Thyroid cancer in children

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***Background*: Thyroid cancer is an uncommon childhood malignancy usually related to radiation exposure and/or genetic predisposition, such as MEN syndromes. This review article will discuss the etiology and genetic factors contributing to carcinoma of the thyroid in children as well as the literature on appropriate surgical treatment of these patients.**

***Data resources*: The surgical literature was reviewed in regard to the management of children with thyroid cancer.**

***Results*: Children most often present with a thyroid mass and diagnosis is made via fine needle aspiration or surgical excision. Treatment consists primarily of surgical resection though there is controversy over the extent of excision necessary for proper oncologic treatment. An emerging consensus is developing that outcome is improved with radioiodine treatment after surgery.**

***Conclusions*: Early aggressive treatment and frequent long-term follow up is essential in the management of these children with thyroid cancer, and most patients can be successfully cured of their disease.**

World J Pediatr 2005;2:94-97

***Key words*: thyroid cancer; RET gene; thyroidectomy**

Review article

Introduction

Carcinoma of the thyroid gland is relatively unusual in children. Carcinoma of the thyroid can be divided histologically into papillary, follicular, medullary, and undifferentiated varieties; papillary carcinoma is the most common form. Approximately 10% of all malignant thyroid tumors occur in children, representing only about 3% of all childhood malignancies. Population studies in Wales and Los Angeles found that the yearly incidence of thyroid carcinoma is between 1 and 2 cases per million individuals younger than 20 years of age.[1,2] The peak incidence of thyroid cancer in children occurs between 10-18 years of age, and females outnumber males 2 to 1 in children above the age of 10. In children under the age of 10, males tend to outnumber females.

With the decreasing use of radiation to treat benign disease, the incidence of thyroid tumors in children has decreased. Radiation as a cause of thyroid cancer was again highlighted by the marked increase of such tumors noted in the Republic of Belarus following the 1986 Chernobyl nuclear power plant catastrophe.[3,4] About four years after the accident, the Belarus population experienced a 62-fold increase in thyroid tumor. The children affected by the Chernobyl incident were noted to have a higher incidence of tumors arising in younger children with an equal male to female ratio of disease. The thyroid tumors noted were usually aggressive papillary carcinomas with intraglandular tumor spread, local soft tissue invasion, and nodal metastases and were more frequently associated with thyroid autoimmunity.[3,4]

Treatment for previous childhood malignancy increases the incidence of thyroid carcinoma. In one study, after treatment for childhood tumors, 9% of secondary malignancies were thyroid cancers.[5] The most common first malignancy is Hodgkin's lymphoma, its treatment leads to subsequent development of thyroid nodules and thyroid cancer. Most thyroid neoplasms follow the previous use of radiation especially to the neck. Not only radiation but also alkylating agents predispose to thyroid cancer. The median interval from radiation therapy to the recognition of thyroid disease is about 13.0 years,[6] illustrating the need for careful surveillance of the children who have been successfully treated for cancer. In these patients, disease was confined to the neck and did not develop into progressive or recurrent disease.[6]

The rearranged during transfection (RET) gene appears to be one of the genetic keys responsible for thyroid cancer. The RET protooncogene is a receptor tyrosine kinase molecule located on chromosome ten and gene rearrangement is associated with papillary cancers.

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Table 1. Clinical aspects of differentiated thyroid cancer in children

	Harness et al, 1992	Samuel and Sharma, 1991	Newman et al, 1998	Astl et al, 2004
No. of patients	89	59	329	32
Mean age	12.8	NA	15.2	NA
Percentage of females	81	66	76	86
Histology				
Papillary	83	37	297	25
Follicular	6	19	32	4
Medullary	0	1	0	3
Other	0	2	0	0
Percentage for metastasis	88	50	74	46**
Surgical procedures				
Total thyroidectomy	79	49	178	29
Subtotal thyroidectomy	5	*	55	2
Lobectomy or others	5	0	96	0
Lymph node procedures	75	NA	255	11
Percentage for radiotherapy	82	71	43	87
Median follow-up (y)	NA	11	11.3	NA
Percentage for cancer mortality	2.2		0.7	0

*: unsubgrouped children receiving total or near-total thyroidectomy; **: Data on metastasis are available from 26 of the 32 patients; NA: data not available.

