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Endocrine malignancies: From pathophysiology to current clinical and surgical therapeutic approaches

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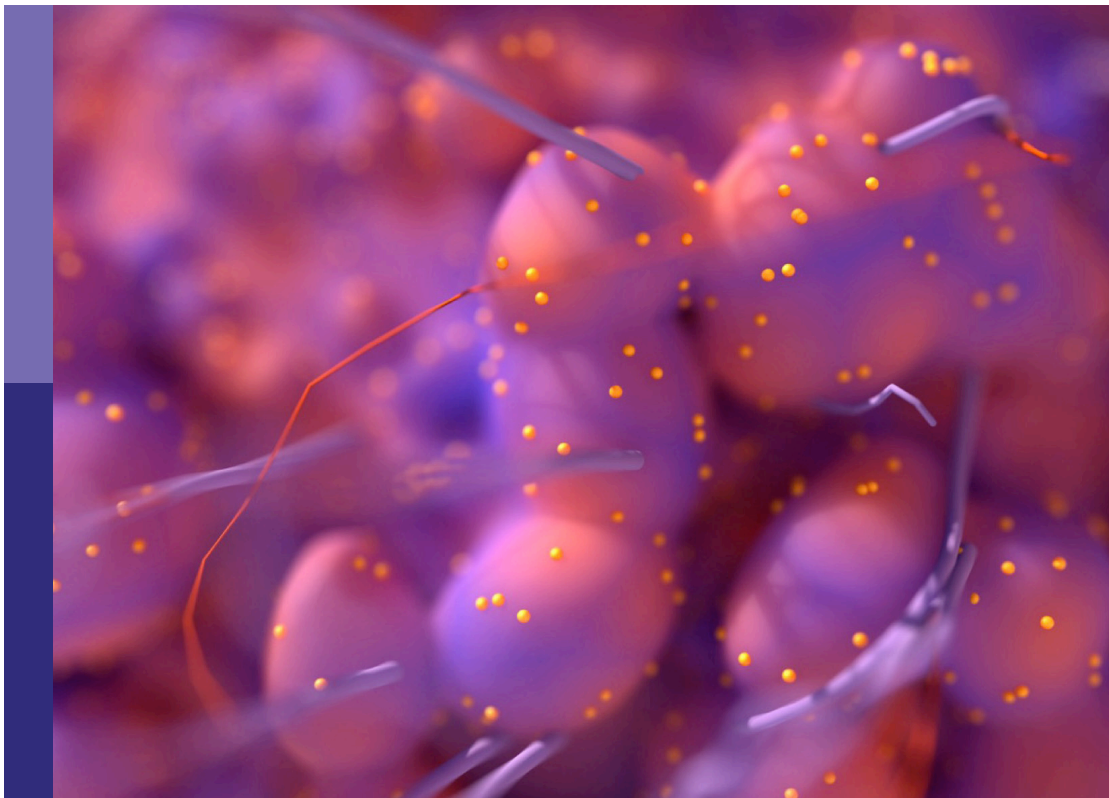

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Endocrine malignancies: From pathophysiology to current clinical and surgical therapeutic approaches

Topic editors

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Editorial: Endocrine malignancies: from pathophysiology to current clinical and surgical therapeutic approaches

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KEYWORDS

endocrine tumor, thyroid, parathyroid, adrenal gland, endocrine surgery

Editorial on the Research Topic
Endocrine malignancies: from pathophysiology to current clinical and surgical therapeutic approaches

Endocrine tumors of the thyroid, parathyroid, and adrenal glands are a significant and complex medical issue that affects millions of people worldwide. These tumors can lead to a variety of serious conditions, including hyperthyroidism, hypothyroidism, hyperparathyroidism (1), and pheochromocytoma (2); moreover endocrine tumors can be benign or malignant, and their diagnosis and treatment require a multidisciplinary approach involving endocrinologists, radiologists (3), pathologists, and surgeons. In recent years, significant progress has been made in our understanding of the pathophysiology of endocrine tumors, as well as in the development of new diagnostic and therapeutic approaches. Hence, this Research Topic aims to provide an up-to-date overview of endocrine tumors, from their pathophysiology to current clinical and surgical therapeutic approaches. The Research Topic includes contributions from leading experts in the field, covering a broad range of topics related to endocrine tumors. The articles in this Research Topic cover the variability of development and the importance of the latest advances in managing thyroid tumors and its debated topics such as lymph node metastasis, central neck dissection, micrometastasis and ectopic tumors.

From the application of the 2015 American Thyroid Association (ATA) guidelines, Wu et al. have retrospectively analyzed a large cohort of differentiated thyroid cancer patients from Wuhan Union Hospital (WHUH), finding that among all factors, age <35 years, clinical N1, and ultrasound reported local invasion had high positive predictive value to predict patients who should undergo total thyroidectomy; as regard Authors have suggested two new models of management, evaluating nodule size (cut off 4 cm), age (cut off 35 years old) in order to achieve better sensibility and sensitivity.

With the aim to develop the nomograms for Lateral Lymph Node Metastasis (LLNM) and to determine predictive factors in patients with papillary thyroid carcinoma and microcarcinoma, Feng et al. reviewed the medical records of a large cohort of patients.

Authors suggest treatment protocols for postoperative management of PTC patients with different risks.

The lymph node metastases of papillary thyroid cancer represent another important topic since they can have different locations and the management of these patients and their follow-up must have particular attention.

Wang et al. conducted a metanalysis to study the relationship between pretracheal and/or prelaryngeal lymph node metastasis and paratracheal and lateral lymph node metastasis; while a singular clinical case of papillary thyroid microcarcinoma patient with skip lymph node metastasis (lateral cervical lymph node metastasis without central lymph node metastasis) and multiple distant metastasis in lung and bone has reported by Jiang et al.

Papillary thyroid cancer is a disease that can also affect children. Ngo et al. has evaluated Pediatric Papillary Thyroid Cancer, rare condition, especially regarding safety of prophylactic central neck dissection (CND) respect of disease-free survival (DFS), pointing out that this procedure is associated with increased DFS and not with increased rates of complications after surgery.

Thyroid cancer can be ectopic although rare (0.3%–0.5% of thyroid cancer). Fu et al. performed a literature review reporting 132 clinical cases of Ectopic Thyroid Cancer (ECT), adding the personal case report of 13-years-old girl with thyroid cancer of the deep surface of the tongue base. Authors stated that surgery with complete resection is the main treatment for ETC.

The Research Topic also includes an interesting perspective of current surgical innovations for thyroid cancer management, highlighting the latest surgical techniques and strategies.

Zhang et al. has researched further studies to examine the effect of selective inferior parathyroid gland autotransplantation on central lymph node dissection (CLND) and incidence of postoperative hypoparathyroidism in patients undergoing endoscopic radical resection of thyroid carcinoma. These Authors have suggested that in patients undergoing endoscopic radical resection of thyroid carcinoma, the parathyroid autotransplantation is more beneficial to postoperative parathyroid glands function recovery, effectively preventing postoperative permanent hypoparathyroidism.

Princi et al. critically examined the experience of the intraoperative nerve monitoring (IONM), an innovative surgical instrument, in a referral center for thyroid and parathyroid surgery. Princi et al. reported surgical outcomes comparing two groups of patients (IONM group and control group). They reported no differences in terms of temporary or definitive recurrent laryngeal nerve injury and stated that routine use of IOMN increases the surgery cost, but overall, it leads to the reduction of both operating times and length of Hospital stay.

Other topics covered in this Research Topic include the treatment of parathyroid tumors. Alberti et al. performed a systematic review of published cases of metastatic parathyroid carcinoma. It has a poor prognosis and the main goals of treatment are to neutralize tumor growth and control hypercalcemia; nevertheless uncontrolled hyperparathyroidism remain the main cause of death. The study emphasized surgery of metastases as the best approach, with a better OS; target therapies and immunotherapy deserve to be extensively tested.

At last, but not least, the Research Topic includes some valuable experiences in the treatment of adrenal tumors and the importance of multidisciplinary care in managing these complex conditions.

Luo et al. described two cases: 50-year-old which developed acute respiratory distress syndrome (ARDS) requiring mechanical ventilation after pheochromocytoma rupture; 46-year-old woman admitted in hospital for pulmonary edema after intrauterine device removal (by hysteroscopy) and occasional find of pheochromocytoma; in both cases laparoscopic adrenalectomy was associated to success after adequate preoperative medical management.

Dong et al. have evaluated 5 cases and analyzed the literature on the management of oncocytic adrenocortical neoplasms, rare and mostly benign tumors, underlining that the surgical resection is the main treatment method, but a careful pathological examination and close follow-up are needed to confirm the prognosis.

Overall, this Research Topic has provided a valuable resource for clinicians and researchers working in the field of endocrine tumors. We hope that readers appreciated this Research Topic "*Endocrine tumors: from pathophysiology to current clinical and surgical therapeutic approaches*." By bringing together the latest research and clinical knowledge, we hope we have advanced our understanding of these complex neoplasms and improved outcomes for patients with endocrine tumors.

Author contributions

Article writing: MT and LP; draft manuscript preparation: MT. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CASE REPORT
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Diagnosis and Treatment of Adrenocortical Oncocytoma: Case Report of Five Cases and Review of the Literature

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Objective: To investigate the diagnosis and treatment of adrenocortical oncocytoma, and have a literature of review.

Materials and Methods: The clinical data of 5 cases of adrenocortical oncocytoma treated in our hospital was retrospectively analyzed. The clinical manifestations, imaging examination, endocrine examination, and pathological results were analyzed respectively.

Results: Oncocytic adrenocortical neoplasms are extremely rare. Oncocytic adrenocortical neoplasms are usually discovered incidentally, only the tumors with endocrine function could exhibit specific manifestations. No specific imageological features of oncocytic adrenocortical neoplasms have been found.

Conclusions: The diagnosis of adrenocortical oncocytoma mainly depends on the pathological examination. Surgical resection is the main treatment method.

Keywords: adrenocortical oncocytoma, treatment, endocrine examination, pathology, surgery

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INTRODUCTION

The oncocytic adrenocortical neoplasm is a rare tumor of the adrenal gland. Since it was first reported in 1986 (1), there has been serial case reports to try to illuminate this rare tumor. However, there is still rather little information available, especially the pathological and follow-up data, to illustrate the biological behavior of this particular tumor. The origin, biological behavior, diagnostic criteria, and prognosis of oncocytic adrenocortical neoplasm remain controversial. Here, we report 5 cases with oncocytic adrenocortical neoplasm and try to summarize its clinical and pathological manifestations, diagnostic criteria, surgical treatment, and prognosis. Written informed consent was obtained from the participant for the publication of this case report and any potentially-identifying information/images.

MATERIALS AND METHODS

The demographic and clinical data of 5 patients with oncocytic adrenocortical neoplasms, diagnosed and surgical treated at the department of urology in Peking Union College Hospital, between April 2005 and July 2018, were retrospectively analyzed.

As showed in **Table 1**, there were 1 male and 4 females. The age ranged from 17 to 63 y. Only one patient found the tumor incidentally during the healthy examination, 2 cases discovered the tumor

during body check for none specific symptoms of palpation or flank pain and the other 2 cases were diagnosed the adrenal tumor during evaluation of the Cushing syndrome, whose urinary free cortisol were significantly elevated. Case 4 underwent resection of left adrenal oncocytoma (10*8*6cm) 6 years ago. She felt flank pain before abdominal CT confirmed the recurrence of tumor near the left kidney and in the abdominal wall. Case 5 manifested virilization besides Cushing syndrome, such as hairy face, rough skin, and irregular menstruation, whose serum testosterone level rose. The cortisol, aldosterone, and catecholamine metabolites were normal except for Cushing Syndrome cases. Except case 1, the tumor size of the other 4 cases were more than 6 cm. Three cases underwent laparoscopic adrenal tumor resection, and 2 patients underwent open surgery of adrenal tumors. All procedures were successfully performed and no complications occurred. The tumor specimens were carefully examined and pathological report indicated adrenocortical oncocytoma in all cases, 2 of which were uncertain malignant potential according the Lin-Weiss-Bisceglia system (2). All the patients were regularly followed up. The follow-up ranged from 7 to 154 months. The virilization and Cushing syndrome disappeared and the serum cortisol and testosterone returned to the normal during the follow-up. There were no local recurrence and distant metastases in all cases.

The characteristics of the patients were showed in **Table 1**. The CT scan of case 5 showed the tumor located between the liver and kidney without normal adrenal gland left. The enhancement was heterogeneous **(Figure 1).** The tumor of case 5 was rounded and encapsulated, whose cut section was yellow-brown. HE staining showed the tumor cells were highly eosinophilic and arranged in a solid pattern (**Figures 2**–**4**). The study is approved by institutional review board of Peking Union Medical College Hospital.

DISCUSSION

Oncocytic neoplasms are tumors where granular eosinophilic cytoplasmic cells resulting from accumulation of mitochondria are the dominant cell type. They are mostly benign tumors and usually arising in the kidney, salivary gland, and pituitary. But according to a series of case reports, it seems that oncocytic neoplasms could originate from any organ, including adrenal gland, thyroid, parathyroid gland, thymus, stomach, liver, pancreas, breast, upper respiratory tract, and so on. (3, 4) The oncocytic neoplasms may share similar molecular alterations and biological features despite originating from different organs (5, 6).

Oncocytic adrenocortical neoplasms are extremely rare. There has been nearly 200 cases since this rare disease was first reported in 1986 (1). Adrenocortical oncocytomas could happen in a large age range, from adolescent to elderly people. This disease has a female dominance of about 2.5:1 and a left-side dominance of about 3.5:1 (4, 7). Our results are consistent with the literature. The age ranged from 17 to 63 years old. 4/5 of the cases were female and 4/5 of the tumors located at the left side.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

TABLE 1 | Clinical information of the patients.

Case	Age(y)	Gender	Symptoms	Hormones						Pathology									Follow-up
				24h UFC	NE	E	DA	T	DS	Ald	Surgical approach	Tumor size	Tumor site	Tumor weight	Malignant	Melan-A	Synaptophysin	α -inhibin	Calretinin	Vimentin	Ki-67	
1	23	F	Cushing syndrome	218.1	15	2.68	237.6	–	–	13.7	Laparoscopic	3*2.5*2	Left	11	Benign	None	None	None	None	None	None	154
2	63	F	Palpitation	116.6	18.51	1.85	187.92	–	–	11.5	Laparoscopic	7*6.5*4	Left	76	Benign	None	None	None	None	None	None	81
3	50	M	None	85.93	21.69	3.56	225.69	–	–	15.1	Laparoscopic	6*6*5.5	Left	127.1	UMP	+	+	–	+/–	+	10%	30
4	55	F	Flank pain, post-op of left adrenal oncocytoma for 6 years	36.96	–	–	–	–	–	–	Open surgical	8.8*7.8*7, 2.6*2.1*1.5	Left kidney, abdominal wall	–	benign	–	+	–	+	+	1%	19
5	17	F	Virilization, Cushing syndrome	265.76	17.72	1.9	159.87	2.55	1291.9	23.54	Open surgical	10*7*6	Right	183.6	UMP	+	+	+	+	–	3%	7

(UMP uncertain malignant potential), 24h UFC, 24 h urinary free cortisol; NE, Norepinephrine; E, epinephrine; DA, Dopamine; T, testosterone; DS, Dihydrotestosterone; Ald, aldosterone.

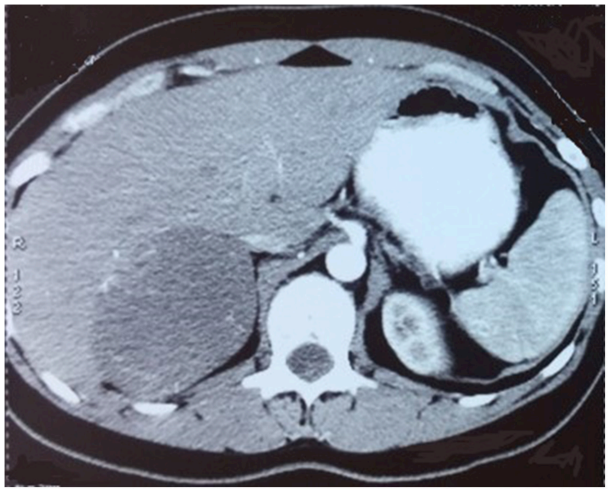

FIGURE 1 | CT scan showed a round mass between liver and right kidney with heterogeneous enhancement.

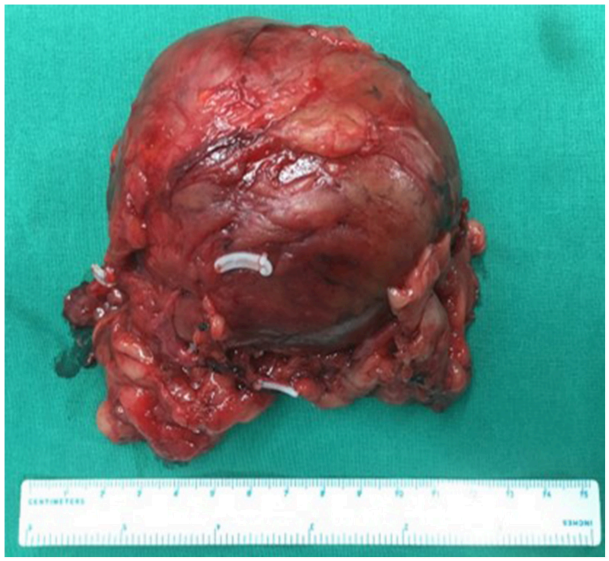

FIGURE 2 | Adrenal oncocytoma is a rounded and encapsulated mass (10*7*6 cm), with yellow-brown cut section. Microscopically, tumor cells are highly eosinophilic and arranged in a solid pattern.

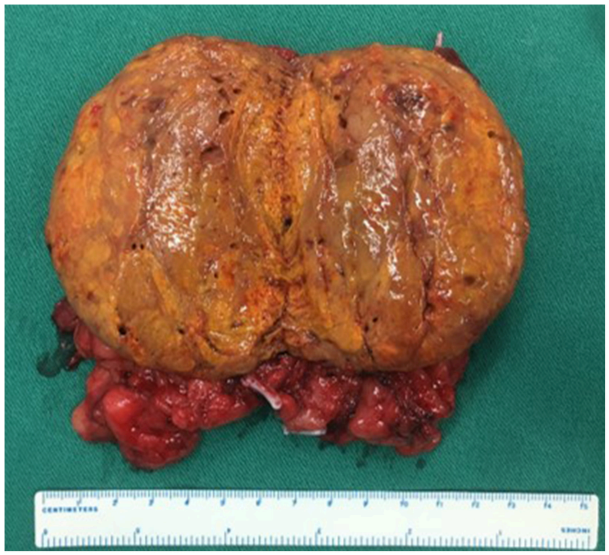

FIGURE 3 | Same as **Figure 2**.

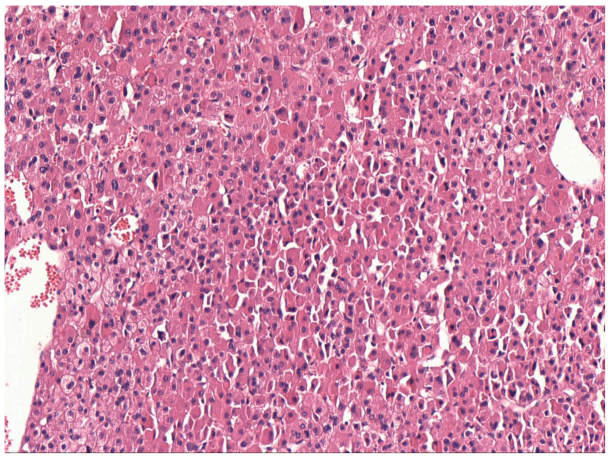

FIGURE 4 | Same as **Figure 2**.

Oncocytic adrenocortical neoplasms are usually discovered incidentally during routine body check without clinical manifestations (8). Only minority of patients may have non-specific symptoms such as abdominal pain, nausea, hypertension and so on (9, 10). Only the tumors with endocrine function could exhibit specific manifestations, such as virilization, feminization, and Cushing syndrome, while most oncocytic adrenocortical neoplasms show no function. There were also studies showed that nearly 30% of oncocytic adrenocortical neoplasms were functional (7). In this study, only one patient showed no symptom. Two patients had non-specific symptoms including abdominal pain and palpitation. And another two patients showed virilization and Cushing syndrome. So oncocytic adrenocortical neoplasms might be functional tumors.

No specific imageological features of oncocytic adrenocortical neoplasms have been found. Benign oncocytic adrenocortical neoplasms may be distinguishable from lipid-rich but not lipid -poor adenomas on CT examination. Malignant ones demonstrate similar features with adrenocortical carcinomas, such as large size, necrosis, and lower percentage enhancement washout, which makes differentiation through CT very difficult. So there were no CT or MRI criteria available to help differentiate benign from malignant tumors (11). There are also no specific signs in MRI and ultrasound (4, 12). Then the imaging examination is mainly used to confirm the location of the tumor and useless to differentiate

benign or malignant. In this series, only case 1 exhibited homogeneous enhancement and the other 4 cases were heterogeneous enhancement.

The diagnosis of adrenocortical oncocytoma mainly depends on the pathological examination. Fine-needle aspiration cytology seems to be useful to confirm the diagnosis preoperatively, but because of the large tumor size and possible heterogeneous areas, this technique may not characterize the tumor and increase the risk of needle tract implantation metastases in case of malignancy (13, 14). The section of benign tumors is usually golden or brownish yellow and the malignant tumors are mostly ashes red or fish-meat like (12). The Weiss system has been adopted as the standard criteria for the assessment and categorization of adrenocortical neoplasms (15). But because of the lack of reported cases of oncocytic neoplasms of the adrenal gland and the follow-up data, Lin-Weiss-Bisceglia system was put up to revise the former criteria to help diagnose this unique tumor (16). The major criteria include mitotic rate more than 5 mitotic figures per 50 high-power fields, atypical mitoses and venous invasion. The minor criteria include large tumor (>10 cm and/or >200 g), necrosis, capsular invasion, and sinusoidal invasion. Presence of any major criteria would be diagnosed as malignant and presence of any minor criteria would be diagnosed as borderline or uncertain malignant potential, while presence of none of major or minor criteria would be diagnosed as benign (2). In our series, 3 cases were benign and the other 2 were uncertain malignant potential according to the modified Weiss system. The case 3 is special, which seems to be malignant as the tumor recurred in the left kidney and abdominal wall after 6 years of resection of left adrenal oncocytoma. There has been 19 months after the second surgery and no recurrence was found. The detailed biological behavior of this tumor remains unknown.

The therapy of oncocytic adrenocortical neoplasms mainly relies on the surgical resection. With the development of laparoscopic technique, the laparoscopic surgery is becoming more and more popular (17, 18). It was suggested to perform the laparotomy when the tumor size was more than 6 cm to obtain a complete resection without tumor rupture. In this study, 2 cases with tumor size more than 6 cm were performed laparoscopic surgery and there is no recurrence after 30 and 81 months follow-up. For the metastatic tumors, surgery is recommended if the metastasis is restricted and could be safely resected (19, 20). In this study, after complete resection of the recurrent tumors, the case 4 has a very good prognosis with no recurrence for nearly 1.5 years.

The oncocytic adrenocortical neoplasms are rare and mostly benign tumors. Surgical resection is the main treatment method. Careful pathological examination and close follow-up are needed to confirm the prognosis.

ETHICS STATEMENT

The study is approved by institutional review board of Peking Union Medical College Hospital. Written informed consent was obtained from the participant for the publication of this case report and any potentially-identifying information/images.

AUTHOR CONTRIBUTIONS

DD and XL write the manuscript. ZJ revise the manuscript. HL review the manuscript.

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Reevaluation of Criteria and Establishment of Models for Total Thyroidectomy in Differentiated Thyroid Cancer

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Wu Z, Xiao Y, Ming J, Xiong Y, Wang S, Ruan S and Huang T (2021) Reevaluation of Criteria and Establishment of Models for Total Thyroidectomy in Differentiated Thyroid Cancer. Front. Oncol. 11:691341. doi: 10.3389/fonc.2021.691341

Introduction: After the publication of the 2015 American Thyroid Association (ATA) guidelines, the indication for total thyroidectomy (TT) was reported to be underestimated before surgery, which may lead to a substantial rate of secondary completion thyroidectomy (CTx).

Methods and Materials: We retrospectively analyzed differentiated thyroid cancer patients from Wuhan Union Hospital (WHUH). Univariate analysis was performed to evaluate all preoperative and intraoperative factors. New models were picked out by comminating and arranging all significant factors and were compared with ATA and National Comprehensive Cancer Network (NCCN) guidelines in the multicenter prospective Differentiated Thyroid Cancer in China (DTCC) cohort.

Results: A total of 5,331 patients from WHUH were included. Pre- and intraoperative criteria individually identified 906 (17.0%) and 213 (4.0%) patients eligible for TT. Among all factors, age <35 years old, clinical N1, and ultrasound reported local invasion had high positive predictive value to predict patients who should undergo TT. Accordingly, we established two new models that minorly revised ATA guidelines but performed much better. Model 1 replaced "nodule size >4 cm" with "age <35 years old" and achieved significant increase in the sensitivity (WHUH, 0.711 *vs.* 0.484; DTCC, 0.675 *vs.* 0.351). Model 2 simultaneously demands the presence of "nodule size >4 cm" and "age <35 years old," which had a significant increase in the specificity (WHUH, 0.905 *vs.* 0.818; DTCC, 0.729 *vs.* 0.643).

Conclusion: All high-risk factors had limited predictive ability. Our model added young age as a new criterion for total thyroidectomy to get a higher diagnostic value than the guidelines.

Keywords: thyroid cancer, thyroidectomy, preoperative, risk factors, model

INTRODUCTION

Differentiated thyroid cancer (DTC) is one of the most rapidly growing malignancies globally in recent years (1–3), and surgery plays a significant role in the treatment for DTC patients. Both the 2015 American Thyroid Association (ATA) and 2018 National Comprehensive Cancer Network (NCCN) revised the guidelines, which narrowed the indication of surgery for DTC and brought considerable controversies about the reasonable treatment for thyroid cancer (4, 5) (**Supplementary Table**). All those altering based no significant prognosis difference between total thyroidectomy (TT) and thyroid lobectomy (6, 7), the effectiveness of complete thyroidectomy (CTx, secondary surgery), and the cautious choice of iodine 131 treatment (8, 9). They recommended that TT is limited to fewer high-risk populations, including a family history of thyroid cancer, radiation history, extrathyroidal extension (ETE), tumor size >4 cm, and clinical lymph node metastasis (cN1). DTC patients without these high-risk factors first should undergo thyroid lobectomy. If postoperative pathology reported risk factors such as aggressive histology, these patients have to undergo secondary CTx. These guidelines presented surgeons a dilemma raised in previous studies that 30–40% of patients who were not eligible for TT need to undergo secondary surgery (10, 11). This brings potential patients' complaints, economic losses, complications, and anesthesia risks.

Although the guidelines proposed many pre- and intraoperative factors, the accuracy and reliability of these factors to decide TT and eliminate the need for CTx have been studied less. Our study analyzed the clinical–pathological data of thyroid cancer patients from Wuhan Union Hospital (WHUH) and evaluated all the factors' ability to predict reasonable TT. Finally, we tried to develop and validate new models to indicate TT by a new algorithm.

METHODS

Clinical–Pathological Data

The training set was from the Union Hospital of Tongji Medical College of Huazhong University of Science and Technology (Wuhan Union Hospital, WHUH) for retrospective analysis. WHUH database included registered thyroid cancer patients from 2008 to 2018. The validation cohort is from the Differentiated Thyroid Cancer in China (DTCC) study [registered at ClinicalTrials.gov (NCT02638077)], which included thyroid cancer patients from nine hospitals with high thyroid surgery volume from 2014 to 2016. All patients were confirmed DTC through pathology assessment of preoperative core needle puncture (CNP) or intraoperative frozen section, and thyroidectomy was completed by experienced thyroid surgeons. Our database recorded mainly, first, age at first diagnosis, gender, family history of malignant tumor, history of another malignant tumor; second, preoperative status of lymph nodes (LN) including central and lateral compartments. Clinical N1 refers to N1a (suspicious central LN metastasis) or (and) N1b (suspicious lateral neck LN metastasis). Third are the intraoperative evaluations recorded by the surgeons, including LN dissection scope and visual inspected tumor invasion. Fourth are the postoperative pathological data including tumor size, pathological subtypes, ETE (excluding capsule invasion), and number of involved LN.

The study inclusion criteria were adult patients (age ≥18 years and ≤65 years old at the date of surgery) who underwent TT and were confirmed DTC by the pathological diagnosis. We excluded any patient who did not have preoperative ultrasound reports and those with distant metastatic disease. Notability, maximum thyroid nodule size was not available in a few included patients' ultrasound results. **Figure 1A** provides a flowchart showing the WHUH and DTCC screening.

The study was performed in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethical Committee of the Union Hospital, Tongji Medical College of Huazhong University of Science and Technology (No. 0304-01). The informed consent for data publication was not required for this study's retrospective nature.

Evaluation of Preoperative and Intraoperative Factors

Univariate analysis was performed to identify the significant correlation between pre- or intraoperative clinical characteristics and high-risk pathological results. We applied two methods to evaluate the ability of each factor to predict the TT. First, the positive predictive value (PPV) indicates the likelihood that someone with preoperative high-risk factors actually should undergo the TT. Factors with high PPV can identify patients who require TT. Thus, it will be sufficient to follow up any positive result of these high PPV factors to obtain an accurate assessment of TT.

Second, all patients are divided into two groups according to whether they need TT based on postoperative ATA risk factors. We performed t-tests (continuous variable) or chi-square tests (categorical variable) for each pre- or intraoperative factor between these two groups. Significant factors ($p < 0.001$) were identified as effective criteria to distinguish whether patients require TT.

Construction of New Predictive Models

After screening all factors through two kinds of univariate analysis above, several significant preoperative (Pre-op) or intraoperative (Intra-op) factors were selected for further model construction. Then, these significant factors were randomly arranged and combined through R programming to construct numerous multivariate models, containing one or all possible risk factors. The logical relationship between factors in models could be "AND" (true if both factors are true) and "OR" (true if either factor is true). Therefore, each model can be described as an expression, such as "① OR ②" and "① AND ②" (NCCN guidelines). In total, the R program randomly generated 3,840 models according to the above method. Then, we selected models in the top 10 percentile of both sensitivity and specificity among all models and sorted these models according to the area

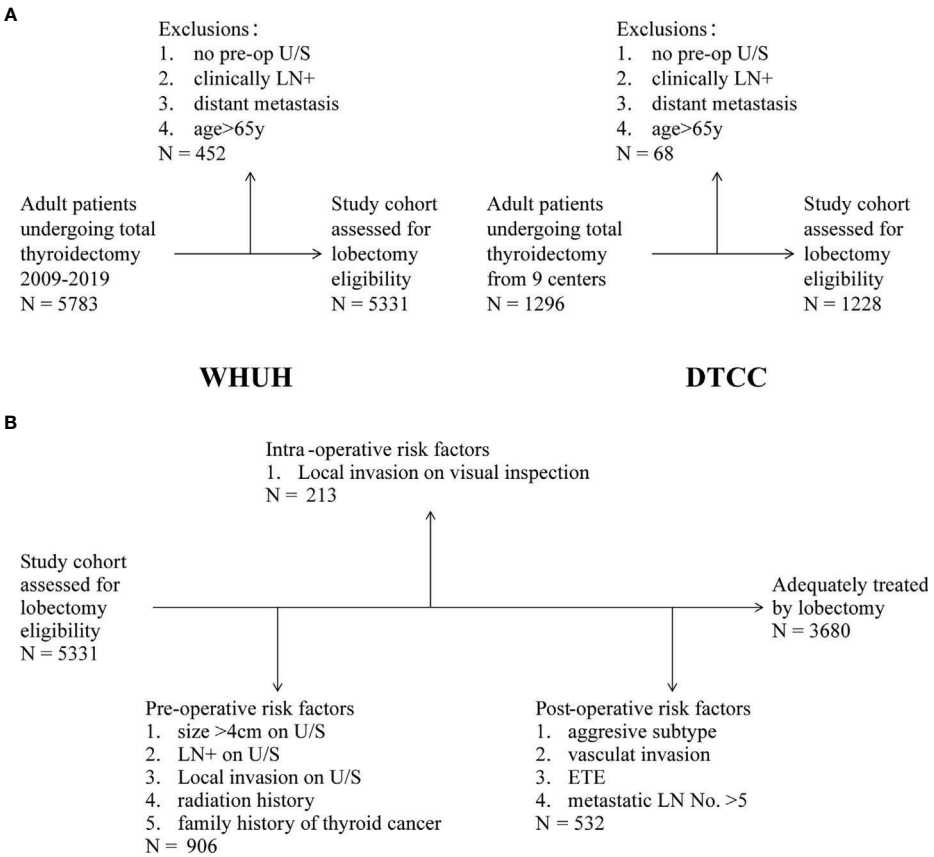


FIGURE 1 | **(A)** Inclusion and exclusion criteria in WHUH database and DTCC cohort. **(B)** Patients with eligibilities to total thyroidectomy (TT) in the different evaluation stages.

under curve (AUC). In summary, this study established the two models with the best performance. Internal sets from WHUH and external sets from DTCC were used to validate both new models, namely, ATA and NCCN guidelines.

Statistical Analysis

The clinicopathological characteristics of patients in two databases were presented by t-test (continuous variable) or chi-square test (categorical variable). All statistical analyses were performed using SPSS version 23.0 (SPSS, Chicago, IL, USA) or R software version 3.2.1 (http://www.r-project.org). All p values were two-sided; $p < 0.05$ is considered statistically significant.

RESULTS

Clinical–Pathological Data Including WHUH Database and DTCC Cohort

A total of 5,331 differentiated thyroid cancer patients were included after excluding 452 ineligible patients in the database from WHUH. As shown in **Table 1**, the average age was 43.8 ± 10.3 years old, and 4,126 (77.4%) were female. Meanwhile, there were 4,909 (92.1%) patients who underwent LN dissection, including 4,882 (91.6%) patients with central compartments and 1,019 (19.1%) patients with neck lateral compartments.

In the DTCC cohort, 1,228 included patients underwent TT. The average age was 41.0 ± 10.5 years old. The percentage of female patients accounted for 71.4% (877), and 1,190 (96.9%) patients underwent LN dissection, among which 1,126 (91.7%) and 581 (47.3%) patients individually underwent central and neck lateral compartment LN dissection. Postoperative pathology revealed that ETE occurred in 336 patients (27.4%), and LN metastasis occurred in 989 patients (80.5%).

Patients Eligible for Total Thyroidectomy

As shown in **Figure 1B**, the preoperative criteria identified 906 (17.0%) people eligible for TT, which consisted of 46 (5.1%) patients with family history of thyroid cancer, 484 (53.4%) patients with ultrasound (U/S)-reported tumor larger than 4 cm, 394 (43.5%) patients with clinical N1, and 57 (6.3%) patients with local invasion (including capsule invasion). A total of 3,014 (56.5%) patients need to undergo TT because of bilateral nodules according to the NCCN guideline. **Supplementary Figure 1** shows the composition relationship between preoperative risk factors. In the remaining 4,425 patients who were prepared for lobectomy, 213 (4.0%) patients were transferred to TT because of

TABLE 1 | Baseline characteristics in development cohort and validation cohort.

		Union Hospital	DTCC	*p*-value
No. of patients		5331	1228	
Gender	**Male**	1,198 (22.5%)	351 (28.6%)	0.001*
	Female	4,126 (77.4%)	877 (71.4%)	
	Not known	7 (0.1%)	0	
Mean age, years	**Years (SD)**	43.8 (10.3)	41.0 (10.5)	0.024*
Family history of thyroid cancer	**Yes**	46 (0.9%)	29 (2.4%)	0.001*
	No	5,285 (99.1%)	1,198 (97.6%)	
	Not known	0	1 (0.1%)	
Clinical N stage	**N1**	394 (7.4%)	470 (38.3%)	0.001*
	N0	4,937 (92.6%)	727 (59.2%)	
	Not known	0	31 (2.5%)	
Maximum tumor size, cm	**≤4**	5,041 (94.6%)	1,210 (98.5%)	0.583
	>4	36 (0.7%)	17 (1.4%)	
	Not known	254 (4.8%)	1 (0.1%)	
LN metastasis, No.	**0**	2,731 (51.2%)	239 (19.5%)	0.001*
	1~5	1,786 (33.5%)	562 (45.8%)	
	>5	814 (15.3%)	427 (34.8%)	
Pathology ETE	**Yes**	187 (3.5%)	336 (27.4%)	0.001*
	No	4,956 (93.0%)	892 (72.6%)	
	Not known	188 (3.5%)	0	

*$p < 0.05$.
SD, standard deviation.

local invasion on visual inspection during operation. Results of the intraoperative frozen sections were not considered because of their overlap with postoperative pathology reports. In summary, in our WHUH database, preoperative clinical characteristics and intraoperative findings can identify 1,119 (21.0%) patients, and the remaining 4,212 patients were eligible for thyroid lobectomy. However, the postoperative pathological results showed that 12.6% (532/4,212) patients had indications of CTx theoretically for high-risk factors after thyroid lobectomy. For instance, 79 (1.9%) patients had ETE (muscle, recurrent laryngeal nerve, and blood vessel), and 1,914 (45.4%) "lobectomy" patients had LN metastasis, of which 467 (11.1%) patients had metastatic LNs >5. Finally, after identifying the pathology, it is sufficient for 31.0% (1,651/5,331) of the patients to perform TT.

In the overall cohort from WHUH, the rate of LN metastasis was 48.8% (2,600/5,331), the proportion of >5 metastatic LNs was 15.3% (814/5,331), the proportion of ETE was 3.5% (187/5331), and 947 (17.8%) patients were identified with intermediate-/high-risk thyroid cancer according to postoperative pathological diagnosis. Therefore, 62.9% (704/1,119) of patients who underwent TT were only identified as low-risk thyroid cancers after the surgery according to the ATA guideline.

Evaluation of Pre-/Intraoperative Factors Based on Postoperative Pathology

We evaluated the prediction ability of several pre-/intra-operative factors for each postoperative risk factor in the ATA or NCCN guidelines. First, among 1,108 patients with age <35 years old, there were 799 patients with LN metastasis, of which 370 patients had >5 metastatic LNs. Tumor size >4 cm and ETE were individually found in 12 and 34 patients. In total, 388 patients belonged to the high-risk subtype based on ATA guidelines. Second, in 394 patients with clinical N1, 341 patients were confirmed LN metastasis in the postoperative pathology, of which 228 patients had > 5 metastatic LNs. Other eight patients belonged to the high-risk subtype because of other factors. Third, 57 patients reported that thyroid tumors invaded the capsule or extraglandular tissues by U/S. Only 10 patients had ETE among 29 patients with the ATA risk factors in the postoperative pathology. In comparison, 45 patients had LN metastasis, of which 21 patients had metastatic LNs >5. Fourth, among 46 patients with a family history of thyroid cancer, 12 patients were classified into the intermediate-/high-risk group, including 9 patients with metastatic LNs >5, 3 patients with ETE, and 1 patient with tumor >4 cm (5). In 484 patients with thyroid nodules >4 cm reported by U/S, only 20 patients had tumor nodules >4 cm in postoperative pathology, 33 patients had ETE, and 90 patients had metastatic LNs >5. In total, 112 patients were identified with intermediate-/high-risk thyroid cancer according to ATA.

Positive predictive value (PPV) was used to evaluate pre- and intraoperative characteristics and is shown in the heat map (**Figure 2**). Several factors were found to be a good predictor of TT based on the ATA guideline, including age <35 years (PPV, 35.0%), clinical N1 (PPV, 59.9%), and U/S-reported local invasion (PPV, 50.9%). However, some guideline suggested factors that performed unsatisfactorily, such as family history of thyroid cancer (PPV, 26.1%), bilateral nodules (PPV, 16.3%), and nodule size >4cm (PPV, 22.4%).

