

Relationship between sonographic features, clinicopathological characteristics and lymph node metastasis of papillary thyroid carcinoma in children

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Summary

Objective: This study aimed to evaluate the relationship between sonographic features, clinicopathological characteristics and lymph node metastasis (LNM) of papillary thyroid carcinoma (PTC) in children (≤ 18 years). **Subject and method:** A total of 46 pediatric patients who were histopathologically diagnosed with PTC from January 2015 to March 2022 were included in this study. The preoperative ultrasonography, histological, and LNM features after surgery were retrospectively analyzed. **Result:** PTC in children accounted for 0.6% of all PTC, with a higher rate of females (67.4%), aged 15-18 years was 71.7%. The tumors were mostly classic type (87.0%), tumor size $> 10\text{mm}$ (76.1%), with high rates of central and lateral LNM (69.6% and 45.7%, respectively). Central LNM was significantly related to extrathyroidal extension (ETE). A significant relationship was observed between lateral LNM and tumor size, multifocality, ETE, intrathyroidal spread, microcalcification, and abnormal lymph nodes on ultrasound. **Conclusion:** Central and lateral LNM in pediatric PTC were common (69.6% and 45.7%, respectively). Several sonographic and clinicopathologic features had a significant relationship with LNM, especially lateral LNM. Patients with risk factors should undergo both clinical and neck ultrasound examinations in order to find evidence of LNM.

Keywords: Sonographic, clinicopathological, papillary thyroid carcinoma, lymph node metastasis, pediatric.

1. Background

According to the American Thyroid Association, pediatric thyroid carcinoma (TC) is defined as TC in children aged 18 years and younger, and represents 1.8% of all thyroid malignancies diagnosed, with 5.9 cases per million people annually [1, 2]. Papillary thyroid carcinoma (PTC) accounts for over 90% of differentiated TC in children, often presented by thyroid tumors or metastatic cervical lymph nodes [3, 7]. The incidence of pediatric PTC is increasing [3].

PTC in children often has more aggressive features with large tumors, extrathyroidal extension, and high rates of lymph node metastasis (LNM) and distant metastasis [5-8]. However, pediatric PTC has a good prognosis, with 30-year survival ranging from 99 to 100% [3]. LNM is frequent in pediatric PTC, up to 70.7% of Vietnamese patients [7]. LNM is a risk factor for tumor recurrence and distant metastasis [7, 8]. It is important to identify patients at risk of LNM to choose the appropriate surgical approach, avoiding tumor recurrence and second surgery.

There have been some studies on TC in Vietnamese children [7-9]. However, the studies on sonographic characteristics, histopathology, and the relationship between these features and LNM have

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still been limited. Our study aims to determine the relationship between sonographic characteristics, clinicopathological features and LNM of PTC in children.

2. Subject and method

2.1. Subject

We collected patients (age ≤ 18 years) who underwent thyroidectomy at the 108 Military Central Hospital from January 2015 to March 2022. All of the patients were pathologically diagnosed with PTC.

We excluded patients whose criteria were as follows: 1) age over 18 years; 2) histological type is not PTC; 3) history of thyroid surgery.

Finally, a total of 46 pediatric PTCs were enrolled in this study.

2.2. Method

A cross-sectional, descriptive study.

Clinicopathological and sonographic features were recorded, including age, gender, tumor size, multifocality, histological types, extrathyroidal extension (ETE), intrathyroidal spread, vascular invasion and the LNM, echogenicity, microcalcification in the tumor, and abnormal lymph nodes on ultrasound.

Age, gender, tumor size, number of tumors, and sonographic features were collected through medical records and pathology reports.

Histological subtypes, ETE, intrathyroidal spread, vascular invasion, and the LNM were evaluated by experienced pathologists from the Department of Pathology.

Histological subtypes were classified according to WHO 2017.

Tumor size was determined as the maximal dimension of the tumor. Multifocality was defined as having two or more tumors in the thyroid gland. In the case of multifocal lesions, the tumor size and pathological and sonographic features were determined by the largest tumor.

The ETE was reported when the tumor invades adjacent structures, including perithyroid tissue, strap muscle, trachea, larynx, esophagus, recurrent laryngeal nerve, prevertebral fascia, or encasing carotid artery or mediastinal vessels.

