# Head and Neck Tumors

# 24

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Tumors of the head and neck present particular challenges for the pediatric surgeon asked to evaluate them. A working knowledge of the embryology, anatomy, physiology and pathophysiology of the head and neck is needed. While the majority of these tumors are benign, an understanding of the fundamentals of surgical oncology is needed when approaching these tumors to ensure proper assessment and treatment.

The head and neck are formed from mesenchymal cells that develop from the paraxial and lateral plate mesoderm, neural crest, and ectodermal placodes in early fetal development. The paraxial mesoderm makes somites and somitomeres which develop into part of the floor and meninges of the brain, the occipital lobe, and the muscle and connective tissue of the face. The lateral plate mesoderm develops into the laryngeal cartilage and connective tissue of the neck. The neural crest cells develop into the brain, the optic cup, the midface, and the pharyngeal arches.

The pharyngeal arches are separated by pharyngeal pouches and clefts. Each arch has a nerve and an artery, and develops into muscle, cartilage and connective tissue. The arterial supply develops when the embryological heart is caudally displaced. Normal anatomy and its variants depend on selective fusion or atrophy of these arteries. In contrast to the arterial supply, the venous system is more variable in the size of the vessels and their course. The branches and connections of the internal, external, and anterior jugular veins provide the venous drainage for the head and neck.

The pharyngeal pouches develop into endocrine glands and the middle ear. Pouch 1 develops into the middle ear and the auditory tube. Pouch 2 develops into the palatine tonsil. Pouch 3 develops into the inferior parathyroid glands and the thymus. Pouches 4 and 5 develop into the superior parathyroid glands. The pharyngeal cleft develops into the external auditory meatus. The thyroid gland is not derived from a pouch but rather develops as an epithelial proliferation from the endoderm of the floor of the pharynx and descends along the thyroglossal tract to the level of the laryngeal primordium.

The thoracic duct and the right lymphatic duct drain lymph from the head and neck. The right side of the head and neck, right upper extremity and the right thorax are drained by the right lymphatic duct which empties near the junction of the right subclavian and right internal jugular veins. The lower extremities, abdomen, and the left side of the head and neck are drained by the thoracic duct which passes posterior to the left common carotid artery and the left vagus nerve as it passes from the right to the left side of the body. The thoracic duct then arches anterosuperiorly and laterally between the left internal jugular vein and anterior scalene muscle to terminate near the junction of the left internal jugular and left subclavian veins. Valves present at the junction of each duct prevent reflux of venous blood. Small anastomotic connections between the two lymphatic ductal systems become important when obstruction or injury to one duct occurs.

The neck is divided based on anatomic triangles that are defined by the angle of the jaw, the clavicle, and the trapezius. Knowing the anatomical triangles of the neck is essential for both properly assessing and determining the prognosis of disease (Fig. 24.1, Table 24.1). The anterior and posterior triangles are separated by the sternocleidomastoid muscle. This muscle extends from medial clavicle to the mastoid bone. The anterior triangle is subdivided into four smaller triangles by the digastric, stylohyoid, and omohyoid muscles. These muscles then create the submandibular, carotid, submental, and inferior carotid triangles. The posterior triangle is divided into the superior occipital triangle and an inferior subclavian triangle by the omohyoid muscle. The triangles with the most lymph nodes include submandibular, submental, anterior cervical, superficial cervical, and deep cervical node groups. Table 24.2 listed common developmental anomalies that present as masses in the head and neck.

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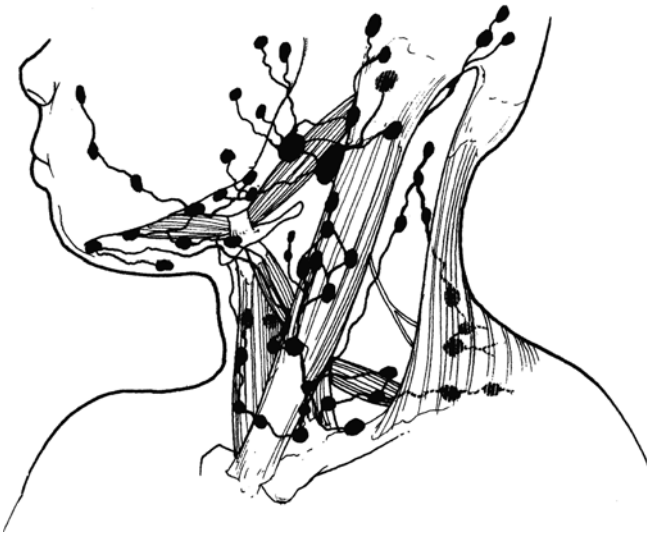

**Fig. 24.1** Muscular triangles and associated lymphatics and lymph nodes of the head and neck

**Table 24.1** Muscular triangles of the neck

| | Posterior triangle | Anterior triangle |
|---|---|---|
| Boundaries | | |
| Posterior | Trapezius muscle | Sternocleidomastoid muscle |
| Anterior | Stemocleidomastoid muscle | Midline of neck |
| Floor | Deep layer cervical fascia | Mylohyoid, hyoglossus, thyrohyoid, pharyngeal constrictor muscles |
| Roof | Superficial cervical fascia | Superficial cervical fascia, platysma muscle |
| Contents | Subclavian artery | Carotid artery |
| | Brachial plexus | Internal jugular vein |
| | Spinal accessory nerve | Submandibular gland |
| | Posterior cervical lymph nodes | Vagus nerve, recurrent laryngeal nerve, lymphatic tissue |
| Subtriangles | Occipital | Submandibular |
| | Subclavian | Carotid, submental, muscular |

## Cervical Adenopathy

Cervical adenopathy is a common finding in pediatric patients and is usually the result of inflammatory processes. In one study, lymphadenopathy was noted in 44 % of children under 5 presenting for a well child check and 64 % of children presenting for a sick visit [1]. However, only 11–30 % of biopsied lymph nodes harbor a malignant process [2–5]. Self-limited, non-specific adenitis from adenovirus, rhinovirus and enterovirus infection of the upper respiratory tract is most common. Up to 3 % of cases are due to cat scratch disease [6]. Measles, mumps, Epstein-Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), herpes virus, tuberculosis, parasitic, bacterial, and other viral infection may also cause cervical adenopathy. Non-infectious inflammatory disorders such as Kawasaki's disease, lupus, Langerhans cell histiocytosis, hemophagocytic lymphohistiocytosis, Castleman's disease, Rosai-Dorfman disease, Kikuchi's disease, Churg-Strauss syndrome, and sarcoidosis may also cause adenopathy.

**Table 24.2** Congenital anomalies presenting as head or neck masses

| Anomaly | Origin |
|---|---|
| Lymphovascular malformation (cystic hygroma) | Abnormal lymphatic drainage, abnormal lymphatic formation |
| Lymphangioma | Abnormal development of arterial, venous and lymphatic channels |
| Second branchial cleft, cyst sinus, or fistula | Failure of obliteration of cervical sinus |
| Thyroglossal duct cyst | Failure of thyroglossal tract obliteration |
| Lingual thyroid | Failure of thyroid descent |
| Thymic cyst | Thymic remnant |

Lymphadenopathy is the initial finding in most malignancies of the head and neck in children [5, 7]. A thorough history and physical exam must be performed. Concerns in the history must include: location and duration of symptoms, associated systemic symptoms, sick contacts, animal exposure, trauma, immunization status, medications, recent travel, dental problems, and diet, including ingestion of unpasteurized animal products and undercooked meat. Often, there are no signs of inflammation, fevers, or upper respiratory symptoms. Malignancy should be suspected for all rapidly growing lymph nodes especially those occurring in the supraclavicular and posterior cervical triangle regions. Factors noted to be predictive of malignancy include nodes greater than 3 cm, supraclavicular or fixed nodes, and abnormal chest x-ray [3].

Fine need aspiration (FNA) is a tool often used in evaluating lymphadenopathy not responsive to antibiotic therapy. The data supporting FNA utilization is found mostly in the adult literature and its use in the pediatric population is limited [8–10]. To perform an FNA an experienced pathologist is needed not only for proper tissue procurement but also for appropriate tissue diagnosis. An 18–22-gauge needle with an attached syringe is inserted into the mass. Once the needle is in the mass, gentle aspiration is performed. The needle is then passed repeatedly through the mass from various angles while applying gentle suction. The tissue is then placed on a slide and stained. Ultrasound or CT guidance may be used for accurate mass localization which is particularly helpful with deep masses of the neck.

**Fig. 24.2** Excisional biopsy of a neck mass. Masses and lymph nodes are completely removed without damaging vital structures. Illustration depicts a mass being dissected from the spinal accessory nerve

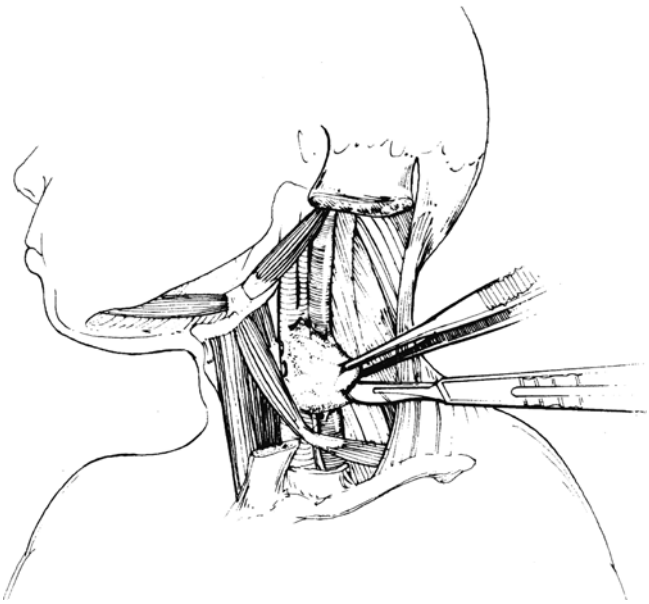

**Fig. 24.3** Incisional biopsy of a neck mass. Illustration shows mass encasing the carotid sheath

Cervical lymphadenopathy is usually a result of acute adenitis. In up to two-thirds of these cases, an FNA can reveal the causative agent [11, 12]. The FNA tissue is usually sent for gram stain and cultures including aerobic, anaerobic, fungi, and mycobacteria. An acid-fast stain may also be used if clinically indicated. Serum serologic testing (Bartonella, tuberculosis, EBV, CMV, HIV, syphilis, etc.…) may also be performed as indicated by the history and examination. When malignancy is suspected, a FNA may or may not be sufficient depending on the underlying diagnosis. Open surgical biopsy is indicated in the following cases: refractory systemic symptoms, hard or fixed lesions, supraclavicular nodes, abnormal chest x-ray or CBC, or rapid growth or disease progression without evidence of inflammation.

When deciding which node should be excised, it is generally best to remove the largest accessible node. In order to perform a lymph node excision, a small incision should be made over the suspicious nodule. Careful dissection with meticulous hemostasis should be performed, being careful to avoid capsule rupture (Fig. 24.2). If the tissues are matted or the node is fixed to surrounding vital structures, an incisional biopsy may be needed (Fig. 24.3). Keep in mind, the node may invade surrounding nerves and vessels, increasing the risk of iatrogenic injury. Since exposure may be difficult especially for deeper lymph nodes, a self-retaining retractor may be helpful. Care should also be taken to avoid damage to adjacent vital structures. Once the node is removed, the wound should be irrigated and the platysma reapproximated with interrupted absorbable suture. The skin is usually closed using an absorbable suture in a subcuticular pattern.

Once the lymph node is removed, it should be kept sterile and moist. The pathologist should be contacted to ensure proper stains and cultures are performed given the patient's clinical history. Part of the node should be sent for gram stain and aerobic, anaerobic, and fungal cultures. A fresh frozen sample may also be sent for histology and staining though a definitive diagnosis requires a permanent section. Proper communication with pathology will ensure that adequate tissue has been obtained for all infectious, immunologic, cytogenetic, and molecular studies requested.

## Hodgkin's Disease

Hodgkin's disease (HD) or Hodgkin's lymphoma is a malignant lymphoma common in children and in adults over the age of 50. In 1932, Thomas Hodgkin first described seven of his patient who all had grossly abnormal lymph glands [13]. Following the description of the pathognomonic multinuclear giant cells by Sternberg in 1898 and subsequently illustrated by Reed in 1902, the cells have become known as Reed-Sternberg cells (Fig. 24.4) [14, 15].

Hodgkin's disease is the most common childhood lymphoma with an overall incidence of 1.2 per 100,000 in the US [16]. The age at presentation has a bimodal distribution with a peak in adolescents and young adults and another in adults over the age of 50. In developing countries, children especially boys are affected at a younger age but Hodgkin's disease is still uncommon before the age of 5 [17]. In childhood there is a male to female ratio of 0.9 but this varies based on age with a male to female ratio of 5.3 in children less than 5 and a ratio of 0.8 in children 15–19 years of age [16, 17]. Relatives of patients with Hodgkin's disease are at

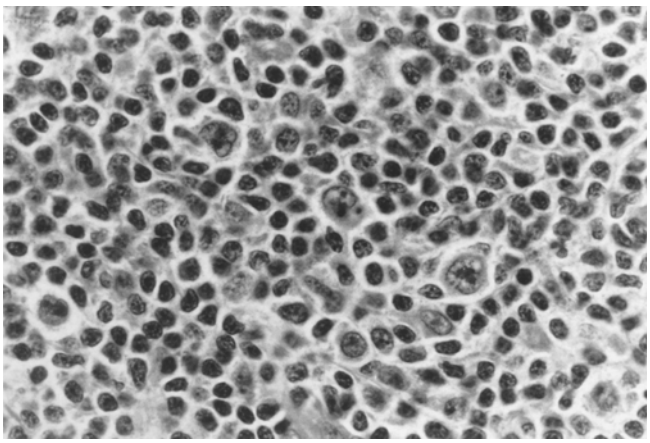

**Fig. 24.4** Photomicrograph demonstrating multiple multinucleated Reed-Sternberg cells of Hodgkin's disease

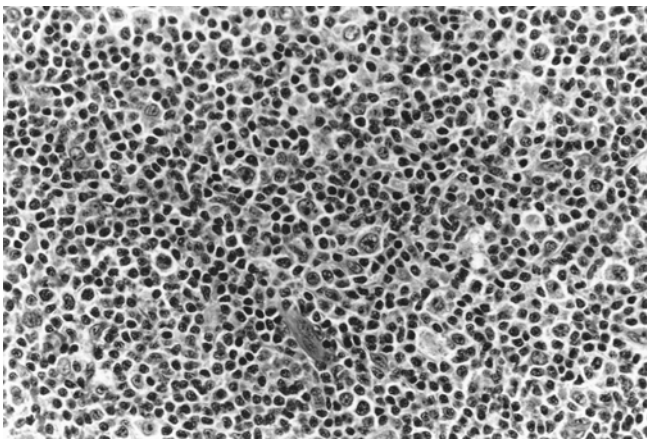

**Fig. 24.5** Photomicrograph demonstrating nodular lymphocyte predominant Hodgkin's disease

a slightly increased risk for the disease with familial forms accounting for 4.5 % of all cases. Clusters of Hodgkin's disease have also been reported [17–20]. Hodgkin's disease is more common in patients with impaired immune systems and/or a history of exposure to viruses such as EBV, CMV or herpes virus 6 [21, 22].

## Pathology and Genetics

On pathologic examination, Reed-Sternberg cells are pathognomonic for Hodgkin's disease though account for only 1 % of the lymphoid tissue on examination. The lymph nodes also display reactive lymphocytes, macrophages, plasma cells, fibrous stroma and collagen. Two common classification systems are the Rye classification and the WHO classification both of which are based on the relative proportion of various cells on histologic examination. The Rye classification divides Hodgkin's disease into nodular sclerosis (50–60 %), mixed cellularity (20–30 %), lymphocyte predominant (10–15 %), and lymphocyte depletion (10 %) [23]. The WHO classification divides Hodgkin's into classical HD and nodular lymphocyte predominant HD [24]. In nodular lymphocyte predominant HD, most HRS cells express B-cell surface markers such as CD19 and CD20. Nodular lymphocyte predominant HD accounts for only 5–10 % of HD [24].

The most common histologic subtype in children is the nodular sclerosing variety representing ~70–80 % of adolescent HD and 50 % of HD in children under 10 years of age [16]. On histologic examination thick collagen bands divide the lymphoid tissue into nodules that are full of lacunar cells, a Reed-Sternberg variant, surrounded by clear space, lymphocytes, eosinophils, and histiocytes (Fig. 24.5). In the mixed cellularity subtype, there are a larger number of malignant cells with occasional necrosis. This mixed cellularity subtype is more common in younger children (30–35 %) and less common in adolescents (10 %). The lymphocyte predominant subtype, which is associated with early diagnosis and good prognosis, contains mature lymphocytes, benign histiocytes, and an occasional Reed Sternberg cell. The lymphocyte depletion variant as the name implies has few lymphocytes and increased Reed-Sternberg cells. Although this variant is rare in children, it is usually diagnosed at an advanced stage and has a poor prognosis.

