Thyroid Cancer in Children

4

Daniel J. Ledbetter

This chapter reviews thyroid cancer in children. It concentrates on differentiated thyroid cancer that arises from thyroid follicle cells, especially papillary thyroid cancer. The other major differentiated thyroid cancer, follicular cell carcinoma, is also discussed but other thyroid cancers are only briefly mentioned. Medullary carcinoma of the thyroid is discussed in Chap. 31, Multiple Endocrine Neoplasia Type 2.

Discussions of thyroid cancer in children are often dominated by extrapolations of data from adults because thyroid cancer is so much more common in adults than children. But thyroid cancer in children is not the same as thyroid cancer in adults. There are different etiologies, risk factors, clinical presentations, and natural histories. The unique aspects of thyroid cancer in children have been recognized and in 2015 the American Thyroid Association published specific recommendations regarding the evaluation and management of thyroid cancer in children 18 years of age and younger [1]. This chapter will review some of those recommendations.

As for many surgical conditions, the lack of controlled trials for patients with thyroid cancer has led to treatment recommendations that are largely based on upon the consensus of experts [1, 2]. As a general rule, treatment of thyroid cancer typically consists of initial operation to remove gross disease in the neck and then radioactive iodine (I-131) is given to patients who have residual disease or to patients who are at a significant risk for recurrent disease [3, 4]. Unlike many other childhood cancers, chemotherapy and external beam radiation are generally not effective against thyroid cancer.

Incidence

Thyroid cancer is an example of a common clinical scenario in pediatric surgery—it is not a rare problem in children, but the absolute number of children affected is small when compared to the number of adults. A report examining more than 30 years of data from the Surveillance, Epidemiology, and End Results (SEER) registry identified 1753 patients younger than 20 years old with thyroid carcinoma and calculated the annual incidence in this age group to be 0.5 cases per 100,000 people [5]. Over the duration of the study, the incidence of thyroid cancer in children steadily increased by 1.1% per year. This increasing incidence in children is consistent with the findings that the overall incidence of thyroid carcinoma has more than doubled from 1975 to 2001 [6].

The relatively low incidence of the thyroid cancer in children can be considered from different perspectives. First, when looking at all patients with thyroid cancer, children are a definite minority, with patients under 20 years of age accounting for less than 2% of patients with a new

D.J. Ledbetter (✉)
Seattle Children's Hospital, 4800 Sand Point Way NE, PO Box 5371/M/S OA.9.220, Seattle, WA 98105, USA
e-mail: dan.ledbetter@seattlechildrens.org

D.J. Ledbetter and P.R.V. Johnson (eds.), *Endocrine Surgery in Children*,
DOI 10.1007/978-3-662-54256-9_4

diagnosis of differentiated thyroid cancer [1, 4]. However, from the perspective of malignancy in the young, thyroid cancer is an important problem.

Among young people the risk of thyroid cancer is directly related to increasing age. Thyroid cancers make up less than 1% of malignant tumors in children younger than 10 years of age but they are much more common in adolescents. In children aged 15–19 years thyroid cancer accounts for 7.5% of all cancers making it the 8th most common malignancy in that age group (and the second most common in girls) and in young adults 20–24 years old thyroid cancer accounts for 10.5% of all cancers making it the third most common cancer in that age group [5, 7].

These incidence figures translate to between 300 and 400 young people with new diagnoses of thyroid cancer each year in the United States. When compared to the roughly 500 new cases of Wilms tumor each year it is apparent that thyroid cancer is a relatively common pediatric tumor requiring surgery [4]. However, the relative frequency that patients with thyroid cancer are seen at any individual pediatric center varies widely depending upon referral patterns and the number of adolescents cared for by that center.

Epidemiology

As with adults, pediatric patients diagnosed with thyroid carcinoma are more likely to be female than male [8, 9]. This female gender predominance is more marked with increasing age. Children younger than 10 years of age with thyroid cancer are only slightly more likely to be female with a gender distribution of 1.2–1.6 girls: 1 boy, while for children aged 10–14 years the ratio is 3.3 girls: 1 boy, and for those aged 15–19 years old the gender distribution is 5.2 girls: 1 boy [10]. Although the data is not as robust in children there are differences in the racial distribution of thyroid carcinoma in adults indicating a higher frequency of diagnosis in Non-Hispanic whites relative to African-Americans [11, 12].

Etiology

Although the cause of most thyroid cancers is unknown, there is an increased risk of thyroid cancer with radiation exposure and in some genetic syndromes.

Risk of Thyroid Cancer After Radiation Exposure

Radiation exposure is the best-known environmental risk factor for developing thyroid cancer. The majority of thyroid cancers that develop after radiation exposure are papillary carcinomas [13]. The magnitude of the risk of thyroid malignancy after radiation exposure is related to the age of the patient at the time of the exposure, the radiation dose, and associated conditions and treatments.

The sensitivity of the thyroid gland to irradiation is higher in younger patients [13–15] and the increased risk is especially marked with radiation doses at or above 20–29 Gy [16].

Radiation exposure can be classified as either low- or high dose. Low-dose exposures include [1] therapeutic irradiation for benign conditions such as hemangiomas, enlarged tonsils, or thymic hyperplasia and [2] living in the vicinity of nuclear accidents such as Chernobyl or in areas impacted by atomic bombs. High-dose exposure occurs with radiation treatment for malignancy. The risk of malignancy is higher with higher radiation doses.

Although the cumulative incidence of thyroid malignancy following medical treatment is low, the incidence of thyroid cancer was found to be higher than expected in cohort analyses of survivors of other childhood cancer [17]. The increased risk of thyroid cancer in individuals who have had radiation exposure to their thyroid during childhood has led to recommendations for long-term thyroid ultrasound surveillance of these patients to detect thyroid nodules [18].

