It is often noted during a bath or by the pediatrician at a routine visit and the mass may be considerable in size. This is in marked contrast with neuroblastoma which is seen in the same age group, but frequently presents with pain, often from osseous metastasis. Wilms tumor may also be associated with hematuria, but with a much lower frequency than is seen with renal cell carcinoma. Rarer presentations are with hypertension or fever. Occasionally a child may suffer abdominal trauma and present with pain and an abdominal mass out of proportion to that expected based on the severity of the injury. Radiographic examination will reveal a mass which can not be attributed to the trauma alone.

Treatment

All children treated on protocols of the NWTSG/COG, UKCCSG, and SIOP received adjuvant chemotherapy for Wilms tumor based on the early work of Sidney Farber which demonstrated the efficacy of this approach. Optimal chemotherapy regimens have been established by a series of well-designed randomized studies primarily performed by the NWTSG/COG in the United States and Canada and SIOP in Europe. Only in the last decade has a trial been performed in which adjuvant therapy was not used in a small proportion of children with extremely low risk tumors. Surgery continues to play a critical role in the treatment of Wilms tumor despite advances in chemotherapy. Accurate staging and safe and complete resection of the tumor are key elements in achieving cure. Local control is rarely achieved by chemotherapy and radiotherapy alone.

Chemotherapy

Wilms tumor was the first malignant pediatric solid tumor with a demonstrated response to dactinomycin [47]. Many additional effective agents have been subsequently identified: vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide.

Children with stage I tumors were treated on the third NWTSG protocol (NWTS-3) with an 11-week regimen of vincristine and dactinomycin without abdominal radiation based on the results of the initial two studies. The 4-year relapse-free survival (RFS) and overall survival (OS) were 89.0 and 95.6 % respectively [38]. The other three stages were treated on a regimen which involved randomization of two or four arms (Table 12.5). This study supported the addition of doxorubicin to the treatment of children with stage III tumors, but did not demonstrate any benefit to the addition of doxorubicin or radiotherapy for children with stage II tumors or benefit from the addition of cyclophosphamide to the treatment of children with stage IV tumors.

NWTS-4 built upon the lessons learned from the prior studies and addressed the issue of whether dose intensification could be safely utilized to decrease the number of visits for chemotherapy and yet maintain the favorable results previously achieved. Dactinomycin and doxorubicin were administered in single moderately high doses compared with the traditional divided dose regimens for each drug. This study also evaluated the use of two lengths of duration for the administration of chemotherapy: a short course (18–26 weeks depending on the regimen and stage) versus a long course (54–66 weeks). The findings of this study were that the pulse-intensive regimens actually produced less hematologic toxicity than the standard regimens allowing greater dose intensity with comparable outcomes [61, 64]. The second randomization demonstrated no benefit in any of the stages to the long interval of therapy over the short interval [60]. Survival results for patients with favorable histology Wilms tumor from NWTS-4 are shown in Fig. 12.9 [27, 61, 84].

Stage I favorable histology tumors (FH) with a specimen weight less than 550 g in children younger than 24 months (very low risk Wilms tumors-VLRWT) were treated on NWTS-5 by resection alone. This arm of the study was closed early when the rate of relapse exceeded the stringent criteria of the protocol. These criteria were established on an expected salvage rate of 50 % for children who relapsed based on prior experience. The goal of the study was to achieve at least a 95 % overall survival rate for this cohort of children. After this arm of the study was closed, children were subsequently treated with the standard therapy of actinomycin D and vincristine (EE4A). A long-term analysis of this cohort of children revealed a much higher than anticipated salvage rate for the chemotherapy naïve patients who relapsed. While the EFS for the children treated with surgery alone was lower (84 %) than for the children treated with chemotherapy (97 %), the dOS was not different 98 % versus 99 % respectively [80].

A component of the current COG study of renal tumors is again evaluating therapy for this cohort of children with surgery alone. It is hoped that it will confirm these results and avoid the use of adjuvant chemotherapy and its potential toxicity, primarily sinusoidal obstruction syndrome, in this young group of children. To be eligible for this study, infants must have lymph nodes sampled to confirm their stage I status. Genetic analyses of subsets of the very low risk tumors have demonstrated distinctive gene expression, histologic and clinical features [132]. This study used global gene expression analysis with immunohistochemistry and tissue

Table 12.5 Randomization for favorable histology Wilms tumors on NWTS-3

	Treatment	Results	
Stage	4-year DFS	4-year OS	
II	Vcr, Dac	87.4 %	91.1 %
	Vcr, Dac + XRT (20 Gy abd)	NS	NS
	Vcr, Dac, Dox	NS	NS
	Vcr, Dac, Dox + XRT (20 Gy abd)	NS	NS
III	Vcr, Dac + XRT (10 Gy abd)	Improved survival with addition of doxorubicin	
	Vcr, Dac + XRT (20 Gy abd)		
	Vcr, Dac, Dox + XRT (10 Gy abd)	82.0 %	90.9 %
	Vcr, Dac, Dox + XRT (20 Gy abd)	No difference in local recurrence between 10 and 20 Gy	
VI	Vcr, Dac, Dox	79.0 %	80.9 %
	Vcr, Dac, Dox, Cyclo	NS improvement from the addition of cyclophosphamide	
	All abd XRT 20 Gy &		
	Pulmonary XRT 12 Gy		

Data from D'Angio et al. [38]

Vcr vincristine, *Dac* dactinomycin, *XRT* radiotherapy, *abd* abdomen, *Dox* doxorubicin, *Cyclo* cyclophosphamide, *NS* not statistically significant

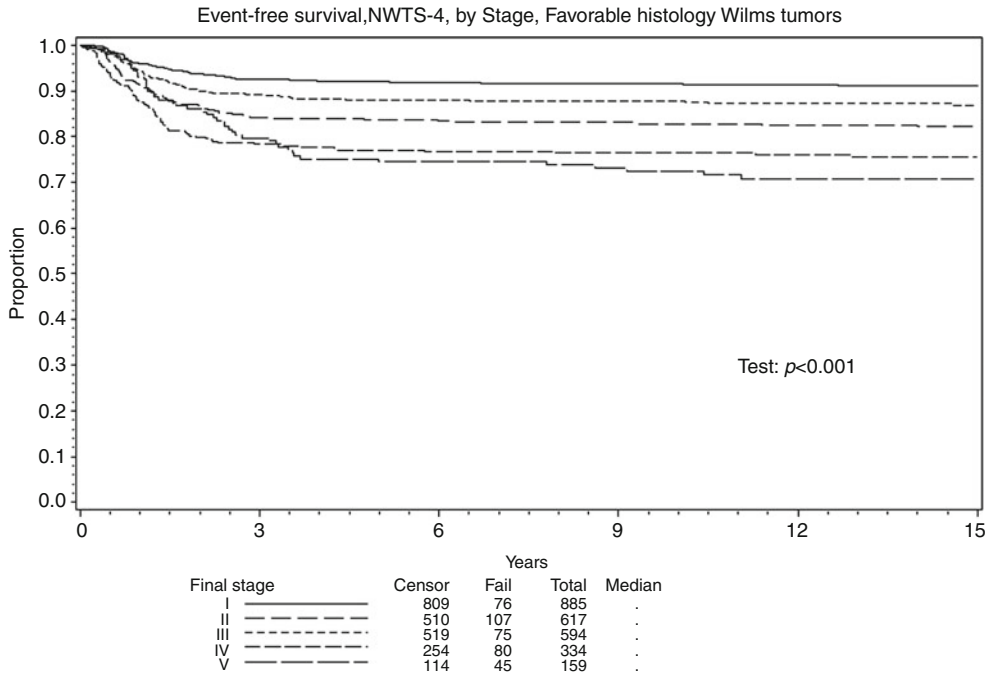

Fig. 12.9 Kaplan-Meier estimates of event-free survival for favorable histology (FH) Wilms tumor patients by Stage

microarray from tumors of children treated in the NWTS-5 study. Two subsets of children comprising 56 % of the very low risk Wilms tumors that have pathologic and molecular differences and apparent risk of relapse. One cluster included nine tumors with tubular differentiated histology, paucity of nephrogenic rests, and lack of LOH for 1p, 16q, and 11p, absence of relapse and a unique gene expression profile consistent with arrest following mesenchymal to epithelial transition. The second cluster included 13 tumors with mixed histology, intralobar rests, and decreased expression of *WT1*; three of six relapses occurred in this cluster. Dr. Perlman and colleagues subsequently demonstrated in 2011 that *WT1* mutation and 11p15 loss of heterozygosity were associated with relapse in patients with very low risk Wilms tumors who do not receive chemotherapy [131].[2] These exciting translational findings may provide meaningful biomarkers to further identify appropriate patients for reduced chemotherapy. Tumors from the VLRWT cohort show an increased frequency of the *WT1* mutation and 11p15 imprinting patterns than reported in Wilms tumors of all ages. This data, furthermore, provides a fertile area of investigation for understanding the cellular mechanisms of metastasis [80, 131, 169].

A recent analysis of patients with favorable histology stage II and III Wilms tumors treated on NWTS-3 and 4 assessed the efficacy of the addition of doxorubicin [27]. While no benefit was seen in the Stage II patients, an increase in the 8-year EFS and OS of randomized patients was seen for those with Stage III disease who received doxorubicin, actinomycin D, and vincristine (84 and 89 %) compared with those who received actinomycin D and vincristine alone (74 and 83 %). When a large group of nonrandomized patients were added to the analysis, the beneficial effect on OS was not seen. This addition of nonrandomized patients unfortunately added some question of bias.

The goal of NWTS-5 was to evaluate preliminary findings from pilot studies that loss of heterozygosity (LOH) for chromosomes 1p and 16q were associated with an adverse prognosis. To most efficiently address this question, it was the first study from NWTSG which did not involve randomization of treatment. This study demonstrated that LOH at either site in children with favorable histology stage I and II was predictive of decreased EFS and in children with stage III and IV disease the presence of LOH at both sites was predictive [73] (Fig. 12.10a, b). A subsequent analysis has suggested that expression of telomerase RNA may also be an adverse prognostic factor for favorable histology Wilms tumor, but confirmatory studies will be required [45].

Treatment of children with anaplastic tumors with standard therapy has resulted in a high rate of failure. Hence, in sequential studies therapy has been intensified. Review of the NWTS-3 and four studies demonstrated that children with focal anaplasia have an excellent outcome when treated with vincristine, doxorubicin, and dactinomycin [57]. The addition of cyclophosphamide to this regimen improved the 4-year relapse-free survival in children with diffuse anaplasia with stages II to IV disease from 27.2 to 54.8 %. Subsequent studies in NWTS-5 have further intensified therapy with the use of doxorubicin, cyclophosphamide, vincristine, and etoposide.,

[2]Pearlman et al. [131].

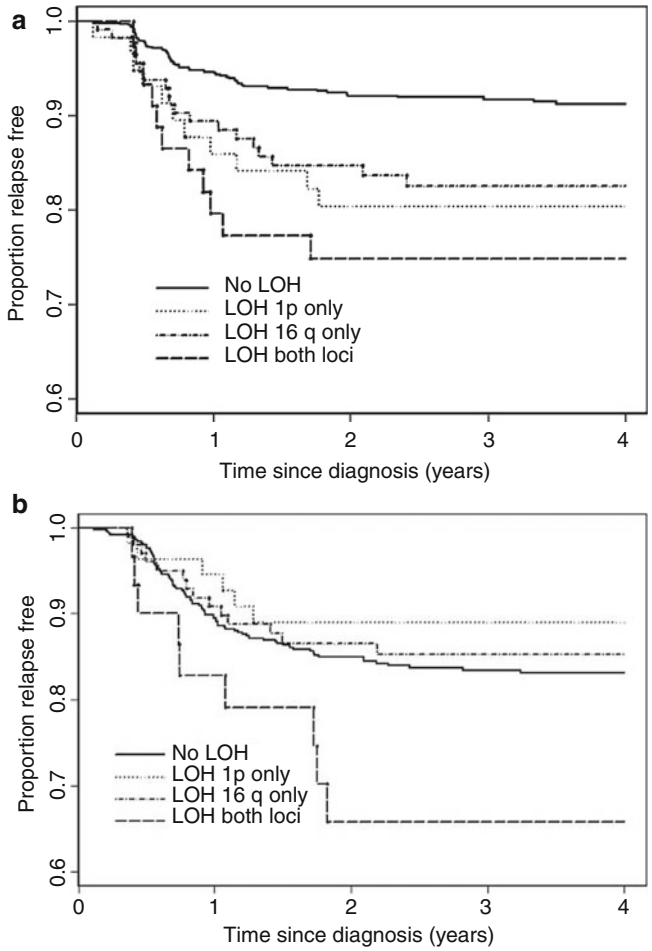

Fig. 12.10 (**a**) Relapse free survival by joint loss of heterozygosity at chromosomes 1p and 16q for stage I–II favorable histology Wilms tumor patients from NWTS-5. (**b**) Relapse free survival by joint loss of heterozygosity at chromosomes 1p and 16q for stage III–IV favorable histology Wilms tumor patients from NWTS-5 (Reproduced by permission of the American Society of Clinical Oncology)

The 4 years EFS and OS of stage I patients were 69.5 and 82.6 % respectively compared with the same survivals for stage I favorable histology of 92.4 and 98.3 % [45]. The EFS progressively declined for increasing stage from 82.6 % for stage II, 64.7 % for stage III and only 33.3 % for stage IV. Clearly even with this intensification of therapy patients with anaplasia do not fare well.

Metastatic pulmonary disease remains an adverse prognostic factor. Recent studies have addressed the management of patients with tumors that extend beyond the kidney by extension or metastasis. Grundy and co-authors (Grundy et al., *Pediatric Blood Cancer* March 15, 2012 epub, personal communication) analyzed the outcome of patients from NWTS-4 and 5 with metastatic lung lesions. Earlier NWTS studies used plain chest radiographs (CXR) to guide treatment. The advent of CT scanning led to detection of smaller lesions and posed the question of how best to treat patients who had lesions detected only by CT. Review of the 231 patients with lung lesions detected by CXR and 186 by CT only was performed. Of the CT only patients, 37 received 2 drugs (vincristine/actinomycin D) and the remainder received 3 drugs (vincristine/actinomycin D/doxorubicin) as was suggested by the protocol for patients with pulmonary metastases shown by CXR. One hundred and one patients did not receive lung irradiation. Five-year EFS was significantly greater for CT only patients receiving 3 drugs with or without radiation compared to 2 drugs (80 % vs. 56 %; $p<0.004$). There was, however, no difference in 5-year OS between the 2 and 3 drug subsets 87 % vs 86 %; $p=0.91$ There was also no significant difference in EFS (82 % vs 72 %, $p=0.13$) or OS (91 % vs. 83 %; $p=0.46$) for CT only patients whether they received lung irradiation or not. These results suggest that CT only lung lesion patients have improved EFS but not OS from the addition of doxorubicin, but receive no obvious benefit from pulmonary radiation. The results of this retrospective study suggest that CT-only lung lesions do have clinical significance in patients with favorable histology Wilms tumour; CT-only lung lesions should not be disregarded in patients who would otherwise receive 2-drug therapy, because the addition of doxorubicin to chemotherapy may reduce the risk for recurrent disease. The current COG study is designed to further address these issues in children with pulmonary metastasis. Specifically, one of the primary objectives of the current COG protocol is to demonstrate that patients with Stage IV FHWT and pulmonary metastases only, who have complete resolution of the pulmonary lesions after 6 weeks of DD-4A chemotherapy (vincristine, dactinomycin, and doxorubicin), so called Rapid Complete Responders (RCR) will have at least an 85 % 4-year EFS after therapy with additional DD-4A and without whole lung radiation. Those who do not have resolution of pulmonary disease by week 6, Slow Incomplete Responders (SIR), will have a 4 year EFS of 85 % with the addition of cyclophosphamide and etoposide to a modified Regimen DD-4A (Regimen M). The rationale for this study came in part from the SIOP 9 study where preoperative chemotherapy for Stage IV FHWT demonstrated a 5 year relapse free survival of 62.5 %. Seventy percent of patients were spared whole lung radiation based on complete resolution of pulmonary metastases after 6 weeks of prenephrectomy chemotherapy [188].

Doxorubicin was found to be particularly effective in the treatment of clear cell sarcoma of the kidney [5, 59]. However, the results have remained below those of standard histology Wilms tumors. No benefit was seen to pulse intensive administration of the agents and there was no difference in survival at 5 and 8 years between patients treated for 6 or 15 months [162]. Treatment on NWTS-5 consisted of vincristine, doxorubicin, cyclophosphamide alternating with cyclophosphamide and etoposide for 24 weeks with local

radiotherapy. An overall 5-year EFS and survival of 79 and 89 % were achieved, but survival results remained very stage dependent: stage I – 100 %, II – 87 %, III – 74 % and IV – 36 % [161]. The most frequent site of relapse was the brain in 11 of 21 cases.

Relapse occurs in about 15 % of children with WT, but if it occurs, it is a very adverse predictor of outcome with long-term survival less than 30 % [74, 133].[3, 4] Treatment of Wilms tumor relapsing after initial treatment with vincristine and actinomycin D was reported by Green and co-authors from the NWTS-5 study [66].[5] In this study, a uniform treatment for patients with relapse was utilized. Seventy-two patients relapsed after immediate nephrectomy, initial chemotherapy with vincristine (VCR) and actinomycin D and no radiation. Relapse treatment included surgical excision when feasible, radiation therapy and alternating courses of VCR, doxorubicin and cyclophosphamide and etoposide and cyclophosphamide. The lung was the solitary site of relapse in 31 patients. EFS 4 years after relapse were 71.4 % and OS 81.8 % for all patients and 67.8 and 81 % for those who relapsed only to their lungs. The most frequent toxicity was hematologic. This data demonstrated that a significant proportion of children with Wilms tumor who relapse after initial treatment with VCR and actinomycin D can be successfully salvaged. A corollary study was published by Malogolowkin and associates in 2008 reporting the treatment of Wilms tumor relapsing after initial treatment with vincristine, actinomycin D and doxorubicin (VAD)and radiation therapy (DD-4A) in NWTS-5 [113].[6] Alternating cycles of cyclophosphamide/etoposide and carboplatin/etoposide were used in 60 patients; the lung was the only site of relapse for 33 and other sites included the operative bed (7), the abdomen (6) and the liver (6). Four year EFS and OS were 42.3 and 48 % for all patients and 48.9 and 52.8 % for patients with only pulmonary relapse. Thrombocytopenia was the most prevalent toxicity. Therefore, approximately half of the children with unilateral WT who relapse after initial VAD and radiation can be successfully treated [66, 113].

Rhabdoid tumors have remained the most resistant to cure of all pediatric renal tumors. Analysis of 142 children treated on NWTS-1-5 showed an overall survival of 23.2 % at 4 years [177]. Survival was stage dependent and children with stage I/II disease had a 41.8 % 4-year survival while children with stage III, IV or V tumors had a 15.9 % 4-year survival. Survival was also clearly related to the age at presentation with the 4-year survival worst for those 0–5 months of age at diagnosis (8.8 %) and best for those over 2 years of age (41.1 %). NWTS-5 used an intensive therapy with carboplatin, etoposide and cyclophosphamide. Unfortunately, no improvement in survival occurred with the series of treatments from NWTS-1 to 5 and no survival benefit was demonstrated with the use of doxorubicin.

Preoperative Chemotherapy

SIOP has promoted the use of preoperative treatment of children with Wilms tumor with radiotherapy or chemotherapy since the early 1970s. Histologic confirmation of the diagnosis before therapy is not routinely recommended by SIOP. This approach has several risks. First, is the potential for administration of chemotherapy for benign disease. Second, modification of tumor histology by the chemotherapy may occur. Third, staging information may be lost. Fourth, a malignant rhabdoid tumor of the kidney or clear cell sarcoma may be present which will not respond to standard therapies and may in fact progress. Treatment without an initial diagnosis is difficult to sustain when NWTSG/COG and SIOP studies have demonstrated a 7.6–9.9 % rate of benign or altered malignant diagnosis in children with a prenephrectomy diagnosis of Wilms tumor [40, 193]. The United Kingdom Children's Cancer Study Group in a recent report identified 12 % of cases which were clinically and radiographically consistent with Wilms tumor, but had other diagnosis established by biopsy [185]. The histologic diagnosis following preoperative treatment in a group of children followed by NWTSG did not appear distorted by treatment, but it is less certain that staging is not altered [194].

The major driving force for the use of preoperative therapy by SIOP was the high rate of operative tumor rupture which occurred in their early series in which patients did not receive preliminary treatment. The rupture rate decreased from 33 % (20 of 60) to 4 % (3 of 72) with preoperative abdominal irradiation (20 Gy) in the first randomized SIOP study of renal tumors (SIOP 1) begun in 1971 [107]. It must be noted, however, that 33 % is an extremely high frequency of rupture. Survival was not affected by the decrease in operative rupture and the incidence of local recurrence was not reported. In NWTS-1 and -2, operative rupture occurred in 22 % and 12 % of children, respectively [39, 40]. In a subsequent SIOP randomized study of Wilms tumors begun in 1977 (SIOP 5), the rate of rupture was essentially the same for children receiving abdominal irradiation (20 Gy) and dactinomycin (9 %, 7 of 76) or a combination of vincristine and dactinomycin (6 %, 5 of 88) [29, 108]. Radiotherapy after resection was based on the stage of the tumors, with stage I receiving no postoperative radiation and stage II and III patients receiving 15 Gy in the group treated initially with radiotherapy and 30 Gy in those treated initially with chemotherapy. In SIOP 6, begun in 1980, all patients received initial preoperative chemotherapy (vincristine and dactinomycin). Radiotherapy was administered after resection to those children with stage IIN1 and stage III disease. Children

[3] Grundy et al. [74].

[4] Pinkerton et al. [134].

[5] Green et al. [66].

[6] Malogolowkin et al. [113].

with stage IIN0 (lymph node negative) were randomized to receive either 20 Gy of radiotherapy versus no radiation to the tumor bed. All children received vincristine and dactinomycin for 38 weeks. After pretreatment 52 % of cases were stage I and there was a low frequency of rupture (7 %). The radiotherapy randomization was halted after 108 children were randomized, 58 to radiotherapy and chemotherapy and 50 to chemotherapy alone. Six local recurrences occurred in the 50 children who did not receive radiotherapy versus no recurrences in the group which did. These results suggested that prenephrectomy treatment altered the pathologic findings which would have led to a diagnosis of stage IIN1 or stage III disease (i.e. lymph node involvement or capsular penetration) and to the standard administration of local irradiation. Extended follow-up studies of these children showed ultimately no statistical difference in survival, as those with relapse had more treatment alternatives [92, 179]. The SIOP-6 protocol also extended chemotherapy to infants over 6 months of age [34]. The overall favorable outcome was not improved, and an unacceptable toxicity occurred in the young infants. In the SIOP-9 study, a reduced dose in infants was recommended.

In the SIOP 9 study initiated in 1987 there was a randomization between 4 and 8 weeks of preoperative therapy with actinomycin D and vincristine to determine if the additional 4 weeks of therapy produced a larger proportion of stage I tumors [178]. This study also replaced postoperative radiotherapy in stage II node negative children with administration of an anthracycline, epirubicin. Preoperative treatment consisted of four weekly courses of vincristine and two 3-day courses of dactinomycin each 2 weeks versus 8 weeks of the identical therapy for patients without distant metastasis. No advantage was seen from the extended therapy in terms of staging at resection between the 4-week and 8-week courses: stage I 64 versus 62 %, or of intraoperative tumor rupture: 1 versus 3 % [56]. (Fig. 12.11) Therapy after resection was based on the pathologic findings. Children with stage I disease and favorable or anaplastic histology received vincristine and dactinomycin for 17 weeks. Those with stage II and III tumors with favorable histology received vincristine, dactinomycin and epirubicin for 27 weeks with no abdominal radiotherapy for stage II NO disease or with 15 Gy of abdominal irradiation in cases of stages IIN1 and III disease. This therapy resulted in a 2-year EFS of 84 versus 83 % for the 4 and 8-week therapies and OS of 92 and 87 % respectively. Children with metastatic disease received 6 weeks of therapy including weekly vincristine, three courses of dactinomycin, and two courses of epirubicin on weeks one and six. The tumor size decreased by more than 50 % in 52 % of the cases and during the second 4 weeks of therapy there was another 50 % reduction in 33 % of the cases (Fig. 12.11). Inappropriate preoperative therapy was given to 5.5 % of the cases including 1.6 % who proved to have benign lesions or malignant lesions not expected to respond to the therapy including neuroblastoma, lymphoma, malignant rhabdoid tumors of the kidney and renal carcinomas. In SIOP 9 the surgery related complications were reported to be 8 % [55]. In this treatment regimen patients with *post therapy* stage II disease receive an anthracycline while on the NWTS studies patients with stage II disease receive vincristine and dactinomycin alone. In SIOP 9, an evaluation of children with completely necrotic tumors at the time of resection demonstrated that they had an extremely favorable prognosis [21]. Complete necrosis was seen in 10 % of 599 children enrolled into the study; 37 children with stages I to III disease and 22 with stage IV disease. Disease free survival was 98 % at 5 years for this cohort versus 90 % for the other patients on SIOP 9. The only death

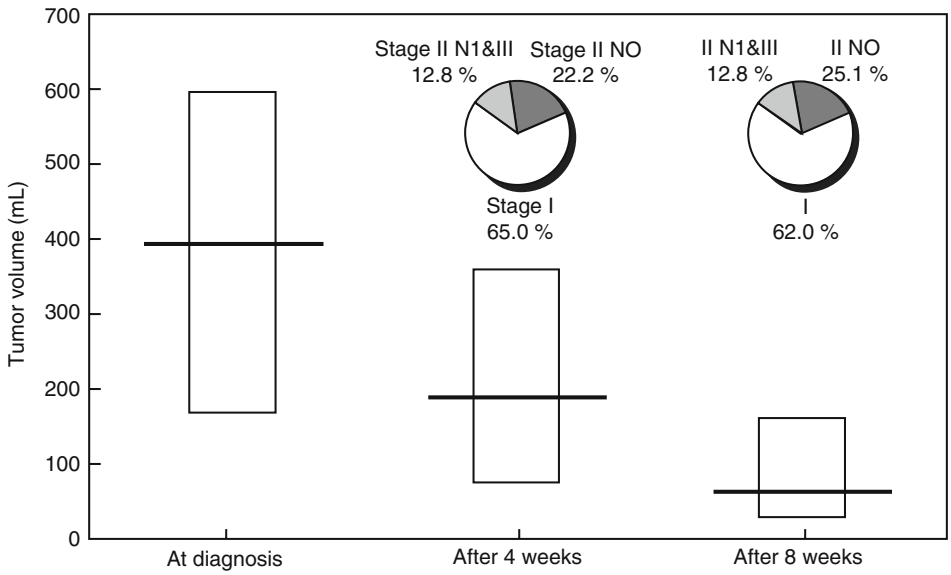

Fig. 12.11 Diagram of the results from the GPOH subgroup of SIOP-9 demonstrates the progressive decrease in the volume of the renal tumors after 4 and 8 weeks of preoperative chemotherapy. The pie charts demonstrate the distribution of tumor stages which reveal an increase in low stage I tumors compared with historical controls (not shown) (Reprinted from Graff et al. [56] with permission from Elsevier.)

in the stage I to III group was a toxic death and survival was 100 % in the stage IV group.

The goal of both NWTSG and SIOP has been to decrease the intensity of therapy and yet achieve the maximum long-term survival. Both groups have decreased the amount of radiotherapy utilized during the course of their studies. Among the children with unilateral nonmetastatic favorable histology Wilms tumors, 24 % of those enrolled in NWTS (275 of 1,160) were given radiation therapy and 18 % of those in SIOP (81 of 447) have received radiotherapy in the most recent studies [65]. SIOP has elected, however, to utilize an anthracycline rather than radiotherapy for their *post chemotherapy* stage IIN0 patients in whom excessive local relapse occurred without additional therapy. This results in around 48 % of patients on SIOP studies with unilateral nonmetastatic, favorable histology patients receiving an anthracycline which is significantly greater than the 24 % of comparable patients on NWTSG regimens.

Complications of Chemotherapy

Significant complications have occurred in some children treated with doxorubicin, particularly cardiomyopathy [68, 115]. The cumulative frequency of congestive heart failure in children treated on NWTS-1 to 4 was 4.4 % at 20 years after diagnosis for those treated initially with doxorubicin, although recent estimates of the 20-year risk of congestive heart failure for children treated on NWTS-3 and 4 is now reported as 1.2 % [27]. The relative risk was increased for females, by cumulative dose of doxorubicin, by use of pulmonary irradiation, and irradiation of the left renal fossa. Subclinical echocardiographic abnormalities have been demonstrated in children who received as little as 45 mg/m^2 of doxorubicin [109]. Only long-term follow-up of children who have received doxorubicin will document what dose, if any, is free of implications.

Second malignant neoplasms are also a concern. NWTSG has reported a 1.6 % incidence of second malignant neoplasms occurring by 15 years after treatment [28]. The incidence correlated with prior treatment of relapsed tumor, the amount of abdominal radiation, and the use of doxorubicin. Acute myelogenous leukemia was seen in patients whose treatment included either doxorubicin or etoposide [167].

While renal failure can be produced by bilateral nephrectomy, it also results from the nephropathy associated with several of the genetic syndromes. A significant incidence of renal failure results from FSGS in children with WAGR syndrome and from diffuse mesangial sclerosis in children with Denys-Drash syndrome. The cumulative incidence of end stage renal failure at 20 years after diagnosis of unilateral Wilms tumor was 74 % for 17 patients with the Denys-Drash syndrome, 36 % for 37 patients with WAGR, 7 % for 125 males with hypospadias or cryptorchidism and 0.6 % for 5,347 patients without any of the other conditions [26] (Fig. 12.12a). In children with bilateral tumors all of these incidences are increased: 50 % for the Denys-Drash syndrome, 90 % for WAGR, 25 % for associated genitourinary abnormalities, and 12 % for those without associated conditions (Fig. 12.12b).

End stage renal disease (ESRD) in patients with Wilms tumor was assessed in a study by Breslow and associates from the NWTSG. The risk of ESRD is exceptionally low for the majority of WT patients. Those with WAGR, DDS or associated GU anomalies should be screened indefinitely to address impaired renal function.

The risk factors for ESRD in non-WT1 related syndromes were recently described by Lange and colleagues. The cumulative incidence of ESRD due to chronic renal failure (CRF) 20 years after WT diagnosis was 0.7 %; for ESRD due to progressive BWT it was 4 % at 3 years post WT diagnosis in synchronous BWT and 19.3 % in metachronous BWT. Metachronous BWT is associated with high rates of

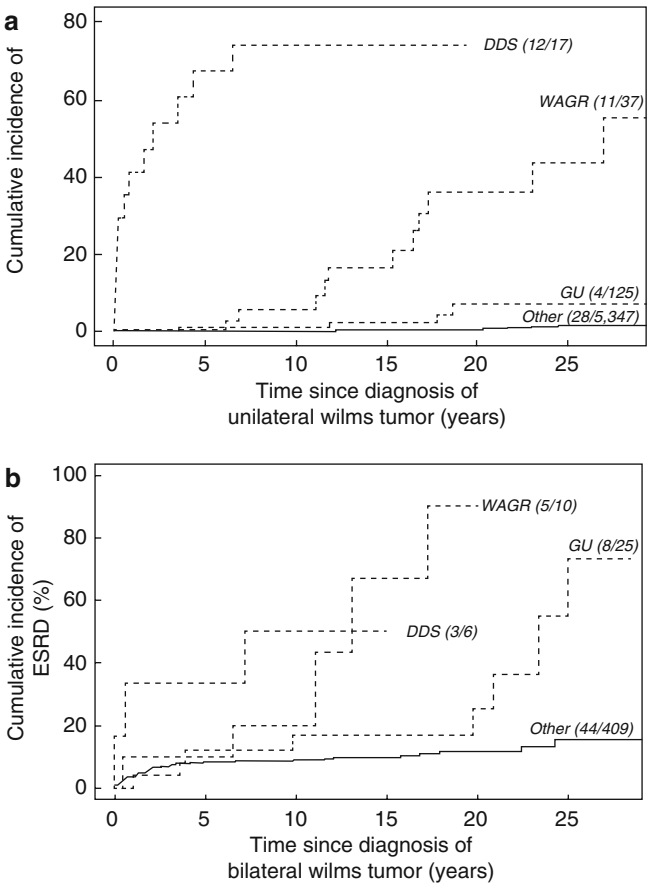

Fig. 12.12 (**a**) Cumulative incidence of end stage renal disease (*ESRD*) in children with unilateral Wilms tumor with Denys-Drash syndrome (*DDS*), WAGR syndrome, associated genitourinary anomalies (*GU*) and other anomalies (*Other*) over time. (**b**) Similar plot of children with bilateral Wilms tumors. In both groups of children a very significant incidence of ESRD is documented (Reprinted from Breslow et al. [26], with permission from the American Urological Association)

ESRD due to surgery for progressive WT. Characteristics associated with WT1 etiology (stromal predominant histology HR 6.4 % 95 % CI p < .001, intralobar nephrogenic rests HR of 5.9 to no rests (95 % CI p = .001 and early onset WT <24 month had a HR of 1.7 relative to appearance at 24–48 months and 2.8 relative to >48 months p = .003 for trend) markedly increased the risk of ESRD due to chronic renal failure despite an overall low risk in non-WT1 syndromic patients. A recent analysis of treatment and outcomes overall for end stage renal disease following Wilms tumor was reported by Grigoriev and co-authors. Time to transplant, graft failure and survival outcomes from 173 children form NWTS were examined. Fifty-five patients who developed ESRD from progressive bilateral WT experienced high early mortality from WT that limited the opportunity for transplant (47 % at 5 years) and survival (44 % at 10 years) in comparison with population controls. The 118 patients who developed ESRD due to other causes (chronic kidney disease) many of whom had WT associated anomalies had transplant (77 % at 5 years) and survival (73 % at 10 years) outcomes no worse than for population controls. Graft failure was similar to controls for both groups. Given the continued high mortality in patients with ESRD and the dramatic improvement in outlook following kidney transplant, the authors suggest a re-evalution of the current guidelines for a 2 year delay in transplant following WT treatment [70, 102].

Late effects are an important element in the treatment of childhood malignancy. Termuhlen and associates recently reported 25 year follow-up of childhood Wilms tumor survivors from the Childhood Cancer Survival Study [175].[7] The cumulative incidence of all versus severe health conditions was 65.4 and 24.2 % at 25 years. Hazard ratios (HR) were 2.0, 95 % CI 1.8–2.3 for grades 1–4 and 4.7, 95 % CI 3.6–6.1 for grades 3 and 4 compared to a sibling group. WT survivors reported more adverse general health status than sibling group prevalence ratio 1.7, 95 % CI 1.2–2.4, but mental health status, socioeconomic status and health care utilization were similar. The cumulative incidence of second malignant neoplasm (SMN) was 3.0 % (95 % CI 1.9–4.0) and mortality was 6.1 % (95 % CI 4.7–7.4 %). This excludes non-melanoma skin cancer. The most common SMN's were soft tissue sarcoma in six, five confirmed breast cancers, one osteogenic sarcoma and one Ewing sarcoma. Radiation exposure increased the likelihood of congestive heart failure (CHF) in patients who received no doxorubicin HR 6.6; 95 % CI, 1.6–28.3 in patients who received <250 mg/m^2 doxorubicin HR 13.0, 95 % CI 1.9–89.7; and in those who received >250 doxorubicin HR 18.3 % 95 % CI 3.8–88.2, SMN (standardized incidence ratio [SIR] 9.0; 95 % CI 3.9–17.7 with and 4.9; 95 % CI 1.8–10.6 without doxorubicin) and death. Long-term survivors of WT treated between 1970 and 1986 are at increased risk of treatment related morbidity and mortality now 25 years from diagnosis. Other complications identified in patients after treatment for Wilms tumor include diffuse interstitial pneumonitis, loss of stature, and difficulties with pregnancy which are primarily related to abdominal and pelvic irradiation [67, 69, 83, 96].

[7] Termuhlen et al. [175].

Surgery

The NWTSG has advocated initial resection of the tumor in all of its protocols. Despite the fact that most Wilms tumors present as a large mass, resection is generally feasible. Wilms tumor, in contrast with neuroblastoma, is much less likely to invade surrounding organs and lymph nodes which complicate the resection. Children undergoing initial nephrectomy in NWTS-3, demonstrated a complication rate of 19.8 % in a group that was very closely followed. [146] The most frequent complication was intestinal obstruction occurring in 6.9 % of the children followed by extensive intraoperative hemorrhage (>50 ml/kg of body weight) occurring in 5.8 % [148]. Injuries to other visceral organs (1 %) and extensive vascular injuries (1.4 %) were much less frequent. Nine deaths were attributed to surgical complications (0.5 %), only one of which was intraoperative. The factors which were associated with an increased risk of surgical complications were advanced-stage local disease, intravascular extension of the tumor, and resection of other organs. "Adherent" organs were often found not to be invaded by the tumor, but rather compressed, distorted or adherent without actual tumor infiltration. Extensive resection involving removal of other organs or procedures which are of a magnitude to be life threatening, should be aborted and a biopsy obtained of the tumor and regional lymph nodes, followed by administration of chemotherapy prior to a second attempt at resection. Following this algorithm, 93 % of 131 children enrolled in NWTS-3 who were initially judged as "unresectable" at surgery or by imaging studies were successfully resected after initial chemotherapy and/or irradiation [150]. Only eight children with tumors that grew or failed to respond did not undergo subsequent nephrectomy.

Complications in the NWTS-4 study have also been assessed [151]. Surgeons were discouraged from performing extensive operations on children in this study involving resection of adjacent organs or massive tumors. Complications occurred in 12.7 % of a random sample of 534 of the 3,335 patients treated on this study. Again, intestinal obstruction was the most frequent complication (5.1 %) followed by extensive hemorrhage (1.9 %), wound infection (1.9 %) and vascular injury (1.5 %). The factors associated with an increased risk of complications were again assessed. Intravascular extension into the inferior vena cava or atrium and nephrectomy performed through a flank or paramedian

incision were both significant factors. Tumor diameter greater or equal to 10 cm was also associated with increased complications. Finally, the risk of complications was increased if the resection was performed by a general surgeon rather than a pediatric surgeon or pediatric urologist. SIOP reported a complication rate of 8 % in a recent study involving 598 patients registered on SIOP-9. These patients were pretreated with vincristine, dactinomycin and epirubicin or doxorubicin prior to nephrectomy [55]. The most frequent events were small bowel obstruction (3.7 %) and tumor rupture (2.8 %). The later is not reported as a complication in the NWTS reviews. Other complications occurred in 2.0 % of patients.

Surgical Details

Radiographic imaging is critical prior to resection of a renal tumor. The most important factors to assess in these studies are the presence of two functioning kidneys, contralateral tumor, and evidence of intravascular extension of the tumor. Intraoperative and not preoperative identification of intravascular extension has been associated with an increased incidence of surgical complications [123]. The organ of origin of the tumor can be determined in most cases with the differential diagnosis generally between neuroblastoma and Wilms tumor. This can generally be determined by the configuration of the kidney and the mass. In neuroblastoma the mass will generally indent the kidney while in Wilms tumor the mass will arise from within the kidney and distort its internal configuration. Often a thin rim of renal parenchyma can be seen extending over the neoplasm in Wilms tumor (Fig. 12.13). Intraabdominal staging has been difficult to assess radiographically unless there is extensive lymph node involvement or intrahepatic metastasis. A radiograph of the chest and computed tomography (CT scan) will determine the presence of pulmonary metastasis. Bone scans and brain scans are routinely performed only if the renal tumor proves to be a clear cell sarcoma or rhabdoid tumor.

Renal tumors must be resected through an adequate subcostal or thoracoabdominal incision. Struggling through an inadequate incision will often result in rupture of the tumor both increasing the stage of the tumor and the risk for intraabdominal recurrence [164]. A flank incision should not be used for resection in pediatric renal tumors because of the limited exposure it provides.

The abdomen should be explored including inspection for hepatic metastasis and intraperitoneal spread. The vena cava, if it is accessible, should also be palpated to assess for intravascular extension of tumor. The contralateral kidney should be palpated for tumor, although it is not currently recommended that the kidney be completely exposed and visualized. Exploration of the contralateral kidney with opening of

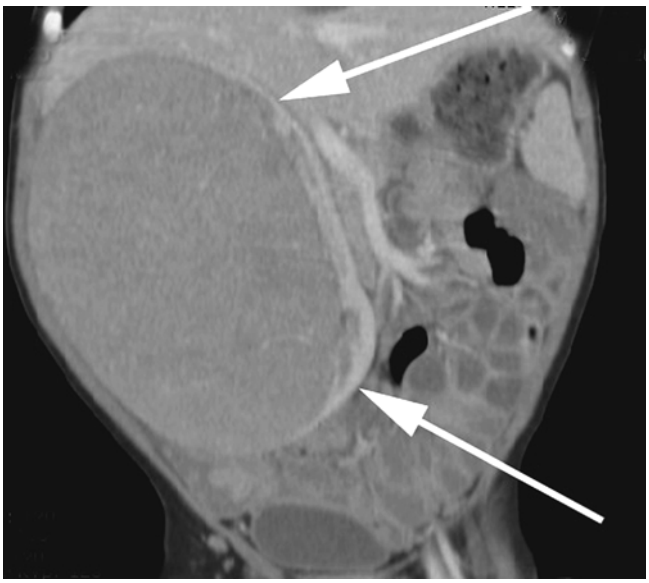

Fig. 12.13 CT scan of a 6 month old infant with Wilms tumor which demonstrates in the coronal reformats the classic finding of intrarenal tumors; a margin of renal parenchyma enveloping the tumor (*arrows*)

Gerota's fascia was recommended by the NWTSG based on the 5 % occurrence of synchronous lesions. In NWTS-2 and 3 contralateral involvement was not detected before exploration by intravenous pyelography (IVP) or CT scan in approximately one-third of the children with bilateral tumors [20]. Review of children with bilateral tumors treated on NWTS-4 identified only nine of 122 children in whom the diagnosis of bilateral disease was missed by the preoperative imaging studies (CT scan, ultrasonography, or MRI) [144]. All but one of these lesions were small: five were less than 1 cm and three were 1–3 cm in diameter. Recent review of this material, however, has suggested that some of the small lesions on the contralateral kidney which were initially thought to be small Wilms tumors would now be more correctly defined as hyperplastic nephrogenic rests [141]. The overall outcome of children with these small lesions was also extremely favorable with no recurrences [26].

The colon is then mobilized off the anterior aspect of the kidney and the renal mass. Although early descriptions of resection recommended initial control of the renal hilum, this is often not feasible with extremely large tumors and must await mobilization of the mass to allow exposure of the hilum [104]. Premature attempts at vascular control, particularly of left sided tumors, may result in ligation of the superior mesenteric artery [149]. Biopsy of the renal mass should not be performed unless the decision is to not proceed with a complete resection. Biopsy will contaminate the peritoneum and increase the stage of the tumor to stage III.

Biopsy of lymph nodes in the renal hilum and along the vena cava or aorta is critical for adequate staging. Even in children with stage IV disease, local staging is critical as it

will determine whether or not abdominal radiotherapy is utilized in most cooperative group protocols. Studies have demonstrated that the surgeon's gross inspection and assessment of lymph nodes does not reliably correspond with the pathologic involvement of tumor with false negative and false positive rates of 31.3 and 18.1 % respectively [126]. An increased incidence of local recurrence occurred in children enrolled in NWTS-4 in whom biopsy of lymph nodes was not performed, particularly stage I cases [164]. This suggested that under treatment of local disease in these children due to inadequate staging resulted in an increased frequency of local relapse. While grossly involved lymph nodes are generally resected, an extensive retroperitoneal lymph node resection has not been demonstrated to improve local control or survival [93].

As the tumor is mobilized, the ureter is divided close to the bladder to avoid creating a "diverticulum" on the bladder which might make the child susceptible to recurrent urinary tract infection. This will also assure that any extension of tumor into the ureter is entirely resected. Gross hematuria in children with Wilms tumor is infrequent, but its occurrence suggests extensive involvement of the renal pelvis with possible extension into the ureter. Ritchey and co-authors reported ureteral extension to occur in approximately 2 % of patients with Wilms tumor from NWTS studies 3, 4 and 5. The diagnosis should be suspected in patients with gross hematuria, hydronephrosis or a nonfunctioning kidney. Cystoscopy with retrograde ureterogram may aid in preoperative diagnosis in these patients. Preoperative diagnosis is important since complete resection of the involved portion of ureter at the time of nephrectomy is essential for local control avoiding residual disease and the need for radiation therapy [143].

If the tumor involves the upper pole, the adrenal gland is generally resected to achieve adequate margins around the tumor and also to obtain periaortic or pericaval lymph node tissue. In children with lower pole lesions, the adrenal gland may be preserved [164].

The factors associated with an increased risk of local recurrence are stage III disease, unfavorable histology (especially diffuse anaplasia), failure to biopsy local lymph nodes and tumor rupture during surgery [164]. The only factors over which the surgeon has control are biopsy of the lymph nodes and rupture of the tumor. Multiple regression analysis adjusting for the combined effects of histology, lymph node involvement and age reveal that tumor spillage posed the highest relative risk of local recurrence in children with stage II disease who received less intensive therapy. Most tumor ruptures occur during mobilization of the posterior aspect of the tumor where it is adherent to the diaphragm. An adequate incision and resection of a segment of the adherent diaphragm can often prevent rupture.

Resection of adjacent organs (liver, spleen, or pancreas) or resection of massive Wilms tumors were discouraged in the recent NWTSG studies and the current COG studies based on prior results. Such extensive resections are associated with a significant increase in surgical complications [146]. Only in this situation should the primary tumor be biopsied along with perihilar and periaortic/pericaval lymph nodes. Preoperative evaluation of children with renal tumors must include studies of coagulation. "Acquired" von Willebrand disease has been seen in children with Wilms tumor which can produce problems with hemostasis if it is not identified and treated appropriately prior to surgery [6].

Preoperative Therapy

Preoperative treatment of Wilms tumor is generally accepted in certain circumstances in the North American studies: occurrence of Wilms tumor in a solitary kidney, bilateral renal tumors, intravascular extension of the tumor above the intrahepatic vena cava, and respiratory distress from extensive metastatic tumor in the lungs. Pretreatment biopsy should be obtained. Percutaneous biopsy is often utilized although needle tract seeding has been reported [106]. The aim of treatment (prior to surgical resection in the bilateral tumors and tumor in a solitary kidney) is to preserve maximum renal parenchyma and function. A horseshoe kidney is often not recognized prior to surgical exploration in many cases; the large size of the tumor often distorts the anatomy concealing its presence [125]. An increased incidence of urine leak and ureteral injury occur in this situation due to the aberrant anatomy of the collecting systems and vascular supply. Although growth of the remaining kidney has been documented (achieving 180 % volume augmentation), the occurrence of focal segmental glomerulosclerosis has been reported in children with a unilateral kidney [44, 176]. In the NWTS 1–4 population, the incidence of renal failure following unilateral nephrectomy was only 0.25 % [145]. Studies from Europe on pretreatment of unilateral Wilms tumor have demonstrated that in most instances a nephrectomy is still required rather than a partial nephrectomy because of the extent of tumor involvement in the kidney at presentation [181].

The efficacy of preoperative chemotherapy in allowing the safe performance of partial nephrectomy for Wilms tumor has been evaluated by several centers. McLorie and associates in Toronto obtained percutaneous biopsy in 37 children with Wilms tumor and then administered multiagent chemotherapy for 4–6 weeks. A partial nephrectomy was then performed in nine children (four with unilateral and five with bilateral tumors) [117]. Two children suffered intra-abdominal relapse. Only 4 of the 30 unilateral tumors (13.3 %) were amenable to a partial nephrectomy. Another analysis of the feasibility of partial nephrectomies was performed at St. Jude Children's Research Hospital [190].

Preoperative CT scans of 43 children with nonmetastatic unilateral Wilms tumor were reviewed retrospectively. Criteria utilized to determine if a partial nephrectomy would have been feasible were involvement by the tumor of one pole and less than one-third of the kidney, a functioning kidney, no involvement of the collecting system or renal vein, and clear margins between the tumor and surrounding structures. Utilizing these criteria, only 2 of 43 scans (4.7 %) suggested partial nephrectomy was feasible. The primary concerns regarding use of preoperative chemotherapy to create "resectable" small tumors is that these children with small tumors at presentation may be curable by surgical resection alone [36, 119]. Beckwith also reported a 40 % incidence of nephrogenic rests in unilateral Wilms tumor specimens raising the concern for an increased number of metachronous tumors if partial nephrectomies are performed [13]. While the role of partial nephrectomy has been suggested in children with Beckwith-Wiedemann syndrome, hemihypertrophy or WAGR in whom smaller tumors may be identified by prospective screening, the efficacy of this approach has not been established [118].

Bilateral Wilms Tumor

Bilateral Wilms tumor (BWT) presents a unique clinical challenge juxtaposing the competing priorities to maximize preservation of renal parenchyma to prevent renal failure and to achieve complete surgical resection to cure the malignancy. Children with bilateral tumors are generally younger than those with unilateral lesions with a mean age of 25 versus 44 months [25]. Preservation of renal parenchyma is a critical issue for these children. In previous studies, patients were treated as followed only with guidelines given, but they were not enrolled on a specific protocol. For the first time COG now has an open protocol for children with bilateral Wilms tumors. Recently the NWTS-4 experience with 188 synchronous BWT patients was reported by Hamilton and coauthors [79].

Guidelines for the 188 BWT included initial biopsy followed by chemotherapy. One hundred and ninety-five kidneys in 123 patients had initial open biopsy; 44 kidneys in 31 patients had needle biopsies. Although pre-resection chemotherapy was recommended, 87 kidneys in 83 patients were managed by primary resection. Complete nephrectomy in 48, 31 partial wedge nephrectomies and 8 enucleations. No initial surgery was performed in 45 kidneys. Relapse or progression of disease occurred in 54 children. End stage renal failure occurred in 23 children, 6 had bilateral nephrectomies. The 8 year EFS for BWT with FH was 74 % and OS was 89 %; for BWT with unfavorable histology, EFS was 40 %, OS was 45 %. Anaplasia was diagnosed after completion of initial chemotherapy in 14 patients. The average time interval from the start of chemotherapy to diagnosis of anaplasia was 390 days (range 44–1925 days). The analysis of NWTS-4 BWT showed that preservation of renal parenchyma is possible after initial pre-operative chemotherapy. The incidence of renal failure remained significantly higher (12 %) than in unilateral patients (1 %) [79].

The current COG BWT protocol includes upfront intensification of triple agent initial chemotherapy, requires second look surgery at 6 weeks for patients whose tumors do not respond (<50 % reduction in volume of the tumor) and definitive surgery or open biopsy at 12 weeks. Adjuvant chemotherapy following resection will be modified based on histology. The goal of earlier surgery is to address possible under treatment of anaplastic tumors and obviate prolonged treatment for differentiated or necrotic tumors. BWT with anaplastic tumors were not identified by needle biopsy and discordance of the pathology in the two tumors was present in 80 % (20/24) on final tissue diagnosis. It is important to emphasize the requirement to biopsy all tumors as "discordant" pathology does occur with a favorable lesion on one side and unfavorable lesion (generally anaplastic) in the other. Davidoff et al published a single institution series where ten patients with BWT all had successful nephron sparing surgery. Many of these children had very large tumors even after preoperative chemotherapy, this emphasizes that it is easy to underestimate the amount of renal parenchyma that can be salvaged when compressed and distorted by a large tumor [41]. Parenchymal sparing surgery is advocated with partial nephrectomy or wedge excision preferred if it will not compromise tumor resection and negative margins are established [41, 79]. Ninety-eight children with bilateral Wilms tumors underwent a partial nephrectomy of 134 kidneys during NWTS-4 [84]. Complete resection of gross disease was accomplished in 118 (88 %) of the 134 kidneys. A higher incidence of positive surgical margins (16 %, 19/134) and local tumor recurrence (8.2 %, 11/134) was seen in this group of children. These were justified by the attempt to preserve renal tissue and avoid renal failure. Overall, portions of 72 % of the kidneys were preserved and the 4-year survival rate was 81.7 %.

In the NWTSG review of renal failure in 55 children from NWTS 1–4, 39 children had bilateral tumor involvement. Increasing efforts to preserve renal parenchyma in bilateral cases in the sequence of the NWTSG studies resulted in a decline in the incidence of renal failure from 16.4 % in NWTS-1 and -2 to 9.9 % in NWTS-3 and 3.8 % in NWTS-4 [146]. Although the incidence may increase in the more recent studies as children age, this declining frequency is also due in part to increased attempts to save part of the kidneys by initial treatment of the tumor with chemotherapy. Preliminary treatment in most cases following biopsy and staging will produce shrinkage of the tumor and facilitate its resection with preservation of a portion of the

kidney. Bilateral lesions are rarely seen in association with clear cell sarcoma or rhabdoid tumors of the kidney The United Kingdom Children's Cancer Study Group (UKCCSG) has also reported attempts at maximal preservation of renal parenchyma with preoperative chemotherapy [98]. Survival was equivalent for those with initial resection versus preoperative chemotherapy, but greater preservation of renal parenchyma was seen in those treated with initial chemotherapy. Radiation has been advocated to prevent relapse in children with partial nephrectomy for bilateral disease, but irradiation will impair the ability of the kidney to grow [128, 169].

The presence of rhabdomyomatous histology has been associated with poor response to preoperative chemotherapy as defined by decrease in size on radiographic evaluation, but it has been found to be associated with favorable survival [2].

Intravascular Extension

Intravascular extension of a tumor thrombus occurs in 4 % of children with Wilms tumor. Identification of vascular extension by preoperative radiographic studies or early in the surgical exploration is critical to avoid a tumor embolus during mobilization of the kidney. Ultrasonography is probably more sensitive than is computed tomography (CT scan). The presence of intravascular extension does not affect the prognosis of the tumor as long as it is successfully resected [147]. Traditionally, intravascular extension has been managed by nephrectomy with resection of the tumor thrombus extending into the renal vein or vena cava. Cardiopulmonary bypass has been required for children with atrial extension of the tumor thrombus, but is associated with a significant incidence of complications (70 %) [123].

A similar review of children treated in the United Kingdom with extensive intravascular involvement also demonstrated a decrease in the extent of vascular involvement in 16 of 21 children and showed that children receiving preoperative chemotherapy had a better outcome [121].

More recently, a review of all of the children treated on NWTS-4 identified 165 of 2,731 patients (6 %) with intravascular extension into the IVC (134 patients) or atrium (31 patients) [166]. Sixty-nine of these patients received preoperative chemotherapy (55 with IVC extension and 14 with atrial extension). Five complications were encountered during preoperative chemotherapy including tumor embolism and tumor progression in one patient each, and three patients developed adult respiratory distress syndrome, one of which was fatal. Intravascular extension of the tumor regressed in 39 of 49 children with comparable pre- and post-therapy radiographic studies, including regression of the tumor thrombus in 7 of 12 from an atrial location avoiding the need for cardiopulmonary bypass. A high frequency of surgical complications occurred in these patients, 36.7 % in the children with atrial extension and 17.2 % in those with IVC extension. The frequency of surgical complications was 26 % in the primary resection group versus 13.2 % in children with preoperative therapy. When all the complications were considered including those which occurred during preoperative chemotherapy (one of those five also had a surgical complication), the incidence of complications among those receiving preoperative therapy was not statistically different from the incidence among those who underwent primary resection, although most of the severe complications occurred in the primary resection group. Preoperative therapy clearly facilitated surgical resection by decreasing the extent of the tumor thrombus.

Surgery Alone for Select Favorable Wilms Tumors-Very Low Risk Wilms Tumors (VLRWT)

A small group of children with Wilms tumor may require only resection of the primary tumor and kidney without adjuvant treatment. These VLRWT are defined as stage I favorable histology tumors weighing under 550 g occurring in children less than 2 years of age Review of children with these tumors registered in the NWTSG studies were revealed a 4-year relapse-free survival exceeding 90 %, suggesting that they could be selected for treatment with surgery alone [69]. A similar review by the United Kingdom Children's Cancer Study Group in which children with stage I tumors received only vincristine "monotherapy", also demonstrated that infants under 2 years of age had particularly favorable 4-year EFS and OS of 93.2 % and 98.1 % respectively [134].

A pathologic review of children treated on NWTS-4 also demonstrated that children under 2 years of age and specimen weight of less than 550 g was highly associated with the absence of adverse microsubstaging variables [58]. A prospective pilot study of this question was performed at Children's Hospital in Boston. Eight children with stage I disease who were under 2 years of age with unilateral, favorable histology tumors with a combined tumor and kidney weight under 550 g were resected and followed without adjuvant therapy [103]. One child developed a metachronous tumor cured by resection and chemotherapy. Continued evaluation of this series showed no episodes of local recurrence [165].

One component of NWTS-5 was a trial of surgery only for children under 2 years of age with small (<550 g tumor and kidney) stage I favorable histology tumors. Seventy-five infants were enrolled in this study [62]. Three infants developed metachronous, contralateral Wilms tumors and eight relapsed 0.3–1.05 years after diagnosis. The sites of relapse were pulmonary (5 cases) and operative bed (3 cases). The 2-year disease-free survival including both relapse and meta-

chronous tumors was 86.5 %. The 2-year survival rate was 100 % with a median follow-up of 2.8 years. The 2-year disease-free survival excluding metachronous tumors was 89.2 %, and the 2-year cumulative risk of metachronous contralateral Wilms tumor was 3.1 %. The stopping rule for the study required closure after these 75 infants were enrolled, but continuing evaluation of this cohort has demonstrated that they have done very well with a high rate of salvage for recurrence as they were previously untreated with chemotherapy [163].

Shamberger and co-authors recently published long term follow-up for this surgical cohort. The median follow-up of surviving patients was 8.2 years for surgery only (range, 1.9–11.8 years) and 5.2 years for the EE4A group (range, 1.6–8.9 years). The estimated 5-year EFS for surgery only was 84 % (95 % confidence interval [CI]: 73 %, 91 %); for the EE4A patients it was 97 % (95 % CI: 92 %, 99 %, P = 0.002). One death was observed in each treatment group. The estimated 5-year OS was 98 % (95 % CI: 87 %, 99 %) for surgery only and 99 % (95 % CI: 94 %, 99 %) for EE4A (P = 0.70). This exciting report demonstrates that the surgery-only EFS was lower than anticipated but, coupled with a much higher than anticipated salvage rate of the chemotherapy naive patients whose disease recurred, led to an observed long-term OS equivalent to that seen with 2-drug chemotherapy. This approach to the treatment of patients with VLRWT eliminates the toxic side-effects of chemotherapy for a large majority of patients. A follow-up study is underway to confirm these findings [163].

Neonatal Wilms Tumor

Wilms tumor occurs rarely in the neonate. A review of the 3,340 children entered into the NWTS studies from 1969 to 1984 revealed only 27 neonates (≤30 days old) with renal tumors (0.8 %) [86]. Over half of the neonates (18) had mesoblastic nephroma and four others had non-neoplastic lesions. One infant had a malignant rhabdoid tumor and four had Wilms tumors. All of these children with Wilms tumor had favorable histology tumors without metastasis. They did well, receiving a variety of treatments ranging from surgery alone to 15 months of three-drug therapy. A subsequent report of 15 cases of Wilms tumor occurring in neonates in the first 30 days of life again demonstrated favorable histology tumors and absence of metastatic disease [142]. Ten of these infants received postoperative chemotherapy and five were followed without additional treatment. Only one of these five children recurred in the renal fossa and lungs and ultimately succumbed to her disease at 16 months of age. The other children are all disease-free at a median follow-up of 31 months.

Extra-renal Wilms Tumor

An extra-renal site of primary Wilms tumor is uncommon. These extra-renal tumors behave identically to tumors arising within the kidney and should be treated both locally and systemically based on the same criteria [3, 35]. Common sites of occurrence of extra-renal Wilms include the retroperitoneum, inguinal canal, scrotum, and vagina. Rare sites are the uterus, cervix, ovary and the presacral space.

The foresight to bank tumor specimens and meticulous data collection from well designed international clinical trials has enabled excellent overall outcomes for children with Wilms tumor and provided fertile substrate for analysis to allow for dedicated scientists and clinicians to maintain the status of Wilms tumor as the paradigm for translational science and multimodal cancer care. Future efforts will focus on unlocking the cellular mechanisms of metastasis and clinical efforts will remain focused on minimizing toxicity and improving outcomes for patients with unfavorable histology tumors and recurrent disease.

Renal Cell Carcinoma

Children with renal cell carcinoma are generally older than those with Wilms tumor, and frequently present with symptoms of flank pain and gross hematuria [100]. Radiographically they are indistinguishable from Wilms tumor. Renal cell carcinoma in children displays gross and microscopic pathologic features similar to those seen in tumors occurring in adults (Fig. 12.14a–c). Clinical stage at the time of diagnosis is the most important prognostic factor and the identification of renal vascular invasion did not appear to be an adverse predictor. Radical nephrectomy and regional lymphadenectomy remain the primary modality for cure and children with distant spread have a grave prognosis. The mean age for presentation with renal cell carcinoma in a pediatric population was 14 years. Overall survival is much worse than for Wilms tumor with only a 30 % 5-year survival in a recent series. Analysis of multiple factors including age, tumor size, location, and histology failed to demonstrate they were predictors of survival. Only stage and achieving complete tumor resection were meaningful prognostic factors. Survival was 60 % in children with complete resection of the primary tumor and zero in those with only partial resection. While survival by stage was well documented with 92.5 % for stage I, 84.5 % for II, 72.7 % for III and 12.7 % for IV, it should be noted that those with positive nodes but no distant metastasis had survival rates three times that of adult historical controls [53]. Renal cell carcinoma is remarkably resistant to chemotherapy preventing cure in most children who present with metastatic disease [120]. Ten to twenty percent of patients have nodal involvement identified at surgery, but lack evidence of distant

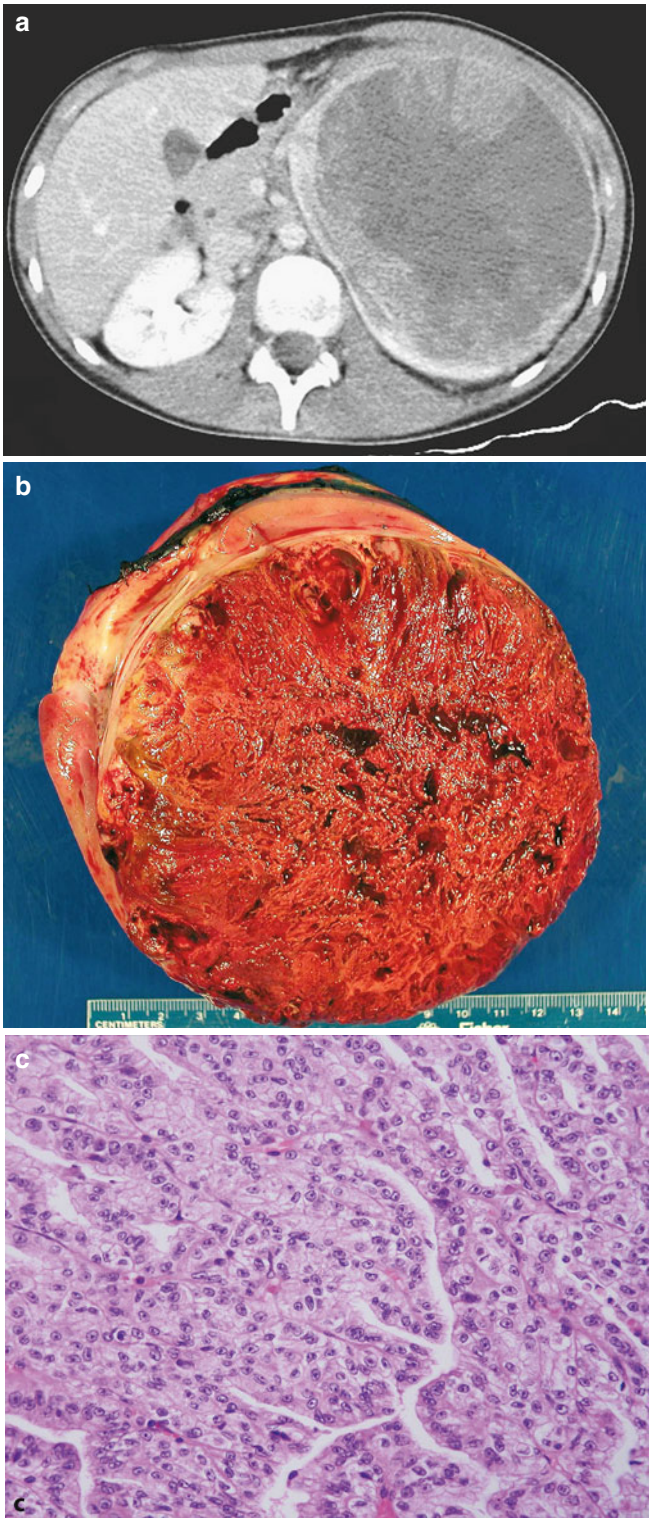

Fig. 12.14 (**a**) CT scan of a 13 year old female who presented with a palpable left flank mass. Wilms tumor and renal cell carcinoma can not be distinguished based on the appearance of the tumor on radiographic studies. (**b**) Cut surface demonstrates a large renal tumor with areas of focal necrosis surrounded by an attenuated renal tissue. (**c**) Microscopic findings of this tumor were consistent with renal cell carcinoma

metastatic disease. In a review of children receiving adjuvant therapy, no benefit could be defined for its use [53].

Nephron-sparing surgery has been utilized in patients with small polar lesions in whom there is no evidence of a multicentric tumor. In these selected cases with tumors less than 4 cm and a normal contralateral kidney, the risk of local recurrence is reported to be 2 % or less which is comparable to the frequency of metachronous recurrence in the contralateral kidney after a unilateral radical nephrectomy.

The occurrence of late relapses long after nephrectomy, prolonged stability of disease in the absence of systemic therapy and rare cases of spontaneous regression of tumors have stimulated an interest in immunotherapy comparable to that utilized in melanoma. Trials of immuno-modulating therapy with interferon-alpha and interleukin-2 (IL-2) have demonstrated some efficacy, but maintenance of a durable cure has been elusive [52]. One trial randomized 294 patients with advanced stage renal cell carcinoma to receive placebo or 9 months of subcutaneous lymphoblastoid interferon. Regrettably, similar recurrence rates occurred in the two groups and worse survival was seen in those randomized to interferon [52]. With the significant toxicity involved with immunotherapy, demonstration of improved survival in randomized trails will be required before this can be adopted as standard therapy.

Mesoblastic Nephroma

Congenital mesoblastic nephroma, also referred to as fetal renal hamartoma or leiomyomatous hamartoma, is the most common renal tumor identified in the neonatal period. Although it was initially diagnosed and treated as a congenital Wilms tumor, mesoblastic nephroma was defined as a distinct entity in 1967 [23]. Mesoblastic nephromas present most frequently in the neonatal period as a palpable flank mass which can be massive in size (Fig. 12.15a). Additional symptoms seen at presentation include hematuria, hypertension, vomiting, and jaundice [85].

Mesoblastic nephroma accounted for 2.8 % of 1,905 renal tumors submitted to the early NWTSG studies. Grossly, these tumors generally have a homogeneous rubbery appearance resembling a uterine fibroid in color and consistency although cystic variants are seen (Fig. 12.15b). Microscopically they are composed of sheets of fibrous or mesenchymal stroma within which bizarre and dysplastic tubules and glomeruli are irregularly scattered [22]. The tumor can invade intact renal parenchyma, and extra-renal infiltration into the perihilar connective tissues is common. The histologic subtypes of this tumor include: the classic type (24 % of cases), the cellular type (66 %), and the mixed type (10 %). The pluripotency of these tumors is revealed by

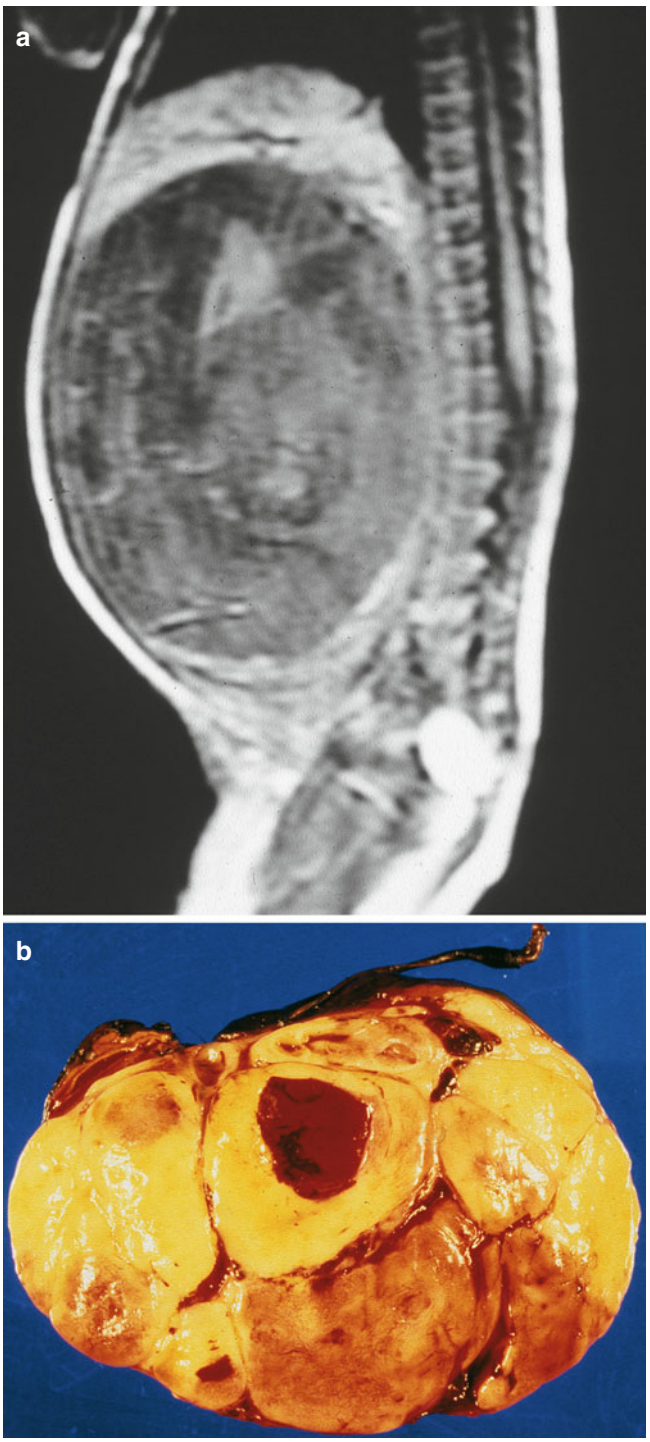

Fig. 12.15 (**a**) Sagittal views of an MRI scan of a newborn infant with a massive renal tumor. (**b**) Cut surface of the tumor shows the classic appearance of rubbery tissue without necrosis consistent with a mesoblastic nephroma

their differentiation into angiomatoid patterns, cartilaginous nests, and their elicitation of intratumoral hematopoiesis in addition to the tiny nephroblastic epithelial foci.

A characteristic chromosomal translocation, t(12;15)(p13;q25), has been described which results in fusion of the *ETV6* (also known as *TEL*) gene from 12p13 with the *NRTK3* neurotrophin-3 receptor gene (also know as *TRKC*) from 15q25 [170, 171]. This results in a chimeric RNA which is characteristic of both infantile fibrosarcoma and the cellular variant of congenital mesoblastic nephroma. This may be of assistance in differentiating the cellular variant from other lesions which must be considered in the differential diagnosis including clear cell sarcoma and rhabdoid tumors of the kidney. It also suggests a close relation between infantile fibrosarcoma and the cellular variant of mesoblastic nephroma [4].

Nephrectomy alone usually cures this tumor. Resection should include generous margins around all gross tumor to avoid local recurrence. Particular attention should be paid to the medial aspect of the kidney including the hilum and great vessels because of this tumor's proclivity to extend into the perirenal soft tissues. Several children have been reported with local recurrence [7] or metastasis to the brain, bones, lungs and heart. [10, 81, 158, 183] In some of these cases, the histology has revealed an unusual degree of mesenchymal cell immaturity and hypercellularity suggesting a more aggressive tumor [22]. These rare occurrences, however, support the concept that mesoblastic nephroma cannot be considered as a simple hamartoma and that complete nephrectomy with negative pathologic margins for tumor is critical in all cases.

In a series of 51 children with mesoblastic nephroma identified in the NWTSG series, adequate operative excision was achieved in 43 of 51 children while eight had local extension and ten had tumor spillage during resection [85]. The use of adjuvant therapy in these cases depended upon the era in which the children were treated. Twenty-three infants treated primarily after 1978 had surgical resection alone. Prior to 1978, 24 had surgery plus chemotherapy and, before 1976, four children also received irradiation. Survival was excellent in this entire group and only one child succumbed to sepsis during chemotherapy. One child recurred at 6 months despite receiving dactinomycin and vincristine. The tumor was surgically re-excised and the child was treated with cyclophosphamide and doxorubicin, and remained without disease 18 months later.

A SIOP study of 29 children with mesoblastic nephroma confirmed the early age at which this tumor is seen. There were only five infants older than 4 months at presentation in the series [156]. Five infants with the cellular type of tumor received some chemotherapy. Two infants in this series died from sepsis following surgery, but the remainder are alive and free of disease 4 years following surgery. Again this tumor was noted to infiltrate the renal hilum or perirenal tissue.

A neonate with an extensively infiltrating tumor was treated with eight weekly courses of vincristine prior to resection [30]. The tumor regressed with treatment, facilitating its resection and cure.

Beckwith has reported the largest cohort of children with recurrent or metastatic lesions from his large collected series [10]. Twenty-four cases of aggressive tumor were seen in a series of 330 mesoblastic nephromas. Of these cases, 8 had metastatic disease, 17 had relapse in the peritoneum or retroperitoneum, and 6 of the infants have succumbed with persistent disease. Recurrences occurred in children following initial chemotherapy or irradiation, which suggests that conventional adjuvant therapy may not decrease the incidence of relapse. Histologic criteria were not helpful in predicting outcome. Beckwith supports aggressive surgical attempts to remove all gross tumor and stresses the need for close monitoring for 1 year following surgery. Relapse was apparent in 23 of the 24 cases within 11 months of resection. Ultrasonography of the local site is adequate and scans for metastatic disease are unrewarding.

Cystic Nephroma

Cystic nephroma is indistinguishable grossly and radiographically from its malignant neoplastic cousins, cystic partially-differentiated nephroblastoma (CPDN) and cystic nephroblastoma. All lesions are composed of purely cystic masses characterized by multiple thin-walled septations. In cystic nephroma, the septations are lined by flattened, cuboidal or hobnail epithelium and are composed entirely of differentiated tissues without blastemal or other embryonal elements which are the distinguishing characteristic of CPDN [94]. While the term "multilocular cyst of the kidney" has been employed, "cystic nephroma" is preferred because the lesion appears to be neoplastic and not congenital. In the cystic nephroblastoma or cystic Wilms tumor there are solid nodules on the septae of blastemal or embryonal elements characteristic of Wilms tumor. An unexplained synchronous occurrence has been reported of cystic nephroma and pleuropulmonary blastoma [43, 90].

These lesions should not be confused with cystic clear cell sarcoma, cystic mesoblastic nephroma, or multicystic dysplastic kidney [1]. Cystic nephroma, CPND and cystic nephroblastoma can be distinguished from multicystic dysplastic kidney because they are confined only to a portion of the kidney with normal renal parenchyma being identified while the cystic changes of multicystic dysplastic kidney almost always involve the entire kidney (its etiology is early *in utero* urinary tract obstruction). Contralateral renal anomalies are frequent in dysplastic kidneys including ureteropelvic junction obstruction and reflux. Multicystic dysplastic kidney is often identified antenatally or in the newborn period while the other lesions occur later.

Generally, nephrectomy will be curative in both cystic nephroma and CPDN [94]. Twenty-three children with these cystic lesions were identified in the NWTSG series: 5 with cystic nephroma and 18 with CDPN. Only one case of CPDN had local recurrence and there were no distant metastases. A more recent review of the NWTSG files of the CPDN cases has again confirmed that primary resection appears to be adequate for all lesions removed intact [19]. In cases where the lesion is isolated to one pole of the kidney, a partial nephrectomy may be considered, however, it must be remembered that these tumors can resemble cystic variants of clear cell sarcoma of the kidney which carry an entirely different prognosis [9, 173]. This is the major concern regarding the use of nephron sparing surgery as suggested by some for these cystic lesions [154].

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Nephron-Sparing Surgery

13

Denis Andrew Cozzi and Francesco Cozzi

Introduction

Wilms tumor (WT) represents the most common form of childhood kidney cancer. Since the 1980s, the 5-year survival rate for this relatively rare tumor has been consistently above 90 % [1]. Most of the dramatic improvements in survival of these children have been achieved by results from randomized clinical studies conducted primarily by two large collaborative groups, i.e. the National Wilms Tumor Study (NWTS) Group, which is now part of the Children's Oncology Group (COG), and the Société Internationale d'Oncologie Pédiatrique (SIOP).

Amongst the well standardized multimodal treatment of WT, surgery still plays a pivotal role. Radical nephrectomy (RN) is currently considered as the procedure of choice, because it allows excision of the primary tumor with a wide surgical margin and most of the patients are believed to have another good kidney. Nephron-sparing surgery (NSS) plays instead a lesser role and is predominantly confined to patients with bilateral Wilms tumor (bWT). Indeed, the rationale for NSS is to limit potential long-term morbidity by maximizing the preservation of functional renal parenchyma.

In patients with bWT, the increased risk of renal insufficiency is well documented. In contrast, the risk of developing progressive renal dysfunction in nephrectomized children with normal contralateral kidney is considered clinically irrelevant to date.

We reviewed the current status of NSS for primary renal tumors during childhood. Included issues will focus on contemporary indications, technical considerations and patient outcomes. Additionally, we made an attempt to summarize existing data on the potential risk of renal dysfunction carried by nephrectomized children in the setting of a normally functioning contralateral kidney.

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Current Indications for Nephron-Sparing Surgery

Acceptable indications for NSS may be divided into three categories including absolute or imperative, relative, and elective indications.

Absolute indications to make an attempt to preserve as much functional renal parenchyma as possible include tumors involving an anatomically or functionally solitary kidney due to unilateral renal agenesis, previous contralateral nephrectomy or irreversible impairment of contralateral renal function due to a benign disorder. However, synchronous bilateral tumor involvement (i.e., stage V), which is reported to occur in 3.6–8 % of the cases, represents the commonest absolute indication for NSS in children. The increased risk of end stage renal disease (ESRD) in this subset of patients is well documented and reported to be as high as 10 % in the most recent review of the NWTS Group experience [2].

In 1957, Rickham reported the first case of bWT treaded with nephrectomy coupled with tumor excision on the other side, followed by radiotherapy [3]. Approximately 20 years later, Wiener reported the first case of bWT treated with staged bilateral partial nephrectomies, emphasizing the use of preoperative chemotherapy to shrink the tumors and, therefore, to facilitate surgery [4].

Because of a great appreciation of the potential for renal failure, the management of bWT has further evolved over the ensuing decades by using more effective, multimodality therapy. This strategy has resulted in a significant increase of patients treated with bilateral NSS. However, the percentage of patients who had at least one kidney removed has remained remarkably high over the years on both sides of the Atlantic, with about 50 % of children with bWT still nephrectomized [5].

Indeed, there are many factors that contribute to the low rate of NSS. The response to chemotherapy may be minimal in some cases, particularly with tumors that have a predominantly stromal pattern [6]. The surgeon is often faced with a

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large tumor that appears to replace the entire kidney. Additionally, many of these tumors are centrally located and extend into the renal hilum. However, at the time of exploration such lesions often compress an unexpected good amount of viable renal parenchyma, as demonstrated by Davidoff et al. [7]. In their study, they attempted to perform bilateral NSS in a consecutive series of patients with bWT following preoperative chemotherapy using a 3-drug regimen. They strongly recommended to attempt NSS on both kidneys in patients with bWT, despite preoperative imaging studies suggesting that the lesions are inoperable. The concept of resectability should not be influenced by tumor size or anatomy has also been promoted by Fuchs et al. [8] in their report on the feasibility of NSS in patients with large, centrally located bWT.

Notably, the increased risk of positive renal margins and subsequent local recurrence rate, which in recent reports varies between 11.6 and 14 %, does not seem to adversely affect the excellent survival rate of patients with bWT [9, 10].

Nonetheless, it is not easy to establish whether new tumors are the result of residual disease or de novo tumors that have developed from other sites. These patients have multifocal disease and a high incidence of nephrogenic rests. Indeed, most of these rests can be eradicated with chemotherapy and radiotherapy. Additionally, a second look, and if necessary, third-look procedures may result in preservation of functioning renal tissue [11]. However, the outlook of patients with unfavorable histology, such as diffuse anaplasia, is significantly poorer than that of patients with favorable histology. These patients would be best served with early surgery for local tumor control, given the chemoresistance of the anaplastic cells. In the bilateral tumor protocol that is being developed by the COG, a 3-drug regimen is being considered at diagnosis for all patients with bWT. The rationale is to decrease the time interval from diagnosis to definitive surgery in these patients. In many patients, these tumors do not respond well in terms of reduced volume, and the treating institution will opt to intensify therapy before proceeding with surgery. The expectation is that intensification of therapy will reduce tumor size further, allowing the patient to undergo NSS. Additionally, starting therapy with three drugs could eliminate some of the delay in patients with unfavorable histology, prompting earlier interval incisional biopsy or tumor resection [12].

There are clinical scenarios where NSS is reasonably indicated due to coexisting urologic (e.g., horseshoe kidney, hypospadias and cryptorchidism association) or medical (e.g., Denys-Drash syndrome) conditions predisposing to future renal failure. Another subgroup of patients who may well benefit from NSS are those children at increased risk for development of a metachronous WT. Patients with aniridia and a number of overgrowth syndromes, such as the Beckwith-Wiedemann syndrome or idiopathic hemihypertrophy, have multicentric disease due to an increased incidence of nephrogenic rests in comparison to patients with unilateral WT not associated with congenital anomalies. Beckwith et al. [13] suggested that the presence of multiple nephrogenic rests (i.e. microscopic nephroblastomatosis) within the normal renal parenchyma surrounding the tumor is associated with a higher risk of subsequent tumor development in the contralateral kidney.

A report from the NWTS Group confirmed this hypothesis and identified infants younger than 12 months as a subset of patients at higher risk of carrying microscopic nephroblastomatosis, thus at increased risk of metachronous WT [14]. For these patients, NSS might be an option if nephrogenic rests are demonstrated before or at surgery [14].

The COG Renal Tumor Committee has recently considered eligible for NSS patients with unilateral disease known to be at risk for ESRD or metachronous bWT (i.e., AREN0534 protocol). For these patients with bilaterally-predisposed unilateral WT (uWT) the protocol recommends preoperative chemotherapy followed by renal sparing surgery. Also the current SIOP protocol (2001) is collecting data on NSS for patients with uWT and contralateral urological and nephrological disorders, or genetic syndromes predisposing WT in the opposite kidney. Additionally, the SIOP protocol has designed a special appendix for the management of hyperplastic nephroblastomatosis. Hyperplastic nephrogenic rests can be diagnosed at imaging as homogeneous solid masses, which do not enhance after contrast administration. Beckwith first considered hyperplastic nephroblastomatosis as a precursor lesion of WT, and, therefore, advised the use of preoperative chemotherapy followed by NSS in view of the potential risk for these patients to develop a metachronous tumor [15]. However, whether hyperplastic nephroblastomatosis really portended a significant higher risk of metachronous WT had not been adequately investigated. Subsequently, Perlman et al. [16] found that of 52 patients with initial diagnosis of hyperplastic nephroblastomatosis, 24 patients developed a WT. Additionally, of 23 collected cases of hyperplastic nephroblastomatosis diagnosed by preoperative imaging or at surgery, 14 presented with bWT (11 synchronous, and 3 metachronous) and 6 with uWT [17]. These clinical data strongly suggested that hyperplastic nephroblastomatosis portends a significant risk of WT in both kidneys, and such risk is much higher than that reported in children with microscopic nephroblastomatosis [17]. Therefore, NSS seems appropriate in children with WT associated with hyperplastic nephrogenic rests. Accordingly, the SIOP protocol recommends NSS for the treatment of uWT associated with hyperplastic nephroblastomatosis. However, we limited the indication of NSS to stage I nonanaplastic, uWT associated with hyperplastic nephroblastomatosis [17]. This prudential approach seems appropriate, given the higher prevalence of anaplastic WT in patients with hyperplastic nephroblastomatosis [16].

Whether NSS is a reasonable alternative to nephrectomy in other patients with WT in the setting of a normal contralateral kidney remains a matter of debate. The main issue against such approach is that there is no convincing evidence that 50 % reduction of renal mass is associated with increased risk of renal failure. It is the opinion of the COG Renal Tumor Committee that NSS for uWT and normal contralateral kidney should still be considered investigational at present [18]. Also the SIOP protocol does not recommend NSS for uWT and normal opposite kidney, but aims to collect data on those so treated patients, provided that the suggested contraindications are respected. In children with uWT, the other main issue against NSS refers to the potential oncological risk of increasing the local recurrence rate and, therefore, decreasing the disease-free survival rate. In an attempt to answer this question, in 1992 we started a prospective study investigating whether NSS was feasible and effective in select children with WT and a normal contralateral kidney [19]. Our study protocol was then revised few years later [20]. Preoperative chemotherapy was routinely administered, except in select instances. NSS was considered only for patients with stage I disease, which was established at surgery on frozen section of specimens from renal and periaortic lymph nodes, specimens from perirenal fat and resection margin. Since the initiation of our study to December 2011, 44 children with unilateral primary renal tumor have been treated at our Institution. Of these, 31 patients underwent RN and 13 received NSS. Although we intended to treat with NSS only patients with stage I disease, we recently come across a patient whose final histology documented tumor infiltration of the renal sinus, i.e. Stage II. All our patients are currently alive and event-free at a mean follow-up of 12 years. Additionally, all our kidney remnants retained their function when assessed by DMSA scan, and some of them contributed for more than 40 % of the overall renal function. We then demonstrated that not only NSS is oncologically safe, but has also a renal advantage over nephrectomy (this issue will be discussed in detail later in the chapter).

To date, only case reports and limited single institution case series studies have dealt with truly elective NSS for children with uWT. We recently collected 124 of such patients [5]. Interestingly, the vast majority of them belonged to European Union countries, where WT is mostly pretreated with chemotherapy, which was used in about 75 % of the entire series. Sixty patients had postoperative stage I "intermediate-risk" ("favorable") histology WT. Local relapse occurred in 4 (6.6 %) of them, all of whom were successfully cured by completion nephrectomy. At a mean follow-up of 4 years, all patients survived without disease, except one who died with no evidence of local recurrence. These figures well compare with the reported crude survival rate of children with postoperative stage I "Intermediate-risk" WT treated by RN [21].

A similar literature review on elective NSS for uWT has been recently conducted by Cost et al. [22]. Analyzed parameters included tumor stage, presence, timing and location of disease recurrence, and overall survival. Eighty-two patients had adequate data for analysis, and outcomes were compared with a cohort of patients managed with RN for non-syndromic uWT at the authors' institution. Overall, there were no statistically significant differences in the oncologic outcomes amongst the two groups. However, when patients were stratified into stage of disease, it became apparent that NSS compared favorably against RN only for the localized disease (i.e., Stages I & II).

It is generally believed that only a minority of patients with uWT would be considered candidates for elective NSS, typically due to the large size and location of many Wilms tumors. With an objective of investigating WT pathological characteristics that may impact the efficacy of NSS, Cost et al. [23] reviewed pathology specimens at their institution from patients undergoing RN for nonmetastatic uWT. Ideal candidates were defined as those having a unifocal mass outside the renal hilum, sparing a third or more of the kidney, favorable histology, no signs of renal sinus or segmental vascular invasion, no metastatic lymph nodes or gross regional disease, and a distinct interface on pathological review between tumor and remaining parenchyma. In total, 19 (24.4 %) of the 78 reviewed patients met all of aforementioned pathological criteria as ideal candidates for partial nephrectomy. The authors concluded that as many as 1 in 4 children undergoing surgery for nonmetastatic uWT have postresection pathological tumor characteristics favorable for NSS. Of note, none of their patients received preoperative chemotherapy, which if used routinely, may increase the potential number of candidates for NSS, as shown in a similar study reported by Guglielmi et al. [24]. Interestingly, Moorman-Voesterman et al. [25] found that the feasibility of NSS may be predictable on preoperative imaging studies with 80 % sensitivity, 97 % specificity, and 87 % accuracy, especially in those patients pretreated with chemotherapy. In their experience, partial nephrectomy was feasible in 7 of 90 (7.7 %) consecutive cases of histology-proven uWT. In their series, NSS was performed in children with tumors involving only 1 pole and occupying less than 1/3 of the kidney. A similar study has been recently conducted by the COG on the image based feasibility of NSS in a select group of patients with very low risk uWT [26]. According to their study protocol, 5 of the 60 patients (8 %) were candidates for NSS. The authors concluded that, as it is unclear whether preoperative chemotherapy can increase the number of patients eligible for NSS, the shift from current COG protocols regarding uWT does not appear desirable [26].

Finally, we believe that NSS is also advisable for unilateral cystic nephroma or cystic partially differentiated nephroblastoma. These rare lesions have a favorable

outcome and may be preoperatively diagnosed by CT scan, which shows multiple cystic spaces with thin walls and no solid component. The differential diagnosis can be made intraoperatively by frozen sections of the excised tumor: the finding of blastemal elements within the septa of the lesion will clinch the diagnosis of cystic partially differentiated nephroblastoma [27].

Evaluation and Operative Considerations

NSS is technically more challenging than en bloc removal of the kidney by RN and, therefore, it requires a more detailed understanding of renal anatomy. Knowledge of the relationship of the tumor and its vascular supply to the collecting system and adjacent normal renal parenchyma is essential for preoperative assessment.

Advances in helical computer tomography (CT) and computer technology now allow the production of high quality 3-D images of the renal vasculature and soft tissue anatomy, and provide a topographical road map of the renal surface with multiplanar views of the intrarenal anatomy. The data from 3-D CT integrate essential information from angiography, venography, excretory urography and conventional 2-D CT into a single preoperative staging test that may decrease the need for more invasive imaging (Fig. 13.1).

Our standardized technique of NSS for unilateral primary renal tumors has been previously described in detail [5]. In the case of bWT, a staged procedure with the less involved side done first is commonly recommended. When partial nephrectomy is precluded on 1 side due to tumor size or anatomy, initial partial nephrectomy is usually performed as a separate procedure on the less involved side, followed by contralateral RN. However, we prefer to attempt bilateral NSS during a single operation and to first approach the kidney with the larger tumor burden, as also advocated by others [7, 8]. Our surgical conduct does not change significantly whether the tumor is affecting one or both kidneys simultaneously. In both instances, the surgical approach requires adherence to the basic surgical principles of early vascular control, avoidance of renal ischemia, complete tumor excision with negative margins, precise closure of the collecting system, careful hemostasis and closure of the renal defect. Partial nephrectomy is the NSS procedure of choice, because complete excision of the tumor with a rim of normal renal tissue should duplicate the oncological principles underlying RN (Figs. 13.1, 13.2, and 13.3). Surgical options include typical or atypical segmental resections, and heminephrectomy, which some authors have successfully carried out also in the longitudinal plane [8]. Tumor enucleation is another NSS surgical option, which involves circumferential incision of the renal capsule and blunt shelling out of the tumor along the plane of its pseudocapsule (Fig. 13.4). The advantage of this procedure is the ease of removing tumors at any location on the kidney with maximum preservation of normal renal parenchyma. However, the main concern regarding this surgical technique is the risk of leaving residual microscopic tumor behind and, therefore, circumferential margins must be assessed meticulously if a tumor is enucleated. Penetration of the pseudocapsule is a fairly frequent event, which has been reported in about 27 % of patients with WT [28]. The potential local tumor spillage carried by tumor enucleation results in a change from stage I to stage II, due to flank contamination by tumor [29]. However, there is collateral evidence from the NWTS that, in absence of anaplasia, an adjuvant two-drug chemotherapy without radiotherapy may provide satisfactory coverage in such circumstances [30]. Another major concern regarding enucleation is that, in those patients who do not have integrity of pseudocapsule, the attempt to enucleate the tumor will result in tumor rupture. In our technique, the tumor is walled off from the peritoneal cavity and, if an inadvertent rupture occurs complete, tumor nephrectomy can then by accomplished with a rather small risk of local spillage. Nonetheless, leaving a macroscopic residue should be avoided because stage III requires radiotherapy, which may thwart the advantage of NSS. Therefore, true indications for tumor enucleation are restricted to large tumors centrally located, benign lesions such as cystic nephroma, and complex bWT. In the letter subgroup of patients, if partial nephrectomy is not feasible and anaplasia can be ruled out, we believe that a more liberal use of enucleation is justified to decrease the number of nephrectomised patients. With regard to the risk of anaplasia, it is worth remembering that children under the age of 3 years carry a very low risk of anaplasia, especially if they have bWT [20].

Finally, ex vivo tumor resection followed by autotransplantation represents an invasive technique, which has been reported in only few cases characterized by exceptionally large and anatomically challenging bWT [31, 32].

Preoperative hydration may be useful to ensure optimal renal perfusion at operation. The operation starts entering the abdominal cavity via a generous transverse trans-peritoneal incision to allow adequate exposure. The colon and its mesentery are mobilized from the anterior surface of the kidney. After opening the Gerota's fascia, the kidney is freed from the surrounding fatty tissue. Only the Gerota's fascia and the perirenal fat adherent to the surface of the tumor are left intact to be removed later along with the tumor. Intraoperative real-time ultrasonography may sometimes be useful to obtain information about tumor depth and extension into the parenchyma, distance from the adjacent calyx, and location of any prominent vessels around the periphery of the tumor. Although intraoperative ultrasound is not clearly better than CT, we found it especially useful for identifying small, unrecognized intrarenal tumors.

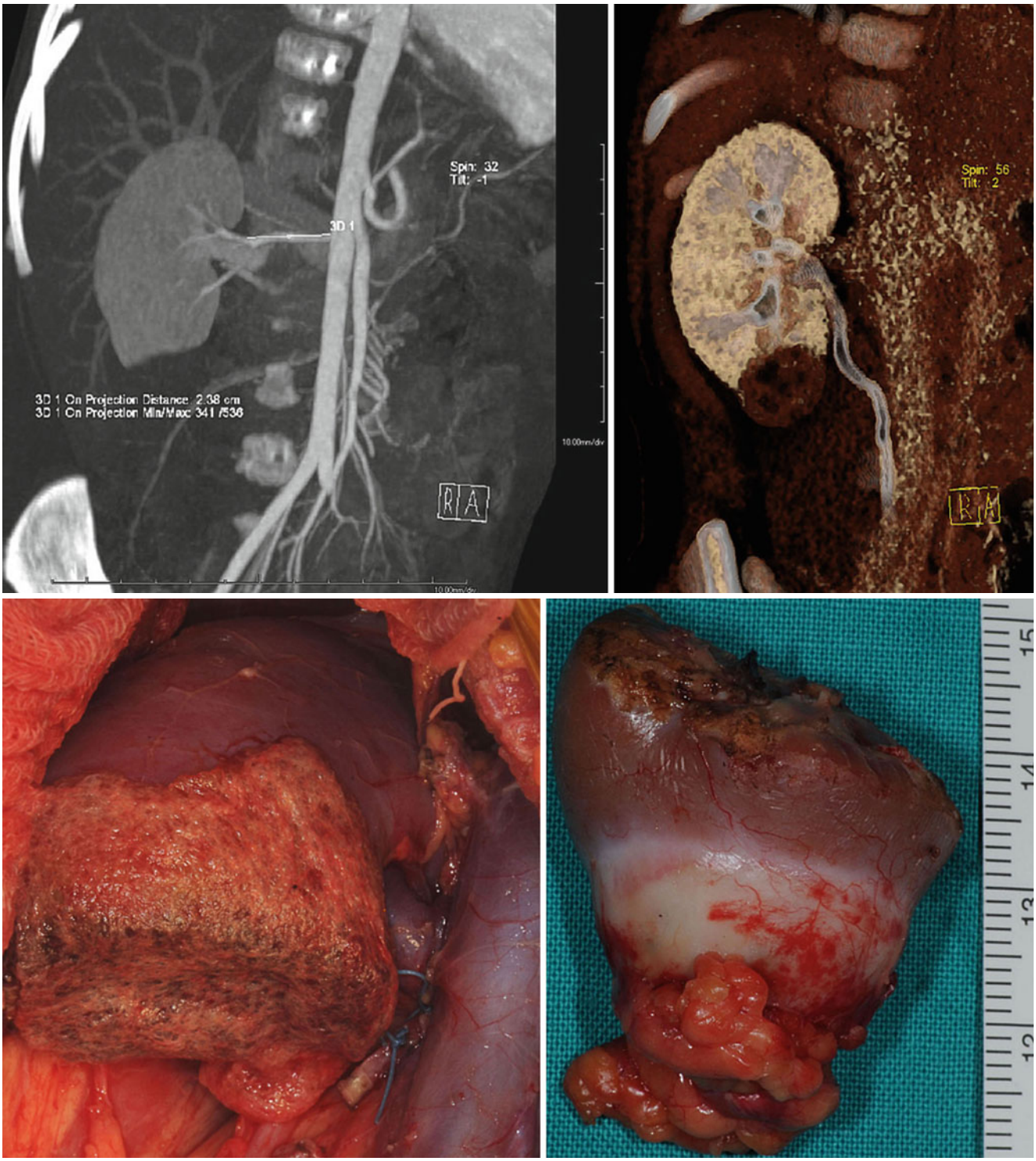

Fig. 13.1 Preoperative, 3-D helical CT coronal views of a small WT sited in the lower pole of the right kidney (*top row*). Intraoperative view of the kidney remnant after partial nephrectomy, and gross appearance of the resected specimen including 1 cm of normal parenchyma around the tumor (*bottom row*). The bloody surface of the kidney remnant was covered with a TachoSil® sponge to assure additional hemostasis

We then take biopsies of perirenal fat and regional lymph nodes, which are sent for multiple frozen sections to establish an intraoperative pathological staging. The affected kidney is walled off from the peritoneal cavity using moist laparotomy sponges to avoid dissemination in case of inadvertent spillage of the tumor. When NSS is performed using renal artery occlusion, intravenous mannitol and furosemide, given 5–10 min before vascular clamping, may prevent

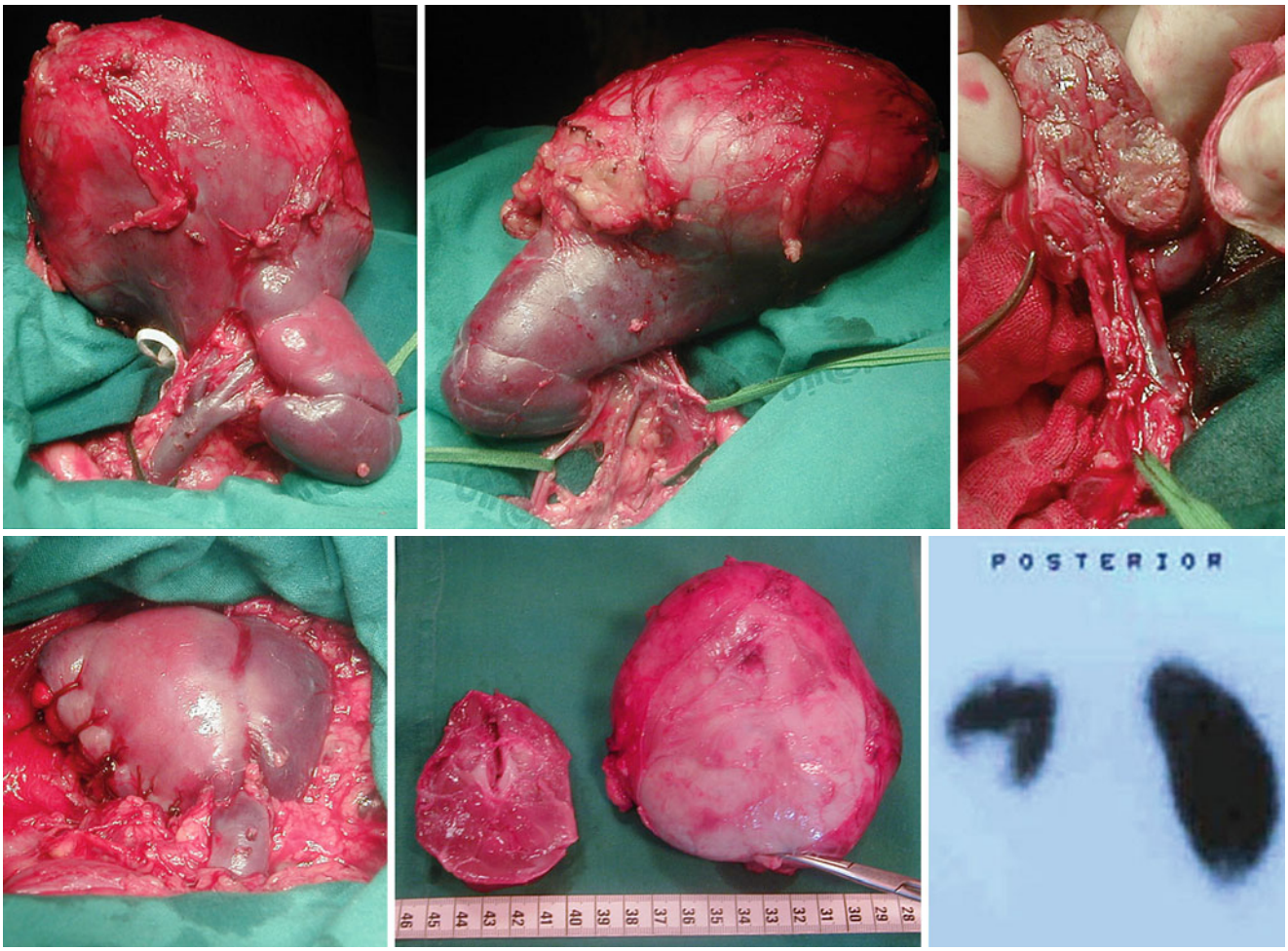

Fig. 13.2 Anterior and posterior intraoperative views of a large WT sited in the upper pole of the left kidney (*top row*). Note a clear groove demarcating the upper third from the lower two-thirds of the kidney. Hemostasis during partial nephrectomy was achieved by simple finger compression, without clamping of the vascular pedicle (*top row*). Intraoperative view of the kidney remnant showing a good blood supply, and gross appearance of the resected specimen with a satisfactory rim of negative resection margin, which included the upper pole calyx (*bottom row*). At 2 years' follow-up, the kidney remnant is well functioning with a 30 % split function on DMSA scan (*bottom row*)

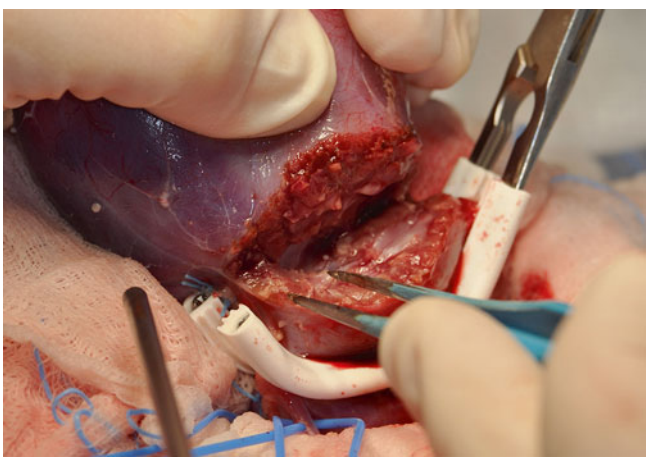

Fig. 13.3 Right partial nephrectomy performed with bipolar forceps. Note the bloodless field obtained by gentle compression of the remaining kidney using a Satinsky clamp with tips covered with rubber tubing

ischemic renal damage by decreasing intracellular edema and intrarenal resistance. Systemic or regional anticoagulation to prevent intrarenal vascular thrombosis does not appear to be necessary.

Current clinical data support a safe warm ischemia time limit of 30 min in patients with normal preoperative kidney function. To date, no scientifically rigorous clinical study has established a warm ischemia dose–response curve. Additionally, no algorithm exists to predict the risk of acute kidney injury and chronic kidney disease in patients undergoing transient warm ischemia [33]. If the warm ischemia time is anticipated to last longer than 30 min, alternatives to prolong the ischemia tolerance of the kidney include surface cooling and perfusion hypothermia. Surface cooling with ice slush affords at least 1 h of safe occlusion of renal artery, although there is some risk of renal cortical necrosis. Surface hypothermia is instituted immediately after vascular

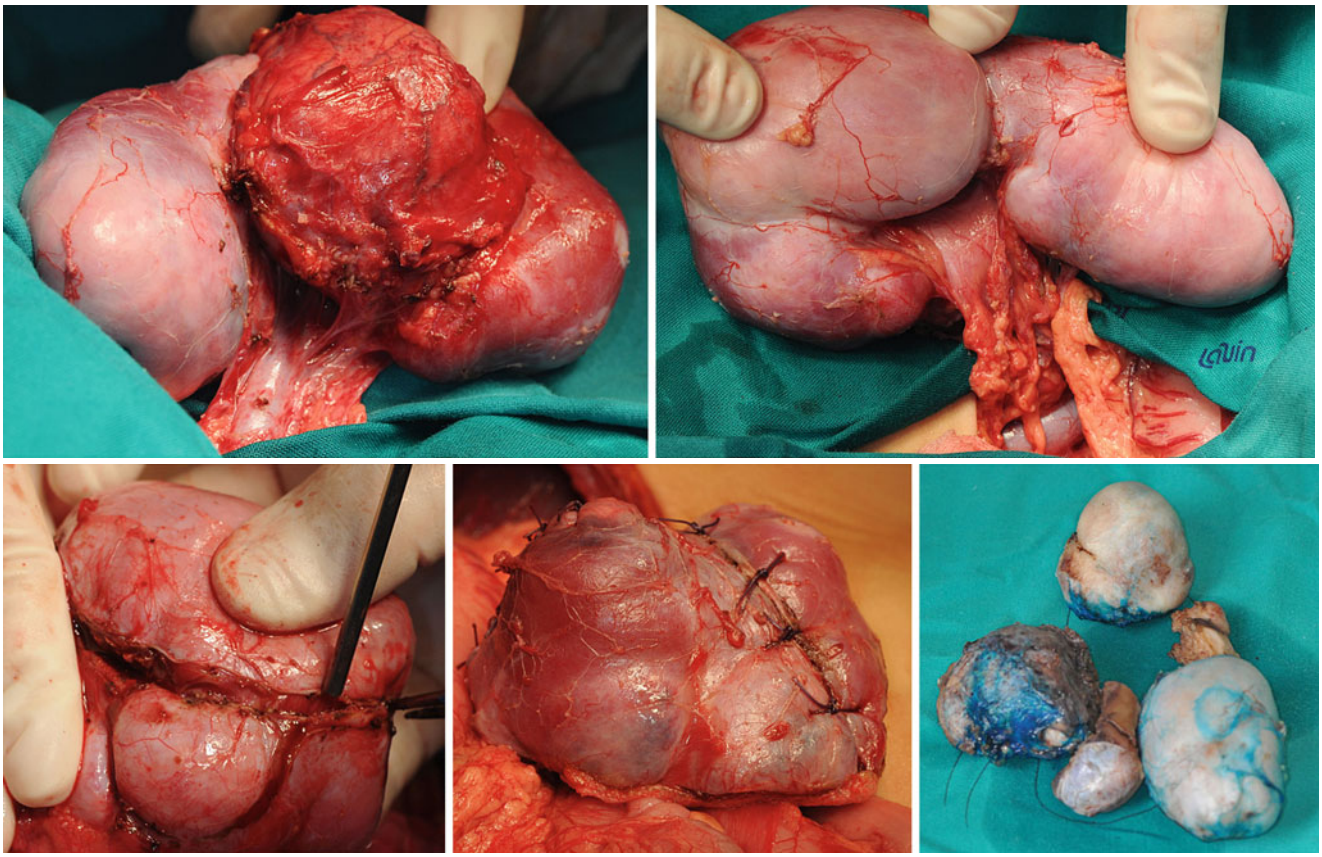

Fig. 13.4 Anterior and posterior intraoperative views of multiple tumors distorting the outline and invading the hilum of the left kidney in a patient with bWT (*top row*). To maximize preservation of normal renal parenchyma, multiple tumor enucleations were accomplished by circumferential incision of the renal capsule and blunt shelling out of the tumor along the plane of its pseudocapsule (*bottom row*). Re-approximation of the cut surface, so that the kidney retains a more reniform contour, and gross appearance of all the resected tumors (*bottom row*)

clamping and maintained for 10 min to decrease core temperature to 15–20 C before commencing tumor resection. Clamping and unclamping the artery should be avoided and may cause reperfusion injury. In situ cold perfusion with intracellular hyperosmolar solutions commonly used during organ transplantation represents another option to allow for a long period of renal ischemia in complex NSS procedures. Although advocators consider in situ perfusion a valid alternative to the rather invasive ex situ bench surgery with kidney autotransplantation, in children such technique has been reported only in a case with bWT [34]. Additionally, there is no evidence that in situ cold perfusion allows for a longer interval of renal protection than the ice slush cooling technique. Finally, the required arteriotomy and venotomy for continuous perfusion portent the risk of renal artery thrombosis, and tumor spillage from the renal vein.

In our technique, hemostasis during NSS is controlled by compression on the renal parenchyma, exerted either manually or using a large vascular clamp (Fig. 13.3). The renal vascular pedicle is encircled with a vessel loop to provide rapid access and clamping of the blood supply, if needed. Generally, the capsule of the kidney is circumferentially scored with an electrocautery to outline the planned extent of resection. If a tumor feeding vessel exists, its preliminary ligation allows for easier demarcation of the resection line and the normal-appearing parenchyma, of which 0.5–1 cm margin around the tumor should be included in the resected specimen. Frozen sections of the tumor base are obtained to confirm a negative margin and to evaluate the histology. Small bleeding is controlled using bipolar forceps or an argon beam device, whereas larger vessels are suture-ligated using fine non-absorbable suture material. The collecting system, if entered, is also closed with fine non-absorbable suture. A watertight closure of the collecting system is essential to prevent urinary fistula formation.

Indeed, bleeding control and repair of the collecting system remain the two most significant challenges facing the surgeon during NSS. In the past decades, a wide variety of new surgical devices for dissection and hemostasis has been developed, along with a dizzying array of hemostatic agents and sealants to assist with hemostasis of the transected renal surface and promote optimal wound healing [35–37]. Current indications for the use and choice of such hemostatic agents are driven mostly by surgeon preference. We have recently

used TachoSil®, that is an absorbable collagen sponge coated with human fibrinogen and thrombin [38]. The sponge is held against the renal parenchyma with a gentle pressure using a moist pad. Upon contact with blood or other fluids, TachoSil® mimics the last step of the clotting cascade producing a fibrin clot in 3–5 min. We found that TachoSil® is an effective and ready-to-use alternative to conventional techniques currently used to control mild to moderate bleeding. Additionally, another attractive promise of this agent is its sealing property, which may represent a valid support against urinary leakage when the collecting system is entered [39]. Other commonly used hemostatic products are based on oxidized regenerated methylcellulose, which are rolled up to form a surgical bolster. The letter is secured into the tumor bed by sutures, and allows for both hemostasis and re-approximation of the kidney remnant. We do not routinely place urinary stent or surgical drain. However, if a major reconstruction is anticipated, the placement of a double-J ureteral stent and a Jackson-Pratt drain in the perinephric space for 5–7 days seems wise. The operation is completed by careful reapproximation of the Gerota's fascia over the kidney remnant, to maintain tissue planes and simplify re-exploration, if needed.

Postoperative adverse events after NSS include urinary fistula, prolonged acute tubular necrosis, and hemorrhage. Urinary fistula is the most common renal related complication after NSS, and usually well responds to conservative management. We often documented a small fluid collection around the operated kidney, and found that all collections spontaneously resolved within 4 weeks of surgery. At times, a Foley catheter placement and/or insertion of a ureteral stent may be considered. If urinoma develops, percutaneous drainage may be necessary. Prolonged acute tubular necrosis with or without acute renal failure is the second most common complication after NSS, and such event is likely underreported. The primary etiology is ischemic renal injury and a decreased renal mass, although other causes of acute tubular necrosis/acute renal failure must be considered, including pre-renal and post-renal causes. Operative considerations to help avoid acute tubular necrosis/acute renal failure include vigorous hydration, the administration of mannitol to promote a brisk intraoperative diuresis, and a short warm ischemia time. Notably, we did not encountered such complication, and hypothesized that our technique of bleeding control by using compression of the renal parenchyma is likely less physiologically disruptive than hilar vascular clamping or cooling.

Bleeding after NSS may be acute or delayed, and occasionally requires re-exploration. Careful intraoperative attention to hemostasis and precise reconstruction of the kidney remnant is mandatory to avoid this and other complications.

Postoperative follow-up after NSS involves a baseline ultrasonography obtained within the first 2 weeks of surgery. The investigation is then repeated monthly during the first postoperative year, along with a chest X-ray every 3 months, and an CT every 6 months [19]. 99mTechnetium dimercaptosuccinic acid (DMSA) renal scintigraphy for the quantification of the differential function of each kidney may be performed after 1 year of surgery. Yearly blood and urine tests are carried out, including the calculation of the estimated glomerular filtration rate.

Influence of Surgical Approach on Renal Function of Children with Unilateral Renal Tumor: A Personal Perspective

Cross-sectional renal function studies suggest that children undergoing nephrectomy for a variety of oncological and non-oncological indications present a post-operative compensatory increase in glomerular filtration rate (GFR) at approximately 90 ml/min/1.73 m^2, that is 75 % of the GFR of subjects with two healthy kidneys [40, 41]. The reduced GFR remains stable up to the age of 30 years and then starts to decline at a rate of 1.5 ml/min/1.73 m^2/year, that is a rate of decline which allows to prevent renal failure for another 50 years [41]. Based on these data and on the increased potential for local recurrence, NSS is not recommended in children with uWT who are not at risk to develop a tumor in the contralateral kidney.

This well accepted concept has been challenged by two consecutive studies of renal function after RN or NSS in the same cohort of children with unilateral renal tumor at a mean follow-up of 6 and 12 years, respectively [42, 43]. To compare the results of these two studies, as a surrogate of renal function, we used the estimated glomerular filtration rate (eGFR) which is a better marker compared to serum creatinine standard deviation scores. The novel and surprising finding was that about 50 % of 25 children with unilateral renal tumor presented before surgery a mild renal dysfunction, defined as a GFR between 60 and 89 ml/min/1.73 m^2. Accordingly, the mean ± SD estimated GFR (eGFR) at diagnosis, taken as control value before surgery, was 78.2 ± 24.1 ml/min/1.73 m^2 for 15 children undergoing RN, and 88.7 ± 26.7 ml/min/1.73 m^2 for 10 children undergoing NSS (Fig. 13.5). Before surgery this difference was not statistically significant ($p = 0.32$). After surgery the 10 children undergoing NSS presented a satisfactory post-operative increase in mean eGFR up to 106.2 ± 24.1 ml/min/1.73 m^2 at the second study; and only one patient presented a mild dysfunction after a bilateral NSS for a metachronous WT. Conversely, the 15 children undergoing RN presented an inadequate post-operative increase in mean eGFR up to 88.6 ± 13.5 ml/min/1.73 m^2 at the second study (Fig. 13.5). The mean eGFR of patients undergoing NSS was significantly higher than that of patients undergoing nephrectomy at first and second study (Fig. 13.5).

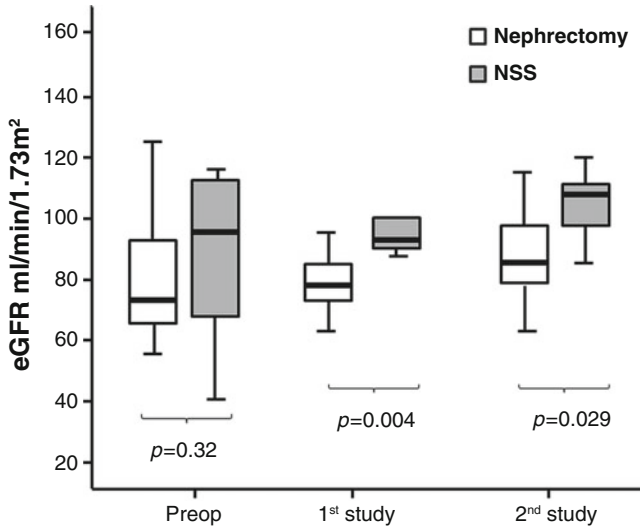

Fig. 13.5 Estimated GFR at 1st and 2nd study in 15 children undergoing nephrectomy and ten children undergoing NSS. *Box plots* indicate the upper and lower quartiles and ranges; the near *bar* is the median

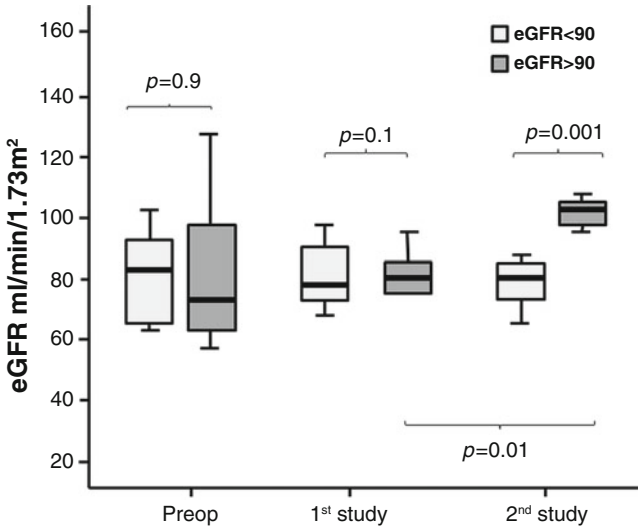

Fig. 13.6 Estimated GFR at 1st and 2nd study in 8 and 7 nephrectomized patients with or without renal dysfunction, respectively

The significant difference between the two groups at second study was mainly due to the presence of eight children, who after nephrectomy presented a mild renal dysfunction as a result of a negligible increase in eGFR, probably due to a reduced nephron endowment (Fig. 13.6). The other seven children presented after the first study a significant increase in mean eGFR up to values similar to those of subjects with two healthy kidneys (Fig. 13.6).

Until recently, the main focus of ablative renal surgery has been to prevent the need for renal replacement therapy. However, during the last decade several population studies have emphasized that also mild renal dysfunctions should be regarded as an independent risk factor for late morbidity and mortality. A recent meta-analysis, by using a novel method to summarize the published results, has come to the conclusion that an eGFR <90 ml/min/1.73 m^2 is associated with 5 % increased risk of both major vascular events and death in patients aged 20–39 years, and with 20–30 % increased risk in patients aged 70 years [44]. Therefore, the conclusion of our second study was that preservation of renal function, if associated with oncological safety, should impact the management of children with unilateral renal tumor, especially those with a reduced renal function reserve capacity [43].

Main limitations of our two studies on renal function in children with unilateral renal tumors include a small sample size and a relatively short follow-up. Therefore, we recently made a cross-sectional and longitudinal study of renal function in 60 children treated by nephrectomy and 12 treated by NSS during the last 50 years at our institution [45]. Table 13.1 shows the results of the cross-sectional study. Of 12 children undergoing NSS, only one, who underwent a bilateral NSS, presented a mild renal dysfunction. Conversely, nephrectomized patients presented 43 % of mild renal dysfunctions up to the third decade of life, and 78 % of mild-to-moderate renal dysfunctions between the fourth and sixth decade of life. The increasing onset of new renal dysfunctions with aging was statistically significant (p = 0.02) [45].

The longitudinal renal function study confirmed that of 50 children with available eGFR at the diagnosis, 30 (59 %) had a pre-existing mild dysfunction. In addition, the longitudinal study of renal function confirmed the progressive renal function decline after the third decade of life, associated with new onset of renal dysfunctions in about 80 % of the patients during the fifth decade after nephrectomy. As a 50-year-old patient nephrectomized during childhood for a renal tumor can expect to live another three decades, it seems reasonable to speculate that many patients will experience a moderate-to-severe renal dysfunction. These observations in children with unilateral renal tumor parallel those in large series of adults with renal carcinoma. More than half of the adult population with unilateral renal carcinoma presents a pre-existing mild renal dysfunction; in addition, 20–25 % of these patients present a moderate renal dysfunction, defined as eGFR between 30 and 59 ml/min/1.73 m^2 [46–48]. It is not yet established if the pre-existing dysfunctions are the result of pre-existing co-morbidities which may increase the risk of kidney cancer, or if the dysfunctions are caused by the tumor itself [49]. In children, the absence of renal function loss following nephrectomy and the increase in renal function following NSS suggest that renal tumor can cause a renal function loss.

About 65 % of adults with a renal cortical tumor develop a new moderate renal dysfunction after nephrectomy, whereas only about 20 % of these patients develop a new moderate renal dysfunction after NSS (p = 0.0001). Therefore, in adults

Table 13.1 Estimated GFR in 12 patients with an age between 2 and 25 years treated by NSS (Group A), 42 nephrectomized patients with an age between 2 and 29 years (Group B), and 18 nephrectomized patients with an age between 33 and 51 years (Group C)

eGFR	Group A	Group B	Group C
ml/min/1.73 m^2	N° 12 (%)	N° 42 (%)	N° 18 (%)
>90	11 (92)	24 (57)[a]	4 (22)[b]
60–89	1 (8)	18 (43)	11 (61)
<59	–	–	3 (17)

[a]Group A *vs* Group B: p = 0.03

[b]Group B *vs* Group C: p = 0.02

with small renal cortical tumors nephrectomy should not be considered as the treatment of choice [47].

Based on these data, the concept that in children with unilateral kidney tumor the renal function after nephrectomy is well preserved in long-term follow-up should be revised. Even kidney donors, who are carefully screened for renal dysfunctions and other medical co-morbidities, are at increased long-term risk for end-stage renal disease, cardiovascular, and all-cause mortality [50].

Treatment options that provide equivalentt medical oncological results associated with a better preservation of renal function are desirable also for children with unilateral renal tumor not at risk of developing a contralateral renal tumor.

Conclusions

The future of NSS is currently evolving, and enthusiasm has been stimulated by several trends, including advances in renal imaging, improved surgical techniques and methods to prevent ischemic renal injury, better postoperative management, such as renal replacement therapy, and long-term prospective cancer-free survival data.

In 1950, Vermooten laid the foundation for modern NSS for renal neoplasms in adulthood. He stated "There are certain instances, when, for the patient's well being, it is unwise to do a nephrectomy, even in the presence of a malignant growth involving the kidney. The question is, whether such a procedure is ever justifiable when the opposite kidney is normal. I am inclined to think that in certain circumstances it may be." [51]. Partial nephrectomy has now become a standard surgical approach in adults, accounting for almost half of all operations for kidney tumors. There is every reason to believe that a similar scenario may well unfold in the pediatric population, provided there are practitioners willing to initiate these clinical studies. The increasing evidence that global renal function is better preserved with 2 rather than only 1 kidney will certainly lead to a more aggressive nephron-sparing surgical approach, not only in children with synchronous bWT. With further experience, the role of NSS for select patients with unilateral WT and normal opposite kidney will increase in scope and application. Small tumors, which are more and more diagnosed on imaging studies, should be certainly treated with a renal sparing approach. Also larger tumors at presentation may be amenable to NSS, because significant reduction in tumor burden may be expected using preoperative chemotherapy. Therefore, preoperative chemotherapy represents a fundamental prerequisite to increase the number of patients with uWT undergoing NSS. Since compelling data are now available that the risk of clinically relevant renal dysfunction in uWT and normal contralateral kidney is significantly higher than what has been previously believed [42, 43], a renal sparing surgical approach should not be considered investigational any longer.

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Neuroblastoma and Other Adrenal Tumors

14

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Abbreviations

3F8	A murine IgG3 monoclonal antibody that binds to GD2
ACTH	Adrenocorticotropic hormone
ALK	Anaplastic lymphoma kinase
BDNF	Brain-derived neurotrophic factor
CCG	Children's Cancer Group
COG	Children's Oncology Group
CT	Computed tomography
CYP	Cytochrome P
DHEA	dehydroepiandrosterone
FISH	Fluorescence in situ hybridization
GCSF	Granulocyte colony stimulating factor
GD2	Disialyl ganglioside 2
GDNF	Glial cell line-derived neurotrophic factor
HVA	Homovanillic acid
IL-2	Interleukin 2
INPC	International Neuroblastoma Pathology Committee
INSS	International Neuroblastoma Staging System
IV	intravenous
LDH	Lactate dehydrogenase
LOH	Loss of heterozygosity
MEN	Multiple endocrine neoplasia
MIBG	Metaiodobenzylguanidine
MRI	Magnetic resonance imaging
NF1	Neurofibromatosis type I
NGF	Nerve growth factor
N-MYC	Myelocytomatosis viral related oncogene neuroblastoma derived
PCR	Polymerase chain reaction
PNET	Primitive neuro-ectodermal tumor
RET	"rearranged during transfection"
TNM	Tumor-node-metastasis
TRK-NGF	Tyrosine kinase receptor-nerve growth factor
TRKS	Tyrosine kinase family of receptors
VEGF	Vascular endothelial growth factor
VMA	Vanillylmandelic acid

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Adrenal Tumors

This chapter addresses the medical presentation and surgical management of malignant adrenal disease. Neuroblastoma is the most common adrenal neoplasm in the pediatric population, accounting for 97 % of adrenal neoplasms in children less than 15 months old. It is 50 times more common than pheochromocytoma, the next most common tumor. The good prognosis associated with early-stage, biologically favorable disease, with a survival rate of more than 90 %, stands in dramatic contradistinction to the poor prognosis associated with metastatic or biologically unfavorable presentations. Other adrenal neoplasms are very rare: malignant adrenocortical disease accounts for less than 0.2 % of all pediatric tumors and only 6 % of adrenal tumors.

Embryology

The adrenal gland is composed of two endocrine tissues of differing embryonic origin, the medulla and the cortex. The adrenal cortex is formed from cells of the mesoderm while the adrenal medulla develops from neural crest cells. The adrenal cortex may be divided into three zones: (1) the zona glomerulosa, the outermost zone of the cortex responsible for the synthesis of aldosterone; (2) the zona fasciculata, the largest of the zones of the cortex, the cells of which produce cortisol; and (3) the zona reticularis, the innermost and smallest of the zones and the producer of adrenal androgens. The adrenal medulla is comprised of neuroendocrine (chromaffin) and glial cells.

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Development of the adrenal gland begins at 3–4 weeks of gestation, just cephalad to the developing mesonephros. During the following 2–3 weeks, cells of the adrenal cortex and steroidogenic gonadal cells will differentiate from a common precursor. The gonadal cells will begin their caudal migration, while the cells that ultimately form the zona reticularis migrate dorsally into the retroperitoneum. Over the next several weeks, the inner cortex enlarges rapidly to form the fetal zone (the outer subcapsular rim remains as the definitive zone). At the same time, neural crest cells formed from ventrolateral migration of neuro-ectodermal cells of the neural tube give rise to sensory ganglia of cranial and spinal nerves and migrate along the neuraxis to form the sympathetic ganglia. By the seventh week of gestation, neural crest cells from sympathetic ganglia follow tropic signals to populate the medial side of the developing medulla. These cells will make and store catecholamines. Throughout gestation, the fetal cortex will continue to differentiate. By 1 year of age, the final architecture of the adrenal gland is present, with 3 layers of adrenal cortex surrounding the mature cells of the adrenal medulla [1].

During embryogenesis, primordial adrenal cells may migrate caudally with other cells of the gonadal ridge. This migration accounts for the presence of accessory adrenal tissue in the retroperitoneum along the course of descent of the ovaries and testes.

Neuroblastoma

History

Perhaps the earliest description of neuroblastoma was penned in 1864 by the famous pathologist Rodolf Virchow, who described it as an abdominal glioma [2]. In 1901, William Pepper published findings from a series of infants with hepatic metastatic disease from an adrenal primary tumor without bony metastasis, providing an accurate description of 4S disease [3, 4]. Six years later, Robert Hutchison reported a series of children with adrenal tumors and orbital and skull metastases, representing what is contemporarily recognized as Stage 4 disease [3, 5]. Dr. James Wright in 1910 was the first to use the term "neuroblastoma" to describe an adrenal tumor of primitive neural cell origin organized into rosettes identical to fetal adrenal tissue [6]. The phenomenon of tumor maturation and differentiation, another significant component of the infantile presentation of neuroblastoma, was reported by Cushing and Wolbach in 1927 [7].

Gross recognized that surgical resection alone was curative in most cases of small tumors isolated to the adrenal, but was insufficient for larger tumors or metastatic disease [8]. In the 1950s and 1960s, pioneering treatments at Boston Children's Hospital in radiotherapy by Martin H. (Dick) Wittenborg and in chemotherapy by Sidney Farber improved survival over surgical resection alone [8, 9]. Nonetheless, certain subsets of patients with neuroblastoma continued to experience a high mortality despite aggressive multimodality treatment. Over the past three decades, this observation has led to efforts to profile a tumor's behavior, based upon histologic and biologic risk factors, and to develop treatment algorithms based upon these risk factors. Today, most children under 1 year of age or with low- or intermediate-risk tumors continue to have a good prognosis with successful treatments, but over 40 % of patients will present with metastatic disease. Of those with metastatic disease, fewer than half will survive more than 5 years [10].

Incidence

Neuroblastoma is the most common extracranial solid tumor of childhood. Approximately 650 children are diagnosed each year, constituting an annual incidence of 9.5 per million children. This represents 8 % of all pediatric solid tumors; however, neuroblastoma causes 15 % of solid tumor-related deaths. Although the median age at diagnosis is 2 years, approximately 40 % of neuroblastoma cases are diagnosed in the first year of life, making it the most common cancer of infancy (children <1 year), with an incidence rate approximately double that of leukemia. Sixteen percent of infant neuroblastomas are diagnosed during the first month of life and 41 % are found by 3 months of age [11]. These numbers appear to be stable to slightly increasing over a 21-year observation period.

Risk Factors

There have been many reports of environmental factors and/or medical conditions associated with the development of neuroblastoma. Most of these studies do not have enough statistical power or data collection to establish a definitive link. A few reports have demonstrated a dose–response relationship with maternal alcohol consumption [12, 13]. Paternal exposures to such occupational hazards as pesticides and electromagnetic fields have also been implicated [14, 15]. Maternal use of recreational drugs, as well as amphetamines, phenytoin for seizures, diuretics, or treatments for vaginal infections, have been associated with increased risk [12, 13, 16]. Use of sex hormones and fertility drugs, however, has been only superficially linked with the development of neuroblastoma, as have intrapartum maternal anemia, maternal hypertension, neonatal respiratory distress, and 1-min Apgar score less than 7 [17, 18]. In infants diagnosed with neuroblastoma at younger than 6 months, neuroblastoma was associated with a high birth weight,

increased maternal weight gain, maternal hypertension, advanced maternal age, and respiratory distress [19]. These associations were not found in older infants and children diagnosed with neuroblastoma. At least one study has reported an inverse relationship between the duration of breastfeeding and the development of neuroblastoma [20]. Folic acid, long known to protect against neural tube defects, has also been linked in one Canadian study to a 60 % reduction in incidence rates of neuroblastoma after folic acid fortification of flour was initiated [21]. All of these studies lack sufficient patient populations and/or statistical power to unequivocally link these factors to an increased risk of neuroblastoma. This does not preclude a possible role of environmental factors, but to date no strong environmental exposure or factor has been identified.

Associated Syndromes and Heredity

The vast majority of cases of neuroblastoma are sporadic without clear genetic precedent. About 1–2 % of diagnosed children have a history of another family member with neuroblastoma. The appearance of neuroblastoma in monozygotic twins has been rarely reported [22]. It has been speculated that this coexistence represents twin–twin placental metastasis rather than a genetic syndrome [23, 24]. It should be emphasized to parents that siblings and future offspring are only at minimal risk for future development of disease [22].

Neuroblastoma is most often an isolated diagnosis; however, it more rarely occurs in association with other neurocristopathies, such as Hirschsprung disease, central hypoventilation syndrome (Ondine's curse), neurofibromatosis (von Recklinghausen disease), and hypomelanosis of Ito [25–28]. It is also one of several tumors of infancy (also including Wilms, hepatoblastoma, and adrenal corticocarcinoma) associated with overgrowth syndromes and hemihypertrophy.

Clinical Presentation

Tumor symptoms are variable and depend on the age of the patient at diagnosis, the site of origin, and the presence of metastatic involvement. Most neuroblastomas are found in children less than 1 year of age. Cases of perinatal neuroblastoma can be seen on fetal ultrasound by about 33 weeks of gestation [29]. Sixty-five percent of neuroblastomas (90 % of those diagnosed during the first month of life) originate within the abdomen in the adrenal gland [29]. The organ of Zuckerkandl in the pelvis near the aortic bifurcation is the second most common location for tumors of abdominal origin. Outside the abdomen, thoracic and cervical paraspinal tumors are the next most common locations of origin. Symptoms vary with location of the primary mass.

An abdominal primary can present with abdominal pain, increasing abdominal girth/distention or changes in bowel or dietary habits. Patients with severe distention may even present with respiratory distress secondary to massive liver involvement, impaired diaphragm movement, and abdominal cavity volume loss (Fig. 14.1). Tumors arising within the organ of Zuckerkandl may involve the small bowel and/or the bladder, resulting in dysfunction and possible urinary or gastrointestinal obstruction [30]. Paraspinal tumor can invade neural foramina and/or nerve plexus, resulting in paresthesias and possible paralysis. Dural involvement can cause spinal cord compression, requiring emergent steroid and chemotherapy treatments.

Multifocal neuroblastoma is rare and usually presents in infants, for whom the prognosis is surprisingly good [31]. As noted above, fetal neuroblastomas are frequently noted as incidental findings on ultrasound, but there can be associated maternal signs and symptoms correlating with disease. Signs of catecholamine excess, such as excessive sweating,

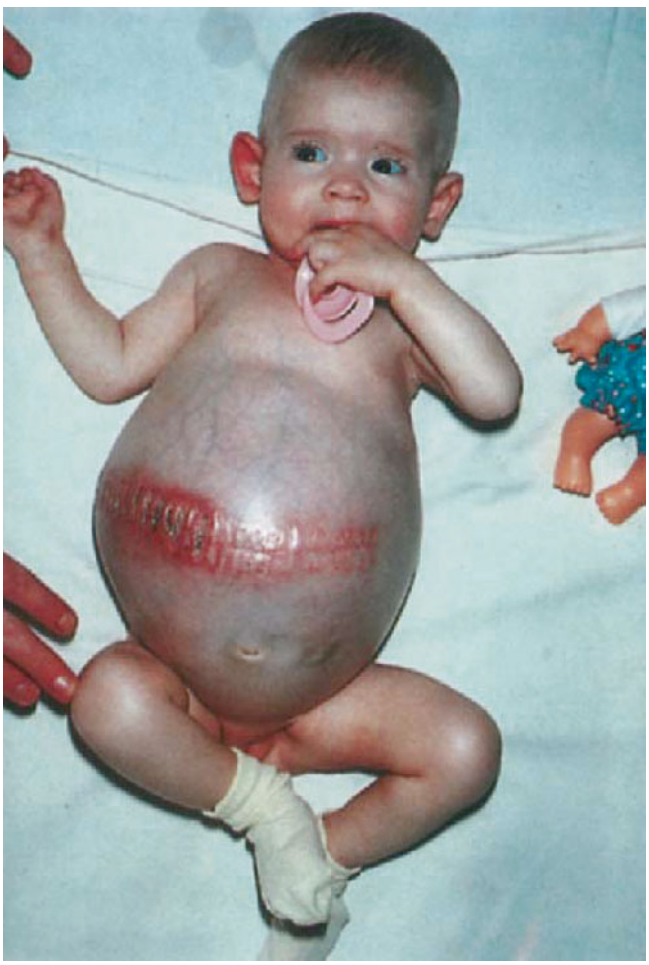

Fig. 14.1 Marked abdominal distention from Stage 4S neuroblastoma

headaches, flushing, or anxiety, may be seen in the mother, although no study has examined the presence of urine catecholamines to supplement diagnosis [32, 33]. Pre-eclampsia has been associated with widely disseminated fetal neuroblastoma. Large tumor size or metastatic involvement of the placenta is associated with the development of fetal hydrops [29, 31, 33]. Treatment algorithms involve serial ultrasounds for stable pregnancies to tocolytics and steroids in cases of pre-eclampsia and fetal hydrops [33].

In neuroblastoma presenting postnatally, metastatic disease infiltrating bone and bone marrow may result in a presentation of generalized bone pain and limping. Marrow involvement can lead to anemia, leukopenia, and thrombocytosis with resultant weakness, infection, and abnormal bleeding or bruising [30]. Patients with Stage 4S disease characteristically present with nontender subcutaneous nodules that have a purple/blue or gray color to them ("blueberry muffin" nodules). These represent metastatic deposits of neuroblastoma cells. Spread of metastases to the periorbital and retrobulbar areas of the eyes may present with the appearance of "raccoon eyes" and give the impression of facial trauma to the child (Fig. 14.2).

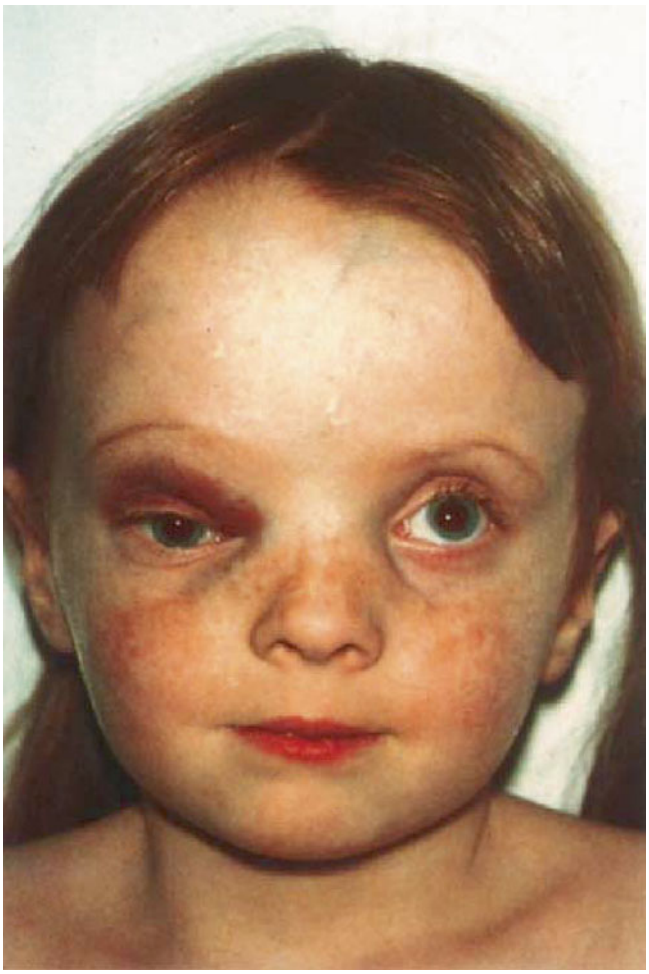

Fig. 14.2 "Raccoon eyes" caused by retrobulbar and periorbital metastasis

Diagnostic Workup

As with all medical conditions, the evaluation of suspected neuroblastoma should commence with a detailed history and physical examination, including a thorough assessment of the primary tumor site, evaluation of palpable lymph node basins, and a complete neurologic examination to rule out spinal cord or nerve root involvement. In addition to basic laboratory investigations including serum electrolytes, complete blood count, and coagulation studies, serum lactate dehydrogenase (LDH) and ferritin should be obtained. Elevated levels of serum LDH >1,000 U/L and ferritin levels >142 ng/mL have been associated with adverse outcomes of disease, most likely representing increased tumor burden [34]. Additional markers that are commonly elevated in neuroblastoma include neuron-specific enolase, chromogranin A, synaptophysin, tyrosine hydroxylase, protein gene product 9.5, ganglioside GD2, and NB84; however, these are not commonly included as part of the initial workup.

The accurate diagnosis of neuroblastoma requires a pathologist familiar with these tumors as well as other small, round, blue-cell tumors such as lymphomas, neuroectodermal tumors, and rhabdomyosarcoma. The minimum international criteria for the establishment of diagnosis is either a tissue biopsy with histologic confirmation or the presence of unequivocal tumor cells within a bone marrow biopsy/aspirate *and* increased levels of urinary catecholamine metabolites [35]. Immunohistochemistry and genetic analysis of biopsied tissue have become increasingly important additional procedures that are performed at diagnosis, as discussed earlier in this chapter. Elevations of urinary catecholamines are evident in 90–95 % of all neuroblastomas. The two most common metabolites present are vanillylmandelic acid (VMA) and homovanillic acid (HVA), which are metabolites of dopamine and norepinephrine, respectively [30]. Levels of these metabolites are age-specific and can be altered with renal function impairment or excessive dietary intake of amine-rich foods, such as bananas, in infants [36]. A number of initiatives have been undertaken internationally to conduct mass screening of VMA and HVA levels in the pediatric population to detect neuroblastoma [37–40]. These efforts have resulted in increases in the measured incidence of neuroblastoma, especially among the perinatal and infant populations, but there have been no reductions in overall mortality [37, 41, 42], nor any reduction in the incidence of advanced-stage disease within the countries that have performed screening [38]. As a result, mass population screening for neuroblastoma has proven to be neither cost-effective

nor useful in lowering mortality from advanced disease and is not recommended.

Metastatic disease is present at the time of diagnosis in greater than 50 % of patients with neuroblastoma. Therefore, bilateral bone marrow aspirates and/or biopsies must be performed in all newly diagnosed patients to determine the extent of disease. Imaging studies of the primary tumor site via computed tomography (CT) or magnetic resonance imaging (MRI) are valuable in establishing baseline measurements of tumor size, as well as detecting any metastatic disease within the chest or abdomen (Figs. 14.3 and 14.4). CT scans are the preferred method for evaluation of chest and abdominal tumors, while MRI has its greatest usefulness in the evaluation of paraspinal tumors. Metaiodobenzylguanidine (MIBG) scan or other bone scans are utilized with increasing frequency to screen for bony disease. MIBG scans use a radiolabeled isotope that is the structural homolog of norepinephrine to visualize regions with adrenergic activity, including neuroblastic tumors (Fig. 14.5). ^{123}I-labeled MIBG is more sensitive and specific for metastatic disease than ^{131}I-MIBG and has become part of the standard evaluation of new patients with neuroblastoma [43]. In addition, MIBG scans can be used

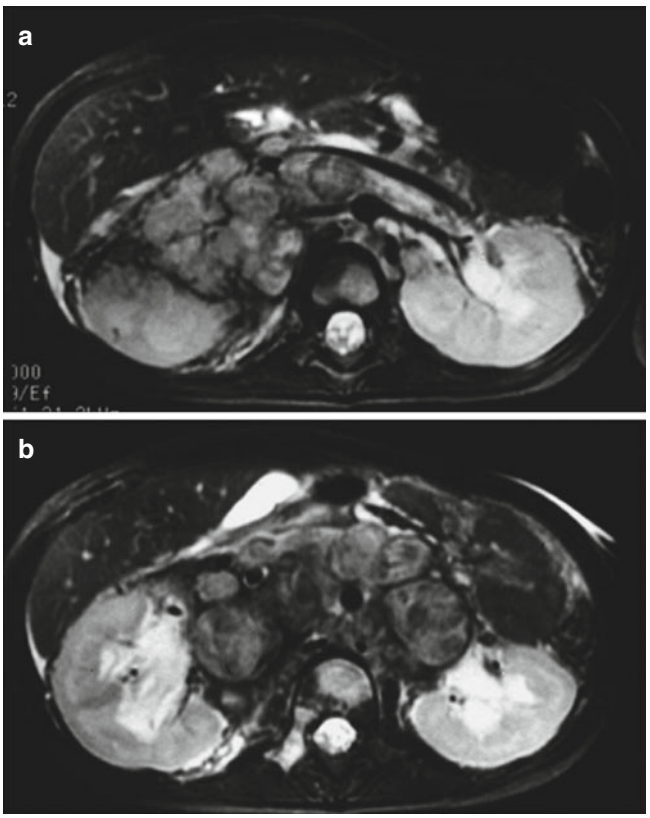

Fig. 14.3 (**a**, **b**) Axial weighted MRI demonstrating right adrenal mass with bulky, conglomerate adenopathy encasing the bilateral renal vessels and aorta. Bone marrow involvement is seen in the right posterior vertebral element and vertebral body

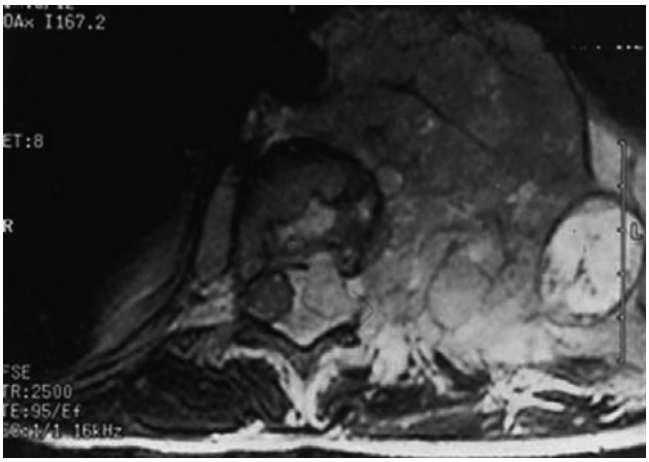

Fig. 14.4 Axial T2 weighted MRI demonstrates a displaced spinal cord with tumor extension through the neuroforamina. The aorta is also encased

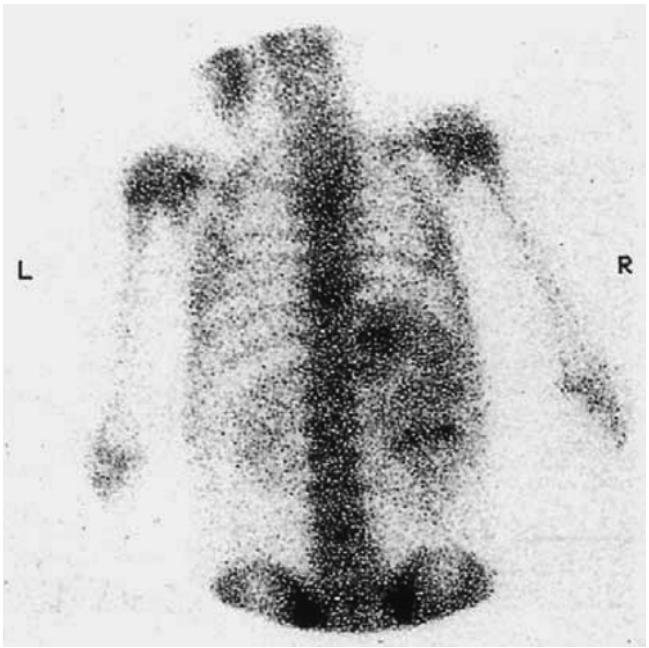

Fig. 14.5 MIBG scan demonstrating increased uptake within a left adrenal tumor

to evaluate the effectiveness of therapy in high-risk patients and may be able to detect residual bone marrow or cortical disease not otherwise visible with other imaging modalities [44]. Approximately 10–20 % of metastatic neuroblastoma is MIBG-negative. In these patients, a bone scan using technetium-99m (^{99m}Tc)-diphosphonate can be used to evaluate for osteolytic lesions. Additionally, there has been recent interest in the use of positron emission tomography (PET) scanning for the detection of non-MIBG avid disease and in the follow-up of high-risk patients after resection [45–47].

Histopathology

Histologic and molecular analysis of neuroblastoma cells has become an important factor in the evaluation of patients and in treatment planning. An open biopsy is usually recommended instead of fine needle biopsy to ensure that an adequate sample of tissue is obtained and to preserve histologic architecture. However, in some centers, multiple needle biopsies have provided adequate diagnostic tissue.

Histology

Histologically, neuroblastoma is composed of two principal cell populations: neuroblasts, which differentiate into neurons and glia, and Schwann cells, which form the supporting stroma. Neuroblasts are small, round blue cells with hyperchromatic nuclei and scant cytoplasm. Neuritic processes (neuropil) and neuroblasts may be organized into Homer-Wright pseudorosettes (Fig. 14.6a–c). Histologically, the tumor must be differentiated from other small, round blue-cell tumors, of which Ewing's sarcoma, primitive neuroectodermal tumors (PNET), lymphoma, and rhabdomyosarcoma are notable examples (Fig. 14.6d). Neuroblastomas stain positive for neural proteins and filaments.

Neuroblastoma represents the most malignant end of a spectrum of peripheral neuroblastic tumors that also includes ganglioneuroma and ganglioneuroblastoma. These tumors are distinguished by their degree of neuronal differentiation, which can range from fully differentiated, mature neurons to immature, undifferentiated neuroblasts (Fig. 14.6e). A single specimen may contain more than one degree of differentiation. In general, the amount of Schwannian stroma increases with differentiation. Patients with stroma-rich, differentiated tumors have a better prognosis than those with stroma-poor, undifferentiated tumors. A rare subtype of undifferentiated neuroblastoma has recently been identified and is characterized by larger-than-normal cells with sharply outlined nuclear membranes and 1–4 prominent nucleoli [48]. The cell enlargement and greater number of prominent nucleoli in neuroblastoma have been correlated with amplification of the *N-myc* oncogene [49] (Fig. 14.6f). Patients with such "large cell neuroblastoma," in contrast to those with traditional undifferentiated neuroblastoma, generally present with the disease at an older age and have a higher rate of metastatic disease and a much poorer outcome.

Of the various proposed histologic classification schemes, the Shimada index has become the most widely used and accepted. It categorizes neuroblastoma into favorable or unfavorable histology based on the age of the patient, the mitotic-karyorrhexis index (an aggregate count of the number of cells per high-powered field undergoing mitosis and nuclear degradation), the extent (rich versus poor) and pattern (nodular versus non-nodular) of the Schwannian stromal component, and the degree of cellular differentiation [50]. Numerous studies have shown that this classification correlates significantly with disease prognosis and outcome [34, 51–53]. Since 1994, the International Neuroblastoma Pathology Committee (INPC) has standardized the terminology and diagnostic criteria for peripheral neuroblastic tumors, adopting a modified Shimada classification system [50]. The INPC system for neuroblastic tumors includes four pathologic categories: neuroblastoma; ganglioneuroblastoma, intermixed; ganglioneuroblastoma, nodular; and ganglioneuroma. Tumors are then subclassified as either favorable or unfavorable with the goal of meaningful prognostication between groups.

Ganglioneuroma is a stroma-dominant tumor with two subtypes: maturing and mature. These subtypes are distinguished based on the degree of differentiation of the ganglion cells present within the tumor. Ganglioneuroblastoma is classified as intermixed or nodular. The intermixed tumors are Schwannian stroma-rich and feature incomplete neuronal maturation with foci of neuroblastic cells in varying degrees of differentiation. Nodular tumors contain macroscopic, hemorrhagic neuroblastomatous nodules that coincide with a background of ganglioneuroma or ganglioneuroblastoma, intermixed.

Neuroblastoma is defined as Schwannian stroma-poor and is categorized according to three specific subtypes: differentiating, poorly differentiated, and undifferentiated. Differentiating neuroblastoma contains neuroblasts with abundant neuropil and 5 % or more of the cells exhibiting differentiation. Poorly differentiated neuroblastoma contains neuroblastic cells with a background of neuropil. Undifferentiated neuroblastoma is a rare subtype containing undifferentiated neuroblastic cells; these tumors often require additional testing beyond histopathologic analysis to confirm the diagnosis.

Biologic Features

Scientific investigations of the unusual and variable biology of neuroblastoma have led to the development of numerous cellular and molecular assays to improve the accuracy of prognostication. Associations have been found between biologic features and disease aggressiveness, response to chemotherapy, survival, and relapse rates. Shimada classification, DNA index, deletions of genetic material on chromosomes 1p or11q, gain of 17q, and *N-myc* amplification have all been found to be independent prognostic variables in disease progression and outcome; of these, *N-myc* amplification has the greatest predictive value for relapse and disease-related mortality [34, 35, 54–56].

N-myc is an oncogene located on chromosome 2p that acts as a transcriptional regulator in the developing nervous system and plays a role in cell proliferation, growth, apopto-

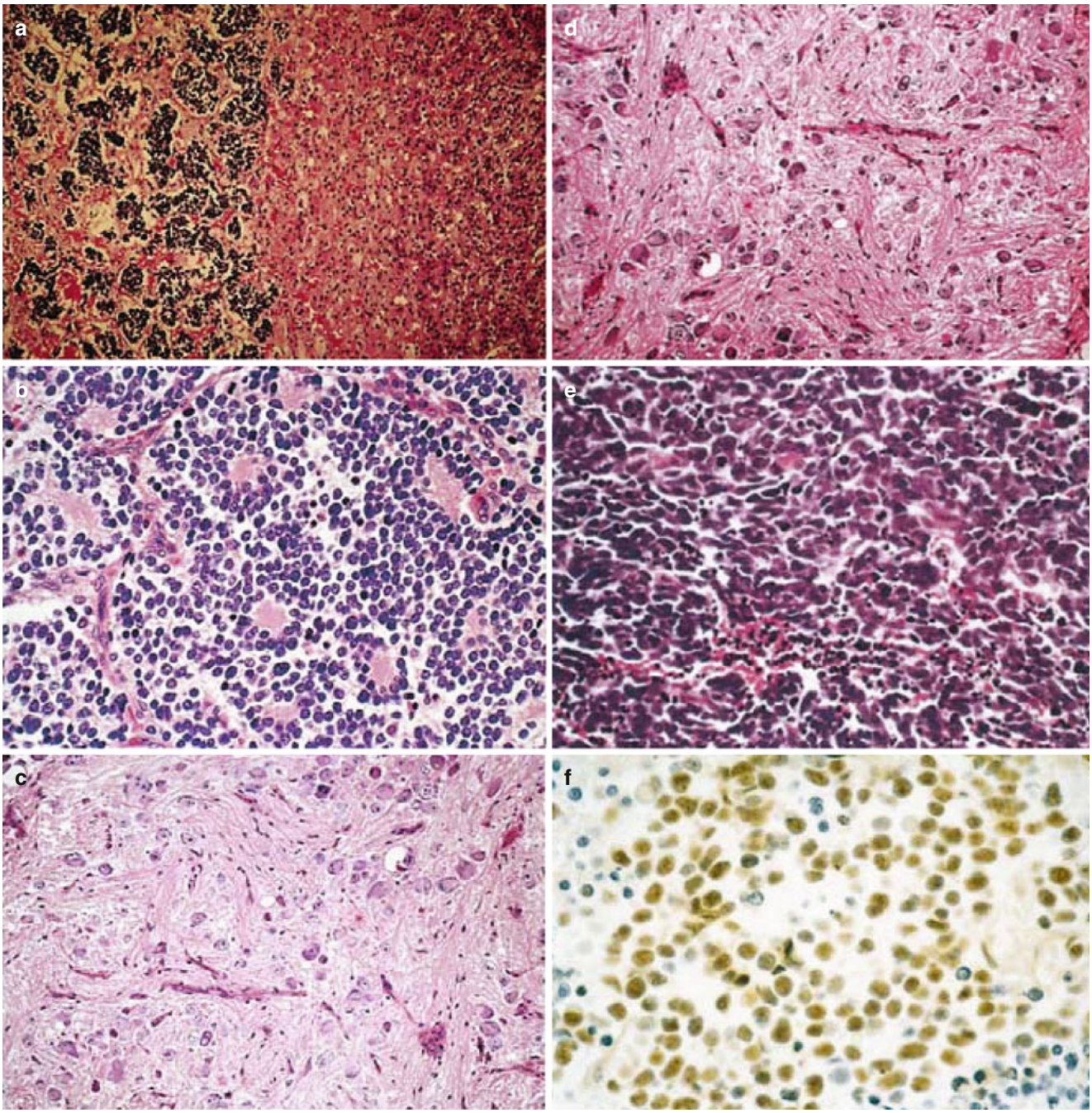

Fig. 14.6 (**a**) Neuroblastoma *in situ*. (**b**) Photomicrograph of neuroblastoma showing small uniform cells with dense, darkly staining nuclei, scant cytoplasm, and Homer-Wright pseudorosettes. (**c**) Photomicrograph of ganglioneuroblastoma showing islands of neuroblastoma cells surrounded by ganglioneuroma. (**d**) Photomicrograph of mature ganglion cells, Schwann cells, and neuropil. (**e**) Undifferentiated small round cell tumor. (**f**) N-*myc* stain of neuroblastoma

sis, and differentiation [57]. Overexpression of *N-myc* has been shown affect multiple pathways regulating cellular function including a direct tumorigenic effect via cooperation with the BMI1 and ALK oncogenes and activation of angiogenic pathways [58–62]. Amplification of the *myc* oncogene in both cultured cells and murine models induces malignant transformation, providing further evidence of a direct link of this gene with tumorigenesis [63]. Detection of amplification can be accomplished by a variety of techniques including polymerase chain reaction (PCR), Southern blot, fluorescent in situ hybridization (FISH), and immunohistochemistry (Fig. 14.7). Most centers and cooperative groups consider 10 or more copies of *N-myc* detected by FISH to be consistent with genomic amplification (Fig. 14.8). The

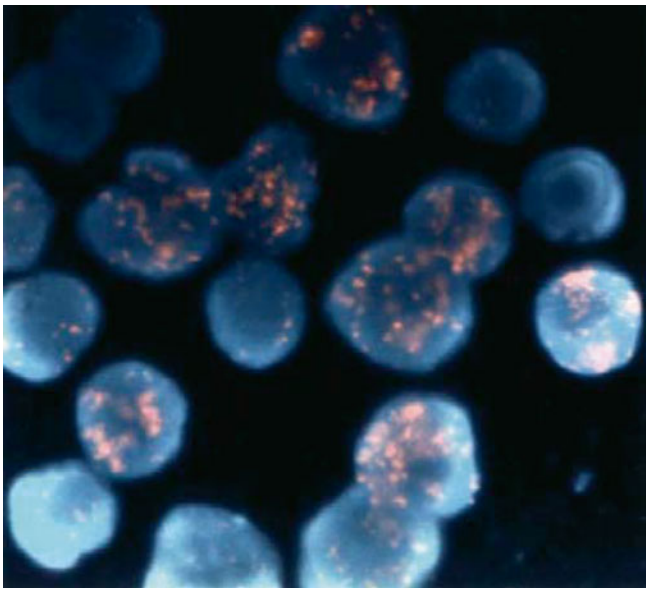

Fig. 14.7 Fluorescent *in situ* hybridization (FISH) showing N-*myc* amplification in tumor cells

excess number of *N-myc* genes usually leads to a higher level of expression of N-Myc protein, but it appears that the amplification itself rather than the overexpression is the predominant adverse factor [34, 64–66].

In approximately 30 % of neuroblastoma cases, *N-myc* amplification is present. Amplification is much more likely in advanced-stage (40–45 %) versus low-stage neuroblastoma (5–10 %). When present in low-stage disease, however, it may predict poorer survival and outcome. Overall, patients with *N-myc* amplification experience rapid disease progression, and 90 % will die of disease progression regardless of therapy provided.

The DNA index (DNA ploidy) has become an important indicator of disease responsiveness. The DNA index refers to the amount of DNA within the nucleus of the cell compared to expected amounts. This is usually measured via flow cytometry or cytogenetic analysis. Patients with hyperdiploid tumors (defined as DNA index >1, but not including tetraploid tumors, which appear to behave as diploid) have better response to chemotherapy, present with lower disease stage, and have an improved overall outcome [35, 67, 68]. This improvement in outcome is especially noted in the infant population [67]. Conversely, the opposite is true for diploid tumor specimens. Hyperdiploidy rarely occurs with *N-myc* amplification, but when it does, it appears that the effects of amplification outweigh the more favorable prognosis of the DNA hyperploidy [55].

Neurotrophin signaling pathways, which play a role in neuronal differentiation, growth, tropism, and apoptosis have also been implicated in the pathogenesis of neuroblastoma. The neurotrophin tyrosine kinase family of receptors (TRKS) is comprised of transmembrane proteins that induce cellular changes when bound by their ligands: NGF, BDNF, and GDNF. There are three subtypes of receptors found, TRK-A, TRK-B, and TRK-C. Expression of TRK-A on the cells of neuroblastoma has been found to correlate with a good prognosis, younger age, and tumor regression. Lack of TRK-A is seen with overexpression of N-myc and consequently carries a poorer prognosis [69–72]. These data suggest that the TRK-A/NGF pathway plays a role in the neuroblastoma differentiation and programmed cell death seen in the regression of tumors among infants. The presence of TRK-B is associated with such chromosomal abnormalities as gain of 17q and loss of heterozygosity for 14q. TRK-B expression is seen in many tumors that have a poor outcome and may correlate with *N-myc* amplification [69–73]. Reports have also shown that TRK-B activation can have a role in chemotherapeutic resistance within these tumors [74, 75]. TRK-C is seen in tumors with favorable prognosis and no *N-myc* amplification [76]. The balance of expression of these three tyrosine kinase receptors may be the most important factor in maintaining a favorable prognosis and disease regression [77].

Chromosomal aberrations in neuroblastoma are frequently present. Loss of heterozygosity and deletion of chromosome 1p occur in 30–50 % of neuroblastomas, more commonly in tumors of diploid karyotype [78, 79]. These aberrations correlate strongly with *N-myc* amplification and poor prognosis [80–83], and it is possible that this chromosomal region may contain a gene that suppresses N-MYC protein function or *N-MYC* amplification. Loss of 1p is a risk factor for disease progression and is found in very few low-stage tumors. Some investigators have suggested that identification of this abnormality should promote upstaging of a low-risk tumor to a higher grouping for more intensive therapy [82, 84].

Gain on chromosome 17q is the most common genetic abnormality in primary neuroblastoma. This region houses the survivin gene, an inhibitor of apoptosis, and its overexpression is an adverse prognostic factor correlating with advanced age at diagnosis, *N-myc* amplification with 1p deletion, and increased relapse rates [85–87]. Similar to *N-myc*, gene amplification of this region, rather than gene expression, appears to be correlated to poor prognosis and higher stage [88].

Various other genes and chromosomal abnormalities have been reported including deletions of 11q and 14q, as well as *bcl-2* overexpression, *ras* expression, *ret* expression, and telomerase activity. Of these, loss of heterozygosity at 11q is used most frequently in a clinical setting to provide additional prognostic information. In *N-myc* non-amplified patients with stage 2 or 3 disease (to be discussed below), the presence of an 11q aberration was the most highly prognostic factor conferring additional disease-specific mortality and a worse prognosis [89].

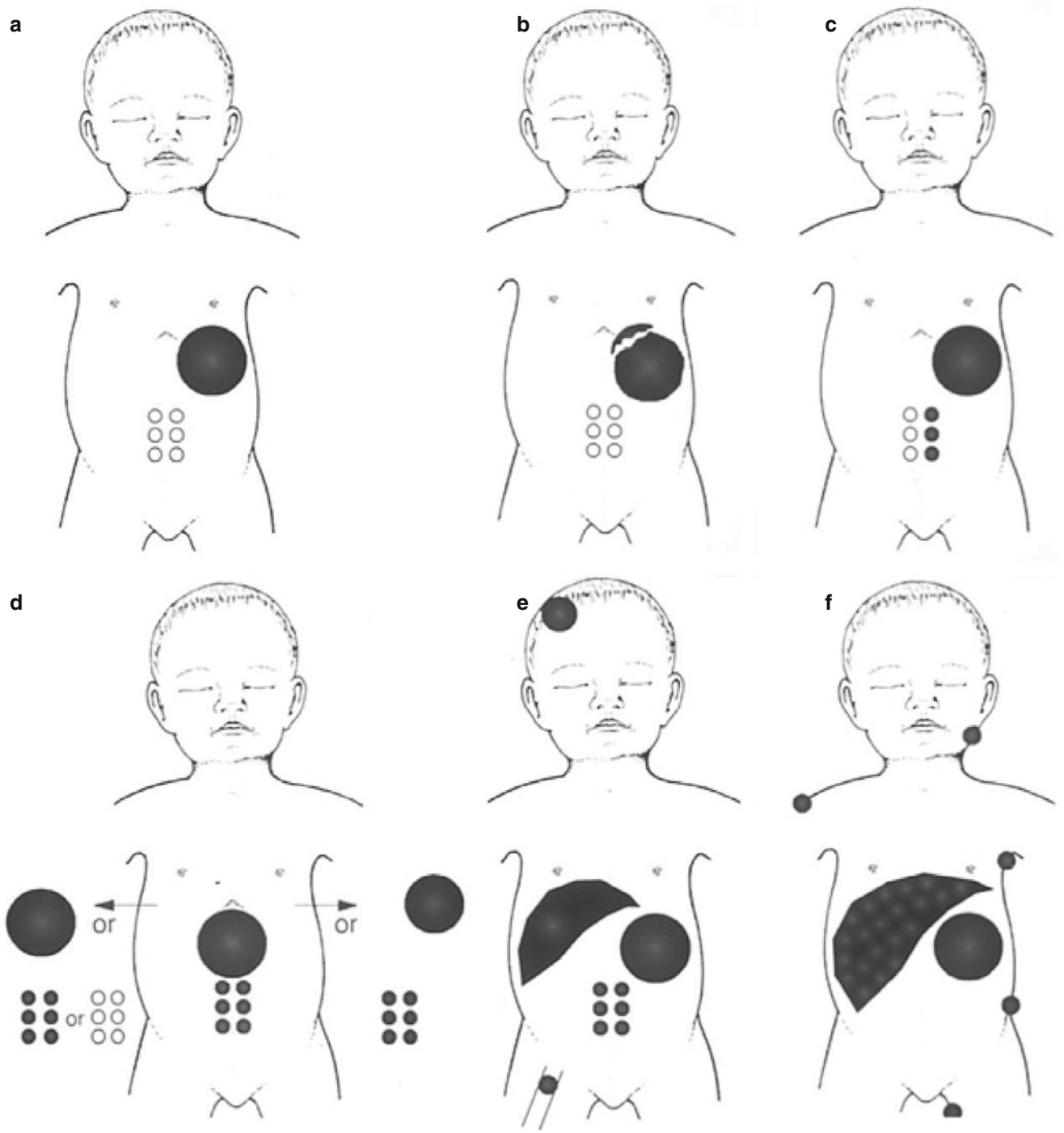

Fig. 14.8 International Neuroblastoma Staging System (INSS). (**a**) Stage 1: Completely resected localized tumor confined to the area of origin with negative lymph nodes. (**b**) Stage 2A: Incompletely resected localized tumor with negative lymph nodes. (**c**) Stage 2B: Unilateral tumor with complete or incomplete resection; positive ipsilateral lymph nodes, contralateral lymph nodes negative. (**d**) Stage 3: Large ipsilateral tumor crossing the midline with or without positive regional lymph node involvement; or a unilateral tumor with positive contralateral lymph nodes; or a midline tumor with bilateral regional lymph node involvement. Midline is defined as the vertebral column. (**e**) Stage 4: Metastatic tumor spread to distant organs, lymph nodes, and bone marrow. (**f**) Stage 4S: Subset of Stage 4 patients who are less that 1 year of age and present with a localized tumor with limited tumor dissemination to the liver, skin, and/or bone marrow

Staging

Multiple staging systems have evolved since the mid-twentieth century in an attempt to stratify patients at presentation into clinical risk groups from which different treatment strategies can be applied. Notable systems include the Evans classification [90], the St. Jude system [91], the Union for International Cancer Control's tumor-node-metastasis (TNM) system, and

the International Neuroblastoma Staging System (INSS) [35]. The INSS was established in 1989 (revised in 1993) and is currently the most accepted and widely used staging system in North America and Europe (Fig. 14.8). Under this system, a fully resected localized tumor constitutes Stage 1 disease. Stage 2 disease is divided into 2A (localized disease with incomplete resection) and 2B (unilateral disease with positive ipsilateral lymph nodes). Stage 3 disease represents a primary tumor crossing the midline (as defined by the vertebral column) or a unilateral tumor with positive contralateral lymph nodes. Any tumor originating from the midline with bilateral lymph node involvement is also Stage 3. Patients with disease metastatic to distant organs, lymph nodes, bone, or bone marrow have Stage 4 disease. Stage 4S represents a subtype of Stage 4 disease reserved for infants and children less than 1 year of age with localized primary tumors, minimal marrow involvement, and metastasis limited to the skin and liver. This pattern of disease spread has been associated with a favorable outcome with intervention typically reserved for patients with massive hepatomegaly causing respiratory distress and abdominal compartment syndrome [92–94].

One of the criticisms of the INSS lies in its relatively subjective staging. A large tumor originating from the intra-abdominal sympathetic chain may be classified as Stage 3 by one surgeon who deems it too large to resect, Stage 2A by another who attempts resection but leaves disease, and as Stage 1 by a third surgeon able to achieve complete resection. In each of these cases, the underlying tumor biology remains the same and the discriminatory power of risk stratification suffers.

INRG Classification

In 2009, a novel staging system was proposed by the International Neuroblastoma Research Group (INRG), with the intent of including preoperative imaging features and the tumor's genetic profile into a consensus approach for pretreatment risk stratification [89, 95]. This multinational research group analyzed the statistical and clinical significance of 13 prognostic factors distilled from a cohort of 8,800 children from North America, Europe, Australia, and Japan. Of these factors, INSS Stage, age, histologic category, tumor differentiation, *N-myc* status, chromosome 11q status, and DNA ploidy emerged as the most statistically and clinically relevant. Coupled with the absence (L1) or presence (L2) of image-defined risk factors (IDRF) (Tables 14.1 and 14.2) reflecting radiographic assessment of vascular of nerve encasement, patients are stratified into 16 pretreatment groups and classified as very low risk (>85 % 5-year event-free survival), low risk (>75 to ≤85 % 5-year event-free survival), intermediate risk (>50 to ≤75 % 5-year event-free survival), and high risk (<50 % event-free survival) (Table 14.3). Metastatic tumors are categorized as stage M, and infants younger than 18 months at diagnosis with metastatic disease limited to the skin, liver, or bone marrow are categorized as stage MS.

Risk Groups

To guide physicians in treatment planning, a risk stratification system has been developed in which patients are assigned to one of three risk groups: low, intermediate, or high risk. These groupings are based upon the success of administered treatments and survival rates. The benefit of risk grouping is to provide the patient with the best possible treatment plan while minimizing the need for toxic therapies.

In North America, risk grouping is based on recommendations of the Children's Oncology Group (COG) schema (Table 14.4). Three groups, comprising low-, intermediate-, or high-risk patients, were based on overall survival rates of >90 %, 70–90 %, and <30 %, respectively, at 3 years after diagnosis. The intermediate risk group has three tiers. The patient's risk group assignment is determined by INSS stage, age, *N-myc* status, Shimada histologic classification, and DNA ploidy. More recently, risk stratification has also incorporated analysis of 1p or 11q loss of heterozygosity (LOH) into treatment protocol assignment. The presence of LOH and all children missing data on chromosomal imbalance are upgraded to the next treatment group.

Low Risk

Definition

All patients with INSS Stage 1 disease are considered low-risk patients, regardless of age, *N-myc* status, Shimada class, or DNA ploidy. All INSS Stage 2A/2B patients with greater than 50 % tumor resection are also in this group with the exception of those who have *N-myc* amplification. Stage 4S patients (who by definition are <1 year of age) who are without *N-myc* amplification, have a favorable Shimada histology, and are hyperdiploid are also in this group.

Treatment

Patients in this group have a survival rate of >90 %. Patients with INSS Stage 1 disease can be treated with surgery alone without the need for adjuvant chemotherapy [96, 97]. Relapse following excision can be successfully treated with chemotherapy at that time to induce remission. Small, localized tumors discovered at birth or during the prenatal period can potentially be observed as they tend to spontaneously regress [98]. Observation of perinatal tumors was studied in a recently closed COG trial, ANBLOOP2. Eligible infants were younger than 6 months with <16 cm^3 solid tumor or <64 cm^3 cystic tumor limited to the adrenal gland. The results

Table 14.1 Image-defined risk factors in neuroblastic tumors

Ipsilateral tumor extension within two body compartments
Neck-chest, chest-abdomen, abdomen-pelvis
Neck
Tumor encasing carotid and/or vertebral artery and/or internal jugular vein
Tumor extending to base of skull
Tumor compressing the trachea
Cervico-thoracic junction
Tumor encasing brachial plexus roots
Tumor encasing subclavian vessels and/or vertebral and/or carotid artery
Tumor compressing the trachea
Thorax
Tumor encasing the aorta and/or major branches
Tumor compressing the trachea and/or principal bronchi
Lower mediastinal tumor, infiltrating the cost-vertebral junction between T9 and T12
Thoraco-abdominal
Tumor encasing the aorta and/or vena cava
Abdomen/pelvis
Tumor infiltrating the porta hepatis and/or the hepatoduodenal ligament
Tumor encasing branches of the superior mesenteric artery at the mesenteric root
Tumor encasing the origin of the coeliac axis, and/or of the superior mesenteric artery
Tumor invading one or both renal pedicles
Tumor encasing the aorta and/or vena cava
Tumor encasing the iliac vessels
Pelvic tumor crossing the sciatic notch
Intraspinal tumor extension whatever the location provided that:
More than one third of the spinal canal in the axial plane is invaded and/or the perimedullary leptomeningeal spaces are not visible and/or the spinal cord signal is abnormal
Infiltration of adjacent organs/structures
Pericardium, diaphragm, kidney, liver, duodeno-pancreatic block, and mesentery
Conditions to be recorded, but not considered image-defined risk factors
Multifocal primary tumors
Pleural effusion, with or without malignant cells
Ascites, with or without malignant cells

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Table 14.2 International Neuroblastoma Risk Group Staging System

Stage	Description
L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment
L2	Locoregional tumor with presence of one or more image-defined risk factors
M	Distant metastatic disease (except stage MS)
MS	Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow

Note: Patients with multifocal primary tumors should be staged according to the greatest extent of disease as defined in the table
From Monclair et al. [95]. Used with permission

of this study have yet to be published, but preliminary analysis suggests these children have an overall excellent prognosis and resection may be limited to those who have evidence of disease progression on serial imaging or biochemical analysis.

Stage 2A/2B low-risk tumors are also treated with initial surgery without the need for preoperative chemotherapy. Overall survival in these patients is >90 % with surgery alone [99, 100]. The application of chemotherapy is reserved for patients in whom <50 % of tumor was resected (Group B intermediate risk) or in patients who possess severe organ/life-threatening symptoms [100]. Chemotherapy consists of a platin agent (usually carboplatin), cyclophosphamide, doxorubicin, and etoposide. This regimen is administered for 6–24 weeks, with dose levels dependent upon the extent of disease and patient age/weight. Radiation therapy is rarely given in this group and is reserved only for tumors presenting with life-threatening symptoms or spinal cord compression. Treatment of children with low-risk Stage 4S disease has been controversial

Table 14.3 International Neuroblastoma Risk Group (INRG) pretreatment classification

INRG stage	Age (months)	Histologic category	Grade of tumor differentiation	*MYCN*	11q aberration	Ploidy	Pretreatment risk group
L1/L2		GN maturing; GNB intermixed					A Very low
L1		Any, except GN maturing or GNB intermixed		NA			B Very low
				Amp			K High
L2	<18	Any, except GN maturing or GNB intermixed		NA	No		D Low
					Yes		G Intermediate
	≥18	GNB nodular; neuroblastoma	Differentiating	NA	No		E Low
					Yes		H Intermediate
			Poorly differentiated or undifferentiated	NA			
				Amp			N High
M	<18				NA	Hyperdiploid	F Low
	<12				NA	Diploid	I Intermediate
	12 to <18				NA	Diploid	J Intermediate
	<18				Amp		O High
	≥18						P High
MS	<18			NA	No		C Very low
					Yes		Q High
				Amp			R High

From Cohn et al. [89]. Used with permission

in the past and is dependent upon the clinical presentation of the patient. These tumors have favorable biologic features and survival rates of 80–95 %. Children who are asymptomatic with disease appear to have a good outcome when treated with supportive care alone, as some of these tumors can undergo spontaneous regression [94, 101–103]. Of the patients who do present with symptoms, these can be managed with minimal low-dose chemotherapy; resection of the primary tumor does not appear to improve outcome or survival. Some infants with Stage 4S disease may present with extensive and diffuse liver involvement that can cause respiratory compromise and symptoms of abdominal compartment syndrome with decreased venous return and renal impairment. These patients may require ventilator support and abdominal decompression surgery in addition to systemic chemotherapy and radiation therapy to the liver.

Intermediate Risk

Definition

The intermediate risk category consists of a heterogeneous group of patients including non-NMYC amplified, incompletely (<50 %) resected INSS Stage 2A/2B disease, ages 0–12 years, all INSS Stage 3 non-NMYC amplified less than 1.5 years and those aged 0–12 years Stage 3 non-NMYC amplified tumors with favorable histology. Additionally, INSS Stage 4 patients who are <1 year of age without NMYC amplification are intermediate risk regardless of other tumor biology features. Non-NMYC amplified Stage 4 patients 1–1.5 years with favorable histology and a hyperdiploid DNA index are also placed in this category. INSS Stage 4S patients are upgraded to intermediate risk if they lack *N-myc* amplification but have either unfavorable Shimada histology OR near-diploid DNA status. If no tissue was obtained for evaluation, or if the patient is symptomatic, Stage 4S infants are also treated on an intermediate risk protocol.

Treatment

Intermediate-risk patients, as a group, maintain an overall rate of survival greater than 90 %. Variations in survival in this group appear to be related to patient age and tumor biology, with patients less than 1 year of age, or tumors with more favorable characteristics, having higher rates of treatment success [99, 104, 105]. Historically, all patients in this group have received surgery and chemotherapy as the primary modalities of treatment. The goal of the COG A3961 study, conducted from 1998 to 2006, was to maintain an overall cure rate of >90 % while minimizing short-term and long-term chemotherapeutic morbidity. Patients with favorable histology received 4 cycles (12 weeks) of low-dose cyclophosphamide, doxorubicin, carboplatin, and etoposide, and those with unfavorable histology received 8 cycles (24 weeks) of the same therapy [33]. Radiotherapy was reserved for patients demonstrating disease progression or for those with unresectable tumors at the completion of chemotherapy. The recently published results of this study

Table 14.4 Children's Oncology Group risk stratification for neuroblastoma

Risk stratification		INSS stage	Age	Biology
Low				
	Group 1			
		1	Any	Any
		2A/2B (>50 % resected)	Any	*N-myc* NA, any histology/ploidy
		4S	<365 days	*N-myc* NA, FH, DI > 1
Intermediate				
	Group 2			
		2A/2B (<50 % resected or biopsy only)	0–12 years	*N-myc* NA, any histology/ploidy
		3	<365 days	*N-myc* NA, FH, DI > 1[a]
		3	>365 days–12 years	*N-myc* NA, FH[a]
		4S (symptomatic)	<365 days	*N-myc* NA, FH, DI > 1[a]
	Group 3			
		3	<365 days	*N-myc* NA, either UH or DI = 1[a]
		4	<365 days	*N-myc* NA, FH, DI > 1[a]
		4S	<365 days	*N-myc* NA, either UH, DI = 1[a] or unknown biology
	Group 4			
		4	<365 days	*N-myc* NA, either DI = 1 or UH
		3	365 to <547 days	*N-myc* NA, UH, any ploidy
		4	365 to <547 days	*N-myc* NA, FH, DI > 1
High				
		2A/2B, 3, 4, 4S	Any	*N-myc* amplified, any histology/ploidy
		3	>547 days	*N-myc* NA, UH, any ploidy
		4	365 to <547 days	*N-myc* NA, UH or DI = 1
		4	>547 days	Any

DI DNA Index, *FH* favorable histology, *INSS* International Neuroblastoma Staging System, *N-myc NA N-myc* not amplified, *UH* unfavorable histology

[a]If tumor contains chromosomal 1p LOH or unb11qLOH, or if data are missing, treatment assignment is upgraded to next group

Adapted from Davidoff [121]. Used with permission

demonstrated an overall 3-year survival rate of 96 %, with 98 % survival among patients with favorable histology and 93 % among those with unfavorable histology [106].

One current COG protocol (ANBL0531) seeks to further stratify patients with intermediate risk and to reduce therapy for patients with favorable biology. Genetic characterization based on tumor ploidy and LOH at 1p or 11q, in addition to patient age and tumor histology, was used to define 3 separate tiers of intermediate-risk therapy. For many patients, it was possible to administer a chemotherapy dose lower than that given in the A3961 protocol. Patients with LOH at chromosome 1p or 11q, however, are not eligible for dose reduction and are upgraded to the next level of therapy [83]. Additionally, tumor ploidy has a particular impact on Stage 4 patients in that DNA diploidy predicts early treatment failures [107]. These patients receive more dose-intensive chemotherapy than their hyperdiploid counterparts (Table 14.4).

As the mainstay of therapy in the treatment of local neuroblastoma, surgical intervention also has a role in both diagnosis and treatment of intermediate-risk neuroblastoma. In patients deemed to have an initially unresectable tumor, chemotherapy is recommended to avoid organ loss or other intraoperative morbidity [108]. In these cases, histologic assessment and biologic testing should be performed on an adequate tissue sample of the suspected neuroblastoma, obtained from either an open or minimally invasive biopsy. Vascular access for chemotherapy may also be obtained at the time of biopsy. Following a chemotherapeutic response (most commonly after the completion of cycle 4 or 5 on the COG protocol), resection of the primary tumor is attempted with the goal of removing all gross visible disease, while preserving end-organ and neurologic function. This may require an incomplete resection, leaving residual disease on essential anatomic structures. The surgical approach depends upon the location of the primary tumor and the experience of the operating surgeon. At our institution, we recommend a thoracoabdominal incision for adrenal or abdominal sympathetic-chain primaries, a midline incision

for pelvic tumors, an open thoracotomy for thoracic tumors, and a modified radical neck incision for cervical chain tumors. Laparoscopic adrenalectomy has been reported in the literature for small, localized, well-encapsulated tumors [109], but no studies have been conducted to compare this approach to open resection or to examine its effectiveness on long-term survival and local recurrence rates. Resection and staging of retroperitoneal lymph nodes are limited by this approach as well.

The role of surgical intervention in intermediate-risk neuroblastoma is under continuous re-evaluation and can vary according to differences in tumor biology. There may be a subset of patients with intermediate-risk disease for whom surgical resection alone is curative. A recent study by Kushner et al. has also shown that a subset of Stage 4 patients without *N-myc* amplification and without extensive bone marrow involvement may do well without any cytotoxic therapy [103]. On the other hand, resection of the primary tumor is no longer required in infants with Stage 4S disease [102].

Radiation therapy is reserved for residual disease after administration of a full course of chemotherapy or for symptomatic patients not responding to initial chemotherapy. This is typically limited to patients with respiratory distress from 4S disease, and to patients with spinal cord compression from epidural disease.

High Risk

Definition

All INSS Stage 4 patients >1.5 years of age fall into this grouping as well as Stage 4 patients <1.5 year with *N-myc* amplification. Stage 3 patients of any age with *N-myc* amplification are defined as high risk as well. Stage 3 patients >1 year old without *N-myc* amplification but who have an unfavorable Shimada histology are upgraded to the high-risk category. Patients with INSS Stage 2A/2B are upgraded to high risk if they are >1 year old and possess both *N-myc* amplification and an unfavorable Shimada histology. Any Stage 4S patient with *N-myc* amplification is upgraded to high risk. Despite aggressive therapies, survival in this group continues to be poor, with long-term survival rates of 10–30 % in cooperative group studies. However, small inroads are being made in certain subsets of high-risk patients; for example, survival for Stage 3 patients with current intensive therapy has been improved to approximately 60 % [30].

Treatment

Therapy for high-risk patients consists of intensive chemotherapy (induction followed by myeloablative consolidation) with surgery and radiation for local tumor control, followed by maintenance therapy.

Induction Chemotherapy: The goal of induction chemotherapy is to induce tumor remission, decrease tumor growth, and improve tumor resectability. Response rates vary from 60 to 90 %. Common agents for induction include cyclophosphamide, ifosfamide, cis/carboplatin, vincristine, doxorubicin, and etoposide. Kushner et al. demonstrated a highly effective protocol of cyclophosphamide, vincristine, and doxorubicin alternating with cycles of cisplatin and etoposide [110]. Additional benefits of intensive induction chemotherapy include the elimination of tumor from the bone marrow prior to cell harvest for autologous transplantation. Stem cell harvest typically occurs following the second cycle of induction chemotherapy.

The response rate of tumor to induction therapy appears to correlate with outcome and chances for long-term disease-free survival. One European study of 549 high-risk patients showed that failure to clear cortical bone lesions and bone marrow involvement following high-intensity induction chemotherapy were independent adverse prognostic factors [111]. In addition, the response of MIBG scintigraphy following therapy has been shown to highly correlate with treatment outcome [45, 112, 113].

Myeloablative Consolidation Therapy: Following surgical resection of the primary disease site and any sites of bulky metastatic disease (usually following the fourth or fifth cycle of induction chemotherapy), high-risk patients undergo myeloablative consolidation therapy with the goal of destroying any remaining tumor cells. The use of consolidation therapy has significantly improved progression-free survival in these patients. The European Neuroblastoma Group reported a dramatic improvement in survival among patients who received consolidation therapy, increasing from 6 months to 23 months for patients who received no additional therapy [114]. Likewise, the Children's Oncology Group reported a 34 % rate of 3-year event-free survival in a group of high-risk patients who received high-dose myeloablative consolidation therapy with autologous transplant, compared with 22 % among patients treated with nonmyeloablative consolidation therapy ($p=0.034$) [10]. Myeloablative consolidation therapy is now recommended for all high-risk patients, except for those receiving treatment under specialized protocols.

Bone Marrow/Stem Cell Transplantation: The ability to reconstitute bone marrow by stem cell transplant (or rescue) has facilitated the successful use of myeloablative chemotherapy [115], and the tumor-free survival and relapse rates achieved appear to be uninfluenced by the type of bone marrow transplant received (autologous vs. allogeneic) [116]. Due to advances in transplant methodology, however, autologous transplant is a safer and more feasible method. Stem cells can now be obtained through peripheral blood stem cell collection instead of traditional bone marrow harvest. Allogeneic transplant has been associated with

higher toxicity rates, death, and rejection, and is no longer recommended [117].

Because neuroblastoma cells can be detected within blood samples of patients via PCR analysis in concentrations of 1 per million and because the majority of high-risk neuroblastoma patients have metastatic disease to the bone marrow at diagnosis, the Children's Oncology Group examined whether reinfusion of small numbers of tumor cells during transplant contributed to systemic relapse [118–120]. COG A3973 was designed as a randomized study of purged vs unpurged peripheral blood stem cell transplant following dose-intensive induction therapy for high-risk neuroblastoma. This study was closed early when interim analysis showed no difference between children receiving either purged or unpurged cells [121]. The current high-risk COG protocol (ANB0532), which opened to accrual in 2007, is examining whether further intensification of myeloablative therapy into 2 (tandem) consolidations confers additional survival benefit.

Surgery: In the past, the use of aggressive surgical resection in high-risk patients, especially those with Stage 4 disease, has been highly controversial. There are no prospective studies demonstrating efficacy of primary site excision in preventing local recurrence or reducing metastatic spread of disease. Retrospective cooperative group reviews have come to conflicting conclusions. A few recent studies have shown an improvement in survival rates with more extensive surgery and better response to chemotherapy [122–124]. In an analysis of 141 patients with Stage 4 disease (not adjusted for tumor biology), La Quaglia et al. showed that overall survival was increased from 11 to 50 % and that the probability of local recurrence decreased from 50 to 10 % in patients who had gross total resection compared with those who did not. Other studies have shown that failure to control the primary site of disease is a leading cause of disease progression and can lead to further systemic spread [125, 126]. As a result of these findings, the COG recommends aggressive surgical removal of all primary tumor and locoregional disease in all neuroblastoma patients older than 1 year. Tumor resection is typically attempted after the fifth cycle of chemotherapy, although some institutions recommend resection earlier in the course of care—either as an upfront procedure, or when chemotherapy has sufficiently reduced the tumor burden (often after the second or third cycle) [127, 128]. Several studies have suggested that upfront resection (if feasible) may result in a better survival outcome than delayed resection following chemotherapy [127].

Radiotherapy: Because neuroblastoma is a radiosensitive tumor, radiotherapy is currently recommended for all high-risk patients after surgery, regardless of the presence of gross or microscopic residual disease, to reduce the incidence of primary local relapse [129]. According to current COG protocols, the target field is determined by adding a 1.5-cm margin to the radiographic boundaries of the tumor at the time of the completion of induction therapy. If induction therapy resulted in a complete response, 21.6 Gy is administered to the primary site of disease. In the presence of gross residual disease, an additional 14.4 Gy is given, for a total of 36 Gy. Sites of metastatic lesions should also be targeted prior to consolidation therapy and stem cell transplant.

Radiotherapy has been shown to benefit select 4S patients and patients with symptomatic spinal cord compression. A typical dose of 20 cGy is administered to the abdomen or thoracic cavities. Total-body irradiation prior to bone marrow transplant has been used in the past to ablate the marrow but is no longer a part of any protocols. The use of intraoperative radiotherapy is being explored for the delivery of higher doses of radiation to the tumor bed with less toxicity [130–132]. Although the optimal dose response curve has yet to be finalized, these studies have shown improved local control.

Maintenance Therapy: Efforts have been made to develop therapies that will improve progression-free survival following treatment. Because retinoic acid can induce differentiation of neuroblastoma cells into benign cells in culture, the CCG-3891 and subsequent trials randomized patients to either receive 6 months of 13-cis-retinoic acid following completion of chemotherapy or no further therapy [10, 133–136]. The patients who received retinoic acid experienced significant improvement in 3-year event-free survival. Furthermore, it appears that retinoic acid administered as high-dose pulse therapy is more efficacious than low-dose continuous infusions [135]. Adverse effects from extended retinoid treatment are generally mild and include dry skin, oral fissures, cheilitis, and headaches. Currently, it is recommended that all high-risk patients receive 6 months of treatment with 13-cis-retinoic acid following chemo- and myeloablative therapies.

Special Circumstances

Opsoclonus/Myoclonus: Between 1.8 and 3 % of children with neuroblastoma present with a paraneoplastic syndrome consisting of symptoms related to opsoclonus/myoclonus and/or ataxia [137]. This syndrome classically causes rapid bursts of chaotic eye movements, irregular jerking movements of the muscles, and ataxia. The mechanism for this syndrome has not been fully elucidated, but it appears to be an immunologic mechanism related to intrathecally secreted B-cell activating factor and high levels of anticerebellar granular neuron antibodies in the presence of a tumor that is densely infiltrated with lymphocytes [138–140]. Although opsoclonus is uncommon among neuroblastoma patients, approximately 50 % of patients who present with opsoclonus will have neuroblastoma [141]. Most patients with this syndrome tend to have localized disease and favorable oncologic outcome [142]. Neurologic function remains poor,

however, as this syndrome tends to be pervasive despite tumor removal and can be associated with neurologic and cognitive deficits, as well as psychomotor retardation [138]. In a recent Italian study, 75 % of patients with opsoclonus/myoclonus syndrome had abnormal neurologic findings at a median follow-up of 7.4 years with a median full-scale intelligence quotient of 78 [143]. Treatment with adrenocorticotropic hormone (ACTH) and corticosteroids is standard therapy and is effective in some cases. However, dose tapering is commonly associated with relapse, and reduction of symptoms is not necessarily correlated to improvement in long-term outcome [140]. In patients with disease that is unresponsive to ACTH or corticosteroids, plasmapheresis and intravenous gamma-globulin have been effective [142–144]. An ongoing randomized prospective COG trial (ANBL00P3) is currently evaluating the effectiveness of immunosuppressive therapy combined with cyclophosphamide use. In addition, the study will examine how the addition of intravenous gammaglobulin improves response rates, as well as long-term outcomes from this syndrome. Research groups led by Pranzatelli and Tate have found that the addition of rituximab to ACTH and intravenous immunoglobulin resulted in symptomatic improvement in all patients undergoing treatment, with a 17 % rate of relapse at 6 months, compared with relapse rates of 75 % on other standard therapy [145, 146].

Spinal Cord Compression: Immediate treatment should be initiated for neuroblastoma with symptomatic spinal cord compression. Symptoms can include paralysis or paresthesia, incontinence, and bladder dysfunction. Functional limitation appears to be mitigated with rapid intervention. Decompression of the cord is warranted and may be accomplished via laminotomy, radiation, or chemotherapy. The three techniques appear to have similar outcomes, but surgery may result in scoliosis later in life [147, 148]. Since most patients will probably require chemotherapy, with or without surgery, COG currently recommends treatment with chemotherapy first, with surgery reserved for patients who do not improve [149–151]. The risk of scoliosis is directly related to the use of laminectomy and the radiation dose level.

Fetal and Perinatal Tumors: The diagnosis of neuroblastoma within the fetal and perinatal population has increased dramatically over the past few decades with improvements in obstetric ultrasound technology. Over 90 % are located within the adrenal gland (two-thirds of these are right-sided) with most being localized INSS Stage 1 or 2 tumors [152–154]. Average fetal diagnosis occurs at 33 weeks [29]. The health and well-being of the mother are of paramount importance, and pregnancies can be carried to term as long as there are no complications from pre-eclampsia or fetal hydrops. The growth of detected masses can be monitored with serial ultrasounds at scheduled visits. Maternal or fetal distress after 28 weeks of gestation should prompt the use of tocolytics, as well as steroids for fetal lung maturity, with a planned delivery as soon as possible [33]. Published data on these patients have shown that the vast majority of these tumors have favorable biologic profiles with no *N-myc* amplification [152–154]. Treatment for these neonates should be based upon COG risk grouping, with the majority falling into the low-risk group. These patients do very well with surgery alone and have an associated survival of 96 % and an event-free survival of 91 % [29].

Because the biological aggressiveness of these tumors is low and the long-term outcome is often favorable, observation has also been recommended as an option for managing these patients. The presumption is that these tumors will regress and newborns will be spared the invasiveness and potential complications of surgery. Tumors less than 5 cm indicate a likelihood of low-stage disease, which can be followed via serial ultrasound to monitor for tumor growth and spread [29]. VMA and HVA levels can also be monitored as a relative indicator for tumor growth and spread. Studies have shown that patients monitored with this approach continue to have good survival rates, with two-thirds of patients avoiding surgery secondary to tumor regression. In those patients with visible tumor growth on ultrasound, successful surgical resection was possible without any upstaging of disease. Chemotherapy is still effective as salvage if needed [29, 155, 156]. The COG is currently conducting a prospective single-arm clinical trial to evaluate observation as a management option in perinatal neuroblastoma patients. While the results have yet to be published, accrual has been completed and early analyses support nonoperative management of small tumors.

Recurrent Neuroblastoma

Recurrence of neuroblastoma is highly dependent upon the patient's initial stage of disease and tumor biology as well as upon the extent of resection and previous treatment received. Treatment of recurrent disease is determined by risk group assessment at the time of diagnosis in addition to the patient's age and tumor biology at time of recurrence. Attempts should be made to obtain new tissue samples for biological analysis of the recurrence and comparison to the initial tumor. Widespread recurrence has a poor prognosis despite aggressive therapy [157, 158]. Central nervous system disease is more common with recurrence and may be seen in 5–10 % of cases [159, 160].

Low-risk Disease: Low-risk patients with local-regional recurrence are treated with resection if possible. If a gross total resection is done, then no further treatment is needed. If less than a total resection is obtained, then 12 weeks of chemotherapy is warranted. If the tumor pathology reveals unfavorable biological markers and a total resection cannot be performed,

then 24 weeks of chemotherapy should be administered. If there is local recurrence with unfavorable Shimada classification or *N-myc* amplification, then the prognosis is poor and the patient will require aggressive high-dose chemotherapy. Any child initially classified as low-risk who is older than 1 year at the time of recurrence has a poor prognosis and needs aggressive therapy; myeloablative protocols with retinoic acid may improve outcome [10].

In low-risk patients, metastatic recurrence is treated according to the pattern of disease spread, tumor biology, and age of the patient. Patients younger than 1 year with favorable tumor biology and a 4S pattern of disease spread are observed if the recurrence occurs within 3 months of initial diagnosis. If metastatic disease progresses after 3 months or if the initial recurrence was not in a 4S pattern, then the primary tumor is resected and patients receive 12–24 weeks of chemotherapy. If the metastatic tumor is found to have any unfavorable tumor biology, then initial resection is followed by 24 weeks of chemotherapy.

Intermediate-risk Disease: Intermediate-risk patients with a recurrence are also treated based upon the time to recurrence and tumor biology. If the local-regional recurrence occurs more than 3 months after completion of chemotherapy and has favorable biologic characteristics, then resection is the primary method of treatment. If total resection of all gross disease is not possible, then 12 weeks of additional chemotherapy is given. If the recurrence is metastatic or has occurred less than 3 months following completion of the primary treatment or has unfavorable biology, patient outcome is poor. These patients should be treated with aggressive high-dose chemotherapy, myeloablative therapy, and retinoic acid.

High-risk Disease: Any recurrence in a high-risk patient is associated with a very poor prognosis. Because conventional therapy protocols have been unsuccessful in these patients, they should be considered for phase 1 or 2 clinical trials.

Experimental Treatments

While early and intermediate-stage neuroblastomas are associated with high cure rates, overall survival for high-risk and relapsed neuroblastoma remains poor. Considerable research efforts are devoted to the development of novel treatment strategies. ^{131}I-MIBG may be used to deliver targeted radiotherapy to tumor cells while avoiding toxicity to surrounding organs and tissues. Response rates in chemoresistant tumors are as high as 46 %, with the greatest benefits seen in older patients (adolescents and adults), who comprise a notoriously difficult-to-treat population [161, 162]. Another radioactive isotope, ^{125}I-MIBG, may preferentially treat micrometastatic and bone marrow disease [121]. The chemotherapeutic agents topotecan and irinotecan have demonstrated activity against neuroblastoma refractory to other treatments [163–165]. COG is currently investigating the combination of irinotecan plus temozolomide as salvage therapy [166]. Another agent used at some centers is etoposide, an oral topoisomerase II inhibitor that has shown some effect in refractory and relapsed patients [167].

Targeted immunologic therapies, including the use of monoclonal antibodies, cytokine therapies, and vaccines, are also under investigation. GD2 is a tumor-associated ganglioside, which is the predominant antigen in neuroblastoma cells. In clinical trials, 3F8, the monoclonal antibody against GD2, was shown to induce a 40 % response in chemorefractory neuroblastoma [168–170]. In the COG trial ANBLOO32, 3F8 used in conjunction with granulocyte colony stimulating factor (GCSF), interleukin-2 (IL-2), and cis-retinoic acid was associated with superior event-free survival (66 % at 2 years vs 46 %) and improved overall survival (86 % vs 75 % at 2 years) over cis-retinoic acid alone [170]. The currently known limitations of these therapies are the risk of allergic reactions and severe immune symptoms, such as fever, pain, and skin irritation.

Recently, activating mutations in the tyrosine kinase domain of the *ALK* (anaplastic lymphoma kinase) oncogene were identified in both hereditary (80 %) and sporadic (7–8 %) neuroblastoma with a possible cooperative effect with *N-myc* [60]. In zebrafish studies, *ALK* prevented apoptosis in *N-myc*–driven over-expansion of sympathoadrenal neuroblasts [61, 62]. A clinical COG Phase I/II trial targeting ALK with crizotinib, an orally available small-molecule inhibitor of ALK, is currently being tested in relapsed and refractory solid tumors [171].

Ongoing research is also investigating the value of anti-angiogenic therapy in the treatment of neuroblastomas, as these tumors are frequently well-vascularized. Animal studies using antibodies against vascular endothelial growth factor (VEGF) or the multitargeted receptor tyrosine kinase inhibitor sunitinib have shown modest promise as single-agent therapy and as sensitizing agents that enhance activity of traditional chemotherapeutic drugs [172–176]. Other potential therapeutic agents include tyrosine kinase inhibitors to affect the TRK-NGF pathway, direct targeting of *N-myc*–amplified cells, microtubule-binding antimitotic agents, histone deacetylators, and the creation of chimeric antibodies to deliver cytotoxic drugs [177, 178].

Other Adrenal Tumors

Other masses of the adrenal gland are rare during childhood and often result in endocrinologic hyperactivity disorders. Pheochromocytomas typically oversecrete catecholamines, while tumors of the adrenal cortex may result in Cushing's syndrome from excess steroid production.

Pheochromocytoma

Pheochromocytoma, a catecholamine-secreting tumor arising from chromaffin cells, is most commonly found in the adrenal medulla, but may arise anywhere along the abdominal sympathetic chain, the periadrenal region, urinary bladder or ureteral walls, thoracic cavity, mediastinum, or in the organ of Zuckerkandl at the aortic bifurcation. Approximately 10 % present during childhood (usually between ages 6 and 14 years), and they are more commonly right-sided, although approximately 20 % are bilateral [180, 181]. Greater than one-third of cases may involve sites of extra-adrenal disease, in clear variance with the adult population, in which only 10 % of tumors are found outside the adrenal gland, where they are frequently termed paragangliomas [181–184]. The organ of Zuckerkandl is the most common site of extra-adrenal tumors [185–187].

The clinical manifestations of pheochromocytoma are attributable to catecholamine excess. Hypertension is invariably present; however, children, unlike adults, tend to demonstrate sustained rather than paroxysmal hypertension. Approximately 1 % of the cases of childhood hypertension can be attributed to pheochromocytoma [179]. Headaches, dizziness, palpitations, abdominal pain, pallor, sweating, thirst, polyuria, and vomiting may also be present. Convulsions and hypertensive encephalopathy occur with much greater frequency than in the adult population, likely secondary to sustained hypertension [179, 184, 188]. In severe cases, precordial pain radiating to the arms may be present, along with pulmonary edema, cardiac hypertrophy, and hepatic congestion. Due to hypermetabolism, weight gain may be poor despite good appetite. Ophthalmoscopic examination may reveal papilledema and retinal hemorrhages. Additionally, proteinuria may be present. Gross hematuria suggests that the tumor is in the bladder wall.

Elevated urinary catecholamines (VMA, HMA, and urine metanephrines) are the hallmark of pheochromocytoma. A linear relationship has been demonstrated between the amount of VMA and size of the pheochromocytoma. Plasma catecholamines are also elevated, but baseline measurements of catecholamines are most accurate in a calm, cooperative patient; obtaining accurate baseline levels from a frightened child undergoing phlebotomy may not be possible. In contrast to adults who have elevations in both norepinephrine and epinephrine metabolites, children with pheochromocytoma predominantly excrete norepinephrine. Patients with paragangliomas present with exclusively high norepinephrine levels, as they lack the enzyme to convert norepinephrine to epinephrine.

Once a diagnosis is confirmed, a CT scan of the chest/abdomen/pelvis should be performed to evaluate the location and extent of disease. The use of ^{131}I-MIBG scans can be useful to confirm adrenal uptake and help identify any sites of extra-adrenal disease [184].

Pheochromocytomas most commonly occur as a sporadic tumor. However, there are also multiple genetic associations. In some families, pheochromocytoma may be inherited as an autosomal dominant trait. They may also be associated with neurofibromatosis, von Hippel-Lindau disease, and as a component of multiple endocrine neoplasia (MEN) types 2A and 2B [189]. Among patients with MEN type 2, bilaterality is much more common and the risk of developing a contralateral tumor following a unilateral adrenalectomy is approximately 50 % [190]. The *NF1* gene maps to chromosome 17, and germline mutations of the *RET* proto-oncogene map to chromosome 10. Mutations within the RET proto-oncogene of MEN patients appears to be the basis for the increased susceptibility to tumor development. Pheochromocytoma is also associated with tuberous sclerosis, Sturge-Weber syndrome, and ataxia telangiectasia.

Unlike the adult version of this tumor, it appears that these tumors in children, even when they occur sporadically, may have an underlying genetic origin. A recent report looking at 270 sporadic pheochromocytomas identified germline mutations of known susceptibility genes in approximately 24 % of cases. This value rose to 70 % in children under 10 years of age [191]. Germline mutations in the succinate dehydrogenase gene (SDHD) have been found responsible for upto 40 % of familial and 5 % of sporadic cases of pheochromocytoma and paraganglioma. Genetic screening should be considered for all patients less than10 years of age who are diagnosed with pheochromocytoma.

Surgical extirpation is the mainstay of treatment but must be approached cautiously, as intraoperative release of catecholamines by manipulation of the tumor may be fatal. Improvements in perioperative medical and anesthetic care have reduced operative mortality from 25 to 40 % in the past to less than 10 % today. Preoperative alpha and beta blockade and volume loading are imperative for least a week prior to operation. Usually 0.2–0.5 mg/kg of phenoxybenzamine is given in a divided dose twice a day until surgery. This is increased gradually until blood pressure is controlled or a maximum dose of 3 mg/kg is reached. Beta blockade should not begin until alpha blockade is achieved. Intraoperatively, an arterial and central venous catheter should be placed and rapidly acting IV drips of sodium nitroprusside, nitroglycerin, phenylephrine, and esmolol should be available for quick titration if needed for hemodynamic stabilization. Blood pressure support may be required postoperatively until homeostasis is regained. Historically, open adrenalectomy was the procedure of choice for this disease. However, given the small size of these tumors in children, as well as their frequent benign nature, most surgeons now opt to perform a laparoscopic resection [184, 192–194]. Documented benefits of the laparoscopic approach include fewer complications,

less time in operating room, less pain, and shorter hospital stays. Both transperitoneal and retroperitoneal approaches have been described, with the lateral transperitoneal approach appearing to be the most popular.

It is difficult to determine malignancy histologically, and there is no currently accepted staging system for pheochromocytoma; the only true criteria for malignancy is the presence metastatic disease or local invasiveness that precludes complete resection. In adults, approximately 10 % of pheochromocytomas are malignant; it is thought that the rate of malignancy in children is lower, probably closer to 3 %. Extra-adrenal sites are more likely to harbor malignancy. Prolonged follow-up is necessary as metachronous occurrence of multifocal disease may become manifest many years after the original operation.

Adrenocortical Carcinoma

Tumors of the adrenal cortex are rare within the pediatric population, comprising less than 0.5 % of all childhood neoplasms [195] and only 6 % of all pediatric adrenal tumors [196]. They are most common in children less than 10 years of age. Up to 10 % are bilateral. Greater than 90 % present with signs or symptoms of endocrine hyperfunction. There is a well-documented association with hemihypertrophy and Beckwith-Wiedemann syndrome, as well as with congenital defects of the genitourinary tract and hamartomatous defects [197–199]. Adrenal carcinoma has been associated with mutations in p53 (on chromosome 17), loss of heterozygosity of chromosomes 2, 4, 11, and 18, and overexpression of the IGF2 gene. Mutation of R337H in the p53 gene has been found to correlate with the development of adrenocortical carcinoma in a region of Brazil [200]. The 5-year survival rate for carcinomas tends to be more favorable than in adults, where it is approximately 40 %.

Most adrenocortical tumors demonstrate virilizing features with accelerated growth velocity and muscle development, acne, penile enlargement or clitoral hypertrophy, hirsutism, and deepening of the voice [201–203]. In addition, Cushing's syndrome may also be present with the characteristic signs of hypertension, central obesity, moon face, and buffalo hump. Serum levels of dehydroepiandrosterone (DHEA) and its derivatives DHEA sulfate and androstenedione are often markedly elevated. Urinary 17-ketosteroids are increased. Malignant tumors often have a deficiency of 11B-hydroxylase activity and secrete increased amounts of deoxycorticosterone resulting in hypertension. Feminizing tumors presenting with gynecomastia or premature thelarche are far less common. High levels of aromatase activity and expression of the CYP19 (*P450arom*) gene, absent in normal adrenal tissue, are found in these tumors. CT scan or MRI of the abdomen and pelvis should be performed in all children in whom the diagnosis is suspected to identify the location and size of the primary tumor. In addition, CT scan of the chest is helpful to locate any sites of metastasis [201]. The most common sites of metastatic disease are the lung, liver, and lymph nodes.

Treatment is surgical; both laparoscopic and open approaches have been described [203–205]. Incomplete resection, tumors greater than 100 g or larger than 200 cm^3, age >3.5 years, symptoms present for >6 months, and a marked increase in urinary 17-ketosteroids and 17-hydroxysteroids have been associated with a poor prognosis [206]. Perioperative replacement of steroids is necessary due to the suppressed hypothalamic-pituitary-adrenal axis and the abrupt removal of the endogenous source of excess steroid production. Gross removal of all tumor should be the goal of surgery, even at the expense of nearby structures as patients with incomplete resections have been shown to have a poorer prognosis [189]. Aneuploid tumors, identified by flow cytometric analysis of DNA content, have been discovered to be more aggressive and have a poorer prognosis [207, 208]. Postoperatively, patients should be monitored by frequent measurement of androgens and imaging studies.

Staging of adrenal cortical carcinoma is based on the TNM classification determined by the size of the primary tumor, degree of local invasion, and spread to lymph nodes or distant sites. Stage 1 and 2 patients have localized disease to the adrenal gland without evidence of invasion or regional/distant spread. These patients are treated primarily with complete resection without the need for additional adjuvant therapies. Stage 3 disease consists of tumors that have invaded the surrounding adrenal fat or those associated with positive local regional lymph nodes. Stage 4 disease is characterized by local invasion of tumor into adjacent structures, positive lymph nodes, or distant metastatic spread of disease. In addition to the surgical resection of the primary site, metastatic disease, most commonly involving liver, lung, or regional lymph nodes, should be treated with metastasectomy if technically feasible [209].

Non-surgical treatment options are limited. External-beam radiation has not demonstrated efficacy. Systemic chemotherapy with mitotane, an adrenolytic agent, and agents which interfere with steroid synthesis (ketoconazole, aminoglutethimide, and metyrapone) may relieve symptoms of steroid excess, but achieve a clinical response in less than 30 % of patients [210–212]. Cisplatin, alone and in combination with carboplatin/etoposide has also been reported to be effective in some cases [213–217].

A current Phase 3 COG trial (ARAR0332) is evaluating patient outcomes in the treatment of adrenal cortical carcinoma with surgery plus regional lymph node dissection and multi-agent chemotherapy. All Stage 1 and 2 patients will receive treatment with surgery alone. Stage 2 patients will

also undergo an extended regional lymph node dissection. Stage 3 and 4 patients will undergo surgery with the addition of multiagent chemotherapy consisting of cisplatin (50 mg/m^2), etoposide (100 mg/m^2), and doxorubicin (25 mg/m^2) for 8 cycles as well as mitotane administration daily for 8 months. Endpoints of this study will look at outcomes, success of surgery, toxicity from chemotherapy, and the incidence of germline/genetic mutations.

Aldosteronoma

Aldosterone-secreting adenomas have been reported in children as young as 3 years of age. The tumors are typically unilateral and are associated with a female gender distribution. Bilateral micronodular adrenocortical hyperplasia is more common in older children and favors males. Hyperaldosteronism is characterized by hypertension, hypokalemia, and suppression of the renin-angiotensin system. Headache, dizziness, muscle fatigue, tetany, and growth failure may be presenting symptoms. Like other adrenal adenomas, the treatment of aldosteronomas is surgical removal. Hyperaldosteronism caused by bilateral adrenal hyperplasia is treated with mineralocorticoid antagonists (spironolactone or eplerenone). Antihypertensive agents such as amiloride should be added as necessary [218, 219].

Adrenal Adenoma

Adenomas are benign masses that are likely to be responsible for over-secretion of endogenous steroids (Cushing's syndrome) [220] as well as rare cases of aldosterone oversecretion (Conn's syndrome) [218, 219]. Symptoms from these tumors are associated with excessive hormonal secretion such as virilization, hypertension, and hypercortisolism. High concentrations of plasma and urinary cortisol levels are detected along with low levels of adrenocorticotropic hormone levels consistent with a functional adrenal mass. Diagnosis can be confirmed with CT or MRI scanning of the abdomen and pelvis to determine the location and size of the mass. There are no clear differentiating radiologic features to establish benign versus malignant disease, though larger-size masses tend towards malignancy [221]. As such, all adrenal adenomas should be resected and may be performed via laparoscopic techniques based upon the success of these procedures in adults.

Adrenal Calcification

Adrenal calcification is commonly detected on routine imaging. The most common cause of adrenal calcification is neonatal hemorrhage; therefore, a careful history should be taken regarding a history of anoxia or trauma at birth. Neuroblastomas, ganglioneuromas, cortical carcinomas, pheochromocytomas, and adrenal cysts may cause calcification. Such calcification is typically unilateral and can be seen within the underlying mass on imaging. In locations where tuberculosis is endemic, tuberculous calcification within the adrenals is common. Finally, extensive bilateral calcifications are common in infants with Wolman disease, a metabolic disorder characterized by a deficiency of lysosomal acid lipase.

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Gastrointestinal Tumors in Children

15

Alan P. Ladd and Jay L. Grosfeld

Introduction

The presentation of a gastrointestinal tumor remains a rarity in even the dedicated practices of surgery for children. Data remains scarce as to the true incidence of primary gastrointestinal (GI) tumors in children. Primary tumors of the GI tract are estimated to compose less than 5 % of all pediatric neoplasms; however, this estimation of prevalence reflects the population occurrences of the 1950s [1, 2]. More conclusive and contemporary data depict the incidence of GI malignancies at 0.027 cases per million in 2005, but are limited to the occurrence of solid malignancies of children [3]. Estimates as to the prevalence of primary GI malignancies with the incorporation of GI-associated lymphomas approach 1.0–1.2 % of all pediatric malignancies [4, 5]. The scarcity of published reviews or comprehensive population datasets of GI malignancies has led to the inability to thoroughly study and devise treatment algorithms for the majority of these tumors, and continues to promote the presentation of the multitude of these cases as small, retrospective case reports in the literature. Conclusive statements as to the natural history or summative outcomes for these GI-associated tumors cannot be derived other than mere generalizations from presentations of heterogenous patient cohorts.

Larger reviews of GI-related neoplasms in children note the occurrence of malignant tumors throughout the gastrointestinal tract, from the level of the esophagus to that of the rectum. In these comprehensive series, lymphomas compose 74–82 % of the GI-related malignancies described [3, 4, 6]. In reference to the remaining primary malignancies of the GI tract, the review of Zhuge et al. of the solid GI malignancies represents the most detailed depiction of their occurrence. Through a 32-year review of the Surveillance, Epidemiology, and End Results (SEER) database, a distribution of carcinomas, sarcomas and neuroendocrine tumors has been identified at 41 %, 43.8 %, and 10.5 %, respectively, among tumors of the foregut and small intestine [3]. No study to date has reflected on the occurrence of colorectal malignancies in children to this published prevalence data but approaches 5.5 % among all tumors in smaller, single-institution series [4].

Noting the scarcity of primary gastrointestinal tumors within the alimentary tract, formal comments as to the natural presentation of these masses are limited. The clinical presentation of these tumors, which arise anywhere from the level of the esophagus to the rectum, is either incidental or based on symptoms related to the mass or mass-effect of the tumor. The majority of tumor presenting symptoms includes abdominal pain (71 %) and vomiting (47 %) [4]. Few tumors present as an incidental abdominal mass (4 %), as occult gastrointestinal bleeding (7 %), or with signs of intestinal obstruction (7 %). Up to a quarter of these tumors may lead to intestinal obstruction by comprising the pathologic leadpoint of an intussusception process. Site of origin of this heterogenic population of tumors plays as much a role in their presenting complaints and symptoms, as the pathology involved with the tumor.

The tumors of the gastrointestinal tract can best be categorized based on their cellular differentiation. Extrapolating the described histologic coding of tumors utilized by Zhuge et al., based on the International Classification of Disease for Oncology, the tumors can be categorized as follows, by relative prevalence (among adult patients) [3, 6]:

Lymphoma
- Burkitts lymphoma
- Non-Hodgkins, Non-Burkitts lymphoma

Sarcoma
- Gastrointestinal stroma sarcoma (GIST)
- Leiomyosarcomas
- Peripheral or Primitive neuroectodermal tumor
- Rhabdomyosarcoma, spindle cell or NOS

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- Myosarcoma
- Ewing's sarcoma
- Epithelioid sarcoma
- Spindle cell carcinoma
- Sarcoma, NOS

Carcinoma
- Adenocarcinoma and mixed subtypes
- Signet ring cell carcinoma
- Mucinous and Mucin-producing adenocarcinoma
- Carcinoma, diffuse-type or NOS
- Squamous cell carcinoma

Neuroendocrine Tumor (NET)
- Carcinoid tumor, malignant
- Carcinoid tumor, benign
- Neuroendocrine carcinoma

Teratoma
- Malignant
- Benign

Hyperplastic Stromal tumor, benign
- Inflammatory pseudotumors
- Peutz-Jeghers polyposis
- Juvenile polyps/hamartomas
- Leiomyoma
- Neurofibroma
- Ganglioneuroma
- Hemangioma

Lymphoma

Given the significant proportion of the body's immunologic function that is supported by the gastrointestinal tract, the high occurrence of lymphomas as GI-related malignancies may be anticipated. Though the discussion of lymphoma is covered elsewhere in this text, a few unique aspects of GI-related lymphoma is provided.

Non-Hodgkin's lymphoma is the most common malignancy affecting the gastrointestinal tract in children. These hematologic tumors, including Burkitt's lymphoma, currently comprise greater than 70 % of reported gastrointestinal malignancies [3, 4, 6]. Burkitt's lymphoma is the most common tumor of the small intestine, composing more than 90 % of small intestinal lymphoma, and comprises the second most common malignancy of the colon, behind adenocarcinoma [4, 6]. Gastrointestinal lymphomas may occur anywhere along the GI tract, but usually occur in the region of the terminal ileum and ileocecal valve [4, 6]. Their presentation is often marked by the presence of intestinal obstruction or the identification of an idiopathic, intraabdominal mass. Obstructive symptoms are either from their involvement in an intussusception process or from direct occlusion of the intestinal lumen. Surgical management of these lesions is directed at either complete resection or palliative intervention for relief of associated signs of obstruction prior to systemic chemotherapy.

Isolated gastric lymphomas in children are similar in apparent etiology to those noted in adults, with a high association with *Helicobacter pylori* colonization. The mucosa-associated lymphoid tissue lymphoma (MALToma) is felt to result from the progressive, malignant degeneration of the stomach mucosa from the *H. pylori* infection, with rare cases of metastasis. Specific treatment for the MALToma relies on the focused treatment of the infectious *H. pylori* organism, with the use of systemic chemotherapy in the treatment of recurrent or metastatic disease [7, 8].

Gastrointestinal Stromal Tumor

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumor in adults. However, in children these tumors are quite rare. Through reported retrospective case-series at large-volume, pediatric centers with oncologic expertise, the reported incidence of these tumors lie between 0.02 and 0.08 cases per million children [9, 10]. Through 2007, reported registries from the SEER database had only identified 20 cases among patients less than 19 years of age. These tumors appear to have distinct differences in their genetic predisposition as compared to the defined GIST tumors of adulthood. As identified by Pappo et al, the occurrence of the commonly identified KIT and PDGFR protooncogenes in 90 % of adult GIST tumors is not found in similarly identified stromal tumors in children. In contrast, the rate of such oncogene expression in childhood tumors is only found in approximately 15 % [9, 11].

Presenting signs and surgical management are discussed in Chap. 27 of this text, for reference. With surgical resection, 5-year survival is reported between 91 and 100 % [9].

Leiomyosarcoma/Leiomyoma

Since the identification in 1998 of receptor tyrosine kinase KIT expression by GIST tumors and the determination of KIT expression as the major immunophenotypic criteria for GIST diagnosis, the diagnoses of leiomyosarcoma (LMS), leiomyomas, and leiomyoblastomas from all prior case reports have come into question [12–14]. The prior determinations that 7 % of childhood malignancies were comprised of soft tissue sarcomas and that those with intestinal involvement made up 2 % of this category, may be overestimates for the true incidence of these non-KIT tumors [15, 16]. In two contemporary publications that clearly delineate between GIST and LMS among the stromal tumors of the gastrointestinal tract, the ratio of occurrence approaches 2:1 in children

[14, 17]. All published information and characterizations of LMS and leiomyomas, especially of the stomach, from case series prior to 2000 must be scrutinized.

LMS and leiomyomas are tumors with typical features of smooth muscle differentiation, with LMS representing the malignant variant. Histologic characterization of LMS includes interlacing spindle cells with eosinophilic cytoplasm, paranuclear vacuoles, and blunt-ended nuclei; along with alpha-actin or muscle-specific actin, vimentin, desmin, and A-SMA expression by immunohistochemical staining [14, 18, 19]. The identification of malignancy and determination of leiomyoma from leiomyosarcoma incorporates the parameters of the number of mitoses per high-powered fields, presence of metastasis, cellular atypia, tumor necrosis and myxoid changes [6, 20, 21]. These immunohistochemical and histologic characteristics are also essential in differentiating LMS tumors from GISTs, rhabdomyosarcomas, malignant peripheral nerve sheath tumors, myofibroblastic proliferation, and other sarcomas [14, 16].

Outside of the stomach where gastrointestinal stromal tumors are nearly all GIST tumors, the occurrence of LMS is felt to occur anywhere along the gastrointestinal tract, with cases often involving the small intestine. Their presenting symptoms range from presentation with intestinal obstruction, perforation or visceral complaints from that of a mass lesion, to the development of occult or active hemorrhage associated with ulceration and tumor necrosis [21].

Complete surgical excision of these lesions remains the goal of treatment. Wide local excision for tumors of suspected malignancy is recommended along with assessment of the associated lymph node basin. Investigation for metastasis should be part of the intervention, though the prevalence of metastases is much less in children, when compared to that of adults [6]. Based on outcomes from adult series, the use of adjuvant chemotherapy may be beneficial in children with residual LMS disease. Current treatment regimens employ doxorubicin and/or ifosfamide-based chemotherapy. The use of radiotherapy has only been anecdotal for treatment of gastrointestinal malignancies in children [6, 14]. Based on results from pediatric case series that incorporate outcomes from gastrointestinal LMS, survival is approximately 59 %, with variable disease-free duration periods of 5 months to 21 years [14, 22–24].

Colonic Carcinomas

The occurrence of colorectal carcinoma is second only to primary liver malignancies as the most common solid malignancy of the gastrointestinal tract. From contemporary reviews of national databases, the annual incidence of these tumors is between 0.2 and 1 per million population, with a steady rate of occurrence over the last two decades [25–27]. Though historic references have depicted a higher occurrence of carcinomas of the colon in males, more recent, large population-based reports note a near equal or slightly greater predilection (1.5:1) in the male gender. Of patients younger than 20 years of age, the greatest incidence lies in those children 15–20 years of age [28].

No clear predominant histology of colorectal carcinoma in children can be concluded from the current literature. In the largest study to date, based on the United States' SEER database published from April 2008, adenocarcinoma comprised 58 % of the cases of colonic carcinoma, with mucinous and signet ring adenocarcinomas accounting for the remaining 42 % in that series. The prevalence of these subtypes of carcinoma was greater than that for carcinoid tumors of the colon by 1.8:1 [25]. These data stand in contrast to large series, single-institutional data noting a higher prevalence of mucinous adenocarcinomas in up to 60–80 % of those cases [28, 29]. By comparison, the presence of mucinous carcinoma in adult colorectal carcinoma only approaches 5–15 % [26].

Etiology for carcinoma of the colon in children is majorly sporadic [30]. In contrast to a report by Durno et al. where over 60 % of pediatric and adolescent cases (younger than 24 years) were shown to have a hereditary risk factor, other international series report the occurrence of predisposing factors to be between 10 and 30 % [29, 31, 32]. Autosomal dominant syndromes including hereditary nonpolyposis colon cancer, familial adenomatous polyposis, juvenile polyposis syndrome, and Peutz-Jeghers syndrome are felt to carry an increased susceptibility for the development of carcinoma of the colon in younger patients, but have been rarely reported in larger case-series. Additionally, chronic colitis from affliction with ulcerative colitis is implicated in the development of colon cancer [31, 33, 34]. The rare presence of predisposing factors is in sharp contrast to the often preexisting occurrence of an adenomatous polyp leading to colon cancer in adults [30].

The presentation of children with carcinoma of the colon is often depicted with abdominal pain in 80–85 %. Additional symptoms often include vomiting or signs of distal intestinal obstruction (50–57 %), constipation (33 %) or diarrhea (28 %), and hematochezia or rectal bleeding in 25–30 % [28, 29]. The lack of specificity of these symptom profiles and lack of suspicion for malignancy as a probable etiology results in symptom duration approaching 3–6 months prior to actual diagnosis [26, 28]. Physical examination of these afflicted children rarely discerns malignancy as the etiology prior to either endoscopic or laparotomy assessment leading to diagnosis. The presence of either a palpable mass or fullness to the abdomen or rectum has been identified in up to 26 % of the children [28]. Thus, no clear algorithm for a common diagnostic pathway of assessment can be recommended outside of the acute

evaluation of more foreboding diagnoses of obstruction, mass, or rectal bleeding in patients demonstrating such findings. An additional unique feature of this class of malignancies in children, from that of adults, lies in their location of colon involvement. In children, the location within the colon most involved with tumor is that of the right colon in 46 %, left colon in 20 % and rectum/anus in an additional 15 % of cases [25]. This may then be associated with the lack of symptoms earlier in the course of disease and potentially affect timing of presentation.

The primary goal of treatment in children with the diagnosis of colonic carcinoma remains that of complete surgical extirpation. The majority of cases present as advanced disease in children with lymphatic involvement or disseminated disease reported in approximately 80 % of all cases [28, 29, 32]. Unfortunately, with the high prevalence of advanced disease encountered with this malignancy, adjuvant chemotherapy is required in the care of most juvenile patients. The standard in chemotherapy is identical to that for adult patients with the use of fluorouracil-based chemotherapy. Since 1986, routine recommendations have been made for the additional use of leucovorin in the treatment of unresectable or metastatic disease. Reported usage of radiation therapy has only been recommended in lower colonic and rectal malignancies, with utilization in less than 15 % of patients [25, 28].

Based upon overall data from the SEER database, 5- and 10-year disease free survival, including all tumors of the colon and rectum, is 61 % and 57.9 %, respectively. Segregating the outcomes based upon the presence of adenocarcinoma, mucinous adenocarcinoma and signet ring carcinoma, the 5- and 10-year disease free survivals are 55 % and 45 %, 33 % and 25.7 %, and 18.5 % and 17 %, respectively for tumor histology [25]. This survival has shown improvement for adenocarcinoma, with improved 5- and 10-year survivals during the latest decade since 1993 at 58.2 % and 49 %, as compared to the prior two decades reviewed. With regards to significant factors as determinants of improved outcome based on multivariate analysis, complete surgical resection and tumor stage were independent predictors of outcome, with the presence of signet ring histology proven as a predictor of worse outcome for this pediatric population [25]. Overall these outcomes for adenocarcinoma of the colon and rectum are worse than that reported for older patients, with a 75 % 5-year survival [35].

The evaluation and treatment of colorectal carcinoma in children especially with its presence at a young age requires additional consideration of familial germline mutation. The evaluation for the conditions of familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer (HNPCC) should be performed in afflicted children. The identification of these germline mutations of the APC gene or MLH1 and MSH2 in these childhood cohorts, respectively, should be utilized as the basis for additional genetic testing and sibling screening [30].

Neuroendocrine/Carcinoid Tumor

Neuroendocrine tumors (NET), including carcinoid tumor, comprise a subset of a larger categorization of tumors deemed gastroenteropancreatic neuroendocrine neoplasms (GEP-NEN) based on their common origin from neuroendocrine cells of the gastroenteropancreatic system. Thus, this larger category of GEP-NEN tumors includes islet cell tumor, gastrinoma, glucagonoma, VIPoma (vasoactive intestinal polypeptide-producing tumor), and non-functional gastroenteropancreatic tumors. The most supported theory as to the cell of origin for these tumors has been put forth by Gosset and Masson in which they hypothesized that the Kulchitsky cell with its argentaffin properties most resembled these tumors [36, 37].

Neuroendocrine tumors of the gastrointestinal tract are quite rare in children and are estimated to comprise 0.08 % of all malignancies encountered at tertiary care, pediatric hospitals [37]. Though impossible to extrapolate an accurate tumor incidence from the variety of small-series, case-reports that outline the presentation of these tumors in children; larger, population-based databases of tumors within North America and Europe place the relative contemporary incidence of these tumors to 1.3–2.6 cases per 100,000 population per year, having increased from 0.3 three decades prior [38, 39]. In two, larger pediatric case-series, the proportion of carcinoid tumors among all gastrointestinal tumors in children, ranged from 3.4 to 16.2 % [39, 40]. In comparison, NETs comprise only 0.8 % of all recorded GI tumors in adult cancer registries in England.

Globally, GEP-NENs are currently classified by the 2010 World Health Organization classification for all such tumors. This classification maintains the information for differentiation and proliferation of the neoplasms and includes the TNM (Tumor, Node, Metastasis) staging classification. The 2010 classification makes the assumption that all GEP-NENs are potentially malignant, with the categorization dependent on the probability of metastasization. Tumors are classified by the combination of information on the extent of their mitotic activity and the relative presence of Ki-67 index, an immunohistochemistry marker of cellular proliferation. Well-differentiated tumors, as carcinoid tumors, are classified as low-grade neuroendocrine tumors. Neuroendocrine carcinomas refer to either intermediate- or poorly-differentiated neuroendocrine neoplasms and are designated as intermediate- or high-grade neoplasm classifications [40–42].

Gastroenteropancreatic neuroendocrine neoplasms present with a wide variety of signs and symptoms, often deter-

mined by their degree of hormonal activity and occasionally by their mass-effect. Gastrinomas, which stimulate the production of gastric acid within the stomach through an unregulated gastrin response, will often produce symptoms of gastroesophageal reflux or findings of recurrent duodenal ulcerations. VIPomas are often diagnosed by their production of a watery diarrhea and will result in significant clinical dehydration. Symptoms of diarrhea, stomach cramps and flushing are the classic presentation of functionally active carcinoid tumors that have metastasized, allowing for a systemic-effect to their serotonin release and avoidance of liver-associated first-pass degradation [41]. Though these above symptom constellations are classic for the presentation of these often hormonally active tumors in adults, their presentation in children are much less predictable. Through the numerous case-series published on the presentation of these tumors within pediatric populations, their spectrum of presenting symptoms include localized or non-localized abdominal pain and occasional concerns for an acute abdomen [37, 43], colicky abdominal pain, episodic bilious or non-bilious emesis, an abdominal mass, anorexia [44], rectal bleeding [45, 46], fever, and nausea [47]. The classic presentation with a "carcinoid syndrome" of flushing and diarrhea was not reflected among these case reports of children, most likely related to the extremely rare presentation of these tumors with a metastatic process in children. As in adults, these tumors have been described at each portion of the gastrointestinal tract, but the majority has been reported to be within the appendix, found either incidentally or with clinical signs of appendicitis.

The majority of reported NET/carcinoid tumors in children are diagnosed incidentally and rarely based upon symptoms of carcinoid syndrome. These classic symptoms of cutaneous flushing, diarrhea, or asthma-like respiratory distress are quite rare in children with NET tumors. Evaluation of NET as a tumor with functional serotonin hypersecretion is often secondary to resection of the incidental tumor. Whether performed as part of the pre-operative or post-operative assessment, 24-h urine collection for 5-hydroxyindolacetic acid (5-HIAA) and Chromogranin-A serum levels should be determined. These levels do not portend a high degree of specificity for NET tumors but may reflect overall tumor mass and the presence of metastatic disease. In addition, elevations in these markers at time of diagnosis offer an additional avenue for surveillance for tumor recurrence [6, 40, 41, 48].

The imaging assessment of NETs remains a process of multi-modality interrogation for the primary tumor site and/or the presence of metastatic disease. A standard modality in assessment for primary tumor location remains transverse imaging with computed tomography (CT). Despite its broad utilization, CT alone allows for location of the primary tumor in 22–45 % of patients [41]. The sensitivity in the determination of metastatic disease, usually to the liver, reaches 79 % for CT and is improved to 95 % with the utilization of MRI. Nuclear medicine modalities offer additional routes for tumor localization. Scintigraphy utilizing somatostatin receptor analogs allows for improvement in the sensitivity of evaluation for metastatic disease. ^{99m}Technetium bone scan should be utilized in patients with bone pain or for determination of potential metastasis to bone or spine. Newer modalities of Indium (^{111}In)-labeled octreotide and gadolinium (^{68}Ga) based positron emission tomography (PET) scanning are showing improved quality and sensitivity and may offer future options for radioactive somatostatin-receptor guided treatment [41, 49].

The operative management for NETs continues to reflect the standards of oncological resection for tumors arising in pediatric and adult patients. There are no evidence-based guidelines for the surgical management of these tumors given their rarity in adults and children. The standard goal of surgical intervention remains surgical extirpation, especially in cases of unknown metastatic involvement. Resection of involved small intestine and colon requires the concurrent resection of associated lymphatic drainage and regional lymphadenectomy. For the more common lesion of the appendix, those tumors less than 1 cm in size without serosal or mesenteric fat involvement require no more than simple appendectomy if clear margins can be maintained. But, for tumors with invasion of the serosa or beyond or for lesions greater than 2 cm, standard practice recommends the addition of a right hemicolectomy for local control [43]. For lesions of the duodenum and pancreas, the radical nature of potential surgical resection should be balanced against the potential for exocrine or endocrine insufficiency. Organ-preservation is often recommended for sporadic cases of NETs; whereas, syndromic associations, as in MEN-1, often support more radical intervention [41]. Cytoreduction techniques in cases of metastatic NETs have proven improvement in symptoms of carcinoid syndrome, especially with liver involvement [50].

Adjuvant treatment for NETs remains focused on reduction of systemic symptoms from metastatic disease. The use of somatostatin analogues has been well described in the treatment of metastatic disease with the goal of carcinoid symptom reduction, with reported symptomatic improvement in 64 % [14]. Recent studies have also identified the inhibiting effect of these somatostatin analogs toward tumor proliferation with improvement in progression-free survival versus placebo-controlled subjects [41, 51, 52].

Because of the rarity of these tumors in the pediatric population, summative outcome data is not available. The major positive prognostic factors in the management of these tumors remain the absence of metastatic disease and the ability to achieve local disease extirpation. Fortunately, few children present with disease metastasis and are cured with

tumor resection. Those reported with metastatic disease are often well controlled with somatostatin analogues, with reports of mortality being quite rare. In review of data from the US SEER database that is inclusive of adult and pediatric patients, 5-year survival rates for tumor involvement of the gastrointestinal system are 76.3 % for localized disease, 69.4 % for regional disease and 40.9 % for disease with distant involvement. For appendiceal primaries the 5-year survival rates are 80.8 %, 88.1 % and 9.6 %, respectively [39].

Gastrointestinal Teratoma

Teratomas are embryonal neoplasms that are composed of all three germinal cell layers, which include ectoderm, endoderm and mesoderm, and are derived from totipotent, primordial germ cells [53]. Teratomas are classified by the World Health Organization as a histologic category of germ cell neoplasms, based on this cellular origination. Those that arise within the gastrointestinal tract are classified as extragonadal teratomas, which also include the more frequent locations of the sacrococcygeal area, retroperitoneum, mediastinum, and neck regions [54, 55].

Teratomas of the gastrointestinal (GI) tract are quite rare. Though there are reports of teratomas involving various regions of the gastrointestinal tract, including the stomach, ileum, colon and rectum, the vast majority of reported cases are of a gastric location [54, 56–58]. Gastric teratomas, themselves, are extremely rare and compose less than 1–2.5 % of all teratomas [54, 59, 60]. In a recent review of the reported world literature by Gupta et al, a total of 102 gastric teratoma cases were identified over the timeframe of 1966–2000. Of these reported cases, over 90 % occurred in male children [53].

Presentation of GI teratomas is often depicted by its relative mass effect and impact on the associated gastrointestinal tract. Initial presentation is usually as a palpable abdominal mass or with abdominal distension, with or without vomiting from extrinsic or intrinsic GI obstruction. Intramural components of the tumor may ulcerate or hemorrhage, leading to rare reports of hematemesis, hematochezia or melena in infancy and childhood [61–64]. Gastric teratomas may present with dehydration secondary to vomiting from extrinsic obstruction. Only individual cases of GI perforation have been attributed to rupture of a gastric teratoma [65].

Gross categorization of teratomas divides them into mature, immature and malignant forms. Mature teratomas are comprised entirely of differentiated tissues of the germinal cell layers. Immature forms of teratoma are defined by their incorporation of incompletely differentiated, fetal tissue elements. Malignant classification is determined by the presence of malignant tissue elements, such as yolk-sac, germinoma, choriocarcinoma, and embryonal carcinoma [53]. The majority of teratomas, including those of GI origin, are mature in nature. Malignancy has been documented in only rare, individual case reports within the pediatric literature. Unlike teratomas of sacrococcygeal origin, GI teratomas are not felt to have the potential for malignant degeneration [53].

Given their common presentation as palpable abdominal tumors, the differential for these types of tumors will include neuroblastoma, hepatoblastoma and mesoblastic nephroma. Evaluation with abdominal roentgenography may be suggestive of teratoma by the presence of globular calcifications (35–60 %), versus smaller calcifications of neuroblastoma. Diagnostic evaluation with the use of ultrasonography, computed tomography or magnetic resonance imaging will allow for improved delineation of the tissue of origin and allows for exclusion of similar mass-type lesions of the abdomen [53, 61]. This imaging will also allow for the identification of characteristics of GI teratoma that include cystic and solid areas within the tumor and any evidence for direct tissue invasion, though rare.

The complete surgical excision of GI teratomas is curative. Given the documented extreme rarity of GI teratoma malignancy, margins of excision should be kept to a minimum, as technically feasible [53, 54, 61]. Primary reconstructive surgery following resection of gastric or intestinal tumors should be achievable. Recurrence following resection is quite rare, but ongoing follow-up and surveillance for recurrent disease following resection is recommended. At this current time, there are no evidenced-based recommendations for the timing of follow-up assessment.

As malignancy of GI teratomas is defined by the presence of malignant elements of fetal tissue origin, the use of alpha-fetoprotein (AFP) is important in patient surveillance. AFP is produced by tissues of the fetal liver, yolk sac and gastrointestinal tract [53, 66]. Though proven to be present in a majority of malignant non-GI teratomas in children, AFP has been identified in benign cases, as well. As AFP cannot be utilized as a predictor of malignancy, its role in patient follow-up is important, especially in those cases of age-normalized elevations seen pre-operatively. Increasing titers following resection may depict the presence of recurrence or residual tumor [53, 67].

Outcomes from primary resection of GI teratomas remain curative in the cases of all mature and the majority of immature tumors. In these cases, no adjuvant therapy is needed. Similar treatment is advocated by Marina et al in the treatment of all immature teratomas. They recommend the ongoing surveillance of these tumors with immature elements, with adjuvant chemotherapy only advocated by evidence of tumor recurrence [68]. Varied reports in the literature promote the use of adjuvant chemotherapy for the higher grade, immature forms and malignant tumors, as based on extrapolation of treatment from gonadal teratomas. Cisplatin-based chemotherapy is utilized in these patients based on the constellation of factors, including incomplete resection, lymph node involvement, metastases, and grade of immaturity [69–71].

No recommendations or reports are present for the use of radiation therapy for GI teratoma.

Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumor (IMT) is the current term most accepted to describe a neoplastic process composed of spindle cells, myofibroblasts, plasma cells and histiocytes. The various terms previously utilized to describe this tumor were inflammatory pseudotumor, pseudosarcomatous myofibroblastic proliferation, plasma cell granuloma, xanthomatous pseudotumor, inflammatory myofibrohistiocytic proliferation, and inflammatory fibrosarcoma [72, 73]. These tumors are often of pulmonary origin, but have been described in all tissues and locations, including the brain, eye, pericardium, heart, trachea, lymph nodes, bladder, pelvis and gastrointestinal tract, omentum, retroperitoneum and extremities [72, 74, 75]. The most common site of occurrence outside of the lungs is within the gastrointestinal mesentery and omentum, accounting for 45 % of extrapulmonary cases [76, 77]. Their occurrence within the gastrointestinal tract, especially within pediatric patients, remain rare with the true incidence being unknown. Within the gastrointestinal system, a greater number of cases are seen within the stomach in children. Numerous reports depict a slightly higher predilection of these tumors, either gastrointestinal or overall, in the female children [72, 78].

The true etiology of IMTs remains unknown. Two disparate thought patterns have emerged regarding the origin of these tumors as either a neoplastic origin or a process secondary to infection, trauma or inflammation [72, 79–81]. Each of these early theories draws support from the various histologic features of the tumor, with its combination of lymphocyte, histiocyte, and plasmocyte infiltrates within tumors as well as their heterogeneous orientation and density of fibroblasts and the occasional presence of mitotic activity and/or tissue necrosis [76, 78]. No direct correlation has been made to tumor development secondary to EBV or human herpes virus infection, or from exposure to infection by organisms such as Helicobacter pylori [73, 78, 79]. More recent immunohistochemical characterization of these tumors shows expression of cellular markers that include anaplastic lymphoma kinase (ALK), gene rearrangements on chromosome 2, clonal chromosome abnormalities and DNA aneuploidy. These findings support a neoplastic origin of the tumors and possible neoplastic potential has been contemplated [76, 79, 82–86]. A subpopulation of these tumors with more aggressive behavior of multi-recurrent, multi-centric and metastatic disease has been described [72, 76, 79, 87, 88]. With these reports of greater aggressive and malignant behavior, a consensus is emerging that IMTs represent a spectrum of tumors along an interrelated myfibroblastic continuum that may extend to the emerging pathologic identity of inflammatory fibrosarcoma [79, 87, 88].

The clinical presentation for IMT varies widely and is most dependent upon the site of origin for these tumors. Common constitutional symptoms of fever and weakness occur in most patients [7] while weight loss and night sweats have been seen in 15–30 % [79, 89]. For gastrointestinal IMTs, the clinical presentation often includes an abdominal mass, abdominal pain or upper gastrointestinal bleeding. Mass effect and the associated compression on the intestinal tract may present as symptoms of abdominal pain or vomiting from variable degrees of intestinal compression and/or obstruction. The presence of metastasis is infrequent at the time of diagnosis and is less than 5 % for all IMTs [85, 90]. Laboratory findings also remain nonspecific, often noting a hypochromic microcytic anemia, elevated platelet count, elevated erythrocyte sedimentation rate and occasional leukocytosis [73, 78, 79]. These laboratory findings are often seen to resolve in most cases following tumor resection and are often followed during post-operative surveillance for evidence of either recurrence or metastasis.

Diagnostic imaging for children afflicted with these tumors will correlate with the interrogation of presenting symptoms. Evaluation that leads to abdominal radiographs may depict circumscribed, amorphous calcifications within an IMT, in addition to the variable signs of gastrointestinal obstruction or intestinal displacement by a soft tissue mass. Interrogation of these masses with ultrasonography and computed tomography of the abdomen often demonstrate solid, well-demarcated masses which may also characterize them as multilobulated and/or heterogeneous masses. Tumor infiltration may be represented on these imaging modalities but is a rare finding [73, 91, 92].

Based upon the imaging alone, the presumptive diagnoses are often soft tissue sarcomas, lymphoma, and sometimes neuroblastoma [73, 91, 92]. With histologic evaluation and the identification of compact spindle cell arrangement, soft tissue sarcomas such as leiomyosarcoma, fibrosarcoma, rhabdomyosarcoma, and malignant fibrous histiocytoma will remain in the differential until immunohistochemical evaluation is performed [73, 93]. With recognition of inflammatory cell infiltrates, the differential may be expanded to the inflammatory subgroup of gastrointestinal autonomic nerve tumors or gastric inflammatory fibroid polyps [93–96]. The underlying histologic findings of a paucity of mitotic figures with the absence of anaplasia, the infiltration of lymphocytes and plasma cells among the bundles of spindle cells [73], and the suggestive immunohistochemical staining for membrane proteins all lead to the eventual diagnosis of IMT [79]. These immunohistochemical features often include immunopositivity with anti-smooth muscle actin, calponin, muscle-specific actin, and variable positivity with desmin and ALK-1 [79].

The goal of treatment of these tumors within the gastrointestinal tract or its associated mesentery or omentum lies in their complete surgical resection. Full resection appears to be the "gold standard" in their treatment [72, 79], with few cases of recurrence or metastatic potential being identified in the literature [75, 90]. Complete resection of any recurrent disease has also been supported, noting the low mitotic index characterizing the majority of these tumors and their poor response to adjuvant therapies of radiation, immunomodulation, or chemotherapy [72, 73, 79, 82]. Tumor regression with steroidal or non-steroidal anti-inflammatory drug use has been documented, and the use of cyclooxygenase 2 (COX-2) inhibition in unresectable or recurrent disease has been supported by the Children's Oncology Group [79, 97, 98].

In cases of complete surgical excision, complete cure is obtained in greater than 60 % of cases. Recurrences have been documented in 18–40 % of IMTs overall, with tumors of gastrointestinal origin demonstrating the higher recurrence rates [72, 73, 99]. Though most of the recurrences occur within the first year of surgery, recurrence has been identified up to 9 years following surgery [81, 100, 101]. Despite this, there remain no clinical or molecular markers for recurrence or metastasis for this tumor [76, 79] or for its sarcomatoid transformation noted in case reports [30]. Purported factors for the elevated risk of IMT recurrence include those of extra-pulmonary origin, size greater than 8 cm, or evidence of local invasion [72, 79, 87]. Though tumor size, degree of cellularity and mitotic rate do not relate to prognosis, findings of nuclear atypia, DNA aneuploidy, and p53 expression do suggest a more aggressive clinical course [74, 83, 102]. Mortality rates from tumor recurrences are 5–7 % [72, 86]. These recurrences have been demonstrated to present as metastases to the lung and brain, along with adjacent organ involvement of the liver, spleen, kidney, pancreas and adrenal gland [76, 94]. Based on the largely sporadic nature of local tumor or metastatic recurrence, a defined plan of post-operative surveillance has not been determined, but loco-regional interrogation along with pulmonary field assessment can be rationalized for those children with more "aggressive" tumors.

Polyps/Polyposis Syndromes

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is the most common of all polyposis syndromes. It has an incidence of 1 in 8000 to 10,000. For the majority of patients it is inherited as an autosomal dominant trait with mutations in the adenomatosis polyposis coli gene, though 20–30 % of the mutations are *de novo* mutations [103–105]. The polyposis is characterized by hundreds to thousands of adenomatous polyps distributed throughout the colon. A related polyposis condition with autosomal recessive pattern of inheritance and a milder phenotypic presentation with regards to number of polyps present is seen in individuals with a defect in the *MYH* gene on chromosome 1p34 [106].

The polyposis of FAP may include polyps of the stomach and duodenum in approximately 45 % of children [104]. The colorectal adenomas have a significant risk of progression to adenocarcinoma by the third decade of life and for duodenal adenocarcinoma in up to 10 % of those afflicted. Individuals with FAP are also at risk for a variety of other carcinomas and sarcomas involving the thyroid gland, brain, the soft tissue, as well as a 1 % risk of hepatoblastoma in early childhood [103].

Presenting conditions for FAP are usually either presymptomatic presentation of an individual with an afflicted family member or presentation based on clinical symptoms of rectal bleeding or related symptoms [104]. Genetic screening for the APC mutation is usually recommended by 10–12 years of age for children within an APC kindred. Endoscopic surveillance should begin with lower endoscopy at the same age range, with screening upper endoscopy performed upon identification of colonic adenomas. Screenings should include biopsy of the lesions to identify development of dysplasia. Average age for the presentation of adenomas is 16 years.

The presence of an APC mutation necessitates eventual surgical intervention for this genetic disorder. A total proctocolectomy with ileal pouch-anal anastomosis is recommended to eradicate the colonic mucosa, once adenomas are identified during screening and when physiologically appropriate in a growing adolescent [103]. Surveillance of the upper gastrointestinal tract should continue life-long and should be repeated every 1–5 years, depending on the number of lesions [104].

Juvenile Polyps/Polyposis

Juvenile polyps are hamartomatous lesions that may present in up to 2 % of children within the first decade of life, by an average of 5–6 years. In most childhood cases these will be solitary polyps, though two or more polyps may be present in 58 %. These polyps typically occur in the colon, with two-thirds beyond the splenic flexure. These polyps rarely harbor pathologic changes and can be removed endoscopically with no additional surveillance required if there is no evidence for polyposis [103].

The term juvenile polyposis describes the presence of tens to hundreds of polyps that are found in the colon, as well as in the small intestine and stomach, on occasion. It is a rare autosomal dominant syndrome with an incidence of approximately 1 in 100,000 [104]. The underlying genetic

defects for juvenile polyposis lie within defects of transforming growth factor-beta or bone morphogenetic protein signaling and may be present in 40–60 % of cases. These polyps usually occur in the colon but may occur in the stomach, small intestine and duodenum [6, 103, 107].

Three versions of polyposis have been described. In polyposis of infancy, the extent of polyposis often leads to diarrhea with a protein-losing enteropathy and hemorrhage that can portend death by 2 years of age. Juvenile polyposis coli and diffuse juvenile polyposis identify polyposes either within the colon or diffusely within the gastrointestinal tract, respectively. Symptoms for these disorders are often occult gastrointestinal bleeding and anemia, with occasional development of intussusception or prolapse. For these conditions of polyposis, repeated endoscopic polypectomies or isolated surgical resections are required for control of the clinical symptoms. Rare reports have identified adenomatous changes or carcinoma degeneration within juvenile polyposis, thus upper and lower endoscopic surveillance should be performed [107, 108].

Peutz-Jeghers Polyposis

Peutz-Jeghers syndrome is an autosomal dominant disorder that is characterized by mucocutaneous pigmentation of the buccal, labial and anal regions of the body that is associated with hamartomatous polyps of the gastrointestinal tract [107]. Hamartomas often involve the jejunum, as well as the remainder of the gastrointestinal tract [103]. A majority of individuals afflicted with this syndrome will develop symptomatic polyposis by 20 years of age. Symptoms associated with the polyposis often include abdominal pain, intussusception and/or gastrointestinal bleeding [109]. The incidence for the syndrome is approximately 1 in 200,000 and is caused by a germline mutation in the LKB-1 gene with *de novo* mutations occurring in 25 % [104].

The polyps associated with this syndrome are at risk for malignant degeneration, with a lifetime risk of malignancy of 90 % [104]. Endoscopic surveillance with colonoscopy should be performed every 3 years following the onset of symptoms and diagnosis of the polyposis. Upper endoscopy and upper intestinal contrast study should also be performed biannually [104, 110].

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Liver Tumors in Children

16

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Abbreviations

AFP	Alpha Fetoprotein
AMKL	Acute Megakaryoblastic Leukemia
CHIC	Children's Hepatic tumor International Collaboration
COG	Children's Oncology Group
ENCCA	European Network for Cancer Research in Children and Adolescents
FL-HCC	Fibrolamellar hepatocellular carcinoma
FNH	Focal nodular hyperplasia
GCTs	Teratoma (germ cell tumors)
GPOH	German Pediatric Oncology Hematology Study Group
HACE	Hepatic Arterial chemo-Embolization
HB	Hepatoblastoma
HCC	Hepatocellular Carcinoma
HC-NOS	Hepatocellular Neoplasm-Not otherwise specified
HLH	Hemophagocytic Lymphohistiocytosis
IMT	Inflammatory myofibroblastic tumor
JPLT	Japanese Pediatric Liver Tumors Study Group
LCH	Langerhahn's Cell Histiocytosis
LRN	Large regenerative nodules
NOS	Heptocellular tumor Not otherwise specified
NRH	Nodular regenerative hyperplasia
PEI	Percutaneous ethanol injection
PLUTO	Pediatric Liver Unresectable Tumor Observatory
POST-TEXT	POST-Treatment EXTent of tumor
PRETEXT	PRE-Treatment EXTent of tumor
RFA	Radiofrequency ablation
SIOPEL	Liver Tumor Study group of the Societe International Oncologie Pediatriqe
SPLIT	Study of Pediatric Liver Transplantation
TACE	Trans-Arterial chemoembolization
TCLT	Transitional cell liver tumor
TPN	Total Parenteral Nutrition
USL	Undifferentiated sarcoma of the liver
VLBW	Very Low Birth Weight
VOD	Hepatic veno-occlusive disease

Chemotherapy abbreviations see legend for Table 16.9

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Historical Context

As recently as the 1960s, surgical resection of malignant liver tumors in children carried a high perioperative mortality of over 30 %, mostly due to hemorrhage [1]. Increasing knowledge of segmental liver anatomy [2] and more sophisticated perioperative management reduced surgical morbidity, and yet operative mortality remained over 10 % in Exelby's 1974 landmark survey of the American Academy of Pediatrics Surgical Section. In this era, before the introduction of cisplatin based chemotherapy and modern surgical techniques, complete operative excision carried a high risk of morbidity and mortality, but offered the only chance for cure [3]. Maneuvers introduced to minimize bleeding including the Pringle maneuver (clamping of the afferent vascular pedicle), total vascular occlusion (clamping of the aorta and clamping or balloon occlusion of the inferior vena cava), hypothermic and hypotensive anesthesia [4], and preresection ligation of the hepatic inflow and outflow vasculature. A decade later, Price reports in 1982 a series of 11 resections for hepatic neo-

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plasia in children with no operative deaths [5]. The increasing use of preoperative chemotherapy was perhaps even more important than the advances in surgical technique.

Our sophistication with chemotherapy for HB, and adjuvant use of antiangiogenic regimens for HCC continues to evolve. One key advance of chemotherapy has been in a neoadjuvant setting to shrink the tumor and enable complete and safe surgical resection. In addition to the two most common malignant liver tumors in children, Hepatoblastoma (HB) and Hepatocellular Carcinoma (HCC) there are a host of benign tumors and more rare malignant liver tumors which may appear in children. The past three decades have brought significant advances in our epidemiology diagnostic acumen with latest generation radiographic imaging and percutaneous biopsy as well as landmark advances in both chemotherapy and surgical technique [6].

