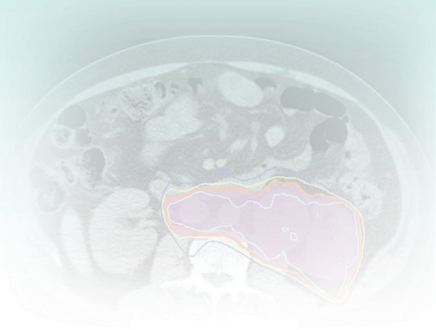
CHAPTER

75 Rare Pediatric Tumors



Luke E. Pater and John Breneman

INCIDENCE

Hepatic tumors: 1.6 per million; male predominance.

Germ cell tumors: 3% of childhood malignancies; female predominance.

Juvenile nasopharyngeal angiofibroma: 0.05% of head and neck tumors.

Pleuropulmonary blastoma: Extremely rare.

Hemangioma and lymphangioma: Hemangiomas: 1% of infants; lymphangiomas: 0.01% of infants.

Diffuse, small, round cell tumor: Extremely rare; primarily affects young males.

Langerhans cell histiocytosis: 1 million to 5 per million; slight male predominance.

Nasopharyngeal cancer: 1% of pediatric cancers; 2:1 male predominance.

BIOLOGIC CHARACTERISTICS

Hepatic tumors: Fetal-type hepatoblasts with sinusoidal hematopoiesis; typically alpha-fetoprotein positive.

Germ cell tumors: Vary widely from undifferentiated germinomas to benign well-differentiated teratomas.

Juvenile nasopharyngeal angiofibroma: Mixed endothelial-lined vessels and fibrous stroma; β-catenin mutations seen in 75%.

Pleuropulmonary blastoma: Mixed blastemal and sarcomatous elements with cystic and solid morphologies. Solid variants behave more aggressively.

Hemangioma and lymphangioma: Abnormal dilated blood or lymph vessels.

Diffuse, small, round cell tumor: Small, round blue cells with collagen dense stroma.

Langerhans cell histiocytosis: Dendritic histiocytes; CD207, S-100, and CD1a positive.

Nasopharyngeal cancer: Mostly lymphoepithelioma; Epstein-Barr virus related.

STAGING

Hepatic tumors: Right upper quadrant ultrasonography, magnetic resonance imaging/computed tomography (MRI/CT) of liver, CT of chest, alpha-fetoprotein level.

Germ cell tumors: Ultrasonography of primary tumor, CT of chest, abdomen, and pelvis; alpha-fetoprotein, β-human chorionic gonadotropin, and lactate dehydrogenase levels.

Juvenile nasopharyngeal angiofibroma: Angiography and CT or MRI of the head.

Pleuropulmonary blastoma: CT of the chest, abdomen, and pelvis; MRI of the brain.

Hemangioma and lymphangioma: CT or MRI of affected site; angiography in selected cases.

Diffuse, small, round cell tumor: CT with intravenous and oral contrast enhancement.

Langerhans cell histiocytosis: Skeletal survey, chest radiography, CT, bone scintigraphy.

Nasopharyngeal cancer: Nasopharyngoscopy, positron emission tomography (PET)/CT, MRI, blood chemistries, and dental and endocrine evaluation.

PRIMARY THERAPY

Hepatic tumors: Neoadjuvant chemotherapy and surgery; overall survival (OS) is about 65% for hepatoblastoma and 25% for hepatocellular carcinoma.

Germ cell tumors: Surgery alone for teratomas or stage I tumors; others get surgery plus chemotherapy. Cure rate is more than 90%.

Juvenile nasopharyngeal angiofibroma: Surgical resection controls approximately 70% of tumors.

Pleuropulmonary blastoma: Surgical resection; cure obtained in 80% of type I tumors and 45% of types II and III tumors.

Hemangioma and lymphangioma: Surgical resection; local control achieved in most patients.

Diffuse, small, round cell tumor: Surgical resection; cure is uncommon.

Langerhans cell histiocytosis: Varies by extent of disease.

Nasopharyngeal cancer: Radiotherapy (RT) with OS of 51% to 95% and relapse-free survival of 36% to 91%

ADJUVANT THERAPY

Hepatic tumors: Cisplatin-based chemotherapy.

Germ cell tumors: Cisplatin/etoposide/bleomycin (PEB) chemotherapy for three to four cycles.

Juvenile nasopharyngeal angiofibroma: Consider RT with 36 Gy to 40 Gy.

Pleuropulmonary blastoma: Chemotherapy with ifosfamide/vincristine/dactinomycin (Actinomycin-D)/doxorubicin (IVADo) or similar regimen.

Hemangioma and lymphangioma: None.

Diffuse, small, round cell tumor: Chemotherapy with alkylating regimen and whole-abdomen irradiation.

Langerhans cell histiocytosis: Surgery, chemotherapy, RT, or corticosteroids.

Nasopharyngeal cancer: Neoadjuvant or adjuvant chemotherapy.

THERAPY FOR LOCALLY ADVANCED DISEASE

Hepatic tumors: Neoadjuvant chemotherapy, surgery, possible liver transplantation; consider RT if unresectable.

Germ cell tumors: Neoadjuvant chemotherapy plus surgery.

Juvenile nasopharyngeal angiofibroma: RT with 36 Gy to 40 Gy controls approximately 80% of tumors.

Pleuropulmonary blastoma: Neoadjuvant chemotherapy with delayed resection. Consider RT with 44 Gy.

Hemangioma and lymphangioma: Surgery, embolization, corticosteroids.

Diffuse, small, round cell tumor: Neoadjuvant chemotherapy, surgical debulking.

Langerhans cell histiocytosis: Low-dose RT or chemotherapy.

Nasopharyngeal cancer: Most disease is locally advanced and treated with chemoradiation.

PALLIATION

Hepatic tumors: Chemotherapy or RT.

Germ cell tumors: Consider RT or additional chemotherapy.

Juvenile nasopharyngeal angiofibroma: Consider diethylstilbestrol or flutamide. Cytotoxic chemotherapy may be effective.

Pleuropulmonary blastoma: RT for brain metastases and symptomatic bone metastases.

Hemangioma and lymphangioma: Consider RT with 10 Gy to 25 Gy for life-threatening conditions.

Diffuse, small, round cell tumor: RT for symptomatic disease.

Langerhans cell histiocytosis: Low-dose RT or chemotherapy.

PRIMARY LIVER TUMORS OF CHILDHOOD

Etiology and Epidemiology

Primary malignant liver tumors (PMLT) in children are rare malignancies representing ~1% of pediatric cancers. They are comprised almost entirely of hepatoblastoma (HBL) and hepatocellular carcinoma (HCC). In people younger than 20 years old, 67% of PMLTs are HBL and 31% are HCC.[1] Age-adjusted rates show a slight male-to-female predisposition for both HBL and HCC.[1,2] HBL has been associated with prematurity, low birth weight, fetal alcohol syndrome, use of maternal oral contraceptives, Beckwith–Wiedemann syndrome, hemihypertrophy, and familial adenomatous polyposis.[3-8] HCC is strongly associated with hepatitis B virus (HBV) as well as α_1-antitrypsin deficiency, hereditary tyrosinemia, extrahepatic biliary a tresia, Fanconi anemia, ataxia-telangiectasia, Sotos syndrome, glucose-6-phosphatase deficiency, congenital hepatic fibrosis, Byler disease, and Wilson disease.[3,9]

Biologic Characteristics and Molecular Biology

There is no familial clustering of HBL, though genetic syndromes are associated with approximately 15% of cases.[10] Familial adenomatous polyposis coli (FAP) with the heritable mutation of the adenomatous polyposis coli (APC) gene has been associated with risk of HBL[11,12] as have been Beckwith–Wiedemann, Sotos syndrome, and Simpson–Golabi–Behmel syndrome. Trisomy 18 has been observed in HBL, particularly in females and patients with multifocal tumors. Other cytogenetic findings in HBL include gains of chromosomes 2, 8, or 20 and loss of 18.[13-16] Mutations of β-catenin and phosphatidylinositol-3-kinase have been reported in sporadic cases,[17,18] as well as differential expression of imprinted genes and altered methylation of gene promoters.[19-21]

HBV is associated with nearly all cases of HCC in areas endemic for HBV.[22] Molecular hybridization reveals incorporation of viral DNA into both malignant and adjacent benign liver cells. The time to development of HCC in children after HBV infection is known to be shorter in children than in adults.

Pathology and Pathways of Spread

HBL is an embryonal tumor thought to arise from a hepatocyte precursor cell, and accounts for 60% to 75% of PMLTs of childhood.[23,24] Two subtypes are recognized; epithelial and mixed, with epithelial type further divided into fetal, embryonal, macrotrabecular, small-cell undifferentiated (SCU), and cholangioblastic variants. The SCU variant has a particularly poor prognosis and is often viewed distinctly for treatment decisions. Within the mixed type, stromal and teratoid variants are identified.[25]

There is a strong relationship between HCC and preexistent hepatic disease or cirrhosis. Fibrolamellar HCC is a variant found in approximately one third of pediatric HCC and typically in cases without preexisting liver disease.[25] This variant has sometimes been reported to have a higher rate of resectability and improved clinical outcome, though this was not supported by the Pediatric Intergroup Hepatoma INT-0098 results.[26]

Clinical Manifestations, Patient Evaluation, and Staging

The majority of children with PMLTs present with a painless right upper quadrant abdominal mass. Additional findings may include abdominal enlargement, pain, anorexia with associated weight loss, nausea, emesis, fever, and jaundice.

Initial evaluation consists of abdominal ultrasound with characteristic findings of a solid intrahepatic mass. Subsequent evaluation should include dual-phase CT of the abdomen and pelvis or axial and coronal MRI with gadolinium at arterial, portal venous, and equilibrium phases. CT of the chest is also required because lung metastases are present in approximately 20% of HBL cases and 30% of HCC cases. Bone scan is reserved for symptomatic patients.[27-29] Laboratory evaluation includes: complete blood count (CBC), differential, platelets, urinalysis, electrolytes including calcium, phosphate, magnesium, creatinine, ALT/AST, bilirubin and total protein/albumin. Alpha-fetoprotein (AFP) is elevated in approximately 90% of patients with HBL and between 60% and 80% of patients with HCC.[28,30] AFP levels less than 100 ng/mL have been associated with poor prognosis.

PMLTs of childhood are typically staged using the Children's Oncology Group Staging system (Table 75-1) and the PRETEXT surgical staging system (Figure 75-1). The PRETEXT staging is based on the number and relative locations of involved liver segments on preoperative imaging. The left lobe of the liver consists of a lateral sector (segments 2 and 3) and a medial sector (segment 4), whereas the right lobe is divided in an anterior sector (segments 5 and 8) and a posterior sector (segments 6 and 7). The number of affected liver

TABLE 75-1 Children's Oncology Group Staging System for Hepatoblastoma

Stage	Description
I	Completely resected localized tumors
II	Grossly resected tumors with microscopic residual tumor
III	Unresectable tumors (measurable residual tumor or abdominal lymph node involvement)
IV	Distant metastases

From Schnater JM, Kohler SE, Lamers WH, et al: Where do we stand with hepatoblastoma? A review. Cancer 98:668–678, 2003.

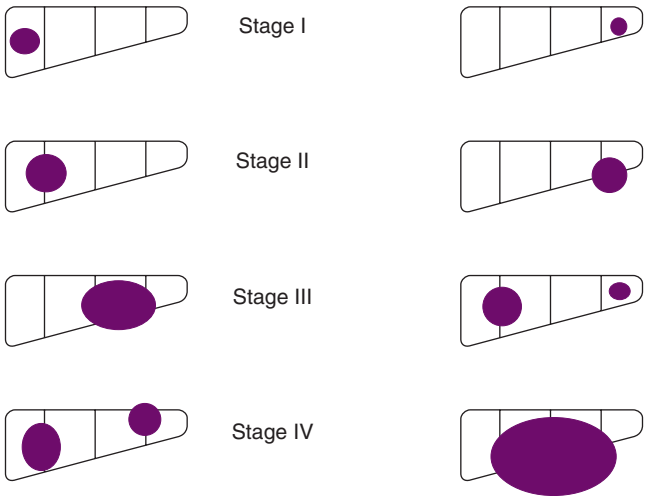


Figure 75-1 PRETEXT surgical staging system for hepatoblastoma. *Adapted from Schnater JM, Aronson DC, Plaschkes J, et al: Surgical view of the treatment of patients with hepatoblastoma. Results from the first prospective trial of the International Society of Pediatric Oncology Liver Tumor Study Group. Cancer 94:1111–1120, 2001.*

sectors determines the PRETEXT category.[27] Staging using the same criteria applied after two to four cycles of chemotherapy is referred to as POST-TEXT. Additional staging notations can be made for involvement of the vena cava or all three hepatic veins (+V), involvement of the portal vein bifurcation or both right and left portal veins (+P), involvement of the caudate lobe (+C), extrahepatic contiguous tumor (+E), and distant metastatic disease (+M).

Primary and Adjuvant Therapy and Results

Surgical resection is the primary treatment modality for PMLTs of childhood and provides the only potential for cure. Approximately half of patients with HBL are able to undergo complete resection at the time of diagnosis. Because HBL is highly chemosensitive, many patients are treated with neoadjuvant chemotherapy, which increases resectability to approximately 75%. Patients with HBL undergoing complete resection have an event-free survival (EFS) of approximately 90%.

The SIOPEL-1 trial reported by the International Society of Paediatric Oncology (SIOP) evaluated the use of four to six courses of preoperative cisplatin and doxorubicin. Eighty-two percent of patients showed at least a partial response and 77% achieved complete resection. The 5-year EFS and OS were 66% and 75%, respectively.[29] The third study of the International Society of Paediatric Oncology Epithelial Liver Tumor Group (SIOPEL-3) randomized patients to cisplatin alone versus cisplatin plus doxorubicin for three cycles preoperatively, followed by two postoperative cycles in children with HBL involving three or fewer liver segments and an alpha-fetoprotein level greater than 100 ng/mL. Outcomes at 3 years were identical: 95% and 93% underwent complete resection in the respective chemotherapy arms, and OS was 95% and 93%, respectively. Grade-3 and grade-4 toxicities were significantly more common in the combination arm.[31]

An analysis of stage I pure fetal histology (PFH) HBL treated with complete surgical resection only on Children's Oncology Group Study P9645 showed all patients free of disease at a median follow-up of 4.9 years.[26]

Children with HCC on the SIOPEL-1 trial presented with more advanced disease and fared significantly worse than patients with HBL. Partial response to neoadjuvant chemotherapy was seen in 49%, and complete resection was achieved in only 36%; 5-year OS and EFS were 28% and 17%, respectively.[28] The Pediatric Intergroup Hepatoma Protocol INT-0098 randomized patients with HCC to postoperative cisplatin/vincristine/5-fluorouracil versus cisplatin and doxorubicin. There was no difference in outcome between the treatment regimens, and the overall 5-year EFS was 17% (75% for stage I, 8% for stage II, and 0% for stage IV).[28] Subsequent SIOPEL studies evaluated a regimen of cisplatin and carboplatin, with no substantial improvement in outcome.[28]

The current COG study reduces chemotherapy for patients with low-risk disease with stage I non-pure fetal histology, non-SCU HBL or stage II non-SCU HBL to two adjuvant cycles of cisplatin, 5-flouorouracil and vincristine (C5V). Intermediate-risk cases with stage I SCU, stage II SCU, or any stage III are given six cycles of C5V + doxorubicin (C5VD).

Locally Advanced Disease and Palliation

Patients with high-risk HBL include those with stage IV disease as well as patients with any stage of HBL or initial AFP under 100 ng/mL. The Pediatric Oncology Group study 9345 treated children with unresectable or metastatic HBL with neoadjuvant carboplatin and C5VD, followed by surgery when feasible, or with high-dose cisplatin and etoposide. Thirty-six percent of patients with stage IV disease were able to undergo subsequent resection. For patients able to undergo resection, 5-years EFS was 79%.[32] The recent SIOPEL-4 trial was a single-arm prospective study for high-risk HBL using neoadjuvant dose-dense cisplatin plus doxorubicin. This approach yielded good outcomes with 74% of children able to undergo complete resection and an 83% 3-year OS.[33] Other approaches include orthotopic liver transplantation when disease is unresectable, with documented long-term survival in a limited number of patients.[27,32]

The approach for patients with metastatic disease uses neoadjuvant chemotherapy followed by surgery, if possible, and consideration of metastectomy if local control is achievable. For patients considered for orthotopic liver transplantation, radiographic clearance of metastatic disease must be confirmed before transplant.