Such rearrangement can place RET adjacent to various ubiquitously expressed genes. The fusion genes are termed RET/PTC, and they exhibit increased expression of the tyrosine kinase activity of the molecule. These genetic rearrangements involving RET are especially frequent in radiation induced thyroid tumors. Following the Chernobyl accident, 62% of children from Belarus with thyroid cancer were found to exhibit RET fusion genes.[7] In some studies, the particular RET fusion gene combination has been correlated with particular histologic subtypes. For example, inversion of chromosome 10, PTC1, is more often associated with papillary carcinoma that tends to be more slow growing with clearer differentiation while PTC3 is more often associated with follicular carcinoma which tends to grow more quickly, more aggressively, and with less differentiation.[8]

Clinical examination

Clinically, thyroid carcinoma usually presents as a thyroid mass, an enlarged cervical lymph node, or with both of these findings. Physical exam findings concerning for malignancy include firm nodule and nodule that are fixed to surrounding structures. Table 1 lists clinical characteristics of differentiated thyroid carcinoma from various clinical series.[9-12] The pathologic diagnosis can either be established using thin-needle aspiration cytology or by frozen-section though there is some controversy over the accuracy of frozen-sections in evaluating follicular lesions. As shown in Table 1, most of these patients will have papillary thyroid carcinoma. Prior to surgery, most children should have a thyroid scan, to determine if the thyroid mass contains functioning thyroid tissue. Ultrasound can also be helpful to determine if a lesion is cystic and/or serve as a guide during the surgical.[13]

The lung is the most common site for metastases, aside from lymph nodes, with an incidence of about 6% at diagnosis.[14,15] In such cases, there is nearly always significant cervical lymph node metastases. Radioiodine scanning is required in these patients since the sensitivity of plain chest X-ray films to demonstrate pulmonary metastases is only about 60%.[14] Though, radioiodine scanning has its limitations as well. If there is a significant residual thyroid gland remaining in the neck, radioiodine scanning may be falsely negative. For this reason, aggressive thyroid resection in children with differentiated thyroid cancer is recommended.[16]

Surgical treatment

Since there are no prospective clinical trials to compare surgical management of thyroid cancer in children, there is some controversy over the best surgical management of these patients. The prognosis of these patients tends to be good regardless of the surgical technique employed.[11] Aggressive resection including total thyroidectomy, with lymph node dissection if the regional nodes are involved, has shown to increase local control of the tumor.[9,11,17,18] Radioiodine ablative therapy is most effective after total thyroidectomy since there is less thyroid tissue to absorb radionuclide. Also, if total thyroidectomy is performed, serum thyroglobulin levels may be used to monitor for tumor recurrence.

On the other hand, differentiated thyroid carcinoma in children is a relatively indolent disease and survival is apparently not related to the extent of gland removal so total thyroidectomy is not necessarily required.[15,19] With total thyroidectomy, there is an increased incidence of major surgical complications, including injury to the recurrent laryngeal nerve and hypoparathryoidism. The reported incidence of recurrent laryngeal nerve injury is 0-24%[9] and the reported frequency of permanent hypocalcemia is 6%-27%.[9,19,20] Such complications are reported to occur less commonly in the more recent clinical series.[9]

Currently, a consensus is immerging that aggressive resection for differentiated thyroid cancer in children is the best surgically management.[16] This treatment probably best consists of a near total thyroidectomy and modified neck dissection to remove gross disease if necessary. After surgical resection, I^{131} remnant ablation and long-term suppressive thyroxin therapy are used to treat residual disease and prevent recurrence. In these patients it is especially important to remove as much of the thyroid gland as possible to allow subsequent scanning and retreatment with radioiodine as necessitated

by tumor recurrence. Residual tumor may be treated with radioiodine so even tumors involving the recurrent laryngeal nerve need not be aggressively resected. The nerve may be spared and residual tumor treated.

Prevention of surgical complications and recurrence

The most serious complications of thyroid resection are recurrent laryngeal nerve injury and permanent hypoparathryoidism. The risk of these complications increases with the extent of the surgical procedure and younger age of the patient.[19] To prevent damage to the recurrent laryngeal nerve, intraoperative nerve stimulation has been used to identify the nerve intraoperatively. A recent report demonstrated the usefulness of this technique in children.[21] To reduce the likelihood of hypoparathyroidism, the inferior thyroid artery should be ligated near the thyroid capsule.[22] Autotransplantation of one or more parathyroid glands is a way to preserve parathyroid function. The parathyroid gland can be transplanted into the sternocleidomastoid muscle or into the nondominant forearm.[23,24] If parathyroid gland perfusion is compromised during the dissection, then one should immediately autotransplant the gland into the nearby sternocleidomastoid muscle.

