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Developments in diagnosis and management of thyroid cancer

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Carlotta Giani, Carla Colombo and
Joana Simões-Pereira

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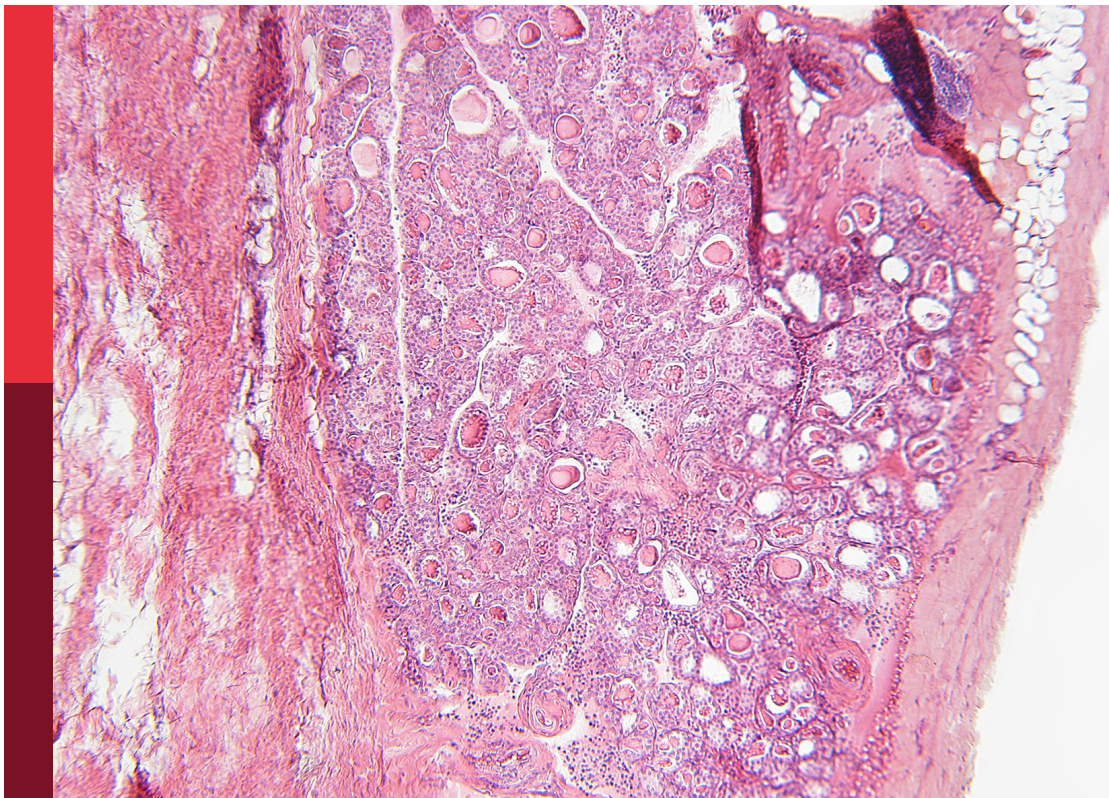

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Developments in diagnosis and management of thyroid cancer

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Pretracheal Lymph Node Subdivison in Predicting Contralateral Central Lymph Node Metastasis for Unilateral Papillary Thyroid Carcinoma: Preliminary Results

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Background: The aims of this study were to assess the clinical value of pretracheal lymph node subdivision in identifying patients with contralateral central lymph node metastasis (CLNM) and risk factors for occult contralateral CLNM in unilateral PTC.

Methods: A total of 139 unilateral PTC patients with a clinically node-negative neck (cN0) who underwent bilateral central neck dissection (CND) were prospectively enrolled. Intraoperatively, the pretracheal region was further divided into ipsilateral and contralateral subregions. Ipsilateral and contralateral pretracheal lymph nodes (LNs) as well as other CLNs (prelaryngeal, ipsilateral paratracheal and contralateral paratracheal) were labeled separately and sent for pathological examination. Demographic and clinicopathologic variables were analyzed to identify factors predictive of contralateral CLNM.

Results: Of 139 patients, bilateral CLNM was present in 37 (26.6%) patients. Contralateral pretracheal LNM was significantly associated with contralateral CLNM. In multivariate analysis, prelaryngeal LNM (P = 0.004, odds ratio = 3.457) and contralateral pretracheal LNM (P = 0.006, odds ratio = 3.362) were identified as risk factors for contralateral CLNM. Neither neck recurrence nor distant metastasis was observed within the mean follow-up duration of 9.1 ± 1.8 months.

Conclusions: In most unilateral cN0 PTCs, performing ipsilateral CND is appropriate, while patients presenting with evident nodal disease intraoperatively or preoperatively in the contralateral central neck should undergo bilateral CND. Intraoperative re-evaluation of prelaryngeal and contralateral pretracheal LNs may be helpful in determining the extent of CND.

Keywords: pretracheal lymph node, central neck dissection, papillary thyroid carcinoma, central lymph node metastasis, clinically node-negative neck

INTRODUCTION

Despite the excellent overall prognosis, papillary thyroid carcinoma (PTC) is characterized by early regional lymph node metastasis (LNM), and the central neck compartment (level VI) is usually the first involved region. Central lymph node metastasis (CLNM) has been reported in 30%–90% of patients who undergo elective central neck dissection (CND) (1, 2). Ipsilateral CND is considered necessary for patients with suspicious nodal metastasis, but when to perform contralateral CND in unilateral PTC is controversial. Bilateral CND has been recommended by some endocrine surgeons because it can enable complete nodal dissection, which may reduce the risk of locoregional recurrence and distant metastasis (3–5). In fact, however, most patients with unilateral PTC only have ipsilateral CLNM without contralateral CLNM. On the other hand, bilateral CND is associated with a higher rate of surgical complications such as hypoparathyroidism and recurrent laryngeal nerve injury, even if it is performed in experienced hands (6, 7). Nonetheless, the risk of nodal metastasis and locoregional recurrence in the contralateral central neck cannot be neglected (8). It is important to understand the characteristics and prognosis of CLNM in unilateral PTC. Therefore, accurate assessment of patients at high risk of CLNM, especially contralateral CLNM, may facilitate determining the appropriate extent of CND, which could decrease unnecessary morbidities caused by bilateral CND.

Pretracheal lymph nodes (LNs) have been found to be closely connected with ipsilateral/contralateral central lymph nodes (CLNs) (9). Although some studies have investigated the risk factors for contralateral CLNM, there have been few studies evaluating whether pretracheal LNs could be used as sentinel LNs that aid in identifying patients with occult contralateral CLNM. In this study, we hypothesized that pretracheal LN subdivision could be of value for the identification of PTC patients with occult contralateral CLNM.

The aims of the present study were to evaluate the clinical value of pretracheal LN subdivision to aid in surgical decision-making regarding the extent of CND and risk factors for occult contralateral CLNM in unilateral PTC.

MATERIALS AND METHODS

Patient Population

From October 2019 to December 2020, 193 patients consented to undergo pretracheal LN subdivision, total thyroidectomy and bilateral CND for the treatment of PTC in our institution. All patients had a preoperative diagnosis of PTC, and no suspicious neck LNs were detected by palpation or ultrasound (US) perioperatively (cN0). Patients with the following were excluded from this study: history of previous thyroidectomy, non-PTC carcinoma, PTC variants, isthmus tumor, bilateral tumors, and lateral neck dissection. Finally, 139 patients were prospectively enrolled in this study. This study was approved by the Institutional Review Board of West China Hospital, Sichuan University (IRB-HX2019012), and all patients provided written informed consent.

Surgical Procedures

A standardized surgical procedure was carried out in the present study to minimize morbidities and ensure comprehensive removal of LNs in the central compartment. CND was defined as a level VI dissection extending superiorly to the hyoid bone, inferiorly to the suprasternal notch, laterally to the carotid sheaths, and dorsally to the prevertebral fascia. Bilateral CND included the removal of prelaryngeal, pretracheal, and both the paratracheal nodes on the side of the tumor and contralateral to the tumor (10). Moreover, pretracheal LNs are further divided into ipsilateral pretracheal LNs and contralateral pretracheal LNs intraoperatively based on the middle line of the anterior wall of the trachea (**Figure 1**).

Histopathological Examination of Surgical Specimens

LNs in each subsite of the central compartment were separated and labeled after dissection and sent for pathological examination along with the resection thyroid specimens. Thyroid specimens and dissected LNs were microscopically examined by two or more experienced pathologists. The following factors were assessed: primary tumor size, multifocality, capsular invasion, extrathyroidal extension (ETE), chronic lymphocytic thyroiditis, the number of metastatic LNs, and the total number of LNs in each subsite. The pathological stage of thyroid cancer was determined in accordance with the 8th edition of the American Joint Committee on Cancer Staging Manual (11).

Postoperative Management and Follow-Up

Postoperative serum calcium and intact parathyroid hormone concentrations were measured in all patients. Patients who developed hypocalcemia were treated with oral calcium and vitamin D supplements, and those who developed significant symptoms were administered intravenous calcium gluconate. Transient hypocalcemia was defined as an ionized serum calcium concentration of <2.1 mmol/L and the calcium level recovered to normal within 6 months, while permanent hypocalcemia was defined as an ionized serum calcium concentration that remained below normal at ≥6 months after surgery and required oral calcium and vitamin D supplementation. Preoperative fibrolaryngoscopic examination was performed for each patient, while postoperative examination was selectively performed in the case who developed hoarseness after surgery. Vocal cord palsy that lasted for 6 months postoperatively was regarded as permanent. All patients received thyroid-stimulating hormone suppression therapy after surgery and underwent regular follow-up at 6-to 12-month intervals with clinical evaluation including serum thyroglobulin (Tg) level, ultrasonography (US) and CT. Locoregional recurrence was defined as the presence of tumors or metastatic LNs on cytological diagnosis. Radioactive iodine (RAI) therapy was performed based on tumor stage and risk factors, in accordance with the American Thyroid Association guidelines (10).

Statistical Analysis

Statistical analyses were performed using SPSS software (version 19.0, IBM Corp, Armonk, NY, USA), and a P value <0.05 was

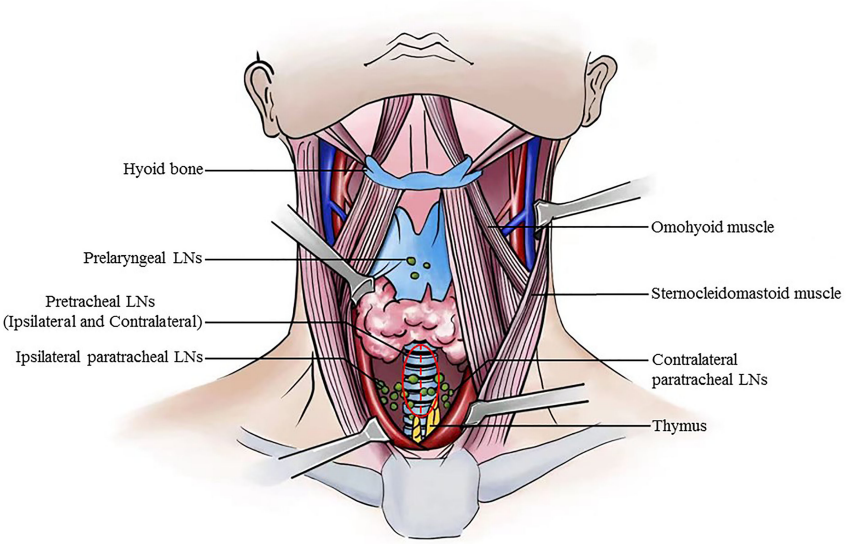

FIGURE 1 | Illustration of pretracheal lymph node subdivision in the central compartment.

considered to be statistically significant. Continuous variables are presented as the mean ± standard deviation (SD), and categorical variables are presented as numbers with percentages (%). Student's t-test was used for continuous variables, and the chi-square test was used for categorical variables in univariate analysis. Multivariate analysis was performed by binary logistic regression to determine if the clinicopathological characteristics were risk factors for contralateral CLNM.

RESULTS

Clinicopathological Characteristics of 139 PTC Patients Who Underwent Total Thyroidectomy With Bilateral CND

The demographics and clinical data of the 139 patients (34 men and 105 women) are summarized in **Table 1**. The median age was 39 years (range, 18–72 years). Of these 139 patients, 89.9% (125/139) were <55 years old, and 10.1% (14/139) were ≥55 years old. The mean ± SD size of the primary tumor was 1.3 ± 0.7 cm (range, 0.6–3.7 cm). Fifty-six (40.3%) patients had a primary tumor ≤1 cm, and 83 (59.7%) patients had a primary tumor >1 cm. Multifocality was observed in 33 (23.7%) patients, capsular invasion was found in 66 (47.5%) patients, and ETE was confirmed in 31 (22.3%) patients. The mean ± SD number of dissected nodes was 5.4 ± 3.2 in the ipsilateral paratracheal region, 3.8 ± 3.0 in the contralateral paratracheal region, 1.4 ± 1.2 in the prelaryngeal region, and 3.8 ± 2.2 in the pretracheal region. One hundred and three (73.4%) patients had pretracheal LNM, 47 (33.8%) patients had prelaryngeal LNM, 88 (63.3%) patients had ipsilateral CLNM, and 37 (26.6%) patients had bilateral CLNM. Among these patients, 7 (5.0%) patients had isolated contralateral CLNM.

Risk Factors for Contralateral CLN Metastasis in 139 PTC Patients

In univariate analysis, prelaryngeal LNM (P = 0.002) and ipsilateral paratracheal LNM (P = 0.009) were significantly associated with contralateral CLNM (**Table 2**). Moreover, contralateral pretracheal LNM (P = 0.001) was significantly associated with contralateral CLNM, while pretracheal LNM was not associated with contralateral CLNM. Among patients with central lymph node metastasis, contralateral pretracheal lymph node positivity was significantly associated with patient age (P = 0.034) (**Table 3**). In multivariate analysis, prelaryngeal LNM (P = 0.004, odds ratio = 3.457) and contralateral pretracheal LNM (P = 0.006, odds ratio = 3.362) were independent predictive factors for contralateral CLNM (**Table 4**).

Postoperative Morbidities and RAI Therapy

Forty-five (32.4%) of 139 patients developed postoperative hypocalcemia and they all recovered within 6 months. Five patients developed hoarseness and were confirmed to have vocal cord palsy by fibrolaryngoscopic examination. Four of the 5 patients recovered to normal cord mobility within 6 months. Forty-nine (35.3%) patients received RAI therapy (100–150 mCi) after surgery, and no patient had neck recurrence (central or lateral) or distant metastasis during the mean follow-up duration of 9.1 ± 1.8 months (range, 6–20 months).

DISCUSSION

In most patients with PTC, cervical nodal metastasis generally occurs in a stepwise sequential fashion (12). Tumors located in the upper part of the thyroid and the pyramidal lobe usually first

TABLE 1 | Clinicopathologic characteristics of patients.

Variables	
Total number of patients	139
Age, median, yrs	39 (18–72)
<55 y/≥55 y, *n* (%)	125 (89.9)/14 (10.1)
Gender, *n* (%)	
Female	105 (75.5)
Male	34 (24.5)
Primary tumor size, cm	1.3±0.7 (0.6–3.7)
≤1 cm/>1 cm, *n* (%)	56 (40.3)/83 (59.7)
Multifocality, *n* (%)	33 (23.7)
Chronic lymphocytic thyroiditis, *n* (%)	43 (30.9)
Capsular invasion, *n* (%)	66 (47.5)
Extrathyroidal extension, *n* (%)	31 (22.3)
Prelaryngeal LNM, *n* (%)	47 (33.8)
Pretracheal LNM, *n* (%)	102 (73.4)
Ipsilateral pretracheal LNM, *n* (%)	73 (52.5)
Contralateral pretracheal LNM, *n* (%)	62 (44.6)
Ipsilateral CLNM, *n* (%)	88 (63.3)
Contralateral CLNM, *n* (%)	37 (26.6)
CLNM, central lymph node metastasis; LNM, lymph node metastasis.	

CLNM, central lymph node metastasis; LNM, lymph node metastasis.

TABLE 2 | Univariate analysis of clinicopathologic characteristics for contralateral CLNM.

	Contralateral CLNM, *n* (%)	*P*
Age, yrs		1.000*
<55	33 (26.4)	
≥55	4 (28.6)	
Gender		0.118
Female	25 (23.8)	
Male	12 (35.3)	
Primary tumor size, cm		0.126
≤1	11 (19.6)	
>1	26 (31.3)	
Capsular invasion		0.291
Yes	22 (33.3)	
No	10 (23.8)	
Extrathyroidal extension		0.422
Yes	5 (16.1)	
No	10 (23.8)	
Multifocality		0.922
Yes	9 (27.3)	
No	28 (26.4)	
Chronic lymphocytic thyroiditis		0.289
Yes	14 (32.6)	
No	23 (24.0)	
Prelaryngeal LNM		0.002
Yes	20 (42.6)	
No	17 (18.5)	
Pretracheal LNM		0.216
Yes	30 (29.4)	
No	7 (18.9)	
Ipsilateral CLNM		0.009
Yes	30 (34.1)	
No	7 (13.7)	
Ipsilateral pretracheal LNM		0.17
Yes	23 (31.5)	
No	14 (21.2)	
Contralateral pretracheal LNM		0.001
Yes	25 (40.3)	
No	12 (15.6)	

*CLNM, central lymph node metastasis; LNM, lymph node metastasis. *Fisher's exact test.*

TABLE 3 | Characteristics of contralateral pretracheal lymph node positivity in patients with contralateral CLNM.

	Patients with contralateral CLNM		
	Contralateral pretracheal lymph node-positive (*n* = 25)	Contralateral pretracheal lymph node-negative (*n* = 12)	*P*
Mean age, yrs	38.5 ± 12.3	37.6 ± 7.3	0.034
≥55 years, *n* (%)	4 (16.0)	0	0.142*
Female, *n* (%)	17 (68.0)	8 (66.7)	0.935*
Primary tumor size (range), cm	1.49 ± 0.65	1.58 ± 1.1	0.108
≥1 cm, *n* (%)	18 (72.0)	8 (66.7)	0.740*
Multifocality, *n* (%)	8 (32.0)	1 (8.3)	0.220*
Extrathyroidal extension, *n* (%)	2 (8.0)	3 (25.0)	0.251*
Prelaryngeal LNM, *n* (%)	13 (52.0)	7 (58.3)	0.717
Ipsilateral CLNM, *n* (%)	22 (88.0)	8 (66.7)	0.183*
Ipsilateral pretracheal LNM, *n* (%)	18 (72.0)	5 (41.7)	0.146*

*CLNM, central lymph node metastasis; LNM, lymph node metastasis. *Fisher's exact test.*

TABLE 4 | Multivariate analysis of risk factors for contralateral CLNM.

	β (SE)	*P*	OR	95% CI (OR)	
				Lower	Upper
Prelaryngeal LNM	1.240 (0.430)	0.004	3.457	1.489	8.026
Contralateral pretracheal LNM	1.213 (0.445)	0.006	3.362	1.407	8.037
Ipsilateral CLNM	0.758 (0.500)	0.13	2.133	0.8	5.685
Constant	-2.665 (0.500)				

CI, confidence interval; CLNM, central lymph node metastasis; LNM, lymph node metastasis; OR, odds ratio; SE, standard error.

metastasize to prelaryngeal and carotid triangular LNs, and those located in the middle and lower parts of the thyroid generally first metastasize to ipsilateral CLNs or pretracheal LNs. To the best of our knowledge, the majority of published studies reported that the region ipsilateral to the tumor is the most common metastatic region (2, 13, 14). In contrast, the results of this study showed that the subsite with the highest rate of LNM in the central neck was the pretracheal region (73.4%), followed by the ipsilateral paratracheal region (63.3%).

A few studies have described the pros and cons of prophylactic CND. Some endocrine surgeons recommended performing bilateral CND as comprehensive dissection of CLNs may reduce the risk of locoregional recurrence and facilitate achieving low Tg levels (1, 15–17). In contrast, others performed unilateral CND because most patients with unilateral PTC have a lower rate of contralateral CLNM. They argued that bilateral CND did not significantly improve survival but may increase the risk of postoperative morbidities (18, 19). The incidence of LNM to the contralateral paratracheal region in cN0 PTC patients has been reported to range from 9.8% to 30.6% (20–23). In the present study, we found that the rate of contralateral CLNM was 26.6% (37/139). Our findings also demonstrated that the incidence of contralateral CLNM was relatively low in unilateral cN0 PTC patients. Thus, the surgical extent of ipsilateral CND is sufficient for most unilateral PTCs.

However, ipsilateral CND means that there is a potential risk of locoregional recurrence in the contralateral paratracheal region. An accurate assessment of cervical lymph node status is the key to reducing the risk of locoregional recurrence and surgical complications. Preoperative US is helpful in detecting metastatic LNs in the neck, but the sensitivity is relatively low because of the overlying thyroid gland and trachea (24). In fact, a large proportion of PTC patients with node negative on preoperative US or palpation were found to have cervical LNM on pathological examination after surgery (24, 25). A few studies have suggested some risk factors for predicting contralateral CLNM in cN0 PTC (13, 14, 20–22). A multicenter study reported that contralateral CLNM was associated with ipsilateral paratracheal LNM (20). In another study, pretracheal and prelaryngeal LNM independently predicted contralateral CLNM (26). The results of this study also showed that patients with prelaryngeal LN involvement had a significantly higher rate of contralateral CLNM, and prelaryngeal LNM was an independent risk factor for contralateral CLNM. Recently, some endocrine surgeons have further investigated the value of intraoperative re-evaluation of prelaryngeal and pretracheal LNs through frozen section examination (FSE) in the decision-making of bilateral CND and found that FSE is a safe and effective strategy to decrease the need for a second-step CND (27, 28).

Theoretically, the risk of contralateral CLNM will increase when pretracheal LNs are positive. However, in our study, pretracheal LN metastasis was not associated with contralateral CLNM. In contrast, contralateral pretracheal LNM was significantly associated with contralateral CLNM, and contralateral pretracheal LNM was an independent predictor for contralateral CLNM. Our data suggest that pretracheal LN subdivision has potential value for clinical application, which is helpful for surgeons to determine the extent of CND. To the best of our knowledge, this was the first study assessing

contralateral pretracheal LNM in predicting contralateral CLNM in unilateral cN0 PTC. Based on the results of our study, contralateral pretracheal LNs could be considered sentinel compartments in bilateral CND, and intraoperative FSE should be considered and performed. Locoregional recurrence after CND remains a critical issue in PTC, although the prognostic relevance of microscopic CLNM to recurrence is likely minimal in most cases. Unfortunately, we were unable to determine whether prophylactic contralateral CND is essential in patients with microscopic CLNM since there was a lack of comparison of the cohort group and a short follow-up period in this study. Therefore, we suggest that PTC patients with unilateral tumors presenting with evident nodal disease intraoperatively or preoperatively in the contralateral central neck should undergo therapeutic bilateral CND. Otherwise, ipsilateral CND may be appropriate.

It is evident that there are several limitations in this study. First, although it is conducted prospectively, a small sample size without comparative analysis cannot be overlooked. Further prospective, randomized trials with large sample size are warranted to validate the value of this intraoperative decision-making approach. Second, a longer follow-up duration is required to assess locoregional recurrence and survival. In spite of these limitations, our study has the merit of including cN0 PTC patients operated on with the same therapeutic protocol in the same institution.

CONCLUSIONS

Patients with unilateral PTC are at a relatively low risk of contralateral CLNM and CND limited to the ipsilateral side is appropriate. The results of the present study suggest that prelaryngeal LNM or contralateral pretracheal LNM increases the likelihood of contralateral CLNM. Therefore, intraoperative assessment of prelaryngeal and contralateral pretracheal LNs by using FSE is able to decide whether to perform contralateral CND in patients with unilateral PTC.

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 Institutional Review Board of West China Hospital, Sichuan University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JZ, designed and conceptualized the study. AS, FL and JZ, conducted the study. WL and LZ, collected the data. QC and YL, data analysis and manuscript writing. JZ and AS, interpreted data and refined the manuscript. All authors contributed to the study and approved the submitted version.

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Combined fine-needle aspiration and selective intraoperative frozen section to optimize prediction of malignant thyroid nodules: A retrospective cohort study of more than 3000 patients

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Background: Preoperative fine-needle aspiration (FNA) is widely used to differentiate malignant from benign thyroid nodules, while intraoperative frozen sections (FS) are suggested as a systematic supplement for intraoperative decision-making, but limitations still remain for both procedures.

Methods: Medical records of 3807 patients with thyroid nodules who underwent both pathological diagnoses (FS and FNA) at our hospital were reviewed. The diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of FNA and FS were also evaluated. We further designed an optimal integration scheme (FNA+selective FS) to predict thyroid nodule malignancy. Finally, the efficiency of the proposed integrated diagnostic model was validated using an independent external cohort.

Results: For distinguishing malignant nodules, FNA had an accuracy of 90.3%, sensitivity of 90.7%, specificity of 85.2%, PPV of 98.8% and NPV of 40.4%. In contrast, the FS represented higher discriminative power (Accuracy, 94.5%; Sensitivity, 94.1%; Specificity, 100%; PPV, 100%; and NPV, 55.6%). we proposed the selective usage of FS (removed nodules with Bethesda category VI from routine FS, ~1/3 of total). The integrated new diagnostic model of FNA plus selective FS (FNA+sFS) achieved accuracy of 96.9%, sensitivity of 97.3%, specificity of 92%, PPV of 99.4%, and NPV of 71.6% (NRI=0.135, 95% CI 0.103-0.167, P <0.001) and was successfully applied to an external cohort (N=554).

Conclusion: Compared with the FNA diagnostic system, FS has an increased ability to distinguish benign and malignant thyroid nodules. The newly proposed integrated diagnostic model of FNA + selective FS can optimize the accuracy of diagnosis.

KEYWORDS

FNA, FS, thyroid nodule, prediction, diagnostic model

Introduction

The incidence of thyroid cancer, the most common endocrine malignancy, has been on an upward trend worldwide in recent decades (1, 2). New cases in China are estimated to be 90,000 per year and increasing significantly (3, 4). With the extensive use of high-resolution B-ultrasound in recent years, thyroid nodules can easily be detected in up to 60%-70% of the population, especially in Asian countries (5, 6). Because most of these nodules are benign and require no further treatment, researchers and clinicians have invested much effort in optimizing the filtering process to rule out malignant nodules.

The accurate screening of malignant nodules has long been a major challenge in the management of thyroid disease. For suspicious nodules detected by B-ultrasound, guidelines in every country differ in diagnostic methods such as fine-needle aspiration (FNA) and frozen sections (FS) (7–9). FNA is the most widely used procedure for cytology, which is defined by the Bethesda system depending on the probability of malignancy (10).

FNA can distinguish approximately 75%-80% of nodules, while the remaining 20%-25% remain indeterminate. Some other supplementary molecular tools can help "rule out" (Afirma GSC) or "rule in" (Thyroseq v3) malignancy in such cases, however, it can only validate 50%-60% of these indeterminate nodules and is unavailable in many countries (11, 12). Intraoperative FS is another widely performed diagnostic procedure which provides a quick intraoperative assessment of nuclear features of thyroid nodules (9). It is routinely used in a lot of countries including China, but the real clinical value and necessity of FS is still highly debated, especially in high Bethesda categories such as Bethesda V and VI (13, 14).

To evaluate the clinical values of fine needle aspiration and intraoperative frozen sections, we retrospectively analyzed 3807 patients who underwent thyroidectomy at our hospital with complete pathological information of FNA, FS, and final pathology (FP) from 2012 to 2016. With the validation of each diagnostic procedure, we propose a modified prediction pathway of "FNA+ selective FS" to optimize predictive accuracy and medical cost efficiency.

Materials and methods

Patients

This study included patients who underwent thyroid surgery between January 2012 and December 2016 at the First Affiliated Hospital of Zhejiang University School of Medicine. To explore the pathological consistency among FNA, FS, and FP of thyroid nodules, inclusion and exclusion criteria were defined and are listed in Figure 1. Patients who did not undergo FNA or FS were excluded from the study. Similarly, an independent cohort of patients who underwent thyroid surgery at Hangzhou First People's Hospital, Zhejiang Province, China (from May 2015 to March 2020) was included in this study according to the procedures described above. This study was approved by the Institutional Review Board of the First Affiliated Hospital of Zhejiang University School of Medicine and Hangzhou First People's Hospital. The requirement for informed consent was waived because of the retrospective nature of the study. Clinicopathological data were collected, including age at surgery, sex, nodule size measured in fresh specimens, bilaterality, multifocality, and pathology at diagnosis (FNA, FS, and FP). All the patients involved are Chinese population.

Preoperative FNA and intraoperative FS evaluation

FNA biopsy is used to obtain cells from nodules in the thyroid gland. Pathologists subsequently make a diagnosis based on the biopsy samples. The Bethesda category was applied for FNA diagnosis (Bethesda I for nondiagnostic/unsatisfactory, II for benign, III for atypia of undetermined significance/follicular lesion of undetermined significance, IV for follicular neoplasm/suspicious for follicular neoplasm, V for suspicious for malignancy, and VI for malignancy). At our hospital, we conduct FNA mostly for patients with a thyroid imaging reporting and data system (TI-RADS) 4a and above. Notably, nodules highly suspicious for adenoma were not recommended for FNA. After the nodules were surgically resected, the pathologists immediately made an intraoperative FS diagnosis of the specimens. The FS diagnosis was stratified into malignancy, suspicious for malignancy, benign, and indeterminate.

Statistical analysis

Categorical variables were compared using the $\chi 2$ test. A Sankey diagram was generated to visualize the shifts in diagnosis between FNA and FS, as well as FS and FP. The accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using standard formulae. In addition, the net reclassification index (NRI) was used to evaluate whether one model led to a better reclassification of patients than another model, using previously described (15, 16). Statistical analyses were conducted using SAS (version 9.4; SAS Institute, Inc., Cary, NC, USA) or R (version 3.5.2). $P < 0.05$.

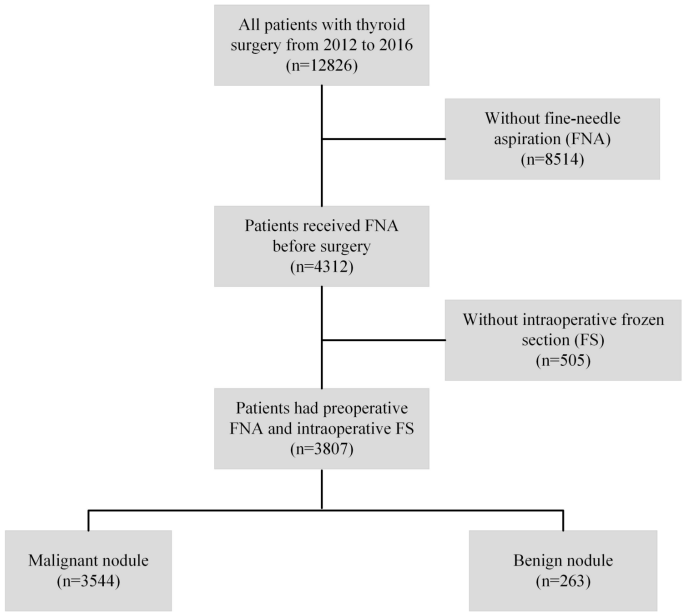

FIGURE 1
Study cohort flowchart.

Results

Clinicopathologic characteristics of patients

Between January 2012 and December 2016, 12826 patients underwent thyroid surgery at the First Affiliated Hospital of the Zhejiang University School of Medicine. 3807 patients with thyroid nodules who underwent all three pathological diagnoses (FS, FNA, and FP) in our hospital were included in our analysis. The demographic and clinicopathological characteristics of the patients are summarized in Table 1. The cohort included 2870 (75.4%) women and 937 (24.6%) men. Patients aged < 55 years accounted for 77.5% of the study

TABLE 1 Clinicopathologic characteristics of the 3807 patients who met inclusion criteria.

	Final pathology						
	Total (n=3807)		Malignancy (n=3544)		Benign (n=263)		
Variables	No.	%	No.	%	No.	%	P value
Age (years)							<0.001
<55	2949	77.5	2790	78.7	159	60.5	
≥55	858	22.5	754	21.3	104	39.5	
Sex							0.013
Female	2870	75.4	2655	74.9	215	81.7	
Male	937	24.6	889	25.1	48	18.3	
Diameter (mm)#							<0.001
<5	829	21.8	812	22.9	17	6.5	
5-10	1747	45.9	1652	46.6	95	36.1	
≥10	1231	32.3	1080	30.5	151	57.4	
Bilaterality							
Yes	NA	NA	735	20.7	NA	NA	
No	NA	NA	2809	79.3	NA	NA	

(Continued)

TABLE 1 Continued

	Final pathology						
	Total (n=3807)		Malignancy (n=3544)		Benign (n=263)		
Variables	No.	%	No.	%	No.	%	P value
multifocality							
Yes	NA	NA	1071	30.2	NA	NA	
No	NA	NA	2473	69.8	NA	NA	

#, The diameter of nodules which underwent FNA; N/A, Not Applicable

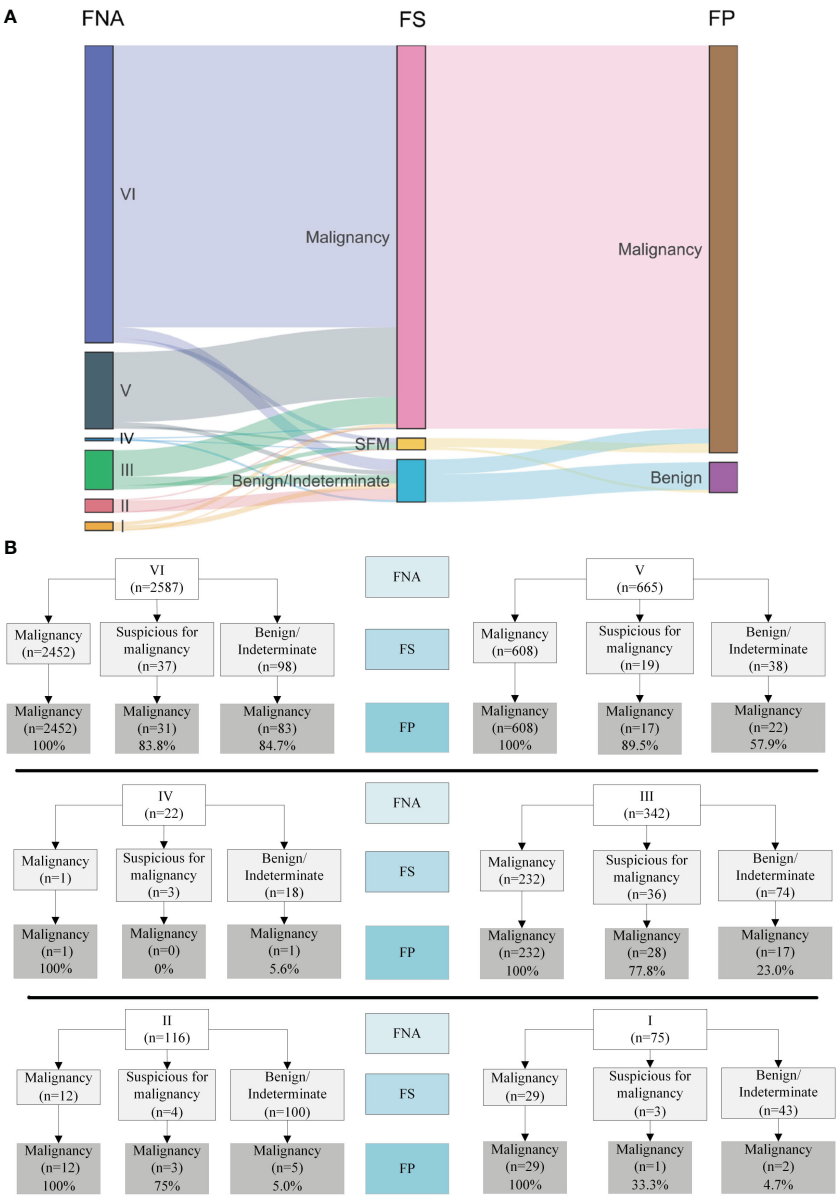

FIGURE 2
Visualization of the shifts of diagnosis among FNA, FS and FP. **(A)** Sankey diagram. **(B)** Details of the shifts. FNA I, II, III, IV, V, VI represents Bethesda category I (Nondiagnostic/unsatisfactory), II (Benign), III (atypia of undetermined significance/follicular lesion of undetermined significance), IV (follicular neoplasm/suspicious for follicular neoplasm), V (suspicious for malignancy) and VI (malignant).

population. There were 829 (21.8%) patients whose FNA nodules had a diameter < 5 mm, 1747 (45.9%) had a diameter between 5 and 10 mm, and 1231 (32.3%) had a diameter ≥10 mm. Bilateral tumors were observed in 735 (20.7%) patients, and multifocal tumors were observed in 1071 (30.2%) patients with malignant pathology.

Visualization of diagnosis shifts amongst FNA, FS and FP

A Sankey diagram was generated to visualize shifts in diagnosis among FNA, FS, and FP (Figure 2A). As shown in Figure 2B, most patients with Bethesda categories VI (2452/2587, 94.8%) and V (608/665, 91.4%) were classified as malignant when evaluated with FS. Notably, 67.8% (232/342) of the patients with Bethesda category III were also classified as having malignant nodules through FS. In addition, 9.7% (371/3807) of the patients were diagnosed with Benign or indeterminate FS histology (Figure 2 and Table 2). Among the 371 patients, 98, 38, 18, 74, 100, and 43 patients were from Bethesda categories VI, V, IV, III, II, and I, respectively (Figure 2B).

The malignancy rates were 99.2% (2566/2587), 97.3% (647/665), 9.1% (2/22), 81% (277/342), 17.2% (20/116), and 42.7% (32/75) for Bethesda categories VI, V, IV, III, II, and I, respectively (Table 2). Surprisingly, we found that all nodules that were malignant in FS were eventually diagnosed as malignant (100%, 3334/3334). Meanwhile, among the nodules classified as suspicious for malignancy, benign, and indeterminate through FS, the malignancy rates were 78.4% (80/102), 34.5% (126/365), and 66.7% (4/6), respectively.

Diagnostic accuracy fine-needle aspiration, frozen section and final pathology

To evaluate the ability of FNA and FS to distinguish between benign and malignant thyroid nodules, we compared the diagnosis of FNA and FS with that of the final pathological diagnosis (FP). When malignancy and nodules suspicious for malignancy were considered as the final malignancy diagnosis, the FNA diagnostic system achieved optimal discriminative power (accuracy, 90.3%; sensitivity, 90.7%; specificity, 85.2%; PPV, 98.8%; NPV, 40.4%) (Figure 3A). Similarly, the best model of the FS diagnostic system for distinguishing benign from malignant nodules had an accuracy of 94.5%, sensitivity of 94.1%, specificity of 100%, PPV of 100%, and NPV of 55.6% (Figure 3B).

To seek an alternative scheme, a flowchart of FNA+selective FS (FNA+sFS) was designed (Figure 3C), and only 32% of patients (1220/3807, Bethesda category I-V) needed to undergo FS for the construction of FNA+sFS. When reclassified according to FNA+sFS, the malignancy rates for malignancy, suspicion of malignancy, benign, and indeterminate were 99.4% (3448/3469), 75.4% (49/65), 16.7% (45/269), and 50% (2/4), respectively (Table 3). We found that the best FNA+sFS model had an accuracy of 96.9%, sensitivity of 97.3%, specificity of 92%, PPV of 99.4%, and NPV of 71.6% (all $P < 0.05$, Figure 3D). A comparison of the best models among FNA, FS, and FNA+sFS is shown in Figure 3E. Compared with the FNA diagnostic system, the FS correctly reclassified 18.2% of patients (NRI=0.182, 95% CI 0.138-0.227, $P < 0.001$). The new proposed scheme, FNA+sFS, also performed much better than FNA alone (NRI=0.135, 95% CI 0.103-0.167, $P < 0.001$, Figure 3F).