The age-dependent sensitivity of the thyroid to the carcinogenic effects of radiation has also been noted with exposure to I-131. In adults

treated with I-131 there seems to be a minimally increased risk of future thyroid cancer, whereas children and even adolescents seem to have an increased risk. The risk is even more substantial if the child was younger than 10 years at the time exposure [19]. The clinical relevance of this increased risk was demonstrated by the epidemic of papillary thyroid cancer among children exposed to I-131 after the Chernobyl nuclear reactor accident in 1986 [20]. Even though radiation-related papillary thyroid cancers look more aggressive histologically and have higher recurrence rates, the overall patient survival with these tumors is similar to tumors not associated with radiation exposure [21].

Risk of Thyroid Cancer in Syndromes

Thyroid cancers are associated with several genetic syndromes including multiple endocrine neoplasia, familial adenomatous polyposis, PTEN hamartoma tumor syndromes, the Carney complex, DICER1 syndrome, and familial non medullary thyroid carcinoma (FNMTC).

Multiple endocrine neoplasia (MEN) type IIA, MEN IIB, and familial medullary thyroid cancer, are autosomal dominant syndromes caused by mutations in the RET proto-oncogene. These syndromes are associated with a very high risk of medullary carcinoma of the thyroid. These syndromes and medullary thyroid carcinoma are discussed in more detail is in Chap. 31.

The autosomal dominant syndrome of familial adenomatous polyposis (FAP) is caused by mutations in the adenomatous polyposis coli (APC) gene. The subset of patients with FAP who have extraintestinal manifestations of their APC mutation are often labeled as having Gardner syndrome. Patients with FAP/Gardner syndrome are at increased risk of developing thyroid cancer at a relatively young age. The thyroid cancer is usually papillary carcinoma and the mean age at diagnosis is 33 years. Because of their relatively high risk of developing thyroid cancer it is recommended that patients with FAP/Gardner syndrome have regular ultrasound screening for thyroid nodules [22].

Mutations in the protein tyrosine phosphatase and tensin (PTEN) gene are associated with a group of rare conditions known as PTEN hamartoma tumor syndromes. The best-described PTEN hamartoma tumor syndrome is Cowden syndrome, which is an autosomal dominant syndrome of macrocephaly, multiple hamartomas, and characteristic skin abnormalities such as trichilemmomas. Patients with Cowden syndrome have an increased risk of differentiated thyroid cancer that can present in childhood. This risk has led to ultrasound screening for thyroid abnormalities [23–25].

The Carney complex is an autosomal dominant syndrome of abnormal skin pigmentation (lentigenes and blue nevi) and an increased risk of endocrine and nonendocrine tumors. The most common endocrine tumor in Carney complex is primary pigmented nodular adrenocortical disease (PPNAD), which can cause Cushing's syndrome. Patients with the Carney complex also have an increased risk of thyroid adenomas and carcinomas [26].

DICER1 syndrome is a rare, autosomal dominant syndrome that increases the affected individuals' risk of developing a variety of unusual benign and malignant tumors at a young age. The most common tumor that develops in DICER1 syndrome is pleuropulmonary blastoma, which usually presents before 6 years of age [27]. Patients with DICER1 are also at risk for including ovarian sex cord stromal tumors, cystic nephroma, multinodular goiter, and differentiated thyroid cancer [28]. Most patients with DICER1 do not develop tumors.

A child with a sibling or a parent with a differentiated thyroid cancer has an increased risk of developing a differentiated thyroid cancer. These patients with familial non-medullary thyroid cancer (FNMTC) may account for up to 5% of all patients with differentiated thyroid cancers [29]. There is probably more than one genetic pathway to explain the increased risk of differentiated thyroid cancer within certain families and it is an area of ongoing investigation [30]. Although controversial, patients with FNMTC seem to be more likely to present with multifocal, bilateral, disease and to present with lymph node involvement at diagnosis [31].

Pathology

The pathologic classification and histologic definition of types of thyroid cancers is from the World Health Organization (WHO) and is the same in children and adults [32]. The overwhelming majority of thyroid tumors in children are differentiated thyroid cancers that arise from thyroid follicular cells. In the SEER registry report mentioned previously, more than 90% of the 1753 children and adolescents had differentiated thyroid cancers and most of those were papillary thyroid cancer (Table 4.1) [5]. Other series from around the world suggest that papillary thyroid cancer accounts is even more prevalent that the SEER report suggests with 90–95% of childhood thyroid cancer [33–35]. The other major differentiated thyroid cancer, follicular cancer, accounts for most of the rest of thyroid cancers [5]. Other thyroid cancers including medullary thyroid cancer and poorly differentiated or anaplastic thyroid cancer are rare.

Papillary Thyroid Cancer

Pathologic features of papillary thyroid cancer include psammoma bodies and nuclear ground glass appearance, longitudinal grooves, and inclusions [32]. Histologic subtypes of papillary thyroid cancer seen in children include classic, solid, follicular, and diffuse sclerosing variants. The diffuse sclerosing variant is important to consider because it is more common in children, especially younger children, than in adults and it has a unique clinical presentation of enlargement of an entire thyroid lobe or the entire gland rather than as a nodule within the gland [36]. The relative prevalence of this variant has led to the recommendation that children presenting with diffusely enlarged thyroid glands or lobes have ultrasound imaging to evaluate for findings of malignancy [1].

Table 4.1 Histologic types of thyroid cancers in children from SEER registry report

83% papillary
60% papillary
23% follicular variant of papillary
10% follicular thyroid cancer
5% medullary
2% other

From Ref. [5], with permission

Papillary thyroid cancer is often multifocal (30–60%) and bilateral (30%) and neck lymph node metastases are present in at least 30–60% of children at diagnosis [37–40]. Pulmonary metastases are also common (10–25%) in children at diagnosis, usually when neck lymph nodes metastases are present [41, 42]. Overall, at the time of diagnosis, children with papillary thyroid cancer are more likely than adults to have tumor extending beyond the capsule of the thyroid, regional lymph node metastases, and pulmonary metastases, even when controlled for tumor size and histology [37–39, 41, 42]. But despite having more advanced disease at the time they present, children with papillary thyroid cancer have an excellent prognosis.