Construction of Risk Model and Validation in External Cohort

Univariate analysis showed (**Figure 3**) that a large number of potential factors had significant associations with intermediate- or high-risk thyroid cancer, including demographic data (age and gender), preoperative ultrasound (tumor size, tumor calcification, local invasion, and suspicious central/lateral compartment LN metastasis), and intraoperative ETE (all $p <$ 0.001). After selections through univariate analyses above, eight

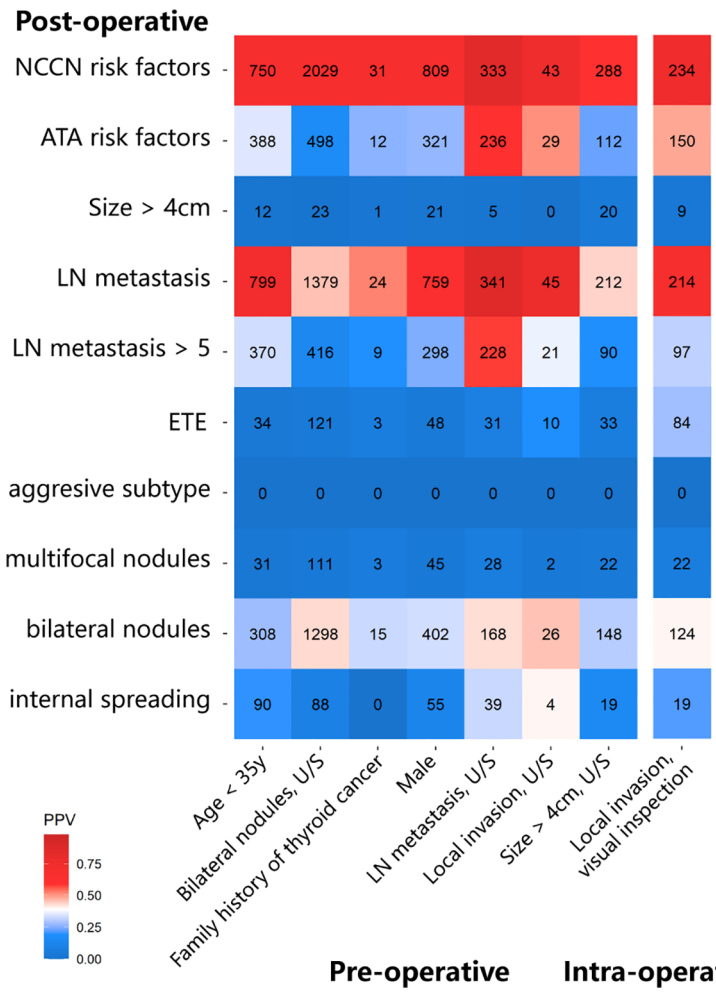


FIGURE 2 | The heatmap shows the positive predictive value (PPV) of pre-/intra-operative factors to predict each postoperative intermediate-/high-risk factor.

preoperative (Pre-op) or intraoperative (Intra-op) factors were identified with good predictive ability to TT, including (1) Pre-op, age < 35 years old; (2) Pre-op, bilateral nodules, U/S; (3) Pre-op, male gender; (4) Pre-op, LN metastasis; (5) Pre-op, size > 4 cm, U/S; (6) Pre-op, family history of thyroid cancer; (7) Pre-op, local invasion, U/S; and (8) Intra-op: local invasion and visual inspection.

Then, we evaluated two models from ATA and NCCN guidelines to predict the TT before the end of surgery. ATA models were defined as "(4) OR (5) OR (6) OR (7) OR (8)" through logical expression. In the training sets (**Figure 4A**), the ATA model performed well in specificity (0.839) but unsatisfactory in sensitivity (0.438). Compared with the ATA model, the NCCN model supplements factor (3) as the indication of TT, which also expressed as "(3) OR (4) OR (5) OR (6) OR (7) OR (8)". Then, specificity (0.289) drops sharply in spite of a relative increase in sensitivity (0.779).

In order to obtain models with better performance than guidelines, we randomly arrange and combine eight significant factors as reported in the method section and thus picked out two models through comprehensively evaluating sensitivity, specificity, and AUC (**Figure 4A**). On the basis of ATA guidelines, Model 1 (① OR ④ OR ⑤ OR ⑥ OR ⑦ OR ⑧) replaced low PPV factor (⑤) with high PPV factor (①) as the standard of TT. Model 1 achieved a significant increase in the sensitivity (0.711) and a minor decrease in the specificity (0.687) compared with ATA guidelines. In Model 2 [(④ OR (① AND ⑤) OR ⑥ OR ⑦ OR ⑧], when other factors in the ATA guideline did not exist, patients underwent the TT only if both two factors (① AND ⑤) are true. Model 2 had a significant increase in the specificity (0.915) and a minor decrease in the sensitivity (0.424) compared with ATA guidelines.

Finally, we assess these models in an external validation cohort from the DTCC project (**Figure 4B**). The sensitivity of ATA and NCCN guidelines is individually 0.351 and 0.754, and the specificity is 0.643 and 0.388, respectively. Consistent with the training sets, new model 1 performed well in sensitivity (0.675), and model 2 was good at specificity (0.729). Notability, both new models 1 (0.649) and 2 (0.593) achieved increased AUC than ATA (0.523) and NCCN (0.577) guidelines.

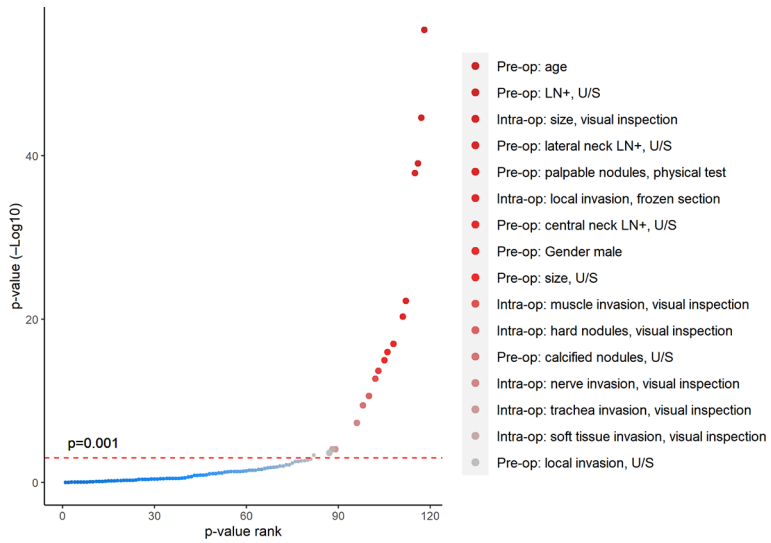
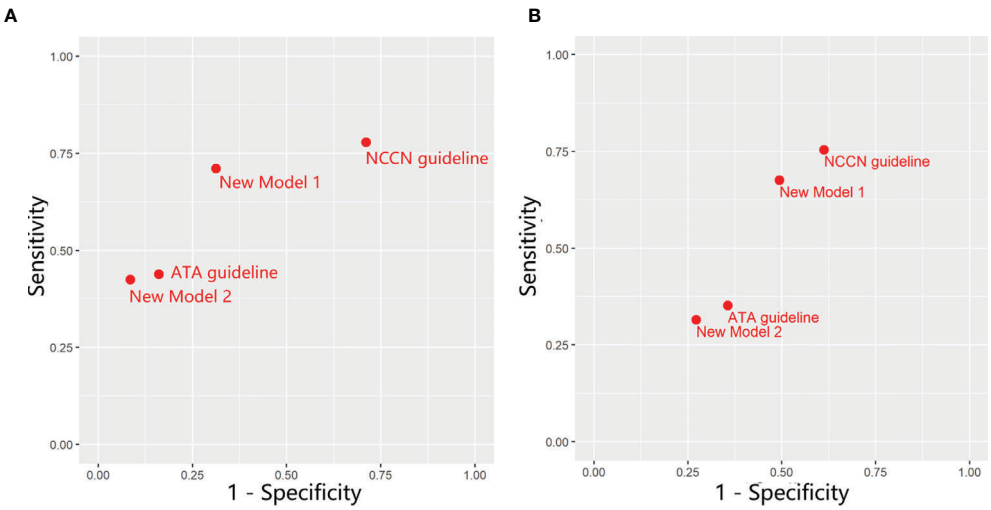


FIGURE 3 | Univariate analysis showed significant correlations between clinical characteristics and high-risk pathological results. All patients are divided into two groups according to whether they need the TT based on postoperative ATA risk factors. p-value was calculated for each pre-/intraoperative factor through t-test (continuous variable) or chi-square test (categorical variable) between these two groups. All factors were ranked along the X-axis from larger to smaller p-values, with significant factors shown in red dots ($p < 0.001$).



Model	Sensitivity	Specificity	AUC
ATA guideline	0.438	0.839	0.758
NCCN guideline	0.779	0.289	0.635
New Model 1	0.711	0.687	0.809
New Model 2	0.424	0.915	0.799

Model	Sensitivity	Specificity	AUC
ATA guideline	0.351	0.643	0.523
NCCN guideline	0.754	0.388	0.577
New Model 1	0.675	0.506	0.649
New Model 2	0.314	0.729	0.593

FIGURE 4 | The ability of varying models for predicting reasonable total thyroidectomy in the training sets **(A)** and validation sets **(B)**.

DISCUSSION

The surgical scope to thyroid cancer had experienced a process from "large to small" (10–12). Concerns about overtreatment further limited total thyroidectomy (TT) and prophylactic central LN dissection in DTC patients. The guidelines changed indications for TT based on evidence from the National Cancer Data Base (NCBD) and the Surveillance, Epidemiology, and End

Results (SEER) database of the United States (6, 7, 13). However, the predictive ability of these preoperative risk factors for reasonable TT needs to be reexamined, and studies for evaluating preoperative TT indication based on large and multicenter cohorts were rare. Our retrospective study, which included the most extensive samples in China, evaluated the ability of pre-/intraoperative factors as indications for TT and developed new diagnostic models that were validated well in the DTCC cohort. In our database from WHUH, 12.6% of patients with low-risk DTCs initially meeting the criteria for lobectomy would ultimately require their entire thyroid to be removed. In contrast, 62.9% of patients who received TT because of pre-/intraoperative risk factors were found to be overtreated after the surgery.

Preoperative Lymph Node Metastasis

In all preoperative risk factors, clinical N1 had the highest PPV for predicting the intermediate–high-risk thyroid cancer. In our study, in 394 patients with U/S reported cN1, 86.5% of patients were confirmed to have LN metastasis, and about 70% of the patients were intermediate-/high-risk patients. Meanwhile, cN1 can predict metastatic LN >5 (57.87%), which was a leading cause for CTx after lobectomy. LN metastasis is an independent risk factor of the prognosis of thyroid cancer patients (14, 15). As an indispensable role in predicting TT, the status of LN was most likely to be underestimated in patients thought to be eligible for lobectomy. U/S is a widely used method to diagnose cN1 (16), but it is challenging to detect metastatic LNs in the central compartment. As a supplement, previous studies had developed several models for predicting LN metastasis, which indicated body mass index (BMI), age, and tumor size as potential risk factors (17, 18). However, the actual predictive value needs more validations. In addition, intraoperative lymph node frozen inspection was not applied in the majority of Chinese hospitals, and previous research recommended that it should be regarded as clinical LN metastasis and be applied as effective criteria for intraoperative conversion from lobectomy to TT (11). In our cohort, a high proportion of metastatic LNs was detected due to a high rate of prophylactic central LN dissection in the past 10 years. However, it is worth to be noted that prophylactic central LN dissection may significantly increase the rate of temporary recurrent nerve injury and hypoparathyroidism, especially in the older group (19). Intraoperative neuromonitoring, with good sensitivity and negative predictive value, may detect proximal recurrent nerve injury. Oral calcium and vitamin D supplements were able to prevent laboratory hypocalcemia and hypocalcemia symptoms for transient parathyroid gland injury (20, 21).

Tumor Size

The tumor size constitutes an essential part of the indication for TT, while T stage was also an independent risk factor for both survival and recurrence (22, 23). In our results, tumor size may be the most overestimated preoperative risk factor. Patients with nodule size >4 cm accounted for 53.4% of all patients who were eligible for TT, the highest percentage among all preoperative factors. However, the postoperative pathology showed that only 4.1% of patients had tumor size more than 4 cm, and only 23.1% of patients were classified into intermediate–high risk. The main reason is that U/S often reports a larger tumor size compared with pathology sections (24, 25). Deveci et al. also reported that the concordance of thyroid nodule >1.0 cm measured by U/S and gross pathology examination is ≤50% (25).

Other Factors

Although U/S has a high sensitivity for the detection of ETE (26), it is difficult to distinguish between ETE and capsular invasion. Therefore, preoperative capsular invasion under U/S was also considered to be eligible for TT. Thyroid cancers with only capsular or the perithyroidal soft tissue invasion were classified as low risk because of their minimal prognosis influence (27, 28). In our study, 45 patients were found to have LN metastasis among 57 patients with U/S-reported invasion. Our finding also corroborated the previous results that ETE were associated with LN metastasis (29). In addition, thyroid cancer family history had an unsatisfactory PPV for intermediate–high-risk thyroid cancer. Relatives with low grades of thyroid cancer (ep. microcarcinoma) or distant relationship might rarely influence the patient (30).

A New Algorithm for Constructing Models

In our database, we also presented the differences of ATA and NCCN guidelines. In both WHUH database and DTCC cohort, ATA guidelines had higher specificity compared with NCCN guidelines, which means that patients eligible for lobectomy are more likely to have low-risk characteristics. However, NCCN has a higher sensitivity, owing to contralateral thyroid nodules as one of the TT criteria. It has been reported that 16%–30% of the patients with bilateral nodules were diagnosed with incident malignant contralateral tumor (31–33). According to the ATA guideline, 17.16% of patients need TT at the first surgery in our database. However, the proportion of patients who need TT would increase by more than three times (56.89%) if NCCN criteria were rigorously implemented.

Our study developed a new algorithm for constructing models. We randomly arranged and combined all significant clinical factors into numerous models. Then, models with good performance were selected, compared with old guidelines in the training set, and validated in DTCC cohorts. The major pros and cons of this new algorithm are as follows: (1) new models are expressed as logical relationships ("AND" and "OR"), which have similar structures with guidelines and are suitable for clinical application. In contrast, scoring systems such as nomograms require much mathematical calculation. (2) All possible combinations of these risk factors were automatically generated and filtered through computer programs. No models will be missed like forward or backward methods. (3) This algorithm can only be applied for categorical variables, while threshold values should be set for continuous variables. Notably, almost all risk factors for predicting TT were categorical variables.

The main change in the new model was age, as the threshold value 35 years old was from the largest AUC, which leads the new model to obtain higher sensitivity and specificity. Young age was found highly related to intermediate–high thyroid cancer in

previous retrospective studies (34, 35), which suggested a high risk of recurrence. Hye-Seon Oh et al. also found that young and male patients should be recommended active surgery for more frequent large-volume LNM (36). Age is an essential factor influencing the prognosis of thyroid cancer. Thyroid tumors in the younger patients (<25 years old) and the older (>65–70 years old) group had been reported to have a more invasive behavior, which seems rational to undergo central LN dissection. However, it deserved personalized processing to balance the risk and quality of elderly patients' life after prophylactic central LN dissection (19). Meanwhile, all the evidence between the clinical model and invasive differentiated thyroid cancer need validation from molecular diagnosis and mechanism experiments (37).

Limitation

First, the proportion of preoperative intermediate–high-risk patients may be underestimated because potential risk factors like neck radiation history were not fully recorded in the WHUH database. Although we have recorded radiotherapy history, it is difficult for retrospective studies to obtain the history of neck radiation examination. Second, some aggressive histology subtypes (ep. hobnail variant of PTC) were not reported by postoperative pathology, leading to underestimating the proportion of high-risk patients. Third, the lack of molecular markers of thyroid cancer hinders the preoperative decision on the resection scope of thyroid cancer. More preoperative serum results such as platelet counts and thyroid autoantibodies are correlated with recurrence of thyroid cancer, which would be potential parameters for managing total thyroidectomy in the future (38, 39).

CONCLUSION

Age <35 years old, LN metastasis, and U/S reported local invasion was found to be a good predictor of total thyroidectomy (TT) based on the ATA guideline. Our model added young age as a new criterion for TT and had a higher diagnostic value in the training and validation cohort.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be available under reasonable requests.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of the Union Hospital, Tongji Medical College of Huazhong University of Science and Technology (No. 0304-01). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

ZW and YXX conceived of the study and analysis plan. JM, YQX, SW, and SR collected data. ZW analyzed the data. YXX wrote the first draft of the manuscript. TH had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.691341/full#supplementary-material

Supplementary Figure 1 | The number of patients with one or more preoperative factors.

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CASE REPORT
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Case Report: Surgical Intervention Under Pheochromocytoma Multisystem Crisis: Timing and Approach

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Background: Progressive multiple organ failures still occur in some patients with pheochromocytoma multisystem crisis (PMC) despite α- and β-blockade being used, and emergency adrenalectomy may lead to rapid hemodynamic stabilization and recovery. Therefore, the optimal timing and surgical approach under PMC remain controversial.

Case Presentation: A 50-year-old man presented with persistent chest pain accompanied by vomiting and headache. CT showed a right adrenal mass, and plasma catecholamine levels were significantly elevated. Phenoxybenzamine was used, but his symptoms were aggravated. He progressed to acute respiratory distress syndrome (ARDS) and received mechanical ventilation. Reexamination of CT showed pheochromocytoma rupture. Emergency pheochromocytoma resection was performed on the 5th day, and he was discharged on the 21st day. A 46-year-old woman was admitted for intrauterine device removal and received hysteroscopy under intravenous anesthesia. She presented with dyspnea, fluctuating blood pressure, and loss of consciousness 9 h after hysteroscopy surgery. CT showed a left adrenal mass, and plasma catecholamine levels were significantly elevated. Her condition fluctuated and could not meet the preoperative preparation criteria for pheochromocytoma despite adequate doses of α-blockade and β-blockade were taken. Furthermore, her lung condition worsened due to recurrent crises and pulmonary edema. After multidisciplinary discussions, laparoscopic left adrenalectomy with venoarterial extracorporeal membrane oxygenation (VA-ECMO) support was performed on the 28th day, and she was discharged on the 69th day.

Conclusion: Elective surgical resection is the essential therapy for PMC with adequate preoperative medical management. Emergency surgery is recommended for patients who fail to achieve medical stabilization or progressive organ dysfunction within 1 week, especially those with tumor rupture and uncontrolled bleeding. The laparoscopic approach may represent an option even under PMC.

Keywords: pheochromocytoma multisystem crisis, VA-ECMO, emergency surgery, laparoscopy, pheochromocytoma

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INTRODUCTION

Pheochromocytoma multisystem crisis (PMC) is a rare, life-threatening condition inducing hemodynamic instability and multiple organ failures caused by the excessive release of catecholamine (1–3). The management of pheochromocytoma crisis includes initial medical stabilization, followed by appropriate α-blockade and fluid resuscitation before surgery (4, 5). However, progressive multiple organ failures still occur in some patients despite the use of α-blockade and β-blockade. Emergency adrenalectomy may lead to rapid hemodynamic stabilization and recovery, even though some are extracorporeal membrane oxygenation (ECMO)-assisted emergency adrenalectomy (2, 6, 7). However, the optimal timing of surgery under PMC remains controversial (2, 8). Minimally invasive surgery (laparoscopic or robotic) is considered the preferred surgical technique for small (<6 cm), non-invasive pheochromocytoma (1, 4); however, whether the laparoscopic approach suits patients with PMC also remains controversial (6). We present two cases combined with a literature review to determine the optimal timing and approach for surgery with unstable PMC.

CASE PRESENTATION

Patient 1

A 50-year-old man presented with persistent chest pain accompanied by vomiting and headache for 5 h. He had a history of hypertension, which was well controlled by nifedipine, but he had not undergone a specialist examination to exclude secondary hypertension. His body temperature was 36.8°C, his blood pressure was 192/132 mmHg, his pulse rate was 95 bpm, and his respiratory rate was 20/min on admission. Serum cardiac markers showed 1.8 ng/ml of creatine kinase-MB (CK-MB), 287 ng/ml of myoglobin (MYO), 0.21 ng/ml of troponin (TNI), and 9.8 pg/ml of B-type natriuretic peptide (BNP). Routine blood tests showed that the total white blood cell count was 20.97×10^9/L. Electrocardiography showed that the ST segment changed. The diagnosis was considered acute non-ST-segment elevation myocardial infarction, and emergency coronary angiography was performed; however, the coronary artery was not stenosis. Subsequent CT showed a 7.1 cm × 6.6 cm, round, right adrenal mass (**Figure 1A**). Plasma catecholamine metabolite levels (MNs) were significantly elevated (metanephrine, 573.5 ng/L; normetanephrine, 2,941.6 ng/L). Phenoxybenzamine (initial dose 10 mg, Q8 h) was used for preoperative preparation.

During hospitalization, the pain was aggravated and spread throughout the abdomen, accompanied by severe fluctuations in blood pressure and heart rate (**Figure 1B**). Furthermore, he progressed to acute respiratory distress syndrome (ARDS) and received tracheal intubation and mechanical ventilation on the 3rd day, and his hemoglobin decreased gradually from 159 g/L at admission to 75 g/L before surgery. CT reexamination showed pheochromocytoma rupture and hemorrhage (**Figure 1C**), and the retroperitoneal hematoma was increased after 1 day (**Figure 1D**). On the 5th day after admission, an emergency pheochromocytoma resection was performed with massive blood infusion. Pathological examination confirmed the diagnosis of pheochromocytoma rupture and hemorrhage. Plasma MN levels returned to normal ranges (metanephrine, 106.9 ng/L; normetanephrine, 80.5 ng/L). After 10 days of postoperative intensive care treatment and 6 days of general treatment, he was discharged on the 21st day of hospitalization. After discharge, his blood pressure returned to normal, and he did not need antihypertensive medication.

Patient 2

A 46-year-old woman without a history of hypertension was admitted for removal of the intrauterine device and received a hysteroscopy under intravenous anesthesia. Transient ventricular tachycardia occurred during the operation. The patient experienced severe nausea and vomiting after surgery, which were considered side effects of anesthesia, until she presented with dyspnea, crackle, hypoxia, and fluctuating blood pressure and lost consciousness 9 h after hysteroscopy surgery. Her blood pressure fluctuated from 99/74 to 144/115 mmHg, and her pulse rate was 130–140 bpm (**Figure 2A**). Arterial blood gas analysis indicated severe acidosis (pH 7.0, 52 mmHg PO_2, 51 mmHg PCO_2). She received tracheal intubation and mechanical ventilation immediately. Large amounts of yellow fluid continued to drain out of her airway, and she was transferred to the intensive care unit (ICU). The total amount of leukocytes was significantly increased to 41.5×10^9/L, procalcitonin was increased to 177.99 ng/ml, and plasma cardiac troponin was 8.668 ng/ml. During hospitalization in the ICU, her blood pressure fluctuated between 204/120 and 77/52 mmHg. Her condition was accompanied by coagulation disorders, renal failure, and liver dysfunction, and she received hemodialysis and blood transfusion. CT showed a 6.6 cm × 5.7 cm, round, central necrosis adrenal mass with an enhancing rim on the left side (**Figure 2B**).

PMC was considered, and plasma MN results (metanephrine, 3,221.27 ng/L; normetanephrine, 10,785.34 ng/L) confirmed the diagnosis. Phentolamine and esmolol were administered with continuous infusion, and blood volume expansion was performed. Her condition gradually stabilized. All indices improved significantly, and the tracheal catheter was removed on the 6th day after admission to the ICU (**Figure 2C**). However, her condition worsened 2 days later when her leukocyte count (26.34×10^9/L) and plasma MNs (metanephrine, 2,466.31 ng/L; normetanephrine, 3,214.03 ng/L) significantly increased (**Figure 2C**). Her condition fluctuated, and she was not able to reach the preoperative preparation criteria for pheochromocytoma despite the administration of adequate doses of α-blockade and β-blockade. Furthermore, her lung condition worsened due to recurrent acute pulmonary edema and fibrosis (**Figure 2D**). After multidisciplinary discussions, an emergency left adrenalectomy with venoarterial extracorporeal membrane oxygenation (VA-ECMO) support was decided. Because of the trauma of open surgery and literature reports (6), we chose to use the laparoscopy approach first and prepared

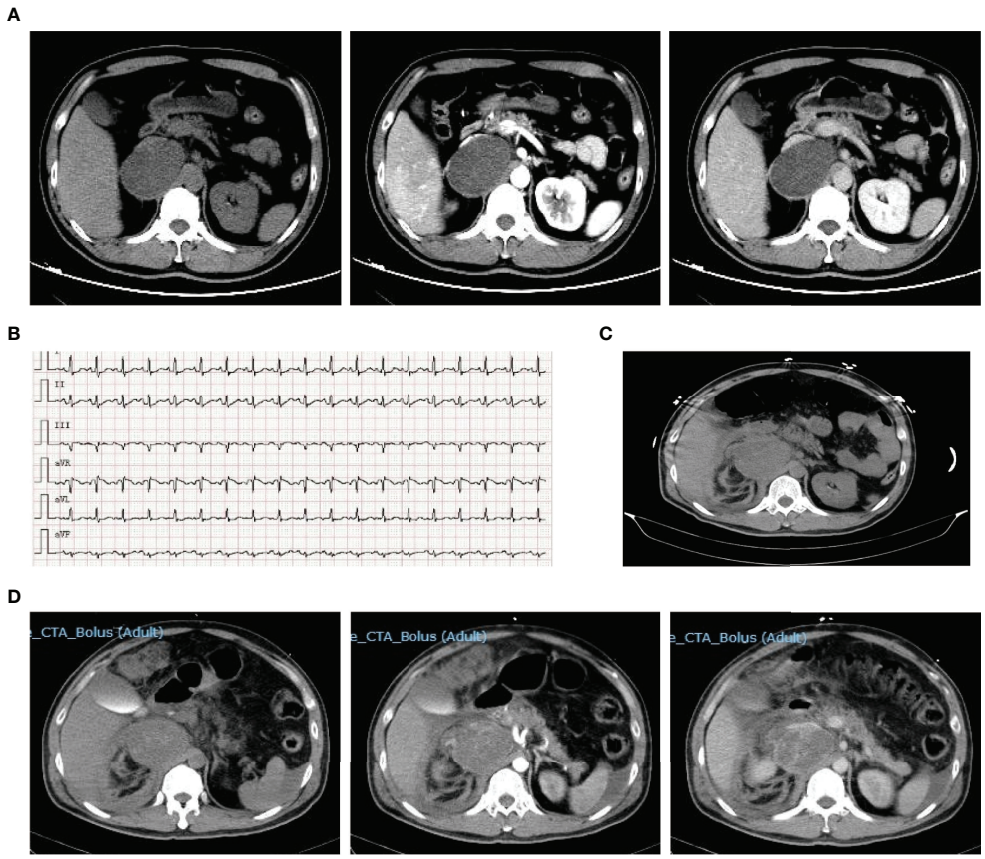

FIGURE 1 | Representative images of patient 1. Contrast-enhanced CT on admission showed right adrenal mass **(A)**. ECG on the 3rd day showed tachycardia **(B)**. CT scan on the 3rd day showed pheochromocytoma rupture and hemorrhage **(C)**. Reexamination enhanced CT showed retroperitoneal hematoma on the 4th day **(D)**.

to open on the 28th day (**Figure 2E**). Pathology confirmed pheochromocytoma with hemorrhage, and plasma MN levels returned to normal ranges (metanephrine, 95.26 ng/L; normetanephrine, 118.99 ng/L). VA-ECMO was removed 6 days later, but mechanical ventilation lasted 20 more days after surgery. A long rehabilitation period was required due to pulmonary fibrosis. The patient was discharged on the 69th day for further pulmonary rehabilitation.

DISCUSSION

Pheochromocytomas and paragangliomas (PPGLs) are catecholamine-secreting neuroendocrine tumors (9). Excessive catecholamines released in a short period will cause a PPGL crisis, and the incidence ranges from 3% to 18% (1, 5, 10, 11). The clinical presentation of the PPGL crisis is widely variable and non-specific, and the classic triad, which consists of episodic headache, diaphoresis, and tachycardia, is only noted in some patients (10, 12). In our cases, patient 1 presented with chest pain, and patient 2 presented with nausea and vomiting as the initial clinical manifestations. Whitelaw divided the PPGL crisis into two types. Type A is described as a more limited crisis without sustained hypotension, whereas type B is described as a severe presentation with sustained hypotension, shock, and multiorgan dysfunction known as PMC (12).

PMC is a critical and lethal emergency, and organ-specific mechanical support is needed, including mechanical ventilation (85%), circulatory support (vasoactive drugs in 68% and ECMO in 41%), and renal replacement therapy (24%) (2, 7). Despite the use of the rescue methods noted above, the mortality of PMC remains high (15%–30%) (1, 7, 12).

Curative surgical resection is an essential treatment for PPGLs, and preoperative pharmacologic preparation (7–14 days) and fluid resuscitation are recommended (4, 5). Most PMC cases will be well controlled after internal medical treatment followed by sufficient α-blockade before surgery (5, 13). Emergency surgery is defined as taking inadequate α-blockade (time and dose) and failing to achieve medical stabilization before operation (5). However, in the case of life-threatening PMC with extreme hemodynamic fluctuations, emergency surgery may achieve hemodynamic stabilization rapidly (1, 2, 14, 15). In addition, surgery with ECMO support will improve the safety of the procedure (6, 7, 16). Delayed

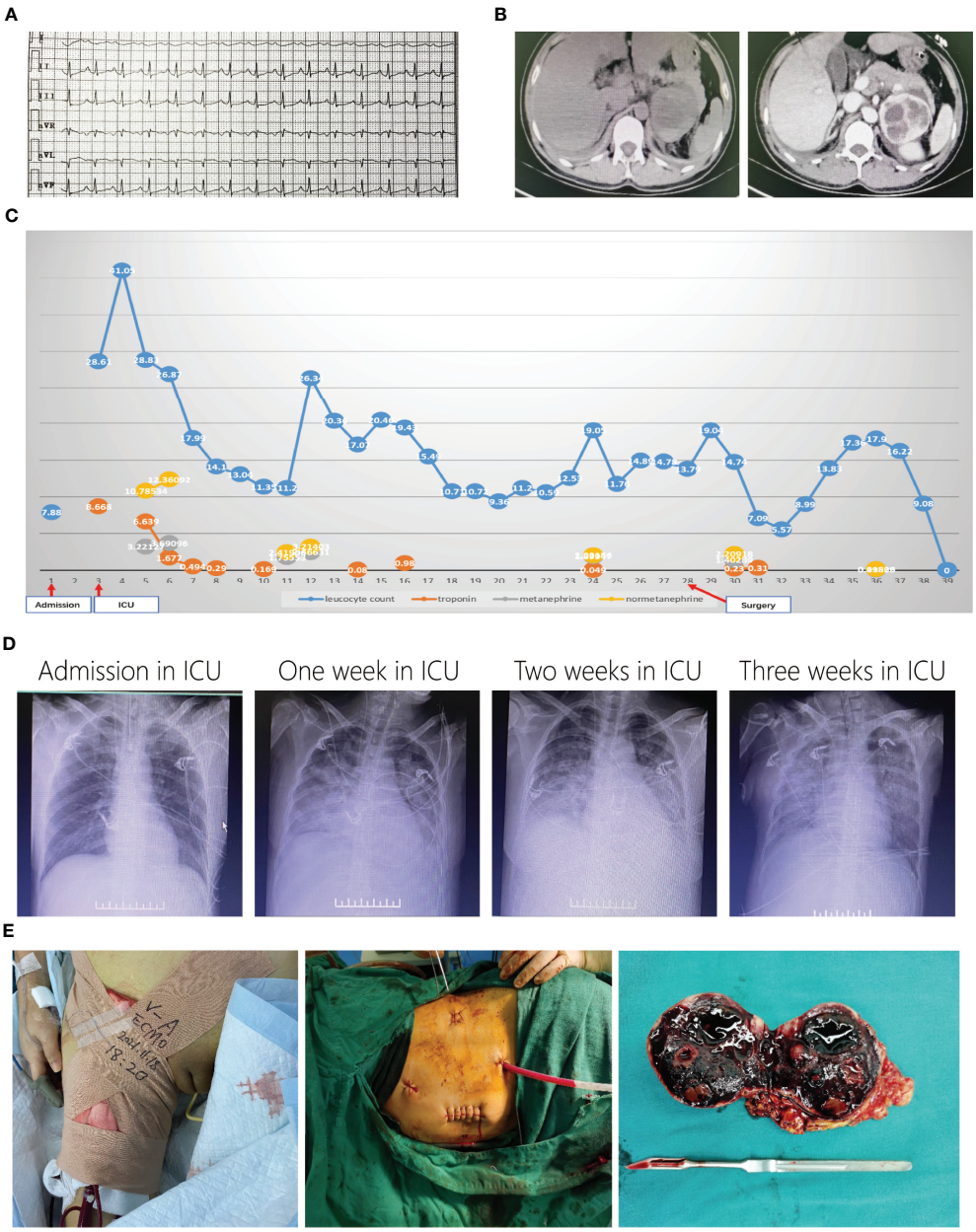

FIGURE 2 | Representative images of patient 2. ECG showed tachycardia when admission in ICU **(A)**. Enhanced CT showed left right adrenal mass **(B)**. Curves of leukocyte count, troponin, metanephrine and normetanephrine showed recurrent crisis happened several times **(C)**. Chest X-ray changes after admission in ICU **(D)**. Laparoscopic surgery with ECMO support **(E)**.

surgery may have a risk of recurrent crises, further organ failure, and more complications (7). In our report, patient 1 received emergency surgery due to tumor rupture and hemorrhage and recovered rapidly. Patient 2 experienced recurrent crises despite adequate α-blockade and β-blockade were used. Surgery was eventually performed under VA-ECMO but prolonged the hospitalization time and caused pulmonary fibrosis; thus, the recovery time was prolonged. Therefore, the optimal timing of surgery under life-threatening conditions remains controversial.

A previous cohort study and review of the literature suggested that emergency resection of pheochromocytoma should be avoided due to the high surgical mortality of 18% (5). However, most deaths occurred before 1990, and the mortality after 1990 was only 1 in 18 cases (6%). We performed a search of the English literature and identified 13 patients who presented with PMC and received emergency pheochromocytoma resection after 2010. All these patients were alive, including 4 who underwent surgery with the support of ECMO (1, 2, 6, 7, 14,

15). Furthermore, we extracted literature with specific data (**Table 1**). All cases were prepared by α-blockade for 1 to 20 days. Three patients underwent surgery within a week and were discharged earlier, whereas the other 3 patients who received longer preparation had longer hospitalization times and more complications. Therefore, the optimal timing of surgery is crucial. Emergency surgery enables rapid recovery, but with a high risk. Deferring surgery may cause the development of recurrent crises and further organ dysfunction. Because most cases will reach medical stabilization within 3–5 days after comprehensive treatment (5, 13), we recommend that emergency surgery should be performed if medical stabilization is not achieved or progressive organ dysfunction occurs within 1 week of treatment. In addition, tumor rupture and uncontrolled bleeding are strong indications for emergency surgery (5, 10).

Minimally invasive surgery (laparoscopic or robotic) is the preferred approach for patients with pheochromocytomas (diameter <6 cm), even in patients presenting with pheochromocytoma crisis after medical stabilization (5, 17). However, the choice of a surgical approach varies according to the adrenal mass presentation, patient fitness for surgery, type and size of the tumor, surgeon's experience, and hospital resources (17, 18). Therefore, a tumor size over 6 cm is not a contraindication for minimally invasive surgery. Choudhary reported that emergency laparoscopic surgery could also be performed on patients with uncontrolled PMC with the support of ECMO, despite the patient receiving secondary surgery for bleeding (6). Our case also showed that the laparoscopic approach might be an optional choice in unstable patients with PMC; however, open surgery should be considered the first choice for ruptured tumors (18), like in patient 1. The indications of surgical approaches during PMC are still not clear, mostly depending on the surgeon's experience and multidisciplinary cooperation.

We presented 2 different cases with PMC. Patient 1 received emergency surgery due to intraperitoneal bleeding and recovered rapidly. Patient 2 experienced recurrent crises during preparation for surgery. Emergency surgery was eventually performed, but prolonged hospitalization and rehabilitation were required. Emergency surgery is recommended for patients with uncontrolled extreme hemodynamic fluctuations, progressive organ dysfunction, and tumor bleeding.

CONCLUSION

PMC is a rare condition with variable manifestations, and elective surgical resection is an essential therapy with adequate preoperative medical management and involves the use of alpha-blocking agents. Emergency surgery is recommended for patients who fail to achieve medical stabilization or progressive organ dysfunction within 1 week, especially for patients with tumor rupture and uncontrolled bleeding. The laparoscopic approach may represent an option even under PMC. Due to the rarity of

TABLE 1 | Emergency surgery under pheochromocytoma multisystem crisis in literature of recent years.

Author	Gender	Age (years)	Crisis manifestations				Tumor size (cm)	Duration of α-blockade before surgery (days)	Time from crisis to surgery (days)	Surgery approach	ECMO support	Complications	Duration of ICU stay (days)	Duration of hospital stay (days)	Outcome
			Severe hypertension/ hypotension	Cardiac crisis	Pulmonary crisis	Other organ crisis									
Bekelaar T 2021 (2)	M	49	Yes	Yes	No	Renal, liver	Left, 5.7	1	1	Open	No	No	16	24	Alive
Choudhary M 2021 (6)	M	30	No	Yes	Yes	Renal	Right, 6.9	10	37	Laparoscopic	Yes	Reoperation of bleeding	N/A	75	Alive
UCHIDA N 2010 (15)	F	52	Yes	Yes	Yes	Renal	Left, 6	N/A	11	Open	No	N/A	N/A	106	Alive
Kakoki K 2015 (14)	M	70	No	Yes	Yes	Renal, liver	Left, 12	5	5	Open	No	N/A	N/A	42	Alive
Present case 1, 2022	M	50	No	Yes	Yes	Bleeding	Right, 7.1	3	5	Open	No	No	13	21	Alive
Present case 2, 2022	F	46	No	Yes	Yes	Renal, liver	Left, 6.6	20	26	Laparoscopic	Yes	Pulmonary fibrosis	46	69	Alive

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; N/A, not applicable.

PMC, a large, randomized, and multicenter trial is needed to identify the best treatment and the optimal timing for surgery.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the participant(s) for the publication of this case report.

AUTHOR CONTRIBUTIONS

DW and SL contributed to the conception and design of the study. SL and QC collected the data. SL and DW wrote the manuscript. All authors contributed to manuscript revision and read and approved the submitted version

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Prophylactic Central Neck Dissection to Improve Disease-Free Survival in Pediatric Papillary Thyroid Cancer

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Background: Pediatric PTC is a rare disease. Although, the prognosis is excellent and the mortality rate is low, the role of prophylactic central neck dissection is still the subject of debate. The aim was to evaluate both the role and safety of prophylactic central neck dissection (CND) in managing pediatric papillary thyroid cancer (PTC), especially in respect of disease-free survival (DFS).

Patients and Methods: In this retrospective study, we collected 54 pediatric cN0 PTC patients (≤ 18 years of age) who were treated from January 2014 to January 2021 at a high-volume thyroid surgery center. Patients were divided into two groups based on the status of prophylactic CND. We analyzed the factors related to the clinicopathological features and recurrence of PTC in children.

Results: Of the 54 cN0 patients, 35 underwent prophylactic CND and 19 patients did not undergo prophylactic CND. The two groups were similar in clinical and pathologic features, such as age, gender, tumor size, multifocal status, and follow-up time. The average DFS was 84.4 ± 2.7 months. Log-rank tests on Kaplan-Meier curves revealed that age, gender, tumor size, multifocality, and extrathyroid extension did not relate to DFS time. Furthermore, DFS time was not affected by the extent of thyroidectomy (p=0.07) or RAI treatment (p=0.21). Prophylactic CND was found to increase DFS time for pediatric patients with cN0 PTC (p = 0.003). There was no statistically significant difference in complications such as transient hypocalcemia (p=0.15) and transient recurrent laryngeal nerve injury (p=0.37) between the prophylactic CND group and the no-prophylactic CND group.

Conclusion: Prophylactic CND was found to be associated with increased DFS and not with increased rates of complications after surgery.

Keywords: prophylactic central neck dissection (CND), pediatric thyroid cancer, papillary thyroid cancer (PTC), pediatric thyroid surgery, pediatric thyroid carcinoma

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INTRODUCTION

Most pediatric thyroid cancers are differentiated thyroid cancer (DTC), with papillary thyroid cancer (PTC) comprising 90% of DTC. According to the American Thyroid Association, pediatric thyroid cancer (PTC) is a rare disease but with incidence increasing by approximately 3% annually (1). PTC accounts for approximately 1.5 percent of all malignancies in the under-18 age group, with an age-adjusted incidence of 4.8 to 5.9 per 1,000,000 people (2).

Compared to adults, thyroid cancer in children more commonly presents at an advanced stage, with increased extrathyroidal extension, cervical lymph node metastasis, and distant metastasis (3, 4). However, the prognosis is excellent and the mortality rate is low, although optimal treatment strategies for children with PTC remain controversial (1, 5). Specifically, the role of prophylactic central neck dissection (CND) is still the subject of debate. Several studies have shown that prophylactic CND improves disease-free survival (6–8). On the other hand, prophylactic CND is associated with increased complications, such as hypoparathyroidism and recurrent laryngeal nerve injury, that negatively affect quality of life, especially in children (1). Thus, we aim to assess the role of prophylactic CND in the management of PTC in children, as well as the potential risks after surgery.

PATIENTS AND METHODS

Patients

In this retrospective study, we collected 54 pediatric papillary thyroid cancer patients with cN0 stage cancer who were treated from January 2014 to January 2021 at the National Cancer Hospital (a high-volume thyroid surgery center in Vietnam with 1500-1800 thyroid surgeries in adults and 20-30 operations for thyroid cancer in children annually). The study was conducted after obtaining informed consent from patients and their parents in compliance with ethical guidelines. This study was approved by the institution's ethics committee and research board.

Patient selection criteria: pediatric PTC patients (≤ 18 years of age) who had no neck lymph node metastases (cN0), as shown by both ultrasonography and clinical examination; a pathology finding after surgery of PTC: total thyroidectomy and prophylactic CND on children with stage cT3-4N0M0 PTC or bilateral tumors; total thyroidectomy or lobectomy plus isthmusectomy with or without prophylactic central cervical lymph node dissection on children with unilateral PTC at stage cT1-2N0M0.

Patient exclusion criteria: patients with distant metastases, recurrence, or a history of previous thyroid surgery.

