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Improving quality of life in patients with differentiated thyroid cancer

Edited by
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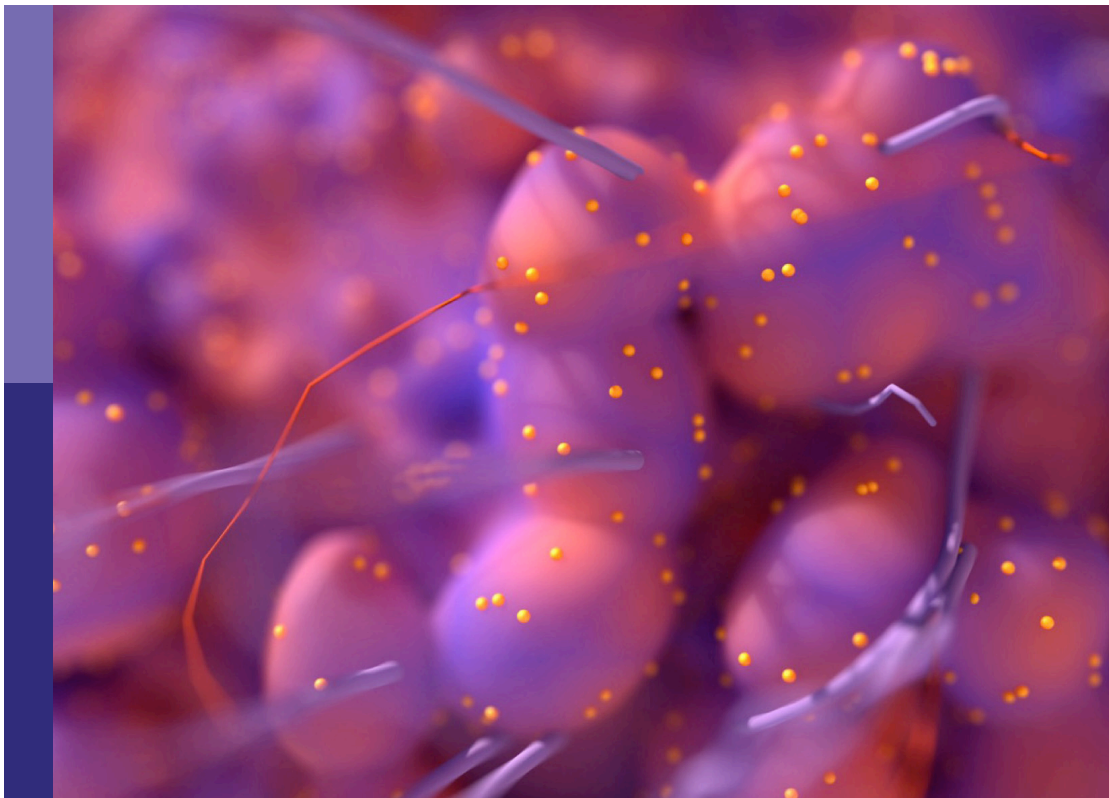

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Improving quality of life in patients with differentiated thyroid cancer

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Table of contents

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Editorial: Improving quality of life in patients with differentiated thyroid cancer

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thyroid cancer, nerve monitoring, quality of life, thyroidectomy, neck dissection

Editorial on the Research Topic
Improving quality of life in patients with differentiated thyroid cancer

Differentiated thyroid carcinoma (DTC) is on the rise worldwide and ranks first among endocrine cancers (1). The survival rate of DTC patients has increased in recent decades with the development of multidisciplinary screening and treatment methods (2). Thyroid cancer is most commonly diagnosed in women in their 40s, which means that these women live longer after completing treatment (3). The increase in thyroid cancer is mainly due to the discovery of thyroid microcarcinoma, and despite the increase in diagnoses, survival rates have not changed (4). This continued increase in new thyroid cancer cases and the known excellent prognosis for well-differentiated thyroid cancer have led to an increasing focus on the quality of life of thyroid cancer patients, rather than just complete removal of the tumour and adjuvant treatments.

Major efforts have been made to reduce the surgical burden in low-risk tumours and in diagnostic procedures. Other surgical contraventions, such as the role of central neck dissection, especially prophylactically, has been questioned given its risk-benefit ratio; the role of active survival in low-risk DTC; non-surgical interventions such as radiofrequency and thermal ablations are among the studies included in these current Research Topics. Other aspects relate to the use of technology to minimise potential complications and adverse outcomes of thyroid surgery - use of intraoperative nerve monitoring to reduce recurrent laryngeal nerve injury, remote surgical approaches that avoid visible neck scars, and more.

After completion of primary treatment, patients with DTC can usually remain healthy and return to their former lives (3, 4). However, in the transitional phase after completion of primary treatment, DTC patients may suffer varying degrees of long-term physical, social and psychological problems that make their survival much more difficult (2). Although some cancer-related problems diminish over time, some DTC patients struggle with physical (dysphonia, hypocalcaemia, pain, dysphagia), psychological (anxiety, depression, fear) and social (avoidance, re-employment) problems related to the treatment consequences (1–4). These problems affect the adaptability and quality of life of DTC patients learning to live with cancer and represent a major challenge in the recovery process (1) (Figure 1).

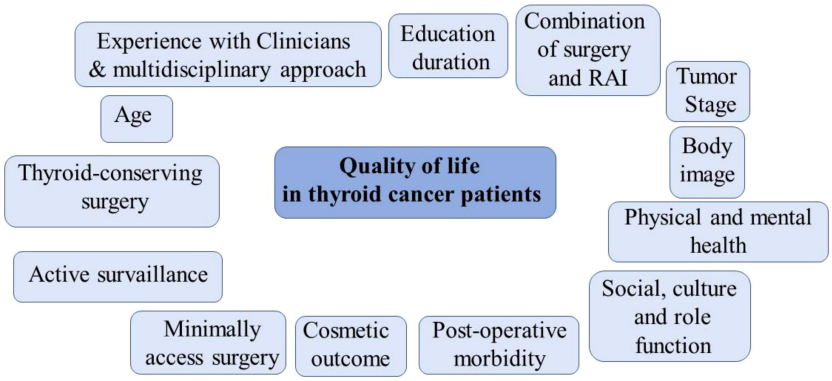

FIGURE 1
Factors influencing quality of life in thyroid cancer patients.

In addition to objective factors that have an obvious impact on quality of life, such as postoperative complications, recurrence, etc., subjective quality of life, i.e. patient-centred factors in treatment options for DTC, has become an important topic in recent clinical trials (1–4). This index distinguishes between general and disease-specific quality of life in terms of the spectrum of life domains affected. General quality of life should encompass all areas of life, while disease-specific quality of life focuses on the effects of disease and therapy (consequences).

Factors influencing the quality of life of DTC patients include physical and psychological symptoms, self-efficacy and social support (2, 3). Close counselling and education of DTC patients, care and symptom control have been shown to be particularly important (1–4). Particular attention needs to be paid to the early management of postoperative morbidity (1–4). Postoperative management has improved, but long-term data, especially on quality of life, are needed (5, 6).

The more severe the symptoms in DTC patients, the greater the psychological distress, the lower the physical and social functioning and the poorer the overall quality of life (7). Social support, such as feeling protected or receiving help from others, helps survivors to actively manage their health problems and find positive meaning in life, which ultimately improves their quality of life (1, 8, 9).

The concept of quality of life is currently gaining importance in the evaluation of treatment procedures (10). When comparing multiple treatments, standardisation is needed to account for the heterogeneity of patient cohorts. Analogous to relative survival in DTC epidemiology, the measured QoL scores should be set in relation to the age- and gender-specific reference of the general population to show the actual effect of the respective disease and its treatment.

Physicians should discuss the expected outcomes after thyroid surgery with patients in order to increase patient satisfaction and quality of life through detailed information.

Author contributions

AK, OC and GD: writing and revising the manuscript. 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.

Publisher's note

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SYSTEMATIC REVIEW
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Prophylactic Central Neck Dissection for cN1b Papillary Thyroid Carcinoma: A Systematic Review and Meta-Analysis

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Background: The value of prophylactic central neck dissection (PCND) for papillary thyroid carcinoma (PTC) with clinically evident lateral cervical lymph node metastases (cN1b) remains unclear. Therefore, a systematic review and meta-analysis was conducted to assess the efficacy and safety of PCND.

Methods: A comprehensive systematic search was conducted on PubMed, Web of Science, Cochrane library and Embase databases up to September 2021 to identify eligible studies. Controlled clinical trials assessing therapeutic effects and safety of PCND for cN1b PTC patients were included. The risk of bias for each cohort study was assessed using the Newcastle-Ottawa Scale (NOS). The primary outcomes were indexes related to the locoregional recurrence (LRR) and surgical complications. Review Manager software V5.4.0 was used for statistical analysis. A fixed effects model was adopted for the data without heterogeneity, otherwise a random effects model was used.

Results: We included 4 retrospective cohort studies, which comprised 483 PTC patients. There was no statistically significant difference in the central neck recurrence (CNR) (10.2% vs. 3.8%, relative risk (RR) = 1.82; 95%CI 0.90–3.67; P = 0.09), lateral neck recurrence (LNR) (5.1% vs. 7.7%, RR = 0.47; 95% CI 0.13–1.74; P = 0.26), and overall recurrence (OR) (18.9% vs. 16.9%, RR = 0.77; 95%CI 0.34–1.76; P = 0.54), between LND + PCND group and LND group. Simultaneously, PCND increased the risk of permanent hypoparathyroidism (11.4% vs. 4.5%, RR = 2.70, 95%CI 1.05–6.94; P = 0.04) and overall complications (17.0% vs. 5.3%, RR = 3.28; 95%CI 1.37–7.86; P = 0.008).

Conclusions: This meta-analysis showed that PCND did not have any advantage in preventing LRR for cN1b PTC. Meanwhile, PCND may result in the increased rate of surgical complications. However, the current evidence is limited and more clinical trials are still needed to further clarify the true role of PCND.

Systematic Review Registration: https://www.crd.york.ac.uk/PROSPERO/, CRD42021281825.

Keywords: prophylactic central neck dissection (PCND), papillary thyroid carcinoma (PTC), lateral neck dissection (LND), lateral cervical lymph node metastases, locoregional recurrence, total thyroidectomy (TT)

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INTRODUCTION

Thyroid cancer is the most common malignant tumor in the endocrine system and head and neck tumors, causing586,000 cases worldwide and ranking 9th in incidence in 2020 (1). Papillary thyroid carcinoma (PTC) accounts for the vast majority of thyroid cancers. Regional lymph node metastases (LNM) are very common in patients with PTC (up to 80%), especially in the central compartment of the neck (2, 3). LNM have been reported in association with a higher rate of locoregional recurrence (LRR) (4). Surgical resection of clinically nodal-positive disease (cN1) in PTC is considered to make improvement to the results of both recurrence and survival. Therefore, it is generally believed that therapeutic cervical lymph node dissection is indicated in PTC patients with cN1. However, the effect on long-term outcome of prophylactic central neck dissection (PCND) in PTC patients without clinically evident nodal metastasis (cN0) remains unclear, and the 2021 National Comprehensive Cancer Network (NCCN) and the 2015 American Thyroid Association (ATA) guidelines do not recommend that routine PCND should be performed in all these PTC patients with cN0 (5, 6).

There is a generally accepted assumption that cervical LNM in PTC patients follow the gradual progression of LNM from the central to lateral compartment and lymph nodes skip metastases to the lateral compartment are present only in a small number of PTC patients (7, 8). Therefore, some surgeons have advocated routine PCND in PTC patients with clinically evident lateral cervical LNM (cN1b) combined with total thyroidectomy (TT) and lateral neck dissection (LND) (9). Moreover, the 2021 NCCN and the 2015 ATA guidelines suggest that PCND should be taken into consideration in PTC patients with cN1b (5, 6). However, this suggestion is relatively weak and based on low quality evidence, and the value of PCND remains unclear.

Surgery in the central compartment of neck may result in some complications. The majority of these complications are injuries of the parathyroid glands and recurrent laryngeal nerves, which will lead to temporary or permanent hypoparathyroidism and hoarseness of voice. As is well known, the extent of initial surgery of thyroid and lymph nodes should be based on evidence of long-term benefits in terms of improvements of local control or survival, while minimizing the risk of complications. Hence, for these PTC patients with cN1b but no clinically evident central compartment LNM on preoperative imaging or intraoperative evaluation, we should weigh the potential benefits of PCND against the risks. This systematic review and meta-analysis was conducted to evaluate the LRR and complications rates of TT + LND versus TT + LND + PCND.

METHODS

Study Protocol and Registration

This systematic review and meta-analysis was performed in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (**Figure 1**). The study protocol was registered on PROSPERO with No. CRD42021281825.

Search Strategy

Eligible studies were identified by a comprehensive systematic search on the PubMed, Web of Science, Cochrane library and Embase databases up to September 2021. The search strings used a combination of the terms "papillary thyroid cancer", "well-differentiated thyroid carcinoma", "lateral neck dissection", "elective central neck dissection", "prophylactic central neck dissection", and logical word "OR" or "AND".

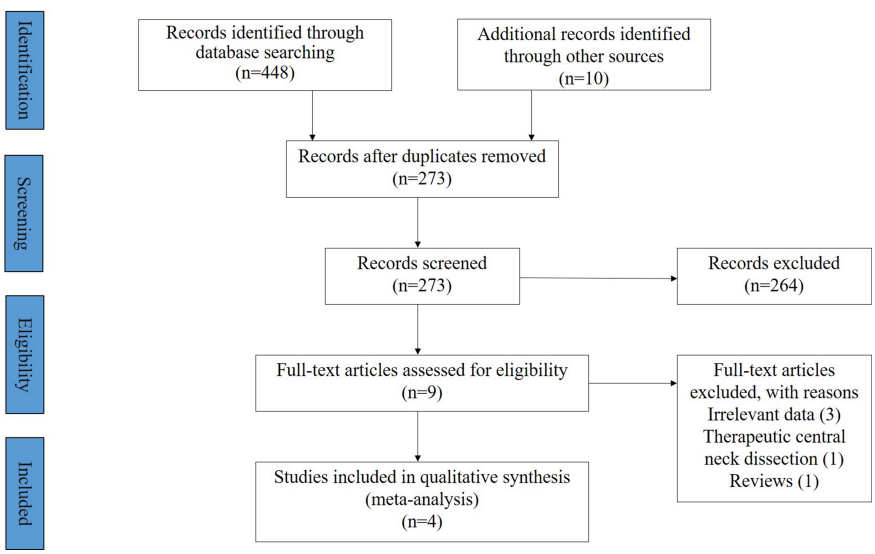

FIGURE 1 | Flowchart of article selection according to PRISMA statement.

Study Selection

Two investigators independently used search strategies to retrieve study titles and abstracts. The inclusion criteria for the articles were as follows (1): articles published in English, (2) PTC patients diagnosed with lateral compartment LNM, (3) two groups that compared TT + LND with TT + LND + PCND in study. The exclusion criteria were as follows: (1) lack of preoperative assessment of central compartment lymph nodes, (2) preoperative diagnosis of central compartment LNM, and (3) insufficient demographic and clinical data. Letters to editors, case reports, meeting abstracts, review articles and incomplete studies were also excluded. In addition, both investigators also reviewed the reference lists of included articles to identify additional relevant articles. All of the potentially eligible articles were identified, and any disagreements between the two investigators were resolved through a discussion and by consensus with a third investigator.

Data Extraction and Quality Assessment

Two investigators independently completed extraction of the following data from included articles based on a standardized template: first author, year, country, study design, study period, follow up, sample size, age, sex, tumor size, extrathyroidal extension, incidence of central LNM, radioactive iodine (RAI) treatment, number of LRR, site of LRR, and surgical complications. For cohort studies, quality assessment and analysis of risk of bias were conducted by Y-xQ and Z-zZ using Newcastle-Ottawa Scale (NOS) independently. This scale awards a maximum of nine points. A score of ≥7 is considered to indicate high quality.

Statistical Analysis

Review Manager software V5.4.0 (The Cochrane Collaboration, 2020) was used for statistical analysis. Heterogeneity among studies was assessed by the heterogeneity test with the I^2 statistic. I^2 >50% was considered significant heterogeneity. A fixed effects model was adopted for the data without heterogeneity in the meta-analysis, otherwise a random effects model was used for the significantly heterogeneous data. The difference between the two groups was quantified by the terms of relative risk (RR) along with 95% confidence interval (CI), and $P < 0.05$ was considered to be significance.

RESULTS

Study Selection

The detail of the article selection process is described as a flow chart (**Figure 1**). Our search strategy retrieved a total of 458 articles, and 273 unique articles were retained after removing the duplicates. After reviewing the titles and abstracts according to the inclusion and exclusion criteria, 9 potentially eligible articles were obtained and reviewed in full text. Of these 9 articles, 5 were subsequently excluded for various reasons, and finally 4 retrospective cohort studies involving 483 PTC cases were included in the meta-analysis (286 in the LND group and 197 in the LND + PCND group) (10–13).

Study Characteristics and Quality

The characteristics of these included studies are summarized in **Table 1**. The years of publication of the included articles ranged from 2013 to 2020. Two studies were conducted in the Israel (10, 13), one in the USA (12), and one in Italy (11). All studies underwent a preoperative imaging procedure for central compartment lymph node assessment by ultrasonography, CT scan, or MRI scan, and two studies also performed an intraoperative evaluation. All studies made a comparison of

TABLE 1 | Detailed characteristics of studies included in the meta-analysis.

Study	Year	Country	Study design	Study period	Follow up (mean, month)	Sample size	Age (mean, year)	Sex (M/F)	Tumor size ≤4cm, n (%)	Extrathyroidal extension, n (%)	Incidence of central LNM, n (%)	Radioactive iodine treatment, n (%)
Trivizki et al.	2013	Israel	RCS	2000–2010	44	LND + PCND: 34	47	17/17	17 (50.0)	13 (38.2)	24 (70.6)	34 (100)
						LND: 17	44	11/6	10 (58.8)	5 (29.4)		17 (100)
Napoli et al.	2020	Italy	RCS	2004–2015	67.9	LND + PCND: 54	42	13/41	49 (90.7)	34 (63.0)	47 (87.0)	54 (100)
						LND: 115	45	45/70	108 (93.9)	68 (59.1)		115 (100)
Harries et al.	2020	USA	RCS	1986–2015	65	LND + PCND: 49	49	19/30	48 (98.0)	/	37 (75.5)	38 (77.6)
						LND: 103	49	46/57	99 (96.1)	/		73 (70.9)
Carmel-Neiderman et al.	2020	Israel	RCS	1998–2015	124	LND + PCND: 60	48	37/23	/	34 (56.7)	/	59 (98.3)
						LND: 51	53	30/21	/	22 (46.8)		51 (100)

RCS, retrospective cohort study; LND, lateral neck dissection; PCND, prophylactic central neck dissection; LMN, lymph node metastasis.

gender ratio, age, tumor size, multifocality, extrathyroidal extension, metastatic lateral cervical lymph nodes, maximum size of metastatic lateral cervical lymph nodes, and RAI treatment between the two groups. Three studies showed a high incidence of central LNM ranging from 70.6 to 87.0%. The follow-up period ranged from 44 to 124 months. Recurrence of disease was determined by cervical imaging evaluation or serum thyroglobulin level and pathologically confirmed (if possible). Quality assessment is shown in **Table 2**. The exposed (patients underwent PCND) and nonexposed cohorts in all included studies were considered good representatives. The main outcomes of interest were LRR and complications. The distribution of preoperative clinical and demographic characteristics was comparable between these two groups, but the status of lateral cervical lymph nodes in each cohort was not compared in the Carmel-Neiderman et al. study. The assessment of outcome was obtained from laboratory and imaging data. All studies provided the complete follow-up of all patients, but the mean follow-up period was less than 10 years in three studies, which was considered insufficient.

Recurrence

All studies reported data for central neck recurrence (CNR), 20 patients in the LND + PCND group and 11 patients in the LND group. There was no statistically significant difference between the two groups in the CNR (10.2% vs. 3.8%, RR = 1.82; 95%CI 0.90–3.67; P = 0.09; I^2 = 0%). Three studies described lateral neck recurrence (LNR) (10–12), 7 patients in the LND + PCND group and 18 patients in the LND group. The rate of LRR in the lateral neck region was also similar between the two groups (5.1% vs. 7.7%, RR = 0.47; 95%CI 0.13–1.74; P = 0.26; I2 = 52%) (10–12). Moreover, we evaluated the overall recurrence (OR) in three studies involving 331 patients (148 received LND + PCND and 183 received LND). A total of 28 patients in total relapsed in the LND + PCND group and 31 patients in the LND group. There was no statistically significant difference between the two groups in OR (18.9% vs. 16.9%, RR = 0.77; 95%CI 0.34–1.76; P = 0.54; I^2 = 59%) (10, 11, 13). Therefore, the outcomes of this meta-analysis suggested no statistically significant difference between the two groups in LRR and OR (**Table 3** and **Figure 2**).

Surgical Complications

Data regarding to permanent laryngeal nerve palsy was reported in three studies, 8 patients in the LND + PCND group and 2 patients in the LND group. Prevalence of laryngeal nerve injury in the LND + PCND group and LND group was 5.4% (8/148) and 1.1% (2/183), respectively. Although the incidence of permanent laryngeal nerve palsy in the LND + PCND group was higher than that of the LND group, the outcome of this meta-analysis suggested no statistically significant difference (5.4% vs. 1.1%, RR = 3.40; 95%CI 0.83–13.94; P = 0.09; I2 = 0%). Data of permanent hypoparathyroidism and overall complications was reported in two studies (10, 11). A total of 10 patients presented permanent hypoparathyroidism in the LND + PCND group while 6 patients in the LND group, indicating a higher rate of permanent hypoparathyroidism in the LND + PCND group (11.4% vs. 4.5%, RR = 2.70, 95%CI 1.05–6.94; P = 0.04; I^2 = 0%). A similar result was obtained for overall complications (17.0% vs. 5.3%, RR = 3.28; 95%CI 1.37–7.86; P = 0.008; I2 = 0%) (**Table 4** and **Figure 3**).

DISCUSSION

Nowadays, the management of cervical lymph node dissection in the treatment of PTC is still one of most controversial issues. As everyone knows that therapeutic lymph node dissection for PTC patients will remove all metastatic lymphoid tissue and reduce the LRR rate. However, there is still a lack of sufficient evidence regarding the confirmation of the efficacy and benefit of PCND for PTC patients. Nowadays, the role of PCND in PTC patients with cN0 has been elaborately investigated. Some studies suggested that PCND in cN0 cases would make improvements to locoregional control and disease-specific survival (14–18). Conversely, other studies suggested that PCND did not improve the long-term prognosis, but increased the risk of complications (19–24). The difference between the same approach and the results of these studies, may be potentially settled in a prospective randomized controlled trial. However, the ATA investigation revealed that it was not feasible to conduct such a large prospective randomized controlled trial of PCND in

TABLE 2 | Quality assessment of cohort studies.

Study	Representativeness of the exposed cohort	Selection of control	Ascertainment of exposure	Outcome of interest not present at the start of the study	Comparability of controls	Outcome assessment	Sufficient follow-up duration	Adequacy of follow-up	Overall bias
Trivizki et al.	★	★	★	★	★★	★	–	★	8/9
Napoli et al.	★	★	★	★	★★	★	–	★	8/9
Harries et al.	★	★	★	★	★★	★	–	★	8/9
Carmel-Neiderman et al.	★	★	★	★	★	★	★	★	8/9

The ★ means one point and the ★★ means two points.

TABLE 3 | Details for recurrence of included studies.

Study	Group	CNR, n (%)	LNR, n (%)	OR, n (%)
Trivizki et al.	LND + PCND	3 (8.8)	2 (5.9)	6 (17.6)
	LND	2 (11.8)	6 (35.3)	6 (35.3)
Napoli et al.	LND + PCND	1 (1.9)	1 (1.9)	3 (5.6)
	LND	2 (1.7)	5 (4.3)	14 (12.2)
Harries et al.	LND + PCND	3 (6.1)	4 (8.2)	/
	LND	2 (1.9)	7 (6.8)	/
Carmel-Neiderman et al.	LND + PCND	13 (21.7)	/	19 (31.7)
	LND	5 (9.8)	/	11 (21.6)

LND, lateral neck dissection; PCND, prophylactic central neck dissection; CNR, central neck recurrence; LNR, lateral neck recurrence; OR, overall recurrence.

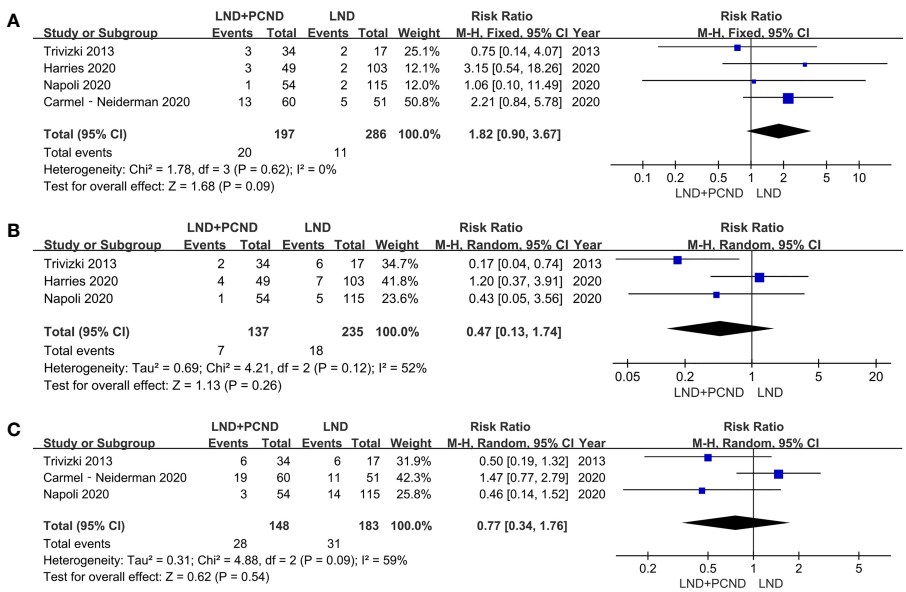

FIGURE 2 | Forest plot showing a meta-analysis of locoregional recurrence (LRR) for included studies. **(A)** Central neck recurrence; **(B)** Lateral neck recurrence; **(C)** overall recurrence.

TABLE 4 | Details for surgical complications of included studies.

Study	Group	Permanent laryngeal nerve palsy, n (%)	Permanent hypoparathyroidism, n (%)	Overall complications, n (%)
Trivizki et al.	LND + PCND	2 (5.9)	2 (5.9)	5 (14.7)
	LND	0 (0.0)	1 (5.9)	1 (5.9)
Napoli et al.	LND + PCND	2 (3.7)	8 (14.8)	10 (18.5)
	LND	1 (0.9)	5 (4.3)	6 (5.2)
Harries et al.	LND + PCND	/	/	/
	LND	/	/	/
Carmel-Neiderman et al.	LND + PCND	4 (6.7)	/	/
	LND	1 (2.0)	/	/

LND, lateral neck dissection; PCND, prophylactic central neck dissection.

PTC patients with cN0 (25). At present, the ATA and NCCN guidelines recommend that PCND should be considered in PTC patients with cN0 with advanced tumor or PTC patients with cN1b (5, 6). However, this recommendation is weak and the evidence is of low quality. The present study showed that a very select group of PTC patients with cN1b but no clinically evident central compartment lymph nodes involvement, might not require routine PCND. The additional procedure does not decrease the rate of LRR and OR, but it is accompanied by complications.

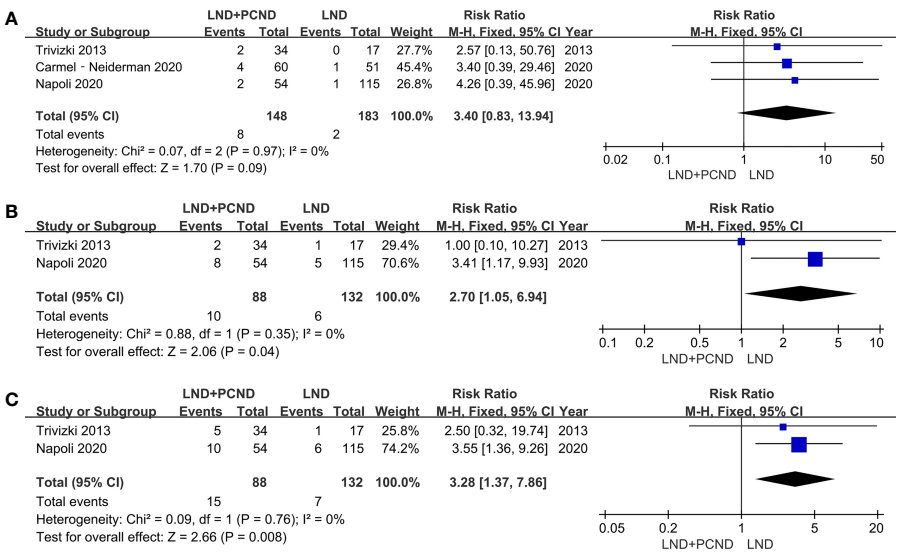

FIGURE 3 | Forest plot showing a meta-analysis of postoperative complications for included studies. **(A)** Permanent laryngeal nerve palsy; **(B)** permanent hypoparathyroidism; **(C)** overall complications.

As we all know, regional LNM are very common in PTC patients. Studies have suggested that occult metastases can be found in the central compartment in 40–70% of cases (4, 11, 26). Due to the high rate of occult metastases, PCND may convert many patients from cN0 to pathologic N1a. However, occult metastases do not carry the similar recurrence risk compared with that of clinically detectable macro-metastases (2). The accurate staging information of lymph nodes may be helpful in the selection of adjuvant therapy in PTC patients with cN0, but it is almost useless for these PTC patients with cN1b. These patients will undergo adjuvant RAI treatment and suppression treatment followed surgery in accordance with the ATA guidelines (6). Adjuvant RAI treatment can improve the lymph node failure-free survival in all lymph node categories, and the greatest therapeutic benefits have been observed in patients with cN1b disease (27, 28). Clinically occult lymph node metastasis can also be successfully treated with adjuvant RAI treatment, with an improvement of 10-year lymph node failure-free survival rate from 82.3 to 95% and overall survival rate more than 90% in PTC patients with cN0 (27, 29). Therefore, adjuvant RAI treatment can contain the LRR and might be used as an alternative to PCND.

Additionally, the potential complications of PCND should not be overlooked. In this study, there was a significantly higher rate of permanent hypoparathyroidism in these patients treated with PCND. In fact, it is a quite common phenomenon that PCND leads to a high proportion of both transient and permanent hypoparathyroidism. The reason may be that the inferior parathyroid glands are removed or devascularized unintentionally during the procedure of PCND. Previous literatures also suggest that PTC patients who underwent PCND had a significantly higher incidence rate of permanent hypoparathyroidism compared with those patients managed without PCND (4.11–19.4% VS. 1.95–8%) (24, 30, 31). Although, there was no statistically significant difference in permanent laryngeal nerve palsy by the meta-analysis, the rate of permanent laryngeal nerve palsy following PCND is 3.7–6.7% compared with 0–2.0% in patients managed without PCND. Nowadays, intraoperative laryngeal nerve monitoring has been widely used for reducing the incidence of recurrent laryngeal nerve injury, and some intraoperative parathyroid identification techniques will be helpful to protect the parathyroid in surgery (32, 33). However, the extent of initial surgery should ultimately be determined by oncological benefit.

We acknowledge that there are several limitations in this meta-analysis. Firstly, only 4 articles were included in this meta-analysis and all studies were of retrospective design with small simple size, which limited our ability to draw firm conclusions from the data. Secondly, since PTC may relapse 10 to 20 years after initial treatment, long-term follow-up is necessary to compare the recurrence rate instead of only about 5 years follow-up. Thirdly, the quality of the included studies was not high. Selection bias or other confounding factors might be included and affect the reliability of the final results. Fourthly, because only articles in English were reviewed and included, some non-English articles may have been excluded from the present study.

CONCLUSIONS

In conclusion, this meta-analysis did not demonstrate any advantage in performing PCND in cN1b PTC patients without clinical evidence of central neck involvement for preventing LRR, even in the central region. Furthermore, PCND may result in the increased rate of surgical complications, including a higher rate

of permanent hypoparathyroidism and overall complications. We recommend that PCND should not be routinely performed in PTC patients with cN1b, especially for these patients without any clinically evident central neck involvement. However, the current evidence is limited and we need more evidence from multicenter, prospective, randomized, controlled clinical trials to further clarify the true role of PCND in PTC patients with cN1b.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

Study conception and design: B-jX and X-qY. Acquisition of data: X-qY, Z-zZ, and W-jY. Analysis and interpretation of data: Z-sM, M-lC and X-qY. Drafting of manuscript: X-qY, Z-zZ. Critical revision of manuscript: B-jX. All authors contributed to the article and approved the submitted version.

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Predictive Factors for Recurrence of Papillary Thyroid Carcinoma in Children and Adolescents

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Background: The incidence of papillary thyroid carcinoma (PTC) in children and adolescents has increased, but the data on long-term outcomes are limited. There are few literatures on the clinicopathological characteristics and prognosis of PTC in children and adolescents in China. Therefore, it is necessary to identify clinicopathological features to precisely predict clinical prognosis and to help choose the optimal method and perform the best therapeutic regimen.

Methods: This study was a retrospective analysis of patients undergoing thyroidectomy at Tianjin Medical University Cancer Institute and Hospital. We analyzed the factors related to the clinicopathological features and prognosis of PTC in children and adolescents.

Results: A total of 95 juvenile PTC patients who underwent thyroidectomy were enrolled. Our research found that patients with younger age (<14 years) were predominantly multifocal and have positive preoperative thyroglobulin (Tg) and higher recurrence rate, and their number of lymph node metastases (LNMs) was more than that of the older group (14–18 years). Maximal tumor size >2 cm, T stage, and multifocality were the risk factors for LNM and the number of LNM ($p < 0.05$). Multivariate analysis displayed the number of central LNM as the independent risk factor for lateral LNM, and multifocality was the independent risk factor for the number of central and lateral LNM. Younger age at diagnosis, positive preoperative thyroid-stimulating hormone (TSH), maximal tumor size >2 cm, lateral LNM, number of LNM, N staging, and American Thyroid Association (ATA) pediatric risk were related to poor prognosis in PTC patients ($p < 0.05$). Cox regression analysis found that younger age at diagnosis and positive preoperative TSH were independent risk factors for recurrence of PTC in children and adolescents.

Conclusions: Our study showed that the clinicopathological characteristics of younger age compared with older age were as follows: highly aggressive, prone to metastases, and higher recurrence rate. In our opinion, patients with characteristics such as younger age at diagnosis, positive preoperative TSH, maximal tumor size >2 cm, lateral LNM, and number of LNM >5 may be considered for prophylactic or therapeutic dissection of

additional metastatic LNs by high-volume surgeons to prevent and reduce the recurrence rate of patients during long-term follow-up.

Keywords: papillary thyroid carcinoma, children and adolescents, lymph node metastases, recurrence, prognosis

INTRODUCTION

Thyroid carcinoma is rare in children and adolescents, but the occurrence has been steadily rising worldwide in the past decades (1, 2). Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer in children and adolescents, which accounts for 90% (3, 4). Although the prognosis of pediatric patients with PTC is excellent and the mortality rate is low, they have higher rates of cervical lymph node metastases (LNMs), extrathyroidal extension (ETE), distant metastasis, and recurrence than the adults (5–8). Furthermore, a second operation for relapsed patients has a great impact on the quality of life of children and adolescents with PTC. In this setting, optimal treatment strategies for children and adolescents with PTC remain controversial. Therefore, recognizing the risk of recurrence of each patient may avoid an ineffective cure. PTC in children and adolescents has an increasing incidence, but long-term prognosis data are limited. Thence, recording the prognosis and identifying the predictors of PTC recurrence are of great clinical value in this age group.

There are few literatures on the clinicopathological characteristics and prognosis in children and adolescents with PTC in China. Therefore, identifying clinicopathological features to predict clinical prognosis and to help choose the optimal method and perform the best therapeutic regimen is crucial. For this reason, we carried out this study to find out the clinicopathological features and clinical outcomes of PTC in children and adolescents in China. According to the recent American Thyroid Association (ATA) guidelines (3), patients below 18 years with PTC were included in our study.

METHODS

Study Population

This retrospective study was conducted at a single center institution; 95 patients who underwent initial thyroidectomy at Tianjin Medical University Cancer Hospital were recruited from January 2000 to August 2018. All patients met the following criteria: 1) they have confirmed PTC after thyroidectomy; 2) their age at diagnosis ≤18 years; 3) their tumors did not merge with other tumors; 4) they did not have a history of thyroidectomy or radiotherapy of the head and neck region; and 5) their medical records were complete. This study was approved by the Ethical Committee of the Tianjin Medical University Cancer Institute and Hospital.

Clinicopathological Variables

Patient characteristics such as age at diagnosis, gender, serological test [e.g., thyroid peroxidase antibody (TPOAb), thyroglobulin antibody (TgAb), thyroid-stimulating hormone (TSH), and thyroglobulin (Tg)], surgery approach, lymph node dissection, pathological characteristics of maximal tumor size, bilaterality, ETE, multifocality, LNM and the number of LNM, and postoperative histological type were recorded completely. The normal ranges of TPOAb, TgAb, TSH, and Tg were 0–9 IU/ml, 0–4.1 IU/ml, 0.27–4.20 mlU/L, and 1.4–78 μg/L, respectively. The histological diagnoses were confirmed by 2 independent pathologists at our institution. TPOAb, TgAb, TSH, and Tg were considered positive when its result was over the upper range. Multifocality was considered if there are two or more tumor foci within the thyroid. Bilaterality was defined if tumors were located in both lobes. The ATA initial risk stratification (3) was performed considering the characteristics of recurrent tumors. Low risk was defined as disease grossly confined to the thyroid with N0/Nx disease or patients with incidental N1a disease (microscopic metastasis to a small number of central neck lymph nodes). Intermediate risk was defined as extensive N1a or minimal N1b disease, and high risk was defined as a regionally extensive disease (extensive N1b) or locally invasive disease (T4 tumors), with or without distant metastasis.

Postoperative Follow-Up

The primary outcome was recurrence of disease in our study, which was assessed from records of basal or stimulated Tg, postoperative neck ultrasonography, ^{131}I whole-body scans, and LN biopsies and pathologically diagnosed after the second operation. Disease-free survival (DFS) is defined as the time interval from thyroidectomy to detection of recurrent PTC. The follow-up period of each patient was defined as the length of time from the initial therapy to the last known contact, which was recorded by viewing the medical history or calling the patient.

Statistical Analysis

Statistical analysis was performed by using the SPSS v26.0 (Chicago, IL, USA). Results of continuous variables were reported as mean ± SD or median values and ranges, and categorical variables were reported as absolute numbers and percentages. Intergroup differences were assessed with the independent-samples t-test or the Mann–Whitney U test (continuous variables) and the χ^2-test with Yates's correction or Fisher's exact test (categorical variables), as appropriate. Recurrence-free survival plots were constructed by using the

Abbreviations: PTC, papillary thyroid carcinoma; ETE, extrathyroidal extension; ATA, American Thyroid Association; DFS, disease-free survival; TSH, thyroid-stimulating hormone; Tg, thyroglobulin; TPOAb, thyroid peroxidase antibody; TgAb, thyroglobulin antibody; LNM, lymph node metastases; LN, lymph node; LND, lymph node dissection; CLND, central lymph node dissection; MRND, modified radical neck dissection; HR, hazard ratio; OR, odds ratio; CND, central neck dissection; CAEK, guidelines from the German Association of Endocrine Surgeons; TT, total thyroidectomy; NTT, non-total thyroidectomy.

Kaplan–Meier method, and groups were compared by using log-rank tests. The Cox hazards regression model was used in multivariate analysis; the hazard ratio (HR) with the 95% CI was presented. A value of $p < 0.05$ was considered statistically significant. All data were analyzed anonymously.

RESULTS

Study Populations

A total of 95 PTC patients, children and adolescents, who underwent thyroidectomy were recruited. The features of patients are given in **Table 1**. The study patients consisted of 64 girls (67.4%) and 31 boys (32.6%) with a median age of 14 years (range: 5–18 years). Thyroid involvement was multifocal in 57 patients (60.0%) and bilateral in 33 patients (34.7%). ETE was documented in the tumors of 67 patients (70.5%). A total of 18 patients underwent unilateral central lymph node dissection (CLND), 28 patients underwent unilateral modified radical neck dissection (MRND), 12 patients underwent unilateral MRND plus contralateral CLND, 6 patients underwent bilateral CLND, and 31 patients underwent bilateral MRND. A total of 84 had central LNM (88.4%), and 66 had lateral LNM (69.5%). The median (range) number of total LN dissected was 39 (0–136), and total LNM was 11 (0–44). During a mean follow-up of 63 months (2–193 months), 26.3% of patients were classified into low-risk groups, 24.2% into intermediate-risk groups, and 49.5% into high-risk groups according to the ATA pediatric risk stratification. A total of 29 patients (30.5%) had a recurrence.

Comparison Between Clinicopathological Features With Different Age Groups in Children and Adolescents With Papillary Thyroid Carcinoma

We compared the clinicopathological features between different age groups (<14 and 14–18 years). We observed that there were statistically significant differences between multifocality, preoperative TSH level, surgical approach, LN dissection, the number of LND and LNM, and recurrence (**Table 2**). Our research showed that patients in the younger group (<14 years) were predominantly multifocal ($p = 0.020$), their preoperative Tg was often abnormal ($p = 0.032$), and they had more LND and LNM and higher recurrence rate than the older group (14–18 years) ($p < 0.05$). Moreover, the DFS rate was significantly different between different age groups ($p < 0.001$, **Figure 1A**).

TABLE 1 | Characteristics of the study patients.

Characteristics	Value	Characteristics	Value
Age at diagnosis		Bilaterality	
<14 years	36 (37.9)	Yes	33 (34.7)
14–18 years	59 (62.1)	No	62 (65.3)
Gender		Central LNM	
Female	64 (67.4)	Yes	84 (88.4)
Male	31 (32.6)	No	11 (11.6)
Preoperative TPOAb level		Lateral LNM	
Positive	29 (30.5)	Yes	66 (69.5)
Negative	66 (69.5)	No	29 (30.5)
Preoperative TgAb level		N stage	
Positive	25 (26.3)	N0	6 (6.3)
Negative	70 (73.7)	N1a	23 (24.2)
Preoperative TSH level		N1b	66 (69.5)
Positive	19 (20.0)	Surgical approach	
Negative	76 (80.0)	Total bilateral thyroidectomy	41 (43.2)
Preoperative Tg level		Ipsilateral glandular lobe plus isthmus resection	42 (44.2)
Positive	34 (35.8)	Subtotal thyroidectomy	12 (12.6)
Negative	61 (64.2)	Lymph node dissection	
Maximal tumor size		Unilateral CLND	18 (18.9)
≤2 cm	40 (42.1)	Unilateral MRND	28 (29.5)
>2 cm	55 (57.9)	Unilateral MRND, plus contralateral CLND	12 (12.6)
T stage		Bilateral CLND	6 (6.3)
T1a	5 (5.3)	Bilateral MRND	31 (32.6)
T1b	35 (36.8)	No. of total LND	39 (0-136)
T2	49 (51.6)	No. of total LNM	11 (0-44)
T3	6 (6.3)	ATA pediatric risk	
Multifocality		Low	25 (26.3)
Yes	57 (60.0)	Intermediate	23 (24.2)
No	38 (40.0)	High	47 (49.5)
Extrathyroidal extension		Recurrence	
Yes	67 (70.5)	Yes	29 (30.5)
No	28 (29.5)	No	66 (69.5)

TPOAb, thyroid peroxidase antibody; TgAb, thyroglobulin antibody; TSH, thyroid-stimulating hormone; Tg, thyroglobulin; LNM, lymph node metastases; CLND, central lymph node dissection; MRND, modified radical neck dissection; LND, lymph node dissection; ATA, American Thyroid Association.

TABLE 2 | Comparison of clinicopathological features of PTC in children and adolescents with different age groups.

Variables	<14 years (n = 36)	14–18 years (n = 59)	p-Value
Gender			
Male	12 (33.3)	19 (32.2)	0.909
Female	24 (66.7)	40 (67.8)	
Maximal tumor size			
≤2 cm	11 (30.6)	29 (49.2)	0.075
>2 cm	25 (69.4)	30 (50.8)	
T stage			
T1a	0 (0.0)	5 (8.5)	0.167
T1b	11 (30.6)	24 (40.7)	
T2	22 (61.1)	27 (45.8)	
T3	3 (8.3)	3 (5.1)	
Central LNM			
Yes	35 (97.2)	49 (83.1)	0.078
No	1 (2.8)	10 (16.9)	
Lateral LNM			
Yes	29 (80.6)	37 (62.7)	0.067
No	7 (19.4)	22 (37.2)	
N stage			
N0	1 (2.8)	5 (8.5)	0.209
N1a	6 (16.7)	17 (28.8)	
N1b	29 (80.6)	37 (62.7)	
Multifocality			
Yes	27 (75.0)	30 (50.8)	0.020
No	9 (25.0)	29 (49.2)	
Extrathyroidal extension			
Yes	25 (69.4)	42 (71.2)	0.857
No	11 (30.6)	17 (28.8)	
Bilaterality			
Yes	16 (44.4)	42 (71.2)	0.121
No	20 (55.6)	17 (28.8)	
Preoperative TSH level	6.6 ± 16.5	2.9 ± 2.1	0.032
Preoperative Tg level	125.3 ± 203.5	129.3 ± 166.9	0.419
Surgical approach			
Total bilateral thyroidectomy	23 (63.9)	18 (30.5)	<0.001
Ipsilateral glandular lobe plus isthmus resection	7 (19.4)	35 (59.3)	
Subtotal thyroidectomy	6 (16.7)	6 (10.2)	
Lymph node dissection			
Unilateral CLND	4 (11.1)	14 (23.7)	0.003
Unilateral MRND	7 (19.4)	21 (35.6)	
Unilateral MRND, plus contralateral CLND	2 (5.6)	10 (16.9)	
Bilateral CLND	3 (8.3)	3 (5.1)	
Bilateral MRND	20 (55.6)	11 (18.6)	
Number of central LND	12.6 ± 6.8	7.9 ± 5.2	<0.001
Number of lateral LND	45.9 ± 33.8	26.2 ± 25.3	0.002
Number of LND	58.5 ± 37.0	34.1 ± 27.3	0.001
Number of central LN metastases	7.1 ± 4.3	4.6 ± 3.8	0.005
Number of lateral LN metastases	10.7 ± 8.6	5.3 ± 6.7	0.002
Number of LN metastases	17.7 ± 11.8	10.0 ± 8.6	0.001
ATA pediatric risk			0.089
Low	7 (19.4)	18 (30.5)	
Intermediate	6 (16.7)	17 (28.8)	
High	23 (63.9)	24 (40.7)	
Recurrence			
Yes	19 (52.8)	10 (16.9)	<0.001
No	17 (47.2)	49 (83.1)	

LNM, lymph node metastases; TSH, thyroid-stimulating hormone; Tg, thyroglobulin; CLND, central lymph node dissection; MRND, modified radical neck dissection; LND, lymph node dissection; ATA, American Thyroid Association.

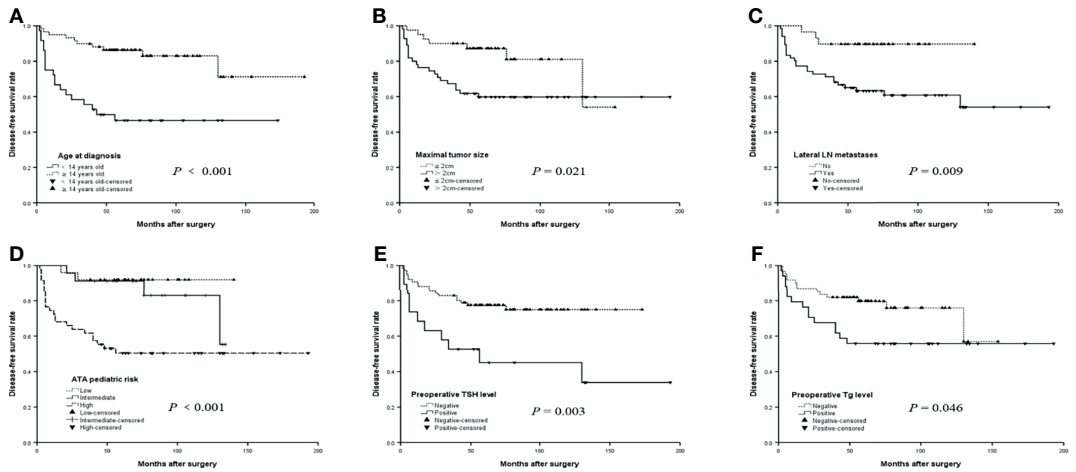

FIGURE 1 | The disease-free survival (DFS) curves of risk factors for recurrence in children and adolescents with papillary thyroid carcinoma (PTC). **(A)** The DFS curves of age at diagnosis in children and adolescents with PTC. **(B)** The DFS curves of maximal tumor size in children and adolescents with PTC. **(C)** The DFS curves of lateral LN metastases in children and adolescents with PTC. **(D)** The DFS curves of ATA pediatric in children and adolescents with PTC. **(E)** The DFS curves of Preoperative TSH level in children and adolescents with PTC. **(F)** The DFS curves of Preoperative Tg level in children and adolescents with PTC.

TABLE 3 | Univariate and multivariate analyses of risk factors of cervical lymph node metastases.

Variables	Univariate		Multivariate		
	OR (95%)	p-Value	OR	95% CI	p-Value
Central LNM					
Maximal tumor size >2 cm	4.333 (1.071–17.539)	0.040			
T stage	2.647 (1.031–6.800)	0.043			
Multifocality	1.950 (0.550–6.915)	0.301			
Extrathyroidal extension	0.885 (0.217–3.614)	0.865			
Bilaterality	0.600 (0.168–2.138)	0.431			
Lateral LNM					
Maximal tumor size >2 cm	4.071 (1.615–10.262)	0.003			
T stage	2.763 (1.361–5.607)	0.005			
Central LNM	3.183 (0.885–11.447)	0.076			
Number of central LNM	8.482 (2.651–27.136)	<0.001			
Multifocality	2.462 (1.008–6.012)	0.048	6.237	1.747–22.266	0.005
Extrathyroidal extension	1.113 (0.430–2.879)	0.825			
Bilaterality	1.270 (0.500–3.228)	0.616			

OR, odds ratio; LNM, lymph node metastases.

Analysis of the Risk Factors of Cervical Lymph Node Metastases in Children and Adolescents With Papillary Thyroid Carcinoma

As shown in **Table 3**, we analyzed the risk factors of LNM in children and adolescents with PTC and found that maximal tumor size >2 cm (p = 0.040) and T stage (p = 0.043) were the risk factors for central LNM. At the same time, our study showed that maximal tumor size >2 cm (p = 0.003), T stage (p = 0.005), number of central LNM (p < 0.001), and multifocality (p = 0.048) were the risk factors for lateral LNM. Multivariate analysis displayed that only the number of central LNM (OR 6.237, p = 0.005) was the independent risk factor for lateral LNM.

We further analyzed the relationship between clinicopathological features and the number of LNM. There was a significant difference in age at diagnosis, maximal tumor size >2 cm, T stage, and multifocality in the number of central LNM (p < 0.05). Our study also revealed that age at diagnosis, maximal tumor size >2 cm, T stage, the number of central LNM, and multifocality were the risk factors for the number of lateral LNM that approached statistical significance (p < 0.05). Moreover, multivariate analysis showed that multifocality (OR 3.575, p = 0.011; OR 3.175, p = 0.023) was the independent risk factor for the number of central and lateral LNM, respectively (**Table 4**).

TABLE 4 | Factors related to the number of positive cervical lymph node metastasis (≤5 vs. >5).

Variables	Univariate			Multivariate		
	OR	95% CI	p-Value	OR	95% CI	p-Value
Number of central LNM						
Gender	0.433	0.181–1.039	0.061			
Age at diagnosis	0.326	0.138–0.771	0.011			
Maximal tumor size >2 cm	3.405	1.420–8.169	0.006			
T stage	3.193	1.563–6.524	0.001			
Multifocality	4.431	1.776–11.053	0.001	3.575	1.331–9.601	0.011
Extrathyroidal extension	1.331	0.542–3.266	0.533			
Bilaterality	1.572	0.672–3.681	0.297			
Preoperative TPOAb level	0.690	0.283–1.684	0.415			
Preoperative TgAb level	0.498	0.190–1.304	0.156			
Preoperative TSH level	1.528	0.557–4.191	0.410			
Preoperative Tg level	1.08	0.462–2.526	0.859			
Number of lateral LNM						
Gender	0.727	0.307–1.719	0.467			
Age at diagnosis	0.388	0.165–0.912	0.030			
Maximal tumor size >2 cm	6.167	2.480–15.331	<0.001			
T stage	3.558	1.724–7.340	0.001			
Central LNM	2.933	0.728–11.827	0.130			
Number of central LNM	6.517	2.639–16.092	<0.001			
Multifocality	4.208	1.739–10.183	0.001	3.175	1.171–8.608	0.023
Extrathyroidal extension	0.971	0.402–2.345	0.947			
Bilaterality	1.366	0.585–3.187	0.471			
Preoperative TPOAb level	0.933	0.390–2.236	0.877			
Preoperative TgAb level	0.742	0.296–1.859	0.524			
Preoperative TSH level	2.676	0.920–7.786	0.071			
Preoperative Tg level	1.994	0.844–4.713	0.116			

OR, odds ratio; LNM, lymph node metastases; TPOAb, thyroid peroxidase antibody; TgAb, thyroglobulin antibody; TSH, thyroid-stimulating hormone; Tg, thyroglobulin.

Multivariate Analysis for Variables Associated With Papillary Thyroid Carcinoma Recurrence of Children and Adolescents

During a mean follow-up of 63 (2–193) months, 29 patients (30.5%) had a recurrence. The results of multivariate analysis for recurrence were summarized after adjusting for other clinicopathological factors, including age at diagnosis, gender, preoperative TPOAb, TgAb, TSH and Tg levels, multifocality, maximal tumor size, T stage, cervical LNM, N stage, and number of LNM. The results showed that age at diagnosis, positive preoperative TSH, maximal tumor size >2 cm, lateral LNM, number of LNM >5, N stage, and ATA pediatric risk were associated with poor prognosis in PTC patients with statistical significance ($p < 0.05$). Cox regression analysis found that

TABLE 5 | Cox proportional hazards regression analysis for variables associated with PTC recurrence.

Variables	Univariate			Multivariate		
	HR	95% CI	p-Value	HR	95% CI	p-Value
<14 years old	4.150	1.924–8.953	<0.001	4.859	1.912–12.350	0.001
Positive preoperative TPOAb level	0.419	0.160–1.100	0.077			
Positive preoperative TgAb level	0.538	0.205–1.411	0.208			
Positive preoperative TSH level	2.961	1.389–6.314	0.005	2.416	1.077–5.420	0.032
Positive preoperative Tg level	2.068	0.994–4.301	0.052			
Maximal tumor size >2 cm	2.61	1.113–6.119	0.027			
T stage	1.691	0.985–2.905	0.057			
Number of central LNM>5	2.719	1.262–5.855	0.011			
Number of lateral LNM>5	5.031	2.044–12.388	<0.001			
Lateral LNM	4.322	1.306–14.309	0.017			
N stage	3.911	1.270–12.044	0.017			
Multifocality	1.982	0.878–4.477	0.100			
Extrathyroidal extension	0.950	0.418–2.158	0.903			
Bilaterality	0.556	0.237–1.302	0.176			
ATA pediatric risk	3.056	1.591–5.871	0.001			

HR, hazard ratio; TPOAb, thyroid peroxidase antibody; TgAb, thyroglobulin antibody; TSH, thyroid-stimulating hormone; Tg, thyroglobulin; LNM, lymph node metastases; ATA, American Thyroid Association.

younger age (<14 years) at diagnosis (HR 4.859, p = 0.001) and positive preoperative TSH (HR 2.416, p = 0.032) were independent risk factors for recurrence in children and adolescents with PTC (**Table 5**).

The survival curves of DFS stratified by the presence of age at diagnosis, maximal tumor size, lateral LNM, the ATA pediatric risk stratification, preoperative TSH, and Tg are shown in **Figure 1**. The differences were significant in the age at diagnosis (p < 0.001, log-rank), maximal tumor size (p = 0.021, log-rank), lateral LNM (p = 0.009, log-rank), and ATA pediatric risk (p < 0.001, log-rank) in terms of the median DFS of patients with PTC (**Figures 1A–D**). The patients with positive preoperative TSH had a shorter median DFS (90.2 months) than the patients with negative preoperative TSH (136.0 months) (p = 0.003, log-rank) (**Figure 1E**). The median DFS was 116.4 months for patients with positive preoperative Tg and 119.1 months for patients with negative preoperative Tg (p = 0.046, log-rank) (**Figure 1F**).

DISCUSSION

Thyroid carcinoma is rare in children and adolescents, which accounts for 0.5%–3% (9), but the occurrence has been rising recently. Children and adolescents with PTC have unique biological characteristics; it has been proposed in the literature that they are more likely to have stronger invasiveness, higher LNM, and recurrence rate (10, 11). Therefore, it is necessary to do further research on the clinicopathological characteristics and prognosis of this age group to provide evidence for the clinical development of diagnosis and treatment plans. Thence, a central purpose of our study was to probe the relevant factors that influence the clinicopathological characteristics and prognosis significant in PTC of children and adolescents.

Previous studies have shown that PTC in children and adolescents has unique clinicopathological features. In order to explore the similarities and differences in clinicopathological features and prognosis of PTC between children and adolescents, we compared clinicopathological features between the younger group (<14 years) and the older group (14–18 years). Park et al. (12) showed that younger age was associated with more extensive forms of PTC, such as high ETE, multifocality, bilaterality, and maximal tumor size. Consistent with the results of Park, our study found that the cancer foci in the younger group were more aggressive and mainly multifocal, the preoperative TSH levels were often abnormal, the number of LN dissected and LN metastases were more than those of the older age groups, and the difference approached statistical significance (p < 0.05). Moreover, our study indicated that the recurrence rate of 52.8% in the younger age group was much higher than 16.9% in the older age group, similar to other research findings that children (<10 or <15 years) had a higher recurrence rate (13, 14). But others did not confirm this relationship (15). Therefore, further research is needed to confirm this conclusion.

The prevalence was reported in about 95% of neck LNM of PTC in children and adolescents (7, 8), and the presence of LNM has a significant impact on the recurrence rate (16, 17). However, due to the low incidence of PTC in children and adolescents and limited literature on the risk factors for LNM in this age group, it is necessary to do further study of the risk factors of LNM of PTC in children and adolescents. Our study found that maximal tumor size >2 cm and T stage were associated with central LNM (p < 0.05) and that maximal tumor size >2 cm, T stage, number of central LNM, and multifocality were the risk factors related to lateral LNM (p < 0.05), consistent with the report of the present study (18, 19). Moreover, multivariate analysis results showed that the number of central LNM (OR 6.237 p = 0.005) was an independent risk factor for lateral LNM, in line with other research findings (16). Our study displayed that ETE was not an independent risk factor for lateral LNM, which may be because the association between ETE and LNM was based on tumor size. Our research results demonstrated that the lateral LNM of PTC was also mainly related to factors delegating tumor aggressiveness and progression in children and adolescents.

The above results showed that the number of central LNM was an independent risk factor for lateral LNM. In order to explore the related factors that affect the number of LNM of PTC in children and adolescents, we divided the number of LNM into two groups (≤5 and>5). Univariate analysis results displayed that age at diagnosis, maximal tumor size >2 cm, T stage, and multifocality were the risk factors of the number of central and lateral LNM (p < 0.05). Moreover, central LNM and the number of central LNM were also the risk factors of the number of lateral LNM (p < 0.05). Multivariate analysis results showed that only multifocality (OR 3.175 p = 0.023) was an independent risk factor for the number of lateral LNM. Therefore, patients with the above characteristics may consider prophylactic LN dissection.

The recurrence rate of PTC in children and adolescents is high, and the second operation for recurrence has a greater impact on this age group. Because of an increasing incidence of PTC in this age group, documentation of the prognosis and identification of predictors of DFS are of great clinical value. Our results showed that age at diagnosis, positive preoperative TSH level, maximal tumor size >2 cm, number of central and lateral LNM, lateral LNM, and N staging were risk factors for recurrence, similar to other research findings (20–22). In addition, we also found that the ATA pediatric risk stratification had predictive value for recurrent PTC patients in children and adolescents, the same results as other scholars' research (22, 23). Multivariate analysis demonstrated that younger age (<14 years) at diagnosis and positive preoperative TSH were independent risk factors for recurrence, which were consistent with the results of other studies (20–25). The prognosis of pediatric PTC is generally excellent. However, factors such as younger age, positive preoperative TSH levels, maximal tumor size >2 cm, lateral LNM, and number of central and lateral LNM are more prone for disease recurrence and should always be considered in the management of these patients.

The related research suggested that, in children, prophylactic central neck dissection (CND) was associated with increased DFS,

as high as 95% at 5 and 10 years (26). Another study showed that prophylactic CND may reduce the risk for reoperation that was as high as 77% in those without CND (27). Some researchers advised that high-volume surgeons can carry out a safe total thyroidectomy (TT) or non-total thyroidectomy (NTT) and routine central CND (28). Both the CAEK and ATA recommended that on pediatric thyroid cancer for patients with PTC and no clinical evidence of gross extrathyroidal invasion and/or locoregional metastasis, prophylactic CND may be selectively considered based upon tumor focality, size, and the experience of the surgeon (29, 30). Our study suggested that patients with features of risk factors for recurrence such as younger age, positive preoperative TSH, maximal tumor size >2 cm, lateral LNM, and number of LNM >5 may be considered prophylactic or therapeutic dissection of additional metastatic LNs by high-volume surgeons to prevent and reduce the recurrence rate of patients during long-term follow-up.

There are some limitations in our study: 1) this is a single-center retrospective study; and 2) pathological subtypes and BRAF mutation status were not considered in this study. These limitations need to be improved in the future.

CONCLUSIONS

In our study cohort, the clinicopathological characteristics of younger age (<14 years) were highly aggressive and prone to metastases, the preoperative TSH were mostly abnormal, and the recurrence rate was much higher than that of older age (14–21 years). Tumor size and T stage were risk factors for neck LNM; central LNM, the number of central LNM, and multifocality were risk factors for lateral LNM. Moreover, multivariate analysis showed the number of central LNM was an independent risk factor for lateral LNM. Univariate analysis results showed that younger age (<14 years) at diagnosis, positive preoperative TSH, maximal tumor size >2 cm, lateral LNM, number of LNM, N staging, and ATA pediatric risk were associated with poor prognosis of PTC in children and adolescents. Cox regression analysis found that younger age (<14 years) at diagnosis and positive preoperative TSH were independent risk factors for recurrence of PTC in children and adolescents. Therefore, patients with characteristics such as younger age (<14 years) at diagnosis, positive preoperative TSH, maximal tumor size >2 cm, lateral LNM, and number of LNM >5 may be considered for prophylactic or therapeutic dissection of additional metastatic LNs by high-volume surgeons to prevent and reduce the recurrence rate of patients during long-term follow-up.

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 Ethical Committee of the Tianjin Medical University Cancer Institute and Hospital. The patients provided written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YG and DH: conceptualization, data collection and analysis, methodology, and drafting of the manuscript. YH: conceptualization, data collection and analysis, and methodology. XW and JZ: conceptualization and methodology. JW: conceptualization and manuscript review and editing. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Cause of Death Among Patients With Thyroid Cancer: A Population-Based Study

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Background: Over the last decades, the number of patients diagnosed with thyroid carcinoma has been increasing, highlighting the importance of comprehensively evaluating causes of death among these patients. This study aimed to comprehensively characterize the risk of death and causes of death in patients with thyroid carcinoma.

Methods: A total of 183,641 patients diagnosed with an index thyroid tumor were identified from the Surveillance, Epidemiology, and End Result database (1975–2016). Standardized mortality rates (SMRs) for non-cancer deaths were calculated to evaluate mortality risk and to compare mortality risks with the cancer-free US population. Cumulative mortality rates were calculated to explore the factors associated with higher risk of deaths.

Results: There were 22,386 deaths recorded during follow-up, of which only 31.0% were due to thyroid cancer and 46.4% due to non-cancer causes. Non-cancer mortality risk among patients with thyroid cancer was nearly 1.6-fold (SMR=1.59) that of the general population. Cardiovascular diseases were the leading cause of non-cancer deaths, accounting for 21.3% of all deaths in thyroid cancer patients. Non-cancer causes were the dominant cause of death in thyroid cancer survivors as of the third year post-diagnosis. We found that males with thyroid cancer had a higher risk of all-cause mortality compared with females. The risk of suicide was highest in the first post-diagnostic year (<1 year: SMR=1.51). The long-term risk of Alzheimer's disease was notably increased in thyroid cancer patients (>5 years: SMR=8.27).

Conclusion: Non-cancer comorbidities have become the major risks of death in patients with thyroid tumor in the US, as opposed to death from the tumor itself. Clinicians and researchers should be aware of these risk trends in order to conduct timely intervention strategies.

Keywords: thyroid cancer (TC), cause of death, epidemiology, population-based study, SEER (Surveillance Epidemiology and End Results) database

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INTRODUCTION

Global morbidity due to thyroid tumors has risen notably in the last three decades (1). There were approximately 586,202 incident thyroid cancer cases and 43,646 thyroid cancer deaths worldwide in 2020 (2). This increasing incidence has been referred to as an epidemic of increasing surveillance and overdiagnosis; however, research indicates that this might also reflect a real increase in new cases of thyroid tumor (3–5). Due to the tremendous progress in cancer screening techniques and the increasing popularization of routine physical examinations in recent decades, a larger number of subclinical lesions have been detected. This has contributed to the high prevalence of low-risk, non-lethal tumors.

Improvements in the detection of thyroid tumors and therapeutic strategies have likewise resulted in favorable prognoses and low mortality rates for this disease (5). Hence, disease morbidity is incomparably higher than mortality for thyroid cancer and the population of cancer survivors continues to grow. However, although this disease presents with a relatively low mortality rate, the social burden caused by thyroid cancer has increased sharply. In addition to the direct and indirect medical, financial, and social costs of thyroid cancer, the long-term impacts of tumors may be multifaceted and complex. Thus, medical and epidemiologic research is necessary to elucidate the comprehensive medical and social costs of this disease.

One important change brought about by the rising population of cancer survivors is the increasing prevalence of deaths from causes other than the index carcinoma, including subsequent second or multiple primary cancers (6) and non-cancer comorbidities (7, 8). Some non-cancer comorbidities, including cardiovascular diseases (9, 10), infectious diseases (11), accidents (12), peptic ulcers (13), as well as suicides (14), have been reported as major threats to cancer patients' health, survivorship, and quality of life. In addition, the risk of non-cancer comorbidities is increased as a consequence of the malignancy itself as well as the treatments administered. For example, an increased risk of non-cancer death immediately after cancer diagnosis has been reported (15). Although a few studies have evaluated the causes of death amongst patients with thyroid carcinoma (including Korea and Taiwan), the range of causes of death evaluated in these studies was much less comprehensive than in the current study and the sample sizes were small (16, 17). Moreover, the scope of these studies was limited (i.e., only a few common causes of death were evaluated). A comprehensive evaluation of the causes of death in patients with thyroid carcinoma is urgently needed. This will help researchers and clinicians identify patients at high risk of death and the particular causes of death for these patients.

The goal of this study was to comprehensively describe the distribution of cause of death in thyroid cancer patients with the purpose of providing constructive evidence for the health management of patients with thyroid tumors as well as optimization of their survival and quality of life.

MATERIALS AND METHODS

Study Population and Data Source

This retrospective cohort study was conducted using data from the Surveillance, Epidemiology, and End Results (SEER) program, covering approximately 48.0% of the US population. Spanning over four decades, the SEER program routinely collects individual data on demographics, tumor morphology, stage at diagnosis, anatomic site, therapeutic modalities, and follow-up data for a range of cancer patients (18). In addition, due to its population-based program design, data from the SEER program can be used for comparisons with the general population, and thus are viable for estimating cancer incidence, mortality, and survival (19).

All thyroid cancer patients (site code C73.9) detected between 1975 and 2016 were retrieved from the SEER 18 database (i.e., the 2018 submission) (20). Only patients with an index thyroid malignancy were included in this study. Patients whose diagnoses were extracted from their death certificates and whose follow-up information was incomplete were excluded (see **Figure S1** for details). For comparison, we extracted age-, sex-, race-, and year-specific death data for the general US population between 1975 and 2016 (21, 22).

Since the SEER is a publicly available database, access to the data required a signed research data agreement form. Institutional review board approval and the need for informed consent were waived for data obtained from the SEER database, as the study did not involve new experiments on human subjects and all data were anonymized.

Study Variables

For all patients, follow-up began at the time that the thyroid malignancy was detected and ended at the time of death from various causes, the finish of the research period (December 31, 2016), or due to early withdrawal. We extracted patients' demographic and clinical information, including age, sex, race, marital status, age at diagnosis, survival time, stage at diagnosis, and therapy modality (i.e., surgery, radiotherapy, or chemotherapy), from the SEER database. Causes of death were classified into three chief categories: the index (thyroid) cancer, a non-index cancer (i.e., secondary or subsequent primary cancers), and non-cancer causes of death. According to the SEER cause-specific death classification variables evaluated herein, non-cancer deaths were classified into 26 categories (23, 24). Non-cancer deaths were additionally classified into seven major categories: cardiovascular disease, infectious disease, respiratory disease, kidney disease, gastrointestinal disease, external injury, and other causes. Deaths from tumors with a histology of "*in situ*, benign, or unknown behavior neoplasm" were not considered non-cancer deaths in our study. For patients who died within 1 month post-diagnosis, the SEER project recorded their survival months as 0 months. Given that the survival time of this category of patients varied from 0 to 29 days, we converted their survival months to the median of this duration (namely, 0.5 months).

Statistical Analysis

We calculated mortality risks due to the index cancer, non-index cancers, and non-cancer causes of death in patients with thyroid carcinoma. For non-cancer causes of death, standardized mortality ratios (SMRs) were assumed to be the ratio of the death toll for patients with thyroid carcinoma to that of the general population. The calculation method for SMRs and associated 95% confidence intervals (CIs) with respect to non-cancer causes of death was as previously described (11, 25–27).

SMRs were calculated as the ratio of the observed number of deaths in cancer patients to the expected number of deaths in the cancer-free population, which had a similar demographic structure in terms of sex, age, race, and the calendar year of study evaluations. For age and years of cancer diagnosis, the values obtained were used herein when the patients are detected with malignancy, and 5-year categories were created in the course of standardization. Associated 95% CIs were calculated using a Poisson distribution (25, 28). SMRs were not available for cancer-associated deaths, since SMRs are calculated based on an assumption that regards the general population as a cancer-free cohort (8). Based on this assumption, the cancer-free general population will not die from cancer; thus, the cancer-associated mortality in this population could not be estimated. The cumulative mortality rate (CMR) was calculated to determine those patients with thyroid carcinoma who were at higher risk of death (11). The JoinPoint model was used to calculated the annual percentage change (APC) of deaths from different causes, and test the statistical significance of trends in cause of death among thyroid cancer patients. An average APC was further calculated to summarize the trend over the entire time period (29).

R statistical software (30) (version 3.52; The R Project for Statistical Computing, Vienna, Austria) and SEER*Stat software version 8.3.6 (21) (National Cancer Institute, Bethesda, MD, USA) were used for all data analyses. All hypothesis tests were two-sided, with a P value of <0.05 set as the level of statistical significance.

RESULTS

Our study retrospectively reviewed and analyzed 183,641 US patients, diagnosed with an index thyroid carcinoma, with a median follow-up time of 6.9 years (range: 0–41.9 years). The majority of thyroid cancer patients were diagnosed at ages 40–59 years (44.1%). Female patients remarkably outnumbered male patients (76.6% *vs.* 23.4%). A majority of thyroid malignancies were detected before progressing to an advanced stage (localized, 55.8%; regional, 31.5%), while only a few thyroid cancer patients were diagnosed with advanced-stage disease (distant, 4.1%). Both surgery and radiotherapy are common treatments for thyroid cancer. In this population, the surgery rate was 95.7% and radiotherapy rate was 45.8%, while chemotherapy was less frequently applied (1.0%) (**Table 1**).

Causes of Death Among Patients With Thyroid Carcinoma

There were 22,386 individuals in total who died during follow-up, contributing to an all-cause mortality rate of 13.68.1 per 100,000 person-years. Among all deaths, 46.4% died from non-cancer causes (n=10,387, mortality rate: 634.8 per 100,000 person-years), 31.0% died from thyroid cancer (n=6,936, mortality rate: 423.9 per 100,000 person-years), and 22.6% died from other cancers (n=5,063, mortality rate: 309.4 per 100,000 person-years) (**Tables 1**, **2**). Cardiovascular disease caused the majority of non-cancer deaths (21.3%), followed by infectious diseases (3.3%) and external injuries (3.3%).

Compared with the cancer-free population, the risk of mortality due to any type of non-cancer comorbidity was significantly greater in patients with a cancer history (SMR: 1.59; 95% CI: 1.56–1.62). Moreover, the risk of mortality due to particular non-cancer causes, including Alzheimer's disease (SMR: 2.96; 95% CI: 2.66–3.29), hypertension (SMR: 2.41; 95% CI: 2.06–2.83), and renal disease (SMR: 2.37; 95% CI: 2.11–2.65) was significantly greater in patients with a cancer history (**Table 2**).

Trends in Cause of Death Among Patients With Thyroid Carcinoma

We observed a rising trend in the proportion of non-cancer deaths in patients with thyroid carcinomas diagnosed between 1975 and 2016, whereas the proportion of deaths caused by thyroid cancer showed a rapid downward trend. More specifically, thyroid malignancy became the most common cause of death amongst patients with carcinoma thyroid malignancy between 1975 and 1990, while non-cancer causes were the major causes of death for persons with a history of thyroid malignancy between 1990 and 2016. The number of deaths from non-index cancers increased over this time (**Figure 1A**).

We further used JoinPoint model to test the trends in cause of death among thyroid cancer patients (**Figure S2**). The index-cancer deaths remained stable from 1975 to 1980 (APC=-0.64, p=0.6), decreased 6.24% annually from 1981 to 1985 (APC=-6.24, p<0.001), and then decreased 2.41% annually from 1985 to 2016 (APC=-2.41, p<0.001). This resulted in an average APC of -3.05 (p<0.001). Non-cancer deaths increased without statistical significance from 1975 to 1977 (APC=66.0, p=0.09), increased 2.48% annually from 1977 to 1997 (APC=2.48, p<0.001), and increased 1.09% annually from 1997 to 2016 (APC=1.09, p<0.001). This resulted in an average APC of 4.26 (p<0.001) (**Figure S2**).

A total of 21.8% (n=4,890) of deaths occurred within the first post-diagnostic year, 24.0% (n=5,369) occurred within 1–5 years after cancer diagnosis, and 54.2% (n=12,128) occurred more than 5 years post-diagnosis (**Table 3**). There was an increasing trend in the proportion of non-cancer deaths in patients with thyroid carcinoma over time (i.e., years after diagnosis), while the number of individuals who died from thyroid malignancy showed a rapid downward trend. Thyroid tumor has become the dominant cause of death in persons with thyroid malignancy within the first few years after diagnosis. However, as of the third post-diagnostic year, non-cancer causes became the dominant causes of death in survivors with a history of thyroid malignancy (**Figure 1B**). Non-cancer comorbidities were responsible for most deaths among long-term cancer survivors (**Figure 1B**). Within the first post-diagnostic year, 66.1% of deaths were attributed to thyroid cancer, whereas 22.5% were attributed to non-cancer causes. For persons who had a cancer history of more than 5 years, only 15.2% died from thyroid malignancy, while 57% of deaths were attributed to non-cancer causes (**Table 3**).

Overall, the SMRs for non-cancer deaths decreased during the first 5 years post-diagnosis. Mortality risks increased with prolonged survival time and were highest after 5 years post thyroid cancer diagnosis, with an associated SMR of 2.26 (95%

TABLE 1 | Characteristics of patients diagnosed with first primary thyroid cancer from 1975 to 2016 in the SEER program.

Characteristics	No. of patients (%)	Total follow-up time (person-years)	No. of deaths (%)	Non-cancer deaths		
				No. of observed deaths (%)	No. of expected deaths (%)	SMR (95% CI)
All	183,641 (100.0%)	1,636,233	22,386 (100.0%)	10,387 (100.0%)	6,530.5	1.59 (1.56-1.62)
Age						
0-19	4,212 (2.3%)	49,098	89 (0.4%)	43 (0.4%)	19.5	2.21 (1.64-2.98)
20-39	54,971 (29.9%)	602,516	1,521 (6.8%)	814 (7.8%)	466.8	1.74 (1.63-1.87)
40-59	80,946 (44.1%)	710,440	6,751 (30.2%)	3,026 (29.1%)	1,728.0	1.75 (1.69-1.81)
60-79	38,622 (21.0%)	256,000	10,739 (48.0%)	5,030 (48.4%)	3,042.1	1.65 (1.61-1.70)
80+	4,890 (2.7%)	18,178	3,286 (14.7%)	1,474 (14.2%)	1,274.1	1.16 (1.10-1.22)
Sex						
Female	140,744 (76.6%)	1,270,557	14,208 (63.5%)	6,787 (65.3%)	4,110.8	1.65 (1.61-1.69)
Male	42,897 (23.4%)	365,676	8,178 (36.5%)	3,600 (34.7%)	2,419.6	1.49 (1.44-1.54)
Race						
White	148,868 (81.1%)	1,350,401	18,272 (81.6%)	8,507 (81.9%)	5,477.6	1.55 (1.52-1.59)
Black	12,058 (6.6%)	95,546	1,819 (8.1%)	941 (9.1%)	594.9	1.58 (1.48-1.69)
Other	22,715 (12.4%)	190,286	2,295 (10.3%)	939 (9.0%)	458.0	2.05 (1.92-2.19)
Year of diagnosis						
1975-1989	13,292 (7.2%)	333,786	5,672 (25.3%)	3,004 (28.9%)	1,039.4	2.89 (2.79-3.00)
1990-1999	18,643 (10.2%)	327,165	4,745 (21.2%)	2,205 (21.2%)	1,161.0	1.90 (1.82-1.98)
2000-2009	72,984 (39.7%)	735,679	8,951 (40.0%)	4,115 (39.6%)	3,184.9	1.29 (1.25-1.33)
2010-2016	78,722 (42.9%)	239,602	3,018 (13.5%)	1,063 (10.2%)	1,145.1	0.93 (0.87-0.99)
Marital status						
Married	112,649 (61.3%)	1,050,292	12,467 (55.7%)	5,606 (54.0%)	3,913.2	1.43 (1.40-1.47)
Unmarried	61,646 (33.6%)	521,789	9,034 (40.4%)	4,333 (41.7%)	2,344.9	1.85 (1.79-1.90)
Unknown	9,346 (5.1%)	64,152	885 (4.0%)	448 (4.3%)	272.3	1.65 (1.50-1.80)
Stage						
In situ	85 (0.05%)	1,127	14 (0.06%)	9 (0.1%)	3.9	2.28 (1.19-4.38)
Localized	102,400 (55.8%)	998,109	9,288 (41.5%)	6,006 (57.8%)	3,895.5	1.54 (1.50-1.58)
Regional	57,935 (31.5%)	547,367	7,711 (34.4%)	3,266 (31.4%)	2,121.5	1.54 (1.49-1.59)
Distant	7,442 (4.1%)	44,710	4,104 (18.3%)	629 (6.1%)	272.3	2.31 (2.14-2.50)
Unstaged	15,779 (8.6%)	44,919	1,269 (5.7%)	477 (4.6%)	237.2	2.01 (1.84-2.20)
Surgery						
Yes	175,800 (95.7%)	1,599,400	18,607 (83.1%)	9,391 (90.4%)	6,196.7	1.52 (1.49-1.55)
No	7,043 (3.8%)	31,686	3,562 (15.9%)	934 (9.0%)	301.4	3.10 (2.91-3.30)
Unknown	798 (0.4%)	5,147	217 (1.0%)	62 (0.6%)	32.4	1.92 (1.49-2.46)
Radiotherapy						
Yes	84,122 (45.8%)	728,512	9,503 (42.5%)	3,420 (32.9%)	2,660.1	1.29 (1.24-1.33)
No/Unknown	99,519 (54.2%)	907,721	12,883 (57.5%)	6,967 (67.1%)	3,870.4	1.80 (1.76-1.84)
Chemotherapy						
Yes	1,891 (1.0%)	6,948	1,361 (6.1%)	101 (1.0%)	44.7	2.26 (1.86-2.75)
No/Unknown	181,750 (99.0%)	1,629,285	21,025 (93.9%)	10,286 (99.0%)	6,485.8	1.59 (1.56-1.62)

CI: 2.21–2.32). This increasing trend was observed for most causes of death and was highest for Alzheimer's disease (5+ years: SMR: 8.27; 95% CI: 7.37–9.28). However, the SMR for suicide (1 year: SMR: 1.51; 95% CI: 1.04–2.20) as well as for death from aortic aneurysm and dissection (1 year: SMR: 3.66; 95% CI: 2.41–5.56) in the first post-diagnostic year were the highest compared with other timeframes during the entire follow-up period (**Table 3**).

Mortality Rates for Patients With Thyroid Tumors

With all causes combined, the 1-year CMR for thyroid cancer patients was 2.2%, whereas the 5-year all-cause CMR was 5.9%, and the 10-year all-cause CMR was 11.0%. When performing cause-specific analyses, we observed that the CMR for thyroid cancer was higher than other for causes in the first few years after diagnosis, while the CMR for non-cancer causes of death overtook that of thyroid cancer, and non-cancer deaths were the most common approximately 8 years following cancer diagnosis (**Figure 2**).

In addition, we conducted secondary CMR analyses using different variables to determine the subpopulations at higher risk of death among the evaluated thyroid cancer patients. We observed that, although the number of male patients diagnosed with thyroid malignancy was much lower than that of female patients (**Table 1**), males were under greater threat of death from nearly all causes compared with females ($p<0.001$ for all causes of death) (**Figure 3**). Older age was associated with a higher CMR for all causes of death (**Figure S3**), and black patients had higher a CMR for deaths from thyroid cancer ($p<0.001$), non-index cancers ($p<0.001$), infectious diseases ($p=0.002$), cardiovascular diseases ($p<0.001$), and renal diseases ($p<0.001$) compared with white patients. The variances between black and white patients in terms of the CMR for respiratory diseases ($p=0.2$), gastrointestinal diseases

TABLE 2 | Cause of death among patients with thyroid cancer in the SEER 18 program.