## Clinical Presentation

More than 90 % of Hodgkin's patients present with painless lymphadenopathy, and greater than 80 % of these cases involve the cervical and supraclavicular lymph nodes. The nodes are firm, rubbery and can be single or multiple. On physical examination, hepatic or splenic enlargement may be noted suggesting metastatic disease. Patients with mediastinal involvement may present with cough, stridor, dyspnea, dysphagia, or superior vena cava (SVC) syndrome due to compression of the airway, esophagus, or blood vessels. Children with mediastinal HD may occasionally present with hypertrophic osteoarthropathy, characterized by excessive skin and bone on the distal parts of their extremities [25, 26]. Patients with retropharyngeal lymphoma may present with an acute airway obstruction (Fig. 24.6). If a transoral needle biopsy is attempted, rapid tumor enlargement may occur leading to airway obstruction. Up to one-third of all patients present with systemic symptoms of fever, night sweats, weight loss, fatigue and pruritis. The pattern of fever is variable, and weeks of high fevers can be separated by afebrile periods. Only 20 % of children have the fevers and night sweats common to many adult patients with HD [27–29]. Patients may present with various immunologic disorders such as treatment-resistant idiopathic thrombocytopenic purpura (ITP), Coombs'-positive hemolytic anemia, or rarely

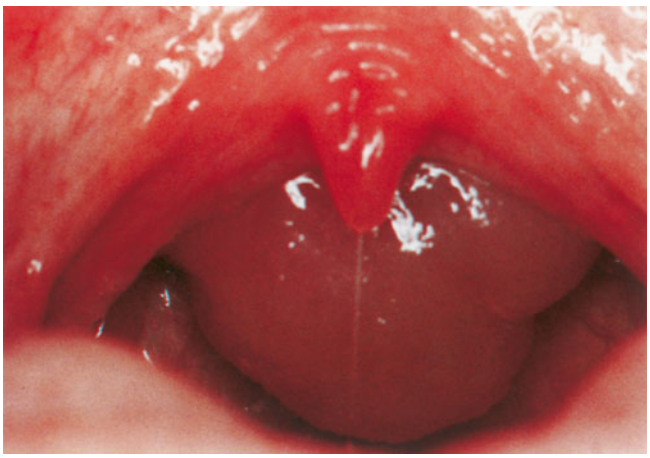

**Fig. 24.6** Lymphoma of the nasopharynx

autoimmune neutropenia [28, 30]. In Hodgkin's patients, ITP may occur at any time including at diagnosis, during treatment, and even after splenectomy [31, 32].

## Diagnostic Evaluation

The diagnosis of Hodgkin's disease can be made only after histologic examination of an affected lymph node. This node must show classic HRS cells or their variants for a diagnosis of HD, and further subclassification requires information about the architecture and proportions of various cells including HRS cells, lymphocytes, eosinophils, neutrophils, and collagen [33]. In order to obtain enough tissue with proper preservation of lymph node architecture, an open biopsy is often performed. Successful diagnosis for lymphomas may be done using core needle biopsies or even fine needle aspiration with flow cytometry in experienced centers [34, 35]. Excisional biopsy is usually performed. If the node cannot be removed without damage to surrounding vital structures, incisional biopsy is appropriate. If Reed-Sternberg cells are seen, a diagnosis may be made on frozen sections though more tissue should be sent for routine staining, immunophenotyping, and cytogenetic analysis.

Prior to lymph node excision, a patient must be assessed for mediastinal masses. Intubation of a patient with a large anterior mediastinal mass may result in acute respiratory failure due to compression of the mass on the trachea after voluntary respirations have ceased. It is essential that a CXR be obtain prior to surgical intervention. If the CXR is suspicious, a chest CT should be performed. If significant airway compression is noted on exam or radiography, other methods of diagnose such as flow cytometry, bone marrow biopsy, and/or thoracentesis should be employed. If a diagnosis still cannot be obtained, consideration of empiric treatment verse lymph node biopsy while sitting upright under local anesthesia may be considered [36].

Laboratory studies include a complete blood cell count with white blood cell differential, erythrocyte sedimentation rate, serum alkaline phosphatase, renal and liver function tests, lactate dehydrogenase, urinalysis, and baseline thyroid function tests. Hodgkin's lymphoma spreads initially to contiguous lymph nodes and later can involve liver, lung, bone marrow and the central nervous system so further workup should focus on these areas. Imaging studies include anteroposterior (AP) and lateral chest radiographs, computed tomography (CT) scans of the high neck, chest, abdomen and pelvis, CT of the primary site and PET scan. A chest x-ray provides information on mediastinal involvement which may be present in up to 75 % of children. Chest CT provides information about pulmonary as well as mediastinal involvement. In addition to pulmonary metastasis, HD can affect the chest wall, pleura and pericardium [37, 38]. As an alternative or adjunct to CT scanning, MRI may be used [39]. PET is especially useful to evaluate response to therapy since it can differentiate fibrosis from active disease and can be helpful in assessing response to treatment [40, 41]. Both a bone marrow aspirate and biopsy are necessary for advanced stage disease and in all stages with systemic symptoms though its utility in early Hodgkin's is unclear.

## Staging

Both children and adults with Hodgkin's disease are staged based on the Ann Arbor Classification system (Table 24.3) [42]. This classification system incorporates numbers of lymph nodes involved, location of affected lymph nodes, extranodal involvement, and systemic symptoms [42, 43]. Subclassification A indicates asymptomatic disease while subclassification B indicates symptoms including fever, night sweats and unexplained weight loss of at least 10 % of body weight over a 6-month period. Improved imaging and use of systemic chemotherapy in all HD patients has made staging laparotomy unnecessary. Laparotomy/ laparoscopy may be helpful in the following situations: intraabdominal lymph node between 1 and 3 cm, focal splenic abnormalities, focal hepatic abnormalities, and areas of abdominal uptake on gallium scan not otherwise explainable. Focal hepatic abnormalities may be best assessed by CT-guided needle biopsy. When staging laparotomy is/was performed, it involved splenectomy, liver biopsy, and sampling of splenic hilar, celiac, porta hepatis, mesenteric, iliac and para-aortic lymph nodes though these criteria were not universal.

## Management

Hodgkin's disease should be managed with a multidisciplinary approach at a pediatric oncology center. Hodgkin's is

**Table 24.3** Ann Arbor staging classification for Hodgkin's disease [42]

| Stage | Definition |
|---|---|
| I | Involvement of single lymph node region (I) or of a single extralymphatic organ or site ($I_E$) |
| II | Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and one or more lymph node regions on the same side of the diaphragm ($II_E$) |
| III | Involvement of lymph node regions on both sides of the diaphragm (III), which may also involve the spleen ($III_s$), an extralymphatic organ or site ($III_E$) or both (IIISE) |
| IV | Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node involvement |
| A | No systemic symptoms |
| B | Presence of systemic symptoms prior to admission including unexplained fever, night sweats, or weight loss greater than 10 % of body weight in 6 months prior to diagnosis |

sensitive to both chemotherapy and radiation. Previously HD was treated with high-dose radiation therapy and later stage disease was treated with MAPP (mechlorethamine, vincristine, procarbazine, prednisone) and radiation [44]. Concerns existed over the long-term effects of this high dose radiation and chemotherapy on growth and development as well as the development of secondary malignancies.

Current recommendations for the treatment of HD include chemotherapy for all stages. Early stage Hodgkin's disease (clinical stage I and IIA) is well controlled by chemotherapy followed by field radiation. Multiple chemotherapeutic regimes have been used in early stage HD with good results. Cycles of VAMP (vinblastine, doxorubicin, methotrexate, prednisone) followed by field ration between 15 and 25.5 Gy showed a 99 % and 96 % disease free 5-year and 10 year survival, respectively [45]. Treatment with OPPA (vincristine, procarbazine, prednisone, doxorubicin in males) and OEPA (vincristine, etoposide, prednisone, doxorubicin) followed by field radiation of 25–35 Gy has also been used with a 99 and 94 % 5-year disease free survival respectively [46].

Hodgkin's patients considered to have advanced disease include: patients with stage IIIa, IIIb, or IV; patients with B-symptoms; or patients with a mediastinal mass greater than one-third the diameter of the chest. Treatment for these patients includes various chemotherapy combinations and various levels of field radiation. Current treatment regimes may be found on the National Cancer Institute (NCI) website and the Children's Oncology Group (COG) website. Traditionally these patients were treated with MOPP and ABVD in addition to field radiation of 20–35 Gy with a 5-year disease free survival of 87–93 % [47]. Radiation dosing was based on response to chemotherapy. With more recent treatment regimes, patient may have a 5-year survival of 95–96 % [46, 48]. This treatment may be tailored based on response and gender [49]. Patients with refractory or relapsing disease of treated with a variety of second line chemotherapy protocols with or without subsequent autologous cell transplantation [50, 51]. Other chemotherapeutic combinations are under investigation with the goal of decreasing drug toxicities and secondary malignancies.

The initial complete remission response rate for all stages of Hodgkin's disease is over 90 %. For stage I or IIA Hodgkin's disease, 5 year disease-free survival for children is approximately 93–99 % [46, 52]. For patients with advance stage Hodgkin's disease the 5 year survival is 87–97 % with a 5 year event free survival of 88 % [46, 47]. Factors that predict a poorer prognosis include male gender, disease stage IIB, IIIB, or IV, bulky mediastinal disease, WBC >13,500/μL, and hemoglobin <11.0 g/dl. Using a point system, giving 1 point for each of the above-mentioned criteria, 5-year disease free survival is 94, 85, 71, and 49 % for 0–1, 2, 3, and 4–5 points respectively [53].

After remission, patients need lifelong close follow-up for recurrent disease and long-term effects of chemotherapy and radiation. When relapse does occur, it is usually within the first 3 years and in associated with a poor prognosis [54]. Treatment for recurrent Hodgkin's disease includes another combination chemotherapy and/or autologous bone marrow or stem cell transplantation. Long-term complications of the radiation and chemotherapeutic interventions include impaired growth, thyroid dysfunction, gonadal dysfunction, cardiopulmonary toxicity, and strokes. Up to 7.6 % of HD survivors will have a secondary malignancy at 20 years. These secondary malignancies most often include thyroid cancer, breast cancer, and sarcomas [55, 56].

## Non-Hodgkin's Lymphoma

Childhood non-Hodgkin's lymphoma (NHL) accounts for 10 % of all pediatric malignancies and about 25 % of all head and neck malignancies. The head and neck is the primary site for NHL 10–15 % of the time, and is most commonly located in the lateral cervical lymphatic chain. Up to 30 % of primary head and neck NHL are extranodal and include lymphoid tissue in Waldeyer's ring, the orbit, mandible, sinuses, salivary gland, and thyroid gland. NHL accounts for approximately 750–800 new cases a year in the United States. Burkitt's and Burkitt-like tumors are most common in 5–14 year olds and diffuse large cell lymphomas are most com-

mon in 15–19 year olds. It is uncommon in children under the age of 3. NHL is twice as common in whites and 2–3 times more common in boys [57].

There is a form of endemic Burkitt's lymphoma in Equatorial African which is distinctive from the sporadic Burkitt's lymphoma noted in the rest of the world. In Africa, endemic Burkitt's lymphoma has an annual incidence of 10 per 100,000 and is associated with EBV in 95 % of cases. It most commonly present as a mass in the jaw, abdomen, orbit, central nervous system, and paranasal sinuses [58]. Sporadic Burkitt's has an annual incidence of 2 per 100,000 children, with only a 15 % association with EBV and more commonly presents in the abdomen, bone marrow, and nasopharynx. In addition to EBV, other immunodeficiency syndromes such as ataxia-telangiectasia, Wiskott-Aldrich syndrome, and X-linked lymphoproliferative syndrome are associated with NHL [59]. There is also an increased incidence of NHL in children receiving immunosuppressive therapy and those with AIDS. Up to 1.6 % of children with HIV will develop lymphoma, with Burkitt's or large cell being the most common [60]. HIV and other viral pathogens, immunosuppressive states, environmental toxins, and commercial products such as hair dyes have been associated with Burkitt's lymphoma.

## Pathology and Genetics

Childhood NHL consists of three major subtypes: mature B-cell NHL (Burkitt, diffuse large B-cell lymphoma), lymphoblastic lymphoma, and anaplastic large cell lymphoma. There is also lymphoproliferative disease associated with immunodeficiency in children and other rare NHL in children including pediatric follicular lymphoma, peripheral T-cell lymphoma, and others more common in adults. The World Health Organization has developed a classification system that divides common pediatric lymphomas based on their phenotype and differentiation [61]. On histologic examination, lymphoma cells replace normal lymph node tissue. In the head and neck region, the most common lymphoma is B cell lymphoma specifically small-cell noncleaved lymphoma. Histologically, the cells are undifferentiated, small, round lymphoid cells with detectable surface immunoglobulin. This uniform shape and size gives a 'starry-sky' histology classic for Burkitt's lymphoma as shown in Fig. 24.7.

Both B and T cell lymphomas are associated the known chromosomal translocations affecting DNA binding transcription factors [62]. Up to 85 % of Burkitt's patients have a t(8;14)(q24;q11) translocation resulting in transfer of the c-myc oncogene from chromosome 8 to the site of the immunoglobulin heavy chain locus on chromosome 14 [63]. This translocation causes activation of c-myc and increased proliferation of lymphoma cells. The location of the breakpoint on chromosome 8 is variable suggesting different molecular subtypes of Burkitt's lymphoma based on different mechanism of c-myc activation [59, 64–66]. In North American Burkitt's lymphoma, the breakpoint is within the c-myc gene in more than 50 % of tumors [59, 67, 68]. Less commonly t(8;22) and t(2;8) results in translocation of lambda and kappa immunologic light chain genes, respectively, to a region distal to the c-myc gene on chromosome 8 [69, 70]. Chromosomal abnormalities have also been noted in patients with T cell lymphoblastic lymphoma including deletions of TAL1, TCR, HOX11, and RHOMB genes [71, 72].

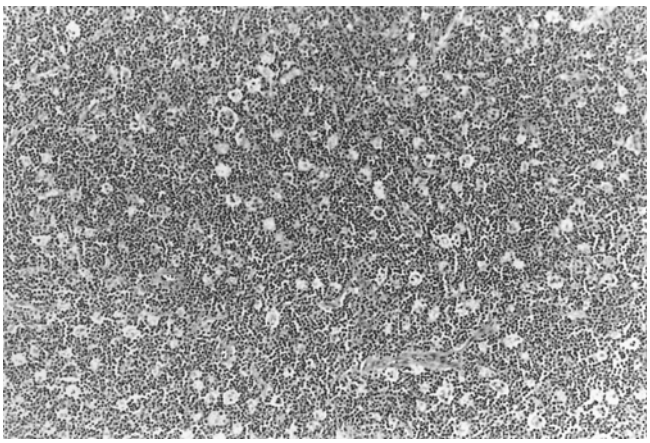

**Fig. 24.7** Photomicrograph demonstrating Burkitt's lymphoma with classic 'starry-sky' histology

## Clinical Presentation

Initially the NHL mass is painless but as rapid growth or compression of surrounding structures occurs, symptoms can develop. Symptoms are based on location of the primary tumor. Cervical NHL may produce neck pain, dysphagia, or dyspnea as tracheal or esophageal compression occurs. Rapidly enlarging tumors may produce mediastinal compression and associated respiratory distress or superior vena caval obstruction. Burkitt's lymphoma in Equatorial Africa most frequently presents with jaw involvement, especially in younger children. Jaw involvement in less common (~15 %) in sporadic Burkitt's lymphoma is not age-related [73, 74]. Children often have extranodal disease at the time of presentation which includes abdominal involvement (31 %), mediastinal involvement (26 %), or head and neck involvement (29 %). Central nervous system (CNS) and bone marrow involvement may also occur [63, 70]. Systemic symptoms are not as common in NHL as in Hodgkin's disease but are a poor prognostic sign.

## Diagnostic Evaluation

As with Hodgkin's lymphoma, an open biopsy should be performed to establish the diagnosis. An open excisional biopsy, or in the case of matted nodes, an incision biopsy, is usually needed to provide an adequate sample for histology, cytogenetics, flow cytometry, and molecular pathology. As with Hodgkin's disease, fine needle aspiration does not provide an adequate sample, and core biopsy may be done at centers with expertise in this area. Recommended laboratory studies include a complete blood cell count with white blood cell differential, erythrocyte sedimentation rate, serum alkaline phosphatase, renal and liver function tests, lactate dehydrogenase, urinalysis, uric acid levels, phosphate levels, and baseline thyroid function tests. Imaging studies should include anteroposterior (AP) and lateral chest radiographs, CT scans of the high neck, chest, abdomen and pelvis, bone scan, and CT/MRI of the primary site. A chest x-ray provides information on mediastinal involvement. Chest CT also provides information about pulmonary as well as mediastinal involvement. PET scan are being used with increasing frequency especially in adults though its use in pediatric is still growing [75, 76]. Both a bone marrow aspirate and biopsy are necessary for staging of the disease. A lumbar puncture is also needed to evaluate for CNS involvement.