Abnormal lymph nodes on ultrasound were recorded when the lymph nodes had features such as microcalcification and loss of structure.

Metastatic lymph nodes were diagnosed based on histopathology, when tumor cells or papillae were observed in the removed lymph nodes.

2.3. Statistical analysis

Categorical variables were presented by numbers and percentages. Univariate regression analysis was used to evaluate the relationship between LNM and risk factors. We used IBM SPSS Statistics software version 26.0 for statistical analysis. A statistically significant difference was recorded when the P-value was less than 0.05.

3. Result

From January 2015 to March 2022, we recorded 7502 patients with PTC. Among them, 46 patients were children, accounting for 0.6%.

3.1. Clinicopathological and sonographic characteristics of pediatric PTC

Table 1. Clinicopathological and sonographic features of pediatric PTC

Features	Category	Number	Percentage (%)
Age (years)	< 15	13	28.3
	15-18	33	71.7
Gender	Female	31	67.4
	Male	15	32.6

Features	Category	Number	Percentage (%)
Tumor size (mm)	≤ 10	11	23.9
	> 10	35	76.1
Tumor location	Left lobe	14	30.4
	Right lobe	23	50.0
	Isthmus	1	2.2
	Bilaterality	8	17.4
Multifocality	Absent	36	78.3
	Present	10	21.7
Histopathological type	Classical type	40	87.0
	Other types	6	13.0
Extrathyroidal extension	Absent	19	41.3
	Present	27	58.7
Intrathyroidal spread	Absent	31	67.4
	Present	15	32.6
Vascular invasion	Absent	39	84.8
	Present	7	15.2
Echogenicity	Hypoechoic	32	69.6
	Hyperechonic	11	23.9
	Isoechonic	3	6.5
Margin	Regular	10	21.7
	Irregular	36	78.3
Microcalcification	Absent	14	30.4
	Present	32	69.6
LNM on ultrasound	Absent	17	37.0
	Normal lymph nodes	7	15.2
	Abnormal lymph nodes	22	47.8
LNM	Absent	11	23.9
	Central LNM (only)	14	30.5
	Central and lateral LNM	18	39.1
	Lateral LNM (only)	3	6.5
Number of lymph node remove (mean ± SD)		16.35 ± 17.13	
Number of LNM (mean ± SD)		7.89 ± 8.87	

Most patients were female (67.4%), aged 15-18 years (71.7%). The tumors were mostly > 10mm in size (76.1%), classical type (87.0%), with high rates of central and lateral LNM (69.6% and 45.7%, respectively).

The rates of ETE, intrathyroidal spread, and vascular invasion were 58.7%, 32.6%, and 15.2%, respectively.

The majority of pediatric PTCs were characterized by hypoechoic echogenicity (69.6%), irregular margins (78.3%), and microcalcification (69.6%).

There were 29 patients (63.0%) whose cervical lymph nodes could be detected on ultrasound. Among these patients, 22 cases (47.8%) had abnormal lymph nodes.

3.2. The relationship between LNM and clinicopathological and sonographic features

Table 2. The relationship between LNM and clinicopathological and sonographic features