Cause of death	Cancer population		General population		SMR (95% CI)
	No. of observed deaths (%)	Mortality rates (per 100,000 person-years)	No. of expected deaths (%)	Mortality rates (per 100,000 person-years)	
All causes	22,386 (100.0%)	1368.1	NA	NA	NA
Index cancer	6,936 (31.0%)	423.9	NA	NA	NA
Non-index cancer	5,063 (22.6%)	309.4	NA	NA	NA
Noncancer cause of death	10,387 (46.4%)	634.8	6,530.5	399.1	1.59 (1.56-1.62)
Infectious diseases	735 (3.3%)	44.9	441.0	26.9	1.67 (1.55-1.79)
Pneumonia and influenza	366 (1.6%)	22.4	185.0	11.3	1.98 (1.79-2.19)
Syphilis	0 (0.0%)	0.0	0.1	0.005	0.00 (NA)
Tuberculosis	5 (0.02%)	0.3	5.2	0.3	0.97 (0.40-2.33)
Septicemia	209 (0.9%)	12.8	111.4	6.8	1.88 (1.64-2.15)
Other infectious diseases	155 (0.7%)	9.5	138.6	8.5	1.12 (0.96-1.31)
Cardiovascular diseases	4,767 (21.3%)	291.3	2,994.9	183.0	1.59 (1.55-1.64)
Diseases of heart	3,554 (15.9%)	217.2	2,313.8	141.4	1.54 (1.49-1.59)
Hypertension without heart disease	152 (0.7%)	9.3	63.1	3.9	2.41 (2.06-2.83)
Aortic aneurysm and dissection	76 (0.3%)	4.6	50.0	3.1	1.52 (1.21-1.90)
Atherosclerosis	63 (0.3%)	3.9	32.0	2.0	1.97 (1.54-2.52)
Cerebrovascular diseases	880 (3.9%)	53.8	501.3	30.6	1.76 (1.64-1.88)
Other diseases of arteries, arterioles, capillaries	42 (0.2%)	2.6	33.9	2.1	1.24 (0.92-1.68)
Respiratory diseases	608 (2.7%)	37.2	459.1	28.1	1.32 (1.22-1.43)
Chronic obstructive pulmonary disease and allied Cond	608 (2.7%)	37.2	459.1	28.1	1.32 (1.22-1.43)
Gastrointestinal diseases	176 (0.8%)	10.8	200.3	12.2	0.88 (0.76-1.02)
Stomach and duodenal ulcers	18 (0.08%)	1.1	16.7	1.0	1.08 (0.68-1.71)
Chronic liver disease and cirrhosis	158 (0.7%)	9.7	183.4	11.2	0.86 (0.74-1.01)
Renal diseases	301 (1.3%)	18.4	127.1	7.8	2.37 (2.11-2.65)
Nephritis, nephrotic syndrome and nephrosis	301 (1.3%)	18.4	127.1	7.8	2.37 (2.11-2.65)
External injuries	736 (3.3%)	45.0	739.6	45.2	1.00 (0.93-1.07)
Accidents and adverse effects	540 (2.4%)	33.0	491.8	30.1	1.10 (1.01-1.19)
Suicide and self-inflicted injury	164 (0.7%)	10.0	175.4	10.7	0.93 (0.80-1.09)
Homicide and legal intervention	32 (0.14%)	2.0	72.3	4.4	0.44 (0.31-0.63)
Other cause of death	3,064 (13.7%)	187.3	1,568.3	95.8	1.95 (1.89-2.02)
Alzheimers (ICD-9 and 10 only)	341 (1.5%)	20.8	115.2	7.0	2.96 (2.66-3.29)
Diabetes mellitus	482 (2.2%)	29.5	290.2	17.7	1.66 (1.52-1.82)
Congenital anomalies	19 (0.08%)	1.2	23.6	1.4	0.81 (0.51-1.26)
Certain conditions originating in perinatal period	2 (0.01%)	0.1	0.1	0.007	16.4 (4.11-65.8)
Complications of pregnancy, childbirth, puerperium	5 (0.02%)	0.3	4.7	0.3	1.07 (0.44-2.56)
Symptoms, signs and ill-defined conditions	166 (0.7%)	10.1	102.9	6.3	1.61 (1.39-1.88)
Other cause of death	2,049 (9.2%)	125.2	1,030.9	63.0	1.99 (1.90-2.08)

NA, not applicable.

(p=0.8), or external injuries (p=0.5) showed no statistical significance (**Figure S4**). Advanced disease stages were associated with a significantly higher CMR for nearly all causes of death (**Figure S5**).

We found that surgical interventions reduced the CMR for all causes of death in patients with thyroid malignancy (p<0.001) (**Figure 4**). Radiotherapy reduced the CMR for nearly all causes of deaths in thyroid malignancy, with the exception of non-index cancers (**Figure 5**). Comparisons between patients who underwent radiotherapy and those who did not showed no statistically significant differences in variances in the CMR (p=0.06) (**Figure 5**). CMR analyses with respect to chemotherapy were not performed in the current study because of the low prevalence of this intervention (**Table 1**).

DISCUSSION

In the current research, we summarized the spectrum of causes of death amongst approximately 183,000 US patients with thyroid carcinoma. The research has revealed that the proportion of non-cancer deaths occurring in patients with thyroid carcinoma exceeded the proportion of index-cancer deaths (i.e., deaths from thyroid malignancy), and that the risk of mortality from non-cancer comorbidities was nearly 1.6-fold that of the cancer-free population.

We have demonstrated that non-cancer comorbidities may be the dominant cause of death in thyroid cancer patients, as has been previously reported for other cancers. More and more research has emphasized the importance of non-cancer

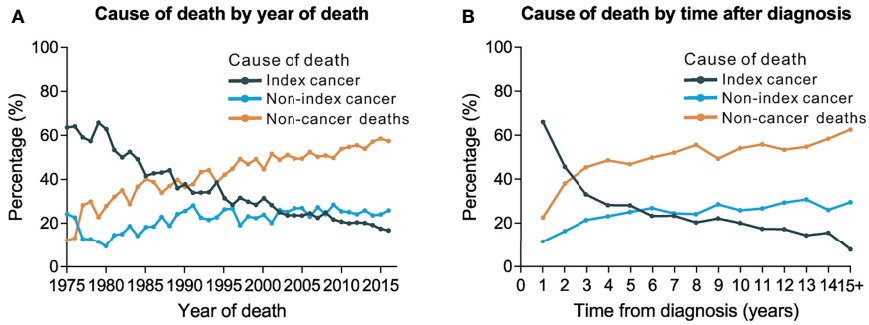

FIGURE 1 | Trends of cause of death by year of death and time after diagnosis. **(A)** Trends of cause of death by year of death among patients with thyroid cancer. **(B)** Trends of cause of death by time after diagnosis.

TABLE 3 | Cause of death among patients with thyroid cancer by time after diagnosis.

Cause of deaths	Time after cancer diagnosis					
	With 12 months		12 to 60 months		More than 60 months	
	No. of deaths (%)	SMR (95% CI)	No. of deaths (%)	SMR (95% CI)	No. of deaths (%)	SMR (95% CI)
All causes	4,890 (100.0%)	NA	5,369 (100.0%)	NA	12,128 (100.0%)	NA
Index cancer	3,230 (66.1%)	NA	1,863 (34.7%)	NA	1,843 (15.2%)	NA
Non-index cancer	559 (11.4%)	NA	1,129 (21.0%)	NA	3,375 (27.8%)	NA
Noncancer cause of death	1,101 (22.5%)	1.31 (1.24-1.39)	2,376 (44.3%)	0.90 (0.87-0.94)	6,910 (57.0%)	2.26 (2.21-2.32)
Infectious diseases	90 (1.8%)	1.60 (1.30-1.96)	176 (3.3%)	0.99 (0.85-1.15)	469 (3.9%)	2.27 (2.07-2.49)
Pneumonia and influenza	42 (0.9%)	1.65 (1.22-2.24)	78 (1.5%)	1.01 (0.81-1.27)	246 (2.0%)	2.97 (2.62-3.37)
Syphilis	0 (0.0%)	0.00 (0.00-NA)	0 (0.0%)	0.00 (0.00-NA)	0 (0.0%)	0.00 (0.00-NA)
Tuberculosis	0 (0.0%)	0.00 (0.00-NA)	2 (0.04%)	1.21 (0.30-4.84)	3 (0.02%)	0.99 (0.32-3.08)
Septicemia	23 (0.5%)	1.46 (0.97-2.19)	57 (1.1%)	1.16 (0.89-1.50)	129 (1.1%)	2.77 (2.33-3.30)
Other infectious diseases	25 (0.5%)	1.70 (1.15-2.52)	39 (0.7%)	0.78 (0.57-1.06)	91 (0.8%)	1.23 (1.00-1.52)
Cardiovascular diseases	526 (10.8%)	1.38 (1.26-1.50)	1,088 (20.3%)	0.91 (0.86-0.97)	3,153 (26.0%)	2.23 (2.15-2.30)
Diseases of heart	390 (8.0%)	1.34 (1.21-1.48)	835 (15.6%)	0.91 (0.85-0.97)	2,329 (19.2%)	2.11 (2.02-2.20)
Hypertension without heart disease	17 (0.3%)	1.74 (1.08-2.79)	33 (0.6%)	1.14 (0.81-1.60)	102 (0.8%)	4.21 (3.47-5.11)
Aortic aneurysm and dissection	22 (0.4%)	3.66 (2.41-5.56)	16 (0.3%)	0.82 (0.50-1.33)	38 (0.3%)	1.56 (1.13-2.14)
Atherosclerosis	10 (0.2%)	2.24 (1.21-4.17)	14 (0.3%)	1.06 (0.63-1.79)	39 (0.3%)	2.72 (1.98-3.72)
Cerebrovascular diseases	81 (1.7%)	1.24 (0.99-1.54)	182 (3.4%)	0.90 (0.77-1.04)	617 (5.1%)	2.65 (2.45-2.87)
Other diseases of arteries, arterioles, capillaries	6 (0.1%)	1.40 (0.63-3.12)	8 (0.1%)	0.59 (0.30-1.19)	28 (0.2%)	1.74 (1.20-2.52)
Respiratory diseases	60 (1.2%)	0.95 (0.74-1.22)	137 (2.6%)	0.69 (0.58-0.82)	411 (3.4%)	2.08 (1.89-2.29)
Chronic obstructive pulmonary disease and allied Cond	60 (1.2%)	0.95 (0.74-1.22)	137 (2.6%)	0.69 (0.58-0.82)	411 (3.4%)	2.08 (1.89-2.29)
Gastrointestinal diseases	18 (0.4%)	0.81 (0.51-1.29)	44 (0.8%)	0.60 (0.44-0.80)	114 (0.9%)	1.09 (0.91-1.31)
Stomach and duodenal ulcers	1 (0.02%)	0.52 (0.07-3.67)	4 (0.07%)	0.64 (0.24-1.71)	13 (0.1%)	1.53 (0.89-2.63)
Chronic liver disease and cirrhosis	17 (0.3%)	0.84 (0.52-1.35)	40 (0.7%)	0.59 (0.43-0.81)	101 (0.8%)	1.06 (0.87-1.28)
Renal diseases	36 (0.7%)	1.96 (1.41-2.72)	68 (1.3%)	1.21 (0.95-1.53)	197 (1.6%)	3.75 (3.26-4.31)
Nephritis, nephrotic syndrome and nephrosis	36 (0.7%)	1.96 (1.41-2.72)	68 (1.3%)	1.21 (0.95-1.53)	197 (1.6%)	3.75 (3.26-4.31)
External injuries	84 (1.7%)	1.08 (0.87-1.33)	215 (4.0%)	0.82 (0.72-0.94)	437 (3.6%)	1.09 (1.00-1.20)
Accidents and adverse effects	53 (1.1%)	0.97 (0.74-1.27)	152 (2.8%)	0.84 (0.72-0.99)	335 (2.8%)	1.30 (1.17-1.45)
Suicide and self-inflicted injury	27 (0.6%)	1.51 (1.04-2.20)	45 (0.8%)	0.74 (0.55-0.99)	92 (0.8%)	0.95 (0.78-1.17)
Homicide and legal intervention	4 (0.1%)	0.70 (0.26-1.85)	18 (0.3%)	0.86 (0.54-1.37)	10 (0.08%)	0.22 (0.12-0.41)
Other cause of death	287 (5.9%)	1.31 (1.16-1.47)	648 (12.1%)	0.97 (0.89-1.04)	2,129 (17.6%)	3.14 (3.01-3.28)
Alzheimers (ICD-9 and 10 only)	8 (0.2%)	0.37 (0.19-0.75)	43 (0.8%)	0.73 (0.54-0.99)	290 (2.4%)	8.27 (7.37-9.28)
Diabetes mellitus	39 (0.8%)	1.05 (0.77-1.44)	113 (2.1%)	0.95 (0.79-1.14)	330 (2.7%)	2.46 (2.21-2.74)
Congenital anomalies	4 (0.1%)	1.65 (0.62-4.41)	5 (0.1%)	0.60 (0.25-1.45)	10 (0.08%)	0.78 (0.42-1.45)
Certain conditions originating in perinatal period	0 (0.0%)	NA	2 (0.04%)	32.6 (8.14-130.2)	0 (0.0%)	NA
Complications of pregnancy, childbirth, puerperium	1 (0.02%)	1.92 (0.27-13.66)	2 (0.04%)	1.16 (0.29-4.63)	2 (0.02%)	0.82 (0.21-3.28)
Symptoms, signs and ill-defined conditions	18 (0.4%)	1.43 (0.90-2.27)	33 (0.6%)	0.83 (0.59-1.17)	115 (0.9%)	2.28 (1.90-2.73)
Other cause of death	217 (4.4%)	1.49 (1.30-1.70)	450 (8.4%)	1.01 (0.92-1.11)	1,382 (11.4%)	3.13 (2.97-3.30)

NA, not applicable.

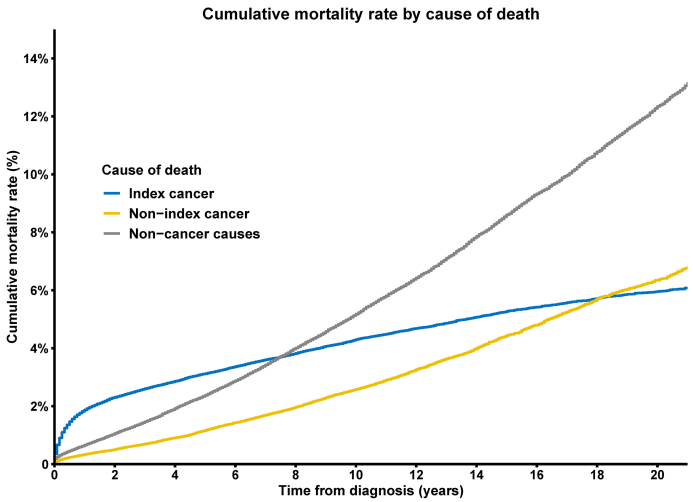

FIGURE 2 | Cumulative mortality rate of deaths from index cancer, non-index cancer and other non-cancer causes among patients with thyroid cancer.

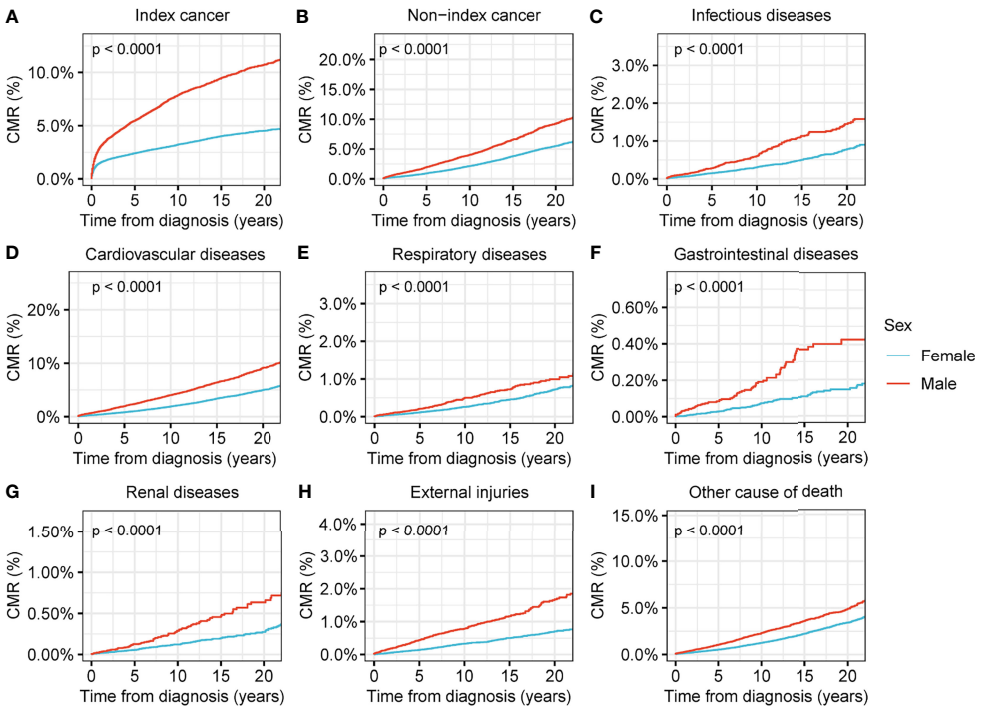

FIGURE 3 | Cumulative mortality rate (CMR) among patients with thyroid cancer by sex. **(A)** CMR from index cancer among patients with thyroid cancer by sex. **(B)** CMR from non-index cancer among patients with thyroid cancer by sex. **(C)** CMR from infectious diseases among patients with thyroid cancer by sex. **(D)** CMR from cardiovascular diseases among patients with thyroid cancer by sex. **(E)** CMR from respiratory diseases among patients with thyroid cancer by sex. **(F)** CMR from gastrointestinal diseases among patients with thyroid cancer by sex. **(G)** CMR from renal diseases among patients with thyroid cancer by sex. **(H)** CMR from external injuries among patients with thyroid cancer by sex. **(I)** CMR from other non-cancer causes among patients with thyroid cancer by sex.

comorbidities in the healthcare of patients with cancer (7, 8, 31, 32). In certain types of malignancy, including breast malignancy (31), colorectal malignancy (8), and prostate malignancy (32), non-cancer comorbidities have become the dominant cause of death in recent decades. This research adds to this finding. This important role of non-cancer deaths in thyroid cancer patients could partly be interpreted by the relatively favorable prognosis for differentiated thyroid carcinoma (33). The reduction in the

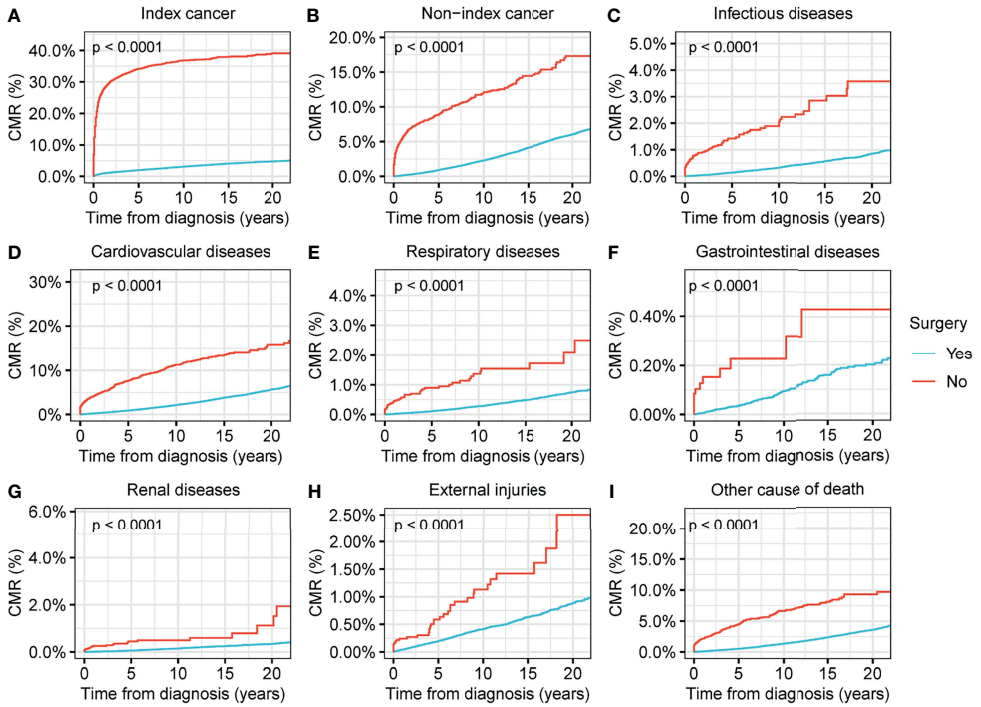

FIGURE 4 | Cumulative mortality rate (CMR) among patients with thyroid cancer by surgery. **(A)** CMR from index cancer among patients with thyroid cancer by surgery. **(B)** CMR from non-index cancer among patients with thyroid cancer by surgery. **(C)** CMR from infectious diseases among patients with thyroid cancer by surgery. **(D)** CMR from cardiovascular diseases among patients with thyroid cancer by surgery. **(E)** CMR from respiratory diseases among patients with thyroid cancer by surgery. **(F)** CMR from gastrointestinal diseases among patients with thyroid cancer by surgery. **(G)** CMR from renal diseases among patients with thyroid cancer by surgery. **(H)** CMR from external injuries among patients with thyroid cancer by surgery. **(I)** CMR from other non-cancer causes among patients with thyroid cancer by surgery.

index-cancer deaths in thyroid cancer should be attributed to the tremendous advances achieved in the detection and treatments of this disease, even over-diagnosis and over-diagnosis in some low-risk cases (34). Recently, personalized medicine, in which a person's prevention, screening, and treatment are optimized by more effective strategies based on genetic information and other personalized characteristics, become a new trend in the management of thyroid carcinomas (33, 35). The management of thyroid carcinomas switch from "one size fits all" therapeutic measures that included total thyroidectomy, radioiodine and TSH suppression, to much more personalized strategies that currently include lobectomy or just active surveillance for low-risk of recurrence thyroid patients (33, 35). In addition, personalized medicine provides new directions for treatment of non-cancer comorbidities in thyroid cancer patients, because the non-cancer comorbidities are also highly individualized and might be distinct across patients.

Our results demonstrate that the risk of nearly all types of non-cancer comorbidities increases with prolonged follow-up time. Advances in early detection have led to an increasing proportion of patients diagnosed at an early stage. Our data showed that only 4% of thyroid malignancies were diagnosed with a distant metastatic tumor. The high early detection rate and generally favorable prognosis for this disease contribute to the increasing prevalence of long-term thyroid cancer survivors. This emphasized the importance of uncovering the detailed causes of death in these long-term malignancy patients, as a cancer history will meaningfully alter the distribution of causes of death among these individuals and will inform interventions with respect to mitigating mortality risk and promoting survivorship and quality of life (7, 8, 31, 32). Our work, as well as that of prior studies, shows that cancer and its treatments may increase the short- and long-term risks of non-cancer death (7, 15).

Cardiovascular disease was responsible for more than one-fifth of all deaths among thyroid cancer patients in this study, making it a significant cause of death among patients with thyroid carcinoma. Earlier findings and cutting-edge treatment guidelines indicated that receiving radioactive iodine for thyroid cancer is related to an elevated incidence of cardiovascular disease, and persistent thyroxine exposure and/or thyroid-stimulating hormone restraining therapy increase the risk of cardiovascular-specific mortality, by impairing large arteries, stiffening small arteries (accepted as a surrogate marker for cardiovascular disease), and leading to hypertension and/or cardiac arrhythmias (36–41). In addition, thyroid cancer patients often receive doses of thyroid hormones that are slightly higher than their daily needs (i.e., suppressive thyroid hormone therapy) in an endeavor to decrease the development of any thyroid malignancy cells following the preliminary course of

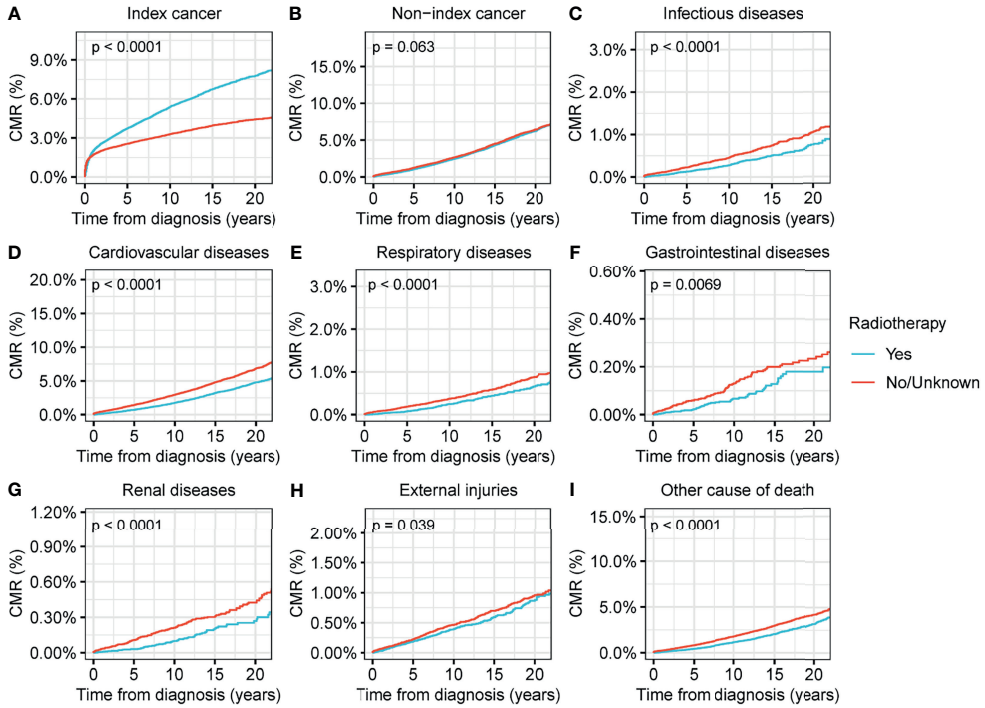

FIGURE 5 | Cumulative mortality rate (CMR) among patients with thyroid cancer by radiotherapy. **(A)** CMR from index cancer among patients with thyroid cancer by radiotherapy. **(B)** CMR from non-index cancer among patients with thyroid cancer by radiotherapy. **(C)** CMR from infectious diseases among patients with thyroid cancer by radiotherapy. **(D)** CMR from cardiovascular diseases among patients with thyroid cancer by radiotherapy. **(E)** CMR from respiratory diseases among patients with thyroid cancer by radiotherapy. **(F)** CMR from gastrointestinal diseases among patients with thyroid cancer by radiotherapy. **(G)** CMR from renal diseases among patients with thyroid cancer by surgery. **(H)** CMR from external injuries among patients with thyroid cancer by radiotherapy. **(I)** CMR from other non-cancer causes among patients with thyroid cancer by radiotherapy.

treatment. We acknowledge that patients who receive high doses of thyroid hormone replacement for a long time are at increased risk of bone loss and heart rhythm changes (i.e., atrial fibrillation) (38).

In this study, we observed a remarkably elevated mortality risk due to hypertension in patients with thyroid carcinoma. Previous research has likewise uncovered a high incidence of hypertension among patients with thyroid carcinoma (23). Patients with thyroid dysfunction (both hypothyroidism and hyperthyroidism) also show an increased prevalence of hypertension (42, 43), and some novel thyroid cancer therapies may likewise add to the possibility of developing hypertension in patients with thyroid malignancy. For example, levantinib is a newly developed molecularly targeted agent for iodine-refractory differentiated thyroid cancer (44), and studies to date demonstrate that most of the patients treated with levantinib had concomitant hypertension (45).

Although thyroid cancer was diagnosed less frequently in male patients, we observed a higher rate of mortality from nearly all causes in male patients with thyroid malignancy in this study. Studies have demonstrated that thyroid malignancy characteristically presents at a more advanced stage and there is a worse tumor prognosis in males (46, 47). Research on the influence of sex hormones on thyroid malignancy has continued to be inconclusive, while plenty of experimental research studies have indicated that estrogen and other hormones and their receptors may lead to tumorigenesis and tumor progression (46, 47).

Interestingly, we discovered that the incidence of suicide was highest within the first post-diagnostic year, consistent with previous pan-cancer studies (14, 26). Prior studies have suggested that suicide risk varies according to the malignant potential of the cancer (26). Our results indicate that thyroid cancer, whose prognosis is more favorable, are also associated with an elevated risk of suicide. External injuries (i.e., mainly due to accidents and suicides) were the third leading non-cancer cause of death in our study, suggesting the great importance of ensuring the safety of thyroid cancer survivors and to avoid the occurrence of external injuries in this population.

We found a remarkably increased risk of mortality from Alzheimer's diseases in long-term thyroid malignancy patients. The thyroid gland plays crucial role in the regulation of metabolism, growth, and development of various tissues, organs, systems, including the central nervous system (48). Accumulating evidence has demonstrated the importance of thyroid function in the development of Alzheimer's disease, while Alzheimer's disease also leads to a significant increase in the morbidity of thyroid dysfunction (49). Although many

studies have confirmed that thyroid function is significantly associated with cognitive impairment, the underlying mechanisms are not well understood (49). Some studies hypothesized that the crucial role that thyroid function plays in the pathogenesis of Alzheimer's disease is achieved by affecting the metabolism of Aβ and p-tau (48, 49). Hyperthyroidism as well as hypothyroidism can induce hippocampus degeneration and impair cognition through a reduction in long-term potentiation (48–52). The relationships between thyroid function and Alzheimer's disease provide new therapeutic strategies for Alzheimer's disease. Understanding the underlying mechanisms will help in providing novel approaches for the management of patients with Alzheimer's disease. Our results demonstrate that thyroid malignancy, as a major type of thyroid dysfunction, might also be related to the long-term possibility of Alzheimer's disease. We conclude that this information should be common knowledge (gained through continuing education) among clinicians and researchers, and targeted interventions should be applied aggressively and consistently in order to mitigate this risk.

Our study had several limitations. First, the SEER 2018 database lacks information on patient comorbidities and family history, as well as detailed information on therapy, all of which may have an impact on thyroid cancer prognoses. Therefore, deeper and more comprehensive analyses, including risk stratification and the assessment of the impact of the aforementioned factors were impossible to conduct herein. Second, there is a possibility of misclassification with respect to cause of death that is inherent to epidemiologic research, and there is some reporting bias associated with death certificates. However, the SEER database uses a systematic and standard data collection procedure in order to ensure the accuracy of cause of death determinations (12), thereby substantially mitigating the possible impacts of these potential biases on study results and interpretation. Nevertheless, the strengths of the current study were the large-scale study cohort and the detailed cause-of-death records, which enabled us to comprehensively analyze the cause of death among patients with thyroid malignancy. Our study can provide guidance for future research, as well as guide clinicians to achieve better long-term outcomes in patients with thyroid carcinoma.

CONCLUSION

Non-cancer causes of death have replaced primary index malignancy as the main cause of death amongst patients with thyroid carcinoma in the US. We clarified that patients with thyroid carcinoma have a higher risk of non-cancer deaths than the cancer-free population. As the survival time of patients with thyroid carcinoma increases, non-cancer deaths will increase in this population and the relative risk of mortality from various causes will increase exponentially. Hence, clinicians should practice careful chronic disease management for patients with thyroid malignancy. In the early phase following malignancy diagnosis, it is necessary to provide appropriate and comprehensive education and psychological counseling to patients in order to prevent the occurrence of depression and suicide. As the survival period is extended, attention should be paid to lifestyle improvements and the rational use of tumor drugs to prevent Alzheimer's disease and other non-cancer diseases. Our findings can guide the direction of future research studies and inform future medical guidelines.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/.

AUTHOR CONTRIBUTIONS

Research designer: HL and YZ. Collecting, analyzing and interpreting data: YZ, QW, ZZ, HL and JN. The main contributors to writing manuscripts: HL, QW, ZZ, HL and JN. The final draft read and approved by all authors.

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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.2022.852347/full#supplementary-material

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Core Needle Biopsy Can Early and Precisely Identify Large Thyroid Masses

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Background: Large thyroid masses, particularly if rapidly growing, are often characterized by compression and infiltration of the vital structures of the neck. Therefore, an early and precise diagnosis, not only of malignancy but also of histotype, is mandatory to set up the right therapy. The aim of this study was to evaluate the diagnostic performance of fine needle aspiration cytology (FNAC) and core needle biopsy (CNB) in this setting.

Patients and Methods: We prospectively evaluated 95 patients with large and rapidly growing thyroid masses admitted to the University Hospital of Pisa between April 2014 and January 2020. All patients were submitted to FNAC and CNB in the same session. The ability of both procedures to diagnose the malignancy of the lesions, particularly the histotype, and to obtain sufficient material to perform molecular analysis was evaluated.

Results: FNAC obtained adequate tumor sample to reach a diagnosis in 76 of 95 (80%) patients, while a higher percentage was obtained with CNB (92/95, 96.8%). FNAC was able to identify the malignancy of the lesion in 74 of 95 (77.9%) cases, but only in 16 of 74 (21.6%) cases was it able to define the histotype. CNB was able to define the malignancy of the lesion in all but three cases (92/95, 96.8%), and in all specimens, the histotype was identified. Moreover, in all cases, the material extracted from CNB was optimal to perform molecular analysis. No surgery-related complications were experienced with both procedures.

Conclusions: CNB is a rapid and safe procedure with higher performance compared to FNAC in identifying the histotype of large and rapidly growing thyroid masses. Moreover, adequate material can be obtained to characterize the molecular profile for the treatment of potentially lethal cancers. In the era of precision medicine, CNB should be introduced in routine clinical practice as a key procedure for an early diagnosis and therapy of these diseases.

Keywords: anaplastic thyroid carcinoma, poorly differentiated thyroid carcinoma, core needle biopsy, fine needle aspiration cytology, thyroid lymphoma

INTRODUCTION

Large thyroid masses, particularly if rapidly growing, are often life-threatening events because of the mechanical compression and/or infiltration of the vital structures of the neck (1–3). The most common is anaplastic thyroid carcinoma (ATC), which often appears with hoarseness, cervical pain, dysphagia, dyspnea, and stridor (4, 5). Moreover, beyond local compression, ATC is characterized by high rates of distant metastases and rapidly fatal clinical outcomes (6), and most patients die within 6 months from the diagnosis (1, 7). Conversely, large thyroid masses other than ATC are not necessarily life threatening and can be successfully treated with specific therapies. A clear identification of the histology of these masses is essential to select the most appropriate therapeutic approach (8–10).

All ATC cases are defined as stage IV and primary tumor considered T4 by the American Joint Committee on Cancer (11). According to the American Thyroid Association (12), the therapeutic options include radical surgery, if possible, external radiotherapy, and/or chemotherapy, which should be combined to maximize the disease control (3, 13, 14).

Since ATC is highly aggressive, a rapid diagnosis and treatment should be mandatory. Moreover, since other thyroid masses can have similar clinical presentation, but different outcomes, differentiating ATC from thyroid lymphoma (TL), poorly differentiated thyroid cancer (PDTC), and thyroid gland metastases (TGM) could improve the therapeutic approach and survival (8).

Currently, fine needle aspiration cytology (FNAC) is the most common diagnostic procedure (3), but it has shown several limitations particularly in the identification of ATC or TL (15–17). Therefore, patients with a suspicion of ATC or TL frequently require a surgical conventional biopsy, with more time elapsed to achieve the correct diagnosis (18). Moreover, in the case of surgical conventional biopsy, particularly in ATC, the surgical wound does not quickly heal, thus leading to a further delay in beginning potential treatments.

Core needle biopsy (CNB) represents a minimally invasive, safe, and accurate procedure providing a histological sample, which retains not only its cytologic appearance but also the tissue architecture. CNB has been suggested as a complementary method to FNAC, mainly to overcome possible inconclusive diagnosis (19). Accordingly, FNAC can play an important diagnostic role in the initial evaluation of ATC, but CNB may be necessary for definitive diagnosis and to perform molecular analysis (3). To our knowledge, no studies comparing the sensitivity of FNAC and CNB, on the same patient, in the diagnostic accuracy for detecting the malignancy of large thyroid masses and discriminating the histology have been performed.

The aim of this prospective study was to compare the diagnostic performance of FNAC and CNB in a large series of patients, thus exploring the possibility that CNB could be the first and main diagnostic tool in the presence of a large and rapidly growing thyroid mass.

PATIENTS AND METHODS

We prospectively collected the data of 95 consecutive patients with large thyroid masses admitted to either the Endocrine Unit or the Endocrine Surgery Unit of the University Hospital of Pisa between April 2014 and January 2020.

The study was conducted according to the guidelines of the Declaration of Helsinki, approved by the local Ethical Committee (CEAVNO, Comitato Etico Area Vasta Nord Ovest). For the policy of the University Hospital, all patients signed an informed consent both for the performance of invasive procedures and for the use of their data for scientific purposes.

Preparation for FNAC and CNB

All patients were submitted to routine blood evaluation and coagulation tests, and the medical history and hemorrhagic risk were carefully evaluated. When receiving antiplatelet or anticoagulation therapy, the diagnostic procedures were still performed, without withdrawal. Only warfarin was discontinued up to 3 days before the procedure. No antibiotics and/or analgesics were used after the procedures.

For each patient, a total body spiral computed tomography (CT) scan with intravenous contrast medium, particularly focused on the neck–mediastinum, was performed. Bronchoscopy and esophagoscopy were performed, if needed.

As per protocol, all patients were submitted to FNAC and CNB in the same time session.

Neck Ultrasound and CT Scan

An Aloka ProSound Alpha-5sv ultrasound system with a 7.5- to 12-MHz linear transducer (Hitachi Aloka Medical, LTD., Tokyo, Japan) was used for the neck ultrasound (neck US) examination. Neck US assessment is necessary to evaluate the composition and vascularity of the lesion in order to avoid necrotic spaces and vascular bundle and to select the most appropriate area of the mass for tissue sampling. For both procedures, a trans-isthmic or a lateral approach was performed according to each specific case.

A Lightspeed 16 RT, Lightspeed 64 VCT, and a Discovery HD 750 CT scan (GE Medical Systems, Waukesha, WI, USA) was used in patients scanned in our institution. Images of the total body CT scan were utilized for the evaluation of the tumor dimension; the presence of necrosis and/or calcifications; esophageal, tracheal, or laryngeal invasion; vascular involvement; and lymph node and/or distant metastases.

FNAC Procedure

Local anesthesia with 1% lidocaine was applied just before performing both FNAC and CNB, and a 2- to 3-mm skin incision was performed using no. 11 surgical blade, specifically for the aim of this study.

US-guided FNAC was performed with a 21-gauge needle using a 10- or 20-ml syringe with standard aspiration technique. During FNA, four to eight needle passes were performed during one single puncture in the analyzed nodule. The appropriateness of the material obtained by FNA was evaluated on site by the endocrinologist or the surgeon who performed the procedure

and was then used to prepare smears, which were examined by pathologists after staining with hematoxylin and eosin.

Cytological results were classified based on the Italian Consensus (20). Accordingly, the samples were defined as non-diagnostic if they were "inadequate", when biased by smearing and/or fixing and/or staining artifacts or by obscuring blood, or "non-representative", when the number of epithelial cells collected from the mass was insufficient for a definitive diagnosis. After FNA, we immediately performed CNB using the same skin incision.

CNB Procedure

CNB was performed using a 16-gauge disposable double-component spring-activated needle. The needle was positioned above the mass, in the same point of the previous FNAC, and was pushed to shoot the cutting cannula. The entire procedure was US guided. The biopsy needles were about 100 mm long. In all cases, we used a 2.0-cm excursion needle. Usually, two or three core samples were picked up from the same skin incision and fixed with 10% formaldehyde solution. After biopsy, the skin incision was dabbed and disinfected, but not sutured. Immediately after CNB, a manual compression of the neck was applied by the patient, and all patients were observed in hospital for the following 20–30 minutes.

Both procedures, FNAC and CNB, were conducted in Fowler's position to avoid respiratory failure.

Cytological and Histological Analyses

FNAC and CNB were analyzed by three different pathologists (LT, CU, and FB) in a double-blinded protocol. Immunohistochemical analyses were performed on each tissue sample obtained by CNB using the VENTANA BenchMark immunostaining system (Ventana Medical Systems, Tucson, AZ, USA). From formalin-fixed and paraffin-embedded specimens, tissue sections (3–5 mm) were deparaffinized and processed. Different panels of immunostaining were performed according to the morphological aspect on tissue section.

Since a greater amount of tissue was obtained by CNB, we decided to perform immunohistochemical and molecular analyses only on CNB samples.

Molecular Analysis Data Collection

Molecular analysis of samples was not an aim of this study and was not performed systematically. However, we collected the available data found in the pathological report for a descriptive analysis. From 2018, genetic analysis for potential actionable mutations, such as *BRAF* V600E first and then *RET/PTC* and *NTRK* rearrangements, has been performed (21–24). Moreover, in some cases, other oncogenes, especially those beneficial for a differential diagnosis, were analyzed. Good quality DNA and RNA extracted from CNB were obtained and were used to perform molecular analysis. We then performed real-time PCR to analyze codons 600 and 601 of the *BRAF* gene (EasyPGX® ready THYROID), *RET/PTC* 1–3, *NTRK* 1–3, and *PAX8/PPAR* gamma rearrangements (EasyPGX® ready *NTRK* and THYROID Fusion). Analysis of the *TERT* gene promoter hotspot mutations C228T and C250T and the *TP53* gene mutations in exons 4–9 was performed on specific request, not in all cases, using direct Sanger sequencing. The MassARRAY system (Sequenom, San Diego, CA, USA) was utilized for the evaluation of exons 18–21 of the *EGFR* gene, exon 20 of the *HER-2* gene, and exons 9 and 20 of the *PIK3CA* gene. Fluorescence *in situ* hybridization (FISH) analysis was conducted for *ROS1* rearrangement (Vysis 6q22 ROS1 Break Apart FISH Probe Kit), MYC translocation (Vysis MYC Break Apart FISH Probe Kit), and BCL2 translocation (Vysis BCL2 Break Apart FISH Probe Kit (all from Abbott Laboratories, Chicago, IL, USA).

Statistical Analysis

Data are presented as median and interquartile range (IQR) or as frequency (percentage). Diagnostic accuracy was evaluated for both procedures. The χ^2 test was used to assess differences between the categorical variables in both procedures. A p-value <0.05 was considered statistically significant. Statistical analysis was performed with SPSS 21.0 software (IBM Corp., Armonk, NY, USA).

RESULTS

At the time of enrollment, patients had a median age of 70 years (IQR = 58–79 years, range = 28–91 years), and 55 out of 95 (57.9%) were women (**Table 1**).

CT Scan Results

In 19 out of 95 (20%) cases, CT scan was not performed in our hospital, and images were evaluated at the time of procedures by the medical team involved in the treatment of the patients. Conversely, 76 of 95 (80%) patients had the CT scan done in our hospital, and images were reviewed by a dedicated radiologist (RC); the radiological features of the neck mass of these patients are reported in **Table 1**.

The median estimated volume of the thyroid gland, including the surrounding parenchyma not involved in the neoplasia, was 114.5 ml (IQR = 48.25–232.5), while that of the malignant lesion was 106.5 ml (IQR = 40.5–210.75). In most cases, the CT scan showed the invasion of some structures of the neck (73.7%), and about half of them revealed the presence of intratumoral macro- or microcalcifications (50%) and necrosis (63.2%). Lymph node (80.3%) and distant (55.3%) metastases were already present at diagnosis.

The correlation of the results of CT scan with those of FNAC, CNB, and specific immunohistochemical staining for ATC, PDTC, TL, and TGM of lung adenocarcinoma is shown in **Figure 1**.

FNAC and CNB Results

We firstly analyzed the ability of both FNA and CNB to provide adequate tumor samples to reach a diagnosis. Enough and adequate material to perform the cytological analysis was obtained in 76 out of 95 (80%) FNA specimens. A significantly higher percentage of good quality tissue, defined as a minimum 20% of tumor content in the specimens, was obtained with CNB (92/95, 96.8%; $p < 0.01$).

TABLE 1 | Epidemiological features of the study group (n = 95) and CT scan features of the 76 patients (76/95, 80%) with large thyroid masses who had a CT scan in our department.

Features			*n* (%)
Sex		M	40 (42.1)
		F	55 (57.9)
Age (years)		Median = 70 years (IQR = 58–79, range = 28–91)	
Volume (ml) (n = 76, 80%)		Thyroid gland including surrounding parenchyma	114.5
		Malignant lesion alone	106.5
CT scan features (n = 76, 80%)	Infiltration	Absent	20 (26.3)
		Esophagus	3 (3.9)
		Trachea	4 (5.3)
		Vascular	12 (15.8)
		Esophagus and trachea	11 (14.5)
		Esophagus and vascular	2 (2.6)
		Trachea and vascular	8 (10.5)
		Esophagus, trachea, and vascular	16 (21.1)
	Calcifications	Absent	38 (50)
		Micro	16 (21.1)
		Macro	22 (28.9)
	Necrosis	Absent	28 (36.8)
		Present	48 (63.2)
	Lymph node metastases	Absent	15 (19.7)
		Present	61 (80.3)
	Distant metastases	Absent	33 (43.4)
		Present	42 (55.3)
	Site of distant metastases	Lung	33 (78.7)
		Liver	3 (7.1)
		Bone	–
		Lung and liver	3 (7.1)
		Other	3 (7.1)

Using this material, immunohistochemistry was performed in 89 of 95 (93.7%) cases, which was useful to the pathologists in clarifying the diagnosis in 88 of 89 (98.9%) cases. The main immunohistochemical markers evaluated according to the histotype revealed by CNB are reported in **Table 2**. The molecular analysis performed in 17 cases is reported in **Table 3**.

A comparison of the cytological results of FNAC and the histological results of CNB is reported in **Table 4**. FNAC was able to identify a malignant lesion in 74 of 95 (77.9%) cases: in 12 out of 74 (16.2%), it provided suspicion for malignancy (TIR 4); in 54 of 74 (73%), it was definitively positive for malignancy (TIR 5); and in 8 of 74 (10.8%) cases, it was suggestive for TL. In 19 (20%) cases, FNAC was not diagnostic (TIR 1), likely due to the presence of necrotic material and inflammatory cells not clearly identifiable during the neck US; in two cases (2.1%), an indeterminate cytology was obtained (TIR 3).

Conversely, CNB was able to diagnose the malignant lesion in all but three cases (92/95, 96.8%). As expected, in all diagnostic specimens, CNB was able to define the histotype of the malignancy, while FNAC did it in 16 of 74 (21.6%) cases ($p < 0.01$) (**Figure 2**).

ATC was diagnosed overall in 35 out of 95 (36.8%) cases by CNB. Conversely, FNAC was suspicious for or diagnostic of malignancy in most of the ATCs identified by CNB (29/35, 82.9%), but the specific diagnosis of ATC was only made in six of them (17.1%).

Similarly, FNAC was suspicious for or diagnostic of malignancy in 23 of 27 (85.2%) PDTCs identified by CNB, but the specific diagnosis of PDTC could not be established in any of them based on the cytological specimen.

Of the 13 cases of TL, 12 were correctly identified by CNB (92.3%). On the other hand, FNAC provided the correct diagnosis of TL in seven cases (53.8%), and another one (7.7%) was classified as thyroid malignancy (TIR 5), but it was not diagnostic in the other five (38.4%).

Six cases in the whole series had TGM (6.3%), and CNB showed that they were metastases from the kidney, colon, lung (two cases), and breast (two cases). Conversely, FNAC was inconclusive (TIR 1) in three cases, suspicious for malignancy in one case, and positive for malignancy in two cases, but in all of them, FNAC did not perform a correct histological diagnosis, only predicted it correctly.

Moreover, several other rare neck cancers (12/95, 12.6%) were diagnosed in our series (**Table 4**). In 9 out of 12 cases, FNAC was able to identify the malignancy of the lesion and, in two of them, also suggested the presence of squamous cell carcinoma. Conversely, in all cases of rare neck cancers, CNB correctly identified both the malignancy of the lesion and the histotype.

Comparison of the Results of CNB, FNAC, and Histology

In 24 of 95 (25.2%) patients, surgery was performed because there was no preoperative evidence of cervical bundle and massive esophageal and/or tracheal infiltration, as assessed by CT scan, bronchoscopy, and esophagoscopy. In this subgroup, we compared the histology and the results of both CNB and FNAC.

As shown in **Table 5**, in 20 out of 24 (83.3%) cases, the CNB results were concordant with those of histology, while in 3 of 24

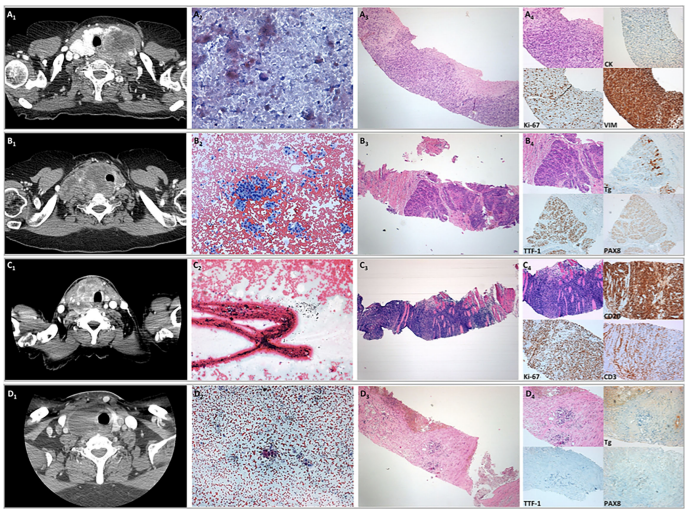

FIGURE 1 | Correlation of the results of CT scan with those of fine needle aspiration cytology (FNAC), core needle biopsy (CNB), and specific immunohistochemical staining for anaplastic thyroid carcinoma (ATC), poorly differentiated thyroid cancer (PDTC), thyroid lymphoma (TL), and thyroid gland metastases (TGM) of lung adenocarcinoma. **(A)** Representative cytological and histological images of a case of ATC. (*A1*) CT scan with i.v contrast imaging. (*A2*) FNAC sample showing a few isolated atypical cells in a necrotic background (original magnification, ×40; Papanicolaou staining). (*A3*) CNB provided a tissue fragment composed of malignant undifferentiated neoplasia (original magnifications, ×4 and ×10; H&E staining). (*A4*) Immunohistochemical staining showing neoplastic cells with a high proliferative index, immunoreactivity for vimentin, and patchy weak immunopositivity for cytokeratins. **(B)** Representative cytological and histological images of a case of poorly differentiated thyroid carcinoma. (*B1*) CT scan with i.v contrast imaging. (*B2*) FNAC sample showing numerous groups of follicular cells with moderate nuclear atypia (original magnification, ×10; Papanicolaou staining). (*B3*) CNB showing neoplastic cells arranged in solid and trabecular architecture (original magnifications, ×4 and ×10; H&E staining). (*B4*) Immunohistochemical staining showing focal weak immunoreactivity for thyroglobulin and diffuse immunoreactivity for TTF-1 and PAX8. **(C)** Representative cytological and histological images of a case of TL. (*C1*) CT scan with i.v. contrast imaging. (*C2*) FNAC sample not diagnostic for the presence of extensive crush artifacts (original magnification, ×20; Papanicolaou staining). (*C3*) CNB provided a fragment of tissue composed of muscular tissue with intense lymphoid infiltration (original magnifications, ×4 and ×10; H&E staining). (*C4*) Immunohistochemical staining showing that neoplastic cells were CD20 positive and CD3 negative with high proliferative indices compatible with B-cell lymphoma. **(D)** Representative cytological and histological images of a case of carcinoma of extra-thyroid origin. (*D1*) CT scan with i.v contrast imaging. (*D2*) FNAC sample showing a few groups of epithelial cells with marked nuclear atypia (original magnifications, ×10 and ×40 in the *insert*; Papanicolaou staining). (*D3*) CNB showing a few clusters of neoplastic cells interspersed in fibrotic stroma (original magnifications, ×4 and ×10; H&E staining). (*D4*) Immunohistochemical staining showing the absence of immunoreactivity for thyroglobulin, TTF-1, and PAX8, suggesting an extra-thyroid origin.

(12.5%) cases, CNB showed a PDTC, but the histology demonstrated the presence of ATC. In only one case of those treated with surgery was the material obtained by CNB inadequate to reach a specific histological diagnosis.

Regarding FNAC, the cytological material was inadequate to reach a diagnosis in three cases (TIR 1), in one case showed an indeterminate lesion (TIR 3), and in 20 out of 24 (83.3%) cases was suggestive or suspicious for malignancy not further characterized. Overall, the ability of FNAC to define the histotype concordantly with histology was observed in only three cases (12.5%) (**Table 5**).

Complications Related to FNAC or CNB

In our series, no complications related to FNAC and CNB were experienced during and after the procedures.

DISCUSSION

Large thyroid masses, particularly if rapidly growing, represent a clinical challenge as they are often related to life-threatening events. In order to quickly reach a diagnosis and carry out appropriate treatments, several procedures have been proposed (3, 25). Surgical conventional biopsy achieves diagnosis in almost all cases, but it has several limitations. It may increase the morbidity and mortality, especially in the elderly, is time-consuming, is invasive, may cause tissue damage, and often requires hospital admission, general anesthesia, and potential transfer to the intensive care unit. Therefore, due to the surgical risk, this approach is not be suitable for all patients (26). Conversely, FNAC is usually the first type of biopsy chosen because it is more immediate, is performed without general anesthesia, and can allow the diagnosis of malignancy in >60% of ATC cases (27, 28). However, cytology, particularly in rare and high-grade malignant neoplasms, does not often give information about the histotype of the tumor, which is, indeed, necessary for the planning of further therapeutic procedures (29). Because of the presence of necrotic material and inflammatory cells in aspirates, we also had 20% of non-diagnostic cases, a higher prevalence when compared to the non-diagnostic FNAC commonly observed when thyroid nodules were submitted to the procedure in our center (30). This percentage of non-diagnostic cases could potentially be reduced by using cell block specimens on the FNA material. However, this is not a routine procedure,

TABLE 2 | Panel of the main immunohistochemical markers evaluated in our series of rapidly growing thyroid masses according to histology diagnosed by CNB (*n* = 89).

		ATC[a] (*n* = 33)	PDTC[a] (*n* = 26)	TL (*n* = 12)	SCC[b] (*n* = 7)	TGM (*n* = 6)	Other cancers (*n* = 5)
Pan-cytokeratins	+++	3 (9.1%)	4 (15.4%)	–	1 (14.3%)	2 (33.3%)	1 (20%)
	+/–	1 (3%)	–	–	–	1 (16.7%)	–
	Negative	10 (30.3%)	–	4 (33.3%)	1 (14.3%)	–	1 (20%)
	Not performed	19 (57.6%)	22 (84.6%)	8 (66.7%)	5 (71.4%)	3 (50%)	3 (60%)
Cytokeratin CAM 5.2	+++	12 (36.4%)	7 (26.9%)	–	3 (42.8%)	2 (33.3%)	–
	+/–	11 (33.3%)	1 (3.8%)	–	–	1 (16.7%)	–
	Negative	8 (24.2%)	1 (3.8%)	2 (16.7%)	–	1 (16.7%)	4 (80%)
	Not performed	2 (6.1%)	17 (65.4%)	10 (83.3%)	4 (57.2%)	2 (33.3%)	1 (20%)
Tg	+++	–	5 (15.2%)	–	–	–	–
	+/–	–	5 (15.2%)	–	–	–	–
	Negative	32 (97%)	16 (61.5%)	2 (16.7%)	7 (100%)	6 (100%)	5 (100%)
	Not performed	1 (3%)	–	10 (83.3%)	–	–	–
TTF-1	+++	1 (3%)	12 (46.2%)	–	–	–	–
	+/–	1 (3%)	2 (7.7%)	–	–	–	–
	Negative	30 (91%)	11 (42.3%)	1 (8.3%)	7 (100%)	6 (100%)	5 (100%)
	Not performed	1 (3%)	1 (3.8%)	11 (91.7%)	–	–	–
PAX-8	+++	3 (9.1%)	8 (30.8%)	–	–	–	–
	+/–	–	1 (3.8%)	–	2 (28.6%)	–	–
	Negative	7 (21.2%)	3 (11.5%)	–	–	2 (33.3%)	3 (60%)
	Not performed	23 (69.7%)	14 (53.8%)	12 (100%)	5 (71.4%)	4 (66.7%)	2 (40%)
PAX-5	+++	–	–	3 (25%)	–	–	–
	+/–	–	–	3 (25%)	2 (28.6%)	–	–
	Negative	–	–	–	–	–	–
	Not performed	33 (100%)	26 (100%)	6 (50%)	5 (71.4%)	6 (100%)	5 (80%)
Ki-67	>30%	7 (21.2%)	2 (7.7%)	7 (58.3%)	1 (14.3%)	–	1 (20%)
	5–30%	–	–	–	–	–	1 (20%)
	<5%	–	–	–	–	–	1 (20%)
	Not performed	26 (78.8%)	24 (92.3%)	5 (41.7%)	6 (85.6%)	6 (100%)	2 (40%)
CD45, other lymphoid markers	+++	–	–	12 (100%)	–	–	–
	+/–	–	–	–	–	–	–
	Negative	8 (24.2%)	1 (3.8%)	–	–	1 (16.7%)	–
	Not performed	25 (75.8%)	25 (96.2%)	–	7 (100%)	5 (83.3%)	5 (100%)

Other cancers include: angiosarcoma (n = 2), undifferentiated mesenchymal neoplasia (n = 2), and plasmacytoma (n = 1). +++ indicates positive staining; +/– indicates focal positive staining; and – indicates negative staining.

CNB, core needle biopsy; ATC, anaplastic thyroid cancer; PDTC, poorly differentiated thyroid cancer; TL, thyroid lymphoma; SCC, squamous cell carcinoma; TGM, thyroid gland metastasis; TTF-1, thyroid transcription factor 1.

[a]*In two ATC cases and one PDTC case, immunohistochemistry was not performed.*

[b]*In SCC, positivity for p40 and p63 was demonstrated in all CNB procedures.*

TABLE 3 | Results of the molecular analysis of 17 cases.

Histotype	Molecular analysis results[a]
ATC	*BRAF*, *H-RAS*, *K-RAS*, and *N-RAS* negative
ATC	*BRAF*, *H-RAS*, *K-RAS*, and *N-RAS*, and *RET/PTC* negative
ATC	*N-RAS* positive; *BRAF*, *H-RAS*, *K-RAS*, and *RET/PTC* negative
ATC	*N-RAS* positive; *BRAF*, *H-RAS*, *K-RAS*, *RET/PTC*, and *TERT* negative
ATC	*BRAF*, *H-RAS*, *H-RAS*, and *N-RAS* negative
ATC	*BRAF*, *H-RAS*, *K-RAS*, and *N-RAS* negative
PDTC	*BRAF*, *H-RAS*, *K-RAS*, *N-RAS*, *EGFR*, *HER-2*, and *PIK3CA* negative
PDTC	*NTRK* fusion (40% of the analyzed cells) positive; *BRAF*, *H-RAS*, *K-RAS*, *N-RAS*, and *TERT* negative
PDTC	*K-RAS* positive; *EGFR* negative
PDTC	*BRAF*, *H-RAS*, *K-RAS*, and *N-RAS* negative
PDTC	*BRAF*, *H-RAS*, *K-RAS*, *N-RAS*, *NTRK1/2/3*, *RET/PTC*, *PAX8/PPAR* gamma, and *TP53* negative
PDTC	*RET/PTC*, *ROS1*, and *EGFR* negative
PDTC	*BRAF*, *K-RAS*, and *EGFR* negative
PDTC	*BRAF* positive
TGM from colon carcinoma	*BRAF*, *H-RAS*, and *N-RAS* negative
TGM from lung carcinoma	*BRAF*, *K-RAS*, *EGFR*, *RET*, and *ROS-1* negative
TL	*MYC* translocation positive; *BCL* translocation negative

ATC, anaplastic thyroid carcinoma; PDTC, poorly differentiated thyroid carcinoma; TGM, thyroid gland metastasis; TL, thyroid lymphoma.

[a]*Specific molecular profiling was performed according to the histotype.*

TABLE 4 | Comparison of the results of FNAC and CNB in rapidly growing thyroid masses (n = 95).

			CNB						Total
			ATC	PDTC	TL	TGM[a]	Other Cancers[b]	Not Diagnostic	
FNAC	TIR 1	Not diagnostic	5	4	5	3	2	–	19 (20%)
	TIR 2	Benign	–	–	–	–	–	–	–
	TIR 3	Indeterminate	1	–	–	–	1	–	2 (2.1%)
	TIR 4	Suspicious carcinoma	4	4	–	1	2	1	12 (12.6%)
	TIR 5	ATC	6	–	–	–			55 (57.9%)
		Malignant neoplasia	19	19	1	2	5	1	
		Squamous cell carcinoma	–	–	–	–	2		
	TL		–	–	6	–	–	1	7 (7.4%)
Total			35 (36.8%)	27 (28.4%)	12 (12.6%)	6 (6.3%)	12 (12.6%)	3 (3.2%)	95 (100%)

FNAC, fine needle aspiration cytology; CNB, core needle biopsy; ATC, anaplastic thyroid carcinoma; PDTC, poorly differentiated thyroid carcinoma; TL, thyroid lymphoma; TGM, thyroid gland metastases.

[a]*Kidney, colon, lung (n = 2) and breast (n = 2).*

[b]*Angiosarcoma (n = 2), undifferentiated mesenchymal neoplasia (n = 2), squamous cell carcinoma (n = 7), and plasmacytoma (n = 1).*

the rate of non-diagnostic results could be slightly reduced (31), and, although commonly applied in our center in lung and liver lesions, it is not performed on thyroid nodules.

Several types of neoplasia were diagnosed in our series. Indeed, beyond ATC and PDTC, the most frequently diagnosed neoplasia on CNB (36.8% and 28.4%, respectively), TL (13.7%), TGM (6.3%), and other rare neck cancers (12.6%), such as angiosarcoma, mesenchymal neoplasia, squamous cell carcinoma, and plasmacytoma, were also diagnosed. Similar results were reported by Choi et al. (32), who performed FNAC and CNB in a series of 52 thyroid nodules clinically suspicious for TGM. Unlike in our study, FNAC and CNB were not performed in all cases; nevertheless, their study demonstrated the higher sensitivity of CNB *vs.* FNAC in the diagnosis of TGM.

It was clearly demonstrated that 18.9% (18/95) of these masses, although localized in the thyroid, were indeed either metastases from other types of tumors or quite rare tumors. However, none of them was identified by FNAC, but were clearly recognized by CNB, which is a true biopsy and allows the pathologist to perform immunohistochemistry, which can better characterize the origin of the tumor (33).

The role of CNB compared to FNAC has already been explored in the diagnosis of thyroid nodules, particularly in cytologically indeterminate lesions. Na et al. (34) evaluated 161 patients with indeterminate cytology and confirmed the higher sensitivity of CNB compared to FNAC in detecting malignancy. However, in our experience, the CNB procedure required that the nodule dimension be ≥3 cm, thus representing a limitation in its routine application. The higher sensitivity of CNB compared to FNAC in detecting malignancy was also confirmed in other human tumors (35–38).

Regarding large neck masses, in particular ATC, Ha et al. (26) evaluated the diagnostic performance of FNAC and CNB in a series of patients with ATC or TL. However, FNAC was performed in 83.8% and CNB in only 32.2% of the study group. The authors obtained 100% and 90.9% positive predictive values for CNB and FNAC in diagnosing ATC, respectively. In our series, the positive predictive values for ATC diagnosis were 100% and 17.1% and for TL diagnosis

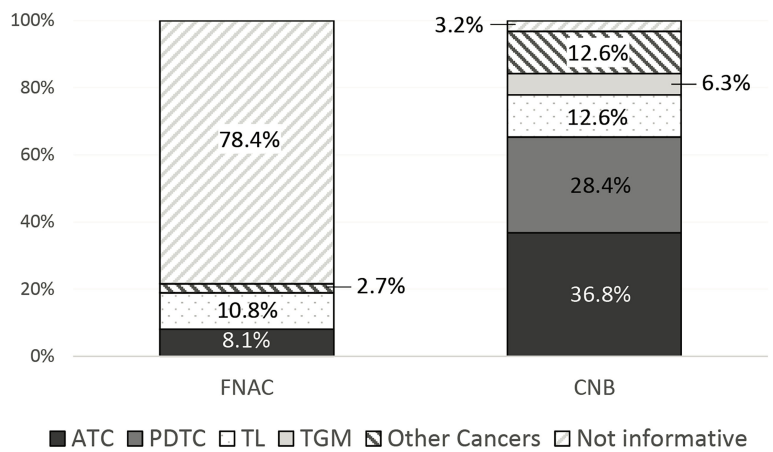

FIGURE 2 | Diagnostic ability of fine needle aspiration cytology (FNAC) and core needle biopsy (CNB) in identifying tumor histotype.

TABLE 5 | Diagnostic performance of FNAC and CNB compared with histology in patients treated with surgery (n = 24).

Patient	Age (years)	Sex	FNAC	FNAC histotype definition	CNB	CNB histotype definition	Histology
1	63	F	TIR 3	No	Undifferentiated mesenchymal neoplasia	Yes	Undifferentiated mesenchymal neoplasia
2	63	M	TIR 4	No	SCC	Yes	SCC
3	57	F	TIR 5	No	PDTC	Yes	PDTC
4	60	M	TIR 4	No	PDTC	Yes	PDTC
5	70	F	TIR 5	No	PDTC	Yes	PDTC
6	68	M	TIR 5	No	PDTC	Yes	PDTC
7	56	F	TIR 5	No	PDTC	Yes	PDTC
8	33	M	TIR 5	No	PDTC	Yes	PDTC
9	70	M	TIR 5	No	PDTC	Yes	PDTC
10	62	M	TIR 5	No	PDTC	Yes	PDTC
11	45	M	TIR 5	**Yes**	PDTC	Yes	PDTC
12	40	M	TIR 4	**Yes**	Not diagnostic	No	PDTC
13	82	M	TIR 1	No	PDTC	Yes	ATC
14	70	F	TIR 4	No	PDTC	Yes	ATC
15	53	F	TIR 4	No	PDTC	Yes	ATC
16	78	M	TIR 1	No	ATC	Yes	ATC
17	68	M	TIR 4	No	ATC	Yes	ATC
18	62	F	TIR 1	No	ATC	Yes	ATC
19	52	F	TIR 5	No	ATC	Yes	ATC
20	72	F	TIR 5	**Yes**	ATC	Yes	ATC
21	63	F	TIR 4	No	ATC	Yes	ATC
22	58	F	TIR 5	No	ATC	Yes	ATC
23	91	F	TIR 5	No	ATC	Yes	ATC
24	47	F	TIR 5	No	ATC	Yes	ATC

FNAC, fine needle aspiration cytology; CNB, core needle biopsy; ATC, anaplastic thyroid carcinoma; PDTC, poorly differentiated thyroid carcinoma; SCC, squamous cell carcinoma.

were 92.3% and 61.5% for CNB and FNAC, respectively. Moreover, unlike in our study, their data were retrospectively collected, CNB was performed in only a minority of cases, and only in a few patients (8.1%) were CNB and FNAC simultaneously performed.

In our series, in the 24 cases submitted to surgery, the correlation between the CNB and histology results was very high since in only 12% of the cases was it slightly discordant. This could be, at least in part, due to the heterogeneity of the ATC, being either of pure anaplastic origin or deriving from the dedifferentiation of a preexisting PTC (3). In any case, this discordance did not play any role in the management of the patients. In the era of precision medicine, in which treatments are targeted against specific genes and mutations of the tumor, the ability to perform a rapid and correct histological diagnosis cannot be overlooked. Indeed, particularly in ATC cases, in which a definitive cure is unlikely with standard treatments, the molecular signature of the neoplasia could improve the outcome of patients harboring actionable mutations (i.e., *BRAF* V600E) (24, 39), as well as in a neoadjuvant setting (40). In our series, although the material obtained from CNB was optimal to perform molecular analysis in most cases (96.8%), it was performed in only 17.9%. This quite low frequency of analyzed cases is not unexpected since the knowledge about the impact of molecular analysis on the treatment of patients with ATC is quite recent (41). Molecular analysis could also be performed on cytological material (42); however, in several cases, cytology does not provide correct information on the histotype, limiting the choice of genetic profile to be analyzed. Conversely, when the histology is known, as in most cases of CNB, a specific molecular profile can be studied, being different not only according to different tumors (43) but also in the context of different thyroid tumors (44, 45). Accordingly, in metastatic malignancies for which the primary site is unknown, the key role of CNB compared to FNAC has been clearly demonstrated, both in clarifying the primary site of the tumor and in obtaining sufficient material to perform the molecular analysis (8, 46).

CNB is a safe and well-tolerated procedure associated with a low incidence of complications when performed in expert hands (47). However, several potential complications have been reported, such as hematoma, voice change, infection, edema, vasovagal reaction, hemoptysis, and dysphagia (34, 48, 49). In a large single-center study, in which CNB was performed on 6,687 thyroid nodules, very few major (0.06%) and minor (0.79%) complications were described (50). Also, in other studies, low rates of major complications, such as bleeding and tumor cell seeding, were observed (51).

These findings are in accordance with our experience, although in the different setting of large thyroid masses, we did not experience any complications related to the CNB procedure. However, to minimize complications, CNB should be performed by well-trained physicians, under real-time US guidance and with a good awareness of neck anatomy and potential complications (52).

To our knowledge, this is the first prospective study comparing the diagnostic performance of FNAC and CNB in a large series of rapidly growing thyroid masses. The main limitation of our study was that it was performed in a tertiary referral center for the treatment of thyroid cancer, therefore making our results not completely reproducible in routine clinical practice. However, it is recommended that these rare thyroid masses should be managed in referral centers able to perform these kinds of procedures. Conversely, the strengths of

this study included the large number of patients enrolled; the use of neck US to identify the areas suitable for biopsy, avoiding the presence of tissue necrosis and inflammation; and the simultaneous use of both FNAC and CNB on the same patient, at the same time, from the same skin incision.

CONCLUSIONS

In conclusion, our study demonstrates that CNB is a safe procedure able to optimize the diagnostic times and to obtain an early histological diagnosis, which is fundamental to starting an early and specific treatment. Moreover, the CNB sample can also be immediately analyzed for its molecular profile, with the great advantage that, if a druggable mutation is revealed, a more specific and active drug can be immediately started. This evidence strongly supports the official introduction of CNB in routine clinical practice for the diagnosis of large and rapidly growing thyroid masses.

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 Comitato Etico Area Vasta Nord Ovest (CEAVNO). The patients/participants provided written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AM, LDN, RE, and GM: conceptualization, methodology and data curation. LDN, AA, PP, CEA, and GM: surgical procedures. RC: imaging revision. LT, CU, and FB: cytological and histological analysis. AM and LDN: formal analysis. AM, LDN, AA, PP, CEA, EM, RE, and GM: investigation. AM, LDN, and RE: writing—original draft preparation. All authors: writing—review and editing. RE and GM: supervision. All authors contributed to the article and have read and approved the submitted version.

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Aggressiveness of Differentiated Thyroid Carcinoma in Pediatric Patients Younger Than 16 years: A Propensity Score-Matched Analysis

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Background: The biological behavior of thyroid cancer in children has been known to be different from that in adults. We sought to understand the differences between DTC presentation in pediatric (<16 years) and adult patients, to guide better prognosis and clinical treatments.

Methods: This retrospective study included 48 pediatric patients younger than 16 years who underwent initial thyroid surgery and were diagnosed with DTC between January 1992 and December 2014 at Yonsei University in Seoul, South Korea. For a 1:4 propensity score-matched analysis, adult patients with matched sex and cancer size were included.

Results: The mean age was 12.54 ± 3.01 years. Total thyroidectomy (70.8%) without lateral lymph node dissection (47.9%) was the most commonly performed surgery. Central (73.9%) and lateral neck node metastases (62.5%) were common; distant metastasis was observed in 2 (4.2%) patients and recurrence occurred in 11 (22.9%). In propensity score-matched analysis, central lymph node metastasis and lateral neck node metastasis were significantly more frequent in pediatric patients. Symptoms were more common in the pediatric group than in the adult group ($p < 0.001$). In stratified cox regression, pediatric patients were more likely to experience recurrence [HR 5.339 (1.239–23.007)]. In stratified log-rank analysis, recurrence-free survival was significantly different between the adult and pediatric groups ($p = 0.0209$).

Conclusion: DTC in the pediatric group revealed more aggressive patterns than in the adult group with the same cancer size. Central lymph node metastasis and lateral neck node metastasis were more frequent. Stratified log-rank analysis revealed that recurrence was significantly higher in pediatric patients than in matched adult patients.

Keywords: thyroid cancer, pediatric thyroid cancer, differentiated thyroid cancer, propensity score matched analysis, papillary thyroid cancer

INTRODUCTION

Among thyroid carcinomas, differentiated thyroid cancer (DTC) in childhood is one of the most common endocrine cancers in pediatric patients, accounting for 90%–95% of all pediatric thyroid carcinomas (1, 2). The most common histopathological diagnosis is papillary carcinoma, followed by follicular variant of papillary thyroid carcinoma. In 66% of the reports, multifocality has been reported (3). Since it only accounts for 1.8% of all thyroid malignancies, the treatment approaches historically have been extrapolated only from adult experiences (4, 5).

The incidence of pediatric DTC has been increasing gradually for the last few decades both in Korea and throughout the world (6–10). Its incidence is almost always higher in female patients (8). The increasing incidence has been reported to be associated with radiation exposure in children (11, 12). Many reports focused on the occurrence of papillary thyroid cancer (PTC) after the nuclear reactor accident in Chernobyl in 1986 (13–15). Treatment for a prior malignancy and a history of thyroiditis were identified as common features of pediatric thyroid cancer, suggesting thyroid cancer as a second malignancy in childhood cancer survivors (16).

The biological behavior of pediatric thyroid cancer is known to be different from that in adult patients; it has been suggested that it presents at a more advanced stage in prepuberty than in puberty (17). Younger pediatric patients are associated with a larger mean tumor size, more aggressive pathological features, and higher incidence of loco-regional and distant metastasis (18, 19). The patients first presented with symptoms such as neck swelling with a palpable mass or discomfort (3, 20).

Until now, the reported risk factors for poor prognosis are younger age, male sex, large primary tumor size, extrathyroidal tumor extension, palpable lymph nodes, distant metastases at diagnosis, and diffuse sclerosing pathology (19, 21). Despite the aggressive disease presentation and higher risk of recurrence, pediatric thyroid cancer is associated with an excellent prognosis (22–25).

Total thyroidectomy and radioactive iodine are recommended as the best management options to reduce the incidence of lung metastasis (22. One study also suggests more extensive cervical lymph node dissection with thyroid stimulating hormone (TSH) suppression therapy since young patients present with more lymph node metastasis (19). Treatment for pediatric thyroid cancer is still controversial because of these reasons.

Most previous studies on pediatric thyroid cancer also included adolescent patients; thus, we aimed to study DTC features in pediatric patients younger than 16 years.

MATERIAL AND METHODS

Study Patients

This retrospective cohort study initially included 48 pediatric patients (<16 years of age) who underwent initial thyroid surgery and were diagnosed with DTC between January 1992 to December 2014 at Yonsei University in Seoul, South Korea. Four patients were excluded from the study since they had missing information regarding pathology and clinical characteristics, i.e., a total of 48. Since the electronic chart system was introduced only in 2003, adult patients were enrolled from January 2003 to December 2014 for propensity score-matched analysis. To minimize the bias from differences in follow-up duration, for the matched analysis, data of only pediatric patients from January 2003 to December 2014 were analyzed, amounting to 37 patients in total.

Ethics Consideration

Written informed consent by the patients was waived due to the retrospective nature of the study. The study protocol was approved by the Institutional Review Board of Yonsei University (IRB 3-2019-0281), Seoul, South Korea.

Statistical Analysis

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R statistics 4.0.2 (http://www.r-project.org). We conducted 1:4 matching using propensity score, selecting adult patients with the same tumor size and sex.

Continuous variables included mean and standard deviation, and categorical variables included frequency and percentage. To compare continuous and categorical variables between two groups, a generalized estimated equation was used. Recurrence-free survival curves were plotted using the Kaplan-Meier method, and the stratified log-rank test was performed to compare the recurrence rate between pediatric and adult patients. To evaluate risk factors for recurrence, stratified Cox regression was performed and are presented as hazard ratio (HR) and 95% confidence interval (CI). P-values of <0.05 were deemed to indicate statistical significance.

RESULTS

The baseline clinical characteristics of the 48 included patients are shown in **Table 1**. The incidence of DTC was higher in female patients (77.1%), and the mean age was 12.54 ± 3.01 years.

The most common presenting symptom was a neck mass (60.4%). Most of the patients (85.4%) did not have a family history of thyroid cancer. Total thyroidectomy (70.8%) without lateral lymph node dissection (47.9%) was the most commonly performed surgery. Papillary thyroid cancer (87.5%) followed by follicular cancer (12.5%) were the most common diagnoses. Central (73.9%) and lateral neck node metastases (62.5%) were common. Further, distant metastasis was observed in 2 (4.2%) patients and recurrence occurred in 11 (22.9%) patients.

We performed 1:4 propensity score matching with adult patients with matched sex and tumor size; the results are shown in **Table 2**. Pediatric patients were more likely to be symptomatic than adult patients ($p < 0.001$). There were no differences regarding family history and surgical extent. Histology was not significantly different when distinguished into papillary and follicular cancer. However, further dividing into histological variants of papillary thyroid cancer showed significant difference. Diffuse sclerosing variant of papillary thyroid carcinoma was more frequent in pediatric thyroid cancer [9/34 (26.5%) vs 6/145 (4.1%)]. Central lymph node metastasis [27 (73.0%) vs 69 (46.6%)] and lateral neck node metastasis were significantly more frequent in pediatric patients than in matched adult patients. There were no significant differences in distant metastasis and use of RAI therapy. Recurrence was significantly more frequent in pediatric patients than in adult patients (13.5% vs 2%, $p = 0.0131$).

In univariable stratified cox regression analysis, pediatric patients were more likely to experience recurrence. Pediatric patients had approximately 5.4 times the risk of recurrence than adult patients [HR 5.339 (1.239–23.007)]. Multiplicity of disease was associated with recurrence compared with a single disease [HR 264.171 (3.219–21678.05)]. In multivariable analysis, only multiplicity was associated with recurrence (**Table 3**).

In stratified log-rank analysis, recurrence-free survival was significantly different between the adult and pediatric groups ($p = 0.0209$; **Figure 1**).

TABLE 1 | The baseline clinical characteristics of 48 pediatric patients.

Clinicopathologic features		N=48 (%)
Age (years)		12.54 ± 3.01
Sex	**Male**	11 (22.9)
	Female	37 (77.1)
Tumor size (cm)		2.42 ± 1.45
Presenting symptom	**None**	18 (37.5)
	Mass	29 (60.4)
Family History	**No**	41 (85.4)
	Thyroid cancer	4 (8.3)
	Non-thyroid cancer	3 (6.3)
OP	**Less than total**	14 (29.1)
	Total	34 (70.8)
LND	**None**	23 (47.9)
	Unilateral	14 (29.2)
	Ubilateral	6 (12.5)
	Selective	2 (4.2)
	mediastinal	3 (6.3)
Histology	**Papillary**	42 (87.5)
	Conventional	29/42 (69.0)
	Diffuse sclerosing variant	10/42 (23.8)
	Not otherwise specified	3/10 (7.2)
	Follicular	6 (12.5)
Central node metastasis		34 (73.9)
Lateral neck node metastasis		30 (62.5)
Distant metastasis		2 (4.2)
RAI therapy		31 (64.6)
Recurrence		11 (22.9)
F/u months		158 ± 83

DISCUSSION

To the best of our knowledge, this is the first study to examine such a large number of young pediatric patients under the age of 16 years with propensity score matching. Previous studies also included adolescent patients and did not consist of pediatric patients solely (8, 16, 20, 26, 27).

Pediatric DTC is an uncommon malignancy. Although the disease is more aggressive and presents at more advanced stages in this group, the overall prognosis is known to be excellent. Our results show that pediatric patients younger than 16 years have a higher risk of recurrence than adult patients with the same tumor size and matched sex. Pediatric patients showed significantly more central node metastasis and lateral neck node metastasis, which could have had an impact on the higher recurrence probability.

Pediatric patients were reported to have larger lesions than adult patients (median 23.6 vs 19.3 mm), with more frequent lymph node metastases (67.8% vs 42.1%) and distant metastases (19, 28). In this study, pediatric patients were matched to adult patients with the same tumor size to overcome this difference. Young patients were significantly more likely to undergo second treatment such as surgery and radiotherapy. The rate of mutations in the proto-oncogene BRAF was significantly higher in adult patients than that in pediatric patients with PTC (28).

Sherman et al. (29) noted the significance of tumor size; the small size of the thyroid gland in children can lead to earlier extrathyroidal spread of the disease. However, extrathyroidal extension was not more frequent in our study. Reports have shown that although DTC presented more aggressively at the time of diagnosis in children, intensive management elicits a similar clinical outcome in both children and young adults (18, 22). A study comparing patients younger than 10 years, and pediatric patients older than 10 and younger than 18 years, noted no significant differences in tumor size or aggressiveness; they suggested that younger children are more likely to have lymph node metastasis at presentation as well as subsequent metastases (16, 25). Our study showed that pediatric patients showed more aggressive patterns than adult patients with the same cancer size with more frequent central node and lateral node metastasis. More than half of the pediatric patients presented with cervical lymph node metastasis.

Lee et al. showed that the younger the patient at diagnosis, the higher the percentage of PTC, multifocality, ETE, LN metastasis, and lung metastasis. The age at diagnosis was not a predictor of

TABLE 2 | 1:4 Propensity score-matched GEE analysis.

		Pediatric (N=37)	Adult (N=148)	p-value
Age		12.76 ± 2.65	45.67 ± 13.19	<0.001
Sex	Male	7 (18.9)	31 (20.95)	>0.9999
	female	30 (81.1)	117 (79.05)	>0.9999
Size (cm)		2.22 ± 1.43	2.23 ± 1.43	>0.9999
Presenting symptom				<0.001
	None	17 (45.9)	120 (81.1)	
	Mass	19 (51.4)	25 (16.9)	
	Hoarseness	0	3 (2.0)	
	Other	1 (2.7)	0 (0.0)	
Family history				0.402
	No	30 (81.1)	134 (90.5)	
	Thyroid cancer	4 (10.8)	7 (4.7)	
	Non-thyroid cancer	3 (8.1)	7 (4.7)	
OP				0.561
	Less than total	9 (24.3)	30 (20.3)	
	Total	28 (75.7)	118 (79.7)	
LND				<0.001
	None	18 (48.7)	111 (75.1)	
	Unilateral	8 (21.6)	27 (18.2)	
	Bilateral	6 (16.2)	7 (4.7)	
	selective	2 (5.4)	0	
	mediastinal	3 (8.1)	3 (2.0)	
Histology				0.072
	Papillary	34 (91.9)	145 (98.0)	
	Conventional	24/34 (70.6)	111/145 (76.6)	<0.001
	Diffuse sclerosing variant	9/34 (26.5)	6/145 (4.1)	
	Follicular variant	0	22/145 (15.2)	
	others	0	6/145 (4.1)	
	Not otherwise specified	1/34 (2.9)	0/145	
	Follicular	3 (8.1)	3 (2.0)	
Multiplicity				0.836
	No	25 (67.6)	102 (68.9)	
	Unilateral	4 (10.8)	11 (7.4)	
	Bilateral	8 (21.62)	35 (23.7)	
T stage				0.317
T1		10 (27.0)	35 (23.6)	
T2		2 (5.4)	21 (14.2)	
T3		24 (64.9)	81 (54.7)	
T4		1 (2.7)	11 (7.4)	
Central node metastasis (N1a)		27 (73.0))	69 (46.6)	0.0008
Lateral neck node metastasis (N1b)		24 (64.9)	37 (25.0)	<0.001
Distant metastasis (M1)		1 (2.7)	3 (2.0)	0.817
RAI therapy		25 (67.6)	114 (77.0)	0.210
Recurrence		5 (13.5)	3 (2.0)	0.0131
Time to recur (days)		1323 ± 1384	678 ± 182	0.2497
F/u months (days)		3688 ± 1281	2695 ± 1143	<0.001

recurrence-free survival, suggesting that multifocality rather than age at diagnosis is an important predictor for recurrence (20). Chaukar et al. suggested a correlation between hormonal influence during puberty and an increased risk of thyroid carcinoma. They observed a near equal distribution of female and male patients in the prepubertal age group (1.5:1), whereas the ratio in patients of 13 to 17 years of age was 3:1, which could suggest a hormonal influence. Since thyroid carcinoma is known to be TSH-dependent, any condition leading to an increase in circulating TSH level in the blood may be associated with an increased risk of thyroid cancer (22). Another study showed that female patients predominantly presented with DTC, although the ratio in the young group was higher, suggesting an association with sex hormone factors (19).

Race was identified as an independent predictor in multivariate analysis, suggesting that non-Caucasian patients are at higher risk of recurrence than Caucasians. Pediatric PTC was associated with lateral node involvement (30). This could somehow explain the higher incidence of recurrent pediatric cancer in our study since our study population only comprised Korean patients, and pediatric patients showed frequent lateral lymph node involvement.

In our study, central lymph node metastasis and lateral neck node metastasis were more frequent. An aggressive operative approach to lymph node resection in experienced hands may be safer when considering complication and recurrence rates compared with less complete resection at a lower volume center (30).

TABLE 3 | Stratified Cox regression to evaluate risk factors for recurrence.