Prognostic factors include age, site of disease, chromosomal abnormalities, tumor burden, and response to therapy. Adolescents and infants tend to have a worse outcome compared to other children [77, 78]. Patients with low-stage disease tend to do better while those with CNS involvement and more advanced disease tend to have worst outcomes [79–81]. Abnormalities of 7q or deletion of 13q have worse outcomes [82, 83] LDH as a surrogate for tumor burden is associated with worse outcomes. As expected poor responders have a worse response with a 30 % event free survival [84].

## Staging

Classification and The St. Jude's Staging system is used to characterize NHL (Table 24.4) [85]. Tumor burden as measured by disease stage, serum LDH, and serum IL2 have all been shown to predict outcome [86–88]. Each category of NHL has typical immuno-phenotype, presentation, chromosomal translocation, and genes affected (Table 24.5).

## Treatment

Treatment protocols for NHL are based on histologic subtype and disease stage. Chemotherapy remains the primary treatment for all histologic variants and stages of NHL. Radiation therapy is reserved for cases of relapse, CNS involvement, and emergency situations such as airway compromise due to mediastinal involvement. In general, surgery is used for diagnosis and perhaps in an emergent setting such as airway compromise. In the absence of surgical emergencies, there is no role for debulking procedures.

Due to rapid turnover of lymphoblasts, patients often present with hyperuricemia, hyperphosphatemia, and renal dysfunction. As chemotherapy is begun, tumor lysis syndrome may occur which is characterized by a rapid lysis of tumor cells resulting in increase uric acid, phosphate, potassium, and purines in the blood and thus renal tubules that may result in increasing renal dysfunction. Patients must be aggressively hydrated before and during chemotherapy. Alkalization of the urine and allopurinol may be helpful in the treatment of hyperuricemia. In some cases, dialysis may be required to manage the renal failure associated with severe tumor lysis syndrome.

For limited disease (stage 1 and 2), treatment consists CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) or COMP (cyclophosphamide, vincristine, methotrexate, prednisone) which both result in a 5 year survival rate of 85–95 % [89–96]. For advanced disease with high tumor burden, high dose regimens and the addition chemotherapy has improved survival rates from 20 % to around 80 % in recent years [89, 96–98]. High stage B-cell NHL with a multi-drug regime have 80–90 % long term survival [80, 84]. For patients with CNS involvement, intrathecal chemotherapy is added to the traditional chemotherapeutic regime.

For Burkitt's lymphoma, patients receive 2–6 months of with COMP and high dose methotrexate and/or cytarabine or

**Table 24.4** St. Jude system for non-Hodgkin's lymphoma [85]

| Stage | Definition |
|---|---|
| I | Single nodal or extranodal tumor site, excluding mediastinum or abdomen |
| II | Single extranodal tumor with regional lymph node involvement; two or more nodal areas on the same side of diaphragm; two single extranodal tumors with or without regional lymph node involvement on same side of the diaphragm; |
| | Primary gastrointestinal tract tumor with or without associated mesenteric node involvement grossly resected |
| III | On both sides of the diaphragm: two single extranodal tumors; two or more nodal areas All primary intrathoracic tumors |
| | All extensive, unresectable primary intra-abdominal disease |
| | All primary paraspinal or epidural tumors |
| IV | Any of the above with initial CNS and/or bone marrow involvement |

**Table 24.5** Major histopathological categories of non-Hodgkin lymphoma in children and adolescents [209]

| Category (WHO classification/updated REAL) | Category (working formulation) | Immuno-phenotype | Clinical presentation | Chromosome translocation | Genes affected |
|---|---|---|---|---|---|
| Burkitt and Burkitt-like lymphomas | ML small noncleaved cell | Mature B cell | Intra-abdominal (sporadic), head and neck (non-jaw, sporadic), jaw (endemic), bone marrow, CNS | t(8;14)(q24;q32), t(2;8)(p11;q24), t(8;22)(q24;q11) | C-MYC, IGH, IGK, IGL |
| Diffuse large B-cell lymphoma | ML large cell | Mature B cell; maybe CD30+ | Nodal, abdominal, bone, primary CNS (when associated with immunodeficiency), mediastinal | No consistent cytogenetic abnormality identified | |
| Lymphoblastic lymphoma, precursor T-cell leukemia, or precursor B-cell lymphoma | Lymphoblastic convoluted and non-convoluted | Pre-T cell | Mediastinal, bone marrow | MTS1/p16ink4a; Deletion TAL1 t(1;14)(p34;q11), t(11;14)(p13;q11) | TAL1, TCRAO, RHOMB1, HOX11 |
| | | Pre-B cell | Skin, bone, mediastinal | | |
| Anaplastic large cell lymphoma, systemic | ML immunoblastic or ML large | CD30+ (Ki-1+) | Variable, but systemic symptoms often prominent | t(2;5)(p23;q35); less common variant translocations involving ALK | ALK, NPM |
| | | T cell or null cell | | | |
| Anaplastic large cell lymphoma, cutaneous | | CD30+ (Ki-usually) | Skin only; single or multiple lesions | Lacks t(2;5) | |
| | | T cell | | | |

Adapted from Percy et al. [16]
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*CNS* central nervous system, *ML* malignant lymphoma, *REAL* Revised European-American Lymphoma, *WHO* World Health Organization

**Table 24.6** Standard treatment options for low-stage non-Hodgkin lymphoma [209]

| Disease | Treatment options |
|---|---|
| Burkitt lymphoma or diffuse large B-cell lymphoma (DLBCL) (completely resected) | GER-GPOH-NHL-BFM-95 (R1): two cycles of chemotherapy |
| | COG-C5961 (FAB/LMB-96) (Group A): two cycles of chemotherapy |
| Burkitt lymphoma or DLBCL (nonresected stage I/II) | GER-GPOH-NHL-BFM-95 (R2): prephase + four cycles of chemotherapy (4-h methotrexate infusion) |
| | COG-C5961 (FAB/LMB-96) (Group B): prephase + four cycles of chemotherapy (reduced-intensity arm) |
| | POG-8314/POG-8719: three cycles of chemotherapy (no radiation or maintenance therapy) |
| Lymphoblastic lymphoma | GER-GPOH-NHL-BFM-95: induction, consolidation, intensification, and maintenance therapy (2 years of total therapy); ALL-type induction and consolidation, high-dose methotrexate courses × 4, and ALL-type maintenance therapy (2 years of total therapy) |
| Anaplastic large cell lymphoma | POG-8314/POG-8719: three cycles of chemotherapy (no radiation or maintenance therapy) |
| | GER-GPOH-NHL-BFM-90: prephase + three cycles of chemotherapy (only for completely resected disease). |
| | FRE-IGR-ALCL99: prephase + six cycles of chemotherapy (for disease not completely resected) |

Permission pending from NCI

by the addition of etoposide and ifosfamide [89, 90, 94]. Large cell lymphoma is treated with a CHOP combination resulting in a 50–70 % event free survival rate 3 years [99–102]. Research is underway examining the benefits of methotrexate, cytarabine, ifosfamide, and carboplatin.

Chemotherapy options based on specific diagnosis (including Burkitt's lymphoma, diffuse large B cell lymphoma, lymphoblastic lymphoma, anaplastic large cell lymphoma) are outline in Table 24.6. Further details on current treatment regimes may be found on the National Cancer Institute (NCI) website and the Children's Oncology Group (COG) website.

Overall, treatment for lymphoblastic lymphoma has improved 5 year survival to 90 % [79, 103]. With current treatment regimes, high-stage anaplastic large cell lymphoma has disease free survival rates of 60–75 % [104, 105] Cure rates for limited disease are greater than 90 % and range from 60 to 90 % for advanced disease [52, 79, 96, 106]. Current therapy for recurrent NHL includes chemotherapy and possible bone marrow transplantation but overall prognosis is poor [64, 67, 107, 108].

## Thyroid Tumors

Thyroid cancer represents about 3 % of all childhood malignancies and 7 % of cancers arising in the head and neck with an incidence of 0.54 per 100,000. Due to improved detection and stable mortality, the prevalence of thyroid cancer has increased [109–111]. The peak incidence of thyroid cancer in children occurs between 10 and 18 years of age, and females outnumber males 2:1 over the age of 10. In children under the age of 10, males tend to outnumber females. In younger children (age 0–4), medullary thyroid carcinoma is more common. As age increase, incidence of papillary histology increases.

The development of thyroid cancer is associated with radiation exposure. With decreasing use of radiation for benign disease, the incidence of thyroid cancer has decreased. Historically, up to 80 % of all new cases of thyroid cancer are related previous radiation to the neck for a variety of benign disorders including enlarged thymus, hypertrophied tonsils and adenoids, hemangiomas, nevi, eczema and cervical adenitis [112]. Diagnostic radiation exposure has been associated with increased incidence of cancer. Prenatal exposure to diagnostic radiation increases risk of childhood cancer by 1.4–2.1 fold [113]. The use of computed tomography (CT) scan is estimated to increase risk of cancer by as much as one fatal cancer for each 1000 CT scans [114]. For head and neck CT scans in children, the estimated increased risk of thyroid cancer is 65 per million patients [115]. Due to this increased risk of cancer associated with diagnostic imaging, there is increased attention to decreasing images if possible or at least decreasing intensity of radiation dose or area of imaging when possible.

Treatment for previous childhood malignancy is associated with an increased incidence of thyroid carcinoma. Most commonly these children had Hodgkin's lymphoma, whose treatment leads to the development of thyroid nodules and thyroid cancer [116, 117]. Up to 50 % of children receiving irradiation and chemotherapy for Hodgkin's disease, leukemia and other head and neck malignancies develop elevated thyroid stimulating hormone (TSH) levels within 1 year of treatment [117, 118]. Not only radiation but also alkylating agents predispose to thyroid cancer. The latency between previous treatment and development of thyroid cancer is up to 25–30 years which emphasizes the importance of continued followed in these patients [119–121]. Increased radiation dose, female gender, and age (12–16 years) were associated with increased incidence of secondary malignancy [122].

The association of thyroid cancer and radiation exposure was again demonstrated in the Republic of Belarus after the 1986 Chernobyl nuclear power plant catastrophe [123, 124]. Within 4 years after the accident, a 62-fold increase in thyroid tumors was noted. After a decade, there was a 10 fold increase in aggressive papillary carcinomas in these children [125]. These children were noted to have aggressive papillary carcinomas in younger children with an equal prevalence in males and females [126]. Factors for the development of thyroid cancer following radiation exposure include higher radiation doses, young age at radiation initiation and female sex.

## Pathology and Genetics

The histologic subtypes of thyroid cancer include papillary or mixed (70–80 %), follicular (20 %) medullary (5–10 %) and rarely, anaplastic [119, 121, 127, 128]. Histologically, papillary carcinoma will consist of papillae of epithelial cells arranged often with lymphocytic infiltrates and psammoma bodies (Fig. 24.8). In follicular carcinoma, malignant adenomatous cell form follicles with nuclear abnormalities, capsular invasion or vascular invasion. Any tumor with papillary components is considered a papillary carcinoma. If follicular characteristics are also present, it is considered a papillary tumor with follicular architecture (Fig. 24.9). Approximately 5 % of thyroid carcinomas are medullary thyroid carcinoma (MTC) that arises from the parafollicular C cells, derived from neural crest cells (Fig. 24.10). Histologically, these tumors have granular cytoplasm with islets of regular, undifferentiated cells.

The RET (REarranged during Transfection) gene plays an important role in the development of thyroid cancer. The RET proto-oncogene is a receptor tyrosine kinase molecule located on chromosome ten that signals via the MAPK pathway. RET gene rearrangement is associated with papillary thyroid cancers. These rearrangements place RET adjacent to various ubiquitously expressed genes. The fusion genes are termed RET/PTC, and they exhibit increased expression of tyrosine kinase with histologic and prognostic significance. The most common is RET/PTC1 and RET/PTC3. PTC 1 is associated with papillary carcinoma and is more

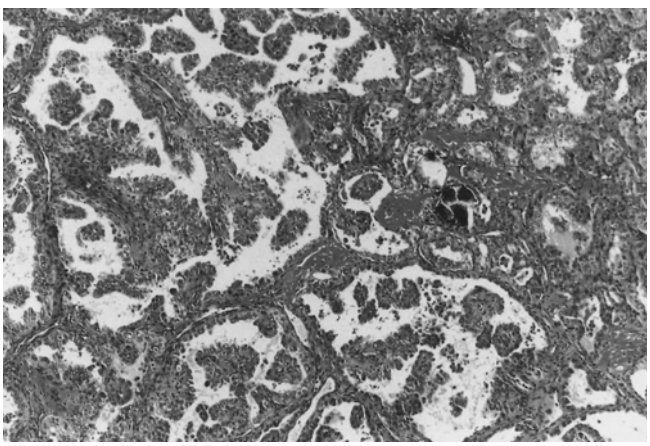

**Fig. 24.8** Photomicrograph demonstrating papillary thyroid carcinoma with papillary architecture

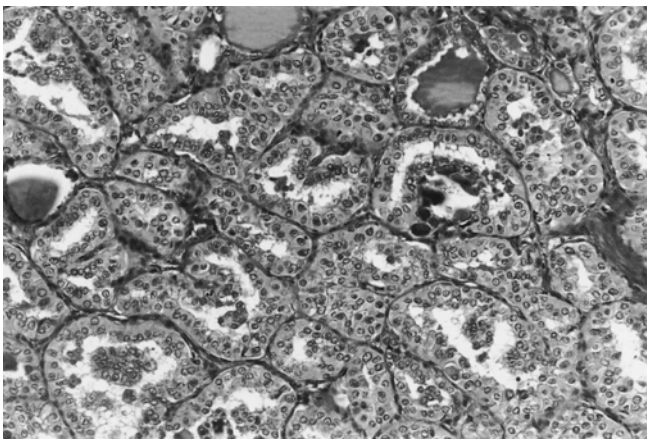

**Fig. 24.9** Photomicrograph demonstrating follicular variant of papillary thyroid carcinoma

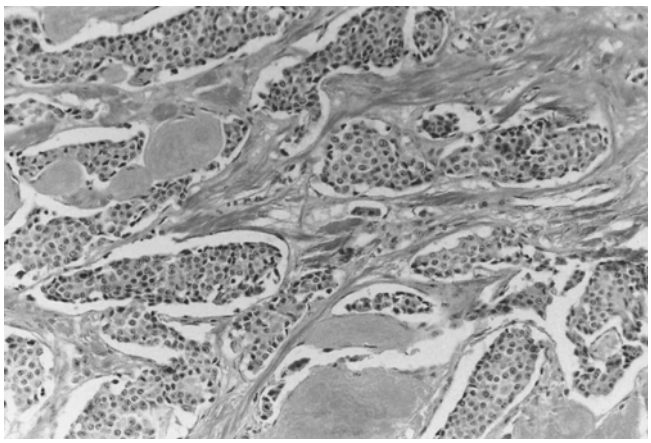

**Fig. 24.10** Photomicrograph demonstrating medullary thyroid carcinoma with amyloid stroma and epithelial cytology

differentiated and slow growing while PTC2 is associated with more aggressive less differentiated follicular carcinoma [129]. RET/PTC rearrangements are found in 40–70 % of pediatric thyroid cancer patients [130].

This RET gene rearrangement occur in 5–80 % of radiation induced thyroid tumors [129–133]. Some studies suggest that particular RET fusion gene combination are correlated with particular histologic subtypes. For example, one particular inversion of chromosome 10, PTC1, is more often associated with papillary carcinoma that tends to be more slow growing with clearer differentiation while PTC3 is more often associated with follicular carcinoma which tends to grow more quickly, more aggressively, and with less differentiation [129]. Other genetic alterations include increased copy numbers and deletions of various chromosomes, and gene alterations including CAMK2N1, AK1, DHRS3, and PDE9A [126]. Recent studies are investigating the specific gene expression signature of post-radiation induced thyroid tumors [134].

Medullary thyroid carcinoma (MTC) may occur sporadically, in patients having multiple endocrine neoplasia (MEN) type 2A or 2B, or in the familial medullary thyroid carcinoma (FMTC) syndrome. As in papillary thyroid cancer, the RET proto-oncogene also plays an important role in the development of medullary thyroid carcinoma as well as MEN syndromes in general [135–137]. These RET mutations affect the development of neural crest derived tissues. Various RET mutation may be found in as many as s 40 % of sporadic non-familial medullary thyroid carcinomas. Medullary thyroid carcinoma is usually the first tumor to develop in MEN 2 patients and is often the cause of death in these patients. Most patients with MEN 2B have a germline mutation of methionine to threonine at codon 918 (M918T). Mutation of alanine to phenylalanine at codon 883 (A883F) has also recently been identified and is associated with a more indolent form of medullary thyroid carcinoma [138].

## Clinical Presentation

Patients usually presents with a thyroid mass, an enlarged cervical lymph node, or with both of these findings. Physical exam findings concerning for malignancy include firm nodule and nodule that are fixed to surrounding structures. Palpable cervical adenopathy is present in up to two-thirds of cases and adenopathy may be the only indication of thyroid cancer even in the absences of a thyroid nodule [128]. Other symptoms may include dysphagia, dyspnea or dysphonia if tracheal or esophageal compression has occurred [120, 127, 139, 140]. Hoarseness indicates compression or invasion of the recurrent laryngeal nerve.