Irradiation Techniques

RT is infrequently used in the treatment of PMLTs. Habrand et al used doses of 25 Gy to 45 Gy in conjunction with chemotherapy in a heterogeneous group of 15 patients; 11 with documented HBL, 2 with HCC, and 2 with unknown pathology. Those with inoperable HBL or minimal (<2 cm) disease postoperatively showed a possible benefit of radiotherapy. No benefit was seen for patients with HCC.[34] There are few current indications for hepatic irradiation or treatment beyond palliation to metastatic sites with HBL or HCC. The current Children's Oncology Group HBL study specifically excludes use of RT. It is clear that the RT dose ranges noted previously are less than those now known to be necessary in adults with HCC. Modern techniques of respiratory gating and stereotactic techniques may provide for additional options for RT of pediatric liver tumors in select cases.

Treatment Algorithms, Controversies, Challenges, and Future Possibilities

The cornerstone of treatment for PMLTs is surgical resection. Most children are treated with neoadjuvant and adjuvant platinum-based chemotherapy because of bulky disease. Orthotopic liver transplantation can provide cures for selected patients in whom resection is not possible. Investigational treatments for HBL include chemoembolization, stereotactic

radiosurgery to focal liver lesions, angiogenesis inhibitors, and biologic agents.

PEDIATRIC EXTRACRANIAL GERM CELL TUMORS

Etiology and Epidemiology

Germ cell tumors (GCTs) can be either malignant or benign and are thought to arise from primitive germ cells that fail to undergo complete differentiation. These tumors are found within the ovary and testis, but also among midline structures such as the sacrococcygeal region, retroperitoneum, mediastinum, and the pineal gland. The rationale for their distribution is attributed to embryologic development as cells migrate from the allantoic stock to the genital ridge, coming to rest as the genitalia.[35]

GCTs account for approximately 3% of all pediatric malignancies[35] and are the most common malignancy in neonates.[36] The overall incidence of GCTs is higher in females, but males are more at risk for malignant GCTs.[37] A bimodal age distribution is noted with peaks at 2 and 20 years of age.

Prevention and Early Detection

Several risk factors have been identified for these rare tumors. Intersex disorders of pseudohermaphroditism, androgen insensitivity, and 5α-reductase deficiency are associated with risk of gonadoblastoma, which can transform into GCT.[38] Undescended testis increases the incidence of testicular GCT to 30 to 50 times the incidence in the general population. This risk is even higher for intraabdominal testis.[39-41]

Biologic Characteristics and Molecular Biology

Pediatric GCTs are genetically distinct from adult GCTs. More than 80% of adult GCTs have isochromosome 12p and many of the remaining display amplification of 12p. These are infrequently observed abnormalities in pediatric GCTs,[42-44] where aberrations on chromosome 1 and 6 are more commonly identified.[43,44]

Pathology and Pathways of Spread

GCTs comprise a spectrum of entities from benign to malignant, with elements of multiple histologic types present in 25% of cases.[45] The most common pediatric GCT is the teratoma, which is composed of tissue from more than one embryonic layer. Teratomas can be either mature, consisting of well-differentiated tissues, or immature, consisting of immature elements (most commonly neuroepithelial tissue).

Yolk sac or endodermal sinus tumors are highly malignant, occur most commonly in the ovary, testis, and sacrococcygeal region and secrete alpha-fetoprotein. Histologically they show classic perivascular formations called Schiller-Duval bodies. Embryonal carcinomas are composed of large, pleomorphic undifferentiated cells. They often occur in combination with endodermal sinus tumors. Choriocarcinomas are rare tumors composed of malignant cytotrophoblasts and syncytiotrophoblasts. They typically secrete β-human chorionic gonadotropin. All three of these GCT types are highly undifferentiated tumors with the propensity to metastasize to lung, liver, bone, and lymph nodes. In a series of 95 patients with sacrococcygeal endodermal sinus tumors,[45] 15% had positive lymph nodes at diagnosis and 35% had distant metastases.

Tumors of undifferentiated germ epithelium are named according to the site of origin: seminomas originate in the testis, dysgerminomas in the ovary, and germinomas in the brain. Seminoma and dysgerminoma are infrequent in childhood.

Clinical Manifestations, Patient Evaluations, and Staging

Clinical manifestations of GCTs are largely dependent on the location of the tumor. The most common location for pediatric extracranial GCTs is the sacrococcygeal region, and because of their early presentation, they may sometimes be identified by fetal ultrasound. Older children more commonly present with large pelvic masses, with malignant degeneration often seen in children over 6 months to 12 months of age. The ovaries, testes, and mediastinum are also common sites, but GCTs can occur in the retroperitoneum, neck, stomach, and vagina as well. Laboratory evaluation includes complete blood count with differential, urinalysis, tumor markers (AFP, β-human chorionic gonadotropin, lactic dehydrogenase, CA-125), electrolytes, creatinine, bilirubin, ALT, alkaline phosphatase, total protein, albumin, phosphorus, magnesium, and calcium. Diagnostic imaging should include chest/abdomen/pelvis CT or MRI and often bone scan. Tumor marker profiles are indicative of different histologies as noted in Table 75-2.

Sacrococcygeal tumors are staged according to the Altman classification. Type I tumors are predominantly external projecting from the sacrococcygeal region and presenting with distortion of the buttocks. Type II tumors are predominantly external but also have a large intrapelvic component. Type III tumors are predominantly intrapelvic with a small external component, and Type IV tumors are entirely internal with no external or buttock component.[46]

Other GCTs are staged according to their site of origin as defined by the Children's Cancer Group and Pediatric Oncology Group staging system outlined in Table 75-3.

Primary Therapy, Adjuvant Therapy, and Results

Primary therapy is dictated by the resectability of the presenting lesion as well as the histology and thus anticipated response to adjuvant therapy options. For most malignant tumors a multidisciplinary approach combining surgery and

TABLE 75-2 Profiles of Germ Cell Tumor Histologies

	AFP	β-HCG	Chemosensitivity	Radiosensitivity
Teratoma				
Mature	—	—	—	—
Immature	–/+	—	—	—
Endodermal sinus tumor	+++	—	+++	—
Choriocarcinoma	—	+++	+++	—
Embryonal carcinoma	—	—	—	—
Seminoma/germinoma	—	+	+++	+++

TABLE 75-3 Children's Cancer Group and Pediatric Oncology Group Staging System for Pediatric Germ Cell Tumors

Stage	Description
OVARIAN	
I	Limited to ovary (ovaries), peritoneal washings negative, tumor markers normal after appropriate half-life
II	Microscopic residual or positive lymph nodes (<2 cm), peritoneal washing negative, tumor markers positive or negative
III	Lymph node involvement >2 cm, gross residual disease, biopsy only, contiguous visceral involvement, peritoneal washings positive, tumor markers positive or negative
IV	Distant metastases
TESTICULAR	
I	Limited to testis, tumor marker normal after appropriate half-life, completely resected with high inguinal orchiectomy
II	Transscrotal orchiectomy, microscopic disease in scrotum or high in spermatic cord, retroperitoneal lymph node <2 cm, increased tumor marker after appropriate half-life
III	Retroperitoneal lymph node >2 cm, no visceral of extraabdominal involvement
IV	Distant metastases
EXTRAGONADAL	
I	Complete resection at any site, negative margins, coccygectomy for sacrococcygeal sites
II	Microscopic residual, lymph nodes negative
III	Gross residual or biopsy only, regional lymph nodes positive or negative
IV	Distant metastases

cisplatin-based chemotherapy (often similar to the adult PEB regimen of cisplatin, etoposide, and bleomycin) is standard.

Sacrococcygeal teratomas are approached with the goal to preserve the levator ani musculature and external sphincter using an inverted-V incision. Inadequate surgery has proven deleterious with a 37% local recurrence rate if the coccyx is spared inappropriately.[47]

Ovarian GCTs are chemosensitive and a conservative surgical approach is usually indicated. Resection of the primary tumor sparing the fallopian tumor if possible is combined with collection of ascites and examination and palpation of the peritoneal surfaces, retroperitoneal lymph nodes, omentum, and the contralateral ovary.[48] These fertility-sparring approaches have cure rates of approximately 95% with 80% of patients preserving reproductive function.[49]

Testicular tumors are removed via a high inguinal incision with high inguinal orchiectomy performed for malignant lesions and a more conservative tumor enucleation for teratoma.

Adjuvant therapy for extracranial GCTs is based on the stage, degree of resection, and histologic subtype (Table 75-4). Observation is recommended following resection of mature and immature teratomas with reported survivals of 82% to 100%.[47]

Resection of sacrococcygeal tumors with negative margins provides cure rates in excess of 90%, though this falls to 75% to 85% in the setting of microscopically involved margins, and 40% for macroscopic residual tumor.[50] There is minimal guidance for the use of RT in the adjuvant setting. A dose of ≥45 Gy

TABLE 75-4 General Treatment Guidelines for Extracranial Germ Cell Tumors

LOW-RISK DISEASE	
All teratomas Stage I gonadal Stage I extragonadal	Surgery and observation
INTERMEDIATE-RISK DISK	
Stages II-IV gonadal Stage II extragonadal	Surgery with adjuvant chemotherapy
HIGH-RISK DISEASE	
Stages III-IV extragonadal	Surgery with adjuvant chemotherapy
INITIAL UNRESECTABLE OR BIOPSY ONLY	Neoadjuvant chemotherapy followed by second surgery, followed by adjuvant chemotherapy for residual pathologic disease

appears reasonable based on a report by Schneider et al.[51] Platinum-based chemotherapy has been advocated for patients with recurrent immature teratomas based on the POG 9048/CCG 8891 trial. Four of five patients with recurrence were rendered disease-free using this salvage approach.[52]

Locally Advanced Disease and Palliation

With a primary goal of resection, bulky and locally invasive disease is treated with neoadjuvant chemotherapy followed by surgery or second-look surgery as appropriate.

The POG 9049/CCG 8882 trial[53] randomized patients with stages III and IV gonadal and stages I to IV extragonadal GCTs to high-dose PEB versus standard-dose PEB with a 6-year EFS of 89.6% versus 80.5% but no benefit in OS. Progressive and metastatic GCTs often respond to cisplatin, paclitaxel, and ifosfamide regimens.[53] The COG AGCT0521 study used the regimen with carboplatin substituted for cisplatin with the goal to improve the toxicity profile. The addition of hyperthermia to resection for relapsed disease is being explored.[54]

Irradiation Techniques

The role of RT for GCTs has diminished significantly owing to the effectiveness of current chemotherapy regimens. RT is now used only in the setting of unresectable disease that is unresponsive to chemotherapy or in the setting of relapse. Radiation doses of ≥40 Gy are typically used.[51]

Treatment Algorithms, Controversies, Challenges, and Future Possibilities

Surgical resection is the first line of treatment with chemotherapy given neoadjuvantly to achieve this goal when possible and in cases of recurrent or metastatic disease. PEB chemotherapy is the currently recommended regimen for patients presenting as locally advanced or metastatic tumor with OS approaching 75%. Because of the high curability of these tumors, current protocols are seeking to decrease toxicity of therapy using algorithms based on histology, site, stage, and genetic aberrations to provide risk-adapted therapy.

JUVENILE NASOPHARYNGEAL ANGIOFIBROMA

Etiology and Epidemiology

Juvenile nasopharyngeal angiofibroma (JNA) is a highly vascular tumor that is histologically benign but locally invasive.

JNA occurs almost exclusively in adolescent boys and young adult men, suggesting a prominent hormonal role in the tumor's etiology; the average age at diagnosis is 17 years.[55,56] The incidence of this tumor is approximately 3.7 per million in the population at risk.[57] There is an increased incidence of JNA in patients with familial adenomatous polyposis, suggesting a connection to the β-catenin pathway.[58]

Biologic Characteristics and Molecular Biology

Both androgen and estrogen receptors have been demonstrated in JNAs.[59,60] Recently, estrogen beta-adrenergic receptors have been found in a high percentage of JNAs. Schlauder et al[60] have postulated that the presence of aromatase in tumor cells converts endogenous androgens to estrogens, causing tumor growth via an autocrine-like mechanism.[61] Most tumors stain for vascular endothelial growth factor, and approximately 40% have a GSTM1 mutation.[62]

Pathology and Pathways of Spread

JNA is a benign tumor, although its exact nature is controversial. Some have suggested that it is a vascular hamartoma and similar to a hemangioma,[63] but others believe it is neoplastic.[64] Histologically, tumors are composed of fibrous connective tissue with abundant endothelium-lined vascular spaces.[63] Localization of β-catenin to tumor stromal cells suggests these may be the neoplastic component rather than the endothelial cells.[65] Tumors typically arise from the superior margin of the sphenopalatine foramen and invade laterally through the pterygomaxillary fissure toward the infratemporal fossa.[55] Intracranial extension is seen in up to a third of cases, although actual dural invasion is uncommon.[66,67] Tumors can be locally invasive of bone and extend into the parapharyngeal spaces, paranasal sinuses, orbit, and base of skull. This pattern of spread predicts for a high risk of local recurrence.[67] Blood supply is primarily from the internal maxillary arteries of the external carotid system.

Clinical Manifestations, Patient Evaluation, and Staging

Presenting symptoms include recurrent painless spontaneous epistaxis, nasal obstruction, nasal discharge, a reduced sense of smell, snoring, headache, cranial nerve palsies, and facial swelling.[56] Angiography is essential to define the tumor's blood supply for planning surgery and, typically, for preoperative embolization to decrease surgical blood loss. There are usually multiple tortuous feeding vessels with a dense, homogeneous blush in the capillary phase.[68] CT and MRI help define the anatomic extent of the enhancing tumor. Distant metastases do not occur, so systemic evaluation is not required. Biopsy can be hazardous owing to the tumor's vascularity; not all authors require biopsy confirmation before treatment if clinical and radiographic data are consistent with the diagnosis.[69]

Several staging systems have been proposed (Table 75-5). Most are designed to guide decisions regarding the resectability and optimal surgical approach to the tumor rather than to predict prognosis.[69-73]

TABLE 75-5 Staging Systems for Juvenile Nasopharyngeal Angiofibroma

ANDREWS STAGING SYSTEM[36]	
Stage I	Tumor limited to the nasal cavity and nasopharynx
Stage II	Tumor extension into the pterygopalatine fossa, or maxillary, sphenoidal, or ethmoidal sinuses
Stage IIIa	Extension into the orbit or infratemporal fossa without intracranial extension
Stage IIIb	Stage IIIa with minimal extradural intracranial extension
Stage IVa	Extensive extradural intracranial or intradural extension
Stage IVb	Extension into cavernous sinus, pituitary, or optic chiasm
CARRILLO STAGING SYSTEM[34]	
Stage I	Tumor limited to nasopharynx, nasal fossae, maxillary antrum, anterior ethmoid cells, and sphenoidal sinus
Stage IIa	Invasion to pterygomaxillary fossae or infratemporal fossae anterior to pterygoid plates, with major diameter <6 cm
Stage IIb	Invasion to pterygomaxillary fossae or infratemporal fossae anterior to pterygoid plates, with major diameter ≥6 cm
Stage III	Invasion to infratemporal fossae posterior to pterygoid plates or posterior ethmoid cells
Stage IV	Extensive skull base invasion >2 cm or intracranial invasion
CHANDLER STAGING SYSTEM[37]	
Stage I	Tumor confined to the nasopharynx
Stage II	Tumor extending into the nasal cavity or sphenoidal sinus
Stage III	Tumor involvement of one or more of the maxillary or ethmoidal sinuses, pterygomaxillary and infratemporal fossae, and orbit or cheek
Stage IV	Tumor extending into the cranial cavity
FISCH STAGING SYSTEM[35]	
Type I	Tumor limited to the nasopharynx and nasal cavity with no bone destruction
Type II	Tumors invading the pterygomaxillary fossa and the maxillary, ethmoidal, and sphenoidal sinuses with bone destruction
Type III	Tumors invading the infratemporal fossa, orbit, and parasellar region remaining lateral to the cavernous sinus
Type IV	Tumors with massive invasion of the cavernous sinus, optic chiasmal region, or pituitary fossa

Primary and Adjuvant Therapy and Results

Surgical removal, often preceded by tumor embolization, is the primary treatment for JNA. A craniofacial approach is used for locally advanced tumors. Endoscopic techniques have less morbidity and are effective for earlier-stage lesions.[55] Gross total removal is usually curative.[66] A number of cases prove not to be amenable to complete resection; depending on case selection, there is a rate of local recurrence after surgery that approximates 20% to 40%, with most recurrences occurring in large, incompletely resected lesions.[55,56] Moderate doses of RT may be indicated for postoperative residual tumor, although observation is more often considered because spontaneous involution of tumor is a well-recognized phenomenon.[74,75] Most recurrences present within a year of surgery. The risk of recurrence is greatest in patients with large tumors that erode the skull base, young age at presentation, and irradiated tumors that are slow to regress.[68,76] There are

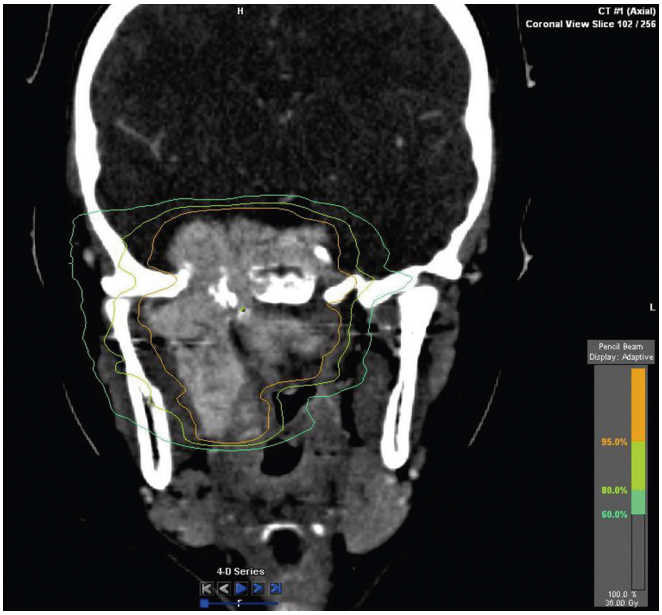


Figure 75-2 Intensity-modulated radiation therapy (IMRT) isodose plan for a patient with juvenile nasopharyngeal angiofibroma.

currently no indications for adjuvant chemotherapy after initial resection.

