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Original Article

Adolescents Who Underwent Thyroid Surgeries for Thyroid Cancers and Masses

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Abstract

Objective: To define clinical presentation, surgical complications, characteristics and survival of thyroid carcinoma (TC) and benign masses in children. ***Methods:*** Twenty-five paediatric patients underwent thyroid surgery for thyroid masses and TC in 13 years. Retrospectively evaluated medical data included sex, clinicopathologic characteristics, surgery type, postoperative complications, recurrences, and survival rate. Correlations between age, sex, complaint and diagnosis were done using Pearson's t test. ***Results:*** The female to male ratio was 3.1:1. The mean age at diagnosis was 16.2 years (range, 5-18 years)(median age=17). A neck mass was the most common complaint (80%). The other patient presented aslymphadenopathy of the supraclavicular region (n=1), neck pain (n=3) and thyroid mass with previous history of exposure to ionising radiation and was receiving chemotherapy for Hodgkin's lymphoma. Seventeen patients were diagnosed with papillary TC, one with follicular TC, four with follicular adenoma, two with thyroiditis, and one with thyroid Burkitt's lymphoma. Surgical treatment consisted of simpletotal thyroidectomy (n=13), total thyroidectomy with modified radical neck node dissection (n=6), and less than total thyroidectomy (n=6). After the total thyroidectomy, surgical resection for recurrence was performed four of the patients with TC. Postoperative radioactive iodine ablation was administered to 15 of the 18 patients with TC (83.3%) after surgical therapy. Mean follow-up duration was 4.2 years (range, 0.5-10 years) and no patients died of TC. Recurrence occurred in five patients (27.7%). Seven patients (38.8%) experienced postoperative hypocalcaemia. One patient who had undergone bilateral neck dissection was found to have a left thoracic duct injury, which was surgically treated. There is no gender differences in complaint and diagnosis ($p>0.05$). ***Conclusion:*** Thyroid carcinoma develops more aggressively and with more recurrences in children. Thus, secondary operations are often required for recurrence and neck dissection. Given the lack of an adequate case load in paediatric clinics, it is vital that surgery be performed by experienced physicians to lessen complications.

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Introduction

Thyroid carcinoma (TC) is uncommon in childhood and adolescence, constituting 0%-3% of all paediatric malignancies.[1,2] Sporadic differentiated TC's are the most common endocrine malignancies in children, and a female preponderance exists among postpubertal children. Follicular TC is less common than papillary TC in paediatric patients, while anaplastic and undifferentiated thyroid carcinomas are extremely rare.[3,4] Paediatric TC differs from

adult TC in clinical manifestations and clinical outcomes. Despite an overall survival rate exceeding 95%, paediatric TC is often more advanced with lymph node and pulmonary metastasis at diagnosis and postoperative local recurrence is more frequent than in adults. However, although their disease stage is frequently advanced, paediatric patients have an excellent prognosis and a low mortality rate.[5]

Our clinic has seen an increasing number of cases of thyroid masses during the last 5 years, and 18 of the cases mentioned below have been observed within this timeframe. This increase of TC is due to effect of Chernobyl Nuclear explotion an frequent use of ultrasonography. Although our clinic is a large centre, some of the assistants may have graduated without seeing even a single thyroid case 2 or 3 years ago. Compared with adult clinics, we have fewer cases and thus less experience in managing patients with thyroid masses; to compensate for this, we enlisted outside assistance from surgeons who normally operate on adults for our first cases.

With this study, we wished to analyse the factors such as age, sex, initial complaint affecting morbidity in children undergoing surgery for a thyroid mass. Thyroidectomies performed by experienced operators in adult patients are associated with fewer complications than are paediatric thyroidectomies. Even in the largest series covering 30-40 years, only 50-100 operations were performed in children. Therefore, studies carried out in children have vital importance.

