Rare Tumors in Pediatric Oncology

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7.1 Introduction

We define rare tumors in pediatric oncology arbitrarily as including the following histologies: retinoblastoma, nasopharyngeal carcinoma, desmoid, non-CNS germ cell tumors, liver tumors, pleuropulmonary blastoma (PPB), chordoma, malignant peripheral nerve sheath tumors, and for some, the true connective tissue tumors. Relative to adult tumors, practically every tumor in this text could be considered rare but these histologies are rare even within the scope of pediatric care.

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Because radiation therapy is not typically used with non-CNS germ cell tumors, PPB and liver tumors, and because connective tissue tumors (sarcomas) will be the focus of Chapter 4, we will focus on retinoblastoma, nasopharyngeal carcinoma, and desmoid tumors. For diseases that occur commonly in adults but rarely in children such as breast cancer, we will not cover the diseases in detail. Adult techniques are used with special anatomic considerations that apply to children on a case by case basis. For even more rare tumors, a large number of registries exist worldwide (Rare tumor registries in the United States 2010; Rare Disease Registries in Europe 2015).

Because these tumors are so rare, the Children's Oncology Group (COG) established a committee dedicated to their study in 2002. No single institution in the world can accrue enough patients to study and make progress in the treatment of these "orphan" diseases. The COG formed in 2002 from the Pediatric Oncology Group (POG) and the Children's Cancer Group (CCG) and each of these smaller groups had established committees studying single classes of rare tumors. Other international organizations exist for the same reason. The first European meeting on rare pediatric tumors took place in Padua, Italy on June 26, 2008 and included teams from Italy (TREP, founded in 2000), the UK (founded in 1998), Poland (PRTS, founded in

T.E. Merchant, R.-D. Kortmann (eds.), *Pediatric Radiation Oncology*, Pediatric Oncology,
https://doi.org/10.1007/978-3-319-43545-9_7

2005), Germany (German Rare Tumor Working Party, founded in 2008), and France.

7.2 Retinoblastoma

Retinoblastoma (RB) makes up less than 3% of the diagnosis of cancer in children less than 15 years of age in the United States (US). In the first year of life, however, it makes up 11% of cancer diagnoses. About two-thirds of all cases occur in those under the age of 2 years and 95% in those under the age of 5 years. In the US, incidence of RB remains relatively unchanged over the 20 year period from 1975 to 1995. In the US, the incidence remained balanced during this timeframe between whites and blacks and between males and females at about 3.7 cases per million children (Ries et al. 1999). In the US that equates to about 350 cases per year and about 5000–8000 cases worldwide.

7.2.1 History

The first known evidence of man knowing about ocular tumors may have come in the form of a sculpture found in Peru from almost 2000 years ago showing an ocular tumor. A terracotta figure from the Meyer-Steineg collection from the Island of Kos in Greece is thought by art historians to demonstrate retinoblastoma in the right eye of a child (Gmek and Gourevitch 2000). Meyer-Steineg found instruments of ophthalmological use from around the second century BCE from excavations on Kos (Jackson et al. 1913).

The first written, Western description of retinoblastoma is credited to the Dutch anatomist Peiter Pauw's notes from 1597 describing a 3 year old boy with a rapidly-growing, large ocular tumor (Kivela and Polkunen 2003). This same case was republished by Bartolini in 1657 and again in the nineteenth century by the German Julius Hirschberg, and then in the twentieth century by Edwin Dunphy as part of his 1963 Edward Jackson Lecture in Boston. Pauw was a professor of anatomy in the Academy in Leiden and the description came from a postmortem examination in the form of his autopsy notes.

Hayes then published an article about a bilateral case in 1767 entitled "The Case of a Diseased Eye Communicated to Mr. William Hunter by Mr. Hayes, Surgeon" (Hayes 1767). It was at about this time that the clinical sign we now associate with retinoblastoma, leukocoria, was first described in the literature. The first person to strongly correlate the clinical sign with the diseases strongly was Georg Joseph Beer in Vienna (Beer 1813). Around the same time a Scottish surgeon based in London named James Wardrop described retinoblastoma in a treatise that was focused on assembling all the known data on retinoblastoma at the time in one place. He concluded that because it was very different in terms of the age when it was found, being in children, that it was a different disease than that found in adults. He was likely the first to ascribe the source of the disease to the retina based on his dissections. His work summarized the natural progression of the disease in a manner that is felt to be essentially that of today's clinic. He is perhaps best known for being the first to champion enucleation (Wardrop 1809).

Enucleation was slow to become accepted because general anesthesia did not come into use until chloroform was discovered. Anesthesia in the form of chloroform and the invention of the ophthalmoscope in 1847 by Babbage (Lyons 1940) permitted a diagnosis at an early enough point to allow for enucleation. Surgical techniques evolved reflecting improved understanding of the natural patterns of spread of the disease with survival rates rising from 5% in 1869 (Hirschberg 1869) to 57% in 1916 (Leber 1911).

The first likely case of radiation's use for retinoblastoma was performed by H.L. Hilgartner in Austin, Texas in 1903 for a three and half year old with bilateral disease. He treated the patient with 84 fractions and the patient was lost to follow-up. The right eye was larger and "became shrunken" while the left eye lesion was smaller and was described as "resorbed" (Hilgartner 1903). Schonberg then presented a series of three papers looking at the long term outcome of a 2 year old girl with bilateral disease in which one eye was surgically managed and the less advanced eye was treated with radiation, a strategy still in

use today (Schoenberg 1927a). At 10 years the child had useful vision (Schoenberg 1927b) but at 25 years the child developed a sarcoma that ultimately spread and took her life (Reese 1951). Perhaps the most famous of the early reporters of radiation was Frederick Herman Verhoeff of the Massachusetts Eye and Ear Infirmary. He reported the case of a 17-month old boy treated in 1917 for a massive left sided lesion without success and then to the right side for an early lesion treated with an anterior chamber sparing technique. That child did well until 1977 when a basal cell carcinoma developed on the lid; it recurred and later a squamous cell carcinoma arose in the lid region as well.

Modern approaches to the treatment of retinoblastoma parallel the fields of surgery, pediatric oncology, and pediatric radiation oncology. The use of brachytherapy was first used in 1930 by Moore via a radon seed (Moore 1931). Kupfer used chemotherapy and radiation together for the first time in the treatment of retinoblastoma in 1953 (Kupfer 1953). Local and system therapy development continues unabated to this day.

7.2.2 Pathology

Retinoblastoma source, as noted above, was first described as arising from the retina by Wardrop in 1809 (Wardrop 1809). This was in debate until work from Paris by Robin and Nysten in 1815 confirmed the source to be the retina (Robin and Nysten 1815). In Berlin, Virchow theorized that the cell of origin was glial, but this was based on flawed Golgi staining techniques of the period (Virchow 1864). Other, more accurate methods of the time based on stains, were inconclusive. Despite an unclear link between retinoblastoma and glial cells, Bailey and Cushing described relationships between retinoblastoma cells and medulloblastoma and "neuro-epitheliomas" (Bailey and Cushing 1926).

Research expanded greatly with the development of cell line and placement of retinoblastoma cells into nude mice (Mcfall et al. 1977). Manipulation of retinoblastoma cells was able to achieve differentiation into different tissues of the retina making the source of the retinoblastoma cell uncertain, save to be pluripotent in nature (Kynthsis et al. 1984).

Retinoblastoma at surgery is soft and friable when resected and is often necrotic and calcified, suggesting that it rapidly outgrows its blood supply. Because of this, it often disseminates in the vitreous and retina and forms small white dots, or seeds, when visually examined in vivo. These cases can be difficult to tell apart from multifocal disease (Sang and Albert 1982). Under the microscope, distinctive Flexner-Wintersteiner rosettes can be seen. They are specific to retinoblastoma and consist of a circle of low columnar cells arranged around an eosinophilic membrane-defined lumen centrally. This membrane is similar to the normal membrane at the outer edge of the normal retina. Homer-Wright rosettes consisting of irregular circles of cells surrounding tangles of fibrils that are lacking the eosinophilic internal membrane can also be seen in retinoblastoma but are more commonly seen in neuroblastoma.

A variant of retinoblastoma made of cells that have a distinctive *fleur de lis* pattern of larger cells made up of abundant, eosinophilic cytoplasm. These are called retinocytomas or retinomas. Cells can exhibit more specific characteristics of cell types of the normal retina including photoreceptor-like 9-0 microtubules, neurosecretory granules, synaptic ribbons, and abundant cytoplasmic microtubules.

7.2.3 Genetics and Molecular Pathophysiology

The current understanding of retinoblastoma, that it has both a germ line and a spontaneous pattern of inheritance, was not understood in the nineteenth century because survival was uncommon. Cases exist with family histories suggestive of retinoblastoma's heritability, but as late as 1905 published essays suggest that no such proof of retinoblastoma being inherited existed (Owens 1905). As more patients survived, some had children, had offspring, and data was collected on the patterns of spread and presentation of the

disease. The real breakthrough in the understanding of retinoblastoma and to some degree in human cancer genetics came in 1971 when A.G. Knudeson, Jr. published his paper on the inheritance patterns seen in retinoblastoma using mathematical modeling based on Poisson distribution analysis. From this work came the now famous "two-hit" hypothesis that described the germ line and spontaneous mutation patterns of presentation and inheritance (Knudeson 1971). Knudeson's work fueled a search for the possible retinoblastoma gene that lasted until 1986 when RB1 (the gene's name) became the first cancer gene to be discovered existing on the long arm of chromosome 13, now known to be 13q14 (Friend et al. 1986).

The protein encoded by RB1 is a phosphoprotein expressed in all adult human tissues and consists of 928 amino acids and weighs 110 kDa. The protein is a regulator of the cell cycle at the transition from G1 to S-phase. Normal RB1 presumably is associated with regulation of the cell cycle where mutated RB1 cells lack control of entry into S-phase and more rapid cell cycling results. Normal RB1 is bound to the protein E2F and when it is phosphorylated, releases E2F allowing E2F to bind to DNA and stimulate DNA transcription (Goodrich et al. 1991).

The RB1 gene is large covering over 200 kilobases and containing 27 exons. Mutations have been described across the gene without clear hotspots being defined. Paternal allele's are more commonly involved in the first hit (Zhu et al. 1989). Penetrance of the trait is over 90%.

The second hit occurs in both germinal and non-germinal cases. It is usually chromosomal in nature and may reflect the effects of the first hit and reflects recombination errors. It occurs in much higher frequency than the first hit and appears to be more susceptible to environmental agents (Zhu et al. 1992). New methods are looking at peripheral blood in the diagnosis of RB1 and can tell if loss of heterozygosity has occurred (Ruiz Del Rio et al. 2015).

After both "hits" to the RB1 gene are present, the cells rapidly accumulate genetic damage and tumors develop. Not much is understood because no animal model for retinoblastoma exists at present. Pure knock-out mice for RB1 die at gestational day 14 due to hematopoietic and neuronal failure. A conditionally RB1-deleted p107-deficient mouse model does exist, but this is not like human retinoblastoma and is unlikely to reflect the clinical pathology seen in human retinoblastoma cleanly. The pathways involved downstream of RB1 include p14ARF, MDM2, MDM4). Human tumors express wild type p53, but changes to MDM2/MDM4 may lead to blockage of the p53 pathway (Laurie et al. 2006). RB1 cells typically show losses at 16q1 and amplifications and gains at 1q and 6p.

7.2.4 Genetic Counseling, Etiology, and Unusual Variants

Today patients are counseled that retinoblastoma comes in two main forms, an inherited or germinal form and a spontaneous or non-germinal form. In the inherited, germ-line form both copies of chromosome 13 harbor the mutated gene. Both eyes are affected in 85% of germinal cases and the presentation is in younger children, often under 1 year of age. When both eyes are affected, the mean number of tumors spread across both eyes is five. When in only one eye it is usually multifocal. Eight percent of those with a germ-line mutation have a positive family history of retinoblastoma. The spontaneous form of the disease always happens in one eye and it is uni-focal even if it can appear via instability to be multifocal due to tumor splitting apart and forming large numbers of "seeds" as noted above (Chintagumpala et al. 2007).

The following is a general map of risks based on class of family member:

1. Children of those with retinoblastoma
   (a) If a parent has bilateral disease the risk is 45%.
   (b) If the parent has unilateral disease, the risk is 5%.
      i. Family history positive: the risk remains 45%.
      ii. Family history negative, less than 2%.

2. Siblings of those with retinoblastoma
   (a) Bilateral sibling with a family history, the risk is 45%.
   (b) Unilateral sibling with a family history, the risk is 30%.
   (c) Without family history, the risk is 2% for those with siblings with bilateral disease and 1% with unilateral disease.

It is important to educate the family on the significance of each form of retinoblastoma, to understand the genetic consequences and to understand the risk to family members in the process of planning families. All patients should undergo genetic testing. Because testing is evolving, it is likely that at least two if not more different tests will be performed to analyze a patient's genetics. Additionally, screening for expected tumors associated with retinoblastoma and its treatment is important. Graphical tools have been developed to assist families in understanding the subtleties of a retinoblastoma diagnosis regardless of educational level.

Retinoblastoma is more frequent in Africa, India, and in Native Americans at about 6–10 cases per million) (Chantada et al. 1999). Most of these are unilateral. Most of the patients have the abnormality on the paternal chromosome. Even in wealthy, industrialized countries the disease is more common amongst those of lower financial class and educational status. These data suggest an environmental etiology, but it is unclear what environmental element is at work (Bunin et al. 1989). Hypotheses have been put forward involving diet, HPV virus exposure, and by extension the incidence of cervical cancer and HPV exposure at delivery (Orjuela et al. 2000). Mouse models support a possible HPV etiology (Griep et al. 1998) and about one-third of cases have detectable HPV detected upon genomic evaluation of tumor specimens. Other epidemiologic associations include *in vitro* fertilization (Moll et al. 2003; Cruysberg et al. 2002) and sunlight (Jemal et al. 2000) exposure.