Objectives

The aim of this study was to evaluate the role of prophylactic CND in managing pediatric PTC, especially in respect of recurrence of the disease. We also investigated the safety of prophylactic CND, specifically, postoperative complications related to the treatment.

Treatment

Before surgery: initial evaluation of children with PTC included a detailed clinical examination, neck ultrasound, laryngoscopy to examine the function of the vocal cords, blood tests (TSH, FT4) to evaluate thyroid gland activity, and serum Tg and anti-Tg. All the children underwent fine-needle aspiration biopsy which revealed PTC. A neck ultrasound scan was performed by two experienced radiologists to confirm that there were no neck lymph node metastases.

Surgery: all the children were operated on by the same high-volume surgical team.

Post-operative treatment: radioactive iodine (RAI) therapy was used, based on the American Thyroid Association's treatment guidelines and the results of Multidisciplinary Thyroid Meeting consultations at our hospital.[1] The dose of RAI therapy for children is 1 mCi/kg body weight.

Follow-up

Transient hypoparathyroidism was defined as a serum calcium concentration below 8 mg/dL or when patients had symptomatic hypocalcemia less than 6 months after surgery. Patients who had hypocalcemia after more than 6 months were classified as having permanent hypoparathyroidism. Transient recurrent laryngeal nerve injury was confirmed by a laryngoscopic diagnosis after surgery and when both vocal cord functions recovered fully within 6 months of surgery. Children were classified as having permanent recurrent laryngeal nerve injury if these findings persisted beyond 6 months.

Clinical examination, neck ultrasound, and biochemical assessment (serum Tg and anti-Tg) were performed on the children every three months for the first two years, every six months up to five years, and then once a year. After RAI treatment, TSH-stimulated Tg and whole-body iodine scans were used to evaluate the effectiveness of the therapy.

The post-treatment response was evaluated according to the American Thyroid Association guidelines for children with PTC published in 2016 (1). Disease-free survival (DFS) is defined as the time interval from initial therapy to detection of recurrent PTC. Local recurrence is defined as evidence of PTC in the neck region detected by imaging (CT, MRI, PET/CT, etc.) and confirmed by fine-needle aspiration biopsy. Distant metastasis is defined as PTC identified outside the neck by an imaging study (CT, PET, whole-body iodine scan, etc.) or biopsy. Serum shTSH-stimulated Tg or unstimulated Tg and anti-Tg were assessed to assist in diagnosing distant metastatic disease.

Statistical Analysis

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) version 25.0 (IBM Corp. IMB SPSS Statistics, Armonk, NY). Results of continuous variables are expressed as mean ± SD (min, max) and for categorical variables as absolute numbers or percentages. When comparing categorical data, the χ^2 test or, if deemed appropriate, Fisher's exact test were used, while the T-test was used to compare continuous data. Factors associated with recurrent disease were examined by univariate Cox analysis. A p-value of less than 0.05 was considered significant.

RESULTS

Of the 54 patients in our study, the majority were female (accounting for 77.8%) and aged 15 years or older (accounting for 79.6%). None of the patients had any family history of cancer or prior neck radiation therapy. The average tumor size was 15.9 ± 7.8 mm (4 - 35 mm). Most tumors were over 10 mm (72.2%) and TIRADS 5 (75.9%). Only five patients had multifocal cancer, and seven had an extrathyroid extension. Stage T1a, T1b, T2, T3b accounted for 27.8%, 33.3%, 25.9%, and 13.0%, respectively. Of the 54 patients, 38.9% underwent lobectomy plus isthmusectomy and 61.1% underwent total thyroidectomy **Table 1**.

TABLE 1 | Clinicopathological features of cN0 papillary thyroid cancer in children.

Features	Distributions (n=54), %
Gender, n (%)	
Female	42 (77.8)
Male	12 (22.2)
Age, mean (SD)[a]	16.0 ± 2.5
< 15	11 (20.4)
≥ 15	43 (79.6)
History, n (%)	
Previous radiation exposure	0 (0)
Normal	54 (100)
Tumor size (mm)	
Mean ± SD: 15.9 ± 7.8 (4 – 35)	
≤ 10 mm	15 (27.8)
> 10 mm	39 (72.2)
Location, n (%)	
Right lobe	28 (51.9)
Left lobe	23 (42.6)
Both lobes	3 (5.5)
Multifocality, n (%)	
Uni focus	49 (90.7)
Multi foci	5 (9.3)
TIRADS, n (%)	
TIRADS 4	13 (24.1)
TIRADS 5	41(75.9)
Extrathyroidal extension, n (%)	
Yes	7 (13.0)
No	47 (87.0)
Primary tumor (T), n (%)	
T1a	15 (27.8)
T1b	18 (33.3)
T2	14 (25.9)
T3b	7 (13.0)
Regional lymph nodes (N), n (%)	
N0	27 (50.0)
N1a	27 (50.0)
Distant metastasis (M), n (%)	
Yes (Lung)	0 (0)
No	54 (100)
Type of thyroidectomy, n (%)	
Lobectomy	21 (38.9)
Total thyroidectomy	33 (61.1)
Radioactive Iodine, n (%)	
Yes	28 (51.9)
No	26 (48.1)
Prophylactic central neck dissection, n (%)	
Yes	35 (64.8)
No	19 (35.2)

[a]*SD, standard deviation.*

Patients were divided into two groups based on the status of prophylactic CND. Of the 54 cN0 patients, 35 underwent prophylactic CND (prophylactic CND group) (accounting for 64.8%) and 19 patients did not undergo prophylactic CND (no-prophylactic CND group, accounting for 35.2%). The two groups were similar in clinical and pathologic features, such as age, gender, tumor size, multifocal status, and follow-up time. However, extrathyroidal extension, total thyroidectomy, RAI treatment, and central lymph node metastasis were significantly more frequent in the prophylactic group (**Table 2**). RAI therapy was indicated significantly more often in the prophylactic group (68.6% vs 21.1%, p=0.001). Furthermore, the patients who underwent prophylactic CND had significantly lower rates of recurrence than the no-prophylactic CND group at the same follow-up time (2.9% vs 31.6%, $p < 0.006$).

Recurrence

There was no significant difference in follow-up time between the two groups (71.7 ± 10.6 months vs 71.3 ± 15.3 months, $p = 0.905$). Of the 54 patients, seven patients had locoregional recurrence within the follow-up time. Of these, all had central lymph node metastasis. In addition, only two patients were found to have lateral compartment as well as central compartment recurrence. The average DFS was 84.4 ± 2.7 months **Figure 1**. Log-rank tests on Kaplan-Meier curves revealed that age, gender, tumor size, multifocality, and extrathyroid extension did not relate to DFS time. Univariate analysis showed that DFS time was not affected by the extent of thyroidectomy or RAI treatment (**Table 3**). Both univariate analysis and multivariate analysis show that prophylactic CND increased DFS time for pediatric patients with cN0 PTC (**Tables 3**, **4**). Kaplan Meier curves show that patients who underwent prophylactic CND had a significantly better DFS than those who did not ($p = 0.03$; **Figure 2**).

Safety of Prophylactic CND

To determine the effectiveness of prophylactic CND, associated complications were analyzed. Hypoparathyroidism and recurrent laryngeal nerve injury are two major consequences of thyroid surgery that have a negative impact on a child's quality of life. There was no statistically significant difference in complications between the prophylactic CND group and the no-prophylactic CND group in terms of temporary hypoparathyroidism (20% vs 5.3%, $p = 0.145$), temporary recurrent laryngeal nerve injury (20% vs 10.5%, $p = 0.372$), postoperative bleeding, permanent hypoparathyroidism, or permanent recurrent laryngeal nerve injury (**Table 5**).

DISCUSSION

The rate of Central Lymph Node Metastasis in Pediatric Patients With cN0 PTC Undergoing Prophylactic CND

In our study, 35 pediatric patients with cN0 PTC underwent prophylactic CND. Of these, 27 patients were found to have central lymph node metastasis, accounting for 77.1%. The rate of

TABLE 2 | Clinicopathological features according to prophylactic central neck dissection.

Variables	Prophylactic CND (n=35)	No prophylactic CND (n=19)	P-value
Age (years)			
< 15	7 (20%)	4 (21.1%)	p = 0.927
≥ 15	28 (80%)	15 (78.9%)	
Gender, n (%)			
Female	26 (74.3%)	16 (84.2%)	p = 0.402
Male	9 (25.7%)	3 (15.8%)	
Tumor size, n (%)			
≤ 10 mm	7 (20%)	2 (10.5%)	p = 0.372
> 10 mm	28 (80%)	17 (89.5%)	
Mutifocality, n (%)			
Uni focus	32 (91.4%)	17 (89.5%)	p = 0.813
Multi foci	3 (8.6%)	2 (10.5%)	
Extrathyroidal extension, n (%)			
Yes	7 (20%)	0 (0%)	p = 0.037
No	28 (80%)	19 (100%)	
Type of thyroidectomy, n (%)			
Lobectomy	5 (14.3%)	16 (84.2%)	p < 0.001
Total thyroidectomy	30 (85.7%)	3 (15.8%)	
Regional lymph nodes (N), n (%)			
N0	8 (22.9%)	19 (100%)	p < 0.001
N1a	27 (77.1%)	0 (0%)	
Radioactive Iodine, n (%)			
Yes	24 (68.6%)	4 (21.1%)	p = 0.001
No	11 (31.4%)	15 (78.9%)	
Follow-up, months	71.7 ± 10.6	71.3 ± 15.3	p = 0.905
Recurrent disease, n (%)			
Yes	1 (2.9%)	6 (31.6%)	p = 0.006
No	34 (97.1%)	13 (68.4%)	

CND, central neck dissection.

central lymph node metastasis in children with the cN0 disease has been shown to be higher than in other age groups (9). In a meta-analysis of 17 studies, Hughes et al. found the rate in other age groups to be approximately 50% (10). In a meta-analysis of 31 studies involving 37,355 patients with cN0 PTC in various age groups, the rate of central lymph node metastasis was reported as 26.4% (11). Thus, the rate of central lymph node metastasis in cN0 pediatric patients is extremely high, which may suggest that prophylactic CND is beneficial in the treatment of PTC in children.

Disease-Free Survival and Prophylactic CND

Despite more widespread disease at discovery compared to adults, children with thyroid cancer have higher survival rates, even in those with distant metastasis or recurrent disease. In follow-up, seven patients (13.0%) experienced recurrence in cervical lymph

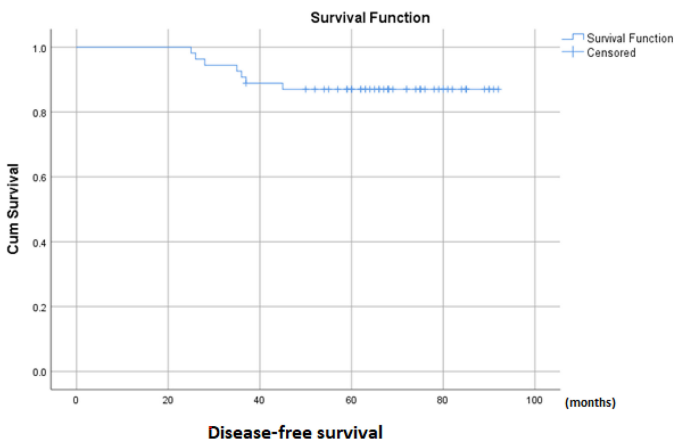


FIGURE 1 | Kaplan–Meier curves estimating disease-free survival of pediatric cN0 papillary thyroid cancer.

TABLE 3 | Univariate analysis of risk factors for recurrence in pediatric patients.

Variables	P value
Age (years)	p = 0.596
Gender	p = 0.699
Tumor size ≤ 10 mm	p = 0.219
Mutifocality	p = 0.382
Extrathyroidal extension	p = 0.858
Type of thyroidectomy	p = 0.069
Radioactive Iodine	p = 0.214
Prophylactic central neck dissection	p = 0.003

TABLE 4 | Multivariate analysis of risk factors for recurrence in pediatric patients.

Variables	P value
Type of thyroidectomy	p = 0.693
Radioactive Iodine	p = 0.815
Prophylactic central neck dissection	p = 0.035

nodes but had no distant metastases. Total thyroidectomy (if not already removed), cervical lymphadenectomy, and iodine 131 therapy were performed on these patients. Kaplan Meier curves show that the DFS time was 84.4 ± 2.7 months, and the 3-year and 5-year DFS rates were 89% and 87%, respectively..

Most studies report recurrence rates of 20% to 40% 10 years after initial treatment of the disease (5, 12–15). Mechteld et al. found that 72 children with DTC (<18 years) who were treated at a single institution between 2003 and 2018 had a median DFS time of 36.7 months, with a 1-year recurrence-free survival (RFS) rate of 93% and a 5-year RFS of 87% (16). A national multicenter retrospective review of 250 pediatric patients treated for PTC in Italy with an average follow-up of 5.8 years found that the rate of recurrent disease was 12% (30/250). Of the 30 recurrent patients, 12 experienced recurrence in the first year and eight in the second year. The main location of recurrence was the cervical lymph nodes (accounting for 56.7%), followed by lung metastases (23.3%), and the thyroid bed (20%) (14).

The utility of prophylactic CND in children with PTC is uncertain. The increased incidence of central cervical metastasis in pediatric patients suggests that prophylactic CND should be considered at the time of initial surgery for children with PTC. On the other hand, lymph node dissection increases complications that negatively affect quality of life, especially in children. Thus, a balance has to be found between the advantages and disadvantages of prophylactic CND in the treatment of PTC in children.

Age, gender, tumor size, multifocality, extrathyroid extension, extent of thyroidectomy and RAI treatment were found not to be related to RFS rates. Importantly, pediatric patients who underwent prophylactic CND show significantly better RFS rates. Moreover, prophylactic CND allows for more accurate staging of the tumor, ensuring better assessment of the N status. The rate of central lymph node metastasis was significantly higher in the prophylactic CND group than in the other group, but more patients underwent RAI therapy after surgery in the prophylactic CND group (p=0.001). However, DFS time was not affected by RAI treatment.

Complications

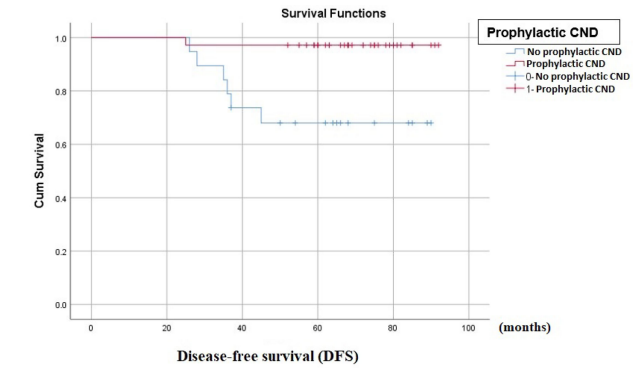
Multiple studies have established that complication rates after pediatric thyroidectomy are higher than after similar surgery in adult patients. Because pediatric patients generally have an excellent life expectancy, even in the setting of advanced disease, they are at risk of enduring the long-term effects of these complications, particularly those involving calcium metabolism and airway compromise. According to current guidelines for the treatment of thyroid cancer, pediatric thyroid surgery should ideally be performed by high-volume surgeons. In our hospital, a high-volume thyroid surgery center in Vietnam with 1500-1800 thyroid surgeries in adults and 20-30 operations for thyroid cancer in children annually, the rate of postoperative complications is low. The most common complications after thyroidectomy are hypoparathyroidism and vocal fold paralysis. Our results show that the rate of temporary hypoparathyroidism is 14.8%, and there were no cases of permanent hypoparathyroidism. Also, 16.7% of the cases exhibited temporary recurrent laryngeal nerve damage, but there were no cases of permanent recurrent laryngeal nerve damage. In our high-volume center, the proportion of complications is lower than in other surgery centers. Mechteld et al. found a rate of hypocalcemia of 37.5%, with long-term hypoparathyroidism persisting in 18 patients (25.0%) (16). In a 21-year study of 184 PTC patients, transient and permanent hypoparathyroidism occurred in 33.1% and 3.3% of cases, respectively (17).

More importantly, there is no statistically significant difference in complications between the prophylactic CND group and the no-prophylactic CND group in terms of temporary hypoparathyroidism (20% vs 5.3%, p = 0.145), temporary recurrent laryngeal nerve injury (20% vs 10.5%, p = 0.372), postoperative bleeding, permanent hypoparathyroidism, or permanent recurrent laryngeal nerve injury.

This study had some limitations. First, this was a single center, retrospective study. Second, the number of pediatric patients with cN0 was small. Patients were not randomized, and groups were not equal in risk, as PTC is a rare disease that more commonly presents at an advanced stage with cervical lymph node metastasis. Third, the prognosis is excellent in children and recurrences can appear up to 10 years after treatment; thus, additional long-term follow-up would be needed to confirm these findings. These limitations need to be addressed in the future. Nonetheless, this was the first article reporting the role of prophylactic CND in the management of cN0 PTC in children, to the best of our knowledge. All patients had undergone high-volume thyroid surgery, and complications can be minimized to improve the treatment of thyroid cancer, especially in pediatric patients.

CONCLUSION

In summary, prophylactic CND was found to be associated with increased DFS but not with increased rates of complications after surgery. To the best of our knowledge, this is the first article reporting the role of prophylactic CND in the management of



Features	DFS, months	p
Prophylactic CND	90.1 ± 1.9	**p = 0.003**
No prophylactic CND	72.3 ± 6.0	

CND, central neck dissection

FIGURE 2 | Kaplan–Meier curves estimating disease-free survival according to surgical procedure.

TABLE 5 | Postoperative complications for patients with cN0 pediatric thyroid carcinoma.

Postoperative complications	Prophylactic CND n, (%)	No prophylactic CND n, %	p, Univariable Model OR (95% CI)
Transient hypocalcemia	7 (20%)	1 (5.3%)	p = 0.145
Permanent hypocalcemia	0	0	N/A
Transient RLN injury	7 (20%)	2 (10.5%)	p = 0.372
Permanent RLN injury	0	0	N/A
Postoperative bleeding	0	0	N/A

CND, central neck dissection; RLN, recurrent laryngeal nerve.

cN0 PTC in children. However, larger sample size studies with long-term follow-up are needed to explore further the role of prophylactic CND in treating pediatric patients with PTC.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available. Requests to access the datasets should be directed to duyyhn@gmail.com.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Vietnam National Cancer Hospital's ethics committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

DN: study design, performance of the study, data collection, statistical analysis, interpretation, and manuscript writing. DN, DL: data analysis and interpretation. DL performance of the study and data collection. DN, DL, and QL: performance of the study. All authors participated in the critical review and approval of the final manuscript.

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Clinical application of parathyroid autotransplantation in endoscopic radical resection of thyroid carcinoma

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Purpose: This study aimed to examine the effect of selective inferior parathyroid gland autotransplantation on central lymph node dissection (CLND) and incidence of postoperative hypoparathyroidism in patients undergoing endoscopic radical resection of thyroid carcinoma.

Methods: The data of 310 patients undergoing endoscopic radical resection of thyroid carcinoma will be retrospectively analyzed. The patients will be divided into the experimental group and the control group according to whether they combined with parathyroid autotransplantation. Statistics of the incidence rate of postoperative hypoparathyroidism, the concentration of PTH and Calcium in the systemic circulation at different time points in the two groups, the concentration of PTH in the cubital fossa vein in the transplantation region in the experimental group, and the number of central lymph nodes and positive lymph nodes dissection will be carried out.

Results: The incidence rate of temporary and permanent hypoparathyroidism in the experimental group was 33.75% and 0.625%, respectively, and in the control group was 22% and 5%, respectively; its difference was statistically significant (X^2 = 10.255, P=0.006). Parathyroid autotransplantation increased incidence of transient hypoparathyroidism (OR, 1.806; CI, 1.088-2.998; P=0.022), and lower incidence of permanent hypoparathyroidism (OR, 0.112; CI, 0.014-0.904; P=0.040). The diameters of thyroid cancer nodules was not associated with the occurrence of transient hypoparathyroidism (OR, 0.769; CI, 0.467-1.265; P=0.301) or permanent hypoparathyroidism (OR, 1.434; CI, 0.316-6.515; P=0.641). Comparison of systemic circulation PTH, between the two groups showed that the PTH of patients in the experimental group was higher than that in the control group from 1 week to 12 months after the operation, and the difference was statistically significant (P<0.05). In the experimental group, from 1 week to 12 months after surgery, PTH concentrations was significantly higher in the cubital fossa of the transplantation side than in the contralateral side, and the differences were statistically significant (P<0.05). The mean number of central lymph node dissected per patient was significantly higher in the experimental group (7.94 ±

3.03 vs. 6.99 ± 2.86; P <0.05); The mean number of positive nodes per patient was significantly higher in the experimental group (3.16 ± 1.86 vs. 2.53 ± 1.59; P <0.05).

Conclusions: In endoscopic radical resection of thyroid carcinoma, parathyroid autotransplantation is more beneficial to postoperative parathyroid glands function recovery, effectively preventing postoperative permanent hypoparathyroidism and realizing more thorough CLND.

KEYWORDS

endoscopic radical resection of thyroid carcinoma, parathyroid autotransplantation, transient hypoparathyroidism, permanent hypoparathyroidism, central lymph node dissection

Introduction

Thyroid cancer is the most common malignant tumor of the endocrine system. Its incidence has been increasing in recent years (1, 2). Bilateral thyroidectomy combined with CLND is a common surgical treatment approach (3). Because of standardization of thyroid disease diagnosis and treatment and an increasing demand for better cosmetic outcomes, more patients and surgeons are selecting endoscopic radical resection, which has become one of the primary surgical methods for thyroid cancer (4, 5). However, this operation is associated with a high risk of parathyroid gland injury. Hypoparathyroidism resulting from damage to the parathyroid gland blood supply or inadvertent parathyroid gland removal can occur, even when the procedure is performed by an experienced specialist (6). Distinguishing the inferior parathyroid glands from enlarged lymph nodes is challenging (7). Retention of the inferior parathyroid glands may limit the extent of thyroidectomy and the thoroughness of CLND, which can lead to postoperative recurrence and metastasis (8). Although in situ gland preservation is one option to preserve parathyroid function, selective inferior gland autotransplantation is another for cases in which the gland is damaged or removed (9). In such cases, we try to preserve all parathyroid glands in situ whenever possible, and when the inferior parathyroid glands are incorrectly incised intraoperatively or when the surgeon judges that their blood supply is impaired, we will selectively transplant one of the inferior parathyroid glands to the non-dominant forearm brachioradialis muscle, leaving the rest of the parathyroid glands in situ, and assess postoperative graft survival by measuring parathyroid hormone (PTH) concentration in venous blood obtained from cubital fossa veins (10, 11). This study aimed to examine the effect of selective inferior parathyroid gland autotransplantation on lymph node dissection and incidence of postoperative hypoparathyroidism in patients undergoing endoscopic radical resection of thyroid carcinoma.

Method

Patients

The medical records of all patients who underwent endoscopic radical resection of thyroid carcinoma at Gansu Provincial People's Hospital from January 2019 to April 2021 were reviewed. All patients underwent preoperative neck ultrasonography, computed tomography, or examination of fine needle aspiration cytology that was consistent with American Thyroid Association (ATA) guidelines for the diagnosis of papillary thyroid carcinoma (PTC) (12). Diagnoses were confirmed by histopathological examination of the surgical specimen. Endoscopic bilateral thyroidectomy was performed for confirmed PTC larger than 1 cm, or older age (>45 years), or with gross extrathyroidal extension, or bilateral foci, or lymph node metastasis, or distant metastasis. We excluded patients with incomplete data, abnormal preoperative parathyroid hormone or calcium concentrations, liver or kidney dysfunction, or a history of neck surgery or radiation therapy. We also excluded those who underwent lateral neck dissection and patients who did not follow up regularly. Patients who underwent endoscopic radical resection of thyroid carcinoma and parathyroid auto transplantation were considered the experimental group. Those who underwent endoscopic radical resection alone were considered the control group.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Gansu Provincial People's Hospital (No.2022-195). All patients provided written informed consent.

Operation methods

A single surgical team performed all operations. Endoscopic bilateral thyroidectomy and CLND using the complete areola

approach were performed. After exposing the thyroid lobes unilaterally, 0.2 mL of a suspension of nano-sized carbon particles was injected percutaneously into the gland (13): the thyroid gland stains black, while the parathyroid gland does not (Figure 1). The trachea and recurrent laryngeal nerve were then carefully dissected and the lobes of the thyroid were removed (Figure 2). The procedure was repeated contralaterally was performed. For papillary thyroid carcinoma, preventive CLND is routinely performed. (Figure 3). Number of central lymph nodes dissected and number of positive lymph nodes were counted. The diameters of thyroid cancer nodules in the two groups after surgery were counted (the diameter of the largest nodule was evaluated in patients with more than one nodule. In the presence of more than one nodule located side by side, the total diameter of the nodules was evaluated.), with 1 cm as the boundary, and the number of patients with thyroid cancer nodules < 1 cm and ≥ 1 cm were counted respectively.

The superior parathyroid gland is always preserved in situ during surgery, and the inferior parathyroid glands is preserved in situ whenever possible. All parathyroid in situ preservation surgery was used as the control group, and the operation in which the inferior parathyroid gland was incised by mistake or the blood supply was damaged and could not be preserved in situ was set as the experimental group. The surgeon determines the in situ viability of the inferior parathyroid glands and selectively transplants one of the inferior parathyroid gland, this condition is called selective parathyroid autotransplantation. Damaged glands or those removed by mistake were placed in a beaker. After injection of 1 mL 0.9% sodium chloride solution was injected into the tissue, it was cut into pieces and homogenized. The PTH immune gold technique (14) was used to confirm parathyroid tissue. The gland suspension was then implanted into the brachioradialis muscle of the non-dominant forearm via injection (Figure 4).

Postoperative protocol

After the operation, calcium and calcitriol supplements were administered (15) and systemic PTH and calcium concentrations were measured. If both were in the normal range (PTH, 16–88 pg/mL; calcium, 2.11–2.52 mmol/L), calcium supplementation was ceased. Hypoparathyroidism was defined as PTH <16 pg/mL or calcium <2.11 mmol/L. Permanent hypoparathyroidism was defined as hypoparathyroidism that persisted >6 months after surgery. According to the 2015 American Thyroid Association (ATA) guidelines (12), Routinely reviewing serum thyroglobulin (Tg), serum thyroglobulin antibodies (Tg-ab) (serum Tg and Tg-ab should be assessed longitudinally in the same laboratory and using the same assay for a given patient)and neck ultrasound after the operation to assess the risk of postoperative disease recurrence. Systemic PTH and calcium concentration were measured before and 1 day, 1 week, 1 month, 3 months, 6 months, and 12 months after surgery. In the experimental group, PTH concentration was measured in venous blood sampled from a cubital fossa vein adjacent to the transplantation site before and 1 day, 1 week, 1 month, 3 months, 6 months, and 12 months after surgery. These measurements were compared with those taken from the cubital fossa contralateral to the parathyroid transplantation site.

Statistical analysis

Statistical analyses were performed using SPSS software version 22.0 (IBM Corp., Armonk, NY, USA). Categorical data are expressed as numbers with percentage and were compared using the chi-square or Fisher's exact test. Continuous data with a normal or near-normal distribution are expressed as means

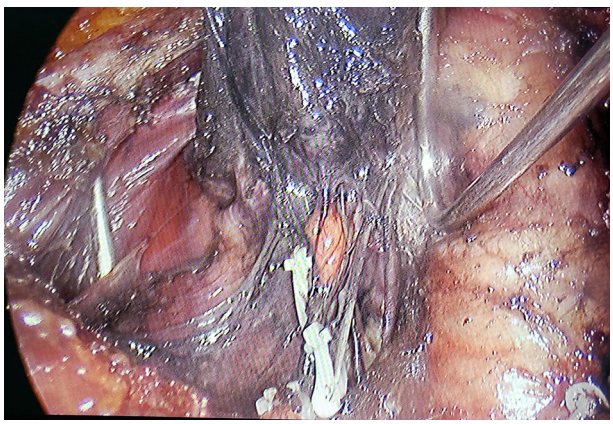

FIGURE 1
"Negative imaging" of parathyroid glands.

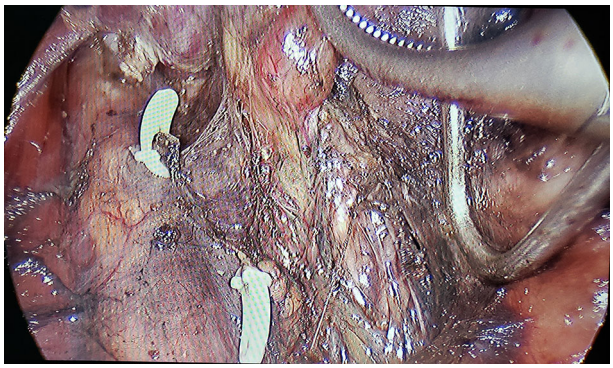

FIGURE 2
Trachea, nerve, blood vessel, parathyroid, imaging.

with standard deviation and were compared using the independent sample t test or corrected t test, depending on group variance. Risk factors for transient and permanent hypoparathyroidism were identified using logistic regression with results presented as odds ratios (ORs) with 95% confidence interval (CI). P <0.05 was considered significant.

Results

General data

In total, 310 patients were included for analysis, 160 in the experimental group and 150 in the control group. The experimental group included 21 men and 139 women with mean age 43.68 ± 10.48 years (range, 22–77). In the control group, 26 were men and 124 were women; mean age was 43.01 ± 11.33 years (range, 20–72). As shown in Table 1, patient characteristics did not significantly differ between the groups.

Hypoparathyroidism data

A total of 55 patients in the experimental group developed hypoparathyroidism: 54 cases (33.75%) were transient and one (0.625%) was permanent. The single permanent hypoparathyroidism patient recovered normalized PTH secretion 12 months after surgery. In the control group, 39 patients developed hypoparathyroidism: 33 cases (22%) were transient and 8 cases (5%) were permanent. Four of the Eight permanent cases recovered normal PTH secretion 12 months after surgery. The incidence of transient hypoparathyroidism was higher in the experimental group than in the control group; however, the incidence of permanent hypoparathyroidism was higher in the control group. The difference between groups was significant (X2 = 10.255; P = 0.006; Table 1). In univariate analysis, parathyroid autotransplantation increased incidence of transient hypoparathyroidism (OR,1.806;Cl,1.088-2.998; P=0.022),and lower incidence of permanent hypoparathyroidism (OR,0.112;Cl,0.014-0.904;P=0.040) (Table 2).

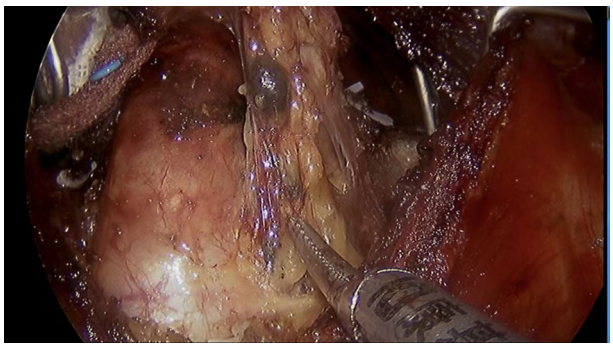

FIGURE 3
Black-stained central lymph node.

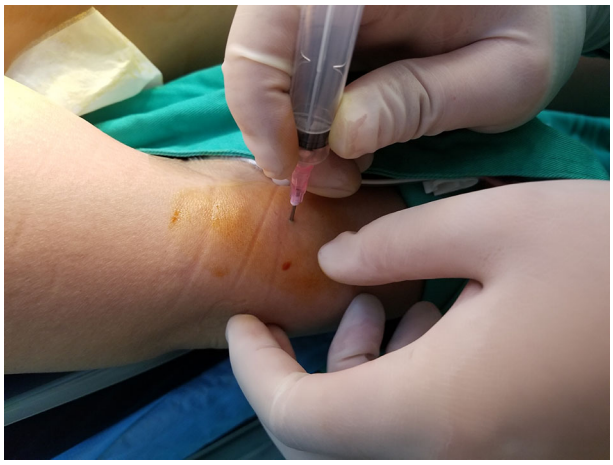

FIGURE 4
Forearm brachioradialis muscle by homogenate injection.

TABLE 1 General data, surgical biochemical data and postoperative pathology of patients.

Grouping	Experimental group	Control Group	t/X^2	P
Age	43.68 ± 10.48	43.01 ± 11.33	T = 0.534	0.594
Gender			X^2 = 1.066	0.302
Male	21 (13.13%)	26 (17.33%)		
Female	139 (86.87%)	124 (82.67%)		
Hypoparathyroidism after operation			X^2 = 10.255	0.006
Transient hypoparathyroidism	54 (33.75%)	33 (22%)		
Permanent hypoparathyroidism	1 (0.625%)	8 (5%)		
PTH (pg/mL, $\bar{X}$ ± S)				
Per	58.67 ± 12.33	57.35 ± 11.28	T = 0.978	0.329
Post 1 day	19.05 ± 6.05	19.48 ± 6.12	T = 0.622	0.535
Post 1 week	24.59 ± 6.68	20.06 ± 6.12	T = 6.211	0.000
Post 1 month	37.71 ± 13.32	28.87 ± 9.36	T = 6.787	0.000
Post 3 months	47.76 ± 13.71	34.03 ± 10.01	T = 10.110	0.000
Post 6 months	48.80 ± 13.35	37.55 ± 9.81	T = 8.490	0.000
Post 12 months	49.73 ± 14.76	39.65 ± 9.78	T = 7.127	0.000
Ca^{2+} (mmol/L, $\bar{X}$ ± S)				
Per	2.33 ± 0.09	2.32 ± 0.08	T = 0.343	0.732
Post 1 day	2.16 ± 0.11	2.14 ± 0.07	T = 1.871	0.062
Post 1 week	2.17 ± 0.05	2.16 ± 0.05	T = 1.426	0.155
Post 1 month	2.23 ± 0.06	2.20 ± 0.07	T = 4.953	0.000
Post 3 months	2.26 ± 0.06	2.23 ± 0.06	T = 4.862	0.000
Post 6 months	2.32 ± 0.06	2.26 ± 0.08	T = 6.421	0.000
Post 12 months	2.32 ± 0.06	2.29 ± 0.08	T = 3.804	0.000
The diameters of thyroid cancer nodules	0.94 ± 0.41	0.91 ± 0.43	T = 0.529	0.597
Lymph nodes dissection				
Number of central lymph nodes dissection	7.94 ± 3.03	6.99 ± 2.86	T = 2.833	0.005
Number of positive lymph nodes	3.16 ± 1.86	2.53 ± 1.59	T = 3.160	0.002

Note: Per, per-operative; Post, post-operative.

Systemic PTH and calcium concentrations before and after surgery

Systemic PTH concentration did not significantly differ between the groups before surgery. After surgery, PTH concentration was significantly higher in the experimental group, except on day 1 (Table 1). In the experimental group, PTH concentration significantly differed between before surgery and 1 day after, 1 day and 1 week after, 1 week and 1 month after, and 1 month and 3 months after surgery($P<0.05$); the concentration did not significantly differ between 3 months and 6 months after surgery($P>0.05$). In the control group, PTH concentration did not significantly differ between 6 months and 12 months after surgery($P<0.05$) (Table 3). Six months after surgery, PTH secretion in the experimental and control groups had recovered to 83.16% and 65.48% of preoperative baseline, respectively.

Systemic calcium concentration did not significantly differ between the groups before surgery. After surgery, calcium concentration was significantly higher in the experimental group, except on day 1 and week 1 (Table 1).

Postoperative specimens

In the experimental and control groups, the number of central lymph nodes dissected was 1271 and 1049, respectively. The mean number of central lymph node dissected per patient was significantly higher in the experimental group (7.94 ± 3.03 vs. 6.99 ± 2.86; $P<0.05$). The number of positive lymph nodes in the experimental and control groups was 505 and 380, respectively. The mean number of positive nodes per patient was significantly higher in the experimental group (3.16 ± 1.86 vs. 2.53 ± 1.59; $P<0.05$; Table 1). The average diameter of thyroid cancer nodules in the experimental group was (0.94 ± 0.41) cm, and that in the control group was (0.91 ± 0.43) cm. There wasdid not significantly differ in the average diameter of thyroid cancer nodules between the two groups ($P>0.05$) (Table 1). There were 150 patients with the diameters of thyroid cancer nodules ≥1cm in the two groups, 38 patients had transient hypoparathyroidism after surgery, and 4 patients had permanent hypoparathyroidism. There were 160 cases of the diameters of thyroid cancer nodules <1cm, 49 cases of transient hypoparathyroidism after operation, 3 cases of permanent hypoparathyroidism. In univariate analysis, The diameters of thyroid cancer nodules was not associated with the occurrence of transient hypoparathyroidism (OR, 0.769; Cl, 0.467-1.265; $P=0.301$) or permanent hypoparathyroidism (OR, 1.434; Cl, 0.316-6.515; $P=0.641$) (Table 4).

Postoperative cubital fossa venous PTH concentration in the experimental group

In the experimental group, cubital fossa venous blood PTH concentration did not significantly differ between the transplantation side and the contralateral side 1 day after surgery ($P>0.05$). From 1 week to 12 months after surgery, serum PTH in the transplantation region was significantly higher than that in the non-transplantation region, and the differences were statistically significant ($P<0.05$). PTH concentration increased in both the transplantation and contralateral sides as time progressed to a peak at 6 months; then, the concentration began to decline (Table 5).

Discussion

Hypoparathyroidism is a common complication of endoscopic radical resection of thyroid carcinoma (16) and may be transient or permanent. In the former, transient hypocalcemia is treated using calcium supplementation and patient quality of life is not significantly affected. The latter causes permanent hypocalcemia, which may lead to abnormal calcification in the brain, kidney, eyes, blood vessels, and other systems (17, 18), which will seriously increase patients' disease and economic burden. The incidence of hypoparathyroidism after thyroid surgery varies considerably (19). Reported incidence rates of transient hypoparathyroidism range from 5.49% to 67.69%; those for permanent hypoparathyroidism range from 0% to 20% (16, 20, 21). This problem is caused by a number of factors (22, 23), one of which is that the definition of the timing of hypoparathyroidism is still being explored. The guidelines of the European Society of Endocrinology (24) and the ATA (25) define permanent hypoparathyroidism as a low PTH concentration 6 months after surgery. However, Kim et al. (26) showed that some patients diagnosed with permanent hypoparathyroidism eventually recover normal PTH secretion. Qiu et al. (27) found that 45.2% of patients were misdiagnosed with permanent hypoparathyroidism when 6 months was used as the cutoff point to define permanence. In our study, the one

TABLE 2 Parathyroid autotransplantation and risk of hypoparathyroidism.

Grouping	Experimental group	Control Group	OR (95%Cl)	P
Transient hypoparathyroidism	54 (33.75%)	33 (22%)	1.806 (1.088-2.998)	0.022
Permanent hypoparathyroidism	1 (0.625%)	8 (5%)	0.112 (0.014-0.904)	0.040

TABLE 3 Comparing the PTH between the two time points of the same group(pg/mL, X±S)

time point	Experimental group			Control Group		
	PTH	T	P	PTH	T	P
Per VS Post 1 day	(58.67 ± 12.33) VS (19.05 ± 6.05)	36.479	0.000	(57.35 ± 11.28) VS (19.48 ± 6.12)	36.131	0.000
Post 1 day VS Post 1 week	(19.05 ± 6.05) VS (24.59 ± 6.68)	7.772	0.000	(19.48 ± 6.12) VS (20.06 ± 6.12)	0.821	0.412
Post 1 week VS Post 1 month	(24.59 ± 6.68) VS (37.71 ± 13.32)	11.133	0.000	(20.06 ± 6.12) VS (28.87 ± 9.36)	9.654	0.000
Post 1 month VS Post 3 months	(37.71 ± 13.32) VS (47.76 ± 13.71)	6.650	0.000	(28.87 ± 9.36) VS (34.03 ± 10.01)	4.611	0.000
Post 3 months VS Post 6 months	(47.76 ± 13.71) VS (48.80 ± 13.35)	0.690	0.491	(34.03 ± 10.01) VS (37.55 ± 9.81)	3.076	0.002
Post 6 months VS Post 12 months	(48.80 ± 13.35) VS (49.73 ± 14.76)	0.588	0.557	(37.55 ± 9.81) VS (39.65 ± 9.78)	1.851	0.065

Note: Per, per-operative; Post, post-operative.

patient (100%) in the experimental group who developed permanent hypoparathyroidism eventually recovered normal PTH secretion 12 months after surgery. In the control group, four of the eight patients who developed it (50%) recovered normal secretory function at 12 months. The reason for the difference in functional recovery between groups is probably related to the lower surface area of the transplanted gland compared with the in situ gland: the angiogenic response to establish gland perfusion is more robust and rapid for a gland with lower surface area (28). Parathyroid glands' surface area in the transplantation region was lesser, which was more likely to occur angiogenic reactions with surrounding tissues, realizing the reconstruction of the blood supply system. However, in-situ reserved parathyroid glands in the control group did not have a normal secretory function, their body surface area was larger, and the angiogenesis was slower, so the parathyroid glands' function recovered in the control group was more complicated than that in the experimental group. Previous studies have shown that parathyroid functional recovery is a dynamic process that may occur over a long period after thyroid surgery (29).