The validation of FNA+sFS in an independent cohort

Finally, an independent validation cohort of 554 patients from Hangzhou First People's Hospital, Zhejiang Province, China (from May 2015 to March 2020) was included in this study and analyzed in accordance with the procedures described above (Figure 4). When FNA+sFS was applied to the independent validation set from the

TABLE 2 The distribution of final benign and malignant diagnoses among two diagnostic system.

Diagnosis Category	Final Pathology				
	Malignancy		Benign		Total
	No.	%	No.	%	(N = 3807)
FNA					
Malignant (VI)	2566	99.2	21	0.8	2587
SFM (V)	647	97.3	18	2.7	665
FN/SFN (IV)	2	9.1	20	90.9	22
AUS/FLUS (III)	277	81	65	19	342
Benign (II)	20	17.2	96	82.8	116
Nondiagnostic/unsatisfactory (I)	32	42.7	43	57.3	75
FS					
Malignancy	3334	100	0	0	3334
Suspicious for malignancy	80	78.4	22	21.6	102
Benign	126	34.5	239	65.5	365
Indeterminate	4	66.7	2	33.3	6

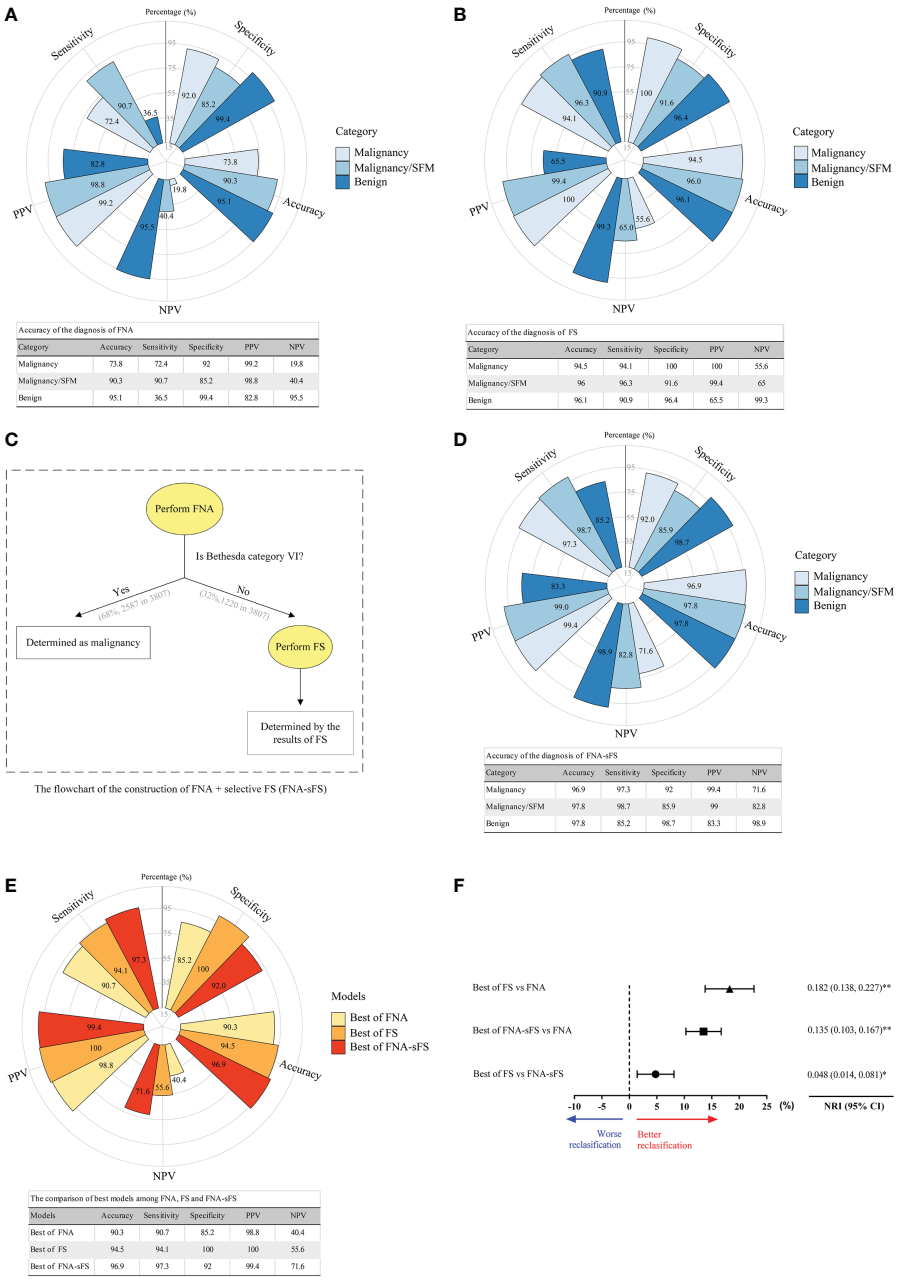

FIGURE 3
Accuracy comparison of the diagnosis of FNA, FS and modified diagnostic model (FNA+sFS). **(A)** Accuracy of the diagnosis of FNA. (All values shown as percent). **(B)** Accuracy of the diagnosis of FS. **(C)** The flowchart for FNA+ Selective FS (FNA+sFS). **(D)** Accuracy of the diagnosis using FNA+sFS. **(E, F)** The comparison of best models among FNA, FS and FNA+sFS. NRI, net reclassification index. * P < 0.05; ** P < 0.05. NPV, negative predictive value; PPV, positive predictive value.

Hangzhou First People's Hospital cohort (N=554), it displayed a discriminatory capability with an accuracy of 89%, sensitivity of 92.6%, specificity of 68.3%, PPV of 94.4%, and NPV of 61.5%, which was significantly better than FNA only (NRI=0.188, 95% CI 0.116-0.259, P <0.001) and not inferior to FS (P = 0.137).

Discussion

Distinguishing malignant nodules from benign nodules plays an important role in thyroid disease management, especially in avoiding overtreatment and potential surgical complications. FNA and FS are well-established diagnostic procedures for malignancy prediction; however, their accuracy and necessity are still debated. We validated the clinical significance of FNA and FS in a large cohort of 3837 patients. We propose a combined FNA+sFS strategy to better balance the diagnostic accuracy and medical cost efficiency.

Diagnostic FNA has long been recommended as the first choice of treatment for nodules suspected to be malignant. In our cohort, it is notable that FNA alone can achieve 90.3% accuracy and 90.7% sensitivity when malignancy and suspicious for malignancy are classified as positive, which influenced the routine use of FNA as

TABLE 3 The distribution of final benign and malignant diagnoses in new diagnostic system.

Diagnosis Category	Final Pathology				Total
	Malignancy		Benign		
	No.	%	No.	%	(N = 3807)
FNA+sFS					
Malignancy	3448	99.4	21	0.6	3469
Suspicious for malignancy	49	75.4	16	24.6	65
Benign	45	16.7	224	83.3	269
Indeterminate	2	50	2	50	4

the first-line screening tool. However, we also observed that the specificity of FNA was only 85.2%. The undetermined cases may need a repeat aspiration or molecular tools to help decision-making (17). A previous study of a large sample size suggested repeat fine-needle aspiration of the atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) nodules did not promote detection of malignancy (18). Additional molecular tools such as Afirma GSC and Thyroseq v3 only had probability of correct

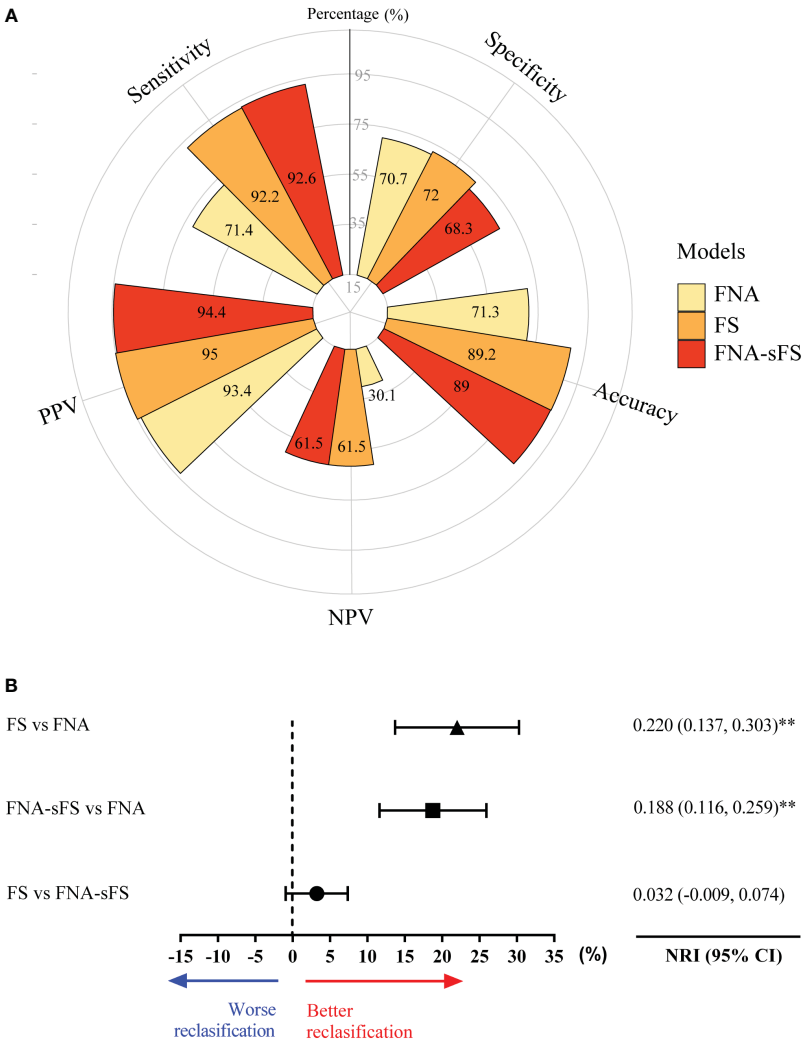

FIGURE 4
The validation of discriminatory capability of FNA+sFS in an independent cohort. **(A)** The comparison of best models among FNA, FS and FNA+sFS in an independent validation cohort. **(B)** The forest plot shows FNA-SF has better reclassification capacity than FNA and FS is also better than FNA, while there is no statistically difference between FNA-SF and FNA. NRI, net reclassification; ** P < 0.05. NPV, negative predictive value; PPV, positive predictive value.

diagnosis of 63.7% and 73.2% with expenses of $17,873 and $14,277 per each correct case (19). Molecular tools are inaccessible in many countries including China. Additionally, patients may refuse repetitive aspiration for various reasons.

Intraoperative FS was another option for secondary confirmation. FSs are routinely used in China and other Asian countries (13, 20, 21). For patients with intermediate and nondiagnostic FNA cytopathology, FS might help to confirm the necessity of total thyroidectomy and central neck lymph node dissection. A retrospective study of 662 patients by Chang et al. demonstrated that FS could lead to a correct diagnosis in 78.9% of lesions, while FNA was only 21.1% (22). Sandrine Estebe et al. found that unnecessary total thyroidectomy and two-stage surgery rates would decrease from 3.6% and 7.7% to 0% and 5.2%, respectively with FS (23). On the other hand, Reema Mallick et al. explored the usefulness of FS and found that intraoperative management was changed in only 2.1% of their cohort and therefore did not recommend its routine use (24). In the present study, we validated the accuracy and necessity of FS by using a fairly large sample size of 3807 patients. FSs demonstrated an overall 18% extra reclassification better than FNA, which confirms the clinical value and necessity of FS, with all categories benefiting.

Our data showed a high malignancy rate of 99.7% in FNA category VI. A meta-analysis by Nguyen Truong Phan Xuan et al. also demonstrated an extremely high malignancy rate of 98.1% % Bethesda VI nodules in Asian countries (20). Therefore, it is reasonable not to apply FS to this subset of patients. Some previous studies also suggested eliminating the use of FS in high categories of FNA, which is in agreement with our strategy of leaving Bethesda VI nodules from the frozen section procedure (25, 26). For nodules with FNA categories I-V, we further investigated the necessity of performing FS with FNA and found that selective FS could raise the rate of correct reclassification by 15% in comparison to FNA only (accuracy 96.9%, sensitivity 97.3%, specificity 92%, PPV 99.4%, and NPV 71.6%). Besides, the cost of FNA was nearly 170 USD and the cost of FS was about 20 USD for each specimen. The potential benefits of the FNA+selective FS would decrease about 1/3 usage of FS while keeping high discriminative power with accuracy of 96.9%, sensitivity of 97.3%, specificity of 92%, PPV of 99.4% and NPV of 71.6%.

Our study had some limitations. First, we did not include molecular tools to increase the accuracy of the prediction. Supplementary molecular tools, such as Afirma GSC or Thyroseq v3, are not currently available in China. In addition, as a retrospective analysis, although we involved an analysis of an external independent cohort consisting of 554 cases from another large clinical center, there is still room for further analysis to approach the highest level of reliability. We recommend setting up a prospective multicenter randomized clinical trial (RCT) with detailed pathology subtypes and supplementary molecular information to optimize our "FNA + selective FS" system in the future.

In summary, our study retrospectively evaluated the clinical value of fine needle aspiration and intraoperative frozen sections in a large sample size of 3837 patients. We propose a modified thyroid nodule prediction method of "Combined FNA and selective FS," which helps clarify the clinical criterion of FS usage with consideration of both diagnostic accuracy and medical efficiency.

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 Institutional Review Board of the First Affiliated Hospital of Zhejiang University School of Medicine Institutional Review Board of Hangzhou First People's Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZM, YD, LW, WW and LT designed the current study and wrote the manuscript. ZM, YD and LW conducted the statistical analyses. ZM, YD, LW, YZ, GW, QY and JW created the original databases to collect the clinicopathological data. WW, DL and LT reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

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Prospective study and proposal of an outcome predictive nomogram in a consecutive prospective series of differentiated thyroid cancer based on the new ATA risk categories and TNM

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Introduction: The personalized management of differentiated thyroid cancer (DTC) is currently based on the postoperative TNM staging system and the ATA risk stratification system (RSS), both updated in 2018 and 2015, respectively.

Purpose: We aimed to evaluate the impact of the last two editions of TNM and ATA RSS in the prediction of persistent/recurrent disease in a large series of DTC patients.

Patients and methods: Our prospective study included 451 patients undergone thyroidectomy for DTC. We classified the patients according to TNM (both VIII and VII ed.) and stratified them according to the ATA RSS (both 2015 and 2009). We then evaluated the response to the initial therapy after 12-18 months according to the ATA "ongoing" risk stratification, and analyzed the variables associated with persistent/recurrent disease by multivariate analysis.

Results: The performance of the last two ATA RSSs was not significantly different. By staging patients according to the VIII or VII TNM editions, we found significant differences only in the distribution of patients with structural disease classified in stages III and IV. At multivariate analysis, only T-status and N-status were independently associated with persistent/recurrent disease. Overall, ATA RSSs and TNMs showed low predictive power in terms of persistent/recurrent disease (by Harrell's test).

Conclusions: In our series of DTC patients, the new ATA RSS as well as the VIII TNM staging provided no additional benefit compared to the previous editions. Moreover, the VIII TNM staging system may underestimate disease severity in patients with large and numerous lymph node metastases at diagnosis.

KEYWORDS

differentiated thyroid cancer, thyroid cancer outcome, thyroid cancer risk factors, persistent or recurrent disease, TNM staging system, risk stratification system TNM staging and ATA risk stratification systems

1 Introduction

Thyroid cancer (TC) is the most common endocrine malignancy, representing about 90% of cases. TC is the most rapidly increasing cancer in the United States, where its incidence increased by 211% in the years 1975-2013; however, due in part to the adoption of more conservative diagnostic criteria, the incidence rate declined by 2.5% per year from 2014 to 2018 (1). The mortality from TC is very low and the death rate increased slightly during 2008 to 2017 (0.6% per year) despite earlier diagnosis and better treatment. In recent years TC death rate appears fairly stable (1). The prognosis of differentiated thyroid cancer (DTC) is excellent with a 5-year survival rate of 99-100% for localized, 98% for regional and 53% for metastatic disease (2).

In 2015 the American Thyroid Association (ATA) guidelines for DTC management (3) introduced a new risk stratification system, which included some supplementary prognostic factors such as lymph node characteristics (number, size and extranodal extension), mutational status, and foci's number of vascular invasion. However, as stated in the ATA guidelines "the incremental benefit of adding these specific prognostic variables to the 2009 initial risk stratification system has not been established" and the added value of this modification has not yet been validated.

The TNM classification has also been updated in 2018 to better predict DTC survival (4). As a result of the changes, the eighth edition of the TNM results in the downstaging of a significant percentage of patients to more accurately indicate the low specific risk of death. Currently, the appropriate clinical-therapeutic management of TC requires post-surgical TNM staging to predict survival, and the assessment of the risk of persistent/recurrent disease according to the ATA risk stratification system. During the follow-up this risk is also regularly re-evaluated according to the "ongoing risk stratification" (3) based on the measurement of thyroglobulin (Tg), thyroglobulin antibodies (TgAb), neck ultrasound, post-131-I WBS, other imaging evaluation as required.

As expected, a more personalized and accurate assessment of the risk of persistent or recurrent disease and death from TC has a significant impact on the initial treatment decision (extension of thyroid and/or lymph node surgery, need for radioactive iodine ablation/therapy, need for TSH suppressive therapy) and appropriate management strategies during short and long-term follow-up.

In the present study we prospectively evaluated, in a continuous series of 451 DTC patients, the variables associated with persistent/recurrent disease (biochemical and structural) and the predictive power of the different ATA risk categories and TNM staging systems. Our findings may help establishing a tailored treatment management based on tumor and patient characteristics.

2 Patients and methods

We studied a consecutive series of 451 DTC patients undergone thyroidectomy with or without lymphnode dissection from October 2017 to February 2020 and followed up at our thyroid outpatients' clinic. The median follow-up was 20.5 (IQR 14.7-27.4) months.

We staged the tumors according to the 7th and 8 th TNM editions: T (the greatest size of the primary tumor) and N (regional lymphnodes metastases) through histology. We indicated N0 when all removed lymphnodes were negative or if there is no radiological or clinical evidence of lymphnode metastasis, N1a if only the central compartment (levels VI-VII) is involved and N1b if latero-cervical nodes (levels I–V) were positive. M (distant metastases) was evaluated according to the post-surgical 131I-whole body scan (WBS) and/or other imaging evidence.

Disease status was evaluated in all patients through neck ultrasound and Tg and TgAb determination after surgery and periodically during the follow-up (every 3-6 or 12 months).

After 12-18 months from the first evaluation, the response to initial therapy (surgery with or without iodine treatment) was assessed with neck ultrasound and both serum Tg and TgAb measurements, either basal or TSH stimulated (L-thyroxine, LT4withdrawal or rhTSH injection) in radioiodine treated patients. According to their response to the initial therapy (ongoing stratification) patients were re-classified as excellent response (ER), indeterminate (IR), biochemical incomplete (BIR) or structural incomplete response (SIR).

Subsequent follow-up was modulated based on the initial risk evaluation and the first treatment response.

The level of TSH-suppression was based according to the ATA guidelines: substitutive LT4 therapy in low-risk patients without

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evidence of disease; mild TSH suppression (0.1-0.4 mU/L) in intermediate risk patients or biochemical disease; complete suppression (< 0.1 mU/L) in high risk patients and/or if structural disease.

All patients with the evidence of persistent or recurrent disease underwent additional morphological exams (computed assisted tomography (CT scan), magnetic resonance imaging, bone scan, positron emission tomography). If patients were not cured, further treatments such as radioiodine treatment therapy, other surgeries or different therapies) were brought off.

3 Statistical analysis

Categorical variables were expressed as frequencies and percentages; quantitative normally distributed ones as mean ± standard deviation (SD) and non-normally distributed ones as median with interquartile range (IQR). The normality was verified through the Kolmogorov-Smirnov test.

The Chi-square test with Yates's correction or Fisher's test were used to analyze the categorical variables. Multivariate analysis was outbrought off through the logistic regression including only significant variables for recurrent/persistent disease at univariate analysis.

The predictive power of the different ATA risk categories and TNM staging systems at short-term re-evaluation was assessed by the Harrell's C concordance index (C-index).

A nomogram was implemented based on the parameters that resulted significantly associated with the risk of recurrent/persistent disease at the multivariate logistic regression analysis, with a risk score for predicting the probability of persistent and recurrent disease.

TABLE 1 Clinical and histopathological characteristics of the 451 DTC patients.

	n.	(%)
Patients (n.)	451	
Follow-up median (IQR) (months)*	20.5 (14.7-27.4)	
Age median (IQR) (y)	47.5 (36.9-57.8)	
Gender		
F/M (ratio)	324/127 (2.6/1)	
Histotypes		
Papillary	433	96.0
Follicular	12	2.7
Papillary-follicular	4	0.9
Poorly-differentiated	2	0.4
M1	11	2.4
Minimal extrathyroid extension (ETE)	97	21.5
Multifocality	176	39.0

* Follow-up minimum 6 months.

A p-value <0.05 was considered statistically significant for all analyses. Data analysis was performed using the Stata software version 16.

4 Results

Clinical and histopathological characteristics are shown in Table 1. Most patients were females with a F/M ratio of 2.6/1.0. Median age at diagnosis was 47.5 yrs (IQR 36.9-57.8). Histotype was papillary in almost all cases (96%). 14.2% of patients had an aggressive PTC variant (diffuse sclerosing, tall cell, insular or columnar).

Eleven patients (2.4%) had distant metastases at diagnosis (10 lung metastases and 1 with lung and bone metastases).

Minimal extrathyroid extension was present in 21.5% and multifocality in 39.0% of patients.

Most patients fell into the T1 and T2 categories, especially with the new TNM staging system; 26.8% of patients had central (N1a) and 13.7% latero-cervical lymphnode metastases (N1b).

Two hundred seventy-seven (61.4%) patients were treated with 131I with different activities: 85 patients with 30 mCi, 186 patients with 100 mCi, 3 patients with 50 mCi, 1 patient with 70 mCi, 1 patient with 150 mCi e another 1 with 200 mCi. 156 patients were treated after L-T4 withdrawal and 121 after rhTSH administration. Six (1.3%) patients required another surgical treatment in the neck and 6 (1.3%) patients underwent to a second 131I treatment after about 12 months from the first.

4.1 TNM staging system and risk stratification system

TNM, staging (VII and VIII editions) and Risk stratification classifications are shown in Table 2.

Applying VII TNM staging system 60% tumors were T1a and T1b,instead applying VIII TNM more than ¾ of the patients (77.4%) fall into this category. This different percentage depends mainly on the removal of minimal extrathyroid extension from T3 classification.

Regarding the lymph node status, applying VII TNM staging 12.0% patients were N0 47.5% Nx; instead applying VIII TNM staging almost 60% of cases were N0a or N0b (268, 59.4%) (due to the removal of Nx in the new TNM system). Thesame percentages were in N1a and N1b classes.

Six patients presented latero-cervical metastases without involvement of the central compartment (skip metastases).

Patients were also staged comparing VII vs VII TNM staging system (Figure 1): most patients fell into stage I using both classifications, respectively 71.9% vs 86.5%.Using VIII TNM edition there was a significative downstaging in all categories (about 30%), mostly from stage III and IVA into stage I and II.

At initial evaluation, patients were subdivided into three different risk categories with few variations in percentage due mainly to the lymph node number and size categorization using 2009 or 2015 ATA risk stratification: 42.8% and 45.5% low, 54.8%

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TABLE 2 TNM, staging (VII and VIII editions) and risk categories (2009 and 2015) of the 451 DTC patients.

		n.	(%)			n.	(%)
TNM (VII ed.)				TNM (VIII ed.)			
T status (T)				T status (T)			
T1a		166	36.8	T1a		206	45.7
T1b		105	23.3	T1b		143	31.7
T2		56	12.4	T2		73	16.2
T3		113	25.1	T3a		5	1.1
T4a		5	1.1	T3b		13	2.9
Tx		6	1.3	T4a		5	1.1
				Tx		6	1.3
N status (N)				N status (N)			
N0		54	12.0	N0a		124	27.5
N1a		121	26.8	N0b		144	31.9
N1b		62	13.7	N1a		121	26.8
Nx		214	47.5	N1b		62	13.7
Staging (VII ed.)				Staging (VIII ed.)			
<45	I	202	44.8	<55	I	298	66.1
	II	4	0.9		II	10	2.2
≥45	I	122	27.1	≥55	I	92	20.4
	II	19	4.2		II	39	8.6
	III	62	13.7		III	5	1.1
	IVA	34	7.5		IVA	0	
	IVB	0			IVB	7	1.6
	IVC	8	1.8				
Risk categories at first evaluation 2009 guidelines				Risk categories at first evaluation 2015 guidelines			
Low		193	42.8	Low		205	45.5
Intermediate		247	54.8	Intermediate		231	51.2
High		11	2.4	High		15	3.3

and 51.2% intermediate and 2.4% and 3.3% high risk according to respectively 2009 and 2015 ATA risk system.

4.2 Response to initial therapy, 12-18 months after initial treatment, in all patients

After initial treatment, 63.9% of patients presented with excellent response. However, 35 patients (not ablated) had basal Tg between 0.2 and 1 ng/mL, stable and compatible with small thyroid remnant. After 12-18 months from initial treatment, just over a third of patients (36.1%) were not cured.

In particular 82 patients presented an indeterminate response (68 patients had indeterminate Tg or TgAb and 14 patients non-specific finding at neck ultrasound or CTscan). Five patients had biochemical incomplete response and 76 patients structural incomplete response (52 had lymph node metastases, almost all small in number and size; 10 lung metastases; 1 only bone metastases and 5 lung and bone metastases, 5 lung and LN metastases, 2 lung, bone and local disease).

4.2.1 Response to initial therapy according to ATA risk categories

As expected, the percentage of patients with an excellent response decreased through risk categories, being less frequent in intermediate- and mostly high-risk patients with both ATA risk categories (Figure 2).

In low risk patients, no significant difference was found in both TNM: approximately 72% had an ER, 19% IR, 1% BIR and 7.8% SIR.

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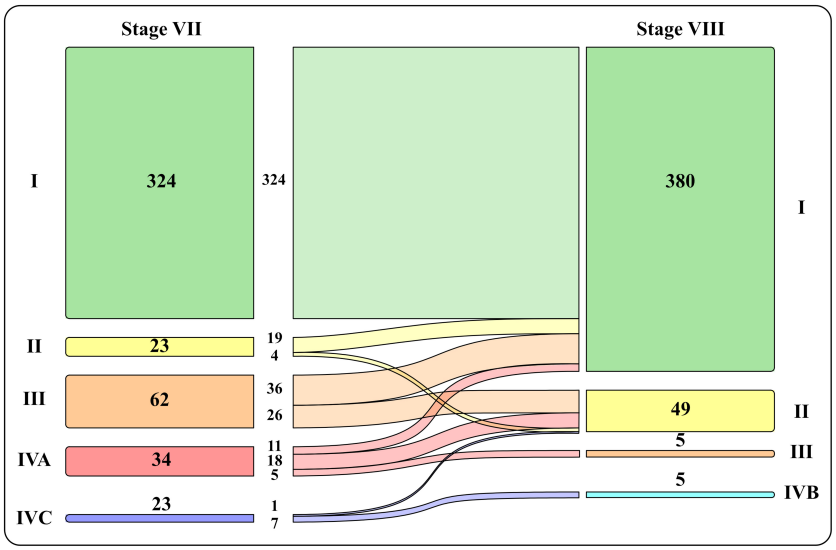

FIGURE 1
Graphic representation of patients' distribution into the four stages with VII vs VII TNM staging system.

Also in intermediate risk patients, no significant difference was found: approximately 60% ER, 17.5% IR, 1% BIR and 21% SIR.

Instead in high risk patients, 20% vs 9.1% had ER, 13.3% vs 9.1% an IR and 66.7% vs 81.8% SIR, respectively using 2009 and 2015 ATA risk stratification.

The results did not change after analysing classic PTC subtype and all DTC separately.

4.3 Structural disease after 12-18 months after initial treatment according to VII vs VIII TNM staging

As expected, the percentage of patients with structural disease increases through the stages mostly using VIII TNM ed. (Figure 3).

Comparing the two TNM editions, a similar percentage of disease was observed in stage I and II both using VII or VIII TNM edition instead a significant difference in stage III and IV, respectively p=0.004 and 0.04.

4.4 Predictors of persistent/recurrent disease at 12-18 months after first treatment

Risk factors of persistent disease (either morphologic or biochemical) at last disease assessment are presented in Table 3.

At univariate analysis, the factors associated to the presence of disease were: T status, the presence of lymph node metastasis, both in the central compartment and in lateral compartments (N1a and N1b status), the presence of more than five lymph node metastases, ATA risk intermediate or high and radioiodine treatment therapy.

At multivariate analysis, both T status and lateral lymph node metastasis were patient features independently predicting persistent/recurrent disease (higher O.R. for N1b= 3.07, p<0.001).

Taking into account only structural incomplete response (SIR) at univariate analysis, the factors associated to the presence of persistent disease are, beyond the same risk factors of above, were male gender and multifocality. At multivariate analysis T status and lateral-lymph node were independent predictors of disease (Table 4).

Since the multivariate analysis showed that lymph node metastases have a significant impact to predict persistent/

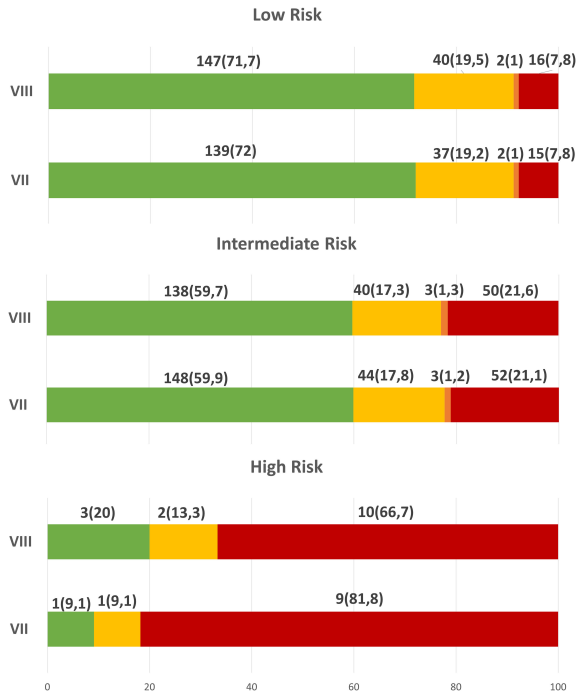

FIGURE 2
Response to initial therapy, 12-18 months after initial treatment, according to ATA risk categories.

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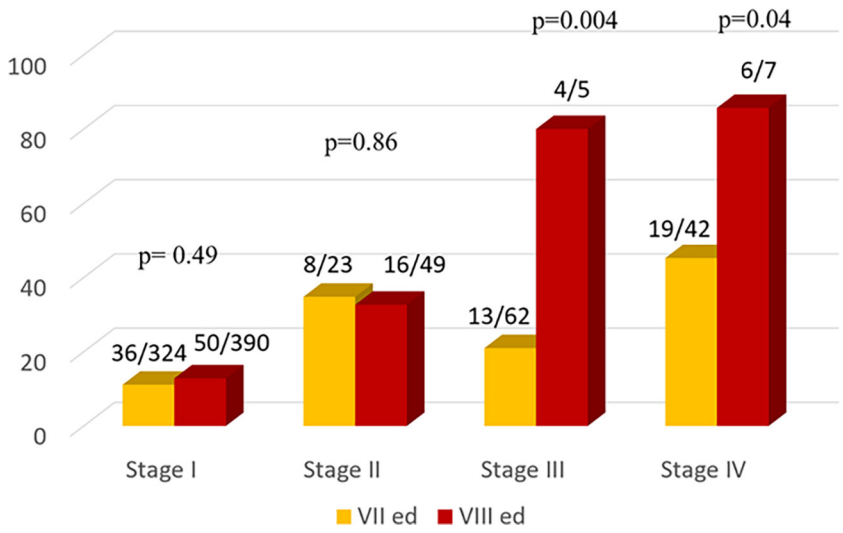

FIGURE 3
Comparison of the Number of Patients with structural disease according to the Seventh (yellow bars) and Eighth (red bars) TNM Editions.

recurrent disease, LN characteristics (localization and number) have been investigated in detail.

As expected not only the presence of positive LN (N1a + N1b vs N0/Nx), but also the number of nodal metastases and their location (N1b vs N1a) were relevant risk factors for persistent/recurrent disease persistence at 12-18 months after first treatment.

Persistent disease was significantly higher in N1 vs N0a/N0b patients (47% vs 28.7%, p<0.001).

Analyzing the number of nodal metastases, using the cut off of 5 positive nodes, the likelihood of persistent disease was higher for patients with > 5 vs ≤ 5 metastatic lymph nodes or negative lymph node (respectively 64.6%, 40.8% and 28.7%) (p<0.001) (Table 3).

As for lymph node location (N1a or N1b), the frequency of disease at 12-18 months after first treatment progressively increased from 28.7% in N0a/N0b to 40.5% in N1a and to 59.7% in N1b (OR 1.69 and 3.67 and p=0.02 and <0.001, respectively) (Table 3).

Analyzing the number and location of nodal metastases, for 121 N1a patients, the probability of persistent disease was higher when more than 5 lymph nodes were involved (7/13 cases, 53.8%) compared with ≤5 lymph nodes involved (42/108, 38.9%); this difference was not statistically significant (p=0.30).

For 62 N1b patients, the probability of persistent disease was sensibly higher when more than 5 lymph nodes were involved (24/35, 68.5%) compared with ≤ 5 lymph nodes involved (13/27, 48.1%); also this difference was not statistically significant (p=0.10).

4.5 Predictive power of risk stratification system (ATA 2009 vs. ATA 2015) and TNM staging system (VII vs. VIII edition)

To evaluate the accuracy of the prediction of the different ATA risk stratification systems (2009 vs. 2015) we calculated the Harrell C concordance index (C-index) considering the disease events at 18-24 months of re-evaluation. We found no differences in predictive power between the ATA 2009 and ATA 2015 criteria for biochemical and structural disease (C-index = 0.576 and 0.574, respectively for ATA 2009 and ATA 2015).

This still held true when only patients with structural disease were considered (C-index = 0.656 and 0.657, respectively for ATA 2009 and ATA 2015).

Similarly, the VII and the VIII TNM staging system resulted to have a similar and low predictive power (C-index = 0.560 vs 0.570, for the VII and the VIII edition, respectively).

4.6 Development of a nomogram to predict persistent/recurrent disease

A nomogram incorporating all the significant parameters was constructed based on the multivariate logistic model identified in Table 3. For each parameter we obtained a corresponding prognostic points as shown in Figure 4. The point values for all predictor variables were summed to reach a total score. This value was plotted on the total score axis and a vertical line drawn from this axis straight up that indicates the patient's probability of persistent/recurrent disease at re-evaluation after the first therapy.

5 Discussion

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy (5). The most frequent histotype (over 85%) is papillary (PTC). DTC incidence was quite stable until 1990s and in recent decades has rapidly grown, more than any other cancer (6), mainly due low-risk thyroid cancer increasing (https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2022.html) (1).

DTC's prognosis is generally excellent., but in some patients tumors are aggressive with poor outcome.During 2008 to 2017

(0.6% per year) TC's death rate increased slightly but appears to have stabilized in recent years.

It is not known if the incrising incidence of PTC is true or whether it is due to the overdiagnosis of indolent PTCs.

Finding the variables identifying these tumors is a major issue to decide the appropriate management.

The American Thryoid Association (3) introduced a new risk stratification system with additional prognostic variables. Moreover, to better predict DTC survival, also the TNM classification was updated in 2018. A significant number of patients were downstaged by the 8th edition (TNM-8) into lower stages to more accurately reflect the low risk of dying, but underestimating the risk of persistent/recurrent disease and death in some patients due to the fact that all young patients without distant metastases fall into stage I.

The changed risk stratification and TNM staging have a significant consequences on the earliest therapeutic judgment and subsequent follow-up management.

Concerning the risk stratification, different data have been published. In Steinschneider et al. data (7) approximately 70% of

TABLE 3 Risk factors of disease (biochemical and structural) at 12-18 months after primary treatment.

Variable	Biochemical and structural disease	Univariate analysis OR [95%CI]	p	Multivariate analysis OR [95%CI]	p
Age - < 55 years - ≥ 55 years	105/308 (34.1) 58/143 (40.6)	1.32 (0.88-1.99)	0,18		
Gender - Female - Male	112/324 (34.6) 51/127 (40.2)	1.27 (0.83-1.94)	0.27		
Lymph node surgery at primary treatment - Performed - Not performed	117/307 (38.1) 46/144 (31.9)	1.31 (0.86-2.0)	0.20		
Aggressive histology - No - Yes	139/387 (35.9) 24/64 (37.5)	1.07 (0.62-1.85)	0.80		
T status - T1a - T1b - T2 - T3a - T3b - T4a	61/206 (29.6) 49/143 (34.3) 38/73 (52.1) 0/5 8/13 (61.5) 3/5 (60.0)	1.24 (0.78-1.96) 2.58 (1.49-4.46) 3.80 (1.20-12.09) 3.57 (0.58-21.88)	0.36 <0.001 0.01 0.14	0.99 (0.61-1.61) 2.11 (1.19-3.74) 2.54 (0.77-8.35) 2.96 (0.48-18.46)	0.98 0.009 0.12 0.24
Multifocal - No - Yes	92/274 (33.6) 70/176 (39.8)	1.31 (0.88-1.93)	0.18		
Extra thyroidal invasion - No - minimal	123/355 (34.6) 40/96 (41.7)	1.35 (0.85-2.14)	0.20		
Lymph node metastases - Absent -Present	77/268 (28.7) 86/183 (47.0)	2.20 (1.48-3.26)	<0.0001	Not included	
Number of N1 at primary surgery - N0a/N0b - ≤5 N1 - >5 N1	77/268 (28.7) 55/135 (40.7) 31/48 (64.6)	1.71 (1.10-2.65) 4.52 (2.37-8.65)	0.016 0.0000	Not included	
Location of N1 at primary surgery - N0a/N0b - N1a - N1b	77/268 (28.7) 49/121 (40.5) 37/62 (59.7)	1.69 (1.08-2.65) 3.67 (2.07-6.51)	0.02 0.0000	1.40 (0.87-2.25) 3.07 (1.68-5.62)	0.16 <0.001
ATA risk stratification - Low - Intermediate - High	58/205 (28.3) 93/231 (40.3) 12/15 (80.0)	1.71 (1.14-2.55) 10.14 (2.76-37.24)	0.008 0.0000	Not included	
Radioiodine treatment - Not performed - Performed	37/174 (21.3) 126/277 (45.5)	3.09 (2.00-4.77)	0.0000	Not included	

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TABLE 4 Risk factors of structural disease at the 12-18 months assessment after primary treatment.

