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HEAD & NECK

Pediatric thyroid surgery: experience in 75 consecutive thyroidectomies

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Abstract

Objectives The main objective of this study is to report our experience in a university hospital in the surgical management of thyroid disease in pediatric patients. We also aim to analyze the results and evaluate the efficacy of fine-needle aspiration biopsy (FNAB) and frozen section analysis.

Methods A retrospective review of thyroid surgeries from January 1997 to December 2017 was conducted. Patients aged under 18 who underwent total or partial thyroidectomy were included. The indication of the surgery, the investigation results, the surgical technique used and the final diagnosis were reviewed and analyzed.

Results A total of 75 patients were included. 80% ($n=60$) were females and 20% ($n=15$) were males. The average age was 13.3 years ± 3.76 and age range was 3–18 years. The indication for thyroidectomy was thyroid nodule in 80% ($n=60$), Grave's disease in 13.3% ($n=10$), multiple endocrine neoplasm type II (MEN II) in 6.7% (n. 5). FNAB was done in 42.7% ($n=32/75$) with sensitivity and specificity of 62.50% and 94.4%, respectively, the positive predictive value was 83.3% and the negative predictive value was 85%. Frozen section, which is a quick intraoperative micro and/or macroscopic examination, was done in 66.7% ($n=50/75$). It was malignant in 12% ($n=6/50$) and was benign in 88% ($n=44/50$). Among benign results, nine ($n=9/44$) patients had malignant disease in final pathological diagnosis. Its sensitivity and specificity were 40% and 100%, respectively, the positive predictive value and the negative predictive value were 100% and 79.6%, respectively. Total thyroidectomy was done in 54.7% ($n=41/75$) and partial thyroidectomy was done in 45.3% ($n=34/75$). Of the 75 patients, 29.3% ($n=22$) had thyroid carcinoma on final pathological analysis.

Conclusion Thyroid diseases that require surgical intervention are rare in pediatric populations. However, when surgery is indicated, there is higher risk of malignancy compared to adults. Our study showed that FNAB has a lower specificity and sensitivity compared to adults, and that surgical decision should be made considering all investigations. We also showed that frozen section is considered primarily for papillary thyroid carcinoma but is not reliable for follicular carcinoma or Bethesda IV. Finally, thyroid surgery in children and adolescents must be part of global multidisciplinary management.

Keywords Thyroidectomy · Child · Thyroid nodule · Differentiated thyroid cancer · Fine-needle aspiration biopsy · Frozen section

Introduction

Thyroid cancer is rare in pediatric patients; thus, its reported incidence is inconsistent. In the United States, the incidence among people under 20 years is 1.8% [1] and represent 5% of pediatric head and neck malignancies [2]. Thyroid nodules are palpable in 0.5–2% of pediatric patients in comparison to 35% in adult patients [2–4]. The risk of malignancy in pediatric thyroid nodules is reported to be between 9.2 and 50% with an average risk of 26.4% [4, 5], whereas this risk is 5% for adults [2, 4]. Pediatric thyroid malignancy has also

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been shown to have an increased risk of regional and distant metastasis [4]. Even though the management of thyroid nodules in pediatric patients is the same as for the adult patients [4], they are at higher risk for long-term harm from overly aggressive treatment [1].

The main objective of this study is to report our experience in a university hospital in the surgical management of thyroid disease in pediatric patients. We also aim to analyze the results and evaluate the efficacy of fine-needle aspiration biopsy (FNAB) and frozen section analysis.

Methods

A retrospective analysis of thyroid surgery from 1997 to 2017 was conducted. Consecutive patients under the age of 18 who underwent partial or total thyroidectomy in ENT ($n=51$) and General Surgery ($n=24$) departments were included. The search of patients was done by the informatics department using the hospital medical records for the criteria mentioned above.

The surgical indication was clearly stated by the surgeon in the patient medical records.

Evaluation of voice hoarseness was reviewed. In ENT department, laryngoscopy was systematically performed for all patients preoperatively and in the first day postoperatively. In general surgery department, laryngoscopy is performed only postoperatively in case of voice hoarseness or respiratory distress.

Fine-needle aspiration biopsy was done by the radiologist under ultrasound and the specimen was sent to pathology laboratory for analysis. Bethesda system was used to describe FNAB results by the pathologist. When Bethesda system was not defined in the primary report, it was secondarily reviewed by a pathologist to define Bethesda grade (Table 1).