Differential Diagnosis

Most solid hepatic masses in children, contrary to adults, are malignant lesions, however sometimes they represent rare benign diagnoses. The differential diagnosis of liver tumors in children includes epithelial tumors, mixed epithelial and mesenchymal tumors, mesenchymal tumors, germ cell tumors, and metastatic or secondary tumors. Following these broad categories a new consensus classification for pediatric liver tumors was recently developed [7]. This consensus classification is the product of the International Liver Tumors Pathology Symposium sponsored by the Children's Oncology Group (COG) in Los Angeles in March of 2011, and subsequent International Pediatric Liver tumors Biology Symposium sponsored by the Liver Tumor Study group of the Societe International Oncologie Pediatriqe (SIOPEL) and European Network for Cancer Research in Children and Adolescents (ENCCA) in Paris October 2011 (Table 16.1) [8, 9]. More rarely one may encounter metastatic lesions or contiguous invasion from primary pediatric solid tumors such as neuroblastoma, Wilms' tumor, or pancreatoblastoma. Hepatic involvement in hematologic malignancies such as hemophagocytic lymphohistiocytosis (HLH), langerhahn's cell histiocytosis (LCH), and megakaryoblastic leukemia may occasionally mimic a primary hepatic malignancy. A variety of benign tumors can also occur in this age group the most common of which are benign vascular tumors [9] (Fig. 16.1). Other benign tumors include mesenchymal hamartoma, biliary cystadenoma, hepatic adenoma, focal nodular hyperplasia (FNH), macroregenerative nodules, dysplastic nodules, germ cell tumors, and inflammatory myofibroblastic tumors [10]. Non neoplastic masses such as vascular malformations, congenital and acquired cysts, abscess, hematoma, and fatty infiltration of the liver may occasionally be confused with liver tumors (Fig. 16.2). Hepatic hematoma or infarction should be suspected in any child with a history of hepatic trauma or in newborns with sepsis and coagulopathy; especially if there is

Table 16.1 Pediatric tumors of the liver, international consensus classification [7]

Epithelial tumors
Hepatocellular
Malignant
Hepatoblastoma (epithelial variants)
Pure fetal hepatoblastoma with low mitotic activity
Fetal, pleomorphic *(vs pleomorphic epithelial component)*
Fetal, cholangioblastic variant
Epithelial mixed (fetal, embryonal, small cell)
Small cell component, INI+/–
Hepatocellular carcinoma
Fibrolamellar HCC
Transitional tumors of the liver
Hepatoblastoma with HCC component
Benign
Hepatocellular adenoma (adenomatosis)
Focal nodular hyperplasia
Macroregenerative nodules
Premalignant lesions
Dysplastic nodules (low grade and high grade)
Biliary
Bile duct adenoma (biliary cystadenoma)
Cholangiocarcinoma
Mixed hepatocellular and biliary
Combined hepatocellular-cholangiocarcinoma
Mixed epithelial/mesenchymal or uncertain origin
Hepatoblastoma mixed
Epithelial and mesenchymal
Teratoid hepatoblastoma
Malignant rhabdoid tumor
INI– (documented *INI* mut)
INI+
Nested epithelial stromal tumor
Mesenchymal tumors
Malignant
Embryonal sarcoma
Rhabdomyosarcoma
Epithelial hemangioendothelioma
Angiosarcoma (adult type)
Synovial sarcoma
Other (DSRCT, PNET, NUT carcinoma…)
Benign
Infantile hemangioma
Cavernous hemangioma
Mesenchymal hamartoma
Germ cell tumors
Teratoma
Yolk sac tumor
Metastatic (secondary)
Metastatic
Hepatic involvement hematologic malignancy
Acute myeloid leukemia
Megakaryoblastic leukemia (M7)
Hemophagocystic lymphohistiocytosis (HLH)
Langerhahn's cell histiocytosis (LCH)

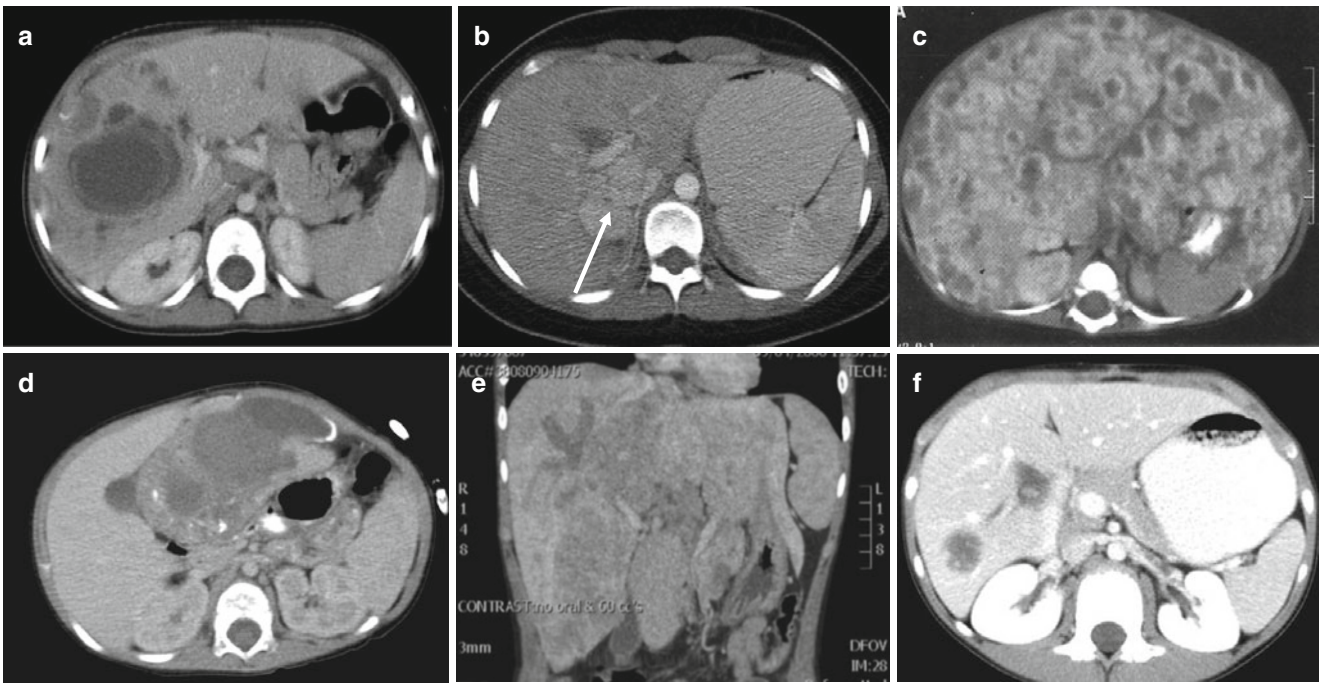

Fig. 16.1 Radiographic appearance of the most common hepatic benign and malignant neoplastic masses of the liver in children. (**a**) Mesenchymal hamartoma a complex multicystic mass with solid septae; (**b**) Focal nodular hyperplasia with arrow pointing to classic stellate central scar; (**c**) Diffuse infantile hepatic hemangioma with multiple nodules showing peripheral contrast enhancement; (**d**) PRETEXT II Hepatoblastoma; (**e**) PRETEXT IV + P hepatocellular carcinoma with involvement of main portal vein; (**f**) Metastatic tumor, two nodules of metastatic colorectal carcinoma in right anterior and posterior sections

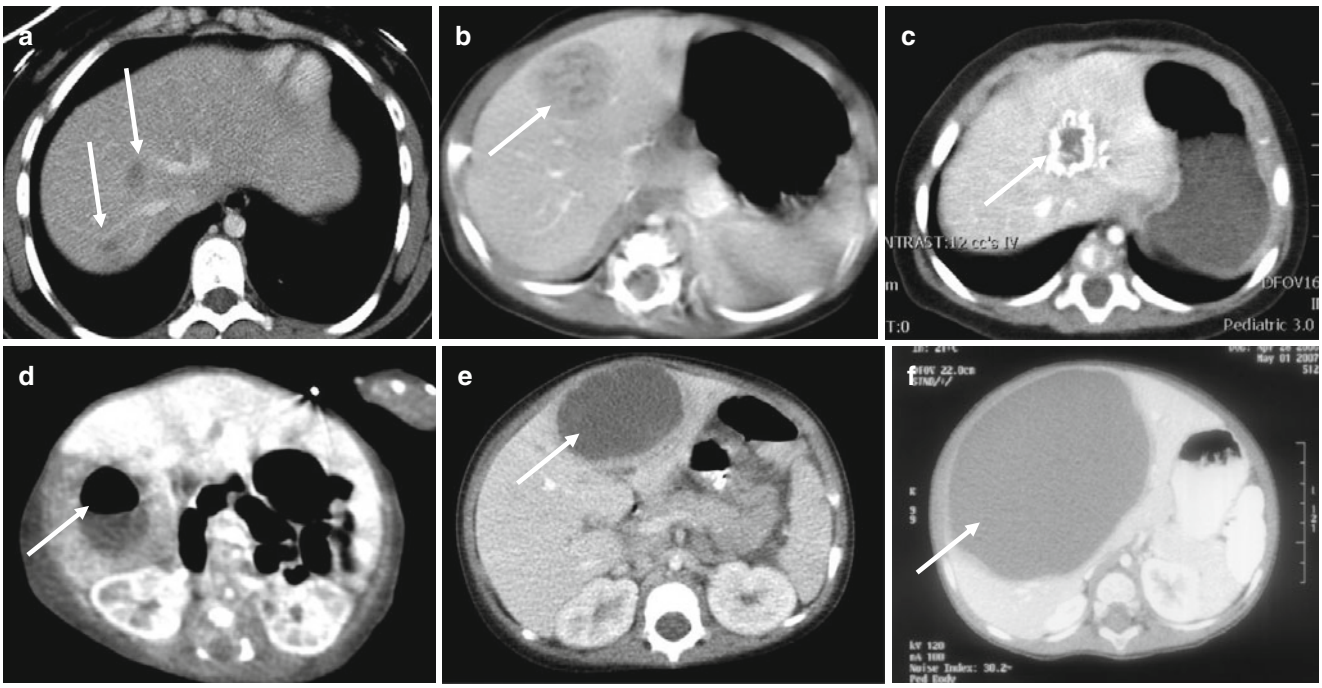

Fig. 16.2 Differential diagnosis: Radiographic appearance of non-neoplastic masses and cysts. (**a**) Multiple small bacterial abscess in a child with chronic granulomatous disease; (**b**) Inspissated bile lake in a child with biliary atresia and cholangitis; (**c**) organizing hematoma in a newborn with sepsis and coagulopathy; (**d**) infarction of right lobe liver and hepatic abscess (with air fluid level) in a premature baby with necrotizing enterocolitis; (**e**) acquired cyst is an amoebic abscess in a toddler with fever; (**f**) congenital cyst is a ciliated foregut cyst in an infant with abdominal distension and feeding difficulties

Table 16.2 Differential diagnosis based upon age at diagnosis [11, 12]

Age group	Malignant	Benign
Infant/toddler	Hepatoblastoma 43 % Rhabdoid tumor 1 % Malignant germ cell 1 %	Hemangioma/vascular 14 % Mesenchymal hamartoma 6 % Teratoma 1 %
School age/adolescent	Hepatocellular (transitional or HC-NOS tumors) 23 % Sarcomas 7 %	Focal nodular hyperplasia 3 % Hepatic adenoma 1 %

a history of perinatal birth trauma, thrombocytopenia, or hemodynamic collapse requiring cardiopulmonary resuscitation. Congenital liver cysts are rare and represent a spectrum ranging from large simple cysts, intrahepatic choledochal cyst, and ciliated hepatic foregut cyst. Acquired cysts might be bacterial, hydatid, or amoebic abscess.

Age at presentation and level of alpha fetoprotein (AFP) are frequent keys to differential diagnosis [11, 12] (Table 16.2). HB is most common in very young children; more than 80 % of children with HB are under the age of 3 at diagnosis [13]. More rare malignant liver tumors in infants and toddlers are teratoma, rhabdoid tumor, and biliary rhabdomyosarcoma [9]. Benign tumors in infants and toddlers may be infantile hepatic hemangioma or mesenchymal hamartoma. In older children and adolescents the main malignant liver tumors are HCC and undifferentiated sarcoma of the liver. HCC in this age group is comprised of an heterogeneous group of tumors, including tumors with features of both HB and HCC, *de novo* HCC tumors, HCC developing on an underlying metabolic or cirrhotic liver disease, and fibrolamellar carcinomas [14, 15]. Tumors in older children with features of both HB and HCC were previously, and somewhat imprecisely, dubbed "transitional cell liver tumors (or TCLT)." The new international consensus classification designates these tumors as [7]. The median age at diagnosis for HCC is about 12 years, but HCC has been described in children as young as 5 [16, 17].

High AFP favors a malignant diagnosis of HB. AFP is sometimes, but not always, elevated in HCC, and is less specific. Other conditions are sometimes associated with an elevated AFP level and this may lead to errors in diagnosis in the absence of a biopsy. Elevated AFP may be associated with other tumor types including germ cell tumors and benign liver tumors such as mesenchymal hamartoma [18] and infantile hemangioma [19]. Other conditions such as viral hepatits or tyrosinemia may be associated with a high AFP [20]. In these situations the AFP level is usually not as high as in HB. Alternatively high AFP is a nonspecific finding in infants as the high fetal AFP levels gradually decline to postnatal levels by 6–8 months of age. Consequently in children younger than 1 year it may be difficult to distinguish physiologic elevation of AFP from AFP secreted by a malignant tumor. Moreover, AFP is often secreted at very high levels in the regenerating liver and/or after ischemic liver injury. A spontaneous decline in the AFP level without any treatment is a good argument in favor of physiologic, not neoplastic, origin. Low AFP is seen in some children with HCC, and other malignant liver tumors like rhabdoid and sarcomas, and benign tumors. Beware that a false low AFP level may sometimes be seen in HB due to lab error. This lab error called the "Hook effect" is a problem that can occur in the presence of extremely high AFP overwhelming the assay technique and generating an erroneously low result [21].

Regardless of the AFP level, unless the tumor has unequivocal radiographic characteristics of a benign tumor, such as an infantile hemangioma, biopsy is recommended. Ultrasound guided or CT guided percutaneous biopsy by co-axial technique is the most common approach to tumor biopsy, except in situations where a larger amount of tissue is desired for biologic study and genetic testing. In patients with high AFP level the main aim is to distinguish between HB, transitional liver tumor, and HCC. In patients with normal AFP the main aim is to distinguish benign tumors, from rhabdoid tumor, fibrolamellar HCC, sarcomas, and metastatic tumors.

Malignant Tumors

Hepatoblastoma (HB)

Epidemiology, Biology, Genetics

The incidence of hepatoblastoma (HB) throughout the world is fairly constant at 0.5 ± 1.5 cases per million children and the male: female ratio of HB is 2:1 [6]. HB is the cause of 80 % of all malignant liver neoplasms in children and accounts for 91 % of the malignant tumors in children younger than 5 years [22]. Epidemiological studies in the United States describe an incidence of 0.7 cases per one million per year [6, 22]. HB rates have increased from 0.6 to 1.2 per million in the past two decades [23]. An increase in the incidence of malignant tumors in the United States has been described between 1973 and 1977 and between 1993 and 1997. HB rates increased (from 0.6 to 1.2 cases per one million population), suggesting that the improved survival rates of extremely premature babies (birth weight <1500 g) has led to a new population of children having increased susceptibility to HB.

The etiology of HB is largely unknown. It is considered to be an embryonic tumor that probably arises from hepatoblasts present in the liver during embryonal life [24]. HB is well-

Table 16.3 Constitutional genetic syndromes associated with pediatric liver tumors [21, 25, 28–34]

Disease tumor type	Gene (chromosome locus)
Familial adenomatous polyposis	*APC (5q21.22) p57KIP2, others*
Beckwith-Wiedemann syndrome	*(11p15.5)*
Li-Fraumeni syndrome	*TP53, others (17p13)*
Trisomy 18	*18*
Glycogen storage disease type I	Glucose-6-phosphatase
Hereditary tyrosinemia	Fumarylaceto-acetate hydrolase
Alagille syndrome	*JAG1*
PFIC (familial cholestatic syndromes)	*FIC1, BSEP*
Neurofibromatosis	*NF-1*
Ataxia–telangiectasia	*ATM*
Fanconi anemia	*FAA, FAC, others*
Tuberous sclerosis	*TSC1, TSC2*

known to be associated with several constitutional genetic syndromes and malformations including Beckwith-Wiedemann syndrome, familial intrahepatic cholestasis, renal or adrenal agenesis, fetal alcohol syndrome, and Prader-Willi syndrome [21, 25] (Table 16.3). Beckwith-Wiedemann syndrome, which shows a loss of heterozygosity at the p57(KIP2) sites located at the chromosomal locus 11p15.5 [26, 27], is characterized by an overgrowth syndrome, an umbilical defect (either an umbilical hernia or omphalocele) and macroglossia Cases of HB have also been associated with hemihypertrophy, total parenteral nutrition (TPN) related cholestasis, and Type 1 glycogen storage disease [28]. Environmental factors including maternal use of oral contraceptives, exposure to metals and smoking may play a role in the occurrence of HB [29, 30]. Familial case reports of HB with FAP are striking and suggest a role in the pathogenesis of HB for chromosomes 5 and 11 [31]. Additional screening for cases in FAP kindred families is recommended by testing for germline mutations in the APC tumor suppressor gene [31, 32]. Germline APC mutations are not commonly seen in children with sporadic HB [33, 34]. Recurring translocations involving 1q12-21 have been described [35].

It is apparent that very low birth weight (VLBW), generally defined as <1500 g, is a potent risk factor for HB which is independently associated with congenital abnormalities [21, 23]. Since these babies have many problems associated with prematurity that require various treatments including total parenteral nutrition, phototherapy, and administration of numerous drugs, some component of these treatments for prematurity appears to be carcinogenic of hepatoblasts. The odds ratio (OR) of the occurrence of HB was 17.18 for babies weighing less than 1500 g compared to an OR of 1.56 for those weighing more than 2500 g with a 95 % confidence interval [23]. Preterm and very low birthweight babies may be exposed to potential newborn intensive care risk factors such as light, oxygen, irradiation, plastics, medications, and total parenteral nutrition [36].

Of several distinct developmentally regulated pathways known to be active in HB, such as IGF2/H19 [37–39], Notch [40], hypermethylation of RASSF1A [41], 4q deletion [42], and Wnt/β-catenin [43, 44]. The Wnt/β-catenin pathway that is most closely implicated in its origin [45]. Nuclear and cytoplasmic accumulations of β-catenin whose oncogenic mutations are associated with chromosomal instability and abnormalities of the Wnt/β-catenin signaling pathway, are seen in patients with HB and may contribute to tumorigenesis [44]. Such aberrant Wnt signaling is a hallmark of HB [46]. Several previous studies of sporadic HB have identified mutations or deletions clustered in exon 3 of *CTNNB1*, the gene for β-catenin [46–48]. Wnt ligand binding site coding at exon 3 is required for β-catenin degradation by serine/threonine phosphorylation of β-catenin using the APC/Axin/GSK3β protein complex. Therefore, mutation or absence of this site leads to β-catenin cytoplasmic accumulation. Accumulated β-catenin binds TCF/LEF transcription factors, translocates to the nucleus and activates the expression of many target genes, including those involved in cell proliferation (e.g. c-myc and cyclin D1), anti-apoptosis (e.g. survivin), invasion (e.g. matrix metalloproteinases) and angiogenesis (e.g. VEGF) [43, 45]. Since the Wnt signaling pathway plays an important role in embryonic development, this pathway appears to have an important role in the tumorigenesis of HB. A significant increase in the risk of HB has been noted in families with familial adenomatous polyposis and Gardner's syndrome [35], which is related to APC gene mutations, which is one of destabilized proteins of β-catenin. Survivors of HB who have this particular syndrome are at risk for developing familial adenomatous polyposis at a young age.

Activation of telomerase, which maintain telomere length and is required for cell immortalization, was reported as the prognostic factor of HB [49, 50]. Recently, TERT (telomerase reverse transcriptase), a catalytic component of human telomerase, was identified as one of cofactors of β-catenin to

bind TCF/LEF transcription factors. Therefore, telomerase activation might activate the expression of many target genes of Wnt signals. Interestingly, expression levels of Wnt signal target genes were more elevated TERT activated tumors in the comparison with others regardless β-catenin mutations, suggesting that TERT may be one of the strong activators of LEF/TCF factors. TERT promoter contains MYC binding sites. The highly malignant HB shows significantly high expression of *MYC* and *MYC*-related genes [51]. Since MYC will be activated as one of Wnt signal target genes, TERT expression might be activated by MYC, suggesting that vicious cycle may exist in HB and contributes to develop the highly malignant HB [48]. Recently, Hedgehog signaling and IGF/PI3K/AKT signaling, whose aberrations have been reported previously, were identified as the simulating pathway of Wnt signaling. Therefore, high activation of Wnt signaling by complicated pathways might be strongly correlated with the malignancy of HB.

Pathology

Guidelines for the optimal gross and histologic work-up of HB have been formulated in a College of American Pathologists protocol [52]. A detailed gross description should include information about what Couinaud segments are involved, number and size of tumor nodules, multifocality, macroscopic vascular involvement including detailed analysis of portal vein, hepatic vein, and or retrohepatic vena cava involvement. For the evaluation of surgical resection margins and the assessment of microscopic residual disease, it is recommended that surgeons and pathologists work closely together using colored sutures and/or inking to identify critical margin areas especially as they relate to the vascular and biliary trees. Untreated HB is solitary in about 80 % of patients, multifocal in about 20 %, and located in the right lobe in about 60 %. The color of the cut surface is often variegated as a result of necrosis and hemorrhage. Pure fetal HB will have the tan color of normal liver. Tumors which have been pretreated with chemotherapy are usually firm, well-delineated with whitish fibrotic areas and calcifications.

An internationally agreed upon pathologic classification of the histologic subtypes of hepatoblastoma has recently been [7] (Table 16.4). Subtypes are rarely homogeneous and about 85 % of all HB contain at least some fetal and embryonal components [53, 55]. In pure fetal histology (PFH) also referred to as "well differentiated fetal" there is very little mitotic activity and the tumors appear to carry a very favor-

Table 16.4 International consensus classification histologic subtypes hepatoblastoma [7]

Epithelial	Subtype/definition	Mixed	Subtype/definition
Fetal	**Well-differentiated** Uniform (10–20 μm diameter), round nuclei, cords with minimal mitotic activity, EMH[a]	Stromal derivatives	Spindle cells ("blastema"), osteoid, skeletal muscle, cartilage
	Crowded or mitotically active (>2 per 10 400× microscopic fields); conspicuous nucleoli (usually less glycogen)	Teratoid	Mixed, plus primitive endoderm; neural derivatives, melanin, squamous and glandular elements
	Pleomorphic, poorly differentiated Moderate anisonucleosis, high N/C, nucleoli		
	Anaplastic Marked nuclear enlargement and pleomorphism, hyperchromasia, abnormal mitoses		
Embryonal	10–15 μm diameter, high N/C, angular, primitive tubules, EMH		
Macrotrabecular	Epithelial HB (fetal or embryonal) growing in clusters of >5 cells between sinusoids		
Small cell undifferentiated (SCU)	(5–10 μm diameter) no architectural pattern, minimal pale amphophilic cytoplasm, round to oval nuclei with fine chromatin and inconspicuous nucleoli, +/– mitoses; +/– INI[b]		
Cholangioblastic	Bile ducts, usually at periphery of epithelial islands, can predominate		

[a]*EMH* extramedullary hematopoiesis

[b]Pure small cell undifferentiated needs to be differentiated from malignant rhabdoid tumors (discohesive, eccentric irregular nuclei, prominent nucleoli, abundant cytoplasmic filaments including cytokeratin and vimentin, negative nuclear INI)

able prognosis. Other subtypes of fetal HB include "crowded"/mitotically active, pleomorphic/poorly differentiated, and anaplastic as defined in Table 16.4. The embryonal pattern almost always occurs in combination with fetal components and areas of tumor with transition from fetal to embryonal cells are common. In contrast to fetal tumors, with predominantly embryonal tumors bile production and extramedullary hematopoiesis are rare. Macrotrabecules are 10–20 or more cells thick and the cells in the macrotrabecular part may be fetal, embryonal, or indistinguishable from those of adult type HCC and the cell type of predominance is sometimes used to further subclassify this type [56]. Originally termed "anaplastic", Haas et al [57] proposed the term small cell undifferentiated (SCU) subtype in 1989. Sometimes found in only a few small foci within the tumor, this subtype may portend a poor prognosis. Clearly the prognosis is poor when SCU A subis the dominant histologic phenotype. The impact of an isolated focus of SCU histology upon prognosis is not yet clear, and it is being studied in the current COG trial AHEP-0731. Some SCU HB displays rhabdoid features and shares lack of INI1 expression with malignant rhabdoid tumors [58]. A large proportion of HB (about 45 % when examined after chemotherapy) reveal a mixed epithelial and mesenchymal phenotype. The mixed phenotype can be further subdivided into those where stromal derivatives vs teratoid features are dominant. Osteoid-like bone formation more commonly present after chemotherapy is felt by some to be induced by exposure to chemotherapy [54].

Imaging, Staging, PRETEXT, Risk Group Stratification

Radiographic Imaging

Appropriate, high quality radiographic imaging remains an essential diagnostic and preoperative step in the treatment of all liver tumors, particularly malignant ones. However it is usually difficult to establish the true nature of a lesion based on imaging alone. Radiographically hepatocellular carcinoma (HCC) in otherwise normal (non-cirrhotic) liver of the pediatric patient is difficult to distinguish from hepatoblastoma. Both tumors are typically large (unless HCC is detected by screening in a cirrhotic patient). While HCC is more commonly multifocal, HB may be multifocal as well. In both diagnoses there may be calcification, venous invasion, and lung metastases. Other forms of metastases (for example to bone) are rare in hepatoblastoma and favor a diagnosis of HCC or rhabdoid. Identification of a central fibrous "scar" suggests fibrolamellar carcinoma or focal nodular hyperplasia (FNH) [59, 60].

Usually, the first method used in imaging of liver masses is abdominal ultrasound (US) which will localize the tumor within the liver and offer some clues regarding its possible character. The typical sonographic appearance of HB and HCC is of a large, heterogeneous (usually predominantly hyperechoic), and vascular mass. The use of US contrast agents in children is currently experimental, but the results in adults suggest that they may be helpful for identifying and characterizing hypervascular liver lesions [61]. In the immediate preoperative assessment of patients with vascular involvement, Doppler US is particularly valuable in helping to differentiate between overt vascular invasion and thrombus versus vessel compression by mass effect. In such cases it is very helpful, when the surgeon is present at the US examination time.

The gold standards of hepatic imaging are the triphasic contrast-enhanced abdominal computed tomography (CT) and the MR with hepatocyte specific contrast agents such as diffusion weighted sequences and delayed hepatobiliary phase imaging with hepocyte specific contrast agents gadoxetate disodium or gabobenate dimeglumine. With contrast CT, the three phases correspond to arterial phase and venous phase and delayed phase imaging. The arterial phase shows the hepatic arterial supply to the liver and may be useful for the detection of small hypervascular lesions, for example small HCC or metastatic lesions [62]. Images in the venous phase usually maximize the margins of primary tumors and are best for assessment of portal and hepatic venous involvement; the hepatic veins usually opacify with contrast almost simultaneously with the portal veins. If for some reason only one scan is to be performed, it should be done in the portal venous phase [63]. In addition, in every case of a suspicion of a malignant lesion, high resolution spiral chest CT should be performed in order to visualize potential lung metastases. With the new generation of CT scanners there is a slight risk of overdiagnosis of very small lesions (below 0.5–1 cm) which in fact may rather represent benign lesions rather than true metastatic foci and even, if they are neoplastic in origin, their clinical significance may be controversial [64, 65]. One should also keep in mind relatively frequent occurrence of lung atelectases in basal lung segments in children undergoing CT under general anesthesia.

An alternative and excellent imaging technique for liver tumors is magnetic resonance (MRI) with hepatocyte specific contrast administration. MRI is prone to motion artifact in small children and its accessibility may be limited due to costs resulting from the need for prolonged general anesthesia with special equipment being capable to work under strong magnetic field. The appearance of HB on both CT and MRI is generally a sharply circumscribed mass that is slightly hypoattenuating relative to the adjacent liver parenchyma on unenhanced and contrast-enhanced images [66]. Calcifications are seen quite frequently. On MRI, HB is homogeneously slightly hypointense on T1-weighted images and hyperintense on T2-weighted images relative to adjacent liver parenchyma [66]. Mixed tumors demonstrate more

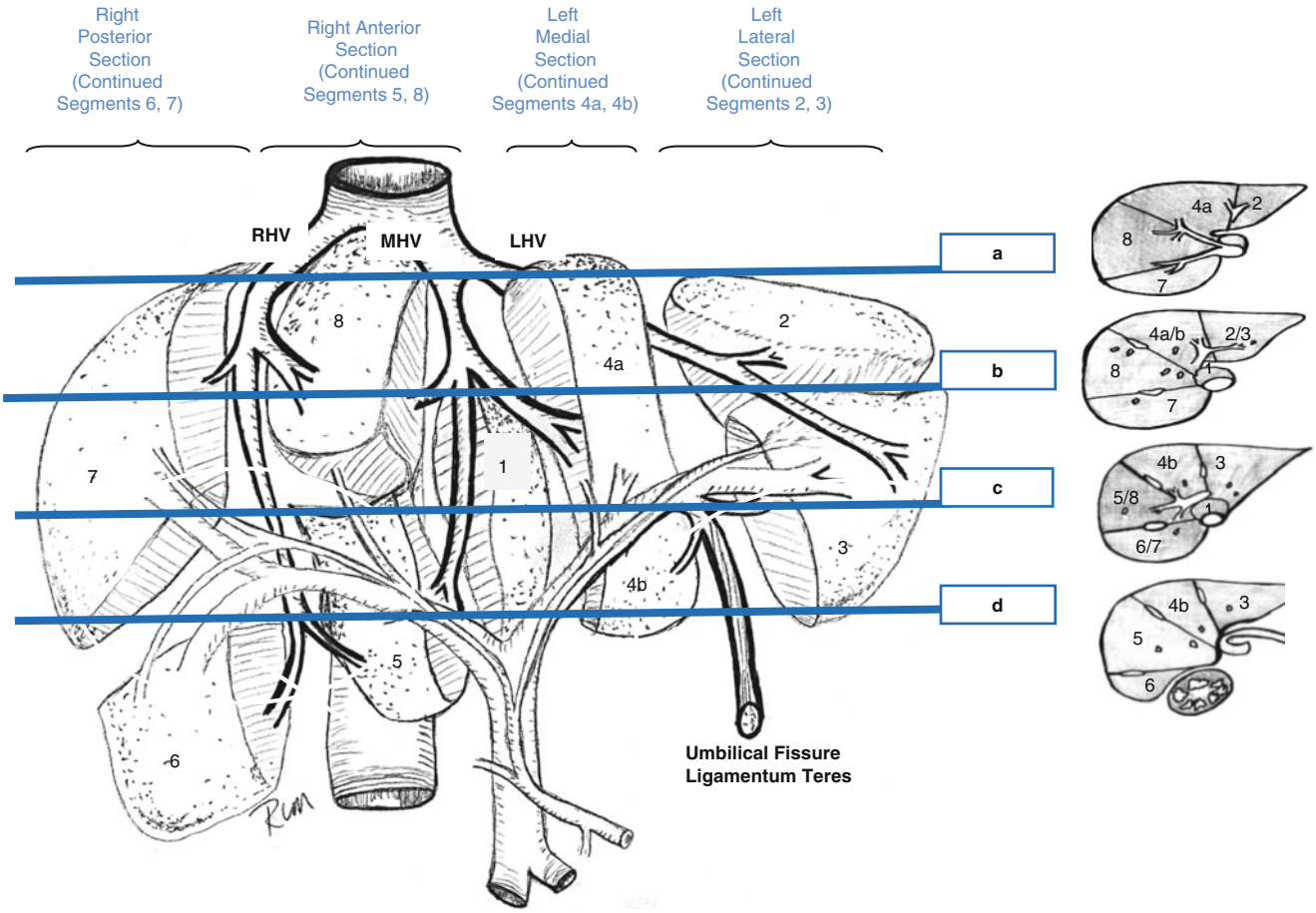

Fig. 16.3 Segmental anatomy of the liver. (**a**) Axial view at the level of the hepatic venous confluence with the suprahepatic venacava; (**b**) Axial view at the level of the left portal vein; (**c**) Axial view at the level of the right portal vein; (**d**) Axial view at the level of the mail portal vein. Numbers 1–8 denote continued segments

heterogeneous signal intensity characteristics [66]. HCCs are heterogeneous (but predominantly hypointense) on T1-weighted images, and mildly hyperintense in comparison with normal liver on T2-weighted images [67]. Contrast-enhanced T1-weighted HCC images show a similar pattern to CT, with early arterial enhancement and reduced signal intensity in the portal venous phase [68]. Recently there has been a whole generation of new, more selective contrast agents used with MRI. In adults, the use of newer contrast agents such as ferucarbotran [69] and mangafodipir [70] may increase the sensitivity of NMR for the detection of HCC, but the results are inconsistent [71]. Experience with the MR contrast agent gadalinium gababinate dimegluonone gd-EOB-DTPA Premovistan Europe Sovist in SUA was recently reported in pediatric HB [72]. The full potential of gd-EOB-DTPA is in evaluation study to date. However, this has clearly shown anatomic differentiation of benign versus malignant tumors with a clarity that is unobtainable with standard contrast agents [73]. There are case reports using positron emission tomography (PET-scan) in detection of recurrent HB, especially when standard imaging (US, CT, MRI) is negative and AFP rises, however false negative and false positive results have been reported [74]. PET-CT is more commonly used nowadays in adult HCC diagnosis, prognostication and staging, however pediatric experience with this modality is very limited.

PRETEXT Group and PRETEXT Annotation Factors

Starting with SIOPEL 1, the cardinal feature of all SIOPEL liver tumor trials has been the use of preoperative neoadjuvant chemotherapy. Such approach required introduction of the preoperative tumor staging system which was called PRETEXT (PRE-Treatment EXTent of tumor). PRETEXT is based upon the segmental anatomy of the liver It has been described in detail in several publications [75–77] (Fig. 16.3). In short it describes the number of contiguous uninvolved liver sections, as well as presence of extrahepatic disease or vascular involvement coded by additional letters (V, P, E, M, C) (Fig. 16.4) (Table 16.5). In addition to risk stratification, PRETEXT has been used to determine tumor resectability and to assess tumor response to neoadjuvant chemotherapy [78, 79]. PRETEXT system applied prior to surgical resec-

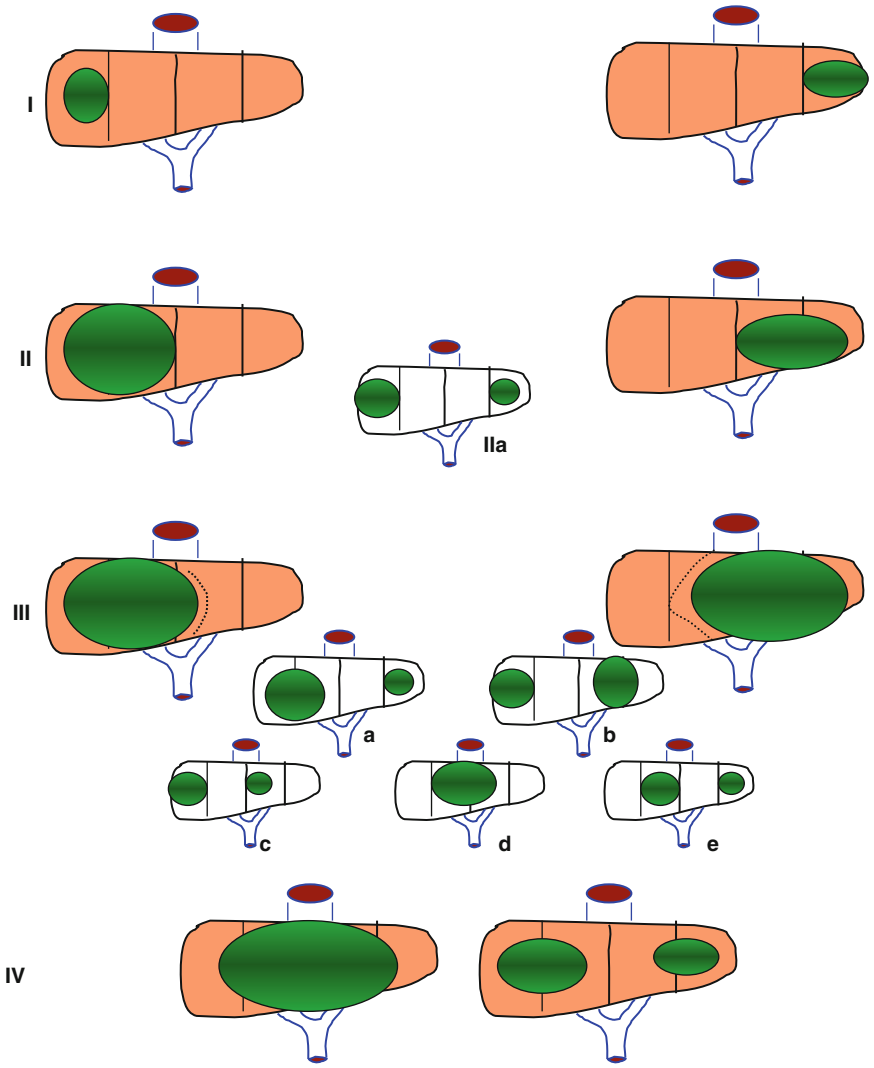

Fig. 16.4 PRETEXT and POST-TEXT groups I, II, III, and IV. Multifocal PRETEXT is IIa. Central or multifocal PRETEXT III is IIIa-e. PREEXT denoted prior to chemotherapy as "PRE-Treatment Extent of disease". POST-TEXT denotes imaging after chemotherapy as "POST-Treatment Extent of Disease"

Table 16.5 PRETEXT/POST-TEXT group (I, II, II, IV) and annotation (V, P, E, M, C, F, R) definitions

PRETEXT/POST-TEXT group	Definition
I	One section involved Three adjoining sections are tumor free
II	One or two sections involved Two adjoining sections are tumor free
III	Two or three sections involved One adjoining section is tumor free
IV	Four sections involved
Annotation:	
V	Venous involvement, V, denotes vascular involvement of the retrohepatic vena cava or involvement of ALL THREE major hepatic veins (right, middle, and left)
P	Portal involvement, P, denotes vascular involvement of the main portal vein and/or BOTH right and left portal veins
E	Extrahepatic involvement of a contiguous structure such as the diaphragm, abdominal wall, stomach, colon, etc.
M	Distant metastatic disease (usually lungs, occasionally bone or brain)
C	Caudate lobe
F	Multifocal tumor nodules
R	Tumor Ruptured at diagnosis

Table 16.6 Use of PRETEXT in risk stratification schemes of the major study groups

	COG-AHEP0731	SIOPEL-3,4,&6	GPOH-HB99	JPLT-2
Very low risk	PRETEXT I or II, pure fetal histology, primary resection			
Low risk/standard risk	PRETEXT I or II Any histology Primary resection	PRETEXT I, II, III	PRETEXT I, II, III	PRETEXT I, II, III
Intermediate-risk	PRETEXT II, III, IV Unresectable at diagnosis V+, P+, E+ SCU			PRETEXT IV Any PRETEXT with rupture, N1, P2, P2a, V3, V3a multifocal
High-risk	Any PRETEXT M+ : AFP level < 100 ng/ml	Any PRETEXT V+, P+, E+, M+ SCU AFP level < 100 ng/ml Rupture	Any PRETEXT V + E + P + M+ Multifocal	Any PRETEXT M1, N2 AFP level < 100 ng/ml

tion but after preoperative chemotherapy has been called POST-TEXT [76]. The precise definitions of vascular involvement differ somewhat between the SIOPEL and COG use of PRETEXT.

PRETEXT has been shown to be of moderate accuracy with a tendency to overstage patients, showed good reproducibility and superior predictive value for survival and possibility to monitor treatment response [75]. It is currently applied in all hepatoblastoma trials and indeed PRETEXT system has been accepted by all major international liver tumors study groups [80]. In HCC where some children may have concomitant hepatic cirrhosis, factors related to possible impairment of liver function should be taken into account in assessing the patient's resectability.

RISK GROUP Stratification

Risk group stratification has differed between the different study groups: COG, SIOPEL, GPOH, and JPLT (Table 16.6). Historically COG used the Evans staging system that relies upon the results of an attempt at surgical resection at diagnosis in all patients. In the current COG trial, AHEP-0731, the risk stratification is a hybrid of the traditional Evan's stage, PRETEXT resectability, AFP level at diagnosis, and presence or absence of unfavorable histologic subtype [81]. After SIOPEL 1, subsequent SIOPEL studies used two risk categories, standard and high risk based upon PRETEXT, presence of metastases and vascular invasion on imaging [82]. With the SIOPEL 3 and 4 studies low AFP tumors (<100 ng/ml) and spontaneously ruptured tumors were added to the high risk category showed that in addition to PRETEXT group, multifocalty AFP level, SCU histology, age over 5 where prognostically important. Recent prognostic analysis performed on the basis of the SIOPEL 2 and 3 trials [84]. An international cooperative effort by COG, SIOPEL, GPOH, and JPLT and coined the Children's Hepatic tumor International Collaboration (CHIC) has been established to identify and adopt an international risk group stratification schema which will be used by all study groups in the future [81]. The initial step in working towards this international risk stratification schema involved establishment of a large cooperative database housing outcome data from all of the multicenter trials shown in Table 16.8 and containing fully annotated data for 1605 patients. This database was then interrogated by univariate and multivariate analysis to yield risk groups comprised of multiple constellations of pretreatment prognostic risk factors (Table 16.7). The international multicenter trial groups are now in the process of integrating these statistical groups of prognostic factors into a global risk stratification scheme that will be used by all trial groups in the future.

Chemotherapy

The introduction of chemotherapy in the multidisciplinary treatment strategy for hepatoblastoma changed the prognosis dramatically. Cisplatin turned out to be the most effective tool. Chemotherapy regimens that included cisplatin achieved response rates up to 97 % which led to a resection rate of up to 80 % [83, 85–94]. Summary results of the major international trials over the past two decades are shown in Table 16.8. The SIOPEL group could even show that the treatment of standard risk hepatoblastoma with six courses of cisplatin monotherapy is equal to the treatment with the combination of cisplatin and doxorubicin [90]. Either used alone, or in combination with doxorubicin, etoposide, 5-fluorouracil, pirarubicin or vincristine, cisplatin has become the gold-standard for the treatment of hepatoblastoma. The different study groups developed on the basis of their experience risk adapted treatment strategies. In the current COG (Children's Oncology Group) study AHEP-0731 low risk patients receive two courses adjuvant cisplatin, vincristine and 5-fluorouracil (C5V). Intermediate risk patients receive neoadjuvant C5V plus doxorubicin (C5V-D), two to four course preoperative and two courses postoperative. High risk patients receive an upfront win-

Table 16.7 Summary results of hepatoblastoma cooperative trials

Study	Chemotherapy	Number of patients	Outcomes
INT0098 (CCG/POG) [85] 1989–1992	C5V vs. CDDP/DOXO	Stage: I/II: 50; Stage III: 83; Stage IV: 40	4-Year EFS/OS: I/II = 88 %/100 % vs. 96 %/96 %; III = 60 %/68 % vs. 68 %/71 %; IV = 14 %/33 % vs. 37 %/42 %
P9645 (COG) [86] 1999–2002	C5V vs. CDDP/CARBO[a]	Stage: I/II: pending publication Stage II = 38; Stage IV = 50	1-Year EFS: Stage III/IV: C5V 51 %; CDDP/Carbo 37 %
HB 94 (GPOH) [87] 1994–1997	I/II: IFOS/CDDP/DOXO; III/IV: IFOS/ CDDP/DOXO + VP/CARBO	Stage: I: 27; II: 3; III: 25; IV: 14	4-Year EFS/OS: I = 89 %/96 %; II = 100 %/100 %; III = 68 %/76 %; IV = 21 %/36 %
HB 99 (GPOH) [88] 1999–2004	SR: IPA; HR: CARBO/VP16	SR: 58 HR: 42	3-Year EFS/OS: SR: 90 %/88 %; HR: 52 %/55 %
SIOPEL 2 [89] 1994–1998	SR: PLADO; HR:CDDP/CARBO/ DOXO	PRETEXT: I = 6; II = 36; III = 25; IV = 21; Mets: 25	3-Year EFS/OS: SR: 73 %/91 %; HR: IV = 48 %/61 %; HR Mets: 36 %/44 %
SIOPEL 3 [90, 91] 1998–2006	SR: CDDP vs. PLADO; HR: SUPERPLADO	SR: PRETEXT I = 18; II = 133; III = 104; HR: PRETEXT IV = 74; +VPE = 70; mets = 70; AFP <100 = 12	3-Year EFS/OS: SR: CDDP 83 %/95 %; PLADO 85 %/93 %; HR: overall 65 %/69 %; mets 57 %/63 %
SIOPEL 4 [92] 2005–2009	HR: Block A: Weekly; CDDP/3 weekly DOXO; Block B CARBO/DOX	PRETEXT: I = 2; II = 17; III = 27; IV = 16; Mets: 39	3-Year EFS/OS: All HR = 76 %/83 %; HR: IV = 75 %/88 %; HR Mets: 77 %/79 %
JPLT 1 [93] 1991–1999	I/II: CDDP(30)/THPA-DOXO; III/IV: CDDP(60)/THPA-DOXO	Stage: I: 9; II: 32; IIIa: 48; IIIb 25; IV: 20	5-Year EFS/OS: I = ? /100 %; II = ?/76 %; IIa = ?/50 %; IIIb = ?/64 %; IV = ?/77 %
JPLT 2 [94] 1999–2010	I: low-dose CDDP Pirarubicin; II–IV: CITA Mets: High dose + stem cell transplant	Stage: *n* = 212; PRETEXT I:; II:; III ; IV	5-Year EFS/OS: I = ?/100 %; II = ?/89 %; III = ?/93 %; IV = ?/63 %; Mets 32 %

AFP alphafetoprotein, *CARBO* carboplatin, *CCG* Children's Cancer Group, *CDDP* cisplatin, *EFS* event-free survival, *C5V* cisplain + 5-flurouracil (5FU) + vincristin, *DOXO* doxorubicin, *OS* overall survival, *PLADO* cisplatin + doxorubicin, *POG* Pediatric Oncology Group SR, standard risk, *SUPERPLADO* cisplain + doxorubicin + carboplatin
[a]Study closed early because of inferior results CDDP/CARBO arm

Table 16.8 Multivariate analysis of risk groups in the Children's Hepatic tumor International Collaboration (CHIC) database [81]

PRETEXT	Age (years)	AFP	Other risk factors[a] (0, 1, ≥ 2)	#Patients in CHIC database[b]	5y-EFS
I & II	<3	>100	0	375	92 %
III	<1	>1,000	0	125	91 %
I & II	<3	>100	≥1	50	76 %
I & II	3–5	>100	Any	53	74 %
III	<1	>1,000	≥1	43	83–86 %
III	>1	>1,000	0	134	87 %
III	>1	>1,000	1	42	74 %
IV	<3	>100	0	58	77 %
I & II	>6	>100	Any	28	51 %
III	Any	100–1,000	Any	28	61 %
IV	<3	>100	1	59	66 %
III	>1	>1,000	>1	24	50 %
IV	<3	>100	>1	32	46 %
IV	>3	>100	Any	40	31 %
M+ (any PRETEXT)	Any	>100	Any and/or PRETEXT4	259	18–48 %
AFP <100 (any PRETEXT)	Any	–	Any	65	36 %

[a]Other Risk Factors statistically significant in multivariate analysis: (a) multifocal tumor, (b) major venous involvement +V (all three hepatic veins or IVC); (c) major venous involvement +P (portal bifurcation or both portal veins); (d) extrahepatic contiguous tumor extension +E; (e) Tumor rupture
[b]CHIC database includes patients from COG (INT-0098; P9645); SIOPEL (SIOPEL-2; SIOPEL-3SR, SIOPEL-3HR); JPLT (JPLT1; JPLT 2); and GPOH (HB89; HB 99)

Table 16.9 Current chemotherapy recommendations of the different study groups [81]

Study group	Risk group	Chemotherapy	Surgery
COG (AHEP 0731)	Very low risk	None	Primary
	Low risk	CDDP, 5FU, VCR × 2	Primary
	Intermediate risk	CDDP, 5FU, VCR, Doxo × 6–8	After 2–4 courses
	High risk	VCR, Irinotecan, Temsirolumus × 2 CDDP, 5FU, VCR, Doxo × 6	After 4–6 courses
SIOPEL (SIOPEL 6) (SIOPEL 3 HR)	Standard risk High risk	CDDP × 6 CDDP × 5 alternating Carbo/Doxo × 5	After 4 courses After 7 courses
GPOH	Standard risk	CDDP, Doxo × 3–4	After 2–3 courses
	High risk	CDDP × 5 alternating Carbo/Doxo × 5 (SIOPEL 3 HR)	After 5–7 courses
JPLT (JPLT 2)	PRETEXT I	CDDP, Pira × 4	Primary
	PRETEXT II	CDDP, Pira × 6	After 2 courses
	PRETEXT III/IV all V+P+E+	CDDP, Pira × 5–6 or CDDP, Pira × 2+Ifo/Carbo/Pira/Eto × 3–4	After 3–4 courses
	All PRETEXT M+	Additional high dose Eto/Carbo/Mel	After 4 courses

COG Children's Oncology Group, *SIOPEL* International Society for Pediatric Oncology, *GPOH* German Society for Pediatric Oncology, *JPLT* Japanese Study Group for Pediatric Liver Tumor, *CDDP* cisplatin, *5FU* 5-fluorouracil, *VCR* vincristine, *Doxo* doxorubicin, *Carbo* carbopaltin, *Pira* pirarubicin, *Eto* etoposide, *STS* sodium-thiosulfate, *Mel* melphalan

dow with vincristine and irinotecan in the first cohort of the study. Once this cohort is complete, a second cohort will receive an upfront experimental window of vincristine/irinotecan/temsirolimus. In both of these study cohorts the upfront experimental window will be followed by six courses of C5V-D, alternated every two courses with vincristine/ irinotecan or vincristine/ irinotecan/ temsirolimus in responders. If possible the tumor resection should be performed after four courses of the standard C5V-D backbone therapy. The aim of this study is to achieve with this risk adapted treatment a decrease in chemotherapy toxicity, while maintaining or improving the event free survival [95]. The current SIOPEL study for standard risk hepatoblastoma SIOPEL 6 uses the cisplatin monotherapy in six courses, already used in the previous SIOPEL 3 standard risk study. The patients are randomized for the additional administration of sodium thiosulfate (STS). The aim of this study is to assess the efficiency of STS preventing hearing loss, a frequent toxic side effect of cisplatin, and to evaluate the influence of STS on the tumor response to cisplatin. For high risk patients the SIOPEL 4 study investigated an intensified application of chemotherapy with weekly alternating cisplatin and doxorubicin/carboplatin. The results are promising but still with a short follow up. The interim recommendation of the SIOPEL is the chemotherapy strategy according to the SIOPEL 3 high risk study: High-risk patients are treated with cisplatin alternating every 2 weeks with doxorubicin/carboplatin for seven neoadjuvant and three adjuvant courses [83]. The recommendations of the other groups are listed in (Table 16.9).

So far, no controlled comparison has been done between the therapeutic strategies of SIOPEL and COG, primary chemotherapy for-all versus primary surgery for some. In terms of overall survival rates, the results of the different study groups have been more or less comparable. The improved results seen over the past two decades highlight some important lessons learned: (1) SIOPEL 4 weekly dose compressed chemotherapy, while toxic, is curing metastatic patients previously thought to be incurable; (2) In children not responding to chemotherapy, alternative chemotherapy and surgical resection of pulmonary metastatic disease should be considered; (3) After tumors have shown a good response to chemotherapy, the presence of a positive microscopic margin may not always portend a poor prognosis; (4) Liver transplant or complex resection (e.g., mesohepatectomy or resection with major venous resection and reconstruction) should be considered in every child with unresectable HB (about 15 % of cases) [79, 81, 93, 97].

Chemotherapy Toxicity

As cisplatin is the most important agent in the treatment of hepatoblastoma, cisplatin induced ototoxicity is a serious problem in the therapy of hepatoblatoma. Sixty percent of children treated with cisplatin develop some degree of bilateral hearing loss. The hearing loss is permanent and may have a delayed onset [96–100]. The risk of developing ototoxicity increases with lower age and a higher cumulative cisplatin dose, particularly when a dose of 400 mg/m^2 or more was reached [99, 100]. Different attempts have been made by the multicenter trial groups to reduce the risk of ototoxicity. The previously conducted COG study, COG P9645, tested amifostine in a randomized trial but failed to find significant otoprotection with this agent [101]. The current standard risk SIOPEL trial, SIOPEL 6, is investigating the potential otoprotective effect of sodium thiosulfate, which competitively binds at the cisplatin receptor site [83, 102, 103]. There are concerns that sodium thiosulfate, as a competitive receptor binder, could reduce the chemotherapy efficacy of cisplatin on the tumor, and results of this ongoing trial are pending at this time. Rather than added a chemoprotectant, the current COG trial, AHEP0731, attempts to reduce cisplatin toxicity by limiting the extended use of cisplatin in

low-risk patients, and using less platinum intensive regimens in intermediate/high risk patients.

Doxorubicin, also frequently used in the therapy of hepatoblastoma, can cause early and late onset of cardiac failure. The damage may be clinically significant only after years. The cumulative incidence of cardiac failure may not have a plateau, and can continue to be clinically significant several years after treatment [104].

Surgery

Surgical Guidelines COG

Contrary to early trials in America where decisions about surgical resection were made by individual surgeons, and hence were subjective and highly variable, the surgical guidelines of the current COG trial AHEP-0731 uses PRETEXT to define the recommended timing and extent of surgical resection. Surgical resection is recommended at diagnosis for PRETEXT I and II with clear venous margins on radiographic imaging. Surgical resection is after neoadjuvant chemotherapy for PRETEXT III (with POST-TEXT I, II or III with no major venous involvement -V and -P). Complete resection with liver transplant or extreme resection is recommended for POSTTEXT III +V +P, PRETEXT III extensive multifocal and for any PRETEXT IV [79, 105]. Resection at diagnosis is recommended only when a segmentectomy or a standard lobectomy will predictably yield a complete resection—i.e., PRETEXT I or II tumors based upon review of the diagnostic radiographic imaging.

Surgical Guidelines SIOPEL

SIOPEL and GPOH study groups recommend neoadjuvant chemotherapy be given to *all* patients with a rare patient going directly to transplant depending upon the recommendation of the transplant center [95].

Technique and Timing of Surgical Resection

Surgical approach differs somewhat between various international study groups and between HB and HCC. SIOPEL group favors initial biopsy followed by preoperative chemotherapy, while American COG group prefers primary resection in some cases with small localized tumors [78]. Current COG surgical guidelines recommend: (1) lobectomy or segmentectomy at diagnosis for PRETEXT I and II; (2) lobectomy or trisegmentectomy after neoadjuvant chemotherapy for POST-TEXT II or III which do not have macroscopic venous involvement (V-,P-); and (3) extreme/complex resection or liver transplant after neoadjuvant chemotherapy for POST-TEXT III with macroscopic venous involvement (V+, P+) or POST-TEXT IV. There is an option for resection of intermediate risk tumors after 2, rather than 4, cycles of chemotherapy given evidence that the majority of the chemotherapy response occurs in the first two neoadjuvant cycles [79, 106]. German GPOH group has recently joined the SIOPEL but in past it used to stand somewhere in between advocating primary resection in the small liver tumors and neoadjuvant chemotherapy in all others. Many surgeons reported that tumor resection after preoperative chemotherapy was easier due to its more solid character and better demarcation from the surrounding healthy liver tissue, as well as less bleeding, although the latter was not proven [77]. Although, no controlled comparison has been made between the therapeutic strategies of SIOPEL and COG, overall treatment results have been largely comparable between both study groups.

Biopsy

Throughout consecutive trials diagnostic biopsy in hepatoblastoma has proven to be safe and reliable [77, 83]. There were no episodes of tumor seeding. Biopsy-related complications were infrequent (7 % in SIOPEL 1) and minor only, which mostly did not require any treatment. Initially open biopsy was advocated but now closed needle biopsy under ultrasonographic or laparoscopic guidance is preferred [83]. In the past COG recommended exploratory laparotomy, attempted surgical resection, and open biopsy in all patients. With refinements in preoperative imaging this has become unnecessary in many patients. Laparotomy and resection at diagnosis is recommended in patients with PRETEXT I and PRETEXT II tumors as long as a safe, margin free resection by either segmentectomy or standard anatomic lobectomy is felt to be feasible. If not, percutaneous or laparoscopic biopsy is generally performed. Biopsy is important in ruling out benign tumors such as infantile hemangioma in the youngest patients, in ruling out transitional HB/HCC tumors in intermediate age children, and in ruling out HCC in the older children. Real time ultrasound guidance makes liver tumor biopsy safer. The aim is to obtain sufficient tissue to allow an accurate diagnosis, whilst avoiding complications. Risk can be further minimized by using a percutaneous coaxial technique because it allows multiple samples to be obtained with a single tissue path. The biopsy tract may be embolized through the outer needle with a throbogenic plug of gelatin foam. Whenever possible, the outer needle should be passed through unaffected liver for a short distance to minimize the possibility of tumor seeding. Great care should be taken, however, to avoid crossing, and therefore possible contaminating, segments of liver that will not be resected at subsequent surgery and the surgeon is encouraged to discuss this in detail with the interventional radiologist prior to the procedure [107]. If any question remains about possibility of obtaining a safe path, laparoscopic biopsy with a tru-cut protecting needle is recommended. Sufficient tissue for pathologic subtyping and biologic study with percutaneous co-axial approach is of paramount importance. It has been postulated that even a small focus of small cell undifferenti-

ated (SCU) histology could affect tumor prognosis in a histologically heterogenous tumor. If any doubt about the adequacy of tissue for analysis is raised, an open biopsy is recommended. Recommendations from 2011 International Pathology Consensus Conference are for a minimum of 5-8 cores. At least 2 or 3 (or more) cores should be frozen for biology and one core or adjacent normal liver should be frozen.

Operative Technique

In general anatomic hepatic resections according to the segmental scheme of Couinaud, refined by Bismuth in the 80s are recommended as segmentectomies, hemihepatectomies and extended hepatectomies. As a general rule, POST-TEXT I tumors can be resected with a segmentectomy, if applicable, and POST-TEXT II ones with a standard hemihepatectomy. POST-TEXT III tumors are resected with extended hemihepatectomy or central hepatectomy. Any tumor with invasion of all major hepatic vessels as shown per imaging (+V, +P) or extensive liver involvement (PRETEXT IV) should be referred to a center with experience in liver resection and liver transplant [78, 79, 96, 108–110].

Atypical, non-anatomic, or wedge resections are not recommended. In two consecutive GPOH multicenter trials, HB89 and HB94, 38 % of the patients with an atypical resection were found to have post resection residual tumor and this was associated with a worse outcome [111]. This may be due to the known role of hepatocyte growth factor (HGF) stimulating post resection residual tumor cell proliferation [112]. Atypical liver resections should be used in selected cases only, mainly of multifocal tumors, when liver transplantation is not an option [113]. In any case adequate resection planning is crucial, which may be supported not only by the proper preoperative imaging, but also augmented with the special rendering software. This service is currently offered by the German company MeVis (MeVis Medical Solutions AG, Bremen, Germany) and it has also been recently developed by the French IRCAD (Research Institute Against digestive Cancer, Strasbourg, France). It may be very useful in cases of extensive tumors with vascular involvement, especially that it has been shown that liver anatomy and segmental division is correct in about 75–80 % of cases [114]. Not infrequently liver segments can receive the portal flow from the contralateral portal branch.

The ultimate goal of surgical resection is to achieve complete margin negative tumor clearance. Data from SIOPEL where patients have received preoperative chemotherapy suggest that any cleared margin (even <1 cm) might be acceptable [96, 110, 115]. No similar data exists for resection of a tumor at diagnosis and margins ≥1 cm are desirable if resection is done prior to chemotherapy. Patients should be referred to experienced medical-surgical Liver Specialty Centers with all technologies for major hepatic resections available and also access to liver transplantation. Hepatic resection begins with mobilization and anatomic definition of the extent of the tumor and satellite lesions, if any. Liver vascular supply should be identified before parenchymal dissection. Hepatic veins are preferentially secured suprahepatically prior to parenchymal dissection. If for some reason in extreme cases they are not able to be secured before parenchymal dissection they can be accessed and secured through liver parenchyma in the final phase of resection. This latter approach to the hepatic veins, while feasible, risks substantial increases in blood loss. Parenchymal dissection is done along the line of ischemia Blood loss can be minimized by adherence to above technical principles, as well as maintenance of a low central venous pressure with Trendelenburg position or application of the Pringle maneuver in the parenchymal phase of the resection which can be done safely up to 30–45 min. In special cases, total vascular exclusion of the liver can be used. Warm ischemia time should not exceed 30 min. In general, interrupted ischemia limited to 10–15 min with intervening 5–10 min periods of reperfusion is better tolerated continuous ischemia intervals [116]. Specialized equipment, such as ultrasonic CUSA-type dissector, water knife (Hydro-jet, ERBE), argon or infrared beam coagulator and intraoperative ultrasonography is usually very helpful in liver resections. Intraoperative ultrasound examination can determine safe resection plane assuring complete tumor removal and reliable detection and complete resection of satellite lesions [117, 118]. Topical thrombostatic agents, such as fibrin glue or special sponge sealants, are used for coverage of the hepatic resection plane.

Microscopic positive tumor margin after HB resection does not seem to guarantee a poor prognosis. In SIOPEL 1 trial only 2 of 16 patients (13 %), who died, had microscopic positive margin [77]. In SIOPEL 2 microscopic positive margin was identified in 13 SR patients and all 13 are long term survivors, even though 8 of them did not receive any additional treatment than prescribed by the protocol [89]. In the SIOPEL 3 SR arm only 2 out of the 28 patients with microscopic positive margin suffered an event and actually one of those was of higher risk of tumor relapse because of the initial intra-peritoneal tumor spillage [90]. Thus, it seems that microscopic positive margin does not confer worse prognosis per se. Beware that all of the data is from patients who have received preoperative chemotherapy, and that this has NOT been the experience in chemo-resistant tumors like HCC. Hence, radical tumor excision is recommended in every case.

Surgical Treatment Options for Preoperative Tumor Rupture

Bleeding from a preoperative tumor rupture occurs in about 2–3 % of HB. Intracapsular hematoma may tamponade the bleeding. Occasionally there may be an uncontained rupture

that decompresses into the peritoneal cavity presenting with uncontrolled bleeding and hypovolemic shock. Correction of clotting factors should be followed either by percutaneous embolization. Operative control of the hemorrhage may be necessary when percutaneous embolization is not immediately available [119]. Inadvertent injury to vital structures can be minimized if heroic, uncontrolled procedures are avoided. It is particularly important to avoid, if possible, massive blood loss, as massive blood transfusion during liver tumor resection has been correlated with an increased risk of tumor recurrence [120], surgical complication, and mortality.

Surgical Complications

Potential surgical complications include bleeding, impairment of blood flow in or out of the liver, bile blockage or leak, liver failure, infection, and others listed in [78] (Table 16.10). Bleeding from needle biopsy can almost always be stopped with correction of clotting factors and with direct pressure. In contrast, massive bleeding during complex tumor resection may be life threatening. Bleeding risk is minimized by avoiding inappropriate aggressive attempts at tumor resection in proximity to major vessels [117, 120]. In the event of a failed initial resection, reoperation is associated with increased perihepatic bleeding with adhesions to the diaphragm, retroperitoneum, and right adrenal gland. Unrecognized anatomic origin of a replaced right or left hepatic artery may lead to bleeding or inappropriate ligation. Normal liver can occasionally survive permanent interruption of arterial or portal venous inflow, but not both [121]. In the rare instance that both portal and arterial inflow of the remaining liver tissue has been disrupted, survival requires immediate revascularization or transplant. Loss of adequate venous drainage from the residual liver remnant will cause congestion and some loss of parenchymal viability. It's important to prevent inadvertent hepatic venous occlusion with ill-placed sutures into the hepatic parenchyma in an attempt to control bleeding. Potential causes of postoperative liver failure include small liver remnant, liver devascularization, interruption of venous drainage, excessive liver warm ischemia due to prolonged vascular occlusion or massive bleeding, major bile duct obstruction, halogenated anesthetic agents, viral infections, and drug reactions. Unless definitive signs of improvement are seen in the first few days, liver transplantation may need to be considered.

Intraoperative cardiac arrest occurs in 1–2 % of major liver resection procedures. The most common cause is uncontrolled massive blood loss. Close communication between the operative surgeon and anesthesiologist is of paramount importance in not allowing the patient to develop life-threatening hypovolemia, acidosis, and coagulopathy. Cardiac arrest may also occur from tumor emboli or, more commonly, an air embolus from an uncontrolled hole in the IVC or major hepatic vein. Risk of an air embolism can be minimized by the use of higher PEEP (Positive End-Expiratory Pressure) settings during the suprahepatic vein and IVC dissection portion of the procedure. It is also very important to preoperatively evaluate cardiac function in all

Table 16.10 Potential surgical complications of major liver resection

Type of surgical complication	Most common	Less common Regularly reported
Bleeding	Intraoperative hemorrhage Postoperative hemorrhage	Intraoperative cardiac arrest Hepatic hematoma Hemobilia Gastrointestinal bleeding Side effects of massive transfusion
Blood flow	Postoperative sequelae of intraoperative inflow and outflow obstruction	Venous outflow obstruction Hepatic artery injury or thrombosis Portal venous injury or thrombosis Hepatic necrosis
Liver failure	Coagulopathy Hypoglycemia Ascites	Too small-for-size liver remnant (<25 % of normal liver, <50–60 % cirrhotic liver)—isn't this a cause, rather than an effect?? Encephalopathy
Bile drainage	Bile leak Biliary stricture	Bile fistula Biloma Bile peritonitis Cholangitis
Infection	Wound infection Hepatic or perihepatic abscess Pneumonia	Sepsis Cholangitis Peritonitis
Miscellaneous	Adhesive bowel obstruction Pleural effusion	Diaphragm injury Wound dehiscence Recurrent or persistent tumor

patients who have been treated with doxorubicin as their post-chemotherapy cardiac function may be compromised and their ability to tolerate hypovolumic stress decreased.

Bile leak occurs in 10–12 % of cases and its frequency has not decreased over the years [112]. The bile ducts, particularly at the level of the hilum, are more easily disrupted than the vessels. If a minor injury is recognized it can usually be directly repaired. Major injury with loss of ductal wall, complete division, or loss of length mandates debridement back to healthy, well-perfused ducts and drainage with a Roux-en-y limb of jejunum. Bile leak from the cut surface is minimized by close inspection and avoiding non-anatomic resection. When any question of potential leak exists a retrograde cholangiogram, before closure of the abdominal wall, is recommended both to detect leaking biliary radicals and confirm appropriate drainage of all remaining segments. Although placing drains at the time of operation does not lessen the rate of bile leakage, it does facilitate postoperative management in the event of a leak. Bile leaks that do not respond to appropriate drainage may be associated with distal obstruction, such as a retained section of viable liver excluded from the biliary drainage system, iatrogenic occlusion (clip, ligature, thermal injury), hematoma, stone, residual obstructing tumor, or ischemic stricture. Appropriate time for reoperation is unclear as wait-and-see treatment is successful in most cases. An adult review recommends that patients with drainage output greater than 100 mL 10 days of bile leakage diagnosis should be scheduled for interventional treatments [112]. No such comparable data exist for children.

Liver Transplant for HB

Cases of "unresectable" hepatoblastoma (HB) due to involvement of the entire liver, extensive multifocality, or major hepatic venous or portal venous involvement comprise 10–20 % of all HB treated in multicenter trials [102]. The best results for high risk HB reported to date were in SIOPEL 4, and these improvements in outcome seen in the high risk group appear to be at least partly due to an increase in the use of liver transplant [79, 92]. The recommendations for transplant used in this most recent studies are: (a) tumor clearly involving all four sections of the liver, especially those with extensive multifocality as judged by MRI or CT angiography; (b) tumor location so close to both main portal vessels at the hilum of the liver and/or all three hepatic veins that it is unlikely that a tumor-free excision plane will be achieved without risking life threatening hemorrhage. These patients should be identified early in their treatment and their clinical course and imaging followed closely throughout their initial chemotherapy, in conjunction with a liver specialty surgeon.

The following guidelines have been developed over the years and are currently recommended by COG, SIOPEL, and GPOH. It is important that consultation with a transplant center with special expertise in pediatric liver surgery be considered early in the treatment in order to prevent delays and unwanted extended courses of chemotherapy while awaiting resection and transplantation. Most of these patients should be treated with standard on-study chemotherapy protocols with the same number of cycles of chemotherapy, before and after transplant, as patients submitted to partial hepatectomy. An occasional patient with an extensively multifocal PRETEXT IV, or with tumor thrombosis in the main portal vein, might be recommended for primary transplant with minimal preoperative chemotherapy [109].

Multifocal PRETEXT IV

Multifocal PRETEXT IV HB in the absence of any metastatic disease after chemotherapy (POST-TEXT IV, multifocal, –M) is a clear indication for liver transplantation. Clinicians should resist the temptation to intensify chemotherapy in a vain effort to avoid transplant because of the high likelihood of inducing tumor resistance to chemotherapy [123]. Apparent clearance of tumor nodules from one section of liver after preoperative chemotherapy should not distract from transplant because of the high probability of persistent microscopic viable neoplastic cells despite radiographic "clearance" [79, 123]. COG and SIOPEL recommend transplant in these patients, although there are controversial reports of successful piecemeal resections of such tumors [93, 114, 115].

Solitary PRETEXT IV

Large solitary PRETEXT IV tumors usually have neoadjuvant chemotherapy and many of these tumors may "downstage" to a POST-TEXT III with clear retraction of the tumor from the anatomic border of one lateral section and would allow performance of a trisectionectomy. A POST-TEXT IV, –M tumor is a clear indication for transplant.

PRETEXT III +P, +V

In a subgroup of PRETEXT III tumors there will be major vascular invasion that does not clear with neoadjuvant chemotherapy. A POST-TEXT III tumor with persistent +V and/or +P that may preclude safe and prudent performance of a extended hepatectomy. Resection in the face of major venous invasion runs the risk of leaving viable neoplastic tissue behind if the surgeon must peel off viable tumor directly from the involved vein. Some have argued in favor of venous resection and reconstruction ("extreme" or "complex" resection) as opposed to transplant in these cases. There are no trials comparing the results of partial resection with extensive venous dissection versus complete resection with transplantation. Again, clinicians should resist the temptation to intensify chemotherapy in a vain effort to avoid transplant because of the high likelihood of inducing tumor resistance to chemotherapy and worsening outcome [122]. Complex

resection carries an increased risk of surgical complication, including bleeding and/or venous outflow obstruction and positive tumor margin [80]. Whether resection is partial, or complete with transplant, any suspicious invasion of the retrohepatic vena cava should be resected "en bloc" and reconstructed either with autologous internal jugular vein, donor iliac vein, or a preserved cadaveric whole organ with donor IVC.

Transplant in Patients with Pulmonary Metastatic Tumor at Diagnosis

An absolute contraindication to liver transplant is persistent pulmonary metastases nonresponsive to neoadjuvant chemotherapy and not amenable to surgical resection. The tumor should show at least partial response to chemotherapy (decrease in tumor size, decrease in serum AFP, and decrease in size or disappearance of pulmonary nodules). Unresponsive or progressive metastatic disease in the face of neoadjuvant chemotherapy is a relative contraindication to transplant because even if the nodules can be surgically resected microscopic foci of chemoresistant tumor are highly probable [79, 109, 124]. Lung metastasis that do respond to chemotherapy, but do not entirely clear, should be surgically resected [79, 125]. Some have advocated sternotomy and bilateral lung palpation, rather than unilateral wedge resection, although this remains controversial.

Rescue Transplant for Relapse or Persistent Tumor

Multiple series have shown superior outcome with primary transplant (about 80 % overall survival) compared to rescue transplant (about 30–40 % overall) [108, 126–130]. The basis for this is undoubtedly multifactorial but two important concerns are the likelihood of chemotherapy resistance in relapse tumors [123, 131, 132], and the debilitated state of the patients when transplanted in the face of end-stage disease.

Pediatric Liver Unresectable Tumor Observatory (PLUTO)

SIOPEL, together with support from COG, GPOH, Study of Pediatric Liver Transplantation (SPLIT), and individual pediatric liver transplant centers all over the world, has established a worldwide electronic registry for liver transplant for childhood tumors (hepatoblastoma, hepatocellular carcinoma, infantile hemangioma, and others) [108]. The link to obtain a password to register patients on this database can be accessed via the PLUTO Registry Website: http://pluto.cineca.org

Surgery for Local Relapse in the Liver

Management of relapse tumor has varied across study groups [131, 132]. In SIOPEL studies, only 5 % of patients who had achieved a complete remission and a local relapse and were treated with salvage chemotherapy and surgery [131]. In JPLT 1 four locally relapsed patients underwent a redo liver resection with short-term survival (17 months) in all four, long-term follow-up not reported [133]. In the liver transplant experience overall survival for "rescue" transplant, transplant for a local relapse, was 30 %, compared to 82 % for patients transplanted at the first operation. PET CT has begun to be used in pediatric surgical oncology of solid tumors although experience is limited; caution is warranted as false positive results are possible in normally regenerating liver

Hepatic Arterial Chemo-embolization (HACE) and Trans-arterial Chemoembolization (TACE)

HACE/TACE is occasionally used in children with HB whose tumors remain unresectable after chemotherapy AND who are not liver transplant candidates due to uncontrollable extrahepatic tumor. Recently available doxorubicin eluting beads are a particularly attractive option for embolization in this situation. TACE, however, is more common in HCC and is discussed below in the HCC surgical discussion.

Hepatocellular Carcinoma

Epidemiology, Biology, Genetics

Hepatocellular carcinoma (HCC) accounts for about 87 % of the malignant liver tumors of children between 15 and 19 years of age [134]. In most countries HCC is less common than HB, but there is considerable geographic variation with rates ranging from 0.2 per million in England and Wales to 2.1 per million children in Hong Kong. Hepatitis B and C viral infections are the most common cause of chronic liver diseases and hepatocellular carcinoma in adult. In pediatric HCCs, most pediatric HCCs are "de novo" cases, usually not related to hepatitis B and C viral infections, but in some Asian populations e.g. Hong Kong and Taiwan HCC occurs more frequently due to the high infectious rates of hepatitis virus [135]. Recent decline in HCC may be attributed to immunization of infants against perinatal transmission of hepatitis virus.

There are two distinct groups of HCC patients in childhood: sporadic or "denovo" HCCs without preceding liver disease and those developed in the context of chronic or congenital liver disease. The former group typically affects older children and shows a relatively poor outcome, while HCC developing in congenital liver diseases [94, 136, 137] are sometimes diagnosed as tiny nascent nodules in the resected liver at liver transplantation [138]. Some biologic differences may exist between HCCs developing in adults and children. Kim and colleagues [139] have observed that expression of cyclin 1 was lower and LOH higher at 13q in pediatric malignancies. Fibrolamellar carcinoma is a rare primary malignant liver neoplasm that usually affects ado-

lescents and young adults with no underlying liver disease and the lack of cirrhosis [15]. This expresses markers associated with both biliary (CK7 and epithelial membrane antigen) and hepatocytic (heppar-1 and glypican-3) differentiation, as well as markers associated with hepatic progenitor cells (CK19 and EpCAM) and stem cells (CD133 and CD44), indicating that subsets of HB and HCC share a molecular pathway in their pathogenesis. Genetic alterations seen in fibrolamellar carcinoma include gains in 1q and 8q and loss of 18q [140], and a recently reported DNAJBI-PRKACA chimeric transcript [141].

Pathology

In the pediatric age group, more than two-thirds of HCC occur in children older than 10 years of age, but only 0.5–1 % of all HCC manifest before 20 years of age, and very few HCCs are diagnosed in children less than 5 years old. About 20–35 % of children with HCC have underlying chronic liver disease. It is still disputed whether "adult-type" HCC in children is the same or a different disease. Zimmermann and others have suggested that HCC forms a tumor family, consisting of adult-type HCC and its variants, fibrolamellar HCC, and a novel entity occurring in older children and young adolescents with features of both hepatoblastoma and hepatocellular type histologies [7]. The gross presentation is in the form of solitary or multiple (multifocal) lesions. Solitary tumors display four main growth patterns, expanding (or pushing) mass lesions, pedunculated (or hanging) lesions, invading tumors with poor delineation, and mutifocal tumors resembling metastatic disease. These growth patterns exert a considerable influence on the surgical resectability of the tumors.

Fibrolamellar Hepatocellular Carcinoma (FL-HCC)

This tumor usually arises in non-cirrhotic livers of adolescents or young adult patients and is encountered more frequently in Western countries [15]. Overall, FL-HCC accounts for less than 10 % of all HCCs. Unlike adult HCC where fibrolamellar has a better prognosis, recent review of fibrolamellar HCC in the SIOPEL experience shows no improved outcome with this subtype in pediatric patients [143]. FL-HCC shows vascular invasion in up to 35 % of cases, frequently metastasizes into locoregional lymph nodes (about 50 % of cases), and tends to show unusual spreading patterns, including intraperitoneal spread. FL-HCC is typically a solitary lesion which has a predilection for the left liver lobe (two-thirds; unusual for hepatic primary tumors). It reveals well-defined margins and a central scar in 70 %. The cut surface often shows a firm and tan to brown tissue with radiating septa, sometimes closely resembling focal nodular hyperplasia. Histologically the cells form strands embedded in the typical fibrosclerotic stroma which may form a central stellate scar. Typically, cells of FL-HCC show marked immunostaining for cytokeratin 7 [7, 55].

Transitional Liver Cell Tumor (TLCT)

TLCT is now called Hepatocellular neoplasm - Not Otherwise Specified (HC-NOS) by the Pediatric Consensus Classification [7]. The term, transitional, had previously been used to denote a putative intermediate position of the tumor cells between hepatoblasts and more mature hepatocyte-like cells although significant confusion regarding the exact histology still exists [7]. These tumors are highly aggressive lesions that have a treatment response pattern clearly different from hepatoblastoma [14]. The usual presentation is that of a large or very large solitary hepatic tumor (mostly in the right liver lobe), commonly associated with very high serum AFP levels. Grossly, the tumors display an expanding growth pattern and sometimes exhibit a large central necrosis. Histologically, the tumor cells vary between and HCC-type cell and cells found in hepatoblastoma, sometimes with formation of multinuclear giant cells.

PRETEXT and Staging HCC

No staging or grading system has been found that accurately predicts prognosis in pediatric HCC. In the pediatric multicenter trials, PRETEXT has been used because of its utility in HB and the crossover between these two tumors in the intermediate age group. The Edmondson and Steiner histologic grading system seems to add prognostic value to the 6th edition of the TNM grading system in adults [142]. Neither COG nor SIOPEL has current open trials for HCC, although an international cooperative trial is in the planning stages. Prior trials in the USA have used the traditional Evan's staging system (I, II, III, IV) [17], but current discussions with colleagues describing the extent of tumor involvement of the liver are based upon PRETEXT to aid in making key decisions about surgical resectability. In HCC where some children may have concomitant hepatic cirrhosis, factors related to possible impairment of liver function should be taken into account in assessing the patient's resectability.

Chemotherapy

Chemotherapy for HCC is discussed controversially. In adult HCC no or little response to chemotherapy is described. Gemcitabine plus oxicisplatin has recently been reported in a large multicenter trial in adults, although no such comparable data exists in children [144]. Children have usually been treated in the last years according to hepatoblastoma trials where cisplatin or carboplatin was combined with one or more drugs (doxorubicin, 5 FU, vincristine, etoposide). It has been postulated that the response rate to chemotherapy is higher in children and in about 1/3 of the children who have preoperative chemotherapy will get a complete resection [16] (Table 16.11). Better chemotherapy response in children may be due to the higher rate of "de novo" tumors with normal liver function and the transitional liver cell tumors

Table 16.11 Chemotherapy for pediatric hepatocellular carcinoma (HCC) [16, 17]

Trial	Chemotherapy	Partial response rate (%)
INT 0098	Cisplatin, doxorubicin versus Cisplatin, vincristine, 5-fluorouracil	16
SIOPEL 1	Cisplatin, doxorubicin (PLADO)	49
SIOPEL 2	Cisplatin, carboplatin, doxorubicin	50
JPLT	Cisplatin, tetrahydropyranyl-adriamycin	32
HB 99 (GPOH)	Carboplatin, etoposide with stem cell transplantation	47

(TLCT) described by Prokurat et al [14]. The true advantage of the use of adjuvant chemotherapy for stage I disease is unknown [17].

Antiangiogenesis, Sorafanib

Despite a moderate response rate to chemotherapy in children with HCC, the overall survival rates are still extremely poor. Novel therapeutic approaches were investigated over the last years in HCC in adults. The recent adult experience with Sorafenib, a multikinase inhibitor with anti-angiogenic and anti-proliferative activities has been most promising. It demonstrated a significantly improved time to tumor progression (median 5.5 months vs. 2.8 months) and OS time (10.7 months vs. 7.9 months) in prospective trials in the treatment of HCC in adults with unresectable tumors [145, 146]. Sorafenib in combination with doxorubicin demonstrated a significantly better progression free survival compared with doxorubicin and placebo [147]. Information about novel therapeutic approaches in childhood HCC is rare. One series of 12 children with HCC treated with Sorafenib in combination with PLADO (cisplatin, doxorubicin) showed a promising approach in childhood HCC: Four of seven patients with unresectable tumors had a partial response and two of them achieved resectability [148].

Other antiangiogenic agents, epidermal growth factor receptor (EGFR) inhibitors and mTOR inhibitors where evaluated in phase II and III studies in HCC in adults: Bevacizumab (VEGF antibody), sunitib (multikinase inhibitor), brivanib (VEGFR inhibitor), erlotinib (EGFR inhibitor), cetuximab (EGFR antibody) [148]. Bevacizumab was the most promising agent especially in combination with erlotinib with a response rate of 25 % In adult tumors the combination of cetuximab with gemcitabine/oxaliplatin (GEMOX) achieved a response rate of 20 % [149].

Surgery

The technical aspects of liver surgery have been discussed in detail above in the surgical section dealing with hepatoblastoma. Topics above with particular relevance to pediatric HCC include biopsy, resectability, surgical technique, HACE/TACE, preoperative portal vein embolization, and surgical complications of liver surgery. Given the poor response of HCC to chemotherapy and radiation, the mainstay of treatment is surgery. This means that in contrast to hepatoblastoma a primary radical tumor resection should be attempted whenever possible, and patients with the clinical constellation for advanced HCC should always be treated in consultation with a specialized center with experience in childhood liver surgery.

In HCC patients with hepatic cirrhosis, the liver remnant volume calculation is essential and can be predicted by CT scan and/or MRI. In childhood, the usual limit for resection (a ratio obtained dividing the remnant liver volume by the patient body weight) can be exceeded from the usual 0.8 value to 0.6 and even more. Sampling of lymph nodes from the hepato-duodenal ligament should be performed in every HCC case, as their involvement is relatively frequent and has a significant impact on prognosis. In general in HCC, extended lymphadenectomy of the hepatic pedicle is recommended.

When an older child or a young adult presents with a resectable tumor thought most likely to be HCC, primary resection should be attempted. Although all studies have confirmed the importance of complete tumor resection for obtaining cure, less than 20 % of patients are amenable to initial surgery. After HCC resection the 5-year survival is on average of 35–51 %, while recurrence-rate is about 20–30 % at the same interval and with little change in the last decade [134]. This is on the contrary to survival rates in completely resected HB that exceed the range of 90 % [102].

Liver Transplant for HCC in Children

The role of liver transplantation in pediatric HCC is in greater evolution than in pediatric HB and because of HCC's relative chemoresistance transplantation may offer an important chance for cure with tumor confined to the liver [150–152]. Transplant is absolutely contraindicated in the presence of any extrahepatic tumor, even in the occasional patient where it clears with chemotherapy. Some argue that an exception might be made in the intermediate case of children with transitional cell liver tumors. Outcome for transplant in adult HCC has improved over the years due to our recognition that strict selection criteria, Milan or UCSF criteria, are important in preventing post-transplant tumor relapse. However, Milan criteria are NOT strictly applied in pediatric HCC [151, 153]. This is because of increased chance of respon-

siveness to chemotherapy, and studies which fail to show a correlation between survival and Milan criteria in children [154, 155]. Despite the excellent overall survival in this pediatric series, the only child in their series who fulfilled all four criteria was a child with tyrosinemia with a small incidental tumor found on surveillance screening. In view of the lack of improvement in results from conventional treatment of pediatric HCC over the past two decades, most pediatric transplant surgeons will offer transplantation to children with large denovo tumors, regardless of size, as long as there is no evidence of extrahepatic spread.

TACE/HACE with Doxorubicin Beads or Yttrium Radioactive Beads

Hepatic arterial chemoembolization (HACE), also called transarterial chemoembolization (TACE), is an established method of treatment of HCC in adults. Experience with TACE in children is limited [156–159]. It has been used not only in pediatric HCC, but also in a small number of children with HB [156–159]. TACE produces a marked reduction in tumor size associated with a significantly decreased AFP levels and tumor necrosis. In the reported experience TACE rendered resectable 2 out of 3 pediatric HCCs or served successfully as a bridge to OLT in three other pediatric cases [159]. According to the report of Li, tumor shrinkage after TACE ranged from 19.0 to 82.0 %, with a mean value of 59.2 % [158]. AFP levels decreased 99.0–29.0 % from initial levels, with a mean decrease of 60.0 %. TACE allowed for the subsequent complete surgical resection in 13 HB cases and the other three underwent partial resection [158]. One patient received successful orthotopic liver transplantation after receiving TACE therapy. Pathological examination showed that the mean percentage of necrotic area in the surgical specimens was 87 %. In Xuewu's experience 6 out of 8 children (75 %) had a marked response after the first TACE and were judged as being surgically resectable, but one boy died of pneumonia just before the scheduled operation, while another boy preferred further TACE [160]. On the other hand, severe complications, such as pulmonary embolism, have been associated with this technique [156]. Although complications with the older lipiodol/cytostatics (doxorubicin, cisplatin and sometimes mitomycin or vincristine with a possible addition of verapamil to break potential tumor resistance) emulsion technique were more frequent, chemoembolization is now possible with doxorubicin loaded capsules of the prolonged release or spheres which develop radiation effect. Embolizing agents are usually Gelfoam or Spongostan particles, or steel coils.

TACE may be of particular use in children with advanced HCC where treatment options are very limited. In some cases tumor resection not only might become possible, but also technically facilitated as tumors become firm and calcified. Main indications for TACE are: a bridge to liver transplantation (while waiting for a liver donor to become available) or to resection (with an attempted conversion of non-operable, systemically chemoresistant tumors to resectability). Potential advantages of TACE include the delivery of a higher concentration of cytotoxic drugs to the tumor, which is mostly vascularized by the hepatic artery branches, prolonged "dwell time" of drug in the tumor and reduced systemic toxicity. TACE may be particularly safe in children and adolescents with HCC who do not have cirrhosis. However, TACE requires high technical expertise in radiology suited with large volume of interventional procedures. The effectiveness of TACE is limited by the development of neovascularity in the periphery of the tumor [161, 162]. The procedure should be repeated every 4–6 weeks.

Pre-operative Portal Venous Embolization

Portal venous embolization has been used in adults with HCC to induce hypertrophy of the remaining liver remnant [163], and reported experimentally in children. This technique may be particularly useful in children with large tumors. The portal venous branch on the side of the tumor is cannulated percutaneously and polyvinyl alcohol and coils are inserted to induce portal vein occlusion under fluoroscopic control. This has a dual effect of alcohol thrombosis of the embolized tumor and compensatory hypertrophy of the unharmed opposite liver lobe increasing the potential hepatic functional reserve in patients with cirrhosis and underlying liver dysfunction in preparation for hepatic resection of the tumor

Percutaneous Ablative Therapies

Ablative percutaneous methods of local control are more relevant to pediatric HCC than HB, as HCC is more often advanced at diagnosis, and therapy often more directed toward palliation than cure. Available ablative therapies include percutaneous radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI), and cryotherapy. Cryotherapy refers to cold injury produced by cryoprobe delivery of liquid nitrogen and although once popular in adults, it has now fallen out of favor due to superior results achieved with RFA and PEI. In most cases, these treatment approaches are palliative and are suitable for smaller size tumors only, generally below 3–4 cm maximum diameter. RFA provides slightly better tumor kill than PEI (90 % versus 80 % complete tumor necrosis) with less sessions (mean of 1.2 versus 4.8) [164]. It is also associated with fewer side effects; thus in many centers, RFA is now preferred over PEI; however, RFA is contraindicated in lesions located adjacent to the major biliary ducts or to bowel loops. Complications of these ablative techniques occur in about 8–9 % of cases, mainly in the form of pain, fever, bleeding, tumor seeding,

and gastrointestinal perforation [165]. Percutaneous ablation has not been well studied in children.

Rhabdoid Tumor

The definition of a rhabdoid tumor classically relies on a characteristic morphology and loss of hSNF5/INI1 tumor suppressor gene expression [166]. In cases lacking the typical histological features, the loss of expression of the INI1 gene product is the essential diagnostic tool. Although pediatric rhabdoid tumors are most common in the kidney and brain, they do occur at other sites including the mediastinum and liver. When primary to the liver, rhabdoid tumor is difficult to distinguish from the small cell undifferentiated (SCU) variant of hepatoblastoma (HB) [58]. Given the aggressive biologic behavior and poor prognosis seen with the SCU variant of HB, it has been suggested that tumors previously classified as SCU-HB were actually hepatic rhabdoid tumors. The differentiation of an SCU-HB from a rhabdoid tumor is challenging and is important in terms of research, but possibly clinically irrelevant at present as both are biologically aggressive with poor response to chemotherapy. Malignant rhabdoid tumor of the liver is a rare and aggressive tumor of toddlers and school age children which may present with spontaneous rupture [167]. These rare tumors are often chemoresistant and fatal, although a recent case report documents the potential for cure with multimodal therapy including ifosfamide, vincristine, and actinomycin D [168]. As with all locally aggressive liver tumors that respond poorly to chemotherapy, the most important treatment goal is complete surgical excision.

Hepatic Sarcomas

Primary hepatic sarcomas are rare, and their outcome depends primarily on tumor histology, sensitivity to chemotherapy and/or radiotherapy, and the ability to achieve complete tumor resection [169].

Biliary Rhabdomyosarcoma

The classic presentation of biliary rhabdomyosarcoma is in young children (average 3 ½ years) with jaundice and abdominal pain, and is often associated with abdominal distension, vomiting, and fever [170]. Histology is either embryonal or botryoid, both histologic subtypes of rhabdomyosarcoma that have a favorable prognosis. It is important to definitively distinguish in differentiated embryonal sarcoma the cuniform biliary rhabdomyoscarcoma as patients with UESL are often erroneously included on COG RMS protocols [171]. Because the tumor most often involves the central biliary tree and porta hepatis, the ability to achieve gross total resection is rare. Fortunately the tumor is often sensitive to both chemotherapy and radiation and long-term survival is seen in 60–70 % of patients. Surgical intervention has two goals: to establish an accurate diagnosis and to determine the local-regional extent of disease. Although chemotherapy is generally effective at relief of the associated biliary obstruction, patients remain at risk for biliary sepsis until the obstruction abates as the tumor shrinks with chemotherapy.

Undifferentiated Embryonal Sarcoma of the Liver

The undifferentiated embryonal sarcoma of the liver (UESL) is an aggressive hepatic tumor of mesenchymal origin. It accounts for about 5–15 % hepatic tumors in childhood [172, 173]. The typical presentation is an 8–18 year old with a liver mass, nausea, vomiting, jaundice, fever, and weight loss. PET CT has been reported to monitor treatment response as recent significant improvement in survival has been seen with chemotherapy, aggressive surgery, and salvage radiotherapy [173]. On MRI the tumor is heterogeneous with focal areas of T1 hyperintensity and T2 hypointensity. On CT, the prominent myxoid stroma has high water content and cystic appearance. The peripheral rim of dense enhancement corresponds to the pseudo capsule [66]. Diagnosis often requires an open biopsy because needle aspiration or true cut biopsy frequently yields only necrotic material [174]. Histologically, the UESL is a mesenchymal lesion with polygonal spindle cells, stellate cells, highly polymorphous cells and a variable component of myxoid stroma. Multiple eosinophilic globular inclusions in giant cells are typical for UESL. Sometimes also dilated bile ducts are present, especially in the peripheral areas. Immunohistochemical analysis shows that the tumor stains positively for vimentin, alpha-1 antitrypsin [171]. UESL has been reported to arise within mesenchymal hamartoma, an hypthosis that was recently shown to be associated with t (11, 19) (q11; q13.4) translocation [175, 176].

The best chance of cure is achieved with a multidisciplinary treatment strategy based on neoadjuvant and adjuvant chemotherapy, surgical resection, and sometimes radiotherapy. The chemotherapy regimens are usually based on guidelines designed for childhood sarcomas, including vincristin (V), actinomycin D (A), cyclophosphamid (C), ifosfamide (I), Doxorubicin (A) (CWS Protocol: VA, VAI, VAIA; IRS protocol: VAC) [171, 172]. The unresectable tumors are treated with neoadjuvant chemotherapy followed by delayed surgery and postoperative chemotherapy, and about two-thirds will show tumor shrinkage after neoadjuvant chemotherapy [174, 177].

Liver transplantation is a treatment option to achieve a complete resection after neoadjuvant chemotherapy [173, 178]. Cure is usually possible following complete tumor resection. Patients with unresectable tumor after chemother-

apy, multifocal or ruptured tumor and patients with distant metastases have been associated with a poor prognosis. The overall survival in single institution series in the last years was 70–100 % [172–174, 179].

Angiosarcoma

Although rare, the authors' personal experience, and multiple case reports in the literature, support the potential for malignant transformation of an infantile hepatic hemangioma to angiosarcoma [180, 181]. Histologic verification of malignancy can be difficult and angiosarcoma should be suspected if the biologic behavior of an infantile hepatic hemangioma shows unusual progression or recurrence after a period of relative quiescence. Relatively chemoresistant, prognosis is generally poor unless diagnosed early. There are case reports of successful transplantation.

Metastatic and Other Malignant Tumors Involving the Liver

Metastatic Liver Tumors

In children, especially infants, hepatic metastasis is sometimes detected in neuroblastoma. Patients with neuroblastoma younger than 12 months of age with metastases limited to liver, skin, and bone marrow is called a stage 4S and have better outcomes than infants with stage 4 disease [182]. The majority of 4S liver tumors will regress spontaneously, even when persistent, and may not require aggressive therapy [182]. Multiple solid tumors of childhood are known to metastasize to the liver including: germ cell tumors (GCTs), neuroendocrine pancreatic tumors, pancreatoblastoma, gastrointestinal stromal tumor, desmoplastic small round cell tumor, nephroblastoma, and brain tumors, especially glioblastoma, and medulloblastoma [183–185]. In cases with metastasies to the liver or lung, chemotherapy, radiotherapy, and surgical approaches have not been standardized. Neoadjuvant chemotherapy often yields a partial response; however, tumors may remain surgically unresectable. An aggressive approach to treatment is required to maximize long-term remission, and multiple case reports document occasional survivors after hepatic metastasectomy.

Hepatic Involvement in Hematologic Malignancies

Hemophagocytic Lymphohistiocytosis (HLH)

Hemophagocytic lymphohistiocytosis (HLH) may occasionally present as an abnormal liver mass in a newborn with coagulopathy. Predisposing factors include familial, herpes simplex virus, and severe combined immunodeficiency [186]. Diagnostic criteria according to HLH-2004 include fever, splenomegaly, bicytopenia, hypotriglyceridemia, hypofibrinogenemia, hemophagocytosis, low NK cell activity, hyperferritinemi a, and high IL-2 receptor levels [187]. Treatment is with combination chemo-immunotherapy, including etoposide, dexamethasone, cyclosporine A, and anticipated mortality of about 40 % is increased if the diagnosis or appropriate therapy is delayed.

Langerhans' Cell Histiocytosis (LCH)

Morphologic changes and clinical findings in Langerhans' cell histiocytosis (LCH) of the liver may resemble primary sclerosing cholangitis or a chronic non-suppurative destructive cholangitis [188]. Therefore, LCH is an important differential diagnosis of chronic destructive cholangitis with cholestatic liver disease, especially in children and young adults. Other involved organs include bone, pituitary, thyroid, lungs [189]. The diagnosis can be verified by S-100 and CD-1a immunohistochemistry. There have been rare reports of pediatric liver transplantation in toddlers with multisystem LCH who developed end stage liver disease despite intensive chemotherapy [190, 191].

Acute Megakaryoblastic Leukemia (AMKL)

Rarely congenital acute megakaryoblastic leukemia (AMKL) may present isolated to the liver with ascites caused by massive infiltration of hepatic sinusoids by leukemic cells [192]. The bone marrow by microscopy and flow cytometry and the peripheral blood smear may not initially show the presence of blasts. Because the marrow fibrosis may not manifest until after the massive hepatic infiltration it may initially be difficult to diagnosis as leukemia. In most children with liver involvement the spleen, lymph nodes, and marrow will also be involved at diagnosis. But even in these cases the diagnosis may be difficult, both clinically and pathologically, and the hepatic and lymph node involvement is not uncommonly misinterpreted as solid tumor [193].

Hepatic Veno-occlusive Disease (VOD)

VOD is a major manifestation of liver toxicity associated with conventional and high-dose chemotherapy in children affected by hematologic malignancies and certain solid tumors [194]. Clinically, patients present with jaundice, painful hepatomegaly, and fluid retention, which may evolve into multi-organ failure, a hallmark of severe disease. The pathogenesis is complex and not completely understood, but the damage to sinusoidal endothelium, typically caused by toxic metabolites released from antineoplastic drugs, is thought to play a crucial role, together with cytokine activation, immune deregulation, and coagulopathy [195]. This results in primarily vascular changes in the liver affecting small hepatic venules (VOD), sinusoids (sinusoidal dilatation, peliosis, and perisinusoidal fibrosis) and the portal vein and its branches. Diagnosis is based on clinical criteria supported by characteristic ultrasound findings, with the gold standard investigation being hepatic-venous pressure gradi-

ent measurement and biopsy. The most convincing approach is the use of defibrotide, a novel oligonucleotide with antithrombotic and antiplatelet aggregating properties, as well as endothelial-stabilizing effects. This agent, together with other specific forms of supportive care, has shown efficacy in the treatment of established VOD and promising results in the prevention of VOD in pediatric patients receiving chemotherapy [196].

Liver Tumors as Secondary Malignancies

Secondary liver tumors, especially focal nodular hyperplasia, have been reported in children previously treated with chemotherapy and radiotherapy for tumors including neuroblastoma, leukemia, germ cell tumor, and Ewing's sarcoma [81, 197]. Another case report of FNH in a child with a history of stage IV neuroblastoma showed foci of small cell undifferentiated hepatoblastoma in the resection specimen so very close follow-up is necessary if treatment of the FNH is nonoperative [198]. Although it is difficult to conclude that a specific chemotherapy agents or radiotherapy can cause FNH, liver tumors have been recognized as potential late effects and/or secondary malignancies in children who have previously undergone chemotherapy and radiation as toddlers.

Benign Tumors

Benign Epithelial Tumors

Benign epithelial tumors that are common in adults may infrequently occur in childhood. These include focal nodular hyperplasia (FNH), nodular regenerative hyperplasia (NRH), large regenerative nodules (LRN), and hepatic adenoma. All are composed of hyperplastic hepatocytes similar to surrounding liver parenchyma and may be difficult to discern at imaging [66]. Preferential hepatic arterial phase enhancement helps distinguish FNH and hepatic adenoma from uninvolved liver. Hepatic adenoma often has intracellular fat and a propensity for intratumoral hemorrhage, neither of which are seen in FNH. Unlike adenoma, FNH often contains enough Kupffer cells to show uptake at sulfur colloid scintigraphy. Nodular regenerative hyperplasia is often associated with portal hypertension.

Focal Nodular Hyperplasia

Focal nodular hyperplasia (FNH) may be diagnosed at any age, from newborns to the elderly. In children, it usually is diagnosed between 2 and 5 years of age [199]. It is a benign epithelial tumor that has been referred to by various names in the literature including benign hepatoma, solitary hyperplastic nodule, focal cirrhosis, cholangiohepatoma, and even mixed adenoma. FNH has been seen in association a variety of different conditions and situations including previous trauma to the liver [200], other liver tumors [201], hemochromatosis [202], Klinefelter's syndrome [203], itraconazole [204], smoking [205], oral contraceptives [205], congenital absence of the portal vein (Abernathy syndrome) [206] and a history of pediatric treatment with chemotherapy for a Wilms tumor or neuroblastoma [198, 207]. Focal nodular hyperplasia is a well-circumscribed, lobulated lesion whose typical architecture on gross examination consists of bile ducts and a central stellate scar containing blood vessels that supply the hyperplastic process. Usually, there is no real capsule, but often the fibrous tissue surrounds the liver in lesions varying in size from a few millimeters to more than 20 cm in diameter and may be single or multiple. Microscopically, the proliferating cells are practically identical to the surrounding hepatocytes.

Like other benign liver tumors, small lesions may be asymptomatic incidental findings. Larger lesions may occasionally present with mass symptoms, usually abdominal pain. The diagnosis of FNH is suggested by the ultrasonographic appearance of a well-demarcated, hyperechoic and homogenous lesion; the tumor may be much more evident on CTA or MRA after intravenous contrast enhancement; and usually has normal accumulation of ^{99m}Tc sulfur colloid on liver scintigraphy. Old case reports have reported false positive imaging with ^{9m}Tc sulfur colloid, but recent review has shown that the diagnosis of FNH by imaging alone without biopsy can be highly specific, and MRI was the most sensitive study [208, 209]. In fact, FNH can be a radiographic chameleon, and although a radiographic "central stellate scar" is a pathognemonic finding, it is lacking in 40–50 % of patients. Spontaneous regression is rare although it may be seen after cessation of oral contraceptives. Asymptomatic patients do not require resection. Symptomatic patients in whom the diagnosis of malignancy has not been definitively ruled out will require surgical excision. Symptomatic patients in whom the benign diagnosis has been confirmed may be candidates for ablative therapy with transcatheter arterial embolization [210].

Macroregenerative Nodules

Nodular regenerative hyperplasia (NRH) are macroregenerative nodules in a non-cirrhotic liver. This is a rare entity of unknown etiology but has been associated in children with a variety of other diseases and drugs. In about half of the children there is some component of associated portal hypertension. Nodular regenerative hyperplasia has been reported in children with portal hypertension and hepatopulmonary syndrome, celiac disease, mimicking metastatic nodules in children with prior treatment of Wilms' tumor or Neuroblastoma, azathioprine treatment of inflammatory bowel disease intrahepatic occlusive venopathy in children treated with six thioguanine for acute lymphoblastic leukemia, Budd-Chiari Syndrome, pulmonary arterial hypertension and connective tissue disorders, chronic granulomatous disease, and a spec-

trum of other disorders many of which involve some sort of perturbation of the hepatic vasculature [211]. Radiologically its nodular appearance may look like neoplasia and open wedge biopsy is occasionally required to definitively rule out malignancy [212]. Prognosis in the absence of portal hypertension is good and complications are rare.

The group in Pittsburgh feels that nodular regenerative hyperplasia (NRH) and large regenerative nodules (LRN) are distinct types of hepatocellular nodules with terminology that has historically often been used interchangeably in the literature [213]. NRH and LRN may have different predisposing factors and imaging findings. Nodular regenerative hyperplasia (NRH) is often associated with portal hypertension, organ transplantation, myeloproliferative disease, or autoimmune processes. The nodules in NRH typically do NOT enhance. Although Rha et al. report a child with NRH secondary to Budd Chiari, the group from Pittsburgh refer to these enhancing lesions in Budd Chiari as LRN [213]. The differentiation may be important if there is a suspicion of malignant degeneration of the nodule and biopsy may be necessary.

Hepatic (Hepatocellular) Adenoma

Hepatocellular adenomas are benign liver neoplasms with specific but varied histopathologic findings and tumor biology. Recent studies of their genetic and histopathic features lead to categorization into three distinct subgroups: (A) inflammatory hepatocellular adenomas; (B) hepatocyte nuclear factor 1x-mutated hepatocellular adenomas; and (C) B-catenin-mutated hepatocellular adenomas. Treatment depends upon subtype and an algorithm was recently proposed in a comprehensive review [214]. The differential diagnosis from focal nodular hyperplasia (FNH) remains a challenge. Other associations have been reported with glycogen storage disease types 1 and 3, galactosemia, hyperthyroidism, polycythemia, diabetes, Fanconi's anemia, polycystic ovary syndrome, and contraceptives or anabolic steroids. When associated with oral contraceptives or anabolic steroids the tumor may regress with cessation of the hormonal therapy. Persistent or progressive adenomas are at risk of rupture and bleeding and surgical excision is often recommended. Alternative contemporary management may include percutaneous radiofrequency ablation [215].

In patients with glycogen storage disease type 1A multiple adenomas may develop progressively in about 50 % of patients. In these patients there is a risk of hepatocellular carcinoma in up to 18 % of patients and HCC has been reported as early as 6 years of age. These patients need to be monitored very closely with serial AFP, radiographic imaging, and biopsy if any question of HCC is raised [216]. In glycogen storage 1A patients in whom the adenomas are multiple and growing, liver transplant not only corrects the underlying metabolic disorder, but also eliminates the risk of tumor rupture, and eliminates the risk of HCC. Apart from the special circumstance of glycogen storage disease, surgical excision has been recommended for lesions >5 cm, dysplastic foci, enlarging size or features of malignant change on imaging, B catenin activation, male gender [216].

Mesenchymal Hamartoma

Although mesenchymal hamartoma of the liver is the second most common benign liver tumor in children, its biology and pathogenesis are poorly understood [174]. Historically, mesenchymal hamartoma has been described in the literature by various names including pseudocystic mesenchymal tumor, hepatic and giant cell lymphangioma, cystic hamartoma, bile cell fibroadenoma, hamartoma, and cavernous lymphangiomatoid tumor. Edmondson recognized these to be similar lesions and described them as mesenchymal hamartoma in 1956. Mesenchymal hamartoma typically presents before 2 years of age with abdominal swelling as the initial symptom. Before sophisticated diagnostic imaging became so readily accessible, many of these tumors became very large, eventually presenting with mass effect such as vena cava compression, feeding difficulties, and respiratory distress. With the widespread use of ultrasound and CT these tumors are now usually detected early as a palpable mass in an otherwise asymptomatic child. The alpha-fetoprotein (AFP) may be variably elevated in this tumor confounding the differentiation from hepatoblastoma. The pathogenesis of mesenchymal hamartoma is unclear. The three leading theories postulate (1) abnormal embryologic development of the mesenchyme producing obstruction of the developing biliary tree that results in cystic, anaplastic, and proliferating bile ducts with most of the proliferative growth just before or after birth, because no mesenchymal mitotic activity in seen histologically [169]; (2) Abnormal development of blood supply with ischemic necrosis and reactive cystic changes [217]; (3) Abnormal proliferation of embryologic hepatic mesenchyme with increased expression of fibroblast growth factor −2 (FGF-2) [218]. Microscopically, the tissue consists of a mixture of bile ducts, liver cell cysts, and mesenchyme. The cysts may simply be dilated bile ducts, dilated lymphatics, or amorphous fluid surrounded by mesenchyme. Elongated or tortuous bile ducts surrounded by connective tissue are unevenly distributed with the bile ducts at the periphery often exhibiting active proliferation [169].

Mesenchymal hamartoma is more common in the right lobe of the liver, although any lobe may be involved. On ultrasonography one sees multiple echogenic cysts although, if the cysts are small, the entire tumor may appear as an echogenic mass. The typical CT scan shows a well-circumscribed, multilocular, multicystic mass that contains low-density cysts separated by solid septae and stroma The stroma and septae may be vascular and occasionally show contrast enhancement on CT scan similar to that seen in infantile hepatic hemangioma. When the cysts are small the tumor may appear solid rather than cystic and biopsy is

required to rule out malignancy. Occasionally a highly vascular tumor in a neonate may present with hydrops, high output heart failure, and respiratory distress [219]. More commonly the tumor tends to increase in size during the first several months of life and subsequently may either stabilize, continue to grow or undergo spontaneous regression.

Traditionally, the surgical treatment has been complete tumor excision, either nonanatomically with a rim of normal tissue or as an anatomic hepatic lobectomy. If the tumor is considered unresectable, the surgical options include enucleation and marsupialization. Although facile, marsupialization may result in tumor recurrence [220]. Management continues to evolve, however, with debate in the literature regarding the advisability of nonoperative management in the asymptomatic patient [221]. Caution is warranted if expectant management is chosen due to reports of malignant transformation or association with undifferentiated (embryonal) sarcoma [174, 222–224].

Hepatobiliary Cystadenoma

Hepatobiliary Cystadenoma is a benign liver tumor most commonly found in middle-aged women. Rare case reports include a 4-year-old boy who had a large mucin-hypersecreting hepatobiliary cystadenoma [225, 226]. The tumor in this little boy caused a hepato-colo-cutaneous fistula, which produced a large amount of external fluid loss. Total excision and repair of the fistula was possible after shrinkage of the tumor with the use of selective embolization of the feeding artery by interventional radiology [226].

Benign Vascular Tumors

Infantile Hepatic Hemangioma

Infantile hemangioma is the most common benign tumor of the liver in infancy [9] illustrates the striking variability of three subtypes focal, multifocal, and diffuse. Many focal lesions are often discovered incidentally and are localized and small enough to be of little clinical significance. Symptoms seen with larger lesions may include abdominal distention, hepatomegaly, congestive heart failure, vomiting, anemia, thrombocytopenia and consumptive coagulopathy, jaundice secondary to biliary obstruction, and associated cutaneous or visceral hemangiomas [227]. The diagnosis of infantile hepatic hemangioma is usually straightforward and based on the combination of clinical symptoms and radiographic appearance on ultrasound and CT scan. Contrast enhanced CT scan shows an area of diminished density, and after bolus injection of intravenous contrast there is contrast enhancement from the periphery toward the center of the lesion, and, after a short delay, there essentially is complete isodense filling of the lesion and liver. MRA has been used in complex cases to identify atypical radiographic features that may portend a poor prognosis [28]. Unfavorable radiographic features include: central varix with arteriovenous shunt, central necrosis or thrombosis, and diffuse hemangiomatous involvement of the liver with abdominal vascular compression [28]. Arterial angiography may be used in infants with refractory symptoms in whom either hepatic artery ligation or embolization is considered. If a definitive diagnosis of simple infantile hepatic hemangioma can be made radiographically, management can be noninvasive because spontaneous regression occurs in most cases—especially those with focal tumors. The terminology is confusing, however, with different authors often using the terms hepatic hemangioma, infantile hepatic hemangioma, infantile hepatic hemangioendothelioma (IHEE), and kaposiform hemangioendothelioma interchangeably [228]. A European pathologic classification recognizes two types in infantile hepatic hemantioendothelioma (IHEE). Type I is more common is composed of a single layer of plump but bland endothelial cells with rare mitotic figures. Type 2 has more pleomorphic endothelial cells and is considered by some to be a low-grade angiosarcoma [229].

A treatment algorithm has been proposed by the vascular anomalies treatment center at Boston Children's Hospital and can be reached at www.liverhemangioma.org (Fig. 16.5). Treatment in this algorithm is based upon whether or not the tumor is solitary, multifocal, or diffuse [230, 231] whose radiographic appearance is shown in Fig. 16.6. About 65 % of

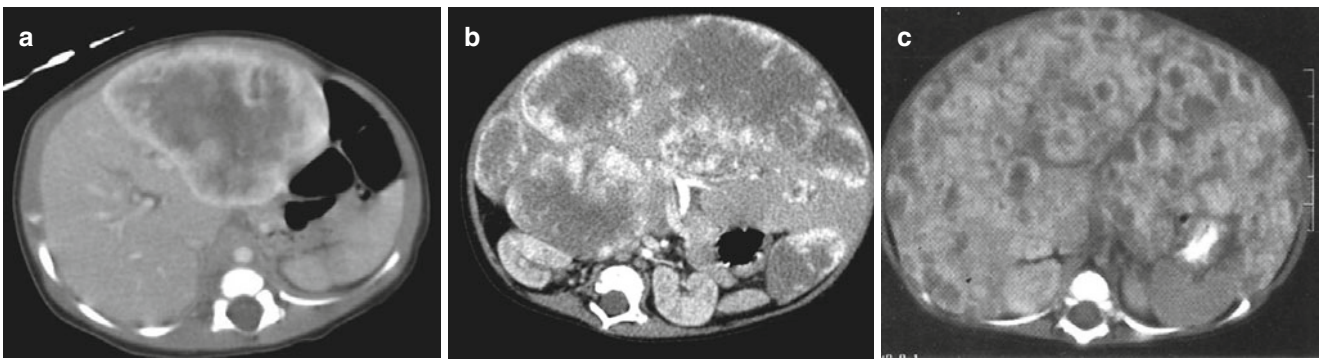

Fig. 16.5 Three subtypes of infantile hepatic hemangioma: (**a**) focal, (**b**) multifocal, and (**c**) diffuse

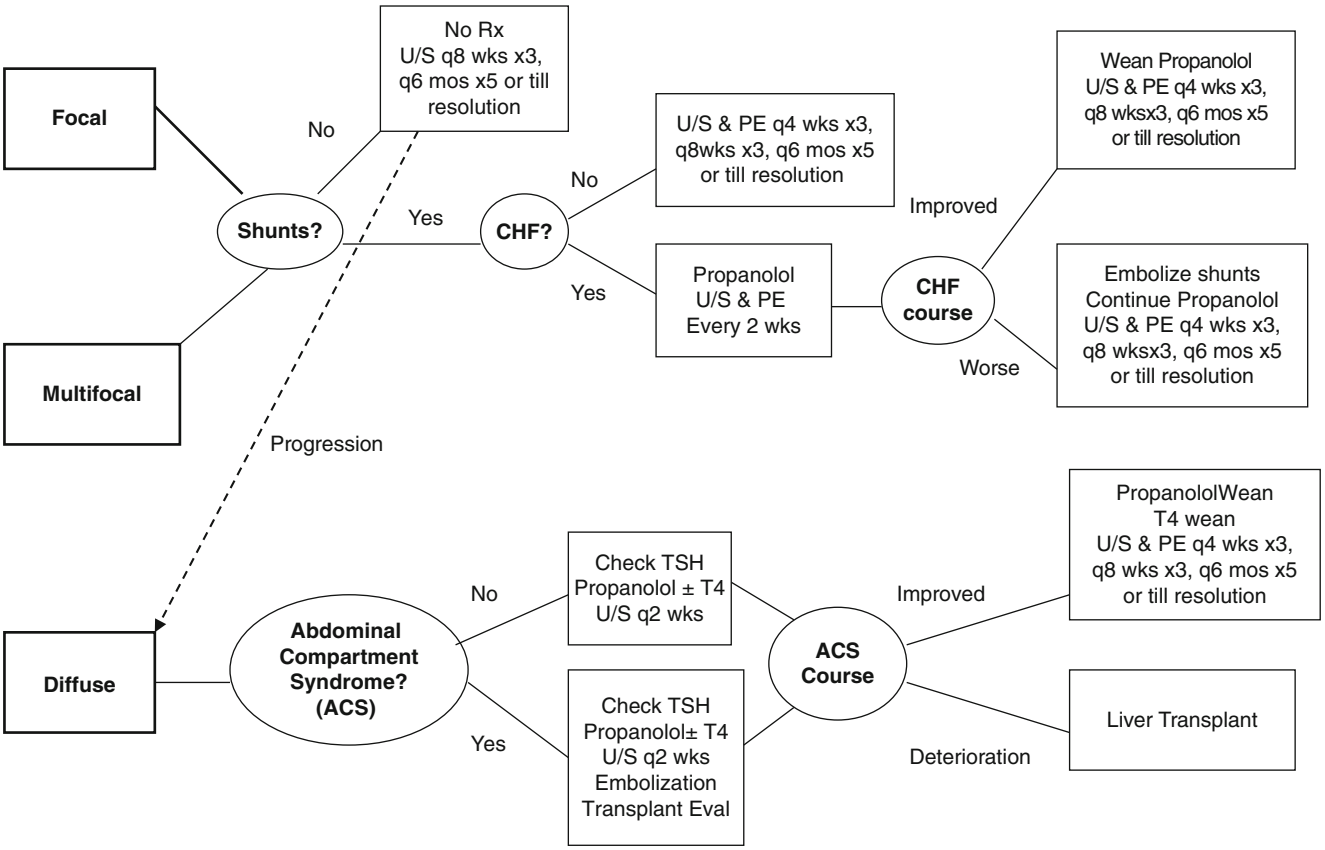

Fig. 16.6 Treatment algorithm: infantile hepatic hemangioma (Adapted from Fishman et al., www.liverhemangioma.com)

tumors are solitary or unifocal with a survival of 86 % and death usually not caused by the tumor but by a co-morbidities [9]. 35 % of tumors are multifocal or diffuse with a survival somewhere between 60 and 100 % with death usually secondary to cardiorespiratory compromise caused tumors refractory to medical and interventional management [9, 231, 232]. Sometimes a large rapidly growing infantile hepatic hemangioma can be life-threatening with intractable high-output cardiac failure from intrahepatic arteriovenous shunting, intraperitoneal hemorrhage, respiratory distress as a result of pulmonary congestion, and massive hepatomegaly compressing abdominal vasculature and producing abdominal compartment syndrome. Historically, the initial medical intervention for symptomatic tumors has been corticosteroids although many are increasingly choosing to start with propranolol [241]. Other medical treatment options exist, although no single treatment has been shown to be universally effective. Congestive heart failure is treated with supportive care, digitalis and diuretics. Anemia and coagulopathy are treated with corrective blood product replacement therapy. Both success and complete failure have been reported variously with many other treatments including epsilon-aminocaproic acid, tranexamic acid, low-molecular-weight heparin, vincristine, cyclophosphamide, interferon 2-alpha, AGM-1470, and newer generation antiangiogenic drugs [233–236]. The angiogenesis inhibitor interferon-alpha may be clinically efficacious, however it must be avoided or used with great caution in children less than 1 year of age because of the risk of producing an irreversible spastic diplegia [237]. Recent studies have shown that the large tumors may produce antibodies to TSH and screening to rule out secondary hypothyroidism is recommended [238]. Treatment is with thyroid hormone replacement therapy and reports demonstrate resolution of the hypothyroidism after liver transplantation in cases that fail medical management [239]. Most recently propranolol has been shown to inhibit the growth of infantile hemangioma [240]. Potential explanations for the therapeutic effect of propranolol, a non-selective beta-blocker, include vasoconstriction, decreased expression of VEGF and bFGF genes through down-regulation of the RAF-mitogen activated protein kinase pathway, and the triggering of apoptosis of capillary endothelial cells [240, 241]. Although rare, malignant transformation to angiosarcoma has been reported and close followup is recommended [180, 181, 242, 243].

In infants who fail medical management, symptomatic solitary tumors may be treated by excision, hepatic arterial ligation or selective angiographic embolization. Although potentially hazardous, hepatic arterial embolization can be especially help-

ful in tumors causing high output cardiac failure due to arteriovenous shunts within the tumor [232]. Orthotopic liver transplantation may be life-saving for cases with diffuse angiomatous change in which the lesion is progressive with intractable high-output cardiac failure, abdominal compartment syndrome, and failure of lesser treatment options.

Kaposiform Hemangioendothelioma

The term "hemangioendothelioma" is sometimes used in the literature when describing a tumor that seems more consistent with a diffuse infantile hemangioma of the liver and hence the terminology can be confusing. Nevertheless, a biologically distinct tumor of infants presenting in the first year of life is kaposiform hemangioendothelioma which may involve the retroperitoneum, extremities, neck or chest wall. Isolated liver involvement is not seen; rather retroperitoneal tumors expand without regard to anatomic planes and may encase the porta hepatis and directly invade the liver, pancreas, mesocolon, colon, and kidneys [244, 245]. Kaposiform Hemangioendothelioma is biologically aggressive, and Kasabach Merritt phenomenon is common with a life threatening coagulopathy and thrombocytopenia. Platelets are consumed by the tumor with a half-life of 1–24 h, and platelet transfusions may actually promote tumor growth through intralesional clotting and the release of vascular endothelial growth factors such as platelet derived growth factor (PDGF). Because of these phenomena, platelet transfusions should only be given when the patient is actively bleeding or as a preparation for surgery [246]. Tumor growth can be so rapid that it causes fibrosis and destruction of the neighboring tissues and mortality ranges from 12 to 24 % for tumors at all sites [244, 247], but may be as high as 60 % for those tumors involving the retroperitoneum due to porta hepatis vascular and biliary obstruction [244]. Successful treatment has been reported with alpha-interferon [248], however, in tumors refractory to antiangiogenic therapy, multidrug chemotherapy regimens may be required and success has been reported with propranolol and vincristine combined with cyclophosphamide, actinomycin D, and methotrexate [246].

Epithelioid Hemangioendothelioma

Epithelioid hemangioendotherlioma is a slow growing vascular tumor which consists of endothelial cells that morphologically resemble epithelial cells. Mainly a tumor in adults, pediatric cases are rare and usually involve children in their teenage years.

Hepatic Teratoma

Primary teratomas (germ cell tumors: GCTs) are rare neoplasms (incidence 0.7/100.000 children/year) with tissue derivatives of all three germ layers [249]. Teratomas mostly occur in the ovaries, the sacrococcygeal region, the testes, and the central nerves system and GCTs of the liver is extremely rare, and accounts for <1 % of all liver neoplasms [250, 251]. Most of them are in children aged <3 years old, and about half of these tumors have been malignant, about half benign [252]. The characteristic histological finding is the predominance of hepatic tissue in the resected specimen. Malignant GCTs have been reported as teratoma [253, 254], choriocarcinoma [255, 256] or yolk sac tumor [251]. Serum AFP levels are sometimes elevated because it is produced by yolk sac, embryonal liver, and embryonal gastrointestinal tract.

Inflammatory Myofibroblastic Tumor

In past inflammatory myofibroblastic tumor (IMT) was often called Inflammatory Pseudotumor. These tumors are usually found in children and young adults and, although most frequently occur in the lungs, can occupy the liver, too [257–260]. Fever, abdominal pain, weight loss and anemia are typical clinical symptoms of IMTs. In some cases of hepatic hilar localization obstructive jaundice develops [257]. There are no specific imaging features of IMT. Thus, surgical biopsy is needed for the final diagnosis. Since the microscopic diagnosis may be quite difficult primary excisional biopsy may be the best option.

Pathologically IMT is a non-neoplastic solid mass consisting of proliferated myofibroblasts with a various degree of infiltration with inflammatory cells. Plasma cells are often predominant. Myofibroblasts are spindle cells sharing features of smooth muscle cells and fibroblasts and stain positively for vimentin, actin, and keratin in most cases [261]. The differential diagnosis are lymphomas and granulomatous lesions. Particularly, when multinucleated giant cells and foamy histiocytes are found [262]. The stroma is typically quite fibrotic with a laminated appearance or dense sclerotic zones, which can be confused with sarcomas [262]. IMT etiology is still largely unclear [257, 262]. There have been several hypotheses like atypical inflammatory response, infectious processes (such as Epstein-Barr virus) [258, 261, 263–265]. These theories are supported by hypergammaglobulinemia or immunologic deficits found in some patients [266]. Recent findings identified clonal, nonrandom, balanced chromosomal translocations resulting in rearrangement of the ALK gene in 50 % of patients [267]. Up to 70 % of IMTs are positive for ALK-1, a tyrosine kinase oncogene found to be rearranged in anaplastic large-cell lymphoma, rhabdomyosarcoma, and peripheral nerve sheath tumor, suggesting that IMTs may represent rather true neoplastic pathway than reactive proliferation. For this reason some are classified as low-grade sarcomas with myofibroblastic differentiation and the World Health

Organization classification puts them among, so called intermediate neoplasms [267]. This is further supported by the fact that some IMTs have a potential for local recurrence or even distant metastases [267]. DNA aneuploidy was identified as another denominator of the malignant IMT behavior [268]. In fact IMTs may be quite a heterogenous group. Surgical excision has been a cornerstone of therapy for IMTs, although spontaneous or antibiotic- and steroid-induced regressions have been noted [262]. Recently, also the use of non-steroid antiinflammatory drugs and imatinib has been tested with some success [267].

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Pancreatic Neoplasms in Children

17

N. Scott Adzick and Pablo Laje

Introduction

Almost all of the different types of neoplasms that commonly occur in the adult population have been reported in children and must be included in the differential diagnosis of a pancreatic mass in a child. Pancreatic neoplasms in children are very uncommon, representing less than 1 % of all solid tumors. According to the Surveillance, Epidemiology and End Results (SEER-17) registry of the National Cancer Institute (NCI), between 1973 and 2007 only 73 cases of pancreatic malignant neoplasms in patients younger than 19 years were reported, which represents an incidence of 0.02 cases per 100,000 people per year [1]. The female to male ratio was 1.7/1. This database is the most accurate source of epidemiologic data available, but it does not include benign neoplasms. Because of their rarity, our understanding of the natural history of pancreatic neoplasms in children is limited, and for the same reason therapeutic protocols in general and chemotherapy regimens for malignant neoplasms in particular are not standardized.

In general, pancreatic neoplasms in children have an overall better prognosis than in adults, and the benign/malignant ratio is significantly higher. Nonetheless, some pancreatic tumors in children are very aggressive, unresectable at diagnosis and have a poor survival rate. Complete surgical resection is the key in the treatment of all pancreatic neoplasms in children, but unfortunately is rarely achieved in cases of poorly differentiated infiltrative neoplasms.

The pancreas can develop primary neoplasms but can also contain secondary neoplasms (i.e. metastasis of distant primary neoplasms), non-neoplastic solid lesions (e.g. lymphangiomas, focal lesions of congenital hyperinsulinism), and non-neoplastic cysts (e.g. choledochal cysts, enteric duplication cysts, pseudocysts).

Among all different types of pancreatic neoplasms in children, pancreatoblastoma (PBT) and solid-pseudopapillary tumor (SPPT) are the most common ones in the first and second decade of life, respectively. The most common signs at presentation are abdominal pain or a palpable abdominal mass. Jaundice is rarely the presenting sign in children.

Classification and Staging

The classification of pancreatic neoplasms was muddled due to overlapping terminology, but this changed over the past decade due to advances in histopathology and molecular diagnosis. The most recent classification accepted worldwide is the one developed and released by the World Health Organization in 2010 which divides pancreatic neoplasms by cell line of origin, histological configuration, and degree of cellular dysplasia (for pre-malignant lesions) (Table 17.1) [2].

Pancreatic neoplasms are initially divided into *epithelial* and *non-epithelial* categories. Epithelial tumors are those with a cell line that resembles the lining of the pancreatic ducts ("ductal" differentiation, typically mucin-producing cells), the lining of the pancreatic acini ("acinar" differentiation, typically enzyme-producing cells), or the cells that form the islets of Langerhans ("endocrine" differentiation, which can be functional or non-functional). Non-epithelial tumors are those that arise from tissue of mesenchymal or ectodermal origin (e.g. liposarcomas, myosarcomas, primitive neuroectodermal tumors), which are extremely rare. Many pancreatic neoplasms are invariably cystic or solid in nature. However, solid neoplasms can develop cystic changes due to ductal obstruction or tissue degeneration, which represents a diagnostic challenge.

The staging system for pancreatic neoplasms in children is based on the TNM classification and follows the criteria used in the adult population (Table 17.2).

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Table 17.1 Classification of pancreatic tumors

Invasive Ductal Adenocarcinoma	**Acinar Cell Neoplasms**
Conventional	Cystadenoma
Atypical Histologic Variants	Carcinoma
Pancreatic Intraepithelial Neoplasia (PanIN)	Cystadenocarcinoma
1A	**Serous Neoplasms**
1B	Cystadenoma
2	Cystadenocarcinoma
3	Solid serous adenoma
Intraductal Neoplasms	**Pancreatic Endocrine Neoplasms**
Intraductal papillary-mucinous neoplasms	Well differentiated
With low, moderate or high-grade dysplasia	*Functional*
With invasive carcinoma	*Non-functional*
Intraductal tubular neoplasms	Poorly differentiated
With low, moderate or high-grade dysplasia	**Solid Pseudopapillary Tumor**
With invasive carcinoma	**Pancreatoblastoma**
Mucinous Cystic Neoplasms	**Mesenchymal Neoplasms**
With low, moderate or high-grade dysplasia	**Secondary Neoplasms**
With invasive carcinoma	

International Agency for Research on Cancer, World Health Organization, 2010

Table 17.2 TNM classification and staging system of pancreatic neoplasms

T – Primary tumor			
TX:	Cannot be assessed		
T0:	No evidence of primary tumor		
Tis:	Carcinoma in situ – PanIN3		
T1:	Limited to the pancreas ≤ 2 cm[a]		
T2:	Limited to the pancreas > 2 cm[a]		
T3:	Tumor extends beyond the pancreas		
T4:	Tumor involves celiac trunk or SMA[b]		
N – Regional lymph nodes			
NX:	Cannot be assessed		
N0	No lymph node metastasis		
N1	Lymph node metastasis		
M – Distant metastasis			
M0:	No distant metastasis		
M1:	Distant metastasis		
Staging	**T**	**N**	**M**
Stage 0:	Is	0	0
Stage 1A:	1	0	0
Stage 1B:	2	0	0
Stage 2A:	3	0	0
Stage 2B:	1, 2, 3	1	0
Stage 3:	4	Any	0
Stage 4:	Any	Any	1

[a]Maximum diameter

[b]Superior mesenteric artery

Individual Neoplasms

Pancreatoblastoma

Pancreatoblastoma (PBT) is the most common pancreatic neoplasm in the first decade of life, and it affects males four times more frequently than females. The mean age at presentation is around 4–5 years, the vast majority of cases occur before 10 years, and very rarely it occurs in adults [3]. PBT belongs to a group of neoplasms called "embryonal tumors", which occur mainly in children and appear to arise from multipotent stem cells. Nephroblastoma (Wilms tumor), hepatoblastoma and neuroblastoma are embryonal tumors, among others. Embryonal tumors appear to share some genetic features. The most striking similarity is the loss of heterozygosity (LOH) of different regions of the short arm of

chromosome 11, which affects the expression of imprinted genes that regulate cell proliferation. The 11p15.5 locus has two imprinted genes: insulin-like growth factor 2 (IGF2) and H19, which have opposite roles in cell proliferation. The IGF2 gene is only expressed from the paternal allele (the maternal allele is silent), whereas the H19 gene is only expressed from the maternal allele (the paternal allele is silent). IGF2 and H19 must be expressed in balance in order to maintain a normal cellular proliferation rate. LOH of the region 11p15.5 with the subsequent imbalance in the IGF2/H19 expression has been demonstrated in cases of nephroblastoma, hepatoblastoma, PBT, and interestingly in the focal form of congenital hyperinsulinism which is characterized by an abnormal proliferation of cells in the form of an adenomatous hyperplasia [4, 5]. Additionally, the LOH of the 11p15.5 region is one of the key features of Beckwith-Wiedemann syndrome, which is associated with disorders of cell proliferation (macroglossia, hemihypertrophy, and hyperinsulinism due to islet cell hyperplasia) and embryonal tumors. PBT is a solid epithelial tumor with cells that have usually some degree of differentiation towards acinar lineage, and much less frequently towards ductal or endocrine lineages. Cells are divided in lobules separated by stromal bands. The pathognomonic feature of PBT is the squamoid corpuscle, which is a cluster of spindle-shaped cells of unknown origin (Fig. 17.1). Because of the acinar-type differentiation, PBT cells are usually positive for lipase and trypsin immunostaining. PBT develops more frequently in the head of the pancreas (60 %) than the body or tail (40 %), and extremely rarely it can occur in ectopic locations. The most common form of presentation is an incidentally found abdominal mass and less commonly abdominal pain. Despite the usually large size at presentation, jaundice is rarely the initial sign of a PBT. There are anecdotal reports of functional PBT detected by a paraneoplasic syndrome [6], and in very rare instances PBT presented as a congenital pancreatic mass (mainly cystic) in patients who had Beckwith-Wiedemann syndrome [7]. Alpha-fetoprotein is elevated in approximately 30 % of PBT, and can be used as a long-term follow-up marker of disease status. On imaging studies PBT usually present as a heterogeneous large mass. Some tumors are well-circumscribed and lobulated, and other tumors are completely infiltrative (Fig. 17.2). Calcifications are frequent. Complete surgical resection, if possible, is the treatment of choice, even if an aggressive surgical intervention is required. Infiltrative tumors that are unresectable at presentation can respond to neoadjuvant therapy and undergo surgical resection afterwards. There is no standard chemotherapy protocol for the treatment of PBT, but the most significant responses have been observed after multiple cycles of Cisplatin and Doxorubicin (Fig. 17.2) [8]. Adjuvant therapy is also recommended for Stage III and IV tumors. The role of radiotherapy remains unclear but there is evidence that it might be useful as adjuvant therapy or for local recurrences [9]. Local recurrences are not uncommon even in cases that were macroscopically completely resected. The prognosis is generally good in cases that present without metastasis and can be resected completely, which according to different series occurs in 60–70 % of the cases. For the other 30–40 % of patients who present with stage IV disease, the overall survival rate is poor: <50 % at 5 years. The most common sites of PBT metastasis are liver and lung.

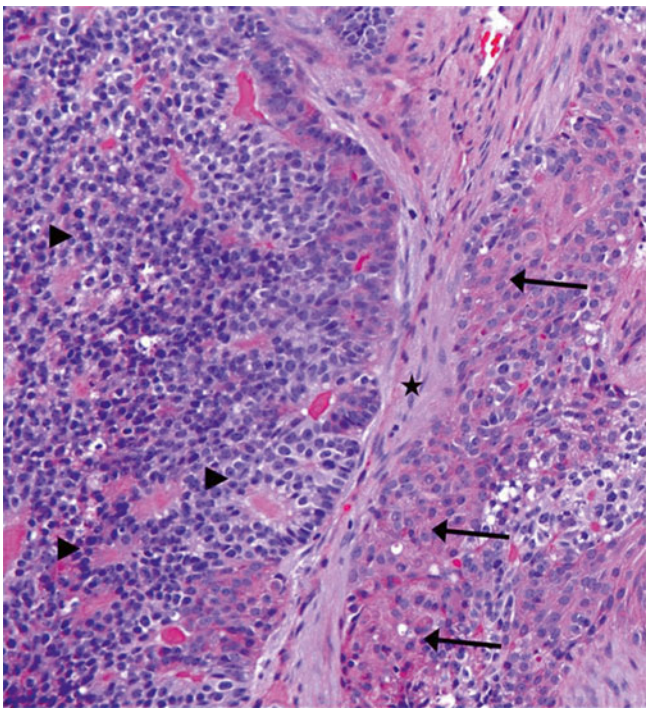

Fig. 17.1 Pancreatoblastoma. Hematoxylin and eosin, 40×. Acinar differentiation (*arrowheads*), squamoid corpuscles (*arrows*) and stromal band (*star*)

Solid Pseudopapillary Neoplasm

Initially described in 1959 by Frantz, this neoplasm has had several different synonyms (solid and papillary tumor, solid-cystic tumor, papillary-cystic tumor and Frantz's tumor) all of which have been replaced by the current term "solid pseudopapillary neoplasm" (SPPN) [10]. SPPN is the most common pancreatic neoplasm in the second decade of life and it affects females 10 times more frequently than males. The mean age at presentation is approximately 20–30 years. SPPN is considered a malignant neoplasm due to its ability to form metastases (which are present at the time of diagnosis in 10–15 % of the cases (Stage IV), but usually has a remarkably benign behavior. SPPN is an epithelial solid tumor that invariably develops significant cystic degeneration. The cellular lineage of origin is unknown. Cells are

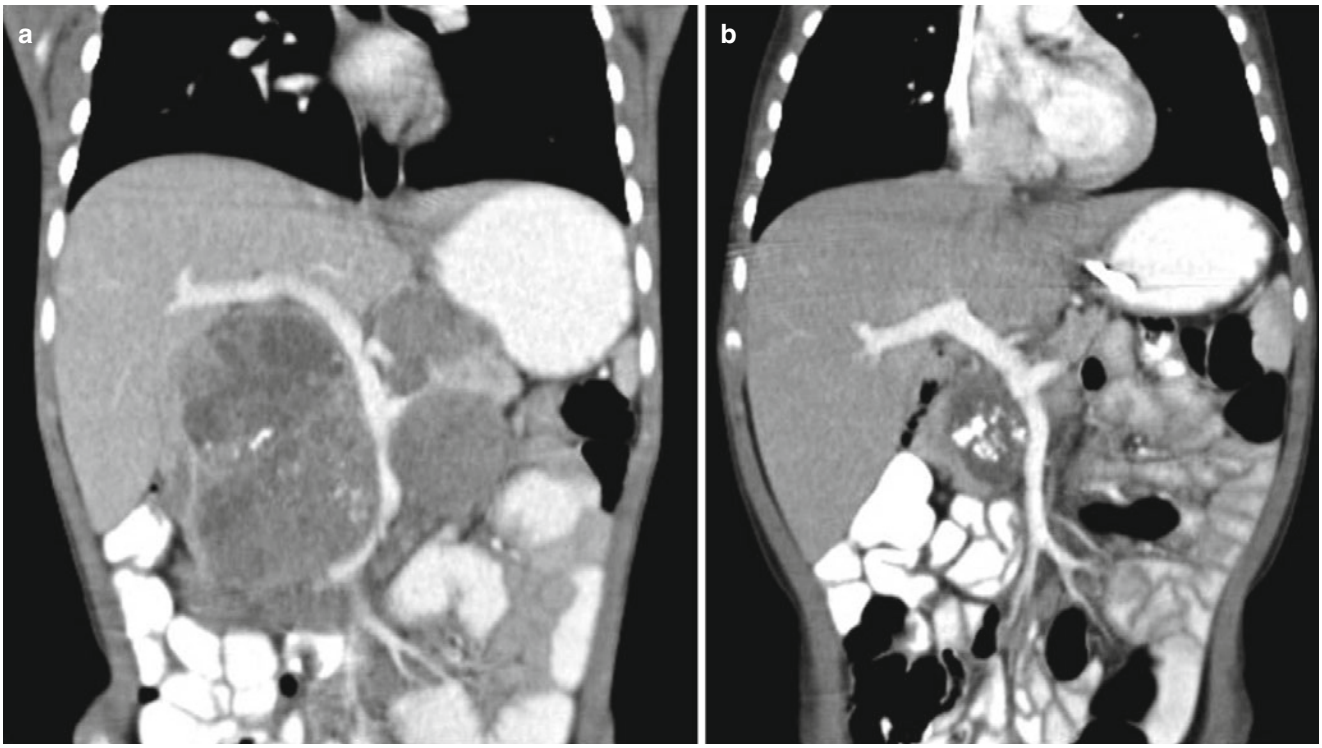

Fig. 17.2 Large PBT at the head of the pancreas with calcifications in a 4-year-old male who presented with abdominal pain (**a**). Initially unresectable and stage IV (lung metastasis). It shrunk significantly after several cycles of cisplatin and doxorubicin (**b**) after which he underwent a Whipple procedure

consistently negative for mucin, enzymes and hormones, which supports the theory that SPPN arises from an embryonal pancreatic pluripotent cell. Other histochemical markers such as neuron-specific enolase, beta-catenin, vimentin and progesterone receptors are frequently positive but non-specific. A particular dot-like intracytoplasmatic expression of CD99 appears to be highly specific for SPPN [11]. Common serum tumor markers (e.g. CA 19–9, CEA, CA 125) are consistently negative in patients with SPPN and there are no known specific serum markers. Most SPPN are located in the body/tail of the pancreas, but they can also occur in the head, and very rarely in extrapancreatic locations [12]. Macroscopically, SPPN has mixed solid and cystic areas. Histologically, SPPN has a very characteristic appearance of solid areas mixed with areas of poorly cohesive cells that form pseudopapillae around thin blood vessels (Fig. 17.3). Vascular or neural invasion are unusual findings in SPPN. On imaging studies, SPPN are usually large (several centimeters in diameter) and heterogeneous, but encapsulated and well demarcated from the surrounding structures (Fig. 17.4). Areas of cystic degeneration are invariably present in SPPN, whereas calcifications are present in a minority of cases. The most common signs of presentation are abdominal pain or an incidentally found abdominal mass, but jaundice is also common in tumors located in the pancreatic head (Fig. 17.4). Preoperative cytological diagnosis by percutaneous or endoscopic biopsy is feasible but has a sensitivity of only 50–75 %. The mainstay treatment of SPPN is surgical resection, which should be as complete as possible even in Stage IV cases. While some authors have reported satisfactory outcomes with incomplete resections in some patients (on < 10-year follow-up), the need for an aggressive surgical approach is supported by numerous reports in the literature [13–15]. Simple enucleation and incomplete resections are associated with more frequent local recurrences and a poorer prognosis [15]. Distal pancreatectomy is the procedure of choice for pancreatic body/tail tumors, and pancreaticoduodenectomy is the procedure of choice for pancreatic head tumors. Lymph node involvement is very rare in SPPN and therefore radical lymphadenectomy is not required. Distant metastases (Stage IV) are present in 10–15 % of the cases at initial presentation, and the most common metastatic sites are the liver and the peritoneum. Interestingly, metastases can develop many years after initial complete resection [16]. When feasible, metastases should be surgically resected; otherwise chemotherapy is the treatment of choice. Chemotherapy has also been used as single or neoadjuvant therapy in cases that were deemed unresectable, and in cases of aggressive local recurrences, but its role in less aggressive tumors is not defined [17, 18]. Radiotherapy and hormonal therapies (i.e. anti-progesterone due to the frequent presence of progesterone receptors) have been used in the past without

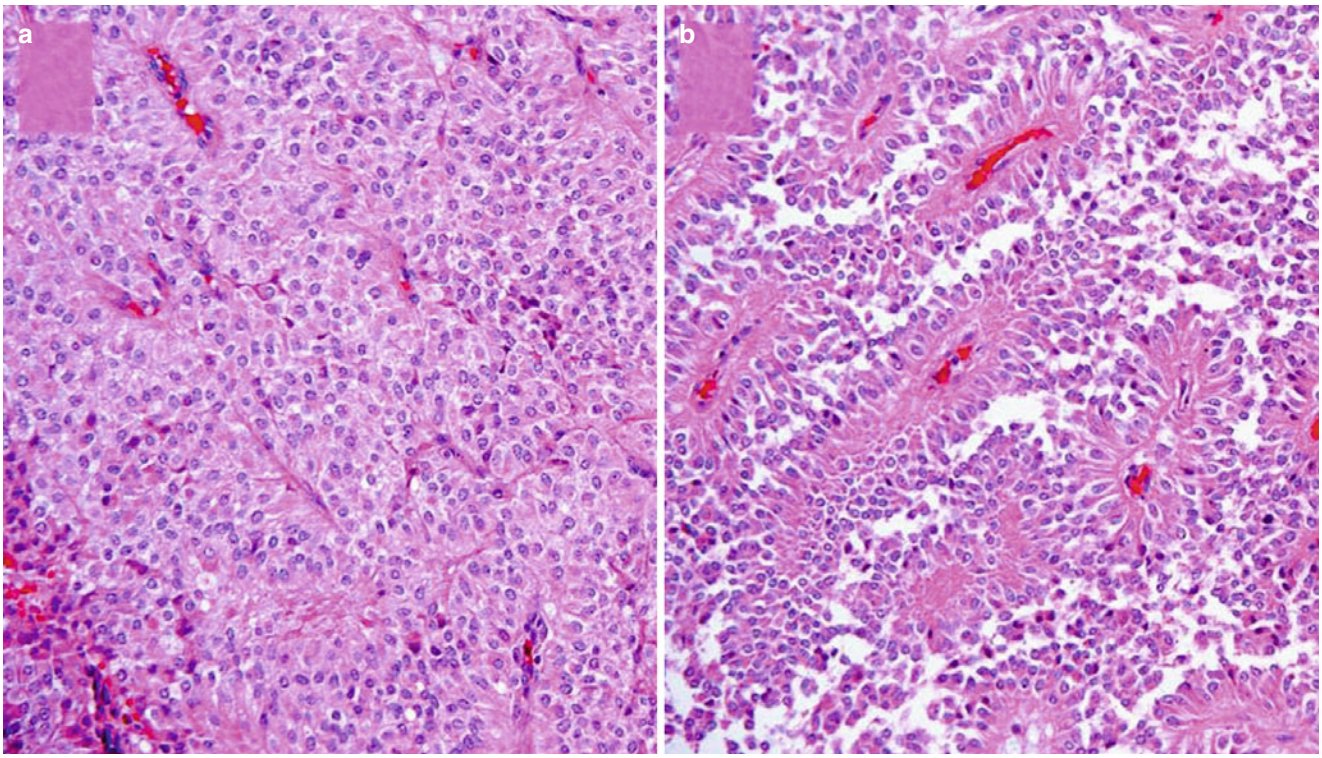

Fig. 17.3 Solid pseudopapillary neoplasm (SPPN). These heterogeneous neoplasms combine solid regions of homogeneous cells (**a**) and pseudopapillary regions where poorly cohesive cells surround small and thin blood vessels (**b**)

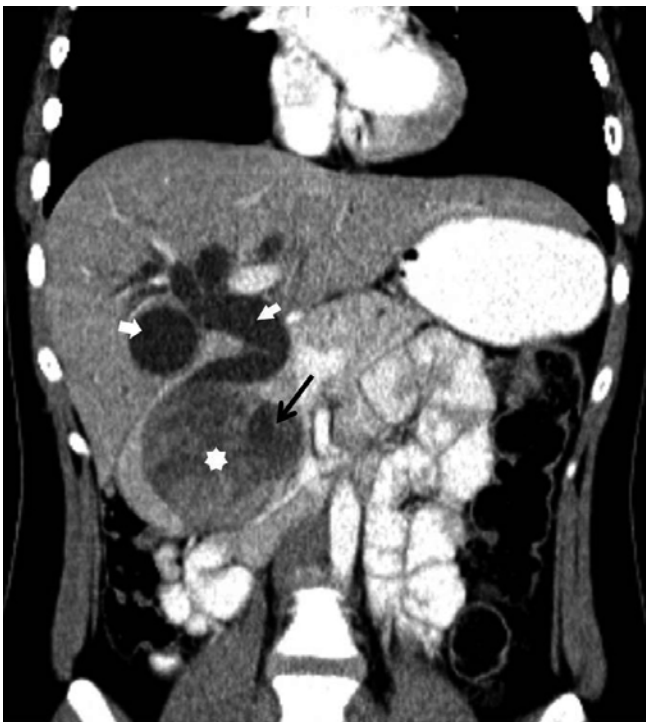

Fig. 17.4 Solid pseudopapillary neoplasm in the pancreatic head in a 16-year-old female. The tumor (*star*) is heterogeneous and well demarcated, and has an area of cystic degeneration (*black arrow*). It caused significant biliary obstruction (*white arrows*); jaundice was the sign of presentation

salutary effect and have been abandoned as therapeutic options in patients with SPPN. The prognosis of SPPN is favorable, with an overall survival rate greater than 90 %, even in cases that are Stage IV at presentation and in those who develop metachronous metastases. There is a subset of SPPN, however, that is very aggressive and undergoes sarcomatous degeneration, with invasion of adjacent organs, neural and vascular elements. Factors that appear to be related to a more aggressive behavior are male gender, infiltrative growth pattern, nuclear pleomorphism, vascular invasion and extrapancreatic invasion [13].

Acinar Cell Neoplasms

Acinar cell neoplasms are a group of epithelial pancreatic tumors that arise from cells that resemble normal acinar cells, produce pancreatic exocrine enzymes and are positive for exocrine enzymes or enzyme-like markers on immunohistochemical staining. This group of neoplasms includes cystic lesions (cystadenoma and cystadenocarcinoma) and solid lesions (acinar cell carcinoma and a very rare subset of carcinomas of acinar, ductal and or endocrine mixed differentiation). *Acinar cell cystadenoma* is a very rare, benign and cystic pancreatic neoplasm. The cysts are lined by acinar cells and the fluid inside the cysts is rich in amylase and

lipase. By definition, cells have no atypia, do not cross the basal membrane and are positive for trypsin and chymotrypsin on immunohistochemical staining. They can be unilocular or more commonly multilocular. There have been only a handful of cases of pediatric acinar cystadenomas reported in the literature, therefore, there is no standardized treatment [19, 20]. Cases that are easily resectable should be resected, and cases that occupy a large segment of the pancreas and would require an extensive pancreatic resection might be amenable to observation only after a biopsy diagnosis. In *acinar cell cystadenocarcinomas* the cysts are lined by cells that have nuclear and cytoplasmatic atypia, and have the potential to metastasize. First described in 1981, only a few cases have been reported in the literature, and the occurrence in pediatric patients is anecdotal [21, 22]. *Acinar cell carcinoma* (ACC) is relatively common within the uncommon malignant pancreatic tumors in children, and it has been extensively reported in the literature [23, 24]. ACC is an aggressive neoplasm that affects males more frequently than females. Early metastases are common (>50 % at the time of diagnosis, mainly in the liver). The prognosis is relatively poor, compared to PBT and SPPN, but it appears to be better in children than in adults (where the 5-year survival rate is <5 %). ACC can be asymptomatic and found incidentally, can produce pain and weight loss, and can also be functional and produce paraneoplasic syndromes like Cushing's and lipase hypersecretion syndrome (subcutaneous fat necrosis, bone infarcts and polyarthralgia) [25–27]. ACC is mainly a solid tumor, but some cystic degenerative changes are not uncommon. Most ACC are located in the head of the pancreas and are large at diagnosis. Alpha-fetoprotein is frequently elevated. Histologically, the cells can have an acinar arrangement or, less frequently, a completely solid arrangement. Cells are almost always positive for trypsin, chymotrypsin, and lipase. ACC can be confused with PBT on histologic analysis due to the marked acinar differentiation of some PBT. The absence of squamoid corpuscles favors the diagnosis of ACC. ACC also share some genetic features with PBT in that studies have shown a high frequency of loss of heterozygosity of the region 11p which is a frequent feature of all embryonal tumors [28]. A combination of surgery and chemotherapy offers the best outcome in ACC. Nevertheless, even patients with no metastases at presentation and a complete surgical resection have a high incidence of distant and local recurrence and a very poor survival rate.

Invasive Ductal Adenocarcinoma

By far the most common malignant pancreatic neoplasm in the adult population (>90 %), ductal adenocarcinomas (DAC) are very rare in children. Few pediatric cases have been reported in the literature, and almost all of them where diagnosed as Stage IV and had an eventual fatal outcome [23, 24, 29, 30]. Most DAC are solid and located in the pancreatic head. Rapid local invasion and early distant spreading are the rule, with 80 % of cases being unresectable at presentation. The most common sites of metastases are liver, lungs, lymph nodes and bone. Most cases of pancreatic DAC are sporadic, but up to 10 % of cases have a familial history of the disease. A number of syndromes like Fanconi's anemia, Peutz-Jeghers (PJ) and most importantly hereditary pancreatitis (HP) have been associated with a higher incidence of pancreatic DAC (up to 40 % of patients with HP and 70 % of patients with PJ will eventually develop pancreatic DAC). Pancreatic DAC is associated with "pre-malignant" lesions, particularly *pancreatic intraepithelial neoplasia* (PanIN) and *intraductal neoplasms*. On imaging studies pancreatic DAC are irregular, heterogeneous, infiltrative lesions, typically hypodense on contrast-enhanced computed tomography and hypointense on magnetic resonance. Macroscopically pancreatic DAC are firm and hard tumors. Histologically there is a *conventional* type (the most frequent) and several different variants (colloid, hepatoid, adenosquamous, and others) but their clinical significance in children is unknown. The neoplastic tissue consists of a tubular proliferation within a desmoplastic stroma that infiltrates the non-neoplastic ducts, islets of Langerhans and acini. Immunohistochemical markers consistently positive in DAC are mucin (particularly MUC1, 3 and 5), the glycoproteins CA19-9, CEA and CA125, and the cytokeratins (CK) 7, 8 and 18. None of them is, however, an unequivocal indicator of DAC. The genetic background of DAC has been extensively studied in the adult population. The most common anomalies involve mutations on the oncogene KRAS and the tumor suppressor genes p53, p16 and DPC4. The treatment of choice is surgery, but a complete resection is rarely achieved. Chemotherapy is used in unresectable cases but there are no standardized protocols in children. The survival rate is very poor, with a median of less than 20 months from the time of diagnosis [23, 24, 30].

Pancreatic Intraepithelial Neoplasia

Pancreatic Intraepithelial Neoplasia (PanIN) is a group of *microscopic* lesions confined to the epithelium of the pancreatic ducts that are precursors of invasive carcinomas. These lesions are classified by the degree of atypia in PanIN 1A, 1B, 2 and 3 (Table 17.3). PanIN are found incidentally in normal pancreatic specimens and in pancreatic specimens that contain neoplastic or non-neoplastic lesions and typically more than one PanIN is present within the same specimen. These lesions are well-known to progress gradually from grade 1A to 3 and eventually turn into invasive ductal

Table 17.3 Classification of Pancreatic Intraepithelial Neoplasia (PanIN)

PanIN	Features	Previous name
1A	Columnar cells; no nuclear atypia	Metaplasia
1B	Papillary architecture; no nuclear atypia	Dysplasia
2	Papillary; moderate nuclear atypia	Dysplasia
3	Papillary; significant nuclear atypia	Carcinoma in situ

carcinomas. They can be found in children, and are particularly frequent in those with hereditary pancreatitis, where PanIN of all grades have been observed in patients as young as 7 years [31, 32].

Intraductal Pancreatic Neoplasms

Pancreatic Intraductal Neoplasms are a group of *macroscopic* (>1 cm in diameter by definition) lesions that arise from the epithelium of the main pancreatic duct (rarely from branches) and are precursors of invasive carcinoma. They are different than PanIN due to the size and the fact that pancreatic intraductal neoplasms are not clinically silent and can be seen on imaging studies. There are two different types: "*papillary-mucinous*" and "*tubular*". Intraductal papillary-mucinous neoplasm (IPMN) is a tumor frequently found in men in their 7th & 8th decade, but has been reported in children [33]. It consists of a proliferation of mucin-producing cells in a papillary pattern. Since the lesion commonly involves the main pancreatic duct, mucin can be seen draining through the ampulla of Vater by endoscopy. The mucinous cells have different degrees of atypia and are graded in "low-grade dysplasia", "moderate-grade dysplasia", "high-grade dysplasia" and "carcinoma in-situ". Cells are ductal in nature, therefore are frequently positive for CEA, CA19-9 and MUC5. Most IPMN develop in the pancreatic head. The treatment of choice is complete surgical resection. Non-invasive cases have a very good prognosis, where cases with an associated invasive carcinoma have a poorer outcome.

Mucinous Cystic Neoplasms (MCN)

MCNs are a group of cystic premalignant lesions characterized by a proliferation of mucin-producing ductal-like cells embedded in an "ovarian stroma" that do not involve the common bile duct (as opposed to IPMN). Cells can have a different degree of atypia and are graded accordingly (low-grade, moderate-grade, high-grade dysplasia and carcinoma in situ). Most MCN occur in the distal pancreas of women in their 3rd and 4th decades of life. All forms of non-invasive MCN used to be termed "mucinous cystadenomas", whereas cases associated with an invasive carcinoma were termed "mucinous cystadenocarcinomas". Both terms are currently abandoned. Several cases of non-invasive and invasive MCN have been reported in children [34–36].

Serous Neoplasms

Serous neoplasms are a group of cystic lesions that are relatively common in adults. The most common entity is the *serous cystadenoma*, which is benign in nature and has been reported in children [37]. It is composed of multiple microcysts (<1 cm in diameter; rarely macrocysts) lined by cuboidal cells with acinar resemblance but without complete acinar differentiation. The fluid within the cysts does not contain enzymes or mucin. Macroscopically they are well-circumscribed lesions and the definitive treatment is surgical excision. The malignant version, *serous cystadenocarcinoma* has the potential to metastasize, and has not been reported in children.

Mesenchymal Neoplasms

Mesenchymal neoplasms of the pancreas are extremely rare and their incidence in the pediatric population is anecdotal. The group includes, among others, schwannoma (a mostly benign neoplasm that arise from the cells of Schwann, described in adolescents), lymphangioma (generally cystic), Ewing sarcoma (a malignant neoplasm that belongs to the family of "small- round-blue-cell tumors", affects primarily teenagers and occurs as a result of a translocation between chromosomes, which fuses the EWS gene [chromosome 22] to the FLI1 gene [chromosome 11]), primitive neuroectodermal tumor (PNET; a malignant neoplasm that shares genetic features with Ewing sarcoma and is also frequent in children) and lymphoma [38–42].

Pancreatic Lymphoma

Pancreatic involvement in cases of systemic lymphoma is not unusual, whereas primary pancreatic lymphomas are extremely rare. There have been a few reports of primary pancreatic lymphoma in children, all of which occurred in the pancreatic head and presented with abdominal pain and pancreatitis [43, 44]. Chemotherapy with or without stem-cell transplantation is the main treatment in these cases, and the role for surgery is limited. We cared for a 3-year-old with

a stage IV primary pancreatic natural-killer T-cell lymphoma who presented with pancreatitis and cholestasis and responded to several cycles of intense chemotherapy (unpublished data) (Fig. 17.5). No such case has been reported in the literature.

Pancreatic Endocrine Neoplasms

Pancreatic endocrine neoplasms (PEN) are relatively frequent tumors in adults and, as expected, rare in children. There has recently been a proposal to rename this group of entities pancreatic "neuroendocrine tumors" (NET). The key feature of this group of neoplasm is the production of hormones or hormone-like bioamines. The group is divided into *well-differentiated* versus *poorly-differentiated* lesions (based on their histological features), and into *functional* versus *non-functional* lesions (based on the clinical effects of hormone hypersecretion). The vast majority of PENs are well-differentiated, characterized by a proliferation of uniform cells with normal-appearing nuclei and, by definition, less than 20 mitoses per 10 high power fields (HPF). The minority of PEN is poorly-differentiated, characterized by an infiltrative proliferation of irregular cells with marked nuclear atypia and, by definition, more than 20 mitoses per 10 HPF (these neoplasms are also called "*neuroendocrine carcinomas*" and are further divided into small-cell and large-cell types). Despite the apparently clear distinction between well- and poorly-differentiated neoplasms, determining the benign or malignant character of an endocrine neoplasm is not always straightforward in the absence of obvious metastases. This is a particularly critical issue in cases of functional neoplasms. Functional neoplasms are typically detected early in their development due to the paraneoplasic syndrome, which can lead to therapeutic approaches that are not extensive enough. Factors associated with a more aggressive behavior are: size (< or>2 cm in diameter), the presence of necrosis, vascular or neural invasion and local invasion. Some poorly-differentiated PEN are very aggressive, metastasize early and have an invariable fatal outcome.

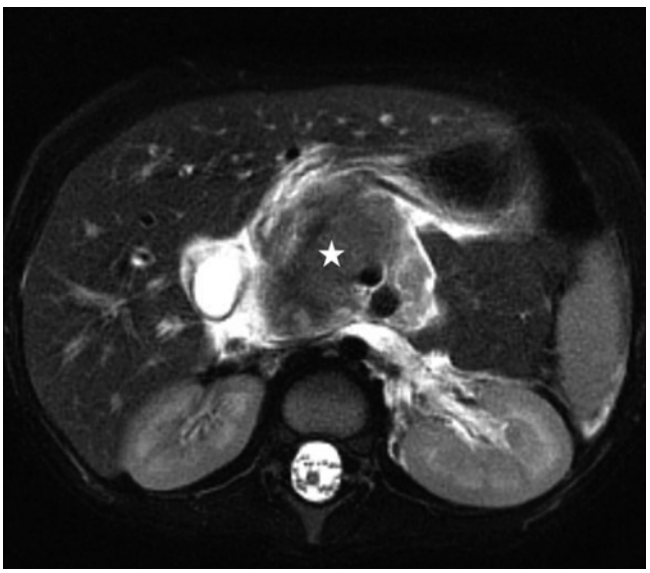

Fig. 17.5 Magnetic resonance of a 3-year-old male with a Natural Killer/T-cell lymphoma located at the head of the pancreas (*white star*) that presented with pancreatitis and cholestasis. The tumor responded to several cycles of chemotherapy

Most PEN are *functional* (65 %), producing the typical paraneoplasic syndrome associated with the hypersecretion of the particular hormone produced. The nomenclature of these lesions is based on the clinical picture and not on the immunohistochemical (IHC) markers (e.g., a PEN that stains positive for insulin but does not produce symptoms is not an insulinoma). Non-functional PEN produce hormone precursors that can be detected by IHC. These tend to be detected later in their development due to the absence of early clinical signs. The most commonly produced hormones are insulin, gastrin, glucagon, vasoactive intestinal peptide (VIP), somatostatin, pancreatic polypeptide (PP), and somatostatin.

In adults, approximately 90 % of PEN are sporadic and 10 % are syndromic, but in children the percentage of syndromic cases is higher. The syndromes that are most commonly associated to PEN are Von Hippel–Lindau (VHL; autosomal dominant; caused by a mutation in a tumor suppressor gene in chromosome 3p25.3), tuberous sclerosis (TSC; caused by mutations in tumor suppressor genes located in chromosomes 9 and 16), and multiple endocrine neoplasia type I (MEN1 or Wermer's syndrome; autosomal dominant, caused by a mutation in the tumor suppressor "*MEN1*" gene located in 11q13 and characterized by parathyroid, gastropancreatic and pituitary tumors) [45–47]. Patients with syndromic PEN can develop multiple synchronous lesions that produce the same or different hormones, and are always at risk for metachronous neoplasms. Macroscopically, well-differentiated PEN are well-demarcated, homogeneous and soft. Poorly-differentiated PEN, on the other hand, are firm, infiltrative and have areas of necrosis. By IHC, PEN lesions are positive for chromogranin A and synaptophysin. The treatment of PEN is complete surgical resection. Chemotherapy is used in unresectable cases and in cases of disseminated disease. Functional tumors may need symptomatic treatment prior to surgery (e.g. proton-pump inhibitors in cases of Zollinger-Ellison). PEN are generally small (particularly the functional ones) at the time of diagnosis, and preoperative localization is not always achieved. A variety of non-invasive and invasive imaging techniques are used for this purpose, however, up to 50 % of the patients are surgically explored without a preoperative tumor location. Ultrasound, endoscopic ultrasound,

intraoperative ultrasound, computed tomography, magnetic resonance, positron-emission tomography, and invasive vascular studies are commonly used in adults and children and have different degrees of accuracy [48–51].

Insulinoma

Insulinomas are neoplasms that arise from the insulin-producing beta-cells of the islets of Langerhans. There are numerous cases reported in children, and the incidence is similar in males and females. The vast majority are benign (>90 %), but malignant stage IV cases with aggressive behavior have been described [52]. Clinically, insulinomas manifest with "Whipple's triad": symptoms of hypoglycemia (e.g. syncope, seizures), hypoketonemic hypoglycemia (insulin inhibits the production of ketonic bodies) and rapid resolution of the symptoms with glucose intake. Most insulinomas in children are sporadic, and 20–25 % are syndromic (mostly associated with MEN1). Most insulinomas are small (<2 cm) at the time of diagnosis and their preoperative identification can be challenging, often requiring a variety of radiologic tests. Larger lesions can be sometimes identified with standard techniques (Fig. 17.6), but this does not occur often. Among all the optional imaging studies, sterile intraoperative ultrasound (combined with direct palpation) has the highest rate of success. Intraoperative ultrasound can also be used, as shown in Fig. 17.7, for targeted needle localization. The treatment of insulinomas usually starts by counteracting the effects of the insulin hypersecretion by means of a high intravenous glucose infusion and hyperglycemic drugs like diazoxide (an agonist of the potassium channel located on the cytoplasmatic membrane of the beta cells, which causes hyperpolarization and inhibition of insulin release) or somatostatin analogs (e.g. octreotide; direct inhibitor of the voltage-dependent calcium channels of the beta cell membrane, which are required for the last phase in the secretion of insulin). Once the patient is euglycemic and all imaging tests are complete, the next step in the treatment is the complete surgical excision of the insulinoma. If preoperative localization is not possible, all efforts should be made to identify the insulinoma intraoperatively by means of inspection, palpation, and ultrasound. If despite all efforts the insulinoma is not found, a sequential pancreatectomy starting at the pancreatic tail can be considered, measuring plasma insulin levels after the resection of each small segment. However a fair balance between the potential side-effects of

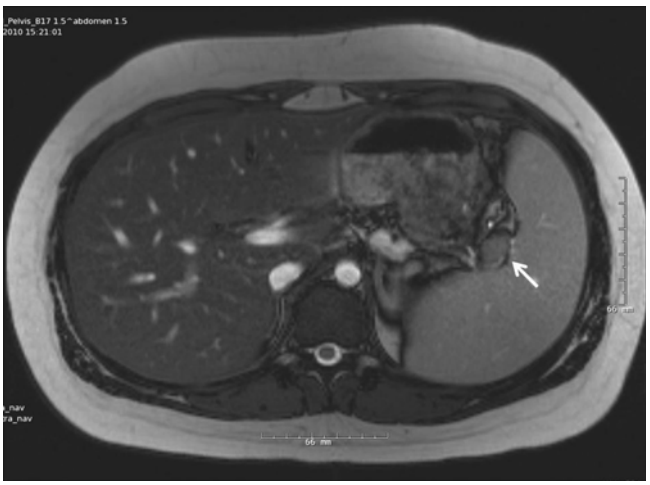

Fig. 17.6 Abdominal MRI of a 13-year-old male with MEN1 showing a relatively large insulinoma in the splenic helium. This patient had multiple synchronous smaller insulinomas and glucagonomas

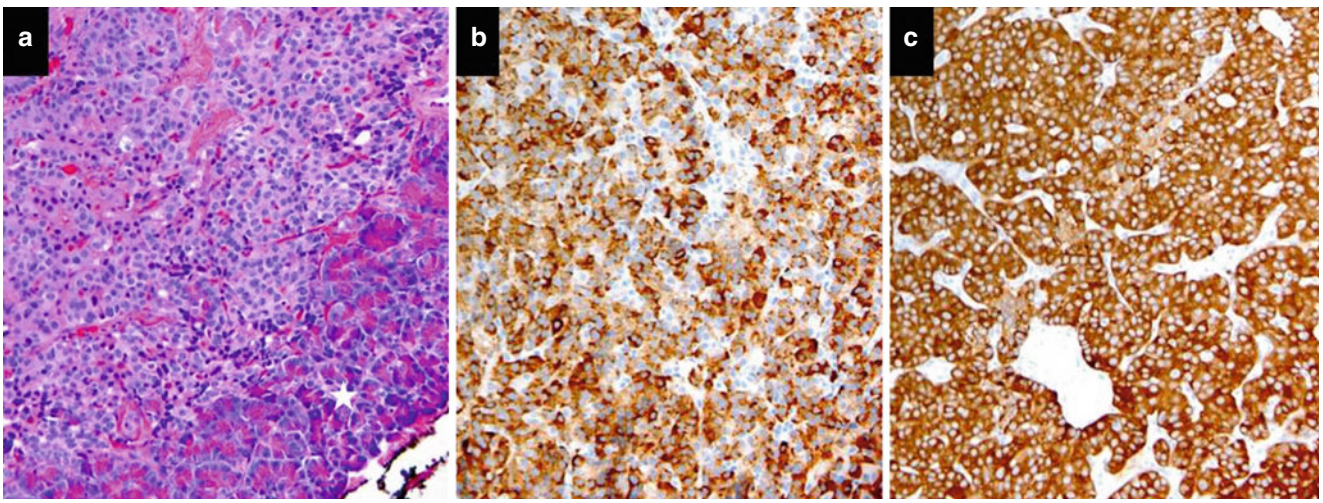

Fig. 17.7 Insulinoma. (**a**) the neoplastic cells do not respect the normal pancreatic lobulations and do not proliferate around the normal pancreatic tissue; instead, normal elements are displaced to the periphery (white star). (**b**) cells stain positive for synaptophysin. (**c**) cells stain positive for insulin

an extensive non-curative pancreatectomy if no change in insulin levels is seen after several resections (head/neck/proximal body insulinomas) versus continuing medical treatment should be thoroughly evaluated. Complete resection of the insulinoma by enucleation or segmental resection is curative in non-syndromic cases. In syndromic cases, on the other hand, tiny undetectable synchronous insulinomas can be present which prevent a lasting cure despite complete resection of an identified insulinoma. Additionally, in syndromic cases recurrences can occur at any time later in life and close surveillance is required. In a series of 8 patients treated over a 5-year period at the Children's Hospital of Philadelphia, one patient had MEN1 and a previous insulinoma resection, no cases of malignancy were seen, and all patients were cured after surgery (data not published). Chemotherapy is a therapeutic option in cases of disseminated disease, which has a very poor outcome. Histologically, insulinomas consist of a proliferation of homogeneous cells that do not respect the limits and anatomy of the pancreatic lobules, displacing the normal elements towards the periphery (Fig. 17.7).

Gastrinoma

Gastrinomas in children have been reported numerous times. They can be sporadic (75 % of cases) or related to MEN1 syndrome (25 % of cases) [53]. Gastrinoma is the most common pancreaticoduodenal neuroendocrine neoplasia in patients with MEN1. Most of them are malignant (80 %), with metastasis to the liver and lymph nodes present at diagnosis. Clinically, gastrinomas manifest with Zollinger-Ellison syndrome, a severe form of peptic ulcer disease. The diagnosis is done by a combination of clinical signs and an elevated serum gastrin level (>500 pg/ml). Preoperative imaging studies must be done to localize the neoplasm. Scintigraphy with labeled octreotide is particularly helpful [54]. The treatment starts with the administration of histamine H2-receptor blockers, proton-pump inhibitors and octreotide, to decrease the gastrin secretion and the acid production. Surgical resection is the next step, which may be achieved by enucleation or a segmental resection. Neoadjuvant or adjuvant chemotherapy is indicated in unresectable tumors and disseminated disease.

VIPoma

Neuroendocrine tumors that overproduce vasoactive intestinal peptide (VIP) causing signs and symptoms are called VIPomas. They can be pancreatic or extra-pancreatic. The clinical picture is called Verner-Morrison syndrome. The vast majority of VIPomas are located in the pancreas, and in rare cases they occur in the retroperitoneum. They can be sporadic or associated with MEN1 syndrome, but the number of reported cases in children is too low to establish reliable demographic or epidemiologic data. In adults, 60–80 % of VIPomas are metastatic at the time of presentation. Both benign and malignant VIPomas have been reported in children [55, 56]. These tumors, when located in the pancreas, arise from neural crest-derived cells present in the pancreatic islets. The hypersecretion of VIP produces *w*atery diarrhea, *d*ehydration), *h*ypokalemia and *a*chlorhydria (the so-called "WDHA-syndrome"). Acidosis, vasodilatation (flushing and hypotension), hypercalcemia and hyperglycemia may also be present. The treatment is complete surgical resection, when possible.

Glucagonoma

Glucagonomas are rare neoplasms that arise from the alpha cells of the islets of Langerhans. The overproduction of glucagon produces a constellation of metabolic effects that are similar to those of diabetes mellitus: hyperglycemia, lipolysis and gluconeogenesis, resulting in pronounced weight loss. Another typical finding in patients with glucagonomas is n*ecrotizing migratory erythema*, a blistering rash that spreads across the skin of the lower abdomen and pelvis. In the adult population, the majority of glucagonomas are malignant. Glucagonomas can be sporadic or associated with MEN1 syndrome. They can co-exist with insulinomas in patients with MEN1. Histologically, the proliferating cells displace the normal pancreatic elements to the periphery, forming well-demarcated lesions (Fig. 17.8). The treatment of choice is the complete surgical resection. Sterile intraoperative ultrasound is helpful for the localization of small, previously undetected lesions (Fig. 17.9).

Congenital Hyperinsulinism

Congenital Hyperinsulinism (HI) is the most frequent cause of persistent, long-term hypoglycemia in newborns and infants, and can lead to severe and irreversible brain damage and developmental delay. It is a rare congenital disorder of glucose metabolism that has an estimated incidence of 1 to 1.4 cases per 50,000 live births, leading to about 80–120 new cases in the United States each year [57, 58]. An incidence as high as 1 in 2500 live births has been reported in populations with high consanguinity like Arabians and Ashkenazi Jews. Inappropriate oversecretion of insulin is the hallmark of HI, and the genetic background is quite variable. Depending on the genetic mutation, babies with HI may be treated medically or may require surgery as either palliative treatment or as a definitive cure. The diagnosis of HI is confirmed when

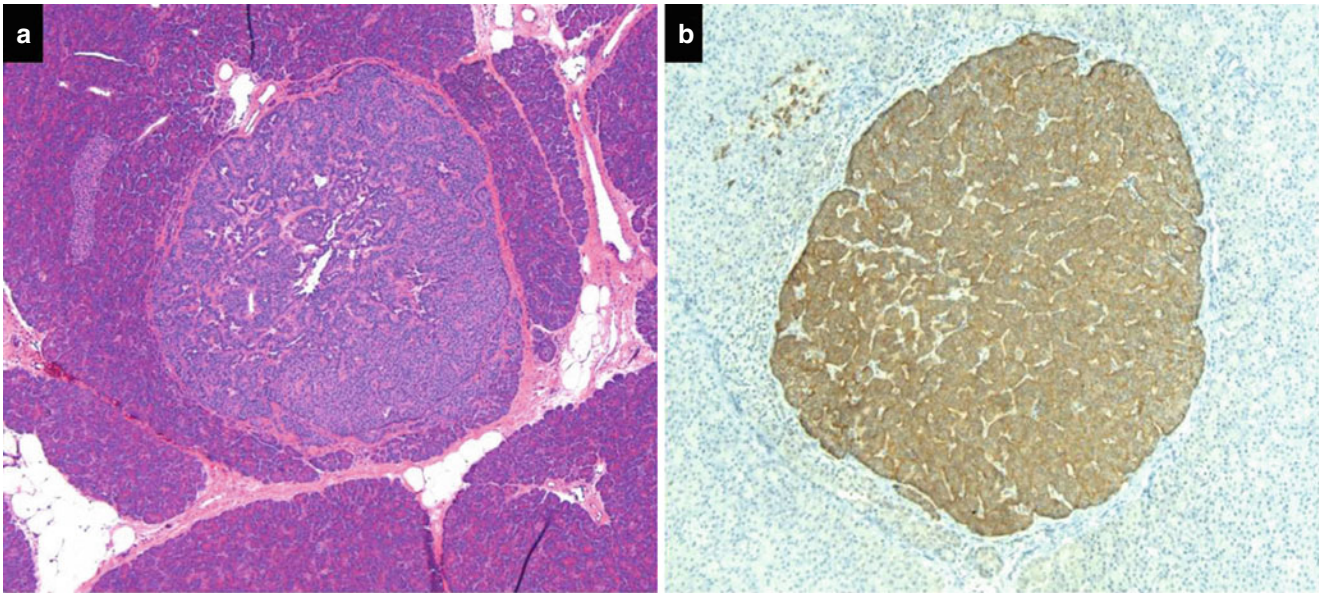

Fig. 17.8 Glucagonoma. (**a**) The neoplastic cells displace the normal pancreatic elements to the periphery and form a well-circumscribed lesion. (**b**) Cells are positive for glucagon by IHC

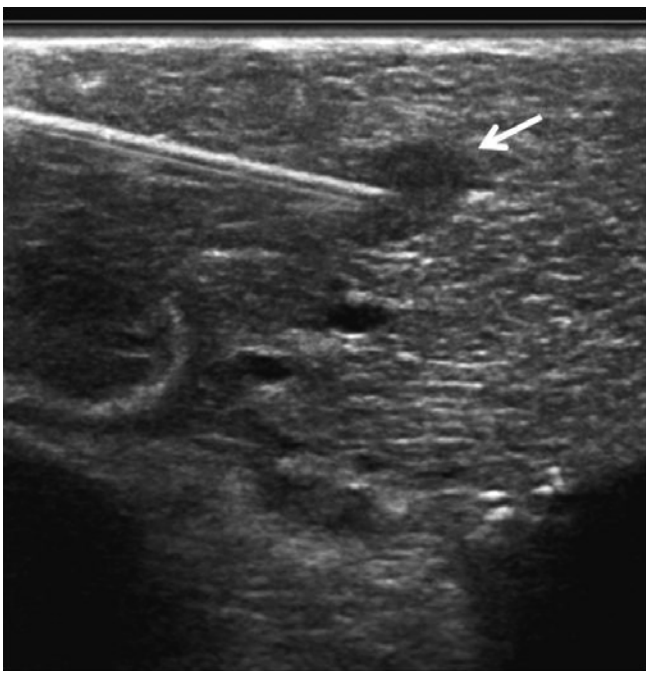

Fig. 17.9 Intra-operative ultrasound-guided needle localization of a 7×6×5 mm, 1 cm deep nonpalpable glucagonoma in the pancreatic head of an 11-year-old female with MEN1. She had a previous insulinoma resected 4 years previously

all of the following metabolic criteria are present: (1) fasting *and* postprandial hypoglycemia with unsuppressed hyperinsulinism (neonatal hypoglycemia is generally defined as a glucose plasma level of <50 mg/dl after the first 24 h of life with an insulin level >36 pmol/L), (2) suppression of lipolysis and suppression of ketogenesis at the time of the hypoglycemia (lipolysis and hepatic ketogenesis are part of the normal physiologic response to hypoglycemia, and are physiologically inhibited by insulin), and (3) a positive glycemic response to a dose of glucagon, which is a direct insulin antagonist (glucose must increase by 30–50 mg/dl after 0.25–1 mg of intravenous glucagon). These criteria must be present for a prolonged period of time and outside certain clinical circumstances such as perinatal stress.

There are two major histological forms of HI: *focal* and *diffuse*, which have an identical clinical course, a completely different genetic background and a completely different surgical management strategy. Focal disease consists of a single focus of adenomatous islet cell hyperplasia surrounded by normal lobular pancreatic tissue. Focal lesions respect the limits of the pancreatic lobules, as opposed to insulinomas which are well demarcated and displace the normal pancreatic structures to the periphery. The beta cells within the focal lesion have an enlarged cytoplasm and typically normal nuclei, although some can have nucleomegaly. They accumulate in central clusters, surrounded by non-beta islet cells. The endocrine cells in the focal lesions push the exocrine components toward the periphery, but there are always some exocrine acinar and ductal cells intermixed within the endocrine cells (Fig. 17.10a). The size of a focal lesion is variable, from a few millimeters in diameter to much greater than a centimeter. It can be located in the surface of the pancreas, or deep within the organ. Superficial lesions can often be identified visually by subtle differences in color and/or by palpation since focal lesions tend to be firmer than the normal pancreas. In our extensive experience at the Congenital Hyperinsulinism Center at The Children's Hospital of

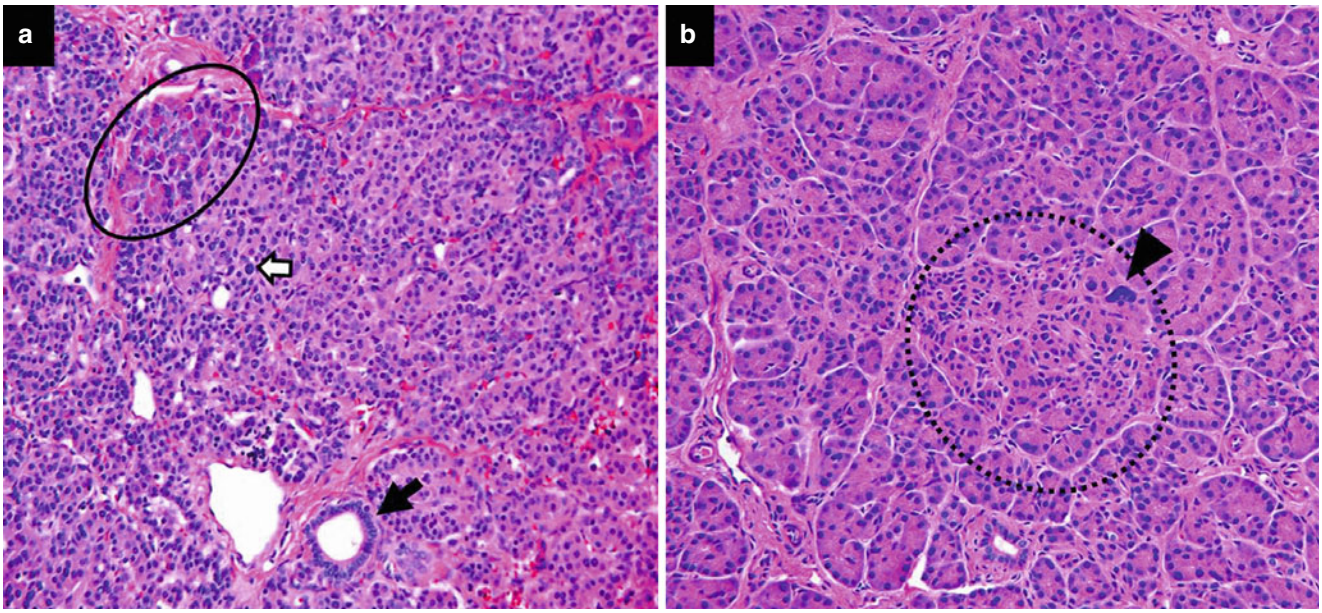

Fig. 17.10 (**a**) Focal lesion of congenital hyperinsulinism (HI). The lesion contains normal pancreatic acinar (*black circle*) and ductal (*black arrow*) components intermixed with the proliferating abnormal endocrine cells, which rarely have nucleomegaly (*white arrow*). (**b**) Diffuse form of HI. There is no endocrine proliferation. The islet of Langerhans (*dotted circle*) is surrounded by normal acinar and ductal components. The characteristic feature is the presence of nucleomegaly (*black arrowhead*)

Philadelphia we have been able to identify the focal lesion by visualization and/or palpation in approximately two-thirds of the cases. Focal lesions can be located anywhere in the pancreas. In our series of more than 170 focal lesions treated by partial pancreatectomy, the distribution was 45 % in the pancreatic head, 25 % in the neck/body, 15 % in the tail, and 15 % in other location, which included focal lesions unusually large that extended beyond a single pancreatic segment, and very rarely lesions that within ectopic pancreatic tissue [59]. In the diffuse form of the disease, most, if not all, beta cells are abnormal throughout the organ, but there is no abnormal endocrine proliferation. The hallmark feature of the beta cells in diffuse HI is nucleomegaly (Fig. 17.10b). Other nuclear abnormalities (e.g. abnormal shape, pseudoinclusions) might also be present. The total number of endocrine cells in pancreases with diffuse HI is not different than in pancreases from euglycemic age-match individuals. The distribution of the abnormal cells is not always homogeneous. In some cases cells with clear nucleomegaly can be very concentrated in one area and very sparse in another area of the same specimen, intermixed with beta cells that do not look histologically abnormal. Of *all* patients with HI, 30–40 % have focal disease and 60–70 % have diffuse disease. Among patients who require surgery (which represent approximately 60 % of all HI patients), in our experience 55 % have focal disease and 45 % have diffuse disease.

From a management standpoint, HI is divided in two groups: diazoxide-*responsive* and diazoxide-*resistant*. The key drug in the treatment of HI is diazoxide, which inhibits insulin secretion by binding and activating the ATP-dependent potassium channel (K-ATP) of the beta-cell cytoplasmatic membrane. In order to be effective the channel (which has two subunits) must be structurally normal and functional. Since the most common causes of HI involve defects in the genes that encode the subunits of the channel (SUR1 and Kir6.2), the majority of HI cases do not respond to diazoxide. The ones that respond to diazoxide are those caused by mutations in other genes. In our experience with more than 450 patients with HI, only 33 % were diazoxide-responsive, whereas 67 % were diazoxide-*resistant*. Most of diazoxide-*resistant* patients require surgery, unless they are deemed not surgical candidates (e.g. multiple prior abdominal surgeries).

To date, about 50 % of patients with HI have a known genetic mutation. The most frequent mutations cause a loss of function in the K-ATP channel. This channel is composed of the two subunits SUR1 and Kir6.2, which are encoded by two genes located next to each other in the p15.4 region of the chromosome 11: ABCC8 and KCNJ11. The *diffuse* form of HI occurs most frequently as a consequence of mutations of the SUR1/Kir6.2 complex inherited in a recessive manner [60]. There are currently more than 200 known mutations in the ABCC8 and KCNJ11 genes. Very rare mutations of the SUR1 gene inherited in a dominant manner and compound heterozygous mutations in the ABCC8/KCNJ11 genes have been identified as a cause of diffuse HI, but the clinical presentation of these patients is milder than patients with recessive disease and respond partially to diazoxide. Diffuse

disease can also occur due to mutations in other genes: glucokinase (GK; 7p15.3-p15.1), glutamate dehydrogenase (GDH; GLUD1; 10q23.3), short-chain L-3-hydroxyacyl-CoA dehydrogenase (SCHAD; 4q22–26), hepatocyte nuclear factor 4a (HNF4A; 20q12–13.1), and the mitochondrial uncoupling protein 2 (UCP2; 11q13). Their pathophysiologic mechanisms are not yet well understood, and their age at onset and clinical presentation is variable. The *focal* form occurs when an individual with a constitutional paternally inherited mutation in the SUR1/Kir6.2 complex loses the normal maternal allele (an event called "loss of heterozygosity") in a group of pancreatic beta cells (a "two-hit" phenomenon), which not only oversecrete insulin but will also develop an adenomatous hyperplastic proliferation pattern. The 11p15 region has several genes subject to genomic imprinting. The loss of the maternal 11p15 not only affects the expression of the ABCC8/KCNJ11 genes (not imprinted), but also affects the expression of the maternal tumor suppressor gene H19 and the cell cycle regulator $p57^{kip2}$ (region 11p15.5). The tumor suppressor gene H19 (strongly imprinted and of exclusively maternal monoallelic expression) exerts an antagonistic effect on the insulin-like growth factor 2 (IGF2) expressed from the paternal allele. The imbalance between IGF2 and H19 is the reason for the adenomatous proliferation of the affected cells. The loss of the maternal allele in a focal lesion can be evidenced by genetic testing and immunohistochemistry (decreased $p57^{kip2}$ staining within the focal lesion) [61]. With regard to the ABCC8/KCNJ11 genes, some cases have only the single abnormal paternal allele, whereas some patients have a duplication of the abnormal allele, which is called uniparental paternal isodisomy. When a baby is diagnosed with HI in the absence of a family history, the parents and the patient must undergo genetic testing. In cases of diazoxide-*responsive* disease, the genetic testing is not urgent and even with the newest technology can take several weeks. In diazoxide-*resistant* cases, which theoretically have a mutation in the SUR1/Kir6.2 complex, the genetic testing becomes more critical because it can help in the differential diagnosis of diffuse versus focal disease, determine the need for imaging studies, and provide prognostic information.

The management of babies with HI starts by providing enough glucose to maintain normoglycemia. This is usually achieved by a combination of high glucose intravenous infusion and frequent enteral feeds. Along with supportive glucose administration, hyperglycemic drugs must be initiated. The first line drug is diazoxide. (an agonist of the K-ATP channel). Diazoxide is not effective in patients with recessively inherited mutations in the ABCC8/KCNJ11 complex and severe HI, but it is effective (at variable levels) in patients with dominant mutations in the ABCC8/KCNJ11 complex, patients with compound heterozygous ABCC8/KCNJ11 mutations, syndromic HI cases and patients with mutations in most of the other HI-related genes of dominant inheritance known to date. After 5 days of diazoxide administration the response is evaluated by a fasting test, off intravenous glucose and off all other hyperglycemic medications. Patients with the ability to maintain a plasma glucose level >70 mg/dl for at least 12 h are considered diazoxide-*responsive*. For these patients, an adequate feeding regimen is established and they are discharged home on long-term diazoxide treatment. Patients who cannot maintain glucose levels above 70 mg/dl for 12 h are presumed to have recessively-inherited disease and are considered diazoxide-*resistant*. In these patients, diazoxide is discontinued, the glucose infusion is re-established, and preoperative planning starts. A variety of alternative drugs can be tried in these patients, but mainly as stabilizing agents prior to surgical intervention. Octreotide (a synthetic long-acting somatostatin analog that inhibits insulin secretion by a direct inhibition of voltage-dependent calcium channels) is generally administered subcutaneously every 6–8 h, but can also be given in a continuous intravenous infusion. The dose must always be titrated up due to rapid tachyphylaxis. Patients with a partial response to diazoxide and some patients with persistent hypoglycemia after a near-total pancreatectomy have been successfully managed at home by a combination of long-term subcutaneous octreotide (twice daily) and a very strict feeding regimen via a gastrostomy. However, octreotide is not recommended for long-term treatment due to its many potential adverse effects, some of which can be life-threatening [5]. Glucagon, a natural insulin antagonist that elevates the plasma glucose levels by activating the enzyme phosphorilase A, which catalyzes the degradation of glycogen in the liver can be used to rescue patients from severe hypoglycemic episodes, but it is not suitable for long-term management.

In terms of preoperative planning in patients with diazoxide-resistant HI, the most relevant step is to differentiate between *diffuse* and *focal* disease because the surgical strategy is radically different. Ideally, through genetic testing two K-ATP channel mutations are found (one from each parent) confirming diffuse disease, or only one mutation of paternal origin is found, possibly consistent with focal disease (the identification of a mutation in the paternal line does not exclude the possibility of a disease-causing postzygotic mutation on the maternal line resulting in diffuse HI not reflected in peripheral blood leukocytes) [62]. Patients with genetically confirmed recessive K-ATP-related diffuse disease do not need preoperative imaging and undergo a near-total pancreatectomy if they cannot be managed with medical therapy. All other patients need preoperative imaging to localize the suspected focal lesion or to help in the differential diagnosis of focal versus diffuse disease when the genetic background is unknown or unclear. Conventional non-invasive image studies have been used to try to distinguish between focal and diffuse disease or to localize genetically

suspected focal lesions, but are not helpful. Invasive interventional tests (arterial stimulation with venous sampling [ASVS] and transhepatic portal venous sampling [THPVS]) were developed in the late 1980s and were used until 2004 [63, 64]. These techniques take several hours to perform, are technically very demanding, and their sensitivity and specificity for distinguishing between focal and diffuse disease are limited [65]. They have been largely replaced by what is now considered the gold-standard imaging study: ^{18}fluoro-L-3-4 dihydroxyphenylalanine positron emission tomography merged with a low-radiation computerized tomography (^{18}F-PET/CT). The study was originally developed in the late 1990s for the detection of tumors of neuroendocrine origin in adults, and has been used in HI patients since 2004 [66–69]. At CHOP, the isotope ^{18}F-DOPA is administered in children under an FDA-approved Investigational New Drug (IND) protocol and the approval of the Institutional Review Board. The isotope has a half-life of 110 min, and is manufactured on the day of the study in the Cyclotron Facility of the University of Pennsylvania. The dose is 0.08–0.16 mCi/kg, given by slow intravenous infusion within 2–3 h of its preparation. All glycemic medications must be stopped prior to the study. The study is done under general anesthesia in a hybrid scanner that initially captures the nuclear signal and then generates a low-radiation CT scan of the abdomen without changing the patient's position. The nuclear signal is captured at 10-min intervals during only the first 50 min post injection because after that time the tracer accumulates in the liver, gallbladder, biliary tree and duodenal lumen, which can lead to false positive images. Focal lesions are seen as bright spots over a darker background, whereas in cases of diffuse disease the tracer is homogeneously distributed throughout the organ (Fig. 17.11). In our experience with more than 160 studies, the sensitivity of the ^{18}F-PET/CT to detect a focal lesion has been 85 %. In the 15 % that were erroneously diagnosed as diffuse disease, the focal lesions were particularly small (although the size of the lesion does not necessarily correlates with the intensity of the signal), were obscured by the signal of the left kidney, or were an atypical case in which the focal lesion occupied most of the pancreas. When a focal lesion is identified on the ^{18}F-PET/CT, the correlation with the actual location determined during the surgery is nearly 100 %. The algorithm for the management of patients with HI is described in Fig. 17.12.

All open operations are approached using a transverse supraumbilical laparotomy. The pancreas is completely exposed by an extended Kocher maneuver, entry into the lesser sac, and mobilization of the inferior border. The spleen is not mobilized. The pancreas is inspected under 3.5× loupe magnification in an attempt to visualize a focal lesion, and it is also palpated. If no focal lesion is identified, then 2–3 mm biopsies are taken from the pancreatic head, body, and tail. Patients with diffuse HI confirmed by intraoperative frozen analysis undergo near-total (95–98 %) pancreatectomy, which involves the resection of the entire pancreas leaving only a tiny residual piece of pancreatic tissue between the common bile duct and the duodenal wall. The intrapancreatic segment of the common bile duct (CBD) must be completely dissected for an adequate near-total pancreatectomy to be performed. To help with the dissection of the CBD, we place a vessel loop around the extrapancreatic distal CBD and then swing that within the duodenal C-loop to trace the CBD through the head of the pancreas until it enters the duodenum. This maneuver is not needed if the CBD follows a course posterior to the pancreatic head. In children with diffuse disease treated by near-total pancreatectomy, a gastrostomy tube is also placed to provide enteral access for glucose or feeds if needed. When the intraoperative biopsies demonstrate normal pancreatic histology, a further search for the focal lesion using the preoperative localization data is conducted. Additional biopsies of suspicious areas are obtained until the focal lesion is identified by frozen section. Expert pediatric pathologic interpretation is vitally important. Focal lesions tend to be less than 10 mm in diameter (although they can be much larger) and frequently are irregularly shaped. Some lesions have octopus-like tentacles that make imperative the intraoperative confirmation of clear margins by frozen section analysis. Focal lesions often have subtle differences in their appearance compared to normal tissue, or may feel firmer than the surrounding normal pancreas (Fig. 17.13). The preoperative PET/CT study greatly facilitates the search. We have been able to identify by visualization and/or palpation approximately two-thirds of all focal lesions. Focal lesions, however, can be buried within the pancreas and be impossible to see or feel. Once the focal lesion is identified, a partial pancreatectomy is performed using frozen sections of margins to ensure a complete resection. Small and superficial lesions in the body or tail can be treated by simple resection. Deep periductal lesions in the body and tail usually are treated by distal pancreatectomy. Superficial and small lesions in the head of the pancreas can also be treated by simple resection. On the other hand, deep pancreatic head lesions close to the common bile duct and pancreatic duct can be tricky to excise completely, particularly if there are ramifications of diseased tissue that emanate from the lesion. To ensure complete lesion resection in these challenging cases, we remove most or all of the pancreatic head followed by Roux-en-Y pancreaticojejunostomy to drain the remaining pancreatic body and tail. By doing this, the endocrine and exocrine functions of the remaining normal pancreas are preserved. In our experience, this approach has been needed in about 40 % of focal lesions within the pancreatic head. The end of a retrocolic, 25 cm-long Roux-en-Y jejunal limb is meticulously anastomosed to the capsule of the pancreatic body (just *beyond* the cut surface of the pancreas) with fine interrupted 5-O monofilament suture to

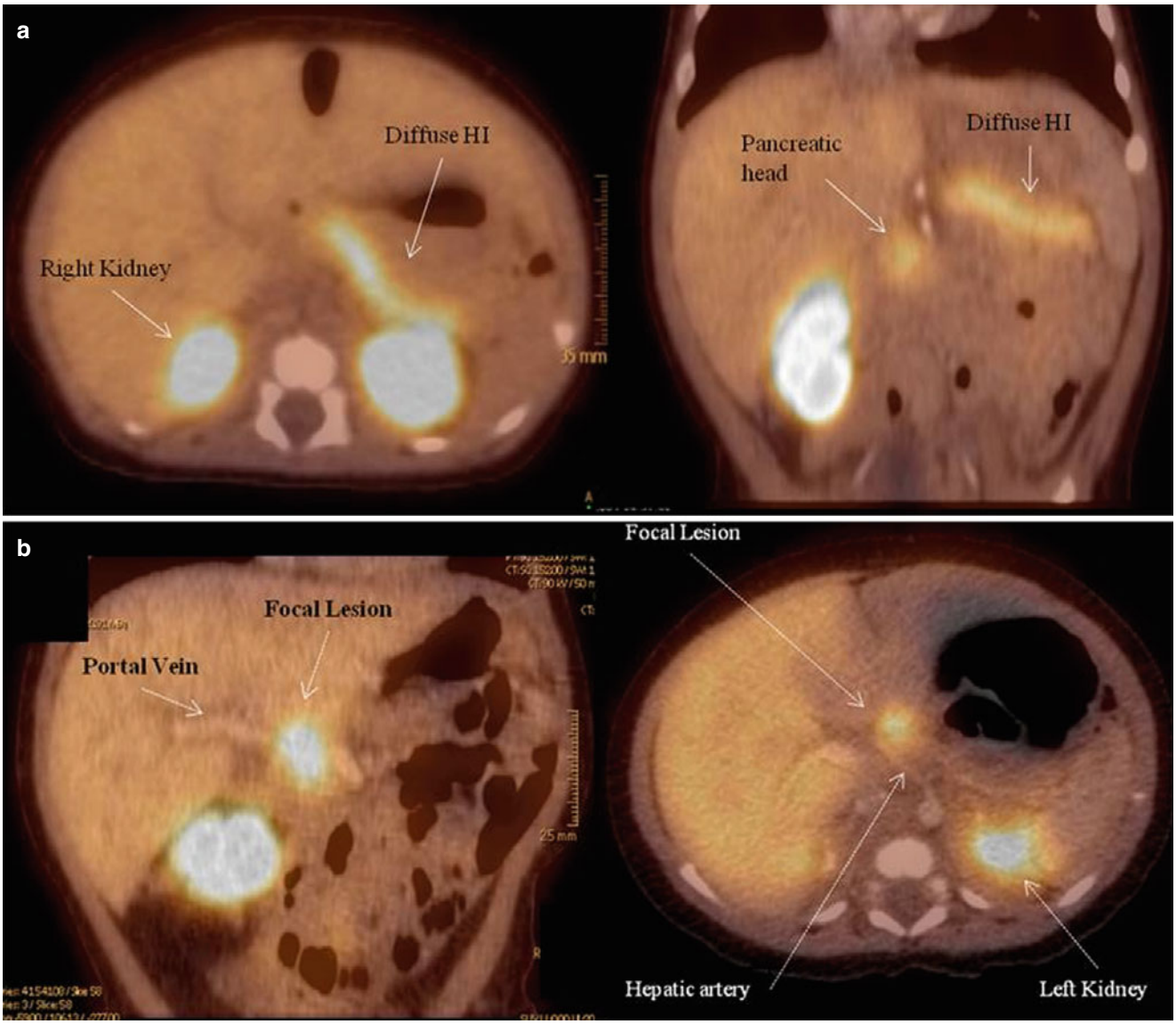

Fig. 17.11 ^{18}Fluoro-L-3-4 dihydroxyphenylalanine positron emission tomography merged with a low-radiation computerized tomography (^{18}F-PET/CT). (**a**) Diffuse disease: the entire pancreas uptakes the tracer homogeneously. (**b**) Focal disease: the lesion is a discrete bright spot in the pancreatic head over a darker background

effectively tuck the cut end of the pancreas into the jejunal lumen. The omentum is then freed from the transverse colon, wrapped around the anastomosis and sutured into place for additional security. Rarely, a focal lesion in the head will extend into the duodenal wall in which case a Whipple procedure may be needed. In cases of near-total or pancreatic head resections it is important to preserve the gastroduodenal artery as well as the vessels supplying the third and fourth portion of the duodenum (superior and inferior pancreaticoduodenal arteries) to avoid duodenal ischemia [70]. We do not use drains after any pancreatic resection for HI. We have used laparoscopy in babies with HI. In cases of focal disease of the body or tail, the approach is straightforward. To facilitate pancreatic body and tail exposure during laparoscopy, it is useful to sew the stomach up to the anterior abdominal wall using 2–3 transabdominal sutures to the anterior gastric wall close to the greater curvature. The carbon dioxide pneumoperitoneum further suspends the stomach anteriorly and also helps to expose the pancreatic body and tail. The laparoscopic procedure is performed via four 3–5 mm ports, and this permits biopsies, complete resection of a visible peripherally located focal lesion, or a distal pancreatectomy if needed. The major drawback to the laparoscopic approach is that there is little tactile feedback to help locate a non-visible focal lesion. Near-total pancreatectomies and pancreatic head resections are significantly more demanding by laparoscopy than by open surgery, and while they are technically feasible, their complication rate such as bleeding and

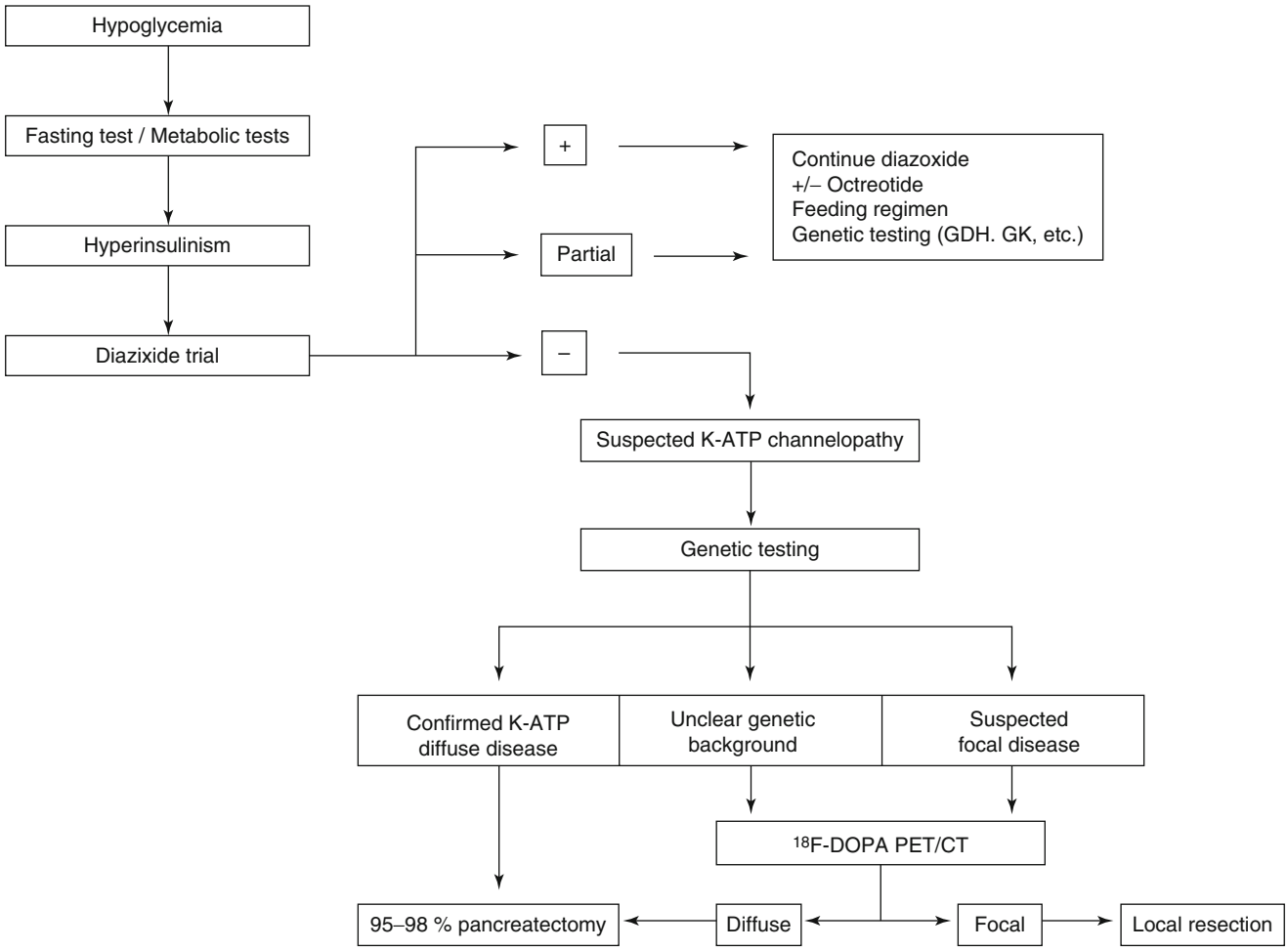

Fig. 17.12 Current algorithm for the management of patients with congenital hyperinsulinism

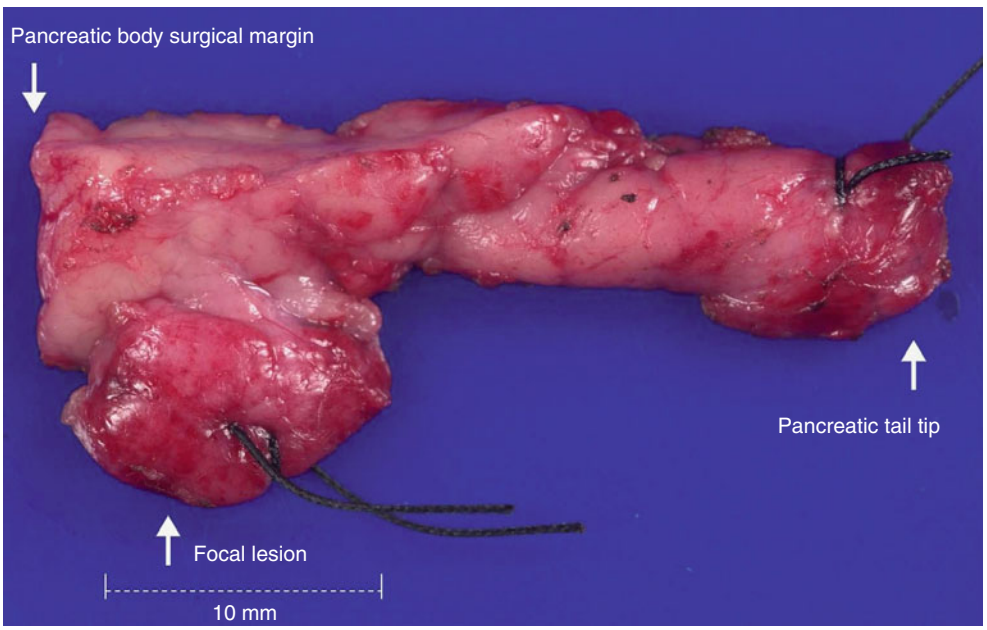

Fig. 17.13 Distal pancreatectomy specimen with an easy to see exophytic focal lesion on the inferior edge of the pancreatic body

common bile duct injury is higher. The effectiveness of this approach is currently not as good as the open approach given that most reported cases are actually 75–90 % pancreatectomies because the CBD is not dissected [71–73].

Postoperative pain is managed by an epidural infusion of bupivacaine (kept for 3–4 days) and intravenous narcotics if needed. Patients are kept NPO until bowel function resumes. The intravenous GIR is re-started at a low dose and advanced to 8 mg/kg/min over the first 24–36 h after the surgery. Plasma glucose levels are measured hourly in the beginning and spaced out as they become stable. If the plasma glucose levels are excessively high (>400 mg/dl) an intravenous insulin infusion is started. The immediate postoperative oscillations in the plasma glucose levels are not reflective of the eventual long-term outcome, because factors like surgical stress and pain can affect glucose homeostasis. When bowel function is evident, enteral feeds are restarted. We start with 1/3 of the goal volume and advance daily by thirds. Simultaneously, the GIR is gradually weaned as the feeding volume increases. When patients are exclusively on enteral feeds, a "cure" fasting test is performed. If patients are able to maintain euglycemia for 18 h, they are considered completely cured. If the time to hypoglycemia is less than 18 h the next step is to determine a regimen of frequent feeds and short fasting periods that will allow the patient to be managed safely at home. Patients that are unable to be weaned from the intravenous glucose infusion rate are obviously not cured and will need further assessment. The complication rate after pancreatic surgery for HI is low, in our experience. General complications are bowel obstruction due to adhesions and small intestine to small intestine intussusception, which generally occurs within the first 2 postoperative weeks [74]. Specific complications include chyle leaks, pancreatic leaks, and CBD injuries, all of which are very rare.

In our experience with more than 325 pancreatectomies, about 95 % of patients with focal disease are cured after surgery. The remaining 5 % require support with a strict feeding regimen, and are presumed to be secondary to microscopic residual disease. In cases of diffuse HI, approximately 50 % of cases continue to have hypoglycemia after surgery and may require supportive management with octreotide and frequent feeds (these patients, despite not being cured, are much easier to manage than before the surgery), 25 % develop diabetes requiring insulin, and 25 % of diffuse HI cases are well controlled with no medications. Long-term follow-up is mandatory since insulin-dependent diabetes can develop even several years after the pancreatectomy.

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Genito-Urinary Tumours

18

Hélène Martelli and Christine Haie-Meder

Abbreviations

AFP	Alpha foeto protein
BP	Bladder Prostate
BT	Brachytherapy
COG	Children Oncology Group
CT scan	Computerized Tomography scan
CT	Chemotherapy
DES	Diethylstilbestrol
EBRT	External Beam Radiotherapy
EpSSG	European Paediatric Soft Tissue Sarcoma Group
GCT	Germ Cell Tumour
Gy	Grays
HCG	Hormon chorionic gonadotropic
IGR	Institut Gustave Roussy
IRS	Intergroup Rhabdomyosarcoma Study
LDR	Low dose rate
MGCT	Malignant Germ Cell Tumour
MMT	Malignant Mesenchymal Tumours
MRI	Magnetic Resonance Imaging
PRE	Primary Reexcision
RMS	Rhabdomyosarcoma
SIOP	International Society of Paediatric Oncology

Genitourinary tumours occur in the pediatric ages from birth to adolescence, and pediatric surgeons as well as pediatric urologists or urologists may be in charge of these patients.

They can be divided into tumours of the urinary tract and tumours of the genital organs. Renal and ovarian tumours will be excluded from this chapter and we will focus on bladder-prostate tumours, female genital tract (vulva, vagina and uterus) and scrotal tumours (testicular and paratesticular tumours).

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Bladder-Prostate Tumours

Bladder-prostate (BP) tumours mainly consist of malignant mesenchymal tumours (MMT), especially rhabdomyosarcoma (RMS). In very rare cases and often at pathology examination, an inflammatory myofibroblastic tumour is diagnosed [1]. Benign lesions such as vascular malformations [2, 3], or fibroepithelial polyp [4] are also very rare.

Clinical and Radiological Evaluation

Bladder and prostate tumours occur most commonly in young children but can be seen at any age in childhood. They grow rapidly and present as a lower abdominal mass. Because of the location at the outlet of the bladder they may cause difficulties with urination by obstructing flow. The child will complain of dysuria, present with hematuria or may develop an acute bladder urinary retention. Constipation is frequently associated with urinary symptoms. A pelvic mass is often palpable, extending to the umbilicus and/or the perineum, making the true site of origin difficult to determine.

Any mass detected on physical examination should be evaluated with an abdominal/pelvic ultrasound. Better additional valuable information can be obtained by magnetic resonance imaging (MRI) than with computerized tomography (CT scan). The tumour develops either from the prostate area or from the bladder wall or both with no possibility to properly detect the exact origin. Typically the prostate tumour develops under the bladder neck, with considerable lengthening of the posterior urethra (Fig. 18.1). The bladder tumour develops inside the bladder cavity, with multiple grapes implantation around the bladder neck (Fig. 18.2).

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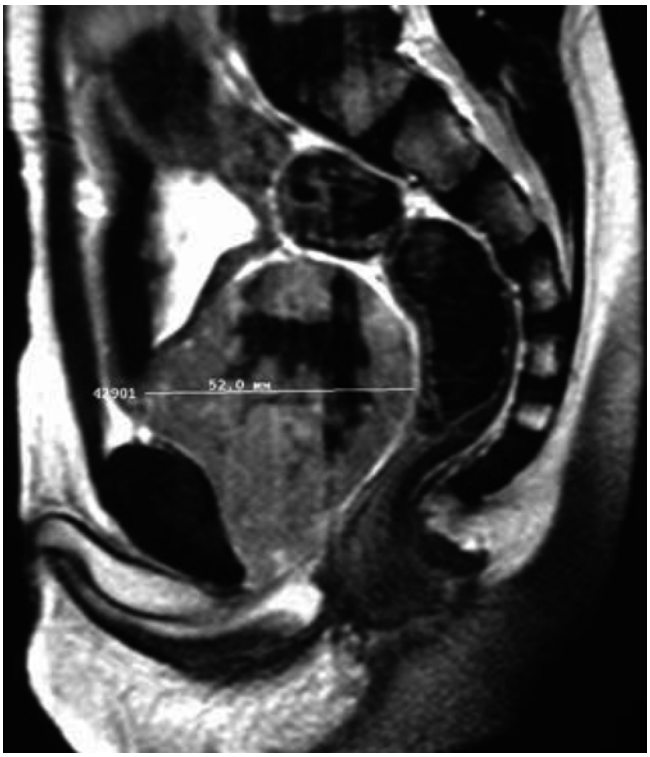

Fig. 18.1 Prostatic RMS in a 4 year-old boy (Sagittal T1 weighted MRI)

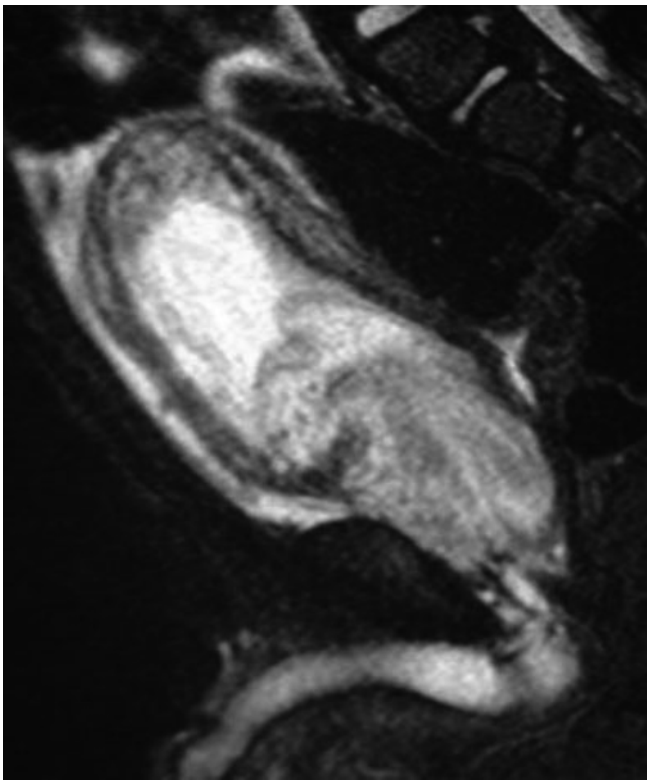

Fig. 18.2 Bladder neck and urethra RMS in a 2 year-old boy (Sagittal T2 weighted MRI)

Sometimes, the invasion of the trigona and ureteral meati leads to uretero hydronephrosis and acute renal failure.

Diagnosis: Primary Surgery/Biopsy

Bladder catheter (urethral catheter is preferred to suprapubic tube to avoid bladder wall contamination) is usually inserted to relieve bladder obstruction. If both ureteral meati are involved with bilateral hydronephrosis, percutaneous nephrostomy may also be necessary.

Primary complete R0 resection by partial cystectomy is rarely feasible except for small tumour of the bladder dome which does not represent a frequent site of tumour. In all other cases, the diagnosis is made by a biopsy, either by cystoscopy or by tru cut (4–6 cores) or surgical biopsy of the mass. In all cases, enough material is necessary for diagnosis, immunochemistry, central review, biological studies and frozen storage.

Pathology and Initial Chemotherapy

Bladder-prostate RMS bear usually a favourable histology i.e. botrioid (within the bladder cavity) or embryonal histological subtypes. Alveolar histology is very rare in bladder-prostate sites [5, 6].

After initial biopsy, the patient is considered as Intergroup Rhabdomyosarcoma Study (IRS) III group and treated by chemotherapy (CT) according to the prognosis group. Bladder-prostate is considered as an unfavourable site. The Children Oncology Group (COG) and the European paediatric Soft tissue Sarcoma Group (EpSSG) protocols are based on prognostic factors including age, site, size, histology, nodal involvement and IRS group.

Delayed Local Treatment

Most often, due to its chemosensitivity to drugs such as Cyclophosphamide, Vincristine, Actinomycin D and Doxorubicine, the tumour begins to shrink after the first course of CT.

Usually it is possible to remove the bladder catheter after some courses of CT except in case of a polypoid tumour protruding into the bladder neck.

Local treatment is necessary in all cases except if the patient is in complete clinical and radiological remission after CT in the EpSSG protocol [7]. In MMT 84, 89 and 95 studies of the International Society of Paediatric Oncology (SIOP), among 119 long term survivors, one patient was cured by initial partial cystectomy and 10 patients did not receive any local treatment after initial biopsy and CT [8].

Most often, local treatment is necessary for a residual mass after initial CT. Bladder-prostate is a challenging site in term of local treatment aiming at avoiding mutilating radical surgery such as total cystectomy and/or total prostatectomy without jeopardizing survival. Bladder preservation has increased in IRS studies from 23 % in IRS I study [9] to 60 % in IRS III study [10] and 83 % in IRS IV study [11]. Bladder preservation, however, does not mean normal bladder function: only 36 of the 55 survivors who retained their bladder, had normal bladder function in IRS IV study [11]. Moreover, all but 4 patients received external radiotherapy and bladder function may be affected by fibrosis as a late effect of radiotherapy. Total prostatectomy with or without bladder neck resection conveys a very high risk of incontinence when performed in very young children [12] and partial prostatectomy alone is associated with a very high risk of local relapse [13]. COG protocols include external beam radiotherapy (EBRT) for all patients with BP RMS except those with complete resection of the primary tumour at diagnosis (IRS group I patients) [14]. EBRT is also recommended in German protocols for children older than 1 year [15].

Brachytherapy (BT) is an alternative to EBRT and has been used for a long time in France in the multimodal treatment of BP RMS in order to avoid long term sequelae of EBRT in very young children less than 3 years of age [16, 17]. Proton therapy has also been proposed in very young patients, providing evidence of significant dose savings to normal structures compared to intensity modulation radiation therapy [18] and may be an alternative to BT [19].

Indications for local treatment can be summarised as follow:

- When the tumour involves the main bladder volume from the bladder neck to the trigona and above, the only reasonable treatment is a total cystectomy (Figs. 18.3 and 18.4).
- When the tumour is developed above the bladder neck, a partial cystectomy or hemi-trigonectomy with ureteral reimplantation is feasible with clear margins.
- When the tumour is confined to the prostate area (prostate and/or posterior urethra) and/or to the base of the bladder (bladder neck area and trigona) two options are possible: a total prostatectomy with or without resection of the bladder neck is a radical, mutilating procedure leading to incontinence and impotence in most cases [20–22]. Partial prostatectomy is not recommended because of a very high risk of local relapse (4 among 5 patients in SIOP MMT 84–89 studies) [13]. The second option is a combined treatment associating conservative surgery (partial prostatectomy and/or partial cystectomy without interruption of the urethra) with or without ureteral reimplantation, with interstitial BT [23]. One mandatory criteria to decide this procedure is to have no extension in the bladder above the level of the trigona, assuming that BT could sterilize any residual tumour of the prostate and/or of the bladder neck but could not reach tumour cells at a higher level in the bladder

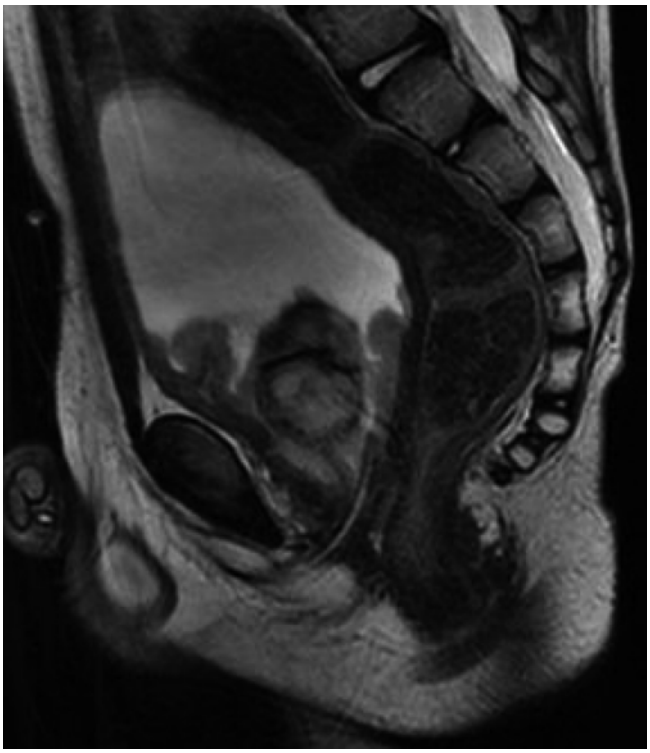

Fig. 18.3 Bladder RMS at diagnosis in a 4 year-old boy (T2 weighted MRI)

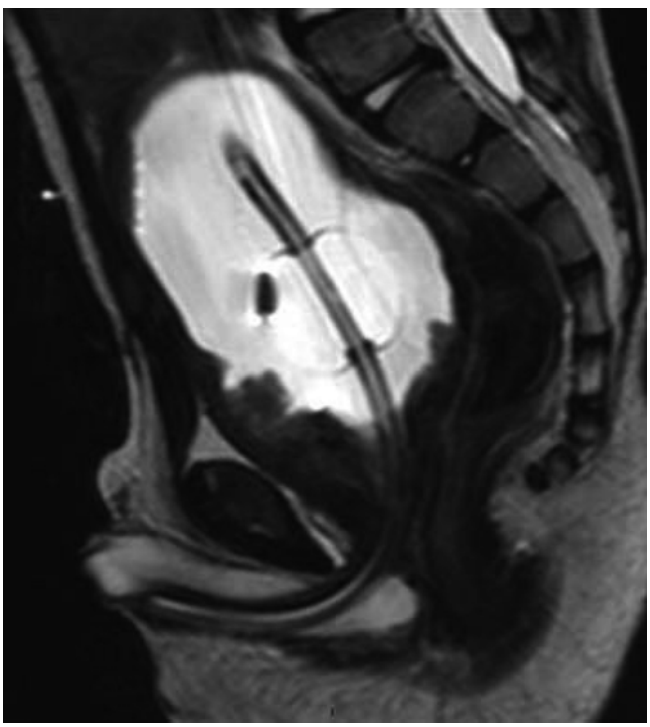

Fig. 18.4 After 8 courses of chemotherapy, the tumour volume has decreased but the implantation of the tumour is very large, assessed by frozen biopsies during surgery: a total cystectomy is necessary

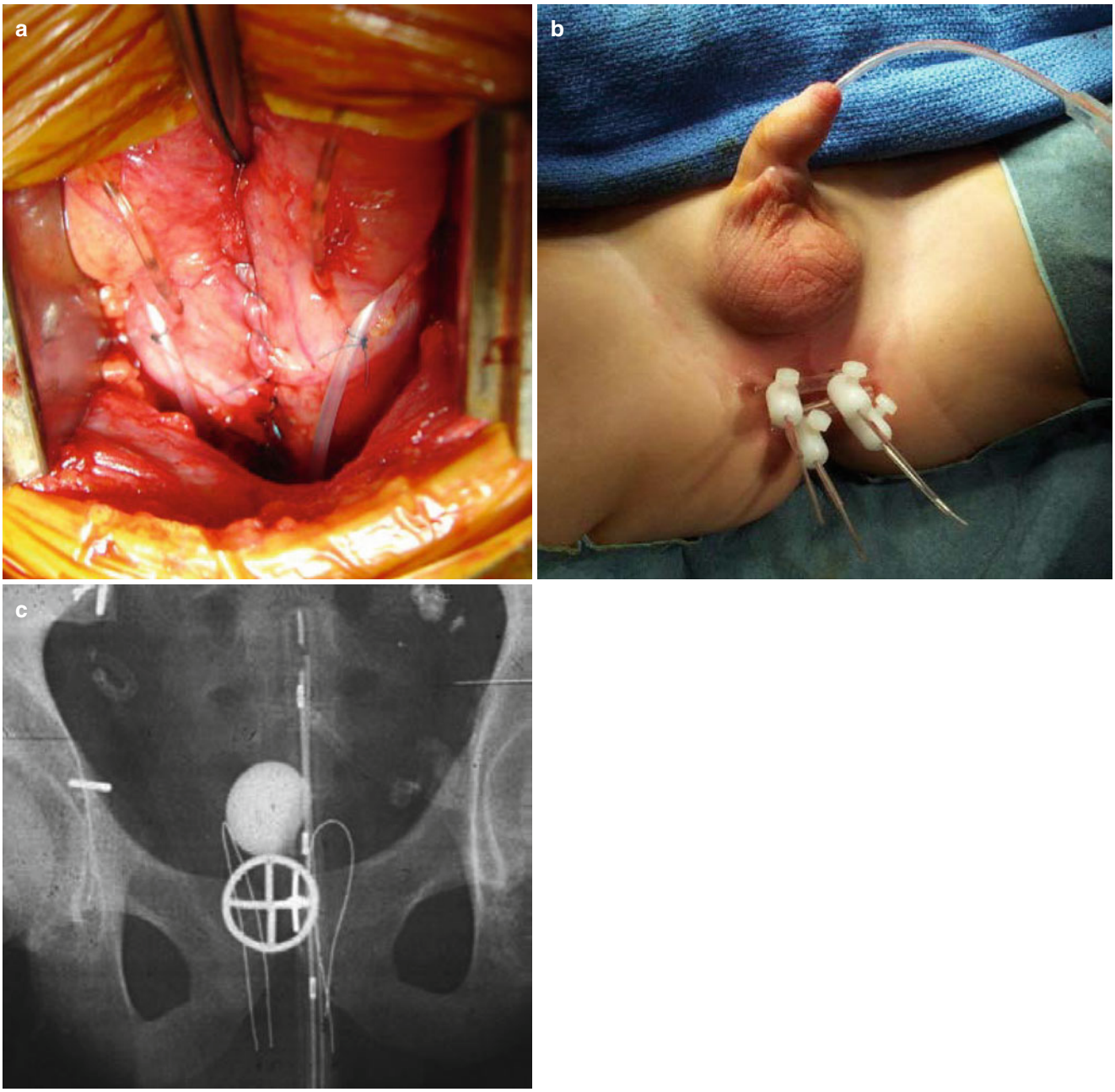

Fig. 18.5 (**a**) Operative view of the bladder with ureteral catheters and catheters encompassing the bladder neck for brachytherapy (**b**): the catheters for brachytherapy are introduced through the perineum (**c**): plain X rays of the pelvis with brachytherapy catheters and balloon of the bladder catheter filled with contrast

wall. When the tumour response to CT is estimated insufficient to perform a conservative procedure, the CT may be continued for 2–3 courses and a new evaluation is performed afterwards. Especially for bladder tumours, the parents and the child are always informed that the conservative procedure might be not feasible due to unexpected operative findings and/or results of frozen sections and that a total cystectomy may be finally decided and immediately performed.

Implantation of the plastic catheters for BT are always done as a per-operative procedure. The BT technique depends on the tumour location. For bladder and prostate tumours, plastic catheters are implanted through a perineal approach consisting of two loops encompassing the prostate and the bladder neck. If necessary, plastic catheters are maintained by a suture at the level of the loop bridge in order to avoid catheter geographical modification (Fig. 18.5a–c). For bladder

tumours, the technique consists of two loops encompassing the partial cystectomy scar.

After 5–7 days following the surgical procedure, children are transferred to a BT department. X-rays are performed with dummy sources to decide upon radioactive source length, according to histopathological findings and application geometry. In low dose-rate BT, Iridium wires are manually loaded. The dosimetry is performed using the Paris system rules. A total dose of 60 Gy is delivered with a dose-rate of 10 Gy per day. Systematic X-rays are performed during the BT procedure once a week in order to detect a potential source displacement which could impact the dosimetry decision. Nowadays, low dose-rate BT is replaced by pulse dose-rate BT.

In a recent paper [21], we reported on 26 males treated with this conservative combined treatment from 1991 to 2007. Until September 2011, 60 patients (54 males, 6 girls) have been treated with this combined treatment. Fifty-two patients had a localized tumour (with only biopsy at diagnosis), 6 were metastatic at diagnosis and 2 patients were treated at time of relapse. Five-year overall survival is 92 % and event free survival is 83 %. With a median follow-up of 5 years (range: 5 months- 15 years), 56 patients are alive, 53 in first complete remission and 3 after local relapse (one within the BT field). Three males had a secondary total cystectomy, 2 for local relapse and 1 for bladder dysfunction. The third boy with local relapse out of the BT field underwent a redo conservative approach with partial prostatectomy and BT. Functional results seems very encouraging since among 27 patients older than 6, 21 have a normal clinical bladder function (normal continence and no difficulty in bladder emptying), 6 have some diurnal dribbling, all males have normal erection. Urodynamic studies have been performed in 5 patients with diurnal dribbling with various results (1 normal, 2 vesical sphincter dyssynergia, 1 decreased bladder compliance, 1 sphincter insufficiency, no decrease of bladder capacity). Long term functional sequaelae are currently under study in the older patients. Results of a quality of life study for males with more than 5 years of follow-up are very encouraging with 82 % of patients who answered the questionnaire (14 among 17 patients) with normal quality of life [24].

Recently, for 3 very young males (less than 4 years of age) with tumours involving the prostate and the whole bladder, we decided to perform a total cystectomy, without prostatectomy (in order to avoid impotence), with BT of the prostate left in place.

A bladder dysfunction may appear after resection of a prostatic tumour with close dissection of the posterior bladder wall, leading to a neurogenic bladder. We recently experienced this problem for two males who underwent the resection of a prostatic tumour, larger than 5 cm, with ligation of the ureters at their entrance into the bladder and cleavage of the tumour from the posterior wall of the trigona and peri-urethral macroscopic residuum treated by brachytherapy. These two patients are cured but complain of dysuria with a non compliant and hyperactive bladder at urodynamic studies and need intermittent catheterisation with drugs.

In conclusion, due to the very young age of males with BP RMS, local treatment is very difficult and should include all techniques which could decrease the burden of therapy and the long term sequelae.

Tumours of the Female Genital Tract

Tumours arising in the female genital tract (uterus, vagina and vulva) are mainly represented by rhabdomyosarcoma (RMS) and germ cell tumours (GCT). Both tumours develop in very young girls, less than 3 years but RMS may occur also in adolescents.

Rhabdomyosarcoma of the Female Genital Tract

This tumour arises from the vaginal wall with one or several implantation points and fulfils the vaginal cavity, coming out from the vulva like grapes which may be found by the parents in the nappies (Fig. 18.6).

It may also present as a unique polyp of the uterine cervix or involve the whole uterus cavity. MRI and vaginoscopy are mandatory as initial exams.

Except for small polyps of the cervix which may be completely resected, a biopsy only is usually performed at

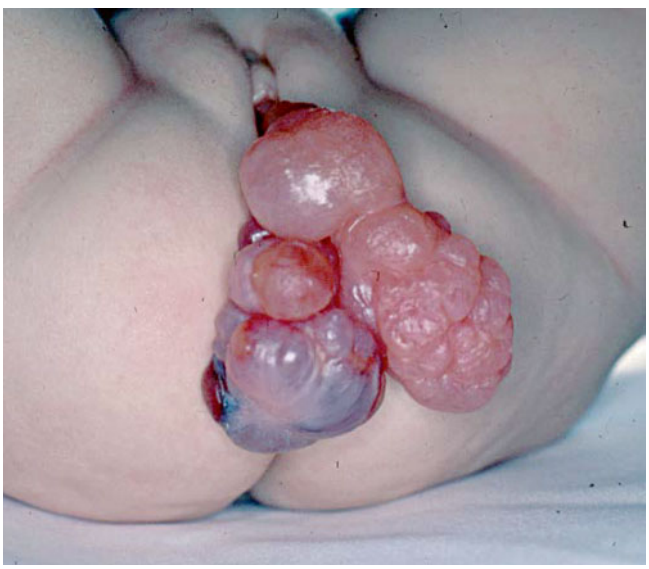

Fig. 18.6 vaginal RMS in a 12 months old girl

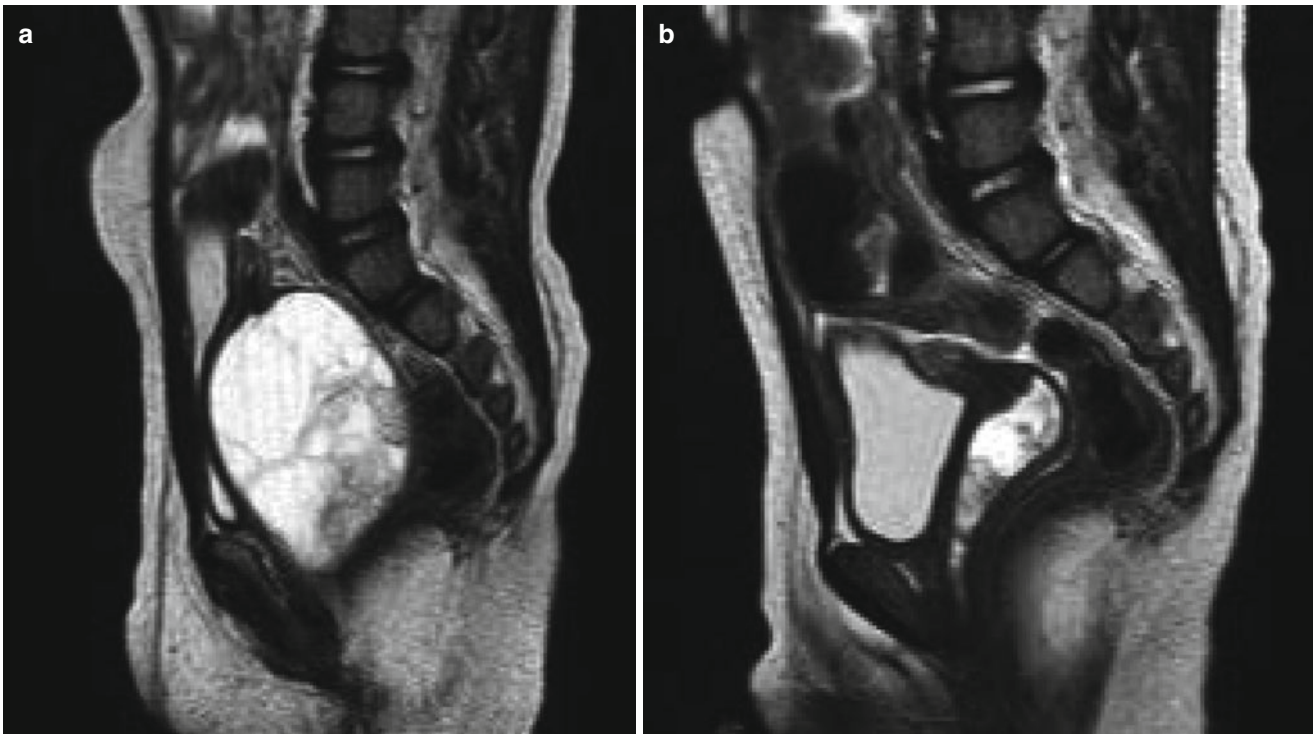

Fig. 18.7 (**a**) Vaginal RMS at diagnosis (Sagittal T2 weighted MRI). (**b**) After 6 courses of chemotherapy, persistent vaginal tumour with multifocal implantation

diagnosis. Histopathology reveals an embryonal or a botrioid RMS, alveolar histology is very rare at this site. Female genital tract is considered as a favourable site in all studies, with very good response to chemotherapy, allowing to decrease local therapy without jeopardizing survival [25, 26]. As for bladder-prostate RMS, all protocols are based on prognostic factors including age, site, size, histology, nodal involvement and IRS group.

After chemotherapy, the tumour may completely disappear, and complete remission is assessed by vaginoscopy and biopsies of any residuum. If biopsies are negative for tumour cells, a local treatment may be avoided but a close follow-up with vaginoscopy every 3 months for at least 2 years, is mandatory. In SIOP studies MMT 84, 89 and 95, among 71 girls treated for a female genital tract RMS, 65 were alive with a median follow-up of 8 years (range: 1–16 years) and 26 (40 %) were cured with chemotherapy alone without any local treatment [26, 27].

When a residual tumour is observed at MRI and vaginoscopy and confirmed at histopathology, a local treatment is necessary (Fig. 18.7a, b). Partial vaginectomy is rarely feasible with clear margins because of possible multifocal implantation of the tumour.

In case of tumour arising in the upper third of the vagina and lower part of the uterine cervix, a trachelectomy is feasible especially in adolescent girls [28].

For vulvo-vaginal and/or cervical tumours, an alternative to total vulvo-vaginectomy and hysterectomy, is represented by brachytherapy (BT). Reported experiences focusing on RMS BT of the female genital tract are rare. Generally, the

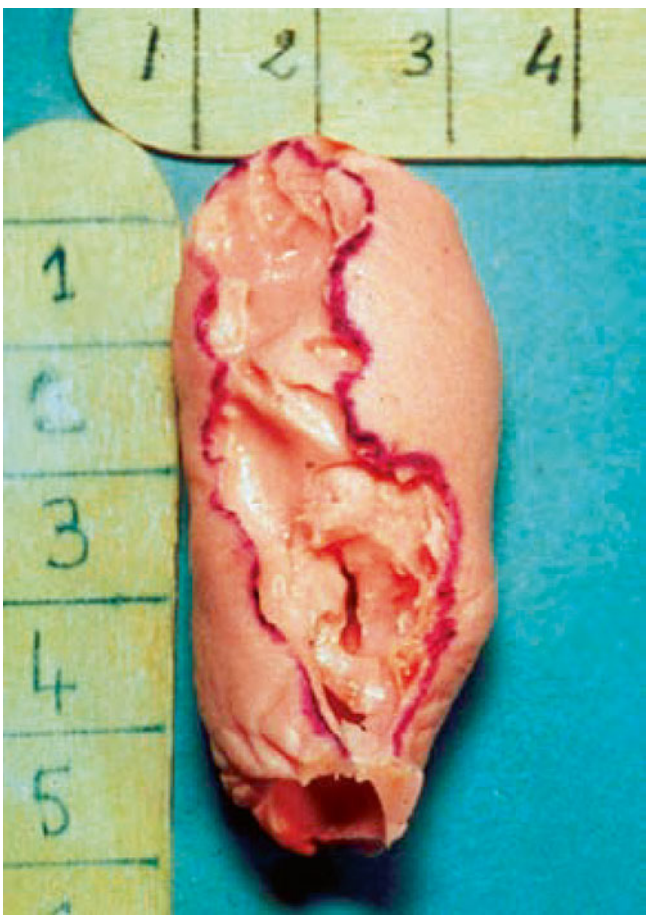

Fig. 18.8 Vaginal impression after solidification of liquid paste injected into the vagina

Fig. 18.9 Vaginal mould with plastic catheters loaded with radioactive material

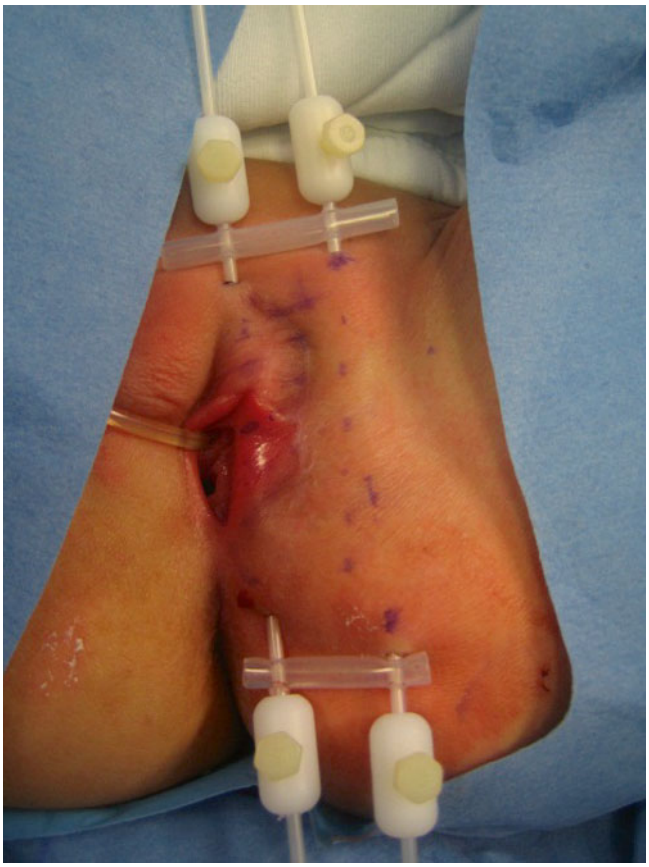

Fig. 18.10 Interstitial BT for a vulval location

BT techniques used in children do not differ greatly from those used in adults. Most reported children have been treated at the Institute Gustave Roussy (IGR) in France. The reason is linked to the specificity of such treatments needing techniques adapted to the anatomy of children and targeted at the tumour. At IGR, the technique of gynaecological BT has always been anatomy-adapted with the use of the mould applicator for both cervical or vaginal RMS. The first step consists of a vaginal impression that accurately shows the topography and extension of the tumour as well as the anatomy of the vagina (Fig. 18.8).

This procedure is performed under general anaesthesia. It represents an essential step in tumour assessment. Therefore, if feasible, it is systematically integrated into the initial tumour assessment and repeated after chemotherapy. A vaginal mould is then made from the vaginal impression. This moulded applicator is individually adapted and allows a ballistic selectivity of the vaginal implant, even for very irregular target volumes, while sparing the organs at risk (Fig. 18.9).

Young girls are usually treated with low-dose-rate (LDR) BT. Older girls can be treated with pulsed-dose-rate BT. For LDR BT, the radioactive material consists of manually loaded iridium-192 (^{192}Ir) wires. Endocavitary BT is done in vaginal, cervical, and uterine RMS localisations. In vulval RMS locations, interstitial BT is used and the implantation respects the rules of the Paris system, with a provisional implant accounting for the tumour size in all 3 dimensions (Fig. 18.10).

For highly infiltrating tumours, a treatment combining interstitial implants and intracavitary BT may be needed.

A dose of 50–60 Gy is delivered in 5–6 days. Ovaries transposition is performed, when necessary, before the BT, using a laparoscopic technique of temporary transposition [29].

In 2006, Magné and colleagues [30] reported an update and reappraisal of the BT experience at IGR in the management of vulval and vaginal RMS, focusing on long-term outcome. Thirty-nine girls treated from 1971 to 2005, with BT as a part of treatment, were retrospectively analysed. Of these patients, 20 were treated before 1990, with the initial tumoural extension included in the BT volume. After 1990, only residual disease was included in the BT -treated volume. The median age was 16.3 months at diagnosis and median follow-up was 8.4 years (range 10 months to 30 years), and RMS was strictly located in the vagina of 26 girls and vulva of six girls. Five-year overall survival was 91 %. Between the two groups (before and after 1990), a substantial difference was seen in rates of acute and long-term sequelae.

Among the 20 patients treated before 1990, 15 (75 %) presented sequelae of vaginal or urethral sclerosis and stenosis. After 1990, only four patients (20 %) had this problem.

In conclusion, girls with female genital tract RMS are highly curable with a multidisciplinary approach and BT is a good alternative to EBRT in term of local treatment.

Malignant Germ Cell Tumours (MGC) of the Vagina

MGC tumours localized to the vagina are rare, occurring in very young girls before 3 years of age. They are mainly represented by vitellin tumours (secreting alpha-foeto-protein (AFP). The tumour, encased in the vaginal wall, is revealed by vaginal bleeding and sometimes dysuria or constipation and is easily palpable at rectal examination. Opposite to RMS nothing is protruding out of the vulva. Usually the diagnosis is made by imaging (ultrasound and MRI) and increased level of serum AFP (Fig. 18.11). If the level of AFP is not very high, compared to the physiological level of AFP in a very young girl, a biopsy can be performed under vaginoscopy.

Surgery is not recommended at diagnosis except for biopsy. Treatment is represented by platinum-based chemotherapy [31, 32]. Usually the tumour decreases considerably, confirmed by the normalization of serum AFP. A vaginoscopy is mandatory, even if the AFP is normal to detect any residual disease. In case of residual disease, even if a biopsy is negative for tumour cells, a surgical resection is recommended, with partial vaginectomy, through an abdominal approach id the tumour is in the upper half of the vagina, or through a perineal approach in other cases. If the residuum is not accessible to a conservative surgery, endocavitary BT is a good alternative to total vaginectomy. In the French study TGM 95 (1995–2005), 7 girls were treated for a vitellin tumour of the vagina [33]. Median age at diagnosis was 9 months (6–14 months). AFP was increased in all girls but 6 had a biopsy to confirm histology. All girls received chemotherapy according to the TGM 95 protocol, including cisplatinum. After normalization of AFP, all girls underwent the surgical removal of a small residuum by partial vaginectomy, 1 with partial resection of the cervix. Four girls were operated through an abdominal approach and 3 through a perineal approach. Only 1 patient had positive tumour cells in the resected specimen and underwent post operative chemotherapy. All girls are in first complete remission with a median follow-up of 8 years. One girl was reported as cured with chemotherapy alone in 2006 [34]. Close follow-up with AFP level is mandatory. A vaginoscopy is necessary, after several years, to control the absence of adhesions of the vaginal wall.

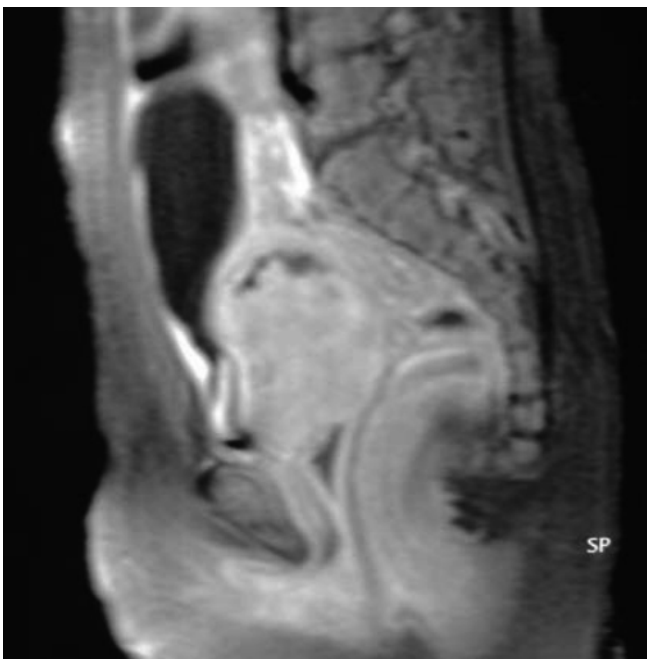

Fig. 18.11 Vitellin tumour of the upper third of the vagina (sagittal T1 weighted MRI)

Clear Cell Adenocarcinoma of the Vagina

This very rare tumour occurs only in pre adolescent or adolescent girls and was mainly due to the administration of Dietylstilbestrol (DES) during mother's pregnancy to prevent premature delivery (DES syndrome). This treatment has stopped in the seventies. The tumour is revealed by genital bleeding, often taken for irregular first menstruations and diagnosed with a delay. The tumour is developed in the upper part of the vagina or in the uterus cervix, infiltrating the parameters. An abdominal CT scan is mandatory to detect metastatic iliac lymphnode involvement.

These tumours are not chemosensitive. Treatment was based on surgery and/or radiotherapy, consisting either in radical hysterectomy and vaginectomy associated with lymphadenectomy, or less aggressive surgery with radiotherapy [35, 36]. Today, the current approach for small tumours is represented by a trachelectomy extended to the parameters, associated with lymphadenectomy. This technique has been described as a case report in a 12 year-old girl with rhabdomyosarcoma of the cervix [25].

Scrotal Tumours

Almost all scrotal tumours are testicular tumours (94 % in the American pre pubertal testicular Tumour registry), tumours of the envelops (mainly paratesticular rhabdomyosarcoma) representing around 6 % [37]. Benign tumours represent more than half of prepubertal testicular tumours [38].

Scrotal tumours in children and adolescents present usually as a painless, solid mass. In young males, the discovery of a scrotal mass by the parents, leads to a medical consultation before metastasis spread. On the contrary, modest adolescent will hire this mass during a long time and signs and symptoms, revealing local invasive tumour and retroperitoneal lymphnode involvement may occur. When the physical examination is equivocal, ultrasound is an excellent tool for distinguishing intratesticular from extratesticular masses. AFP level should be measured urgently (HCG is not necessary because choriocarcinoma is not observed in pre-pubertal males).

Except for tumours in children older than 6 months with elevated AFP levels (who most likely harbor yolk sac tumours), the initial surgical management of a prepubertal testis tumour is excisional biopsy (enucleation) with frozen section analysis. This strategy is supported by the fact that, compared with adult tumours, for which inguinal orchiectomy is standard surgical management, a high percentage of prepubertal tumours are benign.

The exploration is accomplished through an inguinal incision with occlusion of the testicular vessels. If the frozen section reveals a likely malignancy, the entire testis is removed with high ligation of the cord. If a benign histology is confirmed (usually teratoma), the remaining testis is closed and returned to the scrotum. The management of teratoma is completely different in adults (considered as a malignant tumour) since 88 % of testes with a teratoma harbor carcinoma in situ elsewhere in the testis [39]. In children, with the exception of 1 case, no such finding has been evident [40].

Completely different is the management of paratesticular tumours which are mainly paratesticular RMS. Benign scrotal tumours are exceptional (lipoblastoma [41], hemangioma [42]). Surgery of paratesticular RMS represents the cornerstone of treatment and all studies recommend radical orchidectomy with high section of the spermatic cord via an inguinal incision [43, 44]. Patients with suspected or definite tumour residuals after initial surgery (especially after scrotal approach) require primary re-excision (PRE) in order to achieve a microscopically complete resection. PRE should be performed through an inguinal approach and hemiscrotectomy is necessary if there is a doubt about scrotal contamination. A primary combined inguinal and scrotal approach is sometimes indicated if the tumour is too large to deliver into the inguinal incision without risk of rupture. The current European rhabdomyosarcoma trial (EpSSG RMS 2005) stipulates these guidelines [45]. In this study patients with an initial scrotal approach who don't undergo hemiscrotectomy with a PRE, must be upstaged and receive a more aggressive chemotherapy.

In conclusion, local treatment is a key point in the multidisciplinary approach of genito-urinary tumours in children. The goal to decrease the burden of local therapy and avoid long term sequelae without jeopardizing survival is obtained by adequate surgical procedures, associated or not with complementary radiotherapy techniques.

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Malignant Germ Cell Tumors

19

Frederick J. Rescorla

Introduction

Germ cell tumors are a relatively uncommon group of neoplasms which can have a variety of presentations affecting the fetus, infant, child, and adolescent. They are interesting for several reasons: in children the extragonadal site predominates compared with gonadal locations; the most common malignant histology is yolk sac tumor which has alpha fetoprotein as a sensitive marker; the survival has been excellent in the era of cooperative group trials utilizing cisplatin, etoposide and bleomycin; and, based on the effectiveness of chemotherapy, neoadjuvant therapy followed by surgery is indicated to avoid excision of normal structures in unresectable cases.

The location of the tumor often determines the timing of presentation. For instance, with vaginal lesions, bleeding often occurs relatively early in the disease progression and these tumors rarely have metastases at diagnosis [53]. In comparison, sacrococcygeal and retroperitoneal abdominal tumors often achieve a large size prior to the onset of symptoms and the rate of metastases in these tumors is over 50 % [11, 52]. Ovarian tumors can achieve a large size before presentation due to the size of the pelvis whereas testes tumors are usually diagnosed at a much smaller size. The histologic variants also differ by site and age. Among the extragonadal sites, yolk sac histology predominates in the younger children which include all of the sacrococcygeal and genital tumors. In mediastinal tumors a significant proportion are older children and the histology is more varied including germinoma, choriocarcinoma and mixed tumors with either benign and malignant or multiple malignant components. In the prepubertal testes tumors yolk sac predominates whereas in puberty there is wide histologic variation.

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Embryology and Classification

Germ cell tumors are thought to arise from arrested or aberrant migration of common progenitor cells. These primordial cells originate near the allantois of the embryonic yolk sac endoderm and migrate to the genital ridge at 4–5 weeks gestation. Germ cell migration is thought to be mediated by c-KIT receptors and stem cell factors [38, 64] and arrest of this process is thought to lead to germ cells at nongonadal sites like the retroperitoneum. Aberrant migration can lead to germ cells at sites such as the sacrococcygeal region, neck, and mediastinum.

The totipotential nature of these cells allows a wide variety of tumors (Fig. 19.1) [65]. Seminoma or dysgerminoma is rare before puberty but occurs at gonadal sites in adolescence. Embryonal carcinoma can further differentiate into embryonic tumors such as mature and immature teratomas or the more malignant extra-embryonic tumors such as a yolk sac or choriocarcinoma. Most childhood germ cell tumors are benign, comprising mature and immature teratomas. Teratomas contain elements from one or more of the embryonic germ layers and contain tissue foreign to the site of origin [20, 41]. Immature teratomas contain primitive neuroepithelium and are graded between I and III [48]. The Pediatric Oncology Group (POG)/Children's Cancer Group (COG) intergroup studies have confirmed the role of complete surgical excision alone as treatment for pediatric immature teratoma regardless of histologic grade [18, 45]. These studies have however noted an association between grade III immature teratoma and microscopic foci of yolk sac tumor emphasizing the need for thorough histologic evaluation of all germ cell tumors.

Yolk sac tumor (also called endodermal sinus tumor) is the most common malignant histologic variant in infancy and childhood and can develop metastases to lymph nodes or lungs. Other malignant histologic types include choriocarcinoma and embryonal carcinoma. Malignant elements coexist in approximately 25 % of pediatric germ cell tumors [29] and benign elements (teratoma) are often present with

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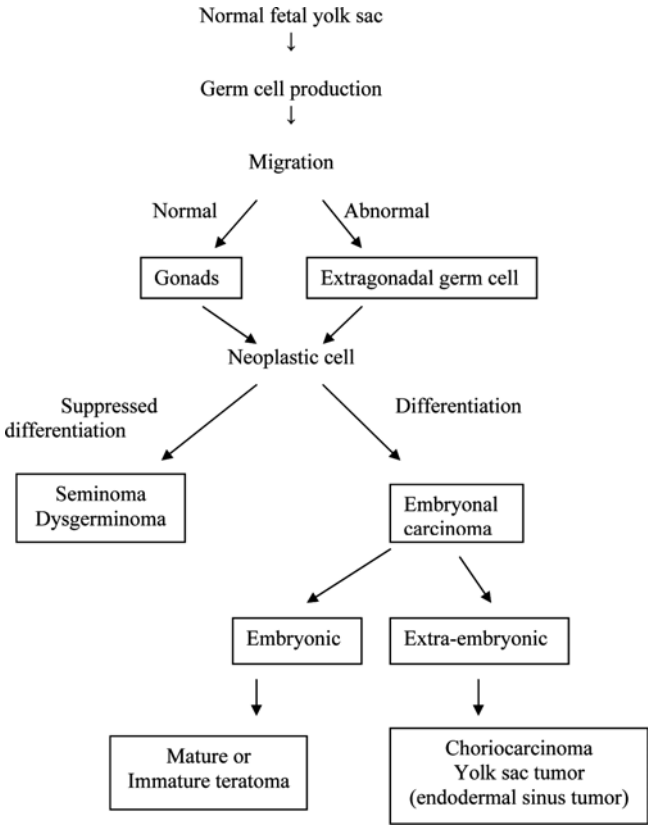

Fig. 19.1 Classification system for development of germ cell tumors

malignant tumors particularly in the mediastinum [10] and ovary [12].