Follicular Thyroid Cancer

Follicular thyroid cancer is relatively rare [5] and it is usually seen in adolescents rather than younger children. Unlike papillary cancer there is less of a female preponderance [41] and its incidence seems to be decreasing rather than increasing [43]. The risk factors for developing follicular thyroid cancer are different than the risk factors for developing papillary thyroid cancer with iodine deficiency related to follicular thyroid cancer but not papillary cancer [44, 45] and radiation exposure related to papillary thyroid cancer but not follicular cancer [37]. Follicular thyroid cancers are common thyroid tumors in the PTEN syndromes so patients with follicular thyroid cancers should be closely evaluated for PTEN syndromes [25].

Follicular neoplasms are typically encapsulated. The cytological features of follicular thyroid cancers and benign follicular adenomas are identical and it is only possible to make the diagnosis of malignancy when there is tumor invasion through the capsule or into blood

vessels. This explains why FNA can only identify a follicular tumor and not a follicular malignancy. Histologic subtypes of follicular thyroid cancer include Hürthle cell, clear cell, and insular variants. These less differentiated variants are all rare in children [46] and tend to be associated with more aggressive disease and a worse prognosis in adults [47].

The clinical presentation and behavior of follicular thyroid cancer are distinct from the more common papillary thyroid cancer with fewer neck lymph metastases but rather a propensity for hematogenous spread and lung metastases. Follicular and papillary thyroid cancers have the same excellent prognosis [5].

Other Thyroid Cancers

Other, non-differentiated thyroid cancers in children include medullary and anaplastic thyroid cancer and lymphomas. Medullary thyroid cancer derives from parafollicular C cells that produce calcitonin rather than follicular cells that produce thyroid hormones. This tumor is reviewed in Chap. 31.

Anaplastic thyroid cancer accounts for <2% of thyroid cancers of all ages. It is mainly a disease of the elderly with the large majority of afflicted patients more than 60 years of age. Anaplastic thyroid cancer is very rare in children. Histologically, it is undifferentiated and similar to non-Hodgkin lymphoma, medullary thyroid carcinoma, the insular variant of follicular thyroid carcinoma, and poorly differentiated carcinoma that has metastasized to the thyroid. Modern immunohistochemistry techniques should make diagnostic confusion less likely. Anaplastic thyroid cancer is also functionally primitive and it does not concentrate iodine so radioactive iodine is not useful for treatment. Anaplastic thyroid cancer grows rapidly, invades locally, and often presents with symptoms such as dysphagia and hoarseness. More than 40% of patients have distant metastatic disease when they present. It is a deadly disease with more than 80% of patients dead within a year of diagnosis and most are dead within 6 months [48].

Lymphoma of the thyroid is rare in adults and children. It usually presents as a relatively rapidly enlarging neck mass in a patient with a history of Hashimoto's thyroiditis. Pathologically, lymphomas of the thyroid are usually large B-cell lymphomas, but other types of lymphoma are possible. The diagnosis of lymphoma can be made by fine-needle aspiration biopsy by an experienced pathologist. Surgery is limited to the biopsy and treatment consists of chemotherapy and radiation depending upon the type of lymphoma [49].

Clinical Presentations of Thyroid Cancer

Thyroid cancer usually presents as a thyroid nodule or an enlarged thyroid gland that may be noticed by the patient or the patient's family or is found on routine physical exam. Thyroid nodules may not be visible or palpable and only be discovered on imaging studies done for screening purposes or for other reasons. Significant thyroid nodules are usually evaluated by fine needle aspiration (FNA) that allows for risk stratification that defines a risk of malignancy. For more on the evaluation of thyroid nodules see Chap. 3.

Thyroid cancer may also be discovered in the surgical specimen after resection of part or all the thyroid gland done for diagnosis of a thyroid nodule or for a benign disease. Finally, thyroid cancer can present with a neck lymph node metastasis or even distant metastatic disease. As noted previously, children and especially younger children are more likely than adults to present with advanced disease [37, 41, 50].

Evaluation

The preoperative evaluation (or staging) of a patient with thyroid cancer usually begins during the evaluation of a patient's thyroid nodule (see Chap. 3). A full history and physical examination should be done with directed questioning about symptoms of hoarseness, voice change, dysphagia, neck pain, and the onset and rapidity

of growth of any neck mass. Any history of radiation exposure and family history of thyroid cancer or any malignancy should be noted. A full physical exam should be done with special attention to the thyroid gland and neck lymph nodes. If not already done, thyroid function tests should be obtained.

Critical for preoperative staging is a high-quality ultrasound of the thyroid gland and the entire neck with the goal of identifying cervical lymph node metastases that would dictate the performance of a neck dissection at the time of thyroid resection. If there is bulky lymphadenopathy or if there are any concerns about local invasion of the trachea, esophagus, or recurrent laryngeal nerve then more detailed imaging of the neck should be done with either a CT scan with contrast or MRI [1]. The potential disadvantage of a CT scan with (iodinated) contrast is that the iodine load given could delay postoperative staging and treatment with radioactive iodine. When abnormal lymph nodes are seen on imaging then FNA should be done to confirm the presence of metastases.

Nuclear medicine thyroid scans are not usually indicated preoperatively, except in the early evaluation of an undiagnosed thyroid nodule in a patient with a low TSH. If there is cervical lymph node metastases then a chest X-ray or a chest CT scan could be considered, although any lung metastases would probably be identified on the postoperative radioactive iodine scan.

Treatment

Children with thyroid cancer have been treated by a variety of methods over the last 50 years with very high survival rates, even though recurrent disease and persistent is relatively common. The goal of current treatment is to maintain the very low disease-specific mortality that has been has been obtained in the past while minimizing the complications and morbidity associated with treatment. The treatment of children with thyroid cancer is best done by an experienced, multidisciplinary team of medical and surgical specialists working in an environment with all the resources and personnel to care for children [1]. The team approach is essential in all phases of treatment because the evaluation, surgical treatment, medical treatment, and long-term follow-up are closely linked and interdependent.

