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ORIGINAL ARTICLE

Surgical treatment of pediatric and adolescent papillary thyroid cancer: a retrospective study of 54 patients in a single center

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KEYWORDS
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Abstract

Objective: In 2015, American Thyroid Association (ATA) issued the first version of *Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer.* The purpose of this study is to evaluate whether the ATA pediatric guidelines recommended surgical approach for the patient can be applied to surgical treatment of pediatric PTC in China.

Method: From April 2012 to December 2020, clinical data of children (≤18 years) with PTC consecutively admitted and treated with initial surgery in the study's department were retrospectively reviewed.

Results: The authors found that the central lymph node metastasis (CLNM) rate was significantly higher than that in the lateral neck (83.33 % vs 62.96%, χ^2 = 5.704, p = 0.017) .The lymph node metastasis rate was significantly lower in cN1b (-) patients than in cN1b (+) patient (55.00% vs 100.00%, χ^2 = 15.263, p = 0.000); Meanwhile, the CLNM and LLNM rates of ipsilateral were significantly higher than those of contralateral central compartment (83.33%vs 57.41%, χ^2 = 8.704, p = 0.003). Lymph nodes of 51 lateral lymph node dissection (LND) were analyzed, which revealed the LNM rate of cN1b (-) patients was significantly lower than that of cN1b (+) patients (55.00% vs. 100.00%, χ^2 = 15.263, p = 0.000).

Conclusion: Children and adolescents have a higher rate of lymph node metastasis at the time of diagnosis. TT should be conducted in the majority of children with PTC. CND should be routinely performed; therapeutic LND is recommended for children with cN1b (+).

Introduction

Differentiated thyroid cancer (DTC) is a rare disease in children and adolescents and contributes to about 1.4% of all pediatric malignancies. Furthermore, its incidence is

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rising.[1,2] The majority of thyroid cancer in children is DTC, including papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). Children are not small adults; as compared with adults, children PTC is characterized by larger tumor in size, higher prevalence of extrathyroidal extension (ETE) and lymph node metastasis (LNM) at the time of diagnosis.[3] As PTC is rare in children, treatment approaches for pediatric PTC are historically extrapolated from adult experience.[4,5] In 2015, ATA issued the first version of *Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer,*[6] which was confined to patients $\leq$ 18 years of age.

As a result, this project retrospectively analyzed the clinical data of 54 children (aged $\leq$ 18) with PTC consecutively enrolled within the last 8 years and followed-up, only then did the authors believe that the majority of pediatric PTC should perform total thyroidectomy (TT, routine prophylactic CND and Therapeutic LND.

Materials and method

Patients

The authors retrospectively reviewed the medical records of 54 pediatric patients aged $\leq$18 years at the time of their initial visits and who were diagnosed with papillary thyroid carcinoma from April 2012 to December 2020 at the Department of Thyroid Surgery, the first affiliated Hospital of Kunming Medical University.

Management protocol

All patients underwent preoperative physical examination, fine needle aspiration (FNA) and high-resolution ultrasonography (US) evaluations of the thyroid gland and neck lymph nodes. Enhanced contrast CT scan was performed in patients with large primary tumor or extensive lymph node metastasis.

TT was performed for children with bilateral tumors, multifocal tumors, primary tumors with T3 or T4 lesions, and clinical evidence of lymph node involvement or distant metastasis. Hemi-thyroidectomy (thyroid lobectomy with isthmusectomy) was selectively conducted in children with intrathyroidal solitary tumor $<$ 1cm and no evidence of lymph node metastasis.

CND was routinely performed in children with PTC confirmed by intraoperative frozen section, including therapeutic and prophylactic CND. Bilateral CND was performed in patients who underwent TT, but ipsilateral CND was performed in patients with lobectomy. CND was implemented according to the CND consensus issued by ATA in 2009.[7]

Therapeutic lateral neck dissection was performed in patients with clinically apparent lateral nodal disease, which was defined as cN1b (+). cN1b (+) was diagnosed by preoperative physical examination, US, FNAB and intraoperative inspection, whereas no clinically apparent lateral nodal disease was defined as cN1b (-). The scope of LND includes selective lateral neck dissection (SLND) in levels II-V or super-selective lateral neck dissection (SSLND) in levels II-IV or levels III-IV. The LND specimens were separated according to neck levels before being sent to the department of pathology.[8]

Individualized THS suppression therapy was performed in all patients with L-T4. Radioactive iodine therapy is recommended for children with T4, N1b or M1 disease. All patients were followed up regularly. Recurrences were defined as structural recurrence, and biochemical recurrences were excluded.