Variable	Univariable model		Multivariable model	
	HR (95%CI)	p-value	HR (95%CI)	p-value
Pediatric patient (age 0-15)				
No	Ref			
Yes	5.339 (1.239-23.007)	0.0246	2.937 (0.233-36.974)	0.4045
OP name				
Less than total	Ref			
Total	6.213 (0.193-200.173)	0.3026		
Histology				
Papillary	Ref			
Follicular	0.474 (0.005-46.611)	0.7498		
Central lymph node metastasis				
No	Ref			
Yes	13.094 (0.565-303.675)	0.1088		
Lateral lymph node metastasis				
No	Ref			
Yes	17.617 (0.801-387.621)	0.0689		
Multiplicity				
No	ref			
Unilateral	264.171 (3.219-21678.05)	0.0131	55.092 (1.640-1850.663)	0.0254
Bilateral	18.946 (0.780-460.079)	0.0707	6.712 (0.491-91.702)	0.1535

In young children, more stable and progressive disease forms were noted, showing higher cure rates in adolescents (19). Disease-free survival was significantly shorter in the children group than that in the adolescent group, but no significant difference was found in cancer-specific survival between these two groups (25). A previous study on the initial and dynamic risk stratification of pediatric patients showed that reflecting the extent of disease by tumor size, localized invasion, and the number and size of cervical LN metastases was useful for predicting the risk of structurally persistent or recurrent disease (31). Using the Kaplan-Meier analysis, we observed that the incidence of recurrence was significantly higher in the pediatric group than in the matched adult group.

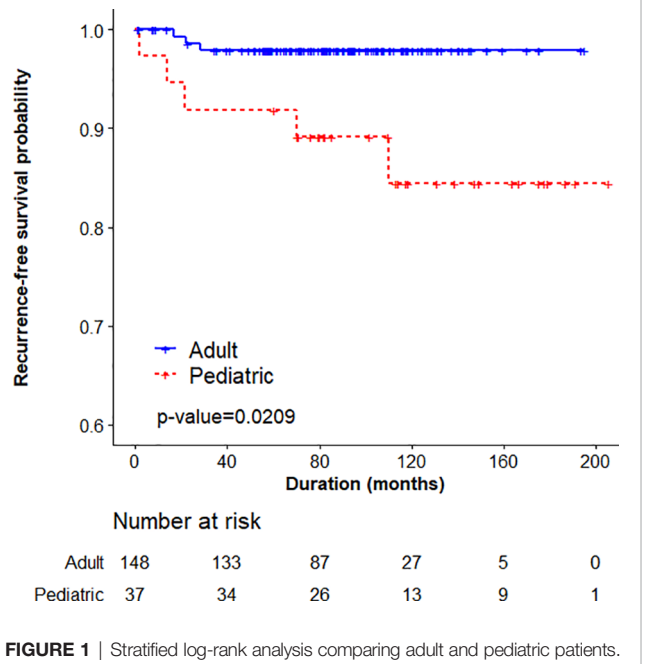

FIGURE 1 | Stratified log-rank analysis comparing adult and pediatric patients.

According to the ATA management guidelines for children, total thyroidectomy remains the treatment of choice for pediatric patients with thyroid cancer (32). A study reported that comparable surgical outcome was seen with lobectomy instead of total thyroidectomy in patients with limited disease, such as those with tumors smaller than 2 cm, no lymph node metastasis, and no multifocal disease (27). Considering our results wherein the mean tumor size was 2.33 ± 1.39 cm and the fact that the central node metastasis (73.9%) and lateral neck node metastasis (64.6%) rates were quite high, patients suitable for lobectomy may be rare. Our results suggest that young patients should undergo more thorough preoperative analysis to decide the extent of surgery since loco-regional and distant metastasis may be more frequent.

This study has several limitations, including small sample size, single institution and limitations inherent to retrospective nature of the study. Molecular analysis should be included in future studies.

CONCLUSION

Pediatric patients showed more aggressive patterns than adult patients with the same cancer size. Central lymph node metastasis and lateral neck node metastasis were more frequent. Recurrence was more significantly observed in stratified log-rank analysis in pediatric patients than in matched adult patients.

There is a need for prospective, collaborative multicenter studies. Future prospective multicenter pediatric studies are required to answer questions regarding the natural history of this condition in pediatric patients.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: personal data. Requests to access these datasets should be directed to kimsuy@aumc.ac.kr.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Yonsei University (IRB 3-2019-0281), Seoul, South Korea. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SYK, YSL, SMK, HSC, CSP contributed to the conception and design of the study. SYK, HJY and HC organized the database. SL and SJ performed the statistical analyses. SYK wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Preoperative Thyroid Peroxidase Antibody Predicts Recurrence in Papillary Thyroid Carcinoma: A Consecutive Study With 5,770 Cases

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Background: Thyroid autoimmunity is common in papillary thyroid carcinoma (PTC) and was believed to confer a better prognosis; however, controversy still remains. This study aimed to investigate the prognostic value of chronic lymphocytic thyroiditis (CLT) and preoperative thyroid peroxidase antibody (TPOAb) in PTC patients.

Methods: A retrospective analysis was performed on 5,770 PTC patients who underwent surgical treatment with pathologically confirmed PTC in our institution between 2012 to 2016. The patients were divided into groups with respect to the coexistence of CLT or preoperative TPOAb levels. The clinicopathological characteristics and disease-free survival (DFS) rates were compared between the groups.

Results: The coexistence of CLT was likely to have bilateral, multifocal tumors. Particularly, PTC patients with TPOAb++ (>1,000 IU/L) had a larger tumor size (p = 0.007) and higher rates of bilaterality and multifocality than those with TPOAb– (TPOAb< 100 IU/L), while for lymph node metastasis and extrathyroidal extension, there is no statistical difference. Tumor recurrence was found in 15 of 425 (3.5%), 9 of 436 (2.1%), and 56 of 3,519 (1.6%) patients with TPOAb++, TPOAb+, and TPOAb–, respectively (p = 0.017). On univariate analysis, TPOAb++ was correlated with tumor recurrence, with a hazard ratio of 2.20 [95% confidence interval (CI), 1.25–3.89], which remained as an independent risk factor at 1.98 (95% CI, 1.10–3.55) on multivariate analysis. PTC patients with TPOAb++ had the lowest DFS rates (96.5 *vs.* 97.9 *vs.* 98.4%, p = 0.020).

Conclusion: CLT is not a protective factor in PTC patients. We provide initial evidence that the preoperative TPOAb instead predicts recurrence in papillary thyroid carcinoma.

Keywords: thyroid peroxidase antibody, papillary thyroid carcinoma, recurrence, chronic lymphocytic thyroiditis, autoimmune thyroiditis

INTRODUCTION

Thyroid cancer ranks as the most common endocrine malignancy, and its overall incidence increases annually (1, 2). Papillary thyroid carcinoma (PTC) is the predominant histological type, representing more than 90% of all thyroid cancer cases (3). Chronic lymphocytic thyroiditis (CLT) is an autoimmune disease accompanied by the presence of thyroid autoantibody in the blood plasma (4). The prevalence of CLT in PTC has been reported to range from 5 to 38% (5–7). However, the relationship between CLT and PTC remains in dispute. Early studies suggested that preexisting CLT promoted the tumorigenesis of PTC (8–10), but it appeared to confer a better prognosis (8, 11–15). In contrast, some other studies showed that CLT did not interfere with prognosis or even predicted poorer outcomes (16–18).

Thyroid peroxidase antibody (TPOAb) is a serological marker of CLT (19). Its levels can be measured preoperatively and quantitatively and may represent the degree of thyroid inflammation (19, 20). An elevated TPOAb level has been reported to be potentially associated with the development of thyroid cancer (21). However, whether preoperative TPOAb levels correlate with recurrence in PTC patients remains unclear.

In the current study, we aimed to investigate the clinical value of coexistent CLT in a cohort of 5,770 consecutive PTC patients. We also evaluated the clinicopathologic and prognostic significance of preoperative TPOAb levels in these cases. The large sample size provided us with an opportunity to study the prognostic effect of TPOAb levels in PTCs.

MATERIALS AND METHODS

Subjects

The medical records of 6,723 patients who underwent total or hemithyroidectomy with a final histopathological diagnosis of PTC at the First Affiliated Hospital, Zhejiang University School of Medicine (Hangzhou, China), from 2012 to 2016, were retrospectively reviewed. In total, 190 patients with a history of thyroidectomy, 141 patients with a history of thyroid disease or radiation exposure, and 622 patients lacking preoperative TPOAb levels were excluded. A total of 5,770 patients were finally included in the retrospective study (**Figure 1**). Among them, 2,775 (48.1%) cases underwent hemi-thyroidectomy, and 2,995 (51.9%) cases underwent total thyroidectomy. This study was approved by the Institutional Review Board of the First Affiliated Hospital, Zhejiang University School of Medicine.

Data Collection

The following clinical variables were collected from the registry: age, gender, preoperative serum levels of free triiodothyronine (FT3), free thyroxine (FT4), thyrotrophin (TSH), and TPOAb. TPOAb was measured by an automated chemiluminescent immunoassay system (Advia Centaur; Siemens, Munich, Germany) at 1 to 2 days before surgery. The postoperative pathological reports, including tumor size, bilaterality, multifocality, extrathyroidal extension (ETE), lymph node metastasis (LNM), and tumor stage (AJCC 8th), were also studied. According to previous studies, CLT was diagnosed based on either preoperative TPOAb higher than 100 IU/L or the presence of diffuse lymphocytic infiltration in the surrounding thyroid tissue (12, 22). For multifocal tumors, the maximum diameter was recognized as the tumor size. Additionally, we defined TPOAb+ when its serum level fell in between 100 and 1,000 IU/L (100 < TPOAb ≤ 1,000 IU/L) and defined TPOAb++ when the serum level was 10 times higher than the normal value (TPOAb > 1,000 IU/L). The normal ranges for the serum levels of FT4, FT3, TSH, and TPOAb were 10.45–24.38 pmol/L, 2.77–6.31 pmol/L, 0.380–4.340 mIU/L, and 0–100.0 IU/L, respectively, at our institution.

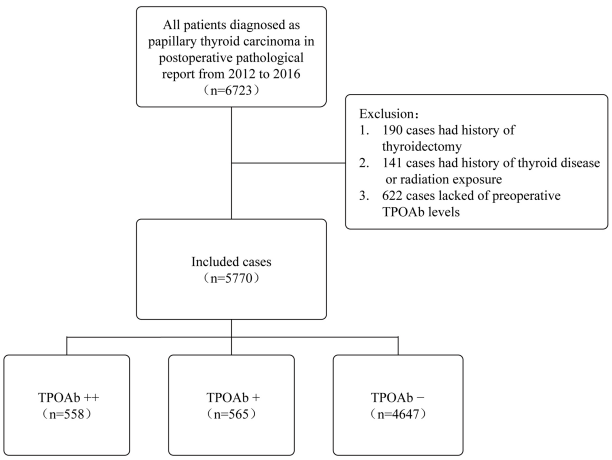

FIGURE 1 | Case selection process for this study. TPOAb, thyroid peroxidase antibody; TPOAb−, 0 < TPOAb ≤ 100 IU/L; TPOAb+, 100 < TPOAb ≤ 1,000 IU/L; TPOAb++, TPOAb > 1,000 IU/L.

At the end of the study, 4,380 patients were available for survival analysis. These patients were followed postoperatively with measurements of serum thyroglobulin and thyroglobulin antibody, neck ultrasound, and iodine-131 whole-body scans to monitor for disease recurrence and survival. The mean follow-up was 3.5 years (range, 1–5 years). A total of 696 (15.9%) cases received adjuvant radioactive iodine (RAI) treatment. Moreover, 80 of 4,380 patients (1.8%) were diagnosed with recurrent disease or metastases, including 17 in the thyroid bed, 60 in the cervical lymph nodes, and 3 with lung metastases. In most patients, recurrence was confirmed by pathologic examination, while 10 patients were diagnosed based on increased thyroglobulin levels and imaging evidence from iodine-131 scans.

Groups and Comparisons

The clinicopathological features and disease outcomes were assessed between the 2 groups according to the coexistence of CLT or not. Based on the preoperative TPOAb levels, we also divided all PTC patients into those with TPOAb−, TPOAb+, and TPOAb++ to investigate the prognostic values of different preoperative TPOAb levels.

Statistical Analysis

The SPSS 25.0 software was used for all statistical analysis. Statistical significance was defined as a 2-tailed *p*-value of less than 0.05. Continuous variables were presented as mean ± SD, and categorical variables were presented as the number of cases, with percentage (%). Pearson's chi-square test was used for categorical variables, and Student's *t*-test or one-way analysis of variance was used for continuous variables. The variables associated with clinical outcomes were evaluated using Cox proportional hazard models in univariate/multivariate analyses. Disease-free survival (DFS) curves were constructed using the Kaplan–Meier method, and the log-rank test was used to compare DFS.

RESULTS

Coexistent CLT Did Not Predict a Better Outcome in PTC Patients

CLT was present in 1,482 of 5,770 (25.7%) PTC patients, and their clinicopathologic characteristics are shown in **Table 1**. The PTC patients with CLT were significantly correlated with a younger age (43.9 ± 11.6 *vs.* 45.6 ± 11.8, $p < 0.001$), female gender (88.2 *vs.* 71.5%, $p < 0.001$), more bilateral (25.1 *vs.* 20.6%, $p < 0.001$) and multifocal (35.2 *vs.* 28.5%, $p < 0.001$) tumors as well as a higher proportion of early stage (AJCC 8th stage I: 93.6 *vs.* 91.3%, $p = 0.005$). No difference was observed between the 2 groups regarding the prevalence of ETE (10.1 *vs.* 10.3%, $p = 0.819$) and the frequency of LNM (39.8 *vs.* 38.1%, $p = 0.239$). For disease recurrence, however, we even found that PTC patients with CLT had a relatively higher recurrence rate than those without CLT, with borderline significance (2.5 *vs.* 1.6%, $p = 0.059$).

Preoperative TPOAb Levels Correlate With Aggressive Clinicopathological Features

TPOAb is the best serological marker of CLT. To further investigate the role of CLT in PTC, we stratified the PTC patients into TPOAb++, TPOAb+, and TPOAb− groups according to the preoperative TPOAb levels (**Table 2**). PTCs with higher TPOAb levels tended to exhibit a younger age (42.8 ± 11.7 *vs.* 44.5 ± 11.3 *vs.* 45.5 ± 11.8, $p < 0.001$), female preponderance (86.9% *vs.* 86.7% *vs.* 73.1%, $p < 0.001$), higher rates of bilaterality (28.7% *vs.* 24.4% *vs.* 20.6%, $p < 0.001$) and multifocality (38.2% *vs.* 35.4% *vs.* 28.6%, $p < 0.001$). However, there was no difference among the 3 groups regarding the prevalence of ETE (8.8% *vs.* 11.5% *vs.* 10.3%, $p = 0.320$) or LNM (40.1% *vs.* 39.3% *vs.* 38.2%, $p = 0.632$). Furthermore, we found that TPOAb ++ group was significantly characterized by younger age, female preponderance and more aggressive features: higher rates of bilaterality, multifocality, tumor size ≥ 10mm and recurrence. Additionally, we compared the levels of TPOAb with the pathological features on inflammation degree. Oxyphilic metaplasia, follicular atrophy or follicular disruption, which indicate high degree of thyroid inflammation (19), were more frequently found in TPOAb++ group. Accompanied higher TSH levels indicated more severe destruction of thyroid follicular cells in these patients. (**Supplementary Table S1**).

TABLE 1 | Clinicopathologic features of PTC patients with and without CLT.

Variables	PTC with CLT (*n* = 1,482)	PTC alone (*n* = 4,288)	*p*
Age (years)			
Mean ± SD	43.9 ± 11.6	45.6 ± 11.8	<0.001[a]
Age <55 years	1,217 (82.1%)	3,272 (76.3%)	<0.001[b]
Female, %	1,307 (88.2%)	3,064 (71.5%)	<0.001[b]
Bilaterality, %	372 (25.1%)	882 (20.6%)	<0.001[b]
Multifocality, %	522 (35.2%)	1,222 (28.5%)	<0.001[b]
Tumor sizec, *D* ≥10 mm, %	561 (37.9%)	1,425 (33.2%)	0.001[b]
ETE, %	150 (10.1%)	443 (10.3%)	0.819[b]
LNM, %	590 (39.8%)	1,633 (38.1%)	0.239[b]
AJCC 8th I, %	1,387 (93.6%)	3,913 (91.3%)	0.005[b]
Recurrence, %	28/1,132 (2.5%)	52/3,248 (1.6%)	0.059[b]

Statistically significant differences were defined as p < 0.05.

PTC, papillary thyroid carcinoma; CLT, chronic lymphocytic thyroiditis; D, diameter; ETE, extrathyroidal extension; LNM, lymph node metastasis.

[a]*Student's t-test.*

[b]*Pearson's chi-square test.*

Preoperative TPOAb ++ Was an Independent Risk Factor for Disease Recurrence

We then investigated the prognostic value of preoperative TPOAb levels. Tumor recurrence was found in 15 of 425 (3.5%), 9 of 436 (2.1%), and 56 of 3,519 (1.6%) PTC patients in the TPOAb++, TPOAb+, and TPOAb− groups, respectively ($p = 0.017$, **Table 2**). Univariate analysis revealed that age <55, bilaterality, multifocality, tumor size ≥10 mm, ETE, LNM, total thyroidectomy, RAI, and TPOAb++ were significantly associated with tumor recurrence (**Table 3**). By multivariate Cox analysis, LNM [hazard ratio (HR), 3.90; 95% CI, 1.20–8.00; $p < 0.001$], RAI (HR, 4.06; 95% CI, 2.20–7.49; $p < 0.001$), and TPOAb++ (HR, 1.98; 95% CI, 1.10–3.55; $p = 0.023$) were identified as independent risk factors for tumor recurrence.

Furthermore, we compared the Kaplan–Meier DFS curves with respect to the risk factors identified above. The 3.5-year DFS rates of those patients with tumor size ≥10 mm (96.5 *vs.* 99.1%, $p < 0.001$, shown in **Figure 2A**), ETE (95.4 *vs.* 98.5%, $p < 0.001$, shown in **Figure 2B**), and LNM (96.0 *vs.* 99.6%, $p < 0.001$, shown in **Figure 2C**) were significantly lower than those of the control group. It is noteworthy that the lowest DFS curve was documented in the TPOAb++ group compared with the TPOAb+ and TPOAb− groups (96.5 *vs.* 97.9% *vs.* 98.4%, $p = 0.020$, shown in **Figure 2D**).

DISCUSSION

CLT is frequently found in PTC, but its prognostic implication in PTC remains an active focus of research and is still under debate. Previous studies displayed that coexistent CLT was associated with a lower rate of ETE and lymph node metastasis in PTC

TABLE 2 | Clinicopathologic features of patients with PTC stratified by the status of TPOAb.

Variables	TPOAb			*P*	*p* for TPOAb–[a] *vs.*	
	++ (*n* = 558)	+ (*n* = 565)	– (*n* = 4647)		TPOAb+[a]	TPOAb++[a]
Age (years)						
Mean ± SD	42.8 ± 11.7	44.5 ± 11.3	45.5 ± 11.8	<0.001[b]	0.066	<0.001
Age <55 years	474 (84.9%)	463 (81.9%)	3,552 (76.4%)	<0.001[c]	0.003	<0.001
Female, %	485 (86.9%)	490 (86.7%)	3,396 (73.1%)	<0.001[c]	<0.001	<0.001
Bilaterality, %	160 (28.7%)	138 (24.4%)	956 (20.6%)	<0.001[c]	0.034	<0.001
Multifocality, %	213 (38.2%)	200 (35.4%)	1,331 (28.6%)	<0.001[c]	0.001	<0.001
Tumor size, *D* ≥10 mm	221 (39.6%)	208 (36.8%)	1,557 (33.5%)	0.007[c]	0.117	0.004
ETE, %	49 (8.8%)	65 (11.5%)	479 (10.3%)	0.320[c]	0.380	0.259
LNM, %	224 (40.1%)	222 (39.3%)	1,777 (38.2%)	0.632[c]	0.627	0.589
AJCC 8th I, %	530 (95.0%)	528 (93.5%)	4,242 (91.3%)	0.004[c]	0.081	0.003
Recurrence, %	15/425 (3.5%)	9/436 (2.1%)	56/3,519 (1.6%)	0.017[c]	0.408	0.005
TSH	2.20 (0.01–62.07)	1.94 (0.01–28.00)	1.66 (0.01–45.16)	<0.001[d]	<0.001	<0.001
FT4	15.0 (5.5–24.6)	15.4 (7.31–29.1)	15.4 (4.4–50.6)	<0.001[d]	0.353	0.043
FT3	4.7 (1.9–9.8)	4.7 (3.2–9.0)	4.8 (2.8–20.1)	<0.001[d]	<0.001	0.750

Statistically significant differences were defined as p < 0.05.

PTC, papillary thyroid carcinoma; TPOAb, thyroid peroxidase antibody; D, diameter; ETE, extrathyroidal extension; LNM, lymph node metastasis.

[a]*TPOAb–, 0 < TPOAb ≤ 100 IU/L; TPOAb+, 100 < TPOAb ≤ 1,000 IU/L; TPOAb++, TPOAb > 1,000 IU/L.*

[b]*One-way analysis of variance.*

[c]*Pearson's chi-square test.*

[d]*Mann–Whitney U-test.*

TABLE 3 | Association between recurrence and TPOAb levels of PTC patients.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*p*
Age <55	2.43 (1.17–5.04)	0.017	1.69 (0.80–3.56)	0.165
Female	0.77 (0.48–1.24)	0.278	0.96 (0.59–1.57)	0.871
Bilaterality	2.31 (1.48–3.61)	<0.001	0.77 (0.38–1.59)	0.484
Multifocality	2.46 (1.59–3.82)	<0.001	1.66 (0.82–3.37)	0.161
Tumor size, *D* ≥10 mm	3.70 (2.33–5.88)	<0.001	1.44 (0.85–2.43)	0.172
ETE	3.24 (1.97–5.34)	<0.001	1.44 (0.84–2.47)	0.191
LNM	9.82 (5.20–18.56)	<0.001	3.90 (1.20–8.00)	<0.001
Total thyroidectomy	3.49 (2.016–6.032)	<0.001	1.08 (0.54–2.16)	0.820
RAI	10.32 (6.49–16.41)	<0.001	4.06 (2.20–7.49)	<0.001
TPOAb+[a]	1.29 (0.64–2.61)	0.479	1.19 (0.58–2.44)	0.634
TPOAb++[a]	2.20 (1.25–3.89)	0.007	1.98 (1.10–3.55)	0.023

Statistically significant differences were defined as p < 0.05.

TPOAb, thyroid peroxidase antibody; PTC, papillary thyroid carcinoma; D, diameter; ETE, extrathyroidal extension; LNM, lymph node metastasis; RAI, radioactive iodine treatment.

[a]*TPOAb– is the reference for TPOAb+ and TPOAb++; TPOAb–, 0 < TPOAb ≤ 100 IU/L; TPOAb+: 100 < TPOAb ≤ 1,000 IU/L; TPOAb++: TPOAb > 1,000 IU/L.*

patients (12, 23), while very recently, Lee et al. found more frequent multifocality and ETE in PTC patients coexisting with CLT, but with a similar recurrence rate than those without CLT (17). In the present study with 5,770 cases, we demonstrated that CLT was not a protective factor for PTC patients. Coexistent CLT was instead attributed to a larger tumor size, bilaterality, multifocality, and a relatively lower DFS rate. Notably, a high preoperative TPOAb level (>1,000 IU/L) was identified as an independent risk factor for tumor recurrence in PTC patients. Our findings may be partially explained by a recent study which implied that lymphovascular and perineural invasion was more common in the PTCs with CLT group (24).

TPOAb is measurable preoperatively and regarded as a sensitive marker of CLT or thyroid autoimmunity (25). The discrepancy concerning the role of coexistent CLT in predicting the prognosis of PTC could partially result from the different degree of thyroid inflammation. Previous studies showed that an elevated TPOAb level might contribute to the development of thyroid cancer (26, 27), while a recent meta-analysis found that although positive TPOAb was associated with an increased risk of thyroid cancer, this association did not exist in some subgroups (28). They argued that the relation between positive TPOAb and the risk of thyroid cancer remained to be elucidated (28). On the other hand, elevated TPOAb appeared as a protective factor for lymph node metastasis (21, 29). However, Shen et al. argued that TPOAb positivity was a risk indicator for more metastatic cervical lymph nodes (30). Recently, Song et al. demonstrated that positive TPOAb was associated with less tumor recurrence in PTC patients (31). Not conducting a subgroup analysis according to the TPOAb values might account in part for these inconsistent conclusions. The levels of TPOAb have been demonstrated to correlate with the degree

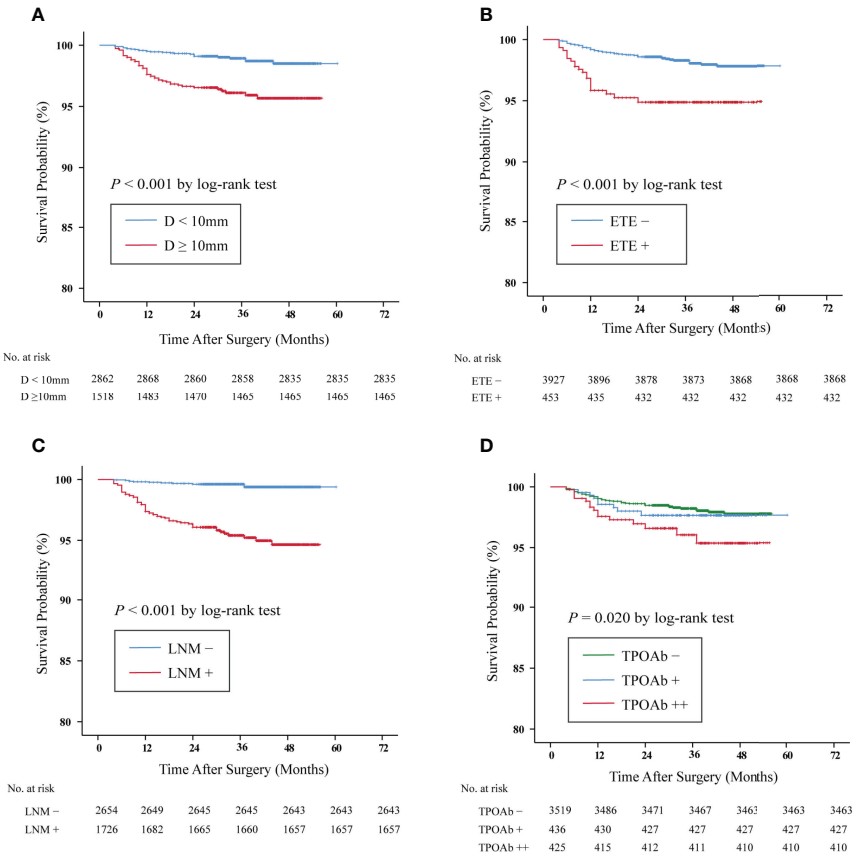

FIGURE 2 | Kaplan–Meier survival curves of disease-free survival (DFS) in papillary thyroid carcinoma (PTC) patients. The DFS rates of PTC patients with **(A)** tumor size ≥10 mm *vs.* <10 mm: 96.5 *vs.* 99.1%, $p < 0.001$. **(B)** Extrathyroidal extension (ETE) + *vs.* ETE–, 95.4 *vs.* 98.5%, $p < 0.001$. **(C)** Lymph node metastasis (LNM)+ *vs.* LNM–: 96.0 *vs.* 99.6%, $p < 0.001$. **(D)** The DFS rates of the TPOAb++ group were significantly lower than those of the TPOAb– group ($p = 0.020$ by log-rank test, TPOAb++ *vs.* TPOAb –, $p = 0.005$; TPOAb++ *vs.* TPOAb+, $p = 0.195$; TPOAb+ *vs.* TPOAb–, $p = 0.476$). TPOAb–, 0 < TPOAb ≤ 100 IU/L; TPOAb+, 100 < TPOAb ≤ 1,000 IU/L; TPOAb++, TPOAb > 1,000 IU/L.

of thyroid inflammation in autoimmune thyroiditis (19, 20). A higher level of TPOAb may represent a severe degree of inflammation. Here we graded the severity of autoimmune inflammation by preoperative TPOAb levels and found that TPOAb++ was an independent risk factor for disease recurrence. PTC patients with TPOAb++ exhibited the shortest DFS, indicating that a higher degree of thyroid inflammation could predict tumor recurrence in PTC patients.

The extent of initial thyroidectomy is a major concern when treating PTC patients, and it is usually determined by multiple factors. Here we found a much higher incidence of bilaterality and multifocality in patients with CLT (25.1 *vs.* 20.6 and 35.2 *vs.* 28.5%, respectively). Particularly, in patients with TPOAb++, the possibility of bilaterality and multifocality was as high as 28.7 and 38.2%. Therefore, total thyroidectomy may be favored in these PTC patients. However, it seems not rational to perform a more aggressive prophylactic cervical lymph node dissection for PTCs with CLT since the rate for lymph node metastasis was almost the same as that of patients without CLT (39.8 *vs.*38.1%).

The current study has some certain limitations. Primarily, it is a retrospective, single-institution study. In addition, because of the favorable prognosis of PTC, our follow-up period is not long enough to uncover the true prognostic significance. We plan to continue this study to obtain longer outcomes. Another limitation is that we do not have thyroglobulin antibody data, which could serve as another clinical marker for CLT (32). Lastly, the current study lacks information of genetic alterations like BRAF and RET/PTC rearrangements, which correlate with CLT and may impact the patients' outcomes.

In conclusion, our large retrospective cohort study demonstrated that CLT is not a protective factor in PTC patients. We instead provide new evidence that a high TPOAb level (>1,000 IU/L) correlates aggressive features, including larger tumor size, bilaterality, and multifocality, and is an independent risk factor for tumor recurrence. Hence, a preoperative evaluation of the TPOAb level is worthwhile for risk stratification and post-treatment surveillance in PTC patients.

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 Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

WW, LW, SC, LT, and ZL designed the current study and wrote the manuscript. WW, LW, ZM, and YD conducted the statistical analyses. WW, LW, SC, XS, ZM, YD, ZC, YC, JR, JY, JZ, and XT created the original databases to collect the clinicopathological data. TF, ZL, and LT reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Relationship Between Thyroid Autoantibodies and Recurrence of Papillary Thyroid Carcinoma in Children and Adolescents

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Background: Numerous studies reported connection between papillary thyroid carcinoma (PTC) and thyroid autoantibody in adults, but few of them have investigated whether there is a similar link in children and adolescents. The purpose of this research was to explore the relationship between clinicopathological features, prognosis and preoperative thyroid peroxidase antibody (TPOAb) as well as thyroglobulin antibody (TgAb) status in children and adolescents with PTC.

Methods : This study retrospectively reviewed 179 patients of PTC who underwent a thyroidectomy from January 2000 to June 2021 at Tianjin Medical University Cancer Hospital. We compared preoperative TgAb and TPOAb status with the clinicopathological features and prognosis of children and adolescents with PTC in different age groups.

Results: Patients with positive preoperative TPOAb and TgAb had lower recurrence rate in the younger group (*P* = 0.006, 0.047, respectively). Patients with positive TPOAb preoperatively had normal level of preoperative Tg and less cervical LNM than patients with negative TPOAb in children and adolescents (P < 0.05). Positive TPOAb preoperatively of PTC patients had a longer median DFS (113.4 months) than negative TPOAb (64.9 months) (P = 0.009, log-rank). Univariate analyses showed age, maximal tumor size, T stage, multifocality, lateral LNM and N staging were predictors for cancer recurrence in children and adolescents (P<0.05). Cox regression analysis found younger age (HR 0.224, P < 0.001), lateral LNM (HR 0.137, P = 0.010), N stage (HR 30.356, P < 0.001) were independent risk factors for recurrence.

Conclusions: Our study found that presence of preoperative TPOAb and TgAb could serve as novel prognostic factors for predicting recurrence of PTC in children.

Keywords: papillary thyroid carcinoma, children and adolescents, thyroid peroxidase antibody, thyroglobulin antibody, recurrence

Abbreviations: PTC, papillary thyroid carcinoma; TPOAb, thyroid peroxidase antibody; TgAb, thyroglobulin antibody; TSH, thyroid-stimulating hormone; Tg, thyroglobulin; LNM, lymph node metastases; ETE, extrathyroidal extension; TNM, tumour-node-metastasis; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; CV, coefficient of variation.

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INTRODUCTION

Thyroid carcinoma is less common in children and adolescents with around 0.5-3%, but the incidence has been steadily rising recently (1). Papillary thyroid carcinoma (PTC) is the most common type of thyroid carcinoma in both children and adults, with around 90% (2). The most common thyroid autoimmune disease among children with thyroiditis is Hashimoto's thyroiditis (HT) (3), which is characterized by high titers of thyroid autoantibodies (4). Thyroid autoantibodies are usually present in the serum of HT patients, with 70-80% for thyroglobulin antibody (TgAb) and 90-95% for thyroid peroxidase antibody (TPOAb), considered to be sensitive markers for HT (5). TgAb and TPOAb positivity rate were significantly increasing in patients with PTC (6). The association between HT and PTC has been studied since the first report in 1955 by Dailey (7). However, the link between thyroid autoantibodies, clinicopathologic and prognosis remain equivocal. Paparodis et al. proposed high levels of TPOAb seemed to prevent PTC (8). Conversely, Adhami' study (9) suggested positive TgAb was connected with lymph node metastases in PTC patients. Iliadou et al. (10) showed that thyroid carcinoma with HT presented more frequently invasive characteristics in children and adolescents (≤ 21years). The above findings demonstrated the inconsistent conclusions about connection between HT and PTC may be due to different antibody status, and the exact association is currently unclear. Thence, further researches on the effect of preoperative TPOAb and TgAb on the development and prognosis of PTC are needed.

Many studies have reported the relationship between HT and PTC in adults, but few researches have investigated whether there is a similar link in children and adolescents. Due to the low incidence of thyroid carcinoma, there have rarely retrospective studies of this age group in China that little is known about the clinical implication of preoperative thyroid autoantibodies. The study aimed to explore the connection between clinicopathological features, prognosis with preoperative TgAb and TPOAb status in children and adolescents with PTC. Relevant literature defined 21 as the age of separation between adults and adolescents (10, 11), which provides a basis for selecting and grouping of children and adolescents in this study.

METHODS

Study Population

This study retrospectively reviewed 179 PTC patients who underwent initial thyroidectomy enrolled from January 2000 to June 2021 that carried out at Tianjin Medical University Cancer Hospital. All patients met the following criteria: (1) their age at diagnosis ≤ 21 years old; (2) histologically proven PTC after thyroidectomy; (3) thyroid-stimulating hormone (TSH), thyroglobulin (Tg), TPOAb and TgAb were measured before thyroidectomy. The exclusion criteria were the following: (1) they merged with other tumors; (2) they had serious medical record deficiency. The studies involving human participants were reviewed and approved by the Ethical Committee of the Tianjin Medical University Cancer Institute and Hospital. The patients provided written informed consent to participate in this study.

Clinicopathological Variables

Patients' characteristics such as age, gender, preoperative TPOAb, TgAb, TSH and Tg levels in the serum, postoperative histological type, pathological characteristics of maximal tumor size, bilaterality, multifocality, extrathyroidal extension (ETE), lymph nodes metastases (LNM) (N1a-central LNM, N1b-lateral LNM) were recorded. Serum TPOAb, TgAb, TSH and Tg were measured on a Roche Cobas immunology analyzer (Switzerland) using the electrochemiluminescence immunoassay (ECLIA) method. The normal ranges for serum levels of TPOAb, TgAb, TSH and Tg were 0–9 IU/mL, 0–4.1 IU/mL, 0.27–4.20 mlU/L, -1.4–78 ug/L, respectively. The intra-assay coefficient of variation (CV) values of serum TPOAb, TgAb, TSH and Tg were 2.4% to 5.6%, 1.3% to 4.9%, 3% to 4% and 1.6% to 4.1%, respectively, whereas the interassay CV values were 3.2% to 5.7%, 2.1% to 6.9%, 4% to 6% and 1.3% to 5.8%, respectively. TPOAb, TgAb, TSH and Tg were considered positive when their serum level was over the upper range. TNM staging was based on the 8th edition of the American Joint Committee on Cancer TNM staging system (12).

Postoperative Follow-Up

The primary outcome was recurrence of disease. The primary imaging modality was ultrasonography during follow-up. When a suspected recurrent lesion (thyroid bed or lymphadenopathy) was identified by imaging and fine-needle aspiration cytology, then surgery was performed to remove the disease and confirm the diagnosis. Elevated serum Tg and TgAb levels without clinical evidence of structural disease were defined as isolated biochemical recurrence and were not classified as true recurrence (13, 14). Disease-free survival (DFS) was defined as the time interval from thyroidectomy to detect PTC recurrence. Follow-up for each patient could be recorded by reviewing records or by calling the patients.

Statistical Analysis

Data analysis was performed by using SPSS v.26.0 (Chicago, IL, USA). Categorical variables were reported as absolute numbers and percentages, continuous variables were reported as a mean ± standard deviation or median and range. Differences between groups were assessed using the χ^2 statistic and Fisher's exact test (categorical variables) or the independent-samples t-test (continuous variables). The Kaplan-Meier method and log-rank test were used to analyze time-dependent variables. The Cox hazard regression model was used for multivariate analysis, expressed as hazard ratio (HR) with the 95%CI. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Study Populations

This study included preoperative TgAb and TPOAb data from 179 children and adolescents with PTC after thyroidectomy. The

features of patients were given in **Table 1**. Patients consisted of 131 girls (73.2%) and 48 boys (26.8%). Thyroid involvement was multifocal in 97 patients (54.2%) and bilateral in 61 patients (34.1%). ETE was documented of 129 patients (72.1%). A total of 154 had central LNM (86.0%), 111 had lateral LNM (62.0%). During a mean follow-up of 74 months (2-225 months), 40 patients (22.3%) had a recurrence.

Relationship Between Preoperative Thyroid Autoantibodies and Clinicopathologic Features of PTC in Different Age Groups

Divided patients into two groups according to relevant literature (15–17): the younger group (< 14 years old) and the older group (14-21 years old). We analyzed the relationship between TgAb, TPOAb and clinicopathological features of PTC patients.

We found that patients with positive preoperative TgAb were predominant female compared with negative TgAb patients in all patients and the older group, and preoperative Tg was usually within the normal range in all groups ($P < 0.05$). Moreover, the recurrence rate of positive preoperative TgAb patients was lower than negative TgAb patients in the younger group ($P = 0.047$) (**Table 2**).

As shown in **Table 3**, our findings suggested that positive preoperative TPOAb patients had normal level of preoperative Tg and less cervical LNM than patients with negative TPOAb in all patients and the older group ($P < 0.05$). In addition, patients with positive TPOAb had lower recurrence rate in the younger group ($P = 0.006$).

Multivariate Analysis for Variables Associated With PTC Recurrence

During a mean follow-up of 74 months (2-225 months), 40 patients (22.3%) had a recurrence: 31 (77.5%) were negative preoperative TgAb and 30 (75.0%) were negative preoperative TPOAb. Moreover, this study showed that DFS rate at 3 years (DFSR-3y), DFSR-5y, -10y, -15y, and -20y were 84.4%, 80.3%, 75.5%, 71.9%, and 71.9%, respectively (**Figure 1**).

The survival curves of DFS of preoperative TgAb and TPOAb status in the younger group were shown in **Figure 1**. The median DFS was 97.4 months for patients with positive preoperative TgAb and 69.8 months for patients with negative TgAb (**Figure 2A**) ($P = 0.053$, log-rank). Patients with positive TPOAb had longer median DFS (113.4 months) than negative TPOAb patients (64.9 months) (**Figures 2B**) ($P = 0.009$, log-rank).

TABLE 1 | Characteristics of the study patients.

Characteristics	N (%)	Characteristics	N (%)
Gender		**ETE**	
Female	131 (73.2)	Yes	129 (72.1)
Male	48 (26.8)	No	50 (27.9)
Age at diagnosis		**Preoperative TPOAb**	
<14 years	36 (20.1)	Positive	64 (35.8)
14-21 years	143 (79.9)	Negative	115 (64.2)
Maximal tumor size		**Preoperative TgAb**	
≤ 2cm	89 (49.7)	Positive	53 (29.6)
>2cm	90 (50.3)	Negative	126 (70.4)
T staging		**Preoperative TSH**	
T1a	18 (10.1)	Positive	30 (16.8)
T1b	70 (39.1)	Negative	149 (83.2)
T2	78 (43.6)	**Preoperative Tg**	
T3	13 (7.3)	Positive	56 (31.3)
Central LNM		Negative	123 (68.7)
Yes	154 (86.0)	**TNM staging**	
No	25 (14.0)	I	179 (100.0)
Lateral LNM		**Surgical approach**	
Yes	111 (62.0)	Total thyroidectomy	64 (35.8)
No	68 (38.0)	Sub-total thyroidectomy	25 (14.0)
Cervical LNM		Ipsilateral glandular lobe plus isthmus resection	90 (50.3)
Yes	162 (90.5)	**Lymph node dissection**	
No	17 (9.5)	Unilateral CLND	44 (24.6)
N staging		Unilateral MRND	62 (34.6)
N0	17 (9.5)	Unilateral MRND, plus contralateral CLND	19 (10.6)
N1a	46 (25.7)	Bilateral CLND	12 (6.7)
N1b	116 (64.8)	Bilateral MRND	42 (23.5)
Bilaterality		**RAI ablation**	
Yes	61 (34.1)	Yes	29 (16.2)
No	118 (65.9)	No	150 (83.8)
Multifocality		**Recurrence**	
Yes	97 (54.2)	Yes	40 (22.3)
No	82 (45.8)	No	139 (77.7)

LNM, lymph node metastases; ETE, extrathyroidal extension; TPOAb, thyroid peroxidase antibody; TgAb, thyroglobulin antibody; TSH, thyroid-stimulating hormone; Tg, thyroglobulin; TNM, tumour-node-metastasis; CLND, central lymph node dissection; MRND, modified radical neck dissection; RAI, radioactive iodine.

TABLE 2 | Clinicopathologic features of PTC patients with positive and negative TgAb in different age groups.

Variables	Total (n=179)			< 14 years (n=36)			14–21 years (n=143)		
	TgAb+	TgAb-	*P* value	TgAb+	TgAb-	*P* value	TgAb+	TgAb-	*P* value
Gender (n, %)									
female	45 (84.9)	86 (68.3)	0.022*	8 (61.5)	16 (69.6)	0.902	37 (92.5)	70 (68.0)	0.002*
male	8 (15.1)	40 (31.7)		5 (38.5)	7 (30.4)		3 (7.5)	33 (32.0	
Preoperative Tg									
positive	4 (7.5)	52 (41.3)	< 0.001*	1 (7.7)	12 (52.2)	0.021*	3 (7.5)	40 (38.8)	< 0.001*
negative	49 (92.5)	74 (58.7)		12 (92.3)	11 (47.8)		37 (92.5)	63 (61.2)	
Maximal tumor size									
≤ 2cm	27 (50.9)	62 (49.2)	0.832	5 (38.5)	6 (26.1)	0.691	22 (55.0)	56 (54.4)	0.946
>2cm	26 (49.1)	64 (50.8)		8 (61.5)	17 (73.9)		18 (45.0)	47 (45.6)	
Multifocality	27 (50.9)	70 (55.6)	0.572	10 (76.9)	17 (73.9)	1.000	17 (42.5)	53 (51.5)	0.336
Bilaterality	21 (39.6)	40 (31.7)	0.310	7 (53.8)	9 (39.1)	0.393	14 (35.0)	31 (30.1)	0.571
ETE	36 (67.9)	93 (73.8)	0.423	9 (69.2)	16 (69.6)	1.000	27 (67.5)	77 (74.8)	0.382
Cervical LNM	47 (88.7)	115 (91.3)	0.589	13 (100.0)	22 (95.7)	1.000	34 (85.0)	93 (90.3)	0.545
Central LNM	46 (86.8)	108 (85.7)	0.849	13 (100.0)	22 (95.7)	1.000	33 (82.5)	86 (83.5)	0.886
Lateral LNM	31 (58.5)	80 (63.5)	0.529	9 (69.2)	20 (87.0)	0.225	22 (55.0)	60 (58.3)	0.724
RAI ablation	7 (13.2)	22 (17.5)	0.481	2 (15.4)	8 (34.8)	0.389	5 (12.5)	14 (13.6)	0.863
Recurrence	9 (17.0)	31 (24.6)	0.264	4 (30.8)	15 (65.2)	0.047*	5 (12.50	16 (15.5)	0.645

*TgAb, thyroglobulin antibody; Tg, thyroglobulin; ETE, extrathyroidal extension; LNM, lymph node metastases; TNM, tumour-node-metastasis; RAI, radioactive iodine; *P < 0.05.*

The median DFS did not differ significantly by TgAb and TPOAb status in the older group (**Figures 3A**, **B**) (*P*>0.05, log-rank). In addition, the median DFS was 152.4 months for positive TgAb patients and 169.6 months for those negative TgAb, 173.7 months for positive TPOAb patients and 164.7 months for those negative TPOAb. The differences were also not significant in all patients with PTC (**Figures 4A**, **B**) (*P*>0.05, log-rank).

After adjusting for other clinicopathological factors (age, gender, cervical LNM, multifocality, T stage, N stage, maximal tumor size, etc.), we summarized the outcomes of multivariate analysis of the association of preoperative TgAb and TPOAb with cancer recurrence. The results in **Table 4** showed risk factors (age, maximal tumor size, T stage, multifocality, lateral LNM, N stage, preoperative TSH and Tg level) were predictors for cancer recurrence in children and adolescents (P < 0.05). Moreover, preoperative positive TPOAb was associated with better prognosis in the younger group (P = 0.021). Cox regression analysis found that younger age (HR 0.224, P < 0.001), lateral LNM (HR 0.137, P = 0.010), N stage (HR 30.356, P < 0.001) were independent risk factors for recurrence of PTC in children and adolescents.

DISCUSSION

The National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) results (2) showed that approximately 90% of thyroid carcinoma pathological types were PTC in children and adolescents, consistent with adults. However, children and

TABLE 3 | Clinicopathologic features of PTC patients with positive and negative TPOAb in different age groups.

Variables	Total (n=179)			< 14 years (n=36)			14–21 years (n=143)		
	TPOAb+	TPOAb-	*P* value	TPOAb+	TPOAb-	*P* value	TPOAb+	TPOAb-	*P* value
Gender (n, %)									
female	51 (79.7)	80 (69.6)	0.143	7 (63.6)	17 (68.0)	1.000	44 (83.0)	63 (70.0)	0.083
male	13 (20.3)	35 (30.4)		4 (36.4)	8 (32.0)		9 (17.0)	27 (30.0)	
Preoperative Tg									
positive	9 (14.1)	47 (40.9)	< 0.001*	1 (9.10	12 (48.0)	0.063	8 (15.1)	35 (38.9)	0.003*
negative	55 (85.9)	68 (59.1)		10 (90.0)	13 (52.0)		45 (84.9)	55 (61.1)	
Maximal tumor size									
≤ 2cm	29 (45.3)	60 (52.2)	0.379	4 (36.4)	7 (28.0)	0.913	25 (47.2)	53 (58.9)	0.147
>2cm	35 (54.7)	55 (47.8)		7 (63.6)	18 (72.0)		28 (52.8)	37 (41.1)	
Multifocality	34 (53.1)	63 (54.8)	0.831	9 (81.8)	18 (72.0)	0.835	25 (47.2)	45 (50.0)	0.744
Bilaterality	25 (39.1)	36 (31.3)	0.294	7 (63.6)	9 (36.0)	0.241	18 (34.0)	27 (30.0)	0.622
ETE	44 (68.8)	85 (73.9)	0.461	8 (72.7)	17 (68.0)	1.000	36 (67.9)	68 (75.6)	0.322
Cervical LNM	54 (84.4)	108 (93.9)	0.037*	11 (100.0)	24 (96.0)	1.000	43 (81.1)	84 (93.3)	0.025*
Central LNM	51 (79.7)	103 (89.6)	0.068	11 (100.0)	24 (96.0)	1.000	40 (75.5)	79 (87.8)	0.057
Lateral LNM	36 (56.3)	75 (65.2)	0.236	7 (63.6)	22 (88.0)	0.167	29 (54.7)	53 (58.9)	0.626
RAI ablation	6 (9.4)	23 (20.0)	0.064	1 (9.1)	9 (36.0)	0.209	5 (9.4)	14 (15.6)	0.298
Recurrence	10 (14.3)	30 (26.1)	0.107	2 (18.2)	17 (68.0)	0.006*	8 (15.1)	13 (14.4)	0.916

*TPOAb, thyroid peroxidase antibody; Tg, thyroglobulin; ETE, extrathyroidal extension; LNM, lymph node metastases; TNM, tumour-node-metastasis; RAI, radioactive iodine; * P < 0.05.*

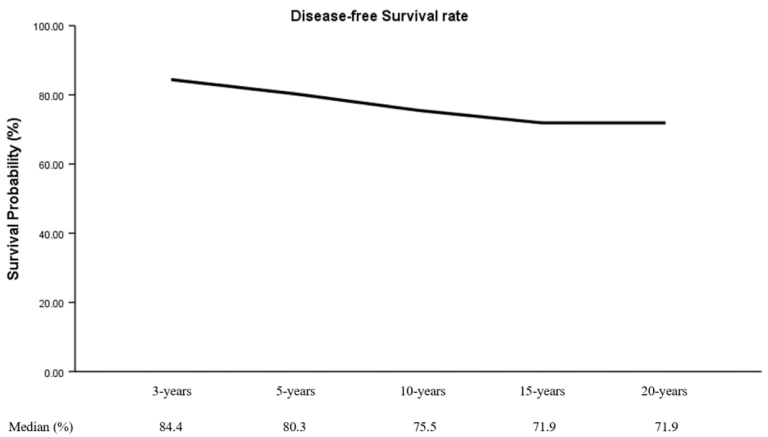

FIGURE 1 | Tendency chart of pooled DFS rate.

adolescents with PTC have their own unique biological characteristics (18), being highly aggressive, prone to metastases and high recurrence rate. Therefore, it is necessary to further study the clinicopathological features of this age group to provide a basis for clinical diagnosis and treatment. The Adham's and Shan's studies have shown thyroid autoantibody were significantly associated with development and prognosis of PTC (9, 19). However, different autoantibody status may have different effects on PTC, and the relationship between PTC and autoantibodies in children and adolescents is still debated (20, 21). Thence, this study was aimed to investigate whether preoperative autoantibody can predict clinicopathologic features and prognosis of PTC in children and adolescents.

Association between thyroid autoantibodies and clinicopathologic features, such as tumor size, bilaterality, multifocality, ETE, and LNM still remain equivocal. Song' study showed PTC patients with positive TgAb and TPOAb had better clinicopathologic features (22). But Li et al. suggested the presence of antibodies did not affect the tumor size (19). Consistent with previous studies that there was no difference in ETE, multifocality between different TgAb and TPOAb status of PTC patients (23, 24), our findings suggested both preoperative TgAb and TPOAb were not associated with multifocality, bilaterality, and ETE of PTC patients. We analyzed the differences in clinicopathological characteristics of different autoantibody status in different age groups, which showed preoperative positive TgAb and TPOAb have been associated with better prognosis in younger children ($P < 0.05$). In the older group, preoperative positive TgAb patients were more female, and preoperative Tg was usually within the normal range compared to negative TgAb patients ($P < 0.05$). Preoperative positive TPOAb patients often had normal preoperative Tg level and less cervical LNM compared to negative TPOAb patients ($P < 0.05$). In this study, 45 patients presented both TgAb and TPOAb. We further analyzed preoperative Tg levels in four antibody status and found that there were differences between groups, which suggested that the observation of Tg levels in different TPOAb status may be affected by TgAb status. Therefore, it is necessary to measure TPOAb and TgAb levels preoperatively simultaneously.

Cervical LNM is known to be a key predictor of recurrence in PTC patients (25). However, association between thyroid autoantibodies and cervical LNM in PTC patients is still controversial. Jo's study (23) indicated that positive TgAb patients had a significantly increased risk of cervical LNM ($P = 0.010$). In contrast, other researchers reported no difference in LNM between positive and negative TgAb patients with PTC (20). On the other hand, Li et al. (19) pointed positive TPOAb reduced the risk of cervical LNM in patients with PTC. But Lee et al. (24) grouped 1879 patients with PTC based on the presence of TPOAb, and found no difference in LNM between positive and negative TPOAb groups. However, we analyzed preoperative

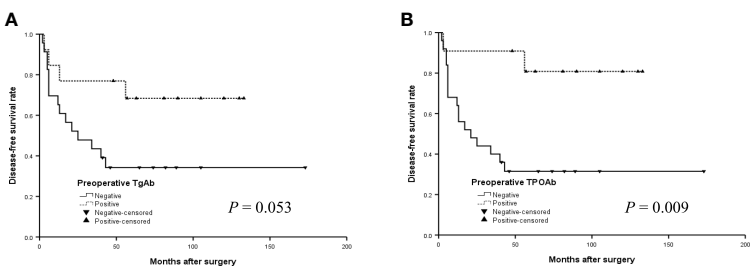

FIGURE 2 | The disease-free survival (DFS) curves of the positive or negative preoperative TgAb **(A)** and TPOAb **(B)** in the younger group (< 14 years) with PTC.

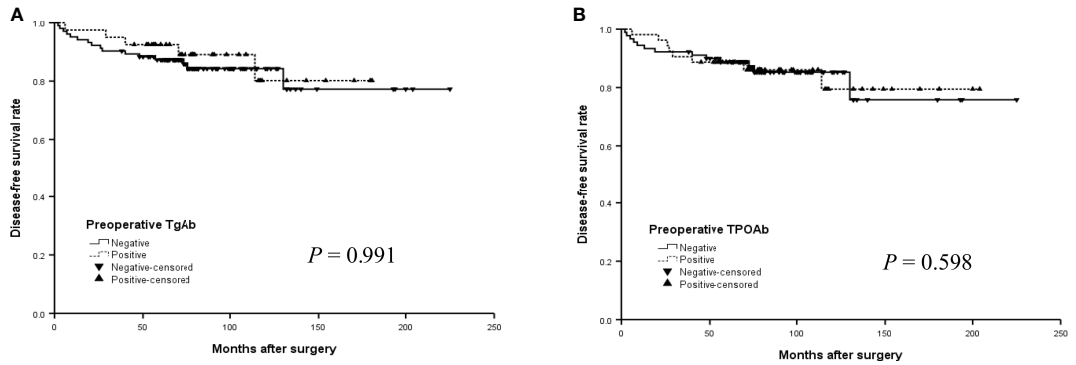

FIGURE 3 | The disease-free survival (DFS) curves of the positive or negative preoperative TgAb **(A)** and TPOAb **(B)** in the older group (14 -21 years) with PTC.

TgAb and TPOAb levels of 179 PTC patients and found that patients with preoperative positive TPOAb had less LNM in children and adolescents ($P < 0.05$). Therefore, the effect of preoperative TgAb and TPOAb on LNM in children and adolescents with PTC still needs to include more cases for further research.

Our study showed that thyroid autoantibodies were associated with better clinicopathologic features in children and adolescents with PTC. The possible potential mechanism was that TgAb could specifically recognize epitopes on the Tg of PTC patients to cause tumor epitope-specific immune responses, increase the destruction of cancer cells and exert its protective effect by regulating the tumor microenvironment (26, 27). TPOAb may mediate by complement-mediated cell death and/or antibody-dependent cytotoxicity to exert its anti-cancer effect (28). Positive TgAb and TPOAb were associated with an increasing number of tumor-associated lymphocyte proliferating cells, which showing better primary tumor characteristics and disease-free survival in children and adolescents with PTC (29). The study has certain clinical value, but unfortunately, the relevant mechanism was not found in this paper. Therefore, the potential mechanism between preoperative TgAb, TPOAb and PTC in children and adolescents needs further research.

PTC in children and adolescents is less common, but the recurrence rate is high (16.7-31.6%) (30–32). The results of our study showed that 40 patients (22.3%) had a recurrence, which was similar to Rubinstein's study (33). Currently, the impact of preoperative TgAb and TPOAb on the prognosis of PTC patients remains controversial (22, 34, 35). Song et al. (20) revealed patients with positive TPOAb were associated with better DFS. But Durante et al. (36) evaluated 1,240 patients from 10 hospitals and indicated recurrence was more common in positive TgAb patients. McLeod et al. (37) showed TgAb status was not associated with DFS or overall survival. However, the aforementioned studies consisted of data from postoperative patients. Therefore, it is necessary to research the relationship between preoperative TgAb as well as TPOAb and prognosis in patients with PTC. Our study found preoperative positive TgAb and TPOAb were protective factor for recurrence in younger group ($P < 0.05$). But the results of univariate analyses showed that cancer recurrence were not associated with TgAb and TPOAb status in the older group ($P>0.05$). Therefore, more cases need to be included for further research.

Preoperative TPOAb and TgAb levels in the serum were relatively stable. Our study showed patients with preoperative positive TgAb and TPOAb had lower recurrence rate in the younger group of PTC patients, which was similar to other research findings (20, 38). Some studies suggested that postoperative TgAb levels may predict recurrence (36, 39), but postoperative antibodies were easily affected by other factors (which may be because cervical lymph nodes initiate and

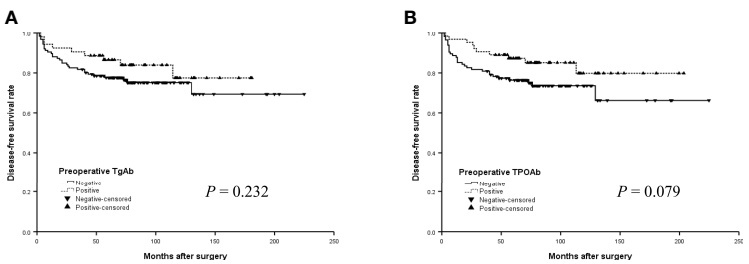

FIGURE 4 | The disease-free survival (DFS) curves of the positive or negative preoperative TgAb **(A)** and TPOAb **(B)** in all patients with PTC.

TABLE 4 | Cox proportional hazard regression analysis for variables associated with PTC recurrence at different ages.

Variables	Univariate			Multivariate		
	HR	95%CI	*P* value	HR	95%CI	*P* value
<14 years old group						
Positive preoperative TPOAb	0.176	0.040-0.771	0.021*			Ns
Positive preoperative TgAb	0.355	0.117-1.078	0.068			Ns
14-21years old group						
Positive preoperative TPOAb	0.995	0.412-2.405	0.991			Ns
Positive preoperative TgAb	0.764	0.280-2.086	0.599			Ns
All patients						
The younger age	0.198	0.106-0.37	< 0.001*	0.224	0.110-0.455	< 0.001*
Positive preoperative TPOAb	0.533	0.260-1.091	0.085			Ns
Positive preoperative TgAb	0.639	0.304-1.343	0.237			Ns
Positive preoperative TSH	2.024	1.008-4.064	0.047*			Ns
Positive preoperative Tg	1.941	1.04-3.623	0.037*			Ns
Maximal tumor size>2cm	2.883	1.438-5.782	0.003*			Ns
T stage	1.659	1.105-2.490	0.015*			Ns
Multifocality	2.271	1.154-4.469	0.018*			Ns
Lateral LNM	3.258	1.440-7.370	0.005*	0.137	0.030-0.622	0.010*
N stage	6.264	2.058-19.062	0.001*	30.356	6.044-152.479	< 0.001*

*TPOAb, thyroid peroxidase antibody; TgAb, thyroglobulin antibody; TSH, thyroid-stimulating hormone; Tg, thyroglobulin; LNM, lymph node metastases; *P < 0.05.*

disseminate the autoimmune response or reflect the persistence of Tg in antigen-presenting cells (40, 41)), which may lead to inaccurate results. In some patients with positive TgAb preoperatively, the postoperative antibody level will decline over time, and it will turn negative after about 3 years (42, 43). Some studies showed that TgAb may persist for years after thyroidectomy, without clear evidence of persistent disease (40, 41). Therefore, it is necessary to further study the preoperative TgAb level and regularly measure TgAb postoperatively to evaluate the prognostic value of the change of postoperative TgAb in PTC patients with preoperative positive TgAb.

There have some limitations in this study. The retrospective study was conducted in a single center that might limit the general applicability of our findings. Therefore, further large-sample studies are needed to evaluate the effect of thyroid autoantibodies on LNM and recurrence.

CONCLUSIONS

In conclusion, we found that presence of preoperative TPOAb and TgAb could serve as novel prognostic factors for predicting recurrence of PTC in children. Further studies are needed to measure TPOAb and TgAb periodically to confirm the prognostic value of postoperative changes in TPOAb and TgAb with positive preoperative TPOAb and TgAb in PTC patients.

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

The studies involving human participants were reviewed and approved by the Ethical Committee of the Tianjin Medical University Cancer Institute and Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

DH: Conceptualization, data collection and analysis, methodology, and drafting the manuscript. JTZ, JMZ: Conceptualization, data collection and analysis, and methodology. XQ, JZZ: Conceptualization and methodology. XZ, MG: Conceptualization, and manuscript review and editing. All authors contributed to the article and approved the submitted version.

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The Specifically Androgen-Regulated Gene (SARG) Promotes Papillary Thyroid Carcinoma (PTC) Lymphatic Metastasis Through Vascular Endothelial Growth Factor C (VEGF-C) and VEGF Receptor 3 (VEGFR-3) Axis

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The papillary thyroid carcinoma (PTC) metastasizes through lymphatic spread, but the follicular thyroid cancer (FTC) metastasis occurs by following hematogenous spread. To date, the molecular mechanism underlying different metastatic routes between PTC and FTC is still unclear. Here, we showed that specifically androgen-regulated gene (SARG) was significantly up-regulated in PTC, while obviously down-regulated in FTC through analyzing the Gene Expression Omnibus (GEO) database. Immunohistochemistry assay verified that the PTC lymph node metastasis was associated with higher levels of SARG protein in clinical PTC patient samples. SARG-knockdown decreased TPC-1 and CGTH-W3 cells viability and migration significantly. On the contrary, SARG-overexpressed PTC cells possessed more aggressive migratory ability and viability. *In vivo*, SARG overexpression dramatically promoted popliteal lymph node metastasis of xenografts from TPC-1 cells mouse footpad transplanting. Mechanistically, SARG overexpression and knockdown significantly increased and decreased the expression of vascular endothelial growth factor C (VEGF-C) and VEGF receptor 3 (VEGFR-3), respectively, thereby facilitating or inhibiting the tube formation in HUVECs. The tube formation experiment showed that SARG overexpression and knockdown promoted or inhibited the number of tube formations in HUVEC cells, respectively. Taken together, we showed for the first time the differential expression profile of SARG between PTC and FTC, and SARG promotes PTC lymphatic metastasis *via* VEGF-C/VEGFR-3 signal. It indicates that SARG may represent a target for clinical intervention in lymphatic metastasis of PTC.

Keywords: papillary thyroid carcinoma (PTC), lymphatic metastasis, specifically androgen-regulated gene (SARG), vascular endothelial growth factor, VEGF-C

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INTRODUCTION

Thyroid cancer is the most common endocrine malignancy, and its global incidence increases year by year due to heavy use of diagnostic imaging and surveillance (1, 2). Differentiated thyroid cancer (DTC) including papillary thyroid carcinoma (PTC) and follicular thyroid cancer (FTC) accounts for more than 90% of all thyroid cancers (3). They tend to be easier to treat than other types but display different routes of metastasis.

PTC is the most common subtype of thyroid cancer with the best overall prognosis, accounting for approximately 70% of cases, although 15% PTCs show higher aggressiveness and poorer outcomes (4). Of PTC patients 20%-90% occur in regional lymph node (LN) metastasis and 10%-15% of patients appear as distant metastasis, which negatively impacts the overall survival (5). Unlike PTC, which tends to metastasize to lymph nodes, FTC tends to metastasize to remote organs especially lungs and bones by the hematogenous route (6). However, the mechanism of different metastatic pathways between PTC and FTC is still unclear.

The specifically androgen-regulated gene (SARG) protein is located in the cytoplasm and has a length of 601 amino acids with two isoforms as the result of alternative splicing. The expression of SARG is up-regulated by androgen, but not by glucocorticoids (7). There are few reports about its function now because the amino acid composition of SARG does not indicate motifs that could predict its function. Parsana et al. (8) discovered SARG was a novel epithelial to mesenchymal transition (EMT) gene whose decreased expression is associated with poor prognosis in lung and prostate cancer patients. However, whether and how the mechanism of SARG regulates the progression of thyroid cancer is currently unclear.

In the present study, we explored the expression profile of SARG between PTC and FTC, then further investigated its roles in PTC metastasis occurring by following lymphatic spread.

MATERIALS AND METHODS

GEO Data

GSE 33630 and GSE82208 Series were downloaded from the GEO database (http://www.ncbi.nlm.nih.gov/geo/) including 45 normal thyroid tissues, 49 papillary thyroid carcinoma, and 27 follicular thyroid cancer tissues. The differentially expressed genes (DEGs) were performed using the edgeR package in the R language (https://bioconductor.org/packages/edgeR/), setting P-value < 0.01 and log2 |FC| > 1 as the threshold.

Cell Culture and Reagents

CGTH-W3 and TPC-1 cells were obtained from Taizhou Central Hospital. 293T human kidney epithelial cell line was purchased from the Chinese Academy of Sciences Type Culture Collection (CASTCC). CGTH-W3 cells were maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum (FBS) while TPC-1 and HEK-293T cells were grown in DMEM containing 10% FBS. Cells were cultured at 37°C in a humidified incubator with 95% air and 5% CO_2. The polybrene was purchased from MCE (Shanghai, China). The pLenti-EF1a-EGFP-P2A-Puro-CMV-SARG-Flag plasmid was designed and was synthesized from OBiO Biotechnology Corp, Ltd. (Shanghai, China). The pMDG2.G and psPAX2 plasmids for lentivirus assembling were obtained from Addgene.

Immunohistochemistry

Thyroid samples of patients were collected by the Taizhou Central Hospital. Immunohistochemistry was performed as follows. Sample sections were dewaxed with xylene, hydrated with ethanol, then run through an antigen repair protocol. Endogenous peroxidases were neutralized by 0.3% H_2O_2 in dH_2O for 10 min. After washing, slides were blocked with 10% ready-to-use goat serum for 0.5 h at room temperature. Tissue sections were incubated with the primary antibodies(SARG, Proteintech; VEGF-C, Proteintech; VEGFR3, Proteintech) overnight. After washing with PBS, samples were incubated with HRP anti-rabbit IgG (1:200) at room temperature for 30 min and diaminobenzidine (DAB) was used as a sensitive chromogen and then counterstained with hematoxylin. Slides were analyzed by taking photos with a microscope (BX53, Olympus, Japan).

Lentivirus-Mediated Transfection

For lentivirus transfection, pLenti-CMV-SARG plasmids (2.5 μg) with a mixture of packaging plasmids (0.75 μg pMD2.G, 1.90 μg psPAX2) were co-transfected into HEK293T cells by using Lipofectamine 2000 (Invitrogen). Infection efficiency was evaluated by observing the percentage of the green fluorescent protein (GFP) expression by inverted fluorescence microscope. The viral supernatant was collected 48-72 h post-transfection. Viral supernatant supplemented with polybrene 8 μg/mL (Sigma-Aldrich) was added to cells. Forty-eight hours after the addition of viruses, SARG-GFP-infected cells were selected with puromycin (MCE). The expression of SARG was confirmed by real-time qPCR and Western blotting.

Transfection of siRNA

The synthetic siRNAs targeting VEGF-C and negative control were obtained from Gene Pharma. Sequences are as follows: 5'-GCCGAUGCAUGUCUAAACUTT-3' (VEGF-C); 5'-UUCUCCGAACGUGUCACGUTT-3' (negative control). Transfection is at 60-70% cell density using Lipofectamine 2000 (Invitrogen) with a final siRNA concentration of 100 nM.

Real-Time qPCR

Total RNAs were harvested by using the Trizol reagent according to the manufacturer's instructions, then reverse transcription was performed by the reverse transcription kit (Takara Biotechnology Co., Ltd.) to obtain the cDNA. The synthetized cDNA was amplified by real-time qPCR using a SARG-specific primer, CAGTCTCAACCAGGTACACAC (forward), TAG TCGGCTGTTTGGGTCCT (reverse); VEGF-C primer, GGCT GGCAACATAACAGAGAA (forward), CCCCACATCTATA CACACCTCC (reverse); VEGFR3 primer, AGGGAGACGC CCTTTCATG (forward), GAGGGCTCTTTGGTCAAGCA (reverse); GAPDH primer, GCACCGTCAAGGCTGAGAAC

(forward), GCCTTCTCCATGGTGGTGAA (reverse). Real-time qPCR cycles were the following: 95°C for 30 s (step 1), 40 cycles of 95°C for 5 s, 60°C for 30 s (step 2), and then 95°C for 15 s, 60°C for 60 s, and 95°C for 15 s (step 3). The target gene expression was calculated by the 2−ΔΔCt method with the following formula: ΔΔCt=ΔCt sample−ΔCt control gene wherein ΔCt =Ct target gene − Ct internal reference.

Western Blotting

Cells were harvest with RIPA lysis solution (Beyotime, China). The total protein concentration was quantified by the BCA method (Thermo Fisher Scientific, Inc.). Western blotting (immunoblotting) was conducted in accordance with a standard experimental procedure. Total protein was separated by 10% SDS-polyacrylamide gel and transferred onto PVDF membranes. The membranes were blocked with 5% nonfat dry milk in TBST (40 mM Tris–HCl, 0.5 M NaCl, 0.1 Tween-20, pH 7.4) at room temperature for 2 h. Primary antibodies (SARG, Proteintech; VEGF-C, Proteintech; VEGFR-3, ABACM; ERK1/2, Proteintech; Phosphorylated-p44/42 ERK1/2, Cell Signaling Technology; GAPDH, Santa Cruz Biotechnology) were diluted in the antibody diluent at 4°C overnight, and secondary antibodies (anti-rabbit 1:10000 and anti-mouse 1:10000) were diluted in TBST for 1 h at room temperature. The detection and quantification of protein bands were captured with the Image Quant LAS 4000 Mini Imager (GE Healthcare Bio-Sciences).

Cell Viability

Cell viabilities were measured using the MTT assay. Cells were digested for single-cell suspensions and seeded in 96-well plate with a density of 1000 cells per well. Four compound holes were set for each group. After culturing for 4 h, 24 h, 48 h, 72 h, and 96 h, 10 μL MTT (5 mg/ml) reagent was added into each well and incubated at 37°C for 4 h. Then, the supernatant fractions were removed and 150 μL dimethyl sulfoxide (DMSO) was added to each well to solubilize the crystals. Absorbance at OD 490 nm was recorded.

Cell Migration Assay

Cell migration was investigated with a pore size of 8 μm Transwell system (Costar). Cells were resuspended into single cells in serum-free medium and cell density was adjusted to 5 × 105 cells/mL. There was 100-μl single cell suspension added to the upper chamber, while in the lower chamber, 500-μL culture medium with 10% FBS was added. After incubation for 12 h at 37°C, cells in the lower chamber were fixed by 70% methanol and stained with 0.1% crystal violet. A total of 5 fields of view were randomly chosen and the numbers of migrated cells were counted under a microscope.

Popliteal Lymph Node Metastasis Assay

All animal experiments were conducted following appropriate guidelines. The present study was ethically approved by the Medical Ethics Committee of Taizhou University College of Medicine. Female BALB/c nude mice (4 to 5 weeks old) were purchased from Beijing Vital River Laboratory Animal Technology (Hangzhou, China). The mice were randomly divided into 2 groups of 5 mice each in a cage. A total of 10 female mice weighing 15-20 g were housed in sterile cages at 20°C under a 12:12 h light–dark cycle. All experiments were performed according to the Institutional Ethical Guidelines. Lentivirus-transduced parallel-controlled or SARG-overexpressed TPC-1 cells (2×10^6 cells) stably expressing GFP were inoculated into the mouse footpads. After 5 weeks, the fluorescence signals of the primary tumors and the popliteal lymph nodes were detected by an *in vivo* imaging system (Aniview 100, Biolight Biotechnology, Guangzhou). Another 3 weeks later, the popliteal lymph nodes were harvested and fixed in formalin. Tissues were dehydrated and embedded in melted paraffin wax, the resulting block was mounted on a microtome and cut into thin slices. The slices were affixed to microscope slides at which point the wax was removed with a solvent and the tissue slices attached to the slides were rehydrated and were ready for H&E staining.

Tube Formation Assay

The 48-well plates were coated with 100 μL Matrigel (BD Biosciences, US) per well and maintained at 37°C for 30 min, then Lentivirus-transduced parallel-controlled or SARG-overexpressed HUVEC cells 4×10^4 were added to wells which were re-suspended in 100 μL complete DMEM medium and incubated at 37°C for 4 or 6 h. Fluorescence microscopy (IX73 Olympus, Japan) was applied to collect the photos with cellSens Standard 1.9 software used to measure the numbers of tubule branches.

Statistical Analysis

All statistical analyses were carried out in GraphPad Prism version 8.0 (GraphPad Software, Inc.) Statistical significance was tested by Student's t-test between =2 groups. Chi-squared test was used to determine whether there is a statistically significant difference in popliteal lymph node metastasis status between the control and SARG overexpressed cells. Results were shown as Mean ± Standard Deviation (Mean ± SD). Differences were considered statistically significant at * $P < 0.05$ and ** $P < 0.01$.

RESULTS

SARG Expression Levels Were Upregulated in PTC and Associated With Lymph Node Metastasis Status

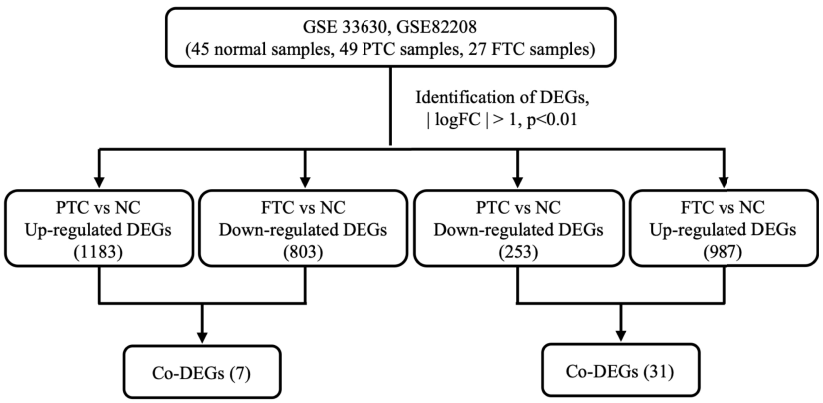
To explore the expression profile of SARG between PTC and FTC, we downloaded GSE 33630 and GSE82208 Series with the same platform using Affymetrix Human Genome U133 Plus 2.0 Array. There were 45 normal thyroid tissues, 49 papillary thyroid carcinoma, and 27 follicular thyroid cancer tissues included in the GEO database to perform the edgeR package. mRNAs showing log2|FC|>1 and p<0.01 were considered differentially expressed genes by following the analysis schedule as shown in **Figure 1A**. Through a comparison of the gene mRNA levels in

cancer and normal tissues, 1183 DEGs and 987 DEGs were screened out with higher mRNA levels in PTC and FTC, respectively, than in normal tissues, while 803 genes and 253 genes expressed lower levels in PTC and FTC, respectively, compared to normal tissues (**Figure 1A**). We further screened out 7 DEGs showing increased profiles in PTC while decreased expression in FTC including SARG. The gene list is shown in **Figure 1B**.

TCGA database analysis confirmed most types of PTCs showed higher levels of SARG than normal thyroid tissues (**Figure 1C**), and more interestingly, even follicular papillary thyroid carcinoma expressed lower SARG mRNA levels (**Figure 1D**). Furthermore, expression of SARG in PTC based on nodal metastasis status in TCGA database analysis showed that PTC with higher SARG levels was associated with more aggressive nodal metastasis (**Figure 1E**).

To determine whether SARG was involved in the regulation of lymph node metastasis of PTC, we evaluated the differential expression profile of SARG between tissue specimens with positive lymph node metastasis and tissue specimens with

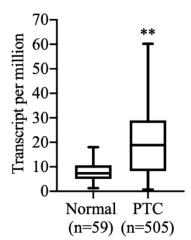
A



B

Genes	logFC, (p<0.01)	
	PTC vs NC	FTC vs NC
Synaptotagmin like 5 (SYTL5)	4.22	-1.65
FAM20A golgi associated secretory pathway pseudokinasa (FAM20A)	2.89	-1.56
Ubiquitin conjugating enzyme E2 Q family like 1 (UBE2QL1)	1.88	-1.54
Specifical androgen-regulated gene (SARG)	1.90	-1.17
Cytoplasmic FMR1 interacting protein 2 (CYFIP2)	1.24	-1.10
Sialic acid binding Ig like lectin 15 (SIGLEC15)	1.43	-1.84
Iroquois homeobox 3 (IRX3)	1.22	-2.80

C



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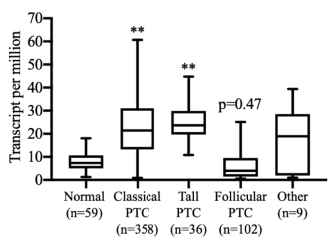

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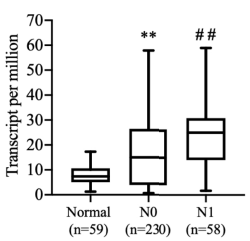


FIGURE 1 | Finding SARG overexpression associated with lymph node metastasis of PTC by analysis of GEO and TCGA database. **(A)** Brief scheme for screening the DEGs between PTC and FTC by GEO database analysis. **(B)** The list of 7 genes is up-regulated in PTC and down-regulated in FTC. **(C)** The expression of SARG between PTC and normal thyroid tissue from TCGA database. **, p<0.01 compared with Normal. **(D)** Expression of SARG in PTC based on tumor histology. **, p<0.01 compared with Normal. **(E)** Expression of SARG in PTC based on nodal metastasis status, **, p<0.01 compared with Normal; ##p<0.01 compared with N0, N0: no regional lymph node metastasis, N1: thyroid cancer with lymph node metastases in the axillary region. SARG, specifically androgen-regulated gene; PTC, papillary thyroid carcinoma; GEO, Gene Expression Omnibus; TCGA, The Cancer Genome Atlas; FTC, follicular thyroid carcinoma; DEGs, differentially expressed genes.

negative lymph node metastasis by immunohistochemistry. The results showed that SARG exhibited higher expression in lymph node-positive tissue specimens than that in lymph node-negative tissue specimens (**Figure 2**). Altogether, overexpression of SARG may exert crucial effects on the growth and progression of PTC.

SARG Overexpression Promoted Cell Viability and Migration in TPC-1 and CGTH-W3 Cells

To better investigate the role of SARG in PTC progression, we constructed SARG-overexpressed cell lines using the lentivirus system in TPC-1 and CGTH-W3 cells that were PTC cell lines. As shown in **Figures 3A, B**, SARG protein and mRNA levels were increased obviously in TPC-1 and CGTH-W3 cells transfected with pLenti-CMV SARG. Consequently, cells transfected with pLenti-CMV SARG grew faster than control cells in MTT assay (**Figure 3C**). Furthermore, the results of transwell migration assay showed that SARG overexpression could raise cell migration in TPC-1 and CGTH-W3 cells (**Figure 3D**).

SARG Knockdown Inhibited Cell Viability and Migration in TPC-1 and CGTH-W3 Cells

To further determine the role of SARG in PTC progression, TPC-1 and CGTH-W3 thyroid cancer cells lines were transfected with shRNA targeting SARG using the lentivirus system to knockdown SARG. As shown in **Figures 4A, B**, the Western blot and real-time qPCR results showed that SARG-shRNA transfection significantly down-regulated the protein and mRNA level of SARG. MTT cell viability assay data indicated that down-regulation of SARG significantly inhibited cell survival in TPC-1 and CGTH-W3 cells (**Figure 4C**). Transwell

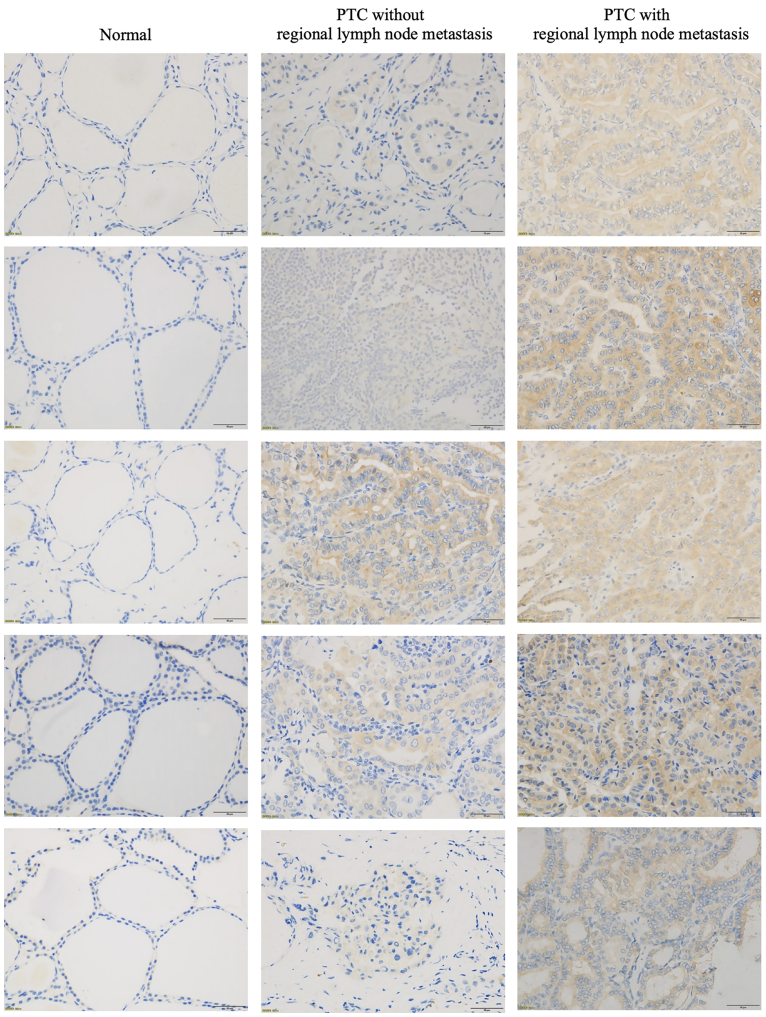


FIGURE 2 | Representative immunohistochemistry assay images of SARG staining in thyroid normal tissues, PTC tissue without regional lymph node metastasis, and PTC tissue with lateral cervical lymph node metastasis. SARG, specifically androgen-regulated gene; PTC, papillary thyroid carcinoma.