The lung is the most common site for metastases, aside from lymph nodes, with an incidence of about 6 % at diagnosis [141, 142]. This is often accompanied by cervical lymph node metastases. Up to 50 % of patients with papillary tumors have metastases to local cervical or mediastinal lymph nodes at the time of diagnosis [143]. Follicular tumors have less local lymph node disease but increased bone metastases. Cervical adenopathy and/or distant metastases are usually the first sign of medullary thyroid carcinoma.

Patients with MEN often have a delayed diagnosis due to vague initial symptoms. Studies have found that during the first year of life, less than 20 % of carriers were found to have typical MEN 2B phenotypes. Characteristics that were described included constipation and inability to cry tears. The median age of diagnosis of MTC was 13–16 years in the M918T carriers [144, 145]. One-third of patients had MEN diagnosis before surgery while two-thirds were diagnosed postoperatively [145]. Once diagnosis was made, patients presented with oral symptoms (96 %), ocular abnormalities (91 %), GI symptoms (71 %), musculoskeletal anomalies (75 %), and pheochromocytomas (28 %) [144].

With delay in diagnosis, these patient tended to present with more advanced tumor, nodes, and metastases with higher levels of preoperative calcitonin levels. Early detection and family screening are needed to improve treatment and survival.

## Diagnostic Evaluation

Initial evaluation of a thyroid mass should begin with thyroid function tests, which are normal in the majority of cases. Laboratory values include thyroid-stimulating hormone (TSH), T3, T4, urine calcium, and calcitonin. Imaging of a suspicious nodule usually starts with an ultrasound study. An ultrasound can determine lesion characteristics, identify abnormal lymph nodes, and serve as a guide for surgery [146].

The pathologic diagnosis can either be established using thin-needle aspiration cytology or by frozen-section though there is some controversy over the accuracy of frozen-sections in evaluating follicular lesions. The use of FNA in the adult population is well established and has decreased the incidence of thyroidectomy for benign conditions and has increased the number of surgical patients with carcinoma [146, 147]. The sensitivity and specificity of FNA in prediction malignancy is 88 % and 84 % respectively [148]. Limitations of FNA include a false negative rate from 1 to 6 %, availability of an experienced cytopathologist, and an inability to differentiate benign from malignant follicular lesions.

Since the pattern of thyroid disease in adolescents is similar to that in adults, FNA is an acceptable way to evaluate thyroid nodules in this population and has been demonstrated useful in older children [149–151]. In children younger than 13 years of age, aspiration is more difficult to perform and the pattern of benign disease is different than in adults. The natural history of these lesions and the safety of a non-operative approach is unknown. Therefore, FNA should probably not be used in young children, and all children younger than 13 years of age should undergo surgical excision. A FNA may reveal cancer, a benign lesion, or a lesion suspicious for cancer. As with adults, benign nodules may be followed with serial physical and ultrasound examinations; resection is indicated if the nodule increases in size. Surgical resection is indicated for all malignant or suspicious nodules.

## Staging

Thyroid cancer staging is based on the American Joint Committee on Cancer (AJCC) staging by TNM classification (Table 24.7 [152]).

## Management

Since there are no prospective clinical trials compare surgical management of thyroid cancer in children, there is some controversy over the best surgical management of these patients. If the cytology of the thyroid mass is benign, observation with serial US every 6–18 months is recommended. If the lesion is stable, one may observe with US. If the lesion enlarges over time, repeat FNA is warranted. If a benign lesion is causing compressive symptoms or cosmetic deformation, excision should be considered. If a benign lesion continues to grow after repeated FNA biopsies, resection may be considered [153].

If repeat FNA of a lesion in an adolescent reveals non-diagnostic aspirates, the surgeon needs to weight the risks and benefits of close observation verse surgical resection. If the FNA is suspicious for papillary thyroid cancer, surgical excision is recommended. If there is a solitary indeterminate nodule present, lobectomy is recommended. If the patient presents with an indeterminate nodule >4 cm, atypia, family history, radiation history, or bilateral disease, a thyroidectomy is recommended. Lobectomy may be considered sufficient if the lesion is less than 1 cm, low risk pathology, unifocal, intrathyroidal papillary carcinoma, no family history, no radiation history, and normal nodes [153].

For differentiated thyroid carcinoma the most commonly recommended surgical options include either total or subtotal thyroidectomy. There is no difference in mortality or morbidity in patients having a total or subtotal thyroidectomy. The mortality rates ranges from 0 to 17 % up to 28 years after treatment [119, 121, 128, 140]. Aggressive resection including total thyroidectomy, with lymph node dissection if the regional nodes are involved, has shown to increase local control of the tumor [119, 121, 128, 154]. Prophylactic central compartment dissection is recommended for papillary thyroid cancer that is T3 or T4. Therapeutic central lymph node dissection is recommended if positive nodes in that compartment. Lateral neck dissection is recommended if clinically positive or biopsy positive nodes are noted. Radioiodine ablative therapy is also most effective after total thyroidectomy since there is less thyroid tissue to absorb radionuclide. Also, if total thyroidectomy is performed, serum thyroglobulin levels may be used to monitor for tumor recurrence.

However, differentiated thyroid carcinoma in children is a relatively indolent disease and survival is apparently not related to the extent of gland removal so total thyroidectomy is not necessarily required [119–121, 128, 140]. With total thyroidectomy, there is an increased incidence of major surgical complications, including injury to the recurrent laryngeal nerve 0–24 % and hypoparathyroidism [121, 128, 141, 155]. Currently, a consensus is immerging that aggressive resection for differentiated thyroid cancer in children is the

**Table 24.7** The American Joint Committee on Cancer (AJCC) has designated staging by TNM classification to define thyroid cancer [153].

| Primary tumor (T)[a] | | | |
|---|---|---|---|
| TX | Primary tumor cannot be assessed. | | |
| T0 | No evidence of primary tumor. | | |
| T1 | Tumor ≤2 cm in greatest dimension limited to the thyroid. | | |
| T1a | Tumor ≤1 cm, limited to the thyroid. | | |
| T1b | Tumor >1 cm but ≤2 cm in greatest dimension, limited to the thyroid. | | |
| T2 | Tumor >2 cm but ≤4 cm in greatest dimension, limited to the thyroid. | | |
| T3 | Tumor >4 cm in greatest dimension limited to the thyroid or any tumor with minimal extrathyroid extension (e.g., extension to sternothyroid muscle or perithyroid soft tissues). | | |
| T4a | Moderately advanced disease. | | |
| | Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve. | | |
| T4b | Very advanced disease. | | |
| | Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels. | | |
| T4a[b] | Intrathyroidal anaplastic carcinoma. | | |
| T4b[b] | Anaplastic carcinoma with gross extrathyroid extension. | | |
| Regional lymph nodes (N)[c] | | | |
| NX | Regional lymph nodes cannot be assessed. | | |
| N0 | No regional lymph node metastasis. | | |
| N1 | Regional lymph node metastasis. | | |
| N1a | Metastases to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes). | | |
| N1b | Metastases to unilateral, bilateral, or contralateral cervical (Levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (Level VII). | | |
| Distant metastasis (M) | | | |
| M0 | No distant metastasis. | | |
| M1 | Distant metastasis. | | |
| Anatomic stage/Prognostic groups[d] | | | |
| Stage | T | N | M |
| *Papillary or follicular* (*differentiated*) | | | |
| Younger than 45 years | | | |
| I | Any T | Any N | M0 |
| II | Any T | Any N | M1 |
| 45 years and older | | | |
| I | T1 | N0 | M0 |
| II | T2 | N0 | M0 |
| III | T3 | N0 | M0 |
| | T1 | N1a | M0 |
| | T2 | N1a | M0 |
| | T3 | N1a | M0 |
| IVA | T4a | N0 | M0 |
| | T4a | N1a | M0 |
| | T1 | N1b | M0 |
| | T2 | N1b | M0 |
| | T3 | N1b | M0 |
| | T4a | N1b | M0 |
| IVB | T4b | Any N | M0 |
| Stage IVC | Any T | Any N | M1 |
| *Medullary carcinoma* (*all age groups*) | | | |
| I | T1 | N0 | M0 |
| II | T2 | N0 | M0 |
| | T3 | N0 | M0 |

(continued)

**Table 24.7** (continued)

| Anatomic stage/Prognostic groups[d] | | | |
|---|---|---|---|
| Stage | T | N | M |
| III | T1 | N1a | M0 |
| | T1 | N1a | M0 |
| | T2 | N1a | M0 |
| | T3 | N1a | M0 |
| IVA | T4a | N0 | M0 |
| | T4a | N1a | M0 |
| | T1 | N1b | M0 |
| | T2 | N1b | M0 |
| | T3 | N1b | M0 |
| | T4a | N1b | M0 |
| | Stage IVB | T4b | Any N |
| IVB | T4b | Any N | M0 |
| IVC | Any T | Any N | M1 |
| *Anaplastic carcinoma*[e] | | | |
| IVA | T4a | Any N | M0 |
| IVB | T4b | Any N | M0 |
| IVC | Any T | Any N | M1 |

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[a]All categories may be subdivided: (s) solitary tumor and (m) multifocal tumor (the largest determines the classification)

[b]All anaplastic carcinomas are considered T4 tumors

[c]Regional lymph nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes

[d]Separate stage groupings are recommended for papillary or follicular (differentiated), medullary, and anaplastic (undifferentiated) carcinoma

[e]All anaplastic carcinomas are considered Stage IV

best surgically management in accordance with ATA guidelines [153]. Currently, it is recommended that children with differentiated thyroid carcinoma undergo near total thyroidectomy and modified neck dissection to remove gross disease if necessary. After surgical resection, $^{I131}$ remnant ablation and long-term suppressive thyroxin therapy may be used to treat residual disease and prevent recurrence. I131 is recommended for patients with known distant metastasis, gross extrathyroidal extension of the tumor regardless of tumor size, or primary tumor >4 cm. RAI (radioactive iodine) may be used in select patients with tumors 1–4 cm confined to the thyroid in patients that have lymph node metastasis or who are otherwise considered high risk. RAI is not recommended for lesions less than or equal to 1 cm, intrathyroidal disease, or multifocal cancer when all foci are less than 1 cm without high risk features. Since residual tumor may be treated with radioiodine, tumors involving the recurrent laryngeal nerve need not be aggressively resected. The nerve may be spared and residual tumor treated.

Recurrent laryngeal nerve injury and permanent hypoparathyroidism are the two most concerning iatrogenic injuries following thyroid resection [119–121, 128, 140]. These risks increase with the extent of resection and younger age of the patient [121]. To prevent damage to the recurrent laryngeal nerve, the nerve should be identified along its entire course and be seen entering the larynx. Intraoperative nerve stimulation is often used in the adult population to trace the course of the nerve and a recent report demonstrated the usefulness of this technique in children. The parathyroid glands should also be protected. If there is any question as to the viability of the parathyroid glands, they should be autotransplanted into the sternocleidomastoid muscle or nondominant forearm. A near total thyroidectomy leaving a few grams of tissue adjacent to the recurrent laryngeal nerve and the superior parathyroid gland should help prevent damage to these structures.

The technique for thyroidectomy is demonstrated in Fig. 24.11a–g. The patient is placed in a supine position initially with the neck extended by placing towel rolls beneath the shoulder. An incision is made 2–3 cm above the sternal notch in a skin crease (Fig. 24.11a). Dissection is carried down through the platysma muscle. Subplatysmal flaps are elevated superiorly to the thyroid notch and inferiorly to the sternal notch (Fig. 24.11b). The strap muscles are separated, not divided, in the midline to expose the thyroid gland (Fig. 24.11c). Crossing branches of the anterior jugular vein may need to be divided. Exposure of the desired lobe is obtained by retracting the strap muscles laterally. If the tumor has invaded the surrounding strap muscle, the strap muscles should be removed en bloc with the thyroid nodule. Ligation of the middle thyroid veins on the anterolateral surface in the middle of the thyroid gland to allows for proper mobilization (Fig. 24.11d). Prior to mobilizing the superior pole, the recurrent laryngeal nerve is identified. The thyroid

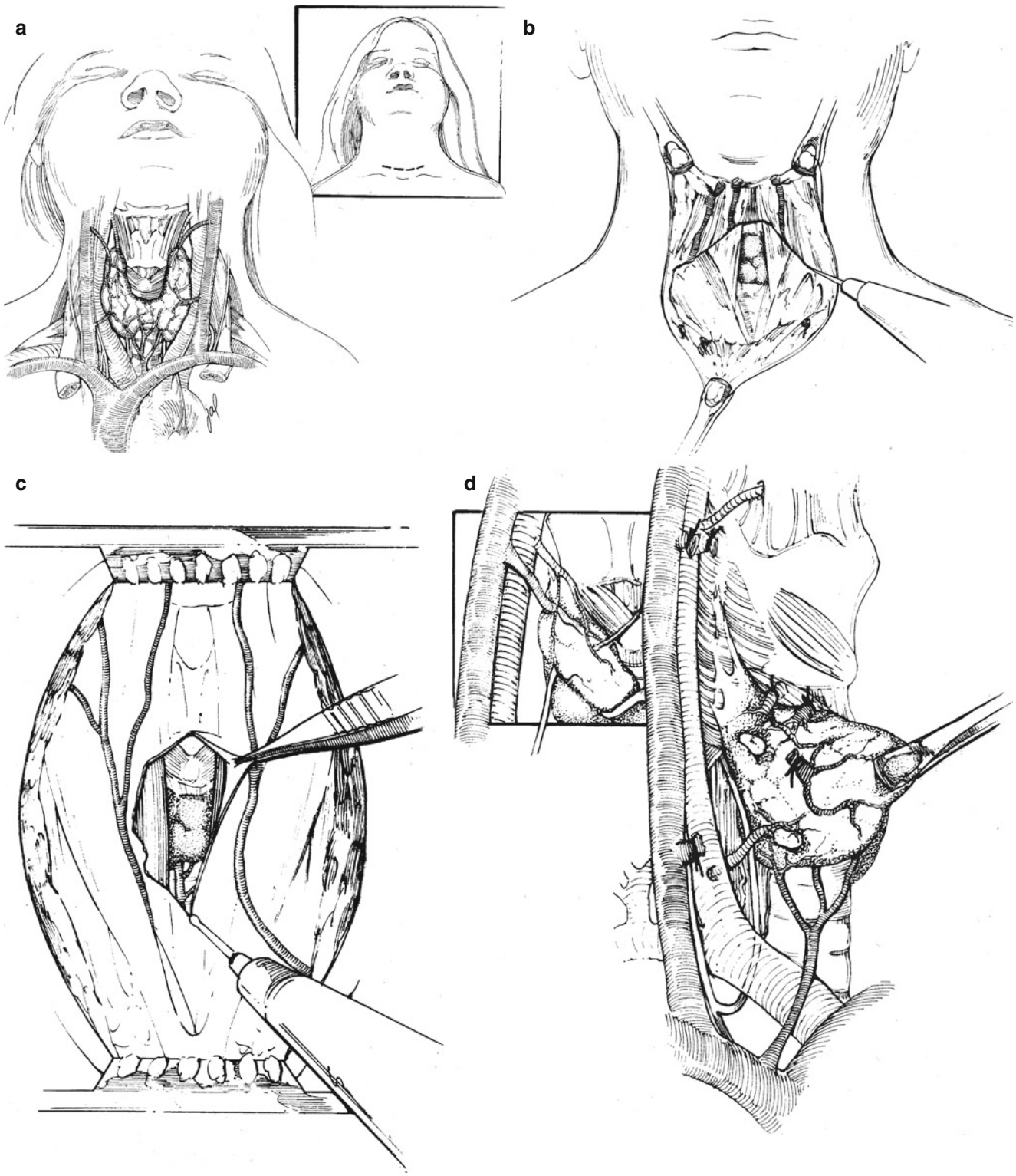


**Fig. 24.11** (**a**) Thyroidectomy. Normal position of the thyroid gland. *Inset* illustrates site for skin incision. (**b**) Thyroidectomy. Elevation of subplatysmal flaps to thyroid notch, superiorly and sternal notch inferiorly. (**c**) Thyroidectomy. The thyroid gland is exposed by separating the strap muscles in the midline. (**d**) Thyroidectomy. Mobilization of the thyroid gland. The middle thyroid vein had been ligated and divided, the recurrent laryngeal nerve identified and the superior pole mobilized. Inset illustrates the superior thyroid artery and vein. Superior pole vessels are divided individually, close to the thyroid gland, to avoid injury to the external branch of the superior thyroid nerve. (**e**) Thyroidectomy. Division of the inferior thyroid artery. The relationship between the inferior thyroid artery and recurrent laryngeal nerve (encircled the suture) is defined. The parathyroid glands are identified and preserved by dividing branches of the artery as they enter the thyroid gland. (**f**) Thyroid lobectomy. Transection of thyroid gland. The recurrent laryngeal nerve is identified along its entire course prior to the division of the ligament of Berry. The thyroid is dissected from the pretracheal fascia and divided at the junction of the isthmus and contralateral lobe. (**g**) Thyroid lobectomy. Appearance following right thyroid lobectomy. The recurrent laryngeal nerve and parathyroid glands are preserved