The protocol of this study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Kunming Medical University, and the study was performed in accordance with the Declaration of Helsinki.

Statistical analysis

SPSS17.0 statistical software was employed for data analysis. Continuous data were reported as mean $\pm$ standard deviation. Categorical variables were analyzed using Pearson's chi-square test. Two-sided p values < 0.05 were considered statistically significant.

Results

Clinical characteristics of the patients

The patient characteristics are shown in Table 1. 47 females and 7 males, with an average age of 14.93 $\pm$ 3.01 years. The average disease course was 15.55 months. The majority of children (50 cases) had classic PTC. The average tumor size was 2.12 $\pm$ 1.14cm. 37 cases (68.52%) had a solitary lesion, and 17 patients (31.48%) had two lesions or more.

According to the 8th version of the AJCC tumor node metastasis (TNM) classification system, with proportions of T1, T2, T3 and T4 at 40.74%, 16.67%, 25.93%, and 16.67%, respectively. At presentation, 45 patients (83.33%) had N1a disease, and 34 patients (62.96%) had N1b disease. Lung metastasis was found in 4 children (7.41%).

Lymph node metastasis based on T stage

The authors analyzed the relationship between T stage and lymph node metastasis (Table 2) and observed that CLNM rate and LLNM rate increased with the increase of T stage of the tumor. Postoperative pathology revealed significantly higher CLNM rate than LLNM rate (83.33% vs 62.96%, χ^2 = 5.704, p = 0.017). No skip metastasis was observed. LNM rate peaked to 100% in patients with T3 or T4 disease.

Lymph node metastasis based on clinical N stage, surgical approaches

The authors analyzed the relationship between clinical N stage, surgical approaches and LNM (Table 3), which revealed the LNM rate of cN1b(-) patients was significantly lower than that of cN1b (+) patients (55.00% vs. 100.00%, χ^2 = 15.263, p = 0.000). CLNM and LLNM rates of cN1b (+) patients were both peaked to 100.00%. Meanwhile, the CLNM and LLNM rates of ipsilateral were significantly higher than those of contralateral central compartment (83.33%vs 57.41%, χ^2 = 8.704, p = 0.003) and contralateral lateral compartment (62.96% vs 31.48%, χ^2 = 10.737, p = 0.001).

Table 1 Patients' characteristics.

Characteristics	No. of patients	%
Pathological type		
Classical PTC	50	92.59%
Diffuse sclerosing variant	3	5.55%
Insular variant	1	1.85%
Multifocality		
Single	37	68.52%
Multiple (≥2)	17	31.48%
Tumor location		
Unilateral	40	74.07%
Left lobe	23	42.59%
Right lobe	17	31.48%
Bilateral	14	25.93%
Tumor size		
≤ 1 cm	13	21.07%
> 1, ≤ 2 cm	17	31.48%
> 2, ≤ 4 cm	21	38.89
> 4 cm	3	5.56%
Extrathyroidal extension		
Yes	23	42.59%
No	31	57.41%
T classification		
T1	22	40.74%
T1a	8	14.81%
T1b	14	25.93%
T2	9	16.67%
T3	14	25.93%
T3a	1	1.85%
T3b	13	24.07%
T4a	9	16.67%
T4a	9	16.67%
T4b	0	0
N classification [a]		
N0	9	16.67%
N1a	45	83.33%
N1b	34	62.96%
M classification [b]		
M0	50	92.59%
M1	4	7.41%

[a] For N classification, N0 no any evidence of regional lymph node metastasis; N1a and N1b were proved pathologically.
[b] For M classification, M0 no any evidence of distant metastasis; M1 was confirmed by Rx-WBS.

Lymph node metastasis rate in different lateral levels

The authors analyzed the LNM rate of 51 LNDs from cN1b(+) 34 patients by different levels (Table 4), and observed the lowest LNM rate in Level V (15.69%), which was significantly lower than that in Level II, III, and IV (χ^2 = 33.443, p = 0.000; χ^2 = 60.016, p = 0.000; χ^2 = 45.351, p = 0.000). The LNM rate in Level III was significantly higher than that in Level II (92.16% vs. 2.55%, χ^2 = 6.746, p = 0.009), but no significant difference between sub-Level IIa and Level IIb was observed. The authors also observed no significant difference in metastasis rate between Level III and Level IV (p = 0.138).