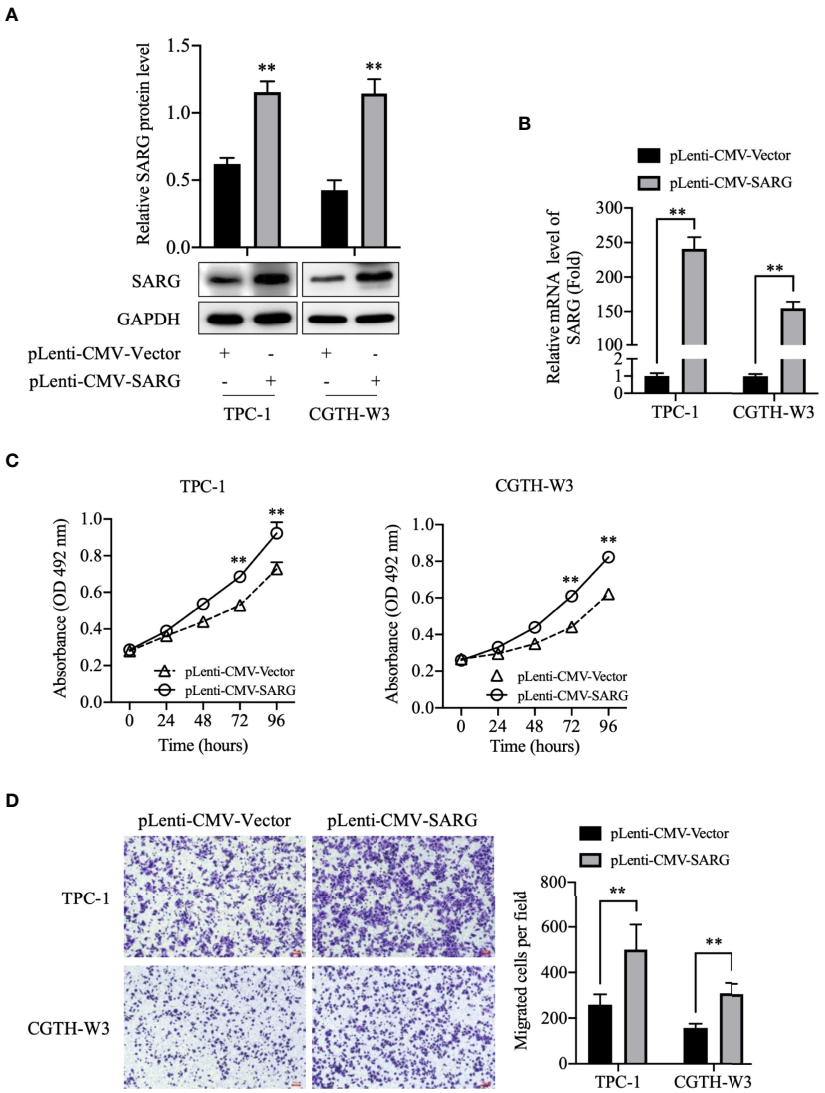


FIGURE 3 | SARG overexpression promoted PTC cells proliferation and migration. **(A)** SARG protein expression in TPC-1 and CGTH-W3 cells was significantly increased after being transfected with pLenti-CMV-SARG plasmid. GAPDH was used as a loading control, whereas pLenti-CMV-vector was used as the negative control. **(B)** SARG overexpression efficiency was evaluated by reverse transcription-quantitative PCR, with all expression levels normalized to those of GAPDH. Data are presented as fold changes relative to the SARG levels in control cells. **(C)** SARG overexpression could increase TPC-1 and CGTH-W3 cells proliferation. **(D)** SARG overexpression promoted TPC-1 and CGTH-W3 cells migration in transwell assay. SARG, specifically androgen-regulated gene. **, p<0.01 pLenti-CMV-Vector.

cell migration assay results showed that down-regulation of SARG reduced the cell migration in TPC-1 and CGTH-W3 cells (**Figure 4D**).

SARG Overexpression Promoted Popliteal Lymph Node Metastasis of PTC Cells Footpad Xenografts in Mice

To further validate the role of SARG in PTC metastasis, *in vivo* experiments were performed. TPC-1 cells overexpressing SARG were injected subcutaneously into the footpads of nude mice. As expected, in comparison to mouse xenografts bearing TPC-1 cells transfected with control vectors, xenografts bearing TPC-1 cells overexpressing SARG showed grossly lymphatic spread being detected by an *in vivo* imaging system as early as 5 weeks later after cell injection (**Figure 5A**). Meanwhile, metastasis in the lymph nodes of mice bearing PTC cells was apparent in H&E staining of lymph node tissue sections (**Figure 5B**). A total of 75% popliteal lymph nodes in mice bearing SARG overexpressing xenografts contain tumor cells, whereas the rate of metastasis to popliteal lymph node was only 20% in mice bearing pLenti-CMV vector plasmid xenografts. There was a significant difference between the vector control and SARG overexpressed group in the popliteal lymph node metastasis rate based on the χ^2 test (**Figure 5C**).

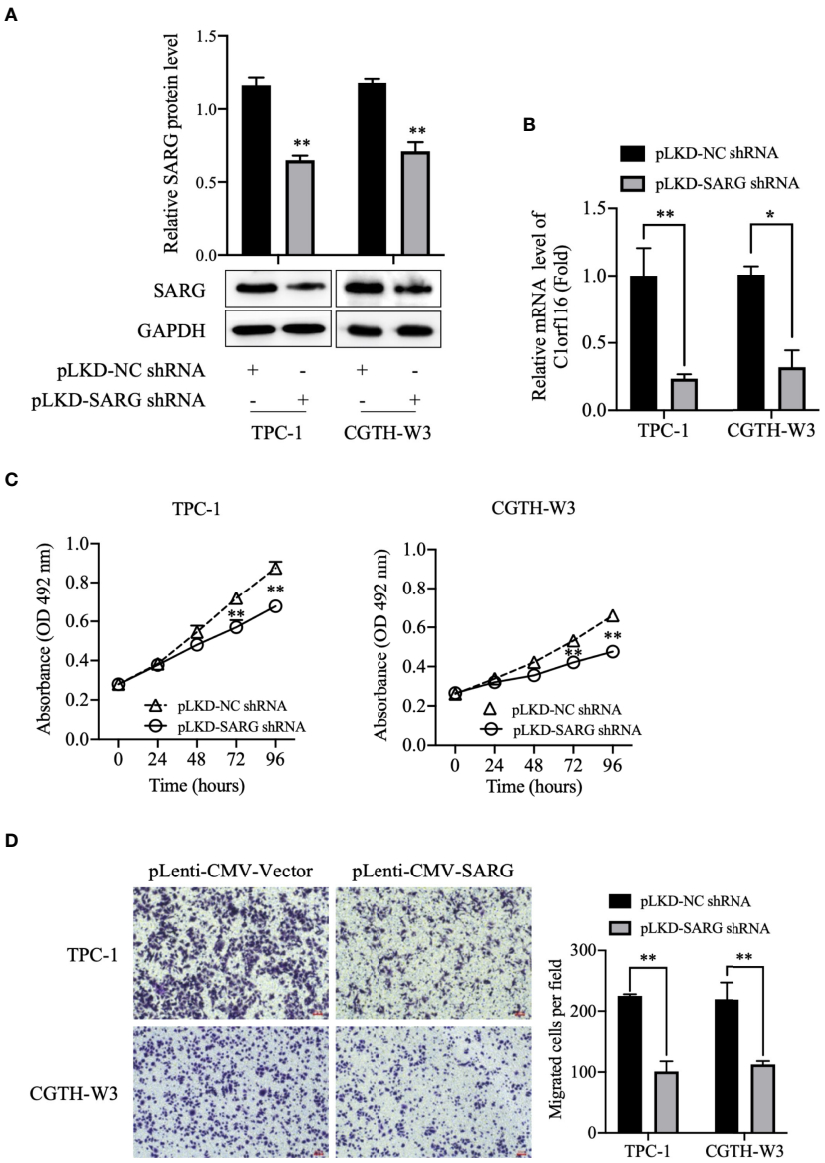
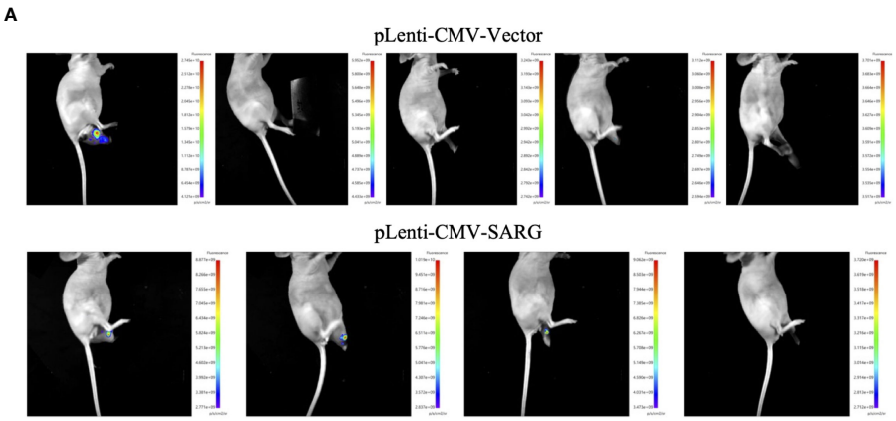


FIGURE 4 | SARG knockdown impaired PTC cells proliferation and migration. **(A)** SARG protein expression in TPC-1 and CGTH-W3 cells was significantly decreased after being transfected with SARG-shRNA. GAPDH was used as a loading control, whereas NC-shRNA was used as the negative control. **(B)** SARG knockdown efficiency was evaluated by reverse transcription-quantitative PCR, with all expression levels normalized to those of GAPDH. Data are presented as fold changes relative to the SARG levels in control cells. **(C)** SARG knockdown could reduce TPC-1 and CGTH-W3 cells proliferation. **(D)** SARG knockdown inhibited TPC-1 and CGTH-W3 cells migration in transwell assay. SARG, specifically androgen-regulated gene. *, $p<0.05$, **, $p<0.01$ compared with NC shRNA.

SARG Was Involved in VEGF-C and VEGFR-3 Regulation

VEGF-C/VEGFR3 axis has been recognized as a critical regulator of lymph node metastasis (9). We also confirmed that VEGF-C and VEGFR3 exhibited higher expression in PTC tissue compared to normal thyroid tissue, and it was highly expressed in lymph node-positive tissue specimens than in lymph node-negative tissue specimens (**Figure 6**). To explore the molecular mechanisms underlying the role of SARG in PTC metastasis, VEGF-C/VEGFR-3 protein levels were measured upon SARG overexpression or knockdown. Western blotting analysis revealed that SARG overexpression increased VEGF-C and VEGFR-3 protein levels in TPC-1 and CGTH-W3 cells (**Figure 7A**). Whereas SARG ablation drastically suppressed the expression of VEGF-C and VEGFR-3 (**Figure 7B**). Furthermore, immunohistochemical experiments were used to detect VEGF-C and VEGFR3 in all the primary xenografts of nude mice. As shown in **Figure 8**, VEGF-C and VEGFR3 expression were upregulated in the SARG overexpressed group than that in the vector control group.

A



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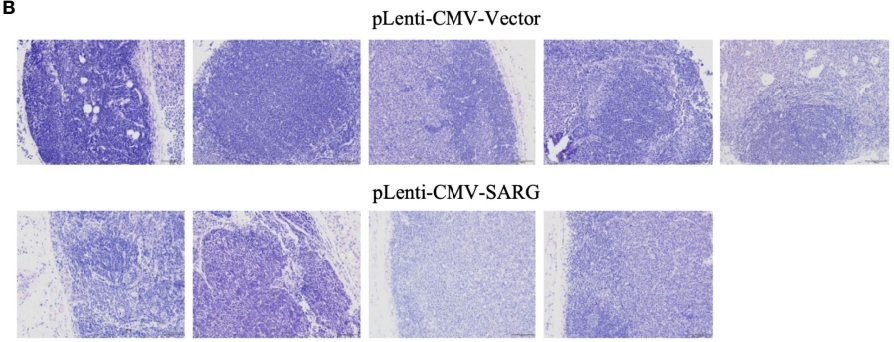

C

Groups	Popliteal lymph node metastasis status	
pLenti-CMV-Vector	No	4
	Yes	1
pLenti-CMV-SARG	No	1
	Yes	3
	Chi-square	2.723
	P value	0.0495

FIGURE 5 | SARG overexpression promoted popliteal lymph node metastasis of PTC cells footpad xenografts in mice. **(A)** TPC-1 cells overexpressed SARG were injected subcutaneously into the footpads of nude mice, 5 weeks later, lymphatic spread was detected by bioluminescence imaging. **(B)** Hematoxylin and eosin staining of popliteal lymph node at the termination. Scale bars, 100 μm. **(C)** χ^2 test of the popliteal lymph node metastasis rate.

A previous study indicated that VEGF-C stimulated lymphatic endothelial cells migration by activating both ERK pathways (10). VEGF-C binds to VEGFR3 and then activates the ERK pathway, which is critical for endothelial and cancer cell survival and progression. Therefore, we observed how the phosphorylated ERK1/2 protein changed after up-regulation or knock-down of SARG. As shown in **Figure 7A**, the protein level of phosphorylated ERK1/2 was increased in SARG-overexpressing TPC-1 and CGTH-W3 cells, while knockdown of SARG showed the contrary results (**Figure 7B**). Tube formation assays were then performed to assess whether SARG could regulate lymphangiogenesis in HUVECs. As shown in **Figure 7C**, SARG over-expression notably promoted lymphangiogenesis in HUVECs. We could find about 12 closed tubes in the vector control group cells under microscope, while there were about 21 closed tubes in SARG overexpressed cells. On the contrary, SARG knockdown dampened lymphangiogenesis (**Figure 7D**).

We test the change of SARG function after knockdown of VEGFC. As shown in **Figures 9A, B**, SARG-siRNA enhances VEGF-C siRNA mediated migration down-regulation.

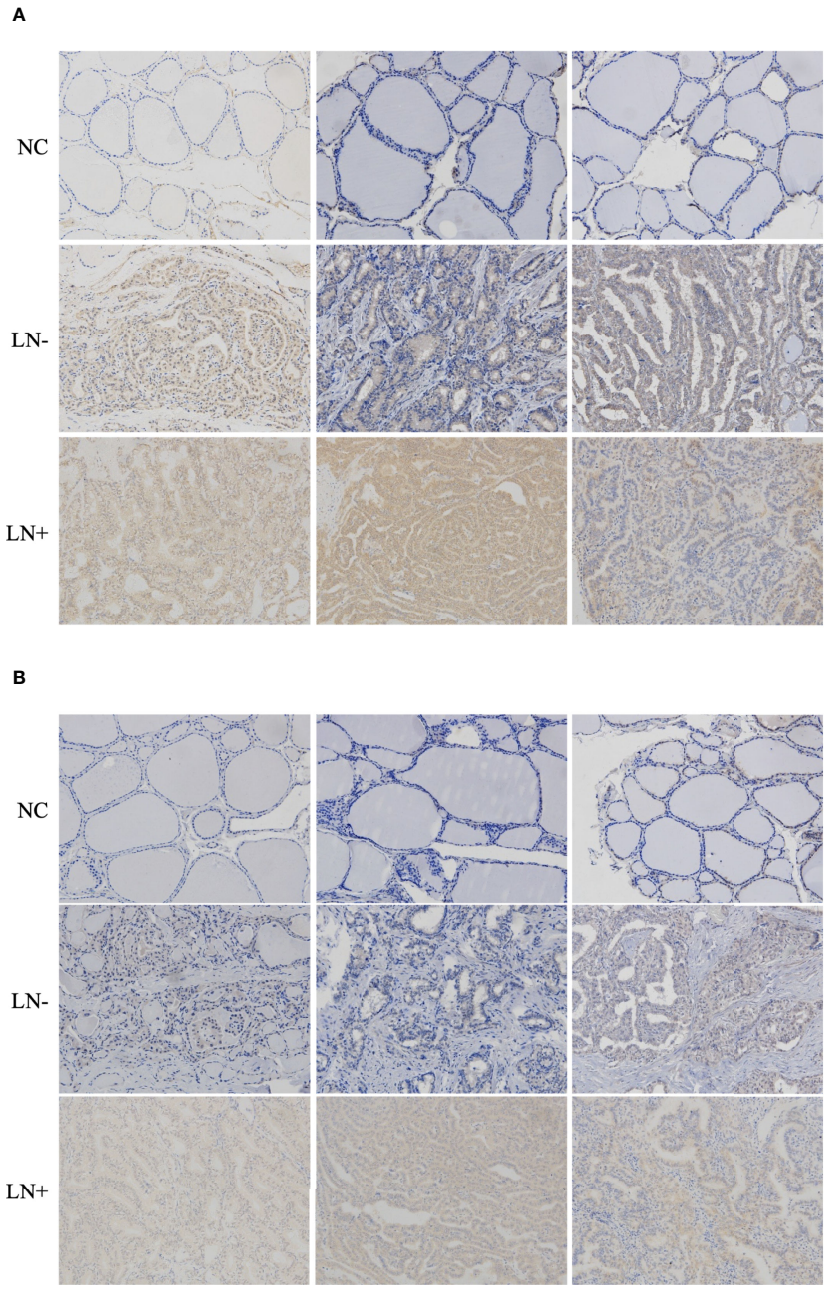

FIGURE 6 | Representative immunohistochemistry assay images of VEGF-C **(A)** and VEGFR3 **(B)** staining in thyroid normal tissues, PTC tissue without regional lymph node metastasis, and PTC tissue with lateral cervical lymph node metastasis. VEGF-C, vascular endothelial growth factor C; VEGFR-3, vascular endothelial growth factor receptor 3; PTC, papillary thyroid carcinoma.

DISCUSSION

In the present study, we found 7 DEGs showing increased profiles in PTC while decreased expression in FTC by analyzing GEO database. Previous preliminary experiments found that down-regulation of SARG would reduce the expression of VEGFR3 in PTC cells, suggesting that SARG may play a role in PTC lymphatic metastasis. To date, there is no published research article about its roles in thyroid cancer. We further showed that SARG has a different expression profile between PTC and FTC by analyzing GEO and TCGA database. We observed here higher levels of SARG in PTC samples with regional lymph node metastasis than those without regional lymph node metastasis. SARG knockdown inhibited PTC cell viability and migration *in vitro*, while its overexpression promoted PTC cell viability, migration *in vitro*, and popliteal

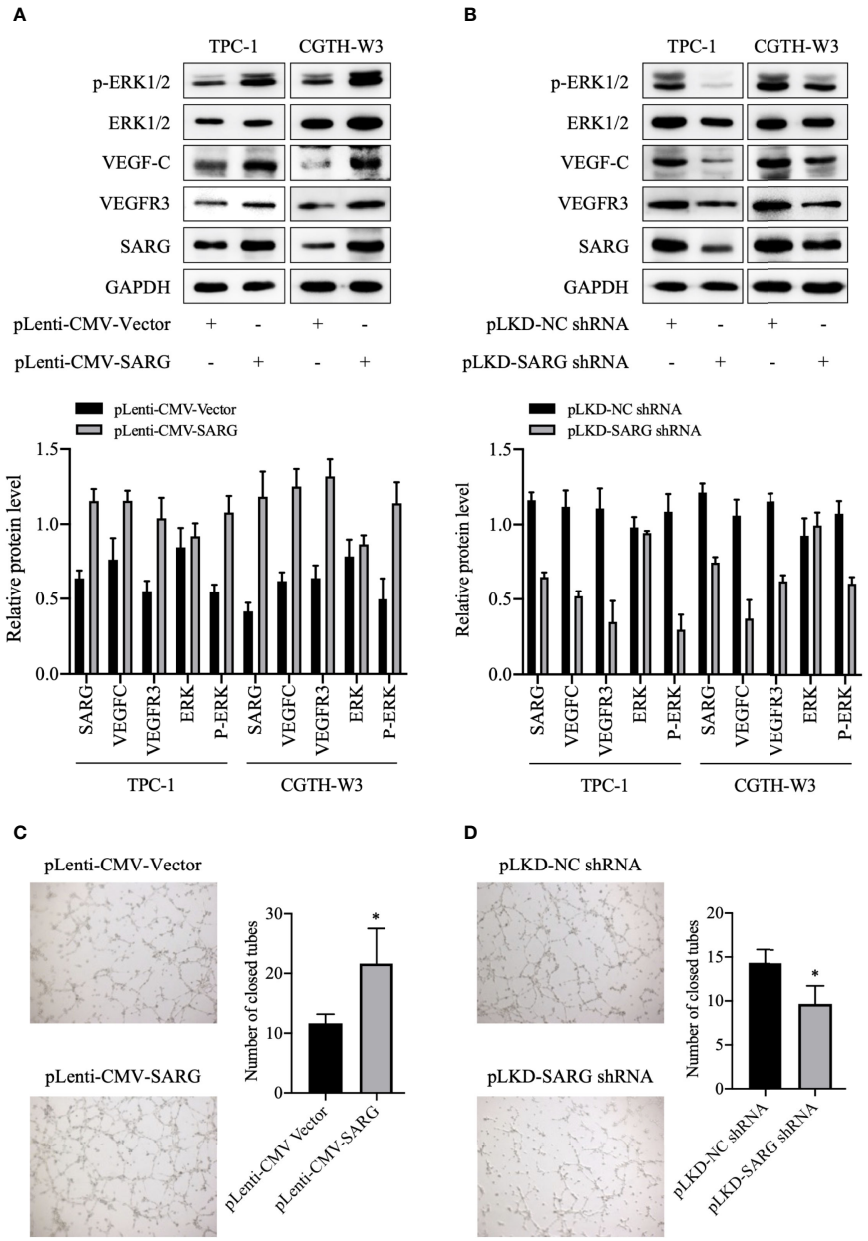

FIGURE 7 | SARG was involved in VEGFC/VEGFR3 regulation and HUVEC tube formation. **(A, B)** VEGF-C and VEGFR3 levels were analyzed by immunoblotting upon SARG overexpression or knockdown, with GAPDH used as the loading control. **(C, D)** The tube formation ability of HUVECs was detected by tube formation assay. * p<0.05 compared with NC-shRNA. SARG, specifically androgen-regulated gene; VEGF-C, vascular endothelial growth factor C; VEGFR-3, vascular endothelial growth factor receptor 3.

lymph nodes metastasis in mice footpad xenografts model. Our primary data provide a new point to study the molecular mechanisms whereby SARG modulates lymphatic metastasis of PTC.

Due to the wide application of diagnostic imaging and fine-needle aspiration biopsy in thyroid nodules, the incidence of thyroid cancer, a common endocrine tumor, has gradually increased in recent years (11). There are 567,000 cases of thyroid cancer worldwide, ranking ninth in incidence (12). Papillary thyroid carcinoma is the most common histological subtype. Although PTC is generally considered to be an indolent tumor, some patients have central lymph node metastasis and cervical lymph node metastasis. Patients with lymph nodes tend to have a high recurrence rate and low survival rate (13). The molecular mechanism of PTC lymph node metastasis is still unclear. In this study, we analyzed the GEO database and found that the expression of SARG was in up-regulated PTC, while down-regulated in FTC. In IHC assay, there were higher levels of

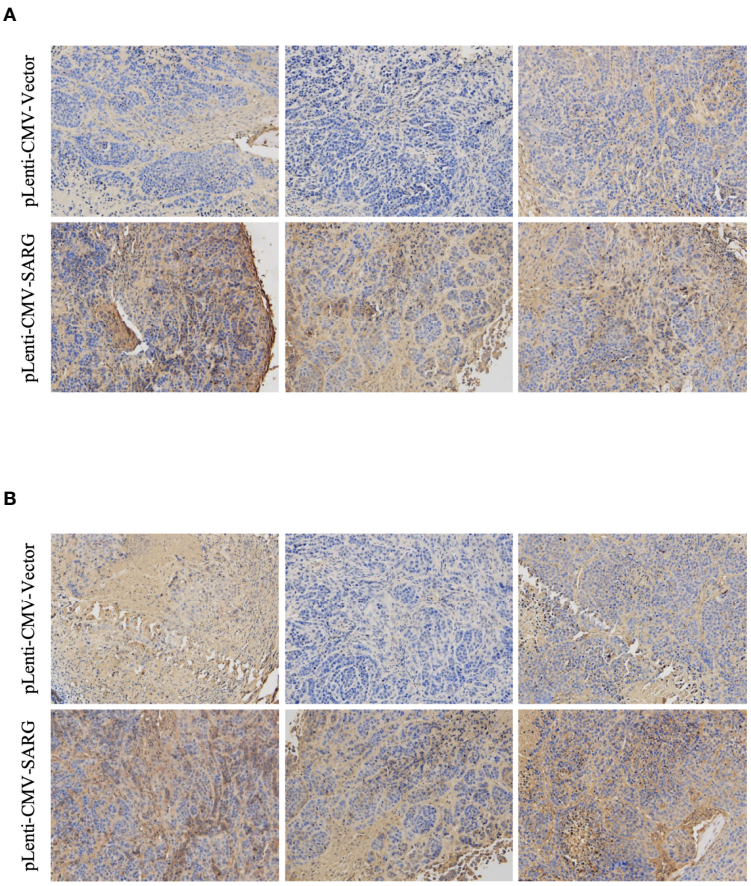

FIGURE 8 | Representative immunohistochemistry assay images of VEGF-C **(A)** and VEGFR3 **(B)** staining in TPC-1 xenografts tissue transfected with vector control plasmids or SARG overexpressing plasmids. VEGF-C, vascular endothelial growth factor C; VEGFR-3, vascular endothelial growth factor receptor 3; SARG, specifically androgen-regulated gene.

SARG in PTC samples with regional lymph node metastasis than those without regional lymph node metastasis, which indicates that SARG might be involved in the regulation of PTC metastasis *via* lymphatic spread.

SARG was first found highly expressed in prostate cancer, its down-regulation induced epithelial to mesenchymal transition in epithelial prostate cancer cell line PC3 cells, suggesting that it may be a new EMT regulatory factor (8). However, there are no reports about its role in other tumors, including thyroid cancer. Here, we showed that SARG knockdown reduced TPC-1 and CGTH-W3 cells viability and migration *in vitro*. On the contrary, SARG overexpression promoted the PTC cells viability and migratory ability in TPC-1 and CGTH-W3 cells by MTT and transwell assay *in vitro*, and the growth of footpad PTC xenograft and popliteal lymph node metastasis in nude mice. Overall, these findings indicate that SARG accelerates tumorigenesis and lymph node metastasis of PTC.

Lymph angiogenesis, an early metastatic event, is considered a necessary condition for lymph node metastasis and is a powerful prognostic indicator for patients with thyroid cancer (14, 15). In addition, lymphangiogenic growth factors and receptors are essential for regulating the mechanism of lymph angiogenesis. Cancer cells secrete lymphangiogenic growth factors to promote the spread of tumor cells to lymph nodes and induce the formation of new lymphatic vessels (16). VEGF-C/D and VEGFR3 signaling has been found to be the most important pathway of lymph angiogenesis (17). VEGF-C first induces the activation of VEGFR3, which leads to the phosphorylation of serine kinases ERK, and ultimately promotes the proliferation, migration, and survival of lymphatic endothelial cells (18). VEGF-C is a lymphatic vessel-specific growth factor, which is increased in expression in various human tumors, including patients with lymph node metastasis of thyroid cancer (19, 20). Here, we show that SARG overexpression or knockdown increases or decreases VEGF-C and VEGFR3 levels, respectively, in PTC cells. Our study shows for the first time that SARG may act by regulating the VEGF-C/VEGFR3 axis in thyroid cancer cells.

In summary, we show SARG is differently expressed in between PTC and FTC tissues. SARG promotes PTC lymphatic metastasis by regulating VEGF-C/VEGFR3 axis (**Figure 9C**). Additional molecular research is needed to understand how SARG regulates VEGF-C and VEGFR3.

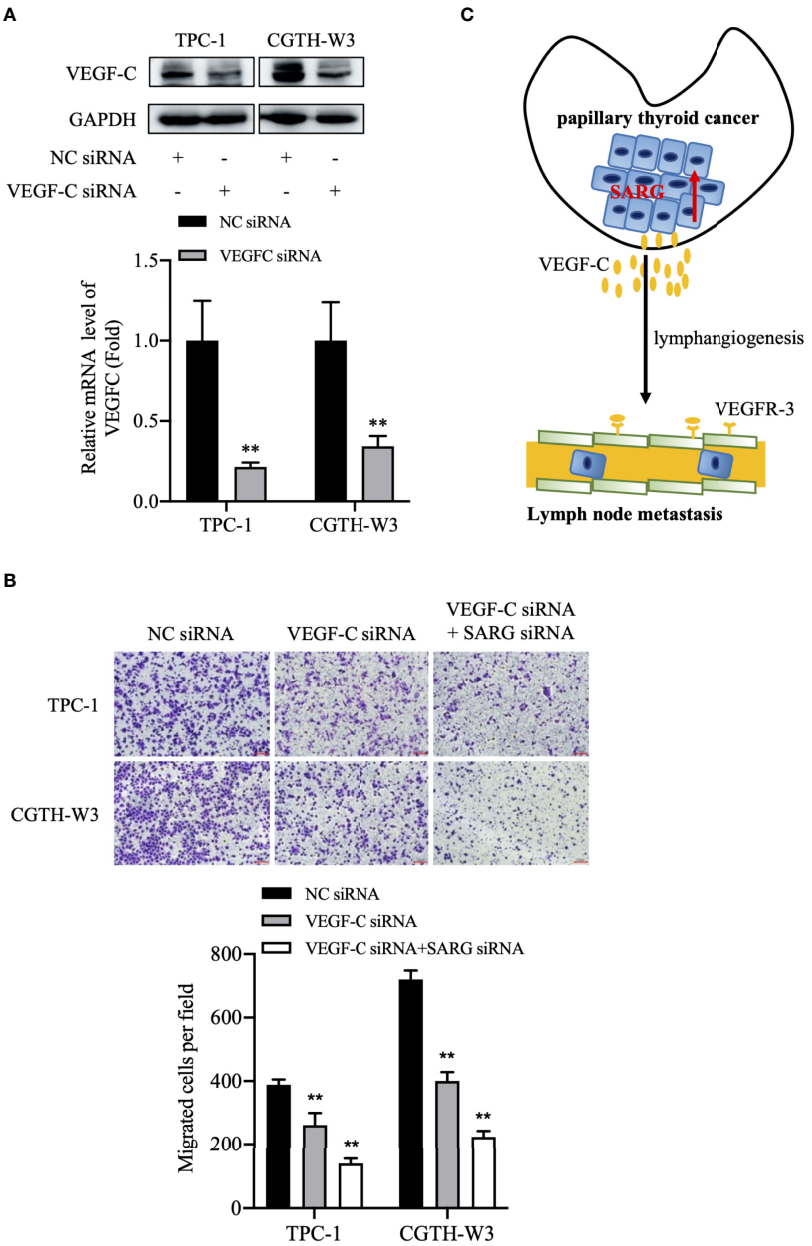

FIGURE 9 | The putative model of lymphatic metastasis mediated by SARG in PTC. **(A)** VEGF-C protein expression in TPC-1 and CGTH-W3 cells was significantly decreased after being transfected with VEGF-C siRNA. GAPDH was used as a loading control, whereas NC siRNA was used as the negative control. **(B)** Knocking down VEGF-C promoted then anti-migration activity of SARG-siRNA in PTC cells. ** p<0.01 compared with NC-siRNA. C, SARG was upregulated in PTC and could upregulate VEGF-C expression in PTC cells, then promoted lymphangiogenesis and lymph node metastasis. PTC, papillary thyroid carcinoma; SARG, specifically androgen-regulated gene; VEGF-C, vascular endothelial growth factor C.

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

The present study was ethically approved by the Medical Ethics Committee of Taizhou University College of Medicine.

AUTHOR CONTRIBUTIONS

S-JX, GC, YL, S-JP, L-LX and SC performed data analysis, data interpretation, and wrote the manuscript; X-FD, B-QD, Z-MW, BJ, X-XC, D-HW, Y-YC, Y-YT, and S-JX conducted the experiment. W-JZ assisted with GEO database analysis. All authors contributed to the article and approved the submitted version.

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Surgical Methods and Social Factors Are Associated With Long-Term Survival in Follicular Thyroid Carcinoma: Construction and Validation of a Prognostic Model Based on Machine Learning Algorithms

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Background: This study aimed to establish and verify an effective machine learning (ML) model to predict the prognosis of follicular thyroid cancer (FTC), and compare it with the eighth edition of the American Joint Committee on Cancer (AJCC) model.

Methods: Kaplan-Meier method and Cox regression model were used to analyze the risk factors of cancer-specific survival (CSS). Propensity-score matching (PSM) was used to adjust the confounding factors of different surgeries. Nine different ML algorithms, including eXtreme Gradient Boosting (XGBoost), Light Gradient Boosting Machine (LightGBM), Random Forests (RF), Logistic Regression (LR), Adaptive Boosting (AdaBoost), Gaussian Naive Bayes (GaussianNB), K-Nearest Neighbor (KNN), Support Vector Machine (SVM) and Multi-Layer Perceptron (MLP),were used to build prognostic models of FTC.10-fold cross-validation and SHapley Additive exPlanations were used to train and visualize the optimal ML model.The AJCC model was built by multivariate Cox regression and visualized through nomogram. The performance of the XGBoost model and AJCC model was mainly assessed using the area under the receiver operating characteristic (AUROC).

Results: Multivariate Cox regression showed that age, surgical methods, marital status, T classification, N classification and M classification were independent risk factors of CSS. Among different surgeries, the prognosis of one-sided thyroid lobectomy plus isthmectomy (LO plus IO) was the best, followed by total thyroidectomy (hazard ratios: One-sided thyroid LO plus IO, 0.086[95% confidence interval (CI),0.025-0.290], $P<0.001$; total thyroidectomy (TT), 0.490[95%CI,0.295-0.814], $P=0.006$). PSM analysis proved that one-sided thyroid LO plus IO, TT, and partial thyroidectomy had no significant differences

in long-term prognosis. Our study also revealed that married patients had better prognosis than single, widowed and separated patients (hazard ratios: single, 1.686 [95%CI,1.146-2.479], *P*=0.008; widowed, 1.671[95%CI,1.163-2.402], *P*=0.006; separated, 4.306[95%CI,2.039-9.093], *P*<0.001). Among different ML algorithms, the XGBoost model had the best performance, followed by Gaussian NB, RF, LR, MLP, LightGBM, AdaBoost, KNN and SVM. In predicting FTC prognosis, the predictive performance of the XGBoost model was relatively better than the AJCC model (AUROC: 0.886 vs. 0.814).

Conclusion: For high-risk groups, effective surgical methods and well marital status can improve the prognosis of FTC. Compared with the traditional AJCC model, the XGBoost model has relatively better prediction accuracy and clinical usage.

Keywords: follicular thyroid carcinoma, machine learning, surgical methods, marital status, prognostic model, AJCC (TNM) staging system

INTRODUCTION

Thyroid carcinoma (TC) is a common endocrine malignant tumor. In recent years, the incidence of TC has been rising sharply worldwide (1, 2). A study from Lim et al. found (3) that between 1974 and 2013, the total incidence of TC in the United States increased by 3% every year. The prognosis of follicular thyroid cancer (FTC) is affected by many factors. However, most current clinical researches focused on papillary thyroid cancer (PTC) and differentiated thyroid cancer (DTC) (4–7), and there is still a lack of large-sample retrospective cohort studies on the prognosis of FTC.

As we all know, surgery is the main method to treat TC, while different surgical methods have different effects on tumor prognosis. On the one hand, there is the possibility of overtreatment. On the other hand, there is the risk of local recurrence caused by conservative surgery. A study by O'Neill etal. (8) revealed that hemithyroidectomy might be the most appropriate treatment for patients with minimally invasive FTC who were younger than 45 years old without vascular invasion. Nixon et al. (9)also confirmed that, for patients with T1T2N0 well differentiated thyroid cancer (WDTC), total thyroidectomy (TT) does not appear to have any benefit in terms of survival compared with patients undergoing thyroid lobectomy. For pT1T2N0 WDTC patients, lobectomy alone is safe and effective (9). On the contrary, a study from Bilimoria et al. (10) indicated that compared with other surgical methods, patients undergoing TT had better survival outcomes and a lower risk of death. However, at present, for the question which surgical method is the best for improving the prognosis of patients, there is still a lack of long-term follow-up study. In recent years, some studies have indicated that sociological factors such as marital status have important impacts on TC (11, 12), but this effect is unclear in patients suffering from FTC only. Other prognostic factors of FTC, such as race, histological type, regional environment, and lymphadenectomy also need to be considered.

With the continuous development of science and technology, artificial intelligence (AI) has been widely used in the medical field. As a branch of AI, machine learning (ML) plays a vital role in disease prevention, screening and diagnosis (13–21). Unfortunately, there is no effective FTC prognostic model based on ML algorithms.The purpose of this study was to review our experience in FTC and assess risk factors for poor prognosis based on initial clinical, sociodemographic and histopathological characteristics. In particular, we aimed to determine whether the FTC patients undergoing only one-sided thyroidlobectomy and isthmectomy (LO plus IO) were sufficient for treatment, explore the relationship between marital status and FTC-specific survival. In the eighth edition of the American Joint Committee on Cancer (AJCC) staging system (22), there are some changes to the TNM staging. However, the role of these new changes in predicting the prognosis of FTC still remains unclear. The ML models were used to predict the prognosis of FTC and compared with the AJCC model. The data for our study came from the database of Surveillance, Epidemiology, and End Results (SEER) and are maintained by the American cancer institute. The SEER database accumulates the survival and prognosis of a large number of rare tumors through long-term follow-up, which provides a valuable opportunity to analyze the prognosis of FTC.

PATIENTS AND METHODS

Data Sources and Study Population

The data were obtained from the SEER database that is also named "Incidence-SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases (1973–2015)". SEER*Stat 8.3.5 software was used for data acquisition. The information of the SEER database comes from 21 cancer registries and covers more than 28% of cases in the United States (https://seer.cancer.gov/). The subjects of the study were patients who were diagnosed with FTC from 2004 to 2015 in 18 regions of the

United States and they were included in the SEER database.It should be noted that the relevant information such as tumor size and degree of capsular invasion was not included in the database until 2004, so the time range of our study was selected from 2004 to 2015. Inclusion criteria: ① There was no restriction on age and gender. ② The histological type was FTC. Exclusion criteria: ① Unknown information/not applicable. ② FTC was not diagnosed as first tumor. ③ FTC was not the main cause of death. The detailed research process was shown in **Figure 1**. The study was deemed to be exempt from formal review, because it used publicly available and confirmed data and gave up the informed consent that was approved by the relevant institutional review board.

Data Selection and Definition

Based on a large amount of literature reading and expert knowledge, the research variables related to the prognosis of FTC were determined. According to the SEER usage guidelines and the Collaborative Stage Data Collection System (CS Manual Online Help: https://web2.facs.org/cstage202/thyroid/

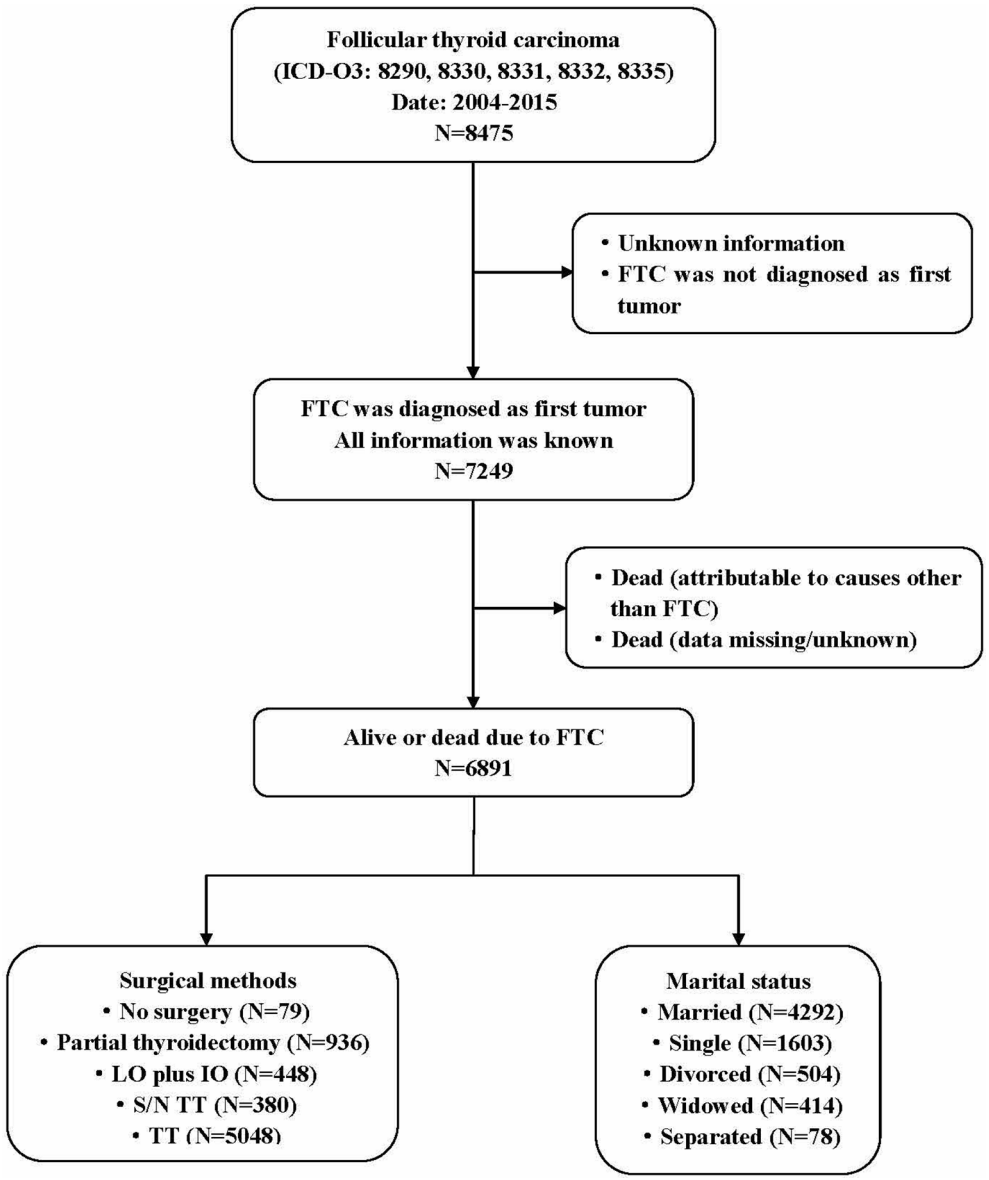

FIGURE 1 | Flow diagram of study design. The data from 6891 patients diagnosed with primary FTC between 2004 and 2015 were included in the study. The study met the Consolidated Standards of Reporting Trials (CONSORT) diagram detailing the study inclusion criteria. Partial thyroidectomy include one-sided thyroid lobectomy or lesion resection. FTC, Follicular thyroid carcinoma; LO plus IO, Lobectomy plus isthmectomy; S/N TT, Subtotal or near total thyroidectomy; TT, Total thyroidectomy.

Thyroidschema.html), the information in the SEER database was extracted. In this study, a total of eleven variables closely related to FTC prognosis were included. Variables include sex, age at diagnosis, race, marital status, histological type, region, surgical methods, lymphadenectomy, T classification, N classification, and M classification.

The definition and classification criteria of FTC and its subtypes refer to the histology codes from International Classification of Diseases for Oncology, Third Revision (ICD-O-3) published by the World Health Organization (WHO) in 2008. FTC includes common subtype (8330), oxyphilic variant (8290), well differentiated subtype (8331), trabecular variant (8332), and minimally invasive subtype (8335). FTC was divided into two major categories based on the histological characteristics of tumors: Classic subtype (8330, 8331, 8332, 8335) and oxyphilic variant (8290). It should be noted that the fourth edition of the WHO new pathological classification of thyroid tumors in 2017 reclassified Hürthle cell carcinoma (HCC)/oxyphilic variant as an independent disease type. At present, the clinical, pathological and molecular characteristics of HCC and FTC are still controversial, and there is a lack of large-scale tumor prognosis cohort studies. Therefore, in this study, HCC was still used as an independent subtype of FTC for prognostic analysis. According to the treatment methods, surgical methods were divided into five categories: no surgery on the primary site, partial thyroidectomy (lobectomy or lesion resection), one-sided thyroid LO plus IO, subtotal or near total thyroidectomy (S/N TT), and TT. Marital status was classified on the basis of the status at diagnosis but not specified. Marital status was divided into married, widowed, separated, divorced, and single (unmarried) status. Lymph node dissection was divided into three categories: no lymph node dissection, one to three regional lymph nodes dissection, and four or more regional lymph nodes dissection. According to the eighth edition of the AJCC cancer staging guidelines (22), age at diagnosis and TNM staging were classified. The patient's attribution area was divided into East, Pacific Coast, Northern Plains, and Southwest in the United States based on the region where the patient's tumor was registered. The races were divided into three categories, namely white, black and other. Other races include American indian, Alaska native, Asian or Pacific islander. The data were removed from the cohort with missing original information and data that were not statistically significant due to the small sample size.The extraction, definition, and classification of the data were completed by two collaborators (Yaqian Mao and Yanling Huang), and the resulting differences were resolved through discussion.

Feature Selection and Model Construction

Univariate and multivariate survival analysis were assessed by Cox proportional-hazards model. The proportional hazards assumption was evaluated by schoenfeld residuals (23). Based on the results of multivariate survival analysis, nine commonly used ML algorithms in the medical were chosen to construct prognostic models for FTC. The end point was the patient's survival status (ie, survival or death) at the end of the 143-month follow-up. The nine ML classifiers include eXtreme Gradient Boosting (XGBoost), Light Gradient Boosting Machine (LightGBM), Random Forests (RF), Logistic Regression (LR), Adaptive Boosting (AdaBoost), Gaussian Naive Bayes (Gaussian NB), K-Nearest Neighbor (KNN), Support Vector Machine (SVM) and Multi-Layer Perceptron (MLP). The SHapley Additive exPlanations (SHAP) method was used to explain the visualization of the model. The goal of SHAP is to explain the prediction of ML by calculating the contribution of each feature to the prediction result, and it is also the most commonly used black box model interpretation method at present (24, 25). The AJCC model was built by the multivariate COX regression analysis, and the R package, named "rms", "foreign", "survival" and "survivalROC", were used to calculate the AUROC value and draw the nomogram and calibration curve.

As an integrated learning algorithm, XGBoost combines the predictions from an ensemble of weak regression trees that are added sequentially to the model to maximize predictive performance and minimize model complexity (26). At the same time, XGBoost adds a complexity control model and learns from RF to reduce the calculation, thus making the model not easy to be over-fitting.As a Gradient Boosted Decision Tree (GBDT) algorithm (27), LightGBM uses a histogram-based algorithm to speed up the training process, reduces memory consumption, and combines advanced network communication to optimize parallel learning that is called the parallel voting decision tree algorithm. RF, an ensemble learning algorithm, is a combination recognition model formed by combining multiple decision trees (28, 29). The accuracy of RF classification is relatively high, it is not easy to be over-fitting, and the anti-noise ability is strong, which is easy to implement, but the amount of calculation is relatively large. NB estimates the conditional probability of each category under each feature by assuming that P (x/yi) obeys Gaussian distribution (ie, normal distribution). The NB classifier is widely used in many classification tasks, because its performance is comparable to state-of-the-art classifiers, and it is simple to implement and fast to execute (30, 31). The advantage of the Gaussian NB model is that it has a stable classification efficiency and a relatively simple algorithm, and performs well on small-scale data. LR is one of the most commonly used binary classification algorithms, and is the gold standard for analyzing binary classification medical data (32, 33), because it can not only provide prediction results, but also provide additional information about the prediction results, such as the odds ratio (OR) of the diagnosis and the 95% confidence interval (CI) (34). AdaBoost is a typical boosting algorithm. Using "reweighting", that is, in each round of the training process, each training sample is provided a new weight according to the sample distribution. By reducing the classification error of individual learner each time, the importance of good individual learner is increased, and the final integrated learner is obtained (35). MLP is a

forward structure of artificial neural network (ANN) that is generalized by perceptron. It integrates the neuron model in the perceptron algorithm and overcomes the weakness of the perceptron to recognize linearly inseparable data, and it has the ability to quickly solve complex problems. The ML approach of MLP-ANN is derived from the basic structure of artificial neurons, and the function of the network depends on the training they receive. This training is based on the presentation of real-world examples and simulates the learning process of a system by determining the differences between the response given by the network and the expected behavior (36, 37). KNN means that in the feature space, if most of the k nearest (ie nearest neighbors in the feature space) samples near a sample belong to a certain category, the sample also belongs to this category (38). The advantages of KNN model are high accurate and insensitive to outliers, and no data input assumptions. SVM, an efficient way to build classifiers, aims to create a decision boundary between two classes, thus making it possible to predict labels from one or more feature vectors (39). Combining multiple parameter values, using the SVM classification algorithm in a nonlinear space enables efficient data classification. Compared with other ML methods, SVM is very powerful in identifying subtle patterns in complex datasets, which can be used for tumor prediction (40), genetic screening (41), and drug applications (42, 43).

Resampling method was used to train and test ML classifiers. Model performance evaluation was mainly conducted through the area under the receiver operating characteristic curve (AUROC), accuracy, sensitivity, specificity, and negative predictive value (NPV). Among them, the classifier with the largest AUROC value was selected as the best model.Then, the optimal model was trained through 10-fold cross-validation,so as to improve its prediction accuracy and applicability. The following packages of Python were used for ML model construction and optimization, including "sklearn.linear model", "sklearn.ensemble", "xgboost1.2.1", "lightgbm 3.2.1", "sklearn 0.22.1", "shap 0.39.0", etc.

Statistical Methods

All statistical analyses in our study were performed using the IBM SPSS software (version 25.0 for windows, SPSS Inc., Chicago, IL, USA), R software (version 3.6.3, https://www.r-project.org/) and Python software (version 3.6.13, https://www.python.org/). In the baseline analysis, categorical variables were represented by counts and proportions, and differences between groups were analyzed using Pearson chi-square tests. In order to reduce the model error caused by the mutual influence between variables, correlation analysis on the data was carried out and showed by heat map. In addition, the variance inflation factor (VIF) was also used to assess the multicollinearity between variables. The relationship between significant variables and cancer-specific survival (CSS) was calculated using the Kaplan-Meier method, and the log-rank test was used to compare distribution differences. CSS was calculated with the cumulative incidence. In order to further adjust the potential bias in our cohort, the propensity score matching (PSM) method was used to match one-sided thyroid LO plus IO with other surgical methods and non-surgical cases. The PSM method is a statistical method for matching the treatment group and the control group, so that the clinical indicators of the research object are comparable to balance variables and reduce bias (44). All statistical analysis adopted two-sided test, and *P* values less than 0.05 indicated significant.

RESULTS

Baseline Characteristics

A total of 6891 FTC patients were included in this study, including 4930 female patients and 1961 male patients, with a median follow-up time of 64 months (range, 29 to100 months). The baseline characteristics of all FTC patients were shown in **Table 1**, and the detailed research flowchart was shown in **Figure 1**.

Feature Variable Screening

This study initially included eleven variables based on professional knowledge. Correlation test was performed among all variables, and the correlation heat map showed that there was no significant correlation among them (**Figure 2**). The VIF of all variables was less than 10, which indicated that there was no multicollinearity among the variables. **Figure 3** indicates the proportional hazard hypothesis test of Cox regression. The results revealed that all residual fitting curves of each variable were close to the level, so it was suitable for the Cox model.

Univariate and Multivariate Cox Regression Analysis

In univariate analysis, compared with patients who did not undergo surgery, patients who received surgery were closely related to CSS improvements (hazard ratios[HRs]: One-sided thyroid LO plus IO, 0.008[95%CI,0.002-0.027]; TT, 0.041 [95%CI,0.028-0.059]; partial thyroidectomy, 0.026[95% CI,0.015-0.046]; S/N TT, 0.048[95%CI,0.027-0.086]; *P* values<0.001 for all comparisons, **Table 2**). Compared with married patients (living with their spouse), patients who were widowed and separated were closely related to CSS deterioration (HRs: Widowed, 5.601[95%CI,4.070-7.708]; separated, 3.839[95%CI,1.875-7.860]; all *P* values<0.001, **Table 2**). The significant variables ($P<0.05$) in the univariate analysis were incorporated into the multivariate analysis. Finally, a total of six variables were included in the Cox regression model (**Table 2**). Among different surgeries, the prognosis of one-sided thyroid LO plus IO (HR, 0.086[95% CI,0.025-0.290], $P<0.001$) was the best, followed by TT (HR, 0.490[95%CI,0.295-0.814], $P=0.006$). Among different marital

TABLE 1 | Demographic characteristics of the participants.

Characteristics	Total 6891	Survival 6650	Death 241	X^2	*P* -Value
Age (y), No.(%)				379.980	<0.001
<25	396 (5.747)	394 (5.925)	2 (0.830)		
25-40	1444 (20.955)	1435 (21.579)	9 (3.734)		
40-55	2244 (32.564)	2210 (33.233)	34 (14.108)		
55~70	1890 (27.427)	1815 (27.293)	75 (31.120)		
70~85	851 (12.349)	749 (11.263)	102 (42.324)		
≥85	66 (0.958)	47 (0.707)	19 (7.884)		
Sex, No.(%)				13.644	<0.001
Female	4930 (71.543)	4783 (71.925)	147 (60.996)		
Male	1961 (28.457)	1867 (28.075)	94 (39.004)		
Race, No.(%)				2.406	0.300
White	5488 (79.640)	5304 (79.759)	184 (76.349)		
Black	786 (11.406)	757 (11.383)	29 (12.033)		
Other*	617 (8.954)	589 (8.857)	28 (11.618)		
Marital status, No.(%)				146.498	<0.001
Married	4292 (62.284)	4176 (62.797)	116 (48.133)		
Single	1603 (23.262)	1562 (23.489)	41 (17.012)		
Divorced	504 (7.314)	484 (7.278)	20 (8.299)		
Widowed	414 (6.008)	358 (5.383)	56 (23.237)		
Separated	78 (1.132)	70 (1.053)	8 (3.320)		
Region, No.(%)				0.928	0.819
East	2863 (41.547)	2769 (41.639)	94 (39.004)		
Pacific Coast	3076 (44.638)	2966 (44.602)	110 (45.643)		
Northern Plains	575 (8.344)	552 (8.301)	23 (9.544)		
Southwest	377 (5.471)	363 (5.459)	14 (5.809)		
Histology, No.(%)				10.652	0.001
Classic subtype	4905 (71.180)	4756 (71.519)	149 (61.826)		
HCC/Oxyphilic variant	1986 (28.820)	1894 (28.481)	92 (38.174)		
Surgical methods, No.(%)				383.321	<0.001
No surgery	79 (1.146)	45 (0.677)	34 (14.108)		
Partial thyroidectomy	936 (13.583)	916 (13.774)	20 (8.299)		
One-sided thyroid LO plus IO	448 (6.501)	445 (6.692)	3 (1.245)		
S/N TT	380 (5.514)	363 (5.459)	17 (7.054)		
TT	5048 (73.255)	4881 (73.398)	167 (69.295)		
Lymphadenectomy, No.(%)				24.013	<0.001
None	4871 (70.686)	4717 (70.932)	154 (63.900)		
1 to 3 regional lymph nodes	1460 (21.187)	1413 (21.248)	47 (19.502)		
4 or more regional lymph nodes	560 (8.127)	520 (7.820)	40 (16.598)		
T classification, No.(%)				901.804	<0.001
T1	1635 (23.727)	1618 (24.331)	17 (7.054)		
T2	2772 (40.226)	2737 (41.158)	35 (14.523)		
T3	2299 (33.362)	2188 (32.902)	111 (46.058)		
T4	185 (2.685)	107 (1.609)	78 (32.365)		
N classification, No.(%)				522.532	<0.001
N0	6687 (97.040)	6506 (97.835)	181 (75.104)		
N1a	110 (1.596)	91 (1.368)	19 (7.884)		
N1b	94 (1.364)	53 (0.797)	41 (17.012)		
M classification, No.(%)				1344.483	<0.001
M0	6667 (96.749)	6533 (98.241)	134 (55.602)		
M1	224 (3.251)	117 (1.759)	107 (44.398)		
AJCC 8th Edition, No.(%)				1680.481	<0.001
I	5585 (81.048)	5531 (83.173)	54 (22.407)		
II	1035 (15.020)	974 (14.647)	61 (25.311)		
III	44 (0.639)	33 (0.496)	11 (4.564)		
IVa	45 (0.653)	23 (0.346)	22 (9.129)		
IVb	182 (2.641)	89 (1.338)	93 (38.589)		

**Other include American indian/Alaska native, Asian or Pacific islander; Partial thyroidectomy include lobectomy or lesion resection.*

HCC, Hürthle cell carcinoma; LO plus IO, Lobectomy plus isthmectomy; S/N TT, Subtotal or near total thyroidectomy; TT, Total thyroidectomy; AJCC, American Joint Committee on Cancer.

status, married patients had better prognosis than patients with single (HR,1.686[95%CI,1.146-2.479], *P*=0.008), widowed(HR,1.671[95%CI,1.163-2.402], *P*=0.006), and separated (HR, 4.306[95%CI,2.039-9.093], *P*<0.001) patients.

Kaplan-Meier Survival Analysis

The influences of significant prognostic factors on the FTC were shown in the Kaplan-Meier survival plots (**Figures 4A–F**). In addition, Kaplan-Meier survival analysis was also performed for

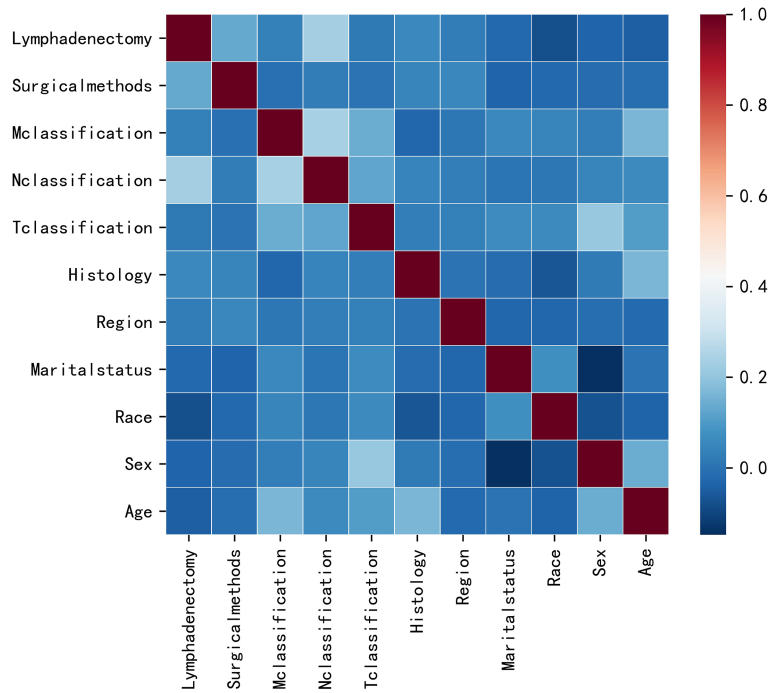

FIGURE 2 | Results of correlation analysis between all variables.

patients whose lesions were only confined to the unilateral thyroid capsule and without distant metastasis (**Figure 5A**). The results showed that compared with patients who did not undergo surgery, patients who underwent surgery had a better prognosis. Propensity scores were used to match one-sided thyroid LO plus IO with other different treatments. The effects of different surgical methods after PSM on FTC prognosis were also described using Kaplan-Meier survival plots (**Figures 5B–F**).The results proved that one-sided LO plus IO, TT, and partial thyroidectomy had no significant differences in long-term prognosis.One-sided thyroid LO plus IO had a relatively better prognosis compared with patients without surgery and those who received S/N TT. The mean survival time and variable settings for each prognostic factor in the Kaplan-Meier curve (**Figures 4**, **5**) were shown in **Table 3**.

Machine Learning Model and AJCC Model

Table 4 and **Figures 6A–C** display the performance of nine different ML methods. According to the analysis results of the training set and the test set, it was found that the XGBoost model had the best performance. **Figures 6D–H** shows the ranking of variable importance for the five main ML classifiers. All the five ML models showed that age, surgical methods, marital status, T classification, N classification, and M classification were the most important variables affecting the prognosis of FTC. **Figures 7A, B** exhibit the ROC curves of the XGBoost model in the training set and the validation set after 10-fold cross-validation. It can be seen from **Figure 7C** that when the learning curves of the training set and the validation set tend to be the same, the performance of the XGBoost model is the best, and its best AUROC value in the test set is 0.886 (**Figure 7D**). At this time, the parameter settings of the XGBoost model were: Objective: Reg: Logistic, learning_rate: 0.03, max_depth: 3, min_child_weight: 1, reg_lambda: 1. **Figure 7E** shows the calibration plot of XGBoost model, and **Figure 7F** is a SHAP summary of the FTC prognostic model.The higher the SHAP feature value is, the redder the dot color is in the graph, and the lower the SHAP feature value is, the bluer thedot color is in the graph. As shown in the Figure, the larger the value of T classification is, the higher the risk of death in patients of FTC is. A total of four variables were included in the eighth edition of the AJCC cancer staging system, namely age at diagnosis, T classification, N classification, and M classification. The AJCC model was visualized through the nomogram, and the AUROC value of the model was 0.814 (**Figure 8**).

DISCUSSION

In this study, it was observed that treatment methods (different surgical methods or active surveillance) and marital status were important prognostic factors related to CSS based on univariate and multivariate Cox regression model. Our results reshaped the traditional view that TT was the standard for treating FTC.

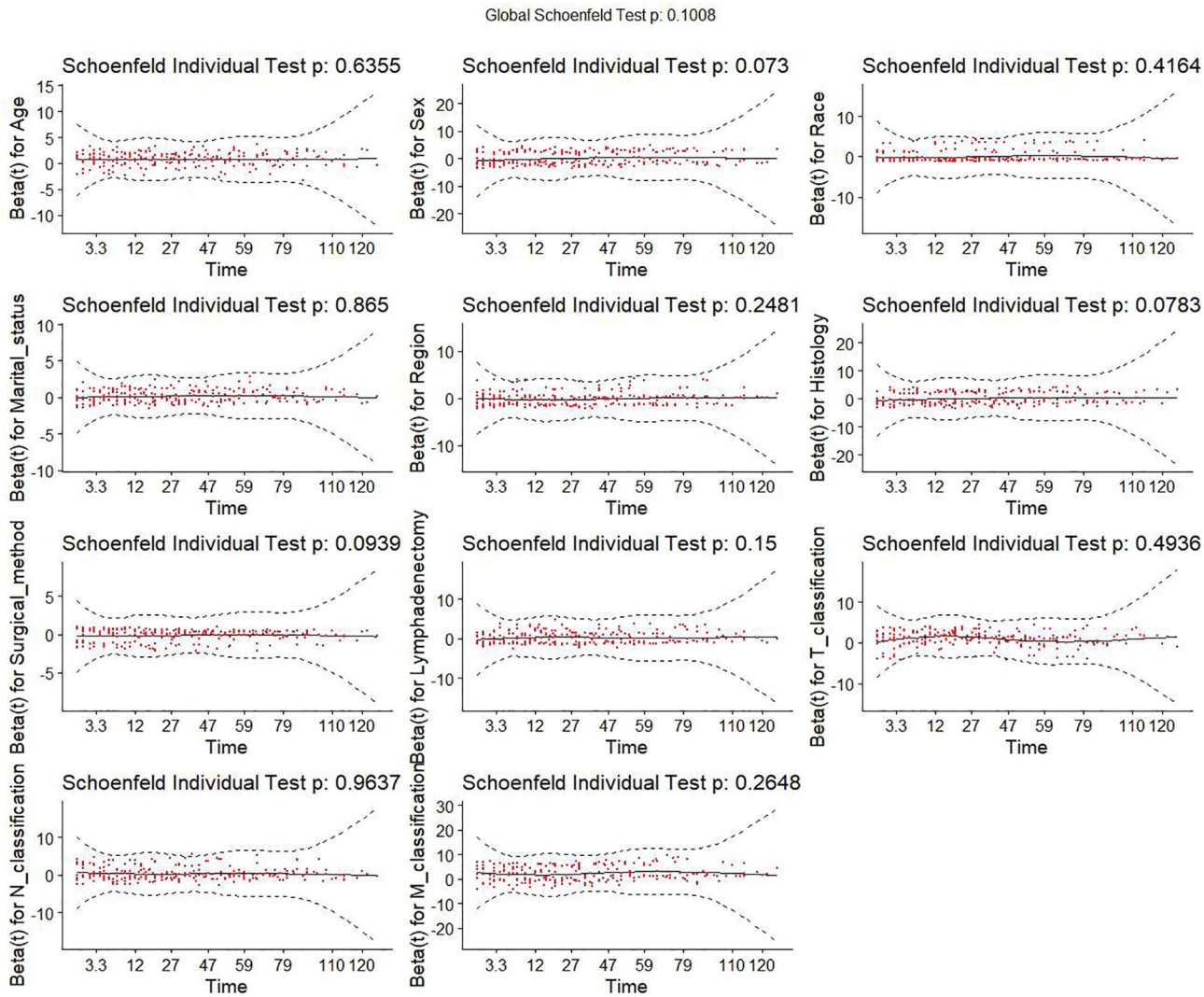

FIGURE 3 | Proportional hazard assumption test of all variables. Y-axis is the beta values for each variable. X-axis is the observed survival time in month. Red dots are the residuals of beta values of different variables. Black solid line is the fitting curve of all residuals. Dashed lines are the lower and upper limits of the 95% confidence interval of all residuals.

The results of multivariate Cox regression were used to construct ML models for FTC patients. The variables in the ML models include age, surgical methods, marital status, T classification, N classification and M classification. As far as we know, this is the first article that uses different ML methods and AJCC cancer staging system to predict the long-term survival of FTC. Our study showed that the XGBoost model appears to have better predictive accuracy than the traditional AJCC cancer staging system.

The analysis of prognostic factors of TC is necessary, especially for FTC patients with relatively high mortality and prone to distant metastases. Unfortunately, due to the lack of clinical data (Because compared with PTC, the prevalence and awareness of FTC is lower) and the low incidence of end-point events, it is difficult to establish prognostic model for CSS of FTC. Secondly, most prediction models or staging systems currently used in clinical practice are for individuals with DTC (including PTC and FTC), medullary cancer and undifferentiated cancer, rather than FTC patients. Thirdly, the predictors of these models mainly include age at diagnosis, tumor size, lymph nodes and distant metastasis, while ignoring other common factors that may affect the prognosis of FTC, such as sociological factors and surgical methods.Therefore, we hold the view that establishing a complete prognostic model for FTC patients has important clinical significance.

As a classic statistical method that is often used to develop clinical prognostic models, Cox regression belongs to regression analysis, which predicts event probability by selecting and using

TABLE 2 | Univariate and multivariable analysis of cancer-specific survival in follicular thyroid cancer.

Characteristics	Univariate Survival Analysis		Multivariable Survival Analysis	
	Hazard Ratio (95%CI)	*P* Value	Hazard Ratio (95%CI)	*P* Value
Age (y), No.(%)				
<25	1 [Reference]	NA	1 [Reference]	NA
25-40	1.210 (0.262-5.602)	0.807	1.332 (0.284-6.257)	0.716
40-55	2.870 (0.689-11.946)	0.147	2.878 (0.674-12.294)	0.154
55-70	8.018 (1.969-32.653)	0.004	5.269 (1.248-22.253)	0.024
70-85	27.555 (6.798-111.692)	<0.001	14.962 (3.523-63.541)	<0.001
≥85	94.026 (21.872-404.217)	<0.001	32.086 (6.993-147.217)	<0.001
Sex, No.(%)				
Female	1.637 (1.264-2.121)	<0.001	1.241 (0.935-1.647)	0.136
Race, No.(%)				
White	1 [Reference]	NA		
Black	1.150 (0.777-1.701)	0.485		
Other*	1.407 (0.946-2.095)	0.092		
Marital status, No.(%)				
Married	1 [Reference]	NA	1 [Reference]	NA
Single	1.003 (0.703-1.432)	0.986	1.686 (1.146-2.479)	0.008
Divorced	1.499 (0.933-2.409)	0.095	1.396 (0.860-2.265)	0.177
Widowed	5.601 (4.070-7.708)	<0.001	1.671 (1.163-2.402)	0.006
Separated	3.839 (1.875-7.860)	<0.001	4.306 (2.039-9.093)	<0.001
Region, No.(%)				
East	1 [Reference]	NA		
Pacific Coast	1.116 (0.84-1.4708)	0.434		
Northern Plains	1.207 (0.765-1.904)	0.419		
Southwest	1.172 (0.668-2.054)	0.580		
Histology, No.(%)				
Classic subtype	1 [Reference]	NA	1 [Reference]	NA
HCC/Oxyphilic variant	1.461 (1.127-1.895)	0.004	1.136 (0.861-1.499)	0.366
Surgical methods, No.(%)				
No surgery	1 [Reference]	NA	1 [Reference]	NA
Partial thyroidectomy	0.026 (0.015-0.046)	<0.001	0.551 (0.280-1.081)	0.083
One-sided thyroid LO plus IO	0.008 (0.002-0.027)	<0.001	0.086 (0.025-0.290)	<0.001
S/N TT	0.048 (0.027-0.086)	<0.001	0.661 (0.331-1.321)	0.241
TT	0.041 (0.028-0.059)	<0.001	0.490 (0.295-0.814)	0.006
Lymphadenectomy, No.(%)				
None	1 [Reference]	NA	1 [Reference]	NA
1 to 3 regional lymph nodes	1.081 (0.780-1.500)	0.639	1.031 (0.720-1.477)	0.868
4 or more regional lymph nodes	2.673 (1.886-3.788)	<0.001	1.366 (0.893-2.090)	0.151
T classification, No.(%)				
T1	1 [Reference]	NA	1 [Reference]	NA
T2	1.213 (0.679-2.165)	0.514	1.224 (0.684-2.193)	0.496
T3	4.948 (2.969-8.244)	<0.001	3.146 (1.870-5.291)	<0.001
T4	54.331 (32.134-91.861)	<0.001	10.955 (6.211-19.322)	<0.001
N classification, No.(%)				
N0	1 [Reference]	NA	1 [Reference]	NA
N1a	7.716 (4.807-12.384)	<0.001	1.670 (0.954-2.924)	0.072
N1b	22.403 (15.937-31.492)	<0.001	2.248 (1.476-3.424)	<0.001
M classification, No.(%)				
M0	1 [Reference]	NA	1 [Reference]	NA
M1	38.357 (29.599-49.706)	<0.001	9.214 (6.669-12.729)	<0.001

**Other include American indian/Alaska native, Asian or Pacific islander; Partial thyroidectomy include lobectomy or lesion resection.*

HCC, Hürthle cell carcinoma; CI, Confidence interval; NA, Not applicable; LO plus IO, Lobectomy plus isthmectomy; S/N TT, Subtotal or near total thyroidectomy; TT, Total thyroidectomy.

a small number of variables. Most importantly, Cox regression considers the time of the event in its prediction process, and the model performance is better. Meanwhile, it can express the patient's predictive effect in a simple and easy-to-interpret form (HR), and visualize it in the form of a nomogram. Therefore, Cox regression was used as a method of variable screening and a modeling tool for traditional cancer staging systems. In clinical practice, the current eighth edition AJCC cancer staging system is a widely used and accepted model (22). It is worth noting that in this staging system, FTC is usually studied in combination with PTC (ie, DTC). Therefore, the clinical prognosis model of FTC was constructed based on the eighth edition of the AJCC staging system. With the continuous development of the precision medicine field, people have put

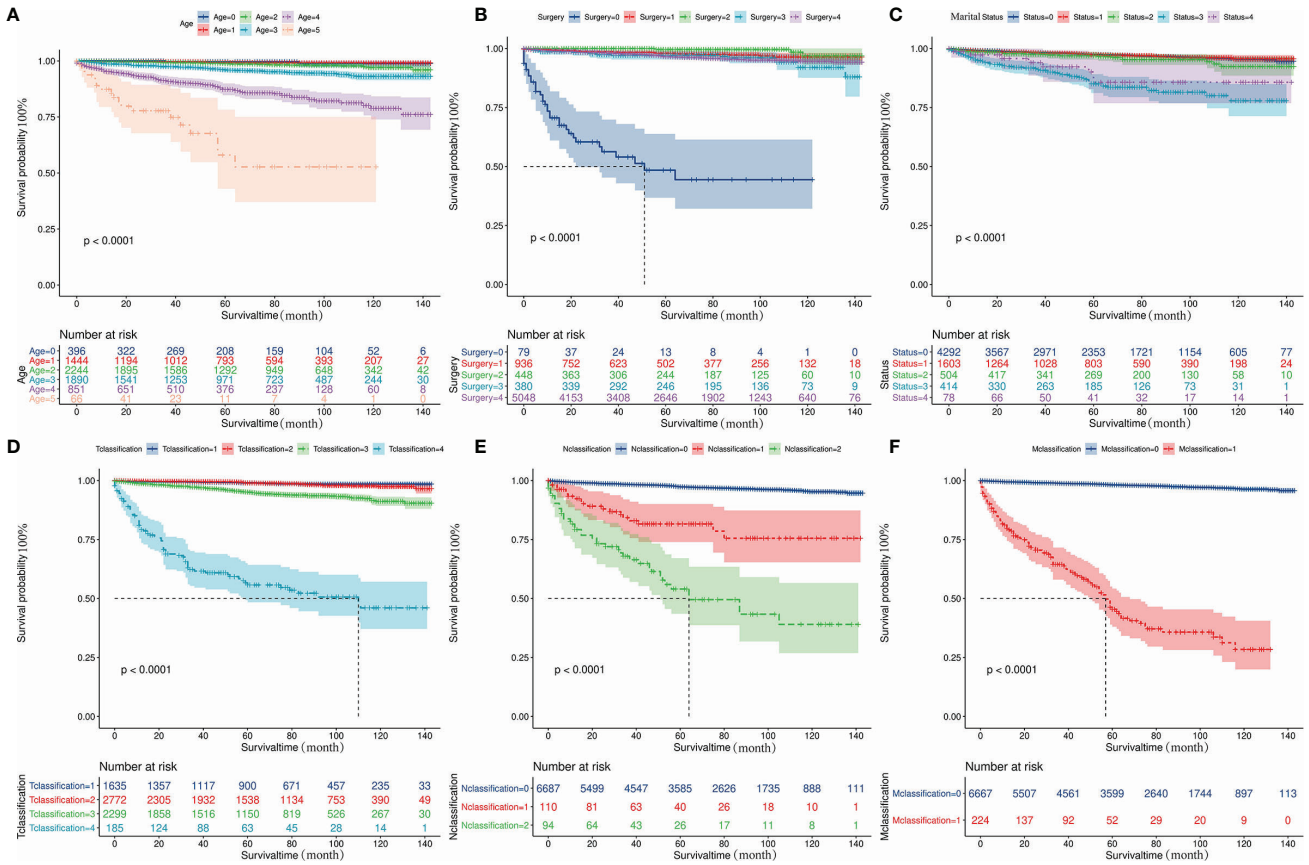

FIGURE 4 | Kaplan-Meier curves depicting cancer-specific survival of important prognostic factors. **(A)** The effect of diagnosis age on the prognosis of patients with FTC. **(B)** The effect of surgical methods on the prognosis of patients with FTC. **(C)** The effect of marital status on the prognosis of patients with FTC. **(D)** The effect of T classification on the prognosis of patients with FTC. **(E)** The effect of N classification on the prognosis of patients with FTC. **(F)** The effect of M classification on the prognosis of patients with FTC. FTC, Follicular thyroid cancer.

forward higher requirements for the accuracy and applicability of various models. Some studies have proved that ML has stronger data processing and knowledge acquisition capabilities compared with traditional statistics. Obviously, this innovative method is an important tool in the field of precision medicine, and helps to choose the best diagnosis and treatment strategy.

In this study, nine different novel ML algorithms were applied to construct the prognostic model of FTC. According to some research, the XGBoost model had better predictive performance than other predictive models, no matter in the training set or the test set. Most importantly, it seems to have better prediction accuracy than the traditional AJCC model. XGBoost is a boosted tree model. The applied algorithm is based on the improvement of GBDT. It can be used to solve classification problems as well as regression problems. In recent years, more and more clinical studies have used the XGBoost algorithm for disease screening, prevention and diagnosis, with positive results. A study from Wu et al. (45) revealed that in determining the clinical prognosis of young hypertensive patients, the XGBoost model was comparable to the Cox regression method and better than the recalibrated Framingham Risk Score model. Hou et al. (46) used XGBoost to develop an ML method to predict the 30-day mortality of sepsis patients. This studies illustrated that the XGBoost model has the best predictive value (AUC,0.857[95% CI,0.839-0.876]) compared with the traditional LR model (AUC,0.819[95%CI, 0.800-0.838]) and simplified acute physiological score II (SAPS II) score prediction model (AUC,0.797[95%CI, 0.781-0.813]). In addition, the research conducted by Zheng et al. (47) also demonstrated that the XGBoost model based on real-world evidence had good predictive performance in predicting the blood concentration of tacrolimus, which could provide guidance for the adjustment of the plan in clinical practice. Five commonly used ML algorithms were used to rank FTC's risk factors in importance. The research results showed that age, surgical methods, marital status, T classification, N classification and M classification were important variables that affect the prognosis of FTC, which was consistent with the analysis results of multivariate Cox regression. It is worth noting that the risk factors of age, T classification, N classification and M classification have been

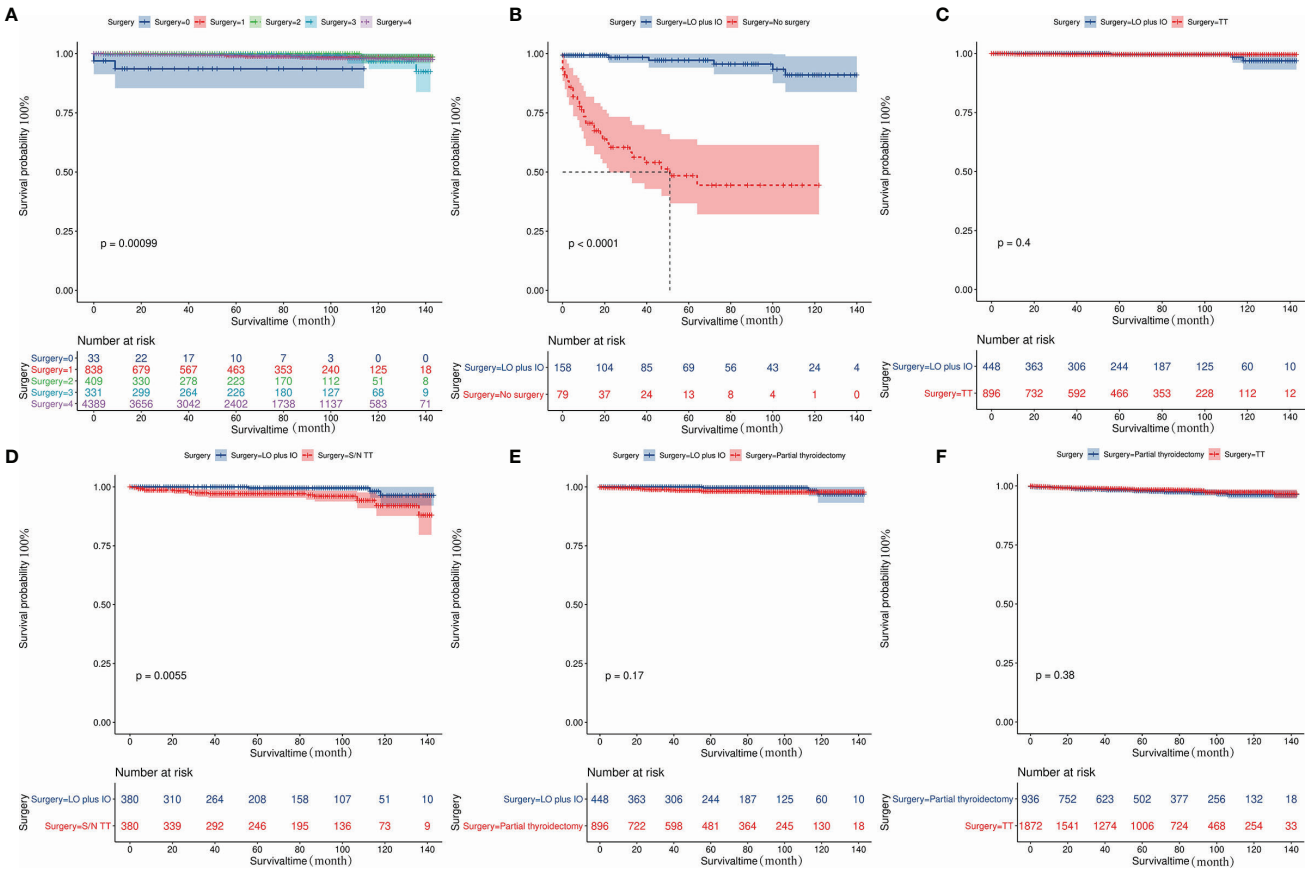

FIGURE 5 | Kaplan-Meier curves depicting cancer-specific survival of different surgical methods in patients. **(A)** indicates the Kaplan-Meier analysis results of different surgical methods in patients with lesions confined to unilateral thyroid capsule and without distant metastasis. **(B-F)** Indicates the Kaplan-Meier analysis results of different surgical methods on tumor prognosis after propensity score matching. The results showed that one-sided LO plus IO, TT, and partial thyroidectomy had no significant difference in long-term prognosis; One-sided thyroid LO+IO had a relatively better prognosis compared with patients without surgery and those who received S/N TT: **(B)** No surgery cases matched to one-sided thyroid LO plus IO (1:2, *P*<0.001). **(C)** TT cases matched to one-sided thyroid LO plus IO (2:1, *P*=0.4); **(D)** S/N TT cases matched to one-sided thyroid LO plus IO (1:1, *P*<0.005); **(E)** Partial thyroidectomy cases matched to one-sided thyroid LO plus IO (2:1, *P*=0.17). **(F)** Partial thyroidectomy cases matched to TT (1:2, *P*=0.38). FTC, Follicular thyroid carcinoma; LO plus IO, Lobectomy plus isthmectomy; S/N TT, Subtotal or near total thyroidectomy; TT, Total thyroidectomy.

fully discussed in previous observational studies (48, 49), but the impacts of different surgical methods and sociological factors (marital status) on the prognosis of FTC are still unknown. So, we conducted a detailed analysis on these variables.

Surgery is the main way to treat TC, but the choice of surgical method is still controversial (9, 10, 50). Since FTC is more aggressive than PTC, early treatment is essential to improve the prognosis of FTC patients. Our research confirmed that whether it was univariate or multivariate analysis, surgical methods had high HR values, which suggested that surgeries were important prognostic indicators of FTC. FTC is mostly unilateral lesions, and TT can lead to permanent hypothyroidism or even hypoparathyroidism, which seriously affects the quality of patient's life. Therefore, some scholars suggested that patients with FTC with a single lesion on one side and no high-risk factors can perform one-sided thyroid LO plus IO (51, 52). Some scholars also argued that as long as the tumor was confined to one lobe, TT should also be performed (51). For this reason, we performed Kaplan-Meier survival analysis for 6000 patients whose lesions were only confined to the unilateral capsule and no distant metastasis. The results revealed that one-sided thyroid LO plus IO was still the best treatment, followed by local surgical excision, TT and S/N TT (Log Rank=18.49, *P*=0.001). In order to further control the confounding, a PSM analysis was conducted, and the results proved that one-sided thyroid LO plus IO, TT, and local surgical excision had no significant differences in long-term prognosis. It should be noted that the type of initial surgical intervention should consider all risk factors such as tumor size, lymph node metastasis and distant metastasis, which is the primary factor in determining the type of treatment. The subjects included in this study were mainly FTC patients with early non-lymph node and distant metastases. Compared with

TABLE 3 | CSS survival time and variable assignment for each significant prognostic factor in Kaplan-Meier analysis results.

