Original Article

Impact of intraoperative frozen section pathology on the treatment outcome of unilateral papillary thyroid microcarcinoma and its influencing factors—a retrospective cohort study

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Background: Most patients with papillary thyroid carcinoma have a good prognosis. Excessive resection of thyroid and cervical lymph nodes is an important reason for affecting the quality of life of patients after surgery. Intraoperative rapid frozen pathological examination is an important step in the development of a surgical plan for thyroid cancer (especially micropapillary carcinoma); however, whether it affects the treatment outcome remains unclear.

Methods: The clinicopathological data of papillary thyroid microcarcinoma (PTMC) patients who underwent surgery in our center from 1 January 2021 to 31 December 2021 were retrospectively analyzed. Patients with unilateral low-risk PTMC who underwent radical surgery were selected as the main research subjects. The negative results of intraoperative frozen section of the central lymph node (CLN) of the affected side were the experimental group, and the positive results were the control group. Subjects with lesions larger than 10 mm and those who did not undergo intraoperative frozen section pathological examination were excluded. After excluding other risk factors for recurrence, we calculated the proportion of patients requiring radioactive iodine (RAI) treatment among those with metastases detected by intraoperative rapid frozen section pathology and its influencing factors. Patient data were analysed using SPSS version 20. Continuous variables were presented as means when symmetrical or as medians and ranges when asymmetrical. Categorical variables were presented as proportions. A P value <0.05 was considered significant.

Results: A total of 564 PTMC patients were included, among whom 122 patients (21.6%) underwent total thyroidectomy due to the presence of metastases in the ipsilateral CLNs. Compared with the experimental group, the patients with male, young age and tumor located in the middle and lower pole in the control group had higher lymph node metastasis (P<0.05).

Conclusions: The proportion of patients requiring postoperative RAI treatment for unilateral low-risk PTMC is relatively low, and the possibility that an intraoperative frozen pathological finding will change the treatment outcome is low. However, the need for postoperative RAI therapy notably increases when the intraoperative frozen pathological analysis reveals ipsilateral CLN metastases, especially in males, younger patients, and/or patients with lesions located in the middle and lower poles.

Keywords: Intraoperative frozen section pathology; papillary thyroid microcarcinoma (PTMC); low risk; unilateral; treatment outcome

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Introduction

Thyroid cancer is the most common malignancy of the endocrine system and has attracted great attention worldwide due to its rapidly increasing incidence, although its mortality remains stable (1). Globally, the estimated number of new cases of thyroid cancer in 2020 was about 580,000, ranking 11th among all cancers (2). According to the data released by the National Cancer Center of China, the number of new thyroid cancer cases in China in 2016 was 202,600, with a male-to-female ratio of about 1:3 (3). Over one third of new cases were papillary thyroid microcarcinoma (PTMC), which are 1 cm or less in size (4). Most of these malignancies are indolent and have a good prognosis.

The treatment of thyroid cancer is surgery-based comprehensive treatment, and surgical resection is the basis of subsequent treatment. However, the scope of surgical resection and neck lymph node dissection is still controversial, because under the premise of the same treatment effect, the larger the scope of surgery, the greater the possibility of more complications after surgery, and some complications may accompany the patient for life, or even change his life trajectory. Rapid intraoperative frozen pathological examination is an important strategy to control the scope of surgery and reduce excessive resection.

Ultrasound is an important tool in the preoperative diagnosis of thyroid nodules (5). Although fine needle aspiration (FNA) is the gold standard for identifying benign and malignant nodules, the cell populations obtained after puncture bear a high probability of being unable to distinguish benign and malignant nodules. Even in large tertiary hospitals in China, genetic testing may be required to confirm the diagnosis.

Therefore, intraoperative rapid frozen section pathological examination is favored in departments of thyroid cancer surgery. This technique can not only distinguish the benign and malignant nature of thyroid lesions but also identify lymph node metastases, thus playing an important role in the surgical decision-making. For unilateral low-risk PTMC, if the preoperative clinical assessment shows that the cervical lymph node is negative (cN_0), ipsilateral thyroid lobectomy with isthmusectomy will be planned; meanwhile, prophylactic dissection of the central lymph nodes (CLNs) at the affected side will be performed under the premise of safety (6). It has been reported that the probability of CLN metastases could reach 43%, even in cN_0 patients (7). Although such a high probability is not typical, it highlights the importance to identify any possible CLN metastasis at the affected side, to circumvent undertreatment. When a CLN metastasis occurs, the purpose of total thyroidectomy is to prepare for possible postoperative radioactive iodine (RAI) therapy. Unfortunately, few studies have investigated the proportion of patients requiring iodine therapy following total thyroidectomy and its influencing factors. In other words, it is currently unknown whether the intraoperative rapid frozen pathological examination will change the treatment outcome. Here, we retrospectively analyzed the data of unilateral low-risk PTMC patients who underwent surgery in our hospital and evaluated the impact of intraoperative frozen pathological examination on the outcome of PTMC treatment. We present the following article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-519/rc).