Variable	Structural disease n.76	Univariate analysis OR [95%CI]	p	Multivariate analysis OR [95%CI]	p
Age - < 55 years - ≥ 55 years	51/308 (16.6) 25/143 (17.5)	1.07 (0.63-1.81)	0.80		
Gender - Female - Male	46/324 (14.2) 30/127 (23.6)	1.87 (1.12-3.13)	0.016	1.63 (0.92-2.90)	0.09
Lymph node surgery - Performed - Not performed	57/307 (18.6) 19/144 (13.2)	0.67 (0.38-1.17)	0.155		
Aggressive histology - No - Yes	63/387 (16.3) 13/64 (20.3)	1.31 (0.67-2.55)	0.42		
T status - T1a - T1b - T2 - T3a - T3b - T4a	23/206 (11.2) 21/143 (14.7) 21/73 (28.8) 0/5 (0.0) 5/13 (38.5) 3/5 (60.0)	1.37 (0.73-2.58) 3.21 (1.65-6.26) 4.97 (1.50-16.49) 11.93 (1.89-75.22)	0.33 <0.001 0.004 0.001	1.12 (0.58-2.18) 2.76 (1.37-5.56) 3.18 (0.82-12.34) 10.85 (1.60-73.52)	0.73 0.005 0.09 0.01
Multifocal - No - Yes	38/274 (13.9) 37/176 (21.0)	1.65 (1.00-2.72)	0.04	1.16 (0.66-2.04)	0.60
Extra thyroidal invasion - No - minimal	54/355 (15.2) 22/96 (22.9)	1.66 (0.95-2.89)	0.07		
Lymph node metastases - Absent - Present	30/268 (11.2) 46/183 (25.1)	2.66 (1.61-4.42)	<0.001	Not included	
Number of N1 at primary surgery - N0a/N0b - ≤5 N1 - >5 N1	30/268 (11.2) 53/130 (40.8) 31/48 (64.6)	5.46 (3.26-9.15) 14.47 (7.16-29.22)	<0.001 <0.001	Not included	
Location of N1 at primary surgery - N0a/N0b - N1a - N1b	30/268 (11.2) 28/121 (23.1) 16/62 (25.8)	2.39 (1.35-4.22) 2.76 (1.39-5.47)	0.002 0.002	1.59 (0.84-3.03) 4.04 (2.00-8.13)	0.15 <0.001
ATA risk stratification - Low - Intermediate - High	16/205 (7.8) 50/231 (21.6) 10/15 (66.7)	3.26 (1.79-5.94) 23.63 (7.20-77.55)	<0.001 <0.001	Not included	
Radioiodine treatment - Not performed - Performed	8/174 (4.6) 68/277 (24.5)	6.75 (3.16-14.44)	<0.001	Not included	

patients were low risk, 25% intermediate and 5.2% high risk patients. Instead, in our data showed fewer patients in low category (45%) and higher in intermediate risk (51%) than in literature with no significant difference between 2009 and 2015 risk stratification.

Regarding the staging, a large proportion of patients were downstaged in the 8th edition (30-40%) vs the 7th one, mostly due to the increasing of the age cut-off to 55 years, the down-classification of T3 disease, and the overall downstaging of lymphnode metastases (4, 7–9), with a minimal impact on the expected 10-year disease-specific survival despite the large proportion of shifted patients to stage I and II. Kim et al. (4) found that 41% of patiens were downstaged and inevitably more patients with recurrences or deaths were found in the lower stages: 17% of patients downstaged from stage III to II had recurrent disease, 25% and 13.6% died in the group downstaged respectively from stage IV to III and from stage IV to II.

Also our data shows an important downstaging (about 30%) mostly from staging III and IVA to I, II and III. In particular the downstaging concerned 82.6% of stage II (into stage I), 100% of stage III (into stage I and II) and 100% of stage IV (into stage I, II and III).

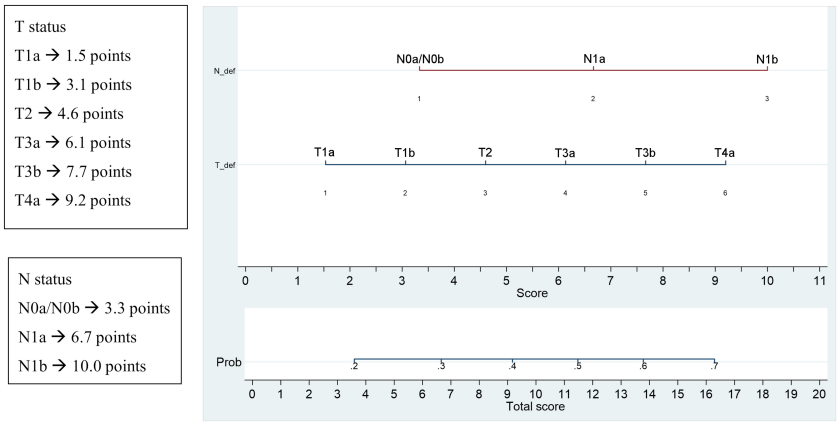

FIGURE 4
Significant parameters at multivariate and corresponding prognostic points and nomogram for the prediction of persistent/recurrent disease on the basis of clinical and histological characteristics.

Evaluating the different response at initial therapy (dynamic or ongoing risk stratification), a paper published 10 years ago by Tuttle et al. (10) found an ER in 86% of low risk patients, in 57% of intermediate-risk and in 14% in the high-risk. In 11% of low-risk patients, 22% in intermediate-risk and 14% in high-risk had BIR and 3% of patients in the low-risk, 21% in the intermediate-risk, and 72% in the high-risk had SIR.

Another paper evaluating 441 patients (7) showed that the proportion of intermediate/high-risk patients in stages I–II increased considerably according to TNM-8 and that patients downstaged in stage II with TNM-8 had more lymphnode metastases, surgeries, disease persistence and an increased disease-specific mortality (non-significant) vs to TNM-7. They found a similar rates of persistent and recurrent disease in stage I in both TNM editions, but higher in stages II ($p = 0.05$) and III ($p = 0.03$) in TNM-8 vs TNM-7Therefore the new TNM guaranteed a more accurate system to assess mortality and persistence disease but that the severity, mainly in in stage II patients or in the 45–55-year old group, should not be underestimated as a result of the important downstaging of some particular groups of patients.

In the present study, after initial treatment, 63.9% of patients presented ER and 36.1% patients were not cured, of which half presented an IR, a little less cases SIR and few patients BIR.

Our data are different compared to previous data mostly for lower percentage of the ER in low risk patients (71.7%), due to an higher number of patients IR (19.5% of low risk patients, 17.3% in intermediate-risk patients and in 13.3% of the high-risk patients) and very lower percentage of patients with BIR (1% in the low-risk, 1.3% in the intermediate-risk and 0% in the high-risk group); regarding SIR the rate are similar to the other paper (in 7.8% in the low-risk, 21.6% in the intermediate-risk, and 66.7% in the high-risk group).

Moreover in our patients the rates of structural disease in stage I and II was similar in both editions and it was significantly higher in stages III ($p = 0.004$) and IV ($p = 0.04$) in VIII compared to VII edition.

Another issue still to be validated is the timing of the re-evaluation. Based on our data, it seems that the restaging at 12-18 months could be too early as many patients with indeterminate response could change into excellent response (for example for TgAb still positive but stable or declining). This hypothesis will be evaluated by extending the follow-up.

Concerning the risk factors, most reports show that age, gender, aggressive variants, tumor size, lymphnode metastases are the most important predictors of outcome (3).

In a recent paper in 2020, Shin et al. (11) found that at at multivariate analysis tumour size > 4 cm, multifocality and nodal factors were the independent factors of recurrence free survival.

In our data only tumor size and lymph node metastases independently predicted short term outcome, instead the other risk factors were not statistically significant. In fact, tumor size is an independent risk factors from T2 up to T4a both for recurrent/persistent disease (biochemical and structural) and for only structural disease.

In a retrospective analysis of 574 patients with PTC, Tran et al. (12) found that tumor size predicted recurrence-free survival on multivariate analysis and Pellegriti et al. (13) showed that tumor size (≤1.0 cm versus. 1.1–1.5 cm) was not predictive of recurrence. Nguyen et al. (14) showed that, in SEER database, the10-year relative survival rates for tumors sized 1.5 cm or larger and tumors less than 1.5 cm were 95.4% and 99.8%, respectively.

Regarding lymph node metastases, their clinical relevance in PTC has been a debated matter for decades (15, 16). To date, the LN metastases impact at diagnosis on recurrence's risk is well documented in many papers, including a recent study of our group (17, 18). For many years, however, only neck lymhpnode metastases, without other specified variables, was evaluated as a PTC prognostic factor.

The impact of neck metastatic LN on PTC risk stratification was better defined in 2015 ATA guidelines, in which additional informations, as the number, size or extranodal extension of metastatic lymhpnodes, were included in the evaluation. To date,

these additional characteristics have not been validated and their relevance in defining the recurrence risk has yet to be quantified.

In our series the positivity of lymph node metastases, the number (≤5 or >5) and the location (N1a and N1b) are effective predictors of the outcome of the patients at 12-18 months after the first treatment, both for recurrent/persistent disease (biochemical and structural) and for only structural disease.

Data on the location of metastases, N1a or N1b, were judged insufficient to include this information in the clinicopathologic variables to estimate the risk in PTC (3) (recommendation #48, [B20], paragraph 1, line 16).

In a recent publication of our group (19), N1b worsened the prognosis and may be related to the appearance of distant metastases, which are considered the best surrogate index for cancer-specific death.

N1b status could be a marker of more aggressive or more advanced disease at diagnosis in PTC patients and associated with other ones (as molecular alterations) of cancer aggressiveness.

Concerning the mETE, its role on disease specific survival (DSS) and on overall survival (OS) have been evaluated by several studies but it's still consider a controversial prognostic factor. Some authors (19–22) showed similar clinical outcomes.However, Castagna et al. (23) showed poorer outcome, in term of persistent/recurrent structural disease and tumor-related death in patients with mETE vs tumors >1.5 cm without extrathyroid extension (11.8% vs. 5.1%), concluding that only small mETE cancers should be consider at low-risk.

Recently, an expansion of TNM-8 has been published (Telescoping) to test he subcategories, according to the mETE, to get a better estimate of the prognosis and to plan the follow-up management.In the next few years, the impact of mETE for each tumor class will be available.

Comparing disease specific survival (DSS) between TNM VII vs VIII ed, Tam et al. (20) concluded that DSS in both TNM editions is similar, although through the updated TNM-8 the 10-year DSS appears more proper between stages. For stages I–IV with TNM-7 the 10-year DSS ranged from 100% to 82.6% ($p < 0.001$) and the 10-year OS from 95.8% to 59.7% while with TNM-8 from 99.8% to 71.9% ($p < 0.001$) and from 94.3% to 34.6%, respectively.

Contrasting, results from Chung et al. (21), analyzing a large series of 3,176 DTC patients, and Jeon et al. (22), investigating the predictive capability of DSS of TNM-8 compared to TNM-7 in 1,613 DTC patients, showed that TNM-8 has a higher power to differentiate patients in each stage and to predict also the DSS.

Although therefore with the TNM-8 an improved assignment of patients at high risk of dying from DTC into more advanced stages of disease seems evident, on the other hand, leads to the erroneuous belief that the disease is less aggressive. Nearly 50% of the cancer-related deaths are involve patients in stages I-II, compared to none with the TNM-7 (7). Having thyroid cancer a very low mortality, in some patients the risk of death is not always related to recurrence's risk.

Recently, several studies showed a better predictability for the new TNM (6, 24). A more accurate survival predictions is suggested when TNM-8 is applied, due to the downstaging of a significant number of patients (about 30%).

In our data, being the median follow-up of 20.5 months, mortality was not assessed so an analysis evaluating the presence of distant metastases, good surrogate for predicting mortality, was carried out. The C-Harrel test to evaluated the power to predict disease after short follow-up found no difference using VII and VIII TNM editions (both for biochemical and structural disease and also for structural disease).

Lastly, generally, cancer nomograms are prediction tools to assess the risk based on specific patient's and tumor's characteristics and to predict the likely outcomes of different therapies. By integrating different prognostic variables, the nomogramhas the ability to create an individual numerical probability of a clinical event, useful to improve disease prognostication and therefore a personalized follow-up.

In literature, recently, several nomograms for prediction the risk of death from thyroid cancer have been proposed (23, 25). In 2016 Lang et al. (24) validated a nomogram for PTC patients with an excellent discriminating skill and accuracy in predicting 10-years-disease-specific death and recurrence. In 2017 two nomograms were proposed (26), one for regional recurrence-free survival and one for distant recurrence-free survival prediction with a C-index of 0.72 and 0.83, respectively.

Also the nomogram elaborated by our data could be useful to plan an individualized follow-up for each patient based on the score obtained from the risk calculation. The limit of this system is the lack of external validation

In conclusion, although the new TNM-8 compared to the previous TNM edition would seem to better discriminate the disease-specific death, in some patients (as N1b at diagnosis, mainly if numerous and large) could underestimate the severity of disease due to the significant downstaging and bring to a non-negligible treatment burden. In fact while in the TNM-7 N1b patients were included in advanced risk categories, the new TNM-VIII does not discriminate the death rate according to the lymphnode location, downstaging some patients (particularly old patients and/or N1b) decreasing the discriminating ability for the few patients with a negative outcome, despite categorized as stage II. Therefore, a careful follow-up is needed for downstaged patients.

Further prospective studies are needed to better define the real effectiveness of the 2015 ATA risk stratification system and the VIII TNM staging system.

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 Comitato Etico Catania 2 A.O. Garibaldi in Catania Piazza Santa Maria del Gesù, 5 95124 Catania. The patients/participants provided their written informed consent to participate in this study.

Author contributions

I) Conception and design: GS and GP. (II) Collection and assembly of data: GS, GD, MR, AB and GP. (III) Data analysis and interpretation: GS and GP. (IV) Manuscript writing: GS and GP. (V) Final approval of manuscript: All authors. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

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Log odds of negative lymph nodes/T stage ratio (LONT): A new prognostic tool for differentiated thyroid cancer without metastases in patients aged 55 and older

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Background: The optimal approach to assess the postoperative status of lymph nodes in differentiated thyroid cancer (DTC) remains controversial. Our aim was to determine if the log odds of negative lymph nodes/T stage ratio (LONT) could serve as a new prognostic and predictive tool for DTC without metastases in patients aged ≥ 55 years.

Methods: The Surveillance, Epidemiology, and End Results (SEER) database was used to study the role of LONT in patients aged ≥55 years diagnosed with DTC without metastases. The primary outcome was overall survival (OS). The Kaplan-Meier method and the Cox proportional hazard regression model were used to calculate the outcome. Moreover, the robustness of research findings was evaluated using sensitivity analyses.

Results: A total of 21,172 DTC patients aged ≥55 years without distant metastasis were enrolled. Multivariate Cox regression analyses and a "floating absolute risk" analysis showed that a LONT ≥0.920 (vs. -0.56 to 0.92) was a protective factor for OS in DTC patients. Sensitivity analyses revealed an E-value of 1.98 for the obtained LONT value. In subgroup analyses, LONT was correlated significantly with OS in different subgroups of negative lymph nodes, stage-I–II subgroups and the N0 subgroup. The conditional probability of survival of DTC improved with prolonged survival time in the LONT ≥0.920 group.

Conclusion: A high LONT was associated with longer OS compared with low LONT in patients aged ≥55 years with non-metastatic DTC. LONT could provide valuable information for undertaking postoperative evaluations.

KEYWORDS

DTC, LONT, negative lymph nodes, negative lymph nodes/T stage, prognosis

1 Introduction

Thyroid cancer (TC) is the most common malignant tumor of the endocrine system. According to the origin of the tumor and the variability in differentiation, the pathologic type of >90% of TCs is differentiated thyroid cancer (DTC), including papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) (1). Thyroidectomy and standardized dissection of lymph nodes in the neck are the first-line treatments for DTC (2, 3).

Tumor-node-metastasis (TNM) staging for TC is important because it is used to guide the treatment and prognosis of patients. However, this system focuses only on the depth of tumor invasion, number of lymph-node metastases, and presence of distant metastases, while prognoses vary even among patients with TC at identical stages. Therefore, developing a more intricate and detailed method of prognostic evaluation may help to accurately predict the outcome, and choose a more targeted and rational individualized treatment protocol.

The main factors influencing DTC outcomes are age and TNM stage. Age is an independent risk factor for disease-specific survival (DSS) in TC patients (4, 5). The eighth version of the Thyroid Cancer Staging System set by the American Joint Committee on Cancer (AJCC) continues to adopt anatomic staging based on T, N and M. The diagnostic cutoff point for age required for the prognosis increases from 45 to 55 years (6). Metastasis in the lymph nodes in the neck is a risk factor for recurrence and shortened survival in patients with TC. However, the strategy for dissection of these lymph nodes is controversial (7–11). Often, dissection of regional lymph nodes for DTC is based on individualized treatment with varying degrees of dissection, which challenges the objective assessment of the postoperative status of lymph nodes. With respect to lymph-node management in DTC, postoperative evaluation of lymph-node status is influenced by multiple factors such as the surgical approach. The number of positive lymph nodes, examination of lymph nodes (ELN) and the number of negative lymph nodes (NLN) are classical evaluation indicators of lymph-node status, which are associated with survival in gastric (12), colorectal (13, 14), and breast cancer (15).

Log odds of negative lymph nodes/T stage ratio (LONT) refers to information on the disease stage and is used to quantify the degree of lymph-node dissection. NLNs represent the total level of lateral neck dissection (LND) and the T stage represents disease severity. NLNs adjusted according to the T stage denote the relative number of NLNs removed from each patient. A high value of LONT indicates more NLNs obtained, while a low LONT value means that fewer NLNs were obtained. Therefore, LONT can be used to compare the relative levels of LND among patients. Different TNM stages, ELNs, or NLNs, and the same LONT denote the same risk level (16). Studies have shown that risk stratification using LONT in patients after surgery for gastric cancer reflects disease severity and integrates the prognostic information of the degree of lymph-node dissection, while being closely related to the treatment outcome (16). However, studies using LONT to investigate TC are lacking, and the prognostic value of LONT in TC patients remains unknown.

To address this, we retrospectively analyzed clinical-pathology data in 21,172 patients with DTC who underwent resection based on the Surveillance, Epidemiology, and End Results (SEER) database of the US National Cancer Institute (Bethesda, MD, USA). We aimed to investigate the effect of LONT on the prognosis of DTC patients aged ≥55 years without metastasis at the first visit using the Kaplan–Meier method, and a Cox regression analysis. Moreover, the robustness of research findings was evaluated by sensitivity analysis and calculation of E-values. This is the minimum strength of association (risk ratio scale) that an unmeasured confounder would need to have with both exposure and the outcome to fully explain the specific exposure-outcome association.

2 Materials and methods

2.1 Data source and cohorts

A population-based study was undertaken retrospectively using data from the SEER database using SEER*Stat 8.3.9. From 2010 to 2015, patients aged 55 and older diagnosed with non-metastatic DTC were evaluated. The exploration was based on the SEER database, which discloses the demographic features, clinicopathological characteristics, and survival information of patients. As the data were derived from anonymous public databases, ethical approval was not sought or needed.

The inclusion criteria were: (1) diagnosis of TC without metastasis; (2) age ≥55 years; (3) histology type included International Classification of Diseases for Oncology, third edition (ICD-O-3) code 8050/3 (papillary carcinoma, not otherwise specified (NOS)), 8260/3 (papillary adenocarcinoma, NOS), 8290/3 (oxyphilic adenocarcinoma), 8330/3 (follicular adenocarcinoma, NOS), 8331/3 (follicular adenocarcinoma, well differentiated), 8335/3 (follicular carcinoma, minimally invasive), 8340/3 (papillary carcinoma, follicular variant), 8341/3 (papillary microcarcinoma), 8342/3 (papillary carcinoma, oxyphilic cell), 8343/3 (papillary carcinoma, encapsulated), and 8344/3 (papillary carcinoma, columnar cell); (4) history of total thyroidectomy.

The exclusion criteria were: (1) unknown number of examined or positive regional lymph nodes; (2) unknown T, N, and M stages; (3) incomplete information on age, sex, ethnicity, tumor diameter, survival, and vital signs; (4) T0 and T4 stages.

2.2 Definition of LONT

"LONT" is defined as the log odds of (negative lymph nodes +1)/T stage ratio. The description of LONT calculation is as follows:

$$log^{(NLNs+1)/T\ stage}$$

T stages T1a, T1b, T2, T3, T4a, and T4b are assigned as 1, 2, 3, 4, 5, and 6, respectively. NLNs denote the ELNs minus the count of positive lymph nodes. The value of one is added for NLNs to avoid the occurrence of zero. A restricted cubic spline was used to assess

the association between LONT and survival to avoid assuming it was a simple linear association. LONT was categorized if non-linearity was detected. The optimal thresholds for LONT were determined on the result of restricted cubic spline.

2.3 Selection of variables

The main variables extracted from the SEER database were "age at the diagnosis", "sex", "ethnicity", "marital status at the diagnosis", "year of the diagnosis", "stage group, derived from AJCC seventh edition (2010–2015)", "T stage derived from AJCC seventh edition (2010–2015)", "N stage derived from AJCC seventh edition (2010–2015)", "M stage derived from AJCC seventh edition (2010–2015)", "tumor grade", "radiotherapy recode", "chemotherapy recode", "CS tumor size", "first indicator of primary malignancy", "SEER cause-specific death classification", "survival in months", "vital signs", and "histology type (based on ICD-O-3)". The histology type includes papillary carcinoma (PC), follicular adenocarcinoma (FC), papillary carcinoma, follicular variant (PCFV), Papillary microcarcinoma (PMC).

2.4 Statistical analyses

Categorical demographic (ethnicity, sex) and clinical data was analyzed by the chi-square test. The designated outcome was overall survival (OS). Survival curves were constructed using the Kaplan-Meier method. The log-rank test was undertaken to compare various subgroups. Univariate and multivariate Cox proportional hazards tests were conducted for OS using the "survival" package in R 4.0.1 (R Institute for Statistical Computing, Vienna, Austria). For comparisons involving multiple groups, 95% confidence intervals (CIs) were calculated using the floating absolute risks (FAR) method to enable valid comparisons between any two groups and not only with the reference group (17). Stratified analyses were conducted with Cox models; hazard ratios (HR), and 95% CIs were calculated for subgroups. The "conditional probability of survival" was defined as the probability of surviving to "Y" years after the diagnosis given survival to "X" (X< Y) years. Additionally, it can describe in detail the survival of patients at different time stages (18). Further analyses of E-value sensitivity were conducted to evaluate the robustness of the association to unmeasured confounding using the "E-Value" package within R. Statistical analyses were also conducted employing R. $P < 0.05$ (two-tailed) was considered significant.

3 Results

3.1 The relationship between LONT and survival

The restricted cubic spline curve showed that LONT had a nonlinear association with survival. HR for death was lowest near the LONT of -0.586, with a gradual rise after 0.920 (Figure S1). Then, optimal LONT thresholds were identified and the cohort was separated into three groups: LONT< -0.586, -0.586≤ LONT<0.920, and LONT ≥0.920.

3.2 Baseline population demographics

A total of 21,172 patients aged ≥55 years diagnosed with TC without metastasis between 2010 and 2015 were enrolled. There was no significant difference between the three groups in the distribution of sequence number and multiple primary tumors. Detailed information about the demographic and clinicopathological characteristics of patients is shown in Table 1.

3.3 OS

Survival analyses using the Kaplan-Meier method revealed a significantly poor OS ($P < 0.001$) for patients with low LONT

TABLE 1 Demographic and clinicopathologic characteristics of the study cohort.

Variables	Total (n = 21172)	LONT< -0.586 (n = 7343)	0.586≤LONT< 0.920 (n = 9911)	LONT≥0.920 (n = 3918)	p
Age, n (%)					< 0.001
55~65	12592(59)	4101(56)	5954 (60)	2537 (65)	
66~74	5919 (28)	2065(28)	2868 (29)	986 (25)	
≥75	2661 (13)	1177(16)	1089 (11)	395 (10)	
Sex, n (%)					< 0.001
Female	15097(71)	4912(67)	7417 (75)	2768 (71)	
Male	6075 (29)	2431(33)	2494 (25)	1150 (29)	
Race, n (%)					< 0.001
Black	1433 (7)	598 (8)	694 (7)	141 (4)	
Others	2281 (11)	887 (12)	978 (10)	416 (11)	
White	17458(82)	5858(80)	8239 (83)	3361 (86)	

(Continued)

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TABLE 1 Continued

Variables	Total (n = 21172)	LONT< -0.586 (n = 7343)	0.586≤LONT< 0.920 (n = 9911)	LONT≥0.920 (n = 3918)	p
Marital status, n (%)					0.001
Divorced/separated	2073 (10)	710 (10)	999 (10)	364 (9)	
Married	13334(63)	4512(61)	6266 (63)	2556 (65)	
Single/Unmarried	2386 (11)	876 (12)	1085 (11)	425 (11)	
Widowed/Others	3379 (16)	1245(17)	1561 (16)	573 (15)	
Diagnosis, n (%)					0.026
2010	2995 (14)	1101(15)	1391 (14)	503 (13)	
2011	3341 (16)	1182(16)	1578 (16)	581 (15)	
2012	3431 (16)	1161(16)	1622 (16)	648 (17)	
2013	3717 (18)	1235(17)	1770 (18)	712 (18)	
2014	3812 (18)	1306(18)	1788 (18)	718 (18)	
2015	3876 (18)	1358(18)	1762 (18)	756 (19)	
AJCC, n (%)					< 0.001
I	11006(53)	2223(31)	6885 (70)	1898 (49)	
II	2606 (12)	1568(22)	864 (9)	174 (5)	
III	5318 (25)	2995(41)	1610 (16)	713 (19)	
IV	2020 (10)	491 (7)	465 (5)	1064 (28)	
AJCC.T, n (%)					< 0.001
T1a	7805 (37)	0 (0)	5864 (59)	1941 (50)	
T1b	4642 (22)	2392(33)	1499 (15)	751 (19)	
T2	3072 (15)	1666(23)	1063 (11)	343 (9)	
T3	4886 (23)	2918(40)	1270 (13)	698 (18)	
T4a	552 (3)	261 (4)	153 (2)	138 (4)	
T4b	215 (1)	106 (1)	62 (1)	47 (1)	
AJCC.N, n (%)					< 0.001
N0	17156(81)	6421(87)	8530 (86)	2205 (56)	
N1	4016 (19)	922 (13)	1381 (14)	1713 (44)	
Grade, n (%)					< 0.001
I~II	5183 (24)	1890(26)	2320 (23)	973 (25)	
III~IV	274 (1)	137 (2)	78 (1)	59 (2)	
Unknown	15715(74)	5316(72)	7513 (76)	2886 (74)	
Tumor Size, n (%)					< 0.001
~1cm	7404 (35)	283 (4)	5421 (55)	1700 (43)	
1~2cm	6424 (30)	2914(40)	2303 (23)	1207 (31)	
2~4cm	4917 (23)	2542(35)	1663 (17)	712 (18)	
4+cm	2427 (11)	1604(22)	524 (5)	299 (8)	
Hist Type, n (%)					< 0.001
PC	11216(53)	3387(46)	5348 (54)	2481 (63)	

(Continued)

TABLE 1 Continued

Variables	Total (n = 21172)	LONT< -0.586 (n = 7343)	0.586≤LONT< 0.920 (n = 9911)	LONT≥0.920 (n = 3918)	p
FC	950 (4)	669 (9)	235 (2)	46 (1)	
PCFV	7170 (34)	2660(36)	3407 (34)	1103 (28)	
PMC	788 (4)	48 (1)	597 (6)	143 (4)	
Others	1048 (5)	579 (8)	324 (3)	145 (4)	
Sequence Number, n (%)					0.309
NO	17006(80)	5856(80)	7993 (81)	3157 (81)	
YES	4166 (20)	1487(20)	1918 (19)	761 (19)	
Multiple Primary Tumors, n (%)					0.234
NO	15444(73)	5304(72)	7269 (73)	2871 (73)	
YES	5728 (27)	2039(28)	2642 (27)	1047 (27)	
NLN, n (%)					< 0.001
0	11254(53)	6538(89)	4716 (48)	0 (0)	
1~8	7829 (37)	805 (11)	5098 (51)	1926 (49)	
≥9	2089 (10)	0 (0)	97 (1)	1992 (51)	
Chemotherapy, n (%)					< 0.001
NO	21100(100)	7312(100)	9893 (100)	3895 (99)	
YES	72 (0)	31 (0)	18 (0)	23 (1)	
Radiation, n (%)					< 0.001
NO&Unknown	11061(52)	2743 (37)	6266 (63)	2052 (52)	
YES	10111(48)	4600 (63)	3645 (37)	1866 (48)	

(Figure 1). Univariate and multivariate analyses were undertaken using data from all patients to assess the potential prognostic factors. In the univariate Cox regression analysis, the following factors were associated with shortened OS: age groups of 66–74 years and >75 years (*vs.* 55–65 years), male sex, black ethnicity (*vs.* white ethnicity), marital status of widowed/other (*vs.* married), grade of II, III, or IV (*vs.* I), stage of T2, T3, T4a, or T4b (*vs.* Ia), N1 stage (*vs.* N0), grade of III–IV (*vs.* I–II), tumor diameter of 2–4 cm or >4 cm (*vs.*<1 cm), multiple primary tumors, and high NLNs. LONT >0.920 was an independent protective factor for OS (HR, 0.756; 95%CI, 0.589–0.97, P =0.028) based on multivariate Cox regression analyses after adjustment for baseline demographic and clinical features (Figure 2). The floating absolute risk method provides the variance in the logarithm of the hazard ratio for each category (including the reference category) to facilitate comparisons among the different LONT categories (Table 2). Compared with the OS values of the -0.586 to 0.920 group, the adjusted HR for LONT >0.920 was 0.756 (95%CI, 0.589–0.97). Stratified analyses showed the HRs for OS across two LONT groups stratified by demographic and clinicopathologic features (Figure S2). The association between LONT and OS remained significant for male sex (P =0.026), black ethnicity (P =0.033), marital status divorced/separated (P =0.015), T4b stage (P =0.005), N status (P<0.001), grade of III–IV (P<0.001), and tumor diameter >4 cm (P<0.001).

3.4 Sensitivity analyses

Analyses undertaken using the FAR method yielded results similar to multivariate Cox regression analyses for OS. Sensitivity analyses for E-values were also conducted to evaluate the robustness of the association to unmeasured confounding (Figure S3). E-values (95% CI) were calculated for LONT ≥0.920 (*vs.* -0.586 to 0.920), 75 years of age and 66–74 years (*vs.* 55–65 years), sex, black ethnicity (*vs.* white ethnicity), married marital status (*vs.* other), multiple primary tumors, tumor diameter of >4 cm and 2–4 cm (*vs.*<1 cm), histology type of papillary microcarcinoma (*vs.* papillary carcinoma, NOS, and papillary adenocarcinoma, NOS), grade of III–IV (*vs.* I–II), T4b stage (*vs.* T1a stage), N status, chemotherapy, and radiotherapy. The respective values were as follows:1.976 (1.209-2.786), 6.410(5.466-7.5), 2.629(2.168-3.141), 2.247(1.881-2.643), 2.334(1.728-3.027), 2.06(1.641-2.512), 1.892(1.293-2.51), 1.821(1.24-2.4), 5.249(4.613-5.96), 3.731(2.518-5.355), 2.140

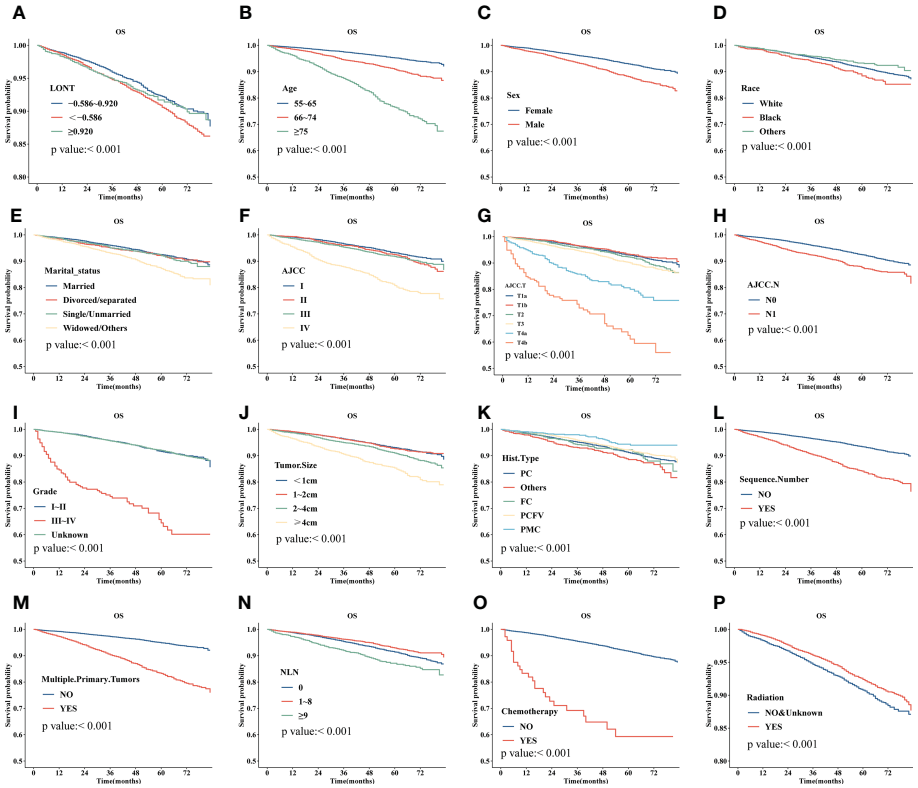

FIGURE 1
Kaplan–Meier plot for overall survival (OS) for LONT **(A)**, age **(B)**, sex **(C)**, ethnicity **(D)**, marital status **(E)**, stage (based on AJCC system) **(F)**, T stage (based on AJCC system) **(G)**, N (based on AJCC system) **(H)**, tumor grade **(I)**, tumor diameter **(J)**, histology type **(K)**, sequence number **(L)**, multiple primary tumors **(M)**, NLNs **(N)**, chemotherapy **(O)**, and radiotherapy **(P)** of patients with differentiated thyroid cancer without metastases aged 55 years and older.

(1.143-3.241), 2.635(1.483-4.16), 4.041(2.879-5.555), 5.021(3-8.107), 3.332(1.702-5.831), 2.616(1.913-3.451), 5.021(3-8.107), and 2.750(2.326-3.218).

3.5 Conditional probability of survival

Figure 3 shows the conditional probability of survival at various time points for the study cohort combining LONT< -0.586 (Figure 3A), -0.586≤ LONT<0.920 (Figure 3B), and LONT ≥0.920 (Figure 3C) separately. In the LONT ≥0.920 group, the annual conditional probability of survival increased with OS. From a 92% chance of survival immediately after the diagnosis, the probability of OS at 1, 2, 3, and 4 years after the diagnosis increased by 93%, 95%, 97%, and 98%, respectively. The probability of OS the following year decreased from 98% to 96% at 3 years and 5 years, respectively.

4 Discussion

The TNM staging system contains only certain characteristic indicators of tumors. For example, lymph-node status is one of the most important predictors for patients with DTC. We comprehensively analyzed the information on the number of NLNs and tumor stage after surgery. LONT was proposed as an indicator to quantify the degree of lymph-node dissection and disease severity intraoperatively and to predict the survival of patients with DTC. We undertook retrospective data analyses of 21,172 patients with DTC aged ≥55 years without distant metastasis. Multivariate COX regression analyses and FAR analyses showed that LONT ≥0.920 (*vs.* -0.56 to 0.92) was a protective factor for OS in patients with DTC. Sensitivity analyses demonstrated that with an E-value of 1.98 for LONT ≥0.920 (vs. -0.56 to 0.92), the results were stable even in the presence of unmeasured confounding factors. Subgroup analyses revealed that LONT correlated significantly with OS in different NLN subgroups, stage-I–II subgroups, and the N0 subgroup. The conditional probability of survival of patients with DTC improved with a prolonged survival time in the LONT ≥0.920 group.

Furthermore, an accurate prognosis for patients with TC s crucial for the postoperative treatment and follow-up plan. The TNM staging system set by the AJCC is the most widely used system for prognostic assessment. Age at TC diagnosis is an independent predictor of DSS (19, 20). The eighth version of the AJCC staging system for TC continues to adopt anatomic staging based on T, N and M. However, a cutoff for the age at the DTC diagnosis from 45 to 55 years is the best single time point for the prognostic model (4–6, 21). Patients with DTC aged ≥55 years with stage-I–IVa disease were included in our study; their prognosis is quite heterogeneous, with 10-year DSS fluctuating between 50% and 100% according to data from the AJCC staging system. These patients may achieve optimal surgical results and longer OS after additional treatment,

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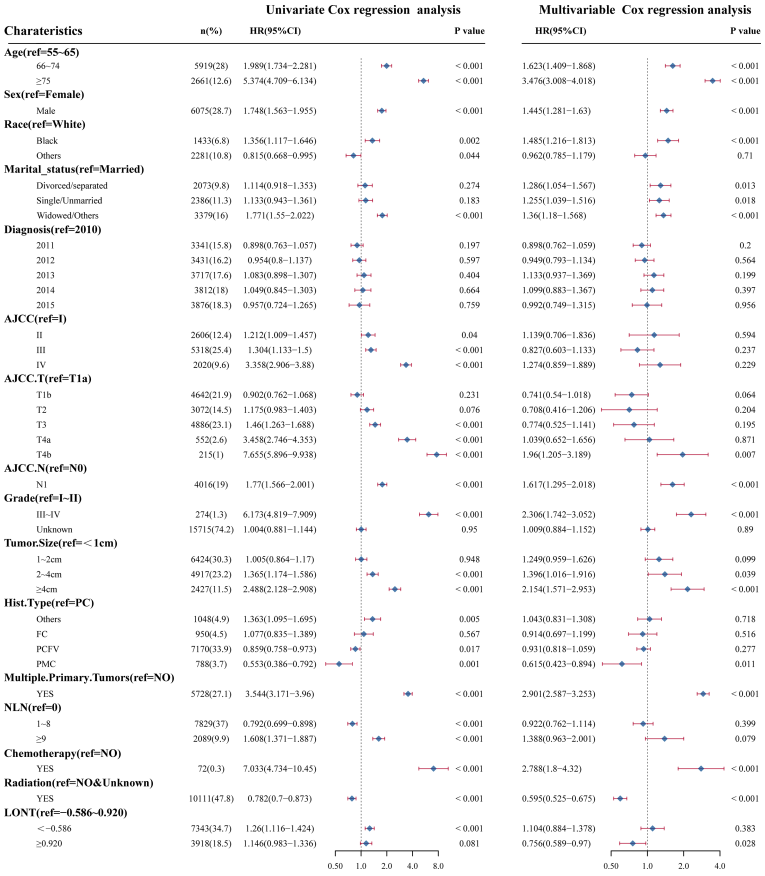

FIGURE 2
Univariate Cox regression analyses and multivariate Cox regression analyses for LONT and clinical features. Forest plot of hazard ratios demonstrating the results of Cox regression analyses. The dashed line denotes where HR = 1.

TABLE 2 Adjusted Hazard Ratios for OS to patients with different LONT by floating absolute risk methods.

	LONT		
	0.586≤ LONT< 0.920 (n = 9911)	LONT≥ 0.920 (n = 3918)	LONT< -0.586 (n = 7343)
Hazard ratio	1	0.756	1.104
95% CI, with floating absolute risk	–	0.589-0.970	0.884-1.378
95% CI, without floating absolute risk	–	0.577-0.991	0.864-1.411

but older patients with DTC tend to seek medical treatment late and often have comorbidities. Therefore, the risk of metastasis and disease recurrence is higher in older patients. Certain studies have found that survival in DTC patients aged<55 years is similar to that in patients with stage-III TC, and significantly lower than that in patients aged ≥55 years with stage-II TC (22, 23).

In the present study, age remained an independent predictor in the multivariate Cox regression mode. Older patients with DTC had to be stratified further according to the diameter of the primary tumor and lymph-node status. The location of metastatic lymph nodes does not affect the prognosis of older patients, while other indicators such as the number and maximum diameter of the primary tumor, maximum diameter of metastases, and external invasion of lymph nodes have been postulated as potential prognostic factors (24, 25).