Genetics and Risk Factors

Children with intersex disorders, undescended testes, and Klinefelter's syndrome associated with thoracic teratoma have an increased risk of germ cell tumors. Children with intersex disorders have an increased risk of developing gonadoblastoma, an in situ lesion with the capability of transforming into dysgerminoma, yolk sac tumor, immature teratoma, or choriocarcinoma [56]. The presence of a Y chromosome is thought to be the risk factor and thus includes male pseudohermaphrodites (under-androgenized males) with testosterone deficiency, androgen insensitivity syndrome, or 5α reductase deficiency as well as mixed gonadal dysgenesis [56]. The risk of malignancy in complete androgen insensitivity is approximately 3.6 % at age 20 and 22 % at age 30 [44]. Gonadectomy is recommended in these children.

The occurrence of testicular cancer is also increased in boys with undescended testes. Approximately 0.4 % of the general population has undescended testes; however, the incidence among males with testicular cancer is 3.5–12 % [26]. In addition, the risk appears even higher with intra-abdominal testes as Campbell [14] notes that this site accounts for only 14.3 % of undescended testes but 48.5 % of the tumors in undescended testes. In addition, the contralateral testes are also at increased risk as 20 % of tumors in patients with undescended testes occur in the contralateral scrotal testes [35]. Seminomas occur with an increased frequency in the undescended testes compared with descended testes [63]. Although some have noted a decreased rate of seminoma after orchiopexy [36], the effect of orchiopexy on the rate of testicular cancer is not known.

Tumor Markers

Yolk sac tumors are the most common histologic type of malignant germ cell tumor in childhood and serum alpha-fetoprotein (AFP) levels should be obtained at the time of presentation. Persistently elevated levels after surgery are suggestive of residual disease whereas elevations after an initial drop can indicate progressive or recurrent disease.

AFP is normally elevated in fetal life and as synthesis does not stop completely at birth, the half-life, which is usually considered to be 5 days, may vary during the first few months of life [67]. AFP levels should drop to normal by 9 months of age [66]. Choriocarcinoma, although less common, has human chorionic gonadotropin (hCG) as an easily identifiable marker. The half-life of hCG is 16 h. Lactate dehydrogenase is elevated in many germ cell tumors; however, is a nonspecific marker.

Extragonadal Germ Cell Tumors

Extragonadal tumors account for approximately two-thirds of pediatric germ cell tumors compared to only 5–10 % in adults [50]. The sacrococcygeal site is the most common, followed by the anterior mediastinum, pineal, retroperitoneum, and less commonly the neck, stomach and vagina. The current staging system utilized by the Children's Oncology Group (COG) for extragonadal tumors is listed in Table 19.1. The overall risk-based treatment scheme is listed in Table 19.2.

Sacrococcygeal Tumors

Sacrococcygeal tumors are relatively rare, affecting approximately 1:35,000 live births [57]. They occur more commonly in girls (70–80 %) and they usually present in one of two clinical patterns: neonates with large predominately benign tumors (mature and immature teratomas) (Fig. 19.2); or, infants and children between birth and 4 years of age with primarily pelvic, malignant (yolk sac) tumors (Fig. 19.3).

Table 19.1 Children's Oncology Group staging system for malignant extragonadal tumors in childhood

Stage I	Complete resection at any site, coccygectomy for sacrococcygeal site, negative tumor margins
Stage II	Microscopic residual; lymph nodes negative
Stage III	Lymph node involvement with metastatic disease. Gross residual or biopsy only; retroperitoneal nodes negative or positive
Stage IV	Distant metastases, including liver

Table 19.2 COG Study AGCT 0132 (2003–2011)

Low risk		
Stage I	Testes	Surgery
Stage I	Ovary	Alone
All immature	Teratomas	
Intermediate risk		
Stage II–III	Ovary	PEB × 3
Stage II–IV	Testes	
Stage I–II	Extragonadal	
High risk (off study)		
Stage III–IV	Extragonadal	PEB × 4
Stage IV	Ovary	

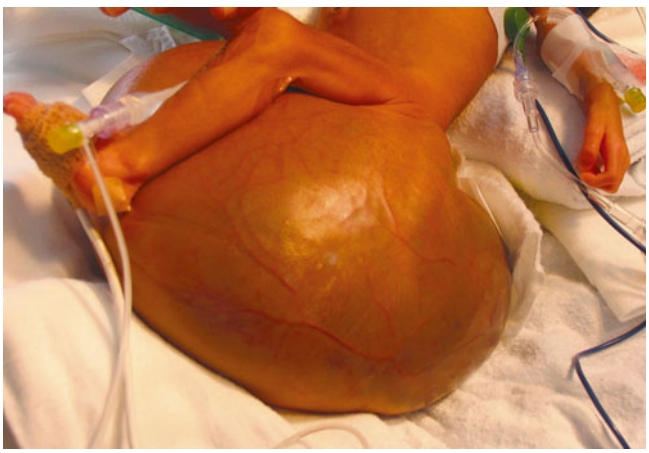

Fig. 19.2 A large Type I sacrococcygeal teratoma

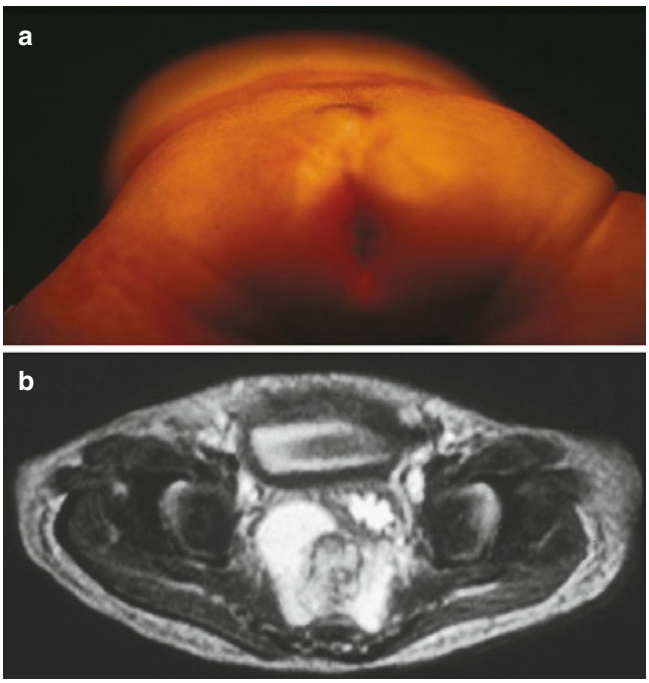

Fig. 19.3 A 2 month old boy with a malignant sacrococcygeal tumor. (**a**) Photograph of small external portion. (**b**) MRI scan demonstrating a pelvic tumor

Sacrococcygeal teratomas can also be noted in utero and if the lesion is greater than 5 cm in size abdominal delivery should be considered in order to avoid dystocia and tumor rupture [25]. High output cardiac failure can also occur due to shunting leading to fetal hydrops [13]. Detection early in gestation and hydrops are ominous and properly selected fetuses may benefit from fetal resection or intervention. Adzick et al. [1] reported the first successful fetal resection. Makin et al. [40] reported 41 antenatally diagnosed SCTs and performed fetal intervention in 12, including cyst drainage to facilitate delivery or relieve bladder obstruction and laser ablation or alcohol sclerosis for hydrops. Although the overall survival for antenatally diagnosed lesions was 77 %, the survival for fetal intervention was 50 % and only 14 % for fetal intervention for hydrops. One recent study noted that the survival for prenatally detected lesions was highest for small lesions (<10 cm) or larger predominantly cystic tumors (100 %), whereas the survival was lowest (48 %) in the large (>10 cm) lesions with increased vascularity, vascular steal syndrome, or rapid growth [7]. Adzick and colleagues currently recommend fetal resection for high-output failure less than 28 weeks gestation and consideration of ex utero intrapartum therapy (EXIT) in those between 28 and 36 weeks [55].

Altman et al. (in a survey of the Surgical Section of the American Academy of Pediatrics) developed a classification system which is widely utilized today (Fig. 19.4) [2]. In this survey the rate of malignancy was higher in older infants (<2 months, 7 % girls and 10 % boys malignant; >2 months, 48 % girls and 67 % boys malignant). Malignancy rates in children presenting after the newborn period in many series is as high as 90 % [22,

51]. The higher malignancy rate with the less apparent lesions may be due to an error in the initial diagnosis which is most commonly confused with a neural defect. In addition, many older infants may have no external mass and symptoms may develop later as the mass enlarges, frequently leading to constipation and urinary tract dysfunction.

An interesting group of children, first reported by Ashcraft and Holder, present with an autosomal dominant condition consisting of the triad of presacral teratomas, anal stenosis,

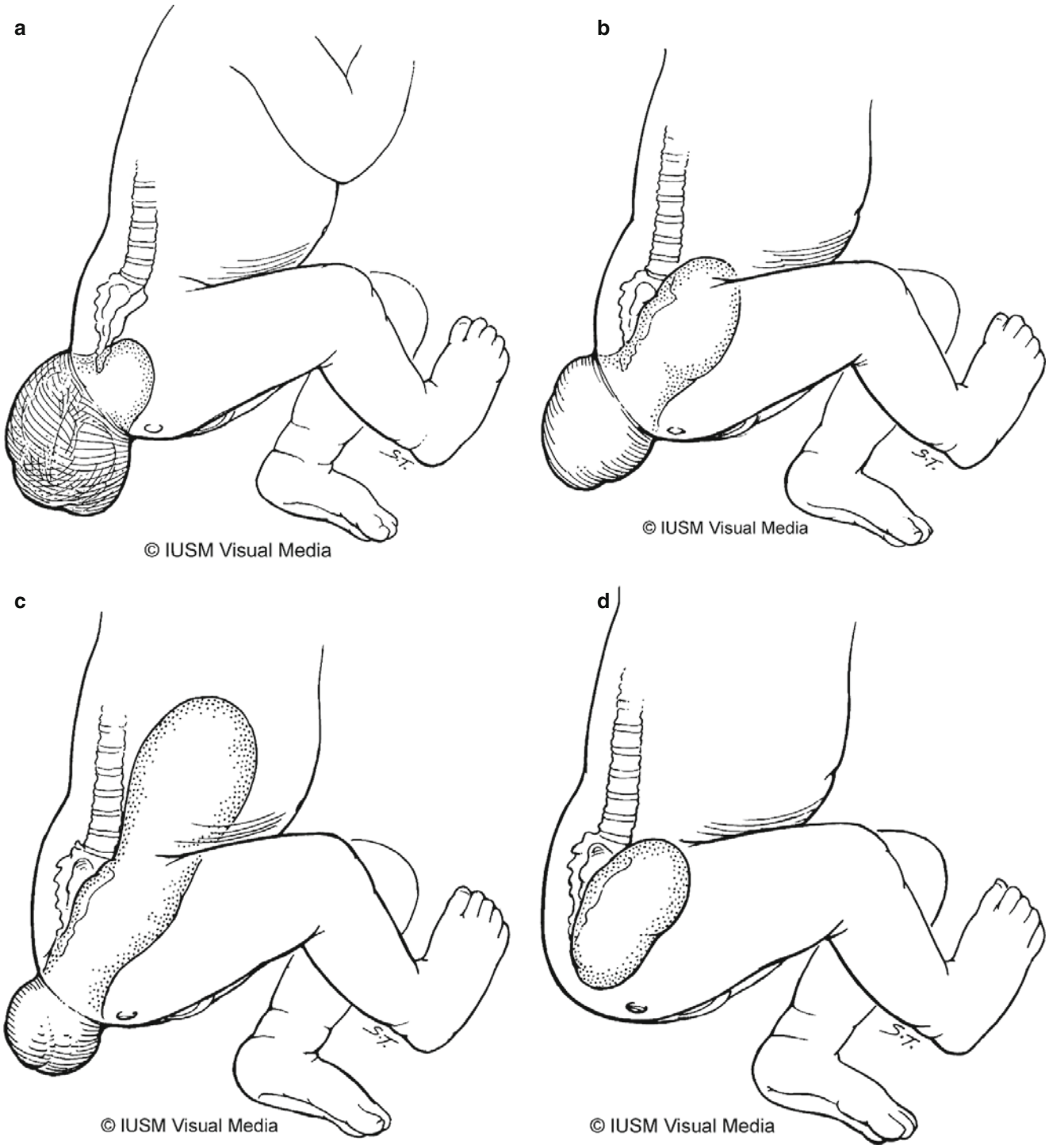

Fig. 19.4 Classification of sacrococcygeal teratomas based on Altman's study. (**a**) Type I (46.7 %) is predominantly external. (**b**) Type II (34.7 %) is external with intrapelvic extension. (**c**) Type III (8.8 %) is visible externally but predominantly pelvic and abdominal. (**d**) Type IV (9.8 %) is entirely presacral

and sacral defects [3]. Currarino et al. [17] suggested that adhesions between endoderm and neural ectoderm form, causing a split notochord resulting in this association of defects.

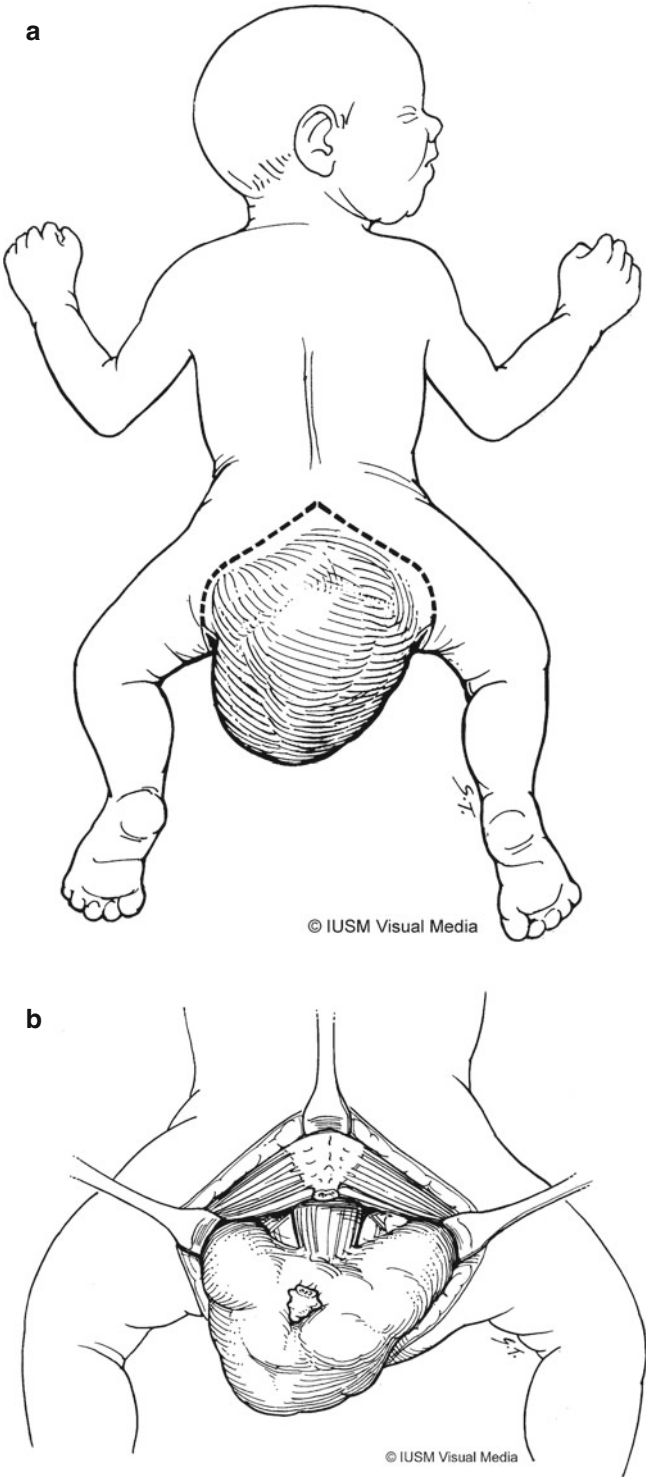

Fig. 19.5 Operative excision of (**a**): Sacrococcygeal teratoma in a neonate with an inverted "V" incision. (**b**) The tumor along with the coccyx is excised, taking care to avoid injury to the rectum

Prior to surgical resection of a neonatal tumor, the degree of pelvic and abdominal extension should be determined by ultrasound, CT, or MRI. In cases with significant pelvic extension, an abdominal approach (open or laparoscopic) may be needed to mobilize the pelvic component and divide the middle sacral artery. In addition, in high vascular flow lesions it may be useful to gain control of the distal aorta in order to allow temporary vascular occlusion if bleeding is encountered [37]. The lesion can be excised with the child in the prone position (Fig. 19.5). Excision of the coccyx is an essential part of the procedure as Gross et al. [31] initially reported a 37 % recurrence rate when the coccyx was not removed. Closure of the wound can be accomplished by bringing the apex of the anterior inverted "V" incision to the open of the posterior portion as demonstrated in Fig. 19.6. This brings the rectum back to a more posterior location from its original displaced position. Sometimes this closure leaves unsightly protruding tissue laterally, and on alternative closure reported by Fishman et al. [24] involved closure bringing the ventral portion of the lateral flaps to a more central posterior.

Most neonates have mature or immature teratomas and are managed with observation during the first few days of life. Operative resection is usually carried out in the first week of life. Recurrent tumors are noted in 4–21 % of these cases [8, 51] and 50 % of these are malignant. The development of malignancy may be the result of a pathologic sampling error which missed an initial malignancy or incomplete resection that leaves a small malignant focus. Follow-up should include serial serum AFP levels to ensure return to normal by 9 months of age as well as follow-up serum AFP levels and rectal examination every 3 months to 3 years of age.

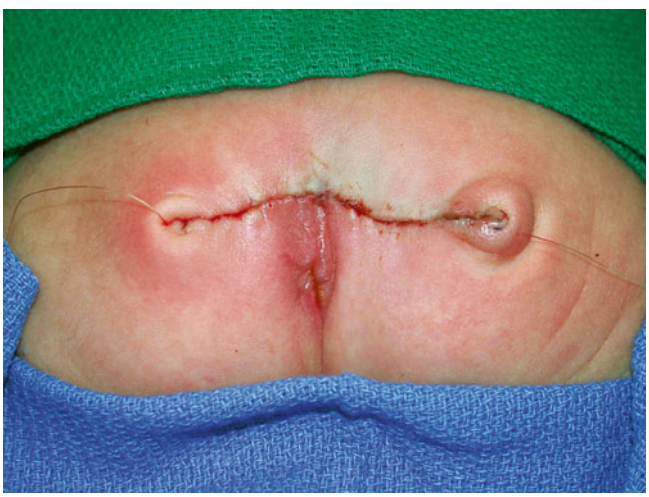

Fig. 19.6 Transverse closure (**a**) and (**b**) use of closure which brings excessive ventral tissue to a more central location leaving two right angled buttock scars

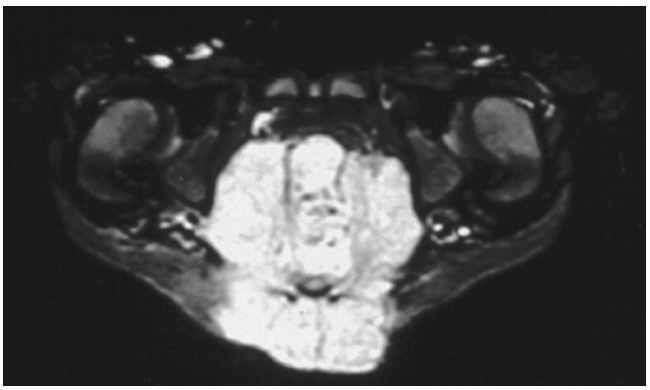

Fig. 19.7 Appearance of a large unresectable sacrococcygeal yolk sac tumor treated successfully with biopsy, neoadjuvant chemotherapy and subsequent excision

Older infants and children with primarily malignant presacral tumors can be approached in a similar fashion; however, due to extensive abdominal extension, initial resection is often not possible and biopsy and neoadjuvant chemotherapy with cisplatin, etoposide, and bleomycin are utilized (Fig. 19.7). The introduction of platinum-based therapy in the late 1970s has significantly improved the survival of these malignant tumors. Schropp et al. [57] noted an 11 % survival prior to 1978 and 86 % after 1978 with the use of platinum-containing therapy.

The POG/CCG intergroup study of 74 infants with malignant sacrococcygeal tumors comprised 62 girls and 12 boys with a median age of 21 months [52]. Fifty-nine percent had metastatic disease at diagnosis and the initial procedure was biopsy in 45 and resection in 29. All patients received chemotherapy with etoposide, bleomycin, and either standard or high-dose cisplatin. The overall 4-year event-free survival (EFS) and survival were 84 ± 6 % and 90 ± 4 %, respectively. There was no difference in survival based on presence or absence of metastases, initial or delayed resection, or dose of cisplatin. This study confirmed the effective role of neoadjuvant chemotherapy in initially unresectable cases. Long-term follow-up of the newborn and older children is necessary as neuropathic bladder or bowel abnormalities have been reported in 11–41 % of patients [28, 42, 43]. A recent long-term study observed that 9 % of the patients had involuntary bowel movements, 13 % soiling, 16 % constipation, and that 30 % lacked urinary control, all factors correlating adversely with quality of life [21].

Abdominal/Retroperitoneal

Abdominal and retroperitoneal sites account for approximately 4 % of pediatric germ cell tumors [11]. Most tumors at these sites are benign with malignancy occurring in 15 % of cases. The POG/CCG study included 25 children with 80 % less than 5 years of age [11]. The most common symptoms were abdominal or back pain followed by fever, weight loss, constipation, or an acute abdomen. Elevated AFP was the most common marker abnormality as yolk sac tumor was identified in 19, and in four with components of choriocarcinoma, beta HCG was elevated. Most had advanced unresectable disease and 17 had metastatic disease at diagnosis.

Although the majority of patients could only undergo debulking or biopsy, the postchemotherapy outcome was excellent. Four with initial biopsy only had no tumor residual tumor after chemotherapy and 13, with subsequent surgery, had complete resection. The 6-year EFS was 82.8 ± 10.9 % and overall survival 87.6 ± 9.3 %. This is compared to a mortality of over 80 % prior to the advent of cisplatin-based chemotherapy [30]. Based on this study primary excision should be performed if a complete resection can be accomplished without removing normal structures. Otherwise, initial biopsy with neoadjuvant chemotherapy will usually allow a secondary resection.

An interesting subgroup of these tumors is the infantile choriocarcinoma syndrome in which infants present in the first 7 months of life with anemia and hepatomegaly. Tumor production of ß-HCG in these infants can lead to precocious puberty. These tumors are thought to arise as primary placental tumors with metastasis to the fetal liver. The mother must also be followed as metastatic disease has occurred in the mother [11].

Growing Teratoma

A rare but important clinical scenario involves the enlargement of benign elements of a tumor, mature or immature teratomas referred to as the "growing treatoma syndrome" [39]. The child in Fig. 19.8a had a extensive tumor and biopsy demonstrated immature teratoma and the serum AFP was normal for the age of the child. The child received chemotherapy for a presumed germ cell malignancy and unfortunately the benign elements continued to grow (Fig. 19.8b) making subsequent resection more difficult than at initial presentation. Initial resection and avoidance of chemotherapy in lack of definite malignancy is important in the management of germ cell tumors.

Mediastinal

The mediastinal site for germ cell tumors accounts for approximately 6–18 % of all pediatric mediastinal tumors

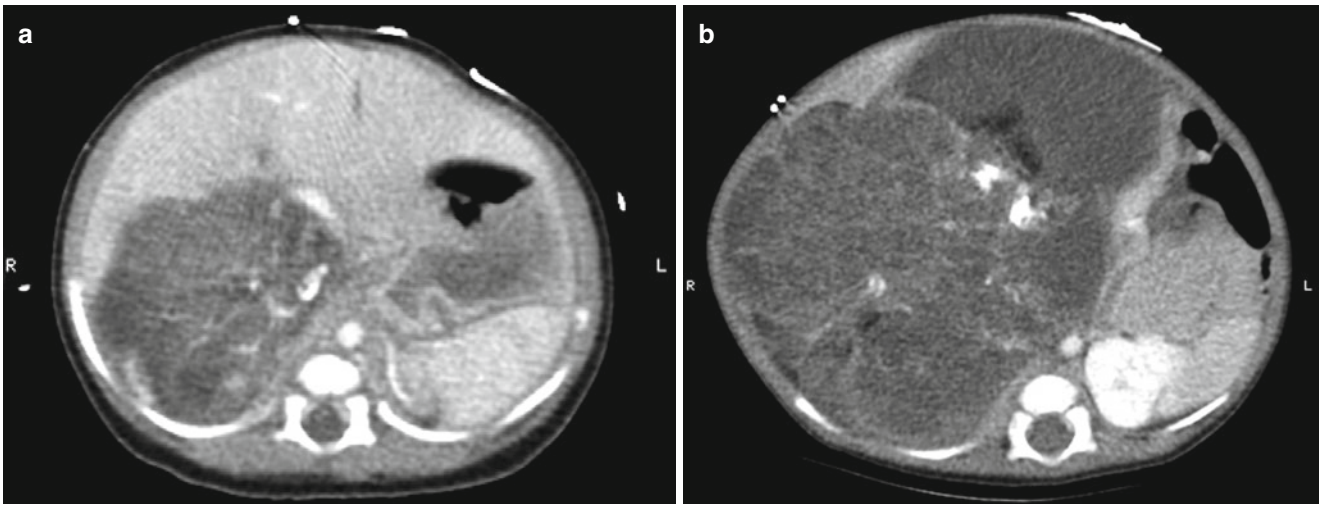

Fig. 19.8 Growing Teratoma. (**a**) A 4-weeks old child with a large tumor. Biopsy demonstrated immature teratoma. (**b**) Three months later, significant tumor growth

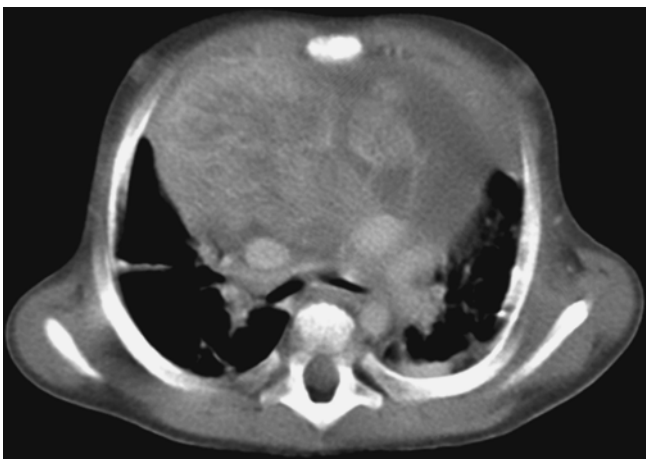

Fig. 19.9 CT scan of a large mediastinal germ cell tumor with airway compromise

and of these 86 % are benign [9, 30]. Many of these tumors achieve a large size prior to detection probably due to the lack of confining boundaries (Fig. 19.9). The clinical presentation is usually respiratory distress in younger children whereas older patients present with chest pain, precocious puberty or facial fullness reflective of venous obstruction. Malignant mediastinal germ cell tumors are more commonly in males and an association with Klinefelter's syndrome has been noted. The presence of hypogonadism, relative increase in leg length compared with overall stature and mild developmental delay should lead to the consideration of Klinefelter's syndrome [10, 39]. Mediastinal germ cell tumors are also associated with hematologic malignancies including leukemia and erythrophagocytic syndrome.

There were 36 patients in the POG/CCG study [10]. Tumor marker elevations included 29 with increased serum AFP and 16 with elevated serum ß-hCG. The histology was more heterogeneous than other extragonadal sites with yolk sac tumor found among the children less than 5 years whereas older patients had yolk sac tumors as well as germinoma, choriocarcinoma, and mixed tumors.

Fourteen children underwent resection at diagnosis followed by chemotherapy with 12 survivors. Eighteen children underwent biopsy followed by neoadjuvant chemotherapy and subsequent resection with 13 survivors.

Biopsy technique options include image-guided or open technique using the Chamberlain anterior approach or standard thoracotomy. Eight of ten image-guided biopsies in the POG/CCG study were successful. In this study both resection at diagnosis and post chemotherapy was frequently difficult due to adherence to the thymus, pericardium, superior vena cava, innominate vein, subclavian artery, aorta, vagus and phrenic nerves, as well as lung. Occasional sacrifice of these structures is needed to accomplish a complete resection. Resections were accomplished most frequently (20/31) by median sternotomy followed by thoracotomy (11/31).

Anterior mediastinal tumors pose unique anesthetic risks and careful preoperative assessment should be performed to determine the form of anesthetic. There is a risk for cardiopulmonary arrest with induction of anesthesia due to tracheal compression [32, 49]. Greater than 35–50 % tracheal compression is associated with increased morbidity [4, 60]. If significant airway compression is present, a percutaneous image-guided biopsy with local anesthesia with or without sedation may allow confirmation of malignancy and administration of neoad-

juvant chemotherapy to decrease tumor size prior to resection.

The survival on the POG/CCG study was 71 ± 10 %, which is lower than the other extragonadal sites, with all deaths occurring in boys over 15 years of age. Interestingly, no death occurred in patients with yolk sac tumors. In some patients with mixed tumors, the benign elements (teratoma) may persist or enlarge as the malignant elements shrink with chemotherapy, the "Growing Teratoma Syndrome." In the POG/CCG study over half of the postchemotherapy specimens contained mature and immature teratoma [10]. In view of the high rate of viable germ cell tumors, complete resection of any residual tumor present after completion of chemotherapy should be performed.

Genital

Primary germ cell tumors of the genital region are rare, primarily occurring in girls less than 3 years of age [16, 47]. Presenting signs and symptoms include most commonly vaginal bleeding followed by a pelvic mass or urinary obstruction (Fig. 19.10) [53]. This lesion can be confused with the botryoides type of embryonal rhabdomyosarcoma. Older reports utilizing surgery and VAC (vincristine, dactinomycin, and cyclophosphamide) reported 67 % survival [16] whereas the POG/CCG report of 13 children (12 vaginal, 1 penile) utilizing a neoadjuvant approach with etoposide, bleomycin and either standard or high-dose cisplatin reported a 4-year survival of 91.7 % [53]. Genital preservation was possible in 11 of 12 survivors. In view of this data, initial biopsy, neoadjuvant therapy and postchemotherapy evaluation usually demonstrates significant shrinkage. In the POG/CCG study, 9 of 11 treated with neoadjuvant therapy had residual masses including one with progression, one had residual yolk sac tumor, and seven with necrotic nonviable residual [53].

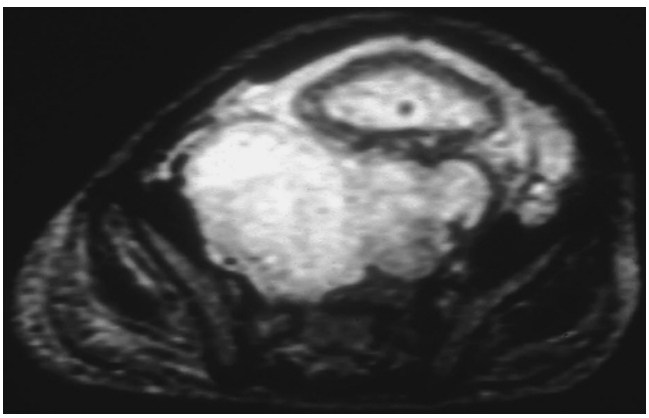

Fig. 19.10 CT scan demonstrating a pelvic mass associated with a vaginal germ cell tumor

Cervicofacial Teratoma

Nearly all of these lesions present in the neonatal period, one-third with airway obstruction, and most are benign mature or immature teratomas [5]. Large fetal tumors can cause hydrops and fetal demise whereas some have been salvaged with fetal resection. Fetal resection should be considered if hydrops develops prior to 28 weeks gestation [33]. An EXIT procedure with the potential for intubation, tracheostomy or resection while on placental support should be considered for those without hydrops.

Testes

Most boys present with a testicular mass allowing preoperative evaluation; however, some present with an acute scrotum with signs and symptoms of torsion, hydrocele, or hernia leading to intraoperative diagnosis and evaluation. A scrotal ultrasound may demonstrate a solitary mass in a child presenting with a testicular swelling or mass. If a discrete mass is noted along with normal-appearing testes, this may represent a testicular teratoma and enucleation is considered adequate therapy. Although the incidence of malignancy in prepubertal testes masses is not known, one report observed that 74 % were benign with 48 % teratomas and only 5 % yolk sac tumors [59]. These benign lesions would not be associated with an elevated serum AFP level. Diagnostic work-up should include determination of serum markers and an abdominal and chest CT. The initial diagnostic procedure is a transinguinal exploration with occlusion of the spermatic vessels at the internal ring prior to mobilization of the testes. If a solitary mass is noted, it should be excised with ligation of the entire spermatic cord at the level of the internal ring. Children with no other evidence of disease are followed with serum AFP levels and if these decline to normal appropriately, are considered Stage I (Table 19.3). The role of observation alone in the management of Stage I testes was confirmed in the CCG/POG study of 63 Stage I tumors [58]. This study excluded boys older than 10 years and therefore consisted entirely of patients with yolk sac tumors. The 6-year survival rate was 100 % and EFS 78.5 % ± 7.0 %. Most recurrences occurred within 6 months and all were salvaged with chemotherapy. Of interest, transcrotal violation was associated with a significantly increased rate of recurrence. Most (85 %) of children will present with Stage I disease compared to only 35 % of adults [23, 34]. The predominant histology in these prepubertal children is yolk sac tumor and thus serum AFP levels are elevated.

Table 19.3 Children's Oncology Group staging system for testes tumors

Stage I	Limited to testis (testes), completely resected by high inguinal orchiectomy; no clinical, radiographic, or histologic evidence of disease beyond testes. Patients with normal or unknown tumor markers at diagnosis must have a negative ipsilateral retroperitoneal node sampling to confirm Stage I disease if radiographic studies demonstrate lymph nodes >2 cm
Stage II	Transscrotal orchiectomy; microscopic disease in scrotum or high in spermatic cord (≤5 cm from proximal end)
Stage III	Retroperitoneal lymph node involvement, but no visceral or extra-abdominal involvement. Lymph nodes >4 cm by CT or >2 cm and <4 cm with biopsy proof
Stage IV	Distant metastases, including liver

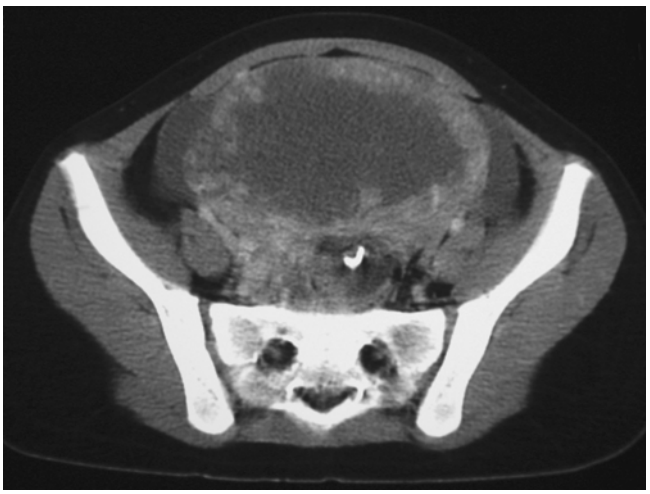

Fig. 19.11 CT scan of a large malignant ovarian mixed yolk sac tumor and teratoma with solid and cystic components

If preoperative evaluation reveals retroperitoneal disease (Stage III) or pulmonary metastases (Stage IV), an initial inguinal orchiectomy is still performed followed by chemotherapy (Table 19.2). Residual disease should be excised and if viable tumor is present, additional chemotherapy administered. The survival of Stage II tumors treated with postoperative chemotherapy although small (n = 17) was 100 % [54]. The survival of Stage III and IV patients treated with chemotherapy was still very high with a 6-year overall survival and EFS of 100 and 94.1 % for Stage III and 90.6 and 88.3 % for Stage IV [19].

Ovary

Ovarian tumors are one of the more common germ cell tumors in female children and adolescents. Of all ovarian masses, most (80 %) are benign (epithelial cysts, teratomas, immature teratomas) often with predominantly cystic components (Fig. 19.11). Symptoms include pain, distention, or the presence of a mass. Less common presentations include acute abdomen secondary to torsion or tumor rupture and precocious puberty.

Although a low risk of malignancy (2 %) is quoted in adult series [15, 46, 62], caution must be taken as many

Table 19.4 Children's Oncology Group operative guideline for ovary tumors

1. Collect ascites or peritoneal washings for cytology
2. Examine entire peritoneal surface and liver; excise suspicious lesions
3. Unilateral oophorectomy
4. Wedge biopsy of contralateral ovary, only if suspicious
5. Omental inspection and excision if adherent or contains nodules
6. Biopsy of suspicious or enlarged retoperitoneal or pelvic lymph nodes

tumors have solid and cystic components. Billmire et al. [12] reported the CCG/POG experience with 131 children and adolescent girls which is the largest series in the era of modern chemotherapy. In this report 57 % of the tumors had cystic components, thus highlighting the difficulty of determining malignancy preoperatively. The mean age was 11.9 years. In addition, the histology showed mixed tumors in most, with teratoma coexisting with malignant elements in 60 girls.

The 6-year EFS and survival by Stage in the POG/CCG study were: Stage I 95, 95.1 %; Stage II 87.5, 93.8 %; Stage III 96.6, 97.3 %; and Stage IV 86.7, 93.3 %. In view of the excellent survival of Stage I tumors, the excellent survival of Stage I girls with microscopic yolk sac tumors treated with surgery alone [18] as well as two series of Stage I girls treated with surgery alone with a 67 % EFS and 97.4 % OS [6, 29], the recently completed COG study treated Stage I ovarian tumors with observation. Unfortunately the low risk arm was closed early due to a greater than anticipated rate of recurrence for Stage I ovarian tumors (<70 % EFS) [27]. The OS was still 95 % due to successful salvage with chemotherapy in most of the girls. The current staging procedure is listed in Table 19.4 and the staging system in Table 19.5. The current recommended therapy is surgery alone for Stage I ovarian tumors.

Tumors with extensive involvement of other structures may be initially managed with biopsy and postchemotherapy excision. Radical removal of the uterus is not recommended. The current recommendation for bilateral tumors is to attempt ovarian preservation if possible on the least involved side, particularly if a plane of demarcation exists between the tumor and normal ovarian tissue. These findings and conclusions are consistent with other germ cell tumors

Table 19.5 Children's Oncology Group staging system for ovary tumors

Stage I	Limited to ovary (peritoneal evaluation should be negative). No clinical, radiographic, or histologic evidence of disease beyond the ovaries
Stage II	Microscopic residual; peritoneal evaluation negative
Stage III	Lymph node involvement; gross residual or biopsy only; contiguous visceral involvement (omentum, instestine, bladder); peritoneal evaluation positive for malignancy
Stage IV	Distant metastases, including liver

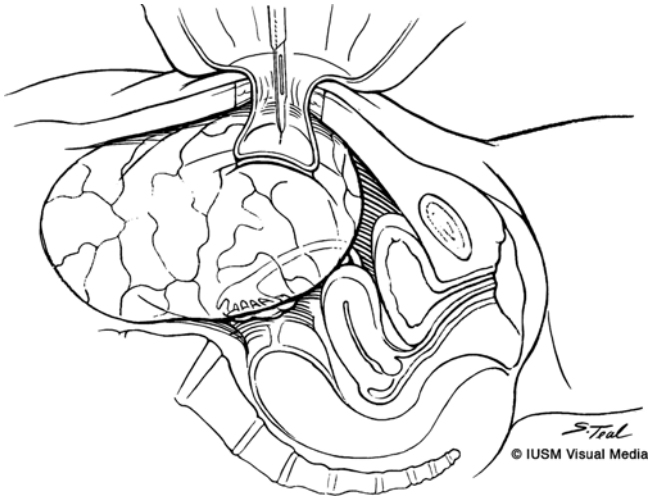

Fig. 19.12 Illustration of technique involving fixation of a plastic sheet to a large benign cystic ovarian tumor with decompression without spill

reflective of effective chemotherapy to increase the success of conservative surgery.

Many adolescents present with primarily cystic lesions and most of these are benign. Laparoscopy has been widely utilized in the management of ovarian lesions in childhood, adolescents, and adults. The main controversy surrounds the ability to perform a cancer type procedure in cases where the exact tumor histology (benign vs. malignant) cannot be determined preoperatively. If the lesion is primarily solid or if the serum markers are elevated, an open procedure is indicated. If the serum markers are normal and the lesion is primarily cystic, particularly if there is a very large cystic component, a less invasive technique may be considered; however, avoidance of tumor spill must be assured. One minimal access procedure involves laparoscopic excision of the tumor from its attachments, placement in a retrieval bag, and delivering the neck of the bag outside of the abdominal cavity through the umbilical opening. The cyst is then punctured, the fluid removed and the cystic lesion, contained within the bag removed without spill and sent for pathologic examination. In the second technique, useful for giant cysts, the cyst is exposed through an approximate 5-cm incision, a bag glued to the cyst with cyanoacrylate adhesive as described by Shozu et al. [61]. The cyst is then incised by cutting through the center of the bag-cyst interface, the fluid removed without spill, and the decompressed cyst then removed from the abdominal cavity (Fig. 19.12). The remainder of the standard procedure, peritoneal/ascitic fluid sampling, omental inspection, and excision and evaluation of the peritoneal surface can be performed laparoscopically. The only aspect which cannot be accomplished is palpation of retroperitoneal nodes, although depending on the size and habitus of the child or adolescent, a small incision may allow this to be accomplished.

Conclusion

The survival for pediatric germ cell tumors has dramatically improved since the introduction of platinum-based therapy in the 1970s. The survival for Stage I gonadal tumors and all immature teratomas at any site is excellent and these are managed by surgical excision and subsequent observation. The survival for intermediate-risk tumors including Stage II-IV testes, Stage II-III ovarian and Stage I-II extragonadal is also very high and reductions in therapy have been possible based on cooperative pediatric trials conducted in the 1990s. The survival for high-risk tumors, Stage III-IV extragonadal and Stage IV ovarian is lower and these have been managed with longer courses of chemotherapy. The current treatment as outlined in Table 19.2 is reflective of a risk based approach.

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Soft Tissue Sarcoma

20

Mary T. Austin and Richard J. Andrassy

Abbreviations

AIEOP	Associazione Italiana di Ematologiae Oncologia Pedaitrica
AJCC	American Joint Commission on Cancer
ASPS	Alveolar soft part sarcoma
ATFS	"Adult type" fibrosarcoma
BSA	Body surface area
COG	Children's Oncology Group
COG-STS	Children's Oncology Group Soft Tissue Sarcoma Committee
COL1A1	Collagen type 1, alpha 1 gene
CT	Computerized tomography
DFSP	Dermatofibrosarcoma protuberans
Dox	Doxorubicin
DSRCT	Desmoplastic small round cell tumor
E	Etoposide
EFS	Event free survival
EWS	Ewing sarcoma gene
FDG	Fluorine-18-fluorodeoxyglucose
FDG-PET	Fluorodeoxyglucose positron emission tomography
FHT	Fibrohistiocytic tumors
FISH	Fluorescent in situ hybridization
FNCLCC	French Federation of Cancer Centers Sarcoma Group
FSRT	Fractionated stereotactic radiotherapy
HART	Hyperfractionated accelerated radiotherapy
HIPEC	Hyperthermic intraperitoneal chemotherapy
I	Ifosfamide
IFS	Infantile fibrosarcoma
IGF-II	Insulin-like growth factor-2
IGF-IR	Insulin-like growth factor-1 receptor
IMRT	Intensity-modulated radiation therapy
IRS	Intergroup Rhabdomyosarcoma Group
IRSG	Intergroup Rhabdomyosarcoma Study Group
LOH	Loss of heterozygosity
MFH	Malignant fibrous histiocytoma
MMS	Mohs micrographic surgery
MPNST	Malignant peripheral nerve sheath tumor
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NF1	Neurofibromatosis type 1
NOS	Not otherwise specified
NRSTS	Nonrhabdomyosarcoma soft tissue sarcomas
OS	Overall Survival
PCR	Polymerase chain reaction
PDGF	Platelet-derived growth factor
PDGFB	Platelet-derived growth factor beta
PET	Positron emission tomography
PFS	Progression-free survival
POG	Pediatric Oncology Group
PRE	Pre-treatment re-excision
RMS	Rhabdomyosarcoma
RT	Radiation therapy
SEER	Surveillance Epidemiology and End Results
STS	Soft tissue sarcomas
STSC	Soft Tissue Sarcoma Committee
VA	Vincristine (V) actinomycin D (A)
VAC	Vincristine (V) actinomycin D (A), and cyclophosphamide (C)
WHO	World Health Organization
WLE	Wide local excision
WT1	Wilms' tumor gene 1

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Introduction

Pediatric sarcomas are typically divided into soft tissue sarcomas and bone sarcomas. The original distinction of soft tissue sarcomas and bone sarcomas from epithelial and hematopoietic tumors is attributed to Virchow who, in the middle 1850s, propounded his theory of "cellular pathology" ascribing the origin of tumors to specific types of cells [1]. The soft-tissue sarcomas (STS) of childhood are a relatively rare and heterogeneous group of tumors that arise primarily from connective tissue and may develop in any site of the body. In the US, 850–900 children less than 20 years of age are diagnosed with STS which accounts for 7.4 % of all cancers in this population of patients [2].

STS are extra skeletal malignant tumors of mesenchymal cell origin. They are classified according to the normal tissue they resemble – for example, rhabdomyosarcoma (skeletal muscle), leiomyosarcoma (smooth muscle), fibrosarcoma and malignant fibrous histiocytoma (connective tissue), neurofibrosarcoma or malignant peripheral nerve sheath tumor (MPNST) (nervous tissue), liposarcoma (adipose), synovial sarcoma (synovium), and angiosarcoma (blood and/or lymphatic vessels). Other sarcomas include rare entities such as alveolar soft-part sarcoma, clear cell sarcoma, desmoid tumor, desmoplastic small round cell tumor, epithelioid sarcoma, extraosseous Ewing's sarcoma, mesenchymal chondrosarcoma, perivascular epithelioid cell neoplasms (PEComas), plexiform histiocytic tumor and undifferentiated soft tissue sarcomas.

Rhabdomyosarcoma (Greek for rhabdos, "rod", mys "muscle", sarkos "flesh") (RMS) is the most common STS among children and adolescents accounting for 40 % of tumors in persons <20 years old [3]. RMS arises from embryonic mesenchyme with the potential to differentiate into skeletal muscle. STS differ widely in their response to therapy, and in children, STS are generally classified as either RMS or Nonrhabdomyosarcoma soft tissue sarcomas (NRSTS) with the NRSTS further divided into multiple histologic subtypes as listed above. RMS are the only STS that are found more commonly in children than adults [3] and therefore, much of our knowledge regarding these tumors is based on findings from pediatric studies. NRSTS are much more common in adults and thus most of the information on the natural history and treatment of these tumors is based on findings from adult studies. The information provided in this chapter is based on the most up-to-date management approaches for each disease entity. However, it remains unclear whether the clinical behavior of a given STS is independent of age and thus whether or not children and adults should be managed similarly. An international trial of pediatric soft tissue sarcomas conducted by the Children's Oncology Group was the first to examine the outcome of pediatric adolescent and young adult patients with NRSTS treated with an adult protocol. Results are pending.

Nonrhabdomyosarcoma Soft Tissue Sarcomas

Epidemiology

In the US, 500–550 children <20 years old are diagnosed with NRSTS each year accounting for approximately 4 % of all childhood cancers [4]. In children, NRSTS have a bimodal age distribution with peaks in infancy and adolescence. However, the distribution of patient age at diagnosis and gender varies among the histologic subtypes. For example, fibrosarcoma is more common in infants, whereas synovial sarcoma and MPNST are more frequently encountered in older children and adults [2, 5]. Black children have a slightly higher incidence than white children [2]. There is a slight male predominance (1.5:1) for all types of STS except alveolar soft part sarcoma and leiomyosarcoma which are seen more frequently in females [3]. The incidence of NRSTS in children and adolescents in the US is 6.6 per million person years and represents 4.5 % of all childhood malignancies [6]. There is no evidence that the incidence of NRSTS is increasing [6]. However, the 5- and 10-year overall survival of children and adolescents with NRSTS is also unchanged at 78 % and 74 %, respectively [6].

Although the majority of patients with NRSTS have no identifiable etiology, a few genetic and environmental factors have been associated with the development of NRSTS. Genetic conditions associated with NRSTS include LiFraumeni syndrome [7], hereditary retinoblastoma [8], neurofibromatosis type 1 [9], Gorlin syndrome [10], and Werner syndrome [11]. Patients with Li-Fraumeni syndrome, a rare autosomal dominant disease characterized by germ line p53 mutations, have an increased risk for development of soft tissue tumors, bone sarcomas, breast cancer, brain tumors and acute leukemia [12, 13]. Approximately half of all patients with MPNST are diagnosed in patients with neurofibromatosis Type 1, (NF-1, VonRecklinghausen's disease) [14] and 2–13 % of patients with NF-1 will develop a MPNST [14–18]. Desmoid tumors occur in 4–20 % of all patients with familial Gardner syndrome [19–21]. Leiomyosarcomas have been linked to Epstein-Barr virus infection in patients with AIDS [22]. Chronic lymphedema is a risk factor for the development of lymphangiosarcoma [23]. Therapeutic radiation doses result in a cumulative incidence of in-field sarcomas in 1–2 % of long-term cancer survivors 10–15 years after therapy [24, 25], with malignant fibrous histiocytoma being the most common.

Clinical Presentation

NRSTS usually present as a painless, enlarging mass in the extremities, back, flank or abdominal wall. Although NRSTS may arise anywhere in the body, intra-abdominal NRSTS are quite rare. Systemic symptoms such as fever and weight loss are rare. Symptoms usually develop due to invasion or compression of adjacent neurovascular structures [26]. In a review of 575 patients age <21 years with STS including 212 patients with NRSTS, the extremities were the most common site of presentation and swelling was the main presenting sign or symptom [27]. In this study, the symptom interval ranged between 1 and 60 months with a longer symptom interval occurring in older patients with larger tumors, extremity primaries, and NRSTS histology [27]. In addition, the risk of death increased significantly the longer the symptom [27]. Approximately 15 % of patients present with metastatic disease most commonly in the lungs [28]. Bone, liver, brain and subcutaneous metastases have been reported; however, bone marrow involvement is exceedingly rare [28]. Thus, as with most malignancies, early and accurate diagnosis is key.

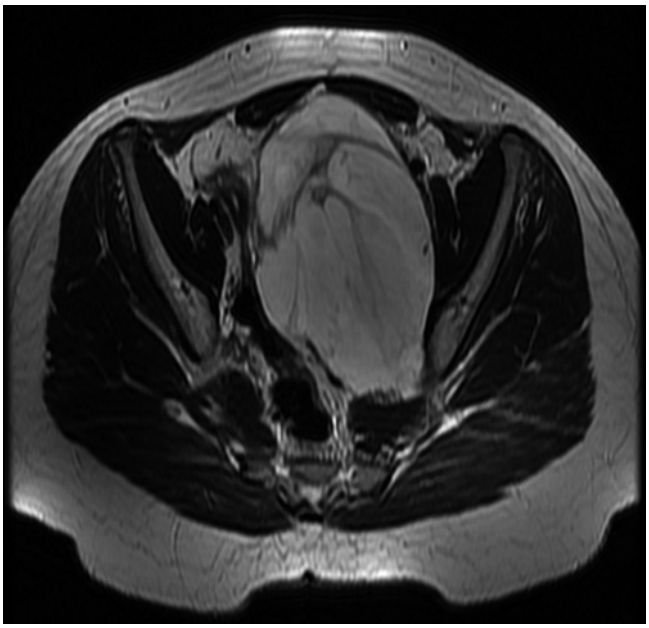

Fig. 20.1 A 17 year-old girl presented with pain in her left thigh. MRI abdomen showed a large pelvic mass. She underwent incomplete resection of a myxoid liposarcoma with pleomorphic elements followed by second look operation and resection of metastatic disease with hyperthermic intraperitoneal chemotherapy (HIPEC)

Diagnosis

NRSTS are a large, heterogenous group of malignancies composed of cells similar to mesenchymal cells. Although NRSTS are easily distinguished from RMS, type classification of these tumors is often difficult. For a suspicious lesion, an adequate tumor specimen must be obtained to identify the histologic subtype and grade of NRSTS. Incisional biopsy is preferred but multiple core needle biopsies may be sufficient [29]. The biopsy should not compromise subsequent wide local excision. For example, longitudinal incisions are preferred in the extremity to allow for excision of the biopsy tract at the time of definitive resection. Inappropriately placed incisions at any location make resection or rotational or advancement flap closure more difficult. Image guidance using ultrasound, computed tomography scan or magnetic resonance imaging (MRI) may be necessary [30].

The pathologist plays a key role in the diagnosis and thus future management of the patient with NRSTS. The initial approach to the fresh pathology specimen is crucial and appropriate specimen handling includes triage for diagnostic and prognostic studies including routine histopathology and immunohistochemistry, cytogenetic and molecular studies, flow cytometry, and electron microscopy. Reverse transcriptase polymerase chain reaction (RT-PCR), biochemical, and microarray gene product analyses may aid in diagnosis. Cytogenetic imprints allow for fluorescent in situ hybridization (FISH) evaluation of mutated genes, tumor defining translocations, and other cytogenetic abnormalities.

Many NRSTS are characterized by chromosomal abnormalities. Despite their complexity, NRSTS may be divided into two groups: those with histology-specific chromosomal rearrangements and those with evidence of widespread genomic instability [26]. The tumors with histology-specific chromosomal rearrangements usually consist of balanced translocations which may lead to fusion of two disparate genes. The resulting fusion transcript is easily detected using polymerase chain reaction-based techniques which facilitates diagnosis of these tumors. Table 20.1 summarizes the genetic aberrations in NRSTS.

If possible, it is preferred to perform diagnostic imaging prior to any surgical intervention. Imaging studies are a valuable tool in staging and preoperative planning and provide baseline measurements for assessment of the response to therapy. Magnetic resonance imaging is the modality of choice as it provides excellent soft tissue definition and provides clear visualization of regional lymph node enlargement if present (Fig. 20.1). Gadolinium-enhanced MRI improves the signal intensity on T1 weighted images and may help distinguish cystic versus necrotic areas as well as highlight the vascularity of the tumor and its relationship to nearby neurovascular structures [31]. Computed tomography may be more useful for tumors within the chest and abdomen/pelvis or in evaluating for lung metastases. Although Fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) has not been used routinely in pediatric NRSTS, it may prove to be a useful tool in evaluating tumor response to adjuvant therapy.

Table 20.1 Genetic aberrations in NRSTS

Histology	Genetic aberration
Alveolar soft part sarcoma	der (17)t(x;17)(p11.2;q25) with *ASPL-TFE3* fusion
Clear cell sarcoma	t(12;22)(q13;q12) with *EWS-ATF1* fusion
Dermatofibrosarcoma	t(17;22)(q21;q13) with *COL1A1-PDGFB* fusion
Desmoplastic small round cell tumor	t(11;22)(p13;q12) with *EWS-WT1* fusion
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12) with *EWS-CHN* fusion
Infantile fibrosarcoma	t(12;15)(p13;q25) with *ETV6-NTRK3* fusion; trisomy 8, 11, 17, 20
Inflammatory myofibroblastic tumor	2p23 rearrangement with *ALK* fusion to *TPM3*, *TPM4*, clathrin, and other genes
Leiomyosarcoma	Complex abnormalities
Low-grade fibromyxoid sarcoma	t(7;16)(q34;p11) with *FUS-BBF2H7* fusion
Malignant fibrous histiocytoma	Complex abnormalities
Malignant peripheral nerve sheath tumor	Complex abnormalities
Myxoid liposarcoma	t(12:16)(q13;p11) with *DDIT2*(*CHOP*)-*FUS* fusion; t(12;22)(q13;q12) with *DDIT3-EWS* fusion
Rhabdoid tumor	Deletion of 22q with *HSNF5*(*INI1* deletion or mutation
Synovial sarcoma	T(X;18)(p11;q11) with *SYT-SSX* fusion; *MYCN* overexpression

Prognostic Factors

There are few prospective studies on NRSTS in children and adolescents [32–34], and therefore, most of our understanding of the factors that influence prognosis are based on retrospective case series and adult studies. Factors shown to impact survival in pediatric NRSTS patients include the extent of disease (metastatic versus non-metastatic), histologic grade, size of the primary tumor, and extent of resection [26]. Tumor resectability and the presence or absence of metastases are the most important prognostic factors. The clinical outcome for completely resected NRSTS's is quite good but more than 20 % of these patients eventually develop disease recurrence and ultimately die due to their disease [34–36]. Risk factors for recurrence are important in determining prognosis, therapy and intensity of therapy. Tumor size and grade predict early relapse, whereas surgical margin status predicts late relapse [37].

These factors may be used to classify tumors as high, intermediate or low risk. Children with metastatic disease are high risk and overall survival is approximately 15 %. Intermediate risk includes patients with unresectable tumors or tumors that are both high grade and >5 cm in maximal diameter. The survival for intermediate risk patients is approximately 50 %. Low-risk tumors are resectable tumors that are either high grade and <5 cm in maximal diameter or low grade and any size. Survival for low risk patients is approximately 90 %. Other factors that may influence survival include microscopic surgical margin, primary site with visceral tumors associated with a worse prognosis, and age with age >10 years as an adverse factor in patients with unresectable tumors [26]. It was based on this risk classification by Spunt and colleagues, the first prospective international trial of pediatric adolescent and young adult NRSTS was conducted by the Children's Oncology group. Long term results from this study are pending.

The most important factor related to local control is extent of resection rather than tumor grade or size. A negative microscopic margin is associated with the lowest risk for local recurrence followed by microscopic residual disease. Patients with gross residual disease are unlikely to achieve local control. Radiotherapy has been shown to decrease local recurrence in patients with microscopic residual disease.

Metastatic disease at the time of initial presentation occurs in approximately 15 % of children with NRSTS [28]. The lung is the most common site of distant metastases, although metastases to bone, liver, and mesentery have also been reported. Regional lymph node spread is rare with most histologic subtypes; however, it may occur in high-grade lesions, synovial sarcoma, angiosarcoma, and epithelioid sarcoma. The prognosis of patients with lymphatic metastases is similar to patients with metastatic disease at other sites.

Staging

Despite the importance of clinical staging in predicting outcome and determining the most effective therapy, there is no validated pediatric NRSTS staging system. In the past, the Intergroup Rhabdomyosarcoma Study Group's surgicopathologic staging system for rhabdomyosarcoma has been used [38]. This staging system will be described in greater detail in the RMS section of this chapter. However, this system fails to account for tumor grade and size which are known to be important prognostic factors in NSRTS.

Although the American Joint Commission on Cancer (AJCC) staging system that is used in adults has not been validated in pediatric studies, the current Children's Oncology Group (COG) trial is using the AJCC staging sys-

Table 20.2 NRSTS pathologic grading system

Grade 1
Angiomatoid malignant fibrous histiocytoma
Deep-seated dermatofibrosarcoma protuberans
Myxoid chondrosarcoma
Myxoid and well-differentiated liposarcoma
Well-differentiated or infantile (≤4 years old) fibrosarcoma
Well-differentiated or infantile (≤4 years old) hemangiopericytoma
Well-differentiated malignant peripheral nerve sheat tumor
Grade 2
Less than 15 % of the surface area shows necrosis
Mitotic count <5 mitotic figures per 10 high-power fields using a ×40 objective
Nuclear atypia is not marked
Tumor is not markedly cellular
Grade 3
Alveolar soft part sarcoma
Clear cell sarcoma
Desmoplastic small round cell tumor
Epithelioid sarcoma
Extraskeletal osteogenic sarcoma
Malignant triton tumor
Mesenchymal chondrosarcoma
Malignant triton tumor
Pleomorphic or round cell liposarcoma
Synovial sarcoma
Undifferentiated sarcoma
Any other sarcoma not in grade 1 with >15 % necrosis and/or ≥5 mitotic figures per 10 high-power fields using a ×40 objective

tem [39]. The AJCC system designates stage based on four criteria including tumor size (< or >5 cm in greatest diameter and superficial or deep), nodal status, metastasis, and tumor grade (well-differentiated, moderately differentiated, or poorly differentiated). Other staging systems commonly used in adult soft tissue sarcomas include those developed by the Memorial Sloan-Kettering Cancer Center [40] and the Musculoskeletal Tumor Society [41]. The system most useful for pediatric NRSTS is not yet determined as none of the adult systems include the unique pediatric histologic subtypes.

In 1986, the Pediatric Oncology Group (POG) conducted a prospective study to evaluate a pediatric NRSTS grading system based primarily on the National Cancer Institute (NCI) system [42, 43]. The NCI system stratifies STS into three different grades based on histologic subtype and a composite of histopathologic parameters that includes tumor necrosis, cellularity, pleomorphism, and mitotic activity [42]. The POG study identified three different tumor grades based on histopathologic subtype, amount of necrosis, number of mitoses, and cellular pleomorphism [43]. Table 20.2 describes the POG grading system.

The grading system used by the French Federation of Cancer Centers Sarcoma Group (FNCLCC) is based on tumor differentiation, mitotic count and necrosis. Although early evidence suggested that the FNCLCC grading system better predicted risk of metastases and mortality when compared to the NCI grading system [44, 45], a more recent study showed both systems to provide an adequate prognostic measure of outcome for pediatric NRSTS [46]. A subset of cases with intermediate prognosis was graded differently by the two systems and included the following histologic subtypes: synovial sarcoma, sarcoma not otherwise specified, alveolar soft part sarcoma, and MPNST [46]. In this study, mitotic index appeared to be the key parameter in grading pediatric NRSTS [46].

Treatment

Given the rarity of the disease, all children, adolescents and young adults with NRSTS should be treated using a multidisciplinary approach that includes pediatric oncologists, surgeons and radiotherapists. In addition, these patients should be considered for entry into institutional or national treatment protocols. Multimodality therapy offers the best chance for a successful outcome. Although the evaluation and treatment of NRSTS is similar in children and adults, several important differences need to be considered. In some young patients, the biology of the tumor seems to be less aggressive, while

the complications of adjuvant therapy may be greater (i.e., radiation induced injury). The long-term effects on growth and second malignancies need to be weighed against the potential benefits of the treatment [47–54]. In general, NSRTS are relatively resistant to chemotherapy and radiotherapy, and therefore, complete surgical resection remains the mainstay of therapy and should be attempted whenever feasible without causing undue loss of tissue or function.

Surgery

Complete surgical resection is the cornerstone to curative therapy in pediatric NRSTS, and therefore, every effort should be made to resect the primary tumor with negative margins before or after chemotherapy. Surgical approach is site specific and tumor size is also important in determining the surgical approach as well as the timing of surgery. Tumor size is a known prognostic variable in NRSTS [55], and therefore, the size of the mass partially determines the surgical approach. Although the AJCC staging system uses a tumor diameter of 5 cm as the cut off between T1 and T2 lesions, this size cut off may not be applicable in children of all ages. Ferrari and colleagues developed a formula to estimate the equivalent size tumor in a child using actual tumor size and adjusting for body surface area (BSA) [55]. The formula is applicable to infants and young children (age < 5 years) with tumors less than 5 cm in size [55]. If a tumor is suspicious for malignancy and either >5 cm in greatest diameter or > infant/toddler equivalent to 5 cm, the tumor should be biopsied to determine the histology prior to proceeding with definitive resection [56].

Although wide local excision is the optimal approach, the amount of tumor free margin necessary is not precisely known and controversy remains in defining an adequate margin. Historically, the standard margin in adults was 2 cm with local recurrence rates of 10–15 % [57]. However, in young children and patients with tumors in locations such as the head and neck, mediastinum, or retroperitoneum, a 2 cm margin may lead to excessively mutilating surgical procedures. The 2 cm margin may not be feasible in locations limited by neurovascular bundles such as tumors arising in the popliteal or antecubital fossa, groin or posterior thigh. In a small series of pediatric patients with NRSTS, Blakely and colleagues found that a pathological resection margin of >1 cm reduced local recurrence in patients with both low- and high-grade tumors [58]. In a similar retrospective review, it was shown that the presence of positive or negative margins is more important than the depth of the margins [35].

In general, close margins are preferred near neurovascular bundles and other vital structures rather than primarily resecting these structures. For extremity tumors, limb salvage by intracompartmental resection has evolved along with improved multimodality therapy. Mutilating resections should only be considered after poor response to radiation other treatment. An adequate wide resection includes the tumor, its pseudocapsule, and a margin of normal tissue removed in all directions enbloc. Since there have been no prospective randomized studies on margin size in NRSTS, a negative margin of at least a centimeter is recommended. Complete R0 resections will not require radiation. Whereas unresectable tumors receive preoperative radiation. R1 resections require post-operative radiation.

It is important to be aware that some tumors, such as synovial sarcoma, have a pseudocapsule and if the operating surgeon fails to recognize it, he/she may inappropriately shell out the tumor leaving behind a positive microscopic margin. Local recurrence rates are extremely high in these circumstances. Patients who present following an unplanned initial resection should be considered for pretreatment re-excision [59]. In these patients, the incidence of residual tumor is high and a negative margin may be achieved with pretreatment re-excision [59]. Pathologic examination or post-operative imaging suggestive of residual tumor should prompt the surgeon to recommend pretreatment re-excision of the primary site to ensure local control.

Lymph Node Dissection

In general, regional lymph node metastases at diagnosis are rare in NRSTS. However, several histologic subtypes require lymph node for staging and include RMS, synovial sarcoma, epithelioid sarcoma and clear cell sarcoma. In synovial sarcoma, regional disease is noted in 20 % of pediatric patients registered in the Surveillance, Epidemiology and End Results (SEER) dataset [60]. Another study suggests lymph node involvement is more common in patients with epithelioid sarcoma and clear cell sarcoma compared to other histologic subtypes [61]. If lymph nodes are clinically enlarged as determined by physical exam or imaging studies, fine needle aspiration or open biopsy may be performed. For clinically negative lymph nodes in patients with extremity primaries, sentinel lymph node biopsy is the preferred method to evaluate the lymphatic basin [56]. Several studies describe sentinel lymph node mapping in pediatric sarcoma patients [62–64]. Sentinel lymph node biopsy is often performed at the time of wide local excision. The primary tumor is injected with a technetium-labeled sulfur colloid and isosulfan blue dye (Lymphazurin). Intraoperatively, a radioisotope detector is used to localize the sentinel node and a small skin incision is made overlying the area of maximal signal. The radioisotope detector in combination with the blue dye is used to identify the sentinel lymph node(s) within the lymphatic

basin. The sentinel lymph node(s) is/are excised and submitted for pathologic review.

Although the identification of positive lymph nodes contributes to staging, it remains unclear as to whether completion lymph node dissection improves survival. Few studies evaluate the role of therapeutic regional lymph node dissection for patients with NRSTS [65, 66]. Riad and colleagues demonstrated a modest improvement in 5-year survival in patients with extremity STS who had resection of involved lymph nodes versus those treated without surgery [66]. Thus, in the setting of a positive sentinel lymph node(s) or clinically positive nodal disease, a formal lymph node dissection may be considered for extremity STS.

Resection of Metastatic Disease

Depending on the histologic subtype, 2–33 % of pediatric patients with NRSTS develop distant disease with most metastases occurring in the lungs [67]. Most studies evaluating the effectiveness of pulmonary metastatectomy in STS include only adult patients. With complete resection of all pulmonary metastases, the 3-year survival is 46–54 % in adults with metastatic STS [68–70]. A recent review suggests that selected patients with a maximum of two pulmonary nodules may benefit from a thoracoscopic versus an open approach for pulmonary metastatectomy [71]. In addition, Weiser and colleagues showed survival benefit with repeat resection of pulmonary metastases in those patients with completely resectable disease [72]. In this study, other prognostic factors associated with a poor outcome included ≥ nodules, largest metastases >2 cm in size, and high-grade primary tumor histology [72]. To date, few studies have evaluated the benefit of pulmonary metastatectomy in pediatric patients with STS [73, 74]. However, a small proportion of patients with metastatic disease may be cured if all distant metastases are completely resected. This is primarily true for patients with low grade NRSTS. In pediatric patients with low grade tumors and metastasis, effort should be made to resect any metastatic disease. Thus, pulmonary mestatectomy is advocated as an adjunct to multimodality therapy in children and adolescents with NRSTS.

NRSTS Pediatric Histologies

The most common NRSTS in the pediatric and adolescent population is synovial sarcoma, followed by undifferentiated, or unclassified sarcoma. These as well as more rare NRSTS will be discussed.

Alveolar Soft Part Sarcoma

Alveolar soft part sarcoma (ASPS) is a rare sarcoma accounting for 5 % of pediatric NRSTS with an age-adjusted incidence rate of 0.1 per million [1]. The median age at diagnosis is 25 years (range 0–84 years) and it occurs more commonly in females than males (1.6:1) [3]. ASPS is considered to be a tumor of uncertain differentiation with no specific cell lineage identified to date [75]. However, ASPS is characterized by an unbalanced recurrent translocation t(X;17)(p11;q25) which juxtaposes the *ASPSCR1* gene with the *TFE3* gene [76, 77].

In children and adolescents, the tumor most commonly arises in the extremities (55 %) followed by the head and neck (28 %), and trunk (15 %) [3]. However, it may present in any region of the body including sites such as the tongue, orbit, heart, and lung [78–81]. The clinical course is often indolent and the primary tumor may grow for years prior to definitive diagnosis. Approximately 23 % of pediatric patients present with distant metastases [3]. The most common metastatic site is the lung, followed by brain, bone, and lymph nodes [82].

Complete resection with negative microscopic margins of localized ASPS is key to achieving long term survival [83]. Thus, it is imperative that patients undergo preoperative imaging, usually MRI, with consideration of fine-needle aspiration or core biopsy prior to definitive surgery. Unlike other NRSTS, ASPS may be diagnosed by fine-needle aspiration due to the presence of intracellular crystals [84–88]. Approximately 17 % of patients present with regional disease [3], and there are a few reports of the use of sentinel lymph node biopsy in these patients [62, 89]. If complete excision of the primary tumor is not feasible, radiation therapy should be considered. Although ASPS is considered chemoresistent, there are reports of benefit with neoadjuvant chemotherapy to induce tumor shrinkage and improve resectability in patients who initially present with unresectable tumors [83]. The value of adjuvant chemotherapy in completely resected ASPS is not proven. There are a few reports of objective responses to biologic agents including interferon-alpha, bevacizumab, and sunitinib [90–94]. Radiotherapy may improve local control in patients with incompletely resected primary and/or metastatic tumors [83, 95]. ASPS is associated with an indolent clinical course and metastases may occur after prolonged disease-free intervals.

Pediatric ASPS is associated with a better prognosis compared to adults. In a population-based study using SEER data, the 5-year relative survival for patients age 0–9 years and 10–19 years was 100 % and 91 %, respectively [3]. In a pediatric series with a median follow-up of 74 months, the 5-year overall was 80 % for the entire cohort and 91 % for patients with localized disease [83]. In this series, tumor size

significantly impacted survival [83]. All patients with tumors ≤5 cm were alive at 5 years compared to only 31 % of patients with tumors >5 cm [83]. Other series have also shown tumor size to be the most important factor related to survival and the likelihood of metastases [95–97].

Desmoplastic Small Round Cell Tumor

Desmoplastic small round cell tumor (DSRCT) is a rare aggressive malignancy that occurs in children, adolescents and young adults. The majority of patients are Caucasian (85 %) with a strong predication for males (10:1) [98]. Although rare, increasing numbers of patients have been diagnosed with DSRCT following the discovery of its specific chromosomal translocation t(11;22)(p13;q12) involving fusion of the Ewing sarcoma gene (EWS) and the Wilms' tumor gene (WT1) [99, 100].

Most commonly, patients present with crampy abdominal pain associated with an abdominal mass [98]. Other symptoms include constipation, weight loss, abdominal distension, jaundice and ascites [98]. DSRCT has a propensity for serosal surfaces, most notably the peritoneal cavity. At diagnosis, patients often present with diffuse abdominal metastatic disease with tumor sizes ranging from 1 mm to confluent sheets and nodules up to 20 cm or greater [101]. DSRCT may spread to the lymph nodes as well as metastasize to distant sites including the liver, intrathoracic cavity, mediastinum, pleura, paratesticular and soft tissues.

The diagnostic evaluation includes CT or MRI of the abdomen and pelvis which often shows multiple nodules studding the peritoneal cavity. Percutaneous or open biopsy is indicated and the specimen should be submitted for immunohistochemistry and cytogenetics. The characteristic translocation is diagnostic of DSRCT. Additional imaging should include chest CT and whole body PET to be performed as part of the staging workup [102].

Complete surgical resection is rarely possible but if achieved, it improves survival in this disease with an otherwise dismal prognosis. Lal and colleagues showed significant survival benefit for patients receiving gross surgical resection compared to patients without resection (3-year survival of 58 % versus 0, respectively) [98]. In this study, 3-year survival was also significantly improved in patients who underwent multimodal therapy including induction chemotherapy, surgical debulking and radiotherapy, compared to patients who did not receive all three modalities [98]. The overall response of DSRCT to conventional chemotherapy is poor and durable remissions are rare. However, agents with known activity in DSRCT are similar to those used in Ewing's sarcoma and should include an alkylator-based regimen with either cyclophosphamide or ifosfamide. A recently described approach includes neoadjuvant chemotherapy followed by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) using cisplatin followed by adjuvant chemotherapy and abdominal radiation [103]. In this study, the 3-year survival was greatest for patients who received HIPEC (71 %) [103]. In addition, disease free survival at 12 months was 53 % for patients who received HIPEC and cytoreductive surgery compared to only 14 % in the patients who underwent surgical debulking without HIPEC [103].

Despite multimodal aggressive treatment strategies including chemotherapy regimens active in Ewing's sarcoma, aggressive debulking surgery, whole abdominal radiation, myeloablative and chemotherapy with autologous stem cell transplant, DSRCT survival remains poor. Many present with lymph node involvement and/or distant parenchymal disease at diagnosis [98]. Overall, 3- and 5- year survival is 44 % and 15 %, respectively [98].

Infantile Fibrosarcoma

Fibrosarcoma is a rare STS that represents approximately 10 % of pediatric STS [3]. However, it is the most common NRSTS in children less than 1 year of age accounting for approximately 25 % of cases [104]. Fibrosarcoma has two peaks of incidence in the pediatric population: infants and young children (infantile fibrosarcoma, IFS) and older children usually between ages 10 and 15 years ("adult type" fibrosarcoma, ATFS). IF is histologically indistinguishable from ATFS. However, IF is characterized by a specific translocation t(12;15)(p13;q25) resulting in *ETV6-NTRK3* fusion gene which differentiates it from other spincle cell neoplasms of childhood [105].

Despite the histologic similarity, the IF and ATFS behave quite differently. IF occurs almost exclusively in children younger than 2 years with the majority diagnosed either antenatally or during the first 3 months of life [106]. IF most commonly presents as an enlarging soft tissue mass involving the extremities with approximately one-third of patients presenting with a tumor >5 cm [106]. Tumor growth may be rapid and the tumor is often highly vascularized and may mimic benign vascular lesions. ATFS is most often diagnosed in patients 10–15 years old and more often presents in axial sites [107].

The goal of treatment for both IF and ATFS is complete non-mutilating excision of the tumor. In IF, the benefit of chemotherapy is not clear. However, initial non-mutilating resection is feasible in less than 25 % of infants. In the majority of infants, neoadjuvant chemotherapy may allow for a more conservative surgical approach [108]. Orbach and colleagues reported a 75 % response rate to chemotherapy in patients with IF [106]. In ATFS, aggressive surgical resection is also the treatment of choice. However, neoadjuvant is

indicated in patients who present with inoperable tumors and adjuvant chemotherapy should be given in all cases due to the frequent occurrence of micro metastases [107]. Radiation therapy is also indicated in ATFS for patients with microscopic or macroscopic residual disease after resection [107]. For both IF and ATFS, mutilating surgery is recommended only for patients with a poor response after neoadjuvant chemotherapy or in the case of local relapse.

Despite a reported local recurrence rate up to 50 %, IF rarely metastasizes (<10 % cases). It is associated with an excellent prognosis and a 5-year overall survival of 80–90 % [104, 106]. Spontaneous regression of incompletely resection IF have been reported. ATFS is more aggressive and often presents with distant metastases most commonly to the lungs. Survival is similar to adults with fibrosarcoma with a 10-year overall survival of 51 [107].

Fibrohistiocytic Tumors

Fibrohistiocytic tumors (FHT) in children and adolescents are a heterogeneous group of tumors that vary in malignant potential from benign (fibrous histiocytoma or dermatofibroma) to intermediate (dermatofibrosarcoma protruberans) to high grade (undifferentiated pleomorphic sarcoma or malignant fibrous histocytoma). These tumors consist of fibroblasts, myofibroblasts, and histiocytes-dendritic cells with a variable inflammatory component of lymphocytes and eosinophils [109]. They more commonly present in adults with a median age of 57 years [3]. Only 3.7 % occur in pediatric and adolescent patients [3].

Dermatofibrosarcoma protuberans (DFSP) is a FHT with low-grade malignant potential. It most commonly occurs in adults with a peak incidence in the second to fifth decade of life [110]. It is relatively rare in children with age-adjusted incidence of 1 per million in persons less than 20 years of age [2]. DFSP may present in infancy as a congenital lesion, and these tumors are often initially misdiagnosed as a vascular malformation. The clinical appearance of DFSP is heterogeneous and lesions may appear as sclerotic, atrophic, macular or nodular with variation in color from bluish, violaceous, and erythematous to flesh-colored, gray or black. Although the majority of DFSP in children occur on the trunk and proximal extremities, they may occur anywhere and the diagnosis should not be excluded based on anatomic location of the tumor.

Due to the infiltrating growth pattern and potential for extension into deeper tissues including fascia and bone, preoperative imaging with MRI is recommended [111]. The current standard treatment for DFSP recommended by the National Comprehensive Cancer Network (NCCN) is wide local excision (WLE) with 2- to 4-cm margins or Mohs micrographic surgery (MMS) [112]. Several studies have compared the two techniques. In a retrospective review of 79 patients who underwent WLE or modified MMS, Paradisi and colleagues found a significantly lower local recurrence rate associated with MMS compared to WLE (1.3 % versus 20.7 %) [113]. The disadvantage of MMS is the need for specialized equipment and technicians as well as the longer procedure time.

DFSP is associated with a translocation between platelet-derived growth factor beta (*PDGFB*, 22q13.1) and type 1 collagen (*COL1A1*, 17q21 ~ 22) leading to a fusion protein (PDGFB) which stimulates the PDGF receptor [114]. Imatinib mesylate is a tyrosine kinase inhibitor that exhibits activity against many proteins including PDGF receptors. Recently, Gooskens and colleagues reported efficacy of imatinib mesylate in children with DFSP [115]. The current NCCN guidelines recommend radiation therapy or imatinib for patients without clear surgical margins, local recurrence or concern for metastases [112].

DFSP may be locally aggressive and is likely to recur if incompletely excised. Fibrosarcomatous change occurs in 4.7 % of cases and increases the likelihood of metastases [116]. Although metastases occur in approximately 5 % of patients, the relative 5- and 15-year survivals for DFSP are excellent (99.2 % and 97.2 %, respectively) [110].

MFH was first described in the 1960's as a pleomorphic spindle cell neoplasm with fibroblastic and histiocytic differentiation. It eventually became the most common STS in adults; however, in recent years, both its histogenesis and validity as a clinicopathologic entity have been questioned. The World Health Organization (WHO) now includes MFH as a subtype of undifferentiated pleomorphic sarcoma. The WHO also reclassified both the plexiform and angiomatoid subtypes as fibrohistiocytic tumors of intermediate malignancy termed plexiform histiocytic tumor and angiomatoid fibrous histiocytoma, respectively. These tumors are quite rare in children and described only in a few case series in the literature [117–121]. The most common primary sites of disease are the head and neck and extremities; however, these tumors may originate from other locations including the orbit, cranial cavity, kidney and retroperitoneum [117, 118, 120, 122]. For MFH, clinical group III (macroscopic residual disease) or IV (distant metastases), tumor invasion and size >5 cm were associated with a worse prognosis [117]. The 5-year survival and event free survival (EFS) estimates for patients with MFH is 76.5 % ± 11.2 % and 70.6 % ± 12.1 %, respectively. The 5-year survival and EFS estimates were both 100 % ± 0 % for patients with plexiform histiocytic tumor and angiomatoid fibrous histiocytoma [117]. Significant prognostic factors included the ability to resect with adequate margins, tumor size, and recurrence. The use of chemotherapy and radiation was not found to improve survival although this may be affected by patient selection with larger and more aggressive lesions receiving chemotherapy

and radiation. Prospective trials of preoperative and post operation radiation as well as adjunctive chemotherapy for high-grade lesions are ongoing.

Leiomyosarcoma

Malignant smooth muscle tumors are uncommon and are particularly rare in childhood. In a recent review of 1,175 extremity soft tissue sarcomas in children and young adults, only 25 cases of leiomyosarcoma were identified) [67]. Only 0.9 % of leiomyosarcoma cases occur in patients less than 20 years old [3], and the incidence is 0.3 per 1 million persons age less than 20 years in the United States [2].

In children and young adults, the most common site of presentation is intra-abdominal followed by extremities, trunk and head and neck [3]. However, there are reports of tumors occurring in the oral cavity [123], parotid gland [124], esophagus [125], heart [126, 127], lung [128–130], pancreas [131], and mesentery [132]. There are several reports of a link between EBV and leiomyosarcoma in children with acquired immunodeficiency syndrome [133–135]. It is also known to occur as a second malignancy, most commonly occurring in a prior radiation field [136]. Hereditary retinoblastoma is a known risk factor for the development of secondary neoplasms [137]. Although the most common soft tissue secondary malignancy in patients with a history of hereditary retinoblastoma is osteosarcoma, there are several reports of leiomyosarcoma developing both within and outside the field of prior radiation [136, 138]. These include several cases of patients with leiomyosarcoma of the urinary bladder [139, 140].

Complete surgical resection is the mainstay of treatment for leiomyosarcoma, and the role of adjuvant chemotherapy and radiation therapy is not well established [141, 142]. The Soft Tissue Sarcoma Italian Cooperative Group reported a 5-year EFS and OS of 56 % and 73 %, respectively, in 16 pediatric patients with leiomyosarcoma [142]. Late recurrences are known to occur and often lead to death [141]. Thus, long-term follow-up and surveillance is mandatory.

Liposarcoma

Although liposarcoma is one of the most common malignant soft tissue tumors in adults, it is exceedingly rare in the pediatric population accounting for less than 3 % of all pediatric sarcomas. The incidence in the United States is 0.1 per 1 million persons less than 20 years old [2]. Alaggio and colleagues published one of the largest case series in a review of 82 less than 22 years old diagnosed with liposarcoma between 1997 and 2007 [143].

Liposarcomas may occur in any location but most commonly present on the extremities and trunk (Fig. 20.1) [3]. They may be divided into the following histologic subtypes: conventional myxoid and round cell liposarcoma, spindle cell myxoid liposarcoma, pleomorphic myxoid liposarcoma, atypical lipomatous neoplasm and dedifferentiated liposarcoma, and conventional pleomorphic liposarcoma [143]. Liposarcoma is rare in children. The conventional myxoid and round cell, spindle cell myxoid and pleomorphic myxoid liposarcomas account for more than 90 % of cases in children and young adults [143]. Pure myxoid liposarcomas are characterized by a t(12;16)(q13;p11) translocation [2]. The most common sites are the lower extremity and trunk including the retroperitoneum, and most present with localized disease [3]. Metastases are present in less than 5 % of cases [3].

Complete surgical resection is the standard treatment for liposarcoma. In a multi-institutional review of 33 pediatric and young adult patients, complete surgical resection was the sole treatment modality for 13 patients (39 %) including 11 patients with myxoid tumors [144]. Surgical resection followed by adjuvant radiation therapy was used in 8 cases (24 %) and adjuvant chemotherapy in addition to surgery and radiation was used in 7 cases (21 %). The estimated 5- and 10-year OS for the entire cohort was 89 % and 64 %, respectively; however, patients with myxoid or well-differentiated histology fared better with 5-year OS 100 % versus 54 % for those patients with pleomorphic histology [144]. Alaggio and colleagues found similar excellent survival in patients with myxoid liposarcoma [143].

Malignant Peripheral Nerve Sheath Tumor (MPNST)

MPNST's primarily occur in adults and only 10 % of cases are diagnosed in the first two decades of life [3]. They account for 5 % of STS's in children and occur more commonly in children with neurofibromatosis type 1 (NF1) [3, 145]. They most commonly present with an enlarging soft tissue mass in the trunk, extremities or head and neck region, with or without pain and dysesthesia. A nerve of origin may be identified in 70 % of cases [146]. The most common primary site is the extremities followed by the trunk and head and neck [3, 146].

Approximately 40 % of MPNST's develop in a preexisting neurofibroma, most often occurring in patients with NF1 [146]. The association between MPNST and NF1 is well established [9, 147, 148]. NF1 is present in more than 40 % of pediatric patients with MSPNT, and the lifelong risk of patients with NF1 developing MPNST is estimated at 8–13 % [145, 149]. NF1, also called von Recklinghausen or peripheral neurofibromatosis, is a relatively common autosomal dominant disorder with an incidence of approximately

1 in 3,000 live births [9]. The syndrome is characterized by learning disabilities, multiple café-au-lait spots, axillary or inguinal freckling, neurofibromas, iris hamartomas, and bony lesions [145, 150]. MPNST's usually occur at an earlier age in patients with NF1 than in patients without the syndrome. In a recent study, the median age at diagnosis was 27 years for patients with NF1 compared to 40 years in patients without NF1 [151].

Surgical resection is the mainstay of treatment for MSPNT and the role of adjuvant chemotherapy and radiation remains unclear. However, a recent international review of 167 pediatric patients with MSPNT assessed the value of chemotherapy and radiotherapy in the treatment of these patients [146]. In this study, chemotherapy was administered to 74 % of patients and radiotherapy to 38 %. The estimated 5-year OS and progression-free survival (PFS) was 51 % and 37 %, respectively. A multivariate analysis identified absence of NF1, tumors confined to the organ or tissue of origin, IRS groups I and II, and extremity primary as independent favorable predictors for OS. A trend toward benefit of radiation therapy after initial resection was observed, and the overall response rate to primary chemotherapy for group III patients was 45 %. However, the rate of response to chemotherapy was significantly lower in NF1 patients (17.6 % versus 55.3 %) [146].

Synovial Sarcoma

Although rare, synovial sarcomas are the most common NRSTS diagnosed in children and adolescents and account for 8 % of STSs in this population with an age-adjusted incidence of 0.7 per 1 million [2, 3]. It is exceedingly rare in young children with the majority of cases diagnosed in the second decade. It is slightly more common in males, and 75 % of patients present with an extremity primary [3].

Despite its name, synovial sarcoma does not arise from synovial tissues but may occur anywhere in the body (Fig. 20.2). They are malignant, high-grade, soft tissue neoplasms that may be subdivided into monophasic, biphasic and poorly differentiated subtypes. It is a clinically, morphologically, and genetically distinct sarcoma characterized by a specific chromosomal translocation t(x;18)(p11.2;q11.2) which is found in all morphologic subtypes [152, 153]. Approximately 10 % of patients present with distant disease [3], and the lung is the most common site of distant metastases. However, unlike most other NRSTS, synovial sarcoma may spread to regional lymph nodes [154] with 23 % presenting with regional disease [3].

The most important aspect of treatment is surgical resection with negative histological margins. In addition, sentinel lymph node biopsy should be considered given the incidence of nodal disease at presentation [155, 156]. Radiation therapy is indicated after incomplete surgical resection and may also be used preoperatively to facilitate complete surgical resection [157, 158]. In a pooled analysis of pediatric NRSTS from the United States and Europe, Ferrari and colleagues showed the use of radiotherapy to correlate with better survival after incomplete resection but it offered no benefit after complete resection [159]. In a retrospective review of 219 children and adolescents with synovial sarcoma, radiation therapy was independently associated with improved overall survival and event-free survival as well as decreased time to local recurrence [160]. However, it is important to consider the long-term effects of radiation therapy especially for young children. Several studies show minimal benefit of radiation therapy for patients with IRS group I and even IRS group II tumors with small tumor size [161, 162].

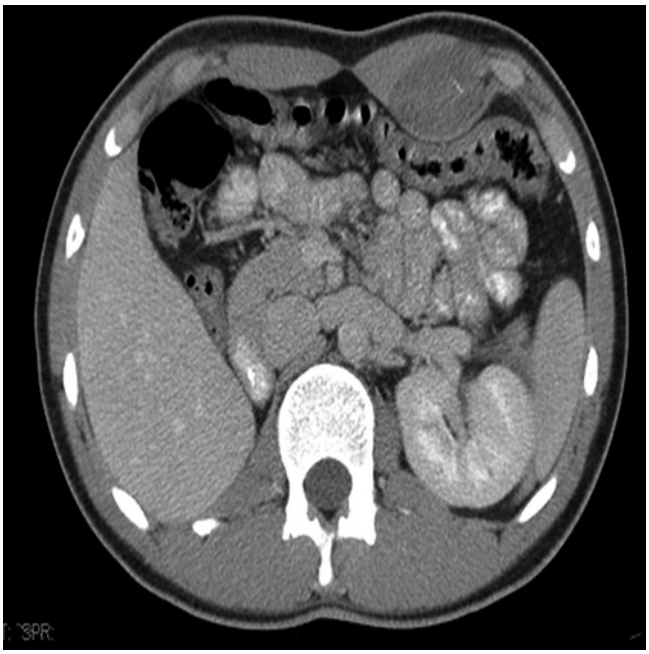

Fig. 20.2 A 16 year-old boy presented with a painless bump on his left abdominal wall. A CT abdomen (shown here) demonstrates a 5.1×3.2 cm anterior abdominal wall mass. He underwent incisional biopsy followed by complete resection for synovial sarcoma

Although synovial sarcoma is considered more chemo sensitive than many other NRSTS, the role of adjuvant chemotherapy remains controversial. In 1993, a German prospective trial suggested benefit of multi-agent chemotherapy and radiation therapy in the treatment of children and adolescents with synovial sarcoma [163]. However, Okcu and colleagues showed no significant differences in outcome between patients treated with or without chemotherapy for all patients with localized disease [160]. In the results of the pooled analysis from the US and Europe, major and minor responses to chemotherapy were seen in 40 % and 19 % of the 107 patients with synovial sarcoma, respectively [159]. In addition, survival was significantly better for patients who

had a major response to chemotherapy and/or received a complete tumor resection [159].

The estimated 5-year cancer-specific survival for children and adolescents with synovial sarcoma is 83 % compared to 62 % for adults [60]. Other important factors that influence overall and event-free survival include tumor size, invasiveness, IRS group, and primary site [60, 158, 160–162, 164]. Several studies show tumor size >5 cm to predict a worse event-free and overall survival [60, 158, 164]; however, other studies suggest tumor invasiveness is the more important factor predicting event-free and overall survival [160–162]. Axial sites, especially head and neck, are associated with a worse prognosis than extremity synovial sarcoma [160, 161, 164]. Ferrari and colleagues evaluated salvage rates and prognostic factors after relapse in 118 children and adolescents with initially localized synovial sarcoma [165]. Relapse occurred in 44 cases (37 %) with local relapse in 15 and metastatic in 29. Overall survival was 29.7 % and 21 % 5 and 10 years after relapsing, respectively, and was influenced by the timing and type of relapse as well as the chance of secondary remission [165]. Thus, it is important to consider surgical resection of locally recurrent and metastatic disease if complete resection is achievable. Late recurrences may occur and therefore, follow-up is recommended every 2 months for 1 year, then every 6 months for 2 years and every year thereafter.

Rhabdomyosarcoma

Epidemiology

Rhabdomyosarcoma (Greek for *rhabdos*, "rod"; mys, "muscle"; sarkos "flesh") is a primary malignancy in children and adolescents that arises from embryonic mesenchyme with the potential to differentiate into skeletal muscle. Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma accounting for approximately 60 % of soft tissues sarcomas in children and adolescents [3]. It is the third most common extra cranial solid tumor of childhood after neuroblastoma and Wilms' tumor. The annual incidence in children and adolescents (<20 years of age) is 4.4 per million children with approximately 350 new cases per year in the United States [166]. There is a slight male predominance (1.4:1), and it occurs more commonly in Caucasians than non-Caucasians (3.6:1) [166]. The median age at diagnosis is 7 years and most (62 %) are younger than 10 years of age [166].

Thirty percent of RMS patients have an associated congenital anomaly with genitourinary, central nervous system and gastrointestinal anomalies being the most common [167]. Although most cases of RMS occur sporadically, the disease is associated with familial syndromes. Neurofibromatosis-1 (NF-1), Rubinstein-Taybi syndrome, Beckwith-Wiedemann syndrome, Costello syndrome, Noonan syndrome, and Gorlin basal cell nevus syndrome have all been described in children with RMS [167–170]. Li-Fraumeni syndrome, a hereditary cancer syndrome first described in 1969, is an autosomal-dominant disorder usually associated with a germline mutation of p53 [13, 167, 171–173]. Li-Fraumeni syndrome is defined as the following: (1) a person diagnosed with sarcoma before the age of 45, and (2) a first degree relative diagnosed with any cancer before age 45, and (3) a first degree or second degree relative diagnosed with any cancer before age 45 or diagnosed with sarcoma at any age. Patients with this syndrome often present with RMS at an early age and have a family history of cancers including breast cancer, brain tumors, leukemia, adrenal cortical carcinoma, soft tissue and bone sarcomas.

Although no specific carcinogens have been identified that cause RMS, the use of marijuana or cocaine during pregnancy may be environmental factors that contribute to the pathogenesis of RMS. Other associations including fetal alcohol syndrome and maternal exposure to radiation have been suggested [174, 175]. A recent study examined the correlation between birth weight and the risk of RMS showing that high birth weight and large size for gestational age increased the risk of RMS [176].

Pathology

RMS is a highly malignant mesenchymal tumor classified as a small, round, blue cell tumor of childhood, a category that also includes neuroblastoma, Ewing's sarcoma, small cell osteogenic sarcoma, non-Hodgkin's lymphoma and leukemia. A combination of light microscopy, immunohistochemical techniques, electron microscopy, and molecular genetic techniques is useful in determining the tumor type. In RMS, light microscopy identifies cross-striations or characteristic rhabdomyoblasts [177, 178]. Immunohistochemical studies including staining for muscle-specific myosin and actin, desmin, myoglobin, z-band protein and Myo-D, may also support the diagnosis of RMS [179, 180].

Six major pathologic subtypes of RMS are outlined by the International Classification of RMS (presented in order of decreasing 5-year survival): (1) embryonal, botryoid; (2) embryonal, spindle cell; (3) embryonal, not otherwise specified (NOS); (4) alveolar, NOS or solid variant; (5) diffuse anaplasia and (6) undifferentiated sarcoma [181]. Although the prognostic value of specific histologic subtypes has varied between studies, each subtype is generally associated with a prognostic group as shown in Table 20.3. There is controversy as to whether the histologic subtype or the site of tumor most strongly influences prognosis.

Each of the two major subtypes of RMS, embryonal and alveolar, has a characteristic histological appearance. The

Table 20.3 International histopathologic classification for childhood rhabdomyosarcoma

Superior prognosis
Botryoid RMS
Spindle cell RMS
Intermediate prognosis
Embryonal RMS
Poor prognosis
Alveolar RMS
Diffuse anaplasia
Undifferentiated sarcoma

embryonal subtype is the most common subtype in children accounting for 68 % of all RMS in children and adolescents <20 years of age [166]. Although they may occur in any site, embryonal RMS typically arise in the head and neck region or genitourinary tract. The botryoid subtype represents 10 % of all RMS and is associated with an excellent 5-year survival rate (95 %). This subtype occurs in hollow organs arising under the mucosal surface of body orifices such as the vagina, bladder, nasopharynx and biliar tract. It is characterized on gross examination as resembling a "cluster of grapes." The spindle-cell subtype arises most often in the paratesticular region but may also occur in the head and neck, especially the orbit, and the extremities [181, 182].

The alveolar subtype accounts for 31 % of all RMS and most frequently arises in the extremities, trunk and perineum [166]. This subtype is seen more often in adolescents and is associated with a poor prognosis [183]. The alveolar variant is characterized by a prominent alveolar arrangement of stroma and dense, small, round tumor cells resembling lung tissue. To be designated as alveolar, the tumor must have greater than 50 % alveolar elements otherwise it is considered embryonal.

Pleomorphic RMS typically occurs in adults >45 years of age and is rarely seen in children. In adults, it is associated with a very poor prognosis. In children, pleomorphic RMS is often not pure and may be accompanied by embryonal type histologic foci [184]. In children, these tumors are most often classified as anaplastic [185]. These tumors account for only 1 % of RMS in children and adolescents [166]. Undifferentiated sarcoma is a poorly defined category of sarcomas whose cells show no evidence of myogenesis or other differentiation [181, 182].

Molecular Biology

The two histologic subtypes of RMS, embryonal and alveolar, have distinct genetic alterations that are useful in diagnosis and may play a role in the pathogenesis of these tumors. In approximately 80 % of cases, embryonal RMS is characterized by loss of heterozygosity (LOH) at the 11p15 locus. This is the location of the insulin-like growth factor-2 (IGF-II) gene and LOH results in overexpression of the gene [186]. IGF-II has been shown to stimulate the growth of rhabdomyosarcoma cells, whereas the blockade of this factor using monoclonal antibodies inhibits tumor growth both in vitro and in vivo [177]. Several other solid tumors are associated with genomic deletions on the short arm of chromosome 11, including Wilms' tumor, hepatoblastoma, and neuroblastoma.

In approximately 80 % of alveolar RMS, a unique translocation occurs between the *FKHR* gene (a member of the forkhead family of transcription factors) on chromosome 13 and either the *PAX3* gene on chromosome 2, t(2;13)(q35;q14), or the *PAX7* gene on chromosome 1, t(1;13)(p36;q14) [187]. *PAX3-FKHR* is more common than *PAX7-FKHR* fusion (59 % versus 19 %) and is associated with a worse overall survival [188]. *PAX3-FKHR* fusion occurs in older patients and is associated with a higher incidence of invasive tumor [189]. Polymerase chain reaction (PCR) assays are now available that allow confirmation of the diagnosis of alveolar RMS based on the presence of these fusion genes [187, 190–192]. However, approximately 20 % of alveolar RMS are translocation negative and by gene array analysis, these fusion negative tumors more closely resemble embryonal RMS with a similar prognosis [193, 194]. Thus, it has been proposed that RMS should be divided into *PAX-FKHR* fusion-positive and – negative tumors rather than alveolar and embryonal histologies. In future COG studies, RMS tumors will risk classify based on fusion status, instead of histologically.

Clinical Presentation

The clinical presentation of RMS is variable and depends on the tumor site, patient age and the presence or absence of metastases. Although adults most commonly present with extremity tumors, RMS may occur in any site in the body except bone. In children and adolescents, the most common sites are the head and neck and the genitourinary tract, with only 20 % of cases occurring in the extremities. Most symp-

toms are secondary to local mass affect and are specific to the primary tumor location. Thirty-five percent of RMS occurs in the head and neck region, 22 % in the genitourinary tract and 14 % in the extremities [166]. The presentation for each primary site will be discussed later in the chapter. There are no classic paraneoplastic syndromes associated with RMS. More than 60 % of patients present with advanced disease including 36 % with regional disease and 30 % with distant metastases [166]. Isolated lung metastases are unusual and should be biopsied to prove disease.

Neonatal presentation of RMS is extremely rare with only 14 cases (0.4 % of patients in IRS I-IV) reported in the literature [195]. They tend to be embryonal botryoid or undifferentiated histology. Children <1 year old accounted for only 6 % of cases in SEER registry data [166].

Diagnosis

The diagnosis of rhabdomyosarcoma usually is made by direct open biopsy. Initial biopsy is generally incisional except in small lesions in which case excisional biopsy is possible. It is important to recognize that the tumor may have a pseudocapsule and if the lesion is "shelled out," the surgeon may have a false notion that the tumor was completely excised. An incisional biopsy requires that the biopsy tract be excised at the time of resection. Therefore, it is imperative that careful thought be used in deciding the orientation of the biopsy incision. Extremity lesions should be biopsied through a longitudinal incision only (Fig. 20.3).

If an excisional biopsy is performed, surgical margins should be carefully marked to allow re-resection if the biopsy results reveal a positive margin. If biopsy margins are not carefully marked on the specimen and the resection bed (usually by sutures or clips), the ability of the surgeon to subsequently obtain negative margins at the time of re-resection is severely compromised. Several grams of tissue are required for histologic and cytologic diagnosis and classification, and therefore, open biopsy is preferred.

Prior to definitive surgery, a full evaluation including imaging, laboratory studies, and bone marrow evaluation should be performed (Table 20.4). Standard laboratory studies include complete blood counts, electrolytes, renal function tests, liver function tests and urinalysis. Imaging of the primary tumor should be performed with either Cat Scan (CT) or MRI depending on the primary tumor site. MRI is preferable for extremity, pelvic and paraspinal tumors whereas CT is valuable for the evaluation of bone erosion and abdominal lymphadenopathy [196].

Evaluation of regional and distant lymph nodes by clinical and radiographic studies (CT or MRI) should be performed. A CT of the abdomen and pelvis should be performed for all lower extremity and genitourinary primary tumors.

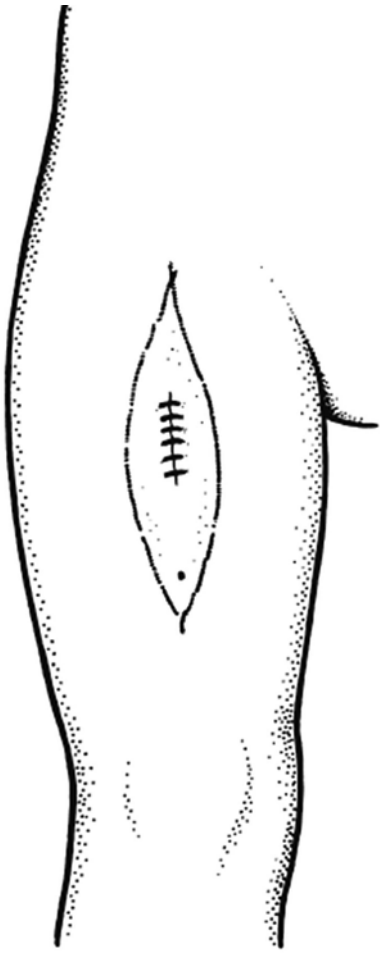

Fig. 20.3 Longitudinal biopsy incision with outline of WLE if necessary

Table 20.4 Diagnostic and preoperative evaluation

History and physical examination
Laboratory studies (cbc/differential, LFTs, electrolytes, creatinine, urinalysis)
CT or MRI of primary tumor
CT chest
Bone marrow biopsy and aspiration
Bone scan
CT abdomen and pelvis (for lower extremity and genitourinary tumors only)
MRI head (for parameningeal tumors only)
Lumbar puncture for CSF cytology (for parameningeal tumors only)
EKG or echocardiogram (selective)

The use of FDG-PET has been widely used in the adult population with sarcoma to determine extent of disease [197, 198]. However, the experience with FDG-PET in children is limited [199–201]. This modality may prove useful in the clinical determination of the extent of disease and improve pretreatment staging thus altering treatment for patients (Fig. 20.4) [196].

Evaluation for metastatic disease includes a bone marrow biopsy and aspirate, bone scan, CT chest, and lumbar puncture for cerebrospinal fluid collection (for parameningeal tumors only).

Pretreatment Staging, Clinical Grouping, and Risk Group Classification

RMS staging is determined by the site and size of the primary tumor, the degree of tumor invasion, nodal status, and the presence of absence of metastases. The staging of RMS is complex and requires three steps:

1. Assigning a pretreatment stage.
2. Assigning a local tumor surgical-pathologic group.
3. Assigning a risk group.

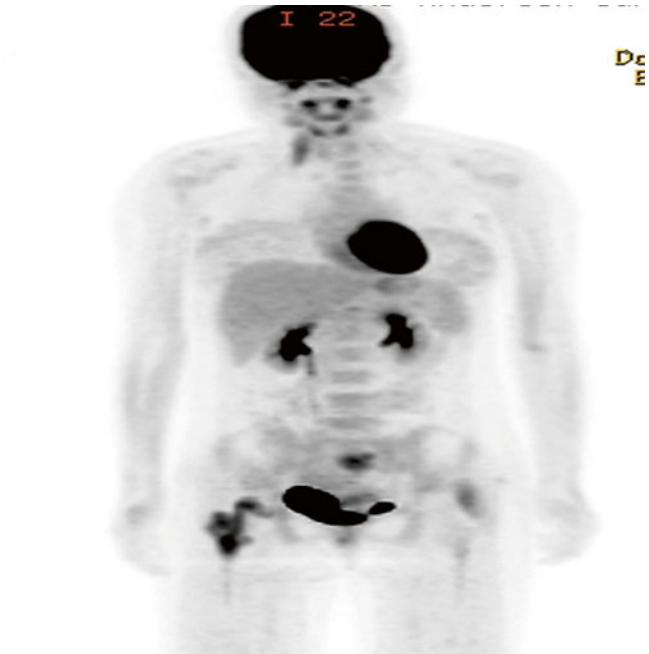

Fig. 20.4 A 18 year-old girl presented with metastatic alveolar RMS. PET CT showed multiple metabolically active sites of metastases including a metastasis in the right proximal femur with extension into the surrounding soft tissues

The Children's Oncology Group Soft Tissue Sarcoma Committee (COG-STS) protocols for RMS use a TNM-based pretreatment staging system that incorporates surgical-pathologic group, primary tumor site, tumor size, regional lymph node status, and the presence or absence of distant metastases (Table 20.5) [202, 203]. The genitourinary tract, biliary tract, nonparameningeal head and neck and orbit are considered favorable primary tumor sites. All other sites are considered unfavorable (Table 20.6). The pretreatment staging system is used to stratify the extent of the disease for different treatment regimens as well as compare outcomes for patients receiving protocol-based treatment.

The extent of residual disease after resection is an important prognostic factor for RMS. The surgical-pathologic or clinical group is based on the completeness of surgical resection and the presence or absence of lymphatic or distant spread after pathologic examination of the surgical specimens (Table 20.7). The clinical group was developed by the Intergroup Rhabdomyosarcoma Group (IRS), and used in the IRS-1, IRS-II and IRS-III studies as the basis for treatment assignment. This is a postsurgical staging system and provides an important adjunct to the pretreatment staging system. However, it does not take into account the biological nature or natural history of the tumor.

The COG-STS developed a risk-stratification system that incorporates pretreatment stage and clinical group in order to classify patients as low, intermediate or high risk (Table 20.8). The treatment assignment in current COG-STS protocols for RMS is based on risk group. This system reliably predicts

Table 20.5 TNM pretreatment staging classification for rhabdomyosarcoma

Stage	Sites	T	Size	N	M
1	Favorable sites	T_1 or T_2	a or b	N_0 or N_1 or N_x	M_0
2	Unfavorable sites	T_1 or T_2	a	N_0 or N_x	M_0
3	Unfavorable sites	T_1 or T_2	a	N_1	M_0
–	–	–	b	N_0 or N_1 or N_x	M_0
4	Any site	T_1 or T_2	a or b	N_0 or N_1 or N_x	M_1

T_1 Tumor confined to anatomic site of origin, T_2 Tumor extension and/or fixed to surrounding tissues, a ≤ 5 cm, b > 5 cm, N_0 Regional nodes not clinically involved, N_1 Regional nodes clinically involved by tumor, N_x Clinical status of regional nodes unknown, M_0 No distant metastases, M_1 Metastasis present

Table 20.6 Favorable and unfavorable anatomic sites for rhabdomyosarcoma

Favorable sites	Unfavorable sites
Orbit	Any site other than favorable
Nonparameningeal head and neck	–
Genitourinary (other than kidney, bladder and prostate)	–
Biliary tract	–

Table 20.7 Clinical grouping for patients with rhabdomyosarcoma

Clinical group	Definition
I	Localized disease, complete resection, negative margins, no regional lymph node involvement
II	Localized disease, grossly removed with microscopic disease at the margin and/or grossly removed but involved regional lymph nodes
III	Localized disease with gross residual disease after incomplete resection or biopsy only
IV	Distant metastasis present at diagnosis

Table 20.8 Rhabdomyosarcoma risk group classification

Risk group	Histology	Pretreatment stage	Clinical group
Low risk	Embryonal	1	I, II, III
–	Embryonal	2, 3	I, II
Intermediate risk	Embryonal	2, 3	III
–	Alveolar	1, 2, 3	I, II, III
High risk	Embryonal or Alveolar	4	IV

patient outcomes and allows correlation between intensity of therapy and outcome.

Treatment

Prior to the introduction of radiation and chemotherapy, surgical resection was the only treatment option for patients with RMS and radical, often mutilating, excision was the standard approach to these tumors. Survival rates were overall poor and ranged from 7 to 70 % depending on the site of disease [204]. In 1950, Stobbe and colleagues demonstrated improvement in outcome in head and neck sites when radiation therapy was added after incompletely resected RMS [205]. In 1961, Pinkel and Pinkren advocated adjuvant chemotherapy and radiation after complete surgical resection [206]. These early studies marked the beginning of the multimodal approach to solid tumors.

Recognizing the value of multimodality therapy and the rarity of these tumors, the first Intergroup Rhabdomyosarcoma Study Group (IRSG) was established in 1972 to investigate the therapy and biology of RMS and undifferentiated sarcoma in previously untreated patients less than 21 years of age. Since then, the IRSG conduced five successive clinical protocols involving almost 5000 patients between 1972 and 1997: IRS-I, 1972–1978; IRS-II, 1978–1984; IRS-III, 1984–1991, IRS-IV Pilot (for patients with advanced disease only), 1987–1991; IRS IV, 1991–1997 [1, 2, 12, 17, 24, 25, 207]. The results from these studies formed the foundation for IRS-V which opened in 1997 and used the concept of risk stratification to conduct separate studies based on clinical and biologic prognostic factors. In 2000, the Children's Oncology Group was established, and the work of the IRSG was continued by the COG Soft Tissue Sarcoma (COG-STS) committee [208].

The approach to the treatment of RMS has been multimodal for more than 30 years. The surgical treatment of the disease has been progressively less mutilating and less aggressive while maintaining excellent survival as seen in earlier studies.

Surgical Treatment

Primary Resection

The primary goal of surgical treatment for RMS is complete resection of the primary tumor with a surrounding rim of normal tissue. The prognosis for patients with RMS is closely linked to the amount of residual disease present after resection, and complete tumor resection, with no microscopic residual disease, offers the best chance for cure. The surgical approach depends on primary tumor site, size, presence or absence of lymph node involvement and distant metastases. The surgical treatment of RMS is site-specific; however, the general principles include complete wide excision of the primary tumor and surrounding uninvolved margins while preserving cosmesis and function. There is little data to support the minimal size of the circumferential margin but 0.5 cm is considered adequate [196]. Adequate margins of uninvolved tissue are required unless excision would compromise adjacent organs, result in loss of function, poor cosmesis, or are not technically feasible.

The margins should be marked and oriented at the operative field to allow precise evaluation by the pathologist. If a positive margin is suspected, intraoperative biopsies should be performed around the resection margin to establish a negative microscopic margin. Unresectable microscopic or gross residual disease should be marked with titanium clips in the tumor bed to direct radiotherapy and guide future re-excision.

A pre-treatment re-excision (PRE) is recommended in the following situations: (1) if only a biopsy was performed of a resectable tumor, (2) a non-oncologic operation was per-

formed, or (3) the status of the margins is unclear. A PRE consists of complete wide re-excision of the prior operative site with pathologically confirmed negative margins. PRE is performed prior to initiation of adjuvant therapy. Patients who undergo PRE with complete excision (clinical group 1) have a similar outcome to patients who are clinical group 1 after initial resection [209].

Lymph Node Evaluation

Lymph node status is an important prognostic factor in RMS and directly impacts risk-based treatment strategies. Approximately 1/3 of patients present with regional nodal disease [166], and positive lymph node status is an independently poor prognostic factor for both failure-free survival and overall survival [210, 211]. Thus, it is imperative that regional lymph nodes be assessed both clinically and radiographically. Any suspicious lymph node requires pathologic confirmation. In addition, RMS patients with extremity tumors, primary tumors of the perineum and paratesticular tumors in children>10 years old should undergo routine surgical evaluation of regional lymph nodes even if there is no clinically or radiographically suspicious disease [212–214]. These sites are associated with a high incidence of nodal disease and false-negative imaging and therefore, pathologic evaluation of the regional nodal basin is required. If the regional lymph nodes are involved, distal nodes must be sampled to determine metastatic disease. However, complete lymph node removal has no therapeutic benefit [215].

Sentinel lymph node biopsy allows adequate, and possibly superior, staging compared to traditional lymph node sampling while limiting operative morbidity [64, 213]. Sentinel lymph-node mapping uses a vital dye such as Lymphazurin® blue along with radio labeled technetium sulfur colloid to localize the regional node(s) most likely to contain metastatic foci [64]. The surgeon removes the sentinel node and the pathologist determines whether the sentinel node contains tumor cells. The sentinel node reflects the status of the nodal basin and therefore, if the sentinel node is positive, the nodal basin is irradiated. Sentinel lymph node biopsies are now part of the required evaluation for extremity RMS patients enrolled on COG studies.

Second Look Operation

It is common that the size, invasion and location of primary RMS tumors prohibit complete resection. Following initial adjuvant therapy with intensive multi-agent chemotherapy with or without radiation, repeat imaging with CT or MRI is performed. If residual tumor is present on imaging or the outcome of therapy is questionable, a second look operation should be considered [216, 217]. Similar to the initial resection, the primary goals of a second look operation is to remove any residual tumor and achieve a complete resection without compromising function or cosmesis. The use of second look operations was evaluated in IRS-III and found to be beneficial for clinical group II patients [218–221]. Second look operations resulted in reclassification of 75 % of partial responders to complete responders after excision of residual tumor, and 12 % of complete responders were found to harbor residual tumor. Thus, imaging studies are not always reliable in determining response to therapy. The survival rate of complete responders and those reclassified from partial responders to complete responders was similar [220, 221]. Second look operations were most effective in extremity and truncal tumors and least useful for head and neck tumors.

The second look operation will also determine the pathologic response to initial therapy prior to administering additional therapy. In IRS-IV, patients with viable tumor present at the second look operation had shorter event-free survival rates than those without viable tumor; however, there was no difference in overall survival [222]. Second look surgery is much less beneficial in children with metastatic disease.

Surgical Treatment of Recurrent and Metastatic Disease

Despite success in primary treatment of RMS, survival after relapse remains very poor. Approximately 30 % of RMS patients develop relapse, and 50–95 % of relapsed patients ultimately die of progressive disease [223]. There is little evidence that surgical resection contributes to improved survival in relapsed RMS. A report from MD Anderson Cancer Center suggests that resection of recurrent RMS confers a 5-year survival of 37 % compared to 8 % survival in patients without aggressive resection; however, the study is limited by a small sample size and the inherent biases associated with a retrospective study design [224]. It is recommended that treatment for locally recurrent disease be determined according to risk stratification. For relapsed patients with more favorable disease, intensive multi-agent chemotherapy followed by radiation and/or surgical resection is appropriate. For patients with less favorable disease, initial dose-intensified chemotherapy and maintenance chemotherapy or experimental therapies may be offered [223].

Metastatic disease most commonly involves the lung (58 %), bone (33 %), regional lymph nodes (33 %), liver (22 %), and brain (20 %) [225]. The role of surgery in the treatment of metastatic disease remains unclear [226]. Primary resection of metastatic disease at diagnosis is rarely indicated. In IRS-IV, 24 % of patients developed isolated lung metastases. A diagnostic biopsy followed by intensive salvage multimodality therapy was used for most of these patients. There was no survival advantage for biopsy confirmed versus radiographically diagnosed lung metastases [226]. The European multicenter, multinational, study group recently reviewed four consecutive trials to determine the impact of local control of pulmonary metastases in patients with metastatic embryonal RMS limited to the lungs [227].

The group reported a 38 % 5-year event-free survival for the entire cohort and did not identify any survival benefit for local control of pulmonary metastases [227].

Chemotherapy

Currently, all patients with RMS receive chemotherapy and the intensity and duration of chemotherapy are dependent on the risk group classification (Table 20.3). Standard therapeutic regimens consist of a combination of vincristine (V), actinomycin D (A), and cyclophosphamide (C) commonly referred to VAC. Other agents with known activity against RMS include doxorubicin (Dox), ifosfamide (I), and etoposide (E). Although significant advancement has been made in improving outcomes of patients with local and regional disease, little improvement has been seen in children with advanced RMS. This is primarily due to the failure of new chemotherapy agents and protocols to improve significantly upon the standard treatment regimens.

VAC has been the gold standard for combination chemotherapy in the treatment of most cases of RMS. Large randomized cooperative trials have allowed for modifications of this combination of agents tailored to specific subgroups according to clinical group and site of disease. A recent COG trial (COG-D9602) stratified patients with low risk embryonal RMS into two groups: subgroup A (Stage 1 Group I/IIA, Stage 2 Group I, and Stage 1 Group 3 orbit only) and subgroup B (Stage 1 Group IIB/C, Stage 1 Group III non-orbit, Stage 2 Group II, and Stage 3 Group I/II disease) [228]. Subgroup A patients received VA with or without radiation and subgroup B received VAC and a reduced dose of radiation. The 5-year overall failure free survival and overall survival were 88 % and 97 %, respectively, for subgroup A, and 85 % and 93 %, respectively, for subgroup B. Thus, two - or three-drug regiments (VA and VAC) with and without radiation therapy are considered standard treatment for specific subgroups of low-risk patients.

The standard chemotherapy combination for children with intermediate risk RMS is VAC. In IRS-IV, intermediate risk patients were randomized to receive either standard VAC or one of two other chemotherapy regimens with ifosfamide as the alkylating agent [229]. The outcomes for both groups were similar and standard VAC treatment was easier to administer [229]. Although cyclophosphamide and topotecan demonstrated substantial activity in patients with recurrent disease and newly diagnosed patients with metastatic RMS, there was no benefit for the addition of these drugs in patients with intermediate risk RMS [230, 231]. In certain intermediate risk patients, dose intensification using known active chemotherapeutic agents should be considered. A comparison of patients treated on IRS-IV with higher doses of cyclophosphamide compared to patients treated on IRS-III with lower doses of cyclosphosphamide suggested some benefit of higher doses in certain groups of intermediate risk patients [232]. These included patients with tumors at favorable sites and positive lymph nodes, patients with gross residual disease and patients with tumors at unfavorable sites with complete gross resection. Dose intensification was not beneficial for patients with unresected embryonal RMS at unfavorable sites [233]. Dose intensification of vincristine and actinomycin-D is not possible due to neurotoxic and hepatotoxic effects [196].

High risk patients have metastatic disease at presentation. These patients have a very poor prognosis despite aggressive therapy. The standard treatment for children with metastatic RMS is VAC. Despite many clinical trials attempting to improve outcome by the addition or substitution of new agents to the standard VAC regimen, no chemotherapy regimens have been more effective than VAC in the treatment of metastatic RMS [196, 234–239]. High-dose chemotherapy followed by autologous stem cell transplant for metastatic RMS fails to offer benefit [240, 241].

Radiotherapy

Radiotherapy is an important component of the multimodality treatment approach in RMS and has improved both local control and outcome for patients with the disease. It is an effective method for achieving local control in patients with microscopic or gross residual disease following biopsy, surgical resection or chemotherapy. In a recent review of patients with microscopic residual disease, local recurrence was due to noncompliance with guidelines or omission of radiation therapy (RT) in more than 50 % of group II patients [242].

RT is tailored for specific sites and extent of disease, but in general, all patients except those with group I embryonal tumors, receive RT. Several prior studies evaluated the radiation dose and method of administration necessary to achieve local control of the tumor [243–245]. Current radiation doses range from 36 to 50 Gy, and the dose depends primarily on the amount of residual disease following primary surgical resection. In patients with group II disease, low dose radiation (40 Gy) is associated with local control rates of ≥90 % [244]. For patients with gross residual disease (group III), radiation doses are usually higher (40–50 Gy). There is no benefit to hyperfractionated RT (59.4 Gy) compared to conventional, once-daily RT (50.4 Gy) [243].

The radiation treatment volume should be determined prior to surgical resection of the primary tumor and is based upon the extent of tumor at diagnosis. A margin of 2 cm is recommended and should include clinically involved regional lymph nodes [245]. In general, multiagent chemotherapy is given for 1–3 months prior to RT followed by 5–6 weeks of RT during which time chemotherapy is modified to avoid radio sensitizing agents such as doxorubicin and actinomycin-D.

RT in very young patients is especially challenging given the long-term sequela associated with RT [246]. The late effects are site-dependent. In the head and neck region, xerostomia, dental problems, facial growth retardation, neuroendocrine dysfunction, and vision and hearing loss may occur [247, 248]. For abdominal and pelvic sites, bowel obstruction and infertility as well as growth retardation are a concern [249]. Extremity RT is associated with fractures, growth retardation, fibrosis, atrophy and peripheral nerve damage [250]. However, the greatest long-term impact of RT may be its association with late secondary malignancies [251].

Thus, it is important to consider techniques that allow delivery of radiation specifically to the tumor while minimizing radiation to surrounding tissues. These techniques include conformal RT, intensity-modulated RD (IMRT), proton-beam RT, and brachytherapy. All of these techniques have been studied in the treatment of RMS. In conformal RT, a computer generates a 3-dimensional image of the tumor and allows the radiologist to administer higher doses of radiation to the tumor while sparing surrounding tissues [252]. IMRT uses computer-controlled linear accelerators to deliver precise radiation doses specifically to the tumor or areas within the tumor [253]. Proton-beam therapy targets tumor cell with streams of charged particles that have very little lateral dispersion and therefore significantly limit damage to surrounding tissues [254, 255]. Brachytherapy, using either intracavitary or interstitial implants, allows local delivery of RT and has been used in the treatment of head and neck, vaginal and vulvar, and select bladder and prostate RMS [256–259].

Management by Site

Head and Neck

Head and neck RMS accounts for 35 % of childhood RMS and the incidence is increasing with an annual percentage change of 1.16 % between 1973 and 2007 [260]. Head and neck RMS is divided into three subtypes: orbital, parameningeal (ear, mastoid, nasal cavity, paranasal sinuses, infratemporal fossa, and pterygopalatine fossa), and nonorbital nonparameningeal (oral cavity, larynx, parotid region, cheek, scalp and soft tissues of the neck). The orbit and nonparameningeal sites are considered favorable whereas nonparameningeal sites are unfavorable and associated with early recurrences and a poor prognosis.

Of head and neck RMS, 25 % occur in the orbit which is associated with a good prognosis [166, 260]. Orbital RMS usually presents in the first decade of life and boys are more commonly affected than girls [261]. The most common presenting symptoms are rapid onset and progression of proptosis and globe displacement [261]. However, the clinical presentation is dependent on the location of the tumor within the orbit and its rate of growth [261]. Although CT and MRI are important tools for preoperative planning and evaluating residual or recurrent disease, incisional biopsy is essential for definitive diagnosis. The majority of patients present with localized disease (61 %) with less than 10 % having metastatic disease [260]. Patients with localized orbital RMS have an excellent overall survival regardless of the extent of initial surgical resection with a 5-year overall survival rate of 89 % [251]. Thus, the mainstay of treatment for orbital RMS is a of combination chemotherapy and radiation therapy. Orbital exenteration is rarely performed and is confined to cases with recurrent disease [262].

While it is well established that complete surgical resection with negative margins offers the best chance for local control in patients with RMS, the multi-disciplinary approach to therapy has allowed less-aggressive surgical procedures while maintaining an excellent prognosis for most patients with head and neck RMS. When feasible, wide excision is indicated, however, it is often either not possible or would result in significant functional and/or cosmetic impairment. The possibility of achieving negative margins is usually restricted to small, superficial tumors [263]. After reviewing the literature, Gradoni and colleagues outlined an algorithm for the role of surgery in nonorbital head and neck RMS (Table 20.9) [264].

Table 20.9 The role of surgery in nonorbital head and neck RMS (Gradoni Surgical Oncology 2010)

Biopsy	All patients with suspected RMS
Primary surgical resection	For patients with alveolar RMS if Complete resection achievable No major functional or cosmetic consequences No high-risk features of meningeal involvement present
Surgical resection after primary chemoradiation	All patients with RMS in whom clinical and radiological re-staging shows resectable residual tumor.
Debulking surgery	Palliative and urgent situations only
Neck dissection	Alveolar RMS at the same time as surgical resection of primary tumor (not indicated for embryonal RMS)
Salvage surgery after locoregional relapse	Efficacy is limited but success reported for late relapses of embryonal RMS
Metastatectomy	Consider for limited pulmonary metastases

Parameningeal tumors account for 44 % of head and neck RMS and are associated with a poor prognosis compared to orbital and nonorbital, nonparameningeal head and neck RMS [260]. More than 50 % present with regional disease and 28 % present with metastases [260]. Paramenigeal tumors tend to recur locally and spread intracranially. High-risk features include intracranial extension, cranial base erosion, cranial nerve palsy and positive cerebrospinal fluid at cytology [265]. All patients with suspected parameningeal RMS should undergo MRI with contrast of the primary site followed by CT with contrast of the same region if skull erosion and/or transdural extension is equivocal on MRI (Fig. 20.5a, b). The cerebrosopinal fluid should be sent for cytology. For most parameningeal tumors, surgical resection is reserved for salvage for recurrent disease after chemoradiation or for tumors that fail to respond to chemoradiotherapy. Achieving negative margins is often difficult and possible in less than 50 % of cases [266]. Sentinel lymph node biopsy has been described as a useful tool in the staging of parameningeal RMS [267].

With intensive chemotherapy and hyperfractionated accelerated radiotherapy (HART), 5-year overall survival increased from 40 to 72 % in a series of 109 children with non-metastatic parameningeal RMS registered in the Associazione Italiana di Ematologiae Oncologia Pedaitrica (AIEOP) Soft Tissue Sarcoma Committee (STSC) protocols from 1975 to 2005 [268]. In this series, delayed surgery after initial chemoradiotherapy was associated with a better prognosis [268]. In a review of 611 patients with localized parameningeal RMS entered on IRS II-IV protocols, overall 5-year survival was 73 % and did not differ between protocol era [265]. Favorable prognostic factors included age <10 years, primary tumor in the nasopahrynx/nasal cavity, middle ear/mastoid or parpharyngeal areas ("better" sites) and no meningeal involvement [269]. Treatment was initial biopsy or surgical resection followed by multi-agent chemotherapy (vincristine, dactinomycin and cyclophosphamide) and radiation therapy [269]. Raney and colleagues also reviewed 91 patients with metastatic parameningeal RMS enrolled on IRS II-IV protocols [270]. They noted that tumors arising in "better" versus "worse" (infratemporal-pterygopalatine area) sites and embryonal versus other histology are associated with improved 10-year failure free survival [270]. In this series of patients with metastatic disease, estimated 10-year failure-free and overall survival was 32 % and 33 %, respectively [270].

Nonorbital, nonparameningeal sites include superficial and deep tumors that do not impinge on the meninges and account for approximately 30 % of head and neck RMS. The majority of patients present with either local (33 %) or regional disease (37 %) with only 20 % presenting with distant metastases [260]. If feasible, wide excision of the primary tumor and ipsilateral neck lymph node sampling of clinically involved lymph nodes is indicated [270]. Given anatomic constraints, narrow resection margins (<1 mm) are acceptable. Children and adolescents with localized nonorbital, nonparameningeal head and neck RMS entered on IRS III-IV protocols received a combination of vincristine and dactinomycin ± cyclophosphamide (VAC) with or without radiation therapy [32]. Five-year overall survival for these patients was 83 % [32].

In summary, modern protocols for head and neck RMS are comprised of chemotherapy and radiotherapy ± surgical resection depending on the primary site and extent of disease. Recently, a few reports have shown benefit with modern radiation therapy techniques including intensity modulated radiotherapy (IMRT), fractionated stereotactic radiotherapy (FSRT), and proton radiotherapy in the treatment of head and neck RMS [255, 271]. These modalities offer the advantage of delivery of high radiation doses to a defined target volume while sparing surrounding organs at risk. This may prove particularly beneficial in the pediatric population in whom conventional radiation therapy is often associated with long-term toxic effects.

Genitourinary Sites

Rhabdomyosarcoma is the most common malignancy of the pelvic structures in children usually affecting children age 2–4 and 15–19 years old. Approximately 22 % of RMS cases arise from genitourinary sites [166]. These sites include the bladder, prostate, paratesticular areas, vulva, vagina, uterus, and rarely, the kidneys or ureter. Vulvar, vaginal, uterine and paratesticular tumors are considered favorable sites and account for approximately 60 % of genitourinary RMS. Less common, bladder, prostate and kidney are considered unfavorable sites [166]. Embryonal histology accounts for 90 % of genitourinary RMS and has a more favorable prognosis than alveolar pathology (82 % versus 65 % 5-year EFS) [210]. The diagnostic and therapeutic management of genitourinary RMS depends on the primary site of disease.

Bladder and Prostate

Bladder and prostate RMS account for 2 % and 4 % of RMS patients, respectively. These tumors usually presents with gross hematuria, urinary retention or urgency and ultrasound may be the initial imaging modality performed. CT or MRI of the abdomen and pelvis determines the extent of the primary tumor and provides visualization of retroperitoneal lymph nodes. The majority of bladder and prostate RMS are embryonal histology (71 %) followed by botryoid (20 %) and alveolar (2 %) histologies [182].

The initial surgical approach is usually limited to biopsy. Biopsy may be performed cystoscopically but care must be taken to obtain adequate tissue for diagnosis and minimize

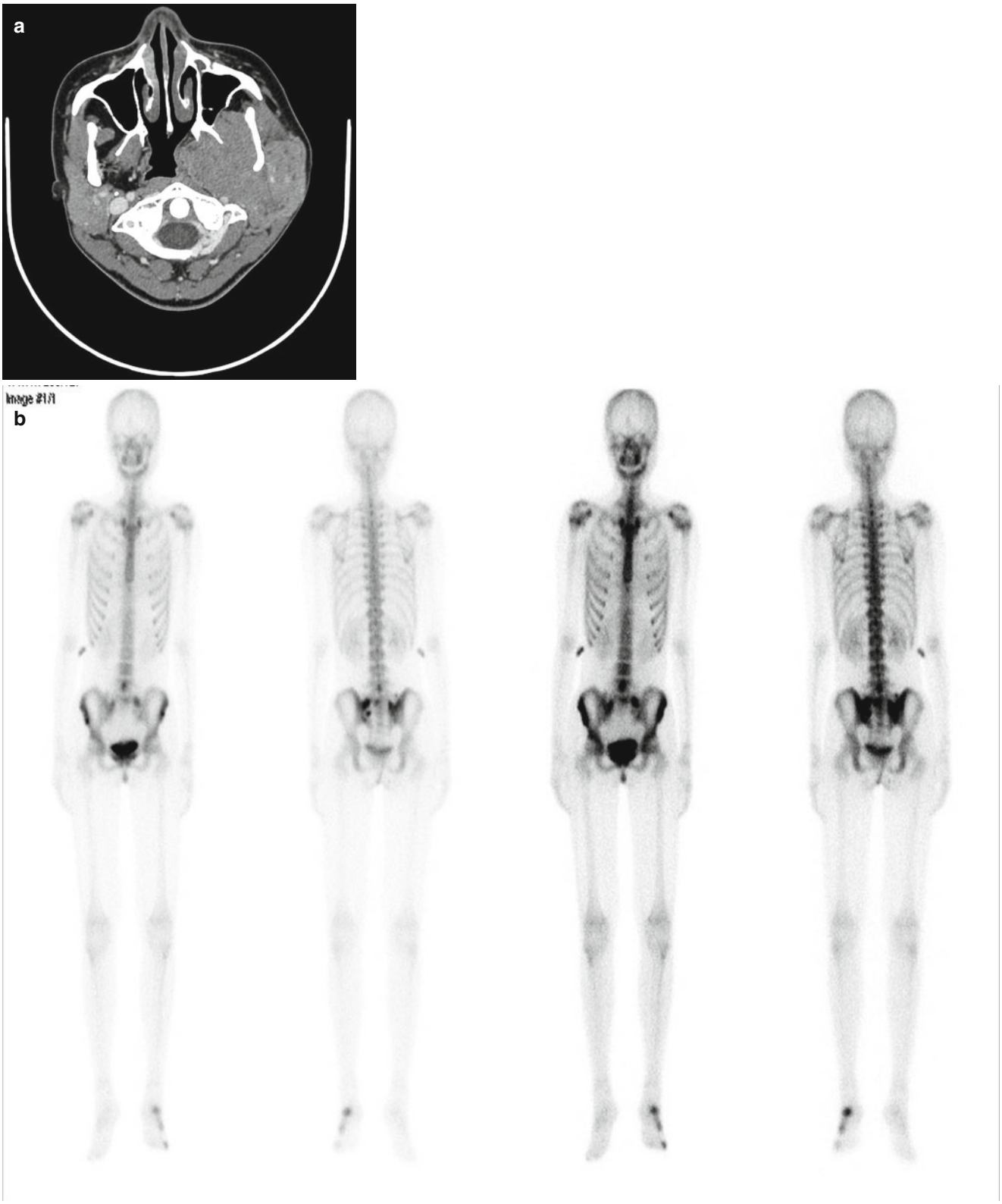

Fig. 20.5 (**a**) A 17 year-old girl presented with a enlarging left cheek mass. CT head and neck demonstrated 5.6×6.4 cm mass in the left masticular space. Biopsy confirmed embryonal RMS. (**b**) A bone scan performed at the time of diagnosis was remarkable for a L5 metastatic lesion

cautery artifact. Alternatively, open biopsy may be performed. In patients who present with ureteral obstruction, internal ureteral stents and/or percutaneous nephrostomy tubes may be necessary; however suprapubic catheters should be avoided due to the risk of seeding the tract with tumor [272]. The major goal of surgery is complete tumor resection with bladder salvage which is achieved in 50–65 % of patients [272–274]. In rare cases, the tumor is confined to the dome of the bladder and is amenable to complete resection with bladder preservation. Neoadjuvant chemotherapy and radiation have decreased the rate of exenterative cystectomy to approximately 30 % [275–277]. However, distal bladder tumors involving the trigone frequently require ureteral reimplantation and/or bladder augmentation. Conservative, delayed surgery performed after intensive chemotherapy with or without radiotherapy yields a better cure rate while maintaining a high rate of bladder salvage in children with prostatic RMS [278]. Pelvic exenteration is reserved for local control when residual viable tumor remains after chemotherapy and radiotherapy. Lymph nodes are involved in 20 % of cases. It is important to examine the retroperitoneum and remove any enlarged lymph nodes [279].

The timing of local control remains controversial and residual mass on imaging does not always represent viable tumor. The tumor may involute or differentiate into mature rhabdomyoblasts. In IRS III, 36 % of patients with no radiographic response were found to be in complete remission at the time of second-look surgery [280]. It has been suggested that bladder and prostate RMS <5 cm in size with embryonal histology may be successfully treated with chemotherapy alone [281].

Overall survival for bladder RMS is good - 82 % at 6 years in the IRS-IV study [229]. It is often difficult to differentiate between bladder and prostate RMS due to their anatomic proximity and tendency to present as large tumors. However, in patients in whom that differentiation is possible, it is clear that prostate RMS has a worse prognosis compared to bladder RMS [166]. Although bladder preservation is often achieved, half of patients will have reduced bladder capacity and only 55 % have normal bladder function [273, 282]. Sexual dysfunction may also be affected [283].

Paratesticular

Paratesticular RMS represents 7 % of all childhood RMS and 12 % of childhood scrotal tumors [213]. Most patients present with a painless scrotal mass. The standard of care is radical orchiectomy via an inguinal approach with resection of the spermatic cord to the level of the internal inguinal ring [196] (Fig. 20.6). The proximal spermatic cord should be evaluated and show no tumor on frozen section [279]. If tumor is present, a higher ligation is performed. When scrotal radiation therapy is planned, the contralateral testis may be temporarily transposed to the adjacent thigh to avoid the radiation field. In general, biopsy is unnecessary and should be avoided. If trans-scrotal biopsy or resection is performed, it may result in tumor seeding, and hemiscrotectomy or hemiscrotal radiation is required [284].

The incidence of nodal metastatic disease for paratesticular RMS is 26 % [285, 286]. Thus, all patients should undergo thin-cut (3.8 to 5.0 mm) abdominal and pelvic CT scans to evaluate nodal involvement. The incidence of lymph node metastases is higher in patients >10 years old and CT may not adequately predict lymph node involvement in these patients [212]. Therefore, a staging ipsilateral retroperitoneal lymph node dissection is required for all children >10 years old on IRSG and COG-STS studies. However, node dissection is not routine in Europe for adolescents with resected paratesticular RMS. All patients with enlarged lymph nodes on imaging irrespective of age should undergo retroperitoneal lymph node sampling and further therapy depends on lymph node status. For patients >10 years old and primary tumor >5 cm, ipsilateral retroperitoneal lymph node dissection up to the level of the renal hilum is recommended. This procedure may be performed laparoscopically by experienced surgeons [287]. Positive suprarenal lymph nodes are considered distant metastases and these patients are considered clinical group IV [196]. It is important to note that retroperitoneal lymph node dissection may be associated with significant morbidity including loss of ejaculatory function, lower extremity

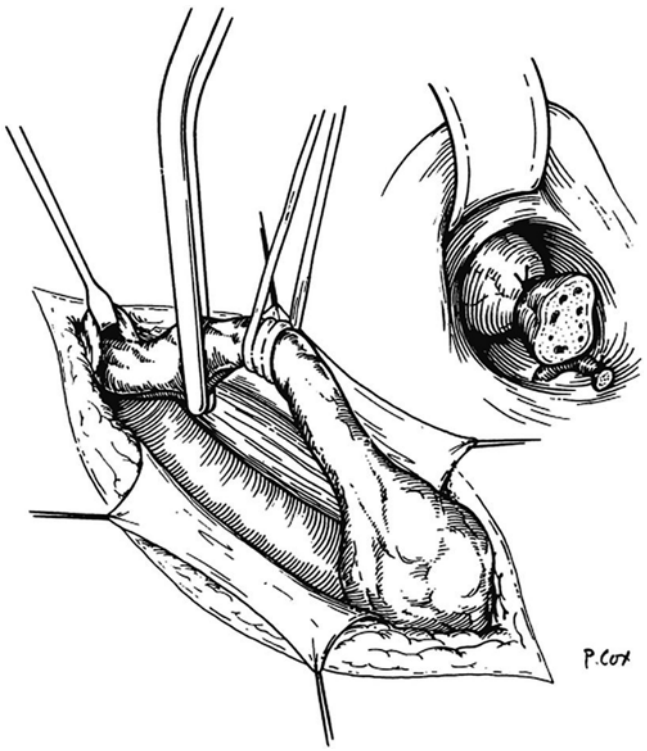

Fig. 20.6 Proximal control of the spermatic cord and orchiectomy through an inguinal incision

lymphedema, and intestinal obstruction [288]. Inguinal nodes are rarely involved and biopsy is performed only if the nodes are clinically positive or if the scrotum is invaded by tumor. Inguinal lymph node involvement is considered distant metastasis and thus, the patient is clinical group IV.

Most paratesticular RMS are embryonal, nonmetastatic, and highly curable with multimodal therapy including surgery, multiagent chemotherapy, and, for patients with retroperitoneal lymph node involvement or incompletely resected disease, radiation therapy [289]. The 3-year failure-free survival rate for paratesticular RMS is >81 % for all patients and >90 % for patients <10 years old [229]. Patients >10 years old and those with tumors >5 cm have significantly worse overall and event-free survival rates [290, 291].

Vulva, Vagina, and Uterus

Vulvo-vaginal and uterine RMS is the most common malignancy of the pediatric female genital system. Approximately half of all cases in the female genital tract arise in the vagina. This tumor generally presents in the first few years of life, with vaginal bleeding or blood-tinged discharge (66 %) and/or a vaginal mass (39 %) [292]. If the tumor arises from the vulva, it consists of a firm nodule embedded in the labial folds, or it may be periclitoric in location. On occasion, it may present as a labial hematoma related to trauma. Diagnosis is confirmed by vulvar or transvaginal incisional or excisional biopsy. Vaginal lesions usually have embryonal or botryoid embryonal histology and are associated with an excellent prognosis [178, 292–294]. Vulvar lesions may have alveolar histology, but most are localized and have a good prognosis. Thus, vulvar, vaginal and uterine RMS are considered favorable sites.

The management of these tumors has evolved from radical resection including pelvic exenteration in the 1970s and early 1980s to neoadjuvant chemotherapy followed by local control with surgery or radiotherapy in the past two decades [295]. The general management principles include biopsy and staging followed by chemotherapy as directed by pretreatment stage and clinical group. There is no role for initial management with radical surgery such as vaginectomy or hysterectomy [178]. Patients are followed with routine abdominal and pelvic MRI to determine tumor response and detect recurrence. Second look operations with biopsy and cystoscopy are common. Rhabdomyoblasts are evidence of chemotherapy response and should be treated with additional chemotherapy rather than surgical excision [178].

Vaginectomy and hysterectomy are performed only for persistent or recurrent disease, and vaginal and uterine salvage are achieved in greater than 40 % of cases [292]. If unresponsive to chemotherapy, primary uterine tumors require hysterectomy with preservation of the distal vagina and ovaries. Oophorectomy is only indicated for cases with direct tumor extension into the ovary. Lymph node involvement is very rare (5 %) and thus, pelvic lymph node dissection is not indicated [279, 296]. It is important to consider surgically relocating the ovaries to preserve fertility in girls who will receive radiation therapy to the lower abdomen and pelvis. In a recent COG-STS study, there was an unacceptably high rate of local relapse in patients with clinical group III vaginal tumors who did not receive radiation therapy, and therefore, it is recommended that all patients with residual, viable tumor receive radiation therapy [296, 297].

Prognosis for patients with loco-regional disease only is excellent with an estimated 5-year survival of 87 % [295]. However, more than half of women surviving treatment for pelvic RMS will have long-term endocrine, gastrointestinal, musculoskeletal, and urologic complications which commonly occur in the radiation field [298]. In addition, surgical complications may include rectovaginal fistula, vesicovaginal fistula, and urinary incontinence all of which are associated with significant morbidity [292].

Extremity

The most common extremity sarcoma in children is NRSTS accounting for 79 % of cases [67]. Only 21 % of extremity sarcomas in children and adolescents are RMS. The extremity is the primary site in 14 % of childhood RMS, and most are alveolar histology [3, 166]. The median age at presentation is 6 years, and it is evenly distributed between males and females [215]. Most children present with a painless mass or swelling but they may also present with a limp. The extremity is an unfavorable site, and therefore, all extremity RMS is at least a pretreatment stage 2 or greater. Approximately 30 % of patients present with nodal involvement and 35 % with distant metastases [67].

The initial workup includes a MRI of the primary tumor. CT is valuable to evaluate bone erosion and/or abdominal lymphadenopathy. Others suggest that ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) may improve pretreatment staging by evaluating for regional and distant metastases as well as detect viable disease or recurrence in a previously operated field [199–201, 299–302]. Incisional or excisional biopsy should be performed through a longitudinal or axial incision to allow for wide local excision of the primary tumor. The primary goal is wide and complete resection of the primary tumor with a surrounding rim of normal tissue while preserving form and function. There is no evidence that margins greater than 5 mm offer any advantage. In general, only pretreatment stage 2 (size <5 cm and no clinical evidence of nodal involvement) are amenable to primary surgical resection and even this is dependent on the location of the primary tumor. Amputation is rarely indicated except for bulky recurrent or persistent disease. Careful determination of margin status is extremely important, and re-resection

at initial or subsequent operation is warranted if a positive margin is present or suspected. Hays and colleagues demonstrated that patients with node negative extremity and trunk sarcomas who underwent re-excision for microscopic residual tumor had a significant survival advantage compared to patients who did not undergo re-excision or were reported to have no residual tumor after initial resection [209]. Thus, it is important to consider re-excision of the primary site after initial surgical resection for all node negative clinical group I and II patients.

For patients with tumors >5 cm or anatomic sites not amenable to primary surgical resection (hand, foot, groin, antecubital or popliteal fossa), an initial incisional biopsy is indicated. After diagnostic confirmation, the patient will receive multi-agent chemotherapy ± radiation therapy followed by a second-look procedure and resection of residual disease. Primary tumors of the hand and foot are especially challenging, and although current recommendations for local therapy include resection only if function can be preserved, some children still undergo amputation [303]. La and colleagues showed excellent local control using radiation therapy for patients with nonmetasatic RMS of the hand and feet [304]. They recommend either radiation therapy or definitive surgical resection that maintains form and function rather than amputation as primary local therapy in patients with hand or foot RMS [304].

Extremity RMS often has nodal involvement (30 %) which necessitates evaluation of the regional lymph nodes in staging of the tumor [166]. In a review of patients enrolled in IRS-IV, Neville and colleagues found that 50 % of biopsied lymph nodes were positive and that 17 % of patients with clinically negative lymph nodes were found to have microscopic nodal disease [215]. Nodal status is a significant predictor of failure-free and overall survival in patients with extremity RMS [215, 305]. Thus, it is imperative to adequately assess nodal involvement in extremity RMS as it will have significant prognostic and therapeutic implications. The COG-STS committee recommends evaluation of axillary nodes for patients with upper extremity tumors and inguinal and femoral triangle nodes for lower extremity tumors. If clinically positive nodes are present, biopsy of more proximal nodes is indicated. In-transit nodal disease may also play an important role. Failure to either sample or radiate the in-transit nodal site(s) is associated with an increase in in-transit failure (15 % versus 0 %) [304, 306]. Sentinel lymph node mapping has been used successfully to determine regional nodal involvement in children with extremity sarcomas [62, 63]. It offers a less invasive, but reliable alternative to aggressive or random lymph node sampling.

Despite intensive efforts of IRSG and now the COG-STS committee, outcome for children with extremity RMS remains suboptimal compared to children with RMS in more favorable sites. Overall 5-year survival is 56 % for all patients and 74 % for patients without metastatic disease [67, 307, 308]. Pretreatment stage and clinical group are highly predictive of failure-free survival in patients with extremity RMS [215]. Patients with complete resection or microscopic residual tumor have significantly better 3-year failure free survival compared to patients with advanced disease (clinical group I 3-year FFS 91 %, II 72 %, III 50 %, and IV 23 %) [215]. In a recent review of patients treated on IRS III and IV protocols, the 5-year failure-free survival was 31 % for patients with clinical group III alveolar or undifferentiated RMS at unfavorable sites and regional nodal involvement which is similar to patients with metastatic disease [210].

Other Sites

Trunk

RMS of the trunk comprises 27 % of childhood RMS cases and includes chest wall, intra-thoracic, paraspinal, and abdominal wall tumors [166]. Of truncal RMS, the chest wall is the most common primary site accounting for 61 % of cases [309]. These tumors usually present as asymptomatic, expanding soft tissue masses. The histology is more commonly alveolar and associated with a poor prognosis [310].

Although surgical excision is the mainstay of local disease control, it may not be feasible. In general, the surgical management of patients with truncal RMS should follow the guidelines used for extremity tumors which include wide local excision with negative margins and assessment of regional nodal status. Primary surgical resection is preferred in tumors <5 cm if negative microscopic margins are expected. It may be useful to perform preoperative lymphoscintigraphy and consider SLNB for patients with truncal RMS as the primary lymphatic drainage basin for truncal sites is often unclear. Very large truncal masses should undergo incisional biopsy followed by neoadjuvant chemotherapy prior to resection. For chest wall lesions, the biopsy should be performed longitudinal to the ribs.

For chest wall tumors, the resection includes the previous biopsy site (if present) and involved chest wall muscles, ribs, and underlying lung. On a review of COG data, the local recurrence of chest wall RMS is no different with an R0 compared to an R1 resection. Because of the efficacy of chemotherapy, microscopically positive margins did not affect outcome. Resection of rib periosteum instead of the entire rib, in select cases, should be considered [222]. Chest wall reconstruction often requires the use of prosthetic mesh, myocutaneous flaps and/or titanium ribs [214]. Thoracoscopy may be useful in determining the extent of pleural involvement and tumor extension to underlying lung [196]. Although RT may improve local control, it is associated with significant morbidity in this region including pulmonary fibrosis, decreased lung capacity, restrictive effects and scoliosis [311].

Paraspinal RMS is rare accounting for 3.3 % of cases entered on IRS I and II. These tumors present as an enlarging mass in the paravertebral muscle area and often invade the spinal extradural space [312]. They must be distinguished from extra-osseous Ewing's sarcoma which is more common in this area. Most patients present with tumors >5 cm and require neoadjuvant chemotherapy followed by surgical resection and postoperative RT.

Biliary Tract

Biliary RMS accounts for <1 % of all RMS. It usually presents at a young age (median 3.4 years) with jaundice and abdominal pain or swelling [313]. The histology is usually boytryoid which responds well to chemotherapy and RT without the need for aggressive surgical resection [314, 315]. Total resection is rarely feasible; however, the outcome is usually good despite residual disease after surgical resection. In a review of biliary RMS patients treated on IRS I-IV, Spunt and colleagues found that complete resection was rarely possible, external biliary drains significantly increased the risk of postoperative infectious complications and in general, the tumors responded well to multiagent chemotherapy and did not require aggressive surgical intervention [315].

Retroperitoneum and Pelvis

RMS of the retroperitoneum and pelvis are often unresectable at presentation due to the massive size of the tumor and extension into vital organs or vessels (Fig. 20.7a, b) [316]. More than 90 % of patients present with either clinical group III or IV disease [317]. Thus, initial biopsy is performed followed by neoadjuvant chemotherapy with or without RT then complete surgical resection. If possible, complete surgical resection offers a significant survival advantage compared to no surgical resection (73 % versus 34–44 %) [316]. In a review of IRS III-IV patients with group III retroperitoneal RMS, age <10 years at diagnosis and embryonal histology were favorable prognostic factors and in these patients, debulking prior to chemotherapy and RT proved beneficial [317]. Other studies have suggested that debulking of more than 50 % of tumor prior to the initiation of chemotherapy and RT is beneficial in patients with retroperitoneal and pelvic RMS [318]. The alternative is surgical resection following neoadjuvant chemotherapy.

Perineum and Perianal

Rhabdomyosarcoma (RMS) of the perineum or anus is a rare sarcoma of childhood that usually presents with advanced stage disease and a relatively poor prognosis. Although perineal and anal RMS is most often alveolar, histology does not affect overall survival for this site [196]. The majority (64 %) of patients present with clinical group III or IV disease and 50 % have lymph node involvement [319]. Late presentation can be due to unrecognized mass, or a perianal mass mistaken for an abscess or hemorrhoids. Resection is often challenging due to the proximity to the urethra and anorectum. It is important to preserve anal sphincter function and consider diversion for anorectal obstruction due to tumor. Regional lymph node evaluation with biopsy of clinically suspicious nodes or SLNB in cases without suspicious nodes is recommended. Age <10 years is an independent predictor of survival (71 % 5-year overall survival compared to 20 % for patients ≥10 years of age) [319].

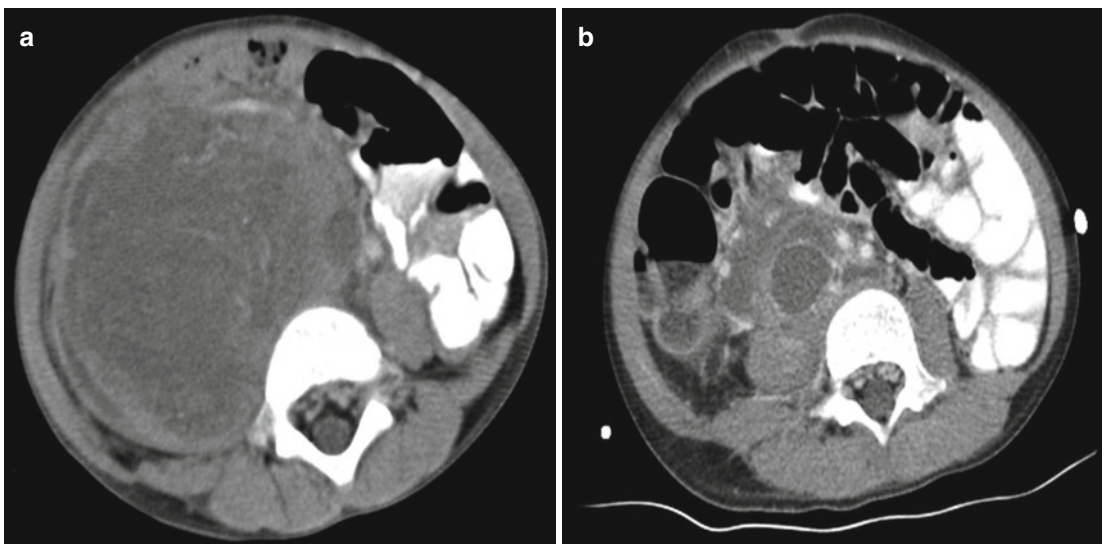

Fig. 20.7 (**a**) A 3 year-old girl presented with an enlarging, painless abdominal mass. CT abdomen and pelvis confirmed an 11.5×9.5×9.5 cm right retroperitoneal mass encasing the abdominal aorta. Open biopsy showed embryonal RMS, and she was started on VAC for stage 2, clinical group III, intermediate risk RMS. (**b**) Despite an initial response to chemotherapy and RT (shown in image), she developed progression intra-abdominal disease and later died

Outcome and Future Research

The overall 5-year survival for children and adolescents with RMS is 60 %; however, the prognosis for childhood RMS is multifactorial and cannot be summarized in a single survival statistic. Although metasatic disease is the single most important predictor of outcome, other factors play a significant role including patient age, tumor primary site and size, resectability, histopathologic subtype, and time to relapse [269, 320]. Biologic characteristics of the tumor cells, such as *PAX* gene rearrangements, are also important determinants of outcome [189]. Children ages 1–9 years have the best prognosis compared to infants and adolescents [229, 321, 322]. Tumor size is an integral prognostic indicator for RMS, and therefore, plays a major role in clinical grouping [55]. Patients with smaller tumors (≤5 cm) have improved survival compared to larger tumors; however, there is some evidence that the 5 cm cutoff used for adults may not be ideal for small children [55]. These factors are important in the designation of treatment groups for risk-based therapy.

Overall, FFS rates for the patients treated on IRS-IV did not differ from results in IRS-III (FFS rate 76 % versus 77 % for IRS-III and IV, respectively) [229]. FFS rates were improved for patients with embryonal rhabdomyosarcoma treated on IRS-IV compared to those of similar patients treated on IRS-III (3-year FFS rates, 83 % versus 74 %). The improvement seemed to be restricted to patients with stage II or stage II/III, clinical group I/II embryonal RMS. The sites of treatment failure were local in 93 patients (51 %), regional in 30 (17 %), and distant in 58 (32 %). Salvage therapy after relapse differed by group. Forty-one percent of the patients with group I/II tumors, compared with 22 % of those with group III tumors, were alive 3 years after relapse [229].

Overall survival for patients with low risk RMS is excellent. The results of IRS III-IV show that patients with non-metastatic tumors of embryonal histology arising from favorable sites (stage 1) and those with tumors in unfavorable sites (stages 2 and 3) that are grossly resected (clinical groups 1 and II) have very high 5-year failure-free survival (approximately 83 %) and overall survival (approximately 95 %) [229, 280, 320]. Thus, current research focuses on dose reduction in systemic therapy to hopefully decrease short- and long-term side effects while maintaining excellent survival for low risk RMS.

The overall survival for recurrent RMS is very poor. Approximately 30 % of patients with RMS will relapse, and 50–95 % of these patients die of progressive disease [280, 320, 323, 324]. In the IRS III, IV, and IV pilot, the 5-year survival for patients who experienced relapse after treatment was less than 20 %. Surgical resection did not impact survival in these patients. However, the results from other single-center studies support the use of aggressive surgical resection in select patients with relapsed RMS [318].

The overall trend has been an increase in survival for each subsequent IRS study; however very little if any progress has been made in the treatment of high risk RMS. Approximately 15 % of patients with RMS present with metastases at diagnosis [280]. Despite aggressive multimodality therapy, 3-year failure free survival is only 25 % in patients with metastatic disease [280, 324, 325]. Prognosis is slightly improved for patients with two or fewer metastatic sites and embryonal histology [226]. The current COG high risk protocol (ARST08P1) is evaluating the feasibility of using a fully human IgG1 monoclonal antibody targeting the Insulin-like Growth Factor-1 receptor (IGF-IR) as well as the addition of temozolamide, an alkylating agent, to the regimen with vincristine and irinotecan based on the synergistic effect of temozolamide plus irinotecan.

Multimodality therapy has improved outcomes for most children diagnosed with RMS. However, much work remains in the efforts to improve survival for patients with high risk disease. In the future, clinical trials will likely focus on the molecular biology that drives tumor behavior. All newly diagnosed patients with RMS should be considered for enrollment in ongoing biology and clinical trials. The surgeon plays a key role and must facilitate the collection and submission of fresh tissue for biology protocols. The success of these efforts will depend on the active participation of physicians from a multitude of disciplines including oncology, radiation therapy, and surgery. In the future, it may be possible to develop customized clinical therapies that improve survival in children and adolescents with RMS.

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Lymphoma

21

Deborah F. Billmire

Childhood Lymphoma

Although treatment of lymphoma in children is primarily medical in nature, the pediatric surgeon plays an important role in establishing the diagnosis and also has an impact on the timely initiation of chemotherapy for these rapidly growing tumors. The surgeon's contributions are crucial to successful management. He or she must be aware of the clinical presentations of lymphoma so that the diagnosis is considered and tissue is appropriately handled. Fresh specimens should be submitted to the pathologist so that all testing can be accomplished to properly assign subtype and staging. The appropriate decision regarding biopsy versus resection must be made. Resection of major organs is generally unnecessary and major procedures may also entail morbidity that would delay initiation of chemotherapy. On the other hand, resection of localized tumors in some cases may reduce or eliminate the need for chemotherapy with its associated organ toxicity. The potential hazards of anesthesia should be recognized in certain situations and the possible use of less invasive diagnostic tools such as examination of pleural and ascitic fluids should be considered. Proper handling of tissue and prompt initiation of chemotherapy will allow for optimal response to therapy for these children.

Several classifications for the subtypes of lymphoma have evolved over time. Increasingly, the emphasis is on versions that rely on immunophenotypic descriptions. This allows subtyping of lymphoma based on biologic properties and provides a mechanism for more targeted therapy. The World Health Organization (WHO) classification revised in 2008 is most often used [26]. Clinically, childhood lymphoma is divided into two major categories, Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). Although there is some overlap in presentation, the clinical features of non-Hodgkin's lymphoma are much more varied. The management and prognosis of these two categories are also different, and each category will be discussed separately.

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Hodgkin's Disease

Hodgkin's disease accounts for approximately 6 % of childhood cancer and 40 % of pediatric lymphoma. The incidence varies from 0.3 to 3 per 100,000 person years [32]. The incidence of Hodgkin's disease increases with age and most pediatric cases occur in adolescents (Fig. 21.1). Hodgkin's disease is uncommon in children less than 10 years of age in the United States [66]. It occurs more frequently in males, particularly at younger ages. The histologic subtype also varies with age. Younger children are more likely to have lymphocyte-predominant or mixed cellularity. Adolescents most often have nodular sclerosing histology.

Histology/Tumor Markers

Hodgkin's disease is characterized on histologic examination by the Reed-Sternberg cell. This is a multinucleated giant cell with two prominent nucleoli that have a characteristic appearance said to resemble "owl eyes". These neoplastic cells are found in an inflammatory milieu including infiltrating lymphoid cells, plasma cells and fibrous stroma that constitute the bulk of the enlarged node. There are four major subtypes of classic Hodgkin's disease that are defined by the relative proportions of normal lymphocytes to Reed-Sternberg cells. These subtypes are lymphocyte predominant, mixed cellularity, lymphocyte depleted and nodular sclerosing. Prognosis worsens with decrease in the proportion of lymphocytes.

The Reed Sternberg cell has its origin from preapoptotic germinal center B cells. Similar to those non-Hodgkin's

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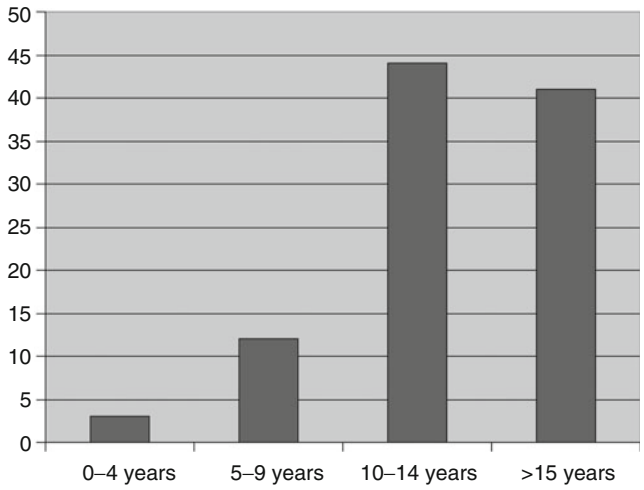

Fig. 21.1 Incidence of Hodgkin's lymphoma by age [48]

lymphomas that arise from B cell origin, there is an association of Hodgkin's disease with Ebstein Barr virus (EBV). EBV genetic material is found in up to 40 % of children with Hodgkin's disease. It is most common in children less than 10 years and is usually seen in those with the mixed cellularity subtype. It is seldom found in those with nodular sclerosing histology. Nearly all classic Hodgkin's lymphomas express CD30. The B cell markers CD45, CD19 and CD79A are usually negative [70].

A fifth subtype of Hodgkin's lymphoma is Nodular Lymphocyte-Predominant Hodgkin's Lymphoma (NLPHL). This subtype is recognized histologically by the presence of cells known as "popcorn" cells. They are large cells with multi-lobed nuclei that express B-cell antigens such as CD19, CD20, CD 22 and CD 79A. In contrast to classic Hodgkin's, the oncogenes OCT-2 and BOB.1 are expressed in NLPHL [67].

Diagnostic Evaluation and Staging System

Children with Hodgkin's disease most often present with enlarged, rubbery nodes in the cervical or supraclavicular region. A complete physical examination with attention to all nodal areas as well as a careful examination of the abdomen should be performed. Blood work should include complete blood count, erythrocyte sedimentation rate, renal and hepatic function studies and alkaline phosphatase. Imaging studies should include chest x-ray and CT scans of the chest, abdomen and pelvis. Bone scan should be performed in those with elevated alkaline phosphatase. Current protocols also employ gallium or positron emission tomography (PET) scans (Fig. 21.2). The fluorodeoxyglucose (FDG) PET scan has become the preferred modality for both initial diagnosis and follow-up scans because of its higher

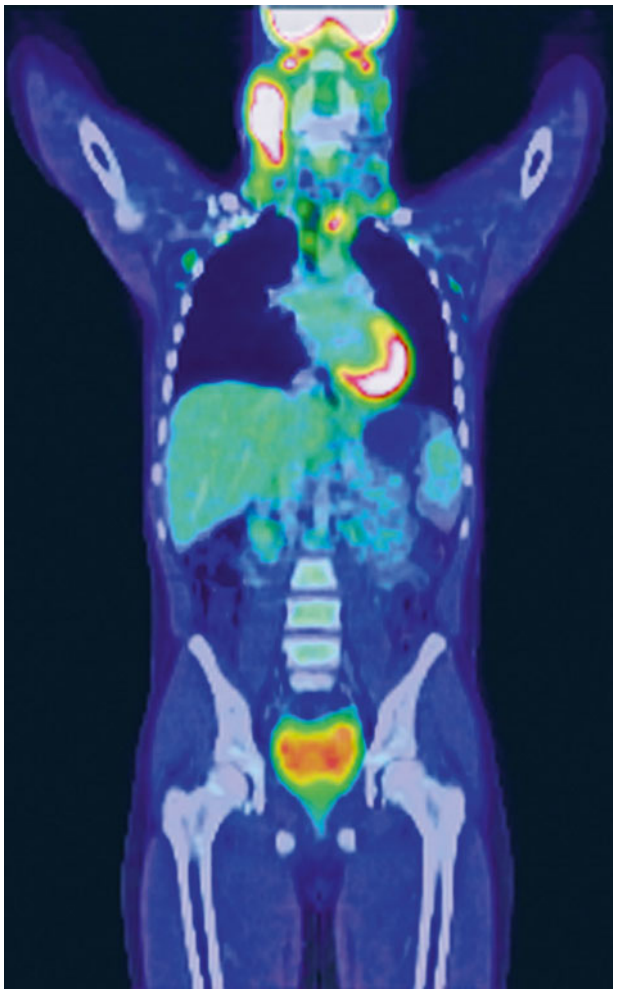

Fig. 21.2 PET-CT scan of mediastinal non-Hodgkin's lymphoma

resolution, 1 day scan time and improved detection of disease below the diaphragm [15]. One study of combined PET/CT scanning in childhood lymphoma (both Hodgkin's and nonHodgkin's) noted better predictive value of negative scans than positive scans when used for follow-up imaging and recommended caution in interpretation of equivocal and positive scans [56]. In patients with stage III or IV disease and those with symptoms of fever or night sweats, bone marrow aspiration and biopsy are also needed. Staging laparotomy is no longer used in pediatric Hodgkin's lymphoma since all current pediatric protocols employ systemic chemotherapy.

The staging system for Hodgkin's disease is based on the revised Ann Arbor system [37]. (Table 21.1) Patients are also given a designation of A or B based on symptomatic criteria. Patients with unexplained weight loss of greater than 10 % of body weight in the 6 months preceding diagnosis, unexplained fevers greater than 38° centigrade for greater than 3 days, or drenching night sweats are assigned to category B. All others are assigned to category A.

Table 21.1 Cotswold modification of the Ann Arbor staging system for Hodgkin's lymphoma [37]

Stage I	Involvement of single lymph node region (I) or localized involvement of a single extralymphatic organ or site (IE)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized contiguous involvement of a single extralymphatic organ or site and its regional lymph node(s) with involvement of one or more lymph node regions on the same side of the diaphragm (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized contiguous involvement of an extralymphatic organ or site (IIIE), by involvement of the spleen (IIIS), or both (IIIE + S)
Stage IV	Disseminated (multifocal) involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement

Clinical Presentation/Surgical Issues

In contrast to non-Hodgkin's lymphoma, Hodgkin's disease occurs primarily in nodal anatomic sites and tends to follow an orderly anatomic progression. There are 20 defined areas of nodal groupings (Table 21.2). Painless, rubbery enlargement of cervical or supraclavicular nodes is the most common presenting complaint and is seen in 80 % of patients. Primary presentation as axillary or groin adenopathy is far less common and occurs in less than 3 % of children (Fig. 21.3). The release of lymphocytokines by the Reed Sternberg cells produces systemic symptoms in up to one third of patients. These symptoms include fever, night sweats and weight loss as described above.

The surgeon's role is to provide adequate tissue for diagnostic studies with minimal morbidity, and to provide staging information in selected subgroups. In general, an incisional or excisional biopsy of involved nodes is preferred. Use of cautery should be avoided on the tissue to be submitted to minimize coagulation artifact. Fine needle biopsies do not provide sufficient tissue for complete histologic and biologic studies, but core needle biopsies may be utilized when other approaches may be too hazardous (Fig. 21.4).

Mediastinal involvement occurs in two thirds of patients at presentation and is relevant to prognosis. A ratio of maximal diameter of the mass to the thoracic cavity greater than 1:3 on posterior-anterior chest x-ray is associated with worsened prognosis [32]. The possibility of a mediastinal mass is a particularly important factor for the surgeon to be aware of in patients with lymphoma. In patients presenting with cervical or supraclavicular adenopathy, the status of the mediastinum must be assessed prior to anesthesia for biopsy. For those patients that present with an isolated mediastinal mass, a search should be made for more accessible disease outside the mediastinum for biopsy under local anesthesia [51]. If a pleural effusion is present, the fluid may be aspirated for cytology, but this is usually more successful in non-Hodgkin's lymphoma. The potential hazards of anesthesia must be considered prior to biopsy. It is well recognized that anterior mediastinal masses of all types pose a risk for respiratory or hemodynamic collapse under general anesthesia and multiple fatal cases have been reported. Loss of ventilation occurs

Table 21.2 Defined nodal groupings for Hodgkin's lymphoma

Peripheral regions
Right neck; cervical, supraclavicular occipital, and preauricular
Left neck; cervical, supraclavicular occipital, and pre-auricular
Right infraclavicular
Left infraclavicular
Right axilla and pectoral
Left axilla and pectoral
Right epitrochlear and brachial
Left epitrochlear and brachial
Central regions
Waldeyer's ring (including base of tongue)
Mediastinum (including paratracheal)
Hilar
Mesenteric
Para-aortic (including retrocrural, portal and celiac)
Splenic/splenic hilar
Lower regions
Right iliac
Left iliac
Right inguinal and femoral
Left inguinal and femoral
Right popliteal
Left popliteal

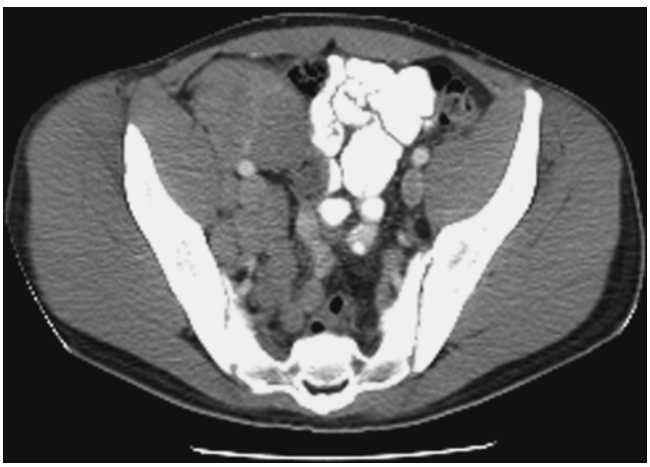

Fig. 21.3 CT scan demonstrating primary iliac nodal presentation of Hodgkin's lymphoma

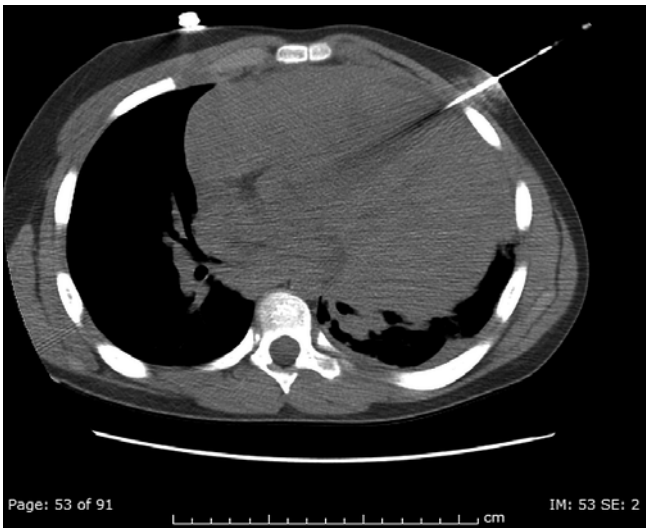

Fig. 21.4 Patient with large mediastinal mass undergoing core needle biopsy under local anesthesia

at several levels. This may include severe narrowing of the trachea and bronchi and is further compromised under anesthesia by loss of smooth muscle airway tone causing distal collapse well beyond reach of a mechanical airway [57]. Encasement of the pulmonary arteries may also occur leading to mortality despite adequate airway control. Clinical symptomatology does not provide a reliable assessment of risk, but the presence of orthopnea is considered to be of particular concern [62]. Objective parameters such as peak expiratory flow rate less than 50 % and tracheal cross section than 50 % of predicted are felt to be predictors of high risk as described by Shamberger [64, 65]. Peak expiratory flow rate (PEFR) is easily done at the bedside and should be measured in the supine position as well as upright. The tracheal cross section should be calculated from the CT scan using an imaging window level of 450 and compared to the graph of normal values provided by Shamberger. Significant variance occurs when different CT window levels are used and calculations become unreliable [57]. In patients considered to be at high risk for general anesthesia, consideration should be given to biopsy in the upright position under local anesthesia or to prebiopsy radiation with shielding of selected nodes. Fine needle biopsy provided adequate tissue for diagnosis of lymphoma in up to 83 % of pediatric patients in one series [71], but subtyping to determine therapy cannot be done with this type of tissue sample. In a large review of surgical quality assurance from the Children's Oncology Group, technique of tissue acquisition was reviewed for accuracy and complications. Accuracy was 98.5 % for open biopsy, 80 % for core needle biopsy, 60 % for thoracoscopic or laparoscopic biopsy, and 25 % for fine needle biopsy. The most common complication was inadequate sampling [12]. Once diagnosis is definitive and therapy is initiated, clinical

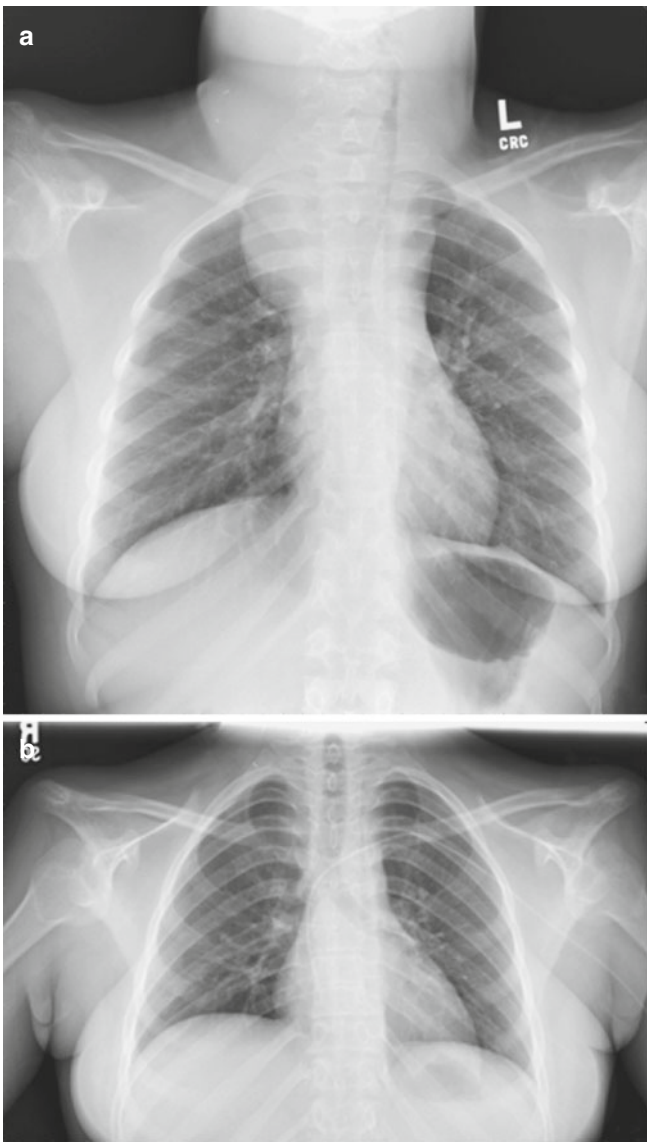

Fig. 21.5 Mediastinal Hodgkin's lymphoma demonstrating tracheal compression at diagnosis (**a**) relieved after one cycle of chemotherapy (**b**)

response is rapid. Chemotherapy can be initiated through a peripherally inserted central catheter and within one or two cycles, general anesthesia can be safely undertaken to provide a more convenient central access with subcutaneous reservoir (Fig. 21.5a, b).

Although staging laparotomy is no longer performed for pediatric Hodgkin's disease, the concept of oophoropexy may still be relevant in certain patients. Radiation of the pelvic nodes (inverted Y field) or central pelvis may be employed in select cases. It is well known that pelvic radiation may result in premature ovarian failure with loss of fertility and endocrine function. This risk is directly related to radiation dose with consistent loss of ovarian function from single doses of 800 cGy or fractionated doses of 1500 cGy [74]. The risk is inversely proportional to age at the time of treatment, thus

putting younger patients at the highest concern for sterility and impact of loss of hormonal function.

Radiation doses for treatment of Hodgkin's disease typically involve 20–35 Gy. Prior to the development of oophoropexy for this problem, loss of ovarian function was almost universal. Oophoropexy, usually performed at the time of staging laparotomy, resulted in preservation of ovarian function in 0–66 % of women [16, 34, 69, 74]. Limited data on efficacy of oophoropexy is available in the pediatric age group. In 1992, Hays' report on staging procedures for advanced pediatric Hodgkin's disease included seven girls that had pelvic radiation to 21 Gy. Two had no oophoropexy and had delayed or no menarche. All five who had oophoropexy had normal menses [20]. In 1992, Williams and Mendenhall reported a laparoscopic technique for oophoropexy in patients planned to undergo inverted Y pelvic radiation for Hodgkin's disease [74]. Helpful operative details and illustrations are provided in the report. The ovaries are pexed together in the midline posterior to the uterus. The medial and lateral borders of each ovary are marked with clips for assistance in defining the radiation field by imaging. These authors provided a follow-up review of 12 patients in 1999 and stressed several points [75]. They cited reports by other authors [19] of clip separation and recommended ultrasound imaging shortly before radiation to confirm that the clips remain associated with the ovaries. They also described two patients in their series that had previously undergone open oophoropexy at the time of initial staging laparotomy. Laparoscopy was done as a second procedure 5 and 6 months later respectively (just prior to radiation), and demonstrated that the ovaries had migrated back to their original positions. It was recommended that the oophoropexy be done in close proximity to the planned radiation to minimize time for migration of the ovaries. Finally, they also noted ovarian failure despite oophoropexy in four of five patients that had received six or more cycles of chemotherapy. Females that are to undergo radiation therapy to the central pelvis would need to have the ovaries pexed laterally to the pelvic sidewalls.

Treatment

Although primary treatment for Hodgkin's disease has been highly successful (90–95 % survival) since the 1980s, the therapeutic strategies have been in constant evolution. Initial successful treatment for localized Hodgkin's lymphoma involved targeted radiation therapy in both adults and children with doses ranging from 35 to 40 Gy [73]. This management strategy required accurate assessment of spread of disease at diagnosis for success. The concept of staging laparotomy including extensive nodal sampling and splenectomy was developed to confirm extent of disease in the abdomen. From this body of experience, it was learned that staging laparotomy resulted in restaging (up or down) in 25–40 % of patients [6, 73] that had been clinically staged by CT scan and lymphangiography. A study of modified staging laparotomy for pediatric Hodgkin's disease by Hays et al. [21], revealed no therapeutic benefit to staging laparotomy and a complication rate of 2.8–6 % [6, 21]. In addition, there was a long term risk of post-splenectomy sepsis.

The recognition that high dose radiation in the growing child had unacceptable musculoskeletal and cardiac toxicity led to the adoption of chemotherapy for all stages of disease in children. As this provided systemic treatment, staging laparotomy became unnecessary and treatment protocols were based on other parameters defining extent of disease. Risk factors such as tumor burden, presence of B symptoms, male gender and sedimentation rate were included in risk stratification.

Chemotherapy agents recognized to be effective in treating Hodgkin's lymphoma include steroids, vinca alkaloids, antimetabolites and alkalating agents as well as several other drugs. Multiple different combinations of these agents have been used in combination to achieve optimal response with reduced morbidity. Radiation protocols have been modified to consist of low dose involved field radiation therapy (LD-IFRT) using 15–25 Gy.

Long-term follow-up has continued to reveal toxicities of the various chemotherapy agents as well as a significant incidence of second malignancies. Current trials are evaluating the success and comparative morbidity of various regimens with or without low dose involved field radiation [24, 30]. It has been observed in some trials that early responders to chemotherapy have better outcome and this has been incorporated as a decision factor to randomize whether or not to use radiation therapy.

Unlike many other pediatric tumors, the salvage rate for relapsed HD is quite high. This provides another area for controversy and discussion. Second courses of therapy carry an additional risk of toxicity and late second malignancy. Outcome goals must include not only short term success but also long term survival and quality of life.

Prognosis and Long-Term Effects

Survival rates for pediatric Hodgkin's disease have been greater than 90 % since the mid 1980s and provide a growing population of long-term cancer survivors. Long-term follow-up has revealed an increased risk for a spectrum of second malignancies with variable survival. In 1989, Meadows estimated the cumulative probability of any second neoplasm after treatment of pediatric Hodgkin's disease to be 20 % after 20 years of follow-up [42]. A more recent follow-up study from Bhatia et al on behalf of the Late Effects Study Group looked at 1380 children who had been treated for

Hodgkin's disease and noted 88 s neoplasms with an actuarial incidence of 7 % at 15 years after diagnosis [4]. Many of these neoplasms can be linked to specific treatment components and the risk of second neoplasm appears to be greater in children than adults. Recognition of these associations has stimulated the ongoing modifications of treatment protocols for pediatric Hodgkin's disease in an effort to balance short-term success with long-term outcome. The long latency for secondary solid tumors in particular makes this a challenging task with continued need for ongoing long-term follow-up.

Secondary leukemia, myelodysplastic syndrome and non-Hodgkin's lymphoma all occur with increased risk after treatment of pediatric HD and carry a poor prognosis. The use of alkylating agents is strongly liked to secondary leukemia and has been variably liked to myelodysplastic syndrome and NHL in some studies [36].

Most solid tumors have a latency period of greater than 10 years. Breast cancer is well recognized as a secondary neoplasm of increased risk after treatment of pediatric Hodgkin's disease [53]. It is most strongly linked to radiation therapy with greatest risk when dose is greater than 40 Gy. These malignancies are often bilateral and are in the radiation field in the medial breast or upper outer quadrant. Radiation therapy during puberty or young adulthood appears to increase the relative risk, presumably due to the proliferative state of the hormonally sensitive tissue. Chemotherapy and splenectomy may also be risk factors [36]. It is recommended that girls treated for pediatric HD be followed with annual breast exams until 25 years. Surveillance should then increase to include breast examination every 6 months and yearly mammography for those that received radiation therapy [36]. Secondary thyroid cancer is also linked to radiation therapy and is the second most common solid secondary cancer. Solid tumors of the gastrointestinal tract also occur with increased risk, particularly colorectal and gastric. The latency period is 10–20 years and symptoms are generally absent until advanced stages. It is recommended that monitoring surveillance be done beginning 15 years after radiation or at age 35 years (whichever is later) [36]. Lung cancer also carries an increase in relative risk. This is markedly potentiated by smoking and increases the relative risk by an additional 20 fold [36]. Secondary sarcomas have a relative increase in risk by 10–14.9 fold. Radiation and alkylating agents are both liked to bone tumors in particular, and these tumors are most likely to occur during the adolescent growth spurt.

Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma accounts for approximately 60 % of pediatric lymphomas [59]. The vast majority are high grade tumors with rapid growth. The incidence of non-Hodgkin's lymphoma increases steadily with age. There has been a 30 % increase in the annual incidence of pediatric lymphoma in the United States during the period from 1973 to 1991. European data also show an annual increase in incidence of childhood non-Hodgkin's lymphoma over the period from 1988 through 1997 [25].

Histology/Tumor Markers

Non-Hodgkin's lymphomas are classified pathologically by a combination of morphologic and immmunophenotypic features. There are three main subcategories based on cell differentiation (precursor or mature) and cell of origin (B cell, T cell or NK cell). Mature B-cell NHL includes both Burkitt's and diffuse large B-cell lymphoma (DLBCL). Lymphoblastic lymphoma derives from precursor T cells in the majority of cases but also includes those with precursor B-cells. Anaplastic large cell lymphoma (ALCL) includes those lymphomas that arise from mature T cells and null cells. These three subgroups account for the majority of NHL cases in children. Follicular and mucosa associated lymphoid tissue (MALT) lymphomas are rare categories with a more favorable prognosis.

Mature B-cell Lymphomas

This subcategory includes those previously referred to as "undifferentiated lymphomas" and accounts for 40–50 % of NHL in children. The most common varieties are Burkitt's and Burkitt's-like lymphomas that have small, noncleaved cells on histologic examination. Burkitt's lymphoma typically has what has been called a "starry sky" appearance due to the presence of interspersed benign histiocytes among the neoplastic cells. Immunophenotypically these tumors are distinguished by positive staining for the markers CD10, CD20, and CD 22 [59]. They are negative for the enzyme TdT. They occur at many sites and most of the abdominal non-Hodgkin's lymphomas fall into this subgroup. Diffuse large B-cell lymphomas (DLBCL) are also in this subcategory. A subset of DLBCL presenting as isolated mediastinal disease in adolescents is seen and carries a poor prognosis [60].

Lymphoblastic Lymphomas

Lymphoblastic lymphomas account for 20 % of childhood NHL [59]. These tumors are of precursor cell origin. Up to 75 % arise from T-cell precursors and account for the majority of NHL presenting in the mediastinum. Immunophenotypically, these tumors are characterized by positive staining for the enzyme TdT, a known T cell characteristic.

Anaplastic Large Cell Lymphomas

Most of these lymphomas are of mature T cell origin and all are CD30 positive. They account for 10 % of childhood NHL. They occur at both nodal and extra nodal sites.

Follicular

Follicular lymphomas are rare and account for less than 2 % of pediatric non-Hodkgin's lymphoma [2]. They are of B cell origin and are characterized by follicular architecture on histologic examination. Immunophenotypic features include positive staining for CD20 and bcl-6. Most also show CD10 positivity. The most common anatomic primary site for these lymphomas is the head and neck region. Follicular lymphoma in children is usually low stage and has a favorable prognosis with complete excision only. In contrast to adults, Bcl-2 expression is noted in a minority of cases. One pediatric series has shown that Bcl-2 expression is associated with disseminated disease and poor prognosis [38].

MALT

Mucosa associated lymphoid tissue (MALT) lymphomas are seen in up to 40 % of NHL in adults but are rare in children [9]. They account for only 0.1 % of pediatric NHL. They are of B cell origin and occur in extra nodal tissue with heterogeneous small B cells growing in marginal zones. Most are associated with chronic infection or autoimmune diseases. As in adults, the most common location is in the gastric lining and is associated with *Helicobacter pylori* infection. Treatment of the *H pylori* infection is generally curative. The second most common location in children is in the parotid gland in association with HIV infection and may also respond to therapy directed at *H pylori* [44]. Two pediatric cases involving the minor salivary gland of the lip and one of the appendix in otherwise healthy children have been reported and responded to local excision only [5, 41, 44].

Diagnostic Evaluation/Staging System

Evaluation of the child with suspected or confirmed non-Hodgkin's lymphoma begins with a complete physical examination with particular attention to nodal areas. Involved peripheral nodes may provide a preferred means of tissue diagnosis with extensive chest or abdominal primary tumors. Laboratory evaluation should include complete blood count with differential, electrolytes, renal panel, urinalysis and liver function studies. Lactic dehydrogenase (LDH) and uric acid are helpful as indices of metabolic turnover and LDH is recognized as a marker of tumor burden and prognosis [59]. Disease should be sought in diffuse sites including bilateral bone marrow aspirates, spinal fluid examination, chest x-ray and CT scan of the neck, chest, abdomen and pelvis. Bone scan should also be performed. As in Hodgkin's disease, FDG-PET scans are also employed for staging and follow-up in some pediatric non-Hodgkin's lymphoma protocols [23]. Immune deficiency states are known to increase the risk of lymphoma and testing for human immunodeficiency virus should also be done.

Table 21.3 Murphy staging system for non-Hodgkin's lymphoma [47]

Stage	Criteria for extent of disease
Localized	
I	A single tumor (extranodal) or single anatomic area (nodal) with the exclusion of mediastinum or abdomen
II	A single tumor (extranodal) with regional node involvement
	Two or more nodal areas on the same side of the diaphragm
	Two single (extranodal) tumors with or without regional node involvement on the same side of the diaphragm
	A primary gastrointestinal tumor, usually in the ileocecal area, with or without involvement of associated mesenteria nodes only, grossly completely resected
Disseminated	
III	Two single tumors (extranodal) on opposite sides of the diaphragm
	Two or more nodal areas above and below the diaphragm
	All primary intra-thoracic tumors (mediastinal, pleural, thymic)
	All extensive primary intra-abdominal disease
	All parasipnal or epidural tumors, regardless of other tumor site(s)
IV	Any of the above with initial CNS and/or bone marrow involvement

The staging system employed for non-Hodgkin's lymphoma is shown in Table 21.3.

Although staging is undertaken at diagnosis, these should all be considered widespread tumors at diagnosis with an aggressive potential for rapid growth.

Clinical Presentation and Surgical Issues

The majority of childhood non-Hodgkin's lymphoma presents in extranodal sites. A review of 80 consecutive cases of pediatric NHL from St. Bartholomew's Hospital in London [50] noted a primary site in peripheral lymph nodes in only 19 % of cases. The abdomen was the most common presenting site in 26 % of children followed by extranodal head and neck (23 %), and mediastinum (20 %). Rare sites including gonads, genitals, skin (Fig. 21.6) and bone accounted for 13 % of children. All four cases of cutaneous lymphoma in Ng's series had localized disease only. Central nervous system disease may be asymptomatic or present with cranial nerve palsy. Involvement of the tonsils may also occur presenting with asymmetric enlargement or with other areas of disease. On rare occasions, isolated tonsillar involvement may be an unexpected finding. A review of routine tonsillectomy specimens by Garavello [18] revealed 2 cases of non-Hodgkin's lymphoma in 1123 specimens

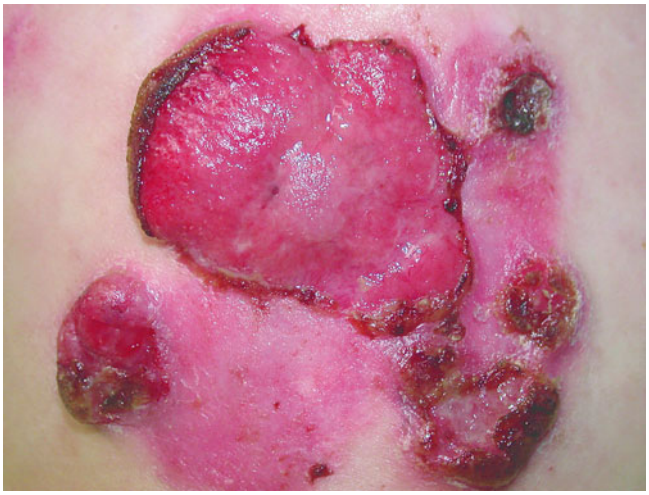

Fig. 21.6 Isolated cutaneous lymphoma

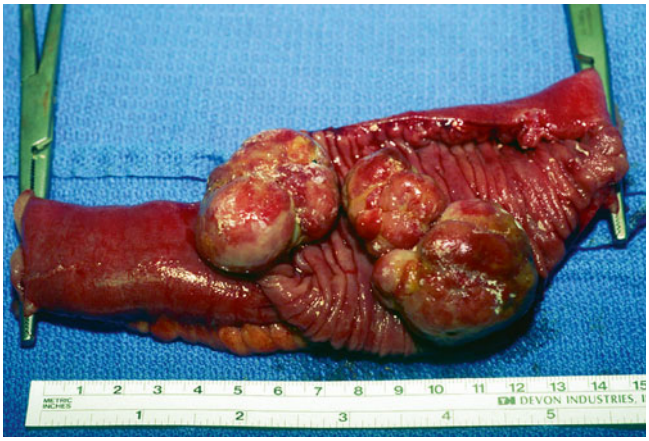

Fig. 21.7 Non-Hodgkin's lymphoma presenting as a cecal mass

(.18 %) from routine pediatric tonsillectomy without clinical suspicion.

Mediastinum

Mediastinal involvement occurs in about 20 % of pediatric cases of non-Hodgkin's lymphoma. These are mainly lymphoblastic lymphomas of T cell origin but diffuse large B-cell lymphomas are also seen. Clinical complaints may include symptoms of upper respiratory infection, chest pain, cough, shortness of breath or signs of superior vena cava syndrome. These masses occur in the anterior mediastinum and carry the same anesthetic risks as described in the section on mediastinal Hodgkin's. Careful physical examination should be done to search for extra thoracic involvement for diagnosis. Pleural effusions are frequently seen (11 % of Ng's series) [50] and thoracentesis may provide adequate material for diagnosis [8, 59]. Pericardial effusions may also occur and sometimes result in cardiac tamponade. In contrast to adult malignancy-associated tamponade, pediatric tamponade is effectively treated with percutaneous drainage [43]. Adult malignant effusions are usually a manifestation of end stage disease and tend to loculate unless treated by pericardial window. Pediatric malignancy-associated tamponade usually has negative cytology and responds well to percutaneous drainage alone. In Medary's study, catheters remained in place for a mean of 5 days and were successfully discontinued without recurrence [43].

Abdomen

Non-Hodgkin's lymphoma presents as an abdominal primary site in 30 % [50, 59] of children. It is more common in males than females by a ratio of three to one. Age distribution is broad with nearly equal incidence in children less than 10 years (44 %) and 10–20 years (56 %) [27]. The most common complaint is abdominal pain that has been present for several weeks before diagnosis [14]. Weight loss occurs in nearly half of patients and nausea and vomiting are common. A palpable mass is found in one third of cases. Those children that present with colicky abdominal pain and heme positive stools may have intussusception from an intramural mass in the distal ileum or cecum (Fig. 21.7). Fever is seen in 26 % of children and an initial diagnosis of appendicitis may be made. In Fleming's consecutive series of 58 children with NHL of the abdomen a preoperative diagnosis of lymphoma was made in only one child [14]. Most patients had a preoperative diagnosis of periappendiceal abcess or idiopathic intussusception. The multi-center Childrens Cancer Study Group experience reported by LaQuaglia et al. [33], revealed a similar pattern with correct preoperative diagnosis in 15 % of patients. In this series, more than half of children had an urgent operation and most of those were felt to have appendicitis or intussusception.

The surgeon's approach to non-Hodgkin's lymphoma in the abdomen will be dictated by the clinical scenario and anatomic findings. Approximately half of the cases will involve the gastrointestinal tract and the vast majority of those will arise in the distal ileum or the right colon [14]. Most of the gastrointestinal lymphomas will present as an acute abdomen due to tenderness or obstruction and many are focal lesions that are amenable to straightforward resection with anastomosis. It is important for the surgeon to consider the possibility of lymphoma so that the tissue will be properly handled for histopathology and biologic studies. The remaining abdominal lymphomas will usually involve diffuse retroperitoneal spread (Fig. 21.8) or include direct infiltration of intraabdominal viscera precluding a complete resection. When this finding is discovered intraoperatively, a limited biopsy should be undertaken to allow accurate diagnosis and prompt initiation of chemotherapy. Subtotal resection and debulking procedures should be discouraged. Previous recommendations for debulking in the 1980s [39, 77] based on limited retrospective reviews were

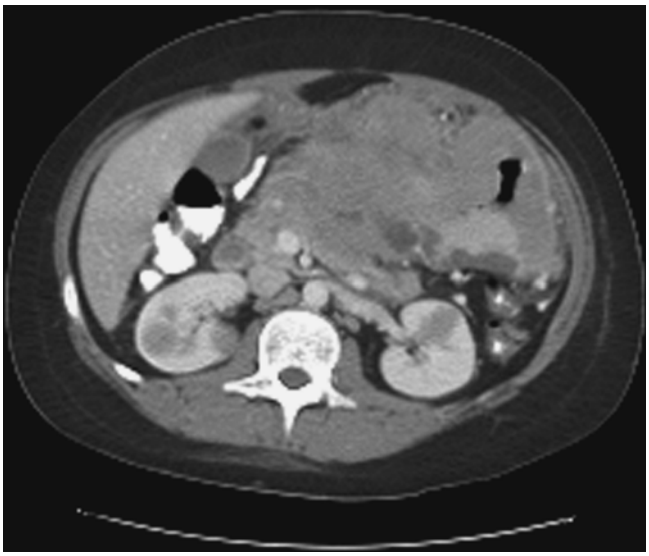

Fig. 21.8 CT scan demonstrating diffuse abdominal non-Hodgkin's lymphoma

not confirmed in pediatric studies reported in the 1990s [17, 63, 68]. Surgical complications that lead to a delay in initiation of chemotherapy are felt to contribute to increased mortality risk [68]. Perforation of the bowel is also associated with a poor prognosis [76] and may occur either spontaneously or secondary to surgical biopsy. Second look procedures after induction chemotherapy should also be discouraged with studies showing either continued unresectability of the mass or necrotic tumor only [28, 63].

If an abdominal mass is discovered prior to laparotomy, the possibility of lymphoma should be considered and a search made for extra-abdominal tissue for biopsy. If ascites is present consideration should be given to paracentesis if possible. The diagnosis of NHL has been made by examination of peritoneal cytology in several cases [72] avoiding the need for more invasive procedures and potential complications.

Other abdominal presentations of non-Hodgkin's lymphoma are seen in a small number of cases. Primary involvement of the stomach is common in adults but was found in only one of 58 children in the St. Jude series [14]. There is usually diffuse infiltration of the gastric wall (Fig. 21.9) and thickened folds may be seen [31].

Jaundice often accompanies abdominal lymphoma, but is the presenting symptom in a minority of cases [13, 52, 55]. The liver itself may be the primary site with multiple parenchymal nodules [54]. Most cases are due to obstructive jaundice either from pancreatic involvement causing ampullary obstruction or from peri-portal adenopathy causing extrinsic compression of the common duct. Diagnosis has been made using peritoneal cytology, endoscopic biopsy, needle biopsy and open biopsy. Percutaneous transhepatic drainage has been associated with complication of persistent biliary fistula

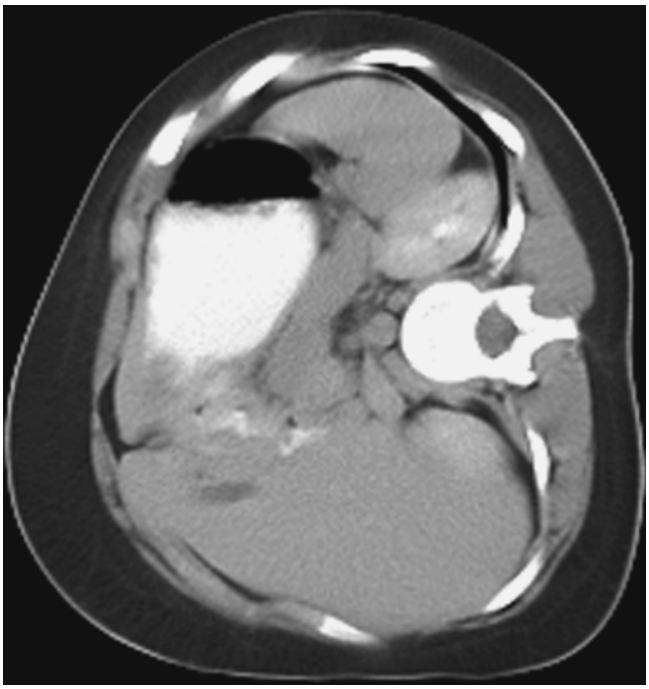

Fig. 21.9 CT scan demonstrating thickened gastric wall due to diffuse infiltration with non-Hodgkin's lymphoma

causing delay in chemotherapy and is not recommended [72]. As in adults [13], the rapid response of the tumor bulk to chemotherapy will allow early relief of obstruction.

Renal involvement with lymphoma is seen in approximately 4–27 % of children [50] and may consist of diffuse involvement or focal lesions. Isolated involvement of the kidney may occur with clinical complaints of flank pain and hematuria. Asymptomatic hypertension has been reported as a presentation of renal lymphoma in children [3, 11].

Other rare abdominal sites include the female pelvic viscera. Primary ovarian lymphomas may present with ovarian enlargement [1]. They have generally been treated by excision and chemotherapy. Although some have questioned the ovary as a primary site, the ovaries have been shown to have small foci of lymphatic tissue in 54 % of females in an autopsy series [45]. Well documented cases of isolated ovarian involvement with follow-up have been reported [45]. In a series of 101 pediatric ovarian neoplasms from New Guinea, 3 % were due to Burkitt's lymphoma [61]. Diffuse uterine enlargement from lymphoma has also been reported presenting as an abdominal mass in two young children [40, 46]. Both had additional sites of involvement (renal, CNS). In each case, diagnosis was made by uterine biopsy and the lymphoma was of B cell origin.

Testis

Infiltration of the testis by lymphoma (Fig. 21.10) is seen in 3–12 % of children with non-Hodgkin's lymphoma at diagnosis [10] and may be treated by systemic chemotherapy.

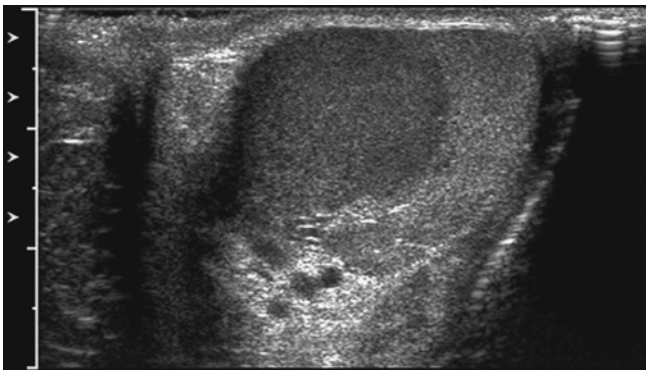

Fig. 21.10 Ultrasound imaging of testicular infiltration due to non-Hodgkin's lymphoma that manifested as testicular enlargement

Radiation therapy has been used in some protocols due to the concern of the testis as a "sanctuary site" less accessible to chemotherapy. A report by Dalle et al. in 2001 [10] summarized the French experience with testicular involvement in childhood B cell lymphoma and acute lymphocytic leukemia. Testicular involvement at diagnosis was noted in 30 boys (5.3 % of males). Involvement of other anatomic sites was present in all but one boy. Testicular enlargement was the presenting complaint in five of the boys and all underwent diagnostic orchiectomy. The remaining boys were noted to have testicular involvement, but presented with other complaints and underwent testicular biopsy or clinical confirmation only. All were treated with chemotherapy and none received radiation. Clinical regression of testicular involvement was seen in all patients and there were no episodes of testicular relapse. Survival was not influenced by the presence of testicular involvement. The authors concluded that systemic chemotherapy is sufficient for B cell non-Hodgkin's lymphoma in boys and that a careful search should be made for additional sites of disease in boys that present with testicular masses. In rare cases, primary lymphoma arising in the testis will present as testicular enlargement and diagnosis will be made at the time of biopsy or orchiectomy. Both follicular and Burkitt's lymphomas have been reported in children as a primary site [22, 29]. In general, these tumors are treated by orchiectomy and chemotherapy. Successful treatment by orchiectomy alone has been reported in a 3 year old boy with stage I follicular lymphoma of the testis [22].

Treatment

Non-Hodgkin's lymphoma is considered a systemic disease in all patients and chemotherapy is the cornerstone of successful treatment. As in many other childhood cancers, there has been a remarkable evolution in treatment regimens since the 1960s with continued improvement due to multicenter, cooperative trials. Increasing knowledge of tumor biology has allowed recognition of differential sensitivity to chemotherapeutic agents among various phenotypic subgroups and risk group stratification. As survival improves for certain subgroups, attention may be refocused on reduction of treatment morbidity and long-term consequences. The surgeon's role in providing adequate tissue for accurate diagnosis and biologic studies is crucial in determining the appropriate chemotherapy regimen. It is important to minimize surgical morbidity so that chemotherapy can begin promptly for these tumors since they have such a rapid growth fraction.

Current chemotherapy for NHL is based on attention to histology, immunophenotype, extent of disease and central nervous system prophylaxis.

Children with low stage (I-II) disease have an excellent overall prognosis with multi-agent chemotherapy but patients with lymphoblastic lymphoma require a more aggressive and longer regimen to achieve success.

Children with advanced stage (III-IV) disease are treated with longer multiagent regimens and prognosis varies with subtype. Patients with Mature B-cell and lymphoblastic lymphomas have long term survival greater than 80 %. Those with anaplastic large cell lymphoma have disease free survival of 60–75 [58]. Central nervous system prophylaxis with intrathecal chemotherapy is given to most patients. If CNS involvement is present at diagnosis, cranial irradiation is usually administered.

The role of radiation therapy outside the central nervous system is limited to only a few situations for childhood NHL. It is occasionally used as emergent therapy for critical airway compression due to mediastinal tumors with shielding of nodal areas planned for biopsy and for massive testicular involvement.

The use of bone marrow transplantation for some types of non-Hodgkin's lymphoma is also under investigation in some centers [7, 35].

Treatment of Relapsed NHL

Unlike Hodgkin's disease, the salvage rate for relapse in non-Hodgkin's lymphoma is poor. Current clinical trials include a variety of high dose chemotherapy combinations and may also include bone marrow transplant [49].

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Melanoma and Other Skin Cancers

22

Stuart B. Watson

Melanoma

Cutaneous melanoma is a life threatening skin cancer that has greatly increased in incidence in recent times, becoming a common cancer in young adults, and an increasing problem in children and adolescents. Awareness of melanoma amongst clinicians and the public is of great importance as early diagnosis results in a far higher chance of curative treatment by relatively simple surgery [1, 2]. Melanoma in pre-pubescent children often presents with an atypical appearance that can cause difficulty in diagnosis [3, 4].

Epidemiology and Predisposing Conditions

Melanoma accounts for between 1 and 3 % of childhood cancers. Presentation of melanoma in childhood is significantly more common in adolescence than in pre-pubertal children with about 85–90.5 % of childhood melanomata presenting in the second decade of life [5, 6]. As such, it is a relatively rare childhood cancer, but there has been a substantial increase in the incidence of melanoma over the last four decades. In the USA, the incidence in children and adolescents increased at an average of 2.9 % per year between 1973 and 2001 [1]. Even more dramatic increases in incidence in young people have been observed with, for example, a doubling of the incidence in Sweden between the 1970s and 1980s [7]. The survival of young people with melanoma is improving but it remains a major threat to life. Overall, in the United States, melanoma in the first two decades of life was found (by year 2005) to have a 93.6 % 5 year survival [8].

Melanoma is most prevalent in white populations living in areas with high levels of solar exposure. Episodes of sunburn and cumulative exposure to solar radiation are important environmental risk factors and these have probably been responsible for the increased incidence of the disease. There is recent evidence that the rate of increase of incidence is slowing, possibly secondary to the implementation of public health campaigns to reduce sun exposure [9, 10].

Known significant risk factors for developing a malignant melanoma in childhood are: a family history of melanoma; vulnerable skin type (pale, tending to freckling, fair or red hair); and increased numbers of various types of pigmented naevi, especially dysplastic naevi [11–13]. The role of sun exposure in causing childhood melanoma is not clear, but the incidence of melanoma in white children in Queensland was found to be six times that in the United Kingdom [14]. Other conditions that significantly increase risk of developing melanoma include immunosuppression, previous presentation of a different cancer, albinism, xeroderma pigmentosum and retinoblastoma.

The commonest predisposing lesion for melanoma in childhood is a congenital melanocytic naevus (CMN). Management of these remains a matter of debate. CMN have been classified as small (<1.5 cm), medium (1.5–19.9 cm) and large/giant (20 cm and above). Increasingly it is being accepted that these sizes are gauged as projected adult size (PAS). Series have shown that up to 50 % of melanomata in prepubescent children arise in medium to giant CMN [15]. Large CMN have been shown to carry a substantial risk of malignant change. Risk of malignant change in small CMN is uncertain, but is likely to be greater than that of the general population [16].

In the past it had been widely accepted that attempts should be made to remove large and giant congenital naevi before puberty to reduce the risk of malignant change. However, recent studies have shown incidence of cutaneous melanoma in CMN of around 2 % or lower [17–19]. Evidence from a large prospective study has shown the following: 1.9 % of congenital melanocytic naevi produced malignant melanoma; lightening of pigmentation occurred in many

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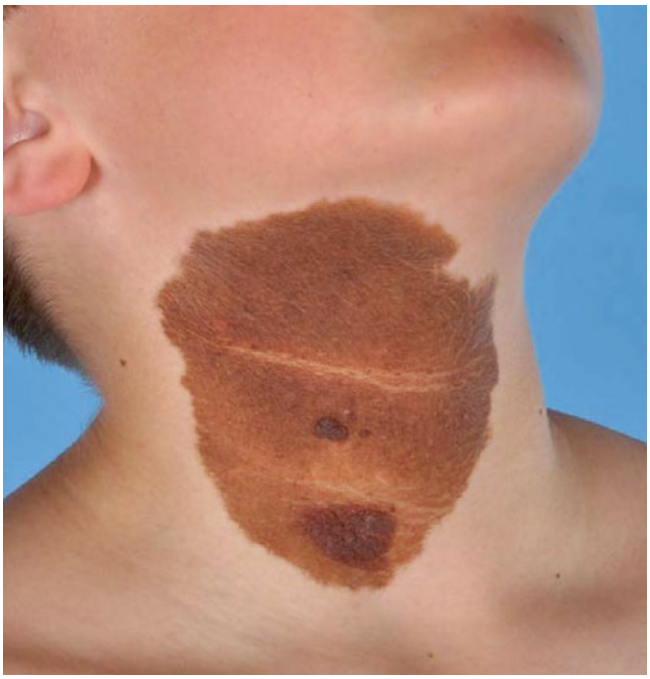

Fig. 22.1 Medium sized congenital melanocytic naevus

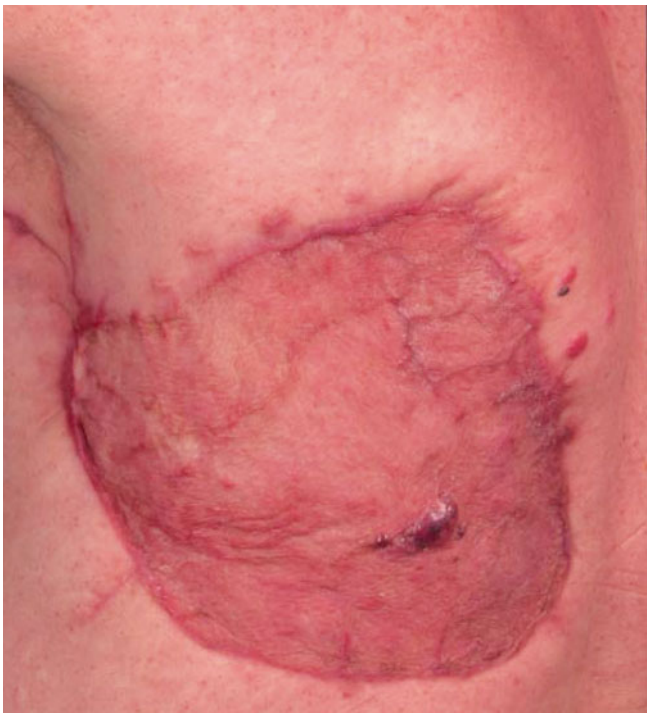

Fig. 22.2 Recurrent melanoma deep to previous excision of melanoma arising in congenital melanocytic naevus

lesions; there was no evidence of reduction in melanoma risk by excision and there was possible evidence of stimulation to increased growth of lesions by surgery [20]. In addition the significant incidence of central nervous system (CNS) complications (18 %) and presence of non-melanoma tumours supports a move towards the primary treatment plan for large and medium CMN being close observation by a skilled multidisciplinary team rather than surgery in all cases [21]. However, there are strong psychosocial reasons for removing CMN (Fig. 22.1). Removal of medium/large CMN requires reconstructive techniques such as tissue expansion, skin grafting or serial excision [22]. It is important to counsel families that surgery does not always succeed in obviating melanoma risk because of the likelihood that naevus cells will remain at distant sites or in the depths of the lesion (Fig. 22.2).

Genetics and Pathology

A family history of melanoma is a significant risk factor for childhood melanoma (25.6 % of patients shown to have family history) [23]. A number of specific gene abnormalities have been associated with familial melanoma. The strongest association is with CDKN2A gene mutations that were found in families presenting with familial melanoma [24]. Other gene abnormalities associated with melanoma include CDK4, ARF and MC1R [25]. However, whilst these gene abnormalities produce a high risk of melanoma in affected families, they are only associated with a small proportion of the total numbers of melanomas [26]. Also, CDKN2A and CDK4 abnormalities are only present in a small proportion of young people with melanoma [27, 28]. Accordingly, the strongest influence of genetic factors in melanoma risk for children seems to be in broad phenotypic characteristics such as fair freckled skin, rather than specific known genetic abnormalities.

Melanoma develops from melanocyte transformation and invasion either de novo or in a pre-existing naevus [29]. Gene mutations including those of *BRAF* and N-RAS are associated with uncontrolled growth of melanocytes, initially in a radial-growth phase (lateral, superficial), and later in a vertical growth phase. Radial growth phase co-relates with a histological appearance of in situ or very superficial melanoma, and vertical growth phase with invasive malignancy which can metastasise [30].

The commonest clinico-pathological subtypes of melanoma are superficial spreading or nodular melanomas. These subtypes are both found in children. Other subtypes may include the following [31].

Common

Spitzoid melanoma is a specific sub-type resembling Spitz naevus, characterized by epithelioid or spindle cells and with specific molecular features [32]. Difficulty in distinguishing benign from malignant Spitzoid lesions has been illustrated by studies showing significant numbers of both false positive

and negative results [33–35]. Not uncommonly, review by several pathologists or a pathology panel is required, and even with specialist pathology review, it is often not possible to determine whether a lesion is a melanoma [36]. Recent advances have improved the methods of differentiating between spitz naevi, atypical spitzoid tumours (of uncertain malignant potential) and melanomas. Molecular pathology of the primary lesion and sentinel lymph node biopsy may be used to elucidate diagnosis in the difficult lesion, but the use of the latter remains controversial, as it is possible that benign naevus cells may be found in lymph nodes [37]. Atypical spitzoid tumours should be followed up as for malignant melanoma.

Rare

- Acrallentiginous melanoma may occur on the hands and feet of young people of African race.
- Small cell melanoma is typically found on the scalp or in a large CMN. It tends to be aggressive with a poor prognosis [38]
- Malignant blue naevus resembles a benign hamartoma. It tends to have a poor prognosis [39].
- 'Animal' type melanoma is a pigment-secreting lesion, which tends to grow deep in the dermis, but may have a relatively good prognosis [40]

Lentigo maligna melanoma is a typical adult subtype which does not tend to occur in childhood, because of aetiology of prolonged sun exposure.

Clinical Presentation

Clinical diagnosis of melanoma in children (especially prepubescent) can be difficult, with lesions commonly appearing atypical in comparison to diagnostic criteria for adults. Lesions presenting with an atypical appearance tend to be amelanotic, with a pink or red surface, and may mimic pyogenic granuloma, keloid scar or even a wart. There may be a more regular border and/or surface than is usually seen with malignant melanoma [41] (Figs. 22.3 and 22.4). However, this has not been found in all clinical series, especially in series with a preponderance of adolescents [15]. The following adult diagnostic criteria are often applicable and should be used as indicators for excision biopsy: the ABCDE criteria or the seven point checklist are useful for clinicians and patients to recognize features of suspicion [42, 43] (Figs. 22.5 and 22.6; Table 22.1).

Ultimately, a safety-first policy should be followed and any doubtful lesion excised to avoid undue diagnostic delay. It is likely that a very significant number of benign lesions will have to be removed to achieve diagnosis of childhood melanoma at an early stage [44].

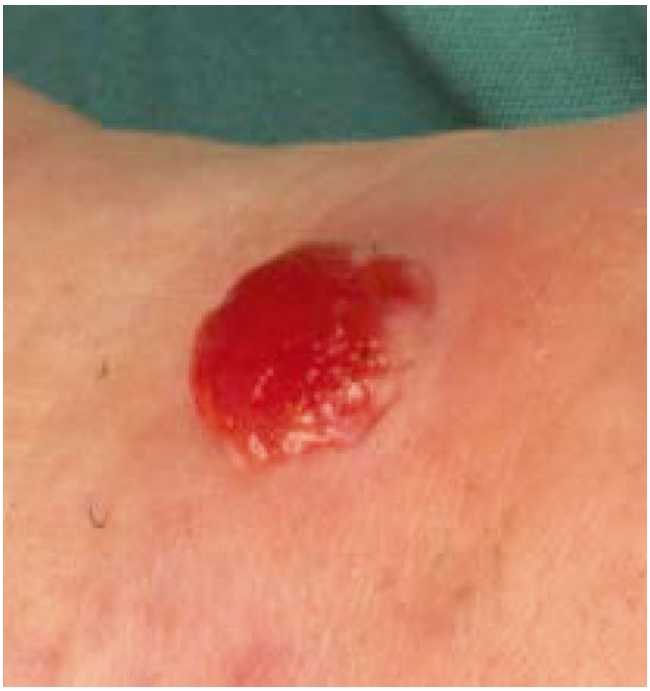

Fig. 22.3 Atypical appearance of melanoma in pre-pubescent child. Raised, smooth and amelanotic

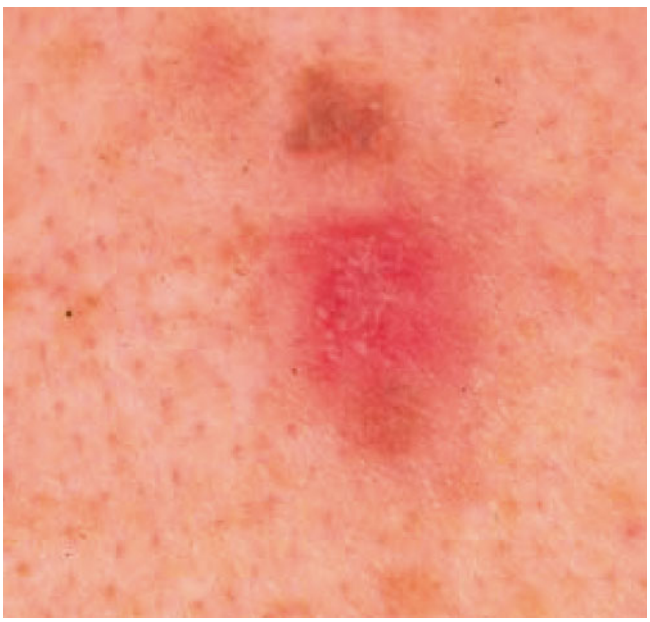

Fig. 22.4 Superficial amelanotic melanoma

Melanoma in childhood may be classified as presenting in pre- or post-pubescent children. Melanomas in the prepubescent group are further sub-classified into congenital, infantile (birth to 1 year) and melanoma of childhood (1 year to puberty). Congenital and infantile melanoma are extremely rare and are most strongly associated with congenital pigmented naevi [27].

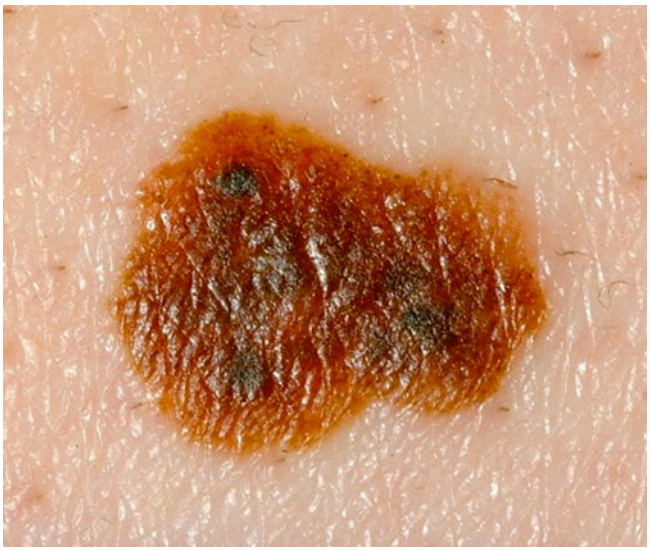

Fig. 22.5 Superficial spreading melanoma in adolescent

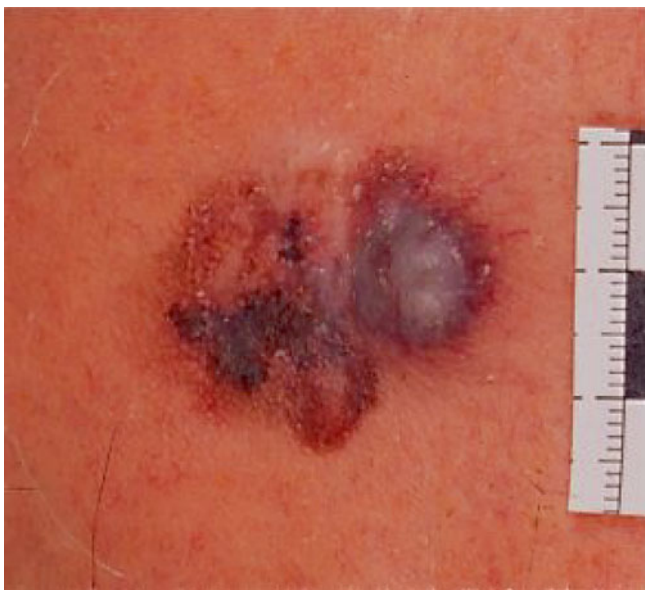

Fig. 22.6 Nodular Malignant Melanoma

Occasionally, children present with ocular melanoma (3 % of childhood melanomas) or melanoma of unknown primary (0.7 %) [6]. Rarely, children may present with oral mucosal melanoma.

Staging

Staging of melanoma guides treatment and prognosis and is detailed in the most recent American Joint Committee on Cancer (AJCC) classification. Staging of the primary melanoma is based on Breslow thickness of the lesion, with additional factors worsening prognosis being ulceration and/or high mitotic rate [45, 46]. Melanoma typically metastasises first to regional lymph node and later to distant sites and this is reflected in the staging system (Tables 22.2 and 22.3) [46].

Previously, Clark level of dermal invasion was used too, but whilst this is still widely reported in pathology and is of interest in assessing a tumour, it has not been shown to confer sufficient prognostic information and has been withdrawn from the staging system [47].

Prognosis of melanoma in children is similar to that in adults [23, 48]. Pre-pubescent children tend to present with more advanced disease than older children and adults The thickness of the primary melanoma may have little bearing on prognosis in children of under 10 years [6].

Table 22.1 Diagnostic criteria for malignant melanoma

ABCDE
(A) Asymmetry
(B) Border irregularity
(C) Colour variation
(D) Diameter of 6 mm or greater
(E) Evolution
Seven point checklist features (One major feature or three minor features)
Major:
Change in size
Irregular shape
Irregular colour
Minor:
Largest diameter 7 mm or greater
Inflammation
Oozing
Change in sensation
'Atypical' appearance in some lesions in pre-pubertal children
Raised red/pink nodule often smooth
Well defined border
May resemble pyogenic granuloma or keloid
Increasing size
Parental concern regarding unexplained lesion

Refs [3, 42, 43].

Imaging

Imaging is not indicated in adults with Stage I, II or IIIa melanoma as the pick up rate for scans in these patients is low, and false positive rate is significant [49, 50]. The mainstay of imaging for Stage IIIb/c and IV melanoma is Computerized Tomography of lungs, liver, brain and deep nodes (eg iliac and aortic for lower limb melanoma) However, there is no definitive guideline for imaging in children, and it is possible that a lower threshold for imaging for distant metastases may be appropriate in young children who tend to present with more advanced disease.

Ultrasound scanning is useful for localizing enlarged lymph nodes for fine needle aspiration biopsy. It may also be more sensitive than CT for assessing hepatic lesions.

Table 22.2 AJCC TNM staging

Classification	Thickness (mm)	Ulceration status/mitoses
T		
Tin situ	Not applicable	Not applicable
T1	≤1.00	(a) Without ulceration and mitosis $<1/mm^2$ (b) With ulceration or mitoses $\geq 1/mm^2$
T2	1.01–2.00	(a) Without ulceration
		(b) With ulceration
T3	2.01–4.00	(a) Without ulceration
		(b) With ulceration
T4	>4.00	(a) Without ulceration
		(b) With ulceration
N	No. of Metastatic Nodes	Nodal Metastatic Burden
N0	0	NA
N1	1	(a) Micrometastasis (SLNB)
		(b) Macrometastasis (palpable node)
N2	2–3	(a) Micrometastasis (SLNB)
		(b) Macrometastasis (palpable nodes)
		(c) In transit metastases/satellites without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in transit metastases/ satellites with metastatic nodes	
M	Site	Serum Lactate Dehydrogenase
M0	No distant metastases	Not applicable
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

Positron Emission Tomography (PET) scanning may occasionally be useful for distinguishing distant metastases and lymphadenopathy.

Surgery

Whenever possible, excision biopsy with a margin of 2 mm should be the diagnostic technique of choice to provide optimum histological analysis. This is essential to provide the most accurate information regarding tumor thickness on which staging and prognosis of the primary melanoma is based [51]. Incisional biopsy does not allow the pathologist to provide diagnostic information with anything like the same measure of accuracy, although in large lesions, it may be the rational first option. Curettage excisions are all but useless for melanoma histopathology and should be strictly avoided.

Treatment plans for established melanoma in children are the same as for adults.

Surgical excision remains the most effective treatment for malignant melanoma and is the only treatment regularly associated with long term control of the disease. Adequate surgical excision of the primary melanoma is determined by a measured surgical margin from the visible edge of the lesion (excision margin). The extent of the excision margin has been the subject of much debate and investigation. The ideal excision margin remains unproven, with a paucity of controlled clinical trials [52]. However, there are widely adopted guidelines that follow a principle whereby the thicker the melanoma, the wider the excision. A widely used guideline is: for in situ melanoma, 5 mm minimum margin; invasive melanoma less than 1 mm Breslow thickness, 1 mm margin; for lesions of thickness 1.01–2 mm, a margin of 1–2 cm; for lesions of 2.1–4 mm thickness, a margin of 2 cm; lesions >4 mm, a margin of 3 cm [49] (Table 22.4).

Occasionally clinicians, patients and families face difficult decisions regarding excision margins for a melanoma presenting close to an important facial feature such as the eye. In such circumstances, it is reasonable to compromise on initial margin, after appropriate discussion with patient and/or family. If pathology shows incomplete excision, more radical surgery is required.

Table 22.3 AJCC Staging

	Clinical staging				Pathologic staging		
	T	N	M		T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III	Any T	N>N0	M0	IIIA	T1-4a	N1a	M0
					T1-4a	N2a	M0
				IIIB	T1-4b	N1a	M0
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a	N2c	M0
				IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					T1-4b	N2c	M0
					Any T	N3	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

Table 22.4 Excision margins

Excision margins for primary melanoma	
Breslow thickness	Excision margin
In situ	5 mm margin
<1 mm or =1 mm	1 cm
1.01–2 mm	1–2 cm
2.1–4 mm	2–3 cm
>4 mm	3 cm

Optimum depth of excision of the primary lesion remains unproven. A straightforward strategy for planning depth of excision is to remove the full thickness of the subcutaneous fat. Melanoma presenting in large congenital melanocytic naevus may invade deeper.

Defects after wide excision often require skin grafting; a long scar to provide direct closure or a flap repair, and careful discussion with family and patient is necessary to prepare them for the outcome. Future revisionary surgery with serial excision or tissue expansion may be indicated if a skin grafted defect is unsightly or symptomatic.

The last 20 years has seen a great deal of investigation into the value of sentinel lymph node biopsy (SLNB) in staging and treatment of melanoma. SLNB stages lymph node metastasis, which is one of the most important prognostic criteria. Initial hopes that making earlier diagnosis of lymph node metastasis by SLNB would lead to enhanced survival have not come to fruition. Controversy exists as to whether SLNB leads to enhanced disease free survival, and whether it should be a standard of care [53, 54]. Further results of long-term trials are awaited. However, it has become a standard of care for staging of melanoma of Breslow thickness 1–4 mm in the AJCC classification and in United Kingdom guidelines for melanoma management, it has been deemed appropriate to offer to all patients (Fig. 22.7).

Studies of childhood melanoma have shown a higher yield of positive sentinel nodes in melanoma of 1–4 mm thickness than are found in adults, which possibly strengthens the case for undertaking sentinel node biopsy in children [55, 56]. Additionally, it is possible, though not proven, that children and adolescents may have a better response to adjuvant biological (immunotherapy) or possibly chemotherapy agents for stage III disease, so it may be significantly in the interest to have their disease accurately staged to allow treatment, especially if that treatment is part of a controlled clinical trial. However, sentinel node has, as yet shown no convincing benefit for eventual disease outcome, and it is important that families are counseled to this effect, and also of the risk of complication from the surgery.

With a positive sentinel node biopsy, or palpable lymphadenopathy confirmed as melanoma by fine needle aspirate or biopsy (Stage III disease), a patient generally proceeds to regional lymphadenectomy. Five-year survival for this group of patients is of the order of 39 %, so there is a chance of prolonged disease free survival [57].

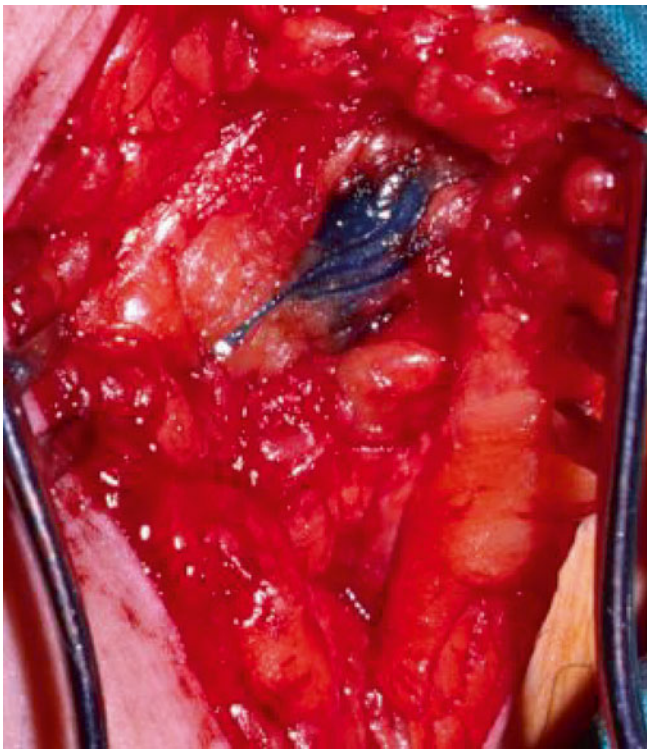

Fig. 22.7 Sentinel node biopsy using blue dye and Technetium colloid techniques

Other indications for surgery are for in-transit metastases, for symptom control in multiple cutaneous metastases and rarely for isolated distant metastases.

An essential adjunct to surgery for melanoma (and atypical spitzoid tumours) is regular clinical follow-up, which in the paediatric population should extend for much longer than the guideline of 5 years for adults.

Non-surgical Treatment

No adjuvant therapy has been shown to convey a definite survival advantage for melanoma.

The most widely used treatment has been Interferon alpha, which has shown benefit in Stage III melanoma in adults in some trials [58]. Studies of children with stage III melanoma (lymph node metastasis) treated with high dose Interferon have shown the treatment to be tolerated acceptably [59, 60]. However, whilst widely used, efficacy of Interferon remains in doubt. A variety of other immunotherapy agents have been/are used on a trial basis, but are unproven.

Chemotherapy has not been shown to convey an advantage as an adjuvant treatment, but it is the treatment of choice in established distant metastatic disease, and whilst responses in adult patients are often poor, there are reports of good responses to chemotherapy in children [61, 62].

Radiotherapy has a role in palliative treatment of symptomatic distant metastases and has been trialed recently for lymph node basins at high risk of local recurrence after lymphadenectomy (where extracapsular spread is present), showing reduced local relapse rates [63]. However there is no evidence that this conveys a survival advantage.

Great efforts have been made to produce a successful melanoma vaccine, but so far, these have not come to fruition.

Non-melanoma Skin Cancers

The term non-melanoma skin cancer is a catchall term that is used regularly when reporting cancers. It groups together the more common malignant epithelial skin tumours of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) with a disparate group of rarer tumours arising from the wide variety of other tissues present in the skin such as sarcomas and lymphomas. The term reflects the reporting of skin cancer statistics and the fact that melanoma is a common skin malignancy that causes significant mortality, whereas other forms of skin malignancy are either rare or have a much lower rate of mortality.

Epidemiology

BCCs and SCCs are very common skin cancers in older adults with fair skin [64, 65]. The main risk factor for their development is prolonged ultraviolet (UV) light exposure that causes cumulative damage to DNA [66, 67]. This makes them much less common in children. In fact they account for half as many cases as melanoma in children whereas over all ages they account for nearly ten times as many [68–71]. The annual rate in children up to the age of 14 is around 1 per million. Reporting of non-melanoma skin cancers is notoriously low probably because they are very common but the figures in children are more likely to be accurate. BCCs make constitute about 50 % of cases and the remainder is mainly made up of SCC and dermatofibrosarcoma protuberans. There are a few predisposing conditions which permit the development of these tumours either through a genetic predisposition for the formation of malignancy or a complete failure to protect against damage from even the most minimal amount of UV exposure.

Pre-disposing Conditions and Lesions

Gorlin Syndrome/Naevoid Basal Cell Carcinoma Syndrome

Gorlin syndrome is the eponymous name for naevoid basal cell carcinoma syndrome. It is a rare (1 in 50,000–150,000)

genetic condition with autosomal dominant inheritance, complete penetrance and variable expression [72]. It is characterised by mandibular cysts, ovarian fibromas and the development of multiple basal cell carcinomas that start to appear around the time of puberty. The underlying genetic abnormality is a mutation of the *PTCH* (patched) gene found on chromosome arm 9q. *PTCH* is an inhibitor of the hedgehog signaling pathway that causes cell growth [73, 74]. *PTCH* mutation is common is sporadic BCCs. UV exposure seems to also play a role in the development of these tumours because they still occur predominantly on sun exposed sites [75].

Epidermodysplasia Verruciformis

Epidermodysplasia verruciformis is a rare genetic disorder that is inherited in an autosomal recessive or more rarely X-linked manner [76, 77]. It predisposes affected individuals to chronic infection with human papillomavirus (HPV) [78]. This causes widespread viral warts. The lifetime risk of skin cancer, usually SCC, is 30–70 % [79]. These usually arise in sun-exposed sites suggesting that the combination of HPV and UV exposure is synergistic. They may arise as de-novo lesions or from existing papillomas. There are over 30 HPV subtypes but HPV-5 and HPV-8 are the most commonly identified in the SCCs [80]. The most commonly identified underlying genetic abnormality is mutation of the EVER1 & EVER2 genes on 17q25, although this only accounts for around 75 % of cases [81, 82]. The exact mechanism by which this allows HPV infection is not yet fully understood but the genes code for proteins that play a role in zinc storage within the cell and there absence may permit easier viral access to zinc that is required for viral replication [83].

Xeroderma Pigmentosum

This is a rare genetic condition that is inherited in an autosomal recessive manner. The underlying deficit is in nucleotide excision repair, which is the process by which UV damage to DNA is repaired [84]. At least seven different genes (XPA-XPG) have been identified that are involved in this process and any one of theses may be at fault. This is reflected in a spectrum of clinical disease. The frequency is about 1 in 250,000 in the USA & Europe. Japan has a higher incidence at around 1 in 40,000 and the black Maori Mayotte population 1 in 5000 [85–87]. The condition is characterised by early erythema, scaling and freckles followed by poikiloderma [88]. Affected individuals are predisposed to all skin malignancies and may present as early as 4 years old. They appear predominantly on sun-exposed sites.

Albinism

Albinism is an inherited disorder of partial or complete failure of melanin production. It may affect the eyes only or eyes and skin [89, 90]. There is a variety of underlying genetic defects that predispose to the condition for the cutaneous forms. These are defects of OCA1 – OCA3 genes which code for tyrosinase, P protein and tyrosinase-related protein respectively. These proteins are required for various steps in melanin synthesis. Melanin is the main UV absorbing protein in the skin and its (relative) absence predisposes the individual to UV damage. The incidence is around 1 in 17,000.

Ferguson-Smith Disease/Multiple Self-Healing Squamous Epithelioma

Ferguson-Smith disease is a rare genetic disorder that is inherited in an autosomal dominant manner [91, 92]. The disease can be traced back to one Scottish family in the eighteenth century. It is characterised by the development of multiple self-healing squamous cell carcinomas or keratoacanthomas. The underlying genetic defect has been mapped to chromosome 9q22-q3, which is a similar region to XPA and PTCH but a specific gene has not been identified [73, 93]. The tumours usually start to present in the second decade of life and despite the fact that they are 'self-healing', surgery is frequently considered because the scar from self-healing can be unsightly or there is diagnostic uncertainty.

Sebaceous Naevus

Sebaceous naevus of Jadassohn is a hamartoma of sebaceous glands, which is present in about 1 in 350 newborns. They are known to have a potential for malignant and benign tumour transformation that can occur in childhood [94]. The most common malignant tumour is basal cell carcinoma but the frequency of transformation into these tumours is not accurately known. Historic studies had suggested rates a high as 22 % but more recent data suggests much lower rates of around 2 % [95]. There is a lack of prospectively collected information and most evidence is based on cases series that have presented for excision and likely therefore to be bias toward lesions that have already started to show malignant change. Excision is often performed because of the potential for malignancy or because of areas of alopecia on the scalp where the lesions frequently occur [94] (Fig. 22.8).

Immunosuppression

Depression of a normal immune response is a feature that is commonly present in the development of skin cancer. Some of the conditions listed above contribute to a failure of a normal immune response but there are also a number of other causes of immunosuppression in children that may allow development of cutaneous malignancies. The blunted immune response may be due to infection such as HIV, treatment such as Immunosuppression for transplant or haematological malignancies or a congenital immunodeficiency [96–100]. The possibility of malignancy should be taken seriously for any new skin lesions on any child who is immunosupressed for any reason.

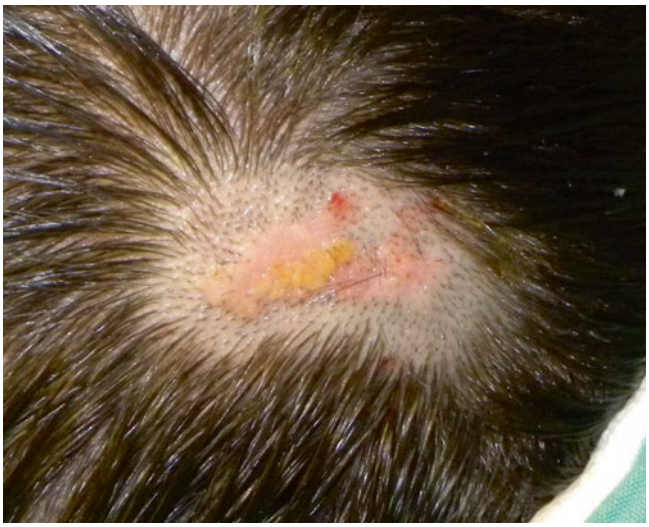

Fig. 22.8 Sebaceous Naevus

Basal Cell Carcinoma

Pathology

Three specific areas of DNA damage are believed to have roles in the development of BCC. Firstly damage to PTCH gene permits up-regulation of the hedgehog signalling pathway which allows cell proliferation [101, 102]. Secondly damage to the tumour suppressor gene TP-53 [102]. Thirdly damage to the smoothened receptor complex gene which forms part of the hedgehog signalling pathway [103]. Further to these areas of damage, which permit tumour development, there is also believed to be a component of immunosuppression from UV damage to Langerhans cells in the skin that means that a normal immune response to the tumours is not present.

Clinical Presentation

BCCs present with a variety of appearances, depending upon the subtype. Nodular BCCs present as papulonodular or cystic nodular lesions, superficial BCCs as erythematous foci and infiltrative as destructive ulcers (hence the common name 'Rodent Ulcer') or pale foci with areas of induration [104]. A 'pearly' edge and telangactasia are common and may be observes with all types. They are slow growing tumours and often the history is of a lesion gradually increasing in size over many months. Patients will not infrequently describe an episode of minor trauma at the site that initiated the lesion but it is unclear whether this is truly an initiating factor or if the early lesion is easily caught on something and traumatised, thereby drawing attention to it.

Staging

BCCs share an AJCC (American Joint Committee on Cancer) staging system with SCC. In most clinical cases however the most important factor in determining management is the morphological classification of the tumour. There have been a variety of classification systems produced over the years these are based on the histopathological morphology. The three most common types, which account for more than 80 % of cases, are nodular, superficial and infiltrative or morphoeic. To these are added a wide variety of other described variants including micronodular, pigmented, adenomatoid, granular, clear cell, giant cell, signet cell, adenoid, keratotic, pleomorphic, follicular, infundibulo-cystic, basal cell carcinomas with variable adnexal differentiation including eccrine, apocrine and sebaceous, with matricial differentiation, with myoepithelial differentiation and basal cell carcinoma with neuroendocrine differentiation. In addition to theses are BCCs with areas of squamous differentiation to which the undefined term 'baso-sqamous' is often applied. These tumours are believed to have a higher metastatic rate and may represent tumours that behave at least in part like squamous cell carcinomas [105, 106]. It may be in fact that these are the only type of BCC that does metastasise. The overall metastatic rate for BCC is around 0.1 % [107].

The nodular types have a well-defined margin that permits easy recognition of the extent of the tumour and therefore is associated with low recurrence rates following surgical excision [108]. The infiltrative, superficial and mirconodular types have poorly defined edges which mean that identification of the extent of the tumour is difficult to identify although this can be improved by the use of dermatoscopes or loupes. Recurrence rates are higher with these types of tumor and because of the irregular growth patterns histopathological examination of the tumour margin becomes less reliable in confirming adequacy of excision. Recurrence rates can be as high as 9 % with a histological clearance margin of 0.75 mm.

Imaging

Since the vast majority of BCCs present as small lesions, confined to soft tissue and do not metastasise, imaging is rarely of benefit. The neglected or recurrent BCC however represents a different entity as these tumours do have a potential for destructive invasion of tissue. Bony invasion in the head and neck is not uncommon and best represented by CT scanning. MRI provides a useful adjunct for cases that demonstrate peri-neural invasion where a significant extension along a cranial nerve can be identified.

Surgical Management

Although other treatment modalities exist for BCC, surgery remains the treatment of choice. In cases where the diagnosis has been made on clinical grounds excision biopsy can be performed or excision can follow a diagnostic biopsy. Surgical excision margins for BCCs are small in comparison to many other tumours although in recent years the recommendation has increased stepwise from 2 to 3 to 4 mm for small (<2 cm) clinically well-defined (nodular) lesions [109]. This correlates with a 95 % clearance rate on histopathology. Poorly defined and larger lesions require margins of at least 5 mm and some studies indicate that a margin of 15 mm may be required to achieve a clearance rate of 95 % [110]. In the vast majority of cases the tumour has less vertical growth and a cuff of subcutaneous fat provides deep clearance, however, at sites of anatomical fusion planes, such as the alar base and pre-auricular area, the tumour may grow along these planes necessitating deeper excision. At some sites e.g., on the dorsum of the nose there is little subcutaneous tissue but excision at the next anatomical plane such as the perichondrium usually provides adequate clearance unless it is obviously breached. Such excisions may be reported with clearance as little at 0.1 mm at the deep margin but the tumour usually has some respect for tissue planes and in this scenario is acceptable.

Despite the concern that may be present following incomplete resection not all tumours will recur. In fact when only a lateral resection margin is incompletely excised about 1 in 5 will recur whereas deep margin involvement is associated with a 1 in 3 chance of recurrence [108]. The risk is highest when both lateral and deep margins are involved. The decision to observe or re-excise will be dependent upon the margin involved, the location of the tumour and the relative risk to the adjacent structures if the become involved with tumour.

Mohs' Surgery

Mohs' surgery is a technique by which tumours are excised in a stepwise fashion with a minimal margin and full face frozen section examination by the operating surgeon. It permits the tumour to be excised with a minimal margin but known pathological clearance. The two main benefits of this technique are low recurrence rates and the possibility of tissue preservation when compared to standard surgical excision. It is however a time consuming technique and in a child would almost certainly require prolonged general anaesthesia. Its use is mostly limited to tumours where the margin is very poorly defined and where tissue preservation around specific cosmetically or functionally important structures usually around the central face is desired [109].

Non-surgical Treatment

BCCs respond well to a multitude of treatments, which may in some cases be used instead of or as an adjunct to surgery [109]. Radiotherapy has cure rates similar to surgery but by comparison involves many more trips to hospital, does not provide histopathological confirmation of excision and the long term cosmetic outcome is generally felt to be less favourable with radiation sequalae of telangactasia and dermatofibrosis worsening over time against surgical scars that improve with time. It does provide a good adjunct to BCCs that are difficult to clear surgically or recur despite apparent adequate clearance [111–116].

Photodynamic therapy (PDT) can be applied well to superficial BCCs. The technique involves the use of a photosensitising agent followed by intense light therapy. Again the technique is time consuming and does not provide histopathological confirmation of excision [117–121].

The topical immune response modifier imiquimod is useful for superficial BCCs with the same caveats as PDT. It may also be used post operatively where small residual components of superficial BCC are present at margins [122–124].

Squamous Cell Carcinoma

Pathology

The main recognised area of damage in SCC is the TP53 tumour suppressor gene [125, 126]. This is usually damage done by UV exposure. It is accompanied by UV damage to Langerhans cells causing a blunted immune response to tumours and by damage to other genes including *P16* (INK4a). *P14* (ARF) [127], *BCL2*, *RAS*, *EGFR and COX* [127–129]. Immunosupression increases the risk of development of these tumours significantly whether through the use of drugs post-transplant, HIV infection, haematological malignancy or treatment thereof [98–100].

Clinical Presentation

The tumours frequently present as an erythematous cutaneous nodule or an erythematous plaque (photos needed). It may be fleshy in appearance or covered with keratin. The keratin covering, which suggests a more well-differentiated tumour, may be a friable mass that falls off regularly or can be cohesive enough to produce a keratin horn (Fig. 22.9). The tumours may also have a ulcerated, sloughy centre (Fig. 22.10). The rate of growth is variable and may be over weeks or months. Keratoacanthomas present with a rapid growth phase, of about 6 weeks and a typical volcanic appearance with a keratin plug in the

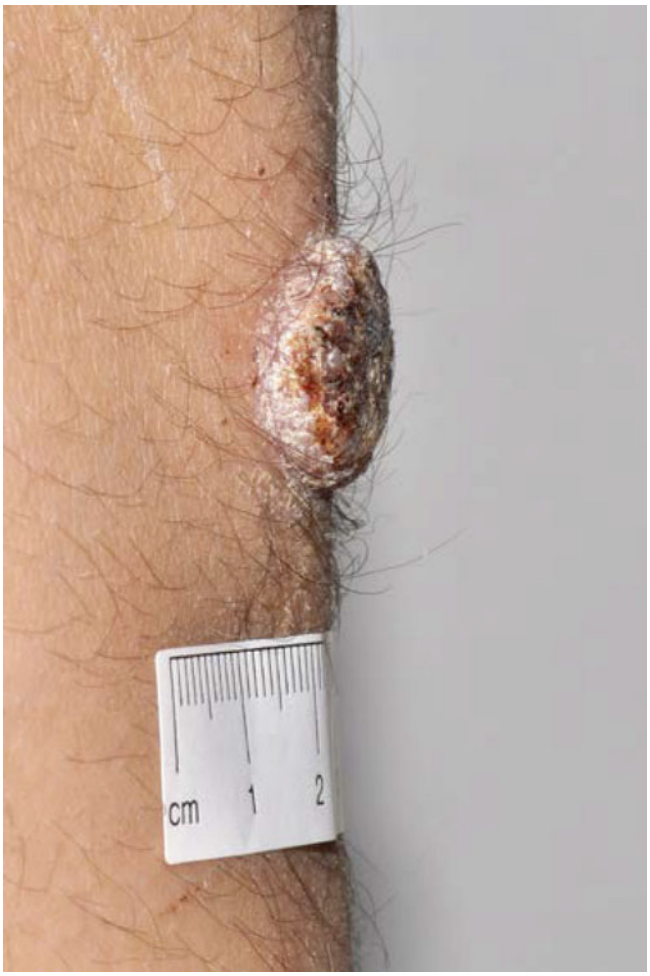

Fig. 22.9 Hyperkeratotic SCC on leg of 12 year old boy with idiopathic immunodeficiency

centre. This is followed by a 6 week period of involution and complete resolution of the tumour with potential for poor scar formation. Clinically and histologically they are very difficult to distinguish from a fast growing well-differentiated SCC.

Staging

Cutaneous SCCs rarely metastasise (0.5–2 %) [130–132] to the regional lymph node basins and staging investigations are rarely necessary. The risk of metastasis is increased by several factors; >2 mm thickness (Breslow thickness); Clark level ≥ IV; Perineural invasion; Primary site ear; Primary site non-hair-bearing lip; Poorly differentiated or undifferentiated. The staging system is available on the AJCC website. Clinical examination of the regional lymph nodes should be performed at the time of presentation and at follow up visits and clinically enlarged nodes require histological examination. Initially this is most easily performed by fine needle

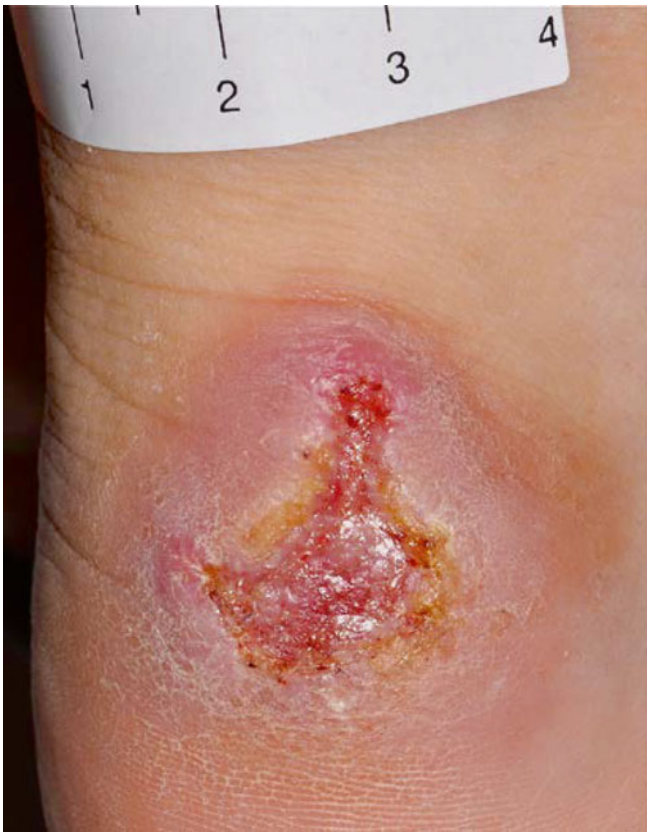

Fig. 22.10 Ulcerated SCC on heel of patient of Fig. 22.9

aspiration (FNA) with or without ultrasound guidance. Formal excision of the lymph node may be required if the result of the FNA is uncertain. In the head and neck region it is known that excision of a single lymph node where SCC has extra-capsular spread is likely to lead to tumour spill and a poorer prognosis and therefore where FNA is inconclusive clearance of a single level en bloc should be performed to obtain material for examination.

Imaging

Most tumours are recognised at an early stage where they involve the skin and subcutaneous tissues only and imaging of the primary tumour is rarely necessary. Neglected tumours with bony involvement will benefit from CT scanning and in tumours involving specific soft tissue structures such as cranial nerves or parotid, MRI scanning can help identify the extent of tumour spread. Ultrasound is particularly useful in examining lymph nodes and the use of colour power doppler can help differentiate between node that contain metastatic spread and those that are enlarged for other causes [133]. The operating surgeon may however find the images produced by CT more useful in planning surgery [134].

Surgical Management

Surgical lateral excision margin recommendations are 4 mm and 6 mm for tumours <2 cm and >2 cm respectively [135]. This gives approximately 95 % clearance. Deep margins are mostly commonly a mobile wad of subcutaneous fat overlying the tumour base. At sites where there is little or no fat present or the tumour has invaded deeply, a clean anatomical plane is the preferred excision margin. Mohs' surgery is also applicable to SCC with the same advantages and disadvantages as BCC [136, 137]. In view of the potential risk of metastasis and local recurrence following incomplete excision, re-excision is advocated whenever possible.

There is no compelling evidence that the benefit of elective lymph node dissections outweighs the morbidity. Sentinel node biopsy is being investigated as a staging tool for high risk SCC but as yet there is no evidence that its use improves outcome for patients over a wait and see policy [138].

Non-surgical Treatment

Surgery remains the treatment of choice for SCC. Histological confirmation of complete excision gives the best chance of cure and reassures both the clinician and patient. The tumour are radiosensitive and cure rates of 90 % have been demonstrated where it has been used as primary treatment modality but the long term cosmetic out come is typically less favourable than surgery [139]. It can be used well as an adjunct to surgery with positive margins at the primary site when further resection is difficult and has demonstrated better disease control following lymphadenectomy where the neck staging is N1 with extra-capsular spread or worse. Cryotherapy and curettage & cautery have both demonstrated good short-term control in low-risk, small, well-differentiated lesions but require experienced practitioners [135]. Topical therapies of imiquimod, 5-fluorouracil, photodynamic therapy and intra-lesional interferon alpha have also been reported but lack evidence to support their routine use.

Dermatofibrosarcoma Protruberans

Epidemiology

Dermatofibrosarcoma protuberans (DFSP) is a rare primary dermal sarcoma. It may account for 13 % of childhood skin cancers [70] although is most common between the ages of 20 and 50. It may have a slightly higher rate of occurrence in females. The disease is recognised to have a high propensity for local recurrence but low incidence of metastatic spread (1–4 %) and hence survival is high at over 99 % over 5 years for all ages [140]. UV exposure is not thought to play a role in development.

Pathology

DFSP on a cellular level resembles three different cell types fibroblastic, histiocytic, and neuroectodermal [141]. It is possible, but not conclusively established, that they therefore arise from undifferentiated mesenchymal cells, which are the precursors of all three types. The tumour cells appear to be driven by platelet-derived growth factor, which seems to derive from a translocation of genes 17 & 22 [142]. This places the gene for a type 1 collagen adjacent to part of the platelet derived growth factor molecule [143, 144]. This leads to formation of excess platelet derived growth factor.

Clinical Presentation

The tumours are very slow growing and often fairly innocuous. The history is usually of a small plaque that appeared many months or years ago and has gradually enlarged to form a lumpy patch [141].

Staging

There is no recognised staging system.

Imaging

Imaging is not usually required. Larger or recurrent tumours may benefit from CT scanning if bony involvement is suspected or MRI to help delineate extensive or specific soft tissue involvement depending upon tumour site and planned procedures.

Surgical Management

The tumour has an infiltrative growth pattern that extends well beyond clinically apparent disease and thus 3 cm resection margins are advised although even with this local recurrence rates around 15 % are observed [145, 146]. Recommended deep excision is to include the next anatomical plane beyond the clinically apparent extent of disease. Mohs' surgical excision has been shown to reduce local recurrence to about 1 % although the same caveats apply as previously stated [147].

Non-surgical Treatment

Radiotherapy has been used for primary treatment historically but its role now is predominantly in reducing recurrence in cases where surgical resection margins are positive or close and re-resection is not pursued.