Methods

Participants

We performed a retrospective cohort study of PTMC patients who underwent surgery in our center between 1 January 2021 and 31 December 2021 (*Figure 1*). Since the objective of our study was to establish a longitudinal association between intraoperative rapid frozen section pathology and patient outcomes, only cases (n=1,229) with thyroid cancer who were hospitalized in our hospital's general surgery department and had an accurate preoperative assessment of the lesion from our imaging center were enrolled. We excluded 611 patients who met any of the following exclusion criteria: no surgery (n=17); coexisting malignancies (n=11); other pathological subtypes (n=26); lesions greater than 1 cm (n=489); lesions invading the capsule (n=52); lymph node metastases confirmed by preoperative puncture (n=8); and coronavirus disease 2019 (COVID-19) vaccination within 1 month before surgery (n=8). Subsequently, 54 participants who did not undergo intraoperative rapid frozen section pathology and only had postoperative pathology results were ruled out. Thus, 564 participants with unilateral low-risk PTMC who had negative ipsilateral CLNs on preoperative imaging assessment and underwent intraoperative rapid frozen section pathology of the ipsilateral CLNs entered the final analysis.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study

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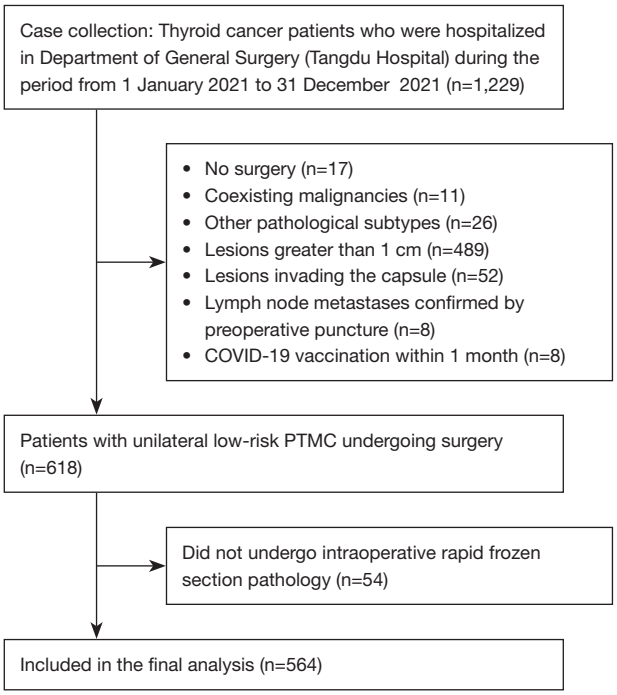

Figure 1 The flowchart of patient enrollment. COVID-19, coronavirus disease 2019; PTMC, papillary thyroid microcarcinoma.

was approved by the Ethics Review Committee of Tangdu Hospital (ethical approval number: 202203-27), and written informed consent was provided by all participants.

Data collection

The collected information included gender, age, body mass index (BMI), largest diameter/location/number of the lesions, preoperative imaging assessment of the ipsilateral CLNs, surgical procedures, intraoperative rapid frozen section pathology of lymph nodes, and postoperative pathology of lymph nodes. The BMI was calculated using the following formula: weight (kg)/[height (m)]^2. The tumor location was divided into upper, middle, and lower poles according to preoperative imaging and intraoperative anatomic findings. The number of tumors included single nodule (n=1) and multiple nodules (≥2). Thyroid surgical treatment methods included ipsilateral thyroid lobectomy with isthmusectomy (when no CLN metastasis was seen at the affected side) and total thyroidectomy (when CLN metastases were found at the affected side). Lymph node dissection methods included ipsilateral CLN dissection (when no metastases were found in the ipsilateral CLNs and there were no macroscopically enlarged lymph nodes), bilateral CLN dissection (when no metastases but macroscopic lymph nodes were found in the ipsilateral CLNs), and dissection of CLNs and lateral cervical lymph nodes (LCLNs; when there were metastases and macroscopically enlarged lymph nodes in the ipsilateral CLNs). The results of intraoperative frozen section pathology of lymph nodes, including "No metastasis found" and "Metastasis found", were reported by the pathology center via telephone and recorded in the operation records. For the postoperative pathology of the lymph nodes, the pathology center provided a hardcopy report, containing information including the total number of lymph nodes resected and the number of metastatic lymph nodes (including micro-metastases and macro-metastases).