Studies have shown (26–28) that the prognosis of patients with N1b-stage disease is significantly worse than that of patients with N1a-stage disease. Metastasis to lateral-neck lymph nodes is an independent risk factor for death. Moreover, indicators related to lymph-node metastasis are associated with outcomes in patients with DTC (29–31). The number of lymph nodes and the number of NLNs may reflect the degree of lymph-node dissection required. Certain studies have suggested that with greater ELNs (32) or NLNs (33), fewer micro-metastases will be missed in the lymph nodes. ELNs and NLNs are independent prognostic factors for lung (34),

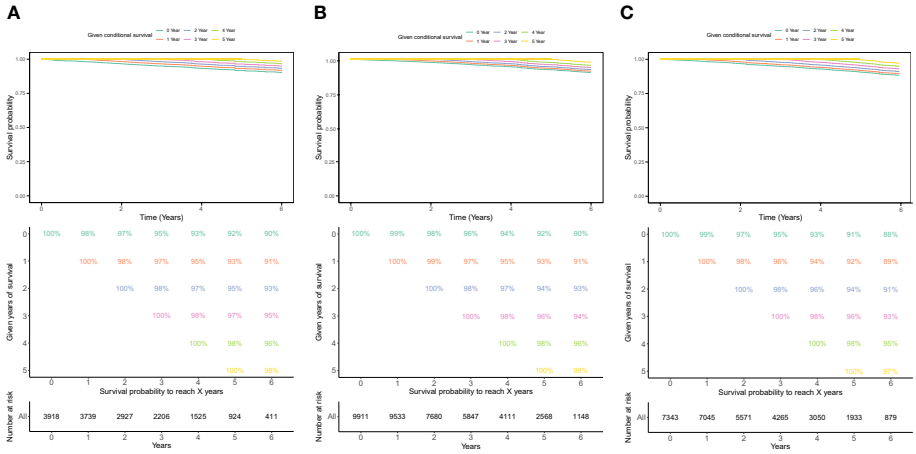

FIGURE 3
The conditional probability of survival of LONT ≥0.920 **(A)**, -0.586≤ LONT<0.920 **(B)**, and LONT<-0.586 **(C)**.

breast (35), and esophageal cancer (32). However, whether there are differences in DTC outcomes for different combinations of lymph-node metastasis-related indicators remains unknown.

The predictive value of tumor diameter-related parameters is controversial, but most scholars agree that a large primary tumor diameter is a clinicopathologic risk factor associated with poor DTC outcomes (36). The tumor diameter was<2 cm in 65% of patients in the present study. One meta-analysis (36) showed that patients with a tumor diameter between 1 cm and 2 cm had a greater risk of postoperative recurrence and death compared to that in patients with a tumor diameter<1 cm. Bilimoria et al. (37) undertook a retrospective study involving 52,173 patients with PTC. Compared with those who underwent total thyroidectomy, patients with a tumor diameter 1–2 cm had insufficient initial treatment, suffered recurrence, and had a poor prognosis. In the AJCC staging system, tumor diameter is not completely equivalent to the T stage, which integrates tumor diameter and gross extrathyroidal extension. Song and colleagues performed a study involving 3,104 patients undergoing thyroid surgery. The DSS of patients with gross extrathyroidal extension was significantly lower than that of patients with stage-T3 disease (38). The authors suggested adjusting the classification of patients with tumor diameter ≤4 cm from stage T3b toT2 to obtain more accurate survival predictions.

In our study, LONT comprised the number of lymph-nodes examined, the number of positive lymph nodes, and the T stage, which integrated the details of tumor diameter and gross extrathyroidal extension. LONT reflected the disease status after surgery and provided information on the degree of lymph-node dissection. In TC, the information required for complete staging may not be available for perioperative thyroidectomy. The eighth version of TNM staging by the AJCC states that information obtained within four months after the surgical procedure can be used to update T, N, and M stages. It also promotes clinical application of LONT and provides additional data for the individualized diagnosis and treatment of TC.

The current study is the first to apply LONT to quantify the relative degree of lymph-node dissection. LONT provides information on postoperative lymph-node dissection and T stage. The prognostic evaluation of patients with M0 disease and identical ELNs or NLNs is a powerful tool. The pattern of lymph-node metastasis varies among different pathologic types. More than 90% of DTC is PTC. Compared with FTC, metastasis to lymph nodes in the neck in PTC is more common and may often occur early. In one large-cohort study, the prevalence of lymph-node metastasis in PTC cases was ≤22% (39). Treatment of metastases in lymph nodes in the lateral neck in patients with DTC remains controversial. With respect to analyses of efficacy and economic perspectives, prospective studies to demonstrate the impact of different surgical scopes on the prognosis are difficult to conduct. Glover et al. (24) stated that safe implementation of prophylactic central neck dissection by an experienced surgeon can compensate for the unreliability of preoperative and intraoperative assessments of lymph-node metastasis in the central compartment. This approach can avoid the regional recurrence caused by insufficient dissection due to a narrow surgical scope and obtain more accurate PTC stages (40), reduce postoperative thyroglobulin levels, reduce the requirement for reoperation (41), reduce the risk of recurrence, and improve the OS (42). However, some studies have shown occult lymph-node metastases have a limited impact upon survival and recurrence (9). Prophylactic LND in patients with negative clinical lymph-node metastasis (cN0) expands the surgical scope and increases the risk of injuring blood vessels, nerves, and lymphatic vessels in the lateral neck (43). *Guidelines for the Diagnosis and Treatment of Adult Thyroid Nodules and Differentiated Thyroid Cancer* (44) published by the American Thyroid Association in 2015 recommend that conventional therapeutic LND of lymph nodes should not be carried out for patients with cN0 disease. Moreover, therapeutic LND should be undertaken for patients with DTC exhibiting lateral-neck-lymph node metastases (cN1b) by clinical and/or preoperative and intraoperative assessments. In contrast, this study proposes LONT as a new prognostic index, which does not consider the surgical approach/procedure, thus avoiding the impact of different surgical methods, while focusing on postoperative outcomes. Subgroup analyses in the present study showed a survival benefit with high LONT in patients with stage-I–II disease and N0 status. Hence, disease severity should not be underestimated in low-risk patients, and follow-up monitoring must be strengthened.

In addition, we revealed that high LONT prolonged OS significantly through adjustment of demographic and clinicopathologic factors. A high LONT value suggested a significant survival benefit. Specifically, higher the LONT values reflected, lower T stages, and fewer lymph nodes involved. Stroup and colleagues (45) retrospectively evaluated 20,513 women with DTC aged ≥40 years. They found OS and DSS to be shorter in the "regional" group (tumor confined to the thyroid gland and soft tissue) than in the "localized" group (confined to the thyroid gland). The difference in life expectancy of patients with DTC (pT1–3, pN0–1, M0) is not significant compared with that in the treated general population (46). The reason for this observation may be that the long-term survival of TC patients has been improved along with the screening and early treatment of TC. Furthermore, most studies have not distinguished subgroups by age.

Nevertheless, our study had several limitations. First, despite being based on a large cohort, our study was limited by its retrospective nature. Second, there was a selection bias for patients with TC. Third, LONT accounts for the degree of lymph-node dissection but cannot fully evaluate the success of surgical treatment or provide information on complications. Fourth, information on subsequent treatment, such as specific regimen and dose of radiotherapy and chemotherapy was not available. Fifth, the population consisted of middle-aged and older patients (≥55 years). Therefore, the results cannot be generalized to younger patient groups. Sixth, whether patients received targeted therapy or immunotherapy based on the molecular properties of TC was unknown, as we did not possess the information on their biomolecular markers. Finally, the postoperative pathology data on vascular invasion, nerve invasion, and condition of the incisal edge were not available.

5 Conclusions

LONT is a new prognostic indicator reflecting the relative degree of LND in different patients. It can predict the OS in patients aged ≥55 years without distant metastases undergoing surgical treatment regardless of preoperative and intraoperative outcomes. It could provide more valuable information for clinicians to conduct postoperative evaluations.

Data availability statement

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

Author contributions

XW: Writing – original draft (lead); writing – review and editing (equal input); formal analysis (equal input). YW: Visualization (equal input); formal analysis (equal input). XL: Visualization (equal input); formal analysis (equal input). JH: Writing – review and editing (equal input). MZ: Conceptualization (lead); writing – review and editing (equal input). 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/fendo.2023.1132687/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Association of LONT with OS.

SUPPLEMENTARY FIGURE 2
Subgroup analyses for LONT.

SUPPLEMENTARY FIGURE 3
E-value of LONT and clinical features in sensitivity analyses.

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Active surveillance in differentiated thyroid cancer: a strategy applicable to all treatment categories response

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Currently, the differentiated thyroid cancer (DTC) management is shifted toward a tailored approach based on the estimated risks of recurrence and disease-specific mortality. While the current recommendations on the management of metastatic and progressive DTC are clear and unambiguous, the management of slowly progressive or indeterminate disease varies according to different centers and different physicians. In this context, active surveillance (AS) becomes the main tool for clinicians, allowing them to plan a personalized therapeutic strategy, based on the risk of an unfavorable prognosis, and to avoid unnecessary treatment. This review analyzes the main possible scenarios in treated DTC patients who could take advantage of AS.

KEYWORDS

thyroid cancer, active surveillance, rate of growth, recurrence, radioiodine

Introduction

The current knowledge on differentiated thyroid cancer (DTC) requires a shift into precision medicine. Closely tailoring medical decisions, treatments, and practices should be based on individualized risk estimates. Furthermore, the last American Thyroid Association guidelines (1) and Italian Expert Consensus (2) for the diagnosis and management of DTC reviewed the traditional *one-size-fits-all* approach, turning it into an individualized management of DTC patients, focused on the estimated risks of recurrence (1) and disease-specific mortality (3). DTC usually has a good outcome with a disease-free survival of approximately 98% and a very low rate of disease-specific mortality (4). Because of this, some years ago, experts have advocated a conservative management approach in selected patients with low-volume tumor burden or slow-progressing DTC (5). Following that, current guidelines (1) have expanded the concept

of active surveillance (AS) in DTC management, initially applied mainly to the management of intrathyroidal microcarcinoma (mPTC) (6–11).

As defined by the National Cancer Institute, AS is "a treatment plan that involves closely watching a patient condition but not giving any treatment unless there are changes in test results that show the condition is getting worse" (https://www.cancer.gov/publications/dictionaries/cancer-terms). AS consists of periodical programmed physical examinations, blood tests, and imaging tests that are essential to early detect disease progression and to immediately plan therapies, avoiding either under- or overtreatment. According to this definition, AS is clearly different from both the "watchful waiting" approach, which is a relatively passive follow-up strategy with interventions being triggered by symptoms, and "follow-up care" that involves medical checkups over time in cured patients after treatment, with the purpose of checking disease recurrence (12).

While the management of metastatic and progressive DTC patients is much more clear and requires treatment, the main challenge is to identify the DTC patients (with any grade of persistent disease) who do not need active treatment and could benefit from AS. In some cases, immediate treatment could cause more harm than good, and even it could not be curative. While the current guidelines are available since 2016, in some areas, the management of DTC still diverges from the international indications, and in particular, AS is not considered a feasible and safe strategy (13).

In this review, we discuss the main possible scenarios in treated DTC patients, other than mPTC, who could take advantage of AS. Our objective is to show the relevance of AS in clinical practice, underlining its safety, appropriateness, and effectiveness in selected patients.

Management of DTC patients not cured by initial treatment

According to the most recent guidelines, DTC (1) patients who did not obtain an excellent response to the initial treatment (i.e., total thyroidectomy *plus* remnant radio-ablation) can be classified into three categories as reported in Table 1. These patients should continue with regular checkups but not necessarily have additional treatment. Here, we describe how to tailor the AS according to these categories of DTC patients.

Patients with an indeterminate response to initial treatment

The indeterminate category has biochemical, morphological, or functional findings that physicians could not classify as either absence or persistence of disease (1). Sub-centimetric thyroid bed nodules or indeterminate cervical lymph nodes (Figure 1A), faint uptake in the thyroid bed (Figure 1B), or non-specific abnormalities on imaging are in this group. Patients with detectable non-stimulated thyroglobulin (Tg) values, but less than 1 ng/ml, stimulated Tg values between 1 and 10 ng/ml, and stable or

TABLE 1 Response to therapy reclassification in patients with differentiated thyroid cancer treated with total thyroidectomy and radioiodine remnant ablation (1).

Category	Definition
Excellent response	Negative imaging *and* *either* suppressed Tg < 0.2 ng/ml *or* TSH-stimulated Tg < 1 ng/ml
Biochemical incomplete response	Negative imaging *and* Suppressed Tg ≥ 1 ng/ml *or* Stimulated Tg ≥ 10 ng/ml *or* Rising anti-Tg antibody levels
Structural incomplete response	Structural or functional evidence of disease, with any Tg level, with or without anti-Tg antibodies
Indeterminate response	Nonspecific findings on imaging studies, *or* Faint uptake in thyroid bed on RAI scanning, *or* Non stimulated Tg detectable, but <1 ng/ml, *or* Stimulated Tg detectable, but <10 ng/ml, *or* Anti-Tg antibodies stable or declining in the absence of structural or functional disease

Tg, thyroglobulin; TSH, thyrotropine.

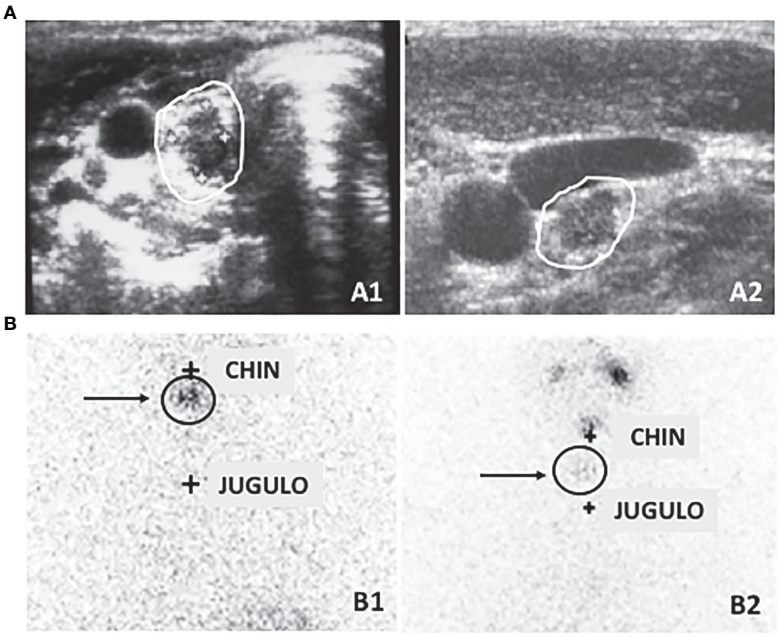

FIGURE 1
(A) Neck ultrasound can detect small lesions that cannot be clearly interpreted as normal or pathological lesions such as sub-centimetric thyroid bed lesion (A1) referable to either thyroid remnant tissue or cancer persistence and indeterminate small cervical lymph nodes (A2). **(B)** Similarly, thyroid bed scintigraphy can detect faint uptake in the thyroid bed that can be due to both a normal remnant or a local persistence or recurrence of the disease (B1) or a small lymph node (B2).

decreasing Tg antibodies (TgAb)[1] in the absence of structural disease are also in this category (1).

The prevalence of indeterminate response (IR) after initial treatment ranges from 4% to 30% and is lower in ATA high-risk patients and increases progressively in intermediate- and low-risk patients (14, 15). Patients treated with either total thyroidectomy or lobectomy alone have a similar rate of IR in different series (16, 17). The nonspecific findings either remain stable or resolve during prolonged observation in most patients, without additional treatment (15, 18). No deaths have been notified in patients with IR up to 10 years of follow-up (14, 16, 17, 19), regardless of the type of initial treatment and the ATA risk category. Conversely, only up to 14% of patients with IR to initial treatment was confirmed to have a persistence of disease, either biochemical or structural, after a median of 6–10 years (16, 17, 19, 20), and this probability increased progressively according to initial risk category (14).

Including a multitude of nonspecific findings, highly different from each other, there is no single strategy to manage patients with IR and they require an even more personalized and tailored approach based on the individual characteristics. In this setting, the trend of serum Tg and TgAb over time (21) should be taken into consideration to identify changes in clinical picture. The evaluation of the serum Tg must also take into consideration the TSH values since there is a strict correlation between these two parameters (21). This is not the case for serum TgAb that can be considered a Tg surrogate marker (22), but independent from TSH values.

Neck ultrasound (US) is the main non-invasive tool in the management of these patients, since the major risk of structural recurrence is in the neck. Unfortunately, by definition, the IR category includes cases with neck lymph nodes not clearly malignant but, at the same time, not clearly inflammatory (Figure 1A). Most of them could be clinically irrelevant, considering the low prevalence of enlarging nodules, the slow growth rate, and the rarity of local complications (23–25). In these cases, routine fine needle aspiration (FNA) is not appropriate. Nevertheless, it should be considered in lymph nodes greater than 1 cm and increasing in size over a couple of evaluations, especially if, in case of a positive FNA result, a modification in management would be applied (1). Whenever a lymph node FNA is planned, a concomitant measurement of Tg in the washout of the needle used for the procedure should also be performed (26).

In these patients, AS is the only available strategy able to identify the minority of patients requiring further therapies. Once-a-year check including clinical and biochemical (i.e., serum Tg, TgAb, TSH; free T4) evaluations plus a neck US should be performed at least for the first 5 years for those at higher risk of recurrence, and then continued every 18–24 months.

Patients with a biochemical incomplete response to initial treatment

Abnormal basal or stimulated Tg or elevated values of TgAb without clear evidence of structural disease define the biochemical

1 In the same assay over time.

incomplete response (BIR) after TT and radioiodine remnant ablation (RRA). Up to 18 months after initial therapy, BIR is found in 10%–20% of DTC patients, and, at variance with IR, the prevalence is similar in all ATA risk categories (1).

Up to 70% of these patients reach the excellent response criteria and the clinical remission over time, without any additional treatment. Moreover, approximately 20%–30% maintain a stable Tg level without structural evidence of disease for many years. Only less than 20% develop a structural disease within 5–10 years (14, 15, 19, 27–29). Moreover, the probability of achieving undetectable Tg could depend on initial risk stratification, which is higher in ATA low-risk patients than in ATA intermediate- and high-risk patients (14). Clinical outcome is generally good in these patients and no deaths have been reported over 10 years of follow-up (14, 15, 19, 27–29). These data suggest that patients with BIR after initial treatment can be managed through AS using Tg and TgAb trends and neck US, without additional interventions to determine whether they will spontaneously reach an excellent response to treatment.

During AS, a sustained increasing Tg trend is strongly suggestive of persistent disease, which should require additional evaluation (1, 30). The doubling time (DT) of serum Tg values is also an important prognostic factor, since prolonged Tg DT (>2 years) is associated with a favorable outcome (31). It is worth pointing out that instead of considering an initial elevated Tg (both basal and stimulated) as a specific marker of persistent disease (30), it should be regarded as an alert sign indicating the need for further evaluation in a patient subset, since the predictive positive value of a single basal value of Tg is low (32–34). Similarly, the increase in the TgAb trend is a warning sign, suggesting the possibility of disease persistence (35, 36). Since TgAb usually disappears 3 years after thyroid ablation (22), its persistence for a long period after initial treatment or its progressive rise, confirmed in at least two to three measurements performed during 1 year of follow up, indicates the presence of a Tg source and consequently could reflect the persistence or recurrence of DTC. In this context, it is crucial to note that Tg or TgAb trends are more helpful than a single determination in predicting disease remission or progression (19, 30, 35). Moreover, Tg and TgAb should always be measured simultaneously, using the same methods over time, to ensure comparability (1).

Recently, after the limitation to RRA use and the promotion to lobectomy for selected patients, the role of Tg and TgAb measurements had to be reassessed (1). In these cases, the Tg level closely depends on the volume of residual thyroid tissue, and it is highly variable from person to person. A Tg value able to discriminate residual thyroid tissue from recurrent or persistent DTC has not been established after surgery alone (1, 18, 37), and the stimulated Tg is worthless in these patients (38). Interestingly, most patients who did not undergo RRA experienced the natural fall of both Tg and TgAb over time in different published series (18, 37, 39–43). Ideally, the residual thyroid tissue could sustain the antigenic stimulus, affecting the disappearance of the serum TgAb. The residual thyroid tissue after TT is probably minimal, and it could not maintain the antigenic stimulus, thus determining the loss of TgAb. Moreover, the initial TgAb levels and degree of lymphocytic infiltration could influence the time to TgAb disappearance (42); thus, the role of Tg and TgAb trend, but not the single value, could also be a surrogate marker in non-ablated patients (1, 16, 18, 37). The disappearance process takes time, especially for TgAb, and during this period, patients should be followed up with AS. The observation of a natural decline or stabilization of serum Tg and/or TgAb represents a positive result, while their progressive increase represents an alert sign, and it should prompt further investigations. Furthermore, in patients treated with lobectomy, Tg and TgAb measurement is useless, because we are not able to determine how much of the total Tg and TgAb depend on residual lobe or on persistent disease (1, 18, 37). In this latter group of patients, neck US becomes fundamental during AS for the early identification of both neck lymph node metastases and/or tumoral foci in the unresected lobe.

Also, in patients with BIR, AS is a useful option to reduce overtreatment and, at the same time, to early identify the few real structural recurrences. Periodic evaluations (every 6–12 months during the first 5 years and then every 18–24 months) based on Tg, TgAb measurement, and neck US allow physicians to discern low and stable Tg or TgAb trend to increasing levels. Additional evaluations should be reserved for those patients showing a rise in Tg or TgAb, shown in two or more consecutive measurements over time. DTC patients treated with TT only but not RRA or even with lobectomy had a good prognosis *per se*. The concept of BIR is useless in these cases since these patients should be considered cured until proven otherwise and neck US remains the most informative and sensitive tool in their management.

Patients with structural incomplete response to initial treatment

Structural incomplete response (SIR) identifies a cohort of DTC patients who have not been cured after initial treatment and have evidence of structural disease either immediately after TT or after RRA as shown by post-therapeutic whole-body scan (ptWBS). SIR includes both patients with biopsy-proven disease and patients with structural or functional metastases assessed on clinical scenarios [i.e., positive ptWBS, positron emission tomography with 2-deoxy-2-fluorine-18fluoro-D-glucose (18FDG-PET), computed tomography (CT) scan, etc.].

Fifty percent to 85% of SIR patients continue to have a persistent disease despite additional therapies (15, 19). Consequently, it confirms the highest risk of disease-specific mortality, which is 11% and 57% for lymph node metastases and distant metastases, respectively. The prevalence of SIR is proportional to ATA risk stratification, being higher in ATA high-risk patients than in ATA intermediate- and low-risk patients (1) in whom it is really very rare (44).

Patients with SIR may be led to further therapies or AS, depending on multiple factors, including the size, location, proximity to vital structures, rate of growth, RAI avidity, and a balance between the risks and the efficacy of therapies. Here, we describe the different possibilities and approaches of AS in SIR patients according to the site of the structural disease.

Cervical lymph node metastases

Cervical lymph nodes represent the most common site of persistent and recurrent DTC, occurring in up to 30% of DTC patients and 75% of ATA high-risk patients, especially in those with lymph node metastases at diagnosis (1, 45). Additionally, the number and the size of the involved lymph nodes and the extracapsular extension are risk factors for persistent or recurrent disease (46–48).

Neck US is the most sensitive tool to distinguish persistent or recurrent lymph node metastases (Figure 2A) from enlarged inflammatory lymph nodes (Figure 2B) that are characterized by well-recognized pathological features (Table 2) (49, 50). In particular, neck US can detect small lymph node metastases in the absence of detectable levels of serum Tg, thus being a fundamental tool in the AS of these patients (38, 51). At the same time, it has been demonstrated that the use of neck US increases the incidence of persistent or recurrent lymph node metastases, likely clinically irrelevant, without changing the disease-specific mortality (4, 52). For this reason, neck US interpretation should not be left to the radiologist but a clinical interpretation should always be performed by the specialist who is following the patient and is aware of their disease status.

Current ATA guidelines (1) recommend performing neck US to evaluate cervical lymph nodes, and their progression, at 6 to 12 months and then periodically. While resection of large, clinically apparent loco-regional metastases often provides a clinical benefit, it remains unclear whether resection of persistent or recurrent small-volume disease, identified using highly sensitive tools, provides any meaningful clinical benefit. The prevalence of increasing lymph nodes is low, the growth rate is slow as well, and the local complication during AS is rare (53). Moreover, the cure rate after lymph node metastasis re-operation ranges from 20% to 50% in different series, and some cases are required to repeat more than one surgery to achieve disease remission (24, 54–60). Furthermore, up to 30% of patients experience recurrent or persistent lymph node metastases after the second neck dissection (56–58, 60). On the other hand, the surgery failed to remove lymph node metastasis, especially the smallest ones, in up to 10% of patients, despite having biopsy-proven metastases (54, 60). Moreover, up to 15% of patients showed a negative surgical exploration (57, 58). Although neck surgery is relatively safe in expert hands, each surgery carries a significant risk of complications, set as 9% of permanent complications in referral centers (55, 58, 59, 61). Re-operation for recurrent or persistent lymph node metastases is associated with high risks of major and permanent complications, due to the fibrotic tissue and the

TABLE 2 Ultrasound features of normal *vs.* abnormal lymph nodes (49).

Normal lymph nodes	Abnormal lymph nodes
Ovoid shape	Round shape
Normal size	Microcalcifications
Preserved hilum	Cystic components
Absent or hilar vascularization	Increased vascularization
	Increased short axis
	Irregular borders
	Hypoechogenicity

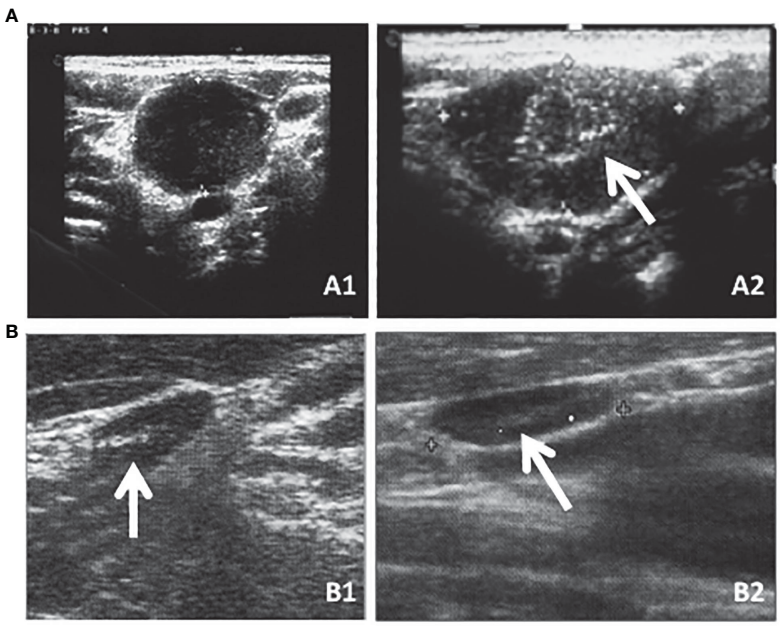

FIGURE 2
Neck US is the most sensitive tool to distinguish persistent or recurrent lymph node metastases [**(A)** (A1) transversal and (A2) longitudinal sections] that are characterized by well-recognized pathological features (e.g., round shape as shown in A1 or microcalcifications as indicated by the arrow in A2) from enlarged inflammatory lymph nodes [**(B)** (B1) transversal and (B2) longitudinal sections] that are oblong in shape and with an evident hylum as indicated by the arrows in both B1 and B2.

disruption of the normal anatomic planes after the initial surgery (62).

For all the above-mentioned reasons, abnormal lymph nodes less than 1 cm in the smallest diameter at neck US are candidates for AS and no treatment. Neck US evaluation should be performed every 6–12 months according to the rate of growth, if any, and simultaneously, a biochemical evaluation of TSH, Free T4, and mainly Tg and TgAb is indicated. Routine FNA is not appropriate, but it might be useful in well-proven progressive lymph nodes greater than 1.0–1.5 cm, in which the FNA results, combined with the results of the Tg measurement in the washout of the needle used for FNA (26), will lead to an appropriate and reasonable therapeutic intervention.

Distant metastases

Up to 5%–10% of SIR patients may have distant metastasis at diagnosis and 5%–10% may develop distant metastases during follow-up. Almost all distant metastases are in the lungs, while a smaller number is in the bones, brain, and liver. Distant metastases are the most frequent cause of disease-specific mortality, especially in older patients. While 10-year survival rates >95% have been documented in young patients with distant metastases, a median 10-year survival rate of <50% can be expected in older patients with distant metastases (63–66). Ten-year overall survival drops to 10% when distant metastases are not responsive to radioiodine therapy (67) and overall survival is significantly worse in patients with bone or brain metastases (68, 69).

Patients with SIR should be regularly assessed by biochemical and appropriate imaging evaluation to plan a personalized strategy. In this setting, Tg could estimate the tumor burden, and Tg doubling time (DT) may represent a prognostic factor since a short Tg DT (<6 months) is associated with a poor outcome (31). In contrast, an incongruous reduction in serum Tg with no concomitant decrease or with an increase in tumor size could be due to a dedifferentiation of the tumoral cells and suggests a radioiodine refractory disease. Cross-sectional imaging provides the most precise information on tumor burden, proximity to contiguous structures, and tumor growth. DT of distant metastases is also a good prognostic indicator of overall survival in patients with metastatic DTC: a shorter DT correlates with a worse overall survival (70). Positron emission tomography (18FDG) may provide additional prognostic information, since 18FDG-PET positive lesions usually have a more aggressive behavior (71, 72).

Two-thirds of patients with metastatic disease demonstrate substantial uptake of radioiodine, but only 42% of them demonstrate structural resolution of disease, and fewer than 10% demonstrate complete resolution of both biochemical and structural disease (67, 68, 73). Moreover, patients who are not responsive to radioiodine treatment have a poor prognosis and a reduced life expectancy (67). For these patients, the probability of obtaining a remission of disease with further radioiodine treatment is low and other strategies should be evaluated.

Radioiodine refractory metastatic patients require a multidisciplinary approach, since a myriad of aspects should be assessed to guarantee a tailored and integrated management, based on the high risk of adverse outcome. However, not all patients with structural radioiodine refractory disease require immediate treatment. Patients with asymptomatic, stable, or slowly progressive diseases are candidates for AS since they may not require initiation of therapy until tumors reach a critical volume, patients experience symptoms, or vital structures are involved. Treating a small, stable, and asymptomatic disease could expose patients to treatment's adverse events without giving them a real prognostic improvement. These patients are candidates for AS with 6-month evaluations including the measurement of serum Tg and calculation of its DT (74), as well as the measurement of TgAb especially for those cases with elevated levels whose trend must be accurately evaluated (74). According to the increasing trend of these serum markers, total body CT scans associated in some cases with 18-FDG-PET should be performed to verify the tumor burden increase (74). Further therapy can be considered when tumor burden becomes clinically significant and tumor progression needs to be documented (70), because the benefit of treatment is demonstrated only in this setting (1, 75–77), and it justifies the potential related adverse events of therapy (78, 79).

In case of stable disease without symptoms, with a slow progression, and without life-threatening lesions, risk about systemic treatment outweighs the benefit and AS can provide a prolonged period of symptom-free disease, without side effects of treatments.

The complexity of these situations and the availability of prospective clinical trials should encourage physicians to refer such patients to tertiary centers with specific expertise.

Conclusions

In clinical practice, AS is the main tool enabling physicians to optimize therapy planning and prevent side effects from unnecessary treatments. AS can ensure appropriate timing and a personalized approach for an active treatment and, at the same time, avoids unnecessary treatment for patients who would not require additional therapy.

AS is indicated as first-line management for patients with a detectable Tg value or TgAb without structural disease and also for those with small, isolated cervical lymph node metastases, especially in cases previously submitted to nodal compartment resection. AS can also be applied in cases of slowly progressing and asymptomatic distant metastases given that the risk of progression or local invasion is low, and the risk of adverse events outweighs the benefit of treatment.

Author contributions

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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Predicting ^{18}F-FDG SUVs of metastatic pulmonary nodes from CT images in patients with differentiated thyroid cancer by using a convolutional neural network

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Purpose: The aim of this study was to predict standard uptake values (SUVs) from computed tomography (CT) images of patients with lung metastases from differentiated thyroid cancer (DTC-LM).

Methods: We proposed a novel SUVs prediction model using 18-layer Residual Network for generating SUVmax, SUVmean, SUVmin of metastatic pulmonary nodes from CT images of patients with DTC-LM. Nuclear medicine specialists outlined the metastatic pulmonary as primary set. The best model parameters were obtained after five-fold cross-validation on the training and validation set, further evaluated in independent test set. Mean absolute error (MAE), mean squared error (MSE), and mean relative error (MRE) were used to assess the performance of regression task. Specificity, sensitivity, F1 score, positive predictive value, negative predictive value and accuracy were used for classification task. The correlation between predicted and actual SUVs was analyzed.

Results: A total of 3407 nodes from 74 patients with DTC-LM were collected in this study. On the independent test set, the average MAE, MSE and MRE was 0.3843, 1.0133, 0.3491 respectively, and the accuracy was 88.26%. Our proposed model achieved high metric scores (MAE=0.3843, MSE=1.0113, MRE=34.91%) compared with other backbones. The predicted SUVmax (R^2 = 0.8987), SUVmean (R^2 = 0.8346), SUVmin (R^2 = 0.7373) were all significantly correlated with actual SUVs.

Conclusion: The novel approach proposed in this study provides new ideas for the application of predicting SUVs for metastatic pulmonary nodes in DTC patients.

KEYWORDS

standard uptake value, lung metastases, differentiated thyroid cancer, prediction model, convolutional neural network

1 Introduction

Thyroid cancer is the most common malignancy in the endocrine system (1). In China, it accounts for 4.7% of all cancer incidence and is expected to have 224,023 new patients in 2022 (2). Thyroid cancer is divided into subspecies of differentiated thyroid carcinoma (DTC), anaplastic thyroid carcinoma (ATC), and medullary thyroid carcinoma (MTC). DTC mainly includes papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC) and Hürthle cell carcinoma, which accounts for 94% of thyroid cancer and has a relatively good prognosis after standardized treatment (3, 4). However, it has been reported in the literature that 5%-25% of DTC patients can develop distant metastasis (5, 6), with lung metastases being the most common, accounting for 55%-85% of cases (7–10). In addition, respiratory failure due to pulmonary metastases may be the leading cause of death in patients with lung metastases from differentiated thyroid cancer (DTC-LM), with approximately 50% of patients dying within 10 years (11, 12).

Based on iodine uptake capacity (9), lung metastases from DTC can be classified as ^{131}I-avid and non ^{131}I-avid (13). 18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is mainly considered for high-risk DTC-LM patients with elevated thyroglobulin (Tg) and negative ^{131}I whole-body scan (14). It can not only detect lung metastases with high sensitivity and specificity, but also predict the potential poor outcome of ^{131}I therapy in ^{18}F-FDG positive lesions (15, 16).

^{18}F-FDG PET/CT is becoming more commonly used in clinical practice. However, the total cost of this examination ranged from 7,000 to 10,000 RMB, which hampers the implementation of PET/CT units and imposes a heavy financial burden on patients (17). According to the World Health Organization's Global Atlas of Medical Devices, only 3% of upper-middle income, and 4% of lower-middle income countries possesses at least one PET scanner per million people. Furthermore, 95% of low income countries and 92% of lower-middle income countries don't have an available PET/CT unit (18). Compared to PET/CT, CT scans are much more prevalent, especially in some developing countries. In China, the number of PET/CT was only 0.3 units per million people, which is much less than the 18 CT units per million people. To sum up, CT is a widespread and cost-effective alternative that can be used as a routinely used technique to analyze pulmonary nodules.

Artificial intelligence (AI) algorithms, especially deep learning, have an excellent performance in medical image analysis because of its ability to integrate vast datasets. Convolutional neural network (CNN) is one of the representative algorithms of deep learning. It has attracted more attention in radiological image processing with its powerful deep structure representation capability. CNN trained on millions of photographic images can be applied to medical images through transfer learning (19). The development of AI can be applied clinically to improve patient care by providing accurate and efficient decision support (20, 21).

In this study, we proposed a model with 18-layer Residual Network (ResNet-18) based on CNN to predict standard uptake values (SUVs) of pulmonary metastatic nodules in patients with DTC-LM from CT images. The proposed model can extract features of lung metastases automatically and predict the SUVmax, SUVmean and SUVmin based on CT images. Applying AI methods to CT images of patients with DTC-LM to achieve SUV prediction has great clinical implications.

2 Methods

2.1 Datasets

The data used in this study were retrospectively derived from the Department of Nuclear Medicine, Shanghai Sixth People's Hospital from November 2014 to September 2021. The patients who satisfied the following criteria were finally enrolled: (1) differentiated thyroid carcer confirmed by pathological results after total or near total thyroidectomy; (2) all patients included had underwent ^{18}F-FDG PET/CT scan; (3) more than three pulmonary nodes detected by ^{18}F-FDG PET/CT and no suspected other primary tumor was found; (4) thyroid stimulating hormone (TSH)-suppressed Tg >1 ng/ml or TSH-stimulated Tg >10 ng/ml, or Tg antibody (TgAb) >100 IU/ml; (5) metastatic pulmonary nodes were confirmed on ^{131}I-SPECT/CT scan after radioiodine therapy; (6) or pathologically proved metastatic pulmonary nodes from DTC. Exclusion criteria were as following: (1) with history of other malignancies; (2) other primary tumor confirmed by PET/CT images; (3) low-quality images; (4) loss of follow-up and unnecessary information.

^{18}F-FDG PET/CT images were acquired according to standardized scanning protocols at our institution. All patients fasted and underwent PET/CT scans 60 minutes after receiving intravenous injection of a dose of 3.7 MBq ^{18}F-FDG per kilogram of body weight. PET/CT equipment manufactured by GE Healthcare was used to generate the images. CT scanning was first performed for attenuation correction and anatomical localization, followed by PET emission scan to show ^{18}F-FDG uptake, and PET/CT fusion images were displayed after processing. Nuclear medicine physicians measure SUV from the images at the workstation. This study was approved by the ethics committee of Shanghai Sixth People's Hospital.

2.2 Network architecture

To predict SUVs from CT images, the following points have to be considered: (1) DTC-LM patient's metastatic pulmonary nodules should first be manually outlined by the specialists in the department of nuclear medicine as the regions of interest (ROI). (2) The original input CT image should be separated from the PET/CT images, which means does not contain PET images. (3) The CT images are grayscale images, which contain less information. The information of focused features such as pixel values need to be extracted to predict SUVs. Therefore, it is important to consider

pixel values in the preprocess, the network structure, and loss function. Based on the above considerations, we designed this framework as in Figure 1 to implement the prediction of SUVs from CT images.