Long-term follow up in these patients is critical, considering the recurrence rate of thyroid cancer is about 30% after 20 years.[11,18,19] In a retrospective study of 329 children treated for differentiated thyroid cancer, there was multivariate analysis of the factors predicting early disease recurrence.[11] The only disease or treatment features significantly predictive of early recurrence were a lower age at diagnosis and the presence of residual neck disease after surgery. Factors not affecting progression-free survival included size of tumor, local extension of tumor, lymph node involvement, metastases, extent of thyroid surgery, use of I^{131} radiotherapy in the initial management, or the antecedent exposure to radiation.[11] The overall progression-free survival of patients with differentiated thyroid cancer in this series was 67% at 10 years and 60% at 20 years after diagnosis.

Follow up for these patients includes an I^{131} whole body scan and chest CT scan performed approximately six weeks after the thyroid resection to detect residual tumor remaining in the neck and in the lungs.[16] Remaining thyroid tissue and any metastatic disease should be treated with radioiodine which can be repeated as needed.[9] Yearly diagnostic radioiodine scans and thyroglobulin level should be conducted to monitor for recurrence. Elevated thyroglobulin values should raise the suspicion for recurrent disease though the diagnostic accuracy of thyroglobulin is limited in children having residual thyroid tissue and in those who are taking thyroid hormone supplementation.[25] To increase the sensitivity of thyroglobulin measurements for residual or recurrent thyroid cancer, the thyroid stimulating hormone (TSH) can be raised by inducing a short period of iatrogenic hypothyroidism or by the administration of recombinant human TSH.[16]

Thyroid medullary carcinoma

While most thyroid carcinomas in children are papillary or follicular, approximately 5% are medullary carcinomas that arise from the parafollicular C-cells. Medullary thyroid carcinoma (MTC) may occur sporadically in patients having multiple endocrine neoplasia (MEN) type 2A or 2B or in the familial medullary thyroid carcinoma (FMTC) syndrome. The RET protooncogene is important in the development of medullary thyroid carcinoma. Various mutations in RET have been shown to be responsible for the multiple endocrine neoplasia type 2 syndromes, MEN 2A, MEN 2B, and FMTC. These RET mutations affect the development of neural crest derived tissues. Moreover, as many as 40% of sporadic non-familial medullary thyroid carcinomas possess RET mutations.[26]

Medullary thyroid carcinoma is usually first detected after spread to lymph nodes or distant metastases.[27] Surgical resection is the only effective treatment of this tumor. Therefore early detection is essential to a successful treatment. Current management of MTC in children from families having the MEN 2 syndrome relies on the presymptomatic detection of the RET protooncogene mutation responsible for the disease, followed by prophylactic total thyroidectomy by about the age of 5 years, before the cancer spreads beyond the thyroid gland.[28] MTC is usually the first tumor to develop in MEN patients.[29] Those children who have a prophylactic thyroidecomy owing to the presence of a RET mutation, 80% will already have foci of medullary carcinoma within the thyroid gland.[30] Because of the increased virulence of medullary thyroid cancer especially in children with MEN 2B, prophylactic thyroidectomy may be recommended in infancy.

Although thyroid cancer in children is relatively uncommon, it is vital that physicians caring for children remain aware of its diagnosis and treatment. Radiation exposure, use of alkylating agents, and genetic syndromes such as MEN and FMTC can dramatically increase the risk of thyroid cancer. Aggressive surgical treatment is gaining favor, although specific tumor factors are not to be underestimated. Although the course is indolent, disease recurrence is fairly common, and

long-term follow up is an essential part of the successful treatment. Further studies, specifically randomized prospective trials, are needed to prove the best surgical intervention for these patients.

Funding: None.
Ethical approval: Not needed.
Competing interest: No benefits in any form have been received or will be received from any commercial party related directly or indirectly to the subject of this article.
Contributors: DD wrote the first draft of this paper. All authors contributed to the intellectual content and approved the final version. MAS is the guarantor.

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Received September 6, 2005
Accepted after revision October 8, 2005