The clinical picture of retinoblastoma is not limited to the development of tumors. Unilateral, non-inherited forms of the disease can present as phenotypically normal. Bilateral (inherited) cases usually present with small lesions in the RB1 gene than cannot be detected. In 5% of cases, however, karyotyping can detect areas of loss and larger areas of loss are correlated with more severe degrees of abnormality (Baud et al. 1999) in what is a constellation of a 13q-loss phenotype:

- Short nose
- Different degrees of mental retardation
- Anteverted ear lobes
- High and broad forehead (frontal bossing)
- Prominent philtrum
- Some have overlapping digits
- Some have microcephaly
- Some have bone growth plate fusion delay

A rare variant of retinoblastoma is the so-called "tri-lateral" retinoblastoma where lesions exist in both orbit and in the pineal region (75–80%) or another suprasellar or parasellar location (20–25%). The intracranial portion presents about 20 months after the bilateral disease is known. The patients have been treated as stage IV extra-ocular retinoblastomas on recent COG trials. They represent primitive neuroectodermal tumors (PNETs) with pathological finding suggesting a possible retinal germinal layer origin. It has been suggested that the decrease in diagnosis of trilateral retinoblastoma may be as a result of an increase in use of early chemotherapy for bilateral disease, making the development of the later-onset brain lesion less likely. Pineal cysts form in cases where chemotherapy has been used and this may represent treated sublinical disease (Popovic et al. 2007; Beck Popovic et al. 2006).

7.2.5 Diagnosis

The diagnosis if retinoblastoma is made initially via careful clinical examination. If a family history of retinoblastoma is known, screening is done so

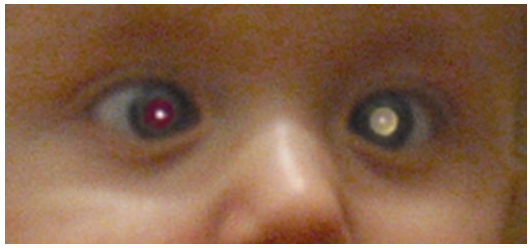


Fig. 7.1 Leukocoria in the left eye from retinoblastoma. Source: Wikipedia, public domain image, submitted by J. Morley-Smith. 2008

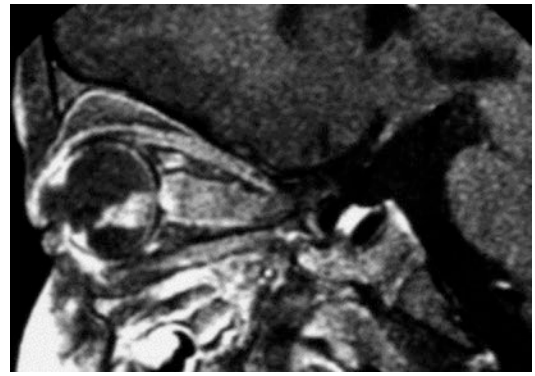


Fig. 7.2 This sagittal T1 enhanced MRI images shows involvement of the optic nerve by tumor. (Public domain Wikipedia)

as to capture the disease as early as possible so as to preserve vision for as long as possible. After an initial clinical exam is done, often driven by leukocoria (Fig. 7.1), examination under anesthesia with a fully dilated pupil is the standard approach used. Mechanical manipulation of the sclera (indentation) is necessary in order to fully visualize the complete retinal surface.

Tumors fall within one of two general categories: endophytic or exophytic. Endophytic tumors grow inward and may seed the vitreous cavity while exophytic tumors grow into the subretinal space causing detachment and can seed into this space. Ophthalmologists document their findings with very detailed hand drawings that to this day are really superior to anything developed in terms of compact documentation. Tumor size, number, location, retinal detachment, the presence and locations of seeds, and the degree of sub-retinal fluid are all part of complete documentation. Additionally, wide-angle retinal imaging, such as provided by the RetCam®, is currently is being used to capture up to 130° angles of view.

For staging purposes, multi-dimensional ultrasound, thin-slice computed tomography (CT), and thin-slice orbital magnetic resonance imaging (MRI) of the orbits are collected (Fig. 7.2).

Using these images, extra-ocular extension is evaluated and if seen, further directed studies are undertaken. Figure 7.2 shows a sagittal MRI from a patient with optic nerve involvement (Aerts et al. 2006). Because 10–15% of patients have metastatic disease, it can be necessary to perform full systemic workups. The findings typically seen with metastatic disease include invasion of the optic nerve beyond the lamina cribrosa, invasion of the iris or ciliary bodies, deep choroidal or scleral invasion, and other direct features of extra-ocular invasion. A full neck examination is indicated in all cases once disease outside of the orbit is suspected. Cerebral spinal fluid, bone scan, and volumetric imaging based on standard principles are indicated in the context of suspected extra-ocular disease.

A partial listing of the differential diagnoses for diseases of the orbit:

- congenital cataract (leukocoria can be present)
- hamartoma (endophytic), choroiditis (exophytic)
- Coat's disease (unilateral telangiectatic retinal blood vessels associated with retinal detachment causing leukocoria and a yellow exudate)
- retinopathy of prematurity (with retinal detachment causing leukocoria)
- retinal astrocytoma, retinoma (benign variant of retinoblastoma)
- persistent hyperplastic primary vitreous

- toxocariasis (associated with endophthalmitis with a resultant membrane formation that can make the pupil appear white)
- Bloch-Sulzberger disease (*incontinentia pigmenti*, and X-linked dominant disease that affects females and which is characterized by a vesiculobullous dermatitis and which may include deformities of the teeth and the CNS including retinal detachment which can cause leukocoria)
- retinal dysphasia (can be unilateral or bilateral)
- Patau's syndrome
  - Norrie's disease
  - Edward's syndrome
  - others
- metastatic disease

7.2.6 Staging

The staging of retinoblastoma that is most accepted currently is the Reese-Ellsworth (R-E) grouping system (Table 7.1). The system was originally used to predict the outcome after external beam radiation therapy and divides each eye into one of five groups based on tumor size, tumor locations, number of lesions, and the presence or absence of vitreous seeding.

Because treatment has shifted from external beam therapy, a new staging system has begun to be used that is simpler and more applicable to current therapy: the International Classification of Retinoblastoma system (Table 7.2). The basis of this system is the extent of seeding into the vitreous and the extra-retinal space rather than tumor size or tumor number and this system (Shields et al. 2006) is the system currently in widest use and is felt to be a better predictor of outcome than the previously used Reese-Ellsworth system. These staging systems are based on an intact eye.

If a patient has undergone enucleation, pathologic data unavailable otherwise are able to influence staging and management of the patient: choroidal involvement, optic nerve extension, and metastatic disease are examples of these data. Surgeons and pediatric oncologists collaborated to form a new, international staging system based on this more complete set of data (Chantada et al. 2006) (Table 7.3). The most common pattern of spread for retinoblastoma is as follows: intraocular, to scleral invasion, to orbital content invasion, to lymphangetic spread to the pre-auricular lymph nodes, to the cerebral-spinal spread, and finally to hematogenous spread.

Table 7.1 Reese-Ellsworth grouping system of retinoblastoma

Reese-Ellsworth classification for conservative treatment of retinoblastoma (Shields et al. 2006)		
Group	Likelihood of globe salvage	Features
I	Very favorable	(a) Solitary tumor, less than 4 disc diameters in size, at or behind the equator
		(b) Multiple tumors, none more than 4 disc diameters in size, all at or behind the equator
II	Favorable	(a) Solitary tumor, 4–10 disc diameters in size, at or behind the equator
		(b) Multiple tumors, 4–10 disc diameters in size, at or behind the equator
III	Doubtful	(a) Any lesion anterior to the equator
		(b) Solitary lesion larger than 10 disc diameters behind the equator
IV	Unfavorable	(a) Multiple tumors, some larger than 10 disc diameters in size
		(b) Any lesion extending anterior to the ora serrata
V	Very unfavorable	(a) Massive tumors involving over half of the retina
		(b) Vitreous seeding

Table 7.2 The international staging system for retinoblastoma

The international classification (staging) system for retinoblastoma (Shields et al. 2006)			
Group	Subgroup	Features	Details
A	A	Small tumor	Small tumors ≤3 mm in basal diameter or thickness and without Group B features
B	B	Larger tumor	Tumors >3 mm in basal diameter or thickness
		Near disc (Juxtapapillary)	Distance to disc ≤1.5 mm
		Macular (near fovea)	Distance to fovea ≤3 mm
		Subretinal Fluid	Clear subretinal fluid ≤3 mm to margin
C		Focal seeds	Tumor with
	C1		Subretinal seeds ≤3 mm away
	C2		Vitreous seeds ≤3 mm away
	C3		Both C1 and C2
D		Diffuse seeds	Tumor with
	D1		Subretinal seeds >3 mm away
	D2		Vitreous seeds >3 mm away
	D3		Both D1 and D2
E	E	Extensive disease	Occupying over 50% of the globe Neovascular glaucoma Opaque media from hemorrhage in anterior chamber, vitreous, or subretinal space Invasion of postlaminar optic nerve, choroid (>2 mm), sclera, or anterior chamber

Table 7.3 New international staging system of classifying retinoblastoma (Chantada et al. 2006)

International classification of retinoblastoma (Chantada et al. 2006)			
Stage	Likelihood of globe salvage	Features	
0	Treated conservatively		
I	Eye enucleated, completely resected histologically		
II	Eye enucleated, microscopic residual tumor		
III	Regional extension	(a) Overt orbital disease	
		(b) Preauricular or cervical lymph node extension	
IV	Metastatic disease	(a) Hematogenous metastasis (without CNS involvement)	1. Single lesion
			2. Multiple lesions
		(b) CNS extension (with or without any other site(s) of regional or metastatic disease)	1. Prechiasmatic lesion
			2. CNS mass
			3. Leptomeningeal and CSF disease

7.2.7 Treatment

Treatment is individualized based on stage (Chantada and Schaiquevich 2015). Focus is first paid to preventing loss of life and then it is paid to preventing loss of vision. The radiation oncologist extends this to think about avoiding second malignancy, avoidance of late effects with organs at risk and disfigurement. The extent of disease, whether one or both eyes are involved, and stage affect the overall approach used in a case. The overall approach to treatment is not dissimilar to that used with most primary brain tumors in that it is team-based. It is, however, different in that primary management of these tumors has historically been the domain of the ophthalmologists because the follow-up and evaluation of intact orbits demands a formal exam under anesthesia in the operating room.

1. Surgery

   For any patient with disease limited to the eye, enucleation is an option and when local options fail, or vision has been lost, and tumor is still limited to the eye this can often be the optimal salvage option in that it avoids the use of radiation with its inherent risk of subsequent second cancers. Enucleation should be performed in an oncologically experienced surgeon's hands in that the orbit should be kept intact if at all possible to avoid seeding. Additionally, for staging purposes, a long section of optic nerve should be removed intact. This is typically 10–20 mm in length. During enucleation, an implant for the orbit is fitted by the surgeon. Muscle attachment is performed in a fashion to optimize later placement of a more realistic, ceramic globe. Ocularists use digital technology mixed with hand painting to make ceramic implants that look extremely realistic. These are changed with time as a child grows.
2. Non-radiation local therapies

   When disease is limited to the contents of the orbit, saving useful vision is the goal of the team treating the child. This becomes crucial when one eye has already been enucleated. Therapy is typically reserved for small 3–6 mm lesions and is used in combination with chemotherapy.

   Cryotherapy is used for small peripheral and equatorial tumors that are less than 2 mm thick and typically under 4 mm in cross section at the base. Patients get 1 or 2 monthly sessions of triple freeze-thaw cycles and control is excellent. This is an approach used in many locations and is relatively well tolerated by patients.

   Photocoagulation using a laser such as an Argon laser treats tumors less than 2.5 mm high and 4.5 mm wide. It also can treat neovascularization induced by radiotherapy. Treatments take one, two, or three sessions typically. Complications can include focal scarring of the retina (Lavinsky et al. 2013).

   The use of heat is also used in the form of transpapillary thermotherapy. Temperatures of 40 to just under 60 C are used for 5–20 min (higher temperatures are used for shorter time periods). Lasers are typically used to deliver this energy. When used with chemotherapy for intraocular tumors, control rates can be as high as 80%. The drugs used include carboplatin, vincristine, and etoposide. Complications can occur and are related to destabilization (detachment) of the retina, local scarring, and retinal tearing (Schueler et al. 2003).
3. Chemotherapy

   Chemotherapy in the traditional intravenous sense is used with local therapy, when patients have bilateral disease, extra-ocular disease, or intra-ocular disease with high risk features. The agents in use include etoposide, cyclophosphamide, doxorubicin, vincristine, ifosfamide, and the platinums (Rodriguez-Galindo et al. 2007; Ghassemi and Khodabande 2015; Chantada and Schaiquevich 2015).

   Work pioneered in Japan evaluated the use of melphalan via intravitreal and intraarterial (IA) routes as a means to treat disease with chemotherapy while avoiding radiation therapy in the context of advanced or recurrent localized disease (Kaneko and Suzuki 2003). Preclinical data suggested that intravitreal

melphalan and thermotherapy interacted in a synergistic fashion (Inomata and Kaneko 1987). Responses with intravitreal chemotherapy and hyperthermia were confirmed in the clinic in patients with progressive disease (Kaneko and Suzuki 2003). Kaneko et al. moved toward IA delivery of melphalan into the ipsilateral carotid artery. This method was improved via the use of balloon catheter usage to direct the drug into the ophthalmic artery by the team lead by Mohri (1993). Abramson et al. reported a modification of this technique that involved cannulation of the ophthalmic artery via a microcatheter and high salvage rates have been reported by the group (Abramson et al. 2008). This last method is the current method being used on the open COG IA protocol for retinoblastoma (Abramson et al. 2010). Data regarding the toxicity of this approach is currently under active investigation (Rizzuti et al. 2008; Wilson et al. 2011). It has been shown in animal models that this approach, currently perhaps the most promising method that can treat advanced local disease successfully without external beam radiation therapy, may cause significant changes to occur in the tissues of the orbit (Steinle et al. 2012; Tse et al. 2013, 2015).