2.3 Image preprocessing

The PET/CT images of the patients included in this study were stored in DICOM format. The CT image matrix was 512 × 512 with

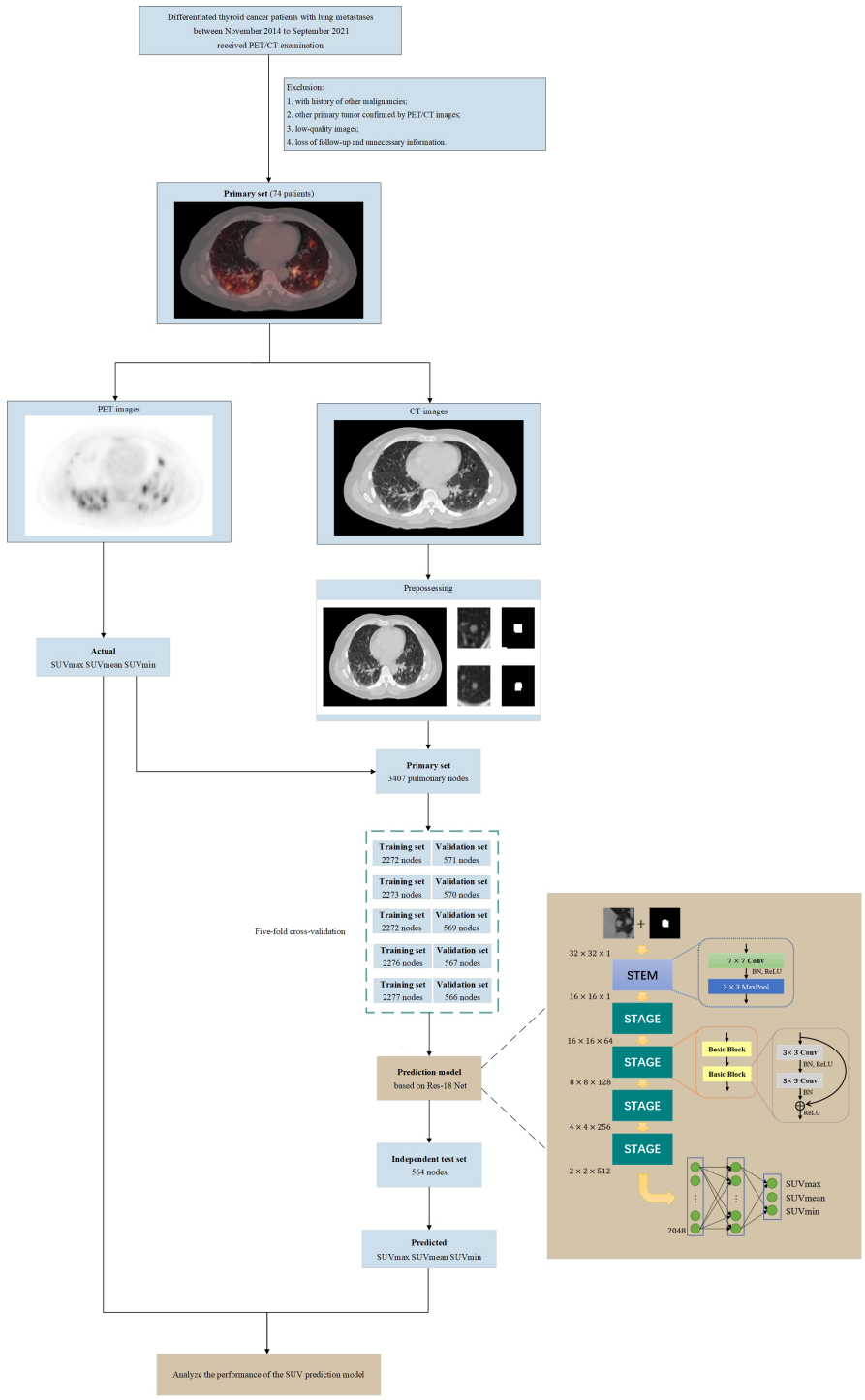

FIGURE 1
Flowchart of our study (including patient selection and exclusion criteria, image pre-processing, architecture of the SUV prediction model and model training, validation, testing).

a thickness of 1.25 mm, and the PET image matrix was 128 × 128 with a thickness of 3.27 mm. We used Algorithm 1 to preprocess the CT images in DICOM format. We also converted the pixel values of PET images in DICOM format to SUVs according to the calculation method provided by GE health care. The PET images were resampled using the SimpleITK tool to make the spatial resolution consistent with the CT images.

Input: DICOM file for CT D_{dcm}
Window center W_c and window width W_w
Output: D_{out}
1. read *Pixel Array*, *Rescale Slope* and *Rescale Intercept* from D_{dcm}
2. $HounsfieldUnit = PixelArray \times RescaleSlope + Rescale\ Intercept$;
3. $top = W_c + W_w \star 0.5$;
4. $bottom = W_c - W_w \star 0.5$;;
5. **for each** *hu* in *Hounsfield Unit* **do**
6. $$hu = \begin{cases} top & if\ hu \geq top \\ bottom & if\ hu \leq bottom; \\ hu & otherwise \end{cases}$$
7. $hu = hu \div (top - bottom)$;
8. **end**
9. **return** *Hounsfield Unit;*

ALGORITHM 1
Normalize based window center and width.

To protect patients' privacy and uniform the image size, we first removed all the information related to the patient from the image includes age, name and patient number. The ROI of each lung nodule were then created manually by a specialist in the department of nuclear medicine. Finally, we obtained images of 3407 lung nodules of different sizes. We preprocessed each image of labeled lung nodules as shown in Supplementary Figure 1. The purpose of this was to remove irrelevant areas and interference markers to prevent the adverse effect of noise on performance. The labeled lung nodule was first positioned and then cropped it into an image of 32 × 32 pixels centered on the lung nodule. If the labeled lung nodule was larger than 32 × 32 pixels, a square was cropped out with the longest edge of the lung nodule region and resize to 32 × 32 pixels. If there were multiple pulmonary nodules in the cropped slice, we first found the labeled pulmonary nodule by the algorithm, used it as an image center and cropped it a pixel of 32 × 32. Then we set the pixel value to one for the labeled pulmonary nodes in the image, while the other regions outside the labeled pulmonary nodes were filled with pixel value zero. Finally, an image of 32 × 32 pixels containing a single pulmonary nodule was input into the regression prediction part of the model for predicting SUVs.

2.4 Model structure

In this study, we used 34-layer Residual Network (ResNet-34) as the backbone part of the network, which composed of one 7 × 7 convolutional layer, eight basic blocks, one max pooling layers, and two fully connected layers to realize the automatic prediction of SUVs on CT images. The STEM contains a 7 × 7 convolutional layer, and a max pooling layer. It is worth noting that we have made minor changes to the STEM part of the model. The input to the model was the normalized CT data with the labeled data, calculated as follows:

$$input = (D_{out} + mask) \star 0.5$$

Where, D_{out} represents the normalized CT image, mask is the labeled data.

Each STAGE contained two basic blocks. Unlike conventional CNN stacked by multiple convolutional layers and pooling layers, each basic block was composed of two 3 × 3 convolutional layers and a short connection. In the basic block, activation function uses ReLU. Shortcut connections can make the deep network easier to optimize and solve the degradation problem caused by deep networks. Finally, there were two fully connected layers that collect and classify the extracted features. The first fully connected layer was followed by the Gaussian Error Linear Unit (GeLU) function and the Dropout layer, and the second fully connected layer was followed by the Dropout layer. The dimensions of feature maps after each layer were shown in Supplementary Table 1.

2.5 Experimental settings and evaluation indicators

We randomly split the dataset into two subsets, a training and validation set containing 2843 nodes and an independent test set containing 564 nodes. For the training, we used L1 Loss function and the standard stochastic gradient descent (SGD) optimizer with a momentum of 0.8, and a weight decay of 0.0005. The batch size was set to 32, and the dropout rate was set to 0. The training epoch was set to 200. The learning rate will be multiplied by 0.1 at the half and three-quarters of the training epoch.

To evaluate the prediction effect of each model objectively and select the final model, we performed five-fold cross-validation of the model. The training and validation set was divided into five nonoverlapping subdatasets randomly. Then the model was trained and validated five times. Four subdatasets were used to train the model, and the remaining one subset is used to validate the model's performance. Moreover, each model needed to be trained and validated five times, and the independent test set was also used to test the model's performance.

Besides, we applied multiple evaluation indicators to estimate the performance of the model. The performance of the regression task was quantified by three metrics: mean absolute error (MAE), mean squared error (MSE), and mean relative error (MRE).

MAE measured the average absolute error between the predicted value and the actual SUVs on the dataset, while MRE measured the average relative error. MSE reflected the absolute deviation of the predicted value from the actual SUVs. They were defined as follows:

MAE

$$= \frac{\sum_{i=1}^{n} |predicted_i - actual_i|}{n}$$

MSE=

$$\sqrt{\frac{\sum_{i=1}^{n} (predicted_i - actual_i)^2}{n}}$$

MRE=

$$\frac{\sum_{i=1}^{n} \frac{|predicted_i - actual_i|}{predicted_i}}{n}$$

In these equations above, n represents the number of images (equal to 3407 in our experiment), $predicted_i$, represents the predicted SUVs of i-th nodes, while $actual_i$ represents the actual SUVs.

To further measure the performance of the model, we classified the SUV according to different intervals, using classification metrics to measure. The performance of the classification task was evaluated using standard metrics including specificity, sensitivity, F1 score, positive predictive value (PPV), negative predictive value (NPV) and accuracy. They derived from true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) as follows:

$$\text{Specificity} = \text{TN}/(\text{TN}+\text{FP})$$

$$\text{Sensitivity} = \text{TP}/(\text{TP}+\text{FN})$$

$$\text{F1 score} = (2 \times \text{PPV} \times \text{Sensitivity})/(\text{PPV}+\text{Sensitivity})$$

$$\text{PPV} = \text{TP}/(\text{TP}+\text{FP})$$

$$\text{NPV} = \text{TN}/(\text{TN}+\text{FN})$$

$$\text{Accuracy} = (\text{Sensitivity}+\text{Specificity})/2$$

2.6 Statistical analysis

The DICOM files of PET/CT were preprocessed using Python toolkits such as Numpy 1.22.3, SimpleITK 2.1.1.1, OpenCV-python 4.6.0.66 and Pydicom 2.3.0. The deep learning network was implemented in Python using PyTorch 1.8.0. The deep learning models were trained, validated and tested on a server with an NVIDIA Tesla V100 PCIe 32GB and an Intel Xeon Gold 5115 CPU. Correlation analysis was performed in the statistical software GraphPad Prism 9.

3 Results

3.1 Patient and image characteristics

The number of patients analyzed in the study was 74, including 46 males and 28 females, The youngest of them was 11 years old and the oldest was 82, with a mean age of 55.2 years. The clinical characteristics of the patients were shown in Table 1. The collected dataset contained 3407 PET/CT images of pulmonary nodules correctly marked by the nuclear medicine specialists. Each contained an 32 × 32 CT image and an 32 × 32 annotated image. The median maximum diameter of these nodules was 9.77mm and the median actual SUVmax, SUVmean, SUVmin measured by PET images were 1.31, 1.06, 0.81, respectively. Their distribution was shown in Figure 2.

3.2 Performance in regression task

The performance of our proposed model in regression task was shown in Table 2. The average MAE, MSE and MRE of SUVmax, SUVmean and SUVmin on five-fold cross-validation set was 0.3493, 1.0880 and 0.3236 respectively. The average MAE, MSE and MRE of SUVmax, SUVmean and SUVmin on independent test set was 0.3843, 1.0133 and 0.3491 respectively.

3.3 Correlation between the predicted SUVs with actual SUVs

We evaluated the correlation between the predicted SUVs with actual SUVs of each node in the independent test set (Figure 3). SUVmax (R^2 = 0.8987, P<0.001), SUVmean (R^2 = 0.8346, P<0.001),

TABLE 1 Patients' clinical characteristics.

Characteristics	Total (n=74)
Gender	
Males	28 (37.8%)
Females	46 (62.2%)
Age (years)	57 (45,66)
Pathological types	
PTC	56 (75.7%)
FTC	15 (20.3%)
PDTC	3 (4.1%)
Tg level* (ng/ml)	147.60 (23.03,815.00)
TgAb level# (IU/ml)	11.80 (10.54,18.68)
TSH level** (mU/l)	0.10 (0.02,2.44)
Maximum Diameter (mm)	9.77 (7.87,12.49)
Actual SUVmax	1.31 (0.87,2.20)
Actual SUVmax	1.31 (0.87,2.20)
Actual SUVmean	1.06 (0.75,1.63)
Actual SUVmin	0.81 (0.59,1.14)

Values are presented as number (percentage) or median (Q25, Q75).
PTC, papillary thyroid carcinoma; FTC, follicular thyroid carcinoma; PDTC, poor differentiated thyroid carcinoma; Tg, thyroglobulin; TgAb, thyroglobulin antibody; TSH, thyroid stimulating hormone; SUV, standard uptake value.
*Tg <0.040 was calculated as 0.04 ng/ml, Tg >25000 ng/ml was calculated as 25000 ng/ml
#TgAb<10 IU/ml was calculated as 10 IU/ml, TgAb>4000 UI/ml was calculated as 4000 IU/ml.
**TSH<0.005 mU/l was calculated as 0.005 mU/l.

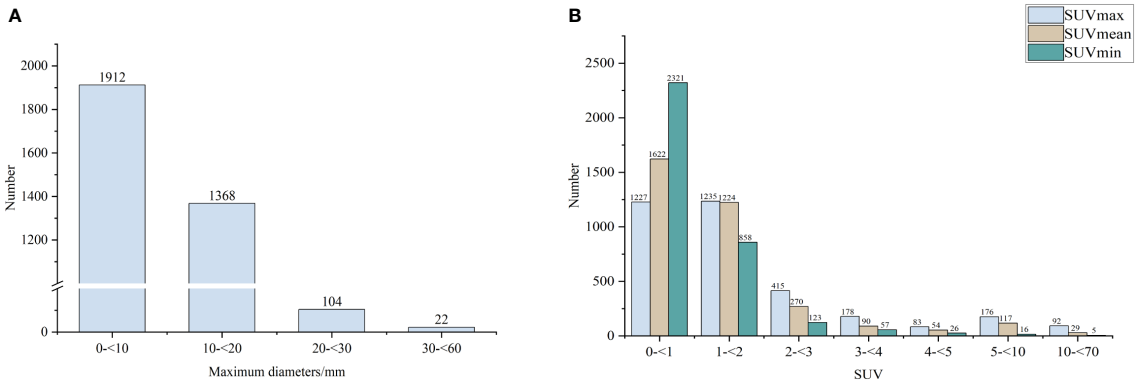

FIGURE 2
The distribution of maximum diameters **(A)** and SUV **(B)** of the nodes.

SUVmin (R^2 = 0.7373, P<0.001) were found to be significantly and positively correlated for all of them.

3.4 Performance in classification task

The performance of our proposed model in classification task was shown in Table 3. The classification task was calculated after we perform coarse classification according to four intervals based on the SUVmax predicted by the model and the real SUVmax. In the classification task of dividing the actual value of SUVmax into four intervals $[0, 2.5)$, $[2.5, 5)$, $[5, 10)$ and $[10, +\infty)$, the accuracy is 89.87% on the five-fold cross-validation set and 88.26% on the independent test set.

3.5 Models with different backbones

We compared the proposed model with convolutional neural networks using ResNet, DenseNet, EfficientNet and ConvNexXt as

TABLE 2 Performance of the SUV prediction model in the regression task.

Metric	Five-fold cross-validation				Independent test			
	SUVmax	SUVmean	SUVmin	AVG	SUVmax	SUVmean	SUVmin	AVG
MAE	0.5344 (0.4839, 0.5889)	0.3240 (0.2958, 0.3539)	0.1895 (0.1759, 0.2039)	0.3493 (0.3194, 0.3810)	0.5894 (0.5403, 0.6416)	0.3536 (0.3279, 0.3806)	0.2100 (0.1972, 0.2234)	0.3843 (0.3563, 0.4139)
MSE	2.3494 (1.5690, 3.3032)	0.7323 (0.5315, 0.9684)	0.1821 (0.1397, 0.2301)	1.0880 (0.7551, 1.4902)	2.2289 (1.6079, 2.9677)	0.6341 (0.4998, 0.7852)	0.1708 (0.1400, 0.2047)	1.0133 (0.7576, 1.3081)
MRE	36.41% (27.09%, 51.97%)	31.89% (23.22%, 46.26%)	28.76% (20.91%, 41.78%)	32.36% (23.80%, 46.64%)	38.37% (33.12%, 44.36%)	34.19% (29.04%, 40.10%)	32.17% (27.11%, 38.03%)	34.91% (29.81%, 40.75%)

Results are presented as values (95% Confidence Interval).
SUV, standard uptake value; AVG, average; MAE, mean absolute error; MSE, mean square error; MRE, mean relative error.

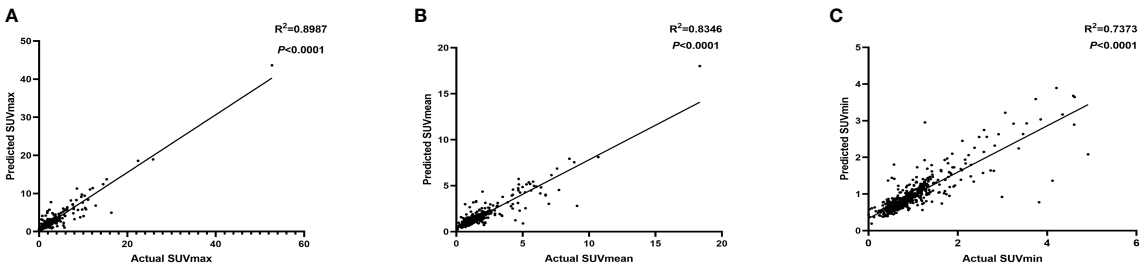

FIGURE 3
The correlation between the predicted SUVmax **(A)**, SUVmean **(B)**, SUVmin **(C)** with actual SUV in independent test set.

TABLE 3 Performance of the SUV prediction model in the classification task.

Metrics	Five-fold cross-validation					Independent test			
	[0,2.5)	[2.5,5)	[5,10)	[10, + ∞		[0,2.5)	[2.5,5)	[5,10)	[10, + ∞
Spec (%)	76.38	95.90	98.44	99.75		71.38	95.41	98.39	99.67
Sen (%)	96.42	65.99	59.89	65.50		95.94	58.89	57.93	58.67
F1 (%)	95.24	67.73	63.52	74.64		94.36	61.86	61.78	68.40
PPV (%)	94.10	70.18	67.81	88.65		92.84	65.20	66.54	83.70
NPV (%)	84.73	95.18	97.83	99.03		81.97	94.07	97.74	98.88
Acc (%)	89.87 (88.74, 90.96)					88.26 (87.06, 89.43)			

Accuracy is presented as values (95% Confidence Interval).
Spec, specificity; Sen, sensitivity; PPV, positive predictive value; NPV, negative predictive value; Acc, accuracy.

backbones on the five-fold cross-validation set and independent test set. The results can be seen in Table 4. The MAE, MSE and MRE in independent test is 0.3843, 1.0113 and 34.91% respectively. Our proposed model with ResNet18 as the backbone performs better compared with other backbones when considering these three metrics together.

3.6 Influence factors of SUVs prediction

We analyzed the correlation between the maximum diameter and actual SUVs with MAE, MRE and MSE in the independent test set (Table 5). The correlation coefficients were 0.190, 0.612, 0.667, 0.557 for MAE, and 0.162, 0.612, 0.610, 0.426 for MSE respectively,

TABLE 4 Comparison of regression performance with other backbones.

Backbone	Five-fold cross-validation			Independent test		
	MAE	MSE	MRE	MAE	MSE	MRE
ResNet18	0.3914	1.2939	33.89%	0.4201	1.2103	39.84%
ResNet34	0.3702	1.0966	33.12%	0.4051	1.1168	36.49%
ResNet50	0.3918	1.4110	34.66%	0.4182	1.1792	37.83%
DenseNet121	0.4188	1.3539	36.20%	0.4778	1.7737	38.99%
DenseNet169	0.4071	1.2794	34.73%	0.4792	1.8015	39.87%
DenseNet201	0.4266	1.4281	35.64%	0.4798	1.6640	41.47%
EfficientNet-B0	0.5449	2.2230	41.38%	0.6038	3.2052	45.26%
EfficientNet-B1	0.5175	2.1594	51.09%	0.5828	2.7543	45.40%
EfficientNet-B2	0.5250	2.4541	39.16%	0.5750	2.6721	43.99%
ConvNeXt-T	0.5883	2.4648	64.47%	0.6319	2.6453	50.72%
ConvNeXt-S	0.5854	2.4439	63.46%	0.6375	2.4818	51.25%
ConvNeXt-B	0.5760	2.4626	60.20%	0.6325	2.6616	51.48%
Proposed model	0.3493	1.0880	32.36%	0.3843	1.0113	34.91%

MAE, mean absolute error, MSE: mean squared error; MRE, mean relative error.

TABLE 5 Correlation analysis of errors.

Correlation coefficient	MAE	MRE	MSE
Maximum diameter	0.190***	-0.041	0.162***
Actual SUVmax	0.612***	-0.046	0.612***
Actual SUVmean	0.667***	-0.074	0.610***
Actual SUVmin	0.557***	-0.118**	0.426***

***$P<0.001$, **$P<0.005$.
MAE, mean absolute error; MRE, mean relative error; MSE, mean squared error; SUV, standard uptake value.

all of which were statistically significant. The correlation coefficients for MRE were not statistically significant.

4 Discussion

In this study, we collected data from 74 patients with DTC-LM and obtained PET/CT images of their 3407 pulmonary metastatic nodules. And, we proposed a model used ResNet-18 as backbone to predict SUVs on CT images for the first time. This CNN architecture was trained and validated using 2843 CT images and tested using 564 images. The experiment showed that our model could predict SUVs effectively. To evaluate the prediction effect of each model objectively, we used five-fold cross-validation and comparative analysis with other mainstream CNN models under three evaluation indicators, including MAE, MSE and MRE. The comparative experiment showed that the performance of model using ResNet-18 as backbone in predicting SUVs from CT images was better than other CNN models.

As one of the most curable cancers, DTC has a favorable prognosis carrying a 10-year overall survival rate of about 90% (22). Although distant metastasis is not a frequent event in DTC, it has adverse impact on survival (23). Specially, DTC-LM patients with ^{18}F-FDG positive/^{131}I negative pulmonary metastases may have shorter survival due to their insensitivity to radioiodine therapy. SUV is the most commonly used semiquantitative tool to measure FDG uptake. It not only reflects the absolute FDG uptake in the tumor, but also assess metabolic changes. Therefore, it is crucial to identity the level of pulmonary metastases FDG uptake in DTC-LM patients to make a therapeutic decision.

Compared to CT and MRI, PET/CT scan may be subject to equipment inaccessibility and the high cost for patients. This scan also requires the injection of ^{18}F-FDG into the body which has a potential radiation risk to the operators. In addition, the distribution and uptake of ^{18}F-FDG could be affected by blood glucose level, making it necessary to control the patient's blood glucose level prior to the scan. These disadvantages hinder its routine implementation into medical field.

Currently, there are many studies on CT-based image recognition and prediction. Wang et al. developed a deep learning model using CT scans efficiently predicted EGFR mutational status in patients with NSCLC (24). Liu et al. developed a CT-based radiomic signature to predict the expression status of the genes encoding E- cadherin, Ki-67, VEGFR2 and EGFR, in patients with gastric cancer (25). To the best of our knowledge, predicting SUVs based on CT images has not been systematically reported. Our study, for the first time, proposed a logical and easy-to-use method to try to predict SUVs of pulmonary metastasis from thyroid cancer by using CT images.

There are still shortcomings in our study. Firstly, the number of lung nodules with large diameters and high SUVs is small, which may affect the generalization ability of this prediction model. Secondly, since only patients with thyroid cancer were included in the current study, the applicability of this model to pulmonary nodes from other malignancies still needs further validation in a larger dataset. In the future, we will continue to collect PET/CT images of metastatic pulmonary nodes and explore SUV prediction model with a better performance. Thirdly, it's hard to explain why morphological features can predict molecular metabolism information. However, metabolic changes of tumor cells may affect their biological behavior and thus could finally alter anatomical imaging findings. So, it is possible that anatomical and metabolic information could be related.

In conclusion, we proposed a model to predict ^{18}F-FDG SUVs of metastatic pulmonary nodes from CT images in patients with differentiated thyroid cancer by using a convolutional neural network for the first time. The novel model proposed in this study provides new ideas for applying artificial intelligence approaches to predict molecular metabolism information from anatomical features and may show good application potential in clinic.

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

CS and XD contributed to conception of the study. YW and LH organized the database. LN and CL designed the model. NJ wrote the first draft of the manuscript. QL and CS revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1127741/full#supplementary-material

SUPPLEMENTARY FIGURE 1
The schematic diagram of the image pre-processing.

SUPPLEMENTARY TABLE 2
Dimensions of feature maps after each layer.

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Clinico-cytopathological subcategorization in thyroid nodules of atypia of undetermined significance/ follicular lesion of undetermined significance using the TIRADS and Bethesda classifications

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Introduction: Bethesda category III – atypia of undetermined significance/ follicular lesion of undetermined significance (AUS/FLUS) is a heterogeneous class of the Bethesda system for thyroid nodules. In order to clarify the therapeutic road for clinicians, this category was subclassified based on the cytopathological features. In this study, we evaluated the risk of malignancy, surgical outcome, demographic characteristics, and correlation of ultrasound features with the final outcome in patients with thyroid nodules based on AUS/ FLUS subclassification.

Method: After evaluating 867 thyroid nodules from three different centers, 70 (8.07%) were initially diagnosed as AUS/FLUS. The cytopathologists re-interpreted the FNA samples and subclassified them into five subcategories: architectural atypia, cytologic atypia, cytologic and architectural atypia, and Hürthle cell AUS/FLUS, and atypia, which was not specified. Based on the suspicious ultrasound features, an appropriate ACR TI-RADS score was allocated to each nodule. Finally, the malignancy rate, surgical outcomes, and ACR TI-RADS scores were evaluated among Bethesda category III nodules.

Results: Among the 70 evaluated nodules, 28 (40%) were subclassified as Hürthle cell AUS/FLUS, 22 (31.42%) as cytologic and architectural atypia, 8 (11.42%) as

architectural atypia, 7 (10%) as cytologic atypia, and 5 (7.14%) as atypia which was not specified. The overall malignancy rate was 34.28%, and the architectural atypia and Hürthle cell nodules displayed lower malignancy compared to other groups (P-Value<0.05). Utilizing ACR TI-RADS scores showed no statistical significance between Bethesda III subcategorization and ACR TI-RADS scores. However, ACR TI-RADS can be a reliable predictor for Hürthle cell AUS/FLU nodules.

Conclusion: ACR TI-RADS helps evaluate malignancy only in the Hürthle cell AUS/FLUS subcategory of AUS/FLUS. Besides, cytopathological reporting based on the suggested AUS/FLUS subclassification could help clinicians take appropriate measures to manage thyroid nodules.

KEYWORDS

thyroid nodule, thyroid neoplasms, fine-needle aspiration, ultrasonography, cytology, Bethesda, AUS/FLUS, TIRADS

1 Introduction

Fine-needle aspiration (FNA) plays a prominent role in managing and work-up of thyroid nodules by approximating the malignancy risk and aiding rational clinical decisions for surgery or observation. In order to provide a standard and uniform reporting system for the cytological evaluation of thyroid nodule FNAs, *the Bethesda System for Reporting Thyroid Cytopathology* (TBSRTC) released a reporting algorithm with six diagnostic categories for FNA specimens (1, 2). Among these six diagnostic categories, Bethesda category III – atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) contains a heterogeneous population of thyroid lesions with a confusingly broad range of malignancy-risk ranging from 10%–30% impeding appropriate consideration for clinical management of patients (3). Therefore, evaluating the malignancy risk for an AUS nodule is problematic since only a subset of patients with AUS nodules have a surgical follow-up. The patients undergoing thyroid resection are a selected population with repeated AUS results or complex clinical or imaging findings. Based on the TBSRTC, 20–25% of this population has cancer after surgery; however, this is undoubtedly overestimated (4, 5). The viable clinical approaches to AUS/FLUS thyroid nodules consist of molecular testing (if available), repeated FNA, and diagnostic surgery with attention to thyroid-stimulating hormone (TSH) levels (6).

Abbreviations: ACR, American College of Radiologists; AUS/FLUS, Atypia of undetermined significance/follicular lesion of undetermined significance; ATA, American Thyroid Association; FNA, Fine-needle aspiration; FTA, follicular thyroid adenomas; FTC, follicular thyroid carcinomas; HIS, Hospital information system; MNG, multinodular goiter; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; papillary thyroid carcinoma (PTC); RAI, Radioactive iodine; TBSRTC, The Bethesda System for Reporting Thyroid Cytopathology; TIRADS, Thyroid Imaging Reporting and Data System; TSH, Thyroid-stimulating hormone; US, Ultrasonography.

Based on the 2nd ed. TBSRTC, AUS/FLUS species are mainly described as thyroid lesions with a comparable proportion of macro- and micro follicles, mild nuclear atypia, wide-ranging oncocytic alteration, and poor fixation (7). Although a prominent population of micro follicles in the FNA sample exists, it does not fulfil the criteria for follicular neoplasm/suspicious for follicular neoplasm. The reason arises from the predominance of micro follicles in a sparse cellular aspirate with slight colloids (4, 5). Notably, AUS and FLUS are considered synonyms; thus, they should not be utilized to represent two different interpretations. In this regard, the 2017 TBSRTC suggests subcategorization for AUS/FLUS to avoid vague descriptors and provide appropriate risk clarification consisting of (a) cytologic atypia, (b) architectural atypia, (c) cytologic and architectural atypia, (d) Hürthle cell AUS/FLUS, (d) atypia, not otherwise specified (1). It has been demonstrated that different atypia patterns of AUS/FLUS are associated with additional malignancy risk. For instance, nuclear atypia has been shown to represent a more prominent malignant risk compared to architectural atypia (8, 9). Therefore, considering other diagnostic approaches would improve risk assessment and patient care.

Several studies have made the possible role of thyroid ultrasonography (US) prominent in the management of AUS/FLUS thyroid nodules (10–12). Introducing Thyroid Imaging Reporting and Data System (TIRADS) by the American College of Radiologists (ACR) has provided a chance to compare the sonographic properties of thyroid nodules with cytological findings to discriminate among benign and malignant thyroid nodules (13). However, to the best of our knowledge, no study has described the correlation of US features (especially by considering TIRADS classification) of thyroid nodules to the Bethesda III subclassifications.

Herein, we have assessed the clinical outcomes of thyroid nodules which are diagnosed with Bethesda III considering its subclassification. Besides, the study has compared the properties of thyroid lesions in different Bethesda III subcategories regarding TIRADS imaging features in order to determine whether TIRADS features and AUS/FLUS subclassification can be used in patient management.

2 Materials and methods

2.1 Patients

The study was performed after approval by the Shahid Beheshti University of Medical Sciences Ethics Committee (Ethics Code: IR.SBMU.MSP.REC.1399.440) and after obtaining informed consent from the patients. This multicentered study was performed mainly in Imam Hossein Educational Hospital, Tehran, Iran, and the data includes FNAs performed at this medical center or outside FNAs interpreted by Imam Hossein Educational Hospital cytopathologists. Two reviewers assessed the records of all patients who underwent thyroid nodules FNA between September 2020 to January 2022 independently. In this regard, FNAs with AUS/FLUS reports were included. Besides, Bethesda III thyroid lesions with previous FNAs representing highly malignant risk (Bethesda Class IV-VI), as well as patients with incomplete documented follow-ups, were excluded. Among 867 screened nodules, 70 reports met the inclusion and exclusion criteria of the study. The demographic properties (age and sex), previous US reports, management plans, and outcomes were collected from the hospital information system (HIS) of evaluated centers. The minimum time for follow-up was six months.

2.2 Fine needle aspiration procedures

Radiologists of evaluated educational centers with at least five years of experience in FNA carried out the procedures. Based on the patient's priority, FNAs were performed with or without an anesthetic (e.g., lidocaine) and repetitive movements of a 25-gauge needle attached to a 2 mL syringe within the nodules under US guidance. The aspirates within the syringe were smeared on appropriate glass slides and immediately fixed with 95% alcohol for Papanicolaou and/or Wright-Giemsa staining.

2.3 Cytopathologic analysis

Four cytopathologists evaluated the interpretation of FNA samples from different centers independently. Besides, another professional cytopathologist assessed the interpreted slides and reviewed the challenging reports. The specimens were allocated into six categories regarding TBSRTC: (a) Bethesda I for nondiagnostic or unsatisfactory slides, (b) Bethesda II for benign lesions, (c) Bethesda III for AUS/FLUS, (d) Bethesda IV for follicular neoplasm or suspicious lesions, (e) Bethesda V for suspicious malignant lesions, and (f) Bethesda VI for malignant nodules (14). After collecting AUS/FLUS specimens, these slides were evaluated and subclassified into five categories based on cytopathological features (Figure 1): (a) Architectural atypia for sparse cellularity along with crowded follicular cells present in trabecular and/or microfollicular positionings, (b) Cytologic atypia for focal, extensive, mild nuclear alteration and/or atypical cyst lining cells, (c) Cytologic and architectural atypia representing with both cytologic atypia and architectural atypia which are discordant, (d) Hürthle cell AUS/FLUS for spare cellular aspirates with exclusive Hürthle cells, (e) Atypia which was not specified (5).

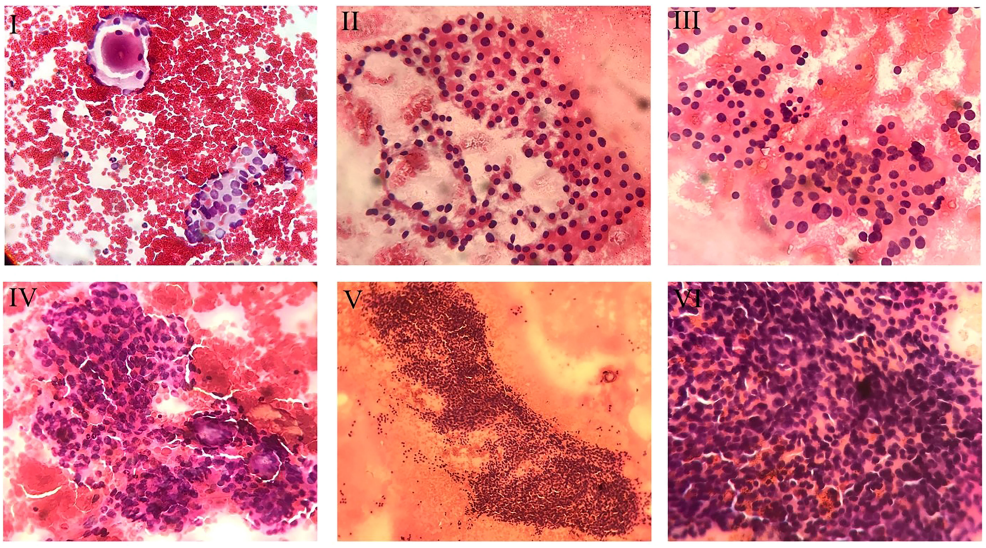

FIGURE 1
Cytopathologic view of different subcategories of AUS/FLUS specimens. I. Cytologic and Architectural Atypia. In the upper left corner, one micro follicle, and in the lower right corner, cellular clusters with pale and enlarged nuclei mimicking papillary carcinoma are noted (Papanicolaou staining, x200). II. Hürthle Cell. Smear exclusively shows the Hürthle cells population (Papanicolaou staining, x200). III. Hürthle Cell and Cytologic atypia. The smear reveals oncocytic follicular cells (Hürthle cells) with some degree of nuclear enlargement (Papanicolaou staining, x200). IV. Architectueal Atypia. showing nuclear crowding and micro follicles (Papanicolaou staining, x200). V. Architectural Atypia. Cellular cluster with nuclear crowding and overlapping is noted (Papanicolaou staining, x100). VI. Architectural Atypia. The smear reveals clusters with nuclear crowding and overlapping (Papanicolaou staining, x400).

2.4 Thyroid ultrasound examination and interpretation

The trained radiologists independently performed the US examinations in evaluated educational centers with at least five years of experience. Besides, another professional radiologist assessed and re-scored the challenging reports. Radiographic features of thyroid nodules were reported regarding ACR TI-RADS comprising: (a) composition, which describes the internal components of a nodule, (b) echogenicity, which shows echogenicity of the nodule components relative to nearby thyroid tissue, (c) shape which describes length to width ratio in anteroposterior to horizontal diameter in the transverse plane, (d) margin which describes border of thyroid nodule and the adjacent thyroid parenchyma or extrathyroidal structures, and (e) echogenic foci defined as markedly enhanced echogenicity of focal regions within a nodule compared to the nearby tissues. The nodules were classified into five TIRADS, including benign (TR1), not suspicious (TR2), mildly suspicious (TR3), moderately suspicious (TR4), and highly suspicious (TR5) (Figure 2) (15).

2.5 Statistical analysis

Our standard data reference consists of FNA reports and permanent section results of surgeries. Nodules with surgical statements declaring neoplasm and/or radioactive iodine (RAI) were considered malignant. In order to describe normal variables, the mean ± standard deviation and for abnormal variables, the Median (IQR) were used. Besides, to compare the variables between the two groups, in the case of normal variables, the independent t-test and, for others, the Mann-Whitney test were used. The Kruskal-Wallis test was used to comparing between more than two groups. The Chi-square test or Fisher's exact test was used in order to compare the categorical variables. P values lower than 0.05 were measured as statistical significance.

3 Results

The mean age of the 70 patients was 46.71 ± 13.52 years ranging from 21 to 83 years. Of the 70 patients who met the appropriate criteria to be included in the study, 60 (85.7%) were women, and 10 (14.3%) were men. In this regard, there is no significant age difference between men and women (P-value = 0.42).

Of the 867 screened thyroid nodules, 76 (8.76%) were initially diagnosed as AUS/FLUS based on the TBSRTC. However, six were excluded due to previous FNAs representing highly malignant risk or incomplete documented follow-up. The AUS/FLUS thyroid lesions were classified based on the Bethesda subcategorization described in the method section. Of 70 AUS/FLUS thyroid nodules, 7 (10%) were subcategorized as cytologic atypia, 8 (11.42%) as architectural atypia, 22 (31.42%) as cytologic and architectural atypia, 28 (40%) as Hürthle cell AUS/FLUS, and 5 (7.14%) as atypia which was not specified. Evaluating the thyroid nodule size showed a statistical significance between nodule size and Bethesda III subcategorization (P-Value<0.05). In this regard, the mean size of thyroid nodules was significantly larger in architectural atypia compared to cytologic atypia (P-Value<0.05) (Table 1).

However, the comparison among other groups did not reveal any significant differences. Although the results demonstrated that larger nodules are more suspicious to be malignant overall (P-Value<0.05), comparing the nodule size among different

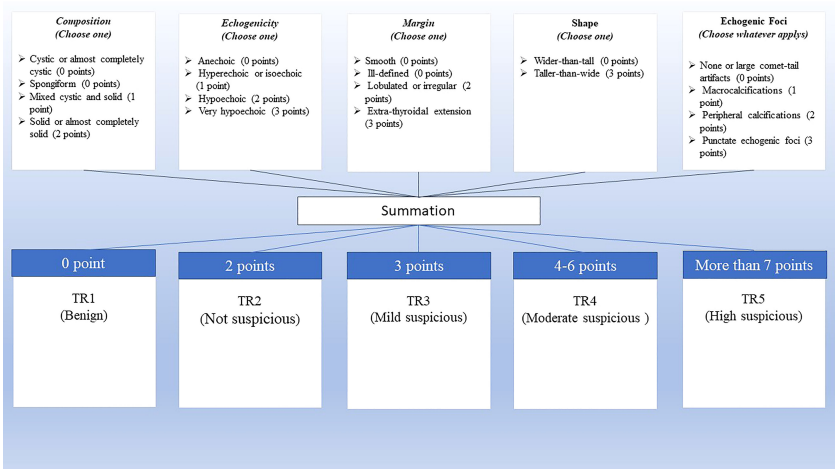

FIGURE 2
ACR TI-RADS scoring. Scoring is calculated based on the five categories of US findings (upper row). A higher cumulative score shows a higher TI-RADS level and a higher probability of malignancy (lower row).

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TABLE 1 Nodule size among subcategories of Bethesda III.

Bethesda Subsection	Nodule size (mm)	[min,max]
Architectural	34.42 ± 15.32	[12.40,55.00]
Cytologic	16.68 ± 16.36	[7.00,53.00]
Cytologic and architectural	23.90 ± 16.29	[5.00,73.00]
Hürthle cell AUS/FLUS	18.63 ± 9.99	[3.00,43.00]
Not specified	16.56 ± 13.93	[8.00,41.00]

subcategories indicated that there is a statistical significance between nodule size and malignancy only in cytologic and architectural atypia subcategory (P-Value<0.05). Table 2 summarizes the demographic differences, including age, sex, and size, between malignant and benign nodules among five subcategories of AUS/FLUS. The results showed no significant difference in age, sex, and risk of malignancy.