Locally Advanced Disease and Palliation

RT can provide effective control for recurrent or large, unresectable tumors. Objective tumor response after RT is typically slow, but ultimate control rates range from 75% to 92%[77]; 90% of responders have no residual tumor 3 years after treatment.[78] Given the strong association of JNA with hormonal receptors, there has been interest in hormonal manipulation for patients with advanced disease. Diethylstilbestrol and flutamide have been used, but results have been inconsistent.[68,79,80] A recent trial supports the use of flutamide in postpubertal patients with 13 of 15 patients showing a partial radiographic response to this agent.[81] Case reports of chemotherapy for recurrent tumor show efficacy for doxorubicin, dactinomycin, vincristine, cyclophosphamide, and cisplatin in selected patients.[82-84]

Techniques of Irradiation

No radiation dose-response curve has been reported for JNA. Local control rates greater than 80% are seen with doses ranging from 30 Gy to 50 Gy,[69,85-89] and a dose of 36 Gy is commonly used. Intensity-modulated RT (IMRT) techniques provide high conformality for sparing of normal structures (Figure 75-2). Stereotactic radiosurgery using single doses of 17 Gy to 20 Gy and hypofractionated RT using 45 Gy in three fractions have been reported effective in small series of patients.[90]

Treatment Algorithms, Controversies, Challenges, and Future Possibilities

Preoperative embolization is followed by maximal surgical resection. Postoperative residual tumor can be observed or treated with RT. Recurrent tumor can be managed with RT. Hormonal manipulation and cytotoxic chemotherapy may be tried for recurrent, refractory disease. The elevated levels of vascular endothelial growth factors in these tumors suggest a potential role for inhibitors of angiogenesis.[91]

PLEUROPULMONARY BLASTOMA

Etiology and Epidemiology

Pleuropulmonary blastoma (PPB) is a dysontogenetic neoplasm of childhood that originates in the lung or pleura.[92] Although rare, it is the most common primary lung tumor in children.[93] It is analogous to other dysontogenetic tumors such as Wilms' tumor, neuroblastoma, and hepatoblastoma.[94]

PPB is thought to progress through a distinct sequence of clinical and pathologic changes beginning as a relatively nonaggressive cystic lesion and subsequently developing into the more malignant mixed cystic/solid and purely solid morphologies.[95] Median age at presentation is 3 years.[96] Younger children typically present with predominantly cystic tumors, whereas older children are more likely to have significant solid components.[97] Boys and girls are equally affected.[97] Siblings of patients with PPB have a higher incidence of PPB than the general population, and mutations of in *DICER1* have been found in many of these families.[98] There is also an increased incidence of other types of dysplasia and neoplasia in relatives of children with PPB.[99]

Prevention and Early Detection

The incidence of PPB in apparently benign lung lesions such as congenital cystic adenomatoid malformations is approximately 4%.[100] However, cystic PPB is clinically indistinguishable from benign cysts, and some authors recommend excision of all such lesions.[101] Further supporting this approach is evidence that PPB can arise de novo from lung cysts, so that resection of these "precancerous" lesions is indicated.[102,103] Others advocate a policy of watchful waiting for purely cystic lesions, only intervening if radiographic changes suggest progression.

Biologic Characteristics and Molecular Biology

Germline mutations of *DICER1*, a gene coding for an endoribonuclease involved in regulation of mesenchymal proliferation, have been identified in families affected by PPB.[98] *TP53* mutations have been described in PPB and may portend a worse prognosis.[104] Polysomy of chromosome 8 has also been noted.[105]

Pathology and Pathways of Spread

Histologically, PPB has small, primitive blastemal cells separated by an uncommitted sarcomatous stroma.[94,97,106] Tumor cells stain with vimentin and may show myogenic differentiation.[93] Rhabdomyoblasts and cartilage nodules are reported in 40% to 50% of patients.[101]

Tumors usually arise in the lung parenchyma. Spread to contiguous structures such as the mediastinum and pleura is associated with a poorer prognosis. Invasion into the chest wall is uncommon.[107] Hematogenous metastases occur, most often to the brain. In one series,[92] the incidence of brain metastases was 11% in mixed cystic/solid tumors and 54% in purely solid tumors.

Clinical Manifestations, Patient Evaluation, and Staging

Presenting symptoms of PPB include cough, dyspnea, wheezing, symptoms of respiratory infection, and occasionally, spontaneous pneumothorax. Chest CT usually reveals a heterogeneous low-attenuation mass with pleural effusion and

mediastinal shift.[107] Differential diagnosis includes rhabdomyosarcoma, Askin tumor, and nonrhabdoid sarcomas; examination of the cystic fluid or solid tumor is required to make a diagnosis. Bone scintigraphy and MRI of the brain should be performed for staging, especially for tumors with a significant solid component.

PPB has no anatomic staging system but is classified into three morphologic types that have prognostic significance. Type I consists of purely cystic tumors, type III lesions are solid tumors, and type II have mixed cystic and solid components.[108] Both type II and type III tumors have significantly poorer prognosis than type I, with an incidence of distant metastases at diagnosis approximating 30%.[96] A fourth type, type Ir (type I, regressed), has been described for cystic lesions without a neoplastic component, hypothesized to have "regressed" from an earlier type I PPB, or alternatively, represent a genetically determined lung cyst that has not yet evolved along a dysplastic path.[109]

Primary and Adjuvant Therapy and Results

Surgery is the cornerstone of management, although most patients cannot undergo gross total resections owing to involvement of critical structures.[96,106] Neoadjuvant chemotherapy can be used in large tumors to render the tumor resectable; adjuvant chemotherapy is often given postoperatively to patients with types II and III tumors. Chemotherapy may improve survival in type I tumors,[95,109] although it is not generally recommended if the tumor is completely resected.[96] Drug regimens parallel those used for other pediatric sarcomas and include ifosfamide/carboplatin/etoposide (ICE regimen), and ifosfamide/vincristine/dactinomycin (Actinomycin-D)/doxorubicin (IVADo regimen). Other active drugs include irinotecan[110] and cisplatin.[97] RT may be indicated in unresectable tumors, although large treatment volumes and young patient age often hinder the use of this modality.[111] Five-year survival rates are approximately 80% for patients with type I tumors and 45% for patients with types II and III.[96,97,106]

Locally Advanced Disease and Palliation

In patients who experience a recurrence, local relapse is somewhat more common than distant failure.[96] When type I tumors recur, they usually recur as types II or III.[95,101] Re-resection should be performed when possible, but second-line chemotherapy is often the primary treatment owing to the extent of disease. RT may be useful for brain metastases and palliation of painful bone lesions.

Irradiation Techniques

Fractionated external beam RT using a dose of 44 Gy has been recommended for incompletely resected tumors, although its role in local control is difficult to assess.[96,106] Normal tissue tolerances may preclude this amount of irradiation; use of a lesser dose may be required in circumstances in which volume and dose exceed organ tolerance. Microscopic margins were controlled in one case report using 36 Gy,[97] but local recurrence was reported after 30 Gy in 10 fractions in a patient with gross tumor.[112] Intracavitary phosphorus-32 has also been used and may contribute to local control in selected patients.[106]

Treatment Algorithms, Controversies, Challenges, and Future Possibilities

Initial resection is performed if possible. Neoadjuvant chemotherapy is used when initially unresectable, followed by delayed surgery. Adjuvant chemotherapy is indicated for most patients. RT should be considered for microscopic or gross residual tumor after surgery. Children should be followed with chest CT at 3-month to 6-month intervals for 2 to 3 years.

HEMANGIOMAS AND LYMPHANGIOMAS

Etiology and Epidemiology

Although often considered together, hemangiomas and lymphangiomas are clinically and histologically distinct entities. Many semidescriptive terms have been applied to these lesions (especially the cutaneous hemangiomas), contributing to confusion regarding their study and management. Synonyms for cutaneous hemangioma include "neonatal stain," "stork bite," "salmon patch," "spider angioma," and "strawberry angioma."

Hemangiomas occur in about 1% of infants, most often during the first few months of life, with about a third of these presenting in the head and neck.[113] Lymphangiomas are much less common, with an incidence between 1 in 6,000 and 1 in 16,000 live births.[114] Half are congenital; 90% are evident before the age of 2 years. Three fourths of lymphangiomas occur in the neck or head areas.

Pathology and Pathways of Spread

Hemangiomas consist of thin-walled vessels lined by endothelial cells and a discontinuous layer of pericytes and reticular fibers.[115] They have been reported to occur in a wide variety of locations, including the skin, liver, bone, central nervous system (CNS), bladder, trachea, and other soft tissues.[116] Lymphangiomas are dilated endothelial-lined lymph channels with thick walls containing smooth muscle.[117] Lymphangiomas can involve the skin, skeletal tissue, spleen, liver, mediastinum, or lung.[118] Hemangiomas and lymphangiomas classically are malformations or low-grade and benign neoplasms with no capacity for metastasis.

Clinical Manifestations, Patient Evaluation, and Staging

Hemangiomas are classified as capillary, cavernous, or mixed, depending on the size of the vessels involved. When they involve the skin, capillary hemangiomas are often raised, circumscribed red lesions. They usually present early in the first year of life, and the great majority undergo spontaneous involution over the subsequent years. They are distinct from vascular malformations such as port-wine stains, which do not regress.[113] Clinical manifestations of hemangiomas are largely dependent on the location of the lesion and can include cosmetic deformity, functional impairment, airway obstruction, bleeding, infection, and high-output cardiac failure. Kasabach–Merritt syndrome describes a giant hemangioma causing thrombocytopenia due to consumption coagulopathy.

Lymphangiomas are also categorized according to the size of the abnormal lymph vessels. Lymphangioma circumscriptum contains relatively small-caliber lymph channels and is usually superficial in location. Cystic hygroma or cavernous lymphangioma consists of large, cystic areas of lymph fluid arising in deeper tissues. Unlike hemangiomas, lymphangiomas do not tend to regress spontaneously and may enlarge during adolescence.[119] Symptoms of lymphangiomas can include disfigurement, pain, infection, and complications of chronic lymph secretion. Lymphangiomas occurring in the mediastinum may cause chylothorax, which can be life threatening.

Classification schemes have been proposed for these lesions, but there is no widely accepted staging system.[115,120]

Primary and Adjuvant Therapy and Results

RT was the mainstay of therapy for both hemangiomas and lymphangiomas through the early 1950s and, in some centers, into the 1970s. Subsequently, the use of RT has been all but abandoned as the natural history of spontaneous involution of hemangiomas was recognized and the late morbidities of RT were reported.[121]

Spontaneous involution will occur in 95% of capillary hemangiomas over the course of several years; most require no treatment.[122] Cavernous hemangiomas do not usually regress spontaneously and require treatment if symptomatic.[115] For symptomatic hemangiomas, topical or intralesional corticosteroids are often the first line of treatment.[123] Systemic corticosteroids are also effective.[113] Surgical resection is an effective treatment in appropriate circumstances. Other treatments include interferon, laser ablation, cryotherapy, compression, electrocautery, and embolization. Other pharmacologic interventions include antiangiogenic and antifibrinolytic agents. Irradiation for hemangiomas with life-threatening complications can be performed and is often effective, with improvement or resolution occurring in more than 80% of patients.[116,124]

Surgical removal of lymphangiomas is curative, although can be cosmetically or functionally morbid in many anatomic sites. Sclerotherapy using agents such as OK-432 or bleomycin is a common nonsurgical treatment, with complete responses seen in about 40% of patients and partial responses in another 40% to 45%.[114] Other nonsurgical therapies include diathermy, cryotherapy, and interferon alfa-2b.[118] RT has also been used with some efficacy in selected patients.[119,125-127]

Locally Advanced Disease and Palliation

Mortality from Kasabach–Merritt syndrome can exceed 10%. Large hemangiomas causing coagulopathy or cardiac failure require aggressive treatment.[128] RT may be useful when other modalities fail.[129] Fractionated RT to doses of 10 Gy to 20 Gy has been effective in these life-threatening situations.[116,124,128,129] Tumors such as lymphangiosarcoma and malignant hemangioendothelioma are highly aggressive neoplasms and require multimodality treatment (Figure 75-3).[130,131]

Irradiation Techniques

Although the efficacy of RT for these conditions is well established, the availability of other effective treatments and the concern for late effects of irradiation in this young patient population appropriately limit RT to a seldom-used option today.[122,132] No definite dose-response relationship has been established for the treatment of hemangiomas, and fractionated radiation doses ranging from 3 Gy to 40 Gy have been recommended.[116,128] Braun-Falco et al[122] reported a large series of patients with hemangiomas; most were treated with fractionated radiation doses between 12 Gy and 25 Gy. Responses were seen in 73% of patients, with complete responses in 50%. Some have reported good results, with lower doses of 3 Gy to 11 Gy,[133] although others recommend a dose of at least 25 Gy.[134] Partial improvement after RT can often be noted within a few weeks, but maximum response can take several months to years.

Lymphangioma has been successfully treated with 10 Gy to 20 Gy of fractionated RT.[119,126,127] Responses can be seen much more quickly in lymphangiomas than in hemangiomas.

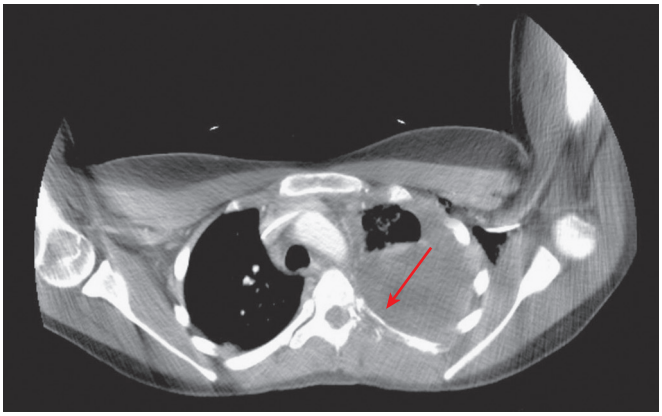


Figure 75-3 Lymphangiosarcoma in a 16-year-old girl arising from a preexisting lymphangioma. The patient's pain and chylous effusion were effectively palliated using 30-Gy radiotherapy. *Arrow* references primary site evident by bony erosion.

Treatment Algorithms, Controversies, Challenges, and Future Possibilities

Observation is usually indicated for hemangiomas. When treatment is required, corticosteroids or locally ablative treatment such as surgery or embolization can be used, as well as systemic agents. RT may be indicated for life-threatening situations. Lymphangioma is usually treated with surgical resection or sclerosing agents such as OK-432. RT, again, is reserved for life-threatening circumstances.

DESMOPLASTIC SMALL ROUND CELL TUMOR

Etiology and Epidemiology

Desmoplastic small round cell tumor (DSCRT) is a rare disease diagnosed in children and young adults at a median age of 22 years (range, 6 years to 49 years). DSCRT was first described by Gerald et al and Park et al in 1991.[135,136] There is a strong male to female predilection ranging from 5:1 to 20:1.[137] Approximately 200 cases have been reported in the literature.[135,138]

Biologic Characteristics and Molecular Biology

A t(11;22)(p13;q12) translocation is the predominant cytogenetic abnormality in DSRCT and breakpoint mapping has demonstrated that all chromosome 11 translocation breakpoints involve intron 7 of the Wilms' tumor gene *WT1*. The *EWS/WT1* fusion gene is used as a specific marker for the diagnosis of DSRCT.[139,140]

Pathology and Pathways of Spread

DSRCT arises from the serosal lining of the body cavities and visceral organs. It is histologically described as nests of small round blue cells separated by desmoplastic stroma. Tumor cells are typically small to medium-sized with round to oval hyperchromatic nuclei and scant to moderate cytoplasm with indistinct cell borders. Larger cells are less commonly present.