FNAB sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) relative to the final pathological diagnosis had been calculated using the same method described by Amrikachi et al. [7]. For statistical analysis, cases with Bethesda IV, V, VI that have malignant lesion in final pathological diagnosis were considered true positive. True negative cases were those with Bethesda II that have benign lesion in final pathological diagnosis. Case with Bethesda II that had malignant lesion were considered false negative. False positive cases were Bethesda IV, V, VI that have benign pathological diagnosis. Bethesda I and III were excluded from the statistical analysis.

Frozen section analysis was done after partial thyroidectomy and described to be either benign or malignant. Sensitivity, specificity, positive and negative predictive values relative to the final pathological diagnosis had been also calculated. Malignant frozen section cases that have malignant lesion in final pathological diagnosis were considered true positive. Benign frozen section cases that have benign lesion in final pathological diagnosis were considered true negative. False positive cases were those that have malignant frozen section results but benign pathological lesion. False negative cases were those that have benign frozen section results but malignant pathological lesion.

Thyroid hormones and calcitonin were requested and followed by pediatric physicians. Thyroid ultrasounds were reviewed to measure the nodules' sizes.

The indication of the surgery, the investigation results, the surgical technique used and the final diagnosis were reviewed and analyzed.

Intraoperative neuromonitoring of the inferior laryngeal nerves was done using a specific endotracheal tube with integrated electrodes (XomedNIM monitoring system, Medtronic Xomed Instrumentation, Saint-Aubin-le-Monial, France).

Table 1 The Bethesda system for reporting thyroid cytopathology: recommended diagnostic categories [6]

I. Nondiagnostic or unsatisfactory
II. Benign
III. Atypia of undetermined significance or follicular lesion of undetermined significance
IV. Follicular neoplasm or suspicious for a follicular neoplasm
V. Suspicious for malignancy
VI. Malignant

Results

A total of 75 patients were identified and included. Sixty patients (80%) were female and fifteen patients (20%) were males. The average age for all patients was 13.3 years ± 3.76 and age range was 3–18 years. The demographic information is summarized in (Table 2).

The surgical indication for either total or partial thyroidectomy were thyroid nodule in 80% ($n=60$), Grave's disease in 13.3% ($n=10$), and multiple endocrine neoplasm type (MEN) II in 6.7% ($n=5$). Among patient with MEN II, two patients had a prophylactic thyroidectomy and did not have medullary carcinoma in the final pathological

Table 2 Demographic information

Total number of patients included	75
Female/male ratio	4/1 (80%/20%)
Fine-needle aspiration biopsy (FNAB)	32 (42.7%)
Frozen section	50 (66.7%)
Thyroid cancer	22 (29.3%)

analysis. However, all patients had a confirmed family history of MEN II. Thyroid carcinoma was found in 28.3% ($n=17/60$) in patients with thyroid nodule. These results are summarized in (Table 3).

Ultrasound results was found in 86.7% ($n=65$). Nodule size was documented in 64.6% ($n=42$) and ranged from 0.6 to 6.8 cm. For thyroid nodules patients, EU-TIRADS scores were not reported. Thyroid hormones were within normal range at time of surgery for all patients. Calcitonin was 15 pg/mL for one patient ($n=1/5$) in NEM II group.

FNAB was done in 53.3% ($n=32/60$) among patients with thyroid nodule. Thirty patients had thyroid nodules and two patients had Grave's disease with a thyroid nodule. Twenty patients had benign FNAB and six patients had suspicious or malignant FNAB. The results are detailed in (Table 4).

The sensitivity and specificity were 62.5% and 94.4%, respectively. The positive predictive value was 83.3% and the negative predictive value was 85%.

We have reviewed the reports of the three patients of Bethesda II that had malignant lesion. The first patient had chronic lymphocytic thyroiditis in FNAB and in final pathology but an associated micro-thyroid papillary carcinoma of 4 mm was also incidentally found. The second patient had epithelial thyroid cells without signs of malignancy in FNAB which can be explained by sampling normal thyroid tissue. The third patient had FNAB described by the cytopathologist to be cytological atypias that need surgical excision and describe it as Bethesda II.

Frozen section analysis was done in 83.3% ($n=50/60$) among patients with thyroid nodule where one patient had Grave's disease with a thyroid nodule. It was malignant in 12% ($n=6/50$) and was benign in 88% ($n=44/50$). Among benign results, nine ($n=9/44$) patients had malignant disease in final pathological diagnosis. Of the nine patients, six patients had follicular carcinoma and three patients had papillary carcinoma, where one of them had micro-carcinoma of 4 mm. The sensitivity and specificity were 40% and 100%, respectively. The positive predictive value and the negative predictive value were 100% and 79.6%, respectively.