There is a general consensus that parathyroid autotransplantation during thyroidectomy increases the risk of transient hypoparathyroidism, but the effect on permanent hypoparathyroidism remains unclear. This is the main controversy of whether to perform parathyroid autotransplantation in thyroidectomy. Ahmed et al. (30) proposed that autologous parathyroid transplantation is the preferred method to ensure good parathyroid function and recommended routine transplantation. Qiu et al. (31) concluded that parathyroid autotransplantation is an independent risk factor for transient hypoparathyroidism but a preventive factor for permanent hypoparathyroidism and recommended selective parathyroid autotransplantation. Su et al. (32) found that parathyroid autotransplantation during thyroidectomy was not associated with the development of permanent postoperative hypoparathyroidism, so it is recommended that parathyroid glands be preserved in situ whenever possible. Some experts (29) even suggest that parathyroid autotransplantation may increase the risk of permanent postoperative hypoparathyroidism. We do not recommend routine parathyroid autotransplantation, but believe that selective parathyroid autotransplantation is the most effective way to salvage injured parathyroid function in cases of intraoperative miscut or injury to avoid permanent postoperative hypoparathyroidism. In our study, the incidence of transient hypoparathyroidism was higher in the experimental group than in the control group (33.75% vs. 22%). However, the incidence of permanent hypoparathyroidism was lower in the experimental group (0.625% vs. 4%); The differences were significant (X2 = 8.327; P = 0.013). In univariate analysis, parathyroid autotransplantation increased incidence of transient hypoparathyroidism (OR,1.806;Cl,1.088-2.998;P=0.022),and lower incidence of permanent hypoparathyroidism (OR,0.151;Cl,0.018-1.269;P=0.046). Selective parathyroid autotransplantation during endoscopic radical resection of thyroid carcinoma is effective in preventing permanent hypoparathyroidism. This is consistent with the findings of Qiu's (31) study. At the same time, we found that the diameters of thyroid cancer nodules was not associated with the occurrence of transient hypoparathyroidism or permanent hypoparathyroidism which was the same conclusion as Yazıcıoğlu et al (22).

Currently, parathyroid function after thyroid surgery is evaluated using clinical symptoms and serum PTH and calcium concentrations (33). In previous studies, the

TABLE 4 The diameters of thyroid cancer nodules and risk of hypoparathyroidism.

Grouping	Diameter ≥ 1cm	Diameter <1 cm	OR (95%Cl)	P
Transient hypoparathyroidism	38 (25.3%)	49 (30.6%)	0.769 (0.467-1.265)	0.301
Permanent hypoparathyroidism	4 (2.6%)	3 (1.88%)	1.434 (0.316-6.515)	0.641

TABLE 5 Comparison between cubital fossa vein PTH in transplantation region and non-transplantation region in the experimental group (pg/mL, X±S).

Grouping	N	Post 1 day	Post 1 week	Post 1 month	Post 3 months	Post 6 months	Post 12 months
Transplantation region	160	20.46 ± 7.45	34.39 ± 10.73	83.77 ± 21.86	99.15 ± 22.92	105.48 ± 22.31	83.53 ± 15.80
Non-transplantation region	160	19.05 ± 6.05	24.39 ± 6.68	37.71 ± 13.32	47.76 ± 13.71	48.79 ± 13.38	49.67 ± 14.89
T		1.862	9.806	22.757	24.345	27.569	19.726
P		0.064	0.000	0.000	0.000	0.000	0.000

Post, post-operative.

sternocleidomastoid muscle was selected as the graft site to avoid making a second surgical incision; however, this method precludes differentiating parathyroid function in the transplantation site and the preserved parathyroid glands (34, 35). Therefore, we selected the brachioradialis in the non-dominant forearm as the graft site. Graft survival was determined when the PTH concentration ratio of the cubital fossa vein in both arms reached 1.5 times (36). One previous study (37) that examined transplantation sites reported that graft function assessment is easiest when the brachioradialis is used and that use of this site is safe and effective. PTH concentration decreased on the first day after surgery in both groups. Since the function of the parathyroid glands retained in-situ could not be wholly predicted, in the experimental group, the transplanted gland required time to establish perfusion (28), the graft had no secretory ability on the first postoperative day, and only the retained in-situ and well-functioning part of the parathyroid glands in both groups secreted PTH. Furthermore, a dilution effect likely occurred in both groups owing to postoperative fluid supplementation. These factors resulted in a significant decrease in serum PTH concentration in the experimental and control groups 1 day after surgery. Systemic PTH concentrations was significantly higher in the experimental group from 1 week to 12 months after surgery. During this time period, PTH concentrations was significantly higher in the cubital fossa of the transplantation side than in the contralateral side, suggesting that the transplanted parathyroid glands survived and began to secrete PTH within a week. This is similar to the findings of Zhang et al. (11), who found that 96.5% demonstrated the first evidence of graft function within 2 weeks, and 3.5% showed graft function 2-8 weeks postoperatively. The mean interval to parathyroid autograft functioning was 1.3 ± 0.9 weeks. However, El-Sharaky (38) observed using electron microscopy for 4 weeks and concluded that the transplanted parathyroid glands became secretory by the second postoperative week and approached a normal state by 4 weeks postoperatively. We found that as the time from transplantation increased, PTH secretory function of the transplanted parathyroid glands increased. Optimal secretion function was reached 6 months after surgery, and then began to gradually decrease to normal by 12 months. We hypothesize that, on the one hand, normal secretory function was restored in the parathyroid glands preserved in situ and the transplanted parathyroid function was inhibited by negative feedback. On the other hand, the body has changed from the compensatory state of the parathyroid glands after the operation to a normal physiological process, whether in-site retained or transplanted parathyroid glands could secrete PTH according to the needs of the body.

By the comparison between 2-time points of the same group, PTH concentration did not significantly differ in the experimental group between 3 months and 6 months after surgery nor in the control group between 6 months and 12 months after surgery. These findings show that functional parathyroid recovery in the experimental group was basically stable 6 months after surgery. In contrast, stable recovery in the control group was not reached until 12 months. Autotransplantation may be more conducive to enabling earlier functional recovery. Qiu et al. (27) also reported the same conclusion. Finally, PTH secretory function recovered to 83.16% of baseline in the experimental group, but only 65.48% of baseline in the control group, further suggesting that autotransplantation is more conducive for postoperative functional recovery. However, parathyroid function remained below baseline in both groups. We speculate that, on the one hand, damaged or disconnected parathyroid glands may have been retained in situ during the operation but their secretory function was impaired. On the other hand, the graft may have lost its secretory function because of insufficient blood supply or fibrosis (26).

Calcium concentration was significantly higher in the experimental group than in the control group 1, 3, 6, and 12 months after surgery. By analyzing the changes in serum PTH and Calcium concentrations in the two groups after the operation, we found that PTH and Calcium increased after the operation did not maintain absolute consistency but existed separation phenomenon. We speculate that PTH mainly increases calcium concentration *via* two mechanisms (39): (1) PTH enhances osteoclast activity to promote release of calcium phosphate into the blood; and (2) PTH enhances calcium reabsorption in renal tubules and stimulates 1,25(OH)2 D3

production in the kidney to affect intestinal calcium absorption. There was a time lag between recovery of serum PTH and calcium concentrations, suggesting that calcium homeostasis mechanisms required time to establish. Furthermore, routine calcium and calcitriol supplementation after surgery caused postoperative calcium testing to be an inaccurate reflection of PTH secretion by the patient. Normalization of postoperative serum calcium concentration with supplementation may have a benefit, as we hypothesize that it puts injured and transplanted parathyroid tissue into a quiescent state, enabling more rapid and robust postoperative recovery of perfusion and function (40). Goltzman et al. (41) found that increased serum calcium and 1,25(OH)2 D3 concentrations can inhibit the transcription and stability of the PTH gene and that sustained hypercalcemia can inhibit parathyroid cell proliferation and reduce volume of functional parathyroid tissue. Therefore, we suggest that postoperative calcium supplementation should be tailored based on biochemical indicators.

The role of preventive CLND in PTC resection is controversial. Although the ATA (12) and National Comprehensive Cancer Network guidelines (42) do not recommend routine dissection, the Japanese Association of Endocrine Surgeons does (43). A recent retrospective study (44) evaluated preventive CLND in patients with PTC and found that preventive CLND can prevent recurrence and improve disease-free survival in patients at intermediate and high risk of recurrence. Therefore, we routinely perform CLND. In our study, the mean numbers of lymph nodes dissected per patient and positive lymph nodes per patient were significantly higher in the experimental group. Analyze the reasons, the inferior parathyroid glands arise from the third pharyngeal pouch based on anatomy (45). Therefore, the location of the inferior parathyroid glands is highly variable, and it is more common in the area between the lower level of the thyroid gland and the thymus. This makes it difficult to differentiate the inferior parathyroid glands from enlarged lymph nodes. In the control group, when the CLND was performed, the operator was relatively conservative in order to protect the inferior parathyroid glands, the scope of the operation was limited, and the number of lymph nodes dissected was limited. In the experimental group, when the CLND was performed, since the inferior parathyroid gland had been transplanted, the operator had no fear of the inferior parathyroid glands being miscut or damaged to the blood supply in this area, so a more thorough and aggressive lymph node dissection could be performed. Therefore, the number of lymph nodes dissected in the central region was more than that in the control group. We conclude that inferior parathyroid gland autotransplantation enables surgeons to achieve more comprehensive CLND, which may reduce the probability of reoperation. This is consistent with the results reported by Wei et al. (8). All patients in our study were followed for 12 months after surgery and no recurrence or metastasis was found. The characteristically slow progression of thyroid cancer and our relatively short follow-up time and small sample size may explain the low recurrence and metastasis rates.

This study has several limitations. First, as a retrospective study, selection bias may have been introduced. Second, the operator's judgment of parathyroid function was subjective to an extent; development of technology that can objectively evaluate parathyroid blood supply is warranted. Near-infrared fluorescent/indocyanine green (NIR/ICG) fluorescence imaging technology is a new research field. After ICG is injected into the human body, the tissue structure can be visualized by NIR. Studies have shown that parathyroid glands with good blood supply can take up ICG imaging, and the fluorescence intensity is positively correlated with the dose of ICG (46). Therefore, the imaging intensity can be used to evaluate the blood supply of the parathyroid glands, so as to evaluate the function of the parathyroid glands and decide whether to perform parathyroid autotransplantation. Its application prospect is worth looking forward to.

Conclusions

Selective inferior parathyroid autotransplantation is effective to prevent permanent hypoparathyroidism when performing endoscopic radical resection of thyroid cancer. However, it is associated with a risk of transient hypoparathyroidism. Strategic transplantation of damaged inferior parathyroid glands or those with poor blood supply is more conducive to early functional recovery of parathyroid secretory function than in situ preservation. Moreover, autotransplantation allows a more thorough CLND, which may reduce recurrence.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the Gansu Provincial People's Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

QZ and K-PQ conceived and designed the research. Z-SW and J-WG collected the data and conducted the research. Y-PZ and W-JC analyzed and interpreted the data. QZ wrote the initial paper. K-PQ revised the paper. QZ and K-PQ had primary responsibility for the final content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The impact of intraoperative "Nerve Monitoring" in a tertiary referral center for thyroid and parathyroid surgery

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The most fearsome complication in thyroid surgery is the temporary or definitive recurrent laryngeal nerve (RLN) injury. The aim of our study was to evaluate the impact of intraoperative neuromonitoring (IONM) on postoperative outcomes after thyroid and parathyroid surgery. From October 2014 to February 2016, a total of 80 consecutive patients, with high risk of RLN injuries, underwent thyroid and parathyroid surgery. They were divided in two groups (IONM group and control group), depending on whether neuromonitoring was used or not. We used the Nerve Integrity Monitoring System (NIM)-Response 3.0® (Medtronic Xomed®). The operation time (p = 0.014). and the length of hospital stay (LOS) (p = 0.14) were shorter in the IONM group. Overall mean follow-up was 96.7 ± 14.3 months. The rate of transient RLN palsy was 2.6% in IONM group and 2.5% in the control group (p = not significant). Only one case of definitive RLN injury was reported in control group. No differences were reported between the two groups in terms of temporary or definitive RLN injury. Routine use of IOMN increases the surgery cost, but overall, it leads to long-term cost savings thanks to the reduction of both operating times (106.3 ± 38.7 vs 128.1 ± 39.3, p: 0.01) and LOS (3.2 ± 1.5 vs 3.7 ± 1.5 days, p = 0.14). Anatomical visualization of RLN remains the gold standard in thyroid and parathyroid surgery. Nevertheless, IONM is proved to be a valid help without the ambition to replace surgeon's experience.

KEYWORDS

thyroid surgery, thyroidectomy, recurrent laryngeal nerve, intraoperative neuromonitoring (IONM), cost analysis, parathyroid surgery

Introduction

Thyroidectomy is one of the most frequent surgical procedures in general surgery Units (1) with about 40.000 thyroidectomies performed in Italy every year (66.66/100.000 inhabitants) (2). Unilateral or bilateral temporary or definitive recurrent laryngeal nerve (RLN) injuries are among the most frightening complications during

thyroidectomy, leading to voice and swallowing alterations (3). In particular, the incidence of temporary unilateral RLN injury ranged from 1% to 20% with a rate between 1% and 2% in high-volume centers (4, 5)

The risk of RLN injury depends on the type of both surgical procedures and pre-operative diagnosis as well as surgeon experience (6). Unfortunately, most of RLN injuries are not visible to the naked human eye: on average only 1/10 lesions can be recognized during surgery (3–6). Moreover, to underline the complexity of this type of surgery, it is necessary to consider some factors that can increase the risk of RLN injury such as redo-surgery, giant or intrathoracic goiter, cancer and previous radiotherapy (7–11), without forgetting that the injury can also occur accidentally due to clamping, stretching, electrocautery or ligature entrapment (5, 12).

There is agreement that the gold standard approach to RLN is the accurate visual identification of the nerve (7, 13). The need of an easier and safer identification and dissection of RLN, also considering legal implications of surgical procedure complications, led some authors to suggest the introduction of routine intraoperative neuromonitoring (IONM) of the RLN during thyroidectomy (14–16). However, the real usefulness of routinely IONM is still debated, especially considering the cost of the equipment (6, 17–22).

The aim of our study was to evaluate the impact of IONM on postoperative outcomes after thyroid and parathyroid surgery for both benign and malignant disorders.

Materials and methods

This was a retrospective single-center study of collected data from patients undergoing thyroid and parathyroid surgery from October 2014 to February 2016 and is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort studies (23).

During the study period, 205 thyroid procedures were performed. The last 40 patients who underwent surgery without IONM (control group) and the first 40 patients who underwent IONM (IONM group), after its introduction into our daily clinical practice, were prospectively selected and included in the study.

All personal, anamnestic, and clinical-laboratory data of the patients were recorded. Anamnesis included the whole past medical history and in particular the pre-operative examination and diagnosis (thyroid fine needle aspiration, hormonal status, pre-operative use of drugs and a complete work-up of the performance status and the presence of eventual comorbidities). Data strictly related to surgery such as ASA score, type and duration of surgery, intraoperative electromyographic data, definitive histological diagnosis, postoperative length of hospital stay, and surgical complications were collected (LOS).

Inclusion criteria

Patients with an increased risk of RLN lesions (10), including pre-operative anatomical abnormalities (non-recurrent nerve), were included in the study. All patients included in the study underwent a preoperative laryngoscopy to assess any lesion or voice alteration.

Pre-operative diagnosis

Based on pre-operative diagnosis, patients were divided as follows: goiter (multinodular, giant goiter, intrathoracic); recurrent goiter; toxic goiter/Plummer's adenoma/Basedow's disease; primary hyperparathyroidism; suspected papillary carcinoma; papillary thyroid carcinoma; thyroid lodge abscess.

Types of surgery

The following different types of surgery were performed: thyroidectomy; completion thyroidectomy; thyroid lobectomy; parathyroidectomy, thyroidectomy, and parathyroidectomy; thyroidectomy and central neck lymphadenectomy (LCC); thyroidectomy with central neck lymphadenectomy and unilateral lateral neck lymphadenectomy (LLC).

All patients received general anaesthesia with endotracheal tube insertion as required by the procedure and the related recommendations (24).

Device monitoring and instrument settings

Nerve Integrity Monitoring System (NIM)-Response 3.0® (Medtronic Xomed®, Jacksonville, Florida, USA; REF 8253002, SN 2NR3-2055) with intermittent and continuous monitoring system was used in all cases. High contrast, digital, colour screen, 1024H × 768W pixels, Touch panel 256H × 256W. Impedance: <5 Ohm. Impedance difference: <1 kOhm. Stimulation level: 0.5 mA–1.5 mA (average 1 mA). Initial post-identification stimulation level: 0.5 mA. Frequency: 30 Hz. Stimulus duration: 100 μs. Minimum event threshold: 100 μV. The skin electrodes were placed in the pre-sternal region. The disposable monopolar (Medtronic Xomed) or polyuse (Neurovision Medical) stimulator probe was placed as a dissection tool.

Standardization of intraoperative monitoring techniques

IONM was performed as previously described (25).

Interpretation of the curve

The amplitude of the electromyography (EMG) curve relating to RLN stimulation depends on the following variables

Contact of the nerve stimulating probe and the presence of loose tissue and fascia covering the nerve, as well as the degree of humidity represented by the presence of blood have to be considered among those factors that may modify the amplitude of the EMG curve relating to RLN stimulation. Indeed, there are many variables that may play a role in the representation of the EMG curve such as the position of the laryngeal electrodes (in the eventuality of a response anywhere stimulated, it is suggested to scuff and reposition the endotracheal tube, because it is probably positioned too caudally), temperature, and dehydration of the nerve. All these eventualities have to be considered and well-known by the operator for a correct interpretation of the EMG curve.

The electrophysiological reference parameters of the intensity of the EMG response were as follows:

- Initial parameters: with mean stimulation at 1 mA, normal mean response of 900 μV (range 500–1800 μV).
- Final parameters: with final stimulation at 1 mA, average normal response of 1200 μV (range 150–5400 μV). Final event threshold averaged 0.37 mA (range 0.15–0.48).
- Parameters highly suggestive of recurrent lesion: with mean stimulation at 1 mA, response <200 μV or percentage reduction >50% compared to pre-dissection baseline control.

Postoperative assessment

Patients with postoperative dysphonia or with significant reduction in EMG signal intensity post-dissection were evaluated with an otolaryngological visit and fibrolaryngoscopy performed on the second postoperative day to assess any lesions or changes in vocal cords motility. Subsequent post-operative checks, in case of dysphonia, were performed one month after surgery with a new phoniatric check-up, and 4–6 months after the operation with a vocal examination and eventual EMG repetition. Transient injury was defined as an injury in which the motility of the vocal cords recovered within 12 months after surgery.

Statistical analysis

The usefulness of the intraoperative neuromonitoring system was assessed within the two groups using the following statistical tools: initially, a univariate analysis was performed on all potential factors, including the use of intraoperative nerve monitoring, influencing the recurrent deficit using Chi-square and Student's t test. Continuous data were expressed as mean ± standard deviation. Multivariate logistic regression was then performed. A value of $p < 0.05$ was considered statistically significant.

Results

Demographic, clinical, and operative characteristics of the included patients are reported in Tables 1–3.

The overall mean operative time was 117.2 ± 40.3 min. In particular, the duration of surgery was 106.3 ± 38.7 min and 128.1 ± 39.3 min ($p = 0.014$) in the IONM group and in the control group, respectively. The median thyroid weight was 36.85 grams (range 8.7–344.2 grams). IONM was performed in nerves at risk.

The length of hospital stay LOS was 3.5 ± 1.5 days. The hospitalization time was shorter in the IONM group (3.2 ±

TABLE 1 Demographic and clinical characteristics of the included patients.

	All patients	C-group	IONM-group	p value
Patients	80	40	40	–
Age (±SD[a]) (range) years	50.6 ± 13.7	49 ± 16.5	51.4 ± 11.4	NS
Male/Female	21 (26.2%)/59 (73.7%)	10 (25%)/ 30 (75%)	11 (27.5%)/29 (72.5%)	NS
Mean follow-up time (±SD[a]) (range) months	96.7 ± 14.3	83.06 ± 5.41	110.30 ± 1.83	NS

[a]SD standard deviation.
NS, not significant.

TABLE 2 Clinical characteristics and presentation of the patients enrolled.

Preoperative Diagnosis	All patients	C-group	IONM-group
Multinodular goiter	36 (45%)	13 (32.5%)	23 (57.5%)
Recurrent goiter	4 (5%)	2 (5%)	2 (5%)
Toxic goiter	9 (11.2%)	3 (7.5%)	6 (15%)
Primary hyperparathyroidism	1 (1.2%)	1 (2.5%)	0
Suspicious thyroid cancer	17 (21.2%)	14 (35%)	3 (7.5%)
Thyroid cancer	12 (15%)	6 (15%)	6 (15%)
Thyroid lodge abscess	1 (1.2%)	1 (2.5%)	0

TABLE 3 Procedures performed.

Surgical procedures	All patients	C-group	IONM-group
Total thyroidectomy	58 (72.5%)	27 (67.5%)	31 (77.5%)
Completion thyroidectomy	4 (5%)	2 (5%)	2 (5%)
Thyroid lobectomy	2 (2.5%)	2 (5%)	0
Parathyroidectomy	1 (1.2%)	1 (2.5%)	0
Total thyroidectomy + Parathyroidectomy	1 (1.2%)	0	1 (2.5%)
Total thyroidectomy + Central Neck lymphadenectomy	11 (13.7%)	6 (15%)	5 (12.5%)
Total thyroidectomy + Central Neck lymphadenectomy + unilateral lateral neck lymphadenectomy	3 (3.7%)	2 (5%)	1 (2.5%)

TABLE 4 Pathological characteristics and follow up of the included patients.

Histology subtypes	All patients 80	C-group 40	IONM-group 40
Struma	37 (46.2%)	15 (37.5%)	22 (55%)
Follicular adenoma	7 (8.7%)	5 (12.5%)	2 (5%)
Parathyroid adenoma	1 (1.2%)	1 (2.5%)	0
Papillary thyroid cancer	27 (33.7%)	14 (35%)	13 (32.5%)
Papillary thyroid cancer + Lymph nodes metastases	5 (6.2%)	4 (10%)	1 (2.5%)
Papillary thyroid cancer + Parathyroid adenoma	1 (1.2%)	0	1 (2.5%)
Microfollicular carcinoma	1 (1.2%)	1 (2.5%)	0
Poor differentiated carcinoma	1 (1.2%)	0	1 (2.5%)

TABLE 5 Procedural details.

Mean operative time (±SD[a]) (range) min	117.2 ± 40.3	106.3 ± 38.7	128.1 ± 39.3	0.014
Mean hospital stay (±SD[a]) (range) days	3.5 ± 1.5	3.2 ± 1.5	3.7 ± 1.5	0.14
Transient laryngeal nerve palsy	4 (2.5%)*	2 (2.6%)*	2 (2.5%)*	0.97
Definitive laryngeal nerve palsy y/n	1 (0.6%)*	0*	1 (1.25%)*	0.32

[a]SD, standard deviation.
*Considering only RLN at risk.

1.5) than in the group without IONM (3.7 ± 1.5) even if this difference was not statistically significant $p = 0.14$.

Pathological characteristics and procedural results were reported in Tables 4, 5.

The mean follow-up was 96.7 ± 14.3 months.

There were 4 cases of transient RLN injury among all the considered nerves (4/157 = 2.5%). In the IONM group the rate of transient RLN injury was 2.6%, while in the group without the use of IONM it was 2.5% ($p = 0.97$).

The four cases were one patient with thyroid carcinoma and one with benign goiter in each group respectively.

In the control group there was only one case of definitive recurrent RLN injury out of the total number of nerves considered (1/157 = 0.6%) $p = 0.32$. In this specific case, the patient was found to have hypomobility of the right vocal cord at otolaryngologic post-operative control; despite this, there was a complete functional recovery of phonatory activity, also reported by the patient, thanks also to early logopedic therapy.

General cost analysis

The cost analysis was based on the economic assessments of the specific period in which the study took place.

The hospitalization of a patient who underwent a traditional total thyroidectomy cost around 2.400 € considering 3 days of hospital stay. These costs comprehend drugs (about 100 €), operating room equipment (about 130 €), diagnostic tests (about 160 €), hospitalization/discharge (about 50 €), ward overheads (about 80 €), medical care (about 250/216 € without and with IONM), nursing care (about 380/328 € without and with IONM), operating room staff (about 450/373 € without and with IONM), and operating room use (about 800/663 € without and with IONM) (26). Moreover, the cost of the intermittent disposable NIM kit, of about 440 €, has to be considered.

The application of IONM technique led to an increase in expenses because of the use of disposable NIM kit. However, reduction in operative time and LOS (even if not statistically significant) led to a reduction in the overall health care expenditure in the long-term.

Lastly, according to the Diagnosis Related Group (DRG), used in Italy to evaluate the reimbursement that each hospital can receive from the National Health System (*Sistema Sanitario Nazionale* or SSN), the average DRG for total thyroidectomy is 3340 €. This value allows us to define how in both groups there was a positive economic balance independent of the use of the IONM.

Discussion

Several international experts highlighted the advantages of a selective use of IONM in case of thyroidectomy for cancer with lymph node dissection, autoimmune pathology, giant goiters, or in redo-surgery (27–31). Nevertheless, its constant application in the clinical practice is still debated (19).

The present study highlights how the use of the IONM, regardless of the malignancy or benignity of the disease,

represents an effective tool to obtain a safer approach and a related overall reduction of health costs. Despite the increased time of setup and increment in costs due to the technology, there is a clear long-term benefit given by the correct intraoperative identification and evaluation of nerves functionality by the routine use of IONM. The benefits are especially evaluated in patients at risk of RLN injury where the visual identification could be more difficult.

Our results were consistent with those described by several authors (9, 24, 25, 32–36).

Calò et al. (25) reported their experience in 2.034 consecutive patients comparing identification alone versus IONM. According to the authors, the use of the IONM did not statistically affect the risk of RLN injury (28 RLN injuries/993 patients in the control group; 23 RLN injuries/1.041 patients in the IONM group) but can be useful in those patients with risk factors.

Staubitz et al. (32) published the results of the EUROCRINE database evaluating the impact of IONM on postoperative vocal cord palsy in 4.598 first-time thyroidectomies performed in 82 hospitals for benign disease between May 2015 and January 2019. There were 50 vocal cord palsies (1.1%) with a lower risk in the IONM group [Odd Ratio (OR) 0.34]. Interestingly, high-volume hospitals had a low injury rate (OR 0.05).

Considering the results obtained in our series, despite the small sample size, we agree with a recent systematic review (35) including 10 articles and 4.460 nerves at risk in the group with visual identification alone and 6.155 nerves at risk in the IONM group. The authors pointed out that the injury rate is lower after IONM in patients undergoing thyroidectomy for malignancy (3.5% vs. 2.1%, $p = 0.050$) with a considerable improvement even in those patients who had to undergo a redo-surgery (7.6% vs. 4.5%, OR: 1.32, $p = 0.021$).

For what concerns cost-benefit analysis of IONM employment versus visual identification of the nerves, Rocke et al. (33) reported a detailed cost utility analysis. They registered a general more cost-effectiveness of the visualization alone with cost savings of $179.40 and $683.20 per patient, but they also reported that if a clinician can, with use of IONM, decrease the rate of RLN injury by 50.4% or more compared with visual identification, selective use of IONM in high-risk cases is most cost-effective and should be suggested.

A recent Cochrane review of Cirocchi et al. (34) regarding the use of IONM or visualization alone in terms of patients' safety, analyzed 4 RCTs including a large population study of 1.558 patients. The authors reported no significant difference between the visualization-only and the IONM techniques in terms of rate of nerve injury, and they recorded a comparable duration of surgery in both cases. Despite these results, the authors reported, among the limitations of the study, a lack of standardization in the collection of data of the various trials that may have influenced the results. As suggested by Cirocchi et al. a well-designed, executed, analyzed and reported RCT with a larger population and longer follow-up, employing the latest IONM technology and applying new surgical techniques is needed.

This study has some limitations. The main limitations are represented by both the retrospective nature of the study and the lack of the use of standardized questionnaires such the Voice Handicap Index-10 (VHI-10) or the Impairment Index-5 (VII-5) valuation questionnaires that could make the results objectified with the existing Literature (36). It was not possible to compare the weight in grams of the thyroid with the postoperative outcomes due to the great variability of the specimen and for the lack of a real definition of weight ranges. Furthermore, the sample size was small, and no statistical matching was performed. However, these limitations were offset by having the procedures performed in a referral center with the observational nature of the data reflecting the current clinical scenario of most of the hospitals distributed worldwide.

Furthermore, considering the incidence of legal malpractice with lawsuit related to the recurrent laryngeal palsy in near of 57% of all cases in a referral center, as reported by Dralle et al. (37), the use of nerve monitoring in selected cases should be advisable even if, as showed by Abadin et al. (38), there is not clear evidence that the "use or nonuse" played a role in malpractice ligation related to thyroid surgery.

Conclusions

The IONM allows a prognostic evaluation of the post-operative vocal cords functioning, preventing the possibility of bilateral damage, and permit to know the exact point and the cause of the RLN injury. However, the visual identification of recurrent laryngeal nerve remains the gold standard in case of neck endocrine surgery even if the use of intra-operative nerve monitoring is advisable.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Comitato Etico Lazio. The patients provided their written informed consent to participate in this study.

Author contributions

PP, GG, SET, FA and CN: substantial contributions to the conception and design of the work, acquisition, analysis, interpretation of data for the work, drafting the work and revising it critically for important intellectual content, final approval of the version to be published, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy, and integrity of any part of the work are appropriately investigated and resolved. AU and MG: substantial contributions to the conception and design of the work, acquisition, analysis, and interpretation of data for the work, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy, and integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Relationship between pretracheal and/or prelaryngeal lymph node metastasis and paratracheal and lateral lymph node metastasis of papillary thyroid carcinoma: A meta-analysis

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Objective: We conducted a meta-analysis to study the relationship between pretracheal and/or prelaryngeal lymph node metastasis and paratracheal and lateral lymph node metastasis in papillary thyroid carcinoma.

Method: A systematic literature search was conducted using PubMed, Embase, and the Cochrane Library electronic databases for studies published up to February 2022. The reference lists of retrieved articles were also reviewed. Two authors independently assessed the methodological quality and extracted the data. A random-effects model was used to calculate the overall pooled relative risk. Publication bias in these studies was evaluated using Egger's test and Begg's test.

Results: Twenty-five independent studies involving 10,525 patients were included in the meta-analysis. The pooled relative risk for ipsilateral and contralateral paratracheal lymph node metastasis was 3.01 (95% confidence interval [CI]: 1.66, 5.45) and 5.68 (95% CI: 2.50, 12.88), respectively, in patients with pretracheal lymph node metastasis. Among patients with prelaryngeal lymph node metastasis, the pooled relative risk for ipsilateral paratracheal and/or pretracheal contralateral paratracheal, and lateral lymph node metastasis was 2.02 (95% CI: 1.90, 2.14), 2.22 (95% CI: 1.34, 3.67), and 3.85 (95% CI: 2.89, 5.14), respectively.

Conclusion: Pretracheal lymph node metastasis and prelaryngeal lymph node metastasis were significantly associated with an increased likelihood of both ipsilateral lymph node metastasis and contralateral paratracheal lymph node

metastasis in papillary thyroid carcinoma. Prelaryngeal lymph node metastasis was positively correlated with the incidence of lateral lymph node metastasis.

KEYWORDS

pretracheal lymph node, prelaryngeal lymph node, paratracheal lymph node, lateral lymph node, papillary thyroid carcinoma, meta-analysis

Introduction

Lymph node metastasis is the most frequent form of metastasis of papillary thyroid carcinoma (PTC), which occurred in 37–61% of patients with clinically negative lymph node (cN0) (1–3). However, there is no consensus on prophylactic central lymph node dissection for low-risk PTC. Routine ipsilateral central lymph node dissection is recommended to be performed for patients with PTC in Chinese Guidelines on the Diagnosis and Treatment of Thyroid Nodules and Differentiated Thyroid Carcinomas (4). The Guidelines for the Management of Thyroid Cancer of the British Thyroid Association indicate that Personalized Decision Making is recommended for patients with non-high-risk PTC with clinically/radiologically uninvolved neck nodes (5). The European Society for Medical Oncology Clinical Practice Guidelines for Diagnosis, Treatment, and Follow-up of Thyroid Cancer indicate that the use of prophylactic central neck dissection for low-risk tumors (T1b–T2, N0) varies across centers (6). However, according to the 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer, prophylactic central neck dissection is not recommended for small (T1 or T2), noninvasive, and clinically node-negative PTC (7). As a result, the indicators of prophylactic central lymph node dissection for low-risk PTC remain unclear.

In recent decades, it has been explored whether the metastasis of the prelaryngeal lymph node, also known as the Delphian lymph node, could be used to predict metastasis in other groups' lymph node, based on its anatomical location. A previous meta-analysis suggested that the risks of central lymph node metastasis and lateral lymph node metastasis were both significantly higher in the prelaryngeal lymph node metastasis group than that in the negative prelaryngeal lymph node group (8). Kim and colleagues confirmed that the specificities of prelaryngeal lymph node metastasis in predicting metastasis in other group lymph nodes were high (9). Because it is located at a similar site, the association between metastasis to the pretracheal lymph node and metastasis to other groups' lymph node has also been investigated previously (10–12).

In order to explore the significance of the combination of prelaryngeal lymph node metastasis and pretracheal lymph node metastasis for predicting metastasis to other groups' lymph node, we conducted this meta-analysis to assess the association of pretracheal and/or prelaryngeal lymph node metastasis with paratracheal and lateral lymph node metastasis in PTC.

Methods

Literature search

A search was independently conducted by two investigators on PubMed, Embase, and the Cochrane Library electronic databases for studies that were published up to 28 February 2022. The search algorithm was ([pretracheal lymph node] or [prelaryngeal lymph node] or [delphian lymph node] or [pre-tracheal lymph node] or [pre-laryngeal lymph node]) AND [thyroid]) for PubMed. The following search terms were used in all fields as a search strategy for Embase (1): pretracheal and pre-tracheal; prelaryngeal and pre-laryngeal; delphian; (2) lymph node, lymph nodes, and (lymph node); (3) thyroid gland, thyroid tumor, thyroid cancer, thyroid neoplasm, thyroid neoplasms, thyroid, thyorids, thyroidal, and thyroideal. For Cochrane Library electronic databases, the search strategy used the following terms as Medical Subject Headings and free word in all fields: (1) pretracheal and pre-tracheal; prelaryngeal and pre-laryngeal; delphian; (2) lymph node, lymph nodes, and (lymph node); (3) thyroid gland, thyroid neoplasms; thyroid, thyorids, thyroidal, and thyroideal. No restrictions were imposed. In addition, we reviewed the reference lists of the retrieved papers and recent reviews.

Study selection

After removing duplication, the acquired studies were screened based on the title and abstract, and the full text was then reviewed. Studies were considered eligible, if they met all the following criteria: (1) the original study was published in English; (2) patients underwent initial thyroid surgery for PTC in the study; (3) the

exposure of interest included prelaryngeal and/or pretracheal lymph node metastasis; (4) the outcome of interest was other groups' lymph node metastasis and/or lateral lymph node metastasis; and (5) relative risk (RR) and the corresponding 95% confidence interval (CI) (or data to calculate these values) were available. Studies were excluded based on the following criteria: (1) Conference Abstract, Review, Case report, and Commentary; (2) those from which data could not be collected adequately.

Data extraction and quality assessment

Two reviewers (BW and C-RZ) independently extracted data using a predefined data extraction form. Data were collected as follows: publication date, first author, type of study, country of origin, study sites and institutes, research period, sample size, preoperative clinical lymph node stage, tumor location, the maximum diameter of tumor, and surgical method, whether patients without prelaryngeal lymph node were included, the number of patients with or without prelaryngeal and/or pretracheal lymph node metastasis, and the number of patients with or without metastasis in other groups' lymph node. The quality of cohort studies was assessed using the Newcastle–Ottawa Scale (NOS), and studies with a NOS score > 5 were considered high-quality studies (13). All disagreements in study selection, data extraction, and quality assessment were discussed and resolved by consensus.

Statistical analysis

Pooled RRs were calculated using a random-effects model (DerSimonian–Laird). Heterogeneity was quantified statistically with the I^2 test. $P < 0.1$ and $I^2 > 50\%$ for heterogeneity was considered significant difference. If there was significant heterogeneity, subgroup analysis was conducted according to the tumor location, or the state of the prelaryngeal lymph node, or the surgical method. Potential publication bias was assessed using Begg's rank correlation test and the Egger linear regression test (14, 15). All analyses were performed using Stata version 14.0 (Stata Corp LP, College Station, TX, USA). Statistical significance was set at $P < 0.05$.

Results

Literature search

The study selection process is illustrated in Figure 1. A total of 295 potentially relevant records were identified by searching these databases. Of these, 176 were retained after duplicates were removed. After the first screening, 124 studies were excluded for various reasons. The remaining 52 studies were assessed *via* full-text screening, and 27 studies were further excluded. Finally, 25 independent studies were included in the meta-analysis.

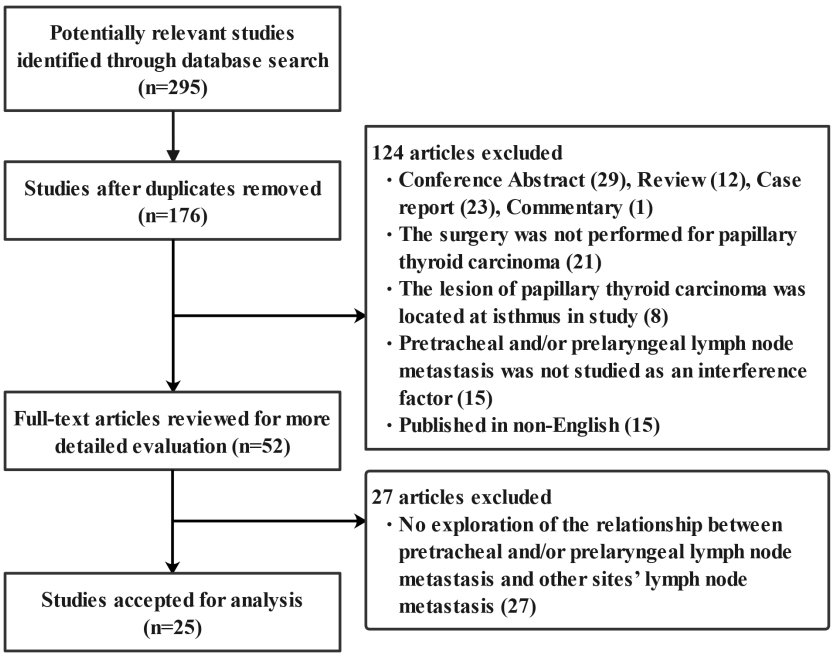

FIGURE 1
Flow chart of study selection.

Study characteristics

Table 1 shows the basic information of the 25 eligible studies (10–12, 16–37). These studies were published between 2011 and 2022. Among the 25 cohort studies, 8 were prospective and 17 were retrospective studies. One, five, and nineteen studies were conducted in America, Korea, and China, respectively. The sample size of these studies varied from 67 to 1,575, and a total of 10,525 patients were included in the analysis. The exposure of interest consisted of prelaryngeal lymph node metastasis, pretracheal lymph node metastasis, and prelaryngeal and/or pretracheal lymph node metastasis. The outcome of interest varied across studies, including ipsilateral paratracheal lymph node metastasis, contralateral paratracheal lymph node metastasis, pretracheal lymph node metastasis, central without prelaryngeal lymph node metastasis, ipsilateral paratracheal and/or pretracheal lymph node metastasis, and lateral lymph node metastasis. According to the NOS score, all included studies were of relatively high quality, with the distribution of the scores ranging from 6 to 8.

Relationship between pretracheal lymph node metastasis and metastasis to other groups' lymph nodes

Three studies explored the relationship between pretracheal lymph node metastasis and ipsilateral paratracheal lymph node metastasis (17, 19, 20). The pooled RR was 3.01 (95% CI: 1.66, 5.45, $p < 0.001$; Figure 2A). Significant heterogeneity was observed ($I^2 = 88.0\%$, $p < 0.001$; Figure 2A). The publication bias, as measured by Begg's test and Egger's test, was not significant ($p > 0.99$, $p = 0.393$, respectively). The relationship between pretracheal lymph node metastasis and contralateral paratracheal lymph node metastasis was investigated in seven studies (10–12, 17, 20, 22, 23), and the pooled RR was 5.68 (95% CI: 2.50, 12.88, $p < 0.001$; Figure 2B). Here, heterogeneity was also significant ($I^2 = 91.5\%$, $p < 0.001$; Figure 2B). Begg's test confirmed that publication bias was not significant ($p = 0.368$), whereas Egger's test yielded the opposite result ($p = 0.003$). When analysis was performed in patients with cN0 unilateral PTC, the pooled RR was 4.97 (95% CI: 2.39, 10.32, $p < 0.001$; $I^2 = 63.0\%$, $p = 0.067$; Figure 2C), and the publication bias was not significant (Begg, $p > 0.99$; Egger, $p = 0.464$).