In brief, the treatment of children with thyroid cancer begins surgery to remove all gross disease in the neck—usually total thyroidectomy [51] and compartmental excision of any involved cervical lymph nodes. Postoperative staging follows surgical resection. Patients found to have persistent local disease or distant metastatic disease and patients who are thought to be at high risk for recurrent disease are treated with radioactive iodine for [3, 4]. The goal of the combination of surgical resection and radioactive iodine is to eliminate all disease that can be detected by diagnostic whole-body radioactive iodine scanning and serum thyroglobulin.

Surgical Treatment

The operations done for treatment of thyroid cancer should be done by a surgeon experienced in thyroid surgery [1], although how these surgeons should be identified is a matter of ongoing debate. The initial operation for a known thyroid cancer is usually a total or near-total thyroidectomy (near-total thyroidectomy defined as preserving 1–2% of the thyroid gland that is adjacent to the recurrent laryngeal nerve or blood supply to the superior parathyroid gland). Total thyroidectomy is now favored over the previously commonly done thyroid lobectomy because of the high risk for bilateral disease (noted previously in Section "Papillary Thyroid Cancer") and the higher risk of local recurrence and later surgical procedures when less than a total thyroidectomy is performed [40, 52, 53]. Total thyroidectomy also makes postoperative follow-up with diagnostic radioactive iodine scans and serum thyroglobulin easier and more reliable. Unilateral thyroid lobectomy is sometimes favored for very small tumors, especially when there is no evidence of disease outside the thyroid gland and future radioactive iodine

imaging and treatment is not likely. The anatomic principles of total thyroidectomy are discussed in detail in Chap. 1.

The most serious complications after total thyroidectomy include hypoparathyroidism and recurrent laryngeal nerve injury. Postoperative hypoparathyroidism with resulting hypocalcemia is caused by resection or devascularization of the parathyroid glands [54]. If devascularization is recognized then the parathyroid gland can be autotransplanted into the sternocleidomastoid muscle [55]. Transient hypocalcemia requiring postoperative treatment with calcitriol (the active form of vitamin D) and calcium is a relatively common problem after total thyroidectomy that can prolong hospitalization while the serum calcium levels stabilize. There are different strategies to deal with this problem including intraoperative monitoring of the parathyroid hormone (PTH) [56] and initiating early, prophylactic treatment of all patients with calcitriol and calcium [57]. Efforts to prevent recurrent laryngeal nerve injury have been concentrated on methods of nerve monitoring which although technically possible have not been found to reliably decrease the risk of nerve injury [58].

Surgery for follicular neoplasms usually consists of an initial thyroid lobectomy. Frozen section may be useful to look for unexpected papillary thyroid cancer but will not be able to differentiate a benign from a malignant follicular tumor. When the follicular neoplasm is benign then no further surgery is needed. When the follicular tumor is malignant then careful consultation with pathology, endocrinology, oncology, and nuclear medicine experts is needed to decide if completion thyroidectomy is needed or if lobectomy will be sufficient resection. Smaller tumors that have minimal evidence of invasion may potentially be treated by lobectomy alone while larger tumors and those that are more invasive histologically are probably best treated by completion thyroidectomy. The usual lack of neck lymph metastases means that neck lymph node dissections are typically not part of surgical treatment of follicular cancer.

The frequent spread of papillary thyroid cancer to neck lymph nodes and the treatment goal of removing gross disease lead to the frequent performance of lymph node resections [40]. These procedures can be therapeutic, prophylactic, unilateral, or bilateral. It is optimal that any lymph node resection be done at the time of the thyroid operation, which is why preoperative assessment of the neck lymph nodes is so important.

When lymph nodes are removed it should be done as "compartment dissection" rather than as "berry-picking", the removal of only obvious, enlarged lymph node [59]. The definition and reporting terminology of neck dissections for thyroid cancer have been standardized [60, 61]. The central neck or anterior compartment is immediately adjacent to the thyroid gland and is designated level VI. Level I is also central but higher in the neck in the submental area (level IA) and submandibular area (level IB). Levels in the lateral neck are II through V. Levels IIA and IIB are the upper jugular group with IIA being anterior (medial) and IIB being posterior (lateral to the spinal accessory nerve). Level III is the middle jugular area from the hyoid bone superiorly to the cricoid cartilage inferiorly. Level IV is the lower jugular area from the cricoid cartilage to the clavicle and Level V is the posterior triangle area (Fig. 4.1).

Papillary thyroid cancer most commonly metastasizes to the central area, level VI, on the same side as the tumor. When there is preoperative evidence of abnormal lymph nodes in the central neck (or in the lateral neck) then central neck dissection is recommended [1, 60]. Unfortunately, neck ultrasound is less reliable at identifying abnormal lymph nodes in the central neck than in the lateral neck [62]. Also, it is not clear if ultrasound size criteria of the tumor or the lymph node that have been used for adults to identify patients at high risk for metastatic disease are applicable to children [63]. Central neck lymph node dissections increase the risk of recurrent laryngeal nerve injury and permanent hypoparathyroidism so there is considerable debate on when and how (unilateral or bilateral) they should be performed [64, 65].