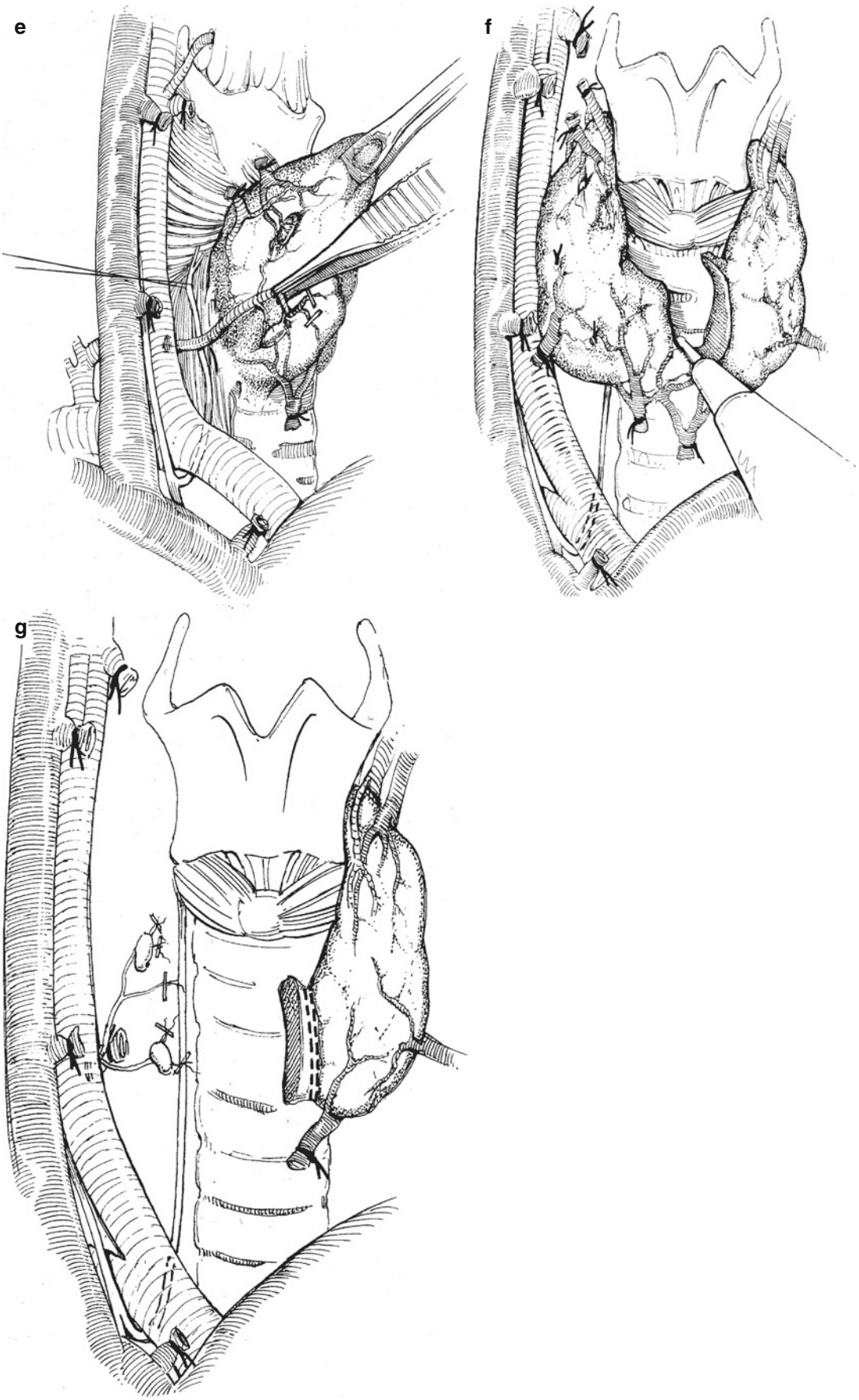


**Fig. 24.11** (continued)

gland is grasped with a Babcock clamp and retracted medially. The recurrent laryngeal nerve is identified by its relationship to the inferior thyroid artery. The right recurrent laryngeal nerve ascends lateral to the tracheal esophageal groove as it passes posterior to the inferior pole of the thyroid. The nerve then travels obliquely, closer toward the gland and crosses the inferior thyroid artery and ascends to enter the larynx. The left recurrent laryngeal nerve arises from the vagus and passes inferior and medial to the aorta and ascends to enter the larynx. The nerve usually travels in the tracheal-esophageal groove but may be more medial on the anterior aspect of the trachea. The nerve may pass over, under or branch around the artery. With the exception of a right non-recurrent laryngeal nerve, there is always a cross point. The nerve should be traced along its anterior plane until it can be seen entering the larynx. The terminal portion of the recurrent laryngeal nerve passes posterior to a lateral extension of thyroid tissue. A neurostimulator may be used to add in recurrent laryngeal nerve localization [156].

This portion of the gland may be left in situ in a near-total thyroidectomy. If medial retraction limits exposure, the superior pole of the gland should be mobilized (Fig. 24.11e). To properly mobilize the superior pole, the thin anterior suspensory muscle over the larynx should be divided. Branches of the superior thyroid vessels are divided close to the thyroid gland below the external branch of the superior thyroid nerve (Fig. 24.11f). Division of the upper pole pedicle between clamps, en mass, results in a high frequency of injury to this nerve and should be avoided. With the superior pole free the gland may be retracted medially.

Finally division of the ligament of Berry, the posteromedial attachment of the thyroid, allows the thyroid to be retracted medially and dissected off of the pretracheal fascia to the isthmus. The recurrent laryngeal nerve courses near this posteromedial attachment so again proper identification of the nerve is essential. A pyramidal lobe, if present should be resected with the specimen. When performing a lobectomy and isthmusectomy, the junction of the isthmus and opposite lobe is transected with electrocautery (Fig. 24.11f, g). For a total thyroidectomy, mobilize the contralateral lobe as described and remove the entire specimen en bloc. Any suspicious lymph nodes should also be removed.

Blood supply to the parathyroid glands usually comes from the inferior thyroid arteries. If these arteries are not properly ligated, the parathyroid glands risk devascularization. In order to prevent this, individual branches of the inferior thyroid artery should be divided distal to the end branches supplying the parathyroid glands and near the thyroid capsule (Fig. 24.11g). The parathyroid glands should then be gently retracted off of the thyroid capsule. Following division of the inferior thyroid artery, the inferior pole vessels are divided. If parathyroid gland perfusion is compromised during the dissection, then one should immediately autotransplant the gland into the nearby sternocleidomastoid muscle [157–159]. Some surgeons advocate routine autotransplantation of one or two parathyroid glands into the sternocleidomastoid muscle or forearm muscle to prevent permanent hypoparathyroidism. Any removed parathyroid glands are placed in a specimen cup of sterile saline submerged in sterile ice until the thyroidectomy is completed.

After hemostasis is assured, the strap muscles are approximated with interrupted absorbable sutures. If complete hemostasis is questionable, a small drain may be placed below the strap muscles and brought out through a separate skin incision. The platysma muscle is closed with interrupted absorbable sutures and the skin closed using a running subcuticular stitch. For parathyroid autotransplantation, the excised parathyroid glands are minced into several small pieces. Within the sternocleidomastoid muscle or forearm muscle, small pockets are created by gently spreading with fine forceps. Two or more pieces of parathyroid tissue are placed in each pocket and marked with a silk suture.

### Postoperative Management

Postoperatively, thyroidectomy patients should be treated with exogenous thyroid hormone to suppress TSH-mediated stimulation of the gland. Patients undergoing total parathyroidectomy with reimplantation often require calcium and vitamin D replacement until the autotransplanted tissue functions adequately [136]. To detect distant metastases or residual disease, radioiodine $^{131}$I scanning should be performed ~6 weeks following surgery and discontinuation of exogenous thyroid replacement. If residual thyroid cancer is detected, then therapeutic doses of $^{131}$I should be administered until all disease is eradicated. RAI is recommended for patients with distant metastatic disease, gross extrathyroidal extension of tumor, for tumor >4 cm. Dome patients with tumors 1–4 cm with lymph node metastasis or high risk features may benefit from RAI. Patients with tumors <1 cm without high risk features do not need RAI [153, 160].

If metastatic disease is present, resection of metastatic disease may be considered. Diagnostic scans (WBS and neck US) are then repeated in 3–12 months. Thyroglobulin levels should also be obtained at 3–12 months; an elevated level should raise the suspicion of recurrent thyroid carcinoma [153, 160–162]. Long term follow up in these patients is critical considering, the recurrence rate of thyroid cancer is about 30 % after 20 years. The overall progression-free survival of patients with differentiated thyroid cancer in this series was 67 % at 10 years and 60 % at 20 years after diagnosis. Factors associated with early recurrence are lower age at diagnosis and presence of residual neck disease.

Current management of MTC in children from families having the MEN 2 syndrome relies on the presymptomatic detection of the RET proto-oncogene mutation responsible for the disease, followed by prophylactic total thyroidectomy

by about the age of 5 years, before the cancer spreads beyond the thyroid gland [163]. MTC is usually the first tumor to develop in MEN patients and of those children who have a prophylactic thyroidectomy due to presence of a RET mutation, 80 % will already have foci of medullary carcinoma within the thyroid gland [136, 164]. Prophylactic thyroidectomy is recommended in infancy for patient with MEN 2B due to the aggressive nature of that subtype of MTC [164–166]. Unfortunately, external beam radiation, and chemotherapy have not been found to be effective in treating MTC, so surgical resection is the only treatment. Patients with MEN 2A have a lifetime risk of hyperparathyroidism of 30 % so at the time of prophylactic thyroidectomy consideration of routine heterotopic autotransplantation should be entertained [133, 164, 167].

The survival for thyroid cancer is quite good with overall mean survival of 30 years. Factors associated with worse outcomes include nonpapillary tumors, male gender, distant metastasis, and nonoperative treatment [110, 168]. Compared to adults, pediatric patients have larger tumors, increased lymph node invasion and distant metastasis. In patients with medullary thyroid cancer, survival was predicted by TNM staging and basal CT level <30 pg/mL [169]. Those patients with class D genotypes, preoperative CT >30 ng/mL, and age >10 years had worse outcomes. The association of radiation iodine with second cancers has lead to further recommendations to avoid radioactive iodine in low risk patients [170, 171].

## Neuroblastoma

Neuroblastoma is the third most common malignancy children and the most common cancer in children less then 1 year of age [172, 173]. The annual incidence of neuroblastoma is about 1 per 100,000 in the United State with 700 new cases each year. The average age at diagnosis in 17.3 months and 40 % are diagnosed before 12 months of age [172–174]. Neuroblastoma is more common in Caucasians than African-Americans (ratio 1.8) in infancy but equivalent after infancy. The male to female ratio is 1.2:1. Primarily tumors of the head and neck region occur in 2–4 % of afflicted children [175]. When disease is noted in the head and neck, it is most commonly metastatic disease. Infants are more likely to present with tumors in the cervical region.

Environmental factors may play a role in the development of neuroblastoma. Maternal opiate use has been associated with neuroblastoma while increased folate intake during pregnancy is associated with a lower incidence [176, 177]. Most neuroblastomas appear to be sporadic though increased incidence is found in children with Turner's syndrome, Hirschsprung's disease, central hypoventilation, and neurofibromatosis type 1 [178, 179]. Familial cases of neuroblastoma have also been reported and appear to be transmitted in an autosomal dominant pattern with variable penetrance [180–182].

### Pathology and Genetics

Neuroblastoma tumors are derived from primordial neural crest cells which populate the adrenal medulla and sympathetic ganglia. Based on maturation and differentiation of these neural crest cells, three histologic patterns of these tumors are noted including neuroblastoma, ganglioneuroblastoma and ganglioneuroma. Neuroblastomas consist of mostly neuroblasts and few stromal cells and are thus characterized as "stromal-poor" [173]. On histologic examination, small, dense, round cells are seen with hyperchromatic nuclei and scant cytoplasm. Electron microscopy, immunohistochemistry, and cytogenetic studies are currently used to diagnose these tumors.

Important biological factors include MYCN status, histopathologic classification, and DNA ploidy. These factors are so significant to outcomes that they are included in the COG staging of these tumors. N-Myc amplification is associated with more advanced disease, rapid tumor progression, and poor outcomes. Chromosome 1 deletions, rearrangements, and translocations have been reported in these patients [183–185]. Deletion of part of chromosome 1p is associated with amplification of N-Myc and is found in up to 25 % of neuroblastomas [185–189]. The smallest common region of loss is 1p36 and is associated with worse outcomes [190]. Deletion of 11q and/or 14q is found in 25–50 % of neuroblastomas and trisomy 17q is found in half of neuroblastomas [191–194]. The amplification of the N-myc proto-oncogene in chromosome 1p deletion and trisomy 17q are both associated with poor prognosis [191, 192, 195–197]. In contrast, expression of the tyrosine kinase receptor gene-A TRK-A is associated with biologically and clinically favorable tumors and good survival [198–201]. DNA ploidy, specifically those with near-triploid have a more favorable clinical prognosis and survival compared to those with near-diploid or near-tetraploid tumors and seems to be most significant in children 12–18 months of age and infants with 4S disease [202, 203].

### Clinical Presentation

Patients usually present with a nontender, firm mass in the lateral neck [175]. If the tumor extends into cervical sympathetic chain, Horner's syndrome (ipsilateral ptosis, miosis, and anhidrosis) may be seen [204, 205]. Heterochromia iridis may be present in children who have congenital or acquired Horner's syndrome [206]. Infant with Horner's syndrome congenital or acquired should under careful exam-

ination and workup for possible neuroblastoma. Metastatic neuroblastoma to the orbits is more common than primary cervical neuroblastoma and may produce proptosis and periorbital ecchymosis. Neuroblastoma may metastasize by lymphatic and/or hematogenous drainage. Cervical neuroblastoma spreads by local invasion of surrounding tissue and shows a high propensity for regional lymph node metastases. Distant disease, bone, and bone marrow involvement is common at presentation.

## Diagnosis

Diagnostic evaluation should include routine blood counts, liver and kidney function test, ferritin levels, and LDH levels. Nearly all neuroblastomas produce catecholamines and their byproducts, homovanillic acid and vanillylmandelic acid can be measured in the urine. In order to assess for the presence of these products, a 24 h urine collection should be obtained. In order to diagnosis neuroblastoma one of the following is needed: a histologic diagnosis of the tumor by microscopy; or evidence of metastases to bone marrow on aspirate with elevation in urine or serum catecholamines [207]. In order to stage a neuroblastoma, the following studies are needed: bilateral iliac crest bone marrow biopsy, bone radiography and a radionuclide or MIBG scan, abdominal CT or MRI, chest x-ray and if positive a chest CT, and a MRI/CT of the head and neck for primary tumors of the head and neck.

## Staging

The most common staging systems for neuroblastoma are the International Neuroblastoma Staging System (INSS) (Table 24.8) and the Children's Oncology Group risk stratification for children (Table 24.9) [207]. When combining the INSS stage, age, MYCN status, INPC classification, and DNA ploidy, an assessment of pretreatment risk can be made (Table 24.9) [208, 209].

## Treatment

Treatment for neuroblastomas arising in the head and neck includes surgery and often chemotherapy. The role of surgery is to establish a tissue diagnosis, stage the tumor, and resect the tumor if possible. For localized cervical neuroblastoma, surgical excision may be curative. When complete surgical excision is possible in stage 1 disease, 5-year survival is 99 % [210–214]. Surgical risk factors for primary resection of localized neuroblastoma for head and neck neuroblastomas include tumor encasing major vessels, tumor extending to base of the skull, compressing the trachea, encasing brachial plexus [215].

Even if complete surgical resection is possible, children identified as intermediate or high-risk need chemotherapy in addition to surgical resection [216]. Multi-agent chemotherapy is used in patients with unresectable disease and advanced disease. Common regimens include cyclophosphamide, ifosfamide, carboplatin or cisplatin, vincristine, doxorubicin, etoposide, topotecan, and adriamycin [209–211, 216–220]. After chemotherapy, surgical resection may be reconsidered [216, 221]. Radiation is used for unresectable tumors of tumors that are not responsive to chemotherapy including incompletely resected cervical neuroblastoma [219, 222, 223].