Relationship between prelaryngeal lymph node metastasis and metastasis to other groups' lymph nodes

Figure 3A shows the results of the pooled RR for central (without prelaryngeal) lymph node metastasis. Sixteen studies were included in the analysis (16, 19–21, 25–29, 31–37). The RRs for the relationship between prelaryngeal lymph node metastasis and central (without prelaryngeal) lymph node metastasis varied from 1.70 to 3.22 across these studies, whereas the pooled RR was 1.96 (95% CI: 1.84, 2.09, $p < 0.001$). Heterogeneity was significant ($I^2 = 57.2\%$, $p = 0.002$), but publication bias was not significant (Begg, $p = 0.166$; Egger, $p = 0.13$). To address the heterogeneity, subgroup analyses were performed for non-bilateral PTC and inclusion or exclusion of cases without prelaryngeal lymph node. The pooled RR for central (without prelaryngeal) lymph node metastasis was 1.88 (95% CI: 1.51, 2.34, $p < 0.001$; $I^2 = 0.0\%$, $p = 0.336$, Figure 3B; Begg, $p > 0.99$; Egger, $p =$ -) in the subgroup of non-bilateral PTC. Additionally, in the subgroup of inclusion and exclusion of cases without prelaryngeal lymph node, the pooled RR was 1.90 (95% CI: 1.76, 2.07, $p < 0.001$; $I^2 = 56.2\%$, $p = 0.033$; Figure 3C; Begg, $p > 0.99$; Egger, $p = 0.924$) and 1.74 (95% CI: 1.59, 1.90, $p < 0.001$; $I^2 = 0.0\%$, $p = 0.786$; Figure 3D; Begg, $p > 0.99$; Egger, $p = 0.394$), respectively.

The pooled RR for ipsilateral paratracheal and/or pretracheal lymph node metastasis is presented in Figure 4A. The risk of ipsilateral paratracheal and/or pretracheal lymph node metastasis for patients with prelaryngeal lymph node metastasis was higher than that for patients without prelaryngeal lymph node metastasis (RR = 2.02, 95% CI: 1.90, 2.14, $p < 0.001$; $I^2 = 0.0\%$, $p = 0.406$; Figure 4A; Begg, $p > 0.99$; Egger, $p = 0.294$). The pooled RR for pretracheal lymph node metastasis was 2.77 (95% CI: 2.06, 3.73, $p < 0.001$; $I^2 = 0.0\%$, $p = 0.995$; Figure 4B; Begg, $p > 0.99$; Egger, $p =$ -). These patients with prelaryngeal lymph node metastasis were also prone to suffer from contralateral paratracheal lymph node metastasis (RR = 2.22, 95% CI: 1.34, 3.67, $p < 0.001$; $I^2 = 84.2\%$, $p = 0.002$; Figure 4C; Begg, $p = 0.452$; Egger, $p = 0.043$). Due to heterogeneity and publication bias, subgroup analysis was performed in patients without lateral lymph node dissection. The pooled RR for contralateral paratracheal lymph node metastasis was 2.57 (95% CI: 1.57, 4.19, $p < 0.001$; $I^2 = 63.1\%$, $p = 0.028$; Figure 4D; Begg, $p = 0.462$; Egger, $p = 0.531$) in this subgroup.

As shown in Figure 5, the pooled RR for lateral lymph node metastasis was 3.85 (95% CI: 2.89, 5.14, $p < 0.001$). Although heterogeneity was significant, the lower CIs of all RRs exceeded 1 ($I^2 = 83.7\%$, $p < 0.001$; Figure 5). No significant publication bias was observed (Begg, $p = 0.373$; Egger, $p = 0.167$).

Relationship between pretracheal and/or prelaryngeal lymph node metastasis and metastasis to other groups' lymph nodes

The result that is presented in Figure 6A combines the RRs for ipsilateral paratracheal lymph node metastasis in patients with pretracheal and/or prelaryngeal lymph node metastasis. The pooled RR was 2.85 (95% CI: 1.59, 5.09, $p < 0.001$; Figure 6A). Heterogeneity was significant ($I^2 = 87.2\%$, $p < 0.001$; Figure 6A). There was no significant publication bias (Begg, $p = 0.734$; Egger,

TABLE 1 The characteristics of included studies.

Study ID	Publication Date	First Author	Type of study	Country/ Region	Institute	Research period	Patients (*n*)	Clinical Stage	Bilateral Lesions	Isthmic Lesion	Existence of Prelaryngeal Lymph Node	Maximum Diameter of Lesion (cm)	Surgical Method	Interference Factors and Outcome Factors		
														PT	PL	PT and/or PL
1	2011	Iyer	Retrospective	American	Memorial Sloan-Kettering Cancer Center	2007.1—2009.12	101	—	NK	NK	NK	—	TT+rPL-LND, eCND, tLLND		Central without PL, Lateral	
2	2011	Roh	Prospective	Korea	Asan Medical Center	2005—2007	184	cN0, unilateral	Accidental Discovery	N	NK	1.5 ± 1.2 (0.4–5.5)	TT+BCND	Ipa, Cpa		Ipa
3	2012	Kim	Retrospective	South Korea	Kosin University College of Medicine	2010.1—2010.10	308	—	NK	NK	N	1.1 ± 0.7 (0.05 – 5.8)	LT/TT+CND ± MRND			Ipa, Cpa, Lateral
4	2013	Lee	Prospective	Korea	Kyung Hee University	—	67	cN0	Y	Y	NK	0.3-5.5	TT+pBCND	Ipa,	Ipa, Cpa, Lateral, PT	Ipa, Cpa
5	2013	Miao	Prospective	China	Third Affiliated Hospital of Harbin Medical University	2007.7—2009.8	184	cN0, unilateral	N	N	NK	0.2-6.8	TT+pBCND	Ipa, Cpa	Ipa, PT	
6	2013	Oh	Retrospective	Korea	Gachon University Gil Hospital	2009.7—2011.12	245	—	Y	NK	N	–	TT+t/pBCND +tLLND		Central without PL, Lateral	
7	2014	Eun	Prospective	Korea	Multitertiary centers: Kyung Hee University School of Medicine, Kyung Hee University School of Medicine at Gangdong, Kangdong Sacred Heart Hospital	—	140	cN0, unilateral	Accidental Discovery	Y	NK	1.4 ± 1.2	TT+pBCND	Cpa		
8	2015	Chen	Retrospective	China	West China Hospital	2011.9—2013.10	218	cN0, unilateral	N	N	Y	≤4.0	TT+pBCND	Cpa	Cpa	
9	2015	Wei	Retrospective	China	West China Hospital	2008.6—2011.6	332	unilateral	N	N	NK	—	NTT/TT+BCND +tLLND			Cpa
10	2017	Chen	Prospective	China	West China Hospital	2011.7—2013.5	153	cN0, unilateral	N	N	Y	>1	TT+pBCND	Cpa	Cpa	Cpa
11	2017	Tan	Retrospective	China	Zhejiang Cancer Hospital	2013.1—2014.6	231	—	Y	NK	Y	—	LT/NTT/TT +ICND/BCND +tLLND		Central without PL, Lateral	
12	2017	Zheng	Retrospective	China	The Affiliated Yantai Yuhuangding Hospital of Qingdao University	2014.8—2016.5	206	—	Y	Y	N	—	STT/NTT/TT +ICND/BCND +tLLND		Ipa+Cpa, Lateral, PT	
13	2019	Wang	Retrospective	China	Changzheng Hospital	2017.7—2018.8	192	—	Y	Y	NK	—	TT+ICND+tCCND +LLND		Central without PL, Lateral	
14	2020	Chen	Retrospective	China	West China Hospital	—	1085	unilateral	N	N	NK	—	TT+BCND+tLLND	Cpa	Cpa	
15	2020	Gong	Retrospective	China	Kunshan Hospital	2014—2018	254	—	N	Y	Y	—	LT/TT+tCND		Ipa+Cpa	

(Continued)

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TABLE 1 Continued

Study ID	Publication Date	First Author	Type of study	Country/ Region	Institute	Research period	Patients (*n*)	Clinical Stage	Bilateral Lesions	Isthmic Lesion	Existence of Prelaryngeal Lymph Node	Maximum Diameter of Lesion (cm)	Surgical Method	Interference Factors and Outcome Factors		
														PT	PL	PT and/or PL
16	2020	He	Retrospective	China	The First Affiliated Hospital, School of Medicine, Zhejiang University	2018.7—2019.3	622	—	Y	Y	NK	—	NK		Central without PL, Lateral	
17	2020	Liu	Prospective	China	Qilu Hospital of Shandong University	2017.1—2019.3	237	cT1N1a/ cT2N1a, unilateral	N	N	NK	1.4 ± 0.8 (0.6~4.0)	TT+BCND	Cpa	Cpa	
18	2020	Zhou	Prospective	China	Qilu Hospital of Shandong University	2017.5—2019.10	242	cN0, unilateral	N	NK	NK	—	TT+BCND			Cpa
19	2021	Li	Retrospective	China	Tianjin Cancer Hospital	2017.6—2019.1	581	—	Y	NK	N	—	LT/TT+ICND +tCPa-CND +tLLND		Central without PL, Lateral	
20	2021	Qi	Retrospective	China	First Affiliated Hospital of Nanchang University	2017.2—2021.6	485	—	Y	Y	N	—	LT/TT+I/BCND +tLLND		Central without PL, Lateral	
21	2021	Yan	Retrospective	China	Tianjin Medical University Cancer Institute and Hospital	2017.8—2020.6	516	—	Y	Y	N	—	LT/TT+I/BCND +tLLND		Central without PL, Lateral	
22	2021	Zhu	Retrospective	China	First Affiliated Hospital of Chongqing Medical University	2013.7—2018.12	1575	—	Y	Y	N	—	LT/TT+ICND+p/ tLLND		PT+Ipa, Lateral	
23	2021	Zhu	Retrospective	China	First Affiliated Hospital of Chongqing Medical University	2016.12—2018.12	1271	cT1~2 N0	Y	Y	NK	≤4	LT/TT+ICND+p/ tLLND		PT+Ipa	
24	2021	Zhu	Retrospective	China	First Affiliated Hospital of Fujian Medical University	2014.1—2015.12	904	—	NK	Y	Y	—	TT/NTT+I/BCND +tLND		PT+Pa, Latreal	
25	2022	Guo	Prospective	China	Fourth Affiliated Hospital of Anhui Medical University	2018.8—2020.2	192	—	NK	NK	NK	—	NK		Central without PL	

NK, not knowledge; LT, lobe thyroidectomy; TT, total thyroidectomy; NTT, near total thyroidectomy; rPL-LND, routinely prelaryngeal lymph node dissection; CND, central lymph node dissection; BCND, bilateral CND; eCND, elective CND; pBCND, prophylactic BCND; tBCND theprapetic BCND; ICND ipisilateral CND; tCCND therapeutic contralateral CND; LLND, lateral lymph node dissection; tLLND, therapeutic LLND; pLLND, prophylactic LLND; MRND modified radical lymph node dissection; PT, pretracheal lymph node; PL, prelaryngeal lymph node; Ipa, ipsilateral paratracheal lymph node; Cpa, contralateral paratracheal lymph node; central, central lymph node; lateral, lateral lymph node.

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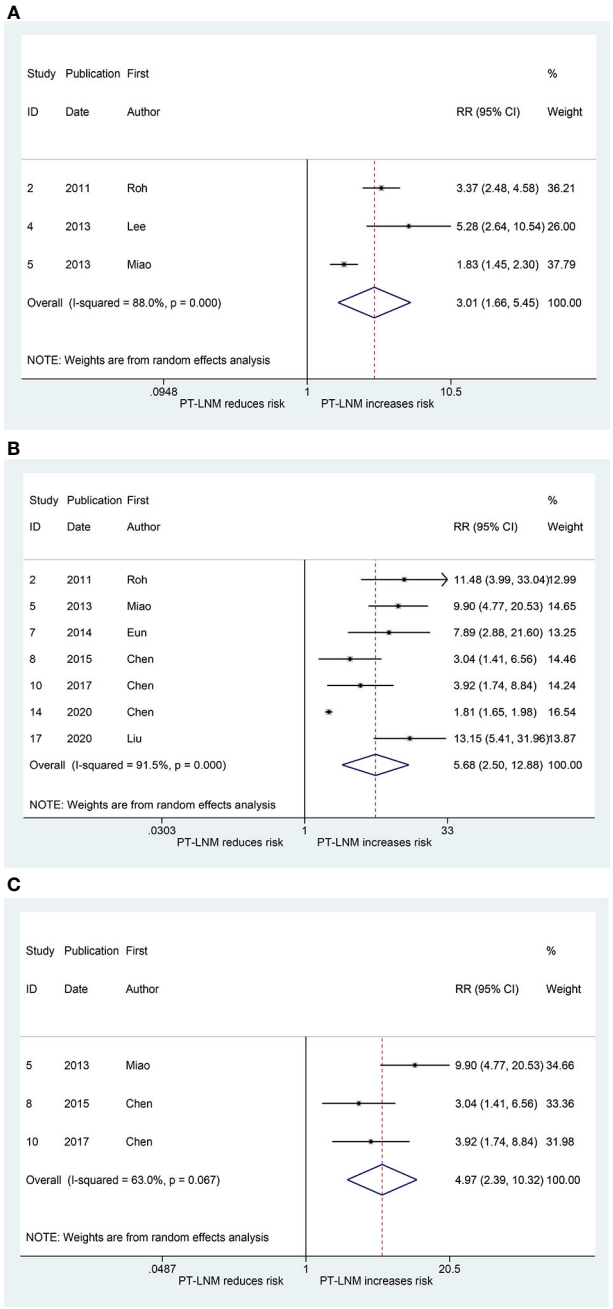

FIGURE 2
The relative risk for other groups' lymph node metastasis in patients with pretracheal lymph node metastasis (PT-LNM). **(A)** Ipsilateral paratracheal lymph node metastasis. **(B)** Contralateral paratracheal lymph node metastasis. **(C)** Contralateral paratracheal lymph node metastasis in patients with unilateral papillary thyroid carcinoma and clinical negative nodes.

p = 0.376). Figure 6B presents the pooled RR related to the pretracheal and/or prelaryngeal lymph node metastasis and the risk of contralateral paratracheal lymph node metastasis; the risk of contralateral paratracheal lymph node metastasis was higher in cases with pretracheal and/or prelaryngeal lymph node metastasis (RR = 5.53, 95% CI: 2.96, 10.32, $p < 0.001$; I^2 = 74.5%, p = 0.004; Figure 6B; Begg, p = 0.462; Egger, p = 0.215). Subgroup analysis was performed in patients who did not undergo lateral lymph node dissection. This confirmed that the risk of contralateral paratracheal lymph node metastasis was further increased in these patients (RR = 9.90, 95% CI: 1.91, 51.34, p = 0.006; I^2 = 81.3%, p = 0.005, Figure 6C; Begg, $p > 0.99$; Egger, p = 0.486).

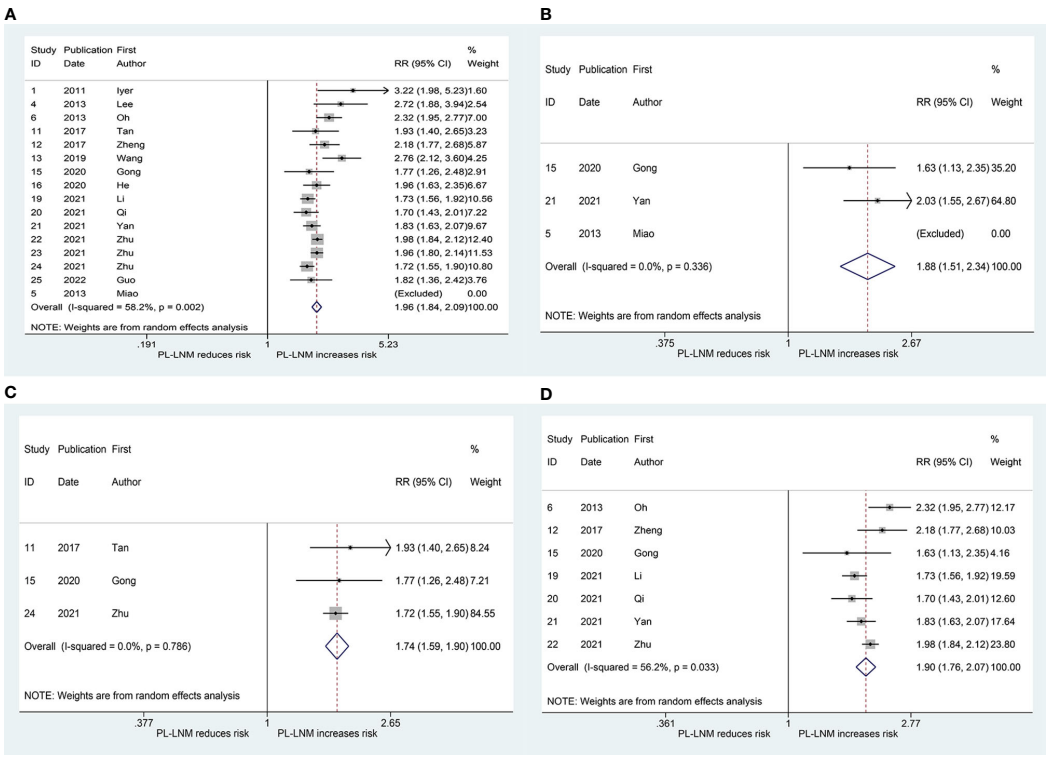

FIGURE 3
The relative risk for central (without prelaryngeal) lymph node metastasis in patients with prelaryngeal lymph node metastasis (PL-LNM). **(A)** The overall. **(B)** Subgroup of non-bilateral papillary thyroid carcinoma. **(C)** Subgroup of inclusion of cases without prelaryngeal lymph node. **(D)** Subgroup of exclusion of cases without prelaryngeal lymph node.

Discussion

The present meta-analysis suggested that pretracheal lymph node metastasis was positively associated with both ipsilateral and contralateral paratracheal lymph node metastasis and that prelaryngeal lymph node metastasis might be a risk factor for central (without prelaryngeal) and lateral lymph node metastasis.

According to the American Thyroid Association Management Guidelines, thyroidectomy without prophylactic central neck dissection is appropriate for small (T1 or T2) and noninvasive clinically node-negative PTC (7). This recommendation was based on the lack of improvement in long-term patient outcomes and an increase in temporary morbidity in these cases (3, 38–40). Similarly, prophylactic central neck dissection for non-high-risk PTC is not routinely performed in Europe (5, 6). Due to their anatomical sites, prelaryngeal and pretracheal lymph nodes can be removed without an increase in complications. Therefore, metastasis to them might be used as an indicator to further screen high-risk PTC.

A recent study indicated that more than 50% of physicians thought that total thyroidectomy for low-risk PTC was not overused, whereas more than 60% of physicians believed that radioiodine for low-risk PTC was overused (41). It implies that, regarding low-risk PTC treatment, conditional total thyroidectomy was acceptable and that radioiodine should be used less frequently. Leboulleux et al. confirmed that the prognoses of nonuse of radioiodine was non-inferior to use of radioiodine in terms of the occurrence of functional, structural, and biologic events at 3 years for patients with pT1N0/x PTC undergoing thyroidectomy (42). Therefore, it might be a better strategy that further distinguishing patients who are able to benefit from radioiodine from patients with low-risk PTC, especially pT2 PTC. In this regard, prelaryngeal and/or pretracheal lymph node metastasis might be used as an indicator.

The thyroid gland has abundant intersecting lymph vessels. Therefore, lymphatic drainage of the thyroid gland is complex, which means that there is no precise sentinel lymph node for thyroid carcinoma. The central lymph node is usually defined as a perithyroidal lymph node, which consists of the prelaryngeal lymph node, pretracheal lymph node, and paratracheal (or

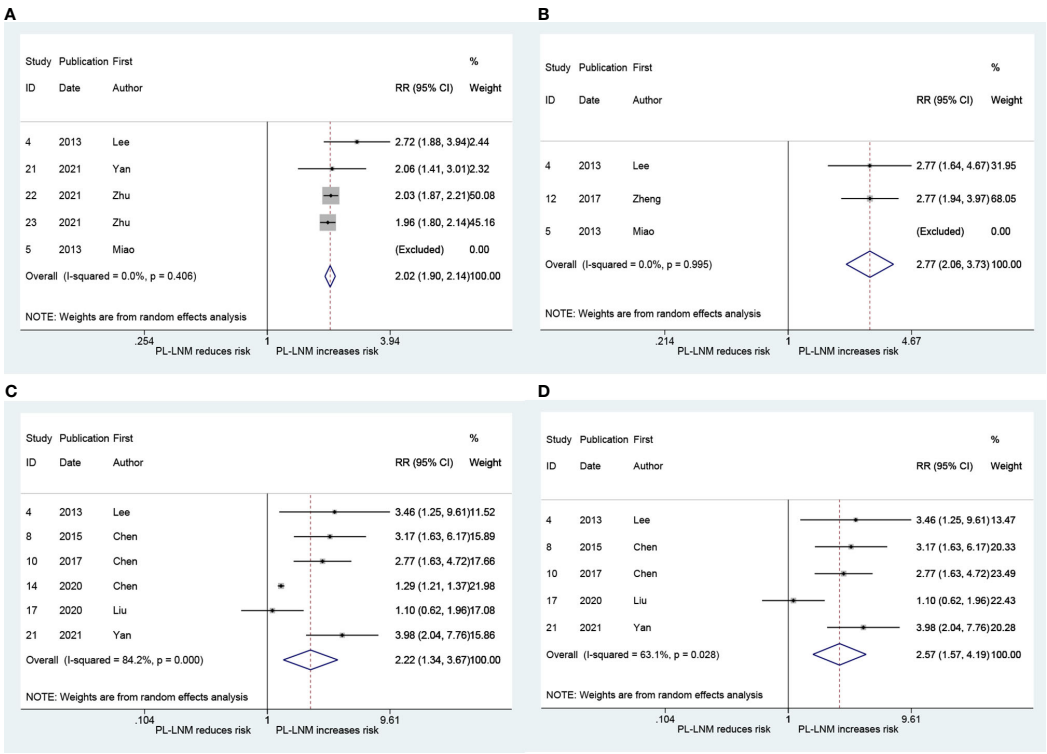

FIGURE 4
The relative risk for other groups' lymph node metastasis in patients with prelaryngeal lymph node metastasis (PL-LNM). **(A)** Ipsilateral paratracheal and/or pretracheal lymph node metastasis. **(B)** Pretracheal lymph node metastasis. **(C)** Contralateral paratracheal lymph node metastasis. **(D)** Contralateral paratracheal lymph node metastasis in the subgroup of patients without lateral lymph node dissection.

trachea-esophageal groove) lymph node (43). However, there is no clear boundary between the pretracheal lymph node and paratracheal lymph node. The pretracheal and ipsilateral paratracheal lymph node metastasis might occur successively or simultaneously. Although it could not be confirmed whether lymph node metastasis occurred earlier in pretracheal or in ipsilateral paratracheal sites, the correlation of lymph node metastasis between the two sites might not be ignored according to our meta-analysis. Pretracheal lymph node metastasis might be considered as an indicator of prophylactic ipsilateral paratracheal lymph node dissection in low-risk PTC.

Contralateral paratracheal lymph node metastasis occurs in 0–21% of patients with unilateral low-risk PTC (12, 17, 20, 24, 30). The meta-analysis suggested that pretracheal lymph node metastasis was positively related to contralateral paratracheal lymph node metastasis after excluding patients with accidental bilateral lobe lesions, isthmic lesions, or preoperative clinical lymph node metastasis. The positive association between contralateral paratracheal lymph node metastasis and pretracheal lymph node metastasis might result from the anatomical site, where the pretracheal lymph node might be one of the stations for metastasis on the way to the contralateral paratracheal lymph node.

Enlightened by the evidence that prelaryngeal lymph node metastasis was a poor prognostic factor in laryngeal and hypopharyngeal cancers, the influence of which in PTC was studied (16, 44, 45). When the number of metastatic lymph nodes exceeds five, it was regarded as an intermediate risk for PTC, which meant that radioiodine adjuvant therapy should be considered (7). A previous meta-analysis showed that prelaryngeal lymph node metastasis was positively associated with central (without prelaryngeal) lymph node metastasis, but it did not examine the effects on subgroups (such as ipsilateral paratracheal, pretracheal and contralateral) of central lymph node metastasis (8). This meta-analysis confirmed that prelaryngeal lymph node metastasis might be a predictor of ipsilateral paratracheal and/or pretracheal lymph node metastasis, pretracheal lymph node metastasis, contralateral lymph node metastasis, and lateral lymph node metastasis. Some previous studies have confirmed that patients with PTC characterized by bilateral lesions, multiple lesions, extrathyroidal extension, lymphovascular invasion, and aggressive pathology are more likely to suffer from prelaryngeal lymph node metastasis (12, 24, 27). In other words, prelaryngeal lymph node metastasis might represent more aggressive invasiveness and be a poor prognostic factor in PTC.

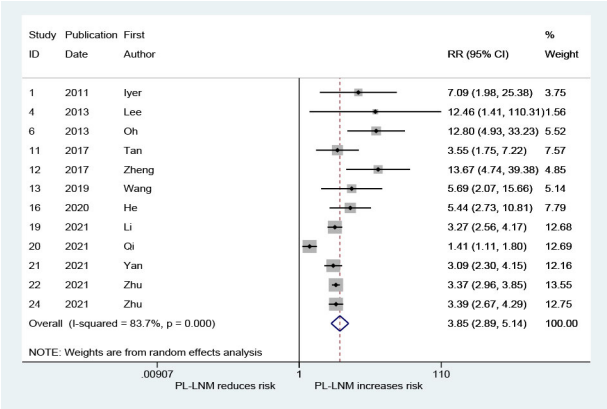

FIGURE 5
The relative risk for lateral lymph node metastasis in patients with prelaryngeal lymph node metastasis (PL-LNM).

The present meta-analysis found that the pooled RRs for ipsilateral and contralateral paratracheal lymph node metastasis in patients with pretracheal and/or prelaryngeal lymph node metastasis were both higher than that in patients with prelaryngeal lymph node metastasis and lower than that in patients with pretracheal lymph node metastasis. In consideration that lateral lymph node metastasis is a risk factor for contralateral paratracheal lymph node metastasis, patients with lateral lymph node dissection were excluded, after which the RR for contralateral paratracheal lymph node metastasis was higher. This phenomenon might suggest that the combination of prelaryngeal and pretracheal lymph node metastasis might be a more valuable predictor than prelaryngeal lymph node metastasis to predict paratracheal lymph node metastasis. Due to a lack of data, the predictive value of simultaneous prelaryngeal and pretracheal lymph node metastasis could not be analyzed, which was speculated more valuable. As for the effect on the lateral lymph node metastasis, no study explored the association.

The existence incidence of prelaryngeal lymph node was 23–76%, and the metastatic incidence was 7.7–30.5% (16, 29, 31, 36). This might be the reason for the lower RRs. A previous meta-analysis suggested that the sensitivities of prelaryngeal lymph node metastasis in predicting contralateral paratracheal, central (without prelaryngeal), and lateral lymph node metastasis were not markedly high (9). The results of the present meta-analysis were consistent with the previous study. Therefore, the states of the combination of prelaryngeal and pretracheal lymph node metastasis might be a more effective prognostic factor and an indicator for paratracheal lymph node dissection. The American Thyroid Association Management Guidelines indicate that clinically involved central nodes are an intermediate risk factor and that central neck dissection should be performed in these patients (7). Similar to the clinically involved central nodes, the prelaryngeal and/or pretracheal lymph node metastasis confirmed by intraoperative frozen biopsy might suggest that central lymph node dissection is necessary and help to further distinguish the relative high-risk PTC from the low-risk PTC.

Substantial heterogeneity was observed among the studies concerning the relationship between pretracheal lymph node metastasis and ipsilateral paratracheal lymph node metastasis, and contralateral paratracheal lymph node metastasis, between prelaryngeal lymph node metastasis and central (without prelaryngeal) lymph node metastasis, and contralateral paratracheal lymph node metastasis, between pretracheal and/or prelaryngeal lymph node metastasis and ipsilateral paratracheal lymph node metastasis, and contralateral lymph node metastasis. Heterogeneity was the major problem that affected the reliability of the pooled effect size in the meta-analysis. The following factors might have influenced the heterogeneity (1): The stages of PTC varied among the included studies. Some studies included patients with PTC with the largest diameter exceeding 4 cm. It is well known that a larger diameter is a poor prognostic factor. Some studies also included patients with cN1 PTC, which already represented an intermediate risk (2). The lesion sites were not completely consistent. Not all studies only included patients with unilateral PTC, some studies included patients with bilateral PTC and/or isthmic PTC, which was a risk factor for prelaryngeal and/or pretracheal lymph node metastasis and then affected relationship and heterogeneity (3). The way to deal with data of patients without prelaryngeal lymph nodes was different among studies. These patients have not been included in analysis in some studies (4). Diverse surgical methods were performed, which might inaccurately determine the status of the lymph node (5). The characteristics of the populations varied in different studies (6). The confounding factors were different

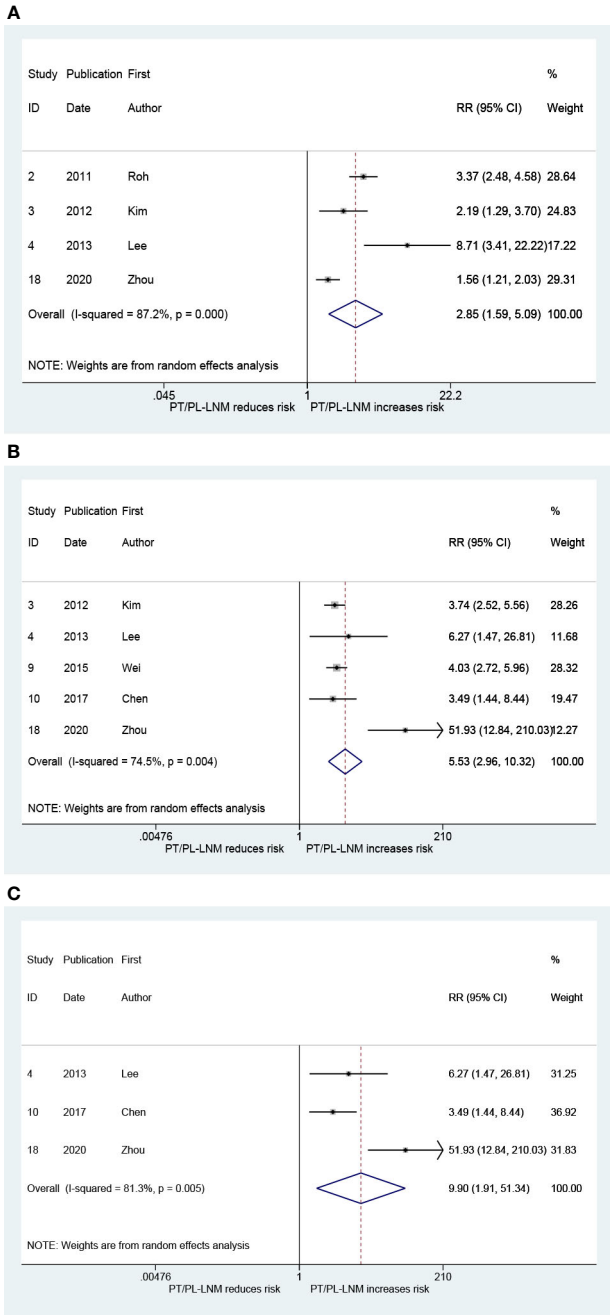

FIGURE 6
The relative risk for other groups' lymph node metastasis in patients with pretracheal and/or prelaryngeal lymph node metastasis (PT/PL-LNM). **(A)** Ipsilateral paratracheal lymph node metastasis. **(B)** Contralateral paratracheal lymph node metastasis. **(C)** Contralateral paratracheal lymph node metastasis in the subgroup of patients without lateral lymph node dissection.

across these studies (7). The quality of studies (NOS scores) was not completely consistent.

There are several limitations to this meta-analysis. First, an analysis could not be performed in patients with unilateral pT1-2 PTC because of the lack of eligible data. Second, although we performed subgroup analysis, the result was always affected by some factors, such as bilateral lesions, isthmic lesions, and lack of information about the existence of prelaryngeal lymph nodes, and the heterogeneity did not always disappear. Third, there was a potential publication bias in studies that explored the relationship between pretracheal lymph node metastasis and contralateral paratracheal lymph node metastasis, and between prelaryngeal

lymph node metastasis and contralateral paratracheal lymph node metastasis, even though they might be addressed by subgroup analysis. Fourth, studies that explored the influence of the combination of pretracheal and prelaryngeal lymph node metastasis are rare. Last, the exclusion of non-English-language studies might lead to bias.

Conclusions

This meta-analysis demonstrated that both pretracheal lymph node metastasis and prelaryngeal lymph node metastasis were significantly associated with an increased possibility of both ipsilateral lymph node metastasis and contralateral paratracheal lymph node metastasis in PTC. A similar result was obtained between pretracheal and/or prelaryngeal lymph node metastasis and paratracheal lymph node metastasis. Moreover, prelaryngeal lymph node metastasis was positively correlated with the incidence of lateral lymph node metastasis. Considering the limited number of studies, it is necessary to conduct more studies that explore the association between the combination of pretracheal and prelaryngeal lymph node metastasis and paratracheal lymph node metastasis, as well as lateral lymph node metastasis in PTC, particularly unilateral pT1-2 PTC.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

Study conception and design: BW, C-RZ, HL, X-MY, and JW. Acquisition of data: BW, C-RZ. Analysis and interpretation of data: BW, C-RZ, and HL. Drafting of manuscript: BW and C-RZ. Critical revision: BW, C-RZ, HL, X-MY, and JW. Final approval of the version to be submitted: BW, C-RZ, HL, X-MY, and JW. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Treatment and outcome of metastatic parathyroid carcinoma: A systematic review and pooled analysis of published cases

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Background: Parathyroid carcinoma (PC) is an extremely rare malignant tumor with an incidence of about 6 new cases per 10 million inhabitants per year. While several papers have been published on treatments and outcomes of PC patients with loco-regional disease, little is known about the prognosis, treatment strategies, and prognostic factors of patients with distant metastasis.

Materials and methods: We performed a systematic review and a pooled analysis of histopathologically confirmed PC cases published in literature using the following keywords: "metastasis–metastatic–secondary nodes" AND "parathyroid carcinoma". Original case reports and case series reporting metastatic parathyroid carcinoma were included. Data from 58 articles were extracted in a piloted form by five reviewers on a shared database.

Results: Seventy-nine patients with metastatic PC were identified between 1898 and 2018. Ten (13%) patients had synchronous metastases, while metachronous metastases occurred in 43 (54%) patients. The remaining 26 patients developed metastatic disease concomitantly to local recurrence. Primary hyperparathyroidism guided the diagnosis of metastatic recurrence in 58 (73%) patients. Surgery was the main primary approach adopted, as it was performed in 43 (54%) patients. Twenty (25%) patients underwent systemic antineoplastic therapy, consisting of chemotherapy, immunotherapy, tyrosine kinase inhibitors, and hexestrol therapy. Bone resorption inhibitors had a limited efficacy in the long-term control of hypercalcemia. After a median follow-up of 37.5 months, 43 (55%) patients died, 22 (51%) due to the consequences of uncontrolled PHPT. The median overall survival was 36 months (range: 1–252). Surgery was associated with a better OS (HR 0.48, 95% CI 0.26–0.88), whereas bone metastases represented a negative prognostic factor (HR 2.7, 95% CI 1.4–5.2).

Conclusion: Metastatic PC has a relatively poor prognosis. The main goals of treatment are to counteract tumor growth and control hypercalcemia. Surgery of metastases is the best approach to achieve rapid control of PHPT and longer survival. Target therapies and immunotherapy deserve to be extensively tested in metastatic PC and strategies to better control hypercalcemia should be implemented.

KEYWORDS

parathyroid carcinoma, pooled analysis, primary hyperparathyroidism, treatment strategy, prognostic factors

Introduction

Parathyroid carcinoma (PC) is an extremely rare malignant tumor with an incidence in the US SEER registry of about 6 new cases per 10 million population per year (1). PC accounts for about 0.005% of all cancers, and its prevalence in patients with primary hyperparathyroidism (PHPT) varies between 0.5% and 5% (2–4). Unlike benign parathyroid tumors, which are more frequent in female patients, PCs have an equal distribution in both sexes with an age at diagnosis between 45 and 55 years (3). PCs generally occur sporadically or less frequently in the context of familiar forms, particularly in 15% of cases of hyperparathyroidism-jaw tumor syndrome (HPT-JT) (hyperparathyroidism associated with ossifying fibroid of the jaw, cysts, and renal tumors) and more rarely in multiple endocrine neoplasia type 1 (MEN1) or type 2A (MEN2A) (5–7).

Approximately 90% of PC patients have symptomatic primary hyperparathyroidism (PHPT) (7). The most frequent symptoms are osteitis fibrosa, nephrolithiasis, neurocognitive disorders, and cardiac arrhythmia, while pancreatitis is less frequent (8–10). Clinical features caused by tumor invasion (neck masses, dysphagia, and hoarseness) are lately observed mainly in non-functioning PC (2), which accounts for less than 10% of all parathyroid carcinomas and occurs in an older population (sixth to seventh decade of life) (11–13).

Due to the early onset of PHPT, PC is usually diagnosed as a local disease and the definitive diagnosis is based on pathological features of capsular invasion, vascular invasion, and mitotic activity (2, 14). Molecular studies on PC have identified three main molecular mutated pathways: CDC73, CCND1, and PI3K/AKT/mTOR (14–17). Dysregulation of these pathways profoundly alters the balance between cell proliferation and apoptosis, and ultimately leads to a competitive growth advantage, metastatic competence, angiogenesis, and resistance to therapy in cancers (14–17).

Surgery is the mainstay of PC management. The gold standard is en bloc resection of all involved tissues and should include at least the PC and the ipsilateral thyroid lobe; the role of the central lymph node dissection is still debated. Surgery must be performed with care to avoid spillage of tumor cells into the surgical field (18).

Survival of PC patients is reportedly heterogeneous (1, 13). The estimated median overall survival is 14.3 years (13), with a 5-year survival rate of 85% and a 10-year survival rate of 49 to 77% (1, 19). Early diagnosis and radical surgery are associated with a better prognosis, while advanced age and lymph node metastases are predictive of a worse outcome (20–22).

The estimated risk of recurrence is 50%–60% at 2–5 years, more frequently in the case of a non-radical surgical approach (1, 22, 23). One-third of patients develop metastases, mainly in lung, liver, or bone (13, 24). The detection of locoregional or distant metastases is based on ultrasound of the neck, CT, or MRI of the chest and abdomen. Among nuclear medicine techniques, limited data are available in the metastatic setting. A total body scan with 99mTc-sestaMIBI and 18-FDG PET/CT may be complementary to conventional imaging in the initial staging, especially in more aggressive and rapidly evolving forms (25, 26).

While several papers have been published on the outcome of patients with early-stage disease, little is known about the prognosis, treatments, and prognostic factors of patients with relapsed and metastatic disease.

It has been reported that morbidity and mortality associated with metastatic PC is in many cases due to PHPT and related complications rather than to tumor progression (20). However, the proportion of patients who die from disease progression and that of patients who die from PHPT are unknown, as well as the impact on patient outcome of debulking surgery, systemic therapies, radiotherapy, and treatments administered to control hypercalcemia.

We systematically reviewed all cases of metastatic PC described in the literature, with the aim to perform a pooled analysis to obtain information on clinicopathological features, treatment strategies, patient outcome, and prognostic factors.

Based on the results obtained, we provided some suggestions on possible clinical approaches.

Methods and materials

Identification of eligible articles and collection

PRISMA checklist was used to present the results of this systematic review

To the extent of the best published literature on metastatic PC, a four-step search strategy was planned. First, we identified the following keywords and MeSH terms in PubMed: "metastasis–metastatic–secondary nodes" AND "parathyroid carcinoma". Secondly, the terms were searched in PubMed. Third, based on our objective, case reports and case series reporting metastatic parathyroid carcinoma were included in this review. Fourth, references to the included articles were scrutinized for additional papers. The last search was performed on 15 December 2021. Only articles that described the clinical history and treatment of individual patients with metastatic parathyroid carcinoma were selected. All articles that did not describe treatments for metastatic disease or did not report outcome or survival were excluded. No restrictions were imposed on publication date or publication status and only English-language articles were selected. The eligibility assessment was performed in an independent and unblinded standardized manner by five reviewers. Disagreements among reviewers were resolved by consensus.

Data were extracted by five reviewers on a shared database with collection and coding rules for the variables explained. After the first data extraction from a sample of included studies, the consistency of the extracted data was assessed to ensure that the reviewers who extracted the data interpreted the forms and draft instructions well. Each reviewer completed data extraction from each article independently. The following data were reported: (1) general information of the paper (first author, journal—the year of publication); (2) patient-disease data at first diagnosis (year of diagnosis, gender, age at diagnosis, clinical presentation, calcium level at diagnosis, PTH level at diagnosis, local–regional–systemic staging assessments, size of T, N-M status, treatment, type of surgery, margin status at the pathological examination, and neck dissection); (3) recurrence data (disease-free interval, site of recurrence, and first treatment of recurrence); (4) metastasis data (interval between first diagnosis and systemic relapse, sites, number, clinical presentation, treatment, chemotherapy drugs, the best response to any systemic lines of therapy, and progression-free survival of any systemic line); (5) hypercalcemia data (signs and symptoms due to hypercalcemia and systemic management of hypercalcemia); and (6) follow-up data (overall survival, follow-up status, and cause of death). If a full paper could not be retrieved, information was extracted from the abstract.