Methods

We examined retrospectively the records of the thyroidectomy patients. Between 1990 and 2013, 25 paediatric patients (patients <18 years of age) underwent thyroid surgery through our paediatric surgical department for primary thyroid masses: papillary TC (PTC, 17 patients), follicular TC (one patient), (only 2 patients stage II others stage I), follicular adenoma (four patients), thyroiditis (two patients), and thyroid lymphoma (one patient). Eighteen of the 25 cases were operated in the last five years. Retrospectively evaluated medical data included sex, age at the diagnosis, pathologic characteristics, type of surgery, postoperative complications, recurrences, and survival rate. Clinicopathologic characteristics include chief complaint at diagnosis, tumour size, extrathyroidal extension, multifocality, bilaterality, family history, thyroiditis, and lymph node involvement. Correlations between age, sex, complaint and diagnosis were done using Pearson's t test. Other parameters could not be tested due to small number of patients or patients meet to a certain group. Thyroid resection consisted of total thyroidectomy and less than total thyroidectomy (unilateral thyroid lobectomy). Recurrent laryngeal nerves (RLN) and parathyroid glands were identified and preserved in all cases. The procedures were performed by the same surgical team. If patients had evidence of lateral lymph node metastasis on preoperative evaluation, modified radical neck dissection was performed. Radioactive iodine ablation (RAI) was performed within 4-6 weeks after surgery for malignant lesions. Serum thyroglobuline (Tg) and Tg antibody levels were measured some suitable preoperative cases and postoperative TC patients. Recurrent/metastatic TC patient and non recurrent/metastatic patient Tg values were compared by T-test. Postoperative RAI was administered to 15 of the 18 patients with malignancies. Because of the 2 patients refused to take RAI and one patients changed to city, RAI did not administer. Total thyroidectomy patients received thyroid-stimulating hormone suppression treatment with levothyroxine. Recurrences after surgery were assessed by regular follow-up every 3 or 6 months.

Results

Main characteristics should be seen in Table 1. Twenty-five patients (19 females, six males; female to male ratio, 3.1:1) underwent surgery for different thyroid masses at our institute. The mean age at diagnosis was 16.2 years (range, 5-18 years), (median age=17 years). There is no gender differences in complaint and diagnosis (female 16.6 years, male 15 years, p=0.34). TSH, fT3 and fT4 levels were in normal limits or all patients were euthyroid. The serum thyroglobulin antibody was increased in 4 of the patients in whom (n=13) it could be obtained (>60 U/ml). Serum Tg level elevated only 6 patients with TC patients before the surgery. Ultrasonography and TSH suppressed, Tg level assessment were performed every 6 months after initial therapy. If the Tg levels is <0.05 ng/ml. It is no disease is present in patients. A neck mass was the most common complaint (n=20, 80%). One patient (4%) was diagnosed with lymphadenopathy of the supraclavicular region, three patients had neck pain (12%), and one patient had a thyroid mass with previous history of exposure to ionising radiation and was receiving chemotherapy for Hodgkin's lymphoma. But control neck ultrasonography was shown TC. There was no difference between complaint and diagnosis to gender. Main complaint of mass was seen 84%