Features	Category	LNM				p value	OR (95%CI)
		Absent		Present			
		n	%	n	%		
Age (years)	< 15	2	18.2	11	31.4	0.401	0.485 (0.09-2.63)
	15-18	9	81.8	24	68.6		
Gender	Female	10	90.9	21	60.0	0.086	6.667 (0.77-58.04)
	Male	1	9.1	14	40.0		
Tumor size (mm)	≤ 10	5	45.5	6	17.1	0.064	4.028 (0.92-17.64)
	> 10	6	54.5	29	82.9		
Tumor location	Left/right lobe/ isthmus	11	100.0	30	85.7	0.999	NA
	Bilaterality	0	0.0	5	14.3		
Multifocality	Absent	10	90.9	26	74.3	0.267	3.462 (0.39-30.96)
	Present	1	9.1	9	25.7		
Histopathological type	Classical type	10	90.9	30	85.7	0.658	1.667 (0.17-16.02)
	Other types	1	9.1	5	14.3		
Extrathyroidal extension	Absent	8	72.7	11	31.4	0.022	5.818 (1.29-26.25)
	Present	3	27.3	24	68.6		
Intrathyroidal spread	Absent	11	100.0	20	57.1	0.998	NA
	Present	0	0.0	15	42.9		
Vascular invasion	Absent	10	90.9	29	82.9	0.524	2.069 (0.22-19.35)
	Present	1	9.1	6	17.1		
Echogenicity	Hypoechoic	7	63.6	25	71.4	0.625	0.700 (0.17-1.93)
	Others	4	36.4	10	28.6		
Margin	Regular	4	36.4	6	17.1	0.187	0.362 (0.08-1.64)
	Irregular	7	63.6	29	82.9		
Microcalcification	Absent	3	27.3	11	31.4	0.794	0.818 (0.18-3.69)
	Present	8	72.7	24	68.6		
Lymph nodes on ultrasound	Absent/Normal	7	63.6	17	48.6	0.386	1.853 (0.46-7.48)
	Abnormal	4	36.4	18	51.4		

The rate of LNM was significantly higher in patients with ETE ($p < 0.05$). There was no relationship between LNM and other features.

Table 3. The relationship between central LNM and clinicopathological and sonographic features

Features	Category	Central LNM				p value	OR (95%CI)
		Absent		Present			
		n	%	n	%		
Age (years)	< 15	4	28.6	9	28.1	0.975	1.02 (0.25-4.11)
	15-18	10	71.4	23	71.9		
Gender	Female	11	78.6	20	62.5	0.291	2.20 (0.51-9.51)
	Male	3	21.4	12	37.5		
Tumor size (mm)	≤ 10	6	42.9	5	15.6	0.054	4.05 (0.97-16.84)
	> 10	8	57.1	27	84.4		
Tumor location	Left/right lobe/ isthmus	12	85.7	29	90.6	0.625	0.621 (0.09-4.20)
	Bilaterality	2	14.3	3	9.4		
Multifocality	Absent	11	78.6	25	78.1	0.973	1.03 (0.22-4.73)
	Present	3	21.4	7	21.9		
Histopathological type	Classical type	13	92.9	27	84.4	0.443	2.41 (0.26-22.77)
	Other types	1	7.1	5	15.6		
Extrathyroidal extension	Absent	9	64.3	10	31.2	0.042	3.96 (1.05-14.89)
	Present	5	35.7	22	68.8		
Intrathyroidal spread	Absent	12	85.7	19	59.4	0.094	4.11 (0.79-21.48)
	Present	2	14.3	13	40.6		
Vascular invasion	Absent	11	78.6	28	87.5	0.443	0.52 (0.10-2.73)
	Present	3	21.4	4	12.5		
Echogenicity	Hypoechoic	10	71.4	22	68.8	0.856	1.136 (0.29-4.52)
	Others	4	28.6	10	31.3		
Margin	Regular	4	28.6	6	18.8	0.460	0.58 (0.13-2.49)
	Irregular	10	71.4	26	81.2		
Microcalcification	Absent	3	21.4	11	34.4	0.384	0.52 (0.12-2.27)
	Present	11	78.6	21	65.6		
Lymph nodes on ultrasound	Absent/Normal	7	50.0	17	53.1	0.845	0.882 (0.25-3.10)
	Abnormal	7	50.0	15	46.9		

The rate of central LNM was significantly higher in patients with ETE ($p < 0.05$). There was no relationship between central LNM and other features.

Table 4. The relationship between lateral lymph node metastasis and some clinicopathological and ultrasound characteristics