Variable assignment	No.(%)	Mean survival time of 143-month, 95%CI	10-year CSS, %	Log Rank	*P*
Age (y)				506.119	<0.001
0: <25	396 (5.747)	142.20 (141.09-143.30)	99%		
1: 25-40	1444 (20.955)	142.08 (141.48-142.68)	99%		
2: 40-55	2244 (32.564)	140.79 (140.06-141.53)	97%		
3: 55-70	1890 (27.427)	136.99 (135.66-138.31)	93%		
4: 70-85	851 (12.349)	123.71 (120.23-127.20)	78%		
5: ≥85	66 (0.958)	79.28 (64.32-94.24)	53%		
Surgical methods				718.331	<0.001
0: No surgery	79 (1.146)	65.00 (51.25-78.75)	41%		
1: Partial thyroidectomy	936 (13.583)	139.79 (138.40-141.18)	96%		
2: One-sided thyroid LO plus IO	448 (6.501)	141.93 (140.74-143.13)	98%		
3: S/N TT	380 (5.514)	136.34 (133.71-138.96)	91%		
4: TT	5048 (73.255)	138.00 (137.26-138.74)	94%		
Marital status				160.665	<0.001
0: Married	4292 (62.284)	139.00 (138.29-139.72)	95%		
1: Single	1603 (23.262)	139.03 (137.84-140.23)	96%		
2: Divorced	504 (7.314)	137.05 (134.52-139.59)	93%		
3: Widowed	414 (6.008)	120.11 (115.34-124.88)	79%		
4: Separated	78 (1.132)	127.33 (117.84-136.82)	84%		
T classification				1149.414	<0.001
0: T1	1635 (23.727)	141.47 (140.75-142.19)	–		
1: T2	2772 (40.226)	141.10 (140.48-141.73)	98%		
2: T3	2299 (33.362)	135.51 (134.16-136.86)	97%		
3: T4	185 (2.685)	83.07 (73.65-92.48)	91%		
N classification				708.276	<0.001
0: N0	6687 (97.040)	138.93 (138.35-139.52)	95%		
1: N1a	110 (1.596)	115.45 (104.69-126.21)	74%		
2: N1b	94 (1.364)	78.36 (64.99-91.73)	40%		
M classification				2038.850	<0.001
0: M0	6667 (96.749)	139.97 (139.46-140.47)	96%		
1: M1	224 (3.251)	66.86 (59.00-74.72)	32%		
Surgical methods[#]				18.490	0.001
0: No surgery	33 (0.55)	107.03 (97.69-116.38)	–		
1: Partial thyroidectomy	838 (13.97)	141.74 (140.82-142.67)	99%		
2: One-sided thyroid LO plus IO	409 (6.82)	142.59 (141.79-143.39)	99%		
3: S/N TT	331 (5.52)	140.28 (138.79-141.78)	95%		
4: TT	4389 (73.15)	141.37 (140.91-141.83)	98%		
Surgical method*				68.939	<0.001
0: No surgery	79 (33.33)	65.00 (51.25-78.75)	41%		
1: One-sided thyroid LO plus IO	158 (66.67)	134.02 (129.35-138.69)	91%		
Surgical method*				0.703	0.402
0: TT	896 (66.67)	142.50 (141.93-143.07)	100%		
1: One-sided thyroid LO plus IO	448 (33.33)	141.93 (140.74-143.13)	98%		
Surgical method*				7.716	0.005
0: S/N TT	380 (50.00)	136.34 (133.71-138.96)	91%		
1: One-sided thyroid LO plus IO	380 (50.00)	141.74 (140.34-143.15)	98%		
Surgical method*				1.916	0.166
0: Partial thyroidectomy	896 (66.67)	140.65 (139.42-141.87)	98%		
1: One-sided thyroid LO plus IO	448 (33.33)	141.93 (140.74-143.13)	98%		
Surgical method*				0.772	0.380
0: Partial thyroidectomy	936 (33.33)	139.79 (138.40-141.18)	96%		
1: TT	1872 (66.67)	140.49 (139.61-141.36)	97%		

[#]*Indicates the Kaplan-Meier analysis results of different surgical methods in patients with lesions confined to unilateral thyroid capsule and without distant metastasis. *Indicates the Kaplan-Meier analysis results of different surgical methods on tumor prognosis after propensity score matching method. It should be noted that the classification items of some variables cannot estimate the 10-year survival rate of CSS due to the insufficient follow-up time and the lack of end-point events, then we use "-" to indicate.*

CSS, Cancer-specific survival; LO plus IO, Lobectomy plus isthmectomy; S/N TT, Subtotal or near total thyroidectomy; TT, Total thyroidectomy; AJCC, American Joint Committee on Cancer.

TT, one-sided thyroid LO plus IO or partial thyroidectomy also can achieve a good prognosis, which is of positive significance for guiding clinical practice.

In recent years, some studies have revealed that marital status is closely related to the prognosis of TC (11, 12, 53) and married TC patients have a significant survival advantage. A study from 126,160 patients with all types of TC showed that widowed or divorced patients were closely related to poor CSS and overall survival (OS) (11). Shi et al. explored 61077 DTC patients and found that widowed patients had a higher tumor mortality in

TABLE 4 | Comparison prediction performances of different ML models, (Mean ± SD).

Machine learning models		Performance				
		AUROC	**Accuracy**	**Sensitivity**	**Specificity**	**NPV**
Training set	XGBoost[a]	0.905 (0.008)	0.915 (0.013)	0.782 (0.021)	0.914 (0.010)	0.991 (0.001)
	LightGBM	0.891 (0.009)	0.919 (0.034)	0.812 (0.023)	0.866 (0.027)	0.989 (0.002)
	LR	0.891 (0.007)	0.872 (0.028)	0.789 (0.036)	0.871 (0.031)	0.991 (0.001)
	RF	0.895 (0.011)	0.912 0.026	0.800 (0.028)	0.879 (0.028)	0.990 (0.002)
	AdaBoost	0.865 (0.005)	0.946 (0.030)	0.794 (0.030)	0.864 (0.018)	0.986 (0.002)
	Gaussian NB	0.892 (0.006)	0.865 (0.026)	0.790 (0.029)	0.867 (0.027)	0.991 (0.001)
	KNN	0.870 (0.015)	0.971 (0.002)	0.793 (0.034)	0.909 (0.027)	0.982 (0.001)
	SVM	0.797 (0.014)	0.940 (0.041)	0.567 (0.042)	0.951 (0.043)	0.984 (0.001)
	MLP	0.894 (0.016)	0.903 (0.024)	0.765 (0.042)	0.905 (0.024)	0.990 (0.001)
Test set	XGBoost[b]	0.904 (0.024)	0.906 (0.025)	0.809 (0.069)	0.903 (0.023)	0.991 (0.003)
	LightGBM	0.887 (0.033)	0.920 (0.046)	0.804 (0.068)	0.883 (0.043)	0.989 (0.002)
	LR	0.897 (0.022)	0.863 (0.036)	0.833 (0.052)	0.862 (0.039)	0.991 (0.003)
	RF	0.900 (0.026)	0.908 (0.047)	0.812 (0.063)	0.887 (0.041)	0.990 (0.002)
	AdaBoost	0.863 (0.038)	0.959 (0.007)	0.772 (0.064)	0.889 (0.046)	0.985 (0.003)
	Gaussian NB	0.904 (0.024)	0.888 (0.029)	0.830 (0.057)	0.885 (0.033)	0.991 (0.003)
	KNN	0.778 (0.020)	0.965 (0.005)	0.619 (0.047)	0.905 (0.032)	0.978 (0.004)
	SVM	0.740 (0.043)	0.954 (0.024)	0.522 (0.091)	0.970 (0.029)	0.981 (0.004)
	MLP	0.896 (0.025)	0.893 (0.044)	0.797 (0.039)	0.893 (0.044)	0.990 (0.003)

[a] indicates that the best performance of the ML classifiers in the training set is XGBoost (ranked mainly according to AUROC value); [b] indicates that the best performance of the ML classifiers in the test set is XGBoost (ranked mainly according to AUROC and accuracy value).

AUROC, Area under the receiver operating characteristic; NPV, Negative predictive value; XGBoost, eXtreme Gradient Boosting; LightGBM, Light Gradient Boosting Machine; LR, Logistic Regression; RF, Random Forests; AdaBoost, Adaptive Boosting; Gaussian NB, Gaussian Naive Bayes; KNN, K-Nearest Neighbor; SVM, Support Vector Machine; MLP, Multi-Layer Perceptron.

DTC (12). A study from Roche et al. indicated that for MTC patients, being married had a protective effect on treatment and overall 5-year survival, but had no effects on CSS (53). In this study, the impacts of marital status on the prognosis of FTC were evaluated. The results found that married people had a better prognosis than single, widowed, and separated patients. More and more studies have shown that a good marital status plays a positive role in the prognosis of tumors, such as bladder cancer (54), oral cancer (55), colorectal cancer (56, 57), chordoma (58), head and neck cancer (59, 60), renal cell carcinoma (61), and so on. The generally accepted explanation for the lower cancer death rate among married people is related to a better socioeconomic status, which is assumed to buffer the impacts of stressful events (62). It is well known that TC is an endocrine-related disease, and mood changes and mental health are closely related to the prognosis of TC. Therefore, we think that providing effective psychological counseling and social support for unmarried, widowed, and separated patients has positive effects on the improvement of the prognosis.

This study also has the following limitations. Firstly, even if the internal differences in baseline characteristics were adjusted through multivariate Cox regression and PSM, these differences still existed to a large extent. Due to the limitation of follow-up time, the longest predicted time point was 143 months. We know that TC has a good prognosis and a high 10-year survival rate, so in future studies, a longer follow-up period should be included. Secondly, the population of this study was mainly from Western countries. Although it included different races, the number of Asians was small. In future research, model verification should be conducted through external populations. Thirdly, we classified the TNM staging of FTC patients with reference to the eighth edition of the AJCC cancer staging guidelines. Owing to the limitations of the database itself, there may be minor discrepancies in tumor staging, which needs to be further improved in future clinical studies.

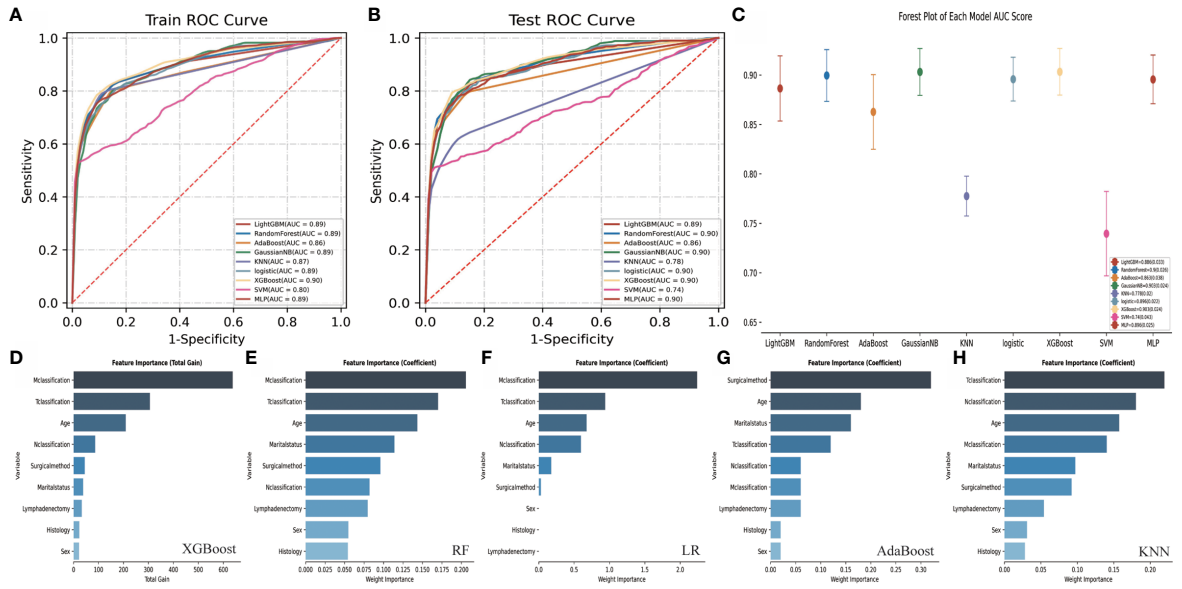

FIGURE 6 | Performance comparison and variable importance ranking of different ML models. **(A)** shows the ROC curve of nine different ML models in the training set. **(B)** shows the ROC curve of nine different ML models in the test set. **(C)** shows the AUROC score forest plot of each model in test set. **(D–H)** show the variable importance ranking of five main ML classifiers. ROC, Receiver operating characteristic; AUROC, Area under the receiver operating characteristic; ML, Machine learning; FTC, Follicular thyroid carcinoma; XGBoost, eXtreme Gradient Boosting; LightGBM, Light Gradient Boosting Machine; LR, Logistic Regression; RF, Random Forests; AdaBoost, Adaptive Boosting; Gaussian NB, Gaussian Naive Bayes; KNN, K-Nearest Neighbor; SVM, Support Vector Machine; MLP, Multi-Layer Perceptron.

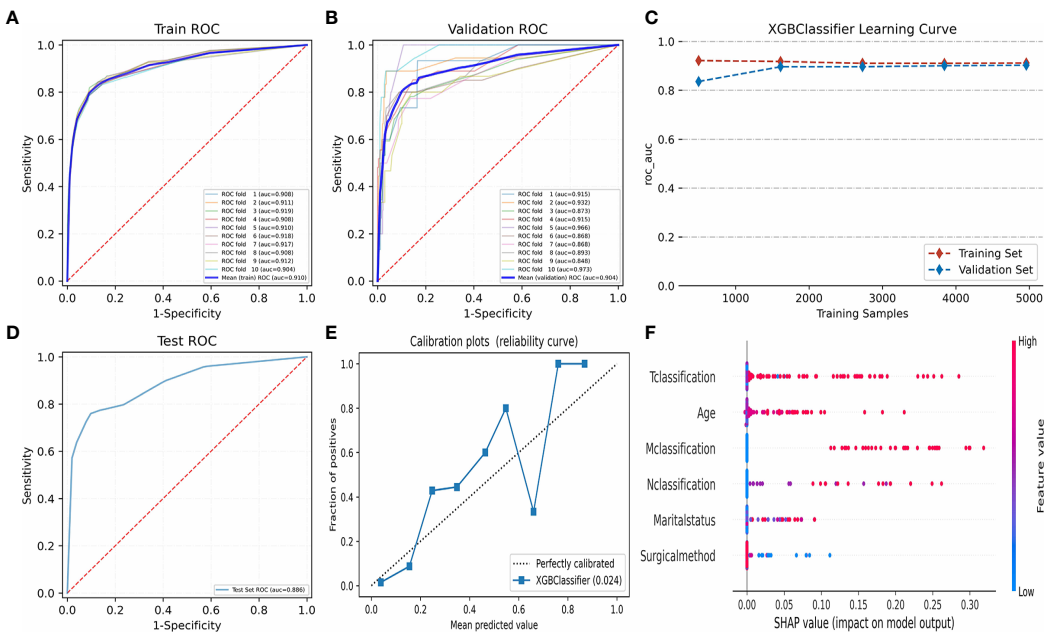

FIGURE 7 | Algorithm optimization and visualization of XGBoost model. **(A–C)** show the fitting optimization process of XGBoost model by 10-fold cross-validation in the training set and verification set. **(D)** shows the AUROC value of XGBoost model in test set. **(E)** shows the calibration plot of XGBoost model. **(F)** shows the SHapley Additive exPlanations of XGBoost model. ROC, Receiver operating characteristic; AUROC, Area under the receiver operating characteristic; XGBoost, eXtreme Gradient Boosting. ROC, Receiver operating characteristic; AUROC, Area under the receiver operating characteristic; XGBoost, eXtreme Gradient Boosting.

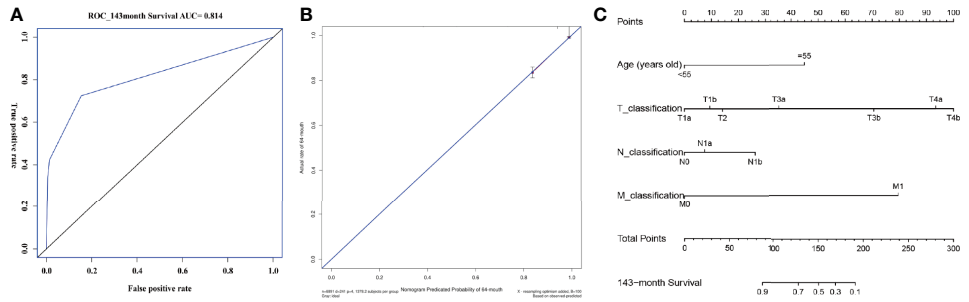

FIGURE 8 | AUROC value, calibration plot and visualization of AJCC model. **(A)** shows the AUROC value of the AJCC model. The y-axis represents the true positive rate of the prognostic prediction, the x-axis represents the false positive rate of the prognostic prediction. The blue solid line represent the predictive performance at 143-month forecast time point. **(B)** shows the calibration plot of the AJCC model. The y-axis represents actual diagnosed cases of FTC, the x-axis represents the nomogram predicated probability. The blue solid line represents a perfect prediction by an ideal model, the red solid line represents the predictive power of the actual model, with the results indicating that a closer fit to the diagonal blue solid line represents a better prediction. **(C)** shows the nomogram of the AJCC model. AUROC, Area under the receiver operating characteristic; AJCC, American Joint Committee on Cancer; FTC: Follicular thyroid carcinoma.

CONCLUSIONS

In summary, the impacts of different surgical methods and marital status on the long-term prognosis of FTC were described. Our studies have proved that for most patients with non-lymph node and distant metastases, one-sided thyroid LO plus IO has a better long-term prognosis. In addition, active and effective social support and companionship can improve the CSS of FTC patients. The XGBoost model can better communicate the prognosis and ultimately promote patient decision-making based on new risk factors.

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

GC had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; Concept and design, YM, GC, JL, YH, LX, WL, JW, HH, and LL; Acquisition, analysis, or interpretation of data, YM, YH, and LX; Drafting of the manuscript, YM, YH, LX, and GC; Critical revision of the manuscript for important intellectual content, YM, WL, JW, GC, JL, HH, and LL; Statistical analysis, YM, YH, and LX; Supervision, GC; All authors contributed to the article and approved the submitted version.

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REVIEW
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Research Review of Thermal Ablation in the Treatment of Papillary Thyroid Carcinoma

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Background: Minimally invasive treatment of thyroid tumors has become increasingly common, but has mainly focused on benign thyroid tumors, whereas thermal ablation of thyroid cancer remains controversial. Clinical studies analyzing the efficacy of thermal ablation of papillary thyroid carcinoma (PTC) have been conducted in several countries to verify its safety. Here, we screened and reviewed recent studies on the efficacy and safety of thermal ablation of PTC as well as psychological assessment, patient prognosis, recurrence, and factors affecting ablation.

Summary: The most significant controversy surrounding ablative treatment of PTC centers on its effectiveness and safety, and >40 studies have been conducted to address this issue. The studies include papillary thyroid microcarcinoma (PTMC) and non-PTMC, single PTC and multiple PTC, and controlled studies of ablative therapy and surgical treatment. In general, ablation techniques can be carefully performed and promoted under certain conditions and with active follow-up of postoperative patients. Ablation is a promising alternative treatment especially in patients who are inoperable.

Conclusions: Clinical studies on PTC ablation have provided new perspectives on local treatment. However, because PTC grows very slowly, it is an indolent tumor; therefore, studies with larger sample sizes and extended post-procedure follow-ups are necessary to confirm the investigators' hypotheses.

Keywords: thyroid cancer, ablation, papillary thyroid carcinoma, thermal ablation, recurrence

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INTRODUCTION

Thyroid cancer is the most common malignant tumor of the head and neck; papillary thyroid carcinoma (PTC) is the most common type, and its incidence is increasing worldwide (1). There are many reasons for the increasing incidence of PTC, among which improved quality of life (QoL), increased health awareness, and the widespread popularity of medical checkups are the main reasons (2–4). A national screening program in South Korea resulted in a 15-fold increase in the

incidence of thyroid cancer over a period of 18 years (5). However, the mortality rate of thyroid cancer has decreased because of the slow progression and low risk of most thyroid cancers. These cancers are referred to as low-risk PTCs, and they are characterized by the absence of significant capsule invasion, extra-thyroidal expansion, lymph node metastasis, and distant metastasis (6). Low-risk PTCs are often detected at autopsy or during physical examination. In recent years, local ablation treatment has been applied to low risk PTCs. The ablation methods include radiofrequency ablation (RFA) microwave ablation (MWA), laser ablation (LA), and ethanol injection, and the first three methods are collectively known as thermal ablation. Thermal ablation only damages the tumor while sparing most of the thyroid glands and periglandular tissues, which opens up a new way of thinking about the treatment of thyroid cancer.

REVIEW

THERMAL ABLATION STUDY OF PAPILLARY THYROID MICROCARCINOMA

Papillary thyroid microcarcinoma (PTMC) is a thyroid cancer of ≤10 mm in diameter and is usually considered to be a very low risk thyroid cancer (7). PTMC is often considered an inert tumor with a favorable prognosis, and several clinical studies have confirmed the stability of PTMC (8). The American Thyroid Association (ATA), the British Thyroid Association, and the European Society for Medical Oncology recommend regular follow-up for low-risk PTMC, which does not require immediate surgery because of its good prognosis (9–11). One study reported a 20-year survival rate of 99% for PTMC (8). Sugitani et al. (12) analyzed 415 asymptomatic patients with PTMC for up to 22 years of follow-up and showed that only 6% of the nodules increased in size, 91% did not change, and 3% showed shrinkage. Similarly, Professor Ito in Japan reported (13) that 1,235 patients with low risk PTMC treated with observational therapy did not develop distant metastases from thyroid cancer and none of the patients died from PTMC over a period of 1.5–19 years. Although the prevailing treatment remains surgery (14–16), some patients are not eligible for surgery because of systemic disease. Furthermore, surgery may lead to recurrent laryngeal nerve paralysis, hypothyroidism, neck scarring, and lifelong medication dependency (17–20). In addition, surgical treatment has the potential to lead to overtreatment of PTMCs. The 2015 ATA guidelines suggest that patients with low risk PTMCs can also be actively monitored (15); however, some patients are unable to undergo long-term follow-up because of anxiety about the disease, and in these cases, ablation of PTMC is a compromise between surgery and observation. A multicenter PTMC ablation study conducted in China that included 11 centers and 725 patients (21) showed a significant reduction in tumor size at 6 months after ablation compared with that before ablation. On ultrasound, 515 (71.0%) PTMCs disappeared completely. Six (0.8%) patients showed disease progression after ablation, including five (0.7%) patients with new PTMCs and one (0.1%) patient with metastasis in the cervical lymph nodes. Increasing evidence supports that RFA, LA, and MWA can effectively treat PTMC with satisfactory clinical results (**Table 1**).

RFA

RFA is a treatment method that introduces electrodes into the lesion area to generate thermal effects by releasing radiofrequency currents, thereby achieving a high local temperature and inducing solidified necrosis and tissue degeneration. RFA is widely used in the treatment of solid tumors, and it has been applied in PTMC since 2016, when RFA was used to ablate 98 PTMCs in 92 patients in China (22). The results of the study showed a 100% volume reduction rate (VRR) at a follow-up of 18 months, with no tumor recurrence or metastasis during the follow-up period. Ultrasound-guided core needle biopsy (CNB) histopathology confirmed the lack of residual tumor or recurrence. The same group then conducted a clinical study with a larger sample size (23) in which RFA was performed on 204 cases of PTMC. The nodules disappeared completely after 24 months of follow-up, the VRR was 100%, and there were only nine cases of mild complications. In 2019 (24), a retrospective analysis of the safety, effectiveness, and long-term efficacy of RFA treatment was performed including 38 PTMC nodules in 37 patients, and similar results were obtained. In addition to studies in China, Korean scholars (25) followed 133 PTMC patients who refused surgery and had a high-risk for surgery for 12 months after RFA; the results showed that 91.4% (139/152) of the tumors disappeared and all patients were free of recurrence and metastasis. The overall complication rate was 3%. PTMC is considered to be an inert cancer, and although some studies have shown complete ablation of RFA with no recurrence, this does not prove the importance of this intervention in the short term. Studies have thus increased the follow-up period and included a larger sample size. Cho et al. (26) reported complete disappearance rates of 98.8% and 100% at 24 and 60 months after RFA for PTMC, respectively, with no local tumor progression, lymph node metastasis, distant metastasis, delayed complications, surgery-related death, or delayed surgery. A 5-year retrospective study of RFA for PTMC was also conducted in China (27), and all nodes were completely absorbed at the end of follow-up, with only 2 patients developing ipsilateral lateral cervical lymph node metastasis. These studies confirm the effectiveness and safety of RFA for the treatment of PTMC.

MWA

Compared with RFA, MWA is a relatively new technique that has been widely used for ablation of various benign and malignant tumors, including benign thyroid tumors (28–30). MWA provides a larger ablation area than RFA, which decreases the time necessary to complete treatment and improves tumor inactivation. MWA is thus less susceptible to heat sink effects.

TABLE 1 | Basic information on PTC ablation studies.

N	Study	Institute	year	Study time	country	Types of nodules	Number of patients	Number of nodules	age	Follow-up time	Type of ablation	Average size	hoarseness	Recovery time for hoarseness	Short-term pain and neck discomfort	Other complications	Transient hematoma	recurrence	Lymph node metastasis	Number of nodules completely disappeared	Nodule disappearance rate
1	(33)	Yantai Affiliated Hospital	2014	2010-2013	CHINA	Single nodule	21	21	52.1 ± 13.6	11(3-22) months	MWA	7.3 ± 3.0	4	3month	most	0	0	0	0	5	19%
2	(22)	General Hospital of Chinese PLA	2016	2013-2014	CHINA	Single and Multiple nodules	92	98	44.7 ± 10.7	3-18 months	RFA	5.6 ± 1.8	4	10min-3h	1	0	0	0	0	10	10.20%
3	(61)	Seoul National University Hospital,	2017	2005-2009	KOREA	Single nodule	6	6	N	48.5 ± 12.3 (36–65) months	RFA	9.2 ± 28	0	N	2	0	0	0	0	4	66%
4	(43)	Rui Jin Hospital	2017	2013-2014 (Duration of treatment)	CHINA	Single nodule	30	30	N	12-24 months	LA	4.8 ± 1.2	0	N	30	1 patient had a decrease in tsh and an increase in t3t4, and recovered within 2 months	0	0	0	30(Contains 20 cases of scar-like areas)	100%
5	(49)	Beijing Friendship Hospital,	2018	2014-2017	CHINA	Single nodule	46	46	43.63 ± 9.27	42 months	MWA	4.49 ± 1.55	2	13month	26	0	0	0	0	7	15%
6	(34)	China-Japan Union Hospital of Jilin University	2018	2013-2014	CHINA	Single and Multiple nodules	15	21	48.0 ± 8.8	36–48 months	MWA	5.8 ± 2.5	1	10min	8	0	0	0	0	20	95.23%
7	(62)	Rui Jin Hospital	2018	2013-2016	CHINA	Single nodule	64	64	42.5 ± 12.3	25.7 ± 8.2 (12–42) months	LA	4.6 ± 1.5	0	N	0	0	0	2	0	64(Contains 13 cases of scar-like areas)	100.00%
8	(24)	Renji Hospital	2019	2014-2017	CHINA	Single and Multiple nodules	37	38	45.14 ± 12.96	12 months	RFA	6.77 ± 1.92	0	N	0	1 patient's t4 increased and recovered after 1 month	0	0	0	37	97.37%
9	(45)	Suzhou Hospital	2019	2016-2017	CHINA	Single nodule	37	37	43.9 ± 17.6	16.5 ± 6.9 (12-24) months	LA	5.1 ± 3.4	0	N	34	1 patient coughed; 1tsh increased, t3t4 decreased, and recovered within 3 months	0	0	1	36(Contains 24 cases of scar-like areas)	86.49%
10	(63)	Beijing Friendship Hospital,	2019	2013-2018	CHINA	Single nodule	168	168	47.36 ± 10.75	753 ± 520 (79–1787) days	MWA		6	Transient	0	1 patient with permanent voice impairment	0	2	5	34	20.24%
11	(25)	Soonchunhyang University Seoul Hospital	2019	2008-2017	KOREA	Single and Multiple nodules	133	152	46 ± 12	39 ± 25 (6-104) months	RFA	4.3 ± 1.4	1	2month	1	0	1	0	0	139	91.40%
12	(37)	China-Japan Union Hospital of Jilin University	2019	2015-2017	CHINA	Single and Multiple nodules	185	206	42.2 ± 11.7	20.7 ± 8.8 (12–36) months	MWA	5.3 ± 1.91	5	1day-4month	21	0	11	1	0	174	84.50%
13	(64)	Cancer Hospital of the University of Chinese Academy of Sciences	2019	2016-2017	CHINA	Single nodule	107	107	44.08 ± 13.13	12–18 (15.14 ± 3.01) months	Thermal ablation	5.9 ± 1.8	0	N	0	0	0	0	0		
14	(50)	Rui Jin Hospital	2019	2014.1-2014.12	CHINA	Single nodule	36	36	41.5 ± 11.3	49.2 ± 4.5 (30–54) months	LA	4.7 ± 1.4	0	0	0	1 patient had a decrease in tsh and an increase in t3t4, and recovered within 2 months		2	1	36(Contains 2 cases of scar-like areas)	100.00%
15	(26)	University of Ulsan College of Medicine, Asan Medical Center	2020	2019-2020	KOREA	Single and Multiple nodules	74	84	46 ± 12	60-124 (72 – 18) months	RFA	4 ± 1.6	1	2month	1	0	2	0	0	84	100%

(Continued)

TABLE 1 | Continued

N	Study	Institute	year	Study time	country	Types of nodules	Number of patients	Number of nodules	age	Follow-up time	Type of ablation	Average size	hoarseness	Recovery time for hoarseness	Short-term pain and neck discomfort	Other complications	Transient hematoma	recurrence	Lymph node metastasis	Number of nodules completely disappeared	Nodule disappearance rate
16	(41)	Dipartimento di Oncologia ed Emato-Oncologia, Università degli Studi di Milano	2020	2018-2020	ITALY	Single nodule	11	11	49.3 ± 8.7	10.2(1.5-12) months	LA+RFA	7.9 ± 1.3	2	N	3	0	0	0	0	N	N
17	(35)	China-Japan Union Hospital of Jilin University	2020	2014-2014	CHINA	Single nodule	41	41	46.10 ± 8.85	>60 months	MWA	2.8-10.0	2	10min, 2m	0	0	0	0	0	40	97.56%
18	(23)	Medical School of Chinese PLA, Beijing	2020	3014-2016	CHINA	Single and Multiple nodules	198	204	42.5 ± 9.5	24-54 months	RFA	6.34 ± 1.8	5	1mon	4	0	0	1	0		almost100%
19	(58)	School of Medicine, Nankai University	2020	2014-2018	CHINA	Single nodule	66	66	41.0 ± 9.2	20.5 ± 7.4 (12–48) months	RFA	13 ± 2	0	N	2	0	0	2	1	38	57.60%
20	(65)	Medical School of Chinese PLA	2020	2016-2018	CHINA	Single and Multiple nodules	202	211	42.79 ± 10.13	24.42 ± 9.15 (3-42) months	RFA	5.35 ± 1.63	0	N	0	0	0	0	0	139	65.88%
21	(36)	Shanghai Tenth People's Hospital,	2020	2010-2018	CHINA	Single nodule	119	119	48.7	37.2 ± 20.9 (12-101) months	MWA	6.9 ± 1.9	8	2-3month	0	4 patients coughed	1	0	1	89	78.10%
22	(48)	General Hospital of Chinese PLA	2020	2013-2013	CHINA	Single nodule	94	94	45.4 ± 10.8	>60 months	RFA	6.14 ± 2.54	0	N	0	0	0	1	0	N	N
23	(66)	Rui Jin Hospital	2020	N	CHINA	Single nodule	34	34	37.9 ± 10.1	18-30 months	MWA	5.0 ± 1.4	0	N	0	0	2	0	0	32	94.12%
						Single nodule	33	33	41.8 ± 13.4		LA	4.5 ± 1.6	1	3month	0	0	1	0	0	27	81.82%
24	(21)	China-Japan Friendship Hospital	2021	2015-2020	CHINA	Single nodule	725	725	46 ± 11	21 ± 13 (6–60) months	Thermal ablation	6.4 ± 1.8	14	1-6month	0	1 case of cough and 1 case of paroxysmal arrhythmia.	4	5	1	515	71.00%
25	(68)	Nankai University	2021	2014-2019	CHINA	Single nodule	95	95	66 ± 4.4	36.6 ± 16.6 (15–74) months	RFA	6.07 ± 1.96	0	N	1	0	0	1	0	44	46.30%
26	(59)	the First Medical Center of the Chinese PLA General Hospital	2021	2014-2019	CHINA	Single nodule	94	94	43.94	12-36 months	RFA	N	2 cases of complications, the specifics are unknown		0	0	0	4	0	94	100%
27	(42)	The Third Xiangya Hospital	2021	2012-2015	CHINA	Single nodule	105	105	44.1± 12.2	65.4 ± 6.3(60-96) months	LA	6.34 ± 2.62	0	N	27	1 patient had a decrease in tsh and an increase in t3t4, and recovered within 3 months	0	1	2	103	100%
28	(52)	First Medical Center of General Hospital of Chinese PLA	2021	2014-2018	CHINA	Single nodule	115	115	44.9 ± 10.4	26(11-60) months	RFA	6.5 ± 1.9	2	1-3month	115	0	0	1	0	115	100%
29	(69)	China-Japan Friendship Hospital	2021	2014-2020	CHINA	Single nodule	106	106	44.39 ± 11.13	25 ± 11 (9–48) months	MWA	7.7 ± 3.5	6	3-6month	0	0	0	2	2	71	70%
30	(70)	Nankai University	2021	2014-2019	CHINA	Single nodule	91	91	40.7 ± 9.3	36 months	RFA	14 ± 2	0	N	2	0	0	3	1	91	100%
31	(71)	The First Medical Center of Chinese PLA General Hospita	2021	2014-2018	CHINA	Single nodule	12	12	41.0 ± 9.2	24.1 ± 6.9 (13–33) months	RFA	15.25	0	N	0	0	0	0	0	2	16.66%

(Continued)

TABLE 1 | Continued

N	Study	Institute	year	Study time	country	Types of nodules	Number of patients	Number of nodules	age	Follow-up time	Type of ablation	Average size	hoarseness	Recovery time for hoarseness	Short-term pain and neck discomfort	Other complications	Transient hematoma	recurrence	Lymph node metastasis	Number of nodules completely disappeared	Nodule disappearance rate
32	(72)	Medical School of Chinese PLA	2021	2014-2017	CHINA	Single nodule	414	414	43.56 ± 9.79	42.15 ± 11.88 (24–69) months	RFA	5.22 ± 1.59	0	N	16	0	0	10	4	336	88.41%
33	(74)	Chinese PLA General Hospital	2021	2014-2018	CHINA	Single nodule	424	424	44.1 ± 9.5	48.1 months	RFA	5	0	N	0	0	0	10	3	383	90.33%
34	(75)	Chinese PLA General Hospital	2021	2014-2018	CHINA	Bilateral	47	100	43.39 ± 9.26	47.77 ± 11.5424-48) months	RFA	4.81 ± 1.57 (0.20–0.93)	0	N	4	0	0	2	0	92	92%
35	(76)	Chinese PLA General Hospital	2021	2014-2018	CHINA	Single nodule	432	432	43.59 ± 9.68	49.25 ± 12.98 (>24) months	RFA	6.03 ± 1.87	0	N	20	0	0	10	5	390	90.28%
						Multiple nodules	55	114	44.09 ± 9.89		RFA	6.29 ± 1.85	0	N	3	0	0	1	1	109	95.61%
36	(77)	Zhejiang University School	2021	2017-2020	CHINA	Single nodule	157	157	45.10 ± 10.25	18-30 months	RFA	5.26 ± 1.74	2	N	0	1 case of transient subclinical addition and subtraction	0	0	0	39	29.30%
37	(27)	The First Affiliated Hospital of Dalian Medical University	2021	2014-2018	CHINA	Single and Multiple nodules	102	109	43 ± 19	60 months	RFA	5. ± 2.9	2	N	0	2 patients had transient subclinical subclinical hypothyroidism; 3 patients had a decrease in tsh and an increase in t3t4, and recovered within 1 week	0	0	2	109	100%
38	(82)	First Medical Center of General Hospital of Chinese PLA	2020	2014-2018	CHINA	Single nodule	112	112	44.9 ± 10.6	13 ~ 60 months	RFA	6.5 ± 1.9	0	N	0	0	0	1	0	112	100%
39	(38)	Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine	2021	N	CHINA	Single nodule	73	73	38.71 ± 11.82	>12 months	MWA	5.8 ± 1.6	1	3month	0	Subclinical addition and subtraction in 2 patients	0	3	3	N	N
40	(60)	The Affiliated Hospital of Qingdao University	2021	2016-2018	CHINA	Single nodule	63	63	43.6 ± 14.2	24 months	MWA	0.45 ± 0.11	Unknown	few days	63	20 patients with hyperthyroidism, including 9 cases of clinical hyperthyroidism and 11 cases of subclinical hyperthyroidism	0	0	0	55	87%

N, This was not reported in the study.

The heat sink effect is an important factor leading to local tumor recurrence after RFA (31, 32), which has increased interest in the MWA technique. The first study of 21 patients with PTMC treated with MWA was conducted and reported in China in 2014 (33). The patients were followed-up for 11 months, and no recurrence or metastasis was detected. Eight of the patients underwent ultrasound-guided biopsy, and the pathology results showed no signs of recurrence; four patients recovered in a short period of time after suffering from hoarseness. Teng et al. used low power MWA (34) to treat 15 patients with a total of 21 nodules. After a follow-up period of 3 years, 20 nodules completely resolved without recurrence. However, studies to date have included a small number of cases and a short follow-up time. The long-term effectiveness and safety of MWA were examined in a study that analyzed 41 cases of PTMC (35); after 60 months of follow-up, the nodule reduction rate was 99.37% ± 4.02%, and no tumor progression was detected during the follow-up period. Yue et al. (36) and Teng DK et al. (37) followed 119 and 185 patients for 2 years after MWA and showed complete absorption rates of 93.9% and 84.5%, respectively; in the former study, one patient developed cervical lymph node metastasis at 26 months of follow-up and underwent successful MWA treatment; in the latter study, only minor complications were observed.

Lu et al. (38) evaluated patients using ultrasonography for up to 24 months after treatment and showed a nodule disappearance rate of 100%. This study performed fine needle aspiration biopsy (FNAB) or CNB of the ablated areas at 3 or 6 months after treatment, and the results showed no atypical or malignant follicular cells by pathological histology. The most common pathological features were fibroblast proliferation (87.18%) and chronic inflammation (82.05%), followed by infarction (53.85%).

LA

Although most of the ablations for low risk PTMC are currently performed by WMA and RFA, another type of thermal ablation, LA, has achieved some efficacy in the treatment of certain systemic tumors. Apini et al. reported (39) a case of a patient with a PTMC of approximately 8 mm in diameter in the thyroid gland that was found on examination due to cirrhotic decompensation combined with renal failure. The patient was treated with LA. FNAB and CNB were performed at 1 and 12 months after PLA, which detected necrotic material and inflammatory cells but no living tumor cells. The nodule was recurrence-free and continued to shrink at 24 months after treatment. Since then, LA has been used for thyroid cancer ablation. Another scholar reported three cases of PTMC treated with LA in 2014 (40). In 2020, an Italian study (41) reported the results of RFA and LA in 11 patients; all patients were free of recurrence and metastasis after surgery; three patients experienced minor postoperative discomfort, which resolved with medication; there were no complications, and patients had a satisfaction score of 10.

A special study on LA was conducted in China (42) including 105 cases of pathologically confirmed solitary PTMC treated with ultrasound-guided LA at Xiangya III Hospital of Central South University. The mean follow-up was >5 years, and the results showed a 100% nodal disappearance rate at 24 months after ablation with no serious complications such as tracheal, esophageal, vascular, or laryngeal nerve injury. Cervical lymph node metastasis occurred in two patients. In 2017, Ruijin Hospital of Shanghai Jiaotong University reported 30 patients treated with LA; at the final follow-up, 10 ablation areas (33.3%) disappeared and 20 ablation areas (66.67%) remained as scar-like lesions, with no post-treatment tumor regrowth detected (43). Institutional studies of cases treated with LA for longer periods were also reported. Kim et al. (44) followed 90 patients for up to 10 years after PTMC ablation and showed a 100% disappearance rate of nodules by 12 months of follow-up. However, after 17–56 months of treatment, five patients (5.5%) developed a new cancerous lesion and one case of lymph node metastasis was found at 2 months after treatment, which was eventually determined to be an undetected cancer site rather than a recurrence. All recurrent patients were treated surgically and remained recurrence-free for 5 years. Ji et al. investigated the effectiveness of ultrasound-guided percutaneous LA for PTMC (45) and achieved similar results. Regarding the pathological features after LA treatment, three cases of thyroid cancer with total thyroidectomy immediately after LA treatment were reported (40), and the pathology showed tissue destruction and charring, complete loss of the entire ablated area and margins of normal tissue surrounding the tumor, and expression of TTF1 and anti-mitochondrial antibodies indicating lack of viability. However, lymph node micrometastases were found in one of the cases. Therefore, the investigators concluded that LA for PTMC should only be used in a subset of designated patients at this stage. In addition, they indicated LA technology may become the first choice for PTMC in the future when precise identification of microlesions in the thyroid and lymph nodes is achieved.

A systematic review of the three methods (RFA/WMA/LA) (46) was performed including 1,187 patients and 1,284 PTMCs, and the results showed that the volume of PTMC was significantly reduced after ablation with all three techniques. MWA was more effective than the other two techniques, but the difference was not statistically significant. There was no difference between the three techniques in terms of complications and recurrence. A meta-analysis also found that LA treatment was less effective for PTMC reduction (47), but the authors concluded that all three techniques are effective and safe for PTMC ablation and can be used as an alternative to surgery in some cases.

A Comparative Study of Thermal Ablation Versus Surgical Procedures

The main treatment for PTMC remains surgical resection; however, thermal ablation has been shown to benefit patients with PTMC as an alternative to surgery. Several studies have been conducted to compare the two treatment modalities (48–53), thermal ablation and surgery, and the results show that thermal ablation has comparable efficacy to surgery in the treatment of PTMC. A meta-analysis including 339 thermal ablation and 314 surgical patients (54) showed no statistically significant differences in the rates of local tumor recurrence,

lymph node metastasis, distant metastasis, and salvage surgery between surgery and ablation. In a long-term follow-up study (27), two patients treated with thermal ablation developed ipsilateral cervical lymph node metastases; however, a study by Myung et al. (55) showed a recurrence rate of 1.4% in patients followed for 5–6 years after surgery. By contrast, ablation does not affect the prognosis of patients treated with or without surgery, and it preserves at least one side of the thyroid gland in most patients. In a related meta-analysis (56), the incidence of temporary laryngeal recurrent nerve injury after thyroidectomy and total thyroidectomy was 10.1 and 8.1%, respectively, and permanent hypocalcemia occurred in 2.8% and 3.3% of patients. In addition, these patients had permanent surgical scarring in the neck, as well as a decrease in QoL because of the need for lifelong medication. RFA treatment can prevent these complications. Another meta-analysis of seven studies including 867 patients (57) showed that thermal ablation is effective for reducing patient complications and decreasing the length of hospital stay, and it is a relatively safe and cost-effective option for the treatment of PTMC.

ABLATION OF PTC (NODULE DIAMETER >1 CM)

Although the use of thermal ablation in the treatment of PTMC is currently in the clinical research stage, advances in technology and the effectiveness and safety of this technique have led scholars to conduct studies on thyroid tumors >1 cm in diameter. In 2020, the Chinese People's Liberation Army General Hospital (58) performed RFA in 66 patients with T1bN0M0 PTC (all refused or were unsuitable for surgery), and the results of the study showed a technical success rate of 100% with no major complications. There was a significant reduction in tumor volume. At the final follow-up, the tumor VRR was 99.11 ± 2.44% (range 92.62%–100%), and 38 cases (57.6%) showed disappearance of tumors. Puncture results at 3 or 6 months after ablation showed malignant cells in two lesions (3.0%) and cervical lymph node metastasis in one case (1.5%). Cao et al. (53) performed RFA and MWA in patients with T1N0M0 PTC who volunteered for ablation or were not suitable for surgical treatment. During a mean follow-up of 22 months, the nodule disappearance rate, the disease progression, and the complication rates were higher in the T1b group than in the T1a group; however, thermal ablation showed effectiveness and safety for T1N0M0 PTC. Studies comparing the efficacy and safety of RFA treatment and surgical resection in patients with T1bN0M0 PTC belonging to different age groups (59) showed that RFA was more cost effective and associated with a shorter operative time than the surgical group, but there was no significant difference in tumor progression and complication rates. In addition, subgroup analyses of patients older than forty-five years and patients younger than forty-five years showed no significant differences in the incidence of tumor progression and complications. Hospitalization costs were higher in older patients than in younger patients in the surgical group, whereas no difference was observed in the RFA group. Ablation of stage T1b thyroid cancer has not been assessed clinically on a large scale, therefore, it cannot be used as an alternative to surgery; however, it has been a local clinical treatment preference for patients who lack indications for surgery.

COMPLICATIONS

The main complications of thermal ablation of thyroid cancer are pain, voice changes, bleeding, and changes in thyroid function. Patients have widespread pain after ablation, with a 100% incidence of postoperative pain demonstrated by Zhou (43), Song (52), and Wang (60). Although criteria for assessing postoperative pain are difficult to establish, the duration of pain was short in all studies, and pain relief occurred within 1 week postoperatively. Hoarseness is one of the most common complications of thermal ablation. The heat generated by RFA or MWA during ablation causes transient damage to the recurrent laryngeal nerve, and some patients experience voice changes, with an incidence of hoarseness of 0%–3.57% and a recovery time of approximately 10 min–6 months (21–27, 33–37, 41–45, 48–54, 58, 59, 61–77). One patient with permanent voice change as a complication was reported. In addition, the rich blood supply to the thyroid gland can lead to transient bleeding at the end of the ablation, although this can be relieved with compression. Finally, a small number of patients experience complications such as altered thyroid function (24, 27, 49, 50, 60, 77) and cough (21, 36, 45) after thermal ablation, which normally resolve during the postoperative period.

RECURRENCE

Recurrence and metastasis after ablative treatment of PTC are major concerns for researchers and clinicians as well as patients. Thermal ablation is a new medical technology and there are many uncertainties. Studies including small sample sizes have shown that a fraction of patients have no recurrence and metastasis (22, 33, 34, 43, 49, 60–62), whereas another fraction of patients experience lymph node metastasis and tumor recurrence (24–27, 42, 52, 58, 69, 76). However, the small sample size of these studies makes it difficult to draw consistent conclusions. A study of unifocal low-risk PTMC that included a large sample showed an overall incidence of local tumor progression of 3.62% at a follow-up time of 42.15 ± 11.88 months (range, 24–69 months) (72). One patient (0.24%) was diagnosed with residual cancer, 4 (0.97%) had lymph node metastasis, and 10 (2.42%) had recurrent PTMC. Of the 10 patients who recurred, one opted for active surveillance and showed stable volume at the 1-year follow-up. Nine patients received additional RFA treatment. All lesions were successfully treated and disappeared at follow-up in seven cases, and no distant metastases were detected. In addition, 70% of recurrent PTMC in this study occurred in the contralateral glandular lobe,

which could suggest that thyroid lobectomy does not prevent recurrence of low-risk PTMC. A controlled study of 884 patients comparing surgery versus ablation (74) showed no significant differences between the surgical and RFA groups in terms of local tumor progression (9/460 [2.0%] vs. 15/424 [3.5%], P = 0.148), LNM (3/460 [0.7%] vs. 4/424 [0.9%], P = 0.914), recurrent PTMC (6/460 [1.3%] vs. 10/424 [2.4%], P = 0.240) and persistent lesions (0/460 [0%] vs. 1/424 [0.2%], P = 0.298). Recurrence was assessed based on relevant imaging examinations at the time of patient follow-up; however, some patients underwent CNB of the ablated central zone, peripheral zone, and surrounding thyroid parenchyma at 3 or 6 months after ablation to assess tumor recurrence (65). The results showed that in 202 patients with low risk PTMC who underwent CNB assessment after ablation, three ablation areas in the peripheral region showed positive biopsy results for CNB. However, early judgment of recurrence could be made when ultrasound images failed to identify CNB but biopsy could. Another study (73) investigated unifocal PTMC and found residual peripheral tumor tissue after CNB puncture, in two patients who subsequently underwent re-RFA.

FACTORS INFLUENCING THE EFFECTIVENESS AND SAFETY OF PTC ABLATION THERAPY

PTC Near the Capsule of the Thyroid Gland

Whether ablation of PTCs located near the thyroid capsule is feasible remains to be determined. The expert consensus on thyroid ablation of the 2019 edition of the Chinese Medical Doctor Association (69) states that the nodule diameter needs to be <5 mm when performing ablation, but the diameter can be 10 mm if the PTC is located near the thyroid capsule. The association of nodules close to the capsule with the risk of metastasis and recurrence remains controversial. A study that included 174 patients (78) showed that the location of nodules within 1.9 mm of the thyroid capsule is associated with increased risk of lymph node metastasis. Another study (79) showed that a shorter distance between the nodule and the thyroid capsule was associated with a higher likelihood of metastasis. In contrast, a study that included 1,922 patients (80) showed that the distance of the tumor from the thyroid capsule was not associated with lymph node metastasis. Therefore, whether the distance between thyroid tumors and the thyroid capsule is related to lymph node metastasis has not been conclusively established, and whether nodes closer to the thyroid capsule should be ablated needs to be further investigated. A clinical study was conducted to answer this question (69). The study included 71 patients with PTC 0–2 mm from the thyroid capsule. The investigators performed PTC ablation and thyroid capsule ablation with a 25 ± 11 month follow-up, and the results showed that all nodules disappeared during the follow-up period, and the incidence of lymph node metastasis and new tumors was 1.9% (2/106). Although the study showed that thermal ablation is safe and feasible for nodes close to the capsule, the safety and efficacy of thermal ablation of nodes close to the capsule needs to be investigated in additional large-sample multicenter studies.

PTC Located in the Isthmus of the Thyroid Gland

Approximately 39.2% of PTCs are located in the isthmus of the thyroid gland, and there are no definitive guidelines regarding the treatment of PTCs in the isthmus (81). Similarly, the expert consensus on thyroid cancer ablation developed by the Chinese Medical Doctor Association clearly states that cancer located in the thyroid isthmus is a contraindication to ablation (69). The isthmus is a flattened gland that is close to the anterior cervical musculature and the trachea, therefore thermal ablation is not indicated because ablation could damage the surrounding tissues if not performed properly. However, whether PTC in the thyroid isthmus is an absolute contraindication to thermal ablation remains unclear. A clinical study enrolled 112 patients with PTC in the isthmus of the thyroid gland to analyze the effect of ablation treatment (82). The results showed that at 18 months after the procedure, the nodules disappeared at a rate of 100% and were even completely absorbed at 1 month after the procedure, although one patient had a recurrence at 7 months after the procedure. The study demonstrated the effectiveness of the thermal ablation technique in the treatment of isthmic nodules. Next, the same group compared thermal ablation with surgery in the treatment of thyroid isthmus nodules (52). There was no metastasis or recurrence except for one patient in the RFA group who recurred. However, the operative time, bleeding, hospital stay, and treatment cost were higher in the surgical group than in the RFA group, and the THYCA-QOL score was significantly higher in the RFA group than in the surgical group. Although ablative treatment for thyroid isthmus nodules has not been reported extensively, the current study shows that thermal ablation can lead to a significant improvement in the postoperative QoL of patients and is an alternative to surgery for PTC in the isthmus.

Age

Although there are indicators or models that can definitively predict issues such as the progression of PTC, age is the only independent prognostic factor affecting thyroid cancer-related mortality (83). Many studies have used 45 years as the cut-off point for staging (84–86). The 5-year survival rate of 65-year-old patients with PTMC who were not treated with surgery is 23% (87).. A clinical study analyzed the outcome and safety of PTMC thermal ablation in patients >55 years of age (68). The results showed that all nodules were completely ablated and the VPR at the last follow-up was 99.78 ± 1.54%; there were no serious complications. One patient developed lymph node metastasis and one had a recurrence, and all were treated with a second RFA with satisfactory results. From the perspective of treatment modality, older patients have more systemic underlying

diseases and are at a greater risk of complications from general anesthesia during surgical procedures. In contrast, ablation techniques commonly use local infiltration anesthesia, which is associated with fewer complications and is safer. A comparison of the efficacy and safety of RFA and surgical resection in patients with T1bN0M0 PTC >45 years of age (59) showed that the prognosis was similar in both groups; however, the overall cost and complications were lower in the ablation group, indicating that RFA may be an effective and safe alternative to surgery for the treatment of patients with T1bN0M0 PTC. The effect of age on the results of thermal ablation needs to be validated over a longer period of time and in larger studies.

Chronic Lymphocytic Thyroiditis (CLT)

CLT is an autoimmune disease characterized by extensive infiltration, fibrosis, and atrophy of the thyroid parenchyma. Approximately 33.3% of PTC cases are associated with CLT (88), and that the coexistence of PTC and CLT is strongly associated with prognosis, lymph node metastasis, and distant metastasis and recurrence rates (89). A study assessing the effect of CLT on the efficacy and safety of thermal ablation in PTMC patients (90) showed that the safety and therapeutic outcomes were not different from those of patients undergoing PTMC alone after ablative treatment for more than 20–48 months. The authors concluded that this study provided a basis for studying the mechanisms of immunomodulation induced by necrosis in thyroid cancer.

Number of PTCs

The current indications for thyroid cancer ablation studies are limited to solitary PTMC. Multiple PTMCs are divided into unilateral glandular lobe with multiple PTMCs and bilateral glandular lobe with at least one nodule, and the incidence of bilateral PTMC is 10%–30% (91). The main treatment for bilateral PTMC is surgery because bilateral PTMC is considered a high risk factor for tumor recurrence (92, 93). However, studies indicate that bilateral lesions are not associated with an increased risk of recurrence (91). Therefore, this issue remains controversial. According to the 8th AJCC/TNM Mortality Risk System and ATA Risk Stratification (14, 94), bilateral PTMC is classified as stage I with a low risk of recurrence. The safety and efficacy of RFA for bilateral PTMC was analyzed in 47 cases (75). The results showed a complete disappearance rate of 92%, but recurrence was observed in two patients. This study demonstrated the safety and efficacy of RFA for the treatment of bilateral PTMC, and the authors concluded that RFA holds promise as an alternative treatment in patients with bilateral PTMC who are not eligible for surgery. In a study by Teng et al. (37), ablation was performed in 18 patients with two or more tumors, but was not reported separately. A recent study included 55 patients with multifocal PTMC and 432 patients with PTMC alone, and a comparative study was performed (76). After 49.25 ± 12.98 months of follow-up, there were no significant differences in VRR, local tumor progression, and recurrence and metastasis rates. The authors concluded that RFA is a promising treatment method after adequate preoperative evaluation.

QUALITY OF LIFE AFTER ABLATION IN PATIENTS WITH PTC

Due to the specificity of thyroid cancer treatment, the QoL of patients after treatment has become an essential and important part of the treatment process. The SF-36 scale and thyroid cancer-specific health-related QoL (HRQoL) questionnaire were administered to 100 PTMC patients after treatment (95). The results showed that the main risk factors affecting QoL in patients with PTMC after ultrasound-guided RFA were female gender, psychological burden, inattention, and neuromuscular system and pharyngeal/oral symptoms. Therefore, preoperative examinations are necessary to assess related symptoms, and psychological intervention should be provided after RFA to improve the QoL of PTMC patients after treatment. A study comparing QoL after surgery and PTMC (96) included 54 patients in the PTMC group and 34 patients in the surgical group. The patients were scored on HRQoL using the 36-item Health Short Form Questionnaire (SF-36), Thyroid Cancer Specific Quality of Life, and Fear of Progression Short Form Questionnaire, and the results showed that ultrasound-guided PTMC ablation treatment was superior to surgery in terms of HRQoL, indirectly suggesting that the ablation patients had a higher postoperative QoL than the surgical group.

CONCLUSIONS

The treatment options for thermal ablation of PTC are still controversial. A growing number of researchers have demonstrated the safety and efficacy of thermal ablation with longer follow-up periods and larger sample sizes. Finally, it is hoped that thermal ablation technology will truly benefit patients with PTC.

After reviewing so many studies, it seems to me that for T1aN0M0 PTC ablation techniques are well established and can achieve essentially the same efficacy and fewer number of complications as surgery during clinical treatment. Several academics are already focusing their research on PTC of T1bN0M0, and I think this will be a focus of future research.

AUTHOR CONTRIBUTIONS

The three authors collected the information together, CC and DO organized and wrote the article, and DX guide the content and writing of the article. DO and CC contributed equally to this work. All authors contributed to the article and approved the submitted version.

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MINI REVIEW
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Daily Management of Patients on Multikinase Inhibitors' Treatment

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In a minority of differentiated thyroid cancer (TC) cases and in a large percentage of poorly differentiated TCs (PDTCs) and anaplastic TCs (ATCs), the prognosis is poor due to the lack of response to conventional treatments. In the last two decades, multikinase inhibitor (MKI) compounds have been developed and demonstrated to be very effective in these aggressive cases. Besides the great efficacy, several adverse events (AEs) have been reported in virtually all patients treated with MKIs, largely overlapping between different compounds and including hypertension, diarrhea, anorexia, decreased weight, fatigue, and proteinuria. Most grade 3–4 adverse reactions occur during the first 6 months of treatment and require dosage reduction and/or drug discontinuation. Due to severity of the AEs related to the treatment with MKIs, a multidisciplinary team is definitely required for the daily management of these patients, for the evaluation of the disease status, and the psychophysical condition. Moreover, it is crucial that the patients could have a facilitated access to reach either specialist doctors or nurses who must have been trained to follow them for their individual clinical complications. The follow-up visits should take place at monthly intervals until the sixth month and then every 1–2 months until the completion of the first year of treatment. The flow chart followed at our tertiary center is reported in the present review as a real-life-based example for the follow-up of patients with advanced TC on MKI treatment.

Keywords: MKI, thyroid cancer, QoL, Lenvatinib, Vandetanib, Cabozantinib, multidisciplinary tumor board, prehabilitation

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INTRODUCTION

Thyroid cancer (TC) has an excellent prognosis, since available treatments, namely, surgery and radiometabolic therapy, are very effective. However, in a minority of differentiated TC cases and in a large percentage of poorly differentiated TCs (PDTCs) or anaplastic TCs (ATCs), the prognosis is poor due to the refractoriness to conventional treatments. In the last two decades, multikinase

inhibitor (MKI) compounds have been developed and demonstrated to be very effective with a long-lasting response to treatment. Unfortunately, since MKIs are cytostatic, they must be chronically administered to patients in order to avoid a sudden growth of metastases upon discontinuation of treatment (1).

Among the different MKIs approved for TC, Lenvatinib (LEN) and Vandetanib (VAN) are the most widely used for radioiodine-refractory advanced differentiated thyroid cancer (RAI-R DTC) and for medullary thyroid cancer (MTC), respectively.

The registration studies reported excellent results regarding the efficacy of LEN: the SELECT study showed a median progression-free survival (PFS) of 19.4 months in the group of patients treated with LEN compared to 3.7 months in the placebo group (2), being similar and even better results reported in following real-life studies (3–16). Similarly, treatment with VAN demonstrated in the registration ZETA study a great efficacy, showing a median PFS of 30.5 months for the VAN group and a median PFS of 19.3 months in the placebo group (17). Of note, VAN had a higher objective response rate (ORR) with respect to placebo even in patients with sporadic disease and without detectable RET mutations. Subsequently, real-life studies confirmed the efficacy of VAN in terms of both ORR and PFS (18–24). More recently, another MKI, Cabozantinib (CABO), was approved for the treatment of advanced MTC and RAI-R DTC. Data obtained from the registration EXAM study showed that the estimated median disease-free survival (DFS) was approximately threefold higher in the CABO arm than in the placebo group (11.2 vs. 4.0 months, respectively) (25) (**Table 1**).

Despite the great efficacy, several adverse events (AEs) have been reported in virtually all patients treated with these MKIs and include hypertension, diarrhea, decreased appetite, decreased weight, fatigue, and proteinuria. Most grade 3–4 adverse reactions occur during the first 6 months of treatment and require dosage reduction and/or drug discontinuation (**Table 1**).

Unfortunately, only few data regarding the quality of life (QoL) of patients during MKI therapy have been reported to date. Jasim et al. evaluated QoL of patients treated with LEN by means of the Linear Analog Self-Assessment (LASA) item on a scale of 0–10, and no variations were found at 2 and 6 months of follow-up, but the drug was discontinued in 28% of cases (26). Two Italian studies evaluated the impact of MKIs treatment on daily life and welfare. Nervo et al. used the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (CTCAE) and the European Quality of Life 5 Dimensions 3 Levels (EQ-5D-3L) questionnaire, providing the EQ-5D index and the EQ visual analogue scale (EQ-VAS). The median EQ-5D index and EQ-VAS scores after 3 months of treatment were lower compared to baseline, but after 12 months, they could be restored, probably as a result of therapy optimization (27). Giani et al. evaluated QoL in 39 patients by using the European Organization for Research and Treatment (EORTC) Quality of Life Questionnaire-Core 30 and the pain visual analogue scale (VAS). Interestingly, no statistically significant differences before, during, and at the end of a 6-month follow-up were found, although a minor improvement of the general health and emotional and cognitive status associated with a slight worsening of the physical role and social functioning was observed (28).

The management of AEs, therefore, emerges as crucial to maintain or improve the eventually decreased QoL of these patients. Few studies evaluated how to optimize the daily management of patients treated with MKIs, suggesting the best approach for clinical practice, aimed to maximally limit dose reductions or treatment discontinuation (29–31).

The availability of a multidisciplinary team (MDT) of healthcare professionals, including endocrinologists, oncologists, nurses, physiotherapists, nutritionists, psychologists, and other health professionals, has been shown to facilitate the management of AEs, thus improving the QoL of these fragile patients (32). Upon the identification of a progressive disease that could benefit from a

TABLE 1 | The main characteristics of the ZETA, EXAM, and SELECT trials, including eligibility criteria and adverse events (AEs).

Drug	Trial	Trialdesign	Patients (n)	Eligibility criteria	All grades AEs (%)		Grade > 3 AEs (%)	
Lenvatinib	SELECT Schlumberger et al., 2015 (2)	Phase III, randomized, double-blind, vs. placebo	261	18 years or older + measurable, pathologically confirmed DTC + 131I-refractory disease	Hypertension Diarrhea Fatigue/asthenia Decreased weight Nausea Stomatitis	67.8 59.4 59 50.2 41 35.6	Fatigue/asthenia Nausea Decreased appetite Decreased weight Hypertension Diarrhea	27.5 13.7 11.5 9.2 9.2 8.4
Vandetanib	ZETA Wells et al., 2011 (17)	Phase III, randomized, double-blind, vs placebo	231	Adults + measurable, unresectable, advanced/ metastatic MTC + performance status ¾ 2 + serum CT ≥ 500 pg/ml	Diarrhea Rash Nausea Hypertension Headache Fatigue	56 45 33 32 26 24	Diarrhea Hypertension QT prolonged Fatigue Decreased appetite Rash	11 9 8 6 4 4
Cabozantinib	EXAM Elisei et al., 2013 (25)	Phase III, randomized, double-blind, vs. placebo	219	Adults + unresectable, advanced/metastatic MTC + disease progression within the prior 14 months	Hypertension Hemorrhage Venous thrombosis GI perforation Non-GI fistula Arterial thrombosis	32.7 25.2 5.6 3.7 3.7 2.3	Hypertension Venous thrombosis Non-GI fistula Hemorrhage GI perforation Arterial thrombosis	8.4 5.6 3.7 3.3 3.3 0.9

MKI treatment, the patient should receive a careful assessment of her/his psychophysical state. A detailed counseling discussion with the patient and the family should be also planned in order to fully describe risks/benefits of the therapy and the possible occurrence of AEs. This would help the patient to fully share the decision to start a chronic treatment and to identify possible AEs in an early phase (**Figure 1**). Recently, prehabilitation practice has been extended to the management of several tumors, including TC. This includes multidisciplinary interventions that aim to enhance patient's functional capacity and to reduce side effects of medical or surgical treatments. As far as patients predicted to be submitted to MKIs are concerned, prehabilitation should include the optimization of the nutritional and of the psychophysical status to be obtained in the weeks/months before the start of treatment.

A MULTIDISCIPLINARY TEAM FOR THE MANAGEMENT OF THE ADVERSE EVENTS

Several adverse events (AEs) have been reported in almost all patients treated with MKIs, most grade 3–4 adverse reactions occurring during the first 6 months of treatment and requiring dosage reduction and/or drug discontinuation.

Gastrointestinal AEs are frequent and significantly reduce the QoL of patients, also compromising their adherence to treatment. Among these, diarrhea is highly prevalent (range, 45%–67% any grade), and decreased appetite/anorexia, nausea and occasionally vomiting are observed, too. To alleviate these symptoms, clinical practice suggests to train the patients to select among foods and preferentially take those less associated with the onset of gastrointestinal symptoms. Since these aliments can have interindividual major differences and can change during the follow-up, a tailored diet should be prepared and modified according to the inputs given by patients. Natural products or supplements (such as Aloe, lactic ferments, and clay) or loperamide should be suggested in case of diarrhea. Hence, patients need to be followed up at baseline and throughout the treatment by expert nutritionists for the setup of appropriate dietary regimens aimed to reduce or avoid weight loss and gastrointestinal AEs, which can have a major impact on the QoL.

Nevertheless, the majority of patients do develop weight loss during MKI therapy, with a multifactorial basis, including decreased appetite, gastrointestinal disorders, dysgeusia, and modifications of the sense of taste. We recently demonstrated that weight loss is mainly associated with fat mass reduction and that leptin parallels the decrease in body mass index (BMI) values, whereas ghrelin levels increase upon BMI decrease, likely leading to the weight stabilization observed after 1 year of treatment (33). Still, the continuous support of an expert nutritionist is needed, possibly integrated with a fitness rehabilitation program to avoid fat-free mass loss. The latter can be a crucial intervention also for the improvement of fatigue, which is another frequent AE of MKI treatment with a strong impact on the QoL and on the fulfillment of the usual daily activities.

We reported the first demonstration (34), recently confirmed by an independent group (35), that fatigue can be frequently related to primary adrenal insufficiency and that, in patients in whom this diagnosis is confirmed, the use of replacement therapy with cortisone acetate significantly improves the symptom. This intervention increases compliance to therapy, avoiding or limiting dose reductions.

Another important and frequent AE is hypertension, which, in some patients, is easily managed with medical monotherapy, in particular by the use of angiotensin-converting enzyme (ACE) inhibitors (which have a beneficial effect on proteinuria, too), while other cases requires the use of multiple drugs to be controlled (e.g., calcium channel blockers or sartanics or diuretics) (36). These patients should be treated by a cardiologist dedicated to MKI-induced hypertension, who will evaluate them before the start

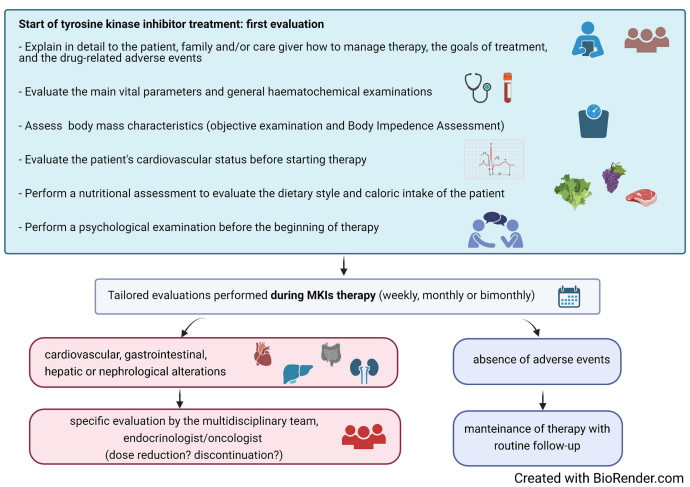

FIGURE 1 | Suggested algorithm for the initial assessment and the follow-up during treatment of patients with advanced thyroid carcinoma treated with multikinase inhibitors (MKIs).

of treatment and during the entire follow-up, with the final aim not to modify antineoplastic treatment due to an unmanageable hypertension.

The majority of MKIs can induce skin alterations of different degrees. It is therefore essential, when the treatment with topical creams (for example those with urea addition to be used for the so-called "hand–foot syndrome") is not enough to reduce the degree of skin lesions, to submit the patient to a specific dermatological examination. For the treatment of this AE, the support of the nursing staff is crucial. Indeed, nurses are fully involved in the management of these fragile patients, since they usually have a more confidential and tight contact with them, thus providing to the clinician valuable information on the general psychophysical state, the adherence to therapy, and any complaint occurring during treatment.

Finally, a psychological support must be always available in the MDT for all patients, but mostly for those who develop mood variability, anxiety, stress, and depression related not only to the neoplastic condition but also to the coexistence of two or more AEs.

DAILY MANAGEMENT OF PATIENTS IN MKI TREATMENT: A SUGGESTED MODEL

Especially during the first 6 months of MKI therapy, patients should be able to promptly and easily reach either specialist doctors or nurses. Indeed, during the first months, MKIs display their maximum efficacy (37), and acute complications such as fistulization upon tumor necrosis can occur. Moreover, the great majority of AEs develop during the first months of treatment.

To this aim, since the start of MKI therapy, patients should be provided with direct phone and email contacts of the whole medical team. As a consequence, each patient, who is completely evaluated at the hospital every 1–2 months, also has a 24-h direct contact and feels fully supported (**Figure 2A**). Even in the absence of complaints, patients like to update the team *via* email, WhatsApp, and Telegram on their health status, and on the positive evolution of AEs. Through these easy contacts, patients can be given dietary advice in case of gastrointestinal AEs, or antihypertensive therapy can be constantly titrated and personalized, thus avoiding a hospital access. In addition, the clinician can monitor on a near-daily basis the body weight's trend in a patient who has developed decreased appetite or nausea or weight loss on MKI treatment.

The Telegram application in particular allows all physicians in the referral team to simultaneously view patient communications and to quickly provide useful and encouraging feedbacks, with the possibility to act on AEs or any complication in a very early phase. On the other hand, patients feel reassured and more prone not to discontinue treatment even in the presence of AEs. Importantly, this way of communication can be considered a training for the younger members of the team who will learn from the more experts how to daily manage these patients.

Later follow-up can be tailored according to the patient's general condition. In principle, hospital visits should be scheduled at close intervals during the first treatment period (e.g., every 7–15 days), subsequently reducing frequency to every 30–60 days. At each time of follow-up, AEs not easily manageable by the treating clinicians (endocrinologists/oncologists) will be treated by a specialized physician (cardiologist, dermatologist, etc.) (**Figure 2B**).

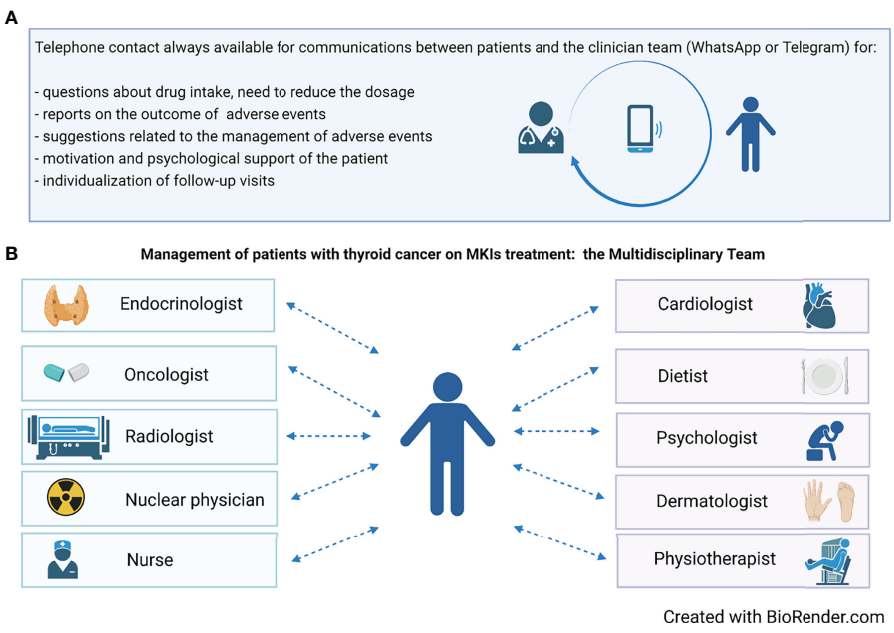

FIGURE 2 | **(A)** The availability of a phone contact is crucial during treatment for an adequate management, aimed to maximally reduce the need for dose reduction or drug discontinuation. **(B)** The composition of the multidisciplinary team involved in the management of patients on MKIs treatment.

DISCUSSION

MKIs provide a useful therapeutic tool for patients with advanced TC, for whom the prognosis was poor until a few years ago. Despite the great efficacy, major limitations exist, such as the need to maintain a chronic treatment and the need to manage several AEs that highly reduce QoL in some patients. In this context, it is worth to note that studies focusing on patients' QoL are still very limited and need to be implemented in the next future.

To manage these patients, a multidisciplinary team is crucial. In particular, the decision on the need to start an MKI treatment, when to start it, and at which dosage must be taken mainly by endocrinology/oncology, radiology, and nuclear medicine specialists in a common board. Thereafter, several other specialists should be involved, including psychologists and nurses.

The patient must feel to be followed up and treated by specialists who are expert on this particular topic and must be always supported in the management of AEs in order to increase the compliance and to reduce the risk of discontinuation of the drug.

Upon the identification of a progressive disease that could benefit from a MKI treatment, the patient should receive a careful assessment of her/his psychophysical state and possibly undergo prehabilitation procedures, and a detailed counseling with the family members should be also planned.

During follow-up, it is crucial for the MDT to manage even daily the communication with the patient, mainly thanks to social networks, such as Telegram or WhatsApp, in order to verify the onset and the degree of AEs and to give a prompt advice. These messaging tools allow clinicians to give continuity of care to patients receiving MKIs and to extend their support beyond the periodic visits to the hospital.

In conclusion, the management of MKI treatment must take advantage of an MDT and of the possible daily connection between clinicians and patients. Every effort should be done in this direction to gain the maximum benefit from these very effective drugs and to reduce the AEs, in order to improve compliance to treatment, thus increasing drug effectiveness and patients' QoL.

AUTHOR CONTRIBUTIONS

This mini-review was conceived and written by CC and LF. All authors contributed to the article and approved the submitted version.

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Nomogram Predicts Overall Survival in Patients With Stage IV Thyroid Cancer (TC): A Population-Based Analysis From the SEER Database

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Background: Stage IV Thyroid cancer (TC) has a relatively poor prognosis and lacks a precise and efficient instrument to forecast prognosis. Our study aimed to construct a nomogram for predicting the prognosis of patients with stage IV TC based on data from the SEER programme.

Methods: We enrolled patients diagnosed with TC from 2004 to 2015 in the study. Furthermore, the median survival time (MST) for the patients equalled 25 months. The patients were split into two groups: the training group and validation group. We used descriptive statistics to calculate demographic and clinical variables, Student's t test was used to describe continuous variables, and the chi-square test was used to describe classified variables. We used the concordance index (C-index) to evaluate discrimination ability and calibration plots to evaluate calibration ability. The improvement of the nomogram compared with the AJCC TNM system was evaluated by the net weight classification index (NRI), comprehensive discriminant rate improvement (IDI) and decision curve analysis (DCA).

Results: There were 3501 patients contained within our cohort, and the median follow-up was 25 months [quartile range (IQR): 6-60] in the whole population, 25 months (IQR: 6-60) in the training cohort, and 25 months (IQR: 5-59) in the validation cohort. The C-index value of the training cohort equalled 0.86 (*95% CI: 0.85-0.87*), and the value of the validation cohort equalled 0.85 *(95% CI: 0.84-0.86).* The NRI values were as follows: training queue: 1.16 for three-year and 1.12 for five-year OS prediction; authentication group: 1.22 for three-year and 1.21 for five-year OS prediction. The IDI values were as follows: training cohort: 0.25 for three-year and 0.21 for five-year OS prediction; validation cohort: 0.27 for three-year and 0.21 for five-year OS prediction. The DCA diagram showed that the nomogram was superior in predicting the three-year and five-year trends.
Conclusions: Our nomogram can be used to forecast the survival of patients with stage IV TC.

Keywords: Thyroid cancer (TC), stage IV, nomogram, overall survival (OS), prognostic model

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INTRODUCTION

Thyroid cancer (TC) is an epidemic in America, and its incidence has grown faster than that of any other cancer since the 1990s (1). An estimated 44,280 new cases occurred in men and women in 2020, with a mortality rate of 4.97%, and this has aroused substantial public concern (2). In the meantime, many patients often develop long-distance metastasis (DMs) or lymphatic metastasis, which in turn leads to a high mortality rate. TC has been classified into four phases, among which stage IV TC varies according to the clinical subtype, including anaplastic carcinoma, medullary thyroid carcinoma (MTC), papillary carcinoma (PTC) and follicular carcinoma (FTC) (3–5). In fact, studies have indicated that TC should be evaluated independently rather than analysing TC without recognizing its pathological type. In fact, all these studies indicate that TC should be studied independently rather than analysing TC without recognizing pathological type (6, 7). Likewise, 5-20% of TC patients might develop DMs resulting in high mortality, which suggests that precise assessment of their prognosis is crucial. At present, there is no individualized model to predict the prognosis of stage IV TC patients (8).

The American Joint Committee on Cancer (AJCC) staging system is the most commonly used tool for evaluating the prognosis of patients with TC. However, this assessment system has many limitations, including low accuracy, disregard of sociodemographic and clinicopathological characteristics (such as time of life, therapy or marital status), and poor performance in predicting individual survival outcomes (9, 10). In conclusion, an individual prediction model is essential for patients with stage IV TC.

Nomograms have been widely used as predictive methods in oncology in recent years. After integrating demographic and clinicopathological characteristics, the nomogram model could be more accurate and personalized than the conventional TNM staging system, and it is convenient for clinicians to predict the prognosis of patients. In our study, we used the Surveillance, Epidemiology, and End Results (SEER) database to establish a nomogram model to predict the prognosis of TC patients (11).

MATERIALS AND METHODS

Data Resource

The recent version of the SEER 18 registries Custom Data (with additional treatment fields) was used as the data source for the present population-based investigation. This database consists of 18 population-based cancer registries and covers approximately 26% of the US population across several geographic regions (12). SEER*-STAT Software version 8.3.9 (Https://seer.cancer.gov/seerstat/) (Information Management Service, Inc. Calverton, MD, USA) was used to generate the case listing. All of the procedures were excluded from the approved guidelines. Informed patient consent was not required to access or use SEER data.

Patients Cohort

Patients diagnosed with TC participated in the study, and the median survival for the patients equalled 25 months. Patients were included according to the following standards: 1) active follow-up to ensure reliable patient status; 2) TNM (American Joint Committee on Cancer, AJCC 6th) stage IV. The criteria for dismissal were as follows: 1) AJCC IV stage and tumour grade are unknown; 2) unknown operation information; and 3) the survival months is zero. After the preliminary filter, 3501 patients with TC were extracted in our cohort. In our study, the demographic and treatment features of patients were confirmed, including ethnicity year of life, time of diagnosis, civil state, operation, radiotherapy and chemotherapy. Tumour specialities consisted of tumour histology, tumour grading, AJCC staging, and prior cancer history. **Figure 1** shows the entire screening process.

Endpoint and Statistical Analysis

Overall survival (OS) is considered the time lag between the date of diagnosis and the date of death due to any reason. We used descriptive statistics to calculate demographic and clinical variables, Student's t test was used to describe continuous variables, and the chi-squared test was used to describe the classified variables. In survival analysis, univariate and multivariate Cox regression analyses were carried out, and the meaningful variables in univariate analysis were included in the multivariate analysis. $P<0.05$ was considered a self-governed risk factor.

Based on the above independent risk factors, a nomogram model was set up. Nomograms estimate probabilities of three and five years. The discriminant ability was evaluated by the harmony index (C index), and the calibration ability was evaluated by a calibration graph. The C-index was on a scale of 0.5 to 1.0, where 0.5 represents random opportunity and 1.0 indicates an exact accouplement. Generally, a C-index greater than 0.7 indicates a reasonable estimation. The improvement of the nomogram compared with the AJCC TNM system was evaluated by the net weight classification index (NRI), comprehensive discriminant rate improvement (IDI) and decision curve analysis (DCA). The NRI and IDI were used to assess improvements in prognosis forecasting and measure the usefulness of a new model (13, 14). DCA is a measurement for assessing the clinical benefit of alternative models and has been applied to nomograms by quantifying net benefits at different threshold probabilities (15, 16). *P values* were two-tailed, and $P < 0.05$ indicated statistical significance. In addition, the above data are analyzed by R Studio.

RESULTS

Baseline Characteristics

Our cohort collected 3501 patients, and the patients were split into two groups: Group 1 was defined as the training group, and Group 2 was defined as the validation group (ratio: 7:3). The median follow-up equalled 25 months [quartile range (IQR): 6-60] in the whole population, 25 months (IQR: 6-60) in the training cohort, and 25 months (IQR: 5-59) in the validation

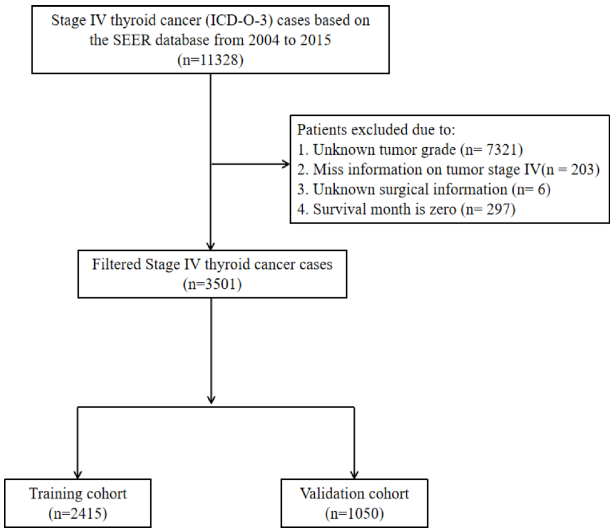

FIGURE 1 | The entire screening process of Patients cohort.

cohort. In the whole population, training and verification teams, the mean ages of patients with TC were 64.5 (± 12.8), 64.5 (± 12.7) and 64.5 (± 12.9) years, respectively. Females(56.5%) and married patients (60.8%) comprised the majority of the cohort. Meanwhile, the whole population had a relatively low rate of moderate (11.9%) and poorly differentiated (16.9%) MTCs. As for histology, MTCs only account for a low ratio of MTCs (3.1%). Moreover, 48.2% of them had tumour stage IVA, and 81.9% of patients had no prior cancer history. In addition, 82.5% and 61.5% of the population received surgery and radiotherapy, respectively, while only 20.2% of patients received chemotherapy. There was no statistical difference between the training and validation cohorts regarding demographic and clinical characteristics ($P > 0.05$), except tumour histology. Detailed information on these TC patients is shown in **Table 1**.

Nomogram Variable Screening Based on Univariate and Multivariate Cox Regression Analysis

We carried out univariate and multivariate analyses sequentially (**Table 2**), and the independent prognostic factors with a significant influence on OS were selected. Univariate analysis showed that 10 variables, such as ethnic lines, time of year, tumour grading, tumour histology, tumour staging, operation, radiotherapy, chemotherapy, prior cancer history and marital status, showed positive statistical significance.

Multivariate Cox proportional risk regression analysis showed that time of life, tumour grading, tumour histology, tumour staging, surgery, radiotherapy and marital status were significantly correlated with OS in the study. In conclusion, the prognostic variables with statistical significance in univariate and multivariate analyses were independent predictive factors for stage IV TC patients.

Nomogram Construction and Validation

Based on screening variables, the nomogram model constructed by Cox proportional hazard regression was used to predict the OS of stage IV TC patients at 3 years and 5 years. As shown in **Figure 2**, screening variables pointed to a score, and a total score was obtained by adding up all of the scores. A nomogram can be used to predict the survival probability of a given patient. Furthermore, most patients in our study had total cumulative points ranging from 300 to 450 (**Figure 2**).

The C-index value equalled 0.86 (95% CI: 0.85-0.87) in the training queue and 0.85 (95% CI: 0.84-0.86) in the validation queue (**Table 3**). The calibration curve of the nomogram also showed high consistency between the nomogram prediction and operating system observed in the training and verification queue for three years and five years (**Figures 3A–D**). In conclusion, the nomogram for TC patients had great discriminative and calibrating abilities.

Nomogram Clinical Value to Compare With AJCC-TNM System Stage

The NRI and IDI were used to compare the accuracy between the nomogram and the AJCC-TNM stage (**Table 3**). In the training cohort, the NRI values for the three-year and five-year OS were 1.16 (95% CI: 1.09-1.23) and 1.12 (95% CI: 1.05-1.19), respectively; the IDI values for the three-year and five-year OS equalled 0.25 (95% CI: 0.21-0.27, P < 0.001) and 0.21 (95% CI: 0.18-0.24, P<0.001), respectively. The validation cohort indicated that the NRI values for the three-year and five-year OS were 1.22 (95% CI: 1.06-1.34) and 1.21 (95% CI: 1.04-1.31), respectively, and the IDI values for the three-year and five-year OS rates were 0.27 (95% CI: 0.22-0.31, P<0.001) and 0.24 (95% CI: 0.19-0.28, P<0.001), respectively.

The clinical benefits of the nomogram were compared with those of the AJCC-TNM system stage. The DCA chart shows

TABLE 1 | The baseline characteristics of patients in the SEER database.