4. Radiation therapy

Radiation therapy has a long history in the treatment of retinoblastoma. The tumor is highly radiosensitive. The first patient treated with a linear accelerator (LINAC) had retinoblastoma and is still alive today with functioning vision. Traditional external beam radiation has fallen out of favor at this time because of the increase in the risk for local second malignancies in this population. It has, for the most part, become the mainstay of salvage if disease cannot be controlled via enucleation alone and of advanced disease (International Staging System stages II, III, and IV). The most common indication for radiation is vitreous and subretinal seeding, but IA therapy is currently being used in this situation on protocol and data from smaller phase I and II studies looks promising for this methodology if the toxicity doesn't turn out to be even worse than with radiation.

The historical dose used to control this disease is 45 Gy at 1.8 Gy per fraction and was the basis of the dose used in the recently closed international COG protocol for extraocular disease. It is likely that 36 Gy is sufficient when chemotherapy is employed and this is likely to be one possible starting point for the next trials in the COG.

There are two types of radiation that are still in common use for retinoblastoma: brachytherapy and proton beam therapy. Traditional photon therapy is still in use and is quite elegant in specialized settings, but it is less commonly used in North America at present due to concerns about integral dose. Electron beam therapy is in use as it has dosimetric advantages in terms of integral dose over photon beam use. Newer methods such as complex three-dimensional compensators can help to make electron beam therapy more conformal.

Brachytherapy in the form of intraocular plaques (Figs. 7.3, 7.4, and 7.5) and in some cases high dose rate brachytherapy using traditional afterloading catheters (Fig. 7.5) is used to keep the integral dose of radiation to a minimum. Brachytherapy has the advantage of being fast, accessible in many radiation centers, and affordable. Plaque therapy is the most common type of radiation used for intraocular disease at this time point in the COG and is a permitted option for local therapy on the current COG IA protocol. Plaque therapy can be used when tumors are 3–15 mm wide, thickness is less than 10–12 mm, and the location is more than 3 mm from the optic nerve and the fovea. The plaque is placed on the sclera in the operating room by the ophthalmologist. It is held in place via sutures. The muscles need to be detached to allow for this. Specialized planning software exists to support plaque brachytherapy including customized template construction for plaque placement via CT based treatment-planning software. The experience of the team is crucial to make this work well (Shields et al. 2001a). Subtle improvements in the process include self-collimating plaques that use clever placement of

sources into wells rather than "atop" the plaque material to decrease scatter and having notched plaques to get near but not "on" the nerve. Radio-isotope selection varies, but iodine is commonly used at present. Control rates in the literature hover between 85 and 90% using plaques (Shields et al. 2001b). Figure 7.3 shows a traditional plaque implant. Figure 7.4 shows a more unusual implant treating the whole eye via a series of four struts anchored to a sutured gold ring encircling the cornea. Figure 7.5 shows an afterloading procedure in sequence. Clearly the scope of options in brachytherapy is broad and crucial to the success of brachytherapy is physician training on the radiation team side and surgical skill and comfort with radiation devices on the surgical side. As is the rule in many parts of radiation oncology, teamwork is of paramount importance.

Proton beam therapy, the second type of common radiation therapy in use today is an improvement relative to other forms of exter-

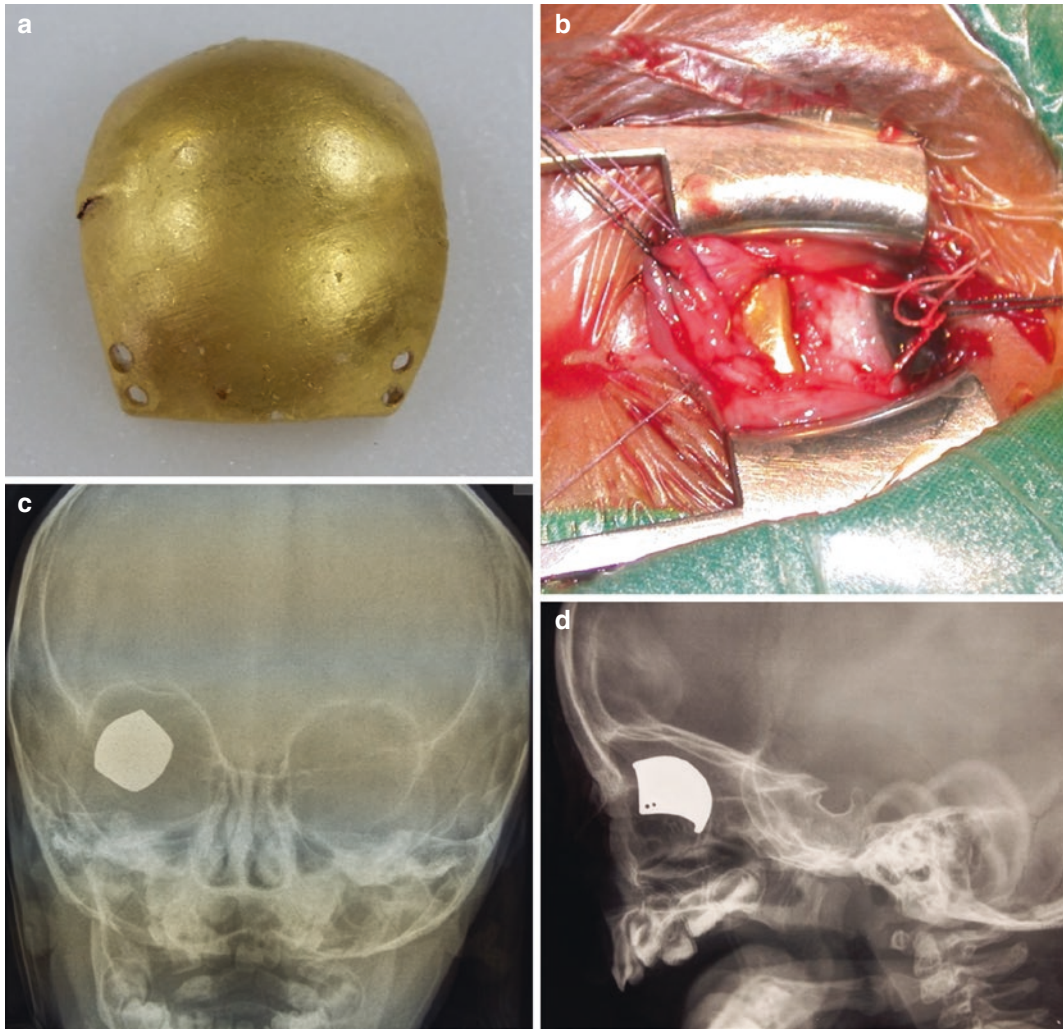


Fig. 7.3 (**a**) Shown is a typical gold plaque used for ocular brachytherapy. (**a**) Shows the outside surface of the plaque and the holes used to thread suture. (**b**) Demonstrates plaque placement in the operating room. (**c**, **d**) Show the placement of the plaque via orthogonal imaging. (**e**) Shows the radiation plan generated via source placement in the plaque. Sources are typically glued to the plaque. (Combined ocular tumor clinic, Groote Schuur Hospital, Cape Town, South Africa)

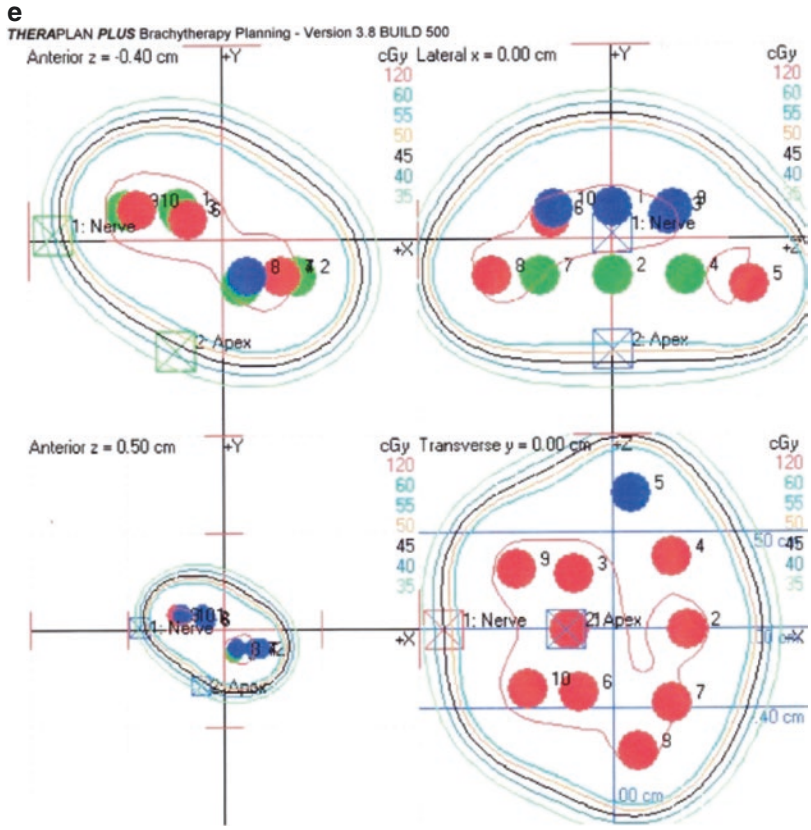


Fig. 7.3 (continued)

nal beam therapy, photons and electrons (Fig. 7.6), because it has a smaller integral dose (Krengli et al. 2005). It is not, however, without significant exposure to normal tissue and the same issues of lens sparing and careful use of ocular immobilization and lens blocking apply to the use of protons. While not a focus of literature to date (Krengli et al. 2005; Mafee et al. 1989), the move from passive scattering and uniform active scattering to spot scanning and intensity modulated proton therapy (IMPT) should, in theory, allow dose to be "wrapped around" the lens. This will require prospective analysis but might be a major indication for the use of IMPT over other forms of proton therapy in this population. Additionally, IMPT should allow lid and lacrimal gland sparing because it allows proximal blocking in addition to distal blocking. Even in the context of extra-ocular disease, given the typical age of the patients, the potential for craniospinal radiation, and the need to control integral dose, proton therapy is likely to be the first choice if any external beam radiation is to be used in a case (Sethi et al. 2014).

7.2.8 Treatment of Unilateral Disease

As noted, enucleation is curative and avoids radiation and systemic chemotherapy's toxicities, but at the cost of full vision. Because vision preservation success has been achieved in bilateral disease, these eyes are offered local therapies, noted above, and systemic therapy as a means to preserve the eye with enucleation being saved for salvage once vision is felt to have been lost.

Ocular preservation is increasingly being used as metachronous contralateral disease can occur, especially in very young children.

Adjuvant therapy is indicated when scleral invasion or tumor extends beyond enucleation along the nerve. Chemotherapy is considered an option rather than enucleation in these cases. In the absence of randomized studies, certain indications consistent with higher risk of extra-ocular disease have become associated with the use of chemotherapy and are currently being studied on active national protocols: retro-laminar and choroidal involvement and sometimes massive choroidal involvement. The standard approach is to use chemotherapy for about 6 months and to use multiple agents. Typical agent combinations include vincristine, doxorubicin, and cyclophosphamide (VDC); vincristine, carboplatin, and etoposide (VCE); hybrids of these two, and recently the use of IA generally with melphalan. On protocol, both local and national, other forms of chemotherapy administration are also under investigation in the unilateral eye.

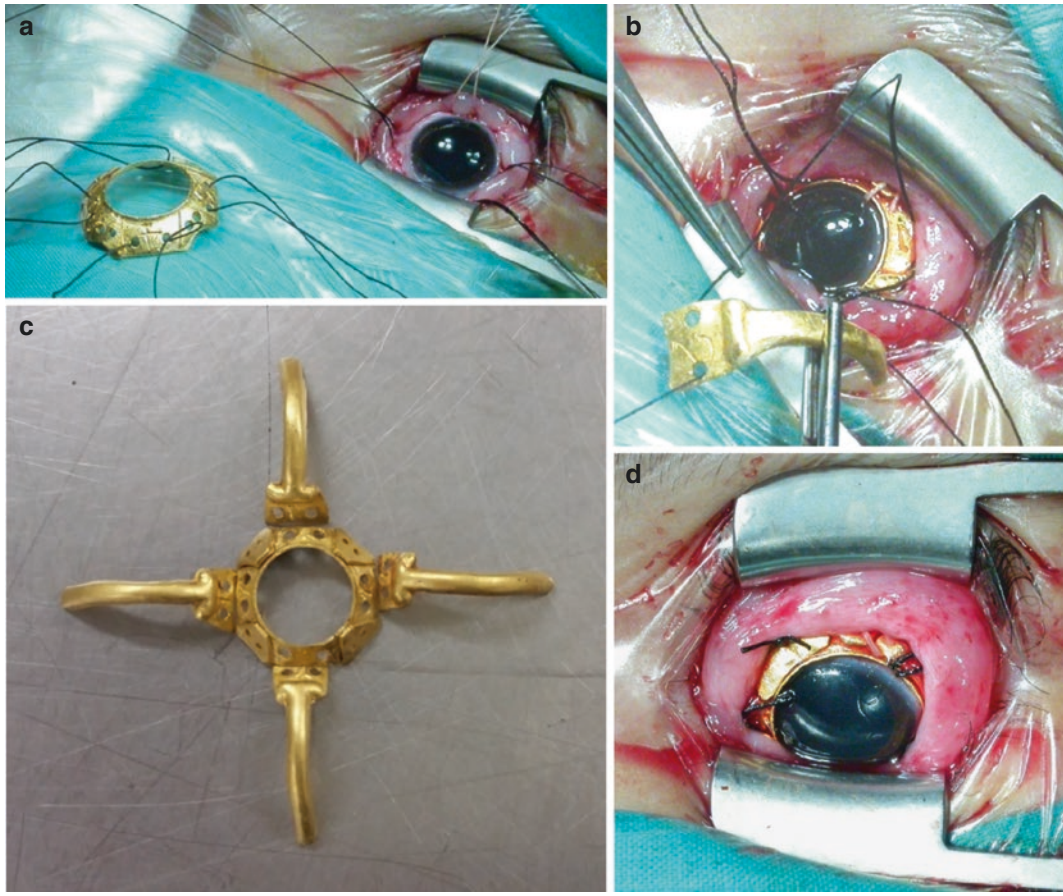


Fig. 7.4 This series of images demonstrates an extremely unusual plaque addressing the orbit volumetrically as a whole. (**a**) Shows the ring of gold that is places around the cornea first. Once the ring is sutured in place, one can see in (**b**) how each "strut" is placed along the curvature of the globe to cover the whole of the orbit. The complete assembly of this device is shown in (**c**). The dosimetry shown in (**d**) demonstrates the effects of the shielding the gold struts give to sources placed on the medial surface of each strut and shows the ability to spare the anterior chamber. In (**e**) the top dosimetry plot shows a "lateral" view of the orbit and the bottom part of the figure shows dose if one were to look right at the patient's pupil toward the fovea. (Combined ocular tumor clinic, Groote Schuur Hospital, Cape Town, South Africa)