Table 1 Main characteristics of the patients

	Age	Sex	Complaint	FNA	Diagnosis	Surgery	Recurrence/ metastasis
1	5	M	Mass	–	Lymphoma	Total thyroidectomy	
2	18	M	Supraclavicular lymph node(+)	Papillary TC	Papillary TC*	Total thyroidectomy +	Operation bed and lateral neck recurrence/Lung metastasis
3	14	F	Mass	Papillary TC	Papillary TC	Total thyroidectomy	
4	15	F	Mass	Papillary TC	Papillary TC	Total thyroidectomy	
5	16	F	Mass	Papillary TC	Papillary TC	Total thyroidectomy	
6	17	F	Neck pain	Colloid mass	Thyroiditis	Less than total thyroidectomy	
7	16	F	Mass	Papillary TC	Papillary TC*	Total thyroidectomy	
8	17	F	Mass	–	Papillary TC	Total thyroidectomy	
9	17	F	Mass	Follicular adenoma	Follicular adenoma	Less than total thyroidectomy	
10	17	F	Mass	Colloid mass	Papillary TC**	Total thyroidectomy +	Lateral neck recurrence
11	16	F	Mass	Follicular TC	Follicular TC*	Total thyroidectomy	
12	17	F	Mass	Follicular adenoma	Follicular adenoma	Less than total thyroidectomy	
13	18	M	Neck pain	Thyroiditis	Thyroiditis	Less than total thyroidectomy	
14	17	M	Previous radiotheraphy for Hodgkin disease	–	Papillary TC	Total thyroidectomy	
15	16	M	Mass	Suspect malignancy	Follicular adenoma	Less than total thyroidectomy	
16	17	F	Neck pain	Papillary TC	Papillary TC	Total thyroidectomy +	Operation recurrence/Cervical node metastasis
17	16	F	Mass	–	Follicular adenoma	Less than total thyroidectomy	
18	17	F	Mass	–	Papillary TC	Total thyroidectomy	
19	18	F	Mass	Papillary TC	Papillary TC	Total thyroidectomy	
20	18	F	Mass	Papillary TC	Papillary TC*	Total thyroidectomy +	Operation bed recurrence
21	16	F	Mass	–	Papillary TC	Total thyroidectomy	
22	16	M	Mass	Papillary TC	Papillary TC	Total thyroidectomy	
23	17	F	Mass	Papillary TC	Papillary TC	Total thyroidectomy	
24	16	F	Mass	Suspect malignancy	Papillary TC	Total thyroidectomy	Lateral neck recurrence
25	18	F	Neck pain	Papillary TC	Papillary TC	Total thyroidectomy	

M=male, F=female, TC=thyroid carcinoma, *=permanent hypocalcaemia, **=thoracic duct injury(+)

in girl and 50% in boy, p=0.94. At the time of surgery, 12 of the patients with malignancies had localised disease in the central neck, while four had lateral and two had bilateral neck node metastasis. Of the 25 patients, 19 underwent fine needle aspiration (FNA), 12 of whom were diagnosed with either papillary TC (n=11) or follicular TC (n=1), while two were diagnosed with a colloidal mass (ultimate diagnosis one thyroiditis and one papillary TC), two with follicular adenomas, two with suspected malignancies (ultimate diagnosis one follicular adenoma and one papillary TC), and one with thyroiditis. FNA did not perform due to clinical advance cases, refuse to this procedure same patients and no experienced staff during the our hospital. It requires expertise for correct diagnosis, which may not be available in all centres. Intraoperative frozen section was done for suspected cases. Positive family history was shown one patient with papillary TC. His father operated for same diagnosis.

Surgical treatment consisted of simple total thyroidectomy (13 patients), total thyroidectomy with modified radical neck node dissection (six patients, 33.3% for TC), and less than total thyroidectomy (six patients). After the total thyroidectomy, supplementary thyroidectomy for recurrence was performed four of the patients with TC. Of the four patients who underwent surgical resection for only tumour recurrence, two had the sclerezon cell type and 2 had the Hurthle cell type.

The mean tumour size was 34.3 mm (range, 6-55 mm). Of the 18 malignant cases, four patients (22.2%) had bilateral disease and six (33.3%) had multifocal disease. Extrathyroidal extension was evident in five cases (27.7%). Four patients displayed lateral neck node metastasis and two displayed bilateral neck node metastasis. The surrounding fat tissues were invaded in three patients. Of the seven patients diagnosed with follicular neoplasia on frozen section (benign or malign lesions?), permenent biopsy was shown three patients had a follicular variant of papillary TC, three had follicular adenomas, and one had follicular TC. Therefore, these four patients with malignant follicular neoplasia on frozen section underwent supplementary thyroidectomy after the exact diagnosis. One patient had recurrent laryngeal nerve invasion, for which the nerve was dissected during the second operation. Recurrent laryngeal nerve palsy did not develop. Two patients had diffuse thyroiditis.