All patients with Bethesda IV and VI had a frozen section done. For patients with Bethesda IV, the first one had papillary carcinoma in both frozen section and final pathologic diagnosis. The second patients did not have signs of malignancy in frozen section but had follicular carcinoma in the final pathological diagnosis. The third patient did not have signs of malignancy in frozen section but had follicular adenoma in the final pathological diagnosis.

Table 4 Fine-needle aspiration biopsy results

FNAB	Final pathological diagnosis	
	Benign	Malignant
Bethesda I ($n=3$)	3	0
Bethesda II ($n=20$)	17	3
Bethesda III ($n=3$)	2	1
Bethesda IV ($n=3$)	1	2
Bethesda V ($n=0$)	0	0
Bethesda VI ($n=3$)	0	3
Total ($n=32$)	23	9

The surgical techniques used for all patients were either partial (lobectomy) or total thyroidectomy. Central and lateral neck dissections were performed when malignancy was found. Total thyroidectomy was performed in 54.7% ($n=41/75$), whereas 13.3% ($n=10/75$) had associated neck dissection. The indications of neck dissection were, thyroid cancer in frozen section intraoperatively in three patients, grossly metastatic adenopathy in four patients, final pathological diagnosis in one patient and preoperative indication for MEN II in two patients. Partial thyroidectomy (lobectomy) was performed in 45.3% ($n=34/75$). Among them, 5.3% ($n=4/75$) had a second stage surgery for totalization and 2.7% ($n=2/75$) had a second stage surgery for totalization with neck dissection. The indications of neck dissection were final pathological diagnosis in one patient, and grossly metastatic adenopathy intraoperatively in one patient. Among partial thyroidectomies, one patient had isthmectomy (excision of the nodule). To analyze the surgical technique used for thyroid nodules and the malignancy incidence, we have excluded patients with Grave's disease and MEN II. The results are summarized in (Table 5).

Intraoperative neuromonitoring of the inferior laryngeal nerves was documented in 42.7% ($n=32/75$).

Regarding post-operative complications, one patient 1.3% ($n=1/75$) had a wound infection. One patient 1.3% ($n=1/75$), who underwent total thyroidectomy with bilateral neck dissection for a papillary carcinoma, had a transient XII paralysis which had rapidly recovered and bilateral recurrent laryngeal nerves paralysis. At follow-up, the right

Table 3 Thyroid cancer incidence relative to the surgical indication

Surgical indication	Benign disease	Malignant disease	Average age (range)
Thyroid nodule 80% ($n=60$)	71.7% ($n=43$)	28.3% ($n=17$)	13.2 ± 3.5 (3–18 years)
Grave's disease 13.3% ($n=10$)	100% ($n=10$)	0%	16.6 ± 1.5 (14–18 years)
Multiple endocrine neoplasm type II 6.7% ($n=5$)	0%	100% ($n=5$)	8.2 ± 3.8 (4–13 years)

Table 5 Surgical technique used for multi-nodular goiter and the final pathological diagnosis results ($n=60$)

Surgical technique	Final pathological diagnosis
Total thyroidectomy 45% ($n=27/60$) Unique 35% ($n=21/60$) With neck dissection 10% ($n=6/60$)	Benign disease 71.7% ($n=43/60$) Malignant disease 28.3% ($n=17/60$)
Partial thyroidectomy 55% ($n=33/60$) Unique 43.3% ($n=26/60$) Second stage totalisation 6.7% ($n=4/60$) Second stage totalisation with neck dissection 3.3% ($n=2/60$)	
Isthmectomy (excision of the nodule) 1.7% ($n=1/60$)	

Table 6 Final pathological diagnosis results ($n=75$)

	Female ($n=60$)	Male ($n=20$)
Benign disease, 70.6% ($n=53$)		
Follicular adenoma, 54.7% ($n=42$)	45.4% ($n=34$)	9.3% ($n=7$)
Grave's disease, 13.3% ($n=10$)	12% ($n=9$)	1.3% ($n=1$)
Teratoma, 1.3% ($n=1$)	1.3% ($n=1$)	0
Ectopic thymic nodule, 1.3% ($n=1$)	1.3% ($n=1$)	0
Malignant disease, 29.3% ($n=22$)		
Papillary carcinoma, 14.7% ($n=11$)	12% ($n=9$)	2.7% ($n=2$)
Follicular carcinoma, 8% ($n=6$)	6.7% ($n=5$)	1.3% ($n=1$)
Medullary carcinoma, 6.7% ($n=5$)	1.3 ($n=1$)	5.4% ($n=4$)
Thyroid carcinoma	25%	30%

vocal cord had recovered but the left vocal cord did not. One patient 1.3% ($n=1/75$), who underwent total thyroidectomy with bilateral neck dissection for MEN II, had dysphonia with paralysis of the right vocal cord. The dysphonia disappeared 3 months later but the patient did not have a fibroscopic laryngeal examination. Among patients that had total thyroidectomy, four patients 9.7% ($n=4/41$) had transient hypoparathyroidism and one patient 2.4% ($n=1/41$) had permanent hypoparathyroidism. Among them, two patients underwent total thyroidectomy for thyroid nodule and three patients underwent total thyroidectomy for Grave's disease.