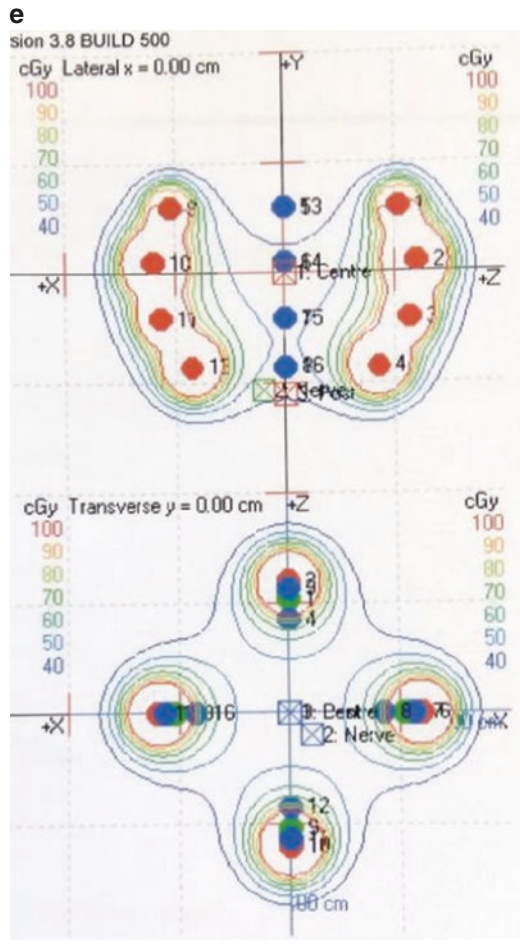


Fig. 7.4 (continued)

7.2.9 Treatment of Bilateral Disease

The current conservative approach using systemic chemotherapy and focal therapies to bilateral disease evolved from the historic approach of enucleation if vision was felt to be impossible to salvage, and external beam radiotherapy if vision might be able to be saved. The high rate of facial deformities in patients treated when very young and the risk of secondary malignancy in the area irradiated, and the advances in the use of chemotherapy and local methods have caused a major shift in the standard approach to these patients. This swing away from the use of radiation is also related to the fact that the risk radiation presents may be age-related and bilateral patients who harbour germline mutations, are typically very young (Abramson and Frank 1998).

The current standard approach in bilateral disease is, therefore, up-front chemotherapy and then sequential local therapy options to both eyes. Chemotherapy is optimized based upon stage with the intensity of therapy mirroring the level of disease. Combinations of vincristine, carboplatin, and etoposide make up the standard backbone of the more aggressive chemotherapy. When eyes are less involved, decreased levels of chemotherapy can be effective. The rates of ocular salvage historically were over 90% in the Group A and B eyes while it was typically over 50% in more advanced eyes with combined radiation therapy. This model may be shifting

toward IA chemotherapy and the early, single institutional data suggest at least equivalent outcomes using IA to these more traditional salvage approaches while fully avoiding radiation therapy and in some cases decreasing systemic toxicity. This is currently under investigation within the COG. Other areas of active investigation in this cohort of patients include intravitreal chemotherapy, subtenon chemotherapy, and other novel delivery approaches that might yield additional options beyond IA chemotherapy when interventional radiology is not available to a center, and when to use IA in combination with other mechanisms of chemotherapy delivery (Mulvihill et al. 2003; Lee et al. 2016; Shields et al. 2014; Seregard et al. 1995).

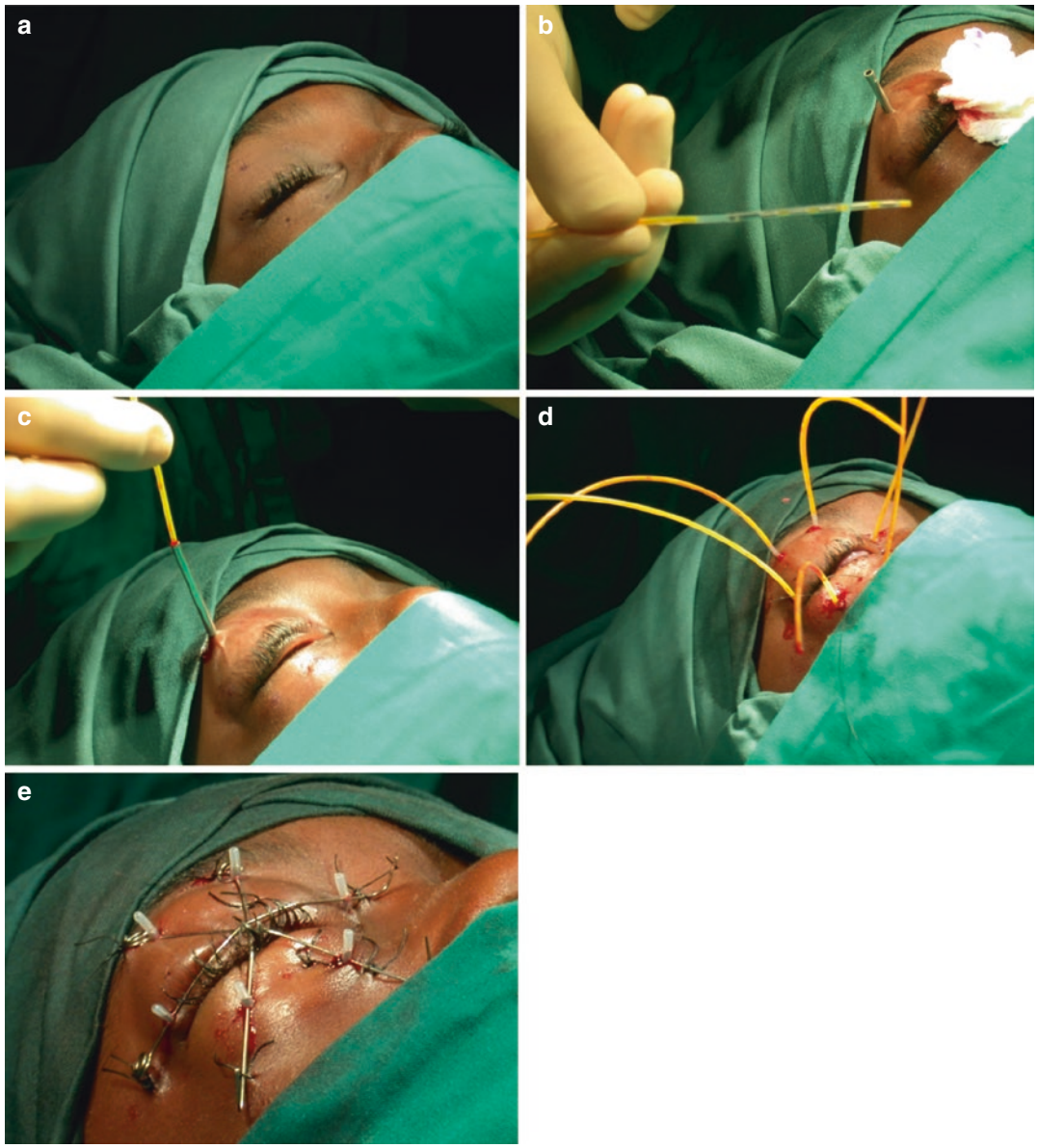


Fig. 7.5 In (**a**–**e**) an after loaded I-125 implant insertion is shown step by step. (**f**) Shows a lateral image of the implant in place and (**g**) shows the dosimetric plan employed in this particular case. (Combined ocular tumor clinic, Groote Schuur Hospital, Cape Town, South Africa)

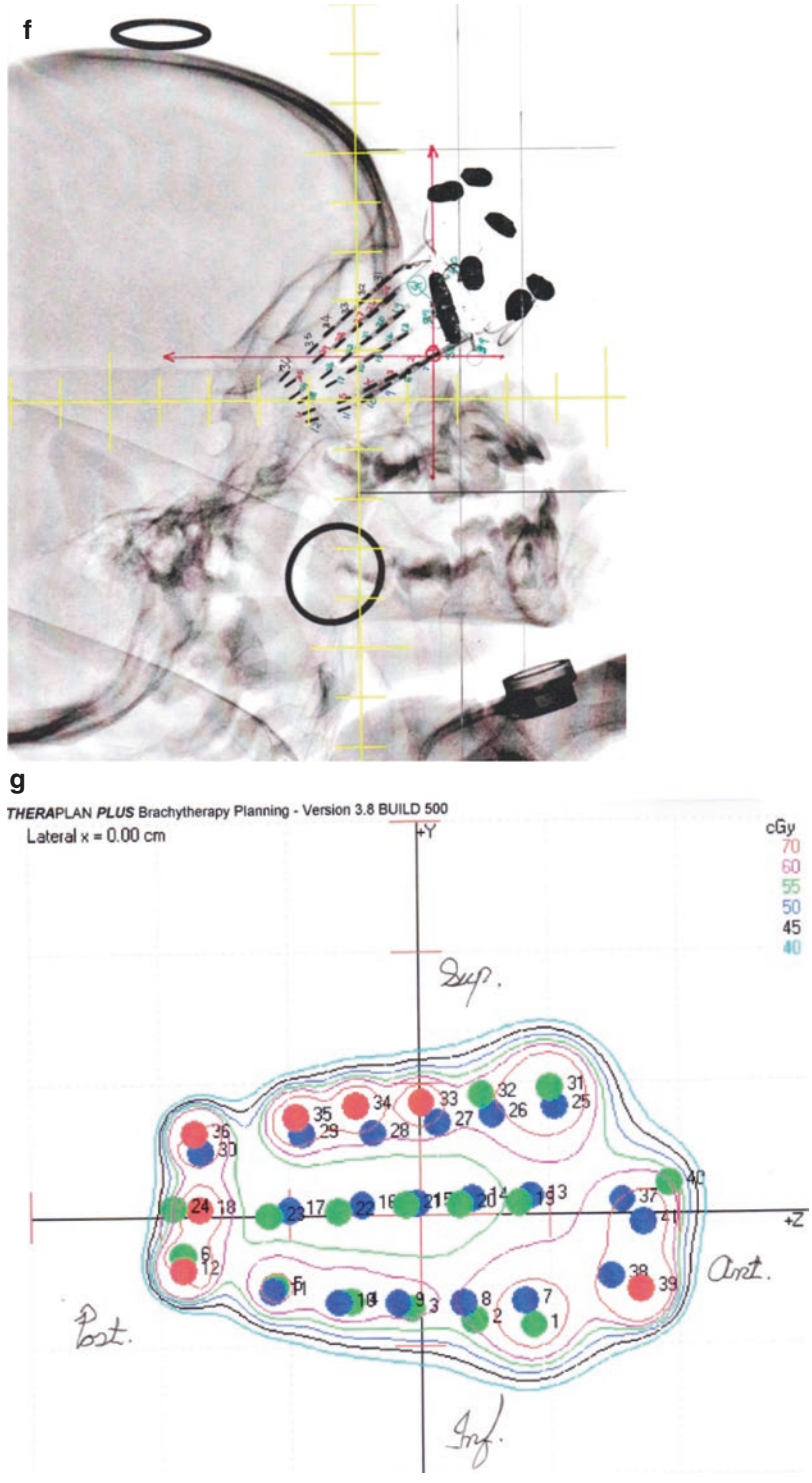


Fig. 7.5 (continued)

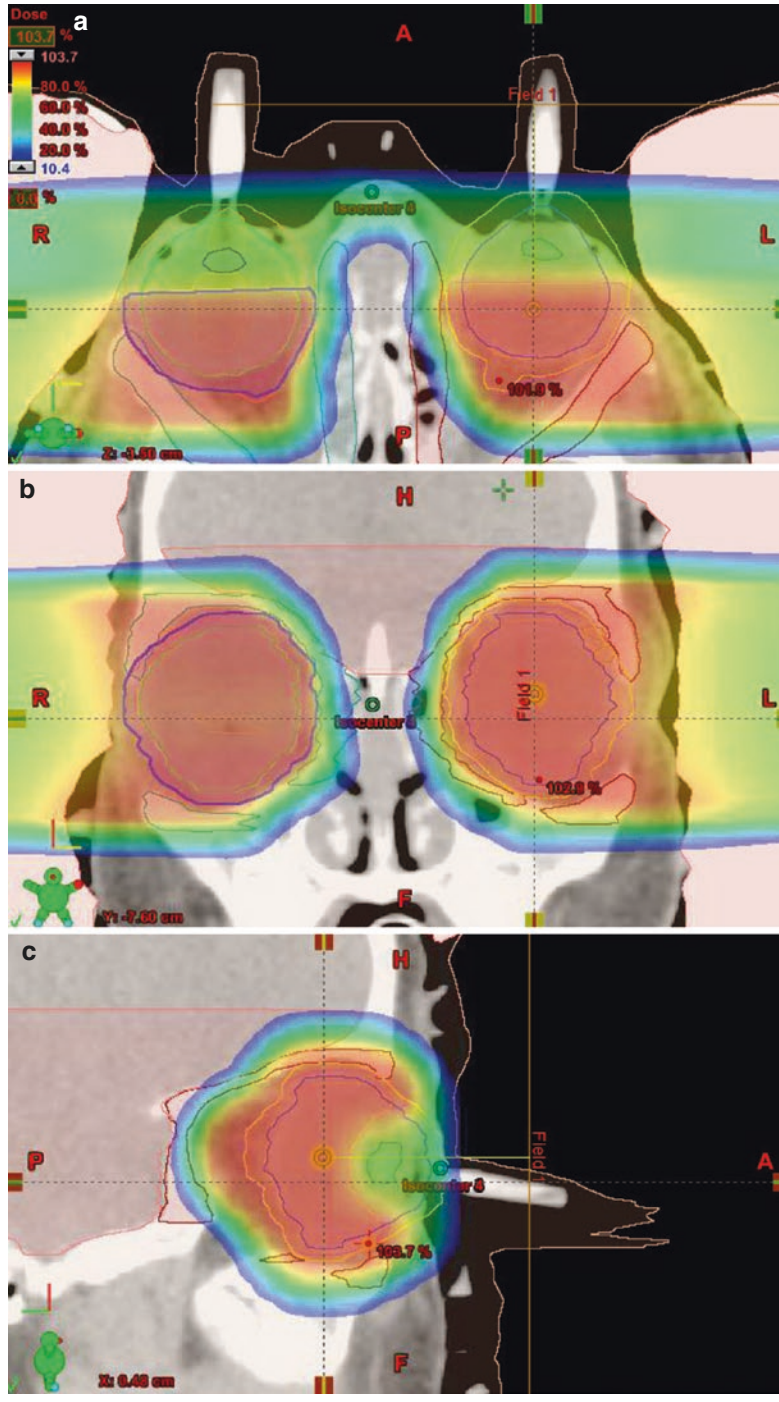


Fig. 7.6 Proton beam therapy to a bilateral case with extraocular, local involvement in each eye requiring radiation. Suction devices are being used to keep the globe still during treatment and are placed each day once the child is asleep. Memory and hormonal centers are able to be spared with the presented dose distribution. The particular case required that the anterior portion of the globes be covered. In this case, dose was limited so as to spare the lens via a cone-down from the entire orbit to the posterior aspect of the orbit as the colorwash demonstrates. Axial (**a**), coronal (**b**), and sagittal (**c**) planes are shown. (Indiana University Proton Therapy Center, Bloomington, Indiana)