Cutaneous Lymphomas

Lymphomas are covered in detail in Chap. 15. Surgery is not standard first line treatment for these tumours but it may be considered in selected localised cases. A 5 mm excision margin is recommended [148, 149].

Cutaneous Angiosarcoma

Angiosarcomas are covered in 16.6.7.3. Cutaneous angiosarcomas are aggressive tumours that are frequently treated with surgery, radiotherapy and chemotherapy. The tumour margin is often difficult to identify and excision is usually performed with a wide (5 cm margin) or frozen section control [150].

Teratomas

Teratomas are covered in Chap. 13. They may involve skin and usually have a clinically obvious margin. Wide excision is not normally required. Excision with a histologically clear margin gives good control.

Juvenile Xanthogranuloma

Juvenile xanthogranulomas are benign skin tumours that appear in children from birth onwards [151]. They usually present as single nodules or papules that may be red or yellow. About 1 in 5 patients have multiple lesions. The incidence peaks around 2 years of age and they are more common in caucasians and in males. The aetiology is not fully understood but they are formed of collections of histiocyte cells possibly from CD4 origin and a failure of cellular apoptosis may play a role [152, 153]. They frequently invade deeper structures [154]. The most common site for presentation is on the head & neck but they can appear anywhere on the skin. Extracutaneous involvement is rare but the eyes and more rarely internal organs may be involved. Although the lesions are benign and will resolve over years, they are often treated for cosmetic or diagnostic reasons. Excision biopsy with a narrow margin usually achieves control but because they can invade deeper structures, radiotherapy or steroids can aid local control (Fig. 22.11).

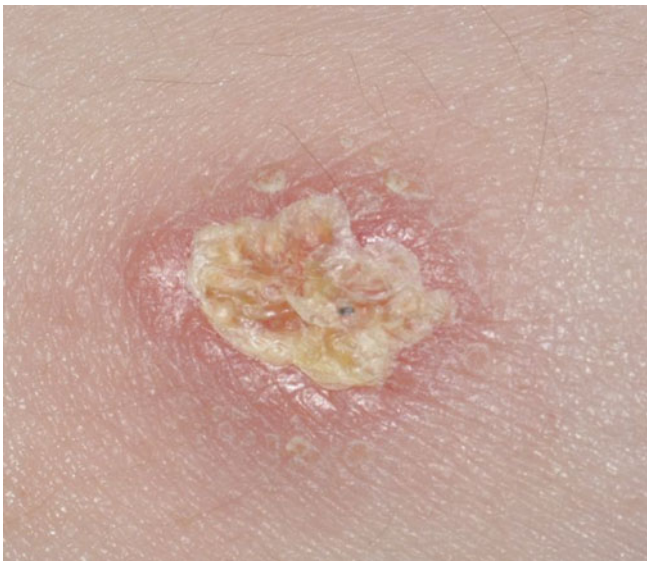

Fig. 22.11 Juvenile xanthogranuloma persistent after radiotherapy

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Bone Tumors; Limb Salvage

23

Stephen R. Cannon

Introduction

Primary bone tumors in children are rare conditions, the upper limb being more rarely affected than the lower limb. The practicing general orthopedic surgeon may not see more than a single case of primary bone tumor over a 5 year period. This rarity makes the recognition—particularly of malignant bone tumors—extremely difficult. Not surprisingly, this leads to difficulties and errors being made in specific treatment. With the establishment of bone tumor/cancer registries, the incidence of malignant primary disease of bone can be seen to be around six cases per million per year. The incidence of osteosarcoma, the most common primary malignant bone tumor, showing peak risks of incidence related to puberty is greatest between 10 and 14 years for girls and between 15 and 18 years for boys [1] (Fig. 23.1).

The most common benign lesion of bone is undoubtedly the solitary osteocartilaginous exostosis (osteochondroma). This condition was first described by Sir Astley Cooper in 1918 [2]. Both solitary exostosis and multiple exostoses (diaphyseal aclasis) may lead to alteration of epiphyseal plate growth and joint subluxation and deformity [3]. Other common benign diseases affecting the skeleton include Ollier's disease [4] which, when associated with soft tissue hemangiomas is termed Maffucci's syndrome [5]. The true incidence of these conditions within the population is unknown, but it is well recognized that the enchondritic element of both syndromes may undergo malignant change [6]. The majority of giant cell tumors are found in the pelvis and lower limbs, although occasionally the distal and proximal radius may be involved. These lesions are, of course, exceedingly rare below the age of 15 years [7]. Of the primary malignant tumors of bone in childhood (Ewing's sarcoma and osteosarcoma), about 12–15 % of cases occur in the upper limb, including the clavicle.

When considering the diagnosis of a bone tumor, it is probably wise to keep the World Health Organization (WHO) classification in mind (Table 23.1). Lesions occurring predominantly in children are highlighted.

Presentation

The diagnosis is often missed simply because it is not considered. It is important to realize that no part of the anatomy is exempt from a bone tumor, and every bone, every muscle and every nerve in all anatomical areas have been recorded as being sites of primary musculoskeletal tumors.

Children often present with symptoms that can be confused with other musculoskeletal injuries. Most children seek medical attention because of pain. The clinician should have a high index of suspicion for pain that is constant, unrelated to

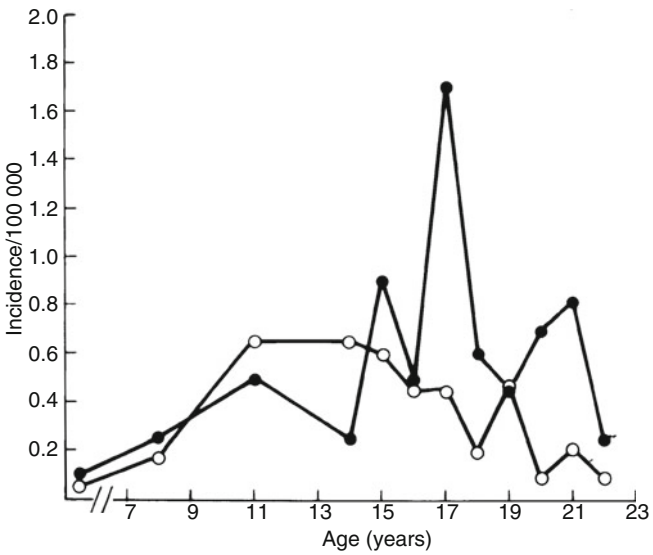

Fig. 23.1 Incidence of osteosarcoma in boys and girls related to age

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Table 23.1 WHO classification of common primary bone tumors

A Bone-forming tumors	
i. Benign	Osteoma
	Osteoid osteoma
	Osteoblastoma
ii. Intermediate	Aggressive (malignant) osteoblastoma
iii. Malignant	Osteosarcoma
	(a) Central (medullary)
	(b) Surface (peripheral)
	Parosteal osteosarcoma
	Periosteal osteosarcoma
	High-grade surface
B Cartilage-forming tumors	
i. Benign	Chondroma
	(a) Enchondroma
	(b) Periosteal (juxtacortical) Osteochondroma (osteocartilaginous exostosis)
	(a) Solitary
	(b) Multiple hereditary
	Chondroblastoma
	Chondromyxoid fibroma
ii. Malignant	Chondrosarcoma
	Dedifferentiated chondrosarcoma
	Mesenchymal chondrosarcoma
	Clear cell chondrosarcoma
C Giant cell tumor (osteoclastoma)	
D Marrow tumors (round cell tumors)	
	Ewing's sarcoma of bone
	Neuroectodermal tumor of bone
	Malignant lymphoma of bone
	Myeloma
E Vascular tumors	
i. Benign	Hemangioma
	Lymphangioma
	Glomus tumor
ii. Intermediate	Hemangioendothelioma
	Hemangiopericytoma
iii. Malignant	Angiosarcoma
	Malignant hemangiopericytoma
F Other connective tissue tumors	
i. Benign	Benign fibrous histiocytoma
	Lipoma
ii. Intermediate	Desmoplastic fibroma
iii. Malignant	Fibrosarcoma
	Malignant fibrous histiocytoma
	Liposarcoma
	Malignant mesenchymoma
	Leiomyosarcoma
	Undifferentiated sarcoma
G Other tumors	
i. Benign	Neurilemmoma
	Neurofibroma
ii. Malignant	Chordoma
	Adamantinoma
H Simple bone cyst	
Aneurysmal bone cyst	
Classification of common primary bone tumors	

activity, and is worse at night. The second most frequent complaint is of swelling. Of particular importance is the rate of tumor growth and whether there has been any relationship to trauma. The third more rare mode of presentation is the occurrence of a pathological fracture. Here, the presence of pain or swelling prior to the fracture is a most important clue to diagnosis. Constitutional symptoms of weight loss and occasionally fever are sinister observations, usually indicative of aggressive disease, often widespread but fortunately rare. Examination of the area complained of is the responsibility of the physician, and the features considered should be: first, is there tenderness and is there increase in the skin temperature? If there is a visible mass, how big is it? Has it changed in size since first noted? The physician should take appropriate measurements. Adjacent joints should be examined for the range of movement and the limb assessed for signs of muscle atrophy. The neurovascular status of the extremity involved should also be assessed. A complete physical examination should also be done, with particular reference to the regional lymph nodes and examination of the chest and abdomen where appropriate. Only after a very thorough history and careful examination should the next investigation, a plain radiograph, be performed.

Radiographic Investigations

The single most important investigation in a suspected bone tumor is the plain radiograph. This investigation may be diagnostic in itself and direct further treatment without additional investigation or indeed the radiograph may alert the surgeon to the possibility of a bone tumor being present. It is also important to emphasize that the radiologist is not a clinician in his own right and requires appropriate information of what the clinician suspects in order to give the best service. The radiograph should be taken in two views at right angles to each other, and when a lesion is recognized the following helpful diagnostic exercise should be undertaken.

1. What is the anatomical site of the lesion? Which bone is it in? Is it in the epiphysis, metaphysis, or diaphysis? Is it in the medullary canal or is it in the cortex, lying on the cortex or surrounding the cortex?
2. What effect is the lesion having on the bone? Is bone being destroyed? Is it a local destruction? Is it permeative or are there moth-eaten changes?
3. What is the bone doing in response to the lesion? Is there an endosteal reaction? Is there a periosteal re action? Is a Codman's triangle, a sunburst pattern, or onion-skinning appearance present?
4. Is there anything about the lesion which is characteristic of a specific tumor? Is it forming new bone? Is there calcification? Does it have a ground glass appearance?

This approach is important, particularly in instances where the initial diagnosis can be safely made on the plain

radiograph alone. Lesions which are inactive, i.e., those that have no symptoms and have a mature reaction around them, can often be observed. Biopsy is usually not necessary. Lesions which appear to be more aggressive, i.e., giant cell tumor or chondroblastoma, may require further evaluation with other radiographic techniques prior to discussing management. In deciding which radiological investigations to acquire, it is useful to communicate with the radiologist which question is being asked. The orthopedic surgeon requires information that answers four questions in order to stage the tumor within the limb.

First, what is the intraosseous extent of the tumor? Second, what is the extraosseous extent of the tumor and what proportion of the lesion is still sub-periosteal? Third, is there any involvement of the adjacent intra-articular structures? Fourth, is the neurovascular bundle involved in the tumor process? If the tumor is malignant, then the clinician needs to know if there is any other bony lesion elsewhere and also if there is any metastatic spread to the lung.

Radio-isotopic technetium 99 m bone scintigraphy can be used both to determine the activity of a primary lesion and to search for other bony lesions. Occasionally the technetium bone scan can reveal the intraosseous extent of a lesion as well as computed tomography (CT) or magnetic resonance imaging (MRI) scanning [8] (Fig. 23.2). Lesions which do not have increased activity on the bone scan are usually benign. The two exceptions to this general rule are myeloma and Langerhans' histiocytosis. Lesions which have increased activity may be benign or malignant. The intensity of uptake is not predictive as to the likelihood of malignancy. Classically, the bone scan appearances of osteosarcoma are of intense activity with an irregular outline [9]. Bone scintigraphy may also on occasion demonstrate pulmonary metastases in instances of osteosarcoma.

Computed tomography is a valuable noninvasive investigation which can determine not only the intramedullary extent of the tumor but also demonstrate extra-osseous extension and the degree of cortical destruction (Fig. 23.3). It may also be used in conjunction with contrast medium to outline the relationship of the tumor to adjacent vascular structures or indeed to represent the vascularity of the lesion itself; CT scan of the lungs is important for accurate staging. Typically, metastases are found in the sub-pleural position (Fig. 23.4), but in spite of the greater sensitivity of this technique the proportion of patients with nor mal chest radiographs at presentation who are subsequently shown to have lung metastases by CT scan is only 10–15 % [10].

Magnetic resonance imaging is now considered the most sensitive single method for assessing intramedullary involvement by tumor [11]. Although both CT and MRI can demonstrate the presence of extra osseous soft tissue extension, MRI is superior to CT in differentiating tumor from adjoining muscle [12, 13] (Fig. 23.5). However, MRI is not as accurate as CT in determining the relationship of a tumor to the cortex of a bone or in evaluating a lesion which is composed of dense bone [14]. In addition, there can be

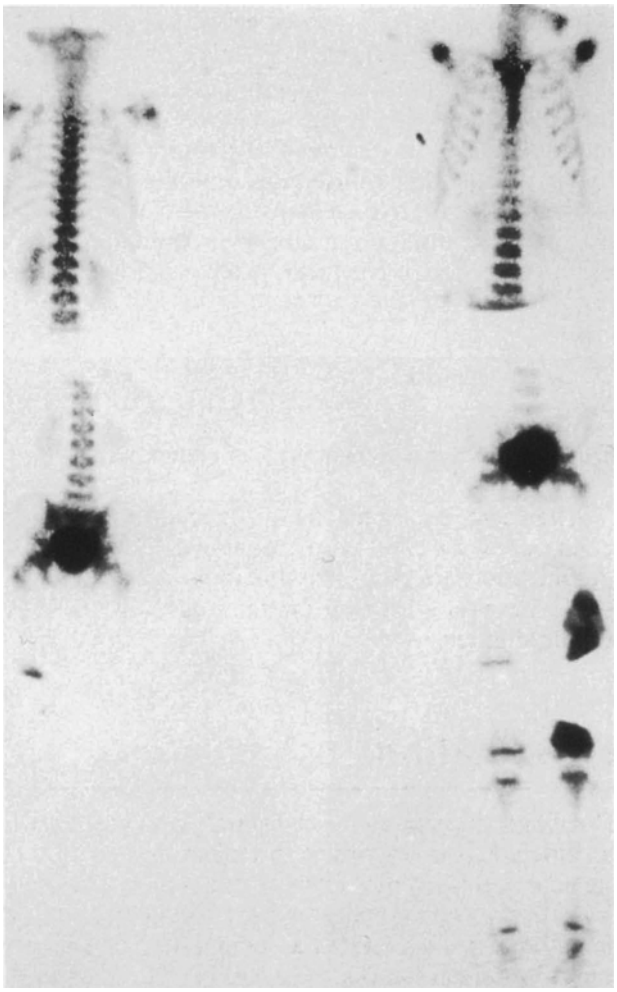

Fig. 23.2 Technetium bone scan of an osteosarcoma showing primary lesion and intraosseous extent

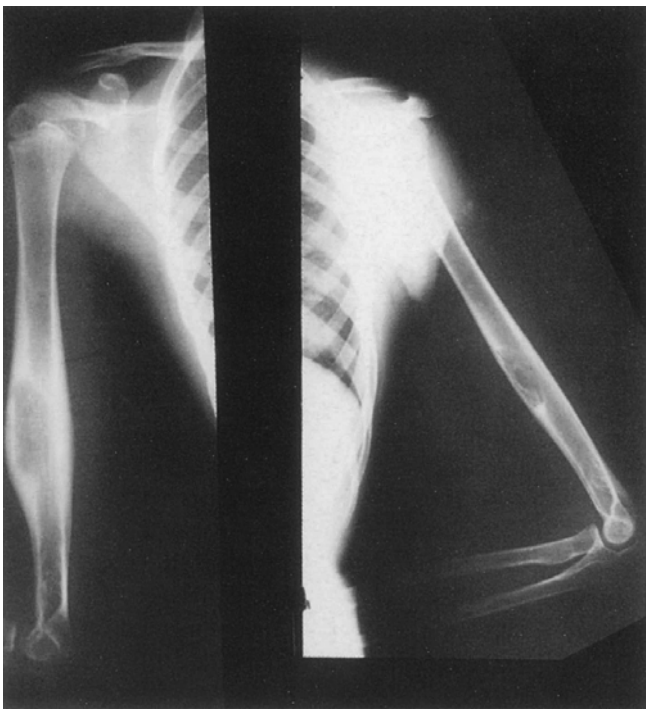

Fig. 23.3 Ewing's sarcoma showing cortical destruction

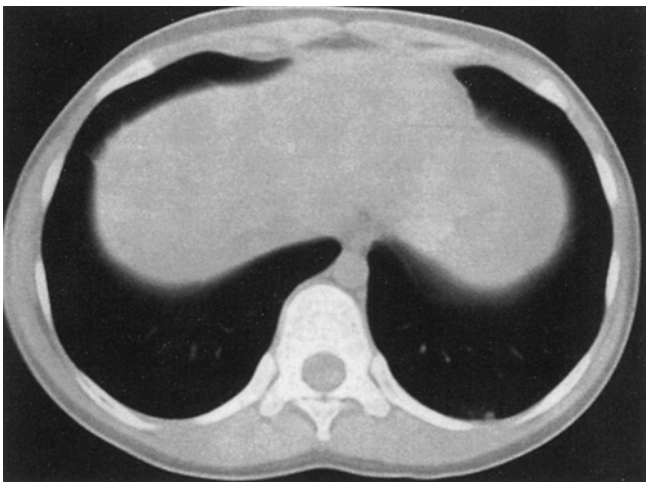

Fig. 23.4 CT scan chest showing multiple subpleural and parenchymal metastases

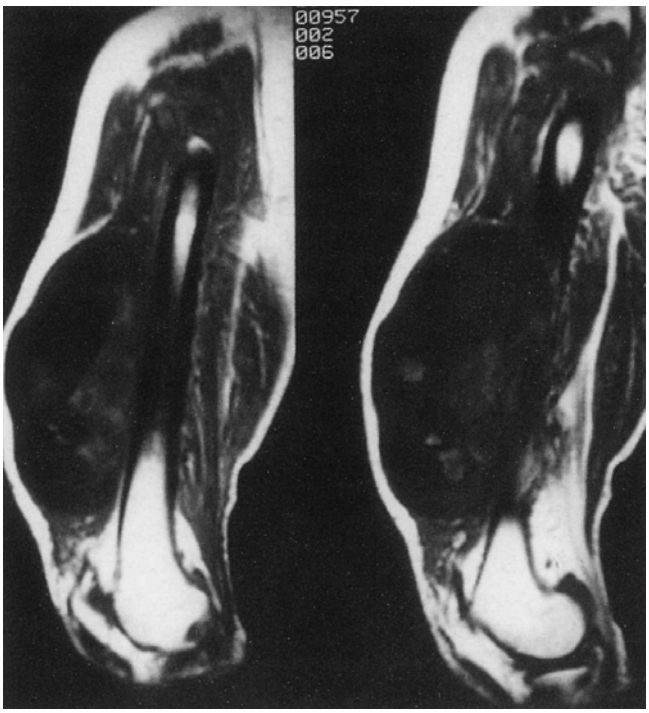

Fig. 23.5 MRI scan of Ewing's sarcoma showing large extraosseous mass

considerable difficulty in differentiating between tumor and peripheral edema in highly malignant tumors. It is also useful to use MRI in delineating the response to treatment by radiotherapy or chemotherapy by documenting reduction in tumoral mass and restoration of normal MRI signals [15].

Despite increasing sophistication of radiological investigations, the radiologist is at best usually only able to offer a differential diagnosis. Osteosarcoma, for example, may be confused with stress fracture, chronic osteomyelitis, ectopic ossification, and other highly malignant tumors that may induce active bone formation such as Ewing's sarcoma. Although the above radiological techniques are usually all that are required in investigation, new techniques such as dynamic MRI, whole body MRI and PET scanning are becoming more prominent and may be useful. Ultimately, however, the diagnosis rests in the hands of the histopathologist and analysis of biopsy material.

Biopsy

Biopsy is the last but perhaps the most critical step in the evaluation of a bone tumor and should only be performed after extremely careful planning [16]. The surgeon who is responsible for the management of the patient with a primary bone tumor should be the individual to decide on the biopsy method and its approach. In a large series of patients with bone tumors, Mankin et al. [17] concluded that the incidence of significant problems in patient management resulting from inappropriate biopsy techniques was 20 % and that the incidence of wound healing complications related to a poorly planned biopsy was similarly high. They further noted that 8 % of biopsies produced a significantly adverse effect on the patient's prognosis and in 5 % led to an unnecessary amputation. Errors in diagnosis leading to inadequate treatment occurred twice as frequently when the initial biopsy was done at the referring hospital rather than a specialist center.

Fine Needle Aspiration (FNA)

This technique, which is generally used in the diagnosis of soft tissue tumors, has also been popularized for initial diagnosis of primary bone tumors, particularly in Sweden [18]. A study of 300 consecutive patients not known to have a previous malignancy or suspected of having a local recurrence was analyzed. The FNA technique itself failed in 18 % of patients. In those patients where material was obtained, 95 % had correct diagnosis. It would appear that chondrosarcoma presented the greatest difficulty in diagnosis and Ewing's sarcoma the least. The only real advantage of FNA is that it can be performed under simple analgesia as an outpatient procedure. It is also worthy of note that FNA in benign bone lesions had a very high incidence of inconclusive results.

Needle Biopsy

Targeted percutaneous needle biopsy using a Jamshidi or similar needle may often be sufficient to yield a diagnosis (Fig. 23.6). The technique is performed under radiological control and has 95 % accuracy when dealing with lesions of the appendicular skeleton [19]. In malignant lesions, the

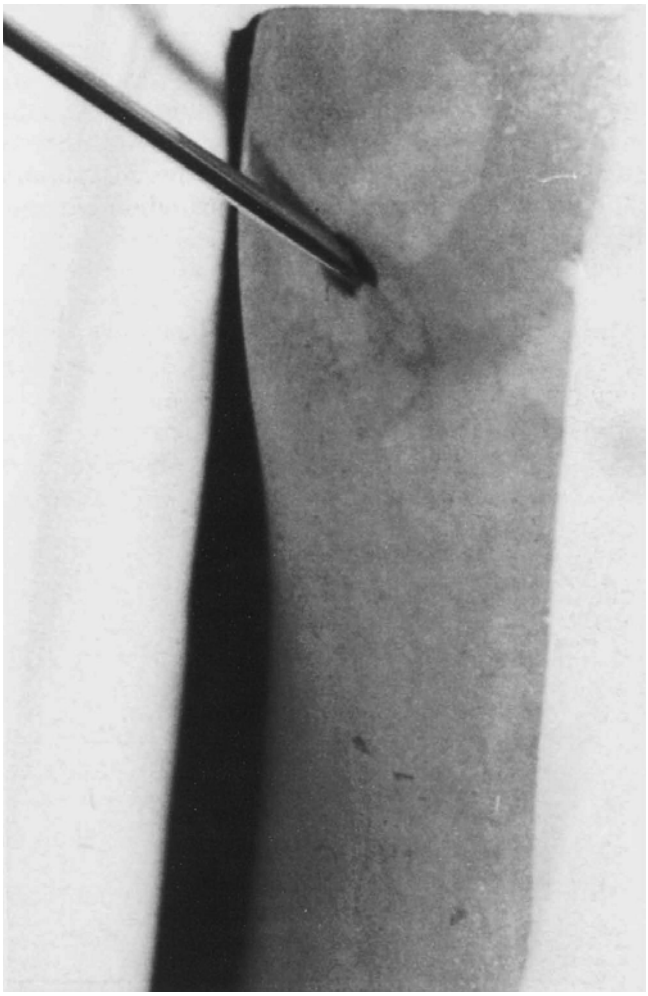

Fig. 23.6 Targeted Jamshidi needle biopsy under radiographic control

needle biopsy tract should be subsequently removed en bloc with the tumor, and this requires a good rapport between surgeon and radiologist. Often, the tract can be marked with Indian ink following completion of the biopsy to facilitate removal. Failure to remove the tract may lead to local recurrence [20]. Although a rapid working diagnosis can often be achieved using frozen section or imprint techniques [21], it is important to emphasize that the analysis of small amounts of histological material requires pathological expertise of the highest caliber and is not, therefore, recommended if such expertise is not readily available.

Incisional Biopsy

Most commonly, biopsy is performed by an open technique, and ideally the biopsy tract should be as small as possible and go directly to bone. Postoperative hemostasis at the operation site is mandatory, and the wound should be closed using a subcuticular suture. It must be remembered that when definitive surgery is performed, the complete biopsy tract and all contaminated tissue must be removed en bloc with the tumor. Failure to do so will significantly increase the risk of local recurrence [22]. The surgeon who performs the open biopsy should keep in mind the definitive procedure that may be required and place the biopsy site accordingly. There is no objection to the use of a tourniquet providing it is released prior to closure and hemostasis obtained. Drains may be used, but they should be brought out close to the wound and in line with it so that excision of the drain tract can also be obtained. There are advocates for closing the biopsy defect in the tumor pseudocapsule with cement, but there is no proof that this lessens contamination and may, if placed under pressure, theoretically further spread the tumor by the intramedullary route.

Excisional Biopsy

Occasionally, an excisional biopsy will be more appropriate than either an incisional or needle biopsy. It is particularly indicated where the lesion is small and can easily be excised, often widely, without significant detriment to the patient's function. Lesions which are obviously applicable to excision biopsy are osteoid osteoma and osteochondroma, and it may also be appropriate in instances of low-grade chondrosarcoma affecting the medulla. It is often difficult to distinguish between active benign cartilage tumors and low-grade chondrosarcomas. When the entire lesion is removed allowing examination of the interface between the tumor, adjacent bone, and soft tissue, the pathologist is usually able to render a better opinion.

It cannot be overemphasized that in children osteomyelitis occurs more commonly than bone tumors. When in doubt material obtained, therefore, should also be sent for Gram staining and culture as well as histological analysis.

Staging Notations

The correlation of information gained from radiological imaging investigations and the biopsy allows classification of a malignant bone tumor into a staging system. The surgical staging system proposed by Enneking et al. is easy to use clinically, and although it suffers from some significant oversimplification, it is generally acceptable [23]. The system is outlined in Table 23.2, and takes into account the three basic features that are recognized as having prognostic importance. These are, first, the histological grade of the tumor, second, its location and, third, the presence or absence of regional or distal metastases. The histological grade is classified as either low grade (G1) or high grade (G2). This grading system does not completely match purely histological grading systems but, in essence, low grade lesions will be the

Table 23.2 Enneking's classification of surgical staging

Stage		Grade	Site	Metastases
I	A	Low (G1)	Intracompartmental (T1)	None (M0)
	B	Low (G1)	Extracompartmental (T2)	None (M0)
II	A	High (G2)	Intracompartmental (T1)	None (M0)
	B	High (G2)	Extracompartmental (T2)	None (M0)
III	A	Low (G1)	Intra- or extra- (T1–T2)	Regional or distant (M1)
	B	High (G2)	Intra- or extra- (T1–T2)	Regional or distant (M1)

equivalent of Broders grade I and some II. The high-grade lesions would all be Broders II, III, and IV [24]. Regarding location, lesions are divided into those occurring in a specific compartment (T1) and those that are extracompartmental in nature (T2). The term "compartments" is defined as an anatomical structure bounded by natural barriers to tumor extension. Thus, a whole bone is considered a compartment as is a functional muscle group bounded by major fascial septa. Tumors spreading beyond these compartments or involving neurovascular structures are classified as extracompartmental. Some anatomical locations such as the axilla, antecubital fossa, periclavicular region, and midhand, are considered extracompartmental ab initio. In the lower limb the popliteal fossa and midfoot are similar problematic areas.

In malignant tumors, metastases occur most frequently to the lungs and they may occasionally occur in bone but are rare in local lymph nodes. When multiple bony lesions are sometimes seen, they are considered examples of multicentric primary tumors, though usually one lesion has the radiological features of a primary lesion and the others have characteristics of secondary intramedullary deposits. Skip lesions of an isolated area of tumor in the same bone as the primary were previously thought to occur in approximately 25 % of cases; more recent data suggests the true incidence is probably much lower [25].

Similar staging systems have been applied to benign disease, but unfortunately they rarely predict the clinical course of the problem. The most predictive element in the course of treatment of benign disease is, in fact, the surgical treatment which is given. For example, wide simple excision of a cartilaginous exostosis will lead to resolution of the problem providing that the cartilage cap is not broken, whereas curettage of a giant cell tumor may result in a local recurrence rate of approximately 20 %. In the upper limb, giant cell tumor commonly affects the distal radius and proximal humerus but tends to occur in only the mature skeleton. On the basis of the radiological appearance, Campanacci et al. [26] proposed four subtypes which redefine the previously proposed terms of latent, active, and aggressive. Unfortunately, grade I often represents a benign fibrous histiocytoma and the other grades do not necessarily predict their clinical behavior. The picture is further complicated by the histological pattern of the tumor. The osteoclasts which are present are now considered to be only markers of the tumor activity, the tumor itself being represented by the stromal background. This background can vary from being very inconspicuous to frankly malignant [27]. This appearance can, of course, profoundly affect the extent of treatment. Primary de novo malignant giant cell tumor is a rare but well-recognized entity. Care is required, particularly in the differentiation of an osteoclastrich osteosarcoma. When diagnosed, the treatment of a malignant giant cell tumor is similar to managing a malignant fibrous tumor.

Treatment of Common Primary Bone Tumors

Benign Bone-Forming Tumors

Osteoma

These usually present as small, painless, slowly enlarging lumps. Although most commonly occurring around the skull, any bone may be affected. The radio logical appearance of an osteoma is a dense well-circumscribed lesion. Treatment is by surgical excision if the patient is symptomatic.

Osteoid Osteoma

This condition usually presents with vague pain, often nocturnal, and relieved characteristically by aspirin and other non-steroidal anti-inflammatory agents [28]. The pain may be associated with tenderness and vaso motor disturbance. Classically, the osteoblastic nidus is within the cortex or spongiosa of long bones. The nidus is less than 1 mm in diameter and induces intense surrounding reactive change (Fig. 23.7). If the nidus is in a subarticular location diagnosis can be difficult, as the reactive changes may not occur. Intracapsular osteoid osteomas around the elbow have been mistaken for tuberculous synovitis [29] and rheumatoid

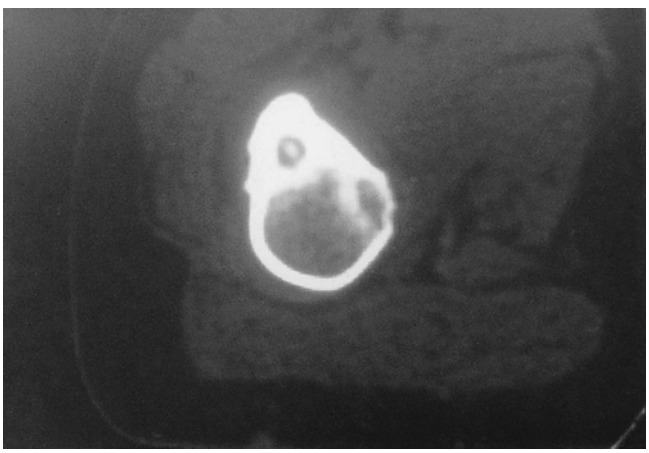

Fig. 23.7 CT radiograph of osteoid osteoma of the femur

arthritis [30]. It is also well recognized that longstanding disease can induce degenerative change [31].

The radiological investigation consists initially of a plain radiograph. This may or may not reveal the characteristic nidus. When marked reactive bone is seen, the differential diagnosis includes bone abscess, sclerosing osteomyelitis of Garré, osteochondritis, and stress fracture [32]. Bone scintigraphy will usually help localize a nidus but is relatively nonspecific. Computed tomography, if applied in close 2 mm sections, will be successful in identifying accurate locations of the nidus prior to surgical resection [33].

The treatment of osteoid osteoma requires excision or ablation of the nidus. As the nidus is surrounded by dense reactive bone this can be difficult to achieve. The traditional approach requires wide exposure with radiological verification of the site. Szypryt et al. [34] have described the use of intraoperative scintigraphy but this is rarely required. Excisional biopsy of the nidus under CT guidance is now performed with success [35] while electrothermal coagulation has also been explored and reported as successful.

The use of radioablation techniques has now become first-line management for the majority of osteoid osteomas, but it can be difficult in some sites, such as adjacent to the spinal column or in the very small epiphyseal areas of bones. Reported rates are of 90 % success with one treatment of radioablation. Five percent of cases require a second attempt at treatment by this technique. Only 5 % require surgical exploration and excision [36].

Osteoblastoma

This lesion has a similar appearance histologically to osteoid osteoma, but is larger and does not induce as much reactive surrounding change. It is an extremely rare lesion affecting mainly the axial skeleton, although any bone may be affected. Patients are predominantly male in their second or third decades [37].

The clinical presentation is of vague pain, less severe than osteoid osteoma, and not particularly relieved by salicylates. Occasionally there may be both swelling and joint dysfunction.

The radiological features classically show an expansile radiolucent lesion, with a thin shell of peripheral new bone.

Treatment consists of either curettage with or without bone grafting or local excision. Local excision results in good local control but reconstruction may be required. This recurrence rate may be as high as 20 % following curettage, but the use of radiotherapy in extraspinal cases is rarely required [38].

Malignant Bone-Forming Tumors

Osteosarcoma

Osteosarcoma is the most common primary malignant bone tumor and can occur at any age, although most cases occur in the first two decades of life [39]. Most commonly affecting the two metaphyseal areas around the knee, the humerus is the third most common site, with tumors often arising at an earlier age than in the lower limb [40].

Osteosarcomas are usually subtyped on the basis of their histological patterns as fibroblastic, chondroblastic, osteoblastic, telangiectatic, or mixed [41]. Although the subtype classification was originally thought to have a bearing on prognosis, carefully controlled studies now suggest that this is not the case. Histological grading is also an unreliable prognostic indication [42].

Patients present usually with a short history of pain followed by swelling, joint dysfunction, and occasionally pathological fracture. The many radiological advances which have occurred in the last decade have allowed very accurate staging of the tumor. The plain radiograph remains the initial diagnostic tool but tends to underestimate the local extent of the tumor. Accurate visualization of cortical destruction and soft tissue spread will be given by CT but this may miss skip lesions in the same bone. It is a useful technique in planning biopsy and local excision [43]. Today, CT of the chest is the accepted staging investigation to assess the potential presence of pulmonary metastases. Local staging of disease now depends heavily on MRI studies, particularly in the T2 mode, which will delineate accurately the intramedullary and soft tissue extent of the lesion; MRI will outline the relationship of the tumor to the adjacent joints and blood vessels (Fig. 23.8).

Preoperative bone scintigraphy using technetium isotopes is useful in identifying skip lesions and metachronous lesions in other bones. The radioisotope scan may also on occasions demonstrate pulmonary metastases [44].

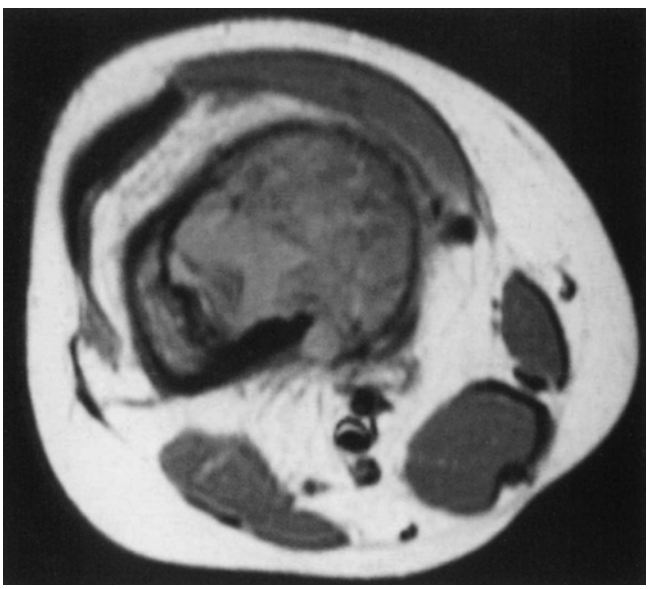

Fig. 23.8 MRI which outlines the relationship of the tumor to the adjacent joints and blood vessels

Having performed the radiological staging procedures, it is necessary to establish the pathological diagnosis. At this stage a biopsy is performed. Many argue that an open biopsy is required. However, Stoker et al. [19] have shown the accuracy of Jamshidi needle biopsy cores obtained in a referral center under local anesthesia and image intensification. More recently similar accuracy has been shown in biopsying the soft tissue component of malignant tumors under ultra sound or MRI [45].

Historically, the early treatment of osteosarcoma was surgical ablation. In the upper limb this required either disarticulation of the shoulder for lesions in the distal humerus or forequarter amputation for more proximal growths. Survival, however, was poor with 5 year survival rates varying between 11 and 25 % [46]. Cade [47] reported an alternative method of treatment employing preoperative radiation followed by surgical ablation only in those cases not developing pulmonary metastases. Many less amputations were performed but the survival rate was unaltered. This was subsequently confirmed by other series [48].

By the early 1970s, it became evident that this appalling survival rate might be improved by the use of adjuvant chemotherapy. Many different protocols were developed, some claiming a very high survival rate [49], but controlled trials of therapies were not performed. In the UK, the Medical Research Council combined with the European Organization for Research into Cancer Treatment (EORTC) set up controlled trials of adjuvant chemotherapy. More recently neoadjuvant chemotherapy has been employed and allows treatment of undetected micrometatases and causes necrosis of the tumor and may allow some shrinkage of the primary tumor. This latter effect may allow easier local resection and reconstruction of the limb. The initial trials compared the effect of Adriamycin (doxorubicin) and cisplatin with or without high-dose methotrexate. The two-drug arm performed better, resulting in a survival rate of 65 % at 5 years. This two-drug arm has been compared with a Rosen T10 regime. The trial has accrued 400 cases. Analysis of them showed no material difference between the two regimes, therefore the two-drug regime is preferred because of less morbidity. A second trial attempting a dose intensification of the two-drug regime, the three courses of chemotherapy being given over 6 weeks as opposed to nine, using rescue by granulocyte cell stimulating factor, has also shown little difference in outcome. A further regime is now in progress which hopes to improve the cure rates of osteosarcoma. The trial is worldwide, involving both European and American oncologists and hopes to improve the outcomes which have been somewhat disappointing over the past 20 years. This randomized trial termed Euramos hopes to herald a new era of clinical investigation into osteosarcoma, which of course should always be treated under the guidance of a specialist team [50].

Surgical intervention is now performed at around the tenth or eleventh week following commencement of chemotherapy and is continued in a randomized manner in the postoperative period. In most cases, a "wide excision" of the tumor is performed outside the tumor pseudocapsule with preservation of the neurovascular bundles, although often in tumors arising in the upper limb the circumflex nerve and the radial nerve may often be sacrificed to allow adequate clearance. Following wide excision functional reconstruction is only possible using either customized endoprostheses or allografts. A recent multi-central pan-European trial has found no significant improvement in either local recurrence or survival in cases treated by chemotherapy.

Parosteal Osteosarcoma

This is a low-grade malignant tumor developing on the external surface of large bones. The disease was first reported by Geschickter and Copeland in 1951 [51]. It has a long natural history and tends to affect patients in the second and third decades of life. Most patients present with a longstanding swelling associated with dull ache. The elbow is only rarely affected.

Treatment consists of wide local resection of the tumor with appropriate reconstruction. It is generally accepted that in most cases chemotherapy is not indicated. Review of the tumor may show high-grade changes in the fibrous elements. These tumors have a poorer prognosis [52], and adjuvant chemotherapy may be indicated. Occasionally, the low-grade component may transform or dedifferentiate to a high-grade osteosarcoma [53]. Treatment for these latter cases is then as for an osteosarcoma (see Chap. 18).

Periosteal Osteosarcoma

This is a very rare tumor; many still doubt its existence, although it probably is a variant of parosteal osteosarcoma with a prominent cartilaginous component [54, 55]. These tumors are usually small unicortical lesions (Fig. 23.9). Treatment is by wide resection and reconstruction where required. Whether chemotherapy is required in their management is still unclear [56].

Benign Cartilage-Forming Tumors

Osteochondroma

These cartilage-capped bony protrusions may develop in any bone derived from cartilage. They are usually discovered in childhood and many are found only as incidental findings on radiography (Fig. 23.10a, b). They are usually painless but pain can be invoked by mechanical irritation or nerve compression. Pseudo aneurysm has also been reported specifically in the popliteal regions [57].

If symptomatic, straightforward excision at the base is curative. If asymptomatic, they can be safely observed. Growth will continue until skeletal maturity. If growth appears to occur after skeletal maturity then malignant transformation must be considered even if the radiographic appearances do

not alter. It is now considered that the size and thickness of the cartilage cap as assessed by MRI or CT is the critical factor. This is of course not visible on plain radiographs.

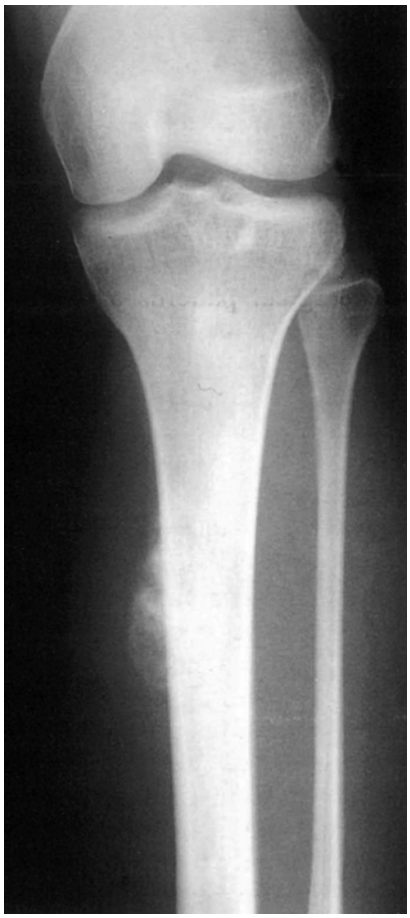

Fig. 23.9 Periosteal osteosarcoma of the tibia

In diaphyseal aclasis the patient may also present with growth abnormality and subluxation of joints. Removal of the lesions is rarely enough and the patients often require major reconstructions to correct the deformities [58]. The patient should be warned specifically of the possibility of malignant change associated with growth after maturity. Known lesions which cannot be palpated should be monitored by radiography. Unfortunately, bone isotope scanning cannot reliably differentiate benign from malignant cartilage lesions, but recent innovations such as PET scanning may be helpful in this regard [59].

Chondroblastoma

This is a rare bone tumor usually located in the epiphyseal plate which is essentially benign. Jaffe and Lichtenstein consider that it is a tumor developed from cartilaginous germ cells, although Higaki considers the cell of origin to be histiocytic [60, 61]. Typically, the patient is in the second decade and is more likely to be male. A long prodromal history is typical and there may be muscle wasting and restriction of joint movement [62]. The most common site of occurrence is the upper humeral epiphyseal plate, although they can be associated with any primary or secondary site of ossification.

Typically, the lesion is radiolucent crossing the growth plate and intralesional calcification can be seen particularly with CT [63] (Fig. 23.10). CT may better illustrate the local invasive properties of the tumor. It is well recognized that chrondroblastoma may be associated with secondary implantations in the lung. These "areas" if resected have a "benign" histological appearance and therefore represent implantation of vascularly transported tumor tissue rather than true metastases.

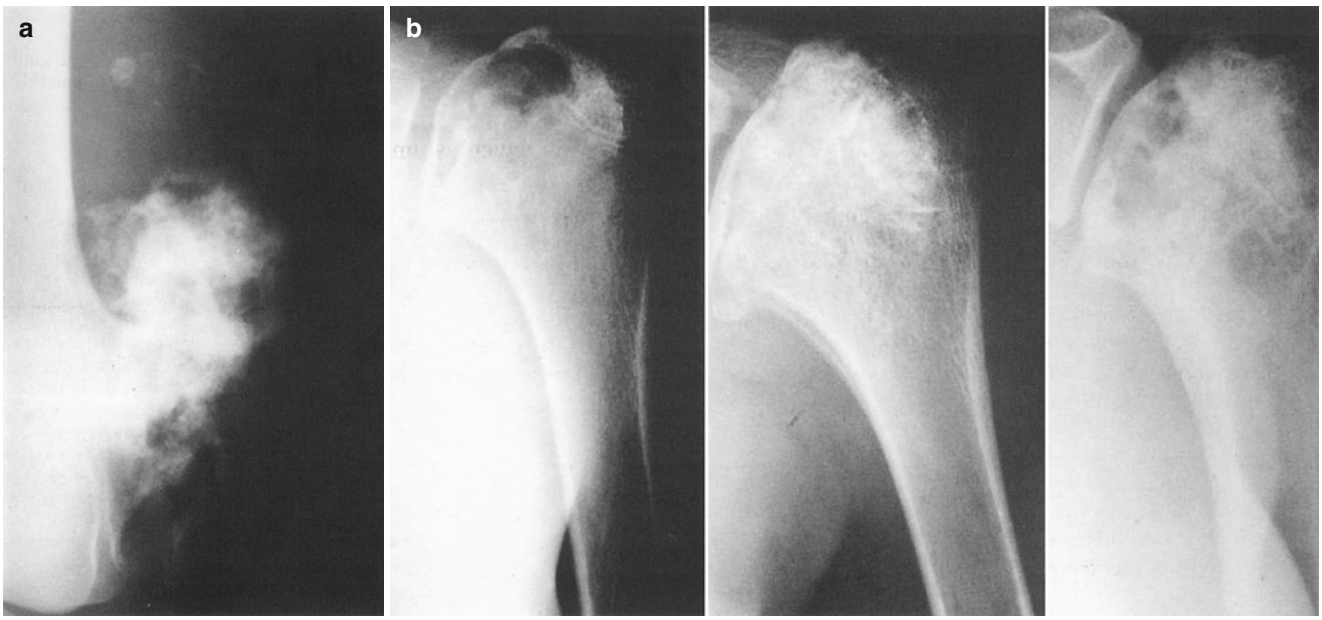

Fig. 23.10 (**a**) Lateral radiograph showing osteochondroma of distal femur. (**b**) AP radiograph of proximal humerus showing chondroblastoma

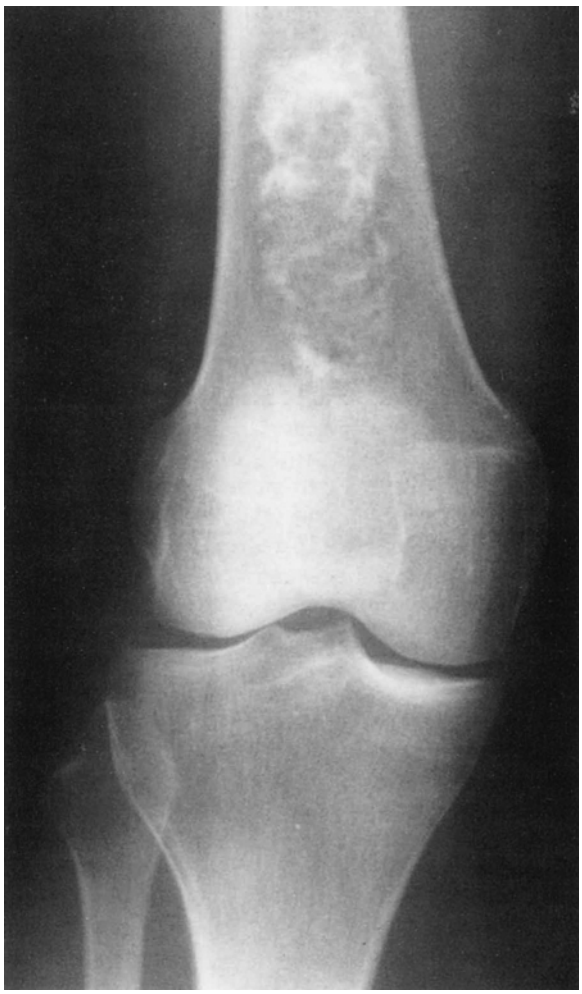

Fig. 23.11 AP radiograph of distal femur showing a chondrosarcoma arising in a pre-existing enchondroma

Treatment of the local lesion is by a combination of curettage and excision of any adjacent soft tissue extension. The outcome is very good but it may recur if not excised totally, and damage may be done to the growth plate. The application of autologous bone graft will lessen the recurrence rate but conversely makes local recurrence more difficult to detect by radiography. The recurrence rate is approximately 20 %, but this may be further reduced by use of cryotherapy and other adjuvants [64].

Chrondromyxoid Fibroma

This is a tumor which arises commonly in the upper tibia. It is most common in the second decade of life but may occur in any decade. There is a long prodromal history, often as long as 2 years [65]. With the exception of the clavicle, all bones can be involved, but it is much more common in the lower limb.

The radiological features are of an eccentric lesion in the metaphyseal area of a long bone. It is well de fined but surrounding sub-periosteal reaction may be slight [66].

As with chondroblastoma, treatment consists of an initial curettage and the recurrence rate can be reduced if the operation is supplemented with an autograft [67].

Malignant Cartilage-Forming Tumors

Chondrosarcoma

Chondrosarcoma is divided into two basic subgroups: primary chondrosarcoma which arises in normal bone, and secondary chondrosarcoma which arises in a pre-existing benign cartilage tumor, usually an enchondroma or cartilage cap of an exostosis. Primary lesions are twice as common. Chondrosarcoma occurs in 25–30 % of cases, secondary to enchondroma or an exostosis. Primary chondrosarcoma rarely occurs in childhood.

Although chondrosarcomas may occur in the young, they predominate after the third decade of life. Both sexes are equally afflicted. Most patients complain of pain but it is well recognized that a presenting mass may be painless [68]. The anatomical distribution favors the axial skeleton, but 10 % of tumors occur in the humerus.

Classically, the radiological appearance is a thick walled radiolucency with irregularly blotchy areas of calcification. On the medullary surfaces the cortex is scalloped and cortical penetration occurs late in the disease. A pre-existing benign tumour (Fig. 23.11) may be difficult to discern.

The only treatment effective in chondrosarcoma is excision, the adequacy of which is important in determining the outcome [69]. The survival outcome is also influenced by the degree of malignancy and the site, patients with pelvic lesions faring far worse than those with upper limb tumor. Although most lesions require excision, preferably of a wide or radical nature, small corticated, low-grade lesions in the elderly may be best served by curettage and adjuvant therapy consisting of cryosurgery, phenolization or "cement" application.

Dedifferentiated Chondrosarcoma

This rare tumor was first described by Dahlin and Be about in 1971 [70]. Additional mesenchymal elements are present in addition to the chondrosarcoma. The humerus is the second most common site. The radio logical appearance may give a clue to the probability of this lesion, which may be represented by a purely lytic expansile area in an otherwise typical chondrosarcoma. The overall poor prognosis of patients with this tumor has led to attempts with the use of chemotherapy as a neoadjuvant therapy in addition to surgery, with little success.

Mesenchymal Chondrosarcoma

This is a further subtype of chondrosarcoma which rarely affects the upper limb. It is characterized by a highly cellular

primitive spindle cell stroma with focal chondroid differentiation [71]. The tumor occurs most frequently in the second decade of life.

In terms of radiography, it is extremely difficult to differentiate the lesion, which may resemble an osteosarcoma as soft tissue extension may be heavily calcified.

Treatment is similar to dedifferentiated chondrosarcoma, consisting of chemotherapy and resection. In Britain, the chemotherapy consists of the agents cisplatin, ifosfamide, and Adriamycin (doxorubicin).

Clear Cell Chondrosarcoma

This is an extremely rare tumor which is rather slow growing, patients often having symptoms for up to 3 years. The most common site is the upper femur but the upper limb may also be affected [72]. The tumor appears as an osteolytic expansile lesion, usually at the proximal end of long bones. Treatment consists of complete surgical excision with reconstruction.

Benign Tumors of Histiocytic or Fibrohistiocytic Origin

Giant Cell Tumor

This is a locally aggressive but essentially benign bone tumor. It accounts for 5 % of all primary bone tumors and afflicts the mature skeleton. There is a slight female predominance [73]. Although commonly affecting the knee, distal radius, and proximal humerus, the elbow region may be affected (Fig. 23.12) and indeed patients with multiple sites have been recorded [74]. All patients suspected of presenting with a giant cell tumor should have hyperparathyroidism excluded by biochemical testing.

Early lesions present radiographically as an expanding lytic lesion, eccentric to the long axis, often with fine trabeculae present. Most investigators believe that the tumor arises in the epiphysis (subarticular region) and extends to involve the metaphysis. Large lesions progress to cortical destruction and joint dysfunction.

On the basis of the radiological appearance, Campanacci et al. [26] have proposed four subtypes which redefine the previously proposed terms of latent, active, and aggressive. Unfortunately, grade I probably often represents benign fibrous histiocytoma and the other grades do not necessarily predict their clinical behavior. The picture is further complicated by the histological pattern of the tumor. The osteoclasts which are present are now considered markers of the true tumor which is represented by the stromal background. This background can vary from being inconspicuous to frankly malignant [27] and thus can profoundly affect treatment.

Another poorly understood phenomenon in these tumors is the likelihood of malignant transformation of a benign tumor either following multiple local recurrences or irradiation treatment [75], and care is required in establishing whether it is true malignant transformation of the giant cell tumor or sarcomatous induction by the radiotherapy when this modality of treatment has been used.

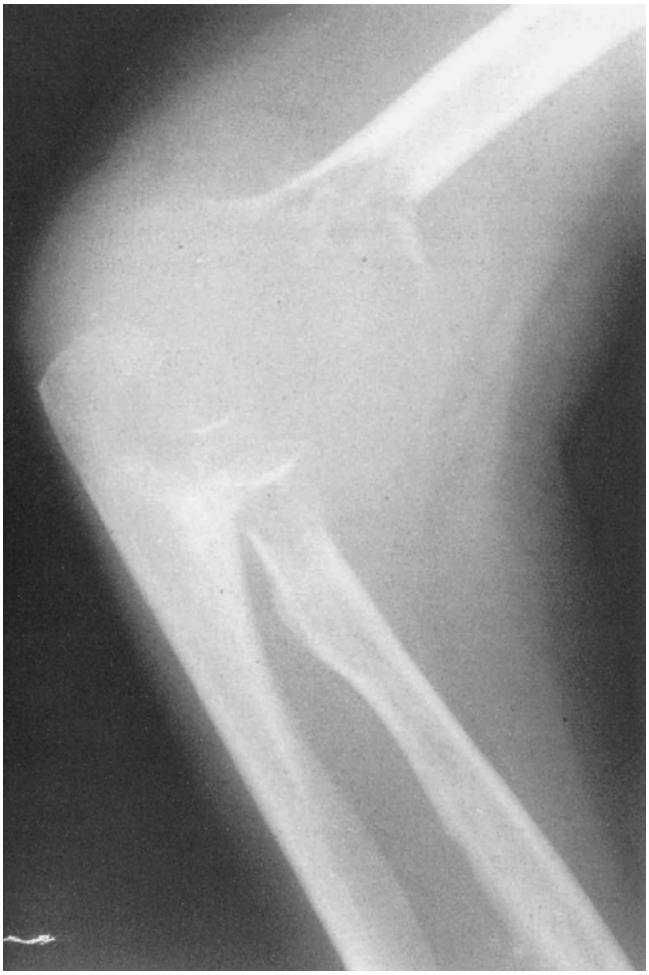

Fig. 23.12 Giant cell tumor: lateral x-ray of elbow joint

Primary de novo malignant giant cell tumor is a rare but well recognized entity, but care is required particularly in the subsequent differentiation of an osteoclast rich osteosarcoma [76]. When diagnosed, their treatment is as for a malignant fibrous tumor (see below).

Given the multiplicity of combinations of local extent and histological appearance, it is difficult to be adamant regarding therapy. It is well recognized that curettage alone has a 20 % or greater local recurrence rate [77]. Recent work by the European Musculoskeletal Oncology Society in a multicenter study suggests that the incidence of recurrence might be halved if adjuvant therapy (phenolization, cryotherapy, or polymethylmethacrylate) is used in combination with intralesional techniques.

Curettage remains the mainstay of treatment; occasionally multiple attempts may be required. Reconstruction may

not always be required after curettage and a number of patients have been treated by simple casting or cast-bracing until infilling of the cavity [78]. If articular failure has occurred by fracture or tumor invasion, then reconstruction with a pros thesis or allograft will be required.

Non-ossifying Fibroma/Benign Fibrous Histiocytoma

Non-ossifying fibroma is generally the term given to a lesion which is larger than a fibrous cortical defect. The term metaphyseal fibrous defect may be used for both. The lesions are extremely common between the ages of 4 and 8 years and can affect any metaphysis [79]. They are rarely seen in adults, which probably reflects the natural history of the condition. Large lesions may be associated with pathological fractures [80].

The radiological features are characteristic, consisting of an eccentric lesion which may involve the cortex situated at the end of the diaphysis. A sclerotic rim is usually seen on the medullary border. Although the lesion does not usually require biopsy, unusual clinical or radiological features may justify the need for needle biopsy.

Treatment in the majority of cases is only observation. Enlargement or pathological fracture will demand curettage or block excision with or without bone grafting. Fractures occasionally lead to obliteration of the lesion [81].

Benign fibrous histiocytoma may have a similar histological picture to a non-ossifying fibroma but tends to occur in older patients and is sited away from the metaphysis. Treatment requires either curettage or block excision.

Malignant Tumors of Histiocytic or Fibrohistiocytic Origin

Malignant Fibrous Histiocytoma

Malignant fibrous histiocytoma was first described by Feldman and Norman in 1972 [82]. It is a high-grade spindle cell lesion of bone which accounts for approximately 5 % of all bone tumors. Although the peak incidence is in the fifth decade, it may occur at any age. Females seem to be preferentially affected in the second decade. Histologically, it resembles its soft tissue counterpart but must be differentiated from this and from fibroblastic subtype of osteosarcoma. The latter may be differentiated by osteoid or alkaline phosphatase production [83]. The clinical presentation is as for other bone tumors, with a usually fairly lengthy duration. The area affected is usually around the knee and the radiographic features are of a tumor with essentially a lytic component with ill-defined margins. Lymph node metastases may occur [84]. Unlike its soft tissue counterpart, malignant fibrous histiocytoma of bone has been shown to respond well to a number of chemotherapeutic agents, including Adriamycin (doxorubicin), ifosfamide, high-dose methotrexate, and cisplatin. Therefore, a combined approach using adjuvant or neoadjuvant chemotherapy, together with adequate surgery, seems the treatment of choice.

Bone Tumors of Vascular Origin

Hemangioendothelioma

Hemangioendothelioma is a locally aggressive non-metastasizing tumor. All age groups can be affected and there is a male predilection. Radiographic appearances are of an osteolytic lesion which may occasionally produce a honeycomb pattern. Treatment is by adequate local surgery. Local recurrence is a problem.

Hemangiopericytoma

This is a low-grade malignant spindle cell tumor rep resenting 0.1 % of malignant bone tumors. It is also more common in males [85]. It again resembles its soft tissue counterpart and presents as an osteolytic bony lesion. The pelvis and lower limbs are more commonly affected. Wide surgical excision is the treatment of choice. The role of chemotherapy or radiotherapy is not yet established. Unfortunately, local recurrence is extremely common and metastases may occur extremely late.

Angiosarcoma

This is the high-grade counterpart of hemangioendothelioma. It is exceedingly rare. Again, wide surgery is the treatment of choice. Vascularity of the tumor may make limb salvage surgery extremely difficult. The tumor is radiosensitive [86]. The role for chemotherapy is not yet established.

Adamantinoma

Adamantinoma is an extremely rare bone tumor which occurs commonly in females, mainly in the second decade of life (Fig. 23.13). The bone which is commonly affected is the tibia [87]. Histologically, there is a mixture of spindle cells forming a fibrous stroma and islands of epithelial-like cells. It often arises in a background of fibrous dysplasia, and a differential diagnosis from metastatic carcinoma in the older patient may be difficult because of the expression of epithelial markers. Occasionally, other long bones can be affected and multi-focality has been recorded. Diagnosis may take many years because of the slow growth of the tumor. Radiologically, the lesion is lytic and well defined. Metastases are only found late in the disease. Treatment is excision, usually involving limb-saving techniques applied after diaphyseal resection and re construction.

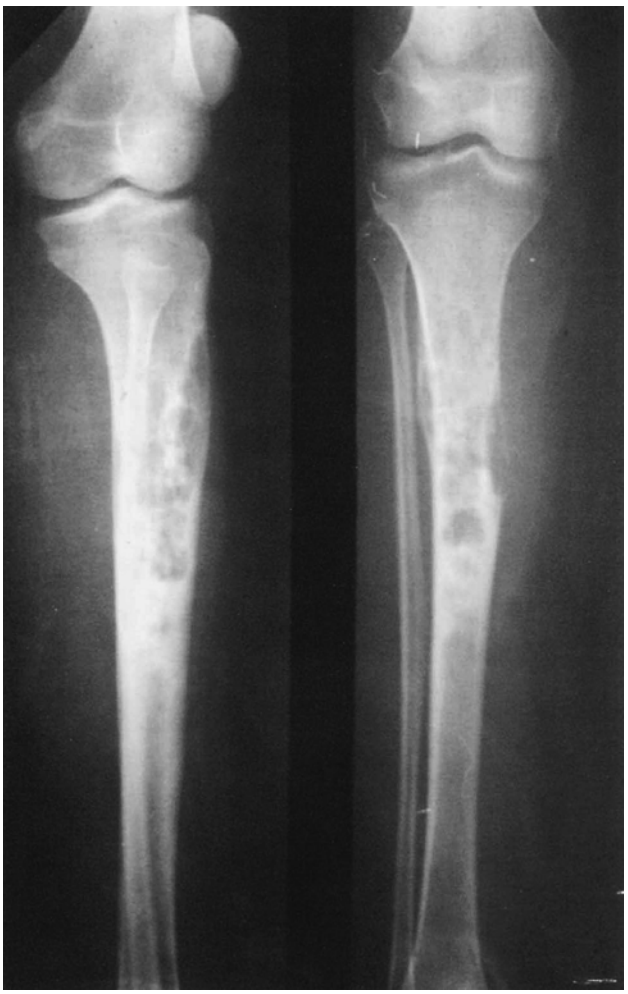

Fig. 23.13 AP and lateral view of adamantinoma of the tibia

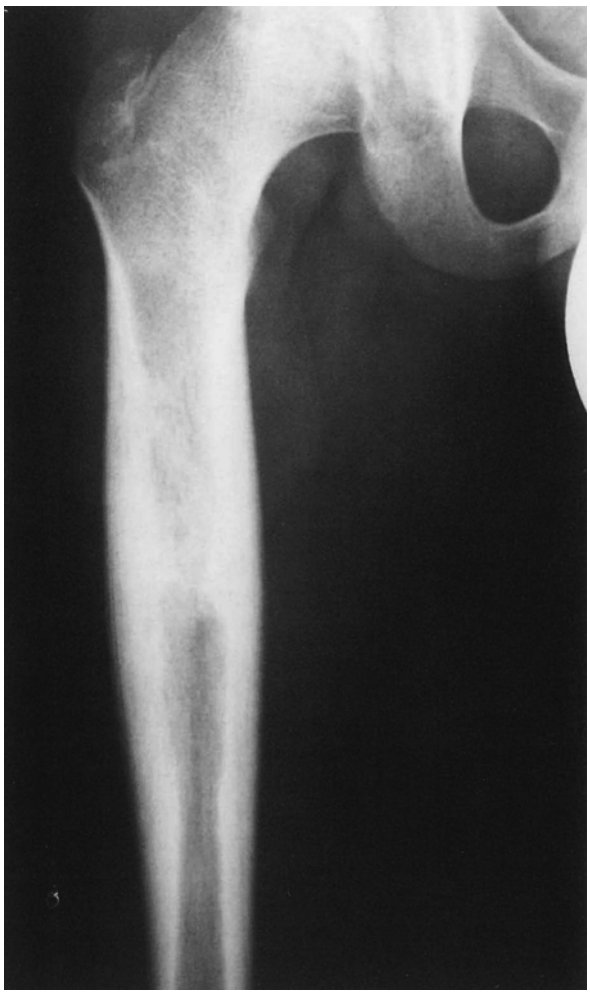

Fig. 23.14 Ewing's sarcoma of the femur exhibiting typical periosteal lamination (onion-skinning)

Ewing's Sarcoma

Ewing's sarcoma is the second most common malignant bone tumor of children and adolescents. Although there is a wide histological spectrum, 10–15 % of tumors fall into the category of malignant round blue cell tumor/Ewing's sarcoma [88]. The mean annual incidence approximates 0.6 per million of the total population [89]. It is rare below the age of 5 years, and the peak incidence is between 10 and 15 years. Male to female ratio is approximately 1.5:1, but this may vary with the age of the patient. Black and Chinese populations are less affected [90]. In addition to the standard presenting features, fever may occur, and this is more likely in patients with advanced or metastatic disease [91]. Pelvis, femur, tibia, and fibula account for 60 % of all primary sites. Although the plain radiographic appearance may be characteristic with a moth-eaten central bony destruction having poorly defined margins and an associated parallel onion-skin periosteal lamination together with a large soft tissue extension, this picture is not always seen (Fig. 23.14). Further investigations are required to confirm the diagnosis. Approximately 20 % of patients present with detectable metastases [92] which may be either pulmonary or be represented by multiple bone/bone mar row involvement. The serum lactate dehydrogenase (LDH) level may be elevated and this is associated with a poor prognostic outcome [93]. Other factors having a favorable influence on prognosis in Ewing's sarcoma are female gender [94], tumor volume at presentation [95], histological type [96], and proven histological response to chemotherapy [97].

Ewing's sarcoma represents a tumor where the utmost collaboration is required between surgeon, radiologist and pathologist. The radiological appearance of osteomyelitis may be very similar, and this can be further complicated if the patient has a leucocytosis and/or fever. The pathologist must differentiate Ewing's tumor from primitive neuroectodermal tumor (PNET) and Askin's tumor, which can be done using neural specific immunohistochemistry. Similar problems may occur in distinguishing the tumor on histological grounds from rhabdomyosarcoma, neuroblastoma lymphoma, and

small cell osteosarcoma. Rarely, primary malignant lymphoma of bone can present without disseminated lymph node or visceral disease. Again, immunohistochemistry using lymphoid markers is helpful in recognizing this category of tumor [98]. Ewing's sarcoma may also present as a extraskeletal lesion without a perceptible bony component. In this variant, there is a higher risk of lymphatic spread; this rare variant is usually treated using the principles employed in embryonal rhabdomyosarcoma [99]. There is no doubt that Ewing's sarcoma is a rapidly disseminating malignancy. Prior to the advent of effective chemotherapy, 90 % of patients died within 5 years. Conventionally, radiotherapy has had a major role in local treatment in Ewing's sarcoma [100]. Although the risk of local failure following radiation alone is difficult to assess, there is increasing evidence that the probability of cure with radiotherapy is related to limited tumor bulk and chemosensitivity as measured by tumor regression [101]. Radiotherapy also can affect growth if the epiphyses are treated leading to limb deformity and length inequality, and radiotherapy around the joints may lead to contracture formation. Radiotherapy in the pelvis may lead to visceral or gonadal damage, although excision alone may be similarly fraught with morbidity [102]. Although the debate continues, it is generally recognized that operative intervention is indicated for the local treatment in Ewing's sarcoma. In the axial skeleton, surgery is rarely indicated but in the pelvis considerable problems may be posed. Certainly, pelvic tumors are usually large and have extensive soft tissue extension invading the pelvic cavity when initially diagnosed. Their prognosis is particularly poor [103]. There is now good evidence that the prognosis of extensive pelvic lesion can be improved when the residual interosseous disease (following chemotherapy) is resected and reconstruction performed. Such resections are rarely "wide" and therefore are usually followed by postoperative radiotherapy. Whether radiotherapy can be omitted in patients who have had a particularly good chemotherapeutic response is the subject of ongoing controlled trials [104]. (For management of Ewing's tumor affecting the chest wall see Chap. 18.)

Simple Bone Cyst (Unicameral Bone Cyst)

These fluid-filled cysts often arise in the metaphyseal region of long bones juxtaposed to the epiphyseal plate. They are usually brought to the patient's attention either by incidental Xray or by pathological fracture. Fracture may lead to resolution of the cyst, but it is also well recognized that a traumatic episode may turn a cystic lesion into an aneurysmal bone cyst [105].

Cysts are commonly found in the proximal humerus and femur but may also occur in both the radius and ulna. They are commonly seen in childhood and adolescence, 90 % of patients being younger than 20 years old. When they do occur in the adult, they tend to occur in either the ilium or os calcis.

Plain radiographs usually show a lesion which has a central medullary location and its length is usually greater than its width (Fig. 23.15). The transverse diameter of the cyst closest to the epiphysis is recognized as being as wide as the epiphysis. With age, the cyst grows towards the diaphysis. This appearance is contrary to an aneurysmal bone cyst (see below), which shows a centrifugal growth pattern. Where the cyst reacts with cancellous bone there is a bony reaction but periosteal reaction is extremely rare. There is no soft tissue component. Further radiological investigation is rarely performed, although it is possible to recognize fluid levels on a CT scan. Treatment can be difficult. Small cysts which are asymptomatic do not require any therapy. However, large cysts may require curettage, bone grafting, en bloc resection, or even nailing. It is now fairly universally accepted following the work of Campanacci et al. [106] that these cysts will respond to an injection of methylprednisolone. If surgery is contemplated, incomplete removal of the cyst lining usually leads to local recurrence. The recurrence rate is much higher in children [107].

Aneurysmal Bone Cyst

These blood-filled expansile lesions present with pain and swelling and may follow a fracture. It is recognized that during pregnancy aneurysmal bone cysts may rapidly enlarge.

It is predominantly a disease of the first three decades of life and occurs equally in both sexes. It can affect any bone and 80 % are recorded as occurring in the upper limb.

The radiological features are of a purely lytic expansile lesion which usually arises in the metaphysis. Extension may occur into the epiphysis when the growth plate has closed [108]. They may grow alarmingly and may mimic malignant tumors (Fig. 23.16). Again, if further radiological investigation is required, the multiple fluid levels seen on CT are practically diagnostic of an aneurysmal bone cyst [109].

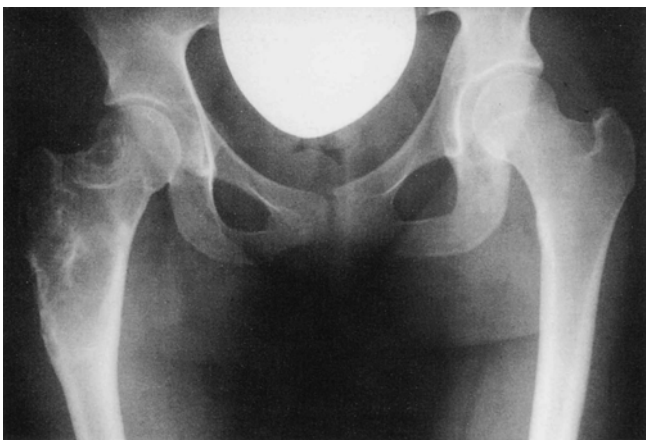

Fig. 23.15 Simple bone cyst proximal femur

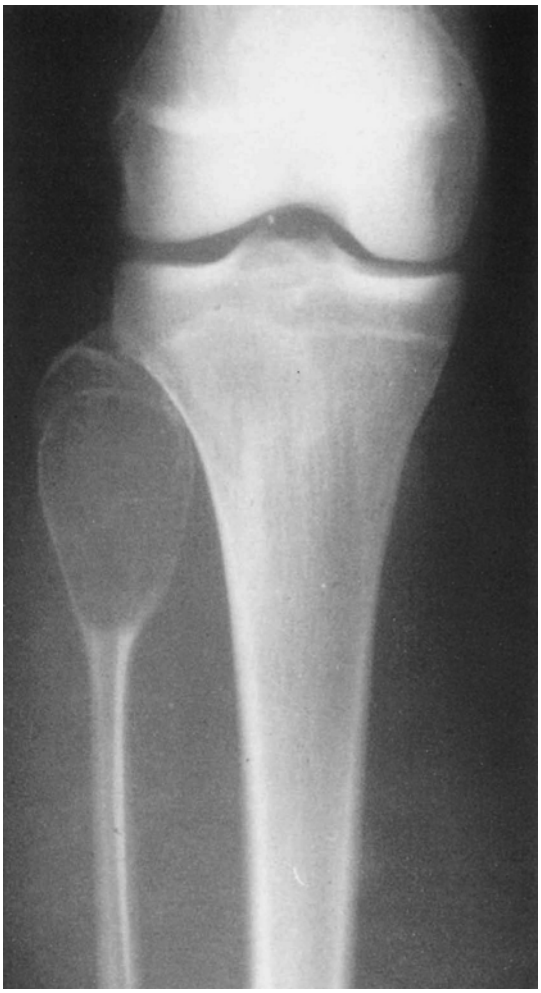

Fig. 23.16 Aneurysmal bone cyst proximal fibula showing large bone expansion

The mainstay of treatment is a combination of curettage and bone grafting. Where the tumor arises in inaccessible sites or where excessive blood loss is feared, arterial embolization may be a helpful adjunct to treatment. In tumors that recur or remain inaccessible, small doses of radiation can be given [110].

Miscellaneous Tumors of Soft Tissue and Bone

Myositis Ossificans

This condition is particularly troublesome when it occurs around the elbow joint. Although it can occur following a single injury, it more usually follows chronic repetitive trauma. The most usual presentation is of a painless mass, although some patients may have considerable soft tissue inflammation and pain. The period of symptoms is usually short.

The radiographic features show no abnormality in the first 2–3 weeks and then speckled calcification becomes evident. A fully mature lesion can usually be seen at around 14 weeks. In general, the diagnosis should be made on clinical and radiological grounds as great care is required in the examination of a biopsy. Unfortunately, myositis ossificans can be easily mistaken for osteogenic sarcoma [111].

Treatment is usually by surgical excision, but this should not be performed until the lesions have matured. Surgical intervention prior to maturity leads to a high rate of local recurrence.

Surgical Management

Embolization

Though angiography is now rarely used in pre-surgical imaging protocols, it can be useful in helping the clinician decide whether a plane of dissection exists between the tumor and the local neurovascular structures and, therefore, allow some limb salvage procedure to be performed. Occasionally, in tumors such as aneurysmal bone cysts, hemangiomas, and vascular osteosarcomas, such as the telangiectatic variety, significant feeding vessels can be recognized. Use of embolization materials injected into these vessels may significantly decrease the vascularity and render excision either possible or more easily accomplished. Embolization may be accompanied by significant pain and discomfort in the affected limb and the procedure should really be timed to allow for surgery to follow within 24 h. Embolization used solely as a method of local treatment is not recommended.

Curettage Alone

Certain benign tumors, notably aneurysmal bone cyst and giant cell tumor, lend themselves to treatment by intralesional removal or curettage. The technique of curettage requires a direct approach to the most weakened part of the cortical bone in expansile lesions or the most anatomically easy access in true intramedullary lesions. A good window of cortical bone is removed to allow adequate visual access to all the various crevices within the medullary cavity. A thorough curettage is performed with a standard bone curette and the cavity is then further debrided using either an osteotome or dental burr. The whole cavity is then thoroughly lavaged with a pressurized pulsed lavage system. Giant cell tumor local recurrence rate as high as 40 % can be recorded with this technique alone. Most surgeons now prefer to add some form of adjuvant therapy; the use of adjuvant therapy will decrease the local rate of recurrence to less than 15 %. Local adjuvants which have been proposed include cryotherapy, phenolization, and the use of cement, the latter having a dual role; first, the hyperthermic

reaction produced in the setting of cement causes local necrosis and further decreases the local recurrence rate, and, second, the cement itself may give immediate structural strength. For the younger patient, most authors prefer to remove the cement after an interval and substitute with bone graft. Lesions sited in the proximal humerus or distal radius are more suited to the simple curettage technique (Fig. 23.17).

Curettage and Bone Graft

When benign tumors occur in the subarticular position, the sub-chondral bone can be eroded and deformity of the articular surface can be encountered (Fig. 23.18). Treatment, therefore, must consist of gaining some mechanical support with either fresh autograft or allograft. The lesion is curettaged in the above manner and then morsellized cancellous auto graft harvested from the iliac crest is inserted into the defect. This will allow reconstitution of the subchondral space and support the articular architecture of the joint (Fig. 23.19). Bone autograft is incorporated relatively quickly. The exact mechanism by which this incorporation occurs is not fully understood but has been previously investigated and reported by Burwell [112]. The initial phase of incorporation in the first 2 weeks is analogous to fracture healing and is equally effective on both cancellous and cortical bone. Osteoblasts are laid down on the surface of the graft, and in the case of cancellous bone the osteoid seen laid down on top of the transplanted trabeculae of bone are rapidly absorbed. Eventually, all the graft of cancellous nature is resorbed. Where cortical fragments exist, the revascularization rate is slower and cortical fragments may be retained even following long-term incorporation. For this reason, cancellous grafting is preferred unless some mechanical strength is required, when cortical or fibular struts may be preferred. In recent years increasing use of bone graft substitute such as ApaPore, a synthetic hydroxy-appetite, have gained increasing amounts of popularity. They obviously avoid the morbidity of donor site harvest and usually incorporate within 6 months.

Excision Alone

Certain benign tumors which occur eccentrically on the bone surface are suitable for simple excision. The most classical variety is a osteochondroma or actively growing exostosis (Fig. 23.20). Here, surgical therapy merely requires resection of the bony stalk of the exostosis at the junction with the host bone. Care must be taken, however, not to spill any of the cartilage fragments, which may lead to local recurrence. The technique of local excision can also be extended to lesions such as non-ossifying fibroma, which occur eccentrically in the metaphysis of bone, and to certain low grade malignant tumors, such as periosteal osteosarcoma, where the resulting defect in the diaphysis may not be great. However, care must always be taken to achieve an

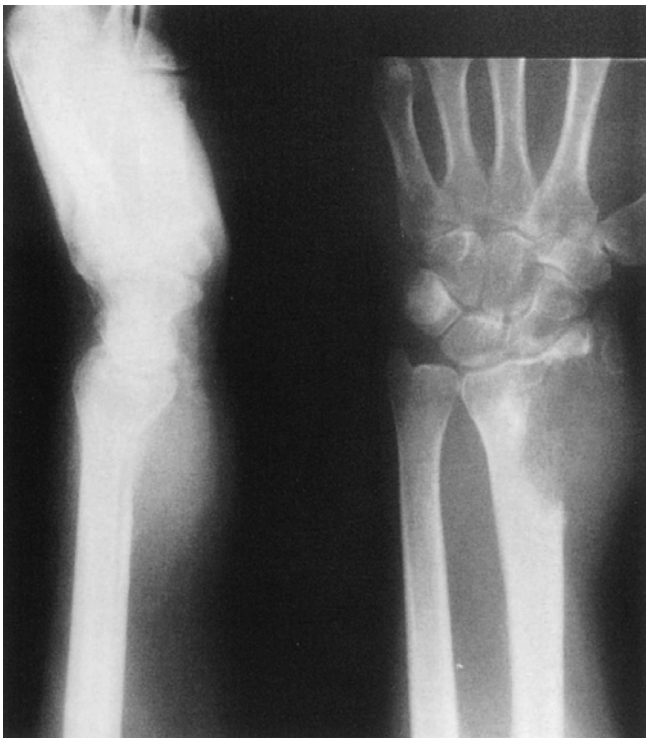

Fig. 23.17 Giant cell tumor of distal radius

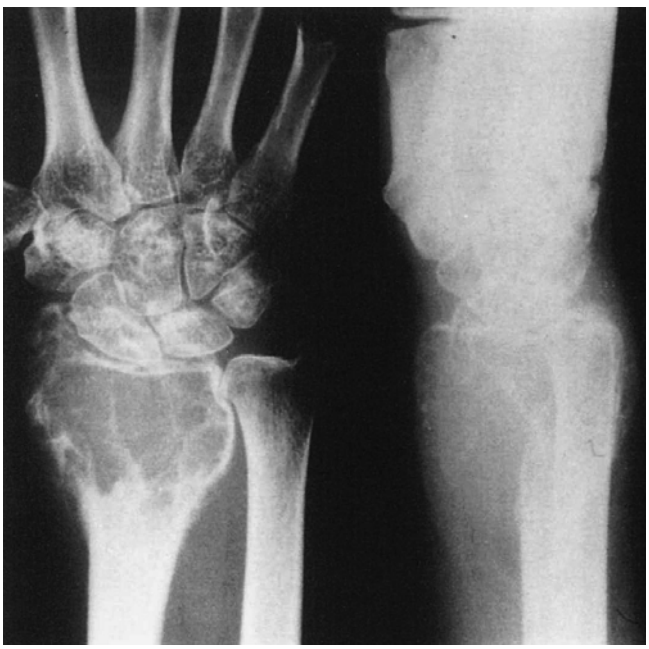

Fig. 23.18 Giant cell tumor of distal radius showing deformity of the articular surface

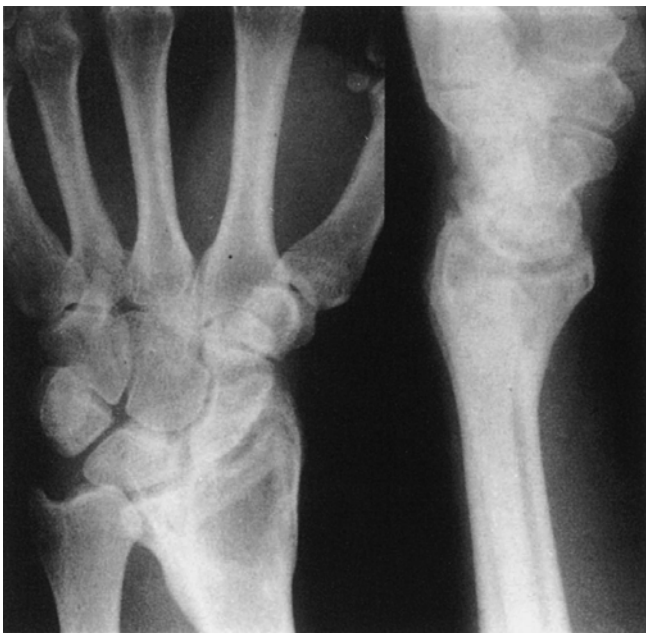

Fig. 23.19 Lesion of distal radius following curettage and bone grafting

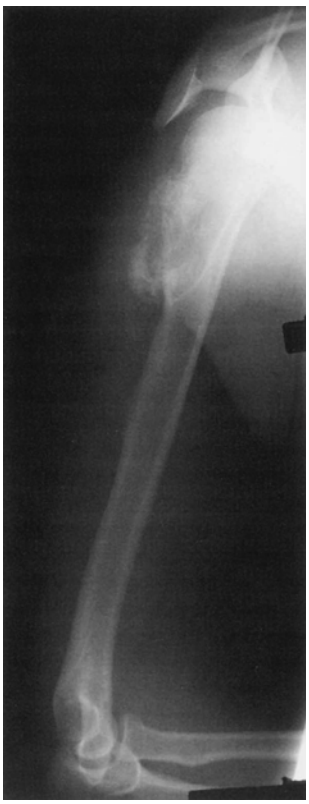

Fig. 23.20 Preoperative Illustrations of a proximal humeral osteochondroma

adequate surgical margin to prevent local recurrence, but most surgical oncologists now believe that the initially reported 5 cm margin is no longer required. Certainly, an adequate rim of normal host bone is all that is necessary, although occasionally this may require grafting techniques to reconstitute the diaphysis (Fig. 23.21).

Osteoarticular Fibular Transplantation

This technique is suitable for fairly large defects which occur following resections of benign or aggressive tumors of the distal radius and proximal humerus. The proximal ipsilateral fibula is harvested and is generally used in a non-vascularized manner. Transplanted to the upper humerus, it will allow a rudimentary shoulder joint which is relatively pain-free, particularly in the younger child. There may also be some hypertrophy of the graft. When used to reconstitute the distal radius, the articular surface is placed adjacent to the scaphoid bone and acts as a structural support and articulation. The fibula is usually plated onto the residual radius and the radial collateral ligament of the wrist reconstituted by using a loop of extensor carpi radialis longus. An illustrative case is seen in Fig. 23.22.

Bone Transportation

This technique originally described by Ilizarov [113], originally used in congenital deformity and post traumatic situations, is now extended to the use of filling postsurgical defects following tumor surgery. The principle is to transport a bone cylinder over the length of the defect and achieve bony closure at the proximal end of the defect by callus distraction and at the distal end of the defect by contact of the cylinder with the host bone. It has significant problems in that it involves prolonged external fixation time of several months, although this is less so in the upper limb. All transport systems suffer from pin track infection and the incidence of this limits the technique to benign tumors. The technique is contraindicated, in my opinion, in malignant tumors where patients are undergoing chemotherapy. Extremely short defects can be managed by acute shortening of the limb followed by reconstitution of the length using a technique of callus distraction (Fig. 23.23). The regenerate bone is often difficult to visualize on plain radiography and the use of ultrasound techniques is indicated to measure the degree and quality of the bone regenerate. In the lower limb, rapid internal fixation and distal bone grafting is recommended, but in the upper limb this does not seem to be a problem. Simple stabilization of the lengthening, which allows the regenerate to mature, appears to be all that is required. The technique is limited to diaphyseal defects. The rate of distraction is usually 1 mm per day, often in four quarter turns of the distracting device [114].

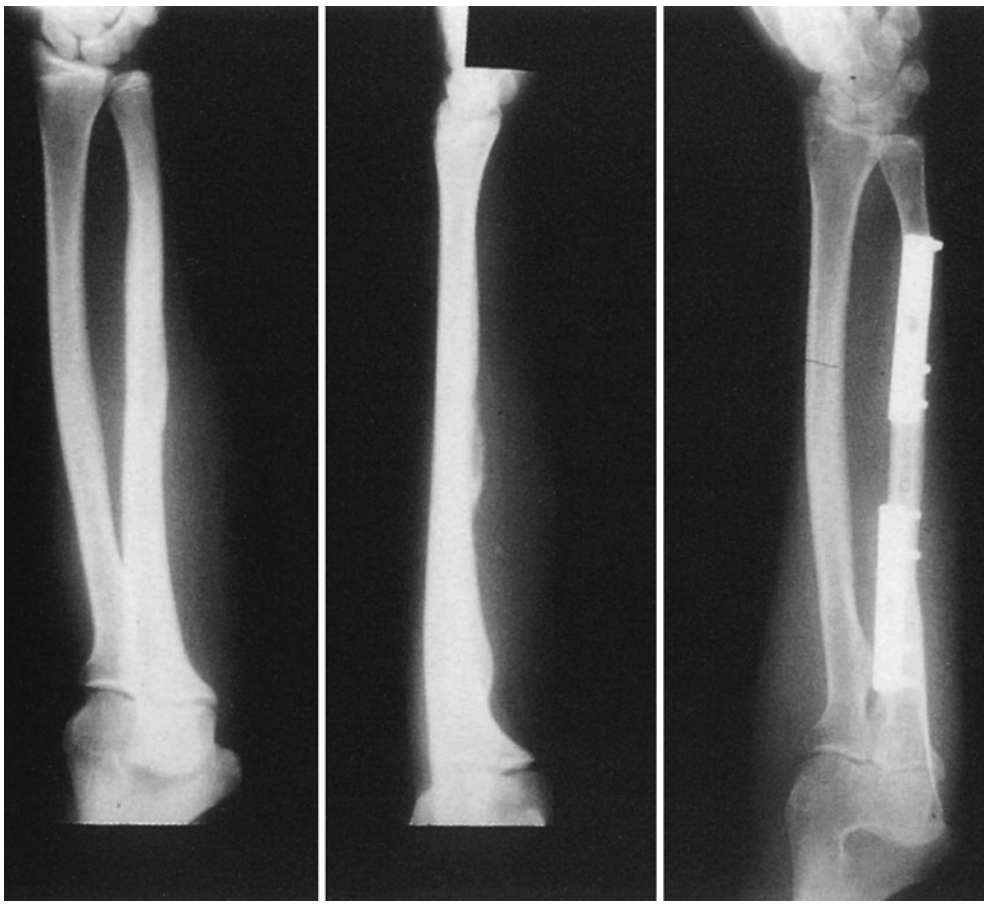

Fig. 23.21 Fibular grafting to reconstitute the diaphysis following tumor excision

Surgery for Large Osteoarticular Defects

When considering whether limb salvage procedures are justified, it has been traditional to consider the long-term oncological result and compare that with results obtained historically with amputation. Subsequent comparisons can be made in four broad areas:

1. Is there any difference in overall survival by patients treated by the two methods?
2. What is the early and late morbidity for each type of reconstruction?
3. Is the function of the salvaged limb satisfactory and does it remain so over a period of prolonged follow up?
4. Are there quality of life issues for patients undergoing limb salvage procedures as opposed to amputation?

Overall Survival

There have been a number of reports from single institutions [115, 116] which have concluded that the performance of limb salvage operations had no effect on the long-term survival of patients. These early reports have been confirmed by a number of multi-institutional reports [117–119]. Simon et al. point out that the local recurrence rate of patients undergoing above-knee amputation for malignant bone tumors around the knee is about 10 %, which is not dissimilar to patients undergoing limb salvage procedures. However, no patients who had a hip disarticulation suffered a local recurrence although at the cost of significant mutilation. Simon [120] reports a study from the Musculoskeletal Tumor Society, where the development of local recurrence was an extremely bad prognostic factor. Sixteen of seventeen people who developed local recurrence following limb salvage or amputation eventually died of their disease. Certainly, local recurrence usually requires amputation if there is no other metastatic disease. Even following amputation it would appear that survival is still unlikely. It is still, however, unclear whether the local recurrence represents poor response of the tumor to neoadjuvant chemotherapeutic agents and hence a poor prognosis or whether it is merely poor surgical decision making. There are, of course, a large number of cases, particularly where local recurrence occurs late and is not associated with metastatic disease, where further limb salvage procedures may be considered.

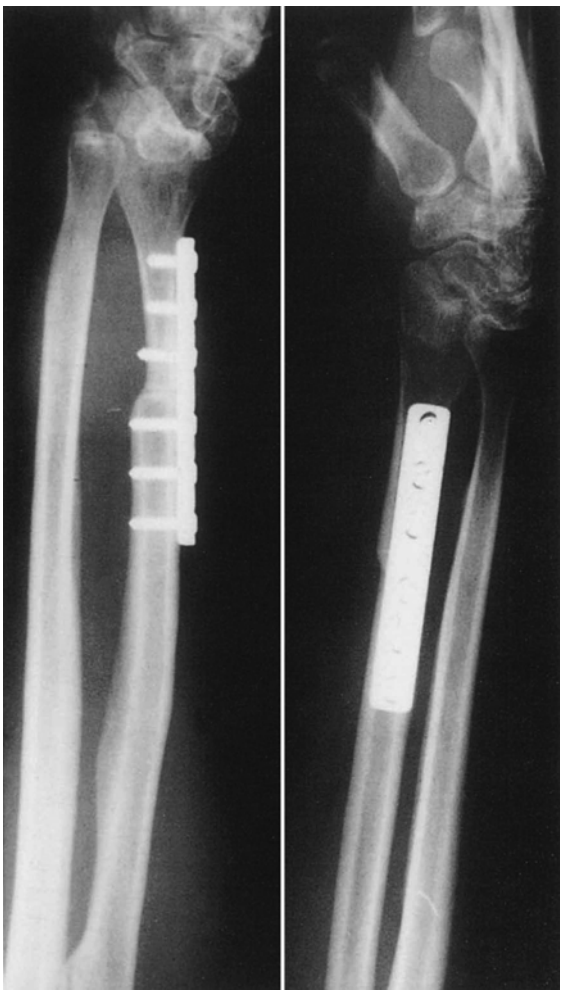

Fig. 23.22 Osteoarticular fibular transplantation of the distal radius in giant cell tumor

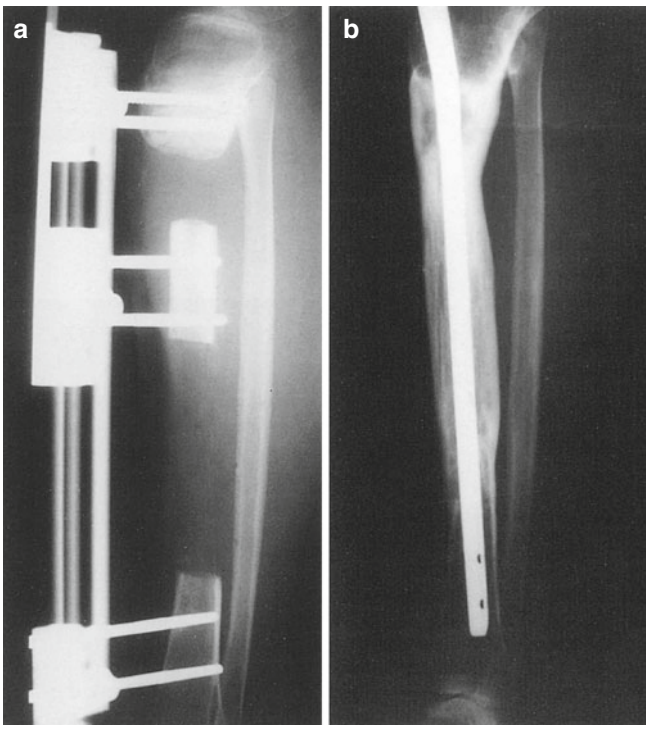

Fig. 23.23 (**a**) Initial radiograph following bone transportation of the tibial diaphysis. (**b**) Final radiograph following bone transportation of the tibial diaphysis

Early Complications

Operations performed for limb salvage are fraught with complications. Acute vascular injury may occasionally occur, and venous thrombosis and pulmonary embolism may be encountered in the early post-operative period. Involvement of neural structures often leads to sacrifice of a nerve during resection of the tumor, but the most worrying complication in the early postoperative period is wound necrosis and sub sequent infection. Loss of cutaneous cover requires urgent soft tissue coverage, often by a local skin flap or rarely by a myocutaneous free flap, so that the method of reconstruction can be covered. If infection ensues, then the complications, particularly where an endoprosthesis has been used, may be devastating. Often the limb requires amputation in the short or medium term. The onset of infection also delays the planned return of the patient to adjuvant chemotherapy.

It is important to emphasize that amputation itself is not without short and long-term complications, and certainly local pressure sores from an external prosthesis, phantom pain, and overgrowth of the stump when amputation is performed in children are recognized complications.

Endoprostheses are now used in a variety of benign and malignant conditions. There is a greater tendency to use them in malignant conditions, often where the patient's survival may be in doubt and hence the patient's longevity limited. Complex reconstructions are rarely justified in this situation. Although techniques such as osteoarticular allografting and bone transportation may be considered in patients with benign or low-grade malignant disease, there are occasions when endoprostheses may be utilized. In our practice, this is usually in periarticular destructive lesions, the most common of which being recurrent giant cell tumor. The frequency of prosthetic utilization in various pathologies is outlined in Fig. 23.24. It can be seen that less than 20 % of patients have a benign condition.

It is well known that most of the malignant bone and joint tumors have a predilection for the lower limb with a few cases occurring in the upper humeral metaphysis. It is therefore not surprising that if the distribution of prosthetic insertion throughout the body is studied, over 80 % of the cases have insertion in the lower limb. The proximal humerus remains the most common site replaced in the upper limb (Fig. 23.25). The foremost commonly replaced areas are therefore, in order of frequency, the distal femur and knee, the proximal femur and

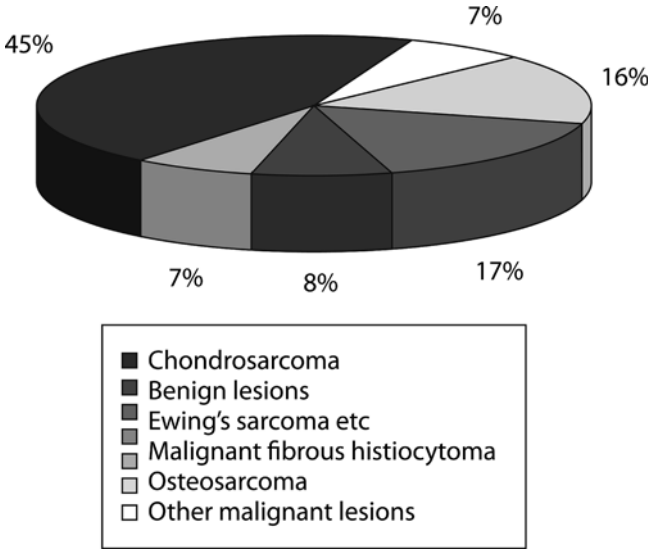

Fig. 23.24 Distribution of prosthetic utilization in various primary bone pathologies

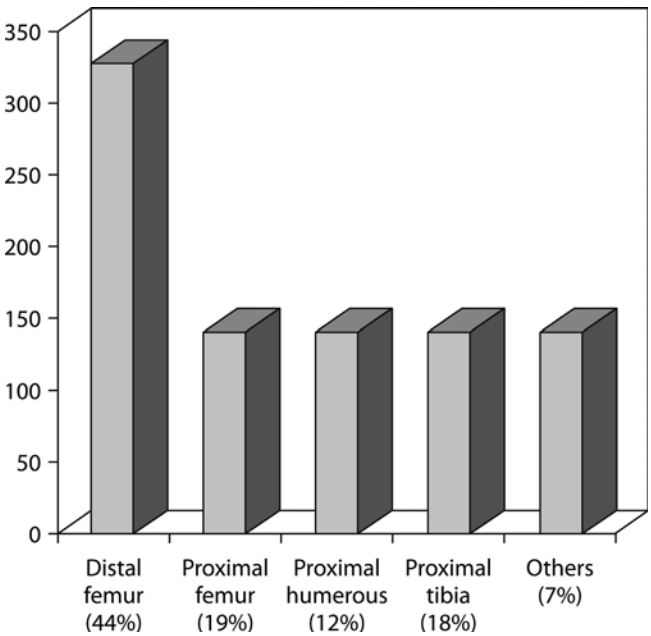

Fig. 23.25 Anatomical distribution of types of prostheses inserted

hip, the proximal tibia and knee and, last, the proximal humerus and shoulder. Occasionally, the diaphysis of femur, tibia, and humerus may be replaced, but these represent only a small fraction of the prostheses inserted. A similar low percentage exists for replacement of the whole bone and adjacent joints.

Allograft Techniques

Allografts suitable for osteoarticular reconstruction are usually only retrieved from deceased donors. This leads to a significant risk of human immunodeficiency virus (HIV) infection and secondary testing of the do nor cannot be accomplished [121]. Such allografts are rarely used in a fresh situation and they must either be frozen with cartilage cryopreservation or freeze dried. Similarly, they must be sterilized by either ethylene oxide or gamma irradiation. Only frozen techniques will allow attempts at cartilage cryopreservation, but frozen and freeze-dried techniques tend to reduce the antigenicity of the allograft. When implanted, the bio logical response to a preserved allograft is, at first, similar to an autograft. However, secondarily, there is an immunological response which causes changes within the graft. The immunological response mounted by the host causes vascular necrosis, which is followed by a second peak of osteoblastic activity at the end of the first 4 weeks. There has been some experimental work by Musculo [122] that suggests tissue typing in allografts will lead to better incorporation. Union of the allograft usually occurs from creeping substitution from the host bone, but there is usually excellent attachment of the soft tissues with the graft. The long-lasting presence of necrotic and revascularizing bone makes allografts more likely to fracture, but this is more of a problem in the lower limb. Strengthening of the allograft may be obtained by adding mechanical support or intramedullary cement. The overall fracture incidence is approximately 16 % [123]. The overall complication rate and long-term function of proximal humeral allografts has been reported by O'Connor et al. [124] and in a nonrandomized comparison of long-term function osteoarticular allograft functioned better than prostheses in the upper humeral position. This essentially has been due to better soft tissue re construction, and conforms with the previous work of Gebhardt et al. [125]. Many of the complications of allograft use in the long term have resulted from the lack of vascularity. Capanna et al. [126], have recently described a technique of using allograft shells combined with a vascularized fibular graft. This has not yet been used in an osteoarticular allograft, but may be of use where a scapulohumeral fusion is employed as the reconstructive method. While Mankin from the USA has popularized the use of cadaveric allografts, and although function in the upper limb is better than in the lower, there remain problems of sizing, stability, fracture, rejection, and degeneration [127, 128].

Endoprosthetic Techniques

Each area which is replaced has its own particular problems, and these are illustrated below.

Case 1

A 12 year old boy presented with a 5 week history of pain and discomfort in the left shoulder which was ignored. While on

holiday he fell from a donkey and sustained a pathological fracture. Staging investigations confirmed a pathological fracture through the left proximal humerus with no evidence of metastatic disease (Fig. 23.26). Biopsy confirmed high-grade osteosarcoma and the patient underwent neoadjuvant chemotherapy. The patient responded to chemotherapy and 6 weeks following the diagnosis underwent resection of the upper left humerus and endoprosthetic replacement (Fig. 23.27). The technical problems in performing upper humeral replacement in such a large tumor are twofold. The first is the proximity of the neurovascular bundle, part of which (the circumflex nerve) is particularly vulnerable as it winds round the surgical neck of the humerus. The second problem is the potential of intracapsular involvement of the glenohumeral joint. Fortunately, extra-articular resection is rarely required and in this case intra-articular resection was performed. There remains considerable debate as to the method of reconstruction of the residual rotator cuff. Early attempts to preserve function by sewing the cuff to a terylene sleeve were met with considerable abrasion debris and sinus formation. Some surgeons still use such a cuff as an artificial capsule over which the rotator cuff is repaired. This technique may lead to considerable stiffness of the glenohumeral joint. Prosthetic replacement of the upper humerus leads to excellent restoration of elbow and hand movement. Shoulder movement, however, remains quite limited. The usual outcome is that rotation is well controlled, although external rotation may be grossly exaggerated. Flexion and abduction are rarely better than 40°, and if the circumflex nerve is sacrificed may not be achieved at all. In manual workers where nerve sacrifice is anticipated, some form of biological or prosthetic arthrodesis of the glenohumeral joint may be a better alternative. Even where the circumflex nerve is preserved, rotator cuff function remains poor, and over time many prostheses sublux into the subacromial space. Early experience with bipolar prostheses where a reverse shoulder mechanism is utilized has shown much better functional movements without the risks of superior or inferior subluxation. The mechanism involves a hemisphere on a spiral component which is screwed into the glenoid with an HA collar. This snap fits into a concave surface inserted on to the upper humerus. Early 5 year results are now available and are encouraging [129].

Case 2

A 12 year old boy presented with a 3 month history of pain and discomfort in the upper left femur. Initial investigation at another hospital showed an abnormal area on plain radiograph and this site underwent open biopsy, which showed Ewing's sarcoma. He was treated with chemotherapy and

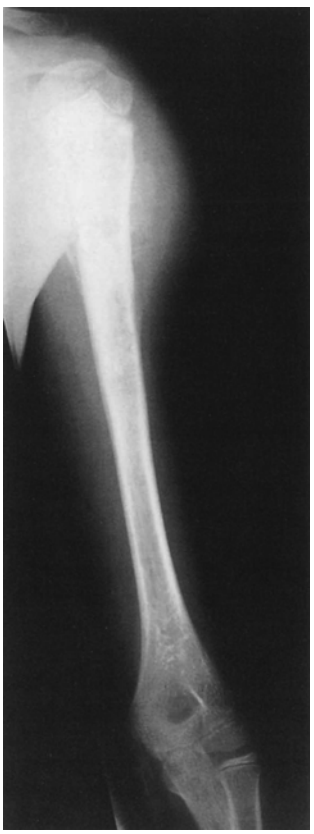

Fig. 23.26 Pathological Fracture through osteosarcoma of the proximal humerus

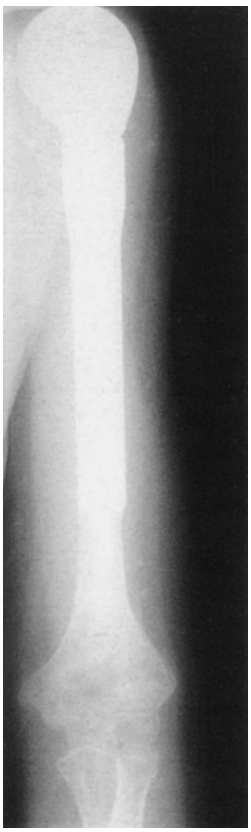

Fig. 23.27 Proximal Humeral prosthetic replacement

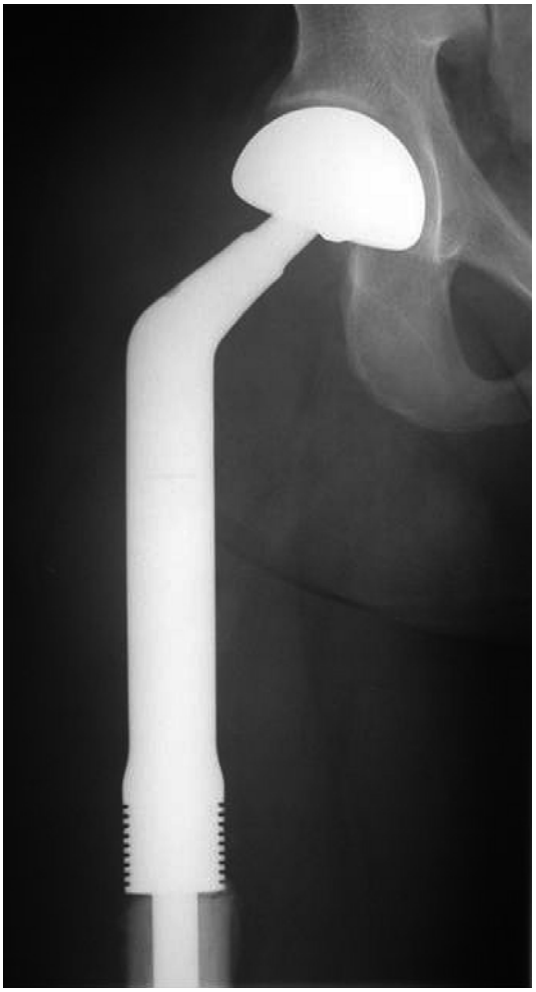

Fig. 23.28 Growing proximal femoral prosthesis with bi-polar head

then underwent an intra-articular resection of the hip joint and upper third of the left femur. The prosthesis was inserted and a bipolar head placed on top of the prosthesis to give acetabular stability. The prosthesis was of an extendible variety (Fig. 23.28). The surgical technique involved detachment of the iliac psoas and all three gluteal muscles. It is usually possible to leave the tensor fascialata intact which preserves innervation. The rest of the vastus muscles remained innervated although the vastus lateralis may be denervated and vastus intermedius is usually excised as a barrier to the tumor. Two methods of reconstruction of the abductor apparatus are possible. Usually the soft tis sue is reconstructed using a nylon weave to connect the muscular structures to the tensor fascia lata. Abduction can be maintained but the altered lever arm means that many patients have a positive Trendelenburg gait. Another technique under investigation involves turning down part of the ilium attached to the anterior fibers of gluteus medius muscle to allow fibrosis of the muscle on to the prosthesis itself. The most frequent complication of this procedure is hip dislocation. The patient is

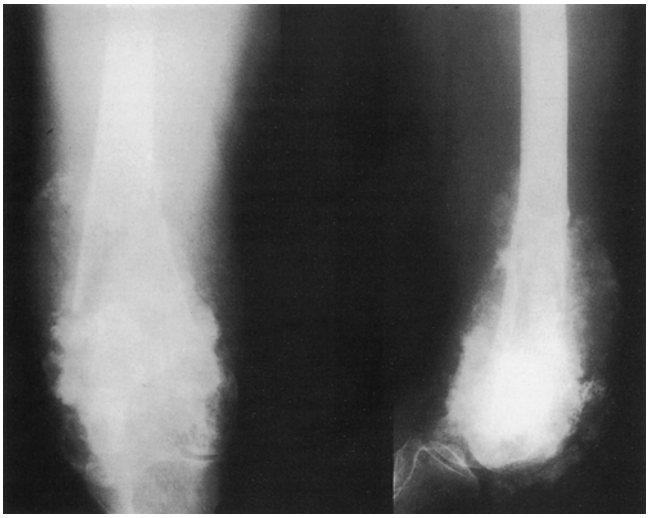

Fig. 23.29 Pathological fracture through osteosarcoma of the right distal femur

advised to use a PoHo type brace for the first 2 months after operation

Case 3

An 8 year old girl presented with a 2 week history of pain in her right distal femur and awoke one morning following a tussle with her sibling in excruciating pain. Plain radiograph confirmed an undisplaced pathological fracture through an osteosarcoma of the distal right femur (Fig. 23.29). Percutaneous needle biopsy performed under general anesthesia confirmed a chondroblastic osteosarcoma. The patient received neoadjuvant chemotherapy and underwent resection of the tumor 6 weeks later. Analysis of the resected specimen confirmed 90 % of the tumor had under gone complete necrosis. It was opted to reconstruct the limb using an uncemented expandable prosthesis (Fig. 23.30). The patient had an uneventful postoperative recovery and is now walking without a limp. Distal femoral replacement remains the most successful area in terms of early function following prosthetic insertion. The anatomy of the region means that the extensor apparatus is rarely severely damaged, and although the gastrocnemius is severely weakened by detachment of their origins, knee flexion can be fully compensated by the hamstrings. Therefore, it is often difficult to tell the operated side when observing gait in such patients. The mechanism used in this case to enable elongation of a prosthesis is termed minimally invasive. Elongation is achieved by insertion of an Allen key to turn a low gear mechanism to achieve elongation of the body of the prosthesis. It is, however, likely that this young lady will require a revision of her prosthesis and perhaps surgical cessation of growth on the opposite limb in order to achieve limb balance at maturity. Over the last 2 years, increasing use of noninvasive magnetic endo-

Fig. 23.30 Uncemented extendible distal femoral and knee prosthesis

prosthesis has been experienced. The prosthesis is similar to the prosthesis described above, but here the elongation is achieved by a motor placed within the body of the prosthesis. Placing the motor in a magnetic field produces a force of around 1500 N, which allows very slow extension of the prosthesis. Some 4 mm of extension will be achieved in 16 min. The slow but strong elongation force is achieved by using an epicyclic gear box. To date the prosthesis is used mainly in the lower limb prosthesis where growth is more important, but experience is just beginning regarding the humerus [130].

Case 4

A 17 year old boy presented with a rapidly enlarging swelling of the left proximal tibia. He denied any pain. Plain radiographs revealed a lytic area of the upper tibia through an area of abnormal bone. Jamshidi needle biopsy performed under local anesthetic confirmed an osteoblastic high-grade osteosarcoma; x-ray showed a typical osteosarcoma with significant soft tissue mass (Fig. 23.31). Further staging investi-

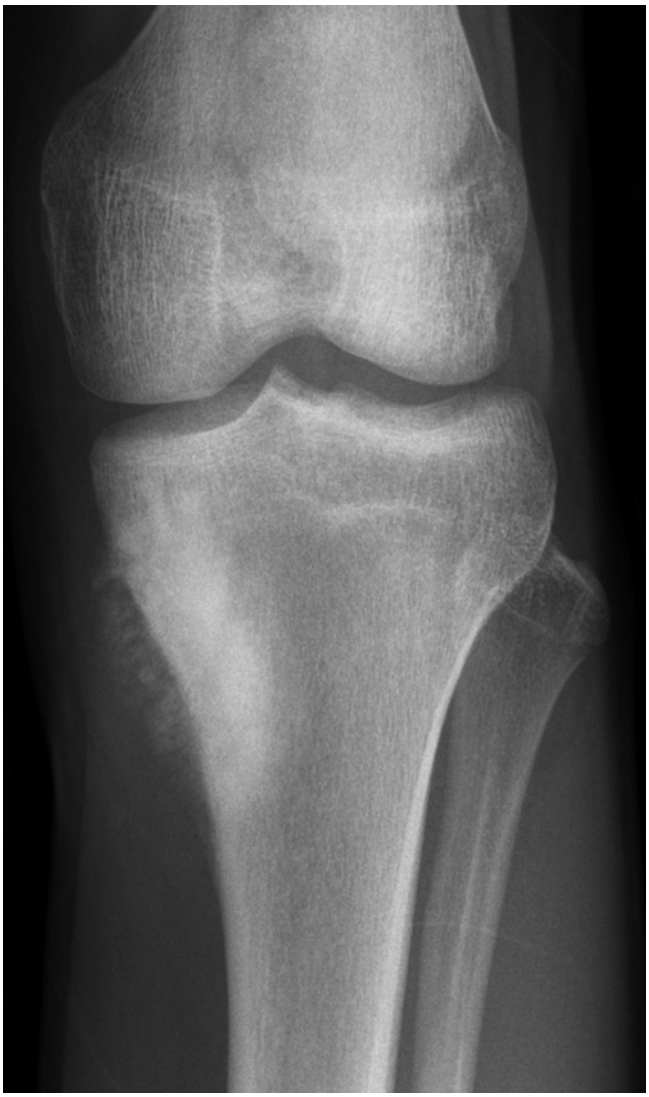

Fig. 23.31 X-ray of osteosarcoma of proximal tibia showing large tumour with soft tissue extension

gations revealed no evidence of metastatic disease. The patient received neoadjuvant chemo therapy, which was uncomplicated, and 6 weeks later underwent prosthetic replacement of the right proximal tibia. The surgical resection of the proximal tibia is fraught with complications. The most important of these as regards long-term function is the detachment of the extensor mechanism. The next most common problem concerns the common peroneal nerve, which usually has to be mobilized and occasionally sacrificed in resection of the tumor. The vascular structures are closely applied to the posterior aspect of the knee and the anterior tibial artery is nearly always sacrificed, as it is grossly adherent to the tumor as it enters the anterior compartment. The early morbidity in these cases, therefore, usually is a combination of arterial ischemia, compartmental syndromes, and nerve palsy. Established neural palsy is, of course, treatable by use of an

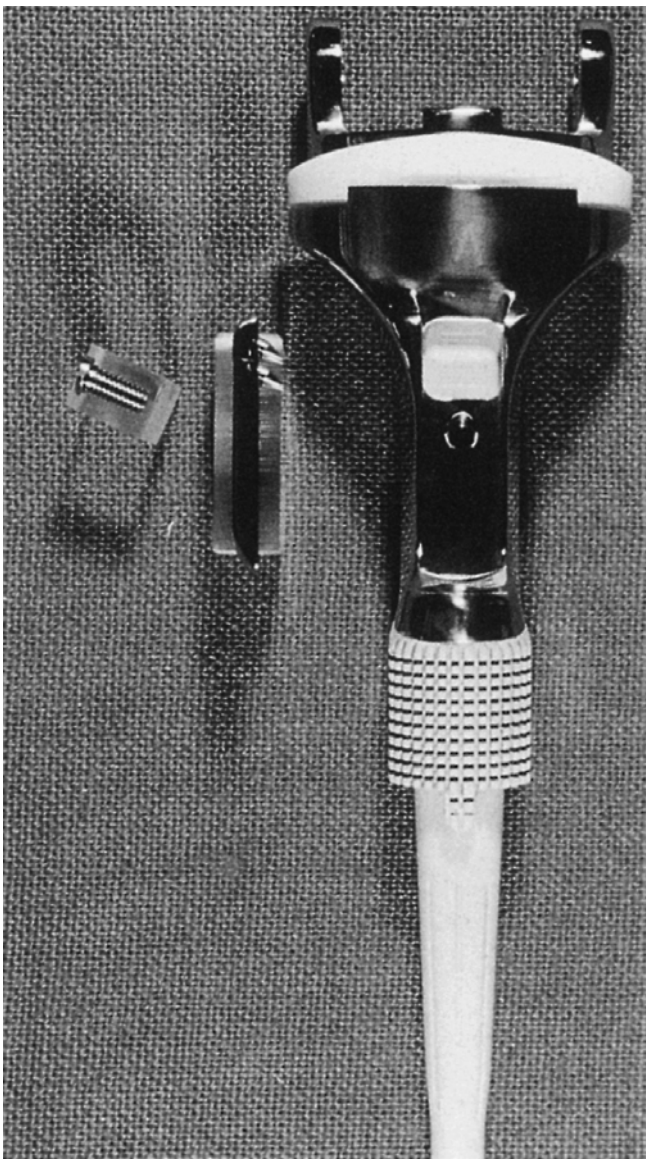

Fig. 23.32 Proximal tibial prosthetic replacement

external ankle-foot orthosis (AFO), ankle arthrodesis or, where appropriate, tendon transfer. In the long term, the major functional disability lies in the weakness of the extensor mechanism. All upper tibial replacements undergo a medial gastrocnemius flap, and this further weakens the flexors of the knee, the long flexors having been previously detached. The extensor mechanism may be reconstructed by simple suture on to the transposed medial head of gastrocnemius, but others prefer a transposition of the upper fibula achieved by multiple osteotomy if this bone is still present or by turndown of a portion of the distal patella (Fig. 23.32).

Postoperative rehabilitation is slow, and the patient is usually kept splinted in extension for a period of 6–8 weeks. The area of reconstruction of the extensor mechanism usually stretches, and the patient usually presents with patella alta and occasionally instability. Few can achieve a straight leg raise, although most achieve a normal walking pattern. This is achieved by throwing the tibia forward following hamstring relaxation and then locking the prosthesis in slight hyper extension.

Amputation and Disarticulation

Despite the current trend to perform limb salvage procedures in malignant disease following neoadjuvant chemotherapy, there are still a proportion of patients who are not suitable for this technique. The present primary amputation rate for musculoskeletal bone tumors at the Royal National Orthopaedic Hospital is 7 %. The indications for primary amputation are as follows:

1. Late presenting tumors with widespread soft tissue contamination, including involvement of the neurovascular bundle, which do not respond to chemotherapy;
2. Difficult anatomical location where tumors surround the neurovascular bundle ab initio;
3. Advancement of tumors despite chemotherapy (poor response to chemotherapy);
4. Wide major displacement and pathological fracture at presentation.

The description of various techniques of amputation is not in the remit of this chapter. However, the most usual lesion which requires amputation is the proximal humeral osteosarcoma where there is widespread involvement of the axillary structures, often with encroachment onto the chest wall. Simple disarticulation of the glenohumeral joint is rarely sufficient in gaining tumor control. These patients unfortunately, require a forequarter amputation procedure.

Management of Local Recurrence

When the first meeting of the International Limb Salvage Association occurred at the Mayo Clinic in 1981, the goal of the symposium was to share experience and focus research into improved results of limb-sparing procedures. At that meeting, the local recurrence rate for all the reported series of limb salvage procedures was 4 %. The society has continued to meet on a twice-yearly basis, and techniques of limb salvage have been popularized. The difficulty is that despite improved imaging techniques, the local recurrence rate for malignant tumors is now 10 % (Enneking WF, personal communication). This seemingly detrimental step in terms of treatment of course results from a vast increase in the number of procedures performed and also a change in patient awareness and demands. Local recurrence usually occurs within 2

years from the primary procedure and the surgeon must be ever aware of its possibility. All limb salvage procedures have in common a very narrow resection margin at the level of the neurovascular bundle. It is not surprising that the majority of local recurrences tend to occur adjacent to this structure. To date, in the series at the Royal National Orthopaedic Hospital, London, we have had only one true recurrence within bone; 50 % of local recurrences, because of involvement of neurovascular bundles, require either disarticulation or an ablative procedure in order to clear the problem. It is important that before undergoing such a procedure the patient is restaged for the presence of metastatic disease. Where local recurrence occurs in tumors not adjacent to neurovascular structures but adjacent to bone, further resection and radiotherapy may be feasible.

Rehabilitation

The majority of limb salvage surgery procedures for primary bone tumors tends to occur in specialized units. Within those units are skilled physiotherapists and occupational therapists who have a wide experience in the rehabilitation of such difficult patients. The aim of biological reconstruction is not to use prolonged immobilization of joints and, therefore, removable splints rather than plaster fixation is generally preferred. Wherever possible, sound primary internal fixation of bone grafts is utilized. There is a continuing debate as to the effect of radiotherapy and chemotherapy upon biological fixation, and this appears to be greater if intra-arterial chemotherapy is considered [131]. Certainly in present regimes patients must be returned for further chemotherapy as rapidly as possible, and where a positive tumor margin is found in the tumor resection, radiotherapy must be considered in addition to attain local control. At present, radiotherapy can be administered in an interval between chemotherapy courses, and occasionally in a hyper-fractionated manner. This is an extremely time consuming and difficult technique, and more traditional approaches have been to delay radiotherapy until primary chemotherapy has been completed. Where patients have received an endoprosthesis, there is no concern regarding union of allograft to host or incorporation of graft, and therefore postoperative oncological management can begin as soon as the wound condition is satisfactory. With endoprosthesis of the proximal humerus, the lack of reliable reattachment of the rotator cuff or denervation or excision of the deltoid leads to significant problems with functional abduction and flexion of the shoulder joint. Although rapid mobilization of the el bow and distal limb is achieved, functional control of the shoulder is only slowly achieved, often not till approximately 6 months. At best, without a rotator cuff, only 40° of flexion and abduction are achieved, although good rotational control of the limb is usually achieved by 6 months. Some early work is being per formed on motorized abductor function by rotatory grafts of innervated latissimus dorsi. Whether this will achieve improved function in the long-term is still unclear. Careful evaluation of the patient is required in the pre-surgical period as arthrodesis of the shoulder is probably more suitable for a manual worker.

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Head and Neck Tumors

24

Diana L. Diesen and Michael A. Skinner

Tumors of the head and neck present particular challenges for the pediatric surgeon asked to evaluate them. A working knowledge of the embryology, anatomy, physiology and pathophysiology of the head and neck is needed. While the majority of these tumors are benign, an understanding of the fundamentals of surgical oncology is needed when approaching these tumors to ensure proper assessment and treatment.

The head and neck are formed from mesenchymal cells that develop from the paraxial and lateral plate mesoderm, neural crest, and ectodermal placodes in early fetal development. The paraxial mesoderm makes somites and somitomeres which develop into part of the floor and meninges of the brain, the occipital lobe, and the muscle and connective tissue of the face. The lateral plate mesoderm develops into the laryngeal cartilage and connective tissue of the neck. The neural crest cells develop into the brain, the optic cup, the midface, and the pharyngeal arches.

The pharyngeal arches are separated by pharyngeal pouches and clefts. Each arch has a nerve and an artery, and develops into muscle, cartilage and connective tissue. The arterial supply develops when the embryological heart is caudally displaced. Normal anatomy and its variants depend on selective fusion or atrophy of these arteries. In contrast to the arterial supply, the venous system is more variable in the size of the vessels and their course. The branches and connections of the internal, external, and anterior jugular veins provide the venous drainage for the head and neck.

The pharyngeal pouches develop into endocrine glands and the middle ear. Pouch 1 develops into the middle ear and the auditory tube. Pouch 2 develops into the palatine tonsil. Pouch 3 develops into the inferior parathyroid glands and the thymus. Pouches 4 and 5 develop into the superior parathyroid glands. The pharyngeal cleft develops into the external auditory meatus. The thyroid gland is not derived from a pouch but rather develops as an epithelial proliferation from the endoderm of the floor of the pharynx and descends along the thyroglossal tract to the level of the laryngeal primordium.

The thoracic duct and the right lymphatic duct drain lymph from the head and neck. The right side of the head and neck, right upper extremity and the right thorax are drained by the right lymphatic duct which empties near the junction of the right subclavian and right internal jugular veins. The lower extremities, abdomen, and the left side of the head and neck are drained by the thoracic duct which passes posterior to the left common carotid artery and the left vagus nerve as it passes from the right to the left side of the body. The thoracic duct then arches anterosuperiorly and laterally between the left internal jugular vein and anterior scalene muscle to terminate near the junction of the left internal jugular and left subclavian veins. Valves present at the junction of each duct prevent reflux of venous blood. Small anastomotic connections between the two lymphatic ductal systems become important when obstruction or injury to one duct occurs.

The neck is divided based on anatomic triangles that are defined by the angle of the jaw, the clavicle, and the trapezius. Knowing the anatomical triangles of the neck is essential for both properly assessing and determining the prognosis of disease (Fig. 24.1, Table 24.1). The anterior and posterior triangles are separated by the sternocleidomastoid muscle. This muscle extends from medial clavicle to the mastoid bone. The anterior triangle is subdivided into four smaller triangles by the digastric, stylohyoid, and omohyoid muscles. These muscles then create the submandibular, carotid, submental, and inferior carotid triangles. The posterior triangle is divided into the superior occipital triangle and an inferior subclavian triangle by the omohyoid muscle. The triangles with the most lymph nodes include submandibular, submental, anterior cervical, superficial cervical, and deep cervical node groups. Table 24.2 listed common developmental anomalies that present as masses in the head and neck.

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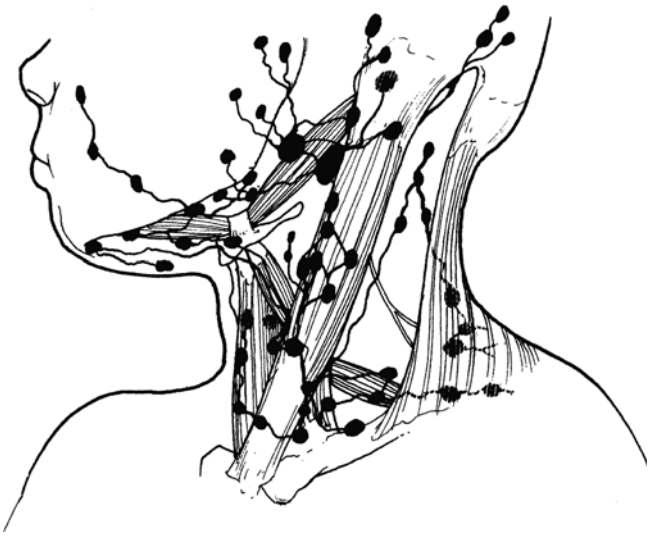

Fig. 24.1 Muscular triangles and associated lymphatics and lymph nodes of the head and neck

Table 24.1 Muscular triangles of the neck

	Posterior triangle	Anterior triangle
Boundaries		
Posterior	Trapezius muscle	Sternocleidomastoid muscle
Anterior	Stemocleidomastoid muscle	Midline of neck
Floor	Deep layer cervical fascia	Mylohyoid, hyoglossus, thyrohyoid, pharyngeal constrictor muscles
Roof	Superficial cervical fascia	Superficial cervical fascia, platysma muscle
Contents	Subclavian artery	Carotid artery
	Brachial plexus	Internal jugular vein
	Spinal accessory nerve	Submandibular gland
	Posterior cervical lymph nodes	Vagus nerve, recurrent laryngeal nerve, lymphatic tissue
Subtriangles	Occipital	Submandibular
	Subclavian	Carotid, submental, muscular

Cervical Adenopathy

Cervical adenopathy is a common finding in pediatric patients and is usually the result of inflammatory processes. In one study, lymphadenopathy was noted in 44 % of children under 5 presenting for a well child check and 64 % of children presenting for a sick visit [1]. However, only 11–30 % of biopsied lymph nodes harbor a malignant process [2–5]. Self-limited, non-specific adenitis from adenovirus, rhinovirus and enterovirus infection of the upper respiratory tract is most common. Up to 3 % of cases are due to cat scratch disease [6]. Measles, mumps, Epstein-Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), herpes virus, tuberculosis, parasitic, bacterial, and other viral infection may also cause cervical adenopathy. Non-infectious inflammatory disorders such as Kawasaki's disease, lupus, Langerhans cell histiocytosis, hemophagocytic lymphohistiocytosis, Castleman's disease, Rosai-Dorfman disease, Kikuchi's disease, Churg-Strauss syndrome, and sarcoidosis may also cause adenopathy.

Table 24.2 Congenital anomalies presenting as head or neck masses

Anomaly	Origin
Lymphovascular malformation (cystic hygroma)	Abnormal lymphatic drainage, abnormal lymphatic formation
Lymphangioma	Abnormal development of arterial, venous and lymphatic channels
Second branchial cleft, cyst sinus, or fistula	Failure of obliteration of cervical sinus
Thyroglossal duct cyst	Failure of thyroglossal tract obliteration
Lingual thyroid	Failure of thyroid descent
Thymic cyst	Thymic remnant

Lymphadenopathy is the initial finding in most malignancies of the head and neck in children [5, 7]. A thorough history and physical exam must be performed. Concerns in the history must include: location and duration of symptoms, associated systemic symptoms, sick contacts, animal exposure, trauma, immunization status, medications, recent travel, dental problems, and diet, including ingestion of unpasteurized animal products and undercooked meat. Often, there are no signs of inflammation, fevers, or upper respiratory symptoms. Malignancy should be suspected for all rapidly growing lymph nodes especially those occurring in the supraclavicular and posterior cervical triangle regions. Factors noted to be predictive of malignancy include nodes greater than 3 cm, supraclavicular or fixed nodes, and abnormal chest x-ray [3].

Fine need aspiration (FNA) is a tool often used in evaluating lymphadenopathy not responsive to antibiotic therapy. The data supporting FNA utilization is found mostly in the adult literature and its use in the pediatric population is limited [8–10]. To perform an FNA an experienced pathologist is needed not only for proper tissue procurement but also for appropriate tissue diagnosis. An 18–22-gauge needle with an attached syringe is inserted into the mass. Once the needle is in the mass, gentle aspiration is performed. The needle is then passed repeatedly through the mass from various angles while applying gentle suction. The tissue is then placed on a slide and stained. Ultrasound or CT guidance may be used for accurate mass localization which is particularly helpful with deep masses of the neck.

Fig. 24.2 Excisional biopsy of a neck mass. Masses and lymph nodes are completely removed without damaging vital structures. Illustration depicts a mass being dissected from the spinal accessory nerve

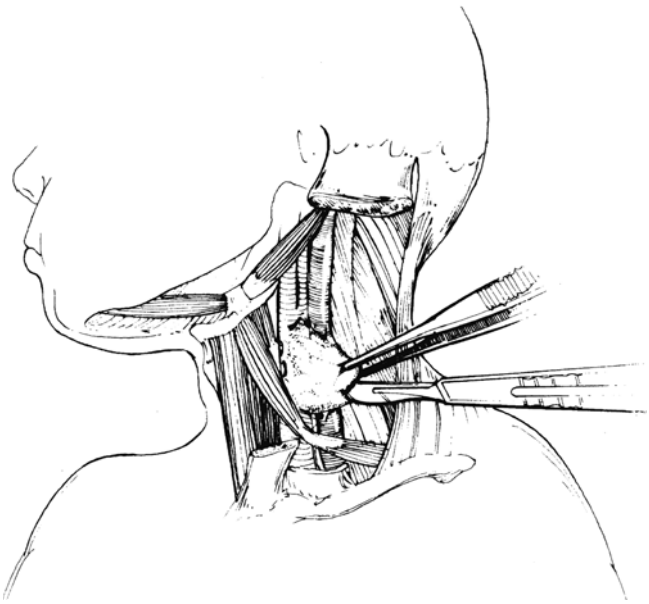

Fig. 24.3 Incisional biopsy of a neck mass. Illustration shows mass encasing the carotid sheath

Cervical lymphadenopathy is usually a result of acute adenitis. In up to two-thirds of these cases, an FNA can reveal the causative agent [11, 12]. The FNA tissue is usually sent for gram stain and cultures including aerobic, anaerobic, fungi, and mycobacteria. An acid-fast stain may also be used if clinically indicated. Serum serologic testing (Bartonella, tuberculosis, EBV, CMV, HIV, syphilis, etc.…) may also be performed as indicated by the history and examination. When malignancy is suspected, a FNA may or may not be sufficient depending on the underlying diagnosis. Open surgical biopsy is indicated in the following cases: refractory systemic symptoms, hard or fixed lesions, supraclavicular nodes, abnormal chest x-ray or CBC, or rapid growth or disease progression without evidence of inflammation.

When deciding which node should be excised, it is generally best to remove the largest accessible node. In order to perform a lymph node excision, a small incision should be made over the suspicious nodule. Careful dissection with meticulous hemostasis should be performed, being careful to avoid capsule rupture (Fig. 24.2). If the tissues are matted or the node is fixed to surrounding vital structures, an incisional biopsy may be needed (Fig. 24.3). Keep in mind, the node may invade surrounding nerves and vessels, increasing the risk of iatrogenic injury. Since exposure may be difficult especially for deeper lymph nodes, a self-retaining retractor may be helpful. Care should also be taken to avoid damage to adjacent vital structures. Once the node is removed, the wound should be irrigated and the platysma reapproximated with interrupted absorbable suture. The skin is usually closed using an absorbable suture in a subcuticular pattern.

Once the lymph node is removed, it should be kept sterile and moist. The pathologist should be contacted to ensure proper stains and cultures are performed given the patient's clinical history. Part of the node should be sent for gram stain and aerobic, anaerobic, and fungal cultures. A fresh frozen sample may also be sent for histology and staining though a definitive diagnosis requires a permanent section. Proper communication with pathology will ensure that adequate tissue has been obtained for all infectious, immunologic, cytogenetic, and molecular studies requested.

Hodgkin's Disease

Hodgkin's disease (HD) or Hodgkin's lymphoma is a malignant lymphoma common in children and in adults over the age of 50. In 1932, Thomas Hodgkin first described seven of his patient who all had grossly abnormal lymph glands [13]. Following the description of the pathognomonic multinuclear giant cells by Sternberg in 1898 and subsequently illustrated by Reed in 1902, the cells have become known as Reed-Sternberg cells (Fig. 24.4) [14, 15].

Hodgkin's disease is the most common childhood lymphoma with an overall incidence of 1.2 per 100,000 in the US [16]. The age at presentation has a bimodal distribution with a peak in adolescents and young adults and another in adults over the age of 50. In developing countries, children especially boys are affected at a younger age but Hodgkin's disease is still uncommon before the age of 5 [17]. In childhood there is a male to female ratio of 0.9 but this varies based on age with a male to female ratio of 5.3 in children less than 5 and a ratio of 0.8 in children 15–19 years of age [16, 17]. Relatives of patients with Hodgkin's disease are at

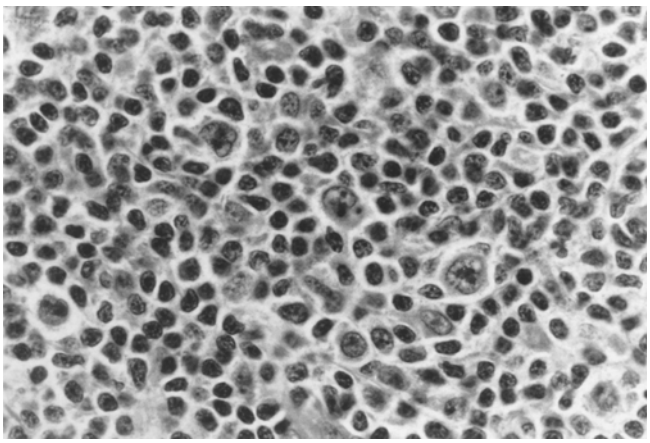

Fig. 24.4 Photomicrograph demonstrating multiple multinucleated Reed-Sternberg cells of Hodgkin's disease

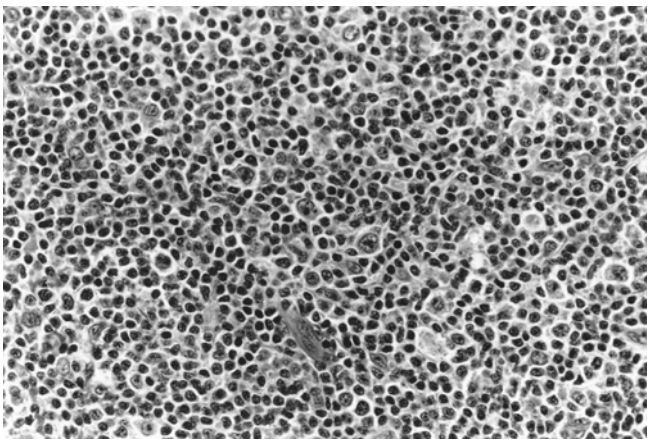

Fig. 24.5 Photomicrograph demonstrating nodular lymphocyte predominant Hodgkin's disease

a slightly increased risk for the disease with familial forms accounting for 4.5 % of all cases. Clusters of Hodgkin's disease have also been reported [17–20]. Hodgkin's disease is more common in patients with impaired immune systems and/or a history of exposure to viruses such as EBV, CMV or herpes virus 6 [21, 22].

Pathology and Genetics

On pathologic examination, Reed-Sternberg cells are pathognomonic for Hodgkin's disease though account for only 1 % of the lymphoid tissue on examination. The lymph nodes also display reactive lymphocytes, macrophages, plasma cells, fibrous stroma and collagen. Two common classification systems are the Rye classification and the WHO classification both of which are based on the relative proportion of various cells on histologic examination. The Rye classification divides Hodgkin's disease into nodular sclerosis (50–60 %), mixed cellularity (20–30 %), lymphocyte predominant (10–15 %), and lymphocyte depletion (10 %) [23]. The WHO classification divides Hodgkin's into classical HD and nodular lymphocyte predominant HD [24]. In nodular lymphocyte predominant HD, most HRS cells express B-cell surface markers such as CD19 and CD20. Nodular lymphocyte predominant HD accounts for only 5–10 % of HD [24].

The most common histologic subtype in children is the nodular sclerosing variety representing ~70–80 % of adolescent HD and 50 % of HD in children under 10 years of age [16]. On histologic examination thick collagen bands divide the lymphoid tissue into nodules that are full of lacunar cells, a Reed-Sternberg variant, surrounded by clear space, lymphocytes, eosinophils, and histiocytes (Fig. 24.5). In the mixed cellularity subtype, there are a larger number of malignant cells with occasional necrosis. This mixed cellularity subtype is more common in younger children (30–35 %) and less common in adolescents (10 %). The lymphocyte predominant subtype, which is associated with early diagnosis and good prognosis, contains mature lymphocytes, benign histiocytes, and an occasional Reed Sternberg cell. The lymphocyte depletion variant as the name implies has few lymphocytes and increased Reed-Sternberg cells. Although this variant is rare in children, it is usually diagnosed at an advanced stage and has a poor prognosis.

Clinical Presentation

More than 90 % of Hodgkin's patients present with painless lymphadenopathy, and greater than 80 % of these cases involve the cervical and supraclavicular lymph nodes. The nodes are firm, rubbery and can be single or multiple. On physical examination, hepatic or splenic enlargement may be noted suggesting metastatic disease. Patients with mediastinal involvement may present with cough, stridor, dyspnea, dysphagia, or superior vena cava (SVC) syndrome due to compression of the airway, esophagus, or blood vessels. Children with mediastinal HD may occasionally present with hypertrophic osteoarthropathy, characterized by excessive skin and bone on the distal parts of their extremities [25, 26]. Patients with retropharyngeal lymphoma may present with an acute airway obstruction (Fig. 24.6). If a transoral needle biopsy is attempted, rapid tumor enlargement may occur leading to airway obstruction. Up to one-third of all patients present with systemic symptoms of fever, night sweats, weight loss, fatigue and pruritis. The pattern of fever is variable, and weeks of high fevers can be separated by afebrile periods. Only 20 % of children have the fevers and night sweats common to many adult patients with HD [27–29]. Patients may present with various immunologic disorders such as treatment-resistant idiopathic thrombocytopenic purpura (ITP), Coombs'-positive hemolytic anemia, or rarely

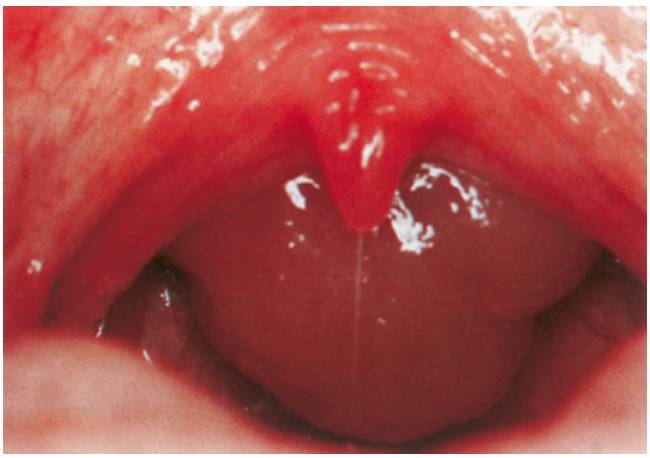

Fig. 24.6 Lymphoma of the nasopharynx

autoimmune neutropenia [28, 30]. In Hodgkin's patients, ITP may occur at any time including at diagnosis, during treatment, and even after splenectomy [31, 32].

Diagnostic Evaluation

The diagnosis of Hodgkin's disease can be made only after histologic examination of an affected lymph node. This node must show classic HRS cells or their variants for a diagnosis of HD, and further subclassification requires information about the architecture and proportions of various cells including HRS cells, lymphocytes, eosinophils, neutrophils, and collagen [33]. In order to obtain enough tissue with proper preservation of lymph node architecture, an open biopsy is often performed. Successful diagnosis for lymphomas may be done using core needle biopsies or even fine needle aspiration with flow cytometry in experienced centers [34, 35]. Excisional biopsy is usually performed. If the node cannot be removed without damage to surrounding vital structures, incisional biopsy is appropriate. If Reed-Sternberg cells are seen, a diagnosis may be made on frozen sections though more tissue should be sent for routine staining, immunophenotyping, and cytogenetic analysis.

Prior to lymph node excision, a patient must be assessed for mediastinal masses. Intubation of a patient with a large anterior mediastinal mass may result in acute respiratory failure due to compression of the mass on the trachea after voluntary respirations have ceased. It is essential that a CXR be obtain prior to surgical intervention. If the CXR is suspicious, a chest CT should be performed. If significant airway compression is noted on exam or radiography, other methods of diagnose such as flow cytometry, bone marrow biopsy, and/or thoracentesis should be employed. If a diagnosis still cannot be obtained, consideration of empiric treatment verse lymph node biopsy while sitting upright under local anesthesia may be considered [36].

Laboratory studies include a complete blood cell count with white blood cell differential, erythrocyte sedimentation rate, serum alkaline phosphatase, renal and liver function tests, lactate dehydrogenase, urinalysis, and baseline thyroid function tests. Hodgkin's lymphoma spreads initially to contiguous lymph nodes and later can involve liver, lung, bone marrow and the central nervous system so further workup should focus on these areas. Imaging studies include anteroposterior (AP) and lateral chest radiographs, computed tomography (CT) scans of the high neck, chest, abdomen and pelvis, CT of the primary site and PET scan. A chest x-ray provides information on mediastinal involvement which may be present in up to 75 % of children. Chest CT provides information about pulmonary as well as mediastinal involvement. In addition to pulmonary metastasis, HD can affect the chest wall, pleura and pericardium [37, 38]. As an alternative or adjunct to CT scanning, MRI may be used [39]. PET is especially useful to evaluate response to therapy since it can differentiate fibrosis from active disease and can be helpful in assessing response to treatment [40, 41]. Both a bone marrow aspirate and biopsy are necessary for advanced stage disease and in all stages with systemic symptoms though its utility in early Hodgkin's is unclear.

Staging

Both children and adults with Hodgkin's disease are staged based on the Ann Arbor Classification system (Table 24.3) [42]. This classification system incorporates numbers of lymph nodes involved, location of affected lymph nodes, extranodal involvement, and systemic symptoms [42, 43]. Subclassification A indicates asymptomatic disease while subclassification B indicates symptoms including fever, night sweats and unexplained weight loss of at least 10 % of body weight over a 6-month period. Improved imaging and use of systemic chemotherapy in all HD patients has made staging laparotomy unnecessary. Laparotomy/ laparoscopy may be helpful in the following situations: intraabdominal lymph node between 1 and 3 cm, focal splenic abnormalities, focal hepatic abnormalities, and areas of abdominal uptake on gallium scan not otherwise explainable. Focal hepatic abnormalities may be best assessed by CT-guided needle biopsy. When staging laparotomy is/was performed, it involved splenectomy, liver biopsy, and sampling of splenic hilar, celiac, porta hepatis, mesenteric, iliac and para-aortic lymph nodes though these criteria were not universal.

Management

Hodgkin's disease should be managed with a multidisciplinary approach at a pediatric oncology center. Hodgkin's is

Table 24.3 Ann Arbor staging classification for Hodgkin's disease [42]

Stage	Definition
I	Involvement of single lymph node region (I) or of a single extralymphatic organ or site (I_E)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (II_E)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also involve the spleen (III_s), an extralymphatic organ or site (III_E) or both (IIISE)
IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node involvement
A	No systemic symptoms
B	Presence of systemic symptoms prior to admission including unexplained fever, night sweats, or weight loss greater than 10 % of body weight in 6 months prior to diagnosis

sensitive to both chemotherapy and radiation. Previously HD was treated with high-dose radiation therapy and later stage disease was treated with MAPP (mechlorethamine, vincristine, procarbazine, prednisone) and radiation [44]. Concerns existed over the long-term effects of this high dose radiation and chemotherapy on growth and development as well as the development of secondary malignancies.

Current recommendations for the treatment of HD include chemotherapy for all stages. Early stage Hodgkin's disease (clinical stage I and IIA) is well controlled by chemotherapy followed by field radiation. Multiple chemotherapeutic regimes have been used in early stage HD with good results. Cycles of VAMP (vinblastine, doxorubicin, methotrexate, prednisone) followed by field ration between 15 and 25.5 Gy showed a 99 % and 96 % disease free 5-year and 10 year survival, respectively [45]. Treatment with OPPA (vincristine, procarbazine, prednisone, doxorubicin in males) and OEPA (vincristine, etoposide, prednisone, doxorubicin) followed by field radiation of 25–35 Gy has also been used with a 99 and 94 % 5-year disease free survival respectively [46].

Hodgkin's patients considered to have advanced disease include: patients with stage IIIa, IIIb, or IV; patients with B-symptoms; or patients with a mediastinal mass greater than one-third the diameter of the chest. Treatment for these patients includes various chemotherapy combinations and various levels of field radiation. Current treatment regimes may be found on the National Cancer Institute (NCI) website and the Children's Oncology Group (COG) website. Traditionally these patients were treated with MOPP and ABVD in addition to field radiation of 20–35 Gy with a 5-year disease free survival of 87–93 % [47]. Radiation dosing was based on response to chemotherapy. With more recent treatment regimes, patient may have a 5-year survival of 95–96 % [46, 48]. This treatment may be tailored based on response and gender [49]. Patients with refractory or relapsing disease of treated with a variety of second line chemotherapy protocols with or without subsequent autologous cell transplantation [50, 51]. Other chemotherapeutic combinations are under investigation with the goal of decreasing drug toxicities and secondary malignancies.

The initial complete remission response rate for all stages of Hodgkin's disease is over 90 %. For stage I or IIA Hodgkin's disease, 5 year disease-free survival for children is approximately 93–99 % [46, 52]. For patients with advance stage Hodgkin's disease the 5 year survival is 87–97 % with a 5 year event free survival of 88 % [46, 47]. Factors that predict a poorer prognosis include male gender, disease stage IIB, IIIB, or IV, bulky mediastinal disease, WBC >13,500/μL, and hemoglobin <11.0 g/dl. Using a point system, giving 1 point for each of the above-mentioned criteria, 5-year disease free survival is 94, 85, 71, and 49 % for 0–1, 2, 3, and 4–5 points respectively [53].

After remission, patients need lifelong close follow-up for recurrent disease and long-term effects of chemotherapy and radiation. When relapse does occur, it is usually within the first 3 years and in associated with a poor prognosis [54]. Treatment for recurrent Hodgkin's disease includes another combination chemotherapy and/or autologous bone marrow or stem cell transplantation. Long-term complications of the radiation and chemotherapeutic interventions include impaired growth, thyroid dysfunction, gonadal dysfunction, cardiopulmonary toxicity, and strokes. Up to 7.6 % of HD survivors will have a secondary malignancy at 20 years. These secondary malignancies most often include thyroid cancer, breast cancer, and sarcomas [55, 56].

Non-Hodgkin's Lymphoma

Childhood non-Hodgkin's lymphoma (NHL) accounts for 10 % of all pediatric malignancies and about 25 % of all head and neck malignancies. The head and neck is the primary site for NHL 10–15 % of the time, and is most commonly located in the lateral cervical lymphatic chain. Up to 30 % of primary head and neck NHL are extranodal and include lymphoid tissue in Waldeyer's ring, the orbit, mandible, sinuses, salivary gland, and thyroid gland. NHL accounts for approximately 750–800 new cases a year in the United States. Burkitt's and Burkitt-like tumors are most common in 5–14 year olds and diffuse large cell lymphomas are most com-

mon in 15–19 year olds. It is uncommon in children under the age of 3. NHL is twice as common in whites and 2–3 times more common in boys [57].

There is a form of endemic Burkitt's lymphoma in Equatorial African which is distinctive from the sporadic Burkitt's lymphoma noted in the rest of the world. In Africa, endemic Burkitt's lymphoma has an annual incidence of 10 per 100,000 and is associated with EBV in 95 % of cases. It most commonly present as a mass in the jaw, abdomen, orbit, central nervous system, and paranasal sinuses [58]. Sporadic Burkitt's has an annual incidence of 2 per 100,000 children, with only a 15 % association with EBV and more commonly presents in the abdomen, bone marrow, and nasopharynx. In addition to EBV, other immunodeficiency syndromes such as ataxia-telangiectasia, Wiskott-Aldrich syndrome, and X-linked lymphoproliferative syndrome are associated with NHL [59]. There is also an increased incidence of NHL in children receiving immunosuppressive therapy and those with AIDS. Up to 1.6 % of children with HIV will develop lymphoma, with Burkitt's or large cell being the most common [60]. HIV and other viral pathogens, immunosuppressive states, environmental toxins, and commercial products such as hair dyes have been associated with Burkitt's lymphoma.

Pathology and Genetics

Childhood NHL consists of three major subtypes: mature B-cell NHL (Burkitt, diffuse large B-cell lymphoma), lymphoblastic lymphoma, and anaplastic large cell lymphoma. There is also lymphoproliferative disease associated with immunodeficiency in children and other rare NHL in children including pediatric follicular lymphoma, peripheral T-cell lymphoma, and others more common in adults. The World Health Organization has developed a classification system that divides common pediatric lymphomas based on their phenotype and differentiation [61]. On histologic examination, lymphoma cells replace normal lymph node tissue. In the head and neck region, the most common lymphoma is B cell lymphoma specifically small-cell noncleaved lymphoma. Histologically, the cells are undifferentiated, small, round lymphoid cells with detectable surface immunoglobulin. This uniform shape and size gives a 'starry-sky' histology classic for Burkitt's lymphoma as shown in Fig. 24.7.

Both B and T cell lymphomas are associated the known chromosomal translocations affecting DNA binding transcription factors [62]. Up to 85 % of Burkitt's patients have a t(8;14)(q24;q11) translocation resulting in transfer of the c-myc oncogene from chromosome 8 to the site of the immunoglobulin heavy chain locus on chromosome 14 [63]. This translocation causes activation of c-myc and increased proliferation of lymphoma cells. The location of the breakpoint on chromosome 8 is variable suggesting different molecular subtypes of Burkitt's lymphoma based on different mechanism of c-myc activation [59, 64–66]. In North American Burkitt's lymphoma, the breakpoint is within the c-myc gene in more than 50 % of tumors [59, 67, 68]. Less commonly t(8;22) and t(2;8) results in translocation of lambda and kappa immunologic light chain genes, respectively, to a region distal to the c-myc gene on chromosome 8 [69, 70]. Chromosomal abnormalities have also been noted in patients with T cell lymphoblastic lymphoma including deletions of TAL1, TCR, HOX11, and RHOMB genes [71, 72].

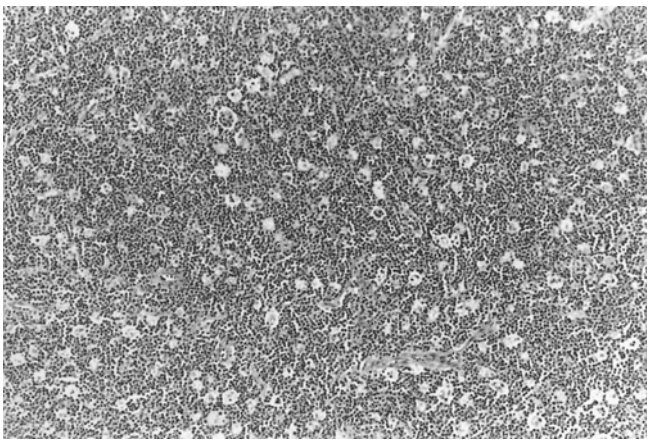

Fig. 24.7 Photomicrograph demonstrating Burkitt's lymphoma with classic 'starry-sky' histology

Clinical Presentation

Initially the NHL mass is painless but as rapid growth or compression of surrounding structures occurs, symptoms can develop. Symptoms are based on location of the primary tumor. Cervical NHL may produce neck pain, dysphagia, or dyspnea as tracheal or esophageal compression occurs. Rapidly enlarging tumors may produce mediastinal compression and associated respiratory distress or superior vena caval obstruction. Burkitt's lymphoma in Equatorial Africa most frequently presents with jaw involvement, especially in younger children. Jaw involvement in less common (~15 %) in sporadic Burkitt's lymphoma is not age-related [73, 74]. Children often have extranodal disease at the time of presentation which includes abdominal involvement (31 %), mediastinal involvement (26 %), or head and neck involvement (29 %). Central nervous system (CNS) and bone marrow involvement may also occur [63, 70]. Systemic symptoms are not as common in NHL as in Hodgkin's disease but are a poor prognostic sign.

Diagnostic Evaluation

As with Hodgkin's lymphoma, an open biopsy should be performed to establish the diagnosis. An open excisional biopsy, or in the case of matted nodes, an incision biopsy, is usually needed to provide an adequate sample for histology, cytogenetics, flow cytometry, and molecular pathology. As with Hodgkin's disease, fine needle aspiration does not provide an adequate sample, and core biopsy may be done at centers with expertise in this area. Recommended laboratory studies include a complete blood cell count with white blood cell differential, erythrocyte sedimentation rate, serum alkaline phosphatase, renal and liver function tests, lactate dehydrogenase, urinalysis, uric acid levels, phosphate levels, and baseline thyroid function tests. Imaging studies should include anteroposterior (AP) and lateral chest radiographs, CT scans of the high neck, chest, abdomen and pelvis, bone scan, and CT/MRI of the primary site. A chest x-ray provides information on mediastinal involvement. Chest CT also provides information about pulmonary as well as mediastinal involvement. PET scan are being used with increasing frequency especially in adults though its use in pediatric is still growing [75, 76]. Both a bone marrow aspirate and biopsy are necessary for staging of the disease. A lumbar puncture is also needed to evaluate for CNS involvement.

Prognostic factors include age, site of disease, chromosomal abnormalities, tumor burden, and response to therapy. Adolescents and infants tend to have a worse outcome compared to other children [77, 78]. Patients with low-stage disease tend to do better while those with CNS involvement and more advanced disease tend to have worst outcomes [79–81]. Abnormalities of 7q or deletion of 13q have worse outcomes [82, 83] LDH as a surrogate for tumor burden is associated with worse outcomes. As expected poor responders have a worse response with a 30 % event free survival [84].

Staging

Classification and The St. Jude's Staging system is used to characterize NHL (Table 24.4) [85]. Tumor burden as measured by disease stage, serum LDH, and serum IL2 have all been shown to predict outcome [86–88]. Each category of NHL has typical immuno-phenotype, presentation, chromosomal translocation, and genes affected (Table 24.5).

Treatment

Treatment protocols for NHL are based on histologic subtype and disease stage. Chemotherapy remains the primary treatment for all histologic variants and stages of NHL. Radiation therapy is reserved for cases of relapse, CNS involvement, and emergency situations such as airway compromise due to mediastinal involvement. In general, surgery is used for diagnosis and perhaps in an emergent setting such as airway compromise. In the absence of surgical emergencies, there is no role for debulking procedures.

Due to rapid turnover of lymphoblasts, patients often present with hyperuricemia, hyperphosphatemia, and renal dysfunction. As chemotherapy is begun, tumor lysis syndrome may occur which is characterized by a rapid lysis of tumor cells resulting in increase uric acid, phosphate, potassium, and purines in the blood and thus renal tubules that may result in increasing renal dysfunction. Patients must be aggressively hydrated before and during chemotherapy. Alkalization of the urine and allopurinol may be helpful in the treatment of hyperuricemia. In some cases, dialysis may be required to manage the renal failure associated with severe tumor lysis syndrome.

For limited disease (stage 1 and 2), treatment consists CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) or COMP (cyclophosphamide, vincristine, methotrexate, prednisone) which both result in a 5 year survival rate of 85–95 % [89–96]. For advanced disease with high tumor burden, high dose regimens and the addition chemotherapy has improved survival rates from 20 % to around 80 % in recent years [89, 96–98]. High stage B-cell NHL with a multi-drug regime have 80–90 % long term survival [80, 84]. For patients with CNS involvement, intrathecal chemotherapy is added to the traditional chemotherapeutic regime.

For Burkitt's lymphoma, patients receive 2–6 months of with COMP and high dose methotrexate and/or cytarabine or

Table 24.4 St. Jude system for non-Hodgkin's lymphoma [85]

Stage	Definition
I	Single nodal or extranodal tumor site, excluding mediastinum or abdomen
II	Single extranodal tumor with regional lymph node involvement; two or more nodal areas on the same side of diaphragm; two single extranodal tumors with or without regional lymph node involvement on same side of the diaphragm;
	Primary gastrointestinal tract tumor with or without associated mesenteric node involvement grossly resected
III	On both sides of the diaphragm: two single extranodal tumors; two or more nodal areas All primary intrathoracic tumors
	All extensive, unresectable primary intra-abdominal disease
	All primary paraspinal or epidural tumors
IV	Any of the above with initial CNS and/or bone marrow involvement

Table 24.5 Major histopathological categories of non-Hodgkin lymphoma in children and adolescents [209]

Category (WHO classification/updated REAL)	Category (working formulation)	Immuno-phenotype	Clinical presentation	Chromosome translocation	Genes affected
Burkitt and Burkitt-like lymphomas	ML small noncleaved cell	Mature B cell	Intra-abdominal (sporadic), head and neck (non-jaw, sporadic), jaw (endemic), bone marrow, CNS	t(8;14)(q24;q32), t(2;8)(p11;q24), t(8;22)(q24;q11)	C-MYC, IGH, IGK, IGL
Diffuse large B-cell lymphoma	ML large cell	Mature B cell; maybe CD30+	Nodal, abdominal, bone, primary CNS (when associated with immunodeficiency), mediastinal	No consistent cytogenetic abnormality identified	
Lymphoblastic lymphoma, precursor T-cell leukemia, or precursor B-cell lymphoma	Lymphoblastic convoluted and non-convoluted	Pre-T cell	Mediastinal, bone marrow	MTS1/p16ink4a; Deletion TAL1 t(1;14)(p34;q11), t(11;14)(p13;q11)	TAL1, TCRAO, RHOMB1, HOX11
		Pre-B cell	Skin, bone, mediastinal		
Anaplastic large cell lymphoma, systemic	ML immunoblastic or ML large	CD30+ (Ki-1+)	Variable, but systemic symptoms often prominent	t(2;5)(p23;q35); less common variant translocations involving ALK	ALK, NPM
		T cell or null cell			
Anaplastic large cell lymphoma, cutaneous		CD30+ (Ki-usually)	Skin only; single or multiple lesions	Lacks t(2;5)	
		T cell			

Adapted from Percy et al. [16]
Permission pending from NCI
CNS central nervous system, *ML* malignant lymphoma, *REAL* Revised European-American Lymphoma, *WHO* World Health Organization

Table 24.6 Standard treatment options for low-stage non-Hodgkin lymphoma [209]

Disease	Treatment options
Burkitt lymphoma or diffuse large B-cell lymphoma (DLBCL) (completely resected)	GER-GPOH-NHL-BFM-95 (R1): two cycles of chemotherapy
	COG-C5961 (FAB/LMB-96) (Group A): two cycles of chemotherapy
Burkitt lymphoma or DLBCL (nonresected stage I/II)	GER-GPOH-NHL-BFM-95 (R2): prephase + four cycles of chemotherapy (4-h methotrexate infusion)
	COG-C5961 (FAB/LMB-96) (Group B): prephase + four cycles of chemotherapy (reduced-intensity arm)
	POG-8314/POG-8719: three cycles of chemotherapy (no radiation or maintenance therapy)
Lymphoblastic lymphoma	GER-GPOH-NHL-BFM-95: induction, consolidation, intensification, and maintenance therapy (2 years of total therapy); ALL-type induction and consolidation, high-dose methotrexate courses × 4, and ALL-type maintenance therapy (2 years of total therapy)
Anaplastic large cell lymphoma	POG-8314/POG-8719: three cycles of chemotherapy (no radiation or maintenance therapy)
	GER-GPOH-NHL-BFM-90: prephase + three cycles of chemotherapy (only for completely resected disease).
	FRE-IGR-ALCL99: prephase + six cycles of chemotherapy (for disease not completely resected)

Permission pending from NCI

by the addition of etoposide and ifosfamide [89, 90, 94]. Large cell lymphoma is treated with a CHOP combination resulting in a 50–70 % event free survival rate 3 years [99–102]. Research is underway examining the benefits of methotrexate, cytarabine, ifosfamide, and carboplatin.

Chemotherapy options based on specific diagnosis (including Burkitt's lymphoma, diffuse large B cell lymphoma, lymphoblastic lymphoma, anaplastic large cell lymphoma) are outline in Table 24.6. Further details on current treatment regimes may be found on the National Cancer Institute (NCI) website and the Children's Oncology Group (COG) website.

Overall, treatment for lymphoblastic lymphoma has improved 5 year survival to 90 % [79, 103]. With current treatment regimes, high-stage anaplastic large cell lymphoma has disease free survival rates of 60–75 % [104, 105] Cure rates for limited disease are greater than 90 % and range from 60 to 90 % for advanced disease [52, 79, 96, 106]. Current therapy for recurrent NHL includes chemotherapy and possible bone marrow transplantation but overall prognosis is poor [64, 67, 107, 108].

Thyroid Tumors

Thyroid cancer represents about 3 % of all childhood malignancies and 7 % of cancers arising in the head and neck with an incidence of 0.54 per 100,000. Due to improved detection and stable mortality, the prevalence of thyroid cancer has increased [109–111]. The peak incidence of thyroid cancer in children occurs between 10 and 18 years of age, and females outnumber males 2:1 over the age of 10. In children under the age of 10, males tend to outnumber females. In younger children (age 0–4), medullary thyroid carcinoma is more common. As age increase, incidence of papillary histology increases.

The development of thyroid cancer is associated with radiation exposure. With decreasing use of radiation for benign disease, the incidence of thyroid cancer has decreased. Historically, up to 80 % of all new cases of thyroid cancer are related previous radiation to the neck for a variety of benign disorders including enlarged thymus, hypertrophied tonsils and adenoids, hemangiomas, nevi, eczema and cervical adenitis [112]. Diagnostic radiation exposure has been associated with increased incidence of cancer. Prenatal exposure to diagnostic radiation increases risk of childhood cancer by 1.4–2.1 fold [113]. The use of computed tomography (CT) scan is estimated to increase risk of cancer by as much as one fatal cancer for each 1000 CT scans [114]. For head and neck CT scans in children, the estimated increased risk of thyroid cancer is 65 per million patients [115]. Due to this increased risk of cancer associated with diagnostic imaging, there is increased attention to decreasing images if possible or at least decreasing intensity of radiation dose or area of imaging when possible.

Treatment for previous childhood malignancy is associated with an increased incidence of thyroid carcinoma. Most commonly these children had Hodgkin's lymphoma, whose treatment leads to the development of thyroid nodules and thyroid cancer [116, 117]. Up to 50 % of children receiving irradiation and chemotherapy for Hodgkin's disease, leukemia and other head and neck malignancies develop elevated thyroid stimulating hormone (TSH) levels within 1 year of treatment [117, 118]. Not only radiation but also alkylating agents predispose to thyroid cancer. The latency between previous treatment and development of thyroid cancer is up to 25–30 years which emphasizes the importance of continued followed in these patients [119–121]. Increased radiation dose, female gender, and age (12–16 years) were associated with increased incidence of secondary malignancy [122].

The association of thyroid cancer and radiation exposure was again demonstrated in the Republic of Belarus after the 1986 Chernobyl nuclear power plant catastrophe [123, 124]. Within 4 years after the accident, a 62-fold increase in thyroid tumors was noted. After a decade, there was a 10 fold increase in aggressive papillary carcinomas in these children [125]. These children were noted to have aggressive papillary carcinomas in younger children with an equal prevalence in males and females [126]. Factors for the development of thyroid cancer following radiation exposure include higher radiation doses, young age at radiation initiation and female sex.

Pathology and Genetics

The histologic subtypes of thyroid cancer include papillary or mixed (70–80 %), follicular (20 %) medullary (5–10 %) and rarely, anaplastic [119, 121, 127, 128]. Histologically, papillary carcinoma will consist of papillae of epithelial cells arranged often with lymphocytic infiltrates and psammoma bodies (Fig. 24.8). In follicular carcinoma, malignant adenomatous cell form follicles with nuclear abnormalities, capsular invasion or vascular invasion. Any tumor with papillary components is considered a papillary carcinoma. If follicular characteristics are also present, it is considered a papillary tumor with follicular architecture (Fig. 24.9). Approximately 5 % of thyroid carcinomas are medullary thyroid carcinoma (MTC) that arises from the parafollicular C cells, derived from neural crest cells (Fig. 24.10). Histologically, these tumors have granular cytoplasm with islets of regular, undifferentiated cells.

The RET (REarranged during Transfection) gene plays an important role in the development of thyroid cancer. The RET proto-oncogene is a receptor tyrosine kinase molecule located on chromosome ten that signals via the MAPK pathway. RET gene rearrangement is associated with papillary thyroid cancers. These rearrangements place RET adjacent to various ubiquitously expressed genes. The fusion genes are termed RET/PTC, and they exhibit increased expression of tyrosine kinase with histologic and prognostic significance. The most common is RET/PTC1 and RET/PTC3. PTC 1 is associated with papillary carcinoma and is more

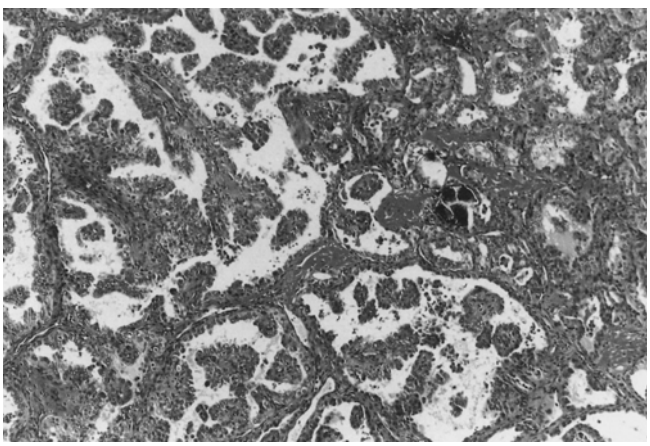

Fig. 24.8 Photomicrograph demonstrating papillary thyroid carcinoma with papillary architecture

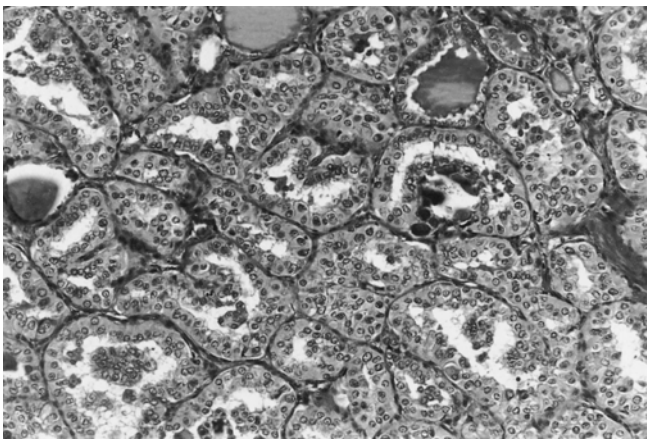

Fig. 24.9 Photomicrograph demonstrating follicular variant of papillary thyroid carcinoma

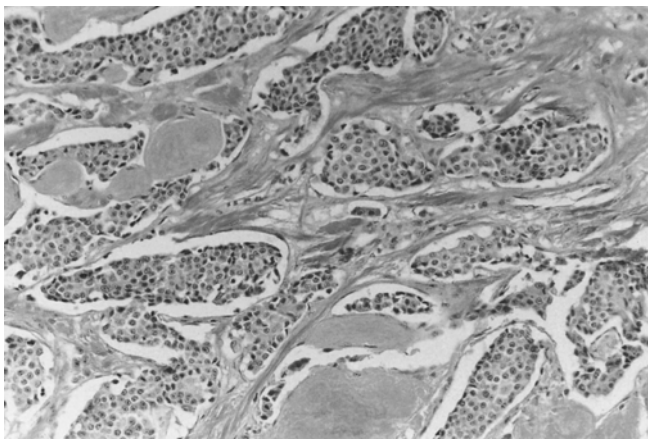

Fig. 24.10 Photomicrograph demonstrating medullary thyroid carcinoma with amyloid stroma and epithelial cytology

differentiated and slow growing while PTC2 is associated with more aggressive less differentiated follicular carcinoma [129]. RET/PTC rearrangements are found in 40–70 % of pediatric thyroid cancer patients [130].

This RET gene rearrangement occur in 5–80 % of radiation induced thyroid tumors [129–133]. Some studies suggest that particular RET fusion gene combination are correlated with particular histologic subtypes. For example, one particular inversion of chromosome 10, PTC1, is more often associated with papillary carcinoma that tends to be more slow growing with clearer differentiation while PTC3 is more often associated with follicular carcinoma which tends to grow more quickly, more aggressively, and with less differentiation [129]. Other genetic alterations include increased copy numbers and deletions of various chromosomes, and gene alterations including CAMK2N1, AK1, DHRS3, and PDE9A [126]. Recent studies are investigating the specific gene expression signature of post-radiation induced thyroid tumors [134].

Medullary thyroid carcinoma (MTC) may occur sporadically, in patients having multiple endocrine neoplasia (MEN) type 2A or 2B, or in the familial medullary thyroid carcinoma (FMTC) syndrome. As in papillary thyroid cancer, the RET proto-oncogene also plays an important role in the development of medullary thyroid carcinoma as well as MEN syndromes in general [135–137]. These RET mutations affect the development of neural crest derived tissues. Various RET mutation may be found in as many as s 40 % of sporadic non-familial medullary thyroid carcinomas. Medullary thyroid carcinoma is usually the first tumor to develop in MEN 2 patients and is often the cause of death in these patients. Most patients with MEN 2B have a germline mutation of methionine to threonine at codon 918 (M918T). Mutation of alanine to phenylalanine at codon 883 (A883F) has also recently been identified and is associated with a more indolent form of medullary thyroid carcinoma [138].

Clinical Presentation

Patients usually presents with a thyroid mass, an enlarged cervical lymph node, or with both of these findings. Physical exam findings concerning for malignancy include firm nodule and nodule that are fixed to surrounding structures. Palpable cervical adenopathy is present in up to two-thirds of cases and adenopathy may be the only indication of thyroid cancer even in the absences of a thyroid nodule [128]. Other symptoms may include dysphagia, dyspnea or dysphonia if tracheal or esophageal compression has occurred [120, 127, 139, 140]. Hoarseness indicates compression or invasion of the recurrent laryngeal nerve.

The lung is the most common site for metastases, aside from lymph nodes, with an incidence of about 6 % at diagnosis [141, 142]. This is often accompanied by cervical lymph node metastases. Up to 50 % of patients with papillary tumors have metastases to local cervical or mediastinal lymph nodes at the time of diagnosis [143]. Follicular tumors have less local lymph node disease but increased bone metastases. Cervical adenopathy and/or distant metastases are usually the first sign of medullary thyroid carcinoma.

Patients with MEN often have a delayed diagnosis due to vague initial symptoms. Studies have found that during the first year of life, less than 20 % of carriers were found to have typical MEN 2B phenotypes. Characteristics that were described included constipation and inability to cry tears. The median age of diagnosis of MTC was 13–16 years in the M918T carriers [144, 145]. One-third of patients had MEN diagnosis before surgery while two-thirds were diagnosed postoperatively [145]. Once diagnosis was made, patients presented with oral symptoms (96 %), ocular abnormalities (91 %), GI symptoms (71 %), musculoskeletal anomalies (75 %), and pheochromocytomas (28 %) [144].

With delay in diagnosis, these patient tended to present with more advanced tumor, nodes, and metastases with higher levels of preoperative calcitonin levels. Early detection and family screening are needed to improve treatment and survival.

Diagnostic Evaluation

Initial evaluation of a thyroid mass should begin with thyroid function tests, which are normal in the majority of cases. Laboratory values include thyroid-stimulating hormone (TSH), T3, T4, urine calcium, and calcitonin. Imaging of a suspicious nodule usually starts with an ultrasound study. An ultrasound can determine lesion characteristics, identify abnormal lymph nodes, and serve as a guide for surgery [146].

The pathologic diagnosis can either be established using thin-needle aspiration cytology or by frozen-section though there is some controversy over the accuracy of frozen-sections in evaluating follicular lesions. The use of FNA in the adult population is well established and has decreased the incidence of thyroidectomy for benign conditions and has increased the number of surgical patients with carcinoma [146, 147]. The sensitivity and specificity of FNA in prediction malignancy is 88 % and 84 % respectively [148]. Limitations of FNA include a false negative rate from 1 to 6 %, availability of an experienced cytopathologist, and an inability to differentiate benign from malignant follicular lesions.

Since the pattern of thyroid disease in adolescents is similar to that in adults, FNA is an acceptable way to evaluate thyroid nodules in this population and has been demonstrated useful in older children [149–151]. In children younger than 13 years of age, aspiration is more difficult to perform and the pattern of benign disease is different than in adults. The natural history of these lesions and the safety of a non-operative approach is unknown. Therefore, FNA should probably not be used in young children, and all children younger than 13 years of age should undergo surgical excision. A FNA may reveal cancer, a benign lesion, or a lesion suspicious for cancer. As with adults, benign nodules may be followed with serial physical and ultrasound examinations; resection is indicated if the nodule increases in size. Surgical resection is indicated for all malignant or suspicious nodules.

Staging

Thyroid cancer staging is based on the American Joint Committee on Cancer (AJCC) staging by TNM classification (Table 24.7 [152]).

Management

Since there are no prospective clinical trials compare surgical management of thyroid cancer in children, there is some controversy over the best surgical management of these patients. If the cytology of the thyroid mass is benign, observation with serial US every 6–18 months is recommended. If the lesion is stable, one may observe with US. If the lesion enlarges over time, repeat FNA is warranted. If a benign lesion is causing compressive symptoms or cosmetic deformation, excision should be considered. If a benign lesion continues to grow after repeated FNA biopsies, resection may be considered [153].

If repeat FNA of a lesion in an adolescent reveals non-diagnostic aspirates, the surgeon needs to weight the risks and benefits of close observation verse surgical resection. If the FNA is suspicious for papillary thyroid cancer, surgical excision is recommended. If there is a solitary indeterminate nodule present, lobectomy is recommended. If the patient presents with an indeterminate nodule >4 cm, atypia, family history, radiation history, or bilateral disease, a thyroidectomy is recommended. Lobectomy may be considered sufficient if the lesion is less than 1 cm, low risk pathology, unifocal, intrathyroidal papillary carcinoma, no family history, no radiation history, and normal nodes [153].

For differentiated thyroid carcinoma the most commonly recommended surgical options include either total or subtotal thyroidectomy. There is no difference in mortality or morbidity in patients having a total or subtotal thyroidectomy. The mortality rates ranges from 0 to 17 % up to 28 years after treatment [119, 121, 128, 140]. Aggressive resection including total thyroidectomy, with lymph node dissection if the regional nodes are involved, has shown to increase local control of the tumor [119, 121, 128, 154]. Prophylactic central compartment dissection is recommended for papillary thyroid cancer that is T3 or T4. Therapeutic central lymph node dissection is recommended if positive nodes in that compartment. Lateral neck dissection is recommended if clinically positive or biopsy positive nodes are noted. Radioiodine ablative therapy is also most effective after total thyroidectomy since there is less thyroid tissue to absorb radionuclide. Also, if total thyroidectomy is performed, serum thyroglobulin levels may be used to monitor for tumor recurrence.

However, differentiated thyroid carcinoma in children is a relatively indolent disease and survival is apparently not related to the extent of gland removal so total thyroidectomy is not necessarily required [119–121, 128, 140]. With total thyroidectomy, there is an increased incidence of major surgical complications, including injury to the recurrent laryngeal nerve 0–24 % and hypoparathyroidism [121, 128, 141, 155]. Currently, a consensus is immerging that aggressive resection for differentiated thyroid cancer in children is the

Table 24.7 The American Joint Committee on Cancer (AJCC) has designated staging by TNM classification to define thyroid cancer [153].

Primary tumor (T)[a]	
TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
T1	Tumor ≤2 cm in greatest dimension limited to the thyroid.
T1a	Tumor ≤1 cm, limited to the thyroid.
T1b	Tumor >1 cm but ≤2 cm in greatest dimension, limited to the thyroid.
T2	Tumor >2 cm but ≤4 cm in greatest dimension, limited to the thyroid.
T3	Tumor >4 cm in greatest dimension limited to the thyroid or any tumor with minimal extrathyroid extension (e.g., extension to sternothyroid muscle or perithyroid soft tissues).
T4a	Moderately advanced disease.
	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve.
T4b	Very advanced disease.
	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels.
T4a[b]	Intrathyroidal anaplastic carcinoma.
T4b[b]	Anaplastic carcinoma with gross extrathyroid extension.
Regional lymph nodes (N)[c]	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Regional lymph node metastasis.
N1a	Metastases to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes).
N1b	Metastases to unilateral, bilateral, or contralateral cervical (Levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (Level VII).
Distant metastasis (M)	
M0	No distant metastasis.
M1	Distant metastasis.

Anatomic stage/Prognostic groups[d]			
Stage	T	N	M
Papillary or follicular (*differentiated*)			
Younger than 45 years			
I	Any T	Any N	M0
II	Any T	Any N	M1
45 years and older			
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1
Medullary carcinoma (*all age groups*)			
I	T1	N0	M0
II	T2	N0	M0
	T3	N0	M0

(continued)

Table 24.7 (continued)

Anatomic stage/Prognostic groups[d]			
Stage	T	N	M
III	T1	N1a	M0
	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
	Stage IVB	T4b	Any N
IVB	T4b	Any N	M0
IVC	Any T	Any N	M1
Anaplastic carcinoma[e]			
IVA	T4a	Any N	M0
IVB	T4b	Any N	M0
IVC	Any T	Any N	M1

Reprint Permission Edge et al. [152]

[a]All categories may be subdivided: (s) solitary tumor and (m) multifocal tumor (the largest determines the classification)

[b]All anaplastic carcinomas are considered T4 tumors

[c]Regional lymph nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes

[d]Separate stage groupings are recommended for papillary or follicular (differentiated), medullary, and anaplastic (undifferentiated) carcinoma

[e]All anaplastic carcinomas are considered Stage IV

best surgically management in accordance with ATA guidelines [153]. Currently, it is recommended that children with differentiated thyroid carcinoma undergo near total thyroidectomy and modified neck dissection to remove gross disease if necessary. After surgical resection, ^{I131} remnant ablation and long-term suppressive thyroxin therapy may be used to treat residual disease and prevent recurrence. I131 is recommended for patients with known distant metastasis, gross extrathyroidal extension of the tumor regardless of tumor size, or primary tumor >4 cm. RAI (radioactive iodine) may be used in select patients with tumors 1–4 cm confined to the thyroid in patients that have lymph node metastasis or who are otherwise considered high risk. RAI is not recommended for lesions less than or equal to 1 cm, intrathyroidal disease, or multifocal cancer when all foci are less than 1 cm without high risk features. Since residual tumor may be treated with radioiodine, tumors involving the recurrent laryngeal nerve need not be aggressively resected. The nerve may be spared and residual tumor treated.

Recurrent laryngeal nerve injury and permanent hypoparathyroidism are the two most concerning iatrogenic injuries following thyroid resection [119–121, 128, 140]. These risks increase with the extent of resection and younger age of the patient [121]. To prevent damage to the recurrent laryngeal nerve, the nerve should be identified along its entire course and be seen entering the larynx. Intraoperative nerve stimulation is often used in the adult population to trace the course of the nerve and a recent report demonstrated the usefulness of this technique in children. The parathyroid glands should also be protected. If there is any question as to the viability of the parathyroid glands, they should be autotransplanted into the sternocleidomastoid muscle or nondominant forearm. A near total thyroidectomy leaving a few grams of tissue adjacent to the recurrent laryngeal nerve and the superior parathyroid gland should help prevent damage to these structures.

The technique for thyroidectomy is demonstrated in Fig. 24.11a–g. The patient is placed in a supine position initially with the neck extended by placing towel rolls beneath the shoulder. An incision is made 2–3 cm above the sternal notch in a skin crease (Fig. 24.11a). Dissection is carried down through the platysma muscle. Subplatysmal flaps are elevated superiorly to the thyroid notch and inferiorly to the sternal notch (Fig. 24.11b). The strap muscles are separated, not divided, in the midline to expose the thyroid gland (Fig. 24.11c). Crossing branches of the anterior jugular vein may need to be divided. Exposure of the desired lobe is obtained by retracting the strap muscles laterally. If the tumor has invaded the surrounding strap muscle, the strap muscles should be removed en bloc with the thyroid nodule. Ligation of the middle thyroid veins on the anterolateral surface in the middle of the thyroid gland to allows for proper mobilization (Fig. 24.11d). Prior to mobilizing the superior pole, the recurrent laryngeal nerve is identified. The thyroid

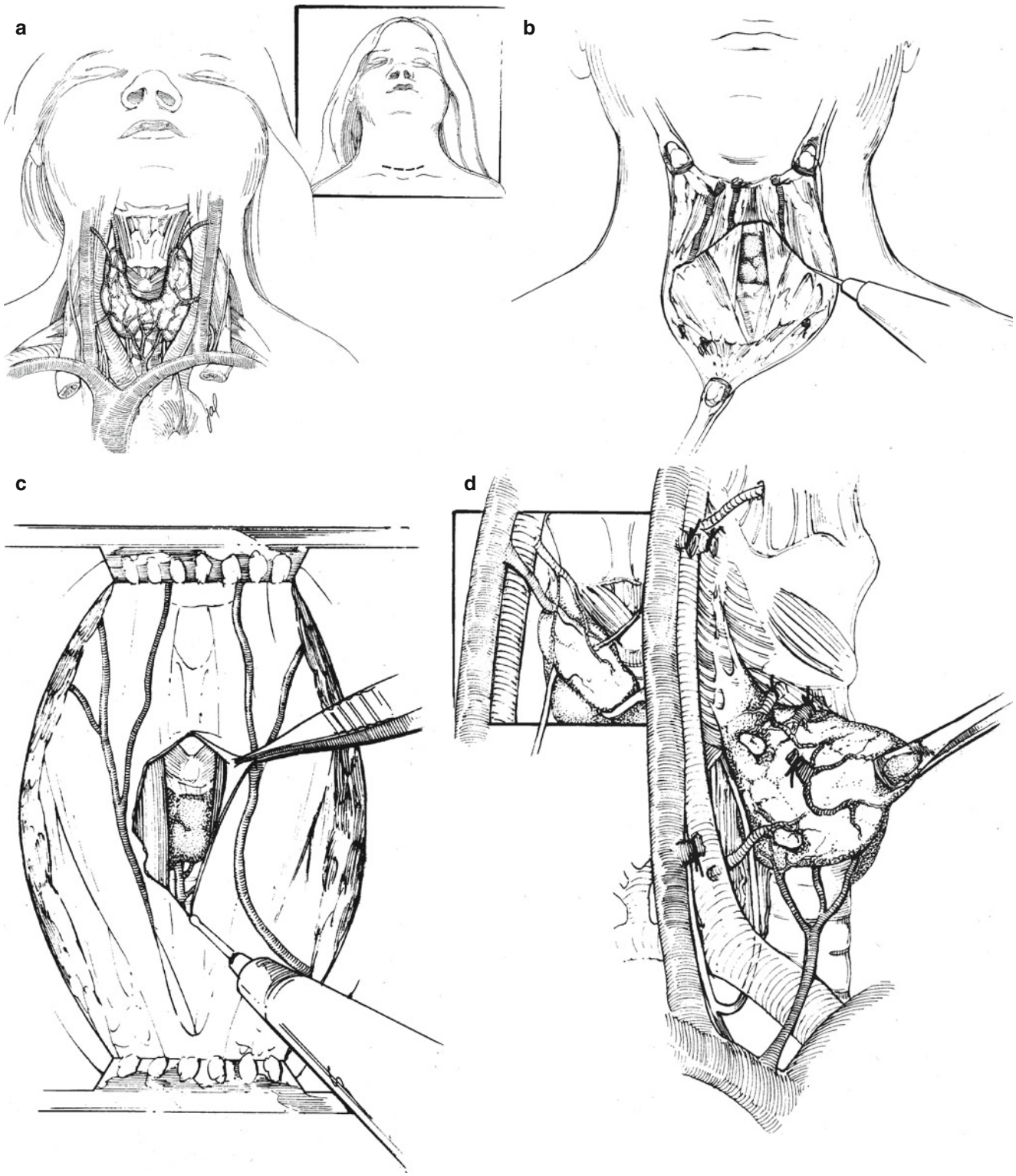

Fig. 24.11 (**a**) Thyroidectomy. Normal position of the thyroid gland. *Inset* illustrates site for skin incision. (**b**) Thyroidectomy. Elevation of subplatysmal flaps to thyroid notch, superiorly and sternal notch inferiorly. (**c**) Thyroidectomy. The thyroid gland is exposed by separating the strap muscles in the midline. (**d**) Thyroidectomy. Mobilization of the thyroid gland. The middle thyroid vein had been ligated and divided, the recurrent laryngeal nerve identified and the superior pole mobilized. Inset illustrates the superior thyroid artery and vein. Superior pole vessels are divided individually, close to the thyroid gland, to avoid injury to the external branch of the superior thyroid nerve. (**e**) Thyroidectomy. Division of the inferior thyroid artery. The relationship between the inferior thyroid artery and recurrent laryngeal nerve (encircled the suture) is defined. The parathyroid glands are identified and preserved by dividing branches of the artery as they enter the thyroid gland. (**f**) Thyroid lobectomy. Transection of thyroid gland. The recurrent laryngeal nerve is identified along its entire course prior to the division of the ligament of Berry. The thyroid is dissected from the pretracheal fascia and divided at the junction of the isthmus and contralateral lobe. (**g**) Thyroid lobectomy. Appearance following right thyroid lobectomy. The recurrent laryngeal nerve and parathyroid glands are preserved

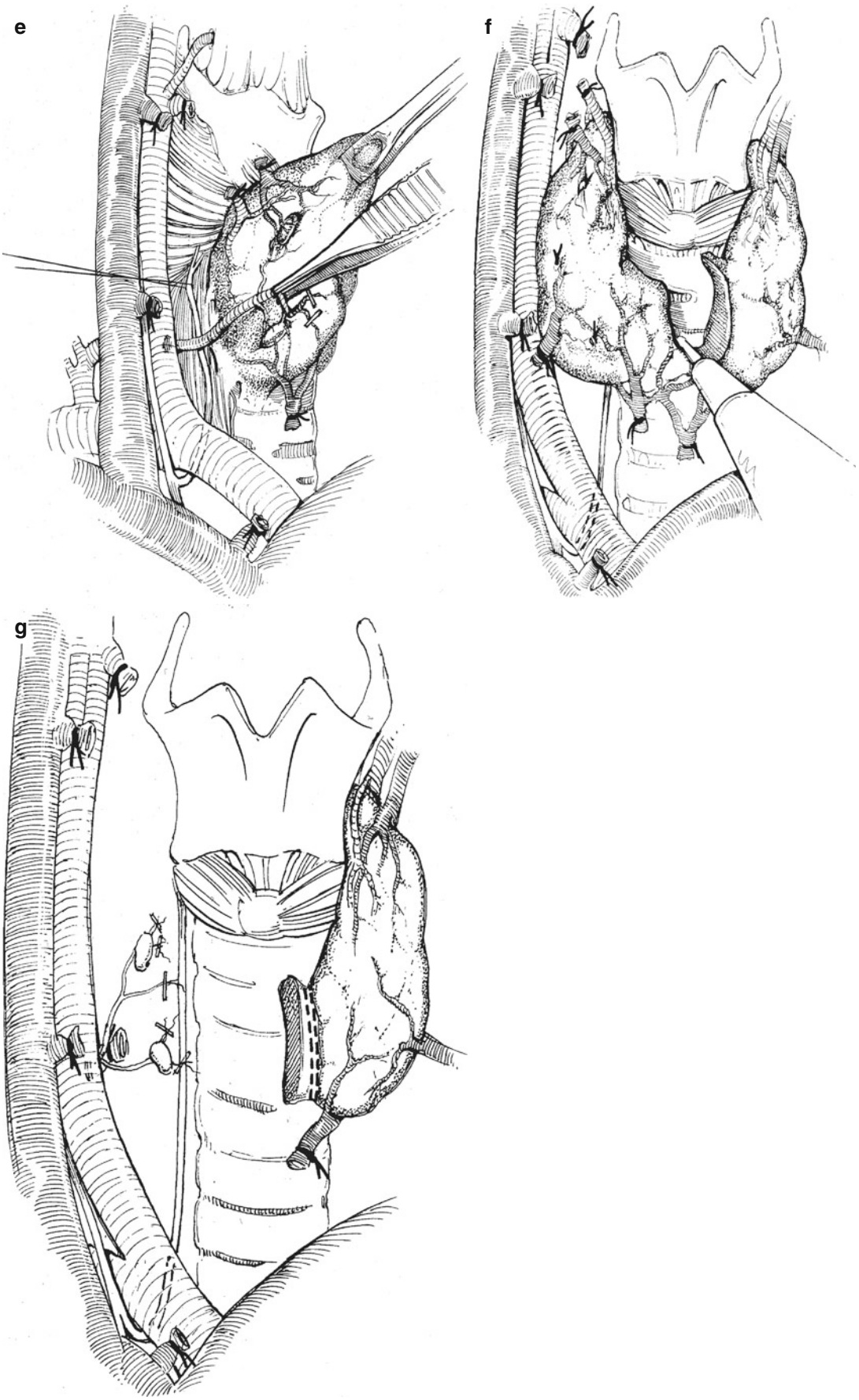

Fig. 24.11 (continued)

gland is grasped with a Babcock clamp and retracted medially. The recurrent laryngeal nerve is identified by its relationship to the inferior thyroid artery. The right recurrent laryngeal nerve ascends lateral to the tracheal esophageal groove as it passes posterior to the inferior pole of the thyroid. The nerve then travels obliquely, closer toward the gland and crosses the inferior thyroid artery and ascends to enter the larynx. The left recurrent laryngeal nerve arises from the vagus and passes inferior and medial to the aorta and ascends to enter the larynx. The nerve usually travels in the tracheal-esophageal groove but may be more medial on the anterior aspect of the trachea. The nerve may pass over, under or branch around the artery. With the exception of a right non-recurrent laryngeal nerve, there is always a cross point. The nerve should be traced along its anterior plane until it can be seen entering the larynx. The terminal portion of the recurrent laryngeal nerve passes posterior to a lateral extension of thyroid tissue. A neurostimulator may be used to add in recurrent laryngeal nerve localization [156].

This portion of the gland may be left in situ in a near-total thyroidectomy. If medial retraction limits exposure, the superior pole of the gland should be mobilized (Fig. 24.11e). To properly mobilize the superior pole, the thin anterior suspensory muscle over the larynx should be divided. Branches of the superior thyroid vessels are divided close to the thyroid gland below the external branch of the superior thyroid nerve (Fig. 24.11f). Division of the upper pole pedicle between clamps, en mass, results in a high frequency of injury to this nerve and should be avoided. With the superior pole free the gland may be retracted medially.

Finally division of the ligament of Berry, the posteromedial attachment of the thyroid, allows the thyroid to be retracted medially and dissected off of the pretracheal fascia to the isthmus. The recurrent laryngeal nerve courses near this posteromedial attachment so again proper identification of the nerve is essential. A pyramidal lobe, if present should be resected with the specimen. When performing a lobectomy and isthmusectomy, the junction of the isthmus and opposite lobe is transected with electrocautery (Fig. 24.11f, g). For a total thyroidectomy, mobilize the contralateral lobe as described and remove the entire specimen en bloc. Any suspicious lymph nodes should also be removed.

Blood supply to the parathyroid glands usually comes from the inferior thyroid arteries. If these arteries are not properly ligated, the parathyroid glands risk devascularization. In order to prevent this, individual branches of the inferior thyroid artery should be divided distal to the end branches supplying the parathyroid glands and near the thyroid capsule (Fig. 24.11g). The parathyroid glands should then be gently retracted off of the thyroid capsule. Following division of the inferior thyroid artery, the inferior pole vessels are divided. If parathyroid gland perfusion is compromised during the dissection, then one should immediately autotransplant the gland into the nearby sternocleidomastoid muscle [157–159]. Some surgeons advocate routine autotransplantation of one or two parathyroid glands into the sternocleidomastoid muscle or forearm muscle to prevent permanent hypoparathyroidism. Any removed parathyroid glands are placed in a specimen cup of sterile saline submerged in sterile ice until the thyroidectomy is completed.

After hemostasis is assured, the strap muscles are approximated with interrupted absorbable sutures. If complete hemostasis is questionable, a small drain may be placed below the strap muscles and brought out through a separate skin incision. The platysma muscle is closed with interrupted absorbable sutures and the skin closed using a running subcuticular stitch. For parathyroid autotransplantation, the excised parathyroid glands are minced into several small pieces. Within the sternocleidomastoid muscle or forearm muscle, small pockets are created by gently spreading with fine forceps. Two or more pieces of parathyroid tissue are placed in each pocket and marked with a silk suture.

Postoperative Management

Postoperatively, thyroidectomy patients should be treated with exogenous thyroid hormone to suppress TSH-mediated stimulation of the gland. Patients undergoing total parathyroidectomy with reimplantation often require calcium and vitamin D replacement until the autotransplanted tissue functions adequately [136]. To detect distant metastases or residual disease, radioiodine ^{131}I scanning should be performed ~6 weeks following surgery and discontinuation of exogenous thyroid replacement. If residual thyroid cancer is detected, then therapeutic doses of ^{131}I should be administered until all disease is eradicated. RAI is recommended for patients with distant metastatic disease, gross extrathyroidal extension of tumor, for tumor >4 cm. Dome patients with tumors 1–4 cm with lymph node metastasis or high risk features may benefit from RAI. Patients with tumors <1 cm without high risk features do not need RAI [153, 160].

If metastatic disease is present, resection of metastatic disease may be considered. Diagnostic scans (WBS and neck US) are then repeated in 3–12 months. Thyroglobulin levels should also be obtained at 3–12 months; an elevated level should raise the suspicion of recurrent thyroid carcinoma [153, 160–162]. Long term follow up in these patients is critical considering, the recurrence rate of thyroid cancer is about 30 % after 20 years. The overall progression-free survival of patients with differentiated thyroid cancer in this series was 67 % at 10 years and 60 % at 20 years after diagnosis. Factors associated with early recurrence are lower age at diagnosis and presence of residual neck disease.

Current management of MTC in children from families having the MEN 2 syndrome relies on the presymptomatic detection of the RET proto-oncogene mutation responsible for the disease, followed by prophylactic total thyroidectomy

by about the age of 5 years, before the cancer spreads beyond the thyroid gland [163]. MTC is usually the first tumor to develop in MEN patients and of those children who have a prophylactic thyroidectomy due to presence of a RET mutation, 80 % will already have foci of medullary carcinoma within the thyroid gland [136, 164]. Prophylactic thyroidectomy is recommended in infancy for patient with MEN 2B due to the aggressive nature of that subtype of MTC [164–166]. Unfortunately, external beam radiation, and chemotherapy have not been found to be effective in treating MTC, so surgical resection is the only treatment. Patients with MEN 2A have a lifetime risk of hyperparathyroidism of 30 % so at the time of prophylactic thyroidectomy consideration of routine heterotopic autotransplantation should be entertained [133, 164, 167].

The survival for thyroid cancer is quite good with overall mean survival of 30 years. Factors associated with worse outcomes include nonpapillary tumors, male gender, distant metastasis, and nonoperative treatment [110, 168]. Compared to adults, pediatric patients have larger tumors, increased lymph node invasion and distant metastasis. In patients with medullary thyroid cancer, survival was predicted by TNM staging and basal CT level <30 pg/mL [169]. Those patients with class D genotypes, preoperative CT >30 ng/mL, and age >10 years had worse outcomes. The association of radiation iodine with second cancers has lead to further recommendations to avoid radioactive iodine in low risk patients [170, 171].

Neuroblastoma

Neuroblastoma is the third most common malignancy children and the most common cancer in children less then 1 year of age [172, 173]. The annual incidence of neuroblastoma is about 1 per 100,000 in the United State with 700 new cases each year. The average age at diagnosis in 17.3 months and 40 % are diagnosed before 12 months of age [172–174]. Neuroblastoma is more common in Caucasians than African-Americans (ratio 1.8) in infancy but equivalent after infancy. The male to female ratio is 1.2:1. Primarily tumors of the head and neck region occur in 2–4 % of afflicted children [175]. When disease is noted in the head and neck, it is most commonly metastatic disease. Infants are more likely to present with tumors in the cervical region.

Environmental factors may play a role in the development of neuroblastoma. Maternal opiate use has been associated with neuroblastoma while increased folate intake during pregnancy is associated with a lower incidence [176, 177]. Most neuroblastomas appear to be sporadic though increased incidence is found in children with Turner's syndrome, Hirschsprung's disease, central hypoventilation, and neurofibromatosis type 1 [178, 179]. Familial cases of neuroblastoma have also been reported and appear to be transmitted in an autosomal dominant pattern with variable penetrance [180–182].

Pathology and Genetics

Neuroblastoma tumors are derived from primordial neural crest cells which populate the adrenal medulla and sympathetic ganglia. Based on maturation and differentiation of these neural crest cells, three histologic patterns of these tumors are noted including neuroblastoma, ganglioneuroblastoma and ganglioneuroma. Neuroblastomas consist of mostly neuroblasts and few stromal cells and are thus characterized as "stromal-poor" [173]. On histologic examination, small, dense, round cells are seen with hyperchromatic nuclei and scant cytoplasm. Electron microscopy, immunohistochemistry, and cytogenetic studies are currently used to diagnose these tumors.

Important biological factors include MYCN status, histopathologic classification, and DNA ploidy. These factors are so significant to outcomes that they are included in the COG staging of these tumors. N-Myc amplification is associated with more advanced disease, rapid tumor progression, and poor outcomes. Chromosome 1 deletions, rearrangements, and translocations have been reported in these patients [183–185]. Deletion of part of chromosome 1p is associated with amplification of N-Myc and is found in up to 25 % of neuroblastomas [185–189]. The smallest common region of loss is 1p36 and is associated with worse outcomes [190]. Deletion of 11q and/or 14q is found in 25–50 % of neuroblastomas and trisomy 17q is found in half of neuroblastomas [191–194]. The amplification of the N-myc proto-oncogene in chromosome 1p deletion and trisomy 17q are both associated with poor prognosis [191, 192, 195–197]. In contrast, expression of the tyrosine kinase receptor gene-A TRK-A is associated with biologically and clinically favorable tumors and good survival [198–201]. DNA ploidy, specifically those with near-triploid have a more favorable clinical prognosis and survival compared to those with near-diploid or near-tetraploid tumors and seems to be most significant in children 12–18 months of age and infants with 4S disease [202, 203].

Clinical Presentation

Patients usually present with a nontender, firm mass in the lateral neck [175]. If the tumor extends into cervical sympathetic chain, Horner's syndrome (ipsilateral ptosis, miosis, and anhidrosis) may be seen [204, 205]. Heterochromia iridis may be present in children who have congenital or acquired Horner's syndrome [206]. Infant with Horner's syndrome congenital or acquired should under careful exam-

ination and workup for possible neuroblastoma. Metastatic neuroblastoma to the orbits is more common than primary cervical neuroblastoma and may produce proptosis and periorbital ecchymosis. Neuroblastoma may metastasize by lymphatic and/or hematogenous drainage. Cervical neuroblastoma spreads by local invasion of surrounding tissue and shows a high propensity for regional lymph node metastases. Distant disease, bone, and bone marrow involvement is common at presentation.

Diagnosis

Diagnostic evaluation should include routine blood counts, liver and kidney function test, ferritin levels, and LDH levels. Nearly all neuroblastomas produce catecholamines and their byproducts, homovanillic acid and vanillylmandelic acid can be measured in the urine. In order to assess for the presence of these products, a 24 h urine collection should be obtained. In order to diagnosis neuroblastoma one of the following is needed: a histologic diagnosis of the tumor by microscopy; or evidence of metastases to bone marrow on aspirate with elevation in urine or serum catecholamines [207]. In order to stage a neuroblastoma, the following studies are needed: bilateral iliac crest bone marrow biopsy, bone radiography and a radionuclide or MIBG scan, abdominal CT or MRI, chest x-ray and if positive a chest CT, and a MRI/CT of the head and neck for primary tumors of the head and neck.

Staging

The most common staging systems for neuroblastoma are the International Neuroblastoma Staging System (INSS) (Table 24.8) and the Children's Oncology Group risk stratification for children (Table 24.9) [207]. When combining the INSS stage, age, MYCN status, INPC classification, and DNA ploidy, an assessment of pretreatment risk can be made (Table 24.9) [208, 209].

Treatment

Treatment for neuroblastomas arising in the head and neck includes surgery and often chemotherapy. The role of surgery is to establish a tissue diagnosis, stage the tumor, and resect the tumor if possible. For localized cervical neuroblastoma, surgical excision may be curative. When complete surgical excision is possible in stage 1 disease, 5-year survival is 99 % [210–214]. Surgical risk factors for primary resection of localized neuroblastoma for head and neck neuroblastomas include tumor encasing major vessels, tumor extending to base of the skull, compressing the trachea, encasing brachial plexus [215].

Even if complete surgical resection is possible, children identified as intermediate or high-risk need chemotherapy in addition to surgical resection [216]. Multi-agent chemotherapy is used in patients with unresectable disease and advanced disease. Common regimens include cyclophosphamide, ifosfamide, carboplatin or cisplatin, vincristine, doxorubicin, etoposide, topotecan, and adriamycin [209–211, 216–220]. After chemotherapy, surgical resection may be reconsidered [216, 221]. Radiation is used for unresectable tumors of tumors that are not responsive to chemotherapy including incompletely resected cervical neuroblastoma [219, 222, 223].

New treatment strategies include immunotherapy, MIBG therapy, differentiating agents, angiogenesis inhibitors, and targeted cell therapy. 131I-MIBG is used in patients with refractory neuroblastoma with a response rate of up to 33 %

Table 24.8 Staging systems for neuroblastoma [209]

International Neuroblastoma Staging System (INSS)	
Stage 1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (i.e., nodes attached to and removed with the primary tumor may be positive).
Stage 2A	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.
Stage 2B	Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically
Stage 3	Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement. The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.
Stage 4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs, except as defined for stage 4S.
Stage 4S	Localized primary tumor, as defined for stage 1, 2A, or 2B, with dissemination limited to skin, liver, and/or bone marrow (by definition limited to infants younger than 12 months) [3]. Marrow involvement should be minimal (i.e., <10 % of total nucleated cells identified as malignant by bone biopsy or by bone marrow aspirate). More extensive bone marrow involvement would be considered stage 4 disease. The results of the mIBG scan, if performed, should be negative for disease in the bone marrow.

Table 24.9 Children's Oncology Group (COG) neuroblastoma low-, intermediate-, and high-risk group assignment schema [209]

INSS stage	Age	MYCN status	INPC classification	DNA ploidy[a]	Risk group
1	0–21 years	Any	Any	Any	Low
2A/2B[b]	<365 days	Any	Any	Any	Low
	≥365 days–21 years	Nonamplified	Any	–	Low
	≥365 days–21 years	Amplified	Favorable	–	Low
	≥365 days–21 years	Amplified	Unfavorable	–	High
3[c]	<365 days	Nonamplified	Any	Any	Intermediate
	<365 days	Amplified	Any	Any	High
	≥365 days–21 years	Nonamplified	Favorable	–	Intermediate
	≥365 days–21 years	Nonamplified	Unfavorable	–	High
	≥365 days–21 years	Amplified	Any	–	High
4[c]	<548 days [14–16]	Nonamplified	Any	Any	Intermediate
	<365 days	Amplified	Any	Any	High
	≥548 days–21 years	Any	Any	–	High
4S[d]	<365 days	Nonamplified	Favorable	>1	Low
	<365 days	Nonamplified	Any	=1	Intermediate
	<365 days	Nonamplified	Unfavorable	Any	Intermediate
	<365 days	Amplified	Any	Any	High

The COG-9641 and COG-A3961 trials established the current standard of care for neuroblastoma patients in terms of risk group assignment and treatment strategies

INPC International Neuroblastoma Pathologic Classification, *INSS* International Neuroblastoma Staging System

[a]DNA Ploidy: DNA Index (DI) >1 is favorable, =1 is unfavorable; hypodiploid tumors (with DI <1) will be treated as a tumor with a DI >1 (DI <1 [hypodiploid] to be considered favorable ploidy)

[b]INSS stage 2A/2B symptomatic patients with spinal cord compression, neurologic deficits, or other symptoms should be treated with immediate chemotherapy for four cycles

[c]INSS stage 3 or stage 4 patients with clinical symptoms as listed above should receive immediate chemotherapy

[d]INSS stage 4S infants with favorable biology and clinical symptoms should be treated with immediate chemotherapy until asymptomatic (2–4 cycles). Clinical symptoms include: respiratory distress with or without hepatomegaly or cord compression and neurologic deficit or inferior vena cava compression and renal ischemia; or genitourinary obstruction; or gastrointestinal obstruction and vomiting; or coagulopathy with significant clinical hemorrhage unresponsive to replacement therapy

[224, 225]. CCG 3891 utilized 13-cis-retinoic acid in maintenance phase with improved results and other retinoids and vitamin A derivatives are under investigation [226]. Other new targets with varying levels of success include ALK inhibition, aurora A kinase inhibition, TRK inhibition, tubulin-binding agents, DNA methylation, histone modification, and miRNAs [215].

Prognosis variables for neuroblastoma include age, stage, N-Myc status, pathology classification, DNA ploidy, location, and metastasis. Infants with primary tumors of the head and neck have a more favorable prognosis. Patients with localized disease that is completely resected have a >90 % survival rate (Fig. 24.12) [227]. Children with intermediate-risk neuroblastoma treated with surgery, chemotherapy, with or without radiation have long-term survival of 90 % [210, 213, 228, 229]. Survival for stage 3 neuroblastoma varies based on age and histologic features [230]. Survival in children with disseminated neuroblastoma (CCG stage IV and POG stage D) is also age dependent but overall survival is ~30 % [221, 231]. When recurrence occurs, the disease is usually widely metastatic and the prognosis is poor.

Rhabdomyosarcoma

Rhabdomyosarcoma is a soft tissue sarcoma that originates from immature mesenchymal cells destined to be striated skeletal muscle. It is the most common soft tissue sarcoma in children accounting for up to 5 % of all childhood cancer and 50–70 % of all sarcomas. It accounts for 20 % of head and neck tumors in children. The annual incidence of rhabdomyosarcoma ranges from 5 to 8 per million children resulting in approximately 350 new cases each year [232, 233]. In the United States, rhabdomyosarcoma is more common in Caucasian children with a 2–3:1 ratio to African American children. The incidence of rhabdomyosarcoma throughout the world varies with increase incidences in Spain and decreased incidences in lower parts of Asia including China, Japan, India, and the Philippines [234, 235]. The incidence of rhabdomyosarcoma appears to be equal in Asian children as compared to Caucasian children in the United States [236]. The incidence is increased in males with a ratio of 1.4:1 but the incidence appears equal in cases of rhabdomyosarcoma of the head and neck [237]. Age of onset has two peak occurrences, the first in children 2–6 years of age and

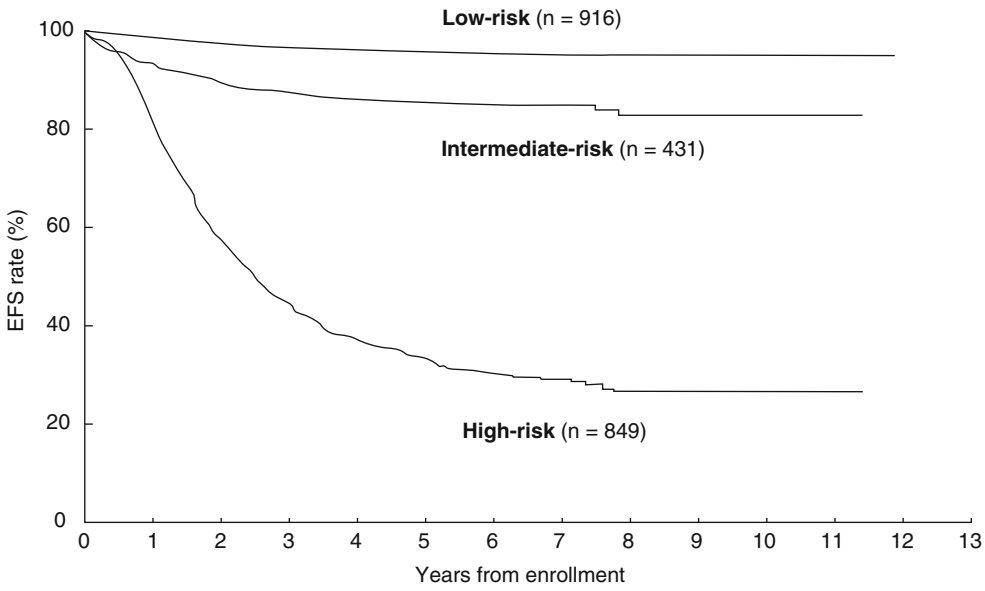

Fig. 24.12 Outcomes for children with low-risk, intermediate risk, and high-risk neuroblastoma [42] (Permission from previously published article: Park et al. [227] with permission from Elsevier)

the second in adolescents 15–19 years old. Two-thirds of the patients are diagnosed younger than 6 years of age [234]. Age-related differences exist for the different sites of primary disease though tumors can arise in any region at any age. Younger children tend to have increased incidence of head and neck and genitourinary rhabdomyosarcoma while older children have an increased incidence of tumors of the extremities and truck and of the male genital tract. For example in patients with orbit RMS, 42 % are aged 5–9 years and in these younger children tumors of the orbit tend to be of the embryonal type. Thirty-five percent of all rhabdomyosarcomas occur in the head and neck.

Most rhabdomyosarcomas are sporadic in occurrence, but some are known to be associated with familial syndromes such as neurofibromatosis, Li-Fraumeni syndrome, Rubinstein-Taybi syndrome, Gorlin basal cell nevus syndrome, Costello syndrome, and Beckwith-Wiedemann syndrome [238–244]. Many children with Li-Fraumeni syndrome in particular are noted to have mutations of p53 tumor suppressor gene which has lead some to speculate that children who develop RMS as a young age should be screened for a p53 mutation. Presence of a p53 mutation may lead one to reduce ionization and/or chemotherapeutic doses that may lead to secondary malignancy though there is no consensus on this topic [245]. Environmental factors that may be associated with the development of RMS including maternal use of marijuana and cocaine, intrauterine radiation exposure, low socioeconomic status, the use of antibiotics soon after birth, and exposure to alkylating agents [19, 246–249]. Relatives of children with rhabdomyosarcoma may be at increased risk for the development of breast cancer, brain tumors, and adrenocortical carcinoma [244, 250–252].

Pathology and Genetics

Rhabdomyosarcomas (RMS) arise from immature mesenchyme cells that were destined to differentiate into muscle. Interestingly, these tumors arise in various locations including areas where striated muscle is not found such as the bladder. On microscopic examination, the cells have immunohistochemical expression of actin, myosin, desmin, myoglobin, Z-band proteins, and/or MyoD with an eosinophilic cytoplasm [253]. Over 99 % of RMS stain for polyclonal desmin, while actin, myogenin and myoglobin are found in 95, 95, and 78 % percent respectively [254]. Myogenin in particular is expressed more often by alveolar RMS. A DNA-binding protein expressed during early myogenesis, MYOD1, is also expressed in these tumors and can be identified by immunohistochemistry and Northern blot analysis [255, 256]. Other immunohistochemical stains may be helpful in identifying RMS. CD99 is a marker used in Ewing sarcoma but is positive in 15 % of RMS patients [257]. Leukocyte common antigen, pan B lymphocyte antibodies, cytokeratin, epithelial membrane antigen, and neural markers such as neuron specific enolase and S-100 protein are positive in 5–20 % of RMS cases. In addition to immunohistochemical staining, transmission electron microscopy (EM) is also useful in identifying myofilament, myotubular intermediate filaments, desmin, actin, and z-bands.

Four histological subtypes of RMS assist in both the categorization and prognosis of patients: embryonal (50 %), botryoides and spindle cell (6 %, 3 %), alveolar (20–30 %), and undifferentiated (10 %). In addition to these four main histological groups, there are RMS tumors that are described as not otherwise specified and diffusely anaplastic (previously pleomorphic) which are associated with poor progno-

sis [258]. The botryoides and spindle class are less common but are associated with the best prognosis. The embryonal RMS group has an intermediate prognosis while the alveolar group has a relatively poor prognosis. Embryonal is most common at birth and decreases into adolescence while alveolar is more common as age increases [259].

The alveolar and embryonal RMS are distinguished based on the architecture of the tumor. Embryonal RMS appears as sheets of rhabdomyoblasts with occasional fusiform cells and no alveolar architecture (Fig. 24.13). The alveolar RMS is characterized by an alveolar architecture with rhabdomyoblasts interspersed among fibrovascular septae [260]. Botryoides RMS whose name means "grape" has the gross appearance of a bunch of grapes. Histologically it is a mass beneath an epithelial layer and subepithelial layer of rhabdomyoblasts. Anaplastic RMS is characterized by atypical mitotic figures and large nuclear size [261, 262].

Cytogenetic and molecular markers have been found in rhabdomyosarcoma that can be useful for classification and prognostication. Up to 80 % of embryonal rhabdomyosarcoma have a loss of heterogeneity at the 11p15 locus near the IGF-II gene. This loss of heterogeneity is suggestive of the presence of a tumor suppressor gene in the region that is disrupted [256, 263, 264]. Overproduction of IGF-II, which is found in both embryonal and alveolar rhabdomyosarcomas, may then stimulate tumor growth [265]. The PAX3-FKHR translocation in alveolar RMS in particular is associated with over expression of IGF-II [266]. Several other genetic mutations are associated with rhabdomyosarcoma including activation and or mutations of the K-ras, N-ras, retinoblastoma, PTCH gene mutations, MDM2, CDK4, p53, and MYCN though the significance of these mutations are yet to been determined [267–271].

In alveolar RMS, the t(2;13)(g37;g14) translocation in which the long arms of chromosome 2 and 13 join to fuse PAX3 and FKHR is diagnostic of the alveolar subtype even in the absence of the characteristic histology (Fig. 24.14) [272, 273]. In particular, the solid alveolar variant may be histologically similar to the embryonal subtype but will possess this translocation. The mechanism by which this translocation produces RMS is unclear but it is postulated that it is due to increased upstream transcription of other genes during development [274–276]. Another translocation t(1;13)(p36;p14) fuses PAX7 and FKHR. This fusion is thought to increase upstream transcription but the mechanism is not fully understood [274]. These markers have been found to have prognostic value as well. For example, PAX7-FKHR

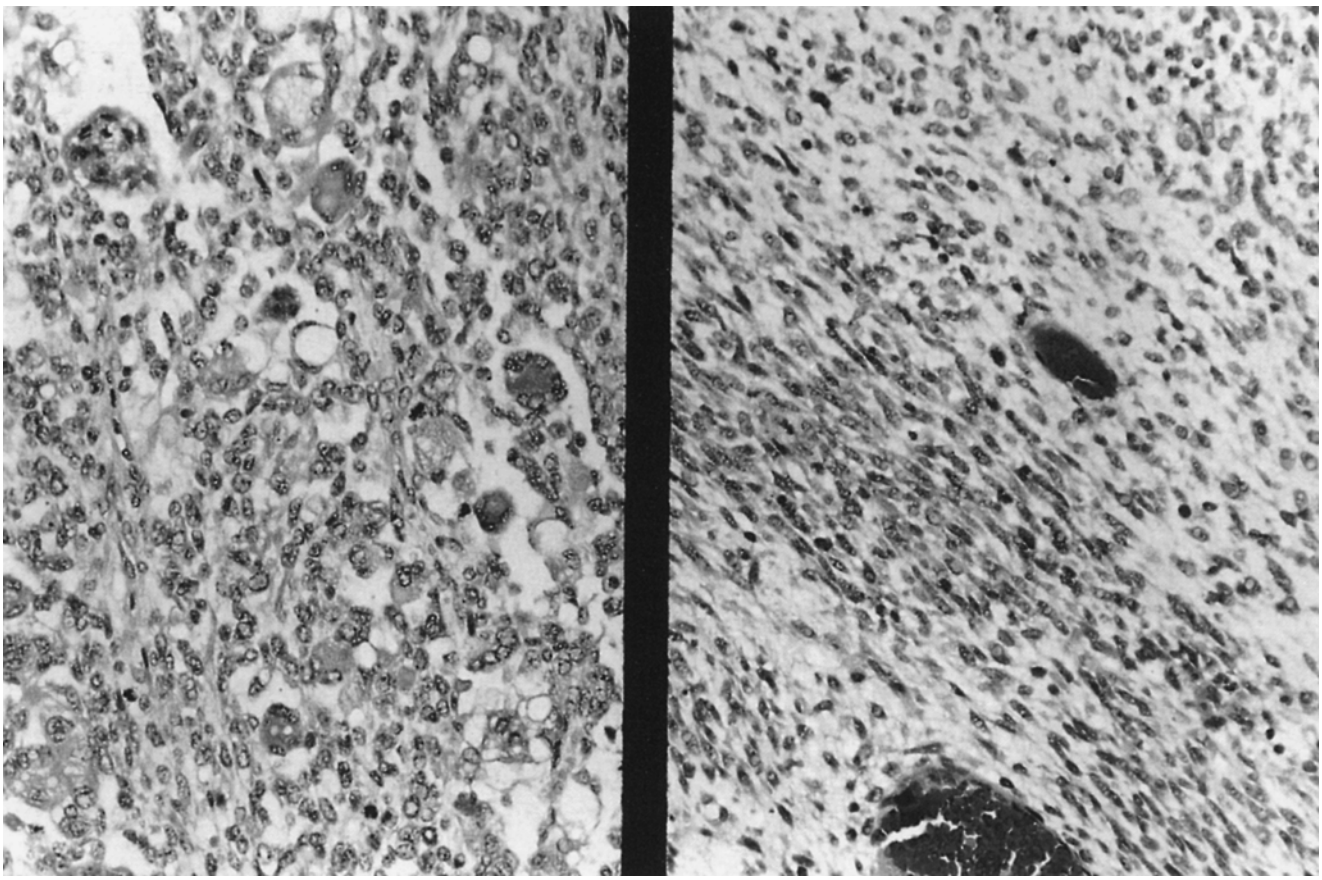

Fig. 24.13 Photomicrograph demonstrating embryonal rhabdomyosarcoma. *Left panel*; round cell rhabdomyosarcoma. *Right panel*; spindle cell rhabdomyosarcoma

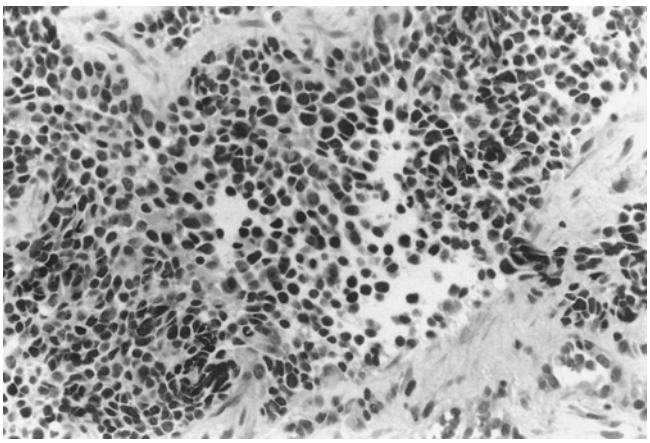

Fig. 24.14 Photomicrograph demonstrating alveolar rhabdomyosarcoma. Note clear areas with alveolar-like appearance

patients tend to be younger patients with extremity lesions that tend to respond favorably to treatment [277, 278].

Clinical Presentation

Thirty-five to forty percent of rhabdomyosarcoma presents in the head and neck, usually as a nontender mass lesion with occasional overlying skin erythema [261, 279, 280]. These tumors tend to arise in the orbit (25 %) and parameningeal sites (50 %) with the remaining 25 % arising in other locations including the scalp, parotid gland, oral cavity, pharynx, and neck [281]. Embryonal rhabdomyosarcoma is more common in the superior nasal quadrant while alveolar is more common in the orbit. An orbital tumor may present with proptosis, periorbital edema, ptosis, and/or opthalmoplegia. Parameningeal or nasopharyngeal tumors present with airway obstruction, local pain, chronic sinusitis and epistaxis. In the case of parmeningeal lesions, cranial nerve palsies may result from direct extension. Middle ear tumors present as a polyploidy mass with earache, otitis media, and discharge which may be hemorrhagic.

Less than one quarter of patients have metastatic disease at diagnosis [277, 282]. When rhabdomyosarcomas does spread, it is either by direct extension or metastasis via lymphatic and/or hematogenous route. Lymphatic metastasis occur less in than 10 % of the cases [283]. Hematogenous spread occurs in 10–20 % of cases and is most often to the lungs (40–50 %), bone marrow (20–30 %), and bone (10 %) [277, 282, 284].

Diagnostic Evaluation

After a thorough history and physical examination, further diagnostic evaluation should include the acquisition of laboratory data. A complete blood count (CBC) may show evidence of anemia due to inflammation and/or pancytopenia due to bone marrow involvement. Liver function tests are necessary to assess for possible metastatic disease to the liver and are necessary prior to administration of potentially hepatotoxic chemotherapy. Renal function tests, electrolytes, serum calcium, magnesium, phosphorous, and uric acid levels are also needed before the administration of potentially toxic chemotherapeutic agents. A urinalysis is also needed to assess for hematuria, which may indicate GU tract involvement.

Imaging studies are important tools to determine the presence of calcifications and bone involvement of the primary tumor and to search for metastatic disease. MRI or occasional CT scans are important to fully assess tumor involvement of the head and neck and serve as a baseline when assessing response to therapy. For tumors of the head and neck in particular, MRI is superior for assessing involvement of adjacent structures and feasibility of resection and should be performed when considering total resection. A CXR and chest CT scan is necessary for evaluation of lung metastases. An abdominal US and/or CT is indicated to evaluate for liver metastasis. While the utility of PET scanning is limited in children, its use in the adult sarcoma population is increasing and FDG-PET may enhance the evaluation of occult metastases, persistent disease, or recurrence [285–287]. A radionuclide bone scan is indicated to assess for bony involvement. Bone marrow biopsies are also necessary to assess for metastatic disease even in patients with normal complete blood counts. In patients with parameningeal RMS a lumbar puncture is indicated to assess for leptomeningeal metastasis.

A biopsy of the tumor is necessary to definitively establish the diagnosis and guide treatment. In order to obtain enough tissue for diagnosis, an open biopsy is often performed, though core needle biopsy is also an alternative. Enough tissue is need for fluorescent in situ hybridization (FISH) and reverse transcriptase–polymerase chain reaction (RT-PCR) testing to assess for the molecular/genetic abnormalities already described.

Staging

Staging and classification of rhabdomyosarcoma is described in a variety of ways. The Intergroup Rhabdomyosarcoma Study divides patients based on the Tumor-Node-Metastasis system (TNM) which includes site of tumor, tissue invasion, tumor size, lymph node involvement and metastatic disease (Table 24.10) [288–290]. The Intergroup Rhabdomyosarcoma (IRS) clinical staging system is shown in Table 24.11 [261, 288, 289]. It divides patients into clinical groups based on the localization of the primary tumor, the extent of surgical resection, and presences of residual disease/metastases [288, 290]. Before treatment is begun, adequate staging must be

Table 24.10 TNM staging system of Intergroup Rhabdomyosarcoma Study IV [288–290]

Stage	Sites	T invasion	T-size	N	M
1	Orbit	T 1 or T2	a or b	N0, N1, Nx	M0
	Head and neck excluding parameningeal				
	Non-bladder, non-prostate genitourinary				
2	Bladder/prostate	T1 or T2	A	N0 or Nx	M0
	Extremity				
	Cranial parameningeal				
	Trunk/retroperitoneum				
3	Bladder/prostate	TI or T2	B	N0, N1, Nx	M0
	Extremity				
	Cranial parameningeal				
	Trunk/retroperitoneum				
4	All sites	T1 or T2	a or b	N0 or NI	M1

A < 5 cm in diameter; b >5 cm in diameter
T tumor, *TI* confined to site of origin, *T2* extension beyond site of origin, *N* regional lymph nodes, *N0* no involvement, *N1* clinically involved, *Nx* status unknown, *M* metastases, *M0* no distant metastases, *M1* distant metastases present

Table 24.11 Intergroup rhabdomyosarcoma clinical Staging system [261, 288, 289, 295, 296]

Clinical group	Extent of disease
I	A. Localized tumor, confined to site of origin, completely resected
	B. Localized tumor, infiltrating beyond site of origin, completely resected
II	A. Localized tumor, gross resection with microscopic residual disease
	B. Locally extensive tumor (positive regional lymph nodes), completely resected
	C. Locally extensive tumor (positive regional lymph nodes), gross resection with microscopic residual disease.
III	A. Gross residual disease following surgical biopsy
	B. Gross residual disease after major resection
IV	Presence of distant metastases, any size primary tumor with or without regional lymph nodes

Table 24.12 Soft Tissue Sarcoma Committee of the Children's Oncology Group: Rhabdomyosarcoma Risk Group Classification [209]

Risk group	Histology	Stage	Group
Low risk	Embryonal	1	I, II, III
	Embryonal	2, 3	I, II
Intermediate risk	Embryonal	2, 3	III
	Alveolar	1, 2, 3	I, II, III
High risk	Embryonal or Alveolar	4	IV

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complete which includes tissue conformation of RMS and TNM staging. Based on stage, clinical group, site, and histology, risk groups assignments may be made (Table 24.12).

Treatment

Rhabdomyosarcoma of the head and neck is often treated with a combination of chemotherapy, radiation, and surgical resection if possible. Surgical resection of head and neck rhabdomyosarcomas should only be undertaken when the entire tumor can be removed with damage to vital structures and without major cosmetic or function deformity. Occasionally superficial tumors of the scalp, ear, cheek, neck, or oropharynx may be completely excised. If complete surgical resection is not possible, chemotherapy and radiation should be administered to shrink the tumor if possible; a complete surgical resection may be possible after treatment. In these cases an incisional biopsy is needed for diagnosis. Random nodal sampling is not indicated. Suspicious lymph nodes should be biopsied for staging purposes, but extensive neck dissections are not indicated. Sentinel lymph node biopsy is being used for extremity and truncal lesions though its role in head and neck RMS has not been assessed [291–293]. There also does not appear to be a role for resection of metastatic lesion such as an isolated pulmonary nodule [294]. For patients with recurrent disease, surgical resection is warranted though again after chemotherapy and radiation if complete excision is not possible.

Chemotherapy and radiation is the mainstay of RMS that is not completely surgically resectable as is the case from most patients with RMS of the head and neck. The standard treatment is a combination of vincristine, actinomycin-D, and cyclophophamide as currently recommended by the Rhabdomyosarcoma Study Group [279, 280, 290, 295, 296]. The IRS – IV patients were divided into prognostic groups

based on clinical and TNM staging. Based on the prognostic staging they were assigned to chemotherapy regimes. Most treatment courses continue for approximately 45 weeks depending on the clinical stage at presentation. Additional agents such as doxorubicin, cisplatin, etoposide, and melphanlan have not been shown to be beneficial though topotecan and irinotecan are under study for patients with resistant tumor and advanced or recurrent disease [261, 279, 280, 296–301].

If residual and or metastatic disease is present, radiation therapy may be added to the above chemotherapeutic regime. Radiation is usually initiated after 2–3 cycles of chemotherapy except in those patients with parameningeal tumors or life-threatening tumors in which radiation is started immediately. Delay of radiation treatment beyond 4 months has been shown to impair local control [302]. Radiation doses vary based on tumor location, extent, and involvement of nodes. For the other clinical groups, local control was achieved with radiation to the primary tumor site in doses of 1.8–2 Gy daily depending on patient age and the size of tumor.

The IRS study group, has noted that radiation was unnecessary for clinical group I embryonal RMA and paratesticular tumors. All other clinical group 1 patients were recommended to have radiation for a total dose of 36 Gy. Those in clinical group II with residual disease after surgery received radiation doses 41.4–45 Gy which increased survival to 75–87 % [303]. In clinical group III, IRS-IV recommends patient with gross residual disease receive 50.4 Gy except in orbital RMS in which 45 Gy is recommended. Patients with parameningeal tumors do benefit from higher radiation doses so the current recommendation is 50.4+ Gy to the site of the tumor with 2 cm margins of normal tissue [302, 304, 305]. Intracranial extension, cranial bone erosion, and/or cranial nerve palsy do not require whole-brain irradiation or intrathecal therapy, though tumor cells in CSF are indications for additional therapy [305]. Intraparenchymal brain metastases may be treated with CNS RT in addition to chemoradiation directed at the primary tumor. Though tumor cells in CSF may signify metastasis, it does not necessarily mean the patient is not treatable. Raney et al. noted that patient without other signs of metastasis were alive 6–16 years after diagnosis [306]. Intracranial extension should receive prompt radiation for delay is associated with worse outcomes [302].

After receiving therapy, patients are reimaged and if residual tumor is noted, resection needs to be entertained. Resection may be a first attempt at an oncologic resection or a second-look operation to confirm/evaluate response and to completely resection disease without loss of function.

For patients with metastatic disease chemoradiation is recommended for the primary and metastatic tumors with organ preservation [307] IMRT or fractionated stereotactic radiation therapy and chemotherapy has been used in patients with rhabdomyosarcoma of the head and neck with good results [308–310].

For patients with orbit tumors and clinical group I (completely excised) head and neck tumors, the 5-year survival is >85 % [279, 290, 296]. For other tumors of the head and neck, the 5-year survival is about 75 %. Relapse has been reported in approximately 1 % of patients after 5 years [279, 290, 296]. When rhabdomyosarcoma recurs, it tends to be more resistant to chemotherapy and radiation and is associated with a poor prognosis. The treatment for recurrent RMS is again chemotherapy, radiation, and surgical resection is possible. There are no clear guidelines on chemotherapeutic regimens and radiation dosing in patients with recurrent rhabdomyosarcoma, but suggestions include vincristine, dactinomycin, and cyclophophamide and also possibly doxorubicin, ifosfamide and etoposide, mesna and actinomycin D [311–316]. Further research is needed to identify better treatment protocols for this treatment resistant group.

Other Soft Tissue Sarcomas

Soft tissue sarcomas other than rhabdomyosarcomas make up 4 % of all tumors in children. These sarcomas are names based on the mature tissue that they resemble though all of these tumors are derived from primitive mesenchymal cells. Those that occur in infants and small children primarily occur in the head and neck region. Soft tissue sarcomas in infants and younger children often have less aggressive behavior and an excellent prognosis with surgery. Sarcomas, which present during adolescence, behave more like tumors in the adult population. Most soft tissue sarcomas present as painless, asymptomatic masses in the neck unless there is compression or invasion of adjacent structures. Because of the rarity of these lesions in childhood, most of the available data for treatment come from the adult population. In general, wide local excision is the treatment of choice. Because of the difficulty in obtaining wide negative margins in the head and neck, adjuvant therapy is often used in conjunction with surgical excision.

Fibrosarcoma

Fibrosarcoma is the most common non-rhabdomyomatous soft tissue sarcoma in children younger than 1 year of age and is the most common soft tissue sarcoma after rhabdomyosarcoma in all children accounting for 11 % of the total [317]. Primary head and neck lesions account for approximately 15–20 % of fibrosarcoma [318]. There is a bimodal age distribution with peaks in infant to 5 years of age and then again between the ages of 10–15 years and is described may be described as infantile or “adult-type” fibrosarcoma. Histologically, fibrosarcoma tumors consist of spindle cells with a characteristic herringbone pattern and it is associated

with ETV6-NTRK3 fusion protein. Fibrosarcomas in the first year of life rarely metastasize and can be treated with wide local excision. Radiation is indicated if complete excision is not possible. Fibrosarcoma tumors in adolescence are more aggressive and require multimodality therapy though utility of adjuvant therapy has not been established. Survival for nonmetastatic tumors ranges from 83 to 92 % in children under 5 years of age and 60 % for those older than 5 years [319–322].

Malignant Peripheral Nerve Sheath Tumor

Malignant peripheral nerve sheath tumors (MPNST) account for 5 % of all soft tissue sarcomas in children and 10 % occur in the head and neck region. They are tumors arising from nerves and express S10 or other neural markers. They can arise from the cranial nerves, cervical plexus, or sympathetic chain. In contrast to most of the other head and neck soft tissue sarcomas, MPNSTs commonly present with pain, paresthesias and muscle weakness. They are associated with neurofibromatosis type I which is characterized by cafe au lait spots, neurofibromas, skeletal dysplasia, and many neoplasms [323]. Half of the patients with MPNST have neurofibromatosis type 1 and 1–2 % of patients with NF 1 will develop MPNST [324]. These lesions are similar in appearance to fibrosarcomas but are far more aggressive. The tumor cells of MPNST, in contrast to fibrosarcoma, are more variable in size and shape and lack a herringbone pattern. Outcome is related to size of tumor, grade, differentiation, surgical resectability, location, comorbidity, and age. The mainstay of therapy is surgical resection if possible [324]. Multimodal therapy including wide surgical excision, radiation, and chemotherapy including vincristine, actinomycin D, cyclophosphamide and doxorubicin (Adriamycin) are recommended though impact of chemotherapy and radiation is debated. Survival is generally good for early stage tumors (50–75 %) and poor for advanced disease (15–30 %) [319].

Synovial Sarcoma

Synovial sarcoma is rare in children but may occur in the head, neck, and trunk in 15–20 % of cases [325–327]. These tumors occur more commonly in older children and young adults and histologically differentiate into a spindle fibrous stroma similar to fibrosarcoma and a glandular component with epithelial differentiation. Synovial sarcomas are separated into monophasic which contain only spindle cell and biphasic which contain both spindle and epithelioid cells. The tumor is associated with t(x;18) translocation with fusion of SYT-SSX1 and SYT-SSX2 proteins. Those patients with a SYT-SSX2 fusion gene have a better prognosis that those with a SYT-SSX1 fusion gene [327]. In contrast to other non-rhabdomyosarcoma soft tissue sarcomas, synovial sarcomas commonly present with both lymph node and lung metastases. Local disease is treated with local excision. The role of chemotherapy and radiation is unclear but often given in combination with surgery. Survival rate depend on tumor location, size, extension, and ability to achieve surgical resection. The 5-year survival rates are greater than 50 % [327–330]

Hemangiopericytoma

Hemangiopericytoma accounts for 3 % of all soft tissue sarcomas and occurs most commonly in the lower extremities and retroperitoneum. These tumors occur rarely in the nasal cavity, paranasal sinuses, orbital region, parotid gland and the neck. It is thought that hemangiopericytomas arise from vascular pericytes or alternatively from mesenchymal cells with pericytic differentiation [331, 332]. Multiple simple and complex genetic translocations have been demonstrated in these tumors [333]. These lesions are classified as benign, malignant, or borderline depending the characteristics of the lesion including tumor size, necrosis, mitotic activity, cellularity, and atypia though universe criteria have not been defined. Wide local excision and postoperative chemotherapy is the recommended treatment. Irradiation is added for incompletely resected tumors. Hemangiopericytomas in infants are associated with a better prognosis than those occurring in older children and adults. The reported 5-year survival rate for these tumors is stage-dependent and ranges from 30 to 70 % [331, 334, 335].

Malignant Fibrous Histiocytoma

Malignant fibrous histiocytomas (MFH) are rare sarcomas with multiple tissue elements that commonly present in the head and neck region. These tumors rarely occur during the first year of life. Ring chromosomes and 19p+ alterations have been observed in these tumors [327, 336, 337]. Microscopically, MFH has multiple cell types, marked cellular pleomorphism and a storiform pattern and resembles fibrosarcoma but lacks a herringbone pattern. Treatment is with wide excision and local irradiation for residual tumor with or without chemotherapy. The 3-year survival for head and neck tumors is greater than 50 % [338–341].

Alveolar Soft Part Sarcoma

Alveolar soft part sarcoma is rare in childhood with an incidence of one per ten million, but when it occurs, it most commonly involves the head and neck. Locations described

include orbit, tongue, thyroid, larynx, buccal space, and paravertebral space. The diagnosis is made based on characteristic light and electron microscopic findings. These tumors possess adenosine triphosphatase and neurosecretory granules suggesting possibly a myogenic and or neuroepithelial origin [342–344]. In addition, immunocytochemical studies overwhelmingly support a myogenic origin [345, 346]. These tumors are associated with chromosomal translocations of t(X;17) on chromosome band 17q25 leading to ASPL-TFE3 fusion protein [327]. These tumors are slow growing and 80 % of children are alive 2 years after diagnosis. Most patients, however, eventually die of the disease. Alveolar soft parts sarcoma in younger children and those arising in the head and neck have a better prognosis. Treatment is with wide local excision. Because these sarcomas are very slow growing tumors, radiation and chemotherapy are reserved for recurrent and distant disease.

Parathyroid Tumors

The parathyroid glands develop at the beginning of the fifth week of gestation in the dorsal portion of the third and fourth pharyngeal pouches. During the sixth week of development, the superior parathyroids arise from the fourth pharyngeal pouch and migrate cephalad and superior. The inferior parathyroid glands arise from the third pair of pharyngeal pouches and migrate inferior and dorsal. Lesions of the parathyroid gland are typically noted in adolescent females and are detected during workup for hypercalcemia. There are many causes of hypercalcemia in children including hyperparathyroidism, sarcoidosis, fat necrosis, familial hypocalciuric hypercalcemia, idiopathic hypercalcemia of infancy, thyrotoxicosis, hypervitaminosis A, hypophosphatasia, prolonged immobilization, and thiazide diuretics to name a few. Hyperparathyroidism may be caused by adenomas or diffuse hyperplasia. Parathyroid carcinoma is extremely rare in this age group. Hyperparathyroidism of infancy is often severe and can be fatal. Half of these patients have a familial component. On pathology, these patients have diffuse hyperplasia. Early treatment is critical for survival.

Patients noted to have hyperparathyroidism need to have calcium levels, PTH levels, and urine calcium measure. Ultrasound of the neck is needed to help localize the lesion. 99T sestamibi scans are 87 % sensitive in preoperative localization of parathyroid adenomas. When ultrasound is combined with sestamibi scan, the sensitivity increases to 96 % [347, 348]. When a solitary adenoma is identified, an excision of the identified adenoma may be performed. Intraoperative PTH (parathyroid hormone) monitoring is needed in order to ensure complete treatment of patients' hyperparathyroidism. A preoperative PTH, 5 min PTH, and 10–15 min PTH should be obtained. A 50 % drop in PTH level should be noted within 10–15 min [349, 350]. If a 50 % drop is note noted, further neck exploration is needed. For patients with parathyroid hyperplasia, a 3.5 gland parathyroidectomy or total thyroidectomy with autotransplant should be performed. Hyperplasia is a feature of patients with MEN syndromes.

Secondary hyperparathyroidism occurs secondary to renal insufficiency or malabsorption. PTH is increased in response to decreased calcium. The treatment of secondary hyperparathyroidism is medical management, though if severe renal osteodystrophy develops, total parathyroidectomy with autotransplantation may be needed. Tertiary hyperparathyroidism is a persistent hyperfunctioning of the parathyroid gland even after inciting stimulus has been removed. This is specifically seen in patients after renal transplant who had chronic renal failure and secondary hyperparathyroidism. These patients have hyperplasia of all four glands may need total parathyroidectomy with autotransplantation if unresponsive to medical management.

Germ Cell Tumors

Germ cell tumors account for about 3 % of neoplasms in children with an incidence of four per million children [351]. Of the germ cells tumors that occur, only 5–10 % occur in the extracranial head and neck region. In general 25–35 % of all germ cell tumors are malignant, though malignant germ tumors of the head and neck are rare [352–354]. Germ cell tumors arise from primitive germ cells and are characterized histologically by the presence of mature tissue from all three germ cell layers. The most common histologic features include skin and cutaneous appendages, adipose tissue, cystic structures and intestinal epithelium. Mature and immature tissue elements are commonly seen in neonatal cervical teratomas.

The majority of cervical germ cell tumors are congenital and present at birth or in early infancy and can be diagnosed by prenatal ultrasound. The anterior lateral neck is the most common site of occurrence though they have also been reported in the pharynx, nasopharynx, paranasal sinuses, skull, and orbit [352, 355–360]. Large congenital lesions may obstruct the pharynx and produce maternal polyhydramnios or non-immune fetal hydrops [353, 354, 359]. Following birth, obstructing tumors produce respiratory distress and dysphagia and may require intubation and emergency surgical tracheostomy. Life threatening airway obstruction has been reported in up to 35 % of cases [352]. These cases may benefit from an EXIT procedure (EX utero Intrapartum Treatment) or OOPS procedure (Operation On Placental Support) at birth to prevent anoxia [361]. Prior to surgical excision proper CT/MRI imaging is important to assess the precise anatomy of the tumor and proximity to

vital structures. Resection may be difficult due to location. If these teratomas recur, reexcision is recommended. Although rare in the cervical region, pure yolk sac tumors (endodermal sinus tumors) or mixed tumors with yolk sac elements behave as malignant tumors and metastases, particularly pulmonary metastasis, from congenital teratomas have been reported [356, 362–364]. There are also reports of mature teratoma of the neck with malignant transformation after incomplete resection [365]. Close followup of these patients is required.

Cervical endodermal sinus tumors have been reported. Serum alpha-fetoprotein levels may be elevated in head and neck tumors with endodermal sinus elements [353, 356, 366]. Excision of benign teratomas results in cure. Malignant lesions are treated with surgical resection if possible followed by a multidrug chemotherapy. Patients with unresectable tumors or residual disease may receive irradiation to the primary tumor site. Most patients initially respond to therapy and estimates of long-term disease free survival in children with unresectable germ cell tumors is around 50 % [365, 367].

Salivary Gland Tumors

Benign and malignant tumors of the salivary glands are rare in children; however when they do occur, the parotid gland is the most common site accounting for approximately 90 % of the cases. Unlike adult salivary gland tumors, pediatric salivary gland tumors have an increased risk of malignancy between 29 and 50 % in various studies [368–370]. Malignant salivary gland tumors are most common in older children and adolescents with a mean age of 13 years [371]. There is a slight female predominance [372–375]. Histologically, salivary neoplasms in children are similar to those seen in adults. The pleomorphic adenoma is the most common benign neoplasm and mucoepidermoid carcinoma the most common salivary gland malignancy [372, 376, 377]. Mucoepidermoid carcinoma (MEC) consists of dermoid and mucus-containing cells. Children tend to present with low or intermediate grade tumors [374]. Low-grade tumors had a decreased rate of recurrence and nodal metastases. It has been suggested that certain tumor makers, specifically PCNA and KI-67 may be linked to high grade MEC though other reviews have not suggested this is not the case [375, 378]. These tumors have been found in children previously treated for childhood cancer with chemotherapy and radiation. Other types of salivary gland tumors include low-grade acinic cell carcinoma, undifferentiated carcinoma, adenocarcinoma, adenoid cystic carcinoma, peripheral neuroectodermal, and malignant mixed tumors all of which occur less commonly [376].

The most common presenting sign in children is a firm preauricular mass. Signs particularly concerning for malignancy are rapid growth, facial weakness or pain and associated lymphadenopathy. Ultrasound, sialogram and CT scan should investigate a swollen parotid gland not suggestive of acute inflammation [379]. A simple hemangioma or lymphangioma should be treated by surgical excision. A pleomorphic adenoma requires a superficial parotidectomy to avoid recurrence. Mucoepidermoid carcinoma requires a total parotidectomy since even well differentiated tumors extend beyond the resection margins. For the soft tissue sarcomas, frozen section allows surface markers, cytogenetic studies and electron microscopy and they are treated appropriately according to the sarcoma or lymphoma protocols as mentioned above.

All firm salivary gland masses should be biopsied [379]. While fine needle aspiration has been used with success in adults, its role in children has not been determined. Incisional biopsy of the parotid gland should be avoided due to the risk of injuring the facial nerve. The only indication for incisional biopsy is for histologic diagnosis of large, unresectable tumors (Fig. 24.15a–d). Superficial or total parotidectomy with preservation of the facial nerve or total excision of the submandibular gland should be the initial procedure. Lymph node dissection is recommended for malignant lesions. Lymphatic metastasis has been report in 37 % of pediatric patients with salivary gland malignancies though only 6 % were noted to have metastatic lymphadenopathy at presentation [376].

In general superficial or total parotidectomy with preservation of the facial nerve is the recommended surgical treatment for salivary gland tumors [380]. Adjuvant radiation can be used for local control of high-grade, high stage tumors or for adenoid cystic carcinoma which are difficult to treat with surgery alone though adjuvant radiation has not been shown benefit long term outcomes [381–383]. Chemotherapy has been used in cases of high-grade or unresectable lesions though its long-term benefits are unknown. The prognosis for low-grade mucoepidermoid carcinoma, acinic cell carcinoma and well-differentiated adenocarcinoma is good, whereas high-grade mucoepidermoid carcinoma, poorly differentiated adenocarcinoma, and undifferentiated tumors do poorly. Mucoepidermoid and acinic cell carcinomas have a 5-year survival of greater than 90 % [384–386]. Survival is related to age with a 50 % 5-year survival in patient 1–4 years old while 95–97 % in patients 10–19 years of age [387].

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC) is rare in childhood with an annual incidence of 0.5 per million children. Approximately 10 % of the cases in the US are in children under the age of 16 [388]. It is slightly more common in males and teenagers of African-American descent [389, 390]. Geographically it is more common in China, southeast Asia, the Mediterranean, and Alaska. This geographic

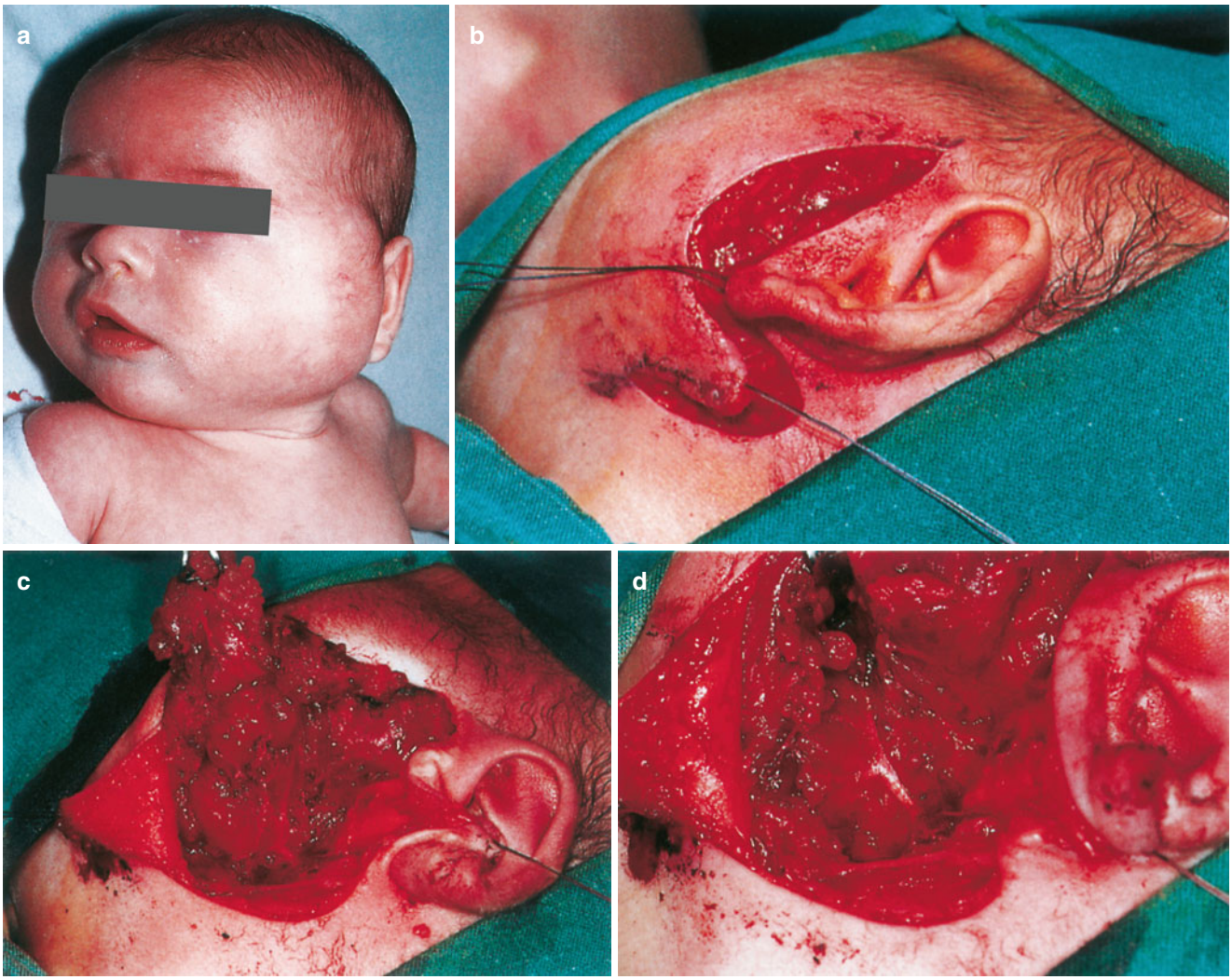

Fig. 24.15 (**a**) Vascular parotid tumor. (**b**) Incision used for exploration. (**c**) Superficial excision of parotid lobe. (**d**) Bed of the tumor showing the intact facial nerve

variation is thought to be due to both genetic and environmental factors. The two different histopathologic variants are squamous cell and undifferentiated carcinoma. Undifferentiated nasopharyngeal carcinoma, also known as lymphoepithelioma, is most common in children and is associated with EBV exposure [391]. NPC is also known to be associated with certain human leukocyte antigens including HLA A2 Bsin2 haplotype, Aw19, Bw46, and B17 [392, 393]. Cytogenetics have linked NPC with inactivation of p53, retinoblastoma (RB2/p130) tumors suppressor genes, and CYP2E1 [393–397].

The most common presenting symptom is a painless neck mass although a child may also have earache, tinnitus, deafness, otalgia, nasal obstruction and epistaxis. At presentation, most children already have metastatic spread to cervical lymph nodes [398]. Auditory symptoms are often the result of persistent middle ear effusion that may have been present for many months prior to diagnosis of nasopharyngeal cancer. As the cancer invades the base of the skull, cranial nerve palsies and head pain may result. Children may also complain of double vision, eye pain, loss of vision, difficulty swallowing, or hoarseness [392, 393, 399, 400]. Sites of distant metastasis include bone, lung, liver, bone marrow and mediastinum [392, 393, 401]. Factors that influenced outcome included age, race, stage, and histologic type [402].

Initial laboratory data should include a complete blood count, serum chemistry, liver function tests and lactic acid dehydrogenase. Elevated LDH levels have been correlated with poor outcomes. Viral capsid antigen IgA and ZEBRA protein concentration should also be measured for baseline tumor markers. Nasopharyngeal examination and biopsy is performed for diagnosis. For diagnosis and staging a CT scan and MRI are useful [403]. MRI is considered better for assessing extent of primary tumor and perineural invasion

while CT is better for detecting bone involvement. PET/CT and MRI are being used more in the pediatric population to further clarify lesions, assess response to therapy and follow-up these patients [404]. In addition, chest x-rays, CT of the chest and abdomen and radionuclide bone scanning should be performed to evaluate for metastatic disease. Bone marrow biopsy and a lumbar puncture should be performed if there is concern for advanced disease.

Undifferentiated nasopharyngeal carcinoma is radiosensitive and responds well to radiotherapy. For metastatic or recurrent NPC, chemotherapy is combined with radiation therapy. Common chemotherapeutic agents include cisplatin, bleomycin, epirubicin, and fluorouracil. The addition of cisplatin based chemotherapy in addition to radiation has increased the overall 5 year survival of children with nasopharyngeal carcinoma approaches from 20–60 % to now 70–90 % [392, 393, 401, 403, 405–407] The NPC-2003-GPOH/DCOG trial assigned patient to neoadjuvant chemotherapy, radiochemotherapy and/or interferon beta. Chemotherapy consisted of cisplatin, 5-FU, and folinic acid with radiation dosing between 54 and 59 Gy with improved outcomes (92 % event free survival and 97 % overall survival at 30 months) [408]. While outcomes have improved, these patients must be followed closely for complication related to therapy including delayed growth, thyroid dysfunction, and second malignancies [402].

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Brain Tumors, Intraocular and Orbital Tumors

25

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In children, brain and spinal cord tumors account for approximately 25 % of all cancer (40–50 % of all pediatric solid tumors). Overall, they are second only to the leukemias in frequency [1, 2]. There have been reports of an increasing incidence of both adult and pediatric brain tumors which may, in part, be due to "detection bias" although some epidemiology groups suggest that the increases are real [3]. The annual incidence is approximately 2–5 cases per 100,000 (1 in 2500 children aged 0–16), which translates to approximately 300–400 new cases being diagnosed in the UK per year [4].

A wide variety of tumor types ranging from the highly malignant to the histologically benign is seen in the pediatric age range. However, prognosis depends not only on histological type but also on the location of the tumor with some low grade tumors (for example, craniopharyngiomas and hypothalamic gliomas) frequently resulting in severe morbidity or sometimes death. Although it is widely taught that infratentorial tumors are more common than supratentorial in the pediatric age group, it can be clearly seen from Table 25.1 that this ratio varies with age. Overall, there seems to be a slight preference for central nervous system (CNS) tumors in males – in particular in some of the more common tumor types – primitive neuroectodermal tumors (PNET), craniopharyngioma, brain stem glioma, ependymoma, and germ cell tumors arising in the pineal region [5] – the most striking sex preference being seen in relatively rare pituitary adenomas with a 7:1 male:female ratio [5].

For the majority of pediatric brain tumors no specific etiological agent or event can be found. Known risk factors include genetic syndromes (such as Neurofibromatosis I and II, basal cell naevus, tuberous sclerosis, Gorlin, Turcott, Li-Fraumeni, and von Hippel-Lindau), which account for 5 % of cases [6], and radiation exposure. Although there has been concern over exposure to low-level electromagnetic radiation (power lines) and from mobile phones, this association remains controversial [7].