Postoperative RAI was administered to 15 of the 18 patients with malignancies (83.3%) following surgical therapy. Because of the 2 patients refused to take RAI and one patients changed to city, RAI did not administer. One patient, aged 5 years, was recorded to have a left thyroid mass in the data; the pathological diagnosis was confirmed as Burkitt's lymphoma. His examination left-sided large firm neck swelling was found. This swelling was presented more acutely with a 1 week. There was no family history, fever and thyroid disorder. Others clinical examinations and laboratory tests were unremarkable. He was treated with chemotherapy for Burkitt's lymphoma and still alive and disease free.

The mean follow-up duration was 4.2 years for all patients (range, 0.5-10 years). Survival rate was 100% for TC patients. There were no death from disease or other causes in follow up time. But event free survival rate for TC patients was 27.7% and Kaplan-Meier event free survival curve could be seen in Figure 1. During the follow-up period, recurrence occurred in five patients. Recurrence occurred in the lateral neck (n=2, 11.1%), the operation bed (n=2, 11.1%), and both the operation bed and lateral neck (n=1, 5.5%). Metastasis was identified in two patients (stage II) while they were waiting for RAI treatment after undergoing thyroidectomy for papillary TC. Metastasis site was lung (n=1, 5.8%) and cervical lymph node (n=1). Serum tg levels were higher (0,1 to >10 ng/ml) in patients with recurrent and metastatic of TC. Serum Tg level was found higher (11.2±10.74 ng/ml) in the group with recurrence/metastasis than in the group without recurrence/metastasis (0.14±0.161), p=0.002. These patients were treated with appropriate therapy, such as completion total thyroidectomy,

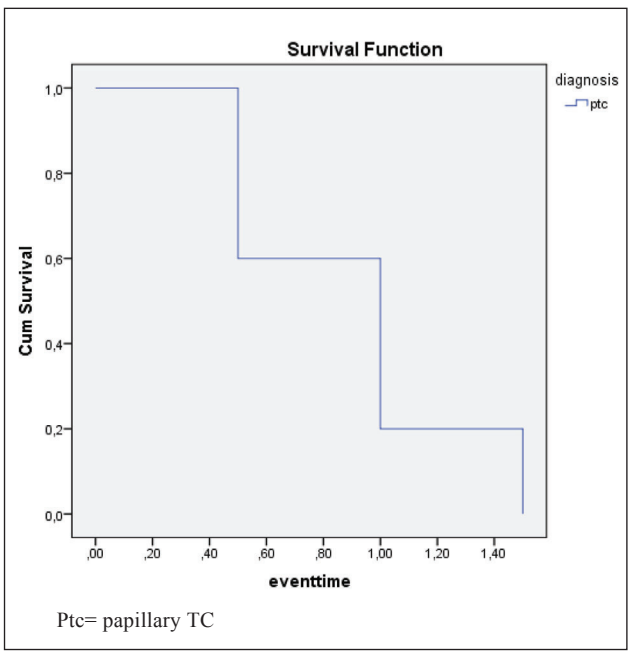

Figure 1 Event free (recurrence and metastasis) survival curve for TC patient (time=year).

modified radical neck dissection, and RAI. No additional treatment was required for any of the follicular adenoma cases. Seven patients (28%) experienced the postoperative complication of hypocalcaemia in 25 cases (transient in three patients and permanent in four [16%]. No recurrent laryngeal nerve injuries, postoperative bleeding, or infections were noted. One patient who had undergone bilateral neck dissection was found to have a left thoracic duct injury, which was appropriately treated.

Discussion

Thyroid carcinoma is uncommon in children and adolescents, accounting for 1.5%-3% of all childhood cancers, with an annual incidence of 0.5 to 1 case per 1 million children.[6] Most affected children are diagnosed during puberty. In patients younger than 18 years, TC behaves differently than in adults; children and adolescents are typically diagnosed at a more advanced stage, with local extension in 20%-60% of cases, cervical lymph node involvement in 40%-80%, and lung metastases in 20%. The course of paediatric TC is also distinct, characterised by frequent local recurrences and the development of new distant metastases. However, the prognosis for children and adolescents with TC is excellent, with an overall survival rate of 95%.[7-9] The reason for this discrepancy is unclear, but some hypotheses have been suggested. The percentage of nondiploid DNA is 10% in children with thyroid cancer, half the rate in adults, which may explain the good prognosis. We did not check our TC patients have nondiploid DNA due to technical shortcomings and lack of sponsor.