7.2.10 Extra-ocular Disease

Four main patterns of spread exist for extra-ocular retinoblastoma "once extra-ocular": local-regional (including down along the optic nerve and the local lymphatics with the first location of drainage being the preauricular lymph nodes), CNS spread with the CSF space, classic metastatic disease via blood to any site in the body, and trilateral disease involving the orbits and the pineal region.

Treatment of extra-ocular disease correlates with two things: the use of external beam radiation and the income status of the population. Firstly, off protocol, the standard approach at this point in time is to treat areas of extra-ocular disease to 39.6–45 Gy at 1.8 Gy/fraction with a 5–10 mm CTV margin and an institutional PTV margin. This includes the use of CSI for CSF positive and trilateral disease with the CSI dose being 36 Gy in 20 fractions. In the recently closed protocol by the COG, ARET0321, patients were randomized to no radiation in stage IV if they had a CR to transplant based on preliminary data from Memorial Sloan Kettering suggesting doing such was safe. Those data are not yet published, so the standard of care is to use radiation, but there may be a move in extra-ocular retinoblastoma to slowly do away with radiation as the data become available.

Extra-ocular retinoblastoma is extremely rare in the United States, Canada, and much of Western Europe, making up less than 5% of all cases of retinoblastoma. In less developed countries, the incidence can be as high as 20–40%. Access to care and screening is felt to be the primary cause of this discrepancy. The difference is so extreme that the ability to conduct studies on this population was likely to have been impossible in the COG without the inclusion of centers in Asia, Africa, and South America (Menon et al. 2000; Antoneli et al. 2003).

1. Loco-regional extra-ocular disease

   Scleral disease is considered extra-ocular because it represents the primary means of tumor getting into the orbit from the globe. It is crucial to treat it as extra-ocular disease. About two-thirds of orbital disease is actually limited to the orbit while the other third represents disease that has spread further and can include the CNS, lymphatic, and hematogenous spread. The overall approach to these cases is to obtain baseline staging data (imaging, CSF status), employ chemotherapy for two to four cycles using a mixture of agents that penetrate the CNS, obtain response imaging data and then perform enucleation to better assess chemotherapy response, then deliver an additional four to six cycles of chemotherapy and complete the local control with radiation therapy at the end. The typical radiation approach is to use 39.6–45 Gy to the orbit. In the special case of local optic nerve involvement with surgical transection, the entire orbit is covered to at least 36 Gy and the optic nerve residual inclusive of the chiasm is treated to 45 Gy in a 9 Gy boost. Orbital exenteration typically is avoided in these cases helping to avoid complex reconstructive surgery (Chantada et al. 2003; Okumoto et al. 2014). Scleral disease is treated in the same way. This remains the standard of care but will likely change over the next several years if data suggesting that radiation may be avoided mature and remain valid.

   When preauricular disease is noted via clinical exam or imaging, coverage of the region takes on the approach used in standard head and neck radiation therapy. If irradiated, the 20% of patients with lymphatic spread have the same control and survival outcomes as those without if radiation is used to cover lymphatic spread (Doz et al. 1994). Data from a good clinical exam and staging imaging quality in this context is critical because one otherwise attempts to avoid excess radiation integral dose.

   Techniques to minimize integral dose are always very prominent in the thought process in this disease and referral to a proton therapy center is not uncommon in these cases. Electron beam therapy is used as well and recent developments in 3D attenuation devices and Monte-Carlo clinical calculation capacity has made this a reasonable option if heavier particle therapy is unavailable.

2. Extra-ocular disease in the central nervous system

   Spread into the CNS is via the optic nerve and outcomes for these cases are poor (Chantada et al. 2003). Protocol management of these cases is suggested given historically poor outcomes even with initial good responses to therapy and CSI is the normal approach taken. The dose employed has varied from 23.4 to 36 Gy with a boost typically up to 45 Gy to areas seen on MRI. The role of transplant has been explored on protocol (Dunkel et al. 2010a; Namouni et al. 1997). The most recent COG protocol allowed a randomization to no radiation use for stage IV cases if a complete response (CR) was observed after transplant using intensive chemotherapy. Until the results of that study are known, off-protocol the standard of care in terms of radiation therapy remains the use of CSI; and it is likely to remain a salvage modality even if the data from the trial support the avoidance of CSI during the initial treatment phase. The use of strategies to avoid integral dose such as the use of proton therapy is indicated in the case of CSI for retinoblastoma.
3. Hematogenous disease

   Much like spread to the CNS, the outcome for spread to areas via the blood such as bones and liver is poor; the literature has more long-term survivors in this category than in CNS spread (Dunkel et al. 2010c). The approach is similar in that chemotherapy is used intensively, but the volume of radiation is limited to the region of the spread plus a reasonable margin, typically 0.5–1.5 cm based on location and nearby organs of risk, to a dose of 45 Gy. Attention to integral dose in these patients still justifies the use of particle therapy in most cases if a good response to chemotherapy has been observed. These cases can be complex and if more than a few lesions are noted, the radiation oncologist may have to stage treatment. The overall approach to these patients is similar to neuroblastoma. Recently, high dose regimens with transplant as rescue have yielded surprisingly good results and some patients with non-skull region bone metastases may not need radiation based on recent work by Memorial Sloan Kettering (Dunkel et al. 2010c). Whether this can be translated into the worldwide community was the subject of COG study ARET0321. It is too soon to evaluate the results of this study but it may turn out that these patients as a group can avoid radiation in specific cases to some metastatic sites.
4. Trilateral retinoblastoma

   Trilateral retinoblastoma is defined as disease in the orbits and the pineal region. It can be seen with only one orbit being involved (Shah et al. 2013). The outcome of these patients is similar to those with more typical CNS metastases and is very poor. Survivors are typically caught early via screening and treated with intensive chemotherapy (Dunkel et al. 2010b). CSI is not always included in the treatment courses of those surviving trilateral disease although new imaging modalities suggest spinal spread is possible in these cases and CSI should be considered (Kamaleshwaran et al. 2014). It is estimated that 1 in 4 cases are found via screening (Kivela 1999). The interval between diagnosis of retinoblastoma and the development of trilateral disease is felt to be rapid, so screening for the first few years after diagnosis is something many groups practice via MRI. The typical approach used is to collect thin slice brain MRI scans every 6 months for 5 years (Pham et al. 2015). Currently the development of pineal gland cysts is being investigated in terms of its relationship with the RB-1 gene. It may be possible in the future to identify those with imaging based changes in the pineal region that do not have retinoblastoma (Pham et al. 2015; Ruiz Del Rio et al. 2014).

7.2.11 Late Effects of Treatment of Retinoblastoma

The immediate late effects of enucleation are loss of vision. The late effects of chemotherapy and radiation therapy are complex and there is a large

amount of data suggesting that both therapies can be quite harmful to this patient population.

Radiation therapy, which is associated with local growth abnormalities and localized secondary malignancies in this population has long been a modality that was targeted for removal from treatment algorithms due to a clear association with late effects (Larson et al. 1990; Newton et al. 1991; Ng et al. 2010). When it needs to be used, some have historically felt that waiting for patients to be over 12 months of age was a reasonable time point due to increased late effects seen in those younger than 12 months of age (Peylan-Ramu et al. 2001). The current use of radiation therapy is limited to plaque therapy and extra-ocular disease. Whenever possible, the use of integral dose variation is minimized via the use of particle therapy. Recent data analysis of the population of the United States supports this general approach (Tamboli et al. 2015).

Cataract in very young patients can be quite complex to manage and it is recommended that patients be referred to national centres of excellence where these patients are seen with regularity. The techniques for managing these cases are complex. It is not uncommon to need revisions of lens as patients age if the orbit grows normally, so using the largest lens possible is the approach typically used by those performing lens replacement surgery (Miller et al. 2005).

Some recently published data from long-term survivor studies in these cohorts suggest that children that are very young are able to re-organize their brains to address areas that may be exposed to low dose radiation and to the loss of visual data in the dimension of learning (Brinkman et al. 2015). Recent work in the study of late effects have seen significant risk to these patients from chemotherapy as well (Choi and Schmidt 2016; Schundeln et al. 2015). The side effects of chemotherapy and radiation are likely additive and the minimization of total exposure in this population is crucial (Shildkrot et al. 2011; Peretz et al. 2001). Even the most promising current management approach to retinoblastoma, the use of IA chemotherapy, may be toxic to these patients and after long term follow-up may be found to be inferior to other modalities (Tse et al. 2015).

7.2.12 The Future of Retinoblastoma Treatment

The focus for retinoblastoma in the future will likely be to use this tumor as a model system to develop and explore targeted therapies because, while complex, the genetics are felt to be far simpler than many other tumors. The RB-1 gene has been mapped and work by multiple labs around the world has synthesized an approachable "map" of genetic targets to test one at a time and in combinations that may allow the field to move away from the more toxic agents in use today. A summary of current concepts is shown in Fig. 7.7 demonstrates some of the signaling pathways active in retinoblastoma (Brennan et al. 2011; Zhang et al. 2012).

7.3 Nasopharyngeal Carcinoma

7.3.1 Introduction and Demographics

Pediatric nasopharyngeal carcinoma (NPC) is a rare disease with distinct differences from its adult counterpart. It is rarer in adolescents and children compared with adults, accounting for <2% of patients with NPC in the SEER registry of North America (Sultan et al. 2010) and <1% of children in the highest risk areas such as Southern China. In these areas there is a unimodal peak of incidence at 50–60 years, however, in Mediterranean countries and North Africa, a second peak in incidence is seen at 10–20 years of age, and in these areas 5–10% of NPC cases occur in children (Berry et al. 1980).

The epidemiology of NPC is complex and poorly understood, incorporating genetic, viral and environmental risk factors (Hu et al. 2013). Exposure to Epstein Barr virus (EBV) appears to be a strong predisposing cause, however, this is not the only risk factor, and genetic and dietary, as well as other factors may also play a role in pathogenesis of this disease.

There are early reports of documented NPC from China, and this region, together with Hong Kong, remains the area of highest worldwide

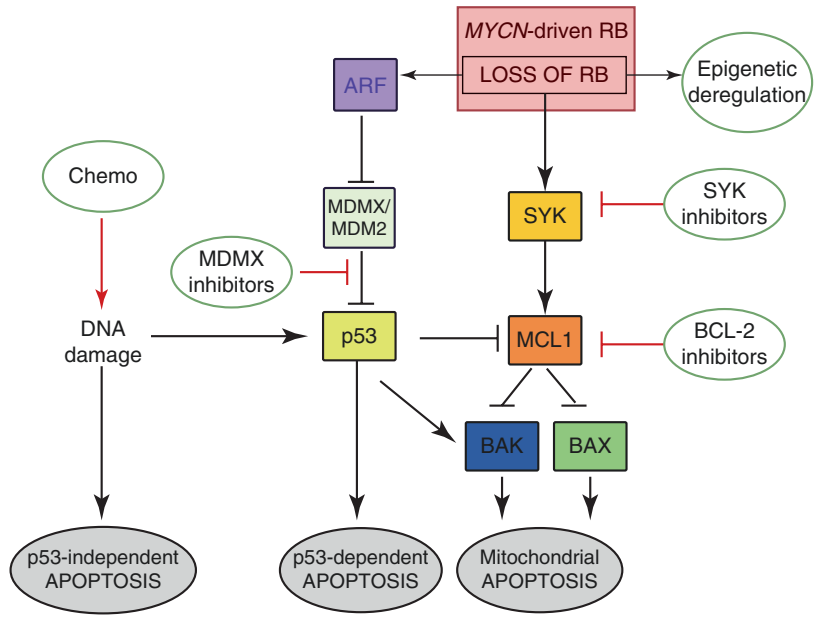


Fig. 7.7 Shown are the various targets that might be available to those seeking to target retinoblastoma in green ovals. (Figure kindly provided by Carlos Rodrigue-Gallindo, M.D. of St. Jude.) The sum of ideas in the figure represents work from multiple laboratories. The figure is relatively simple compared to many other cancers but to date has demonstrated extreme complexity nonetheless

incidence (Chang and Adami 2006). However, even in China, incidence varies greatly, with the highest incidence rates observed in Southern China (>20 per 100,000 person-years) compared with rates of <1 per 100,000 person-years in low incidence areas.