The care of children with CNS tumors has probably changed more in the last 25 years than any other pediatric surgical group. This is due to changes at every stage of patient care:

1. Improvement in diagnostic techniques – computerized tomography (CT) in the 1970s, magnetic resonance imaging (MRI) in the 1980s, and functional imaging in the 1990s – with the ability to map eloquent cortex preoperatively (motor/sensory/visual/speech and memory). In addition, MR spectoroscopy can non-invasively shed light on the possible diagnosis of tumours.
2. Developments in neuroanesthesia (including intra and perioperative monitoring – including the use of "awake procedures" in those old enough to tolerate them). With the patient awake it is possible to map areas of eloquent cortex as well as to undertake sub-cortical mapping of white matter tracts.
3. Advances in surgery (including use of the operating microscope, the ultrasonic aspirator, stereotaxy, endoscopy, intraoperative functional mapping - including motor evoked potentials (MEPs) and somatosensory evoked potentials (SSEPS); – which allow for safer resection particularly of spinal cord and basal ganglia tumours).
4. Developments in adjuvant therapy (including both chemotherapy and radiotherapy, the use of multicenter trials, the recognition of the detrimental effects of radiotherapy on the developing CNS, the use of fractionated

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Table 25.1 Site of tumor by age

Age	% Infratentorial
0–6 months	27
6–12 months	53
12–24 months	74
2–16 years	42

From Greenberg [14], with permission

radiotherapy and stereotactic radiosurgery) and more recently the greater availability of Proton therapy;
5. Improvements in supportive services (physiotherapy; occupational and speech therapy; social, psychological, and educational support; palliative care).

From the surgical perspective, the result has been that a tissue diagnosis can virtually always be achieved regardless of the site and aggressive surgical removal of tumors can usually be attempted. Technology now available aims to use the detail of neuroimaging to help direct the surgeon during the operation. This "neuronavigation" relies on the surgeon registering the patient's head, which is then tracked by infrared cameras. Surgical instruments, fitted with light-emitting diodes, are also tracked as they come into the line of sight of the cameras. The workstation on which the preoperative imaging studies are held will then display where the instrument is within the head and its relationship to the tumor or target. The main drawback of neuronavigation is the fact that the information used is preoperative rather than real time. Intraoperative MRI units (where the patient's head is held within a small MRI magnet or where the operative layout includes a scanner within the operating theatre into which the patient is intermittently placed) are now available but it is yet to be shown that they are cost effective.

Another area of change in the last two decades has been the widespread use of immunohistochemical techniques to further classify poorly differentiated tumors. The World Health Organization (WHO) published a consensus document in 1979, updated in 1993 and again in 2000, giving a standardized reporting system. More recently, it has become clear that in the future CNS tumors may be classified by their molecular genetic profile. Molecular genetics is already important in helping to diagnose rhabdoid tumors/ATRTs (deletions or mutations of the gene hSNF5/INI1) [8], and is of prognostic and therapeutic value in the management of patients with oligodendrogliomas (1p/19q deletion being associated with prolonged survival and chemosensitivity in adults) [9].

Despite these advances, epidemiological data from the UK Childhood Cancer Research Group shows the overall 5 and 10-year survival rates to be approximately 55 % and 50 %, respectively, and there has been little change in the past 10 years. This is in contrast to the substantial rise in survival rates seen over this period in children with leukemia and non-CNS tumors [10]. This and the recent reporting of improved survival statistics on selected tumor subtypes (e.g., medulloblastoma) have emphasized the need for further collaborative studies. In particular it is hoped that the development of biologically directed therapies and the application of functional imaging to increase the safety and extent of surgical excision will result in significant improvements in outcome. In the last few years, trials in adults have shown significant improvements in survival duration in patients with malignant gliomas (using concomitant Temozolomide [11] or intratumoral chemotherapy [12]) and these results have been the first significant improvement in the management of these patients in the last 40 years. Phase III trials of a number of new agents (including gene therapy) are underway in adult patients – although methods of delivery (for example, convection-enhanced delivery) still need further refinement.

Phakomatoses

The phakomatoses (or neurocutaneous syndromes) are a group of conditions in which cutaneous stigmata are associated with CNS abnormalities or tumors. Although considered relatively rare, up to 10 % of all pediatric astrocytomas are associated with neurocutaneous syndromes [13]. Recognition of these syndromes is important as it may alter the indication and goals of surgery. Likewise, an understanding of the natural history and genetics of the disease is essential for dealing with both patient and family.

Neurofibromatoses

This group comprises by far and away the most common type of phakomatosis and the patients fall broadly into two subtypes – neurofibromatosis types 1 and 2 (NF1 and NF2). Previously, NF1 was known as von Recklinghausen's disease and this, with an incidence of approximately 1/3000 births, is responsible for more than 90 % of cases of neurofibromatosis. It shows an autosomal dominant inheritance with almost 100 % penetrance, but up to 50 % of cases represent spontaneous somatic mutations [14] with the gene responsible being located on chromosome 17. Optic pathway tumors are the most common type of tumor seen in NF1 but other low-grade gliomas and meningiomas are also seen. The incidence of CNS tumors is approximately 10 % [14–16].

Similarly, NF2 is also an autosomal dominant condition with the gene probably being on chromosome 22 [14]. The pathological signature of NF2 is the presence of bilateral acoustic neuromas. Although both NF1 and NF2 may be associated with multiple intradural spinal tumors, these are more common in NF2 than in NF1. Other non-CNS tumors also have

an increased frequency in NF2 (including neuroblastoma, sarcoma, leukemia, Wilms' tumor, and ganglioglioma) [14].

The subcutaneous neurofibroma are usually sessile in children but increase in size and in number with puberty and pregnancy and often become pedunculated. These tumors can undergo malignant degeneration in 2–29 % of patients (but usually during adult life) [17]. Congenital neurofibromas are often of the plexiform type with a propensity for the periorbital region where they may be progressive and very vascular. A further orbital problem is the characteristic dysplastic lesion seen in NF1 with sphenoid dysplasia leading to pulsatile exophthalmos, and indeed this may be the presenting sign of NF1 in an infant or young child [15].

Other skeletal lesions include congenital bowing of long bones and pseudoarthrosis, vertebral scalloping and scoliosis. Visual problems as a result of an anterior visual pathway tumor may be the first manifestation of NF1 in a young child and may be quite marked by the time medical attention is sought. As a general rule, tumors affecting the optic nerve tend to present at a slightly older age (early 20s) while chiasmatic tumors most often present in the first decade of life often in association with endocrine disturbance and hydrocephalus [18]. In contrast, the defining characteristic of NF2 is the presence of bilateral acoustic tumors, which usually present in adolescence [14, 16].

Another fundamental difference between NF1 and NF2 is the apparent disorganization of the CNS and the presence of hamartomas, heterotopias and low-grade neoplasms in NF1. Macrocephaly may be seen in three-quarters of patients with NF1 [19] and approximately one-third of NF1 patients are intellectually impaired, probably reflecting this widespread intrinsic cerebral disorganization. In addition, MRI scans frequently show areas of abnormal signal intensity but these remain of unknown significance. In contrast, the brains of patients with NF2 do not show this marked disorganization and cognitive function is usually normal.

Tuberous Sclerosis

Tuberous sclerosis (TS), also known as Bourneville's disease, is inherited as an autosomal dominant trait, although many cases are sporadic [16, 20, 21]. The prevalence is approximately 1/10,000 [20] and the disease usually declares itself in childhood with epilepsy and mental retardation. Non-CNS manifestations include "ash leaf spots," facial angiofibromas ("adenoma sebaceum"), café-au-lait spots, shagreen patches (subependymal fibrosis), subungual fibromas, retinal hamartomas, honeycomb lungs, angiomyolipomas of the kidneys, and cardiac rhabdomyomas. In the CNS there are multiple benign hamartomatous lesions which occur in the lining of the lateral and third ventricles (subependymal nodules) and cortical nodules ("tubers").

The characteristic brain tumor in TS is the subependymal giant cell astrocytomat (SEGA), which is believed to arise from subependymal nodules and nearly always occurs at the Foramen of Monro (Fig. 25.1a, b). The sites of these tumors frequently result in obstructive hydrocephalus, which is the usual cause of presentation. The reported incidence of SEGAs ranges from 7 to 23 % [22]. Pathologically, these are usually low grade giant cell astrocytomas which are benign and therefore the aim of surgery is to establish free communication of the cerebrospinal fluid (CSF) pathways rather than necessarily a total resection, which may be difficult to achieve. Surgery may also be considered for intractable epilepsy if it can be shown that one of the tubers or an abnormal area of brain around the tuber is acting as a focus. More recently the use of Everolimus, a drug which inhibits the mammalian target of rapamycin (a protein regulated by gene products involved in the tuberous sclerosis complex) has been used with some success. However, the role of this targeted drug in TS is not yet defined for treatment of either the epilepsy related to the tubers or for the treatment of an associated SEGA. For the latter, it may well be that Everlimus is useful in decreasing the size and vascularity of the SEGA prior to surgical intervention.

Von Hippel-Lindau Disease

This syndrome consists of CNS hemangioblastomas (usually cerebellar but may be spinal and occasionally supratentorial), in association with angiomatosis retinae, cysts/tumors in various organs and polycythemia [16]. This disease usually presents in adulthood and has an autosomal dominant trait with variable penetrance and a positive family history is only seen in approximately 20 % of cases. The diagnosis is made by the presence of two or more separate characteristic lesions or a single lesion with a positive family history. The most common associated lesions are pheochromocytomas and renal cysts/tumors (renal cell carcinoma being present in approximately 30 % of patients) [16]. Adenomas are also seen in the pancreas, liver, spleen, lung, epididymis and ovaries. The CNS tumors may be multiple and on imaging are usually cystic with a strongly enhancing mural nodule. At surgery, the tumors are highly vascular but usually well demarcated.

Posterior Fossa Tumors

Tumors in this region fall into two distinct groups those arising from the cerebellar hemispheres or the fourth ventricle, and those arising from the brain stem itself. These two distinct groups have different clinical presentations and surgical goals and will therefore be discussed separately.

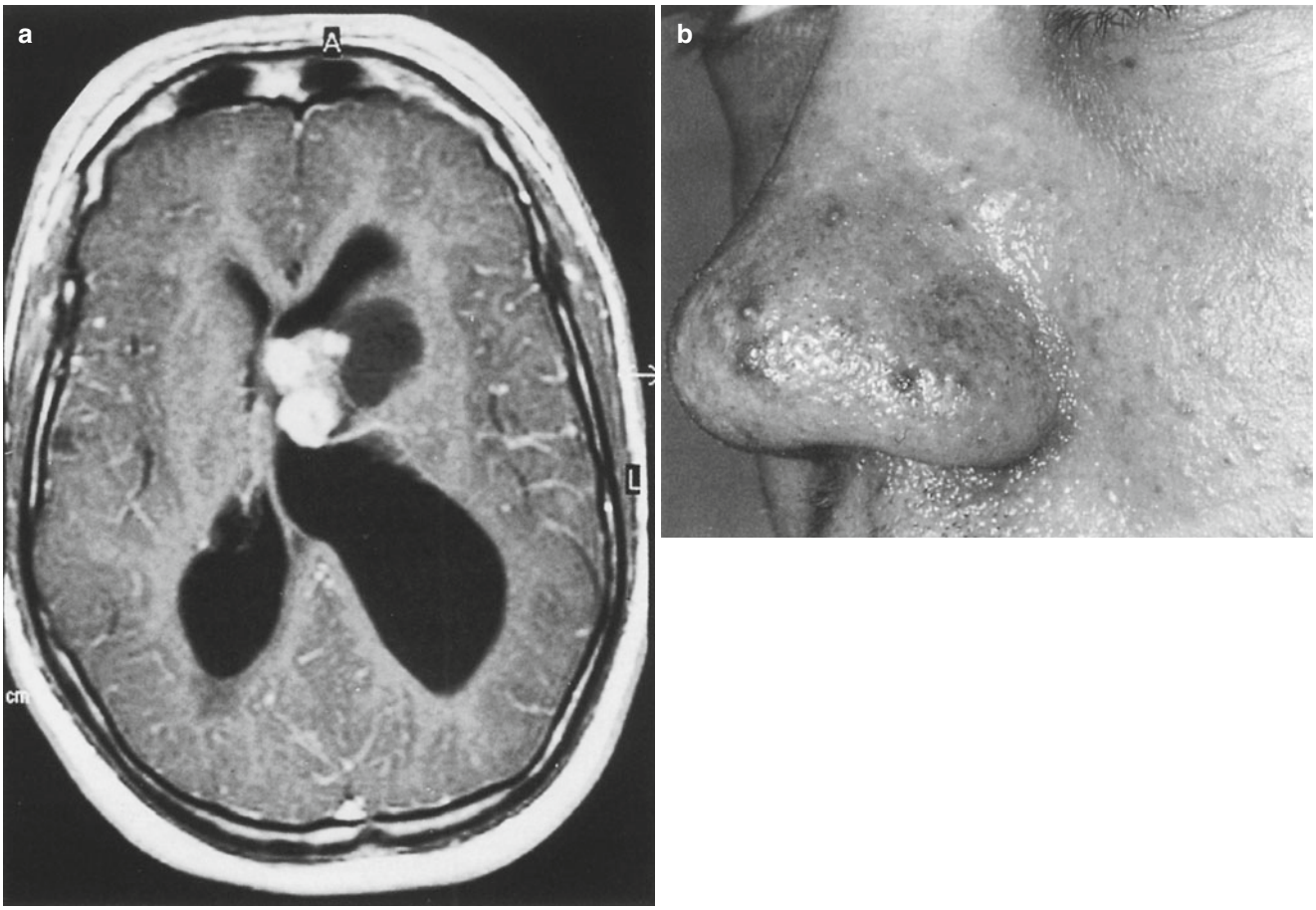

Fig. 25.1 (**a**) Axial T1-weighted MRI with gadolinium showing a giant cell astrocytoma at the Foramen of Monro in an adolescent patient with tuberous sclerosis. (**b**) The classical facial angiofibromas (adenoma sebaceum) of tuberous sclerosis

"Cerebellar" Tumors

Within this group of tumors are included cerebellar astrocytomas, medulloblastomas, and ependymomas. Cranial nerve tumors (for example, acoustic neuromas or 5th nerve tumors) will not be discussed due to their relative rarity in children.

As a group, these tumors usually present once they are large enough to cause hydrocephalus by blocking off the outflow of the fourth ventricle. The duration of symptoms rather than type of symptoms correlate with tumor type. Young children, in whom the sutures have not fused, may present with macrocrania, vomiting, and irritability. In older children headache, classically in the morning, and nausea and vomiting are the usual symptoms. It is not infrequent for patients to have been investigated for gastrointestinal problems prior to having a head scan which shows a tumor. If the cerebellar tonsils have been impacted into the foramen magnum, there may be neck pain or head tilt or even opisthotonus. Clinical examination may reveal papilloedema, a 6th nerve palsy (a false localizing sign due to the hydrocephalus) and by the time patient presents there is normally a degree of ataxia and past pointing. If the hydrocephalus is left untreated, the patient will eventually become comatosed.

From a surgical management point of view, there are two main problems: treatment of the hydrocephalus and surgical removal of the tumor. Although historically there was a vogue to insert ventriculoperitoneal shunts into all these patients prior to tumor removal, with the widespread availability of CT and MR scanning these children have tended to present earlier and the usual practice today is to commence dexamethasone and perform early surgery. If required, an external ventricular drain may be inserted either prior to surgery or at the time of surgery. Alternatively, it is possible to treat the obstructive hydrocephalus (either pre or post-tumour removal) by means of an endoscopic third ventriculostomy (ETV). This procedure basically creates an internal diversion of the CSF in order to bypass the obstruction – by making a hole in the floor of the III ventricle. In the setting of a patient over 1 year of age with obstructive hydrocephalus, the success rate for an ETV is of the order of 70–80 %. Each tumor type will now be dealt with individually.

Cerebellar Astrocytomas

Cerebellar astrocytomas are virtually always of the low-grade (pilocytic) type in children. This tumor type makes up approximately one-third of childhood posterior fossa tumors [23] with patients being slightly older than those with the malignant posterior fossa tumors. Grossly, these tumors are found to lie either in the cerebellar hemisphere or may involve the midline (vermis). They are either cystic (70 %) with a mural nodule or a solid mass (22 %) with multiple cystic areas [24]. Although well demarcated, areas where it may be difficult to obtain a complete removal include extension through the cerebellar peduncles into the brain stem (brain stem invasion being reported in 8 % of cases) [24] or when tumor is found high in the tentorial notch towards the vein of Galen. The microscopic features of these tumors are characteristic with a biphasic pattern of dense and compact areas with elongated (pilocytic cells) that alternate with loose areas containing stellate astrocytes and microcysts [24]. The cells may contain intracytoplasmic eosinophilic inclusions termed Rosenthal bodies. Vascular proliferation may be seen in cerebellar astrocytomas and unlike other gliomas, this does not indicate a more aggressive behavior of the tumor. Calcification may also be seen in these tumors.

On CT scan, hydrocephalus is often present and in the posterior fossa the classical finding is of a cystic tumor with an enhancing nodule. The tumor is iso or hypodense on noncontrasted scans. Occasionally, the cyst wall itself enhances and looks thickened and in these cases, surgical excision of the wall is indicated as it will consist of tumor. However, if the cyst wall does not enhance, then at the time of surgery a thin cyst consisting of gliotic tissue rather than tumor is found. The solid type of tumors can be difficult to differentiate from ependymomas or medulloblastomas. The differential diagnosis of the cystic astrocytoma is with a cystic hemangioblastoma – but the latter are exceptionally rare in the pediatric age group. Today, MRI scanning is usually also obtained as this helps with surgical planning. Cerebellar astrocytomas are usually isoor hypointense on T1-weighted images and hyperintense on T2-weighted images. Additionally, the MRI will often show on the sagittal plane that the tonsils have herniated through the foramen magnum (Fig. 25.2).

The goal of surgery in these patients is total removal of tumor as this is an important prognostic factor. Additionally, if total surgical excision has been performed then no further adjuvant therapy, specifically radiation, is needed [25]. Garcia et al. reviewed 80 children with cerebellar astrocytoma and the recurrence rate was 2.5 % for patients with total removal and 3.5 % for patients who had a subtotal removal. Interestingly, radiation did not affect the outcome of patients who had a subtotal excision [25]. Nonetheless, subtotal resection is compatible with long-term survival [26, 27]. From the Garcia study, the 5-, 10-, and 25-year disease-free survival rates were 92 %, 88 %, and 88 % respectively.

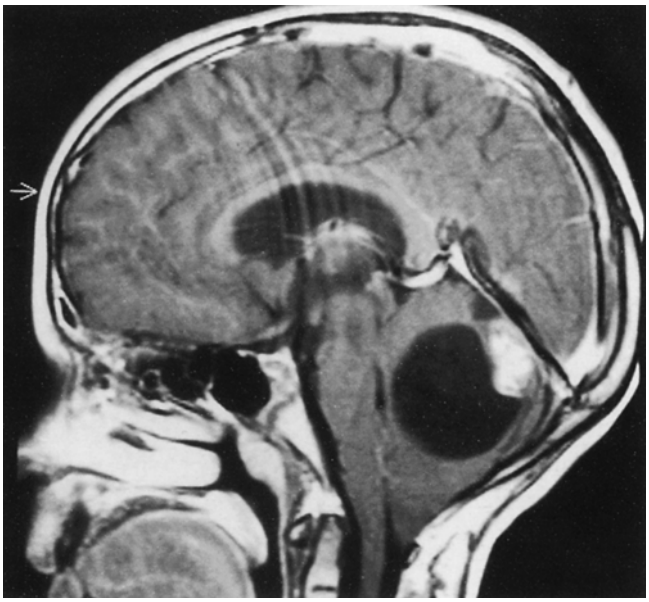

Fig. 25.2 Sagittal T1-weighted MRI with gadolinium showing a large posterior fossa cyst with an enhancing nodule characteristic of a pilocystic astrocytoma. Note that the cerebellar tonsils have herniated through the foramen magnum

There are, however, case reports of recurrence after 36 years [28] and occasionally, malignant change is seen in the recurrence. For these reasons these patients require long-term follow-up, with intermittent scanning. Nonsurgical treatment includes radiation or chemotherapy and is only recommended when there is a recurrence and further surgical excision is not feasible, and/or if the recurrent tumor has a malignant histology [29].

Medulloblastoma

Medulloblastomas were first described in 1925 by Bailey and Cushing, who suggested that these tumors were derived from a primitive pluripotent cell called the medulloblast. This putative cell has never been found but the name has now become entrenched in the neurosurgical literature. More recently, it has been recognized that the medulloblastoma should be classified under the heading of Primative Neuroectodermal Tumor (PNET). Medulloblastoma is the most common malignant CNS tumor in childhood comprising 15–20 % of childhood brain tumors [30] and make up approximately one-third of all posterior fossa tumors in childhood. The peak incidence is between the ages of 3 and 8 years – being slightly younger than the pilocytic astrocytoma age range. However, these tumors may occur in the infancy and are occasionally seen in adults.

Medulloblastomas are most commonly found in the region of the fourth ventricle arising within the vermis. The tumors are reddish in color, friable and frequently vascular. A “desmoplastic” variant has been described which is char-

acterized as being firm and well demarcated but this tends to occur in older children and adults. Recent evidence suggests that this subtype carries a better prognosis compared to classical medulloblastomas [31]. In contrast, large-cell medulloblastoma has been recognized as a distinct subtype which is associated with a poor prognosis [32].

A characteristic of medulloblastoma is the ability to spread via the CSF pathways into the spinal ("drop metastases") or cerebral subarachnoid spaces or within the ventricles. Such dissemination maybe diffuse or nodular and it is reported that 20–30 % of patients with medulloblastoma have seeded within the craniospinal axis at the time of diagnosis [30]. Extraneural metastases are seen in 5 % of patients [2] and this rate of extraneural deposition does not appear to be altered by the use of a (millipore) filter in association with a ventriculoperitoneal shunt.

Histologically, the classic medulloblastoma is composed of densely packed small cells with hyperchromatic nuclei and very little cytoplasm. There are frequent mitoses and rosettes of the Homer-Wright type are seen in about 20 % of cases. Over the last decade cytogenetic and molecular studies have shown that isolated 17p loss and elevated expression of erbB2 and c-myc are associated with a poor prognosis [33].

On CT scanning, medulloblastoma appears as a well-marginated, homogeneously hyperdense mass arising from the vermis and filling the fourth ventricle. The mass typically enhances with contrast and calcification is seen in approximately 15 % of cases [30]. Mild to moderate edema is common around the tumor and hydrocephalus is present in 95 % of patients [30]. The investigation of choice in all posterior fossa lesions is MRI as it gives far better definition and resolution. The tumors are usually hypodense on T1-weighted images and on T2-weighted images but enhancement is still the rule after gadolinium has been injected (Fig. 25.3a, b); MRI is also superior in picking up subarachnoid seeding and spinal metastases.

The aim of surgery is gross total resection but in approximately one-third of cases a medulloblastoma infiltrates the dorsal brain stem and this precludes total removal [34]. These tumors usually require a long incision in the vermis and this may result in transient truncal ataxia and dysconjugate gaze, which usually resolves over a couple of weeks. In patients in whom the tumor has involved the cerebellar peduncle, there may be long-standing ipsilateral dysmetria. Occasionally, patients will suffer with cerebellar mutism, which is poorly understood but tends to resolve over a matter of weeks.

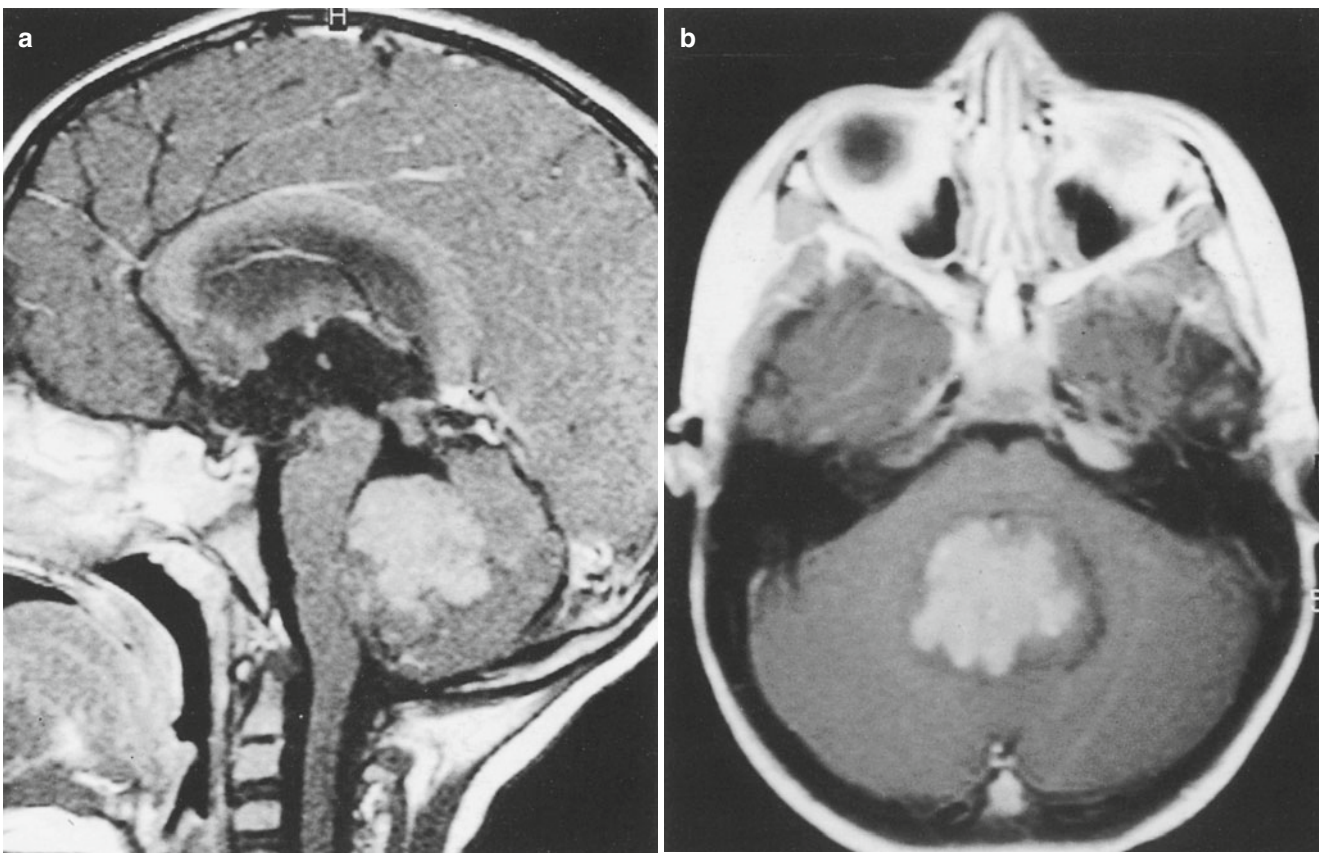

Fig. 25.3 (**a**) Sagittal and (**b**) axial T1-weighted MRI with gadolinium showing a large posterior fossa tumor in the fourth ventricle with variable uptake of contrast. Histologically verified as a medulloblastoma

Prognostic Factors

1. Extent of Surgical Resection. Differing definitions and surgical impressions have made this area fraught when trying to undertake comparative studies. It is now generally accepted that a gross total resection is one at which the surgeon feels there is no tumor left and an early CT or MRI examination with and without contrast fails to show any tumor deposit. A subtotal resection is one in which a small amount of tumor is known to have been left by the surgeon or if a postoperative scan shows a small lump of enhancing tissue in the operative bed (<1.5 cm^2). Using these strict criteria, there does not appear to be a significant difference in outcome between the two groups [30]. In comparison, patients with a partial excision (>1.5 cm^2) or a biopsy alone fare far worse [30].
2. Size/Dissemination. The Chang staging system has been widely employed for many years and characterizes medulloblastoma by tumor size (T stage T1 to T4) and the presence or absence of metastases (M0 to M4). More recently, it has become apparent that preoperative tumor size per se is of no predictive value [30]. However, the presence or absence of dissemination at the time of diagnosis is the most significant factor in predicting the survival of patients with medulloblastoma. It is therefore essential to arrange a preoperative staging spinal MRI. Furthermore, in order to detect M1 disease (malignant cells identified in the CSF) an LP for cytology should be carried out 10–14 days after the posterior fossa surgery.
3. Age. Probably for multifactorial reasons, younger children fare less well than older children with medulloblastoma (Table 25.1). Younger children are more likely to have disseminated disease at the time of diagnosis and younger patients are less likely to receive aggressive treatment due to the adverse effects of radiotherapy.
4. Histology and Molecular Genetics
   Using these three main criteria (gross total/subtotal versus partial/biopsy; <3 years of age versus >3 years of age; no dissemination versus dissemination) patients with medulloblastoma have been subdivided into "average risk" and "high risk" by the American Children's Oncology Group (COG). It can be estimated that for the poorest group, overall survival is approximately 36 % at 5 years with standard postoperative craniospinal axis irradiation, versus 60–80 % for children without adverse risk factors [30, 35].

Adjuvant Therapy. It is quite clear from the literature that medulloblastomas are highly radiosensitive. However, follow-up studies have shown that radio therapy at a young age may have a devastating effect on final neuro and cognitive development. These cognitive sequelae are dependent on age at treatment and dose and field of irradiation given [30, 36]. Thus although the "standard" dose of radiation given to patients with medulloblastoma is 5500 cGy with a dose of 3600 cGy to the neuraxis [30, 37], it is obvious that these dosages are unacceptable to the immature brain and therefore trials have been undertaken using chemotherapeutic agents to see if it is possible to withhold radiation either temporarily or permanently in very young children [38]. In children older than 3 years the addition of chemotherapy to the standard treatment of surgery and radiotherapy has a resulted in improved survival, even in association with reduced radiotherapy dose to the craniospinal axis [35]. Further clinical trials looking at both survival and quality of survival, while employing lower doses of radiotherapy, are underway. Other areas of research interest include the use of hyperfractionated radiation and of stereotactic radiosurgery for small deposits/recurrences [39].

Endocrine dysfunction is another common problem after radiotherapy [40] with hypothyroidism and growth failure being the most common deficiencies. While the use of growth hormone is beneficial, the final height attained is significantly less than the midparental height [41]. Cushingoid appearance associated with the use of steroids is another common problem during treatment.

Medulloblastoma is clearly a chemosensitive tumor, as demonstrated in numerous phase I and II studies carried out at disease relapse [42, 43]. Chemotherapy has also been used as an adjuvant in medulloblastoma therapy for many years. Studies of chemotherapy given after surgery and before radiotherapy ("sandwich chemotherapy") have shown a survival advantage of 14 % at 5 years in patients who received chemotherapy [44]. Standard therapy is, however, to give chemotherapy after completion of radiotherapy as described by Roger Packer and survival is now more than 80 % at 5 years [35]. For various reasons – ranging from earlier diagnosis, to better anesthetic and surgical technique and the use of adjuvant therapy – medulloblastomas are one of the few CNS tumors in which there has been a significant improvement in 5-year survival over the last 20–30 years. At present, 5-year survival rates in the range of 70–80 % are to be expected [30, 35, 45].

Ependymoma

Ependymomas are rare tumors accounting for 6–12 % of brain tumors in childhood (30–35 new cases per year in the UK) [46]. Although they may be found throughout the CNS in children, 70 % of ependymomas occur in the posterior fossa [47]. Half of these tumors present in pre-school children and the posterior fossa tumors occupy the fourth ventricle and extend through the outlets of the fourth ventricle into the cerebellar pontine angles and down over the cervical medullary junction. On CT, the ependymoma is usually

either isoor hyperdense and may show calcification. Enhancement after contrast is variable. Often MRI with its better definition shows more clearly the spread of the tumor over the cervical canal or out of the Foraminae of Luschka (Fig. 25.4). In the preoperative work-up, it is important that a spinal MRI is performed to look for spinal drop deposits.

Histologically, ependymomas are composed of well differentiated cells which are often arranged around blood vessels forming perivascular rosettes. These tumors vary from being well differentiated through to having anaplastic features with high cellularity, pleomorphism, necrosis, and high mitotic activity. However, the significance of the histological changes is yet to be verified as there is only a tendency towards worse prognosis with increasing anaplasia [48]. Until recently, reviews in the literature included the highly malignant ependymoblastoma in the anaplastic group and this adversely skewed the survival curve for these children. The ependymoblastoma is now considered to be an embryonal tumor (a variant of the PNET) [49].

With the ependymoblastoma removed from the heading of anaplastic ependymoma, the survival curves are not dramatically different from those showing more low-grade histological features.

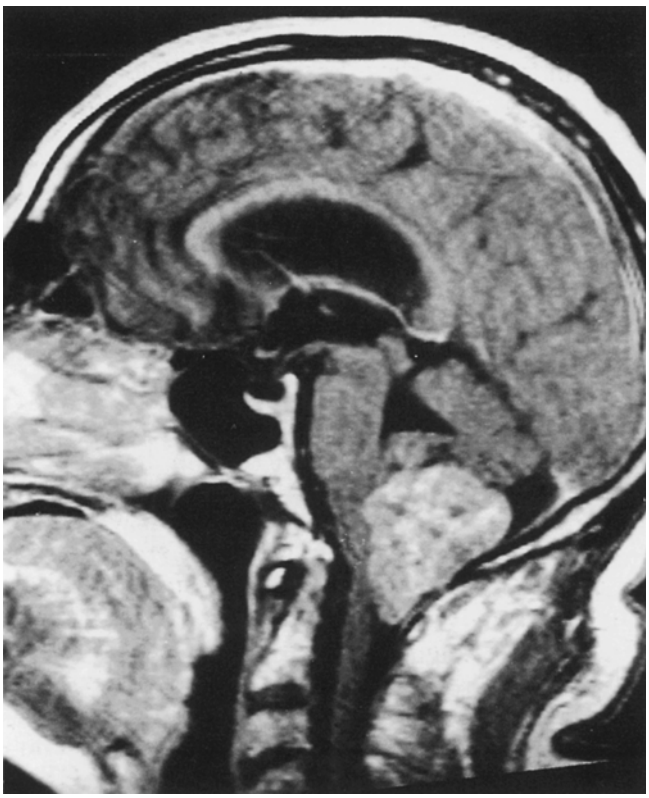

Fig. 25.4 Sagittal T1-weighted MRI with gadolinium showing a large enhancing posterior fossa tumor which has involved the herniated cerebellar tonsils

At the time of surgery, approximately 10–25 % of posterior fossa ependymomas are found to be invading the floor of the fourth ventricle [47, 50]. As with medulloblastomas, the aim of surgery is maximum possible resection without causing neurological deficit. However, due to the frequent extension to the cerebellar pontine (CP) angle, there is a higher incidence of lower cranial nerve palsies after resection. Due to this combination of brain stem invasion and CP angle involvement, the rate of complete resection is relatively low. Recent single institution retrospective studies have emphasized the importance of obtaining gross total removal with 10-year survival rates of over 70 % in patients with radiological confirmation of gross surgical removal [51, 52]. This is to be compared with the 30 % 5-year survival rate usually quoted for this disease [53]. A multivariate analysis of prognostic factors identified complete resection as the most favorable prognostic factor [54]. This importance of complete resection has led to the concept of second look surgery, after treatment with chemotherapy, to allow removal of any residual tumor.

Postoperatively, patients should be imaged within 48 h looking for residual tumor. In the absence of dissemination, radiotherapy is given (5400 cGy to the tumor bed), with spinal radiation only being given to those patients with proven deposits. Results from trials using hyperfractionated and conformal radiotherapy are awaited. In an attempt to avoid radiotherapy in young children various chemotherapeutic trials have been undertaken. There is now evidence that some children can have long-term remission with chemotherapy alone [55] although some children still suffer late recurrences. The approach is still worthwhile in this situation as the chemotherapy can result in very significant delays in the requirement for radiotherapy [56].

Brain Stem Tumors

It is only really since the advent of CT and perhaps even more importantly MRI that the true heterogeneity of this group of tumors has been understood. The classification used here is that based on Abbott et al. [56] and it has allowed for a rational approach to this diverse group of tumors. This has meant that some patients are not subject to any surgical procedures while others are treated aggressively as the underlying tumor may well be benign. The clinical presentation is also somewhat variable and will be discussed with each tumor type.

Diffuse Pontine Glioma

Unfortunately, this is the majority of brain stem tumors (comprising 60–70 % of the New York series) [57]. It was this tumor group with its dismal prognosis that all patients were assumed to have prior to the advent of modern imaging.

The patients present with a short history of ataxia and multiple cranial nerve dysfunction. An MRI scan demonstrates an expanded pons which is hypointense on T1 images (Fig. 25.5a, b). However, the extent of tumor involvement is best appreciated on T2 imaging with the tumor having a hyperintense signal. Enhancement is variable and hydrocephalus is not usually apparent. No treatment has been shown to be effective, with a median survival of 9 months [58]. Radiation has been shown to have a palliative effect and to increase the duration of survival. To date, chemotherapy trials have also failed to demonstrate efficacy but more aggressive regimens and biological "new agents" are currently being evaluated. With the classical MRI picture and clinical history, it is generally agreed that submitting these children to a biopsy is not warranted for diagnosis, although biopsy to obtain tissue for biological studies may be necessary if newer molecular treatments are being considered.

Focal Tumors

These tumors may arise anywhere within the brain stem and may even be partially exophytic into the CSF spaces. These patients usually have histories going back many months or years, and focal neurological signs. The solid portion of these tumors typically enhances with gadolinium. In the presence of progressive symptoms, surgical debulking of these tumors is a feasible option as the histology is usually of a low-grade astrocytoma. Radiotherapy is not indicated and it is feasible to re-operate on these focal tumors to achieve a complete resection. A subset of these focal tumors is the tectal gliomas, which not infrequently will have been initially "misdiagnosed" as a congenital aqueduct stenosis. These tectal gliomas will frequently show calcification on CT scans [59]. These tumors would seem to have a very benign course and can usually be watched with serial imaging (Fig. 25.6).

Exophytic Tumors

These tumors arise from the subependymal glial tissue and fungate into the fourth ventricle [57] with more than 90 % of the tumor residing within the ventricular system. The clinical history is long but because of the potential to cause hydrocephalus, patients with these tumors may present with raised intracranial pressure. Additionally, the site of the tumor may result in intractable vomiting, "failure to thrive" [60], ataxia, and nystagmus. On imaging alone, it can be difficult to differentiate these tumors from medulloblastomas or astrocytomas of the vermis. However, in general, these tumors tend to be isointense and tend to enhance with gadolinium on MRI (Fig. 25.7). The aim of surgery is to shave the tumor flush with the surrounding floor of the fourth ventricle but not to advance ventral to this plain. These tumors are usually

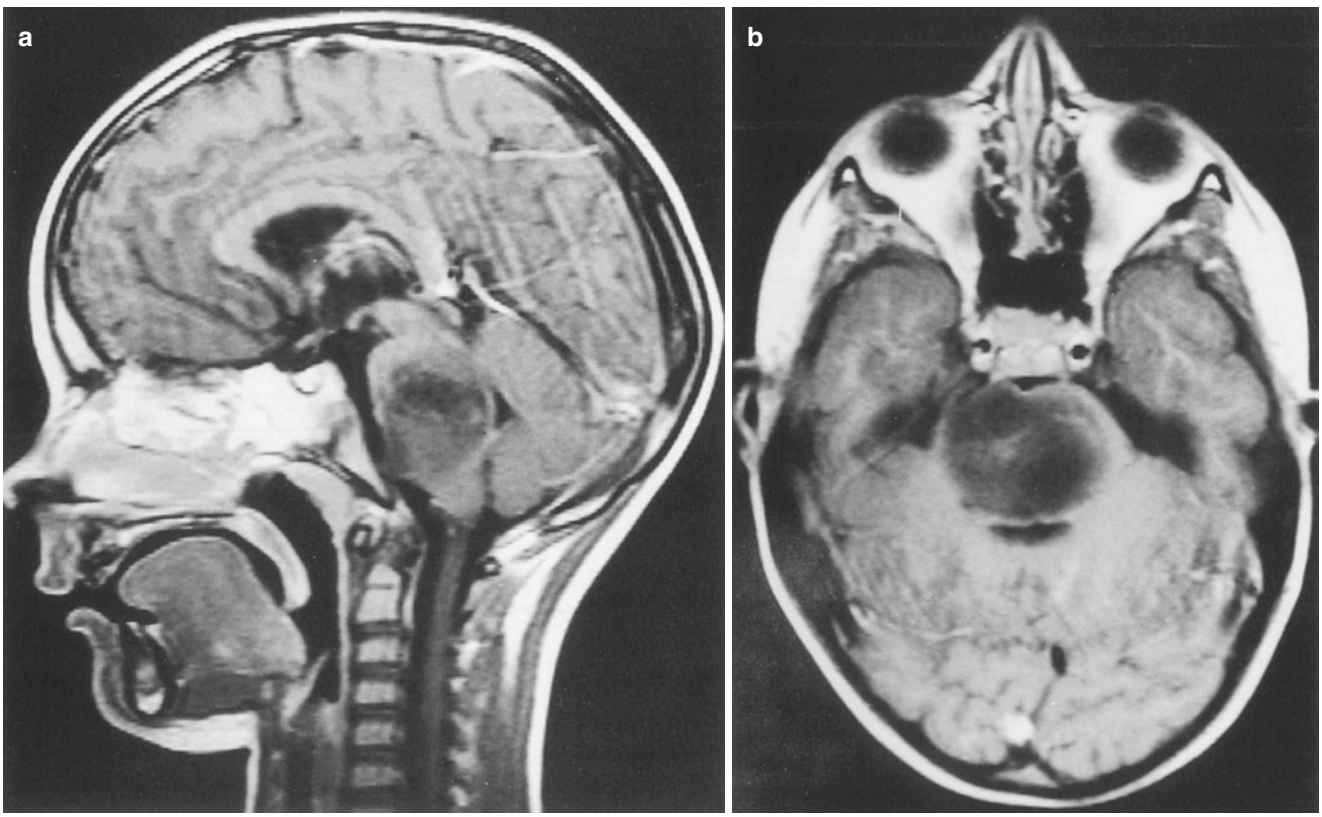

Fig. 25.5 (**a**) Sagittal and (**b**) axial T1-weighted MRI with gadolinium showing massive expansion of the pons by a poorly enhancing tumor – characteristic of a diffuse pontine glioma

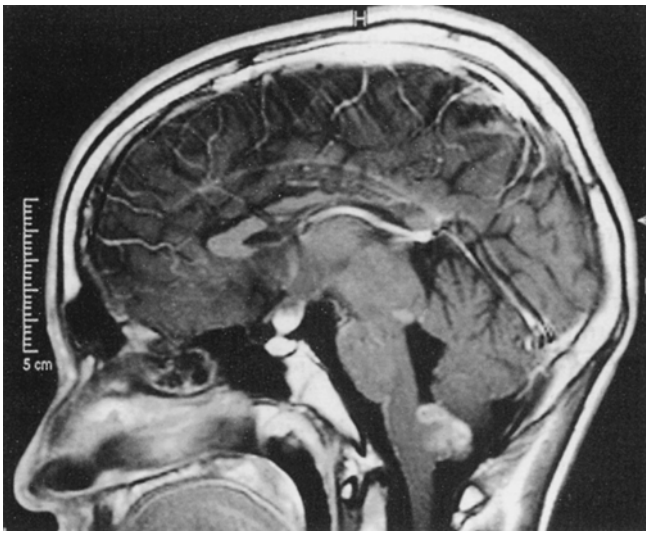

Fig. 25.6 Sagittal T1-weighted MRI with gadolinium showing an exophytic enhancing tumor arising off the medulla. Note also, the tectal plate tumor (with a small area of enhancement) and the enhancing hypothalamic tumor. This 12-year-old boy had presented with hydrocephalus 5 years earlier and on the basis of the CT scan performed at that time, the diagnosis of hydrocephalus secondary to aqueduct stenosis was made. Although asymptomatic, further imaging of the spine revealed another tumor (Fig. 25.9)

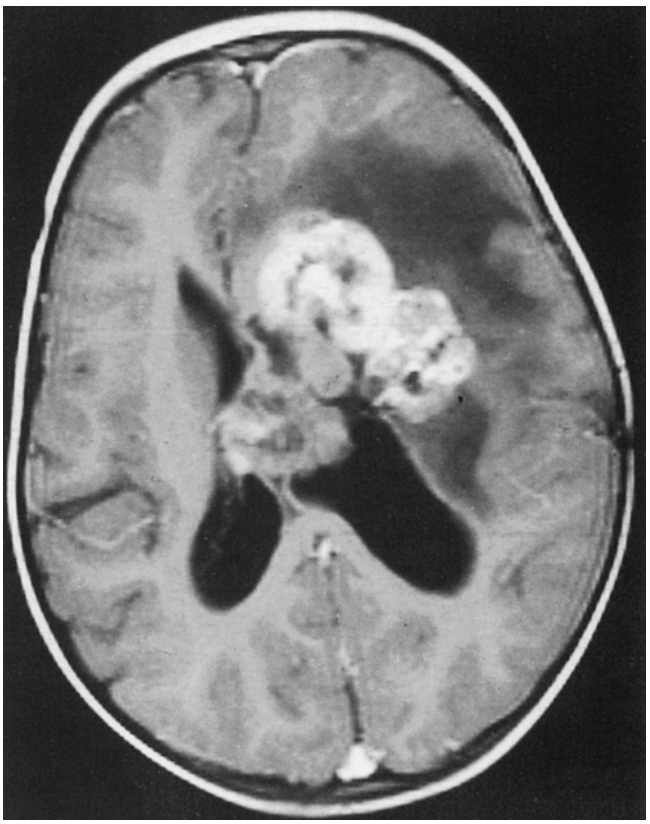

Fig. 25.7 Axial T1-weighted MRI with gadolinium showing a large partially cystic, enhancing tumor involving the parenchyma and with extension into the lateral ventricle. The associated edema is characteristic of a malignant tumor

benign and surgery followed by surveillance with repeat MRI is required. At the time of tumor recurrence, probably the best form of further therapy is repeat operation.

Cervicomedullary Tumor

These glial tumors involve the upper cervical cord/ medulla. In effect, they should be treated like spinal cord tumors, the main difference being that as they have "run out of spinal cord" at the level of the decussating white matter tract, they exophytically grow into the cisterna magna [61]. These patients present with long-standing neck pain and gradually develop myelopathy and sensory dysesthesias. These patients also often exhibit torticollis.

Imaging relies on MRI scanning and this shows an enlarged upper cervical cord with distortion of the medulla, usually with an exophytic component going into the cisterna magna. Enhancement with gadolinium is variable. In general, these tumors are low-grade gliomas although very occasionally malignant spinal cord tumors may mimic these findings.

Again, the aim of surgery is to remove as much tumor as possible without damaging normal neural tissues. The cervical tumor is interparenchymal and this requires a midline myelotomy. The exophytic component of the tumor is dealt with in the normal fashion being wary of vascular damage to the posterior inferior cerebellar artery vessels. Some groups find intraoperative electrophysiological monitoring helpful with this group of patients [57]. Postoperatively, these patients are at risk of respiratory failure and problems with protecting their airway and may require tracheostomy and feeding gastrostomies [57].

Supratentorial Tumors

These tumors usually present clinically with focal neurological signs (e.g., hemiparesis, visual disturbance); or with mass effect either directly due to tumor size or as a result of obstructive hydrocephalus; or with seizures. Supratentorial tumors are a heterogenous group and approximately one-third of these neoplasms involve the cerebral hemisphere [48, 62]. The most common tumor is the low-grade astrocytoma (WHO grade 2), which is composed of fibrillary or protoplasmic neoplastic astrocytes. Other low-grade tumors in this location include juvenile pilocytic astrocytomas (similar to cerebellar astrocytomas), oligodendroglioma, ependymoma, mixed glioma, dysembryoplastic neuroepithelial tumor, and ganglioglioma [48]. During the first 2 years of life, supratentorial tumors are more common than infratentorial and most of these are malignant neoplasms – usually PNETs, choroid plexus carcinomas, or teratomas [48, 63]. Overall, in children, approximately 20 % of supratentorial tumors are malignant neoplasms, the most common being

the malignant glioma. A brief run through the more common hemispheric tumors will be given prior to discussion of other supratentorial tumor types.

Cerebral Hemispheric Tumors

Astrocytomas

This group of tumors comprises one-third of hemisphere neoplasms and shows equal sex distribution with a peak incidence between the ages of 8 and 12 [64, 65]; 10–20 % of these tumors will be juvenile pilocystic astrocytomas (having identical histological makeup as those found in the posterior fossa). Malignant gliomas make up a further 20–30 % and overall, tumor cysts are found in approximately 40 % of children with supratentorial astrocytomas [48]. In adult patients distinct genetic signatures have been found for some glioma tumour types – and these mutations can have some bearing on prognosis. The best characterized of these is the 1p19q co-deletion seen classically in oligodendrogliomas and which confers an improved survival and sensitivity to both chemotherapy and radiotherapy. In high grade gliomas methylation of the gene encoding the repair protein DNA methyltransferase (MGMT) has been shown to correlate with response to Temazolamide. In grade II gliomas (rare in children) TP53 and IDH1 mutations are considered genetic hallmarks in adult patients and when present in GBM specimens implies that the tumour is a "secondary" GBM and has up-graded from a grade II or III tumour. Unfortunately, most of these genetic alterations are commonly not seen in paediatric gliomas – which strengthens the argument that these tumours in children are biologically and clinically different to those seen in adults. One "marker" that is seen in adult and paediatric tumours is the BRAF oncogene – which can be useful in confirming the diagnosis of pilocytic tumours.

Once again, it has been shown that gross total/subtotal (>90 %) resection confers survival advantage over partial resection/biopsy in both low-grade and highgrade tumors [48]. In spite of the benign histology in the low-grade group, only 60–70 % of children will be long-term survivors [48]. This probably reflects the fact that in most series all supratentorial low-grade gliomas are grouped together – including those involving deep vital structure like the hypothalamus and basal ganglia. Nonetheless, the aim of surgery should be to remove as much of the tumor as is safely feasible. The use of radiation postoperatively in these patients with low-grade gliomas is an area of contention. When gross total excision has been accomplished it would seem reasonable to follow these patients with serial imaging. In those patients with partial debulking or biopsy only due to the site of the lesion and in whom clinical progression is occurring, then radiotherapy is indicated. Chemotherapy, using vincristine and carboplatin, is effective and is now used routinely in younger children (less than 8 years of age) and in children with NF1 in whom the use of radiotherapy is to be avoided [66] (Fig. 25.8a–d).

With regard to the malignant tumors, there is clear benefit of adjuvant irradiation and it has been shown that doses of 5400–6000 cGy appear to offer longer survival time than does that under 5000 cGy [67]. Additionally, postirradiation chemotherapy has been shown to significantly increase survival in children with malignant astrocytomas [68] with an increased 5-year survival from 13 % in those patients receiving irradiation only to 43 % in those also receiving a nitrosourea-based regimen. The alkylating agent Temozolomide has been investigated in both adults and children with high-grade glioma but while its use during and following radiotherapy has been shown to increase duration of survival when compared with radiotherapy alone in adults, no such advantage has been shown in children [69–71]. Further trials of new agents are under way at present.

Ependymoma

These tumors make up approximately 10 % of all CNS tumors in childhood, and approximately 30 % are located supratentorially [48]. Over half of ependymomas occur before 2 years of age [48]. Although the posterior fossa ependymoma is located in relation to the fourth ventricle, the supratentorial ones often lie within the parenchyma and are thought to arise from ectopic rests of ependymal cells adjacent to the ventricles. Histologically, supratentorial ependymomas are identical to those found in the posterior fossa (see above). Likewise, the aims of surgery are similar to those of the posterior fossa ependymomas. Imaging of the spine is required to exclude drop metastases. Overall, 5-year disease free survival is better than for the infratentorial tumors and ranges between 40 and 60 % [51, 72, 73], with children with gross total resection faring better and giving recent survival rates of up to 85 %. The use and indications for adjuvant therapy are the same as for infratentorial ependymomas.

Oligodendrogliomas and Oligoastrocytomas

While pure oligodendrogliomas are rare tumors in the pediatric age group (2–3 % of hemispheric tumors) [48], up to 30 % of supratentorial gliomas consist of a mixed population of astrocytes and oligodendrocytes – giving them the term "mixed glioma" or "oligoastrocytoma" [48, 64]. Peak incidence is between 6 and 12 years and there is a strong male predominance [48, 74]. These tumors are usually located in the frontal lobe. Histologically, oligoastrocytomas consist of more than 25 % astrocytes whereas the oligodendrocytomas are uniform monotonous sheets of cells with perinuclear clear zones or halos producing a "fried egg" appearance [48]. Both tumor types are histologically graded in a similar fashion to astrocytomas. There has been great variation in the incidence of this diagnosis in series of patients with glioma, raising the possibility of international differences in the diagnostic criteria.

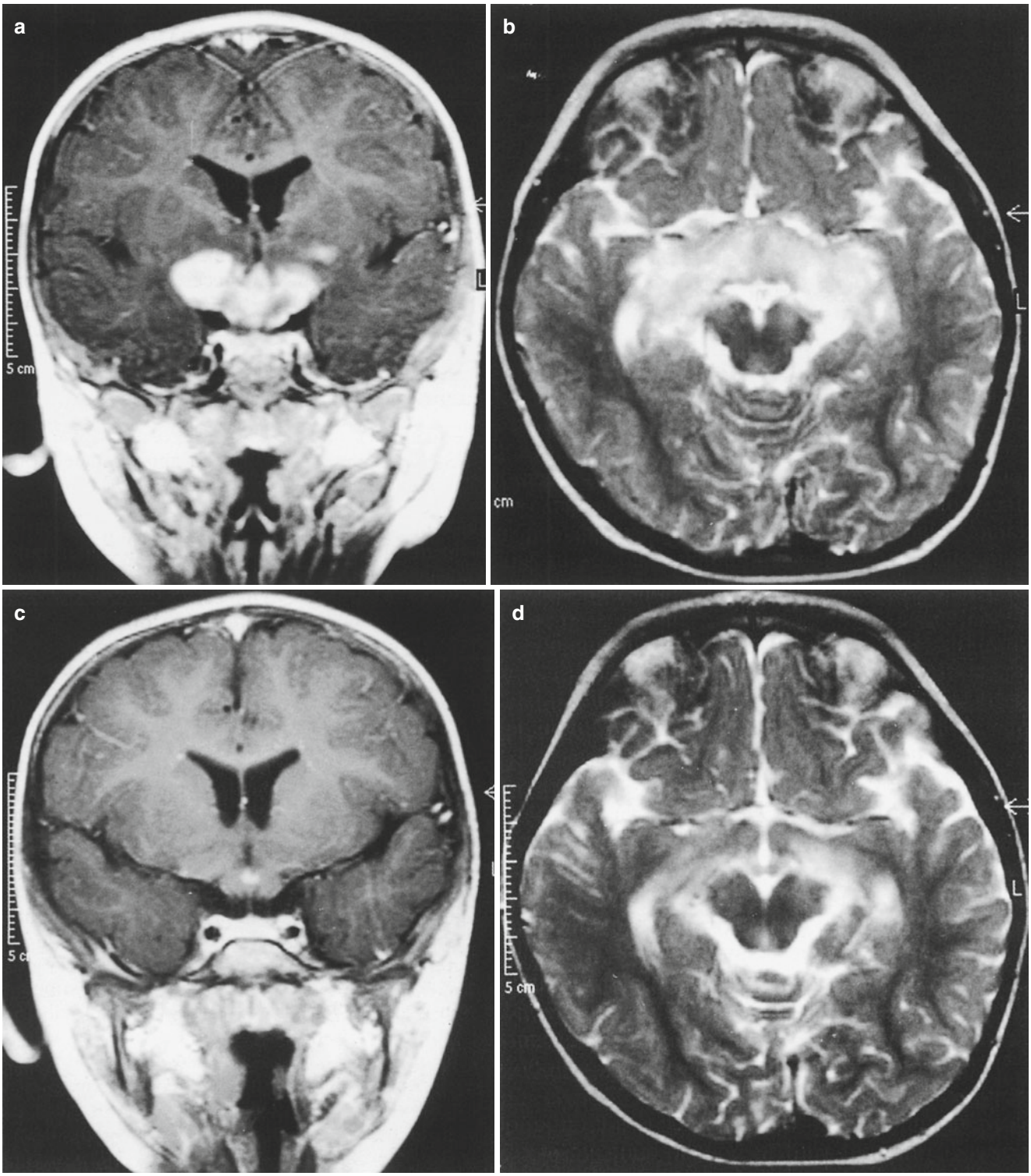

Fig. 25.8 (**a**) Coronal T1-weighted MRI with gadolinium taken at the level of the hypothalamus and third ventricle showing an extensive enhancing tumor – histologically confirmed to be a pilocytic astrocytoma and at surgery found to involve the optic chiasm. (**b**) Axial T2-weighted MRI showing extension of the tumor along the optic radiation. (**c**, **d**) Are comparable MRI scans from the same 2-year-old patient after chemotherapy with the low grade "Baby Brain" protocol – there being a dramatic reduction in tumor bulk

However, recent advances in our understanding of the cytogenetic changes associated with oligodendrogliomas may help rationalize the diagnostic process. In particular, these tumors often show 1p/19q loss and usually do not show p53 mutations. The 1p/19q loss confers survival advantage and sensitivity to chemo-therapy [9]. On CT scan, calcifica-

tion may be present and there is patchy contrast enhancement with both CT and MRI. Tumor cysts are frequent. The aim of surgery is radical resection and the role of irradiation in these tumors is controversial but probably improves survival in subtotally resected anaplastic tumors. The 5-year survival for pure oligodendrogliomas ranges from 75 to 85 % [74, 75]. Malignant mixed tumors fare poorly with similar survival curves to the malignant gliomas.

Ganglioglioma

These tumors are also mixed tumors consisting of neoplastic ganglion cells and astrocytes and make up approximately 5 % of pediatric brain tumors [48]. Histological grading is based on the astrocytic component of the tumor with regard to features of anaplasia. These tumors have a predilection for the medial temporal lobe and usually present with poorly controlled seizure disorders. Males are more commonly affected and the tumors can occur throughout childhood. Use of MRI demonstrates a well-demarcated cystic temporal lobe mass with no edema.

These are indolent tumors but with often devastating social consequences due to the poorly controlled epilepsy. The aim of surgery is therefore to make the diagnosis, but also to relieve epilepsy. In patients with intractable epilepsy, it is therefore important preoperatively to fully assess the origin of the epileptic focus to confirm that this correlates with the MRI lesion. Longterm survival is seen in 75–90 % of patients following radical surgery [75, 76], and radiotherapy is not given in patients who have undergone gross total resection. The role of radiotherapy in patients with a subtotal resection is not yet determined.

Primitive Neuroectodermal Tumors (PNET)

These tumors are identical histologically to the infratentorial medulloblastomas. Imaging studies usually demonstrate large, relatively well-demarcated lesions with mixed enhancement patterns and areas of cysts and calcification and possibly hemorrhage [48] (Fig. 25.7). The aim of surgery is to remove as much tumor as possible and preoperatively; these patients require MRI of the spinal axis. Treatment is similar to that for infratentorial medulloblastomas, but the overall prognosis is poor with less than 30 % surviving 5 years [32]. Treatment is particularly difficult in young children due to the long-term cognitive consequences of radiotherapy to the supratentorial area.

Meningiomas

Although these tumors make up approximately 15 % of adult series, they only constitute approximately 2–3 % in pediatric series [77]. They are more common in females and in adolescence and may be associated with neurofibromatosis. A far higher percentage of pediatric meningiomas are intraventricular (25 %) than in the adult population [48]. As with adult meningiomas, the aim of surgery is total removal including adjacent dura, and long-term survival is expected although recurrence may occur. Occasionally, meningiomas are malignant and may metastasize.

Cerebral Metastases

Although common in adults, these tumors only make up approximately 5 % of pediatric brain tumors [48] with the most common primary tumors being sarcomas. Patients usually have pulmonary metastases by the time they present with CNS involvement and the prognosis is poor with survival being measured in months. Providing the lesion(s) are small (<3 cm) one treatment option for this group of patients is radiosurgery (stereotactically focused high dose single shot radiotherapy).

Midline Tumors

Germ Cell Tumors

Intracranial germ cell tumors (GCTs) account for 30 % of all GCTs and are histologically identical to extracranial GCTs. Table 25.2 shows the histological classification used for GCTs, which tend to occur in midline sites (suprasellar or pineal), although occasionally they may arise within a ventricle, or within the hemisphere [48]. The management of this group of tumors is covered under section "Pineal region tumors".

Optic Nerve/Chiasm and Hypothalamic Gliomas

Tumors occurring on the optic pathways make up approximately 5 % of all pediatric brain tumors [78] and 75 % of these present in the first decade of life. Histologically, these tumors are usually low-grade pilocytic astrocytomas, which very rarely undergo malignant transformation. The tumors may be solid or cystic and are usually fusiform. They may arise primarily in the optic nerve and go on to involve the chiasm or, conversely, they may arise initially in the chiasm and spread to the optic nerves or into the hypothalamus [18]. "Skip" lesions may also be seen along the optic pathways – especially in patients with neurofibromatosis. The symptoms and signs of optic nerve gliomas are dependent upon their

Table 25.2 Histological classification of intracranial germ cell tumors

Germinoma
Embryonal carcinoma
Yolk sac tumor (endodermal tumor) Choriocarcinoma
Teratoma
Immature teratoma
Mature teratoma
Teratoma with malignant change
Mixed germ cell tumor

anatomical location. The main presenting features are visual failure, squint, proptosis, endocrine dysfunction, and hydrocephalus. Overall, these tumors are associated with good long-term survival but this can be accompanied by slow progressive visual deterioration [18].

The treatment of these tumors remains controversial as their natural history is highly unpredictable – with some tumors progressing despite aggressive treatment while others remain indolent indefinitely [18, 78]. Up to one-third of patients with optic nerve gliomas have neurofibromatosis (NF1) and further evidence for this phakomatosis should be sought at presentation. In general, tumors in patients with NFI behave in a more indolent manner.

Patients with tumors within the orbit or on the intracranial optic nerve tend to present at a slightly later age (6 years) than those with chiasmatic tumors (2–4 years) [18, 78, 79]. Unfortunately, these posteriorly located tumors, which often involve the hypothalamus at presentation, are the most common form of optic nerve glioma making up some 60 % [80]. These patients may present with hydrocephalus and/or visual problems and/or pituitary dysfunction and/or hypothalamic dysfunction. The latter classically leading to the diencephalic syndrome (emaciation, pallor, and hyperactivity) seen in up to 20 % of patients under 3 years of age [79]. Other symptoms of hypothalamic involvement include diabetes insipidus, anorexia, obesity, and precocious puberty. These tumors also show markedly varying capacity for progression with some remaining indolent while others rapidly increase in size [81].

The imaging investigation of choice is MRI, which usually shows a hypointense tumor on T1-weighted images with enhancement after gadolinium (Fig. 25.8a–c). On T2, high intensity signal may be seen extending to the lateral geniculate bodies, although whether this represents tumor extension or optic tract edema has not yet been determined [79]. Visual evoked responses may be of assistance in monitoring visual function but are of limited value in screening [78].

Management of these tumors remains controversial but in general, patients with reasonable and/or static visual acuity only require surveillance with regular ophthalmic assessment and imaging. Surgery is reserved for problematic proptosis and tumors which are located within the optic nerve but without evidence of spread towards the optic chiasm. Tumors involving the chiasm/hypothalamus may require debulking if there is evidence of tumor progression or if the tumour is causing hydrocephalus – such surgery aims to debulk the mass but leave tumour near the hypothalamus and chiasm. Additionally, histological verification may be important in order to exclude other causes for a suprasellar mass and in particular ascertain if the tumour is a standard pilocytic glioma or the more aggressive pilomyxoid tumour. Frequently CSF diversion is required for the treatment of hydrocephalus in patients with posteriorly located tumors (and occasionally this may be complicated by the formation of problematic ascites).

The role of adjuvant therapy in the treatment of optic pathway tumors also remains controversial and is limited to patients with clinical and radiographic evidence of progression. The young age of many of the patients considerably limits the use of radiotherapy; nonetheless, Jenkin et al. [79] have shown that for posterior tumors, irradiation is effective with a 75 % 10 year relapse-free survival. Side-effects of irradiation therapy not only include those previously discussed (cognitive impairment, endocrine dysfunction, and secondary malignancy) but also an increased risk of developing Moyamoya phenomenon (cerebral ischemia secondary to spontaneous occlusion of the internal carotid arteries) especially in the setting of NF1 [82]. Of the chemotherapeutic agents available, the nitrosourea-based cytotoxic regimens have been shown to result in symptomatic improvement or stabilization [83]. More recently, carboplatin and vincristine has been reported to be effective in arresting growth in progressive optic gliomas and this is now considered standard treatment for patients with NF1 and young children (less than 8 years) [84] (Fig. 25.8).

Craniopharyngiomas

These tumors make up between 5 and 10 % of pediatric brain tumors and approximately 15 % of all supratentorial tumors [85] and thus are the most common nonglial tumors of childhood. Although 50 % of these tumors occur in adults, the peak incidence for the remainder is between the ages of 5 and 10 years [86].

The origin of these unusual tumors has caused much debate over the years but it is generally accepted that they arise from squamous cell rests of an incompletely involuted hypophyseal–pharyngeal duct [87]. Tumors are usually located in the suprasellar region and expand into the hypothalamus and third ventricle. In addition, they grow into the sella and down between the clivus and the brain stem. Approximately one-third of these tumors are purely cystic, while a quarter are purely solid and the remainder mixed – thus overall nearly three-quarters of the tumors are at least partially cystic [87]. The fluid in these cysts is like "engine oil" and contains variable amounts of protein with suspended cholesterol crystals. Calcification is seen in almost all childhood craniopharyngiomas [86]. Histologically, craniopharyngiomas are composed of epithelial cells and form two distinctive variants – the adamantinous and the squamous papillary type. The adamantinous type are mainly found in childhood and tend to be cystic tumors, with calcification seen on imaging, and which are prone to recur and have a worse overall outcome. The squamous papillary type are usually seen in adults and are generally solid, noncalcified lesions.

Although craniopharyngiomas do not invade neural tissue, they cause an extensive glial reaction – especially around the small finger-like tumor projections which occur within the hypothalamus. Additionally, they frequently are strongly

adherent to major arteries and cranial nerves at the base of the brain – in particular the optic chiasm and tracts, the pituitary stalk, and the arteries of the Circle of Willis. It is this unfortunate combination of benign histology and predisposition to form cysts and dense "adhesions" to vital structures that make these tumors such a surgical challenge.

Clinically, these children usually present with signs of raised intracranial pressure secondary to hydrocephalus. Additionally, disturbances of the hypothalamic–pituitary axis may be noted resulting in short stature, diabetes insipidus, obesity, and delayed or precocious puberty. Children of this age may well not complain of visual problems but on presentation over half of them have evidence of visual disturbance (poor acuity, field defect, diplopia or nystagmus) [85]. Plain x-rays show calcification in 85 % [86] and may also show an enlarged sella. Calcification is also shown by CT scans and the degree of cystic/solid makeup of the tumor and any associated hydrocephalus (Fig. 25.9a, b). Enhancement is intensive but mixed, and coronal scanning may help identify intrasellar extension; MRI is superior to CT for displaying general configuration of the tumor and its relationship to surrounding structures.

The treatment of craniopharyngiomas remains controversial, some proponents advocating aggressive total removal in all children [85, 88], while others consider surgery for craniopharyngiomas as merely palliative and believe that subtotal or partial resection followed by radiation therapy should be the rule [86, 89]. Certainly, if at surgery the hypothalamus is involved, a more conservative approach is warranted to avoid hypothalamic morbidity – as represented by the short, obese, somnolent child. It is becoming more widely accepted that survival and progression-free survival after conservative surgery and radiotherapy are as good as those seen after radical surgery and that there is a lower morbidity associated with the former treatment. However, radiotherapy has its own problems – occasional failure to prevent progression, calcification of the basal ganglia, radiation necrosis (especially of the optic apparatus). Although alternative treatments have been tried (e.g., intracystic injection of radioactive isotopes or bleomycin) these have not been widely adopted [85, 90]. Radiosurgery (single treatment high-dose focused radiotherapy) may have a role in treating small solid tumor remnants situated away from the chiasm [85].

Pineal Region Tumors

While making up less than 1 % of most adult series [91], pineal tumors are responsible for some 3–8 % of childhood brain tumors [92]. Tables 25.2 and 25.3 show the wide vari-

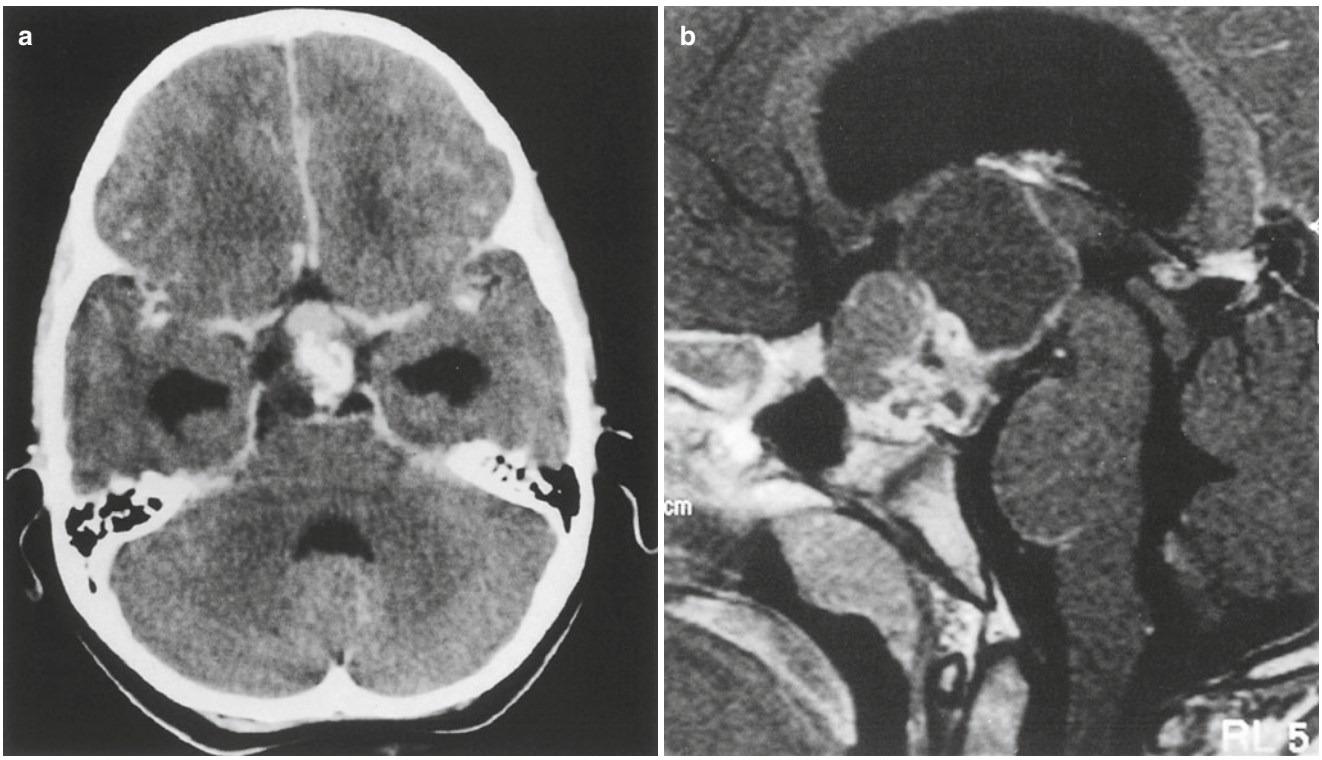

Fig. 25.9 (**a**) Axial CT with contrast showing a partially cystic and partially calcified craniopharyngioma. Note the relationship to the vessels of the Circle of Willis. (**b**) Sagittal T1 weighted MRI shows the extension of the same tumor into the sella turcica, just over the clivus and with a cystic component pushing into the hypothalamus

Table 25.3 Histological variation of tumors found in the pineal region

Tumors of germ cell origin
(see Table 25.2)
Tumors of pineal parenchyma
Pineocytoma
Pineoblastoma
Mixed
Tumors of supportive or adjacent tissues
Gliomas
Ganglioglioma
Meningioma
Non-neoplastic cysts
Pineal cyst
Arachnoid cysts
Vascular lesions
Vein of Galen aneurysm
Arteriovenous malformations
Cavernoma

ety of tumors that may be found at this location; however, between half and three-quarters of all tumors are either germinomas or of astrocytic origin [91]. Historically, surgical morbidity and mortality rates were high and the standard treatment was shunt insertion for the hydrocephalus and "blind" irradiation of the tumor [93–95]. Improvement in surgical instrumentation and the use of various surgical approaches have resulted in a far more favorable experience in recent years with acceptable mortality rates (0–2 %) [91].

Clinically, these children usually present with headache and may have dorsal midbrain syndrome (Parinaud's) consisting of poor upward gaze and difficulty with accommodation. Males are up to four times more likely to develop pineal tumors than females and the average age of presentation is 13 years [91]. Germinomas are particularly prevalent in Japanese adolescent males. Although CT and MRI are useful in delineating the tumor they are not diagnostic (Fig. 25.10). Tumor markers [alpha-fetoprotein (AFP), beta human chorionic gonadatrophin (HCG), and placental alkaline phosphatase (PLAP)] may be raised in both CSF and serum. Preoperative sampling of the CSF is required and at the same time cytology can be undertaken. Raised PLAP is classically seen with germinoma, AFP with yolk sac tumors, and raised HCG with choriocarcinoma.

Due to the wide variability in tumor type – not all of which are radiosensitive – it is now generally accepted that tissue diagnosis is required prior to treatment, the only caveat to this being "secretory tumors" which are positive for AFP or HCG. These markers are only positive in malignant germ cell tumors and many trial protocols would recommend upfront chemotherapy with surgery being reserved for postadjuvant residual tumor. Concern has been raised in the literature on the reliability of histological diagnosis from small specimens obtained by stereotactic biopsy [91] – especially as 15 % of tumors are of mixed histology [96]. Additionally, the site of pineal tumors with their proximity to the deep venous system has resulted in a higher rate of hemorrhage and morbidity with biopsies in this region than in other areas of the brain. For these reasons, open surgical approaches have gained popularity. However, recent reports of stereotactic biopsy in the management of pineal tumors [97] have shown good diagnostic rates and low morbidity and mortality.

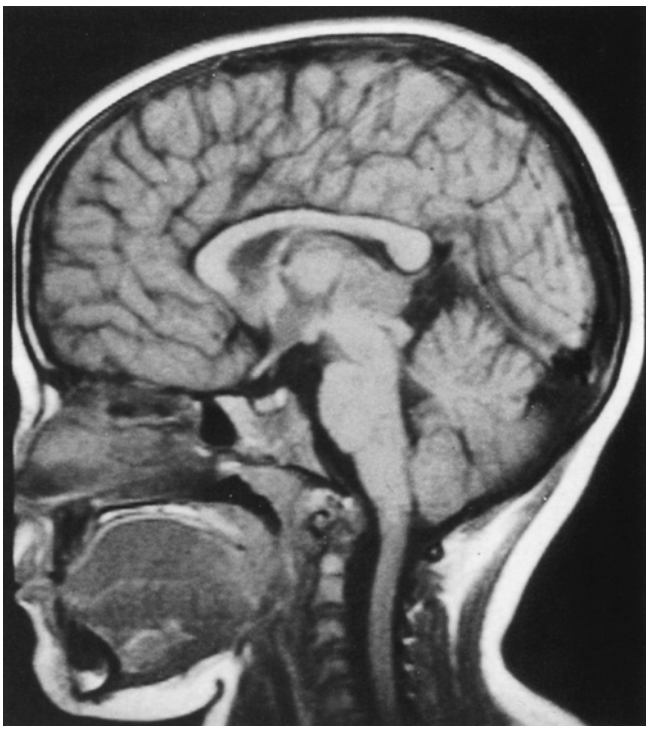

Fig. 25.10 Sagittal T1-weighted MRI showing a pineal tumor compressing the tectal plate. The histology was pineoblastoma

The use of endoscopy in neurosurgery (originally reported in 1923) has increased dramatically over the last two decades, and it is now common practice to treat the hydrocephalus associated with pineal tumors by performing an endoscopic third ventriculostomy (making a small hole through the floor of the third ventricle into the interpeduncular cistern thus bypassing the obstruction at the level of the aqueduct). At the same time, CSF may be obtained for cytology and tumor markers and it may be possible to perform a biopsy of the tumor during the same procedure.

From a surgical perspective, patients with evidence of subependymal seeding or spinal drop metastases require a biopsy (either stereotactic or endoscopic) to obtain a diagnosis. Patients with substantially elevated tumor markers do not require histological confirmation prior to starting treatment. For all other patients, either a biopsy (endoscopic or stereotactic) or an open surgical approach with intraoperative fro-

zen section is required. When the histology is benign, attempt at total removal is undertaken; if the histology is reported as a germinoma, no more than a biopsy is performed; while in those children with malignant pineal region tumors an attempt is made to remove as much tumor as possible.

Postoperative adjuvant therapy is obviously tailored to tumor type with no further treatment being required for benign lesions while radiation and chemotherapy may be required for malignant tumors. The 5-year survival for germinomas treated with radiotherapy is over 90 % and therefore many groups recommend radiotherapy alone [91, 96]. Studies are underway to see if it possible to reduce the volume and dose of radiation in patients with germinomas while preserving high cure rates. Secreting tumors have a far poorer prognosis with radiotherapy alone and therefore the use of adjuvant chemotherapy (in particular using etoposide and platinum agents) is now advocated. CSF markers can be used for tumor surveillance and to assess treatment in this group.

Intraventricular Tumors

As a group, these tumors do not usually present until they have reached sufficient size to obstruct the ventricular system resulting in hydrocephalus. Choroid plexus papillomas may also cause hydrocephalus by overproduction of CSF, although the most likely cause for the hydrocephalus is due to raised protein and cellular debris blocking off CSF absorption. Apart from choroid plexus tumors, the other relatively common tumor types are colloid cysts and the subependymal giant cell astrocytoma. The latter is dealt with under the phakomatoses.

Choroid Plexus Tumors

These relatively rare tumors are histologically divided into choroid plexus papillomas (benign) (Fig. 25.11a) and choroid plexus carcinoma (malignant) (Fig. 25.11b). The latter show focal invasion and dedifferentiation of cells with marked nuclear pleomorphism [98]. Carcinomas tend to be larger at diagnosis than papillomas and they disseminate along CSF pathways. Both appear as reddish/gray frondular tumors which are highly vascular. For this reason, they enhance brightly on MRI and CT. In children, they tend to occur in the lateral ventricle [98] while the fourth ventricle is the more typical site in adults [99].

Choroid plexus tumors usually occur in children under 2 years of age in whom there is a small circulating blood volume. This, in combination with the fact that the vascular supply is usually found deep and medial to the tumor, makes these tumors a significant surgical challenge. Complete surgical resection is curative for the papilloma-type and the only long-term survivals

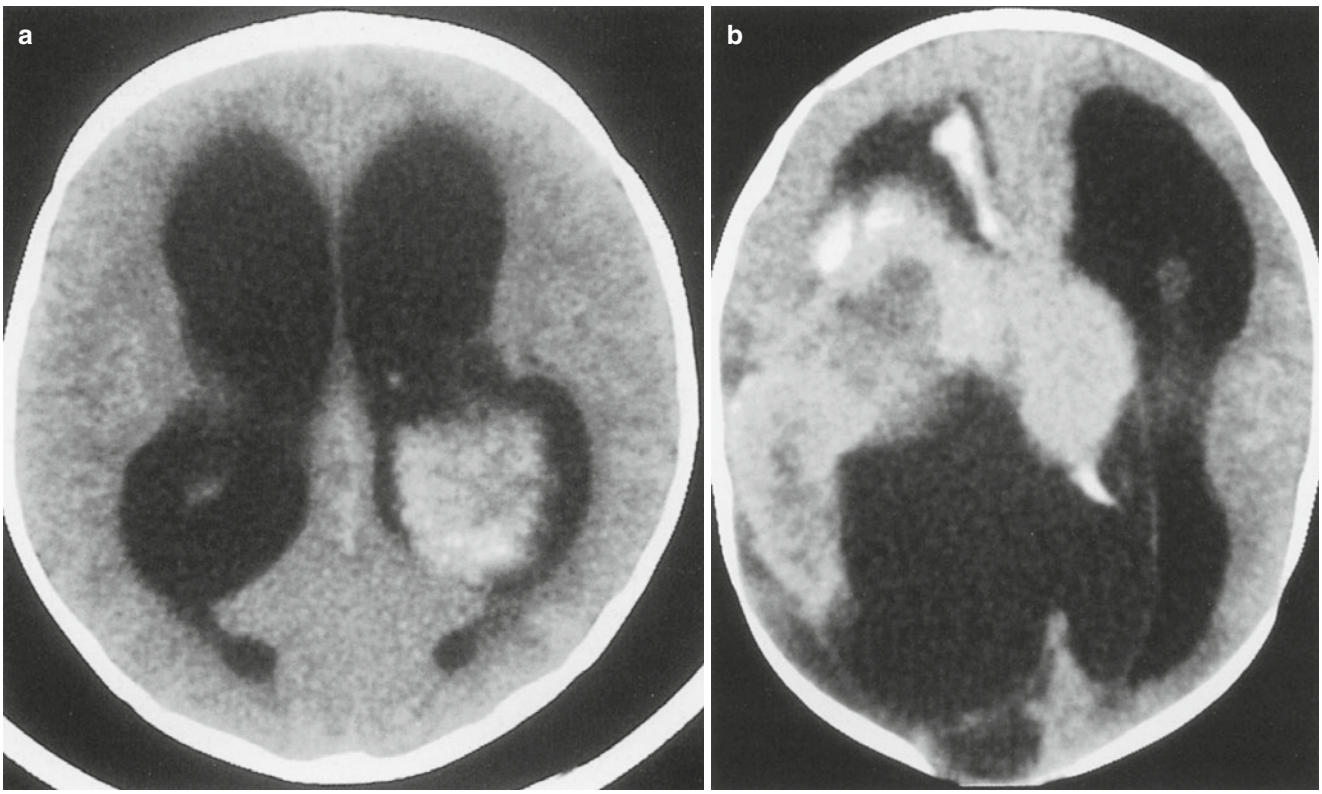

Fig. 25.11 (**a**) CT scan showing benign choroid plexus papilloma. (**b**) CT scan showing choroid plexus carcinoma

reported in the carcinoma-type have occurred after gross total resection and irradiation [100]. The role of presurgical chemotherapy to help devascularize these tumors has been raised by the Toronto group [101] and there are anecdotal reports of success in treating infants with multiagent chemotherapy and of trying to embolise the tumour pre-operatively.

Colloid Cysts

These tumors are rare in childhood but are still occasionally responsible for cases of sudden death. Colloid cysts are benign neuroepithelial cysts whose contents vary from gelatinous to firm in consistency. They are located in the anterior aspect of the third ventricle and may obstruct both Foramen of Munro. It is this site which makes them potentially lethal with their ability to suddenly cause hydrocephalus. Clinically, most patients do not present with acute deterioration or drop attacks but with symptoms of raised intracranial pressure. Various surgical approaches (open via a craniotomy, endoscopic, and stereotactic aspiration) have been advocated for the treatment of these lesions. The role of surgery in truly asymptomatic patients (without hydrocephalus) remains undetermined.

Tumors of the Skull

These "lumps" usually come to light incidentally after minor trauma and 75–90 % [102, 103] are benign with the most common being epidermoid or dermoid tumors and with Langerhans' Cell Histiocytosis being the next largest group.

Dermoid and Epidermoid Tumors of the Skull

Between them, these tumors probably make up less than 1 % of all pediatric brain/skull tumors. Dermoids are usually found around the orbits, around the anterior fontanel and along cranial sutures [103]. These tumors are cysts with stratified keratinizing squamous epithelium forming a capsule of epidermoid and additional dermoid appendages such as hair follicles and sebaceous glands including the walls of dermoids. The tumor usually presents as a painless swelling while those arising around the orbit may present with exophthalmos. Plain x-rays show a rounded erosion of the bone with sclerotic margin while CT scanning shows a lesion which is hypodense. Surgical excision is the treatment of choice.

Fibrous Dysplasia

In this condition, normal bone is replaced by fibrous tissue (fibroblasts and collagen fiber bundles) and the lesion probably represents a developmental defect of mesenchymal tissue [102]. Although occurring in the first few decades of life, lesions are most active during periods of bone growth and during puberty. In nearly 75 % of cases only one bone is involved (the cranium being involved in 10–27 % of cases) (monostotic form) while in the cases where more than one bone is involved (polyostotic) the cranium is involved in over 50 % of cases [102]. If associated with café au lait spots and endocrine dysfunction, the polyostotic form is termed Albright's syndrome. Plain x-ray appearance depends on the amount of bone within the lesion and ranges from radiolucent through to ground-glass or ossified and sclerotic. Growth of the tumor can lead to facial disfigurement or compression of cranial nerves exiting the foramina. Although surgery can be curative, the bones involved often preclude this. These lesions can undergo malignant degeneration to sarcomas (estimated risk of less than 0.5 %) but after radiation, this risk may increase up to 44 % [102].

Langerhans' Cell Histiocytosis (Histiocytosis X)

This refers to a range of proliferative diseases affecting the reticuloendothelial system which results in the formation of tumor-like lesions. The disease spectrum varies from Letterer-Siwe disease in which there is diffuse systemic involvement and which is progressive and often fatal, through an intermediate stage (HandSchüller-Christian disease) in which there is cranial involvement, exophthalmos, and diabetes insipidus; through to eosinophilic granuloma in which solitary lesions are found. The common histological feature is Langerhans' cell histiocytes. In all the conditions, calvarial lesions are the most common and these lesions are usually painful. On plain x-rays they appear punched-out without sclerosis (Fig. 25.12a, b). Diagnosis is obtained at the time of excisional biopsy with curettage. If confirmed, further evaluation (hematological, liver function, chest x-ray and skeletal survey) should be undertaken to determine the extent of active disease. No further treatment is required for single lesions but multiple lesions can be treated with low-dose radiation (300–1000 rads); however, multifocal and multisystem disease requires chemotherapy. After surgical excision of a solitary lesion, continuous followup is necessary as up to one-third of patients can later develop a new lesion after several years [102].

Hemangioma

Pathologically, these are cavernous hemangiomas growing within the diploe and forming a predominantly lytic lesion on plain x-rays. They have the classic sunburst appearance due to radiating bony spicules. Incision and curettage is usually curative.

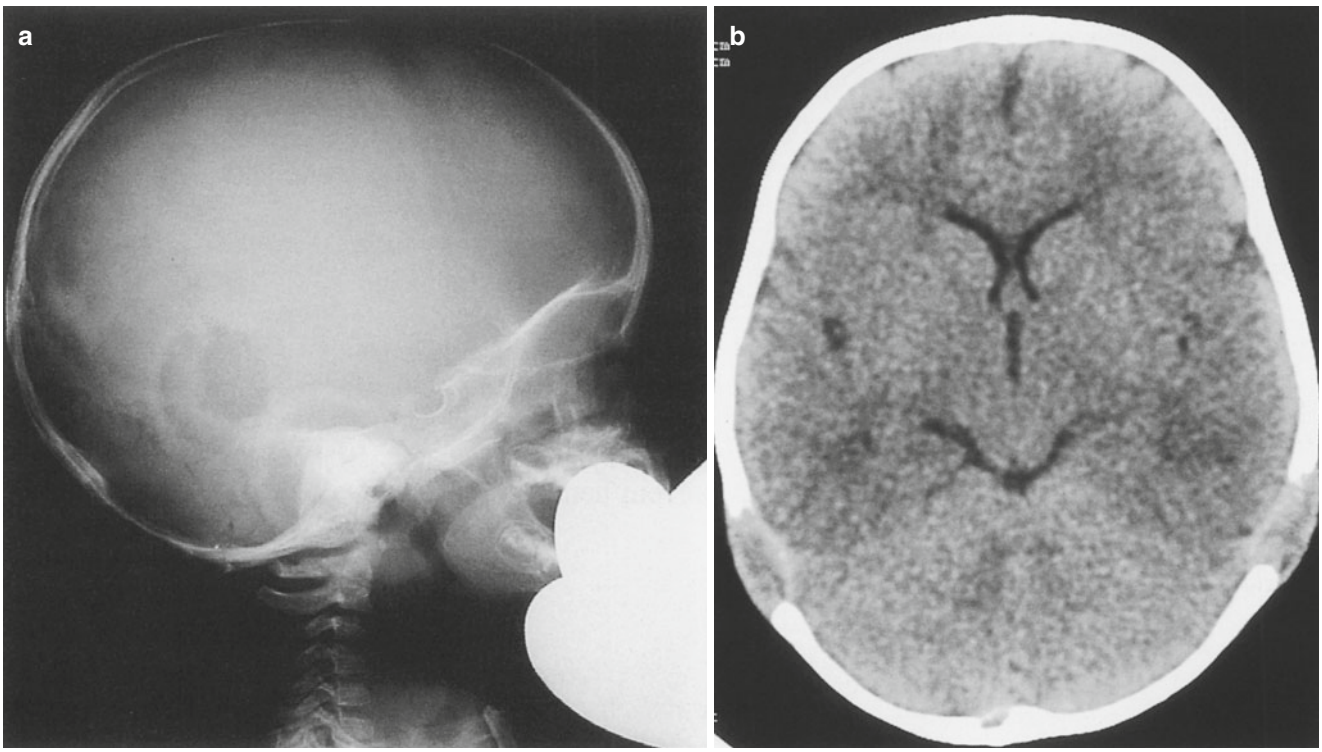

Fig. 25.12 (**a**) Plain x-ray of skull showing punched out lesion of histocytosis on both sides. (**b**) CT scan of the same patient

Osteoma

These are rare, benign, firm, nontender masses which are dense and well demarcated on plain x-ray. If required they can be easily removed.

Aneurysmal Bone Cyst

Although usually a disease of long bones and spine, approximately 5 % occur in the calvarium where they may appear lytic or calcified depending on their age on x-ray. Surgical excision is recommended to prevent hemorrhage after incidental trauma.

Chordomas

These tumors rarely present in childhood but when found in the pediatric population, they are usually located at the skull base involving the clivus and present with lower cranial nerve dysfunction. Metastases to the lung are more frequent in pediatric than in adult patients with chordomas [104]. The investigation of choice to display the tumor extent is MRI. The site makes surgical access difficult but removal has been achieved via far lateral, transoral and more recently endoscopic approaches. Long-term survival for children treated with surgery and radiotherapy approaches 50 % [102]. Proton therapy is thought to be more effective than standard radiation for these tumors.

Malignant Primary and Secondary Tumors

Neuroblastoma, because of its relative frequency, is often seen to metastasize to facial bones and the skull. All forms of sarcoma may be located in the cranium although it is rare for the skull bones to be the primary site.

Spinal Cord Tumors

Spinal cord tumors are divided into extradural and intradural – the latter being further subdivided into those which are intramedullary (meaning within the parenchyma of the spinal cord) and those that are extramedullary. Table 25.4 shows the types of tumor that may present with spinal cord compression (including extradural compression). Most series include all spinal tumors together and also include developmental anomalies – thus making the true incidence of any type difficult to ascertain. Di Lorenzo et al. [104] found a ratio of intracranial to intraspinal tumors of 6.7–1 (making spinal canal tumors some 12–15 % of all nervous system tumors). Nearly 70 % of these were extramedullary and over 40 % of

Table 25.4 Types of tumors causing spinal cord compression

Intradural
Congenital
Dermoid/epidermoid
Teratoma
Extramedullary
Meningioma
Nerve sheath tumors (schwannoma and neurofibroma)
Intramedullary
Primary (glioma, ependymoma, hemangioblastoma)
Metastatic (neural "drop" metastases)
Extradural
Direct Spread
Neural crest tumors (e.g., neuroblastoma)
Soft tissue tumors (e.g., sarcomas)
Bony tumors (benign and malignant)
Metastic

them were extradural. Causes of extradural cord compression include neuroblastomas (Fig. 25.13a–c), tumors of the bony spine and other metastasizing malignancies and these will be discussed in other chapters in this book.

Extramedullary Spinal Tumors

The presenting features depend on the pathology and the age of the child. Delay in diagnosis is the rule rather than the exception. The most common symptom is of pain and motor weakness and in young children the latter may result in regression of ambulatory skills. Sphincter disturbance may also be noticed by delay or regression – although often these symptoms are mistaken as behavioral. Progressive spinal deformity is another method of presentation. Although plain x-rays show abnormalities are present in 50–60 % of extramedullary lesions, the investigation of choice today is MRI.

Epidermoid and Dermoid Tumors

These lesions are generally believed to result from invagination of skin elements during development. However, occasionally, they may arise after multiple lumbar punctures [106]. Histologically, they are similar to their intracranial counterparts. Dermoids are more common in children and both are usually found in the lumbar region often in association with a cutaneous abnormality – hairy patch, port wine, nevus, or dermal sinus. The latter may present with a history of recurrent bouts of meningitis. On MRI scanning, dermoids have the intensity of fat (Fig. 25.14). Complete removal is advocated otherwise recurrence is likely.

Teratoma

These tumors either occur within the spinal canal (usually in the lumbar region) or in the sacrococcygeal area. The latter will not be discussed further here. A third of these tumors arise in children less than 5 years of age [107] and the tumors may be cystic or solid and are usually found in the thoracic or lumbar regions.

Use of MRI shows multiple tissue signals and surgical excision is the treatment of choice with failure of complete removal resulting in recurrence.

Meningioma

Most present in adolescence and usually occur in the thoracic region. Approximately 20 % of cases are associated with NF1 [107] and surgical excision is aimed for with good long-term results but with possibly higher rates of recurrence than that seen in adults [107].

Nerve Sheath Tumors

Schwannomas are composed of Schwann's cells while neurofibromas are a mixture of Schwann's cells and fibroblasts but with an abundance of collagen fibers. These tumors tend to present around puberty and approximately 25 % of them are associated with von Recklinghausen's disease (NF1) [107]. Varying amounts of the tumor may be in the spinal canal with dumb-bell shaped tumors being seen in 20 % of cases. Very occasionally malignant change can occur within them. The investigation of choice is MRI and treatment consists of total removal when feasible.

Hemangioblastoma

Hemangioblastomas may occur as part of von HippelLindau disease and approximately 50 % of spinal hemangioblastomas occur in conjunction with this syndrome. In general, although hemangioblastoma is rare in children, the spinal lesions are more common than cranial [107]. These tumors may be multiple. Treatment is surgical removal.

Metastatic Disease

Extraneural. Involvement of the central nervous system with leukemia is common and may be present at initial diagnosis in up to 30 % of patients with acute myelogenous leukemia (AML) [108]. Without prophylactic treatment, patients with acute lymphocytic leukemia (ALL) will develop CNS disease in 50–80 % of patients [107] but prophylactic treatment reduces this risk to 2–10 %. Leukemia of the CNS presents as either parenchymal or meningeal disease or both and the dural involvement may reach sufficient proportion to produce a mass lesion either within the cranium or within the spinal canal. Hemorrhage can occur from these lesions and infiltration of nerve roots or the spinal cord itself may occur. Diagnosis may be made by CSF cytology and MRI may show meningeal enhancement or masses. Treatment is a combination of radiation and chemotherapy.

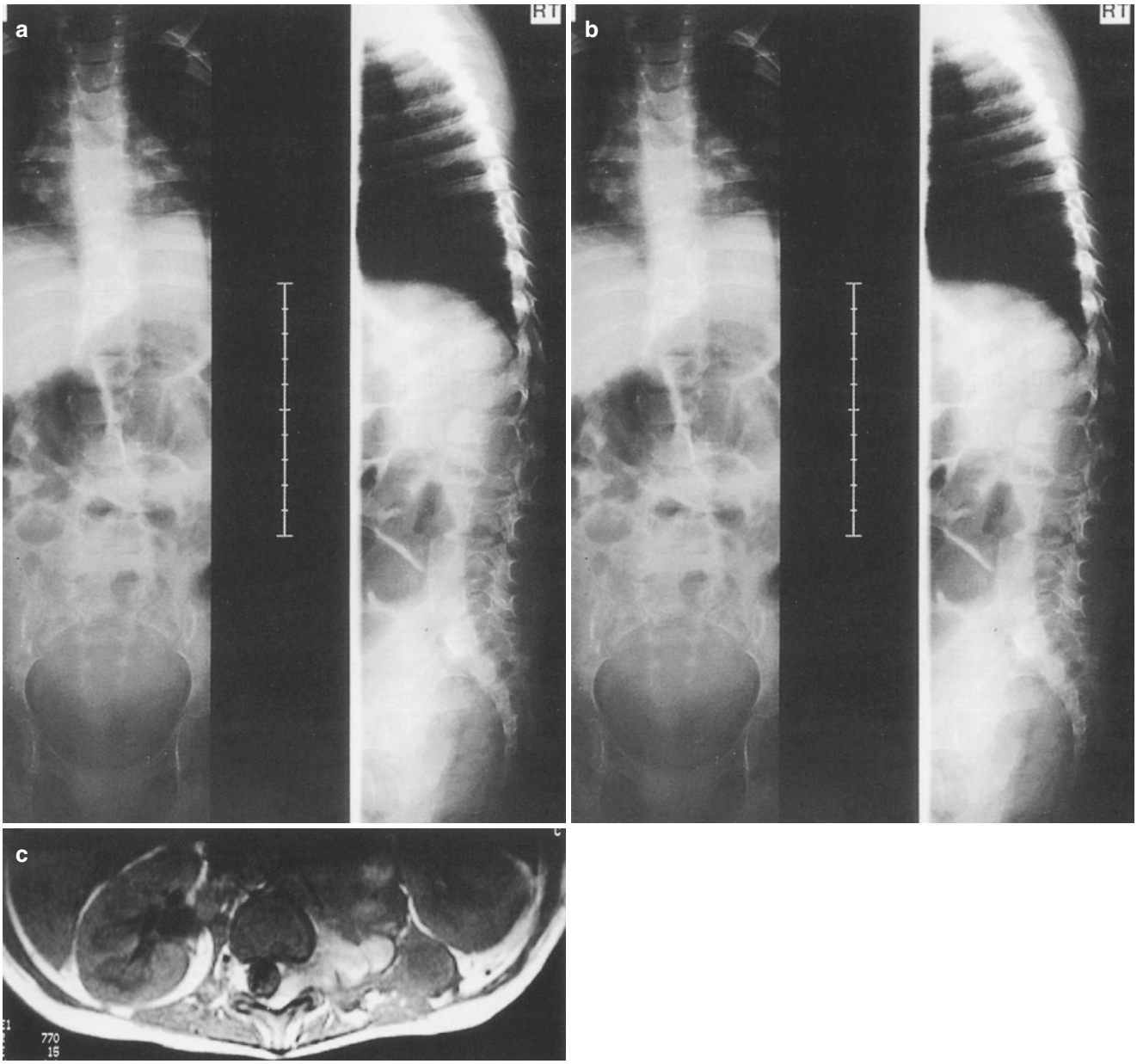

Fig. 25.13 (**a**) Plain anteroposterior and lateral x-rays of a paraplegic 3-year old child showing gross dilation of the nerve root exit foramina. (**b**) Axial and (**c**) sagittal abdominal MRI with gadolinium from the same patient, showing a large enhancing suprarenal mass entering the spinal canal via the left lumbar nerve root foramen. Histologically, this proved to be a ganglioneuroblastoma

Lymphoma can involve the CNS in either primary or secondary fashion. The primary lesions are non-Hodgkins lymphomas and are usually seen in immunocompromised patients [acquired immunodeficiency syndrome (AIDS) or transplant patients], classically being located in the periventricular regions of the cerebral hemispheres. Secondary deposits from both Hodgkin's and non-Hodgkin's lymphomas are seen and are usually extradural – often in the spinal canal. Although generally a medical disease, surgical intervention may be required for acute cord compression not relieved by treatment with chemotherapy.

Neural Origins. The most common causes of drop metastases are PNETs (including the medulloblastomas), anaplastic astrocytomas, ependymomas, and germ cell tumors. Drop metastases are usually seen in the lumbar region. Treatment is generally nonsurgical unless there is a solitary lesion producing acute neurological compression.

Intramedullary Tumors

These relatively uncommon tumors account for only 6 % of central nervous system tumors of childhood [109] and usually occur in adolescence. In the past, these tumors were usually biopsied and given radiotherapy but over the last two

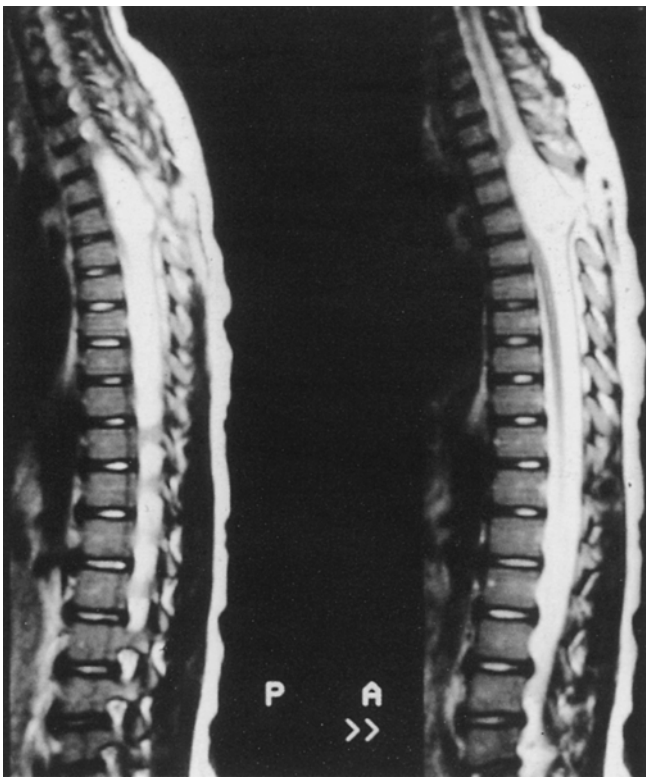

Fig. 25.14 Sagittal T2-weighted MRI of the spine showing a large dermoid (giving the same signal as fat) with marked compression of the spinal cord

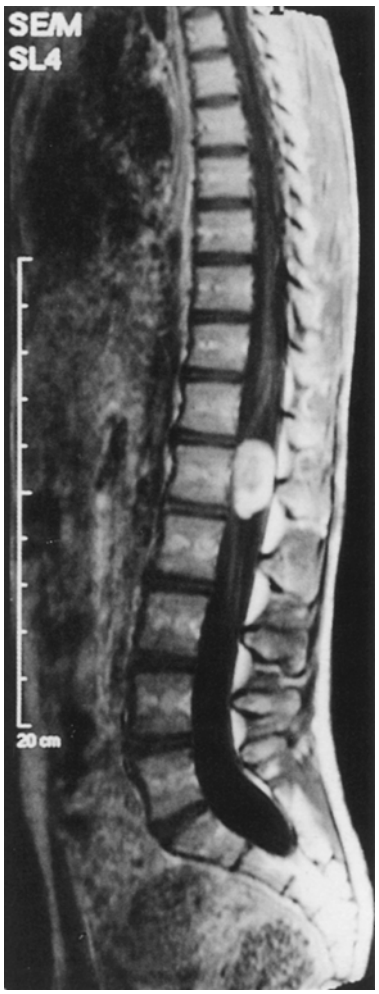

Fig. 25.15 Sagittal T1-weighted MRI of the spine with gadolinium, showing an enhancing tumor arising from the conus

decades, it has become apparent that most of these tumors in children should be treated aggressively surgically.

In the pediatric age range, astrocytomas make up approximately 60 % of the tumors and ependymomas make up less than 30 % (compared with over 50 % in adults) [109]. Within the pediatric population there is also a predilection for the tumors to occur in the cervical region (nearly 50 % versus only 30 % in the adult series) [109]. Interestingly, over 10 % of patients at presentation will have associated hydrocephalus (the cause of which is still debated) [109].

The imaging of these tumors has been revolutionized by MRI, which has shown them to fall into two types – (a) holocord astrocytomas (these in effect are similar to the cystic variety of cerebral astrocytomas with a small solid component associated with a large rostral and caudal cyst which may extend the whole length of the spinal cord), and (b) focal tumors (Fig. 25.15). With the holocord type of tumor, surgery is restricted to removing the solid component and subsequent follow-up studies will show the rostral and caudal cysts to gradually disappear. Likewise, gross total excision of the focal tumor should be undertaken. For both low-grade astrocytomas and ependymomas, no further adjuvant therapy is required. It should also be noted that the success of surgery is directly related to the preoperative neurological status and therefore an expectant policy while a child gradually deteriorates is not in the long-term interest of the patient. Follow-up is required for these patients and if there is recurrence; further surgery is the first line of treatment.

Surveillance is also required to detect delayed spinal deformity which is more likely to occur the higher up the spinal column the tumor is located. The cause of this deformity (kyphosis or scoliosis) is not clear but probably represents a combination of structural damage (laminectomy) and neuromuscular imbalance. Laminoplasty (the re-insertion and holding down of the laminae in their original position after surgery) is now routinely employed (Fig. 25.16) although there is no evidence to date that this decreases the risk of spinal deformity.

Occasionally, the astrocytomas are malignant (usually with a shorter history) and in these cases radical resection is not indicated as not only is the morbidity associated with aggressive surgery far higher, but also there has been no improvement shown in survival after radical surgery. In this group of patients, total neuroaxis radiation is required but the outlook is dismal.

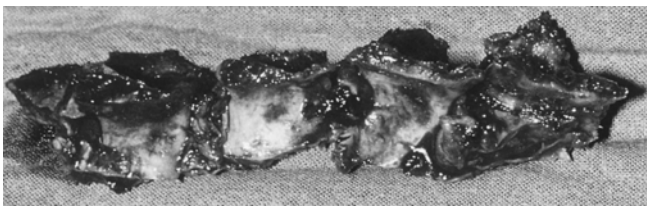

Fig. 25.16 Operative photograph showing four laminae removed en bloc (laminoplasty) which were replaced at the end of the procedure

Intraocular Tumors

Retinoblastoma

Retinoblastoma is the commonest ocular tumor of childhood, affecting one in 20,000 live births worldwide [110], with no racial or gender predilection.

It results from loss of the Rb tumour suppressor gene (Ch13q14). In the genetic (germ-line or heritable) form, every cell is missing one copy of the Rb gene. In the somatic (non heritable) type, a single developing retinal cell loses one copy of the Rb gene during retinal development. This is why genetic cases often have multiple tumours in one or both eyes, and can develop cancers elsewhere, while somatic cases are unilateral and unifocal [111].

Inheritance Patterns

Over 90 % of cases are sporadic. 40 % of all cases are bilateral. Over 90 % of children carrying the Rb gene defect will develop retinoblastoma [111].

Clinical Presentation

Bilateral cases often present early with poor vision, and nystagmus. Unilateral cases usually present later, at 2–3 years, with leukocoria and squint, or with glaucoma, iris heterochromia, phthisis bulbi, orbital inflammation and hyphaema.

Late presentation with proptosis or orbital mass carries a very poor prognosis (Fig. 25.17).

The tumour can spread along the optic nerve, or through the choroid to brain, bones, lungs and abdominal solid organs.

Digital flash photography can highlight the white reflex in some cases, and lead to earlier detection (Fig. 25.18).

The diagnosis of retinoblastoma is essentially clinical, supported by imaging in some cases. Diagnostic biopsy is contra-indicated because of the risk of extra-ocular spread.

The typical findings are one or more round white retinal masses (Fig. 25.19). A characteristic feature is calcification within the tumour on ophthalmoscopy or ultrasonography [16].

Fig. 25.17 Advanced stage retinoblastoma in a child from third world country

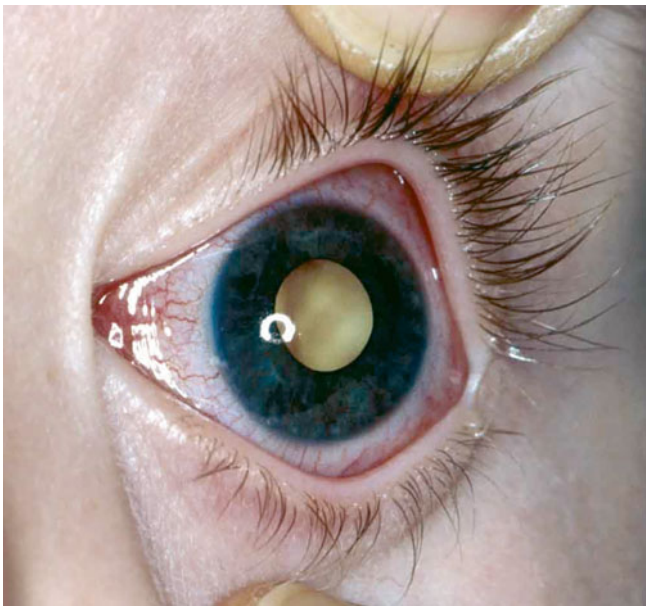

Fig. 25.18 Retinoblastoma presenting with leukocoria of the eye

The diagnosis can be confirmed histologically if the eye is enucleated, with characteristic Flexner–Wintersteiner rosettes, Homer Wright rosettes, and fleurettes (Fig. 25.20).

Genetic Testing

Mutation testing: can be performed on blood, and tumour tissue if available (from the enucleated eye). This helps identify germ line cases and consequently determine risk to the fellow eye and to unaffected relatives.

Differential Diagnosis

Coat's disease, Persistent fetal vasculature (PFV), Retinal dysplasia, congenital retinal infection (e.g., toxocariasis),

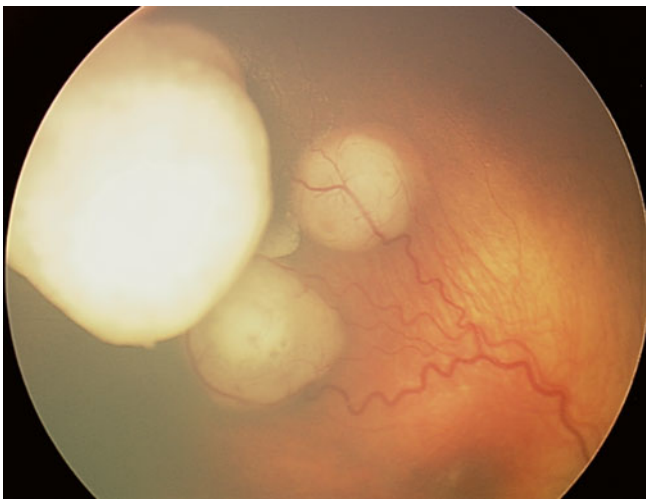

Fig. 25.19 Multiple white retinoblastoma tumours (Retcam photo)

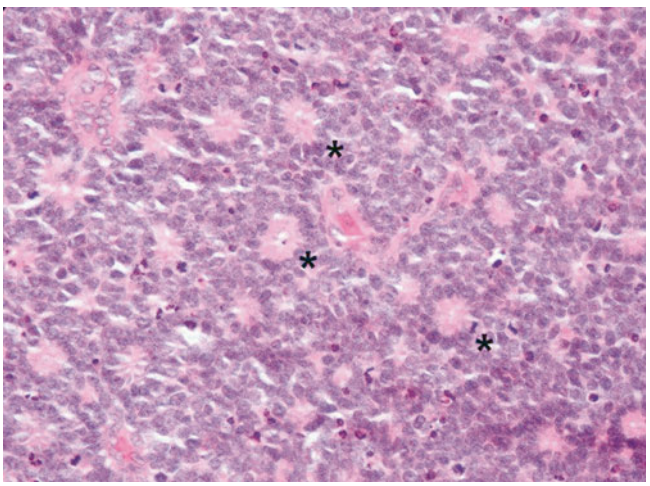

Fig. 25.20 Typical Retinoblastoma with Flexner Wintersteiner rosettes (*asterisks*)

congenital cataracts and glaucoma are all differential diagnoses that can be distinguished on clinical examination [112] (see Table 25.5).

Table 25.5 Table showing a differential diagnostic list of intraocular tumours

Primary ocular disease
Coats disease
Persistent hyperplastic primary
vitreous
Cataract
Coloboma
Retinopathy of prematurity
Myelinated retinal nerve fibers
Osseous choristoma
Infections
Toxoplasmosis Toxocariasis CMV retinitis
Metastatic endophthalmitis
Systemic disorders
Tuberous sclerosis
Norrie's disease
Incontinentia pigmenti
Leukemia
Metastatic malignancies
Other primary ocular tumors
Retinal astrocytomas
Medulloepithelioma
Glioneuroma
Hemangiomas
Retinal pigment hamartomas

Treatment

Retinoblastoma has evolved from a deadly childhood cancer to a largely curable cancer within the past 40 years. Current treatment strategies aim to salvage the eye and provide the best visual outcome possible. This requires significant multidisciplinary input and should be coordinated by a specialised centre.

The various modalities of treatment are:

Chemotherapy: Its main role is to shrink the tumours to a size where laser treatment can be effective (chemoreduction). It is also very effective against vitreous and subretinal disease, and for extraocular involvement and metastases [113].

Chemotherapy can be delivered by 4 routes-Systemic-Common regimens include carboplatin, etoposide, and vincristine (JOE or CEV chemotherapy). There are significant short and long term side effects of chemotherapy, including hearing loss with carboplatin, and nephrotoxicity.

Typically, this involves 4–6 cycles at 3 weekly intervals.

Peri-ocular- subtenon injections of Carboplatin or Topotecan

Intra-arterial- a newer technique involving trans-femoral canulation of the ophthalmic artery to deliver drugs such as Melphalan and Topotecan into the ocular circulation. Generally used as second line treatment for residual/recurrent disease.

Intra-vitreal- direct injection of chemotherapeutic agents into a disease free quadrant of the vitreous after anterior chamber aspiration to soften the eye. This is a new technique which holds promise for vitreous disease which can be difficult to eradicate. Although long term experience is lacking, the initial results are encouraging in selected cases [114].

Laser treatment- suitable for primary treatment of smaller tumours, or larger tumours after (chemoreduction). Laser treatment is however not effective for vitreous seeds.

Laser is delivered through dilated pupils using the indirect ophthalmoscope or microscope. The two common laser

wavelengths are 532 nM green light and 810 nM infrared light (Large spot infrared thermotherapy).

Cryotherapy: trans-scleral delivery results in temperatures of −60 to −80 °C, and is suitable for larger, peripheral tumours.

Radiotherapy: Once the mainstay of treatment, external beam radiotherapy (EBRT, teletherapy) is now reserved for diffuse disease in the only remaining eye, or recurrent disease not responsive to all other forms of treatment. There are significant risks including secondary malignancies in germ line cases, cataracts, dry eyes, soft tissue and bony atrophy.

Plaque brachytherapy involves high dose of radiation to a localized area without the risks of EBRT. It is highly effective against localized vitreous disease and for elevated tumours.

Enucleation: is the treatment of choice for advanced unioocular disease or very advanced eye of bilateral cases.

The eye is sent for histology, and mutation studies. A porous or non porous spherical orbital implant of appropriate size is used depending on the age of the child.

A prosthetic shell painted to match the other eye is fitted in due course for cosmesis.

Treatment Principles

A combination of treatment modalities helps minimize adverse effects.

Examination under anaesthesia (EUA) at decreasing frequency as the child grows older is important for early detection of recurrent or new tumours, with examinations without anaesthesia for older children.

During active treatment, chemotherapy is given over 4–6 cycles at 3–4 weekly intervals, with EUAs before each cycle to monitor response and apply local treatment (laser or cryotherapy). Local treatment may be continued at further EUAs until all tumours are inactive.

Supportive Treatment

Prosthesis fitting for enucleated eyes, psychological support for children and families, protective eye wear for the better/remaining eye during contact sport, long term oncological surveillance especially for germ line cases, and genetic/lifestyle health counseling are all important.

Early Diagnosis- The Role of Imaging and Tissue Sampling

If there is a family history of retinoblastoma there are several options to prevent retinoblastoma or enable early detection

(i) Pre-implantation genetic diagnosis (PIGD) involves screening embryos at the blastocyst stage. Unaffected embryos are selectively implanted ensuring the foetus is born free of the retinoblastoma mutation. Additionally, there is no risk of second cancers, and no risk to future generations. The obvious disadvantage of this technique is the need for in-vitro fertilization (IVF).

(ii) Chorion villous sampling (CVS) or amniocentesis for prenatal RB mutation testing.

(iii) Prenatal ultrasound- in the last few weeks of pregnancy. There is no consensus on the subject of early induction of labour to enable early treatment.

(iv) Cord blood testing for the Rb mutation.

(v) Free fetal DNA testing. This exciting new technique involves testing free (extracellular) fetal DNA which is known to cross the placental barrier. In cases where the mother is healthy and the father is the mutation carrier, maternal blood is tested using DNA amplification. If the mutation is found in maternal blood, one can deduce that it has come from the fetus which must be carrying the mutation. This can then be confirmed at birth with cord blood testing.

Screening for Retinoblastoma

If the mutation for the index case is known, blood testing can be offered to relatives. If the relative is mutation positive or if the mutation is not known for the index case, and risk cannot be excluded, screening exams are offered to enable early detection and treatment.

Screening is not needed if the relative does not carry the mutation.

Prognosis

Most untreated tumours proceed to local invasion and metastasis to cause death within 2 years. Occasionally however, the tumour may spontaneously stop growing to form a retinoma, or necrose to cause phthisis bulbi (shrunken globe).

Most small/medium tumours can be successfully treated while preserving useful vision, and globe salvage is possible in many larger tumours The survival rate varies between as low as 30 % in some developing countries to 95 % in the developed world. Poor prognostic factors include optic nerve involvement and extra-ocular spread.

Recurrence

Recurrence can develop within the eye in previously treated tumours, and regular follow-up examinations are essential. Delayed recurrence in the orbit or distant metastases can occur several years after the initial presentation [33].

Risk of Second Cancers and the Role of Long Term Surveillance

Patients with germ-line mutations are at increased risk of developing secondary malignancies such as pinealblastoma

(trilateral retinoblastoma) osteogenic or soft tissue sarcomas, melanoma and bladder cancer with cumulative risk between 20 and 48 % over 50 years in various studies [115]. This risk is increased with radiation exposure [37]. Patient education and health awareness play a key role in minimising delay in diagnosis and treatment of second malignancies in these patients.

Research Directions

It is likely future research will be directed towards targeted molecular therapy to individualize treatment, exploring biologic treatment eg anti angiogenic agents, growth factors and gene therapy to prevent tumour formation.

Medulloepithelioma

Medulloepithelioma is a rare tumor which arises from undifferentiated nonpigmented ciliary epithelium (though there are isolated reports of pigmented medulloepitheliomas in children). A report in 1988 detailed only 16 medulloepitheliomas recorded at the Institute of Ophthalmology in London over a 25-year period [113]. They can be locally invasive with malignant features and orbital invasion, but distant metastases are uncommon.

They most commonly present between 2 and 4 years of age as a pink-colored mass arising from the iris or ciliary body appearing in the anterior chamber of the eye. Secondary changes such as cataract with reduced vision or iris rubeosis and glaucoma may also be presenting features. Histopathological examination has shown that rubeosis iridis is the most common clinicopathological feature.

More than half of all medulloepitheliomas are classified as benign [115] while the remainder shows cytological features which may resemble neuroblastoma cells, features of embryonal sarcoma, or astrocytoma cells. When histopathology is difficult, because of poor differentiation, diagnosis may be facilitated by the use of immunohistochemistry to identify the neuro-epithelial origin of the tumor [116].

For some tumors local resection with an iridocyclectomy can be curative. Detailed ultrasonographic examination will serve to indicate the extent of the tumor and is a valuable aid in assessing the feasibility of local resection [117].

Successful conservative treatment with local Iodine 125 brachytherapy has also been described [118], but, in most instances, enucleation of the affected eye is necessary. If examination of the enucleated eye shows evidence of extrascleral extension than surgery needs to be followed by postoperative orbital radiotherapy. Rarely, if there is evidence of orbital recurrence, then orbital exenteration may be required.

Malignant Melanoma of the Iris and Choroid

Malignant melanoma of the choroid is the most common primary ocular tumor but rarely affects children. In a series of 3706 consecutive ocular melanomas, only 40 affected individuals were less than 20 years of age and 78 % were between 15 and 20 [119, 125]. Nonetheless, there are isolated reports of very early onset uveal melanoma [120, 126], and it must be considered in the differential diagnosis of retinoblastoma.

Diagnosis is established by identifying the characteristic ultrasonography findings of high internal reflectivity, and fluorescein angiography shows mottled fluorescence in the early phases.

Treatment depends on the size and location of the melanoma, but options include local resection, plaque brachytherapy, transpupillary thermotherapy with the diode laser or, most commonly, enucleation of the affected eye.

Juvenile Xanthogranuloma (JXG)

JXG is a benign inflammatory lesion of the iris and ciliary body containing histiocytes, lymphocytes, and Touton giant cells. Clinically JXG may take the form of a discrete nodule or a diffuse thickened yellow plaque on the iris, and is often associated with an ipsilateral, yellow papular skin lesion. JXG is a notorious cause of spontaneous hyphema (bleeding into the anterior chamber of the eye) in children, and if it shows that tendency, treatment with topical or subconjunctival steroids may be necessary.

Occasionally the uveal tract may become diffusely involved in Letterer-Siwe disease, a systemic histiocytic disorder.

Intraocular Vascular Tumors

Vascular intraocular tumors may appear in isolation or as part of a neurocutaneous syndrome (see section "Phakomatoses").

Choroidal Osteoma

Choroidal osteoma is usually unilateral, and consists of a well-circumscribed, yellow/orange placoid lesion. They show genuine bone formation with osteoblasts, osteocytes, and osteoclasts all present. The bone is laid down in trabeculae and there are intertrabecular marrow spaces.

They require no treatment and are easily identified with CT imaging which shows discrete shield-shaped plaque of calcification in the choroid. It should be considered with differential diagnosis for calcified unilateral retinoblastoma.

Myogenic and Neurogenic Tumors

Myogenic tumors, both leiomyomas and rhabdomyosarcomas, are extremely rare in an intraocular location.

Neurogenic tumors are also extremely rare in this location in childhood. The exceptions are those neurogenic tumors associated with the phakomatoses.

The phakomatoses are a group of disorders in which skin, eye, and central nervous system are involved. Included in this group of disorders are:

- Neurofibromatosis type 1 and 2
- Tuberous sclerosis
- Von Hippell-Lindau syndrome
- Sturge-Weber syndrome
- Klippel-Trenaunay-Weber syndrome
- Wyburn-Mason syndrome

Neurofibromatosis type 1 is a common neurocutaneous condition with an autosomal dominant pattern of inheritance. NF1 has a birth incidence of 1 in 2500 to 1 in 3000; the diagnosis is based on clinical assessment and two or more of the features listed in Table 25.6 are required [121]. The causative mutation occurs on the long arm of chromosome 17 at the q11.2 site and results in underproduction of the tumor suppressor protein neurofibrin [122].

Clinicians should be aware that some individuals with mosaic/segmental NF1 present with six or more café au lait patches and skin fold freckling; however, the skin manifestations are in a restricted segment of the body.

Lisch nodules, a highly characteristic pigmented hamartoma are found in 90–95 % of children by the age of 3 years. Histologically they are a variant of neurofibroma and are of value in establishing the diagnosis but need no intervention.

Plexiform neurofibromas, on the other hand, cause significant morbidity because they are diffuse, grow along the length of a nerve, and may involve multiple nerve branches and plexi. The lesions can be nodular, and multiple discrete tumors may develop on nerve trunks. Plexiform neurofibromas infiltrate surrounding soft tissue and bony hypertrophy is evident in some instances.

Table 25.6 Diagnostic criteria for neurofibromatosis 1

6 or more café au lait macules (>0.5 cm in children or >1.5 cm in adults)
2 or more cutaneous/subcutaneous neurofibromas or one plexiform neurofibroma
Axillary or groin freckling
Optic pathway glioma
2 or more Lisch nodules (iris hamartomas seen on slit lamp examination)
Bony dysplasia (sphenoid wing dysplasia, bowing of long bone +/ pseudarthrosis)
First degree relative with NF1

Facial plexiform neurofibromas causing disfigurement appear during the first 3 years of life and commonly affect the orbits and eyelids. Removal of benign plexiform neurofibromas is difficult due to encroachment of the tumor on surrounding structures and its inherent vascular nature. Life-threatening hemorrhage can occur and expert advice from experienced soft tissue tumor or plastic surgeons is essential before removal. A number of agents (including farnesyl transferase inhibitors, antiangiogenesis drugs, and fibroblast inhibitors) are being used in clinical trials to assess their therapeutic effect on growth of plexiform neurofibromas.

There is an 8–13 % lifetime risk of developing malignant peripheral nerve sheath tumors (MPNST) in NF1, but predominantly in individuals aged 20–35 years. These cancers usually but not invariably, arise in pre-existing plexiform neurofibromas.

Optic pathway gliomas (OPG) are grade 1 pilocytic astrocytomas and are found principally in the optic pathways, brainstem, and cerebellum. They occur in about 15 % of children with NF1, are often asymptomatic and more indolent than their counterparts in the general population. However, some tumors produce impaired visual acuity, abnormal color vision, visual field loss, squint, pupillary abnormalities, optic atrophy, proptosis, and hypothalamic dysfunction. The risk of symptomatic OPG is greatest in children under 7 years and older individuals rarely develop tumors that require medical intervention [123]. If the integrity of the chiasm is threatened by an optic nerve glioma it is necessary to consider reducing the tumor volume with chemotherapy. Occasionally surgery is warranted to deal with severe proptosis with corneal exposure, or to debulk extensive chiasmal gliomas. Radiotherapy is not advocated in young children because of potential second malignancy [130].

Neurofibromatosis Type 2 (NF2) is an autosomal dominant neurocutaneous disease that is clinically and genetically distinct from NF1 and occurs in approximately 1 in 25,000 individuals. It is caused by inactivating mutations on chromosome 22q11.2 and is characterized by bilateral vestibular schwannomas. Affected individuals also develop schwannomas on other cranial, spinal, peripheral, and cutaneous nerves. Café au lait patches are less numerous than in NF1 and the skin lesions are predominantly schwannomas. Slit lamp examination reveals juvenile subcapsular lens opacities in the majority of patients and multiple retinal astrocytomas are much more likely than in NF1 (Figs. 25.21 and 25.22).

Children with Tuberous Sclerosis (TS) show a combination of cutaneous angiofibromas, retinal astrocytic hamartomas, and CNS hamartomas causing developmental delay and epilepsy. The ocular lesions require no treatment and will only cause visual disturbance if they are located at the

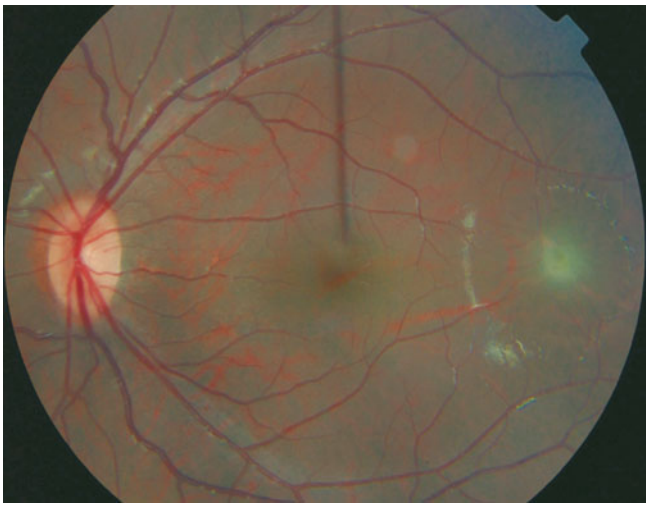

Fig. 25.21 Multiple retinal astrocytomas in neurofibromatosis

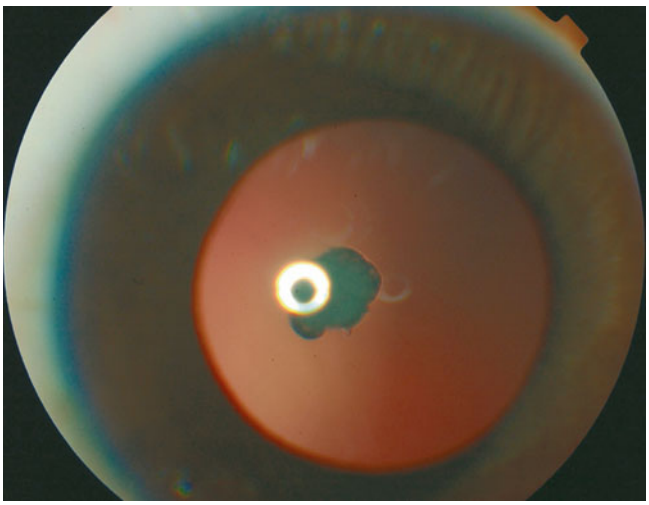

Fig. 25.22 Juvenile subcapsular lens opacities in neurofibromatosis

macula. However, the ophthalmologist may well be the first clinician to recognize the condition, and needs to ensure that a detailed assessment is undertaken, because of the association with renal and cardiac pathology (Fig. 25.23).

Von Hippel-Lindau syndrome is characterized by the formation of retinal capillary angiomas and cerebellar angiomas or hemangioblastomas. The retinal lesion may cause exudation, and since this exudation tends to accumulate at the macula area, it is associated with significant visual loss. In extreme cases the accumulated exudate leads to a retinal detachment, so that treatment at an early stage is desirable.

The aim of treatment is to encourage absorption of the exudate. For lesions between the equator of the globe and the ora serrata, cryotherapy to the base of the hemangioma is most appropriate, using a triple freeze thaw technique. For more posteriorly located tumors isolation with argon laser photocoagulation with later sealing of the feeder vessels is the preferred approach.

The major ophthalmic complication of Sturge-Weber syndrome is glaucoma with up to 30 % of affected children developing glaucoma. The diffuse choroidal hemangioma, which some affected children show, does not require surgical intervention in the vast majority of cases. If it is associated with sight-threatening retinal exudation, then laser photocoagulation, to promote absorption of the exudate, may be attempted.

Orbital Tumors

Orbital tumors in childhood may be benign or malignant; they may be derived from any of the structures within the orbit or they may metastasize to the orbit from a distant site. Table 25.7 reflects the nature and origin of the tumors and is a useful template for this discussion.

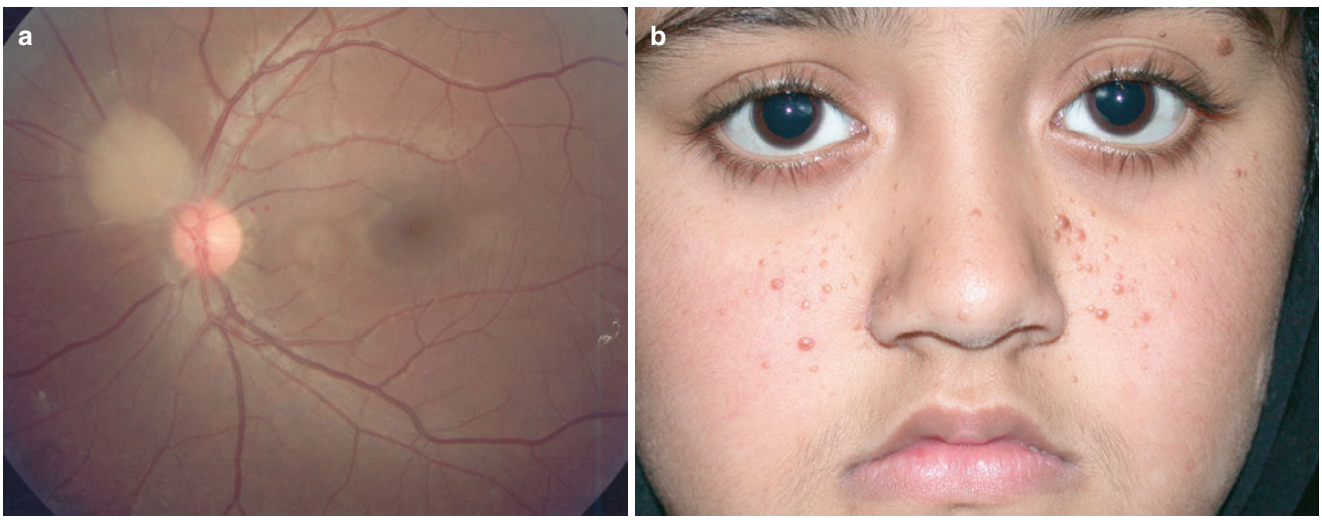

Fig. 25.23 (**a**) Retinal astrocytoma and (**b**) adenoma sebaceum in a child with tuberous sclerosis

Table 25.7 Classification of orbital tumors

Primary benign: Derived from orbital structures
Primary malignant
Secondary benign: Arising from adjacent structures
Secondary malignant
Orbital cysts
Metastatic
Associated with systemic disease

Diagnosis

Regardless of their nature, most orbital tumors present with proptosis and limitation of ocular rotations. Pain and inflammation are more variable symptoms and other signs will depend on the tissue of origin. For example, profound visual loss, pupillary abnormality and optic nerve swelling or atrophy are the hallmarks of optic nerve gliomas but are rarely seen with rhabdomyosarcoma.

Primary Benign Orbital Tumors

Neural
- Optic nerve glioma
- Optic nerve meningioma
- Neurofibroma
- Schwannoma

Vascular
- Capillary hemangioma
- Lymphangioma
- Varix
- AV malformation

Adipose and muscular
- Lipoma
- Myofibroma

Fibrous
- Fibroma
- Fibromyxoma
- Fibrous tissue dysplasia

Osseous and cartilaginous
- Osteoma
- Juvenile ossifying fibroma
- Aneurysmal bone cyst

Optic Nerve Glioma

Optic nerve glioma is the commonest intrinsic tumor of the optic nerve. It typically presents around the age of 5 years with loss of vision, painless axial proptosis, and limited ocular movements. Girls are more commonly affected than boys and up to 50 % of affected children have NF1 [127].

It is a benign, slow growing, low-grade pilocytic astrocytoma and carries a better prognosis when it is associated with NF1 [128]. Occasionally, particularly in younger children, optic nerve glioma shows more aggressive local expansion and these typically are the children likely to need surgical intervention.

The diagnosis is established by imaging which shows a tubular or fusiform swelling of the optic nerve, and characteristic "kinking" of the affected nerve. MRI will show the extent of the tumor, whether there is intracranial extension and any evidence of chiasmal involvement. Visual field testing (in children who are sufficiently cooperative) will identify any involvement of fibers derived from the contralateral optic nerve.

Management consists of observation, including serial visual fields, if the cosmesis is good and there is no threat to the chiasm. Poor vision with severe proptosis, or threatened chiasmal involvement are indication for either chemotherapy (usually with vincristine and carboplatin) or globe sparing optic nerve excision [129, 131]. This surgery can be performed through a lateral orbitotomy if only the orbital portion needs removal, but a craniofacial exposure permits more complete excision of the nerve including the intracranial prechiasmatic portion (Fig. 25.24).

Optic Nerve Meningioma

Optic nerve meningioma is a rare tumor in infants and children. The mean age of presentation is 10 years. It occurs more commonly in males with an increasing incidence with age. The orbit is one of the most common locations. Presentation is of chronic progressive visual loss with mild proptosis associated with diplopia, headache, and ptosis. The tumor is histologically benign but the clinical course tends to be more aggressive in children than in adults. There can be hereditary predisposition and on genetic testing there can be a deletion of part of chromosome 22.

Primary Orbital Cysts

- Dermoid
- Sebaceous
- Hematic
- Hydatid
- Lacrimal duct cyst (Dacryops)
- Microphthalmos with cyst

Fig. 25.24 (**a–c**) Sequence of clinical photos after intralesional injection of triamcinolone and dexamethasone

Malignant Orbital Tumors

Primary Orbital Malignancy
- Rhabdomyosarcoma
- Lacrimal gland adenoid cystic carcinoma
- Sarcoma
- Teratoma

Metastatic orbital malignancy
- Neuroblastoma
- Ewing's sarcoma
- Wilm's tumor

Orbital involvement in systemic malignancy
- Lymphoma
- Leukemia
- Histiocytosis
- Plasmacytosis

Primary Benign Orbital Tumors

- Sinus mucocoele
- Encephalocoele
- Meningocoele

Other Causes of Proptosis in Childhood

Lymphoid
- Benign reactive lymphoid hyperplasia

Histiocytic
- Eosinophilic granuloma

Lacrimal
- Ectopic lacrimal gland
- Lacrimal gland inflammation

Inflammation
- Orbital Pseudotumor
- Orbital myositis
- Wegners
- Sarcoid
- Tuberculosis (Table 25.8)

Table 25.8 Other causes of proptosis in childhood

Lymphoid
Benign reactive lymphoid hyperplasia
Histiocytic
Eosinophilic granuloma
Lacrimal
Ectopic lacrimal gland
Lacrimal gland inflammation
Inflammation
Orbital pseudotumor Orbital myositis Wegners
Sarcoid
Tuberculosis

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Tumors of the Lung and Chest Wall

26

Stephen J. Shochat, Robert C. Shamberger, and Christopher Weldon

Primary pulmonary tumors of the lung are infrequent in infants and children; the majority of pulmonary neoplasms in children are due to metastatic disease. The approximate ratio of primary pulmonary tumors to metastatic neoplasms and non-neoplastic lesions of the lung is 1:5:60 [98]. Although primary pulmonary tumors are rare in children, the majority are malignant. In a review of 383 primary pulmonary neoplasms in children by Hancock et al. [33], 76 % were malignant and 24 % were benign. This incidence is similar to that previously reported by Hartman and Shochat and Weldon and Shamberger [35]. Table 26.1 demonstrates the spectrum of primary pulmonary neoplasms seen in children. This chapter presents the more common benign and malignant primary pulmonary tumors and discusses the management of pulmonary metastatic disease in the pediatric population.

Lung Tumors: Benign

Inflammatory Myofibroblastic Tumor (Plasma Cell Granuloma)

Inflammatory myofibroblastic tumor (IMT) has also been called inflammatory pseudotumor, histiocytoma, and fibrohistiocytoma [46]. This lesion, which is seen frequently in adults, occurs rarely in children younger than 10 years (approximately 8 % of all cases of IMT). However, IMT is the most common benign tumor in children and accounts for slightly more than 50 % of all benign lesions and approximately 20 % of all primary lung tumors [35]. These tumors usually present as peripheral pulmonary masses, but occasionally present as polypoid endobronchial tumors [2, 6]. The pathogenesis of IMT is not well understood, but an antecedent pulmonary infection has been reported in approximately 30 % of cases. The mean age at presentation in children is 7 years, and 35 % of the children are between 1 and 15 years of age (Fig. 26.1) [2, 6, 96]. Many children are asymptomatic at the time of presentation, but fever, cough, pain, hemoptysis, pneumonitis, and dysphagia may be present. The natural history is that of a slow-growing mass starting as a focus of organized pneumonia

Table 26.1 Primary pulmonary neoplasms in children

Type of tumor	No. of patients (%)[a]
Benign (n = 92)	
Plasma cell granuloma	48 (52.2)
Hamartoma	22 (23.9)
Neurogenic tumor	9 (9.8)
Leiomyoma	6 (6.5)
Mucous gland adenoma	3 (3.3)
Myoblastoma	3 (3.3)
Benign teratoma	1 (1.1)
Malignant (n = 291)	
Bronchial "adenoma"	118 (40.5)
Bronchioalveolar carcinoma	49 (16.8)
Pulmonary blastoma	45 (15.5)
Fibrosarcoma	28 (9.6)
Rhabdomyosarcoma	17 (5.8)
Leiomyosarcoma	11 (3.8)
Sarcoma	6 (2.1)
Hemangiopericytoma	4 (1.4)
Plasmacytoma	4 (1.4)
Lymphoma	3 (1.0)
Teratoma	3 (1.0)
Mesenchymoma	2 (1.7)
Myxosarcoma	1 (0.3)

Modified from Hancock et al. [33]
[a]Percent of benign or malignant tumors

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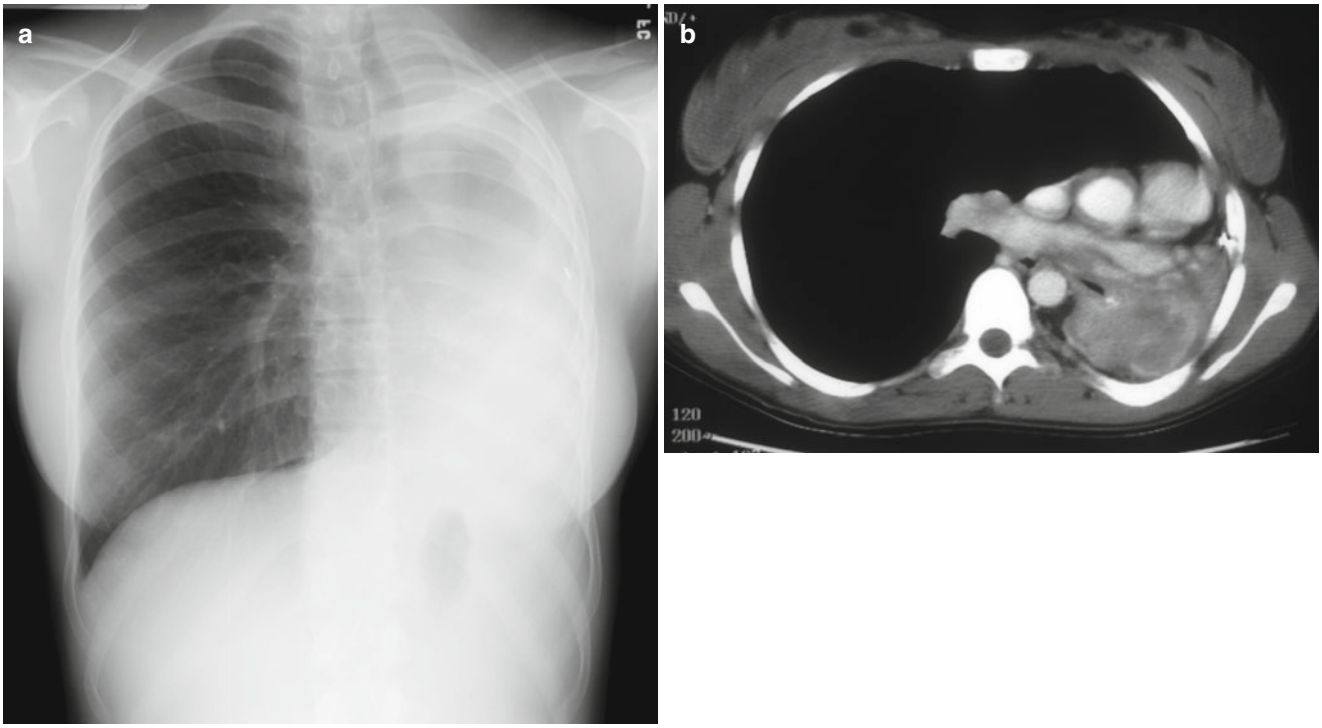


Fig. 26.1 (**a**) Chest radiograph of an 18 year old female who presented with a 6-month history of increasing cough and shortness of breath and recent hemoptysis. Study revealed complete opacification of the left chest. (**b**) Subsequent computed tomography (CT scan) demonstrated occlusion of the mainstem bronchus and a calcified mass in the lung. Pathology on the left lung demonstrated inflammatory myofibroblastic tumor treated with a pneumonectomy

with a tendency for local invasion. However, rare cases of rapid growth have been reported [100]. Extension of the tumor beyond the confines of the lung is common. At least four deaths have been reported due to tracheal obstruction or involvement of the mediastinum by massive lesions.

Treatment consists of a conservative pulmonary resection with removal of all gross disease if possible. Primary hilar adenopathy may be present, and local invasion with disregard for tissue planes mimics malignancy. A frequent problem is establishing the benign nature of the lesion prior to resection. Malignant fibrous histiocytoma of the lung, an extremely rare tumor in children, can mimic IMT radiographically and must be considered in the differential diagnosis [66]. Recurrences following resection occur if the lesion is incompletely resected. Nonsteroidal anti-inflammatory drugs have been used to treat large inoperable lesions, with encouraging results [88].

Hamartoma

Pulmonary hamartoma is the second most frequent benign lesion seen in children. This lesion usually presents as a parenchymal lesion which can be quite large. Approximately one quarter are calcified, and "popcorn-like" calcification is pathognomonic [23]. Two endobronchial lesions have been reported. Four tumors occurring in the neonatal period were quite large and were associated with significant respiratory distress; all were fatal. An interesting association seen in Carney triad is the combination of pulmonary hamartoma, extra-adrenal paraganglioma, and gastrointestinal smooth muscle tumors (GIST); the majority of these patients are young women. The tumors seen in this triad have an unpredictable but often indolent biologic behavior [101]. Conservative pulmonary resection is the treatment of choice; however, lobectomy or even pneumonectomy may be required, especially for large lesions and endobronchial lesions when sleeve resection is not possible or distal parenchyma has been destroyed by chronic obstruction.

Lung Tumors: Malignant

Bronchial Adenoma

Bronchial adenoma is the most frequently encountered primary malignant pulmonary tumor. These are a heterogeneous group of primarily endobronchial lesions. Although adenoma implies a benign process, all varieties of bronchial adenomas occasionally display malignant behavior. There are three histologic types: carcinoid tumor (most common), mucoepidermoid carcinoma, and adenoid cystic carcinoma.

Carcinoid tumors account for 80–85 % of all bronchial adenomas in children [74]. The presenting symptoms are due to bronchial obstruction: cough, recurrent pneumonitis, and hemoptysis (Fig. 26.2a, b). Symptoms are often present for months due to the rarity of this lesion and diagnostic challenges; occasionally, children with wheezing have been treated for asthma, delaying diagnosis as long as 4–5 years. Metastatic lesions are reported in approximately 6 % of cases, and recurrences occur in 2 %. Bronchial lymphadenopathy is often related to chronic inflammation and not to metastatic disease. There is a single report of a child with a carcinoid tumor and metastatic disease who developed the classic carcinoid syndrome [52]. Bronchial adenomas of all histologic types are associated with an excellent prognosis in children, even in the presence of local invasion [86].

Endobronchial biopsy may be hazardous because of the risk of hemorrhage, and endoscopic resection is not recommended due to the risk of tumor remnants in the wall of the bronchus. Bronchography or computed tomography (CT) may be helpful to determine the degree of bronchiectasis distal to the obstruction, because the degree of pulmonary destruction may influence surgical therapy (Fig. 26.2c, d) [3]. However, Tagge et al. [90] described a technique for pulmonary salvage despite significant distal atelectasis. Conservative pulmonary resection with removal of the involved lymphatics is the treatment of choice. Sleeve segmental bronchial resection is possible in children and is the treatment of choice when feasible [27, 45, 75]. Adenoid cystic carcinomas (cylindroma) have a tendency to spread submucosally, and late local recurrence or dissemination has been reported. In addition to *en bloc* resection with hilar lymphadenectomy, an intraoperative examination of the bronchial margins should be carried out if the margins are close to avoid leaving residual tumor. Mucoepidermoid carcinoma of the bronchus has also been described in children as young as 4 years [81], and they are defined as low- or high-grade lesions.

Bronchogenic Carcinoma

Although bronchogenic carcinoma is rare in children, it was the second most common malignant lesion reported by Hancock et al. [33] Interestingly, squamous cell carcinoma was rare, with the majority of tumors being either undifferentiated carcinoma or adenocarcinoma. The term bronchioalveolar carcinoma has been used in most cases [65]. These tumors are associated with both cystic adenomatoid malformations and intrapulmonary bronchogenic cysts. Survivors are rare as mortality exceeds 90 %. The majority of children present with extensive local involvement and/or disseminated disease, and the average survival is only 7 months (Fig. 26.3). Complete resection, followed by adjuvant chemotherapy is recommended for the rare localized lesion.

Pulmonary Blastoma

Pulmonary blastoma is a rare malignant tumor that arises from mesenchymal blastema. This tumor is an aggressive lesion, with metastatic disease at presentation in approximately 20 % of cases [20, 33]. They may arise from the lung, pleura, and mediastinum [69]. These tumors are classified into three types: Type I (purely cystic), Type II (cystic and solid), and Type III (completely solid) [26]. Type I tumors are difficult to distinguish radiographically from cystic adenomatoid malformation (Fig. 26.4a, b) [40]. Occasionally, they may arise in an extralobar sequestration or lung cyst. The majority of cases occur in the right hemithorax. Frequent sites of metastases are the liver, brain, and spinal cord. Local recurrence is frequent, and the mortality rate is approximately 40 % [17, 33, 44]. The majority of children present before 4 years of age, and symptoms include persistent cough, chest pain, episodes of pneumonia that are refractory to antibiotics, and hemoptysis. Diagnosis is established by CT of the chest, bronchoscopy, and biopsy. Because most are located peripherally, resection is usually possible by segmental or lobar resection. The use of multimodal neoadjuvant chemotherapy and radiation following surgical resection has shown promising results in a few patients with extensive disease and dissemination [44, 69]. Dramatic response of the primary may facilitate resection. Chemotherapeutic agents that have been used include actinomycin D, vincristine, cyclophosphamide alternating with courses of doxorubicin, and cisplatin. Histologic evaluation of the tumor shows an exclusive mesenchymal composition, including primitive tubules, immature blastema, and spindle cell stroma. Some demonstrate elements of embryonal rhabdomyosarcoma arising within a multicystic lesion.

An important consideration is the association of primary lung tumors with congenital cystic pulmonary malformations. These lesions may be asymptomatic and be discovered incidentally. In some instances, the natural history of the lung cyst is unknown, and a few may regress [51]. Although some authors recommend simple observation, most pediatric surgeons argue against prolonged observation of cystic lesions because of an increased risk of infection, pneumothorax, sudden cyst enlargement with potential respiratory compromise, and associated malignancy [1, 16, 51, 60, 68, 80, 89]. As mentioned above there is evidence suggesting a relationship between type IV cystic adenomatoid malformation and type I pulmonary blastoma. While complete lobectomy with negative margins is adequate treatment for these patients, close observation is recommended [39, 58, 73]. If patients with asymptomatic cystic malformations are observed without resection, they should be followed closely and evaluated frequently.

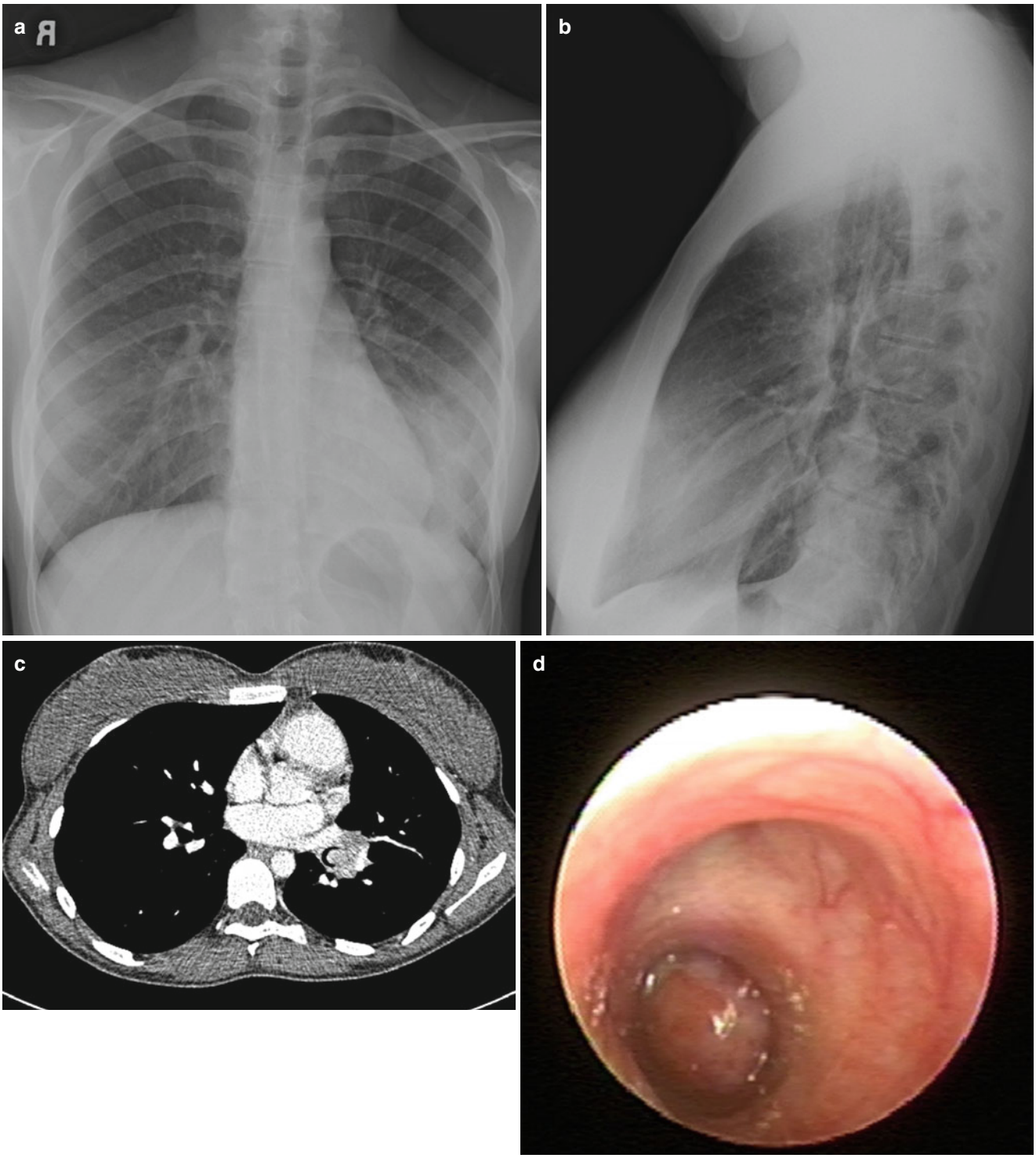


Fig. 26.2 (**a**) This 16-year old female who presented with a pneumonia and pleural effusion which was treated with catheter drainage and antibiotics. Follow-up chest radiographs (**a**, **b**), however, continued to show collapse of the left lower lobe for over a year which led to a CT scan (**c**). This demonstrated an endobronchial lesion extending into the left bronchus intermedius and occluding it with complete collapse of the left lower lobe. Bronchoscopy (**d**) localized the lesion to just distal to the origin of the upper lobe and lingular bronchi

Rhabdomyosarcoma

Rhabdomyosarcoma of the lung is rare and accounts for only 0.5 % of all childhood rhabdomyosarcomas [94]. Many of the lesions are endo-bronchial in origin. This is an important issue because 4 % of benign tumors and 8.6 % of malignant tumors enumerated in Table 26.1 were associated with previously documented cystic malformations [33]. Tumors that developed in these malformations included 11 sarcomas, 9 pulmonary blastomas, 3 bronchogenic carcinomas, and 2 mesenchymomas.

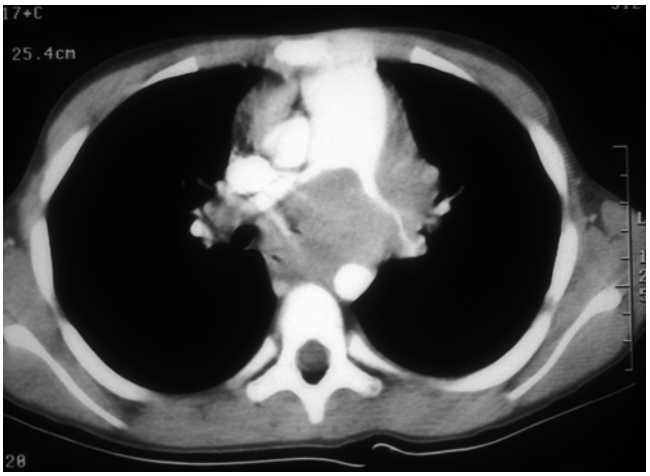


Fig. 26.3 This CT scan of an 8 year old boy who presented with a cough shows a large lesion arising in the hilum of the lung and extending into the mediastinum surrounding the left pulmonary artery. Needle biopsy demonstrated a bronchogenic carcinoma which had a rapidly progressive course despite intensive chemotherapy

Treatment of Metastatic Disease

The histology of the primary tumor and its response to combined-modality therapy govern the management of the pulmonary metastases [48]. Pulmonary metastases should not be resected until the primary tumor is eradicated and other sites of metastatic disease are excluded. Pulmonary metastasectomy is considered most frequently for osteosarcoma [47].

Osteosarcoma

Children with osteosarcoma should be considered for resection of pulmonary metastases once the primary lesion is controlled. The overall disease-free survival is approximately 40 % in children who develop metachronous pulmonary metastases. Multiple factors, such as number of pulmonary nodules and time of recurrence, define the prognosis of children with osteosarcoma and pulmonary metastases [36, 93]. Roth et al. [76] showed that patients with fewer than four pulmonary nodules had an improved survival over those with more than four lesions. According to Goorin et al. [28], a complete resection of all pulmonary lesions is an important determinant of outcome, and penetration through the parietal pleura is associated with an

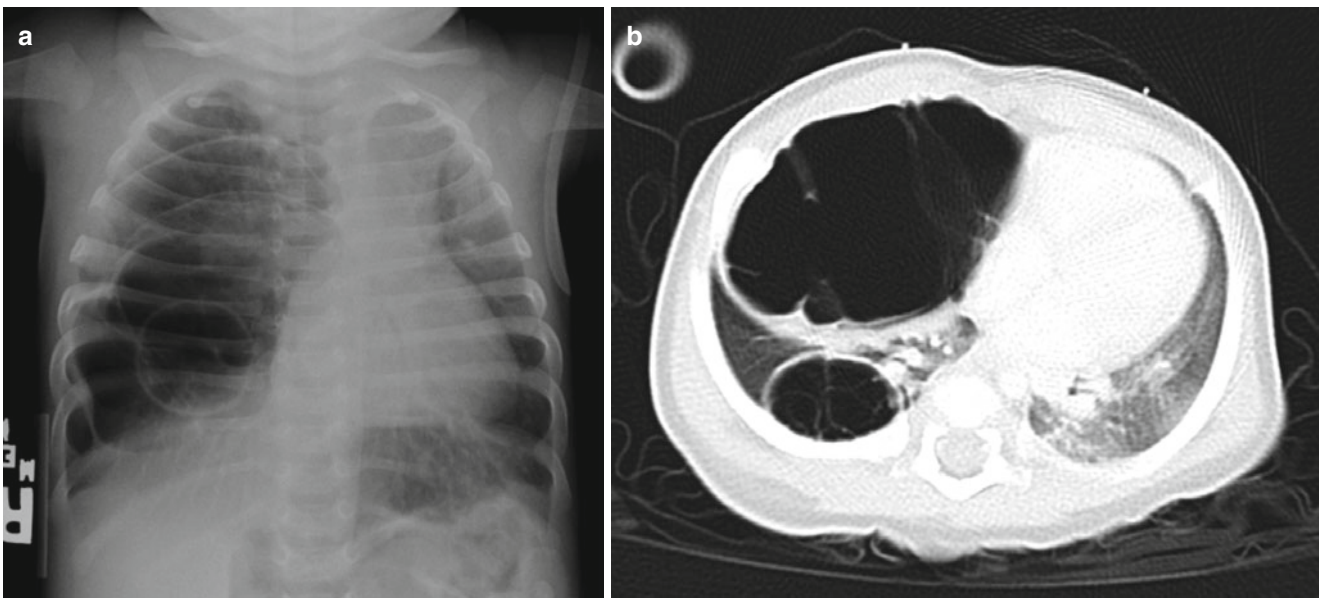


Fig. 26.4 (**a**) Chest radiograph of an 11 year old female who presented with shortness of breath and a cough demonstrated a right sided pulmonary mass. (**b**) Her CT scan revealed a multilobular mass and needle biopsy established the diagnosis of pulmonary blastoma. An extrapleural pneumonectomy and post operative radiotherapy were utilized for local control and she remains free of disease 16 years later

adverse outcome. Although somewhat controversial, the outlook seems to be somewhat improved, even in patients presenting with pulmonary metastases, if all metastatic lesions are resected [59]. Harris et al. [34] reported a 68 % rate of survival in 17 patients with fewer than eight pulmonary nodules at presentation following chemotherapy, resection of the primary tumor, and pulmonary metastasectomy. An aggressive attempt at surgical resection of pulmonary metastases is indicated in osteosarcoma, possibly irrespective of the number of lesions or the interval between presentation and identification of metastases. A number of recent studies have shown a survival advantage in patients with repeated metastasectomy including patients with as many as five recurrences [10, 13, 17].

Soft Tissue Sarcoma

The usefulness of resecting pulmonary metastases in patients with soft tissue sarcoma depends on the histologic subtype. Rarely is pulmonary resection of metastatic lesions required in rhabdomyosarcoma, and resection of pulmonary metastasis in Ewing's sarcoma is not efficacious [38, 48]. Several European protocols are being designed to better define the role of pulmonary resection in Ewing's sarcoma. The remaining sarcomas should be considered for resection if complete excision is possible and the patient's primary tumor .has been completely resected. The time to development of pulmonary metastases, number of lesions, and tumor doubling time are all significant prognostic factors in soft tissue sarcomas. Historically, 10–20 % of these patients can be salvaged by resection of pulmonary metastases [55].

Wilms' Tumor

Rarely is pulmonary resection of metastatic disease required in children with Wilms' tumor. In a review of the National Wilms' Tumor Study by Green et al. [29], no advantage of pulmonary resection was found compared with chemotherapy and radiation therapy alone. In an attempt to avoid pulmonary radiation, deKraker et al. [21] suggested a protocol using primary pulmonary resection after chemotherapy for pulmonary metastases. Only 5 of 36 patients ultimately required resection of pulmonary metastases following chemotherapy, as most patients had a complete response with chemotherapy alone. One encouraging finding was that only 4 of 36 children required whole lung irradiation. Because the results of chemotherapy and whole-lung irradiation are excellent for children with Wilms' tumor and pulmonary metastases, pulmonary resection of metastases should be reserved for selected cases.

Tumors of the Chest Wall

Epidemiology

Tumors of the chest wall are rare in the pediatric population with an incidence of less than 2 % of all tumors in children [24, 50]; up to two-thirds of these lesions are malignant [99]. The majority arise from the bony structures of the chest wall (55 %), as opposed to soft tissue (45 %) [15]. Collectively, a 60 % 5-year overall survival rate for all tumors has been reported, with a recurrence rate of 50 % (local and distant). The 5-year survival rate after relapse is only 17 % [49].

Presentation

Masses of the chest wall typically present with respiratory symptoms or pain, with pain being the most frequent in malignant lesions. Many have extensive protrusion into the pleural cavity with limited if any external findings. In infants and young children the benign lesions are often found incidentally by caregivers, while older children and young adults may present with larger masses that have been present and growing for some time until they produce respiratory symptoms. Incidental discovery on routine chest imaging has been reported to be as high as 20 % [77]. They can be found anywhere on the thorax, and the tissue of origin is generally mesenchymal in nature, regardless of whether the tumors are malignant or benign. Hence, sarcomas are the most common malignant tumors, while carcinomas are almost nonexistent. The symptoms of respiratory compromise or dysfunction – tachypnea, hypoxia, cough, dyspnea on exertion – and these symptoms may have been present for quite a while before seeking medical advice. Symptoms stem from parenchymal compression from the mass intruding into the pleural space and onto the lung or from malignant effusions, both of which interfere with normal respiratory mechanics. Pulmonary function tests may be indicated prior to proceeding with any intervention based on respiratory symptoms.

Diagnostic Adjuncts

Imaging studies should include first, erect, posterior-anterior and lateral chest radiographs to evaluate the location, size, presence of calcifications, osseous involvement, and the presence of pulmonary parenchymal disease. Next, an ultrasound exam is recommended to determine the echo features (solid versus cystic, degree of homogeneity and vascularity of the mass). Axial imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) is performed next. The advantages of CT reside in its ability to clearly define the lung parenchyma and pleural space in relation to the osseous, vas-

cular and soft tissue components of the thorax (and hence mass), and the fact that it is a rapid technique requiring minimal to no sedation, even in the youngest of patients. The negative aspects of CT are the radiation exposure with subsequent risk of a secondary malignancy [12]. The benefits of MRI versus CT include better definition of the soft tissue components, as well as enhanced evaluation of the osseous and neural structures to determine the extent of central or peripheral nerve involvement and/or the presence of skip lesions or metastases. Unfortunately, this technique is time consuming and generally requires sedation or even general anesthesia to obtain optimal studies. Motion artifact from the heart and lungs can also interfere with this technique limiting its utility, but this obstacle is being overcome with the use of cardiac-gated, respiratory-triggered protocols [91, 92]. Diagnosis cannot be established by radiographic studies [91, 92]. Additional imaging studies may be required to assess the presence of metastases in malignant lesions (brain and abdominal CT, bone scan, positron emission tomogram [PET] scan). Recent reports have suggested that the combination of PET and CT scans yields more accurate data in assessing the primary tumor, local and regional lymph node basins, evidence of recurrence and for response to ongoing therapies [72, 79]. Once initial studies have been performed, retrieval of tissue for histopathological evaluation and diagnosis is warranted.

Diagnosis

Biopsy options include small or large specimen approaches. If a mass is small (less than 3 cm) or thought to be benign, then an upfront excisional biopsy may be warranted. However, the incision should be oriented so that a future re-excision can be performed, if needed, without compromising oncologic principles. A rim of normal tissue should be excised circumferentially around the mass. If the mass is large (greater than 4–5 cm), fixed to surrounding structures or involving many structures in the thorax, or if it is considered malignant by imaging, then either an incisional biopsy or core-needle biopsy is warranted. Placing the incision in-line with any future resection is of paramount importance, regardless of the technique utilized, and either approach will yield enough tissue for histopathologic and cytogenetic analyses [41]. Once a diagnosis is confirmed, then disease-specific treatment algorithms may be initiated.

Therapeutic Principles

Though treatment regimens are tumor-specific, there are certain general principles that apply. For malignant lesions, multimodality therapy is the accepted paradigm for the majority of lesions, while simple extirpation is the rule with benign entities. With surgery, the most important concept to emphasize is the need for complete resection with negative pathologic margins to decrease the risk of recurrence and need for subsequent therapy. Surgical extirpation also mandates wound reconstruction. Large defects (greater than 5 cm except for posterior and superior lesions where the defect will be buttressed by the scapula) require the use of prosthetic (rigid [silicone, Teflon (DuPont), methyl methacrylate] or flexible [prolene mesh (Ethicon), PTFE mesh, marlex mesh (Chevron Phillips Chemical), Gore-tex (WL Gore & Associates)]) materials and/or autologous tissues (pedicle or free flaps [latissimus dorsi, rectus abdominis or pectoralis major]) to reconstruct the chest wall to assure normal chest wall mechanics and prevent respiratory embarrassment.

Tumor Types

Chest wall tumors are separated into benign and malignant cohorts (Table 26.2), as well as primary and secondary lesions. Specific tumors and their treatment will be outlined in the subsequent sections.

Chest Wall Tumors: Benign

Aneurismal Bone Cyst (ABCs)

ABCs can be found anywhere on the chest wall, and they generally arise in the ribs. They have characteristic patterns of appearance on both chest radiographs and MRI [91], and they can grow to be quite large producing local destruction to the adjacent tissues (Fig. 26.5a, b). Surgical extirpation with complete excision is the treatment of choice, and recurrence is rare. Histologically, the lesions are blood filled cysts composed of fibrous tissue and giant cells.

Chondroma

Chondromas are slow-growing, painless masses that usually arise in the costal cartilages. On imaging studies, they are lytic lesions with sclerotic margins, and unfortunately, they are difficult to distinguish radiographically from their malignant brethren, chondrosarcomas. Hence, complete resection with a wide margin of normal tissue is advocated [82].

Desmoid

Desmoid tumors are fibrous neoplasms that can be found anywhere in the body. They are thought to be benign, but they have also been reported to undergo malignant

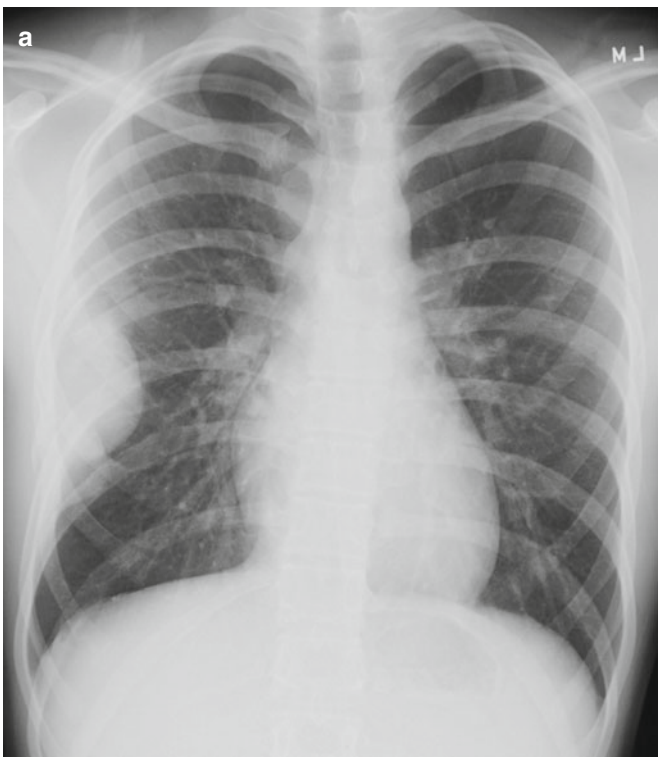
Table 26.2 Pediatric chest wall tumors

Benign
Aneurysmal bone cyst
Chondroma
Desmoid
Fibroma
Fibrous dysplasia
Lipoblastoma
Lipoma
Mesenchymal Hamartoma
Osteochondroma
Osteoma
Vascular malformations
Malignant
Chondrosarcoma
Ewing's Sarcoma Family
Fibrosarcoma
Langerhans cell histiocytosis
Leiomyosarcoma
Leukemia
Liposarcoma
Lymphoma
Neuroblastoma
Rhabdomyosarcoma
Osteosarcoma

degeneration [82]. Desmoid tumors infiltrate adjacent and surrounding tissues, and they are known to travel down fascial planes and to encase neurovascular structures in the mediastinum or the thoracic inlet. MRI is the radiographic procedure of choice to best define the extent of involvement and the structures involved. Treatment is wide local resection with negative margins, but recurrence rates from 10 % (negative margins) to 75 % (positive margins) have been described by some authors [8, 22, 31]. If a complete resection is not feasible and vital structures would be sacrificed during operative extirpation, then multimodality therapy consisting of radiation (50–60 Gy) and cytotoxic (vinblastine and methotrexate) and cytostatic (tamoxifen and diclofenac) chemotherapy is recommended, though the optimal regimen is not well established [7, 53, 54, 85].

Fibrous Dysplasia

Fibrous dysplasia is a benign condition where normal bone is replaced by fibrous tissue. These lesions are generally not large, and patients present with pain, often from a pathologic fracture. On plain radiographs, these lesions are described as lytic in nature with a characteristic "soap bubble" appearance [42]. Treatment is based on symptoms and concerns for



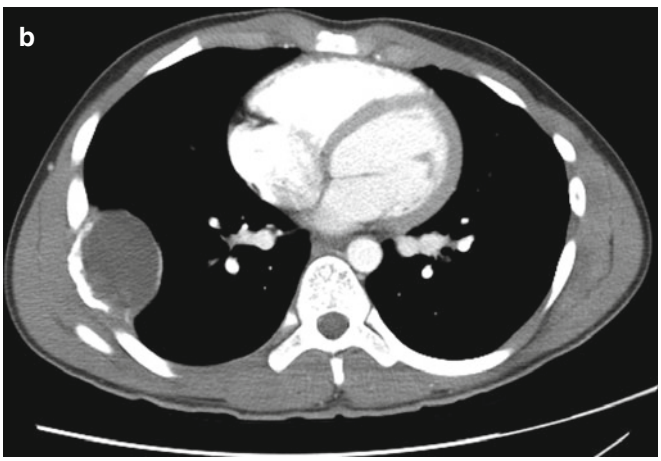


Fig. 26.5 (**a**) Chest radiograph obtained on a 15-year old boy complaining of chest pain after trauma during a hockey match. It revealed a mass lesion based around the 7th rib. (**b**) Follow-up CT scan demonstrated a cavitary lesion of the rib. Because of initial concern regarding malignancy, a percutaneous needle biopsy was obtained but diagnosis was inconclusive. Subsequent open procedure and curettage confirmed a diagnosis of aneurysmal bone cyst

possible fracture secondary to the inherent structural weakness the lesion produces in the bone. Simple excision is the recommended procedure.

Mesenchymal Hamartoma

Mesenchymal hamartomas (MH) are masses found in infants or young children that can also be discovered antenatally. The lesions are generally well circumscribed and though emanating from the chest wall (one or several ribs), they abut or compress, as opposed to invade, thoracic structures (Fig. 26.6a, b). Hence, symptoms at presentation are often from respiratory embarrassment. Parents may also note a palpable mass. These lesions are well defined by radiographic features on cross-sectional imaging, including mineralization and hemorrhagic cystic structures [32]. Histopathologically, these lesions consist of chondroid tissue with blood-filled, endothelial-lined spaces interspersed with osteoclastic giant cells. Treatment strategies have traditionally consisted of complete resection with subsequent chest wall reconstruction, but considering the large size of these lesions and the small volume of the chest cavity in the infants in which they occur, concern over the future complications of scoliosis and respiratory compromise from this approach has been considerable. In light of the fact that they are not know to undergo malignant degeneration [5], expectant observation [71, 83] or other less morbid approaches (radiofrequency ablation [9]) have been described. With expectant observation, the relative size of these lesions decreases as the children grow, resulting in less physiologic impact.

Osteochondroma

Osteochondromas are composed of bony and cartilaginous elements and are more commonly found in males (3:1 ratio) [82]. The lesion can present with pain from a pathologic fracture or compression of nearby nerves, or it can be asymptomatic if it grows into the thoracic cavity. The lesion is well characterized on plain radiographs, and arises from the cortex of the rib at the metaphysis and has a "cartilage cap" [42]. Malignant degeneration has been documented [91], and resection is warranted in all postpubertal patients, with symptoms, or if the mass is growing.

Chest Wall Tumors: Malignant

The majority of malignant tumors in infants and children are sarcomas, and the most common of these tumors will be addressed individually in the following sections.

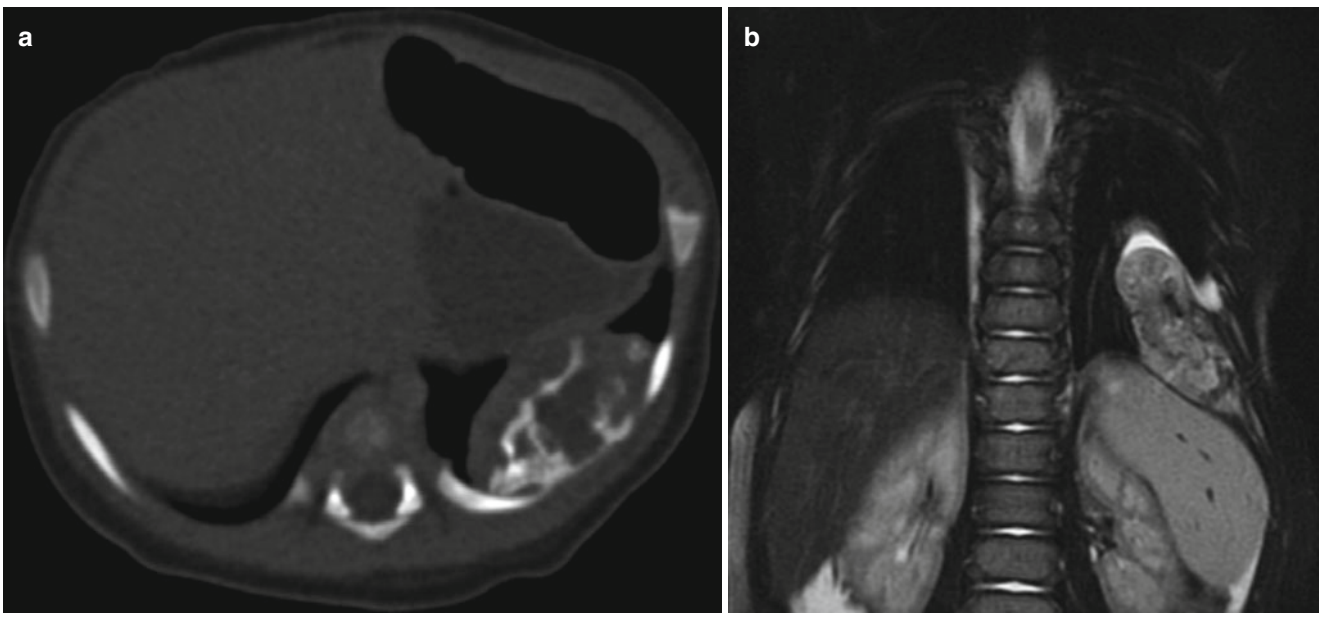


Fig. 26.6 Antenatal ultrasound revealed a calcified chest mass in this infant. Chest radiograph at birth showed partially calcified lesion in the chest and CT scan (**a**) was obtained to better define the lesion. It demonstrated a lesion arising from the ventral aspect of the 10th rib which was heterogeneous with areas of internal spiculated or plate-like ossification/calcification throughout the mass which was felt to be consistent with a mesenchymal hamartoma. MRI obtained at 6 months of age (**b**) demonstrated a heterogeneous mass with amorphous areas of signal void consistent with previously demonstrated calcification. Uptake of contrast was also heterogeneous. This has been followed expectantly and when seen 2 years later the lesion was decreasing in size as the child continued to grow.

Chondrosarcoma (CS)

Chondrosarcomas are derived from cartilaginous elements (costal cartilages) that are the most common primary malignant bone tumor of the chest wall in adults [87], and they are more common in males [82]. CS have been associated with a prior history of trauma [63], as well as being known to form from malignant degeneration of the benign counterpart discussed previously [87]. Some 10 % of patients will present with metastatic disease [15], especially in the lungs and brain. Primary therapeutic intervention is complete surgical resection with a margin of normal tissue of at least 4 cm [82] secondary to the high risk of local recurrence (up to 75 % with positive margins) even with negative margins at the initial operation (10 %) [25]. These tumors are not chemotherapy responsive, and the role of radiation is only for those lesions that are unresectable or with known positive margins. Five-year survival has been reported to be from 60 to 90 % [25, 43], and favorable prognostic factors are the absence of metastases at presentation and a complete resection [15, 25].

Ewing's Sarcoma Family/Primitive Neuroectodermal Tumors (EWS/PNET)

EWS/PNET are the most common malignant chest wall lesion in the pediatric population [83]. They are aggressive tumors requiring multimodality therapy; survival is poor despite intensive therapy, particularly in those who present with metastatic disease. Patients present with respiratory symptoms or pain; metastases to the lung, bone or bone marrow are common (25 %) [15]. EWS/PNET are defined histologically as sheets of small, round cells with scant cytoplasm and are characterized by a balanced gene translocation (EWS/FLI1) (t11:22[q24:q12]) [62]. Imaging studies demonstrate characteristic bony destruction described as lytic or sclerotic lesions [92]. Treatment involves an initial biopsy followed by neoadjuvant chemotherapy (4 cycles) with vincristine, actinomycin, cyclophosphamide, and Adriamycin (Adria-VAC) alternating with etoposide and ifosfamide. This regimen has demonstrated a great deal of success in shrinking the tumor to improve survival and facilitate complete resection [30, 84] (Fig. 26.7a, b). In fact, with the use of neoadjuvant chemotherapy, complete surgical resection with negative margins was possible in 71 % of patients versus 37 % who underwent primary surgical intervention [84]. The extent of surgery should include all involved structures and a soft tissue or osseous margin. Postoperative adjuvant therapy utilizes the same preoperative chemotherapy regimens, but not radiotherapy if complete resection is achieved. This should be the goal, despite the known radiosensitivity of this tumor [97], due to the late effects of radiotherapy (scoliosis, pneumonitis, cardiotoxicity, secondary malignancy, growth retardation, and breast hypoplasia or aplasia) [84]. The use of radiotherapy for residual disease after surgical extirpation, unresectable tumors and for patients who presented with a malignant pleural effusion where is an accepted therapeutic intervention. A recent European consensus conference advocated

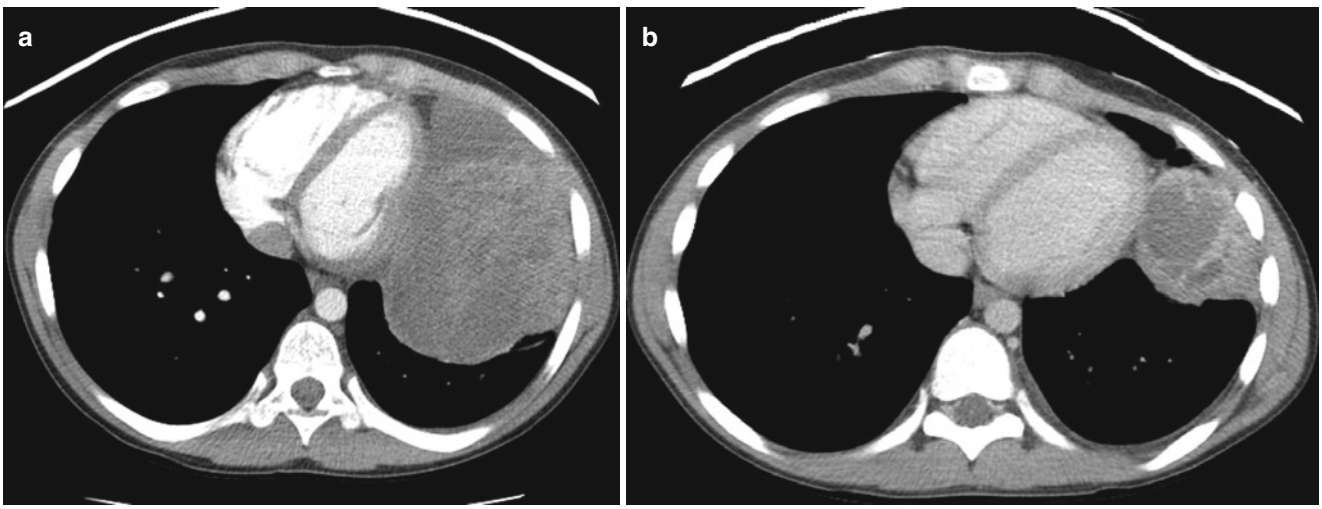


Fig. 26.7 This 10 year old boy presented with left-sided chest pain several days after falling from a tree. Chest radiograph was read as a pulmonary contusion. He had two other episodes of chest pain subsequently and radiographs were felt to demonstrate pneumonias. Six months later a chest radiograph and (**a**) CT scan demonstrated a chest wall mass and open biopsy revealed a Ewing's sarcoma. He received six cycles of 5-drug chemotherapy and the CT scan at that time (**b**) showed remarkable regression of the tumor. Pathology of the resection specimen including portions of three ribs showed no residual tumor

surgery over irradiation in all cases [95]. Five-year overall survival utilizing the above protocol was around 70 % for patients with nonmetastatic disease [14], and the 8-year survival was roughly 30 % for patients with metastatic disease [64]. In patients presenting with metastatic disease, the European Intergroup Cooperative Ewing's Sarcoma Studies Group demonstrated improved survival with the use of myeloablative chemotherapy followed by stem cell rescue at the conclusion of conventional treatment protocols [70].

Fibrosarcoma (FS)

FS (also known as infantile or congenital fibrosarcoma) are malignant tumors found throughout the body in infants that present as large masses that often involve, invade and surround adjacent structures. FS have been found in the chest wall, and several reports have documented the success of multimodality therapy in combating these tumors [57, 67]. FS can be distinguished from other myofibrous and sarcomatous lesions by the presence of a unique gene rearrangement between the TEL gene (12q13) and TRKC gene (15q25) [57]. FS are chemotherapy sensitive, and reports demonstrating the effectiveness of neoadjuvant chemotherapy with vincristine, actinomycin, cyclophosphamide, and Adriamycin followed by surgical extirpation are well accepted (Fig. 26.8a–c) [57, 67]. A recent report [67] from Europe demonstrated that 5-year overall and event-free survival rates were 89 % and 81 %, respectively. The authors report that in their series complete surgical extirpation was rarely feasible, and that conservative surgical approaches should be adopted. Furthermore, 71 % of patients responded to alkylating agent- and anthracycline agent-free regimens, hence, this regimen should be started first to limit long-term toxicity.

Osteosarcoma (OS)

OS of the chest wall can be primary or secondary tumors (prior sites of irradiation or from pre-existing osseous lesions [Paget's disease]) [82]. Lesions are primarily of the

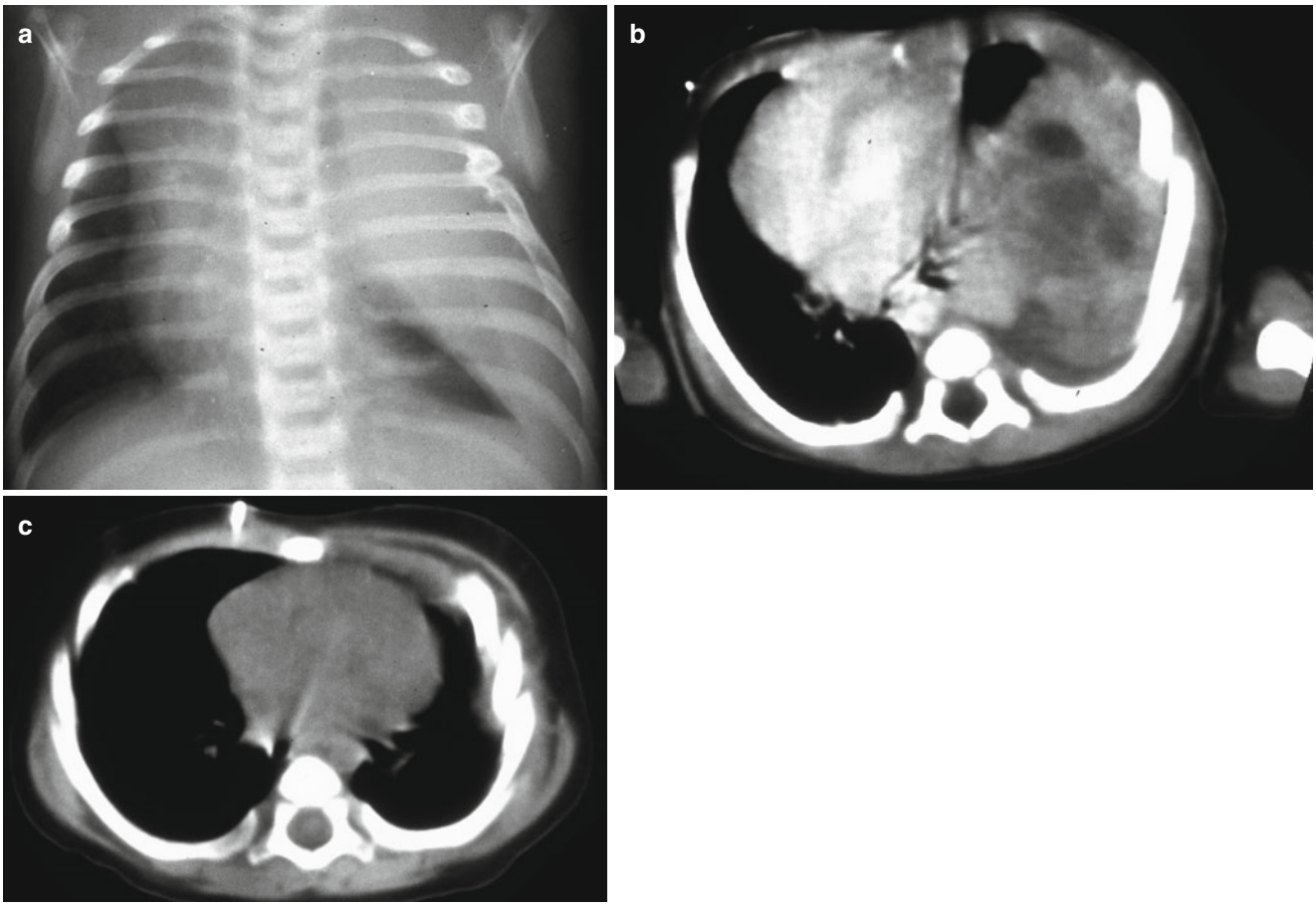


Fig. 26.8 (**a**) Chest radiograph of a newborn with respiratory distress demonstrates a large left pleural "filling defect". (**b**) CT scan demonstrated a solid lesion with some areas of presumed necrosis. Needle biopsy revealed an infantile fibrosarcoma. (**c**) Follow-up CT scan after 5 courses of Adria-VAC (300 mg/m^2 Adriamycin and 2 courses of VAC) produced remarkable regression of the tumor facilitating resection

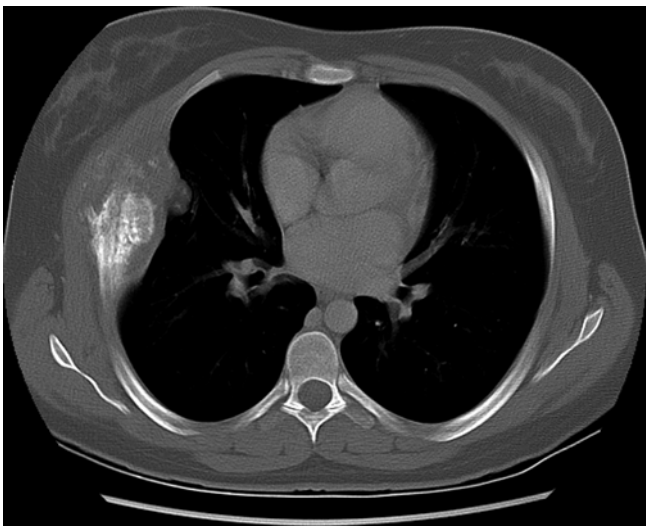


Fig. 26.9 A 15 year old female presented with a 2 month history of stabbing right sided chest pain. Chest radiograph revealed a mass within the thoracic cavity and a subsequent CT scan shown here demonstrated a large mass arising from the right 5th rib with osteoid matrix and irregular well-defined margins. Initial incisional biopsy was not diagnostic, so a resection involving segments of three ribs was performed and it was shown to be an osteosarcoma

ribs (Fig. 26.9), and on imaging, they can be confused with chondrosarcoma [56]. Chest radiographs will demonstrate a "sunburst pattern," and axial imaging concentrating on regional (bony skip lesions) and distant (lung, liver, brain) metastases must be obtained [82]. Pre-therapy biopsy is required to establish the diagnosis, and neoadjuvant therapy precedes extirpative procedures. Overall survival rates are poor (15–20 %) [15], but in the presence of nonmetastatic disease 5-year survival rates can exceed 50 % [15]. Prognosis is related to the presence of metastases, the degree of tumor burden and the response to chemotherapy [11].

Rhabdomyosarcoma (RMS)

RMS of the chest wall is a rare tumor and accounts for no more than 7 % of all RMS in Intergroup Rhabdomyosarcoma Studies (IRS) [4, 19, 61]. The chest wall site is deemed an unfavorable site, and therefore, this is an adverse prognostic factor [4, 61]. Other adverse prognostic factors have been reported to be histopathologic findings (alveolar versus embryonal), tumor burden and size, incomplete resection, and presence of metastatic disease (including lymph node metastases) [4, 18]. Despite advances in the treatment of RMS over the last 40 years, unfavorable sites carry an overall survival of only 55 % (versus 90 % for favorable sites) [4], and those with truncal RMS have been reported to have a failure-free survival rate of no greater than 67 % [78]. These tumors require multimodality therapy, and neoadjuvant chemotherapy followed by surgical extirpation. Radiation is reserved for lesions with positive margins following surgery or unresectable tumors. A report from Saenz and colleagues documented the utility of radiation (median dose of 44 Gy) to salvage some patients with residual disease [78]. However, the necessity for complete surgical resection has been called into question by a recent report from the Children's Oncology Group (COG) [37], in which the outcome of patients enrolled in IRS I-IV with chest wall RMS were analyzed. The report documents that regardless of clinical group (I-III) and other tumor-specific factors (histological subtype, tumor size), the only critical factor to influence failure-free and overall survival was the presence of metastatic disease. In the face of metastases, patients with chest wall RMS had an overall and failure-free survival of 7 % and 7 % versus 49 % and 61 %, respectively, in the cohort without metastases ($p<0.001$). Therefore, the authors suggest where gross total surgical resection will produce significant morbidity or physical debilitation, less aggressive operative approaches should be entertained.

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Mediastinal Tumors

27

Wendy Su and Jean-Martin Laberge

Introduction

Primary mediastinal tumors are uncommon in the pediatric population. Mediastinal masses in children include a wide spectrum of pathology [1], from congenital lesions such as duplication cysts found incidentally, to lymphomas presenting with respiratory collapse. Sixty-five to 80 % of mediastinal lesions are malignant [2–5]; therefore they should be investigated without delay. About 40 % of mediastinal tumors occur in children younger than 2 years old.

Anatomy

One of the most fundamental surgical knowledge is the understanding of anatomy (Fig. 27.1). The best way to approach mediastinal lesions is to consider them by their location, which will also have implication on the optimal surgical approach. The mediastinum is divided into the anterior, middle and posterior compartments based on the lateral chest radiograph. The anterior mediastinum is located between the sternum and the pericardium. It contains the thymus, lymph nodes and fat; and is the most common site of pediatric mediastinal masses. The middle compartment is the busiest containing multiple vital structures including the heart, the trachea, the mainstem bronchi and their associated lymphatics, and the aortic arch and great vessels. This visceral compartment starts from the pericardium and ends posteriorly with the trachea. The posterior compartment extends from behind the trachea to the vertebral bodies and the paravertebral sulcus. The posterior compartment is home to the descending thoracic aorta, autonomic ganglia and nerves, esophagus, thoracic duct, lymph nodes, and fat. A clear understanding of the type of tissues present in each compartment is the key to the logical consideration of the differential diagnosis. Table 27.1 illustrates the different types of tumors common to each of the compartments.

The age of the patient at presentation is also important in the differential diagnosis. Infants and young children are more likely to present with neuroblastomas, lymphangiomas, teratomas, and congenital anomalies such as bronchopulmonary foregut malformations. Lymphomas and benign neurogenic tumors are more common in teenagers. Table 27.2 outlines the relationship between age and differential diagnosis of mediastinal masses.

Anterior mediastinal tumors account for 44 % of all mediastinal lesions [2], and 80 % of these are malignant. The major anterior mediastinal tumors can be characterized by the four "terrible" T's, in the order of frequency: *T*-Cell lymphomas, *T*eratomas and germ cell tumors, *T*hymus, and intrathoracic *T*hyroid. Although a physiologically enlarged thymus is common in children, thymoma and thoracic thyroid are extremely rare in the pediatric population. Cervical lymphatic malformations, commonly known as cystic lymphangiomas or hygromas, can also extend into the superior mediastinum, and rare cases of primary mediastinal lymphangiomas have been reported.

Twenty percent of mediastinal tumors are found in the middle compartment. These are primarily lymphocytic in origin and include Hodgkin's disease and non-Hodgkin's lymphomas. The rare cardiac and pericardial tumors are also found in this compartment.

Posterior mediastinal masses account for 36 % of all mediastinal tumors and two thirds of these are malignant [6]. These tumors usually arise from neurogenic structures located in the paravertebral sulcus; they include neuroblastomas, ganglioneuromas and neurofibromas, and are more commonly seen in infants and toddlers. Other sarcomas or primitive neuroectodermal tumors and, rarely, teratomas can

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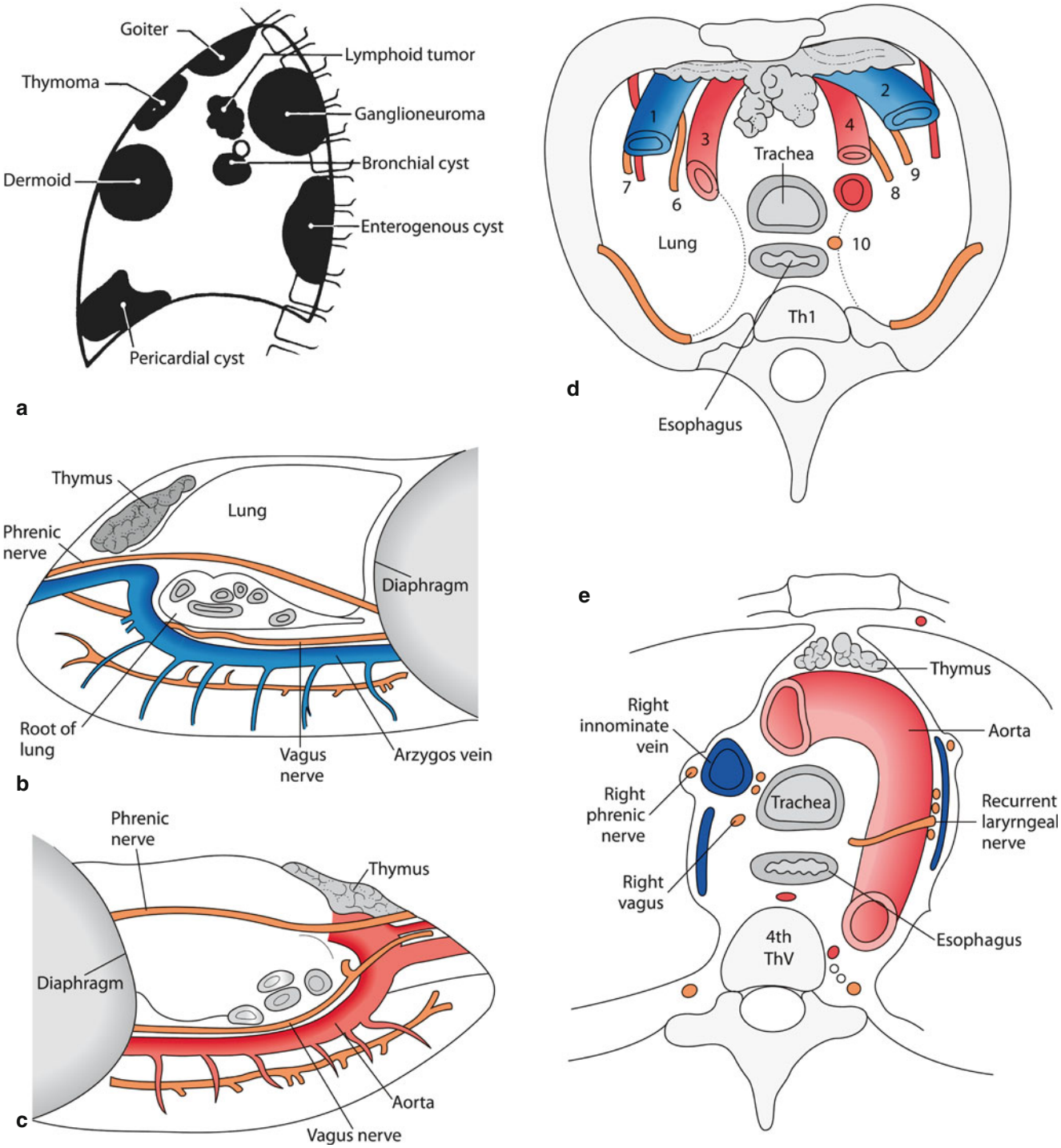

Fig. 27.1 (**a**) Diagram of the mediastinum. (**b**) Right hemi-thorax. (**c**) Left hemi-thorax. (**d**) Structures at the thoracic inlet. *1*+ *2*: Left and right innominate vein; *3*: innominate artery; *4*: left common carotid; *5*: left subclavian artery; *6*: right vagus nerve; *7*: right phrenic nerve; *8*: left vagus nerve; *9*: left phrenic nerve; *10*: recurrent laryngeal nerve; *11*: 1st thoracic nerve. (**e**) Structures at level of 4th thoracic vertebra

also be found in this compartment. Foregut duplications, bronchogenic cysts, pericardial cysts, and extralobar sequestration can be found in both the middle and posterior mediastinum. These are not neoplasms, but they should be considered in the differential diagnosis.

Clinical Presentation and Diagnosis

Clinical Presentation

Mediastinal tumors may be discovered incidentally or present in a wide range of symptomatology, resulting from direct

Table 27.1 Distribution of mediastinal tumors by compartment

Anterior mediastinum	Middle mediastinum	Posterior mediastinum
Lymphomas	Lymphoma	Neuroblastoma
Hodgkin's lymphoma	Lymphangioma	Ganglioneuroma
Non-Hodgkin's lymphoma	Hemangioma	Ganglioneuroblstoma
Germ cell tumors	Pericardial cysts	Schwannoma
Teratomas	Bronchogenic cysts	Neurofibroma
Malignant germ cell tumors	Gorham's Disease	Paraganglionma
Thymus		Primitive neuroectodermal tumor
Thymoma		Esophageal duplications
Thymolipoma		
Vascular malformation		
Lymphangiomas		
Hemangiomas		

Table 27.2 Diagnosis by age (Grosfeld et al.)

Newborns/Infants	Children	Teenagers
Thymus	Thymus	Lymphoma
Lymphangioma	Lymphangioma	Hodgkin's disease
Neuroblastoma	Ganglioneuroma	Teratoma
Teratoma	Inflammatory adenopathy	Ganglioneuroma
Duplication cyst	Neuroblastoma	Germ-cell tumor
Bronchogenic cysts	Teratoma	Schwannoma
Lipoma	Hodgkin's disease	Neurofibroma
Meningocele	Lymphoma	Peripheral neuroectodermal tumor
	Peripheral neuroectodermal tumor	Rhabdomyosarcoma
	Rhabdomyosarcoma	

Reproduced from Grosfeld et al. [2], with permission from Raven Press?

compression, tumor invasion, functional tumor secretion, or paraneoplastic syndrome. Incidental masses found during routine chest radiograph should be investigated without delay, as the incidence of malignancy is high. Mediastinal tumors can present with cadiorespiratory symptoms from direct mass effect. Compression of the trachea or mainstem bronchi can lead to cough, stridor, and dyspnea. Involvement of the superior vena cava (SVC) may lead to the SVC syndrome. Orthopnea and impending respiratory arrest may result from the combination of airway compression, venous obstruction and cardiac dysfunction. Vigilant anesthetic planning is crucial in the management of these patients as discussed in section "Anesthetic consideration for patients with mediastinal tumors".

In addition to the direct mass effect, patients may have symptoms associated with systemic effects of the disease process. Patients with lymphoma may have fever, night sweats, and weight loss. Myasthenia gravis is seen in thymomas, and virilization may be present in germ cell tumors. Posterior mediastinal lesions can present with neurologic symptoms due to intra-spinal extension, or Horner's syndrome resulting from the involvement of the cervicothoracic sympathetic ganglia. Paraneoplastic syndromes such as opsoclonus-myoclonus or watery diarrhea induced by vasoactive intestinal peptide are rare modes of presentation for neurogenic tumors (Fig. 27.2).

Investigation

The definitive diagnosis of a mediastinal tumor should start with a thorough history and physical examination. Close attention to respiratory status and presence of lymphadenopathy is essential. The lateral chest radiograph helps to identify the location of the tumor and guides additional laboratory studies. Complete blood count with differential and comprehensive chemistry panel should be obtained. Urinary catecholamines should be sent in patients with a posterior mediastinal mass, and alpha-fetoprotein (AFP) and beta-human chorionic gonadotropin (β-HCG) should be sent if germ cell tumors are suspected.

CT scan of the chest should be the first diagnostic imaging study to provide more detailed characterization of the tumor and its relationship to the surrounding structures. In the present day technology, the examination can be performed in a matter of seconds and will require no or minimal sedation even in an anxious child [7]. Modern MR imaging is often equivalent to CT in the evaluation of mediastinal masses and avoids radiation. It is also the imaging modality of choice to assess spinal involvement in posterior mediastinal neurogenic tumors [7]. *M*-iodobenzylguanidine (MIBG) scan is a useful nuclear medicine modality in the preoperative staging assessment of suspected neuroblastomas.

Once the specific diagnosis is confirmed, treatment strategies of the mediastinal tumor can be tailored to the disease process. Lymphomas are treated with systemic chemotherapy and

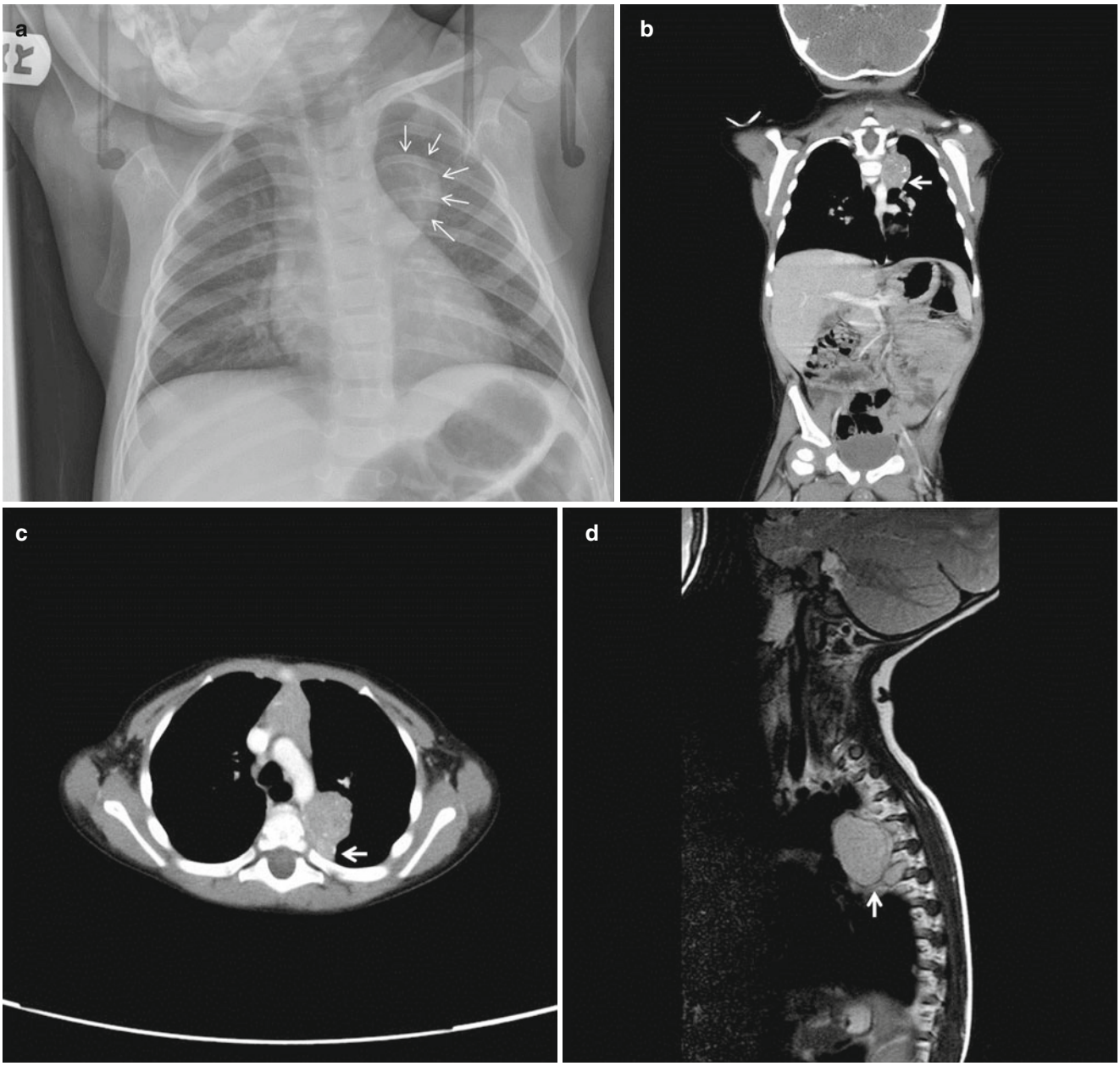

Fig. 27.2 (**a**) A 17 month old boy presented with opsoclonus myoclonus. A brain MRI was negative and a chest radiograph obtained for suspected pneumonia showed a left paravertebral lesion (*arrows*), CT (**b**, **c**) and MRI (**d**) showed a lesion sitting adjacent to but not extending into the spinal canal (*arrow*). The tumor was resected thoracoscopically with concomitant excision of adjacent lymphadenopathy. The final pathology showed neuroblastoma with unfavorable histology and two lymph nodes with metastatic neuroblastoma (INSS stage 2B). He was treated with observation only and received treatment with steroids and IVIG for his opsoclonus/myoclonus, which were slow to resolve despite negative imaging for residual disease 2 years post resection

radiation, and malignant germ cell tumors will benefit from neoadjuvant chemotherapy. Otherwise, surgical resection is the definitive treatment for most mediastinal pathologies.

Anterior Mediastinal Tumors

Children with anterior mediastinal tumors can pose significant challenges in diagnosis and management. An algorithmic approach with multidisciplinary involvement provides the optimal care for these fragile patients [8]. The pediatric surgeon is often called upon to coordinate care between pediatric oncologist, critical care/intensivist, anesthesiologist, and interventional radiologist; and to decide the best approach to obtain adequate tissue for diagnosis in concert with the pathologist. Once a child presents with a symptomatic anterior mediastinal mass, a careful search of extra-mediastinal involvement is essential. The least invasive and lowest risk

procedure should be utilized first [9]. Peripheral blood smear and flow cytometry may be diagnostic of leukemia. Elevated serum AFP will point to yolk-sac germ cell tumors. A mass containing mixed solid/cystic elements and fat on CT scan or MRI will lead to the diagnosis of teratoma. Chest radiograph may reveal pleural effusion, in which case fluid obtained by pleurocentesis can be sent for flow cytometry and cytology. Careful physical examination may reveal cervical lymphadenopathy that can be biopsied under local anesthesia with conscious sedation.

Lymphomas

Malignant lymphoma is the most common mediastinal tumor in children, accounting for approximately 60 % of all pediatric mediastinal lesions. These arise from the thymus and/or the mediastinal lymph nodes. Two-thirds are non-Hodgkin's lymphomas and one-third are Hodgkin's disease [10, 11]. T-cell lymphoblastic lymphomas are the most common histologic subtype of non-Hodgkin's lymphomas, followed by large cell lymphomas [11, 12].

Children with non-Hodgkin's lymphoma frequently present with symptoms related to local compression such as tachypnea, cough, stridor, and occasionally superior vena cava syndrome (Fig. 27.3). Up to 55 % of children with mediastinal Hodgkin's lymphoma have radiographic evidence of tracheal compression (Fig. 27.4) [13]. Pleural effusion and cervical lymphadenopathy are frequently present and should be the first choice for obtaining cells or tissue for diagnosis [14]. These tumors have an excellent response to chemotherapy and radiotherapy despite the fact that disseminated disease is often present [1]. Peripherally-inserted central venous access should be obtained during diagnostic procedures performed under local anesthesia when contraindications to general anesthesia are present. The surgeon's role is to obtain adequate tissue for diagnostic studies with minimal morbidity. Diagnosis and differentiation of histologic subtypes based on immunohistochemistry, cytogenetics and flow cytometry have significant impact on treatment regimen, thus sufficient diagnostic material need to be obtained prior to the initiation of chemotherapy. Recent advancement in molecular genetic testing utilizing fluorescent in situ hybridization and polymerase chain reaction may allow diagnosis with smaller amounts of tissue obtained from percutaneous fine needle aspiration or core biopsies [15, 16]. An open procedure with excision of the entire lymph node provides the best approach for adequate tissue diagnosis and assessment of nodal architecture [11]. However, the risk of anesthetic complication from the mass effect of the large mediastinal mass should be carefully assessed prior to any procedure as discussed in section "Anesthetic consideration for patients with mediastinal tumors".

In patients without extra-thoracic disease, pretreatment with steroids or radiation prior to biopsy may reduce tumor size rapidly and allow for safer anesthesia. However, radiation may significantly alter pathology making the correct diagnosis difficult. In some cases the radiation field can be adjusted to spare an area for later biopsy. Pretreatment with

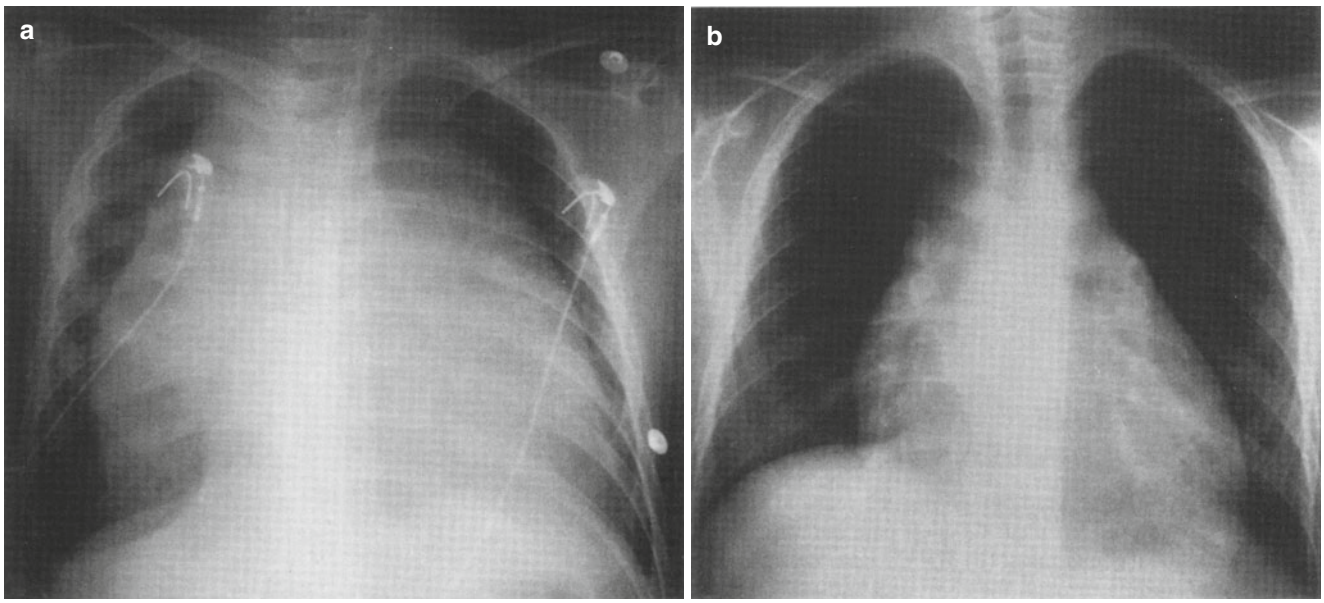

Fig. 27.3 (**a**) Chest radiograph of an 8 year old girl who presented with a 3 week history of wheezing, cough, anorexia and weight loss of 3 kg. The pleural effusion was tapped to avoid biopsy and the diagnosis of acute lymphoblastic lymphoma was obtained. (**b**) Chest radiograph 1 week after the first course of prednisone, vincristine, doxorubicin, methotrexate, and intrathecal cytosine arabinoside (ara-C) demonstrates a dramatic response to therapy

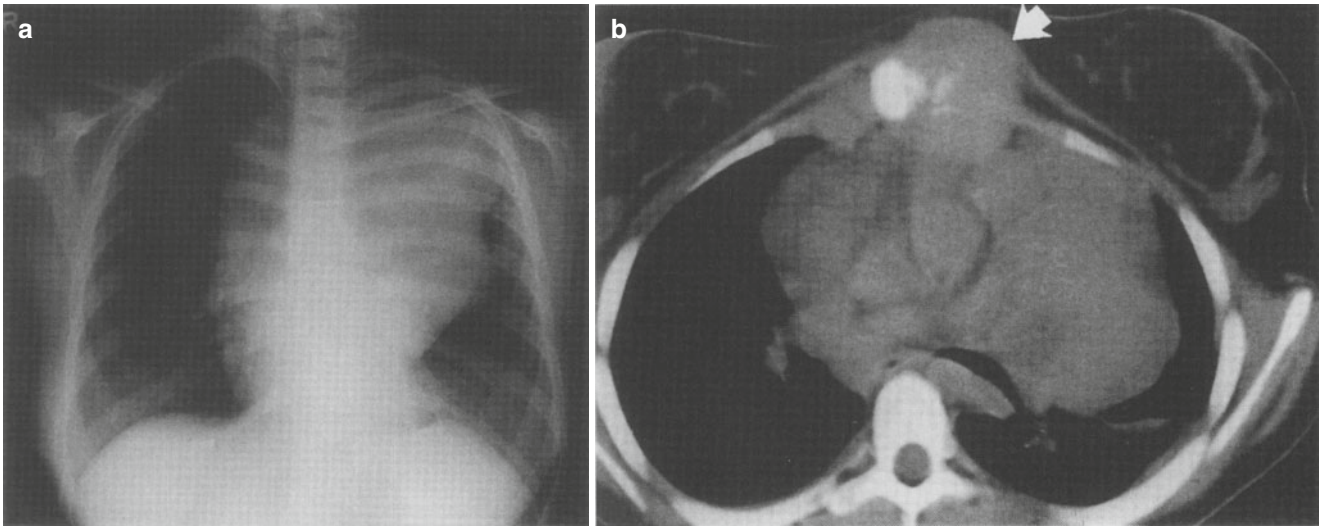

Fig. 27.4 (**a**) Chest radiograph of a 12 year old girl obtained because of mild left pleuritic chest pain demonstrates a large anterior mediastinal mass. (**b**) The CT scan revealed that the mass was eroding through the chest wall and sternum (*arrow*). Because of significant tracheal compression a biopsy was obtained under local anesthesia and Hodgkin's disease was diagnosed

steroids may also ablate tumor and cellular architecture as well as cytogenetic markers, leading to inaccurate diagnosis [17, 18] but may be necessary in the face of overwhelming anesthetic risk.

The staging, treatment and prognosis for lymphomas are discussed in Chap. 20.

Teratomas and Germ Cell Tumors

Germ cell tumors account for 6–18 % of pediatric mediastinal neoplasms [19]; they are the second most common tumor of the anterior mediastinum in children. They are believed to derive from primordial germ cells that missed their "target" during migration and remained in the mediastinum. Eighty-six percent are benign mature teratomas containing all three germinal layers, and the rest contain various malignant components including seminomas and non-seminomas.

Teratomas

Overall, 7–10 % of all teratomas are mediastinal, making this the third most common site after the sacrococcygeal and gonadal primaries [20]. Teratomas may present at any age from infancy to adolescence. The majority are benign, but after adolescence mediastinal teratomas have a high incidence of malignant behavior, which is usually indicated by elevated levels of tumor markers (alpha fetoprotein and beta-HCG) [20]. Immature elements are not of prognostic significance in children under 15 years, but they are associated with local aggressiveness and distant metastases above that age [21, 22]. Most mediastinal teratomas are located in the anterior mediastinum and frequently have large cystic components (Fig. 27.5), but a few have been described in the posterior mediastinum, some with epidural extension. Intrapericardial and intracardiac lesions are also described, the former presenting in utero or at birth with fetal hydrops or massive pericardial effusion [20]. Infants and toddlers with an anterior mediastinal teratoma commonly present with respiratory distress, but in older children, the teratoma may be an incidental finding on chest radiograph. It may also present as a chest wall mass with erosion through the soft tissues (Fig. 27.6), with hemoptysis or trichoptysis from bronchial erosion, with rupture into the pleural cavity, or with cardiac failure [20, 22]. CT scan is the imaging technique of choice in the evaluation of these lesions. It can define the extent of the lesion and possible tracheal compression. A heterogeneous anterior mediastinal mass containing calcification and varying tissue densities including fat is highly suggestive of the diagnosis [23]. Surgical resection via anterior thoracotomy, median sternotomy or thoracoscopy [24] is usually curative, although if present, malignant elements in the tumor will require further therapy.

Malignant Germ Cell Tumors

The mediastinum is the primary site in 4 % of malignant germ cell tumors [25]. These are complex tumors of varied histology with frequent coexistence of benign elements [26]. Malignant components include yolk sac tumors (also known as endodermal sinus tumors), seminomas, dysgerminomas, embryonal carcinomas, and choriocarcinomas [27]. They are more common in boys than girls (3:1). A strong association is found in patients with Klinefelter's syndrome, who often present with precocious puberty from the choriocarcinoma elements [20]. AFP and β-HCG should be obtained preoperatively, as for suspected germ cell tumors in other loca-

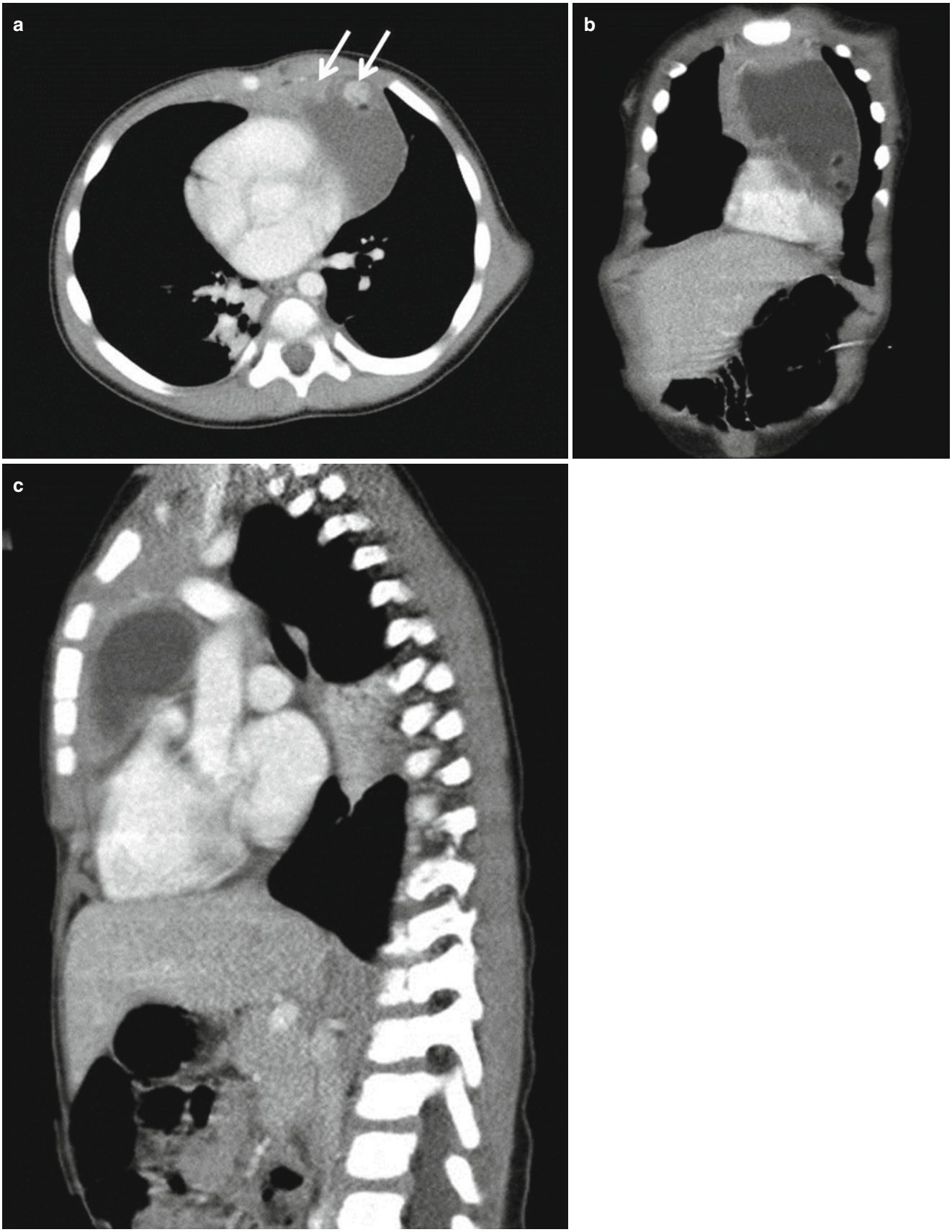

Fig. 27.5 (**a**) Axial, (**b**) coronal, and (**c**) sagittal CT scan of a 22 month old boy presenting with fever, cough, and weight loss. The anterior mediastinal mass is predominately cystic, with small solid components containing calcifications and fat densities (*white arrows*), arising from the thymus. This is highly suggestive of a benign cystic teratoma. The patient underwent complete surgical resection via median sternotomy without additional therapy

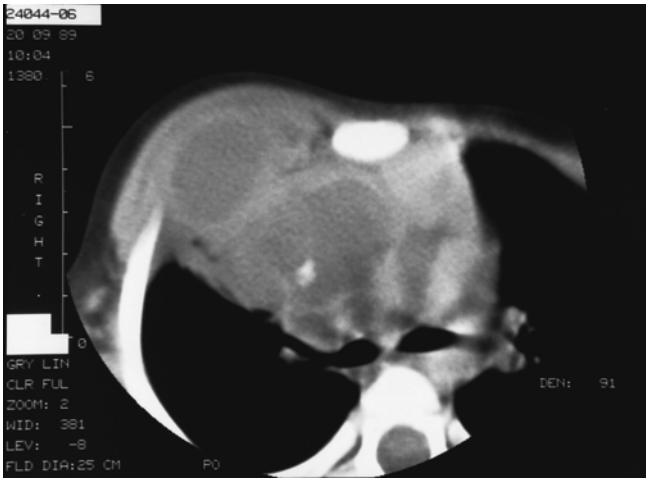

Fig. 27.6 A 2 year old was referred for a 5 cm by 5 cm hard fixed right chest wall mass that appeared suddenly during an upper respiratory infection. The computed tomography scan shows a bilobed lesion that extends through the chest wall and contains a small area of calcification. An incisional biopsy revealed pus-like material, containing ghost cells and calcified debris. Serum markers were normal. Complete excision of the mass required a right anterior thoracotomy and partial resection of an adherent right middle lobe. Pathologic examination revealed a ruptured mature teratoma with marked inflammatory reaction, containing foci of enteric, respiratory, and squamous mucosa; smooth muscle; salivary glands; pancreas; neuroglial tissue; and bone (Reproduced with permission from page 983 of: Laberge et al. [90])

tions. Elevated serum AFP will lead to suspicion of malignant yolk sac component, and high serum β-HCG is likely from the choriocarcinoma elements. Diagnostic biopsy should be obtained for large tumors considered difficult to resect either with image-guided core needle biopsy or via an anterior mediastinal approach [27]. Both can be safely performed under local anesthesia should the patient present with significant respiratory symptoms. The prognosis for patients with malignant germ cell tumors arising in the mediastinum was regarded previously as dismal with only occasional survivors in the pre-chemotherapy era [28, 29]. The POG/CCSG intergroup study demonstrated successful reduction in tumor bulk with neoadjuvant chemotherapy, which allowed complete resection of tumors with malignant components in 82 % of patients [27]. With the combination of multiagent chemotherapy (cisplatin, etoposide and bleomycin) and aggressive surgical resection, the POG/CCSG intergroup study reported 83 % 5-year overall survival and 79 % event-free survival in patients with extragonadal malignant germ cell tumors [29]. Similar results were reported by the United Kingdom Children's Cancer Study Group and the French MGCT study, utilizing carboplatin instead of cisplatin to minimize renal toxicity and hearing loss [30, 31]. However, children older than 12 years of age with thoracic primaries had a six times higher risk of death compared with younger children with other primary sites. An alternative high dose cisplatin regimen offered better event-free survival than standard dose cisplatin, but at the cost of increased treatment related toxicities and secondary malignancies [32].

The management of primary mediastinal germ cell tumors should be conservative at diagnosis, with biopsy only for large tumors. Patients with elevated tumor markers or histologic confirmation of malignancy should receive neoadjuvant chemotherapy prior to attempt at resection. Benign tumors and masses persisting after chemotherapy (often due to coexisting benign teratomatous elements) should be resected aggressively, and an excellent outcome can be expected [33].

Thymic Tumors

Tumors or tumor-like lesions arising from the thymus include thymic hyperplasia, thymic cysts, thymomas, and thymolipomas. These lesions represent less than 5 % of resected mediastinal tumors in children.

Thymic hyperplasia may take the form of lymphoid follicular hyperplasia with or without thymic enlargement. These are often present in autoimmune diseases such as myasthenia gravis and Grave's disease, and associated with a favorable response to thymectomy. True thymic hyperplasia can present as massive hypertrophy in children; surgical resection is only indicated in symptomatic patients when the diagnosis is unclear (Fig. 27.7); otherwise a short course of steroids will shrink the lesion. Thymic rebound hyperplasia is seen in children who have received systemic chemotherapy, usually within 2 years of initiation. It is a self-limited process and spontaneous resolution is expected [34, 35]. The diagnostic dilemma in patients who have been treated for mediastinal lymphoma is to distinguish thymic rebound from recurrent or metastatic tumor. Thymic rebound hyperplasia appears as diffuse enlargement with a fine mixture of fat and lymphoid tissue, a smooth contour, and normal appearing vessels on imaging studies. Recurrent neoplasia usually has a nodular contour and often contains necrotic or calcified foci [36]. Recovery from recent stress such as thermal burn or systemic illness can also result in thymic hyperplasia.

Thymic cysts are thin-walled, usually unilocular cysts containing thymic tissue in the cyst wall. They often extend from the mediastinum to the neck and are benign. Most are asymptomatic but hemorrhage into the cyst cavity or secondary infection may lead to tracheal compression and respiratory distress. Surgical excision is curative in symptomatic patients and is recommended in asymptomatic patients with large cysts to prevent complications.

Thymomas are rare in children as compared to adults, with only 2 % presenting in the first two decades of life. They are usually benign and arise in the upper anterior mediastinum or at

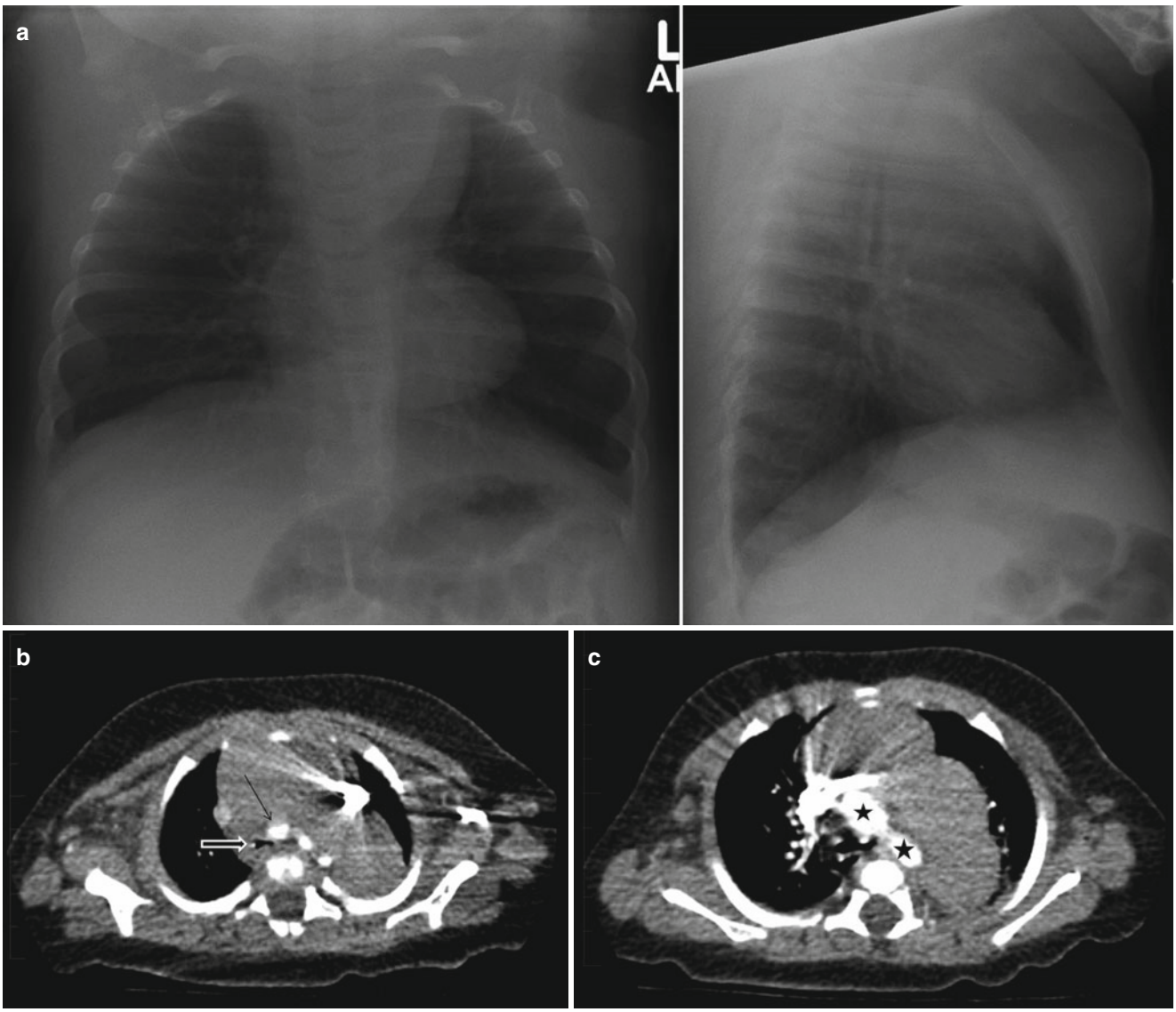

Fig. 27.7 A 4 month old girl presented with stridor and wheezing. (**a**) The chest radiograph showed an anterior mediastinal mass. (**b**) CT scan showed marked compression of the trachea (*thick arrow*) at the level of the brachiocephalic artery (*thin arrow*); artefacts are due to contrast injection in the left arm. (**c**) The mass extended posteriorly, and inferiorly past the level of the aortic arch (*stars*). Repeat CT scan after 2 days of steroids (not shown) showed mild improvement; thymic hyperplasia was suspected but because of diagnostic uncertainty and persistence of symptoms, a thoracoscopic excision was carried out without complications. Pathology confirmed thymic hyperplasia

the base of the neck. Although they may be massive in size, they generally compress adjacent structures rather than invade them. Respiratory distress and superior vena cava syndrome may occur [37]. They are occasionally associated with myasthenia gravis. Surgical resection is curative and recurrence is rare (2 %) [38]. Malignant thymomas are epithelial in nature and invasive as in adults. Aggressive surgical resection is critical as response to chemotherapy and radiotherapy is limited. Resection of lung, pleura, diaphragm, superior vena cava and pericardium may be required to achieve complete surgical extirpation.

Thymolipoma is a rare benign tumor of the thymus that often attains gigantic proportions in clinically asymptomatic patients (Fig. 27.8). Associated conditions such as myasthenia gravis [39], aplastic anemia [40], Graves' disease [41], and Hodgkin's disease [42], although possibly coincidental, have been reported in adult patients. One case of erythrocyte hypoplasia and hypogammaglobulinemia has been reported in a child [43]. Thymolipomas show fatty attenuation mixed with fibrous septae and normal thymic tissue on CT scan; on MRI, they demonstrate high signal intensity on both T1 and T2 weighted images along with strands of lower signal intensity at the fibrous septae [36]. Histologically a thymolipoma is composed of thymic and mature adipose tissue. The tumor usually extends inferiorly to either side of the medias-

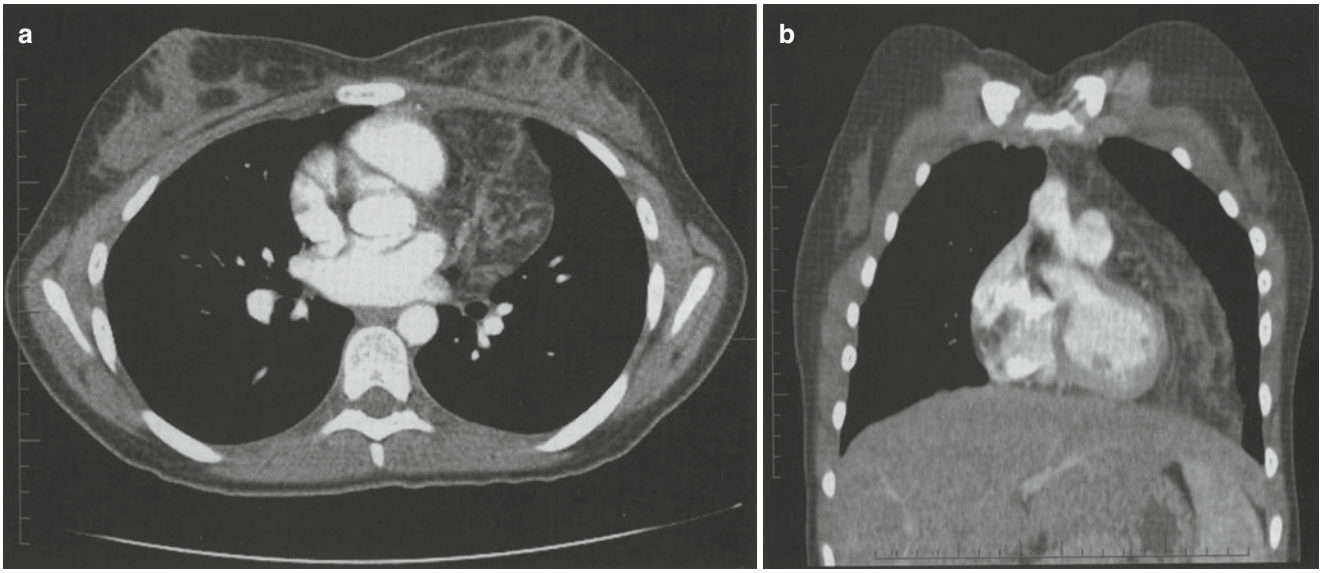

Fig. 27.8 Thymolipoma. This 17 year old girl had an incidental finding of a heterogenous anterior mediastinal mass during investigation of Crohn's disease. (**a**) This axial cut on CT scan shows the soft tissue mass with fat infiltration, to the left of the aortic arch. (**b**) The extent of the mass to the costo-diaphragmatic angle can be appreciated on this coronal reconstruction. A thoracoscopic resection was performed (Courtesy of Dr. Ken Shaw)

tinum. Surgical resection is necessary for definitive diagnosis and can be accomplished thoracoscopically as these tumors tend to be pliable and rarely invade neighboring structures [43, 44].

Lymphangiomas

Lymphatic malformations are the most common vascular anomalies found in the anterior mediastinum. Isolated lymphatic malformations of the mediastinum are rare and can be found in all three compartments. Most mediastinal lymphangiomas are in fact extensions of cervical, axillary or chest wall lesions. These lesions are congenital in nature and are usually asymptomatic; spontaneous resolution is uncommon but has been observed. Symptoms often develop as a result of infection, hemorrhage, or cyst expansion, leading to the need for intervention. Complete surgical resection can be difficult and lead to significant morbidity as these lesions tend to infiltrate between vital structures. Percutaneous aspiration and sclerotherapy has been gaining popularity for both primary and recurrent lesions. Several sclerosing agents have been reported to yield good results, including OK-432, alcoholic solution of zein (Ethibloc), bleomycin and doxycycline [45, 46]. OK-432 is the most commonly reported agent in the literature, favored by Japanese and European surgeons with good to excellent outcomes, but is not clinically available in North America. Alcoholic solution of zein is widely used in Europe and Canada with favorable results as well. However, there is no standardized regimen in the administration of sclerosing therapy as the literature is comprised of mostly case reports and expert opinions [34, 47], and there is limited experience with large mediastinal lesions. Surgical resection remains an excellent option for macrocystic lesions without infiltration of vital structures. A combined thoracoscopic drainage and sclerotherapy is also a viable option for lesions not accessible percutaneously (Fig. 27.9).

Others

Angiofollicular or giant lymph node hyperplasia (also called Castleman's disease) is usually a benign condition, which most commonly affects mediastinal nodes. The grossly enlarged nodes are very vascular on imaging studies. Excisional biopsy is required to differentiate this from lymphoma. The disease sometimes takes a systemic form, in which case the course is complicated with anemia and growth failure. These manifestations sometimes improve with excision of the enlarged node(s) if easily accessible, but aggressive surgical resection should be avoided [48].

Langerhans cell histiocytosis in the mediastinum is usually part of a multifocal systemic disease, but rarely may present as an isolated thymic mass. Superior vena cava syndrome has been described. The prognosis for unifocal mediastinal disease is excellent [37].

Among the less common mediastinal tumors, there are reports of lipomas and lipoblastomas, and rare instances of liposarcoma. Other sarcomas such as rhabdomyosarco-

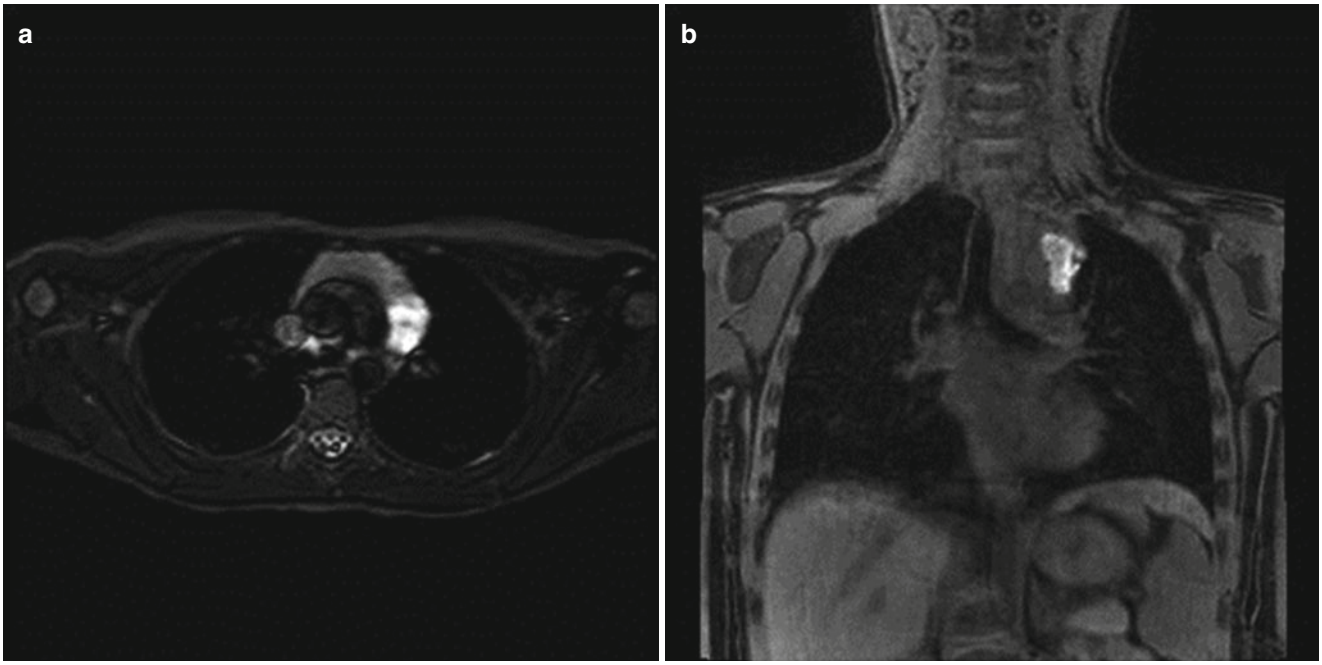

Fig. 27.9 (**a**, **b**) A 7 year old girl had cervical lymphangioma resected 4 years previously. She had remained asymptomatic until she recently presented with prominent left neck and chest wall vessels. A MRI was performed to demonstrate the superior mediastinal mass compressing the left subclavian and innominate veins, with mild tracheal deviation. The lesion was treated with left thoracoscopic drainage and doxycycline sclerotherapy with satisfactory resolution of symptoms (Courtesy of Dr. Wolfgang Stehr)

mas, Ewing tumors, mesenchymomas and other unusual neoplasms may also occur [37]. Rare cases of fibromatosis have also been described in the mediastinum.

Middle Mediastinal Tumors

The middle mediastinum is also known as the visceral compartment, containing the trachea and mainstem bronchi, the heart and the great vessels. Lymphoid tissues are also abundant in this region, thus lymphomas are the most common tumors, often involving both the anterior and middle mediastinum. Benign vascular tumors and lymphatic malformations are also found here. Gorham's disease is worth mentioning; even though it is not a tumor per se, it behaves as one. Gorham's disease or "vanishing bone disease" is a rare disorder of unknown etiology, characterized by proliferation of vascular channels that results in the destruction and resorption of the osseous matrix [49]. Some consider it as an extreme form of lymphangiomatosis [50]. The shoulder and the pelvis are the most commonly affected sites; however, various locations in all of the other areas of the skeleton have also been reported. The disease may present with pain from lytic bony lesions and pathological fractures, or with chylous pericardial or pleural effusions, which may be life-threatening. These effusions may be due to mediastinal extension of the disease process from the involved vertebrae, scapulae, ribs or sternum, or may represent a direct lymphangiomatous involvement of the mediastinum. In general, mediastinal and spinal involvement are associated with a poor prognosis. The treatment is mostly supportive, with isolated trials of radiation therapy, anti-osteoclastic and anti-angiogenic medications including pamidronate, zoledronic acid and alpha-2b interferon [51]. Pleurodesis and pleuroperitoneal shunts may be useful for symptomatic relief. The disease occasionally becomes quiescent after adolescence.

Bronchogenic cysts are benign congenital lesions that can present with symptoms of tracheal compression or recurrent pulmonary infections. The treatment is complete surgical excision [52] (Fig. 27.10).

Posterior Mediastinal Tumors

Neurogenic Tumors

Tumors of neural crest origin are the most common posterior mediastinal lesions. They arise from the sympathetic chain and range from benign ganglioneuroma to malignant neuroblastoma. Twenty percent of neurogenic tumors are located in the mediastinum. Neuroblastoma is the most common tumor and occurs mostly in infants and young children (Table 27.2). Ganglioneuromas present in older

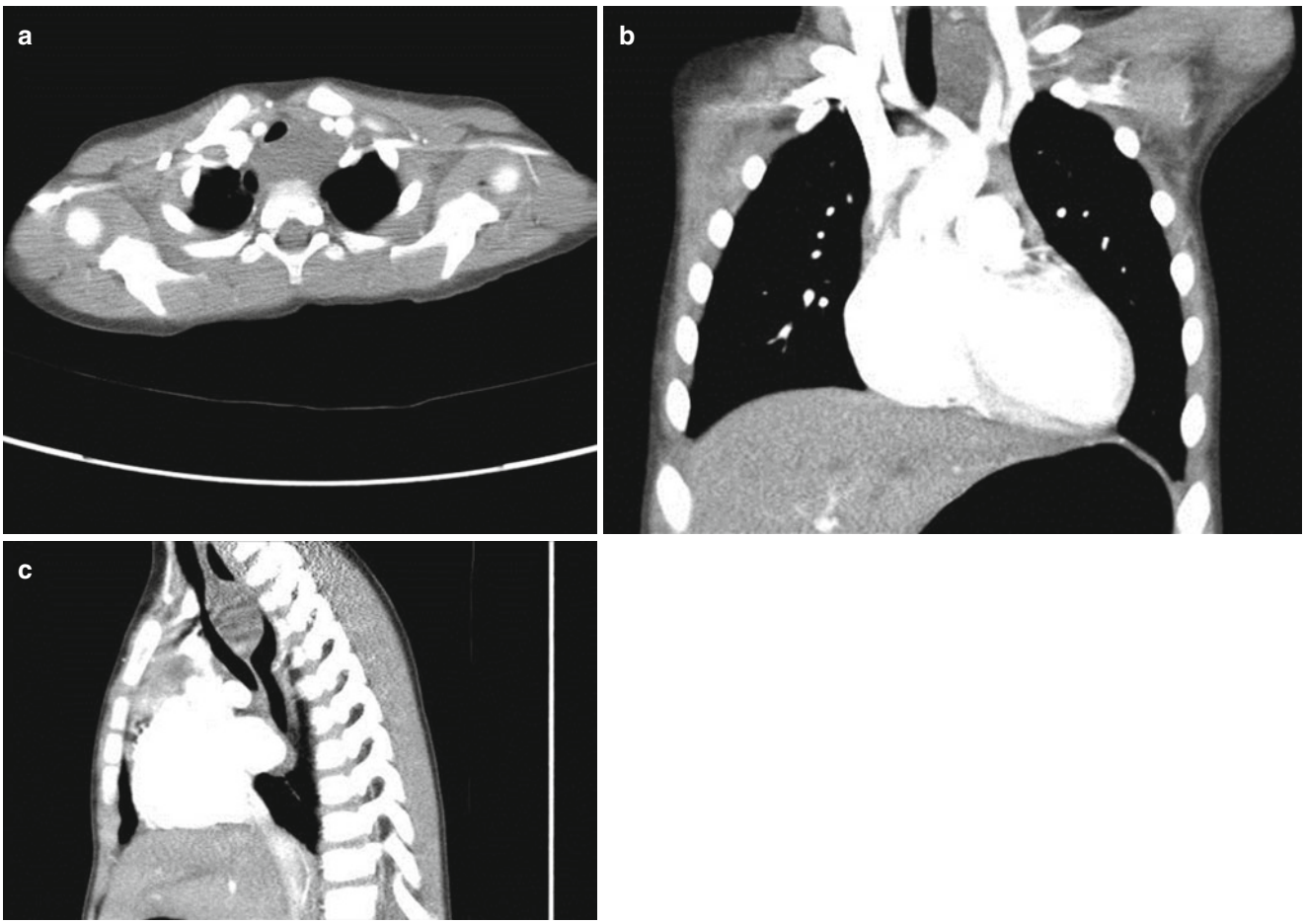

Fig. 27.10 (**a**) Axial, (**b**) coronal, and (**c**) sagittal view. A 2 year old boy presented with chronic cough and mild dysphagia. CT scan revealed a cystic mass in the superior mediastinum partially compressing the trachea anteriorly and the esophagus posteriorly. The patient underwent stepwise general anesthesia, starting with intravenous ketamine and propofol. Once easy masking was established, a fiberoptic intubation was performed and the airway was secured. Patient underwent a left thoracoscopic resection of the lesion and pathology confirmed it to be a bronchogenic cyst

children and teenagers as asymptomatic lesions, which are identified incidentally on chest radiographs obtained for unrelated reasons. Radiographically they appear as paraspinal spindle-shaped lesions and are frequently calcified. Neurogenic tumors may occur anywhere along the paraspinal sulcus from the thoracic inlet to the diaphragm. They can present as incidental paraspinal mass on routine chest radiograph, or can be identified on investigations performed for Horner's syndrome, ataxia or opsoclonus myoclonus. When the tumor extends into the spinal canal, it may present with signs and symptoms of cord compression. Investigations for paraspinal posterior mediastinal masses should include a CT scan or MRI prior to surgical resection to better define the relationship to surrounding structures and assess possible spinal extension (Fig. 27.11). Spot urinary catecholamines should also be obtained. A preoperative MIBG scan is recommended to determine local tumor extent and presence of distant metastases, and will be a useful modality for postoperative monitoring when the tumor is MIBG avid.

Most mediastinal neurogenic tumors are well encapsulated and readily resectable, unlike their abdominal counterparts. Surgical resection is the treatment of choice and is curative for benign lesions such as ganglioneuromas. Several recent series have reported successful thoracoscopic resections, but removal within an endobag is essential to prevent tumor spillage [24]. The tumor can be closely adherent to the posterior part of the ribs and necessitates removal of part of the periosteum. Often it is impossible to avoid leaving small amounts of residual disease along the sympathetic nerve roots as they emerge from the foramina. These areas are simply marked with small titanium clips for future imaging. For upper thoracic neuroblastomas, a temporary or permanent Horner's syndrome is a normal postoperative "complication", especially when present preoperatively. Adequate sampling of ipsilateral lymph nodes is essential to determine

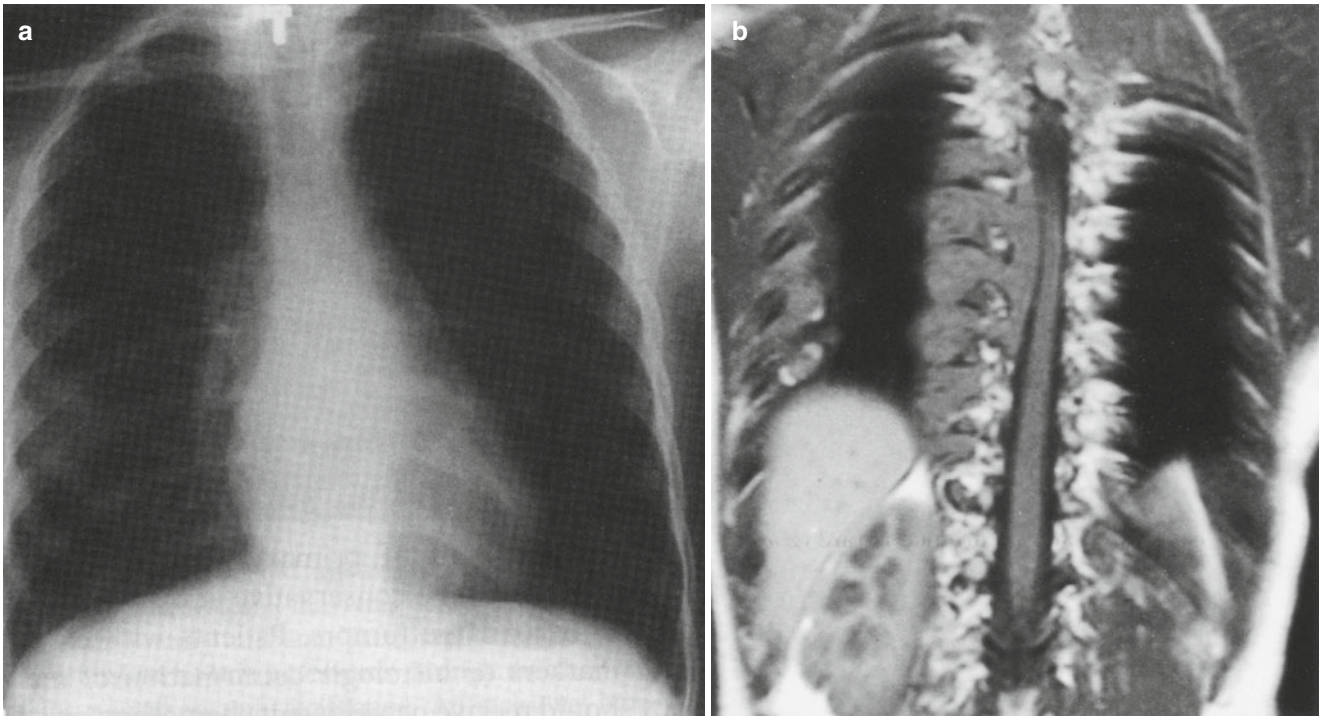

Fig. 27.11 (**a**) Chest radiograph of a 5 year old girl referred for back pain, which demonstrated a minimal right paraspinal mass, but on the MRI scan (**b**) a dramatic extension of the tumor was demonstrated through the spinal foramen, and was compressing the spinal cord, although she had no significant neurological symptoms. A percutaneous needle biopsy demonstrated the tumor to be a neuroblastoma

surgical staging in neuroblastomas, as patients with stage L1 disease according to the International Neuroblastoma Risk Group Staging System (INRGSS) may be observed after a macroscopically complete surgical excision. Ipsilateral nodes are excised if any are visible, but extensive sampling, including contralateral nodes, is not required for thoracic neuroblastomas, unlike for their abdominal counterpart. Patients with thoracic neuroblastomas tend to have a better prognosis (see Chap. 13 for a complete discussion on neuroblastoma).