Intraoperative rapid frozen section pathology

A 6–8 cm arcuate incision was created two transverse fingers above the supraclavicular fossa for dividing the subcutaneous tissue, adipose tissue, and platysma. Skin flaps were mobilized below the platysma, upwards to the upper edge of the thyroid cartilage and downwards to the supraclavicular fossa, with both sides to the medial border of the sternocleidomastoid muscle. The "white line" was divided to retract the strap-like muscles on the affected side. After the lateral side of the thyroid was mobilized, the inferior thyroid vein, middle vein, and superior pole artery and vein were ligated with silk sutures, and then the thyroid isthmus was severed. The upper and lower parathyroid glands and the recurrent laryngeal nerve were identified and carefully protected before the ipsilateral thyroid was resected. The ipsilateral CLNs were dissected, including all the lymphatic and fatty tissues below the thyroid cartilage, above the sternal notch, and within the medial region of the common carotid artery. Any injury to the recurrent laryngeal nerve and parathyroid tissues was avoided throughout the surgical procedure (the above steps were completed by the surgeons). The lymph nodes and adipose tissue were snap-frozen and sliced at –25 ℃ and then fixed with alcohol acetate formalin (AAF) (85 mL of 95% ethanol, 10 mL of 4% neutral formaldehyde, and 5 mL of glacial acetic acid). After nuclear staining in hematoxylin for 30 seconds to 1 minute, the sections were washed in running tap water until they turned "blue". Eosin was used to counterstain the cytoplasm for 5–15 seconds. After washing with tap water, the sections were dehydrated in a graded series of ethanol, treated with xylene, and mounted in neutral resin before the sections were read (all

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Table 1 Basic information of the PTMC patients

Patient characteristics	Negative group (n=442, %)	Positive group (n=122, %)	P value
Gender			
Males (n=152)	96 (63.2)	56 (36.8)	<0.05
Females (n=412)	346 (84.0)	66 (16.0)	>0.05
Age (years) (mean ± SD)	46.2±5.32	45.1±7.86	>0.05
BMI (kg/m^2, mean ± SD)	23.4±1.52	22.2±2.15	>0.05
Maximal tumor diameter (mm, mean ± SD)	6.98±2.32	7.13±1.86	>0.05
Tumor location			
Upper pole (n=98)	80 (81.6)	18 (18.4)	>0.05
Middle pole (n=277)	223 (80.5)	54 (19.5)	>0.05
Lower pole (n=189)	139 (73.5)	50 (26.5)	<0.05
Tumor number			
Single (n=389)	304 (78.1)	85 (21.9)	>0.05
Multiple (≥2, n=175)	138 (78.9)	37 (21.1)	>0.05
Surgical procedure for the thyroid			
Ipsilateral thyroid lobectomy with isthmusectomy (n=442)	442	–	–
Total thyroidectomy (n=122)	–	122	–
Management of lymph nodes			
Ipsilateral CLN dissection (n=486)	432	54	–
Bilateral CLN dissection (n=74)	10	64	–
LCLN & BCLN dissection (n=4)	–	4	–

PTMC, papillary thyroid microcarcinoma; SD, standard deviation; BMI, body mass index; CLN, central lymph node; LCLN, lateral cervical lymph node; BCLN, bilateral cervical lymph node.

the above steps were completed in the pathology center). The cases were divided into 2 groups: the negative group (no metastasis was found in the lymph nodes) and the positive group (metastasis was found in the lymph nodes).

Variables

The primary outcome was the proportion of participants requiring RAI therapy after surgery. According to the relevant guidelines, we defined patients with 5 or more lymph node metastases as those who required postoperative RAI therapy. When the total number of the dissected lymph nodes was below 5, we also considered the percentage of the number of positive lymph nodes to the total number of dissected lymph nodes, and RAI therapy was recommended if the percentage was greater than 50%. If there were no lymph nodes in the dissected tissues, they were excluded from the study.