Features	Category	Lateral LNM				p value	OR (95%CI)
		Absent		Present			
		n	%	n	%		
Age (years)	< 15	5	20.0	8	38.1	0.180	0.41 (0.11-1.52)
	15-18	20	80.0	13	61.9		
Gender	Female	19	76.0	12	57.1	0.179	2.38 (0.67-8.38)
	Male	6	24.0	9	42.9		
Tumor size (mm)	≤ 10	9	36.0	2	9.5	0.049	5.34 (1.01-28.40)
	> 10	16	64.0	19	90.5		
Tumor location	Left/right lobe/isthmus	24	96.0	17	81.0	0.136	5.647 (0.58-55.08)
	Bilaterality	1	4.0	4	19.0		
Multifocality	Absent	23	92.0	13	61.9	0.023	7.08 (1.30-38.44)
	Present	2	8.0	8	38.1		
Histopathological type	Classical type	22	88.0	18	85.7	0.819	1.22 (0.22-6.81)
	Other types	3	12.0	3	14.3		
Extrathyroidal extension	Absent	16	64.0	3	14.3	0.002	10.67 (2.45-46.39)
	Present	9	36.0	18	85.7		
Intrathyroidal spread	Absent	22	88.0	9	42.9	0.003	9.78 (2.22-43.12)
	Present	3	12.0	12	57.1		
Vascular invasion	Absent	23	92.0	16	76.2	0.154	3.59 (0.62-20.88)
	Present	2	8.0	5	23.8		
Echogenicity	Hypoechoic	17	68.0	15	71.4	0.801	0.850 (0.24-3.01)
	Others	8	32.0	6	28.6		
Margin	Regular	18	72.0	18	85.7	0.269	2.33 (0.52-10.48)
	Irregular	7	28.0	3	14.3		
Microcalcification	Absent	11	44.0	3	14.3	0.037	4.71 (1.10-20.20)
	Present	14	56.0	18	85.7		
Lymph nodes on ultrasound	Absent/Normal	20	80.0	4	19.0	<0.001	17.00 (3.93-73.58)
	Abnormal	5	20.0	17	81.0		

The data shows a significant relationship between lateral LNM and tumor size (> 10mm), multifocality, ETE, intrathyroidal spread, microcalcification, and abnormal lymph nodes on ultrasound (all $p < 0.05$).

There was no relationship between lateral LNM and age, gender, histopathological type, vascular invasion, echogenicity, and tumor margin.

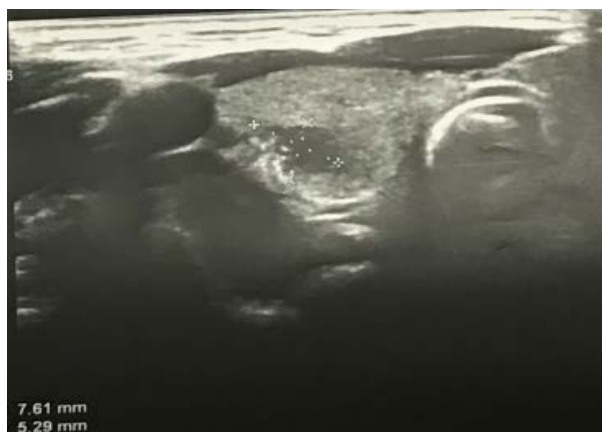


Figure 1. Thyroid nodule with sonographic features: hypoechoic, microcalcifications, irregular margin (BBL, 17 years)

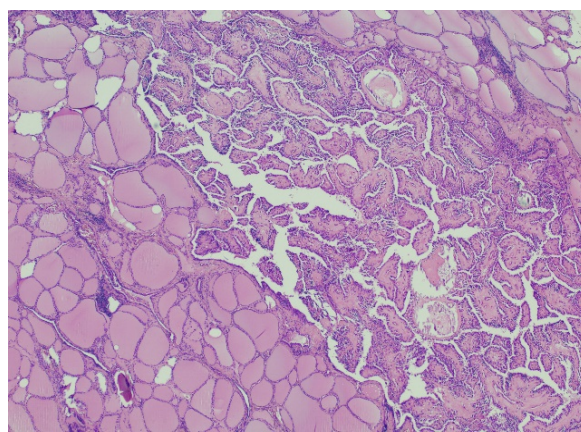


Figure 2. Papillary thyroid carcinoma (HE, 40X, E3792) (BBL, 17 years)



Figure 3. Abnormal lymph node with sonographic features: large size 21x13mm, hypoechoic, irregular margin, loss of structure, microcalcifications (NHQG, 11 years)