Lateral neck dissections are those compartmental lymph node resections beyond the central

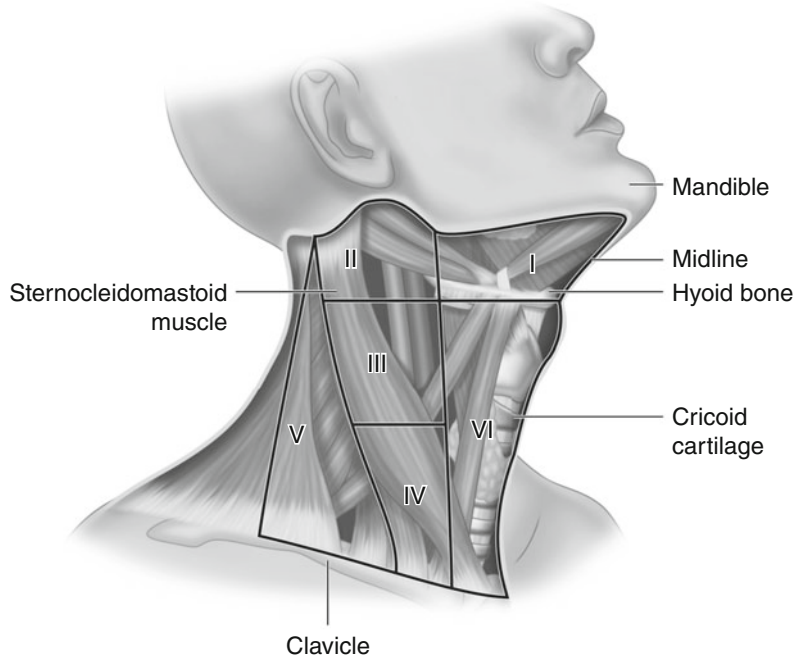

Fig. 4.1 Neck lymph node levels (see text for descriptions)

compartment (level VI). Lateral neck dissections are recommended when there is preoperative evidence of lymph node metastases in those compartments to decrease the chance of persistent and recurrent disease [37, 40]. The dissection can be tailored based on the preoperative staging but often involves levels III, IV, V, and II [66].

Although thyroid surgery in adults is increasingly being done on an outpatient basis, most children, especially younger children and those undergoing a total thyroidectomy with or without neck dissection are admitted after their operation. They are observed for potential bleeding, airway compromise, recurrent laryngeal nerve injury, and hypocalcemia due to hypoparathyroidism. Operative complications are directly related to younger ages and the extent of the operation with recurrent laryngeal nerve injury reported in 3.8% of children 6 years and under, in 1.1% of children 7–12 years, and in 0.6 of patients 13–17 years of age [67]. TSH usually stimulates differentiated thyroid cancer so after surgery thyroid hormone replacement is given to suppress TSH with the target TSH level being lower in patients at higher risk [1].

Postoperative Staging

After the initial operation postop evaluation (staging) is done to identify patients who would benefit from postoperative radioactive iodine treatment and to help define the intensity of follow-up care needed. This staging is dependent upon the surgical pathology, a postoperative diagnostic whole-body radioactive iodine scan, and serum thyroglobulin level [1]. Staging is best done within 12 weeks of surgery.

Pathologic staging for children is a modification of the adult method by the American Thyroid Association that is designed to better risk stratify patients [1]. There are three risk groups—Low, Intermediate, and High [1]. The Low risk group has either no neck lymph node metastases or only microscopic metastases to a small number of central (level VI) lymph nodes. Low-risk patients have a low risk of distant metastases but some risk of recurrent or persistent disease in the neck lymph nodes. Intermediate risk patients have extensive central neck lymph node metastases or minimal lateral compartment neck lymph node metastases. They are also at a low risk for distant metastases but have an increased risk

(compared to Low risk patients) of recurrent or persistent disease in the neck lymph nodes. High-risk patients have locally invasive disease, extensive metastases to lateral compartment lymph nodes, or distant metastases. They have the highest risk of recurrent or persistent regional or distant disease [1].

The staging for Low-risk patients consists of serum thyroglobulin levels while they are euthyroid; i.e., when their TSH is suppressed by their thyroid hormone replacement. Thyroglobulin is a glycoprotein made by follicular cells and follicular cell malignancies and its presence correlates well with the presence and magnitude of metastatic disease in patients who have had their normal thyroid removed [68]. This value can then be followed in the future to observe trends. If the thyroglobulin is initially low and increases over time then it would indicate recurrent disease.

Staging for patients who are Intermediate and High Risk consists of serum thyroglobulin levels when their TSH levels are elevated (the TSH will tend to stimulate any persistent disease) and diagnostic whole-body radioactive iodine (RAI) scans, although some Intermediate risk patients may not need diagnostic scanning [1]. Diagnostic radioactive iodine scans are done with either I-123, which is ideal but more expensive, or I-131, which is the same isotope, used for treatment.

Postoperative Radioactive Iodine Treatment

Radioactive iodine treatment is given to treat known residual or metastatic disease and to prevent recurrent disease [69]. Enthusiasm for its routine use has been tempered by the observation that when children with differentiated thyroid cancer are followed for a very long time that those treated with radioactive iodine have an increase in all-cause mortality compared to those not treated with radioactive iodine. This increased mortality is mainly due to an increased risk second malignancy in those treated with radiation [52, 70].

Radioactive iodine may be given for diagnostic scans (see above) or may be given for treatment. Treatment is with I-131. Radioactive iodine is effective because iodine is markedly concentrated in cells of differentiated thyroid cancers as well as normal thyroid tissue. This concentration of iodine is most pronounced when TSH (thyroid stimulating hormone or thyrotropin) is present at relatively high levels. This requires that the patient either be hypothyroid, raising endogenous TSH levels, or receive recombinant human TSH (rhTSH). In addition, the patient must be in a state of relative iodine deficiency with no recent iodinated contrast and often a low iodine diet [4].

The dosing of radioactive iodine in children requires either an empiric determination based on the patient's size or a more specific determination with calculation of the theoretical maximum dose that will avoid bone marrow toxicity. This specific calculation is known as dosimetry [4]. Radioactive iodine toxicities are mainly to tissues incorporating iodine and consist of—sialadenitis (salivary gland inflammation), xerostomia (dry mouth), dental caries, stomatitis (inflammation of the mouth), dry eyes, and nasolacriminal duct obstruction [71]. Decreased spermatogenesis has been observed in post pubertal males, so sperm banking should be offered.

Outcomes/Complications

Even though children present with more advanced disease than adults they have a better survival. Even with advanced local disease or metastatic disease children with differentiated thyroid cancer have an excellent survival. In the SEER data base study of 1753 children with thyroid cancer those with papillary thyroid cancer had survivals of 98, 97, and 91% at 5, 15, and 30 years [5]. In the same study the survival with follicular thyroid cancer was 96, 95, and 92% at 5, 15, and 30 years [5]. Many series report nearly 100% disease specific survival over 10 and 20 and more years [37, 41, 52]. Even with tumor recurrence and lung metastases prognosis is good.