Characteristics	All cohort		Training cohort		Validition cohort		P-value
	N 3501	% 100	N 2451	% 70.01	N 1050	% 29.99	
Age(mean±SD)	64.5 (±12.8)		64.5 (±12.7)		64.5 (±12.9)		0.98
Race							0.58
Black	222	6.3	162	6.6	60	5.7	
Other	487	13.9	337	13.7	150	14.3	
White	2792	79.7	1952	79.6	840	80	
Sex							0.14
Female	1979	56.5	1365	56.7	614	58.5	
Male	1522	43.5	1086	44.3	436	41.5	
Grade							0.97
Grade I	1211	34.6	780	35.5	341	32.5	
Grade II	417	11.9	288	11.8	129	12.3	
Grade III	592	16.9	412	16.8	180	17.1	
Grade IV	1281	36.6	881	35.9	400	38.1	
Histology							0.02
Anaplastic carcinoma	790	22.6	531	21.7	259	24.7	
Follicular carcinoma	179	5.1	140	5.7	39	3.7	
Medullary carcinoma	108	3.1	81	3.3	27	2.6	
Other	418	11.9	282	11.5	136	13	
Papillary carcinoma	2006	57.3	1417	57.8	589	56.1	
AJCC stage							0.95
IVA	1688	48.2	1179	48.1	509	48.5	
IVB	803	22.9	561	22.9	242	23	
IVC	1010	28.8	711	29	299	28.5	
Surgery							0.11
No	611	17.5	411	16.8	200	19.0	
Yes	2890	82.5	2040	83.2	850	81	
Radiotherapy							0.14
No	1347	28.5	923	37.3	424	40.4	
Yes	2154	61.5	1528	62.3	626	59.6	
Chemotherapy							0.22
No	2794	79.8	1970	80.4	824	78.5	
Yes	707	20.2	481	19.6	226	21.5	
cancer history							0.66
Yes	634	18.1	449	18.3	185	17.6	
No	2867	81.9	2002	81.7	865	82.4	
Marital status							0.53
Married	2128	60.8	1498	61.1	630	60	
Single	1263	36.1	881	35.9	382	36.4	
Unknown	110	3.1	72	2.9	38	3.6	

SEER, Surveillance, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer.

that the nomogram had a certain advantage in predicting 3-year and 5-year OS, as it increased net benefits more than the AJCC-TNM system stage for almost all threshold probabilities in both the training and validation cohorts and with both the treat-all-patients scheme and the treat-none scheme (**Figures 4A–D**). In summary, the abovementioned results indicated that the nomogram model could increase precision and reliability for OS prediction compared with the AJCC-TNM staging system.

DISCUSSION

Stage IV TC is a tumour with a relatively poor prognosis, but it lacks a precise and efficient instrument to forecast prognosis in individual patients in clinical practice, except for the AJCC TNM staging system. On the basis of the records of 3501 patients from the SEER database, our team put up a nomogram model to forecast the three-year and five-year OS of patients with stage IV TC. Seven variables were selected by clinical significance to construct and validate the capability of the model, which could provide the basis for future clinical decisions. Measured by range along nomogram scales, age was the most important prognostic factor, followed by tumour grading, tumour staging, tumour histology, surgery, radiotherapy and marital status. This is the first study to predict the prognosis of patients with stage IV TC, and the population-based nomogram model showed the greatest results.

In our study, prognosis was estimated by OS, which is a common and objective index for patients with stage IV TC. Univariate Cox regression analysis showed that ethnic lines, time of life, tumour grading, tumour histology, tumour staging, operation, radiotherapy, chemotherapy, past cancer history and

TABLE 2 | Cox proportional hazard model of OS.

Characteristics	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Race						
Black		As reference			As reference	
Other	0.68	0.52-0.88	0.003	0.90	0.69-1.18	0.46
White	0.76	0.61-0.94	0.01	0.91	0.73-1.13	0.37
Age	1.05	1.04-1.06	<0.001	1.03	1.02-1.04	<0.001
Sex						
Female	As reference					
Male	0.94	0.84-1.05	0.290			
Grade						
I		As reference			As reference	
II	1.43	1.08-1.91	0.01	1.27	0.95-1.69	0.11
III	5.51	4.5-6.7	<0.001	3.24	2.61-4.02	<0.001
IV	11.05	9.24-13.21	<0.001	5.20	4.17-6.48	<0.001
Histology						
Anaplastic carcinoma	As reference				As reference	
Follicular carcinoma	0.24	0.19-0.31	<0.001	0.56	0.42-0.75	<0.001
Medullary carcinoma	0.22	0.16-0.31	<0.001	0.54	0.37-0.77	<0.001
Other	0.51	0.44-0.6	<0.001	0.77	0.64-0.94	0.01
Papillary carcinoma	0.12	0.11-0.14	<0.001	0.6	0.5-0.72	<0.001
AJCC stage						
IVA		As reference			As reference	
IVB	5.04	4.31-5.89	<0.001	1.99	1.68-2.35	<0.001
IVC	6.92	5.96-8.04	<0.001	3.89	3.31-4.58	<0.001
Surgery						
No		As reference			As reference	
Yes	0.15	0.14-0.17	<0.001	0.64	0.54-0.76	<0.001
Radiotherapy						
No		As reference		As reference		
Yes	0.39	0.35-0.44	<0.001	0.65	0.56-0.74	<0.001
Chemotherapy						
No		As reference		As reference		
Yes	3.21	2.84-3.63	<0.001	1.05	0.91-1.21	0.5
Prior cancer history						
Yes		As reference		As reference		
No	0.75	0.65-0.86	<0.001	0.91	0.79-1.05	0.19
Marital status						
Married		As reference		As reference		
Single	1.48	1.32-1.66	<0.001	1.21	1.07-1.36	0.002
Unknown	0.96	0.67-1.38	0.82	0.83	0.58-1.21	0.34

SEER, Surveillance, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; OS, Overall Survival; BCS, breast conserving surgery; SM, simple mastectomy; RM, radical mastectomy.

marital status were significantly related to OS. To decrease the estimation bias and further confirm the independent prognostic factors on OS for patients with TC, multivariate Cox regression analysis was performed.

After readjusting the demographic, clinicopathological and therapeutic variables, we discovered that time of life, tumour grading, tumour histology, tumour staging, operation, radiotherapy and marital status were still significantly related to OS. Through univariate and multivariate Cox regression analysis, the above 7 variables were selected to build the prediction model.

In conclusion, the nomogram model can be used to predict the survival outcome of various cancers, which integrates clinical and demographic factors to evaluate the risk of specific diseases (10, 17–20). Traditionally, the AJCC-TNM staging system has been the primary choice to predict prognosis and make clinical decisions. However, the prognosis of patients at the same stage is often different because the AJCC-TNM staging system does not comprehensively consider various variables, such as clinical characteristics, treatment methods and sociodemographic characteristics. Therefore, we compared the nomogram, which involves more variables, with the conventional AJCC-TNM staging system. The NRI value and IDI value of the nomogram versus the TNM staging system suggested that the nomogram prediction model had better predictive capability than the TNM staging system alone. Furthermore, DCA curves demonstrated that our model forecasted survival outcome with better clinical value and utility than the conventional staging system. In the validation cohort, the results could also be replicated favourably. In conclusion, our nomogram could provide accurate and individual predictions of OS in patients with TC.

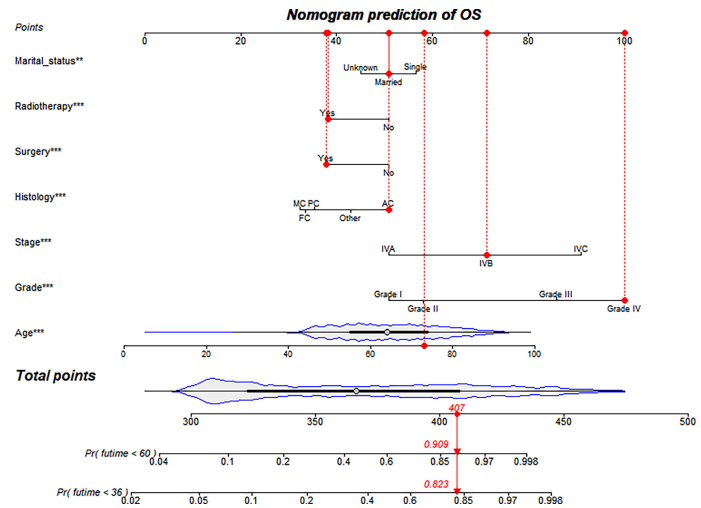

FIGURE 2 | nomogram prediction of OS.

Since many patients with stage IV TC have concerns about balancing the risk of surgery and the chance for a longer life, there is great need to build a scoring system for reference. Using this model, we could easily and precisely predict individual patients' overall death probability at certain time points.

First, different variables pointed to a score according to the top scale, and we drew a vertical line from each prognostic factor to obtain the corresponding points. Second, we obtained a total score by summing all of the scores. Finally, we drew a vertical line from the total points scale to the 3- and 5-year overall death scale to obtain the estimated probabilities of death, and from this we obtained the OS rate. For instance, 73-year-old married patients underwent surgery and radiotherapy, with anaplastic carcinoma and grade II and stage IVB tumours. Since we can estimate from the nomogram graph that the 3-year and 5-year overall death probabilities are 82.3% and 90.9%, the 3-year and 5-year OS rates are 17.7% and 9.1%, respectively.

Although the nomogram performed well, our study did have some limitations, as shown below. First, the nomogram was based on a retrospective study, which could not prove causation and result due to selection bias. Second, we were unable to exclude the impact of potential confounders, such as family history, complications, health conditions, and patient anxiety, which were not covered in the SEER database. Last, a P value < 0.05 was used to determine statistical significance, and no adjustment was made for multiple analyses. The probability of false rejection of invalid hypotheses may have exceeded 0.05. Multicentre clinical trials are needed to evaluate the external utility of our nomogram.

CONCLUSION

Our study aimed to construct a nomogram for predicting prognosis in patients with stage IV TC based on data from the

TABLE 3 | C-index, NRI and IDI of the nomogram and AJCC-TNM stage system in OS prediction for stage IV TC patients.

	Training cohort			Validation cohort		
	Estimate	**95% CI**	**P-value**	**Estimate**	**95% CI**	**P-value**
NRI (vs. AJCC-TNM stage system)						
For 3-year OS	1.16	1.09-1.23		1.22	1.06-1.34	
For 5-year OS	1.12	1.05-1.19		1.21	1.04-1.31	
IDI (vs. AJCC-TNM stage system)						
For 3-year OS	0.25	0.21-0.27	<0.001	0.27	0.22-0.31	<0.001
For 5-year OS	0.21	0.18-0.24	<0.001	0.24	0.19-0.28	<0.001
C-index						
The nomogram	0.86	0.85-0.87		0.85	0.84-0.86	
AJCC-TNM stage system	0.72	0.71-0.73		0.71	0.7-0.72	

AJCC, American Joint Committee on Cancer; OS, Overall survival; TC, Thyroid cancer

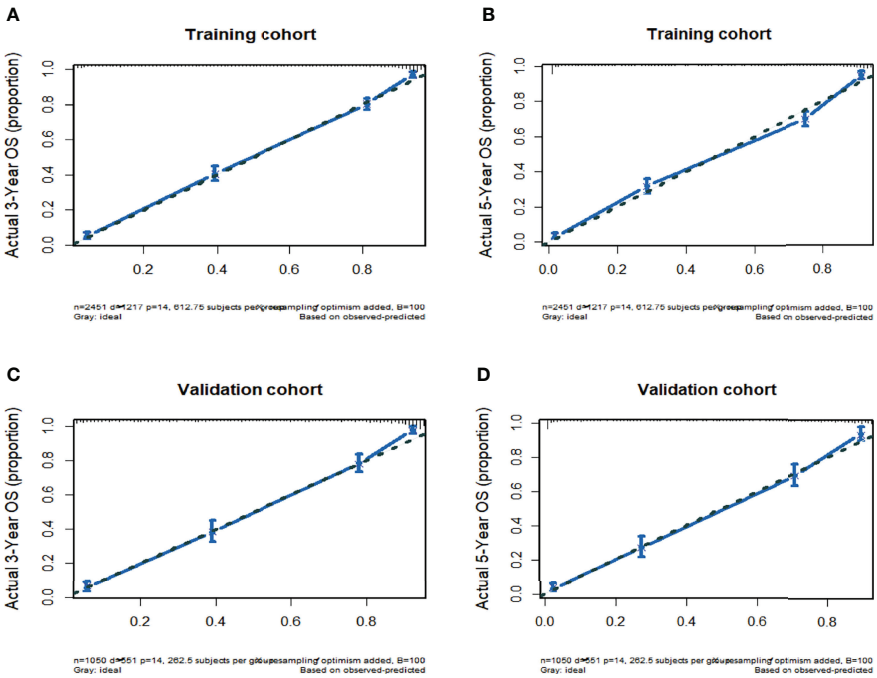

FIGURE 3 | **(A)** Nomogram-Predicted probability of 3-Year OS. **(B)** Nomogram-Predicted probability of 5-Year OS. **(C)** Nomogram-Predicted probability of 3-Year OS. **(D)** Nomogram-Predicted probability of 5-Year OS.

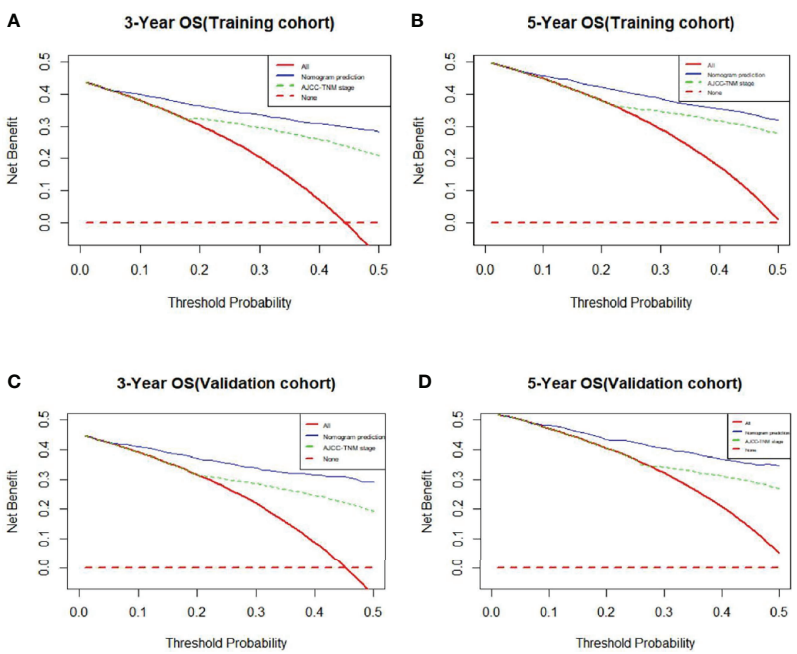

FIGURE 4 | **(A)** 3-Year OS. **(B)** 5-Year OS. **(C)** 3-Year OS. **(D)** 5-Year OS.

SEER programme. Given its favourable clinical utility and accurate prognosis prediction in comparison with the conventional TNM staging system, our nomogram can be used to predict the survival of patients with stage IV TC. However, multicentre clinical validation is also required to evaluate the external utility of our histograms.

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.

AUTHOR CONTRIBUTIONS

TY and TH analysed the data. TH drafted the manuscript. TY generated the figure. MZ and QH edited the manuscript. All authors contributed to the article and approved the submitted version.

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Indoleamine 2,3-Dioxygenase Immune Status as a Potential Biomarker of Radioiodine Efficacy for Advanced Distant Metastatic Differentiated Thyroid Cancer

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Purpose: Host immunity influences the impact of cancer therapy but the effect of immune status in radioiodine (RAI)-treated differentiated thyroid cancer (DTC) remains obscure. Here we investigated indoleamine 2,3-dioxygenase (IDO) activity as a biomarker of response to RAI in patients with distant metastatic DTC (dmDTC).

Methods: Patients with dmDTC receiving RAI were evaluated for serum IDO activity (kynurenine and kynurenine:tryptophan ratio) at baseline and 3 months after RAI. The optimal cut-off value for these biomarkers to predict response was established by receiver operating characteristic analysis. The relationship between disease outcomes, overall survival (OS) and progression-free survival (PFS), and IDO activity levels was studied.

Results: Higher baseline kynurenine:tryptophan ratio (>2.46) was correlated with poorer RAI response as well as shorter median PFS (45 mo versus not reached, p=0.002) and OS (78 mo versus not reached, p=0.035). High baseline kynurenine:tryptophan ratio was also correlated with a reduced number of tumor-infiltrating lymphocytes. Higher post/pre-kynurenine ratio (>1.69) was associated with survival endpoints: shorter median PFS (48 mo versus not reached, p=0.002) and OS (68 mo versus not reached, p=0.010). Favorable baseline and favorable change corresponded with better PFS and OS.

Conclusions: Our results suggest that RAI also alters IDO activity in dmDTC patients. IDO activity could predict progression and survival outcomes for advanced dmDTC patients. Serum IDO biomarker levels could be used to select dmDTC likely to benefit from RAI therapy, although further studies are necessary.

Keywords: differentiated thyroid cancer, radioiodine, indoleamine 2, 3-dioxygenase (IDO), immune suppression, predictive factors

INTRODUCTION

Differentiated thyroid cancer (DTC) is the most common histological and least-aggressive type of thyroid cancer (1). However, 10%–20% of DTC patients develop distant metastatic disease, which is the most frequent cause of disease-specific death (2, 3). Distant metastatic DTC (dmDTC) patients require radioiodine (RAI) therapy at least once during their disease course. Although some patients with iodine-avid distant metastases may benefit from RAI therapy, this therapy is rarely curative (4).

RAI has been reported to activate the host immune system by reducing the secretion of Th2 cytokines [interleukin (IL)-4, IL-5, and IL-13] which might lead to tumor immune escape (5, 6). Therefore, in addition to direct DNA damage and tumor cell death, RAI might enhance antitumor immunity by those immunomodulatory factors in the tumor microenvironment (TME) (7). On the contrary, multiple immune suppressive factors are also activated by radiotherapy which results in aggressive and radiotherapy-resistant tumors with a poor clinical outcome (8). However, the relationship between RAI and blood biomarkers of immune function is not well understood.

Indoleamine-2,3-dioxygenase (IDO) is an intercellular enzyme that catalyzes conversion of tryptophan into kynurenine (9). IDO is expressed in a variety of different malignancies, and currently known as a cancer-related immunosuppressor (10, 11). IDO inhibits T cells by tryptophan depletion in the TME, which activates the amino acid–sensitive general control nonderepressible 2 stress-kinase pathway and causes cell cycle arrest and anergy induction in responding T cells (12). On the other hand, kynurenine, the product of IDO, enters natural killer (NK) cells *via* the aryl hydrocarbon receptor on the surface of NK cells. Kynurenine then decreases NK cells cytotoxicity in TME by inhibiting expression of NK-activating receptors, such as natural killer group 2D and NKp46, *via* signal transducer and activator of transcription (STAT)1 and STAT3 pathways (13). Furthermore, kynurenine and its downstream metabolites promote potent tumor immunosuppression *via* activation or differentiation of regulatory T (Treg) cells and effector T cells (14, 15). High IDO expression is associated with poor clinical outcome in diverse types of solid tumors, including thyroid cancer (16, 17). However, details of IDO activity in DTC have not been fully explored. The role of IDO activity as a biomarker for treatment outcomes and the prognostic significance in dmDTC treated with RAI remains unknown.

In this study, we evaluated the association between blood IDO activity levels and clinical benefit in advanced dmDTC patients treated with RAI. We examined differences in IDO biomarkers, including serum kynurenine and the kynurenine:tryptophan (K/T) ratio, before and 3 months after RAI. We then investigated whether IDO dynamics could represent a potential predictive biomarker for response to RAI. In addition, the association between circulating levels of IDO and overall survival (OS) and progression-free survival (PFS) in patients with dmDTC was studied.

MATERIALS AND METHODS

Patients and Treatment

Patients with advanced dmDTC who received RAI therapy between January 2010 and June 2020 were identified from routine patient documentation at the Department of Nuclear Medicine, Nanjing First Hospital or the Affiliated Hospital of Jiangsu University. All patients signed a written informed consent prior to blood sampling according to the Declaration of Helsinki. This retrospective study was approved by the Institutional Ethics Committees of Nanjing First Hospital and the Affiliated Hospital of Jiangsu University. Baseline fasting blood samples and clinical characteristics of all dmDTC patients were obtained at the time of initial presentation at the hospital for the first cycle of RAI treatment.

Therapeutic Approach and Follow-Up

All patients withdrew levothyroxine and began a low-iodine diet for 3–4 weeks before ^{131}I treatment (thyroid-stimulating hormone reached 85.03 ± 35.37 uIU/mL). The first dose of oral ^{131}I was 150–250 mCi (5.55–9.25 GBq). ^{131}I whole body scan (WBS) was performed 4 days later. Patients with no ^{131}I avid metastasis would be excluded. RAI therapy was repeated if the patient benefited from it, until complete remission or ^{131}I inavidity on WBS. The treatment interval varied from 6 to 12 months, and the treatment was repeated for 2–8 cycles. The cumulative activity of ^{131}I ranged from 11.1 to 57.35 GBq. The follow-up period was 1–11 years with a median of 64 months. Patients were examined 1 month after RAI, and followed up approximately every 3 months during the first year, and every 6 months from the second year thereafter. Post-RAI fasting blood samples of patients were collected at 3 months after the first cycle of RAI.

Efficacy Evaluation

Response to RAI was defined according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Responders were defined as patients with partial and complete responses, and non-responders were patients who had stable or progressive disease. If the patient had no measurable lesions, the response evaluation was based on thyroglobulin (Tg), a DTC tumor biomarker when antithyroglobulin antibody was negative. Compared with pretreatment, patients with a reduction of >25% in Tg levels were considered responders.

Immunohistochemistry

DTC samples were obtained from surgical patients who provided signed informed consent at Nanjing First Hospital, Nanjing, China and Affiliated Hospital of Jiangsu University, Zhenjiang, China. Immunohistochemistry was performed as described previously (18). For immunohistochemistry, a mouse monoclonal anti-CD3 (1: 500, BD Biosciences Pharmingen, San Diego, CA, United States) and a mouse monoclonal anti-CD8 (1:150, BD Biosciences Pharmingen) were used. $CD3^+$ and $CD8^+$ tumor-infiltrating lymphocytes (TILs) were counted in a microscopic field at ×200 in the three independent areas with the most abundant lymphocyte infiltration.

Measurements of Serum Tryptophan and Kynurenine

L-Tryptophan and L-kynurenine (Sigma, St. Louis, MO, USA) were used to construct standard curves. L-tryptophan-d5 and L-kynurenine-d4 (Cambridge Isotope Laboratories, Xenia, OH, USA) were used as internal standards. Tryptophan and kynurenine were measured using ultra-high-performance liquid chromatography (UPLC)–tandem mass spectrometry (MS/MS) (ACQUITY UPLC I-Class/Xevo TQD IVD System, Waters, USA) as described previously (19). Then 400 μL internal standard working solution was added to 150 μL human serum and 150 μL acetonitrile. A series of calibration standard solutions contained a mixture of drug-free serum (150 μL), L-tryptophan/L-kynurenine (150 μL), and internal standard (400 μL) working solution. Then 400 μL supernatant was collected after centrifugation at 12 000 rpm for 10 min and evaporated to dryness in a vacuum centrifugal concentrator. The residual was dissolved by 120 μL 1.2% formic acid. The supernatant was collected after centrifugation at 12 000 rpm for 5 min and injected into the chromatographic system for further analysis.

Tryptophan and kynurenine were analyzed by multiple reaction monitoring mode of MS/MS in positive ion mode. The cone voltage was 15–24 V, collision energy was 22–35 eV and transitions were m/z 205.0→118.0 for L-tryptophan, m/z 209.0→145.98 for L-kynurenine, and m/z 210.03→150.07 for L-tryptophan-d5, m/z 213.01→98.01 for L-kynurenine-d4.

Statistical Analysis

PFS was defined as the time from the start of RAI to documented evidence of progression or death; OS was measured from the start of RAI to the date of death from any cause. The association of IDO checkpoint with RAI treatment response and response rate was assessed by Mann–Whitney U test or chi-square test. Differences between pre- and post-treatment IDO checkpoints were analyzed using a paired t-test. The cutoffs for the prediction of IDO significant biomarker variables were determined by receiver operating characteristic (ROC) curve analysis using response as an event. Kaplan–Meier method and a log-rank test were applied to compare the survival difference between groups. Univariate analysis for progression and survival was performed by Cox proportional hazards regression model. Multivariate analysis by Cox proportional hazards regression model with 95% confidence interval (95% CI) was used to evaluate clinical variables with log-rank $p<0.05$ under univariate analysis as covariants. All statistical analyses were performed with IBM SPSS Statistics version 23.0 (Armonk, NY, USA). Scatter plot figures were generated using GraphPad Prism version 8 (La Jolla, CA, USA).

RESULTS

Patient Characteristics

Of 182 dmDTC patients enrolled, 104 patients (70 female, 34 male) with good-quality samples available for IDO testing formed the primary study population. The age of these patients was 48.7 ± 11.5 years (range 8–72 years). Distant metastasis as the initial evaluation of DTC was discovered in 25 cases (24.0%), and the diagnosis of distant metastasis was established during subsequent follow-up in 79 cases (76.0%). The median age at diagnosis of distant metastasis was 47 ± 11 years (range, 8–70 years). Sixty-five patients were at least 45 years old and 39 were <45 years old at the time of diagnosis. The distribution of pathological types of DTC was as follows: papillary thyroid carcinoma (PTC) in 74 patients (71.2%) and follicular thyroid carcinoma in 30 patients (28.8%). Fifty-five (52.9%) cases had only lung metastasis; 24 (23.1%) only bone metastasis; and 25 (24.0%) either combined lung and bone or other site metastases. Among other site metastases, four patients had mediastinal metastasis, two pleural metastasis, and one liver metastasis. Symptoms or events (like fractures) associated with any-site metastases occurred in 25 cases. **Table 1** shows the demographic and clinical features of the patients.

Prognostic Clinical Factors and Overall Outcomes

Median follow-up time was 64 (95% CI, 56–72) months for all patients. The median PFS was 61 (95% CI, 47–75) months. Univariate analysis showed that the age of onset for distant metastases ($p=0.023$), pathological type ($p=0.018$), extent of metastases ($p=0.042$), whether the distant metastases were the first presentation of DTC ($p=0.012$), were significant risk factors for OS. Patients with younger age at diagnosis, PTC, noncombined site of distant metastasis, and discovery of distant metastases during follow-up had better OS than patients with older age at diagnosis, follicular thyroid carcinoma, combined sites of distant metastases, and discovery of distant metastases at diagnosis or before surgery. However, only age ($p=0.034$), extent of metastases ($p=0.049$), and pathological type ($p=0.008$) were significant for PFS (**Table 1**). These clinical parameters were thus selected as associated covariants for further multivariate analysis of IDO checkpoint biomarkers.

Dynamics of Kynurenine and K/T Ratio at Baseline and Post-RAI

Serum kynurenine and K/T ratio fluctuated at two time points before and after RAI (**Figures 1A, B**). The mean kynurenine concentrations increased after RAI. The K/T ratio post-RAI was also significantly higher than that pre-RAI.

Baseline IDO Biomarkers and Outcomes

The kynurenine levels at baseline did not differ between responders and non-responders. Baseline K/T ratio had a trend to be lower in responders than in non-responders [median 2.15 (range 1.10–3.50) vs. 3.10 (1.14–5.09) ($p<0.001$)] (**Figure 2A**). Using the ROC curve to determine the best value of baseline K/T ratio to predict response, we identified ≤2.46 (area under the curve 0.797, 95% CI 0.703–0.891, $p<0.001$) as the cutoff point that combined maximal sensitivity (65.9%) with best specificity (79.4%) (**Figure 2B**). Adopting the ROC-derived threshold, 63 (60.6%) patients were classified as having low baseline K/T ratio, while 41 (39.4%) were categorized as having high baseline K/T ratio. Response rate was significantly lower in patients with high compared with low baseline

TABLE 1 | Comparison of Overall Survival and Progression Free Survival Based on Clinical Characteristics of dmDTC Patients.

Variables	Patients (n)	Overall Survival			Progression Free Survival		
		Hazard Ratio	(95% CI)	P-value	Hazard Ratio	(95% CI)	P-value
Age at diagnosis (years)							
<45	39						
≥45	65	3.45	(1.18-10.07)	0.023	2.06	(1.06–4.03)	0.034
Gender							
Female	70						
Male	34	1.35	(0.58–3.13)	0.491	1.12	(0.57–2.18)	0.745
Extent of metastases							
Lung only	55			0.042			0.049
Bone only	24	1.48	(0.48–4.54)	0.491	1.09	(0.50–12.38)	0.832
Combined and other sites	25	3.09	(1.26–7.58)	0.014	2.24	(1.13–4.43)	0.021
First presentation							
No	79						
Yes	25	2.76	(1.25–6.10)	0.012	1.69	(0.90–3.17)	0.101
Histologic type							
PTC	74						
FTC	30	2.59	(1.18–5.70)	0.018	2.35	(1.25–4.35)	0.008
Symptoms or events							
No	79						
Yes	25	1.35	(0.67–3.23)	0.34	1.67	(0.92–3.06)	0.094
T stage							
1-2	49						
3-4	55	1.36	(0.62–2.99)	0.45	1.17	(0.64–2.13)	0.607
Positive lymphatic invasion							
No	38						
Yes	66	1.03	(0.46–2.31)	0.94	0.59	(0.31–1.14)	0.115

CI, confidence interval; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma.

K/T ratio (13.5 vs. 47.1%, odds ratio 0.148, 95% CI 0.062–0.356, $p<0.001$) (**Supplementary Figure 1**). No correlation was found between baseline K/T ratio and tumor histological type. The tumors in patients with high baseline K/T ratio showed significantly lower $CD3^+$ and $CD8^+$ TIL numbers compared to the tumors in patients with low baseline K/T ratio ($CD3^+$TILs: 9.07 ± 4.43 vs. 13.22 ± 7.46, $p = 0.002$; $CD8^+$ TILs: 4.05 ± 2.26 vs. 6.29 ± 3.64, $p=0.001$) (**Figures 2C, D**; **Supplementary Figure 2**). Patients with high baseline K/T ratio had shorter PFS than those with low baseline K/T ratio [45 months vs. not reached, hazard ratio (HR) 2.50, 95% CI 1.35–4.63, $p=0.002$], and shorter median OS (78 months vs. not reached, HR 2.32, 95% CI 1.03–5.19, $p=0.035$) (**Figures 2E, F**). In the multivariate Cox regression analysis, elevated baseline K/T ratio correlated significantly with worse OS (HR 5.32; 95% CI, 1.96–14.44; $p=0.001$) and PFS (HR 3.75; 95% CI, 1.87–7.54; $p<0.001$) after adjusting for clinically significant factors (**Table 2**).

Post-RAI IDO Biomarkers and Outcomes

Neither the IDO biomarker (kynurenine or K/T ratio) levels post-RAI nor RAI-induced K/T ratio changes post-RAI differed between responders and non-responders. The RAI-induced post/pre-kynurenine ratio was significantly higher in non-responders compared with responders [median 1.95 μmol/L (range 1.67–4.91) vs. 1.64 μmol/L (range 0.73–2.07), $p=0.028$] (**Figure 3A**). By conducting ROC curve analyses, 1.69 (AUC 0.66, 95%CI 0.56–077, $p=0.005$) was calculated as the best cutoff for post/pre-kynurenine ratio to differentiate responders from non-responders (**Figure 3B**). The sensitivity and specificity of post/

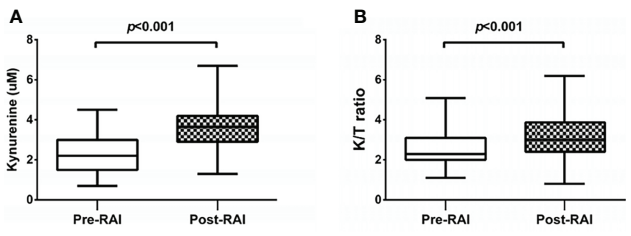

FIGURE 1 | Changes of kynurenine concentrations **(A)** and the K/T ratios [Kynurenine (μM)/Tryptophan(μM) x 10^2] **(B)** in serum samples at pre-RAI and post-RAI time points.

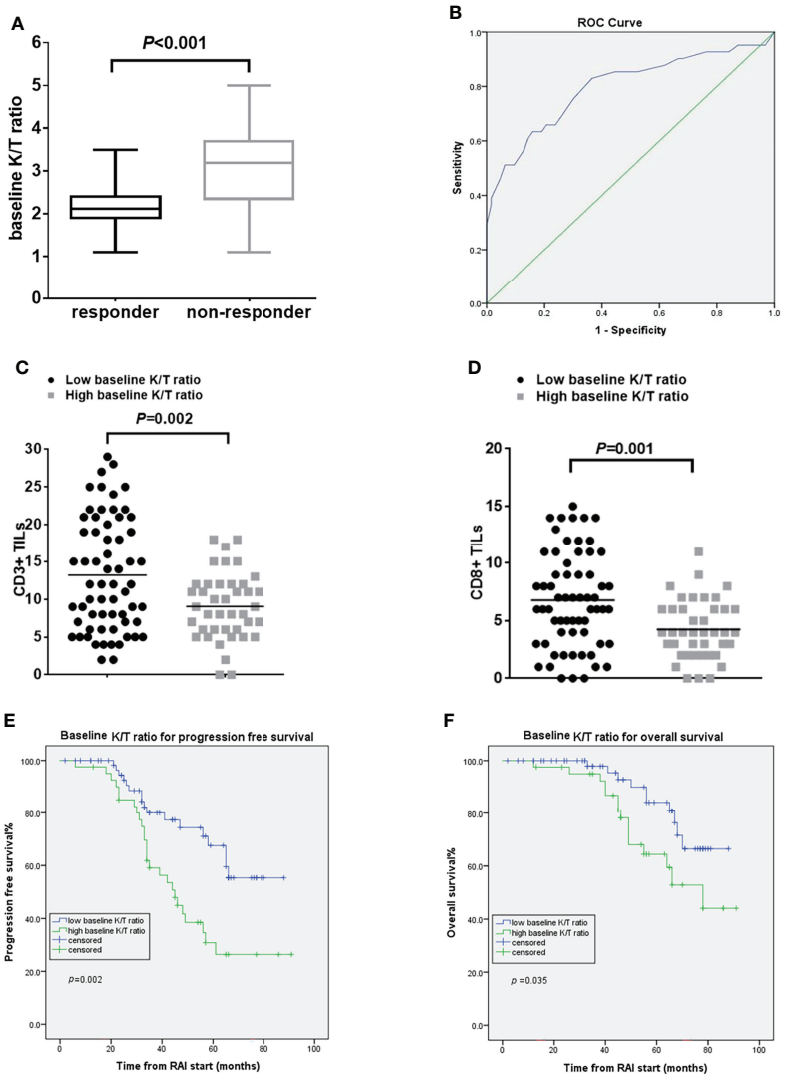

FIGURE 2 | Pre-RAI K/T ratio and treatment outcomes. **(A)** the pre-RAI K/T ratio according to the response to RAI treatment **(B)** ROC curve for pre-RAI K/T ratio in dmDTC patients **(C)** association of baseline K/T ratio with the number of $CD3^+$ TILs **(D)** association of baseline K/T ratio with the number of $CD8^+$ TILs **(E)** PFS curves of the dmDTC patients according to pre-RAI K/T ratio **(F)** OS curves of the dmDTC patients according to pre-RAI K/T ratio.

pre-kynurenine ratio in predicting therapy response were 56.1% and 60.3%, respectively. The response rate was lower in the high than in low post/pre-kynurenine ratio group (13.5 vs. 37.5%, odds ratio 0.319, 95% CI 0.140–0.726, p=0.006) (**Supplementary Figure 3**). No correlation was found between post/pre-kynurenine ratio and tumor histological type. High post/pre-kynurenine ratio correlated significantly with worse PFS (48 months vs. not reached, HR 2.90, 95% CI, 1.48–5.77, p=0.002) and poorer OS (68 months vs. not reached, HR 4.08, 95% CI, 1.40–11.92, p=0.010) (**Figures 3C, D**). The significance of post/pre-kynurenine ratio associated with OS in multivariate Cox regression model was lost when adjusting for clinically significant factors. Otherwise, in the multivariate Cox regression models for PFS, post/pre-kynurenine ratio remained an independently predictive factor (HR 2.76; 95% CI, 1.34–5.71; p=0.006; **Table 2**).

Effects of Combined IDO Biomarkers on OS and PFS

Considering serum K/T ratio at baseline and RAI-induced post/pre-kynurenine ratio change, the 104 evaluable patients were classified into four groups. Group 1 included 36 (34.6%) patients with low baseline K/T ratio and low post/pre-kynurenine ratio. Group 2 included 17 (16.3%) patients with high baseline K/T ratio and low post/baseline kynurenine ratio. Group 3 included 27 (26.0%) patients with low baseline K/T ratio and high post/baseline kynurenine ratio. Group 4 included 24 (23.1%) patients with high baseline K/T ratio and high post/baseline kynurenine

TABLE 2 | Multivariate Analyses of Factors Predicting Overall Survival and Progression Free Survival.

	Overall Survival			Progression Free Survival		
Variables	**Hazard Ratio**	**(95% CI)**	**P-value**	**Hazard Ratio**	**(95% CI)**	**P-value**
Age at diagnosis (years)						
<45						
≥45	3.51	(1.19–10.35)	0.023	2.87	(1.42–5.78)	0.003
Extent of metastases						
Lung only			0.009			0.042
Bone only	0.639	(0.20–2.07)	0.491	0.69	(0.31–1.56)	0.375
Combined and other sites	3.73	(1.38–10.09)	0.010	2.02	(1.00–4.09)	0.050
First presentation						
No						
Yes	2.92	(1.25–6.81)	0.013	2.54	(1.30–4.96)	0.007
baseline K/T ratio						
Low						
High	5.32	(1.96–14.44)	0.001	3.75	(1.87–7.54)	0.000
Post/pre-kynurenine ratio						
Low			–			
High	–	–	–	2.76	(1.34–5.71)	0.006

CI, confidence interval; PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma

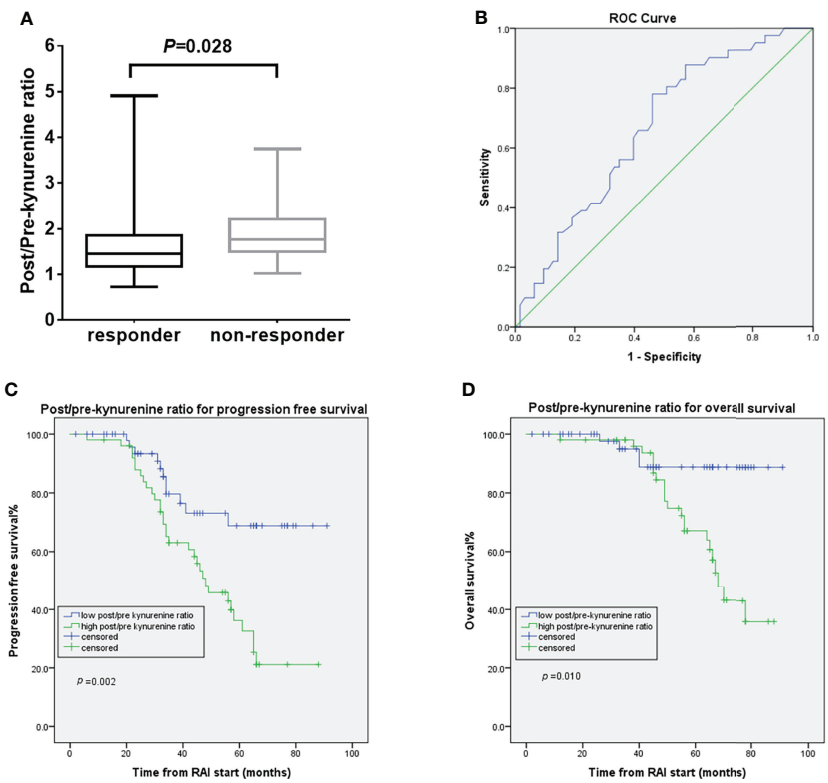

FIGURE 3 | Post/pre-kynurenine ratio and treatment outcomes. **(A)** the post/pre-kynurenine according to the response to RAI treatment **(B)** ROC curve for post/pre-kynurenine in dmDTC patients **(C)** PFS curves of the dmDTC patients according to post/pre-kynurenine **(D)** OS curves of the dmDTC patients according to post/pre-kynurenine.

ratio. There were significant differences in PFS (p=0.001) (**Figure 4A**) and OS (p=0.014) (**Figure 4B**) for these four groups. The median OS and PFS were not reached after 64 months of median follow-up in Groups 1 and 2. Median OS and PFS were 70 months (95% CI 65–75) and 65 months (95% CI 46–84) in Group 3, and 66 months (95% CI 48–84) and 44 months (95% CI 31–57) in Group 4, respectively. Groups 3 and 4 had shorter OS than Group 1 (HR 9.284, 95% CI 1.18–73.32,

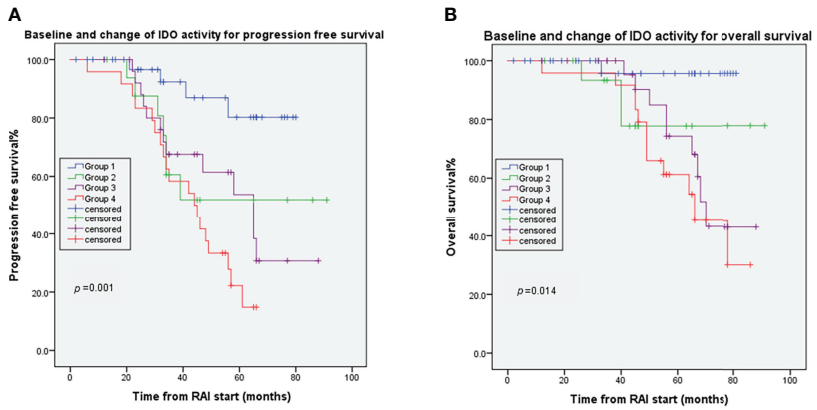

FIGURE 4 | Combined effects of baseline Change of IDO on DTC tumor progression **(A)** and overall survival **(B)**. Group 1: patients with low baseline K/T ratio and low post/pre-kynurenine ratio; Group 2 patients with high baseline K/T ratio and low post/baseline kynurenine ratio; Group 3: patients with low baseline K/T ratio and high post/baseline kynurenine ratio; Group 4: patients with high baseline K/T ratio and high post/baseline kynurenine ratio.

p=0.035; HR 14.08, 95% CI 1.82–108.72, p=0.011, respectively). Groups 2–4 had poorer PFS than Group 1 (HR 3.93, 95% CI 1.14–13.44, p=0.029; HR 4.09, 95% CI 1.33–12.54, p=0.014; HR 7.39, 95% CI 2.49–21.92, p<0.001, respectively).

DISCUSSION

In the present retrospective study, we found that non-responders to RAI had higher serum K/T ratio at baseline compared to responders. Patients with low baseline K/T ratio achieved longer PFS and OS than those harboring high serum baseline K/T ratio.

We hypothesized that IDO activity could be useful to predict response to RAI in dmDTC patients, based on the immunoinhibitory properties of IDO and its function as a potent immune checkpoint in cancer. IDO is highly expressed in DTC tumor tissues (17). IDO activity, as reflected by serum kynurenine levels, was higher in PTC patients than that in healthy controls (20). IDO immune status was also higher in DTC patients with lung metastases than in patients without metastases (21). High expression of IDO in FTC-133 human thyroid cancer cells exerted a strong suppressive action on the proliferation of activated T lymphocytes (17). To the best of our knowledge, this study is the first study to show the predictive value of serum IDO activity biomarkers in patients with DTC.

In our analysis, baseline K/T ratio was an important prognostic marker for dmDTC patients treated with RAI. This is in agreement with previous studies in which baseline IDO activity might have served as prognostic factors treated with chemoradiation (22, 23). IDO controls complement-dependent enhancement of chemoradiation therapy against murine glioblastoma (24). Mouse knockout studies have indicated that IDO promotes breast tumor resistance to chemotherapy *via* immune escape from T-cell-dependent anti-tumor immunity (25). In this study, we analyzed the infiltration of TILs and evaluated the relationship between IDO activity and TIL counts. Interestingly, baseline K/T ratio was negatively related with $CD3^+$ or $CD8^+$ TILs. This is consistent with previous reports showing the immunosuppressive role of IDO enzyme in the malignant tumor disease (26, 27) Thus, our findings demonstrated that IDO activity is associated with the suppressed infiltration of T cells into the tumor tissues, which may contribute to poor response to RAI.

RAI causes DNA double-strand breaks, which can lead to efficient DTC cell killing. Tumor-derived IDO improves DNA damage repair and mediates resistance to chemoradiation in human cancer cells by a steady supply of nicotinamide adenine dinucleotide generated from the IDO downstream metabolic products (28). This is the evidence that IDO promotes cancer survival through another mechanism, independently of the immune system. Our preliminary data provide strong clinical confirmation of the preclinical studies concerning the role of IDO in DTC. More mechanistic investigations are required to confirm these findings.

Another major finding of our study was that RAI induced IDO activity change, reflected by post/pre-kynurenine ratio, was higher in RAI non-responders, with shorter OS and PFS. Most previous studies have shown the relationship between IDO activity at baseline and prognosis of patients with acute myeloid leukemia (29, 30), breast cancer (31), cervical cancer (32), lymphoma (33–35), colorectal cancer (36), glioma (37), lung cancer (22, 23, 38–41), and melanoma (42, 43) (**Table 3**). Only a few studies investigated the relationship between dynamic IDO activity change and outcome of tumor patients after radiotherapy or chemotherapy. One study reported that the K/T ratio was increased in non-small-cell lung cancer (NSCLC) patients after chemoradiation therapy and such an increased IDO activity portended worse OS and PFS (22). Elevated post/pre-kynurenine ratio in stage III NSCLC patients treated with chemoradiation had significantly worse OS (23). Higher serum kynurenine levels after radiotherapy were associated with worse OS in patients with newly diagnosed stage I/II NSCLC (38). As far as we know, there are no studies on the IDO levels in circulation in patients with advanced thyroid cancer. Our study demonstrated that the increase of IDO activity after RAI

TABLE 3 | Prognostic Value of IDO Activity in Different Cancer Types.

Cancer	N (adults)	Serum IDO Markers	Detection method	Prognostic value	Ref.
Acute myeloid leukemia	184	Kyn/Trp ratio	HPLC	Increased Kyn/Trp ratio associated with short OS	(29)
	48	Kyn concentration	HPLC	Increased Kyn levels associated with short OS	(30)
Breast cancer	32	Trp/Kyn ratio	HPLC	Lower Trp/Kyn ratio associated with shorter OS	(31)
Cervical cancer	251	Kyn/Trp ratio	MS	Increased Kyn/Trp ratio associated with short DFS	(32)
T-cell leukemia/ lymphoma	96	Kyn/Trp ratio; Trp concentration	MS	Increased Kyn/Trp ratio and the levels of Kyn associated with short OS	(33)
Follicular lymphoma	110	Kyn/Trp ratio; Trp concentration	MS	Increased Kyn/Trp ratio and the levels of Kyn associated with short OS	(34)
Non-Hodgkin lymphoma	73	Trp concentration	HPLC	Lower Trp levels associated with shorter OS	(35)
Colorectal cancer	66	Trp concentration	HPLC	Lower Trp levels associated with liver metastases and reduced quality of Life	(36)
Glioma	33	Kyn/Trp ratio	HPLC	Increased Kyn/Trp ratio associated with short OS	(37)
Lung cancer	33	Kyn/Trp ratio	MS	Increased Kyn/Trp ratio after induction and chemoradiation therapy associated with short OS and PFS	(22)
	110	Kyn/Trp ratio; Kyn concentration	HPLC	Increased pre-treatment Kyn/Trp ratio and changes in the levels of Kyn after radiation associated with poor OS	(23)
	56	Kyn concentration	HPLC	Increased levels of Kyn post-radiation associated with poor OS	(38)
	104	Kyn/Trp ratio	HPLC	Increased Kyn/Trp ratio pre-treatment associated with short PFS; increased post/pre-Kyn : Trp ratio after radiation associated with OS	(39)
	123	Kyn/Trp ratio	MS	Increased Kyn/Trp ratio associated with short OS	(40)
	252	Kyn/Trp ratio	HPLC	Increased Kyn/Trp associated with decreased efficacy of chemotherapy	(41)
Melanoma	87	Kyn/Trp ratio	HPLC	Increased Kyn/Trp ratio associated with short OS	(42)
	186	Kyn concentration	HPLC	Increased levels of Kyn post-radiation associated with short OS	(43)

Kyn, kynurenine; Trp, tryptophan; HPLC, high performance liquid chromatography; MS, mass spectrometry; Ref., references; OS, overall survival; PFS, progression-free survival.

was related to therapy response in DTC. The possible reason might be that after massive radiosensitive tumor cells killing by ionizing irradiation, the proliferation of radioresistant tumor cells dominate the TME and present an immunosuppressive phenotype, or that RAI directly alters the biological behavior of tumor cells and leads to suppression of the anti-tumor microenvironment. These findings support that in addition to IDO activity at baseline as a prognostic biomarker for DTC patients, RAI therapy might affect host tumor immune microenvironment, modify the therapeutic response, and finally change the prognosis in DTC patients. Further studies are needed to explore the mechanisms of immunoregulation under RAI.

The capability of IDO to predict outcomes of RAI treatment was further confirmed by the combined use of baseline and the change of IDO activity after RAI. Patients who maintained low baseline K/T ratio and low post/pre-kynurenine ratio achieved better PFS and OS than those who maintained high baseline K/T or post/pre-kynurenine ratio. This clinical experience suggests that, on the one hand, the differences in baseline IDO activity of the dmDTC patients would represent individual immune status variation in tumor pathophysiological characteristics. Baseline IDO biomarker might be used to select suitable patients who may benefit from RAI treatment. On the other hand, the change in IDO activity after RAI therapy dynamically reflected the tumor response to RAI in biological behavior and immune environment, allowing for early detection of cases with acquired resistance to RAI.

Regarding RAI-treated DTC patients, Tg has been reported to have prognostic value. Unfortunately, patients with poorly differentiated thyroid carcinoma and those with positive anti-Tg antibody show decreased expression of Tg (44, 45). In those cases, patients cannot be evaluated with Tg (46). Evaluation of other available tissue biomarkers, such as sodium iodine transporter, requires adequate samples that can only be obtained in an invasive manner, and is hindered by spatial and temporal heterogeneity. These data underline the challenge to identify a reliable biomarker among the systemic immune components with a clear predictive value for DTC patients, since the development and maintenance of an immune microenvironment has shown clear associations with individual outcome (47).

This study had some limitations. First, the number of patients was limited, which may affect study results. Second, correlative immunological markers, such as forkhead box P3 expression and other T lymphocyte subset, were not measured, which may help to confirm the putative role of IDO in DTC patients. Third, the cutoff value of IDO biomarker was derived from analysis of the study population and thus needs to be validated in an external series of patients. Finally, IDO1 might act as an immunosuppressor in a context-dependent manner and its expression is induced by specific oncogenes (13). The association between serum IDO biomarker levels and mutations of clinical tumor driver genes involved in DTC initiation and progression was not evaluated in this study.

In conclusion, our study provides clinicians with an independent and significant prognostic biomarker in dmDTC patients treated with RAI. Serum IDO activity could represent a noninvasive dynamic biomarker that is available in every patient, demonstrating disease and evolution of tumor immune environment over time and enabling early detection of cases with immunobiological resistance to RAI. Finally, our findings, if confirmed, may reveal the development of novel multimodality clinical trials using anti-IDO agents that might improve the

efficacy of RAI by blocking the potential immunosuppressive action of IDO.

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

The studies involving human participants were reviewed and approved by the Institutional Ethics Committees of Nanjing First Hospital, the Institutional Ethics Committees of Affiliated Hospital of Jiangsu University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XX, LS, and HZ conceived and designed the study. XX and HZ supervised the study. LS and RD did the statistical analysis. QJ, WW, JZ, and SL contributed to acquisition, analysis, or interpretation of data. XX, LS, RD, QJ, and HZ drafted the manuscript. All authors revised the report and approved the final version before submission.

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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.2022.871792/full#supplementary-material

Supplementary Figure 1 | Response rate in patients with low and high pre-RAI K/T ratio groups.

Supplementary Figure 2 | Representative images of $CD3^+$ and $CD8^+$ tumor-infiltrating lymphocytes in two different with DTC. (patient 1: non-responder;patient 2:responder). Scale bar, 50 μm.

Supplementary Figure 3 | Response rate in patients with low and high post/pre-kynurenine groups.

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Comparison of the Differential Diagnostic Performance of Intravoxel Incoherent Motion Imaging and Diffusion Kurtosis Imaging in Malignant and Benign Thyroid Nodules

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Objective: This study aimed to compare the diagnostic capacity between IVIM and DKI in differentiating malignant from benign thyroid nodules.

Material and Methods: This study is based on magnetic resonance imaging data of the thyroid with histopathology as the reference standard. Spearman analysis was used to assess the relationship of IVIM-derived parameters D, f, D* and the DKI-derived parameters D_{app} and K_{app}. The parameters of IVIM and DKI were compared between the malignant and benign groups. Binary logistic regression analysis was performed to establish the diagnostic model, and receiver operating characteristic (ROC) curve analysis was subsequently performed. The DeLong test was used to compare the diagnostic effectiveness of different prediction models. Spearman analysis was used to assess the relationship of Ki-67 expression and parameters of IVIM and DKI.

Results: Among the 93 nodules, 46 nodules were malignant, and 47 nodules were benign. The D_{app} of DKI-derived parameter was related to the D ($P < 0.001$, $r = 0.863$) of IVIM-derived parameter. The K_{app} of DKI-derived parameter was related to the D ($P < 0.001$, $r = -0.831$) of IVIM-derived parameters. The malignant group had a significantly lower D value ($P < 0.001$) and f value ($P = 0.013$) than the benign group. The malignant group had significantly higher K_{app} and lower D_{app} values (all $P < 0.001$). The D+f had an area under the curve (AUC) of 0.951. The D_{app}+K_{app} had an AUC of 0.943. The D+f+D_{app}+K_{app} had an AUC of 0.954. The DeLong test showed no statistical significance among there prediction models. The D ($P = 0.007$) of IVIM-derived parameters and D_{app} ($P = 0.045$) of DKI-derived parameter were correlated to the Ki-67 expression.

Conclusions: IVIM and DKI were alternative for each other in in differentiating malignant from benign thyroid nodules.

Keywords: magnetic resonance imaging, intravoxel incoherent motion, diffusion kurtosis imaging, thyroid nodules, Ki-67

INTRODUCTION

Thyroid nodules are common in adults. It was reported that incidental thyroid nodules are found on 20% to 67% of ultrasound examinations, up to 25% of contrast-enhanced thoracic computed tomography scans, 16% to 18% of magnetic resonance imaging (MRI) scans, and 1% to 2.3% of positron emission tomography scans (1). Due to avoiding unnecessary surgery, effective diagnostic methods that can provide reliable differentiation between malignant and benign thyroid nodules are urgently needed.

Ultrasound is widely used to detect thyroid nodules and in guidelines for biopsy and clinical therapy, and ultrasound-guided fine needle aspiration biopsy is valuable for the diagnosis of thyroid nodules. Nevertheless, up to 30% of fine needle aspiration biopsies show indeterminate cytology because of the finiteness of the puncture tissue (2). Computed tomography has been used to depict the relationship of the nodule with surrounding structure and lymph node metastasis. However, it is difficult to distinguish between benign and malignant thyroid nodules and poses radiation hazards (3). With the development of MRI techniques, diffusion weighted imaging (DWI) has become a promising modality for thyroid examination in recent years.

Intravoxel incoherent motion (IVIM) and diffusion kurtosis imaging (DKI), as diffusion derivative technology, have shown tremendous clinical potential in thyroid nodules (4–7). IVIM can separate the incoherent motion of water molecules within capillaries from extravascular molecular diffusion (8). IVIM theory could resolve pure diffusion coefficient (D), and perfusion related incoherent microcirculation (D*), separately, while also identifying the microvascular volume fraction (f). DKI can provide a more accurate model of diffusion and capture the non-Gaussian diffusion parameters for tissue heterogeneity (9). DKI theory could resolve the non-Gaussian diffusion coefficient (D_{app}), and the apparent kurtosis coefficient (K_{app}). Past study showed IVIM and DKI provide a more comprehensive description of tissue properties compared to DWI in thyroid (4, 5). However, the differential diagnostic capacity of IVIM and DKI remains to be revealed in patients with thyroid nodules.

Diffusion parameters were considered to reflect the cell size and density, extracellular space and intracellular architecture, which limits the cellular movement of water. Ki-67 is a cell proliferation protein that was related to cell density and extracellular space (10). It is unknown about the relationship between Ki-67 expression and the parameters of IVIM and DKI in thyroid papillary carcinoma.

In this study, we compared the diagnostic performance of IVIM and DKI to differentiate malignant nodules from benign thyroid nodules. In addition, we explored the relationship of Ki-67 expression and parameters of IVIM and DKI in thyroid papillary carcinoma.

MATERIALS AND METHODS

Patient Collection and Thyroid Nodule Selection

This prospective study was approved by the local institutional review board (IRB No. CZLS2021207-A), and written informed consent was obtained from each patient. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). From July 2020 and February 2021, 86 consecutive patients were recruited and underwent thyroid MRI examinations in this study.

The inclusion criterion was as follows: a) no contraindications for MRI examination; b) thyroid nodule excision was planned; c) patients had not needle biopsy or therapy before MRI scan; d) only the biggest nodule was selected when there were more than two nodules in one lobule. The exclusion criterion was as follows: a) IVIM or DKI had worse image quality; b) the nodules were cystic.

Sample Size

There are no generally accepted approaches to estimate the sample size requirements for derivation and validation studies of prediction models, however, we ensured that the study met suggested requirements of having at least 10 events per candidate variable for the derivation of a model and at least 100 events for validation studies.

Examination Method

MRI was performed on a 3.0 T whole body MRI system (SOMATOM Prisma, Siemens Healthineers, Forchheim, Germany) using a third-party 16 channel surface coil (Zhongzhi Medical, Jiangsu, China). The MRI protocol mainly included coronal fast dixion, axial T1 weighted imaging with fat suppression, axial T2 weighted imaging with fat suppression, axial IVIM and DKI. IVIM and DKI were performed using the ZOOMit technique with selective excitation based on parallel radio frequency pulses. The detailed protocol parameters are shown in **Table 1**.

Image Analysis

All IVIM and DKI images were transferred to a workstation (syngo. via Frontier, Siemens Healthineers, Germany) for analysis. IVIM and DKI parameters were measured by observer 1 (LJ, with six years of

Abbreviations: AUC, Area under the curve; DKI, Diffusion kurtosis imaging; DWI, Diffusion weighted imaging; ICC, Interclass correlation coefficient; IVIM, Intravoxel incoherent motion; MRI, Magnetic resonance imaging; ROC, Receiver operating characteristic; ROI, Regions of interest.

TABLE 1 | Imaging parameters of IVIM and DKI.

	IVIM	DKI
TR	4200 ms	4600 ms
TE	72 ms	72 ms
FOV	160 × 58 mm^2	160 × 58 mm^2
Average	2, 2, 2, 2, 4, 6, 9	1, 4, 6, 9
b-value	0, 50, 100, 200, 400, 600, 800 ($\times 10^{-3}$ s/mm^2)	0, 500, 1000, 1500 ($\times 10^{-3}$ s/mm^2)
Matrix size	36 × 110	36 × 110
Thickness	3 mm	3 mm
Intersection gap	0.3 mm	0.3 mm
Examination time	329 s	273 s

IVIM, intravoxel incoherent motion imaging; DKI, diffusion kurtosis imaging; TR, time repetition; TE, time echo; FOV, field of view.

experience in thyroid imaging). The IVIM and DKI parameters of the first 75 nodules were assigned by Observer 2 (JC, with two years of experience in thyroid imaging). The observers were blind to the surgical pathological results. The measurement was repeated one month later by observer 2. Regions of interest (ROI) was freehand drawn along the nodule margin in the largest slice to obtain relevant parameters. ROIs of IVIM and DKI were in the same slice, avoiding cystic, vessel and hemorrhage. The parameters derived from the IVIM were obtained through the previously reported fitting equation: S_b/S_0 = (1 - f) exp (-b D) + f exp (-b D*) (11). The following parameters were calculated: D, D* and f. The parameters derived from the DKI were obtained through the previously reported fitting equation:$S_b = S_0 \exp(-b D_{app} + b^2 D_{app}^2 K_{app}/6)$ (12). The following parameters were calculated: K_{app} and D_{app}. The mean value was recorded for each ROI.

Histopathologic Examination

According to the established convention, histopathologic examination was used as reference standards. Tissue samples of each nodule were obtained from operation. Surgically resected nodules were subjected to intra-operative frozen section analysis for preliminary risk assessment. The final diagnosis was based on postoperative paraffin section pathological examinations. In the event of suspicious malignant samples or atypical samples, immunohistochemical staining was applied to differentiate benign and malignant nodules. All diagnoses were determined by experienced pathologist. According to the pathological results, the nodules were assigned to either the benign or malignant groups.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0, GraphPad Prism 7.0, and R version 4.0.1. The results were considered to be statistically significant at $P < 0.05$. The interclass correlation coefficient (ICC) was used to test the interobserver reliability and intraobserver reliability. The ICC was interpreted as follows: 0.00–0.20, poor correlation; 0.21–0.40, fair correlation; 0.41–0.60, moderate correlation; 0.61–0.80, good correlation; and 0.81–1.00, excellent correlation. The Kolmogorov–Smirnov test was performed to analyze normality. According to the results of the Kolmogorov–Smirnov test, Pearson analysis or Spearman analysis was used to assess the relationship of parameters of IVIM and DKI. The independent Student's t test or Mann–Whitney U test were applied to check whether there were significant differences between the malignant and benign groups. When $P < 0.05$, variables were entered into binary logistic regression analysis. Single parameters and the combination of parameters used to establish the diagnostic model. Receiver operating characteristic (ROC) curve was applied to predict malignant nodules. The DeLong test was used to compare the diagnostic effectiveness of the prediction models. Pearson analysis or spearman analysis was used to assess the relationship of Ki-67 expression and parameters of IVIM and DKI in thyroid papillary carcinoma.

RESULTS

Clinical Data

Of the 86 patients, 7 patients were excluded (2 patients with worse image quality and 5 patients with cystic nodules). Ultimately, among 79 patients with 93 nodules, 59 were female and 20 was males, with ages ranging from 21 to 77 years old. In the malignant group, 26 were female and 14 was males, with ages ranging from 21 to 67 years old. In the benign group, 33 were female and 6 were male, with ages ranging from 21 to 77 years old. There were 46 malignant nodules (44 papillary carcinoma, 1 follicular carcinoma, 1 medullary carcinoma), and 47 benign nodules (24 adenomas, 19 nodular goiters, 2 goiters with adenomatous hyperplasia, 1 subacute thyroiditis, 1 granulomatous inflammation). In the sample, 31patients with papillary carcinoma had the results of Ki-67.

Relationship of Parameters of IVIM and DKI

The reproducibility of the two ROIs for measuring thyroid nodules with IVIM and DKI parameters is summarized in **Table 2**, with good ICC values. The D_{app} of DKI-derived parameter was correlated to the D ($P < 0.001$, r = 863) of IVIM-derived parameter (**Table 3**; **Figure 1**). The K_{app} of DKI-derived parameter was correlated to the D ($P < 0.001$, r = -0.831) of IVIM-derived parameters (**Table 3**, **Figure 1**).

Comparison of IVIM and DKI Parameters Between the Malignant and Benign Groups

The malignant group had a significantly lower D value ($P < 0.001$) and f value ($P = 0.013$) than the benign group (**Table 4**). The D* value was not significantly different between malignant

TABLE 2 | The interobserver and intraobserver reproducibility of measurements of thyroid nodules with IVIM and DKI.

	Interobserver (95% CI)	Intraobserver (95% CI)
D	0.865 (0.794-0.912)	0.928 (0.88-0.954)
D*	0.795 (0.694-0.865)	0.963 (0.943-0.977)
f	0.799 (0.700-0.868)	0.856 (0.781-0.907)
D_{app}	0.872 (0.805-0.917)	0.957 (0.955-0.973)
K_{app}	0.891 (0.833-0.930)	0.954 (0.963-0.985)

IVIM, intravoxel incoherent motion imaging; DKI, diffusion kurtosis imaging; CI, confidence interval; D, true diffusion coefficient; D, pseudodiffusion coefficient; f, perfusion fraction; D_{app}, apparent diffusion coefficient derived from DKI; K_{app}, apparent diffusion kurtosis coefficient.*

TABLE 3 | The correlation analysis of quantification parameters of IVIM and DKI.

	r	*P*
D_{app} VS D	0.863	< 0.001
D_{app} VS D*	0.079	0.450
K_{app} VS D	-0.913	< 0.001
K_{app} VS D*	-0.049	0.643
K_{app} VS f	-0.079	0.447
D_{app} VS K_{app}	-0.831	< 0.001
D VS D*	0.126	0.230
D VS f	0.060	0.569
D* VS f	0.137	0.190

IVIM, intravoxel incoherent motion imaging; DKI, diffusion kurtosis imaging; D, true diffusion coefficient; D, pseudodiffusion coefficient; f, perfusion fraction; D_{app}, apparent diffusion coefficient derived from DKI; K_{app}, apparent diffusion kurtosis coefficient.*

and benign nodules (P = 0.666) (**Table 4**). The malignant group had a significantly higher K_{app} (P < 0.001) and lower D_{app} (P < 0.001) (**Table 4**). The color maps of IVIM- and DKI-derived parameters were shown in **Figures 2**, **3**.

Diagnostic Performance Evaluation

Among the quantification parameters of IVIM, the D value had an area under the curve (AUC) of 0.928, the f value had an AUC of 0.637, and D+f had an AUC of 0.951 in predicting thyroid malignant nodules (**Table 5**). In the quantification parameters of DKI, D_{app} had an AUC of 0.943, K_{app} had an AUC of 0.921, and D_{app}+K_{app} had an AUC of 0.943 in predicting malignant thyroid nodules (**Table 5**). D+f+D_{app}+K_{app} had the highest AUC of 0.954 (**Table 5**). However, the DeLong test shows that there was no statistically significant difference among D+f, D_{app}+K_{app} and D+f +D_{app}+K_{app} (**Table 6**) (**Figure 4**).

Relationship of Ki-67 Expression and Quantification Parameters of IVIM and DKI in Thyroid Papillary Carcinoma

The D (P = 0.007) of IVIM-derived parameters was related to the Ki-67 expression (**Table 7**) (**Figure 5**). The D_{app} (P = 0.045) of DKI-derived parameter was related to the Ki-67 expression (**Table 7**) (**Figure 5**). Representative D maps, D_{app} maps and immunohistochemical staining pictures (**Figures 6**, **7**) were illustrated.

DISCUSSION

It is necessary to differentiate malignant from benign lesions when detecting thyroid nodules using imaging methods. In this study, the DKI-derived parameters were related to the IVIM-derived parameters. The malignant and benign nodules exhibited significantly different D, f, D_{app} and K_{app} values. Moreover, these parameters of IVIM and DKI had comparable differential

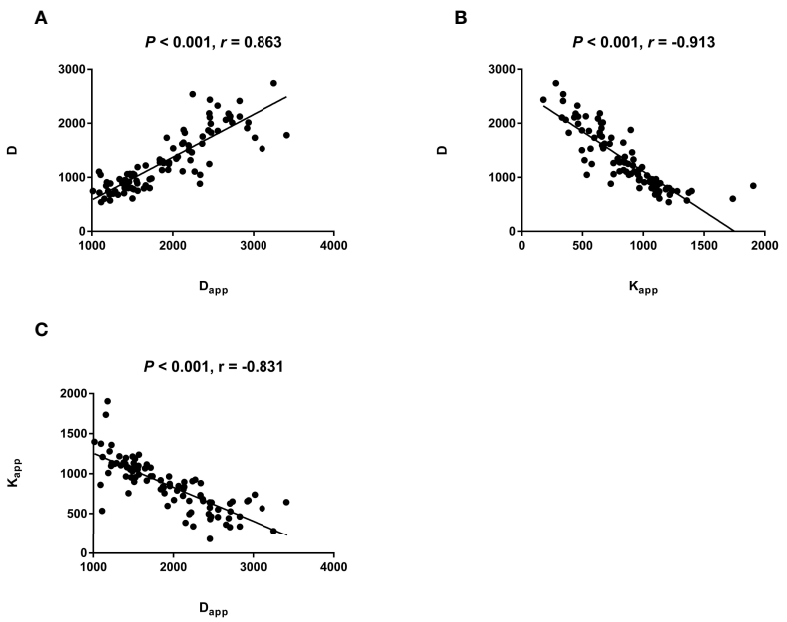

FIGURE 1 | The scatter plot reflecting correlation of quantification parameters between IVIM and DKI.

TABLE 4 | Quantification parameters of IVIM and DKI for the benign and malignant groups.

	Benign group (n = 47)	Malignant group (n = 46)	*P*
D ($\times 10^{-3}$ mm^2/s)	1.71 ± 0.48	0.92 ± 0.22	< 0.001
D* ($\times 10^{-3}$ mm^2/s)	16.56 ± 4.76	16.08 ± 5.92	0.666
f (%)	18.37 ± 0.83	14.54 ± 0.60	0.013
D_{app} ($\times 10^{-3}$ mm^2/s)	2.37 ± 0.46	1.48 ± 0.27	< 0.001
K_{app}	0.65 ± 0.26	1.07 ± 0.22	< 0.001

IVIM, intravoxel incoherent motion imaging; DKI, diffusion kurtosis imaging; D, true diffusion coefficient; D, pseudodiffusion coefficient; f, perfusion fraction; D_{app}, apparent diffusion coefficient derived from DKI; K_{app}, apparent diffusion kurtosis coefficient.*

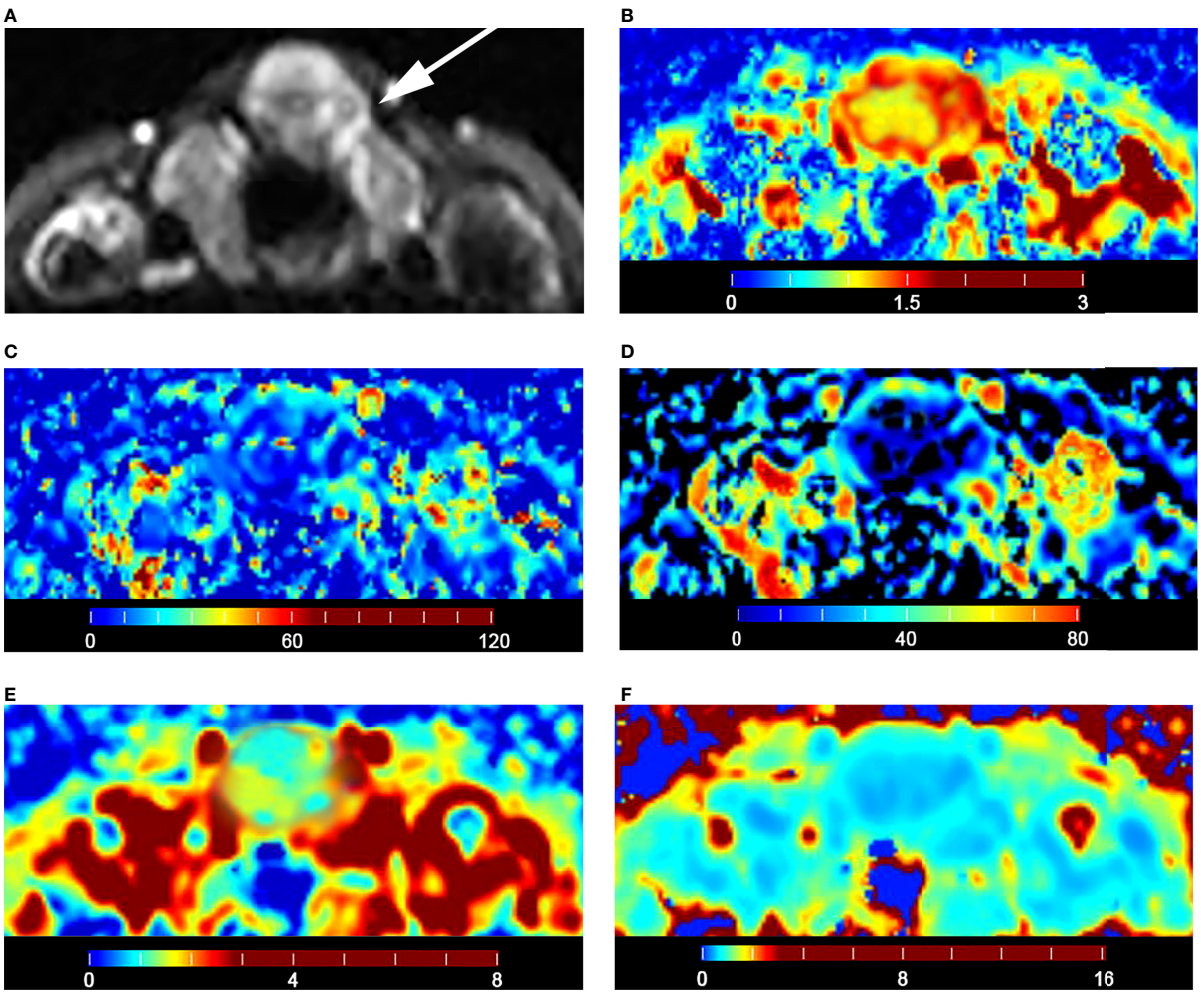

FIGURE 2 | Images of a 36-year-old female with isthmus papillary carcinoma: **(A)** axial diffusion image with b = 0; **(B)** color map of D, D value of lesion is 0.93 × 10^{-3} mm^2/s; **(C)** color map of D*, D* value of lesion is 16.04 × 10^{-3} mm^2/s; **(D)** color map of f, f value of lesion is 14.21%; **(E)** color map of D_{app}, D_{app} value of lesion is 1.53 × 10^{-3} mm^2/s; **(F)** color map of K_{app}, K_{app} value of lesion is 1.05.

diagnostic ability for thyroid nodules. Combination IVIM with DKI cannot improve diagnostic performance. In addition, both DKI-derived parameters and IVIM-derived parameters were related with Ki-67 expression.

IVIM is a noninvasive technique that shows superiority in reflecting tumor cellularity and perfusion without the need for contrast agents. It has already been applied in the differentiation of lung nodules (13), thyroid nodules (14), prostate (15) and brain tumors (16) with good diagnostic performance. In our study, malignant nodules demonstrated lower D values than did benign nodules, which is consistent with previous studies (14, 17). The D value can precisely reflect the true diffusion without the influence of perfusion-related diffusion, which can calculated with the data from b-values higher than 200 mm^2/s using a

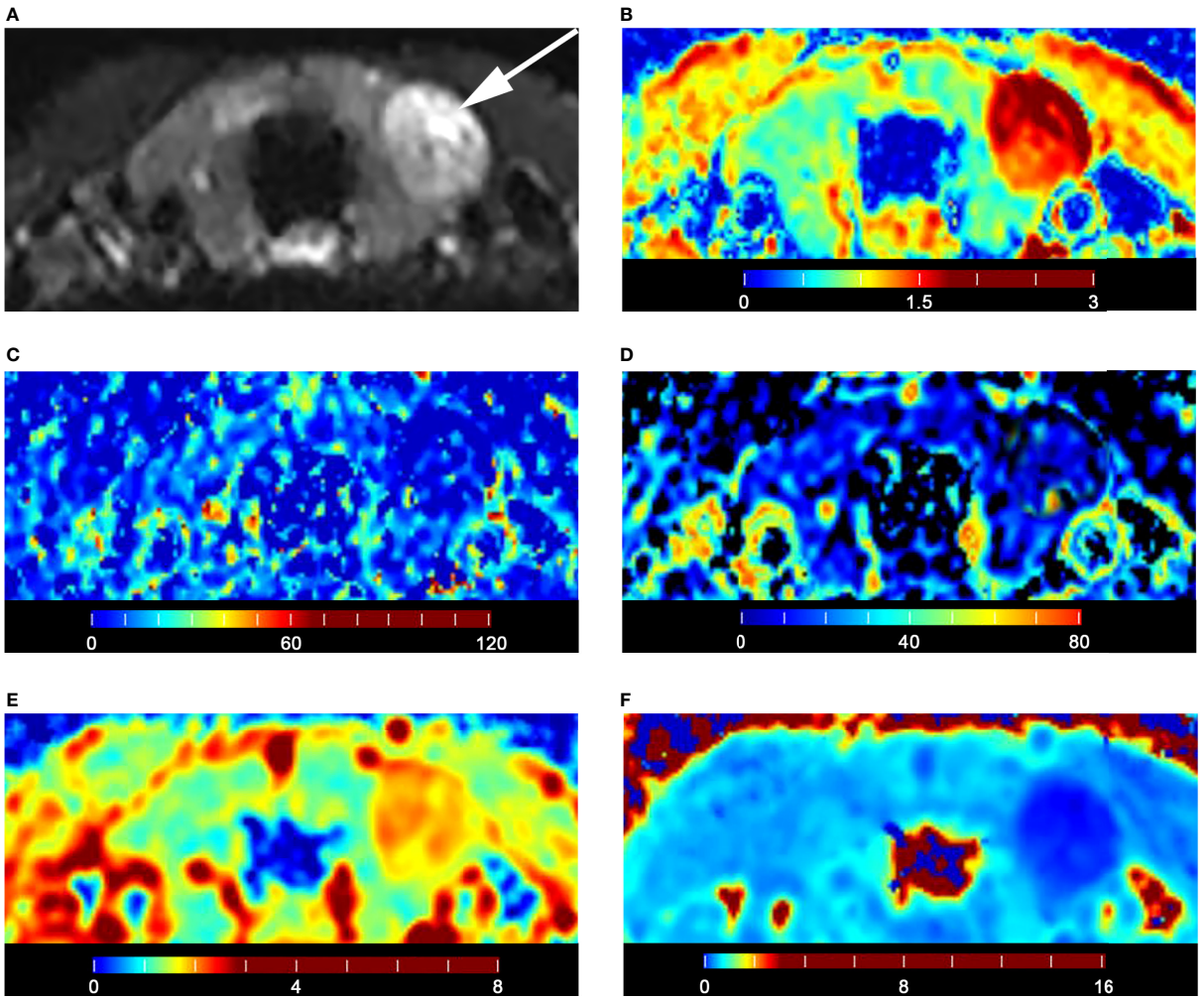

FIGURE 3 | Images of a 28-year-old male with left lobe follicular adenoma: **(A)** axial diffusion image with b = 0; **(B)** color map of D, D value of lesion is 1.79 × 10^{-3} mm^2/s; **(C)** color map of D*, D* value of lesion is 15.74 × 10^{-3} mm^2/s; **(D)** color map of f, f value of lesion is 18.35%; **(E)** color map of D_{app}, D_{app} value of lesion is 2.06 × 10^{-3} mm^2/s; **(F)** color map of K_{app}, K_{app} value of lesion is 0.50.

TABLE 5 | The diagnostic performance of the parameters of IVIM and DKI.

	True positive	False positive	Sensitivity	Specificity	AUC
D	91.30%	8.70%	87.23%	93.48%	0.928
f	63.04%	36.96%	73.91%	53.57%	0.637
D+f	89.13%	10.87%	82.98%	91.30%	0.951
D_{app}	91.30%	8.70%	91.30%	91.49%	0.943
K_{app}	86.96%	13.04%	93.48%	82.98%	0.921
D_{app}+K_{app}	89.13%	10.87%	87.23%	95.65%	0.943
D+f+D_{app}+K_{app}	89.13%	10.87%	93.62%	86.96%	0.954

IVIM, intravoxel incoherent motion imaging; DKI, diffusion kurtosis imaging; AUC, area under the curve; D, true diffusion coefficient; f, perfusion fraction; D_{app}, apparent diffusion coefficient derived from DKI; K_{app}, apparent diffusion kurtosis coefficient.

monoexponential model (18). In addition, malignant nodules demonstrated a significantly lower f value than did benign nodules, but the f value had undesirable differential diagnostic capacity. The f value mainly reflects pseudodiffusion. When the b-value is lower than 200 mm^2/s, the data are fitted to a biexponential model to acquire the f value (19). The ZOOMit technique restricts the b-value to multiples of 50. Therefore, the b-value cannot be set to 10 and 90 mm^2/s, resulting in the worse

TABLE 6 | Comparison of the diagnostic performance between IVIM and DKI for differential diagnosis by DeLong test.

	P
D+f VS D_{app}+K_{app}	0.623
D_{app}+K_{app}+D+f VS D+f	0.736
D_{app}+K_{app}+D+f VS D_{app}+K_{app}	0.325

IVIM, intravoxel incoherent motion imaging; DKI, diffusion kurtosis imaging; D, true diffusion coefficient; f, perfusion fraction; D_{app}, apparent diffusion coefficient derived from DKI; K_{app}, apparent diffusion kurtosis coefficient.

TABLE 7 | The correlation analysis between Ki-67 and quantification parameters of IVIM and DKI in thyroid papillary carcinoma.

	r	*P*
D	-0.475	0.007
D*	0.042	0.824
f	-0.079	0.672
D_{app}	-0.362	0.045
K_{app}	0.284	0.122

IVIM, intravoxel incoherent motion imaging; DKI, diffusion kurtosis imaging; D, true diffusion coefficient; D, pseudodiffusion coefficient; f, perfusion fraction; D_{app}, apparent diffusion coefficient derived from DKI; K_{app}, apparent diffusion kurtosis coefficient.*

differentiation performance. In this study, the D* value was not significantly different between benign and malignant nodules. D* reflects the contribution of perfusion to signal attenuation of the diffusion image (20). It has been reported that the D* value may be unreliable in the IVIM model for differential diagnosis and has poor measurement reproducibility (21).

DKI is a non-Gaussian diffusion weighted analysis method. The diffusion of water molecules in the microenvironment deviates from the mono-exponential Gaussian model at high b-values, leading to inaccurate fitting and poor calculation of the diffusion coefficient. Considering the above factors, a DKI model was developed and showed good diagnostic performance for prostate cancer (22), hepatocellular carcinoma (23), and glioma (24). It has been reported that DKI-derived parameters demonstrated an advantage compared to conventional DWI for thyroid lesion diagnosis (4). Certainly, in this study, there were significant differences in D_{app} and K_{app} values between the benign and malignant nodules, consistent with a previous study

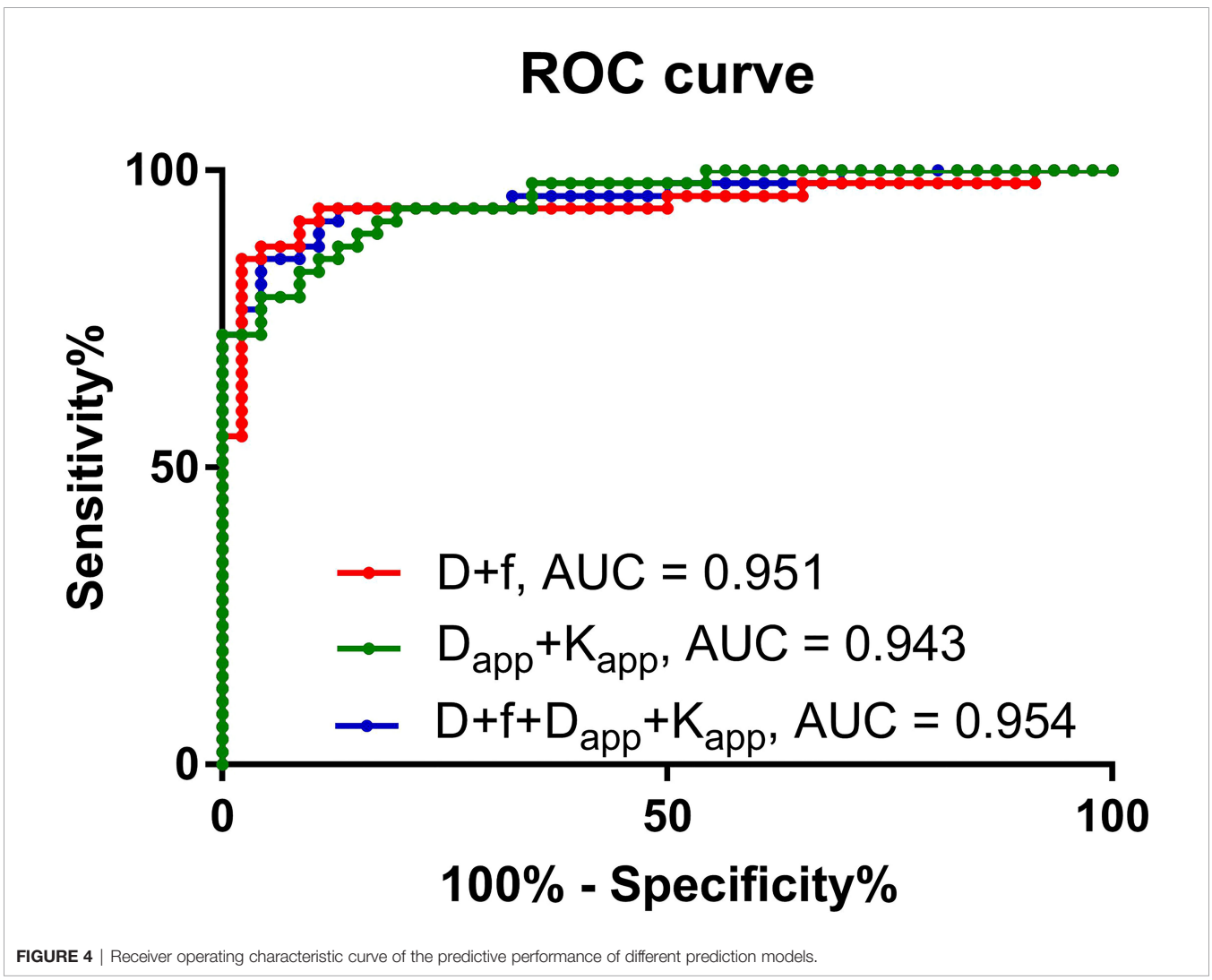

FIGURE 4 | Receiver operating characteristic curve of the predictive performance of different prediction models.