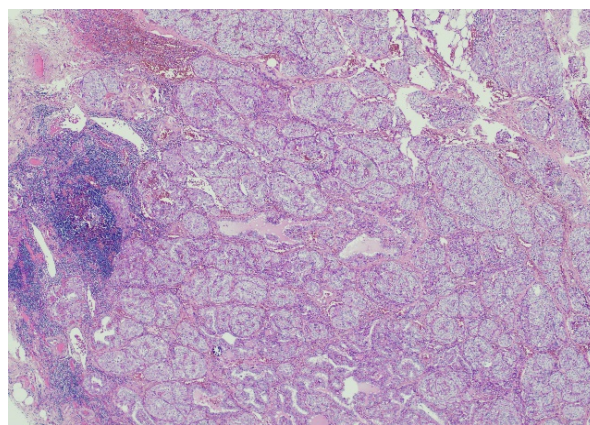


Figure 4. Lymph node metastasis (HE, 40X, 20C5154) (NHQG, 11 years)

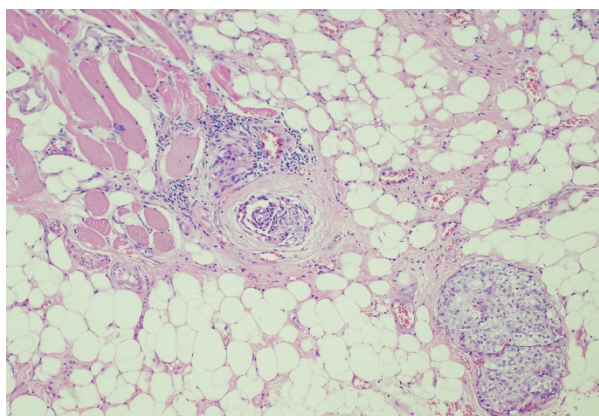


Figure 5. Extrathyroidal extension with fibrofatty tissue and muscle invasion (HE, 100X, 20C5155)

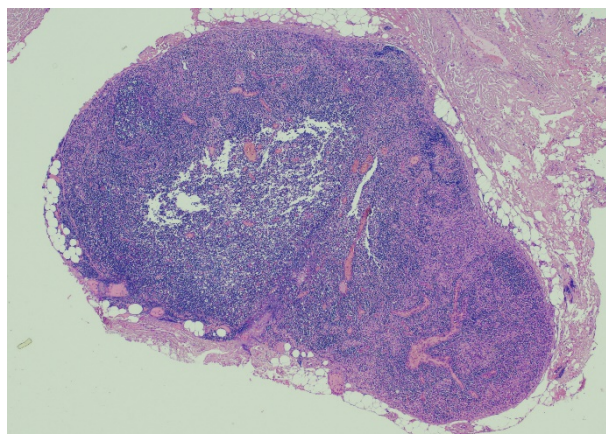


Figure 6. Lymph node without metastasis (HE, 40X, 19A2529)

4. Discussion

4.1. Clinicopathological and sonographic characteristics of PTC in children

PTC is a rare disease in children. The rate of pediatric PTC in our research was 0.6%. The majority of patients were aged between 15 and 18 (71.7%). Females had a higher incidence (67.4%). These findings were consistent with previous studies. Ngo Quoc Duy (2022) showed that in 67.7% of patients aged 15-18 years, the female/male ratio is 2.19/1 [7]. According to Nguyen Van Loc (2021), this data was 69.4% and 4.66/1, respectively [9]. Samuel Golpanian et al. (2016) also showed similar results, with 81.8% of patients being female and 76.7% of those over 15 years old [3].

Table 1 shows that the tumors were mostly > 10mm in size (76.1%). The classical type was the most common (87.0%). High rates of central and lateral LNM were seen (69.6% and 45.7%, respectively). The rates of ETE, intrathyroidal spread, and vascular invasion were 58.7%, 32.6%, and 15.2%, respectively. These were consistent with the known highly aggressive features of pediatric PTC.

Tumor size is an important prognostic factor in PTC as a factor for tumor staging in the TNM classification system. Compared to larger tumors, microcarcinomas (≤ 10 mm in size) usually have less malignancy and a lower rate of LNM [3, 7]. Other authors showed that pediatric PTC had a higher rate of tumors > 10mm in size [3, 6, 7]. The classical subtype is the most common subtype of PTC, accounting for 85-95% [7, 9]. Consistent with this data, the rate of classical PTC in our study was highest at 87%.