New treatment strategies include immunotherapy, MIBG therapy, differentiating agents, angiogenesis inhibitors, and targeted cell therapy. 131I-MIBG is used in patients with refractory neuroblastoma with a response rate of up to 33 %

**Table 24.8** Staging systems for neuroblastoma [209]

| International Neuroblastoma Staging System (INSS) | |
|---|---|
| Stage 1 | Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (i.e., nodes attached to and removed with the primary tumor may be positive). |
| Stage 2A | Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically. |
| Stage 2B | Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically |
| Stage 3 | Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement. The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column. |
| Stage 4 | Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs, except as defined for stage 4S. |
| Stage 4S | Localized primary tumor, as defined for stage 1, 2A, or 2B, with dissemination limited to skin, liver, and/or bone marrow (by definition limited to infants younger than 12 months) [3]. Marrow involvement should be minimal (i.e., <10 % of total nucleated cells identified as malignant by bone biopsy or by bone marrow aspirate). More extensive bone marrow involvement would be considered stage 4 disease. The results of the mIBG scan, if performed, should be negative for disease in the bone marrow. |

**Table 24.9** Children's Oncology Group (COG) neuroblastoma low-, intermediate-, and high-risk group assignment schema [209]

| INSS stage | Age | MYCN status | INPC classification | DNA ploidy[a] | Risk group |
|---|---|---|---|---|---|
| 1 | 0–21 years | Any | Any | Any | Low |
| 2A/2B[b] | <365 days | Any | Any | Any | Low |
| | ≥365 days–21 years | Nonamplified | Any | – | Low |
| | ≥365 days–21 years | Amplified | Favorable | – | Low |
| | ≥365 days–21 years | Amplified | Unfavorable | – | High |
| 3[c] | <365 days | Nonamplified | Any | Any | Intermediate |
| | <365 days | Amplified | Any | Any | High |
| | ≥365 days–21 years | Nonamplified | Favorable | – | Intermediate |
| | ≥365 days–21 years | Nonamplified | Unfavorable | – | High |
| | ≥365 days–21 years | Amplified | Any | – | High |
| 4[c] | <548 days [14–16] | Nonamplified | Any | Any | Intermediate |
| | <365 days | Amplified | Any | Any | High |
| | ≥548 days–21 years | Any | Any | – | High |
| 4S[d] | <365 days | Nonamplified | Favorable | >1 | Low |
| | <365 days | Nonamplified | Any | =1 | Intermediate |
| | <365 days | Nonamplified | Unfavorable | Any | Intermediate |
| | <365 days | Amplified | Any | Any | High |

The COG-9641 and COG-A3961 trials established the current standard of care for neuroblastoma patients in terms of risk group assignment and treatment strategies

*INPC* International Neuroblastoma Pathologic Classification, *INSS* International Neuroblastoma Staging System

[a]DNA Ploidy: DNA Index (DI) >1 is favorable, =1 is unfavorable; hypodiploid tumors (with DI <1) will be treated as a tumor with a DI >1 (DI <1 [hypodiploid] to be considered favorable ploidy)

[b]INSS stage 2A/2B symptomatic patients with spinal cord compression, neurologic deficits, or other symptoms should be treated with immediate chemotherapy for four cycles

[c]INSS stage 3 or stage 4 patients with clinical symptoms as listed above should receive immediate chemotherapy

[d]INSS stage 4S infants with favorable biology and clinical symptoms should be treated with immediate chemotherapy until asymptomatic (2–4 cycles). Clinical symptoms include: respiratory distress with or without hepatomegaly or cord compression and neurologic deficit or inferior vena cava compression and renal ischemia; or genitourinary obstruction; or gastrointestinal obstruction and vomiting; or coagulopathy with significant clinical hemorrhage unresponsive to replacement therapy

[224, 225]. CCG 3891 utilized 13-cis-retinoic acid in maintenance phase with improved results and other retinoids and vitamin A derivatives are under investigation [226]. Other new targets with varying levels of success include ALK inhibition, aurora A kinase inhibition, TRK inhibition, tubulin-binding agents, DNA methylation, histone modification, and miRNAs [215].

Prognosis variables for neuroblastoma include age, stage, N-Myc status, pathology classification, DNA ploidy, location, and metastasis. Infants with primary tumors of the head and neck have a more favorable prognosis. Patients with localized disease that is completely resected have a >90 % survival rate (Fig. 24.12) [227]. Children with intermediate-risk neuroblastoma treated with surgery, chemotherapy, with or without radiation have long-term survival of 90 % [210, 213, 228, 229]. Survival for stage 3 neuroblastoma varies based on age and histologic features [230]. Survival in children with disseminated neuroblastoma (CCG stage IV and POG stage D) is also age dependent but overall survival is ~30 % [221, 231]. When recurrence occurs, the disease is usually widely metastatic and the prognosis is poor.

## Rhabdomyosarcoma

Rhabdomyosarcoma is a soft tissue sarcoma that originates from immature mesenchymal cells destined to be striated skeletal muscle. It is the most common soft tissue sarcoma in children accounting for up to 5 % of all childhood cancer and 50–70 % of all sarcomas. It accounts for 20 % of head and neck tumors in children. The annual incidence of rhabdomyosarcoma ranges from 5 to 8 per million children resulting in approximately 350 new cases each year [232, 233]. In the United States, rhabdomyosarcoma is more common in Caucasian children with a 2–3:1 ratio to African American children. The incidence of rhabdomyosarcoma throughout the world varies with increase incidences in Spain and decreased incidences in lower parts of Asia including China, Japan, India, and the Philippines [234, 235]. The incidence of rhabdomyosarcoma appears to be equal in Asian children as compared to Caucasian children in the United States [236]. The incidence is increased in males with a ratio of 1.4:1 but the incidence appears equal in cases of rhabdomyosarcoma of the head and neck [237]. Age of onset has two peak occurrences, the first in children 2–6 years of age and

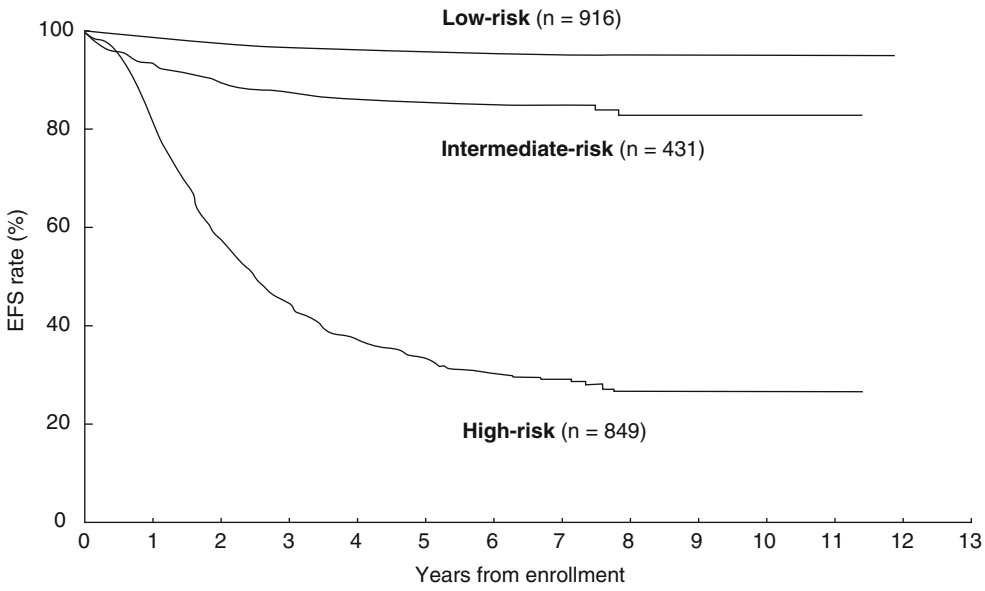


**Fig. 24.12** Outcomes for children with low-risk, intermediate risk, and high-risk neuroblastoma [42] (Permission from previously published article: Park et al. [227] with permission from Elsevier)

the second in adolescents 15–19 years old. Two-thirds of the patients are diagnosed younger than 6 years of age [234]. Age-related differences exist for the different sites of primary disease though tumors can arise in any region at any age. Younger children tend to have increased incidence of head and neck and genitourinary rhabdomyosarcoma while older children have an increased incidence of tumors of the extremities and truck and of the male genital tract. For example in patients with orbit RMS, 42 % are aged 5–9 years and in these younger children tumors of the orbit tend to be of the embryonal type. Thirty-five percent of all rhabdomyosarcomas occur in the head and neck.

Most rhabdomyosarcomas are sporadic in occurrence, but some are known to be associated with familial syndromes such as neurofibromatosis, Li-Fraumeni syndrome, Rubinstein-Taybi syndrome, Gorlin basal cell nevus syndrome, Costello syndrome, and Beckwith-Wiedemann syndrome [238–244]. Many children with Li-Fraumeni syndrome in particular are noted to have mutations of p53 tumor suppressor gene which has lead some to speculate that children who develop RMS as a young age should be screened for a p53 mutation. Presence of a p53 mutation may lead one to reduce ionization and/or chemotherapeutic doses that may lead to secondary malignancy though there is no consensus on this topic [245]. Environmental factors that may be associated with the development of RMS including maternal use of marijuana and cocaine, intrauterine radiation exposure, low socioeconomic status, the use of antibiotics soon after birth, and exposure to alkylating agents [19, 246–249]. Relatives of children with rhabdomyosarcoma may be at increased risk for the development of breast cancer, brain tumors, and adrenocortical carcinoma [244, 250–252].

## Pathology and Genetics

Rhabdomyosarcomas (RMS) arise from immature mesenchyme cells that were destined to differentiate into muscle. Interestingly, these tumors arise in various locations including areas where striated muscle is not found such as the bladder. On microscopic examination, the cells have immunohistochemical expression of actin, myosin, desmin, myoglobin, Z-band proteins, and/or MyoD with an eosinophilic cytoplasm [253]. Over 99 % of RMS stain for polyclonal desmin, while actin, myogenin and myoglobin are found in 95, 95, and 78 % percent respectively [254]. Myogenin in particular is expressed more often by alveolar RMS. A DNA-binding protein expressed during early myogenesis, MYOD1, is also expressed in these tumors and can be identified by immunohistochemistry and Northern blot analysis [255, 256]. Other immunohistochemical stains may be helpful in identifying RMS. CD99 is a marker used in Ewing sarcoma but is positive in 15 % of RMS patients [257]. Leukocyte common antigen, pan B lymphocyte antibodies, cytokeratin, epithelial membrane antigen, and neural markers such as neuron specific enolase and S-100 protein are positive in 5–20 % of RMS cases. In addition to immunohistochemical staining, transmission electron microscopy (EM) is also useful in identifying myofilament, myotubular intermediate filaments, desmin, actin, and z-bands.

Four histological subtypes of RMS assist in both the categorization and prognosis of patients: embryonal (50 %), botryoides and spindle cell (6 %, 3 %), alveolar (20–30 %), and undifferentiated (10 %). In addition to these four main histological groups, there are RMS tumors that are described as not otherwise specified and diffusely anaplastic (previously pleomorphic) which are associated with poor progno-

sis [258]. The botryoides and spindle class are less common but are associated with the best prognosis. The embryonal RMS group has an intermediate prognosis while the alveolar group has a relatively poor prognosis. Embryonal is most common at birth and decreases into adolescence while alveolar is more common as age increases [259].

The alveolar and embryonal RMS are distinguished based on the architecture of the tumor. Embryonal RMS appears as sheets of rhabdomyoblasts with occasional fusiform cells and no alveolar architecture (Fig. 24.13). The alveolar RMS is characterized by an alveolar architecture with rhabdomyoblasts interspersed among fibrovascular septae [260]. Botryoides RMS whose name means "grape" has the gross appearance of a bunch of grapes. Histologically it is a mass beneath an epithelial layer and subepithelial layer of rhabdomyoblasts. Anaplastic RMS is characterized by atypical mitotic figures and large nuclear size [261, 262].

Cytogenetic and molecular markers have been found in rhabdomyosarcoma that can be useful for classification and prognostication. Up to 80 % of embryonal rhabdomyosarcoma have a loss of heterogeneity at the 11p15 locus near the IGF-II gene. This loss of heterogeneity is suggestive of the presence of a tumor suppressor gene in the region that is disrupted [256, 263, 264]. Overproduction of IGF-II, which is found in both embryonal and alveolar rhabdomyosarcomas, may then stimulate tumor growth [265]. The PAX3-FKHR translocation in alveolar RMS in particular is associated with over expression of IGF-II [266]. Several other genetic mutations are associated with rhabdomyosarcoma including activation and or mutations of the K-ras, N-ras, retinoblastoma, PTCH gene mutations, MDM2, CDK4, p53, and MYCN though the significance of these mutations are yet to been determined [267–271].

In alveolar RMS, the t(2;13)(g37;g14) translocation in which the long arms of chromosome 2 and 13 join to fuse PAX3 and FKHR is diagnostic of the alveolar subtype even in the absence of the characteristic histology (Fig. 24.14) [272, 273]. In particular, the solid alveolar variant may be histologically similar to the embryonal subtype but will possess this translocation. The mechanism by which this translocation produces RMS is unclear but it is postulated that it is due to increased upstream transcription of other genes during development [274–276]. Another translocation t(1;13)(p36;p14) fuses PAX7 and FKHR. This fusion is thought to increase upstream transcription but the mechanism is not fully understood [274]. These markers have been found to have prognostic value as well. For example, PAX7-FKHR

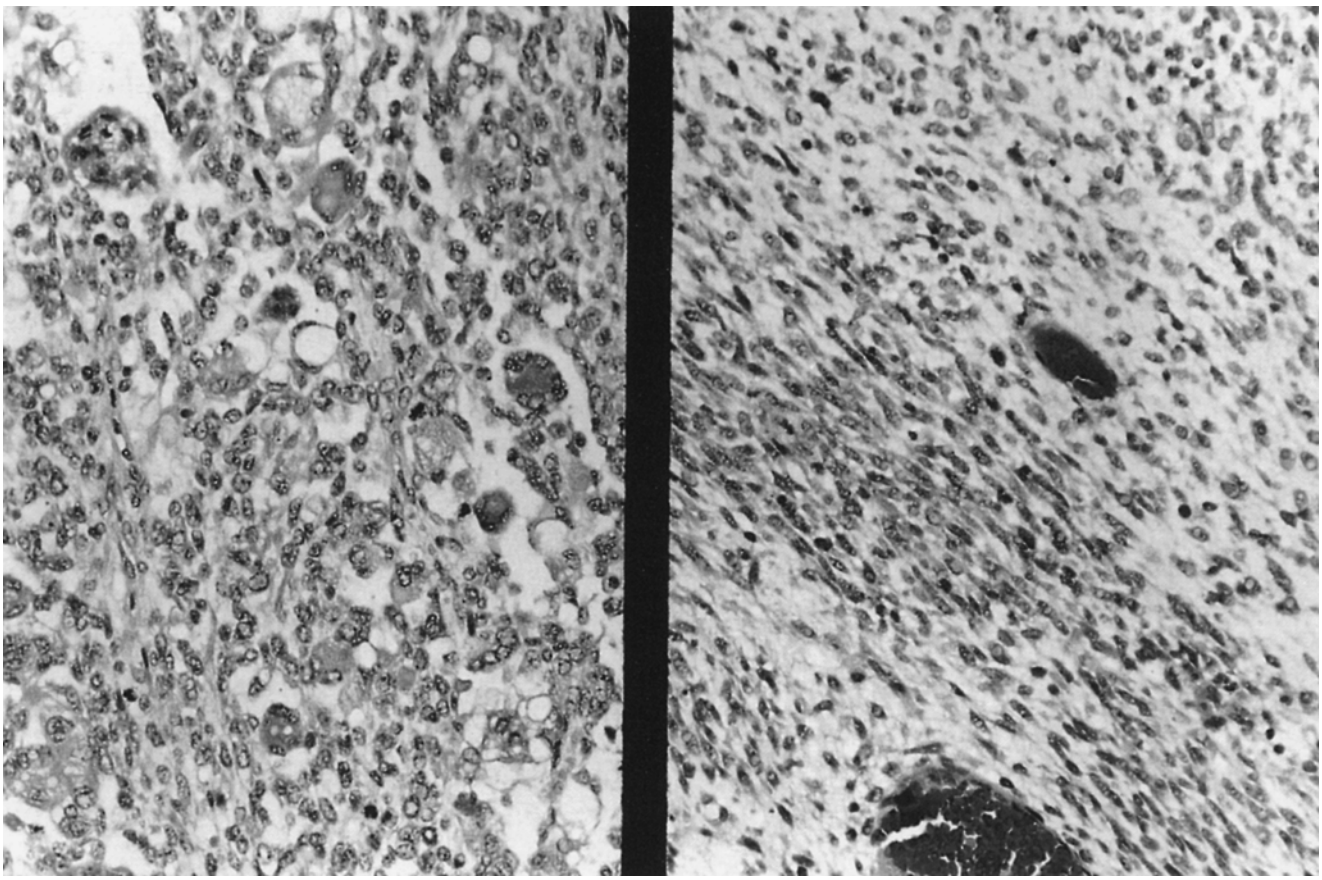

**Fig. 24.13** Photomicrograph demonstrating embryonal rhabdomyosarcoma. *Left panel*; round cell rhabdomyosarcoma. *Right panel*; spindle cell rhabdomyosarcoma

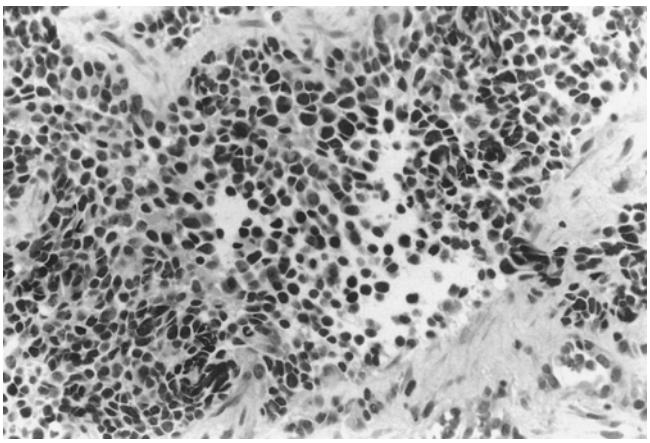

**Fig. 24.14** Photomicrograph demonstrating alveolar rhabdomyosarcoma. Note clear areas with alveolar-like appearance

patients tend to be younger patients with extremity lesions that tend to respond favorably to treatment [277, 278].