7.3.2 Classification of NPC

The WHO has classified NPC into three subtypes (Barnes et al. 2005) (Table 7.4):

In all geographical areas, there is a striking difference in gender distribution with males representing about 66–75% of cases (Sultan et al. 2010; Zheng et al. 1994). In contrast to adults, almost 90% of pediatric patients with NPC have Type III disease (Mertens et al. 1997; Ayan and Altun 1996). Even though children are more likely to present with advanced loco-regional disease, their prognosis is better. Reports from both endemic and non-endemic areas show overall survival rates of children with NPC of approximately 75–80% at 5 years (Sultan et al. 2010). This is despite being treated on a number of differing protocols, mostly adapted from adult treatment strategies (Ozyar et al. 2006).

Another difference between adult and pediatric NPC, is that pediatric survivors of NPC appear to be at a markedly increased risk of developing second cancers. In a SEER study, survivors of childhood NPC had a 41% increased risk of developing a second primary cancer. This concern has been raised in other studies previously (Scelo et al. 2007). Most of the cancers reported were solid cancers of the head and neck region. In addition, a higher than expected rate of late effects were also a concern in these children with xerostomia, deafness, subcutaneous fibrosis, endocrine problems and dental problems being described (Berry et al. 1980; Cheuk et al. 2011; Ozyar et al. 2006). Although some of the studies used less modern techniques of radiotherapy, there was sufficient concern to warrant that current studies look at ways to reduce radiation dose, as well as to employ techniques that limit morbidity (Sultan et al. 2010).

Table 7.4 WHO classification of NPC

Keratinising squamous carcinoma
Non-keratinising carcinoma • Differentiated • Undifferentiated
Basaloid squamous carcinoma

7.3.3 Genetics

1. EBV

The link between EBV and NPC was initially based on the finding of raised IgG and IgA EBV antibodies in NPC patients (Zeng et al. 1985). EBV has a geographical prevalence and primary infection ranges from a mild pyrexial, self-limiting disease in children, to infectious mononucleosis in adults. The virus infects the oropharyngeal epithelium, but also the B-lymphocytes, which act as a source of latent infection and allow dissemination of the virus to other epithelial surfaces (Vokes et al. 1997). Clonal EBV DNA has been shown to be present in NPC tumor cells, and has led to the hypothesis of the virus being the cause of malignant transformation in the cell.

As well as being a causative factor, levels of anti-EBV antibodies have been studied as a possible prognostic indicator in NPC (Neel et al. 1984; De-Vathaire et al. 1988). Twu et al. showed that EBV DNA in plasma may be a reliable indicator of prognosis and other studies have shown a correlation between levels of EBV DNA and staging, recurrence rates and survival in NPC patients (Twu et al. 2007; Ma et al. 2006; Leung et al. 2003).

Other genetic factors may also play a role in development of NPC. Genetic studies in high risk populations, such as the Cantonese people in Southern China and Hong Kong show a possible HLA-associated risk for NPC (Simons et al. 1976). In other high risk groups, such as the Aleut Indians, and North Africans, studies show genetic links to the population in Southern China, (Chang and Adami 2006; Zheng et al. 1994) strengthening this hypothesis.

Some studies also show a relationship between NPC and the consumption of certain preserved or smoked foods, especially in children (Ward et al. 2000).

7.3.4 Work-Up

Because of the anatomical location of the nasopharynx, patients tend to present late. This is particularly true of pediatric patients, many of whom may present with non-specific complaints such as recurrent otitis media (Martin and Shah 1994). However, the commonest presenting complaints in children tend to be neck masses (due to secondary lymphadenopathy) and headache. Due to an abundant lymphatic supply, NPC spreads early to the lymphatics and to bilateral regional lymph nodes which may be very bulky on presentation. Commonly involved are the internal jugular, posterior cervical and retropharyngeal chains of lymph nodes. Some would argue that children and adolescents with unilateral otitis media and significant cervical lymphadenopathy should be subjected to endoscopy if living in a high risk area (Martin and Shah 1994). All patients suspected of having a nasopharyngeal mass should have a complete general physical examination, as well as a detailed head and neck examination, including documentation of any enlarged cervical lymph nodes and careful evaluation for cranial nerve abnormalities. Cranial nerves III to VI are most commonly affected. Endoscopy with biopsy of a visualized lesion is required (Vokes et al. 1997), and in most children this entails an examination under anesthetic. In addition, cross sectional imaging is required to adequately assess extent of disease. EBV-related biomarkers may help in diagnosis but has a greater role in post-treatment surveillance (Lee et al. 2012).

Magnetic resonance imaging (MRI) is regarded as being superior to computed tomography (CT) scans for assessing the local tumor extent and nodal involvement. Fluorodeoxyglucose positron emission tomography (FDG-PET) combined with CT is also useful for assessing adenopathy in the neck, but MRI is superior for assessment of intracranial extent or involvement of the skull-base (Liao et al. 2008).

For the assessment of distant metastases, integrated FDG-PET has been shown to be superior to CT alone or conventional work-up consisting of CT, ultrasound and bone scan. Bone marrow biopsy is indicated in the presence of advanced loco-regional disease, and CSF cytology should be obtained for patients with intracranial extension. Systemic spread of NPC most commonly affects bone, lung, liver and bone marrow (Chua et al. 2009; Ng et al. 2009).

Staging of NPC is the most critical prognostic factor for both primary and recurrent disease in NPC (Lee et al. 2012). The current TNM staging system has been customized for NPC and has been adopted by both the American Joint Committee on Cancer (AJCC) (Edge and Compton 2010) and the Union for International Cancer Control (UICC) (Sobin et al. 2009; Greene and Sobin 2009; AJCC Cancer Staging Manual 2011) (Table 7.5).

In endemic areas, more than 90% of Pediatric NPC patients present with advanced stage disease (stage III and IV disease.) (Yan et al. 2013; Liu et al. 2014). However, in non-endemic countries like USA, this percentage is lower at approximately 77% (Sultan et al. 2010).

Table 7.5 American Joint Committee on cancer staging for NPC (2010)

	TNM staging of nasopharyngeal carcinoma
T1	Tumor confined to nasopharynx or extends to oropharynx and/or nasal cavity without parapharyngeal extension
T2	Tumor with parapharyngeal extension (i.e., posterolateral tumor infiltration beyond pharyngobasilar fascia)
T3	Involving bony structures and/or paranasal sinuses
T4	Intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit or masticator space[a]
N1	Unilateral nodes 6 cm or less, above the supraclavicular fossa, and/or retropharyngeal nodes 7 cm or less (may be uni- or bi-lateral)
N2	Bilateral nodes, 6 cm or less, above the supraclavicular fossa
N3a	Lymph node >6 cm
N3b	Extension to supraclavicular fossa
Mx	Distant metastases not assessed
M0	No distant metastases
M1	Distant metastases

Stage	
I	T1N0
II	T1-2 N1, T2N0
III	T3N0-2, or T1-3N2
IVa	T4N0-2
IVb	N3 disease
IVc	M1

[a]Note that definition of masticator space in this regard refers to tumors extending **beyond** the anterior surface of the lateral pterygoid muscle or lateral extension **beyond** the postero-lateral wall of the maxillary antrum and pterygomaxillary fissure (Lee et al. 2012)

7.3.5 Treatment

In all Pediatric patients with NPC, treatment is given with intent to cure. Because of the rarity of this disease, treatment has traditionally followed principles and guidelines established in adult NPC. However, in several studies, the outcome of children and adolescents with nasopharyngeal carcinoma appears to be superior to that of their adult counterparts with 5 year disease specific survival approximately 20% higher despite children presenting with advanced stage disease (Sultan et al. 2010; Liu et al. 2014).

Because of the anatomical location of NPC, almost all tumors are deemed irresectable at diagnosis and surgery is not indicated except for biopsy. Treatment, therefore, has been limited to radiotherapy and chemotherapy either alone, or in combination, and more recently with immunotherapy. Treatment regimens commonly used in the treatment of Pediatric NPC have generally used one of the following approaches:

1. Radiotherapy alone in early stage disease(unusual in children)
2. Neo-adjuvant(induction) chemotherapy followed by radiotherapy
3. Combined chemo-radiation with or without adjuvant chemotherapy
4. Induction chemotherapy followed by chemo-radiation
5. Chemoradiation followed by immunotherapy

7.3.6 Radiotherapy in NPC

The efficacy of mega-voltage radiotherapy in NPC has been well documented in many studies. In stage I disease, radiotherapy alone is adequate treatment. However, this applies to a very small percentage of children as by far the majority present with advanced disease. In stage III and IV disease, concurrent chemoradiation is the

established treatment regimen. However, treatment of stage II disease is more controversial (Lee et al. 2012).

Equally controversial is the dose of radiotherapy that is required to cure NPC in children. There appears to be a correlation between tumor burden and the dose required for local control, with an estimate of 1% increase in risk of local failure, for every 1 cm^3 increase in volume of tumor (Sze et al. 2004).

Recommended doses for the primary site and other involved nodal sites range from 59.4 to 70 Gy (1.8–2 Gy per fraction) and some studies have shown improved local control when doses >66 Gy are used (Ozyar et al. 2006). However, other studies have shown dose >70 Gy was not associated with a superior outcome, but did cause additional toxicity (Lee et al. 2009a; Hu et al. 2013). Several studies have looked at special techniques such as brachytherapy and stereotactic radiotherapy in an attempt to further boost dose to the gross tumor in NPC. In adults results are variable with some studies showing benefit while others (Rosenblatt et al. 2014) did not, but in children, profound additional toxicity was shown, most notably in terms of temporal lobe necrosis, catastrophic epistaxis (due to petrous internal carotid pseudo-aneurysm rupture) and osteoradionecrosis. Brachytherapy and stereotactic boost are, therefore, not recommended (Lee et al. 2012). Standard doses for the elective treatment of potential risk sites in the neck are treated to a dose of 50–60 Gy.

In the largest review of Pediatric NPC worldwide, the Rare Cancer Network looked at prognostic factors related to local control (LC), loco-regional (LRC) and distant-metastatic relapse-free survival (DMC) l. Multivariate analysis showed a statistically significantly poorer outcome for patients with T3/T4 disease (LRC), patients receiving a total nasopharyngeal dose of <66 Gy (for LC, LRC), age > 14 years (LRC), or male gender (DMC). Patients with N3 disease seemed to have a poorer DFS and OS with nodal bulk playing a major role. Patients who received radiotherapy alone also did worse in terms of DFS (Ozyar et al. 2006).

In contrast, other studies from France have shown that response-adapted, dose-reduced radiotherapy may be possible in about 50% of patients who have a favorable response to neoadjuvant chemotherapy. In these patients, dose reduction to the neck nodes of less than 50 Gy was not associated with an inferior outcome, and had less toxicity (Orbach et al. 2008). However, this is still not considered standard treatment, and at this time high dose radiotherapy (66–70 Gy) combined with chemotherapy is considered to be standard of care (Nasopharyngeal cancer: multi-disciplinary management 2010).

Technique of radiotherapy does seem to play an important role in toxicity of treatment, with several studies showing a reduction in acute grade 3 toxicity as well as a later onset of grade 2 toxicity when advanced treatment planning methods, such as intensity modulated radiotherapy (IMRT) are used (Laskar et al. 2008). IMRT allows better dose conformity and better protection of organs at risk with reduction in trismus and grade 2 xerostomia seen in some studies (Liu et al. 2014). Use of other advanced techniques of radiotherapy such as helical tomotherapy and proton therapy have been reported and may offer dosimetric advantages, but are not considered standard (Lee et al. 2008; Taheri-Kadkhoda et al. 2008).

However, in countries where advanced techniques are not readily available both 3-D conformal radiotherapy and 2-D radiotherapy can be adequately used to treat NPC. Despite the concern that use of IMRT may increase integral dose and therefore cause a greater risk for secondary malignancy, this risk has to be weighed up against the better acute side effect profile of advanced techniques (Hall 2006; Macklis 2006). Figure 7.8 shows an IG-IMRT treatment plan for a child and Fig. 7.9 shows a similar case in a different child where protons were employed.