The search revealed 1,225 potentially relevant articles on metastatic parathyroid carcinoma. Reading the title or abstract, 1,103 studies were excluded for various reasons (e.g., reviews–meta-analysis, no full-text available, *in vitro*, or animal). The full text of the remaining 122 articles was evaluated, and from the references of these studies, 15 additional articles were identified. Seventy-eight articles were excluded because they contained no data on treatment of metastatic disease, outcomes, or follow-up or because of possible duplicate use of data. Finally, data from 59 papers were included in this pooled analysis. Figure 1 depicts the consort diagram.

Statistical analysis

Descriptive statistics consisted of frequency tables of categorical variables and median (ranges) for continuous variables. Normal distribution of continuous variables was assessed by Kolmogorov–Smirnov and Shapiro–Wilk tests, when applicable. Cox proportional hazards models were introduced to investigate possible prognostic factors for overall survival. We accepted a type I error of maximum 5%. All analyses were performed with SPSS (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

Results

We identified 79 patients diagnosed with metastatic PC between 1898 and 2018. Data of 59 of them (74%) were derived from case reports, 14 (18%) from single-institution case series, and 6 (8%) from multicenter series. Table 1 depicts the characteristics of the patients. Forty-two patients (53%) were men and the median age at diagnosis was 45 years (range: 13–71). Five patients had an inherited susceptibility: HPT-JT syndrome in two patients, MEN1 in two patients, and neurofibromatosis 1 (NF1) in one patient. At first presentation, 10 patients (13%) had synchronous metastasis; the remaining 69 underwent surgery as the first approach on the primary tumor and the disease later relapsed with distant metastases ± local recurrence. In 26 patients (33%), metachronous metastasis occurred together with local relapse. The median time from the first diagnosis to metastasis diagnosis [distant metastasis-free survival (DMFS)] was 36 months (range: 1–156; Figure 2A). The most frequent site of metastasis was lung (57 patients, 72%), followed by bone (16 patients, 20%), liver (11 patients, 14%), extra-regional lymph nodes (8 patients, 10%), and brain (7 patients, 9%). At the first diagnosis of metastatic disease, 25 patients (32%) had more than 10 distant nodes, and even 30 patients (38%) had ≤4 nodes. Data

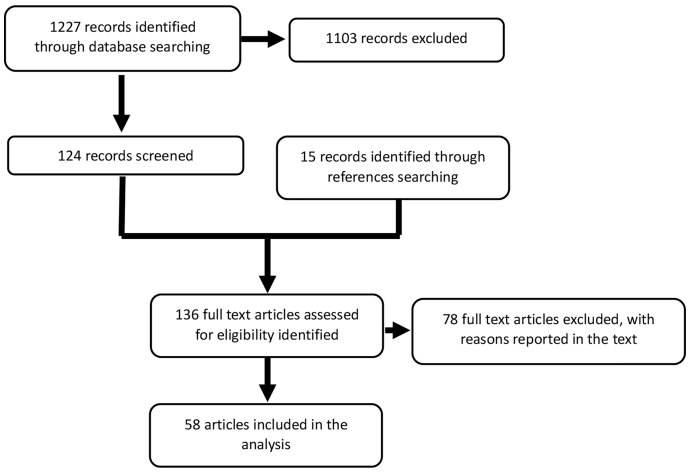

FIGURE 1
Consort diagram. The first search yielded 1,227 papers, 124 of which were relevant to this analysis. Among the references, we identified 15 additional articles. The absence of information on treatment or survival outcome excluded 78 articles. The final analysis included data from 58 articles.

on imaging techniques used for staging were heterogeneous and incomplete.

Strategies to control the tumor growth

Surgery was the primary approach for metastatic disease, as it was performed in 43 patients (54%). Thirty-five of them (81%) underwent resection of lung metastasis, while in six and four patients, surgery was performed on brain and liver metastases, respectively. In nine patients, surgery was followed by radiotherapy. No patients received adjuvant systemic therapy. Radiotherapy alone was the primary approach in 9 patients (12%); 20 patients (25%) underwent a systemic antineoplastic therapy, 11 (55%) of which as a primary approach (Table 2). The remaining 16 patients (20%) received only best supportive care. Systemic antineoplastic therapies consisted in chemotherapy in 10 patients and immunotherapy in 6, while tyrosine kinase inhibitors (TKIs) were prescribed in 5 patients and 2 patients received hexestrol therapy, a nonsteroidal estrogen. Fluorouracil + cyclophosphamide and dacarbazine (DTIC scheme) was the most used chemotherapy regimen. All four patients treated with DTIC achieved a clinical benefit from the therapy (i.e., disease response or stabilization) and median progression-free survival (PFS) was 10 months (range: 4–15 months). Two patients received anthracycline-containing schemes: methotrexate + cyclophosphamide + doxorubicin and lomustine (MAPP scheme) and doxorubicin alone, obtaining a partial response. Six patients treated with different monotherapies (vincristine, nitrogen mustard, paclitaxel, etoposide, cisplatin, capecitabine, and temozolamide) had no benefit from the treatment. Among the five patients treated with TKIs, none had a complete response, while a partial response was obtained in three of the four patients receiving sorafenib and in two patients receiving cabozantinib and regorafenib, respectively. It is noteworthy that regorafenib was administered as a second-line treatment in a patient already treated with sorafenib. Another patient received ramucirumab as a second-line approach, without any benefit. Among the patients receiving immunotherapy, four received an anti-human PTH immunotherapy with prolonged partial response in two patients (PFS of 144 and 32 months), stable disease for 6 months in the third, and PHPT control without tumor regression in the fourth. One patient received unspecified

TABLE 1 Patient characteristics.

Patient features		No. (N = 79)
Age median (range)		45 (13–71)
Sex	Male	42 (53.2%)
PHPT at metastasis presentation		58 (73.4%)
Synchronous metastasis		10 (12.7%)
Metastasis site	Lung	57 (72.2%)
	Liver	11 (13.9%)
	Bone	16 (20.3%)
	Extraregional lymph nodes	8 (10.1%)
	Brain	7 (9%)
Number of distant nodes	1	14 (18.0%)
	2–9	26 (32.9%)
	≥10	25 (31.6%)
	Missing	14 (17.7%)
Signs and symptoms of PHPT	Renal lithiasis	32 (41.6%)
	Nervous symptoms	17 (22.1%)
	Pancreatitis	9 (11.7%)
	Osteitis	28 (36.4%)
	Arrhythmia	4 (5.2%)

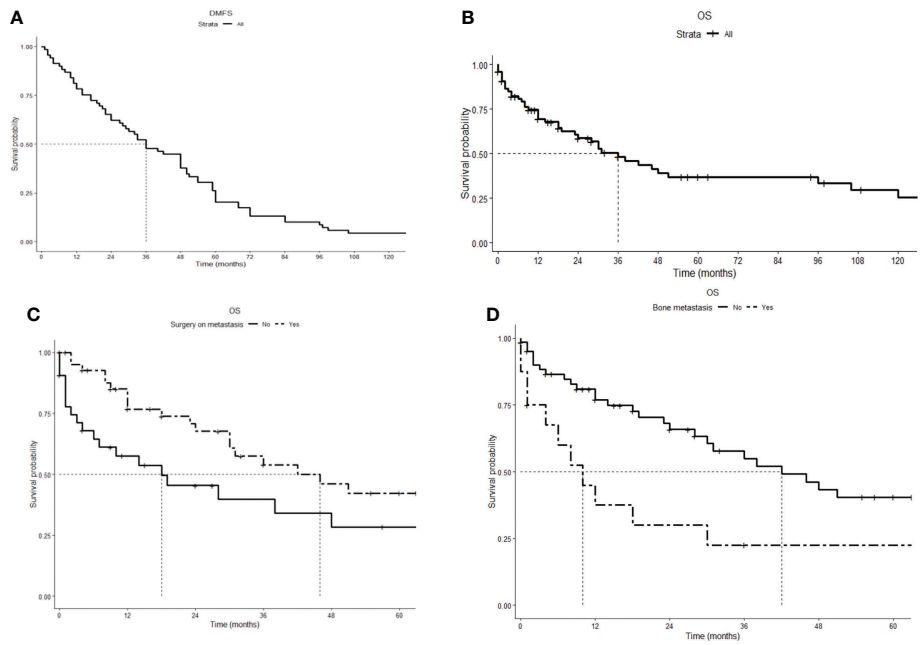

FIGURE 2
Kaplan–Meier survival curves. **(A)** Distant metastasis-free survival (DMFS): Time from the first diagnosis to diagnosis of metastasis, median 36 (range: 1–156) months. **(B)** Overall survival (OS): time from diagnosis of metastasis to death or last follow-up, median 36 (range: 1–252) months. **(C)** Overall survival comparison for cytoreductive surgery (HR 0.49, 95% CI 0.27–0.91). **(D)** Overall survival comparison for bone metastasis (HR 2.6, 95% CI 1.3–5.1).

chemoimmunotherapy without benefit and one patient, with documented microsatellite instability, obtained a partial response lasting 24 months with pembrolizumab. Table 2 summarizes the systemic treatments administered and the relative patient outcomes.

Primary hyperparathyroidism: Features and outcomes

The diagnosis of metastatic disease was associated with PHPT in 58 patients (73%), while 10 (13%) patients reported symptoms caused by tumor invasion (e.g., neck masses, dysphagia, pain, and breathlessness) and 3 patients both. In the remaining eight patients (10%), the diagnosis was incidental during follow up. The median calcium level was 14.5 mg/dl (range: 9.1–22 mg/dl; 1st quartile [Q] 12.9 mg/dl, 2nd Q 14.5 mg/dl, 3rd Q 17 mg/dl, and 4th Q 22 mg/dl). As reported in Table 1, the most frequent symptoms associated with PHPT were, in descending order of frequency, renal lithiasis, nervous symptoms, pancreatitis, osteitis, and arrhythmia. Surgical treatment of metastases was effective in controlling calcium in all 33 patients for whom data were available (missing data for 10 patients). Twenty-five of them achieved normalization of serum calcium levels and the remaining eight patients had a reduction in calcium levels. Of these latter eight patients, five had a persistence of the disease after surgery. Data on the influence of radiotherapy on hypercalcemia were missing. Various systemic therapies were used for hypercalcemia: 24 patients (29%) received bone antiresorptive drugs, which consisted of bisphosphonates in 21 patients and denosumab in 3 patients. Eighteen of these patients (74%) achieved a benefit in controlling hypercalcemia, which was transient in 14 patients, while the duration of hypercalcemia control was missing in 4 patients. The remaining six patients had only transient stability of their calcium values for 2–6 months. Nine patients (12%) received calcitonin and six patients received other hormonal therapies (e.g., somatostatin analog). Two out of three patients had transient control of hypercalcemia after subcutaneous injection of octreotide. In five patients, hypercalcemia was accompanied by severe renal insufficiency requiring dialysis. Only 2 patients received cinacalcet. Due to incomplete records, data on the duration of hypercalcemia control were not analyzed. A logistic regression analysis was performed to test the association of the following variables with hypercalcemia: age, sex, lymph node status, metastasis at first presentation, sites of metastasis, surgery on metastasis, and radiotherapy; an inverse

TABLE 2 Systemic therapies administered.

References	Drug	No. of patients	ORR	Median PFS (m) (range)	Median OS (m) (range)	Best outcome for hypercalcemia
(27, 28)	Estrogen	2	1/2	5.5 (1–10)	76 (72–80)	PR
(29)	Everolimus	1	0/1	2	Na	Na
(8, 30–32)	5FU + cyclophosphamide + dacarbazine	4	3/4	10 (4–15)	95 (35–162*)	CR
(8, 29, 33–35)	Other chemotherapies	6	0/6	2 (1–4)	83.5 (9–144)	PD
(8, 33, 34, 36)	Anthracycline monotherapy	4	1/4	3 (2–16)	23 (17–144)	PD**
(8)	Dacarbazine monotherapy	1	0/1	3	144	PD
(37)	Methotrexate + adriamycin + cyclophosphamide + lomustine	1	1/1	18*	29*	Na
(37, 38)	Immune checkpoint inhibitors	1	1/2	11.5 (2–21*)	14.5	CR
(29, 39)	Sorafenib	4	3/4	10 (3–17*)	22 (Na–22*)	CR
(15)	Cabozantinib	1	1/1	2–3	Na	Na
(15)	Ramucirumab	1	0/1	1	Na	Na
(15)	Regorafenib	1	1/1	2	Na	Na
(40–43)	Anti-PTH vaccine	4	2/4	NR (5–144*)	NR (10–144*)	CR

CR, complete resolution; Na, not assessed; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progression disease; PFS, progression-free survival; PR, partial response.
* Censured.
** The patient, who benefited from chemotherapy, did not have PHPT.
° Other chemotherapies: vincristin, nitrogen mustard, paclitaxel, ethoposide, cisplatin, capecitabin, and temozolamid.

relationship was found with the presence of distant lymph nodes (HR 0.16; 95% CI 0.03–0.83).

Survival analysis

After a median follow-up of 37.5 months, 43 patients (55%) died. The causes of death were as follows: uncontrolled PHPT in 22 patients (51%), tumor progression in 14 patients (32%), and other causes in 3 patients (7%). The cause of death was not specified for four patients. The median overall survival from diagnosis of metastasis to death or last follow-up (OS) was 36 months (range: 1–252; Figure 2B). As reported in Table 3 and Figures 2C, D, cytoreductive surgery had an independent favorable role in predicting patients' OS (HR 0.48, 95% CI 0.26–0.88), while bone metastases had a negative prognostic significance (HR 2.7, 95% CI 1.4–5.2). Information on individual patients can be found in the Supplementary Material.

Discussion

Due to its extreme rarity, few data in the literature are available to guide the diagnosis and treatment of metastatic PC. The present pooled analysis of published cases confirms that PC occurs in patients in the fourth decade of age without difference between the two sexes. In most patients, the symptoms and signs leading to the diagnosis of distant relapse were related to PHPT, although 13% of patients reported symptoms caused by growth of the tumor mass (e.g., neck masses, dysphagia, pain, and breathlessness). These data have important implications on the follow-up of operated patients, which is based on prospective evaluation of blood levels of calcium and parathyroid hormone but should also include periodic radiological evaluations. Since, in the present series, the most frequent site of metastasis was lung, followed by bone, liver, and lymph nodes, a CT scan of the abdomen and thorax may be considered adequate in the follow-up. However, 9% of patients developed brain metastases; thus, a

TABLE 3 Prognostic factors of patients with metastatic parathyroid carcinoma according to univariate and multivariate analyses.

Overall survival		Univariate			Multivariate		
		HR	95% CI	*p*	HR	95% CI	*p*
Lung metastasis	Yes	0.483	0.239–0.976	0.043			
Liver metastasis	Yes	2.415	1.178–4.952	0.016			
Bone metastasis	Yes	2.704	1.395–5.243	0.003	2.303	1.138–4.663	0.020
Surgery on metastasis	Yes	0.478	0.260–0.878	0.017	0.474	0.246–0.912	0.025
Radiotherapy	Yes	2.184	1.131–4.220	0.020			
DMFS	>36 months	0.461	0.237–0.895	0.022			

brain CT and/or MR should be considered in case of appearance of suspicious neurological symptoms. Noteworthy, in 26 patients (33%), distant metastases occurred together with local recurrence; this emphasizes the need to include accurate clinical examination and neck ultrasound in the follow-up. With regard to nuclear medicine techniques, the case series presented in literature suggest that a total body acquisition with 99mTc-sestaMIBI and 18F-FDG PET/CT can be complementary to conventional imaging in the initial staging, especially in more aggressive and rapidly evolving forms (25, 26). However, limited and heterogeneous data are available in the metastatic setting, since only few patients have been evaluated with these techniques. Therefore, we cannot draw any suggestions on the use of nuclear medicine techniques in the follow-up of PC patients after surgery. A frequent question about follow-up is its duration. In the present series, most metastatic recurrences occurred within 60 months; hence, follow-up should be continued for at least 5 years. It should be noted that one patient in this series developed metastases after 13 years, suggesting a possible follow-up extension beyond 5 years in selected cases.

The main goals of treating metastatic PC are to counteract tumor growth and control hypercalcemia. The control of hypercalcemia is of paramount importance, since in this series it was the cause of death in half of the patients. All PC patients with PHPT had at least one metastatic site; however, the extent of disease did not correlate with the severity of hypercalcemia. Therefore, surgery of metastasis with radical intent was effective in controlling hypercalcemia and should be pursued whenever possible, as it allowed rapid control of PHPT and a longer survival. This is relevant as many patients present an oligo metastatic disease at first relapse, and this observation, together with the predilection of the lung as a site of metastasis, favors surgery. If complete excision of all metastases is not possible, local regional treatments, such as radio-frequency ablation, similarly to what is adopted in other tumors, could reasonably be considered, although data on the efficacy of these treatments could not be obtained in this series.

With regard to systemic therapies, long-term control of hypercalcemia in malignancies can be achieved with the use of bone resorption inhibitors such as bisphosphonates and denosumab. In patients with PC-related hypercalcemia, however, the effect of these drugs was transient, and the syndrome was invariably resistant after initial control. Denosumab appears to be effective in patients with zoledronic acid resistance (44), but our case series does not allow us to obtain data in this regard, as only three patients were treated with denosumab. Good results have been obtained with calcimimetic drugs as cinacalcet, which is a recommended treatment (45, 46). However, no information on the effectiveness of this drug on patient outcome is available in this series. Two anecdotal case reports describe a response of hypercalcemia to estrogen therapy (27, 28). Furthermore, two patients had a transient improvement of PHPT in response to somatostatin analogue, but the results with this drug are still debated (47).

The prognosis of patients with metastatic PC was relatively poor, with a median survival of 36 months, but with considerable variability over a range of 1 to 255 months. The independent prognostic parameters were surgery as a favorable factor, underlining the importance of this therapeutic modality in this setting, and bone metastases as a worsening factor. This latter finding is in contrast with what has been observed in other metastatic malignacies (48, 49), in which the presence of visceral metastases plays a major role.

Data on the efficacy of systemic anticancer therapies are scarce and sometimes anecdotal. The few cases treated with chemotherapy have shown activity of alkylating drugs and anthracyclines. Target therapy could be a suitable option and several potentially actionable genomic alterations have been described, including PTEN, NF1, KDR, PIK3CA, and TSC242 (15, 16). In the present series, multikinase inhibitors targeting neoangiogenesis seem promising, as all drugs tested were active, although only five cases were considered. The same applies to immunotherapy, for which it is worth mentioning the interesting results obtained by a vaccine consisting of human and bovine PTH-like immunogenic fragments, which induced the formation of autoantibody against PTH and achieved lasting control of tumor growth and associated malignant hypercalcemia in three cases (40, 41, 50).Based on these very promising results, this treatment strategy deserves to be further tested either alone or in combination with modern checkpoint inhibitors.

In this study, we included the largest number of metastatic PC cases. Previous studies were mostly case reports or case series, and mostly included PC with and without recurrence. We focused on metastatic status, overall survival, and treatment, which were not highlighted in previous studies. To reduce potential bias in the analyses, we undertook a systematic review with the independent application of pre-defined inclusion criteria and data extraction. However, our study has some limitations. Demographics data were only derived from secondary data without standard protocols and from a long period; hence, there was high heterogeneity. Moreover, the study suffered from publication bias.

Conclusion

Metastatic parathyroid carcinoma arises in the fourth decade of age and has a poor prognosis. Increased calcemia and parathormone values lead to diagnosis in most patients, although some report only symptoms caused by the growth of the tumor mass. Oligometastatic lung disease is the most frequent pattern of recurrence, and in about one-third of patients, local recurrence occurs together with distant metastases. The main goals of the treatment are to counteract tumor

TABLE 4 Suggestions for the clinical management of PC patients.

Follow-up of radically resected patients
• After definitive treatment of the local disease, a patient follow-up should be implemented, including physical examination, blood calcium and parathyroid hormone levels, and periodic radiological imaging assessments.
• Periodic radiological evaluations during follow-up should include neck ultrasound, and CT scan of the abdomen and thorax. Brain CT and/or MR should be considered in case of suspicious neurological symptoms.
• Follow-up should be prosecuted for at least 5 years.
• Total body 99mTc-sestaMIBI and/or 18F-FDG PET/CT scans can be complementary to conventional imaging in the initial staging.
Treatment
• Surgery of metastasis should be persecuted as first approach whenever possible.
• If complete removal of all metastases is not possible, other local treatments could reasonably be considered.
• Systemic therapies should be considered in patients not amenable to surgery and/or local regional therapies.
Systemic treatment
• Transient control of hypercalcemia can be achieved with the use of bone resorption inhibitors, such as bisphosphonates and denosumab.
• Calcimimetic drugs, such as cinacalcet, are recommended treatment.
• Dacarbazine and anthracyclines containing schemes are the chemotherapy of choice in the management of metastatic PC.
• Anti-angiogenetic drugs and immunotherapy could also be possible options.

growth and control hypercalcemia. The latter challenge is of paramount importance, as it is the cause of death in at least half of patients. Surgery of metastases is the best approach to achieve rapid control of PHPT and longer survival. When surgery cannot be radical, other complementary local–regional approaches can be used. Systemic therapies should be considered when the disease could not be managed with local ablative treatments. According to the few data in the literature, dacarbazine, anthracyclines, sorafenib, and other antiangiogenetic drugs provided some positive results in the management of metastatic PC. Also, immunotherapy with vaccines based on bovine PTH-like immunogenic fragments seems promising, and this strategy deserves to be tested in association with modern immune checkpoint inhibitors. Based on the results of this systematic review and pooled analysis, we propose a list of suggestions for the management of patients with metastatic PC (Table 4).

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

AA, AB, SG, and PB contributed to conception and design of the study. AA, DS, AT, LL, and CM contributed to the research and extraction of data. MZ performed the statistical analysis. AA, DS, AT, LL, and CM wrote the first draft of the manuscript. MZ wrote a section of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.997009/full#supplementary-material

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Nomograms for the prediction of lateral lymph node metastasis in papillary thyroid carcinoma: Stratification by size

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Background: Lateral lymph node metastasis (LLNM) is a risk factor of poor prognosis in papillary thyroid cancer (PTC). We aimed to determine predictive factors and develop the nomograms for LLNM in patients with papillary thyroid microcarcinoma (PTMC) and macro-PTC.

Methods: We reviewed the medical records of 1,106 patients who underwent surgery between January 2019 and January 2022. Patients were divided into a PTMC and a macro-PTC group. We developed preoperative and postoperative nomograms for predicting LLNM based on results of multivariate analysis. Internal calibration was performed for these models.

Results: The number of metastatic lymph nodes in lateral compartment was higher in macro-PTC patients. LLNM was independently associated with gender, the number of foci, location, shape, and central lymph node metastasis (CLNM) in PTMC patients. For macro-PTC patients, chronic lymphocytic thyroiditis, the number of foci, location, margin, CLNM, and central lymph node ratio were all independent predictors for LLNM. All the above factors were incorporated into nomograms, which showed the perfect discriminative ability.

Conclusion: The diameter of the tumor has an impact on the rate of LLNM. Separate predictive systems should be used for PTMC and macro-PTC patients for more accurate clinical assessment of lateral lymph node status. Through these nomograms, we can not only detect high-risk patients with occult LLNM preoperatively, but also form appropriate treatment protocols for postoperative management of PTC patients with different risks.

KEYWORDS

papillary thyroid carcinoma, papillary thyroid microcarcinoma, lateral lymph node metastasis, nomogram, surgery

Introduction

The incidence of papillary thyroid cancer (PTC), which accounts for approximately 80.0% of thyroid cancers, has been increasing worldwide in recent decades (1). Although most patients with PTC have a good prognosis, the incidence of lymph node metastasis (LNM) is high, ranging from 20% to 90% (2–6). As reported, PTC patients with lateral lymph node metastasis (LLNM) had higher incidence of disease persistence, recurrence, and distant metastasis when compared to patients with or without central lymph node metastasis (CLNM) (7).

Unless suspicious LLNM is confirmed by preoperative fine needle aspiration cytology (FNAC), prophylactic lateral neck dissection (LND) is not recommended for patients with clinically negative (cN0) lateral neck (1). However, the incidence of occult LLNM was reported to be as high as 30.4% among PTC patients (8). Considering the presence of occult LLNM, which was hardly detected in the preoperative period, some patients who undergo thyroidectomy may detect the residual metastatic lymph nodes in the lateral compartment (9). Therefore, establishing predictive models for early detection of LLNM and residual risk is critical.

Tumor size is an important factor among the clinical and pathological features that can be assessed preoperatively and intraoperatively. With the increasing detection rate of papillary thyroid microcarcinoma (PTMC) (≤10 mm diameter) (1), the optimal treatment strategy of PTMC, especially whether PTMC needs surgery, remains controversial. Active surveillance has been recommended as a reasonable alternative approach to immediate surgery for low-risk PTMC according to a 10-year observational study (10). The possibility of LNM during active surveillance is a major concern for clinicians and patients. Clinically apparent lymph nodes re-stratified patients with PTMC from low risk to intermediate risk according to the 2015 American Thyroid Association (ATA) risk stratification (1). In addition, macro-PTC (>10 mm diameter) is more vulnerable to aggression. According to the previous research, tumor size was the best predictor of CLNM and LLNM and was significantly associated with lymph node recurrence (11). Therefore, we assumed that clinicopathological features may be different between PTMC and macro-PTC patients, and the clinical management of PTMC patients should be differentiated from macro-PTC patients.

Unlike previous studies that only determined risk factors of LLNM, we first aimed to investigate the differences in clinicopathological features between PTMC and macro-PTC patients, especially differences in LNM. Then, we aimed to perform subgroup analysis on this basis, investigating the risk factors for LLNM in PTMC and macro-PTC patients, respectively. Finally, we attempted to develop nomograms to predict LLNM. Through these accurate and easy-to-use nomograms, we can proactively detect high-risk patients with occult LLNM preoperatively and form appropriate treatment protocols for postoperative management of PTC patients with different risks.

Materials and methods

Study design

This retrospective study was approved by the Institutional Review Board of Changzhou First People's Hospital, and the need for informed consent was waived due to the retrospective nature of this study. We retrospectively reviewed the medical records of 1,257 patients with pathologically proven PTC who underwent primary surgical treatment at our institution between January 2019 and January 2022. The following exclusion criteria were applied: (1) non-PTCs or other subtypes than classic PTC; (2) history of prior treatment for head and neck cancer; (3) history of cervical radiation exposure in childhood; (4) family history of thyroid cancer; (5) history with other malignancy; (6) incomplete clinical data; (7) loss to follow-up; and (8) patients who underwent non-curative surgery (residual tumor or lymph node detected within 6 months of initial surgery). A total of 1,106 patients were included (Figure 1).

Preoperative examination and surgical procedures

Diagnostic medical sonographers with over 5 years of experience performed the high-resolution neck ultrasound to evaluate the lymph node status and thyroid nodules. Each thyroid nodule would be evaluated by the following features: shape, tumor site, nodular composition, echogenicity, margin, and echogenic foci. Cervical lymph nodes with the following characteristics were suspected of metastases: hyperechoic changes, roundness or necrosis, loss of the fatty hilum, microcalcification, or peripheral vascularity (12). FNAC was conducted to confirm the histopathologic diagnosis preoperatively for suspicious thyroid nodules and lateral lymph nodes.

Total thyroidectomy was performed if the patient had any of the following factors: tumor located in the thyroid isthmus, bilateral multifocality, tumor size >4.0 cm, or 1.0 cm < tumor size ≤ 4.0 cm with risk factors for recurrence, presence of extrathyroidal extension (ETE), and suspicious LLNM preoperatively (1). Otherwise, patients underwent lobectomy plus isthmectomy only. According to the Chinese guidelines for diagnosis and treatment of differentiated thyroids, central neck dissection (CND) was routinely performed for all PTC patients. On the premise of effectively protecting the parathyroid gland and recurrent laryngeal nerve (RLN), ipsilateral CND was performed for ipsilateral lesion; bilateral CND was performed for isthmus lesion and bilateral lesions. For patients with clinically suspicious

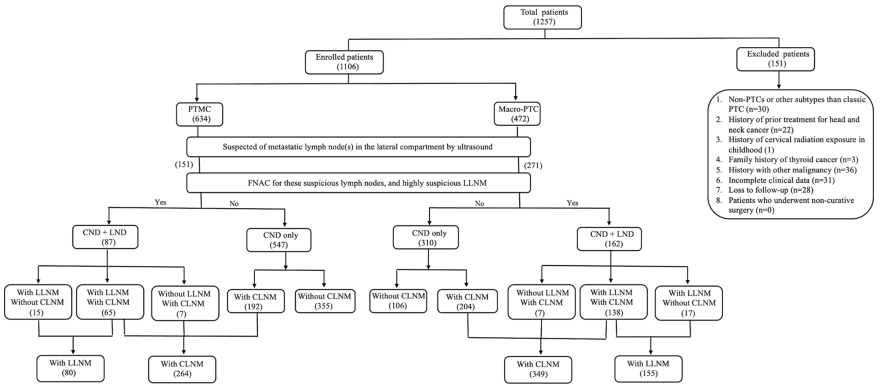

FIGURE 1
Flowchart of the patients enrolled in this study.

unilateral LLNM confirmed by FNAC, total thyroidectomy plus CND and ipsilateral therapeutic lateral neck dissection (LND) was performed. CND included the removal of prelaryngeal, pretracheal, and paratracheal lymph nodes. LND referred to the removal of the lateral lymph nodes, including level II to V, while preserving the spinal accessory nerve, internal jugular vein, or sternocleidomastoid muscle. The status of cervical lymph nodes was confirmed by a final histological examination.

Definitions

Body mass index (BMI) (kg/m^2) was defined as weight (kg) divided by height (m) squared. According to the World Health Organization-BMI standard, enrolled PTC patients were divided into normal (BMI < 25 kg/m^2), overweight (25 ≤ BMI < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2) group. The diagnosis of chronic lymphocytic thyroiditis (CLT) included any of the following: (i) elevated antibodies to thyroid peroxidase level (>50 IU/ml), and/or (ii) findings of diffuse heterogeneity on ultrasound, and/or (iii) diffuse lymphocytic thyroiditis on histopathology (13). ETE was defined as a tumor with capsular abutment of more than 25% of its perimeter on ultrasound (14). The tumor size and location were determined by the largest predominant primary lesion for multifocal lesions. For patients who did not undergo LND, the number of metastatic lymph nodes in lateral compartment was clinically considered to be zero. The central lymph node ratio (CLNR) was calculated as the ratio of metastatic lymph nodes in the central compartment out of the number of dissected lymph nodes in the central compartment.

Postoperative complications

All patients underwent fiber laryngoscope before and after surgery to assess the mobility of vocal cords. Transient RLN injury was regarded as decreased or absence of vocal cord mobility resolving within 6 months of surgery. Impaired vocal cord mobility for more than 6 months after surgery was considered permanent RLN injury. Serum calcium and phosphorus concentrations were measured in all patients after surgery. Transient hypocalcemia was defined as an ionized calcium level <2.10 mmol/L during hospitalization and the calcium level returned to normal within 6 months. Permanent hypoparathyroidism was diagnosed in patients still requiring calcium supplementation more than 6 months after surgery.

Statistical analysis

All statistical analysis was performed by using SPSS Version 25.0 software (Chicago, IL, USA), and R software Version 3.5.3 (The R Foundation for Statistical Computing). Pearson Chi-square test or Fisher's exact test was used for categorical data, and independent *t*-test was used to compare continuous variables. Differences with *p* values less than 0.05 were regarded as significant. Binary logistic regression analysis was conducted to assess independent associations of LLNM with factors found to be statistically significant by univariate analysis. We constructed the risk prediction model Nomogram in R software according to independent factors screened through the logistic regression model. The discriminative power of the nomogram for predicting LLNM was determined using the area under the receiver operating characteristic (ROC) curve, also known as the concordance index, with values ranging from 0.50 to 1.00. To address model overfitting and obtain a relatively unbiased evaluation, we used 1,000 random bootstrap resamples. The calibration of diagnostic nomogram was further evaluated by the calibration chart, which plotted the predicted probability of the nomogram against the observed probability.

Results

Baseline clinicopathological characteristics of PTC patients with different sizes

In our study, 151 PTMC patients and 271 macro-PTC patients were suspected of LLNM by preoperative ultrasound and underwent FNAC for these suspicious lymph nodes. Eighty-seven PTMC patients and 162 macro-PTC patients had high suspicion of LLNM and underwent LND. Postoperative pathology revealed LLNM in 80 PTMC patients and 155 macro-PTC patients (Figure 1).

Table 1 shows the clinicopathological characteristics of the enrolled 1,106 PTC patients in this study. The 1,106 patients consisted of 800 women (72.3%) and 306 men (27.7%). There were 196 patients (17.7%) aged 55 years or older. CLT was present in 370 patients (33.5%) and absent in the remaining 736 patients (66.5%). The number of patients with one, two, and more than two foci in the thyroid gland were 712 (64.4%), 268 (24.2%), and 126 (11.4%), respectively. Tumors located in the upper portion of the thyroid gland were detected in 553 patients (50.0%), and tumors located in the middle/lower lobe of thyroid were detected in 553 patients (50.0%). In this study, tumors located in the isthmus were included in the group with tumors located in the middle pole. There were 74 cases of isthmus tumors, including 44 cases in the PTMC group and 30 cases in the macro-PTC group.

We divided patients into the PTMC group and the macro-PTC group according to the largest diameter of tumor. There were 634 patients in the PTMC group and 472 patients in the macro-PTC group. There was a statistically significant difference between two groups in terms of sex, BMI, number of foci, echogenicity, shape, margin, echogenic foci, CLNM, and LLNM (all $p < 0.05$). The number of removed lymph nodes in the central compartment of macro-PTC patients was more than PTMC patients (8.1 ± 5.1 vs. 7.5 ± 4.6, $p = 0.031$). However, there was no statistical difference in the number of removed lymph nodes in the lateral compartment between the two groups ($p = 0.881$). The number of metastatic lymph nodes in the central compartment and lateral compartment was fewer in the PTMC group when compared with the macro-PTC group (1.2 ± 2.2 vs. 3.1 ± 3.3; 4.3 ± 3.1 vs. 5.6 ± 4.5, respectively, all $p < 0.05$). Figure 2 showed the boxplot of the number of removed and metastatic lymph nodes in the lateral compartment. As for other clinicopathological factors, no significant differences were observed.

Of 634 PTMC patients, 12 patients developed RLN injury (including 7 patients with transient RLN injury and 5 patients with permanent RLN injury). As for 472 macro-PTC patients, 7 patients developed RLN injury (including 4 patients with transient RLN injury and 3 patients with permanent RLN injury). Hypocalcemia occurred in 25 PTMC patients, of whom 19 cases were temporary and 6 cases were permanent. As for macro-PTC patients, 11 cases developed hypocalcemia, including 7 temporary cases and 4 permanent cases. There was no statistical difference in the incidence of RLN injury and hypocalcemia between PTMC and macro-PTC patients.

Prevalence and distribution of metastatic lymph nodes in the lateral neck

As shown in Figure 1, among 634 PTMC patients, 87 patients had suspected metastatic lymph nodes in the lateral compartment, and of 472 macro-PTC patients, 162 patients had suspected metastatic lymph nodes in the lateral compartment. A total of 249 PTC patients underwent the total thyroidectomy plus CND and ipsilateral therapeutic LND. Postoperative pathology showed that 80 PTMC patients developed LLNM, and 155 macro-PTC patients developed LLNM.

Table 2 shows the distribution of metastatic lymph nodes in the lateral compartment of PTMC and macro-PTC patients. Simultaneous lymph node metastasis in level II, III, and IV was the most common in PTMC and macro-PTC patients, which is up to 21.8% and 24.7%, respectively. For the rate of metastatic lymph nodes in the lateral compartment divided by region, level IV metastasis was the most common in PTMC and macro-PTC patients (75.9% for PTMC, 79.6% for macro-PTC), followed by level III metastasis (69.0% for PTMC, 73.5% for macro-PTC); level V metastasis was the least common (20.7% for PTMC, 23.5% for macro-PTC).

Risk factors for LLNM in PTMC patients

We first analyzed the risk factors for LLNM in PTMC patients. As shown in Table 3, LLNM presented the significant association with sex, tumor size, the number of foci, location, shape, echogenic foci, CLNM, and CLNR in the univariate analysis (all $p < 0.05$).

Multivariate logistic regression modeling was further conducted to screen for significant variables associated with LLNM in PTMC patients. Multivariate analysis showed that sex (OR: 2.011, 95% CI: 1.162–3.482, $p = 0.013$), two tumor foci (OR: 2.050, 95% CI: 1.106–3.801, $p = 0.023$), three or more tumor foci (OR: 3.581, 95% CI: 1.667–7.693, $p = 0.001$), tumor located in the upper pole (OR: 2.623, 95% CI: 1.519–4.530, $p = 0.001$), tumor with aspect ratio (A/T) >1 (OR: 2.455, 95% CI: 1.424–4.235, $p = 0.001$), and presence of CLNM (OR: 7.390, 95% CI: 3.903–13.990, $p < 0.001$) remained independent predictors for LLNM in PTMC patients.

Risk factors for LLNM in macro-PTC patients

The relationships between predictive factors and LLNM in macro-PTC patients are presented in Table 4. Sex, BMI, CLT,

TABLE 1 Clinicopathological features of PTC patients with different tumor sizes.

Characteristics	Total	PTMC	Macro-PTC	*p*-value
	1,106	634	472	
Sex				
Male	306 (27.7%)	150 (23.7%)	156 (33.1%)	
Female	800 (72.3%)	484 (76.3%)	316 (66.9%)	0.001
Age (years)				
≥55	196 (17.7%)	113 (17.8%)	83 (17.6%)	
<55	910 (82.3%)	521 (82.2%)	389 (82.4%)	0.918
BMI (kg/m^2)				
Normal	123 (11.1%)	80 (12.6%)	43 (9.1%)	
Overweight	592 (53.5%)	350 (55.2%)	242 (51.3%)	
Obesity	391 (35.4%)	204 (32.2%)	187 (39.6%)	0.018
Diabetes				
Absence	964 (87.2%)	542 (85.5%)	422 (89.4%)	
Presence	142 (12.8%)	92 (14.5%)	50 (10.6%)	0.054
CLT				
Absence	736 (66.5%)	411 (64.8%)	325 (68.9%)	
Presence	370 (33.5%)	223 (35.2%)	147 (31.1%)	0.160
BRAF V600E mutation				
Negative	142 (12.8%)	73 (11.5%)	69 (14.6%)	
Positive	964 (87.2%)	561 (88.5%)	403 (85.4%)	0.127
The number of foci				
1	712 (64.4%)	435 (68.6%)	277 (58.7%)	
2	268 (24.2%)	144 (22.7%)	124 (26.3%)	
3 or more	126 (11.4%)	55 (8.7%)	71 (15.0%)	<0.001
Multifocality				
Solitary	712 (64.4%)	435 (68.6%)	277 (58.7%)	
Ipsilateral multifocality	150 (13.6%)	87 (13.7%)	63 (13.3%)	
Bilateral multifocality	244 (22.1%)	112 (17.7%)	132 (28.0%)	<0.001
Location				
Upper	553 (50.0%)	301 (47.5%)	252 (53.4%)	
Middle/Lower Upper	553 (50.0%)	333 (52.5%)	220 (46.6%)	0.052
Nodular composition				
Mixed cystic and solid	10 (0.9%)	4 (0.6%)	6 (1.3%)	
Solid	1,096 (99.1%)	630 (99.4%)	466 (98.7%)	0.269
Echogenicity				
Hyperechoic or isoechoic	33 (3.0%)	12 (1.9%)	21 (4.4%)	
Hypoechoic	1,057 (95.6%)	616 (97.2%)	441 (93.4%)	
Very hypoechoic	16 (1.4%)	6 (0.9%)	10 (2.1%)	0.012
Shape				
A/T ≤1	710 (64.2%)	455 (71.8%)	255 (54.0%)	
A/T >1	396 (35.8%)	179 (28.2%)	217 (46.0%)	<0.001
Margin				
Smooth	646 (58.4%)	435 (68.6%)	211 (44.7%)	
Lobulated or irregular	289 (26.1%)	131 (20.7%)	158 (33.5%)	
ETE	171 (15.5%)	68 (10.7%)	103 (21.8%)	<0.001
Echogenic foci				
None or large comet-tail artifacts	319 (28.8%)	230 (36.3%)	89 (18.9%)	
Macrocalcifications	67 (6.1%)	36 (5.7%)	31 (6.6%)	

(Continued)

TABLE 1 Continued

Characteristics	Total	PTMC	Macro-PTC	*p*-value
Peripheral calcifications	8 (0.7%)	0 (0.0%)	8 (1.7%)	
Punctate echogenic foci	712 (64.4%)	368 (58.0%)	344 (72.9%)	<0.001
CLNM				
Absence	493 (44.6%)	370 (58.4%)	123 (26.1%)	
Presence	613 (55.4%)	264 (41.6%)	349 (73.9%)	<0.001
LLNM				
Absence	871 (78.8%)	554 (87.4%)	317 (67.2%)	
Presence	235 (21.2%)	80 (12.6%)	155 (32.8%)	<0.001
No. of removed LNs in CC	7.7 ± 4.9 (2–35)	7.5 ± 4.6 (2–25)	8.1 ± 5.1 (2–35)	0.031
No. of metastatic LNs in CC	2.0 ± 2.9 (0–18)	1.2 ± 2.2 (0–15)	3.1 ± 3.3 (0–18)	<0.001
No. of removed LNs in LC*	28.0 ± 10.3 (10–69)	28.1 ± 10.7 (11–57)	27.9 ± 10.2 (10–69)	0.881
No. of metastatic LNs in LC*	5.2 ± 4.1 (0–22)	4.3 ± 3.1 (0–13)	5.6 ± 4.5 (0–22)	0.006

PTC, papillary thyroid carcinoma; PTMC, papillary thyroid microcarcinoma; BMI, body mass index; CLT, chronic lymphocytic thyroiditis; A/T, aspect ratio (height divided by width on transverse views); ETE, extrathyroidal extension; LN, lymph node; CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis; CC, central compartment; LC, lateral compartment.
The categorical variables were expressed as n (%).
The continuous variables were expressed as the mean ± standard deviations (range).
*The number of metastatic and removed lymph nodes in lateral compartment was clinically considered to be zero for patients who did not undergo lateral neck dissection.

tumor size, the number of foci, location, margin, CLNM, and CLNR were all correlated with LLNM by univariate analysis (all $p < 0.05$).