There is often significant heterogeneity in differentiation with immunohistochemical reactivity for epithelium (epithelial membrane antigen), mesenchyme (vimentin), myogen (desmin), and neurons (neuron-specific enolase, CD56).[141]

Clinical Manifestations, Patient Evaluation, and Staging

DSRCT usually presents with diffuse abdominal metastatic disease (Figure 75-4). Extensive peritoneal surface involvement results in poor absorption of intraperitoneal fluid and

the build-up of ascites results in symptoms of abdominal fullness and distension, with constipation, weight loss, loose stool, and jaundice. Other primary sites include bone,[142] paratestes,[143] CNS,[144] kidney,[145] and pleura.[146] Common sites of metastases are the intrathoracic cavity, mediastinum, pleura, paratesticular region, and soft tissues.[138]

Initial work-up includes CT or MRI of the chest, abdomen and pelvis with consideration for PET/CT. Extensive disease at presentation often precludes complete resection leading to open biopsy as the usual diagnostic procedure. Though a staging system has been proposed,[147] none has been widely accepted, and essentially all cases are considered "stage 4" with dissemination at the time of diagnosis.

Primary and Adjuvant Therapy and Results

Although no universally accepted treatment recommendation exists for DSRCT, treatment usually begins with an alkylator-based chemotherapy regimen such as cyclophosphamide, doxorubicin, and vincristine alternating with ifosfamide and etoposide. This is followed by aggressive surgical debulking, whole-abdomen RT and targeted RT to high-risk sites, and autologous stem-cell transplantation. Median survival with this approach is 19 months.[148] Lal et al reported 3-year survival of 58% in patients who underwent aggressive tumor debulking versus 0% for those who did not, illustrating the importance of surgery in the management of DSRCT.[149] Hyperthermic intraperitoneal chemotherapy perfusion, typically with cisplatin, has also been used with reports suggesting a survival benefit with this approach.[138] Liver metastases have been treated using yttrium-90 with radiographic response.[150] Although radiographic and clinical response is frequent with aggressive therapy, long-term prognosis remains poor with 5-year survival of approximately 15%[149,151] (Figure 75-5).

Figure 75-4 Desmoplastic small round cell tumor in a 12-year-old boy. There is extensive caking of the omentum as well as metastases to the liver and spleen.

Irradiation Techniques

RT plays an important role in the trimodality treatment of DSRCT. In a series of patients from Memorial Sloan Kettering Cancer Center, 3-year survival was 55% for those receiving chemotherapy, surgery, and RT versus 27% when fewer than three modalities were used.[149] Because of typical presentation with extensive abdominal disease and serosal spread, whole-abdomen radiotherapy is the most commonly applied approach. Whole-abdomen dose is typically 30 Gy guided primarily by normal tissue tolerance. With IMRT or conformal techniques, boost of gross disease to 45 Gy should be considered. Kidney dose of approximately 15 Gy whole organ and 20 Gy to 50% volume as well as liver dose of 24 Gy whole organ and 30 Gy to 50% volume are typical dose constraints.

Treatment Algorithms, Controversies, Challenges, and Future Possibilities

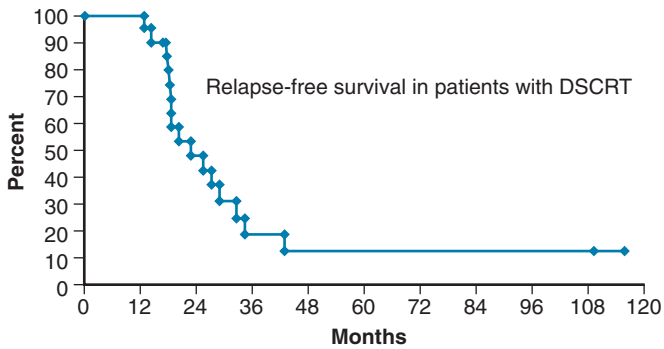
The current treatment algorithm for DSRCT consists of biopsy followed by neoadjuvant chemotherapy, second-look debulking surgery, and whole-abdominal RT with boost to bulk disease. Hyperthemic intraperitoneal chemotherapy is being investigated in Phase II trials and autologous bone marrow transplant has also been used.[147,148,152]

Targeted biologic therapies either upfront or at time of relapse are being considered for immunohistochemically positive for markers such as placental alkaline phosphatase, *ERBB2*, androgen receptor, and c-KIT.[153] Additionally, there are case reports of antitumor activity for bevacizumab[151] and trastuzumab.[153]

LANGERHANS CELL HISTIOCYTOSIS

Etiology and Epidemiology

Langerhans cell histiocytosis (LCH) refers to the spectrum of diseases arising from clonal proliferation of the CD1a and



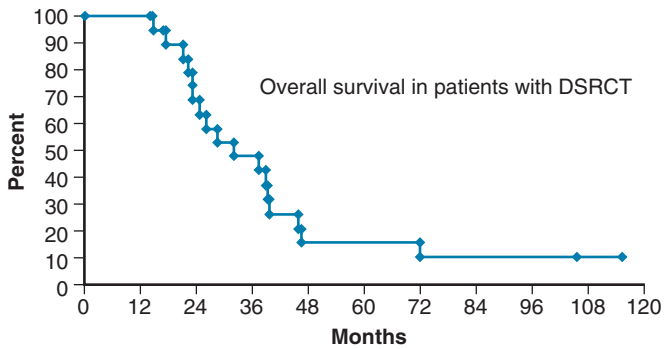


Figure 75-5 Disease-free survival and overall survival for desmoplastic small round cell tumor (DSRCT).
Data from Goodman KA, Wolden SL, La Quaglia MP, et al: Whole abdominopelvic radiotherapy for desmoplastic small round-cell tumor. Int J Radiat Oncolog Biol Phys 54:170–176, 2002.

CD207 positive reticuloendothelial Langerhans cell. The historical name "histiocytosis X" was coined in the 1950s to indicate the histiocytic origin of the disease, with the "X" reflecting the mysterious clinical spectrum of disease presentation.[154] This designation was replaced by the term LCH in 1987.[155] LCH has an incidence of between 1 and 5 cases per million in the United States with approximately 1200 cases diagnosed each year.[156] Most children are under 15 years old at the time of diagnosis with a peak incidence between 1 and 4 years of age. There is a 2:1 male predominance with a slightly higher incidence in Caucasians. The precise etiology of LCH is unknown.[156,157] Some have posited it may be caused by a viral infection, possibly human herpes virus 6 (HHV-6), although this has been disputed. Additionally, abnormalities in the intracellular communication between T cells and macrophages as well as irregularities in cytokine regulations have been proposed as etiologic mechanisms.[158-162]

Biologic Characteristics and Molecular Biology

The origin of LCH is believed to be the epidermal Langerhans cell. A clonal disorder, it is known to spontaneously regress in some patients and prove fatal in others. Most cases arise spontaneously, although there are rare genetic forms of the disease associated with specific cytokine gene variants that tend to occur early with multifocal disease.[163-165]

Pathology and Pathways of Spread

Histiocytic disorders have been classified into three groups by the Histiocyte Society: dendritic cell histiocytosis, macrophage-related disorders, and malignant histiocytosis with LCH falling into the first group.

Although the clinical manifestations of LCH can be quite varied, the pathology has more consistent characteristics. The presence of Langerhans cells is the hallmark of LCH. They are usually accompanied by macrophages, eosinophils, multinucleated giant cells, and T-cells.[166,167] The pathognomonic Langerhans cell is a large ovoid cell with a folded nucleus and a slightly eosinophilic cytoplasm. Birbeck granules can be visualized with electron microscopy. Expression of langerin (CD207) is the most specific marker. Additionally, cytoplasmic S-100 protein positivity and positivity of major histocompatibility (MHC) class II and CD1a are usually present.[168]

Clinical Manifestations, Patient Evaluation, and Staging

LCH is often grouped into three distinct entities that have different clinical presentations and prognoses. These distinctions are somewhat artificial, however, because there is a continuous spectrum of protean disease presentations. Approximately 30% of patients present with unifocal lytic lesions of bone known as eosinophilic granuloma.[169] These lesions occur in older children and commonly involve the skull. They can be painful and cause swelling and fractures, though they may also be incidentally identified.[170] This form of LCH is usually indolent and easily treated. Hand–Schüller–Christian disease is intermediate in severity. It presents as a triad of exophthalmos, skull lesions, and diabetes insipidus and occurs at a somewhat younger age.[171] Letterer–Siwe disease is the most aggressive form of LCH. It is typically seen in children younger than 3 years of age and involves multiple organ systems. Common presentations include splenomegaly, lymphadenopathy, anemia, and blood dyscrasias with diffuse skeletal involvement. These children may have fever, popular rash, and cachexia. The prognosis of this presentation is poor.

There is no uniform staging system for LCH. Children are generally grouped by burden of disease such as number of lesions involved, single or multiple organ involvement, and "non-risk sites" (skin, bone, lymph nodes) versus "risk sites" (liver, spleen, lung, bone marrow). Those with "risk sites" involved are now often considered as having "high-risk" LCH versus others considered to have "low-risk" disease.[169,172] A Turkish study of 217 patients reported 41.5% of patients with single-system disease, 34.1% with multiple-system disease, and 24.4% with multiple-system disease with organ dysfunction.[170]

Workup should include skeletal survey as lesions are typically lytic and bone scintigraphy, although recommended, may not detect some lesions. Visceral disease status is evaluated by CT or MRI of the chest and abdomen, and brain MRI to rule out CNS involvement. PET/CT can be used to assess lymphatic involvement and may be more specific for bony lesions.[173] Bone marrow biopsy is recommended in cases with cytopenias. Diabetes insipidus evaluation via urine specific gravity and osmolality should also be performed. Liver biopsy may be indicated in cases with elevated liver function tests (LFTs). Pulmonary function tests and high-resolution CT are indicated when pulmonary involvement is suspected.

Primary and Adjuvant Therapy and Results

LCH involving a solitary bone may be appropriate for observation as spontaneous regression is possible. More frequently local therapy with surgical curettage or corticosteroid injection is used. RT is effective as well, though less frequently used. These local therapy modalities have an excellent outcome for unifocal disease with a cure rate of 94% reported by Titgemeyer et al.[174] Limited skin involvement can be treated with topical steroids or photodynamic therapy.

Locally Advanced Disease and Palliation

Multifocal disease is treated with systemic therapy. Risk-adapted regimens using combinations of vinblastine, etoposide, and prednisone are usually prescribed.[175] Risk is based on age, extent of multifocal disease, and critical organ involvement. Early response to chemotherapy has been identified as a prognostic indicator with multisite patients responding to therapy at 6 weeks having a 92% OS and non-responders 11% OS.[175] In non-responders and refractory disease, stem-cell transplantation has been used.[176,177]

Irradiation Techniques

The use of radiotherapy in the treatment of LCH has steadily declined because of the effectiveness of alternative treatments and concerns for late RT effects in this young patient population. Current considerations for the use of RT include lesions where surgical intervention would have potential morbidity or in cases of lesions refractory to other treatments. Low-dose RT for bone lesions has been consistently effective with 88% to 96% local control reported for doses of 6 Gy to 15 Gy (median, 9 Gy).[178,179] RT has also been used for diabetes insipidus secondary to LCH. Doses of 15 Gy to 20 Gy to the sellar/hypothalamic area have been used, and when given within 1 to 2 weeks of onset, 25% to 35% of patients show biochemical improvement.[180-182]

Treatment Algorithms, Controversies, Challenges, and Future Possibilities

Overall, most patients enjoy a favorable prognosis. Unfortunately, there are a minority of children (up to 20% to 30%) with

extensive organ involvement who succumb to LCH within 5 years. Targeted therapy and immune modulators have been evaluated in small studies including anti-CD1a antibodies, cytokine inhibitors, alemtuzumab, low-dose oral cyclophosphamide, and all-trans retinoic acid.[183-185] Imatinib and B-raf inhibitors have also been studied.[186-188] The Histiocyte Society and its website is a frequently updated resource for ongoing clinical trials and emerging information on LCH.[189]

NASOPHARYNGEAL CARCINOMA

Etiology and Epidemiology

Pediatric nasopharyngeal carcinoma (PNC) is a rare tumor with an incidence and histologic subtype that varies significantly based on geographic location.[190]

In children, the median age at diagnosis is 13 years and there is a 2:1 male predominance.[191,192] Comparisons are often made between the adult and juvenile variants of nasopharyngeal carcinoma (NPC), and indeed much of the treatment regimens for PNC have been extrapolated from adult data owing to the rarity of the pediatric tumors. The diseases are similar in their relationship to EBV infection, to diets containing nitrites and salted fish, and to the male predominance. Additionally, certain human leukocyte antigen (HLA) subtypes are associated with an increased risk of NPC.[193,194] However, in children, the greatest incidence occurs in the Mediterranean and North America regions rather than China, Southeast Asia, and Alaska; undifferentiated histology is the most common type; and patients present with significantly more advanced disease at diagnosis. In one retrospective series, 92% of pediatric patients had stages III to IV disease versus 67% of adults. However, data show that despite higher stage disease, children have a better overall prognosis in both OS and locoregional disease control.[195-197]

Biologic Characteristics and Molecular Biology

EBV has been a long established etiologic factor for the development of NPC and is associated with 90% of PNCs, particularly the undifferentiated and nonkeratinizing types. The relationship between EBV and NPC was confirmed when EBV DNA was found in neoplastic epithelial cells but was absent in the surrounding lymphocytes.[198] The EBV genome is a double-stranded DNA virus encoding 100 genes, only 10 of which are expressed in latently infected cells in vitro. Of these, six are nuclear proteins (EBNAs), two are latent membrane proteins (LMPs), and two are nontranslated RNA molecules (EBER) that likely aid in cell growth. In NPC, latent membrane protein 1 (LMP1) acts as an oncogene, changing growth patterns and upregulating proteins that inhibit apoptosis, including BCL2.[190] Although BCL-2 is highly expressed in ~80% of adults with NPC, it is likely not associated with pediatric NPC.[199,200] LMP1 also binds to various proteins associated with tumor necrosis factor receptors and is involved in activation of transcription factors, cellular adhesion molecules, and cytokines. *LMP2* is also expressed in NPC and acts by preventing reactivation of the virus by blocking phosphorylation of tyrosine kinases.[190]

NPC development is thought to represent a multistep process initiated most frequently by EBV infection resulting in the expression of *LMP1* and overexpression of *TP53* in the epithelial tumor cells. Additionally, rearrangement of the retinoblastoma tumor suppressor genes, and polymorphism of *CYP2E1* may contribute to tumorigenesis. Genetic gains on chromosome 12 as well as losses on 11q, 13q, and 16q have been associated with invasiveness, whereas *TP53* mutation and altered expression of cadherins are associated with metastasis.[193,201-203] A small proportion of PNC exhibit t(15;19) with the BRD4-NUT oncogene, which perturbs BRD4 functions thus blocking cellular differentiation and contributing to the oncogenic progression in the highly aggressive NUT midline NPC.[204]

Pathology and Pathways of Spread

NPC is grouped into three histiotypes by the World Health Organization (WHO): type I, keratinizing squamous cell carcinoma; type II, nonkeratinizing squamous cell carcinoma; and type III, undifferentiated carcinoma, previously referred to as lymphoepithelioma. Type I shows significant keratin production, is usually seen in adults, and is not usually associated with EBV. Type II is characterized by groups of cells with oval or fusiform nuclei and scant cytoplasm. Type III is an undifferentiated tumor with prominent nonmalignant lymphocytic infiltration. The Cologne modification of the WHO classification further subdivides types II and III; type IIa has pleomorphism without lymphoid infiltration, type IIb has significant lymphoid infiltrate. Type IIIa is characterized by larger, eosinophilic nuclei, and type IIIb has smaller basophilic nuclei. Virtually all PNCs are type III undifferentiated carcinomas.[190,205]

PNC typically originates in the fossa of Rosenmüller, a pharyngeal recess posterolateral to the eustachian tube orifice. Routes of direct spread include the oropharynx or perineural spread along cranial nerves extending to the skull base. The cervical lymph nodes are typically involved early, and less commonly, the spinal accessory chain and retropharyngeal nodes. Most patients present with locoregionally advanced disease; distant metastases at presentation is infrequent. The most frequently affected metastatic sites are the bones, lungs, liver, bone marrow, and mediastinum.[206]

Clinical Manifestations, Patient Evaluation, and Staging

The most common presenting symptom of PNC, occurring in up to 90% of patients, is a painless cervical mass representing lymphadenopathy. Bilateral lymph nodes are often present because of the midline location of the nasopharynx with regional drainage to the internal jugular nodes, the spinal accessory nodes, and the retropharyngeal nodes. Local extension of tumor can cause epistaxis, nasal obstruction, hearing loss, or otitis media from obstruction of the eustachian tubes, which can also lead to ear pain and tinnitus. Base-of-skull invasion can result in headache, facial pain, neck pain, and cranial neuropathies.[190,193,194,207] Uncommonly, the syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been reported and can cause severe hyponatremia.[208] The duration of symptoms before diagnosis ranges from 1 month to 24 months, with an average of 5 months.[190]

Work-up includes history and physical examination with nasopharyngoscopy. Laboratory evaluation consists of CBC, kidney and liver function tests, serum EBV titers, a baseline audiogram, and CT or MRI of the head and neck. CT of the chest and abdomen or, alternatively, PET/CT, is done to screen for distant metastases.[209] Dental and endocrine evaluations should be obtained in preparation for RT and to establish baseline function.