Important factors related to tumor aggressiveness include tumor size, multifocality, ETE, intrathyroidal spread, and vascular invasion. Our study showed high rates of these characteristics, similar to prior studies. Ngo Quoc Duy (2022) indicated that the rate of multifocality was 21.2%, and the data for ETE was 34.3% [7]. The results in a research of Yue Jie et al. (2023) were 26.4% and 52.8%, respectively [5].

The preoperative assessment of newly diagnosed pediatric PTC patients is crucial for optimizing surgical outcomes and medicinal treatment. In all cases, a full neck US utilizing a high-resolution probe and Doppler technique should be obtained by an expert ultrasonographer [2]. All patients in our study had preoperative neck ultrasound. Ultrasound features are shown in Table 2. The majority of patients were presented with hypoechoic echogenicity (69.6%), microcalcification (69.6%), and irregular margins (78.3%). There were 29 patients (63.0%) whose cervical lymph nodes could be detected on ultrasound. Ngo Quoc Duy (2022) studied 99 patients, giving the results: Hypoechoic echogenicity (81.8%), hyperechoic (17.2%), microcalcification (56.6%), TIRAD 4 and TIRAD 5 (94.9%). There were 45 patients (45.5%) whose cervical lymph nodes could be found on ultrasound [7]. Nguyen Van Loc (2021) showed that 31 patients (36.5%) had lymph nodes detected by ultrasound [9].

According to Richman DM et al. (2018), sonographic features associated with malignant nodules in children included larger size, solid parenchyma, taller-than-wide shape, presence of speckled calcifications, irregular margin, and presence of abnormal lymph nodes [10]. Furthermore, Wei-Ping Jiao (2017) showed that hypoechogenicity and irregular margins were strongly associated with PTC [4].

4.2. The relationship between LNM and clinicopathological and sonographic features

LNM is a poor prognostic factor in PTC, especially lateral LNM [2, 8]. Our data reported that the rates of central LNM and lateral LNM were 69.6% and 45.7%, respectively. Central LNM was closely related to ETE. There was no relationship between central LNM and other characteristics. Lateral LNM was significantly associated with tumor size (> 10mm), multifocality, ETE, intrathyroidal spread, microcalcification in the tumor, and abnormal lymph nodes on ultrasound. These results were in agreement with other studies.

Most studies show a high rate of central LNM in over 50% of pediatric PTC patients [5-7, 9]. The rate of lateral LNM in this study was similar to Vietnamese studies [7, 9], higher than the results of Yue Jie (2023) [5] and lower than the results of Soo Young Kim (2022) [6]. The difference may be due to differences in race and lymph node dissection experience of the surgeons.

When investigating the relationship between central and lateral LNM with risk factors, Nguyen Van Loc (2021) noted a higher rate of central LNM in patients with ETE and detectable lymph nodes on ultrasound. While lateral LNM is associated with tumors > 20mm in size, ETE, and lymph nodes detected on ultrasound [9]. Ngo Quoc Duy (2022) showed that there was a relationship between central LNM with age (> 15 years), gender (male), tumor size (>10mm), bilaterality, and ETE. Lateral LNM was closely related to age (> 15 years), multifocality, bilaterality, tumor size (> 10mm), and ETE [7]. Our results were consistent with these findings. However, we did not find a relationship between age, gender and LNM. This results may be due to our sample size being smaller.

Our study has some limitations. Firstly, our study is a retrospective, single-center research and tends to have a selection bias. Secondly, ultrasound features were collected from medical records. Some other important features of ultrasound are not available for analysis, such as the shape of the tumor, vascularity, the size of lymph nodes, etc... Multicenter prospective studies should be performed to further explore these issues.

5. Conclusion

Central and lateral LNM in pediatric PTC were common (69.6% and 45.7%, respectively). Several sonographic and clinicopathologic features had a significant relationship with LNM, especially lateral LNM, including tumor size (> 10mm), multifocality, ETE, intrathyroidal spread, microcalcification, and abnormal lymph nodes on ultrasound. Patients with risk factors should undergo both clinical and neck ultrasound examinations in order to find evidence of LNM.

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