Statistical analysis

The continuous data were presented as mean ± standard deviation and the categorical variables as percentages. The comparisons between negative group and positive groups were based on *t*-test for continuous variables and chi-square test for categorical variables. A P value of <0.05 was considered statistically significant. Statistical analysis was performed using SAS 9.4 software (SAS Institute, Cary, NC, USA).

Results

Table 1 summarizes the baseline characteristics of patients in 2 groups. There were 152 male patients (27.0%) and 412

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Table 2 Relationship between gender and risk of lymph node metastasis

Gender	Number of patients (n)	Number of lymph nodes resected ($\bar{x}$±SD, range)	Number of positive lymph nodes ($\bar{x}$±SD, range)
Males	152	8.9±3.3 [5–25]	2.5±1.1 [1–16]
Females	412	7.6±4.2 [3–20]	1.2±0.4 [1–4]

SD, standard deviation.

Table 3 Relationship between age and risk of lymph node metastasis

Age group (years)	Number of patients (n, %)	Number of patients with positive lymph nodes (n, %)	Number of lymph nodes resected ($\bar{x}$±SD, range)	Number of positive lymph nodes ($\bar{x}$±SD, range)
<30	56 (9.9)	16 (28.6)	10.2±3.7 [5–25]	2.1±2.1 [1–16]
30–39	105 (18.6)	27 (25.7)	8.9±2.7 [6–21]	2.0±1.6 [1–8]
40–49	208 (36.9)	39 (18.8)	7.4±3.6 [3–18]	1.2±1.5 [1–9]
50–59	147 (26.1)	29 (19.7)	7.1±1.1 [4–18]	1.5±1.1 [1–8]
≥60	48 (8.5)	11 (22.9)	7.2±2.0 [4–19]	1.3±2.0 [1–7]

SD, standard deviation.

females (73.0%), with a 1:2.7 male-to-female ratio. The mean age of these was 45.6 years (range, 17 to 79 years). The mean BMI was 22.7 kg/m^2. Most patients (69.0%) had a single lesion, and the remaining patients (31.0%) had 2 or more lesions. About half of the tumor lesions were located in the middle pole, 33.5% in the lower pole, and only 17.4% in the upper pole. The average maximal tumor diameter was 7.02 mm, with the shortest one being 4.96 mm.

Since the lesions were clinically assessed as "low risk", most patients (78.4%) finally underwent ipsilateral thyroid lobectomy with isthmusectomy, and the remaining patients (21.6%) received total thyroidectomy as the intraoperative rapid frozen pathological examination of the ipsilateral CLNs revealed the presence of metastasis. Among the patients who underwent total thyroidectomy, 26 had 5 or more positive lymph nodes, accounting for 21.3% of total thyroidectomy cases or 4.6% of the whole study population. According to the guidelines, these participants required postoperative adjuvant RAI therapy. These guidelines do not recommend dissection of the LCLNs in PTMC patients; in our clinical practice, however, when the CLNs are confirmed to have metastases and the macroscopically enlarged lymph nodes are found during surgery, ipsilateral LCLN dissection will be performed. Among the patients included in this study, 4 patients underwent LCLN dissection, accounting for about 0.7% of the whole study population (*Table 1*).

In addition, 56 male patients had lymph node metastasis, accounting for 36.8% of male participants, which was significantly higher than that (16.0%) of female participants, along with a notably larger average number of metastases (2.5 *vs.* 1.2) (*Table 2*). In addition, we found that younger patients were more likely to have lymph node metastasis and thus require postoperative RAI therapy, which is consistent with previous studies (*Table 3*). Furthermore, tumor location was another factor affecting lymph node metastasis. The risk of ipsilateral CLN metastasis was higher for tumors located in the lower pole (26.5%) than those in in the middle pole (19.5%) or upper pole (18.4%), along with larger number of lymph nodes dissected (*Table 4*). In clinical practice, thyroid cancer associated with Hashimoto's thyroiditis is very common, and these patients usually have many enlarged CLNs. If enlarged lymph nodes are found during surgery, bilateral CLN dissection is routinely performed in our center to avoid possible metastases and undertreatment. Therefore, 74 patients in this study underwent bilateral CLN dissection, and 4 patients received LCLN & BCLN dissection due to the presence of metastases and macroscopically enlarged lymph nodes (*Table 5*).