Staging is based on the American Joint Committee on Cancer staging system for NPC in adults (Table 75-6). The nodal staging for nasopharyngeal tumors takes into account the anatomic level of nodal involvement, an important prognostic factor. Retropharyngeal lymph nodes, regardless of their laterality, are considered N1.[210,211]

TABLE 75-6 Nasopharyngeal Carcinoma Staging: American Joint Committee on Cancer

PRIMARY TUMOR	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Primary tumor confined to nasopharynx, extending to oropharynx, or nasal cavity without parapharyngeal space extension
T2	Tumor extends to soft tissues
T2a	Tumor extends to oropharynx and/or nasal cavity (no parapharyngeal extension)
T2b	Tumor within parapharyngeal space*
T3	Invasion of bone of skull base or paranasal sinuses
T4	Tumor with intracranial extension or cranial nerve involvement, extension to hypopharynx, orbit, or infratemporal fossa/masticator space
REGIONAL LYMPH NODES	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node involvement
N1	Unilateral metastasis ≤6 cm above the supraclavicular fossa and/or unilateral or bilateral retropharyngeal lymph nodes ≤n6 cm
N2	Bilateral lymph node metastasis, ≤6 cm, above the supraclavicular fossa
N3	Metastasis in a lymph node >6 cm or extension to supraclavicular fossa
N3a	>6 cm
N3b	Extension to supraclavicular fossa
DISTANT METASTASES	
M0	No distant metastasis
M1	Distant metastasis
AJCC STAGE	
Stage 0	TisN0M0
Stage I	T1N0M0
Stage IIA	T2aN0M0
Stage IIB	T1-2aN1M0 T2bN0-1M0
Stage III	T1-2a-2bN2M0 T3N0-1-2M0
Stage IVA	T4N0-1-2M0
Stage IVB	T1-4N3M0
Stage IVC	M1

From Edge SB, Byrd DR, Compton CC, et al, editors: AJCC Cancer Staging Handbook, ed 7, New York, 2010, Springer.
**Parapharyngeal extension denotes posterolateral spread of tumor.*

Primary and Adjuvant Therapy and Results

Surgery for PNC is limited by anatomic location and involvement of critical structures, which would usually result in a morbid and incomplete resection. Therefore, RT is the mainstay of therapy for every stage of PNC. PNC is radiosensitive. However, outcome with RT alone has been unsatisfactory, with local recurrence rates of 20% to 60% and rates of distant metastases ranging from 20% to 55%.[212-216] Therefore, combined-modality therapy is most often used.

Treatment of PNC was initially extrapolated from recommendations in the adult literature and cisplatin has been the agent most frequently used in conjunction with RT. This was based primarily on the Intergroup 0099 trial, which compared chemoradiation with RT alone in adults with NPC, delivering 70 Gy with or without cisplatin, followed by three cycles of adjuvant cisplatin and 5-fluorouracil.[217] Three-year progression-free survival was 69% with chemoradiation versus 24% with RT alone, and 3-year OS was 78% versus 47%, respectively. The use of cisplatin was further supported by a meta-analysis of adult patients that reported a 20% survival benefit for concurrent cisplatin with RT versus RT alone.[218]

Historically, PNC was treated with RT alone. OS ranged from 50% to 55% with relapse-free survival of 36% to 75%. RT doses varied significantly from 35 Gy to 86 Gy.[219-221] More recently, combined-modality regimens and advanced RT techniques such as intensity-modulated RT (IMRT) and image-guided RT (IGRT) have improved outcomes for PNC. Ayan et al[222] and Wolden et al[223] reported improved survival after chemoradiation, particularly using neoadjuvant chemotherapy, with OS as high as 76%. Data from these studies also suggested a benefit when radiation doses exceeded 60 Gy. However, the 10-year actuarial rate of severe complications using these radiation doses was 24% including a significant risk of sensorineural hearing loss when the cochlear dose exceeded 48 Gy.[224]

Ozyar et al[195] reported a large, multiinstitutional international review of PNC treated over a 25-year interval which demonstrated the benefit of cisplatin as well as higher RT dose. Overall 5-year survival was 77.4% with DFS of 68.8% after combined irradiation and chemotherapy; the only significant negative prognostic factor for OS and DFS was N3 disease. RT doses less than 66 Gy adversely affected locoregional control, and RT without chemotherapy decreased locoregional control and DFS.

Kupeli et al published their experience treating PNC using RT with concurrent cyclophosphamide versus concurrent vincristine, cyclophosphamide, epirubicin, and dactinomycin (AVAC) versus neoadjuvant cisplatin. OS with neoadjuvant cisplatin was 80% versus 63% with AVAC and 31% with cyclophosphamide.[225]

The Pediatric Oncology Group 9486 study used neoadjuvant chemotherapy (cisplatin, 5-fluorouracil, methotrexate, and leucovorin) followed by RT (50.4 Gy to the upper neck, 45 Gy to the lower neck, and a boost to the primary tumor to a total dose of 61.2 Gy).[226] Four-year EFS and OS was 77% and 75%, respectively.

A prospective German trial tested three cycles of cisplatin, 5-fluorouracil, methotrexate, and leucovorin followed by RT (59.4 Gy) for stages III IV PNC; patients were then maintained on interferon-beta for 6 months. After a median follow-up of 30 months (range, 6 months to 95 months), EFS rate was 92.4%, and OS was 97.1%. Acute toxicity was mainly leucopenia, mucositis, and nausea; late toxicity consisted of hearing loss and hypothyroidism. The excellent outcomes were hypothesized as due, in part, to the administration of interferon-beta during a period of relative immune suppression in EBV-positive NPC.[227]

Factors that correlate with DFS include age, nodal stage, TNM stage, node size, node fixation, radiation dose, and response to neoadjuvant chemotherapy.[228]

Response-adapted RT has been investigated to reduce RT toxicity. Habrand et al[229] used sequential cisplatin-based regimens and response-adapted RT doses of 50 Gy after marked response and 65 Gy to 70 Gy after poor response to chemotherapy. Five-year EFS and OS were 64% and 68%, respectively; locoregional failures were similar between the groups, but the low RT dose group actually had superior OS and EFS, with apparent reduction in late toxicities. Orbach et al[230] reported results of risk-adapted RT following one of three chemotherapy protocols (both neoadjuvant and adjuvant

chemotherapy). Objective response to preirradiation chemotherapy was seen in 78% of cases; those with complete response or good partial response received a reduced dose RT regimen (median dose 47 Gy) to the clinically negative cervical nodes and 59.4 Gy to the primary tumor. Patients not meeting response criteria were given 60 Gy median dose to all involved sites. The 5-year OS was not compromised in the reduced-dose cohort, with OS of 73% at 5 years, local failure rate of 10%, and regional failure rate of 3%.

Irradiation Techniques

Because of the high-risk of lymph node involvement at presentation, RT for PNC targets the primary tumor, clinically involved nodes, and nodal areas at risk. Prophylactic RT includes lymph nodes in the bilateral upper deep jugular, submandibular, subdigastric, midjugular, low jugular and supraclavicular, posterior cervical, and retropharyngeal chains.

The optimal doses to maximize tumor control and minimize toxicity continue to evolve with current recommendation for 60 Gy to 70 Gy to the primary tumor and gross disease and 45 Gy to 50 Gy for at-risk nodal areas. The recent COG protocol ARAR0331 specifies RT alone for stages I and IIa disease to 61.2 Gy and 66.6 Gy, respectively. For advanced disease, patients are given neoadjuvant cisplatin and 5-flourouracil, with responding patients treated to 61.2 Gy versus 70.2 Gy for non-responders.

IMRT allows for sparing of normal tissues with reduced toxicity and superior target coverage. Both acute and long-term toxicity with IMRT are likely improved as compared to other techniques. However, this comes at the expense of increased integral dose and the possibility of increased risk of radiation-induced tumors.[231] Proton therapy has been used for PNC and its use will likely grow because of the inherent decrease in normal tissue exposure with particle therapy.[232]

Simulation should be CT based, with appropriate immobilization and localization techniques. The Children's Oncology Group currently recommends delineation of the gross tumor volume (GTV) based on MRI; lymph nodes larger than 1.5 cm or of any size with a necrotic center are included in the GTV. The clinical target volume (CTV) includes the GTV plus a 1-cm margin, the entire nasopharynx, retropharyngeal nodes, skull base, pterygoid fossa, parapharyngeal space, inferior sphenoidal sinus, and posterior third of the nasal cavity, and maxillary sinuses as well as the bilateral cervical lymphatic levels I to V. The lower halves of levels IV and V can be excluded in patients with early-stage disease. A boost, or second CTV, may include the nasopharynx and residual enhancing disease that remains after neoadjuvant chemotherapy.

Critical normal structures include the spinal cord and brainstem, mandible/temporomandibular joint, temporal lobes, and optic apparatus. Other structures at risk are the parotid gland, oral cavity, larynx, eyes, lens, cochlea, and pituitary. Xerostomia, neck fibrosis, dental caries, chronic sinusitis, chronic serous otitis, trismus, hypopituitarism, hypothyroidism, hypoplasia of facial bones or clavicles, and second malignancies have been well documented[190,223,225] (Table 75-7).

TABLE 75-7 Incidence of Treatment-Related Toxicity in Nasopharyngeal Cancer

Complication	Percentage
Xerostomia	3.5-84
Soft-tissue fibrosis	23-61
Dental caries	7-33
Chronic otitis	18
Hypothyroidism	9.5-12
Trismus	7.1-9
Chronic sinusitis	7
Second malignancy	2-6
Osteoradionecrosis	3
Optic neuritis	3

Treatment Algorithms, Controversies, Challenges, and Future Possibilities

Standard treatment for most PNC is defined as three to four cycles of platinum-based neoadjuvant chemotherapy followed by RT to the primary tumor and regional lymphatics with concurrent cisplatin. This may be followed by additional chemotherapy. Early-stage disease may be considered for RT alone. Dose recommendations will likely continue to evolve with ongoing studies reviewing response-based dosing. IMRT techniques are recommended with the use of proton RT being reported on as well. Future challenges will likely be related to optimal dose definition and using improved RT techniques to minimize toxicity, integration of EBV-directed therapy, and immunomodulation.

CRITICAL REFERENCES

A full list of cited references is published online at www.expertconsult.com.

2. Schnater JM, Kohler SE, Lamers WH, et al: Where do we stand with hepatoblastoma? A review. Cancer 98:668–678, 2003.
15. Tomlinson GE, Douglass EC, Pollock BH, et al: Cytogenetic analysis of a large series of hepatoblastoma: Numerical aberrations with recurring translocations involving 1q12-21. Genes Chromosomes Cancer 44:177–184, 2005.
18. Hartmann W, Kuchler J, Koch A, et al: Activation of phosphatidylinositol-3′-kinase/AKT signaling is essential in hepatoblastoma survival. Clin Cancer Res 15:4538–4545, 2009.
27. Schnater JM, Aronson DC, Plaschkes J, et al: Surgical view of the treatment of patients with hepatoblastoma. Results from the first prospective trial of the International Society of Pediatric Oncology Liver Tumor Study Group. Cancer 94:1111–1120, 2002.
29. Pritchard J, Brown J, Shafford E, et al: Cisplatin, doxorubicin, and delayed surgery for childhood hepatoblastoma. A successful approach. Results of the first prospective study of the International Society of Pediatric Oncology. J Clin Oncol 18:3819–3828, 2000.
31. Perilongo G, Maibach R, Shafford E, et al: Cisplatin versus cisplatin plus doxorubicin for standard-risk hepatoblastoma. N Engl J Med 361:1662–1670, 2009.
32. Katzenstein HM, London WB, Douglass EC, et al: Treatment of unresectable and metastatic hepatoblastoma. A Pediatric Oncology Group phase II study. J Clin Oncol 20:3438–3444, 2002.
33. Zsiro J, Brugieres L, Brock P, et al: Dose-dense cisplatin-based chemotherapy and surgery for children with high-risk hepatoblastoma (SIOPEL-4): A prospective, single-arm, feasibility study. Lancet Oncol 14:834–842, 2013.
35. Rescorla FJ: Pediatric germ cell tumors. Semin Surg Oncol 16:144–158, 1999.
50. Gobel U, Schneider DT, Calaminus G, et al: Multimodality treatment of malignant sacrococcygeal germ cell tumors: A prospective analysis of 66 patients of the German cooperative protocols MAKEI 83/86 and 89. J Clin Oncol 19:1943–1950, 2001.
52. Marina NM, Cushing B, Giller R, et al: Complete surgical excision is effective treatment for children with immature teratomas with or without malignant elements. A Pediatric Oncology Group/Children's Cancer Group Intergroup Study. J Clin Oncol 17:2137–2143, 1999.
53. Cushing B, Giller R, Cullen JW, et al: Randomized comparison of combination chemotherapy with etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with high-risk malignant germ cell tumors. A pediatric intergroup study—Pediatric Oncology Group 9049 and Children's Cancer Group 8882. J Clin Oncol 22:2691–2700, 2004.
57. Boghani Z, Husain Q, Kanumuri VV, et al: Juvenile nasopharyngeal angiofibroma: A systematic review and comparison of endoscopic, endoscopic-assisted, and open resection in 1047 cases. Laryngoscope 123(4):859–869, 2013.
76. Reddy KA, Mendenhall WM, Amdur RJ, et al: Long-term results of radiation therapy for juvenile nasopharyngeal angiofibroma. Am J Otolaryngol 22:172–175, 2001.
77. Chakraborty S, Ghoshal S, Patil VM, et al: Conformal radiotherapy in the treatment of advanced juvenile nasopharyngeal angiofibroma with