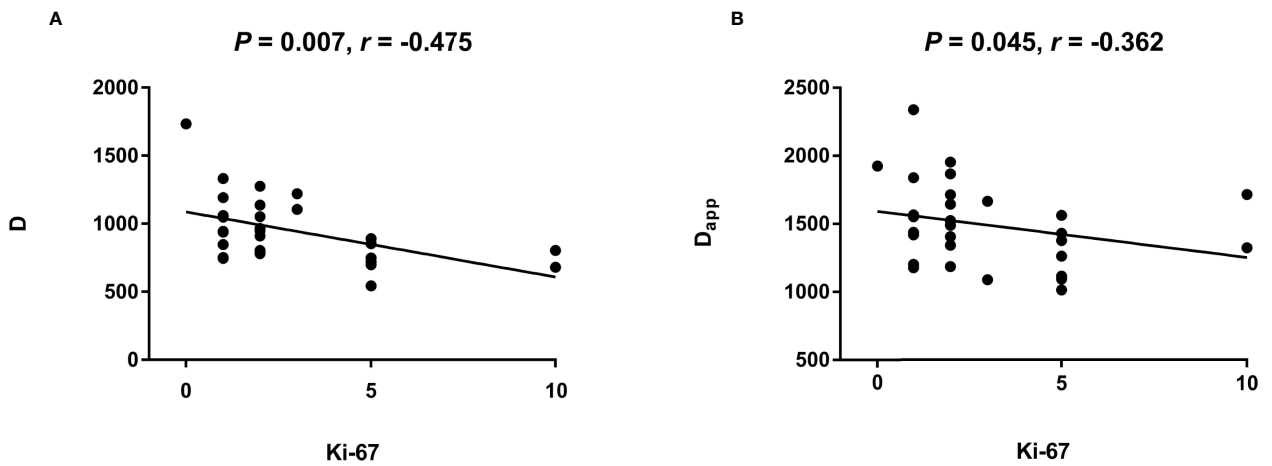

FIGURE 5 | The scatter plot reflecting correlation between Ki-67 and quantification parameters of IVIM and DKI.

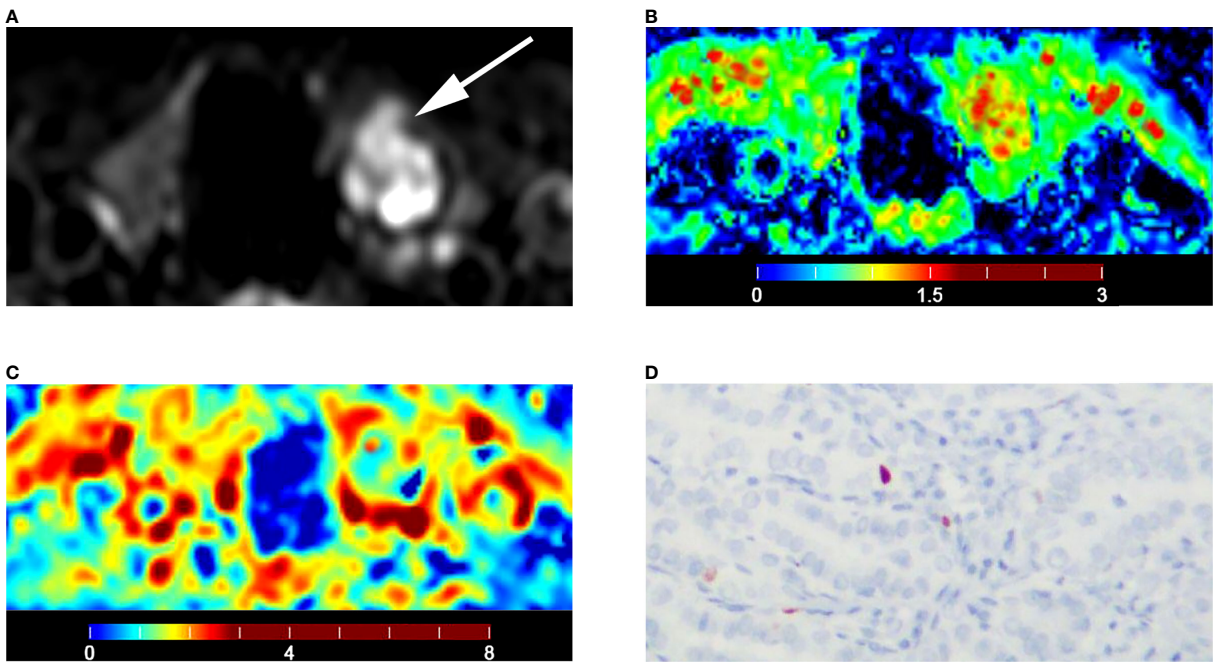

FIGURE 6 | Images of a 55-year-old male with left lobe papillary carcinoma (A-D): **(A)** axial diffusion image with b = 0; **(B)** color map of D, D value of lesion is 1.06 × 10^{-3} mm^2/s; **(C)** color map of D_{app}, D_{app} value of lesion is 1.43 × 10^{-3} mm^2/s; **(D)** Ki-67 expression is 1% in tumor cells.

(4). In the DKI model, restricted diffusion is due to cell proliferation and increases in cellularity, consequently, a reduction in extracellular and intercellular spaces. D_{app} was correlated with extracellular changes, and K_{app} was more sensitive to the intracellular architecture (25). This technique allows for the measurement of the excess diffusion kurtosis of the tissue while quantifying the deviation of tissue diffusion from the standard Gaussian pattern (26). In this respect, this technique is expected to more accurately reflect the microstructural complexity of human tissue (27). Malignant thyroid nodules have lower D_{app} and higher K_{app} values than benign nodules, which means that malignant nodules may have less extracellular space and a tighter intracellular architecture.

Both DKI-derived parameters and IVIM-derived parameters were related with Ki-67 expression. In pathological studies, proliferative activity of cells is often evaluated by the

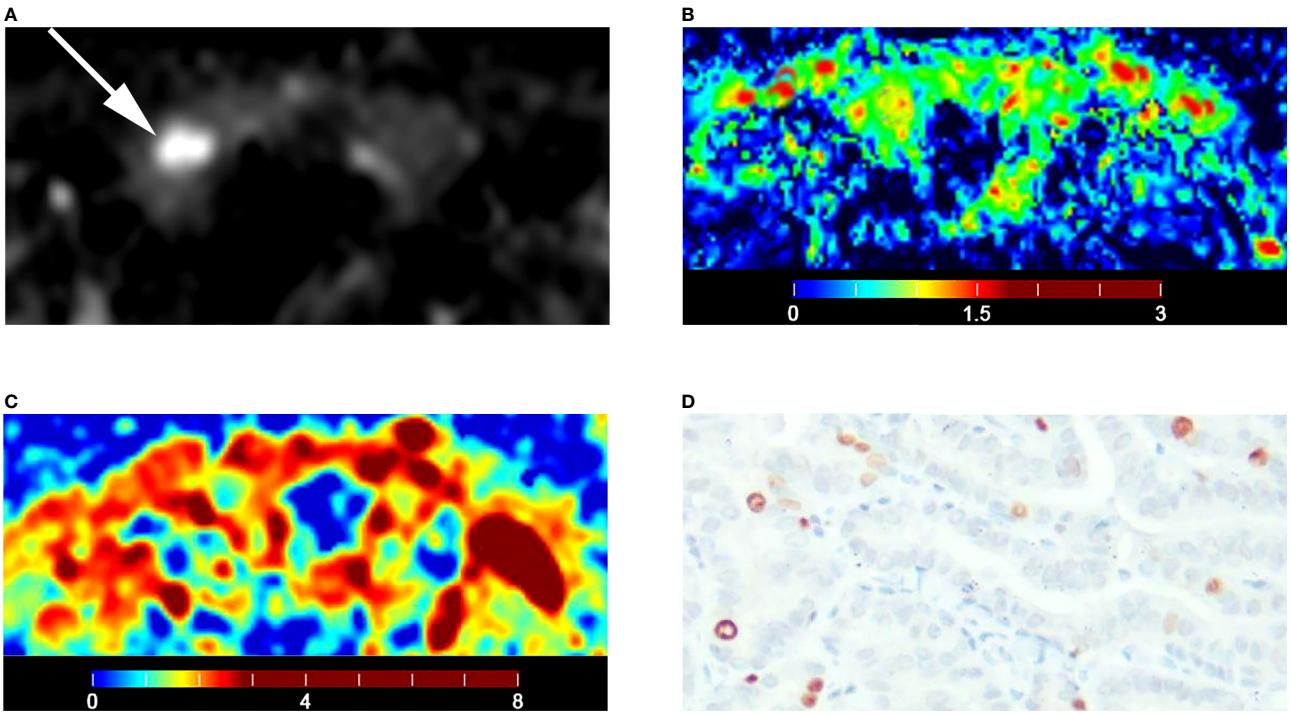

FIGURE 7 | Images of a 51-year-old female with right lobe papillary carcinoma (A-D): **(A)** axial diffusion image with b = 0; **(B)** color map of D, D value of lesion is 0.70×10^{-3} mm^2/s; **(C)** color map of D_{app}, D_{app} value of lesion is 1.26×10^{-3} mm^2/s; **(D)** Ki-67 expression is 5% in tumor cells.

expression of Ki-67, one of the most common proliferation markers that is expressed in all active phases of the cell cycle (28). The D value can precisely reflect the true diffusion without the influence of perfusion-related diffusion. The expression of Ki-67 lead to restricted diffusion, which could result in low D value. In addition, rapid cell proliferation could lead to less extracellular space, which could result in low D_{app}. The strong linear relationship between IVIM-derived parameters and DKI-derived parameters led to the alternative for each other in in differentiating malignant from benign thyroid nodules.

This study does have some limitations. First, the ZOOMit technique restricts the b-value to multiples of 50; otherwise, the f value may have better diagnostic performance. Second, only binary logistic regression was used to build the prediction model. Other statistical models should be introduced in subsequent work. Third, the number of Ki-67 cases is relatively small. A larger patient cohort is needed in future studies to confirm the present results.

CONCLUSIONS

IVIM and DKI showed comparable differential diagnostic capacity in differentiating malignant from benign nodules. Combination IVIM with DKI cannot improve diagnostic performance. The D of IVIM-derived parameters and D_{app} DKI-derived parameter was related to the Ki-67 expression in thyroid papillary carcinoma. In conclusion, IVIM and DKI were alternative for each other in in differentiating malignant from benign thyroid nodules.

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 Chongqing University Cancer Hospital institutional review board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR'S CONTRIBUTIONS

JW contributed to the conception and design of the study, data analysis and writing of the manuscript. LJ and DL contributed to performing the experiments and writing and revising the manuscript. JC, JZ and ML contributed to the data collection. DL, XL and HH contributed to the data analysis and interpretation of the data. JZ is the guarantor of this study

and approved the version to be submitted. All authors accept responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Differences in the clinical characteristics of papillary thyroid microcarcinoma located in the isthmus ≤5 mm and >5mm in diameter

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Background: The optimal treatment of papillary thyroid microcarcinomas (PTMCs) located in the isthmus (iPTMCs) is still controversial. The purpose of this study was to compare the clinicopathologic features of patients with iPTMCs ≤5 mm and >5 mm in diameter after total thyroidectomy, and to identify the risk factors for recurrence in patients with iPTMCs.

Methods: A total of 102 iPTMC patients who underwent total thyroidectomy were reviewed retrospectively. The clinicopathologic characteristics of iPTMCs ≤5 mm group (n = 29) have been compared with a group >5 mm (n = 73). Univariate and multivariate Cox proportional hazard models served to identify risk factors associated with recurrence-free survival (RFS).

Results: Gender (p = 0.033), multifocality (p = 0.041), and central lymph node metastasis (CLNM) (p = 0.009) of patients in the ≤5 mm and >5 mm groups differed significantly. iPTMC patients with age <55 years, male, multiple tumor, and extrathyroidal extension showed comparatively more frequent of CLNM in >5 mm groups. Of the 102 patients, nine (8.8%) developed recurrence during follow-up (median: 49.5 months). The patients with recurrences had comparatively high rates of CLNM (p = 0.038), extranodal invasion (p = 0.018), and more MNCND (Metastasis Nodes for Central Neck dissection) (p = 0.020). A cutoff of MNCND >2.46 was established as the most sensitive and specific level for the prediction of recurrence based on receiver operating characteristic (ROC) curve analyses. Multivariate analysis showed that the number of MNCND ≥3 was an independent predictor of poor RFS (p = 0.028).

Conclusion: We have found that the recurrence rates are similar in patients with iPTMCs ≤5 mm and >5 mm. The iPTMCs >5 mm were more likely to be associated with pathological features such as multifocality and CLNM. The male gender, extrathyroidal extension, and CLNM were associated with recurrence of iPTMCs except for tumor size and multifocality. Higher risk of CLNM should be considered in iPTMC >5 mm when it reaches some risk

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factors. The numbers of MNCND ≥3 may be an independent predictor for recurrence, which could help clinicians for the decision of radioiodine administration and the modulation of follow-up modalities.

KEYWORDS

papillary thyroid microcarcinoma, isthmus, tumor size, clinicopathological features, recurrence

Introduction

Papillary thyroid microcarcinoma (PTMC) is papillary thyroid carcinoma (PTC) with a diameter less than 10 mm. The incidence of PTC has increased rapidly worldwide in recent years (1). About half of the increase being because of PTMC, which has increased more than fourfold over the past 30 years (2, 3). The incidence of PTC arising in the isthmus was reported to be between 2.2% and 12.3% (4, 5). Compared with PTC in other sites, iPTC tended to be smaller in size and had a higher proportion of PTMC.

Until now, the clinical significance of iPTMCs and their optimal surgical strategy remains controversial. The American Thyroid Association (ATA) guidelines include PTMCs of absence of aggressive features in the low-risk category. Previous studies have demonstrated that PTMCs in the isthmus show more aggressive behavior and are more likely to be associated with multifocal disease, lymph node involvement, and capsule invasion than in other thyroid regions (6). Total thyroidectomy is to be considered as an appropriate surgical treatment when the iPTMCs patient falls within the high-risk category (7). However, the patient may be suitable for thyroid isthmusectomy if the iPTMCs are small in size and have no aggressive characteristics (8).

The diagnosis of iPTMC ≤5 mm has increased with the development of diagnostic technology. Meanwhile, the clinical significance of iPTMCs ≤5 mm and their optimal management remain unclear. Some studies have demonstrated that PTMCs ≤5 mm and >5mm in diameter have also been suggested as being important for risk stratification. PTMC >5mm was more likely to have high-risk features (9–12). To our knowledge, the clinicopathologic features and extent of surgery of iPTMCs ≤5 mm and >5 mm remain undetermined. The objective of this study was to evaluate the clinicopathologic characteristics and recurrence rates in patients with iPTMCs ≤5 mm and >5 mm who underwent total thyroidectomy at our institution. Additionally, we sought to investigate the risk factors associated with CLNM and recurrence.

Patients and methods

A total of 102 iPTMC patients (82 women and 20 men) who underwent total thyroidectomy and bilateral central neck dissection between January 2015 and January 2020 in the Department of Thyroid Surgery of the First Affiliated Hospital, School of Medicine, Zhejiang University were analyzed retrospectively. Before surgery, each patient underwent ultrasound-guided fine-needle aspiration biopsy (FNAB). iPTMC was defined as a PTC located in the isthmus less than 1 cm in size according to final pathologic reports. The clinicopathological data of iPTMC patients were analyzed. These patients were classified into two groups: iPTMC ≤5 mm (n = 29) and iPTMC >5 mm (n = 73). This retrospective study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University. Written informed consent was obtained from all patients before the study.

The iPTMC patients in the study met the following inclusion criteria: the center of the tumor located between two imaginary lines perpendicular to the surface of the skin from the most lateral points of the trachea. Patients who underwent unilateral lobectomy or isthmectomy, secondary surgery, and other types of thyroid cancer were excluded. iPTMCs less than 3 mm were also excluded due to the difficulty of preoperative identification. The 8th edition of the American Joint Committee on cancer (AJCC), TNM classification of malignant tumors in 2016 was used to describe and categorize cancer stages. Radio-iodine therapy was not performed postoperatively. All patients received thyroid-stimulating hormone-suppressive therapy after surgery. Postsurgical physical examinations were performed every 3 to 6 months. The mean follow-up period was 45.2 ± 18.0 months (median: 49.5 months). Cervical CT and FNAB were performed during a follow-up to evaluate suspected recurrences. Reoperation was performed on patients' suspected recurrence, and postoperative pathology was confirmed.

Statistical analysis

Statistical analyses were performed using SPSS version 22.0 (SPSS, Chicago, IL). The results were expressed as mean ± SD. Differences between categorical variables were assessed using the Chi-square test or Fisher exact test and continuous variables using Student's t-test. Multivariate recurrence analysis was

conducted using the Cox proportional hazards regression to identify independent prognostic factors. The restricted mean survival time (RMST) was used for survival analysis of variables of CLMN, CLNM ratio, and MNCND, which were not suitable for log-rank test. The time for calculating the RMSTs was set at $t^* = 60$ months. Statistical analysis for cutoff point was assessed by time-dependent ROC curves and was performed using R version 4.2.0 (R Core Team (2022), R Foundation for Statistical Computing, Vienna, Austria), applying the package time ROC for time-dependent ROC analysis. The optimal cutoff point was selected as the closest to (0.1) the criteria. RFS was conducted between the different groups using the Kaplan–Meier analysis, and the differences in curves for each variable were determined by the log-rank test. Results were reported as hazard ratios (HRs) and 95% confidence intervals (95% CI). Differences with $P < 0.05$ were defined as statistically significant.

Results

This study included 102 patients of mean age 42.38 ± 11.38 years (range: 22–77 years). The clinicopathologic features of the two groups are shown in Table 1. There were no significant differences in age, thyroglobulin, and thyroidperoxidase antibodies between the ≤5 mm and >5 mm groups at the time of diagnosis. The mean size of the largest tumor was 4.5 ± 0.69 mm in the ≤5 mm group and 7.8 ± 1.43 mm in the >5 mm group. The rate of female patients in the two groups were 93.1% and 75.3%, respectively ($P = 0.033$). The rates of multifocality (five of 29 [17.2%] *vs.* 27 of 73 [37.0%]; $p = 0.041$) and CLNM (seven of 29 [24.1%] *vs.* 38 of 73 [52.1%]; $p = 0.009$) were significantly lower in the ≤5 mm than in the >5 mm group. However, there were no statistically significant differences in extrathyroidal extension, TNM stage, and recurrence ($p = 0.442$, $p = 0.526$, and $p = 0.733$, respectively). N1a and N1b classifications were observed in 24.1% and 0% in the ≤5 mm group and in 47.9% and 4.1% in the >5 mm group ($p = 0.031$).

While CLNM was more frequent in patients with <55 years (58.7% *vs.* 10.0%, $P = 0.004$), male gender (77.8% *vs.* 43.6%, $P = 0.011$), multifocality tumor (66.7% *vs.* 43.5%, $P = 0.047$), and extrathyroidal extension (72.2% *vs.* 45.5%, $P = 0.043$) in >5 mm group, there were no statistically significant differences in ≤5 mm group (<55 *vs.* ≥55, $P = 0.121$; male *vs.* female, $P = 0.376$; single *vs.* multifocality tumor, $P = 0.362$; extrathyroidal extension present *vs.* absent, $P = 0.554$) (Table 2).

During the follow-up period, nine (8.8%) patients developed recurrence. Table 3 summarizes the nine patients who experienced tumor recurrence. The mean time to recurrence after surgery was 20.2 months (range: 2–50 months). Of these recurrences, the rate of CLNM, multifocality, and extrathyroidal extension was 88.9%, 44.4%, and 55.5%, respectively. All relapsed patients had lateral neck compartment metastases and seven (77.8%) were ipsilateral level III lymph node metastasis. Reoperative surgery was performed in patients with tumor recurrence.

When the nine patients with recurrence were compared with the 93 patients without recurrence in terms of their clinicopathological variables, they were found to be more likely male ($p = 0.049$) and to have higher numbers of extrathyroidal

TABLE 1 Clinical characteristics of patients with papillary thyroid microcarcinoma located in the isthmus by size.

Variables	≤5 mm group (*n*=29)	>5 mm group (*n* =73)	*p* value
Age (mean±SD, years)	45.0±11.5	41.4±11.3	0.150
<55	23 (79.3%)	63 (86.3%)	
≥55	6 (20.7%)	10 (13.7%)	0.277
No. of females, n (%)	27 (93.1%)	55 (75.3%)	0.033
Size of tumor, mm	4.5±0.69	7.8±1.43	—
Multifocality,n (%)	5 (17.2%)	27 (37.0%)	0.041
Extrathyroidal extension,n (%)	6 (20.7%)	18 (24.7%)	0.442
CLNM,n (%)	7 (24.1%)	38 (52.1%)	0.009
Mean no. dissected nodes for CND	6.11±4.23 (1-20)	7.96±5.58 (1-27)	0.118
Mean no. metastasis nodes for CND	0.32±0.61 (0-2)	1.9±3.0 (0-14)	0.006
N classification (N0/N1a/N1b)	22/7/0	35/35/3	0.031
TNM stage (I/II)	29/0	72/1	0.526
Recurrence,n (%)	3 (10.3%)	6 (8.2%)	0.733
TG(mean±SD, ng/mL)	24.5±43.4	37.6±94.7	0.254
TPOAb(mean±SD, IU/mL)	304.1±1233.3	339.9±878.8	0.996

CLNM, Central lymph node metastases; CND, Central neck dissection; TG, Thyroglobulin; TPOAb, Thyroid peroxidase antibody.

TABLE 2 Clinicopathologic factors related to central lymph node metastasis in >5 mm and ≤5 mm group.

Variables	≤5 mm group			>5 mm group		
	No. of patients (n = 29)	CLNM (n =7)	*p* value	No. of patients (n = 73)	CLNM (n =38)	*p* value
Age (years)						
<55	23	7(30.4%)	0.121	63	37(58.7%)	0.004
≥55	6	0(10.0%)		10	1(10.0%)	
Gender						
Male	2	1(50.0%)	0.376	18	14(77.8%)	0.011
Female	27	6(22.2%)		55	24(43.6%)	
Multifocality						
Single tumor	24	5(20.8%)	0.362	46	20(43.5%)	0.047
Multiple tumor	5	2(40.0%)		27	18(66.7%)	
Extrathyroidal extension						
Present	6	2(33.3%)	0.554	18	13(72.2%)	0.043
Absent	23	5(21.7%)		55	25(45.5%)	

CLNM, Central lymph node metastases.

extension ($p = 0.018$), higher numbers of CLNM ($p = 0.038$), and positive lymph nodes ($p = 0.020$; Table 4). ROC curve was performed to assess the recurrence based on the numbers of lymph nodes metastases (Figure 1). The area under the ROC curve (AUC) was 0.729 ($P = 0.0139$), which indicated that the numbers of lymph nodes metastases could accurately predict recurrence in iPTMCs. According to Youden's index, the best cutoff value was 2.46. The sensitivity and specificity was 55.6% and 86.0%, respectively. Univariate analysis revealed that extrathyroidal extension and MNCND ≥3 associated significantly with poor RFS ($p = 0.028$ and $p = 0.008$, respectively). Multivariate analysis showed that MNCND ≥3 remained an independent variable for poor RFS (HR = 4.566 [95% CI 1.181–17.657]; $p = 0.028$) (Table 5).

Figure 2 shows the Kaplan–Meier estimates of RFS in iPTMC patients. Tumor size ≤5 mm patients or >5 mm patients did not have statistical differences for recurrence ($p = 0.711$, HR: 0.771, 95% CI: 0.193–3.088; Figure 2A). Compared with the extrathyroidal extension(-) group, the extrathyroidal extension(+) group had significantly lower RFS ($p = 0.017$, HR: 4.359, 95% CI: 1.17–16.25; Figure 2B). Time-dependent ROC analysis was conducted to clarify the best cutoff point of age and rate of CLNM. The cutoff points of age and CLNM ratio were 42 years and 0.111, respectively. CLNM(+) and CLNM ratio >0.111 was significantly related to the lower RFS ($p = 0.035$, RMST (CLNM[+]): 53.15m, 95% CI: 48.41–57.89, RMST(CLNM[-]): 58.69 m, 95% CI: 56.65–60.74, HR:4.886; $p = 0.024$, RMST (CLNM ratio >0.111): 52.42m, 95% CI: 47.23–57.60, RMST (CLNM ratio ≤0.111): 58.78m, 95% CI: 56.86–60.69, HR:5.873, respectively; Figures 2D, E). However, the cutoff points of age (>42 years and ≤42 years) did not have statistical differences for recurrence ($p = 0.24$; HR: 0.952, 95% CI: 0.892–1.016; Figure 2C). The RFS was significantly lower for the patients of metastasis nodes for CND ≥3 ($p = 0.035$, RMST (MNCND[+]): 48.04 m, 95% CI: 38.84–57.24, RMST (MNCND[-])= 58.15 m, 95% CI: 56.25–60.04, HR: 5.92; Figure 2F).

TABLE 3 Characteristics of the patients with tumor recurrence.

Patient # no.	Age, y	Sex	Size, mm	CLNM (%)	Multifocality	Extrathyroidal extension	Time to disease free survival, m	Recurrence site
1	29	F	3	25%	-	+	2	Level VI lymph node
2	43	M	5	0%	+	-	50	Level III lymph node
3	34	F	3	25%	+	-	18	Level III lymph node
4	30	M	8	54%	+	+	17	Level II, III lymph node
5	32	M	7	100%	-	-	17	Level IV lymph node
6	51	F	10	63%	-	+	4	Level III lymph node
7	31	F	8	13%	-	-	32	Level III lymph node
8	38	M	7	13%	+	+	35	Level III, IV lymph node
9	43	F	6	43%	-	+	7	Level II, III lymph node

CLNM, Central lymph node metastases. + represents multifocal carcinoma or positive for Extrathyroidal extension. - Represents unifocal carcinoma or no Extrathyroidal extension.

TABLE 4 Clinicopathologic factors related to tumor recurrence.

Variables	Recurrence (n =9)	No recurrence (n = 93)	*p* value
Age (years), mean±SD	36.78±7.51	42.92±11.58	0.122
Age <55 years,n (%)	9 (100%)	77 (82.8%)	0.175
Male,n (%)	4 (44.4%)	16 (17.2%)	0.049
CLNM, n (%)	7 (77.8%)	38 (40.9%)	0.038
Multifocality, n (%)	4 (44.4%)	28 (30.1%)	0.376
Extrathyroidal extension, n (%)	5 (55.6%)	19 (20.4%)	0.018
Mean no. dissected nodes for CND	9.33±6.69	7.01±5.22	0.217
Mean no. metastasis nodes for CND	3.33±3.43	1.23±2.45	0.020
Ratio of CLNM	0.34±0.33	0.17±0.27	0.072

CLNM, Central lymph node metastases; CND, Central neck dissection.

Discussion

The studies from the past 5 years have demonstrated that an increasing number of PTCs are being identified, which is based largely on an expansion in the use of diagnostic imaging and surveillance. Generally, most PTCs have an indolent course and an excellent outcome, with a 10-year RFS of 98% and 20-year cause-specific mortality rate of <1% (13, 14). PTCs arising in the thyroid isthmus have been reported in approximately 2.2–12.3% of all PTCs (4, 5). However, iPTCs may have a higher incidence of extrathyroidal invasion, CLNM, and multifocality than PTCs in the lateral lobes, because even a small tumor abuts the trachea and the thyroid capsule (15–18). J. Seok et al. observed that the presence of extrathyroidal extension of iPTC was 73.0%, which is significantly higher compared with PTCs in other sites (57.1%) (16). In the study of Song et al., the rate of CLNM of iPTCs was

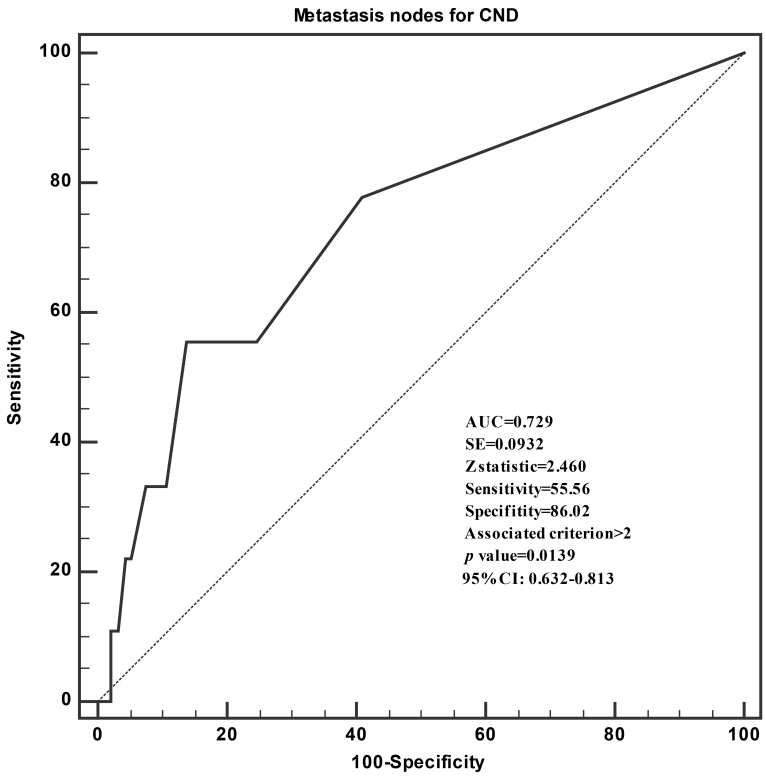

FIGURE 1
Receiver operating characteristic curve analyses of the numbers of lymph nodes metastases for predicting recurrence.

TABLE 5 Univariate and Multivariate Analysis of Variables Associated with tumor recurrence.

Variables	Univariate		Multivariate	
	HR(95% CI)	*p* value	HR(95% CI)	*p* value
Sex, male	1.789 (0.927-3.452)	0.083		
Age, ≥55 years	0.038 (0.000-86.587)	0.407		
Tumor size, >5 mm	0.770 (0.192-3.082)	0.712		
CLNM	4.812 (0.996-23.258)	0.051		
Multifocality	1.608 (0.432-5.993)	0.479		
Extrathyroidal extension	4.351 (1.167-16.214)	0.028	3.173 (0.820-12.272)	0.094
≥3 metastasis nodes for CND	5.880 (1.578-21.913)	0.008	4.566 (1.181-17.657)	0.028

CLNM, Central lymph node metastases; CND, Central neck dissection.

71.1%, higher than that of other PTCs (40.3%) (18). Goldfarb et al. found that the proportion of multifocality was 48.6%, which was higher than in the lobes (39.8%) (6).

At present, there are no clear surgical guidelines for iPTCs, and the focus of debate is mainly on the extent of primary tumor resection. There are no specific guidelines for management of thyroid cancers confined to the thyroid isthmus. Several surgeons recommend that total thyroidectomy could be considered as an appropriate surgical treatment for PTC originating in the isthmus regardless of primary tumor size (6, 7). Only a few studies advocated isthmusectomy or wide field isthmusectomy as a suitable and reasonable surgical procedure for selected patients with small differentiated thyroid cancer limited to the isthmus without lymph node metastasis (8, 19, 20). Although the optimal extent of surgery for PTMC remains unclear, total thyroidectomy reduces tumor recurrence rates in patients with multifocal disease (21). In the current study, the rate of extrathyroidal extension and multifocality of iPTMC was 23.5% and 31.4%, respectively. Therefore, careful ultrasound evaluation should be performed in other sites of thyroid on iPTMCs preoperative for surgical decision-making (5).

The isthmus is located in front of the trachea and, due to its anatomical uniqueness, iPTCs may be detected early. Compared with PTC in other sites, iPTC tended to be smaller in size and had a higher proportion of iPTMC (22). iPTMCs accounted for 41.4–66.3% of all iPTCs (6, 23, 24), higher than that of other PTCs (35.7–48.8%) (25, 26). The ATA guidelines recommend fine-needle aspiration for nodules >5 mm in size when the patient falls within the high-risk category or if ultrasonographic examination shows manifestations that suggest malignancy (27). Previous studies have suggested that the recurrence rates and clinicopathologic features are similar in patients with PTMCs ≤5 mm and >5 mm in the lobes, except for lymph node metastasis and extrathyroidal extension (28, 29). However, the clinical significance and recurrence of iPTMCs ≤5 mm and >5 mm and their optimal management remain unclear. In our study, the rates

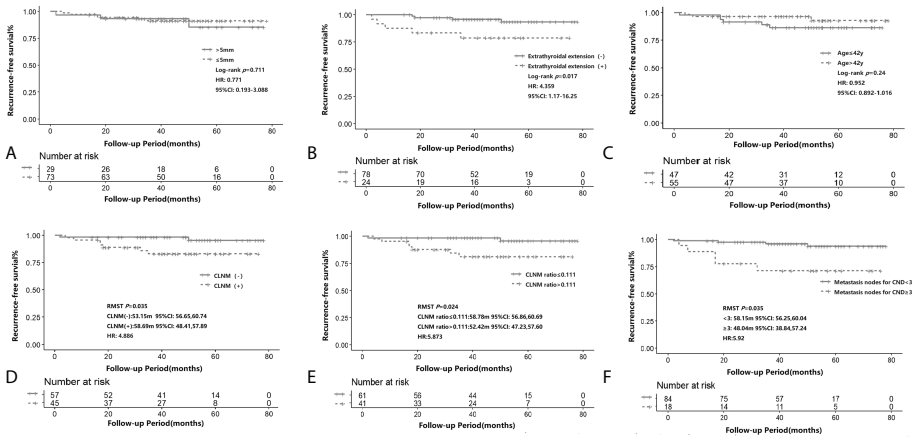

FIGURE 2
Recurrence-free survival according to tumor size (≤5 mm and >5mm) **(A)**, presence of extrathyroidal extension **(B)**, age (≤ 42y and >42y) **(C)**, CLNM **(D)**, CLNM ratio (≤0.111 and >0.111) **(E)** and the number of metastatic lymph nodes (> 2 and ≤2) **(F)** in iPTMC. The Kaplan–Meier method for recurrence with the log-rank test was used for statistical comparisons of **A-C**. The restricted mean survival time (RMST) was used for survival analysis of **D-F**. CLNM, central lymph node metastasis.

of multifocality and CLNM were significantly lower in the ≤5 mm than in the >5 mm group. Female patients of iPTMC ≤5 mm were higher than that in the >5 mm. However, there were no statistically significant differences in extrathyroidal extension and TNM stage. Although male sex, lymph node metastasis, and multifocality are associated with poorer prognosis (30, 31), there were no significant differences in recurrence between the two groups. With a median follow-up of 49.5 months, the RFS of iPTMCs ≤5 mm and >5 mm did not have statistical differences. Time-dependent ROC analysis was conducted to clarify the cutoff point of tumor diameter in the current study. However, there were no statistically significant differences for recurrence.

On the study of Luo et al., tumor size of iPTC >11 mm was significantly associated with lymph node metastasis (23). Wang et al. found that tumor size >7 mm was associated with CLNM (32). Our findings revealed that the incidence of lymph node metastasis was significant high (52.1%) in iPTMC >5 mm group. However, the incidence of CLNM was relatively high in iPTMC >5 mm group when age <55 years, male sex, multiple tumor, and extrathyroidal extension existing showing no significant difference to that of same clinicopathologic factors in iPTMC ≤5 mm group. Therefore, we can infer that when the size of iPTMC is >5 mm, relatively high incidence of lymph node metastasis may occur when reaches certain risk factors. In fact, the correlation between lymph node metastasis and tumor recurrence was reported to be significant. CLNM was considered to be an aggressive clinical feature of PTMC related to higher incidence of recurrence (30, 31, 33). In the present study, the Kaplan–Meier survival analyses indicated that the RFS was better for iPTMCs without CLNM compared with that with CLNM. Of the nine cases of recurrence, one (11.1%) recurrence in a level VI lymph nodes and eight (88.9%) recurrences in lateral neck lymph nodes. Level III lymph nodes metastases accounted for 77.7% of all relapse cases.

With the comparison of clinicopathological variables of patients with and without recurrence, the relapse cases were found to be a higher CLNM (77.8%) and higher numbers of metastasis lymph nodes (p = 0.02). Several studies have found that the risk of recurrence was positively associated with a higher number of lymph nodes metastases at initial surgical operation (34, 35). The presence of >5 metastatic lymph nodes was associated with a significantly worse RFS than patients with <5 metastatic lymph nodes (36, 37). Interestingly, the present study shows that the presence of more than two metastatic lymph nodes is also associated with a significantly worse RFS. Using the existing data of iPTMC, we performed ROC curve analysis between the number of CLNM and recurrence. The AUC value was 0.729, cutoff value was 2.46, sensitivity was 55.6%, and specificity was 86.0%. The Kaplan–Meier survival analyses also indicated the significant differences of RFS between patients with ≥3 and <3 metastatic lymph nodes (p = 0.003). Furthermore, Cox proportional hazards model was used to identify risk factors for recurrence. On univariate analysis, risk factors for recurrence were extrathyroidal extension and ≥3 MNCND. Multivariate analysis indicated that the only independent risk factor for recurrence was ≥3 MNCND (HR, 4.566; 95% confidence interval, 1.18–17.66; p = 0.028). This showed that the model has a certain function in predicting recurrence and help clinicians for the decision of radioiodine administration and the modulation of follow-up modalities.

Our present study had several limitations. First, the sample size of the iPTMC was relatively small, which may cause a selection bias. Second, a relatively short follow-up time may be potential biases affecting the risk factor analyses and results. The retrospective nature of our study may also have led to selective bias. The larger number of patients with a longer period of follow-up is needed to overcome these limitations.

Conclusions

In conclusion, our findings demonstrate that the recurrence rates are similar in patients with iPTMCs ≤5 mm and >5 mm. Nonetheless, iPTMCs >5 mm was more likely to be associated with pathological features such as multifocality and CLNM. Higher risk of CLNM should be considered in evaluation and surgical decision of iPTMC >5 mm when reaches some risk factors. The male gender, extrathyroidal extension, and CLNM were associated with recurrence of iPTMCs except for multifocality. The numbers of metastasis nodes for CND ≥3 may be an independent predictor for recurrence, which could help clinicians for the decision of radioiodine administration and the modulation of follow-up modalities.

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

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

FZ, and YW conceived the idea and designed the research. XX and FL collected data and followed up patients. FZ, LZ and YS participated in statistical analysis and article writing. 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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Nomogram individually predicts the risk for distant metastasis and prognosis value in female differentiated thyroid cancer patients: A SEER-based study

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Objective: Distant metastasis (DM) is an important prognostic factor in differentiated thyroid cancer (DTC) and determines the course of treatment. This study aimed to establish a predictive nomogram model that could individually estimate the risk of DM and analyze the prognosis of female DTC patients (FDTCs).

Materials and methods: A total of 26,998 FDTCs were retrospectively searched from the Surveillance, Epidemiology, and End Results (SEER) database from 2010 to 2018 and randomly divided into validation and training cohorts. Univariate and multivariate analyses were performed to screen for prognostic factors and construct a prediction nomogram. The performance of the nomogram was assessed by the area under the receiver operating characteristic curve (AUC), concordance index (C-index), and a calibration curve. The overall survival (OS) and cancer-specific survival (CSS) were evaluated by Kaplan–Meier (K-M) analysis.

Results: A total of 263 (0.97%) FDTCs were reported to have DM. K-M analysis showed the association of multiple-organ metastases and brain involvement with lower survival rates ($P < 0.001$) in patients. Tumor size, age at diagnosis, thyroidectomy, N1 stage, T3–4 stage, and pathological type were independent predictive factors of DM in FDTCs (all $P < 0.001$). Similarly, age at diagnosis, Black, DM, T3–4 stage, thyroidectomy, and lung metastasis were determined as independent prognostic factors for FDTCs (all $P < 0.001$). Several predictive nomograms were established based on the above factors. The C-index, AUC, and calibration curves demonstrated a good performance of these nomogram models.

Conclusion: Our study was successful in establishing and validating nomograms that could predict DM, as well as CSS and OS in individual patients with FDTC based on a large study cohort. These nomograms could enable surgeons to perform individualized survival evaluation and risk stratification for FDTCs.

KEYWORDS

distant metastasis (DM), differentiated thyroid cancer (DTC), nomogram, overall survival (OS), prognosis

Introduction

Thyroid cancer is one of the most commonly occurring endocrine malignancies, and its incidence has been dramatically increasing worldwide (1–3). Among the histological subtypes of thyroid cancer, differentiated thyroid cancer (DTC) accounts for nearly 90% of all thyroid carcinomas (4). DTC has a favorable prognosis, with a 10-year overall survival rate exceeding 90% (5). Nevertheless, a small number of DTC patients present with distant metastasis (DM) at initial diagnosis, which is the leading cause of thyroid cancer-related mortality (6, 7). The risk factors for DM have been widely discussed in previous studies, but the results were inconsistent in patients with DTC. Liu et al. (8) reported that larger tumor size, lymph node metastasis, male, and histological subtype of follicular thyroid cancer (FTC) significantly increased the risk of DM in patients with DTC. Huy et al. (9) demonstrated that vascular invasion, multifocality, and extrathyroidal extension were independent predictors of DM. Unfortunately, the above studies were retrospective, small-sampled, single-center studies and exhibited a huge heterogeneity. To date, there is no effective method to quantitatively predict DM in DTC patients.

Sex disparity in disease aggressiveness, prognosis, and incidence has been observed in a variety of cancers (10, 11). In thyroid cancer, women are two to three times more likely to develop DTC and present at an earlier stage of disease, than patients with a non-aggressive type of cancer or those diagnosed at a younger age (12). In contrast, men tend to have a more aggressive disease at diagnosis and ultimately suffer higher mortality and lower disease-free survival (13). Therefore, the potential impact of sex disparity on DM should be taken into consideration to reduce the influence of selection bias.

Abbreviations: DM, distant metastasis; FDTC, female differentiated thyroid cancer; AUC, the area under the receiver operating characteristic curve; C-index, concordance index; OS, overall survival; CSS, cancer-specific survival; K-M, Kaplan–Meier; FTC, follicular thyroid cancer; SEER, Surveillance, Epidemiology, and End Results; DCA, decision curve analysis; TMC, thyroid microcarcinoma.

The SEER (https://seer.cancer.gov/) database is a large public database that represents approximately 28% of the US population and provides clinical information about patient demography, tumor morphology, diagnosis, treatment, and prognosis (14). Given the important role of DM in predicting survival outcomes in DTC patients, identifying the patients who have the possibility to develop DM and offering these individuals more aggressive treatments are paramount to achieving the best clinical outcomes. Nomogram is a simple and reliable statistical prediction tool that has been widely used in the clinical setting and is helpful for clinicians to recognize the high-risk female DTC patients (FDTCs) in a visual fashion.

Based on the heterogeneity of thyroid cancer, and multiple available treatment options, it is important to establish predictive models for DM and provide an appropriate therapeutic strategy for FDTCs. Moreover, there is a lack of studies focusing on developing a convenient and accurate risk assessment tool to predict the cancer-specific survival (CSS) and overall survival (OS) in FDTCs. To our knowledge, this is the first study attempting to use a large database to create a prognostic nomogram for FDTCs, which may enable personalized medical decision-making and surveillance more accurately.

Materials and methods

Data source

A retrospective cohort study was conducted by using selected data from the SEER database of the US National Cancer Institute. Our study was approved by the Ethics Committee of Xiangya Hospital of Central South University and conformed to the provisions of the Declaration of Helsinki. We extracted patients diagnosed with DTC (ICD-O-3 codes 8341, 8340,8050, 8260, 8050) from the SEER 21 region during the period 2010–2018. Information for metastatic sites of the lung (Combined Mets at DX-lung), bone (Combined Mets at DX-bone), liver (Combined Mets at DX-liver), and brain

(Combined Mets at DX-brain) was collected since 2010. The inclusion criteria were as follows: (I) diagnosed with DTC at some time from 2010 to 2018; (II) female; (III) active follow-up during the study period; (IV) with a known cause of death. We excluded patients with insufficient or unknown clinicopathologic profile, other types, or undetermined histology of thyroid carcinomas. Finally, a total of 26,998 FDTCs were enrolled in the current study (Figure 1).

Clinical characterization

The variables were extracted from the selected cohorts as follows: demographic variables included race (black, white, other) and age (<55 or ≥55 years); clinicopathological characteristics included T stage (Tx, T0, T1, T2, T3, and T4), N stage (Nx, N0, and N1), M stage (M0 or M1), TNM stage (I, II, III, and IV), summary stage (localized, regional, and distant), tumor size (≤10 or >10 mm), histology type (papillary, papillary with follicular variant, and follicular), median income (<$45,000, $45,000–$65,000, and ≥$65,000), survival months, and vital status. The endpoint of the current study was OS and CSS, which were defined as the duration from the initial diagnosis to all-cause death and the interval from the initial diagnosis to death from DTC, respectively (15). The seventh edition of the TNM classification system was used to stage FDTCs.

Nomogram development

The nomogram was developed based on the results of multivariate analysis by using the "rms" package in R version 3.5.1 (http://www.r-project.org/). The performance of the nomogram was assessed by calibration and discrimination. A calibration plot (1,000 bootstrap resamples) was used to evaluate the discrimination of the model, the Harrell's concordance index (C-index), ranging from 0.5 (indicates absence of discrimination) to 1 (indicates perfect discrimination) (16), which approximately equivalented to the area under the receiver operating characteristic curve (AUC). Furthermore, decision curve analysis (DCA) was employed to evaluate the clinical values and utility of the nomogram by R function "stdca" (17).

Statistical analysis

Statistical analyses were performed in SPSS 22.0 (IBM Corp, USA). Categorical variables were presented as percentage (%), and continuous variables were expressed as the mean ± SD. Chi-square test and t test were used for categorical and continuous variables, respectively. Univariate and multivariate analyses were performed to identify the independent risk factors of DM or prognostic factors of CSS and OS. The Kaplan–Meier (K-M) method was employed to estimate the OS and CSS, and the significance of differences was assessed by log-rank tests. P value < 0.05 (two-sided) represented positive statistical significance.

Results

Clinicopathological features

A total of 26,998 eligible FDTC patients from 2010 to 2018 were identified from the SEER database.

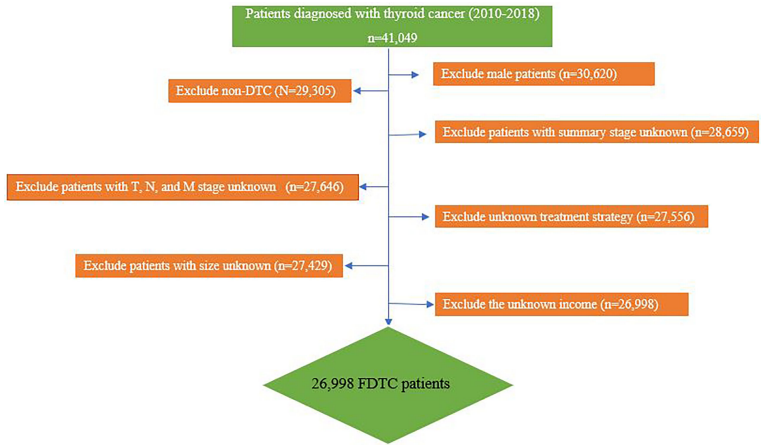

FIGURE 1
Research flowchart.

The clinicopathological characteristics of the patients are displayed in Table 1. In the whole study cohort, 17,629 (65.3%) patients were younger than 55 years. The average age was 47.9 ± 15.13 years, and the majority of the patients were white (21,267, 78.8%) and had a larger tumor size (21,639, 80.2%). Of these, T1 stage (17,175, 63.6%), N0 stage (20,567, 76.2%), M0 stage (26,735, 99.0%), TNM I stage (21,072, 78.1%), and localized (19,039, 70.5%) were more common. Papillary (18,400, 68.2%) was the most common pathological subtype, followed by papillary with follicular variant (7,405, 27.4%) and FTC (1,193, 4.4%). A percentage of 98.4% patients had undergone thyroidectomy. The median follow-up time was 50 months, during which a total of 918 (3.4%) patients had died and 0.65% (176/26,998) patients had died due to DTC. Besides, DM was found in 263 (0.97%) patients, of which 166 patients (0.61%) had lung metastases, 92 patients (0.34%) had bone metastases, 14 patients (0.05%) had liver metastases, and 12 patients (4.96%) had brain metastases. K-M analysis demonstrated that brain metastasis was associated with the worst survival than other metastasis sites ($P < 0.001$, Figure 2A). Compared with single metastasis, multiple metastases were associated with a poorer survival ($P < 0.001$). Interestingly, triple metastases did not reduce the survival time as compared to double metastases (Figure 2B). These results indicated that the pattern of organ-specific metastases had different prognostic values in FDTC.

TABLE 1 Characteristics of 26,998 patients with FDTC in SEER.

Variable	Patient demographics (%)
Age mean ± SD	47.9 ± 15.13
≥55 years	9,369 (34.7)
<55 years	17,629 (65.3)
Race	
White	21,267 (78.8)
Black	2,025 (7.5)
Other	3,706 (13.7)
Tumor size mean ± SD	7.58 ± 11.03
≤1.0 cm	5,359 (19.8)
>1.0 cm	21,639 (80.2)
T stage	
T0	25 (0.1)
Tx	125 (0.5)
T1	17,175 (63.6)
T2	4,481 (16.6)
T3	4,625 (17.1)
T4	567 (2.1)
N stage	
N0	20,567 (76.2)
Nx	445 (1.6)
N1	5,896 (22.2)
M stage	
M0	26,735 (99.0)
M1	263 (1.0)
TNM stage	
I	21,072 (78.1)
II	1,804 (6.7)
III	2,876 (10.7)
IV	1,246 (4.6)
Summary stage	
Localized	19,039 (70.5)
Regional	7,457 (27.6)
Distant	502 (1.9)
Thyroidectomy	26,575 (98.4)
Pathological type	
Papillary	18,400 (68.2)
Papillary with follicular variant	7,405 (27.4)
Follicular	1,193 (4.4)
Median income	
<$45,000	1,249 (4.6)
$45,000-$65,000	8,318 (30.8)
≥$65,000	17,431 (64.6)

FDTC, differentiated thyroid cancer; SEER, Surveillance, Epidemiology, and End Results.

A novel nomogram predicting distant metastasis

Subsequently, 26,998 FDTC patients were randomly divided into validation and training cohorts (Table S1) to formulate and validate the nomogram. The univariate analysis indicated that the age at diagnosis, white, FTC, N1 stage, T3–4 stage, tumor size, thyroidectomy, and thyroid micro-carcinoma (TMC) were significantly associated with DM in the training cohorts (all $P<0.05$). Multivariate logistic regression analysis proved that the age at diagnosis, pathological type, N1 stage, T3–4 stage, thyroidectomy, and tumor size were independent risk factors for DM (all $P<0.05$, Table 2). In terms of the tumor size, an increasing DM risk was detected in patients with a larger tumor size (OR = 1.02, 95% CI = 1.01–1.04, $P = 0.003$). Also, an older age at diagnosis was associated with a higher risk of DM (OR = 1.03, 95% CI = 1.01–1.05, $P = 0.001$). Comparing papillary with follicular variant thyroid cancer, papillary thyroid cancer (PTC) (OR = 0.47, 95% CI = 0.3–0.73, $P< 0.001$) and FTC (OR = 4.73, 95% CI = 2.64–8.5, $P< 0.001$) showed an opposite effect. Thyroidectomy was associated with a significantly lower risk of DM (OR = 0.06, 95% CI = 0.03–0.09, $P< 0.001$). Furthermore, higher N stage (OR = 6.44, 95% CI = 4.21–9.84, $P< 0.001$) and T stage (OR = 2.66, 95% CI = 1.76–3.91, $P< 0.001$) were associated with a higher probability of DM.

In order to assess the risk variables of DM in FDTCs more intuitively, a nomogram model was constructed (Figure 3A). The C-index of nomogram for predicting DM was 0.887 in the training cohort and 0.878 in the validation cohort, respectively.

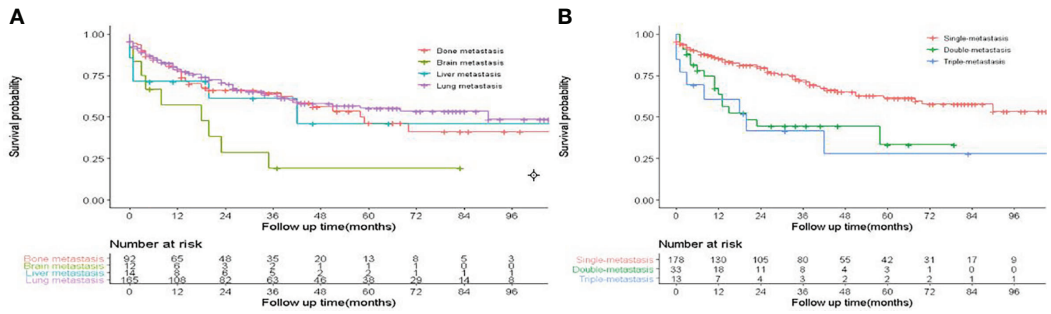

FIGURE 2
Effect of distant metastasis on overall survival in FDTCs. **(A)** The overall survival in different metastasis sites. **(B)** The overall survival of different metastasis patterns.

TABLE 2 Univariate and multivariate logistics regression analyses of the risk factors of DM in the training cohorts.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	OR (95% CI)	*P*
Age mean ± SD	1.06 (1.05-1.07)	<0.001	1.03 (1.01-1.05)	0.001
<55 years	Ref	<0.001	Ref	0.114
≥55 years	4.67 (3.24-6.72)		1.75 (0.87-3.51)	
Race				0.731
White	2.15 (1.13-4.09)	0.02	0.88 (0.42-1.84)	0.939
Black	0.88 (0.3-2.59)	0.82	0.96 (0.31-2.95)	
Other	Ref		Ref	
Pathological type				<0.001
Papillary with follicular variant	Ref	0.64	Ref	<0.001
Papillary	0.91 (0.61-1.36)	<0.001	0.47 (0.3-0.73)	
Follicular	5.04 (3.03-8.39)		4.73 (2.64-8.5)	
T stage				
T0-2	Ref	<0.001	Ref	<0.001
T3-4	5.46 (3.91-7.62)		2.62 (1.76-3.91)	
N stage				
N0/x	Ref	<0.001	Ref	<0.001
N1	3.82 (2.74-5.32)		6.44 (4.21-9.84)	
Thyroidectomy	0.05 (0.03-0.08)	<0.001	0.06 (0.03-0.09)	<0.001
Tumor size	1.04 (1.03-1.04)	<0.001	1.02 (1.01-1.04)	0.003
TMC	2.22 (1.57-3.14)	<0.001	0.69 (0.37-1.3)	0.254
Median income				
<$45,000,	Ref	0.89	Ref	–
$45,000-$65,000	1.07 (0.42-2.74)	0.38	–	–
≥$65,000	1.5 (0.61-3.69)		–	

CI, confidence intervals; TMC, thyroid microcarcinoma; DM, distant metastasis.

The areas under the ROC curves (AUC) in the training and validation cohorts were 0.887 and 0.874, respectively (Figures 3B, C). The AUC combined with the C-index reflected a good discrimination ability of the nomogram. In addition, the calibration plots showed perfect consistency in both the training and validation cohorts (Figure 3D). Finally, DCA indicated that this nomogram had an excellent performance in clinical practice (Figure 3E).

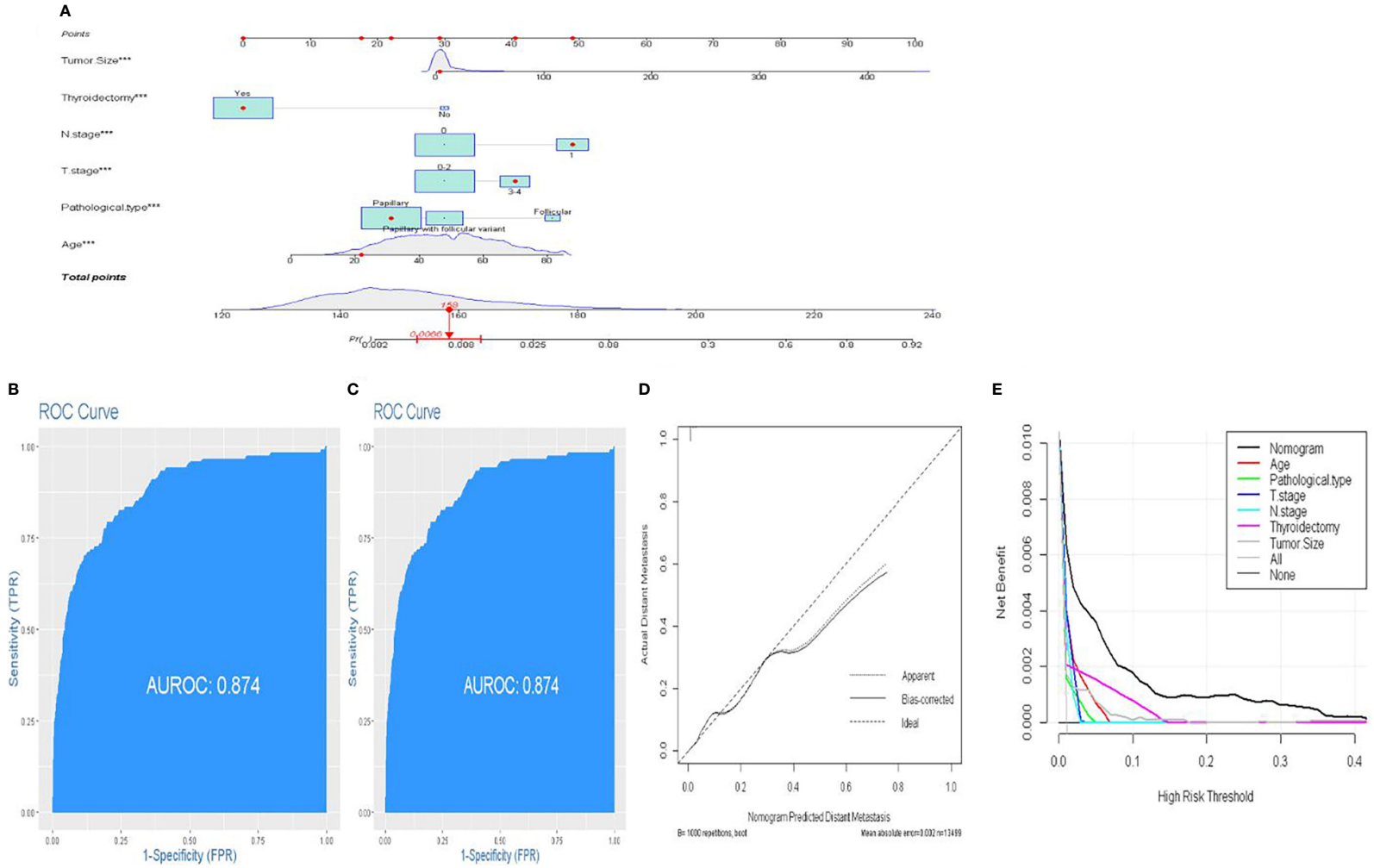

FIGURE 3
A novel nomogram predicting distant metastasis. **(A)** Nomogram predicting the probability of DM. Instructions: Locate the patient characteristics of each variable on its respective axis. Draw a line to the "dot" scale to get a score for each variable. Find the total score on the total score scale based on the sum of the points of all variables. Draw a line to the end scale. **(B, C)** The ROC curve of nomograms in training and validation cohorts. **(D)** Calibration curves of the nomogram for the probability of DM. **(E)** Decision curve analysis for nomogram

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TABLE 3 Univariate and multivariate logistics regression analyses of the risk factors of lung metastasis in FDTC patients.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	OR (95% CI)	*P*
Age mean ± SD	1.07 (1.05-1.08)	< 0.001	1.02 (1.00-1.04)	0.018
<55 years	Ref	< 0.001	Ref	0.005
≥55 years	5.95 (3.55-9.77)		2.5 (1.31-4.74)	
Race				0.687
White	3.37 (1.66-6.87)	< 0.001	1.18 (0.54-2.58)	0.429
Black	0.69 (0.18-2.59)	0.578	0.58 (0.15-2.24)	
Other	Ref		Ref	
Pathological type				0.033
Papillary with follicular variant	Ref	0.414	Ref	< 0.001
Papillary	1.17 (0.8-1.72)	< 0.001	0.64 (0.42-0.96)	
Follicular	5.06 (3.07-8.35)		4.53 (2.59-7.93)	
T stage				
T0-2	Ref	< 0.001	Ref	< 0.001
T3-4	9.05 (6.52-12.56)		4.57 (3.17-6.61)	
N stage				
N0/x	Ref	< 0.001	Ref	< 0.001
N1	5.07 (3.72-6.93)		6.35 (4.33-9.31)	
Thyroidectomy	0.05 (0.03-0.07)	< 0.001	0.07 (0.04-0.11)	< 0.001
Tumor size	1.03 (1.02-1.04)	< 0.001	1.01 (1.00-1.02)	0.004
TMC	2.03 (1.47-2.81)	< 0.001	0.88 (0.55-1.41)	0.591
Median income				
<$45,000,	Ref	0.571	Ref	–
$45,000-$65,000	1.28 (0.55-2.98)	0.543	–	–
≥$65,000	1.29 (0.57-2.94)		–	

CI, confidence intervals; TMC, thyroid microcarcinoma; FDTC, female differentiated thyroid cancer.

An individualized nomogram predicting bone metastasis and lung metastasis

Lung and bone are the most common organs for metastasis in patients with DTC, and metastasis in these organs is known to correlate with a poor prognosis. Next, we developed two predictive nomograms to evaluate the possibility of bone and lung metastasis, respectively. Independent risk factors for bone and lung metastasis were identified by univariate and multivariate analyses. The age at diagnosis, FTC, N1 stage, T3–4 stage, tumor size, and thyroidectomy were identified as significant independent predictors of lung metastasis (all $P<0.05$, Table 3). Similarly, age at diagnosis, FTC, T3–4 stage, tumor size, and thyroidectomy were also identified as independent predictors of bone metastasis (all $P<0.05$, Table 4). These significant independent factors were incorporated to build a nomogram (Figures 4A, B). The C-index value of the nomogram for predicting lung and bone metastasis was 0.914 and 0.884, respectively. Meanwhile, the AUC of the nomogram for predicting lung and bone metastasis was 0.914 and 0.885, respectively (Figures 4C, D), which also *demonstrate*d the accuracy and reliability of the prediction model. The calibration curves showed excellent agreement between the predicted and actual observations (Figures 4E, F).

A prognostic nomogram predicting OS and CSS

The prognostic significance of gender is still controversial, and there is no clinical evidence relating gender with prognosis in FDTCs. To identify the independent prognostic factors associated with the survival of FDTCs, univariate and multivariate Cox analyses were performed. Statistical analyses demonstrated that the age at diagnosis ($P<0.001$), Black ($P = 0.008$), distant metastasis ($P<0.001$), T3–4 stage ($P<0.001$), thyroidectomy ($P<0.001$), tumor size ($P = 0.044$), lung metastasis ($P = 0.005$), and liver metastasis ($P = 0.009$) were independent risk factors for OS (Table 5). Moreover, in the CSS analysis, the age at diagnosis ($P<0.001$), Black ($P = 0.043$), regional ($P = 0.004$), distant metastasis ($P<0.001$), T3–4 stage ($P<0.001$), N1 stage ($P<0.001$), thyroidectomy ($P<0.001$), lung

TABLE 4 Univariate and multivariate logistics regression analyses of the risk factors of bone metastasis in FDTC patients.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	OR (95% CI)	*P*
Age mean ± SD	1.08 (1.07-1.1)	< 0.001	1.04 (1.01-1.06)	0.005
<55 years	Ref	< 0.001	Ref	0.149
≥55 years	8.36 (4.94-14.16)		1.87 (0.8-4.38)	
Race				0.141
White	15.57 (2.17-111.67)	0.006	4.58 (0.6-34.8)	0.254
Black	3.66 (0.33-40.38)	0.289	4.12 (0.36-46.92)	
Other	Ref		Ref	
Pathological type				< 0.001
Papillary with follicular variant	Ref	< 0.001	Ref	< 0.001
Papillary	0.42 (0.25-0.7)	< 0.001	0.31 (0.17-0.54)	
Follicular	7.96 (4.83-13.14)		4.74 (2.76-8.15)	
T stage				
T0-2	Ref	< 0.001	Ref	< 0.001
T3-4	3.71 (2.46-5.59)		2.24 (1.4-3.61)	
N stage				
N0/x	Ref	0.687	–	–
N1	1.1 (0.68-1.78)		–	
Thyroidectomy	0.05 (0.03-0.07)	< 0.001	0.06 (0.04-0.12)	< 0.001
Tumor size	1.03 (1.02-1.04)	< 0.001	1.02 (1.00-1.03)	0.015
TMC	1.86 (1.2-2.9)	0.006	0.81 (0.39-1.69)	0.581
Median income				
<$45,000,	Ref	0.56	Ref	-
$45,000-$65,000	1.65 (0.39-7.04)	0.214	–	-
≥$65,000	2.44 (0.6-9.97)		–	

CI, confidence intervals; TMC, thyroid microcarcinoma; FDTC, female differentiated thyroid cancer.

metastasis (P = 0.003), and bone metastasis (P = 0.009) were significantly associated with CSS (Table 6). The OS and CSS nomograms were constructed based on the independent prognostic factors (Figures 5A, B) and were validated internally. The C-index for the OS nomogram was 0.826, while it was 0.827 for the CSS nomogram. The ROC is plotted in Figure 2, and the AUCs for OS and CSS were 0.818 and 0.961, indicating acceptable discriminations (Figures 5C, D). In addition, the calibration curves indicated an excellent agreement between the actual survival and the predicted results (Figures 5E, F).

Discussion

Overall, DM is uncommon in DTC, and the lung is the most common site for metastasis, followed by the bone, liver, brain, and kidney (18, 19). Thyroid cancer patients who develop DM are reported to have a poor prognosis and low overall survival (20). During the past decades, many studies have focused on identifying the heterogeneous and homogeneous prognosis-related factors of DM, including male gender, tumor size, histology subtype, extrathyroidal extension, age at diagnosis, and lymph node metastasis status (6, 8, 21–24). However, the potential impact of gender disparity on thyroid cancer prognosis was ignored. To the best of our knowledge, our study is the first large-scale analysis that has established an individual nomogram model to assess the prognosis of FDTCs and quantify the risk of DM, specifically regarding lung metastasis and bone metastasis. Our nomogram models would provide a personalized and accurate tool for the clinicians to determine more effective and reasonable treatment strategies for FDTCs.

In the present study, DM was found in 263 (0.97%) patients and the lung (166, 0.61%) was the most frequent organ of metastasis, which was consistent with the previous studies (18, 25, 26). The pathogenesis of metastasis still remains unclear, and DM is known to correlate with a higher mortality rate. In this study, we sought to investigate the effect of different DM sites on survival in patients with DTC to better understand their association with survival outcomes. Our results showed that brain metastasis was associated with a poorer survival rate than the other metastasis sites. Moreover, multiple-organ metastases

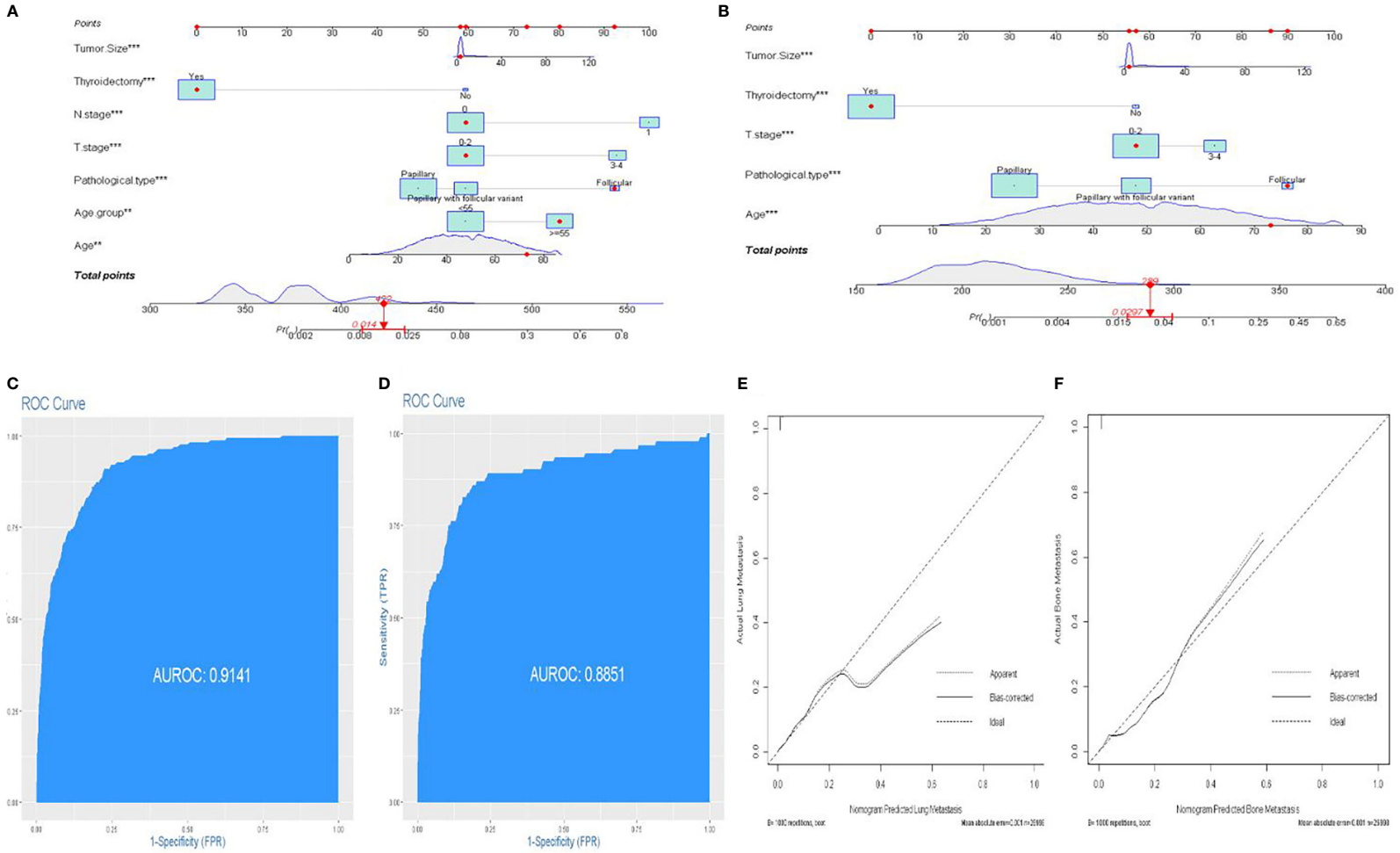

FIGURE 4
An individualized nomogram predicting bone metastasis and lung metastasis. **(A)** Nomogram predicting the probability of lung metastasis. **(B)** Nomogram predicting the probability of bone metastasis. **(C)** The ROC curve of the nomogram with lung metastasis. **(D)** The ROC curve of the nomogram with bone metastasis. **(E, F)** Calibration curves of the nomogram for the probability of lung metastasis and bone metastasis.

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TABLE 5 Univariate and multivariate cox regression analyses of the prognostic factors of OS in FDTC patients.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	OR (95% CI)	*P*
Age mean ± SD	1.09 (1.08-1.11)	< 0.001	1.08 (1.07-1.09)	< 0.001
<55 years	Ref	< 0.001	Ref	0.542
≥55 years	6.9 (5.9-8.06)		0.92 (0.71-1.2)	
Race				0.625
White	3.28 (2.41-4.47)	< 0.001	0.92 (0.65-1.29)	0.008
Black	1.1 (0.67-1.81)	0.714	2.01 (1.2-3.37)	
Other	Ref		Ref	
Pathological type				
Papillary with follicular variant	Ref	0.419	–	–
Papillary	1.06 (0.92-1.23)	0.006	1.01 (0.87-1.17)	0.916
Follicular	1.5 (1.12-2.01)		0.75 (0.54-1.04)	0.084
Summary stage				0.589
Localized	Ref	0.11	Ref	< 0.001
Regional	1.13 (0.97-1.32)	< 0.001	1.06 (0.87-1.28)	
Distant	12.51 (10.42-15.02)		3.24 (2.44-4.32)	
T stage				
T0-2	Ref	< 0.001	Ref	<0.001
T3-4	2.29 (2–2.63)		1.47 (1.23-1.77)	
N stage				
N0/x	Ref	0.063	–	–
N1	1.16 (0.99-1.35)		–	
Thyroidectomy	0.06 (0.05-0.07)	< 0.001	0.18 (0.14-0.22)	< 0.001
Tumor size	1.01 (1.01-1.02)	< 0.001	1.0 (1.01-1.01)	0.044
TMC	1.31 (1.02-1.68)	0.034	0.93 (0.68-1.26)	0.62
Median income				
<$45,000,	Ref	0.157	Ref	-
$45,000-$65,000	0.82 (0.62-1.08)	0.059	–	-
≥$65,000	0.73 (0.56-0.95)		–	
Lung metastasis	17.09 (13.15-22.21)	< 0.001	1.65 (1.16-2.33)	0.005
Bone metastasis	20.53 (14.83-28.43)	< 0.001	1.29 (1.16-2.33)	0.262
Liver metastasis	22.79 (10.21-50.88)	< 0.001	0.3 (0.12-0.74)	0.009
Brain metastasis	55.88 (28.94-107.9)	< 0.001	1.53 (0.72-3.23)	0.264

CI, confidence intervals; TMC, thyroid microcarcinoma; FDTC, female differentiated thyroid cancer; OS, overall survival.

had a poorer survival compared to single-organ metastases ($p < 0.001$). Interestingly, triple-organ metastases did not reduce the OS rate and CSS rate, as compared to double-organ metastases. This can be attributed to the rare incidence of synchronous DM, and majority of DM developed during the clinical follow-up. This is also partially because early identification of DM at the initial diagnosis is difficult, which may lead to an incomplete registration in the SEER database.

In the recent decades, different studies have attempted to identify the risk factors of DM in patients with DTC. A meta-analysis demonstrated male, older age, extrathyroidal extension, vascular invasion, and lymph node metastasis to be significant risk factors for DM (9). The study by Kwon et al. (27). reported radiomics analysis based on grayscale ultrasound to predict DM. Nevertheless, there have been no published studies for predicting DM in female patients with DTC. To our knowledge, this is the first study attempting to identify the risk factors and create a nomogram model for recognizing early DM in FDTCs. Our study showed that the age at diagnosis, FTC, N1 stage, T3–4 stage, tumor size, and thyroidectomy were significantly associated with DM. Therefore, this discrepancy should be taken into consideration when formulating treatment strategies. Lungs and bone are the most common sites for metastasis, which have been reported to be associated with a poor prognosis. Therefore, we investigated the risk factors for bone metastasis and lung metastasis in order to facilitate the

TABLE 6 Univariate and multivariate cox regression analyses of the prognostic factors of CSS in FDTC patients.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	OR (95% CI)	*P*
Age mean ± SD	1.14 (1.11-1.16)	< 0.001	1.09 (1.07-1.11)	< 0.001
<55 years	Ref	< 0.001	Ref	0.686
≥55 years	16.99 (10.43-27.66)		1.17 (0.54-2.54)	
Race		< 0.001		0.53
White	6.83 (2.53-18.42)	0.108	0.7 (0.23-2.15)	0.043
Black	2.82 (0.8-10.01)		3.88 (1.04-14.43)	
Other	Ref		Ref	
Pathological type				
Papillary with follicular variant	Ref	0.007	Ref	–
Papillary	1.72 (1.16-2.55)	< 0.001	1.01 (0.66-1.53)	0.979
Follicular	4.98 (2.9-8.54)		1.18 (0.61-2.3)	0.621
Summary stage		< 0.001		0.004
Localized	Ref	< 0.001	Ref	< 0.001
Regional	6.54 (4.03-10.61)		2.4 (1.32-4.36)	
Distant	184.63 (117.1-191.11)		13.05 (6.87-24.8)	
T stage		< 0.001		< 0.001
T0-2	Ref		Ref	
T3-4	12.55 (8.92-17.65)		3.46 (2.26-5.3)	
N stage		< 0.001		< 0.001
N0/x	Ref		Ref	
N1	4.56 (3.38-6.13)		1.93 (1.34-2.77)	
Thyroidectomy	0.03 (0.02-0.04)	< 0.001	0.2 (0.13-0.31)	< 0.001
Tumor size	1.01 (1.01-1.02)	< 0.001	1.01 (1.01-1.02)	0.057
TMC	2.18 (1.25-3.78)	0.006	2.18 (1.25-3.78)	0.868
Median income				
<$45,000,	Ref	0.996	Ref	–
$45,000-$65,000	1 (0.35-2.88)	0.825	–	–
≥$65,000	1.12 (0.41-3.09)		–	
Lung metastasis	80.28 (57.41-112.3)	< 0.001	1.97 (1.26-3.09)	0.003
Bone metastasis	79.79 (53.45-119.1)	< 0.001	2.22 (1.22-4.04)	0.009
Liver metastasis	86.99 (35.7-212.0)	< 0.001	0.37 (0.13-1.06)	0.065
Brain metastasis	178.2 (83.33-381.2)	< 0.001	0.59 (0.22-1.6)	0.301

CI, confidence intervals; TMC, thyroid microcarcinoma; FDTC, female differentiated thyroid cancer; CSS, cancer-specific survival.

early detection of metastatic lesions. We found that the age at diagnosis, FTC, T3–4 stage, and a larger tumor size were correlated with the development of bone or lung metastasis, which was consistent with previous research (28, 29). FDTCs with these risk variables should be monitored closely during follow-up. More importantly, to improve risk stratification and enable personalized medical decision-making, we developed and validated a predictive nomogram to identify high-risk patients with ease. Meanwhile, this predictive model showed excellent performance in assessing the risk for DM in FDTCs.

Although FDTC has a favorable prognosis, about 30% of the patients experience relapse and metastasis, which indicates the need for an accurate assessment of their prognosis (30). AGES, MACIS, AMES scoring system, and the TNM staging system have been frequently employed for the prognostic stratification of cancer patients (31). However, no scoring system could comprehensively and accurately assess the prognosis of patients of DTC, especially for FDTCs. In the present study, we identified that the age at diagnosis, Black, distant metastasis, T3–4 stage, thyroidectomy, and lung metastasis were independent prognostic factors for OS and CSS in FDTCs. Older age has been widely reported to be associated with a poor prognosis (32, 33). Advanced age was associated with an increased mortality rate. T3–4 stage was an independent prognostic factor whereas the tumor size was not; this might be because the T stage represents the extent of the primary

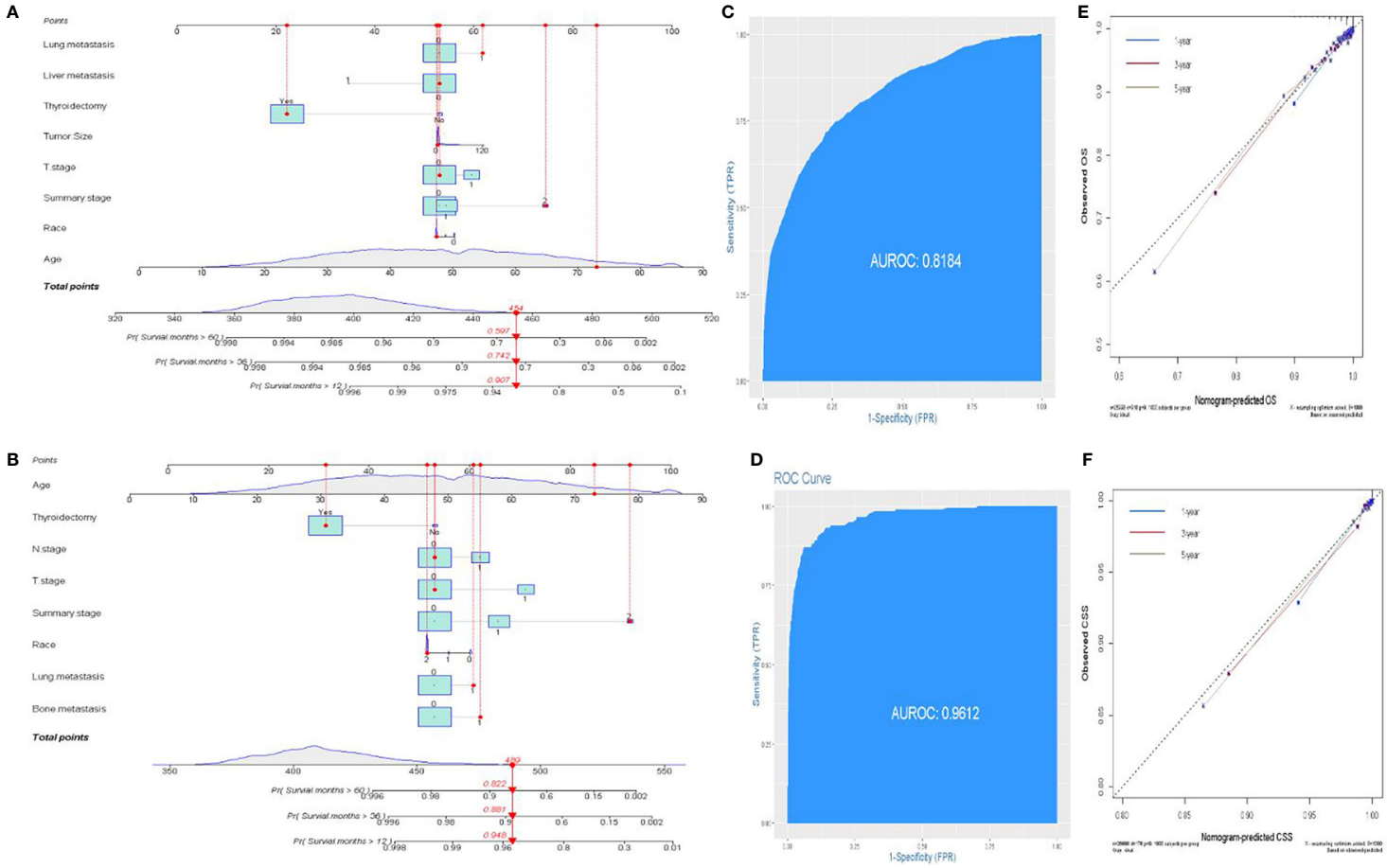

FIGURE 5
Establishment of prognostic nomograms. **(A, B)** Nomogram predicting the probability of OS and CSS. **(C, D)** The ROC curve of the nomogram with OS and CSS. **(E, F)** Calibration curves of the nomogram for the probability of OS and CSS.