The optimal treatment for patients presenting with symptomatic spinal cord compression at diagnosis has evolved. Treatment of the so called 'dumbbell' lesions with significant extension into the spinal canal must first involve control of the spinal lesion by laminectomy/laminotomy, radiation, or chemotherapy [53]. Initial resection of the thoracic component entails the risk of potential swelling of the spinal tumor with worsening of neurologic compression and paralysis [6, 54]. Recent studies from France, Italy and the Pediatric Oncology Group all demonstrated equal efficacy between laminectomy, radiation, and chemotherapy to relieve or improve neurologic deficits. However, patients treated with chemotherapy usually did not require additional treatment and have less orthopedic sequelae, whereas patients treated either with radiotherapy or laminectomy commonly did [55–57]. Although laminotomy may be a worthwhile alternative with fewer sequelae than laminectomy, the current trend is to use chemotherapy for debulking, now that the fear of inducing tumor necrosis, resulting in edema and increased cord compression, has been dispelled. Surgical decompression is reserved for patients who show progressive neurologic deterioration after initiation of chemotherapy [58]. The frequency of complete neurologic recovery in children with intraspinal neuroblastoma inversely correlates with the duration and severity of the presenting neurologic deficits [56], and up to 44 % have permanent disabilities [55].

Prognosis in neuroblastoma is age-dependent, with a better prognosis for infants compared to older children. Intrathoracic neuroblastomas have a more favorable prognosis than abdominal primaries of comparable stage [58, 59]. This is most likely related to the favorable biology of most thoracic neurogenic lesions [60, 61]. In the presence of a maturing ganglioneuroblastoma, it is important to remember that the tumor is as malignant as its most malignant component. A small proportion of older children with thoracic neuroblastoma appear to have a protracted course, with late recurrences and death.

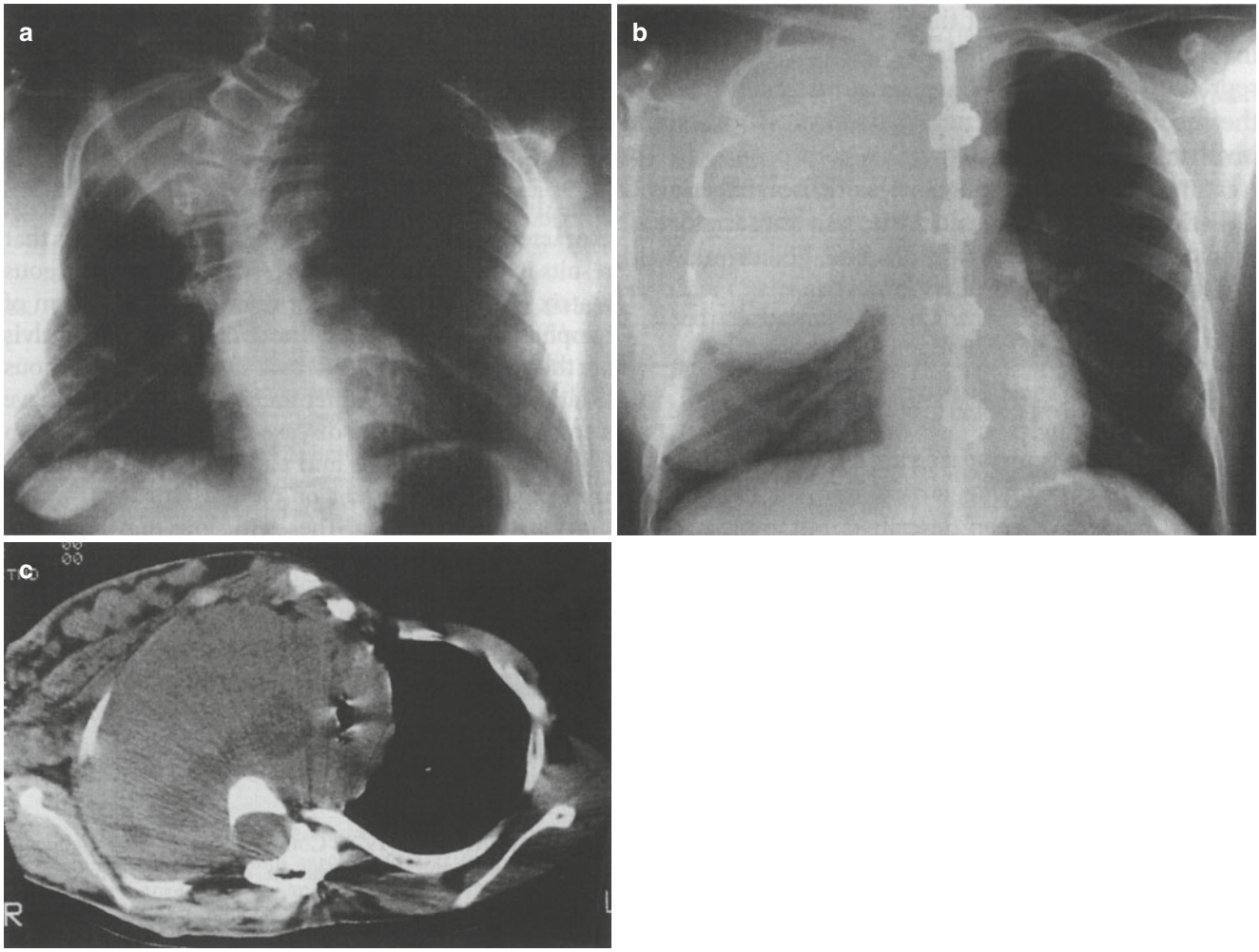

Fig. 27.12 (**a**) Chest radiograph of a 10 year old boy with neurofibromatosis obtained immediately prior to fusion of his spine. The right apical mass had been stable in size. (**b**) Dramatic increase in the size of the apical mass was noted 9 months later. At resection, malignant degeneration into a neurofibrosarcoma was found. Note thinning of the upper ribs as a result of the long-standing neurofibroma. (**c**) CT scan obtained prior to resection demonstrates the large mass displacing the mediastinum to the left, but not compressing the trachea. Multiple subcutaneous neurofibromas are seen in the subcutaneous tissues of the right chest

Others

Plexiform neurofibroma may occur in the mediastinum as an isolated lesion or in patients with neurofibromatosis (NF 1 or von Recklinghausen's disease). Resection is required for isolated lesions in order to obtain a histologic diagnosis [62]. In patients with neurofibromatosis, resection is required if the lesions are symptomatic. Rapid growth usually occurs if there is malignant transformation to malignant peripheral nerve sheath tumor (Fig. 27.12). MRI and PET scan are both useful to detect malignant transformation in NF 1 patients [63, 64].

Pheochromocytoma (also called paraganglioma) can also occur along the sympathetic chain in the neck and mediastinum and produce symptoms of compression as well as flushing and hypertension. This tumor has been described in the anterior mediastinum as well. Regional or distant metastases are seen in 15–20 % of patients [37]. Other rare neurogenic tumors include *neurilemmoma* and malignant *schwannoma*.

Anesthetic Consideration for Patients with Mediastinal Tumors

Risk Assessment

The majority of patients with mediastinal tumors tolerate general anesthesia well with a reported anesthetic complication rate of <10 % [65]. However, respiratory or hemodynamic collapse during induction of general anesthesia is a recognized risk in children with an anterior mediastinal mass. The increased risk is contributed by several factors, and can be understood as restrictive or obstructive ventilatory compromises, decreased venous return and

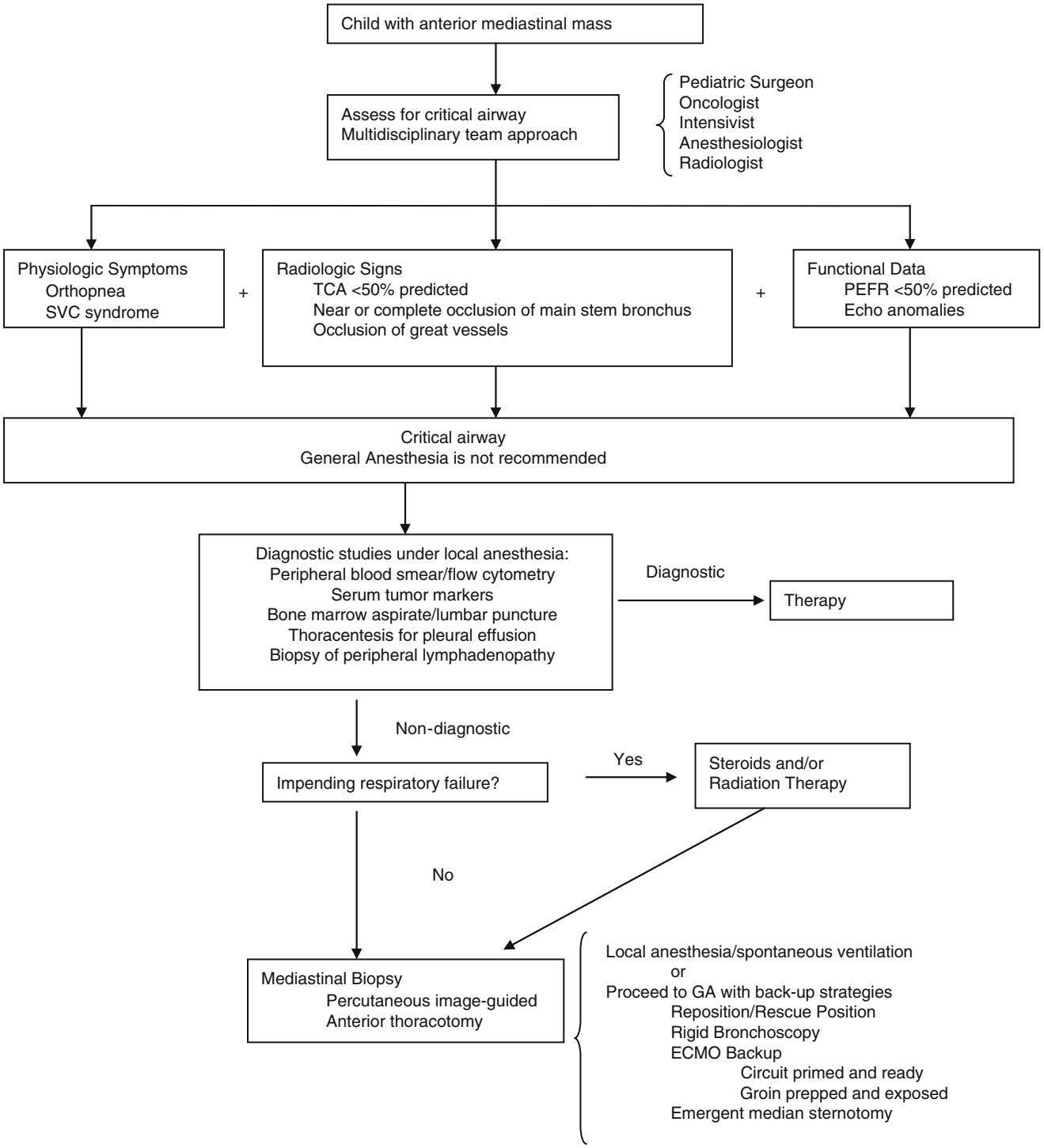

Fig. 27.13 Anesthetic risk assessment and diagnostic approaches for children with an anterior mediastinal mass. *SVC* superior vena cava, *TCA* tracheal cross-sectional area, *PEFR* peak expiratory flow rate

increased pulmonary pressure with right-sided heart failure. Restrictive compromise is contributed by decreased functional residual capacity and decreased lung compliance. Obstructive changes are evident by the decreased airway diameter and worsened under anesthesia by the loss of normal bronchial smooth muscle tone and distal airway collapse.

An algorithm depicting the assessment of critical airway and the appropriate diagnostic procedure is illustrated in Fig. 27.13 [8–10]. Anesthetic risks should be considered

with the combination of clinical, radiological, and functional data. Clinical signs and symptoms alone do not correlate well with anesthetic complications. Several recent studies have also shown that the degree of airway and vascular compression correlates poorly with actual clinical symptoms. [8, 66, 67] The only symptom that is strongly associated with respiratory collapse is orthopnea [5, 68, 69]. Thus patients presenting with orthopnea should avoid general anesthesia for either diagnostic or therapeutic procedures as a general rule.

Historically, children with a mediastinal mass less than one-third of the diameter of the thorax have a low risk of anesthetic complications, and those with a mass greater than 45 % of chest diameter are thought to have the greatest risk [1, 70]. As technology advanced, CT scans became routinely used to define the cross-sectional area of the trachea to assess the relationship to anesthetic risk [69, 71, 72]. Both Azizkhan et al and Shamberger et al suggested that children with tracheal cross-sectional areas (TCA) less than 50 % of predicted should not receive a general anesthetic. A recent retrospective series in the anesthesia literature reported imaging findings of mainstem bronchus compression and great vessel compression, along with orthopnea and upper body edema, as significantly associated with anesthetic complications in children with anterior mediastinal masses [65].

Extensive pulmonary function abnormalities were identified in a group of patients with anterior mediastinal masses prospectively studied [72]. The peak expiratory flow rate (PEFR) in pulmonary function studies is the best parameter in the prediction of anesthetic problems. It provides a quantitative reflection of central airway size. It can be easily performed with a hand-held device and compared with the predicted values [10, 72]. A PEFR of less than 50 % of predicted is associated with increased anesthetic risks [69]. The measurement of pulmonary function in children with anterior mediastinal masses may add valuable information to the anatomic evaluation obtained by CT scan. In particular, it can quantitate the magnitude of pulmonary restriction in relation to the size of the mass and may identify impairment of flow related to compression of airways distal to the carina, which cannot be measured by CT scan. Thus, the clinical, functional, and radiological findings can be incorporated into a simple algorithm to assess anesthetic risk for each individual patient (Fig. 27.13).

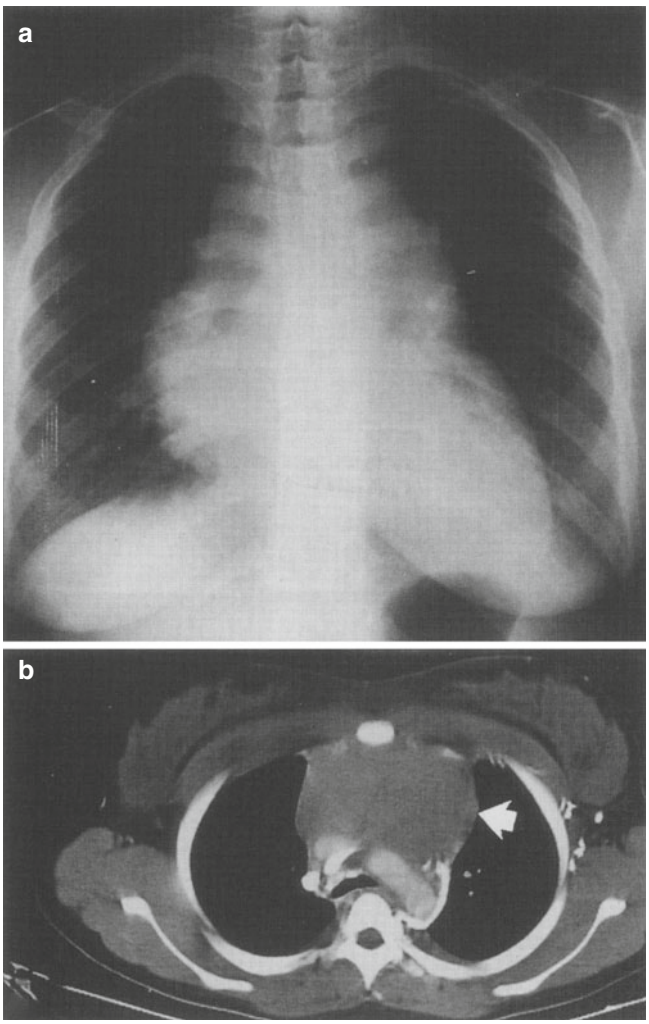

Fig. 27.14 (**a**) Chest radiograph of a 12-year-old girl who presented with facial swelling and plethora. Chest radiograph demonstrated a significant anterior mediastinal mass. Echocardiogram revealed a pericardial effusion and the CT (**b**) revealed a homogeneous anterior mediastinal mass (*arrow*). Her white cell count was 5.1 with a normal differential count. Fluid aspirated from the pericardium, however, had a white cell count of 724,000 and cytology was diagnostic of lymphoblastic leukemia

Alternatives to General Anesthesia for Diagnosis

The least invasive and lowest risk technique should be utilized first to diagnose a mediastinal mass [9]. A multidisciplinary approach in the decision making is essential for optimal patient care. An extra-thoracic approach under local anesthesia can be performed in most patients with anterior mediastinal masses to obtain diagnostic material. This includes cervical or supraclavicular excision of an enlarged lymph node, thoracentesis in the presence of pleural effusion to obtain cells for cytology and flow cytometry [14], and bone marrow aspirate and biopsy since leukemias may present as an anterior mediastinal mass (Fig. 27.14). Fine needle aspiration and core-needle biopsies of mediastinal masses under CT or ultrasound guidance is generally adequate to obtain a pathologic diagnosis, but frequently does not provide sufficient material for histologic subtyping for lymphomas [73–76]. The Chamberlain procedure (anterior thoracotomy

through the bed of the second rib) can be performed under local anesthesia even in children, and should be part of the armamentarium of the pediatric surgeon [77]. Thoracoscopic biopsy requires general anesthesia, and its diagnostic accuracy for lymphoma is still under investigation, despite excellent diagnostic yields for other thoracic lesions using minimally invasive techniques [78, 79]. Careful communication with the pathologist regarding the adequacy of biopsy material is essential when utilizing a minimally invasive technique. [80, 81]

Management of General Anesthesia

Despite the increased anesthetic risk, surgical biopsy or resection under general anesthesia remains the optimal option for some children with mediastinal tumors. Thus, careful preoperative discussion must occur between the surgeon and the anesthesiologist to provide an individualized management plan based on the child's preoperative symptoms and imaging findings (Figs. 27.15 and 27.16). Airway management maybe achieved with awake fiberoptic bronchoscopy using local anesthesia and judicious intravenous sedation. Rigid bronchoscopy performed by the surgeon may be necessary in the event of airway loss, passing the scope beyond a mid-tracheal narrowing or placing it into a patent mainstem bronchus to allow for adequate ventilation until spontaneous ventilation returns. Identifying a "rescue" position preoperatively may be helpful to minimize cardiorespiratory collapse [82].

Extracorporeal Membrane Oxygenation (ECMO) providing cardiopulmonary bypass is the final option in the management of critical mediastinal masses [83–85]. The best time to consider ECMO is prior to anesthesia induction. Cannulation options should be discussed and decided, and a circuit should be primed and ready (Fig. 27.17). A femoral approach with distal limb perfusion is the preferred method as the cervical approach would likely be compromised by the presence of the tumor [85].

Video Assisted Thoracoscopic Surgery (VATS)

Surgical biopsy and resection is essential in the management of pediatric mediastinal tumors. Anterior mediastinal masses are traditionally approached with median sternotomy or anterior thoracotomy, and posterolateral thoracotomy for posterior mediastinal lesions. Increased expertise in minimally invasive surgery has allowed VATS to be applied in the surgical management of mediastinal pathologies.

VATS offers several advantages over traditional open thoracotomy and sternotomy both for the surgeon and the patient. Thoracoscopy provides greater exposure of the entire thoracic and mediastinal compartments and wider area of access. The magnification also gives better anatomic detail. The video monitor affords the anesthesiologists and trainees a better understanding of the procedure. Patient-related advantages include less postoperative pain, less splinting, and less atelectasis [86]. The risk of skeletal deformities such as scoliosis and chest wall asymmetry is minimized with the thoracoscopic approach [87]. Shorter hospital stay and earlier return to normal activity for both patient and parents have been well documented in the literature. Conversely, potential problems with the use of thoracoscopy for biopsy include the inability to palpate lesions, the risk of intrapleural tumor spillage and the development of recurrent disease at the port sites.

Both benign and malignant conditions can be treated with VATS (Figs. 27.2, 27.9, 27.10 and 27.15). Benign mediastinal cysts and tumors can be safely resected with VATS. Biopsy, staging and even curative resection can be achieved with VATS in selected patients with malignant lesions. Even young infants tolerate VATS with few complications. In one report, 38 of 39 procedures were completed successfully using VATS [24]. Diagnosis was obtained in all cases, and complete resection was performed in 33 children who were appropriate candidates.

Relative contraindications for VATS include previous thoracotomy and significant bleeding disorder. Patients with airway compromise from large anterior mediastinal mass may require alternative diagnostic methods.

Single Lung Ventilation

A detailed discussion regarding airway management should be carried out between the surgeon and the anesthesiologist preoperatively. Single lung ventilation is essential to provide optimal exposure of the mediastinum. It can be achieved with double lumen endotracheal tubes in older children, and mainstem intubation or selective contralateral lung ventilation using ipsilateral bronchial blockers for smaller children [88]. The use of low pressure, low flow of CO_2 (3–5 mmHg) also helps to collapse the ipsilateral lung. Placement of a chest tube at the end of the procedure is procedure-dependent and at the discretion of the surgeon.

Positioning and Port Placement

Patients with anterior mediastinal masses should be positioned in a modified supine position with the affected side elevated slightly (15–45°). Patients with posterior masses are positioned in a modified prone position with a similar degree of elevation. Such positioning takes advantage of gravity to allow the lung to fall away from the lesion when the lung is collapsed. Three or four ports are placed between the ante-

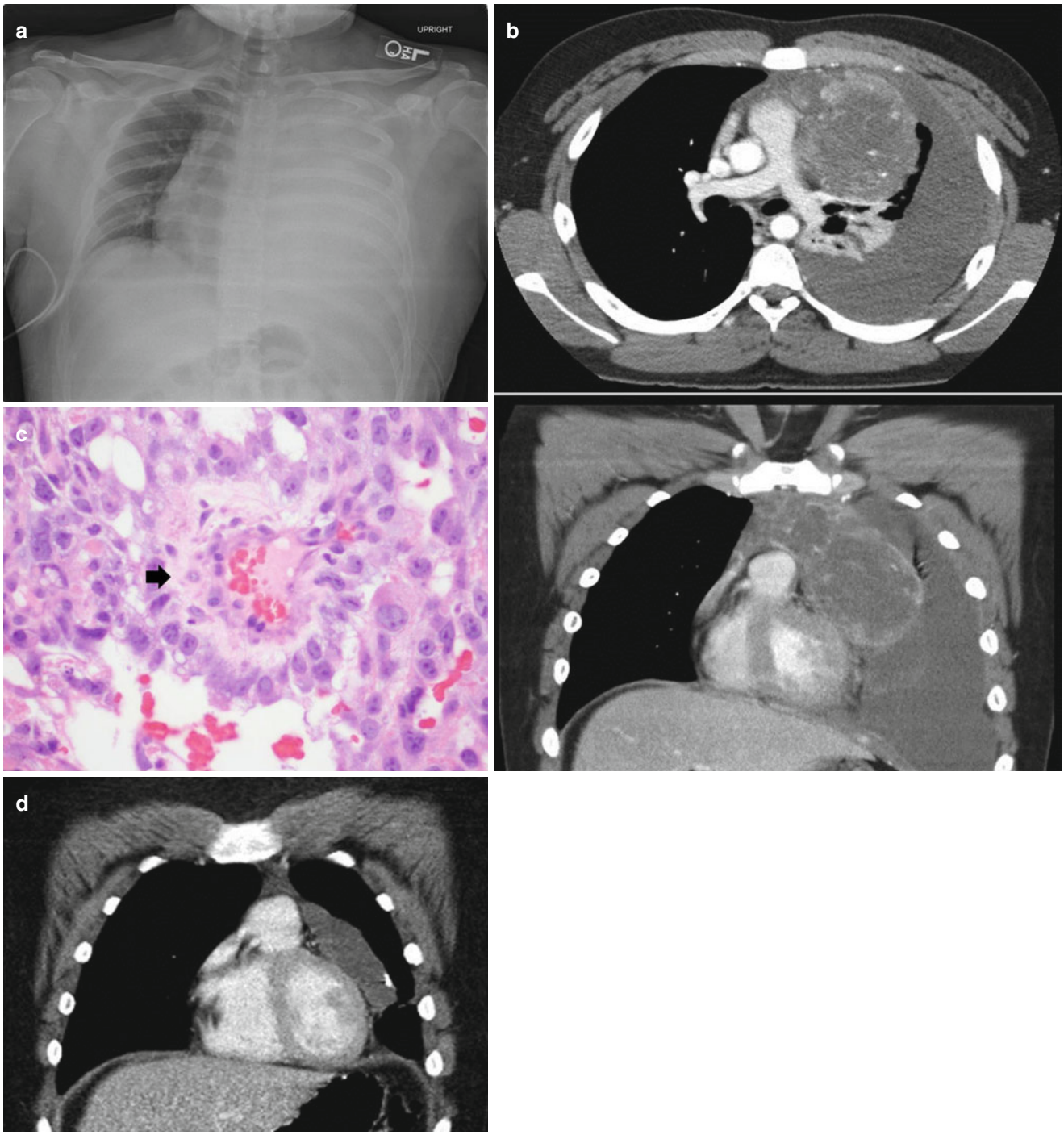

Fig. 27.15 (**a**) Chest radiograph of a 17 year old male with anterior mediastinal mass and left hemothorax presenting with respiratory distress. (**b**) CT scan demonstrating the large anterior mediastinal mass with increased vascularity and associated hemothorax. The airway is patent but the mass is compressing on the pulmonary artery and left atrium. The patient had a chest tube placed which drained mostly sanguinous fluid output; cytology was not diagnostic. After multidisciplinary discussion, thoracoscopic decortication and biopsy were done under general anesthesia. The patient received stepwise anesthetics, starting with Ketamine and propofol, followed by short acting muscle relaxant and endotracheal intubation. The patient tolerated the procedure well. (**c**) Pathology of the biopsy revealed yolk-sac tumor with pathognomonic Schiller-Duval bodies (*black arrow*). (**d**) CT scan 3 months later demonstrating significant reduction of the mass after four cycles of chemotherapy (cisplatin, etopiside, and bleomycin/VP16). The patient underwent complete thoracoscopic resection of the tumor uneventfully (Courtesy of Dr. Christopher Newton)

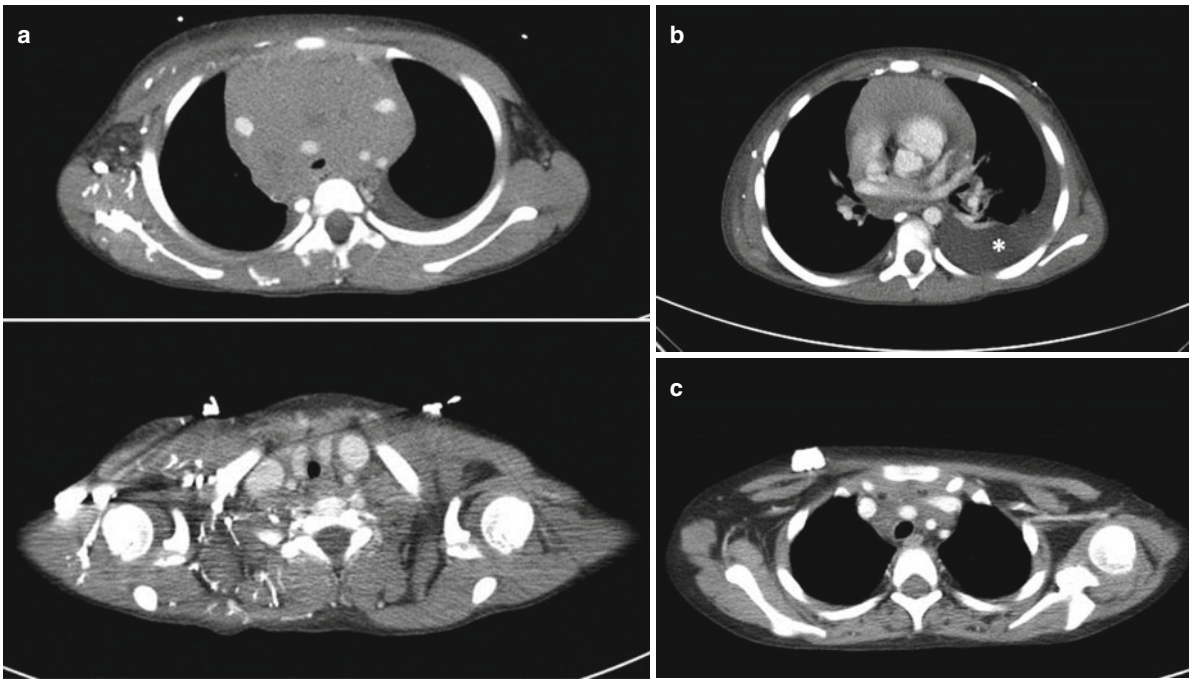

Fig. 27.16 (**a**) CT scan of a 7 year old boy presenting with facial swelling, chest wall spider angiomas, dyspnea and impending respiratory failure. Patient received intravenous methylprednisone and two sessions of radiation therapy. Note the collateral vessels indicative of SVC obstruction consistent with SVC syndrome. Tracheal cross section is 16 mm^2, 23 % of predicted value for age. (**b**) A pleural effusion developed 3 days later (*), thoracentesis was performed under local anesthesia, with child life specialist to distract the patient. However the pleural fluid cell block was non-diagnostic. (**c**) Patient's clinical symptoms improved with the pretreatment although CT finding remained unchanged. He underwent ultrasound guided core needle biopsy of the anterior mediastinal mass under local anesthesia and sedation, while maintaining spontaneous ventilation. The core needle biopsy was diagnotic for lymphoblastic lymphoma. Patient was started on chemotherapy and the CT scan at 4 weeks showed nearly normal anatomy, with tracheal cross section of 76 mm^2, 101 %of predicted

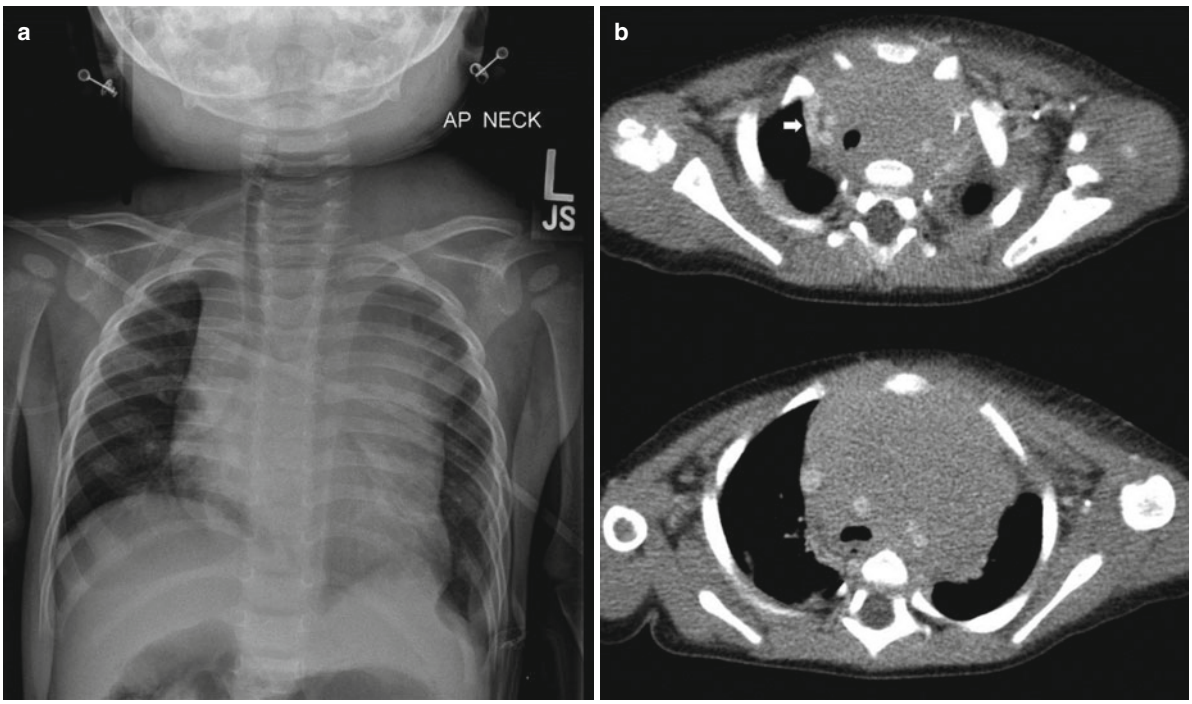

Fig. 27.17 (**a**) Chest radiograph of a 12 month old girl with a large cervical and mediastinal mass suspicious for lymphoma. Note the degree of tracheal deviation. (**b**) CT scan demonstrated significant mediastinal shift and caval compression with suspicion of a thrombus (*white arrow*). The patient underwent biopsy of the cervical lymphadenopathy under local anesthesia and IV sedation in semi-upright position. The patient tolerated the procedure well in the operating room but deteriorated in the PICU. An ECMO circuit was primed with plans for femoral cannulation but the patient tolerated intubation with positive pressure ventilation, and ECMO was eventually not needed

rior and posterior axillary lines. Entry into the thoracic cavity at the fourth or fifth interspace is optimal, as the collapsed lung from single lung ventilation may elevate the ipsilateral diaphragm.

VATS provides a safe and effective approach in the surgical management of mediastinal tumors [89]. This approach is the author's preferred method in appropriate patients with mediastinal masses, as long as basic oncologic surgical principles are upheld without compromising patient safety.

Conclusion

The majority of pediatric mediastinal masses are malignant. Anatomical assessment and knowledge of representative tissue in each compartment will provide an organized approach to the differential diagnosis. Age of the patient, imaging modalities and tumor markers (when present) are additional useful factors. Early diagnosis, resection of non-lymphomatous tumors, and adjunctive treatment can result in improved survival. Careful assessment of anesthetic risk factors in patients with large anterior mediastinal masses can avoid significant anesthetic complications. VATS offers the advantage of smaller incisions, better visualization, and faster recovery with low morbidity. VATS can be used safely in the evaluation and treatment of some mediastinal malignancies.

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Rare Tumors

28

Hugo A. Heij

Definition

When is a tumor called rare? From a practical point of view we will use the definition in this chapter that a tumor is considered "rare" if there is no treatment protocol available. One can derive a very long "list of rarities" from the pediatric pathology literature [1–3], which allows the following subdivided definitions:

1. Rare tumors independent of age.
2. Adult-type tumors in children[1].
3. Rare but typical childhood tumors.
4. Common pediatric tumors with rare histologic features.
5. Common pediatric tumors in rare locations.
6. Seemingly common but in fact rare tumors.
7. Rarely recognized occurrences of common tumors.

In view of the surgical character of this book it seems appropriate to discuss the rare tumors arranged according to their anatomical regions, with special emphasis on the abdominal cavity. The aim of this chapter is not to provide an exhaustive list of all rare tumors, but rather to focus on solid tumors that require surgical treatment. Where possible, guidelines for management will be derived from the available literature. To that purpose, literature searches have been performed in Medline (PubMed) using the type of tumor as MESH term, focusing on reviews. Also, cross references and hand searches of the literature have been done.

[1]Ethical issues may arise in families with a genetic predisposition for malignant tumor. Recently a discussion was published by the committee on bioethics of the American Academy of Pediatric on the pro's and con's of genetic testing of children for adult-type tumors, like familial adenomatous polyposis and breast cancer (Caga-anan et al., *Pediatric* 2012;129:163–7).

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IPSO Rare Tumor Registry

Ten years ago, a registry of rare tumors was instituted by the International Society for Pediatric Surgical Oncology (IPSO). The aims of this registry are to collect data and tissue for research, and to provide information and guidance on the management of patients with rare tumors.

The entries provide an impression (but nothing more exact than an impression) of the epidemiology. For the epidemiology and incidence: see also [2]. Table 28.1 provides an overview of the spectrum of tumors registered.

Benign (Pseudo)Tumors

These are essentially benign tumors and the reason to present them here is because of the confusion that may arise with malignant tumors (Laffan EE. Pediatric soft tissue tumors .., *Radiographics* 2009;e36)

Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumor (IMT) was first described in the lung in 1937, and since then has been reported at various sites. Histopathologically, IMT is a benign solid tumor, mainly composed of spindle-shaped cells, and has a chronic inflammatory component [4]. Synonyms are: inflammatory pseudotumor, pseudosarcomatous myofibroblastic proliferation, plasma cell tumor, xanthomatous pseudotumor, fibroxanthoma, and histiocytoma [4, 5].

The presentation varies according to the location: respiratory symptoms and clubbing in pulmonary IMT; abdominal pain, fever, and weight loss in abdominal IMT [6].

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Table 28.1 Overview of the spectrum of tumors registered with IPSO

Tumor spectrum	
Adrenocortical carcinoma	30
Hamoudi (Frantz) tumor	11
Carcinoid	3
GIST	3
Pancreaticoblastoma	3
Aggressive fibromatosis	3
Pulmonary blastoma	2
Pheochromocytoma	2
Lipoblastoma	2
Chorioncarcinoma liver	2
Desmoplastic tumor abdomen	2
Single entries (n = 25)	
Transitional cell carcinoma	
Spindle epithelial tumor with thymus-like differentiation (SETTLE)	
Seminoma	
Renal cell carcinoma	
Mullerian papilloma	
Mucoepidermoid bronchial carcinoma	
Metanephric adenofibroma	
Mesenchymal hamartoma	
Malignant trophoblastic tumor placental site	
Malignant fibrohistiocytoma	
Malignant nonchromaffinic paraganglioma	
Inflamm. myofibroblastic tumor – pt known with neurofibromatosis	
Infantile fibromatosis	
Hemangiopericytoma (infantile type)	
Granulosa-Theca cell tumor	
Gonadoblastoma	
Follicular thyroid ca (lft)	
FNH (focal nodular hyperplasia)	
Embryonic pancreatic tumor	
Ductal adenocarcinoma of pancreas/hepatoblastoma (fetal type)	
Chondroblastoma	
Chemodectoma	
Angiomyolipoma (Tuberous sclerosis)	
Angiomatoid fibrous histiocytoma	
Adenocarcinoma colon	

With acknowledgement to Dr. D.C. Aronson

Large fibrous inflammatory pseudo-tumors may occur in the mesentery, duodenum, jejunum, pancreas, spleen, and liver [4, 5, 7–9].

Malignant transformation of IMT has been described in a 13-year old boy with NF-1 presenting with a pelvic tumor with liver metastases. Despite resection and chemotherapy, the tumor recurred (Ernst et al., *JBR BTR* 2011)

The most frequent finding is a palpable mass in the abdomen [4, 9–11]. Jaundice was the presenting sign in a 6-year-old boy with IMT in the hilum of the liver [7].

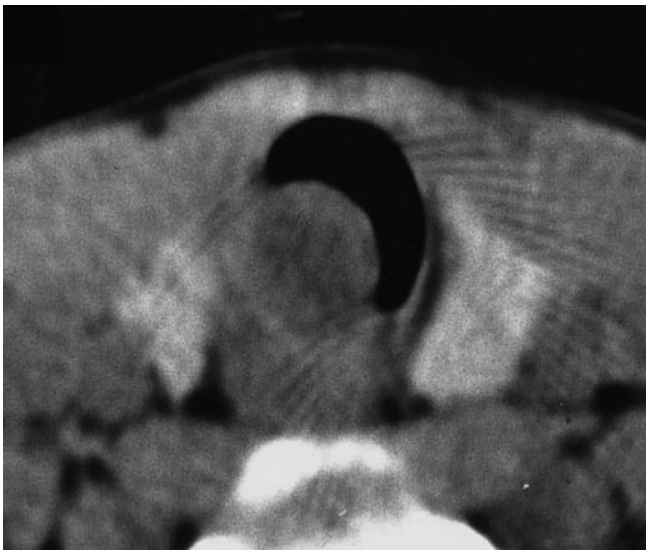

Fig. 28.1 I.M.T. of the trachea. Inflammatory pseudotumor of the trachea (From Bumber et al. [5])

Thoracic IMT has been reported in the heart [12], lung [4], mediastinum, and trachea [5]. A 14-year-old boy with IMT of the trachea underwent successful CO_2-laser excision [5] (Fig. 28.1). Successful diagnosis of IMT by fine needle aspiration cytology (FNAC) with ancillary studies towards ALK and actin expression has been reported (Stoll & Li). ALK expression may also be of prognostic significance as Fragoso et al. (ref) describe seven cases with ALK-negative IMT and a benign course.

The treatment of IMT is complete resection, which may require sacrifice of blood vessels and other vital structures [7, 13]. There are scarce data on recurrence rate, but the available evidence suggests it may be higher than 10 %. Tumors that have ill-defined margins and therefore cannot be resected completely have a higher risk of recurrence [8]. Although usually histologically benign, radiation and cytotoxics have been successfully used in unresectable and recurrent IMT. Corticosteroids have also been advocated under these circumstances [11]. Good response to adjuvant chemotherapy was reported for an unresectable IMT in a 10-year old boy with multiple abdominal tumors (Bertocchini, *JPS* 2011)

Xanthogranulomatous Pyelonephritis

Xanthogranulomatous pyelonephritis (XPN) is a rare destructive inflammatory process. This condition can be mistaken for a Wilms' tumor; however, the radiographic presence of infection and calculi often help to make a preoperative diagnosis of XPN. Treatment is nephrectomy and antibiotic coverage [14].

Juvenile Xanthogranuloma

Juvenile xanthogranuloma (JXG) is a member of the group of histiocytic proliferative disorders. JXG is a usually benign self-limiting disorder presenting as nodular skin lesions. It occurs mainly in the head and neck region and is present at birth in 5–17 % of the cases [15]. In the hand, JXG may arise from the tendon sheath and is called giant cell tumor of the tendon sheath [16].

Disseminated JXG in contrast may involve liver, lungs and CNS, and in young children has a poor prognosis. Various treatments, including surgical resection, have been attempted. Dölken et al. report a 7-month-old girl with life-threatening systemic JXG, including multiple CNS lesions, that responded well to chemotherapy according to the Langerhans cell histiocytosis protocol [17]. The association of JXG and mastocytosis was described recently in a 3-year old girl (Gruber et al., *Int J Dermatol*)

Langerhans' Cell Histiocytosis

Histiocytic and dendritic neoplasms in children are rare. They arise from antigen-processing phagocytes (histiocytes) and antigen-presenting dendritic cells, which are derived from the hemopoietic stem cells. The WHO classification distinguishes six entities, of which Langerhans' cell histiocytosis is the most common. Other types are: Langerhans' cell sarcoma and histiocytic sarcoma. These tumors have been described in the vertebral bodies, responding to irradiation, but later metastasizing to the lung [18]; but also as primary pulmonary cystic lesions with fatal outcome despite chemotherapy [19]; as facial swelling [20] (Fig. 28.2); and as cervical lymphadenopathy, with a favorable response to chemotherapy [21].

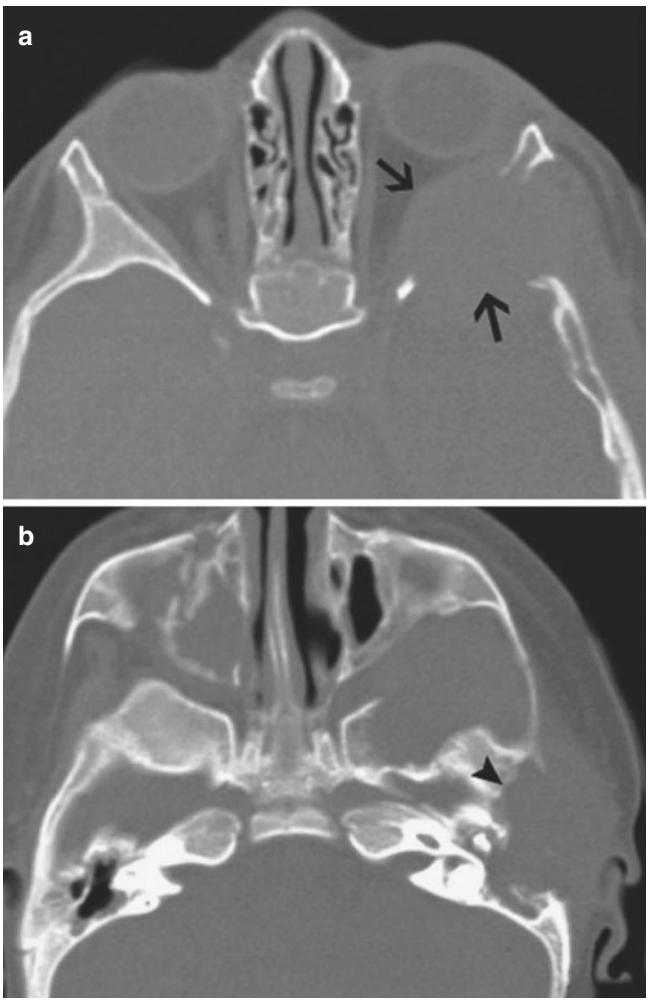

Fig. 28.2 Langerhans cell histiocystosis (**a**) CT scan shows a lytic lesion of the frontal and sphenoid bones (*arrows*) (**b**) CT scan shows destruction of the temporal bone (*arrowhead*)

Association of Malignancy and Langerhans' Cell Histocytosis

A case of simultaneous occurrence of malignant histocytosis and primary gonadal germ cell tumor was reported in an 18-year-old male by Margolin and Tarweek [22]. The testicular cancer was a stage 1 teratocarcinoma with endodermal sinus tumor elements with malignant histocytosis. The patient died despite treatment with chemotherapy.

Two case reports described the association of histocytosis and germ cell tumors. A 14-year-old boy developed fatal malignant histiocytosis of the spleen during cytotoxic treatment for mediastinal immature teratoma which had been excised 11 months before [23]. A 15-year-old boy presented with chest pain and was diagnosed with a mediastinal germ cell tumor and simultaneous histiocytioc sarcoma of the spleen [24]. Recently more report have been published on the association of LCH with nephroblastoma in a 2 years old girl (Narui, *PBC* 2009); neuroblastoma in a 5 year old boy (Rayburg, *PBC* 2009); Broncho- Alvaeolar Carcinoma in a 15-year old male with colonic polyposis (von der Thusen, *JCO* 2011)

Fibromatosis

Fibromatosis in children comprise a wide spectrum of conditions. A fibroblastic stem cell, called collagenoblast with many oncogenic potentials, has been postulated as the common origin of fibromatoses [25].

Infantile digital fibromatosis (Reye tumor) is a benign condition with a tendency to spontaneous regression. Calcifying aponeurotic fibroma is equally benign and requires conservative excision. In newborns, plantar nodules

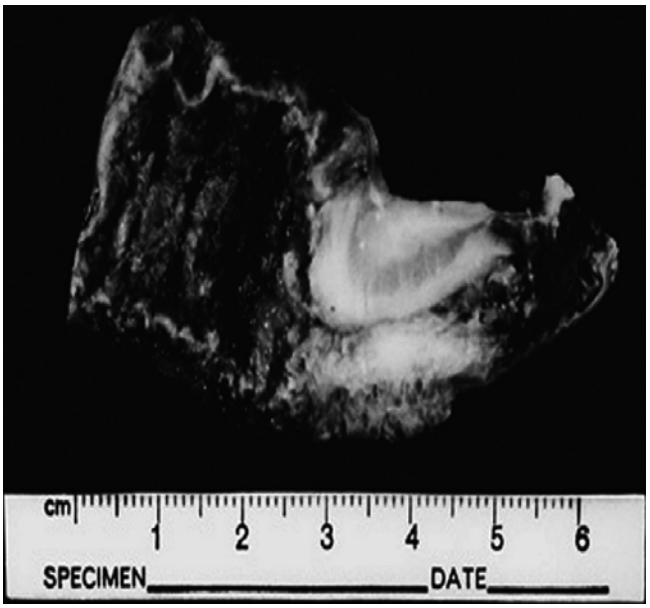

Fig. 28.3 Intestinal fibromatosis. Congenital solitary intestinal fibromatosis (With kind permission from Numanoglu et al. [28]). Review For an overview of the role of imaging, particularly MRI in fibromatosis (see Laffan et al. (2009))

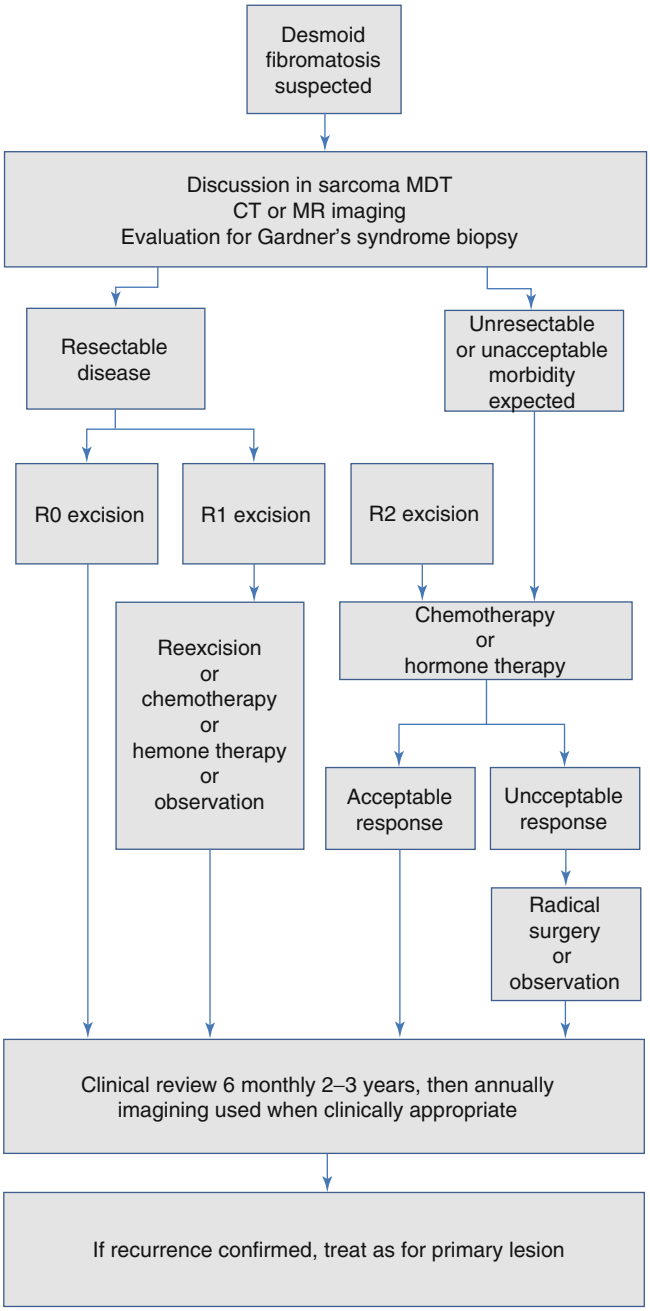

Fig. 28.4 Wilks et al. present a treatment algorithm for facial pediatric desmoids tumors (From *JPRAS* 2011)

have been reported, that are classified as precalcaneal congenital fibrolipomatous hamartoma [26, 27]. At the other end of the spectrum are lesions like: low-grade myofibroblastic sarcoma, plexiform fibrohistiocytic tumor, and congenital and infantile fibrosarcoma that require complete (radical) excision [16].

Congenital intestinal fibromatosis has been reported to cause obstruction (Fig. 28.3) [28]. Aft er excision, the prognosis is good [28, 29].

Aggressive fibromatosis (AF), also called desmoid tumor, arises form the connective tissue of muscles and overlying fascia. The histological features are benign and they do not metastasize, but show local invasiveness and have a tendency to recur. The age distribution peak of pediatric AF is at 8 years (range 0–19). The majority occurs sporadically, but they can be associated with Familial Adenomatous Polyposis (FAP) and Gardner syndrome. The recurrence risk after complete excision is significantly lower than in the case of positive surgical margins [30, 31]. If complete excision is not feasible, as in intra-abdominal, mesenteric tumors, NSAIDs and tamoxifen may be effective [32]. The role of cytotoxic agents (a combination of vincristin, actinomycin-D, and cyclophosphamide, VAC) and radiotherapy, although advocated in cases of positive resection margins, is not defined [31]. Prognostic factors have been described by Salas et al. (*JCO* 2011) and particularly for children by Meazza (*Minerva Pediatr* 2011) and encompass: age, size, site (girdle or intra-abdominal localization) incomplete resection, and beta-catenin activating mutations. Similar findings in pediatric aggressive fibromatosis of head and neck were reported by Sharma et al. Wilks et al. present an algorithm for facial pediatric desmoids tumors (*JPRAS* 2011) (Fig. 28.4).

Mesenteric fibromatosis has been reported in a 13 year-old boy after irradiation for Hodgkin's disease [33].

Another rare variation in the spectrum is DermatoFibroSarcoma Protuberans, DFSP. The pigmented

version is also known as Bednar Tumor. It is a low grade malignancy but with a high risk of local recurrence. Fibrosarcomatous transformation has been reviewed by Voth et al. A good response to imatinib, allowing complete resection of an initially irresectable tumor, has been reported (Gooskens et al., *PBC* 2010).

Fibromatoses in children are difficult to manage for a variety of reasons. They are rare and their clinical behavior is unpredictable. Most cannot be diagnosed without histologic material. Management must therefore be based on an adequate biopsy followed by a detailed discussion between pathologist and surgeon. Although some recur, those that are not malignant are best treated by conservative, nonmutilating excision, with further excision as recurrence occurs. When malignancy is found on biopsy, excision with a margin of normal tissue is necessary. MRI is helpful in planning these procedures. Appropriate staging, including CT-scan of the chest, is indicated [32].

Vascular Tumors

Malignant Vascular Tumors

Malignant vascular tumors (hemangiosarcoma, malignant hemangioendothelioma, and Kaposi sarcoma) are extremely rare in children.

A case of a 13-year-old girl with malignant hemangioendothelioma has been reported. The tumor was treated by surgical excision of the omentum. However, bloody ascites and multiple peritoneal implants were already present [34].

A series of 18 children were described by the combined Italian and German oncology groups [35]. Surgery is the mainstay of treatment, but even with combined treatment of excision, chemotherapy and radiotherapy the 5-year survival was 30 %. A 2-year old girl with rupture of a angiosarcoma of the spleen and liver metastases came into complete remission after splenectomy, partial liver resection, and treatment with VAI [36].

Kaposi sarcoma (KS) is associated with HIV in children in Africa (Fig. 28.5), but less frequently in children in industrialized countries [37]. In Africa, it is now one of the most frequent tumors in children [38]. The Human Herpes Virus 8 (HHV 8) is involved in the pathogenesis [39]. Thalidomide appears a promising and affordable inhibitor of angiogenesis [40].

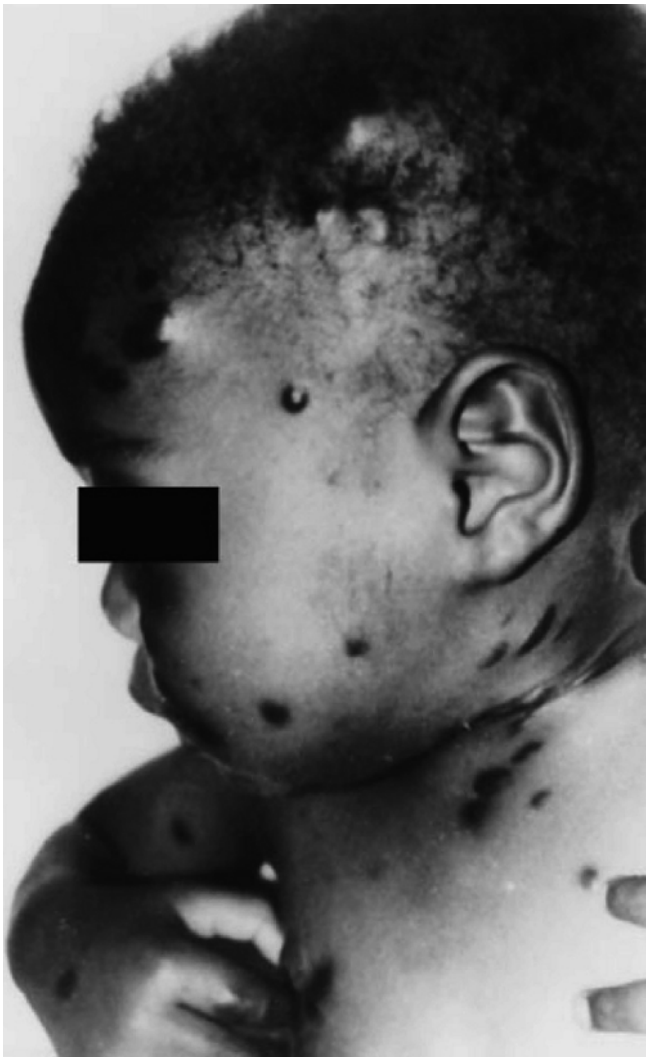

Fig. 28.5 Kaposi's sarcoma (From Manji et al. [38])

Hemangiopericytomas

Hemangiopericytoma (HPC) is a rare tumor that represents 1 % of all vascular tumors and arises not from endothelium but from pericytes, therefore strictly spoken it is not a blood vessel tumor. In children, there are two forms: the infantile (below the age of 12 months) and the adult type. Although histologically this tumor looks aggressive, it behaves in a benign manner. Spontaneous regression has sometimes been observed. HPC can be localized in the heart, lung, retroperitoneum, or the urinary tract and may present as an abdominal mass causing obstructive symptoms. Subcutaneous tumors may not appear vascular. While the tumor is benign, tumor recurrence has been recorded more than 10 years later. Imaging studies may show calcification in the soft tissues. The treatment of choice is complete excision of the tumor, which is followed by complete remission in patients with the infantile type. HPC in older children behaves like the adult type. Adjuvant treatment with VAC and IVA [ifosfamide, vincristine, Adriamycin (doxorubicin)] is advised in patients with irresectable lesions or positive margins [41].

A review from St Jude Children's Hospital (17 children between 1962 and 2009) showed a better clinical behavior than the adult type with chemoresponsiveness and spontaneous regression (Fernandez-Pineda, *JPHO* 2011)

Recently, a malignant Perivascular Epitheloid Cell tumor (PEComa) has been reported in a 2 year old child by Alaggio et al. (*JPS* 2012;47:e31). This family of tumors was first described by Zamboni in 1996, and includes angiomyolipoma, lymphangio-leiomyomatosis, clear cell 'sugar' tumor of the lung, and clear cell myomelanocytic tumor (CCMMT). In this case the tumor was located in the ligamentum teres. After excision, a recurrence showed good response to sirolimus.

Rare Tumors of the Head and Neck

Malignant Mesenchymoma

Malignant mesenchymoma is a rare neoplasm of mesenchymal origin arising in the soft tissues, the extremities, neck, back, sacrum, and occasionally in the mediastinum. See below, the section titled "Ectomesenchymoma."

Brain Metastases in Children

Hematogenous brain metastases are uncommon in children. A literature review revealed an incidence of 4 % in over 2000 reported patients. The incidence varied according to the primary tumor: between 1.3 % in Wilms' tumor, 4.4 % in neuroblastoma, and 13.5 % in germ cell tumor [42]. In the SIOP Wilms' tumor studies between 1971 and 2000, brain metastases were reported in 14 out of 3040 patients (0.5 %). Treatment consisted of multimodal chemotherapy, radiotherapy, and surgery in seven patients. None of the patients survived [43]. In a review of 20 patients reported in the literature, death was recorded in five cases and in the remaining patients survival time of up to 8.5 years was noted [44]. There may be a publication bias in this compiled data since the experience of a single institution with 16 patients with brain metastases from various primary pediatric tumors, reported one survivor at 20 months with alveolar soft part sarcoma [45]. Many of these patients had metastases in multiple organs. In summary, the prognosis of brain metastases from solid tumors in children appears dismal, despite multimodal treatment.

Nasopharyngeal Carcinoma

Epithelial cancers (carcinomas) are the single largest group of rare tumors in children, with an incidence of 2–3 % of all childhood malignancies in the Western population. For most sites incidence increases with age, but nasopharyngeal carcinoma (NPC) has a bimodal age distribution, with an early peak in adolescence. The most common presentation is with cervical lymphadenopathy. The role of surgery is therefore limited to biopsy. Chemotherapy (methotrexate, 5-FU, and cisplatinum) and irradiation achieved a high response rate and sustained remission in 91 % [2]. An increase in the prevalence of squamous cell carcinoma (SCC) in various locations but particularly in the nasopharynx, was reported by Chow et al. Possible causes for this increase are the improved survival of cancer patients who may develop SCC as secondary tumor. (Chow, *JPS* 2007;42:2035–9)

In 1997, Srotjan et al. [46] described five children with nasopharyngeal carcinoma with advanced stage IV tumors that were treated with low irradiation dose adjusted to preradiation neoadjuvant chemotherapy. Tumor control was achieved and acute and long-term morbidity reduced.

Salivary Gland Carcinoma

Carcinoma of the salivary gland is very rare in children [47]. Taylor et al. [48] described 15 such children. The primary site was the parotid gland in 11 cases, submandibular gland in three, base of the tongue in one. Six children were treated with complete excision, one required postoperative radiotherapy, five had partial excision, and four tumors were biopsied only. They concluded that complete excision is the treatment of choice.

Mucoepidermoid carcinoma of the parotid has been reported as secondary malignancy in a 17-year-old boy and a 16-year-old girl, who had been treated for osteosarcoma and Ewing's sarcoma, respectively. Subtotal parotidectomy appeared curative. Mucoepidermoid carcinoma has been reported before as secondary tumor after leukemia or lymphoma treatment, but not in sarcoma patients [49].

Synovial Sarcoma of the Larynx in a Child

Morland et al. [50] reported the first case of synovial sarcoma of the larynx in a child. He was treated with combination chemotherapy and radiotherapy, which led to remission for 3 years. Only six cases have been previously reported.

Rare Tumors of the Chest

Tumors of the Sternum

In addition to malignant bone tumors of the sternum, a deceptive condition called Self Limiting Sternal Tumors of Childhood (SELSTOC) occurs. Te Winkel et al. describe a

series of 14 young children with a rapidly growing sternal mass that disappeared within 6 months. (Te Winkel, *PBC* 2010)

Mediastinum

Thymic lesions consist of tumors, cysts, or hyperplasia. Clinical presentation varies from respiratory symptoms to incidental findings on x-rays. About 30 cases in children have been reported in the literature. Benign thymoma, is, unlike in adults, not always associated with myasthenia or other autoimmune diseases. Complete surgical excision is curative. Multiple localizations have been reported [51]. Malignant thymomas are aggressive and require complete excision.

Stage of the tumor is an independent prognostic factor for survival. Adjuvant chemotherapy and radiotherapy are advocated for invasive tumors [52, 53].

Tracheal and Bronchial Tumors in Children

Primary tumors of the trachea are rare in adults, and even more so in children. Carcinoid represents about one third of the cases, bronchogenic carcinoma one quarter, and mucoepidermoid carcinoma and pleuropulmonary blastoma 9 and 8 %, respectively [54–56].

Diagnosis may be delayed because of lack of awareness. Presentation may be with hemoptysis, pneumonia, and other respiratory symptoms. The diagnosis of carcinoid can be improved by octreotide nuclear scan, as these tumors contain somatostatin receptors. Improved imaging will outline the extent of the tumor and hence guide the surgical treatment, which consists of complete excision, if necessary involving lobectomy or pneumonectomy. Endoscopic treatment of carcinoid is discouraged by most authors [57]. Craig et al. reported on video-assisted thoracoscopic pneumonectomy for bronchial carcinoid affecting the bronchus intermedius in a 14-year-old girl [58].

The outcome of mucoepidermoid carcinoma of the tracheobronchial tree appears good after complete excision [59, 60].

Personal experience

I treated a child with one a couple of years back. It was in the left main bronchus, occluding LLL bronchus totally and wiping out the left lower lobe, but didn't occlude LUL bronchus and extended up into Left main bronchus about 1 cm. I took out the left lower lobe and did a sleeve resection of left main and a bit of LUL bronchus, joining upper lobe bronchus to the residual left main bronchus. Histology was intermediate grade Mucoepidermoid carcinoma, 3 mm clear of all margins, no nodes involved. No chemo or radio therapy and no recurrence now 4 years later.

We tried High Res CT with reconstruction and MRI for follow up, but while they are adequate for nodal or hilar disease, they were not helpful or reliable for mucosal or bronchial wall recurrence. I therefore do regular Bronchoscopies, ceasing at 5 years, which also checks for any stricture formation (none yet). High Res CT subjects them to too much radiation and would only pick up bulky disease in this site, which is a bit late. MRI not really impressive in the bronchus/mediastinum. CXR changes would be too late, so I would encourage you to do Bronchoscopies, probably 3 monthly for a year, 6 monthly for 2 more years then yearly to 5 years. No evidence based support for this, as it is too rare a tumour, but that seems a reasonable protocol. Very curable if recurrence picked up early.

Regards,

Bruce G Currie

Sydney Children's Hospitals Network.

Inflammatory pseudotumor of the trachea has been mentioned above. Cartilaginous neoplasms of the trachea have been described in a child with Mafucci's syndrome, causing obstructive symptoms. Endoscopic laser ablation was successful [61].

Primary Lung Tumors

Primary tumor of the lung is rare in childhood. Yu et al. report the Boston experience with 40 cases in 90 years. The more frequently occurring tumors were: carcinoid (8), IMT (7) and PleuroPulmonary blastoma (6). The mortality was 17.5 % (Yu, *JPS* 2010)

Pleuropulmonary Blastoma

Pleuropulmonary blastoma is a rare malignant primary tumor of the lung in children, but 25 % of cases are extrapulmonary and metastasize mainly to the CNS. A case of extrapulmonary pleuropulmonary blastoma was reported in a child [62]. This tumor is associated with pre-existing cystic lesions of the lung (congenital cystadenomatoid malformation, CCAM). In fact, the extended classification of CCAM (or Congenital Pulmonary Airway Malformation, CPAM) encompasses 5 types, of which type 4 has a histological picture similar to grade 1 PPB. Table 28.2 [63] presents an overview of this classification. The differentiation between PPB and CPAM continues to defy clinicians. There are no reliable characteristic and low-threshold resection of cystic lung lesions is recommended (Oliveira et al., *Eur J Ped Surg* 2011; Nasr et al. *JPS* 2010;45:1086–9).

PPB is also associated with cystic lesions of the kidney: cystic nephroma [64]. Familial cases of this association have been reported [65, 66]. An association with ovarian sex

Table 28.2 An assessment of the expanded classification of congenital adenomatoid malformations and their relationship to malignant transformation

0	1–3 %	Solid; the lungs are small throughout	Bronchial-type airways that have cartilage, smooth muscle, and glands are separated by abundant mesenchymal tissue	Neonates; other malformations; poor prognosis
1	60–70 %	Large cysts (up to 10 cm)	The cysts are lined by pseudostratified ciliated cells that are often interspersed with rows of mucous cells	Presentation may be late; resectable; good prognosis; rare casesshow carcinomatous change
2	10–15 %	Sponge-like composed of multiple small cysts (up to 2 cm) and solid pale tumor-like tissue	The cysts resemble dilated bronchioles separated by normal alveoli; striated muscle in 5 %	Neonates; other malformations; poor prognosis
3	5 %	Solid	There is an excess of bronchiolar structures separated by air spaces that are small, have a cuboidal lining, and resemble late fetal lung	Neonates; poor prognosis
4	15 %	Large cysts (up to 10 cm)	The cysts are lined by a flattened epithelium resting on loose mesenchymal tissue	Neonates and infants; good prognosis

From MacSweeney et al. [63]

cord stromal tumors has been reported by Schultz et al. (*Gynaecol Oncol* 2011). A genetic syndrome has been postulated [67, 68].

The treatment of choice is surgical excision but the prognosis for this type of tumor is poor. Adjuvant chemotherapy has been used successfully in a child with metastatic disease [69]. The registry web site serves as an important resource for physicians and families (http://www.ppbregistry.org).

Cystic Adenomatoid Malformation of the Lung and Malignant Tumors

Apart from PPBs, there are several published cases of other tumors, like mesenchymomas and rhabdomyosarcomas, arising in CCAM [63].

A case of a 22-month-old child with a CCAM who developed rhabdomyosarcoma of the lung was reported by d'Agostino [70]. Among 382 cases of primary pulmonary tumors only 17 had rhabdomyosarcoma, with six of these 17 (35 %) arising in a pre-existing pulmonary cystic malformation [71].

Tumors of the Diaphragm

Primary tumors of the diaphragm are rare, even in adults, with fewer than 200 cases reported. In children these tumors are exceptional, with 41 cases published [72]. The majority [32] was malignant; half of these were rhabdomyosarcomas. A benign Schwannoma was successfully excised in a 13 year old girl. The literature review in this paper focuses on Schwannomas and the diagnosis of diaphragmatic tumors (Hobbs et al., *JPS* 2012) The presentation may be with chest symptoms or with abdominal symptoms. The diagnosis is oft en difficult because of the rarity and localization. The treatment depends on the histological diagnosis. Preoperative chemotherapy may shrink the tumor to allow complete excision [72].

Breast Masses

Epidemiology and Etiology

Malignant tumors of the breast are rare in children and adolescents. In this age group, only one-third arise from primary breast tissue; the rest arise from non-breast tissue (rhabdomyosarcoma) or are metastatic tumors. Predisposing factors are: genetic (BRAC-1 and BRAC-2 mutations, Li-Fraumeni syndrome) or exposure to ionizing radiation, as in survivors of Hodgkin's disease [73]. These patients need careful and frequent follow-up according to a detailed schedule [74].

Sixteen patients under the age of 20 years were seen between 1951 and 1990. Four had benign cystosarcoma phyllodes, one osteosarcoma, and metastatic histocytic lymphoma, one had adenocarcinoma, nine had infiltrating ductal carcinoma, and one had an infiltrating lobular carcinoma in addition to an infiltrating ductal carcinoma. The treatment involved a combination of surgery, radiotherapy, and chemotherapy [75].

Eighteen patients with breast cancer were treated over a 25-year period including 16 females and two males. Primary malignancy presented in two of the patients, metastatic disease in 13, and secondary malignancy in three [76].

Diagnosis

Mammography in young patients is of limited value; ultrasonography, MRI, and PET-scan are more helpful. Fine needle aspiration cytology has a limited role in children because of pain and fear. Excisional biopsies in prepubertal children involves the risk of damage to the breast bud [77].

Treatment

Benign breast masses in adolescent girls are usually fibroadenomas, which may resolve spontaneously. If not excised they should be followed carefully, as ultrasonography cannot

distinguish between fibroadenoma and cystosarcoma phyllodes [77]. Phyllodes is malignant in 25 % of the cases and should be excised completely with a margin of normal tissue [77].

Two young girls with rhabdomyosarcoma of the breast, one primary and one with metastatic, were treated with surgery and chemotherapy respectively [78].

Rare Tumors of the Abdomen

Peritoneum, Omentum, and Mesentery

Primary tumors of these structures are oft en cystic, and benign, with lymphangioma being the most common [79]. Simple surgical excision is the treatment of choice. Peritoneal sarcomas often are very large and pretreatment with neoadjuvant chemotherapy is oft en necessary to render these tumors operable.

Other extremely rare malignant tumors are discussed below.

Peritoneal Mesothelioma

These tumors, although sharing some common histologic features, can vary considerably in biological behavior. Three different types are described: (a) classic, asbestos-related mesothelioma of adults, mainly in the pleural cavity; (b) multicystic mesothelioma, predominantly affecting the pelvic peritoneum of young women and associated with good prognosis [80]; (c) mesothelioma in children, which has an unpredictable behavior [81]. Measuring DNA index by fl ow cytometry can distinguish the cystic (aneuploid) form from the more malignant (diploid) tumors. In only one case, pathologically proven exposure to asbestos fibers has been reported [82].

The treatment of peritoneal mesothelioma depends on the behavior and appearance. Complete surgical removal is often not possible. There are reports that mesothelioma responds to adriamycin alone or in combination with cisplatinum. Intraperitoneal administration of cisplatinum has also been described [81]. Because of the rarity in children, the diagnosis of mesothelioma is rejected even by pathologists in up to 40 % of the cases [83].

Desmoplastic Round Cell Tumors

The group of small, blue cell tumors include neuroblastoma, PNET/Ewing's sarcoma and Desmoplastic Small Round Cell Tumor (DSRCT).

These arise from soft tissues with mesothelial linings, are characterized by male predominance, adolescent onset, and aggressive behavior. The tumors are often intraperitoneal, massive, and tend to metastasize early to lymph nodes, liver, and lungs. The immunohistochemical profile of these tumors is oft en distinctive and reacts to a broad range of antigens. Clinical presentation is usually with a painful mass, but the tumor can also lead to urinary obstruction [84, 85]. Intra-abdominal desmoplastic small round cell tumors may present with retroperitoneal or mesenteric primary with ascites and hepatic metastases. Urogenital involvement has been reported including paratesticular and ovarian localizations [85–87]. Complete surgical excision is usually impossible. Aggressive multidrug chemotherapy can reduce the tumor mass impressively, but the patient remains with residual disease [88].

Kretschmar et al. [89] reported three cases of desmoplastic small cell tumors and reviewed the literature and found 101 cases reported previously which indicated that this tumor is highly malignant and carries a grave prognosis. Only 50 % of cases respond to chemotherapy with a median survival of 17 months.

Molecular genetic studies revealed potential targets for the treatment of DRCT with the PDGF inhibitor SU101 (leflunomide) (Slater and Shipley, *BMJ* 2007)

Lipoblastoma and Liposarcoma

Lipoblastoma is a benign tumor arising from embryonal fat and therefore only occurs in young children. So far, 85 cases have been described, 12 of them presenting with an abdominal mass. The name lipoblastoma may cause confusion with malignant embryonal tumors, and therefore the term infantile lipoma has been proposed [90]. The treatment of choice is excision [91–93].

Only five cases of liposarcoma in childhood have been documented, with two of them arising from the porta hepatis [94–96]. Three of these five children died, one of them developing a recurrence 12 years after an initial favorable response to surgical excision combined with irradiation and chemotherapy.

Gastrointestinal Tract

General

In a recent review, Ladd and Grosfeld [97] presented 58 children and adolescents with gastrointestinal tumors over a 33-year time frame. The average age was 13.8 years; there were 39 malignant and 19 benign tumors. Over half of the children had lymphomas (Burkitt's in 15, and non-Burkitt's, non-Hodgkin's lymphoma in 15). Six patients had colorectal carcinoma, six had neurogenic tumors, four had inflammatory pseudotumors, three presented with Peutz-Jeghers syndrome; there were two children with carcinoid, two with juvenile colonic polyps, two with hemangioma and one each with leukemic infiltrate and gastric leiomyosarcoma.

In a series of 35 patients reported from Turkey, carcinomas of the large bowel and rectum were the most common, comprising about half of this material [98].

In this chapter, malignant and premalignant tumors of the G-I tract will be discussed.

Carcinoma of the Esophagus

Adenocarcinoma of the esophagus has been reported in an 8-year-old boy from India [99]. There was a longstanding history of vomiting, probably due to gastroesphageal reflux. The patient left the hospital without treatment. The authors quote several other case reports of adenocarcinoma in children with Barrett's esophagus.

Smooth Muscle Tumors

In recent years several cases of gastrointestinal smooth muscle tumors, both benign and malignant, have been reported in human immunodeficiency virus (HIV) infected children [100] Another report mentions similar tumors in the lung of a child with clinical HIV infection [101]. Also, abdominal leiomyosarcomas have been described in very long-term survivors of childhood cancer [102].

Leiomyoma and Leiomyoblastoma

These are essentially benign tumors, often occurring at an early age. Symptoms are most commonly caused by complications, such as intestinal obstruction, intussusception, or bleeding. These tumors have been found to occur in the stomach, small intestine, and colon. Usually, excision at the time of treatment of the complication leads to cure [103].

Leiomyosarcoma

Soft tissue sarcoma account for 7 % of all childhood malignancies. Sarcomas with intestinal involvement comprise only 2 % of this latter group. Leiomyoma often invole the stomach, whereas leiomyosarcoma (LMS) are more often found in the jejunum in children [97]. Over half of LMS occur in newborns. Other risk groups are patients with impaired immunity, e.g., after organ transplantation or due to HIV infection [97, 100–102, 104, 105].

LMS is a highly malignant tumor. The Children's Hospital in Boston reported ten; five (50 %) of the children died with metastases. Wide surgical excision is the treatment of choice [106].

Apparently the histological distinction between leiomyosarcoma and leiomyoblastoma is not always easy [107], which could explain why several neonates with "leiomyosarcoma" survived [108, 109].

In total, 27 cases of pediatric intestinal leiomyosarcoma have been reported in the literature. Complete excision and no recurrence after 5 years was achieved. Visceral metastases are atypical [110].

GIST

Gastro Intestinal Stroma Tumor has been recognized as a distinct entity by WHO since 1990. Although predominantly a tumor of adulthood, occurrence in children has been reported by several authors and over 50 pediatric cases can be found in the literature (Hoelwarth ME, personal communication, 2009) [97, 104, 111–113]. Miettinen et al. [114] reported 44 cases of gastric GIST occurring in patients younger than 21 years from the Armed Forces Institute of Pathology.

GIST is a mesenchymal tumor consisting of cells that are very similar to Interstitial Cells of Cajal (ICC), which express the CD 117 antigen, an epitope of the receptor tyrosine kinase KIT, in contrast to smooth muscle tumors like leiomyosarcomas. The great majority of pediatric GIST (88 %) is located in the stomach, but small bowel and colon localizations have been reported [104].

The most common symptoms are pain, anemia due to gastrointestinal bleeding [115], and abdominal masses. The tumor metastasizes to peritoneum, liver, or lymph nodes. Prognostic factors are: mitotic activity, tumor size and tumor site: gastric and colonic tumors have a better outcome than small bowel or mesenteric primaries [110] (Fig. 28.6).

The association of gastric epithelioid leiomyosarcoma (the older name for a GIST), extraadrenal paraganglioma, and pulmonary chondroma was described as Carney's Triad. Two of the triad's components are potentially lethal and it is very important that any patient with any of these tumors should be followed long-term. In 1993, Argos et al. [116] reported on 36 cases of Carney's Triad including their own case of a 12 year-old girl. In Miettinen's series [114] only one out of 44 cases had Carney's triad, but Price found two patients with the triad in the five described [112].

Surgical resection is the mainstay of the treatment of GIST. Complete gross resection is recommended and lymphadenectomy is not warranted [104, 110]. Response to chemotherapy is probably low, but imatinib mesylate, a tyrosine kinase inhibitor has been reported to achieve 50 % response rate [97, 104, 110].

Gastric Teratoma

One hundred and two cases of this usually benign tumor have been reported in the latest review [97]. The majority of the patients are boys, and malignant degeneration has been only rarely described. Abdominal mass, pain, gastric outlet obstruction, or bleeding are presenting symptoms and signs. After complete resection, no recurrences have been described [117] (Fig. 28.7).

Gastric Carcinoma

Fewer than 25 cases of gastric carcinoma in children have been reported [97]. It appears, however, that childhood infection with Helicobacter pylori can play an important causative role in gastric cancer in the adult [118]. Gastric cancer in children has also been described as a secondary tumor aft er treatment for malignant lymphoma [119]. The most common complaints of stomach cancer in childhood are pain and vomiting, along with symptoms suggesting acid peptic disease. Delay in diagnosis is common and can be avoided by

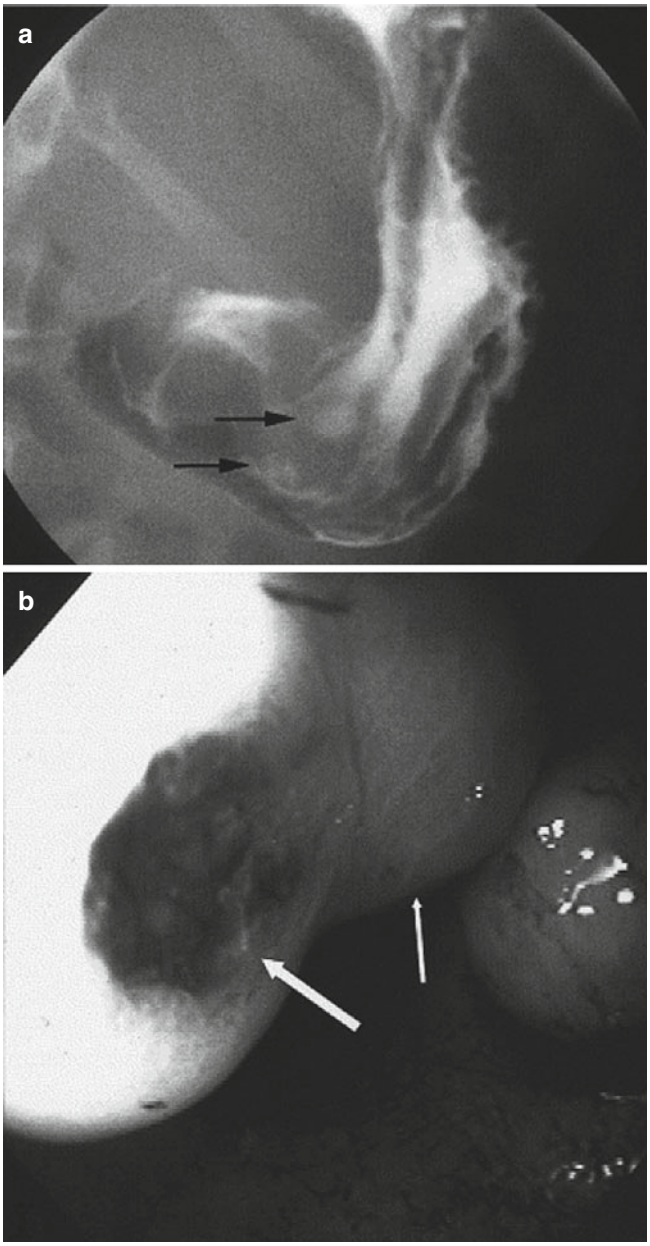

Fig. 28.6 G.I.S.T. Gastrointestinal stromal tumors arising from the stomach (From Durham et al. [110]). (**a**) Upper gastrointestinal series. Distal aspect of stomach shows 2 irregular intragastric filling defects (*arrrows*) in the regio of the antrum of the stomach. (**b**) Upper gastrointestinal endoscopy shows polypoid lesions in the antrum of the stomach with erosion of the surface from a previous episode (*arrows*)

early imaging and endoscopy. Long-term survival is uncommon [120, 121].

The role of chemotherapy and radiation in gastric cancer is still not well defined. Surgery alone may prolong survival. Studies in adults recommend the use of etoposide, doxorubicin (Adriamycin), and cisplatin as primary therapy or combined with surgery and radiation [121]. A 2-year-old boy with pernicious anemia caused by vitamin B12 and iron deficiencies developed atrophic gastritis and gastric carcinoma.

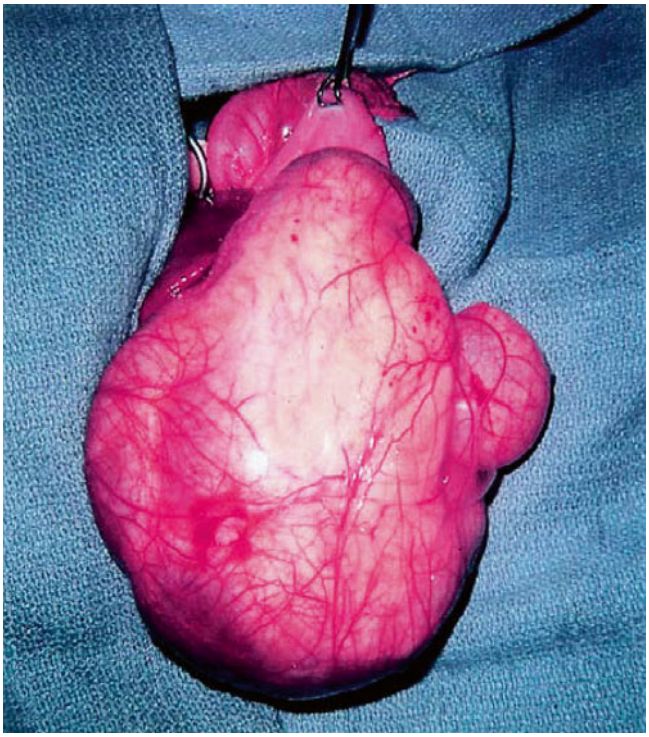

Fig. 28.7 Teratoma of the stomach

This has not been reported previously. Treatment included high subtotal gastrectomy with gastrojejunostomy and resection of associated lymph nodes and omentectomy and 6 months of chemotherapy. Follow-up after 1 year showed no evidence of recurrent disease [122].

Intestinal Polyps and Polyposis Syndromes

Juvenile Polyps

Juvenile polyps are hamartomatous in nature and, although benign, considered by some as a premalignant condition [97]. They occur in about 1 % of children and are usually detected because of complications. Rectal bleeding is most oft en the presenting symptom; however, prolapse of the polyp during defecation or straining may also occur. The majority are single (80 %) and are located in the rectum, but they have also been reported in colon, stomach, duodenum, and ileum [97]. Colonoscopy is recommended for children with unexplained rectal blood loss and normal proctoscopic examination [123, 124]. Solitary polyps should be excised endoscopically. The finding of a solitary rectal polyp is an indication for colonoscopy to exclude polyposis [125].

Generalized Juvenile Polyposis

This uncommon disease is characterized by the development of multiple (50 to more than 200) hamartomatous polyps throughout the intestinal tract, mostly in the large bowel; 85 % of cases occur in children. In half of the cases, there is

a positive family history of polyps or polyposis. The genes involved are SMAD4 on chromosome 18q21.1 or BMPR1A located on the long arm of chromosome 10. The infantile form of this condition is associated with protein-losing enteropathy, anemia, hypoproteinemia, and is often fatal [126]. Eighteen to thirty-five percent of patients with juvenile polyposis develop malignant disease by the age of 35. The treatment of choice is colectomy and an anal sphincter-saving procedure [127].

Peutz-Jeghers Syndrome

Peutz-Jeghers Syndrome (PJS) syndrome is autosomal dominantly inherited with an incidence estimated at 1:120,000. It is characterized by abnormal melanin deposits in the skin, lips, and mucous membranes and the formation of multiple hamartomatous polyps throughout the gastrointestinal tract (Fig. 28.8).

The small bowel is involved in 96 % of cases, the colon in 27 %, the stomach in 24 %, and rectum in 24 %. Labial pigmentation is a reliable clinical marker in 94 % of patients with Peutz-Jeghers syndrome. The causative genetic mutation involves STK11/LKB1 on chromosome 19 [128]. Polyps start to grow in the first decade of life, and 50–60 % of patients will develop symptoms by the age of 20 years.

In a large overview of the material removed by polypectomies in children, Peutz-Jeghers syndrome accounted for 1.73 % of the cases [129]. The complications of bowel obstruction due to intussusception of a polyp and anemia caused by bleeding from these polyps are often noted, sometimes before the typical abnormal pigmentation has developed.

In younger children (below 16 years of age) the gastroduodenal region is frequently the site of the polyps. Apparently these children are at risk for the development of malignant tumors. Two of the 70 patients mentioned earlier developed gastrointestinal adenocarcinoma, perhaps due to degeneration of a polyp, two an ovarian cancer and one a testicular tumor, possibly indicating a genetic disposition. A third case of adenocarcinoma of duodenum and jejunum occuring in an 8-year-old girl with Peutz-Jeghers syndrome was reported later [130]. There is an increased risk of ovarian cancer in relatives of a patient with Peutz-Jeghers syndrome. Whether hamatomatous polyps degenerate into carcinomas (the hamartoma-carcinoma sequence) has been debated. Some investigators consider the polyps as an epiphenomenon to a cancer prone condition [131].

Familial Adenomatous Polyposis (FAP)

This adenomatous autosomal dominant genetic disorder is due to a germline mutation of the APC-gene on chromosome 5q21-22. It is infamous because of its tendency to develop carcinoma of the large bowel, and may cause any

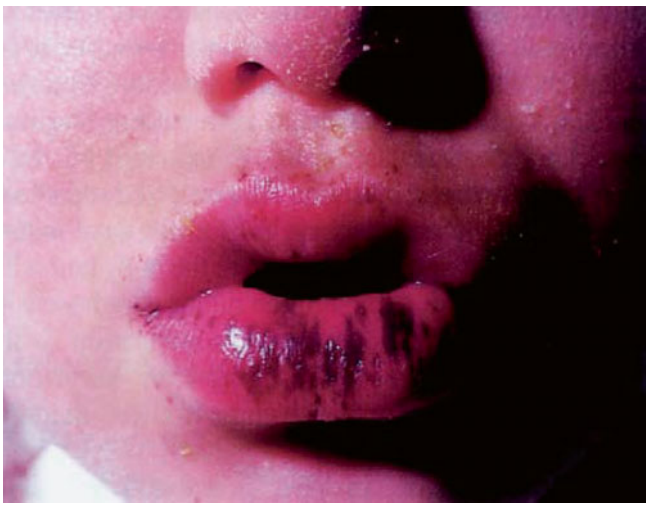

Fig. 28.8 Pigmentations of lips in Peutz Jeghers

significant bowel symptoms during childhood. In families with FAP a colonoscopy is indicated in children before they are 10 years of age [132]. Total colectomy, rectal mucosectomy, and ileoanal anastomosis eliminate the risk for malignant degeneration. Numerous reports have been published on the technical aspects of the ileoanal sphincter-saving operation, which is also applied in patients with ulcerative colitis. Most surgeons prefer the construction of an ileoanal anastomosis, using a "J"-pouch. Early and late complications after these procedures are common and the complication rate can be as high as 41 %. Late complications include inflammation ("pouchitis"), diarrhea, or stasis [133]. These complications occur more often in ulcerative colitis patients, whereas the FAP patients as a general rule fare much better [134].

Children in FAP families also have a tendency towards developing liver tumors (hepatoblastoma) more often than in general population [135]. Another interesting link with familial polyposis is Gardner's syndrome and the familial generalized juvenile polyposis, which by and large probably should be managed in a similar fashion as familal polyposis [136].

Although the risk of colon cancer in children under 15 years of age is very low (6 %), the youngest patient reported was 9 years. Therefore, the timing of colectomy is under debate as dysplasia can be asymptomatic. Vasudevan et al. described a group of 11 children who underwent surgery at a mean age of 13 years. Dysplasia was present in 9 patients (82 %). The authors advocate early operation to prevent malignant degeneration [137].

Colorectal Carcinoma

Uncommon in childhood (less than 1 % of all colonic cancers), this tumor has an extremely poor prognosis. This is due to late detection because of ignoring initial symptoms, a

high percentage of signet ring or anaplastic lesions present, and often regional lymph node metastases (75 % on presentation in the largest published series).

Survival varies from 0 to 25 %. Even in the event of complete resection it would be advisable to give adjuvant therapy with 5-fluorouracil and leucovorinbased cytotoxics in instances of high-grade lesions or regional lymph node involvement [138–140].

Urinary diversion into the sigmoid colon or use of bowel elsewhere in the urinary tract has also been identified as a risk for the development of adenocarcinoma. Although there usually is a time lag of more than 20 years, and therefore the carcinoma will develop beyond childhood, it is a fact to be kept in mind when constructing urinary conduits in children [141]. Experimental evidence suggests that familial polyposis, ulcerative colitis and ureterosigmoidostomies are conditions with an unstable colonic epithelium, which may become dysplastic, and perhaps deteriorate into malignant degeneration [142].

Brown et al. [139] described seven children aged 10–15 years with carcinoma of the colon and rectum. Distant metastases were present in five, and there were no survivors in this series. The youngest patient described was 9 months [97].

Carcinoid Tumors

These tumors appear in the gastrointestinal tract, biliary tree, ovaries, bronchi, lungs, and pancreas. The most common sites are the appendix, followed by small intestine and rectum. In one report a case is described of a carcinoid tumor occurring in a rectal duplication [143]. Appendiceal carcinoid is uncommon in infancy but may occur in late childhood and adolescence. Girls are affected three times as often as boys.

In most patients carcinoid is an incidental finding in the appendix removed for acute or recurrent abdominal pain. Usually the tumor is less than 2 cm in diameter and in 75 % of the cases it is located near the tip of the appendix. Simple appendectomy is curative in these patients. When the tumor is greater than 2 cm in diameter and occurs at the base, or if there is tumor growth beyond the appendix, a more extensive procedure like partial colectomy is indicated [97]. In the largest reported series of 40 cases, no recurrences, metastases, or tumor related deaths were observed [144].

Bile Ducts

Introduction

Two types of tumors occurring in this region deserve mentioning, namely the biliary tract rhabdomyosarcoma and carcinoma arising in the anatomically abnormal bile duct system (Fig. 28.9).

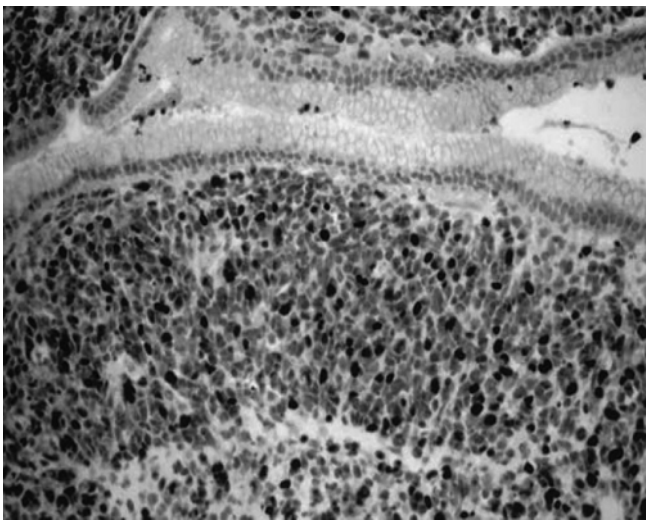

Fig. 28.9 Tumor of CBD. Embryonal rhabdomyosarcoma of the common bile duct mimicking choledochal cyst (From Tireli et al. [145])

Rhabdomyosarcoma

Fewer than 40 cases of rhabdomyosarcoma of the bile ducts have been reported in the literature. The presenting symptom is usually obstructive jaundice [145] (Fig. 28.8).

The diagnosis can be made using abdominal ultrasound, MRI or CT scan. The prognosis for this tumor has been rather poor; 40 % of the cases present with metastases, but local growth is a leading cause of death in most instances [146]. The first large series of ten patients was reported in 1985 [147]. At the time of publication there were four survivors following extensive resection and adjuvant radiation and chemotherapy. An interesting development is a recent report in which after an exploratory operation the patient was treated with chemotherapy which caused a dramatic reduction in tumor size. At a second-look operation complete regression of the tumor was observed. The authors claim that with this approach of aggressive surgery can be prevented [148]. Similar experience was reported by Spunt et al. [149], but this has not been confirmed by other authors [150].

The role of preoperative imaging is uncertain. ERCP was not found to be helpful in the two cases where it was performed [149]. It is not clear whether MRCP is more accurate than CT-scan [150]. Preoperative (PTC) or intraoperative cholangiography can be useful [150].

Carcinoma

The risk of adenocarcinoma developing in a choledochal cyst has been known for many years. A survey of 645 cases of choledochal cyst in Japan treated between 1972 and 1982 disclosed 54 cases (8.4 %) of biliary carcinoma. The incidence varied from 0.3 % in the pediatric population to 15.6 % in the adult cases, indicating that the risk of developing this cancer increases with age [151]. With time, approximately

20–25 % of cases will develop malignancy, which carries a poor prognosis since less than 10 % are resectable [152]. Patients with an anomalous arrangement of the pancreaticobiliary duct system have an increased cellular proliferative activity in the gallbladder mucosa starting in early childhood [153]. It is presumed that complete cyst excision eliminates the risk of malignant degeneration [152].

Pancreaticobiliary maljunction without dilatation of the common duct is very rare, but nevertheless may be associated with carcinoma in later life. Based on experience in a recent series of seven Japanese children with this anomaly, complete excision of common bile duct and gallbladder followed by hepaticojejunostomy is recommended [154].

Pancreas

Introduction

Malignant pancreatic tumors are rare in children. Vossen et al. quote from a Japanese autopsy statistic, that 0.2 % of infant deaths caused by malignant disease are due to pancreatic tumors [155]. A report from Memorial Sloan Kettering describing 17 patients below 21 years in the time period of 33 years between 1967 and 2000, illustrates the spectrum of malignant pancreatic tumors in children. Pancreatoblastoma (5 cases) and solid pseudopapillary or Frantz' tumor (7 cases) were the most frequent. Other tumors were: acinar cell carcinoma (1), nonfunctioning pancreatic endocrine neoplasm (1), malignant VIPoma (1), and PNET (2). The clinical presentation varied: abdominal pain (11), mass (4), anorexia (3). Only three patients were jaundiced [156]. The pancreas may also be the seat of malignant lymphoma, which may be difficult to diagnose [157].

In this section a more detailed description will be given of four types of pancreatic tumors in children:

(a) pancreatoblastoma, (b) solid pseudopapillary or Frantz' tumor, (c) pancreatic ductal Adenocarcinoma, (d) malignant endocrine tumors.

Pancreatoblastoma

Pancreatoblastoma (PB) is a malignant epithelial tumor showing mainly acinar differentiation, but occasionally also containing endocrine and ductal cells. These different cellular elements may derive from a pluripotent "blastomatous" cell. This may also explain the fact that a considerable number of PB express alfafoetoprotein (AFP), and that serum levels are increased in patients with PB. Dhebri et al. have reviewed the literature on 153 cases [158]. Most of the PB occur in early childhood, but 10 % occur in adults. Antenatal diagnosis and successful neonatal management have been reported [159, 160]. The latter patient, and several others in the literature, had the Beckwith-Wiedeman Syndrome (BWS), which is associated with loss of heterozygosity (LOH) on chromosome 11p [161]. The same genetic characteristic has been described in six out of seven patients with PB. Another genetic activation reported in PB is a mutation of the beta-catenin gene [158]. Others have reported multiple chromosomal abnormalities in PB-cells, including MYC-oncogene [162] (Fig. 28.10).

The tumor may arise in any part of the pancreas. The typical mode of presentation is with an abdominal mass, weight loss and pain; jaundice is present in about 10 %. Metastases are present at first diagnosis in 17–35 % of the patients. The diagnosis should be considered on the basis of imaging studies and can be confirmed by fine needle aspiration cytology [163]. The treatment consists of complete resection. If this is not possible, neoadjuvant chemotherapy should be given. Various cytotoxic regimes have been advocated: most contain vincristin and cyclophosphamide or ifosfamide, in combination with either actinomycin-D, cisplatinum, doxorubicin, or bleomycin. Postoperative radiotherapy has been advocated for irresectable or incompletely resected cases. See algorithm in Dhebri et al. [158].

The prognosis in children after complete resection is fairly good, with a reported 5-year survival rate between 50 and 80 % [164].

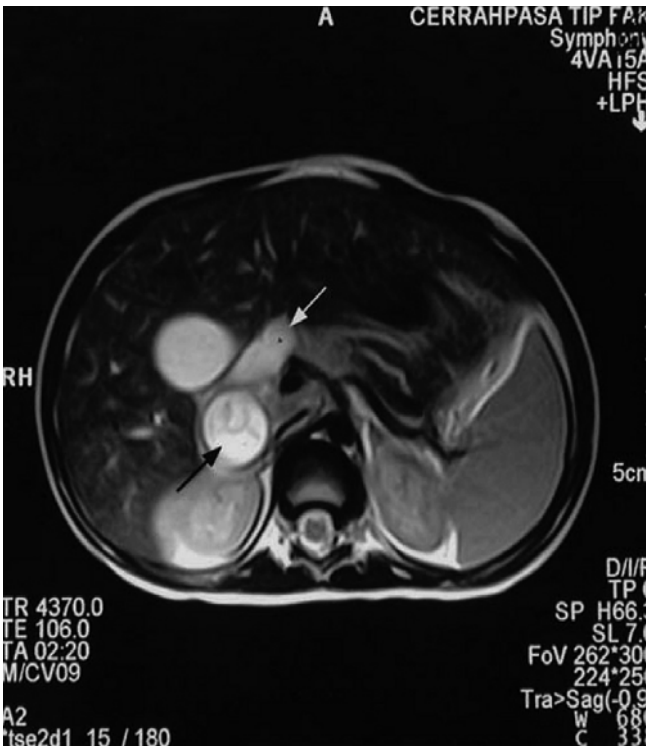

Fig. 28.10 MRI of rhabdomyosarcoma of the common bile duct: *black arrow* points to mass, *white arrow* to CBD (from Tireli [145])

Solid Pseudopapillary Tumor; Papillary Cystic Tumor of the Pancreas; Frantz's Tumor

Solid pseudopapillary tumor of the pancreas (SPTP) is known by several names, including the eponym of the author who first described this tumor in 1959 as a separate entity, V.K. Frantz. Since then, more than 700 cases have been reported in the English literature, their ages ranging between 2 and 85 years, with a mean of 22 years. One hundred sixty-five SPTPs have been reported in children below the age of 18 years. Over 90 % of the tumors occur in females [165, 166]. It has been suggested that SPTP occurs more often in Asians and Africans than in Caucasians [166].

The cell of origin of SPTP is uncertain. Kosmahl et al. [167] performed a comprehensive immunocyto-chemical analysis of 59 tumors and concluded that it is difficult to relate the tumor to epithelial cells, even if a multipotent stem cell origin is considered. On the other hand, SPTP is not a purely endocrine tumor either, both on cytochemical and clinical grounds. The authors postulate that there is a relationship with ovarian rete cells [167]. The tumor may occur in any part of the pancreas, but more often in the tail [167, 168].

The majority of SPTP are localized tumors, particularly in children there are only a few case reports of metastases [169]. Intraperitoneal spread has been observed after abdominal trauma [168]. SPTP is therefore considered as a low-grade malignant tumor.

Most patients present with gastro-intestinal symptoms and a palpable mass. The diagnosis is made by a combination of clinical signs and imaging. Endoscopic ultrasound-guided fine needle aspiration cytology has been advocated, but found conclusive in only a minority of cases [166, 170]. The treatment is complete excision with a margin, but without lymphnode dissection. Intraoperative frozen section is recommended. The prognosis is good in children after complete removal (Fig. 28.11).

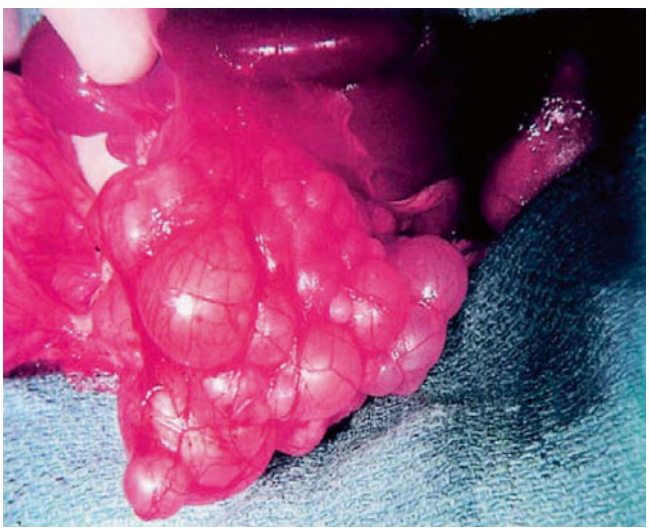

Fig. 28.11 Ectomesenchymoma (From Hajivassiliou et al. [187])

Pancreatic Ductal Adenocarcinoma

Pancreatic ductal adenocarcinoma (PDAC) is a tumor of the elderly that is exceedingly rare in children. Approximately 37 cases have been reported, although some doubt exists whether these were all adenocarcinomas. In a series of 520 pancreatic neoplasms, 404 were PDACs, two occurred in patients younger than 18 years [171]. The presence of an abdominal mass in the epigastrium, abdominal distension, or obstructive jaundice are the common presenting symptoms.

The diagnosis of a panceatic mass can be made with ultrasonography, MRI, or CT scan. Aggressive surgical procedures are recommended when feasible. In the majority of cases pancreatoduodenectomy or distal pancreatectomy are necessary. Even in instances of anaplastic tumors, survival following extirpative resection has been reported. One author claims that all patients in whom a resection was undertaken were long-term survivors, but others found no better outcome in young patients compared to the elderly [171].

Malignant Endocrine Pancreatic Tumors

Whereas in adults, the majority of endocrine pancreatic tumors are insulinomas, which are rarely malignant, in children there is an almost equal distribution of insulinomas and gastrinomas. Unfortunately, most of the insulinomas diagnosed as malignant have already metastasized at diagnosis [155]. Endocrine pancreatic tumors, which are associated with the MEN 1 syndrome, can also be malignant [172]. Malignant endocrine pancreatic tumors have furthermore been reported in children with Tuberous Sclerosis Complex (TSC), an autosomal dominant condition, presenting with epilepsy and mental retardation and known to be associated with benign renal cysts and angiomyolipoma (see also below). TSC1 and TSC2 genes are located on chromosme 9 and 16, respectively. Malignant nonfunctioning islet cell tumors expressing LOH of chromosome 16 (TSC2) were found in two boys [173, 174].

Rare Tumors of the Genitourinary System

Renal Cell Carcinoma

A retrospective analysis of 22 cases of renal cell carcinoma was reported by Aronson et al. [175]. Age, tumor size, location, and histology were found not to be predictors of outcome; tumor stage and complete surgical resection were the only significant prognostic determinants. The overall 5-year survival was 30 %. The survival rate for tumors that were completely resected was 60 % versus 10 % for those lesions incompletely resected.

Attempts to treat these tumors by nephron-sparing surgery have also been reported in children. Cook et al. reported on 15 patients, with a mean age of 7.9 years. Presentation

with hematuria, pain, and polycythemia in 75 %, whereas 25 % were asymptomatic. Treatment consisted of nephrectomy in 10 patients, and partial nephrectomy in five. Excision of metastases was done in 2 patients. Outcome: 13 are in complete remission, and of the three stage IV patients, 1 died and 1 survived with disease. All of the patients with partial nephrectomy are in complete remission. Two editorial comments warn that the long-term outcome of partial nephrectomy in children is unknown, and that the risk of recurrence has to be established in prospective studies.

Renal Cell Carcinoma in Association with Tuberous Sclerosis in Children

Tuberous sclerosis (TS) is an autosomal disorder with incomplete penetrance and variable phenotype (see also section under "Pancreas"). Angiomyolipoma and multiple renal cysts are seen in patients with TS. Cases of renal cell carcinoma in patients with TS are usually multiple and may be bilateral [177].

Transitional Cell Carcinoma of the Bladder

Five boys were reported to have transitional cell carcinoma of the bladder [178] Imaging and urine cytology correlated with cystoscopic and biopsy findings. Ultrasound examination was the most sensitive. A special risk category for bladder tumors are patients with bladder augmentation. Transitional cell carcinoma has been reported in three adults who underwent this procedure for neuropathic bladder [179]. In the discussion of this paper, A.B. Retik states the risk starts to rise after a 10-year lag period, in analogy with the experience in the ureterosigmoidostomy patients.

Cystic Partially Differentiated Nephroblastoma

Cystic partially differentiated nephroblastoma (CPDN) is a rare neoplasm. The tumor consists of well-demarcated cystic lesions of the kidney. Blastemal and other embryonic cells are present in the septa of the cysts; MRI can detect the lesions which are highly suggestive of either CPDN or cystic nephroma [180].

Experience in the NWTSG consists of 21 patients, 13 of whom received cytotoxic drugs whereas eight (all stage I) did not. The outcome was 100 % survival without recurrences. It is concluded that for stage I patients surgical treatment alone is probably sufficient [181].

B Cell Non-Hodgkin's Lymphoma as a Primary Renal Tumor

Primary renal lymphoma is an extremely rare tumor; only about 35 cases are reported in literature. A 6 year-old boy had a unilateral renal tumor which was thought to be a Wilms' tumor. On review of the histology this proved to be a B cell lymphoma [182].

Prostatic Non-Hodgkin's Lymphoma

A T cell non-Hodgkin's lymphoma of the prostate occurred in a child who presented with acute urinary retention and who responded well to treatment with chemotherapy [183].

Testicular Tumors Before Puberty

Twenty-two neonates less than 1 month of age were found to have testis tumors; seven were diagnosed at birth. Cell types included yolk sac tumors in six, and six had gonadal stromal tumors. Six had juvenile granulosa cell tumors, two gonadoblastoma, one teratoma, and one harmartoma. Serum alpha-fetoprotein was normal in ten tested patients. There were no metastases. Seventeen boys were followed up and there was no evidence of disease. Neonatal tumors are rare but should be considered in the differential diagnosis of scrotal masses in the neonate [184].

Testicular tumors are rare in prepubertal children, and the large majority are germ cell tumors. Serum tumor markers should be assessed before operation. If the markers are not elevated and salvageable testis tissue is present on ultrasound, an excisional biopsy with frozen section is advocated. If the tumor is a benign teratoma, the testis can be preserved [185]. Both reports originate from the Prepubertal Testis Tumor Registry (PTTR) created by the Section of Urology of the American Academy of Pediatrics in 1980.

A recent review on testicular and paratesticular tumors in prepubertal boys describes the full spectrum of benign and malignant tumors with recommendations for the management. (Ahmed et al., *The Lancet Oncol* 2010;11:476–83). A more specific overview on sex-cord stromal tumors of testis and ovary in children presents important principles on the surgical management of these tumors (Schultz KAP et al., *J Pediatr Hematol Oncol* 2012;34:S55–63)

Ectomesenchymoma

Ectomesenchymoma is a malignant nonepithelial tumor containing two or more cell-types from ectodermal and mesenchymal origin (Fig. 28.12). Synonyms are: malignant Triton tumor (MTT) and primary osteochondrorhabdomyosarcoma. It is considered a variant of the Malignant Peripheral Nerve Sheath Tumor (MPNST) that contains rhabdomyoblasts [186]. This tumor is associated with Neurofibromatosis type 1 (NF1) and usually develops in these patients before the age of 35 years. It is rare in children, with only 24 cases reported, more than half of them in NF1 patients [186]. Predilection sites are: head and neck, trunk, and extremities.

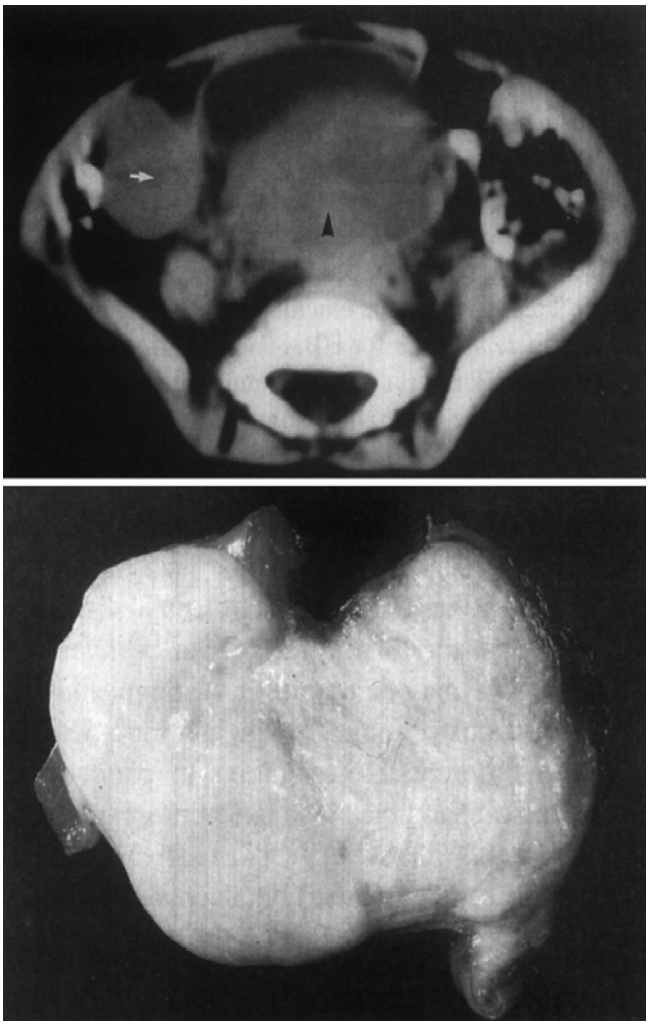

Fig. 28.12 Ectomesenchymoma. Upper picture shows CT-scan with different components (*black and white arrows*), lower picture show cut surface with different differentiations (from Hajivailiou, Figs. 1 and 3)

Hajivassiliou et al. reported a case in a child (gangliorhabdomyosarcoma) with cutaneous nevus syndrome. Review of the literature revealed 35 similar cases [187].

The treatment of MTT consists of wide local excision, the role of chemotherapy is uncertain. The prognosis is grim, with a 5-year survival of 26 % [186].

Malignant ectomesenchymoma of the bone is even more rare. Two children were reported: one 10-year old girl with a tumor of the fibula, and a 15-year-old girl with a tumor of the proximal humerus. A combination therapy of intensive cytotoxics (osteosarcoma protocol) and wide local excision resulted in complete remission in both cases [188–190].

Malignant Melanoma in Children

Malignant melanoma is rare in children, representing 1–3 % of all pediatric malignancies. Two percent of malignant melanomas occur in patients younger than 20 years. Most of pediatric melanomas are seen in adolescents with only 0.3 % in prepubertal children. The incidence is two per million children (below age 15 years), but is rising [191–193].

Certain (skin) conditions predispose to malignant melanoma. Risk factors in addition to exposure to sunlight [193] are:

1. Giant congenital melanocytic nevi (CMN), 5–15 % risk
2. Familial atypical mole/melanoma (FAMM), 100 % risk
3. Treatment with chemotherapy for malignant disease
4. Retinoblastoma
5. Xeroderma pigmentosum, (2000 × increased risk)

Malignant melanoma does occur in prepubertal children. Mones and Ackerman [194] describe a group of 11 children between 1 and 10 years of age, (6 younger than 5 years) with melanoma arising de novo. The diagnosis was missed in all cases, both by the clinician and by the pathologist, and all metastasized. One child died. The melanomas were growing fast, and very thick at the time of diagnosis. Confusion with benign Spitz nevus may arise, and the authors point out that the histopathological criteria for melanoma in young children are not different from those in adults.

Approximately half of melanomas in children arise in association with a pre-existing lesion: about 30 % within giant CMN and 20 % in association with other lesions, like acquired melanocytic nevi or small- or medium-sized CMN [192, 195, 196]. More than half of all melanomas that arise within giant CMNs do so before puberty, whereas melanomas that develop in smaller CMNs often occur after puberty [192]. Prophylactic excision of all giant CMNs, defined as covering 1 % body surface in head and neck and 2 % elsewhere on the body, is therefore recommended [197]. If a nevus changes in size or aspect, starts bleeding or itching, suspicion should arise. In children where melanoma developed in association with a pre-existing nevus, only 7 % of the patients had no signs or symptoms. As the clinical diagnosis is erratic and benign Spitz nevus may be confused with melanoma, the next step is to perform an excisional biopsy of the lesion. If the lesion is smaller than 15 mm, a margin of 1–2 mm is sufficient. It is important to excise the full thickness for adequate staging. Staging depends on the level of penetration (Clarke) or thickness of the lesion (Breslow), and the presence or absence of regional lymphnode and distant metastases. Children (<20 years) were found to have more frequent lymph node metastases than young adults (20–24 years of age), even in non-ulcerated melanoma with <2 mm thickness (Mu et al. *Cancer* 2012;118:2700–7).

The TNM classification of the American Joint Committee on Cancer is shown in Table 28.3 [3]. For adequate staging of lymphnodes, sentinel node biopsy has been advocated [198].

Treatment guidelines are based on the experience in adults. See American Association of Dermatology online guidelines; National Comprehensive Cancer Network Melanoma Panel. Treatment consists of radical excision, with adequate margins. For lesions less than 1 mm

Table 28.3 Staging of melanomas

Primary tumor (T)			
pTX	Primary tumor cannot be assessed		
pTO	No evidence of primary tumor		
pTis	Melanoma in situ		
pTl	Tumor 0.75 mm or less in thickness, or Clark		
	Level II		
pT2	Tumor greater than 0.75 mm but no more than		
	1.5 mm in thickness, or Clark Level III		
pT3	Tumor greater than 1.5 mm but no more than 4 mm in thickness, or Clark Level IV		
pT4	Tumor greater than 4 mm in thickness, or Clark		
	Level V, or satellites present within 2 cm of primary tumor.		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
NO	No evidence of regional lymph node metastasis		
Nl	Metastasis 3 cm or less in greatest dimension in any regional lymph node or nodes		
N2	Metastasis greater than 3 cm in greatest dimension in any regional lymph node or nodes and/or in transit metastasis.		
Distant metastasis (M)			
MX	Presence of distant metastasis cannot be assessed		
MO	No evidence of distant metastasis		
M 1	Distant metastasis present		
Stage grouping			
Stage 1	pTI	NO	MO
	PT2	NO	MO
Stage 2	pT3	NO	MO
Stage 3	pT4	NO	MO
	Any pT	Nl, N2	MO
Stage 4	Any pT	Any N	MO

From Corpron and Andrassy [3]
From Beahrs et al. [199], with permission. I

thickness, 1-cm margin is considered adequate; if 1–4 mm thickness: 2-cm margins, and 3-cm margin for lesions with more than 4 mm depth [3]. Enlarged lymphnodes should be removed by formal regional dissection. Elective lymphnode dissection is of no advantage in lesions of <1 mm thickness nor in lesions of >4 mm depth. For those between 1 and 4 mm, sentinel node biopsy with routine histopathology and immunohistochemistry is advocated. If the sentinel node is positive, a complete regional node dissection is recommended [192].

Although there is no evidence that chemotherapy is useful in adults, there are some encouraging experiences with a combination of vincristin, cyclophosphamide, and dactinomycin in children [192]. Immunotherapy with Interferon alpha 2b has been found effective. The prognosis is determined by the stage, and there is no evidence that children have a different outlook than adults [3, 192, 195, 196].

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Reconstructive Surgery

29

Philip J. Hammond, Stuart Watson, and Stuart O'Toole

Introduction

Appropriate excision of malignant tumours commonly leaves defects that cannot be repaired by direct closure of the tissues. This may apply to the skin, to deeper soft tissues and to bone. Modern surgical treatment is aimed at reconstructing such defects with a variety of autologous tissues or synthetic materials.

Key advantages of reconstruction of defects include: the potential for early post operative radiotherapy or chemotherapy after rapid healing has been achieved by reconstruction of a defect with vascularised tissues; restoration of function; and optimum psychosocial rehabilitation.

Most often, reconstruction of a large tumour excision defect that cannot be directly repaired requires vascularised tissue (a "flap") because the bed of the defect is non-vascularised, and/or a large volume defect is present.

Many other reconstructive options are available for a variety of different indications, including skin grafts, tissue expansion, integrated prosthetics and biosynthetic or wholly synthetic tissue substitutes.

Where possible, a dedicated multidisciplinary team should be available to support the patient and family through the process of excision and reconstruction and to guide decision making in treatment of the patient and disease. It is vital that optimum treatment of the disease is not compromised by reconstructive considerations. With good teamwork, availability of skilled reconstructive surgery can actually enhance disease treatment by allowing excision of large tumours close to vital structures with immediate coverage of the defect: a successful reconstruction can then facilitate optimum post operative radiotherapy in a tumour with a close surgical margin.

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Principles of Patient Care

Where reconstructive flap surgery is planned, it is crucial to explain the plan carefully to the family and to the patient where appropriate. The different treatment options should be discussed. Commonly a variety of different flaps may be available to repair any given defect, and factors of patient/family preference may influence these. Use of pictures and diagrams are useful for children (and adults) in explaining what is to be done. Considerations of sports, hobbies and future career plans are often important in choosing donor sites for tissue used in reconstruction.

Generally, the reconstructive surgeon has the opportunity to help with overall psychological management of the patient and family by providing a positive counterbalance to the stress of coping with malignant disease: discussion about future goals, current sources of enjoyment and methods of helping to maintain or restore these help to direct the family's thoughts towards a positive future and away from fears of a potentially adverse prognosis.

With regard to the surgery itself, it is vital both for the patient/family experience and for the success of the operation to adopt a holistic approach to the surgery: reconstructive flaps are much more prone to failure in patients who are in pain, afraid, dehydrated, cold, in uncomfortable physical positions and uncooperative. These conditions reduce blood flow and increase chances of tissue ischaemia. Accordingly, the anaesthetist, theatre nursing team and postoperative care team are of crucial importance in helping the surgeon to maintain optimum conditions for comfort for the patient and family, and for success of the operation [1].

Where possible, regional anaesthesia should be used for post-operative pain control to allow optimum comfort and

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minimum chance of vascular spasm; nurse controlled or patient controlled analgesia should be provided and titrated; the patient should be kept comfortably warm to avoid vasoconstriction and compensatory hypermetabolism; intravenous fluids should be given to optimise peripheral circulation; care should be taken to prevent post-operative vomiting; reassurance and distraction should be provided to avoid fear; cannulae should be sited for post operative blood sampling to avoid episodes of stressful venepuncture; where possible, dressings should be left undisturbed, and carefully designed splints used to prevent painful movements and ensure optimum positioning; for complex head and neck reconstructions, postoperative ventilation for a few days may be indicated. The overall aim should be to have a calm, comfortable, peaceful patient. Under such circumstances, the success rate of reconstructive flaps in children is very high [2, 3].

In spite of the high success rate of reconstructive surgery in children, it remains extremely important to have a secondary plan in the event of a failed reconstruction. Where at all possible, this eventuality, and the plan for dealing with it should be explained to the family pre-operatively so that trust and accordingly, optimum care of the child, is maintained in the event of a failure. Similarly, complications such as revision of anastomoses, haematoma, seroma and hospital acquired infections should be emphasised to consenting families before complex flap surgery.

Reconstructive Flaps

The simplest flaps are local skin flaps that can be designed using well-established geometric techniques. Examples of these techniques are transposition, V-Y advancement and rotation flaps [4]. In most instances, these techniques are suitable for repair of relatively small defects, and are not widely applicable to tumour surgery in children. However, perforator-based fasciocutaneous flaps may be used for repair of small or moderate sized defects on the limbs (Fig. 29.1). These flaps have the advantage of surgical simplicity combined with good reliability and can be used proximally or distally based [5, 6].

Dramatic developments in knowledge of vascular anatomy in the last 40 years have enabled surgeons to develop a profusion of large named-vessel flaps that can be used to repair substantial defects in any anatomical site. Awareness of the pattern of blood supply in any tissue is the key to safely designing a vascularised tissue transfer. Certain tissues have large, safe vascular pedicles, and as a result can be used reliably for transfer.

Useful classifications of the blood supply of muscles, fasciocutaneous flaps and skin help surgeons to plan safe transfer of any given portion of tissue [7–9].

Ideally, the tissue used for a flap should be able to be harvested without undue aesthetic or functional damage to the patient. This may be dependent on individual patient preference so it is always important to discuss the "cost" of any donor site with the family.

Hand held Doppler or Duplex scanning are extremely useful tools for planning of flap design. In more complex cases, MR or CT angiography may be indicated.

An important factor influencing the choice of donor site is patient positioning during surgery: if a flap can be raised simultaneous to excision of the tumour, this substantially reduces operating time, and potential physiological stress to the patient: accordingly how a patient needs to be positioned to raise a flap may have a material effect on the choice of

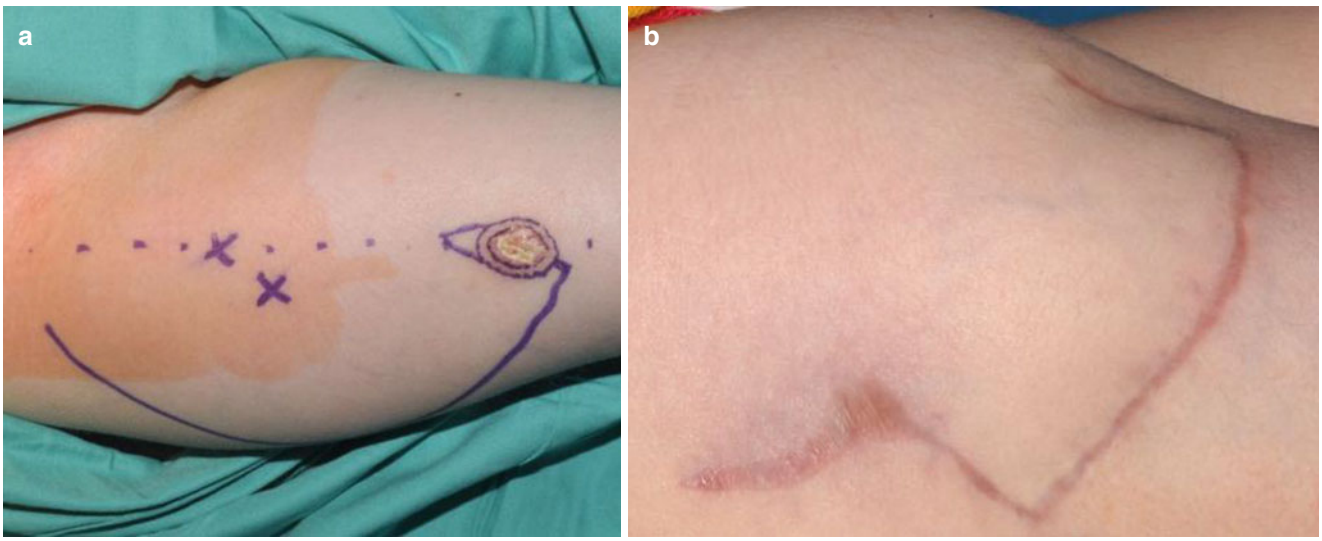


Fig. 29.1 (**a**) Design of rotation flap based on perforator for repair of defect after excision of xanthogranulomaon thigh persistent post-radiotherapy. (**b**) Defect repaired

reconstruction (for example, it is often preferable during excision and reconstruction of defects in the head and neck for the patient to be in the supine position).

There are a number of "workhorse flaps" which are very reliable and have acceptable donor sites. As a result, these flaps are widely used as pedicled or free flaps for tumour reconstruction.

Workhorse Flaps

Latissimus Dorsi

Latissimus dorsi is a large fan shaped muscle that has a consistent large dominant vascular pedicle, the thoracodorsal artery (with its vena comitans). The pedicle is a terminal branch of the subscapular artery and it enters the muscle inferior to the insertion of latissimus, underneath the posterior axillary fold. The muscle arises from the spinous processes of the lower six thoracic vertebrae, the posterior iliac crest and the lowest four ribs and in this area the muscle receives a secondary blood supply from multiple large perforating vessels on its deep surface. Although a very large muscle, it may be harvested with no apparent functional deficit. However, caution should be exercised in use of the flap in patients with interests in sports requiring optimum shoulder function (such as rock climbing or the dominant limb for tennis players).

The flap may be taken as a muscle flap only, or as a musculocutaneous flap, with the potential for a large skin flap. For more complex defects, it is possible to harvest additional tissues with latissimus, such as a portion of serratus anterior muscle or bone from the scapula.

Used as an island pedicled flap based on the thoracodorsal vessels, the flap may cover defects of the chest wall, supraclavicular fossa, neck, lower face, shoulder, arm and elbow [10] (Fig. 29.2). Its reliability when based on this pedicle is near 100 %, with the main potential problem being compression or kinking of the pedicle, which usually manifests as venous congestion.

Latissimus dorsi is possibly the most widely used free flap for large soft tissue defects [11]. For large volume defects, a musculocutaneous flap provides extra volume, and where a thinner flap is required, a thinned muscle only flap covered by a skin graft, may be used, or a portion of the muscle may be harvested; the flap can often be tailored to the defect.

For functional muscle reconstruction in the upper limb, or for facial reanimation, latissimus may be harvested with the thoracodorsal nerve.

The lumbar and paraspinous perforating vessels may be used to supply a turnover muscle flap for coverage of defects of the lower spine. It is necessary to include more than one perforator to safely supply this variant of the flap.

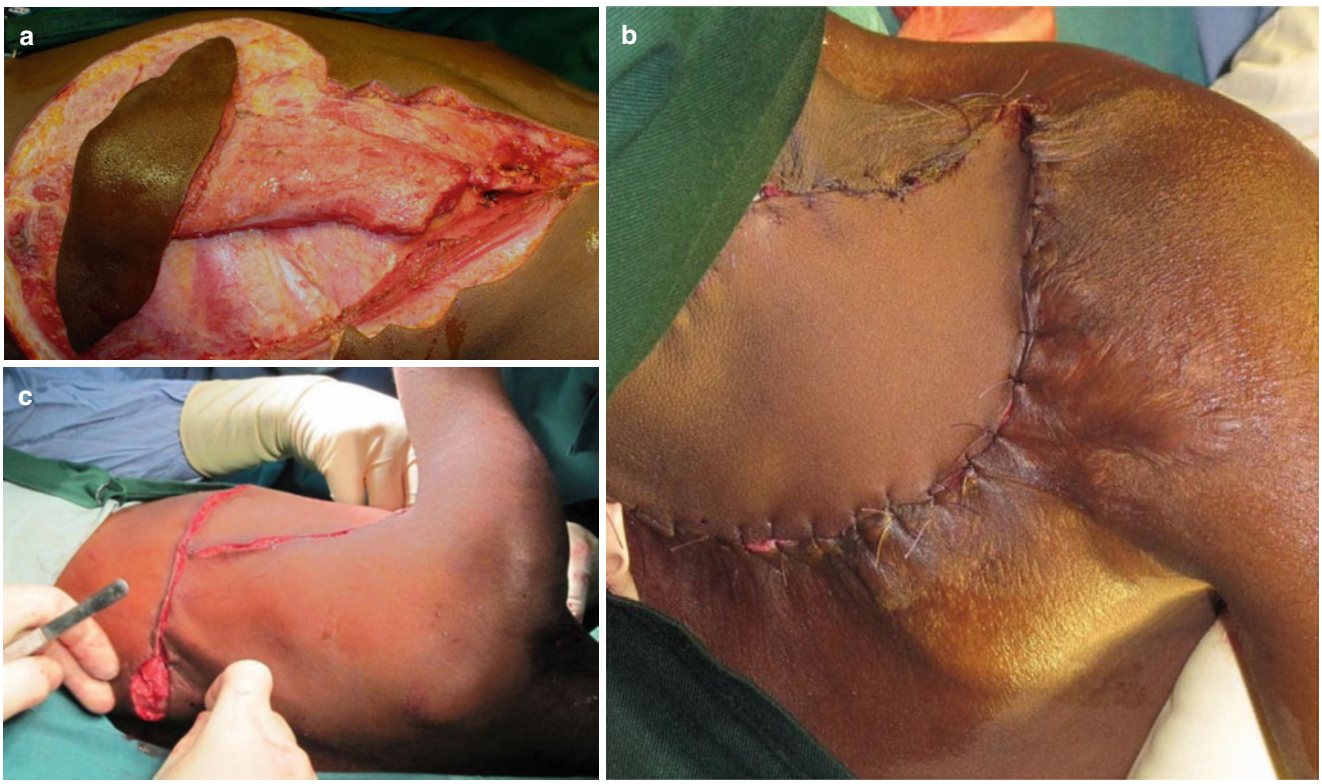


Fig. 29.2 (**a**) An island latissimus dorsi musculocutaneous flap raised on the anterior half of the muscle. (**b**) The flap passed through the axilla to repair a large defect of the anterolateral neck. (**c**) With patient in the lateral position the donor site is closed at the same time as the flap is inset

A further development of the use of the thoracodorsal pedicle is the thoracodorsal artery perforator flap (TAP flap) where a large skin flap may be raised on one of the perforating vessels dissected through, and separated from the muscle. This provides a thin skin flap with a long pedicle, but this procedure is technically much more demanding than elevation of latissimus itself.

Rectus Abdominis

Rectus abdominis is a long, moderately wide, flat muscle that is supplied by two main vascular pedicles that can supply the whole muscle and the overlying skin: the superior epigastric vessels and the deep inferior epigastric vessels. The muscle arises from the fifth to seventh ribs and inserts to the pubic crest.

Harvest of the muscle usually leaves only a modest functional deficit, but may cause an incisional hernia, especially below the arcuate line.

The flap may be used as a pedicled flap based on the superior epigastric artery for coverage of the anterior chest wall and sternum. The safest design of the skin island of the flap when superiorly based is a vertically orientated ellipse over the muscle (vertical rectus abdominis musculocutaneous-VRAM-flap) [12]. It is reasonable to design a more transverse skin island if required, but there is a chance of the contralateral portion of the skin flap having vascular problems, so this should be avoided if possible.

The larger deep inferior epigastric artery supplies a variety of possible designs of musculocutaneous flap skin island, including a vertical, transverse or oblique skin paddle. This allows design of island pedicled flaps to cover large defects of the lower abdomen, hip, lateral buttock, femoral triangle and anterior thigh (Fig. 29.3). It can also cover large perineal defects if passed transperitoneally [13].

The deep inferior epigastric vessels supply a useful variety of potential free flaps including a muscle flap, musculocutaneous flap and perforator-only skin flap (deep inferior epigastric perforator-DIEP flap). These can be designed so as to fill large-volume defects or defects requiring thin skin cover, depending on requirements.

Radial Forearm Flap

The radial forearm flap is based on perforating branches of the radial artery and its venae comitantes that lie in the septum between flexor carpi radialis and brachioradialis on the forearm. Elevation of the flap requires inclusion of the radial artery and venae comitantes. Venous drainage is supplemented by inclusion of volar forearm subcutaneous vein(s) that drain into the cephalic vein proximally. These veins usually drain the skin flap more effectively than the deep veins.

The flap leaves minimal functional deficit, but often leaves marked scarring especially if a large skin flap is harvested, when skin grafting of the defect is required.

The radial forearm flap may be raised as a fasciocutaneous flap; as a skin flap with minimal fascial harvest; or as a fascial flap. Additionally, vascularised bone from the radius may be harvested, and palmaris longus tendon may be used if strong soft tissue is required. Sensation may be provided to a skin flap by use of the lateral cutaneous nerve of forearm, which can be joined with a suitable cutaneous recipient nerve.

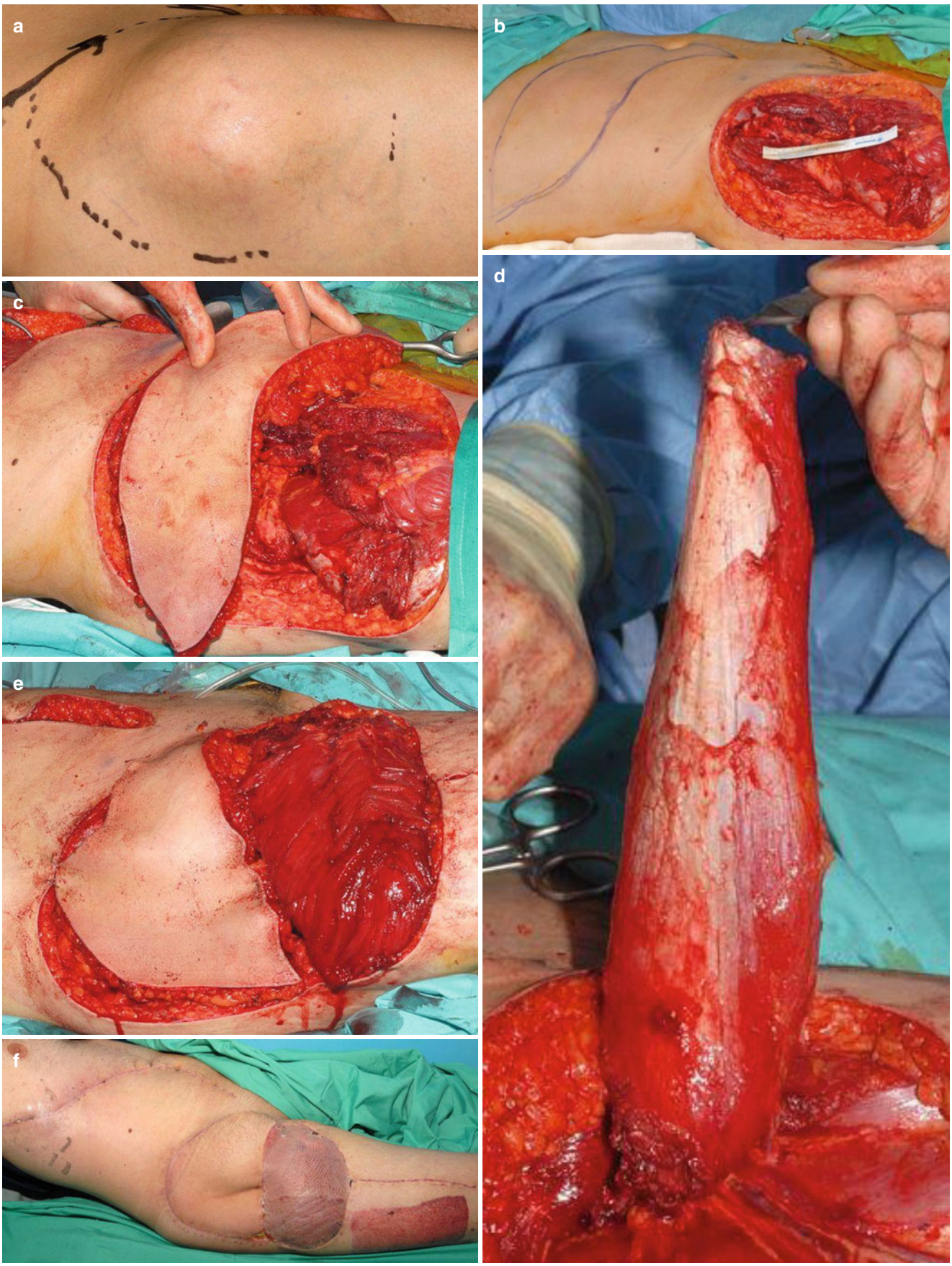
The main indication of the flap in children's tumour surgery is as a free flap used for repair of defects of the head and neck or the peripheries of the limbs where a very reliable free flap, possibly innervated, is required for a challenging defect [14] (Fig. 29.4).

Less often, it is used as a pedicled flap for upper limb reconstruction and may be used proximally or distally based.

Anterolateral Thigh Flap

The anterolateral thigh flap is based on a perforating branch of the descending branch of the lateral circumflex femoral artery [15]. The artery is of large caliber, long and with two large venae comitantes. The flap is based over the septum between the rectus femoris and vastus lateralis muscles. In approximately 35 % of cases, the perforating branch emerges in the septum between the muscles, and in approximately 65 % it emerges through vastus lateralis close to the septum. The surface marking of the perforator is commonly at a point 2 cm below and lateral to the junction of the upper and middle thirds of a line drawn between the anterior superior iliac

Fig. 29.3 (**a**) Large intramuscular sarcoma proximal thigh in an adolescent male. (**b**) 25 cm diameter defect after excision of the sarcoma. An oblique extended rectus abdominis flap is shown planned on the right upper abdomen and lower chest, based on the deep inferior epigastric vessels. (**c**) The rectus abdominis flap is tunneled through the inguinal area to the defect. A further flap is required for the distal part of the defect. (**d**) The origin of rectus femoris muscle has excised with the tumour. The remainder of rectus femoris muscle is islanded on its vascular pedicle. (**e**) The rectus femoris is inset into the distal half of the defect. (**f**) Longer term result showing skin grafting over the rectus femoris and direct closure of the rectus abdominis donor defect (skin graft donor site on thigh *bottom right*)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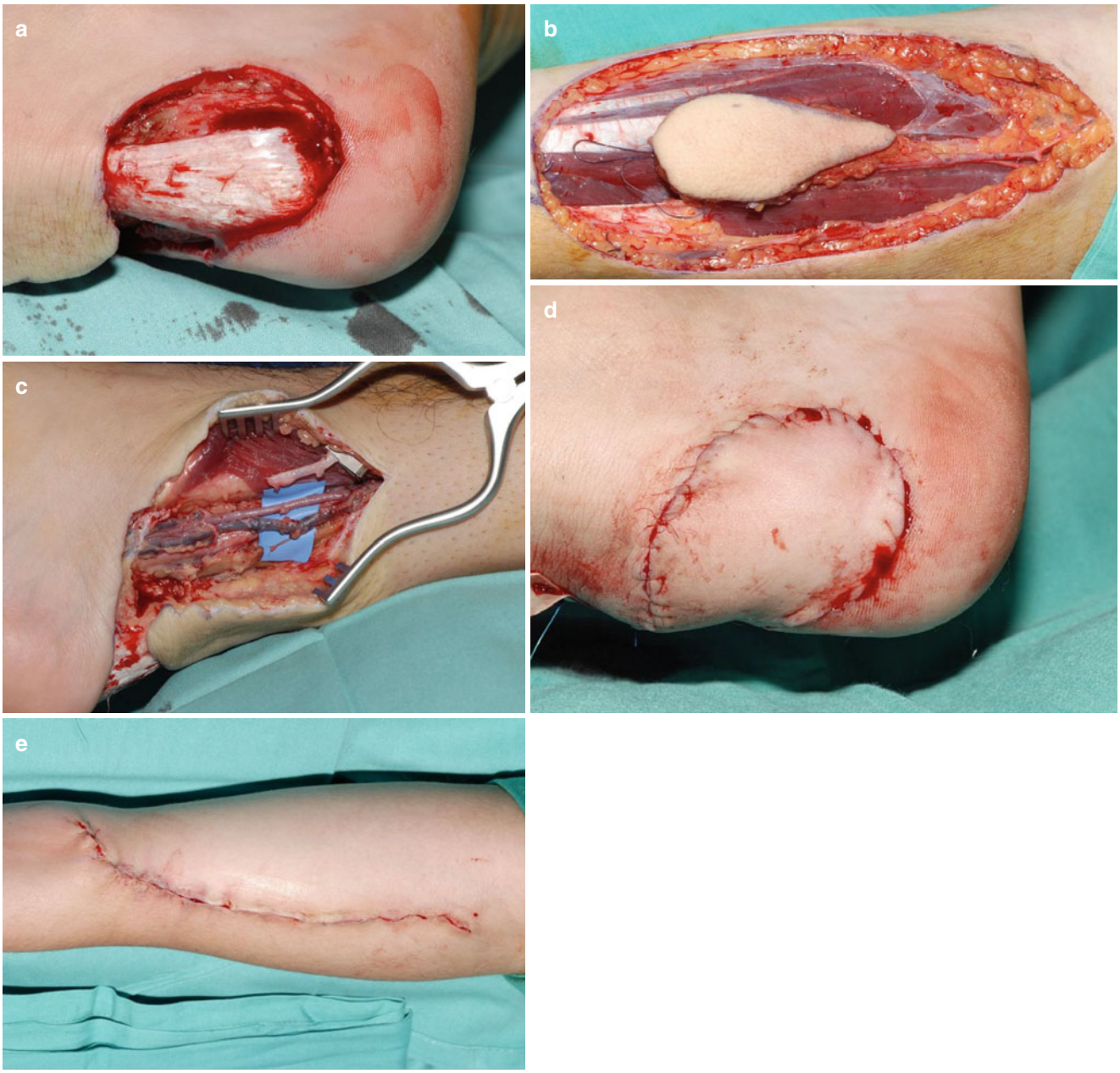

Fig. 29.4 (**a**) Defect after excision SCC heel in boy with immunodeficiency. (**b**) Free radial forearm flap at donor site including lateral cutaneous nerve of forearm to provide optimum sensation. (**c**) Posterior tibial vessels and long saphenous vein exposed for recipient vessels for the free flap. Small branch of tibial nerve used for neurorraphy. (**d**) Flap inset. (**e**) Forearm donor site closed directly

spine and the upper lateral border of the patella. Hand-held Doppler or Duplex ultrasound should be used for confirming the site of the perforator, as it can be variable.

The flap can provide a large island of skin with relatively inconspicuous scarring, and leaves no significant functional deficit, although there is always some numbness in the distribution of the lateral cutaneous nerve of thigh. The skin may be taken with or without fascia, and thinned considerably of subcutaneous fat, depending on thickness of tissue required [16].

The flap provides an excellent donor site for large amounts of vascularised fascia. When harvesting a fascial extension, care should be taken to preserve the small blood vessels on the superficial surface of the fascia (Fig. 29.5). Where additional bulk is required, a portion of vastus lateralis may be harvested [17], but harvest of most of the nerve to vastus lateralis is likely to leave a functional deficit, so this should be avoided unless there is no good alternative.

The anterolateral thigh flap is mainly used as a free flap for head and neck or limb reconstruction. It may be used for

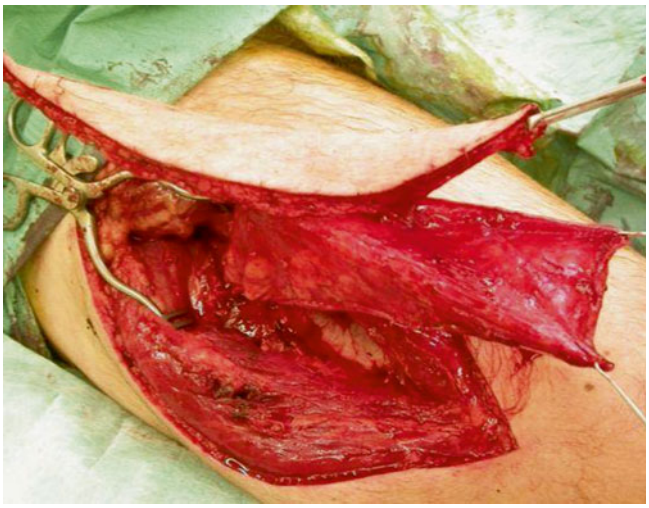

Fig. 29.5 An anterolateral thigh flap at its donor site showing skin flap and large separate fascial flap raised on the same pedicle

reconstruction of the femoral triangle or lower abdomen as an island pedicled flap. Upper abdominal defects requiring fascia are best repaired using the flap as a free flap.

Inclusion and neurorraphy of the lateral cutaneous nerve of the thigh can provide improved sensation to the flap.

Fibula Flap

The fibula flap is probably the most reliable flap for reconstruction of bone defects. It provides the greatest length of bone available for vascularised transfer and has a large consistent vascular pedicle, the peroneal artery and venae comitantes. If a skin island is required, this is planned over the middle third of the fibula, and the perforating vessel(s) identified with Doppler ultrasound. These vessels generally pass posterior to the fibula to the peroneal vessels. Important technical points include the possible requirement for a diastasis screw in the fibula distally if a long length is harvested close to the ankle, and the need for caution near the peroneal nerve.

The fibula can be used as a free flap for a variety of sites, especially for mandibular reconstruction or as a pedicled flap for ipsilateral tibial defects [18–20].

The shaft of the fibula does not grow well. If normal growth is required in a fibula transfer (if the epiphysis of the recipient bone has been excised), the head of the fibula with its epiphyseal plate should be included in the transfer. In this event, it is necessary to raise the anterior tibial artery and vein and appropriate branches to vascularise the fibular head. Elevation of these is technically more challenging than the peroneal vessels and in particular, there is a higher incidence of post operative peroneal nerve problems [21]. However satisfactory growth of the transferred bone may be obtained.

Gracilis Flap

The gracilis flap is probably the most widely used flap for free functional muscle transfer. The muscle is based on its main vascular pedicle, a branch of the medial circumflex femoral artery which runs transversely deep to the adductor longus muscle. The surface marking of the gracilis is just posterior to a line between the adductor tubercle and the medial femoral condyle, and the level of the pedicle is the equivalent of about 8–10 cm distal to the adductor tubercle in an adult. The branch of the obturator nerve that supplies the gracilis runs more obliquely than the vascular pedicle, up towards the obturator foramen.

Harvest of the gracilis leaves no significant functional defect and a well-concealed incision.

The muscle may be used as a muscle or musculocutaneous flap for repair of defects around the perineum. It is used for free functional muscle transfer for facial paralysis and for deficits of hand function and elbow flexion [22].

Gastrocnemius Flaps

The gastrocnemius flaps are very reliable and robust muscle flaps which are used for reconstruction of defects around the knee, especially in association with prosthetic and allograft reconstructions. They are supplied by the medial and lateral sural arteries that are large, short branches of the popliteal artery. When a single flap is required, the medial head is longer and slightly larger than the lateral head and is not close to the peroneal nerve, so this is the usual first choice, unless the defect is predominantly lateral [23].

As long as the soleus muscle remains intact, the functional defect from harvest of both gastrocnemius muscles is not severe, although use of both muscles should be confined to cases where there is no reasonable alternative. Harvest of a single gastrocnemius muscle leaves little function deficit.

The muscles may be raised as muscle-only or musculocutaneous flaps. The latter tend to be bulky, and leave an unsightly skin grafted donor site.

Other Flaps for Tumour Surgery

Numerous other named flaps may be used for reconstructive surgery.

The scapular and parascapular flaps are extremely reliable and large skin flaps based on the circumflex scapular artery. These flaps may also be harvested with a large amount of bone from the scapula and have shown good results in mandibular reconstruction in children [24, 25]. Parascapular and scapular flaps are also useful pedicled for defects around the shoulder, axilla and lower neck.

The free groin flap provides pliable thin skin from an excellent donor site. Excellent results may be obtained from use of this flap in children [26]. However, the vascular pedicle is relatively small, short and variable compared with the typical workhorse flaps, and as a result this flap is less widely used.

For head and neck reconstruction the temporoparietal fascial flap [27] and pectoralis major flap [28] have a variety of indications, and the latter is also useful for reconstruction of defects around the chest wall and axilla/shoulder.

In the inguinal region, femoral triangle and distal thigh, the sartorius muscle turnover flap is a very simple and effective option [29], and for larger, more complex defects, a rectus femoris muscle flap [30] (Fig. 29.3) or tensor fascia latae musculocutaneous flap [31] are very reliable options.

For bone defects the deep circumflex iliac artery (DCIA) flap provides a large amount of vascularised bone [32] and can provide excellent reconstruction of the mandible. However, it is generally regarded as challenging to raise and more prone to complications than the fibula flap or scapular flaps and the donor site can be very problematic.

Rarely used but reliable flaps for "salvage" situations include the deltopectoral flap for neck reconstruction [33], the omentum for chest wall [34] and pedicled groin flap for upper limb [35]. These flaps are "high cost" for the patient in a variety of ways, but may be used to salvage a desperate situation.

Skin Grafting

Excision of skin tumours commonly leaves defects that are suitable for skin grafting. Generally the donor sites for split thickness or full thickness grafts are "low cost" for the patient with relatively unobtrusive scarring. For facial defects, full thickness skin grafts may be taken from the post auricular or supraclavicular areas to provide a reasonable colour match for facial skin (grafts retain colour/texture of donor area). However, skin grafts rarely provide a high quality aesthetic result because of poor contouring, marginal scarring and inconsistency of colour (almost always, the graft looks like a "patch", especially with split skin grafting). Therefore, it is essential that families be carefully advised of the limitations of the outcome of graft reconstructions.

It is not uncommon for children who have had skin graft reconstructions to return in future for revision surgery such as serial excision or tissue expansion to improve the appearance.

A further limitation of skin grafting is the poor tolerance of grafts to radiotherapy. Where possible, graft-only reconstruction should be avoided where postoperative radiotherapy is indicated.

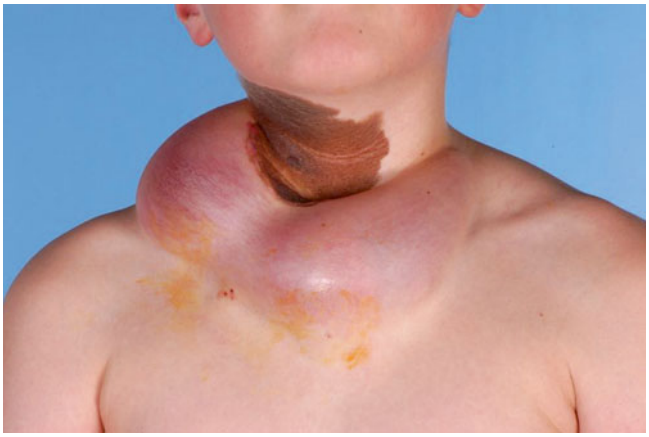

Fig. 29.6 Patient undergoing tissue expansion for removal of large congenital pigmented naevus on neck

Tissue Expansion

Tissue expansion is widely used in children for the elective reconstruction of cutaneous defects, especially in aesthetically important areas such as the face, neck and scalp. Almost always, this is appropriate only for excision of benign lesions such as congenital pigmented naevi [36, 37] (Fig. 29.6). Generally, the minimum time scale for tissue expansion is approximately 2 months between insertion of expander(s) and advancement of the expanded flaps. Accordingly the role of tissue expansion in cancer reconstruction is in secondary reconstruction of scarring and defects after treatment has been completed.

Tissue expansion after radiotherapy carries a high risk of complications and should be avoided unless there is no other useful reconstructive option.

Synthetic Materials

Dermal Regeneration Templates

A number of commercially produced dermal regeneration templates are available for reconstruction of extensive cutaneous defects after skin excision. These tend to be based on animal or cadaver derived collagen that forms a matrix for autologous fibroblasts to regenerate a dermis. The main indication for these in tumour surgery is in removal of giant congenital pigmented naevi [38]. Products are available which give successful graft take rates of approximately 90 % for clean surgical wounds. Thin skin autograft is required to complete the reconstruction and this can be applied on a single stage (immediate) or two-stage (after 2–3 weeks) basis, depending on the product used. Outcomes tend to be equivalent to those of medium thickness split skin grafts, with aesthetic and functional results of moderate quality.

In the event of infection, severe failure of dermal regeneration template may occur, so very careful postoperative management is required.

Occasionally, a dermal replacement may be useful for temporary coverage of a large wound after tumour excision when pathology is uncertain. In this circumstance, a topical negative pressure dressing may be a good option to retain the dermal replacement in position and control the wound until pathology is available and definitive treatment may be carried out.

Synthetic Materials for Chest Wall and Abdominal Reconstruction

Reconstruction of full thickness defects of the chest wall after tumour excision requires a stable skeletal substitute to prevent paradoxical respiration if more then three ribs laterally or if the sternum and costal cartilages are removed. Meshes based on polypropylene or polytetrafluoroethylene (PTFE) may be used to provide skeletal support [39] covered either with direct skin closure, or with a flap such as pectoralis major, latissimus dorsi or rectus abdominis. An absorbable alternative is collagen coated polyglycolic acid mesh [40]. The most extensive bone excisions may require methyl methacrylate cement reinforcement of the chest wall prosthesis [41].

More recently developed biosynthetic materials that may be used to replace bony, muscle or fascial defects of chest wall or abdominal wall include animal derived collagen sheets or mesh. Their principle potential advantages are in having a lower susceptibility to infection because of vascularisation and integration with possible greater potential to allow growth [42].

Chest Wall Reconstruction

Primary thoracic wall malignancies are rare in children and evidence on optimal treatment is often lacking. The most frequently encountered primary tumours are primitive neuroectodermal tumour (PNET/Ewing's sarcoma/Askin's tumour) and rhabdomyosarcoma. Currently, following incisional biopsy for histological diagnosis, thoracic malignancies are frequently treated with neoadjuvant chemotherapy, followed by surgical resection and sometimes local radiotherapy depending on the outcome of multi-disciplinary discussions and clinical trials. Surgical treatment usually implies a conflict between resection margins to ensure adequate excision and large thoracic defects which require complex reconstruction and represent a significant surgical challenge. The defect can either be closed primarily or may require chest wall reconstruction. Reconstruction must take into account the child's quality of life with optimization of functional and cosmetic outcomes whilst avoiding possible subsequent asymmetrical growth, particularly as the prognosis in many tumours has improved in recent years and long-term survival may be anticipated [43]. Some authors have attempted to describe the ideal characteristics of a prosthetic material for chest wall reconstruction: *rigidity* to restore physiological function by providing stability with avoidance of paradoxical chest movement and to protect underlying structures; *inertness* to allow in-growth of host fibrous tissue to reduce the likelihood of infection; *malleability* to allow fashioning to the required shape and size; and *radiolucency* to allow follow-up imaging of the underlying disease process and organs [44]. In adult practice, the use of alloplastic and xenogenic materials as well as muscle flap repair is well established [45]. In children, however, reconstruction must also allow chest wall and lung growth and as such there is a significant risk of scoliosis and respiratory morbidity with reconstruction attempts and loss of function when muscle flaps are used.

Careful pre-operative planning is essential and CT scan and/or MRI will aid in determining the extent of resection required and involvement of deeper structures such as lung and mediastinum. It is essential that consideration is given to the ability of the reconstruction technique to allow wound closure as well as support post-operative respiration and a combined team approach involving anaesthetists, plastic surgeons, intensive care physicians, and physiotherapists will optimize outcome.

Skeletal Reconstruction

Depending on the histopathology resection usually attempts to achieve a disease free margin of ≥2 cm which often results in multiple ribs being resected. The defect site and size are the important factors in surgical reconstruction with skeletal reconstruction required if resection of a full thickness tumour will result in a defect with paradoxical movements. Small defects (involving one to two ribs) can usually be covered with muscle and skin. Posterior skeletal defects may be better tolerated as the scapula provides stability. Resections of the lower ribs can be reconstructed by reapproximating the diaphragm to the lowest remaining rib [46]. Defects involving the sternum/anterior costal attachments may be reconstructed with a rib transposition, by detaching the anterior part of a remaining rib from the sternum and fixing it to the sternum or a residual part of rib in the middle of the defect.

Large defects are generally reconstructed using non-rigid prosthetic materials such as Goretex patch [39], Prolene or Marlex mesh, collagen-coated Vicryl mesh and more recently materials have been used which derive from bovine or porcine collagen (such as Tutopatch). The material is

stretched under adequate tension to bridge the defect to provide rigidity and is secured to the surrounding rib margins with sutures through drill holes or encircling the ribs. When very large defects result in paradoxical movement of the prosthetic patch additional materials may be required to provide rigidity. Such a scaffold may be provided by a titanium bar such as STRATOS™ (Strasbourg Thoracic Osteosyntheses System) or VEPTR™ (vertical expandable prosthetic titanium rib) [47]. A mesh or patch is usually interposed between the titanium bar and the underlying lung to prevent lung herniation. In the presence of local infection or if there is possible contamination of the prosthetic graft a muscular flap is the preferred option or a staged reconstructive procedure may be required. It has been suggested that because prosthetic materials do not grow with the child that they result in more severe scoliosis than if living myocutaneous flaps are used.

Soft Tissue Reconstruction

Following tumour resection with a resultant defect an autogenous muscle graft is often the preferred approach for reconstruction, either with or without concurrent skeletal reconstruction. Myocutaneous flaps may also allow skin coverage in addition to soft tissue. Muscle transposition using latissimus dorsi, pectoralis major, serratus anterior or rectus abdominis are the most common with the choice being dictated by the site and size of defect. Most such flaps depend on the preservation of a vascular pedicle although on occasions a free muscle flap with microvascular anastomosis may be considered. Team working with plastic surgical colleagues is vital to optimize outcome for such complex reconstructive efforts.

Long-Term Complications

Scoliosis following chest wall resection is a commonly documented complication; the protrusion usually being on the side of resection. This tends to be most marked with the resection of posterior and lower ribs and is related to the number of ribs removed. Progression of the scoliosis is observed until skeletal maturity and may be exacerbated by impairment of growth following radiotherapy. The severity of scoliosis can be estimated by measurement of the Cobb angle on chest radiograph. Surgical correction of severe scoliosis may be required with insertion of a Harrington rod or rib expansion devices [48].

A reduction in forced vital capacity (FVC) due to restriction of the chest wall is frequently observed and tends to progress with time; particularly if empyema or radiation have resulted in pleural thickening. Other documented complications have included dislocation of titanium bars, chest wall deformity and bronchopleural fistula [43].

Chemotherapy and radiotherapy result in an increased risk of developing secondary tumours such as sarcomas and leukaemia which mandates long-term follow-up surveillance. Keeping the total dose of irradiation to <60 Gy limits this risk has encouraged efforts to achieve primary surgical resection.

Reconstructive Urology

Introduction

Surgical extirpation was initially the treatment of choice for children with genitourinary malignancies, especially rhabdomyosarcoma [49, 50]. However over the past two decades the operative management of these tumors has become less aggressive with the emphasis now on the preservation of the affected organ where possible [51]. The improved response to chemotherapy along with more effective radiotherapy has allowed this paradigm shift in management. With multimodal therapy, surgery has been delayed until after completion of combined chemotherapy and radiotherapy. This has allowed more limited resections to be performed in those children that have responded well to treatment. Between 1978 and 1991, ten children between 1 and 8 years of age with group III pelvic rhabdomyosarcoma (IRS classification) and considered inoperable at diagnosis were treated primarily with intensive polychemotherapy, complementary radiotherapy and subsequent conservative surgery. Eight of ten children survived free of disease with a functional bladder (range of follow-up 5.7–18.4 years) [49, 50]. This initial experience has been repeated in other series with similar disease free survival rates and bladder preservation [52]. The function of preserved bladders seems to be acceptable although the reduction in bladder capacity in conjunction with radiotherapy means that these bladders have to be followed long-term [53]. It should also be noted that some children will not respond to initial treatment and more radical surgery will be required [54, 55] to achieve disease control.

Before Reconstruction

Reconstruction after treatment for childhood urological malignancy is a challenge for all those involved. Before surgery is considered great care should be taken to ensure that the child and their family are physically and psychologically prepared. The oncological team must ensure that reconstruction will not interfere with the ongoing management and surveillance of the child. A thorough assessment of renal appearance and function must be made including glomerular

function rate if there are any concerns. The overall nutrition of the child must be optimized and assessed to ensure that they are able to cope with the surgery and its implications. Finally the child and family must understand the nature of the surgery and have the appropriate psychosocial support to make its long-term outcome satisfactory.

Options for Reconstruction

There are a vast number of operations described for reconstruction of the bladder, each with its own advocates and perceived benefits. At the risk of over simplification and for the benefit of the non surgical reader we can simplify the choices for reconstruction based on the site and margins of resection for the original bladder tumour. If we divide the bladder into detrusor, trigone (with ureteric orifices) and urethral sphincter complex we can look at the approach to reconstruction in each case. The overriding principal is to provide a container that can store a reasonable amount of urine at a low pressure with mechanism to empty it. If the container cannot be emptied voluntarily then clean intermittent catheterization (CIC) will be required, if this cannot be achieved urethrally then a cutaneous stoma for catheterization will be needed. It should be remembered that, before, during and after urological reconstruction the patient needs to be seen, counseled and supported by a dedicated team of nurse specialists.

Tumours Confined to the Detrusor

Tumours confined to the detrusor muscle, that can be resected easily without affecting the trigone or sphincter mechanism, may not need any further surgery. If the amount of detrusor removed is large then the functional capacity of the bladder may be reduced sufficiently to cause symptoms. The limited paediatric literature, suggest that most children adapt to this reduction in bladder capacity and further surgery is not required [56, 57]. However, in some children surgery to augment the capacity of the bladder may be required. Similarly, children with a fibrosed and contracted bladder resulting from radiotherapy may also benefit from bladder augmentation.

At the time of bladder augmentation the child should be free of neoplastic disease locally and systemically. Intermittent CIC per urethra may be necessary after bladder augmentation and the child and his parents should be aware of the risks and complications related to augmentation and taught how to safely catheterize the new bladder.

Various segments of intestine have historically been used for bladder augmentation (ileum, cecum, ileocecum, sigmoid, stomach etc.) [58]. Intensive research efforts have currently been directed at finding a "tissue engineered" alternative to bowel for use in augmentation [59]. A bioengineered alternative would avoid the complications of using bowel and greatly simplify the surgery required. However, at the present time bowel and more commonly ileum is the tissue of choice and an ileocystoplasty is routinely performed.

Ileocystoplasty

The bladder is mobilized and opened in a sagittal or coronal plane. A 20 cm portion of terminal ileum at least 15 cm from the ileocaecal valve is isolated on its vascular pedicle. The segment of ileum is opened up along its antimesenteric border, for a large augmentation the bowel is fashioned into a cup and anastamosed to the opened bladder.

Trigone

If the trigone is involved then a sub total cystectomy will be required. The majority of the storage capacity of the bladder will have been removed. If the sphincter mechanism is intact, then the operation of choice would be an orthotopic bladder substitution. The storage function of the bladder is performed by a detubalirized section of bowel with the ureters attached. This storage container is anastamosed to the original sphincters, which provide the mechanism for continence. Bladder emptying can be achieved by a combination of relaxing the sphincters and increasing abdominal pressure, although clean intermittent catheterization may be required.

There are a huge variety of operations described in the literature for orthoptic bladder replacement, but they are all based on this principle. The Koch pouch is described to illustrate the principle [60, 61].

Urethral Sphincter and Bladder Neck

If the sphincter mechanism is affected by residual disease then it may need to be resected. In the male child continence can be achieved with just the external sphincter so complete bladder preservation can be achieved after resection of prostatic disease. In a female or a male with widespread disease more radical surgery may be required. The ureters can be anastamosed to an isolated segment of ileum which is formed into a cutaneous stoma, a so called ileal conduit. Alternatively the ureters can be joined to the sigmoid colon to form a utersosigmoidostomy, however the long term risk of malignancy when urine and faeces are mixed in the colon is significant [62].

A more acceptable long-term option is to perform a continent cutaneous diversion. Again there are a whole host of operations described, but they all adhere to a similar principle. A segment of bowel is isolated and formed into a storage chamber, the ureters are joined to this chamber and a continent channel is formed to the abdominal wall skin. This channel is then used for catheterization to empty the neobladder. The Koch Pouch [60] is shown as an example of such a continent diversion where the ileal segment is isolated

on its vascular pedicle, the central part is detubularized and folded twice to create a large pouch. The segment of the ileum at each end of the pouch is intussuscepted to provide a nipple valve to prevent leakage of urine or reflux. The ureters are isolated and anastomosed to the afferent loop. The efferent loop provides the contient catheterizable channel.

Clean Intermittent Catherization

In any reconstructive urological procedure attention must be given to ongoing drainage of the urinary tract. If a continent storage container is used then there must be mechanism put in place to empty the container regularly. In the majority of occasions some form of clean intermittent catheterization (CIC) will be required four to five times per day [63]. CIC can be done via the urethra in some children but often an alternative route for catheterization needs to be explored. Traditionally this involves the use of the appendix, which is tunnelled through the bladder wall to prevent passive leakage of urine and anastomosed to the umbilicus or abdominal wall create a catheterisable stoma (Mitrofanoff principle) [64]. In those patients who have previously had their appendix removed a segment of small bowel is opened on the antimesenteric border and re-anastomosed longitudinally to form a tube. This is referred to as Monti procedure [65].

Long Term Complications of Urological Reconstruction

Surgical Complications

Nearly all of the urological reconstructions described involve the use of a segment of bowel to store urine. Bowel will produce mucous which can be source for infection and stone formation. Ensuring good fluid intake and instituting a policy of regular bladder washouts can reduce the risk of these problems occurring. The continent diversions described also require regular catheterization of their stoma, difficulty in performing catheterization due to stenosis or leakage of urine from the channel are well recognized issues [66, 67].

Renal Function

A child who has undergone urological reconstruction needs to have regular assessment of their renal status. Their kidneys need to be assessed by ultrasound for hydronephrosis and by nuclear medicine studies for scarring. Urea and creatinine should be checked regularly and if there are any concerns a formal assessment of renal function should be undertaken. The commonest reason for a detioration in renal status is a failure of the child to comply with catheterization and inadequate emptying of the neo bladder.

Metabolic Consequences

The use of a bowel segment to store urine can result in the abnormal absorption of electrolytes and the development of hyperchloraemic metabolic acidosis. This in turn can lead to demineralization of bone. Therefore, electrolytes need to be measured regularly and supplemental oral bicarbonate may be required in a minority. If as segment of terminal ileum has been used in the reconstruction then the absorption of B12 may be affected and this should be checked several years after surgery [68].

Tumour Formation

There is evidence in the literature to suggest an association with urological reconstruction and the development of tumours in the neobladder. The risks are difficult to quantify, although the incidence of tumour formation appears to be greater with the use of colon and stomach than for reconstruction with ileum. There are isolated reports of malignancy occurring with bladders that have been augmented with small bowel, but these have occurred in bladders that were chronically inflamed or tuberculous prior to the surgery. The patient should be advised to look out for symptoms such as haematuria and consideration should be given to surveillance by cystoscopy in the long-term follow up of these patients [62, 69, 70].

Vaginal Reconstruction

Vaginal reconstruction may be required in patients who have had their vagina removed after treatment of pelvic malignancy arising either from the vagina or uterus or bladder infiltrating the vagina. However, with current oncological management the vast majority of girls treated for pelvic malignancy will not need any form of reconstructive surgery [71].

For those children that do require vaginal replacement there is huge controversy in the literature over what operation should be performed and when it should be performed. Even if the reader widens their review of the literature to include the requirement for vaginal replacement in other conditions the numbers of cases available for review are small and the advice on management conflicting [72].

A functional vagina that can be joined to any remaining mullerian structures can be achieved by progressive dilation, the use of skin tubes or a segment of bowel. The long-term results of vaginal replacement suggest that although a reasonable functional result can be achieved, repeated surgeries and vaginal self dilation are nearly always required. For this reason alone it is probably advisable to delay surgery until an age where the child can fully participate in her management [73–75].

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Reconstructive Surgery for Bone Tumors

30

Roderick D.D. Duncan

Reconstructive Surgery for Malignant Bone Tumor

The diagnosis and management of bone tumours has been largely covered in the chapter by Mr SR Cannon, but it is important to discuss other recent advances in this field. These include computer assisted surgical techniques and alternatives to endoprosthetic reconstruction. Amputations are less frequently required now than previously, but there are some important considerations in children that need highlighting. Finally, rotationplasty as an alternative to amputation will be discussed. There are parts of the world, for example Europe and North America where this procedure is more widely performed than in other countries, for example the UK. For the correct patient with the correct indications, it can be very successful.

Computer Assisted Navigation in Sarcoma Surgery

A prerequisite for successful tumour surgery is complete removal of the tumour itself. Sometimes defining the limits of the lesion is straightforward using images from staging studies, particularly MRI scans. In certain circumstances it can be very difficult to translate the information from scans to the patient. This is particularly the case when attempting removal of pelvic tumours. Computer assisted surgery is a rapidly evolving field within orthopaedic surgery and is used principally in joint replacement, spinal surgery and cruciate ligament reconstruction to ensure accurate placement of implants. In tumour surgery the navigation techniques can be used to guide bone cuts and to ensure a clear margin. There are a number of different techniques but the principles are similar. Imaging studies are used to identify the boundaries of the tumour and to plan the resection margins. Figure 30.1 shows the result of fusing CT and MR images of a pelvic tumour. Landmarks on the skeleton are identified either preoperatively or intraoperatively, in order to orientate the images. Motion sensors can be attached to surgical instruments (drills and osteotomes) which will show the precise location of the tip of the instrument on the fused CT/MRI image in three dimensions. A recent paper suggests that using computer navigation may improve tumour clearance, but controlled studies have not been published [1].

Advances in Biological Limb Reconstruction Following Resection of Malignant Tumours in Children

There is no doubt that advances in endoprosthetic (EPR) design have improved implant survival and function. Modular systems are available for implantation in adults – EPR components of differing sizes can be kept in theatre and assembled during the procedure to ensure that the final device fits perfectly. In paediatric practice it is more common to have to rely on custom-made implants as modular components of the correct size are less freely available. These implants can be designed to incorporate growth. Implants remain very costly and therefore are not available in all healthcare systems. Failures of endoprosthetic reconstructions are common.

In a review of 2367 EPRs, Henderson et al. examined why EPRs fail. The overall failure rate was 25 % with a mean time to failure of 47 months. The most common reason for failure was infection which occurred in 8 % of all cases but accounted for 34 % of all failures. Other causes were aseptic loosening, periprosthetic fracture and tumour progression [2]. In a series of patients who had an endoprostheses implanted for more than 20 years previously, Grimer et al. found that there was an amputation rate of 12 % and also a cumulative risk of deep infection of 1 % per year

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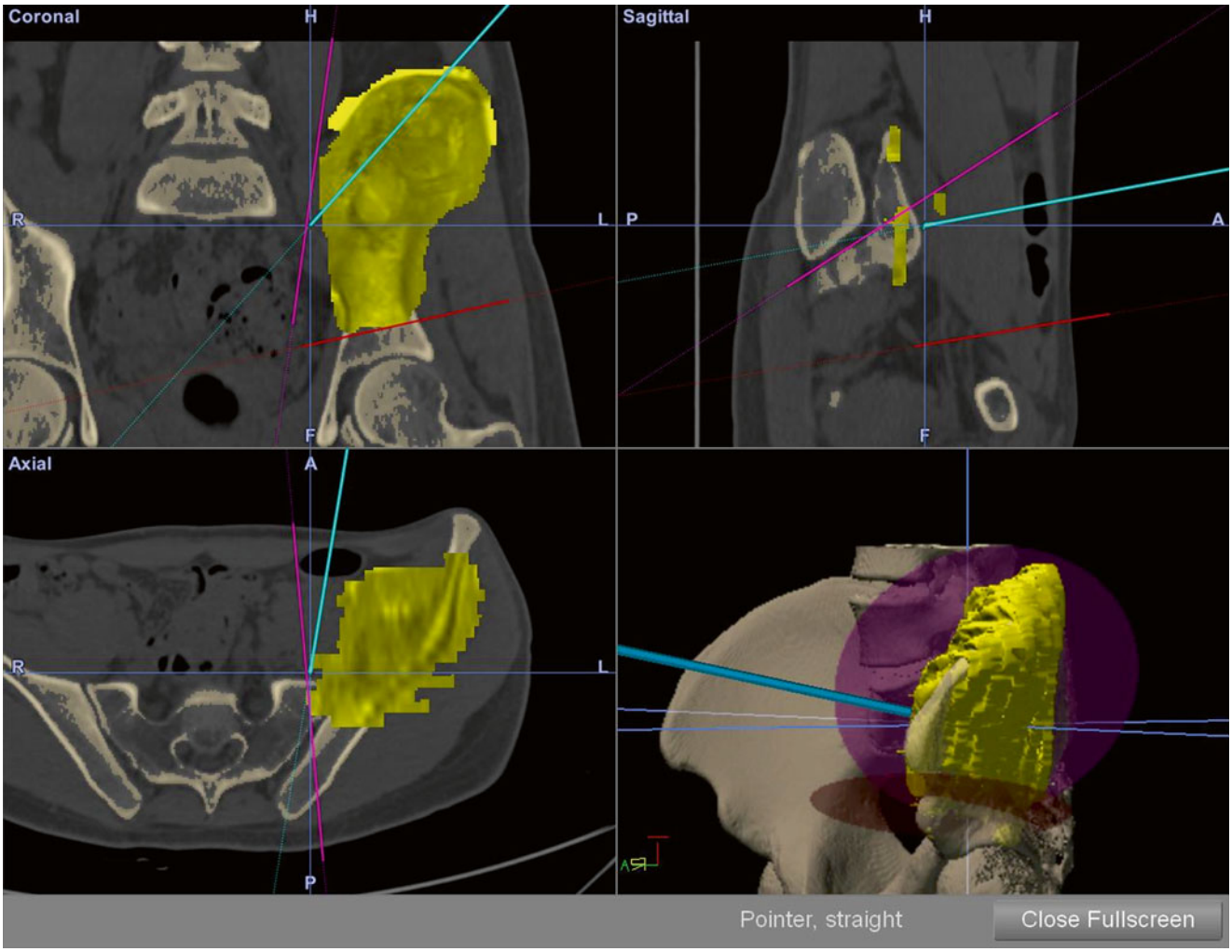

Fig. 30.1 Screen shot from intraoperative resection of a pelvic sarcoma using computer navigation. The intended resection (*yellow*) is planned from both preoperative MRI and CT scans. The planes of resection have been identified and marked (*red and purple lines*). The *blue line* represents the position of a surgical instrument, attached to a motion sensor, being used to resect the tumour (Images courtesy of Mr Ashish Mahendra, Glasgow Royal Infirmary, Glasgow UK)

(Personal communication British Orthopaedic Oncology Society Leicester 2012). Fracture around an endoprosthesis is a concern as long as the EPR is in place and full normal sporting activities, particularly high impact or contact sports, are generally discouraged. Revision of an EPR for fracture is complicated and increases the risk of infection.

Types of Biological Reconstruction

The use of bone to reconstruct defects following tumour resections has been studied for many years in the hope that this will provide a more durable 'biological' reconstruction. The options are to use bulk autograft (vascularised or non vascularised), allograft, a composite reconstruction using both bone and an EPR, or distraction osteogenesis. The latter option has not gained great popularity in the management of malignant tumours outside certain large centres because of the perceived risks of pin-related infection and poor bone formation in a child undergoing chemotherapy. Two recent reports, one on growth plate (physeal) distraction and another on external fixation with or without distraction, suggest that these fears may have been overestimated [3, 4]. It has been found that the use of allograft bone to reconstruct defects which include joint surfaces has not provided a long term solution, with early failure of the articular surface requiring revision. A way around this is to combine allografts and EPRs to create a composite reconstruction. Whether these produce better results in the long term when compared to endoprostheses alone remains to be seen.

Pure biological reconstruction techniques tend to be limited to situations where the host joint surfaces can be retained without compromising the surgical margins. For metaphyseal tumours, the physis may need to be sacrificed.

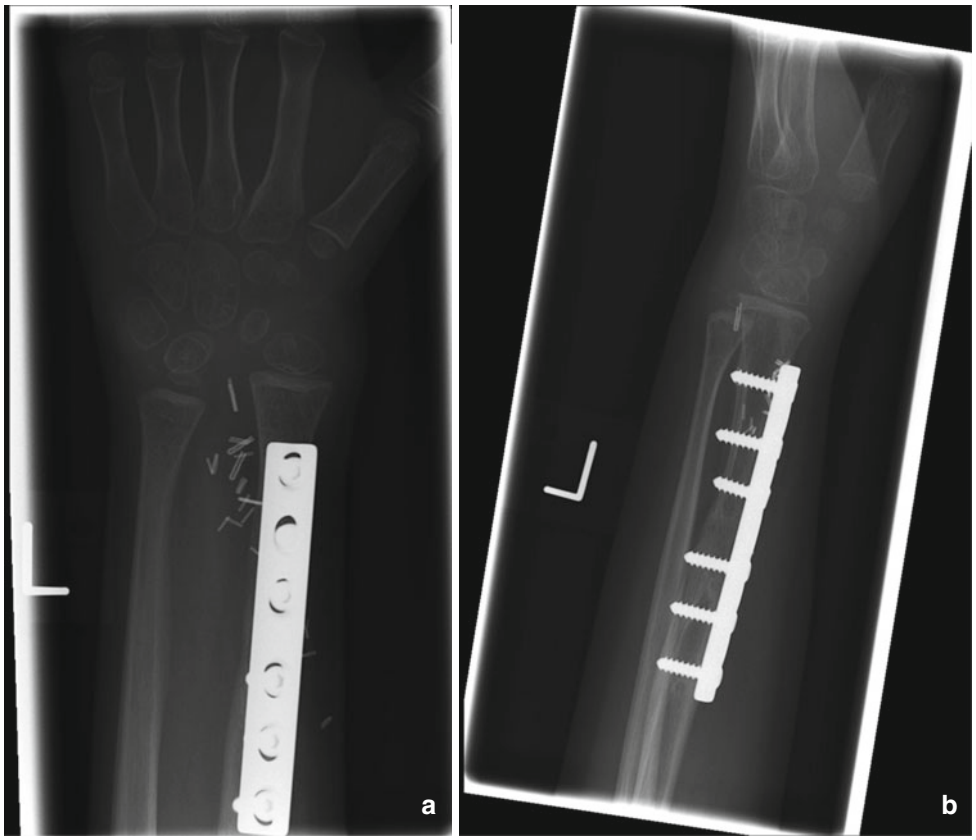

Fig. 30.2 (**a**, **b**) Radiographs from an 8 year old boy who had free transfer of his proximal fibula to the wrist following resection of a recurrent aneurysmal bone cyst. The fibula was mobilised on the anterior tibial artery in order to preserve the physeal blood supply. A faint Harris line can be seen indicating that the transplanted fibula is growing

In certain situations it is possible to reconstruct a defect using a vascularised autograft in which the physeal blood supply is retained. It is therefore possible that the limb will continue to grow. By harvesting the proximal fibula whilst preserving the physeal vessels, the vascularised graft can be used to reconstruct the distal radius for example [5] (Fig. 30.2).

Bulk allografts or autografts can be used in the following circumstances; diaphyseal resections, metaphyseal resections where preservation of the physis is not required (in the older child for example) and following certain pelvic resections. There are cultural objections to allografts is certain parts of the world. Allografts are expensive and not widely available outside centres will well established tissue banks. The use of vascularised autografts is common, with the fibular graft raised on the pedicle of the peroneal artery, being the mainstay. There is a high union rate and it is relatively resistant to infection, but the procedure is technically demanding and can be complicated by late fatigue fracture [6]. The grafts hypertrophy after implantation, but this can take a long time, requiring protected weight bearing or protection with an orthosis. Vascularised fibular grafts can be used for joint arthrodesis (Fig. 30.3).

Extracorporeal Irradiation and Reimplantation

There has been a lot of recent interest in the use of irradiated autografts. The technique of extracorporeal irradiation and reimplantation was first reported in the late 1980s [7]. It involves resection of the malignant tumour with a cuff of normal tissue in order to achieve a wide surgical margin. The specimen is then packed in a sterile container and then irradiated with at least 50 Gy. The original report recommended 300 Gy, but doses between 50 and 300 Gy are reported [6–11]. The soft tissues are removed from the bone either before or after irradiation, the tissues sent for pathological evaluation and the bone is then reimplanted (Figs. 30.4 and 30.5). The dose of irradiation is enough to kill all cells in the host bone, including the tumour cells and delivers a dose which is considerably higher than could be safely delivered by conventional means. The bone is then reimplanted. Plating of the graft is recommended, with either one or two plates [8]. There does not appear to be an increased risk of local recurrence, with rates reported to be less than 10 %. Infection remains a problem, up to 32 % [8], but one group [9] found that the use of vancomycin impregnated cement seemed to be associated with fewer infections.

Ipsilateral or contralateral vascularised fibular transfers have been used to fill the medullary canal – in theory this should encourage union, and may speed up the incorporation of the irradiated autograft. One small study compared irradiated autograft reconstruction with allografts [9]. They found a similar rate of infection and fracture rate, but the non union rate was much higher in the allograft group than the autograft (43 % vs 7 %). The three fractures in the autograft group were treated with casts, but the allografts fractures were fixed and grafted.

A significant criticism of extracorporeal irradiation and reimplantation is that it does not allow complete pathological

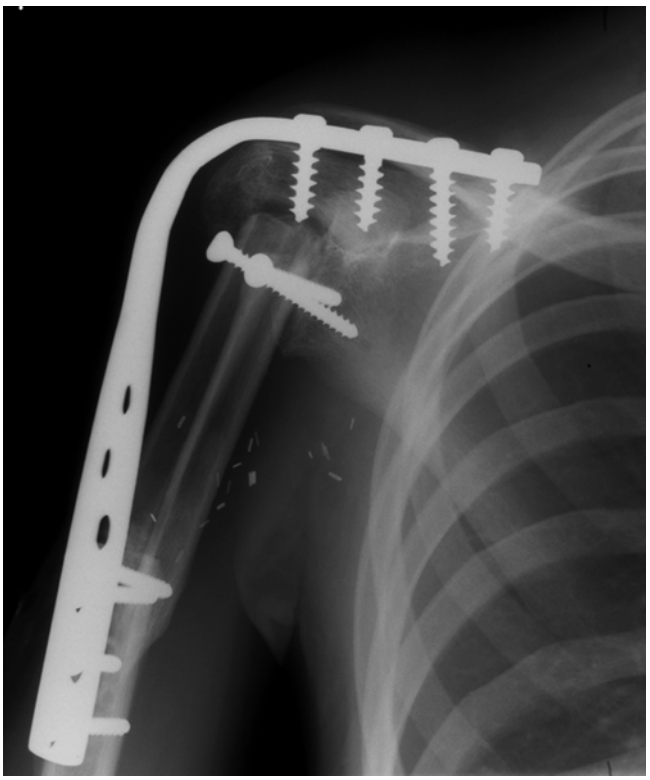

Fig. 30.3 Radiograph of a reconstruction of the shoulder following an intraarticular resection of the proximal humerus for Ewings sarcoma. An arthrodesis was performed using a free vascularised fibular graft, and a contoured plate

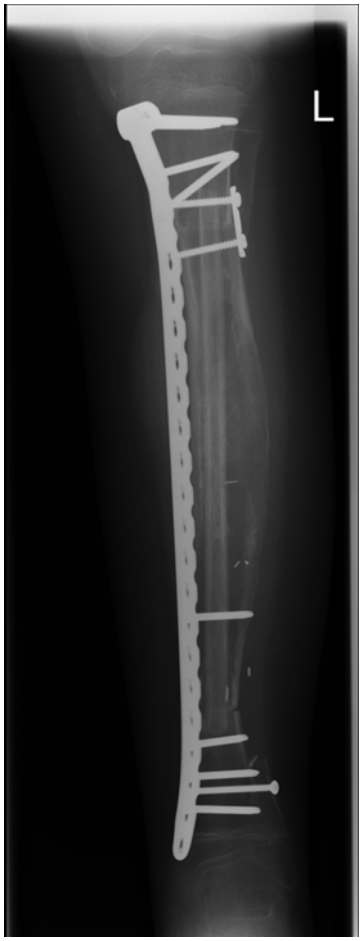

Fig. 30.5 Radiograph of a 9 year old boy who had resection, extracorporeal irradiation and reimplantation of the tibial diaphysis with an ipsilateral vascularised fibular transfer for an adamantinoma

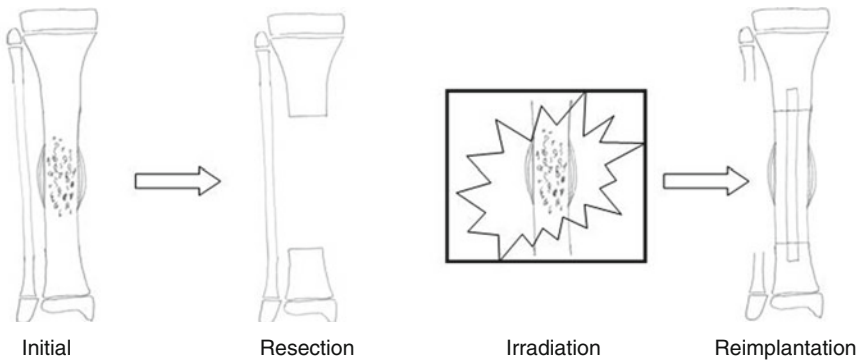

Fig. 30.4 Schematic diagram of the process of resection, extracorporeal irradiation and reimplantation of the tibial diaphysis, with reconstruction incorporating an ipsilateral vascularised fibular transfer

evaluation of the specimen. The soft tissues and marrow from the resection margins can be evaluated, but the estimation of the percentage necrosis is likely to be unreliable. This is a prognostic indicator in those who have had preoperative chemotherapy and, in several clinical trials, used to guide postoperative chemotherapy.

Several other questions also remain such as whether the long term risk of infection is different from that of EPRs, and whether biological reconstructions will eventually become strong enough to permit unrestricted sporting activities. Infection remains a huge problem, but the use of antibiotic impregnated bone grafts is encouraging [12].

Alternatives to Limb Sparing Surgery

Limb sparing surgery is not always feasible in children with malignant tumours of the limb girdles. The primary aim of local treatment for sarcoma is complete tumour clearance including a surrounding cuff of normal tissue. The reconstruction of the resulting defect should result in a well perfused and sensate limb which will allow the child to function as they wish to and which looks good. Ideally the reconstruction should be long-lasting with the risk of as few complications as possible. The majority are treated by limb sparing surgery. Many families expect that their child will be able to take part in normal activities after limb sparing surgery, but this is not always the case. Activity restriction is usually advised after implantation of an endoprosthesis and after biological reconstruction. This may not be easy for children and their families to accept. A fracture following limb salvage can result in an extremely challenging problem, with a significant risk of complications.

An amputation may result in a quality of life which is comparable to that after limb sparing surgery, with little impact on employment, educational attainment, marriage and psychological status. Most large studies have found that physical functioning scores are less for amputees than those having limb salvage, but the differences are much smaller than one might expect [13, 14]. Measuring the health related quality of life of survivors of childhood cancer is more difficult than one might imagine because of the limitations of the tools that are in use and also because of the mechanisms young people adopt to cope with their diagnosis and treatment [15]. The difference in physical functioning between childhood cancer survivors and the normal population becomes more apparent with time [16] which makes it challenging to organise studies with long term follow up. Bone cancer survivors have consistently worse physical functioning scores than other cancer groups [16]. The effect of the type of surgery (limb sparing or amputation) on this particular outcome measure is not yet clear. Again the differences between those undergoing limb salvage, and those undergoing amputation are smaller than one might expect.

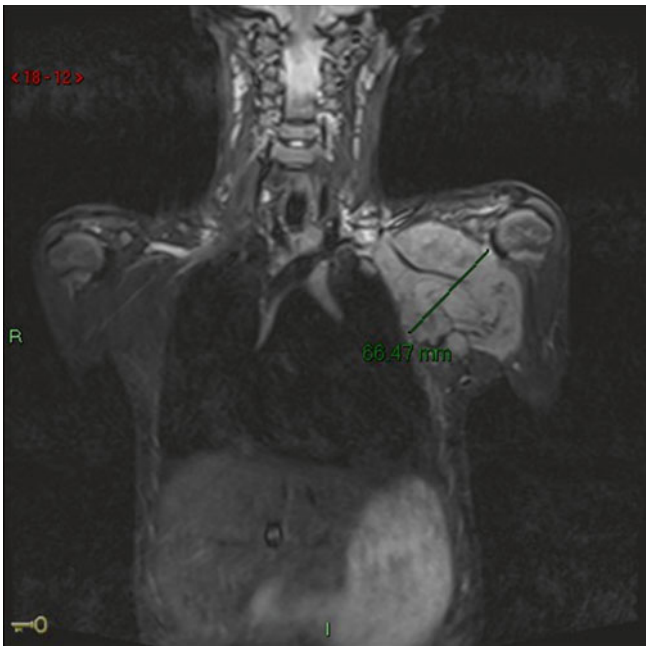

Fig. 30.6 Coronal plane MRI scan of an epithelioid sarcoma of the axilla with the axillary vessels passing straight through the tumour. This tumour could not be treated with limb salvage and the child underwent a modified fore-quarter amputation

In situations where safe removal of the tumour will involve resection of major nerves and vessels or where large amounts of muscle need to be sacrificed, amputation may be the only option for surgical clearance (Fig. 30.6). This is a difficult situation to discuss with families. It is helpful to have a good working relationship with the local prosthetic and psychology services. Children who are being considered for amputation should be offered the opportunity to meet with the prosthetic team pre-operatively and to meet someone who has undergone a similar procedure at a similar age. The best way to utilise psychology services has not been defined – it can be difficult to predict beforehand how children and their families will adjust to the loss of the limb. Some do much better than expected and others do not. One group found that children accept amputation more readily if the child has pain or functional loss before surgery [17]. Throughout treatment for cancer, a supportive family is important. If the family are positive about the amputation as being a curative procedure then this is likely to help the child come to terms with it as well as helping friends and other family members.

Amputation is a particularly difficult issue to discuss with teenagers at a time where concerns regarding body image are heightened. Some will refuse point blank to agree to amputation when limb sparing surgery is not advisable. It is essential to have frank, but sensitive, discussions with the young person to make sure that, if there is a serious risk that the tumour might not be completely removed, they understand the full implications of their decision to refuse amputation. The risks

are of local recurrence and further surgery with the attendant complications. The chances of cure may also be reduced.

Amputation is occasionally performed for recurrent benign disease where there have been multiple attempts at local resection and limb sparing.

Amputations in Children – Surgical Issues

Amputations in adults are most often performed for complications of peripheral vascular disease and for trauma. Careful selection of amputation level and skin flaps is important because of impaired perfusion to the skin. In children who require amputation for cancer, the tissues are usually healthy and wound healing problems are less of a concern. The main surgical difficulty is to provide a stump which is covered by healthy skin and muscle whilst obtaining complete tumour clearance. It is important to liaise with the prosthetic services to ensure that the remaining stump length is adequate for prosthetic fitting. We use 10 cm as the minimum length for a below knee amputation. An alternative is disarticulation through the knee. An ankle disarticulation (Syme's amputation) is an option for children who have tumours of the foot, but the heel pad must be preserved to provide a durable end-bearing stump.

In children with tumours, soft tissue coverage is usually not a problem although sometimes careful planning of the skin flaps is required. The major problem, which is particularly a concern in younger children is that of bone overgrowth. This is common and occurs in between 4 and 35 % of children [18]. It is particularly common after transtibial amputation where it may occur in up to 15 %. After the age of 12 years of age stump overgrowth is less of a problem [19]. It is also less common following transfemoral amputation. It occurs as a result of appositional bone growth. In a sense the bone also appears to outgrow the soft tissue envelope (Fig. 30.7). The padding over an amputation stump reduces over a remarkably short period of time and can result in pain, difficulty in wearing the prosthetic limb and infection of the stump. The incidence of overgrowth can be

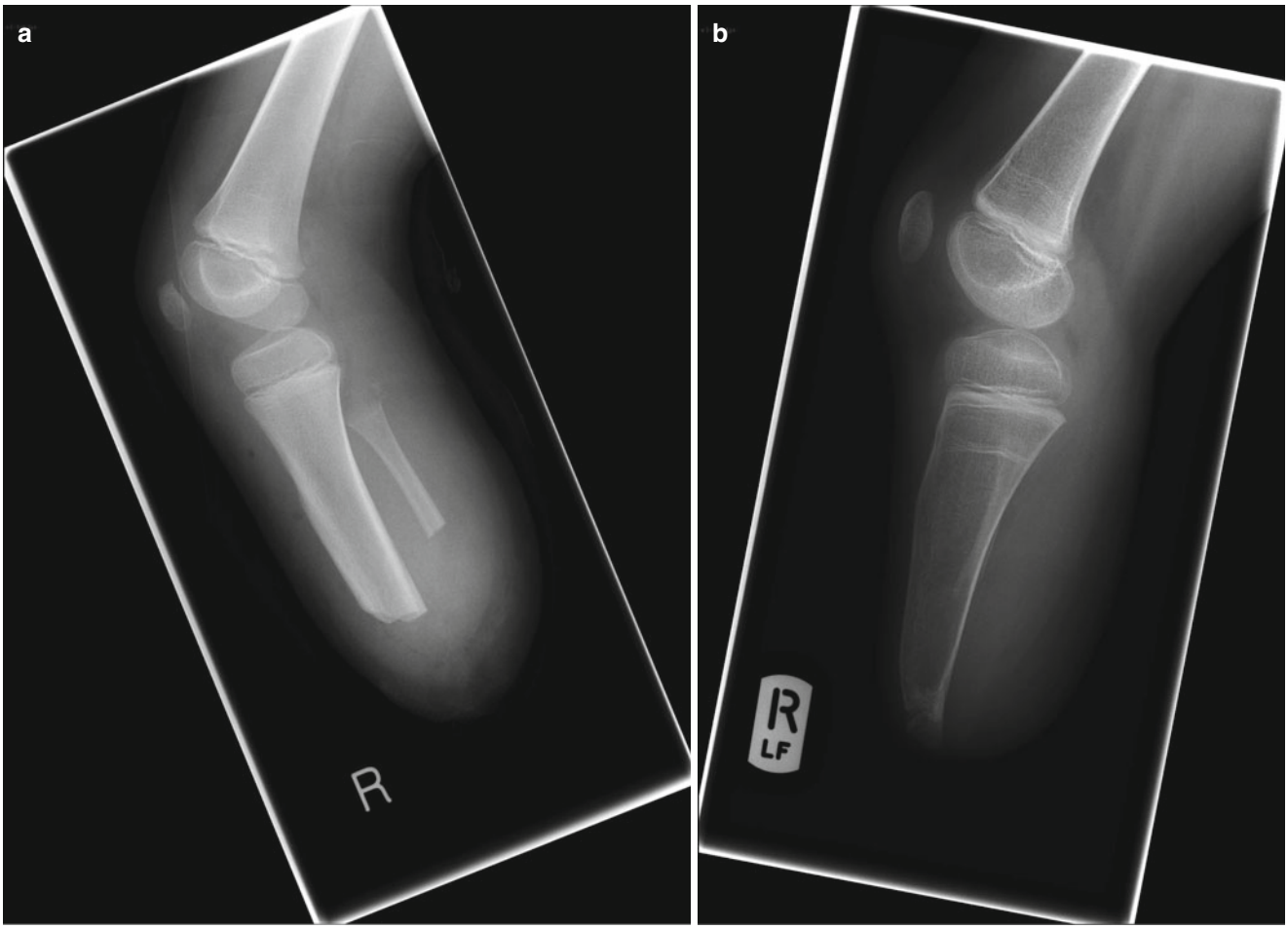

Fig. 30.7 (**a**, **b**) Radiographs of a boy who had a transtibial amputation with capping for an undifferentiated extracompartmental sarcoma of the calcaneus. Note the large soft tissue envelope distal to the tip of the tibia (**a**) and the amount of growth that had occurred 11 months later (**b**) with subsequent reduction in the soft tissue coverage

reduced, but is not abolished, by capping the stump either with autograft from the iliac crest, using a synthetic cap. In a comparative study the rates of revision surgery after simple resection, synthetic capping and biological capping were 86 %, 29 %, and 29 % respectively [20]. Another effective technique is to create a synostosis between the tibia and the fibula (the Ertl procedure) [21].

Rotationplasty

Rotationplasty can be regarded as either a form of amputation or limb salvage of the lower limb. The aim of the procedure is to preserve a functional joint at the level of the opposite knee. The energy involved in walking afterwards is approximately 30 % above normal which is comparable to a below-knee amputation and much better than after an above knee amputation (approximately 70 % more energy utilised compared with normal gait) [22]. It involves resection of a limb segment and rotation of the distal part of the lower limb, placing the ankle joint at the level of the contralateral knee. A prerequisite is that the foot and ankle must retain normal sensation and power after surgery. Vascular resection and reanastomosis can be performed if the femoral or popliteal vessels are involved by tumour, but the common peroneal and posterior tibial components of the sciatic nerve must be preserved. It is most commonly performed for distal femoral tumours as an alternative to above knee amputation, but can also be used for proximal tibial and even tumours of the proximal femur.

It is a valuable reconstructive option in children. A trans-femoral amputation involves sacrifice of the distal femoral growth plate, from which the majority of femoral growth occurs. In a child who has growth remaining in the lower limb, the proximal segment of the amputated lower limb will therefore become relatively shorter over time – an initially adequate stump length will become less. This will have implications for suspension of a prosthesis and lower limb function. Initially, the child may function as expected for a trans-femoral amputee, but with time function may become more like that after a hip disarticulation. Rotationplasty preserves a joint at the level of the knee, so the child will function more like a below knee amputee. An obvious disadvantage is the appearance of the limb. Some suggest that these individuals will have psychological problems because of the appearance of the limb, but this is not supported in the literature. One study of twenty-two patients, studied at least 10 years after surgery, showed values of contentment relating to friends, partnership and sex which were comparable to the normal population. They also had comparable quality of life measured using the EORTC QOL-C30 tool [23]. The mental component scores of the SF-36 tool for measuring quality of life in rotationplasty patients were, in some respects, better than the normal population in one study [24]. Half of one group of young people who had undergone rotationplasty felt that they had no difficulty in initiating intimate relationships or having an active sex life, although some did have concerns. The authors of this study pointed out that problems in this area are not uncommon among conventional amputees [25]. The importance of family, friends and healthcare professionals in facilitating acceptance cannot be over-stressed.

With expert prosthetic management these children can function very well. A study on the sports activity and endurance capacity of sixty-one patients with rotationplasty revealed higher levels of participation in sports than the general population. Most took part in activities such as swimming and cycling, but also soccer and volleyball. Some took part in Alpine skiing, horse riding and badminton. Their findings confirmed the findings of others that their oxygen consumption was higher than that of healthy subjects, but is lower than that of other patients with amputations [26]. Bekkering et al. used an activity monitor and a questionnaire and found no difference in physical activity levels between groups who had undergone limb salvage or amputation/rotationplasty, but the limb salvage patients were better at a timed test on stairs and various walking activities including stepping over 20 cm obstacles [27].

In summary, rotationplasty is a valuable option for treating certain children with malignant disease, particularly those in whom the alternative is an above knee amputation, or where a significant leg length discrepancy is predicted at the end of growth. The recent review by Gupta et al. [28], and descriptions by Winkelmann [29] and Kenan et al. [30] will provide readers with more detailed information regarding the surgical technique.

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Surgical Complications of Childhood Tumors

31

G. Suren Arul

Rare Surgical Presentations of Cancer in Childhood

Most childhood tumors will first present to a physician; some tumors will present in an atypical manner and may mimic a surgical condition. The diagnosis may be missed if the surgeon is not aware of the possibility of cancer. A very great number of rare presentations of childhood cancer have been described in the literature. It is important that the surgeon who is not experienced in the management of childhood cancer is aware that an apparently benign condition could be a manifestation of an underlying malignancy [27, 73] (Table 31.1).

Soft Tissue Complications

Soft tissue problems are a common cause for surgical consultation on the oncology ward. Immunosuppression, steroid-induced skin changes, and prolonged immobilization all contribute to skin infections. These may start as simple localized infections, which may quickly spread into life-threatening problems. Although the conditions outlined below are all related, they do have significant differences, which are reflected in their varying management. Careful clinical diagnosis in conjunction with relevant microbiological, hematological, and biochemical findings is essential.

Cellulitis

Usually soft tissue problems involve no more than simple local infections. However, as these children are often immunosuppressed, a localized infection can quickly spread to a life-threatening cellulitis. Any areas of erythema should be treated suspiciously with swabs of the area and blood cultures being sent. Antibiotics should be employed early in a suspected infection.

Proven cellulitis should be managed by marking the area of erythema so that any progress can be monitored. Intravenous antibiotics are mandatory and should be prescribed after discussion with the infectious disease specialists.

Table 31.1 Surgical presentation of tumors

Presentation	Neoplastic cause	Ref
Acute abdominal pain	Ruptured Wilms' tumor	[45]
	Ruptured liver tumor	
	Appendicular carcinoid, lymphoma	
Intussusception	Hemangioma	[14, 16]
	Ganglioneurofibroma	[97]
	Lymphoma	[29, 113]
Intestinal obstruction	Leiomyoma	[107]
	Esophageal leiomyoma	[13]
	Intestinal fibromatosis	[19]
	Lymphoma	
Gastrointestinal bleeding	Gastric teratoma	[50]
	Typhlitis	[51]
Perianal abscess	Yolk sac tumors	
	Rhabdomyosarcoma	
Biliary obstruction	Hemangioendothelioma	[104]
	Rhabdomyosarcoma	[18]
Hydronephrosis	Neuroblastoma and other pelvic tumors	[43]
Testicular swelling	Primary tumor	
	Leukemia	[86]
	Lymphoma	
Varicocele	Wilms' tumor	[9]
Bronchiectasis	Carcinoid	[116]
Priapism and clitoral engorgement	Congenital myeloid leukemia	

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Superficial Abscesses

Conditions such as paronychia and superficial skin abscesses in the groin or axilla are relatively common. In patients with a normal neutrophil count the treatment of choice is incision and drainage of the area of maximum fluctuation. In the cases of neutropenic patients most abscesses will not contain pus but watery fluid containing no neutrophils. These instances are best treated with antibiotics and granulocyte stimulating factor; any areas of fluctuation can be aspirated with a fine needle to provide fluid for culture and sensitivity testing often without the need for incision and drainage.

Radiation Necrosis

Children receiving radiotherapy may develop radiation necrosis of the skin and soft tissues. This was seen more commonly in treatment protocols that advocated large doses of radiation therapy develop extensive erythema of the skin and skin necrosis to superficial areas in the body. This is no longer the case with current protocols (Fig. 31.1).

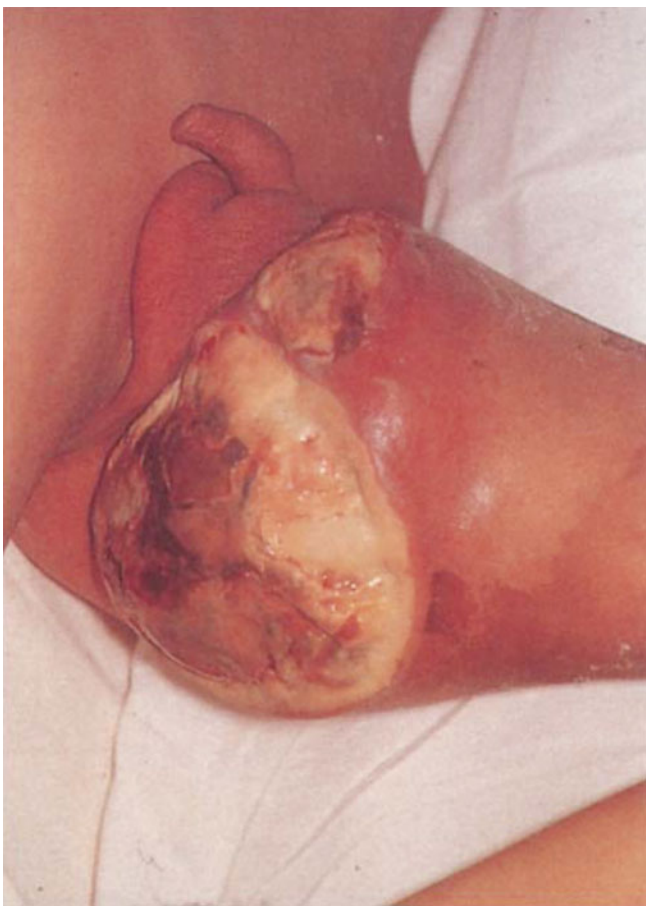

Fig. 31.1 Skin necrosis after chemotherapy and radiotherapy to shrink a rhabdomyosarcoma of the thigh [48]

Necrotizing Fasciitis

Established cellulitis may progress to necrotizing fasciitis. The common forms of this disease are either caused by group A streptococcus or a mixed flora of anaerobic and aerobic bacteria. This later condition is known as Fournier's gangrene if it occurs around the perineum or Meleney's gangrene if it occurs on the abdominal wall (often associated with a recent operation wound).

In this condition the patient is toxic and complains of severe localized pain. The affected area often has a necrotic appearance from the underlying ischemia. Crepitus may be detected on examination. The diagnosis is made clinically. Once diagnosis is established the treatment is broad spectrum antibiotics (aminoglycoside, penicillin, and metronidazole), intravenous fluid resuscitation, and extensive surgical debridement. Numerous debridements are often required, the defect being closed at a later stage with tissue flaps or skin grafts [95, 100].

Neutropenic patients are at particular risk of developing a pseudomonas fasciitis known as ecthyma gangrenosum (Fig. 31.2) [8, 12, 34, 91]. The patient develops black necrotic ulcers on the buttocks and perineal region. These are initially small but without treatment will spread and coalesce. Unlike necrotizing fasciitis, the treatment is primarily medical with an antibiotic regime including aminoglycoside with an antipseudomonal cephalosporin or penicillin; granulocyte colony stimulating factor (GCSF) may help to revive the neutrophil count [4]. Close observation must be kept on the patient.

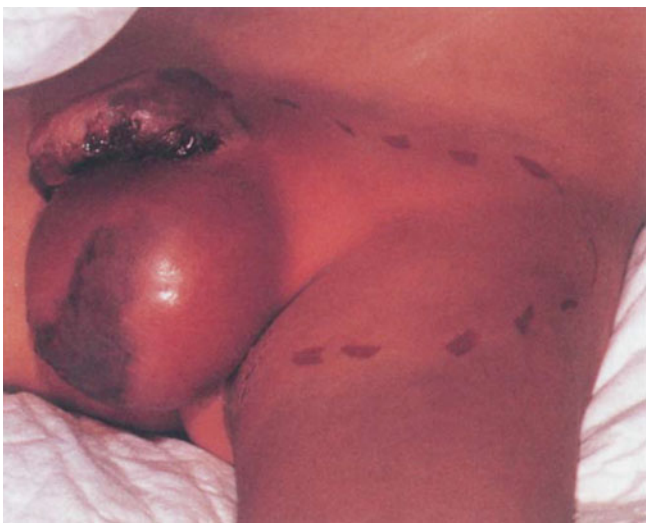

Fig. 31.2 Ecthyma gangrenosum. This 3-year-old boy undergoing treatment of acute lymphoblastic leukemia became profoundly neutropenic 10 days after receiving chemotherapy. He developed a pyrexia and a hot erythematous penis and scrotum with areas of necrosis. Blood cultures and swabs of the area grew Pseudomonas aeruginosa. He was treated with antibiotics and G-CSF and recovered fully without the need for surgical intervention

If large necrotic areas develop then late surgical debridement may be required. Occasionally a diverting colostomy may be necessary.

Compartment Syndrome

Compartment syndrome is a rare problem in childhood and so is often overlooked till a late stage. It can develop in the presence of severe septicemia and shock, particularly after pseudomonas septicemia in the neutropenic patient. In our experience a septic child may complain of lower limb pain; however, as the child is so systematically unwell this can be overlooked. On examination the foot is plantar flexed with tight lower leg muscle compartments. There may be reduced skin sensation over the foot or parasthesia. The pathognomonic sign is extreme pain on the slightest attempt to actively or passively move the foot. Loss of pedal pulses is a late finding. The differential diagnosis is deep vein thrombosis, lower limb cellulitis, or an ischemic arterial problem. The diagnosis is a clinical one; checking compartment pressures and Doppler ultrasound studies can be misleading [80].

Despite the fact that these children are severely ill, surgical decompression under general anesthetic should be performed urgently. All four compartments should be opened right down over the ankle using a medial and lateral incision. The sooner this is done the better the chances of saving the muscles. Though muscle compartments expand markedly after release, use of a loose subdermal tacking suture allows apposition of the wound edge without increasing the compartment pressures. This reduces the need for skin grafting and thus gives a much better cosmetic result. Hemostasis with bipolar diathermy must be done scrupulously as bleeding is a major problem postoperatively. Numerous debridements of dead muscle may be required, although this should be left until demarcation has occurred. Delayed primary closure, tissue flaps, or skin graft may be used subsequently.

Thoracic Complications

Surgeons may be consulted by oncologists for advice and surgical intervention in children with thoracic complications. The most common request is for biopsying of suspicious lesions on a chest radiograph following treatment – the usual histological finding is of a benign lung scar; however, diffuse fibrosis secondary to chemoradiotherapy, recurrence of tumor, or fungal lesion are other important diagnoses. In addition, surgical consultation may be required to help with management of pleural effusions or severe hemoptysis. Other complications that may arise from thoracic structures involved with tumor, or from iatrogenic procedures, e.g., central lines, biopsy, or thoracoscopy or mediastinoscopy include the following.

Superior Vena Caval Syndrome

The patient is unduly distressed following a procedure on the neck, e.g., after insertion of a central venous catheter or a biopsy. There is venous congestion of the face and neck with distended neck veins and petechial hemorrhage. Color Doppler ultrasound is useful to detect thrombosis in the great veins of the neck. Angiography via the catheter may demonstrate thrombus in the superior vena cava. Assessment at a low-radiation dose, 64-slice CT angiography has been helpful in diagnosing this condition [124]. Rarely, surgical intervention is indicated and most can be managed by supportive measures alone including heparin administration and removal of the central line from this location.

Superior Mediastinal Syndrome

This syndrome results in tracheal compression from trauma, biopsy of tumor (e.g., lymphoma of the mediastinum), or after thoracomediostinoscopy. Rapid intubation and treatment with antibiotics is indicated until the syndrome subsides. Rarely, a tracheostomy is indicated if this syndrome develops rapidly and unsuspected.

Pneumomediastinum, Pneumopericardium, and Surgical Emphysema

The "Michelin man" can be a complication after thoracoscopy from damage to the lung or the airway. This can be treated with antibiotics and a chest drain if a tension pneumothorax results. In rare instances this can occur as a complication of high-pressure ventilation therapy with dissection of air into their interstitial spaces.

Cardiac Tamponade

Cardiac tamponade may result after insertion of a central venous line and needs early recognition. Pericardiac drainage and replacement of a central line is needed.

Pleurodesis

Large malignant pleural effusions may cause respiratory embarrassment. If they do not settle with the treatment of the underlying disease they may require pleurodesis. Very little information has been published concerning children with malignant effusions; most pleurodesis has been undertaken for congenital lymphatic problems (chylothorax) or recurrent spontaneous pneumothorax.

Walker-Renard, et al. reviewed all the literature on pleurodesis of malignant lesions [110]. They found that response rates varied from 93 % with talcum powder to 0 % for etoposide. Doxycycline, tetracycline, and bleomycin all had success rates around 60–80 %. Bacillus Calmette-Guérin (BCG) vacine, quinacrine, and thioptepa were not assessed because of the lack of published data.

Talcum powder may be inserted into the pleural cavity using insufflation; this technique is best done under general anesthetic with thoracoscopy [119, 126], although it can be inserted as a talcum slurry by tube thoracostomy under local anesthetic. Adult respiratory distress syndrome (ARDS), pulmonary edema, and granulomatous pneumonitis have all been described as complications developing postoperatively.

Fungal Lung Lesions

Opportunistic fungal infections are an important cause of morbidity and mortality in the immunosuppressed child. Fungal infections include those caused by Candida albicans, Aspergillus, zygomycetes Cryptococcus, and Mycobacterium avium [101]. The usual presentation of pulmonary fungal infection is fever, malaise, cough, or chest pain. Other problems which may develop include progressive respiratory distress or life-threatening hemoptysis.

Plain chest radiography may show a cavitating lesion, a mass, or pulmonary infiltrates, followed by computed tomography (CT) scan to more accurately identify the lesion (Fig. 31.3a, b). Bronchoscopy with bronchioalveolar lavage may demonstrate fungal hyphae. Occasionally, either fine needle aspiration or an open biopsy of the lesion is necessary to achieve a definitive diagnosis. The most frequently identified organism is aspergillus. Treatment begins with appropriate antifungal agents, usually amphotericin B. Removal of the bulk of infected lung tissue improves the chances of eradicating the disease [101].

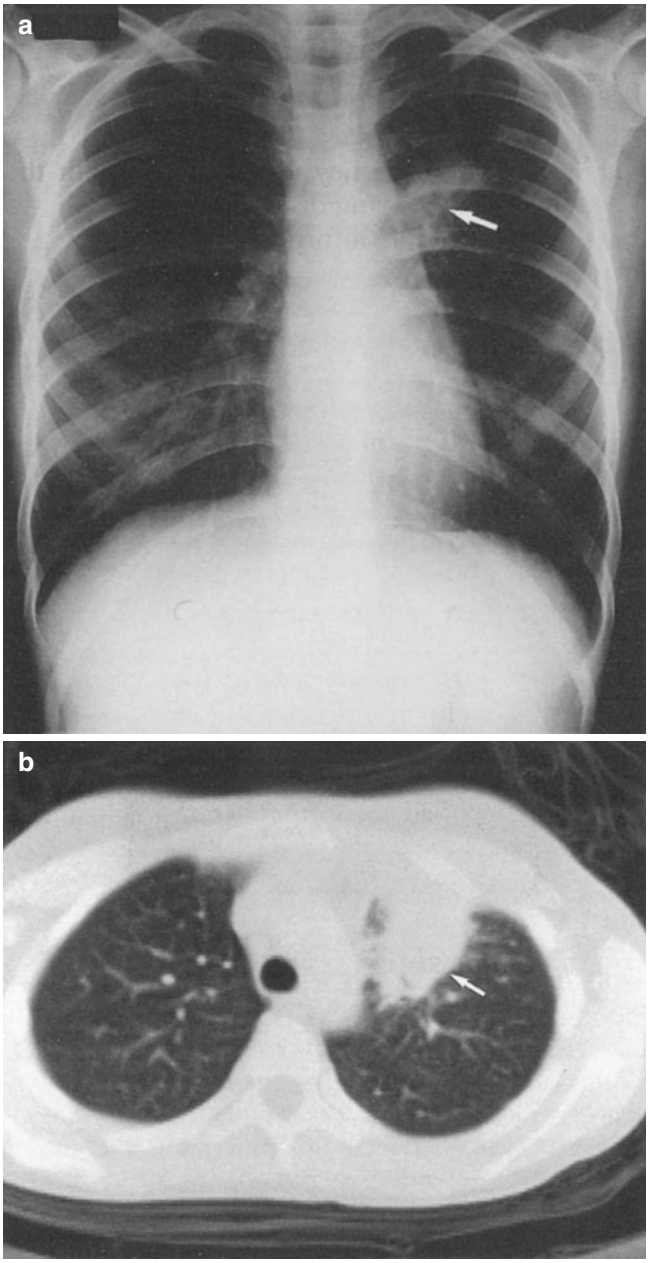

Fig. 31.3 (**a**, **b**) Aspergilloma. This patient, undergoing bone marrow transplantation for a relapsed leukemia, developed an invasive aspergilloma on her left upper lobe bronchus that was gradually eroding into her pulmonary vessels and causing her hemoptysis. Following a lobectomy and removal of the lesion she has made an uneventful recovery. (**a**) Chest x-ray of the patient. (**b**) CT scan of the same patient

Complications of Long Lines

The development of tunneled silastic central venous catheters by Broviac and Hickman are among the most important milestones in the progress of pediatric oncology. However, as with all surgical procedures they are not without significant complications if they are not performed with care by an experienced operator (Table 31.2).

Central venous lines can be placed either as an open cutdown or a percutaneous approach; the percutaneous approach can use either the landmark technique or the ultrasound guided technique. The ultrasound guided percutaneous approach combines the benefits of active visualization of the vein throughout and is gaining more advocates as it is shown the complication risks are reduced [102, 103]. The two major advantages of the ultrasound guided approach are that venous occlusion is much reduced approximately 2–3 % versus upto 25 % for open lines [5] and that redo surgery is significantly more straightforward. See Chap. 27 [64]. Like all procedures the operator will improve with experience and there are significant benefits to be gained from concentrating expertise [120].

Table 31.2 Complications of central venous catheters

	Complications
Insertion	Hemothorax/hemomediastinum
	Secondary tearing of the vein
	Pneumothorax
	Hematoma secondary to thrombocytopenia
	Air embolus
	Cardiac arrhythmias
Usage	Infection
	Thrombosis of tip/vena cava thrombosis/atrial thrombus
	Air embolus
	Line breakage causing bleeding, introduction of infection and air embolus
	Dislodgement
Removal	Air embolus
	Catheter embolus to right side of heart or lungs
	Dislodgement of septic thrombus

Table 31.3 Causes of acute abdominal pain in children with cancer

Diagnosis
Neutropenic enterocolitis
Pseudomembranous colitis (Clostridium difficile)
Cytomegalovirus/adenovirus enteritis
Acute graft-versus-host disease
Peptic ulceration (stress or steroids)
Pancreatitis
Hemorrhagic cystitis
Radiation enteritis
Obstruction
Perforation of bowel
Inflammatory cause
Intestinal lymphoma responding to treatment
Rupture of a Wilms' tumor
Hemorrhage into a tumor causing distension
Hepatic tumors
Sudden hepatomegaly stretching liver capsule
Hypercalcemia of malignancy

Complications of Catheter Removal

It is important to remember that most operative deaths associated with tunneled catheters occur when they are removed. The reasons for this may be that it is considered a simple procedure often attempted on the ward under local anesthetic or in the anesthetic room by the most junior surgeon. If the cuff is easily palpable near the exit site then it can be removed by dissection through the exit but otherwise it needs a further incision to be made over the cuff. The incision and exit site are then sutured closed [33].

Gastrointestinal Complications

Acute Abdominal Pain

Overview

The development of the acute abdomen in a child being treated for neoplastic disease often provides the medical and surgical teams caring for that child with a diagnostic and therapeutic dilemma. The cause of the symptoms may be the same as those in a child of similar age without cancer or it may be related to the treatment of cancer. Even simple conditions may be confused by the immunodeficiency, the use of steroids, or cytotoxic drugs and other factors associated with the cancer and/or its treatment. This may lead to localized conditions becoming generalized and the clinical signs of sepsis and inflammation being masked. In addition, the management decisions are complicated by the fact that many of these children are seriously ill at presentation and wound healing may be impaired.

Assessment of the risks of all possible causes is necessary to determine whether a laparotomy is required or if intensive medical treatment is preferable. The present thinking is that both have their place even for the ill child [88], and hence the medical and surgical teams should work closely together in initial assessment and ongoing management.

Table 31.3 shows the likely causes of acute abdominal pain in children with cancer and a suggested structured approach to their treatment. Specific conditions are discussed in detail below.

The Role of Diagnostic Imaging

Close cooperation with the radiology department is important for the diagnosis of the acute abdomen in children with cancer. While accurate diagnosis is essential, avoidance of invasive or time-consuming investigations is also important in these seriously ill children. Plain abdominal radiograph may show bowel dilatation, mucosal edema, a space-occupying lesion, free air (outlining the bowel wall), or pneumatosis intestinalis. An erect abdominal radiograph may show free air under the diaphragm though it may be normal in over 10 % of bowel perforations; lateral decubitus abdominal radiographs (right side up) may be used in the severely ill patient.

Abdominal ultrasound is an excellent noninvasive method of assessing the bowel for intestinal wall thickness, free fluid, and collections of fluid within the abdomen. Normal colonic wall thickness is $\leq$2 mm [12]. It can also pick up appendicitis, cholecystitis, and pyelonephritis [42, 78]. Ultrasound examination is relatively inexpensive, avoids ionizing radiation, and can be performed at the bedside. However, it must be remembered that ultrasound is operator-dependent and that excessive bowel gas, especially in the older child, can adversely affect the images; hence a negative scan does not necessarily rule out intra-abdominal pathology.

A CT scan is also noninvasive and requires both intravenous and oral contrast. Restless children will require sedation or general anesthetic for the study. In the immunocompromised patient, CT may demonstrate intra-abdominal abscesses, pseudomembranous colitis, typhlitis, graft-versus-host disease, radiation enteritis, and appendicitis [25, 72].

Contrast studies are beneficial in the relatively well child with chronic symptoms especially for diagnosis of strictures or radiation enteritis [70]. However, care must be taken in patients with colitis because of the risk of bowel perforation [69, 109]; for this reason we prefer to use water-soluble non-ionic contrast medium.

The Role of Endoscopy

Surgeons are frequently called on to perform either upper or lower gastrointestinal endoscopy on patients with unexplained abdominal symptoms. The number of causes of abdominal pain or bleeding are numerous and, together with judicious use of diagnostic imaging, endoscopy and relevant biopsies may be essential for accurate diagnosis [7, 67, 87, 89].

Obtaining biopsies at endoscopy is not associated with significant sepsis even in severely immunosuppressed patients [52]. Upper gastrointestinal endoscopy can be used to sclerose esophageal varices or inject bleeding ulcers. Careful performance of colonoscopy in patients with viral colitis, typhlitis, and severe graft-versus-host disease is essential in order to avoid overdistension of the colon and reduce the risk of perforation.

Assessment of Acute Abdominal Pain in the Child with Malignant Disease

1. Full history with particular reference to the time of onset of pain with regard to other treatments, changes in the neutrophil count and changes in other physiological parameters, i.e., pulse, temperature, blood pressure, respiratory rate.
2. Full examination with special regard to the abdomen looking for focal or generalized tenderness and signs of peritonism. Avoid rectal examination in neutropenic patients if possible.
3. Blood tests to include full blood count, urea, electrolytes, amylase, liver function tests. Clotting studies may reveal disseminated intravascular coagulation. Arterial blood gas sample may show signs of an unexpected metabolic acidosis suggesting ischemia or sepsis. Remember that white cell count, C-reactive protein, and erythrocyte sedimentation rate may all be normal in the presence of immunosuppression.
4. Septic screen to include urine, stool, blood cultures, and sometimes lumbar puncture.
5. Diagnostic imaging – see above.

Metabolic Causes of the Acute Abdomen

This usually arises from two main metabolic disorders.

1. Hypercalcemia of malignancy. This can be caused by metastases, osteolytic bone tumors, or humoral factors secreted by endocrine tumors [54], e.g., parathyroid hormone. The symptoms are those of hypercalcemia (weakness, brachycardia, constipation, polyurea, peptic ulceration, and pancreatitis). Fluid resuscitation and pamidonate is of value in the management of acute cancer-related hypercalcemia in children.
2. Tumor lysis syndrome. This was often observed in the treatment of bulky lymphomas following chemotherapy but can occur with any large bulky tumor undergoing necrosis. A rare complication of germ cell tumors and calcium levels should be monitored in all children with solid ovarian masses [120]. The metabolic upset includes hyperuricemia, hyperkalemia, and hyperphosphatemia with hypocalcemia. The patient presents with severe abdominal pain from uric acid crystal crisis, lethargy, andanuria [1, 11, 117, 122, 128]. Calcification of the gastric mucosa has been reported in association with tumor lysis syndrome in a child with non-Hodgkin lymphoma [10].

The management of such a high-risk patient includes intravenous hydration with at least 2–3 l/m^2 over 24 h using quarter strength saline, 5 % dextrose, alkalization of the urine with sodium bicarbonate 100 meq/l titrating the urine to a ph of 7.0–7.5, drug therapy, allopurinol 300–500 mg/m^2 for 3 days to prevent uric acid deposition, and careful monitoring of urine output, ph, urine electrolytes, and urea including calcium and phosphate. Occasionally, dialysis or hemofiltration may be necessary. Recombinant urate oxidase (rasburicase) may be used for prevention and treatment of tumor lysis syndrome in patients with hematological malignancies [112]. Rasburicase is a safe, highly and rapidly effective agent in the treatment and prevention of malignancy-associated acute hyperuricemia and could be considered the treatment of choice to prevent tumor lysis syndrome in children at high risk [81].

Specific Causes of Abdominal Pain

Intestinal Obstruction

Vomiting in a child being treated for malignant disease is very common; however, this must be differentiated from the emesis observed in numerous surgical conditions. Obstruction is due to mechanical blockage of the bowel and is common after operation for tumor [85, 99]. Characteristically vomit is bile-stained (green) in mechanical obstruction and in adynamic paralytic ileus. Auscultation is an important denominator. Table 31.4 shows the causes of intestinal obstruction.

Table 31.4 Causes of obstruction in relation to the bowel wall

Position of obstructing lesion	Diagnosis
Outside the bowel	Mass effect from large intra-abdominal
Tumor (compression)	Postoperative adhesions
In the bowel wall	Primary or secondary tumor within the bowel wall
	Intussusception – after surgery for Wilms' tumor [25], neuroblastoma or other
	Retroperitoneal procedures
	Strictures at an anastomosis, or from radiation enteritis,
	or enterocolitis paralytic ileus Opiate therapy
	Vincristine therapy
	[Adriamycin (doxorubicin)]
	Anticholinergic effects of medication
	Any of the causes
	of intestinal inflammation
	Any cause of intraperitoneal sepsis
Within the lumen	Tumor invasion of the lumen

It must be noted that sometimes a child presents with obstruction due to abdominal lymphoma. There are two clinical scenarios to be aware of. The first is with localized ileocecal disease causing the lead point of an intussusception. In this case localized resection with primary anastomosis is the treatment of choice; biopsy of suspicious mesenteric lymph nodes may also help in staging. If there is diffuse disease then a biopsy alone with intense supportive management is sufficient as the disease will rapidly resolve once chemotherapy is started [16].

Radiation Enteritis

Clinical features. Acute systemic upset, with nausea, vomiting, diarrhea, abdominal pain, and gastrointestinal bleeding; commonly complicates radiotherapy to the abdomen and pelvis. Although these acute symptoms usually resolve relatively quickly, about 5 % of patients progress to chronic complications after the completion of radiotherapy [38, 70, 115, 118, 125]. Radiation damage to the bowel is dose dependent, although other factors such as previous operations, peritonitis, and concurrent chemotherapy (especially actinomycin-D) may all contribute to worsening the long-term problems [24]. More than one complication may occur and new lesions may develop at later stages; radiation enteritis should, therefore, be considered to be a progressive disease [38]. Complications related to the large bowel include proctocolitis, colorectal and anal strictures, rectal ulcers, spontaneous necrosis, and fistulae to bowel, bladder, or vagina. Small bowel complications include bleeding, adhesions, strictures, malabsorption, spontaneous necrosis, fistula, and poor anastomotic healing [115]. Bleeding and fistula or perforation seem to represent the two ends of the spectrum of radiation enteritis suggesting that bleeding represents just mucosal trauma whereas full-thickness bowel wall damage must be present for perforation and fistula formation [38]. Malabsorption of fat, vitamin B12, and calcium may also occur [24, 115].

Diagnosis Diagnosis of the condition can be difficult. A history is important with regard to the time and dosage of radiation. An erect or supine abdominal radiograph may show features of obstruction or perforation. The most important investigations are contrast radiographs, and either small bowel studies or large bowel enemas. Radiological signs of small bowel disease include evidence of submucosal thickening, single or multiple stenoses, adhesions, and sinus or fistula formation [70]. Large bowel strictures usually appear smooth and concentric in outline [115].

Radiation enteritis causes severe villous blunting, distended lymphatics, and replacement of the normal columnar epithelium with cuboidal cells; a pattern consistent with the clinical findings of malabsorption. The submucosal changes include perivascular adventitial fibrosis. Microscopic changes can be found in macroscopically normal bowel [24, 115].

Treatment Radiation enteritis is a progressive disease [118]. Many patients can be treated conservatively; 5–20 % of patients may require surgical intervention [38, 49]. The main indication for surgery is perforation. Patients with strictures are best treated conservatively, initially with bowel rest and decompression followed by low residue diets [24, 118]. If obstruction or fistula makes operative intervention necessary then great care must be taken to handle the bowel gently and avoid resection wherever possible. A high incidence of anastomotic leaks follows bowel resection of irradiated bowel due to a compromised blood supply and poor wound healing. Extensive dissection of adhesions should be avoided and a side-to-side bypass operation considered in some cases. When a resection is inevitable, for instance after perforation or in response to chronic severe blood loss, then more generous resections should be made and the bowel temporarily exteriorized to avoid an anastomosis [38, 118].

Prophylaxis Many techniques have been used to exclude bowel from the pelvis during radiation therapy for pelvic malignancy using omental slings, tissue expanders, and distension of the bladder or retroversion of the uterus. The use of pelvic vicryl mesh placed at the level of the sacral promontory seems to be the best option in children [71]. In a study of eight children undergoing pelvic irradiation for malignancy who had a pelvic mesh placed before radiotherapy, none suffered from radiation enteritis [71].

Adhesive Obstruction Previous laparotomy, intra-abdominal or pelvic irradiation, and intraperitoneal bleeding or sepsis may lead to adhesion formation. Hence, a child with an intra-abdominal tumor is at significant risk of the late complications of adhesion formation. Operation for adhesions caused by radiotherapy is unrewarding and dangerous; the bowel is often unhealthy, easily damaged, and the adhesions rapidly reform. Adhesions secondary to previous operations are best managed conservatively but failure of the obstruction to resolve after 48 h and signs of ischemia are absolute indications for laparotomy.

Treatment of Obstruction in the Terminally Ill Child

Obstruction may occur in the advanced stages of childhood malignancy and although it may be a preterminal event, its management is important for symptom control. Traditional treatment includes stopping oral intake, insertion of a nasogastric tube, decompression, intravenous fluids, and correction of electrolyte abnormalities. Medical management includes anticholinergics, antiemetics, and analgesics. The role of steroids to reduce the degree of perineoplastic inflammation is controversial. Octreotide is a somatostatin analog that stimulates water and electrolyte absorption and inhibits water secretion by the small intestine. It may be useful in the treatment of obstruction and enteric fistulae [111]. Operative intervention with colostomy or bypass procedure may be justified. However, it may be more appropriate to manage these patients with intravenous opiates alone.

Neutropenic Enterocolitis

Though this condition may affect any part of the bowel, the most common area to be affected is the distal ileum and cecum and hence the term "typhlitis" is often used. It describes the clinicopathological syndrome of necrotizing inflammation of the cecum occurring in neutropenic patients. Though many cases of appendicitis complicating neutropenia had been described [30] (usually with fatal results), it was not until 1961 that Amromin first recognized that neutropenic enterocolitis of the cecum was a distinct entity [2, 65].

Incidence Exact incidence rates are difficult to collect because of the paucity of large studies and the difficulties of defining the relevant population. Several series have suggested an overall incidence of approximately 5 % in patients with acute leukemia [32, 74, 92].

Etiology The condition only develops in the presence of profound neutropenia. This may be disease induced [hematological malignancy, aplastic anemia and immunodeficient diseases such as human immunodeficiency virus (HIV)-induced acquired immunodeficiency syndrome (AIDS)] or secondary to drug treatment (chemotherapy for malignancy and bone marrow transplantation). The condition appears to be more common in acute myelogenous leukemia than in other forms [74, 88].

No definite cause has ever been identified but several hypotheses exist. Damage to the bowel mucosa allows invasion by colonic flora. Septicemia can then develop unchecked by the depleted immune system. Later, shock may increase the ischemia and thus perpetuate the vicious cycle. The initial mucosal insult is probably multifactorial including a direct effect of cytotoxic drugs on the mucosa, profound neutropenia, mucosal hemorrhage due to associated thrombocytopenia, stasis, and by changes in the bacterial flora secondary to prophylactic antibiotics [3, 88, 109, 114]. Why the cecum is most commonly affected is not clear though stasis and a relatively poor blood supply are possible explanations.

The theory that leukemic infiltrates of the bowel wall become necrotic in response to chemotherapeutic regimens causing damage to the mucosal wall and local hemorrhage appears plausible but there is little evidence, on microscopic examination, to support it.

Clinical Features Typically a patient undergoing induction chemotherapy is rendered neutropenic and develops problems between day 4 and 14. Symptoms and signs include diarrhea, vomiting, gastrointestinal bleeding, abdominal distension and sepsis. Examination usually reveals an ill patient with pyrexia, tachycardia, hypotension, and peritoneal irritation which may be diffuse or limited to the right iliac fossa [32, 39, 69, 74, 82, 88, 92].

Pathology Grossly edematous cecum, mucosal ulceration, congested mesentery, and hemorrhagic mucosa progressing to full thickness necrosis of the bowel wall are seen at laparotomy. Three characteristic anatomical distributions are seen. First, the necrosis is sharply localized to the cecum with relative preservation of the ileum; second, the cecum is involved in extensive disease with other portions of the colon and small intestine; and third the cecum may contain ulcers which also occur sporadically throughout the intestine [109].

The tissues are edematous and blood vessels are dilated and engorged. Tissue structures appear necrotic and frequently masses of organisms are seen within the lesions. Leukemic infiltration is rarely seen but when present is readily identifiable. The usual microscopic pattern is one of hemorrhagic necrosis involving the mucosa and submucosa with a striking lack of acute inflammatory reaction. Occasionally, an exudate resembling a pseudomembrane and consisting of fibrin and cell debris may be found overlying the most severely ulcerated mucosal surfaces. In later stages the process may progress to full thickness involvement of the bowel wall and perforation.

Differential Diagnosis Causes of acute abdominal pain in these patients include acute appendicitis, pseudomembranous

colitis, intussusception, pancreatitis, and pelvic abscess [32]. However, studies have shown that the most likely cause of diffuse or localized right iliac fossa abdominal pain in neutropenic patients is typhlitis [72, 74, 88, 109].

The most common organism isolated in septic patients with typhlitis is Pseudomonas aeruginosa [69, 109] though other Gram-negative organisms such as Escherichia coli and Klebsiella are also commonly found [32, 88, 92, 93, 114]. Gram-positive bacteria and fungi are occasionally found [32, 39, 109]. It is important to send multiple stool samples for analysis of C. difficile and its toxins to rule out pseudomembranous colitis.

Investigations Blood tests are of little help, except to confirm neutropenia (neutrophils <0.5). Other markers of infection and inflammation can be misleading due to the effects of steroids, cytotoxic drugs, and general bone marrow suppression.

Diagnostic imaging studies are essential. Plain radiographs of the abdomen may show a paucity of bowel gas in the right iliac fossa progressing to a right-sided, ill-defined soft tissue mass due to a fluid-filled atonic cecum [109]. Other signs include small bowel ileus, ascites, and occasionally cecal pneumatosis which may not appear until the terminal stages of the disease process. Contrast enema findings include thickened mucosal folds, "thumb-printing" due to edema of the mucosa and cecal contraction [69]. Filling of the appendix rules out acute appendicitis. Contrast enemas may precipitate perforation of the cecum in the debilitated child [72, 109].

The investigation of choice is abdominal ultrasound [78, 93]. Sonographic features of typhlitis include the so-called target sign of a rounded mass with a highly echogenic center and a wide hypoechoic periphery. Remember that this sign is also seen in malignant tumors of the bowel, intussusception, and bowel infarction [33, 38, 64, 69, 78, 93]. Appendiceal thickening may indicate an increased risk of serious complications from this disease process [66].

If the ultrasound is not diagnostic or there is a suspicion of a more sinister cause then CT scan should be used. It can detect transmural inflammation, cecal wall thickening, soft tissue mass, and pneumatosis [72, 93].

Having ruled out intussusception, the finding of a soft tissue inflammatory mass in the right iliac fossa by ultrasound or CT in a neutropenic patient with pain and sepsis should be considered diagnostic of typhlitis [42, 72, 93].

Management Management of these patients remains controversial, and both surgical [32, 74, 92, 108, 114] and conservative medical management have been advocated [39, 88]. Recently, large series have shown that aggressive medical treatment with bowel rest, fluid resuscitation, and broad spectrum antibiotics together with selective surgical intervention are associated with good outcomes [88, 93]. Children are treated with intravenous fluids and triple antibiotics (benzylpenicillin, netilmicin, and metronidazole) and closely observed with frequent reassessment by the surgical team, for signs of deterioration. Granulocyte colony stimulating factor (GCSF) has been employed to hasten the return of the neutrophils but thus far its benefits in typhlitis have not been confirmed.

The main indication for surgical intervention is perforation; the other indications for operation include persistent gastrointestinal bleeding despite correction of thrombocytopenia and coagulation defects or clinical deterioration despite maximal supportive therapy. The child will benefit from removal of the source of abdominal sepsis by resection of necrotic bowel and peritoneal lavage [31]. It is important to rule out surgically treatable causes such as intussusception or acute appendicitis. Prognosis is better if the patient is in remission at the time of the operation [32].

Using a combination of aggressive medical and selective surgical management the two largest recent studies have shown a mortality of approximately 8 % [88, 93].

Pancreatitis

Pancreatitis may rarely develop in some children with cancer following treatment with L-asparaginase, azathioprine, thiazide diuretics, and corticosteroids [63]. In addition it can complicate raised intracranial pressure [28] or hypercalcemia [6, 63]. After L-asparaginase up to 6.5 % of patients will develop pancreatitis [76]. L-asparaginase induced severe narcotizing pancreatitis has been successfully treated with percutaneous drainage used to flush the infected necrotic parts [5].

Clinical features include severe abdominal pain, vomiting, and shock. Diagnosis is confirmed by a raised serum amylase or lipase level [94]. Full blood count, urea and electrolytes, serum calcium, liver function tests, clotting screen, and an arterial blood gas (ApO_2) should be obtained. Chest radiograph can show signs of adult respiratory distress syndrome (ARDS). The abdomen should be assessed by either ultrasound examination or CT scan [78, 94] evaluated for edema, fluid collection, hemorrhage, necrosis, and other complications of pancreatitis.

Treatment is essentially medical, aimed at correction of the shock-like state of the patient with aggressive fluid resuscitation, nasogastric tube insertion, and drainage bowel rest. Intensive care is required if complications such as severe hypocalcemia, disseminated intravascular coagulation or respiratory distress associated with hypoxia develop [94]. Antibiotics may be required particularly in patients who are immunocompromised. Complications of pancreatitis include pancreatic abscess, which often requires urgent debridement and drainage. Pseudocysts may also occur but often will resolve, although in some instances may require drainage either percutaneously or by operative treatment. Octreotide has been used successfully in a child with L-asparaginase induced hemorrhagic pancreatitis [41].

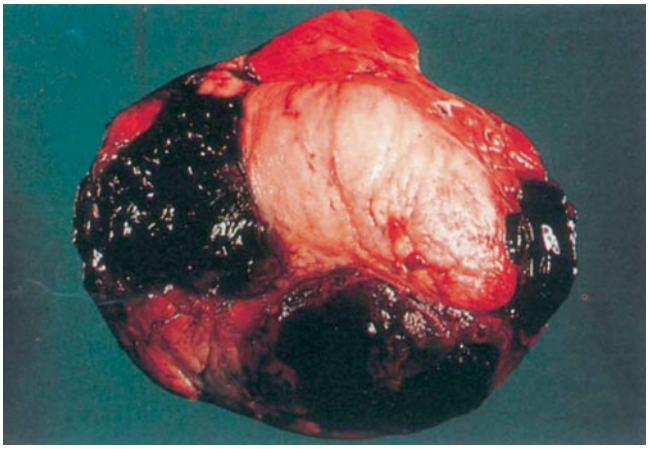

Fig. 31.4 Subcapsular hematoma in a Wilms' tumor. This was about to rupture and had to be removed as an emergency procedure

Cholecystitis

Though rare, cholecystitis should always be considered in the differential diagnosis of the acute abdomen. In particular acute acalculous cholecystitis is associated with stress, sepsis, and co-existing problems such as leukemia [123]. The usual presentation is with rightupper quadrant pain, pyrexia, and vomiting; jaundice and a palpable mass are sometimes found. Diagnosis is confirmed by ultrasonograph demonstration of gallbladder distension, thickening of the gall bladder wall, pericholecystic fluid collection, and lumen sludge. Patients with cholecystitis usually respond to conservative management with intravenous fluids and antibiotics [123]. Unresponsive cases may require percutaneous drainage or cholecystectomy, either laparoscopically or by open surgery.

Ruptured Tumor

Occasionally the cause of the acute abdominal pain is the result of a ruptured tumor. This has been described in patients with Wilms' tumor, hepatoma, neuroblastoma, and B-cell lymphoma. This is often the result of trivial trauma in a child with an unsuspected neoplasm, but can occur spontaneously. Tumor rupture results in a more advanced stage of the disease process and requires more aggressive treatment. Godzinski found that survival after acute nephrectomy for ruptured Wilms' tumor was good but that this was achieved at the expense of long-term morbidity from using doxurubicin (adriamycin) and radiotherapy [45] (Fig. 31.4). An arteriovenous fistula and hemorrhage has been reported as a complication following renal biopsy of a suspected bilateral Wilms' tumor [22].

Gastrointestinal Bleeding

Surgeons are occasionally asked to evaluate children on the oncology unit with gastrointestinal bleeding. This can range from small specks of altered blood to frank life-threatening hemorrhage. A list of conditions associated with gastrointestinal hemorrhage is presented in Table 31.5.

Table 31.5 Causes of gastrointestinal bleeding

Site	Cause
Whole bowel	Tumor infiltration of bowel
	Mucosal ulceration from chemoradiotherapy
	Lymphoma
	Acute graft-versus-host disease
	Thrombocytopenia
	Depletion of clotting factors
Liver	Porto-systemic hypertension and varices Impaired production of clotting factors Veno-occlusive disease
Esophagus	Esophageal varices viral/fungal esophagitis gastroesophageal reflux Mallory-Weiss tears
Stomach and duodenum	Peptic ulceration (stress or steroid induced)
	Gastric erosions
	Gastric antral vascular ectasia
Small bowel	Enteritis (see below)
Large bowel	Neutropenic enterocolitis
	Radiation enteritis
	Infective colitis (cytomegalovirus, herpes simplex virus, adenovirus, cryptosporidia, Giardia, Candida)
	Clostridium difficile infection
Non-oncological causes	Ulcerative colitis
	Meckel's diverticulum
	Anal fissure
	Hemorrhoids
	Intestinal duplication
	Hemangioma

Gastric Antral Vascular Ectasia. This is a condition that is being increasingly reported in BMT patients. It was first described by Rider1 back in 1953 but recently has been noted in patients undergoing transplantation [14, 45]. It causes acute and chronic blood loss, at endoscopy the appearance is of red patches within the stomach. Histology shows dilated submucosal capillaries, fibrin thrombi, and fibromuscular hyperplasia. There should be no evidence of GVHD, infection, or ulceration. Ohashi reported five cases all of whom had received conditioning therapy with busulfan and all had a history of microangiopathy [3]. Treatment was supportive but did not seem to respond to omeprazole in three of the five patients. Selective angiography had suggested high venous pressures so they were tried on the cardio-selective beta blocker Metoprolol with good results.

The Role of Diagnostic Imaging in Acute Gastrointestinal Bleeding

Plain radiographs are rarely useful but may show toxic dilatation of the colon in acute colitis. Contrast studies should be avoided as they yield little useful information and prevent more useful investigations such as angiography.

Angiography and red cell scans are difficult to set up and time consuming and thus should be held in reserve until upper or lower gastrointestinal endoscopy fail to provide a diagnosis. Angiography has the advantage of accurately detecting the site of the bleeding if the rate exceeds 1.0 cc/min and can be used to embolize a bleeding point. The disadvantage of angiography is that it is an invasive procedure. Radiolabeled red cell scan, on the other hand, can be used in cases with a slower bleeding rate (0.5 cc/min) but provides less precise anatomical location of the bleeding point.

The Role of Endoscopy in Acute Gastrointestinal Bleeding

Upper and lower gastrointestinal endoscopy are the most rewarding procedures in detecting the site of bleeding. In a bleeding peptic ulcer endoscopic injection of the ulcer bed with epinephrine and heater probe coagulation may stop the bleeding. In rare instances of liver damage associated with portal hypertension, esophageal varices may be the cause of bleeding and can be injected with sclerosing agents or banded.

Algorithm for Management of Gastrointestinal Bleeding

A recommended algorithm for the management of patients with gastrointestinal bleeding is shown in Fig. 31.5.

Esophagitis in the Immunosuppressed Patient

The esophagus is a frequent site for infection in the immunosuppressed patient. Patients present with dysphagia, retrosternal chest pain, fever, and upper intestinal bleeding. The patient's symptoms, oropharyngeal cultures and esophageal contrast radiography are not predictive of the cause – therefore, accurate diagnosis depends on endoscopy, mucosal biopsy, and brushings of abnormal-appearing areas and cultures [67].

Endoscopic findings range from discreet vesicles in herpes simplex virus (HSV) esophagitis to erosions and a spectrum of findings from esophagitis to gross ulceration which may complicate any infection and is compounded by gastroesophageal reflux. The most common infecting organism was HSV followed by cytomegalovirus (CMV). Fungal infection also occurs and is usually due to Candida albican [67]. Treatment is supportive with adequate analgesia and appropriate antiviral or antifungal therapy.

Infectious Colitis

Immunocompromised patients are at high risk for development of opportunistic infections. Affecting agents include Candida albican, pneumocystitis carnii, C. difficile, cryptosporidia, giardia, CMV, HSV, rotavirus, astrovirus, and adenovirus. Cytomegalovirus infection is particularly associated with colitis and bowel perforation [46]. Investigation of diarrhea includes sending stool culture for anaerobic organisms, C. difficile toxin, and microscopy and culture looking for protozoa, fungi, or viral infestation. Viral infection is of particular importance in the bone marrow transplant patients as clinically it is difficult to differentiate infection from acute graft-versus-host disease. The consequences of increasing the level of immunosuppression to treat graft-versus-host disease, when the patient is actually suffering from viral colitis, can result in a fatality. Sigmoidoscopy or colonoscopy are useful in making the diagnosis by providing biopsies from affected areas of colon for histology [55, 121, 127]. Histological examination of biopsies may show viral inclusion bodies or fungal colonies. Appropriate treatment for proven viral infection is with aciclovir or ganciclovir.

Clostridium-difficile-associated diarrhea is now a common problem in hospitals. Changes in the normal bacterial flora of the colon as a result of antibiotic therapy (especially clindamycin and in infants ampicillin) allows overgrowth of C. difficile with subsequent release of toxins that cause mucosal damage and inflammation [53]. Clinical presentation includes mild to moderate diarrhea, antibiotic-associated colitis with or without pseudomembrane formation, and fulminant colitis (Figs. 31.6 and 31.7). Associated symptoms include abdominal cramps and bloody diarrhea. In instances of fulminating colitis the patient presents with an acute abdomen, fever, tachycardia, and lethargy. Toxic dilatation may develop. Diagnosis depends on demonstration of C. difficile toxins in the stool; sigmoidoscopy or proctoscopy and biopsies may be beneficial as most disease is confined to the rectum or sigmoid. However, in 10 % of cases the colitis is limited to the proximal colon. Unfortunately, colonoscopy in these latter cases, in patients with fulminant colitis, may be complicated by perforation.

The treatment of C. difficile associated colitis is cessation of prior antibiotics, and treatment with vancomycin or flagyl preparations is mandatory. Barrier nursing of infected patients is recommended. Though severe colitis can usually be controlled within 48–72 h with antibiotics and appropriate supportive treatment, in some cases this fails and perforation occurs. Emergency celiotomy is mandatory for instances of proven perforation or severe refractory cases unresponsive to nonoperative management [15, 53] colectomy, ileostomy and construction of a Hartman pouch are often required.

Perianal Lesions

Perianal lesions include localized infections, abscesses, and other causes of inflammation such as graft-versus-host disease and radiation proctitis.

Measures to avoid perianal infections include the following points:

1. Avoid rectal examination and the use of suppositories and enemas.
2. Avoid constipation using laxatives/stool softeners.

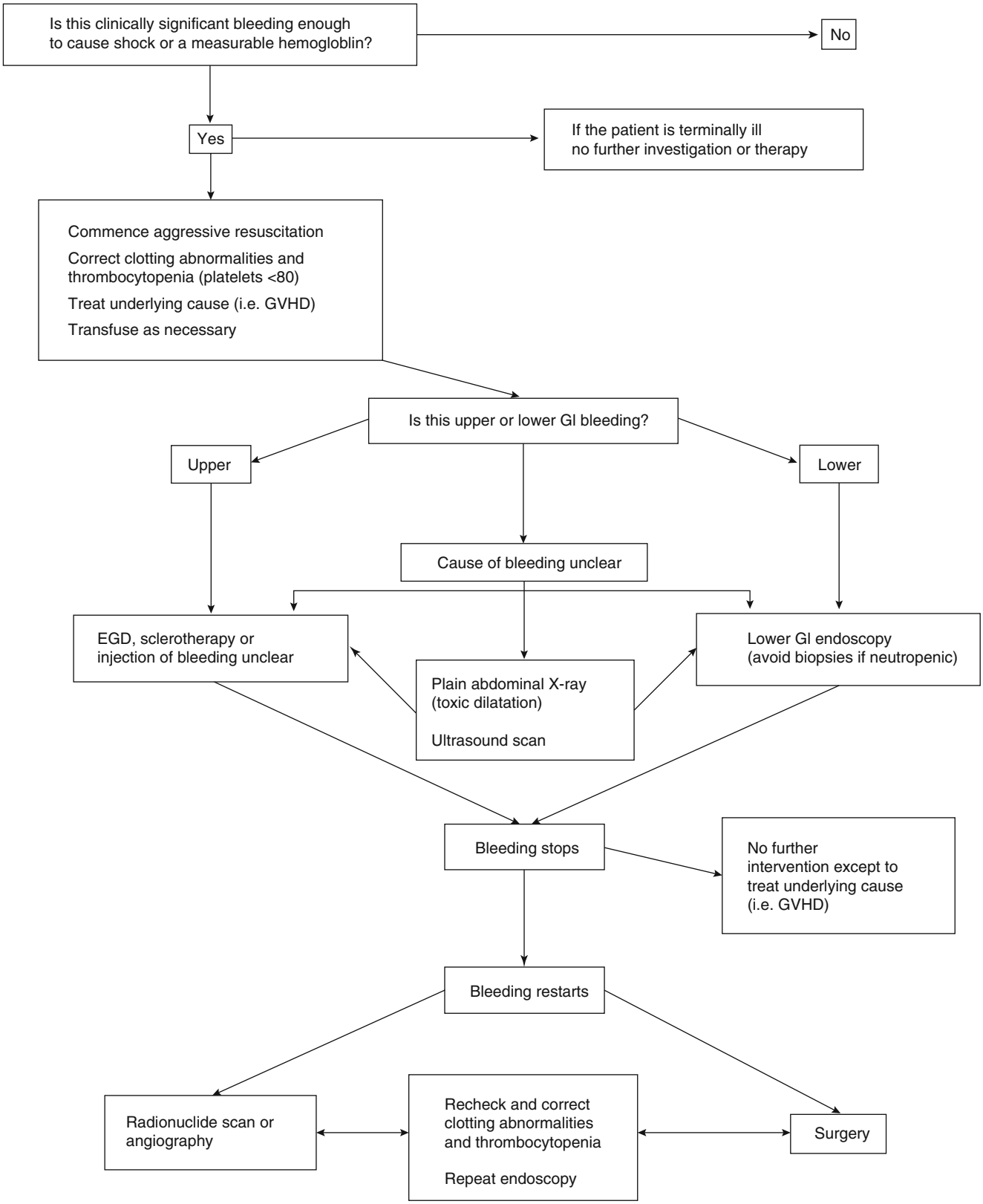

Fig. 31.5 Algorithm for management of gastrointestinal bleeding. *GVHD* graft-versus-host disease, *GI* gastrointestinal, *EGD* esophagogastro-duodenoscopy

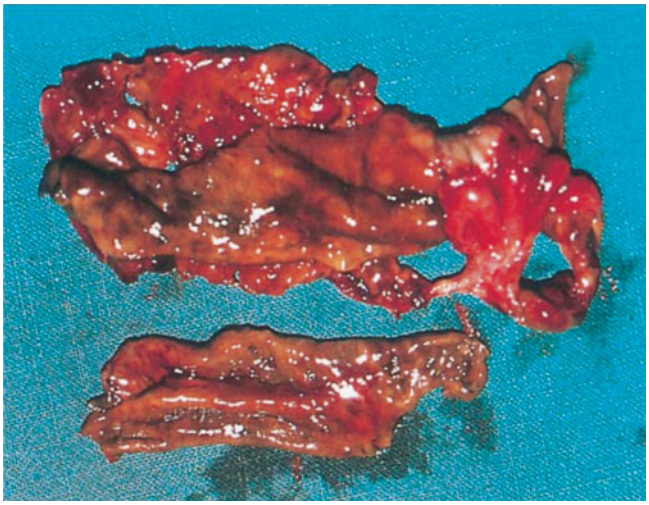

Fig. 31.6 Pseudomembranous colitis

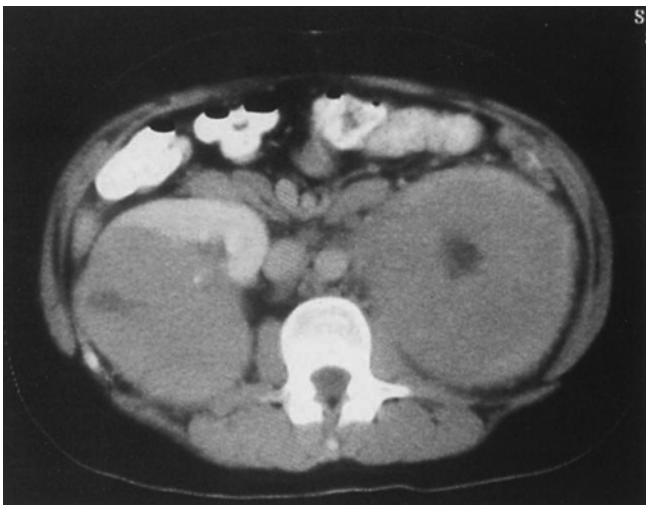

Fig. 31.7 Bilateral infiltration of the kidney in a patient with recurrent T cell lymphoma: CT scan showing both kidneys involved. This patient had to be treated by dialysis for renal failure

3. Avoid diarrhea. Clean perianal skin carefully with water (Sitz baths) and soft cloth. Barrier cream may reduce any skin reaction.