The flow-up documentation showed that among 70 patients, 41 (58.57%) underwent surgery as the final therapeutic decision, while 29 (41.42%) performed repeated follow-up FNAs (active surveillance), which did not convince physicians to use surgery as the therapeutic choice. Among the patient with total or partial thyroid lobectomy, the permanent section analysis showed 16 (39.02%) benign and 25 (60.97%) malignant thyroid nodules. Malignancy rates among these five subcategories of AUS/FLUS showed that there is a statistical significance between the malignancy rate and Bethesda III subcategorization (P-Value <0.05). In this regard, the nodules subclassified into Hürthle cell AUS/FLUS and architectural atypia possess lower malignancy risk compared to other subclassifications (P-Value<0.05) (Table 3).

Evaluating the pathology reports of resected thyroid among patients who underwent surgery revealed that the final diagnoses consisted of papillary thyroid carcinoma (PTC) (51.21%), lymphocytic thyroiditis+multinodular goiter (12.19%), lymphocytic thyroiditis (9.75%), multinodular goiter (MNG) (9.75%), Hürthle cell adenoma (4.87%), Hürthle cell carcinoma (4.87%), and non-invasive follicular thyroid neoplasm with papillary like nuclear features (NIFTP) (2.43%). Figure 3 shows the subcategorization of AUS/FLUS thyroid lesions, clinical decisions, and final pathological outcomes.

In order to compare US characteristics between benign and malignant nodules described as ACR TI-RADS, the scores were evaluated in each subcategorization. The overall malignancy rates among ACR TI-RADS three, four, and five were 19.04%, 38.09%, and 71.42%, respectively. The analysis showed a statistical significance between ACR TI-RADS and malignancy rates (P-Value<0.05). However, no statistical significance was observed between Bethesda III subcategorization and ACR TI-RADS scores (P-Value>0.05). Evaluation of ACR TI-RADS scores among Bethesda III subcategorization regarding the malignancy rate showed that ACR TI-RADS scores statistically are predictive for malignancy only in Hürthle cell AUS/FLU subclassification (P-Value <0.05). Besides, ACR TI-RADS scores three and four were statistically different between malignant and benign nodules in architectural atypia subclassification (P-Value <0.05) (Table 4).

TABLE 2 Demographics of thyroid nodules based on the AUS/FLUS subcategories.

	Architectural			Cytologic			Cytologic and architectural			Hürthle cell AUS/FLUS			Not specified		
	Benign	Malignant	P	Benign	Malignant	P	Benign	Malignant	P	Benign	Malignant	P	Benign	Malignant	P
Age*															
	43.75 ± 14.98	–	–	42.67 ± 8.96	40.75 ± 10.53	0.81	51.11 ± 13.74	41.46 ± 12.99	0.11	49.95 ± 13.42	44.50 ± 6.25	0.35	50.00 ± 28.79	57.00 ± 8.48	0.77
Size*															
	34.42 ± 15.32	–	–	11.33 ± 4.51	11.33 (7,15.8)	0.86	15.56 ± 8.34	29.68 ± 18.15	0.02	17.39 ± 10.36	23.17 ± 7.57	0.09	8.93 ± 0.90	28.00 ± 18.38	0.20
Gender*															
Men	4 (50%)	0	–	1 (33.30%)	0	0.43	1 (11.10%)	0	0.41	2 (9.10%)	0	0.60	1 (33.30%)	1 (50%)	0.70
Women	4 (50%)	0		2 (66.70%)	4 (100%)		8 (88.90%)	13 (100%)		20 (90.90%)	6 (100%)		2 (66.70%)	1 (50%)	

*Normal data are reported with mean ± standard deviation and non-normal data with median (IQR).

TABLE 3 Malignancy risk in different Bethesda III subcategories.

Bethesda III subcategory	Benign	Malignant	Chi-Square Test
Architectural	8/8 (100%)	0/8 (0%)	Value= 4.50 P-Value= 0.03
Cytologic	3/7 (42.85)	4/7 (57.14%)	Value= 0.14 P-Value= 0.70
Cytologic and architectural	9/22 (40.90%)	13/22 (59.09%)	Value= 0.73 P-Value= 0.39
Hürthle cell AUS/FLUS	22/28 (78.57%)	6/28 (21.42%)	Value= 9.14 P-Value= 0.002
Not specified	3/5 (60.00%)	2/5 (40%)	Value= 0.20 P-Value= 0.65

4 Discussion

Several studies have reported an overall rate of malignancy ranging from 10% to 30% in the Bethesda III category of thyroid nodules (1, 3, 16, 17). Besides, TBSRTC 2nd ed revealed a higher risk of malignancy AUS/FLUS thyroid nodules (10-30%) compared to 1st edition (5-15%), showing the heterogeneous nature and outcomes of these nodules. The 2015 American Thyroid Association (ATA) recommend active surveillance, including repeated FNA, molecular testing (like ThyroSeq v.3), or diagnostic lobectomy after considering worrying clinical and sonographic features along with patient preference and feasibility (6). This fact has resulted in severe challenges in patient management and treatment planning. In order to increase the transparency and efficacy of AUS/FLUS thyroid nodules, TBSRTC has introduced a subclassification for the Bethesda III category, which consists of five subcategories based on the cytopathologic interpretation (1, 5). To evaluate clinical approaches, risk of malignancy, and outcome in AUS/FLUS thyroid nodules, we assessed the thyroid nodules regarding the suggested subcategorization of AUS/FLUS. Our study showed that Hürthle cell AUS/FLUS is the most classified lesion, while cytologic and architectural atypia, architectural atypia, cytologic atypia, and atypia were not specified are in the second to fifth positions, respectively. However, considering the malignancy risk, Hürthle cell AUS/FLUS and architectural atypia showed lower malignancy risk compared to other subcategorizations. There are controversial reports on the prevalence of each subclassification and its risk of malignancy. Guleria et al. have shown that cytologic and architectural atypia was the most classified AUS/FLUS lesions, followed by Hürthle cell AUS/FLUS, architectural atypia, atypia which was not specified, and cytologic atypia. Also, they showed that cytologic atypia lesions showed a higher risk of malignancy (18). A meta-analysis by Valderrabano et al. also demonstrated that the malignancy rates were lower for architectural atypia and oncocytic atypia (Hürthle cell). Evaluating the final pathology reports of patients who underwent surgery showed that PTC is the most common diagnosis among AUS/FLUS nodules. In accordance with our study, it has been reported that PTC is the most frequently diagnosed malignancy for AUS/FLUS nodules (19). It seems that nodule size alteration, US follow-up findings, and biochemistry profile persuade clinicians to take surgery as a final therapeutic approach. Reviewing the final diagnosis among the Bethesda III subcategories showed that the Hürthle cell AUS/FLUS as a subcategory and NIFTP as a rare diagnosis are challenging for clinicians and cytopathologists.

As a challenging subcategory of AUS/FLUS, the Hürthle cells are characterized as oncocytes associated with the thyroid epithelial cells displaying plentiful fine cytoplasmic granules around the nucleus due to the presence of oversize, vacuolated, and dilated mitochondria (20,

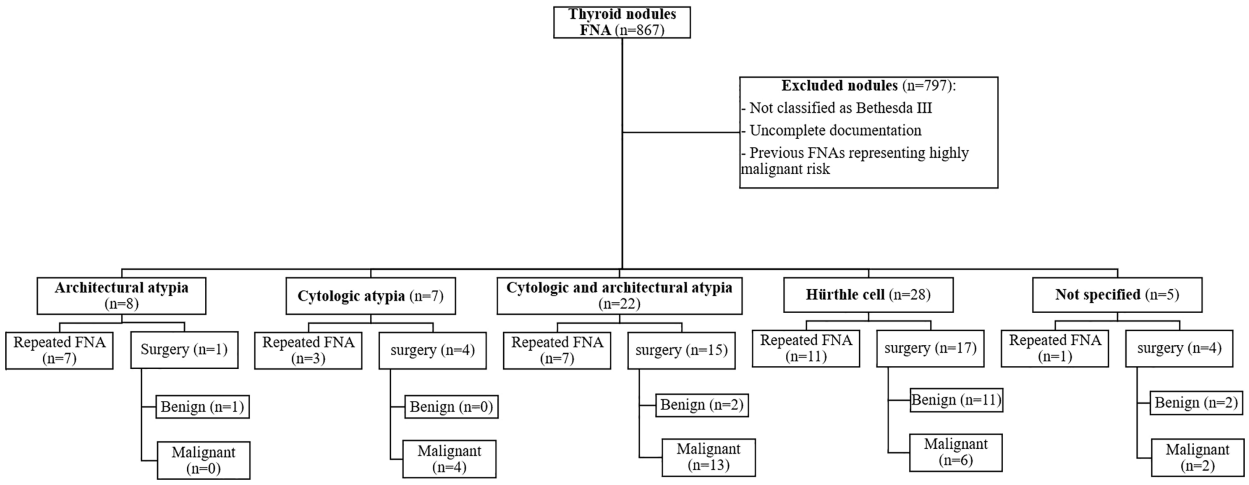

FIGURE 3
Diagram of clinical outcome of thyroid nodules. Among 867 evaluated thyroid nodules, 70 lesions were sub-categorized into architectural atypia, cytologic atypia, cytologic and architectural atypia, Hürthle cell AUS/FLUS, and atypia, not otherwise specified. The outcomes are shown based on surgery or follow-up US-FNA.

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TABLE 4 Bethesda III subcategorization and ACR TI-RADS scores.

	Architectural			Cytologic			Cytologic and architectural			Hürthle cell AUS/FLUS			Not specified		
	Benign	Malignant	P	Benign	Malignant	P	Benign	Malignant	P	Benign	Malignant	P	Benign	Malignant	P
TR3	5	0	–	0	0	1.00	3	3	1.00	8	1	0.02	1	0	–
TR4	3	0	–	3	3	1.00	5	9	0.28	13	2	0.005	2	2	1.00
TR5	0	0	1.00	0	1	–	1	1	1.00	0	4	–	0	0	1.00
Fisher's Exact Test	P_Value =0.72			P_Value=0.65			P_Value = 0.82			P_Value = 0.003			P_Value = 0.66		

21). It has been shown that Hürthle cells can be found both in non-malignant lesions such as Hashimoto's disease, nodular goiter, Graves' disease, radiotherapy or chemotherapy-associated lesions, and also thyroid neoplasms including Hürthle cell adenomas, Hürthle cell carcinomas, follicular thyroid carcinomas (FTC), follicular thyroid adenomas (FTA), and PTC (22). The presence of Hürthle cells in thyroid FNAs persuades cytopathologists to discriminate nonneoplastic (mainly hyperplastic) from neoplastic lesions, that extensively clarifies clinical management approaches.

Based on the BSRTC, the FNA reports of Hürthle cells are primarily classified into the category III or IV (1). An exclusively Hürthle cell specimen can be categorized as AUS/FLUS in patients with MNG and lymphocytic (Hashimoto) thyroiditis, generally considered hyperplastic rather than neoplastic (23). Notably, most malignancies in known Hashimoto thyroiditis patients are considered PTC (24). Thus, reporting Hürthle cell AUS/FLUS as the most common subcategory with various differential diagnoses should be considered carefully to provide detailed information to avoid a needless lobectomy.

Another critical challenge in AUS/FLUS subcategorization is NIFTP, a shallow-risk thyroid lesion mainly subclassified into architectural atypia or cytologic and architectural atypia. It has been shown that up to 20% to 25% of all lesions previously diagnosed as thyroid malignancies should have been categorized as NIFTP (25–27). Any of the six TBSRTC categories may precede a report of NIFTP; however, the most frequent NIFTP report is encountered in the setting of AUS/FLUS (28). NIFTPs have cytologic features similar to PTC except for a follicular architecture and classical papillae of PTC. Therefore, the presence of true papillae with fibrovascular cores and/or psammomatous calcifications will exclude NIFTP diagnosis. Considering the lower risk of malignancy in NIFTP, suspicious US pattern, indeterminate cytology, and *RAS* mutation in ThyroSeq should guide clinicians to NIFTP for considering less aggressive therapeutical approaches (18, 29). Besides, future studies are required to determine whether NIFTP is associated with specific patterns of AUS/FLUS. This may hypothetically persuade efforts to recognize NIFTPs in AUS/FLUS subcategories.

Nodular size is another prominent feature of thyroid nodules. There is a considerable discrepancy in the correlation between thyroid nodule size and malignancy risk. In this study, we have evaluated the size of thyroid nodules among different AUS/FLUS subcategorization. In this regard, nodules classified into architectural atypia (34.42 mm) were significantly larger than cytologic atypia (16.68 mm). Notably, our results showed that nodules classified into architectural atypia display lower malignancy risk than other categories, including those with cytologic atypia. These results are in accordance with previous studies that demonstrated thyroid nodules smaller than 20 mm have a higher malignancy risk than larger lesions (30, 31). On the other hand, comparing the size of malignant and benign nodules in each subclassification of AUS/FLUS showed that malignant nodules (29.68 mm) are larger than benign nodules (15.56 mm) only in the cytologic and architectural atypia subcategory. At the same time, the difference was not significant in other subclassifications. Some reports show that an increase in thyroid nodule size influences cancer risk in a nonlinear fashion with a threshold of 20 mm (32). In order to take appropriate clinical measures for AUS/FLUS thyroid nodules, Sengul et al. have recommended active surveillance for managing these thyroid nodules with a size of 10-15 mm (33). It seems that the size of thyroid nodules is

not an accurate predictive feature for the malignancy risk of the thyroid nodules, and FNA cytology is required besides the size feature (34).

As another risk-evaluating tool, US characteristics have shown an acceptable predictive role in determining the malignancy of thyroid nodules. In this regard, some studies have assessed the predictive role of US features in AUS/FLUS nodules (35, 36). In order to simplify and standardize the evaluation and reporting of US characteristics of a thyroid nodule, the *American College of Radiology* has introduced the ACR TI-RADS reporting system consisting of five grades of malignancy susception (15). ACR TI-RADS has been utilized in evaluating thyroid nodules of different cytopathologic categories and has proven its efficacy in clinical practice (37). However, the predictive role of ACR TI-RADS in AUS/FLUS subclassifications is unclear. In this study, we have shown that ACR TI-RADS is not predictive for Bethesda III subcategorization. Some studies have evaluated the TIRADS score between AUS and FLUS, which has revealed no significant differences between benign and malignant FLUS nodules, while there were significant differences between benign and malignant nodules of the AUS subcategory (2). On the other hand, we have shown that ACR TI-RADS scoring is significantly different between benign and malignant nodules only in Hürthle cell AUS/FLUS subclassification. Słowińska-Klencka et al. assessed the diagnostic effectiveness of EU-TIRADS for Hürthle cell thyroid nodules in Bethesda III-V. They concluded that EU-TIRADS would not assist clinicians in taking the appropriate measure in patients with thyroid Hürthle cell nodules, especially in the Bethesda IV classification. However, we have demonstrated that ACR TI-RADS can be used in Hürthle cell AUS/FLUS thyroid nodules to discriminate between benign and malignant nodules (38).

Our study has some limitations: 1) Although the ratio of AUS/FLUS reports among evaluated nodules was sensible according to previous reports, the number of AUS/FLUS reports in evaluated centers was low. 2) the unavailability of molecular pattering in evaluated centers may influence the final clinical decision in patients with AUS-FLUS nodules. 3) We tried recruiting several expert radiologists and cytopathologists; however, reporting US features and FNA slides is still subjective, and results vary interpretations among radiologists and cytopathologists.

5 Conclusion

In conclusion, we have demonstrated that Hürthle cell AUS/FLUS and architectural atypia showed lower malignancy among different AUS/FLUS subcategorization. Besides, Although ACR TI-RADS cannot be used in sub-categorizing AUS/FLUS lesions, it is predictive of malignancy in Hürthle cell AUS/FLUS subclassification.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author (afsharmoghadam@sbmu.ac.ir).

Ethics statement

The studies involving human participants were reviewed and approved by Shahid Beheshti University of Medical Sciences Ethics Committee (Ethics Code: IR.SBMU.MSP.REC.1399.440). The patients/participants provided their written informed consent to participate in this study.

Author contributions

AB, SR, and NM conceived and designed the analysis AB, SR, AD, and NM collected the data MR, SK, PB, and NM contributed data or analysis tools AB and EE performed the analysis AB, and NM wrote 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

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Patient decision aids for patients with differentiated thyroid carcinoma: development process and alpha and beta testing

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Background: Patient decision aids (PtDAs) are structured clinical tools that facilitate shared decision-making. Two important treatment decisions for patients with differentiated thyroid cancer (DTC), which could benefit from PtDAs, are as follows (1): the extent of surgery decision in patients with low-risk DTC and (2) the decision to start or delay starting the treatment with tyrosine kinase inhibitors (TKIs) in patients with advanced tumors.

Material and methods: PtDAs for these two decisions were developed using the International Patient Decision Aids Standards (IPDAS) quality criteria in an iterative process of prototype development *via* alpha and beta testing by patients and physicians. The information content of the PtDAs was based on the available literature, current guidelines, and patient's needs, preferences, and values.

Results: The web-based PtDAs underwent two rounds of alpha testing, revisions, and beta testing. The PtDAs have the same structure, consisting of six steps: a general introduction, information about the treatment options, comparing the treatment options, knowledge questions, a values clarification exercise, and saving the information. The alpha testing (n = 8 patients, n = 10 physicians) showed that the PtDAs were highly acceptable and usable for decision-making. Results of the beta testing in 20 patients showed that two patients did not use the PtDA; the other 18 patients found that the PtDAs were readable (n = 17) and helpful (n = 14) for decision-making. All patients recommend using the PtDAs.

Conclusions: Evidence-based PtDAs were created for patients with DTC for two different treatment decisions. Our final version was judged to be clear, balanced, and helpful in decision-making.

KEYWORDS

thyroid cancer, shared decision making, surgery, tyrosine kinase inhibitor, decision aid

Introduction

Differentiated thyroid cancer (DTC) is rapidly increasing in incidence throughout the world, mostly as a result of the increased use of diagnostic imaging and surveillance (1–3). Primary treatment for most patients with DTC consists of surgical removal of the thyroid (total thyroidectomy), followed by treatment with radioactive iodide (I^{131}, RAI) to ablate the remaining thyroid remnants or destroy (microscopic) DTC remnants. This is followed by life-long thyroid hormone therapy (4, 5). In patients with low-risk tumors smaller than 1 cm, the removal of only the affected lobe (lobectomy) is currently the standard of care. These patients do not require RAI treatment, and most of them maintain normal thyroid function. Several studies, including a recent meta-analysis (6), suggest that this more conservative approach results in similar long-term outcomes and therefore could be applied also in selected patients with low-risk tumors larger than 1 cm. However, because there are no prospective randomized controlled clinical trials (RCTs), comparing different surgical approaches for patients with low-risk DTC larger than 1 cm, management recommendations are currently based on retrospective data (7). After primary treatment, the majority of patients with DTC have an excellent long-term prognosis (1, 8–11).

Nonetheless, after primary treatment, up to 30% of the DTC patients develop recurrent disease and/or distant metastases. These patients have a less favorable prognosis amounting to an average life expectancy of 3–5 years for those with tumors that are nonresponsive to RAI (12, 13). For patients with metastatic disease, both local and systemic treatments are available, but overall complete remission is only seen in one-third of cases (14) and, while these treatments can improve DTC-related symptoms and disease-free survival, there is no evidence that these treatments result in a clear improvement of the overall survival (OS).

Therefore, for both patients with low-risk DTC and with RAI-refractory advanced DTC, there is a discussion about the optimal treatment strategy that better balances the risks and benefits for the individual patients and their personal preferences. As such, some patients with low-risk DTC might currently undergo overtreatment, which could negatively affect their quality of life (QOL) (6).

The current guidelines of the American Thyroid Association (ATA) state that less aggressive therapy, for example, a thyroid lobectomy and a tailored follow-up, can be equally acceptable and explicitly mention room for patients' preferences (15). Similarly, for asymptomatic or mildly symptomatic RAI- refractory DTC patients, an important unanswered question regards the optimal timing of starting tyrosine kinase inhibitors (TKIs). For those who are asymptomatic or only mildly symptomatic, starting the treatment too early may expose them to side effects and worsen their QOL without evidence of a survival benefit (16). The recent European Thyroid Association (ETA) guidelines state that the decision to start TKIs should include patient-related medical factors and patients' preferences with respect to treatment goals and patient values, and acceptance of adverse effects (17).

Given the different benefits and harms of surgery and TKI treatment, the care for patients with DTC should be better personalized. Patients could be informed using plain-language, evidence-based information about these decisions. Patient decision aids (PtDAs) are suitable instruments to support decision-making. Studies have shown that PtDAs generally improve patient knowledge, result in more realistic patient treatment expectations, increase active patient participation in decision-making, and reduce indecisiveness (4, 18). Currently, no PtDAs for DTC patients for the above-mentioned treatment decisions are available. This study presents the development process and alpha and beta testing of different PtDAs in order to provide decision support for two treatment decisions in patients with DTC (1): the extent of surgery in patients with low-risk DTC larger than 1 cm, and (2) the decision to wait or start with TKIs in patients with asymptomatic or mildly symptomatic advanced, RAI-refractory DTC.

Materials and methods

Development process

The development of the PtDAs was part of the Communication Booster (COMBO) study (NCT03905369), which aimed to develop, evaluate, and implement decision-support tools for DTC patients. Thirteen hospitals (six academic and seven non-academic) in the Netherlands participated, as well as the Dutch patient association "Schildklier Organisatie Nederland (SON)." In the study, we randomized patients into an intervention or control group. Patients in both groups received general information about DTC from their physicians. In addition, the intervention group received also the PtDA. The Medical Ethical Committee (CMO) of the region Arnhem–Nijmegen approved the study protocol (MEC-2018-4521).

The International Patient Decision Aids Standards (IPDAS) were used to guide the development of the PtDAs and were based on behavioral and decision-making theories underlying the Ottawa Decision Support Framework (19–21). To guide the development process, recommendations by Coulter et al. (21) and the Dutch Guideline were consulted (22). The development process is shown in Figure 1 and was performed by a project group consisting of a PhD student who is also a medical doctor (AK), a decision-making scientist (PS), an endocrinologist (RN-M), an implementation scientist (RH), and an oncologist (PO), assisted by a patient and physician expert panel. None of these patients or physicians had any conflicts of interest.

Scope and purpose of PtDAs

The scope and purpose of the PtDAs were defined by the project group. Meetings were held with the project group to reach a consensus on the scope, purpose, and target audience. The main scope was to improve informed choice regarding two different treatment decisions in patients with DTC. Therefore, the project group agreed to develop a PtDA for each treatment decision (Figure 2). The target audience for the first PtDA was defined as patients with low-risk DTC (> 1 cm) according to the ATA criteria

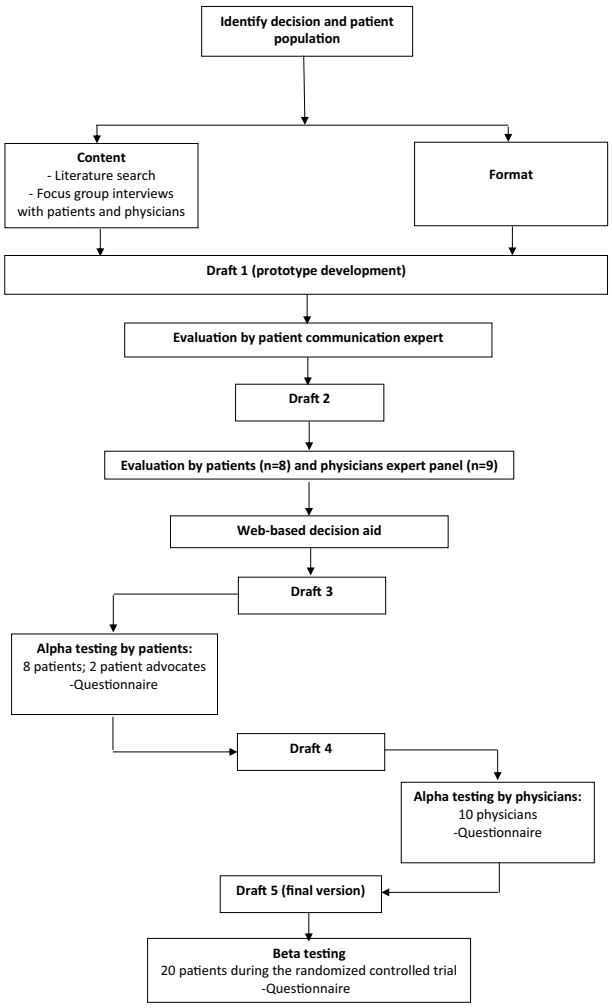

FIGURE 1
Development process of the patient's decision aids.

(15), considering the extent of thyroid surgery. For the second PtDA, the target group consisted of patients with advanced RAI-refractory asymptomatic or mildly symptomatic DTC considering whether to wait or start with TKI treatment.

Content and format

The first part of the COMBO study consisted of a literature review for clinical parameters, resulting in a meta-analysis of the extent of surgery decision (6), followed by focus groups with patients with DTC and physicians (endocrinologists, surgeons, oncologists, nuclear medicine physicians) treating patients with DTC to explore patients' needs, preferences, and values regarding the two treatment decisions, which resulted in a focus group paper (23). Based on the identified needs, guidelines, literature review, and the expertise in the project group, domains were determined that were important for decision-making in this setting: (1) risks and (2) benefits of both treatment decisions; (3) oncological outcomes in both treatment decisions; and (4) patients' personal values in decision-making. For the first three domains, we collected available literature (6, 24–26); for the fourth domain, values mentioned by patients and physicians were extracted from the focus group interviews (23). The development was an iterative process (Figure 1), with the content and format informed by the IPDAS guidelines. An online, web-based format was chosen by the project group to provide a PtDA that is tailored to a treatment decision. This resulted in the prototype draft.

Methods of alpha & beta testing and revision

The first drafts of the two PtDAs ("thyroid lobectomy or total thyroidectomy" and "to wait or start with TKIs") were finished after an iterative process of revising and reviewing the prototype content with the project group. In order to ensure the PtDAs were accessible to a broad audience, these drafts were evaluated on readability by communication experts experienced in increasing readability ("Stichting Makkelijk Lezen") (27). The reading level aimed to enable 95% of the Dutch population to understand the text, level A2-B1, according to the Common European Framework of for Languages (28). This resulted in the second draft (29) (Figure 1).

The second draft was sent by email to two different panels, consisting of eight patients and nine physicians (Figure 1). The eight patients made a decision regarding DTC in the past (four with low-risk DTC and four with advanced disease). The nine physicians

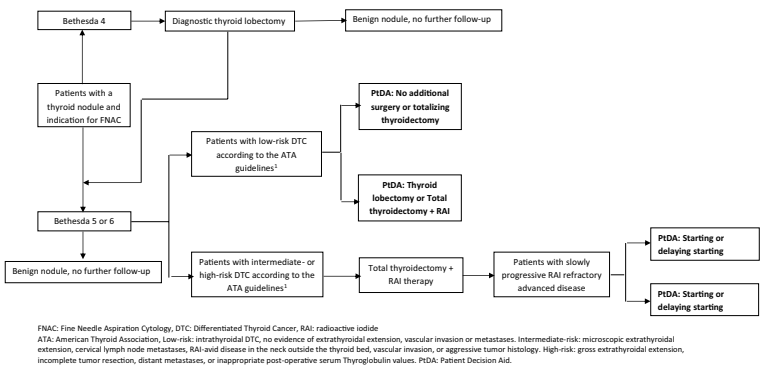

FIGURE 2
Overview of the different decision aids in the Netherlands.

consisted of two endocrinologists, two surgeons, and five oncologists treating patients with DTC. Patients and physicians were asked to evaluate this draft of the PtDA on clear language, content, layout, and comprehensibility. They were recruited from participating Dutch academic hospitals. Feedback on the PtDAs was also given by two patient advocates recruited from the patient association SON (Figure 1). This resulted in a third draft with a web-based format.

This third web-based draft was developed and alpha-tested by patients who made a decision regarding DTC in the past (Figure 1). The patients were recruited by endocrinologists from the participating Dutch academic hospitals, who asked one or two of their patients to participate in a face-to-face interview about the PtDA. After verbal consent, patients were approached by the investigator (AK) by telephone. Eight patients (four with low-risk DTC and four with advanced disease) were willing to participate (Table 1). All interviews were conducted by AK, and further interviews were determined by data saturation. The first part of the interview was unstructured using a think-aloud method (30). The second part was semi-structured, and participants were asked to fill out a questionnaire on content, structure, length, readability, balance, comprehensibility, relevance, reliability, completeness, and usability (Figure 1; Table 2). This resulted in the fourth draft.

TABLE 1 Demographic characteristics of patients and physicians who participated in the alpha testing.

	Patients (*n* = 8)	Physicians (*n* = 10)
Mean age in years (range)	42 (35–72)	45 (36–62)
Sex (*N*, %female)	6	8
Caucasian (*N*, %)	8	10
Level of education		
High school or less	2	
Vocational education	4	
University	2	
Type of treatment		
Surgery		
Thyroid lobectomy	2	
Total thyroidectomy	2	
Systemic therapy		
Lenvatinib	1	
Sorafenib	3	
Type of professional (*N*, %)		
Endocrinologist		2
Surgeon		6
Oncologist		2
Type of hospital (*N*, %)		
Academic		4
Non-academic		6
Years of experience as professional (*N*, %)		
0–5 years		3
5–10 years		2
10–15 years		0
15–20 years		3
>20 years		2

As suggested by Coulter (21), physicians were invited to participate in alpha testing as well. Therefore, the fourth draft was sent to an expert panel of 10 physicians (two endocrinologists, six surgeons, and two oncologists) from academic and nonacademic Dutch hospitals, all specializing in treating patients with DTC. None of them were involved in the initial development of the PtDA. They were asked to assess the PtDA for usability, acceptability of the content and format, practicality of use in the clinical pathways, and their perceived efficacy. They were further asked whether they would be willing to hand out this PtDA to their patients and at what moment in time. Their suggestions were incorporated to create the final fifth version (Figure 1), which was deemed acceptable for clinical use. The number of interviews was, again, determined by data saturation (Figure 1; Table 1). In addition to the quantitative evaluation, the quality of the fourth draft was tested against the IPDAS criteria.

Beta testing

The beta testing, or " real-world testing, " was organized during the ongoing randomized controlled COMBO trial (RCT, NCT03905369). The first 20 participants (Figure 1; Table 3) in the intervention group who received the PtDA and who were not involved in the design phase were asked to evaluate the feasibility of the PtDA with a questionnaire containing questions on usefulness, length, amount of information, comprehensibility, and reliability (Table 4). The quality of the PtDAs was tested using the IPDAS criteria.

Results

Development process

Content and format

Both PtDAs were divided into a general introduction and six steps: general information about DTC; treatment options; comparison of the treatment options; important items; values clarification exercise; and saving the information. The general introduction indicated for whom the PtDA was applicable and contained an explanation of how to use the PtDA. The first step gave general information about DTC. In step 2, the treatment options with the main risks, benefits, and oncological outcomes are presented. In step 3, patients could compare the treatment options. In step 4, patients were asked to answer factual knowledge questions to check for comprehension. Step 5 contained a values clarification exercise with five statements. These were based on patients' values extracted from the focus group interviews (Figure 3) (23). Patients could

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TABLE 2 Alpha testing among DTC patients and physicians treating patients with DTC.

	Draft 3: Low-risk DTC patients (*n* = 4)	Draft 3: Advanced disease patients (*n* = 4)	Draft 4: Physician's low-risk DTC (*n* = 8)	Draft 4: Physician's advanced disease (*n* = 2)
Length				
Too long	0	0	0	0
Too short	0	0	0	0
Just right	4	4	8	2
Amount of information				
Too much	0	0	0	0
Too little	2	0	0	0
Just right	2	4	8	2
Information balanced?				
Yes	3	4	8	2
Biased towards thyroid lobectomy	1		0	
Biased towards total thyroidectomy	0		0	
Biased towards systemic therapy		0		0
Biased towards watchful waiting		0		0
DA is comprehensible in general?				
Good	4	4	5	2
Moderate	0	0	3	0
Bad	0	0	0	0
Risks comprehensible?				
Good	4	4	5	1
Moderate	0	0	3	1
Bad	0	0	0	0
Readability				
Good	4	3	8	2
Moderate	0	1	0	0
Bad	0	0	0	0
DA reliable?				
Yes	3	4	8	2
No	0	0	0	0
Missing	1	0	0	0
Confusing items?				
Yes	0	0	2	0
No	4	4	6	2
Missing items?				
Yes	0	0	0	0
No	4	4	8	2

(Continued)

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TABLE 2 Continued

	Draft 3: Low-risk DTC patients (*n* = 4)	Draft 3: Advanced disease patients (*n* = 4)	Draft 4: Physician's low-risk DTC (*n* = 8)	Draft 4: Physician's advanced disease (*n* = 2)
Navigation through DA?				
Good	4	2	8	2
Moderate	0	2	0	0
Bad	0	0	0	0
Values clarification exercise helpful?				
Yes	4	4	8	2
No	0	0	0	0
DA helpful in decision making?				
Yes	4	4	8	2
No	0	0	0	0
Recommend use of DA?				
Yes	4	4	8	2
No				

indicate the importance of each statement on a four-point Likert importance scale ranging from not important to very important. The next page contained two empty boxes. Box 1 asked patients to tell what matters in their lives in general, and box 2 asked for their concerns regarding treatment. They were also asked to indicate which option they preferred and the strength of this preference. In the last step, patients were stimulated to save their answers using email or printing options and to bring these answers along and discuss them with their physicians in the next consultation.

Patients and physicians' expert panel

The second draft of the extent of surgery PtDA was revised by four patients and three physicians. One patient and all three physicians suggested developing two separate PtDAs for "thyroid lobectomy or total thyroidectomy" and "no additional surgery or totalizing thyroidectomy" because of the different treatment options (Figure 2). Percentages of complications and a note on life-long adjustment difficulties of substitution with thyroid hormones were added.

The second draft of the TKI PtDA was revised by four patients and five physicians. One patient and all five physicians suggested developing two separate PtDAs, one for sorafenib and one for lenvatinib, the two TKIs that are currently approved for use and reimbursed in the Netherlands, because of different outcome percentages and adverse events (Figure 2). More detailed information about the effect of TKIs, adverse events, and information on the palliative character of TKIs were added, as were progression-free survival rates. Both patients and physicians indicated that the general information about DTC was not appropriate for patients with metastatic disease because these patients were already familiar with thyroid cancer, so this information was deleted. In the end, four separate PtDAs for the extent of the surgery decision and the TKI decision were developed (Figure 2). Based on this information, the third draft was developed in the form of web-based PtDAs.

TABLE 3 Demographic characteristics of patients who participated in the beta testing.

	Patients (*n* = 20)
Mean age in years (range)	52.5 (25–73)
Sex (*N*, %female)	14
Level of education	
High school or less	4
Vocational education	12
University	3
Unknown	1
Type of treatment	
Surgery	15
Systemic therapy	5

Results of alpha & beta testing and revision

Alpha testing 1: patients

The third draft was alpha-tested by four patients treated with surgery and four with advanced disease. Their baseline characteristics are presented in Table 1. All patients were satisfied with the content, format, and layout. Length and the amount of information were assessed "just right" by all participants. The information was predominantly judged as balanced and comprehensible, and participants preferred 100-person diagrams for risk communication (31). All participants found the PtDAs useful for decision-making if they had to choose between the

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TABLE 4 Beta testing during the RCT among DTC patients.

	Patients (n=20)
DA used before the conversation with your physician	
Yes	18
No	2
Partly	0
Why not or partly used?	
Too difficult	0
Too much information	0
No time to read the DA	1
No need for a DA	1
	Patients (n=18)
How much time (minutes) did you spend on the DA?	45
Values clarification exercise helpful?	
Yes	15
No	3
Better knowledge after reading the DA?	
Yes	15
No	3
Timing	
Too early	0
Too late	6
Just right	12
Length	
Too long	1
Too short	1
Just right	16
Amount of information	
Too much	0
Too little	2
Just right	16
Information balanced?	
Yes	16
No	2
DA is comprehensible in general?	
Good	16
Moderate	2
Bad	0
Readability	
Too easy	1
Too difficult	0
Just right	17
DA reliable	
Yes	18
No	0
Information in a logical order?	
Yes	17
No	1
Grade (0-10)	
0	0
1	0
2	0
3	0
4	0
5	0
6	2
7	6
8	5
9	4
10	1
Recommend use of DA?	
Yes	18
No	0

(Continued)

TABLE 4 Continued

treatment options. Participants also suggested some minor changes. To improve the relevance of the extent of surgery, they suggested including more general information about low-risk DTC. To increase the usability of the TKI PtDAs, it was suggested to clarify the navigation through the PtDAs. Lastly, to increase readability, one participant suggested changing the colors of the 100-person diagrams. Other results from the questionnaire are shown in Table 2.

Alpha testing 2: physicians

The fourth draft was evaluated by 10 physicians (two endocrinologists, six surgeons, and two oncologists) from academic and nonacademic hospitals, all of whom specialized in treating patients with DTC. Their baseline characteristics are presented in Table 1. Overall, they were satisfied with the content, format, and layout of the PtDAs. Length and the amount of information were assessed "just right" by all physicians.

For the extent of surgery PtDAs, physicians suggested adjusting the surgery time for thyroid lobectomy as compared to total thyroidectomy because the duration of surgery is not the same for

Step 5 'what is important to you?':
You have the choice to remove either half or the entire thyroid gland. Together with your doctor, you may choose the option which suits you best. This depends on what is important to you. Below, you may indicate how important certain statements are to you.

Your doctor invites you to take your answers to the next consultation.

Statement	Not important		Very important	
1. If I have my entire thyroid removed, I have to take thyroid hormone tablets for life.	0	0	0	0
2. Medication adjustment of thyroid hormone can decrease my quality of life.	0	0	0	0
3. If I have half my thyroid removed, I may be able to go home on the same day.	0	0	0	0
4. If I have my entire thyroid removed, I am twice as likely to have (temporary) complications.	0	0	0	0
5. If I have my entire thyroid removed, I can get additional radioactive iodide therapy.	0	0	0	0
6. The chance that my tumor will come back is slightly smaller if the entire thyroid gland is removed followed by additional radioactive iodide therapy.	0	0	0	0

Your doctor or nurse can be more involved if they know what is important in your daily life, for instance your family, work or hobbies. You may enter this below.

Your doctor or nurse can be more involved if they know what concerns you most. You may enter this below.

My choice

You have thought about what is important to you. Which treatment do you prefer at the moment?

0 Thyroid lobectomy
0 Total thyroidectomy
0 Don't know

How strong is the above preference?

0 Not strong 0 Rather strong 0 Strong 0 Very strong

Figure 3. Example of the values clarification exercise of the extent of surgery PtDA (translated from Dutch into English).

FIGURE 3
Example of the values clarification exercise of the extent of surgery PtDA (translated from Dutch into English).

both procedures. There was a discussion about the presented recurrence rates (RR). For the extent of surgery PtDA, physicians suggested reducing the RR for total thyroidectomy from 7% to 4%, based on the following literature regarding the addition of RAI: The mean percentage of RR after the addition of RAI is 4% (32–35). A recent review by Verburg et al. (26) showed that literature published in the last decade offers data that support adjuvant postoperative RAI in DTC patients. Recently, Leboulleux et al. (36) showed in an RCT that the RAI ablation did not result in a significant oncological benefit in patients with low-risk tumors smaller than 2 cm and therefore could possibly be omitted in these cases. The latter represents only a part of the patients targeted by this PtDA, and omitting the RAI ablation for low-risk patients who underwent total thyroidectomy is currently not routinely applied in the Netherlands. All the abovementioned suggestions were admitted in the PtDAs. For the TKI PtDAs, there were no specific suggestions.

Other results from the questionnaire are shown in Table 2. All physicians mentioned that they would recommend the use of the PtDAs. Figure 3 shows the values clarification exercise of the final version of the "thyroid lobectomy or total thyroidectomy" PtDA.