Discussion

The incidence of thyroid cancer has rapidly increased in recent years due to the increased health awareness among

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Table 4 Relationship between tumor location and risk of lymph node metastasis

Tumor location	Number of patients with positive lymph nodes (n, %)	Number of lymph nodes resected ($\bar{x}$±SD, range)	Number of positive lymph nodes ($\bar{x}$±SD, range)
Upper pole (n=98)	18 (18.4)	6.7±2.3 [3–9]	1.4±0.9 [1–7]
Middle pole (n=277)	54 (19.5)	7.4±1.9 [5–25]	1.8±1.2 [1–16]
Lower pole (n=189)	50 (26.5)	7.5±2.2 [5–23]	1.9±2.0 [1–10]

SD, standard deviation.

Table 5 Relationship between the extent of lymph node dissection and the risk of metastasis

Extent of lymph node dissection	Number of patients (n)	Number of patients with positive lymph nodes (n, %)	Number of lymph nodes resected ($\bar{x}$±SD, range)	Number of positive lymph nodes ($\bar{x}$±SD, range)
Ipsilateral CLN dissection	486	54 (11.1)	2.1±0.7 [3–15]	1.3±1.0 [1–7]
Bilateral CLN dissection	74	64 (86.5)	4.5±2.1 [5–20]	2.1±1.5 [1–10]
LCLN & BCLN dissection	4	4 (100.0)	6.7±2.8 [5–25]	5.2±2.6 [5–16]

SD, standard deviation; CLN, central lymph node; LCLN, lateral cervical lymph node; BCLN, bilateral cervical lymph node.

the general population and the huge investment in health care in China (8,9). Teng believes that the increased prevalence of thyroid cancer can be explained by 4 reasons: (I) there is a huge "reservoir" of thyroid cancer in the human body; (II) due to the indolent biological nature of thyroid cancer, the tumor will not progress for a long period of time or progresses slowly; (III) large-scale screening for thyroid nodules and thyroid cancer has been actively carried out in China; and (IV) the resolution of ultrasound has dramatically increased (10). Despite the surge in morbidity of thyroid cancer, there has been no significant increase in mortality; the survival rates of thyroid cancer patients have not notably changed, and the prognosis is good.

Due to the good prognosis of PTMC, whether immediate surgery is required for this condition remains controversial. "Conservative" authors believe that the vast majority of PTMC patients have no symptoms, the tumor progresses slowly, or even does not progress for life. Surgical treatment offered after disease progression will not affect survival outcomes. Thus, conservative treatment should be selected. In contrast, "radicals" argue that although PTMC has a good prognosis, not all patients are in a non-progressive subclinical state; rather, in some cases, PTMCs even have local invasion or lymph node/distant metastasis at early stages (11,12). After a diagnosis of PTMC is made, conservative treatment has strict requirements such as location of the lesions in glands, low-risk pathological subtypes, no signs of lymph node metastasis, and good mental status of the patient. A final decision should be jointly made by clinicians and patients (6). Under the current technical conditions in most hospitals, it is difficult to identify the pathological subtypes of thyroid cancer based on specimens obtained by FNA and therefore conservative treatment can be highly risky for patients with high-risk subtypes. Conservative treatment also faces another challenge: patient acceptance. The Chinese people's fear of cancer is inherent; the mental challenges faced by patients and the societal stigma of the disease can affect the patient's life and work.

For PTMCs requiring surgical treatment, surgery is the key to cure and the basis for subsequent treatments (13). At present, the major controversy is the management of the primary tumor and the cervical lymph nodes (14). The tumor size is not the only indicator for evaluating tumor invasion and metastasis. Clinically, PTMC often invades the capsule or surrounding tissues and may also lead to CLN or even LCLN metastasis. According to the Chinese expert consensus on diagnosis and treatment of PTMC (2016 edition), thyroid lobectomy with isthmusectomy or total/near total thyroidectomy should be reasonably selected for PTMC according to the clinical features and risk of the lesion (6). The guidelines suggest that ipsilateral thyroid lobectomy with isthmusectomy is preferred for PTMC, and the role of total thyroidectomy should not be emphasized. Individualized treatment plans should be formulated according to clinical stages, risk assessment results, and pros

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and cons of different surgical procedures. The willingness of patients may also be considered (6). For the management of cervical lymph nodes, the guidelines recommend that for patients with cN_0 PTMC, prophylactic CLN dissection should be performed when technical support is available; however, prophylactic LCLN dissection is generally not recommended. In fact, the indication of LCLN dissection for PTMC is the presence of preoperatively or intraoperatively confirmed LCLN metastasis. In our current study, the proportion of patients requiring LCLN dissection was very low (about 0.7%) in unilateral low-risk PTMC patients.