Symptomatic perianal infections are a relatively common occurrence in the neutropenic child, complicating 6 % of hospitalized leukemic patients [47]. In the case of the profoundly neutropenic patient, no abscess will develop because of the lack of neutrophils to produce pus. The usual findings are of a mixed culture of colonic organisms [4, 44]. Pseudomonas aeruginosa is particularly pathogenic in this region and may quickly progress to necrotizing fasciitis of the anorectal region [4].

Unlike the patient with an intact immune system where surgical incision and drainage of the abscess forms the basis of treatment, the immunocompromised patient should be treated primarily with broad spectrum antibiotics that cover anaerobic and Gram-negative organisms. The regime used includes intravenous benzylpenicillin, netilmicin, and metronidazole. Granulocyte colony stimulating factor may hasten the return of an immunological response though its role is yet to be proven. Constipation should be treated with stool softeners and laxatives. Pain relief may be required. These patients should be observed closely to make sure that no abscess develops when the neutrophil count rises and that the cellulitis does not spread resulting in a necrotizing fasciitis [4, 44, 77]. Indications for surgical intervention are obvious fluctuation, a significant amount of necrotic tissue, or progression to a necrotizing infection [47, 77]. There appears to be no increased morbidity or mortality in those requiring operation [47, 77]. The usual procedure is drainage of the abscess.

Genitourinary Tract Complications

Renal failure may be a complication seen after many years following treatment with cytotoxic agents and radiotherapy. Patients with neuroblastoma and Wilms' tumor are especially susceptible. Another complication seen in patients receiving therapy for bulky tumor is that of uric acid nephropathy discussed under metabolic causes of the acute abdomen (see "tumor lysis syndrome," above).

Hemorrhagic Cystitis

Hemorrhagic cystitis is a complication resulting from cancer therapy. Several causes have been identified, including alkylating agents, infections, and pelvic irradiation.

The oxazaphosphorine alkylating agents, cyclophosphamide and ifosfamide, are the most important causes. Cyclophosphamide was first introduced as an antineoplastic agent in 1957. Within 2 years Coggins, et al. had reported cases of significant hemorrhagic cystitis (Fig. 31.8) [21]. Acrolein, a liver metabolite of cyclophosphamide produced by microsomal enzymatic hydroxylation, has been identified as the cause of the cystitis. The exact mechanism of action is unknown but contact of acrolein with the urothelium causes sloughing of epithelium, development of inflammatory infiltrates, regeneration of a thinner epithelium, and formation of new blood vessels.

Numerous infectious causes are known. Viral pathogens include BK virus, polyoma virus, adenovirus, and cytomegalovirus. They are thought to be most significant in bone marrow transplant patients who are immunosuppressed and already sensitized by cyclophosphamide. These patients

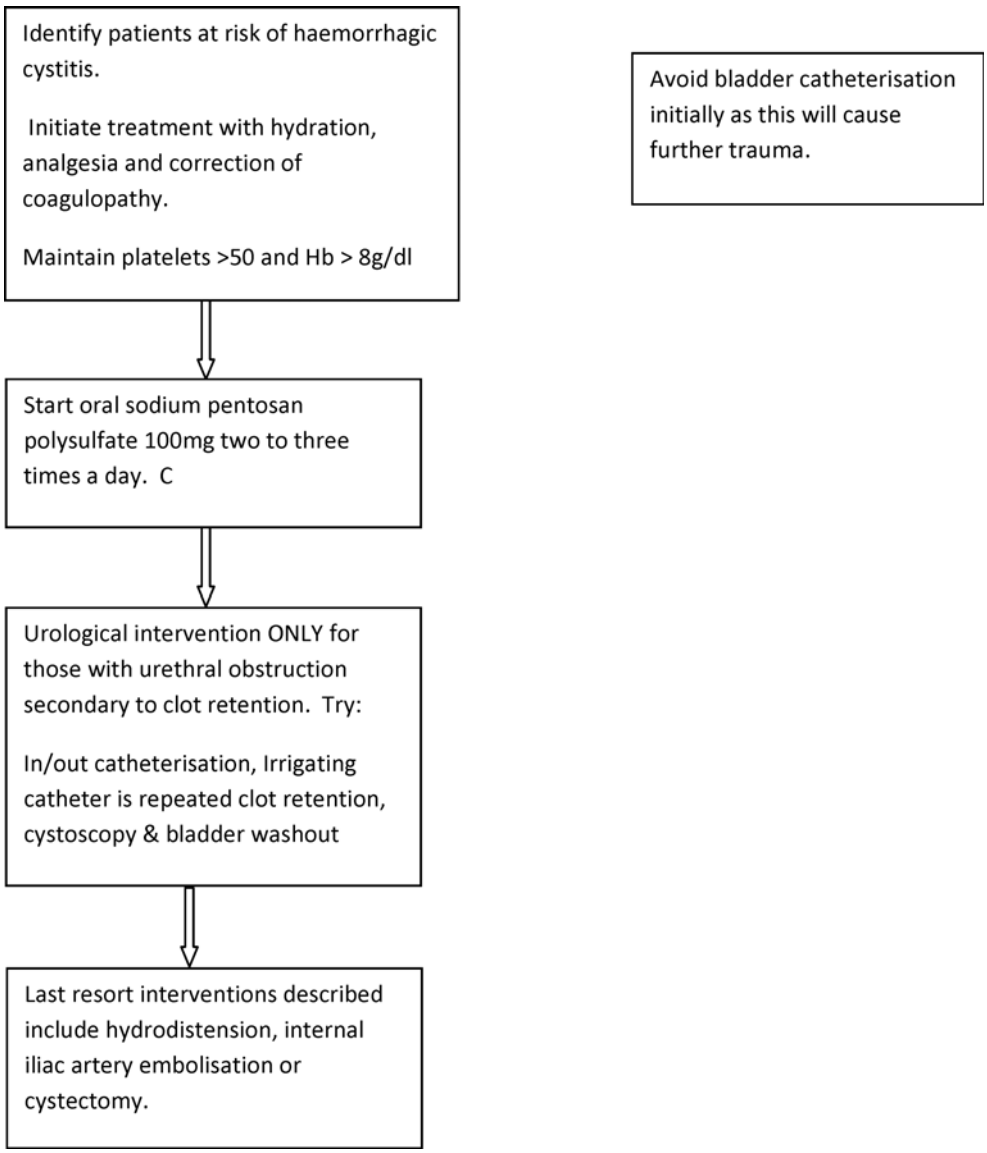

Fig. 31.8 Protocol for management of haemorrhagic cystitis used by Birmingham Children's Hospital since 2007

seem to develop a late hemorrhagic cystitis weeks or months after transplantation – there may be a link with graft-versus-host disease. Bacterial causes include E. coli, Klebsiella and Proteus, and fungal causes such as Candida albicans, Aspergillus fumigatus and Cryptococcus neoformans are also implicated in immunosuppressed patients [98].

Incidence

The incidence of hemorrhagic cystitis ranges from 2 to 40 % in adults; in children this complication seems to be less frequent at around 5–10 % [58]. The complication appears to be more frequent during the summer, suggesting that there may be a link with dehydration.

Clinical Features

The urological side-effects vary from transient irritative voiding symptoms, including urinary frequency, dysuria, urgency, suprapubic discomfort and stangury with microscopic hematuria, to life-threatening hemorrhagic cystitis [60, 96]. Late complications include bladder fibrosis, necrosis, contracture, and vesicoureteric reflux. The onset of symptoms is variable and may occur during the course of therapy or for several months later [60].

Though the severity of hemorrhagic cystitis does not appear to be dose-related, pediatric patients seem to develop cystitis at lower dosage and shorter duration compared with adults – this may be a consequence of the parenteral route of administration used in most children. There is no correlation with age or sex [58, 96]. However, it is a common complication of allogenic blood and marrow transplantation. In a recent paper they concluded it is more prevalent in matched unrelated donors and unrelated cord blood transplantation than matched related donors [31].

Table 31.6 Mesna prophylaxis given for cyclophosphamide therapy at the Bristol Royal Hospital for Sick Children

20 mg/kg of intravenous Mesna in 0.9 % saline given together with the cyclophosphamide over 1 h
76 mg/kg of intravenous Mesna in maintenance fluids (5 % dextrose and 0.225 % saline) over the next 23 h
Each urine is checked by dipstix for microscopic hematuria
If hematuria is found then a further 24 h of Mesna is given
Any further doses of cyclophosphamide receive the same regime

Table 31.7 Patients at risk of developing acute graft-versus-host disease

1. Bone marrow transplant patients [103]
2. Solid organ transplant patients
3. Transfusion of unirradiated blood products in neonates
4. Transfusion of unirradiated blood products in patients receiving immunosuppressive chemoradiotherapy

Diagnosis

The diagnosis is often made clinically. Urine culture must be obtained to rule out infection. Excretory urograms may show anatomical defects and ultrasound can be diagnostic of hemorrhagic cystitis [56]. Urine cytology is frequently used in adults but has not been useful in children. Urine should be examined by electron microscopy for viral infection. Definitive diagnosis requires cystoscopy and biopsy, and can be useful in ruling out other causes.

Prevention

Adequate hydration, diuresis, and frequent bladder voiding all reduce the concentration and the time for which the toxic urine is in contact with the bladder [60, 96]. Care must be taken not to cause overhydration as cyclophosphamide is known to cause damage to renal tubules and inappropriate water retention.

N-Acetyl cysteine and more recently Mesna (2– mercaptoethane sulfate) have been shown to reduce the incidence of cyclophosphamide-related cystitis [60, 98] by binding and inactivating the toxic acrolein (Table 31.6).

Treatment

Many different therapies have been suggested over the last 40 years, few of which have been rigorously tested by randomized controlled trials. Several of the management possibilities have only been described in adults [23, 40, 57, 59–61, 75, 79, 84, 90, 105] (Table 31.7). Fresh frozen plasma, platelets, and blood transfusion should be given as required.

Levine and Richie [60] suggested an algorithm for treatment based on the severity of the disease. Mild acute disease simply requires cessation of cyclophosphamide with good hydration and oral analgesia [58].

Formalin is no longer recommended. A review of the presentations and management of children with hemorrhagic cystitis after bone marrow transplantation at The Royal Hospital for Sick Children, Glasgow during the period between 1990 and 1997 showed only six children who developed the disease. During this 8-year period 91 children received a bone marrow transplant. The mean age was 12 years (range 5–15 years); all had prophylaxis with hydration and Mesna. The presentation of hemorrhagic cystitis occurred on average 40 days after chemotherapy (range 26–40 days) Hemorrhagic cystitis was heralded by a period of microscopic hematuria lasting 4–12 days (mean 9 days) [83]. Use of sodium pentasan polysulfate (SPP) has been described in adults and has subsequently been used with good effect in children at Birmingham Children's Hospital (see their algorithm Fig. 31.8) [27]. The mechanism of sodium pentasan polysufate is taken orally and excreted in the urine and though its mechanism of action is still poorly understood it is thought to reduce the urothelial response to inflammatory stimuli.

In haemorrhagic cystitis the bladder lining becomes markedly inflamed and friable. Catheterization of the bladder may simply exacerbate this and increase bleeding. In is important therefore that the pain associated with inflammation of the bladder is appropriately treated, up to and including opiate infusion. Clot retention should not be over diagnosed. The avoidance of unnecessary urethral catheterization can only be a good thing as it is unpleasant for most children let alone a teenager on chemotherapy. None of the children in the protocol group treated with SPP required catheterization either as a primary treatment or as developed complications requiring urological treatment [27].

Outcome

Although hemorrhagic cystitis secondary to cyclovesicoureteric reflux, bladder irritability and incontinence, and ureteric strictures. Renal function may be compromised by the outflow tract obstruction.

Patients who received more than 50 g of cyclophosphamide probably require long-term surveillance with blood pressure, urinalysis, and assessment of renal function. In addition there is a 4–7 % increased risk of bladder malignancy [98]. The risks are greatest in those patients receiving both cyclophosphamide and pelvic irradiation without any uroprotection with Mesna. Urine cytology can be used for early detection of new bladder malignancy [107]. Abnormal cytology or evidence of gross or microscopic hematuria requires further investigation with cystoscopy, bladder biopsy, and excretion urogram.

Other Conditions Affecting the Genitourinary Tract

Renal involvement in non-Hodgkins lymphoma is associated with a poor prognostic factor and renal function should be

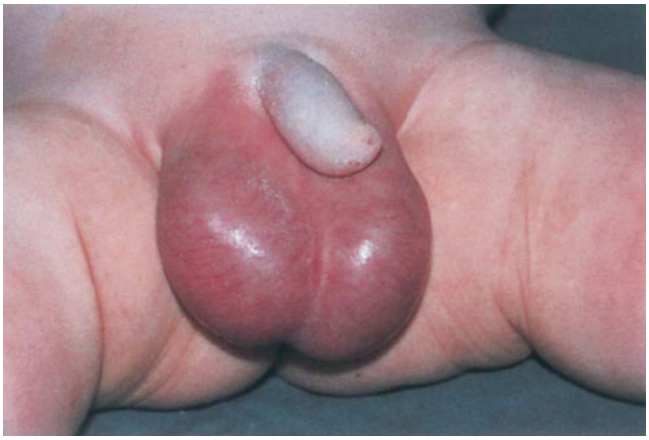

Fig. 31.9 Leukemic infiltration of the testes

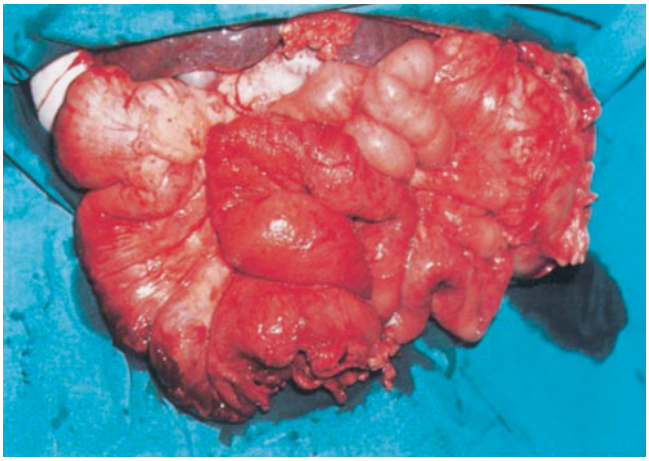

Fig. 31.10 This 4-year-old boy had severe graft-versus-host disease affecting the entire gastrointestinal tract and was managed conservatively for many months. Laparotomy was eventually performed, for persistent intestinal obstruction. Multiple fibrotic strictures were observed and resected. The patient is alive and well 6 years later

monitored closely. Renal dysfunction caused by direct tumor involvement may complicate therapy and shorten survival [17]. Ureteral obstruction may be caused by L-asparaginase, an effective antileukemia and antilymphoma agent as it is toxic to many organ systems. This could be managed by a double J stent [20].

Children with leukemia may present with acute testicular swellings which can be mistaken for other acute scrotal conditions, e.g., torsion of the testes, epididymo-orchitis. These children have leukemic infiltration of the testes (Fig. 31.9) and a biopsy usually confirms the presence of leukemic cells in the testes. This is often a presentation in boys who have had treatment for leukemia and have relapsed after their treatment is finished. The testis is considered a "sanctuary site" for tumor persistence and may require irradiation.

Intestinal Graft-Versus-Host Disease

Graft-versus-host disease is one of the major complications of bone marrow transplantation. The concept behind transplantation of allograft bone marrow is that new T lymphocytes will develop which will recognize the host as "self." However, mature T cells may also be transplanted that have already learned what is "not self" and thus may attack host cells that are covered with "foreign" class I and II major histocompatibility antigens.

Clinical Features

Most patients undergoing bone marrow transplantation will develop graft-versus-host disease without specific anti-graft-versus-host disease prophylaxis, at around 2–5 weeks post-transplant. The severity of disease depends on the closeness of the major histocompatibility match, whether the donor marrow has been T cell depleted, the degree of minor histocompatibility match (related to age, sex, race, etc.), and the type of prophylaxis used.

Table 31.8 Clinical grading of graft-versus-host disease

I	Maculopapular rash <25 % of BSA	2–3	Diarrhea
II	Maculopapular rash 25–50 % of BSA	3–6	Diarrhea
		>1000 ml/day	
III	Generalized erythroderma	6–15	Diarrhea
		>1500 ml/day	
IV	Generalized erythroderma with bulla formation	>15	Severe abdominal pain, and desquamation with or without ileus

The skin, followed by the gastrointestinal tract (Fig. 31.10) and liver are the most commonly affected organs. Cutaneous manifestations include pruritus and a fine erythematous or maculopapular rash. In severe cases blistering and desquamation of the skin may occur. A punch biopsy of the skin is required for definitive diagnosis and grading (Table 31.8) of the histological severity of the graft-versus-host disease. In severe disease, the lung can also be affected (though usually in the more chronic form).

Any area of the alimentary tract from the mouth to the anus can be affected. In one study MacGregor, et al. found that up to 70 % of patients with graft-versus-host disease had some degree of intestinal involvement [62].

The most common manifestations occur in the small bowel and reflect direct effects on the intestine and secondary infections that develop as a consequence of graft-versus-host disease [26, 35, 68, 102, 106]. Symptoms include

nausea, vomiting, abdominal cramps, and diarrhea. The diarrhea may be profuse and cause fluid and electrolyte imbalance. Nutritional problems may occur due to malabsorption and a protein losing enteropathy. Occasionally mucosal casts are passed per rectum. In severe graft-versus-host disease there can be generalized signs of adynamic ileus, peritoneal irritation, gastrointestinal bleeding, and perforation: this suggests full thickness inflammation with ulceration.

Investigations

Investigations include blood tests to assess the severity of electrolyte and serum protein levels with complete blood count and a coagulation profile.

Erect and supine abdominal radiographs may show signs of thumb printing, suggesting mucosal edema; pneumatosis may also be observed as erect chest radiographs (or decubitus abdominal radiographs) may show pneumoperitoneum. Contrast barium enema may show typical signs of gastrointestinal graft-versus-host disease but must be used cautiously in very sick patients because of the risks of perforation [36].

Radiological signs include thickened and effaced mucosal folds, thickened bowel wall and rapid transit. In subacute gastrointestinal graft-versus-host disease the contrast studies show a segmental patchy appearance of ulceration with normal and abnormal areas interspersed [36]. Use of CT scan shows fluid-filled, dilated, poorly opacified bowel loops and characteristic abnormally enhanced, thin mucosa.

Histology of intestinal graft-versus-host disease initially shows necrosis of individual intestinal crypt cells (apoptosis). Progression of disease leads to loss of whole crypts with mucosal denudation and ulceration. In extreme circumstances the entire mucosa may be sloughed off [37].

Endoscopic examination can be very useful. The endoscopic appearance of graft-versus-host disease shows edema, erythema, and frank ulceration but these signs are nonspecific [37]. Mucosal biopsy, however, may be characteristic [102] and can help differentiate graft-versus-host disease from opportunistic infections and other causes of colitis [7, 67]. Upper gastrointestinal biopsies have a higher yield than biopsies from the colon or rectum. However, as the disease is patchy the most affected area of bowel should be examined. Invasive procedures such as endoscopy or biopsy should be undertaken because the benefits are often life saving and the actual risks of serious complication are relatively low [7, 52, 102].

Other Problems in Bone Marrow Transplant Patients

In addition to problems with the gastrointestinal tract, the surgeon is occasionally consulted for advice and requests for biopsies to help diagnose problems in patients with liver and respiratory problems. We recently reviewed liver and lung biopsies taken from bone marrow transplant patients at the Bristol Royal Hospital for Sick Children with undiagnosed findings such as worsening liver function and increasing respiratory distress. Of eight liver biopsies (seven by Tru-cut and one by open operation) three were related to graft-versus-host disease, two were due to viral infection, two were related to transfusion siderosis, and one was an aspergilloma. Two open lung biopsies showed one case of cytomegalovirus pneumonitis and one case of radiation fibrosis. Overall we found the complication rate to be low and a number of unsuspected diagnoses were made that altered future management [42].

Treatment

Once graft-versus-host disease is documented the treatment is essentially medical with administration of high-dose steroid immunosuppression. The prognosis of graft-versus-host disease is worse if skin, gut, and liver are all involved. The only indication for surgical intervention is perforation of the intestine. Severe hemorrhage is best treated by aggressive medical management with correction of clotting abnormalities, platelet transfusion, and endoscopy. The results of surgical resection in the acute phase are universally poor. Once the disease is quiescent the areas of sloughed intestinal mucosa may heal by forming a stricture that may require bowel resection.

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Organ Dysfunction, Second Malignant Neoplasms, and Survival

32

Robert T. Russell and Anna T. Meadows

Introduction

Cancer is the second most common cause of death in children between the ages 1–14 in the United States; it is, surpassed only by accidents [1]. More than 12,000 children are diagnosed with cancer each year in the United States [2]. Nearly one third of cancers diagnosed in children of this age group are leukemias, followed by cancer of the brain and central nervous system (21 %), neuroblastoma (7 %), rhabdomyosarcoma (3 %), Wilms tumors (5 %), and Hodgkin disease (4 %). The most recent SEER data estimates incidence rates for 2005–2009 for childhood cancer (Fig. 32.1). During the last 25 years the 5 year survival rate among children for all cancer sites has improved dramatically from 58 % for patients diagnosed between 1975 and 1977 to 81 % for those diagnosed between 1999 and 2005 [3] (Table 32.1). Most of these 5-year survivors will be cured and will comprise an increasing population of adults. In 2005, there were estimated to be over 325,000 survivors of childhood cancer. Furthermore, 24 % of these survivors had survived more than 30 years since diagnosis and over 25 % were 40 years of age or older [4].

Despite the progress in survival rates for pediatric malignancies, the therapy responsible for this improved survival into adulthood can also lead to long-term health related outcomes, referred to as "late effects" that manifest months to years after completion of cancer treatment. Long term survivors are also likely to develop new cancers as a result of therapy. Some second tumors, such those that occur in the skin or the thyroid can be cured, but sarcomas and leukemia are often fatal. In this chapter, we present what is now known about treatment related organ dysfunction, second malignancies, and long term survival.

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Organ Dysfunction

Neurocognitive Effects

Cranial irradiation (CRT), high dose systemic chemotherapy, and intrathecal chemotherapy all are known to lead to neurocognitive sequelae. These therapies affect survivors of brain tumors, acute lymphoblastic leukemia (ALL), and non-Hodgkin lymphoma (NHL). The pathogenesis of the central nervous system damage is not completely understood. Particular groups of patients who are at greatest risk for these sequelae are those receiving the highest radiation doses, patients younger than age five at treatment, those receiving both CRT and systemic therapy, and children with primary brain tumors [5–8]. Studies have demonstrated that younger children treated for brain tumors may experience significant decline in IQ scores due to irradiation -induced destruction in normal white matter over time. These neurocognitive deficits are most often seen several years following radiation and can be progressive in nature. Studies have demonstrated that the neurocognitive decline over time may reflect the child's inability to acquire new skills and knowledge rather than loss of already acquired skill and knowledge [6, 8–11].

Although the "safe" dose of cranial irradiation in the treatment of children is still debated, it is clear that higher doses have a significant impact on cognition, especially in the younger patients. Silber et al. compared groups of children being treated for ALL and medulloblastoma with three different CRT doses (18 Gy, 22–24 Gy, and 32–40 Gy). He demonstrated that the group treated with the lowest dose of CRT appeared to gain IQ points when compared to the groups with higher doses of CRT. [12] This increase was likely related to the spuriously lower baseline performance. Neuropsychological evaluations are recommended for

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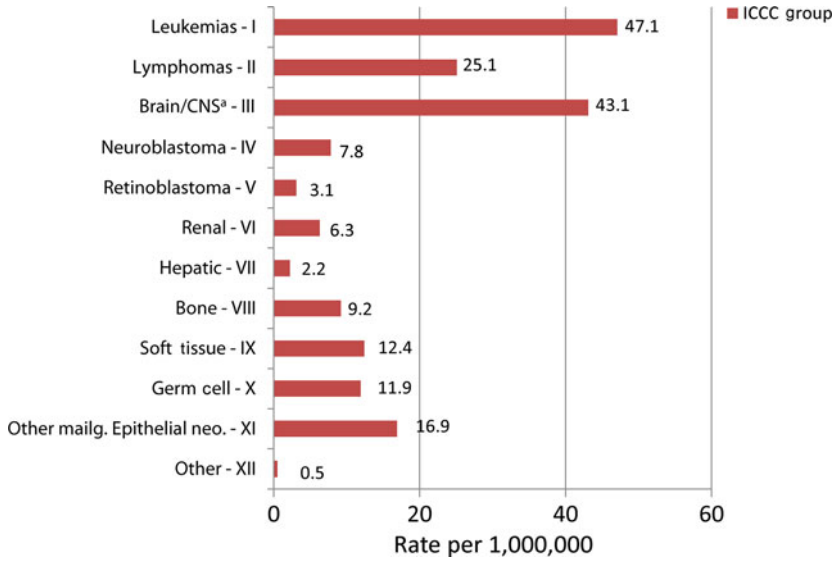

Fig. 32.1 Childhood cancer: SEER incidence rates 2005–2009 by International Classification of Childhood Cancer Group (includes myelodysplastic syndromes and Group III benign brain) under 20 years of age, both sexes, all races). [a]Rate for Group III (Brain/CNS) includes benign brain tumors. Rates are age adjusted to the 2000 US Std Population (19 age groups – census P25-1130). International Classification of Childhood Cancer is based on the ICD-O-3 [113] (Source: SEER 18 areas [San Francisco, Connecticut, Detroit, Hawaii, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJMLA, Kentucky, Louisiana, New Jersey and Georgia excluding ATL/RG])

Table 32.1 Trends in 5-year relative survival rates[a] (%) for children under age 15, 1975–2005

Site	1975–1977	1978–1980	1981–1983	1984–1986	1987–1989	1990–1992	1993–1995	1996–1998	1999–2005
All sites	58	63	67	68	72	76	77	79	81[b]
Acute lymphocytic leukemia	58	66	71	73	78	83	84	87	89[b]
Acute myeloid leukemia	19	26	27	31	37	41	42	49	60[b]
Bone and joint	50	48	57	58	67	67	74	70	72[b]
Brain and other nervous system	57	58	56	62	64	64	70	75	74[b]
Hodgkin lymphoma	81	88	88	91	87	97	95	96	95[b]
Neuroblastoma	52	57	55	52	62	76	67	66	74[b]
Non-Hodgkin lymphoma	44	53	67	70	71	76	81	83	86[b]
Soft tissue	61	75	69	73	66	80	77	70	81[b]
Wilms tumor	73	79	87	91	92	92	92	92	91[b]

Source: Horner et al. [3]
[a]Survival rates are adjusted for normal life expectancy based on follow up of patients through 2006
[b]The difference in rates between 1975–1977 and 1999–2005 is statistically significant ($P<0.05$)

patients when they are in remission and well if the planned therapy might be expected to impact neurocognitive function; repeat testing is recommended at clinically indicated points in their follow-up [13].

The effects of chemotherapy and systemic steroids on neurocognitive function in children with ALL are receiving increasing attention. Central nervous system (CNS) directed chemotherapy has largely replaced cranial irradiation in the treatment of ALL as the detrimental effects of cranial irradiation have become evident. However, there is evidence of long-term neurocognitive deficits in survivors of childhood ALL treated with chemotherapy alone. Although most of the studies found that general intelligence is relatively preserved, there are deficits detected in attention, executive function,

and complex fine-motor functioning. Risk factors for development of these deficits included younger age and female gender [14, 15]. Systemic corticosteroids, typically prednisone or dexamethasone, are an essential component of successful leukemia therapy. Despite their anti-leukemic properties, their potential impact on neurocognitive function has been a concern. However, ALL treatment protocols are increasingly shifting from prednisone to dexamethasone because of the greater therapeutic efficacy and superior CNS penetration of the latter agent [16–18]. However, its superior CNS penetration also raises concerns for its increased potential for neurotoxicity.

Pulmonary

The lungs are susceptible to radiation-induced injury and injury secondary to certain chemotherapeutic agents (bleomycin and high dose alkylating agents). Pulmonary irradiation (RT) is being used less for all lymphomas, but pulmonary metastases from Wilms tumor, rhabdomyosarcoma, and Ewings sarcoma continue to be treated with whole lung RT. Therapy for Hodgkin lymphoma in children has evolved over the years with more emphasis on chemotherapy and lower doses and volumes of RT to mediastinal and nodal disease. Radiation-associated lung damage is related to the total dose received, how the dose is fractionated, the total volume of lung irradiated, and the age at exposure [19, 20]. Radiation-induced lung injury includes an acute phase of radiation pneumonitis occurring 2–6 months following the exposure. This is followed by a late phase characterized by pulmonary fibrosis, which may present with dyspnea and a nonproductive cough [21]. Early studies of children treated for Wilms tumor revealed that radiation treatment at an early age led to significant reductions in lung volume, chest wall compliance and decreased chest wall growth over time [22]. Due to continued refinements in techniques, and to protocols that reduce the dose or eliminate RT, the incidence of radiation-induced pulmonary toxicity had dramatically decreased [23].

Pulmonary toxicity due to chemotherapy, like that associated with RT, also follows a pattern of early interstitial lung injury occurring up to several months after treatment and a late phase of pulmonary fibrosis as the most common sequelae [19]. It has been shown that pulmonary toxicity occurs after exposure to bleomycin, mitomycin-C, nitrosoureas (carmustine and lomustine), busulfan, and cyclophosphamide. The pulmonary toxicities of these agents are usually dose-dependent and can be exacerbated by concurrent or previous RT to the mediastinum [24–26]. Active approaches to decrease chronic pulmonary toxicity of therapy include awareness of cumulative dosage restrictions of offending chemotherapeutic agents, limiting radiation doses, and avoidance of primary and secondhand smoke.

Cardiovascular

The cardiovascular system is sensitive to certain chemotherapeutic agents and affected by mediastinal RT. The anthracyclines (doxorubicin and daunomycin) are most commonly associated with cardiomyopathy. It is estimated that as many as 60 % of childhood cancer survivors have been treated with anthracyclines as they are important in the therapy of sarcomas and neuroblastoma [27]. Anthracycline cardiotoxicity is believed to be from direct myocardial injury by the formation of free radicals. Repeated exposure and continuous myocardial injury leads to ventricular thinning, increased myocardial stress, and decreased ventricular function [28]. There can be early progressive cardiomyopathy that develops during therapy but the major problems become evident years after completion of therapy. The risk of developing cardiomyopathy from anthracyclines is dose-dependent [27]. Although it appears that no dose of anthracycline is free of cardiotoxicity with increasing follow-up, the overall incidence of anthracycline associated congestive heart failure is less than 10 % as long as the cumulative dose is less than 500 mg/m^2 [29, 30]. Additional risk factors have been elucidated that may also contribute to the risk of therapy-related congestive heart failure: younger age at treatment, female gender, pre-existing heart disease, increasing time since treatment, and concomitant mediastinal RT [31, 32].

Efforts to prevent anthracycline cardiotoxicity are being actively explored. Utilization of anthracycline analogs, liposomal preparations, and longer infusion times have not, however, proven to decrease the risk of cardiotoxicity [27, 33]. The most promising cardioprotectant is dexrazoxane, an intracellular iron chelator that scavenges free iron to prevent the formation of anthracycline-iron complexes responsible for myocardial damage. This has been shown to reduce cardiac injury as reflected by elevations in troponins in children undergoing therapy for ALL without reducing the antileukemic effect [34]. The use of angiotensin-converting enzyme (ACE) inhibitors, secondary to their ability to reduce left ventricular afterload and to slow progression of left ventricular dysfunction, has also been studied. A randomized control trial comparing enalapril to placebo demonstrated that ACE inhibitors may not prevent progression in left ventricular dysfunction although they did provide some improvement in afterload reduction [35].

Radiation-associated cardiotoxicity is progressive in survivors and differs from anthracycline cardiotoxicity. Congestive heart failure following mediastinal RT alone is quite rare, but it presents primarily as diastolic dysfunction as opposed to systolic dysfunction seen with anthracycline exposure [36]. RT has been linked to the development of restrictive cardiomyopathy, pericarditis, valvular heart disease, coronary artery disease, and conduction abnormalities

[28, 37, 38]. Coronary heart disease, due to radiation-induced endothelial injury, has been reported following mediastinal RT with a cumulative risk of over 20 % at 20 years, and appears to be dose-related [39, 40].

Gastrointestinal

Gastrointestinal complications in long-term cancer survivors consist of radiation-induced enteritis and fibrosis, chemotherapy and radiation induced hepatopathy, hepatic veno-occlusive disease, and viral hepatitis related to transfusion. Enteritis and fibrosis are the most common complication from radiation and may arise at any site along the gastrointestinal tract. Radiation has been associated with obstruction, ulcers, fistulae, enterocolitis, and incontinence [41]. The stomach and small intestine appear to be more sensitive to radiation that the colon and rectum [42]. Radiation enteritis leading to fibrosis, strictures, and dysmotility has been shown to be dose-dependent with a rate as high as 36 % for fibrosis when the radiation dose exceeds 60 Gy, but children may develop this with doses as low as 20 Gy [43]. Further insult to the gastrointestinal tract by chemotherapy or additional abdominal surgery may lead to clinically significant problems [44]. The effects of radiation are more likely to occur at lower doses if during preceeding surgery, the colon or small intestines are immobilized.

Chronic liver disease in long-term pediatric cancer survivors can be related to radiation or chemotherapy induced hepatic dysfunction, veno-occlusive disease related to therapy for ALL, or transfusion related viral hepatitis. Chronic liver toxicity has been reported in survivors who underwent significant radiation doses to liver [45]. Chemotherapeutic agents, especially methotrexate, in the absence of radiation, can be a late cause of hepatic dysfunction secondary to fibrosis. Hepatic veno-occlusive disease, also known as sinusoidal obstructive syndrome, is a potentially fatal outcome after stem cell transplantation. The mean incidence of veno-occlusive disease is estimated to be 15 %. Well established risk factors for this complication include younger age, hepatic inflammation, fibrosis, cirrhosis, previous abdominal radiation, and repetitive transplantations with myeloablative conditioning regimens. Defibrotide, a polydeoxyribonucleotide with antithrombotic, thrombolytic, and fibrinolytic properties, has been studied in an open-labeled randomized control trial in pediatric stem cell transplantation. This trial demonstrated a decreased incidence of veno-occlusive disease with the use of defibrotide from 20 to 12 % [46]. Finally, viral hepatitis may also be a cause of chronic liver disease in long-term pediatric cancer survivors. Most often this is related to transfusion of blood products prior to routine screening of blood products in 1992. Retrospective series of survivors of childhood cancer treated prior to routine screening of blood products estimated a 17 % rate of seropositivity for hepatitis C, a major risk factor for late onset of cirrhosis [47].

Renal

Cancer treatments associated with long-term renal complications include chemotherapeutic drugs, radiation therapy, and surgical nephrectomy. Certain antibiotics can also exacerbate the effects of chemotherapy. Chemotherapy-induced nephrotoxicity is most commonly seen and can manifest as acute irreversible renal failure, progressive chronic renal failure, or renal tubular dysfunction [48]. The most common nephrotoxic chemotherapeutic agents include cisplatin, carboplatin, ifosfamide, and methotrexate. These specific chemotherapeutic agents are commonly used in pediatric patients with Wilms' tumor, neuroblastoma, osteosarcoma, Ewings sarcoma, retinoblastoma, and germ cell tumors.

Cisplatin, and less so carboplatin, cause glomerular damage and distal renal tubular damage leading to diminished glomerular filtration rate (GFR). Most children receiving cisplatin have some acute loss of renal function, but there is considerable individual variability in severity. Long term recovery or stability of renal function is usually favorable. Electrolyte wasting, specifically a magnesium-wasting tubulopathy, occurs in essentially all patients treated with cisplatin. This may persist in some patients and up to 50 % of patients may require supplementation to prevent associated hypocalemia or hypokalemia [49]. Carboplatin is less nephrotoxic than cisplatin, but myelosuppression is its major dose-limiting side effect. Furthermore, carboplatin has a higher risk of renal insufficiency and tubulopathies when combined with ifosfamide than with cisplatin/ifosfamide combination therapy [50].

Ifosfamide nephrotoxicity most commonly leads to proximal tubular dysfunction, and less often, decreased GFR. During therapy, acute renal tubular dysfunction often resolves prior to the next course; however, permanent and progressive kidney damage may occur [51]. It is estimated that 30 % of children treated with ifosfamide develop a persistent nephropathy, and 5 % develop a clinically significant Fanconi syndrome. This syndrome is caused by treatment related dysfunction of the proximal tubule cells leading to excessive urinary excretion of glucose, protein, phosphate, bicarbonate, and potassium. Growth failure and rickets are sequelae of this syndrome if untreated.

Radiation induced nephropathy may present with azotemia, hypertension, and severe anemia; this may occur months to years after radiation [52]. Due to utilization of abdominal radiation for treatment, most studies examining radiation-associated nephropathy have been conducted in Wilms tumor survivors. Studies demonstrate a prevalence of renal insuffi-

ciency to be 10–12 % in those treated with radiation therapy. Significant nephropathy was seen in those patients who received doses in excess of 20 Gy and those treated with radiation in combination with ifosfamide chemotherapy [53, 54]. The elimination of radiation in early stage disease and the reduction in dose for those patients for whom radiation therapy is recommended has greatly reduced the prevalence of this problem.

The risk of end stage renal disease (ESRD) from surgical nephrectomy is quite low. In a long term follow-up study by The National Wilms Tumor Study Group, the estimated cumulative incidence of ESRD 20 years after diagnosis of unilateral Wilms tumor was 0.6 and 12 % for bilateral disease. This excluded those patients with concomitant genitourinary abnormalities and those with tumor suppressor gene *WT1* [55]. Fortunately, the risk of ESRD is remarkably low for most patients with unilateral Wilms, but a significant number of survivors have subclinical glomerular and tubular damage [56]. Performing nephron-sparing surgery for bilateral disease, avoiding nephrotoxic chemotherapy, and optimizing radiation strategies need to be utilized to decrease the risk of renal impairment.

Auditory Dysfunction

Commonly utilized agents in the management of childhood cancer that are potentially ototoxic include platinum-based chemotherapy, aminoglycoside antibiotics, loop diuretics, and radiation therapy. Each of these agents is capable of causing sensorineural hearing loss alone, and often times several of these agents are utilized in combination increasing the risk of auditory impairment. Specific risk factors for hearing loss as a result of therapy include platinum-based chemotherapy in combination with cranial irradiation, utilization of multiple ototoxic agents in combination, and young age at the time of exposure [57]. Diagnoses commonly associated with hearing loss include brain tumors, germ cell tumors, neuroblastoma, and osteosarcoma.

The mechanism of injury for both platinum- and radiation-induced ototoxicity is due to destruction of cochlear hair cells. Cisplatin and related agents are absorbed by the cochlear hair cells and result in ototoxicity through the production of oxygen free radicals. The initial hearing loss is generally in the high frequency ranges, but as cumulative doses increase there is progression of the injury toward the cochlear apex where lower frequencies are affected [58]. The risk of sensorineural hearing loss is greater for cisplatin than carboplatin (55 vs. 38 %), but the risk significantly escalates in children treated with both agents (84 %) [59].

Radiation-induced cochlear injury, similar to platinum-related ototoxicity, results in a high frequency sensorineural hearing loss. Limiting the radiation dose seen by the cochlea to 35 Gy or less leads to hearing loss in less than 3 % of patients. Mild to moderate hearing loss occurs in over 35 % of children exposed to doses exceeding 60 Gy [60]. Sensorineural hearing loss secondary to cancer related therapies may limit future language development, psychosocial development, and academic achievement [61].

Endocrine Abnormalities

As many as 40 % of childhood cancer survivors may have endocrine disturbances related to their underlying malignancy, radiation therapy, chemotherapy, and/or surgery [62]. These endocrine disturbances include growth hormone deficiency, hypo- and hyperthyroidism, adrenal insufficiency, precocious puberty, gonadotropin deficiency, and gonadal dysfunction [63].

There is a well-established association between cranial radiation and the development of pituitary hormone deficiencies. The growth hormone axis is the most sensitive of hypothalamic functions to radiation and can be affected at radiation doses of 18 Gy [64, 65]. The age of the patient at the time of radiation therapy may affect the degree of hypothalamic-pituitary damage sustained. Studies suggest that younger age at the time of diagnosis and treatment may lead to more deleterious effects on the axis [66]. Growth hormone deficiency is the most common endocrine problem following cranial radiation therapy. Severe growth retardation, defined as height below the 5th percentile, has been observed in as many as 35 % of survivors of childhood brain tumors and in 10–15 % of children treated for leukemia with prophylactic cranial radiation [67, 68]. Until growth is completed, it is recommended that children undergo semi-annual screening for growth failure and endocrine consultations should be obtained for those who are below the third percentile for height or weight, or are growing slower than 4–5 cm per year [63]. The use of recombinant growth hormone supplementation in these children is controversial, especially since there have been some reports that its use is followed by more second cancers than expected [69]. Growth can also be affected by radiation to the spinal axis in the treatment of brain tumors and to the lower extremities in the treatment of sarcomas of bone and soft tissue.

Both precocious puberty and delayed puberty may be a result of cranial radiation (CRT). True precocious puberty, early puberty, and normally-timed puberty with rapid progression have been associated with radiation doses ≥18 Gy. Female gender and younger age at treatment are significant risk factors for these disorders of pubertal development [70]. Furthermore, radiation doses >40 Gy may delay puberty through gonadotropin deficiency [71]. Annual history and physical in childhood cancer survivors treated with CRT along with screening for these disorders has been recommended.

Complications involving the thyroid gland include development of hypothyroidism, hyperthyroidism, and thyroid tumors (benign or malignant.) These thyroid disorders are primarily seen in children treated with radiation. Primary or central hypothyroidism may be seen depending on the radiation field and dose of radiation. Central hypothyroidism following CRT is related to effects on thyrotropin-releasing hormone and thyroid stimulating hormone in children who have received >40 Gy. Hyperthyroidism is observed much less commonly, estimated to be around 5 % of patients after radiation in children treated for Hodgkin lymphoma. Thyroid nodules and cancer may develop after radiation to the thyroid or neck. Recent evidence shows increasing risk of thyroid cancer with doses up to 29 Gy, beyond which the risk declines [72]. As a part of these patients' annual history and physical palpation of the thyroid gland and attention to symptoms of hypo- or hyperthyroidism is recommended.

Gonadal Function

For both males and females, all treatment modalities (chemotherapy, radiation, and surgery) can lead to gonadal dysfunction, whether it is due to germ cell depletion or abnormalities of gonadal endocrine function. In female patients, germ cell failure and ovarian endocrine dysfunction are synchronous. Two forms of premature ovarian failure have been described. Acute ovarian failure occurs in survivors who may lose ovarian function during or shortly after completion of therapy. On the other hand, some survivors who retain ovarian function after completion of therapy may experience premature menopause or menopause well before 40 years of age [73]. In general, older age at treatment, abdominal and pelvic radiation, and chemotherapy with alkylating agents have been associated with increased risk of ovarian failure in female cancer survivors [74].

In a study from the Childhood Cancer Survivor Study (CCSS) concerning ovarian function and reproductive outcomes, it was estimated that 6.3 % of their cohort of female cancer survivors developed acute ovarian failure (AOF). From their multivariable logistic regression model, increasing doses of ovarian irradiation, exposure to procarbazine at any age, and exposure to cyclophosphamide between ages 13–20 were independent risk factors for AOF. Precise data on the incidence of premature menopause and patient/treatment factors associated with the development of premature menopause in survivors of childhood cancer are limited, but it is known that ovarian radiation and alkylating chemotherapy are major risk factors. When comparing a small group of childhood cancer survivors to their siblings, there was an estimated 8 % risk of premature menopause versus 0.8 % in the sibling group. For those patients receiving both abdominal-pelvic radiation and alkylating chemotherapy, the incidence of premature menopause approached 30 % [73]. It should be recognized that those patients experiencing premature menopause are at increased risk of developing a variety of adverse health-related outcomes including osteoporosis, cardiovascular disease, and psychosexual dysfunction. These patients should be appropriately counseled and screened for these adverse health-related outcomes.

Pregnancy Related Outcomes

Following treatment for childhood cancer, concerns linger about the ability to have normal pregnancies and healthy children. This discussion does not include exposure to teratogenic agents during the first trimester of pregnancy. A detailed summary of the effects of chemotherapeutic agents during pregnancy is beyond the scope of this chapter and detailed elsewhere [75]. Long term cancer survivors' concerns focus on whether the therapy they received prior to pregnancy is a risk to their offspring. A recent report from the CCSS reviewed over 4029 pregnancies in 1915 female survivors of childhood cancer. They did not identify excess adverse pregnancy outcomes [73]. Radiation to the pelvis is more likely to result in infertility or pregnancy related complications. Reports from the National Wilms Tumor Study identified an increased risk of perinatal death, prematurity and low birth weight in the offspring of female long-term cancer survivors. They described 427 pregnancies of at least 20 weeks duration in women who had been treated with flank irradiation for Wilms tumor. Malposition of the fetus, premature labor, birth weight less than 2500 g, and gestation less than 36 weeks correlated with radiation in a dose-related manner [76]. A companion study from the CCSS of 6224 male survivors from the age of 15–44, who were not surgically sterile, reported a less likely hazard ratio (0.56) to sire a pregnancy than siblings. Among survivors, the hazard ratio of siring a pregnancy was decreased by radiation therapy to the testes with >7.5 Gy, higher cumulative alkylating agent dose, or treatment with cyclophosphamide or procarbazine [77].

In males, it is possible to have impaired germ cell function (azoospermia) without evidence of gonadal endocrine dysfunction and with considerably less chemotherapy or lower doses of radiation. Sertoli (germ) cells are more sensitive to radiation and cytotoxic effects of chemotherapy than the hormone-producing Leydig cells. Radiation to the testes is known to result in loss of germinal epithelium, decrease in testicular volume, and increase in follicle-stimulating hormone (FSH). These effects are dose dependent and will have differential effects following fractionated exposures of 0.1–6 Gy. At doses from 1 to 3 Gy, azoospermia may be reversible; at doses 3–6 Gy, azoospermia may persist for 3–5 years and less likely to reverse; however, irreversible damage occurs at doses >6 Gy [63, 78].

Chemotherapy induced germ cell injury primarily occurs following treatment with alkylating agents and heavy metals. Many of the agents decrease spermatogenesis in a dose-dependent fashion, regardless of pubertal status at the time of exposure. Among adult males treated for Hodgkin Lymphoma with mechlorethamine, vincristine, prednisone, and procarbazine (MOPP), exposure to five or more cycles has been associated with prolonged or permanent azoospermia in 80–100 % of survivors [79]. However, those patients treated with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) have a 30–50 % risk of azoospermia with a much higher likelihood of recovery when compared to those exposed to MOPP therapy [80]. In those patients treated with cyclophosphamide, gonadal injury has been reported to be reversible in the majority of patients several years after therapy. However, permanent azoospermia is seen in patients receiving higher dose therapy for prolonged intervals [81].

Leydig cell preservation in the setting of abnormal germ cell function in long-term male survivors is increasingly more common. Radiation-related Leydig cell damage is dose-dependent and inversely related to age at treatment. Prepubertal and peripubertal boys treated with testicular radiation doses exceeding 20 Gy for testicular leukemia experienced significant germ cell depletion and were at high risk for delayed sexual maturation. Adolescent and young adult males tolerated fractionated radiation doses greater than 30 Gy to the testes with only 50 % developing Leydig cell failure. It has been demonstrated that utilization of lower fractionated doses (<12 Gy) in prepubertal males led to normal pubertal maturation in most patients, although often with compensated Leydig cell failure [82]. The effect of chemotherapeutic agents on Leydig cell function is less clear. Following MOPP in prepubertal boys, normal pubertal progression and normal adult levels of testosterone are expected. However, gynecomastia with low testosterone and increased luteinizing hormone levels have been reported in similar patients treated in adolescence, and compensated Leydig cell failure without gynecomastia is common in adults [83, 84].

Recognition of these gonadal toxicities of radiation and chemotherapy are important to discuss with patients and their families. These discussions are particularly important in young men and women since they have not yet had children. Sperm banking for adolescent and young adult males is worthwhile and should be encouraged, whereas the value of harvesting and freezing ova for young females is still being studied.

Second Neoplasms

Data from large studies have demonstrated that childhood cancer survivors are at a sixfold increased risk of developing a second cancer, when compared with the general population [85]. The degree of risk and the type of subsequent cancers differ substantially according to type and dose of therapeutic exposures, and the presence of genetic predisposition. The more commonly reported second cancers in these survivors are tumors of the skin, breast, thyroid, bone, gastrointestinal, and genitourinary tract. Three subsets of subsequent neoplasms have been described: (1) malignant neoplasms, those with a behavior code of three as defined by SEER; (2) nonmelanoma skin cancer; and (3) nonmalignant meningioma [86]. Second malignant neoplasms (SMNs) are histologically distinct from the initial cancer and those that develop after completion of treatment for a primary malignancy. The most recent CCSS cumulative incidence estimate of subsequent neoplasms at 30 years after childhood cancer diagnosis is 20.5 %. The 30-year cumulative incidence by subsequent neoplasm subtype was 7.9 % for SMNs, 9.1 % for nonmelanoma skin cancers, and 3.1 % for menigiomas [86]. This CCSS study reported the cumulative incidence of subsequent neoplasms, the risk of subsequent neoplasms compared to the general population, the latency period observed for subsequent neoplasms, and specific risk factors. The 30-year cumulative incidence for subsequent neoplasms was highest for Hodgkin lymphoma and Ewing sarcoma. Female breast cancer and thyroid cancer were the most common subsequent cancers after 30 years. The highest risks for a subsequent neoplasm followed the diagnosis of Hodgkin lymphoma and Ewing sarcoma with standardized incidence ratios (SIR) of 8.7 and 8.5. The median time to the first occurrence of subsequent malignant neoplasms in this study was 17.8 years (range = 5–32 years). The median latency between primary cancer and second malignancy was shortest for leukemia (8.9 years) and longest for small intestine and colorectal cancers (23.1 years) [86]. Other risk factors for any subsequent neoplasm were female sex, older age at primary childhood cancer diagnosis, radiation therapy exposure, and primary diagnosis of Hodgkin lymphoma. For the purposes of this chapter, we will focus on several of the most common SMNs.

Breast Cancer

The British Childhood Cancer Survivor Study (BCCSS) assessed over 8000 females diagnosed with childhood cancer under the age of 15 who had survived at least 5 years from diagnosis. Overall, 81 breast cancers were observed in this cohort where 37.5 were expected. The most common type of breast cancer observed was infiltrating ductal carcinoma in over 70 % of patients. Significantly elevated standardized incidence ratios were found in survivors of Hodgkin's disease, heritable retinoblastoma, bone sarcoma, Wilms tumor, and soft tissue sarcoma [87]. Treatment of the primary cancer with RT was significantly associated with

the development of breast cancer. An elevated risk in young female Hodgkin's disease survivors has been found in many previous studies [85, 88], and there is convincing evidence that this is related to exposure to chest radiation. Consistent with other studies reporting increased risk of cancer among Wilms' tumor survivors [89, 90], the excess risk observed may be related to the radiation scatter dose to the breast tissue from treatment with abdominal irradiation or chest irradiation for lung metastases. Likewise, the risk of bone sarcoma and soft tissue sarcoma is likely related to RT exposure. However, underlying genetic predisposition, i.e., Li-Fraumeni syndrome, cannot be ruled out for increased risk of development of breast cancer in those survivors of bone and tissue sarcoma [89, 90].

Thyroid Cancer

Childhood cancer survivors treated with radiation for their first tumor are at elevated risk for thyroid cancer due to the exquisite sensitivity to radiation of the gland in children [91]. Sklar et al. reported the risk of thyroid cancer in a small cohort of patients with Hodgkin disease to be 18-fold that of the general population [92]. Risk factors for development of thyroid cancer are female sex, exposure to radiation therapy at a young age, and increased time since exposure to radiation [72, 93]. Furthermore, these studies have noted a linear dose–response relationship between thyroid cancer and radiation up to 20 Gy but a decrease in the risk at higher radiation doses. This is believed to be due to cell killing effect at higher doses of radiation [72, 94]. Until recently, there appeared to be no evidence to suggest an association with chemotherapeutic agents; however, Veiga et al. reported an increased risk of thyroid cancer associated with alkylating agents among patients receiving radiation doses up to 20 Gy [95]. The risk decreased with the higher doses of radiation demonstrating a cell kill effect.

Sarcomas

A recent nested case control study of secondary sarcomas by Henderson et al. identifies those patients at risk, details the relationship between chemotherapy and secondary sarcomas, and quantifies the risk related to radiotherapy and secondary sarcomas. They identified 105 secondary sarcomas among the CCSS participants as of February 2007 [96]. The median age of developing secondary sarcomas was 8.6 years and the median interval from first cancer to secondary sarcoma was 11.8 years. Radiation therapy was associated with a significantly increased risk for secondary sarcoma development (odds ratio = 4.1) after adjustment for primary cancer diagnosis, anthracycline exposure, and use of other chemotherapeutic agents. The risk of secondary sarcoma development was 15.6-fold compared to those with no radiation exposure in the group receiving radiation doses between 10 and 29.9 Gy. This risk escalated significantly to 114.1-fold in those patients exposed to radiation doses >50 Gy. Patients with a primary diagnosis of Hodgkin lymphoma or sarcoma were more likely to develop secondary sarcoma. Finally, they identified an increase in secondary sarcoma development related to exposure to anthracyclines after controlling for radiation dose [96]. For secondary sarcomas, the best hope for cure is early detection. This study highlights a specific group of survivors that are at high risk for secondary malignancy and should be under close monitoring by clinicians.

Bone Cancer

The risk of second bone tumors in childhood cancer survivors has been reported to be 133-fold that of the general population, with an estimated cumulative risk of 2.8 % [97]. Patients at a particularly increased risk are survivors of hereditary retinoblastoma, Ewing's sarcoma, and other malignant bone tumors. Data from the BCCSS demonstrated the risk of bone cancer increased substantially with increased cumulative doses of radiation to the bone and increased linearly with increased cumulative dose of alkylating agents [98, 99]. The increased risk for bone and soft tissue sarcomas in retinoblastoma survivors is likely attributable to the known predisposition to second primary cancers among those survivors who carry the germ-line mutation [100–102].

Gastrointestinal and Genitourinary Cancers

The CCSS and BCCSS highlighted the excess risk associated with development of gastrointestinal. Both studies estimated that childhood cancer survivors were 4.6–5 times more likely to develop a gastrointestinal malignancy than the general population [99, 103]. The risk was low among survivors younger than 20 years, but increases substantially with attained age. This risk was observed to be greatest following Wilms tumor and heritable retinoblastoma. Treatment with RT imposed a 3.3 fold risk of developing a subsequent gastrointestinal malignancy [99]. These findings led to recommendations that survivors exposed to more than 30 Gy of abdominal radiation have a colonoscopy at a minimum of every 5 years, starting 10 years after radiation exposure or at age of 35 years, whichever is later. Furthermore, development of genitourinary cancers is four times more likely in survivors than the general population, according to the BCCSS. Survivors of heritable retinoblastoma and those treated with chemotherapy were in the highest risk groups [104].

Leukemia

Early investigation estimated that the cumulative incidence of subsequent leukemia in cancer survivors, predominantly acute myeloid leukemia (AML), plateaus at approximately 2 % 10–15 years after the primary cancer therapy [105]. The majority of these patients were adults who had been treated for Hodgkin disease with the regimen MOPP. This regimen contains two alkylating agents that are known to be leukemogenic. During that last three decades, treatment for children with Hodgkin disease has relied less heavily on large doses of alkylators, with more emphasis on anthracylines in regimens such as ABVD [106]. However, children treated for bone and soft tissue sarcomas have received large doses of alkylating agents and they have experienced an increase in second malignant neoplasms and secondary AML [107, 108].Their treatment also included etoposide, an epipodophyllotoxins which led to many secondary AMLs in children treated for ALL. A more recent report evaluated the 14,358 survivors in the CCSS cohort, all of whom had survived at least 5 years from their primary neoplasm. A total of 96 survivors developed subsequent leukemia; 43 developed subsequent leukemia, 25 occurred 5–10 years, 5 at 10–15 years, and 13 at ≥15 years [109]. The 30-year cumulative incidence for development of subsequent leukemia was 0.31 %. The risk was highest between 5 and 10 years from primary diagnosis. However, contrary to prior reports [105, 110], there was a statistically significant increased risk of subsequent leukemia ≥15 years from primary cancer therapy. Similar to those patients developing leukemia in the first 10 years after diagnosis, those ≥15 years have a poor prognosis with a median survival of 2 years [109].

Life Expectancy for Childhood Cancer Survivors

As noted earlier, the 5-year relative survival rate among children for all cancer sites improved from 58 % for patients diagnosed between 1975 and 1977 to 81 % for those diagnosed between 1999 and 2005 (Table 32.1). Unfortunately, this increased rate of survival does not come without cost; significant long-term morbidity and mortality are associated with treatment of childhood cancer which increases long after completion of therapy. Recent reports from the Childhood Cancer Survivor Study (CCCS) assessing late mortality and late recurrence have begun to investigate these important questions.

The CCCS has analyzed the largest cohort for assessment of late morbidity and mortality among 5-year survivors of childhood and adolescent cancer, including death attributed to treatment-related causes, death related to progression of primary disease, and/or death related to other causes [111]. A comparison of all-cause mortality of 5-year survivors of childhood cancer to age-adjusted expected survival rates for the US population reveals an increased mortality for those with childhood cancer at all-time points up to 30 years from diagnosis. The mortality rates from 5 to 9, 10 to 19, 20 to 29, and 30+ years from diagnosis are 13.57, 6.00, 6.52, and 14.22 deaths per 1000 person-years, compared to expected rates of 0.66, 1.03, 1.44, and 2.07 for the general population [111]. These elevated mortality rates at 20–30 years after cancer diagnosis are associated with all of the above causes.

The mortality rate due to recurrence or progression of primary malignancy is 4.4/1000 person-years. Wasilewski-Masker et al. analyzed the CCCS cohort in an effort to further characterize late recurrence, defined as relapse of primary cancer more than 5 years following diagnosis. The cumulative incidence of late recurrence was 4.4 % at 10 years, 5.6 % at 15 years, and 6.2 % at 20 years for all childhood cancer survivors [112]. The majority of late recurrences (69 %) occurred 5–10 years after diagnosis, but late recurrences continued to occur up to 29 years after the original cancer diagnosis. Male survivors experienced a slightly higher incidence of late recurrences as did all other racial/ethnic groups compared with blacks. Those patients with Ewing sarcoma and astrocytoma were at the highest risk for late recurrence at 20 years (13 and 14.4 %, respectively), while survivors of kidney tumors had the lowest risk for recurrence at 20 years (0.9 %) [112].

Armstrong et al. analyzed standardized mortality ratios (SMRs) following childhood cancer among the CCCS cohort including subsequent malignancy, cardiac, pulmonary, and other medical causes of death. Compared to age-, calendar year-, and sex-specific rates for the US population, survivors of childhood cancer were 15 times more likely to die of a subsequent cancer, 8.8 times more likely to do of a pulmonary event, seven times more likely to die from cardiac-related events, and 2.6 times more likely to die from other medical causes [111]. This highlights the fact that therapies essential for cure of the primary malignancies likely have long-term consequences many years after the risk of primary tumor recurrence has past. Patients originally diagnosed with medulloblastoma, Hodgkin's disease, and Ewing's sarcoma had very high SMRs for death due to second malignancy (23.4, 20, and 20, respectively). SMRs for cardiac-related deaths were elevated in survivors of renal tumors and Hodgkin's disease. This effect is likely due to exposure to anthracycline chemotherapy and chest/pulmonary radiotherapy. Those survivors of acute myeloid leukemia and neuroblastoma were at the highest risk for pulmonary death. Interestingly, no statistically significant elevated SMRs were seen for death due to external causes (motor vehicle accidents, other accidents, and suicide) in this specific population [111] (Fig. 32.2).

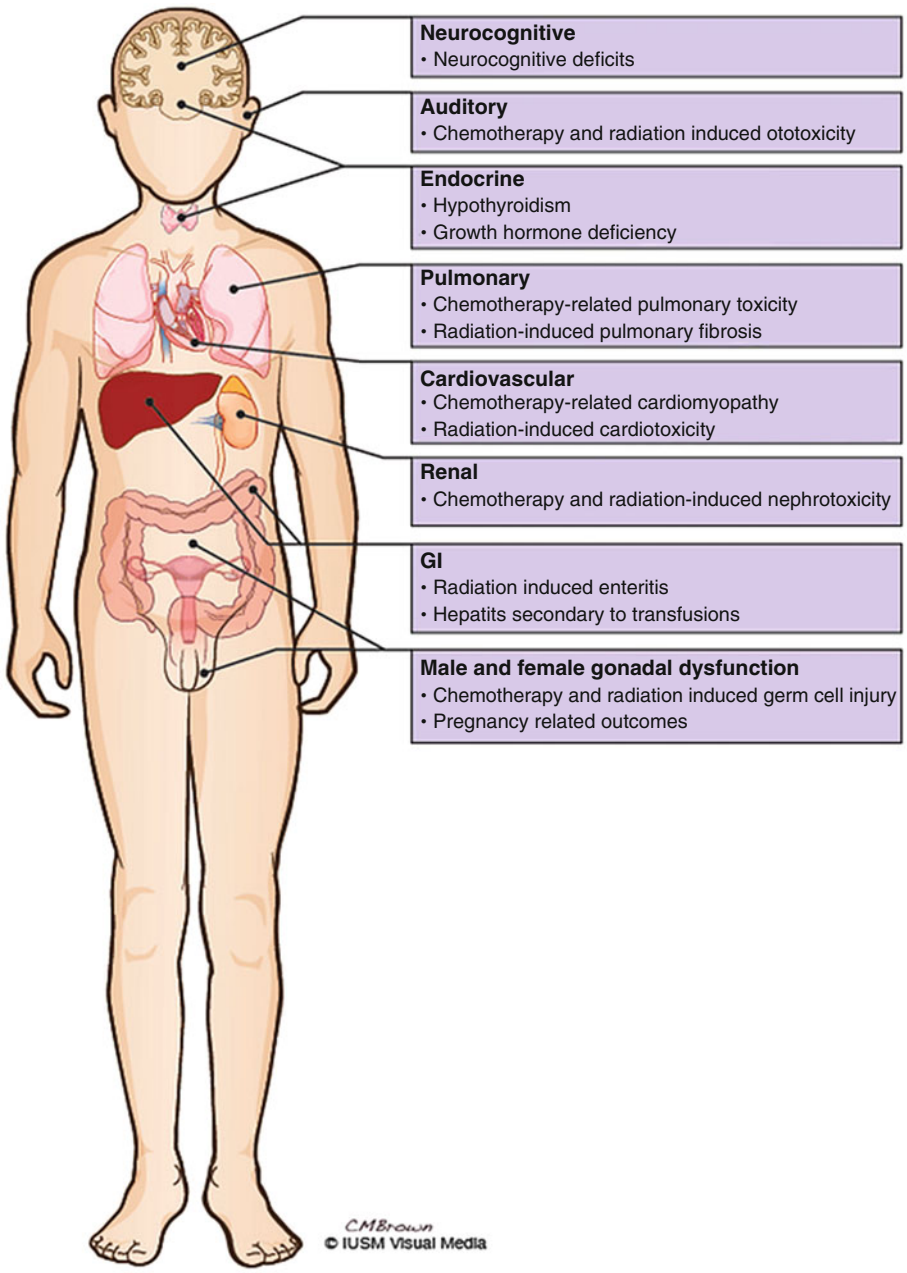

Fig. 32.2 Side effects of chemotherapy and radiotherapy in the pediatric population

Conclusions

Most adult survivors of childhood and adolescent cancer will not be seen during their adult lives by pediatric oncologists or pediatric surgeons. But it is critically important that survivors continue to be monitored and the results of follow up studies be reported. Late effects and chronic health conditions including second malignancies may not become evident until late in the lives of survivors. Since therapy has been altered during the last four decades because of our increased knowledge of late effects, it will also be important to compare the late effects of earlier cohorts with those who may have benefited from more recent, presumably less toxic, therapy.

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Management of Childhood Solid Tumours in Third World Countries

33

Larry Hadley

The concept of the "Third World" is a political construct that through common usage has become synonymous with "developing countries" which is itself a euphemism for "undeveloped countries". The current politically correct, marginally less patronizing, terminology is "resource-poor" countries or "low-income" countries, however they are probably best described as simply "poor".

Within our understanding of these terms there lies a range of economic and social circumstances encompassing the new economic giants of China, Brazil and India as well as the "not-developing" countries of sub-Saharan Africa, but generally these countries are characterized, if not defined, by poverty, a colonial past, poor education standards particularly amongst women, and economic bondage to rich countries [1]. With the exception of Haiti, all not-developing countries are in sub-Saharan Africa (Fig. 33.1).

It can rationally be argued that in such poor countries although the health needs are great childhood solid tumours are not amongst the most pressing. It is undeniable that infectious diseases, poverty and malnutrition are much more important in terms of the numbers of affected children and the morbidity and mortality that they cause [2]. The Millennium Development Goals were established to address these major issues, and although many countries are falling behind their targets, progress is being made [3].

The management of childhood solid tumours however should not be seen in isolation from public health measures to improve the health of populations. Primary Health care initiatives are at least in part designed to identify patients who are suffering from treatable illness that requires more sophisticated management, and to expedite access to the necessary facilities if possible [4]. It must be clearly understood that many, if not most, solid tumours of childhood are treatable and potentially curable diseases, and that energy spent in the management of these children is amply rewarded in terms of quality and length of life and is a cost-effective exercise. Treatment for curable and potentially curable cancers has been described as "a fundamental right of all children in the world" [5]. Cost-effectiveness is maximized by targetting those tumours that occur frequently in a given geographical area, that have a reasonable prognosis and can be treated by regimens that are relatively inexpensive and of low toxicity.

It is difficult to accommodate the wide spectrum of constituencies within the Third World in a single vista and emphasis has been given here, as an exemplar of the Third World, to the most deprived region of the world, sub-Saharan Africa.

Africa is a large continent, larger than United States of America together with the whole of Europe, the Indian subcontinent and Australasia. This vast area is not an homogenous geo-political entity and socio-economic conditions range from the relative wealth of the Arab states in the north and South Africa in the south to include some of the poorest countries on earth. Data relating to Africa are often skewed by inclusion of these relatively wealthy extremes and the true scale of the poverty of sub-Saharan Africa tends to be masked.

Africa is home to 1 billion people with an anticipated increase of 0.5 billion over the next 15 years [6]. It must be remembered that all population increases are children to begin with and already between 40 and 50 % of the total population of sub-Saharan Africa is under 16 years of age [7].

Health Economics

"The African region has 24 % of the burden (of disease) but only 3 % of health workers, commanding less than 1 % of world health expenditure" [8].

The countries of sub-Saharan Africa form part of the "not-developing" world and most are facing their fourth consecutive decade of economic recession [7]. Governments and individ-

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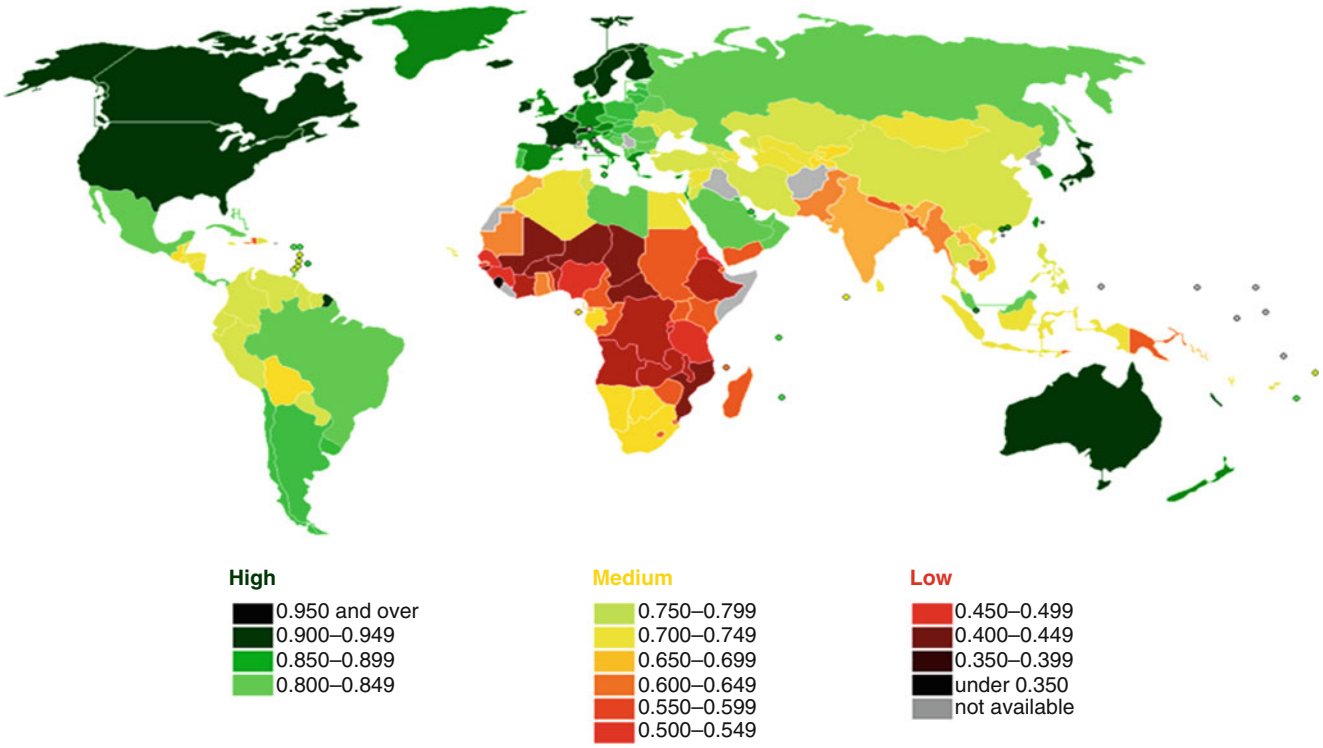

Fig. 33.1 UN map of human development

uals in the region are therefore worse off today than they were in the 1970s. Despite the region being blessed with considerable mineral and oil reserves, suggesting that it is disingenuous to term the region "resource poor", little of the derived benefit filters down to the common man. The desert North African states, although currently plagued with political upheaval, have larger economies based upon oil and agriculture and in most geographical, social, economic and political aspects are quite distinct from the sub-Saharan region.

Along with a failing economy sub-Saharan Africa lacks basic infrastructure and this is particularly acute in the provision of surgical services [9] but these deficiencies are only one reflection of deficiencies in health care in general and fundamental hospital resources such as running water, electricity and oxygen cannot be taken for granted [10, 11].

All health budgets are finite sums of money; some large, some small, but all finite. Because these sums throughout sub-Saharan Africa are meagre, ranging from US$17.00 per person per year in Democratic Republic of Congo to US$819.00 per person in South Africa [12], there is limited funding for any but the most urgent priorities.

Only seven sub-Saharan African countries can afford more than US$100 per person per year for healthcare and 15 countries spend less than the US$58.00 afforded by Haiti [12]. In the United States comparable expenditure is currently US$7285.00 per person, and in the United Kingdom US$3222 [12].

It is facile to suggest that reorganization of a nation's budget would allow health expenditure to rise to any significant degree as health expenditure relative to Gross Domestic Product is higher in several African countries than it is in North America and Europe [13]. The meagre sums available for health care reflect the real poverty of the region. However, the dated perception that governments in Africa are more corrupt and less efficient than anywhere else in the world has led to major donor funding being channeled through NGO's rather than government departments. Not only may this create a policy mismatch between governments and the narrow goals of NGO's but frequently has knock-on effects including the reduction of medical personnel in the health service as they are sucked into the work of NGO's having been tempted by improved emoluments and working conditions [14].

Where governments are short of money individual wealth is negligible and the people of sub-Saharan African countries are typically subsistence farmers with little or no disposable income [15]. Childhood cancer is not perceived to be a healthcare priority in a region struggling to cope with the ravages of malaria, HIV/AIDS and tuberculosis. What little money there is available for health care, including large donor funding, is diverted into these pressing needs through multinational programmes. Wars and famine continue to blight the region, although this is not something unique to Africa, and add to the considerable risks experienced by children.

Survival from childhood cancer has been shown to relate directly to this government health expenditure but is also critically related to the number of physicians relative to the population served [16].

Patterns of Disease

Throughout the subcontinent patterns of malignant disease vary with an obvious increase in the prevalence of Burkitt Lymphoma in the equatorial belt [17] and recent rises in the incidence of non-Hodgkin's Lymphoma and Kaposi Sarcoma in response to the increased prevalence of HIV disease [18, 19]. There has also been an increase in Epstein-Barr related smooth muscle tumours associated with AIDS in both adults and children [20].

There are few population based studies of malignant disease in African children and nearly all data are derived from hospital based registries or pathology databases. Both of these data collection methods have the potential to underestimate the true prevalence of disease within a community and the number of recorded cancers in children is far fewer than would be expected in European or American populations of similar size. So it seems likely that malignant disease in Africa is more common than reported and many children are either choosing not to present for treatment, are being misdiagnosed or are dying of co-morbidity before their malignant disease has become clinically significant. Hospital registries may also be skewed by regional patterns of referral and other micro-environmental factors.

With these limitations in mind, lymphomas now constitute 44 % of malignancies in a hospital based survey in Nigeria [21], 35 % in Sudan [22]. and 54 % in Ghana [23], although a recent report from a second centre in Ghana puts the incidence at 81 % suggesting considerable variations between districts in the same country [24]. Nephroblastoma constitutes 20 %, 13 % and 10 % respectively but has a surprising incidence of 38.4 % in a hospital-based review from Rwanda (Table 33.1) [25].

Such data, and regional variations demand that each centre develops its own data set, must be used to inform strategies to develop effective management but all suggest that surgical oncologists should be an important part of that development. We have learned from the HIV pandemic that patterns of disease also change with time [19], (Table 33.2) and thus data collection and management must be seen as a continual exercise in order to detect such changes. Sub-Saharan Africa has been disproportionately affected by HIV (Fig. 33.2) and even though antiviral therapy is more widely available, thanks in no small part due to NGO's such as the Bill and Melinda

Table 33.1 Prevalence of Wilms' tumour in Africa

Country	Years	Number of tumours	Number of Wilms' tumour	Percentage
Ghana [23]	2006–2010	554	39	7.0
Nigeria (Zaria) [80]	2006–2010	135	13	9.6
Rwanda [25]	2009–2011	133	51	38.4
Sudan [22]	1999–2007	322	43	13.3
Nigeria (Enugu) [21]	2002–2007	174	35	20.1

Table 33.2 Comparative prevalence of different malignancies between periods 1980 and 1982 and 1990–1992

	1980–1982 (pre-HIV epidemic)			1990–1992 (post-HIV epidemic)			
Malignancy	Total no.	Percentage	Prevalence	Total no.	Percentage	Prevalence	p values
Total	118	100	17.1	200	100	2.1	0.03
All lymphomas	48	42.1	7.2	65	32.5	7.1	NS
Non-Hodgkin's lymphoma	25	21.92	3.7	44	22.0	4.8	NS
Burkitt's lymphoma	18	15.78	2.7	11	5.5	1.2	0.05
Hodgkin's lymphoma	6	5.26	0.9	10	5.0	1.1	NS
Retinoblastoma	7	6.14	1.0	26	13.0	2.8	0.02
Kaposi's sarcoma	3	2.63	0.4	39	19.5	4.2	0.000016
Wilms' tumour	8	7.01	1.2	6	3.0	0.66	NS
Nasopharyngeal carcinoma	2	1.75	0.3	4	2.0	0.44	NS
All sarcomas	15	13.15	2.25	21	10.5	2.32	NS
Rhabdomyosarcoma	3	2.63	0.45	12	6.0	1.32	NS
Osteosarcoma	1	0.87	0.15	2	1.0	0.22	NS
Soft tissue sarcoma	9	7.89	1.35	3	1.5	0.33	NS

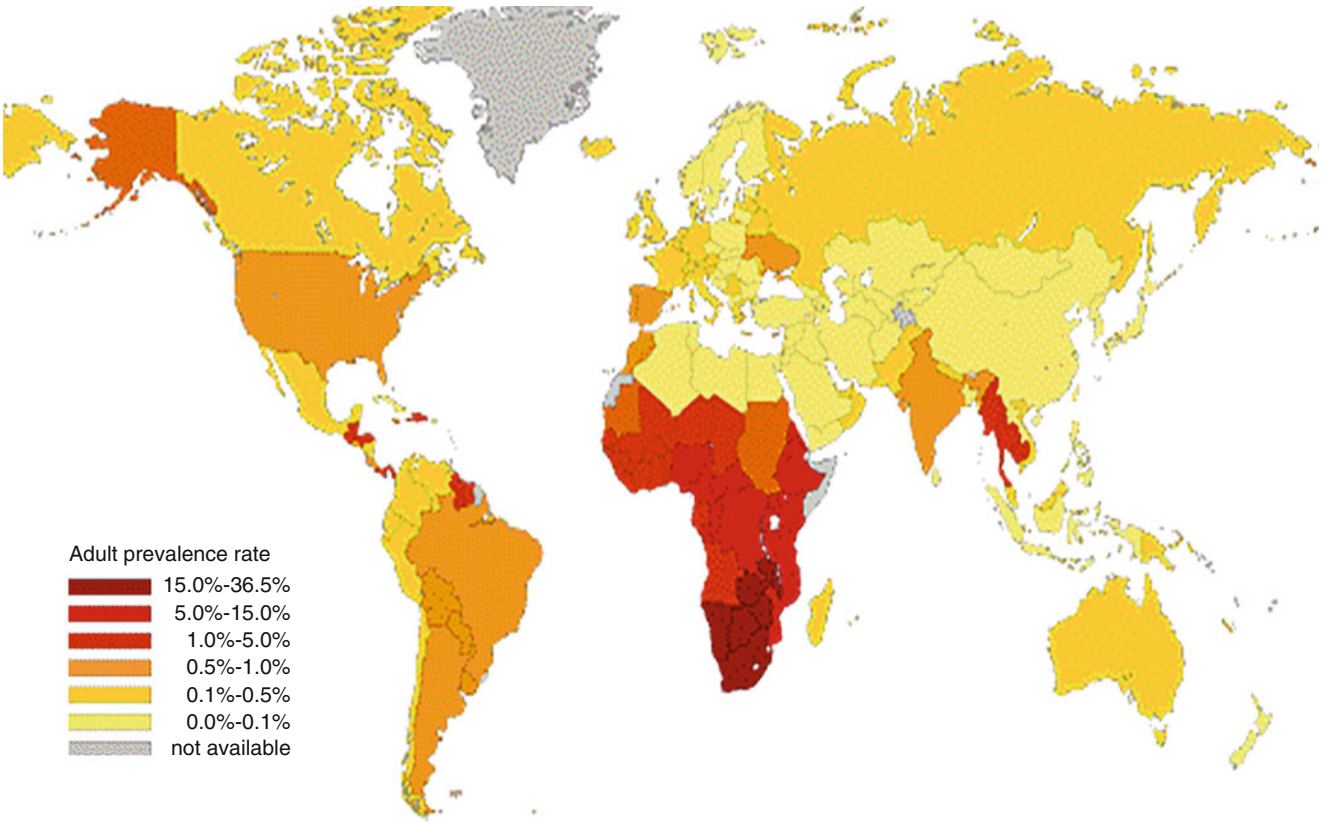

Fig. 33.2 World distribution of HIV

Gates Foundation and the PEPFAR fund, there are still millions of Africans living with the disease untreated. In the KwaZulu-Natal province of South Africa 39.5 % of women attending antenatal clinics were HIV infected in 2010 with an overall prevalence of 15.8 % in the population [26]. Throughout sub-Saharan Africa 35 % of deaths in children under 5 year of age are due to HIV and related diseases and it is estimated that only 10 % of children in need are currently receiving antiviral treatment [27]. Certainly HIV infection dramatically increases the risk of developing certain malignancies, particularly Kaposi Sarcoma [28] but also Burkitt Lymphoma and non-Hodgkin lymphoma [29].

Medical Manpower

It has been clearly established that survival from childhood cancer is related to the relative numbers of medical personnel in a country [15]. The African region has a median of 2.3 doctors per 10,000 of the population but this number is skewed by the well endowed countries of north Africa and the economic giants of the region; Nigeria and South Africa. This median however should be viewed in the context of Europe where the median is 33.3 doctors per 10,000 people and the Americas at 22.5 [30].

Thirty–one of 47 sub-Saharan African countries have fewer than 1 physician per 10,000 population [31]. Numbers range from 0.1 physicians per 10,000 people in Liberia, 0.2 physicians per 10,000 people in Tanzania, Ethiopia and Malawi to 7.7 physicians per 10,000 population in South Africa. These figures should be compared to those of affluent nations such as the UK with 23.0 physicians /10,000 population, the USA with 25.6 and the Netherlands with 31.0 [32]. The World Health Organization considers 2 doctors per 10,000 people to be the minimum required to sustain a primary health care programme [33] and clearly much of sub-Saharan Africa currently lacks the human resources to establish paediatric oncology units using the model favoured by European oncology groups [34].

Countries in Africa have difficulty retaining the doctors that they train and both “push” and “pull” factors led to there being 5334 doctors from sub-Saharan Africa working in the United States of America in 2002 [35]. They represented 6 % of African physicians. The situation has not improved [36]. The channeling of aid through non-governmental organizations rather than through ministries of health allows these NGO’s to attract physicians away from the public service leading to further shortages on the ground [13]. The paucity of medical staff has prompted several countries in Africa to train “tecnicos” or “clinical officers”; people who have no

medical training but who can perform standard operations such as Caesarean Section or skin grafting and the emergency management of trauma, or who have been trained to give anaesthesia [37]. Such use of non-medical personnel who cannot easily migrate might yet be a useful and sustainable model for staffing oncology services in many countries.

In defining the millennium development goals the United Nations targetted the high infant mortality and child mortality figures from sub-Saharan Africa [38] however the contribution of childhood malignancy to this attrition is not felt to be significant [39]. Paediatric oncology care once again has slipped under the radar and avoided prioritization.

Paediatric surgery itself was neglected as a specialty until it was recently demonstrated that 80 % of children in parts of the Third World need some surgical procedure before their 16th birthday [40] and that the primary care of many common disorders is simple surgery. However in sub-Saharan Africa there is a paucity of surgeons in general and paediatric surgeons in particular [31]. There were reportedly only 39 paediatric surgeons in sub-Saharan Africa in 2002 and whilst this number will have risen the majority work in either Nigeria or South Africa [41]. There are .001 Neurosurgeons per 10,000 population in the African region making management of brain tumours difficult, if not impossible, in many countries [8]. Most surgery for children throughout Africa is therefore performed by general surgeons. Along with a shortage of surgical specialists there is a paucity of anaesthetic and support staff, particularly those skilled in the care of infants and small children [42].

Paediatric Oncologists are even rarer and their role in nascent oncology services is being filled by general paediatricians or surgeons [43]. There is an increasing awareness of the lack of surgical capacity generally throughout sub-Saharan Africa [44] and efforts to address the unsustainable resource situation in paediatric oncology are underway through the Francophone GFAOP (Groupe Francais-Africain d'Ocologie Pediatrique) and programmes such as the African Paediatric Fellowship Programme (APFP) in Cape Town, however training local oncologists will take time. There are paediatric oncology centres dotted throughout the continent where facilities may mirror Euro-American centres but they are not the rule.

The establishment of treatment facilities, no matter how basic they may be in comparison to the ideal, is an important stimulus to the development of paediatric services in general and paediatric surgery in particular. Surgeons deal with individuals rather than populations and the ability to offer effective treatment is their *raison d'être.* If this involves stretching the definition of surgical care to encompass the administration of chemotherapy, then this is what must be done. It makes no sense to perform difficult surgery yet have the patient relapse because there is no paediatric oncologist available. As personnel costs weigh heavily on limited health budgets and few oncologists are attracted to areas with no resources, the status quo is likely to last into the middle distance at least, with important implications for the training of personnel for practice in these areas.

Access to Health Care

Given the lack of infrastructure and support for oncology the results of treatment of childhood tumours in Africa are unsurprisingly disappointing. Parents of affected children find support and often symptomatic care from traditional healers such as the isangoma and inyanga of southern Africa. These practitioners are both culturally acceptable and available within the community and even in major urban centres are well patronized. Many patients attend hospitals in desperation only after the traditional healer has patently failed in his attempts at cure [45].

Patients may face lengthy and expensive journeys to access appropriate health services and patients from rural areas are especially disadvantaged [46]. Under these circumstances it may be prudent to admit the child to hospital for the duration of treatment rather than risk default. Additionally, in many countries parents are required to pay for all treatment including laboratory tests, imaging studies and chemotherapy. Impecunious parents are then placed in an unenviable dilemma and may have no alternative but to refuse treatment. The economic straits of the patients also preclude regular follow-up in regions where travel is arduous and expensive [47]. Abandonment is a particular problem throughout Africa but is greatest in countries that require the family to fund investigations and treatment. It is hoped that the recent Kenyan initiative in making cancer care free to the patient will set a precedent for the continent [48].

The Internet

Support structures such as "twinning" with centres in Europe and America are frequently unavailable to African centres, although there are nascent programmes of information exchange within the continent, and some early excursions into training of both doctors and nurses [49]. Throughout Africa internet access is 11.4 % compared to 33.5 % for the rest of the world. Again penetration is uneven with figures of less than 1.0 % in countries such as the Democratic Republic of Congo, Ethiopia, Guinea, Niger, Liberia and Sierra Leone. Data for Africa are skewed by the inclusion of the Mediterranean countries where internet penetration is high (34 % in Tunisia and 41 % in Morocco). Africa as a whole has 15 % of the world's population but only 5.7 % of the world's internet users [6]. Broadband internet penetration is around 0.6 %. These access difficulties, in addition to high

internet service costs make "twinning" most difficult in those areas of arguably the greatest need. Low bandwidth programmes have been used in Paediatric Surgical education within Africa [50] and interactive educational and management meetings are regularly arranged by those countries blessed with broadband access, but there is untold potential for use of the internet for consultation, support and education. The use of mobile phone technology in support of patients on HIV medication or malarial treatment programmes suggest a model for improving patient follow-up at oncology clinics [51].

Co-Morbidity

Centres in Africa are overwhelmed by the numbers of children presenting with advanced disease and significant co-morbidity [52]. Of particular concern is the number of children who are malnourished at presentation either because of a marginal pre-morbid diet or because of the effects of late presentation [53], or both (Fig. 33.3). Malnutrition has a direct effect on the toxicity of treatment, and mortality, requiring that neoadjuvant chemotherapy doses must be reduced [54]. There is some evidence to suggest that in malnourished children with alteration of body composition there are altered pharmacokinetics of chemotherapy drugs that might in part explain this increased toxicity [55]. However chemotherapy in this group of patients is difficult and requires careful monitoring.

It must be clear that malnutrition also increases surgical risk and that pre-operative feeding must be given in conjunction with cytoreductive treatment if peri-operative morbidity is to be minimized. It may be necessary to increase the caloric intake by overnight nasogastric feeds in children who are unable to take adequate amounts orally [56].

Having a solid tumour does not protect a child from his environment and children with tumours, in addition to nutritional support, also need treatment for their malaria, tuberculosis, intestinal parasites, HIV/AIDS and other associated diseases [57]. Associated diseases may make primary assessment more difficult (Fig. 33.4) as well as requiring specific treatment. These features conspire to make biopsy of suspected primary and metastatic lesions more frequently necessary.

Tuberculosis presents particular difficulties in that clinical presentation can mimic malignant disease, the pathologies frequently co-exist and radiology can be confusing. Under these circumstances it may be necessary to biopsy pulmonary or intra-abdominal lesions to correctly stage the disease (Fig. 33.5) [57].

Many patients present with advanced local disease (Fig. 33.6) with displacement of normal anatomy that can be recognized when computerized tomography is available but which might ensnare the surgeon who does not have access

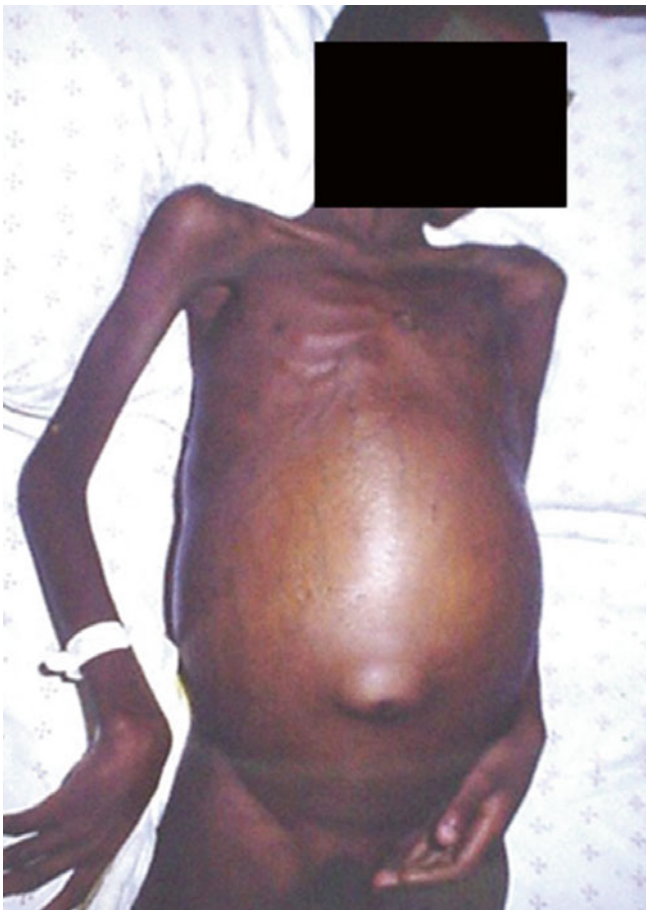

Fig. 33.3 Patient with Wilms' tumour at presentation showing abdominal tumour and signs of malnutrition

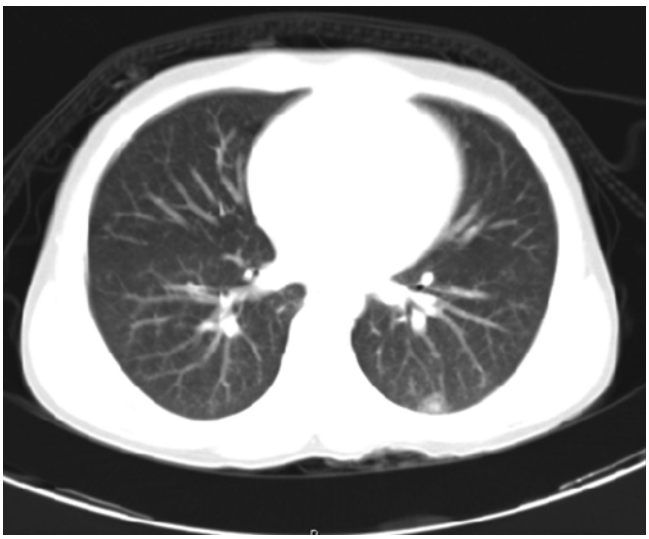

Fig. 33.4 Chest CT image of an HIV infected child with nephroblastoma. Thoracoscopic biopsy confirmed the pulmonary lesion to be schizosomiasis

to this investigation. Advanced local disease may also result in intestinal obstruction (Figs. 33.7 and 33.8) with challenging consequences. These large abdominal masses also alter the mechanics of breathing with frequent basal atelectasis and infection. Metastatic disease is common and often extensive (Fig. 33.9). It would appear that the site of metastatic disease in Wilms' tumour in Africa does not impact on survival [59].

Hypertension is reported in Africa with a far greater frequency than from Europe and America and the sequelae of hypertension; intracranial and cardiac add to the difficulties of treatment (Fig. 33.10) [60].

Other Resource Constraints

Perversely, whilst the expense of newer pharmacological treatments is high, availability of commonly used drugs may be limited because they are *not* expensive and therefore there is little profit to be made by drug manufacturers [61]. There

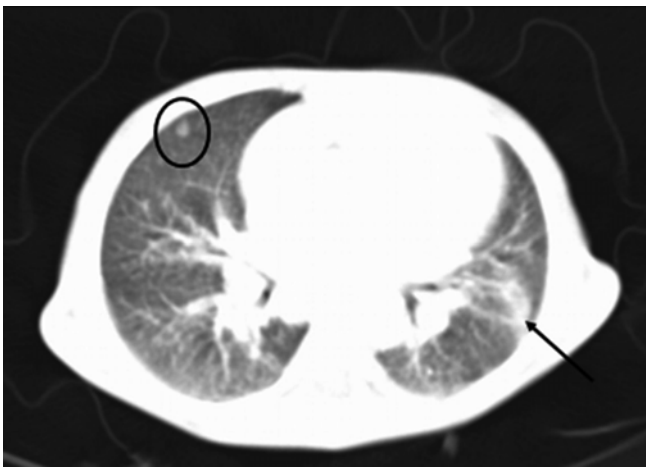

Fig. 33.5 Transverse CT image of patient with nephroblastoma and HIV infection. Note tuberculosis (*arrow*) and intra-pulmonary lymph node (*circled*) showing HIV lymphadenitis on biopsy

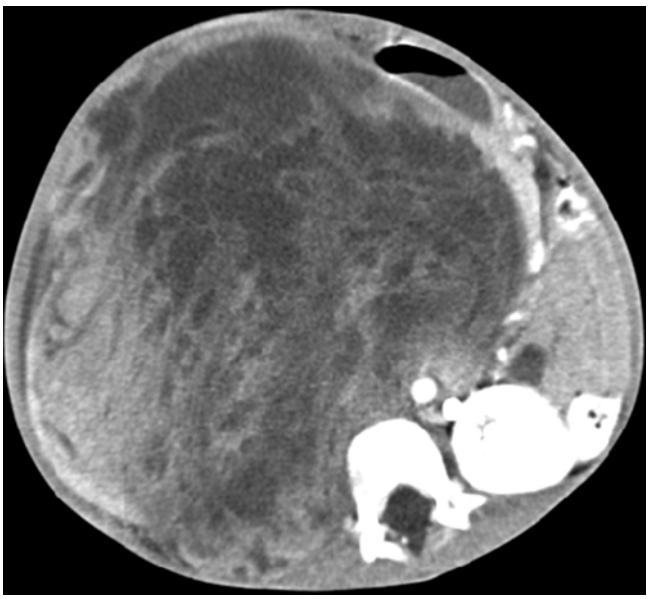

Fig. 33.7 Axial CT image of patient presenting with right sided Wilms' tumour causing duodenal obstruction

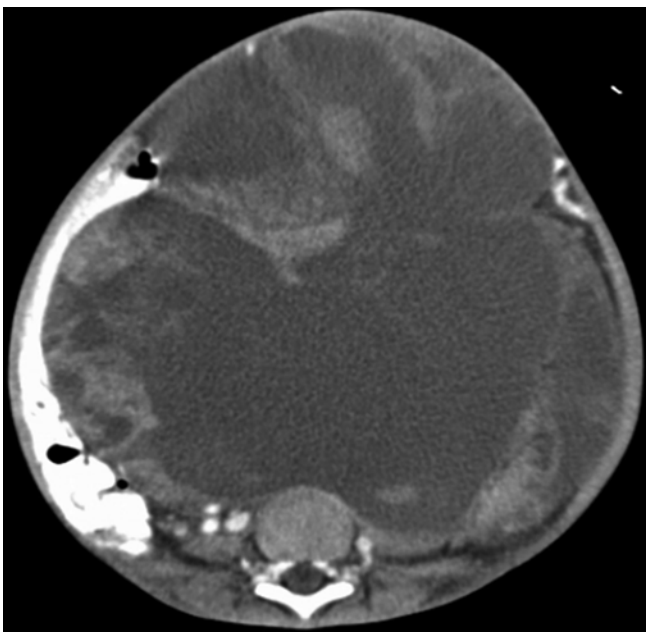

Fig. 33.6 Transverse CT image of patient with typical triphasic Wilms' tumour. The displacement of the common iliac vessels to the right of the lumbar spine can be clearly seen

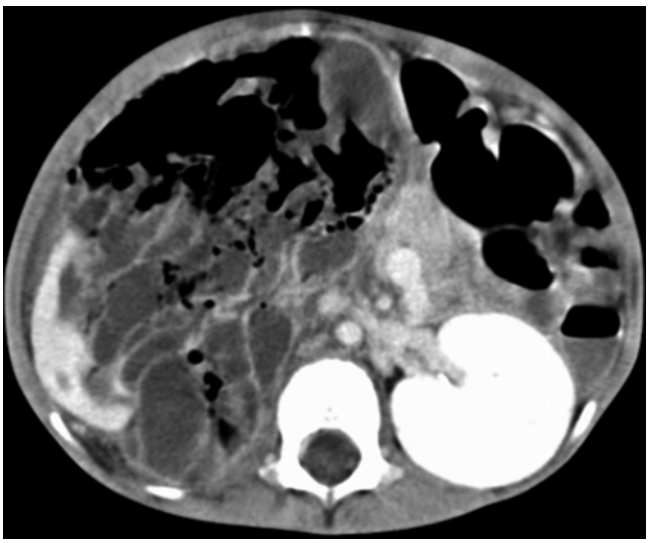

Fig. 33.8 "Pneumo-nephroblastoma" caused by fistulation into the duodenum during neoadjuvant chemotherapy in the patient also illustrated in Fig. 33.7

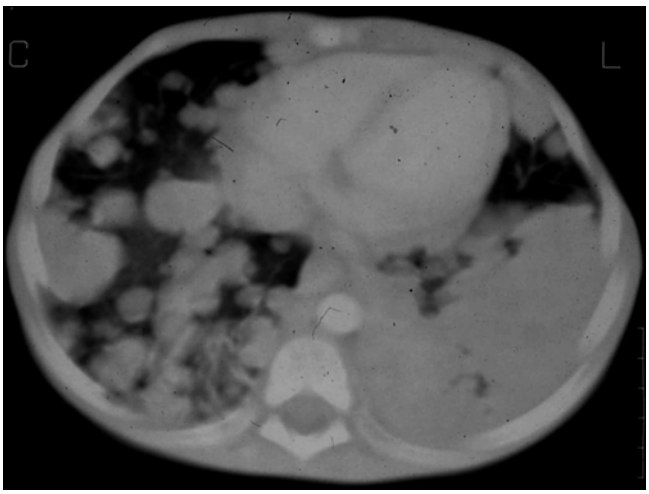

Fig. 33.9 Axial CT image of a patient presenting with Wilms' tumour

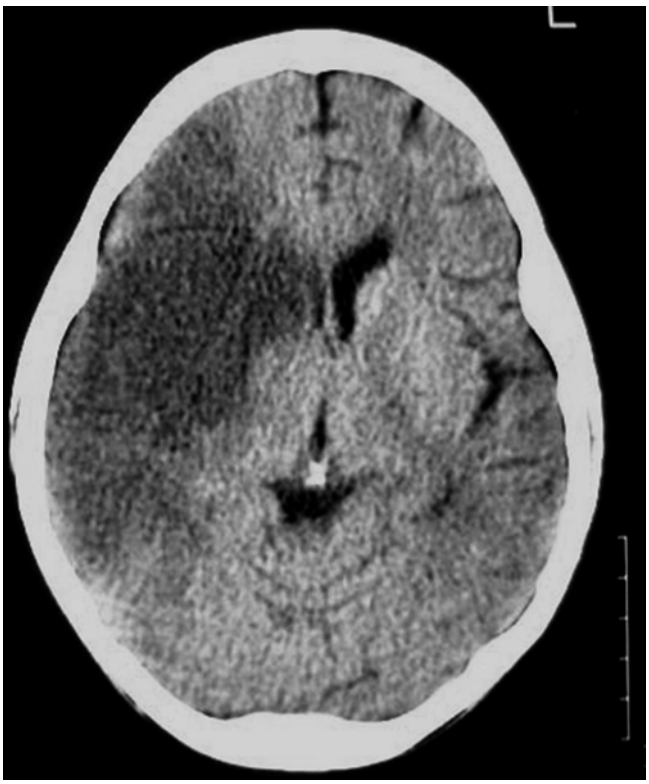

Fig. 33.10 Transverse cranial CT scan of 4-year old patient with Wilms' tumour presenting with hypertension and stroke (Previously published image) [60]

are also difficulties with the regularity of drug supply, storage, affordability and dispensing [62].

Paediatric surgical services are stretched by the conflicting interests of trauma victims, congenital abnormalities, surgical infections, and routine surgical pathology [40]. Cytology and histopathology services are patchy and lengthy reporting times frequently delay the introduction of effective treatment [63].

Blood and blood products, where available, may be unsafe and expensive [64] and oncology surgery can be difficult and time-consuming.

Despite the efforts of the International Atomic Energy Agency through their PACT programme (Programme of Action for Cancer Therapy) radiotherapy is effectively not available in the region [65] and the European norm of one megavoltage machine per 250,000 population is far from being attained [66]. This lack of resource is possibly most keenly felt in attempting to treat children with brain tumours.

So it may be thought that the problems and pressures on surgeons confronting children with malignant disease could hardly be greater but they pale into insignificance compared to the pressures on parents and the patients themselves. In countries in which patients are required to pay for investigation and management or appeal for charity to assist them there may be irresistible financial pressures to refuse treatment. Where distances are vast it may be impossible for a parent to accompany a child to the treatment centre, particularly when there are siblings at home requiring attention. Distance is also a major disincentive to regular follow-up attendance and in Malawi this has been obviated by using GPS technology to locate each patient's dwelling and having a staff member on a motorcycle make rounds and record the survival status of treated children.

What all this means

In an environment characterized by a lack of human and material resources, late presentation of patients, multiple life-limiting co-morbidities and an inability of the patient to comply with treatment and follow-up protocols, some tumours are simply untreatable and therapeutic efforts should be directed at those common tumours that we know have a reasonable prognosis and for which the treatment is manageable within the resources available.

Burkitt's lymphoma is the most frequent malignancy seen in children in equatorial Africa and there have been many studies showing the efficacy of low toxicity regimens that result in an increased overall survival without increasing the risks of treatment related mortality [67]. As endemic Burkitt's lymphoma has no parallel in Europe and America these regimens have had to be designed regionally and the exercise represents a successful collaboration between funders, clinical researchers and patients in need. By demonstrating that collaboration improves results such programmes have stimulated interest in children's cancer that has been traditionally thought to be an insoluble problem.

Nephroblastoma is a tumour that has an excellent survival in patients treated in the developed world with cure rates reportedly between 85 and 95 % on both sides of the Atlantic irrespective of the nature of the primary intervention [68]. In

sub-Saharan Africa survival data, where available, suggest that the outlook for afflicted patients remains dire. In Sudan only 11 % of the inception cohort completed treatment and 27 % received no treatment at all [69]. In Malawi, one of the few sub-Saharan African centres with a Paediatric Oncology Unit, albeit under the guidance of a general paediatrician rather than an oncologist, there has been a measurable increase in survival from the start of the programme [70] and although current Wilms' tumour survival in Malawi is not comparable to European or American data, the fact that progress has been made is encouraging [54]. However the difficulties experienced by the surgeon are exemplified by their report of anaesthetic related death, irresectability and intraoperative tumour rupture. These experiences are by no means unique and are mirrored in reports from Nairobi, Kenya [71] and Nigeria [72]. In western Kenya 2 year overall survival is 33 % [73] as it is in Dar es Salaam, Tanzania [74].

Such experiences inform the decision of many African centres to align themselves with the SIOP philosophy of neoadjuvant chemotherapy [75]. Such a policy has the potential to make primary tumours smaller thereby improving the operative risk profile, it affords a window of opportunity to detect and manage co-morbidities, and offers an in vivo trial of the efficacy of the selected chemotherapy protocol [76]. With tumours that are large at presentation secondary intestinal obstruction is not unusual and dramatic chemotherapy-related complications such as entero-tumoral fistula may tax the attending surgeon (Figs. 33.6 and 33.7).

Whilst certainly true of nephroblastoma the principle of neoadjuvant treatment has been applied to nearly all solid tumours.

Pursuant upon this broad policy, and influenced by the prevalence of second primary pathology such as tuberculosis, pretreatment diagnosis becomes desirable. In some regions where histopathology services are rudimentary or non-existent diagnosis is based on clinical findings and perhaps ultrasound. Of course there will be errors but the frequency of these errors is immeasurable. Where histopathology services are readily available percutaneous needle biopsy is advisable, not in an attempt to define subtleties within a diagnostic group but to exclude non-malignant conditions such as TB [57]. The Collaborative Wilms Tumour Africa Project involving centres in an increasing number of countries demonstrates the ability to cooperate across national borders and language barriers in an attempt to develop regionally relevant policies and protocols [58].

Summary

Sub-Saharan Africa is disadvantaged in terms of both human and material resources and faces multiple pressing health challenges. In resolving these challenges, whilst Africa has no need to reinvent the wheel, importation of European and American models of health care may not be appropriate and culturally and socially acceptable, as well as affordable, models need to be developed.

It is fantasy to think that management and research strategies of the developed world can be applied directly to patients in Africa and it is unlikely that the standards of histopathological diagnosis, of radiology, of laboratory evaluation that are required by European and American protocols are going to be attained in sub-Saharan Africa in the near, or even the distant future.

It is important to adopt a pragmatic approach. Pragmatism dictates that patients with potentially favourable outcomes should be treated as aggressively as circumstances allow and resources should not be expended on patients for whom the outlook in any event is grim [77]. There is little to be gained by offering chemotherapy to patients where there are no laboratory facilities to monitor toxicity, or where blood transfusion is not available should it become necessary. It is unwise to attempt major surgery in the absence of adequate anaesthetic support.

Data acquisition is an important first step in redressing the situation. Regional variation in the prevalence of childhood tumours is great and the impact of HIV on these patterns of disease requires continuous regional study. Diagnosis very often must be made on clinical or simple radiological grounds such as ultrasound scanning performed by the treating physician [68]. This does not devalue the information. The results of such data collection must be published and used to formulate policy and define needs.

Massaging data, by for example excluding from analysis children who die before, or soon after treatment starts, or who abandon treatment or refuse surgery, will increase the apparent overall survival and is always a temptation. However such manipulations mask the true state of affairs. We know how to treat tumours such as Wilms' tumour, the developed world has shown us this. The tragedy of Africa is that children are still dying of the disease. The answers to the problem of late presentation, abandonment and co-morbidity might lie more in the domain of politics rather than oncology but it is important that the oncology community generate data that reflect the true situation so that health administrators can base their decisions on fact.

Treatment options are limited by the drugs available, the general condition of the patient and the clinical skills and facilities available. To insist that chemotherapy administration requires the skill of a paediatric oncologist is not a sensible contribution to progress in Africa where there are few paediatric oncologists and it seems unlikely that there will be an adequate number in the foreseeable future [43]. Just as untrained "tecnicos" can perform skin grafts without medical training so a surgeon or paediatrician can inject chemotherapy and monitor toxicity without being an oncologist.

The current heightened awareness of the inequity of global healthcare resources in general [78], and surgical services in particular [79], augurs well for the future development of appropriate surgical services in Africa. Sharpening the needle-point of surgical expertise will, of itself, not compensate for the major infrastructural deficiencies, but must proceed in tandem with resource development and allow health planners to realize that paediatric surgical oncology is a cost-effective service that can uplift regional services generally.

It is the responsibility of interested parties, whatever their primary field of expertise, to ensure that paediatric surgical oncology remains on the agenda.

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Supportive Care of Children with Cancer

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Jane Belmore

Introduction

Childhood cancer is rare and the causes of most childhood cancers are unknown. The term childhood cancer is defined as tumours affecting those in the population under the age of 15 years. Childhood cancers are different from cancers that affect adults – they generally occur in different parts of the body, look different under a microscope and respond differently to treatment.

Childhood cancers can be grouped into 12 types:

Leukaemias	Retinoblastoma
Lymphomas	Kidney tumors
Brain & CNS tumors	Liver tumors
Sympathetic nervous tumors	Bony tumors
Soft tissue sarcomas	Gonadal & germ cell tumors
Other & unspecified tumors	Carcinomas & melanomas

In the UK around 1500 children are diagnosed with cancer each year. Leukaemia is the most commonly diagnosed cancer in children. Leukaemia and brain tumors account for more than half of all cancers in childhood.

It is largely because of clinical trails that such outstanding progress has been made in the treatment of children's cancers over the last few decades [1].

Clinical Trials

Over the past 30 years, treatment outcomes for pediatric cancer patients has improved dramatically due to the expertise of coordinated, multidisciplinary teams and national cooperative group clinical trials. Without the randomised phase III clinical trials, progress would have stalled and patients would have been locked into ineffectual and excessively morbid cancer treatments as the standard of care [2].

Although the majority of children with cancer will be cured, 20–30 % will still die as a result of refractory disease or complications of treatment [3]. There remains a need for new chemotherapy drugs to reduce morbidity and decrease mortality. Pediatric phase 1 trials are critical for the evaluation of promising new anticancer agents. They determine a safe and appropriate dose and schedule for new anticancer agents that can be subsequently used in phase 11 trials to test for activity against specific childhood cancers. Attention is also being focused on preventing psychosocial, biological and behavioural consequences of cancer treatment [4].

Multidisciplinary Team Working

In the UK, treatment for children with cancer is organised on a regional basis. A highly specialised multidisciplinary team provides the overall care of the child and family, with further care being given by local district hospitals and primary health care teams. The emphasis is very much on having children looked after in their own home as much as possible with routine bloods being done mainly at home by the Children's Community Nurse (CCN) or their own Paediatric Oncology Outreach Nurse Specialist (POONS). Social workers funded by charitable organisations such as CLIC Sargent Cancer Care for Children provide psychosocial and financial support to families.

Multidisciplinary team working is an essential part of principle treatment centres in pediatric oncology and hematology. The composition of MDT's varies with local service provision.

There are many professional disciplines involved in the care of a child with cancer, other than the pediatrician and pediatric medical and surgical oncology specialists, and nurses trained in the care of sick children with cancer. These include the social worker, the play specialist and assistants,

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occupational therapist, physiotherapist, dietician, pharmacist, psychologist, speech therapist, hospital school teacher and others. Both parents need to understand the role each member plays in their child's care.

Play is an important element of normal development, learning, and expression, and is necessary for the sick child whether in hospital or at home. Additionally, focused play helps the child to understand what is to happen to him. The involvement of teachers in the hospital continuing formal education is important for school-age children. Education is a normal part of life and helps to ensure a smooth transition to school and home life.

Good MDT working relies on excellent communication of roles and responsibilities to enable each member to provide the service that they are best placed to deliver, with respect to their professional skills and the individual family concerned. The philosophy of MDT working should be of mutual respect and valuing unique aspects of each team member's contribution to care [5].

Caring for children with cancer is a stressful experience. There should be opportunities for all those professionals involved to interact and discuss needs and changes in the progress of the children in their care. The nature of the treatment means that children and families become well known, and the effects of relapses and deaths can be considerable and should be recognized. Meetings also provide an opportunity to support each other [6]. Psychological support, whether peer group or professional counselling, should be available for caregivers, with complete confidentiality.

Care at Home

Children with cancer have a right to achieve their potential, both during their treatment and in laying foundations for their future. Fulfilling true potential should encompass educational achievement, social achievement and emotional stability, as well as leading a long and healthy life. To help children with cancer to achieve their full potential, a well coordinated, genuinely multi-agency approach should be taken to delivering services.

Children with cancer want to lead ordinary lives, and being at home, or closer to home, gives them the opportunity to do exactly this. To enable children with cancer to spend more time at home, good quality community based care should be available to all children regardless of where they live. All parents have a wealth of knowledge about their child. Indeed, they are the experts about their child's behaviour, likes and dislikes, and daily care, including medical care. Professionals need to work collaboratively with parents in order to be able to tap into this knowledge. They will also need to possess excellent communication and listening skills, in order to enter into meaningful conversations with families [7].

Many centres have developed patterns of working that facilitate some aspects of care being shared with a hospital more local to the child's home, known as "shared care". Shared care can be delivered at different levels dependent on the facilities and expertise available at the local hospital. This arrangement can greatly reduce the disruption to family life, but can cause anxiety for families if communication between care settings is not well managed. Families still have to travel considerable distances for routine tests and care, if these cannot be provided at their local hospital.

All the specialist centres and some of the shared care hospitals have paediatric oncology outreach nurse specialists (POONS) who meet families around the time of diagnosis and help to provide expert clinical care in the community. These services provide continuity for children and families, but the type of service provided varies considerably across the country. Many of these posts have been funded by charities on a pump priming basis and others are part funded by charities indefinitely.

Community children's nursing teams working in partnership with POONS are able to offer a comprehensive range of care and support. Community children's nurses can carry out many routine tests and provide expert clinical care thereby reducing the number of hospital visits and time spent away from home and school. However, these teams are not yet in place in all areas of the country.

Most centres would now strive to have a key worker for every child diagnosed with cancer and their family. The key worker will, in the majority of cases, be a specialist nurse experienced in oncology and attached to a principle treatment centre, most often the POON. The key worker is a navigator, an enabler, a coordinator. The aim of the role is to ensure the provision of holistic care and support to meet the individual needs of the child and family. The specialist nurse key worker may not always deliver care personally, but will be responsible for ensuring the child and their family receive appropriate clinical and non-clinical care at all stages, both in hospital and in the community [8]. It is often not until the child returns home for the first time, be it after a short or long hospitalization, that the full impact of the diagnosis is realised. The parents are suddenly responsible for their child's care. For families who have experienced prolonged inpatient care for their child, returning home can be very daunting, and the confidence of parents may well be somewhat shaken. No longer is there someone easily available to give answers or reassurance, therefore, providing contact telephone numbers at the hospital is essential.

However, the need to get on with family routines is helpful. The child may want to check that nothing has changed in the home during their absence, and often brightens up and eats better and enjoys being in their own environment. Inevitably, there will be a lot of visitors, and the experience of this first return home might possibly not be a quiet one!

The implications and repercussions on family life are considerable, and how each family adjusts will depend upon their normal strategies for living, family dynamics, and the availability of their extended support. The impact is greatest on the immediate family of parents, siblings, and grandparents but uncles, aunts, cousins, friends, schoolmates, neighbours etc. will also be affected. Most will have difficulty in knowing how to handle the situation. Sometimes friends withdraw from the family because they do not know what to say, and are apprehensive about facing a possible outburst of emotion (their own or that of the parents). Others may be unexpectedly helpful. Parents and other relatives may need encouragement to remember that despite the diagnosis of cancer the child is a normal child and requires appropriate disciplines. There is a temptation to give the sick child everything they want, at the cost of others, yet this is not in their best interests.

During hospital contacts, whether as an inpatient or attending the day unit, both children and parents make contacts with other families. Indeed, many friendships develop as time goes on, some lasting throughout a child's cancer journey, and even beyond. This element of support, found by the parents themselves, plays a vital role in helping families cope.

Education

The provision and co-ordination of education for children with cancer is very variable. Children often have difficulty keeping up with schoolwork and teachers do not always understand the difficulties faced by children returning to school [9].

Children over 3 years of age can be involved in a playgroup, nursery or school. Whenever possible the sick child should continue to attend, or at least interact with his peer group so that the eventual return to group/school will be a smooth transition. Children worry about their appearance (alopecia, disfigurement, body weight changes, not being able to keep up etc.) not wanting to be different from their peers. There is also the risk that others may make fun of them. When a return to school is likely, it is helpful for the outreach nurse and/or social worker to have a meeting at the school together with the parents, the child, the teachers and school nurse to provide information and dispel anxieties. This includes information regarding treatment patterns and relevant instructions for specific concerns including anticipated attendance, hair loss, fatigue, levels of concentration and any special equipment required [10].

Additionally, there is an opportunity to decide what to tell the other school children. If given an opportunity to ask questions the affected child would then know how his anxieties would be handled on returning to school. For a child who has had lengthy hospitalizations or has residual disability, the advice and support of an educational psychologist is important. Sometimes a return to part-time studies is relevant and, for a few, home tuition may be appropriate in the short term.

Siblings

Siblings, if not given the opportunity to be involved or informed, will possibly be "attention seeking", demonstrate difficult behavior, or be disruptive [11]. They will feel neglected and isolated if they see little of their parents. However, some will revel in the attention of grandparents, aunts and friends.

School or club activities may be the only "normal time" in their lives during this period, yet disruption here may also be demonstrated. It is wise for a sibling's schoolteacher to be aware of the stress that their pupil is experiencing, as sometimes children will confide in a trusted teacher. When the sick child returns home, parents' loyalties will become divided, but planning special time with the other children is more valuable than gifts.

Children worry about each other and need the opportunity to play together if at all possible. Sometimes children may think they are to blame for their sibling's illness and reassurance is needed to dispel this fear [12]. Long periods of hospitalization can be very difficult, especially when the sick child comes home and re-establishes his position, and siblings are thrown onto a secondary role as the focus of the parent's attention is on the sick child [13]. The sibling's trust in adults can be shaken, particularly if the sick child is taken to hospital; in the middle of the night, with a fever, for example. Good communications within the family is of vital importance in reducing misunderstandings, especially when the sick child has to return to the hospital for further treatment.

Treatment

Chemotherapy

Chemotherapy is drug therapy that is cytotoxic and that prevents malignant cell division and spread. Most chemotherapy agents kill malignant cells in the active dividing phases of the cycle (G1, S, G2, M) by damaging the RNA or DNA that tell the cycle how to copy itself. Non malignant cells that undergo rapid division (e.g., hematopoietic, mucosal and gastrointestinal cells) are not spared as demonstrated by some of the common side effects exhibited (e.g., bone marrow suppression, mucositis) with chemotherapy administration [14].

Radiotherapy

Radiotherapy is the use of ionising radiation to treat malignant disease. Generally, radiotherapy has a diminishing role in the treatment of childhood cancers due to very effective chemotherapy regimens and also the recognition of the late effects of radiotherapy, which is of particular significance to the pediatric patient still in the process of growth and development.

However, radiotherapy is still required for approximately 20 % of children and young people with cancer. It is the main mode of treatment for brain tumours and it plays a significant role in the palliation of symptoms [15].

Surgery

This is well covered in other parts of this book.

Cell and Gene Therapies

A multidisciplinary approach including chemotherapy, radiation, surgery and/or hematopoietic stem cell transplantation (HSCT) has led to a dramatic improvement in the long-term survival for pediatric malignancies over the past 30 years.

Cell and gene therapies would be an appealing addition to the treatment armamentarium of pediatric malignancies because both strategies offer the potential of selectively killing malignant cells, thus reducing short- and long-term side effects. In addition, both therapeutic approaches promise to benefit patients who currently fail multimodal therapy.

However, careful planned clinical trials are needed to validate these novel therapeutic approaches. Cell and gene therapies will most likely not replace convential therapies but will complement them, increasing their potency and, it is hoped, reducing short- and long-term toxicities [16].

Haematopoietic Stem Cell Transplantation

Reconstitution of haematopoiesis via hematopoietic stem cell transplantation (HSCT) is an established treatment approach for many malignant and non-malignant diseases that affect the hematopoietic and immune systems.

- Allogenic transplantation
- In allogenic transplantation, the recipient receives hematopoietic stem cells from a closely matched donor and alloantigens that differ between donor and recipient are targets for T-cell recognition. The most important criteria for choosing an allogenic donor is the degree of histocompatibility with the recipient.
- Autologous transplantation
- The rationale for autologous transplantation is that dose intensification will increase the response rate of chemosensitive tumors. Hematopoietic toxicity is a limiting factor for dose intensification, which can be overcome by harvesting hematopoietic cells and then cryopreserving and reinfusing them after doses of chemotherapy and radiotherapy that would otherwise be lethal or require a prolonged period of recovery.
- Cord blood transplantation
- Another alternative source of stem cells is cord blood. There are several large cord banks where cord blood is collected, cryopreserved, and tested for infectious agents in accordance with standards developed by governmental and specialty oversight organizations. The immediate availability of cryopreserved cord blood eliminates the usual delay in HSCT when unrelated donor marrow is used [17].

Side-Effects of Treatment

The following is just a quick summary of some of the most common side effects seen in pediatric cancer patients.

Nausea and Vomiting

Nausea and vomiting secondary to treatment experienced by pediatric oncology patients can be divided into three major categories:-

Acute: nausea and vomiting experienced in the first 24 h following therapy

Delayed: nausea and vomiting that occurs 24 h following therapy

Anticipatory: nausea and vomiting that occurs prior to the start of subsequent cycles of chemotherapy

Good antiemetic control is best achieved by medicating with appropriate antiemetics prior to the initiation of therapy: it is very difficult to break the cycle of nausea and vomiting once it starts.

Neutropenia

Neutropenia is a natural consequence of chemotherapy treatment. Fever in the child with severe neutropenia is a medical emergency requiring prompt assessment and treatment. Parents need to be extremely vigilant when having a neutropenic child at home.

Biochemical Derangements

Those most frequently observed in children with malignancy include derangements of phosphate and potassium due to tumour lysis syndrome (TLS), hyper- or hyponatremia, hypercalcemia and the consequences of acute nephrotoxicity. Numerous other biochemical abnormalities, with a wide variety of causes, may occur less frequently.

Anaemia

Anaemia in children with malignancy may be caused by bone marrow infiltration or as a result of treatment. Children and adolescents vary greatly in their ability to tolerate anaemia but many will require frequent blood transfusions during their treatment.

Thrombocytopenia

Platelets are essential for normal blood clotting. Thrombocytopenia is usually as a result of treatment or bone marrow infiltration. Children going through treatment will have frequent blood tests so that blood and platelet transfusions are given timeously.

Mucositis

Mucositis is a triad of gastro-intestinal pain, mucosal ulceration and diarrhoea. The management of mucositis is analgesia and the maintenance of hydration/nutrition.

Anorexia and Malnutrition

Reduced oral intake is very common in children with malignancy. This may be due to lack of appetite, change in taste, nausea and vomiting, lethargy or pain. Also repeated hospital stays may interfere with any consistency that can be encouraged at home. Very often children may need help with feeding to maintain an adequate calorific intake. Enteral nutrition may be required via nasogastric or PEG feeding. A paediatric dietician will usually follow up all the children throughout their treatment [18].

Breaking Bad News

Breaking bad news can be difficult for health professionals and it seems few receive specific training for undertaking this challenging task. While doctors have a uniquely important role in breaking bad news it is evident that other health professionals, most frequently nurses, can be equally involved in this encounter [19].

Each situation is unique with each individual child and his/her family armed with their own values, beliefs and knowledge. What is important to the child or young person may differ from the values held by the parents or carers and this may be problematic [20].

Hearing bad news is a very stressful event and a number of coping mechanisms may be used. Traditionally, two ways of coping have been identified [21]. The first of these is problem-focused coping that is concerned with doing something active around the situation, e.g., finding out as much information as possible, seeking social or other support or becoming involved actively in the child's care.

The second mechanism is emotion-focused coping that is aimed at reducing the emotional impact of the stressor. Parents who use this type of coping may utilize defence mechanisms, such as denial or suppression, in order to avoid the situation or may project their feelings onto health professionals. In reality, parents use some facets of both mechanisms although one style takes precedence.

It is very important in these days of multi-layered families that the correct people are present at this initial diagnosis as there is a lot of information to be absorbed. Once the word "cancer" is used it can be difficult for parents to be able to take on board all the other information that they are given.

It is important that undisturbed privacy and adequate time are arranged before disclosing the diagnosis. Some parents will be utterly devastated and shocked at the news, while others might be "relieved" as the period of doubt and waiting for results has ended. Parents need to know the name of the disease or tumor, the prognosis (even if the outlook is poor), that "the best treatment" is available, and who will be looking after their child. The information should be imparted with full disclosure and honesty. An outline of the treatment and what that entails should be presented and ideas of timescales discussed.

At the interview, it is advisable to have a nurse or other support personnel present who stays with the parent offering time for clarification of the information, and answering some of the practical questions, such as what to do about employment, finance and travelling to and from the hospital. In their initial confusion, parents appreciate advice on how to handle the news, how to manage the lives of the other children in the family, and who will be able to stay with the child in hospital. They are likely to have anxieties about guilt ("I should have taken him to the doctor sooner"), or anger over some perceived delay ("I took him to the doctor on several occasions, I knew there was something wrong"). Parents need assurance that they will be kept informed regarding their child's progress.

Parents go through a process of grieving for the loss of their child's health because his/her life is threatened, and they have no control over the situation. Difficult parental behaviour might be demonstrated and could be the result of their effort to regain some control of their lives [22]. Often they feel shock and disbelief, along with a feeling of helplessness, failure and guilt [23]. Many parents value a second opportunity to discuss the details with the consultant a day or so later.

What to Tell the Child

Studies show that children wish to be informed about their illness and plans for treatment [24]. Although children's information needs to be age dependent, most will worry about the impact of the disease and medical treatments on their daily lives and on others around them. Studies also show that if the information, even if unfavourable, is withheld from children, such silence exacerbates the child's fears and fantasies [25]. Involving children in their consultation can improve health outcomes and be empowering for the family. This is considered good practice by the General Medical Council [26].

The child's ability to understand his illness will vary according to his age, and the degree of communication and trust that already exists within the family; however he should have an opportunity to ask his own questions [27].

It is wise to ensure that any question is fully understood before being answered, as children often do not use words in the same way as adults. Even if a parent is not able to answer the child's questions, allowing a discussion with a professional is better than denying the subject or telling lies as the child might find out answers from others.

Children soon learn about their condition and become very knowledgeable about their treatment, who the people are that care for him, the complex names of the drugs and investigations – and possibly what is happening to other children as well!

There are lots of excellent resources available from the various cancer charities or other organisations which are directed at the child or young person themselves so the type, language and format is easily understandable for different age groups.

The Impact of a Cancer Diagnosis

The diagnosis of cancer in childhood has a huge impact on a child, their family and their wider social circle in a number of ways. One of the reasons for this is the treatment process, which often involves complex treatment in specialist centres many miles from home and sometimes leads to being separated from friends and extended family and home for long periods of time. There is also the protracted uncertainty of the outcome of the disease. For most parents the initial diagnosis of cancer is associated with the prospect of their child's death, despite the many assurances that are given.

Children with cancer and their families have diverse health, social, emotional, psychological, educational and employment needs and require a range of specialist and general services to meet these needs over a long period of time. From a health perspective, children require primary services (such as GPs and health visitors), secondary services (such as those provided by local district general hospitals) and tertiary services (delivered by principle treatment centres) throughout their period of care [28].

For most children there will inevitably be short or long periods of hospitalization which means further disruption to the family and its routines, and usually one or other parents will want to stay in hospital with the sick child most of the time. It is vital that parents seek "time out" together to discuss feelings, fears and problems with each other, offering each other mutual support. In some instances they may see little of each other, or even avoid talking about such painful matters.

Parents have the task of explaining the situation to the rest of the wider family, including other children. They also have to arrange care for other children in the family, ensuring they get to school, remain well fed and are escorted to evening activities e.g., sports or visiting friends. Wherever possible it is important for a well sibling to visit the child in hospital. Children have vivid imaginations and they might think that their sibling is not coming home, or that they look worse than they actually are. It is also important for the hospitilized child to see their sibling(s) for reassurance that family life goes on and he or she is not forgotten.

While children respond to treatments differently, in general, they handle chemotherapy, radiotherapy and surgery better than adults. Throughout the child's treatment program, which might last for 6 months to a year or more, it is difficult for families to plan activities together. There is always the threat of a sudden return to hospital because of complications, treatment, tumor recurrence, or pyrexia. It is unwise to organize holidays until the treatment program is completed. Throughout their ordeal the family needs the opportunity to discuss their fears. Many parents may imagine what would happen if their child died, may be convinced that this will happen, and some may even wish to discuss the possibility of death. They need to be encouraged to think positively – a positive and calm attitude in the parent helps the child, yet it is often the attitude of the child itself that helps the parent.

It is important to recognize the cultural and religious needs of families as a little flexibility with treatment may be required. Recognizing these factors and discussing the issues may address these needs. For example, Muslims may wish

privacy next to their child at certain times for prayer. Dietary restriction may be applicable; Jehovah's Witness' may refuse infusion of blood or blood products. There are many aspects of all cultures and religions deserving consideration, and caregivers should be aware of the individual needs. Spiritual support from religious leaders may be helpful [29, 30].

Ongoing communications is vital in maintaining their trust, the family need to be updated frequently about how the disease is responding and what future plans are. Supporting a child through cancer treatment can test families physically, emotionally, socially and financially [31]. Families are offered the services of a CLIC/Sargent social worker who can offer support and advice regarding any issues that may arise including employment, financial affairs or help in filling out various forms required. Parents are very adept at using the internet to search out information or treatments which they think might be applicable to their child.

The counsel and support of the outreach nurse or social worker visiting the home or during the stays in hospital to listen, empathize and guide can provide invaluable support. Other parents in the ward or clinic can be supportive, as they are going through similar experiences. However, one should be sensitive to the additional stress that parents feel when other children in the ward or clinic are very ill or die, as they and their child cannot be shielded from the realities of life.

Adolescents

Adolescence is a distinct developmental life stage that takes place between childhood and adulthood. The key changes during this period are:

- Physical changes, due to puberty
- Psychological changes, such as forming a sense of identity and purpose, incorporating sexual identity, and developing new cognitive skills, including abstract thinking
- Social change, including negotiating increasing levels of independence, and managing new levels of responsibility (for example, many adolescents are themselves carers). Establishing and maintaining positive personal relationships, including sharing and intimacy.

Adolescence involves moving from being a more dependent child to being a more dependent adult. This means learning how to manage separation, choice, independence and loss, including the loss of childhood. How the young person's parents and other adults respond to them during this period can make a significant impact on their life [32].

When cancer strikes, adolescents face even greater difficulties; as illness-related stressors are superimposed on the normal physical and psychological stressors associated with this developmental period [33]. At a time when social emancipation, independence, autonomy, identity, peer relations and career goals are to be established, the diagnosis and treatment of cancer poses a significant threat to the achievement of these developmental tasks [34].

Among adolescents recently diagnosed with cancer they frequently described protecting their parents by not communicating all their concerns, fears and anxieties. They described how they wanted to spare their parents as many stressful events as possible, as they were already overburdened with fears and concerns for them. In many cases, they described a substitute person to communicate with, such as a boy/girl friend, or an extended relative. This altered communication continued, in which full disclosure was not always present among all family members [35].

Loss of self-esteem and confidence in adolescents facing diagnosis and treatment may be profound.

Every day in the UK, seven young people aged 13–24 are told they have cancer. That's about 2100 young people a year. Cancer is the number one cause of non-accidental death in young adults in the UK. Different cancers predominate at different ages: leukaemia, lymphomas and brain tumours in 13–18 year-olds, and lymphomas, carcinomas (soft tissue cancers) and germ cell tumours (e.g., testicular cancer) in 19–24 year-olds. Young people get some of the most aggressive cancers, but because only 0.6 % of all cancers occur in young people, they are often misdiagnosed initially. This decreases their chances of survival and can mean they are excluded from clinical trials.

The Teenage Cancer Trust fund and develop specialist units within NHS hospitals that bring young people together to be treated by teenage cancer experts in an environment tailored to meet their needs. The Teenage Cancer Trust has funded, built and now maintains 28 units across the UK. The charity continues to raise funds to provide the best cancer support and care for young people, whenever and wherever they need it [36].

Transition to Palliative Care

Despite the advances in the treatment of childhood cancer, approximately 30% of children suffering from cancer in the United Kingdom still die as a result of their illness and will require a purely palliative approach to care [37].

When a family is informed that their child is no longer curable, the emotional nature of the discussion can impair their ability to hear and absorb information. It is, however, important that the message is clear. In an attempt to protect the child and family, professionals may disguise information in subtlety. A consequence of this subtlety may be that the message becomes ambiguous. It is therefore important to confirm understanding during and subsequent to the discussion.

Moreover, if further palliative therapy is offered, the nature of the intervention should be reinforced. These initial discussions should be well documented, as it is common for decisions taken at these times to be questioned later [38].

Families can now readily obtain information regarding treatments available internationally via the internet. Even if parents choose not to access additional information, well-meaning relatives or friends frequently do so on their behalf. In consequence, families may present data regarding innovative treatments that are available globally. While it can be difficult to review these candidly, when it is clear to the professional team that cure is no longer possible, such initiatives should be greeted with respect and compassion. Experience indicates that failure to do so may create barriers in palliative care. Parents have the rest of their lives to live and should feel that everything possible has been done to try and achieve a cure for their child. There may be hope to have time for some special experiences or trips, (there is sometimes "a lot of living to do"). Many charities are now available to give children "special wishes". Parents are entering a different period of uncertainty and Family Bereavement Services can offer support in adjusting to the impending loss.

Whether the child will die at home, in a hospice, or hospital should be discussed [39]; the choice is the parents' and they should be reassured that they can change their minds at any time, and their decision will be respected. It may be appropriate to involve the child or young person in the discussion, depending on their knowledge. After, perhaps years of illness working with a particular hospital team, changing supportive caregivers at this time can be very difficult, and it may take a while for parents to feel confident with any change.

Never will a child and family be more in need of compassionate and expert care than when they reach the palliative phase of the disease. It is the responsibility of professionals to ensure that this time in the family and child's life is managed appropriately wherever they choose to receive care.

At Home

The general medical practitioner may have had little input due to the hospital attendance of the child during treatment. He can feel vulnerable, as it is rare for a child to die at home [40]. In advance of palliative care at home, a meeting between the general practitioner and other professionals is considered good practice. Often this meeting will include other members of the primary health care team, and the child's oncology consultant and outreach nurse. It provides an opportunity for discussion of the child's present status, and the potential progress and problems. It is important to identify a key worker and often the outreach nurse will take on this role. The link provided by an outreach nurse enables a smooth transition and coordination of care, promoting confidence, and reducing feelings of isolation [41]. This link also facilitates the availability of oncology consultant advice and possibly a combined home visit with the general practitioner and consultant. Parents need the assurance of continued support, to know where it would come from, and who would provide any equipment that may be needed. The parents should become confident in caring for their child at home. They need to know who to contact if they need help or advice. Identifying a key professional, also known to all team members, prevents confusion [42]. This would usually be the outreach nurse.

The visiting nurse's role is to encourage the parents to do as much of the child's care as they wish and are able. It is important for parents and children to feel that they still have control of their lives, and to organize routines for themselves.

Fear of the unknown and isolation can be very difficult to handle. Some children, with adequate symptom control, may have a fairly long palliative phase and continue with normal activities, including school, right up to weeks or even days before dying, when they enter a terminal phase. During this time there can be a number of positive experiences for the family and considerable fun too, although tinged with obvious sadness.

Usually, the mum ends up being the one the child has increasing dependence upon which can be difficult for the dad both in physical and emotional terms.

Child's Questions

The questions children ask will depend very much on their development, understanding, and prior experience. They often overhear conversations or sense parental anxieties and become aware that circumstances have changed. They may sense that they are not getting better despite treatments and want to know why. In time they adjust, but may be unaware that they might die [43].

Allowing open communication with a very sick child can be frightening. Family members and professionals alike may fear the question "Am I going to die?" It is important to try to confirm what information the child seeks and to establish their current level of knowledge. To respond with questions such as "Have you been worrying that you are dying?" and "What makes you think that?" will allow the child to expand his/her fears and ensure that the right question is answered. Children may merely need reassurance that they are not expected to die imminently. Children who have the strength to ask such questions usually want to discuss the issue, and have the capacity, with support, to cope with the answer [44].

It is important that the subject of death, if asked, is not taboo as this can create other difficulties. Sometimes a child

might simply be trying to feel if it is safe to talk about death. It might be that he just wants the confirmation of love and that he would be missed, or the reassurance that his parents would be alright. The young child could also have feelings of anger, anxiety, fear of separation and being unable to ask questions, so may withdraw feeling insecure [45].

Adolescents may be the most challenging group of patients, as teenagers sometimes appear to consider themselves "immortal" as they often take many risks. They may have feelings of grief (anger, disbelief, anxiety etc.) manifested by verbal outbursts and body language. Some, however, will fully understand the nature of the situation and organize their own funeral [46].

Part of the normal routines for children with cancer are hospital visits to the outpatient department or day care facility. Such visits should continue until they cease to be relevant, or the child and parent no longer wish to attend, or travelling becomes too much of an effort for the child.

School attendance continues to be an important activity for many children with progressive disease. This routine can prompt both social support and normality. Understandably, the inclusion of a dying child within the classroom can be worrying for both the family and teachers. It is the role of the oncology outreach nurse to support staff and facilitate strategies with the school to enable the child to attend, and sustain other pupils. When a child is no longer able to attend school, the support of home tuition services can be of benefit [47].

Many siblings experience intense anticipatory grief before their brother or sister dies, and it is likely that they will continue to grieve for the rest of their lives. Inter-related factors such as children's individuality, the family situation and the home environment shape how siblings grieve. Siblings experience and demonstrate many grief responses, but they do not express emotions in neatly ordered stages. Each sibling responds differently and often they are unable to sustain their emotions for long periods of time, needing to return to "normal" activities.

Children often overhear conversations, or feel a strained atmosphere, and rather than make it worse may seek to move away from the cause, or alternatively may take on more responsibility in their family than they can comfortably manage. It is important to encourage parents to set consistent boundaries for siblings and to reward positive behaviour [48].

Hospice Care

Hospices are used in comparatively few instances for children dying from a malignancy, as most families are not keen to develop new relationships at a late stage of their child's illness, especially if it takes them away from their local community [39]. However, the hospice remains an option for all children requiring palliative care, and provides all the dimensions of palliative care throughout the child's life, in addition to end-of-life care as necessary.

There has been a steady growth in the number of children's hospices over the last 20 years. Children's hospices provide flexible, family-centred care throughout the course of the child's illness and after his/her death. They provide respite, emergency, palliative and bereavement support, together with information, advice and practical assistance. This service is provided by multidisciplinary staff, and is available 365 days a year at no cost to the family. The hospice philosophy is founded on the belief that children and their families should be offered help to achieve a quality of life – physical, emotional and spiritual – throughout a child's lifetime, and to help with bereavement support after the child's death [49].

Symptom Control

The aim of care, as during active treatment, is to allow the fullest quality of life that symptoms and circumstances will permit. It is pertinent to warn parents of any problems that are likely to occur, and some parents may even ask how their child will die and more importantly how will they know when the end is near. While it is not possible to be precise, they are also seeking reassurance that every effort will be made to prevent suffering, and to keep their child at home.

Throughout palliation, medications may well increase in number and complexity in an attempt to control unwanted symptoms. However, it is wise to constantly review the medications prescribed and administered, as subsequent prescriptions may be incompatible, or a previous medicine may become redundant. Medication can become irksome for the child to take, therefore the minimum dose and frequency necessary for comfort and function should be prescribed. The team looking after the child at home also needs to have confidence in the parents' ability to administer medicines appropriately.

Assessment is the foundation of good symptom management. History taking, listening and questioning are crucial to the process.

Young children may not have the verbal or cognitive ability to let carers know about their symptoms. Changes in the child's behaviour may therefore be the best or only indicator. Assessment will consequently rely heavily on parental reporting. Reports should be treated seriously, even if the cause is not readily apparent. Parents express great frustration and guilt when professionals are unwilling to give credence to their findings.

The use of assessment tools can allow children to quantify their symptoms and provide an objective assessment of the baseline severity and the efficacy of any intervention used [50].

Symptom management for children should combine and integrate both pharmacology and non-pharmacological

strategies. It should be recognised that, within the children's palliative care community, complementary and alternative medicine is increasingly being used to the great benefit of children and families.

It is not practical to identify every possible symptom that may occur, therefore only the commonest problems are noted here.

Pain

Pain is one of the symptoms most commonly experienced by children dying of cancer and it is the symptom that parents fear most [51]. Reassurance is needed that every effort will be made to alleviate this symptom. If a child says he has pain, he needs to be believed, and patience applied to discover its cause. Some children behave differently in the presence of pain and caregivers need to recognise body language as the child's energy level diminishes and he becomes quiet and withdrawn or possibly irritable. The cause could be psychological – worry, anxiety, insecurity, or depression, fear for himself or separation from his parents, or "just not himself" and unable to describe how he feels.

The World Health Organisation's analgesic ladder is considered the gold standard in adult palliation, and is also applicable within the paediatric palliative care setting [52]. It is the author's experience that most children will require opioids by continuous infusion as they near the end of life.

Constipation

Usually as a side-effect of opioids and requires that laxatives are started prophylactically and continue to be given regularly. Suppositories and enemas may be required if the problems persists.

Nausea and Vomiting

The vomiting centre in the brain receives stimuli from all areas of the body and brain. Vomiting can be caused by one or many stimuli. The art of diagnosis and treatment is to work out the interruption of which pathway will be the most effective [53]. In end stage care, an anti-emetic can be added to the drugs used for seizure or pain control and given subcutaneously by syringe driver.

Bleeding

As the emphasis of treatment changes to palliation, discussion is needed about the changing criteria for measuring full blood counts and administering blood products. The majority of children, however, do not have significant bleeding problems, despite a low platelet count. More commonly, severe bruising or petechiae are experienced [54].

Seizures

Seizures are commonly seen in central nervous system disease and should be anticipated. Management should therefore be discussed with the family and a clear strategy put in place, including advice on position and medication available. Seizure activity can range from short absences to grand-mal events [55]. Other potential causes of seizure in paediatric palliative care include cerebral metastases, electrolyte imbalance and fever.

Cough

Treatment of the underlying cause is always best, but is not always possible, and symptomatic treatment must start. Simple measures such as physiotherapy with or without postural drainage, correct positioning and humidified air or nebulised saline may work well. However, treatment with a cough suppressant may be needed, starting with codeine, and progressing to morphine linctus [56].

Anorexia

Loss of appetite (anorexia) is common in children in the palliative phase of their disease. There are many factors that contribute to anorexia, either in isolation or combination. Some, such as nausea, vomiting, sore/dry mouth, pain and constipation, may be partly or fully amenable to treatment [55]. The child's nutrition should be maintained, with supplements, if necessary, throughout the period of palliation, whilst naso-gastric feeding needs careful consideration, taking into account the child's general condition, their other symptoms, bulbar function and cultural beliefs. There could come a point when it no longer remains appropriate to encourage a child to eat more than he wishes, but fluid intake should always be encouraged – thirst can be distressing. As the child's activity decreases, the daily calories required becomes reduced; however, this is an area that parents find most distressing, and needs careful explanation.

Bladder Retention

Bladder retention may be painful and if so should be relieved by catheterisation. An indwelling catheter may be necessary in some instances. An indwelling catheter would not mean that the child is either bed- or housebound, although it would mean some readjustment. Urinary infections are painful and distressing and the administration of an appropriate antibiotic is very justified.

"Just in Case" Boxes

Many district nursing teams and palliative care teams now leave boxes or cases in the family's home. These boxes are made up by the hospital pharmacy team and include specific commonly used drugs for palliative care along with the appropriate syringe driver and syringes etc. This allows for a speedy reaction from the nurse to deal with symptoms that may arise especially when a syringe driver is needed for pain

relief. It is also reassuring for the parents to know that these are available in the house. With appropriate anticipatory care, prescriptions can already have been filled in by the doctor.

End of Life Care

Together for Short Lives defines ends end of life care as [57]:

> End of life care that helps all those with advanced, progressive, incurable illness to live as well as possible until they die. It focuses on preparing for an anticipated death and managing the end stage of a terminal medical condition, that includes care during and around the time of death, and immediately afterwards. It enables the supportive and palliative needs of both child/young person and their family to be identified and met throughout the last phase of life into bereavement.

It includes management of pain and other symptoms and provision of psychological, social, spiritual and practical support and support for the family into bereavement. This is not confined to specialist services but includes those services provided by any health or social care professional in any setting.

The key goals in planning for end of life care are:

- Professionals should be open and honest with families when the approach to end of life is recognised.
- Joint planning with families and relevant professionals should take place as soon as possible.
- A written plan of care should be agreed including decisions about methods of resuscitation; emergency services should be informed.
- Care plans should be reviewed and altered to take account of changes.
- There should be 24 h access to pain and symptom control including access to medication.
- Those managing the control of symptoms should be suitably qualified and experienced.
- Emotional and spiritual support should be available to the child and carers.
- Children and families should be supported in their choices and goals for quality of life to the end.

Spiritual Needs of Children and Families

The diagnosis of a life-threatening or life-limiting illness can be devastating for all concerned, life is often turned upside down and the resulting anxiety and uncertainty can have a catastrophic impact on the patient, and their family and friends. In such situations, individuals may start to question the very meaning and purpose of life, challenging long-held beliefs and values in an attempt to make sense of their situation and restore some order to the chaos they may be encountering [58].

For some children and their families, religious belief, practices and customs, with associated teachings and doctrines, will be fundamental to their spirituality and lives. For some children, their spirituality will be intricately woven with a religious belief. This belief may have been inherited or passed down to them from their parents, becoming an essential part of their life, identity and ancestry.

All people working with children in paediatric palliative care need awareness, education and information about the diverse customs and practices connected with the many world religions they might encounter. By developing this awareness, healthcare professionals will be in a better position to offer culturally sensitive, religious and spiritual care and avoid stereotypical assumptions and generalisations [59].

Support for Staff

In our modern system, it has usually been assumed that professional carers are there to look after other people, rather than requiring support themselves. The reality is that pediatric oncology, despite the ever brightening prospects for cure, remains a specialty with high emotional casualties. For some staff, the effects may be very obvious, but for others they may manifest more subtly; they may have difficulty talking to patients or develop tactics to distance themselves from difficult emotional situations. The effectiveness of the team in supporting the family of a child dying from cancer can therefore be imperilled.

The development of such counterproductive tactics can be minimized by the provision of support for the team, particularly during the palliative phase. This can be done through regular input from skilled “supervisors”, and also simply through helping team members feel confident in their own skill. Such confidence comes from adequate education in aspects of listening, communicating effectively and symptom control. Considerable support is now available from specialists in palliative medicine, especially from the adult specialty, but increasingly from specialists in paediatric palliative care [60].

Parents Preparing for the Child’s Death

Many parents of children who die may never have attended a funeral before. They might seek information from the doctor, spiritual advisor, nurse or social worker as to what will happen and how to handle it. It may be helpful to indicate that they might have some difficult questions to ask, and that someone is always available to answer them at any time. Some parents only want to face such questions after the child has died, while others may arrange the funeral in detail well in advance.

Professional carers need to ensure that the child or young person, as well as other family members, feel supported by them at this time. This means taking time to listen to their fears and worries and, if asked, offering gentle suggestions and ideas that may inform their decision making. No life experience will have prepared the child or young person and their family for what is a frightening experience, and, understandably they may turn to professional carers for advice and guidance.

Parents and other family members are often fearful that if they step away from the bedside, they will not be present at the time of the child's death. As such, it is often helpful to let family and loved ones know about the signs of impending death, both to achieve a sense of preparedness about what to expect and to try and judge when presence at the bedside is helpful. It is also critical to warn parents that it may not be possible to know the exact moment of when death will occur.

Some of the signs of impending death are;

- Profound progressive weakness
- Sleeping much of the time
- Little interest in food or drink
- Difficulty in swallowing
- Disorientation to time with increasingly short attention span
- Urinary incontinence or retention
- Oliguria or anuria
- Changes in respiratory rate mottling and cooling of the skin [61]

The need for a professional presence may change; some parents will be confident to have less of a presence, others might wish for more and it is important for the professional to be sensitive to the subtle changes. Professionals should not remove all hope, but guide the change to hope for realistic goals of comfort and support.

After the Child Dies

No matter for how long the child's death has been expected, there is shock at the time of death and behaviour will vary from normality or quiet numbness to hysteria and anything in between. Most parents mange to cope and function. Each parent will probably respond differently at the time of the child's death (and perhaps throughout the bereavement).

The most important message to relay to the parents is that nothing needs to be done in a hurry when their child dies. This is very much a private time for family to say their individual goodbyes. Saying goodbyes and performing rituals are important because they enable parents, siblings and other family members to express their love, sorrow, relief, regrets and share precious memories.

Washing the child for the last time, dressing the child in special clothes, taking photos, playing favorite music, praying together, touching and cuddling the child, talking to the child, taking hand and footprints, cutting a lock of hair and writing a message or poem for the child are all examples of rituals that families have found helpful and necessary. Even in a hospital setting parents should be allowed this opportunity. Parents need time and privacy to say goodbye to their loved one [61].

Support and guidance should be available to the parents from doctors, nurses, religious leaders or funeral directors. It is important for the funeral to be arranged according to the parents' wishes, considering religious or cultural rites and feasibility. Parents should make as many of the arrangements themselves as they wish, rather than have another family member take over the task.

Although the period before the funeral may seem long, this is a valuable adjusting period for the parents, siblings and the rest of the family. The funeral itself is a ceremony that gives the opportunity to openly grieve and say goodbye. At this stage some parents "may not feel anything at all" and function almost as normal (which can be disturbing to other family members), while other bereaved parents may only be able to function with assistance or encouragement.

Losing a child is the worst experience in life. The parent has lost part of himself and some feel physically empty [62, 63]. Grieving is a very tiring exercise. The day no longer has the intense activity and anxiety of caring for the dying child. It takes a lot of effort performing even the simplest tasks, such as making tea, getting out of bed, etc. life seems to have lost its purpose.

Parental self-esteem becomes low, and the feeling of worthlessness is compounded by the fact that despite their efforts their child died [64]. Some people avoid going to the usual shops for fear of meeting someone who does not know that their child has died. One parent might make frequent (even daily) visits to the grave over many months, and another hardly visits at all.

Grief is not a mental illness, though sleeplessness, anxiety, fear, anger and a preoccupation with self can all add up to a feeling of "going mad". These feelings are natural, and when experienced and expressed will become less frequent and begin to subside over time. Talking about them and bringing them into the open is helpful. Expressing grief is cathartic, and attempts to short-circuit these feelings rarely help in the long term and may cause deep-seated problems in the years ahead. If grief is denied, or anger and guilt persist to the exclusion of other feelings, help may be required from a professional counsellor [65].

The future may seem uncertain or even frightening, and a tremendous effort is required just to get through every day. It may take many months before the bereaved person is able to dwell less on the sad events surrounding the death and starts

to function more as they once did, although they will be inevitably changed.

Some parents manage to return to the routine of work quite quickly as often there is a need for financial income. Work may become simply a way to fill in the day, yet concentration is likely to be poor, as the bereaved have difficulty in thinking of anything other than their child. For those who have no employment the days are very long. A Family Bereavement Service facility could help all family members, including children.

Together with the loss of a child goes the loss of future expectations that the child will never now fulfil. Over the next months and years there are anniversaries of what the child did "this time last year", or "should have been doing this year". The loss of their child is felt daily, but the most difficult of all is the birthday. The first anniversary of the death might also be hard, as well as family holidays (such as Christmas or an equivalent). The second year can sometimes be worse than the first. It is not uncommon for a spell of depression to occur at 18 months or even later which friends can find difficult to understand. Time is not "a healer" but provides space to learn to readjust.

Siblings

Siblings of children with palliative care needs have often grown up in the shadow of illness as their parents, as a matter of priority, focus on the needs of their sick child. Siblings' coping mechanisms are affected by their age and stage of development, their understanding of the situation and their past experiences, but mainly from learnt behaviour from within the family. Parents are usually best placed to talk to siblings about what is happening, and members of the multidisciplinary team should enable them to do so, and provide them with information, support and guidance.

It is sensible to allow siblings the choice of seeing the child who has just died, as this can help them understand about death. A straightforward explanation of how their dead sibling looks and feels should be offered before the child makes his decision to see the body or not. If this experience is denied it is possible that the sibling might have worse ideas about death, or later accuse a parent because this choice was not given. Siblings can also have a role in helping to choose clothes and flowers, and maybe what to put in the coffin to accompany the child [66].

When the sick child dies, the sibling suddenly becomes the only focus for the attention of parents (and grandparents, etc.) who may too wrapped up in their own grief to notice this. Children do not like to see their parents sad and crying, and might avoid talking of their dead sibling, yet need to know that crying is allowed. The sibling gets upset and angry too; he might be reluctant to go to bed, might not sleep at night and have nightmares. His behaviour may become difficult and demanding one minute, and happy and playful the next. A young child might cling to his parents, and an older one choose to visit friends (where there is not the sadness of home). Children who are allowed to talk about their dead sibling should adjust well to their new lives without them, although sometimes in later years can experience further difficulties.

Grandparents

Grandparents find the death of a grandchild very difficult to bear. They hurt because they are unable to prevent the pain that their child (the parent) is suffering, and they have their own loss. They wish that they, who have had a full life, could have died instead. The effect of critical illness and loss has seldom been studied in grandparents, but it is imperative for the multidisciplinary team to recognise the active role they often play in family health and illness.

People do not know what to say to those who are bereaved of a child, they cannot risk the tears of the bereaved or possibly their own and may change the subject even when the bereaved themselves mentions the child's name. As a result people can say unhelpful things which can be very hurtful. Worse still is when a friend avoids the bereaved not knowing how to approach, for fear of causing upset.

The Professional

The death of a child invites care-givers to confront and come to terms with their strengths, limitations, and personal suffering. If these are recognized, accepted and processed, then one's vulnerability may become a source of maturity and growth. If left silent, suppressed, unattended or ignored they may become a source of stress, of alienation and occasionally of dysfunction. A functional team enhances in its members, a sense of belonging to a group, which can tolerate suffering, draw upon its strengths, and learn from experience [67].

It is stressful being in the company of those whose child is dying or who has died and professionals cannot support a family in this situation without some emotional involvement themselves.

Factors that have been recognized as helpful in supporting professionals include:

Acknowledging and understanding our own emotions and having somewhere safe to express them; having training in understanding ourselves in relation to this work, and in understanding families' needs in grief and loss; being clear about the boundaries of our roles; being part of a supportive team; and having access to regular support and supervision

where we feel able to be honest and open about how this work affects us [65].

Conclusion

The diagnosis of cancer in a child is devastating news and the family and its individuals will never be the same again. It is not in the natural order of events that a child should die before parents or grandparents and the diagnosis threatens the expectations of life and the future.

Throughout care, communication is vitally important – between professional and child, professional and parent, parent and child, parent and siblings and between professionals. Multidisciplinary support, understanding the implications of the diagnosis, anticipating problems and alleviating them where possible are important adjuvants to care. These things will help families develop and hopefully strengthen, through the experience of the child's survival.

Maintaining normal family routines and relationships, wherever possible, is vital to the function of the family unit, and the success with emotional survival, no matter the outcome. Listening, empathy and support will sustain.

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Long-Term Effects of Childhood Cancer Therapy on Growth and Fertility

35

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Introduction

Survival rates for most childhood malignancies have improved remarkably over the past decade with an overall survival rate for England and Wales for children less than 15 years of age quoted as 75 % (1993 and 1997) [1]. This improvement has been attributed to advances in treatment, better supportive care, and centralizing treatment in specialized centers with entry of patients into clinical trials [2, 3]. Approximately 1 in every 640 individuals in the US between the ages of 20 and 39 years is a survivor of childhood cancer [4]. Long-term survival rates vary with cancer type, demographic characteristics such as age, gender and race, tumor characteristics such as location and extent of disease, morphology, and genetic alterations.

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Attempts to improve survival in poor prognosis groups have led to therapeutic protocols that use more intensive therapy increasing the probability of treatment complications and long-term adverse outcomes in survivors.

With the improvement in survival rates, focus has shifted to minimizing the late effects associated with intense cancer therapy. For example, in the treatment of Wilms' tumor and Hodgkin's lymphoma, survival rates have been maintained despite a reduction in the overall intensity of treatment used for most patients. Reports concerning the frequency and severity of late effects of treatment vary widely and accurate estimates of the incidence and severity are difficult to define. Previous cohort studies have estimated that between 33 and 75 % of adult survivors experience problems [5, 6].

The Childhood Cancer Survivor Study (CCSS) – a large cohort study in the US – found that more than 40 % of survivors of childhood cancer report long-term adverse effects in specific areas of health. Patients treated for soft-tissue sarcomas were identified as among those with the highest risk of such problems [7]. The cohort demonstrated a 10.8-fold excess in overall mortality. Recurrence of the original cancer was the leading cause of death among 5-year survivors, accounting for 67 % of deaths [8]. Nevertheless, the overall proportion of survivors affected is currently relatively small [9].

A recent study looking at the barriers to follow-up care of survivors in the US and the UK found that the majority of survivors are not receiving recommended health care. Key barriers identified included a general lack of awareness of late effects by survivors, a lack of capacity for survivor care within cancer institutions, primary care physicians being unfamiliar with the health care needs of survivors, and a general lack of communication between survivors, cancer centers, and primary care physicians. Strategies to overcome these barriers are being investigated [10].

The late effects of cancer therapy may be subdivided into:

1. Impairment of endocrine function
2. Abnormal growth
3. Sub-fertility

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4. Cardiac and renal complications
5. Pulmonary fibrosis and restrictive lung disease
6. Secondary malignancies
7. Neurological impairment
8. Cognitive decline and psychological effects
9. Reduced quality of life
10. Early death

The risk of late effects are directly related to the treatment received rather than the underlying pathological diagnosis. Their anticipation and detection are essential as they may be amenable to prevention and treatment [11]. The following chapter focuses on impaired endocrine function, abnormal gonadal sub-fertility, and secondary malignancy.

Endocrine Late Effects

Endocrine disturbances have been documented in 20–50 % of childhood cancer survivors resulting from the underlying condition, the nature, and cumulative dosage of cytotoxic chemotherapy, and the dose and schedule of irradiation [12].

Patients with central nervous system tumors are at increased risk with the prevalence of an endocrinopathy documented in more than 70 %. This is often as a result of radiation injury to the hypothalamus, thyroid, or gonads [13].

Endocrine abnormalities often impose a negative impact on growth, body image, sexual function, and quality of life.

The range of endocrine complications includes gonadal damage, thyroid disorders, and dysfunction of the hypothalamic-pituitary axis. Neuroendocrine abnormalities may occur following external radiation for a number of tumors when the hypothalamic-pituitary axis falls within the fields of radiation. Deficiency of one or more anterior pituitary hormones, most commonly growth hormone, has been demonstrated after therapeutic cranial irradiation for primary brain tumors, prophylactic cranial irradiation for acute lymphoblastic lymphoma (ALL), and total body irradiation (TBI) as conditional treatment before bone marrow transplant (BMT).

Direct Radiation Damage to the Hypothalamic Pituitary Axis (HPA)

Following cranial radiotherapy patients are at risk of: growth hormone deficiency, an attenuated pubertal growth spurt, early or delayed puberty, and multiple pituitary hormone deficiencies.

The impact of radiation is dependent on the total dose, fraction size, number of fractions, and the duration of therapy (see Chap. 8). Lower radiation doses are associated with isolated growth hormone deficiency while higher doses may cause panhypopituitarism. A tissue's radiosensitivity is directly proportional to its mitotic activity and inversely proportional to its cellular differentiation. Radiation effects on slowly proliferating tissues such as the brain only become obvious with time.

The pathophysiology of radiation-induced damage has not been completely elucidated. Direct neuronal injury has been proposed to be the main mechanism rather than reduced cerebral blood flow.

The hypothalamus has been shown to be more radiosensitive than the pituitary and is damaged by lower doses of cranial radiation. This is suggested by suppression of insulin-mediated and spontaneous growth hormone secretion following cranial irradiation but preservation of the growth hormone response to hypothalamic-releasing factors [14–16]. Doses of less than 50 Gray (Gy) affect the hypothalamus with subsequent growth hormone deficiency. Higher doses used in the treatment of nasopharyngeal carcinomas and tumors of the base of the skull may cause direct anterior pituitary damage leading to early and multiple pituitary hormone deficits [17–20]. The pituitary hormones are generally lost in the following order: growth hormone, leutenizing hormone/follicle stimulating hormone, ACTH, and thyroid stimulating hormone [21].

Hypothalamic-pituitary dysfunction secondary to radiation is also time dependent [22, 23]. The progressive nature of the hormonal deficits following radiation damage to the hypothalamic-pituitary axis can be attributed to the delayed effects of radiotherapy on the axis or the development of secondary pituitary atrophy following a lack of hypothalamic releasing factors [15, 24, 25].

An additional risk factor is the age of the child at the time of radiotherapy. Younger children have been shown to be more sensitive than older children and adults to radiation-induced damage of the hypothalamic-pituitary axis [26].

Growth Hormone Deficiency

Growth hormone deficiency is usually the first and frequently the only manifestation of neuroendocrine dysfunction following cranial irradiation. It is classically characterized by diminished spontaneous (physiological) growth hormone secretion in the presence of preserved peak responses to provocative tests although the latter will also become abnormal [27].

Growth hormone is usually secreted in an intermittent pulsatile pattern with the majority of secretory bursts during sleep. Spontaneous growth hormone secretion is determined by the number of pulses, pulse amplitude, and the total 24-h integrated GH concentration derived from sampling every 20 min over a 24-h period. The reported frequency of radiation-induced growth hormone deficiency reported will be influenced by the physiological or pharmacological test used. Most prospective studies have used provocative testing and so the true extent of growth hormone deficiency may be underestimated.

The severity and onset of GH deficiency are dose dependent and the incidence increases with time elapsed after irradiation. Virtually all children treated with cranial irradiation doses in excess of 30 Gy will be growth hormone deficient 2 years after treatment. Low-dose cranial irradiation (18–24 Gy) used as CNS-directed therapy in ALL may lead to isolated growth hormone deficiency [28–32]. Isolated growth hormone deficiency has also been documented following total body irradiation with doses as low as 10 Gy [31, 33].

Short stature after cancer treatment has been well documented, particularly following cranial and craniospinal irradiation [34].

The effect of final height is more profound with treatment at a younger age [35].

Outcome in adult height and sitting height is poor in children surviving medulloblastoma due to craniospinal irradiation (CSRT) and chemotherapy. A study at the Children's Hospital of Philadelphia evaluated adult height and sitting height in 51 medulloblastoma patients stratified into four groups: G1, GH-deficient (GHD) patients treated with 23–39 Gy craniospinal radiation but not treated with GH [recombinant human (rh)GH]; G2, patients treated with rhGH; G3, patients who were not GHD; and G4, patients treated with 18 Gy CSRT and rhGH [36].

Sitting height. The sitting heights were available for 35 patients (two in group G1, 26 in group G2, two in group G3, and five in group G4), and the results are shown in Fig. 35.1. Compared with the general population, the sitting heights were impaired in all of the children (total group mean SDS, −2.96; $P<0.0001$). In groups G2 and G4, the mean sitting height SDS were -3.3 ± 1.43 and -1.62 ± 1.16, respectively. Similar to the comparison of standing adult height outcome, the sitting height of group G4 was significantly taller than that of group G2 ($P=0.021$). Therefore, higher dosing of rhGH and reduced CSRT doses improved sitting height, although sitting height SDS was still short in comparison to the normal population. Although limited to two patients, the sitting height SDS for group G3 (non-GHD patients) was −2.0. The adult stature in the entire group G3 was shorter than midparental height and not different from group G2, whose spinal growth was impaired despite rhGH treatment. These observations suggest that despite GH sufficiency in group G3, the loss of stature in comparison to midparental height is due to CSRT injury to spinal growth.

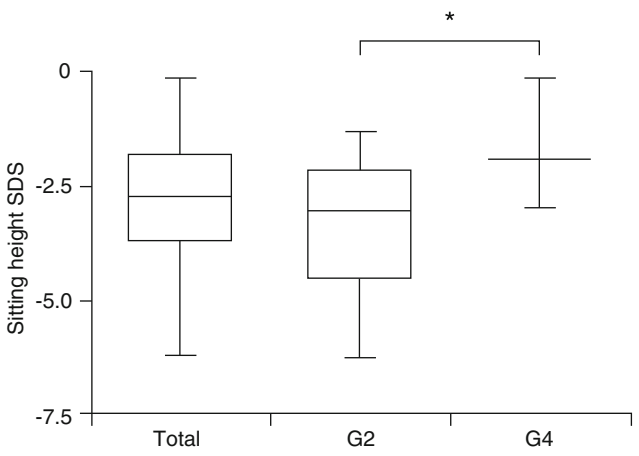

Fig. 35.1 Sitting height outcome. Sitting height SDS in total patients (n=35), in group G2 (n=26), and in group G4 (n=5). The *box and whiskers plot* represents +2 SD and −2 SD (*error bars*), the 25 and 75 % (*box*), and the mean (*horizontal bar*). *, P=0.021

Early diagnosis and treatment is important as response to growth hormone is poorer than in idiopathic growth hormone deficiency especially in children who have received spinal radiotherapy [37].

Growth hormone deficiency is also believed to cause a reduced lean body mass and increased fat mass, metabolic abnormalities including an adverse lipid profile and glucose intolerance, reduction in bone mineral density and impaired quality of life [38–41]. Insulin resistance, impaired glucose tolerance or even type 2 diabetes mellitus have been recently reported in children who have received total body irradiation.

It is well accepted to treat documented growth hormone deficiency in childhood with replacement doses of recombinant human growth hormone. Diagnosis of GH insufficiency can sometimes be problematic at times, however, especially in the early postirradiation period [25]. Measurements of peak growth hormone secretion will miss deficits confined to qualitative, subtle differences in pulsality (neurosecretory dysfunction) [42] and those in whom there is an inability to augment pubertal growth hormone adequately [43, 44]. Measurements of insulin-like growth factors and their binding proteins are unreliable indicators of growth hormone secretion in this situation [45]. A high index of suspicion for growth hormone deficiency is therefore needed following irradiation.

Growth in children is a sensitive marker of growth hormone status. The presence of significant growth deviation over a 1-year period (growth velocity below the 25th percentile) or a drop in height of greater than or equal to one standard deviation is highly suggestive of clinically significant growth hormone deficiency. However, obesity can result in preservation of a normal height velocity with a worsening height prognosis, as can precocious puberty, another common consequence of cranial irradiation in young girls.

Growth monitoring is an essential part of followup of children who have received cranial irradiation as part of treatment. Sitting and standing heights should be measured every 3–6 months. The sitting height is obtained by using a sitting height stadiometer and is particularly important in those who received spinal irradiation. The impact of spinal irradiation on spinal growth is such that greater auxological emphasis must be placed on the leg length changes rather

than the total height. Spinal irradiation will particularly impair late pubertal growth.

With biochemical or clinical evidence of growth hormone deficiency (height velocity <5 cm/year) treatment is usually commenced with recombinant growth hormone as a daily subcutaneous injection. Due to the evolving nature of growth hormone insufficiency it is important that treatment begin as soon as possible.

Growth hormone is potentially mitogenic and concerns have been raised about its use in cancer survivors. However, long-term studies of patients treated with physiological replacement doses of recombinant growth hormone have failed to demonstrate any increased risk of tumor recurrence or increased frequency of second tumors although continued surveillance is needed [46–48].

However, most centers do not advocate introducing therapy within the first 2 years after cancer treatment as this is the time of highest relapse.

Abnormalities of Gonadotrophin Secretion

Gonadotrophin deficiency. Disruption of gonadotrophin secretion generally occurs at radiation doses above 40 Gy [49, 50]. Deficiencies of both follicle-stimulating hormone (FSH) and leutenizing hormone (LH) have been documented. The clinical picture shows considerable variability from subclinical abnormalities detectable only by gonadotrophin releasing hormone (GnRH) testing to a significant reduction in circulating sex hormones levels and delayed puberty. Gonadotrophin deficiency is generally a reflection of hypothalamic dysfunction [51]. It is therefore possible to restore gonadal function and fertility by use of exogenous GnRH replacement therapy. Because of differential sensitivities of testicular and ovarian cell types to cytotoxic chemotherapy or radiotherapy, spontaneous progression through puberty is no guarantee of subsequent fertility.

Precocious puberty. The effect of cerebral irradiation on the hypothalamic-pituitary-gonadal axis (HPGA) is dose dependent. Whereas higher doses cause a deficiency, lower doses can cause premature activation leading to early or precocious puberty. The mechanism for early puberty following irradiation is believed to be secondary to disinhibition of cortical influences on the hypothalamus.

The definition of precocious puberty is the onset of puberty before the age of 8 years in girls and 9 years in boys. This can be distinguished from early puberty, which means onset between 8 and 10 years in girls and 9 and 11 years in boys.

Low-dose cranial irradiation (18–24 Gy) used in central nervous system prophylaxis for ALL has been associated with a higher incidence of early or precocious puberty, an effect seen mainly in girls. No increased frequency of precocious puberty over the normal population has been documented in male ALL survivors [52, 53]. This may reflect sex differences in the control of the onset of puberty (Fig. 35.2).

Ogilvy-Stuart et al. demonstrated that in 46 GHD children previously irradiated for brain tumors (25–47.5 Gy) the onset of puberty occurred at an early age in both sexes and there was a significant linear association between age at irradiation and age at onset of puberty, i.e., the younger the age at irradiation the earlier the onset of puberty [54].

The consequence of early puberty is that of a premature pubertal growth spurt followed by early epiphyseal fusion and a reduction in final adult height.

Children with precocious puberty are also usually growth hormone deficient. Both problems contribute to a poorer prognosis with respect to final height potential by reducing peak height velocity [55], and the time over which childhood growth can take place.

Height loss after radiation has also been shown to be disproportionate with a significant portion being a loss of sitting height [56]. Direct radiation to the spine further disrupts spinal growth with only a partial response to growth hormone therapy, which mainly stimulates long bone growth. Thus, the younger the child at the time of irradiation, the greater the risk of subsequent skeletal disproportion [57].

Close monitoring of these patients is essential after treatment with respect to growth and puberty. Six-monthly clinical assessment of pubertal status is needed as well as auxology measurements. Growth hormone and gonadotrophin secretion and bone age should be done as indicated.

Suppressing pubertal progression and delaying skeletal fusion with GnRH analogues and treatment with growth hormone gives the best prognosis in terms of height potential although the final height achieved is still lower than target [58, 59].

Hypothyroidism. The risk of hypothyroidism following treatment for childhood cancer is related to radiation field, dose, and adjuvant chemotherapy. Chemotherapy alone has not been shown to cause hypothyroidism [60]. Thyroid

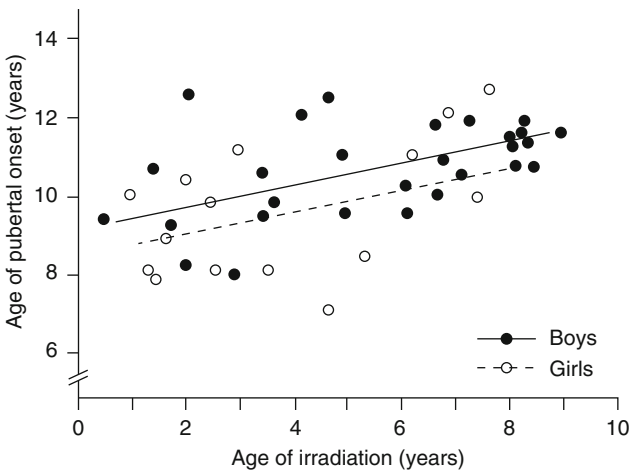

Fig. 35.2 Age at onset of puberty compared with age at irradiation in children treated for brain tumors [54]

dysfunction may occur due to central thyroid stimulating hormone (TSH) deficiency following cranial irradiation, primary end organ damage due to direct irradiation to the gland or a combination of both, for example following craniospinal irradiation or TBI.

TSH deficiency. The hypothalamic pituitary axis and production of TSH appears least vulnerable to radiation damage. The risk of TSH deficiency from cranial irradiation is dose [61] and time related [62] as for other pituitary hormone deficiencies. However, the risk is low. In a survey of 71 children who had been treated with cranial irradiation, 6 % showed evidence of TSH deficiency at a median of 12 years follow up [62]. The risk of TSH deficiency occurs at doses >50 Gy.

End organ damage. The thyroid gland is sensitive to direct irradiation. Hypothyroidism, thyroid nodules, and hyperthyroidism have all been described. Primary hypothyroidism is the most common consequence of direct radiation injury and occurs frequently at doses that exceed 26 Gy. In a population of 1787 adults and children who received neck irradiation for Hodgkin's disease the risk for developing hypothyroidism was 47 % at 27 years [63] and approximately half the patients with thyroid dysfunction were diagnosed in the first 5 years. The presence of thyroid nodules after radiation is very common. The percentage reported with thyroid cancer varies from 14 to 40 %, the risk increasing with time since treatment, and those treated at a young age most at risk [64, 65].

Combined central and primary hypothyroidism. The commonest cause for thyroid dysfunction now seen by the pediatric endocrinologist is due to a combined effect of primary and central dysfunction due to cranial and direct irradiation. The patients most at risk are those who have received craniospinal irradiation for brain tumors. In one study [66] of 119 patients who had been treated as children with craniospinal irradiation, raised TSH levels were seen in 22 % who had received craniospinal irradiation alone and 69 % who had received craniospinal irradiation and chemotherapy. The overall prevalence of primary dysfunction was 28 % compared to 3 % for central dysfunction. In a more recent study evaluating thyroid function in children treated with craniospinal irradiation (36 vs. 23 Gy) with or without chemotherapy, those treated with the lower dose of radiotherapy who also received chemotherapy, and those treated at a younger age, had the highest incidence of hypothyroidism (100 % for those aged <5 years) [67]. There is a risk of primary hypothyroidism after TBI, which may be compounded by a central decline in TSH production. After fractionated TBI the risk is reduced – only 16 % in one study had features of thyroid dysfunction at long-term follow-up [68].

Evaluation of thyroid dysfunction. Biochemical diagnosis of thyroid dysfunction is based on basal thyroid function tests – TSH and free thyroxine (FT4) level. Detection of primary hypothyroidism is relatively easy with rising TSH levels and declining FT4 levels. If there is evidence of increasing TSH levels with persisting normal FT4 levels (compensated primary hypothyroidism), treatment should be started prior to overt hypothyroidism as persistently elevated TSH levels are thought to increase the risk of thyroid cancer.

The diagnosis of central or combined hypothyroidism can be notoriously difficult. Treatment should be considered for individuals at risk who have a low normal or subnormal FT4 level, especially if declining over time, with low, normal, or mildly raised TSH levels, with or without symptoms [69].

Fertility

Direct damage to the gonads may occur due to radiotherapy involving the spine or pelvis or by systemic chemotherapy. This may lead to subfertility or infertility in both males and females.

The Effects of Chemotherapy

The extent of cytotoxic damage to the gonads is dependent on the agent used, the age and sex of the patient, and the dose received. Toxic chemotherapeutic agents include alkylating agents such as the nitrogen mustard compounds (cyclophosphamide, ifosfamide, and melphalan); nitrosoureas (carmustine, CCNU), busulphan, thiotepa, and cisplatin; procarbazine, and etoposide. Alkylating agents act as inhibitors of DNA synthesis and damage those cells with rapid mitotic activity such as the germinal cells of the testicular tubules leading to severe germinal aplasia and oligosper- mia/azoospermia in adulthood [70].

The germinal epithelium is more sensitive to the detrimental effects of chemotherapy than the somatic cells. This means that following gonadotoxic chemotherapy, male patients may become oligospermic or azoospermic but testosterone production by the Leydig cells is unaffected so secondary sexual characteristics develop normally [71, 72]. However, with higher doses of chemotherapy, Leydig cell dysfunction also occurs [73].

Treatment of Hodgkin's lymphoma has traditionally been associated with a high rate of azoospermia due to the use of procarbazine and alkylating agents such as chlorambucil and cyclophosphamide. Newer hybrid regimens have been designed with the above agents being alternated with anthracycline agents resulting in significantly less gonadotoxicity [74].

Ovarian dysfunction has also been documented after chemotherapy with a significant number seen following treatment of Hodgkin's lymphoma [62–65]. Causative agents include procarbazine and the alkylating agents. These effects are age and dose related [75–79].

The Effects of Radiotherapy

The degree of radiation damage depends on the field of treatment, total dose, and fractionation schedule [80–83]. In males, doses as low as 0.1–1.2 Gy can cause Sertoli cell damage with impaired spermatogenesis and with doses greater than 4 Gy leading to permanent infertility [80–82]. Germ cells are more susceptible to radiation damage than somatic cells. Leydig cells responsible for testosterone production in males, are relatively radio-resistant, and are damaged at doses of around 20 Gy in prepubertal boys and up to 30 Gy in sexually mature males [84, 85].

In females, total body, abdominal, or pelvic irradiation may lead to ovarian and uterine damage, the extent being dependent on the radiation dose, fractionation schedule, and age at time of treatment.

The human ovary contains a fixed pool of primordial oocytes maximal at 5 months of gestation, which declines with increasing age in a biexponential manner, eventually leading to menopause at an average of 50–51 years. At this age, approximately 1000 oocytes remain. The number of primordial oocytes present at the time of treatment, together with the dose of radiotherapy received by the ovaries, determines the fertile "window" and the age at which premature ovarian failure occurs [86].

The radiosensitivity of the human oocyte has recently been estimated to be less than 2 Gy [87]. The Faddy-Gosden equation

$$dy / d\text{ay}\, x = -y\left[0.0595 + 3,716 / \left(11,780 + y\right)\right]$$

where x denotes age, $y(x)$ is population at age x, with initial value $y(0) = 701{,}200$; the initial value denotes population at birth provides a mathematical model for calculating the rate of natural follicular decline in women.

A recent study has looked at predicting the age of ovarian failure after radiation based on data obtained from young women who developed ovarian failure after total body irradiation.

It is not possible to diagnose ovarian failure clinically, biochemically, or radiologically before the onset of puberty. The above mathematical model may be useful in predicting the onset of ovarian failure in women receiving radiotherapy [86] (Table 35.1).

Acute ovarian failure, defined as the loss of ovarian function within 5 years of diagnosis, is known to develop in a subset of survivors of pediatric and adolescent cancers. A cohort study with female participants >18 years from the CCSS was conducted looking at incidence and risk factors. Acute ovarian failure developed in small subset (6.3 % of cases) especially in those treated with at least 1000-cGy radiation to the ovaries [88].

Abdominal and pelvic irradiation are used in the treatment of a variety of malignancies such as Wilms' tumor, pelvic rhabdomyosarcoma, and Ewing's sarcoma of the pelvis or spine with dose and volume dependent upon the diagnosis and tumor size. The prevalence of ovarian failure following whole abdominal radiotherapy has been unacceptably high with the majority of patients failing to complete pubertal development without hormone replacement therapy. The introduction of flank irradiation in 1972 has resulted in significantly less pubertal failure but the onset of a premature menopause may occur with time. Irradiation involving the uterus in childhood is associated with an increased incidence of nulliparity. Even if a pregnancy is achieved there is a high incidence of early miscarriage or intrauterine growth retardation with small-for-gestational-age offspring due to problems with uterine blood flow and distensibility [89–91].

Permanent menopause may be induced in women over 40 years of age following gonadal radiotherapy treatment with 6 Gy, while significantly higher doses are required to completely destroy the oocyte pool and induce ovarian failure in younger women and children [92]. This reflects the smaller follicle reserve in older patients and hence increased susceptibility to smaller doses of irradiation.

Determination of the impact of chemotherapy and radiotherapy on gonadal function currently involves regular clinical assessment of pubertal status, biochemical assessment of gonadotrophins and sex steroids, menstrual history in females, and semen analysis in males. It has not been possible to detect early gonadal damage in a prepubertal child due to a lack of a sensitive marker of gonadal function.

Inhibin B is a potential marker of gonadotoxicity in this age group. It is secreted primarily from Sertoli cells in males and developing small antral follicles in females. It plays a key role in spermatogenesis and folliculogenesis in adult males and females, respectively. Gonadotoxic chemotherapy has been shown to be associated with a reduction in inhibin B levels [83]. A pilot study assessing inhibin B in relation to sensitive measurements of gonadotrophins as markers of the early gonadotoxic effects of chemotherapy in prepubertal children treated for cancer found that in prepubertal girls with cancer, chemotherapy is associated with suppression of inhibin B. Sustained suppression following treatment may indicate permanent ovarian damage. In prepubertal boys, chemotherapy had little immediate effect on Sertoli cell production of inhibin B. Inhibin B, together with sensitive measurements of FSH, may be a potential marker of the gonadotoxic effects of chemotherapy in prepubertal children with cancer [84].

Fertility Protection and Preservation

Infertility is functionally defined as the inability to conceive after 1 year of intercourse without contraception. Rates of permanent infertility and compromised fertility after cancer therapy vary and depend on many factors. The effects of chemotherapy and radiation therapy depend on the drug or

Table 35.1 Predicted age at ovarian failure with 95 % confidence limits for ages at treatment from 0 to 30 years and for doses 3, 6, 9, and 12 Gy

	3 Gy			6 Gy			9 Gy			12 Gy		
Age	Low	Mean	High	Low	Mean	High	Low	Mean	High	Low	Mean	High
0	31.2	35.1	39.0	18.7	22.6	26.5	9.8	13.7	17.6	4.0	7.9	11.8
1	31.3	35.2	39.1	19.0	22.9	26.8	10.4	14.3	18.2	4.8	8.7	12.6
2	31.5	35.4	39.3	19.3	23.2	27.1	10.9	14.8	18.7	5.5	9.4	13.3
3	31.6	35.5	39.4	19.7	23.6	27.5	11.5	15.4	19.3	6.2	10.1	14.0
4	31.7	35.6	39.5	20.1	24.0	27.9	12.1	16.0	19.9	6.9	10.8	14.7
5	31.9	35.8	39.7	20.5	24.4	28.3	12.7	16.6	20.5	7.7	11.6	15.5
6	32.1	36.0	39.9	20.9	24.8	28.7	13.3	17.2	21.1	8.4	12.3	16.2
7	32.2	36.1	40.0	21.3	25.2	29.1	13.9	17.8	21.7	9.1	13.0	16.9
8	32.4	36.3	40.2	21.7	25.6	29.5	14.6	18.5	22.4	9.9	13.8	17.7
9	32.6	36.5	40.4	22.1	26.0	29.9	15.2	19.1	23.0	10.6	14.5	18.4
10	32.8	36.7	40.6	22.6	26.5	30.4	15.8	19.7	23.6	11.4	15.3	19.2
11	33.0	36.9	40.8	23.0	26.9	30.8	16.5	20.4	24.3	12.1	16.0	19.9
12	33.2	37.1	41.0	23.5	27.4	31.3	17.1	21.0	24.9	12.9	16.8	20.7
13	33.4	37.3	41.2	23.9	27.8	31.7	17.8	21.7	25.6	13.6	17.5	21.4
14	33.6	37.5	41.4	24.4	28.3	32.2	18.5	22.4	26.3	14.4	18.3	22.2
15	33.9	37.8	41.7	24.9	28.8	32.7	19.1	23.0	26.9	15.1	19.0	22.9
16	34.1	38.0	41.9	25.4	29.3	33.2	19.8	23.7	27.6	15.9	19.8	23.7
17	34.3	38.2	42.1	25.9	29.8	33.7	20.5	24.4	28.3	17.0	20.5	24.4
18	34.6	38.5	42.4	26.4	30.3	34.2	21.2	25.1	29.0	18.0	21.3	25.2
19	34.9	38.8	42.7	27.0	30.9	34.8	21.8	25.7	29.6	19.0	22.0	25.9
20	35.1	39.0	42.9	27.5	31.4	35.3	22.5	26.4	30.3	20.0	22.8	26.7
21	35.4	39.3	43.2	28.0	31.9	35.8	23.2	27.1	31.0	21.0	23.5	27.4
22	35.7	39.6	43.5	28.6	32.5	36.4	23.9	27.8	31.7	22.0	24.3	28.2
23	36.0	39.9	43.8	29.1	33.0	36.9	24.6	28.5	32.4	23.0	25.0	28.9
24	36.3	40.2	44.1	29.7	33.6	37.5	25.3	29.2	33.1	24.0	25.7	29.6
25	36.7	40.6	44.5	30.3	34.2	38.1	25.9	29.8	33.7	25.0	26.5	30.4
26	37.0	40.9	44.8	30.8	34.7	38.6	26.6	30.5	34.4	26.0	27.2	31.1
27	37.3	41.2	45.1	31.4	35.3	39.2	27.3	31.2	35.1	27.0	27.9	31.8
28	37.7	41.6	45.5	32.0	35.9	39.8	28.0	31.9	35.8	28.0	28.7	32.6
29	38.0	41.9	45.8	32.5	36.4	40.3	29.0	32.6	36.5	29.0	29.4	33.3
30	38.3	42.2	46.1	33.1	37.0	40.9	30.0	33.2	37.1	30.0	30.1	34.0

location of the radiation field, dose, dose intensity, method of administration, disease, age, gender, and pretreatment fertility of the patient. Male infertility can result from the disease itself as seen in patients with testicular cancer and Hodgkins lymphoma or more frequently from damage or depletion of germinal stem cells (Table 35.2). Measurable effects of chemotherapy or radiotherapy include compromised sperm number, motility, morphology, and DNA integrity. In females, fertility is affected by any treatment that decreases the number of primordial follicles, affects hormonal balance, or interferes with the functioning of the ovaries, fallopian tubes, uterus, or cervix.

Male and female fertility may be transiently or permanently affected by cancer treatment or only manifest in women later through premature ovarian failure. Female fertility may be compromised despite maintenance or resumption of cyclic menses. Even if women are initially fertile after cancer treatment, the duration of their fertility may be shortened with a premature menopause.

There is a paucity of data regarding rates of male and female infertility following most current cancer treatments and oncologists have difficulty providing precise guidance to patients about their risks for infertility.

A review of current literature by the American Society of Clinical Oncologists assessed cancer patients' interest in fertility preservation, quality of evidence supporting current and forthcoming options for preservation of fertility in men and women, and the role of the oncologist in advising patients.

Available evidence suggests that fertility preservation is very important to many people diagnosed with cancer. Infertility from cancer treatment may be associated with psychosocial distress. Even though cancer survivors can become parents through routes such as adoption and third party reproduction (using gamete donation or a gestational carrier) most prefer to have a biological offspring even if they have concerns about birth defects that could result if the parent

Table 35.2 Best assessment of risk of subfertility following current treatment for childhood cancer by disease

Low risk of subfertility (<20 % risk)	
1.	Acute lymphoblastic leukemia
2.	Wilms' tumor
3.	Soft tissue sarcoma stage 1
4.	Germ cell tumors (with gonadal preservation and no radiotherapy)
5.	Retinoblastoma
6.	Brain tumor
	Surgery only Cranial irradiation <24 Gy
Medium risk of subfertility	
1.	Acute myeloblastic leukemia
2.	Hepatoblastoma
3.	Osteosarcoma
4.	Ewing's sarcoma
5.	Soft tissue sarcoma
6.	Neuroblastoma
7.	Hodgkin's disease – "hybrid therapy"
8.	Brain tumor
	Craniospinal radiotherapy Cranial irradiation >24 Gy
High risk of subfertility (>80 % risk)	
1.	Total body irradiation
2.	Localized radiotherapy; pelvic/testicular
3.	Chemotherapy conditioning for bone marrow transplant
4.	Hodgkin's disease – alkylating agent-based therapy
5.	Soft tissue sarcoma – metastatic
Low risk <20 %, High risk >80 %	

had cancer treatment before conception or anxiety about their own longevity or their child's lifetime cancer risk [93–96].

Parents may also be interested in fertility preservation on behalf of their children with cancer. Impaired future fertility is difficult for children to understand but potentially traumatic for them as adults. The use of established methods of fertility – semen cryopreservation and embryo freezing – in postpubertal minor children requires parental consent. However, the modalities available to prepubertal children to preserve fertility are limited by their sexual immaturity and are essentially experimental.

Advances in assisted reproductive technologies have focused attention on the possibility of preserving gonadal tissue for future use [97–99]. Such technique does raise a number of important legal and ethical issues. Concerns include protection of children's reproductive rights and obtaining valid informed consent both for storage and for future use of cryopreserved material. Given the absence of proven therapeutic benefit and potential risk associated with these procedures, together with the uncertainty of predicting infertility from new chemotherapeutic and reproductive strategies, it is questionable whether such treatment is justified or ethical in children without scientific trials. The technique of autotransplantation in patients following cancer treatment raises the theoretical possibility of reintroduction of malignant cells.

Current recommendations from the American Society of Clinical Oncology suggest that the two methods of fertility preservation with the highest likelihood of success are sperm cryopreservation for postpubertal males and embryo freezing for females. Conservative surgical approaches and transposition of ovaries or gonads or gonadal shielding before radiotherapy may also preserve fertility in selected cases. Other available fertility preservation methods should be considered experimental and be performed in centers with the necessary expertise after due ethical process [100].

Although data are limited, there appears to be no detectable increased risk of disease recurrence associated with most fertility preservation methods and pregnancy even in hormonally sensitive tumors [101, 102].

Aside from hereditary genetic syndromes, there is no evidence that a history of cancer, cancer therapy, or fertility interventions increase the risk of cancer or congenital abnormalities in progeny. Available studies, including large registry studies, have shown no increased risk of genetic abnormalities, birth defects, or cancers in children of cancer survivors [72, 103–107].

Conclusion

Endocrine disturbances are common in childhood cancer survivors with an increased prevalence in patients with central nervous system tumors.

Growth hormone deficiency is the commonest endocrine abnormality following cranial radiotherapy occurring between 2 and 5 years from treatment depending on the dose. Multiple pituitary hormone deficiencies also occur at higher doses. Serial monitoring of height, sitting height, weight, and pubertal staging with calculation and interpretation of height velocity and body mass index are essential to enable anticipation and prompt management of growth and puberty problems.

Fertility in both males and females can be affected by cancer treatment given prepubertally. The two methods of fertility preservation with the highest likelihood of success are sperm cryopreservation for postpubertal males and embryo freezing for females. Oncologists should discuss with families how cancer treatment can affect fertility prior to the commencement of therapy and fertility preservation offered where appropriate and available.

A major challenge for the future remains to maintain a high cure rate for childhood cancers while further reducing endocrine and other late effects associated with therapy.

Second Tumors

Charles Keys Robert Carachi

The survival of childhood cancers has improved greatly in the last 30 years. With better diagnostic and therapeutic regimens most children who are now diagnosed with cancer will have a survival rate at 5 years of approximately 70 % [108]. This improved survival is achieved at the expense of the long-term effects of having a childhood malignancy and their irradiation and chemotherapeutic treatments. These late effects include reduced fertility, cardiovascular morbidity, adverse endocrine function, and psychological effects. The development of a second malignant neoplasm (SMN) is also a well-recognized late outcome.

As more children survive into adulthood the extent of SMNs is becoming more apparent. However, such malignancies are difficult to study for several reasons. They take a long time to develop, which requires long follow-up and retrospective data collection. Furthermore, small cohorts of patients make results difficult to interpret. However, large cancer groups have published data from large cohorts of children with cancer and have identified prevalence rates and general patterns of associated tumors. Also certain risk factors have been found such as genetic susceptibilities, effects of treatment regimens, lifestyle, and environmental factors.

Incidence and Associations

Overall in the US, SMNs in survivors of cancer account for 6–10 % of all cancers [108]. A European cohort study showed an overall incidence of 3 % of developing an SMN after a childhood cancer [109]. More recently a cohort study of over 16,000 patients identified an overall risk of developing an SMN by 25 years as 4.2 % [110] (Table 35.3).

Various patterns of associations between primary and SNMs have been noted.

The association between retinoblastoma and developing an SMN, especially sarcomas, has long been known [112]. The proposed mechanism is a combination of genetic susceptibility and radiotherapy exposure. One study showed a 30-year cumulative incidence of SMN of 35 % in patients who received radiotherapy and 5.8 % in those who did not [113].

Wilms' tumor patients are also known to develop SMNs. One study showed an incidence of 0.4 % [114]. These SNMs tend to be bone and soft tissue sarcomas, and are often in the field of previous irradiation. Acute myeloid leukemia, lymphoma, and brain tumors have also been reported (Figs. 35.3a, b).

Sarcomas have been the subject of many studies occurring either as the primary tumor, which then develop an SMN, or as the SMN following a different primary tumor. Following the treatment of soft tissue sarcomas several SMNs have been recognized including a second sarcoma, brain tumors, leukemias, neuroblastomas, and lymphomas [115].

The risk of SMN following a Ewing sarcoma has been the subject of debate. One recent study reported a relative risk of 12.7 % of developing an SMN at 20 years [116]. A second sarcoma following irradiation accounted for most of these.

Brain tumors are the most common solid tumor of childhood, and SMNs following them are well recognized [117]. The incidence is variable and there can be a wide variety of neoplasms including non-Hodgkins lymphoma, basal cell carcinoma, malignant melanoma, and Kaposi sarcoma.

SMN following lymphoma is also becoming more prevalent. Most patients with Hodgkin's lymphoma can now be cured, making this more common. The risk of lung cancer is significantly increased in patients with previous Hodgkin's disease [118]. Other SMNs include leukemia and cancers of the esophagus, stomach, colon, and breast [119]. Patients with non-Hodgkin's lymphoma have also been shown to have an increased risk of all malignancies, especially leukemia and lung cancer [120]. Hodgkin's disease has also been reported as an SMN following leukemia, but in general this is very rare for reasons that are still unknown [121].

Thyroid neoplasms following radiotherapy for childhood malignancy is a well-established late outcome. Primary malignancies include lymphomas, leukemias, Wilms' tumor, and neuroblastomas. These thyroid neoplasms can be either benign or malignant [65].

Risk Factors/Etiology

The risk of developing an SMN is a balance of genetic predisposition, exposure to previous therapy, lifestyle, and environmental factors.

Table 35.3 First and second tumors associated with risk factors

First tumor	Second tumor	Risk factors
Retinoblastoma	Bone and soft tissue sarcoma, pineal, melanoma	Genetic disease, radiation
Wilms' tumor	Bone and soft tissue sarcoma, leukemia, brain	Radiation
Neuroblastoma	Thyroid, bone and soft tissue sarcoma	Radiation
Sarcomas	Other sarcomas of bone and soft tissues	Radiation; neurofibromatosis
Lymphoma	Leukemia, other lymphoma, sarcoma	Alkylating agents, epipodophyllotoxins; radiation

Adapted from Meadows [111]

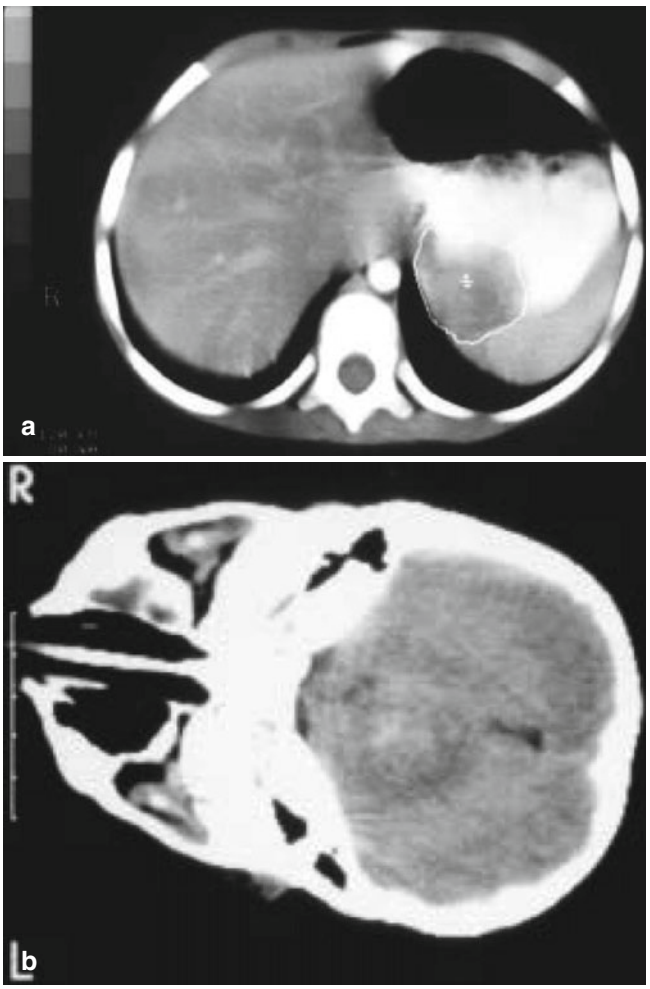

Fig. 35.3 (**a**) This is a CT scan of a 2-year-old boy who presented with a large abdominal mass. He had a large Wilms' tumor on the left side invading the liver. He subsequently was found to have chromosome breakage syndrome when he became unwell following chemo- and radiotherapy. (**b**) Two years later after his treatment was completed, he developed signs of raised intracranial pressure. This CT scan of the brain shows a separate brain tumor. He succumbed shortly after treatment was instituted. His brother also died after treatment for a rhabdomyosarcoma of the head and had a second tumor, a ganglioneuroblastoma of the abdomen discovered at post mortem

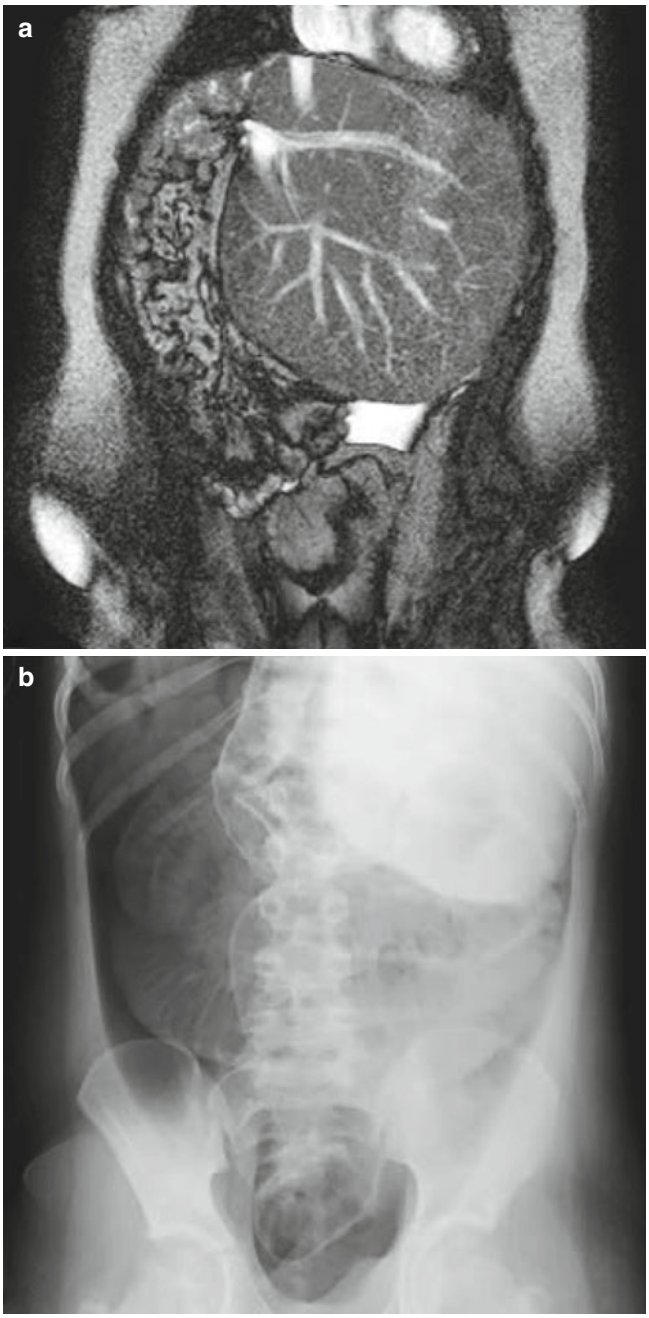

Fig. 35.4 (**a**) This is a scan of a child with a familial rightsided hepatoblastoma that has been successfully resected and following treatment was cured. Genetic studies on the family revealed he had the APC gene mutation. On follow-up 3 years later he developed rectal bleeding. This scan shows compensatory growth of the residual normal left lobe of liver. (**b**) This x-ray demonstrates a complication of a pneumoperitoneum after an attempted biopsy of polyps in the colon. Multiple polyps were encountered. The patient had a total colectomy, and is well

Much has been written about the genetic susceptibility of SMN in children. The risk of developing an SMN is increased in two common pediatric conditions; neurofibromatosis type I, and the genetic form of retinoblastoma [111]. Neurofibromatosis type I is carried by a mutation on chromosome 17 and accounts for 0.5 % of childhood cancers. This gene is associated with an increased risk of developing an SMN.

The genetic form of retinoblastoma involves a constitutional alteration of chromosome 13. These patients have been reported to have a 50 % risk of developing an SMN by 50 years of age [122]. Li-Fraumeni syndrome is a known indicator of cancer manifesting as sarcomas and subsequent risk of SMNs. A germline p53 gene mutation is accountable for this [123].

Other inherited cancer syndromes include multiple endocrine neoplasias and familial adenomatous polyposis. Beckwith-Wiederman syndrome is associated with primary Wilms' tumor and SMN hepatoblastoma (Fig. 35.4a, b). Recent evidence has shown increased RET gene expression in patients who develop thyroid SMN following radiotherapy [124].

Exposure to radiotherapy has long been linked to an increased risk of developing a subsequent neoplasm. Factors that may influence this include age of the child, field of radiation, and dose of irradiation, in addition to the type of primary neoplasm. In general the younger the age at which radiotherapy is received, the greater the risk. Low doses of radiation are associated with thyroid neoplasms [65] and higher doses with sarcomas, although no definite dose threshold has been found [125]. The development of breast tumors following radiation is not thought to be dose related but may be due to a specific susceptibility [126].

Chemotherapy agents are also known to be associated with the development of SMNs. Alkylating agents and epipodophyllotoxins are the most well known and are associated with secondary leukemia [111].

Evidence suggests that the risk of SMN development is further increased with combined radiotherapy and chemotherapy [127, 128].

Summary

As patients with childhood tumors achieve longer survival more SMNs are being seen. These can occur in some well-established patterns that may follow genetic predisposition. They may result as a late effect of exposure to irradiation and some chemotherapeutic agents.

All patients with childhood malignancies require long-term follow-up. Long-term prospective surveillance of all children with malignancies will afford improved understanding of incidence and possible etiology of these SMNs. This may provide the opportunity to prevent and treat these malignancies.

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Minimally Invasive Surgery in the Diagnosis and Treatment of Childhood Cancer

36

George W. Holcomb III and Benno Ure

One of the earliest reports about the use of minimally invasive surgery (MIS) in children described thoracoscopy for evaluation and biopsy of intrathoracic conditions [1]. In that 1979 report, 57 children underwent 65 thoracoscopic procedures. Fifteen of the operations were performed for the diagnosis of an intrathoracic tumor. Three years later, Rodgers and Ryckman described over 150 thoracoscopic operations for evaluation of intrathoracic pathology [2]. Twenty-five of these were undertaken for the potential diagnosis or staging of cancer in patients from 8 months to 18 years of age. Twelve were performed for parenchymal tumors, 11 for mediastinal masses, and two for pleural disease. Interestingly, there were very few publications over the next 10 years describing the use of laparoscopy or thoracoscopy for the treatment of benign or malignant disease in children. With the advent of the MIS revolution in the late 1980s and early 1990s, a number of adult surgeons began to describe their experience using thoracoscopy for lung and esophageal cancers [3–8]. In addition, a number of papers described the utility of laparoscopy in adults for pancreatic, ovarian, gastric and colon cancers [9–17].

The use of MIS in children for benign disease was slow to evolve as was its utilization for malignancies. Over the past 10 years, experience with MIS in children with cancer has grown to the point that this modality can now be considered an acceptable approach for many tumors. In the abdomen, laparoscopy is used primarily for biopsy of new lesions or for second look purposes (Fig. 36.1). In addition, it is being increasingly used for resection of Wilms tumors or other renal lesions which have previously been treated with chemotherapy and have decreased significantly in size [18–20]. This is especially true in Europe where chemotherapy is often given prior to attempted tumor resection. Another optimal candidate is a small baby with a suspected neuroblastoma which is well localized. Although rarely performed, an abdominal staging procedure for Hodgkin's Disease is also a good indication for laparoscopy in children with cancer.

The use of thoracoscopy matured much faster than laparoscopy for malignant disease, primarily due to the fact that biopsy of mediastinal masses or wedge resections of pulmonary lesions are straightforward procedures in children. Also, resection of posterior mediastinal masses can be accomplished thoracoscopically. This chapter will describe the use of laparoscopy and thoracoscopy for children with cancer, the impact of MIS on tumor cell behavior, and will review the recent literature describing these minimally invasive approaches in children with cancer.

Laparoscopy in Pediatric Oncology

The spectrum of malignancies in children for which a laparoscopic biopsy might be useful includes the whole range of pediatric abdominal and retroperitoneal tumors such as neuroblastoma, nephroblastoma, hepatoblastoma, rhabdomyosarcoma, teratoma, lymphoma and several others [21–25]. The feasibility is reported to be excellent with a conversion rate of less than 5 % in some series and a diagnostic accuracy of laparoscopic biopsies for various malignant conditions of up to 100 % [22, 26, 27].

A number of reports have confirmed that laparoscopy is a valid approach for resection of solid malignancies in selected children. However, the feasibility of laparoscopic tumor resection is limited in most reports that include a wide spectrum of tumors. Warmann et al. [22] had to convert in 5 out of 9 resections and Metzelder et al. [25] reported a conversion rate of 42 % with 24 attempted laparoscopic resections of various solid tumors. On the other hand, a 2007 report from Hong Kong described 38 patients over 10 years undergoing laparoscopy for tumor resection [28]. The mean age at operation was 7.5 years (1 day to 15 years). The operation

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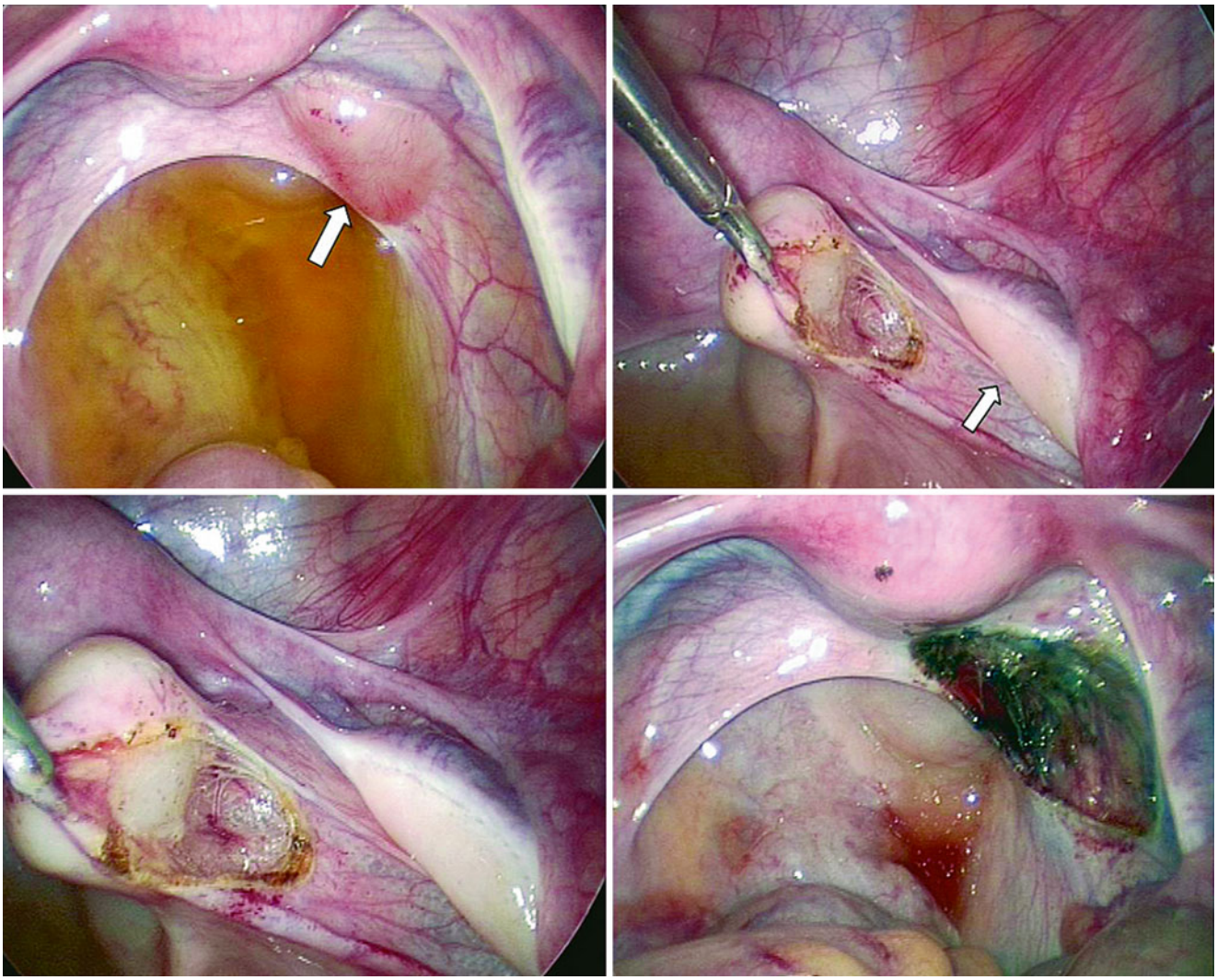

Fig. 36.1 Second-look laparoscopy can be useful after adjuvant therapy in certain circumstances. In this teenage patient who previously had undergone laparotomy and resection of a large germ cell tumor, second-look laparoscopy was performed to determine whether evidence of residual disease existed. *Upper left* , Residual disease is seen along the right pelvic side wall (*white arrow*). *Upper right*, this mass is being resected from the pelvic side wall. Note the normal right ovary (*white arrow*). *Lower left* , further dissection of the mass is achieved. *Lower right*, the mass has been completely excised with hemostasis controlled by cautery. (Reprinted with permission from Pediatric Surgery, 4th edn, Ashcraft , Holcomb, Murphy, eds, Elsevier, 2005, p 676.)

was able to be performed successfully in 30 of the 38 patients. Eight patients required conversion because of limited intraperitoneal space in seven and bleeding in one. Seven of these patients had malignant tumors, and there was no recurrence with an average follow-up of 3.1 years. Similarly, St. Peter et al. reported a low conversion of 10 % for laparoscopic adrenalectomy in 140 children [29].

The patient is usually positioned supine on the operating table, although it may be helpful to place a roll underneath the left or right flank depending on the nature of the laparoscopic operation. For adrenal operations, it is often easier to perform the procedure with the patient positioned in a true lateral position. An orogastric tube should be inserted, and the bladder should be emptied following induction of anesthesia. The bladder can be emptied with a Credé maneuver or a urinary catheter can be introduced if a long procedure is anticipated. For an upper midline abdominal lesion, it is often helpful to place the patient in lithotomy, and the surgeon will stand between the patient's legs, much like for a laparoscopic fundoplication. For a right or left upper abdominal procedure, the patient positioning and location of the personnel should be similar to a laparoscopic cholecystectomy or a splenectomy, respectively.

If the target lesion is in the pelvis, a single monitor is usually needed and positioned at the foot of the bed. The surgeon and assistant stand opposite each other. In general, if the lesion is a left lower abdominal or left pelvic mass, the surgeon should stand on the patient's right side and vice versa for

a right lower abdominal or pelvic mass. For a pelvic lesion, it is important to evacuate the bladder completely so a temporary urinary catheter may be advisable. If a nephrectomy is planned, the patient should be positioned in a 45° or a 90° lateral position, depending on the surgeon's preference.

It is important to use an endoscopic retrieval bag to extract specimens to prevent port site recurrences. No port-site recurrences were observed in any of the larger series of children undergoing laparoscopic resection of neuroblastoma [23, 24, 29]. However, Chui and Lee [30] recently described peritoneal dissemination of a Wilms tumor 3 months after laparoscopic resection and Metzelder and Ure [31] reported on a child with port-site metastasis after biopsy of a Burkitt's lymphoma.

In summary, the laparoscopic approach can be recommended in children with suspected abdominal or retroperitoneal malignancy requiring biopsy. With meticulous selection of patients, the feasibility of laparoscopic resection in children with neuroblastoma and several other types of malignant tumors is excellent. The known short-term benefits of MIS such as less pain and fast recover are obvious, but data on long-term results in larger series of children are needed to establish general recommendations.

Impact of Laparoscopy on Tumor Cell Behavior

The benefits of MIS have been attributed to several underlying mechanisms, including a specific effect on the immune system. Experimental studies have confirmed that MIS interferes with the function of various cell populations which play a key role in the host defense, such as monocytes-macrophages, polymorphnuclear leucocytes and lymphocytes [32, 33]. These specific immunological effects have been attributed to less injury associated with the minimally invasive approach and to metabolic properties of the gas used for the pneumoperitoneum.

Most studies investigating MIS and its effect on tumor biology have focused on laparoscopy. Experimental studies confirm that laparoscopy versus laparotomy and the use of CO_2 versus air for pneumoperitoneum have similar effects, such as a lower migration of polymorphnuclear cells to the abdominal cavity, and lower abdominal macrophage cytokine release [34]. The use of CO_2 during laparoscopy compared to mini-laparotomy with a similar length of abdominal incision was associated with lower circulatory cytokine release, prevented hepatic macrophages from expansion, and preserved normal intraabdominal cell distribution [35]. Effects of CO_2 used for pneumoperitoneum have also been identified in distant organs. The pulmonary macrophage reactive oxygene species release is reduced after pneumoperitoneum with CO_2 compared to air [34]. Besides its effect on macrophage functions, the chemotaxis and migration of polymorphnuclear cells is also blocked by CO_2 [36]. The underlying mechanism of these immune effects is a low pH [37, 38], which is at CO_2 exposed areas of the abdominal cavity during laparoscopy [38]. These effects may even have an impact on survival after sepsis. In a rodent model, CO_2 pneumoperitoneum versus exposure to helium or air significantly reduced the 7 day mortality [39].

Currently, controversy exists about the role of CO_2 in patients with malignant disease. It has been postulated that the alteration of host defense mechanisms may interfere with the clearing of tumor cells spread during the operation. In addition, a direct impact on the behavior of tumor cells has been suggested. The in-vivo behavior of neuroblastoma cells after pneumoperitoneum was investigated by Iwanaka et al. [40] There was no significant difference in survival, tumor growth, or distant metastasis in mice with CO_2 pneumoperitoneum versus laparotomy when the tumor remained untouched. Also, port site recurrences were found to be similar whether biopsies were performed during CO_2 or gasless pneumoperitoneum. On the contrary, Schmidt et al. investigated several pediatric tumor cell lines in-vitro [41]. The proliferation rate of neuroblastoma, hepatoblastoma, hepatocellular carcinoma, and lymphoma cells was significantly reduced for up to 4 days after exposure to CO_2 when compared to air or helium.

CO_2 also causes alterations to the peritoneal surface. Exposure to CO_2 alters the electronmicroscopic structure of mesothelial cell layers and enhances neuroblastoma cell migration through this layer [36]. C-myc and HMCB1 expression of neuroblastoma cells are increased after CO_2 incubation in-vitro [42]. In the mouse model, the incidence of liver metastasis is significantly increased 28 days after CO_2 pneumoperitoneum when compared to laparotomy [43].

It is important to appreciate that these findings might not reflect the clinical environment as children usually receive chemotherapy after the operation. However, as clinical reports on long-term outcomes are scarce and no randomized or controlled clinical trials comparing MIS with conventional surgery have been conducted, definitive recommendations for the use of MIS in children with solid tumors cannot be made. It will be necessary to wait for longer term results.

Thoracoscopy in Pediatric Oncology

The important principles for performing a thoracoscopic operation in a patient with cancer have not changed over the past 15 years. The location of the mass to be biopsied or excised will determine whether or not preoperative localization is needed. Most surface lesions can be visualized at thoracoscopy, and do not need localization. However, if the lesion is small, there should be consideration for preoperative localization as sometimes it can be difficult to visualize a

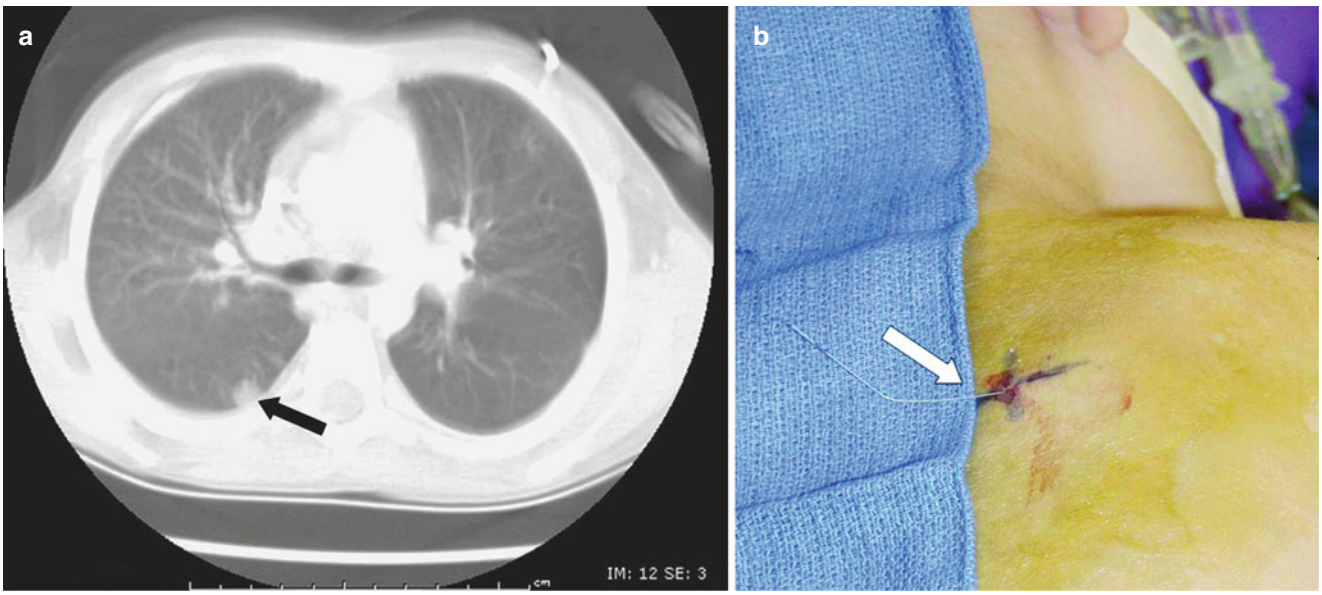

Fig. 36.2 (**a**, **b**) Preoperative localization is important for thoracoscopic operations when compared to the open operation because of the lack of tactile sensation with one's hands. Preoperatively, the patient was noted to have a posterior lung nodule (*black arrow*) (**a**). This lesion was localized preoperatively and the wire is seen exiting the patient' skin (*white arrow*) (**b**)

small lesion on the surface of the lung when the lung is collapsed. Preoperative localization is important for the thoracoscopic procedure as compared with the open operation because of the loss of tactile sensation resulting in the inability to palate the lesion with one's hands. If the lesion is deeper in the parenchyma, preoperative localization should be strongly considered. A number of techniques are possible, including percutaneous placement of a wire into the lesion using CT guidance (Fig. 36.2) [44]. Also, the application of methylene blue or a drop of the patient's own blood may be instilled in the area to be resected in case the wire is dislodged [45, 46]. The use of methylene blue has been banned by many institutions so a blood patch from the patient may be better. It is important not to collapse the lung too quickly following bronchial blockade and insufflation as the wire may become dislodged from the lesion as the lung is pulled away from the chest wall. Localization of parenchymal nodules has also been described using thoracoscopic ultrasound [47].

Another important preoperative consideration is whether or not to use a double lumen endotracheal tube. The smallest double lumen tube is 26 French. Thus, the smallest patient in whom this tube can be utilized is usually 6–8 years of age. Therefore, if a thoracoscopic operation is planned for a younger patient and collapse of the ipsilateral lung is important, other modalities should be considered to effect collapse of the ipsilateral lung. If the patient is undergoing a left thoracoscopic operation, a relatively easy technique is to place an uncuffed endotracheal tube into the right main stem bronchus, which usually allows minimal ventilation into the left lung. If a right thoracoscopy is needed, it is sometimes possible to position an uncuffed endotracheal tube down the left main stem bronchus, although this is not as easy as on the right side. A bronchial blocker can also be introduced down the right main stem bronchus with the endotracheal tube positioned in the trachea to collapse the right lung.

Positive pressure insufflation is a useful technique to create working space in the thoracic cavity. Most surgeons who perform thoracoscopic procedures frequently now use valve cannulas and positive pressure insufflation to effect lung collapse. An insufflation pressure of 6–8 torr usually will result in good parenchymal collapse in most patients. Also, positive pressure helps augment the initial lung collapse if endobronchial blockade is being employed.

An important consideration for a thoracoscopic operation is patient positioning. By positioning the patient on the operating room table in different positions, the surgeon can take advantage of gravity to improve visualization. For an anterior mediastinal lesion, the patient should be placed about 30° supine with a roll under the ipsilateral side. Following lung collapse, the lung should fall more posteriorly and improve visualization of the anterior mediastinum. Conversely, for a posterior mediastinal lesion, the patient should be positioned approximately 30° prone, which allows the lung to fall anterior and improve exposure to the posterior mediastinum (Fig. 36.3). For a parenchymal nodule, the patient can be placed more or less in a 90° decubitus position, although the patient can be tilted anteriorly or posteriorly if the lesion is more posterior or anterior. For a lesion on the diaphragm which requires evaluation for possible biopsy or excision, the patient should be positioned more in a reverse

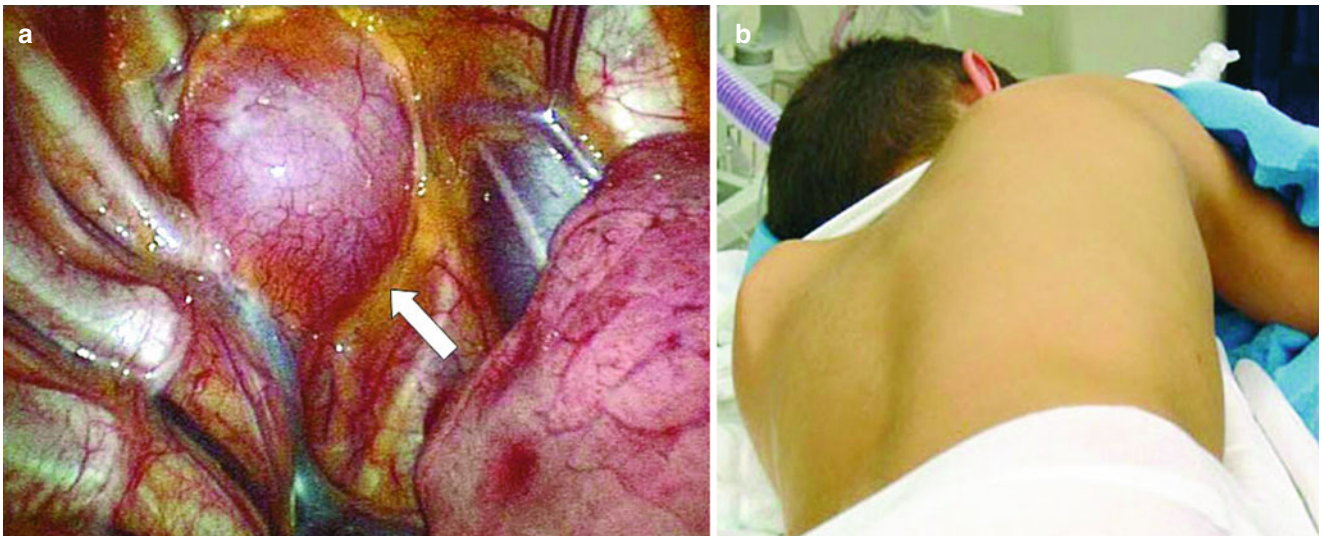

Fig. 36.3 (**a**, **b**) Patient positioning is an important preoperative consideration for a thoracoscopic (or laparoscopic) operation. This teenager had a posterior mediastinal mass (*white arrow*) which turned out to be a ganglioneuroma (**a**). For access to this posterior mediastinal lesion, the patient was placed in a 30° prone position to allow the lung to fall away from the posterior mediastinum (**b**)

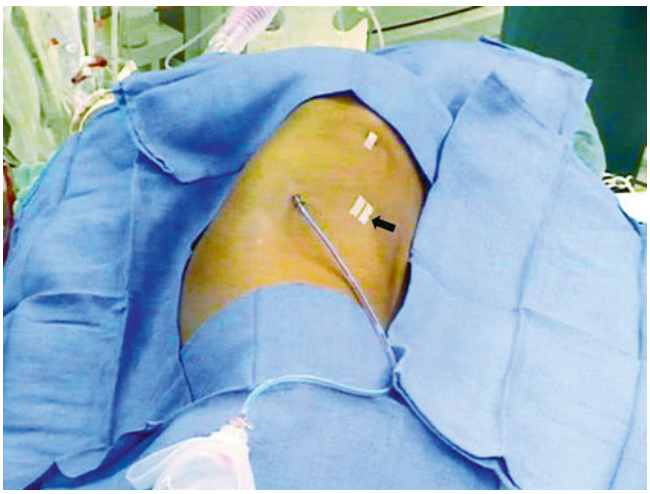

Fig. 36.4 The port positions for a young child undergoing thoracoscopic wedge excision of a metastatic lesion are seen. The largest incision (*arrow*) was positioned as far away from the lesion as possible so that the stapler could be opened within the chest cavity. A small silastic drain was exteriorized through a stab incision

Trendelenburg position to allow the lung to fall away from the diaphragm. Conversely, for a lesion in the apex of the thoracic cavity, the table can be placed more in a head-up position to promote the lung falling more caudal and away from the target area. Positioning of monitors and operating room personnel is the same regardless of whether the operation is for benign or malignant disease.

Another issue in children is whether or not an endoscopic stapler can be utilized for parenchymal resections. For anterior and posterior mediastinal lesions, it is unlikely that a stapler will be needed as there is no need to divide the lung parenchyma. However, for parenchymal disease, a stapler can make the operation safer and more efficacious. On the other hand, the current staplers are made primarily for adult patients, and it is important to modify their use in infants and small children. Therefore, the site for introduction of the stapler should be placed as far away from the lesion as possible in order to be able to introduce the stapler and open the cartridge (Fig. 36.4). It is important to remember that 4–5 cm of the stapler must be in the thoracic cavity before the stapler can be opened. Sometimes, it is necessary to remove the port so that the cartridge can be introduced into the thoracic cavity and opened. The angulated staplers are generally easier to manipulate, ligate, and divide the lung parenchyma (Fig. 36.5). If an additional instrument is needed for retraction, a "stab incision technique" often allows introduction of a 3 or 5 mm instrument without using a cannula. The advantage of using the stab incision technique is that there is greater mobility with an instrument placed directly through the thoracic interspace rather than working through a cannula as angulation and movement of the cannula is often limited by the ribs and size of the interspace. There is rarely a problem with leak of CO_2 through the stab incision if an adequate insufflation flow is used.

Port site metastases remain a concern in these patients, but there are very few literature reports describing this problem. There has been a report of a port site metastases in a child undergoing a thoracoscopic operation for osteogenic sarcoma [48]. However, despite the fact that this problem does not occur as often as initially feared, it is important to place all specimens into an endoscopic retrieval bag for exteriorization (Fig. 36.6). Morcellation

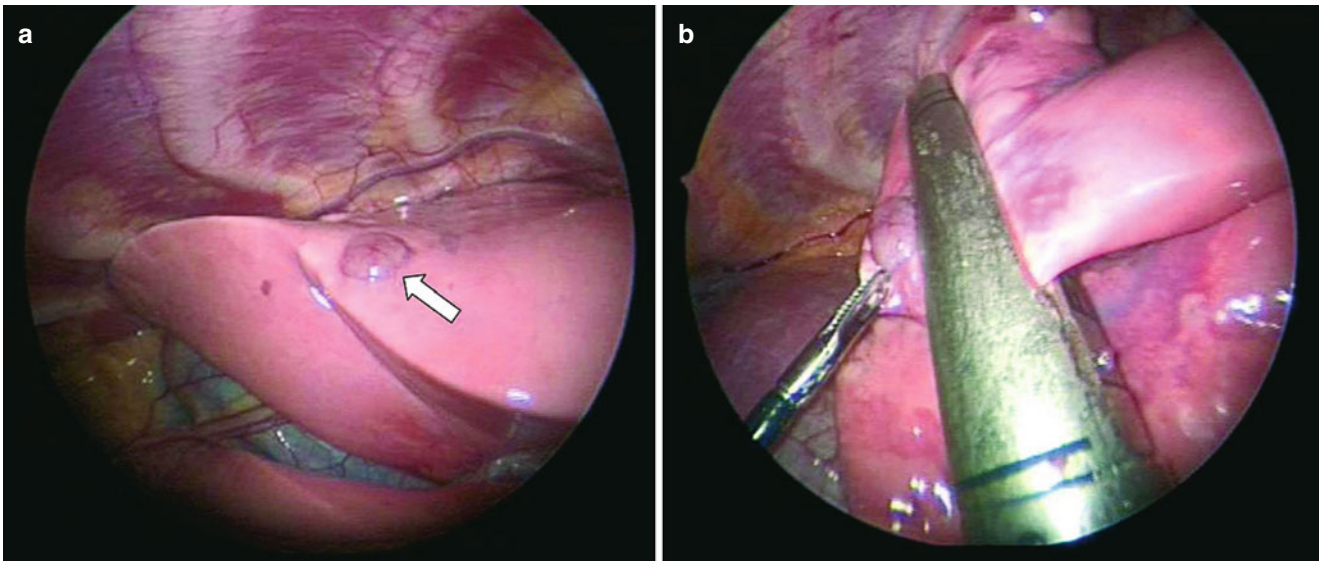

Fig. 36.5 (**a**, **b**) Staplers are the easiest and safest means to extract a pulmonary parenchymal lesion. In this patient with a suspected metastatic Wilms' tumor, the lesion (*arrow*) is seen on the edge of the right upper lobe (**a**). The stapler has been placed across the parenchyma and the lesion has been incorporated in the wedge resection (**b**)

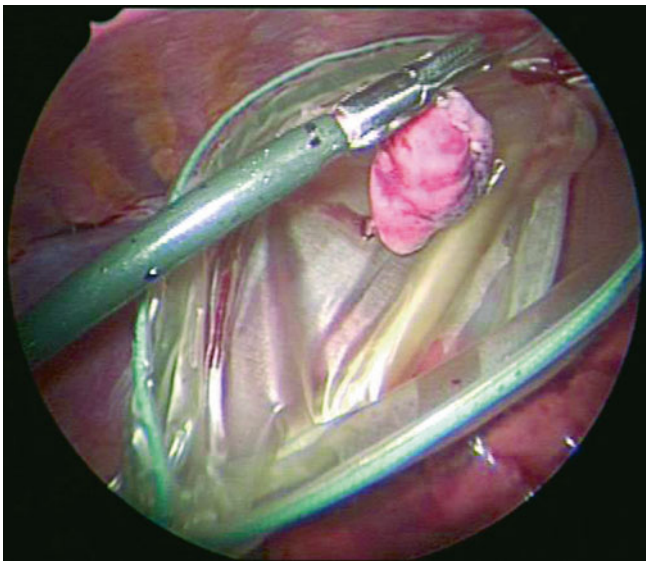

Fig. 36.6 Cancer specimens should be placed into an endoscopic retrieval bag prior to removal from the patient

of cancer specimens is not advisable. Endoscopic retrieval bags are now available in 10 and 15 mm sizes. The 10 mm bag is usually sufficient. It is very important not to extract a specimen that is too large through a small port site as the bag may tear and result in spillage of the specimen which could lead to implantation on the parietal surface of the thoracic cavity or port site recurrences. Therefore, the skin and soft tissue at the site of extraction should be enlarged so the bag and specimen can be exteriorized without tearing the bag.

Literature Review

A 2010 Cochrane review could not come to any definitive conclusion about the efficacy of MIS for patients with cancer because there were no randomized controlled trials or case control trials comparing the open approach versus the minimally invasive approach [49]. Thus, the current literature on this subject comes primarily from retrospective case series and cohort studies.

The first large series describing the use of laparoscopy and thoracoscopy in children with cancer was published in 1995 and described 85 children from 15 CCG (now Children's Oncology Group) institutions who underwent 88 minimally invasive procedures [21]. Twenty-five patients had a laparoscopic operation and 60 patients underwent a total of 63 thoracoscopic procedures. In 2002, Rothenberg and his colleagues described 52 patients undergoing 63 thoracoscopic operations over a 7 year period [50]. Eight patients required conversion to the open approach.

In 2004, the group from St. Jude's Hospital reported 101 patients undergoing 113 minimally invasive operations [23]. Sixty-four patients underwent a laparoscopic operation and 49 had a thoracoscopic procedure. In this series, seven abdominal tumors were excised. In the patients who underwent a thoracoscopic procedure, most of them required wedge resection of a lung nodule. In 14 patients (29 %), the operation had to be converted to an open thoracotomy because of the inability to localize the suspected lesion. None of these patients requiring conversion had undergone attempted preoperative localization.

In a 2007 review, the diagnostic and ablative roles of MIS in children with cancer were evaluated in a consecutive series of 276 patients with cancer [25]. This prospective study included all patients who underwent abdominal and thoracic operations for cancer over a 5 year period. Three hundred and one operations were performed at this single institution and a minimally invasive approach was attempted in 90 of these patients (30 %), and was successful in 69 (77 %) patients. Twenty-one MIS operations for cancer (23 %) were converted to an open procedure. Regarding the abdominal operation, 41 operations for biopsy or staging were attempted laparoscopically and all but six were successfully performed. Twenty-four laparoscopic resections were attempted, and the authors were successful in 14 (58 %). In the chest, thoracoscopy for biopsy was attempted in 14 thoracic operations, and was successful in all but one (93 %). The thoracoscopic approach was attempted in 11 patients for tumor resection, and was successful in seven. Conversions from the MIS approach to the open operation occurred mainly due to limited visibility. Three bleeding complications occurred with one patient requiring a blood transfusion. There were no port site recurrences after a median follow-up of 39 months.

Most reports of laparoscopic tumor resection deal with neuroblastoma. Iwanka and colleagues have described laparoscopic biopsy for neuroblastoma in 25 children and laparoscopic excision in nine patients with localized disease [51]. De Lagausie et al. resected 9 adrenal neuroblastomas and converted one case due to adhesions [52]. Similar success was reported in other small series [53–55]. In their multicenter study, Leclair et al. analyzed 45 children [56]. The conversion rate was 9 %, and the survival rate in children with localized neuroblastoma was 96 % with a median follow-up of 28 months. There was no control group and no information on selection criteria for the laparoscopic approach.

Several authors from Japan have described laparoscopic resection of neuroblastoma identified by mass screening [57, 58]. The feasibility has been excellent with localized disease and well encapsulated tumors with a size of less than 5 cm in diameter. However, the appropriate indication for laparoscopic resection of neuroblastomas identified by mass screening remains a matter of debate. Two Japanese groups have suggested resecting tumors which do not regress for several months or increase in size to more than 5 cm [59, 60]. Other authors have resected smaller neuroblastomas less than 4 cm [61]. Tanaka and co-authors confirmed that over 70 % of 53 patients who fulfilled specific criteria could be observed without surgery and no unfavorable biologic factors were noted in excised tumors [62].

A report from South Korea described 10 children who underwent laparoscopic surgical resection for malignant solid tumors between 2005 and 2010 [63]. Six patients underwent laparoscopic adrenalectomy for neuroblastoma (5) or adrenal cortical carcinoma (l). Two patients underwent laparoscopic partial hepatectomy for hepatoblastoma, one patient underwent laparoscopic salpingo-oophorectomy for yolk sac tumor, and one underwent laparoscopic tumor excision of the rhabdomyosarcoma in the pelvis. Complete resection was achieved in all cases. The tumors ranged from 2.5 to 5.3 cm in maximum diameter. There were no conversions and no postoperative complications or recurrences during the 17.3 month median follow-up.

Several small series of children undergoing laparoscopic nephrectomy for unilateral Wilms tumor have been described. Varlet et al. operated on three children without tumor rupture and event-free survival after 18 months [18]. Duarte et al. reported on 15 cases without information on long-term results [64].

Technical aspects of laparoscopic surgery in children with suspected malignancy include using low pressure pneumoperitoneum to preserve the integrity of the peritoneal cell layers, and minimizing the spread of tumor cells by using retrieval bags. Iwanaka [40] showed experimentally that local or intravenous chemotherapeutic agents, such as cyclophosphamide, reduced the incidence of port-site metastasis from neuroblastoma. The authors therefore recommended chemotherapy as soon as possible after laparoscopic biopsies in children with chemotherapy-sensitive tumors. However, clinical evidence of the advantages of this approach is lacking.

The feasibility of laparoscopic resection for other tumors can only be derived from case reports. Pancreatic tumors including insulinoma [65, 66], pseudopapillary tumors [67], hepatoblastoma [68] renal clear-cell sarcoma [18], and numerous other rare conditions have been successfully resected via laparoscopy. These initial data are encouraging, but long-term follow-up is not yet available.

Although many authors prefer the transabdominal approach for optimal laparoscopic tumor exposition, the transperitoneal route has been also recommended in children with retroperitoneal tumors [69, 70]. On the other hand, Steyaert et al. [71] successfully used a retroperitoneoscopic approach in 10 and Theilen et al. in 16 cases [72]. In this last series, 16 patients with a median age of 16.4 years underwent retroperitoneoscopy between 2004 and 2010 for oncologic disease. Nine patients underwent lymph node sampling, six patients underwent diagnostic biopsy and one patient required resection of a metastatic nodule. Three patients underwent conversion to the open operation. Pampaloni et al. has suggested a transabdominal laparoscopic surgery for right-sided lesions and prefers the retroperitoneoscopic approach for left-sided tumors [73].

Retroperitoneal lymph node dissection (RPLND) is recommended in children 10 years or older with paratesticular rhabdomyosarcoma. Primary tumors greater than 5 cm in size are an additional risk factor for disease recurrence in the

retroperitoneum. Recently, three patients with a mean age of 13.6 years underwent laparoscopic modified RPLND after radical orchiectomy [74]. Their primary testicular masses measured a mean 7.5 cm. The laparoscopic RPLND was performed a mean of 8.6 days after the radical orchiectomy.

A relatively recent report from the Children's Oncology Group Hodgkin's Lymphoma study reviewed 185 patients with Hodgkin's lymphoma with 169 having complete data [75]. Ten of these patients underwent MIS biopsy. An open biopsy was performed in 148 patients, computed tomography-guided core biopsy was performed in five patients, and fine needle aspirations were performed in four patients. There were no staging laparotomies or laparoscopies performed. The diagnostic accuracy was 98.5 % for the open biopsy, 80 % for the core biopsy, 60 % for the thoracoscopic-laparoscopic biopsy and 25 % for the fine needle aspiration.

A number of surgeons have described their experience with thoracoscopy for neurogenic tumors. The group from Great Ormond Street recently described 43 children undergoing thoracoscopic excision of a mediastinal neurogenic tumor [76]. Twenty of these were neuroblastomas, 13 were ganglioneuroblastomas and 10 were ganglioneuromas. Most (86 %) patients were symptomatic with cough, dyspnea, wheezing, spinal compression, dancing eye syndrome and Horner syndrome. Thirty-eight patients underwent an open operation and five underwent a thoracoscopic procedure. Those undergoing thoracoscopy had smaller tumors.

In one institution, a total of 149 cases of neuroblastoma were identified over 17 years [77]. Thirty-seven patients had a tumor located in the thorax. Open thoracotomy was used in 26 cases while the thoracoscopic approach was possible in 11. The authors felt the thoracoscopic approach was effective for this tumor and offered shorter hospitalization and decreased blood loss when compared to open thoracotomy. However, the patients were not matched so that these conclusions may not be valid.

In a multicenter French review of 139 thoracoscopies for either resection or biopsy of pulmonary lesions found the thoracoscopic approach to be safe and effective for the evaluation and resection of solid mediastinal tumors as well as for biopsy and/or resection of metastatic lesions, especially for nephroblastoma [78].

There is no doubt that the minimally invasive approach is beneficial for selected patients with malignancy. It appears especially helpful in patients requiring biopsy or staging. It does not appear to be advantageous for resection of large solid tumors. However, localized tumors which have decreased in size from preoperative chemotherapy are good candidates for the MIS approach. Resection of metastatic nodules in the chest will likely remain the primary utility of thoracoscopy for malignant disease. Patients with neurogenic tumors in the chest are also good candidates, provided that a complete resection can be performed.

Whether the operation is being performed laparoscopically or thoracoscopically, it is important to remember the principles of oncology regarding spillage and port site recurrences. Fortunately, port site recurrences do not appear to be a significant problem for children undergoing the MIS approach for their malignancy.

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New Treatments and New Therapies

37

Edward M. Barksdale Jr. and Iuliana D. Bobanga

Introduction

Recent advances in molecular and cellular biology have opened new avenues for the understanding of the genetic nature of cancer. Emergence of novel treatment approaches over the last 50 years has resulted in significant improvement in the prognosis of childhood cancer. The long-term survival rate for pediatric cancer patients in the 1960s was approximately 20 % and currently is in the range of greater than 75 % [1]. Specifically, the survival in patients with Wilm's tumor has dramatically increased from 30 to 90 % during this period [2]. Despite these impressive trends in survival, little progress has been made in the therapy of many pediatric brain tumors, neuroblastoma, and soft-tissue sarcomas. Furthermore, the focus of mainstream cancer therapies to target the proliferating cells has led to significant side effects in normal developing tissues, organs, and bone marrow predisposing children to growth delay, cognitive impairments, and secondary malignancies [3]. Clearly, strategies that are both more targeted and effective are mandated in these patients.

Enhanced understanding of cancer biology further reinforces the complex and dynamic nature of the genomic events surrounding tumor development, progression, and metastasis. Despite this complexity, there appear to be subsets of molecular, biochemical, cellular, and immunologic traits or fingerprints that characterize all the events in the cell's neoplastic transformation from the normal to the premalignant and then to the malignant phenotype. Hanahan and Weinberg (2000) postulated that cancer was a "manifestation of six essential alterations in cell physiology that collectively dictate malignant growth." These six "hallmarks of cancer" include: (1) autonomous provision of growth signals, (2) resistance to growth inhibitory signals, (3) evasion of apoptosis, (4) replication without limits,(5) sustained angiogenesis, and (6) local tissue invasion and distant metastasis [4]. Recent work over the last three decades gives credence to a possible seventh trait: evasion of host tumor immune detection or immunosurveillance [5]. In this context, the inherent genomic instability of cancers frequently render them rapidly moving targets for therapies directed at only one component of their behavior.

The classic paradigm for cancer therapy consists of radical surgery, multi-agent chemotherapy, and external beam radiation, all directed primarily at limiting the proliferative potential of the cancer cell. Significant strides have been made in the area of cancer immunotherapy, sometimes referred to as the fourth discipline to fight cancer, in addition to surgery, chemotherapy and radiation therapy. This chapter will focus on the emerging therapies and strategies that are in late preclinical phases of development or currently being utilized in early clinical trials. Some of these promising therapies may have applications in the treatment of pediatric solid tumors, while others may remain preclinical yet provide a limited forecast of the possibilities that lie on the horizon of pediatric cancer care. This chapter will specifically focus on immune-based (cellular, vaccine, and monoclonal), anti-angiogenesis, and gene and antisense therapies to provide a conceptual foundation of understanding these novel and emerging cancer strategies. Although these therapies are presented as different subcategories, they are often complementary and overlapping in their application. This is a dynamic and evolving area of combined medical and scientific interest; more detailed reviews of these topics may be obtained in the references.

Immunotherapy

Increased understanding of the molecular, cellular, and immunologic mechanisms of tumor-host interactions has led to greater insights regarding the potential for therapeutic

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manipulation of the immune system to reject invasive and metastatic cancer. Even as early as the late nineteenth century, William Coley, an American surgeon, observed that tumor regression could be mediated by bacterial toxins [7]. Although Burnet hypothesized that cancer occurred due to impairment in immunosurveillance in the mid-twentieth century, the role of the immune system in the pathogenesis of cancer did not gain acceptance until the late twentieth century [8]. A preponderance of evidence now exists that the immune system plays a significant role in cancer biology. This includes the spontaneous regression of certain tumors like neuroblastoma, the presence of antitumor antibodies and immune effector cells in patients with treated tumors, the correlation of lymphocytic infiltration in cancer tissue specimens with survival, the 200-fold increased rate of malignancy in patients with congenital or acquired immunodeficiencies and the fivefold increase in cancer post-transplantation [9–11]. Cancer immunotherapy aims to exploit the specificity and power of the immune system and augment the antitumor immune responses already known to exist [12].

The immune response may be broadly categorized into two interrelated components: innate and adaptive immunity (Fig. 37.1). Innate immunity consists of nonspecific, antigen-independent killing that is mediated by neutrophils, macrophages, monocytes, dendritic cells, natural killer cells, natural killer T cells, ϒδ T cells, eosinophils, and complement activation pathways. Under ideal circumstances, growing tumors provide various "danger" signals which induce inflammation, activate innate effector cells with antitumor activity, and stimulate professional antigen-presenting cells, particularly dendritic cells, to engulf tumor-derived antigens and migrate to draining lymph nodes to trigger an adaptive response by the T and B cells. Adaptive immunity involves antigen-specific immune recognition by T and B cells with subsequent clonal expansion of immune effector ($CD8^+$) and memory and regulatory ($CD4^+$) T cells. Despite this well-synchronized mechanism, the presence of tumor indicates that the immune system has failed to detect or adequately reject the cancer [12]. The immune system has evolved to both recognize self-antigens to avoid their destruction and to delete auto-reactive immune effector cells, a process known as clonal deletion. Many tumors express altered self-antigens that may either evoke an immune response, or due to homology with the native or wild-type protein, induce tolerance. This capacity to discriminate self versus non-self is one of the hallmarks of the immune system and a critical concept in understanding the design, limitations, and side effects of immune-based therapies [13]. Enhancing immune reactivity to malignantly-transformed cells with therapies that exploit known tumor antigens or target the mechanisms of tumor immune evasion while limiting autoimmunity, is the principal goal of cancer immunotherapy [14].

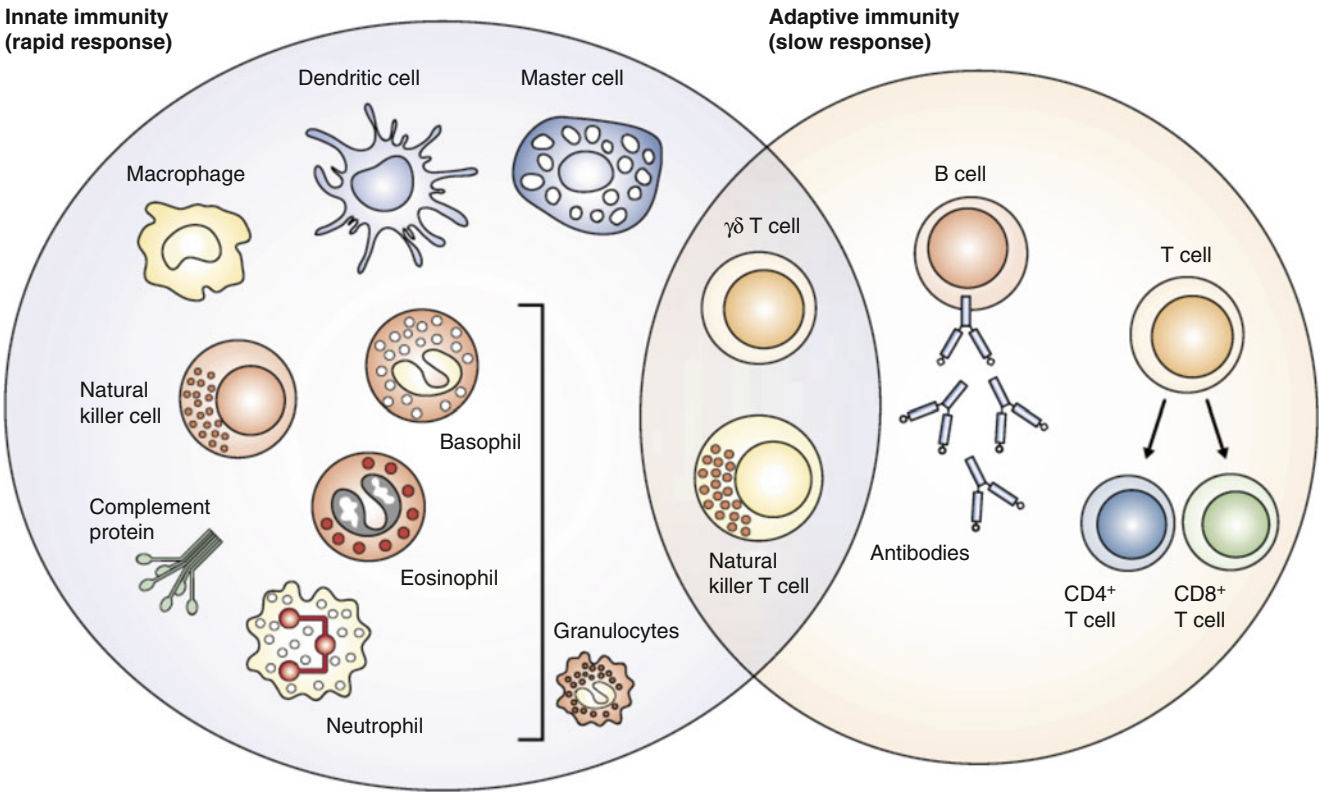

Fig. 37.1 Innate versus adaptive immunity [157]

Table 37.1 General mechanisms that can inhibit antitumor immune reaction in cancer patients

Immune factors	Tumor factors
Low or null frequency of antitumor T cells in vivo	Secretion of immunosuppressive molecules (TGF-beta, IL-10, Arg-1, NO synthase 2)
Low-affinity recognition of self-antigens expressed on tumor cells	Cell surface expression of immunosuppressive ligand (e.g., PD-L1, CTLA-4)
Chronic exposure to tumor antigens with low immunogenicity	Competition for molecules essential for T-cell metabolism and proliferation (e.g., glucose, tryptophan)
Absence of appropriate T-cell priming by immature or nonactivated antigen-presenting cells	Downregulation of MHC and proteins involved in antigen processing and presentation
Immunosuppression of antitumor T cells by regulatory cells (regulatory T cells, cells derived from myeloid lineage)	Heterogeneity of antigen expression in transformed cells constituting the tumor mass, leading to tumor immunoediting

TGF transforming growth factor, *IL-10* interleukin-10, *Arg-1* Arginase-1, *NO* nitric oxyde, *PD-L1* programmed death ligand 1, *CTLA-4* cytotoxic T-lymphocyte Antigen 4, *MHC* major histocompatibility complex [31]

Although many preclinical studies have demonstrated tumor eradication in mice with the use of immunotherapies, progress toward the development of effective antitumor strategies in humans has been limited [15, 16]. The principle barrier to the development of more effective immunotherapies is related to the cancer cell's ability to escape detection or immunosurveillance and the development of tumor-specific immune tolerance. Tumors have evolved numerous mechanisms to induce a state of anergy (Table 37.1). Some of these mechanisms include the downregulation of MHC molecule expression, the loss of tumor antigens, expression of immunosuppressive cytokines (TGF-, IL-10), migration of immunosuppressive T regulatory or suppressor cells to the tumor microenvironment, and the lack of co-stimulatory molecule expression. Another important tolerogenic mechanism is immunoediting, or the selection of tumor cell clones that are not recognized by the antitumor immune response [17–19]. Various immunotherapeutic agents have been developed to circumvent these mechanisms of immune evasion that employ virtually all known immune effector cells [12, 14]. They are often discussed in two broad categories: antibody-based therapies (monoclonal antibodies) and T cell-based therapies (adoptive cell transfer and vaccine based). These categories have expanded to include vaccine adjuvants, dendritic cell activators and growth factors, T-cell stimulators and growth factors, immune checkpoint inhibitors, and agents to neutralize or inhibit suppressive cells, cytokines, and enzymes. Alone, each approach has a limited use in cancer treatment, but in combinations dictated by the biology of the tumor microenvironment, these agents are overwhelmingly likely to have an impact [14].

Pediatric oncology is an attractive target for immune based therapies because of the ability for conventional therapies to establish a state of minimal residual disease (MRD), a setting in which immune-based therapies may be more likely to be effective. Resistance to conventional cancer therapies does not appear to confer resistance to immune-based therapies, thus making immunotherapy an approach that might be integrated into current multimodal regimens or that might have efficacy when used alone [14, 20]. Most of the immune-based therapies have been well-tolerated and have shown promise in the setting of refractory or high-risk malignancies. Some immunotherapies for pediatric malignancies, such as ch14.18 monoclonal antibodies for neuroblastoma and the innate immunity stimulator MTP-PE for osteosarcoma, have already been proven effective in phase III randomized trials and are being incorporated into current anticancer regimens [14, 21, 22].

Monoclonal Antibody Therapy

Three decades ago the technique of monoclonal antibodies (mAbs) was developed and shortly thereafter much enthusiasm emerged about their potential as an anticancer immunotherapy [23]. Despite the initial interest, the early therapeutic agents were marginally effective due to the immunogenicity of the animal-derived antibodies and their direction against ineffective cell targets. These therapies utilized unmodified murine mAbs, which were unable to kill targets due to their inability to fix complement, unable to elicit antibody-dependent cellular cytotoxicity (ADCC) with host mononuclear cells and had limited *in vivo* survival. Furthermore, these antibodies did not target appropriate surface molecules critical to tumor survival, which limited their effectiveness [24, 25]. Present modifications utilizing fully human or humanized monoclonal antibodies (moAbs) directed against cell surface targets like cytokines, growth factors, and death signal receptors have significantly improved the overall effectiveness of these antibodies, making them the most rapidly growing class of immunotherapeutic agents in clinical use [26]. For effective targeting, the targeted antigen should be relatively tumor-specific and highly expressed, with limited shedding, which could act as a decoy for circulating moAbs [27].

Based on the early lessons, various therapeutic strategies have emerged in the current design of moAbs against cancer. MoAbs kill tumor cells via (a) direct tumor cell killing, (b) immune-mediated tumor cell killing and (c) vascular and stromal cell ablation (Fig. 37.2) [24]. Direct tumor cell killing by antibodies can occur through receptor agonist or antagonist activity, induction of apoptosis, or delivery of a payload, such as a drug or cytotoxic agent. Immune-mediated pathways of cell death following binding of the moAb to its target include antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and T cell function regulation [22, 24, 25]. Both ADCC and CDC depend on the key function of the Fc portion of antibodies, which binds effector cells and complement and directs them to the tumor cell. Monoclonal antibodies have also been utilized against host tissue targets like angiogenic molecules or basement membrane proteins. Avastin, a humanized antibody approved for the treatment of metastatic colon cancer, is a potent angiogenesis inhibitor that targets vascular endothelial growth factor [28].