intracranial extension: An institutional experience. Int J Radiat Oncol Biol Phys 80:1398–1404, 2011.
92. Priest JR, Magnuson J, Williams GM, et al: Cerebral metastasis and other central nervous system complications of pleuropulmonary blastoma. Pediatr Blood Cancer 49:266–273, 2007.
97. Parsons SK, Fishman SJ, Hoorntje LE, et al: Aggressive multimodal treatment of pleuropulmonary blastoma. Ann Thorac Surg 72:939–942, 2001.
99. Slade I, Bacchelli C, Davies H, et al: DICER1 syndrome: Clarifying the diagnosis, clinical features and management implications of a pleiotropic tumour predisposition syndrome. J Med Genet 48:273–278, 2011.
106. Priest JR, McDermott MB, Bhatia S, et al: Pleuropulmonary blastoma. A clinicopathologic study of 50 cases. Cancer 80:147–161, 1997.
109. Pleuropulmonary Blastoma Registry. Available online at www.ppbregistry.org.
116. Schild SE, Buskirk SJ, Frick LM, et al: Radiotherapy for large symptomatic hemangiomas. Int J Radiat Oncol Biol Phys 21:729–735, 1991.
119. Johnson DW, Klazynski PT, Gordon WH, et al: Mediastinal lymphangioma and chylothorax. The role of radiotherapy. Ann Thorac Surg 41:325–328, 1986.
124. Ogino I, Torikai K, Kobayasi S, et al: Radiation therapy for life- or function-threatening infant hemangioma. Radiology 218:834–839, 2001.
129. Mitsuhashi N, Furuta M, Sakurai H, et al: Outcome of radiation therapy for patients with Kasabach-Merritt syndrome. Int J Radiat Oncol Biol Phys 39:467–473, 1997.
132. Lindberg S: Radiotherapy of childhood haemangiomas. From active treatment to radiation risk estimates. Radiat Environ Biophys 40:179–189, 2001.
135. Gerald WL, Miller HK, Battifora H, et al: Intra-abdominal desmoplastic small round-cell tumor. Report of 19 cases of a distinctive type of high-grade polyphenotypic malignancy affecting young individuals. Am J Surg Pathol 15:499–513, 1991.
137. Goodman KA, Wolden SL, La Quaglia MP, et al: Whole abdominopelvic radiotherapy for desmoplastic small round-cell tumor. Int J Radiat Oncol Biol Phys 54:170–176, 2002.
138. Hayes-Jordan A, Anderson P: The diagnosis and management of desmoplastic small round cell tumor: A review. Curr Opin Oncol 23:385–389, 2011.
148. Kushner BH, LaQuaglia MP, Wollner N, et al: Desmoplastic small round-cell tumor. Prolonged progression-free survival with aggressive multimodality therapy. J Clin Oncol 14:1526–1531, 1996.
149. Lal DR, Su WT, Wolden SL, et al: Results of multimodal treatment for desmoplastic small round cell tumors. J Pediatr Surg 40:251–255, 2005.
165. Egeler RM, van Halteren AG, Hogendoorn PC, et al: Langerhans cell histiocytosis: Fascinating dynamics of the dendritic cell-macrophage lineage. Immunol Rev 234(1):213–232, 2010.
166. Favara BE, Feller AC, Pauli M, et al: Contemporary classification of histiocytic disorders. The WHO Committee On Histiocytic/Reticulum Cell Proliferations. Reclassification Working Group of the Histiocyte Society. Med Pediatr Oncol 29(3):157–166, 1997.
169. Morimoto A, Ikushima S, Kinugawa N, et al: Improved outcome in the treatment of pediatric multifocal Langerhans cell histiocytosis. Results from the Japan Langerhans Cell Histiocytosis Study Group-96 protocol study. Cancer 107:613–619, 2006.
178. Selch MT, Parker RG: Radiation therapy in the management of Langerhans cell histiocytosis. Med Pediatr Oncol 18:97–102, 1990.
182. Rosenzweig KE, Arceci RJ, Tarbell NJ: Diabetes insipidus secondary to Langerhans' cell histiocytosis: Is radiation therapy indicated? Med Pediatr Oncol 29:36–40, 1997.
189. The Histiocyte Society. Available at www.histiocytesociety.org.
190. Ayan I, Kaytan E, Ayan N: Childhood nasopharyngeal carcinoma: From biology to treatment. Lancet Oncol 4:13–21, 2003.
195. Ozyar E, Selek U, Laskar S, et al: Treatment results of 165 pediatric patients with non-metastatic nasopharyngeal carcinoma. A Rare Cancer Network study. Radiother Oncol 81:39–46, 2006.
196. Downing NL, Wolden S, Wong P, et al: Comparison of treatment results between adult and juvenile nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 75:1064–1070, 2009.
219. Gasparini M, Lombardi F, Rottoli L, et al: Combined radiotherapy and chemotherapy in stage T3 and T4 nasopharyngeal carcinoma in children. J Clin Oncol 6:491–494, 1988.
220. Jenkin RD, Anderson JR, Jereb B, et al: Nasopharyngeal carcinoma—a retrospective review of patients less than thirty years of age. A report of Children's Cancer Study Group. Cancer 47:360–366, 1981.
221. Ingersoll L, Shiao Y, Donaldson S: Nasopharyngeal carcinoma in the young. A combined M.D. Anderson and Stanford experience. Int J Radiat Oncol Biol Phys 19:881–887, 1990.
223. Wolden SL, Steinherz PG, Kraus DH, et al: Improved long-term survival with combined modality therapy for pediatric nasopharynx cancer. Int J Radiat Oncol Biol Phys 46:859–864, 2000.
226. Rodriguez-Galindo C, Wofford M, Castleberry RP, et al: Preradiation chemotherapy with methotrexate, cisplatin, 5-fluorouracil, and leucovorin for pediatric nasopharyngeal carcinoma. Cancer 103:850–857, 2005.
227. Buehrlen M, Zwaan CM, Granzen B, et al: Multimodal treatment, including interferon beta, of nasopharyngeal carcinoma in children and young adults: Preliminary results from the prospective, multicenter study NPC-2003-GPOH/DCOG. Cancer 118(19):4892–4900, 2012.
229. Habrand J, Guillot Valls D, Petras S, et al: Carcinoma of the nasopharynx in children and adolescents treated with initial chemotherapy followed by adapted doses of radiotherapy. Int J Radiat Oncol Biol Phys 60:S247, 2004.
230. Orbach D, Brisse H, Helfre S, et al: Radiation and chemotherapy combination for nasopharyngeal carcinoma in children. Radiotherapy dose adaptation after chemotherapy response to minimize late effects. Pediatr Blood Cancer 50:849–853, 2008.

REFERENCES

1. Darbari A, Sabin KM, Shapir CN, et al: Epidemiology of primary hepatic malignancies in U.S. children. Hepatology 38:560–566, 2003.
2. Schnater JM, Kohler SE, Lamers WH, et al: Where do we stand with hepatoblastoma? A review. Cancer 98:668–678, 2003.
3. Bellani FF, Massimino M: Liver tumors in childhood. Epidemiology and clinics. J Surg Oncol Suppl 3:119–121, 1993.
4. Herzog CE, Andrassy RJ, Farzin E: Childhood cancers: Hepatoblastoma. Oncologist 5:445–453, 2000.
5. DeBaun MR, Tucker MA: Risk of cancer during the first four years of life in children from the Beckwith-Weidemann syndrome registry. J Pediatr 132:398–400, 1998.
6. Giardiello FM, Offerhaus GJ, Krush AJ, et al: Risk of hepatoblastoma in familial adenomatous polyposis. J Pediatr 119:766–768, 1991.
7. Feusner J, Buckley JD, Robison L, et al: Prematurity and hepatoblastoma: More than just an association? J Pediatr 133:585–586, 1998.
8. Ribons LA, Slovis TL: Hepatoblastoma and birth weight. J Pediatr 132:750, 1998.
9. Stocker JT: Hepatic tumors in children. In Suchy FJ, editor: Liver disease in children, St. Louis, 1994, Mosby Year Books, Inc, pp 901–930.
10. Tomlinson GE, Kappler R: Genetics and epigenetics of hepatoblastoma. Pediatr Blood Cancer 59:785–792, 2012.
11. Garber JE, Li FP, Kingston JE, et al: Hepatoblastoma and familial adenomatous polyposis. J Natl Cancer Inst 80:1626–1628, 1998.
12. Oda H, Imai Y, Nakatsuru Y, et al: Somatic mutations of the APC gene in sporadic hepatoblastomas. Cancer Res 56:3320–3323, 1996.
13. Soukup SW, Lampkin BL: Trisomy 2 and 20 in two hepatoblastomas. Genes Chromosomes Cancer 3:231–234, 1991.
14. Tonk VS, Wilson KS, Timmons CF, et al: Trisomy 2, trisomy 20, and del(17p) as sole chromosomal abnormalities in three cases of hepatoblastoma. Genes Chromosomes Cancer 11:199–202, 1994.
15. Tomlinson GE, Douglass EC, Pollock BH, et al: Cytogenetic analysis of a large series of hepatoblastoma: Numerical aberrations with recurring translocations involving 1q12-21. Genes Chromosomes Cancer 44:177–184, 2005.
16. Swarts S, Wisecarver J, Bridge JA: Significance of extra copies of chromosome 20 and the long arm of chromosome 2 in hepatoblastoma. Cancer Genet Cytogenet 91:65–67, 1996.
17. Koch A, Denkhaus D, Albrecht S, et al: Childhood hepatoblastomas frequently carry a mutated degradation targeting box of the beta-catenin gene. Cancer Res 59:269–273, 1999.
18. Hartmann W, Kuchler J, Koch A, et al: Activation of phosphatidylinositol-3′-kinase/AKT signaling is essential in hepatoblastoma survival. Clin Cancer Res 15:4538–4545, 2009.
19. Baylin SB, Ohm JE: Epigenetic gene silencing in cancer—A mechanism for early oncogenic pathway addiction? Nat Rev Cancer 6:107–116, 2006.
20. Gray SG, Eriksson T, Ekstrom C, et al: Altered expression of members of the IGF-axis in hepatoblastomas. Br J Cancer 82:1561–1567, 2000.
21. Hartmann W, Waha A, Koch A, et al: p57(KIP2) is not mutated in hepatoblastoma but shows increased transcriptional activity in a comparative analysis of the three imprinted genes p57(KIP2), IGF2, and H19. Am J Pathol 157:1393–1403, 2000.
22. Chang MH, Chen DS, Hsu HC, et al: Maternal transmission of hepatitis B virus in childhood hepatocellular carcinoma. Cancer 64:2377–2380, 1989.
23. Weinberg AG, Finegold MJ: Primary hepatic tumors of childhood. Hum Pathol 14:512–537, 1983.
24. Stocker JT: Hepatic tumors in children, ed 2, Philadelphia, 2001, Lippincott, Williams and Wilkins.
25. Lopez-Terrada D, Alaggio R, de Davila MT, et al: Towards an international pediatric liver tumor consensus classification: Proceedings of the Los Angeles COG liver tumors symposium. Mod Pathol 2013. epub ahead of print.
26. Katzenstein HM, Krailo MD, Malogolowkin MH, et al: Fibrolamellar hepatocellular carcinoma in children and adolescents. Cancer 97:2006–2012, 2003.
27. Schnater JM, Aronson DC, Plaschkes J, et al: Surgical view of the treatment of patients with hepatoblastoma. Results from the first prospective trial of the International Society of Pediatric Oncology Liver Tumor Study Group. Cancer 94:1111–1120, 2002.
28. Czauderna P, Mackinlay G, Perilongo G, et al: Hepatocellular carcinoma in children. Results of the first prospective study of the International Society of Pediatric Oncology Group. J Clin Oncol 20:2798–2804, 2002.
29. Pritchard J, Brown J, Shafford E, et al: Cisplatin, doxorubicin, and delayed surgery for childhood hepatoblastoma. A successful approach. Results of the first prospective study of the International Society of Pediatric Oncology. J Clin Oncol 18:3819–3828, 2000.
30. Lack EE, Neave C, Vawter GF: Hepatoblastoma. A clinical and pathologic study of 54 cases. Am J Surg Pathol 6:693–705, 1982.
31. Perilongo G, Maibach R, Shafford E, et al: Cisplatin versus cisplatin plus doxorubicin for standard-risk hepatoblastoma. N Engl J Med 361:1662–1670, 2009.
32. Katzenstein HM, London WB, Douglass EC, et al: Treatment of unresectable and metastatic hepatoblastoma. A Pediatric Oncology Group phase II study. J Clin Oncol 20:3438–3444, 2002.
33. Zsiro J, Brugieres L, Brock P, et al: Dose-dense cisplatin-based chemotherapy and surgery for children with high-risk hepatoblastoma (SIOPEL-4): A prospective, single-arm, feasibility study. Lancet Oncol 14:834–842, 2013.
34. Habrand JL, Nehme D, Kalifa C, et al: Is there a place for radiation therapy in the management of hepatoblastomas and hepatocellular carcinomas in children? Int J Radiat Oncol Biol Phys 23:525–531, 1992.
35. Rescorla FJ: Pediatric germ cell tumors. Semin Surg Oncol 16:144–158, 1999.
36. Parkes SE, Muir KR, Southern L, et al: Neonatal tumors: A thirty-year population based study. Med Pediatr Oncol 22:309–317, 1994.
37. Kaatsch P, Kaletsch U, Michaelis J: Annual report 1997; German childhood cancer registry, Mainz, Germany, 1998, Deutsches Kinderkrebsregister.
38. Rutgers JL, Scully RE: Pathology of the testes in intersex syndromes. Semin Diagn Pathol 4:275–291, 1987.
39. Fonkalsrud EW: The undescended testis [Review]. Curr Prob Surg 15:1–56, 1978.
40. Fonkalsrud EW: Current management of the undescended testis. J Pediatr Surg 5:2–7, 1996.
41. Campbell HE: Incidence of malignant growth of the undescended testicle. Arch Surg 44:353–369, 1942.
42. Chaganti RS, Houldsworth J: The cytogenetic theory of the pathogenesis of human adult male germ-cell tumors. APMIS 106:80–83, 1998.
43. Perlman EJ, Cushing B, Hawkins E, et al: Cytogenetic analysis of childhood endodermal sinus tumors: A Pediatric Oncology Group Study. Pediatr Pathol 14:695–708, 1994.
44. Bussey KJ, Lawce HJ, Olson SB, et al: Chromosome abnormalities of eighty-one pediatric germ-cell tumors: Sex-, age-, site-, and histopathology-related differences—a Children's Cancer Group Study. Genes Chromosomes Cancer 25:134–146, 1999.
45. Gobel U, Schneider DT, Calaminus G, et al: Germ-cell tumors in childhood and adolescence. GPOH MAKEI and the MAHO study groups. Ann Oncol 11:263–271, 2000.
46. Schey WL, Shkolnik A, White H: Clinical and radiographic considerations of sacrococcygeal teratomas: An analysis of 26 new cases and review of the literature. Radiology 125:189–195, 1977.
47. Rescorla FJ, Breitfeld PP: Pediatric germ cell tumors. Curr Probl Cancer 23:257–303, 1999.
48. Billmire D, Vinocur C, Rescorla F, et al: Outcome and staging evaluation in malignant germ cell tumors of the ovary in children and adolescents, an intergroup study. J Pediatr Surg 39:424–429, 2004.
49. Gershenson DM: Management of ovarian germ cell tumors. J Clin Oncol 25:2938–2943, 2007.
50. Gobel U, Schneider DT, Calaminus G, et al: Multimodality treatment of malignant sacrococcygeal germ cell tumors: A prospective analysis of 66 patients of the German cooperative protocols MAKEI 83/86 and 89. J Clin Oncol 19:1943–1950, 2001.
51. Schneider DT, Wessalowski R, Calaminus G, et al: Treatment of recurrent malignant sacrococcygeal germ cell tumors: Analysis of 22 patients registered in the German protocols MAKEI 83/86, 89, and 96. J Clin Oncol 19:1951–1960, 2001.
52. Marina NM, Cushing B, Giller R, et al: Complete surgical excision is effective treatment for children with immature teratomas with or without malignant elements. A Pediatric Oncology Group/Children's Cancer Group Intergroup Study. J Clin Oncol 17:2137–2143, 1999.
53. Cushing B, Giller R, Cullen JW, et al: Randomized comparison of combination chemotherapy with etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with high-risk malignant germ cell tumors. A pediatric intergroup study—Pediatric Oncology Group 9049 and Children's Cancer Group 8882. J Clin Oncol 22:2691–2700, 2004.
54. Wessalowski R, Schneider DT, Mils O, et al: Regional deep hyperthermia for salvage treatment of children and adolescents with refractory or recurrent non-testicular malignant germ-cell tumours: An open-label, non-randomised, single-institution, phase 2 study, I. Lancet Oncol 14:843–852, 2013.
55. Bleier BS, Kennedy DW, Palmer JN, et al: Current management of juvenile nasopharyngeal angiofibroma. A tertiary center experience 1999-2007. Am J Rhinol Allergy 23:328–330, 2009.
56. Tang IP, Shashinder S, Gopala Krishnan G, et al: Juvenile nasopharyngeal angiofibroma in a tertiary centre. Ten-year experience. Singapore Med J 50:261–264, 2009.
57. Boghani Z, Husain Q, Kanumuri VV, et al: Juvenile nasopharyngeal angiofibroma: A systematic review and comparison of endoscopic, endoscopic-assisted, and open resection in 1047 cases. Laryngoscope 123(4):859–869, 2013.
58. Valanzano R, Curia MC, Aceto G, et al: Genetic evidence that juvenile nasopharyngeal angiofibroma is an integral FAP tumour. Gut 54:1046–1047, 2005.
59. Hwang HC, Mills SE, Patterson K, et al: Expression of androgen receptors in nasopharyngeal angiofibroma. An immunohistochemical study of 24 cases. Mod Pathol 11:1122–1126, 1998.
60. Schlauder SM, Knapp C, Steffensen TS, et al: Aromatase may play a critical role in the pathogenesis of juvenile nasopharyngeal angiofibroma. Fetal Pediatr Pathol 28:232–238, 2009.
61. Montag AG, Tretiakova M, Richardson M: Steroid hormone receptor expression in nasopharyngeal angiofibromas. Consistent expression of estrogen receptor beta. Am J Clin Pathol 125:832–837, 2006.