Thyroid-stimulating hormone (TSH) may also play a more prominent role as a promoting factor in younger patients. Therefore, postoperative TSH suppression with thyroid hormone replacement is more effective in paediatric patients. Additionally, dedifferentiation from well-differentiated to poorly differentiated carcinoma does not often occur in paediatric thyroid carcinoma.[8,10]

The treatment of paediatric thyroid cancer remains controversial. Because of its low incidence, a prospective trial is difficult to perform. Overall, papillary thyroid cancer demonstrates aggressiveness in 60% of cases, intraglandular dissemination in 40%, and locoregional metastasis in 77%. By observing clinicopathological parameters and their distribution across selected groups, we previously demonstrated that papillary TC behaves more aggressively in younger age groups.[11] Multicentric foci in both thyroid lobes and greater tumour aggressiveness have been identified as risk factors for metastatic development. In a previous report, Dzepina supported the need for total thyroidectomy and meticulous intraoperative exploration of the thyroid bed and lateral neck, with surgical extirpation of all potential microscopic disease foci.[11] Jarzab et al performed a retrospective analysis of 109 patients and found that total thyroidectomy resulted in a 97% disease-free survival at 10 years, whereas non-radical operations were associated with a risk of relapse of 59% at 5 years and 85% at 10 years.[12] Zimmerman et al compared 58 children and 981 adults treated for PTC at their institution. They found that childhood PTC was more often metastatic to the lymph nodes and lungs at presentation and that it more often recurred in the lymph nodes of the neck postoperatively.[8] Thompson and Hay reviewed 21 worldwide studies of thyroid carcinoma and reported on nearly 1800 patients. These authors found that regional nodal metastases were common (range, 27%-100%; median, 60%). Local invasion was noted in 6%-71% of cases (median, 30%) and distant metastases were present in 6%-28%. Tumour recurrence, both locally and at distant sites, was more common in the paediatric group (range, 0%-58%; median, 30%).[1]

Among our paediatric TC patients, 27.7% experienced recurrence, 33.3% had lymph node involvement, and 27.7% had extrathyroidal involvement and bilaterality. We preferred to perform total thyroidectomy on our patients to decrease the risk of metastasis, recurrence, and spread and to avoid the complications often associated with subsequent surgical treatment.

In other studies, while the recurrence rates in the thyroid bed and lymph nodes were 20% and 15%, respectively, these rates were 1% and 4%, respectively, in patients who underwent RAI.[1,13] Therefore, we are trying to decrease the recurrence rate by administering RAI treatment within the first 3 weeks after thyroidectomy. Thyroid cancers are the secondary tumours observed second most commonly in Hodgkin's and non-Hodgkin's lymphomas and third most commonly in leukaemia patients.[14] As in our patients, treatment for thyroid masses that develop in these patients should be administered very quickly and aggressively.

Published reports describing children with TC are very limited, and only a few series have managed to obtain more than 100 patients. Therefore, the reported complication and recurrence rates of paediatric TC patients vary widely. With case series generally consisting of 25 or 30 patients, it takes a long time to reach these numbers; additionally, compared with adults, paediatric follow-up time is shorter. Most paediatric surgeon have not experienced 50 or 100 cases. Considering the possible spread of TC during the diagnostic