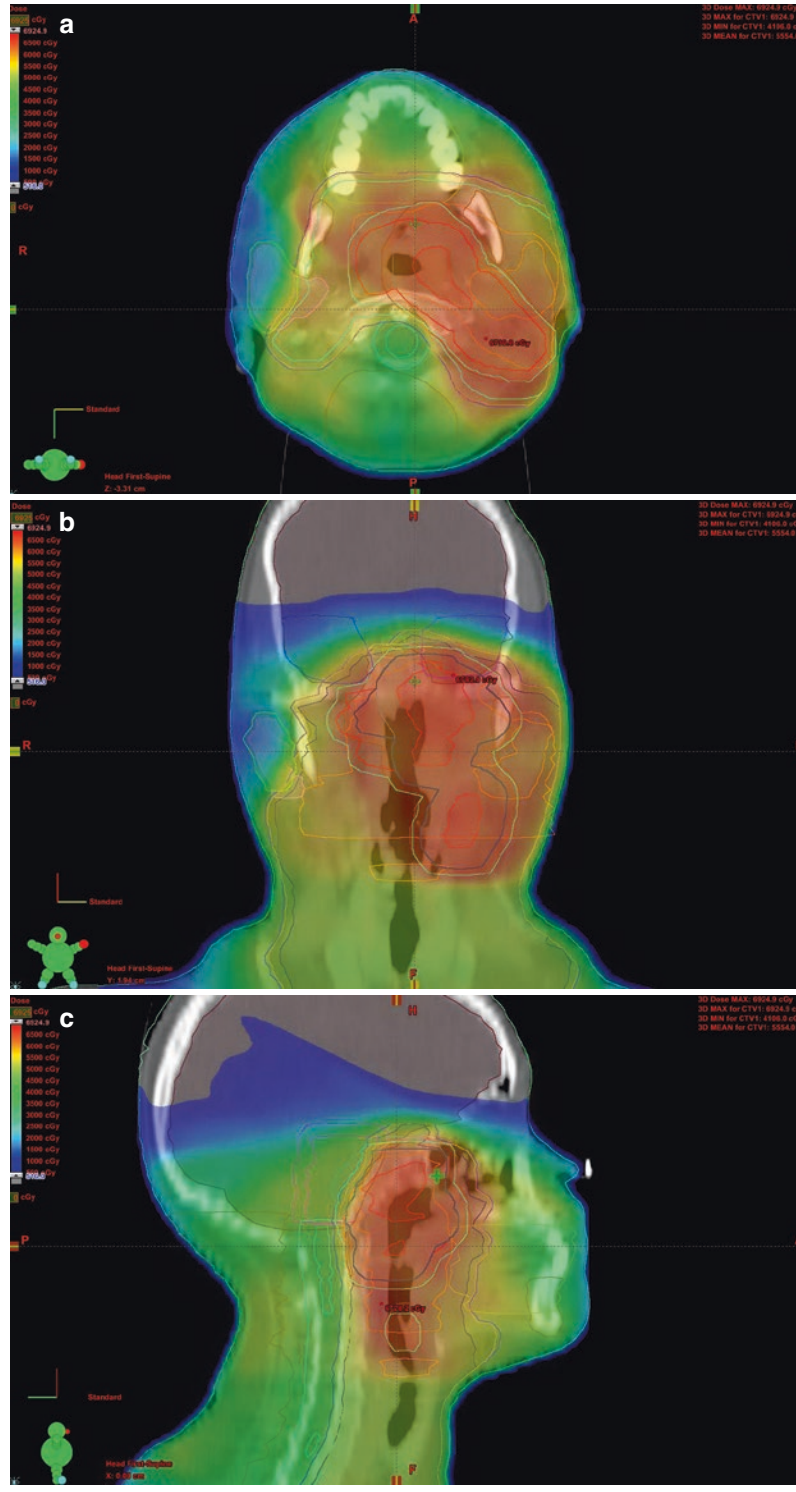


Fig. 7.8 This image-guided intensity modulated radiotherapy (IG-IMRT) plan shows the integral dose delivered with photons in this disease when the necks are treated. Shown are axial (**a**), coronal (**b**), and sagittal (**c**) views of the dose colorwash. (St Jude's children's research centre, Memphis, TN, USA)

Fig. 7.9 This image-guided intensity modulated proton therapy (IG-IMPT) plan shows the integral dose delivered with photons in this disease when the necks are treated. Shown are axial (**a**), coronal (**b**), and sagittal (**c**) views of the dose colorwash. This is a different patient than shown in Fig. 7.8. (St Jude's children's research centre, Memphis, TN, USA)

Table 7.6 Tumor volumes (Lee et al. 2009b) for RT in NPC

	Structures included in volume	Dose required (1.8–2 Gy/#)
Primary disease (GTV) =	Nasopharynx and all involved structures (lymph nodes > 1 cm on CT OR with necrotic centre OR FDG avid on PET OR clinically involved OR endoscopy findings	2.12 Gy per # to 70 Gy 59.4–74 Gy
CTV1 =	GTV+ 5 mm margin	
High risk areas (CTV2) =	CTV1+ 5 mm AND skull-base, clivus, pterygopalatine fossa, parapharyngeal spaces, retropharyngeal nodes, 1/3 to 1/2 of posterior nasal cavity, sphenoid sinus, maxillary sinuses, upper neck nodes to level of hyoid bone	1.8 Gy/# to 59.4 Gy 60 Gy
Prophylactic nodal irradiation (CTV3)	Lower neck and supraclavicular nodes	1.6 Gy/# to 50.4 Gy 50 Gy

7.3.7 Radiotherapy Planning

The treatment volumes required in NPC are extensive owing to the advanced local disease frequently encountered as well as the common involvement of bilateral neck nodes, right down to the supraclavicular nodes bilaterally. Radiotherapy volumes for areas at risk (CTV) are irrespective of planning technique to be used. However, margins applied to this for planning targets volumes (PTV) depend on the frequency and quality of portal imaging available during treatment, and are centre-specific (Table 7.6).

7.3.8 Tumor Volume Delineation

At critical areas e.g., brainstem, margin is reduced to 1 mm.

PTV = CTV2 + 3–5 mm to account for organ motion and set up error.

For IMRT volumes, Anne Lee suggests using the RTOG-0225 study radiotherapy guidelines (Lee et al. 2009b). In this study, radiotherapy was delivered using a simultaneous integrated boost technique, however, caution should be used in children where doses above 2 Gy per fraction, and accelerated fractionation have been related to a marked increase in late effects (Lee et al. 2009a).

Prolongation of treatment time for any reason has repeatedly been shown in several studies to adversely affect local control (Kwong et al. 1997).

7.3.9 Combination Chemotherapy and Radiotherapy in Pediatric NPC

Because the numbers of pediatric NPC are small when compared to the adult disease, many of the large studies are based on extrapolated results from adult studies, despite the histological differences.

In adults, the question regarding the benefit of adding chemotherapy to radiotherapy in treatment of locally advanced NPC was answered in a large meta-analysis where patients from endemic and non-endemic areas were included. The absolute survival befit for the addition of chemotherapy to radiotherapy was 6% at 5 years (improvement of 56–62% with HR = 0.82). The benefit for event-free survival (EFS) was slightly higher at 10%. The greatest effect was seen with concomitant chemoradiotherapy which was the only sequence that achieved significant survival benefit (Baujat et al. 2006).

Concomitant chemo-radiotherapy most frequently uses cisplatin with or without 5-fluorouracil together with radiotherapy in varying schedules (Lee et al. 2012). Controversy remains about the benefit of adding adjuvant chemotherapy to chemoradiation. Although concomitant chemoradiotherapy (CRT) is needed for local control and overall survival, there appears to be some indication that the addition of adjuvant chemotherapy is needed for distant control of NPC (Hui et al. 2009; Lee et al. 2011).

It must be noted that the addition of chemotherapy to radiotherapy is associated with a higher risk of acute toxicities, especially mucositis (Al-Sarraf et al. 1998). In addition, late toxicities such as sensorineural deafness may be worse with CRT compared with radiotherapy alone. Use of advanced radiotherapy techniques such as IMRT may improve this, allowing a lower dose constraint of <47 Gy to the cochleae. A further question surrounds the possible benefit of induction chemotherapy. The theoretical gains of tumor volume reduction, leading to increased minimum tumor dose and improved tumor control probability have been shown in some studies (Lee et al. 2009a). A further practical point in favor of induction chemotherapy in resource-limited settings is that dramatic changes in neck contours can be seen with this schedule prior to radiotherapy cast-fitting and planning, thereby avoiding re-casting and adaptive re-planning to account for this during radiotherapy.

In children, the benefit of concurrent CRT in advanced disease has also been shown in several studies (Bakkal et al. 2007; Cheuk et al. 2011). However, because study numbers are smaller, it is less clear as to whether the addition of adjuvant chemotherapy (or induction chemotherapy) confers any additional benefit (Yan et al. 2013).

7.3.10 Morbidities and Late Effects of Treatment

The commonest morbidities seen in survivors of Pediatric and adolescent NPC are xerostomia, neck fibrosis, hearing loss, trismus, glossolalia, encephalopathy and pituitary hormone deficiency (Yan et al. 2013). The incidence of these morbidities is dose–dependent, with a dose of >68 Gy to the primary associated with all of the above, except for neck fibrosis which was associated with a neck dose of >60 Gy.

7.3.11 Use of Novel Agents

Since routine use of CRT in NPC, distant failure has become the primary cause of death in patients who relapse. Apart from studies looking at improving radiotherapy techniques in order to limit late toxicities, other studies have investigated possible targets for novel therapies. Epidermal growth factor receptor and vascular endothelial growth factor receptor are overexpressed in the majority of NPC cancers (Chua et al. 2004). Studies investigating the possible benefit of the addition of biological agents to chemotherapy as well as immunotherapy and drugs targeting EBV gene products are ongoing (Buehrlen et al. 2012; Yoshizaki et al. 2012).

7.3.12 Recurrent Disease

The majority of recurrences of NPC in children occur within 2 years (Yan et al. 2013). This is earlier than in adult NPC, but in both, distant metastases are the most common pattern of failure, with bone being the commonest site involved. Treatment of recurrent NPC in children depends on the pattern of recurrence. Visceral metastatic disease is treated with chemotherapy whilst bone metastases are treated with concurrent or sequential chemo-radiation. Local recurrence carries a slightly better prognosis than distant metastatic recurrence and patients should be assessed for concurrent chemo-RT strategies. Prognosis after distant recurrence is poor (Yan et al. 2013).

7.4 Desmoid Tumors

7.4.1 Introduction

Desmoid tumors or aggressive fibromatoses are rare benign, non-metastatic but locally invasive tumors that arise from fascial or deep musculoaponeurotic structures in various locations in the body. They represent a monoclonal proliferation derived from mesenchymal stem cells (Wu et al. 2010).

They were first described by McFarlane in 1832 (Macfarlane 1832) but the name “desmoid” was coined by Muller in 1838 from the Greek word “desmos” meaning bond, fastening or tendon-like (Muller 1838). They occur in 2–4 new individuals per million per year and make up 0.03% of all neoplasms and 3% of soft tissue

tumors (Fletcher et al. 2013). Classically they are divided into juvenile and adult-type fibromatoses (Allen 1977) and make up 60% fibrous tumors in childhood (Ayala et al. 1986; Faulkner et al. 1995; Spiegel et al. 1999).

7.4.2 Epidemiology

Two relative incidence peaks are reported in the literature: a pediatric group at 6–15 years, and between puberty and age 40 years in women (Meazza et al. 2009). Up to 30% occur in the first year of life with a peak incidence at 4.5 years and a male predominance (Ayala et al. 1986; Faulkner et al. 1995; Spiegel et al. 1999; Schmidt 1995). They are mainly sporadic where the pathogenesis is most likely multifactorial including genetic predisposition, endocrine factors, trauma (including sites of previous surgery) and exposure to radiation (Meazza et al. 2009). The occasionally seen inherited cases (5%) have been linked to Familial Adenomatous Polyposis in Gardner Syndrome (autosomal dominant) often presenting with aggressive intra-abdominal mesenteric lesions (Lefevre et al. 2008). Most tumors in children tend to be extra-abdominal unlike their adult counterpart (Otero et al. 2015). They are usually solitary but may be multifocal where they tend to develop in the same limb or anatomical region (Häyry and Scheinin 1988).

Pediatric desmoids have a strong tendency to recur locally (24–77%) and may be fatal in abdominal locations or unresectable sites. Risk factors for local recurrence in children include young age, large size (>5 cm), presentation as recurrence, girdle/extremity/intra-abdominal location (abdominal/chest wall locations associated with better local control), involved surgical margins and B-Catenin-activating mutations. Whether local relapse affects survival remains unanswered (Meazza et al. 2011). OS is 90% at 10 years approaching 100% in extra-abdominal cases (16–22).

Historically the biologic and clinical patterns of AF in children have been considered the same as those in adults, and treatment recommendations have, therefore, been similar (Meazza et al. 2009). In an effort to standardize treatment specific to the pediatric population, identify risk factors associated with the abovementioned higher local recurrence rate as well as potential therapeutic targets for intervention, most of the international soft tissue sarcoma cooperative groups are now trying to register patients in databases and protocols. The European pediatric Soft Tissue Sarcoma Study Group (EpSSG NRSTS 2005 protocol) is strongly recommended and will be discussed below within the management section (Meazza et al. 2011).

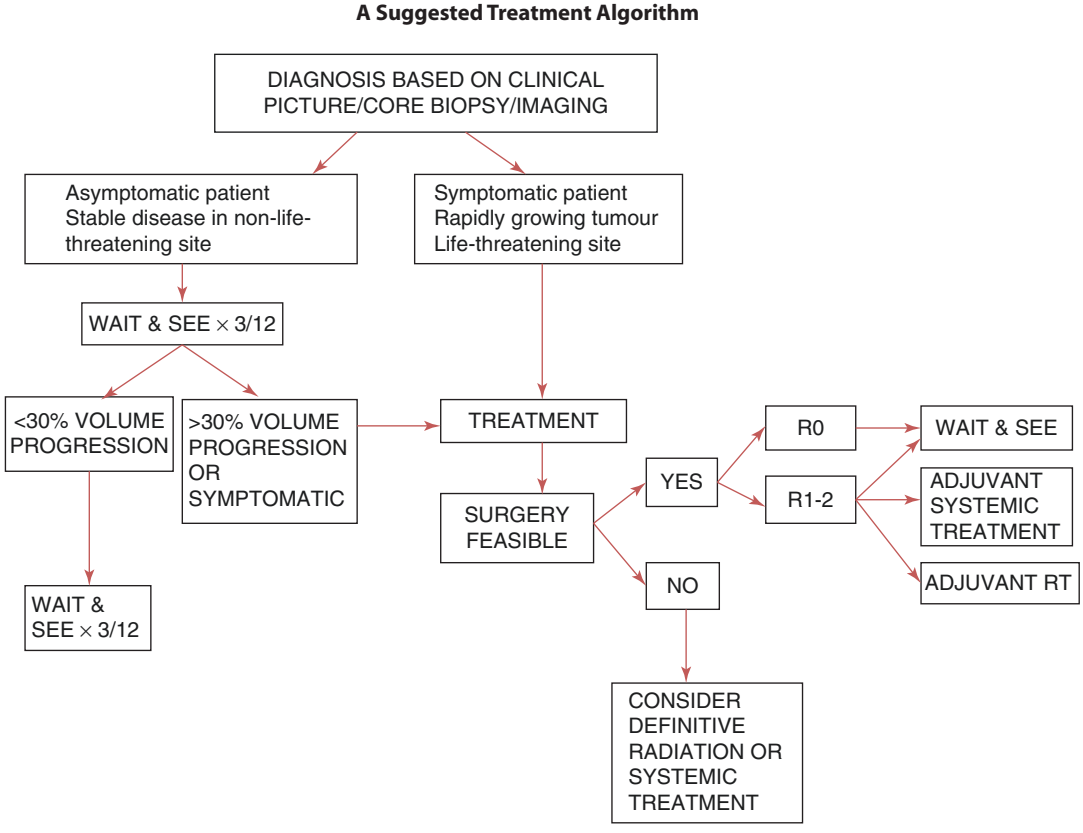
7.4.3 Diagnosis

1. Core biopsy—this is essential for diagnosis and shows an infiltrative lesion made up of uniform spindle cells (myofibroblasts) within a dense collagenous stroma. Tumors stain positive for vimentin with variable expression of muscle-specific actin, desmin and smooth muscle actin (Fletcher et al. 2013; Weiss and Goldblum 2001). Eighty percent express β-catenin, involved in promoting mesenchymal cell proliferation both in FAP-associated desmoids (through germline mutations in APC gene) and sporadic desmoids (through somatic mutations of the β-catenin gene CTNNB1) (Nieuwenhuis et al. 2008; Li et al. 1998; Iwao et al. 1999; Tejpar et al. 1999; Sakorafas et al. 2007). A stronger expression of β-catenin especially associated with p53 positivity may predict high recurrence rate: wild-type β-catenin tumors seem to have better relapse free survival compared to β-catenin mutated tumors (5-year RFS 75% vs. 43%) and may be a useful molecular biomarker of local recurrence (Dômont et al. 2010; Lazar et al. 2008). Gene alterations of chromosomes 8, 20, 6 and 5 are also reported. COX-2 increases growth factor expression e.g., PDGF in desmoids which may be mitogenic for fibroblasts and the tumor suppressor gene Rb1 is lower in this disease and may be involved in pathogenesis (Brandal et al. 2003; Poon et al. 2001; Kong et al. 2004). These molecular aberrations may guide new molecular targets in this disease (Meazza et al. 2011).