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tumor, including the extrathyroidal extension and tumor size. Wen et al. (34)demonstrated that DTC patients that underwent thyroidectomy had improved survival rates, similar to the results from our study. Moreover, DM had a significant adverse impact on the mortality rate, wherein the presence of bone and lung metastasis significantly reduced the FDTC-specific survival rate ($P < 0.001$). Subsequently, we constructed a nomogram model in order to predict the survival rate more accurately. The current nomogram may enable clinicians to identify high-risk FDTCs with a poor prognosis, so that such patients could be provided follow-up surveillance and better therapeutic strategies.

However, the current study had a few limitations. In the first place, the SEER database had some inherent limitations, including the lack of availability of information regarding some of the critical prognostic factors, such as the extent of surgery, margin status, radioiodine dosage, and BRAF V600E. Prognostic factor analysis based on the SEER database was incomplete. Therefore, the nomogram provided a relative clinical guidance value for clinicians and needed to be further improved after adding these relevant data. Besides, we adopted the seventh edition of the TNM classification system to stage FDTCs. The latest edition raised the cutoff age from 45 to 55 years and removed the microscopic extra-thyroidal extension from the T3 disease; these differences affect the accuracy of the nomogram. Third, a total of 26,998 FDTCs were enrolled from 2010 to 2018, leading to some data missing, because the SEER database recorded the metastatic sites from 2010. Furthermore, the novel predictive model was only validated internally; external validation was still necessary. Considering the above limitations, further randomized controlled trials should be recommended to improve the current prognostic nomogram.

In summary, the pattern of distant metastatic organ involvement was associated with variability in CSS and OS in FTDCs. We successfully established and validated nomograms to predict DM, including lung metastasis and bone metastasis, as well as CSS and OS in individual FTDCs, based on a large study cohort. Although some limitations exist in this predictive model, our nomograms provide a personalized, convenient, and visual clinical tool for the assessment of prognosis and risk for DM, which may enable surgeons to conduct individualized survival evaluation and identify the risk for DM in FDTCs.

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 ur study was approved by the Ethics Committee of Xiangya Hospital of Central South University and conformed to the provisions of the Declaration of Helsinki. The patients/participants provided their written informed consent to participate in this study.

Author contributions

WW and ZY designed the study. WW and CS conducted the statistical analysis. WW and CS collected the clinical data. ZY wrote the whole paper. ZY and CS supervised and edited the paper. 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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.800639/full#supplementary-material

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Detection of thyroglobulin in fine-needle aspiration for diagnosis of metastatic lateral cervical lymph nodes in papillary thyroid carcinoma: A retrospective study

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Objective: We analysed the diagnostic performance of thyroglobulin in fine-needle aspiration (FNA-Tg) in the suspicious lateral cervical lymph nodes (CLNs) in patients with papillary thyroid cancer (PTC), proposed the best cutoff value and discussed the factors that may affect the diagnostic value of FNA-Tg.

Methods: In the present study, a retrospective analysis of 403 patients with PTC with 448 suspected lateral CLNs metastasis from October 2019 to May 2021 was performed. The cutoff value according to the receiver operating characteristic (ROC) curve was determined, and the Wilcoxon rank-sum test was used to evaluate the correlation between FNA-Tg and factors.

Results: According to the ROC curve, the cutoff value of FNA-Tg was 3.69 ng/ml (sensitivity, 92.48%; specificity, 75.00%). Patients who underwent total thyroidectomy were excluded. Compared with US and FNAC, the diagnostic performance of FNA-Tg was the greatest, especially for small CLNs (diameter ≤ 1 cm), cystic CLNs, and patients with Hashimoto's thyroiditis (HT). Moreover, FNA-Tg levels were correlated with the presence of HT ($p = 0.003$), the anti-thyroglobulin antibody (Tg-Ab) ($p < 0.001$), the ratio of metastatic lateral CLNs ($p = 0.004$) and Tg assay kits ($p < 0.001$).

Conclusions: FNA-Tg measurement is sensitive enough for diagnosing lateral CLN metastases from PTC, but its diagnostic value is compromised by a number of factors.

KEYWORDS

papillary thyroid carcinoma, thyroglobulin, fine need aspiration, lymph nodes, metastasis

Introduction

Papillary thyroid carcinoma (PTC) accounts for 90% of thyroid cancer diagnoses (1) and has the best prognosis among them. However, metastasis to the cervical lymph nodes (CLNs) occurs in 20–50% of cases, resulting in recurrence (2), and accurate CLN examination is critical to treatment strategy and patient outcome. Ultrasound (US) is widely available, convenient and economical with a high degree of sensitivity (3) but still fails to recognize CLNs of diameter less than 1 cm (4). In addition, the diagnostic value of US is affected by the presence of lymphocytes, variable necrosis and poor epithelial cellularity (5). US-guided fine-needle aspiration of cytology (FNAC) has demonstrated high specificity in detecting solid CLNs. Previous studies have assigned FNAC sensitivity rates of 66–95% and specificity of 40–100% (6–9). However, FNAC detection of CLNs leads to the identification of cystic components, false-negative results and non-diagnostic interpretations due to the lack of epithelial tissue (10, 11). Pacini et al. first proposed the measurement of thyroglobulin in fine-needle aspiration (FNA-Tg) washout fluids in 1992 (12), giving a sensitivity and specificity of 100% and hugely advancing the assessment of CLNs. Both the American Thyroid Association (ATA) and the European Thyroid Association (ETA) guidelines strongly recommend the use of FNA-Tg to evaluate CLNs prior to surgery, especially for patients with suspected recurrence after total thyroidectomy (13, 14). However, no uniform standard for the cutoff value of FNA-Tg for diagnosis of CLN metastasis in PTC exists. The presence or absence of thyroid glands (15), levels of serum-Tg (s-Tg) (16) and levels of anti-thyroglobulin antibody (Tg-Ab) may all affect the diagnostic performance of FNA-Tg (17). Thus, the utility of FNA-Tg, remains controversial.

The aim of the current study was to identify the optimal FNA-Tg cutoff for diagnosis of lateral CLN metastasis in PTC patients. Sensitivity and specificity of US, FNAC and FNA-Tg were examined to compare diagnostic performances. Factors affecting the diagnostic value of FNA-Tg were analyzed to give a reliable basis for clinical diagnosis and application.

Materials and methods

Experimental subjects

A retrospective analysis of 448 lateral CLNs from 403 patients who underwent unilateral or bilateral therapeutic lateral neck dissection with or without thyroidectomy due to recurrence/metastases of PTC between October 2019 and May 2021 at Tianjin Medical University Cancer Institute and Hospital was conducted. Eleven patients underwent unilateral lateral CLN dissection without thyroidectomy due to suspicious recurrence in the CLNs only and had previously received unilateral thyroidectomy. Patients with histories of total thyroidectomy surgery were excluded due to the small sample size and difficulty of obtaining a significant result. Final CLN diagnoses were based on postoperative histopathology.

Ethical approval was granted by Tianjin Cancer Hospital Ethics Committee. No patient had a contraindication to puncture and written informed consent was obtained from all participants prior to the operation.

FNAC and FNA-Tg

All patients underwent US neck examination and suspected malignant lymph nodes were identified according to the following characteristics: calcification, loss of the hilar, focal or diffuse hyperechoic changes, cystic change round shape and abnormal blood flow signal. Suspected malignant lateral CLNs were aspirated 3-5 times each by experienced US experts using a 10 ml syringe carrying a 22-gauge needle under high-frequency US real-time localization. Aspirated tissue from each CLN was smeared onto two to three slides, fixed with 95% ethanol and stained with Papanicolaou staining for cytological diagnosis by an experienced pathologist.

Remaining aspirates on the puncture needle were washed with 1 ml of 0.9% normal saline, collected and tested for Tg concentration over time by chemiluminescence immunoassay (ECLIA), using a commercially available kit (Elecsys Tg II). The measuring range was 0.04–500 ng/ml.

Statistics

Statistical Package for Social Science (SPSS) professional software version 21.0 was used. Taking histopathological results as the gold standard, ROC curves of FNA-TG were drawn and the area under the ROC curve (AUC) calculated. Sensitivity, specificity, positive predictive value (PPV), false predictive value (NPV) and accuracy were calculated to compare the diagnostic value of methods, according to the following formulae: Sensitivity=True positive/(True positive+ False negative); Specificity=True false/(True negative+ False positive); PPV=True positive/(True positive+ False positive); NPV=Ture false/(True negative+ False negative); Accuracy= (True negative+ True positive)/Total. A Wilcoxon rank-sum test was used to evaluate the correlation between FNA-Tg and s-Tg, TPO-Ab and Tg-Ab. A p-value of <0.05 was regarded as statistically significant.

Results

Clinical characteristics and lateral CLNs

A total of 403 patients (129 males and 274 females) with 448 lateral CLNs of median size 1.2 cm (range: 0.4–4.9 cm) were recruited over a 20-month period. Patient mean age was 41.37 years (range: 8–75 years). A total of 398 lateral CLNs were suspected to be malignant from US results and the remaining 50 considered inflammatory. 338 (81.06%) CLNs were suspected of being malignant after FNAC and 38 were benign (9.11%). 72 (16.07%) CLNs could not be accurately characterized due to insufficient samples or inefficient data. The median size of CLNs undiagnosed by FNAC was 1.1 cm and FNA-Tg analysis gave an accuracy of 83.3%, indicating the utility of this measurement in overcoming the drawbacks of FNAC. Final histopathological diagnosis identified 412 (91.96%) of CLNs as metastatic and 36 (8.04%) as benign.

Differences between metastatic and benign lateral CLNs

Post-surgery histopathological analysis allowed the CLNs to be divided into metastatic and benign groups. Mean patient age was younger in the metastatic group (40.9 ± 12.7 years) than in the benign (46.5 ± 12.5 years; p = 0.013). Median CLN size in the metastatic group (1.3 cm) was higher than in the benign group (1.0 cm; p = 0.004). Percentage metastatic lateral CLNs was significantly higher in men (94.59%) than in women (90.67%; p = 0.015) and metastatic CLNs had higher median levels of FNA-Tg (p < 0.001; Figure 1) and s-Tg (p = 0.03) than benign CLNs. Other indicators were not significantly different between the metastatic and benign groups (Table 1).

Cutoff values of FNA-Tg for malignant lateral CLNs

The most appropriate cutoff value for diagnosing metastatic lateral CLNs in PTC was estimated from the ROC curve to be 3.69 ng/ml with an AUC of 0.839 (Figure 2) and sensitivity, specificity and accuracy of 92.48%, 75.00% and 91.07%, respectively. A total of 412 CLNs were histopathologically defined as malignant and 381 (92.48%) had levels of FNA-Tg in excess of 3.69 ng/ml. However, FNA-Tg analysis of the 48 benign CLNs showed only 27 (56.25%) to have low levels. Evaluation of the diagnostic performance of multiple FNA-Tg levels (0.04, 0.1, 0.5, 3.69, 5, 10, 20 and 50) showed that FNA-Tg

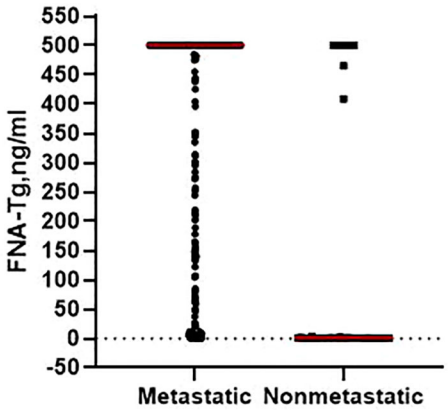

FIGURE 1
The level of FNA-Tg in metastatic and non-metastatic lateral CLNs.

TABLE 1 Difference between metastasis and benign of lateral CLNs.

	Metastasis (412)	Benign (36)	P value
Age, years	40.9 ± 12.7	46.5 ± 12.5	0.013
Sex			0.015
male	140	8	
female	272	28	
Size of tumor, cm, (median, range)	1.1 (0.1-7.0)	0.9 (0.1-2.5)	0.374
Size of CLNs, cm, (median, range)	1.3 (0.4-4.9)	1.0 (0.4-2.7)	0.004
ETE (presence:absence)	49:325 (15.08%)	5:30 (16.67%)	0.843
HT(presence:absence)	114:260 (43.85%)	10:17 (58.82%)	0.477
s-Tg, ng/ml, (median, range)	24.1 (0.04-510)	15.9 (0.14-90)	0.030
TSH, mIU/L, (median, range)	2.1 (0.01-49.6)	2.2 (0.03-6.4)	0.674
Tg-Ab, IU/ml, (median, range)	13.1 (0.92-4000)	14.0 (4.79-4000)	0.178
TPO-Ab, IU/ml, (median, range)	9.0 (0.25-1022)	9.0 (9-375)	0.058
FNA-Tg, ng/ml, (median, range)	500.0 (0.04-500)	0.45 (0.04-500)	<0.001

CLNs, Cervical Lymph Nodes; ETE, Extrathyroidal extension; HT, Hashimoto's thyroiditis; s-Tg, Serum thyroglobulin; FNA-Tg, The measurement of thyroglobulin on fine-needle aspiration; Tg-Ab, anti-thyroglobulin antibody; TPO-Ab, anti-peroxidase antibody.

sensitivity decreased but specificity increased with an increase in the diagnostic threshold (Table 2).

The presence of thyroid glands may cause false positive results and the ratio of FNA-Tg and s-Tg were used as the cutoff value to eliminate the interference of s-Tg. FNA-Tg/s-Tg >1 gave the highest specificity but lower sensitivity (Table 2). We found a higher cutoff value for FNA-Tg (3.69 ng/ml) than that previously reported in the literature (>1 ng/ml). A total of 15 lymph nodes with FNA-Tg values between 1-3.69 ng/ml were found during the current study (Table 3). A comparison of the 1 ng/ml and 3.69 ng/ml cutoff values revealed improved specificity at the expense of lower sensitivity. In summary, we find a cutoff value of 3.69 ng/ml FNA-Tg to be the most appropriate because of its relatively high sensitivity and specificity.

Tg assay kits were changed during the current study with Beckman Access Tg 2 assay (functional sensitivity: 0.1–482 ng/ml) being used between August 2018 and September 2019 and Elecsys Tg 2 assay (functional sensitivity: 0.04–500 ng/ml) between October 2019 and May 2021. Analysis of data collected between August 2018 and September 2019 indicated slightly different FNA-Tg cutoff values derived from the use of the two kits: 3.15 ng/ml vs. 3.69 ng/ml (Figures 3, 4). Median FNA-Tg level was lower when measured by the Beckman Access Tg 2 assay (482 ng/ml) than by the Elecsys Tg 2 assay (500 ng/ml; $p < 0.001$).

Comparison of diagnostic value of US, FNAC and FNA-Tg

Characteristics of suspicious CLNs from US scans included cystic change, calcification or rounded rather than elongated shape, abnormal blood flow, focal or diffuse hyperechoic changes, absence of hilum and irregular margins (18). Sensitivity, specificity, PPV and NPV of US were 90.39%, 30.56%, 93.62% and 22.00%, respectively. PTC-like nuclear features in the follicular cells of LNs, such as nuclear enlargement and overlapping, irregular membrane, grooves and pseudoinclusion bodies with obvious nuclear clearance, led to identification of PTC metastasis by FNAC (19). FNAC showed a sensitivity of 92.39% and a specificity of 52.38% across 448 lateral CLNs. Combining US, FNAC and FNA-Tg gave the highest sensitivity (98.50%) and accuracy (91.53%) but the lowest specificity (13.89%; Table 4).

For 72 CLNs that could not be diagnosed by FNAC, the accuracy of FNA-Tg was up to 83.3%. FNAC specificity and PPV were up to 100% for 55 cystic CLNs identified by US but accuracy (90.38%) and sensitivity (90.00%) were lower than

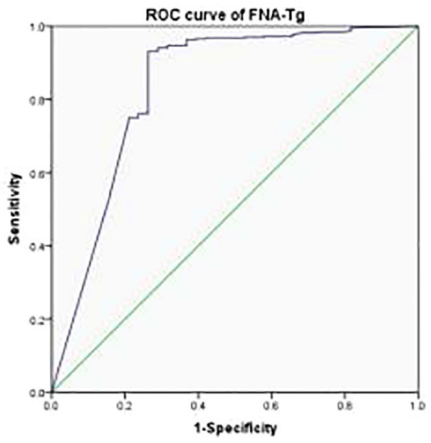

FIGURE 2
The ROC curve of FNA-Tg according to definite status of the 448 lateral CLNs.

TABLE 2 Diagnostic value in different cutoff values of FNA-Tg.

Different cutoff values, ng/ml	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
FNA-Tg (0.04)	99.03	25.00	93.79	69.23	93.08
FNA-Tg (0.1)	97.09	30.56	94.12	47.83	91.74
FNA-Tg (0.5)	95.87	52.78	95.87	52.78	92.41
FNA-Tg (1)	95.39	66.67	97.04	55.81	93.08
FNA-Tg (3.69, ROC)	92.48	75.00	97.69	46.55	91.07
FNA-Tg (5)	91.50	75.00	97.67	43.55	90.18
FNA-Tg (10)	90.29	75.00	97.64	40.30	89.06
FNA-Tg (20)	88.35	75.00	97.59	36.00	87.28
FNA-Tg (50)	87.14	75.00	97.55	38.57	86.16
FNA-Tg/s-Tg>1	85.47	77.78	95.00	34.15	84.82

FNA-Tg, The measurement of thyroglobulin on the fine-needle aspiration; PPV, Positive predictive value; NPV, Negative predictive value.

that of FNA-Tg (94.55% and 98.08%). The accuracy of US (85.87%) and FNAC (88.31%) for the 112 small lymph nodes with diameters less than or equal to 1 cm indicated by US was lower than that of FNA-Tg (92.47%; Table 5). The diagnostic value of FNA-Tg was higher for 124 lateral CLNs with HT than that of FNAC and US, regardless of sensitivity, specificity, PPV, NPV or accuracy.

Factors influencing FNA-Tg diagnostic efficiency

Level of Tg-Ab ($p < 0.001$), presence of HT ($p = 0.003$), lymph node ratio (LNR) ($p < 0.001$) and Tg assay kits ($p < 0.001$) were all found to be related to the level of FNA-Tg (Table 6).

Samples were divided into Tg-Ab positive, Tg-Ab negative and Hashimoto's thyroiditis (HT) positive and HT negative groups, according to the level of antibodies and the HT status. Samples were defined as Tg-Ab positive if levels were greater than or equal to 115 IU/ml. Median Tg-Ab levels were similar in the positive and negative groups but the interquartile range (IQR) was higher in the former (500–6.675) than in the latter (500–441), indicating more concentrated FNA-Tg at 500 ng/ml in patients with negative Tg-Ab. ROC curves demonstrated a lower FNA-Tg cutoff value of in the Tg-Ab-positive group (1.525 ng/ml) than in the negative group (4.165 ng/ml). Similarly, equivalent median FNA-Tg levels were found in the HT-positive and negative groups but the IQR was significantly different (HT positive: 500–104.5 and HT negative: 500–470, $p = 0.003$). The degree of FNA-Tg dispersion was small in the HT-negative group and the cutoff value in patients with HT (1.525 ng/ml) was lower than in patients without HT (4.165 ng/ml). The LNR was determined by dividing the number of invaded CLNs by the total number of removed CLNs and was found to be related to FNA-Tg level ($p < 0.001$). Above a cutoff value equal to the median level of LNR (0.16), FNA-Tg was more concentrated at 500 ng/ml.

None of s-Tg level ($p = 0.104$), CLN characteristics (cystic or solid, $p = 0.54$) or CLN size ($p = 0.071$) affected FNA-Tg level. Postoperative histopathological results divided PTC samples into classic, follicular, Warthin tumor-like and diffuse sclerosing types. Levels of FNA-Tg did not vary according to these different subtypes ($p = 0.885$).

Discussion

Recent evidence has accumulated to suggest that the diagnostic value of FNA-Tg for CLN metastasis was significantly better than that of US and FNAC. A recent meta-analysis of 2257 patients with 2786 suspicious CLNs gave a

TABLE 3 Cases of CLNs with FNA-Tg between 1-3.69 ng/ml.

Number		15
FNAC	Positive	8
	Negative	5
	Inefficient	2
Size of CLNs, cm, (median, range)		1.3 (0.8-2.6)
Pathology	Metastasis	12
	Benign	3

CLNs, Cervical Lymph Nodes; FNAC, Fine needle-aspiration cytology.

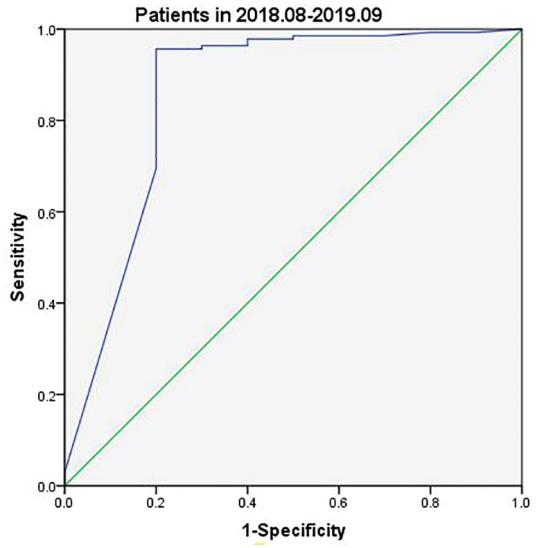

FIGURE 3
The ROC curves of FNA-Tg in different assay kits of Tg (Patients in 2018.08-2019.09).

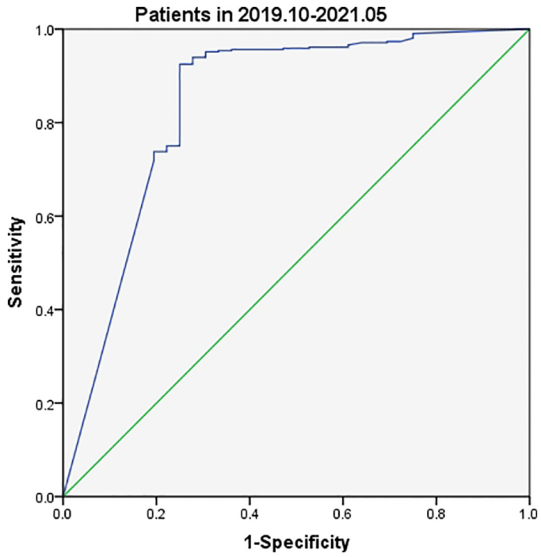

FIGURE 4
The ROC curves of FNA-Tg in different assay kits of Tg (Patients in 2019.10-2021.06).

hierarchy of diagnostic value as follows: a combination of FNAC and FNA-Tg > FNA-Tg > FNAC (20). The current research affirmed the clinical value of FNA-Tg and achievement of the best diagnostic performance by FNA-Tg, FNAC and US. Se Jeong Jeon et al. concluded that FNA-Tg gave superior diagnosis of metastasis in small CLNs (≤5 mm in minimal diameter) (21). Such small nodes are relatively difficult to aspirate and sample by FNAC, complicating the interpretation of cytology results (5). The current study demonstrated a diagnostic accuracy of FNA-Tg of 92.47% for small CLNs (diameter < 1 cm), higher than that of US (85.87%) and FNAC (88.37%). Metastatic CLNs (median, 1.3cm) were found to be bigger than benign CLNs (median, 1.0 cm) and had higher FNA-Tg levels (median: 500 ng/ml vs 0.45 ng/ml) but CLN size was not directly related to FNA-Tg level. We consider FNA-Tg, to be a qualitative rather than quantitative detection indicator. Cystic changes in CLNs were seen as malignant signs by US but presented a challenge for FNAC because of scant cellularity (22). Analysis of the diagnostic value of FNAC and FNA-Tg for cystic CLNs gave higher sensitivity (98.08%) but lower specificity (33.33%) for FNA-Tg compared with FNAC (90.00% and 100%). We strongly recommend the combination of FNA-Tg and FNAC for diagnosis and analysis of cystic CLNs. HT has been frequently associated with PTC occurrence and the interference of large numbers of lymphocytes complicates judgment of CLN characteristics by US and FNAC. Coexistence of PTC and HT among the current cohort was 27.68% (124/448). We found a superior diagnostic performance of FNA-Tg over FNAC for HT patients and a combination of the two methods produce the best results of all.

From the first proposal of FNA-Tg utility in 1992 until the present, no standard for the diagnostic threshold of FNA-Tg has been agreed. A meta-analysis of 24 studies and 2865 LNs showed a range of FNA-Tg cutoff values from 0.2 ng/ml to 50 ng/ml in patients with or without thyroid glands (23) and a cutoff of 1 ng/ml was frequently selected (24, 25). Variations in patient cohorts, different types of washout fluids, different Tg assay kits and the potential impact of some clinical biochemical indicators may all contribute to producing the wide range of values. Central CLNs are subject to interference by thyroid glands and the trachea (26, 27), leading to false-positive results, and we chose to include only lateral CLNs in the current study. The cutoff value of 3.69 ng/ml derived from ROC curve (AUC=0.839) analysis of the present cohort is in agreement with most current research (16, 28) but is lower than some recent values (12, 29). Some studies have proposed that functional assay sensitivity, lower in the early stages, affects cutoff values, explaining the progressive decrease in proposed cutoff values (30). Similar findings were supported by the current study due to the impact of variable Tg assay kits.

Baskin (2004) proposed that serum Tg-Ab had no effect on diagnostic performance because intracellular Tg was not exposed to circulating Tg-Ab (31). In addition, the concentration of FNA-Tg in metastatic CLNs was suggested to be much higher than that of Tg-Ab, leading to saturation of Tg-Ab binding sites and overcoming the interference (19). However, the study of 207 patients with 263 CLNs by Min Ji Jeon et al. demonstrated lower FNA-Tg levels in CLNs from serum Tg-Ab-positive patients than in those from Tg-Ab-negative patients ($p = 0.001$) (17). We confirm the above findings and recommend that a lower cutoff value of FNA-Tg should be used for patients

TABLE 4 Comparison of diagnostic value between US, FNAC and FNA-Tg.

Diagnostic methods	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	AUC(95%CI)
FNA-Tg(3.69, ROC)	92.48	75.00	97.69	46.55	91.07	0.839 (0.754,0.925)
FNAC	92.39	52.38	97.04	28.95	90.16	0.540 (0.414,0.665)
US	90.39	30.56	93.62	22.00	85.52	0.616 (0.522,0.710)
FNAC+US	97.24	20.00	95.09	31.25	92.67	0.787 (0.688,0885)
FNAC+FNA-Tg(3.69)	94.34	60.71	97.09	43.59	92.07	0.815 (0.712,0.918)
US+FNA-Tg(3.69)	98.04	27.78	93.90	55.56	92.34	0.835 (0.753.0.918)
FNAC+US+FNA-Tg(3.69)	98.50	13.89	92.72	45.45	91.53	0.823 (0.725,0.922)

PPV, Positive predictive value; NPV, Negative predictive value; AUC, Area under the curve; US, Ultrasound; FNAC, Fine needle-aspiration cytology; FNA-Tg, The measurement of thyroglobulin on fine-needle aspiration.

with a high level of Tg-Ab. We speculated that the presence of Tg-Ab in CLNs from patients with high serum Tg-Ab may bind to Tg within the CLN, resulting in decreased detection of FNA-Tg. We aim to measure Tg-Ab within CLN tissue in order to confirm or refute our suspicions.

HT may interfere with FNA-Tg levels. The condition is often accompanied by increased Tg-Ab due to a complex autoimmune and inflammatory response which destroys normal follicular cells in the thyroid gland and precipitates the occurrence of tumors (32). Interestingly, patients with higher levels of Tg-Ab or who were positive for HT had similar FNA-Tg cutoff values (1.525 ng/ml) and *vice versa*. The diagnostic performance of FNA-Tg was profoundly affected by the presence of HT. Lower cutoff values of FNA-Tg are advised for HT patients and the combination of FNAC and FNA-Tg recommended for diagnosis of metastatic CLNs. In view of these findings, we recommend that all patients prescribed CLN FNA-Tg measurements also have bloodwork for serum Tg-Ab levels and TPO-Ab to identify HT.

s-Tg has been found to cause false positive FNA-Tg results in many previous studies (9, 33). However, the current study found that s-Tg levels were not related to FNA-Tg levels (p=0.104),in agreement with Anne-Laure Borel et al. (34). Contamination by s-Tg during puncture is likely to be negligible due to extremely high FNA-Tg concentrations (usually higher than the maximum value of the detection range).

LNR was related to FNA-Tg level but when FNA-Tg was very high in the lower internal jugular chain (e.g., 500 ng/ml), CLNs were shown by histopathological analysis to occur in areas other than the lower internal jugular chain. Thus, FNA-Tg measurement does not aid the determination of the extent and area of metastasis. We recommend that the surgeons base treatment decisions on intraoperative findings in combination with preoperative evaluations. FNA-Tg is affected by diverse factors, all of which require consideration by treating physicians.

We acknowledge some limitations to the current study. Patients with histories of total thyroidectomy surgery (only 39) were excluded due to the paucity of data. However, thyroid glands may release Tg, causing contamination during puncture and false positive results. This may result a higher cutoff value in the current study compared with others and we aim to collect more data from patients who have undergone total thyroidectomy to improve cutoff value accuracy. Many patients with an extremely low level of FNA-Tg (such as 0.04 ng/ml) did not have surgical treatment. We were unable to judge whether the CLNs were benign or malignant in these patients. In addition, it has been suggested that FNA causes a surge in s-Tg, illustrating the importance of measuring s-Tg before FNA. No clear chronological order was observed for the examination of patients in the current study and future research should be avoid interference by these factors. Moreover, many patients showed a lower level of FNA-Tg after puncture of the lower internal jugular chain of the neck and CLNs from this area only were resected. Histopathology confirmed the absence of metastasis in this area but whether metastases were present in other areas was unknown. In addition, the current study population was relatively young (mean age: 41.37), with small tumor size (median: 1.1cm) and a high percentage of males (33.04%). This may lead to generalizability bias, as young PTC patients tend to have more aggressive disease with higher rates of regional metastasis and extra-thyroid extension. Therefore, this inevitable bias may lead to different results from other studies. Finally, all patients had more than one suspected malignant CLN

TABLE 5 Different methods to diagnose small CLNs.

Methods	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
FNAC	88.31	50.00	91.89	40.00	83.15
US	85.87	42.86	86.81	40.91	77.78
FNA-Tg	92.47	76.19	94.51	69.57	89.47

PPV, Positive predictive value; NPV, Negative predictive value; US, Ultrasound; FNAC, Fine needle-aspiration cytology; FNA-Tg, The measurement of thyroglobulin on fine-needle aspiration.

TABLE 6 Factors may influence the level of FNA-Tg.

Factors	p Value
Year	0.23
Sex	0.062
s-Tg	0.104
TSH	0.368
Tg-Ab	<0.001
TPO-Ab	0.112
CT	0.099
Size of CLNs	0.071
Characteristics of CLNs (cystic or solid)	0.54
LNR	<0.001
ETE	0.768
Subtypes of PTC	0.885
BRAF	0.365
TNM	0.549
HT	0.003
Types of Tg assay kits	<0.001

CLNs, Cervical Lymph Nodes; ETE, Extrathyroidal extension; HT, Hashimoto's thyroiditis; s-Tg, Serum thyroglobulin; FNA-Tg, The measurement of thyroglobulin on fine-needle aspiration; Tg-Ab, anti-thyroglobulin antibody; TPO-Ab, anti-peroxidase antibody; CT, calcitonin; LNR, the lymph node ratio.

but only one with obvious signs of metastasis was selected for puncture. Punctured CLNs could not be identified during surgeries but resection range ensured that every suspicious CLN was removed. Had labelling of CLNs been possible during surgery, more reliable results may have been obtained.

Conclusions

US guided FNA-Tg was an efficient preoperative diagnostic procedure, showing good performance for PTC patients with suspicious lateral CLNs. The technique depends on the availability of experienced cytopathologists, especially for small or cystic CLNs. Optimal diagnostic value was achieved by a combination of US, FNAC and FNA-Tg. Ideal cut-off values for FNA-Tg require further validation. The presence of HT, high Tg-Ab levels and LNR all affected the level and diagnostic value of FNA-Tg. Different Tg assay kits may produce different cutoff values because of the differences in range and functional sensitivity. The clinical value of FNA-Tg continues to be acknowledged but should only be used as an auxiliary diagnostic method and does not determine the range of surgical removal of CLNs.

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 study involving human participants were reviewed and approved by Tianjin Cancer Hospital Ethics Committee. All patients had no contraindications to puncture and signed informed consent before the operation. The patients provided written informed consent to participate in this study.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by YXW, YSD, HL, KY, JL, QCL, MQZ, BBY, YW, CJ, YSW, and XDW. The first draft of the manuscript was written by XDW, YSD, and HL. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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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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Nomogram for preoperative estimation risk of cervical lymph node metastasis in medullary thyroid carcinoma

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Objectives: Cervical lymph node metastasis (CLNM) is common in medullary thyroid carcinoma (MTC), but how to manage cervical lymph node involvement of clinically negative MTC is still controversial. This study evaluated the preoperative features and developed an ultrasound (US)-based nomogram to preoperatively predict the CLNM of MTC.

Materials and methods: A total of 74 patients with histologically confirmed MTC were included in this retrospective study and assigned to the CLNM-positive group and CLNM-negative group based on the pathology. The associations between CLNM and preoperative clinical and sonographic characteristics (size, location, solid component, shape, margin, echogenicity, calcification, and extracapsular invasion of the tumor) were evaluated by the use of univariable and multivariable logistic regression analysis. A nomogram to predict the risk of the CLNM of MTC was built and assessed in terms of discrimination, calibration, and clinical usefulness.

Results: The nomogram was based on three factors (tumor margin, US-reported suspicious lymph node, and extracapsular invasion US features) and exhibited good discrimination with an area under the curve (AUC) of 0.919 (95% CI, 0.856–0.932). The calibration curves of the nomogram displayed a good agreement between the probability as predicted by the nomogram and the actual CLNM incidence.

Conclusions: We constructed and validated a US-based nomogram to predict the risk of CLNM in MTC patients, which can be easily evaluated before surgery. This model is helpful for clinical decision-making.

KEYWORDS

sporadic medullary thyroid carcinoma, cervical lymph node metastasis, ultrasonography, prevention lymph node dissection, nomogram

Introduction

Medullary thyroid carcinoma (MTC) is a rare disease, amounting to about 2%–5% of all thyroid malignancies globally (1–3). It is characterized by a relatively slow tumor growth but early lymph node (LN) metastasis (LNM), which appeared in 40.0%~66.7% of patients when initially diagnosed, with the predominance of cervical lymph node metastasis (CLNM) (4). In sporadic MTC, the proportion of central and lateral neck LNMs related with T1 tumors is 14% and 11%, respectively; the proportion is 86% and 93%, respectively, with pT4 tumors (5). Palpable thyroid nodules are associated with a 70% rate of CLNM and a 10% rate of distant metastasis (6).

Total thyroidectomy (TT) and dissection of cervical LNs are standard approaches for MTC in light of preoperative serum calcitonin (Ctn) levels, ultrasound (US)-reported suspicious LN findings, and intraoperative or fine-needle aspiration (FNA)-proven CLNM (1, 7, 8). However, there is a disputed topic in performing lateral neck dissection (LND) in patients without evidence of CLNM on preoperative US. More aggressive prophylactic LND may raise the risk of severe nerve injury and hypoparathyroidism without obvious survival benefits (9).

Preoperative imaging plays an important role in the diagnosis and staging of MTC. Although several studies have reported high-risk factors relative to clinical and US features predictive of CLNM in MTC (10–12), the results have been conflicting. In addition, some of the risk factors identified, such as TNM stage, are only available after the operation (13, 14) and cannot help in determining the extent of thyroid surgery. Seeking a suitable and noninvasive approach for evaluating CLNM is therefore of great importance.

For this reason, we constructed and validated a nomogram to predict CLNM based on clinical and US features, a precise, simple, and objective scoring system for preoperatively quantifying the probability of CLNM.

Materials and methods

This retrospective study was approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine, and the requirement for informed consent was waived. We retrospectively evaluated the preoperative clinical and US features for predicting CLNM in patients with pathologically confirmed MTC surgery in our hospital between January 2011 and January 2021. The inclusion criteria of the nodules were as follows: 1) the thyroid US examination was carried in our department within 2 weeks before surgery; 2) patients who underwent initial thyroid surgery with central neck dissection (CND) or modified radical neck dissection during the initial surgery and were pathologically confirmed as MTC; 3) no other treatment before surgery. The exclusion criteria were as follows: 1) patients with distant metastases or accompanied by other malignancies; 2) incomplete or unqualified ultrasound images; 3) patients are treated by chemotherapy or radiotherapy before surgery; 4) for MTC patients without LND, regularly followed up for less than 5 years. According to the above criteria, 74 patients (31 men and 43 women, mean age 43.2 ± 10.9 years) were enrolled. Figure 1 showed the flowchart of the patients enrolled in our study. All patients underwent TT with bilateral CND, 54 (72.9%) patients underwent modified radical neck dissection during the initial surgery, and the remaining 20 MTC patients without LND were regularly followed up for at least 5 years, with a median of 6.7 years [interquartile range (IQR) 5.0–9.3 years]. Among the study subjects, 33 (44.6%)

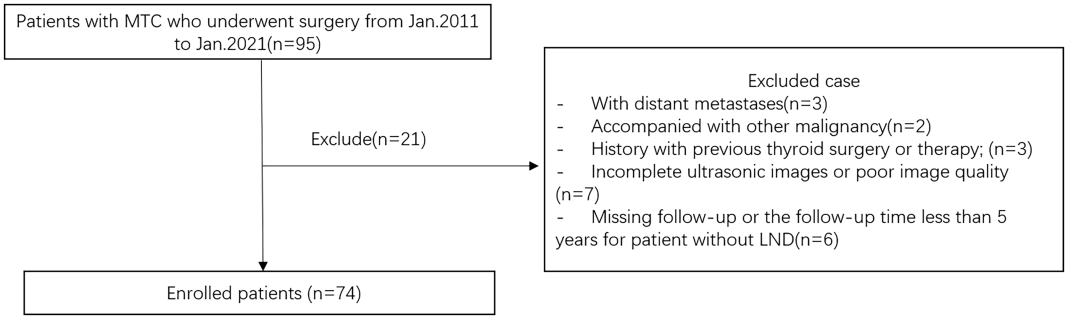

FIGURE 1
Flowchart of the patients enrolled in our study. MTC, medullary thyroid carcinoma; LND, lymph node dissection.

patients were placed in the LNM-negative group and 41 (55.4%) patients were placed in the CLNM-positive group according to the pathology results. All cases were regularly followed.

Requirements for ultrasound images

The US images obtained from the picture archiving and communication system (PACS) workstations should contain the following requirements: 1) including as many malignant characteristics of the tumor as possible in the longitudinal and transverse planes; 2) clearly exhibiting the extent of contact with the adjacent capsule; 3) US findings, including the size, location, solid component, shape, aspect ratio (A/T), margin, echogenicity, echotexture, peripheral halo sign, extracapsular invasion, calcifications, vascularization, suspicious metastatic LNs, Contrast-Enhanced Ultrasound (CEUS) patterns, and elastic scores were independently evaluated, as previously reported (15) by two sonographers with more than 10 years of experience in thyroid US and were blinded to the clinical outcome. In patients with multifocal MTCs, the dimensions of the largest MTC lesion were used. Tumor size was classified according to the maximum diameter. Tumor shape was classified as either oval and round or irregular. The A/T was classified as <1 or ≥1. The internal echogenicity was categorized as hyperechogenicity, isoechogenicity, hypoechogenicity, or marked hypoechogenicity compared with the adjacent cervical muscle. Margins were classified as smooth, lobulated, microlobulated, and spiculated. Calcifications, if present, were classified as microcalcifications, macrocalcifications, or mixed calcifications. Tumor vascularity was assessed by color Doppler flow imaging (CDFI) and classified according to the Adler criteria [16] from 0 to 3. The presence of extracapsular invasion (defined as that the tumor in contact with the adjacent capsule, so that the continuity of the capsule line was interrupted or covered by lesions). In the preoperative assessment of CLNMs, a suspicious LN exhibited the following features: internal microcalcification, loss of hilar echogenicity, exhibition of peripheral flow, and cystic or hyperechoic change. Elastography images were classified according to the scores by Hong et al. (15) into a score of 1–6. In this study, a malignant lesion showing Hong scores of 4–6 was considered as "hard" malignancy and the remaining scores as "soft." The CEUS patterns of the thyroid nodules were classified as hyperenhancement and hypoenhancement.

The clinical characteristics, including gender, age, preoperative Ctn, and carcinoembryonic antigen (CEA), were collected from the electronic medical records. In line with a previous research (16), the thresholds set for Ctn and CEA were as follows: Ctn ≥8.4 pg/ml (men), Ctn ≥5.0 pg/ml (women), and CEA ≥5 ng/ml.

Statistical analysis

The statistical analyses were performed through SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Continuous data are presented as mean ± standard deviation (SD) and compared by using Student's t test. Categorical data were compared using the Pearson chi-square test and Fisher's exact test, and the receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff points for tumor size in US. Variables that proved to be statistically significant on univariate analysis were included in the multivariate logistic regression to evaluate risk factors for CLNM in MTC patients.

A nomogram was built according to the results of the binary logistic regression to assess the risk of CLNM preoperatively by using R software (version 3.5.1). The performance of the nomogram was further evaluated by discrimination and calibration. ROC was employed to test the discriminative power and consensus of our formulated CLNM prediction model. The calibration of the prediction model was carried out by plotting the CLNM-positive predicted probability of the nomogram against the observed probability. In addition, the nomogram was subjected to 1000 bootstrap resamples for internal validation to assess the accuracy of the constructed logistic regression model.

Results

Demographic and clinicopathologic characteristics

All 74 MTC patients, including 31 men and 43 women, were confirmed by surgery and pathology. Among the 74 eligible patients, 41 patients had CLNM [10 patients with central compartment lymph node metastasis (CCLNM), four patients with lateral compartment lymph node metastasis (LCLNM), and 27 patients with both compartment LNM]; the remaining 33 patients showed negative CLNM. Sixty-four patients had measurements of their serum Ctn levels and 62 had measurements of their CEA. In the ROC analysis, the optimal cutoff tumor size in US between the two groups was 2.19 cm [area under the curve (AUC), 0.579; 95% confidence interval (CI), 0.449–0.709]. The baseline characteristics of the patients in each group are presented in Table 1. The level of preoperative serum Ctn was significantly higher in the CLNM-positive group than that in the CLNM-negative group ($p = 0.001$); no significant differences were found between the two groups in terms of age, gender, tumor location, or CEA.

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TABLE 1 Clinical and US imaging characteristics of MTC.

Characteristics	Non-LNM group	LNM group	χ^2	p
Mean age	46.85 ± 14.17	48.95 ± 13.43	0.075	0.785
Preoperative Ctn	270.66 ± 426.32	549.1 ± 697.94	12.47	0.001
Preoperative CEA	103.11 ± 224.35	113.2 ± 232.85	0.052	0.863
Sex			0.007	0.934
Men	14	17		
Women	19	24		
Location 1			2.387	0.122
Left lobe	15	26		
Right lobe	18	15		
Location 2			0.129	0.937
Upper lobe	12	16		
Middle lobe	17	21		
Lower lobe	4	4		
Nodule size			5.734	0.017
≤2.19	4	26		
>2.19	29	15		
Aspect ratio			1.471	0.225
≤1	28	33		
>1	5	11		
Shape			4.062	0.044
Oval and round	19	14		
Irregular	14	27		
Margin			23.467	0
Smooth	6	1		
Lobulated	17	6		
Microlobulated	4	5		
Spiculated	6	29		
Extracapsular invasion			28.48	0
Yes	6	33		
No	27	8		
Echogenicity			1.958	0.376
Markedly hypoechogenic	18	27		
Hypoechogenic	14	14		
Hyperechoic or Isoechoic	1	0		
Composition			0.498	0.48
Solid	28	37		
Mixed	5	4		
Echotexture			2.02	0.155
Homogeneous	6	3		
Heterogeneous	27	38		
Calcification			0.485	0.785
Absent	13	13		
Microcalcification	14	20		
Macrocalcification	6	8		
Peripheral halo sign			1.517	0.218
Absent or fine halo	30	39		
Thick or irregular halo	3	2		
Vascularity			0.659	0.883

(Continued)

TABLE 1 Continued

Characteristics	Non-LNM group	LNM group	χ^2	*p*
0	6	6		
1	6	8		
2	3	6		
3	18	21		
Elastic score			1	0.583
<3	1	0		
≥3	13	10		
CEUS patterns			0.012	0.912
Hypoenhancement	8	6		
Hyperenhancement	3	2		
US-reported LN status			27.43	0
Positive	2	27		
Negative	31	14		

US, ultrasound; MTC, medullary thyroid carcinoma; LNM, lymph node metastasis; Non-LNM, non-lymph node metastasis; Ctn, Calcitonin; CEA, carcino-embryonic antigen; CEUS, Contrast-enhanced Ultrasound; LN, lymph node.

Selected factors for the model

The preoperative sonographic features of MTCs are also described in Table 1. After univariable analysis, MTCs with positive CLNM were more often nodules with a larger size (p = 0.017), irregular shape (p = 0.044), microlobulated or spiculated margin (p < 0.001), extracapsular invasion (p < 0.001), and US-reported suspicious LN (p < 0.001) than those without CLNM. While the variables of echogenicity, solid component, echotexture, presence of calcification, halo sign, vascularity, elastic scores, and CEUS patterns were not significantly different between the two groups (p > 0.05 for all).

After multivariate analysis, extracapsular invasion, margin, and US-reported LN status remained independent predictors for CLNM, as shown in Table 2.

Predictive nomogram for the probability of CLNM

A nomogram was built based on the results of the binary logistic regression that integrated the above three independent preoperative suspicious features for predicting CLNM of the MTC (Figure 2). The value of each of these variables (margin, extracapsular invasion, and US-reported LN status) was proportionally assigned a score based on the point scale. Subsequently, a total score could be obtained by summing up each subject's score and identifying it on the lower total point scale, and the probability of CLNM in each patient can be finally determined. According to the ROC analysis, the nomogram exhibited good discrimination, with an area under the ROC curve of 0.919 (95% CI, 0.856–0.932). A calibration curve of the nomogram exhibits that the predicted value is in good agreement with the actual probability of CLNM with additional 1,000 bootstraps (Figure 3).

An example of the nomogram in use

For example, the risk of CLNM in patient 1 who has a lesion in the right thyroid lobe with spiculated margins, extracapsular invasion, and US-reported suspicious LN (Figures 4A, B) could be calculated to be 98% by drawing a vertical line on the "Total points" scale (Figure 4C). Pathology proves the positive CLNM. In patient 2 who has a nodule in the right lobe with lobulated margins, no US-reported suspicious LNs, and no extracapsular invasion (Figures 4D, E), the risk of CLNM turned out to be about 30% (Figure 4F). Postoperative pathology demonstrated the negative CLNM, although she had a high serum Ctn (>2,000 pg/ml).

TABLE 2 Multivariate analysis of risk variables for CLNM of MTC.

Characteristics	β	Odds ratio (95% CI)	*p*
Extracapsular invasion	1.82	1.39-27.72	0.017
US-reported LN status	2.74	2.21-109.61	0.006
Margin	1.32	1.51-9.35	0.004

LN, lymph node.

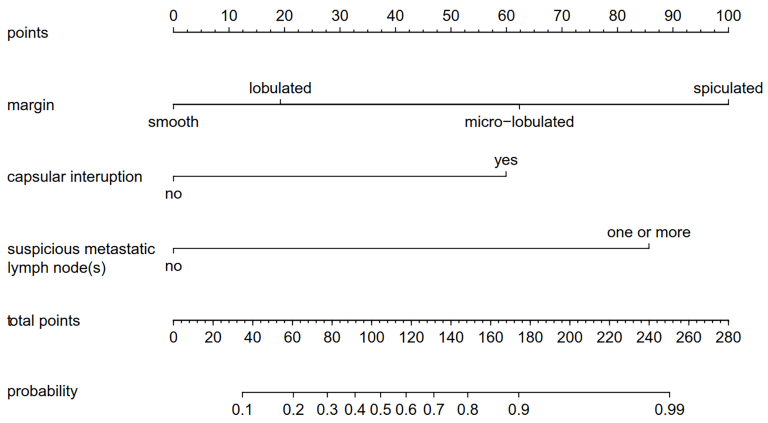

FIGURE 2
A nomogram forecasting the risk of CLNM for patients with MTC. The value of each of these variables was proportionally assigned a score based on the point scale. Subsequently, a total score could be obtained by summing up each subject's score and identifying it on the lower total point scale. The probability of CLNM in each patient can finally be determined. CLNM, cervical lymph node metastasis; MTC, medullary thyroid carcinoma.

Discussion

There are no evident recommendations for deciding the extent of LND in MTC patients with no clinical evidence of CLNM in preoperative images, so the clinical management of these patients can be challenging. Supporters, for example, Al-Qurayshi et al. (17), pointed out that preventive neck dissection upgraded 17.7% and 14.3% of patients to N1A and N1b. A meta-analysis (18) showed that LND was associated with lower mortality, suggesting that preventive LND is beneficial. However, it raises the risk of potential surgical complications such as recurrent laryngeal nerve injury, chylorrhea, and reduced parathyroid function (9). Therefore, an accurate and convenient way to directly assess the preoperative risk of CLNM is urgently needed. Machens et al. (19) found that about 70% of MTC patients with CCLNM had LCLNM, which suggests that for MTC patients with CCLNM, preventive

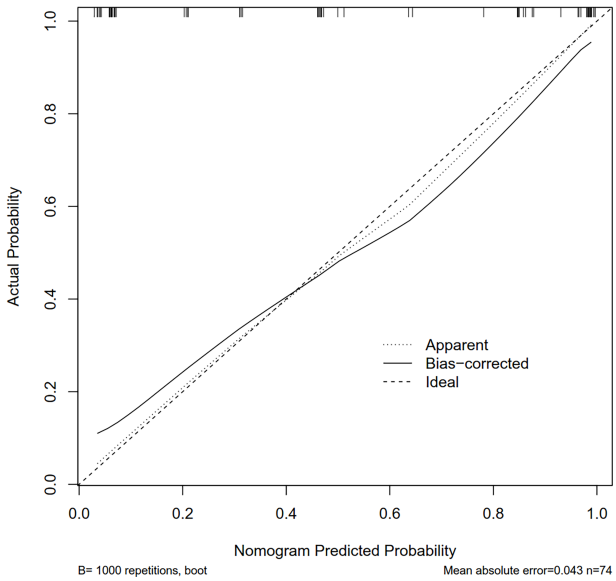

FIGURE 3
The calibration curves for the nomogram. The x-axis represents the nomogram-predicted CLNM probabilities, and y-axis represents the actual probability of CLNM. Perfect prediction would be along the 45-degree line. The solid curve is bias-corrected by bootstrapping (B = 1,000 repetitions), indicating the observed nomogram performance. CLNM, cervical lymph node metastasis; MTC, medullary thyroid carcinoma.

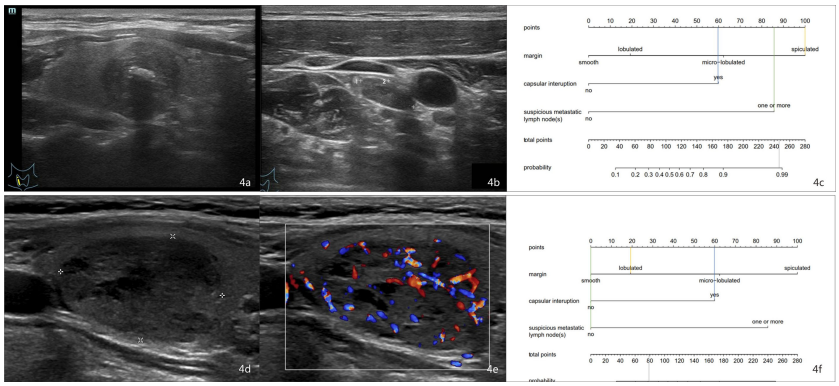

FIGURE 4
Examples of using the nomogram to predict the individual probability of CLNM by drawing straight lines across the diagram. First, draw lines straight upward to the point axis for each factor (margin status, orange line; capsular interruption, blue line; US-reported LN status, green line). Then, calculate total points for each of the predictors. Finally, draw a line (the gray line) straight down to the "Total points" scale to obtain the "Risk" of CLNM. **(A)** A 54-year-old man with MTC. **(B)** A small (size, 1.28 * 0.55 cm) lymph node was discovered, so the score was 85. The margin is spiculated, so the score was 100. The capsule is interrupted, so the score was 60. **(C)** The total point was 245 (100 + 60 + 85). The nomogram displayed that the chance of CLNM was more than 98%. Postoperative histology proved the positive CLNM. **(D, E)** A 60-year-old woman with MTC. The margin is lobulated, so the score was 20. The capsule is interrupted, so the score was 60. No suspicious lymph node was discovered, so the score was 0. The total point was 80 (20 + 60 + 0). **(F)** The probability of CLNM was approximately 30% by projecting a line straight down on the "Total points" scale. Postoperative pathology revealed that the patient has negative CLNM. CLNM, cervical lymph node metastasis; MTC, medullary thyroid carcinoma.

resection of ipsilateral cervical LNs is necessary. The National Comprehensive Cancer Network (NCCN) guidelines suggest that LND should be performed when the primary tumor is more than 1 cm or there is CCLNM (7). Therefore, our research focuses on the related factors of CLNM rather than LCLNM or CCLNM in patients with MTC, so as to provide a basis for preventive LND. Oh et al. (12) indicate that high preoperative Ctn levels (>65 pg/ml) and a larger tumor size (>1.5 cm), irregular shape, spiculated margin, and subcapsular location of the tumor in preoperative neck US are significantly associated with LCLNM of MTCs. MTCs with two or more predictors are at higher risk for LCLNM. MTCs with fewer than two predictors have a very low probability of LCLNM and might be suitable for treatment without prophylactic lateral LND. However, the equal split of the variables in the work of Oh et al. is quite impractical considering the nonlinear relationship between the variable and LCLNM that brought forward further questions about the representativeness of their prediction model for other populations.

The nomogram is a predictive tool that uses a visual chart of a statistical predictive model to solve the complexity of balancing different variables; it also reduces the bias caused by individual abnormal clinical or imaging variables. Moreover, nomograms play important roles in personalized risk stratification and help doctors in choosing the treatments when no guidelines exist, especially in the field of cancer (20). Previous studies (21–24) have demonstrated that nomograms have been useful in predicting CLNM risk in PTC patients, but there were relatively few reports for predicting CLNM risk in MTC patients. In our present study, a noninvasive nomogram model for the preoperative prediction of CLNM of MTC was built using US features. This nomogram model exhibited a satisfying result with a good discriminative ability of a C-index of 0.919 (95% CI, 0.856–0.932) and a good calibration.

According to our findings, tumor margin, US-reported suspicious LNs, and extracapsular invasion were independent risk factors for CLNM of MTC. The presence of ETE in MTC is considered a risk factor for aggressive behavior and CLNM (25–27). The extrathyroidal extension (ETE) is confirmed by postoperative pathology. However, extracapsular invasion, defined as a tumor abutting the thyroid capsule or there was a discontinuity of the capsule, could be a useful preoperative US feature for predicting ETE in pathological reports (28). MTC cancer cells are low-differentiated, highly invasive, and often grow infiltrating. The thyroid capsule can be regarded as a barrier. Once the malignant tissue infiltrates the capsule, it is easy to enter the lymphatic circulation system, which makes it extremely prone to LN and distant metastasis (29). In this study, in MTC patients with CLNM, the invasion of the capsule was significantly higher than that of noninvasive (80.5% vs 18.2%), which indicates that the invasion of the capsule has a greater impact on CLNM. This finding suggests the importance of careful US examination to determine extracapsular invasion of MTCs because of its usefulness in predicting CLNM.

The finding that merits discussion is the potential influence of the tumor margin on CLNM, which is the largest contributor to scores of the US-based model. A lobulated or spiculated margin on a preoperative US image was considered a predictive factor for CLNM in MTC. With significant improvements of ultrasonic resolution and the application of higher-frequency

probes, margin details of thyroid nodules are better exhibited now, which can promote a more nuanced assessment of thyroid lesions. A smooth margin of the tumor was almost found in the CLNM-negative group. When the MTCs present expansile growth, a group of tumor cells "pushing" into surrounding normal thyroid tissue, forming a lobulated margin, this result was consistent with those earlier studies (30–33). When the MTC infiltrated and grew extensively, the boundary presents microlobulated or spiculated, and it was more likely to infiltrate the thyroid capsule and metastasize to adjacent cervical LNs. In this study, CLNM risk increased with the microlobulated or spiculated margin. Therefore, attention should be fixed on the identification of margins.

It is reported that neck ultrasonography demonstrated low sensitivity but high specificity and a positive rate in diagnosing CLNM. Neck US showed only a 6% sensitivity when diagnosing CCLNM (34). Especially, micrometastasis may be hidden by the thyroid tissues. In our study, preoperative US examination found suspicious LNs in 29 cases (29/41, 70.7%) with a relatively low sensitivity (65.9%) but high specificity (93.9%) and positive predictive value (PPV) (93.1%), higher than those in previous studies (85%–88% and 77%–83%, respectively) (35).

In our present study, univariate analysis indicated that the level of preoperative serum Ctn and tumor's size were obviously higher and larger in patients with positive CLNM than those with negative CLNM, which agreed with the previous research that a high preoperative Ctn level is related to the extent of CLNM and poor prognosis in MTC (36–41). However, multivariate analysis showed that they were not independent predictors for predicting CLNM, which may be due to the small sample size; the other reason may be that the level of preoperative serum Ctn and the size of MTC were partially overlapped. With the increase in the diameter of the primary tumor, the basal Ctn level gradually increases, as does the number of LNMs. Therefore, the two factors are strongly correlated.

This study successfully constructed an US-based nomogram, which perfectly stratified patients according to their risk of CLNM and demonstrated a satisfactory performance. We recommend that patients with high scores should undergo prophylactic LCLN dissection to prevent reoperations due to recurrence or metastasis. For patients with low scores, which indicate that they are at low risk of CLNM, prophylactic LCLN dissection should be avoided to reduce unnecessary damage and possible surgical complications. In the American Thyroid Association guidelines, prophylactic LCLN dissection based on the Ctn level is suggested with a Grade I recommendation (recommends neither for nor against it) (1). About 36% of the CLNM-negative patients of this study displayed high preoperative Ctn levels (>150 pg/ml) before the operation, which lead to the LCLN dissection. When the nomogram was used to evaluate the risk of CLNM in each patient, 75% of patients had low scores. This finding indicates that these MTC patients could choose a more suitable surgical strategy if the prediction model is used.

There are some limitations in our study. First, this is a retrospective single-center study that may be affected by selection biases. Second, our study failed to contain a complete biochemical assessment with serum Ctn, CEA levels, and other imaging studies. Third, it is worth noting that our nomograms have not been validated by external cohorts, and we will use other databases for calibration in our future studies.

In conclusion, we established and validated a user-friendly and accurate US-based nomogram for forecasting the probability of CLNM in MTC patients preoperatively, which may guide clinicians in stratifying patients and assist surgeons to choose the appropriate surgical strategy and thus reduce overtreatment of indolent MTC, which is suitable to the current trend toward personalized care.

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

The studies involving human participants were reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

ZL: Collection of data, interpretation of data and drafting the article; YH: Revising the article and provide the acquisition of funding; CY: Collection of data, interpretation of data; YW: Provide patient information and surgical specimens; QY: Provide pathological results; PH: general supervision of the research group. 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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Review: Improving quality of life in patients with differentiated thyroid cancer

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Well differentiated thyroid cancer is a common malignancy diagnosed in young patients. The prognosis tends to be excellent, so years of survivorship is expected with low risk disease. When making treatment decisions, physicians should consider long-term quality of life outcomes when guiding patients. The implications for treating indolent, slow growing tumors are immense and warrant careful consideration for the functioning years ahead. Surgery is the standard of care for most patients, however for a subset of patients, active surveillance is appropriate. For those wishing to treat their cancer in a more active way, novel remote access approaches have emerged to avoid a cervical incision. In the era of "doing less", options have further expanded to include minimally invasive approaches, such as radiofrequency ablation that avoids an incision, time off work, a general anesthetic, and the possibility of post-treatment hypothyroidism. In this narrative review, we examine the health related quality of life effects that surgery has on patients with thyroid cancer, including some of the newer innovations that have been developed to address patient concerns. We also review the impact that less aggressive treatment has on patient care and overall wellbeing in terms of active surveillance, reduced doses of radioactive iodine (RAI) treatment, or minimally invasive techniques such as radiofrequency ablation (RFA) for low risk thyroid disease.

KEYWORDS

thyroid cancer, quality of life, surgery, radiofrequency ablation, active surveillance

Introduction

Well differentiated thyroid cancer (WDTC) is one of the most common neck malignancies in patients under 40 years of age (1). A large number of cancer survivors exist due to the rising incidence of diagnosis at a young age and the excellent long-term survival rate post-surgery. Even though the prognosis is excellent, and the 10 year survival rate exceeds 90%, sometimes the treatment can leave patients with a sequelae that affects their quality of life (1). Upon diagnosis, patients are often counselled that they have a slow growing, indolent cancer with an excellent prognosis. While this holds true for the majority

of patients, this doesn't account for the physical and emotional burden that can occur post-surgery, impairing the ability to socialize or work.

The implications of thyroid cancer treatment are immense and warrant a careful look at the long-term effect on the quality of life in addition to the projected prognosis. Studies have shown that the health related quality of life (HRQOL) of thyroid cancer survivors can be negatively affected for up to 20 years after treatment (2). With the rising number of cases in patients under 45, years of surveillance are required post treatment to monitor for recurrence decades later, to adjust the dose of lifelong thyroid replacement medications, to monitor for side effects of radioactive iodine treatment (RAI) or to address any functional impairment post-surgery such as dysphonia or dysphagia.

There is no one definition of quality of life (QOL). The World Health Organization defines quality of life (QOL) as an individual's perception and expectation of a certain standard of excellence as regards to his/her social and cultural environment (3). This term tends to be multidimensional and is affected by numerous factors such as physical health, psychological state, level of independence, social relationships and is associated with the environment which the person is living in (4). Assessing the QOL post-treatment is an important aspect of cancer care that deserves as much attention as immediate treatment of the disease itself. This aspect of cancer care tends to be more difficult to quantify, however various validated questionnaires have attempted to capture this data. It has been shown that QOL in cancer patients is not predicted by prognosis alone and QOL in thyroid cancer survivors can be worse than in patients with other malignancies who may have a worse prognosis (5). Gamper et al. reinforce the idea that functional impairment related to treatment for thyroid cancer is unrelated to the favorable clinical outcome (6).

Over the past few years there has been an increased focus on the HRQOL of patients with thyroid cancer. This is in response to the relative paucity of data, the years of disease free survival, and a shift towards "doing less". Given that patients with thyroid cancer tend to have a life expectancy that does not impair their survival, ensuring their HRQOL during surveillance plays an important role in their care. In this narrative review, we collate the data on the HRQOL effects of surgery in patients with thyroid cancer, including some of the newer innovations that have been developed to address patient concerns. We also review the impact that less aggressive treatment has on patient care and overall wellbeing in terms of active surveillance, reduced doses of radioactive iodine (RAI) treatment, or minimally invasive techniques such as radiofrequency ablation (RFA) for low risk thyroid disease.

Surgery

Knowledge that thyroid carcinoma is part of a clinical spectrum of low, intermediate and high risk disease is an important aspect for guiding patients through their options for surgery, active surveillance or thermal ablation. Aggressive disease is met with aggressive resection resulting in total thyroidectomy, +/central neck dissection, and even lateral selective neck dissection when warranted, followed by post-operative lifelong levothyroxine replacement, radioactive iodine and external beam radiation in the advanced disease state (1). For the most part, there has been a shift toward less aggressive surgical intervention, reduced RAI use, and less thyroid hormone suppression for lower risk disease (well differentiated thyroid cancer > 1 cm but < 4 cm without extrathyroidal extension, or clinical evidence of cervical lymphadenopathy (cN0) (1). As clinicians, it can be challenging to guide patient decision-making while balancing the risks of disease recurrence and interventions that may affect the long-term quality of life. Most of the time, surgical resection of low risk carcinoma with clear margins leads to cure (7), however complications can and do exist. Even though select patients demonstrate equal oncological control of their cancer with total thyroidectomy or lobectomy, factoring in their quality of life post-surgery is an important determinant to consider when discussing the extent of surgery with patients (8–11).

Completeness of surgical resection is the most important determinant of outcome whereas treatments such as RAI treatment and TSH suppression are reserved as adjuncts to cancer control (8, 9). How much or how little to surgically remove is an important consideration when achieving a favorable long-term outcome that needs to be balanced with an overall well-being. A handful of articles have examined whether there is a difference in the QOL of patients receiving a thyroid lobectomy compared with total thyroidectomy (12, 13) and the results are conflicting. Malterling et al. compared the short and long-term outcomes as well as the quality of life in Swedish patients with papillary and follicular cancer after treatment with total thyroidectomy and post-operative RAI (77 patients) compared with treatment with subtotal thyroidectomy and occasional RAI (53 patients) (12). Overall, no significant difference was found in outcome between the two groups in the 10 year cancer-specific survival rate irrespective of stage. Specifically, aggressive treatment for TNM stage I-II did not confer an advantage and led to more unwanted side effects. The quality of life was assessed by questionnaire 8 to 22 years after their primary operation (88% response rate) and found 7 patients lived with permanent complications including RLN palsy, hypocalcemia and ongoing cancer, or recurrence, however a difference in the quality of life was not appreciated due to the intervention received. No significant difference in mental and physical health was found on SF-36 questionnaire in age- and sex-matched Swedish reference population compared with thyroid cancer patients. This study is limited by a small number and potential bias from years after surgery.

In a larger based study which included 1005 patients with differentiated thyroid cancer, Nickel B. et al, found health related QOL issues in 775 patients (77.1%) after diagnosis and treatment of their cancer (median time between diagnosis and interview was 23.1 weeks (range, 1.9 – 90.9 weeks)) (13). Papillary thyroid cancer was the most common diagnosis (889 of 1003, 88.6%), where roughly half of patients had tumors less than 2 cm in size (564 of 1000, 56.4%), and 791 patients received total thyroidectomy (78.7%). Those patients who had a total thyroidectomy (without neck dissection) were 1.5 times (odds ratio, 1.49; 95% CI, 1.04-2.12) more likely to report health related QOL issue or an adverse effect of treatment compared with patient who underwent hemithyroidectomy. More specifically, the common themes that emerged from patient responses were physical concerns (663, 66.0%), psychological (187, 18.6%), lifestyle (82, 8.2%), or no issue or adverse effect (246, 24.5%). High or very high psychological distress scores (Kessler Psychological Distress Scale) were found compared with the national figures (Australia) (20.6%

vs.11.7%). Examples of the most common physical concerns included; fatigue, low energy levels, voice concerns, difficulties titrating medical levels (13). Other studies have found similar concerns as Nickel B et al, demonstrating that the quality of life issues relevant to thyroid cancer patients cross culturally include fatigue and exhaustion, quality of sleep, employment, social support, fear of cancer progression, fear of second operation, difficulties swallowing and globus sensation (14). Worldwide, the most common theme in thyroid cancer survivors include fatigue and sleep issues (6, 15–17).

Various studies have demonstrated a significant negative impact on patient's QOL when a visible scar is present from a midline anterior neck incision (18, 19). This seems to be more of a cultural phenomenon, and often placement of the surgical scar within an existing natural skin crease can hide the scar nicely, resulting adequate patient satisfaction in most parts of the world (20). Regardless, novel approaches for accessing the thyroid remotely are gaining popularity in certain parts of the world to avoid a visible scar that the traditional surgical approach requires for gland removal. Choi et al. used a Dermatology Life Quality Index (DLQI) to investigate the impact of thyroid scars on the quality of life and found the mean score to be 9.02, similar to that of patients suffering from chronic skin diseases such as psoriasis, vitiligo and severe atopic dermatitis (19). Various remote access techniques have been developed to hide a cutaneous scar in the anterior neck to less visible locations such as under the breast or in the axilla, and more recently intraorally. The transoral endoscopic thyroidectomy vestibular approach (TOETVA) for removal of the thyroid has become a favored approach since it allows the surgeon midline access to the thyroid with little soft tissue dissection, no cutaneous scar, and safe same-day discharge with minimal discomfort for low risk thyroid disease (21–29). Although the operative time is longer with TOETVA, and the costs are greater with remote access techniques, in certain cultures, these are acceptable trade-offs to avoid a visible scar. When the DLQI was applied in the early post-operative period after receiving the transoral vestibular approach, the median score was 3, a significantly favorable outcome compared with an open approach (26). Furthermore, no significant differences in the incidence of major complications between TOETVA and transcervical thyroidectomy (1.5% vs 2.1%, p=0.75) were noted for both benign and low risk malignancy, making it a sound approach in select patients concerned about a visible scar (29, 30). Other reports have demonstrated the safety and efficacy of remote access techniques for eliminating a visible scar (31).

In a retrospective study by Sun H et al., patients with clinically positive central neck nodes and papillary thyroid cancer with tumor sizes < 1.5 cm in the upper pole and < 3 cm in other parts of the thyroid underwent total thyroidectomy with central neck dissection *via* TOETVA compared with open approach by a single surgeon. After propensity score matching, 28 patients underwent TOETVA and 56 patients were included in the conventional open thyroidectomy group (32). In term of oncological control, the mean number of retrieved central lymph nodes (p=0.202), metastatic central lymph nodes (p=0.421), and Tg level without thyroid-stimulating hormone (TSH) stimulation (p=0.686) 3 to 54 months after surgery did not differ between the TOETVA or open conventional group. At least within the short term, this study demonstrates oncological success. In terms of safety, a significant difference was not noted between the rate of transient vocal cord palsy (p=1.000), or transient hypoparathyroidism (p=0.870) between the two groups.

With both TOETVA and the open conventional approach, complications such as permanent recurrent laryngeal nerve (RLN) palsy or permanent hypoparathyroidism are rare but do occur with surgery. For high-volume thyroid surgeons, the open neck approach can result in less than 1% of permanent RLN injury in primary cases, with up to 30% of impaired RLN function after revision thyroid surgery (33, 34). Most of the literature shows comparable rates to the standard open thyroidectomy with no significant difference in safety when the procedure is done with an endoscope or *via* the open approach (32, 35). These numbers are less with thermal ablation for various reasons which include careful patient selection for more anterior based tumors away from the "danger triangle", and low risk carcinomas. The cornerstone of therapy is based on the preoperative decision making which involves balancing the risks and benefits of surgery or any treatment at all. Impaired vocal fold mobility can impact a patient's ability to work or socialize, can result in breathing difficulties in up to 75% of patients during activity, dysphagia in up to 56%, aspiration in as many as 44% of patients creating significant impact to their quality of life (34). Thus, intraoperative nerve monitoring has played an important role for guiding favorable outcomes particularly for advanced malignancy, re-operative surgery or anticipated aberrant anatomy (36).

TOETVA has a few potential complications worth mentioning that do not exist with the open convention approach. For example, transient mental nerve injury can occur during placement of the endoscopic port in the inferior vestibule. In a recent systematic review, mental nerve injury was 5.8% (102/1,887 patients), whereas other reviews report a prevalence ranging 1-5% (35, 37). Skin bruising and dimpling of flap perforation are rare complications with TOETVA, however can be disappointing to a patient who opted for a scarless approach. Another rare (2 out of 1887 patients) but potentially serious complication is a carbon dioxide embolism caused by prolonged high insufflation pressures or a tear in the vessel promoting entrance of C02 into the circulation (35). Other insufflation-related adverse events include pneumomediastinum, pneumothorax or excessive hypercarbia. Gasless TOETVA has also been invented to avoid such complications (38). The literature also describes the unique but rare risk of delayed tracheal rupture caused by accidental dissection, surgical needle puncture, Hegar dilation, trocar placement or thermal injury from the energy device (39). Through careful blunt dissection and use of the energy device these complications can be mitigated.

Chronic hypoparathyroidism post-total thyroidectomy can result in persistent hypocalcemia due to low circulating parathyroid hormone from devascularized or resected parathyroid glands. Symptoms of hypoparathyroidism have been shown to have negative effects across several domains (40). In a questionnaire to 264 hypoparathyroid patients post-thyroid surgery, Buttner et al, found significant impairments in social, physical, cognitive and emotional functioning leading to an impaired quality of life (41). In response to this complication, certain centers are incorporating parathyroid autofluorescence into their practice as a means for improving the detection of these glands over visualization alone (30).

Patients after total thyroidectomy for malignancy require life-long thyroxine replacement and regular evaluation of TSH serum levels as

well as thyroglobulin to screen for recurrence. These simple blood tests are an easy approach for biochemical surveillance. However, a subset of patients experience chronic fatigue syndrome known as asthenia after total thyroidectomy (TT), even if their TSH is within the normal range. In a prospective observational cohort study that included 182 patients, Luddy et al. found that 42% of patients had asthenia after total thyroidectomy (TT) compared with 4% after thyroid lobectomy (TL) on Brief Fatigue Inventory questionnaire more than one year post surgery (42). Patients were also more likely to have asthenia if they had surgery for a malignancy compared with benign disease, with an odds ratio of 10.4 (95% CI 3.86-28.16) when TT was compared to TL for patients with malignancy compared to benign disease (2.05, 95% CI 1.17-3.61) (42). Although the rate of post-operative hypothyroidism after a lobectomy alone varies considerably in the literature, doing less for low risk disease may improve long-term outcome in the correct clinical scenario.

Radioactive iodine treatment

Radioactive iodine (RAI) has been the standard treatment post-thyroidectomy for papillary and follicular thyroid carcinoma for decades (1). Even though RAI administration is relatively routine, it is fraught with early and late side effects, which can impact chewing, speech, taste, saliva, anxiety levels including the risk of a second malignancy (43). Treatment with RAI also delays family planning by a year which can be of concern for women in their prime reproductive years (43). Although the treatment itself has unwanted effects, the side effect with the most impact is the period prior to RAI treatment which requires patients to be rendered hypothyroid, so uptake of RAI was more avid. In the past, the pre-ablation period would lead to significant physical and emotional instability and reduce the QOL in patients during and after treatment as they try to bring their TSH into the normal range. Since the development of recombinant human thyroid stimulating hormone (rhTSH) (also known as thyrogen), this practice has become obsolete, making the process more tolerable. Thus, rhTSH has significantly improved the aftercare post-thyroidectomy as an alternative for thyroid hormone withdrawal pre-RAI ablation.

Post-operative treatment with RAI for low risk well differentiated thyroid cancer is controversial, and has been shown repeatedly that it is unlikely to have any meaningful benefit for papillary microcarcinoma or patients with low risk disease that has no other worrisome features (1, 44–48). Even the dose of RAI has been questioned, leading the American Thyroid Association guidelines to recommend use of a lower dose of RAI in low and intermediate risk disease (1, 49). Studies have shown that the use of high dose RAI (ie.100 mCi) has no advantage for remnant ablation over a lower dose of 30-50 mCi for low to intermediate risk disease (1, 49). Mazzaferri et al. examined the effects of more than 1000 patients treated with RAI following thyroidectomy for WDTC and found a decrease in cancer-related deaths and recurrences in patients who were older than 40 years or who had isolated tumors larger than 1.5 cm compared to those who did not receive RAI (50). Post-operative RAI plays a role in certain clinical scenarios, however in the setting of low risk disease, it's role is minimal in reducing recurrence of thyroid carcinoma.

In a cross-sectional study, Almeida et al. found that patients who received a higher dose of 150 mCi of RAI had significantly worse pain, swallowing, chewing, speech, taste, and anxiety (51). Similarly, Ahn et al. found a decrease in the QOL in patients that were treated with total thyroidectomy (TT) and RAI compared with TT alone (52). Even when a lower dose (median dose was 80 mCi) of RAI was used, patients experience lower scores in QOL measurements, despite matching for TSH, and levels being in the normal range (52). This accumulating evidence has resulted in most North American institutions moving away from treating patients with RAI for low risk disease such as PTMC, or performing total thyroidectomy unless more concerning high risk features are present. In the era of "doing less", selective and judicious administration of RAI can translate to improved well-being post treatment.

Active surveillance

The push to be conservative is based on the notion that "doing less" can lead to a better QOL. However, this warrants a close look at both sides of the issue so the impact imposed by the numerous repeat ultrasounds, biopsies, and bloodwork to actively surveil the patient as well as the emotional and psychological aspects of living with a known cancer is assessed. However, most of the current literature demonstrates significant patient satisfaction in a select group of patients wishing to avoid surgical intervention.

Nakamura et al. compared the quality of life and psychological impact of patients with PTMC who were under active surveillance (AS) and those who underwent immediate surgery (53). In a cross-sectional study, 347 patients with low risk PTMC who underwent AS (n = 298) or immediate surgery (n=49) completed two questionnaires (thyroid cancer-specific health-related QOL (THYCA-QoL) and the Hospital Anxiety and Depression Scale (HADS)) and the results between the two study groups were compared. In the immediate surgery group, the THYCA-QoL questionnaire revealed more complaints about "voice" ($P<0.001$), "psychological" ($P=0.025$), "problems with scar" ($P<0.001$) and "gained weight" ($P=0.047$) than the AS group. In the HADS questionnaire, the AS group had significantly better anxiety ($P=0.020$), depression ($P=0.027$), and total scores ($P=0.014$) than the immediate surgery group. Similar findings have been reported in the literature from patients having undergone immediate surgery compared with AS in terms of fatigue, change of voice and appearance, level of satisfaction with similar self-assessed financial burden (54). Although follow up was for a median of 8 months, studies with longer follow-up periods would be beneficial given that patients tend to live for years with little effect on their survivorship. It may also be that there exists a selection bias in studies such as this.

Using a larger population base, Moon et al. investigated the initial treatment choice on their 2-year QOL in patients with low-risk PTMC (55). In a multicenter prospective cohort study on AS (n=674) of their PTMC compared with those that chose immediate surgery (n=381), including lobectomy or total thyroidectomy, the 2-year QOL was best for patients with the least invasive treatments (n=500 for AS, n=238 lobectomy, n = 79 total thyroidectomy). Of the 674 patients, 101 switched from AS to surgery during the follow up

period. Thirty five of those patients switched treatment to surgery due to disease progression and were found to have a better QOL on questionnaire compared to the 66 subjects that had no disease progression (55). Jeon et al, found similar QOL issues in patients with PTMC that underwent thyroid lobectomy compared with patients who underwent AS. Specific concerns in the thyroid cancer-specific QOL questionnaire demonstrated statistically significant differences between the groups, with greater health related problems in the surgical group in terms of neuromuscular complaints (coef: 4.99 [CI 0.63-10.62], p = 0.0200), throat/mouth problems (coef: 5.28 [CI 0.18-10.38], p=0.043), and scar problems (coef:9.34 [CI 4.38-14.29], p<0.001) (56). Thus, AS is a reasonable option for patients with PTMC who do not wish to endure these possible risks provided they meet the appropriate oncological criteria.

Lubitz et al. looked at patient preferences retrospectively after they had already undergone treatment (most of which had total thyroidectomy), and found that 536 patients of 1546 (35%) would consider the option of AS if this approach was oncologically equivalent (57). The main reason for patients favoring observation was to preserve their quality of life. Thus, if the burden of surveillance or level of worry is not worse than surgical treatment itself, then this approach is sound (58).

Radiofrequency ablation

Radiofrequency Ablation (RFA) has emerged as one of the common ways to thermally ablate thyroid low risk WDTC. Thermal ablation is a third option for patients who are anxious about leaving their low risk thyroid cancer untreated. Other indications include recurrent lymph node metastases in patients whom have had a prior total thyroidectomy and neck dissection for their papillary thyroid cancer who are deemed high risk for reoperation or who do not wish to have repeat surgery (59). The most robust data exists for RFA of PTMC as a safe and effective alternative treatment to AS or surgery who wish to actively treat their microcarcinoma but in a minimally invasive way. The advantages for thermal ablation is that it avoids surgical incision in the neck, takes less operative time, does not require a general anesthetic, allows patients to return to work and routine life, and does not render patients hypothyroid. Thermal ablation is suitable for low risk thyroid cancer, similar to those patients that would qualify for AS but who would like to actively treat their cancer.

The evidence for improved HRQOL in patients who have undergone RFA for their low-risk PMC is beginning to emerge. Lan Y et al. compared patients who underwent US-guided RFA with those that had surgery (TT or Lobectomy) by using three validated questionnaires (Short Form healthy survey (SF-36), thyroid cancer-specific quality of life, and Fear of Progression Questionnaire-Short Form) (60). The results show that the physical wellbeing of patients in the RFA group was better than in the surgery group, with improvement in certain scores for the lobectomy group over the TT group. Specifically, there were significantly less complaints relating to overall symptoms, “problems related to scarring” and “less interest in sex” scale scores of patients treated with RFA compared with surgery. However, there was no significant differences in FOP-Q-SF questionnaire scores between the two groups looking at physical health or the social family domain (p >0.05).

In patients that have undergone conventional thyroidectomy compared with thermal ablation of their benign thyroid nodules, Jin et al. demonstrate that thermal ablation provides improved patient satisfaction, post-operative quality of life, and a shorter hospital stay (61). These immediate benefits are improved in patients with benign nodules, however, broader oncological control and risk of recurrence are factors that play into QOL with cancer patients. This has created creative solutions in certain clinical situations, where RFA can be combined with surgery to achieve improved patient satisfaction. Yuan et al, retrospectively evaluated the quality of life in patients who underwent thyroid lobectomy for their unilateral papillary thyroid carcinoma and RFA for the contralateral benign nodules compared with lobectomy alone (62). Those patients who underwent lobectomy plus RFA were found to have improved symptoms of anxiety, physiological health, psychological and sensory features that were measured *via* questionnaire six months post treatment. Of note, after 4.2 year follow-up nine patients (6.1%) in the lobectomy plus RFA group and seventeen (11.5%) in the thyroid lobectomy alone group underwent completion thyroidectomy (P = 0.100). Whether the combined RFA and surgery option is a sound long-term oncological option still remains to be determined with larger prospective data.

For the most part, patients are cured of their papillary thyroid cancer with total thyroidectomy +/- neck dissection followed by post-operative radioactive iodine treatment, however up to 15-30% of patients can have local recurrences in the previously operated tissue bed and neck (59). The American Thyroid Association guidelines recommend surgery as the treatment of choice for neck lymphadenopathy, but some patients may not wish to endure the risks of reoperation, are unfit for surgery, or are at great risk for reoperation in the neck due to scarring (1). Ultrasound guided percutaneous thermal ablation in the treatment of cervical lymph node metastasis of recurrent papillary thyroid cancer has been shown to be a safe and effective treatment as well as a reasonable option for locally controlling small lesions (59). In a systematic review, patients who had their lymph node metastasis treated for their recurrent papillary thyroid cancer had significantly decreased lymph node volumes, low thyroglobulin levels, with low complication rates after treatment (59). The complication rate was higher when ablation was done in the central region (12%), with an overall complication rate of 5%. The results from minimally invasive techniques are encouraging, but need to be appropriately framed in a discussion with patients regarding immediate as well as long term oncological control.

For centers that are not equipped with thermal ablation, cheaper readily available options for treating recurrent papillary thyroid cancer in a minimally invasive way include ethanol *via* chemical ablation. The literature demonstrates how US guided ethanol treatment of metastatic lymph nodes is an excellent alternative to surgery, provided there are a limited number of metastasis from their PTC (63, 64).

Conclusion

Finding the right balance between oncological control and long term QOL remains an ongoing challenge in thyroid cancer patients. Increasingly, treatment has become more individualized in order to maximize the years of disease free survival in young patients. For low risk well- differentiated thyroid cancer, active surveillance, minimally invasive techniques, such as RFA or ethanol ablation, and even

remote access techniques such as TOETVA are reasonable options in select patients. In an attempt to "do less", to improve the quality of life in patients with papillary thyroid cancer, oncological safety should not be compromised. Technological advancements can enhance a patient's quality of life but further rigorous studies are need to better define the long-term oncological control.

Author contributions

PP-A did the literature review, manuscript writing, editing, and finalization of the manuscript. JR and RT contributed to the editing and finalization of the manuscript. 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.

Publisher's note

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