Recurrences are relatively common and the most important risk factor for disease free survival is the extent of the original operation [40, 52]. Recurrence in the neck can be treated with surgical resection of gross disease if technically possible. Radioactive iodine treatment is given when operation is not deemed to be effective or safe. Pulmonary metastases are treated with radioactive iodine and even though it is persistent the disease may not progress.

References

1. Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenga S, Cerutti JM, Dinauer CA, Hamilton J, Hay ID, Luster M, Parisi MT, Rachmiel M, Thompson GB, Yamashita S. Management guidelines for children with thyroid nodules and differentiated thyroid cancer. Thyroid. 2015;25:716–59.
2. American Thyroid Association Guidelines Taskforce on Thyroid N, Differentiated Thyroid C, Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, Mciver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19:1167–214.
3. Rivkees SA, Mazzaferri EL, Verburg FA, Reiners C, Luster M, Breuer CK, Dinauer CA, Udelsman R. The treatment of differentiated thyroid cancer in children: emphasis on surgical approach and radioactive iodine therapy. Endocr Rev. 2011;32:798–826.
4. Parisi MT, Mankoff D. Differentiated pediatric thyroid cancer: correlates with adult disease, controversies in treatment. Semin Nucl Med. 2007;37:340–56.
5. Hogan AR, Zhuge Y, Perez EA, Koniaris LG, Lew JI, Sola JE. Pediatric thyroid carcinoma: incidence and outcomes in 1753 patients. J Surg Res. 2009;156:167–72.
6. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973–2002. JAMA. 2006;295:2164–7.
7. Wu XC, Chen VW, Steele B, Roffers S, Klotz JB, Correa CN, Carozza SE. Cancer incidence in adolescents and young adults in the United States, 1992–1997. J Adolesc Health. 2003;32:405–15.
8. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin. 2011;61:212–36.
9. Bleyer A, Viny A, Barr R. Cancer in 15- to 29-year-olds by primary site. Oncologist. 2006;11:590–601.
10. Cramer JD, Fu P, Harth KC, Margevicius S, Wilhelm SM. Analysis of the rising incidence of thyroid cancer using the surveillance, epidemiology and end results national cancer data registry. Surgery. 2010;148:1147–52 (discussion 1152–3).
11. Enewold L, Zhu K, Ron E, Marrogi AJ, Stojadinovic A, Peoples GE, Devesa SS. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980–2005. Cancer Epidemiol Biomarkers Prev. 2009;18:784–91.
12. Aschebrook-Kilfoy B, Ward MH, Sabra MM, Devesa SS. Thyroid cancer incidence patterns in the United States by histologic type, 1992–2006. Thyroid. 2011;21:125–34.
13. Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, Schneider AB, Tucker MA, Boice JD Jr. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res. 1995;178:AV43-60.
14. Schonfeld SJ, Lee C, de Gonzalez AB. Medical exposure to radiation and thyroid cancer. Clin Oncol (R Coll Radiol). 2011;244–50.
15. Ron E, Saftlas AF. Head and neck radiation carcinogenesis: epidemiologic evidence. Otolaryngol Head Neck Surg. 1996;115:403–8.
16. Ronckers CM, Sigurdson AJ, Stovall M, Smith SA, Mertens AC, Liu Y, Hammond S, Land CE, Neglia JP, Donaldson SS, Meadows AT, Sklar CA, Robison LL, Inskip PD. Thyroid cancer in childhood cancer survivors: a detailed evaluation of radiation dose response and its modifiers. Radiat Res. 2006;166:618–28.
17. Taylor AJ, Croft AP, Palace AM, Winter DL, Reulen RC, Stiller CA, Stevens MC, Hawkins MM. Risk of thyroid cancer in survivors of childhood cancer: results from the British Childhood Cancer Survivor Study. Int J Cancer. 2009;125:2400–5.
18. Schneider AB, Bekerman C, Leland J, Rosengarten J, Hyun H, Collins B, Shore-Freedman E, Gierlowski TC. Thyroid nodules in the follow-up of irradiated individuals: comparison of thyroid ultrasound with scanning and palpation. J Clin Endocrinol Metab. 1997;82:4020–7.
19. Jacob P, Goulko G, Heidenreich WF, Likhtarev I, Kairo I, Tronko ND, Bogdanova TI, Kenigsberg J, Buglova E, Drozdovitch V, Golovneva A, Demidchik EP, Balonov M, Zvonova I, Beral V. Thyroid cancer risk to children calculated. Nature. 1998;392:31–2.
20. Tronko MD, Howe GR, Bogdanova TI, Bouville AC, Epstein OV, Brill AB, Likhtarev IA, Fink DJ, Markov VV, Greenebaum E, Olijnyk VA, Masnyk IJ, Shpak VM, McConnell RJ, Tereshchenko VP, Robbins J, Zvinchuk OV, Zablotska LB, Hatch M, Luckyanov NK, Ron E, Thomas TL, Voilleque PG, Beebe GW. A cohort study of thyroid cancer and other thyroid diseases after the Chornobyl accident: thyroid cancer in Ukraine detected during first screening. J Natl Cancer Inst. 2006;98:897–903.