## Clinical Presentation

Thirty-five to forty percent of rhabdomyosarcoma presents in the head and neck, usually as a nontender mass lesion with occasional overlying skin erythema [261, 279, 280]. These tumors tend to arise in the orbit (25 %) and parameningeal sites (50 %) with the remaining 25 % arising in other locations including the scalp, parotid gland, oral cavity, pharynx, and neck [281]. Embryonal rhabdomyosarcoma is more common in the superior nasal quadrant while alveolar is more common in the orbit. An orbital tumor may present with proptosis, periorbital edema, ptosis, and/or opthalmoplegia. Parameningeal or nasopharyngeal tumors present with airway obstruction, local pain, chronic sinusitis and epistaxis. In the case of parmeningeal lesions, cranial nerve palsies may result from direct extension. Middle ear tumors present as a polyploidy mass with earache, otitis media, and discharge which may be hemorrhagic.

Less than one quarter of patients have metastatic disease at diagnosis [277, 282]. When rhabdomyosarcomas does spread, it is either by direct extension or metastasis via lymphatic and/or hematogenous route. Lymphatic metastasis occur less in than 10 % of the cases [283]. Hematogenous spread occurs in 10–20 % of cases and is most often to the lungs (40–50 %), bone marrow (20–30 %), and bone (10 %) [277, 282, 284].

## Diagnostic Evaluation

After a thorough history and physical examination, further diagnostic evaluation should include the acquisition of laboratory data. A complete blood count (CBC) may show evidence of anemia due to inflammation and/or pancytopenia due to bone marrow involvement. Liver function tests are necessary to assess for possible metastatic disease to the liver and are necessary prior to administration of potentially hepatotoxic chemotherapy. Renal function tests, electrolytes, serum calcium, magnesium, phosphorous, and uric acid levels are also needed before the administration of potentially toxic chemotherapeutic agents. A urinalysis is also needed to assess for hematuria, which may indicate GU tract involvement.

Imaging studies are important tools to determine the presence of calcifications and bone involvement of the primary tumor and to search for metastatic disease. MRI or occasional CT scans are important to fully assess tumor involvement of the head and neck and serve as a baseline when assessing response to therapy. For tumors of the head and neck in particular, MRI is superior for assessing involvement of adjacent structures and feasibility of resection and should be performed when considering total resection. A CXR and chest CT scan is necessary for evaluation of lung metastases. An abdominal US and/or CT is indicated to evaluate for liver metastasis. While the utility of PET scanning is limited in children, its use in the adult sarcoma population is increasing and FDG-PET may enhance the evaluation of occult metastases, persistent disease, or recurrence [285–287]. A radionuclide bone scan is indicated to assess for bony involvement. Bone marrow biopsies are also necessary to assess for metastatic disease even in patients with normal complete blood counts. In patients with parameningeal RMS a lumbar puncture is indicated to assess for leptomeningeal metastasis.

A biopsy of the tumor is necessary to definitively establish the diagnosis and guide treatment. In order to obtain enough tissue for diagnosis, an open biopsy is often performed, though core needle biopsy is also an alternative. Enough tissue is need for fluorescent in situ hybridization (FISH) and reverse transcriptase–polymerase chain reaction (RT-PCR) testing to assess for the molecular/genetic abnormalities already described.

## Staging

Staging and classification of rhabdomyosarcoma is described in a variety of ways. The Intergroup Rhabdomyosarcoma Study divides patients based on the Tumor-Node-Metastasis system (TNM) which includes site of tumor, tissue invasion, tumor size, lymph node involvement and metastatic disease (Table 24.10) [288–290]. The Intergroup Rhabdomyosarcoma (IRS) clinical staging system is shown in Table 24.11 [261, 288, 289]. It divides patients into clinical groups based on the localization of the primary tumor, the extent of surgical resection, and presences of residual disease/metastases [288, 290]. Before treatment is begun, adequate staging must be

**Table 24.10** TNM staging system of Intergroup Rhabdomyosarcoma Study IV [288–290]

| Stage | Sites | T invasion | T-size | N | M |
|---|---|---|---|---|---|
| 1 | Orbit | T 1 or T2 | a or b | N0, N1, Nx | M0 |
| | Head and neck excluding parameningeal | | | | |
| | Non-bladder, non-prostate genitourinary | | | | |
| 2 | Bladder/prostate | T1 or T2 | A | N0 or Nx | M0 |
| | Extremity | | | | |
| | Cranial parameningeal | | | | |
| | Trunk/retroperitoneum | | | | |
| 3 | Bladder/prostate | TI or T2 | B | N0, N1, Nx | M0 |
| | Extremity | | | | |
| | Cranial parameningeal | | | | |
| | Trunk/retroperitoneum | | | | |
| 4 | All sites | T1 or T2 | a or b | N0 or NI | M1 |

A < 5 cm in diameter; b >5 cm in diameter
*T* tumor, *TI* confined to site of origin, *T2* extension beyond site of origin, *N* regional lymph nodes, *N0* no involvement, *N1* clinically involved, *Nx* status unknown, *M* metastases, *M0* no distant metastases, *M1* distant metastases present

**Table 24.11** Intergroup rhabdomyosarcoma clinical Staging system [261, 288, 289, 295, 296]

| Clinical group | Extent of disease |
|---|---|
| I | A. Localized tumor, confined to site of origin, completely resected |
| | B. Localized tumor, infiltrating beyond site of origin, completely resected |
| II | A. Localized tumor, gross resection with microscopic residual disease |
| | B. Locally extensive tumor (positive regional lymph nodes), completely resected |
| | C. Locally extensive tumor (positive regional lymph nodes), gross resection with microscopic residual disease. |
| III | A. Gross residual disease following surgical biopsy |
| | B. Gross residual disease after major resection |
| IV | Presence of distant metastases, any size primary tumor with or without regional lymph nodes |

**Table 24.12** Soft Tissue Sarcoma Committee of the Children's Oncology Group: Rhabdomyosarcoma Risk Group Classification [209]

| Risk group | Histology | Stage | Group |
|---|---|---|---|
| Low risk | Embryonal | 1 | I, II, III |
| | Embryonal | 2, 3 | I, II |
| Intermediate risk | Embryonal | 2, 3 | III |
| | Alveolar | 1, 2, 3 | I, II, III |
| High risk | Embryonal or Alveolar | 4 | IV |

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complete which includes tissue conformation of RMS and TNM staging. Based on stage, clinical group, site, and histology, risk groups assignments may be made (Table 24.12).

## Treatment

Rhabdomyosarcoma of the head and neck is often treated with a combination of chemotherapy, radiation, and surgical resection if possible. Surgical resection of head and neck rhabdomyosarcomas should only be undertaken when the entire tumor can be removed with damage to vital structures and without major cosmetic or function deformity. Occasionally superficial tumors of the scalp, ear, cheek, neck, or oropharynx may be completely excised. If complete surgical resection is not possible, chemotherapy and radiation should be administered to shrink the tumor if possible; a complete surgical resection may be possible after treatment. In these cases an incisional biopsy is needed for diagnosis. Random nodal sampling is not indicated. Suspicious lymph nodes should be biopsied for staging purposes, but extensive neck dissections are not indicated. Sentinel lymph node biopsy is being used for extremity and truncal lesions though its role in head and neck RMS has not been assessed [291–293]. There also does not appear to be a role for resection of metastatic lesion such as an isolated pulmonary nodule [294]. For patients with recurrent disease, surgical resection is warranted though again after chemotherapy and radiation if complete excision is not possible.

Chemotherapy and radiation is the mainstay of RMS that is not completely surgically resectable as is the case from most patients with RMS of the head and neck. The standard treatment is a combination of vincristine, actinomycin-D, and cyclophophamide as currently recommended by the Rhabdomyosarcoma Study Group [279, 280, 290, 295, 296]. The IRS – IV patients were divided into prognostic groups

based on clinical and TNM staging. Based on the prognostic staging they were assigned to chemotherapy regimes. Most treatment courses continue for approximately 45 weeks depending on the clinical stage at presentation. Additional agents such as doxorubicin, cisplatin, etoposide, and melphanlan have not been shown to be beneficial though topotecan and irinotecan are under study for patients with resistant tumor and advanced or recurrent disease [261, 279, 280, 296–301].

If residual and or metastatic disease is present, radiation therapy may be added to the above chemotherapeutic regime. Radiation is usually initiated after 2–3 cycles of chemotherapy except in those patients with parameningeal tumors or life-threatening tumors in which radiation is started immediately. Delay of radiation treatment beyond 4 months has been shown to impair local control [302]. Radiation doses vary based on tumor location, extent, and involvement of nodes. For the other clinical groups, local control was achieved with radiation to the primary tumor site in doses of 1.8–2 Gy daily depending on patient age and the size of tumor.

The IRS study group, has noted that radiation was unnecessary for clinical group I embryonal RMA and paratesticular tumors. All other clinical group 1 patients were recommended to have radiation for a total dose of 36 Gy. Those in clinical group II with residual disease after surgery received radiation doses 41.4–45 Gy which increased survival to 75–87 % [303]. In clinical group III, IRS-IV recommends patient with gross residual disease receive 50.4 Gy except in orbital RMS in which 45 Gy is recommended. Patients with parameningeal tumors do benefit from higher radiation doses so the current recommendation is 50.4+ Gy to the site of the tumor with 2 cm margins of normal tissue [302, 304, 305]. Intracranial extension, cranial bone erosion, and/or cranial nerve palsy do not require whole-brain irradiation or intrathecal therapy, though tumor cells in CSF are indications for additional therapy [305]. Intraparenchymal brain metastases may be treated with CNS RT in addition to chemoradiation directed at the primary tumor. Though tumor cells in CSF may signify metastasis, it does not necessarily mean the patient is not treatable. Raney et al. noted that patient without other signs of metastasis were alive 6–16 years after diagnosis [306]. Intracranial extension should receive prompt radiation for delay is associated with worse outcomes [302].

After receiving therapy, patients are reimaged and if residual tumor is noted, resection needs to be entertained. Resection may be a first attempt at an oncologic resection or a second-look operation to confirm/evaluate response and to completely resection disease without loss of function.

For patients with metastatic disease chemoradiation is recommended for the primary and metastatic tumors with organ preservation [307] IMRT or fractionated stereotactic radiation therapy and chemotherapy has been used in patients with rhabdomyosarcoma of the head and neck with good results [308–310].

For patients with orbit tumors and clinical group I (completely excised) head and neck tumors, the 5-year survival is >85 % [279, 290, 296]. For other tumors of the head and neck, the 5-year survival is about 75 %. Relapse has been reported in approximately 1 % of patients after 5 years [279, 290, 296]. When rhabdomyosarcoma recurs, it tends to be more resistant to chemotherapy and radiation and is associated with a poor prognosis. The treatment for recurrent RMS is again chemotherapy, radiation, and surgical resection is possible. There are no clear guidelines on chemotherapeutic regimens and radiation dosing in patients with recurrent rhabdomyosarcoma, but suggestions include vincristine, dactinomycin, and cyclophophamide and also possibly doxorubicin, ifosfamide and etoposide, mesna and actinomycin D [311–316]. Further research is needed to identify better treatment protocols for this treatment resistant group.

## Other Soft Tissue Sarcomas

Soft tissue sarcomas other than rhabdomyosarcomas make up 4 % of all tumors in children. These sarcomas are names based on the mature tissue that they resemble though all of these tumors are derived from primitive mesenchymal cells. Those that occur in infants and small children primarily occur in the head and neck region. Soft tissue sarcomas in infants and younger children often have less aggressive behavior and an excellent prognosis with surgery. Sarcomas, which present during adolescence, behave more like tumors in the adult population. Most soft tissue sarcomas present as painless, asymptomatic masses in the neck unless there is compression or invasion of adjacent structures. Because of the rarity of these lesions in childhood, most of the available data for treatment come from the adult population. In general, wide local excision is the treatment of choice. Because of the difficulty in obtaining wide negative margins in the head and neck, adjuvant therapy is often used in conjunction with surgical excision.

### Fibrosarcoma

Fibrosarcoma is the most common non-rhabdomyomatous soft tissue sarcoma in children younger than 1 year of age and is the most common soft tissue sarcoma after rhabdomyosarcoma in all children accounting for 11 % of the total [317]. Primary head and neck lesions account for approximately 15–20 % of fibrosarcoma [318]. There is a bimodal age distribution with peaks in infant to 5 years of age and then again between the ages of 10–15 years and is described may be described as infantile or “adult-type” fibrosarcoma. Histologically, fibrosarcoma tumors consist of spindle cells with a characteristic herringbone pattern and it is associated

with ETV6-NTRK3 fusion protein. Fibrosarcomas in the first year of life rarely metastasize and can be treated with wide local excision. Radiation is indicated if complete excision is not possible. Fibrosarcoma tumors in adolescence are more aggressive and require multimodality therapy though utility of adjuvant therapy has not been established. Survival for nonmetastatic tumors ranges from 83 to 92 % in children under 5 years of age and 60 % for those older than 5 years [319–322].

## Malignant Peripheral Nerve Sheath Tumor

Malignant peripheral nerve sheath tumors (MPNST) account for 5 % of all soft tissue sarcomas in children and 10 % occur in the head and neck region. They are tumors arising from nerves and express S10 or other neural markers. They can arise from the cranial nerves, cervical plexus, or sympathetic chain. In contrast to most of the other head and neck soft tissue sarcomas, MPNSTs commonly present with pain, paresthesias and muscle weakness. They are associated with neurofibromatosis type I which is characterized by cafe au lait spots, neurofibromas, skeletal dysplasia, and many neoplasms [323]. Half of the patients with MPNST have neurofibromatosis type 1 and 1–2 % of patients with NF 1 will develop MPNST [324]. These lesions are similar in appearance to fibrosarcomas but are far more aggressive. The tumor cells of MPNST, in contrast to fibrosarcoma, are more variable in size and shape and lack a herringbone pattern. Outcome is related to size of tumor, grade, differentiation, surgical resectability, location, comorbidity, and age. The mainstay of therapy is surgical resection if possible [324]. Multimodal therapy including wide surgical excision, radiation, and chemotherapy including vincristine, actinomycin D, cyclophosphamide and doxorubicin (Adriamycin) are recommended though impact of chemotherapy and radiation is debated. Survival is generally good for early stage tumors (50–75 %) and poor for advanced disease (15–30 %) [319].

## Synovial Sarcoma

Synovial sarcoma is rare in children but may occur in the head, neck, and trunk in 15–20 % of cases [325–327]. These tumors occur more commonly in older children and young adults and histologically differentiate into a spindle fibrous stroma similar to fibrosarcoma and a glandular component with epithelial differentiation. Synovial sarcomas are separated into monophasic which contain only spindle cell and biphasic which contain both spindle and epithelioid cells. The tumor is associated with t(x;18) translocation with fusion of SYT-SSX1 and SYT-SSX2 proteins. Those patients with a SYT-SSX2 fusion gene have a better prognosis that those with a SYT-SSX1 fusion gene [327]. In contrast to other non-rhabdomyosarcoma soft tissue sarcomas, synovial sarcomas commonly present with both lymph node and lung metastases. Local disease is treated with local excision. The role of chemotherapy and radiation is unclear but often given in combination with surgery. Survival rate depend on tumor location, size, extension, and ability to achieve surgical resection. The 5-year survival rates are greater than 50 % [327–330]

## Hemangiopericytoma

Hemangiopericytoma accounts for 3 % of all soft tissue sarcomas and occurs most commonly in the lower extremities and retroperitoneum. These tumors occur rarely in the nasal cavity, paranasal sinuses, orbital region, parotid gland and the neck. It is thought that hemangiopericytomas arise from vascular pericytes or alternatively from mesenchymal cells with pericytic differentiation [331, 332]. Multiple simple and complex genetic translocations have been demonstrated in these tumors [333]. These lesions are classified as benign, malignant, or borderline depending the characteristics of the lesion including tumor size, necrosis, mitotic activity, cellularity, and atypia though universe criteria have not been defined. Wide local excision and postoperative chemotherapy is the recommended treatment. Irradiation is added for incompletely resected tumors. Hemangiopericytomas in infants are associated with a better prognosis than those occurring in older children and adults. The reported 5-year survival rate for these tumors is stage-dependent and ranges from 30 to 70 % [331, 334, 335].