In addition, the impact of surgery on the quality of life should also be considered. Total thyroidectomy will inevitably lead to lifelong thyroid hormone replacement therapy, and thorough lymph node dissection increases the risk of injury to recurrent laryngeal nerve and parathyroid glands. Therefore, an individualized surgical plan should be developed based on the patient's age, occupation, preoperative imaging findings, and pathological examination results to ensure the safety and effectiveness of the surgery and maintain good quality of life as much as possible. In our center, intraoperative rapid frozen pathological examination is performed for patients with preoperative cN_0 PTMC to identify the status of the ipsilateral CLNs. If the result is negative, ipsilateral thyroid lobectomy with isthmusectomy combined with ipsilateral CLN dissection is performed; if the pathology reveals the presence of metastatic lesions, bilateral CLN dissection with or without LCLN dissection (based on the presence or absence of macroscopically enlarged lymph nodes) is applied.

If the intraoperative frozen pathological examination confirms the presence of ipsilateral CLN metastases, total thyroidectomy may be performed to prepare for the possible postoperative RAI therapy. However, total thyroidectomy is not required if there is no need for postoperative radiotherapy. Therefore, the indications of RAI therapy are another important factor in determining the surgical procedure. In 2022, the European Thyroid Association pointed out in its consensus document on the indications for post-surgical radioiodine therapy in differentiated thyroid cancer that a decision of post-surgical radioiodine therapy should be made based on the following considerations: (I) the initial prognostic indicators for thyroid cancer-related death and recurrence, including surgical and pathological reports; (II) postoperative serum thyroglobulin (Tg) levels; and (III) findings of neck ultrasonography (15). According to the American Thyroid Association, patients with high risk of recurrence have a higher risk of cancer-related death, and postoperative RAI therapy can prolong the disease-free survival (DFS) and overall survival (OS) (16). In patients with intermediate risk of recurrence, the following patient populations may benefit more from RAI therapy: elderly patients; patients with histologically confirmed aggressive lesions; patients with rapidly growing lesions; patients with extraglandular lesions; patients with a large number of positive lymph nodes; and patients with lymph node metastases outside the central area. Therefore, RAI therapy is recommended for these patients. In contrast, RAI therapy is not recommended for patients at low risk of recurrence. According to Chinese guidelines on PTMC, for PTMC patients with metastases (especially distant metastases), radioiodine (I-131) therapy can help eliminate residual lesions or metastases that cannot be surgically removed, alleviate disease conditions, and reduce the risk of PTMC recurrence.

Therefore, postoperative RAI therapy is required for: (I) patients with macroscopically visible tumor lesions invading surrounding tissues; (II) patients with tumor lesions that cannot be completely removed during surgery; and (III) patients with many positive lymph nodes or if the diameters of the involved lymph nodes are large. In our practice, when the intraoperative frozen pathological results indicate that there is metastasis, total thyroidectomy is performed to avoid the phenomenon that patients with many lymph node metastases due to residual glands cannot receive postoperative adjuvant RAI therapy. In fact, RAI therapy can also bring a variety of complications (17). The legitimacy of this strategy must therefore be questioned. Some PTMC patients do not have other risks; only their CLNs have metastasis, and the number of metastases has not reached the indications for RAI therapy. According to the guidelines, these patients have a low risk of recurrence risk; ipsilateral thyroid lobectomy with isthmusectomy will be adequate, and total thyroidectomy is not required. In other words, CLN metastases identified by intraoperative frozen section pathology do not always require subsequent RAI therapy and will not change the treatment strategies. Based on the data from our center in 2021, among 564 patients with preoperatively-assessed cN_0 PTMC (without other risk factors for recurrence), only 26 (4.61%) required postoperative adjuvant RAI therapy because the number of cervical lymph node metastases exceeded 5. Notably, males, younger patients, and those with lesions located in the lower pole were more likely to develop lymph node metastasis, along with a higher possibility of postoperative

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RAI treatment.

For the vast majority of PTMC patients who do not have other risks of recurrence (such as tumor lesions located inside the glands and complete intraoperative resection of lesions), intraoperative rapid frozen pathological examination does not change the patient's treatment outcome, and total thyroidectomy is not required for most patients; rather, ipsilateral thyroid lobectomy with isthmusectomy combined with CLN dissection will be sufficient. However, special attention should be paid to the risk factors affecting lymph node metastasis, including gender, age, and tumor location.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-519/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-22-519/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Review Committee of Tangdu Hospital (ethical approval number: 202203-27), and written informed consent was provided by all participants.

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