Surgical complications

Unilateral recurrent laryngeal nerve was resected in 2 patients due to tumor infiltration. One patient underwent tracheotomy due to temporary paralysis of bilateral recurrent laryngeal nerve. Chylous leakage developed in 2 patients and was cured with non-surgical treatment. No permanent hypoparathyroidism and postoperative bleeding occurred.

Follow-up and outcome

All children were treated with TSH suppression therapy with L-T4. 24 children underwent radioiodine therapy. In this group of children, no patient died of the disease, the median follow-up time was 38.56 months, and 5 patients (9.26%) relapsed and underwent reoperation. The 5 patients with recurrence were 2 cN1b (-) and 3 cN1b (+). The first operation time was 2015, 2018, 2015, 2017 and 2016. Tumor recurrence occurred during the follow-up period, including 3 recurrences in the central area, 5 recurrences in the lateral cervical area, and 1 recurrence in the residual thyroid gland, including overlapping cases. There was no significant difference in reoperation rate between cN1b (-) and cN1b (+) children (9.09 vs. 9.38%, p = 676). There was also no significant difference in recurrence rate between SLND and SSLND groups (0% vs 8.82%, p = 0.287).

Discussion

Surgery is the most important method to treat PTC, which ranges from lobectomy to total thyroidectomy (TT).[9] There were no surgical treatment guidelines specific for children with thyroid carcinoma in China, and only adult guidelines can be referred to. The 2015 ATA pediatric guidelines recommended TT for the majority of children with PTC. And a near-TT or TT can greatly reduce the risk of recurrence and subsequent second surgery.[10,11] TT can also optimize or reduce the utilization of postoperative ^{131}I treatment, and benefits serum Tg as tumor marker to detect recurrent or persistent lesions. In the present study, the bilateral and multifocal lesions were 25.93% and 31.48%, respectively, which was lower than that quoted in ATA children guidelines.

According to ATA adult guidelines,[4] and ATA pediatric guidelines,[6] DTC patients with LNM should be treated with TT. The present study's results revealed that the LNM rate in the central and lateral compartments was 83.33% and 62.96%, respectively. Therefore, based on the high LNM rate, the authors perform TT in most children with PTC.

Although TT is recommended for the majority of children with PTC, the extent of thyroidectomy is still controversial. The main problem is the influence of surgical resection scope on tumor recurrence and potential complications (such as transient/permanent postoperative hypoparathyroidism and recurrent laryngeal nerve injury).[12-14] Wang et al.[13] reported that TT can not reduce recurrence but only increase the surgical complications. Amarasinghe et al.[14] reported that the incidence of residual cancer may increase up to 30% without total thyroidectomy. However, some oncologists advocate bilateral thyroidectomy with the main reasons as follows: (1) the bilateral lobes of the thyroid are

Table 2 Relationship between LNM rate and T stage.

T-stage	N	CLNM [n/%]	LLNM [n/%]	LNM [n/%]
T1	22	14/63.64%	8/36.36%	14/63.64%
T1a	8	3/37.50%	2/25.00%	3/37.50%
T1b	14	11/78.57%	6/42.86%	11/78.57%
T2	9	8/88.89%	5/55.56%	8/88.89%
T3	14	14/100.00%	12/85.71%	14/100.00%
T3a	1	1/100.00%	1/100.00%	1/100.00%
T3b	13	13/100.00%	11/84.61%	13/100.00%
T4	9	9/100.00%	9/100.00%	9/100.00%
T4a	9	9/100.00%	9/100.00%	9/100.00%
T4b	0	—	—	—
Total	54	45/83.33%	34/62.96%[a]	45/83.33%

[a] Compared with CLNM rate, $\chi^2 = 5.704$, $p = 0.017$.

Table 3 Relationship between clinical N stage, surgical approaches and LNM.