## Malignant Fibrous Histiocytoma

Malignant fibrous histiocytomas (MFH) are rare sarcomas with multiple tissue elements that commonly present in the head and neck region. These tumors rarely occur during the first year of life. Ring chromosomes and 19p+ alterations have been observed in these tumors [327, 336, 337]. Microscopically, MFH has multiple cell types, marked cellular pleomorphism and a storiform pattern and resembles fibrosarcoma but lacks a herringbone pattern. Treatment is with wide excision and local irradiation for residual tumor with or without chemotherapy. The 3-year survival for head and neck tumors is greater than 50 % [338–341].

## Alveolar Soft Part Sarcoma

Alveolar soft part sarcoma is rare in childhood with an incidence of one per ten million, but when it occurs, it most commonly involves the head and neck. Locations described

include orbit, tongue, thyroid, larynx, buccal space, and paravertebral space. The diagnosis is made based on characteristic light and electron microscopic findings. These tumors possess adenosine triphosphatase and neurosecretory granules suggesting possibly a myogenic and or neuroepithelial origin [342–344]. In addition, immunocytochemical studies overwhelmingly support a myogenic origin [345, 346]. These tumors are associated with chromosomal translocations of t(X;17) on chromosome band 17q25 leading to ASPL-TFE3 fusion protein [327]. These tumors are slow growing and 80 % of children are alive 2 years after diagnosis. Most patients, however, eventually die of the disease. Alveolar soft parts sarcoma in younger children and those arising in the head and neck have a better prognosis. Treatment is with wide local excision. Because these sarcomas are very slow growing tumors, radiation and chemotherapy are reserved for recurrent and distant disease.

## Parathyroid Tumors

The parathyroid glands develop at the beginning of the fifth week of gestation in the dorsal portion of the third and fourth pharyngeal pouches. During the sixth week of development, the superior parathyroids arise from the fourth pharyngeal pouch and migrate cephalad and superior. The inferior parathyroid glands arise from the third pair of pharyngeal pouches and migrate inferior and dorsal. Lesions of the parathyroid gland are typically noted in adolescent females and are detected during workup for hypercalcemia. There are many causes of hypercalcemia in children including hyperparathyroidism, sarcoidosis, fat necrosis, familial hypocalciuric hypercalcemia, idiopathic hypercalcemia of infancy, thyrotoxicosis, hypervitaminosis A, hypophosphatasia, prolonged immobilization, and thiazide diuretics to name a few. Hyperparathyroidism may be caused by adenomas or diffuse hyperplasia. Parathyroid carcinoma is extremely rare in this age group. Hyperparathyroidism of infancy is often severe and can be fatal. Half of these patients have a familial component. On pathology, these patients have diffuse hyperplasia. Early treatment is critical for survival.

Patients noted to have hyperparathyroidism need to have calcium levels, PTH levels, and urine calcium measure. Ultrasound of the neck is needed to help localize the lesion. 99T sestamibi scans are 87 % sensitive in preoperative localization of parathyroid adenomas. When ultrasound is combined with sestamibi scan, the sensitivity increases to 96 % [347, 348]. When a solitary adenoma is identified, an excision of the identified adenoma may be performed. Intraoperative PTH (parathyroid hormone) monitoring is needed in order to ensure complete treatment of patients' hyperparathyroidism. A preoperative PTH, 5 min PTH, and 10–15 min PTH should be obtained. A 50 % drop in PTH level should be noted within 10–15 min [349, 350]. If a 50 % drop is note noted, further neck exploration is needed. For patients with parathyroid hyperplasia, a 3.5 gland parathyroidectomy or total thyroidectomy with autotransplant should be performed. Hyperplasia is a feature of patients with MEN syndromes.

Secondary hyperparathyroidism occurs secondary to renal insufficiency or malabsorption. PTH is increased in response to decreased calcium. The treatment of secondary hyperparathyroidism is medical management, though if severe renal osteodystrophy develops, total parathyroidectomy with autotransplantation may be needed. Tertiary hyperparathyroidism is a persistent hyperfunctioning of the parathyroid gland even after inciting stimulus has been removed. This is specifically seen in patients after renal transplant who had chronic renal failure and secondary hyperparathyroidism. These patients have hyperplasia of all four glands may need total parathyroidectomy with autotransplantation if unresponsive to medical management.

## Germ Cell Tumors

Germ cell tumors account for about 3 % of neoplasms in children with an incidence of four per million children [351]. Of the germ cells tumors that occur, only 5–10 % occur in the extracranial head and neck region. In general 25–35 % of all germ cell tumors are malignant, though malignant germ tumors of the head and neck are rare [352–354]. Germ cell tumors arise from primitive germ cells and are characterized histologically by the presence of mature tissue from all three germ cell layers. The most common histologic features include skin and cutaneous appendages, adipose tissue, cystic structures and intestinal epithelium. Mature and immature tissue elements are commonly seen in neonatal cervical teratomas.

The majority of cervical germ cell tumors are congenital and present at birth or in early infancy and can be diagnosed by prenatal ultrasound. The anterior lateral neck is the most common site of occurrence though they have also been reported in the pharynx, nasopharynx, paranasal sinuses, skull, and orbit [352, 355–360]. Large congenital lesions may obstruct the pharynx and produce maternal polyhydramnios or non-immune fetal hydrops [353, 354, 359]. Following birth, obstructing tumors produce respiratory distress and dysphagia and may require intubation and emergency surgical tracheostomy. Life threatening airway obstruction has been reported in up to 35 % of cases [352]. These cases may benefit from an EXIT procedure (EX utero Intrapartum Treatment) or OOPS procedure (Operation On Placental Support) at birth to prevent anoxia [361]. Prior to surgical excision proper CT/MRI imaging is important to assess the precise anatomy of the tumor and proximity to

vital structures. Resection may be difficult due to location. If these teratomas recur, reexcision is recommended. Although rare in the cervical region, pure yolk sac tumors (endodermal sinus tumors) or mixed tumors with yolk sac elements behave as malignant tumors and metastases, particularly pulmonary metastasis, from congenital teratomas have been reported [356, 362–364]. There are also reports of mature teratoma of the neck with malignant transformation after incomplete resection [365]. Close followup of these patients is required.

Cervical endodermal sinus tumors have been reported. Serum alpha-fetoprotein levels may be elevated in head and neck tumors with endodermal sinus elements [353, 356, 366]. Excision of benign teratomas results in cure. Malignant lesions are treated with surgical resection if possible followed by a multidrug chemotherapy. Patients with unresectable tumors or residual disease may receive irradiation to the primary tumor site. Most patients initially respond to therapy and estimates of long-term disease free survival in children with unresectable germ cell tumors is around 50 % [365, 367].

## Salivary Gland Tumors

Benign and malignant tumors of the salivary glands are rare in children; however when they do occur, the parotid gland is the most common site accounting for approximately 90 % of the cases. Unlike adult salivary gland tumors, pediatric salivary gland tumors have an increased risk of malignancy between 29 and 50 % in various studies [368–370]. Malignant salivary gland tumors are most common in older children and adolescents with a mean age of 13 years [371]. There is a slight female predominance [372–375]. Histologically, salivary neoplasms in children are similar to those seen in adults. The pleomorphic adenoma is the most common benign neoplasm and mucoepidermoid carcinoma the most common salivary gland malignancy [372, 376, 377]. Mucoepidermoid carcinoma (MEC) consists of dermoid and mucus-containing cells. Children tend to present with low or intermediate grade tumors [374]. Low-grade tumors had a decreased rate of recurrence and nodal metastases. It has been suggested that certain tumor makers, specifically PCNA and KI-67 may be linked to high grade MEC though other reviews have not suggested this is not the case [375, 378]. These tumors have been found in children previously treated for childhood cancer with chemotherapy and radiation. Other types of salivary gland tumors include low-grade acinic cell carcinoma, undifferentiated carcinoma, adenocarcinoma, adenoid cystic carcinoma, peripheral neuroectodermal, and malignant mixed tumors all of which occur less commonly [376].

The most common presenting sign in children is a firm preauricular mass. Signs particularly concerning for malignancy are rapid growth, facial weakness or pain and associated lymphadenopathy. Ultrasound, sialogram and CT scan should investigate a swollen parotid gland not suggestive of acute inflammation [379]. A simple hemangioma or lymphangioma should be treated by surgical excision. A pleomorphic adenoma requires a superficial parotidectomy to avoid recurrence. Mucoepidermoid carcinoma requires a total parotidectomy since even well differentiated tumors extend beyond the resection margins. For the soft tissue sarcomas, frozen section allows surface markers, cytogenetic studies and electron microscopy and they are treated appropriately according to the sarcoma or lymphoma protocols as mentioned above.

All firm salivary gland masses should be biopsied [379]. While fine needle aspiration has been used with success in adults, its role in children has not been determined. Incisional biopsy of the parotid gland should be avoided due to the risk of injuring the facial nerve. The only indication for incisional biopsy is for histologic diagnosis of large, unresectable tumors (Fig. 24.15a–d). Superficial or total parotidectomy with preservation of the facial nerve or total excision of the submandibular gland should be the initial procedure. Lymph node dissection is recommended for malignant lesions. Lymphatic metastasis has been report in 37 % of pediatric patients with salivary gland malignancies though only 6 % were noted to have metastatic lymphadenopathy at presentation [376].

In general superficial or total parotidectomy with preservation of the facial nerve is the recommended surgical treatment for salivary gland tumors [380]. Adjuvant radiation can be used for local control of high-grade, high stage tumors or for adenoid cystic carcinoma which are difficult to treat with surgery alone though adjuvant radiation has not been shown benefit long term outcomes [381–383]. Chemotherapy has been used in cases of high-grade or unresectable lesions though its long-term benefits are unknown. The prognosis for low-grade mucoepidermoid carcinoma, acinic cell carcinoma and well-differentiated adenocarcinoma is good, whereas high-grade mucoepidermoid carcinoma, poorly differentiated adenocarcinoma, and undifferentiated tumors do poorly. Mucoepidermoid and acinic cell carcinomas have a 5-year survival of greater than 90 % [384–386]. Survival is related to age with a 50 % 5-year survival in patient 1–4 years old while 95–97 % in patients 10–19 years of age [387].

## Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC) is rare in childhood with an annual incidence of 0.5 per million children. Approximately 10 % of the cases in the US are in children under the age of 16 [388]. It is slightly more common in males and teenagers of African-American descent [389, 390]. Geographically it is more common in China, southeast Asia, the Mediterranean, and Alaska. This geographic

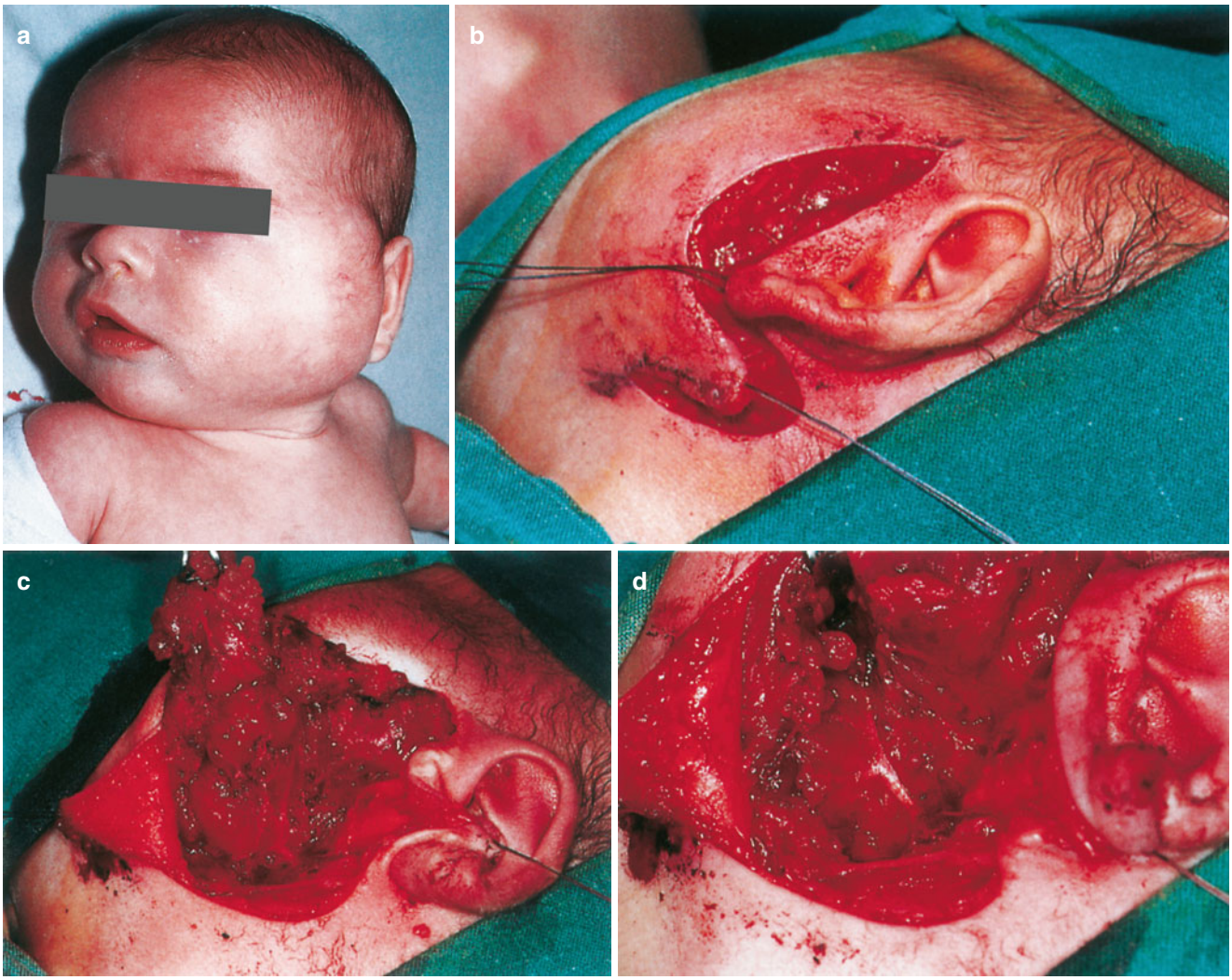


**Fig. 24.15** (**a**) Vascular parotid tumor. (**b**) Incision used for exploration. (**c**) Superficial excision of parotid lobe. (**d**) Bed of the tumor showing the intact facial nerve

variation is thought to be due to both genetic and environmental factors. The two different histopathologic variants are squamous cell and undifferentiated carcinoma. Undifferentiated nasopharyngeal carcinoma, also known as lymphoepithelioma, is most common in children and is associated with EBV exposure [391]. NPC is also known to be associated with certain human leukocyte antigens including HLA A2 Bsin2 haplotype, Aw19, Bw46, and B17 [392, 393]. Cytogenetics have linked NPC with inactivation of p53, retinoblastoma (RB2/p130) tumors suppressor genes, and CYP2E1 [393–397].

The most common presenting symptom is a painless neck mass although a child may also have earache, tinnitus, deafness, otalgia, nasal obstruction and epistaxis. At presentation, most children already have metastatic spread to cervical lymph nodes [398]. Auditory symptoms are often the result of persistent middle ear effusion that may have been present for many months prior to diagnosis of nasopharyngeal cancer. As the cancer invades the base of the skull, cranial nerve palsies and head pain may result. Children may also complain of double vision, eye pain, loss of vision, difficulty swallowing, or hoarseness [392, 393, 399, 400]. Sites of distant metastasis include bone, lung, liver, bone marrow and mediastinum [392, 393, 401]. Factors that influenced outcome included age, race, stage, and histologic type [402].

Initial laboratory data should include a complete blood count, serum chemistry, liver function tests and lactic acid dehydrogenase. Elevated LDH levels have been correlated with poor outcomes. Viral capsid antigen IgA and ZEBRA protein concentration should also be measured for baseline tumor markers. Nasopharyngeal examination and biopsy is performed for diagnosis. For diagnosis and staging a CT scan and MRI are useful [403]. MRI is considered better for assessing extent of primary tumor and perineural invasion

while CT is better for detecting bone involvement. PET/CT and MRI are being used more in the pediatric population to further clarify lesions, assess response to therapy and follow-up these patients [404]. In addition, chest x-rays, CT of the chest and abdomen and radionuclide bone scanning should be performed to evaluate for metastatic disease. Bone marrow biopsy and a lumbar puncture should be performed if there is concern for advanced disease.

Undifferentiated nasopharyngeal carcinoma is radiosensitive and responds well to radiotherapy. For metastatic or recurrent NPC, chemotherapy is combined with radiation therapy. Common chemotherapeutic agents include cisplatin, bleomycin, epirubicin, and fluorouracil. The addition of cisplatin based chemotherapy in addition to radiation has increased the overall 5 year survival of children with nasopharyngeal carcinoma approaches from 20–60 % to now 70–90 % [392, 393, 401, 403, 405–407] The NPC-2003-GPOH/DCOG trial assigned patient to neoadjuvant chemotherapy, radiochemotherapy and/or interferon beta. Chemotherapy consisted of cisplatin, 5-FU, and folinic acid with radiation dosing between 54 and 59 Gy with improved outcomes (92 % event free survival and 97 % overall survival at 30 months) [408]. While outcomes have improved, these patients must be followed closely for complication related to therapy including delayed growth, thyroid dysfunction, and second malignancies [402].

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