Multivariate analysis was performed to determine whether these parameters were independently correlated LLNM in macro-PTC. Absence of CLT (OR: 1.807, 95% CI: 1.080–3.024, $p = 0.024$), three or more tumor foci (OR: 2.588, 95% CI: 1.383–4.841, $p = 0.003$), tumor located in the upper pole (OR: 2.139, 95% CI: 1.360–3.365, $p = 0.001$), lobulated or irregular tumor (OR: 2.378, 95% CI: 1.410–4.009, $p = 0.001$), presence of ETE (OR: 3.691, 95% CI: 2.081–6.549, $p < 0.001$), presence of CLNM (OR: 2.621, 95% CI: 1.273–5.398, $p = 0.009$), and CLNR (OR: 2.359, 95% CI: 1.439–3.866, $p = 0.001$) remained independently predictive of LLNM in macro-PTC patients.

Development of nomograms for predicting LLNM in PTMC and macro-PTC patients

To better predict the individual probability of LLNM, we constructed a series of diagnostic nomograms using independent predictors selected by binary logistic regression analysis to generate a combined measurement (Figure 3). Because none of the leading

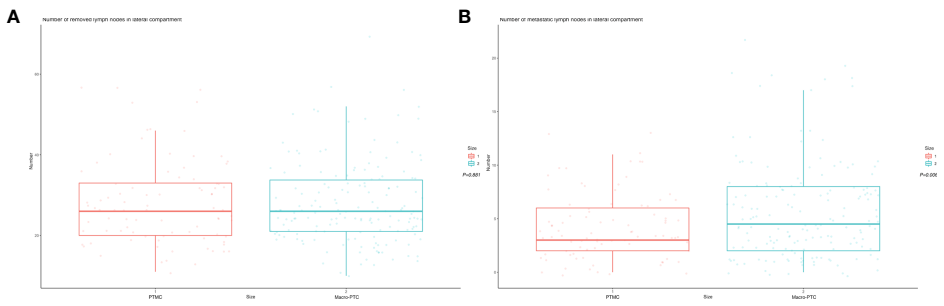

FIGURE 2
Boxplot of number of lymph nodes. **(A)** Number of removed lymph nodes in lateral compartment: PTMC group vs. macro-PTC group: 28.1 ± 10.7 vs. 27.9 ± 10.2, $p = 0.881$; **(B)** number of metastatic lymph nodes in lateral compartment: PTMC group vs. macro-PTC group: 4.3 ± 3.1 vs. 5.6 ± 4.5, $p = 0.006$.

TABLE 2 Distribution of metastatic LNs in the LC of 249 PTC patients who underwent LND.

Distribution of LLNM	PTMC87	Macro-PTC162	*p*-value
Without LLNM	7 (8.0%)	7 (4.3%)	0.353
Single level			
II	1 (1.1%)	0 (0.0%)	0.146
III	7 (8.0%)	15 (9.3%)	0.748
IV	11 (12.6%)	21 (13.0%)	0.943
V	0 (0.0%)	1 (0.6%)	0.353
Two levels			
II+III	3 (3.4%)	5 (3.1%)	0.878
II+IV	6 (6.9%)	5 (3.1%)	0.284
II+V	0 (0.0%)	1 (0.6%)	0.353
III+IV	15 (17.2%)	31 (19.1%)	0.713
III+V	0 (0.0%)	3 (1.9%)	0.504
IV+V	2 (2.3%)	7 (4.3%)	0.646
Three levels			
II+III+IV	19 (21.8%)	40 (24.7%)	0.614
II+III+V	3 (3.4%)	1 (0.6%)	0.099
II+IV+V	0 (0.0%)	1 (0.6%)	0.353
III+IV+V	9 (10.3%)	7 (4.3%)	0.065
Four levels			
II+III+IV+V	4 (4.6%)	17 (10.5%)	0.110
Summary of LLNM			
II	36 (41.4%)	70 (43.2%)	0.781
III	60 (69.0%)	119 (73.5%)	0.452
IV	66 (75.9%)	129 (79.6%)	0.492
V	18 (20.7%)	38 (23.5%)	0.618

LN, lymph node; LC, lateral compartment; LLNM, lateral lymph node metastasis; PTC, papillary thyroid carcinoma; PTMC, papillary thyroid microcarcinoma.

guidelines recommend prophylactic LND, we divided models of LLNM into the preoperative model and the postoperative model for PTMC and macro-PTC patients. Preoperative models (Figures 3A, C) were constructed based on clinical factors, and postoperative models (Figures 3B, D) were constructed based on clinicopathological factors. Detailed factors are listed in the Tables 3 and 4. According to the regression coefficient of LLNM, each variable was proportionally distributed as the point in the range of 0 to 100 in the nomograms. Detailed scores are listed in the Tables 3 and 4. The corresponding probability of LLNM in each person can be determined by adding the total score and positioning it on the scale of the total score.

Internal validation of the prediction nomograms

The ROC analysis for nomograms of LLNM was then performed. Area under curves (AUCs) for the preoperative model and postoperative model for predicting LLNM in PTMC patients were 0.754 and 0.834, respectively (Figures 4A, B). Moreover, for predicting LLNM in macro-PTC patients, AUCs for the preoperative model and postoperative model were 0.753 and 0.797, respectively (Figures 4C, D).

Furthermore, the similar bootstrap resampling procedure was used to conduct the internal calibration plot for established models. The calibration curve of nomograms presented good agreement between the predicted and observed probability of LLNM. After the adjustment for optimism, corrected risks also showed excellent agreement with observed metastasis risk, and only minor discrepancies were observed (Figure 5).

Moreover, we developed the nomogram for LLNM in all PTC patients and compared this nomogram with nomograms for LLNM in PTMC and macro-PTC, respectively (Supplementary Figures 1–3). We found that the AUCs of nomograms for LLNM in PTMC and macro-PTC were higher than that in all PTC patients. It shows that we are correct to develop the nomogram of LLNM separately for PTMC and macro-PTC.

Discussion

LLNM, which is defined as level II–V cervical lymph node involvement, suggests a poor prognosis among PTC patients (7).

TABLE 3 Univariate analysis and multivariate analysis of factors associated with LLNM in patients with PTMC.

Characteristics	LLNM			Multivariate analysis			
	Presence (n = 80)	Absence (n = 554)	p-value	Adjusted OR (95% CI)	p-value	Score[1]	Score[2]
Sex							
Female	33 (41.3%)	117 (21.1%)		Ref		0	0
Male	47 (58.8%)	437 (78.9%)	<0.001	2.011 (1.162–3.482)	0.013	60	35
Age (years)							
≥55	11 (13.8%)	102 (18.4%)					
<55	69 (86.3%)	452 (81.6%)	0.308				
BMI (kg/m^2)							
Normal	4 (5.0%)	76 (13.7%)					
Overweight	50 (62.5%)	300 (54.2%)					
Obesity	26 (32.5%)	178 (32.1%)	0.078				
Diabetes							
Absence	72 (90.0%)	470 (84.8%)					
Presence	8 (10.0%)	84 (15.2%)	0.220				
CLT							
Absence	56 (70.0%)	355 (64.1%)					
Presence	24 (30.0%)	199 (35.9%)	0.300				
BRAF V600E mutation							
Negative	6 (7.5%)	67 (12.1%)					
Positive	74 (92.5%)	487 (87.9%)	0.229				
Maximum tumor size							
≤0.5 cm	7 (8.8%)	119 (21.5%)		Ref			
>0.5 to ≤1 cm	73 (91.3%)	435 (78.5%)	0.008	1.394 (0.575–3.375)	0.462		
The number of foci							
1	41 (51.2%)	394 (71.1%)		Ref		0	0
2	23 (28.7%)	121 (21.8%)		2.050 (1.106–3.801)	0.023	56	36
3 or more	16 (20.0%)	39 (7.0%)	<0.001	3.581 (1.667–7.693)	0.001	100	64
Bilateral tumors							
Absence	64 (80.0%)	458 (82.7%)					
Presence	16 (20.0%)	96 (17.3%)	0.558				
Location							
Middle/Lower	27 (33.8%)	306 (55.2%)		ref		0	0
Upper	53 (66.3%)	248 (44.8%)	<0.001	2.623 (1.519–4.530)	0.001	61	48
Nodular composition							
Mixed cystic and solid	0 (0.0%)	4 (0.7%)					
Solid	80 (100.0%)	550 (99.3%)	0.298				
Echogenicity							
Hyperechoic or isoechoic	0 (0.0%)	12 (2.2%)					
Hypoechoic	78 (97.5%)	538 (97.1%)					
Very hypoechoic	2 (2.5%)	4 (0.7%)	0.084				
Shape							
A/T ≤1	42 (52.5%)	413 (74.5%)		Ref		0	0
A/T >1	38 (47.5%)	141 (25.5%)	<0.001	2.455 (1.424–4.235)	0.001	69	45
Margin							
Smooth	52 (65.0%)	383 (69.1%)					
Lobulated or irregular	21 (26.3%)	110 (19.9%)					
ETE	7 (8.8%)	61 (11.0%)	0.389				
Echogenic foci							

(Continued)

TABLE 3 Continued

Characteristics	LLNM			Multivariate analysis			
	Presence (n = 80)	Absence (n = 554)	p-value	Adjusted OR (95% CI)	p-value	Score[1]	Score[2]
None/large comet-tail artifacts	15 (18.8%)	215 (38.8%)		Ref			
Macrocalcifications	10 (12.5%)	26 (4.7%)		2.378 (0.764–7.403)	0.135		
Peripheral calcifications	0 (0.0%)	0 (0.0%)		–	–		
Punctate echogenic foci	55 (68.8%)	313 (56.5%)	<0.001	1.349 (0.691–2.634)	0.381		
CLNM							
Absence	13 (16.3%)	357 (64.4%)		Ref			0
Presence	67 (83.8%)	197 (35.6%)	<0.001	7.390 (3.903–13.990)	<0.001		100
CLNR							
<0.5	46 (57.5%)	483 (87.2%)		Ref			
≥0.5	34 (42.5%)	71 (12.8%)	<0.001	1.586 (0.869–2.896)	0.133		
Largest size of lymph node in LC							
≤2 cm	63 (78.8%)	453 (81.8%)					
>2 cm	17 (21.3%)	101 (18.2%)	0.517				

LLNM, lateral lymph node metastasis; PTMC, papillary thyroid microcarcinoma; BMI, body mass index; CLT, chronic lymphocytic thyroiditis; A/T, aspect ratio (height divided by width on transverse views); ETE, extrathyroidal extension; CLNM, central lymph node metastasis; CLNR, central lymph node ratio; LC, lateral compartment; OR, odds ratio; CI, confidence interval. The categorical variables were expressed as n (%).
Score[1] represents the preoperative score of the preoperative model.
Score[2] represents the postoperative score of the postoperative model.

TABLE 4 Univariate analysis and multivariate analysis of factors associated with LLNM in patients with macro-PTC.

Characteristics	LLNM			Multivariate analysis			
	Presence (n = 155)	Absence (n = 317)	p-value	Adjusted OR (95% CI)	p-value	Score[1]	Score[2]
Sex							
Female	91 (58.7%)	225 (71.0%)		Ref			
Male	64 (41.3%)	92 (29.0%)	0.008	1.046 (0.646–1.692)	0.855		
Age (years)							
≥55	25 (16.1%)	58 (18.3%)					
<55	130 (83.9%)	259 (81.7%)	0.561				
BMI (kg/m^2)							
Normal	6 (3.9%)	37 (11.7%)		Ref			
Overweight	81 (52.3%)	161 (50.8%)		1.902 (0.703–5.147)	0.205		
Obesity	68 (43.9%)	119 (37.5%)	0.018	2.465 (0.902–6.738)	0.079		
Diabetes							
Absence	138 (89.0%)	284 (89.6%)					
Presence	17 (11.0%)	33 (10.4%)	0.853				
CLT							
Presence	31 (20.0%)	116 (36.6%)		Ref		0	0
Absence	124 (80.0%)	201 (63.4%)	<0.001	1.807 (1.080–3.024)	0.024	48	45
BRAF V600E mutation							
Negative	23 (14.8%)	46 (14.5%)					
Positive	132 (85.2%)	271 (85.5%)	0.925				
Maximum tumor size							
>1 to ≤2 cm	77 (49.7%)	199 (62.8%)		Ref			
>2 to ≤4 cm	67 (43.2%)	98 (30.9%)		1.402 (0.871–2.256)	0.165		
≥4 cm	11 (7.1%)	20 (6.3%)	0.022	1.284 (0.514–3.206)	0.593		

(Continued)

TABLE 4 Continued

Characteristics	LLNM			Multivariate analysis			
	Presence (n = 155)	Absence (n = 317)	p-value	Adjusted OR (95% CI)	p-value	Score[1]	Score[2]
The number of foci							
1	76 (49.0%)	201 (63.4%)		Ref		0	0
2	41 (26.5%)	83 (26.2%)		1.027 (0.614–1.720)	0.918	7	2
3 or more	38 (24.5%)	33 (10.4%)	<0.001	2.588 (1.383–4.841)	0.003	70	73
Bilateral tumors							
Absence	107 (69.0%)	233 (73.5%)					
Presence	48 (31.0%)	84 (26.5%)	0.310				
Location							
Middle/Lower	49 (31.6%)	171 (53.9%)		Ref		0	0
Upper	106 (68.4%)	146 (46.1%)	<0.001	2.139 (1.360–3.365)	0.001	56	58
Nodular composition							
Mixed cystic and solid	2 (1.3%)	4 (1.3%)					
Solid	153 (98.7%)	313 (98.7%)	0.979				
Echogenicity							
Hyperechoic or isoechoic	4 (2.6%)	17 (5.4%)					
Hypoechoic	147 (94.8%)	294 (92.7%)					
Very hypoechoic	4 (2.6%)	6 (1.9%)	0.322				
Shape							
A/T ≤1	90 (58.1%)	165 (52.1%)					
A/T >1	65 (41.9%)	152 (47.9%)	0.218				
Margin							
Smooth	38 (24.5%)	173 (54.6%)		Ref		0	0
Lobulated or irregular	63 (40.6%)	95 (30.0%)		2.378 (1.410–4.009)	0.001	76	66
ETE	54 (34.8%)	49 (15.5%)	<0.001	3.691 (2.081–6.549)	<0.001	100	100
Echogenic foci							
None/large comet-tail artifacts	21 (13.5%)	68 (21.5%)					
Macrocalcifications	14 (9.0%)	17 (5.4%)					
Peripheral calcifications	2 (1.3%)	6 (1.9%)					
Punctate echogenic foci	118 (76.1%)	226 (71.3%)	0.100				
CLNM							
Absence	13 (8.4%)	110 (34.7%)		Ref			0
Presence	142 (91.6%)	207 (65.3%)	<0.001	2.621 (1.273–5.398)	0.009		74
CLNR							
<0.5	52 (33.5%)	219 (69.1%)		Ref			0
≥0.5	103 (66.5%)	98 (30.9%)	<0.001	2.359 (1.439–3.866)	0.001		66
Largest size of lymph node in LC							
≤2 cm	127 (81.9%)	270 (85.2%)					
>2 cm	28 (18.1%)	47 (14.8%)	0.366				

LLNM, lateral lymph node metastasis; PTC, papillary thyroid carcinoma; BMI, body mass index; CLT, chronic lymphocytic thyroiditis; A/T, aspect ratio (height divided by width on transverse views); ETE, extrathyroidal extension; CLNM, central lymph node metastasis; CLNR, central lymph node ratio; LC, lateral compartment; OR, odds ratio; CI, confidence interval. The categorical variables were expressed as n (%).
Score[1] represents the preoperative score of the preoperative model.
Score[2] represents the postoperative score of the postoperative model.

LND is only recommended for PTC patients with positive FNAC-proven LLNM according to the ATA guidelines (1). Notably, ultrasound-guided FNAC is not available in some institutions, and the false-negative rate of FNAC can be as high as 16.7% (15). Accurate evaluation factor for LLNM is necessary for distinguishing high-risk PTC patients.

LNM usually occurs in a stepwise and continuous manner. LLNM usually occurs after CLNM, which explains the higher

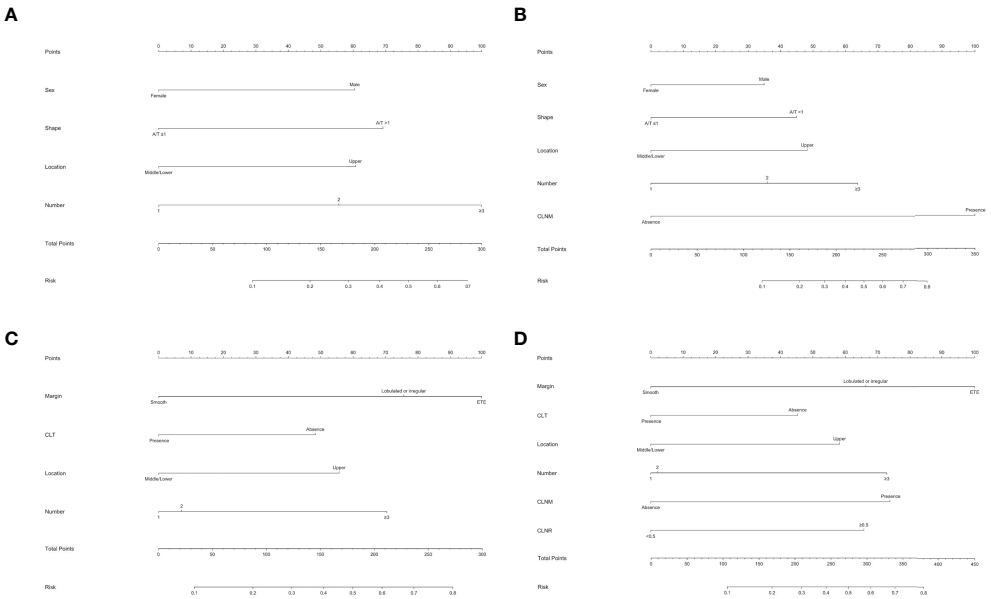

FIGURE 3
Nomogram for predicting LNM in patients with PTC. **(A)** Preoperative nomogram for predicting LLNM in PTMC patients; **(B)** postoperative nomogram for predicting LLNM in PTMC patients; **(C)** preoperative nomogram for predicting LLNM in macro-PTC patients; **(D)** postoperative nomogram for predicting LLNM in macro-PTC patients.

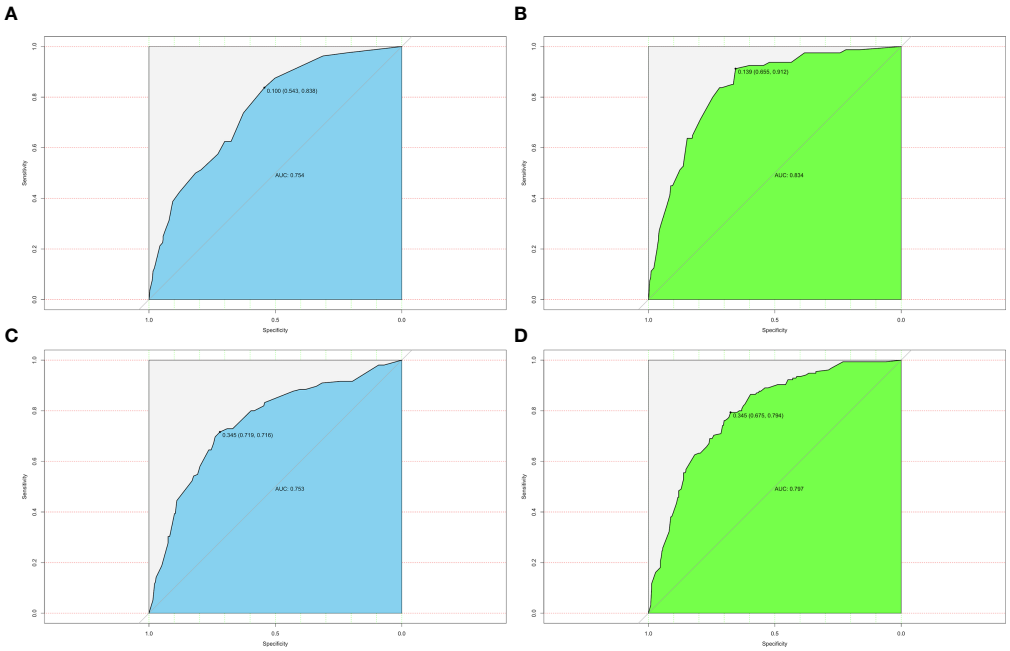

FIGURE 4
ROC curves for different models. **(A)** AUC was 0.754 for the preoperative model of predicting LLNM in PTMC patients; **(B)** AUC was 0.834 for the postoperative model of predicting LLNM in PTMC patients; **(C)** AUC was 0.753 for the preoperative model of predicting LLNM in macro-PTC patients; **(D)** AUC was 0.797 for the postoperative model of predicting LLNM in macro-PTC patients.

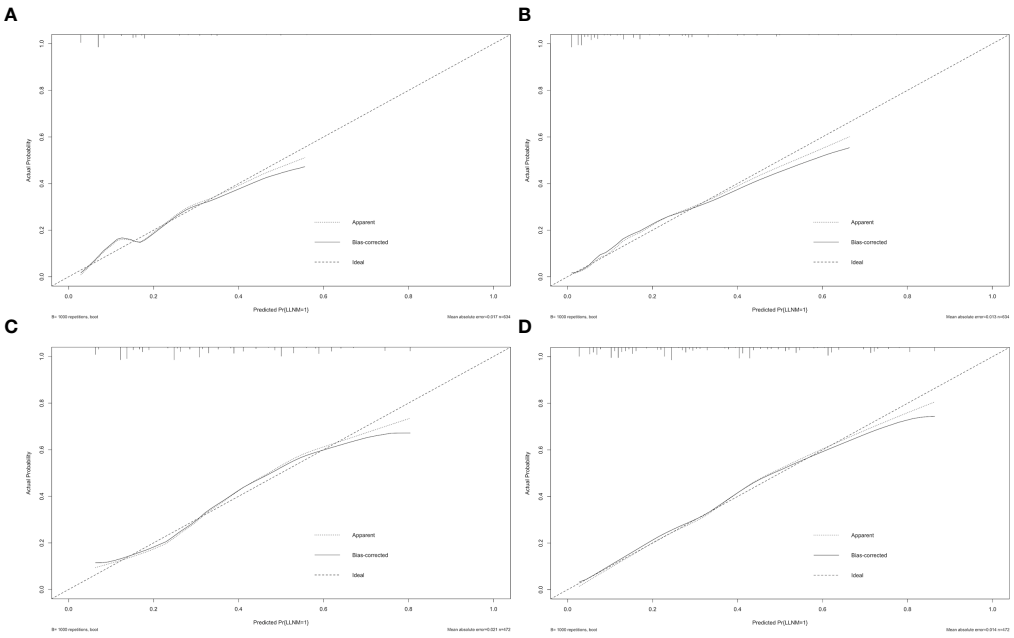

FIGURE 5
Calibration curves of nomograms for predicting LLNM. The diagonal dashed line represents the ideal prediction by the perfect nomogram; the solid line represents the calibration estimate from the internally validated model; the dotted line indicates the apparent predictive accuracy. The closer the solid line is to the dotted line, the stronger the predictive ability of the model. **(A)** Calibration curve for the preoperative model of predicting LLNM in PTMC patients; **(B)** calibration curve for the postoperative model of predicting LLNM in PTMC patients; **(C)** calibration curve for the preoperative model of predicting LLNM in macro-PTC patients; **(D)** calibration curve for the postoperative model of predicting LLNM in macro-PTC patients.

incidence of CLNM than LLNM. However, there are some special cases. For example, 15 (2.4%) and 17 (3.6%) patients in the PTMC and macro-PTC groups developed skip metastasis (negative CLNM with positive LLNM). Patients often had multi-level metastasis, and simultaneous metastasis in levels II, III, and IV was the most common in both PTMC and macro-PTC. Within the lateral cervical lymph node chain, level IV metastasis was consistently the most common in both PTMC and macro-PTC, followed by level III, level II, and level V. These findings were consistent with a previous study (16).

In our study, we found that male gender, multifocality, upper location of tumor, tumor with A/T >1, and presence of CLNM were risk factors for LLNM in PTMC patients. These findings were consistent with published articles. Consistent with a previous study including 1,066 patients with PTMC, our results showed that an increase in the number of tumors led to an increased risk of LLNM (17). Multifocality leading to increased aggressiveness may be due to the fact that multifocal clonal origins result from intraglandular spread of a single primary tumor (18). Liu et al. (19) also found upper portion location was the risk factor for LLNM in PTMC. The lymphatic drainage system of the upper pole differs from that of other parts of the thyroid lobe. Tumors in the upper lobe can spread directly to the ipsilateral lateral chamber through the lymphatic vessels along the superior venous vessels, which lead to the higher rate of LLNM in upper pole location. In addition, in rare cases, some tumors can even bypass the central compartment and directly metastasize to the lateral compartment through these channels, which is known as skip metastasis (20, 21). The diagnosis of PTMC has also improved with the development of ultrasound. However, studies linking LNM to ultrasound features of PTC are limited. We found a significant difference in the probability of developing LLNM in PTMC with A/T >1. Other ultrasound features, such as nodular composition, echogenicity, and echogenic foci, were not associated with LLNM in PTMC patients. In several studies, CLNM was shown to be an important factor for LLNM in PTMC (22, 23), and our study also confirmed this correlation.

Then, we compared the clinicopathological characteristics predictive of LLNM in patients with macro-PTC. Multivariate analyses indicated that absence of CLT, three or more tumor foci, upper location of tumor, lobulated or irregular tumor, presence of ETE, presence of CLNM, and CLNR were all independent predictors for LLNM in macro-PTC patients.

These were consistent with the known high-risk features of macro-PTC. In macro-PTC, risk factors for LLNM such as multifocality, location, and CLNM are also risk factors for LLNM in PTMC. CLT has been considered a risk factor for the development of thyroid malignancy. However, data on the effect of CLT on cervical LNM in PTC were inconsistent. Some studies showed that PTC patients coexistent with CLT had a higher incidence of LNM (24), while others showed the opposite conclusion (25, 26). In our study, the most significant result is the association of CLT with the less frequent LLNM. This result is in agreement with the meta-analysis of Lee et al. (27), that the lymphocytic infiltration counteracts tumor progression. Therefore, we infer that concurrent CLT is a protective factor for macro-PTC patients. As for macro-PTC, ultrasound features, such as lobulated or irregular tumor and presence of ETE, were associated with LLNM. Ultrasound showed high sensitivity (80%) for predicting minimal ETE in PTC patients (28). In this study, a tumor was classified as suspicious for ETE when there is a contact of >25% with the adjacent capsule of PTC. Metastatic ratio could be used to quantitatively evaluate the positive central lymph nodes. We analyzed the metastatic ratio of central lymph nodes and set the cutoff metastatic ratio as 50% according to previous studies (29, 30). We found that CLNR was significantly associated with LLNM in macro-PTC.

Considering none of the leading guidelines to date recommend prophylactic LND, we incorporated all the above factors into nomograms to create possibilities for detecting high-risk patients with occult LLNM preoperatively and providing an individualized plan for postoperative management of PTC patients. Although there was no statistical difference in the incidence of RLN injury and hypocalcemia in PTMC and macro-PTC patients, the incidence of CLNM and LLNM in macro-PTC was much higher than that of PTMC (73.9% vs. 41.6%; 32.8% vs. 12.6%, respectively), indicating that the diameter of the tumor has an impact on the rate of LNM, and separate predictive systems should be used for PTMC and macro-PTC patients for more accurate clinical assessment of lateral lymph node status. We separately established two predictive nomograms to predict LLNM in PTMC patients before and after operation. In the same way, we built predictive nomograms to predict LLNM in macro-PTC patients. All the above nomograms showed excellent precision. In addition, compared with the nomogram for LLNM in all PTC patients, nomograms for LLNM in PTMC and macro-PTC all showed higher AUCs. The largest contributors to nomogram scores differed between PTMC and macro-PTC. The number of foci and CLNM were the largest contributors for the preoperative and postoperative model in PTMC, respectively. As for macro-PTC, the margin was the largest contributor to both preoperative and postoperative models. These findings suggest that preoperative attention should be paid to the number of tumors for PTMC patients, and the preoperative tumor margin status is extremely important for macro-PTC. Experienced sonographers should perform detailed preoperative examinations to detect more suspected lesions in PTMC patients and accurately assess the margin of macro-PTC. Moreover, for candidates of active surveillance of PTMC, we can provide these patients more information to help them decide whether to participate in active surveillance based on the preoperative nomogram. Combined with other risk factors, high-resolution ultrasound by experienced sonographers should be performed to detect small metastatic lymph nodes in the lateral compartment early for patients with a high risk of LLNM according to preoperative nomograms. Experienced surgeons are recommended to perform detailed operations on these patients. Moreover, considering the possibility of performing LND in the future, carbon nanoparticle suspension injection should be used at the first surgery to prevent missing small metastatic lymph nodes. In addition to assisting in preoperative screening high-risk patients of LLNM, our postoperative nomograms may be helpful in detecting the risk of residual LLNM postoperatively for PTC patients who did not undergo LND. For patients with a high risk of LLNM, we can increase the frequency of follow-up and ultrasound, and decrease the cutoff of FNAC for suspicious lymph nodes in the lateral compartment. Adjuvant radioactive iodine should be carried out to detect and address possible residual carcinoma in the lateral compartment when necessary. Unless obvious clinical evidence of LLNM is present, “wait and see” is recommended for patients with a low risk of LLNM.

Despite the fact that some encouraging results were achieved, this study still had some limitations. First, although our study has a large sample size, it is a retrospective study, which is based on single-center data, and tends to have selection biases. The data were extracted from medical records; factors such as extranodal extension of metastatic lymph nodes were not available. Furthermore, different surgeons were involved in the procedure; surgeon-specific factors, such as the number of removed lymph nodes, might affect postoperative outcomes. Third, LND was not routinely performed for all PTC patients in our institution, and occult LLNM may be present. Finally, nomograms in our study were assessed only using the internal validation method. Validation of nomograms may be compromised given the diagnostic patterns in different institutions. Thus, we will conduct prospective multi-center institutional trials in subsequent studies to obtain more objective conclusions.

In conclusion, the diameter of the tumor has an impact on the rate of LLNM. We found that LLNM in PTMC patients was independently related to gender, the number of foci, location, shape, and CLNM. For macro-PTC patients, CLT, the number of foci, location, margin, CLNM, and CLNR were all independent predictors for LLNM. By using the above variables, we constructed nomograms that can not only detect high-risk patients with occult LLNM preoperatively, but also form

appropriate treatment protocols for postoperative management of PTC patients with different risks.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article. The need for informed consent was waived due to the retrospective nature of this study.

Author contributions

J-WF and L-ZH: Writing—original draft, Software, and Data curation. S-YL: Validation, Formal analysis, and Data curation. FW: Conceptualization. JY and JH: Validation and Investigation. ZQ and YJ: Writing—review and editing, Visualization, and Supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.944414/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Nomogram for predicting LLNM in all PTC patients. **(A)** preoperative nomogram; **(B)** postoperative nomogram.

SUPPLEMENTARY FIGURE 2
ROC curves for the model. **(A)** AUC was 0.730 for preoperative model of predicting LLNM in all PTC patients; **(B)** AUC was 0.758 for postoperative model of predicting LLNM in all PTC patients.

SUPPLEMENTARY FIGURE 3
Calibration curves of nomograms for predicting LLNM. **(A)** calibration curve for preoperative model of predicting LLNM in all PTC patients; **(B)** calibration curve for postoperative model of predicting LLNM in all PTC patients.

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Diagnosis and treatment of ectopic thyroid carcinoma: A case report and literature review

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Introduction: Ectopic thyroid cancer (ETC) is primary thyroid cancer occurring in ectopic thyroid tissue, and its incidence rate is approximately 0.3%–0.5% of thyroid cancer. Only approximately 132 cases of ETC have been diagnosed and treated worldwide in the past 110 years, with most of them being adults. Of note, patients with ETC are prone to misdiagnosis and mistreatment.

Case report: This was a 13-year-old adolescent female who reported having a sensation of swallowing obstruction when eating blocky foods. Color Doppler Ultrasound (CDU) found a 2.3 cm ×1.7 cm × 2.1 cm hypoechoic nodule slightly to the right of the deep surface of the tongue base, with a honeycomb shape. Meanwhile, a mixed echogenic nodule of approximately 2.0 cm × 1.9 cm × 2.3 cm was seen deep in the mouth floor, and a very low echogenic region of 1.4 cm × 1.1 cm × 1.8 cm was observed in the nodule. We then performed a fine needle aspiration biopsy (FNAB) of the thyroid nodules guided by CDU, and the results showed papillary thyroid carcinoma (PTC). Then, a local extended resection of the thyroid carcinoma was performed. Bilateral cervical IA and adjacent subhyoid lymph node dissection was performed through a small anterior cervical incision. The patient recovered well, and was discharged on the fifth day after surgery. The patient only took levothyroxine tablets for replacement therapy after surgery. The patient was followed up for 36 months, and the thyroid function remained in the normal range. Reexamination by CDU showed no tumor recurrence, lymph node enlargement, or obvious change in the tongue base ectopic thyroid.

Conclusions: ETC is an extremely rare type of thyroid cancer, which is easy to be misdiagnosed. Preoperative use of CDU, nuclide scanning, computed tomography (CT)/Magnetic resonance imaging (MRI), and FNAB can significantly reduce the misdiagnosis rate of this disease. Surgery is currently the main treatment for ETC. Complete resection still has a high cure rate. For patients with advanced ETC who cannot be completely resected, external

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radiotherapy and targeted therapy can be tried, but the prognosis needs to be verified with more cases in the future.

KEYWORDS

ectopic thyroid, thyroid tumor, thyroid cancer, diagnosis, treatment

Introduction

The ETC refers to primary cancer occurring in ectopic thyroid tissue, and its incidence rate is approximately 0.3–0.5% of thyroid cancer (1). To our knowledge, only approximately 130 cases of ETC have been clearly diagnosed and treated worldwide in the past 110 years, with most of the cases occurring in adults. It is noteworthy that patients with ETC are prone to misdiagnosis and mistreatment. Herein, we report the diagnosis and treatment of the youngest adolescent with ETC to date. In addition, we summarized this ETC's clinical manifestations, diagnosis, and treatment by reviewing previous relevant literature.

Case report

The patient was a 13-year-old adolescent female who reported having a sensation of dysphagia when eating solid foods. The symptoms had been present for approximately 2 years, and the patient had no sore throat, hoarseness, dyspnea, or hemoptysis. By chance, the patient found a mass at the base of her tongue after inserting her fingers into her mouth. She had no past medical history. On physical examination, in addition to the raised mass at the base of the tongue, we found a mass just above the hyoid bone, approximately 2 cm in diameter, with poorly defined boundaries and poor mobility. No definite thyroid was found by palpation in the normal thyroid anatomy area, and no abnormal enlarged lymph nodes were found in the anterior neck and bilateral neck. Initially, the mass at the base of the tongue was the differentially diagnosed as lingual ectopic thyroid, hemangioma, or other possibilities, while the mass around the hyoid bone was diagnosed as a thyroglossal duct cyst, and surgery was recommended.

The patient underwent a series of tests after hospitalization. CDU found a hypoechoic nodule of 2.3 cm × 1.7 cm × 2.1 cm in size, slightly to the right of the deep surface of the tongue base, with a honeycomb shape (Figure 1). As a result, an ectopic thyroid was considered. Moreover, a mixed echogenic nodule of approximately 2.0 cm × 1.9 cm × 2.3 cm in size was found on the deep surface of the mouth floor. Its boundary was unclear, shape was irregular, it was connected to the tongue base mass, and its boundary with the surrounding muscle tissue was unclear (Figure 1). A very low echogenic region of 1.4 cm × 1.1 cm × 1.8 cm was observed in this nodule, suggesting the possibility of an ectopic thyroid with an ETC nodule. There were no abnormal swollen lymph nodes in the bilateral neck. No thyroid tissue was detected in the normal thyroid region. The findings of contrast-enhanced CT scan of the neck were similar to those of CDU (Figure 1). Thyroid function: free triiodinated thyroxine 3.13 pg/ml, free thyroxine 0.83 ng/dl, thyroid-stimulating hormone (TSH) 5.76 mIU/L, thyroglobulin 37.3 ng/ml, anti-thyroglobulin antibody < 5.00 IU/ml, anti-thyroid peroxidase antibody 2.37 IU/ml, parathyroid hormone 70.40 pg/ml, serum calcium < 0.50 pg/ml. Chest X-ray, electrocardiogram, and other auxiliary examinations found no specific abnormalities. Furthermore, we performed FNAB of thyroid nodules guided by CDU, and the results showed papillary thyroid carcinoma (PTC).

Subsequently, we performed a local extended resection of the thyroid carcinoma but preserved the normal thyroid tissue at the base of the tongue. Bilateral cervical IA and adjacent subhyoid lymph node dissection were performed through a small anterior cervical incision. During surgery, we found that the ETC nodule was wrapped by ectopic thyroid tissue on the floor of the mouth and connected with ectopic thyroid tissue at the base of the tongue (Figure 2). No parathyroid glands were found during the surgery. Postoperative pathology showed that the nodules in the ectopic thyroid tissue at the mouth floor were PTC (Figure 2), and 1 of 12 lymph nodes had metastasis. Parathyroid hormone measurements were performed on postoperative days 1 and 3, and the results were normal. The patient recovered well without neck bleeding, facial numbness, or convulsions, and was discharged on the fifth day after surgery. Levothyroxine tablet replacement therapy was started 7 days after surgery. Thyrotropin suppression and radioiodine-131 therapy were not performed.

To date, the patient has been followed up for 36 months, and the thyroid function and TSH are in the normal range. No tumor recurrence or suspicious lymph node metastasis was found by CDU of the neck, and there was no significant change in ectopic thyroid tissue at the base of the tongue. The patient reported being very satisfied with the therapeutic effect.

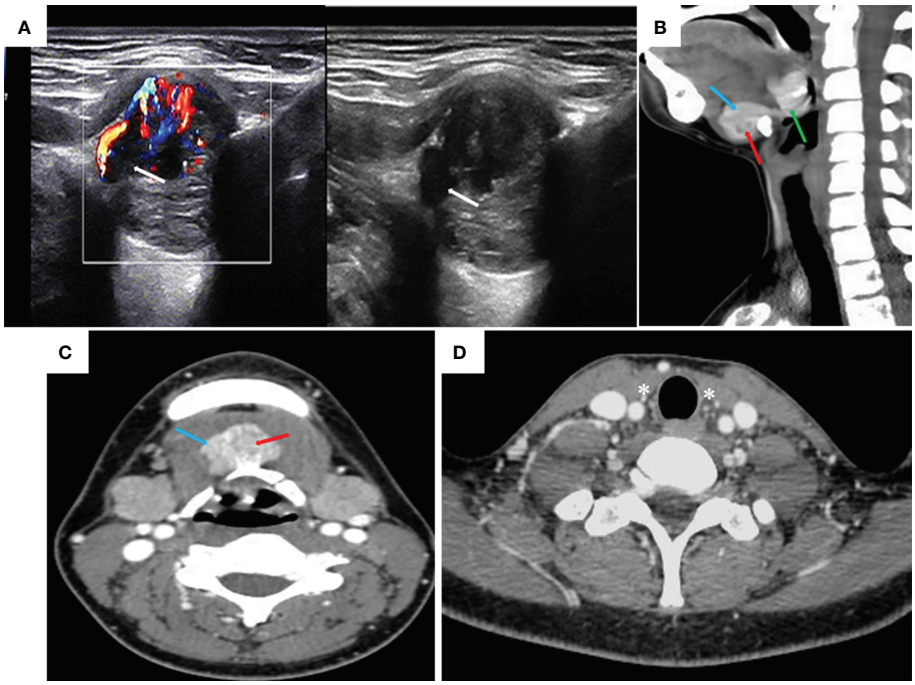

FIGURE 1
Color Doppler ultrasound and contrast-enhanced CT. **(A)** Ectopic thyroid and carcinoma nodule at the floor of the mouth (very hypoechoic area shown by the white arrow). **(B, C)** Ectopic thyroid gland at the base of the tongue, ectopic thyroid gland at the base of the mouth, and a single cancer nodule (the green arrow is the thyroid gland at the base of the tongue, the blue arrow is the thyroid gland at the base of the mouth, and the red arrow is a cancer nodule). **(D)** No thyroid gland in the normal position of the neck (white * area).