Thyroid carcinoma was found in 29.3% ($n=22/75$) in this series. For thyroid nodules patients, thyroid carcinoma is found in 28.3% ($n=17/60$). The final pathological diagnosis is summarized in (Table 6).

Discussion

Pediatric thyroid nodules and thyroid carcinoma are rare entities in the pediatric population. The prevalence of clinical palpable thyroid nodules vary and is documented to be between 0.5 and 2% [2–4] and the echographic prevalence of thyroid nodules is 3% [4]. The prevalence increases with age and there is a female to male preponderance (5:1) during adolescence that is not seen in young children [1]. Our data was consistent with the current reports: 80% of the patients were females and 70% of those with thyroid cancer were females.

Our results demonstrate 29.3% malignancy incidence with papillary carcinoma as the most common malignant histological type which is consistent with the published estimates [1, 4, 5]. Niedziela [5] has reviewed several reports of thyroid carcinoma incidence between 1960 and 2004 and found an overall incidence of 26.4%. In adults, the incidence of thyroid carcinoma is about 5% [4].

The recommendations of The French Society of Endocrinology (*La Société Française d'Endocrinologie*) and The American Thyroid Association Guidelines indicates that surgical approach to thyroid nodules depend on FNAB results [1, 4]. These two recommendations mentioned that the sensitivity and specificity of FNAB in children are reliable and similar to those found in adults [1, 4]. Indeed, many studies have shown that FNABs in adults have almost 100% positive predictive value (PPV) and negative predictive value (NPV) [8]. Layfield et al. [9] states that a benign FNAB has a 100–97% chance of being benign on final pathology (NPV), and a malignant FNAB has a 97–99% chance of predicting malignancy in adults (PPV). However, in pediatric populations, results of FNAB are not as accurate as in adults [7, 10]. Roy et al. found that benign FNAB results that were benign in final pathology were 71% ($n=22/31$) of the time (NPV) and a malignant FNAB that were malignant in final pathology were 94% ($n=30/32$) of the time (PPV) [10]. Amrikachi et al. found a sensitivity and specificity of 100% and 65%, respectively, from 32 thyroidectomies [7]. The PPV and NPV in his study were 70% and 100%, respectively. Corrias et al. found a sensitivity and specificity of 95% and 86.3%, respectively, from 42 thyroidectomies [11]. In our study, the sensitivity and specificity were 62.5% and 100%, respectively, and the PPV was 83.3% and the NPV was 85%. From these results, FNAB in pediatric patients is not as accurate as in adults. However, sensitivity, specificity, PPV and NPV were calculated from patients who underwent thyroidectomy and did not include benign cases that did not have thyroidectomy. When benign thyroid nodule

on FNAB is selected for surgery, it would have been evaluated by physical examination, ultrasound evaluation and thyroid hormone tests. All of these elements contribute to the indication of thyroidectomy for benign thyroid nodule.

Amrikachi et al. [7] mentioned that the reason for a wide range of sensitivity and specificity in children is how the authors define the false positive and false negative which is true for our study as we have not included Bethesda I and III in our calculations.

In our study, if we consider the patient with (chronic lymphocytic thyroiditis) as true negative and exclude the patient with (cytological atypias: Bethesda III) from the statistical calculations, the sensitivity and the specificity would be 83.3% and 94.7%, respectively. Thus, the sensitivity is not high as in adults or as in the study of Corrias et al. [11].

Diagnostic surgery is indicated in Bethesda IV and V and therapeutic surgery is indicated in Bethesda VI [1, 4]. Arguments against the routine use of FNAB in children have included the anatomical/physical limitation of the patient, the need for an experienced cytopathologist, the need for sedation in younger patients, and errors in sampling [10]. In our study, a 16-year-old patient refused FNAB.