2. Imaging:
   (a) **Ultrasound**—findings are non-specific but may be used to direct core biopsy
   (b) **CT Scan**—tends to show a lesion isodense to skeletal muscle but also non-specific
   (c) **MRI**—used for primary diagnosis, to aid surgical staging and for follow up post treatment. The lesion may be well defined or have irregular infiltrative margins. A key diagnostic feature is hypointense bands representing collagen bundles on T2 W images. Moderate to marked gadolinium contrast enhancement is seen except in these collagen bundles. Other possible radiological findings include "split fat sign" which refers to a thin rim of fat surrounding the lesion or a "fascial tail" demonstrating infiltration along the fascia. The more infiltrative the lesion the higher the recurrence rate in children (Romero et al. 1995).
3. If a familial trait is suspected the following is suggested: skull x-ray, panoramic dental X-rays, fundus examination, colonoscopy and gastroscopy, dermatologic exam and referral for genetic counseling (Meazza et al. 2011).

7.4.4 Management

Management of these tumors is challenging and should be individualized. There is no "Gold Standard" strategy shown to lower recurrence rate and decrease long term toxicity yet. Due to the rarity of these tumors it is difficult to conduct randomized controlled trials needed to formulate evidence-based shared treatment guidelines. In children especially, there is a paucity of literature available, limited mainly to one prospective phase II trial (POG 9650 on 28 patients), reports on retrospective studies and review articles (Meazza et al. 2011). Options include surgery, radiation, systemic management or a combination of these, and observation ("wait-and-see" strategy).



7.4.5 Surgery

Surgery remains standard first line treatment and comprises wide local excision aiming for negative microscopic margins. Primary surgery is suggested if complete non-mutilating surgery is potentially feasible or in cases of tumor progression, symptoms or threatening site. Less than 25% microscopic complete resections are seen at diagnosis. Disease control is similar after marginal resection or intralesional surgery/biopsy. The following relapse rates have been reported:

Group I (Complete resections) 22%,
Group II (Marginal resections) 76% and,
Group III (Macroscopic residual disease) 76% (10)

Growth factors released during wound healing post-operatively may actually promote β-catenin activation helping to explain both the high relapse rate and role of surgery in stimulating the onset of desmoids. Because of wide margins, the need for reconstructive surgery is frequent and chronic pain and cosmetic sequelae are common.

7.4.6 Radiation Therapy

Most studies have shown that adjuvant radiation (post-operatively) confers a higher local control rate (Goy et al. 1997; Spear et al. 1998; Ballo et al. 1998). Surgery with adjuvant radiation has been compared to definitive radiation alone by the 2008 Guadagnolo et al. and the 2010 Rödiger et al. studies and reported no statistically significant difference in local control rates at 4 or 10 years (Guadagnolo et al. 2008). Postoperative radiotherapy raises local disease control to a level similar to complete resection (from 46 to 78% in primary tumors and from 18 to 76% in recurrent desmoids).

The decision to offer radiation should be made by both the treating clinician and patient/parents after weighing the potential benefits in local control against the potential toxicity associated with irradiating children. It is recommended that this treatment modality be used as sparingly as possible in children with desmoids tumors (Therasse et al. 2000). The optimal dose, whether definitive or adjuvant, has also not been defined. Total doses between 50–56 Gy in 2 Gy fractions, and fields covering the total tumor or surgical bed plus a margin of at least 5 cm have generally been recommended (Mendenhall et al. 2005; Spear et al. 1998; Ballo et al. 1998; Lewis et al. 1999; Plukker et al. 1995). Delayed second radiation may be considered at disease progression. The main complications of radiation include healing problems, fibrosis, edema, skin ulceration, pathologic fractures, cellulitis, growth abnormalities, neurologic deficits and secondary malignancy (Spear et al. 1998; Ghert et al. 2014). An increase in complications is noted above 56 Gy and in patients younger than 30 years (pediatric population) (Ballo et al. 1999). In contrast to adults, desmoid tumors in children are more likely to recur despite radiotherapy (Meazza et al. 2009; Therasse et al. 2000). The EpSSG guidelines recommend radiation only in select situations: failure to respond to chemotherapy, in unresectable cases, progression despite multiple surgical procedures or as an alternative to mutilating surgery. Figure 7.10 shows a case of a desmoid treated with proton therapy in a teen after multiple prior resections and progressive growth toward the spinal canal.

7.4.7 Systemic Therapy

Systemic treatment may shrink tumors to make them amenable to resection, stop growth or stabilize disease. It may be given upfront as neoadjuvant treatment prior to surgery or radiation (useful in very young children) or in previously treated patients e.g., failure after surgery, radiation or both. Experience is limited in prepubescent children. Due to the slow growth rate of the tumor and slow response to chemotherapy, at least 6 months treatment or up to 12–18 months treatment is recommended. Like adult sarcomas, a general chemo-responsiveness rate of about 40% is noted (Oudot et al. 2012). The Italian Pediatric Series observed an overall response rate of 49% to low dose chemotherapy, a further 38% achieved tumor stabilization and RR <30% with previous exposure to systemic treatment. Meazza et al. provided a useful table of available systemic options adapted below (Meazza et al. 2011).

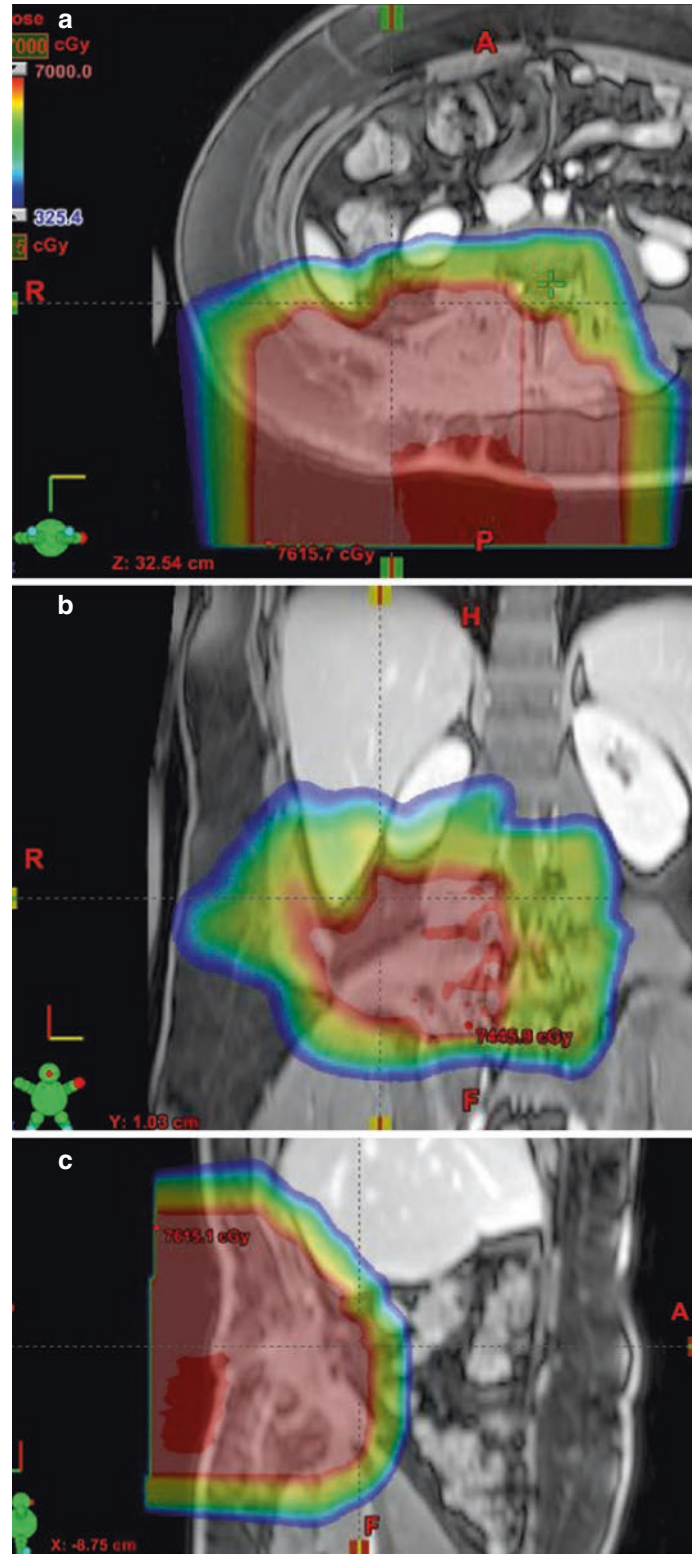


Fig. 7.10 Shown is a proton plan that addressed a desmoid that had recurred a total of four times and surgery options were exhausted given tumor spread to abut the spinal nerve roots and the bowel. A low dose was delivered to a larger volume while a higher dose, in a boost, was delivered to a smaller volume. The patient did not recur in the deep areas where dose was taken to the boost dose. Shown are axial (**a**), coronal (**b**), and sagittal (**c**) views of the dose colorwash. (Indiana University Proton Therapy Center, Bloomington, Indiana)

Serious side effects include fertility problems, cardiotoxicity and secondary malignancies. Wherever possible, children should be enrolled in clinical trials.

7.4.8 Systemic Treatment Options (Adapted from Meazza et al. 2011)

Chemotherapy

Regime	Response RATE
– Methotrexate 30 mg/m^2/week iv + Vinblastine 6 mg/m^2 (max 10 mg)/week iv – Methotrexate 30 mg/m^2/week iv + Vinorelbine 20 mg/m^2/week iv	58% Major/Minor response 42% Stable disease (Meazza et al. 2011, Skapek et al. 2007)
– Vinorelbine 25 mg/m^2/iv (or alternatively, 60 mg/m^2 oral) day 1,8,15 plus oral Cyclophosphamide 25 mg/m^2/day (every day)	
– IVA Regime (Vinc 1.5 mg/m^2 day 1, Actinomycin 1.5 mg/m^2 day 1, Ifosfamide 3 g/m^2 day 1–2) or VAC regime (Vinc 1.5 mg/m^2 day 1, Actinomycin 1.5 mg/m^2 day 1, Cyclophosphamide 1.2 g/m^2 day 1) or VA regime (Vinc 1.5 mg/m^2 and Actinomycin 1.5 mg/m^2) every 21 days	Response Rate 47% (Meazza et al. 2011)
– Pegylated liposomal doxorubicin (20–50 mg/m^2 iv every 3–4 weeks)	
– Hydroxyurea (20 mg/kg/day to start and then 30 mg/kg/day	Partial response 29%, stable disease 50% (preliminary results of N. American study underway) (Meazza et al. 2010, Takemaru et al. 2008)
Targeted therapy	
– Imatinib (400 mg × 2/day) (targets PDGFin desmoids)	Response Rate 10–20% (Heinrich et al. 2004)
– Sorafenib (400 mg day)	Partial Response 25% Stable disease 70% (Gounder et al. 2011)
Hormonal treatment	
– Tamoxifen 5 mg × 2/day if age < 10 years, 10 mg × 2/day if age > 10 years – Toremifene 60 mg × 3/day	Experience is limited in prepubescent children and caution is advised. Common side effects include growth abnormalities, teratogenicity and deep vein thrombosis
Non-steroidal anti-inflammatory drug	
– Sulindac (100–200 mg tablets) at the dose of 4 mg/kg × 2/day or 4 mg/kg twice daily – Celecoxib (100–200 mg capsules) 100 mg twice daily	Antacids, Proton Pump Inhibitors and monitoring of renal function advised in children

7.4.9 Observation

It has been observed that certain desmoid tumors may remain stable for long periods of time and even regress. This has prompted the use of a "wait-and-see" strategy that is more commonly used in adults but may be considered in children for asymptomatic tumors, in non-life-threatening sites, in the absence of marked progression (defined as >30% volume progression). This approach may also provide information on natural tumor biology and growth rate (Wu et al. 2010; Gronchi 2003). These patients should be strictly reviewed every 3–4 months with clinical examinations and MRI scans, preferably by a specialized pediatric sarcoma unit.

7.4.10 Other Options

These include radiofrequency ablation, cryoablation or limb salvage with isolated perfusion but are not widely used (Bocale et al. 2011).

7.4.11 Follow Up

In general this includes rehabilitation of children, aiming for maximal function. Regular physical examinations and appropriate imaging is mandatory.

Conclusions

Desmoids are rare tumors and, therefore, evidence is limited, especially in children. Treatment should be individualized ideally by a specialized pediatric sarcoma or oncology unit. Risks and benefits of each treatment modality should be thoroughly discussed between clinicians, patients and their parents. Future international prospective trials are awaited to further guide management of this chronic disease.

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