Beta testing

The final version was beta- tested during the RCT of the COMBO study. All participants in the intervention group were asked to fill out a questionnaire about the feasibility of the PtDA. A total of 20 participants were already included in this intervention group. Their baseline characteristics are presented in Table 3. Two participants did not use the PtDA. The other 18 participants were satisfied with the content, format, and layout of the PtDAs (Table 4). Length and the amount of information were assessed "just right" by 89% of participants; the median grade was 8 out of 10, and all participants recommended using the PtDA. Almost all suggested handing over the PtDA as early as possible after the diagnosis, ahead of the decision appointment at home, and also to include more details about their current daily life. They also suggested including the option of active surveillance.

IPDAS criteria

The IPDAS collaboration checklist was used to estimate the quality of the PtDAs (20). Of the 64 items on the checklist, 55 quality criteria were applicable to our PtDAs given the scope of the PtDAs. The final version of the PtDAs met 52 out of the 55 applicable IPDAS criteria (95%). Among the 23 criteria for "content," 21 criteria were met. The two unmet criteria were on listing the option of doing nothing and viewing personalized probabilities based on their own situation. Among the 26 criteria in the " development process," 25 were met. The one unmet criterion was the provision of alternative methods to understand the information, such as audio or video options. Lastly, after the beta test, the six criteria for "effectiveness" were all met.

Discussion

This article describes the systematic development and pilot testing of web-based PtDAs for patients with low-risk (> 1 cm) DTC regarding the extent of primary surgery and for patients with advanced disease regarding starting or delaying the start of TKI treatment. We performed alpha testing with patients and physicians and beta testing with patients. To make the PtDA accessible to every eligible patient, it was written in the A2-B1 language level according to the Common European Framework of for Languages (28). The PtDAs were considered clear, balanced, and helpful for decision-making. The amount of information, length, presentation, and clarity of information received positive feedback. None of the participants indicated that the content was confusing. The criteria for evidence-based PtDA development that have been established by the IPDAS were followed (20). Our PtDAs met 52 of 55 quality criteria for content, development process, and effectiveness as formulated in the IPDAS checklist. Patients acting as reviewers who made a treatment decision in the past indicated they would have preferred to use the present PtDAs, if they had been available at the time of decision-making.

Most, but not all, of the IPDAS criteria were met. For example, listing the option of active surveillance was recommended in the IPDAS criteria. However, we did not include active surveillance in the PtDA for the extent of the surgery decision. At this moment, in national and international guidelines, active surveillance for low-risk DTC patients is not mentioned as a primary treatment option. In recent years, there has been emerging evidence on the safety of active surveillance as an option for the management of micro papillary thyroid carcinomas (mPTCs < 1 cm). More research is necessary before including this option in the PtDA for patients with low-risk tumors larger than 1 cm. When available, these data can be incorporated into a future version of the PtDA. Regarding the criteria to provide information on "viewing probabilities based on their own situation," we assessed that based on the current knowledge, we could not provide additional information that might better individualize the prediction of the outcomes. For example, although we hypothesize that in general elderly patients have a higher risk of complications or adverse events, length of hospital stay, and mortality (37), we could not find whether and to what extent the risks are higher specifically in elderly DTC patients. A third criterion we did not meet was "the provision of alternative methods to understand the information, such as audio or video options." Patient participants in our focus group interviews did not prefer audio and/or video options to understand information.

To the best of our knowledge, these are the first documented PtDAs aiming to support DTC patients in these two treatment decisions. Regarding PtDAs in low-risk DTC patients (1–4 cm), there is only one published PtDA focusing on RAI therapy in patients with low-risk papillary thyroid cancer (PTC) (4). This PtDA is limited to the decision to follow or omit RAI treatment after a total thyroidectomy. On the other hand, Brito et al. (38) and Pitt et al. (39, 40) recently developed a treatment choice tool (paper cards) for patients with DTC. These tools included the option of active surveillance, implying that these tools are also useful for informed patients with mPTC. Both tools need further testing before being implemented on a broad scale.

Our PtDAs were designed to facilitate conversations about treatment options for DTC patients in two different treatment decisions. In general, PtDAs have been shown to improve patient knowledge of the health care decision, decrease decisional conflict, and facilitate shared decision-making (18). Patients who use a PtDA are more often satisfied with the choice than those who receive standard counseling (18). However, PtDAs promote conversations between physicians and patients and do not replace the need for a patient–physician consultation. Treatment options still need to be explained to patients to help individualize the trade between harms and benefits according to the patient's specific situation and clinical situation. PtDAs facilitate a preference-based decision in which patient values and preferences are incorporated (41). By clarifying patients' values, PtDAs encourage the treatment option that best fits the patient. Therefore, a values clarification exercise was added asking patients to select arguments for and against a treatment option. Feldman-Stewart et al. showed in an RCT in patients with early-stage prostate cancer that values clarification exercises led to better preparation for decision-making and to less regret at the > 1-year follow-up (42).

Strengths and limitations

A strength of our study is the structured development process of the PtDAs, which systematically uses the input of patients, physicians, and patient advocates. Involving patients in all stages of development yielded important insights. Furthermore, our statements in the values clarification exercise were based on patients' values extracted from the focus group interviews (23). Another strength is that we developed four very specific PtDAs for each of the decision steps to support decision-making for the full decision trajectory of DTC patients.

A limitation in the development process of the PtDAs is the reliability of evidence regarding the information presented about the clinical outcomes of the different options. This limitation is inherent to the lack of prospective trials on head-to-head comparisons of the treatment options, which can provide the highest level of evidence. Nonetheless, shared-decision making is

appropriate for situations where there is insufficient evidence that one option is superior to another, which is also the case for the decisions for which the PtDA has been developed in the present study. Moreover, the information provided in the PtDAs is based on the best available evidence. First, regarding the extent of surgery, only retrospective trials are available, showing no differences in oncological outcomes in terms of RR and OS (6). Second, for the use of TKIs, only two RCTs are available (24, 25). The outcome in terms of OS has not been published yet. Additionally, in daily practice, the effect of TKIs can be different, as the treatment regimens used in practice may differ from regimens used in the RCTs, particularly because of *ad hoc* individualized dose adjustments in patients who are deemed more prone to toxicity or who develop AEs. Furthermore, information desired in rural locations or other countries may differ, potentially making the PtDAs less applicable in settings where less accurate diagnostic tools or less experienced physicians are available. As DTC research continues, new studies may require updating of outcome rates and treatment modalities. Moreover, a prospective randomized controlled trial is ongoing (NCT03905369) investigating the effect and implementation of the PtDAs.

Conclusion

Novel evidence-based PtDAs were created for patients with DTC. These PtDAs were positively evaluated to support patients and physicians in shared decision-making by patients having undergone the treatments, patient advocates, and physicians. The PtDAs address an important need for DTC patients and aim to increase patient knowledge and guide patients toward an informed decision (23). The PtDAs will be made publicly available after the large prospective trial has been completed.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/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

AK: conceptualization (equal), writing —original draft preparation (lead), and writing —review and editing (lead). RH: conceptualization (equal) and writing —review and editing (equal). PO: writing —review and editing (equal). RN-M: conceptualization (equal) and writing —review and editing (equal). PS: conceptualization (equal) and writing —review and editing (equal). COMBO study group: conceptualization (supporting). All authors have read and agreed to the published version of the 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.

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The association between vitamin D supplementation and the long-term prognosis of differentiated thyroid cancer patients: a retrospective observational cohort study with propensity score matching

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Objective: Benefits of vitamin D in various cancers have been reported, but its effects on differentiated thyroid cancer (DTC) have not been established. We aimed to analyze the effect of vitamin D supplementation on the prognosis of DTC.

Methods: A retrospective observational cohort study was conducted on 9,739 DTC patients who underwent thyroidectomy from January 1997 to December 2016. Mortality was classified as all-cause, cancer-related, or thyroid cancer-related. Patients were divided into the "VD group" (supplemented with vitamin D) and the "control group" (without vitamin D supplementation). Propensity score matching was performed in a 1:1 ratio according to age, sex, tumor size, extrathyroidal extension (ETE), and lymph node metastasis (LNM) status, and 3,238 patients were assigned to each group. Kaplan-Meier curves, log-rank test and Cox proportional hazards regression analysis were performed.

Results: The follow-up period was 10.7 ± 4.2 years. Clinicopathological variables between two groups were similar except for all-cause (p<0.001) and total cancer death (p=0.001). From the Kaplan–Meier curve and log-rank test, "VD group" had significantly favorable all-cause (p<0.001) and total cancer mortality (p=0.003), but similar thyroid cancer mortality (p=0.23). In Cox regression, vitamin D intake reduced the risk of all-cause (hazard ratio [HR], 0.617, p=0.001) and total cancer mortality (HR, 0.668, p=0.016) but had no effect on thyroid cancer mortality.

Discussion/conclusion: Vitamin D supplementation was positively associated with all-cause and total cancer mortality in DTC and might be a modifiable prognostic factor for improved survival. Further research will be needed to clarify the effect of vitamin D supplementation on DTC.

KEYWORDS

vitamin D, thyroid carcinoma, propensity score, mortality, cause of death

Introduction

The incidence of thyroid cancer has increased significantly worldwide, and thyroid cancer accounts for 3% of all cancers worldwide (1). Most of the diagnosed thyroid cancers are differentiated thyroid cancer (DTC), including papillary thyroid cancer (80-85%) and follicular thyroid cancer (10-15%), and the prognosis is generally excellent (2, 3). However, recurrence (10-15%) or distant metastasis (5%) may occur in DTC patients even after they have received appropriate treatment such as surgery or radioactive iodine treatment (2).

It has been reported that patients with poor prognostic factors have a higher risk of recurrence and death (4). There are several established prognostic factors in thyroid cancer, such as age, sex, tumor histopathology, tumor size, lymphovascular invasion, extrathyroidal extension (ETE), lymph node metastasis (LNM), distant metastasis, *BRAF* mutation, and *TERT* promoter mutation (3, 5). Since these prognostic factors cannot be modified, many studies are being conducted to explore modifiable prognostic factors in thyroid cancer patients (6, 7).

Vitamin D plays an important role in the body's calcium homeostasis (8). Vitamin D also exerts action in the tumor microenvironment, which is the environment surrounding a tumor and can influence the growth of cancer cells, by inhibiting proliferation, inflammation, invasion, metastasis and angiogenesis and by inducing apoptosis and cell differentiation (3, 8, 9). Several studies have shown that vitamin D supplementation affords good results in the incidence and prognosis of cancer, particularly breast, prostate, and colorectal cancer (10, 11). However, the effects of vitamin D supplementation on the prognosis of cancer are still controversial. One meta-analysis reported that vitamin D intake significantly reduced total cancer mortality by 13%, whereas another meta-analysis reported that vitamin D intake had no effect on reduction in total cancer mortality (12, 13).

Only a few studies have investigated the role of vitamin D in the aggressiveness and prognosis of thyroid cancer. Some studies reported that thyroid cancer patients had lower vitamin D levels, and lower vitamin D levels were associated with advanced thyroid cancer, characterized variably by higher T stage, ETE, and LNM (14, 15). Other studies reported that vitamin D levels had no association with the risk of incidence, advanced stage, or prognostic features of thyroid cancer (16, 17). There have been no studies analyzing the effect of vitamin D supplementation on mortality in thyroid cancer patients. The purpose of this study was to elucidate the potential role of vitamin D supplementation as a modifiable risk factor in the prognosis of thyroid cancer. We hypothesized that vitamin D supplementation would have a positive effect on mortality in thyroid cancer patients.

Methods

We conducted a retrospective observational cohort study. The flow diagram of this study is described in Figure 1. The cohort included patients aged 19 to 70 years who underwent thyroidectomy for DTC, including papillary thyroid cancer, follicular thyroid cancer, and Hürthle cell (oncocytic) thyroid cancer, at Seoul National University Hospital between January 1, 1997, and December 31, 2016. The following patients were excluded from this study: 1) patients with unavailable information on vitamin D intake; 2) patients with vitamin D supplementation after surgery for less than six months; 3) patients with a history of other cancers at the time of diagnosis of thyroid cancer; 4) patients with diseases or conditions that cause hypercalcemia or hypercalciuria (e.g., multiple myeloma, bone metastases, or malignant bone disease); 5) patients with intestinal diseases that could affect serum vitamin D levels (celiac disease, small intestine resorption disease, and a history of small bowel resection); 6) patients taking medications that could affect serum calcium or vitamin D levels; and 7) patients unable to have clinical data collected.

A total of 9,739 patients were eligible for this study. Clinicopathologic and survival status data up to December 31, 2019, were collected. Clinicopathological information, including age at thyroid surgery, sex, operation extent, tumor size, ETE, LNM status, and TNM stage, was collected from electric medical records. Operation extent is grouped into 'TT' and 'less than TT'. 'TT' includes total thyroidectomy and near total thyroidectomy. 'Less than TT' was all surgeries except 'TT'. ETE was confirmed as positive or negative by the final pathological findings, and ETE included microscopic and gross ETE. Data on the survival status of patients, duration of survival, and cause of death were collected from the registered data of the Korea Statistics. The causes of death were classified into the following three categories: 1) all-cause mortality, defined as patient death for any reason; 2) total cancer mortality, defined as patient death related to all malignancies; and

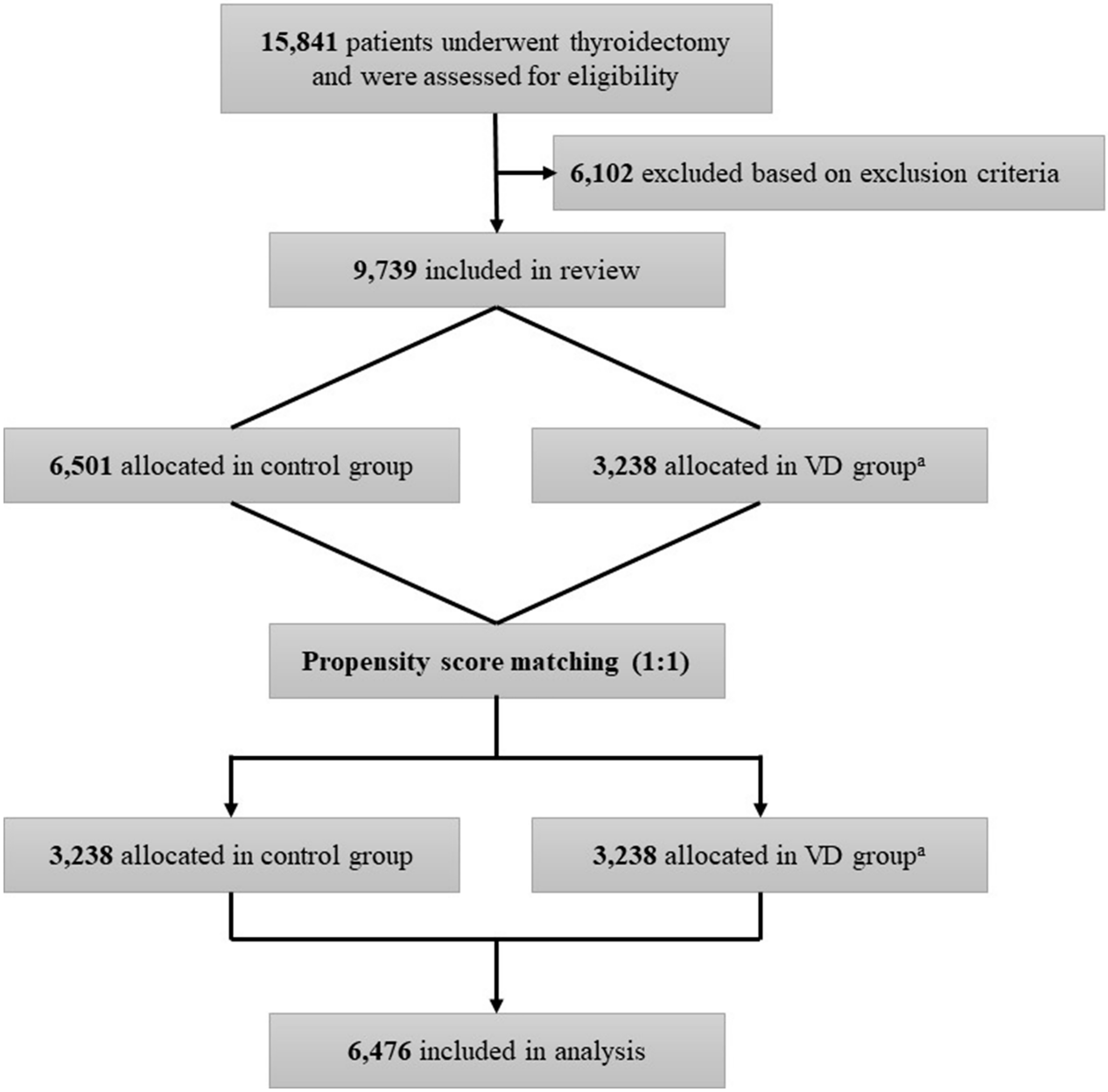

FIGURE 1
Flow chart of the study. [a]VD group is the case group with oral vitamin D supplementation for at least 6 months.

3) thyroid cancer mortality, defined as patient death related to thyroid cancer.

Vitamin D supplementation was defined as taking active or inactive vitamin D orally for any cause. Patients were divided into two groups according to their vitamin D supplementation status: 1) a control group of patients who did not receive vitamin D supplementation after thyroid surgery and 2) a "VD group" of patients who received supplementation with vitamin D for at least 6 months after thyroidectomy.

The consent of participants was waived due to the nature of the retrospective study. The study was approved by the Institutional Review Board (No. 2012-081-1181). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement reporting guideline for observational studies (18).

Statistical analysis

To correct the bias of confounding factors, propensity score matching (PSM) using nearest neighbor matching was introduced. Patients in both groups were matched at a 1:1 ratio based on age at the time of thyroid surgery, sex, tumor size, ETE, and LNM status. Considering collinearity, TNM stage was not included as a covariate, because age, tumor size, LNM, and ETE were included in TNM stage. Continuous variables were analyzed using Student's t

test, and categorical variables were analyzed using the chi-square test. All-cause, total cancer, and thyroid cancer mortality in the control and VD groups were compared using the Kaplan–Meier method and log-rank test. Cox proportional hazards regression analysis was used to analyze independent prognostic factors for all-cause, total cancer, and thyroid cancer mortality in thyroid cancer patients. Statistical significance was set at $p < 0.05$. All statistical procedures were performed using R software (R ver. 4.1.3; R Foundation for Statistical Computing).

Results

Baseline characteristics

The baseline characteristics of the original unmatched cohort and PSM-adjusted cohort are presented in Table 1. A total of 9,739 patients were included in the present study. There were 6,501 (66.8%) patients in the control group and 3,238 (33.2%) in the VD group. Compared to the control group, the VD group in the total cohort demonstrated associations with age at operation (older age), operation extent, ETE, LNM status, and TNM stage (all $p<0.001$). In the control group, higher proportions of patients with all-cause, total cancer, and thyroid cancer mortality were revealed ($p<0.001$, $p=0.002$, and $p=0.388$, respectively). A total of 276 and 77 participants in the control and VD groups, respectively, died during the study period, and the causes of death for each group are summarized in Supplementary Table 1. No significant differences in the causes of death by organ system were observed between the control and VD groups. Supplementary Table 2 summarizes mortality rates based on the extent of the operation and TNM stage in both cohorts. The 'Less than TT' group comprised 940 patients, while the 'TT' group had 8,671 patients. There were no significant differences in the mortality rates of all-cause, total cancer, and thyroid cancer according to operation extent (all p>0.05). The all-cause mortality was 249 (2.9%) in TNM stage I, 96 (9.8%) in TNM stage II, 5 (13.2%) in TNM stage III, and 3 (60.0%) in TNM stage IV. For all cancer mortality rates, the rates in TNM stage I, II III, and IV were 1.8% (n=158), 7.5% (n=74), 13.2% (n=5), and 60.0% (n=3), respectively. In terms of thyroid cancer mortality rates, they were 0.4% (n=39), 2.8% (n=27), 7.9% (n=3), and 60.0% (n=3) in stages I to IV, respectively.

After PSM, 3,238 patients were assigned to each group. The mean ages of patients in the control and VD groups were 48.5 ± 11.1 and 48.6 ± 10.8 years, respectively ($p=0.762$). There were 320 (9.9%) male subjects in the control group and 342 (10.6%) in the VD group ($p=0.389$). The number of patients who underwent total thyroidectomy was 2,806 (88.5%) in control group and 3,092 (95.6%) in VD group ($p<0.001$). Tumor size was not different between the two groups (control, 1.2 ± 1.0 cm vs. VD group, 1.2 ± 0.9 cm, $p=0.613$). ETE was confirmed in 1,953 patients (60.3%) in the control group and in 1,963 patients (60.6%) in the VD group ($p=0.819$). Central and lateral LNM was confirmed in 789 (24.4%) and 602 (18.6%) patients in the control group and in 830 (25.6%) and 582 (18.0%) patients in the VD group, respectively ($p=0.473$). There were more patients with TNM stage I and III in the VD group and more patients with TNM stage II in the control group (p=0.029). The number of patients who died from any cause was 151 (4.7%) in the control group and 77 (2.4%) in the VD group ($p<0.001$). The number of patients who died from total cancer-related causes was 99 (3.1%) in the control group and 57 (1.8%) in the VD group ($p=0.001$). The number of patients who died from thyroid cancer-related causes did not differ between the two groups (control group, n=30 (0.9%) vs. VD group, n=20 (0.6%), $p=0.201$). After conducting PSM, a total of 151 and 77 participants in the control and VD groups, respectively, died during the study period, and there were no significant differences in the causes of death by organ system between the two groups. There were no significant differences in all-cause mortality, total cancer mortality, and thyroid cancer mortality between the two groups classified by extent of operation, with p-values of 0.116, 0.149, and 0.389, respectively. The all-cause mortality was 2.6% (n=146) in stage I, 9.0% (n=74) in stage II, 14.3% (n=5) in stage III, and 60.0% (n=3) in stage I. Regarding the mortality rates for all cancer types, the corresponding rates for stages I, II, III, and IV were 1.6% (n=91), 7.0% (n=57), 14.3% (n=5), and 60.0% (n=3), respectively. The thyroid cancer mortality rates also varied, with rates of 0.4% (n=22), 2.7% (n=22), 8.6% (n=3), and 60.0% (n=3) in stages I to IV, respectively.

Comparisons of mortalities according to vitamin D supplementation

During a median follow-up of 10.7 ± 4.2 years, 228, 156, and 50 patients died from all-cause, total cancer-related, and thyroid cancer-related causes, respectively. The analyses to compare all-cause, total cancer, and thyroid cancer mortality according to vitamin D supplementation are described in Figure 2. Kaplan–Meier survival curves showed that the patients of the VD group had significantly better all-cause mortality than patients of the control group ($p<0.001$). At 5, 10, 15, and 20 years after surgery, the all-cause mortality rates of the control group patients were 1.3%, 3.2%, 6.6%, and 12.7%, respectively, and those of the VD group patients were 0.7%, 2.0%, 4.8%, and 7.5%, respectively. There was also significantly better total cancer mortality among VD group patients than control group patients ($p=0.003$) according to Kaplan–Meier curve analysis. The 5-, 10-, 15-, and 20-year total cancer mortality rates in the control group were 1.0%, 2.4%, 4.4%, and 7.1%, respectively, and those in the VD group were 0.5%, 1.6%, 3.4%, and 5.2%, respectively ($p=0.003$). However, the Kaplan–Meier curve showed no difference in thyroid cancer mortality between the two groups ($p=0.23$). The 5-, 10-, 15-, and 20-year thyroid cancer mortality rates in the control group were 0.3%, 0.7%, 1.5%, and 1.9%, respectively, and those in the VD group were 0.2%, 0.5%, 1.3%, and 2.9%, respectively ($p=0.23$).

Comparative analysis of factors affecting mortality

The results of Cox proportional hazards regression analysis of the effect of vitamin D supplementation on all-cause, total cancer,

TABLE 1 Baseline characteristics of original unmatched cohort and propensity score matching-adjusted cohort.

	Original unmatched cohort			PSM-adjusted cohort[a]		
	Control group (n = 6,501)	VD group[b] (n = 3,238)	*p*-value	Control group (n = 3,238)	VD group[b] (n = 3,238)	*p*-value
Age at operation (years)	46.2 ± 11.5	48.6 ± 10.8	<0.001	48.5 ± 11.1	48.6 ± 10.8	0.762
Sex			<0.001			0.389
Female	5297 (81.5%)	2896 (89.4%)		2918 (90.1%)	2896 (89.4%)	
Male	1204 (18.5%)	342 (10.6%)		320 (9.9%)	342 (10.6%)	
OP extent[c]	(n=6,375)	(n=3,236)	<0.001	(n=3,169)	(n=3,236)	<0.001
TT[d]	5579 (85.8%)	3092 (95.5%)		2806 (88.5%)	3092 (95.6%)	
Less than TT[d]	796 (12.2%)	144 (4.4%)		363 (11.5%)	144 (4.4%)	
Tumor size (cm)	1.2 ± 1.0	1.2 ± 0.9	0.287	1.2 ± 1.0	1.2 ± 0.9	0.613
ETE[e]			<0.001			0.819
No	2962 (45.6%)	1275 (39.4%)		1285 (39.7%)	1275 (39.4%)	
Yes	3539 (54.4%)	1963 (60.6%)		1953 (60.3%)	1963 (60.6%)	
LNM status[f]			<0.001			0.473
No LNM[f]	4019 (61.8%)	1826 (56.4%)		1847 (57.0%)	1826 (56.4%)	
Central LNM[f]	1365 (21.0%)	830 (25.6%)		789 (24.4%)	830 (25.6%)	
Lateral LNM[f]	1117 (17.2%)	582 (18.0%)		602 (18.6%)	582 (18.0%)	
TNM stage			<0.001			0.029
I	5885 (90.5%)	2830 (87.4%)		2787 (86.1%)	2830 (87.4%)	
II	599 (9.2%)	382 (11.8%)		437 (13.5%)	382 (11.8%)	
III	14 (0.2%)	24 (0.7%)		11 (0.3%)	24 (0.7%)	
IV	3 (0.0%)	2 (0.1%)		3 (0.1%)	2 (0.1%)	
Mortality						
All-cause	276 (4.2%)	77 (2.4%)	<0.001	151 (4.7%)	77 (2.4%)	<0.001
Total cancer	183 (2.8%)	57 (1.8%)	0.002	99 (3.1%)	57 (1.8%)	0.001
Thyroid cancer	52 (0.8%)	20 (0.6%)	0.388	30 (0.9%)	20 (0.6%)	0.201

[a]Propensity score matching was performed in a 1:1 ratio based on age at the operation, sex, tumor size, ETE, and LNM status.
[b]The VD group is the case group with oral vitamin D supplementation for at least 6 months.
[c]OP extent, operation extent.
[d]TT, total thyoridectomy.
[e]ETE, extrathyroidal extension, was confirmed by final pathologic results and included microscopic and gross ETE.
[f]LNM status, lymph node metastasis status, was defined as follows according to the final pathological results; i) 'no LNM' indicates no lymph node metastasis, ii) 'central LNM' indicates lymph node metastasis only in the central compartment, and iii) 'lateral LNM' indicates lateral compartment lymph node metastasis regardless of central compartment lymph node metastasis.

and thyroid cancer mortality are summarized in Table 2 and Figure 3. Cox analysis showed that vitamin D supplementation significantly reduced the hazard ratio (HR) for all-cause mortality to 0.572 (95% CI 0.443-0.739, p=0.001) and total cancer mortality to 0.627 (95% CI 0.464-0.847, p=0.016). However, thyroid cancer mortality was not affected by vitamin D supplementation in the Cox analysis. Cox analysis showed that the risk of all-cause mortality increased with age at surgery (HR 1.098, 95% CI 1.082-1.115, p<0.001), male sex (HR 2.009, 95% CI 1.433-2.815, p<0.001), and tumor size (HR 1.372, 95% CI 1.266-1.487, p<0.001). In Cox analysis, total cancer mortality was analyzed for increased risk with the same variables as all-cause mortality, including age at surgery (HR 1.09, 95% CI 1.071-1.109, p<0.001), male sex (HR 2.2, 95% CI 1.488-3.254, p<0.001), and tumor size (HR 1.462, 95% CI 1.34-1.594, p<0.001). According to Cox analysis, thyroid cancer mortality was increased in patients with ETE (HR 2.366, 95% CI 1.103-5.072, p=0.027) as well as in patients with older age at operation (HR 1.111, 95% CI 1.073-1.15, p<0.001), male sex (HR 2.983, 95% CI 1.573-5.656, p=0.001), and larger tumor size (HR 1.797, 95% CI 1.615-1.998, p<0.001).

Discussion

This retrospective cohort study included 9,739 DTC patients with available information on vitamin D supplementation. We

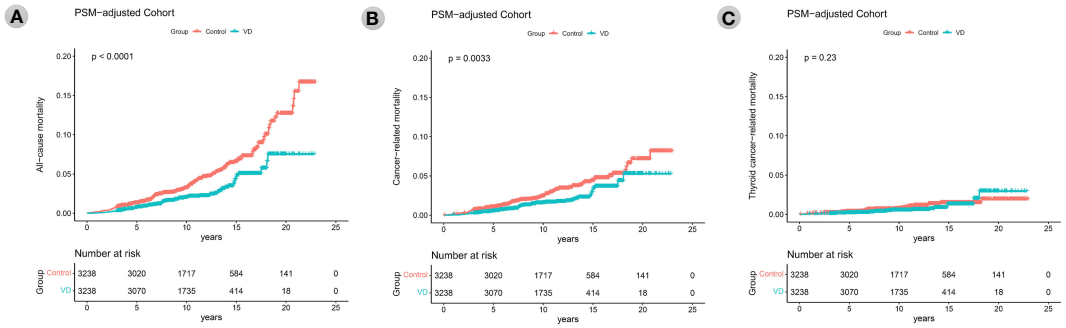

FIGURE 2
Kaplan–Meier survival curves of all-cause mortality **(A)**, total cancer mortality **(B)**, thyroid cancer mortality **(C)** according to the groups (vitamin D supplementation) in the propensity score matching-adjusted cohort. PSM, propensity score matching which was performed in a 1:1 ratio based on age at the operation, sex, tumor size, ETE, and LNM status. VD, VD group which is the case group with oral vitamin D supplementation for at least 6 months.

TABLE 2 Cox proportional hazards regression analysis for all-cause mortality, total cancer mortality and thyroid cancer mortality in thyroid cancer patients in the propensity score matching-adjusted cohort.

	All-cause mortality		Total cancer mortality		Thyroid cancer mortality	
	HR, 95% CI[a]	*p*-value	HR, 95% CI[a]	*p*-value	HR, 95% CI[a]	*p*-value
Vitamin D supplementation	0.617, 0.467-0.814	0.001	0.668, 0.48-0.928	0.016	n/a[b]	n/a[b]
Age at operation (years)	1.098, 1.082-1.115	<0.001	1.09, 1.071-1.109	<0.001	1.111, 1.073-1.15	<0.001
Sex (Male)	2.009, 1.433-2.815	<0.001	2.2, 1.488-3.254	<0.001	2.983, 1.573-5.656	0.001
Tumor size (cm)	1.372, 1.266-1.487	<0.001	1.462, 1.34-1.594	<0.001	1.797, 1.615-1.998	<0.001
ETE[c]	n/a[b]	n/a[b]	n/a[b]	n/a[b]	2.366, 1.103-5.072	0.027

[a]HR, 95% CI, hazard ratio, 95% confidential interval.
[b]n/a, not applicable.
[c]ETE, extrathyroidal extension, was defined according to the final pathologic results and included microscopic and gross ETE.

analyzed mortalities in the context of three categories based on cause of death, providing differentiated information on the effects of vitamin D supplementation on various causes of death. We found that vitamin D supplementation was associated with reduced all-cause and total cancer mortality in patients with DTC. These results suggest that vitamin D supplementation could be a potential prognostic factor in DTC patients. To our knowledge, this is the first study to analyze the effect of vitamin D supplementation on mortality in patients with thyroid cancer. To avoid selection bias, we performed PSM analysis to minimize the influence of potential confounders, including established prognostic factors (age, sex, tumor size, ETE, and LNM) (3, 5). After PSM, 6,476 patients with a median follow-up of 10.7 years were analyzed to evaluate the effect of vitamin D supplementation on mortality in DTC patients. Therefore, the present study with a large sample size and long-term follow-up provides reliable information.

Vitamin D can act in multiple carcinogenesis stages, reduce the invasiveness and metastasis of tumors, and modulate the immune system (12). Francesca cialdai et al. reported potential antineoplastic functions of vitamin D (8). Cell cycle arrest, apoptosis, epithelial-mesenchymal transition, epithelial-mesenchymal transition, CD8+ T-cell infiltration, and anti-inflammation are potential antitumorigenic mechanisms of vitamin D action. Vitamin D regulates multiple signaling pathways through activation of vitamin D receptor (VDR) transcription factor. Phosphoinositide 3-kinase and mitogen-activated protein kinase downstream of ligand-bound VDR can be activated and modulate microRNA expression and cancer stem cell biology. The VDR-retinoid X receptor complex and vitamin D elements in target genes alter gene transcription in response to vitamin D. However, the role of vitamin D in carcinogenesis is still under debate.

The beneficial effect of vitamin D supplementation on cancer mortality was reported in a meta-analysis of 10 randomized controlled trials (summary RR, 0.87; 95% CI, 0.79-0.96) (12). A recent randomized controlled trial (VITAL) also reported that vitamin D supplementation reduced the HR for total cancer mortality to 0.79 and 0.75 at time points other than the first-year and second-year follow-ups (11). However, another randomized controlled trial (D-Health trial) including 21,315 older participants

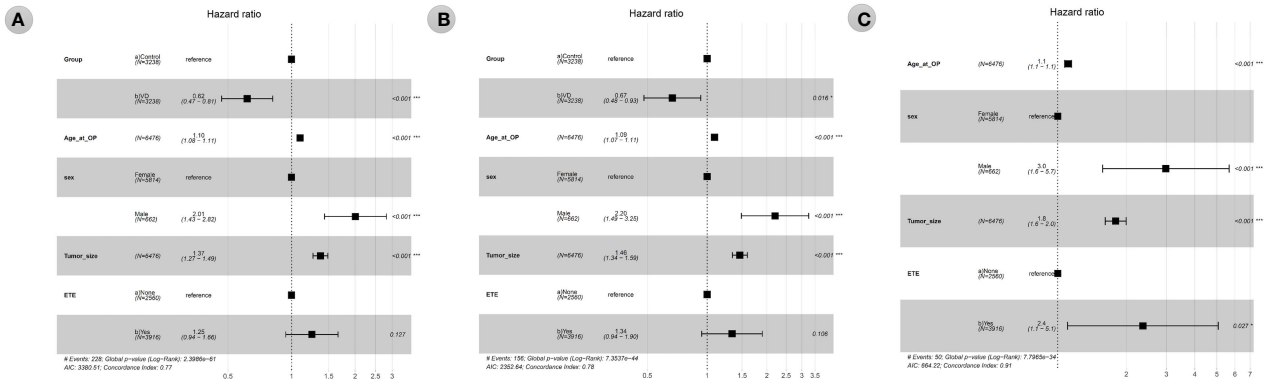

FIGURE 3
1 Forest plot of hazard ratios from multivariable Cox proportional hazards regression analysis of all-cause mortality **(A)**, total cancer mortality **(B)**, thyroid cancer mortality **(C)** according to the groups (vitamin D supplementation) in the propensity score matching-adjusted cohort. VD, VD group which is the case group with oral vitamin D supplementation for at least 6 months. Age_at_OP, Age at operation in years. ETE, extrathyroidal extension, was defined according to the final pathologic results and included microscopic and gross ETE.

(≥60 years) did not show the beneficial effect of vitamin D supplementation for the reduction of all-cause mortality (19). Our study revealed that vitamin D supplementation reduces all-cause and total cancer mortality and supports the efficacy of vitamin D supplementation, albeit to varying degrees.

However, we could not observe a significant improvement in thyroid cancer mortality in thyroid cancer patients who had vitamin D supplementation. Because DTC patients have excellent clinical outcomes, with a 10-year cancer-specific survival of 97.2%, only 50 patients of 6,476 patients died from thyroid cancer during the follow-up period of 10.7 years (20). The nonsignificant result might be attributed to our study being of short a duration to observe sufficient mortality events, considering the very low mortality rate of thyroid cancer.

The VITAL study suggested that the effect of vitamin D intake in reducing metastatic and advanced cancers is due to a general mechanism affecting the body, not a site-specific mechanism (11). The insignificant effects of vitamin D supplementation on the reduction in the risk of thyroid cancer mortality may be due to the lack of a site-specific effect of vitamin D supplementation. Therefore, further studies will be needed to ascertain the effect of vitamin D supplementation with large numbers of patients and long-term follow-up periods, including sufficient numbers of thyroid cancer-specific deaths.

Thyroid cancer was reported to be associated with low levels of vitamin D from the perspective of clinical or pathological aggressiveness *in vitro*, case-control, and cohort studies, and the results varied from study to study (3). Stepien et al. reported that vitamin D levels were lower in thyroid cancer patients than in normal subjects, and Kim et al. reported that patients with lower vitamin D levels were associated with more aggressive features of thyroid cancer (14, 15). However, there were also previous studies that did not show a significant association between vitamin D levels and aggressive characteristics of cancer in thyroid cancer patients (16, 21, 22).

A previous multicenter cohort study showed that older age at diagnosis, male sex, larger tumor size over 2 cm, presence of ETE, lateral cervical LNM, distant metastasis, and TNM stages at diagnosis were independent risk factors for disease-specific mortality in DTC patients (23). Our results suggest that male sex is most likely to be associated with an increased risk of all-cause, total cancer, and thyroid cancer mortality (HR 2.009, HR 2.2, and HR 2.983, respectively). In addition to male sex, large tumor size and old age at time of operation were determined to have a significant positive correlation with increases in all-cause, total cancer, and thyroid cancer mortality. Sex, tumor size, age, and ETE are well-known prognostic factors associated with the aggressiveness and prognosis of thyroid cancer (3, 5). In this study, these factors were adjusted using PSM to confirm an effect of vitamin D on thyroid cancer mortality.

This study has some limitations. First, as this study is a retrospective observational cohort analysis, it was not possible to completely eliminate the potential for selection bias, and the detailed information could not be comprehensively reviewed. Second, we could not analyze the mechanism by which vitamin D positively affects mortality, and the criteria for vitamin D supplementation were not uniform. Third, since the vitamin D level before and after vitamin D supplementation was not included in the analysis, it was not possible to analyze the effect of the vitamin D level or its increase or decrease on the prognosis of thyroid cancer. Fourth, other possible confounding factors, such as socioeconomic status, comorbidity, and lifestyle, were not analyzed. In the future, well-designed studies are needed to analyze the relationship between the prognosis of thyroid cancer patients and vitamin D supplementation regimens.

Conclusion

Vitamin D supplementation was positively associated with all-cause and total cancer mortality in patients with DTC. We suggest that vitamin D supplementation has potential to be a modifiable prognostic predictor regarding reduced mortality in patients with

DTC. Further research will be needed to clarify the effect of vitamin D supplementation on DTC.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the corresponding authors upon request.

Ethics statement

The studies involving human participants were reviewed and approved by Seoul National University Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

(I) Conception and design: SJK, HSC, and YJP. (II) Administrative support: SJK and YJP. (III) Provision of study materials or patients: SJK, SWC, KEL, DJP, and YJP. (IV) Collection and assembly of data: JHA, and HSC. (V) Data analysis and interpretation: JHA, and HSC. (VI) Manuscript writing: all authors. 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/fendo.2023.1163671/full#supplementary-material

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Transiently impaired endothelial function during thyroid hormone withdrawal in differentiated thyroid cancer patients

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Purpose: Endothelial dysfunction, which was associated with chronic hypothyroidism, was an early event in atherosclerosis. Whether short-term hypothyroidism following thyroxine withdrawal during radioiodine (RAI) therapy was associated with endothelial dysfunction in patients with differentiated thyroid cancer (DTC) was unclear. Aim of the study was to assess whether short-term hypothyroidism could impair endothelial function and the accompanied metabolic changes in the whole process of RAI therapy.