ClinicalN Stage	Surgical approaches	N	CLNM [n/%]		LLNM [n/%]		
			Ipsilateral[a]	Contralateral	Ipsilateral[a]	Contralateral	LNM (+) [%]
cN1b (-)	CND	20	11/55.00%	4/20.00%	—-	—-	11/55.00%
	Unilateral CND [b]	10	5/50.00%	—	—-	—-	
	Bilateral CND [c]	10	6/60.00	4/40.00%	—-	—-	
cN1b (+) [d]	LND [e]	34	34/100.00%	27/79.41%	34/100.00%	17/50.00%	34/100.00%[e]
	Unilateral LND	17	17/100.00%	12/70.59%	17/100.00%	—-	
	Bilateral LND	17	17/100.00%	15/88.24%	17/100.00%	17/100.00%	
Total		54	45/83.33%[f]	31/57.41%	34/62.96%[g]	17/31.48%	

[a] In patients with bilateral lesions, the larger side of the tumor is regarded as ipsilateral and the smaller side of the lesion as contralateral.
[b] 2 patients underwent TT with unilateral CND.
[c] 2 patients underwent lobectomy with bilateral CND.
[d] Including 2 patients for subsequent operation developed from cN1b (-) LND includes SSLND and SLND.
[e] Compared with LNM in cN1b (-) patients, p = 0.000.
[f] Compared with contralateral CLNM, p = 0.003.
[g] Compared with contralateral LLNM, p = 0.001.

not separate and are linked to each other into an organ; you must remove the entire organ in order to reduce the cancer relapse; (2) pediatric differentiated thyroid cancer has the characteristics of multifocal lesions. In fact, it is difficult to make accurate risk stratification and the recurrence risk of each patient pre-operatively or intra- operatively. There is no quantitative index to find the best balance between the risks and benefits of surgery.

Table 4 Lymph node metastasis rate in different levels of lateral neck.

		LLNM [n/%]							
		Level II			Level III	Level IV	Level V		
LND	side	II	IIa	IIb			V	Va	Vb
SSLND (III-IV)	6	—-	—-	—-	5 83.33%	5 83.33%	—-	—-	—-
SSLND (II-IV)	11	6 54.55%	6 54.55%	3 27.27%	9 81.82%	8 19.51%	—-	—-	—-
SLND (II-V)	34	31 91.08%	26 76.47%	18 52.94%	33 97.06%	29 85.29%	8 23.53%	2 5.88%	7 20.59%
Total	51	37 72.55%ༀ※	32 59.26%	21 38.89%	47 92.16%[a]	42 82.35%[b]	8 15.69%	2 3.92%	7 13.73%

[a] Compred with LLNM rate in level V, p = 0.000.
[b] Compred with LLNM rate in level III, p = 0.009. (Pathological findings from the second surgery were included in the analysis).

In this study, the authors performed TT for children with bilateral lesions, multifocal tumors, locally advanced (T3 or T4) tumors and clinical evidence of lymph node or distant metastasis. The authors found that only 5 (11.36%) had tumor recurrence during the postoperative follow-up, including 3 recurrences in the central area, 5 recurrences in the lateral cervical area, and 1 recurrence in the residual thyroid gland including. Therefore, the authors believe that the majority of children with PTC should be treated with TT, and lobectomy be considered for a few patients with caution.

Literature reported that PTC in children was more likely to have CLNM,[13,15] which increased the risk of pulmonary metastasis. CND is associated with a decreased risk of locoregional persistent or recurrent disease so as to increase disease-free survival (DFS), as well as the potential to increase the efficacy of 131I treatment.[16] Additionally, some studies have shown that TT with prophylactic CND can increase 5-year and 10-year DFS to 95%.[17] It is recommended in ATA children guidelines that CND should be performed in children with malignant cytology and clinical evidence of gross extrathyroidal invasion and/or locoregional metastasis on preoperative staging or intraoperative findings, and prophylactic ipsilateral or bilateral CND should be selectively considered in patients with no clinical evidence of gross extrathyroidal invasion and/or locoregional metastasis.

Owing to the possibility of permanent hypoparathyroidism following CND, some authors argued that CND in children with DTC is controversial. Unfortunately, there are no intraoperative data that reliably to predict which patient is at increased risk of locoregional metastasis or recurrence. Rubinstein et al.[18] reported that LNM ratio >0.45 may predict the likelihood of recurrence in pediatric PTC patients undergoing TT with prophylactic CND.

CND was routinely performed in the present study, and the results revealed the CLNM rate in ipsilateral and contralateral of the central compartment were 83.33% and 57.41%, respectively, and the CLNM rate in patients with T1, T2, T3 and T4 tumor were 63.64%, 88.89%, 100% and 100%, respectively.