An important mechanism of action used by some moAbs has been the interference with immune regulation of T cell function by blocking T cell inhibitory receptors. CTLA-4 is such a receptor on the surface of T cells that diminishes the autoimmune response. By blocking the receptor with anti-CTLA-4 moAbs, the suppressive signal is inhibited and this leads to an augmentation of T cell-mediated immunity. This has shown antitumor effects in melanoma and prostate cancer in adults and is currently under investigation in a pediatric Phase I trial [29]. Other examples of these agents

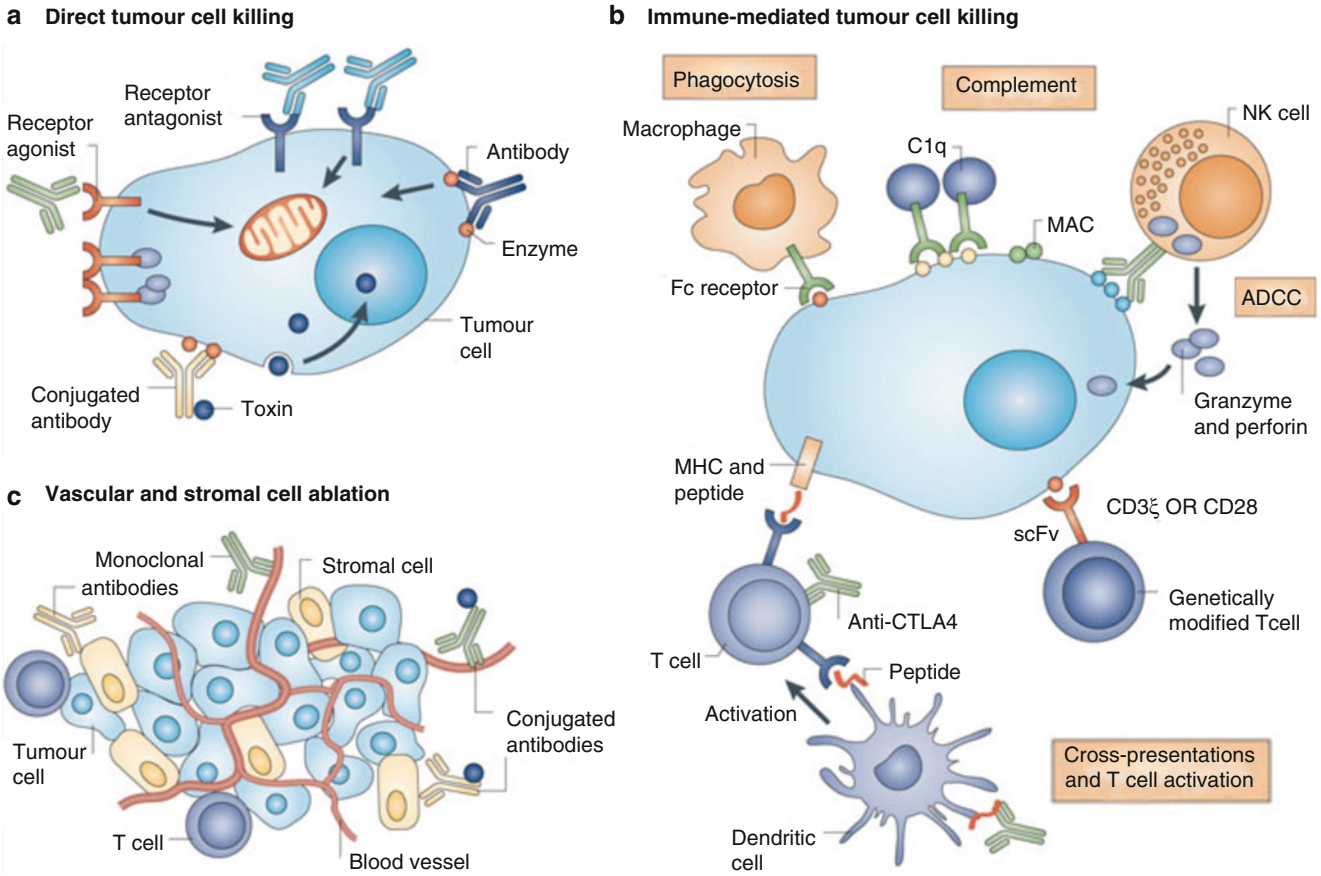

Fig. 37.2 Mechanisms of tumor cell killing by antibodies. (**a**) Direct tumor cell killing can be elicited by receptor agonist activity, such as an antibody binding to a tumor cell surface receptor and activating it, leading to apoptosis (represented by the mitochondrion). It can also be mediated by receptor antagonist activity, such as an antibody binding to a cell surface receptor and blocking dimerization, kinase activation and downstream signaling, leading to reduced proliferation and apoptosis. An antibody binding to an enzyme can lead to neutralization, signaling abrogation and cell death, and conjugated antibodies can be used to deliver a payload (such as a drug, toxin, small interfering RNA or radioisotope) to a tumor cell. (**b**) Immune-mediated tumor cell killing can be carried out by the induction of phagocytosis; complement activation; antibody-dependent cellular cytotoxicity (*ADCC*); genetically modified T cells being targeted to the tumor by single-chain variable fragment (*scFv*); T cells being activated by antibody-mediated cross-presentation of antigen to dendritic cells; and inhibition of T cell inhibitory receptors, such as cytotoxic T lymphocyte-associated antigen 4 (*CTLA4*). (**c**) Vascular and stromal cell ablation can be induced by vasculature receptor antagonism; stromal cell inhibition; delivery of a toxin to stromal cells; and delivery of a toxin to the vasculature. *MAC* membrane attack complex, *MHC* major histocompatibility complex, *NK* natural killer (Adapted from Scott et al. [24])

include anti-PD-L1, which eliminates a negative T-cell receptor signaling pathway, and moAbs that eliminate $CD4^+$ $CD\ 25^+$ regulatory T cells [25].

Several moAbs have been approved for clinical use and well over 100 antibodies are presently being evaluated in therapeutic clinical trials (Table 37.2) [24, 25]. Some of the moAbs currently approved for therapy of solid tumors include Trastuzumab (Hercecptin), a moAb directed against HER-2/neu-positive breast cancer; moAbs against the epidermal growth factor receptor (EGFR), important in some breast and gastrointestinal tumors; and Bevacizumab (Avistin) which targets vascular endothelial growth factor (VEGF). Pediatric solid tumors like sarcomas, neuroblastomas, and gliomas may express similar molecules and may be candidates for treatment with these moAbs. Trastuzumab is currently being explored as a therapy for osteosarcoma [30].

One of the most successful immune therapies in pediatric oncology has been the moAbs targeting the GD2 disialoganglioside in neuroblastoma. It is an ideal target for moAb therapy due to its diffuse expression on nearly all neuroblastoma cells, its lack of shedding from tumor cells and its restricted expression by neuroendocrine tumor cells. Three well-studied moAbs against GD2 – ch14.18, hu14.18, and 3 F8 – have demonstrated response in patients with refractory neuroblastoma and seem to be more effective in a MRD setting than in bulky disease. To enhance the recruitment of effector cells for ADCC, these moAbs have been conjugated to cytokines and growth factors such as IL-2 and GM-CSF. This lead to the creation of "immunocytokines" which work to target the tumor and to transport factors that enhance the immune response within the tumor microenvironment. Great progress has been made with this approach: a Phase III trial with ch14.18 plus GM-CSF and IL-2 versus standard therapy following autologous BMT for high risk neuroblastoma was terminated early due to enhanced event-free and overall survival in the treatment arm [21]. This paves the way for the incorporation of moAbs into regimens for patients with high risk neuroblastoma.

T Cell-Based Therapies

The work pioneered by Rosenberg and others has demonstrated that cells in the immune system can be therapeutically

Table 37.2 Monoclonal antibodies currently FDA approved in oncology and their mechanisms of action

Antibody	Target	FDA-approved indication	Mechanism of action
Naked antibodies: solid malignancies			
Trastuzumab (Herceptin)	ERBB2	ERBB2-positive breast cancer, ERBB2-positive gastric or gastroesophageal junction cancer	Inhibition of ERBB2 signaling and ADCC
Bevacizumab (Avastin)	VEGF	Metastatic colon cancer, advanced NSCLC, progressed glioblastoma, metastatic renal cancer	Inhibition of VEGF signaling
Cetuximab (Erbitux)	EGFR	Squamous cell carcinoma of head and neck, metastatic EGFR-positive colorectal cancer	Inhibition of EGFR signaling and ADCC
Panitumumab (Vectibix)	EGFR	Metastatic EGFR-positive colorectal cancer	Inhibition of EGFR signaling
Ipilimumab (Yervoy)	CTLA-4	Unresectable or metastatic melanoma	Inhibition of CTLA-4 signaling
Naked antibodies: hematologic malignancies			
Rituximab (Mabthera)	CD20	CD20-positive B cell NHL and CLL	ADCC, direct induction of apoptosis and CDC
Alemtuzumab (Campath)	CD52	B cell CLL	Direct induction of apoptosis and CDC
Ofatumumab (Arzerra)	CD20	CLL	ADCC and CDC
Conjugated antibodies: hematologic malignancies			
Brentuzimab vedotin	CD30	Hodgkin's lymphoma, anaplastic lymphoma	Delivery of toxic payload, auristatin toxin
^{90}Y-labelled ibritumomab tiuxetan (Zevalin)	CD20	B cell NHL	Delivery of the radioisotope ^{90}Y
^{131}I-labeled tositumomab (Bexxar)	CD20	CD20-positive follicular NHL	Delivery of the radioisotope ^{131}I, ADCC and direct induction of apoptosis

Adopted from Scott et al. [24]

ADCC antibody-dependent cellular cytotoxicity, *CDC* complement-dependent cytotoxicity, *CLL* chronic lymphocytic leukemia, *CTLA-4* cytotoxic T lymphocyte-associated antigen 4, *EGFR* epidermal growth factor receptor, *FDA* US Food and Drug Administration, *NHL* non-Hodgkin's lymphoma, *NSCLC* non-small cell lung cancer, *VEGF* vascular endothelial growth factor

exploited as anticancer agents. Tumor-reactive $CD8^+$ cytotoxic T lymphocytes (CTLs), $CD4^+$ helper cells, natural killer cells, and antigen presenting cells (dendritic cells, macrophages, etc.) are among the most promising candidates for cell-directed therapies. T lymphocytes have been identified as the dominant cells involved in the rejection of tumors in animal models, thus attempts to develop cell-based immunotherapies in humans have focused on the generation of T cells capable of recognizing antigens expressed by cancers [31].

T-cell activation is a multistage process that first involves antigen-specific engagement of the T cell receptor complex (TCR), which is triggered by the recognition of peptides complexed with MHC Class I or II molecules. The TCR-Ag interaction is facilitated by the engagement of adjacent adhesion molecules like intercellular adhesion molecule 1 (ICAM-1) expressed by the antigen presenting cell (APC) and its specific ligand, leukocyte function antigen 1 (LFA-1) on the T cell, to form a supermolecular activation complex (SMAC) (Fig. 37.3). Costimulation, the binding of other APC surface molecules with their T cell ligands, is required in order to achieve further T cell activation and expansion. The most important of these APC costimulatory signaling molecules are B7.1 and B7.2 which bind CD28 on T cells. Absent or inadequate CD28 signaling/costimulation results in the induction of a tolerogenic response to the specific antigen (Fig. 37.4) [32, 33].

While many tumor-associated antigens that serve as targets for CTLs have been identified, solid cancers in humans grow and metastasize in immunocompetent hosts. Two main reasons explain this: most cancers are weakly or not immunogenic, thus tumor-reacting lymphocytes are few, and those that are present may undergo anergy, and thus become tolerant or are immunosuppressed by systemic factors or molecules in the tumor microenvironment [31]. Multiple mechanisms that result in cancer progressing despite a competent immune system are described in Table 37.1. A subset of T cells, regulatory or suppressor T (T reg) cells, are a functionally distinct population of CD4+ CD25+ immune effector cells that maintain the state of self tolerance and eliminate auto-reactive CTLs, including those that may be directed against tumor antigens. Large numbers of T reg cells have been found in breast, ovarian, pancreatic, and lung cancer and have a strong correlation with poor outcomes [34]. The expression of the transcriptional repressor FOXP3 in $CD4^+CD25^+$ T reg cells creates a microenvironment that favors tumor proliferation through direct effects on CTL and antigen presenting cell trafficking (Fig. 37.5) [35]. Depletion of T reg subsets offers a potential treatment strategy in patients with solid malignancies and high T reg tumor infiltration [36, 37].

Despite the inhibitory mechanisms that result in tumor propagation, T-cell-mediated immunity is the main mechanism by which tumors are rejected in preclinical models [31, 38]. Thus, the goal of cancer immunotherapy is to supply an adequate number of antitumor CTLs with enhanced function in conjuncture with mechanisms that avoid immune suppression and tolerance in the tumor microenvironment. T-cell-based immunotherapies may be categorizes by three major mechanisms: (1) nonspecific immune modulation, (2) active immunization with cancer vaccines, and (3) adoptive immunotherapy, or the transfer of autologous *ex vivo*-stimulated T cells [31].

Nonspecific Immunotherapy

Nonspecific immune therapies aim to stimulate antitumor effector T cells or block the negative checkpoints that inhibit T cell function [31]. Two cytokines have been used as stimulators of effector T cells and are becoming incorporated into standard antitumor therapy: interleukin-2 (IL-2) is FDA

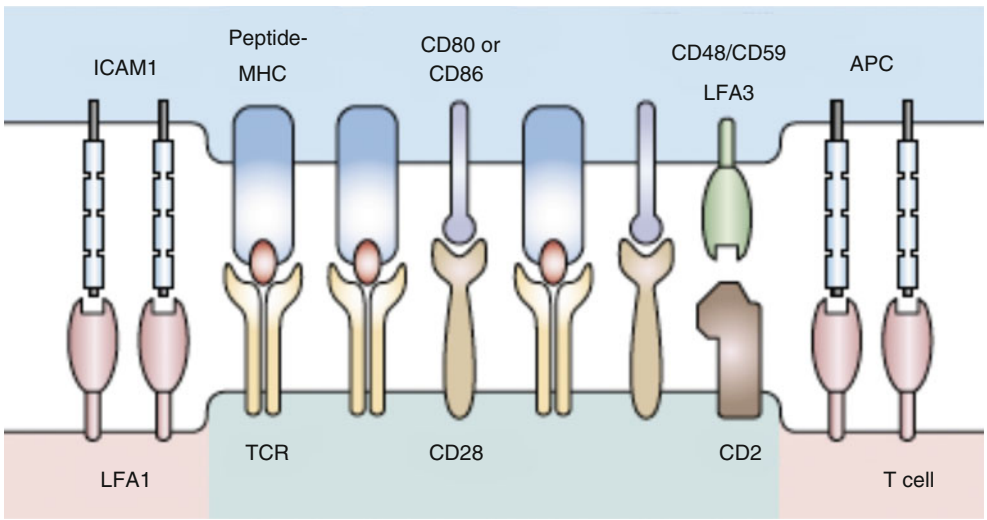

Fig. 37.3 Supermolecular activation complex (SMAC). T cell receptor-antigen-major histocompatibility complex (TCRAg(Peptide)-MHC) binding is facilitated by the engagement of adjacent adhesion molecules like intracellular adhesion molecule 1 (*ICAM-1*), CD 80/CD86, and CD48/CD59 (*LFA-3*) expressed by the antigen-presenting cell to their specific ligands leukocyte function antigen 1 (*LFA-1*), CD2, and CD28 on the T cells respectively to form the supermolecular activation complex (SMAC) or "immunologic synapse" [153]

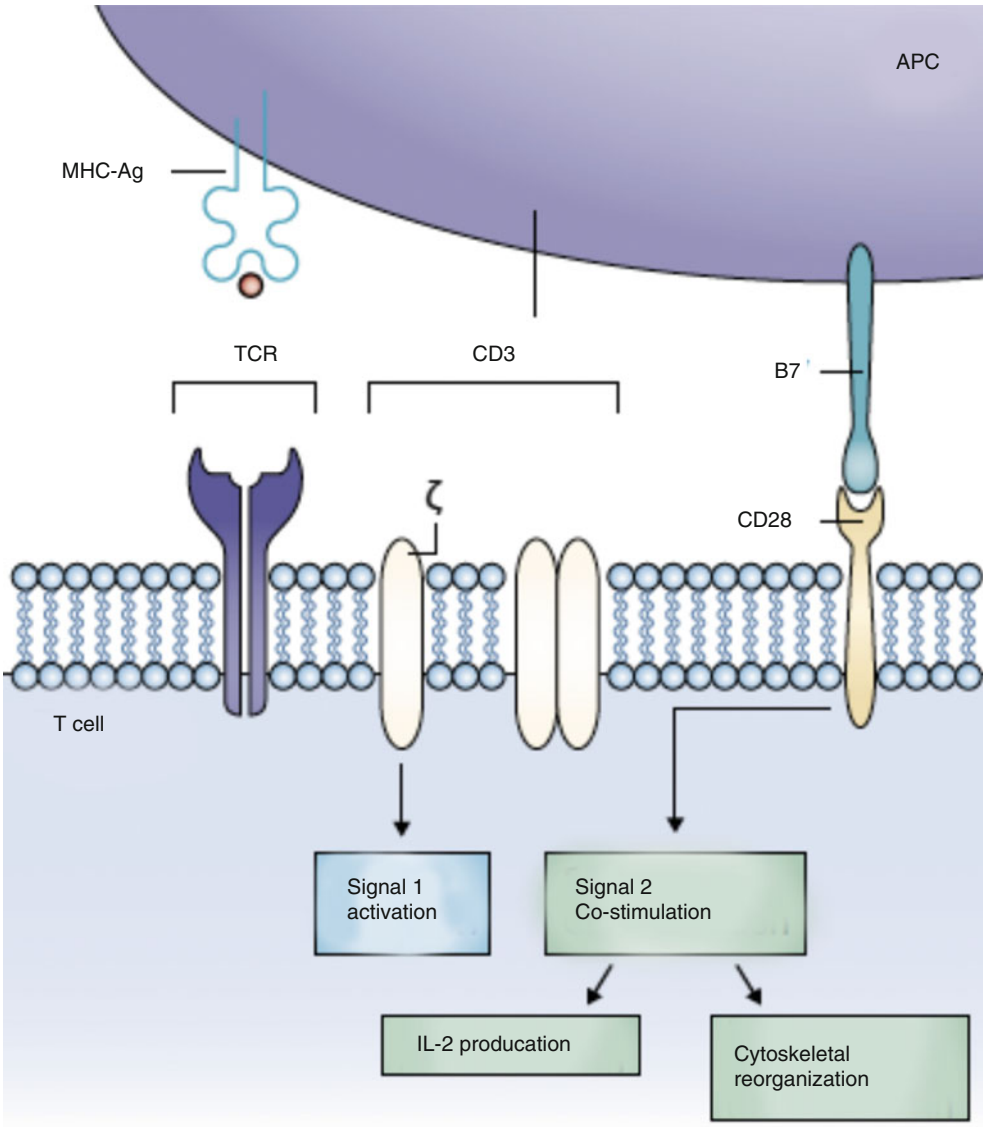

Fig. 37.4 T cell receptor binding and costimulation. T cell activation requires two signals. The first signal occurs when the T cell receptor binds with its specific antigen (*red*) that is presented by the Major Histocompatibility Complex (*MHC*) molecule on the antigen-presenting cell (*APC*) in conjunction with the CD3 proteins expressed adjacent to the receptor. A second signal that is independent of binding must occur to complete the process of activation. This second signal is costimulation, which is initiated by the binding of CD28 receptor for the B7.1 (CD80) and B7.2 (CD86) ligands expressed on the APC. This leads to cytotoxic T cell activation and expansion of T helper cell differentiation and migration. Costimulation also results in the production of antiapoptotic survival factors for lymphocytes. The absence of costimulation/signal 2 leads to the development of anergy or T cell tolerance to the presented antigen [154]

approved for the treatment of metastatic melanoma and renal cancer, and interferon alpha-2-beta (IFNα2β) is FDA-approved for node-positive melanoma patients, hairy cell leukemia, AIDS-related Kaposi's sarcoma and CML [39–41]. IL-2 alone has not been found sufficient to induce regression of other solid cancers, but is also being used as an adjuvant to other immunotherapies. Toxicities associated with IL-2 include capillary leak syndrome and autoimmune effects, such as vitiligo and thyroiditis. Interestingly, the occurrence of autoimmune side effects correlates with cancer regression [42]. IFNα2β is a cytokine produced by lymphocytes, macrophages and dendritic cells primarily in response to viral infections, but has shown activity against a variety of malignancies [31]. Ongoing clinical trials examine the use of IFNα2β in children with melanoma, plexiform neurofibromas and brain tumors and other hematologic malignancies [43].

Activated T cells express surface inhibitory molecules that suppress T cell activity when they bind to their corresponding ligands on immature antigen presenting cells (APCs) or tumor cells (see Fig. 37.11). Monoclonal antibodies against these inhibitory molecules have been developed and shown to be effective for some cancers (Table 37.3, Fig. 37.1). Anti-CTLA-4 moAbs, ipilimumab, works by preventing the binding of CTLA-4 on activated T cells with its ligand, B7, and thus preventing the T cell's inactivation [44]. Ipilimumab was recently FDA-approved as a second-line treatment for patients with metastatic melanoma, but is used with caution due to its severe immune-related toxicities, particularly enterocolitis [45]. A similar mechanism is used to block another inhibitory molecule on activated T cells, PD-1, or its ligand on APCs and tumor cells, PD-L1, with very promising results in multiple advanced solid malignancies [46, 47]. Although nonspecific

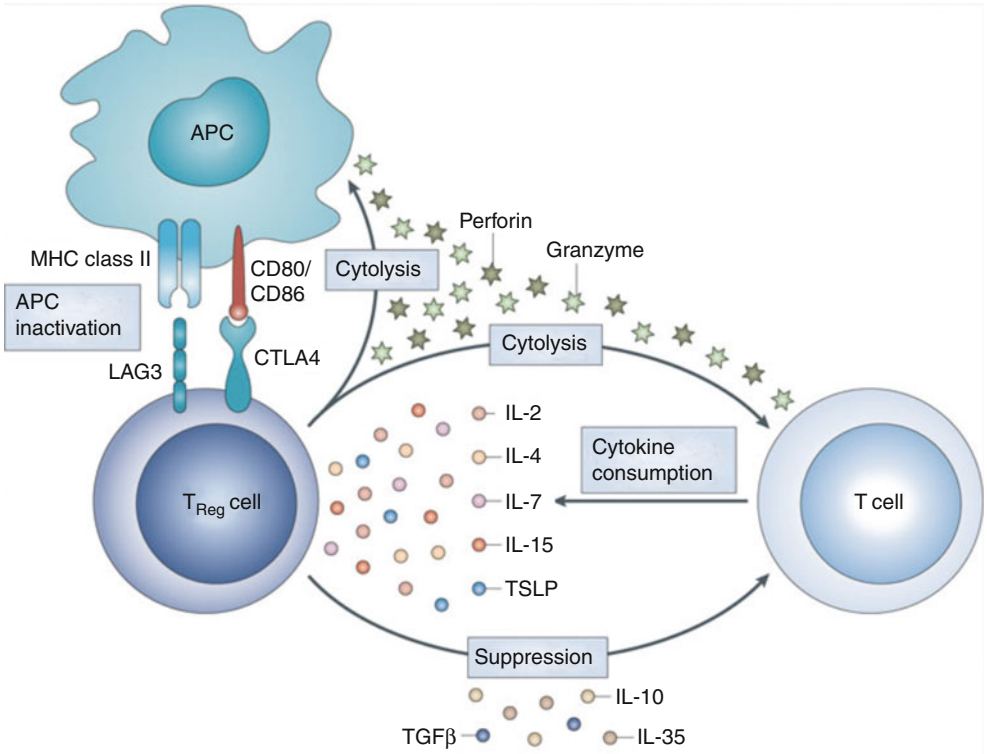

Fig. 37.5 Regulatory T cells (*T regs*) use several mechanisms to suppress conventional T cells. T regs inhibit the maturation of APCs and block the surface expression of MHC molecules and costimulatory molecules CD80 and CD86, thus preventing the interaction between APCs and T cells. T regs can also secrete granzymes and perforin, which causes cytolysis of T cells and APCs. T regs also secrete inhibitory cytokines (transformin growth factor-β (*TGFβ*), interleukin-10 (*IL-10*), *IL35*) that suppress the activation and proliferation of T cells. T regs consume cytokines of the common cytokine receptor γ-chain (γc), which induces the expression of pro-apoptotic proteins within conventional T cells and increases their apoptosis rate. *CTLA4* cytotoxic T lymphocyte antigen 4, *LAG3* lymphocyte activation gene 3, *TSLP* thymic stromal lymphoprotein [159]

Table 37.3 Blockade of negative immunoregulatory checkpoints that impair immunotherapy

Host negative immunoregulatory mechanism	Potential intervention to release checkpoint on the immune response
After interaction with CD80/CD86 family on APCs, negative T cell costimulatory molecule CTLA-4 delivers signals that terminate T cell activation	Antibody-mediated blockade of CTLA-4 enhances anti-tumor immunity induced by vaccine
PD1 interaction with PDL1 or PDL2 inhibits T cell receptor-mediated proliferation and activation of CD4+ T cells	Anti-PDL1 antibody, Anti PD1 antibody
CD4+ CD25+ negative regulatory T cells (suppressor T cells) inhibit antitumor immune response	Oncotoxin (IL-2 diphtheria toxin ONTAK), anti IL-2Rα Pseudomonas toxin (LMB-2), or CD25-directed antibody (PC61) therapy to deplete T regs
IL-2-mediated self-tolerance leads to apoptosis of tumor-specific T cells	IL-15 to facilitate the survival of NK and memory phenotype CD8 T cells in lieu of IL-2
CD4+ NK T cells generate IL-13, which indirectly (via TGB-β) inhibits CD8+ cell-mediated anti-tumor responses. TBG-β is also synthesized directly by tumor cells or host cells via other mechanisms	IL-13Rα IgFc or anti- TBG-β monoclonal antibody

APCs antigen-presenting cells, *PD1* programmed cell death-1, *PDL1* programmed cell death ligand-1, *NK* natural killer, *TGF* transforming growth factor, *CTLA-4* cytotoxic T-lymphocyte antigen-4

immunotherapies have been found to be most effective in metastatic melanoma and renal cancer, other similar inhibitory molecules, along with cytokines that preferentially activate CTLs, such as IL-15, IL-21, and IL-12, are under investigation in these and other solid adult and pediatric tumors [31, 48].

Adoptive Cell Transfer

The efficacy of T cell-based immunotherapies may be limited by the inability to rapidly generate large numbers of antigen-specific T cells *in vivo*. Adoptive T cell transfer allows for generation and expansion of large quantities of

autologous, activated, target-directed T cells [49]. Adoptive cell transfer (ACT) techniques involve three principal steps in order to produce potent antitumor responses: (1) isolation of antitumor T cells from patients with cancer; (2) *ex vivo* expansion and activation of these CTLs; and (3) autologous reinfusion of CTLs with appropriate growth factors (Fig. 37.6) [50]. CTLs recognize antigens secreted by tumors that consist of 8–10 amino acid peptide fragments or epitopes derived from cytoplasmic proteins that have undergone proteosomic degradation. These epitopes are then covalently bound in the cleft of the Class I Human Leukocyte Antigen (HLA), also known as the Major Histocompatibility Complex (MHC) located on APCs, and presented to the complimentary TCR on the CTLs [51]. Two types of autologous T cells are currently used in ACT: (1) tumor-infiltrating lymphocytes (TILs) grown from metastatic tumor nodules, and (2) peripheral blood lymphocytes (PBLs) harvested by leukapheresis and genetically modified to express a TCR or a chimeric antigen receptor (CAR) to a specific tumor antigen [52].

Adoptive Cell Transfer Using Tumor-Infiltrating Lymphocytes (TIL)

One of the greatest successes of ACT has been accomplished in the use of TILs in the treatment of metastatic melanoma, particularly when patients are given an immunodepleting preparation regimen before TIL and IL-2 infusion [53]. This immunodepleting preparation eliminates suppressive T regs as well as other endogenous lymphocytes that compete for growth-promoting chemokines, such as IL-7 and IL-15 [31, 49]. Despite its success in malignant melanoma, the challenge of using TIL for ACT lies in the limited number of patients that are candidates for surgical excision of a tumor metastasis necessary to generate TIL. Furthermore, TIL with demonstrable antitumor activity have rarely been generated from tumors other than melanoma [31].

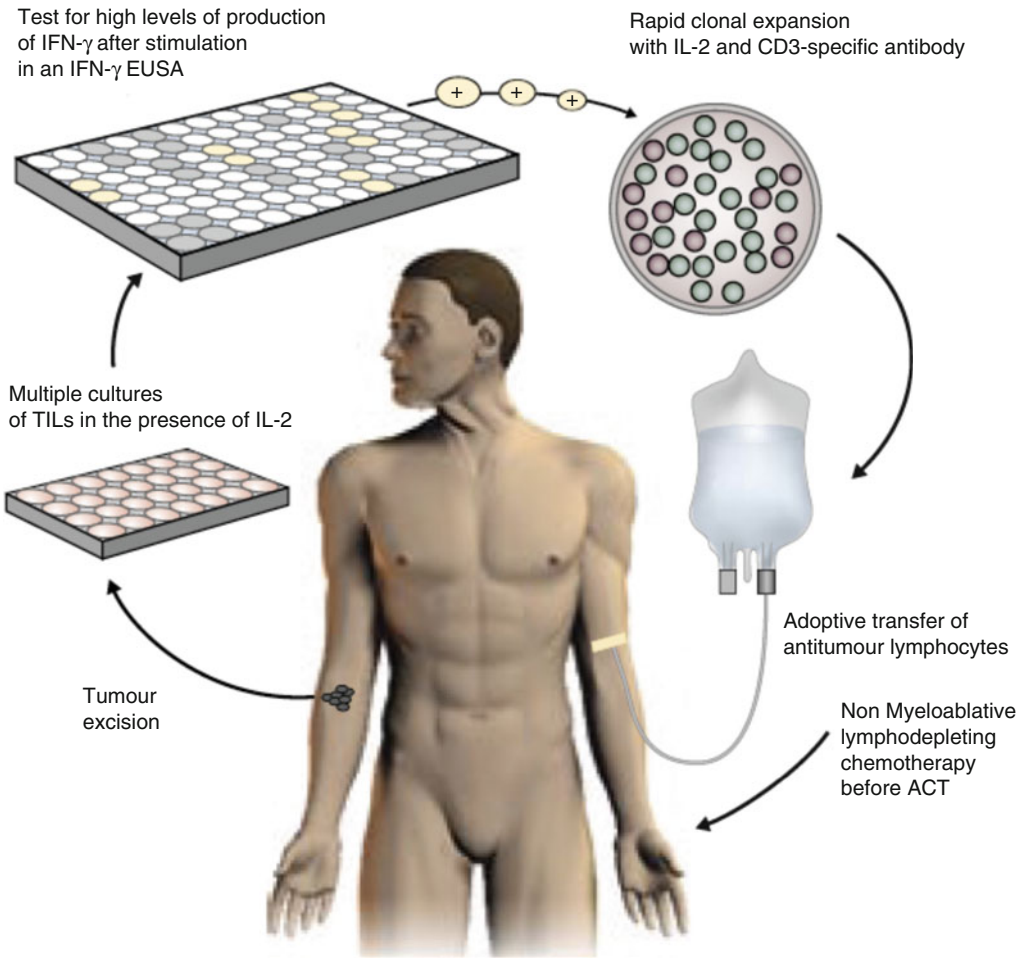

Fig. 37.6 Adoptive Cell Transfer. This technique of immunotherapy involves the isolation from tumor infiltrating leukocytes (*TILs*) of antitumor T cells with high avidity to and high activity against tumor antigens selected and isolated from excised tumor in cancer patients. These TILs are expanded ex-vivo with cytokines like interleukin-2 (IL-1) and T cell clones with high anti-tumor specificity (high level interferon-γ production post-stimulation) are selected and further expanded with IL-2 and activated with anti-CD3 antibody prior to reinfusion. Patients will also receive non-myeloablating lymphodepleting chemotherapy prior to reinfusion of the adoptively transferred T cells (Adopted from Gattinoni et al. [160])

Adoptive Cell Transfer Using Genetically Modified Autologous Peripheral Blood Lymphocytes (PBL)

A new frontier in adoptive immunotherapy has been reached by genetically engineering T cell receptors on cytotoxic T cells. This method creates CTL populations with particular antigen specificities that are expanded *ex vivo* and then administered as adoptive immunotherapy [52]. Both genetically engineered T cell receptors that recognize antigen in an MHC restricted manner, as well as genetically engineered receptors that incorporate the binding sites of moAbs (chimeric antigen receptors or CARs), have been used (Fig. 37.7) [54, 55]. Concern for autoimmune reactions and the restricted interaction of engineered TCRs with peptides presented only by MHC class I molecules limits the effectiveness of engineered TCRs [56]. CARs overcome some of these limitations. They are composed of a single-chain Fv fragment from a monoclonal antibody fused to the intracellular activating signaling chair of the T cell receptor (Fig. 37.8) [14, 31, 54]. These CAR-engineered T cells have the ability to recognize antigen similar to antibodies, directly on tumor cells, following which they become cytotoxic and kill the identified cell (Fig. 37.9) [54]. The advantage of CARs is that they bypass one of the common mechanisms that tumors use to evade the immune response: MHC downregulation.

CAR-transduced cells have been shown to traffic to tumor sites [57, 58]. In children with neuroblastoma, second-generation CARs against GD2 have been studied in clinical trials, where EBV-specific cytotoxic lymphocytes were engineered to recognize GD2. Successful activity against neuroblastoma was found, with 50 % objective responses, including one sustained CR [59]. Clinical trials using engineered T cells and CARs against pediatric malignancies and ongoing for children with ALL, lymphoma, osteosarcoma, medulloblastoma and glioblastoma multiforme [14, 26, 60, 61].

Vaccine Therapy

The holy grail of tumor immunotherapy is the development of a preventive vaccine that will eradicate cancers in a manner

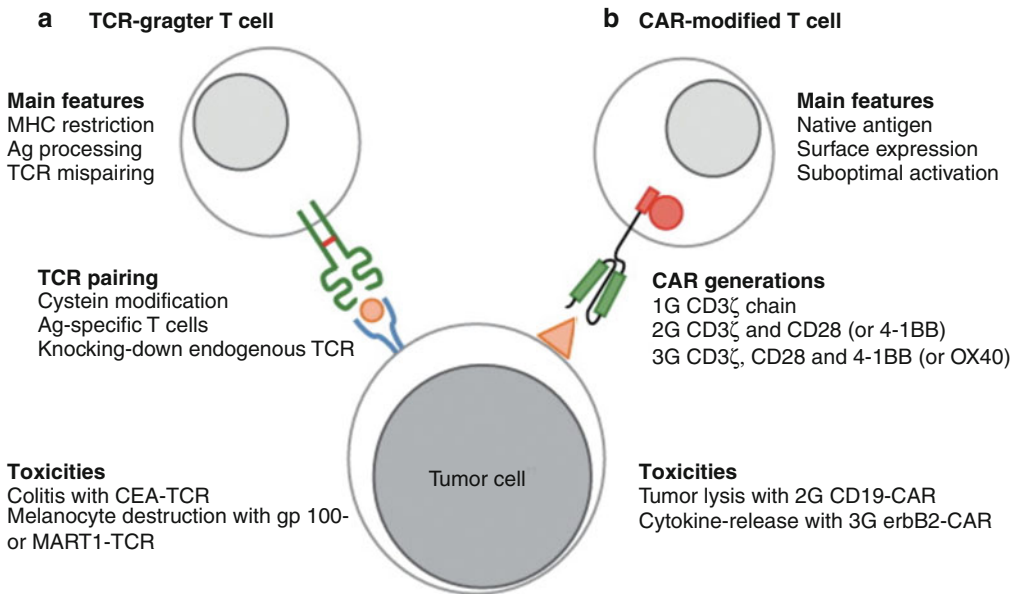

Fig. 37.7 Adoptive cell transfer – the main features of tumor cell recognition by TCR-grafter or CAR-modified T cella. The main features of tumor–cell recognition by TCR-grafted or CAR-modified T cells. (**a**) Tumor–cell recognition by TCR-grafted T cells requires antigen processing and presentation by MHC molecules. Mispairing of the introduced TCR α and β chains with the endogenous chains, however, may lead to the formation of TCRs with unpredicted and potentially dangerous specificities and toxicities, including colitis and destruction of skin, ear and eye melanocytes. To avoid TCR mispairing, different strategies include cysteine modification to additional disulfide bonds between the α and β chain of the desired TCR, transduction of viral specific T cells to reduce the repertoire of potentially mispaired TCRs and knocking down the endogenous TCR by genetic means. (**b**) CAR-modified T cells recognize their target antigen in its native, unprocessed form as it is expressed on the cell surface. Suboptimal activation of lymphocytes by earlier generations of CARs is currently being addressed by the introduction in cis of endogenous signaling domains from co-stimulatory receptors, such as CD28, 4-1BB, or OX40. This created different generations (*G*) of CARs, which are now classified as follows: 1G consisting of the CD3 ζ chain alone and mainly resulting in effector functions; 2G which have the CD3 ζ chain in combination with the intracellular immunoreceptor tyrosine-based activation motif (ITAM) of CD28 or 4-1BB, leading to enhanced cytokine production and proliferation; and 3G with the CD3 ζ chain and CD28 ITAM, plus additional ITAMs from either 4-1BB or OX40, resulting in prolonged survival. Toxicities reported in clinical trials include massive tumor-lysis syndrome and cytokine release storm [55]

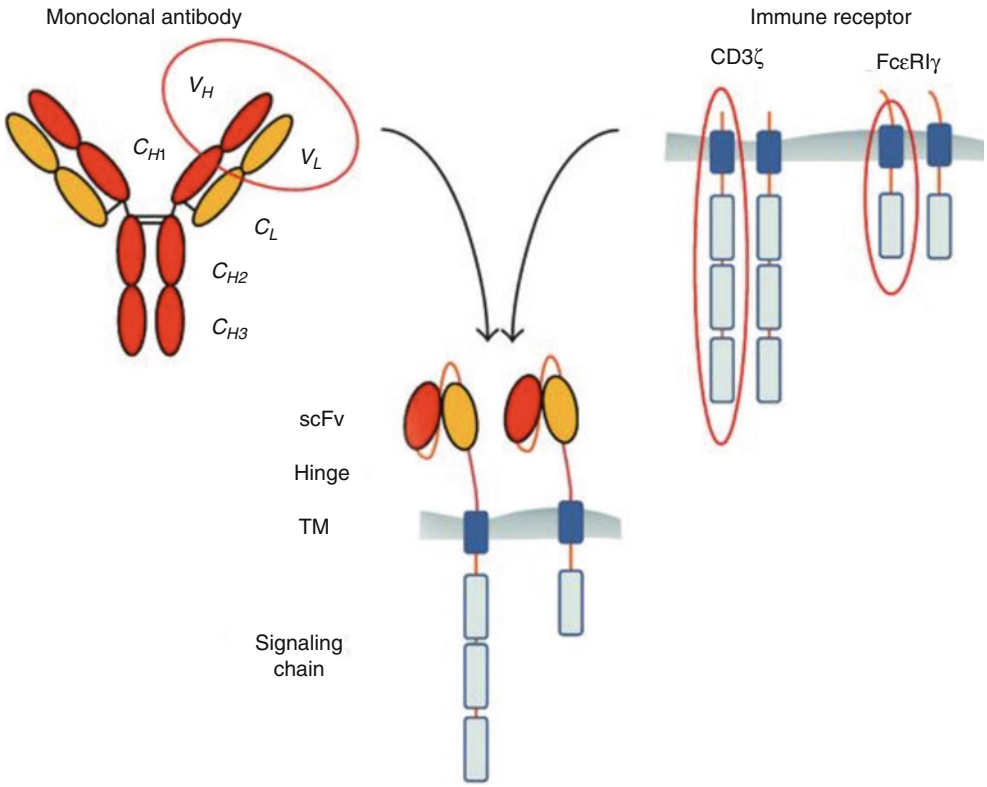

Fig. 37.8 Architecture of chimeric antigen receptors (CARs). CARs are made up of a binding motif, an extracellular hinge and spacer element, a transmembrane region (*TM*), and a signaling endodomain. The binding motif consists of single chain fragment variable (scFv) derived from a tumor associated antigen-specific monoclonal antibody and the signaling domains come from activating and costimulatory immune receptors [54]

analogous to the smallpox vaccine. Although 10–20 % of all human tumors may be caused by viruses and other microorganisms, the vast majority of human malignancies are the result of either exogenous carcinogens or endogenous genomic events that result in malignant transformation [62]. Hepatitis B and Human Papilloma virus vaccines will undoubtedly markedly diminish the worldwide incidence of hepatic and cervical malignancies, respectively [63, 64]. The goal of the ideal vaccine for cancer prevention would provide a sustained response against oncogenesis over the entire life of the individual (Fig. 37.10). These preventive therapies would likely require periodic boosters to both stimulate and maintain immune memory. These vaccines would also need to simultaneously thwart the development of self-reactive clones that would lead to the development of autoimmune disease. The efficacy of this type of vaccine appears to require the coadministration of other immunoadjuvants like cytokines, allogeneic MHC glycoproteins, costimulatory molecules, and microbial CpG. Furthermore, the data support that in order for these preventive vaccines to be effective, they must be initiated early in the process of tumorigenesis [65].

In contrast to preventive vaccines, therapeutic vaccines are more readily applicable to current cancer therapy. Various categories of vaccines exist, including tumor cells (autologous or allogeneic), tumor cell lysates (membrane and heat shock proteins), gene-modified tumor cells (encoding cytokine genes or costimulatory molecules), and tumor-dendritic cell fusion products. Vaccines may also be based on purified antigenic peptides, synthetic peptides, naked DNA, recombinant viruses, and recombinant bacteria (Table 37.4) [65]. The goal of these vaccines is to generate sustained responses to a specific antigen through the formation of immunologic memory. The challenge is that the targeted antigens are often weakly immunogenic tumor-associated antigens, or over-expressed self-antigen whose T cell counterparts are neutralized [14]. Both autologous and allogeneic tumor cell vaccines have been trialed for several decades but are labor intensive and only marginally effective because they fail to evoke sustained anti-tumor immune responses. Many of these trials have utilized melanomas or allogeneic melanoma cell lines [66].

Genetic modification of tumor cells with cytokine genes during vaccine preparation have demonstrated modest effects in several phase I and II clinical trials. These vaccines constructed to express GM-CSF, IL-2, and CD40L have serologic and pathologic evidence of an immune response; however, clinical responses have been marginal [67]. Peptide-based vaccines that contain the appropriate HLA-restricted amino acid sequences can be designed and constructed to improve the binding affinity to T cells. These sequences based on tumor-specific, tumor-unique, and tissue- differentiation antigens can be engineered by markedly enhancing the binding affinity and stability of the TCR-MHC tumor peptide complex, resulting in enhanced antitumor immunity. This involves minimal changes in the amino acids of a specific epitope (peptide sequence). These vaccines are

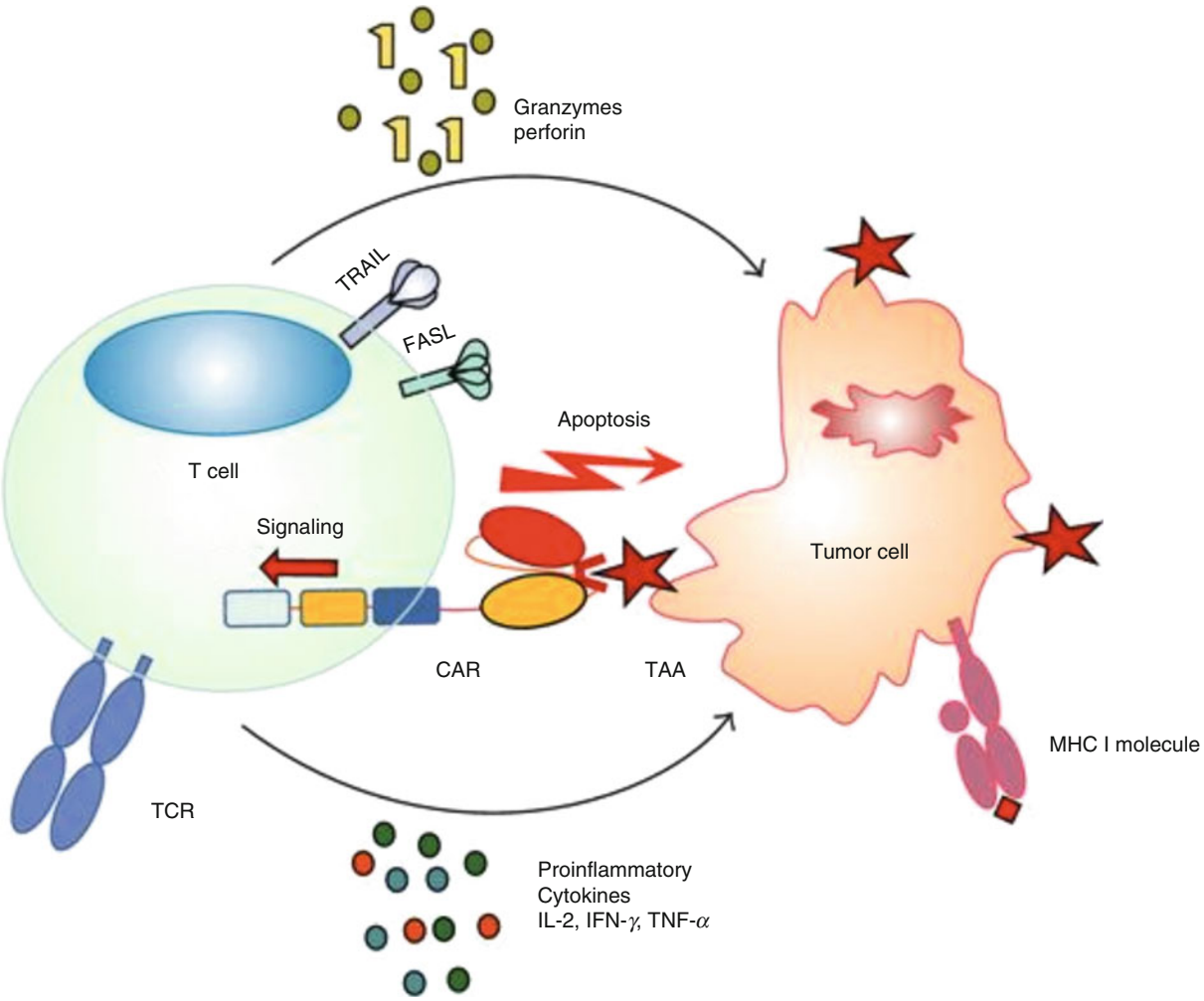

Fig. 37.9 Antitumor effects mediated by CAR-engineered T cells. CAR-modified T cells can recognize tumor cells via binding of the CAR to its tumor-associated antigen (*TAA*) independent of TCR-MHC/peptide interaction from an antigen-presenting cell. As a result, T cells are activated and can eliminate tumor cells by the secretion of perforin and granzymes as well as the expression of Fas Ligand (*FasL*) and tumor necrosis factor-related apoptosis inducing ligand (*TRAIL*). In addition, other tumor-infiltrating immune cells can be activated by the secretion of various proinflammatory cytokines [54]

quite labor intensive and require exact HLA typing and matching with the precise tumor peptide epitope. Examples of these tumor antigens include: [68, 69].

Recent understanding of the role of T cell activation by "professional" antigen presenting cells (monocytes, macrophages, and dendritic cells), the regulation of T cell activation by regulatory T cells, and the role of T cell trafficking and costimulation may lead to further advances in the effectiveness of cellular therapies. Dendritic cells (DC), the most potent antigen presenting cells, hold great promise as an adjuvant immunotherapy or cancer vaccine (Fig. 37.11). Primarily due to the marginal efficacy of other vaccine strategies, DC-based vaccines have emerged as a viable alternative to conventional vaccine strategies. DC, a population of bone-marrow-derived cells, reside in an immature state at peripheral sites where they monitor for environmental alterations such as viral infection or malignant transformation. These changes stimulate antigen uptake via phagocytosis that initiates DC differentiation and proliferation. These APC subsequently migrate to regional lymphoid organs where they present high concentrations of tumor antigens to naive T cells that are then activated. This stimulation of T cell activation, also known as priming, results in numerous CTLs directed against the tumor [70]. DC-based therapies offer several sites for therapeutic manipulation of the cellular immune response (Fig. 37.12). DC may be activated *ex vivo* with agents like GM-CSF, Interleukin-4 (IL-4), or CD-40 L, or DC may be loaded with antigen. Alternatively, DC may be activated *in vivo* by simultaneous injection of tumor peptides with an immune adjuvant like CD-40 antibodies, chemokines, and immunoglobulin G Fc fragment. *Ex vivo* engineering of DC has gained the greatest favor and allows manipulation of

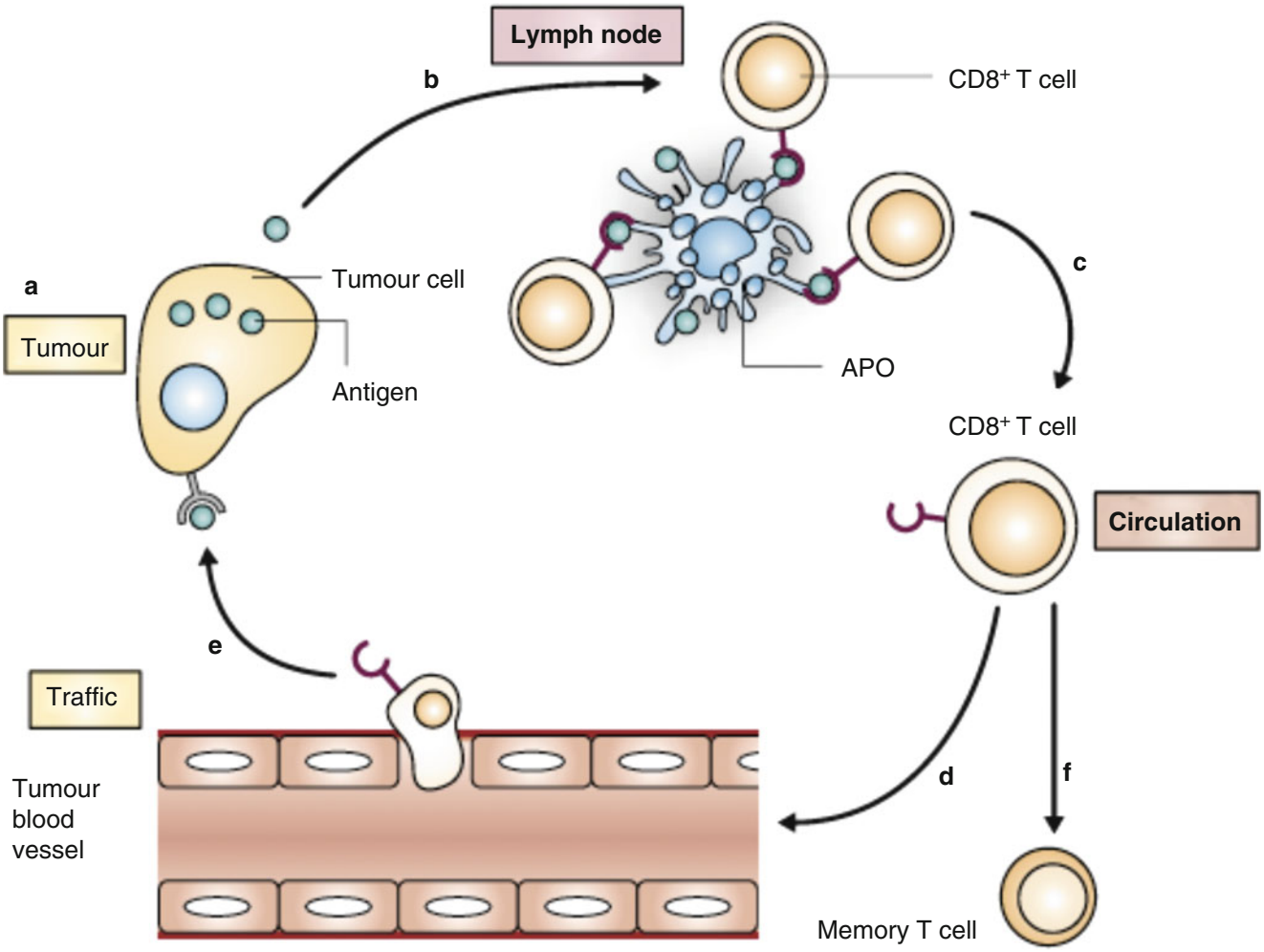

Fig. 37.10 The six steps necessary for an effective antitumor CD8+ T-cell response. Tumor lysis mediated by antigen specific CD8+ T cells is a multistep process. Each of the six steps is an immunoregulatory checkpoint that may be modulated by a host of factors. These steps include: (*a*) expression of peptide antigen by the tumor; (*b*) antigen uptake and processing by antigen-presenting cells (*APC*) and subsequent antigen presentation by the APC to T cells in the lymph node; (*c*) T cell proliferation by tumor antigen specific T cells; (*d*) access to and entry into the tumor; (*e*) evasion by CD8+ cytotoxic T cells by immunosuppressive and immunoregulatory factors in the tumor microenvironment to recognize and lyse their tumor targets; (*f*) generation of memory T cells. Tumor immunotherapy utilizing T-cell-based strategies may fail at each of these critical steps. Advances in the development of immunoassays and immunodiagnostic techniques have not only improved the understanding of antitumor response but have facilitated the development of strategies to overcome the specific factors that may impair the immunotherapeutic response at each of these steps [155]

CD34+ hematopoetic DC progenitors or monocytes that are naive and unexposed to the tolerogenic effects of the tumor microenvironment [71, 72].

Geiger et al. demonstrated that tumor lysate-pulsed DC could be used to safely treat patients with advanced recurrent neuroblastoma that had failed conventional therapy, generate specific antitumor T cell responses, and yield regression of metastatic disease [73]. Other investigators have shown in preclinical models that DC transduced with cytokine genes or coadministered with cytokines may provide potentially effective therapies in neuroblastoma [74–76]. There are several challenges to the adoption of cancer vaccines, especially in pediatric cancers. First, there are multiple sources and methods of vaccine development, as discussed above, and it is unclear which approach, if any, is superior. Second, most pediatric tumors do not have a well-defined optimal antigen for directed targeting. Third, most standard pediatric cancer therapies are highly immunosupressive, requiring a long period of time for immune effector cells to recover and respond to the vaccine. Furthermore, the effect of the vaccine may be too slow to overcome a bulky, rapidly proliferating tumor. Thus, current efforts are focused on identifying appropriate antigens, maximizing the potency of the vaccine itself, administering the vaccines in a setting of MRD and potentially combining vaccines with other immunotherapies [14].

Table 37.4 Key differences between anti-tumor vaccines in cancer therapy and prevention

Antigen	Tissue expression	
	Tumors	Normal tissue
Differentiation antigens (overexpressed)		
Tyrosinase	Melanoma	Melanocytes
MART1/Melan-A	Melanoma	Melanocytes
GP100	Melanoma	Melanocytes
Differentiation antigens (normally expressed)		
Prostate Specific Antigens	Prostate cancer	Prostate
CD20, idiotype	B cell malignancies	B cells
Cancer-testis antigens		
MAGE1, MAGE3	Melanoma, others	Testis, placenta
GAGE and others	Melanoma, others	Testis, placenta
Oncofetal antigens		
CEA	Colon cancer, others	Liver, others
AFP	Liver cancer	–
Mutated antigens		
CASP8	Head and neck cancer	–
CDK4, MUM3	Melanoma	–
Beta-catenin	Melanoma, lung, other	–

Adapted from Yee and Greenberg [161]
Adapted from http://www.angio.org
AFP alpha-fetoprotein, *casp8* caspase-8, *CDK-4* cyclin-dependent kinase-4, *CEA* carcinoembryonic antigen, *GP100* glycoprotein 100, *MAGE* melanoma antigen, *MART1* melanoma associated antigen recognized by T cells 1, *MUM3* melanoma ubiquitous mutated-3

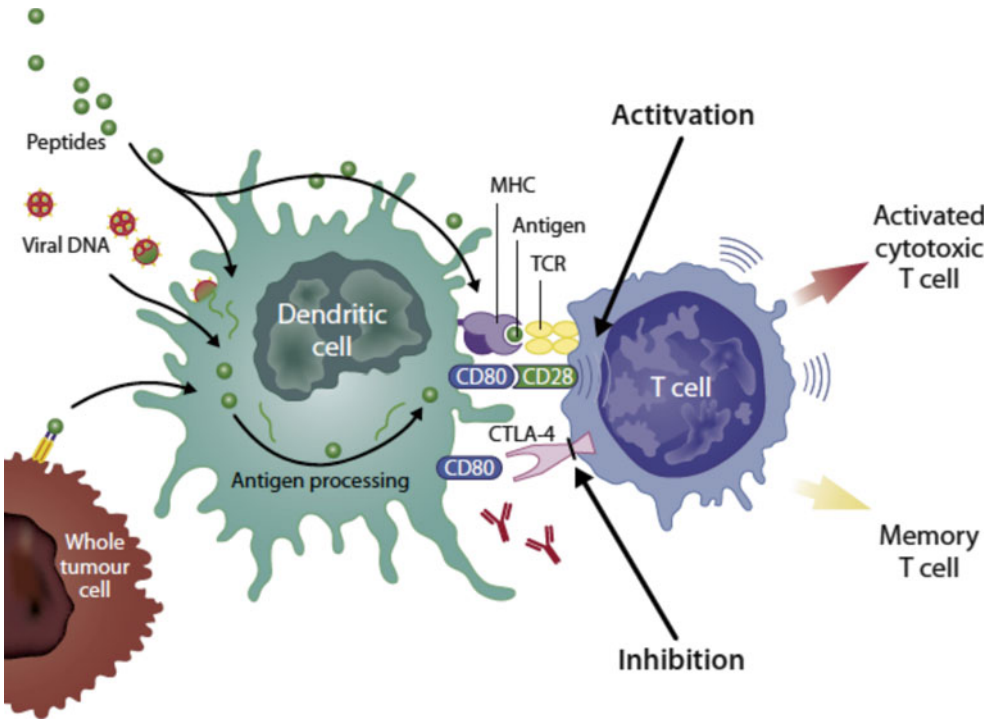

Fig. 37.11 Dendritic cell (antigen-presenting cell)-T cell stimulation. Dendritic cells and other antigen-presenting cells can process antigens such as peptides or whole-tumor cells, can become infected by viral vectors that then express tumor-associated antigens for presentation, or can be *ex vivo* pulsed with peptides then injected. These antigen-presenting cells present antigen to the T cell, causing activation of the T cell. Upon activation, CTLA-4 is upregulated and inhibits prolonged activation of the T cell. Antibodies to CTLA-4 can block the inhibitory signals and cause prolonged activation. *CTLA-4* cytotoxic T-lymphocyte-associated protein 4, *MHC* major histocompatibility complex, *TCR* T-cell receptor [156]

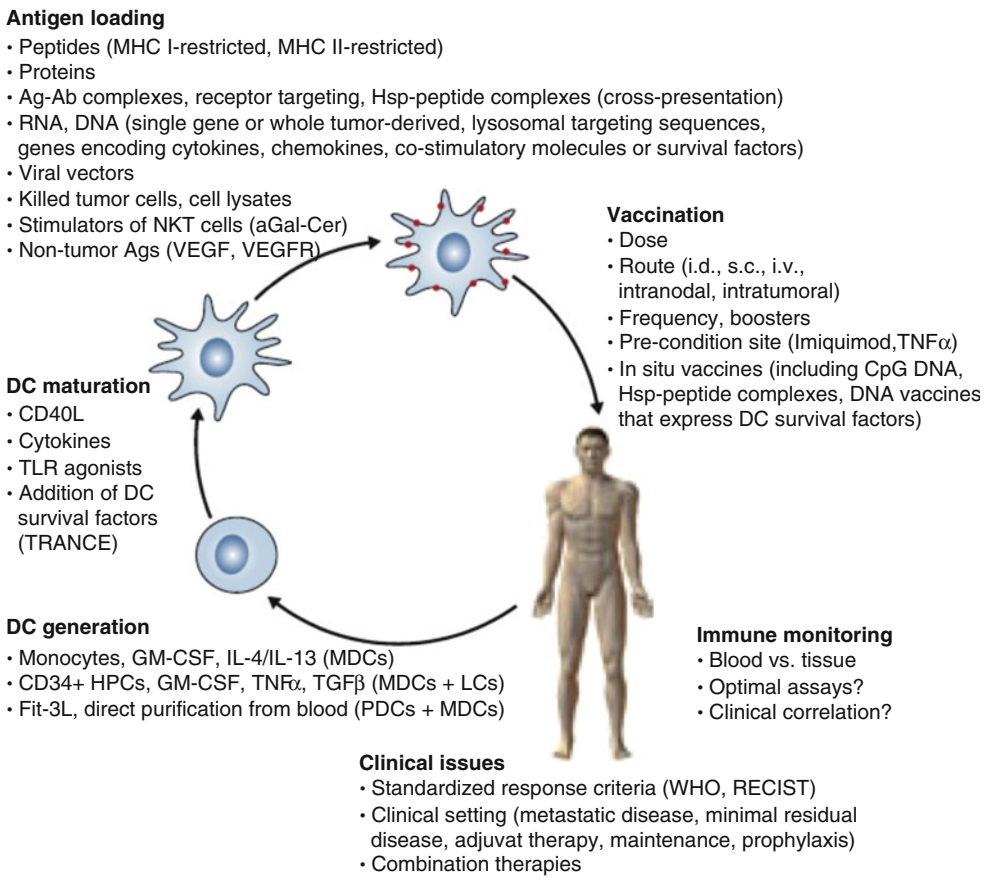

Fig. 37.12 Clinical dendritic cell (*DC*) vaccines. A variety of strategies have been devised to use DC vaccines in the immunotherapy of cancer. DC may be generated (isolated/purified), matured, and antigen loaded *ex vivo*. Generation strategies may result in heterogeneous DC populations that may have varying numbers of macrophages, monocytes, and other immune-effector cells. DC maturation strategies employ the use of various cytokines and other agonistic and survival factors. DCs are then loaded with peptides proteins (antigen), cytokines, chemokines, DC survival factors, factors that stimulate other immune-effector cells or other non-tumor antigens. Following preparation of the DC they may be delivered via a variety of routes and the immune response to therapy may be assessed by various monitoring techniques. The correlation of these monitoring immunologic assays with clinical outcome will determine the true efficacy of these therapies (Adapted from O'Neill et al. [158])

Angiogenesis Inhibitors

Over the last four decades, a large body of work, built on the landmark paper by Dr. Folkman in 1971 has demonstrated that angiogenesis plays a critical role in tumor growth and metastasis in a variety of malignancies, including the pediatric cancers neuroblastoma and nephroblastoma [77, 78]. Because angiogenesis has a more limited role in healthy patients, developing angiogenesis inhibitors is a desirable anti-cancer strategy [79]. Furthermore, while the principle approach of classic anticancer chemotherapy has focused on the cancer cell, which is genetically unstable, and thus a "moving target", the endothelial cell in the tumor microenvironment has greater genomic stability, making it a more susceptible target for therapeutic manipulation [80, 81].

Angiogenesis, a process by which new capillaries develop from existing blood vessels, is a multistep event that consists of local membrane degradation of the endothelial cell tube, endothelial cell invasion of the surrounding stroma, proliferation, migration and differentiation, capillary tube or "sprout" formation and tubular fusion and coalescence to form vascular loops which will allow blood to circulate into the region [82]. While physiologic angiogenesis is a tightly orchestrated process that is regulated by a balance of pro- and anti-angiogenic factors, tumor angiogenesis is erratic, with leaky vessels that are poorly formed [83, 84]. However, the same pro- and anti-angiogenic molecules orchestrate angiogenesis in tumors (Fig. 37.13). Pro-angiogenic molecules, including vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), platelet derived growth factor (PDGF), along with other growth factors, increase the rate of endothelial cell proliferation particularly in ischemic zones even when these factors are systemically administered [84, 85]. Homeostasis of angiogenesis is maintained by the presence of anti-angiogenic factors, such as angiostatin, endostatin, thrombospondin-1, fumagillin [TNP-470],

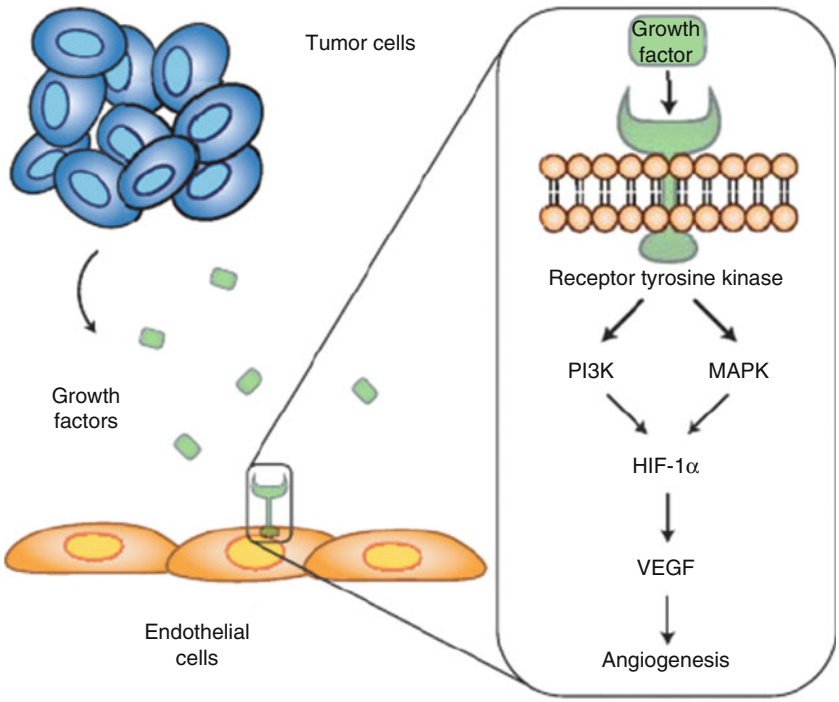

Fig. 37.13 Tumor cells promote angiogenesis. Tumor cells secrete pro-angiogenic growth factors that bind to receptors on dormant endothelial cells lading to a downstream signaling cascade and secretion of vascular endothelial growth factor (*VEGF*). In turn, VEGF causes vasodialation and an increase in vessel permeability. The endothelial cells migrate and proliferate to form new branches from the pre-existing vasculature by detaching from the extracellular matrix and basement membrane [79]

tumstatin and matrix metalloproteinase inhibitors, which physiologically oppose the process [86, 87]. Tumor cell expression of many of the pro-angiogenic factors is regulated by hypoxia through the transcription factor hypoxia-inducible transcription factor (HIF), which is degraded in the presence of oxygen, but prevails in hypoxic conditions and leads to transcription of pro-angiogenic factors like VEGF [88].

The secretion of high levels of pro-angiogenic molecules appears to be a distinct component of the repertoire that every tumor must acquire to survive. Laboratory evidence suggests that this occurs early in the premalignant stages of tumor development and may in fact be the "second hit" or signal that is felt to be necessary for transformation [89]. Each tumor has its own distinct threshold or "angiogenic switch," when the tumor grows and cells in the center of the tumor become hypoxic, stimulating the tumor to produce its own blood supply by shifting the balance between angiogenesis inhibitors and stimulators towards the latter. Thus, it progresses from the non-angiogenic to angiogenic phenotype. This "angiogenic switch" is felt to be a necessary step in malignant transformation and local tissue invasion (Fig. 37.14) [84]. Furthermore, this phenotype increases the potential for metastasis by both enhanced tumor shedding into the general circulation and by the secretion of factors such as proteases that disrupt the basement membrane at distinct sites to allow metastatic growth [90, 91]. A number of studies utilizing advanced techniques of immunohistochemistry to evaluate primary tumors have demonstrated that vessel number and density within the primary tumor correlate with both the metastatic potential and the long-term prognosis for many malignancies [92, 93].

VEGF is the dominant and best studied growth factor that controls angiogenesis through its binding to the VEGF receptor (VEGFR) on endothelial cells, and has an effect on the induction, maintenance and growth of vascular endothelial cells. It is involved in both normal and abnormal angiogenesis. VEGF stimulates endothelial mitogenesis, controls vascular permeability, promotes endothelial survival and stimulates expression of tissue plasminogen activator, urokinase plasminogen activator, collagenases, and matrix metalloproteinases. These enzymes degrade the basement membrane and extracellular matrix—a necessary step for endothelial cell migration [94, 95]. VEGF gene transcription is induced by Hypoxia-inducible factor (HIF), which increases in hypoxic conditions. In addition, cytokines such as EGF and TGF-β also increase VEGF expression [88, 96, 97]. The VEGFR family comprises multiple high-affinity tyrosine kinases that are expressed almost exclusively on vascular endothelium and have an immunoglobulin-like extracellular domain and an intracellular tyrosine kinase domain (Figs. 37.14 and 37.15) [79]. In malignancy, VEGF is highly unregulated, and in some tumors, such as glioma, its overexpression is associated with poor prognosis and reduced survival. It is not produced by endothelial cells, but by tumor cells or stroma, thus having a paracrine mode of action. In breast and prostate cancer, it is further increased by sex steroid hormones [98, 99].

Angiogenesis inhibitors have been shown successful in the treatment of multiple tumor types. Five main categories of angiogenesis inhibitors have been effective in animal models: (1) anti-VEGF monoclonal antibodies (mAbs); (2) VEGF receptor small molecule tyrosine kinase inhibitors and mAbs; (3) soluble VEGF receptors that act as decoys; (4) inhibition of pro-angiogenic molecules that stimulate

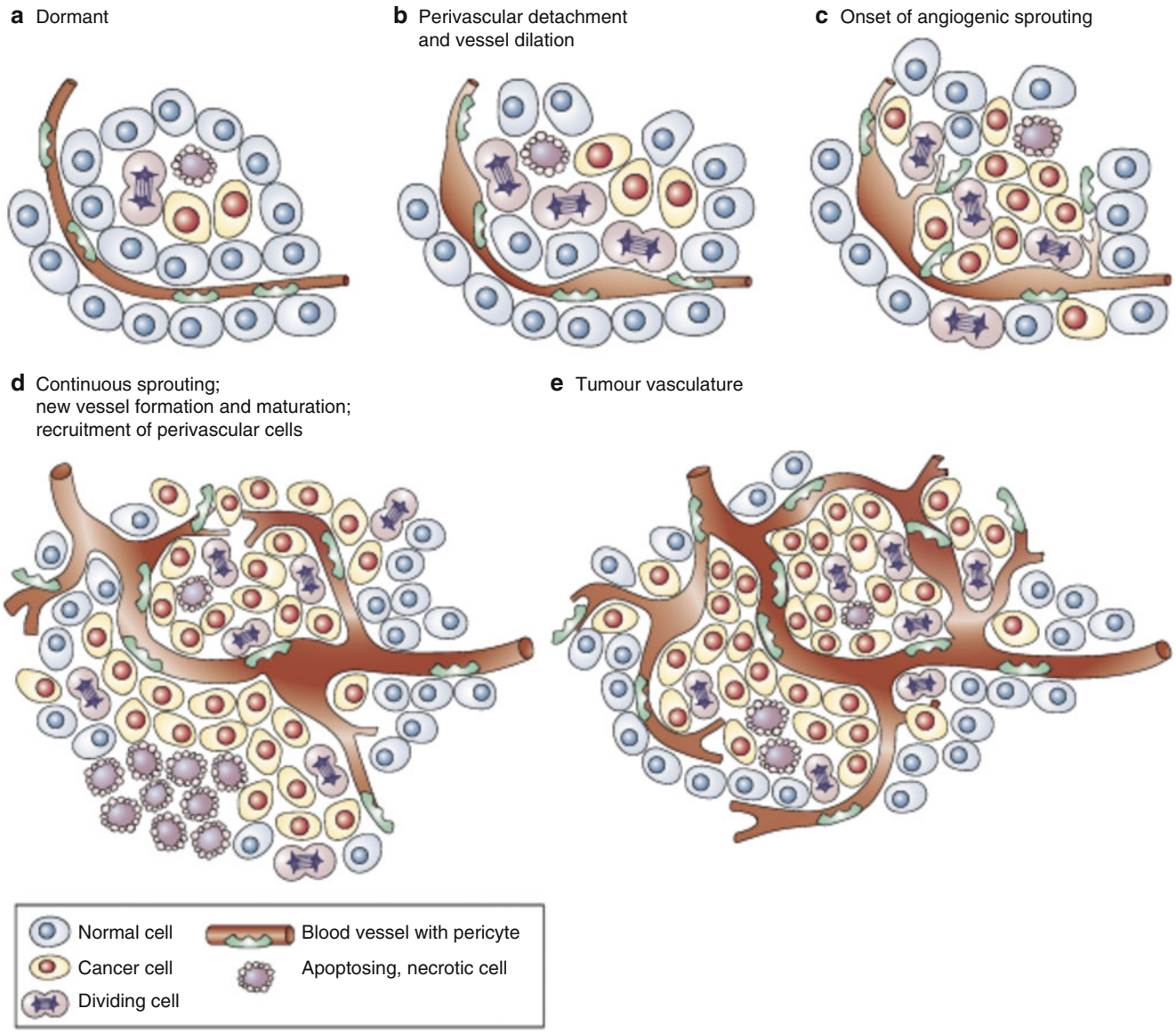

Fig. 37.14 The angiogenic switch. (**a**) Most tumors begin as autonomously dividing cells that reach a steady state between replication and apoptosis and remain as dormant avascular nodules. The angiogenic switch is a critical event in tumor development and progression allowing for exponential tumor growth. This switch begins with (**b**) perivascular detachment and vascular dilatation, followed by the (**c**) onset of angiogenic sprouting, (**d**) neovascular development and growth with associated migration of perivascular cells. A (**e**) neovascular network engulfs the tumor providing critical metabolic substrates to hypoxic and necrotic areas of tissue to further potentiate tumor cell proliferation (Adapted from Jain and Munn [106])

VEGF expression (i.e., EGF, EGFR, PDGF, PDGFR, HIFs, COX-2 inhibitors, and IL-1β); and (5) endogenous angiogenesis inhibitors (i.e., endostatin, angiostatin) (Table 37.5) [100–103]. The effectiveness of angiogenesis inhibitors in the treatment of malignancy is explained by two theories: inhibition of tumor endothelial proliferation and vascular normalization. Intuitively, it is expected that blocking angiogenesis or administering anti-angiogenic compounds results in decreased tumor vasculature. Interestingly, this has been shown in multiple animal models, where 50–60 % of tumor vasculature was lost after VEGF inhibition, but empty sleeves of basement membrane and pericytes were left behind, which resulted in full revascularization by the seventh day after treatment withdrawal. This finding correlates with multiple clinical trials in various solid tumor human malignancies that have equated drug withdrawal (bevacizumab) with disease progression [104]. The second hypothesis explains the greater effectiveness of antiangiogenesis inhibitors when used in combination with conventional chemotherapy instead of monotherapy. The suggested explanation is that VEGF blockade causes a paradoxical "normalization" of tumor vasculature with decreased vessel leakiness, resulting in a temporary improvement of blood flow, and thus chemotherapeutic agents access, to the tumor cells [105, 106]. It is likely that a combination of these two hypotheses is responsible for the effectiveness of these drugs.

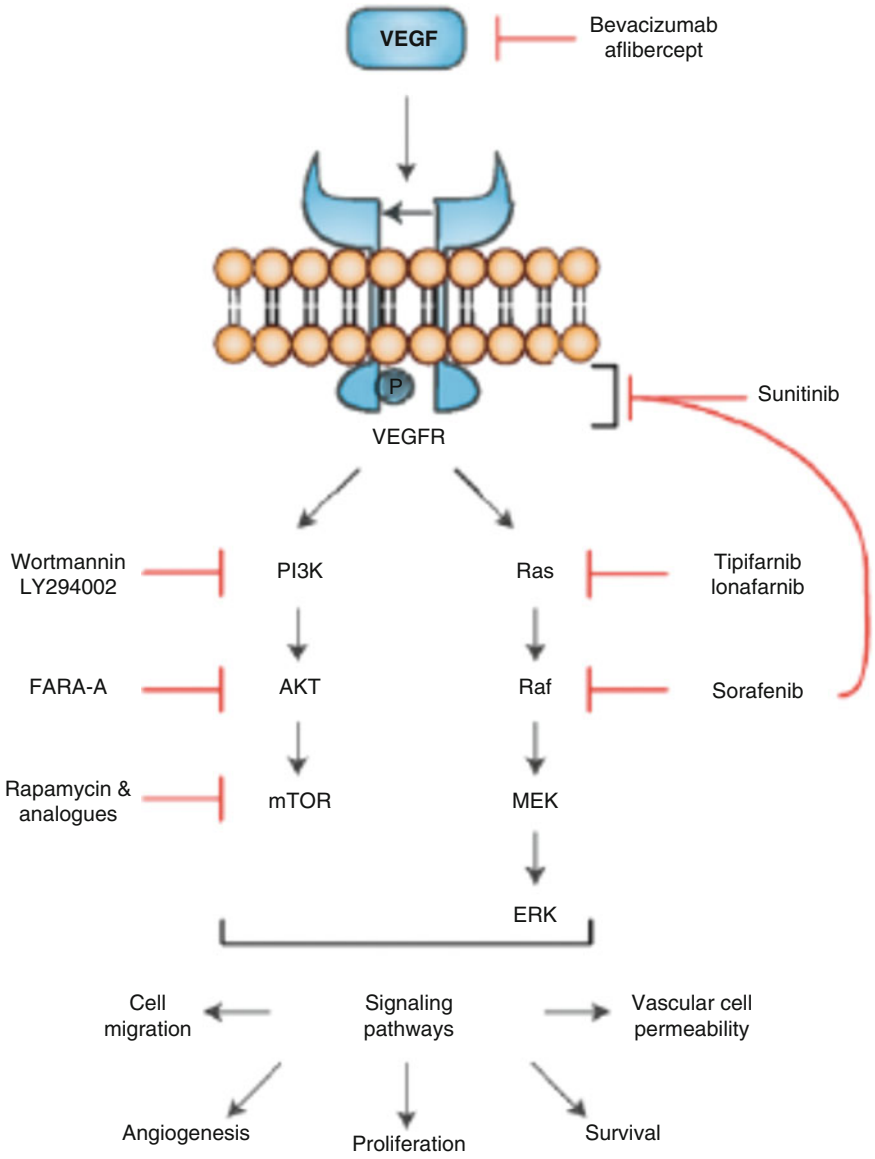

Fig. 37.15 Mechanism of action of vascular endothelial growth factor (*VEGF*). After VEGF binds to the VEGF receptor (*VEGFR*), a tyrosine kinase, dimerization and autophosphorylation of the receptor occur. The phosphorylated receptor then interacts with several signaling molecules, leading to signal transduction, and eventually angiogenesis. Various preclinical and clinical compounds that inhibit angiogenesis at various steps of the pathway are shown [79]

More than a dozen angiogenesis inhibitors have been FDA approved for various malignancies (Table 37.5). Bevacizumab, a humanized monoclonal antibody directed against all isoforms of VEGF-A, was the first to be FDA approved for use in patients with advanced colorectal cancer in 2004, and since then, its indications have broadened to non-small cell lung cancer, breast and renal cell carcinoma and glioblastoma [107, 108]. Another approach to VEGF inhibition is the recombinant fusion protein aflibercept that contains the VEGF-binding domains of two specific VEGF receptors fused to the Fc portion of human IgG, which functions as a soluble "decoy" receptor. Aflibercept has a higher affinity for VEGF than the mAb bevacizumab, thus, it inactivated VEGF and prevents it from binding to its receptor very effectively [109].

Multiple small molecule tyrosine kinase inhibitors have been FDA approved for various malignancies, some of which also have oral availability (Table 37.5). They act by interfering with the VEGFR and other receptors and molecules involved in the VEGFR signal transduction [110]. Angiostatin, a proteolytic fragment of plasminogen, and endostatin, a 20-kD fragment of the basement membrane protein collagen XVIII exemplify naturally-occurring, potent anti-angiogenic effects. They have both exhibited potent antitumor activity against mouse tumor models, and are now undergoing promising early clinical trials [111, 112]. A new approach to targeting tumor vasculature has been the development of vascular disrupting agents (VDAs), which selectively damage the endothelial linings of tumor blood vessels. One of the major VDAs under investigation is combretastatin A4 phosphate, in early clinical

Table 37.5 Angiogenesis inhibitors

Category	Drug name	Mechanism of action	Approved indications
Monoclonal antibody therapy	Bevacizumab (Avastin)	Humanized mAb that binds biologically active forms of VEGF and prevents its interaction with its receptor, thereby inhibiting endothelial cell proliferation and angiogenesis	Metastatic colorectal cancer, NSCLC, advanced breast cancer (Europe), metastatic renal cancer, advanced ovarian cancer (Europe), second-line treatment of glioblastoma
	Aflibercept	Recombinant fusion protein that contains the VEGF-binding domains of two specific VEGF receptors fused to the Fc portion of human IgG, which functions as a soluble "decoy" receptor for VEGF	Metastatic colon cancer, macular degeneration
Small molecule TKIs	Sorafenib (Nexavar)	Small molecule TKI of VEGFR-1, -2, -3, PDGFR-β, and Raf-1	Advanced renal cancer, advanced unresectable hepatocellular cancer
	Sunitinib (Sutent)	Small molecule TKI of VEGFR-1, -2, -3, PDGFR-β, and RET	Advanced renal cell cancer, GIST after progression on imatinib, progressive unresectable or metastatic pancreatic neuroendocrine tumors
	Pazopanib (Votrient)	Small molecule TKI of VEGF, PDGFR and c-kit	Advanced renal cell cancer
	Vandetanib (Caprelsa)	Small molecule TKI of VEGFR and EGFR	Metastatic unresectable medullary thyroid cancer
	Regorafenib (Stivarga)	Oral multikinase inhibitor that targets VEGFR-1, -2, -3, TIE2, PDGFR, and FGFR, kit, RET, RAF, BRAF, and BRAFV600E	Metastatic colorectal cancer who have progressed after all approved standard therapies
	Axitinib (Inlyta)	Oral multikinase inhibitor that targets VEGF-1, -2, -3	Advanced renal cell cancer after failure of one prior systemic therapy
Inhibitors of mTOR	Temsirolimus (Torisel)	Small molecule inhibitor of mTOR, part of the PI-3 kinase/AKT pathway involved in tumor cell proliferation and angiogenesis	Advanced renal cell cancer, relapsed or refractory mantle cell lymphoma, non-hodgkins lymphoma (Europe)
	Everolimus (Afinitor)	Small molecule inhibitor of mTOR, part of the PI-3 kinase/AKT pathway involved in tumor cell proliferation and angiogenesis	Advanced renal cell cancer, advanced unresectable pancreatic neuroendocrine tumors, unresectable subependymal giant cell astrocytoma

Adapted from: http://www.angio.org/understanding/inhib.php
mAb monoclonal antibody, *VEGF/VEGFR* vascular endothelial growth factor/receptor, *TKI* tyrosine kinase inhibitor, *PDGFR* platelet derived growth factor receptor, *FGFR* fibroblast growth factor receptor, *EGFR* endothelial growth factor receptor, *mTOR* mammalian target of rapamycin, *PI3* phosphoinositol-3

trials [79]. As further molecules and regulatory steps of angiogenesis are elucidated, other potential anti-angiogenic targets are discovered and tested as potential anticancer treatments.

Gene Therapy

Gene therapy, the introduction of genetic material into cells for therapeutic indications, may be an important treatment strategy for a variety of malignancies. Gene therapy encompasses a broad spectrum of experimental strategies that all use genetic material to modify cells. Four major categories of anticancer gene therapy exist: (1) gene transfer (2) oncolytic virotherapy, (3) immunotherapy, and (4) bone marrow protection (Fig. 37.16) [113–115]. Gene transfer involves the introduction of new genes into cancerous cells or surrounding tissue to slow cancer growth or cause cell death. Oncolytic virotherapy uses viral particles that selectively replicate within the cancer cell to cause cell death. Immunotherapy uses genetically modified cells and viral particles to stimulate the immune system to recognize and destroy cancer cells [114]. A more detailed discussion of the application of gene therapies as a component of immunotherapy has been discussed above, and encompasses various strategies, from recombinant cancer vaccines to cytokine gene transfer into the tumor cell that will elicit a vigorous antitumor response. The bone marrow protection strategy borrows the multi-drug resistant gene found in cancel cells to transduce bone marrow cells and increase their resistance to chemotherapeutic drugs. Combinations of these approaches have been investigated for various cancer models with mixed success. For example, in lung cancer models, survival benefits have been

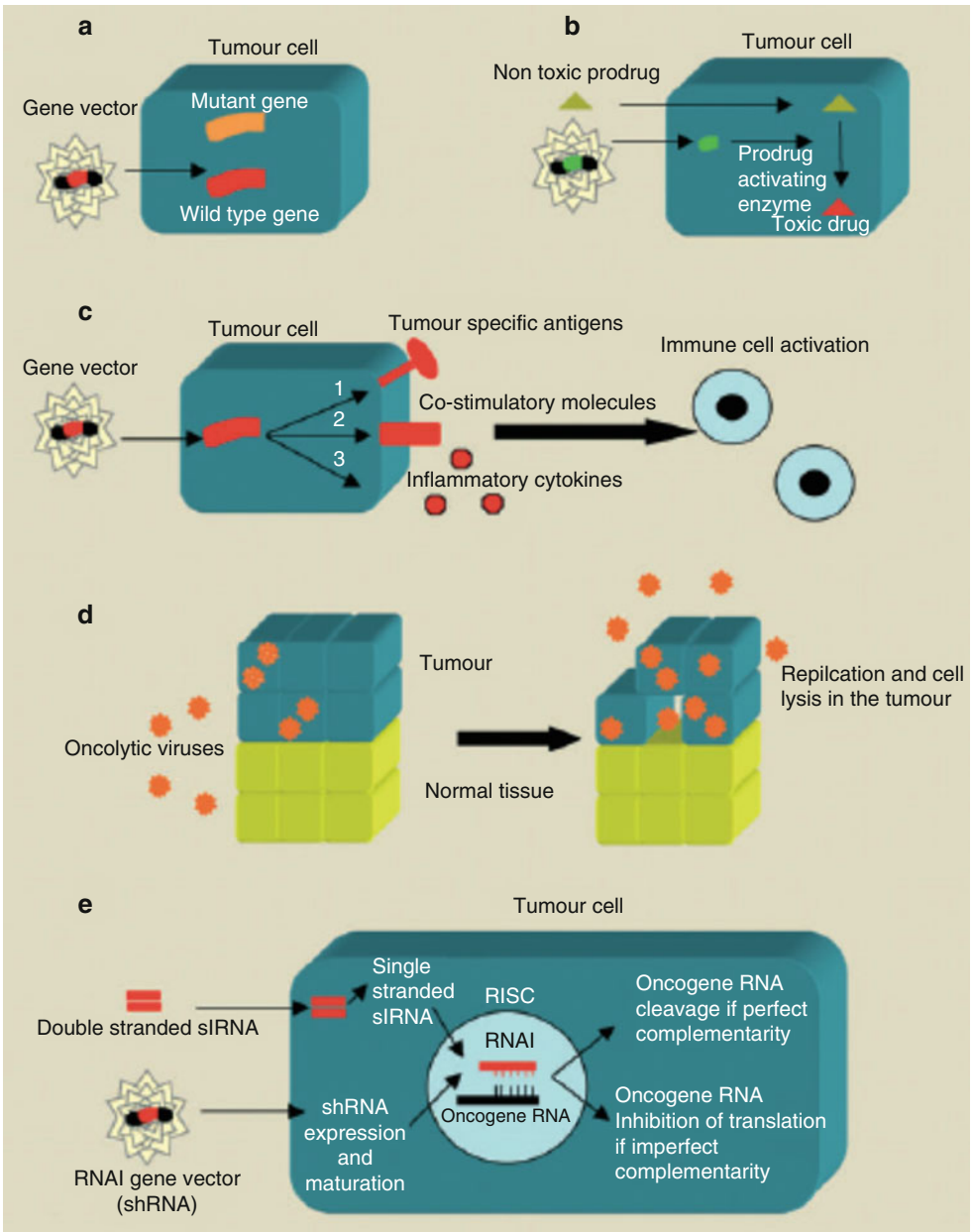

Fig. 37.16 Various types of gene therapy. (**a**) Gene re-expression. The vector carries a wildtype version of a mutated gene into the tumor (**b**) Suicide therapy. The patient first receives a systemic nontoxic prodrug and then the vector carries prodrug-activating enzyme gene directly to the tumor. (**c**) Immune therapy. The vector carries a gene coding (*1*) a specific immunogenic tumor antigen, (*2*) a co-stimulatory signaling molecule, or (*3*) an inflammatory cytokine that all lead to immune system activation and anti-tumor activity. (**d**) Oncolytic viruses. Oncolytic viruses specifically replicate in tumor cells and cause tumor cell lysis and death. (**e**) Therapeutic RNA interference. The small interfering RNA (*siRNA*) or siRNA gene is delivered into the tumor cell. After maturation and incorporation into the RNA-induced silencing complex (*RISC*), siRNA can bind an oncogene RNA, leading to oncogene repression and cell death [115]

demonstrated using gene therapy to create cancer vaccines, target viruses to cancer cells for lysis and death, decrease the blood supply to the tumor, and introduce genes into the cancer cells that cause death or restore normal cellular phenotype [116]. Although clinical trials of various forms of gene therapy have been performed in adults with marginal success, the number of studies in children remain limited due to significant safety considerations [117].

Gene Transfer

The principles of gene transfer: selection of a gene, a vector and a management strategy.

Gene Selection

A large variety of therapeutic genes are under investigation, such as tumor suppressor genes, oncogenes, antiangiogenesis genes, suicide genes, inflammatory cytokines and microRNA genes [115]. Tumor suppressor genes are a category of naturally occurring genes like p53, APC (adenomatosis polyposis coli), RB (retinoblastoma), p16INK4a, PTEN, and p14ARF, that prevent malignant transformation of the host cell. Many cancers result from the loss of function or expression of these genes and hypothetically, the restoration of this single gene will reverse the complex process of tumorigenesis. The delivery of these genes to malignant cells in which their expression is defective or absent results in cell growth arrest, apoptosis, and genomic stability [117].

Two major principles guide this form of gene therapy: (1) delivery of a single gene will induce growth inhibition and/or death in the cancer cell; (2) transgene delivery to adjacent normal tissue will have minimal effects. The effectiveness of this type of therapy is also critically dependent on the delivery of the viral vector to other adjacent tumor cells not directly exposed to the vector to invoke a "by-stander effect." This process may also induce indirect effects on the adjacent normal tissues by impacting the expression of growth factors like IGF-I and VEGF. The inhibition of these substances has negative paracrine effects on growth and survival of normal cells within the tumor microenvironment. This is the critical component of the effective gene therapy utilizing tumor suppressors (Fig. 37.17). The prototype for this form of gene therapy is p53 gene therapy for non-small cell lung cancer, which provided the proof of principle that delivery of the tumor suppressor gene was tumoricidal in vivo [118]. This study demonstrated the safety and efficacy of this approach with one-third of the patients showing a clinical response to treatment. Currently modifications of viral factor delivery systems are being utilized to refine this therapy.

Alternatively, blocking oncogene expression via techniques of antisense oligonucleotides or ribozyme delivery of

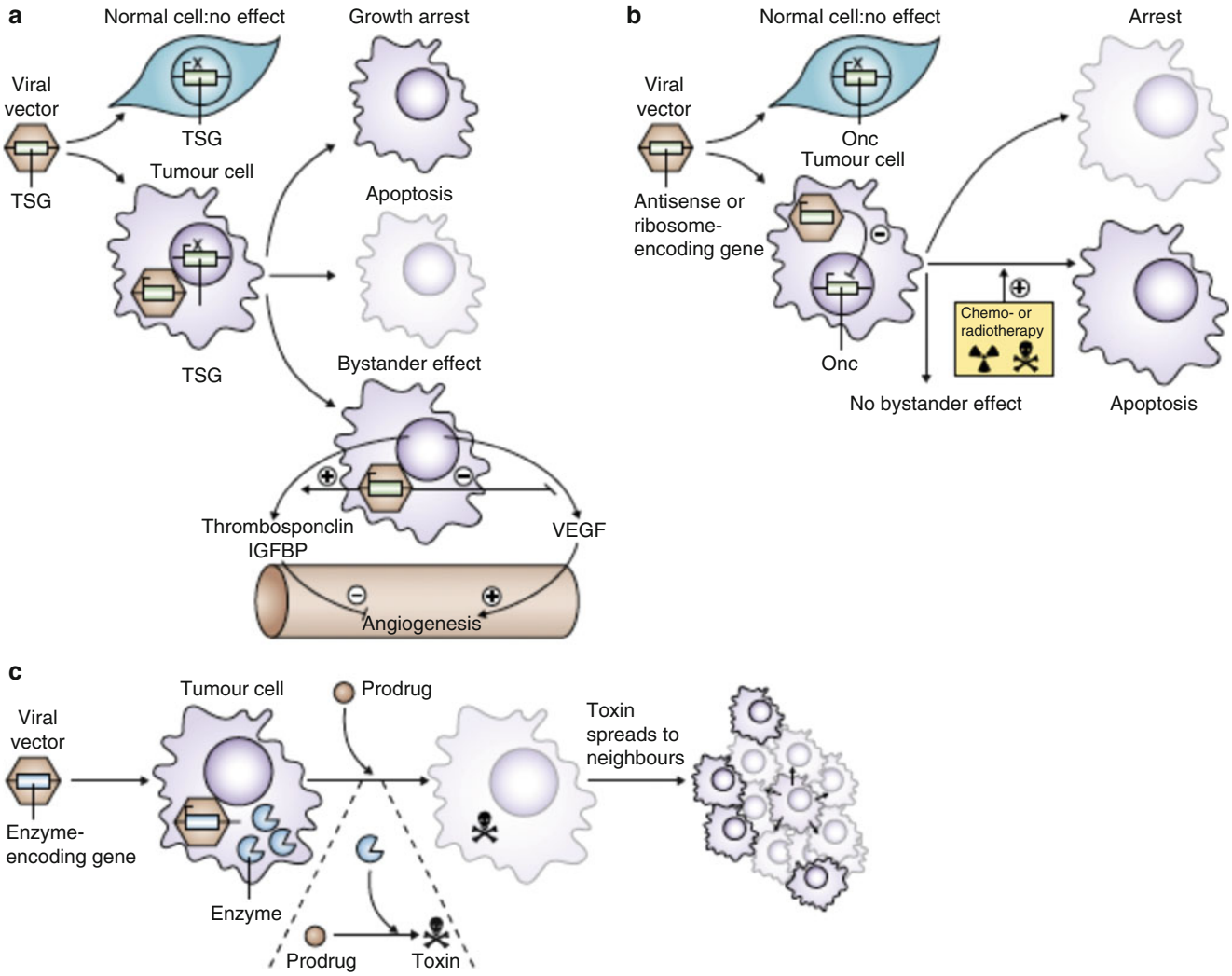

Fig. 37.17 Cancer gene therapy: (**a**) Tumor suppressor gene (TSG) therapy or (**b**) inhibition of oncogene expression. (**a**) Viral vectors encoding tumor suppressor genes are delivered to the tumor microenvironment and will infect normal and tumor cells. They will typically have no effect in normal cells but will induce growth arrest or apoptosis in tumor cells. These TSG may exert innocent bystander effects, e.g., p53 gene therapy which abrogates endothelial vascular endothelial growth factor (*VEGF*) secretion and induces thrombospondin and insulin-like growth factor 1 production (antiangiogenic factors). (**b**) Alternatively, transgene delivery of oncogene inhibitors like antisensene oligonucleotides, which directly inhibit oncogene expression or ribozymes that cleave oncogene transcripts. These may lead to growth arrest, apoptosis or increase chemo- and radiosensitivity of the tumor cells (Adapted from Gilboa [69]). (**c**) Transgene delivery of a suicide gene like a prodrug concerting enzyme may activate toxic metabolites in the infected cell that is cytotoxic to this and nearby cells inducing a "potent bystander effect" (Adapted from Gilboa [69])

suicide genes to cancer cells may be an effective strategy (Fig. 37.17b). Several malignancies depend on oncogene induction for the maintenance of the malignantly transformed state. Disrupting the expression of these genes in select tumors results in the restoration of the nonmalignant phenotype [115].

The delivery of suicide genes to cancer cells is another emerging category of gene therapy for cancer. This technique involves the delivery of enzymes-encoding genes that allow the cancer to metabolize a nontoxic prodrug administered separately into a potent cytotoxic agent (Fig. 37.17c). The most broadly studied enzyme-prodrug combination is herpes simplex virus-thymidine kinase (HSV-tk)-gancicolvir, enzyme-pro- drug combination. The HSV-tk phosphorylated ganciclovir, which results in its incorporation into the host DNA and DNA synthesis inhibition [119]. Other enzyme-prodrug combinations are listed above (Table 37.6). Although the techniques of suicide gene therapy have demonstrated in vitro responses, the clinical efficacy of this therapy has been marginal. This may in large part be secondary to inadequate *in vivo* delivery mechanisms to target all malignant cells, especially in the setting of widespread metastatic disease.

Vectors

The successful introduction of genetic material into eukaryotic cells requires a method that will both insert the genetic material in the particular cell of interest with adequate efficiency and will promote sufficient expression of the gene in the cell type. Although numerous techniques of gene transfer exist, they fall into two major categories: viral (transduction) and non-viral (transfection) techniques. Transduction methods may result in permanent or transient alteration of the host genetic material. Additionally, expression of the transgene may be constitutive or regulated. The principle viral techniques involve retroviruses, adenoviruses, adeno-associated viruses, pox viruses, and herpes simplex viruses. The viral techniques offer ease of in vivo delivery and sustained high level transgene expression, but may interfere with normal cell function or evoke an immune response. Non-viral techniques utilize naked or plasmid DNA, DNA encapsulated in cationic lipids (liposomes) or physical methods like gene gun or hydrodynamic gene transfer techniques to introduce genetic material into the cell. Although non-viral methods of gene delivery offer advantages such as ease of production and diminished toxicity, the efficiency of *in vivo* delivery is diminished and lacks sustained high-level expression (Table 37.7) [113].

Table 37.6 Enzyme-prodrug combinations for suicide gene therapy [113]

Enzyme	Prodrug	Product	Mechanism
HSV-tk	Ganciclovir	Ganciclovir triphosphate	Blocks DNA synthesis
Ctyosine deaminase	5-Fluorocytosine	5-Fluorouracil (5-FU)	Pyrimidine antagonist: blocks DNA and RNA synthesis
Carboxylesterase	CPT-11	SN38	Topoisomerase inhibitor
Cytochrome P450	Cyclophosphamide	Phosphoramide mustard	DNA alkylating agent: blocks DNA synthesis
Purine nucleoside phosphorylase	6-Mercaptopurine-DR	6-Mercaptopurine	Purine antagonist: blocks DNA synthesis

HSV herpes-simplex virus, *CPT-11* camptothecin-11

Table 37.7 Characteristics of vectors used for gene therapy

Vector	Packaging capacity	Ease of production	Integration into host genome	Duration of expression	Transduction of post-mitotic cells	Pre-existing host immunity	Safety concerns	Germline transmission
Nonviral	Unlimited	+++	Rarely	Usually transient	++	None	–	–
Retroviral	8.0 kb	Producer cell lines for onco-retroviral but not lentiviral vectors	Yes	Long-term	++	None	Insertional mutagenesis	–/+
Adenoviral	30.0 kb	+/–	No	Transient	Very efficient	+++	Inflammatory response	–
Adeno-associated virus	4.6 kb	Cumbersome	Rarely	Long-term in post-mitotic cells	Efficient	++	–	+/–
Herpes	150 kb	+/–	No	Transient	++	+++	Inflammatory response	–

Viral vectors have been favored in cancer gene therapy due to their ability to facilitate *in vivo* delivery to a variety of sites and the capacity to maintain prolonged transgene expression. Two categories of viral vectors are recognized: integrating and non-integrating. One of the most common integrating viral methods of gene transfer is through the use of retroviruses. Following cellular entry, the viral RNA undergoes reverse transcription to cDNA by viral reverse transcriptase. Subsequently, the cDNA molecules undergo nuclear translocation via the nucleopore and stable genomic integration. The virally integrated DNA or provirus is then translated into protein [117]. Retroviral vectors are constructed by substituting the gene of interest in the viral protein-coding regions. Packaging of these particles using helper or packaging cell lines that contain structural viral proteins facilitate genomic incorporation [117]. Adenovirus, adeno-associated virus, and herpes virus vectors are incorporated into episomes that are not integrated into the host DNA and are subsequently lost over time. These offer distinct advantages in clinical situations when transient transgene expression is desired.

The most efficient viral vectors for transgene expression are the adenoviruses [113]. These viruses do not require cell division for transduction, may be produced in high titers, transduce with high levels of efficiency without host genomic incorporation (episome), and have high level early transgene expression. Principal limitations of this vector are based on its capacity to provoke a potent antiviral immune response and its hepatic tropism which may augment its toxicity [117]. Furthermore, their episomal location make them useful only for transient gene expression. Recent modifications in their structure to eliminate wild-type genes may render these "designer" adenovirus vectors less immunogenic and allow for more prolonged *in vivo* survival and function [113].

Recombinant adeno-associated viruses (rAAV), members of the parvovirus family, are another category of viruses that may be used as vectors. These non-enveloped, single-stranded, replication-incompetent DNA viruses easily integrate into the host genome but require the co-administration of a helper virus (adenovirus or herpes virus) for replication. The enhanced safety profile, low immunogenicity, ability to transfect non-dividing cells and the ability to achieve long-term expression make these viruses a nearly ideal vector. The production of neutralizing antibodies by some individuals, high titer transduction requirement, limited packaging capacity for genetic material and lack of reliable packaging cells are some of the significant limitations to the utility of this gene therapy vector. Pox viruses, a family of DNA viruses, have a large genomic capacity that permits significant amounts of foreign DNA incorporation. These viruses incorporate into the cytoplasm and are independent of host transcription regulation. They may be engineered to produce large amounts of gene product. These viruses are limited by their low expression of the transgene and host cytolytic properties. Recombinant herpes simplex virus vectors have also been utilized as vectors but are hampered by their induction of a robust inflammatory response. Modifications of the virus and delivery systems may improve this vector strategy [117].

Various non-viral vectors are under investigation as carriers of transgenes. Naked or plasmid DNA is one option which has poor efficacy due to its low cellular uptake and rapid clearance. Thus, it is selectively used in vaccination and immunotherapy strategies, coupled with electroporation, an electrical pulse that transiently increases the permeability of cell membranes and allows for the uptake of naked DNA, *in vitro*. Synthetic vectors like cationic liposomes comprise a lipid bilayer membrane and are amphiphilic, nicely protecting the negatively-charged DNA inside. Their use is limited due to low *in vivo* cellular uptake [120]. Nanoparticles are an emerging class of vectors for gene transfer. Because of the increased permeability of blood vessels in cancer, nanoparticles may extravasate and selectively accumulate in tumors. This theory explaining their affinity towards the tumor microenvironment is called the enhanced permeability and retention (EPR) effect [121, 122].

Strategy

The *ex vivo* strategy consists of cell collection from the patient, followed by culturing and transducing the cells with a vector and then reintroducing the cells into the subject. This strategy is frequently done in immunotherapy, such as adaptive T cell transfer and cancer vaccines. The *in vivo* strategy consists of direct injection of the vector into the subject, either systemically or intra-tumorally, which is the more commonly employed strategy in gene transfer. The advantage of the *ex vivo* strategy involves limitation of dissemination of the vector, while the *in vivo* strategy has the advantage of omitting the cell culturing steps [115].

Oncolytic Virotherapy

Another emerging category of gene therapy for cancer is the use of therapeutic viral infection to treat the cancer. Reports in the mid to late twentieth century utilizing viruses to treat conditions such as cervical cancer emerged as a theoretical approach to care but lacked the molecular or genomic foundation to be advanced into a sound treatment paradigm. Currently, the construction of replication-competent viruses that replicate only in rapidly dividing cells and also lack virulence genes are being safely exploited for anticancer gene therapies. Among these agents are a group of herpes virus mutants G207 and HSV-1716 used in clinical trials to treat malignant glial cell tumors and metastatic melanoma, respectively. Replication of the attenuated adenovirus mutant, ONYX-015, relies on inhibition of p53 function and may be

used to eliminate malignant cells with loss of p53. Normal cells expressing this tumor suppressor prevent replication of this virus [123]. Adenovirus defective in E1A proteins, which typically bind and neutralize RB and its analogues, have also been shown in preclinical trials to selectively kill cells with defective RB [124, 125]. Other viral constructs like the adenovirus Calydon CN706 and others have been designed to exploit tissue-specific regulatory elements in the replication process in areas like the prostate or colon as a means of cancer cell killing [126].

Bone Marrow Protection

Another category of gene therapy involves techniques of chemoprotection to decrease the myeloablative toxicities of chemotherapy. Expression of the multi-drug resistance gene (MDR) makes tumor cells resistant to the effects of chemotherapy by encoding for a transmembrane pump that actively eliminates cytotoxic agents. MDR gene-transduced hematopoietic bone marrow progenitor cells have been shown to have decreased toxic effects [119, 127]. This strategy is still in its early stages of evolution but may hold great promise, particularly in the pediatric population.

Antisense Strategies

One of the major spin-offs of the human genome project has been the improved understanding of the molecular basis for cancer development, progression, and metastasis. Numerous molecular targets have been identified through a variety of genomic and proteomic technologies. Antisense oligonucleotide (ASO) strategies are an emerging novel anticancer therapy based on the specificity of the Watson-Crick base pair interactions [128]. These antisense oligonucleotides are single-stranded, chemically modified, DNA-like molecules that are typically 17–22 nucleotides in length and designed to be complementary to the selected gene's mRNA based on Watson-Crick base pair binding specificity. The native targeted mRNA sequence is termed the "sense" sequence, while the complementary oligodeoxyribonucleotide (oligonucleotide) is the "antisense" sequence. Watson-Crick-specific complementary binding of the mRNA (sense)-DNA (antisensense) complex leads to activation of RNase-H, a ubiquitous intranuclear enzyme, mediated cleavage of the target mRNA. RNase H cleaves the mRNA strand of the mRNA-ASO hybrid, allowing the ASO to bind to another identical mRNA, while the cleaved mRNA undergoes rapid degradation. This technique targets the messenger RNA that encodes the nucleotide sequence that will undergo translation to a specific protein normally upregulated during oncogenesis by the ribosome (Fig. 37.18). Selective partial inhibition or deactivation of this protein then dysregulates growth, differentiation, and apoptosis of the targeted cell [129–131]. Techniques have been developed to specifically target tumor cells with a safe pattern of side effects. Recent studies have demonstrated that this form of therapy may inhibit translation inducing alterations in mRNA transport, modulating or inhibiting mRNA splicing, and arresting translation by triple helix formation [132]. Some of these antisense sequences may contain motifs that possess nonspecific or "off target" effects that are different from its specific target. An example of this is the CpG motif found in some ASOs that have an immunostimulatory activity in addition to its translation inhibitory effect [133].

Double-stranded siRNA (small interfering) also inhibits gene expression by direct Watson-Crick-specific hybridization to a target RNA that leads to posttranscriptional gene silencing. These siRNAs are incorporated into a multiprotein RNA-inducing silencing complex leaving the antisense strand to guide this complex to its homologous RNA targets by endonucleolytic cleavage (Fig. 37.19). Theoretically siRNAs offer superior potency and specificity; however, few biologically active molecules have been identified. Utility of this approach has also been limited by production costs and toxicities [134].

Numerous major barriers currently exist to the clinical applicability of this technique. These include the identification of sites on the mRNA of the particular gene that are accessible, antisense hybridization techniques, methods of delivery to the tissue of origin, *in vivo* stabilization and resistance to degradation, limitation of toxicities, and increasing the affinity to the specific mRNA sequence [128]. Chemical modification of the ASO backbone may lead to improved tissue distribution and bioavailability through increased resistance to nuclease digestion while retaining potent hybridization and RNase-H activity.

Antisense Targets

The elucidation of the role of target genes associated with neoplastic progression produces a growing list of antisense gene candidates. The most promising candidates are the targets that are upregulated during or as a consequence of cancer progression and therapeutic resistance and are not otherwise amenable to inhibition with antibodies or small molecules. Although a number of ASOs have been identified in preclinical models of tumor, only a select group of protein targets have been clinically applicable. Some of these targets include members of the BCL2 family, protein kinase C (PKC) family, the inhibitors of apoptosis family (IAP), and the heat shock protein family. Among the most studied antisense targets are the BCL2 family members (BCL2 and BCL-XL). This class of oncogenes promotes

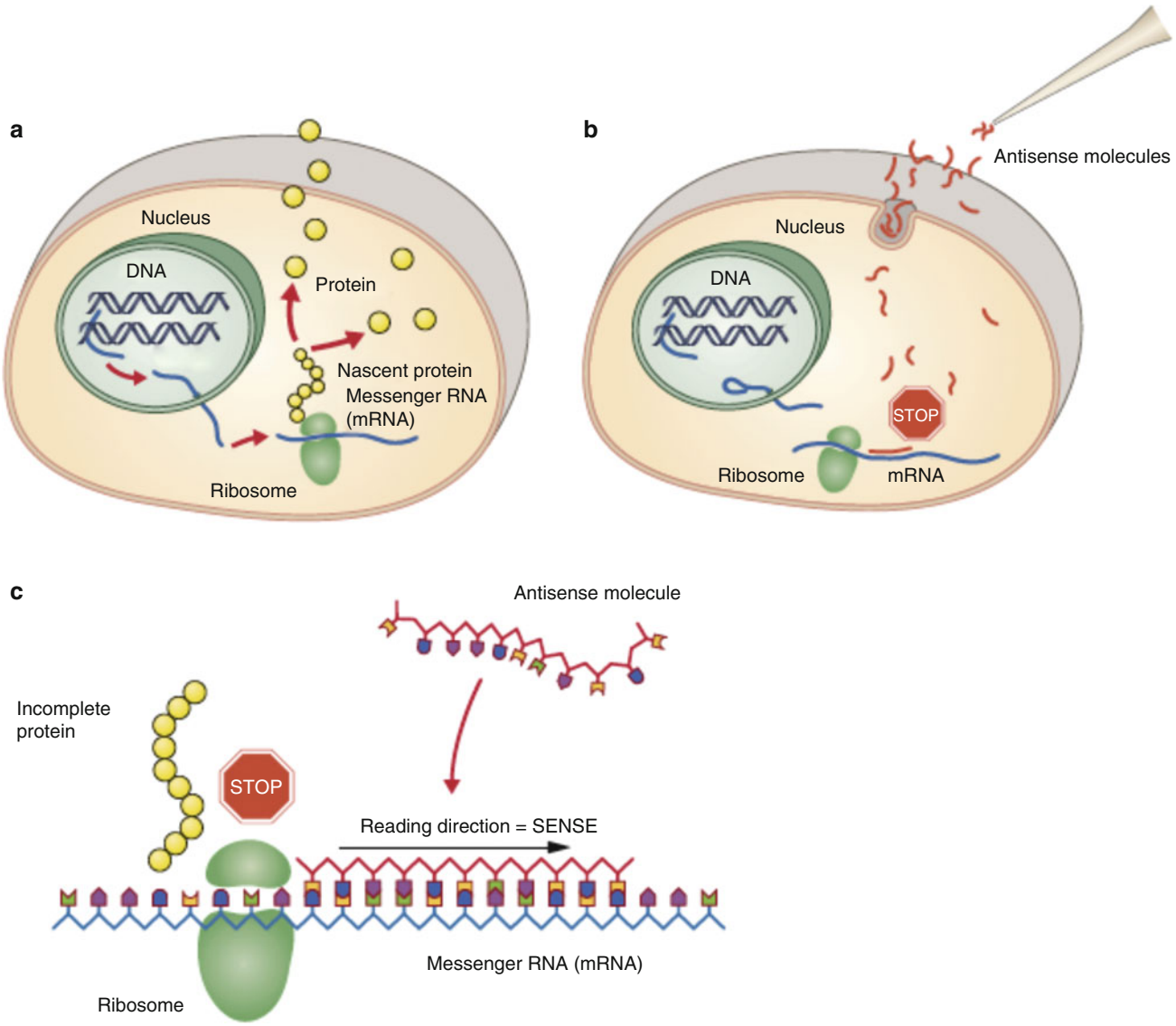

Fig. 37.18 Antisense therapy. (**a**) Genetic alterations in malignantly transformed, stromal or vascular endothelial cells may produce proteins that potentiate the survival and growth of malignancies through the standard sequence of DNA translation to mRNA and mRNA transcription by the ribosome to protein. (**b**) Antisense therapy utilizes the delivery of antisense molecules to the target cell where they bind with mRNA to stop protein transcription. This leads to death or dysfunction of the tumor cell. (**c**) Binding of the antisense nucleotide, which is typically 17–22 nucleotides in length, is designed to be complementary to the selected gene's mRNA based on Watson-Crick base pair binding specificity

tumor progression by inhibiting apoptosis or programmed cell death through BCL-2, a mitochondrial-membrane protein that functions to heterodimerize with BAX and the other proapoptotic regulators, thereby inhibiting the release of cytochrome c from the mitochondria and the subsequent steps of the apoptotic cascade [135]. The selective and competitive dimerization between pairs of these antagonists and agonists of the BCL2 family of proteins determines how a cell responds to an apoptotic signal. BCL-2 overexpression has often been implicated in treatment resistance by tumors. BCL-XL is another antiapoptotic BCL-2 family member that may be coexpressed in some tumors and some may switch between the two pathways [136–140].

Protein Kinase C (PKC) belongs to a class of serine/ threonine kinases that regulate numerous intracellular processes "arising from G-protein-coupled receptors, receptors with tyrosine kinase activity and nonreceptor tyrosine kinases" [141]. Enhanced PKC expression is associated with oncogenesis and multidrug resistance phenotype. PKCα inhibitors block proliferation, affect the growth and survival of tumors, promote apoptosis, and sensitize tumor cells to chemotherapy [142–144].

Survivin, an inhibitor of apoptosis (IAP) gene family, encodes proteins that protect cells from undergoing apoptosis through the inhibition of caspases, the key effector proteins of the apoptotic cell death cascade [145]. This protein

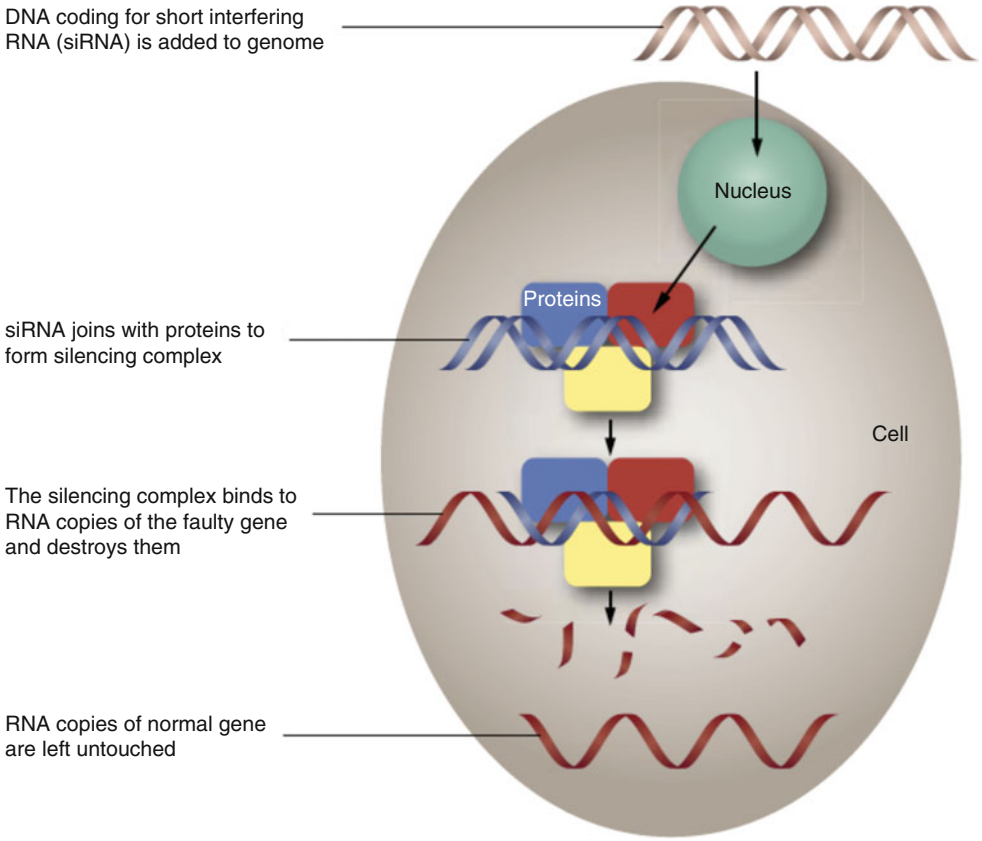

Fig. 37.19 Mechanism of action of double-stranded small-interfering RNA (*siRNA*)

is highly expressed in many adult malignancies including breast, lung, pancreas, colon, and prostate cancers but is largely unexpressed in normal tissue [146, 147]. Survivin is also present in many pediatric brain tumors, soft tissue sarcomas, and neuroblastomas. Overexpression in tumor cells inhibits chemotherapy induced, BAX-induced, and Fas-induced apoptosis. High-level expression is correlated with poor prognosis in solid tumors. Survivin is the fourth most common gene expressed in cancer cells but not in normal tissue. This selectivity of Survivin, in addition to its physiologic functions make it an ideal target for therapeutic antisense interventions [148].

Survivin has been identified in primary pediatric central nervous system tumors, soft tissue sarcomas, and neuroblastoma; however, detailed analysis of these tumors remains quite limited at present. Studies have shown that 10–50 % of medulloblastomas in children may express Survivin and that the level of expression may correlate with both histology and prognosis. Diagnostic and therapeutic implications are emerging from these observations. Over 80 % of rhabdomyosarcoma, the most common pediatric soft tissue sarcoma, may overexpress this molecule. Studies also indicate that Survivin in these tissues may serve as an excellent target for antisense and other RNA silencing technologies. Survivin expression appears to be correlated with unfavorable histology, advanced disease, and poor prognosis in neuroblastoma [149]. Promising results of preclinical data implicate Survivin-targeted strategies utilizing antisense techniques as a feasible approach to therapy in the future [150].

The heat shock proteins (HSP) are a family of highly conserved molecular chaperones that are induced by signals such as hypertension, oxidative stress, activation of Fas death receptor, and cytotoxic drugs that directly interfere with apoptosis. Antisense strategies to target these important molecular chaperones are currently being studied and hold promise in the therapy of some malignancies [151].

Success of antisense therapies will be predicated upon the improved understanding of the relative importance of the identified target, dose optimization and scheduling, successful clinical trial data from sensitive tumors, and rational use of combination regimens. Future antisense techniques are being designed with prolonged *in vivo* half life, improved tissue distribution, increased potency, and decreased toxicity.

Conclusion

The progress made in the last three decades in the understanding of the molecular, genetic, cell signaling, and immunologic foundations has led to significant advances in our efforts to either cure cancer or make it a chronic disease. Many of these novel strategies that have been introduced to adult oncology have only recently begun to be used in the treatment of pediatric malignancies.

It becomes increasingly clear from the adult experience that Ehrlich's "magic bullet" or therapy that will cure all cancer does not yet exist but that the optimal approach to treating malignancy must employ a strategy based on the use of multiple modalities [152]. As our understanding of cancer cell biology and the host response continues to proliferate, these novel and emerging therapeutic strategies will become conventional and new therapies will emerge. Our focus must remain on the close collaboration of scientist and clinician to achieve this goal of a cure or alternatively to convert cancer into a chronic non-fatal disease that can be managed.

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Central Venous Access

38

Gregor M. Walker and Constantinos A. Hajivassiliou

Introduction

Approximately 200,000 central venous lines (CVLs) are inserted in the UK annually and a significant proportion are indwelling lines inserted for the administration of chemotherapy or to serve the other needs of patients with oncological problems.

The advances in cancer care have been paralleled by similar advances in central line design and construction. The history of central access and treatment through indwelling catheters is relatively short: in 1968 Dudrick et al. [1] inserted a catheter in the superior vena cava of beagle puppies that was maintained in situ for a long period. Broviac et al. introduced a catheter suitable for long-term use in 1973 [2], and Hickman modified this in 1975 [3] by increasing catheter wall thickness and lumen diameter. The evolution of materials used to construct these catheters has also been revolutionized by the replacement of thrombogenic, relatively noncompliant, and variably antigenic rubber, nylon, polyvinyl, or polyurethane catheters with those made of silicone, associated with a concomitant decrease in the complication rate and duration of indwelling catheter time.

Multiple lumen catheters have been designed for use in patients requiring long-term simultaneous administration of two or more parenteral solutions, e.g., chemotherapy, antibiotics, antifungal agents, and parenteral nutrition. Since the introduction of intravenous therapy teams, there have been dramatic improvements in catheter and catheter site care, bringing about a reduction in complications [4]. Furthermore, the introduction of fully implantable central access systems (Figs. 38.1 and 38.2) has afforded further benefits, especially freedom of lifestyle, to these patients [5, 6].

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Indications for the Insertion of Central Lines

Patients with oncological problems will almost always require treatment with chemotherapy. Administration of chemotherapy is the most important specific indication for the insertion of a central venous line. However, the needs of cancer patients are oft en quite complex; therefore, a CVL may be required for other uses besides chemotherapy.

Administration of Chemotherapeutic Agents

The use of multiple lumen catheters has been of particular value in patients requiring multimodal treatments. Patients undergoing bone marrow transplantation require vascular access during preparation for transplant, high-dose chemotherapy, and total body irradiation.

Supportive therapy is also required during preparation for engraftment and following transplantation.

Administration of Intravenous Alimentation

Intestinal complications of chemotherapy requiring bowel rest (e.g., typhlitis) or effectively leading to a malabsorption type syndrome occur relatively frequently in neutropenic patients with leukemia during aggressive treatment with chemotherapy [7]. Many children with cancer are malnourished during their induction of chemotherapy, manifesting in weight loss. Their nutritional requirements can be met by parental feeding despite inadequate absorption from the gastrointestinal tract. Nutritional support can also be maintained without the need for long hospital stays through home parenteral nutrition programs.

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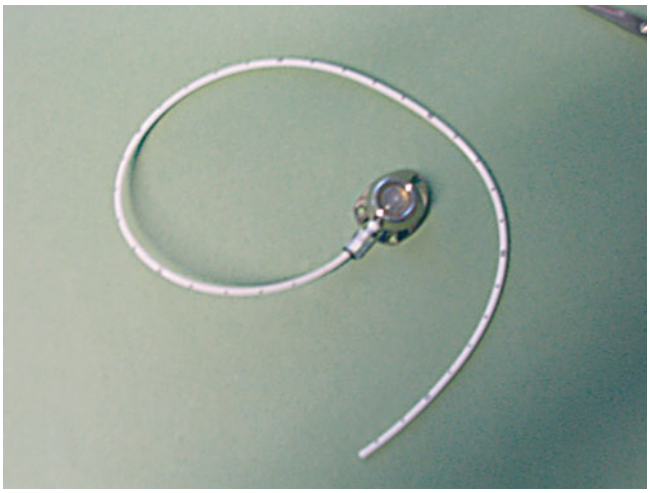

Fig. 38.1 Fully implantable device (port-a-cath) allowing patients a much less restricted lifestyle

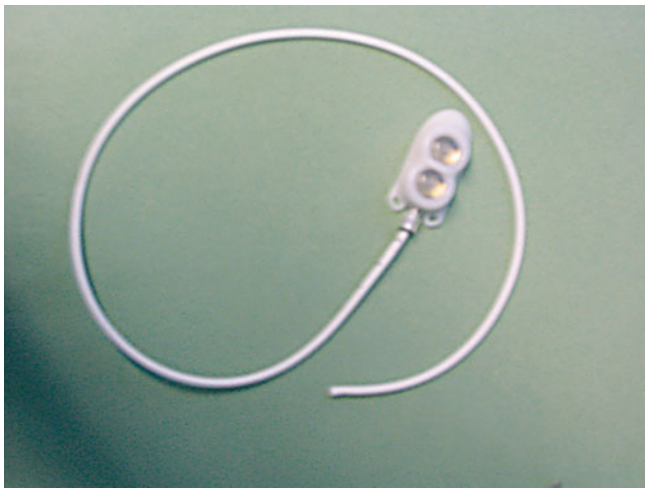

Fig. 38.2 Dual lumen port affording the advantages of double lumen lines in a totally implantable device

Resuscitation

Central access is also invaluable in the intensive care unit and monitoring of these patients, pre- and posttransplantation, during and after major oncological surgery, and in the management of complications such as tumor lysis syndrome.

Monitoring and Repeat Blood Sampling

Monitoring central venous pressure is important in monitoring patients in the intensive care facility or during major surgical procedures. Frequent blood sampling, from the catheter during courses of chemotherapy, avoids the need for frequent venepuncture in the pediatric patient.

Administration of Antibiotics

As many of these patients are immunocompromised, they may require frequent courses of intravenous antibiotics for prolonged periods to manage episodes of systemic sepsis.

Repeated Transfusion of Blood and Blood Products

CVLs are used for the administration of whole blood, packed cells, white cells, platelets, and plasma factors, and plasma may be required in patients with granulocytopenia, immune suppression, and patients with recurrent or chronic blood loss. Central lines are also useful for patients requiring exchange blood transfusions and apheresis.

Hemodialysis

This may be necessary for various reasons [8] and a specially modified large caliber line (semi-rigid dual lumen catheter) can be inserted to allow hemodialysis to be performed. It is possible to use the same tract of an existing central line and sequentially dilate it with special venous dilators to permit insertion of the hemodialysis catheter. This preserves a valuable entry point to the central circulation as oncology patients are likely to require multiple line insertions.

Methods of Venous Access

General Principles Applying to Gaining Intravenous Access: "The 5A's"

- Asepsis
- Antisepsis
- Adequate access
- Anatomical placement
- Avoidance of complications

All the above are self explanatory: aseptic technique should be employed with appropriate antisepsis of the surrounding skin/tissues. Chlorhexidine is superior to betadine as it is associated with a lower incidence of line infection [9]. The line inserted should be adequate for the purpose intended (single/multiple lumen, appropriate diameter, etc.) and should be inserted in the appropriate central location. The operator's experience and appropriate choice of the technique for insertion are also important factors in avoidance of complications.

Peripheral Venous Access

Peripheral venous access is indicated for short-term administration of fluids and drugs. There are a number of advantages over central venous access. There is evidence that drugs administered peripherally reach effective levels as quickly as those given centrally as long as they are flushed with a bolus of saline [10].

The basilic and cephalic veins in the antecubital fossa and the dorsal veins of the hands and feet are usually easily accessible in most patients. The origin of the cephalic vein in the "anatomical snuff box" is a site favored by medical staff, earning it a reputation as the "house-man's vein." Occasionally cannulae may need to be inserted blindly, where no vein is visible or palpable. In this situation veins which are relatively fixed in their position such as the medial cubital vein or the long saphenous vein at the ankle are useful. Different peripheral cannulation sites are more appropriate in different age groups. In neonate and infants, the scalp is a useful alternative site for peripheral access, although it is necessary to shave the hair around the site of insertion.

Some agents when given peripherally can contribute to the development of vasculitis (e.g., calcium, dopamine, chemotherapy agents); however, parenteral nutrition can be successfully administered into peripheral veins. Patients who require only short-term nutritional support are ideal candidates for this peripheral parenteral nutrition. Advantages of using peripheral access include the avoidance of the complications associated with the insertion and the care of central venous cannulae. However, administration of chemotherapy commonly leads to complications if given in the periphery. Other means to reduce the incidence of thrombophlebitis and prolong the life-span of peripheral lines include the simultaneous administration of fat emulsion (intralipid) and the use of a topical vasodilator such as transdermal glycerin trinitrate [11].

Peripheral lines are available in a variety of diameters, each color-coded in a universal manner, regardless of manufacturer. The smallest cannulae have the highest gauge.

Peripherally Sited Central Venous Access

The risks involved in central line insertion can be avoided by using specifically designed silicone catheters that can be placed in a peripheral vein and advanced into a more central position (PIC-line). This allows the administration of solutions that may be venotoxic when given peripherally, but avoids some of the complications associated with central line insertion [12].

Most commercially available long-lines come with an introducing kit. Ideal sites for insertion include the antecubital fossa veins, the femoral vein, or in small children the long saphenous vein at the ankle. To reduce the incidence of complications, if an upper limb vein is used the catheter should be advanced into the superior vena cava, and if a lower limb vein is used it should lie in the external/common iliac vein [13]. There have been recent reports of this type of cannula being associated with cardiac tamponade, after the tip of the line migrated through the wall of the right atrium [14, 15] leading to the recommendation that the tip of the line should rest in the central veins rather than the right atrium. The less compliant polyurethane lines of extremely fi ne caliber (e.g., <2 FG) are most likely to cause this problem, partially due to the high pressure "jetting" effect at the tip of the line [16].

Central Venous Access

Central venous access is indicated if venous access is required for a prolonged period of time, if peripheral access is unsuccessful, or when hypertonic or venotoxic solutions are to be used. Central lines are available in two major forms – polyethylene catheters that are more rigid and suitable for short-term access/monitoring, and silicone catheters that are more suited for long-term use. The complications of central line insertion are listed in Table. 38.1. The site chosen, underlying condition of the patient, and the experience of the clinician determine the incidence of these complications [22]. Junior trainees should be supervised until they feel comfortable and demonstrate competency in carrying out this procedure.

As the list of complications is long, the clinician may be tempted to advise repeated peripheral cannulae. In a large review of 585 children who required venous access, Ziegler et al. found that in 385 with peripheral lines there was a complication rate of 9 %, and in 200 children with central access, the rate was 20 % [23]. However, as the central lines were in place for a longer period than the peripheral lines, the complication rate per patient per day was actually lower in the central line group.

The reported risk of developing a catheter-related infection ranges between 1 and 20 % [17], but this should also be expressed as "per 100 intravascular device days." Infection can be reduced by meticulous aseptic technique at the time of insertion and each time the line is accessed or the dressing damaged at the exit site. A 2 % chlorhexidine solution is an

Table 38.1 Commonest complications of Central Line Insertion

Complication	Incidence [reference]
Infection	1–20 % [17]
Hemorrhage	1–3 % [18]
Dislodgement	7 % [19]
Phlebitis	4 % [18]
Thrombosis	1.5–3 % [18, 19]
Thromboembolism	1 % [18]
Air embolism	Rare (<0.1 %) [20]
Pneumothorax	2 % [21]
Hemothorax	0.2 % [21]

appropriate choice of agent and appears to be superior to betadine [9]. A collagen subcutaneous cuff as found on some central lines can reduce the risk of infection if the patient is nonseptic at the time of insertion [24]. The cuff can also add to the security of the line if inserted to a distance of greater than 2 cm from the exit site [25].

Manufacturers of commercially available central lines are listed in Table. 38.2. A recent modification popularized in the USA is the Groshong valve [26]. This patented system allows the tip of the catheter to be rounded and closed. The valve opens inwards when blood is aspirated and outwards during infusions. It remains closed when the line is not in use so clamping of the line is not necessary. Lines only require flushing once weekly.

There are three main sites commonly used for central lines – the subclavian vein, the femoral vein, and the neck veins (internal and external jugular veins). Each of these sites will be discussed.

Catheterization of the Subclavian Vein

The subclavian vein may be percutaneously catheterized using the Seldinger technique [27]. The apex of the lung lies higher on the left so pneumothorax is a more common complication using this side (Fig. 38.3). Unless there is a suspected cervical spine injury, this technique is facilitated by placing a roll under the thoracic spine, thereby extending it, a head down position to engorge the great veins, and the patient facing towards the contralateral side.

Technique

1. Scrub hands and observe strict aseptic technique.
2. Cleanse the patient's skin with an antiseptic solution and drape appropriately. The wider the sterile field, the better.
3. Infiltrate local anesthetic (e.g., 0.5 % bupivacaine) to an area 0.5 cm below the clavicle just lateral to the mid-clavicular line.
4. Attach a 2.5-ml syringe onto the needle and flush with heparinized saline.
5. Puncture the skin just below the clavicle lateral to the mid-clavicular line and advance the needle superiorly until the clavicle is met. Manipulate the needle to pass under the clavicle and point the tip medially.
6. At this point flush a very small amount of saline through the needle to evacuate any plugs of skin or tissue in the needle.
7. Place a finger of the other hand in the sternal notch, and direct the needle towards this target, gently aspirating the syringe as the needle is advanced.
8. Visualize the needle passing under the clavicle towards the tip of the finger in the sternal notch.
9. Free aspiration of blood indicates the correct position. If this is not achieved, withdraw slowly, while aspirating. Flashback of blood almost invariably occurs as the needle is withdrawn.
10. Once the vein has been accessed, firmly secure the end of the needle with one hand, and with the other remove the syringe. There should be free flow of blood from the end of the needle at this time.

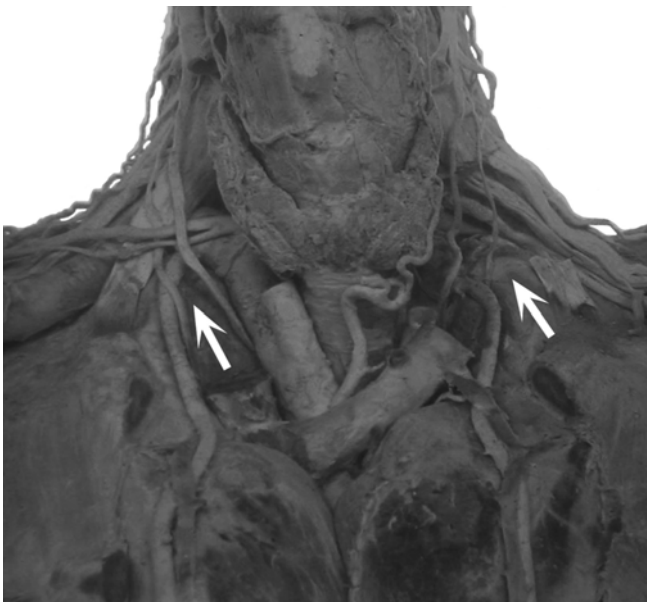

Fig. 38.3 Anatomical specimen of the neck and thoracic inlet showing the protrusion of the apex of the lung/pleura (*arrows*) in close proximity to the sites of percutaneous puncture for accessing the subclavian veins

Table 38.2 A selection of central line Manufacturers

Name	Address	Device
Vygon Corporation	East Rutherford, NJ	Various
Gesco International	San Antonio, TX	Per-Q-Catheter, various
Dow Corning	Ithaca, NY	Various
Pharmacia Inc.	St. Paul, MN	Port-a-cath, various
Bard Corp	Murray Hill, NJ	Various
Cook Inc.	Bloomington, IN	Broviac, various

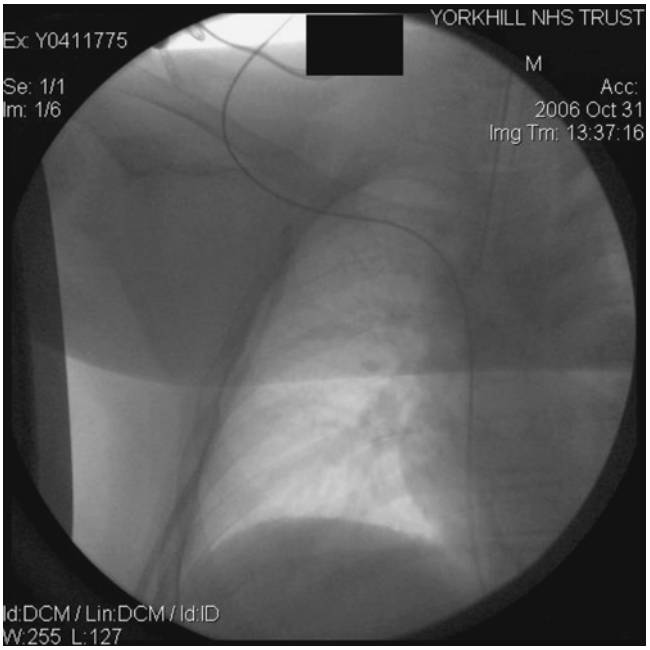

Fig. 38.4 Guidewire passed through needle into the heart. On this occasion it traversed the right atrium and terminated into the IVC and was withdrawn prior to the procedure continuing

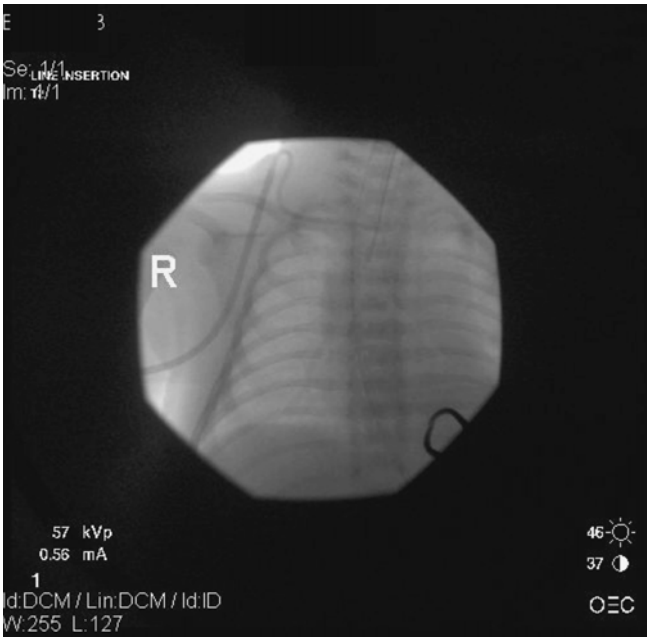

Fig. 38.5 Inappropriate position of CVL tip into the innominate Vein

11. Pass the guidewire through the needle until the tip is in the vena cava (Fig. 38.4). This should pass easily; if this is not the case, this indicates incorrect placement. This part of the procedure should be done with image intensifier help.
12. Remove the needle over the guidewire and make a small skin incision to allow the exit of the tunneling device and catheter and also subsequently the passage of the tissue/venous dilator and split sheath introducer.
13. Tunnel the line from a position lateral to the areola of the breast to the guidewire entry point and cut to size (ideally with the help of the image intensifier).
14. Pass the dilator over the guidewire and with a gentle but fi rm advancing and rotating force, advance the venous dilator/split sheath introducer into the SVC/RA.
15. When the correct position is radiographically confirmed, the guidewire and venous dilator are removed leaving the outside thin split sheath introducer in situ. This allows the tip of the previously tunneled catheter to be advanced to the correct position (SVC/RA junction) and the sheath split and removed while holding the catheter in place.
16. Advance the catheter over the guidewire until it reaches the desired position, then remove the guidewire.
17. Flush all lumina of the line and secure it in place using one of several methods to reduce the chance of displacement and migration [28–30].
18. Confirm that bilateral breath sounds are present.
19. Proper catheter position should be documented in all cases with a chest radiograph as inappropriately positioned lines should be remanipulated (Fig. 38.5).

Catheterization of the Femoral Vein

Percutaneous femoral vein catheterization has been used for long-term venous access (it is also the site of access for many invasive vascular techniques, e.g., cardiac catheterization, embolization, etc.). In the absence of significant abdominal distension the central venous pressure recorded through a femoral line is also an accurate reflection of supradiaphragmatic venous pressure [31]. Although it would seem that femoral lines are more likely to be complicated by infection there is no evidence of this [32]; indeed there is a lower rate of insertion-related complications compared to other sites [21]. Thrombotic complications, however, are more common.

For long-term access, the femoral vein is cannulated by a long saphenous vein cut down at the groin. A subcutaneous tunnel is fashioned to the anterior abdominal wall after the vein is exposed. A cuffed catheter can then be inserted through the tunnel and into the vein and can be advanced to the desired level up to the right atrium (Fig. 38.6).

Catheterization of the Jugular Veins

The external and internal jugular veins can be used for central access. Both can be accessed percutaneously or by an open technique. The external jugular vein is an appropriate site for venous cut down in children under general anesthetic and the number of complications related to insertion is low. Indeed, it is the site of choice for the insertion of the first central line in this institution.

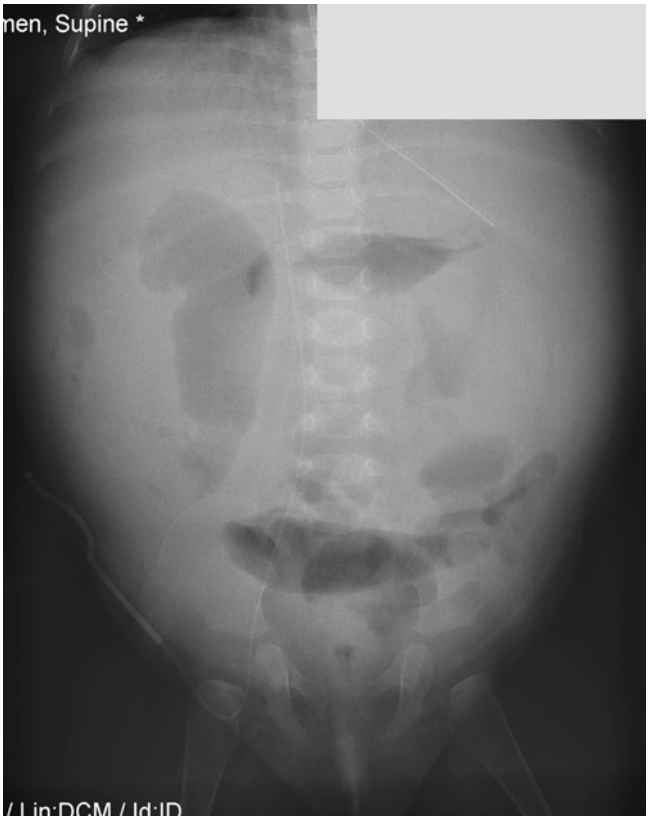

Fig. 38.6 A femoral line placed into the IVC

Percutaneous access of the internal jugular vein is preferably performed on the right. The pathway to the right atrium is straight, and there is virtually no chance of thoracic duct injury. Again, it is best if the patient is placed head down with a roll under the shoulders to extend the neck, with the patient facing the contralateral side. If there is suspected cervical spine trauma this position will not be possible. Recently published guidelines (2002) from the National Institute for Clinical Excellence have recommended the use of 2-dimensional ultrasound to locate the vein prior to percutaneous insertion. This policy increases the success rate of internal jugular venous access in children although the avoidance of arterial injury is not as marked as in adult practice [33]. This technique has also been described with subclavian access [34].

Totally Implantable Devices

These consist of central venous lines that are inserted as documented above but instead of being tunneled to an exit site, a port is buried in a subcutaneous pocket, usually on the lateral chest wall, and secured through small fixing holes in its periphery. The port is a chamber with a self-sealing injection port (Figs. 38.1 and 38.2). A recent addition to the choice of ports is a dual lumen device, with the obvious advantages it affords (Fig. 38.2). The ports are made of stainless steel, titanium alloy or synthetic plastic materials and have a

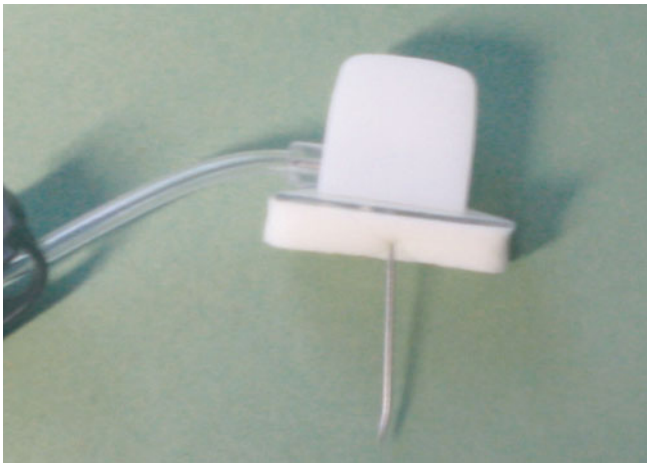

Fig. 38.7 Close up view of the Huber needle, which is constructed in such a way to penetrate the silicone dome of the port reservoir by pushing away the layer of silicone instead of "coring" through its thickness

silicone dome on the anterior surface to allow access. The silicone compound has "bleeding" properties such that after the needle is withdrawn, the access hole seals spontaneously. Access to the port is achieved via a specially designed "non-coring" Huber needle through the skin (Fig. 38.7).

Advantages of implantable devices include decreased infection rate with appropriate care [35], decreased dislodgement rate [25], minimal maintenance [36], and freedom of activities [37]. The most pleasing aspect of these devices to our patients is the ability to continue with normal activities such as swimming and other sports. Although access to the port involves puncturing the overlying skin, this is initially sensitized by using local anesthetic cream (EMLA, Ametop) until the area eventually becomes insensitive as time progresses. The skin, however, may break down over the patch and lead to complications, e.g., infection.

Complications of CVLS and Their Treatment

A central line, however carefully and expertly inserted, is still a foreign body in direct contact with the circulation. Most of the potential complications have already been reported and studied (Table. 38.1), but the clinician should remain vigilant to identify and treat any potential permutation or new complication that may arise. Infection is a serious complication, especially in immunocompromised patients and can be treated aggressively with antibiotics with reasonable success [38], although in the setting of sepsis, 20–60 % of catheters will be removed [35]. Some organisms (e.g., staphylococcus epidermidis [39], pseudomonas species, and candida albicans [40], etc.) are virtually impossible to eradicate and will require line removal and a new line to be inserted. Although some success is reported by replacing the line through the

same tract [41], in severely immunocompromised patients the commonest protocol involves removal of the line, antibiotic administration, and line replacement several days later once the infection is controlled. There is a paucity of published evidence regarding an optimal delay before line reinsertion. Published articles pertain predominantly to the use of short-term central venous lines in the intensive care setting and extrapolation of this evidence to cuffed tunneled lines is tenuous. One controversy with short-term central lines is the practice of routine replacement to prevent catheter-related sepsis. In a telephone survey in 1997, 52 % of intensive care units in the UK had a policy of replacing lines before 7 days [42]. Recommendations from the USA do not support a practice of routine replacement [43].

Another relatively recent advance is the introduction of antibiotic-impregnated lines [44], which are reportedly associated with lower rates of bacterial colonization [45]. Techniques used include bonding minocycline and rifampicin to both internal and external surfaces or chlorhexidine and silver sulfadiazine to the external surface [46]. This technology is widely available with percutaneously inserted central lines rather than tunneled long-term central lines. However, these lines are less compliant as a result of the manufacturing process of impregnation and careful consideration should be made prior to their use.

Hemorrhage can be caused by damage to the vein, inadvertent puncture of an artery or the heart [47], and exacerbated by thrombocytopenia/impaired clotting in pancytopenic patients. While in most cases general measures (mainly local pressure application) suffice, in some, vascular reconstruction/emergency cardiac surgery may be necessary to correct the problem. Mortality is indeed associated with this thankfully rare complication. Phlebitis is rarely observed with correctly positioned central lines and is more commonly the result of peripheral administration (mainly through necessity) of venotoxic solutions or due to displacement of the tip of the central line from the correct position. Thrombosis is also a sequel of the presence of the line in the circulation as such and this may lead to vein stricture and/or thrombosis. Pulmonary embolus is a rare complication usually resulting from the dislodgement of a thrombus from the right atrium (RA). Keeping the catheter tip proximal to the RA avoids this complication.

Prior to each use, the line should be checked for free flow of blood both ways. If in doubt, a chest radiograph and possibly an echocardiogram should be performed to assess the position and presence of thrombus around the line. Early detection and treatment will reduce the chances of thromboembolic complications. Air embolism can occur during insertion of the line or through a breach of the integrity of the line. The former can be avoided if the patient remains in head down position until the line is inserted, flushed, and sealed and the latter by regular careful inspection of the integrity of the line and all obturator parts.

Pneumothorax is a well-recognized, although rare, complication of percutaneous subclavian vein access and all patients/families should be warned about this possibility. If recognized early, it is successfully treated by the insertion of a chest drain. Chylothorax is a very rare complication of central venous access, almost exclusively after left -sided approach due to the proximity of the thoracic duct to the confluence of the internal jugular vein with the left subclavian. It can be avoided by ensuring open approaches remain above the confluence of the two great veins.

If the line is advanced too far (i.e., into the RA), it can cause atrial arrhythmias by interfering with the SA or AV node or ventricular arrhythmias by interfering directly with the ventricular myocardial wall. In such cases, the line should be remanipulated in the correct position as soon as possible. Fracture of the catheter, if complete, can result in the distal segment embolizing into the pulmonary vasculature. This can be successfully retrieved through a transfemoral minimally invasive technique best done in the cardiac catheter suite.

Many unfortunate patients require repeated insertions of central lines over long periods of time and this eventually results in obliteration/thrombosis of the available veins. In order to avoid fruitless invasive explorations, an angiogram would be indicated if a new attempt at central access is required in such a patient. Until recently, the investigation of choice was a formal angiogram, which is associated with a high level of radiation and the possibility of allergic reaction to intravenous contrast, or B-mode ultrasound, but these investigations have now been virtually superseded by detailed MR angiography which can effectively guide the surgeon to the appropriate vessel while at the same time being safer and much less invasive for the patient (Fig. 38.8).

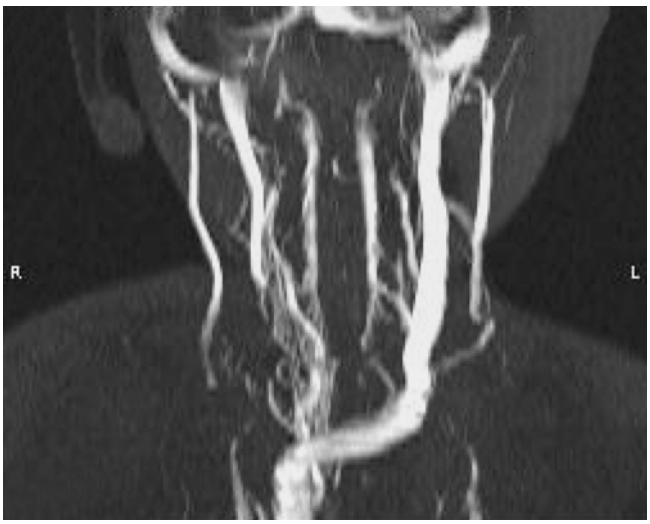

Fig. 38.8 MR venogram showing complete occlusion of the right internal jugular and subclavian veins with the development of tortuous collateral circulation. CVL cannulation was achieved by percutaneous subclavian access of the innominate vein

Summary

Technological advances in material manufacture and design have revolutionized the safety of implantable central lines, by reducing their antigenicity and thrombogenic potential, while at the same time augmenting their longevity in the circulation. Surgical technique has evolved in parallel to allow for safe and minimally invasive placement of these lines that afford a more successful and comfortable method of administering the necessary chemotherapeutic and supportive agents to oncology patients.

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Pain Management

39

John Currie

Introduction

It is one of the "Rights of the Child" not to have to endure pain [1, 2]. In the past there was little knowledge or understanding of pain in children [3]. Many of us were taught that babies do not feel pain. Minor operations such as circumcision were often performed on neonates with no analgesia. We now know this to be a cruel misconception and in fact neonates have an enhanced, more global response to pain. Sensitization of the nervous system by trauma at such an early age can lead to different pain behavior in later life [4]. This global response in neonates is due in part to the poor hyalinization of nerves at this early stage of life, and also to the inability to localize pain until the brain develops a proper body image in the first few months of life.

This better understanding of pediatric pain has led to a revolution in pain management for acute and peri-operative pain in children. Most children's hospitals now have a well established "pain team" who ensure protocols are followed and that pain is adequately assessed and treated. It is from this initiative that the problem of chronic pain in children came to be recognized. These principles have been applied to chronic pain due to terminal disease.

Pain is an adaptive mechanism. Pain is a sensation and a reaction to that sensation. It helps us to avoid noxious stimuli in our environment and protect any injury while healing takes place. Pain is incorporated in our body image, localized and then changes our behavior. Our body image and pain behavior develop throughout childhood. For instance, a child under 5 years of age may describe any pain as "tummy ache" [5]. The pain may be somatic, visceral, or both, each type of pain having a different effect on the child. Somatic pain is easier to incorporate into the body image; a cut or broken arm can be seen. It is part of the body, outside of "self." Visceral pain, on the other hand, is more difficult to visualize. It is mediated mainly by C fiber pathways with anatomical connections into the limbic system. This is more frightening and has a greater emotional response. It is also harder to localize. We do not have a well-developed internal body image. A good example of this is appendicitis, which presents as a central abdominal pain until our nervous system works it all out.

Pain may be useful and protective, and this is easier to tolerate, and usually time limited. Chronic pain can be thought of as "useless" pain. This can lead to more suffering. Suffering is a global concept, associated with negative feeling, and impairs quality of life. This type of pain needs a different approach and this is what is provided by pain clinics in their pain management programs.

If the pain is associated with neoplasia then these negative feelings are enhanced. Any worsening of the pain will be interpreted by the patient and their family as progression of the disease. The final stage is palliative care. Here pain and symptom management is the goal, realizing that a cure is impossible and the outcome hopeless. This situation is obviously very psychologically demanding on staff as well as devastating for the family. The more closely staff are involved with the care of these children then the more difficult this situation will be. Nurses in particular will be in need of psychological support when caring for a dying child.

A palliative care team is extremely valuable for providing objective advice regarding difficult decisions and support to the primary care team. This team should meet regularly in an environment conducive to open discussion, rather than on the ward itself. In our own institution the team consists of our lead oncologist, pain management consultant, liaison psychiatrist, pediatrician, surgeon, and the nurses who coordinate care in the child's home as well as during ward admissions. We find that this approach works well. It is also useful to maintain close contact with the hospital ethics committee for help with end of life decisions and "do not resuscitate" orders.

Pain from childhood tumors is chronic "useless" pain which may develop as the disease progresses to become terminal pain needing palliative care. There may be acute

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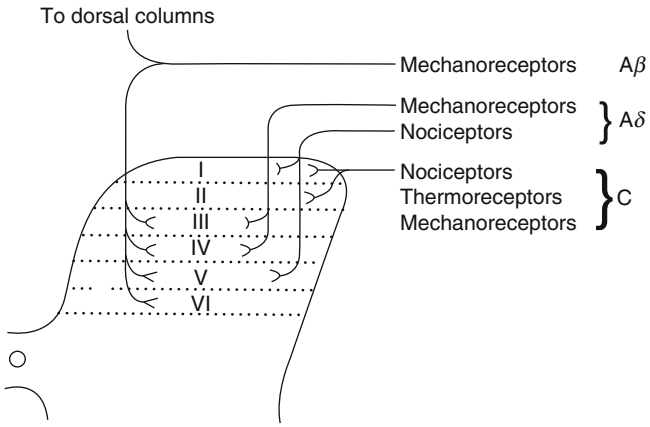

Fig. 39.1 Integration of sensory input in the dorsal horn of the spinal cord

events related to the progression of the disease, such as fractures related to bone metastases, pleuritic pain due to infection, or pain due to lymphoedema, for example.

What do we mean by "chronic pain?" The most widely accepted definition is that of Bonica [6]. He defined chronic pain as:

> Pain which persists a month beyond the usual course of an acute disease or reasonable time for an injury to heal or is associated with a chronological pathological process which causes continuous pain or pain which recurs at intervals for months or years.

In palliative care the ongoing disease process leads to a chronic pain picture which is progressive. The last few years have seen a considerable development in our understanding of pain mechanisms [7]. Laboratory and clinical studies have demonstrated increased spontaneous activity involving both mechanosensitivity and chemosensitivity in damaged peripheral nerves [8]. The consequent increased neural activity effects changes in both the dorsal root ganglion and the dorsal horn of the spinal cord (Fig. 39.1). This is a well-known phenomenon of dorsal horn windup. Abolition of spontaneous activity from damaged nociceptors or nerves may allow remodeling of the dorsal horn, and other areas of the central nervous system, resulting in prolonged pain relief.

This is an example of how the nervous system adapts to a chronic stimulus. The nervous system "learns" and tends to facilitate chronic stimulation. This has led to the concept of the plasticity of the nervous system which is now well established [9–11]. Understanding of the way in which the nervous system adapts to chronic pain inputs has lead to a range of techniques and specific drug treatments for the control of chronic pain [12].

This "learning" takes place throughout the nervous system all the way through to how the body image is mapped into higher centers and hence to consciousness [13] (Fig. 39.2).

Thus the pain may become "neuropathic" (from the Greek "neuro," meaning nerves, and "pathy," meaning abnormality). This is pain either originating from abnormal firing of nerve cells, or abnormal propagation of sensory input so that non-noxious sensations are perceived as painful. This type of pain relies on different transmitters within the nervous system, notably the n-methyl d-aspartate (NMDA), gamma amino butyric acid (GABA), and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) systems [14–16]. Neuropathic pain does not usually respond to conventional analgesic regimes and is opiate resistant.

Management of Pain in the Child with Advanced Malignancy

The effects of a tumor are complex and debilitating. As the tumor grows it may compress local tissues or nerves causing pain. Compression of nerves is a classic way in which neuropathic pain in produced. Indeed, compression by ligature is the most common way of producing an experimental neuropathic pain model. The tumor may also infiltrate into a nerve bundle or plexus causing pain. Infiltration into bone will initially cause painful pressure on the periosteum and may progress to cause pathological fractures. The same is true of bone metastases. Tumors also produce secretions which can act locally or systemically. Locally acting secretions include kallikreins [17, 18] and bradykinin [19, 20], which cause pain in nerve endings adjacent to the tumor. Recent research has focused on the purine pain pathway, mediated by adenosine triphosphate [21–23]. This is particularly interesting with relation to pain caused by tumors due to the very high levels of adenosine triphosphate in cancer cells. Systemically cancers produce substances that alter metabolism and the immune response. This leads to systemic pain, which is not well understood. Pain can also result from recumbence and pressure on thinned and weakened tissues.

Successful management of pain and other symptoms of pediatric tumors demands a team approach. Nurse pain specialists will liaise with the ward teams on a day-to-day basis, and in particular with the home support nurses. This latter group is key to managing pain at home. Most children are

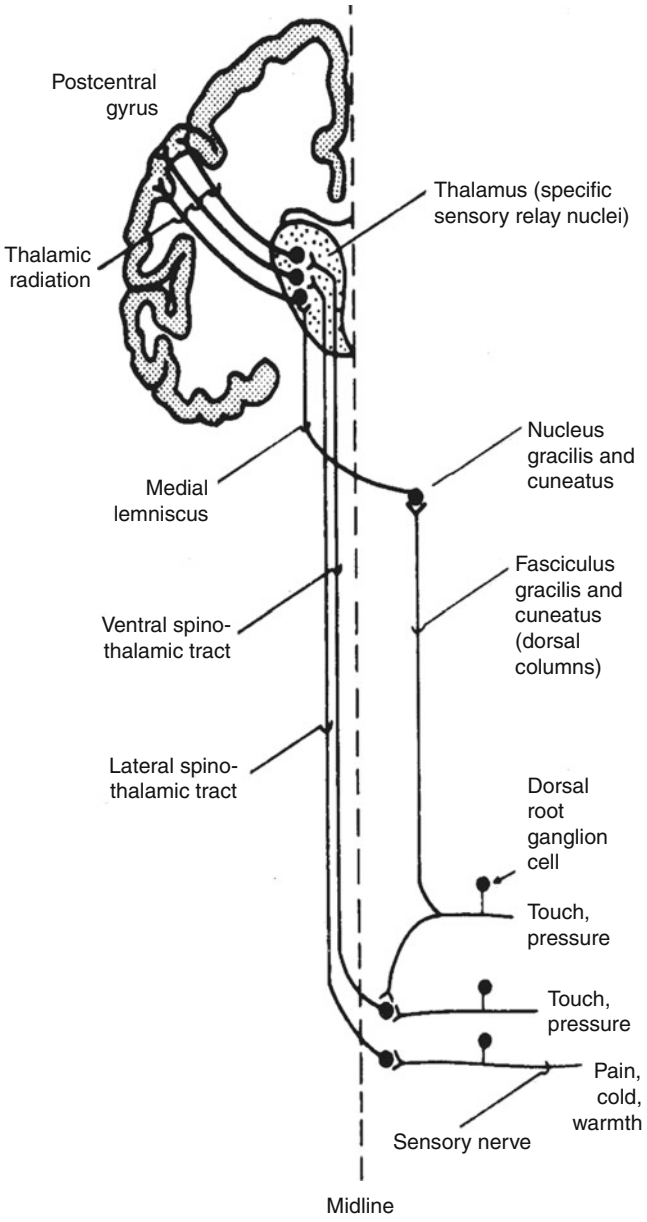

Fig. 39.2 Mapping of the body image through the thalamus to the post central gyrus. The post central gyrus is the area of the sensory cortex where the body is mapped as the homunculus (little man)

better nursed at home with their families where possible. This is particularly true at the end stages of life. The ideal is for the child to die comfortably at home. Other members of the team will include a psychologist and perhaps also a psychiatrist to try to help with the inevitable depression and anxiety. Where a family has a strong religious faith then close involvement with their church and hospital chaplain, etc., is extremely helpful. The physiotherapists can help with stiffness and pain due to recumbence as well as breathing exercises and helping to clear secretions. Any acute exacerbations of pain can be assessed with the help of the diagnostic imaging department to diagnose fractures, effusions, etc.

When assessing a patient with pain due to malignancy, adequate enquiry to obtain information is essential. We use a detailed questionnaire that the child fills in with the help of the family. This can identify the different types of pain the child has, as well as how it changes during each day. A pain diary can help with how the pain is responding to treatment or progressing.

The first step is to try to gain control and break the cycle of pain. Patient-controlled methods are preferably as they give some control to the child. They have something they can do. This can also help allay the fear that the pain may crescendo and become completely uncontrollable. Children often fear what the pain may be like rather than deal with what it is. Anyone who has performed a venipuncture on a child will know this well! A transcutaneous nerve stimulation device is extremely useful and is often our first line of approach. For visceral pain we have found a TSE (Transcutaneous Spinal Electro-analgesia) machine extremely useful. This is coupled with explanation and reassuring the patient and family, i.e., explanation as to why the child has pain, due to the mechanisms we have described, and reassurance that pain does not necessarily mean progression of the disease.

Sometimes more of an intervention event is necessary to break the cycle of pain. This may be a local anesthetic injection or an infusion of medication. It is important to get control of the pain in order to gain the confidence of the child and family.

Then a systematic approach is followed, developing a plan to deal with the pain. This is where the team approach is essential to monitor progress and avoid over treatment. Careful enquiry must be made as to the effect of the pain on the child's sleep pattern. If the child is kept awake or woken by pain, the whole family will be woken and lose sleep. This has a detrimental effect on everyone's mood and ability to cope. Pain relief must be first directed to give the child a good night's sleep. Melatonin is extremely useful for re-establishing normal sleep patterns. After that, pain control at rest is the goal, followed by pain control for whatever activity the child may be capable of. Pain control during all activity may not be possible, but some degree of mobility can usually be achieved, even if only from bed to chair.

Medical Treatment

There is still a place for conventional analgesia regimes. Many children will respond and not progress to the more intractable pain picture. Care must be taken to give adequate analgesic doses of these drugs and to make full use of the synergism between different drug groups. A good example

of this is to combine paracetamol with nonsteroidal anti-inflammatory drugs (NSAIDs).

This represents the first stage of the World Health Organization analgesic ladder (Fig. 39.3). Most units would progress from this first stage to stage three, strong opiates. This bypasses stage two, weak opiates. Stage two is unlikely to control the pain for long, and the side effects of the weak opiates are out of proportion with their efficacy in controlling pain.

Morphine is the standard opiate used and will initially be given intravenously to determine the required dose. This can then be converted to oral morphine given as a long-lasting (continuous) preparation twice daily. Breakthrough pain can be controlled by oral morphine given as the standard preparation. As long as oral intake is possible this is the ideal regime as is effective in most cases. Diamorphine can be used if morphine becomes ineffective, as it is a more powerful analgesic with the added benefit of a more profound anxiolytic action. It is extremely soluble making it the ideal agent for subcutaneous administration usually as an infusion. Fentanyl patches allow opiate absorption without a cannula. Patches are available in different strengths allowing titration of the dose. Each patch will give a steady dose of opiate through the skin for 72 h. Oral morphine can be used for breakthrough effect.

Nerve blocking techniques are useful, and may be peripheral or central. Laboratory and clinical studies have demonstrated increased spontaneous activity involving both mechanosensitivity and chemosensitivity in damaged peripheral nerves. The consequent increased neural activity effects changes in both the dorsal root ganglion and the dorsal horn of the spinal cord [8]. Abolition of spontaneous activity from damaged nociceptors or nerves may allow remodeling of the dorsal horn, and other areas of the central nervous system, resulting in prolonged pain relief. Local anesthetic administered by subcutaneous infiltration or directly to specific nerves can produce long-lasting pain relief for a variety of chronic painful conditions [10, 12]. Pain relief will often last for months [17]. Intrapleural blocks can be very useful for upper abdominal pain as well as pain in the thorax. A catheter can be used and an infusion given. This can be a very useful "event" to gain control of pain that has become intractable.

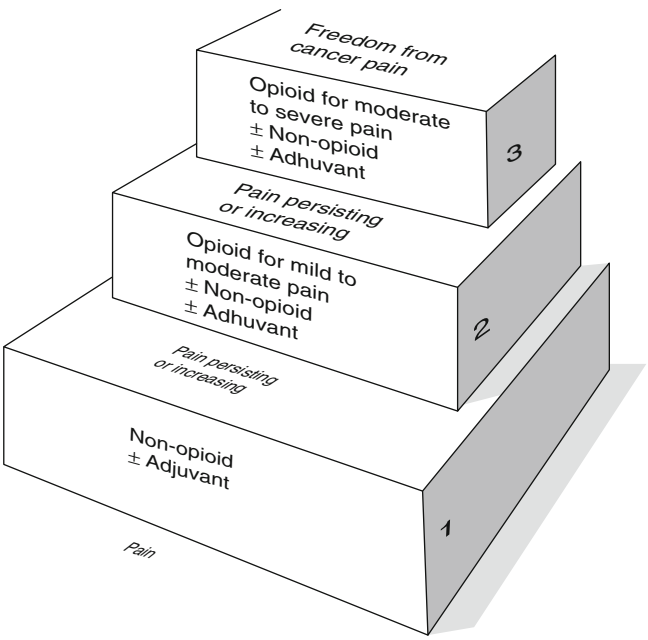

Fig. 39.3 WHO "Pain Ladder"

Many treatments despite involving short-term modification of the neural pathways nevertheless have long-term effects, for example, injecting local anesthetic drugs. We are manipulating the plasticity of the nervous system. I like to think of this as rebooting the system so that the normal program can run. In this computer age children relate well to this analogy.

Some pain may be mediated by the sympathetic nervous system and be helped by sympathetic blockade [24]. A good example is coeliac plexus block for pain mediated by upper abdominal tumors, particularly those affecting the pancreas. We have, in our unit, a particular interest in coeliac plexus block for upper abdominal pain [25, 26] (Figs. 39.4, 39.5, 39.6, and 39.7).

Stellate ganglion block can be very effective in controlling pain mediated by the sympathetic nervous system in the upper quadrants. A block using local anesthetic such as levobupivacaine gives long-term relief and seldom needs to be repeated (Fig. 39.8).

In chronic pain epidural block is often a technique of last resort. The catheter can be tunneled to allow for long-term use. There are difficulties involved in managing a patient with a long-term epidural catheter, but these can be overcome with careful monitoring. These epidural infusions can be successfully managed at home. There are more drug preparations now available for administration by the epidural or caudal route as well as techniques for modification of neuronal function at this level [27, 28]. Catheters can also be placed intrathecally and this is an extremely effective method of achieving pain control [29]. The high risk of infection limits its usefulness [30]. Reservoirs of medication can be implanted under the skin, but this technique is limited by cost not just of the system itself but also in terms of resources to manage it effectively. The most common drugs used in these central blocks are local anesthetics such as levobupivacaine and opiates such as morphine or diamorphine. Adjuvant drugs such as clonidine can enhance the effect of local anesthetic.

The position of the tip of the epidural catheter can be confirmed by radiography or ultrasound to ensure accurate delivery of the medication (Fig. 39.9).

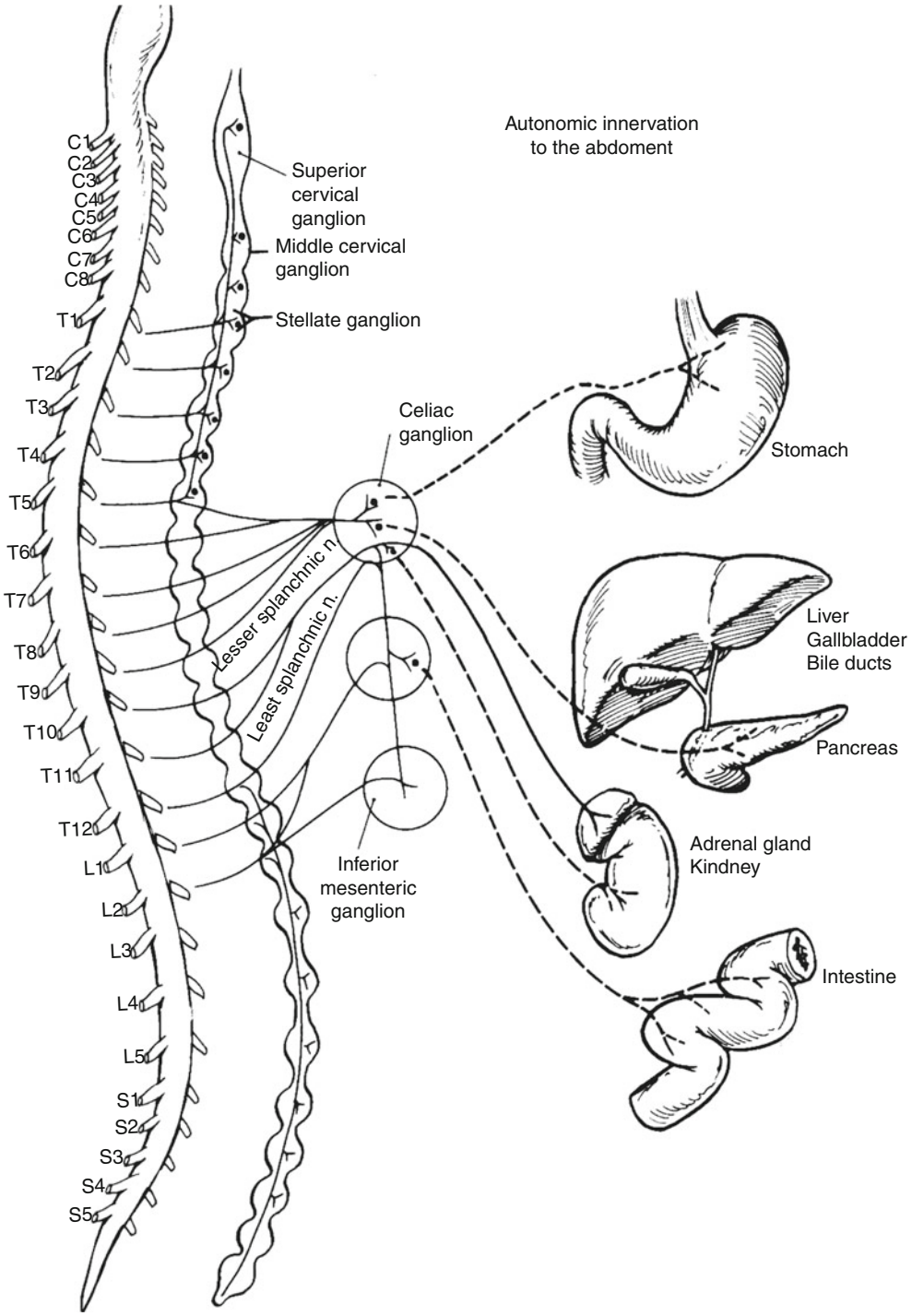

Fig. 39.4 The autonomic innervation of abdominal viscera

Other more invasive techniques may include nerve destruction, but this is seldom employed in children. An exception is ablation of the coeliac plexus after successful block with local anesthetic. A single localized lesion may be the major source of pain, for example, collapse of a vertebra due to tumor infiltration causing pain by nerve compression. This may be treated by injecting polymethyl methacrylate into the vertebra, which hardens and supports the damaged spine. Although obviously rarely used this is an extremely effective technique for controlling this type of very localized pain. We have ourselves used this successfully in a case of vertebral collapse due to hemo-lymphangioma.

The use of other techniques such as acupuncture and aromatherapy can be very effective [27]. Careful patient

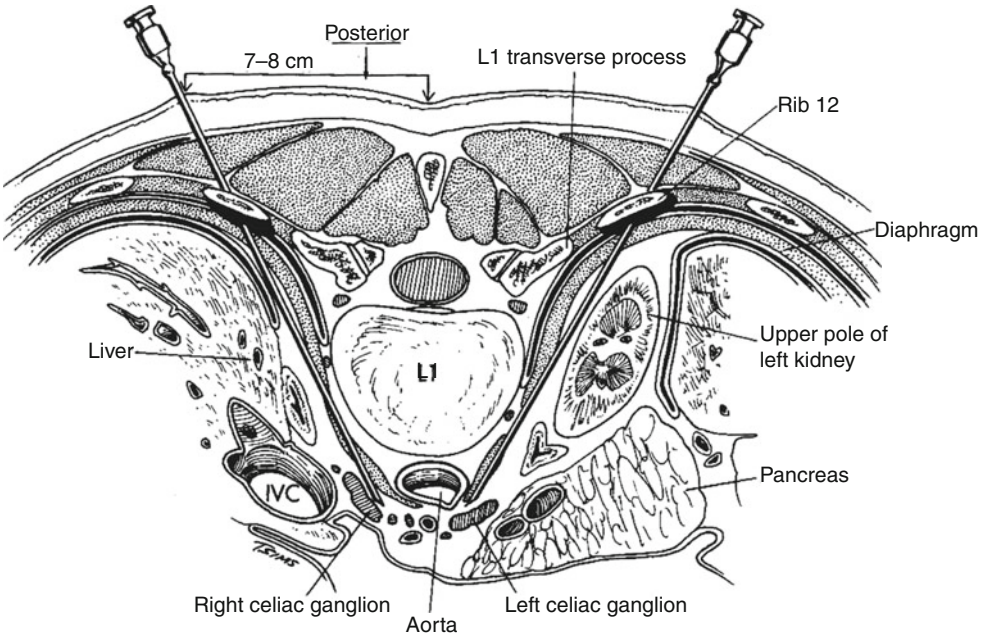

Fig. 39.5 Showing the positioning of the two needles for coeliac plexus (ganglion) block

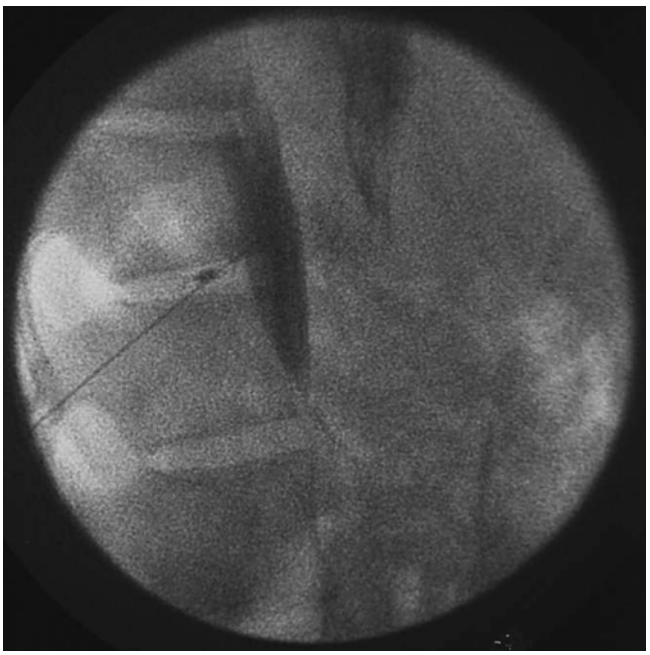

Fig. 39.6 Lateral radiograph showing dye around the aorta at the level of the coeliac ganglion

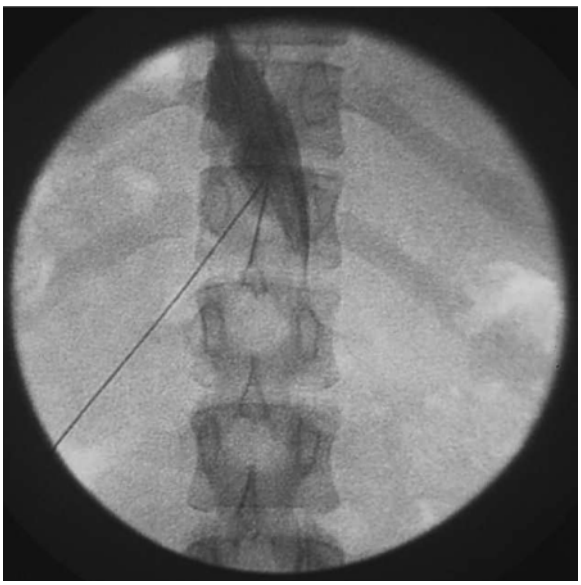

Fig. 39.7 Antero-posterior radiograph showing dye in the midline at T12

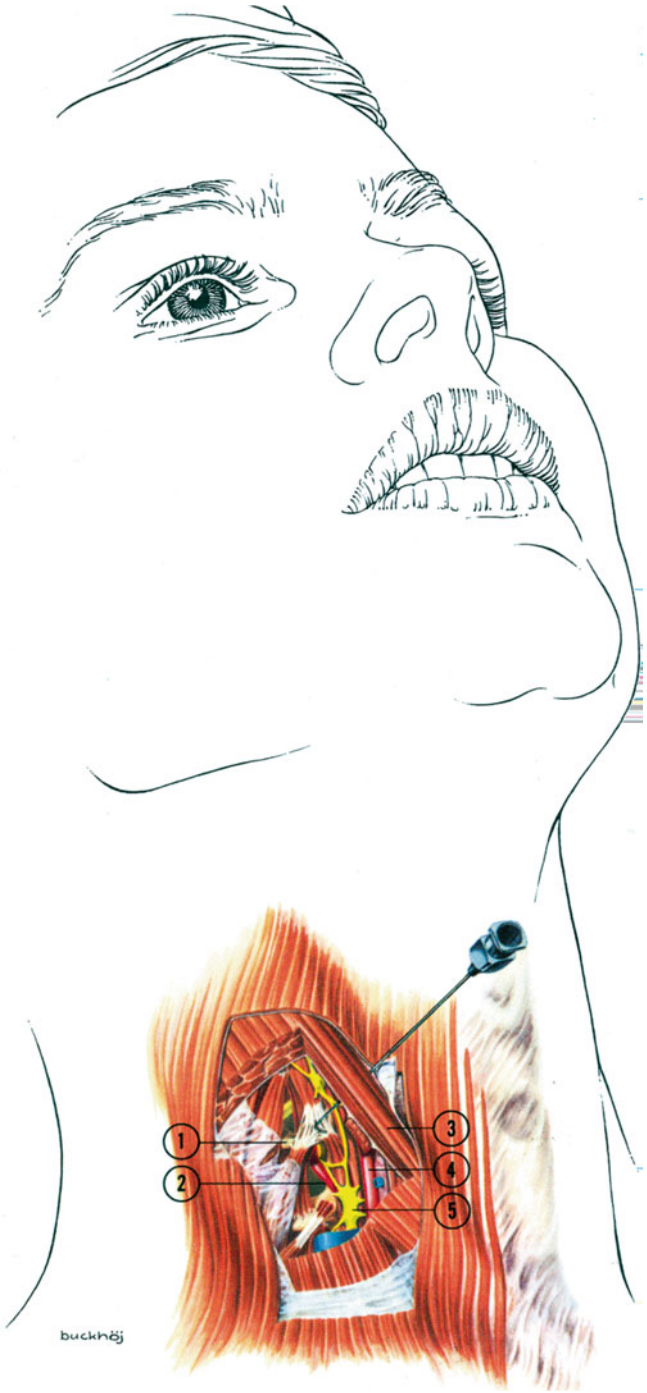

Fig. 39.8 Stellate Ganglion Block, showing the position of the ganglion in the neck and enlarged to show position of the needle adjacent to the ganglion. (*1*) Transverse process of C6, (*2*) Vertebral artery, (*3*) Sternocleidomastoid muscle, (*4*) Common carotid artery, (*5*) Stellate ganglion

selection is important, particularly for acupuncture. Aromatherapy has the major advantage of allowing parental involvement. Modern treatment regimes can lead to excessive "medicalization" of the child. The ability to be involved in care is very valuable to parents.

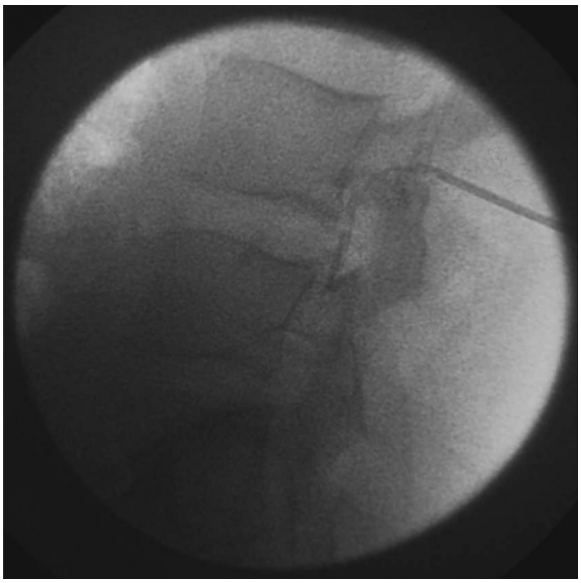

Fig. 39.9 Radiograph of the epidural catheter passing caudad in the epidural space

When the Drugs Don't Work

Most pain related to cancer will be controlled with opiates as the final stage of the analgesic ladder. The palliative team really comes into its own when these standard techniques fail and "the drugs don't work." This is when these more invasive techniques will be employed. Morphine may not control the pain. The pain may be mediated by different pathways particularly if the pain becomes neuropathic. The main pathway in this process is the N-methyl D-aspartate (NMDA) system.

More specific agents are now available for this neuropathic pain and their mechanisms of action are better understood [16, 17]. Our first line treatment for somatic neuropathic pain is gabapentin, lamotrigine being preferred for visceral pain. Ketamine is an excellent NMDA blocker and can be used intravenously or as part of an epidural infusion. Psychological side effects limit its use intrathecally. Methadone is also a very effective NMDA blocking agent, but its usefulness is limited by its narrow therapeutic index and significant side effects.

Other Symptoms

Nausea is a common symptom of cancer pain associated with renal or hepatic dysfunction, chemotherapy, and of course opiates. In children, however, we find that if the dose of opiates is appropriate for the pain then side effects do not present a significant problem. It is only when the dose is escalated in a futile attempt to control pain that has become opiate resistant, that the unwanted effects emerge. Nausea

can be as distressing as the pain itself and should be treated aggressively [36]. The cause should be determined, whether it be due to chemotherapy or metabolic dysfunction. Hypercalcemia, which may occur particularly in metastatic tumors, must always be excluded, as it is a potent cause of vomiting. The antiemetic will be chosen with regard to the cause of vomiting in each particular patient.

Excess secretions can be a major problem in the end stages of palliative care. The child may be too weak to cough and clear normal secretions or infection may lead to increased secretions. This may lead to noisy breathing or indeed choking which is very distressing to relatives and staff caring for the child. Hyoscine usually applied as a patch is very effective in relieving this symptom.

In a pain management program the input of other health care professionals is essential. This is particularly important in palliative care especially at the end of life. Depression and anxiety are features of terminal care in even the youngest of patients. This must be recognized particularly as many of the drugs to help with this can take days to work. A particular feature of palliative care is terminal agitation. The cause of this is multifactorial. Factors include poor metabolism of drugs at the end of life as well as increased anxiety. Nozinan (levomepromazine) is the most effective treatment, and has the added advantage of being an excellent antiemetic.

New drugs on the horizon which may be useful for neuropathic pain are levetiracetam an antiepileptic with a novel mode of action [31], and the AMPA blocking agent Anandamide.

Many of these new techniques and methods have resulted in some ethical dilemmas. For instance, most of the drugs used are not licensed for use in children or are being prescribed for conditions that are "off-license" for that drug.

The Future

There are many promising new developments in the study of chronic pain. We have several new drugs which can be used to modify the method of transmission of chronic pain and research continues in this area. New developments in functional MRI give us a better understanding of the central changes associated with chronic pain and its treatment. Remapping sensory input into consciousness is an exciting possibility [13, 32]. There is also increasing evidence of a genetic basis or predisposition to chronic pain syndromes opening up further avenues of treatment [33–36]. These advances will help us in our understanding of the effects of our therapies on the pain pathways and central pain perception, and may also provide guidence in the choice of appropriate treatment.

The drugs and dosages that we use in our clinic are listed in Table 39.1 [37].

Table 39.1 Drugs and dosages used in author's clinic

Neuropathic pain drugs
These drugs should be titrated slowly up to the effective dose. This will help to avoid unwanted effects. They should not be stopped suddenly, but weaned off gradually. Doses for pain management are generally lower than those used to control epilepsy.
Gabapentin:
>60 kg max dose up to 3600 mg/24 h
<45 kg max dose up to 2400 mg/24 h
<30 kg max dose up to 1200 mg/24 h
<20 kg not recommended
Preparations available: capsules: 100 mg, 300 mg (can be opened & mixed with food, e.g., jam, etc.) Tablets: 600 mg, 800 mg
Amitryptilline: requires ECG before commencement.
>50 kg 25 mg PM – aim for 25 mg BD
<50 kg 10 mg PM – aim for 10 mg BD
<30 kg not recommended
Preparations available: oral solution: 25 mg/ml, 50 mg/5 ml
Tablets: 10 mg, 50 mg
Carbamazepine:
>40 kg 100 mg PM should be effective at this dose
<40 kg not recommended
Preparations available: tablets: 100 mg, 200 mg, 400 mg
Chewtabs (tegretol): 100 mg, 200 mg
Oral solution (tegretol): 100 mg/5 ml
Suppositories (tegretol): 125 mg, 250 mg
Slow release (tegretol retard): 200 mg, 400 mg
Lamotrigine:
>50 kg START 10 mg BD (max 40 mg.BD)
>30 kg START 5 mg BD (Max 25 mg BD)
<30 kg not recommended
Titrate to effect. We start this with child as in-patient as adverse reactions, particularly a rash may be a problem.
Preparations available: tablets: 25 mg, 50 mg, 100 mg, 200 mg
Soluble: 5 mg, 25 mg, 100 mg
Topiramate
>30 kg 2–6 mg/kg per day in two divided doses.
Initiate 25 mg nightly with weekly increments of 1–3 mg/kg withdraw very slowly.
NSAIDs (Non Steroidal Anti Inflammatory Drugs)
Caution if bleeding risk, asthma, atopy, renal dysfunction, GI ulceration/bleeding, on anticoagulants, (avoid if <6 months or weight <10 kg).
Diclofenac:
1 mg/kg up to 8 hourly
Preparations available: tablets: 25 mg, 50 mg
Suppositories: 100 mg
Modified release (diclomax SR): 75 mg
Modified release (voltarol retard): 100 mg
Ibuprofen:
10 mg/kg up to 6 hourly
Preparations available: tablets: 200 mg, 600 mg
Oral suspension: 100 mg/5 ml
Effervescent granules: 600 mg/sachet
Naproxen:
<5 years not recommended
>5 years 10 mg/kg in 2 divided doses
Preparations available: tablets: 250 mg, 500 mg
Oral solution: 125 mg/ml
Suppositories: 500 mg

(continued)

Table 39.1 (continued)

Piroxicam:
<15 kg 5 mg stat
16–25 kg 10 mg daily
26–45 kg 15 mg daily
>46 kg 20 mg daily
Preparations available: capsules: 10 mg, 20 mg
Melts (Feldene): 20 mg
Suppositories: 20 mg
Antiemetics should be chosen in relation to the cause of the vomiting.
Ondansetron: is a specific 5HT three serotonin antagonist.
Dose: 0.1 mg/kg (100 μg) 8 hourly
Preparations available: tablets: 4 mg, 8 mg
Oral lyophilisates (zofran melt): 4 mg, 8 mg
Domperidone: does not readily cross the blood–brain barrier, so causes less central effects. It acts at the chemoreceptor trigger zone.
Dose: 200–400 mcg/kg 4–8 hourly
<20 kg not recommended
Preparations available: tablets: 10 mg
Oral solution: 5 mg/5 ml
Suppositories: 30 mg
Hyoscine: topical hyoscine preferred (Scopoderm TTS):
Dose: >35 kg 1 mg patch
Not recommended <10 years
Preparations available: 1 mg/72 h when in contact with skin.
Metoclopramide
500 micrograms/kg/24 h
Oral or IV
Methotrimeprazine
Excellent for intractable nausea/vomiting. Sedative and useful for “terminal agitation” in palliative care.
Initial dose 0.25 mg/kg daily given in 2 or 3 divided doses. This dosage may be increased gradually until an effective level is reached which should not surpass 40 mg/day for a child less than 12 years of age.
Opioids
Minimum monitoring standard for in-patients. Do not mix opioids or routes of administration.
Loading dose
>3 months old 0.1–0.2 mg/kg (100–200 μg/kg).
Switch to oral as soon as possible.
Oral opioids
MST: opioid naïve child: <15 kg expert use only
15–25 kg: 5 mg BD
25–50 kg: 10 mg BD
>50 kg: 15–20 mg BD
Preparations available: tablets: 5 mg, 10 mg, 30 mg, 100 mg
Sachets: 20 mg, 30 mg, 60 mg, 100 mg, 200 mg
Oramorph: opioid naïve child: one-fifth of total MST dose for breakthrough 4/6 hourly. Preparations available: oral solution: 10 mg/5 ml
If more than 3 doses of oromorph per day add to MST dose by adding total dose of drug to MST dose and divide to 2 equal doses.
Always titrate to effect. Doses may be considerably higher in children who are not opiate naïve.
Diamorphine: extremely soluble and so is useful in small volumes for subcutaneous administration. When converting from morphine start with 1/4 to 1/3 of combined oral MST and oromorph dose
Sevredol: as oromorph, one-fifth of total MST dose for breakthrough 4/6 hourly.
Preparations available: oral solution: tablets: 10 mg, 20 mg
Conversion to MST as per oromorph recommendations.
Oxycontin and oxycodone are alternatives to MST and ORAMORPH

Table 39.1 (continued)

Tramadol: >12 years 50 mg 6 hourly
>60 kg 100 mg 6 hourly
Preparations available: capsules: 50 mg
Soluble: 50 mg
Slow release: 100 mg, 150 mg, 200 mg
Effectiveness limited by high incidence of nausea.
Dihydrocodeine: 0.5–1 mg/kg 6 hourly
Preparations available: tablets: 30 mg
Oral solution: 10 mg/5 ml
Slow release: 60 mg
Topical opioids
Fentanyl: opioid naïve child: 25 mcg/h patch
Under 30 kg: half patch
Under 15 kg: quarter patch
Patch should not be cut but placed over nonporous dressing such as
Tegederm to give desired surface area of patch next to the skin.
Preparation available: patch 25 = 25 mcg/h for 72 h
Patch 50 = 50 mcg/h for 72 h
Patch 75 = 75 mcg/h for 72 h
Patch 100 = 100 mcg/h for 72 h
When starting evaluation of the analgesic effect should not be made before the system has been worn for 24 h to allow the gradual increase in plasma-fentanyl concentration. It also may take 17 h or longer for the plasma-fentanyl concentration to decrease by 50 %. Patches should be changed every 72 h.
NMDA (N-methyl-D-aspartic acid) antagonist
These drugs should only be used by specialists for severe intractable pain.
Ketamine:
Binds to specifically to phencyclidine site (PCP site) of the NMDA receptor-gated channel and blocks NMDA receptors. It can be associated with general disturbances of sensory perception.
This is an anesthetic and adequate training before use is essential.
Sublingual: may be used to test efficacy 1 mg/kg diluted in 5 ml water: spit out after 2 min or if feeling dizzy.
Intravenous: start at 15 mg/kg in 24-h period diluted in normal saline to give dose of 2–4 ml/h. May need up to 25 mg/kg/24 h,
Epidurally: epidural agents must be preservative free. Start with bolus of 0.6 mg/kg and then 0.8–1 mg/kg in 24-h period.
Methadone:
Epidurally: as per epidural ketamine doses

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Paediatric Palliative Care

40

Dermot Murphy

Introduction

Don't you ever laugh as the hearse goes by,
For you may be the next one to die.
They wrap you up in a big white sheet
From your head down to your feet.
They put you in a big black box
And cover you up with dirt and rocks.
All goes well for about a week,
Until your coffin begins to leak.
The worms crawl in, the worms crawl out,
The worms play pinochle in your snout,
They eat your eyes, they eat your nose,
They eat the jelly between your toes.
A big green worm with rolling eyes
Crawls in your stomach and out your eyes.
Your stomach turns a slimy green,
And pus pours out like whipping cream.
You'll spread it on a slice of bread,
And this is what you eat when you are dead. [1] (Child's nursery rhyme parts of which date back to the Crimean War)

Death, much like sex, is a topic that adults find hard to discuss among themselves let alone with their children [2]. The conversation may be painful for both parties and there is a natural desire to protect children from harm. This ignores the fact that death is an integral part of childhood and that a failure to have an open conversation about childhood mortality can lead to significant misunderstandings at both an individual and societal levels.

Service Development and Epidemiology

Paediatric palliative care is an active and total approach to care, from the point of diagnosis or recognition, throughout the child's life, death and beyond. It embraces physical, emotional, social and spiritual elements and focuses on the enhancement of quality of life for the child or young person and support for the family. It includes the management of distressing symptoms, provision of short breaks and care through death and bereavement [3].

This definition has profound implications for the provision, planning and funding of services for children and their families with life limiting or life threatening conditions.

Palliative care for children is a relatively new speciality, with the first children's hospice, Helen House, opening in Oxford (UK) in 1982 [4]. Until the middle of the 1990s there was only one consultant specialising in Paediatric Palliative Medicine in the UK. It is a testament to families and professionals that there has been a massive increase in resource provision since then but it is sobering that there are still less than ten senior doctors with a paediatric training working as consultants in this field in the United Kingdom today.

Cancer is the commonest cause of death in children and the second commonest cause (after accidents and violence) in teenagers and young adults in industrialised countries. Cancer represents approximately 25 % of all childhood deaths. This equates to approximately 250 deaths in children aged under 16 years in a country of 63 million [5]. Death however is a very crude marker of need and it should be emphasised that End of Life Care is a small part of a greater palliative care package.

Models of Disease Trajectory

It is helpful to consider what the disease trajectory for children with a terminal diagnosis is and how it has changed over time. A traditional model views the child's journey as a gradual transition from cure to palliative care but it is also possible to construct a model that is dynamic and more accurately reflects the current situation where a child and family dip in and out of palliative care services as required. In this latter model palliation and curative intent are not seen as distinct,

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separate entities, rather as a reflection of a patient's need at that moment. Both models reflect that palliative and curative care should are two sides of the same coin and there is no defined start or endpoint to palliation (see Fig. 40.1).

Childhood cancer is now probably best thought of as a chronic disease. The majority of relapsed solid tumours still remain incurable but there has been a dramatic increase in the number of options open to families at the time of relapse. It is important to acknowledge that many of these have arisen because families have overcome the fatalistic attitudes of doctors and nurses.

The burden of therapy at the time of relapse should not be under estimated. It may well include further surgery consolidated with myeloablative chemotherapy and stem cell return (an autologous bone marrow transplant), radiotherapy or a phase I/II trial.

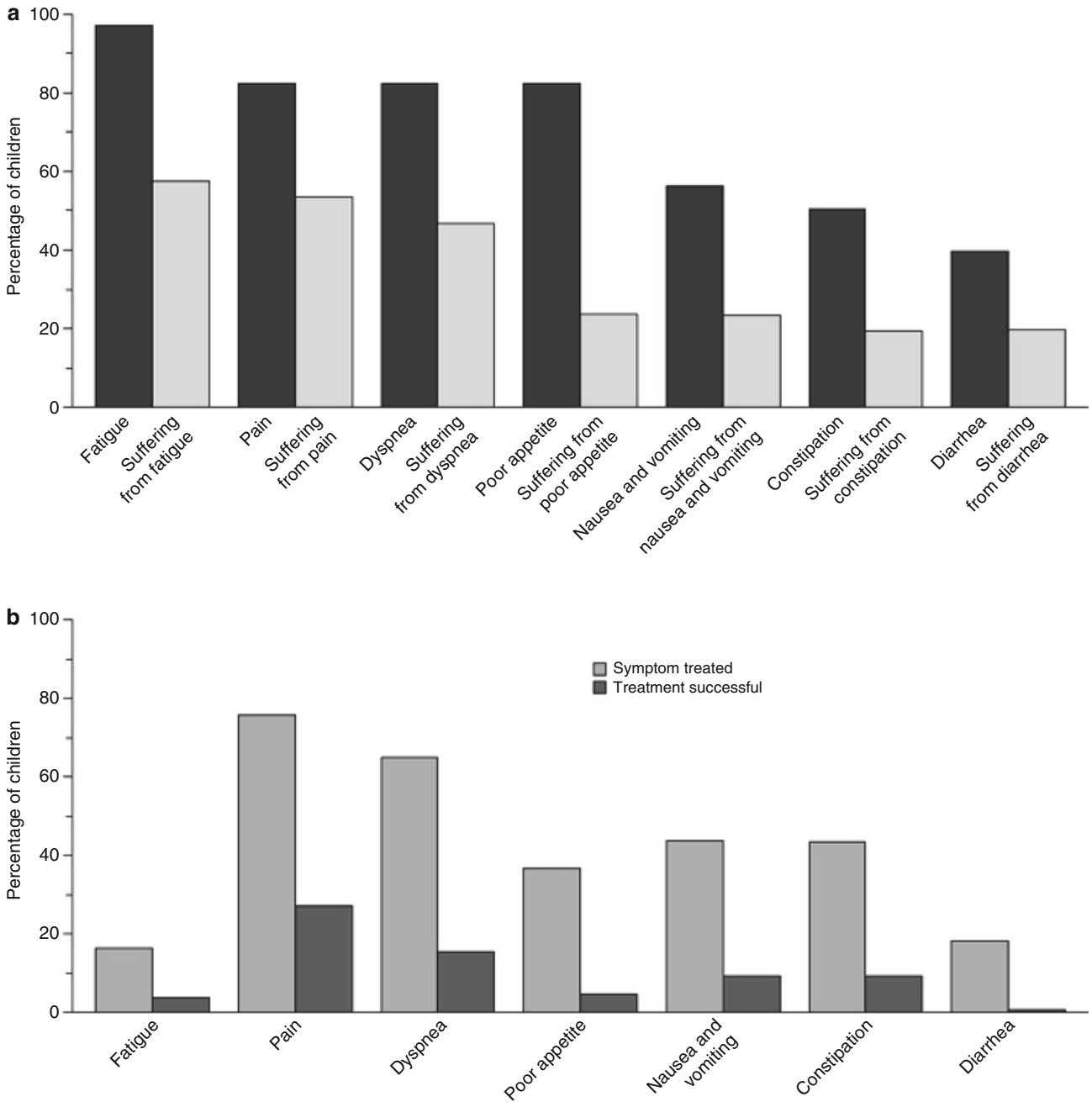

Fig. 40.1 Models of disease trajectory

Symptoms at the End of Life

How a child feels and the burden of care has been well researched on both sides of the Atlantic. Wolfe et al. [6] looked at symptoms at the end of life in children dying in Boston. She noted not only the presence of symptoms but also whether they caused suffering. Her team also showed how limited teams were in treating symptoms that did cause suffering (see Fig. 40.2). Furthermore doctors and nurses were unaware of many of the symptoms families described (see Fig. 40.3).

Liben and Goldman [7] found in a UK study that while the symptom constellation was similar that the presence of a dedicated symptom care team enabled a greater success in managing symptoms at the end of life.

A further UK study [8] showed the symptom constellations differed by tumour type when grouped together by type (solid tumour, brain tumour or leukaemia/lymphoma) Surprisingly the symptoms suffered by children with solid tumours and leukaemias was almost identical while children with brain tumours have their own, unique, pattern of symptoms (See Fig. 40.4).

Symptoms should be actively sought and treated. They will change over time through the evolution of the child's disease. Differing members of the multi disciplinary team should be employed as the child and family will disclose different concerns to different professionals. The response of symptoms to interventions should be also be clearly noted. This process should be repeated frequently. Using the mnemonic "I am fine" will allow a systematic approach (See Fig. 40.5)

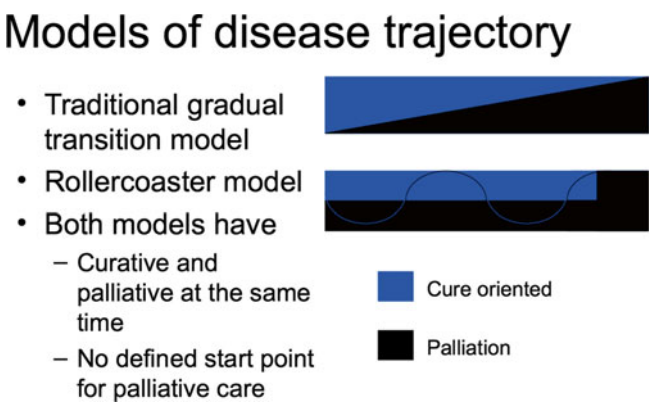

Fig. 40.2 The degree of suffering from and the success of treatment of specific symptoms in the last month of life. Panel **a** shows the percentages of children who, according to parental report, had a specific symptom in the last month of life and who had "a great deal" or "a lot" of suffering as a result. Panel **b** shows the percentages of children who, according to parental report, were treated for a specific symptom in the last month of life, and in whom treatment was successful (rather than "somewhat successful" or "not successful")

Barriers to Care

Access to expertise for children and their families is inequitable even within countries with a socialised health care service [9]. Many factors may be associated with this: personal, cultural, social or institutional. It is crucial that all forms of discrimination should be eliminated for this particularly vulnerable patient group.

If a child wishes to enter a phase I/II trial this should be provided as close to home as possible with a recognition that time is limited. It is difficult to balance the hope that an early phase clinical trial offers with the reality that these will very rarely extend the quality or quantity of life.

Communication

Discussion with the family around the time of relapse is crucial. It should be clear and recognise that the child and family are experts in their own disease. These conversations should be seen as a process rather than a single event and that the parent's and child's needs will need differing approaches even if they have the same requirements.

Fig. 40.3 Discordance between the reports of parents and physicians regarding the children's symptoms in the last month of life. Data were missing for ten children for whom there was no documentation of clinic or hospital visits in the last month of life and for one child whose records were not available for review.*CI* denotes confidence interval. [a]McNemar's test was used

Symptom	Reported by parent but not by physician (N = 92)	Reported by physician but not by parent (N = 92)	Kappa statistic (95 % CI)	P Value[a]
	Number (percent)			
Fatigue	44 (48)	1 (1)	–0.02 (–0.07 to 0.02)	<0.001
Pain	15 (16)	11 (12)	0.10 (–0.12 to 0.32)	0.56
Dyspnea	19 (21)	10 (11)	0.10 (–0.11 to 0.31)	0.14
Poor appetite	33 (36)	1 (1)	0.29 (0.15 to 0.43)	<0.001
Constipation	31 (34)	7 (8)	0.16 (–0.02 to 0.33)	<0.001
Nausea and vomiting	25 (27)	18 (20)	0.06 (–0.14 to 0.26)	0.36
Diarrhea	20 (22)	8 (9)	0.31 (0.12 to 0.51)	0.04

Symptom	Entry into study			Last month of life		
	CNS vs leukernia/ lymphoma	CNS vs othersoild	Leukernia/ lymphoma vs other soild	CNS vs leukernia/ lymphoma	CNS vs other soild	Leukernia/ lymphoma vs other soild
Pain	–	–	–	NS	p < .01	NS
Weakness	p < .05	p < .01	NS	–	–	–
Weight gain	p < .05	p < .01	NS	p < .05	p < .01	NS
Weight loss	–	–	–	NS	p < .01	p < .01
Anorexia	–	–	–	NS	p < .01	p < .01
Swallowing	–	–	–	p < .01	p < .01	NS
Excess secretions	–	–	–	p < .01	p < .01	NS
Headache	p < .05	p < .01	NS	p < .01	p < .01	NS
Dizziness	NS	p < .05	NS	NS	p < .01	NS
Convulsions	–	–	–	NS	p < .01	NS
Mobility	p < .01	p < .01	NS	p < .01	p < .01	NS
Speech	p < .05	p < .01	NS	p < .01	p < .01	NS
Vision/hearing	p < .01	p < .01	NS	p < .01	p < .01	NS
Anemia	p < .01	p < .01	NS	p < .01	p < .01	NS
Bleeding	p < .01	NS	NS	p < .01	p <. 05	NS
No.of significant differences	8	8	0	9	14	2

Fig. 40.4 Significance of differences in symptom prevalence between different tumor groups at entry to study and in the last month of life (adjusted for multiple testing). *NS* indicates not statistically significant

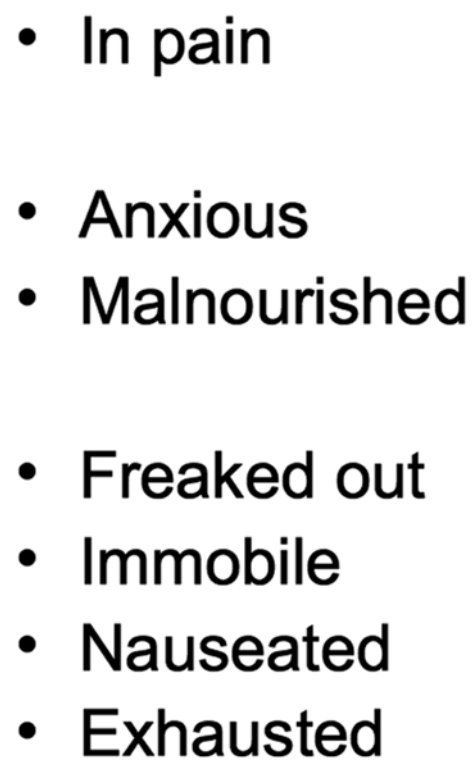

Fig. 40.5 I am fine

It is now almost universal that parents will be part of a wider social network that is world wide and disease specific. They may well have information on very early trials that is not readily available to clinicians. This has shifted the consultation away from a paternalistic "doctor knows best" model into a much more collaborative conversation in which the doctor's role is to interpret the information that patients have and to direct them towards resources they may not have seen. There should be humility on both sides and a recognition that a second opinion may be useful.

Talking to children about dying is often clouded by mutual pretense [10], here each party understands what is happening but doesn't talk about it. Dangerous topics are avoided, space is given to allow individuals to leave conversations if the pretense is in danger of being shattered. This tactic avoids confirmation of a known, terrifying reality for both parties. This may be a perfectly reasonable way to avoid trauma between individuals but may lead to huge misunderstandings and avoidable fear if it is unrecognised by health care professionals.

Guidelines on Talking about Death and Dying

There is no "right way" of talking to children (and to the parents and siblings of children) who are dying. Some general pointers can be noted though. (1) It is of paramount importance is to listen to the child and hear what they are saying (and not saying). (2) Have an understanding that children (and their parents) can hold mutually incompatible rational and scientific thoughts about death and dying at the same time. (3) The need and desire for information will ebb and flow over the disease trajectory. (4) Children want to keep those they care about around them-a desire that makes them unlikely to vocalise their needs if they see this as incompatible with their loved ones wishes.

This doesn't mean the fundamental question is "to tell or not to tell" but rather "what to tell, when to tell and who should tell". Children want to know about what their illness

and will try to figure it out for themselves if they are not told. This is especially important in an era when even toddlers can manipulate iPads. However, even prior to the information revolution, a visit to the play room on a children's cancer ward when parents were not present, would quickly confirm that children readily shared detailed knowledge of their disease and prognosis with one another.

In a situation when parents do not wish to discuss aspects of their child's treatment or death with them it is extraordinarily important and beneficial to find out why. Quite often fundamental misunderstandings about what the prognosis is or what treatment entails are uncovered. Again listening to a parents fears and concerns is vital as is an understanding that communication is a joined up process rather than a series of one off events. It is common that the views of individual parents may diverge, not only from one another but also from their child. It is vital that all sides are heard and respected. It is helpful to open dialogue by acknowledging how difficult and almost unreal, the conversation is. It is often also helpful to refer, at some point during the consultation, to previous experience of looking after families in a similar situation. Statements such as "I have found other parents find it really scary to think about their child's death" or "In the past children have tried to protect their parents in this situation-do you think this is happening" help families to engage in topics that they may be avoiding in a bid to protect themselves, their partner or their children. Asking "How would you like me to explain this to your child" is constructive, helpful and can lead to further clarity. Do not expect to have resolution of all concerns after a single consult. Suggest that further discussions with the child, either with you present or not, may help. This need not be straight away-but the groundwork for all future conversations will have been laid. It is vital to have the child's key worker present at as many of these consultations as possible. The reality though is that a parent or child may take advantage of a "corridor conversation" to garner further thoughts. A regular multi disciplinary team meeting allows information sharing and the planning of further consults. Above all, remember a child's needs may well not reflect your own needs or your perception of what their needs are. They may also be very different from the needs of their parents, siblings and grandparents.

Careful notation of a child's and family's wishes are paramount. This will avoid painful repetition of basic information and inappropriate and unwarranted health care interventions. Scotland is the first country in the world to have a legally mandated end of life care plan for children [11]. It allows clear and precise documentation of what a child and family want to happen at the end of life. It is owned by the family and is carried by them and is seen as a positive intervention. It was deliberately designed to show all professionals (including police, ambulance and school) what will be done rather than what wont be done and is used in community, hospice, hospital, education and home environments. Forms, parent information sheets and education packages are all available on line [12].

Conclusion

Children dying from cancer form a uniquely vulnerable group. They and their families deserve the same rigour of thought and delivery of care as children who have curable disease. They deserve rapid access to the latest information on novel therapies and symptom control. Access to specialized services should be equitable and independent of class, ethnicity, socio-economic status and geography. Care should be of the highest quality and teams providing palliative care should be driven by a strong evidence base and welcome routine external audit of performance. There should be an institutional and governmental agenda to provide safe and sustainable services.

Winston Churchill once remarked that the mark of a country's civilization was the way it cared for its prisoners. This was taken up by John FitzGerald Kennedy and modified to assert that the mark of a country's civilization was the way it cared for its pensioners. In the Twenty-First century surely the mark of a country's civilization is the way it cares for its dying children.

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Medical Law as Applied to Paediatric Oncology Surgery

41

Robert Wheeler

Introduction

To describe the influence of medical law on as wide ranging a topic as paediatric oncology is a significant undertaking. But in a book destined to be read by surgeons working in multiple continents, Nations and States, there is the additional problem of describing the complex variations of the local legal rules existing in the diverse jurisdictions within which the surgeons work. Surgeons working in North America will sympathise with the claim that the heady mixture of (individual) State and Federal law can lead to some legal uncertainties. These are multiplied when considering the fundamental differences between the common law and civil legal systems as they are variously represented across the world.

This chapter is thus determinedly written on the basis on a single jurisdiction [1], that of England and Wales. The intention is to examine in depth the core subjects of capacity, disclosure, and some legal devices to facilitate treatment in this single common law system. The principles behind the rules described echo throughout many jurisdictions, and will, with some modification, be applicable to most.

Capacity to Provide Consent

In paediatric oncology surgery, the majority of patients will be unable to provide their own consent, since they will have insufficient capacity to do so. This burden will thus fall upon their parents, and the effect of this relationship is variously defined in different jurisdictions. In England and Wales, as a result of the Children Act 1989 and its supporting legislation, children are divided into three broad groups. Those under 16 years are presumed to lack capacity to provide consent, although a substantial number at the older end of this age range may rebut this presumption by proving their capacity for the decision that they are being asked to make. The others in this group, who cannot pass this threshold of capacity ('incompetent') need to have their consent provided by a competent person with parental responsibility. Children who are 16 and 17 are in a distinct group, 'young people', in whom the presumption has switched, so the starting position is that they possess capacity to provide consent for treatment. This may be challenged by their parents or clinicians; and this challenge is particularly engaged if the young person refuses to provide consent. On the 18th birthday, adulthood is reached, and the lingering rights of those with parental responsibility are extinguished. In our jurisdiction, the consent (or its refusal) by an adult found to be competent is unlikely to be challenged.

In England, a child is therefore someone who has not yet reached 18 years of age. Legal synonyms include 'minor' and 'infant'. The latter is instructive, since it is derived from the Latin: *Infans*, unable to speak. This reflects the legal rules which prevent children from speaking for themselves in court, although this impediment has been at least partly addressed over the last two decades. Nevertheless, it begs a fundamental question, as to whether children can provide their own consent, or whether they depend upon their parents to provide it for them.

Children under the Age of 16 Who Lack Capacity

This is the simplest group. Although presumed to lack capacity, some will be able to demonstrate their competence to provide independent consent for treatment (vide infra).

For those who cannot, a person with parental responsibility has the right to provide consent where necessary. The child's mother (the woman who gave birth to the baby, rather than the person who provided the egg from which he

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was conceived, if different) has parental responsibility automatically. The child's father gains parental responsibility automatically if he is married to mother at the time of the birth registration, or when they subsequently marry. Since 2003, unmarried fathers also get parental responsibility automatically, when they register the birth. Alternatively, parental responsibility can be acquired by the unmarried father; either with the agreement of the child's mother, or by application to a court.

Parental responsibility is passed to adoptive parents on legal adoption. It may be shared with guardians appointed by parents; with local authorities; and is linked to various legal orders[1].

The person with parental responsibility who provides consent for a child's surgery must act in the child's best interests in so doing. These are usually self evident, and the agreement between parents and surgeon is reached after full disclosure of the relevant information.

Having absorbed this description, the reader may well ask whether a failure accurately to identify the requisite adult with parental responsibility constitutes sub standard care. There is little indication in this jurisdiction to suggest that this is the case, although in general principles, a surgeon would be expected to ensure that the person providing consent has the authority to do so. In the first line of National Health Service consent forms, the signatory is required to assert their status as a person with parental responsibility. Emphatically, surgeons are not required to go behind this assertion, in pursuit of 'proof' of parenthood. We are, after all, surgeons, not police officers or social workers. Furthermore, the disclosure necessary properly to inform the consent for oncological surgery at times requires parents to absorb grave and complex risks. It is the manner and substance of this disclosure, and not the legal status of those who claim parentage of the child, that should be foremost on the surgeon's mind. Nevertheless, if there are reasonable grounds to doubt an assertion of parental responsibility, it may be in the child's best interests to take proportionate steps to clarify the situation.

Parental agreement with a surgical management plan is not invariable. In a case [3] concerning a child with biliary atresia, the clinicians wished to perform a liver transplant, and considered the prospects of success to be good. The parents refused their consent, on the grounds that the surgery was not in the child's best interests. The Court of Appeal held that the assessment of the child's best interests went wider than the narrower medical best interests, and that T's connection with his family held great weight in this regard. Accordingly, the court refused to enforce the hospital's request that the mother would bring T in for surgery. The judgement could be criticised, in failing to differentiate between the interests of the child and those of his mother. However, the case provides an example of the balancing act performed by courts, when faced with dissonance between surgeons and parents.

Such dissonance is foreseeable when dealing with the potential morbidity and mortality associated with major tumour resection, particularly in cases where the anatomical site of the tumour increases the risk of direct trauma to contiguous organs, or to major blood vessels, with resultant fields of ischaemic damage. The excision of neuroblastoma falls into this group; with the attendant risk that resection may not influence the eventual outcome of that child's disease. Irrespective of these risks, parents very rarely baulk at the prospect of resection, focussed as they usually are on removing the primary tumour, and perceiving little alternative to running the risk of perioperative harm.

In cases where there is tangible parental reluctance to consent, it is submitted that a second opinion, to repeat the explicit balancing exercise between the risks and benefits of resection for this particular child will almost always be beneficial, to the child, her parents, and the surgeon involved.

Parental disagreement with a surgical oncology plan is uncommon, but occasionally occurs in relation to the necessity for long term central venous access. Disclosure of the alternatives to any surgical management plan must be provided to ensure that consent is 'informed', and thus valid. In the case of venous access, it may be better to defer the final decision for a long term line by temporising, and suggesting intermediate peripheral access, with a PICC device. In this way, parents, surgeons and patient can mull over the additional risks and benefits of a more permanent device, whilst avoiding delay of early phase treatment.

Children under 16 Who Can Demonstrate Their Capacity

Depending on their maturity and the intervention that is proposed, children from a young age may be able to provide independent consent. A 4 year old may be able to consent to a blood pressure measurement; a 6 year old to a venepuncture; a 10 year old to the removal of a central venous catheter. It is not suggested that the parents should be excluded from this process; such an exclusion would be quite wrong. It is for the family as a whole to decide what part the child's potential capacity should play in the consenting process. But the involvement of children in this process will strengthen the therapeutic relationship, and is to be encouraged.

A child's previous experience is of great importance. It is submitted that following the very recent diagnosis of leukaemia, a 15 year old, who has been healthy up to this point, will be so horrified by the dissolution of his comfortable and well organised life as to be incoherent, and potentially incapable

[1]For a full account see Bainham [2].

of consenting for the necessary tunnelled central venous catheter (CVC). Contrast this child with a 10 year old on the same ward; suffering relapsed leukaemia. He has already undergone three line insertions and two removals. He knows (effectively) everything there is to know about CVC placement; together with the alternatives, complications and disadvantages. Now facing his fourth insertion, he may well be competent to provide independent consent.

Therefore, it is important objectively to determine whether a child of 15 years or younger has capacity to provide independent consent for the proposed intervention.

For this assessment, the *Gillick test* is used, derived from a landmark case where it was established that a child with capacity to provide consent should be allowed to do so, independently of her parents. The test requires that the child has sufficient understanding and intelligence to enable them to understand fully what is involved in a proposed intervention [4]. Thus, if a child can understand:

- That a choice exists
- The nature and purpose of the procedure
- The risks and side effects
- The alternatives to the procedure; and is able:
  - To retain the information long enough…
  - To weigh the information…..
  - To arrive at a decision
  - *And* to be free from undue pressure

Then she would be deemed competent for the proposed intervention. It will be seen that competence rests on intelligence, maturity and experience. Not on age.

Gillick provides a high threshold for consent, consistent with public policy. It would be highly undesirable to allow children to provide consent for interventions which they could not fully understand. The fact that a child has to 'prove' their competence places a barrier to children that is never experienced by adults, whose capacity is presumed. One can only speculate how many adults would 'pass' the test in *Gillick*.

The *Gillick* competent child does not enjoy an equal right to refuse treatment. Only those cases in which the refusal of life-saving treatments in these children is at issue have reached the English courts. But given this opportunity, courts have resolutely denied the (otherwise) competent minor the right to choose death. A 15 year old girl [5] refusing her consent for a life-saving heart transplant had her refusal overridden by the courts. M's reason was that she 'would rather die than have the transplant and have someone else's heart… "I would feel different with someone else's heart…that's a good enough reason not to have a heart transplant, even if it saved my life"….'

The court authorised the operation, as being in her best interests.

In another case [6], a 14 year old girl with serious scalding required a blood transfusion. She was a Jehovah's Witness, and refused the treatment. The court found that even if she had been Gillick competent, her grave condition would have led the court to authorise the transfusion. As it was, the girl was unaware of the manner of death from anaemia, and was basing her views of on those of her congregation, rather than on her own experiences. For these reasons, she was judged incompetent to make this decision for herself.

It must be remembered that the vast majority of Gillick competent children who (successfully) refuse treatment are refusing relatively trivial procedures. You would be entitled to rely upon their parent's consent if necessary, but it is a matter for clinical judgement whether the procedure could be deferred, to allow the child further time to consider, and be reconciled with what is likely to be an inevitable outcome. The problem of refusal in *Gillick* competent children is dealt with in the same way as for the 16 & 17 year age group, below.

Young People of 16 & 17 Years of Age

In this jurisdiction, young people of 16 & 17 years of age are presumed to have the capacity to provide consent for surgical, medical and dental treatment. This was made possible by a law enacted in 1969 [7], which recognised that the decisions that teenagers were taking, irrespective of the law, contrasted sharply with the age of majority (21 years, the legal start of adult life) at the time. The new law reduced the age of majority to 18 years, and introduced the presumption of capacity for 16 & 17 years olds.

What the new law did not do was extend this right to consent for research, or interventions that do not potentially provide direct health benefit to the individual concerned. However, if competent on the basis of the test in *Gillick*, a young person may be able to provide consent for these activities.

Young people of 16 & 17 are thus able to provide consent for treatment in absence of their parents. However, the parental right to provide consent for treatment lasts until the end of childhood. This has the effect of providing a 'safety net'; allowing a 16/17 year old the opportunity of consent for herself; or deferring to her parents, if she sees fit. Once the child reaches adulthood on her 18th birthday, her parents' right disappears. For the rest of her life, she alone can provide consent, either directly, in person; or in some circumstances, by a proxy method, her wishes embodied either in a deputy, or in a document.

If parents and a young person disagree over a matter of consent, it is wise to exercise caution.

If a young person, thus defined, wishes to exercise his right to consent, and his parents oppose the decision, then

you would be entitled to rely on his consent. However, it would be important to understand the basis for this disagreement. For instance, if you suspected that the young person was not competent, you should challenge the presumption. This can simply be done by establishing whether he understands the relevant information; can retain the information, believe it, weigh it up….and communicate his decision. If he can, then he has capacity. But it is still wise to tease out where the problem lies, since this is a most unusual situation, and it would be in the young person's best interests to resolve the issue before surgery, if that is feasible. This is because the value of parental support for their children's treatment is tangible, and severing this support of a child when they may need it could increase their vulnerability.

The problem, reversed, is of a young person who refuses treatment, but who is accompanied by a parent who wants to provide consent. Valid parental consent will make the procedure 'legal', but as with the situation of consent withdrawal, you will still have to make a clinical judgement as to whether proceeding with the treatment against the young person's wishes is both practicable, and in her best interests. In summary, it is recommended that an elective procedure should be abandoned until the dispute is resolved. If emergency treatment is required, but could be administered in a different way which was still consistent with her best interests, the alternative should be explored. If her life or limb is threatened, and there is no choice but to provide a definitive operation, then reluctantly, you may feel the need to restrain and proceed.

In theory, the teenager resisting central venous access to start treatment for a rapidly progressive non-Hodgkin's lymphoma could be an example of this situation. But it should be noted that in reality, the amount of resistance that a child of any age puts up is usually inversely proportional to their malaise and discomfort. In the gravely ill, refusal is rare.

There are those who are gravely ill, but needing urgent rather than emergency treatment. If a 16/17 year old in this category refuses treatment for the preservation of her life, such as the transfusion of blood [8], or feeding [9] (in anorexia), courts have invariably chosen to override the child's autonomy, and provide an order which allows lawful provision of the treatment against the child's wishes. This either upholds the parental wishes for treatment, or overrides parental refusal. These cases are rare, but the timescale within which the decision needs to be made allows sufficient time for the court to be contacted, providing the surgeon with the necessary authority.

In young people with cystic fibrosis who are refusing heart lung transplant in defiance of their parents' wishes, the reality of the situation may make the transplant service accede to the young person's wishes. The necessity for a high degree of compliance with post operative immunosuppression and its attendant management has led the clinicians to take a pragmatic approach, and centres will not attempt to enforce transplantation on the unwilling young person. In the competent young person with re-recurrence of their pulmonary metastases from osteosarcoma, the dogged determination of parents to fight for repetitive surgery is clinically supportable only whilst the patient shares his parents' resolution to fight on.

Disclosure

It is, frankly, trite to assert that in any topic relating to oncology surgery in children, a topic is 'difficult'; since that adjective aptly describes the entire clinical subject. But if there is a place to assign "difficulty", it persuasively sits in disclosure. Those of us familiar with the concept of 'therapeutic privilege' will recall the assertion that information that may distress the patient should be withheld from them; for their own good. The increasing predominance of citizens' autonomy has effectively washed this away. Academic law books no longer refer to therapeutic privilege; or alternatively, it is consigned to an historical reference. Without further discussion, although with some regret, the doctrine, irrevocably synonymous with paternalism, has been discarded.

It is submitted that disclosure in oncology surgery is more difficult than in other forms of surgery. Most of our major procedures are elective. Surgeons dealing with *emergency* life saving surgery have simply that remit; to save life. There is no feasible alternative but to operate, since non operative treatment will end in death. In the emergency situation, society presumes the paramountcy of life, and surgeons rely on the doctrine of necessity. This common law doctrine permits surgeons to save the life or limb of an incompetent person without their consent. Under these desperate circumstances, disclosure assumes a secondary importance.

But the doctrine of necessity has its limits. The unconsented laparotomy for otherwise uncontrollable bleeding does not give the surgeon licence to perform the synchronous excision of an unrelated but obviously malignant ovary, since this would fail to align with the primary purpose, of saving life and limb. This illustrates society's determination to retain individuals' autonomy to make decisions for themselves, whenever possible.

In most non-oncological elective surgery, there is an overwhelming imbalance between benefit and risk. Nuss repair of pectus excavatum, Meckel's diverticulectomy, hypospadias, herniotomy are obviously associated with risk, which must be disclosed, but in reality, the risks are low; and the benefits both obvious, and disproportionately greater.

Not so in elective oncology surgery, where the world literature acknowledges both the inherent risks of damage to

contiguous structures during tumour excision, and the uncertainty of the benefits that may accrue.

This leaves us all with the dilemma of what to tell the parents when seeking their consent for excisional surgery. Do we explicitly acknowledge that their child may die?

The Standard of the Particular Patient

The legal history of disclosure extends over 50 years; with the proposal in North American courts that the standard for valid consent was based on what the particular patient in question wished to know. This was the originally conceived doctrine of 'Informed consent' [10]. There were difficulties with its practical application. A disappointed patient might sue his doctor, on the grounds that he has been given insufficient information about his procedure….and asserting that if he had known the information, he would have refused to proceed. Even with a wide-ranging and comprehensive disclosure of preoperative information by the defendant doctor, a particular nugget of information will go unmentioned. This omitted material, the litigant patient asserts, (in retrospect), was crucial for him to know; and will establish his claim, however rare and obtuse that piece of information might have been. Such a doctrine could leave a door open to unsubstantiated claims, and has not been wholeheartedly supported in English law.

The Professional Standard

The next attempt, 20 years later, at setting a standard for disclosure was to suggest that it should be provided by expert medical evidence, the so-called 'professional' standard, akin to the standard setting in other aspects of clinical care. Although this was accepted for some years, it has fallen into disrepute. Courts became increasingly anxious that doctors were 'protecting their own', and acting in a paternalistic manner by, in effect, telling the patient what he *should* be worried about, rather than asking the patient what worried him.

The Reasonable Patient Standard

Subsequently, English courts' felt able to put themselves in the position of the claimant patient, asking themselves whether, in the circumstances of the case, they would regard the disclosure as adequate? The courts do not feel the need to ask an expert doctor's view on this matter. They consider themselves, as reasoning citizens, amply equipped to set the standard. Thus the stage is set for the 'reasonable patient'. This patient is a fictional creation of the court, imbued with all of the characteristics of the claimant patient, but whose sense of reasonableness is provided by the court. And the reasonable patient is thus employed:

> If there is a significant risk which would affect the judgement of a reasonable patient, then in the normal course it is the responsibility of a doctor to inform the patient of that significant risk, if the information is needed so that the patient can determine… what course he or she should adopt [11].

This leaves open to question what a 'significant risk' entails. However, if you apply your personal criteria to the phrase, you are likely to consider that most of the unintended harms that flow from surgery could be construed as 'significant'. The great difficulty is that there exists a gap between what you, as an experienced clinician (and what an average patient)…. might foresee as the result of surgery.

On how many citizens, that you might encounter walking down your local high street, will it dawn that surgery on a thoracic ganglioneuroma, adjacent to the vertebral column could result in lower limb weakness, or a drooping eyelid? Or that it is foreseeable that percutaneous central venous catheterisation might necessitate a thoracotomy, to stem the haemorrhage? Or that spillage of an ovarian tumour during laparoscopic removal might lead to recurrent or distant disease?

Whilst commonplace knowledge for surgeons, these potentials for disaster are not widely known by those who have not had a medical education.

And that is why they should be disclosed, when obtaining consent.

In addition to this gap in surgical knowledge is the reverse; the recognition that the patient is intimately acquainted with their own circumstances, of which you know little, or nothing. Their academic, sporting and social aspirations may be put at risk by surgical procedures. It is conceded that the priority of oncology surgery is likely to make other considerations peripheral by comparison. Nevertheless, on principle, disclosure of risks, so that the patient can at least decide to take the risk rather than have it imposed unwittingly upon them is consistent with good medical care.

You may not know that the young person with a suspicious posterior triangle lymph node is also a promising boxer, who would not willingly put at risk the functioning of his accessory nerve. He and his family may value a consideration of the alternatives to biopsy of this particular node; perhaps the equally accessible node in the groin? But until they have some awareness of these risks, why would they ask about them?

To address this gap created by a combination of the professional knowledge of the doctor and the patient's personal circumstances, the General Medical Council [12, para 32] makes it clear that the duty to disclose is onerous:

> You must tell patients if an investigation or treatment might result in a serious adverse outcome, even if the likelihood is very small

The risk may be tiny, but of great importance when deciding whether or not to have surgery, which may be elective.

Statistics are a valuable form of description when articulating risk to patients. In a recent case, the court confirmed the importance of comparative statistics when describing alternative procedures that a patient might want to consider in deciding which intervention she should consent for. Faced with a choice between a catheter cerebral angiography and an MR angiogram, the patient was not informed of the comparative risks of stroke [13]. The court held that the patient, as a result, could not provide properly informed consent.

The Numeric Threshold of Risk

The most serious risks faced by the paediatric oncology patient, when facing surgery, are very unusual. Damage to the blood vessels of contiguous organs during a Wilms' nephrectomy; death on the operating table from exsanguination during neuroblastoma excision are both reported, and foreseeable, but mercifully rare. Numerically, the incidence of these catastrophes would be expressed in fractions of a percentage point.

But the most commonly asked question relating to disclosure refers to the importance, or otherwise, of the numeric threshold for risk; how common does a risk have to be before we disclose it to the patient? This is a particularly apposite question for the parents of an oncology parent facing major surgery. Should they be troubled with such unlikely eventualities? Could this aspect of disclosure be placed behind the curtain of a numeric threshold, relieving the surgeon from the obligation of revealing the rarest (and most distressing) potential outcomes?

When describing the risk of a clinical intervention to a patient, there is a common and mistaken supposition by doctors that there exists a numeric threshold of improbability beyond which there is no need to disclose. Where the line should be drawn?

Doctors are comfortable with ubiquitous numeric thresholds to guide their interventions, and depend upon on plasma levels, physiological or radiological measurements to carry a patient across a threshold from non-treatment to treatment.

But the numerical risk of most complications of therapy is usually low, and may not be caught by a realistic threshold. Is it right that such a threshold should (inadvertently) conceal relevant matters from the putative patient's consideration?

Courts have briefly explored the notion of a numeric threshold. In the 1980, a Canadian court [14] held that a 10 % risk should automatically be disclosed when obtaining consent; in this case, to disclose the possibility of a stroke following surgery. This built on the American concept of a material risk, where a reasonable person in the patient's position is likely to attach significance to the risk.

Since then, courts have steadily distanced themselves from a numeric threshold. Three years later, an American [15] case determined that a 200/1 complication rate would not equate to a material risk. A 'landmark' English consent case [16] held that Mrs Sidaway, who had suffered spinal cord damage after surgery, failed to prove that a prudent patient would regard a <1 % complication rate as constituting a significant risk.

In 1997, it was held that there was no certainty that an unqualified duty to disclose a risk of around 1 % existed, in the context of a family who were not told that permanent neurological damage could flow from cardiac transplantation surgery [17]. An Australian case [18] had held that the failure to warn of the 14,000/1 risk of blindness following ophthalmic surgery fell below the reasonable standard of care. From the perspective of English law, this was the death knell of the numeric threshold. To disclose all risks of this frequency would be impractical. The court was demanding that significant risks should be disclosed, irrespective of the likelihood of occurrence. The UK courts followed this lead in 1995 [19], holding that failure to disclose the risk of spontaneous vasectomy reversal (2300/1) equated to substandard care.

The explicit switch from a quantitative to a qualitative approach came in a maternity case [11], when a patient lost her baby. She had reluctantly agreed to the deferral of her delivery, in the absence of full disclosure of the possible consequences of so doing. Lord Woolf, giving the leading judgement, held that it was not necessarily inappropriate to fail to disclose a risk in the order of 0.1–0.2 %; but that the correct standard was to disclose '…. A(ny) significant risk which would affect the judgement of the reasonable patient', as described above.

In a subsequent case [20] where it was held that there was a failure to warn parents of the risk of foetal abnormality of a pregnancy that coincided with maternal chickenpox, the threshold that the disclosure had to satisfy was that of the *patient's* determination of a risk, albeit insubstantial; the court accepted Ld Woolf's dictum proscribing the use of a numeric threshold.

Legal scholars support this trend, warning against reducing the meaning of 'substantial' or 'grave' (or 'significant') to quantifiable (numeric) risks [21], since such reduction misses the central point; that only the patient can judge what risk is material to them, irrespective of its frequency of occurrence.

The concept of a numeric threshold for disclosing risk is therefore outdated from the legal point of view. There is no reference whatsoever to a threshold either from the General Medical Council [12] or the Department of Health [22]; other than to give information about all significant adverse outcomes.

The commonest question asked by surgeons, when discussing the law of consent, is where to draw the line between

matters that must be disclosed, and those that require no mention. Invariably, they demand a numeric threshold, and are disappointed when this is not forthcoming. Although it is understandable that surgeons continue to use this artificial threshold, it is submitted that they should follow the lead of the courts, because a better formula that identifies what needs to be disclosed has been provided for our use.

It is better because it provides an assurance that patients will not be 'ambushed' by a serious complication which the surgeon could foresee, but of which the patient, or her parents, remained oblivious until it was too late for her to avoid it.

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Training in Paediatric Oncology and Tumour Boards

42

Diana McIntosh and Robert Carachi

Training

Training programmes in Paediatric Oncology vary from country to country. The programme presented here is what training a doctor has to undergo in order to be recognised as a fully trained specialist in Paediatric Oncology. There are no training programmes in the UK in Paediatric Surgical Oncology. Trainees in paediatric surgery undergo core surgical training lasting 2–3 years and higher surgical training lasting 6 years. One of their nine topics of competency includes oncological surgery and by their 3rd year they would be expected to biopsy tumours, insert portocaths and insert central lines and Hickman lines for delivery of chemotherapy, both by the open route as well as by ultrasound guided percutaneous route. During their final years of training they will be expected to do a tumour nephrectomy and be part of the team in resecting neuroblastoma and sarcomas.

The European Syllabus recommends a total of 25 cases performed as a first operator or assistant. A general paediatric surgical consultant with an interest in surgical oncology develops expertise by getting involved in all the tumour cases in the hospital, attends the tumour board regularly and is part of the oncology on call team to deliver this service. In addition, attendance at oncology masterclasses and visits to centres overseas, that have a major commitment to tumour surgery. A consultant would try to be a member of one of the Paediatric Tumor bodies i.e., IPSO, SIOP etc.

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Training in Paediatric Oncology

General Paediatric trainees in the UK seeking GMC subspecialist accreditation in Paediatric Oncology must apply via the Royal College of Paediatric Child Health's (RCPCH) National Grid training scheme.

Paediatric Oncology National Training Number (NTN) Grid

The Oncology National Grid Training Scheme began in 2002 and annually recruits a varying number of trainees. Successful applicants require deanery approved Confirmation of Eligibility and should have completed core Specialist Registrar (SpR)/Level 2 Specialist Trainee (ST) training, usually consisting of 6 months neonatal medicine, 6 months community medicine and 12 months general paediatrics. The grid is only open to applications from UK trainees holding a NTN and those in an equivalent training programme within the European Economic Area. Successful candidates should have sufficient time prior to completion of training to ensure all areas outlined in the Oncology Higher Specialist Training Record can be covered. Applications may be considered if candidates have relevant experience prior to grid appointment but this should be discussed with the College Specialist Advisory Committee (CSAC) and approved prospectively. Up to date details of the Grid Application process are found on the RCPCH website http://www.rcpch.ac.uk [1].

Paediatric Oncology Higher Specialist Training Record (HST Record)

The Higher Specialist Training Record outlines learning objectives for higher specialist training in Paediatric Oncology. In addition it serves as a record of learning/experiences for all aspects of training and forms the basis of the portfolio assessment during the Annual National Oncology Review.

Within the HST there are details of the knowledge base trainees are expected to acquire during their training. Documentation of knowledge acquisition with educational supervisor confirmation is required (Table 42.1).

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Table 42.1 Section 4.1 Knowledge Base, Paediatric Oncology HST Record and Portfolio, December 2001

Epidemiology
Incidence and mortality rates for childhood cancer, including ethnic and geographical variability
Aetiological facts and theories
Techniques used in epidemiological studies
National, regional and local cancer registration policies
Biology of normal and malignant cells
Normal cell structure and function
Genetics of normal and malignant cells
Growth kinetics of normal and malignant cells
Normal and abnormal mechanisms of cellular growth control
Principles of cancer treatment
Chemotherapy
Pharmaceutics, pharmacology and toxicity (acute and long term) of individual drugs
Cytotoxic drug preparation, administration and safe handling
Principles and rationale of combination chemotherapy regimens
New drug evaluation – Phase 1 and phase 2 trials
Radiotherapy
Basic radio biology
Planning techniques
Standard treatment strategies and their acute and late toxicities
Principles of less common techniques including brachytherapy, targeting (e.g., MIBG) and radio iodine
Surgery
Principles of biopsy and optimal handling of tissue
For diagnosis and biological studies
Surgical strategies for common solid tumours
Central venous access
Biological and novel therapies
Potential role for biological therapies
Potential models for gene therapy
Supportive care
Blood product usage – risks and policies
Febrile neutropaenia and infection
Nutritional assessment and support
Anti emetic therapy
Techniques for bone marrow support (including growth factors)
Psychological, educational and social support of patient and family
Clinical features of common childhood malignancies
Presenting features of acute leukaemia and common solid tumours, including CNS tumours
Typical features and classification of all common malignancies
Role of biological studies as diagnostic and prognostic aids
Typical features and classification of acute leukaemia
Recognition of bone marrow infiltration by solid tumours
Role of cytogenetics and immunophenotypic analysis
Therapy
Familiarity with current standard therapy plans for all forms of childhood malignancy, including an historical perspective on the evolution of current clinical trials and treatment outcomes
Principles and application of high intensity therapy
Principles and application of allogeneic bone marrow transplantation including matched unrelated transplantation
Oncology emergencies
Septic shock
Tumour lysis
SVC obstruction
Spinal cord compression
Raised ICP
Acquired coagulation disorders
Veno-occlusive disease
Communication and ethical issues
Knowledge of models of consultation
Principles of breaking bad news
Understanding of principles of informed consent
Data protection
Sequelae of treatment (early, intermediate and late)
Endocrine consequences and therapy
Major organ toxicities
Psycho-social problems
Risks of second malignancy
Organisation of LTFU programmes and strategies for surveillance of survivors
Terminal/palliative care
Principles of analgesia and other symptom control
Resources for the support of families at home
Awareness of the role of the Macmillan (or equivalent) nurse team
Awareness of the role offered by hospice care

The following link provides updated details of the Paediatric Oncology curriculum http://www.rcpch.ac.uk/training-examinations-professional-development/postgraduate-training/sub-specialty-training/paedi-12 [2].

Grid Trainee Assessment

In addition to the local Deanery Annual Review where the ARCP for STs/RITA for SpRs is completed, Paediatric Oncology Grid trainees must also undergo a National Oncology Annual Review. These reviews serve to both assess the trainee and provide a forum to discuss any training issues the trainee or CSAC may have.

This rigorous and comprehensive assessment assesses the trainee's knowledge and experience in paediatric oncology to date. The exact format varies but usually consists of two clinical scenario discussions and a critical appraisal of a recent clinically relevant paper chosen by the review panel. The trainee's portfolio is assessed by the CSAC to determine achieved competencies and highlight any training issues. The portfolio is expected to include:

- Reflective summary of training to date
- Personal development plan
- Educational supervisor report

- Ten anonymised clinic letters assessed independently using SAIL method
- Case summary table
- Technical skills log
- Out patient clinic attendance log
- Multidisciplinary Team meeting attendance log
- Long term follow-up clinic log
- Palliative care cases
- Detailed case summaries
- Teaching
- Study Leave
- Details of recent audit and research
- Publications/Abstracts/Presentations

Following completion of the assessment, the CSAC then provide the trainee with an individualised training plan for the forthcoming year.

The review outcome is also fed back to the Educational Supervisor and Head of Training Programme Director at the local Deanery in order to inform their next ARCP/RITA. Updated requirements for the National Annual Review will be provided to the trainee at the time of appointment and when notified of their review.

Paediatric Oncology Trainee Group (POTG)

The POTG is a group of doctors either in grid training posts or other disciplines interested in paediatric oncology. It is recommended that all such trainees join the group. The aim of the group is to promote interest and education in Paediatric Oncology. Regular educational meetings are held at different UK locations with updates given by the RCPCH Paediatric Oncology CSAC representative. The website http://www.cclg.org.uk/ [3] provides details of how to join the POTG. The group welcomes membership from General Paediatric trainees interested in developing an Oncology special interest.

Shared Care

All children with cancer in the UK should undergo the diagnostic process and management planning at a Primary Treatment Centre. However once treatment is established it can be appropriate to deliver care closer to home at a Paediatric Oncology Shared Care Unit. This care is generally delivered by General Paediatricians with a special interest in Paediatric Oncology who liaise closely with the Primary Treatment Centre. General Paediatric trainees wishing to develop an interest in Paediatric Oncology are able to formalise their training by completion of a Special Interest (SPIN) Module. This is in addition to completion of Level 3 competencies in General Paediatrics. The SPIN module serves to standardise the special interest curriculum and takes approximately 12 months to complete. Completion of this module does not alter the Certification of Completion of Training (CCT) which remains in General Paediatrics. Further details on the SPIN modules and application process can be found on RCPCH website http://www.rcpch.ac.uk/ [1].

Tumour Boards

Paediatric malignancy is rare and differs from adult cancers anatomically and pathologically. Clinical presentation of cancer in children is highly variable and can often mimic other more common paediatric conditions providing clinicians with diagnostic challenges. Management of these tumors is often prolonged, complex and multimodal with different tumor types requiring varying combinations of chemotherapy, radiotherapy or surgery. Multiple specialists are required to deliver these highly specialised treatments which are continually evolving. For these reasons Paediatric Oncologists worldwide recognise the need to manage children and young people diagnosed with cancer within multidisciplinary teams.

In the UK, all children and young people diagnosed with haematological, solid and CNS malignancies should be discussed at a Tumour Board (TB) as stated in the National Institute for Clinical Excellence (NICE) Guidance on Improving Outcomes for Children and Young People with Cancer. This is echoed in the Children's Cancer and Leukaemia Group (CCLG) [3] guidelines related to treating children with cancer. Discussion at TB is recommended to be not only at the time of diagnosis but also when undergoing reassessment or at relapse (Fig. 42.1).

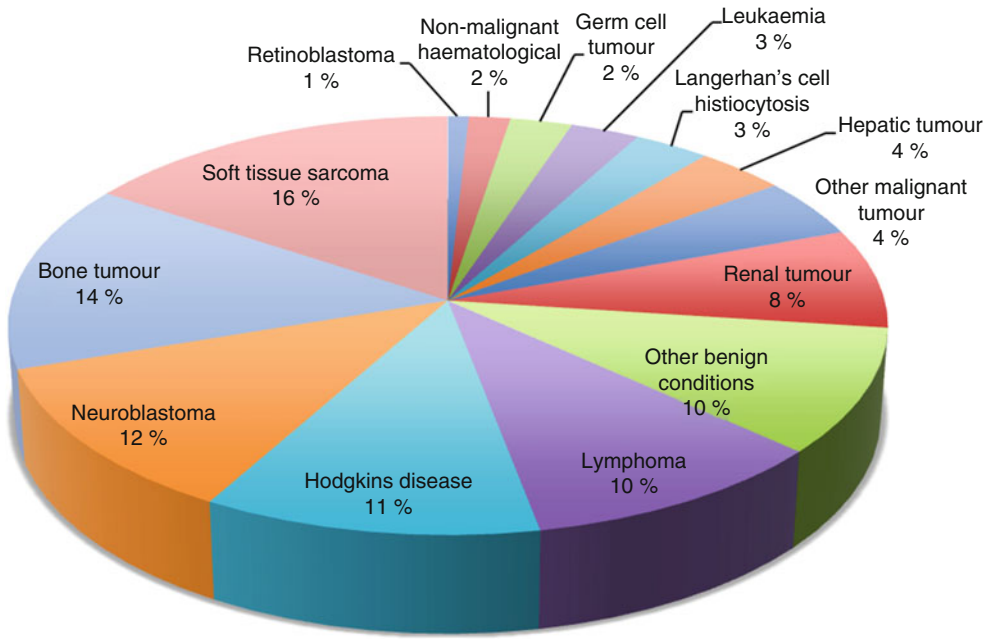
Whilst it is a requirement that all Primary Treatment Centres have a weekly diagnostic and treatment TB meeting, the number and configuration of these meetings may vary.

A Paediatric Oncologist, Paediatric Surgeon and Clinical Oncologist planning and delivering radiotherapy should all be in attendance to coordinate treatment of patients on whom Paediatric Pathologists and Paediatric Radiologists are providing diagnostic information. The TB membership and responsibilities should be explicit with clearly defined clinical and managerial leadership. In addition it is necessary to have adequate administrative support to coordinate meetings and provide secretarial support.

Managing children and young people with cancer using this MDT approach has multiple benefits. In addition to each individual patient being considered from a range of viewpoints and expertise, it promotes learning, offers a greater probability of timely and appropriate treatment and better continuity of care.

Fig. 42.1 Diagnoses discussed at RHSC tumour board 2005–2013

Germ cell tumour	9
Leukaemia	10
Langerhan's cell histiocytosis	11
Hepatic tumour	13
Other malignant tumour	16
Renal tumour	27
Other benign conditions	34
Lymphoma	36
Hodgkins disease	39
Neuroblastoma	41
Bone tumour	51
Soft tissue sarcoma	55
CNS neoplasms	72



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43 International Confederation of Childhood Cancer Parent Organizations Parent Organisations: Partners in the Care for Children with Cancer

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The experience of a child undergoing cancer treatment can be traumatic, distressing and isolating for parents and siblings as well as the patient. The impact on the whole family has been well understood by health professionals for many years, as have the medical needs of the child, but also the necessity to provide services which look after the emotional and social needs of the family of the child. Parent support groups have been formed over the past 30 years to provide information and practical, emotional and financial support for families to enable them to cope with the difficulties associated with lengthy treatment – often many miles from home.

The Childhood Cancer International (CCI) is an international network representing organisations of parents of children with cancer worldwide. Since its founding in 1994, CCI has increased its membership in 2006 from the initial 9 members to 148 member organisations representing parents and children from 81 countries. CCI works closely with other childhood cancer organisations, in particular with the International Society of Paediatric Oncology (SIOP).

CCI's vision is to be recognised world-wide as the body representing families of children with cancer. CCI wants to see a world where the issues faced by children with cancer and their families, both in the short and long-term, are understood by families, healthcare professionals and the wider community to ensure that children receive the best possible care wherever they are in the world at the time of diagnosis and beyond.

CCI's mission is to share information and experiences in order to improve access to the best possible treatment & care for children with cancer everywhere in the world. It does this through an international network of parent support groups and survivor networks with the common goal of providing a voice for the needs of children with cancer and their families and advocating for increased awareness of childhood cancer at both a local and international level. By working in partnership with other child cancer organisations, the need for psycho-social care for the children and their families and the long term issues faced by survivors will be promoted.

CCI's objectives are:

- Education – of parents, survivors, doctors, nurses, psychologists, teachers, etc. Parent organisations can share their special experiential expertise in order to increase each others' knowledge and to help direct services more appropriately.
- Public awareness – of the general public with regard to childhood cancer, the needs of children with cancer and their families, the increased chances of cure, and the continuing need for medical and psychosocial monitoring and support.
- Development – of parent organisations where they not yet exist. This can be at a local and national level. CCI supports and trains parents to create and lead parent organisations and so strengthen this worldwide movement. Parent organisations are encouraged to act as advocates for their children regarding medical and psychosocial care, school and education, insurances etc.
- Advocacy – for adequate medical and psychosocial care, for advance of the cure rates of children with cancer throughout the world and for equal access to insurances and employment of survivors.

In practice, the needs of families and their children differ immensely in the various countries. In the industrialized countries effectively all children get diagnosed and treated. Treatment is provided to similar standards, with more than 70 % of children surviving. Parent organisations can focus

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on psychosocial care – welfare, education, emotional and long-term survivor support.

In lower income countries, most children do not get diagnosed and even if they do, treatment is inadequate or – in the best cases – palliative. Eighty percent of children with cancer in the world fall into this category. Parent organisations in these countries are striving to educate doctors and families about early diagnosis, giving support to help families travel to a centre, and providing the drugs that are essential for treatment.

CCI helps parent organisations develop against this varied background of needs.

CCI Activities to Help Parent Organisations Worldwide to Achieve Their Mission

Information and Sharing

Annual conference – Each year CCI holds an international conference, usually at the occasion as the annual SIOP conference. This enables parent organisations, survivor organisations, support organisations and professionals to meet and take part in lectures, workshops and to informally network.

Regional conferences – CCI also organizes a regional conference wherever the continental SIOP's have their biannual meeting. These meetings provide an excellent forum to discuss the needs of children with cancer and their families a certain part of the world and to tailor informational sessions and workshops to the wishes of parent organisations and health care professionals in that specific region, to share best practices and thus try to jointly find the best strategy. Next to these joint meetings with the medical professionals, CCI organizes other regional conferences in area's where for instance a common culture or language guarantees the best communication.

These conferences also provide a forum for members to meet and share information, experiences and knowledge with other members so that all can benefit from best practise and new ideas including information on, for example:

- How to lobby governments and advocate on behalf of children with cancer
- How to create an awareness of childhood cancer regionally
- Development of parent mentoring and assistance programmes
- Developing and growing parent support groups
- Forming a therapeutic alliance with the medical team on improving conditions and services in the ward

Information – CCI provides a range of information through a number of channels. The CCI E-Newsletter is published monthly and the CCI website is a major resource for parent organisations, and individual parents, throughout the world. It brings together information about parent organisations around the world, contains guidelines for treatment and care and manuals for setting up and running parent organisations and provides links to sites with information of value for parents and their families.

Public Awareness

International Childhood Cancer Day – This annual event on 15th February helps CCI member organisations to raise awareness and funds for use at a local level.

Development

Twinning – There are many examples of parent organisations twinning to provide development support. For example, a resource-rich member providing support to a resource-poor member, or a member with a long experience of an issue supporting another, to avoid "re-inventing the wheel". Often these twinning programmes are jointly run with hospitals in the two different countries.

Local visits – CCI officers visit local parent organisations, often in combination with regional conferences.

Advocacy

CCI is a powerful advocate for the issues and effects of childhood cancer at an international level including long-term impact on survivors – medically, financially and socially and access to treatment and medication, if nut for cure than at least for palliation.

CCI works with SIOP in developing guidelines for professionals and parent organisations to help provide holistic treatment and care.

CCI sits at the table with specialists and reviews ethical and informational aspects of innovative treatment studies.

ICCPO believes that every child deserves the chance to live and therefore helps to improve diagnosis and access to treatment in resource-poor countries. Therefore CCI set up World Child Cancer though which CCI operates to improve childhood cancer care in low and middle income countries.

CCI strives to improve support for survivors and their families to avoid these families being disadvantaged as a result of cancer.

With ever competing demands on governments, it falls to those affected, and those working in this field to advocate the

case for children with cancer. No one is better placed than those who have experienced the trauma of life-threatening illness to a child, or who have had to endure inequality as a result of it.

Local Parent Organisations and Their Activities

Local parent organisations are often linked to a certain treatment centre. Their activities differ according to the needs of parents in different places, and the resources available to them, but in general organisations work in the following areas.

They provide parents with **information** about the disease and the treatment, about psychosocial issues and coping strategies, and about the hospital and the treatment team. They also give information about financial and insurance issues. They do this through arranging presentations, discussion groups, newsletters, brochures, books, resource lists and a website.

Parent organisations provide **financial assistance**, home-from-homes, respite care, and information about practical issues such as home care, school programmes, funeral arrangements. They raise funds to help pay for treatment or to improve the children's ward in the hospital. This kind of practical support is especially seen in less wealthy countries where basic medical treatment and funds to travel to the hospital are lacking.

Most parent organisations offer **social support** through recreational programmes for children, like day trips or camps. Often siblings are involved, and sometimes the entire family. They sometimes fund computer links between ill children and their schoolmates to reduce social isolation.

Parent organisations offer **emotional support** in the form of peer-to-peer counselling. Parents who went through the same are only half a word away. There can be special sessions for mothers and fathers separately, for teenage patients or siblings, and for bereaved parents.

Parent organisations often work with the medical team to improve medical and psychosocial care and create change that will benefit them and their children. This advocacy role has increased over the last decade and today parent organisations are often involved in the design of clinical trials and the improvement or care models in their countries.

National Parent Organisations and Their Activities

National parent organisations generally coordinate and share information and resources among various local groups via meetings, conferences, newsletters and electronic media. They sometimes support local parent organisations by offering a training programme for current and future leaders and volunteers. Often national organisations provide services that would be difficult and costly to organise at each local site, like books, a national newsletter, camps. Many national organisations sponsor an annual conference for all parents or for group representatives.

National organisations often have access to health care policy-makers. They have the ear of national cancer societies and governmental bodies concerned with cancer policy, health benefits, special educational programmes for sick children, funding of childhood cancer research and treatment, etc. They act as advocates, represent parent and survivor concerns and work with national paediatric oncology organisations, nurses, social workers and psychologists. Some are active lobbyists in the legislative arena and with employers and insurance companies.

The size of national organisations varies considerably. They count between 5 and 200 local chapters; some only have one chapter, e.g., the national organisation. They also vary in their annual budget: organisations in many nations, especially those in the less affluent countries, have very minimal funds.

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