62. Maniglia MP, Ribeiro ME, Vodys NM, et al: Molecular pathogenesis of juvenile nasopharyngeal angiofirbroma in Brazilian patients. Pediatr Hematol Oncl 30:616–622, 2013.
63. Liang J, Yi Z, Lianq P: The nature of juvenile nasopharyngeal angiofibroma. Otolaryngol Head Neck Surg 123:475–481, 2000.
64. Abraham SC, Wu TT: Nasopharyngeal angiofibroma. Hum Pathol 32:455, 2001.
65. Abraham SC, Montgomery EA, Giardiello FM, et al: Frequent beta-catenin mutations in juvenile nasopharyngeal angiofibromas. Am J Pathol 158:1073–1078, 2001.
66. Margalit N, Wasserzug O, De-Row A, et al: Surgical treatment of juvenile nasopharyngeal angiofibroma with intracranial extension. J Neurosurg Pediatr 4:113–117, 2009.
67. Herman P, Lot G, Chapot R, et al: Long-term follow-up of juvenile nasopharyngeal angiofibromas. Analysis of recurrences. Laryngoscope 109:140–147, 1999.
68. Grybauskas V, Parker J, Friedman ML: Juvenile nasopharyngeal angiofibroma. Otolaryngol Clin North Am 19:647–657, 1986.
69. Carrillo JF, Maldonado F, Albores O, et al: Juvenile nasopharyngeal angiofibroma. Clinical factors associated with recurrence, and proposal of a staging system. J Surg Oncol 98:75–80, 2008.
70. Fisch U: The infratemporal fossa approach for nasopharyngeal tumors. Laryngoscope 93:36–44, 1983.
71. Andrews JC, Fisch U, Valavanis A, et al: The surgical management of extensive nasopharyngeal angiofibromas with the infratemporal fossa approach. Laryngoscope 99:429–437, 1989.
72. Chandler JR, Goulding R, Moskowitz L, et al: Nasopharyngeal angiofibromas. Staging and management. Ann Otol Rhinol Laryngol 93:322–329, 1984.
73. Radkowski D, McGill T, Healy GB, et al: Angiofibroma. Changes in staging and treatment. Arch Otolaryngol Head Neck Surg 122:122–129, 1996.
74. Spielmann PM, Adamson R, Cheng K, et al: Juvenile nasopharyngeal angiofibroma. Spontaneous resolution. Ear Nose Throat J 87:521–523, 2008.
75. Weprin LS, Siemers PT: Spontaneous regression of juvenile nasopharyngeal angiofibroma. Arch Otolaryngol Head Neck Surg 117:796–799, 1991.
76. Reddy KA, Mendenhall WM, Amdur RJ, et al: Long-term results of radiation therapy for juvenile nasopharyngeal angiofibroma. Am J Otolaryngol 22:172–175, 2001.
77. Chakraborty S, Ghoshal S, Patil VM, et al: Conformal radiotherapy in the treatment of advanced juvenile nasopharyngeal angiofibroma with intracranial extension: An institutional experience. Int J Radiat Oncol Biol Phys 80:1398–1404, 2011.
78. Cummings BJ, Blend R, Keane T, et al: Primary radiation therapy for juvenile nasopharyngeal angiofibroma. Laryngoscope 94:1599–1605, 1984.
79. Labra A, Chavolla-Magana R, Lopez-Ugalde A, et al: Flutamide as a preoperative treatment in juvenile angiofibroma (JA) with intracranial invasion. Report of 7 cases. Otolaryngol Head Neck Surg 130:466–469, 2004.
80. Gates GA, Rice DH, Koopmann CF, Jr, et al: Flutamide-induced regression of angiofibroma. Laryngoscope 102:641–644, 1992.
81. Thakar A, Gupta G, Bhalla AS, et al: Adjuvant therapy with flutamide for presurgical volume reduction in juvenile nasopharyngeal angiofibroma. Head Neck 33:1747–1753, 2011.
82. Schick B, Kahle G, Hassler R, et al: Chemotherapy of juvenile angiofibroma—an alternative? HNO 44:148–152, 1996.
83. Goepfert H, Cangir A, Lee YY: Chemotherapy for aggressive juvenile nasopharyngeal angiofibroma. Arch Otolaryngol 111:285–289, 1985.
84. Goepfert H, Cangir A, Ayala AG, et al: Chemotherapy of locally aggressive head and neck tumors in the pediatric age group. Desmoid fibromatosis and nasopharyngeal angiofibroma. Am J Surg 144:437–444, 1982.
85. Lee JT, Chen P, Safa A, et al: The role of radiation in the treatment of advanced juvenile angiofibroma. Laryngoscope 112:1213–1220, 2002.
86. McAfee WJ, Morris CG, Amdur RJ, et al: Definitive radiotherapy for juvenile nasopharyngeal angiofibroma. Am J Clin Oncol 29:168–170, 2006.
87. Fields JN, Halverson KJ, Devineni VR, et al: Juvenile nasopharyngeal angiofibroma. Efficacy of radiation therapy. Radiology 176:263–265, 1990.
88. Cummings BJ: Juvenile nasopharyngeal angiofibroma. Control rates and treatment costs. Head Neck Surg 3:169–170, 1980.
89. Cummings BJ: The treatment of juvenile nasopharyngeal angiofibroma. The case for radiation therapy. J Laryngol Otol Suppl 8:101–102, 1983.
90. Lopez F, Suarez V, Costales M, et al: Treatment of juvenile angiofibromas: 18-year experience of a single tertiary centre in Spain. Rhinology 50:95–103, 2012.
91. Zhang M, Sun X, Yu H, et al: Biological distinctions between juvenile nasopharyngeal angiofibroma and vascular malformation: An immunohistochemical study. Acta Histochem 113:626–630, 2011.
92. Priest JR, Magnuson J, Williams GM, et al: Cerebral metastasis and other central nervous system complications of pleuropulmonary blastoma. Pediatr Blood Cancer 49:266–273, 2007.
93. Dishop MK, Kuruvilla S: Primary and metastatic lung tumors in the pediatric population. A review and 25-year experience at a large children's hospital. Arch Pathol Lab Med 132:1079–1103, 2008.
94. Manivel JC, Priest JR, Watterson J, et al: Pleuropulmonary blastoma. The so-called pulmonary blastoma of childhood. Cancer 62:1516–1526, 1988.
95. Priest JR, Hill DA, Williams GM, et al: Type I pleuropulmonary blastoma. A report from the International Pleuropulmonary Blastoma Registry. J Clin Oncol 24:4492–4498, 2006.
96. Indolfi P, Bisogno G, Casale F, et al: Prognostic factors in pleuro-pulmonary blastoma. Pediatr Blood Cancer 48:318–323, 2007.
97. Parsons SK, Fishman SJ, Hoorntje LE, et al: Aggressive multimodal treatment of pleuropulmonary blastoma. Ann Thorac Surg 72:939–942, 2001.
98. Hill DA, Ivanovich J, Priest JR, et al: DICER1 mutations in familial pleuropulmonary blastoma. Science 325:965, 2009.
99. Slade I, Bacchelli C, Davies H, et al: DICER1 syndrome: Clarifying the diagnosis, clinical features and management implications of a pleiotropic tumour predisposition syndrome. J Med Genet 48:273–278, 2011.
100. Nasr A, Himidan S, Pastor AC, et al: Is congenital cystic adenomatoid malformation a premalignant lesion for pleuropulmonary blastoma? J Pediatr Surg 45:1086–1089, 2010.
101. Hill DA, Jarzembowski JA, Priest JR, et al: Type I pleuropulmonary blastoma. Pathology and biology study of 51 cases from the International Pleuropulmonary Blastoma Registry. Am J Surg Pathol 32:282–295, 2008.
102. Senac MO, Jr, Wood BP, Isaacs H, et al: Pulmonary blastoma. A rare childhood malignancy. Radiology 179:743–746, 1991.
103. Tagge EP, Mulvihill D, Chandler JC, et al: Childhood pleuropulmonary blastoma. Caution against nonoperative management of congenital lung cysts. J Pediatr Surg 31:187–189, discussion 190, 1996.
104. Kusafuka T, Kuroda S, Inoue M, et al: P53 gene mutations in pleuropulmonary blastomas. Pediatr Hematol Oncol 19:117–128, 2002.
105. Vargas SO, Nose V, Fletcher JA, et al: Gains of chromosome 8 are confined to mesenchymal components in pleuropulmonary blastoma. Pediatr Dev Pathol 4:434–445, 2001.
106. Priest JR, McDermott MB, Bhatia S, et al: Pleuropulmonary blastoma. A clinicopathologic study of 50 cases. Cancer 80:147–161, 1997.
107. Naffaa LN, Donnelly LF: Imaging findings in pleuropulmonary blastoma. Pediatr Radiol 35:387–391, 2005.
108. Fosdal MB: Pleuropulmonary blastoma. J Pediatr Oncol Nurs 25:295–302, 2008.
109. Pleuropulmonary Blastoma Registry. Available online at www.ppbregistry.org.
110. Ohta Y, Fujishima M, Hasegawa H, et al: High therapeutic effectiveness of postoperative irinotecan chemotherapy in a typical case of radiographically and pathologically diagnosed pleuropulmonary blastoma. J Pediatr Hematol Oncol 31:355–358, 2009.
111. Pinarli FG, Oguz A, Ceyda K, et al: Type II pleuropulmonary blastoma responsive to multimodal therapy. Pediatr Hematol Oncol 22:71–76, 2005.
112. Lal P, Sharma DN, Biswal BM, et al: Role of radiotherapy in conjunction with chemotherapy in giant pleuropulmonary blastoma. Indian Pediatr 35:186–188, 1998.
113. Bartlett JA, Riding KH, Salkeld LJ: Management of hemangiomas of the head and neck in children. J Otolaryngol 17:111–120, 1988.
114. Acevedo JL, Shah RK, Brietzke SE: Nonsurgical therapies for lymphangiomas. A systematic review. Otolaryngol Head Neck Surg 138:418–424, 2008.
115. Mulliken JB, Glowacki J: Hemangiomas and vascular malformations in infants and children. A classification based on endothelial characteristics. Plast Reconstr Surg 69:412–422, 1982.
116. Schild SE, Buskirk SJ, Frick LM, et al: Radiotherapy for large symptomatic hemangiomas. Int J Radiat Oncol Biol Phys 21:729–735, 1991.
117. Whimster IW: The pathology of lymphangioma circumscriptum. Br J Dermatol 94:473–486, 1976.
118. Ozeki M, Funato M, Kanda K, et al: Clinical improvement of diffuse lymphangiomatosis with pegylated interferon alfa-2b therapy. Case report and review of the literature. Pediatr Hematol Oncol 24:513–524, 2007.
119. Johnson DW, Klazynski PT, Gordon WH, et al: Mediastinal lymphangioma and chylothorax. The role of radiotherapy. Ann Thorac Surg 41:325–328, 1986.
120. de Serres LM, Sie KC, Richardson MA: Lymphatic malformations of the head and neck. A proposal for staging. Arch Otolaryngol Head Neck Surg 121:577–582, 1995.
121. Costello SA, Seywright M: Postirradiation malignant transformation in benign haemangioma. Eur J Surg Oncol 16:517–519, 1990.
122. Braun-Falco O, Schultze U, Meinhof W, et al: Contact radiotherapy of cutaneous hemangiomas. Therapeutic effects and radiation sequelae in 818 patients. Arch Dermatol Res 253:237–247, 1975.
123. Musumeci ML, Schlecht K, Perrotta R, et al: Management of cutaneous hemangiomas in pediatric patients. Cutis 81:315–322, 2008.
124. Ogino I, Torikai K, Kobayasi S, et al: Radiation therapy for life- or function-threatening infant hemangioma. Radiology 218:834–839, 2001.
125. O'Cathail S, Rostom AY, Johnson ML: Successful control of lymphangioma circumscriptum by superficial X-rays. Br J Dermatol 113:611–615, 1985.
126. Denton AS, Baker-Hines R, Spittle MF: Radiotherapy is a useful treatment for lymphangioma circumscriptum. A report of two patients. Clin Oncol (R Coll Radiol) 8:400–401, 1996.
127. Yildiz F, Atahan IL, Ozyar E, et al: Radiotherapy in congenital vulvar lymphangioma circumscriptum. Int J Gynecol Cancer 18:556–559, 2008.
128. Hesselmann S, Micke O, Marquardt T, et al: Case report: Kasabach-Merritt syndrome. A review of the therapeutic options and a case report of successful treatment with radiotherapy and interferon alpha. Br J Radiol 75:180–184, 2002.
129. Mitsuhashi N, Furuta M, Sakurai H, et al: Outcome of radiation therapy for patients with Kasabach-Merritt syndrome. Int J Radiat Oncol Biol Phys 39:467–473, 1997.