Machens et al.[19] showed that TT plus prophylactic CND could significantly decrease the need for subsequent surgeries, which was as high as 77% for patients without CND. Rubinstein et al.[20] found a trend toward lower recurrence in patients undergoing thyroidectomy with CND compared with thyroidectomy alone in cN1b (-) patients ($p = 0.07$). However, as preoperative ultrasounds and intraoperative palpation are difficult to make an accurate assessment on the lymph node. In the present study, only 12 (22.22%) patients were cN1a (+), and CLNM was confirmed to be 83.33% following routine CND. Recurrences were revealed in the contralateral central compartment in 2 patients who underwent lobectomy with unilateral CND and 1 in the patient underwent TT, bilateral CND and bilateral LND patient. Among these 54 patients who underwent CND, none of the children had permanent hypoparathyroidism, mainly because the surgeons in the study's hospital had solid anatomical knowledge and delicate and skilled surgical operations. In addition, the present study's main research direction is the basic research of parathyroid glands. The authors are well aware of the anatomical location of the parathyroid glands and the importance of parathyroid glands.

Based on the high prevalence of lymph node involvement and difficulties in evaluating the central compartment, the authors suggest prophylactic bilateral CND for PTC children who underwent TT. Otherwise, prophylactic unilateral CND is acceptable for children who underwent lobectomy.

Literature showed that therapeutic LND is associated with a reduction in persistent or recurrent disease and improved DFS in children.[6] The 2015 ATA children guidelines also recommended therapeutic LND, including Levels III, IV, anterior V, and II, and routine prophylactic LND is not recommended.[6] Ito et al.[21] suggested prophylactic LND for children with risk factors of lateral nodes involvement.

In the current study, therapeutic LND (including SSLND or SLND) was performed on the basis of the preoperative evaluation by physical examination, US and CT, and results show that the LLNM rate gradually increased with the increase of T stage, and the LLNM rate in patients with T1, T2, T3 and T4 tumor were 36.36%, 55.56%, 85.71% and 100%, respectively. The present study's results indicate the importance of preoperative evaluation. For this cohort of patients, the present data also revealed 62.96% and 31.48% of LLNM in ipsilateral and contralateral of the lateral neck, respectively. Jeon et al.[22] recently revealed that LLNM were independent predictors for structural persistent or recurrent disease.

The authors observed the lowest LNM rate in Level V (15.69%), which was lower than in Levels II, III and IV ($p = 0.000$). The LNM rate in Level III was significantly higher than in Level II, but no significant difference between sub-Level IIa and IIb. The authors also observed no significant difference in metastasis rate between Level III and Level IV. As it is a retrospective study, some patients underwent SSLND (Levels II-IV dissection in 6 procedures and Levels III-IV dissection in 11 procedures), which was inconsistent with the recommendations of ATA children guideline. This may be due to the arbitrary decision by the surgeon, and someone will argue that the un-dissected nodes with occult metastasis would result in recurrence in patients underwent SSLND. Excellent outcome was reached with 38.56 months of follow-up, no significant difference in reoperation rate was observed between cN1b (-) and cN1b (+) children (9.09 vs 9.38%, $p = 676$), and no difference in recurrence rate between SLND and SSLND groups (0% vs 8.82%, $p = 0.287$) was observed. Such excellent outcome in this study may be due to non-randomized LND procedure or short follow-up time, and this group of patients is also being followed up.

The present research shows that PTC in children and adolescents is characterized by high lymph node metastasis at the time of diagnosis. And the CLNM and LLNM rates increased with the increase of T stage of the primary tumor, and the CLNM and LLNM rates in the ipsilateral side of the primary tumor were significantly higher than those in the contralateral side. Careful preoperative assessment of primary tumor and neck lymph nodes should be carried out to optimize the surgical approach. The majority of pediatric PTC should perform TT. Prophylactic bilateral CND is preferred in patients who underwent TT, and unilateral CND is acceptable in patients with a high risk of surgical complications and those with hemi-thyroidectomy. Therapeutic LND is suggested for children with cN1b (+) patient, SLND (Levels II-V) is preferred other than SSLND (Levels II-IV or Levels III-IV).

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Conflicts of interest

The authors declare no conflicts of interest.

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