21. Schneider AB. Radiation-induced thyroid tumors. Endocrinol Metab Clin North Am. 1990;19:495–508.
22. Herraiz M, Barbesino G, Faquin W, Chan-Smutko G, Patel D, Shannon KM, Daniels GH, Chung DC. Prevalence of thyroid cancer in familial adenomatous polyposis syndrome and the role of screening ultrasound examinations. Clin Gastroenterol Hepatol. 2007;5:367–73.
23. Ngeow J, Mester J, Rybicki LA, Ni Y, Milas M, Eng C. Incidence and clinical characteristics of thyroid cancer in prospective series of individuals with Cowden and Cowden-like syndrome characterized by germline PTEN, SDH, or KLLN alterations. J Clin Endocrinol Metab. 2011;96:E2063–71.
24. Smith JR, Marqusee E, Webb S, Nose V, Fishman SJ, Shamberger RC, Frates MC, Huang SA. Thyroid nodules and cancer in children with PTEN hamartoma tumor syndrome. J Clin Endocrinol Metab. 2011;96:34–7.
25. Hall JE, Abdollahian DJ, Sinard RJ. Thyroid disease associated with Cowden syndrome: a meta-analysis. Head Neck. 2013;35:1189–94.
26. Stratakis CA, Courcoutsakis NA, Abati A, Filie A, Doppman JL, Carney JA, Shawker T. Thyroid gland abnormalities in patients with the syndrome of spotty skin pigmentation, myxomas, endocrine overactivity, and schwannomas (Carney complex). J Clin Endocrinol Metab. 1997;82:2037–43.
27. Doros L, Schultz KA, Stewart DR, Bauer AJ, Williams G, Rossi CT, Carr A, Yang J, Dehner LP, Messinger Y, Hill DA. DICER1-related disorders. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Ledbetter N, Mefford HC, Smith RJH, Stephens K (eds) GeneReviews (R), Seattle, WA; 1993.
28. de Kock L, Sabbaghian N, Soglio DB, Guillerman RP, Park BK, Chami R, Deal CL, Priest JR, Foulkes WD. Exploring the association between DICER1 mutations and differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2014;99:E1072–7.
29. Bonora E, Tallini G, Romeo G. Genetic predisposition to familial nonmedullary thyroid cancer: an update of molecular findings and state-of-the-art studies. J Oncol. 2010;2010:385206.
30. Gara SK, Jia L, Merino MJ, Agarwal SK, Zhang L, Cam M, Patel D, Kebebew E. Germline HABP2 mutation causing familial nonmedullary thyroid cancer. N Engl J Med. 2015;373:448–55.
31. Moses W, Weng J, Kebebew E. Prevalence, clinicopathologic features, and somatic genetic mutation profile in familial versus sporadic nonmedullary thyroid cancer. Thyroid. 2011;21:367–71.
32. Delellis RA. Pathology and genetics of thyroid carcinoma. J Surg Oncol. 2006;94:662–9.
33. Harness JK, Thompson NW, Mcleod MK, Pasieka JL, Fukuuchi A. Differentiated thyroid carcinoma in children and adolescents. World J Surg. 1992;16:547–53 (discussion 553–4).
34. Halac I, Zimmerman D. Thyroid nodules and cancers in children. Endocrinol Metab Clin North Am. 2005;34:725–44, x.
35. Gupta A, Ly S, Castroneves LA, Frates MC, Benson CB, Feldman HA, Wassner AJ, Smith JR, Marqusee E, Alexander EK, Barletta J, Doubilet PM, Peters HE, Webb S, Modi BP, Paltiel HJ, Kozakewich H, Cibas ES, Moore Jr FD, Shamberger RC, Larsen PR, Huang SA. A standardized assessment of thyroid nodules in children confirms higher cancer prevalence than in adults. J Clin Endocrinol Metab. 2013;98:3238–45.
36. Koo JS, Hong S, Park CS. Diffuse sclerosing variant is a major subtype of papillary thyroid carcinoma in the young. Thyroid. 2009;19:1225–31.
37. Demidchik YE, Demidchik EP, Reiners C, Biko J, Mine M, Saenko VA, Yamashita S. Comprehensive clinical assessment of 740 cases of surgically treated thyroid cancer in children of Belarus. Ann Surg. 2006;243:525–32.
38. Zimmerman D, Hay ID, Gough IR, Goellner JR, Ryan JJ, Grant CS, McConahey WM. Papillary thyroid carcinoma in children and adults: long-term follow-up of 1039 patients conservatively treated at one institution during three decades. Surgery. 1988;104:1157–66.
39. Savio R, Gosnell J, Palazzo FF, Sywak M, Agarwal G, Cowell C, Shun A, Robinson B, Delbridge LW. The role of a more extensive surgical approach in the initial multimodality management of papillary thyroid cancer in children. J Pediatr Surg. 2005;40:1696–700.
40. Jarzab B, Handkiewicz Junak D, Wloch J, Kalemba B, Roskosz J, Kukulska A, Puch Z. Multivariate analysis of prognostic factors for differentiated thyroid carcinoma in children. Eur J Nucl Med. 2000;27:833–41.
41. Chow SM, Law SC, Mendenhall WM, Au SK, Yau S, Mang O, Lau WH. Differentiated thyroid carcinoma in childhood and adolescence-clinical course and role of radioiodine. Pediatr Blood Cancer. 2004;42:176–83.
42. Vassilopoulou-Sellin R, Klein MJ, Smith TH, Samaan NA, Frankenthaler RA, Goepfert H, Cangir A, Haynie TP. Pulmonary metastases in children and young adults with differentiated thyroid cancer. Cancer. 1993;71:1348–52.
43. Otto KJ, Lam JS, Macmillan C, Freeman JL. Diminishing diagnosis of follicular thyroid carcinoma. Head Neck. 2010;32:1629–34.
44. McHenry CR, Phitayakorn R. Follicular adenoma and carcinoma of the thyroid gland. Oncologist. 2011;16:585–93.
45. Woodruff SL, Arowolo OA, Akute OO, Afolabi AO, Nwariaku F. Global variation in the pattern of differentiated thyroid cancer. Am J Surg. 2010;200:462–6.
46. Yusuf K, Reyes-Mugica M, Carpenter TO. Insular carcinoma of the thyroid in an adolescent: a case