Frozen section is a quick intraoperative micro-and/or macroscopic examination involving freezing of a surgical tissue fragment and is classically the prime guide to surgical extension [12]. In the literature, mean values of sensitivity and specificity of frozen section were 71% and 98%, respectively [13]. In a recent study of Guevara et al. [12], sensitivity and specificity were 75.4% and 100%, respectively. Our study showed sensitivity and specificity of 40% and 100%. To explain this difference, we reviewed the final pathology of the nine patients ($n = 9/44$) that had benign frozen section. Six patients had follicular carcinoma and three patients had papillary carcinoma, where one of them had micro-carcinoma of 4 mm. It is difficult to detect follicular malignancy in frozen section as it had been explained by Guevara et al. [12] that this neoplasm requires capsule rupture and/or vascular embolism (which are the diagnostic criteria for follicular carcinoma) that are rarely found.

Frozen section analysis is indicated when FNAB results were Bethesda IV and V (suspicious) [12]. It is of limited value in Bethesda IV (follicular neoplasm or suspicious for Hürthle-cell neoplasm) because the histologic characterization of these lesions requires detailed analysis of the tumor capsule for demonstrating capsular and/or vascular invasion—an analysis which is not practical in the daily practice of pathology. For Bethesda VI, Frozen section is not indicated due to high specificity of FNAB [12–14].

Since there are no prospective clinical trials comparing surgical management of thyroid cancer in children, there is some controversy over the best surgical management of these patients. For differentiated thyroid carcinoma the most commonly recommended surgical options include either total or partial thyroidectomy. The mortality rates range from 0 to 17% up to 28 years after treatment [15].

Jocely et al. had concluded in a study on the evolution of thyroid surgery that pediatric thyroid surgery is extremely safe, especially when performed at a high-volume endocrine surgery center [16]. They often select surgical treatment for benign disease and choose total thyroidectomy over limited resection. This may reflect increasing confidence in the safety and efficacy of surgery and reliability of thyroid hormone replacement therapy.

In our series, total thyroidectomy was used for Grave's disease, MEN II and multi-nodular goiter. Partial thyroidectomy with frozen section is used for isolated thyroid nodule. There was no difference in the management between ENT department and general surgery department as the decision for the surgery and the surgical technique to be used is discussed in a multidisciplinary meeting between a pediatric thyroid surgeon and a pediatric endocrinologist. Whether to propose a neck dissection or not is based on the surgical indication, presence of cervical adenopathy on physical examination and/or in imaging studies, presence of thyroid cancer on FNAB, presence of thyroid cancer on frozen section intraoperatively, or presence of thyroid cancer on final pathological diagnosis and its histological characteristics.

Pediatric patients have higher risks of post-operative complications [1, 4]. This increased risk is due to lower incidence of thyroid disease that require surgical intervention and the higher incidence of locoregional lymph node metastasis [1] and related to the anatomy: large head and short neck making the surgical exposition of the thyroid gland difficult [4]. The most common complications after thyroidectomy are hypoparathyroidism and recurrent laryngeal nerve damage [1, 4]. Efremidou et al. [17] reported transient hypoparathyroidism and temporary recurrent laryngeal nerve paralysis in adults following total thyroidectomy at the rate of 7.3% and 1.5%, respectively. Akkari et al. [18] had discussed thyroid surgery in children, its complications and the anatomical variations of the recurrent laryngeal nerve. They found 1.1% ($n = 1/63$) permanent left recurrent laryngeal nerve paralysis and 23.5% ($n = 8/34$) hypoparathyroidism of patients that had total thyroidectomy. In this study, we found 1.1% ($n = 1/75$) bilateral permanent recurrent laryngeal nerve paralysis and 1.3% ($n = 1/75$) temporary recurrent laryngeal nerve paralysis. Transient hypoparathyroidism was found in 9.7% ($n = 4/41$) and permanent hypoparathyroidism was found in 2.4% ($n = 1/41$). Both results are consistent with the published risk of complications (hypoparathyrodism: 5–15%) (surgery specific complications: 1–6%) [1, 4]. In our study, we did not find any difference in the risk of complications comparing to adults.

All patients were followed by a pediatric endocrinologist for management of hormone replacement therapy following total thyroidectomy and for treatment of any post-operative

hypoparathyroidism. Patients with malignant thyroid disease requiring adjuvant radioactive iodine therapy were referred to nuclear medicine department.

Conclusion

Thyroid diseases that require surgical intervention are rare in pediatric populations. However, when surgery is indicated, there is higher risk of malignancy compared to adults. Our study showed that FNAB has a lower specificity and sensitivity compared to adults, and that surgical decision should be made considering all investigations. We also showed that frozen section is considered primarily for papillary thyroid carcinoma but is not reliable for follicular carcinoma or Bethesda IV.

Finally, thyroid surgery in children and adolescents must be part of global multidisciplinary management.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest concerning this article.

Research involving human participants and/ or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

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