Discussion

Occurrence and classification of the ectopic thyroid gland

Ectopic thyroid gland is a rare congenital malformation. The incidence of ectopic thyroid in the general population is approximately 0.3/100,000-1/100000, and the incidence of thyroid disease is approximately 0.01%–0.03%, of which women account for approximately 65%–80%, significantly more than men (2, 3). The disease begins at the embryo stage of human development. In the fourth week of embryonic development, the endodermal epithelial cells between the ventral ends of the first and second pairs of branchial arches proliferate and sag to form a thyroid diverticulum, which further extends into the thyroglossal canal. The thyroglossal canal may extend through the body of the tongue in the anterior direction of hyoid bone and thyroid cartilage to gradually form a solid cell cord. Ectopic thyroid occurs when the cell cord descends abnormally into the 2nd–4th ring of the trachea. Ectopic thyroid can be seen in almost any part of the body. Over 90% of them occur in the tongue (4, 5), followed by the sublingual area, under the jaw area (6), before and after the hyoid bone, the lateral neck, trachea and parotid gland, axillary region, or heart (7–11). This is consistent with our statistical results for ETC. According to the presence or absence of thyroid tissue in the normal anatomical position of the neck, the ectopic thyroid can be divided into two categories: vagal thyroid (absence of thyroid in the normal position and presence of thyroid in the abnormal position) and extra thyroid gland (presence of thyroid in both the normal and abnormal positions).

Manifestations and diagnosis of ETC

The severity of symptoms in the vast majority of patients with ETC is related to the tumor size and anatomical location. When the tumor is large enough, events such as local compression or intracavitary obstruction will occur. When ETC occurs in the head and neck, patients may also present with dizziness, vomiting, sore skin, snoring, hoarseness, irritating cough, dyspnea, sore throat, swallowing obstruction, head and face swelling, and other symptoms (12–15), and it needs to be distinguished from thyroglossal duct cyst (15–17), hemangioma, dermoid cyst, lymphatic tuberculosis, papilloma of the nasal cavity (18), nasopharyngeal carcinoma (19), laryngeal tumor (20, 21), pharyngeal tumor (22), esophageal tumor, lymph node metastasis cancer, and other diseases (23).

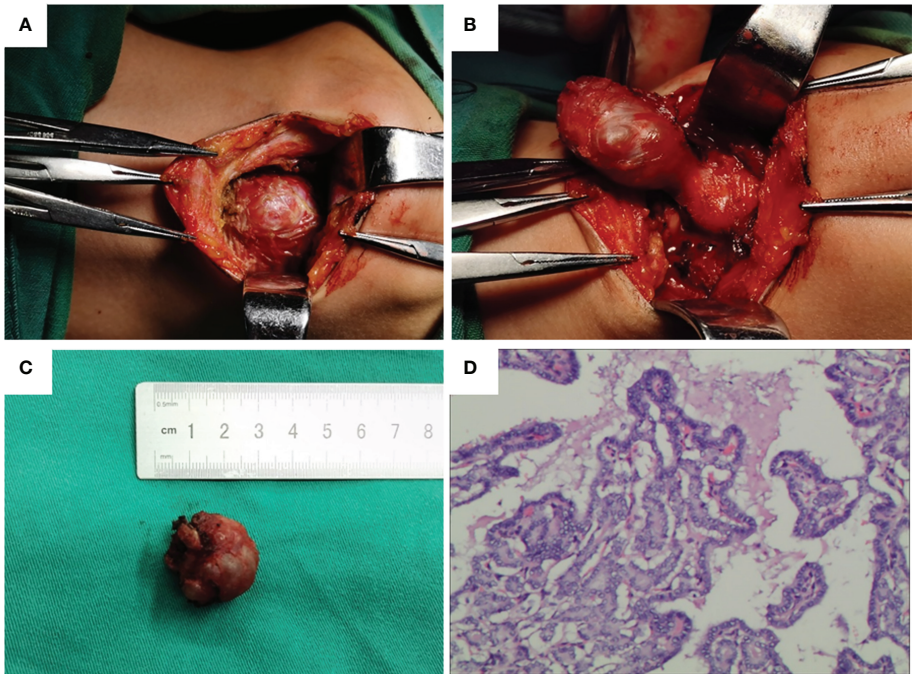

FIGURE 2
Intraoperative findings and postoperative pathology. **(A–C)** Ectopic thyroid and cancer foci in the floor of the mouth. **(D)** Postoperative pathology showed papillary thyroid cancer.

When ETC occurs in the chest and mediastinum, it can be accompanied by hoarseness, dyspnea, eating disorders, and chest deformity, and it should be differentiated from thymoma, teratoma, tracheal tumor, esophageal cancer, and even bone tumor of the chest wall (24–29).. When ETC occurs in the abdominal cavity or pelvic cavity, symptoms such as abdominal pain, abdominal distention, loss of appetite, anemia, defecation disorders (30), and even recurrent urinary tract infections may occur, and it needs to be differentiated from primary and secondary tumors originating from the abdomen and pelvic cavity (31–34).

Among the previously reported ETC cases, the detection rates of CDU, CT/MRI, Radioiodine scan, and FNAB were 81.1%, 78.8%, 20.5%, and 41.0%, respectively. Approximately 60% of the patients were not clearly diagnosed before surgery (Table 1). For patients with suspected ETC, it is important to select appropriate auxiliary examinations in addition to physical examinations. The proportion of patients with ectopic thyroid (or thyroid cancer) complicated with hypothyroidism is relatively high, up to approximately 30%, as reported in the literature (35). Routine assessment of thyroid hormone levels can determine whether patients have hyperthyroidism or hypothyroidism in advance, which can effectively avoid the occurrence of postoperative hyperthyroidism crisis and reduce the risk of hospitalization. We believe that, as with thyroid cancer surgery in general, preoperative and postoperative parathyroid detection may help to better compare the changes in parathyroid function. If necessary, doctors can even choose to perform a 99mTc-sestamibi single-photon emission computed tomography (99mTc-MIBI SPECT) scan before surgery to determine the location and number of parathyroid glands, thereby avoiding the occurrence of permanent parathyroid dysfunction. To the best of our knowledge, although PTC co-exists in over 90% of ETC, medullary thyroid carcinoma has also been reported (36). Thus, calcitonin detection is also necessary. As the preferred method of ETC diagnosis, CDU can confirm the presence of thyroid in the normal position and also make a preliminary judgment on the size, shape, boundary, blood flow, and anatomical relationship with the surrounding structures of the suspicious mass. It should be noted that CDU cannot independently diagnose the presence of ETC but needs to be combined with thyroid radionuclide scanning and FNAB. In particular, CDU is more limited in the diagnosis of ETC in the mediastinum, abdominal cavity, and other parts. When the mass is large, the CDU diagnosis is unclear, or CDU considers ETC as a suspicious mass. CT/MRI scan can clearly show the size, shape, boundary, and the relationship between the surrounding structure of the mass from multiple levels as well as roughly assess the characteristics of the mass according to its tissue density and signal strength (26, 27, 29). When the tumor is located in the mediastinum, chest, or abdominal cavity, CT/MRI can also be selected to determine whether there are adhesions or

TABLE 1 The diagnose and treatment of 132 patients with ectopic thyroid carcinoma.

Area		Number	Diagnose					Treatment				Relapse or metastasis	Total
			CDU	CT/MRI	RAI-S	FNAB	Others	Surgery	RAI-T	RAD	Others		
Head and maxillofacial													6
	Scalp	1	–	1	–	–	–	1	–	–	–	–	
	Skull	2	–	2	–	–	–	2	–	–	–	1	
	Nasopharynx, nasal Septum	2	–	2	–	–	2	2	–	–	–	–	
	Parotid gland	1	–	–	–	–	–	1	–	–	–	1	
Oral cavity, pharynx and neck													107
	Tongue, pharyngeal	63	56	52	18	27	18	59	13	6	5	5	
	Midline of the neck (trachea, larynx, esophagus, etc)	32	27	22	7	15	9	32	7	1	3	2	
	Lateral neck	12	10	8	–	3	–	12	6	–	–	1	
Chest													11
	Mediastinum (esophagus, pericardium, etc.)	8	6	8	1	4	5	8	2	2	2	1	
	Clavicle and chest wall	3	1	2	1	2	2	3	1	2	1	1	
Abdominal and pelvic													8
	Abdominal cavity (liver, rectum)	2	1	2	–	2	2	2	1	–	1	2	
	Pelvic cavity (uterus, ovaries, etc)	6	6	5	–	1	2	6	2	–	1	2	
Total		132	107	104	27	54	40	128	32	11	13	16	132

CDU, Color Doppler ultrasound; CT/MRI, Computed tomography/Magnetic resonance imaging; RAI-S, Radioiodine scan; FNAB, Fine needle aspiration biopsy; RAI-T, Radioiodine-therapy; RAD, Radiotherapy.

any infiltration with the surrounding great vessels, to fully evaluate the surgical risk (37). In case CDU fails to identify the presence of the thyroid, iodine-131 or ^{99}Tcm radionuclide scanning can be very effective for identifying normal or ectopic thyroid tissue and can also clearly display metastatic lesions. However, it is worth noting that some ectopic thyroid functions are low or nonfunctional, and the radioactive nuclide uptake is not obvious, which may lead to misdiagnosis. However, this test is not recommended for routine use because of radiation exposure. To avoid misdiagnosis of the disease, preoperative FNAB guided by CDU can be selected (38), and intraoperative freezing is also feasible. Besides, thyroid globulin levels can be measured to assist in diagnosis when medical conditions allow. When ETC is located in the nasopharynx, trachea, esophagus, cervix, and other special sites, endoscopic assistance can often achieve the purpose of biopsy. For patients with ETC and distant metastasis, whole body bone scans and PET-CT can determine the location and number of metastases. In 2017, Hu et al. reported the first case of ectopic mediastinal PTC using endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for safe and accurate sampling, which we believe is worthy of recommendation (26).

The treatment of ETC

Herein, we summarized the previous treatment methods of 132 ETC patients (Table 1) by reviewing the literature. The proportion of ETC patients receiving surgery, radioiodine, and external radiotherapy was 97.0%, 24.2%, and 8.3%, respectively. The rate of tumor recurrence and metastasis was 12.1%, and only a few studies reported a survival time. We noted that surgery and radioiodine are still the main treatment methods for ETC. A small number of patients with advanced ETC received external radiotherapy or targeted therapy, but the prognosis was poor, and the benefit was little (33). For the surgical treatment of ETC, preoperative consideration should be made based on the classification of the ectopic thyroid, pathological types of cancer foci (e.g., follicular carcinoma, medullary carcinoma, poorly differentiated or undifferentiated carcinoma), location and size

of the cancer foci, patient age, and other factors. For patients requiring iodine-131 postoperative treatment, not only the ectopic thyroid gland should be completely removed, but the normal anatomical location should also be checked for the presence of glands, and if any, the gland should also be removed (39, 40). It should be noted that for ETC located at the base of the tongue and the floor of the mouth, postoperative wound bleeding could easily lead to airway obstruction, and a preoperative temporary tracheotomy should be considered. In the existing case reports, only a few scholars have carefully described the extent of intraoperative lymph node dissection and the number of lymph node metastases. It is still highly controversial whether prophylactic neck dissection or only therapeutic lymph node dissection should be performed in patients with ETC. We found that some scholars did not perform cervical lymph node dissection when removing the primary tumor lesions, and the patients still achieved long-term disease-free survival (41, 42). The extent of lymph node dissection should be determined according to the specific body location and the pathological type of the tumor. For lesions with a low risk of metastasis and recurrence, lymph node dissection may increase the incidence of complications. When dealing with adolescent patients, the formulation of a surgical plan needs to be more cautious, and endocrine dysfunction in the process of growth and development should be avoided as much as possible while taking into account the radical treatment of cancer. The adolescent patient with ectopic thyroid cancer reported in this paper had a small tumor and no obvious extracapsular extension, which is considered to be at low risk of recurrence. Neck lymph node dissection was unnecessary, but the patient's mother strongly requested neck lymph node dissection before surgery. After consultation, we only performed bilateral neck dissection of the IA and subhyoid regions through the small anterior cervical incision, and the final pathology showed that only one metastatic lymph node existed. Finally, attention should be paid to identifying and protecting the parathyroid gland during ETC resection to avoid the occurrence of permanent hypoparathyroidism. Postoperative radioiodine therapy and TSH suppression can be referred to as the treatment of thyroid cancer in general.

Conclusion

ETC is an extremely rare type of thyroid cancer, which is easily misdiagnosed. Preoperative use of CDU, nuclide scanning, CT/MRI, and FNAB can significantly reduce the misdiagnosis rate of this disease. Surgery is currently the main treatment for ETC, and complete resection still has a high cure rate. For patients with advanced ETC who cannot be completely resected, external radiotherapy and targeted therapy can be attempted, but the prognosis needs to be verified with a larger sample in the future.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

GF and FG were responsible for writing the manuscript. GF was responsible for the collection and sorting of patient data. WZ searched and collected a large number of relevant literature. XR and XZ gave professional advice on the writing. ZW and MG made important revisions to the manuscript, gave the final approval to publish the manuscript, and agreed to be responsible for all aspects of the work to ensure that issues relating to the accuracy or completeness of any part of the work are properly investigated and resolved. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Case Report: A papillary thyroid microcarcinoma patient with skip lymph node metastasis and multiple distant metastasis

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Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer. Papillary thyroid microcarcinoma (PTMC) is defined as PTC with a diameter less than 1 centimeter. Most lymph nodes of PTC patients have metastasized to the central neck, and a few lymph nodes have metastasized to the lateral neck. Skip lymph node metastasis, that is, lateral cervical lymph node metastasis without central lymph node metastasis, is even less common. Additionally, distant metastasis of PTMC is also rare, mainly occurring in the lung and bone. Here, we reported a case of PTMC patient with skip lymph node metastasis and multiple distant metastasis. The patient presented with a huge shoulder mass and the primary tumor was found to originate from the thyroid. However, the patient only suffered with PTMC *via* postoperative pathological results, and interestingly, the patient only had skip lymph node metastasis. Thus, we should focus on PTMC patients with lateral cervical lymph nodes metastasis, especially those with skip metastasis. In addition, this case provides a new perspective for us to understand of skip lymph metastasis and distant metastasis of PTMC.

KEYWORDS
papillary thyroid microcarcinoma, skip lymph node metastasis, shoulder metastasis, distant metastasis, case report

Established facts

Papillary thyroid carcinoma (PTC) is the most common endocrine malignant tumor with an increasing incidence.

The incidence of distant metastasis of PTC is less than 5%. The main locations of distant metastases are the pulmonary and bone.

Novel insights

For suspected metastatic lymph nodes, fine needle aspiration cytology (FNAC) combined with the thyroglobulin might be useful.

Inflammation caused by residual sutures is also a factor should not be ignored in thyroid cancer.

Introduction

Thyroid cancer is the most common endocrine malignant tumor, and its incidence rate is rising. Papillary thyroid carcinoma (PTC) is the most common thyroid carcinoma. Papillary

thyroid microcarcinoma (PTMC) is defined as PTC with a diameter less than 1 cm. Although the prognosis of PTC and PTMC is good, patients with advanced PTC can often be found. Skip lymph node metastasis in PTC refers to lateral cervical lymph nodes metastasis without central lymph nodes metastasis, which is a special type of lymph node metastasis (1). Skip lymph node metastasis is rare in PTC, but it affects the prognosis and recurrence of patients (2). Distant metastasis in PTC is also rare, especially the multiple distant metastasis. It occurs in about 2%–13% of patients with PTC and significantly reduces the survival rate of these patients (3). We reported a case of PTMC with skip lymph nodes metastasis and multiple distant metastasis. This case might give us a new understanding of PTMC metastasis and require us to evaluate lymph node metastasis more reasonably, especially for evaluating the skip lymph node metastasis. With the increasing incidence of thyroid cancer, the treatment of thyroid cancer should be more individualized, and elaborate preoperative investigations can help us to diagnose and treat some rare cases.

Case presentation

A 50-year-old woman was admitted to our hospital because of pain in her right humerus for 5 years, swelling with limited movement for 4 years in February 2022. Physical Examination: a huge mass with pain could be seen in the right shoulder, which disrupted the normal shoulder. Superficial varicose veins could be seen on the surface of the mass, without swelling or ulcer. The movement of the right shoulder joint was obviously restricted (**Figure 1A**). Imaging examinations were conducted for the right shoulder of the patient. X-ray, CT and MRI demonstrated a huge soft tissue mass in the upper part of the right humerus, and enlarged lymph nodes in the right supraclavicular fossa, that is, the IV segment of the right lateral neck (**Figures 1B–D**). In addition, multiple solid nodules in both lungs were found by lung CT (**Figures 2A–C**). The ^{18}F-FDG PET/CT image also confirmed the above results (**Figures 1E,F**, **2D**). In order to make a definite diagnosis, the patient underwent the needle biopsy for shoulder mass. The pathological result showed that the shoulder mass was a metastatic tumor, possibly originating from thyroid *via* immunohistochemistry analysis of tissue samples with CK (+), CK7 (+), Ki-67 (10%+), TTF-1(+), TG (+), HPC (−), AFP (−), Syn (−), CgA (−), SATB2 (−), CT (−), p53 (−), NapsinA (−), ER (−), PR (−), CDX2 (−) (**Figure 1G**).

Then, thyroid examinations were carried out. The serum free thyroxine, TSH, A-TG, A-TPO, PTH and calcitonin were all normal. It was worth noting that the serum thyroglobulin was over 10,000 ng/ml. The thyroid contrast-enhanced ultrasound (CE-US) showed 5.3 mm and 8.4 mm nodules in left and right lobes with TI-RADS 5 (**Figures 3A,B**). Metastasis was considered to be in the prelaryngeal lymph node (also called Delphian lymph nodes), rather than in lateral cervical lymph nodes by CE-US. The contrast-enhanced CT of thyroid also showed the nodules in thyroid (**Figures 3C,D**) and enlarged lymph nodes in the right supraclavicular fossa (**Figures 3E,F**). However, the ^{18}F-FDG PET/CT scan did not find any abnormal glucose metabolism in the thyroid gland and central cervical lymph nodes, but did in the right supraclavicular fossa, which was different from CE-US (**Figure 3G**). Finally, total thyroidectomy, central cervical lymph node dissection and right lateral cervical lymph node dissection were performed for the patient in March 2022 (**Figure 4A**). Pathological results show that the nodules in both sides were classical papillary thyroid microcarcinoma (**Figure 4B**). The BRAF-V600E of the patient was wild-type. Additionally, sutures were found in the cancerous nodule in the right lobe, which came from a partial thyroidectomy for a thyroid benign nodule in 2012 (**Figure 4A**). Interestingly, the lymph nodes suspected of metastasis by CE-US did not show metastasis, while the lateral lymph nodes showed metastasis.

Discussion

The incidence of skip lymph node metastasis and distant metastasis in PTC is very low. It is significantly related to the prognosis and recurrence of the patients. Thus, the mentioned patients should be carefully screened, and personalized and collaborative multi-disciplinary care should be given. In this case, the patient who had PTMC with skip lymph node metastasis, huge shoulder metastasis and lung metastasis is very rare. By screening the diagnosis and treatment process, we can have new views on this kind of patients. We will discuss some new insights from the following three angles, including skip lymph node metastasis with inconsistent preoperative results, rare humeral metastasis, and malignant change around residual sutures from previous surgery.

Skip lymph nodes metastasis

Skip lymph nodes metastasis is a special type of lymph node metastasis, which usually refers to lateral cervical lymph node metastasis without central lymph node metastasis (1). The incidence of skip metastases is about 3%–19.7% (2). Generally, the non-invasive examinations used to evaluate lymph node metastasis are imaging examinations, such as ultrasound and CT.

Besides, molecular markers can also be used to predict the lymph node metastasis. TERT promoter mutations and RET/PTC rearrangements were associated with distant metastasis (4–6). Interestingly, BRAF mutations were found to be not related with distant metastasis in PTC (5). Another study found that 25-genes could distinguish N0 and N1 in PTC (7). Additionally, plasma N-glycomics, microRNA-222 and ANGPTL1 were all proved to be biomarkers for predicting lymph node metastasis of PTC (8–10).

In our case, the enlarged prelaryngeal lymph nodes were suspected of metastasis by the thyroid CE-US. ^{18}F-FDG PET/CT image did not show any abnormal glucose metabolism in the thyroid and cervical lymph nodes, but found in the right supraclavicular fossa. The pathological results of the patient demonstrated that there was skip lymph node metastasis in right lateral cervical region IV, which was inconsistent with the thyroid CE-US. Therefore, we need a more effective evaluation method for skip lymph node metastasis. Lee proposed that the location of lymphatic metastasis was related to the location of nodules in the

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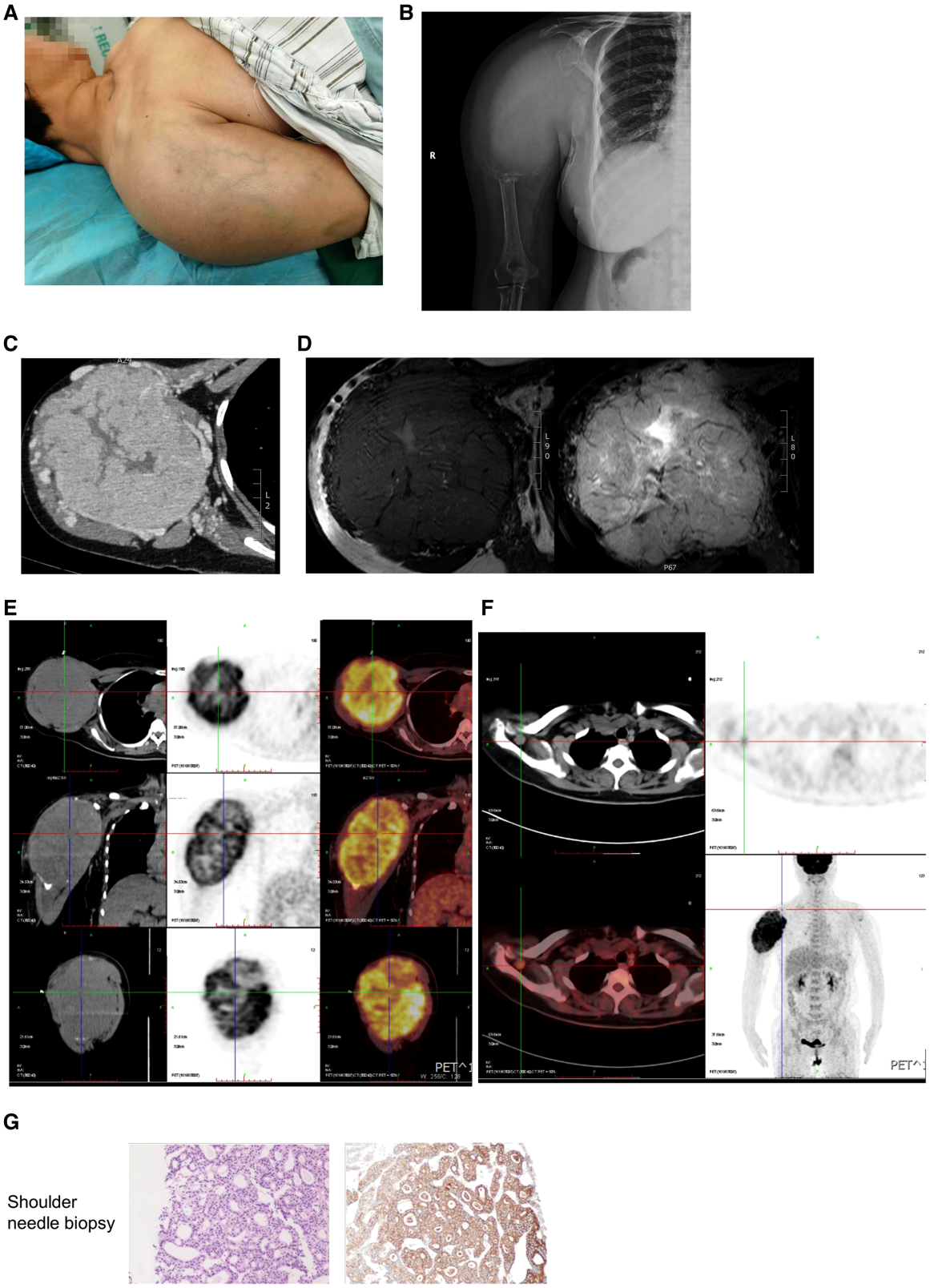

FIGURE 1
Examination and pathology of shoulder tumor. (**A**) The appearance of right shoulder. (**B**) The x-ray of the right humerus showed a vague high-density shadow with unclear boundary, and bone destruction near humerus and scapula. (**C**) Contrast-enhanced CT of the right humerus showed a soft mass replacing the normal bone structure with unclear boundary and dilated blood vessels. (**D**) No normal structure was found in the right humerus, shoulder joint and clavicle by MRI. T1 weighted image shows a mass with low signal intensity. T2 weighted image shows high signal intensity. (**E**,**F**) ^{18}F-FDG PET/CT image showed that increased uptake in shoulder tumor (**E**) and the right supraclavicular fossa (**F**). (**G**) Needle biopsy of shoulder mass.

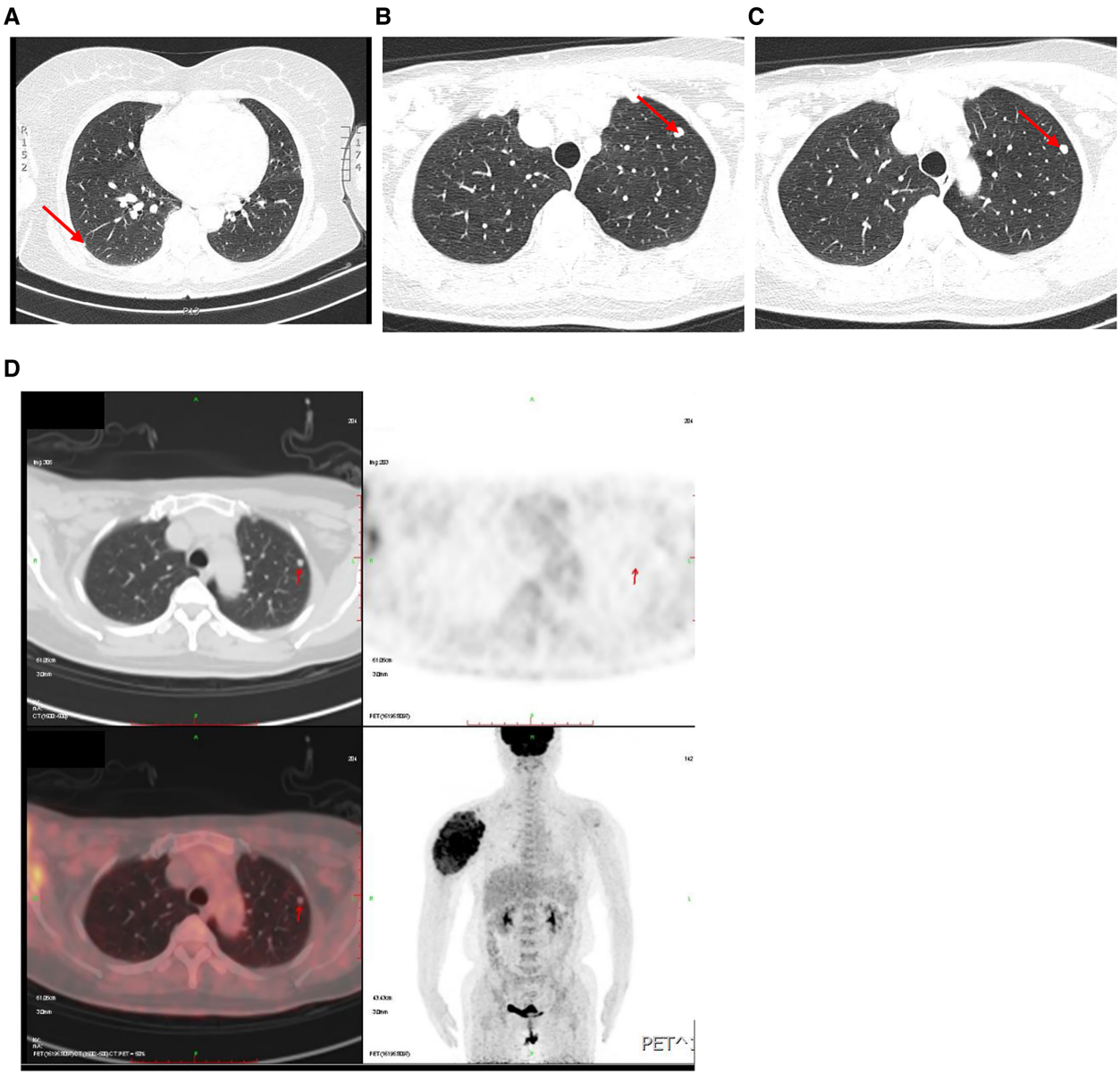

FIGURE 2
Examination of lung. (A–C) High-resolution CT of pulmonary showed multiple solidity nodules. (D) ^{18}F-FDG PET/CT images showed increased uptake in pulmonary nodules.

thyroid gland (11). Another study on skip metastasis in PTC demonstrated that thyroid capsular invasion, multifocality, tumor in the upper portion, and maximum tumor diameter ≥ 1 cm were independent risk factors (12). For suspected metastatic lymph nodes, fine needle aspiration cytology (FANC) combined with the thyroglobulin might be useful (1). For the primary patients with high-risk factors, the lateral cervical lymph nodes should be carefully evaluated to reduce the postoperative recurrence. The research of Hao Fu demonstrated the value of PET/CT in evaluation of lymph nodes and distant metastasis in PTC patients. And the diagnosis performance of gallium 68-labeled fibroblast activation protein inhibitor PET/CT was superior to fluorine 18 fluorodeoxyglucose PET/CT, which we could consider to utilize in advanced PTC patients in further clinical practice (13).

Distant metastasis

The incidence of distant metastasis of PTC is less than 5%. The main sites of distant metastases are the pulmonary and bone, which leads to a significant decline in survival rates (14).

Pulmonary metastasis in PTC is rare. Previous studies found that male, old age, large tumor, extrathyroidal extension and lymph node metastasis were related to pulmonary metastasis (15, 16). Additionally, bilateral lateral lymph node metastasis was also an important risk factor (15). In our case, this patient with the right lateral cervical lymph node metastasis developed pulmonary metastasis. Therefore, lung CT should be included in the preoperative examination, when lateral lymph node metastasis is suspected.

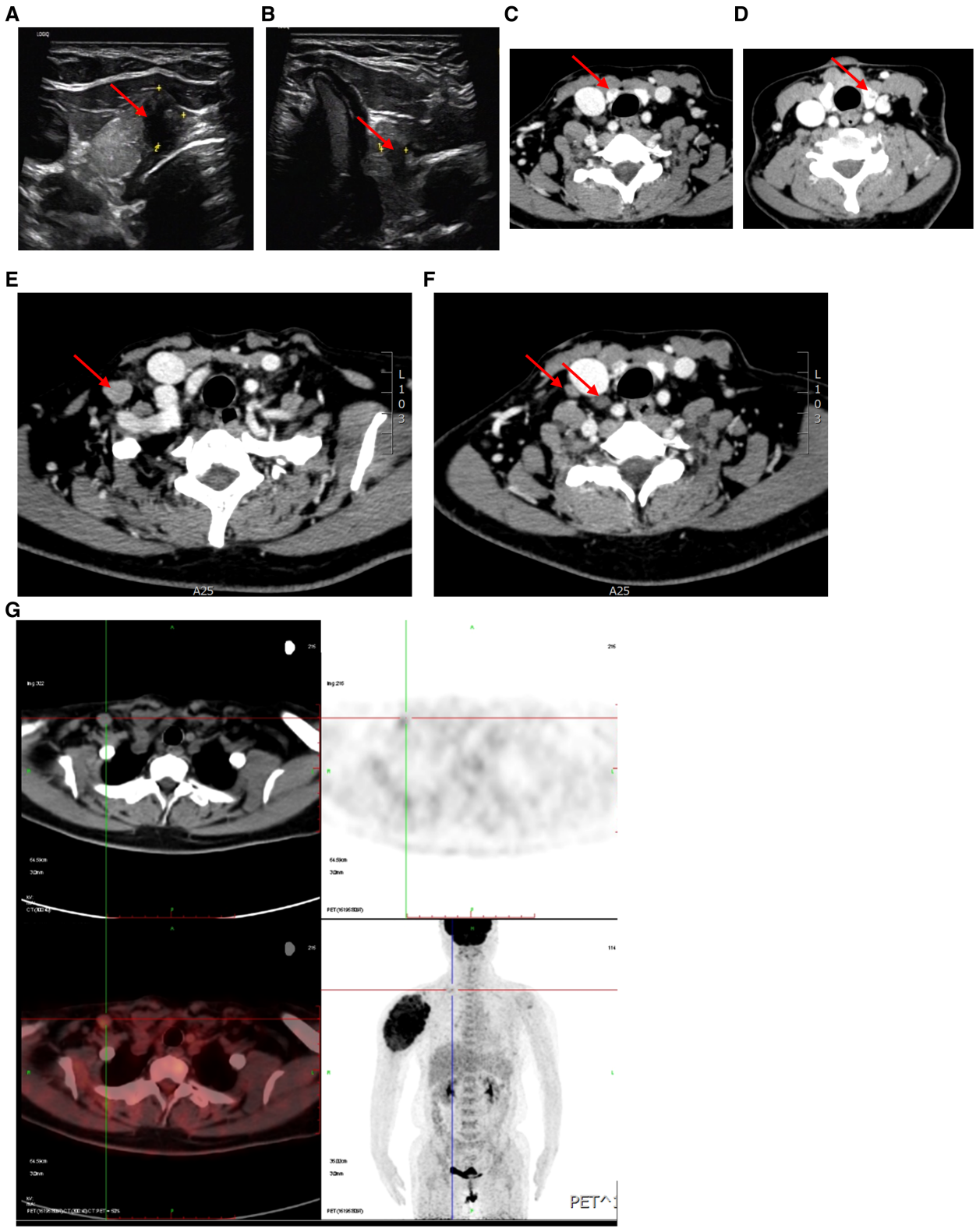

FIGURE 3
Examination of thyroid and cervical lymph nodes. (A,B) CE-US of thyroid showed within the upper portion of the left thyroid lobe was a hypoechoic, taller than wide, irregular nodule (red arrow), deeming it a TI-RADS 5. (C,D) Contrast-enhanced CT of the thyroid identified hypodense nodules within both thyroid lobes. (E,F) CT scan showed high density nodules in the right lateral cervical region. (G) ^{18}F-FDG PET/CT images showed increased uptake in right supraclavicular fossa.

Bone is the second most common metastatic site in PTC, and the mechanism of bone metastasis may be different in different patients. The incidence of bone metastasis is about 2%–13% (3). Bone metastasis mainly occurs in the spine (34.6%), followed by the pelvis (25.5%) (17). Bone metastasis is very insidious. Pain and fracture are the most common clinical manifestations. The most

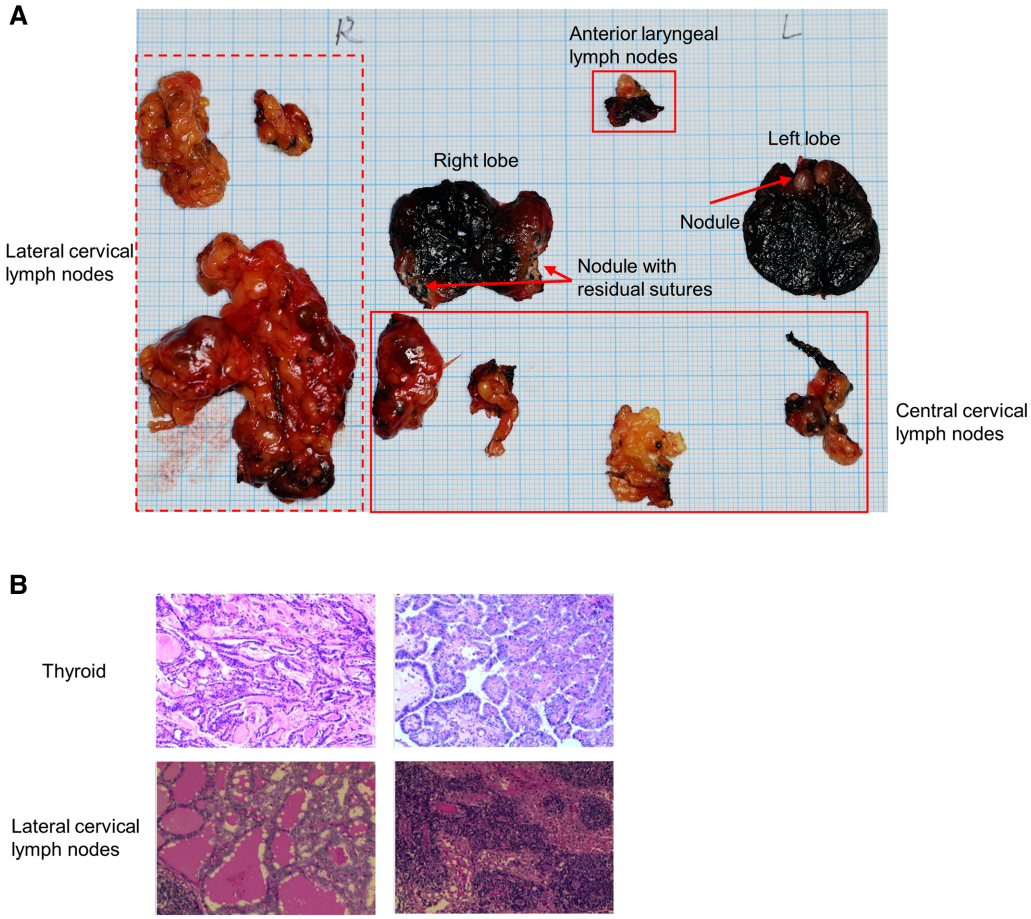

FIGURE 4
Postoperative specimen and pathology. (A) Thyroid and lymph nodes specimen. Dotted line box indicates lateral cervical lymph nodes, solid line box indicates central cervical lymph nodes. (B) Pathology of thyroid and lymph nodes.

convenient method to evaluate bone metastasis is imaging examinations, including x-ray, CT and MRI (18).

In our case, the patient showed obvious pain and swelling in her right shoulder. First of all, we considered that it was a bone tumor. However, the pathological results showed that it originated from thyroid carcinoma. Although this patient suffered with bone metastasis in the upper region of the right humeral, the site was different from the traditional site where bone metastasis occurred. This might be related to risk factors of the patient, especially the skip lymph node metastasis in the lateral cervical region. Recent studies showed that larger tumor size (>4 cm), extrathyroidal extension and lymph node metastasis were independent prognostic factors for bone recurrence. Moreover, large lymph node metastasis was significantly related to bone metastasis. Ito et al. found that lymph node metastases larger than 3 cm was a significant predictor of bone recurrence and also predicted a poor prognosis (19).

In conclusion, early detection for distant metastasis is closely related to the patients' prognosis and survival. Besides, lateral lymph node metastasis plays an important role in distant metastasis.

Malignant changes at residual sutures

The patient reported in this case underwent surgery for a benign thyroid nodule in the right lobe of the thyroid 10 years ago, and residual sutures were seen in the right nodule during this surgery. Unfortunately, pathological results showed that the small lesion around the sutures was PTMC. The malignant nodule was suspected to be related to a long-term inflammatory response caused by residual sutures. There are many reports revealing the relationship between inflammation and postoperative tumor recurrence (20). A study demonstrated that the prognostic score of inflammation was related to distal extrahepatic bile duct cancer after pancreaticoduodenectomy. Further studies have shown that the prognostic score of inflammation was an independent risk factor for recurrence of distal extrahepatic bile duct cancer (21).Thus, inflammation caused by residual sutures is also an influential factor which should not be ignored. In thyroid surgery, we can use the ultrasonic scalpel to hemostasis, and try to avoid using non-absorbable sutures to reduce inflammation caused by suture residues.

Limitations

In the study, we reported a rare case of PTMC with skip lymph node metastasis and multiple distant metastasis. There are some limitations in the case. First, we didn't perform iodine scan and radioactive iodine ablation for this patient. Although MDT was performed on the patient, the patient was unwilling to undergo amputation, which might significantly affect the curative effect. Moreover, we developed the treatment plan through MDT, but the patient did not return after discharge due to her own problems, and result in lacking of follow-up. Second, the lung nodules were not certainly diagnosed as PTC metastasis, but they were highly suspicious. In addition, only BRAF was detected for the patient, and TERT was not detected. Therefore, a more complete examination and follow-up may be more helpful for our understanding of this patient.

Thyroid cancer is an inert tumor with good prognosis, and conventional surgery is suitable for most patients. However, a small proportion of patients may be suffered from skip lymph node metastasis and distant metastasis. For this kind of patients, interdisciplinary consultation for diagnosis and treatment are needed to reduce the risk of recurrence, improve survival rate and improve the quality of life.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

QJ, SL, and YG: performed the surgery. CR, XL, and FY: collected the data of patient. QJ and MZ: drafted the first manuscript. SL, YL, and YG: revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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