report and review of the literature. Curr Opin Pediatr. 2003;15:512–5.
47. Lopez-Penabad L, Chiu AC, Hoff AO, Schultz P, Gaztambide S, Ordonez NG, Sherman SI. Prognostic factors in patients with Hurthle cell neoplasms of the thyroid. Cancer. 2003;97:1186–94.
48. Kebebew E, Greenspan FS, Clark OH, Woeber KA, McMillan A. Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors. Cancer. 2005;103:1330–5.
49. Stein SA, Wartofsky L. Primary thyroid lymphoma: a clinical review. J Clin Endocrinol Metab. 2013;98:3131–8.
50. Lazar L, Lebenthal Y, Steinmetz A, Yackobovitch-Gavan M, Phillip M. Differentiated thyroid carcinoma in pediatric patients: comparison of presentation and course between pre-pubertal children and adolescents. J Pediatr. 2009;154:708–14.
51. Raval MV, Bentrem DJ, Stewart AK, Ko CY, Reynolds M. Utilization of total thyroidectomy for differentiated thyroid cancer in children. Ann Surg Oncol. 2010;17:2545–53.
52. Hay ID, Gonzalez-Losada T, Reinalda MS, Honetschlager JA, Richards ML, Thompson GB. Long-term outcome in 215 children and adolescents with papillary thyroid cancer treated during 1940 through 2008. World J Surg. 2010;34:1192–202.
53. Machens A, Lorenz K, Nguyen Thanh P, Brauckhoff M, Dralle H. Papillary thyroid cancer in children and adolescents does not differ in growth pattern and metastatic behavior. J Pediatr. 2010;157:648–52.
54. Ritter K, Elfenbein D, Schneider DF, Chen H, Sippel RS. Hypoparathyroidism after total thyroidectomy: incidence and resolution. J Surg Res. 2015;197:348–53.
55. Lo CY. Parathyroid autotransplantation during thyroidectomy. ANZ J Surg. 2002;72:902–7.
56. Puzziello A, Gervasi R, Orlando G, Innaro N, Vitale M, Sacco R. Hypocalcaemia after total thyroidectomy: could intact parathyroid hormone be a predictive factor for transient postoperative hypocalcemia? Surgery. 2015;157:344–8.
57. Antakia R, Edafe O, Uttley L, Balasubramanian SP. Effectiveness of preventative and other surgical measures on hypocalcemia following bilateral thyroid surgery: a systematic review and meta-analysis. Thyroid. 2015;25:95–106.
58. Pisanu A, Porceddu G, Podda M, Cois A, Uccheddu A. Systematic review with meta-analysis of studies comparing intraoperative neuromonitoring of recurrent laryngeal nerves versus visualization alone during thyroidectomy. J Surg Res. 2014;188:152–61.
59. Musacchio MJ, Kim AW, Vijungco JD, Prinz RA. Greater local recurrence occurs with "berry picking" than neck dissection in thyroid cancer. Am Surg. 2003;69:191–6 (discussion 196–7).
60. American Thyroid Association Surgery Working G, American Association of Endocrine S, American Academy of OH, Neck S, American H, Neck S, Carty SE, Cooper DS, Doherty GM, Duh QY, Kloos RT, Mandel SJ, Randolph GW, Stack BC, Jr, Steward DL, Terris DJ, Thompson GB, Tufano RP, Tuttle RM, Udelsman R. Consensus statement on the terminology and classification of central neck dissection for thyroid cancer. Thyroid. 2009;19:1153–8.
61. Stack BC, Jr, Ferris RL, Goldenberg D, Haymart M, Shaha A, Sheth S, Sosa JA, Tufano RP, American Thyroid Association Surgical Affairs C. American Thyroid Association consensus review and statement regarding the anatomy, terminology, and rationale for lateral neck dissection in differentiated thyroid cancer. Thyroid. 2012;22:501–8.
62. Solorzano CC, Carneiro DM, Ramirez M, Lee TM, Irvin GL, 3rd. Surgeon-performed ultrasound in the management of thyroid malignancy. Am Surg. 2004;70:576–80 (discussion 580–2).
63. Farahati J, Reiners C, Demidchik EP. Is the UICC/AJCC classification of primary tumor in childhood thyroid carcinoma valid? J Nucl Med. 1999;40:2125.
64. Giordano D, Valcavi R, Thompson GB, Pedroni C, Renna L, Gradoni P, Barbieri V. Complications of central neck dissection in patients with papillary thyroid carcinoma: results of a study on 1087 patients and review of the literature. Thyroid. 2012;22:911–7.
65. Machens A, Elwerr M, Thanh PN, Lorenz K, Schneider R, Dralle H. Impact of central node dissection on postoperative morbidity in pediatric patients with suspected or proven thyroid cancer. Surgery. 2016;160:484–92.
66. Sturgeon C, Yang A, Elaraj D. Surgical management of lymph node compartments in papillary thyroid cancer. Surg Oncol Clin N Am. 2016;25:17–40.
67. Sosa JA, Tuggle CT, Wang TS, Thomas DC, Boudourakis L, Rivkees S, Roman SA. Clinical and economic outcomes of thyroid and parathyroid surgery in children. J Clin Endocrinol Metab. 2008;93:3058–65.
68. Eustatia-Rutten CF, Smit JW, Romijn JA, Van der Kleij-Corssmit EP, Pereira AM, Stokkel MP, Kievit J. Diagnostic value of serum thyroglobulin measurements in the follow-up of differentiated thyroid carcinoma, a structured meta-analysis. Clin Endocrinol (Oxf). 2004;61:61–74.
69. Hung W, Sarlis NJ. Current controversies in the management of pediatric patients with well-differentiated nonmedullary thyroid cancer: a review. Thyroid. 2002;12:683–702.
70. Brown AP, Chen J, Hitchcock YJ, Szabo A, Shrieve DC, Tward JD. The risk of second primary malignancies up to three decades after the treatment of differentiated thyroid cancer. J Clin Endocrinol Metab. 2008;93:504–15.
71. Fard-Esfahani A, Emami-Ardekani A, Fallahi B, Fard-Esfahani P, Beiki D, Hassanzadeh-Rad A, Eftekhari M. Adverse effects of radioactive iodine-131 treatment for differentiated thyroid carcinoma. Nucl Med Commun. 2014;35:808–17.