130. Lezama-del Valle P, Gerald WL, Tsai J, et al: Malignant vascular tumors in young patients. Cancer 83:1634–1639, 1998.
131. Costa MA, Sousa A, Vieira E: Hemangioendothelioma. A rare vascular tumor in childhood and adolescence. Pediatr Hematol Oncol 13:333–337, 1996.
132. Lindberg S: Radiotherapy of childhood haemangiomas. From active treatment to radiation risk estimates. Radiat Environ Biophys 40:179–189, 2001.
133. Chang B, Gu H, Qian H, et al: Treatment of cutaneous hemangiomas with low-dose soft x-ray. Chin Med J (Engl) 110:893–894, 1997.
134. Sealy R, Barry L, Buret E, et al: Cavernous haemangioma of the head and neck in the adult. J R Soc Med 82:198–201, 1989.
135. Gerald WL, Miller HK, Battifora H, et al: Intra-abdominal desmoplastic small round-cell tumor. Report of 19 cases of a distinctive type of high-grade polyphenotypic malignancy affecting young individuals. Am J Surg Pathol 15:499–513, 1991.
136. Park BJ, Alexander HR, Libutti SK, et al: Treatment of primary peritoneal mesothelioma by continuous hyperthermic peritoneal perfusion (CHPP). Ann Surg Oncol 6:582–590, 1999.
137. Goodman KA, Wolden SL, La Quaglia MP, et al: Whole abdominopelvic radiotherapy for desmoplastic small round-cell tumor. Int J Radiat Oncol Biol Phys 54:170–176, 2002.
138. Hayes-Jordan A, Anderson P: The diagnosis and management of desmoplastic small round cell tumor: A review. Curr Opin Oncol 23:385–389, 2011.
139. Barr FG, Chatten J, D'Cruz C, et al: Molecular assays for chromosomal translocations in the diagnosis of pediatric soft tissue tumors. JAMA 273:553–557, 1995.
140. De Alava E, Ladanyi M, Rosai J, et al: Detection of chimeric transcripts in desmoplastic small round cell tumor and related developmental tumors by RT-PCR. Am J Pathol 147:1584–1591, 1995.
141. Nathan JD, Gingalewsik C, Salem RR: Intra-abdominal desmoplastic small round cell tumor. Yale J Biol Med 72:287–293, 1999.
142. Murphy AJ, Bishop K, Pereira C, et al: A new molecular variant of desmoplastic small round cell tumor. Significance of WT1 immunostaining in this entity. Hum Pathol 39:1763–1770, 2008.
143. Cummings TJ, Brown NM, Stenzel TT: TaqMan junction probes and the reverse transcriptase polymerase chain reaction. Detection of alveolar rhabdomyosarcoma, synovial sarcoma, and desmoplastic small round cell tumor. Ann Clin Lab Sci 32:219–224, 2002.
144. Neder L, Scheithauer BW, Turel KE, et al: Desmoplastic small round cell tumor of the central nervous system. Report of two cases and review of the literature. Virchows Arch 454:431–439, 2009.
145. Collardeau-Frachon S, Ranchere-Vince D, Delattre O, et al: Primary desmoplastic small round cell tumor of the kidney. A case report in a 14-year-old girl with molecular confirmation. Pediatr Dev Pathol 10:320–324, 2007.
146. Karavitakis EM, Moschovi M, Stefanaki K, et al: Desmoplastic small round cell tumor of the pleura. Pediatr Blood Cancer 49:335–338, 2007.
147. Hayes-Jordan A, Green H, Fitzgerald N, et al: Novel treatment for desmoplastic small round cell tumor: Hyperthermic intraperitoneal perfusion. J Pediatric Surg 45:1000–1006, 2010.
148. Kushner BH, LaQuaglia MP, Wollner N, et al: Desmoplastic small round-cell tumor. Prolonged progression-free survival with aggressive multimodality therapy. J Clin Oncol 14:1526–1531, 1996.
149. Lal DR, Su WT, Wolden SL, et al: Results of multimodal treatment for desmoplastic small round cell tumors. J Pediatr Surg 40:251–255, 2005.
150. Subbiah V, Murthy R, Anderson PM: 90Y-Yttrium microspheres radioembolotherapy in desmoplastic small round cell tumor hepatic metastases. J Clin Oncol 29:e292–e294, 2011.
151. Saab R, Khoury JD, Krasin M, et al: Desmoplastic small round cell tumor in childhood. The St. Jude Children's Research Hospital Experience. Pediatr Blood Cancer 49:274–279, 2008.
152. Msika S, Gruden E, Sarnacki S, et al: Cytoreductive surgery associated to hyperthermic intraperitoneal chemoperfusion for desmoplastic round small cell tumor with peritoneal carcinomatosis in young patients. J Pediatric Surg 45:1617–1621, 2010.
153. Chalasani P, Shtivelband MI, Cranmer LD: Advanced desmoplastic small round cell tumor. Near complete response with trastuzumab-based chemotherapy. Clin Adv Hematol Oncol 7:473–475, 2009.
154. Lichtenstein L, Histiocytosis X: Integration of eosinophilic granuloma of bone, "Letterer-Siwe disease" and "Schuller-Christian disease" as related manifestations of a single nosologic entity. Arch Pathol 56:84–102, 1953.
155. Broadbent V, Egeler RM, Nesbit ME, Jr: Langerhans cell histiocytosis—clinical and epidemiological aspects. Br J Cancer Suppl 23:S11–S16, 1994.
156. Alston RD, Tatevossian RG, McNally RJ, et al: Incidence and survival of childhood Langerhans cell histiocytosis in Northwest England from 1954 to 1998. Pediatr Blood Cancer 48:555–560, 2007.
157. Grifo AH: Langerhans cell histiocytosis in children. J Pediatr Oncol Nurs 26:41–47, 2009.
158. Andersson By U, Tani E, Andersson U, et al: Tumor necrosis factor, interleukin 11, and leukemia inhibitory factor produced by Langerhans cells in Langerhans cell histiocytosis. J Pediatr Hematol Oncol 26(11):706–711, 2004.
159. Kawakubo Y, Kishimoto H, Sato Y, et al: Human cytomegalovirus infection in foci of Langerhans cell histiocytosis. Virchows Arch 434(2):109–115, 1999.
160. Kannourakis G, Abbas A: The role of cytokines in the pathogenesis of Langerhans cell histiocytosis. Br J Cancer Suppl 23:S37–S40, 1994.
161. Csire M, Mikala G, Jako J, et al: Persistent long-term human herpesvirus 6 (HHV-6) infection in a patient with Langerhans cell histiocytosis. Pathol Oncol Res 13(2):157–160, 2007.
162. Strenger V, Urban C: Chromosomal integration of the HHV-6 genome as a possible cause of persistent HHV-6 detection in a patient with Langerhans cell histiocytosis. Pathol Oncol Res 16(1):125–126, 2010.
163. De Filippi P, Badulli C, Cuccia M, et al: Specific polymorphisms of cytokine genes are associated with different risks to develop single-system or multisystem childhood Langerhans cell histiocytosis. Br J Haematol 132:784–787, 2006.
164. Merad M, Ginhoux F, Collin M: Origin, homeostasis and function of Langerhans cells and other langerin-expressing dendritic cells. Nat Rev Immunol 8(12):935–947, 2008.
165. Egeler RM, van Halteren AG, Hogendoorn PC, et al: Langerhans cell histiocytosis: Fascinating dynamics of the dendritic cell-macrophage lineage. Immunol Rev 234(1):213–232, 2010.
166. Favara BE, Feller AC, Pauli M, et al: Contemporary classification of histiocytic disorders. The WHO Committee On Histiocytic/Reticulum Cell Proliferations. Reclassification Working Group of the Histiocyte Society. Med Pediatr Oncol 29(3):157–166, 1997.
167. Weitzman S, Egeler RM: Langerhans cell histiocytosis: Update for the pediatrician. Curr Opin Pediatr 20(1):23–29, 2008.
168. Valladeau J, Ravel O, Dezutter-Dambuyant C, et al: Langerin, a novel C-type lectin specific to Langerhans cells, is an endocytic receptor that induces the formation of Birbeck granules. Immunity 12(1):71–81, 2000.
169. Morimoto A, Ikushima S, Kinugawa N, et al: Improved outcome in the treatment of pediatric multifocal Langerhans cell histiocytosis. Results from the Japan Langerhans Cell Histiocytosis Study Group-96 protocol study. Cancer 107:613–619, 2006.
170. Yagci B, Varan A, Caglar M, et al: Langerhans cell histiocytosis. Retrospective analysis of 217 cases in a single center. Pediatr Hematol Oncol 25:399–408, 2008.
171. Buckwalter JA, Brandser E, Robinson RA: The variable presentation and natural history of Langerhans cell histiocytosis. Iowa Orthop J 19:99–105, 1999.
172. Gasent Blesa JM, Alberola Candel V, Solano Vercet C, et al: Langerhans cell histiocytosis. Clin Transl Oncol 10:688–696, 2008.
173. Phillips M, Allen C, Gerson P, et al: Comparison of FDG-PET scans to conventional radiography and bone scans in management of Langerhans cell histiocytosis. Pediatr Blood Cancer 52(1):97–101, 2009.
174. Titgemeyer C, Grois N, Minkov M, et al: Pattern and course of single-system disease in Langerhans cell histiocytosis data from the DAL-HX 83- and 90-study. Med Pediatr Oncol 37:108–114, 2001.
175. Gadner H, Heitger A, Grois N, et al: Treatment strategy for disseminated Langerhans cell histiocytosis. DAL HX-83 Study Group. Med Pediatr Oncol 23:72–80, 1994.
176. Kudo K, Ohga S, Morimoto A, et al: Improved outcome of refractory Langerhans cell histiocytosis in children with hematopoietic stem cell transplantation in Japan. Bone Marrow Transplant 45:901–906, 2010.
177. Kesik V, Citak C, Kismet E, et al: Hematopoietic stem cell transplantation in Langerhans cell histiocytosis. Case report and review of the literature. Pediatr Transplant 13:371–374, 2009.
178. Selch MT, Parker RG: Radiation therapy in the management of Langerhans cell histiocytosis. Med Pediatr Oncol 18:97–102, 1990.
179. Olschewski T, Seegenschmiedt MH: Radiotherapy for bony manifestations of Langerhans cell histiocytosis. Review and proposal for an international registry. Strahlenther Onkol 182:72–79, 2006.
180. Demiral AN: The role of radiotherapy in the management of diabetes insipidus caused by Langerhans cell histiocytosis. J BUON 7:217–219, 2002.
181. Isoo A, Ueki K, Ishida T, et al: Langerhans cell histiocytosis limited to the pituitary-hypothalamic axis—two case reports. Neurol Med Chir (Tokyo) 40:532–535, 2000.
182. Rosenzweig KE, Arceci RJ, Tarbell NJ: Diabetes insipidus secondary to Langerhans' cell histiocytosis: Is radiation therapy indicated? Med Pediatr Oncol 29:36–40, 1997.
183. Jordan MB, McClain KL, Yan X, et al: Anti-CD52 antibody, alemtuzumab, binds to Langerhans cells in Langerhans cell histiocytosis. Pediatr Blood Cancer 44(3):251–254, 2005.
184. Idbaih A, Donadieu J, Barthez MA, et al: Retinoic acid therapy in "degenerative-like" neuro-Langerhans cell histiocytosis: A prospective pilot study. Pediatr Blood Cancer 43(1):55–58, 2004.
185. Nakajima K, Morisawa R, Kodama H, et al: Successful treatment with cyclophosphamide of Langerhans cell histiocytosis involving the skin and lymph nodes in an adult patient. Clin Exp Dermatol 35(7):791–792, 2010.
186. Wagner C, Mohme H, Kromer-Olbrisch T, et al: Langerhans cell histiocytosis: Treatment failure with imatinib. Arch Dermatol 145(8):949–950, 2009.
187. Montella L, Insabato L, Palmieri G: Imatinib mesylate for cerebral Langerhans'-cell histiocytosis. N Engl J Med 351(10):1034–1035, 2004.
188. Badalian-Very G, Vergilio JA, Degar BA, et al: Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood 116:1919–1923, 2010.
189. The Histiocyte Society. Available at www.histiocytesociety.org.
190. Ayan I, Kaytan E, Ayan N: Childhood nasopharyngeal carcinoma: From biology to treatment. Lancet Oncol 4:13–21, 2003.
191. Plowman PN: Rare tumors. In Pinkerton CR, Plowman PN, editors: Paediatric oncology, ed 2, Cambridge, 1997, Chapman and Hall, pp 561–575.

192. Ayan I, Altun M: Nasopharyngeal carcinoma in children: Retrospective review of 50 patients. Int J Radiat Oncol Biol Phys 35:485–492, 1996.
193. Vokes EE, Liebowitz DN, Weichselbaum RR: Nasopharyngeal carcinoma. Lancet 350:1087–1091, 1997.
194. Cvitkovic E, Bachouchi M, Armand JP: Nasopharyngeal carcinoma. Biology, natural history, and therapeutic implications. Hematol Oncol Clin North Am 5:821–838, 1991.
195. Ozyar E, Selek U, Laskar S, et al: Treatment results of 165 pediatric patients with non-metastatic nasopharyngeal carcinoma. A Rare Cancer Network study. Radiother Oncol 81:39–46, 2006.
196. Downing NL, Wolden S, Wong P, et al: Comparison of treatment results between adult and juvenile nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 75:1064–1070, 2009.
197. Bar-Sela G, Ben Arush MW, Sabo E, et al: Pediatric nasopharyngeal carcinoma. Better prognosis and increased c-Kit expression as compared to adults. Pediatr Blood Cancer 45:291–297, 2005.
198. Hawkins EP, Krischer JP, Smith BE, et al: Nasopharyngeal carcinoma in children—a retrospective review and demonstration of Epstein-Barr viral genomes in tumor cell cytoplasm. A report of the Pediatric Oncology Group. Hum Pathol 21:805–810, 1990.
199. Preciado MV, Chabay PA, Matteo EN, et al: Epstein Barr virus associated pediatric nasopharyngeal carcinoma: Its correlation with p53 and BCL-2 expression. Med Pediatr Oncol 38:345–348, 2002.
200. Lu QL, Elia G, Lucas S, et al: BCL-2 protooncogene expression in Epstein Barr virus association nasopharyngeal carcinoma. Int J Cancer 53:29–35, 1993.
201. Claudio PP, Howard CM, Fu Y, et al: Mutations in the retinoblastoma-related gene RB2/p130 in primary nasopharyngeal carcinoma. Cancer Res 60:8–12, 2000.
202. Sheu LF, Chen A, Meng CL, et al: Analysis of bcl-2 expression in normal, inflamed, dysplastic nasopharyngeal epithelia, and nasopharyngeal carcinoma. Association with p53 expression. Hum Pathol 28:556–562, 1997.
203. Hildesheim A, Anderson LM, Chen CJ, et al: CYP2E1 genetic polymorphisms and risk of nasopharyngeal carcinoma in Taiwan. J Natl Cancer Inst 89:1207–1212, 1997.
204. Yan J, Diaz J, Jiao J, et al: Perturbation of BRD4 protein function by BRD4-NUT protein abrogates cellular differentiation in NUT midline carcinoma. J Biol Chem 286(31):27663–27675, 2011.
205. Mertens R, Granzen B, Lassay L, et al: Nasopharyngeal carcinoma in childhood and adolescence. Concept and preliminary results of the cooperative GPOH study NPC-91. Gesellschaft fur Padiatrische Onkologie und Hamatologie. Cancer 80:951–959, 1997.
206. Douglass E: Management of infrequent cancers of childhood. In Pizzo P, editor: Principles and practice of pediatric oncology, ed 3, Philadelphia, 1997, Lippincott-Raven, pp 977–1003.
207. Polychronopoulou S, Kostaridou S, Panagiotou JP, et al: Nasopharyngeal carcinoma in childhood and adolescence. A single institution's experience with treatment modalities during the last 15 years. Pediatr Hematol Oncol 21:393–402, 2004.
208. Krmar RT, Ferraris JR, Ruiz SE, et al: Syndrome of inappropriate secretion of antidiuretic hormone in nasopharynx carcinoma. Pediatr Nephrol 11:502–503, 1997.
209. Cheuk DK, Sabin ND, Hossain M, et al: PET/CT for staging and follow-up of pediatric nasopharyngeal carcinoma. Eur J Nucl Med Mol Imaging 39(7):1097–1106, 2012.
210. American Joint Committee on Cancer: AJCC cancer staging manual, ed 7, New York, 2010, Springer.
211. Chu A, Flynn MB, Achino E, et al: Irradiation of nasopharyngeal carcinoma: Correlations with treatment factor and stage. Int J Radiat Oncol Biol Phys 10:2241–2249, 1984.
212. Hoppe RT, Goffinet DR, Bagshaw MA: Carcinoma of the nasopharynx: Eighteen years' experience with megavoltage radiation therapy. Cancer 37:2605, 1976.
213. Mesic JB, Fletcher GH, Goepfert H: Megavoltage irradaition of epithelial tumors of the nasopharynx. Int J Radiat Oncol Biol Phys 7:447–453, 1981.
214. Sanguineti G, Geara F, Garden A, et al: Carcinoma of the nasopharynx treated by radiotherapy alone: Determinants of local and regional control. Int J Radiat Oncol Biol Phys 37:983–996, 1997.
215. Bailet JW, Mark RJ, Abemayor E, et al: Nasopharyngeal carcinoma: Treatment results with primary radiation therapy. Laryngoscope 102:965–972, 1992.
216. Vikram B, Strong EW, Manolatos S, et al: Improved survival in carcinoma of the nasopharynx. Head Neck Surg 7:123–128, 1984.
217. Al-Sarraf M, LeBlanc M, Giri PG, et al: Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer. Phase III randomized Intergroup study 0099. J Clin Oncol 16:1310–1317, 1998.
218. Langendijk JA, Leemans CR, Buter J, et al: The additional value of chemotherapy to radiotherapy in locally advanced nasopharyngeal carcinoma. A meta-analysis of the published literature. J Clin Oncol 22:4604–4612, 2004.
219. Gasparini M, Lombardi F, Rottoli L, et al: Combined radiotherapy and chemotherapy in stage T3 and T4 nasopharyngeal carcinoma in children. J Clin Oncol 6:491–494, 1988.
220. Jenkin RD, Anderson JR, Jereb B, et al: Nasopharyngeal carcinoma—a retrospective review of patients less than thirty years of age. A report of Children's Cancer Study Group. Cancer 47:360–366, 1981.
221. Ingersoll L, Shiao Y, Donaldson S: Nasopharyngeal carcinoma in the young. A combined M.D. Anderson and Stanford experience. Int J Radiat Oncol Biol Phys 19:881–887, 1990.
222. Ayan I, Altun M: Nasopharyngeal carcinoma in children. Retrospective review of 50 patients. Int J Radiat Oncol Biol Phys 35:485–492, 1996.
223. Wolden SL, Steinherz PG, Kraus DH, et al: Improved long-term survival with combined modality therapy for pediatric nasopharynx cancer. Int J Radiat Oncol Biol Phys 46:859–864, 2000.
224. Chen WC, Jackson A, Budnick AS, et al: Sensorineural hearing loss in combined modality treatment of nasopharyngeal carcinoma. Cancer 106(4):820–829, 2000.
225. Kupeli S, Varan A, Ozyar E, et al: Treatment results of 84 patients with nasopharyngeal carcinoma in childhood. Pediatr Blood Cancer 46:454–458, 2006.
226. Rodriguez-Galindo C, Wofford M, Castleberry RP, et al: Preradiation chemotherapy with methotrexate, cisplatin, 5-fluorouracil, and leucovorin for pediatric nasopharyngeal carcinoma. Cancer 103:850–857, 2005.
227. Buehrlen M, Zwaan CM, Granzen B, et al: Multimodal treatment, including interferon beta, of nasopharyngeal carcinoma in children and young adults: Preliminary results from the prospective, multicenter study NPC-2003-GPOH/DCOG. Cancer 118(19):4892–4900, 2012.
228. Laskar S, Sanghavi V, Muckaden MA, et al: Nasopharyngeal carcinoma in children. Ten years' experience at the Tata Memorial Hospital, Mumbai. Int J Radiat Oncol Biol Phys 58:189–195, 2004.
229. Habrand J, Guillot Valls D, Petras S, et al: Carcinoma of the nasopharynx in children and adolescents treated with initial chemotherapy followed by adapted doses of radiotherapy. Int J Radiat Oncol Biol Phys 60:S247, 2004.
230. Orbach D, Brisse H, Helfre S, et al: Radiation and chemotherapy combination for nasopharyngeal carcinoma in children. Radiotherapy dose adaptation after chemotherapy response to minimize late effects. Pediatr Blood Cancer 50:849–853, 2008.
231. Varan A, Ozyar E, Corapcioglu F, et al: Pediatric and young adult nasopharyngeal carcinoma patients treated with preradiation cisplatin and docetaxel chemotherapy. Int J Radiat Oncol Biol Phys 73:1116–1120, 2009.
232. Oshiro Y, Sugahara S, Fukushima T, et al: Pediatric nasopharyngeal carcinoma treated with proton beam therapy. Two case reports. Acta Oncol 50(3):470–473, 2011.