process, the recurrence frequency, paranoid nodules, and the proximity of anatomic structures such as the RLN, inexperience may pose a significant problem for the patient. Even the 68-year series of children under 21 performed at the Mayo clinic had only 215 cases (three patients annually), where two paediatric series revealed complication rates ranging from 0%-40% for RLN injury and 0%-32% for permanent hypoparathyroidism.[1,15] In addition, surgical complications increase with a decrease in age. This results depend on both paediatric surgeon perfom thyroidectomy fewer than adult surgeon and small size organ, tissue and nerve. A United States-based study showed that children aged 0-6 years have a higher complication rate (22%) than older children (15% for 7-12 years and 11% for 13-17 years). In general, children have higher complication rates than adults after thyroidectomy (9.1% versus 6.3%).[16] This same study emphasized that performance of the operation by an experienced surgeon who executes 30 or more thyroid operations a year will decrease complications to the minimum.[16]

Considering that 518 thyroid operations were carried out in 22 months (per an article written at our facility) in adult patients at our institution, the difference in the experience level with adults versus children is clear. Seven patients had postoperative hypocalcaemia (28%) and was permenant in (16%) in our series. RLN injury was observed 11% and was permenant 1%, 29% postoperative hypocalcaemia and 5% major complications (tracheostomy, Horner syndrome) were reported under 21 age patients in La Quaglia et al series. They had claimed for higher complication rate this age group patients with differentiated TC who presented with parenchymal metastasis.[5] In this series, the rate of persistent hypoparathyroidism was 0.7% and the RLN injury rate was 1.3%, which are quite low compared with other paediatric series.[17] The fact that our study had a 0% rate of RLN injury can be explained by the fact that our clinical operation for first cases were performed together with experienced endocrine adult surgeons and that we involved ear-nose-throat surgeons in neck dissections when required. Most of the remaining cases were operated by us.

As a result of this study, we concluded that recurrence and lymphatic metastasis are frequently observed in children with thyroid cancer. Therefore, in total thyroidectomy and neck dissection if lymph node metastase are seen in imaging or during the surgery should be carried out. Moreover, post surgical RAI treatment should be given for microcarcinomas, lymp node and distant metastases involvement and residual disease and TSH supression should also be administered (Figure 2).

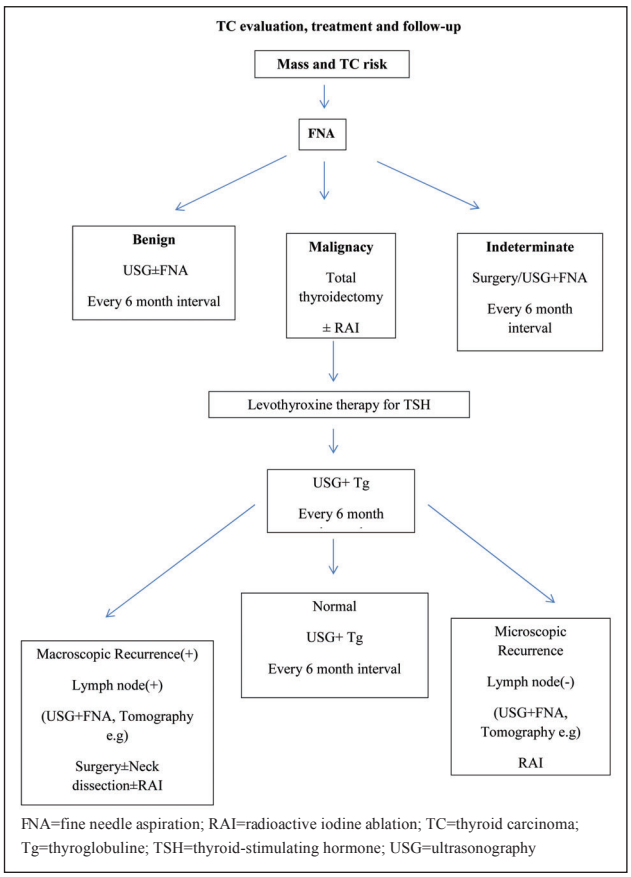

Figure 2 Simple algorithm for TC patients (adopted from Rivkees et al article).[14]

Declaration of Interest

The authors declare that there is no conflict of interest.

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