Methods: We recruited fifty-one patients who underwent total thyroidectomy surgery and would accept RAI therapy for DTC. We analyzed thyroid function, endothelial function and serum lipids levels of the patients at three time points: the day before thyroxine withdrawal(P_1), the day before ^{131}I administration(P_2) and 4-6 weeks after RAI therapy(P_3). A high-resolution ultrasound named flow-mediated dilation (FMD) was used to measure endothelial function of the patients.

Results: We analyzed the changes of FMD, thyroid function and lipids at three time points. FMD(P_2) decreased significantly compared to FMD(P_1) (P_1vsP_2, 8.05 ± 1.55vs 7.26 ± 1.50, p<0.001). There was no significant difference between FMD (P_3) and FMD(P_1) after restoring TSH (thyroid stimulating hormone) suppression therapy (P_1 vs P3, 8.05 ± 1.55 vs 7.79 ± 1.38, p=0.146). Among all parameters, the change of low-density lipoprotein (ΔLDL) was the only factor correlated negatively with the change of FMD (ΔFMD) throughout the RAI therapy process ($P_{1\text{-}2}$, r=-0.326, p=0.020; $P_{2\text{-}3}$, r=-0.306, p=0.029).

Conclusion: Endothelial function was transiently impaired in DTC patients at short-term hypothyroidism state during the RAI therapy, and immediately returned to the initial state after restoring TSH suppression therapy.

KEYWORDS

endothelial dysfunction, lipids, differentiated thyroid cancer, radioiodine therapy, flow-mediated dilation

Introduction

The frequency of diagnosis of differentiated thyroid cancer (DTC), the most common subtype of thyroid cancer and the most common endocrine malignancy, continues to rise as a result of the widespread use of diagnostic imaging and surveillance (1–3). However, the mortality rate associated with DTC remains low, relative to that associated with other cancers, because of the indolence of thyroid cancer and the availability of effective treatments (4). Radioiodine (RAI) treatment is an effective method of treating potential remnant cancer tissue and metastases following surgery (5). High concentrations of thyroid stimulating hormone (TSH) (>30 mIU/L) are required for RAI therapy to be performed, because this increases the ^{131}I uptake by thyroid cancer tissue. A sufficient serum TSH concentration is usually achieved in clinical practice by the withdrawal of thyroid hormone for 3–4 weeks. Therefore, patients experience short-term hypothyroidism during RAI therapy (6).

The association between hypothyroidism and cardiovascular (CV) diseases is well established, with reports dating as far back as 1878, when thyroid function tests were not available (7). It has been shown that patients with overt hypothyroidism frequently experience pericardium effusion, cardiac enlargement, and atherosclerosis (8). Hypothyroidism has been demonstrated to be an independent risk factor for atherosclerosis (9), the potential mediators of which include dyslipidemia, hypercoagulability, arterial stiffness, obesity, and endothelial dysfunction (10). The endothelial dysfunction, first reported in 1995, is an early stage in the development of atherosclerosis, and is associated with a higher risk of CV events (11). The endothelium plays important roles in modulating vascular tone by synthesizing and releasing an array of endothelium-derived relaxing factors, including vasodilator prostaglandins, NO, and endothelium-dependent hyperpolarization factors, as well as endothelium-derived contracting factors (12). Endothelial cells, forming a continuous monolayer along the inner surface of arteries, are activated by thyroid hormone through its binding to thyroid hormone receptors, which are expressed on both the myocardial and vascular endothelium. This leads to the production of nitric oxide (NO), the most important vasodilator substance, causing the relaxation of vascular smooth muscle cells and arterial dilatation (12–15). The relationship between hypothyroidism and endothelial dysfunction has now been thoroughly studied. It was well established that chronic hypothyroidism caused endothelial dysfunction by reducing NO availability (16–18). And subclinical hypothyroidism patients, patients with a TSH level>10 mIU/L and normal thyroid hormone levels, had a higher risk of developing heart failure (19). But it is unclear whether short-term hypothyroidism has similar effects like subclinical hypothyroidism or chronic hypothyroidism patients.

Endothelial function can be assessed using flow-mediated dilation (FMD) that measures flow-mediated changes in brachial artery diameter induced by short term ischemia. Flow-mediated changes are endothelium-dependent, largely NO-mediated dilatation of arteries in response to artificially induced increases in blood flow induced shear stress. The brachial artery is occluded by the inflated cuff for 5 min, and the shear-induced NO would increase and the vasodilation of the brachial artery would be induced after the cuff deflated. We calculated FMD by the percentage flow-mediated dilation index (FMD%), which is defined as the largest relative change in arterial diameter (20). FMD is affected by CV risk factors and independently predicts the outcome of CV diseases, which is worthy of greater attention in patients with hypothyroidism (21, 22). There were many tools to assess endothelial function including measuring the percent of change in blood flow following heat-mediated vasodilation using laser Doppler flowmetry (10) and peripheral arterial tonometry measuring finger microvascular function. An interesting study compared three noninvasively methods assessing endothelial function and FMD was proven to be a good tool (23).

In the present study, we aimed to determine whether short-term hypothyroidism caused by the thyroxine withdrawal during RAI therapy impaired endothelial function in patients with DTC. Because short-term hypothyroidism was usually accompanied by an abnormal lipid profile (24), we also evaluated the relationships between endothelial function and circulating lipid concentrations.

Materials and methods

Patients and RAI procedure

The present study was conducted at the Shanghai Jiao Tong University Affiliated Sixth People's Hospital and was approved by the local ethics committee. We evaluated patients after they had undergone total thyroidectomy and would accept RAI therapy between March and December 2021 in the Nuclear Medicine Department of Shanghai Sixth People's Hospital. Patients who satisfied the following criteria were considered for inclusion: they (i) had DTC, confirmed by pathological examination; (ii) underwent total thyroidectomy, and (iii) had never previously undergone RAI therapy. Of the 73 patients who satisfied these criteria, 22 were excluded because of insufficient circulating TSH concentrations (n=2) or missing follow-up data (n=20). Thus, 51 patients who were to undergo RAI therapy were recruited prospectively. All of these had their thyroxine withdrawn for 3–4 weeks prior to RAI to increase their serum TSH concentrations. Their thyroid function and circulating thyroglobulin (Tg) and anti-thyroglobulin antibody (TgAb) concentrations were routinely tested prior to RAI therapy, and neck ultrasonography and chest computed tomography were also performed. An oral dose of ^{131}I (30–200 mCi) was empirically administered to the participants, who underwent a ^{131}I whole-body scan (^{131}I-WBS) 3 days after radioiodine administration. All the participants restarted their TSH suppression therapy 2 days after RAI therapy at the same doses that they had been administering before thyroxine withdrawn.

Measurements of thyroid function and serum lipid concentrations

Thyroid function and serum lipid concentrations were tested at three time points: the day before thyroxine withdrawal (P_1), the day before ^{131}I administration (P_2), and 4–6 weeks after RAI therapy

(P_3). The serum concentrations of the following were measured to assess thyroid function: free triiodothyronine (FT_3), free thyroxine (FT_4), Tg, TgAb, and TSH. The serum concentrations of triglycerides, cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol were measured.

Assessment of endothelial function

Endothelial function was evaluated at three time points. FMD, a non-invasive means of assessing peripheral artery endothelium-dependent dilation using ultrasonography, was used to determine the effect of short-term hypothyroidism on the endothelial function of patients with DTC. FMD was performed according to previously published guidelines (21): the participants fasted for 6 hours, avoided exercise for 24 hours, and refrained from the consumption of caffeine, vitamin C, and alcohol for 12 hours prior to the procedure. If the participants were taking medication for the treatment of underlying diseases, such as hypertension and diabetes, the assessment was performed four half-lives after the preceding dose. The participants relaxed in a quiet, temperature-controlled room for at least 10 minutes before the procedure, to reduce their mental stress level and minimize the effects of any previous physical activity. During the FMD procedure, the blood pressure of each participant was measured using their right arm while in sitting position. To evaluate the brachial artery, a cuff was wrapped around the extended right forearm of each participant while they were in a supine position, an ultrasonographic transducer was applied 3–5 cm above the antecubital fossa, and the baseline diameter of the artery was measured. The cuff was then inflated to a pressure 50 mmHg higher than the participant's systolic blood pressure (SBP) for 5 minutes, then the recovery of the arterial diameter was monitored on cuff deflation, and the post-ischemic diameter was recorded. The FMD of the brachial artery was calculated as (post-ischemia diameter – baseline diameter)/baseline diameter × 100%. The FMD procedure was performed by a physician with at least 3 years of experience in the use of an Omron UNEXEF38G system, with a probe frequency of 10 MHz. FMD was measured twice for each participant at an interval of 20 minutes, and the mean value was used in further analyses.

Statistical analysis

Parameters are summarized as mean±standard deviation (SD) or median and interquartile range for continuous data, and as counts or proportions for categorical data. The changes in continuous datasets during therapy were compared using repeated measures analysis of variance (ANOVA) or Friedman's two-way analysis of variance by rank, as appropriate [general linear model procedure in SPSS]. Prior to performing ANOVA, the assumption of sphericity was tested using Mauchly's test, and when the sphericity assumption was not met, the multivariate test statistic was determined using Wilks's lambda test. After Friedman analysis, comparisons between P_1, P_2, and P_3 were performed using repeated Wilcoxon signed rank tests, with the application of the Bonferroni correction to the level of significance for paired groups. Comparisons of categorical data between P_1, P_2, and P_3 were made using the χ^2 test. Results were considered statistically significant when $p<0.05$. Data were analyzed using SPSS v.12.0 for Windows (Chicago, IL, USA).

Results

Clinical characteristics of the patients

Fifty-one patients were studied, and their clinical characteristics are shown in Table 1. The patients had a male-to-female ratio of 1:1.8 and their mean age was 35.3±9.7 years. 50 patients had been diagnosed with papillary thyroid cancer; 39 with classic phenotypes and 11 with variant phenotypes. 1 patient had been diagnosed with follicular thyroid cancer. Their mean body mass index (BMI) was 23.4±3.5 kg/m^2, and 1 patient had BMI <18 kg/m^2 and 19 patients had BMI >24 kg/m^2. 11 patients had CV risk factors (hypertension, smoking, and hyperlipidemia, n=2; diabetes, smoking, and hyperlipidemia, n=1; hypertension and diabetes, n=1; hypertension, n=2; hyperlipidemia, n=5; smoking, n=1). The serum concentration of TSH was >30 mIU/L in all of the patients on the day of ^{131}I administration. ^{131}I (30–200 mCi) was empirically administered on the basis on the patient's serum Tg and TgAb concentrations and the results of neck ultrasonography and chest computed tomography. 36 patients were given ^{131}I (£100mCi) and the others ^{131}I (>100mCi). Post-therapeutic ^{131}I-WBS showed that 4 patients had metastases (2 had lymph node metastases and 2 had lung metastases).

Changes in thyroid function, vascular parameters, and lipid concentrations

The thyroid function, vascular, and lipid data at the 3 time points were displayed in Table 2. The serum concentrations of TSH and Tg significantly increased between P_1 and P_2 and then decreased between P_2 and P_3, while the serum concentrations of FT_3 and FT_4 showed the opposite trends. These changes imply that the patients experienced a change from subclinical or clinical hyperthyroidism to overt hypothyroidism, but returned to their initial states after the RAI therapy.

The serum concentrations of lipids (triglyceride, total cholesterol, LDL cholesterol, and HDL cholesterol) were all higher at P_2 than at P_1, reflecting thyroxine withdrawal. After the patients restarted their TSH suppression therapy, their serum lipid concentrations decreased, such that they were significantly lower at P_3 than at P_2. Vascular parameters, including SBP, diastolic blood pressure, and baseline diameter, showed similar change to the lipids. However, there were no significant differences in thyroid function, vascular parameters, or lipid concentrations between P_1 and P_3.

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TABLE 1 Clinical characteristics of patients.

Patient characteristics	Total sample (N=51)
Age (y) (Mean ± SD)	35.3 ± 9.7
≤55	49(96.1%)
>55	2(3.9%)
Sex (Female)	33(64.7%)
Pathological classification	
PTC(Classic phenotype)	39(76.4%)
PTC(Variant phenotype)	11(21.6%)
FTC	1(2.0)
BMI (kg/m^2)	23.4 ± 3.5
<18	1(2.0%)
18-24	31(60.8%)
>24	19(37.2%)
Cardiovascular risk factors	
Hypertension	4(7.8%)
Diabetes	2(3.9%)
Hyperlipidemia	8(15.6%)
Smoking	4(7.8%)
None	40(78.4%)
ATA Risk Stratification system (2015)	
Low	12(23.5%)
Intermediate	36(70.6%)
High	3(5.9%)
TNM stage*	
I	49(96.1%)
II	2(3.9%)
RAI dose (mCi)	
≤100	36(70.6%)
>100	15(29.4%)
^{131}I-WBS	
Residual thyroid tissue	47(88.3%)
Lymph node metastasis	2(3.9%)
Lung metastasis	2(3.9%)

BMI, body mass index; PTC, papillary thyroid carcinoma; ^{131}I-WBS, ^{131}I-whole body scan; RAI, radioactive iodine.
* Tumor-node-metastasis (TNM staging is determined by eighth American Joint Cancer Committee TNM staging system).

Changes in endothelial function

Endothelial function during the various states of thyroid function was assessed by FMD using ultrasonographic imaging, and the results are shown in Figure 1 and Table 2. We found that the FMD of the patients was lower at P_2 than at P_1 (7.26±1.50 *vs.* 8.05±1.55, p<0.001), but increased when subclinical or clinical hyperthyroidism developed after the recommencement of TSH suppression therapy, at P_3 (7.79 ± 1.38 *vs.* 7.26 ± 1.50, p=0.002). There was no significant difference in FMD between P_1 and P_3 (8.05 ± 1.55 *vs.* 7.79 ± 1.38, p=0.438). This implies that there was a temporary induction of endothelial dysfunction when the serum TSH concentration increased during the preparation for RAI therapy, which was followed by a gradual recovery when thyroxine therapy was subsequently reinstated.

The relationships between the changes in FMD and serum lipid concentrations during the RAI therapy are shown in Table 3. Because of the complexity of the changes in thyroid hormones, we simplified the process into three stages (P_{1-2}, P_{2-3} and P_{1-3}) and analyzed the relationships separately. We found that the change in FMD (ΔFMD) negatively correlated with the change in LDL cholesterol concentration (ΔLDL) during two stages (P_{1-2}, r= −0.326,p=0.020; P_{2-3}, r=−0.306, p=0.029) and the correlation plots were shown in Figure 2.

12 of the patients showed decreases in FMD of >1% between P_1 and P_3. It has been reported that every 1% decrease in FMD was associated with an increase in the incidence of CV events (25, 26). Therefore, we defined a decrease in FMD of >1% as reduced value and placed these 12 participants into a reduced group, and the other 39 into an unreduced group, and compared the clinical characteristics of the two groups. The results were shown in Table 4. there were no significant differences in the baseline characteristics in the two groups (age, sex, prevalence of CV risk factors, and BMI).

Discussion

In the present study, 51 patients underwent total thyroidectomy for DTC and would accept RAI therapy and experience a short-term hypothyroidism were recruited and most of them were younger than 55 years old except for 2 patients. We have shown that the hypothyroidism which develops following thyroxine withdrawal during RAI therapy caused transient endothelial dysfunction in patients with DTC, and that this was reversed after the reinstatement of TSH suppression therapy. The lipid profile of patients changed alongside these fluctuations in serum thyroid hormone concentrations during the whole process, and the changes in LDL cholesterol negatively correlated with the changes in FMD. In addition, when we compared reduced group with unreduced group, we did not find significant difference in baseline characteristics between the two groups.

DTC accounts for >95% of cases of thyroid cancer, but is associated with a relatively good prognosis because of the availability of effective treatments based on thyroidectomy. TSH suppression, accompanied by thyroid hormone supplementation, is recommended by the American Thyroid Association, which means that patients are in a state of subclinical or clinical hyperthyroidism during the TSH suppression therapy (6). RAI is an effective method of treating thyroid cancer, but requires a sufficient serum TSH

TABLE 2 Changes of thyroid function, vascular parameters and lipids.

Characteristics	P1	P2	P3	*p-value*
FMD (%)	8.05 ± 1.55	7.26 ± 1.50*	7.79 ± 1.38	<0.001
Baseline diameter (mm)	2.96 ± 0.57	3.20 ± 0.61*	2.98 ± 0.57	<0.001
SBP (mmHg)	123.1 ± 14.5	120.6 ± 16.1*	117.5 ± 12.7	<0.001
DBP (mmHg)	74.9 ± 9.3	77.3 ± 14.0*	73.2 ± 8.2	0.029
Cholesterol (mmol/L)	4.49[3.79-5.06]	6.22[5.46-7.14]*	4.33[3.79-4.92]	<0.001
Triglyceride (mmol/L)	1.07 [0.75-1.66]	1.71[1.06-2.86]*	1.10[0.81-1.56]	<0.001
HDL-Chol (mmol/L)	1.23 ± 0.34	1.43 ± 0.37*	1.16 ± 0.32	<0.001
LDL-Chol (mmol/L)	2.74 ± 0.76	3.67 ± 1.04*	2.65 ± 0.76	<0.001
FT3 (pmol/L)	4.94 ± 0.94	1.28[1.01-2.00]*	5.27 ± 0.84	<0.001
FT4 (pmol/L)	22.62 ± 4.43	2.261.40-3.21]*	24.60[22.40-28.00]	<0.001
Tg (ng/mL)	0.54[0.04-2.58]	4.20[0.45-30.60]*	0.29[0.04-1.95]	<0.001
TgAb (KIU/L)	14.2[11.6-98.5]	14.3[11.8-124]	14.8[11.7-154.0]	0.783
TSH (mIU/L)	0.32[0.05-1.59]	100.00 [82.90-100.00]*	0.53[0.20-1.65]	<0.001

FMD, flow-mediated dilation; SBP, systolic blood pressure; DBP, diastolic blood pressure; FT_3, free triiodothyronine; FT_4, free thyroxine; TSH, thyroid stimulating hormone; HDL, high density lipoprotein; LDL, low density lipoprotein; Tg, thyroglobulin; TgAb, anti-thyroglobulin antibody.
All comparisons made to P_1:*:p<0.05.

concentration, which is usually achieved in the clinic by thyroid hormone withdrawal, such that patients preparing for RAI therapy are hypothyroid during the process of thyroid hormone withdrawal (27). Therefore, these patients experience a change from subclinical or clinical hyperthyroidism to short-term hypothyroidism, and then return to their initial states during the whole RAI therapy process.

Thyroid dysfunction is closely associated with CV disease. It is well known that long-term hypothyroidism is associated with atherosclerosis, with potential mechanisms consisting of hypercholesterolemia, hypertension, and endothelial dysfunction (9). Endothelial dysfunction is an early event in atherosclerosis, and plays an important role in the regulation of hemostasis and thrombosis, local vascular tone, redox balance, and the orchestration of acute and chronic inflammatory reactions within the arterial wall (14). Short-term hypothyroidism were also associated with undesirable cardiovascular effects (28). Endothelial function can be non-invasively assessed using FMD, which is the endothelium-dependent, largely NO-mediated

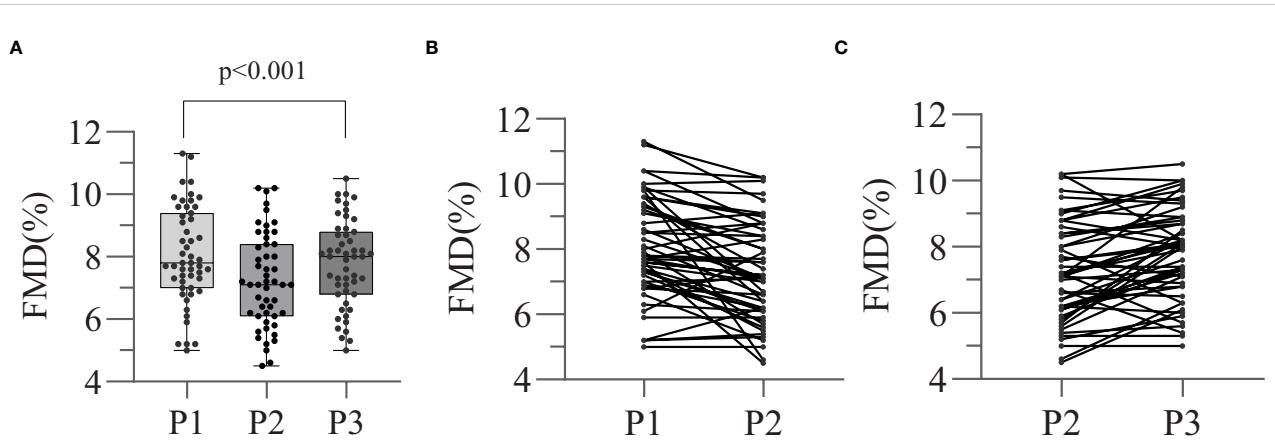

FIGURE 1
Effect of thyroid dysfunction on endothelial function in different stages. Flow-mediated arterial dilatation (FMD) (endothelin-dependent vasodilatation) was measured at each of the three stages (P_1, P_2, P_3). Different FMD values between three stages were compared by means of repeated measures ANOVA **(A)**. The trends of changing in FMD values of $P_{1\text{-}2}$ **(B)** and $P_{2\text{-}3}$ **(C)** were also showed separately.

TABLE 3 The correlation between the changes of FMD (%) and the corresponding changes of lipids and thyroid hormones.

	ΔFMD_{1-2}		ΔFMD_{2-3}		ΔFMD_{1-3}	
	R	*p-value*	R	*p-value*	R	*p-value*
ΔCholesterol (mmol/L)	-0.22	0.130	-0.31	0.030*	-0.18	0.218
ΔTriglyceride (mmol/L)	-0.24	0.083	-0.07	0.640	-0.02	0.899
ΔHDL-Chol (mmol/L)	0.11	0.456	-0.12	0.419	-0.13	0.380
ΔLDL-Chol (mmol/L)	-0.33	0.020*	-0.31	0.029*	-0.20	0.169
ΔFT_3 (pmol/L)	-0.42	0.770	-0.05	0.709	0.08	0.586
ΔFT4(pmol/L)	-0.12	0.407	0.06	0.703	0.01	0.956
ΔTg (ng/mL)	0.07	0.607	0.10	0.509	-0.08	0.558
ΔTSH (mIU/L)	-0.02	0.910	-0.06	0.695	0.05	0.748

FMD, flow-mediated dilation; TSH, thyroid stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; HDL, high density lipoprotein; LDL, low density lipoprotein; Tg, thyroglobulin.
*:p<0.05.

dilatation of arteries in response to induced increases in blood flow and shear stress (29). In the present study, we had characterized the changes in FMD in patients with DTC at the various thyroid function states experienced during the RAI therapy. We found that FMD decreased when overt hypothyroidism developed in patients preparing for RAI therapy and recovered after TSH suppression therapy was restarted. Although differences in this trend existed between the patients, the small sample size prevented definitive conclusions being drawn regarding these.

Erbil et al. recruited 22 patients with non-toxic multinodular goitre treated by total or near-total thyroidectomy and compared the endothelial function of them at different thyroid function states. In this research, endothelial function was impaired caused by the short-term hypothyroidism in the patients and persisted for at least 3 months, and total cholesterol and TSH were independent determinants of it (30). Chang et al. found that the short-term hypothyroidism could cause the clinical, biochemical and cardiovascular changes in DTC patients, but endothelial dysfunction did not present in the patients (31). The different of these studies may be attributed to the individual specificity of the patients with a small sample size and the different research time points, but these researches showed same opinion that short-term hypothyroidism did not cause permanent impairment to patients. Nevertheless, long-term TSH suppression therapy using supraphysiologic thyroid hormone treatment increased heart rate and left ventricular mass led to myocardial strain and impaired diastolic function and reduced arterial elasticity (32). The increased cardiovascular morbidity was confined to patients with a mean TSH level below 0.1mIU/L, but no correlation with the cumulative RAI dose was observed for the risk of all-cause mortality in patients treated with RAI ablation (33). Patients with thyroid cancer usually underwent both long-term supraphysiologic thyroid hormone treatment and transient iatrogenic hypothyroidism. According to our research and the studies above, long-term supraphysiologic thyroid hormone treatment may be more responsible for the developing of cardiovascular issues and needed to be further explored. Then we defined participants who had an FMD at P_3 that was >1% lower than that at P_1 as being reduced and the others as being unreduced. The two groups had no significant difference in baseline characteristics, but there was a tendency that patients in reduced group had more invasive PTC subtypes which needed to be further explored. A study with a wide range of ages and larger sample size may be helpful to figure out the difference between two groups.

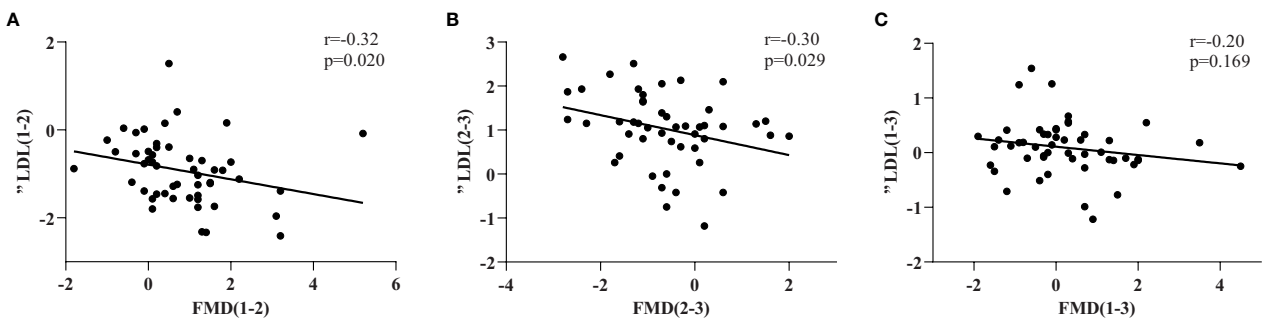

FIGURE 2
ΔFMD(%) and the correlation with the corresponding change of LDL(ΔLDL) in three stages **(A–C)**.FMD(%) was measured as described in the Methods section and expressed as percentage variation in brachial artery diameter induced by 5 minutes of ischemia.

TABLE 4 The baseline characteristics(P_1) between Reduced group and Unreduced group.

Baseline characteristics (P_1)	Reduced group (n=12)	Unreduced group (n=39)	*p-value*
Age (y)	38.42 ± 11.00	35.46 ± 9.26	0.359
Sex (Female)	7(58.3%)	26(66.7%)	0.855
BMI (kg/m^2)	23.51 ± 3.55	23.41 ± 3.48	0.934
CV risk factors	3(25.0%)	8(20.5%)	0.744
PTC (Classic phenotype)	7(58.3%)	32(82.1%)	0.090
RAI dose (£100mCi)	11(91.7%)	25(64.1%)	0.081
ATA Risk Stratification system (Low/Intermediate/High)	3/9/0	9/27/3	0.616

RAI, radioactive iodine; CV, cardiovascular; *: p<0.05.

Previous studies have shown that overt hypothyroidism affects the lipid profiles of patients (34, 35). Consistent with these, we have shown that overt hypothyroidism is associated with changes in serum lipid concentrations (triglyceride, total cholesterol, LDL cholesterol, and HDL cholesterol), but that the serum concentrations of lipids returned to their initial levels after TSH suppression therapy was reinstated. It was worth noting that the change in LDL cholesterol was the only change that correlated with the change in FMD throughout the process of RAI therapy. Although TSH concentration changed during the process, it showed no relationship with the change in FMD, which contrasted with the findings of previous studies, because it was previously reported that the HDL cholesterol concentration is the only independent determinant of FMD (36). Thus, the mechanism that was responsible for the change in FMD during RAI therapy requires further research. The change in LDL cholesterol concentration was found to correlate with the change in FMD across the period of the present study, and therefore the changes in LDL cholesterol that occur during RAI therapy are worthy of further research. In addition, the use of medication might be considered to avoid the sharp rise in LDL cholesterol that occurs in patients during hospitalization to keep the endothelial function. Besides, we only recruited 2 patients older than 55, so whether the endothelial function changes of them differed from young patients were unclear. Vascular endothelial dysfunction is regarded as a primary phenotypic expression of normal human aging. Decreased blood vessel density and endothelial cell subset dynamics appeared during ageing of the endocrine system (37). Another study found the loss of vascular abundance accompanied by the decline in pericytes is a key feature of aging tissues (38). The capacity of expansion of lymphatic vessels is also impaired in aged animals (39). Chronological age steadily impairs endothelial function through reduced endothelial nitric oxide synthase (eNOS) expression/action, accelerated NO degradation and so on (40). The cellular, molecular, and functional changes that occur in the endothelium during ageing can be contributed to the development of cardiovascular diseases (41). So high-quality studies with enough sample size are needed to classify the changes of endothelial function in patients older than 55.

There were several limitations to the present study. Almost all of the patients recruited were younger than 55 from only one medical center making the results applicable more to young patients than old patients. So, multicenter studies with larger sample size from and a wide range of ages should be conducted to verify the appropriateness of our conclusions and extrapolate them to all of the DTC patients. Besides, we only investigated the short-term effects of a single short period of hypothyroidism on endothelial function. However, patients with advanced diseases generally require multiple rounds of RAI therapy, meaning that they can experience several periods of short-term hypothyroidism. It is unknown whether multiple short periods of hypothyroidism can cause permanent damage to vascular endothelial function. We will enlarge the follow-up time and keep tracking the patients to fill this gap in the future work. Furthermore, FMD assesses endothelial-dependent dilatation, whereas nitroglycerin-mediated dilatation (NMD) assesses endothelial-independent dilatation, and in the present study, we did not measure NMD. However, many previous studies have shown that there is no relationship between changes in thyroid function and NMD (16, 17), and nitroglycerin can induce severe hypotension (28). Therefore, we believe that the lack of NMD measurements is not of great importance. Lastly, we only used one tool named FMD to assess the macrovascular endothelial function of the brachial artery of the patients. FMD index did not represent all aspects of endothelial dysfunction and long-term potential effects of the short-term hypothyroidism in patients may exist and needed to be explored.

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 Shanghai Jiao Tong University Affiliated Sixth People's Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of

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

Author contributions

L-YH: Data curation, Formal analysis, Investigation, Writing – original draft. XL, GQ-Z: Data curation, Supervision. CX, C-TS, H-JS: Writing – review and editing.

W-KW, Z-LQ, Q-YL: Resources, review and editing, Supervision, Conceptualization. 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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Review article: new treatments for advanced differentiated thyroid cancers and potential mechanisms of drug resistance

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The treatment of advanced, radioiodine refractory, differentiated thyroid cancers (RR-DTCs) has undergone major advancements in the last decade, causing a paradigm shift in the management and prognosis of these patients. Better understanding of the molecular drivers of tumorigenesis and access to next generation sequencing of tumors have led to the development and Food and Drug Administration (FDA)-approval of numerous targeted therapies for RR-DTCs, including antiangiogenic multikinase inhibitors, and more recently, fusion-specific kinase inhibitors such as RET inhibitors and NTRK inhibitors. BRAF + MEK inhibitors have also been approved for *BRAF*-mutated solid tumors and are routinely used in RR-DTCs in many centers. However, none of the currently available treatments are curative, and most patients will ultimately show progression. Current research efforts are therefore focused on identifying resistance mechanisms to tyrosine kinase inhibitors and ways to overcome them. Various novel treatment strategies are under investigation, including immunotherapy, redifferentiation therapy, and second-generation kinase inhibitors. In this review, we will discuss currently available drugs for advanced RR-DTCs, potential mechanisms of drug resistance and future therapeutic avenues.

KEYWORDS

drug resistance, immunotherapy, neoadjuvant, metastatic thyroid cancer, radioiodine refractoriness, tyrosine kinase inhibitor, novel treatments

Introduction

Differentiated thyroid cancers (DTCs) have an excellent prognosis in most patients, with an overall 5-year relative survival rate of 98.4% according to the SEER database (1). However, a subtype of patients, representing 5-10% of all DTCs, will develop distant metastasis, most frequently in the lungs and bones (2). Prognosis remains favorable as long

as metastatic disease is radioiodine-avid (3). Yet, 50% of metastatic DTCs are refractory to radioactive iodine (RAI), which is associated with poor outcomes and a 10-year survival rate of about 10% (4). On the other hand, many patients with advanced radioiodine refractory DTC (RR-DTC) can have an indolent or slowly progressive disease for many years. Thus, as multiple advances have been made in the treatment of advanced RR-DTCs in the last decade with multiple new therapeutic options, current challenges include identifying the appropriate timing for treatment initiation as well as choice of the right therapy.

When to treat RR-DTC

The first step in treating advanced DTCs is to properly identify radioiodine refractory disease. In fact, until disease is considered unresponsive to RAI, ^{131}I remains the gold standard in the treatment of metastatic advanced disease (3). However, taking into account the toxicity associated with high cumulative doses of RAI, it is crucial to properly identify when this therapy is no longer beneficial to the patient. The definition of RR-DTC can be challenging in clinical practice and remains somehow controversial. In most publications (2–6), RAI-refractory (RAI-R) disease is defined as either: (1) absence of RAI uptake outside the thyroid bed on the first posttherapy whole body scan, (2) loss of RAI concentration in a tumor tissue which was previously proved as RAI-avid, (3) concentration of RAI in some tumor lesions but not in others, and (4) progression of metastatic disease despite significant concentration of RAI, within a relevant time frame, usually considered as 6-12 months after ^{131}I therapy. A fifth criterion which is highly debated is disease progression in a patient who has received ≥ 600 millicuries (mCi) of ^{131}I. This is based on a single study which showed no further complete remissions after a cumulative dose of 22.2 GBq (600 mCi) (7). Therefore, factors such as response to previous therapies, duration of response, RAI uptake on diagnostic whole-body scan as well as previous treatment toxicity and patient preference should all be taken into account when considering if additional RAI therapy is indicated, rather than cumulative dose alone. Finally, ^{18}F-FDG PET/CT could also be useful in identifying RAI-R disease. For instance, a study showed that a SUVmax greater than 4.0 in ^{18}F-FDG avid metastases has a sensitivity of 75.3% and a specificity of 56.7 for predicting absence of ^{131}I avidity (8).

Although associated with risk of progression and poorer prognosis, not all RAI-R disease needs immediate therapy. In fact, RAI-R metastatic DTCs can have an asymptomatic and indolent clinical course for several years. Such patients can be managed with active surveillance and TSH suppression alone as long as disease is asymptomatic, there is no or minimal progression, and tumor burden is low (2–4, 9). Active surveillance includes regular cross-sectional imaging of known sites of distant disease (every 3-12 months), serum thyroglobulin (Tg) and Tg antibody measurement, and as needed ^{18}FDG-PET/CT whole body imaging, especially when Tg levels are increasing without explanation from cross-sectional imaging (2, 3, 9).

During this surveillance period, various scenarios can occur. First, disease can remain stable and asymptomatic, thus requiring no further intervention. Alternatively, there can be significant progression in one single lesion putting the patient at risk of complications or symptoms. This should be managed by locoregional therapy when feasible, including external beam radiation, stereotactic radiosurgery, thermal ablation, transarterial chemoembolization, and/or surgery (2, 3, 9). Finally, when local therapies are not feasible, or there is tumor progression despite local therapy, or there is significant disease progression in multiple lesions affecting more than one organ, then systemic therapy with kinase inhibitors becomes indicated (9).

Molecular basis of differentiated thyroid cancer

Selecting the right kinase inhibitor to treat advanced progressive RR-DTC requires a comprehensive knowledge of the genetic alterations underlying these tumors. In fact, over the last decade, better understanding of the molecular mechanisms driving DTCs and RAI refractoriness has allowed the development of multiple targeted therapeutic agents (Figure 1).

The mitogen-activated protein kinase (MAPK) pathway is central to the pathogenesis of papillary thyroid carcinomas (PTCs). Mutually exclusive activating somatic alterations of genes encoding effectors in this pathway were found to represent over 80% of the known genetic alterations in these tumors in The Cancer Genome Atlas (TCGA) (10). *BRAF* V600E oncogenic mutations are the most frequent, encountered in about 60% of PTCs, followed by *RAS* point mutations and *RET* fusions (10). Rearrangements involving *ALK* and *NTRK* genes encoding tyrosine kinase receptors have also been described and are of particular interest since therapies targeting these mutations are now available (5, 11, 12). When no mutation in the MAPK pathway is identified, alterations in members of the phosphoinositide 3-kinase (PI3K) pathway are usually detected, including *PTEN*, *PIK3CA* and *AKT1* mutations, although those are relatively rare (5, 10). *EIF1AX* has been described as a novel driver oncogene in approximate 1% of PTCs using the TCGA, and is mutually exclusive with MAPK mutations (10). Other mutations occasionally encountered in PTCs include fusions involving *BRAF, THADA, MET, FGFR2 and ROS1* (10, 13).

Mutation profile can help predict tumor behavior and RAI refractoriness (14). In fact, it has been well described that tumors driven by *BRAF* V600E mutations exhibit high MAPK-signaling output and significant reduction in the expression of genes responsible for iodine uptake and metabolism, such as the sodium-iodide symporter (NIS) (10, 11). Tumors harboring *BRAF* V600E mutations had a significantly lower differentiation score in the TCGA cohort when compared to those with *RAS* mutations (10), explaining the decreased RAI uptake and responsiveness seen in *BRAF*-mutant tumors. A mouse model developed by Chakravarty and colleagues (15), in which oncogenic expression of *BRAF* V600E in thyroid follicular cells is inducible by

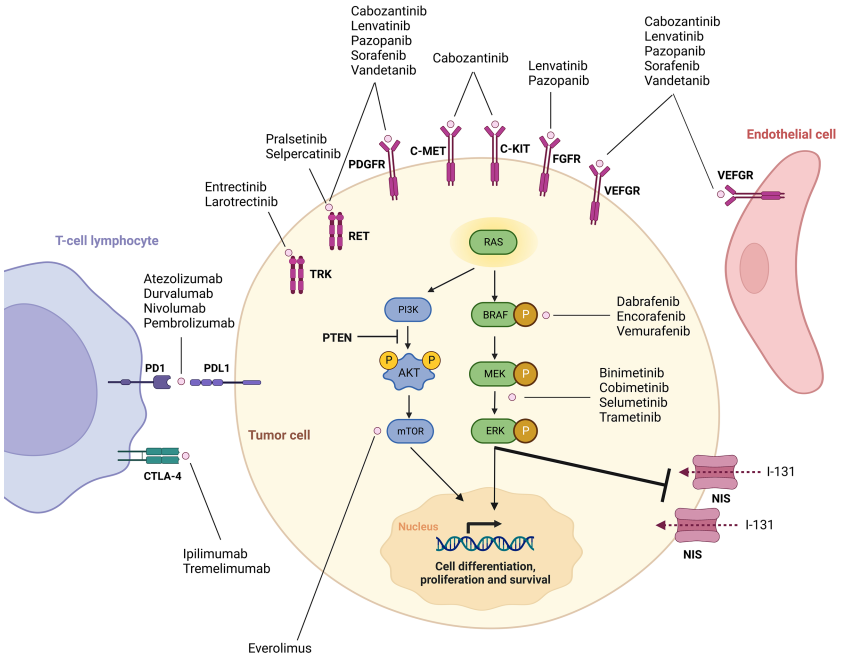

FIGURE 1
Overview of mechanisms of tumorigenesis in differentiated thyroid cancer and targets of currently available drugs. Adapted from Cabanillas et al., Targeted Therapy for Advanced Thyroid Cancer: Kinase Inhibitors and Beyod. Endocr Rev. 2019;40(6):1573-604. By permission of Oxford University Press, License# 5497811051598.

doxycycline administration, supports this observation. Following induction of *BRAF* V600E expression, mice developed high-grade PTCs with increased MAPK transcriptional output and impairment of thyroid-specific gene expression, including near complete loss of NIS. Nevertheless, given the high frequency of *BRAF* mutations in PTC, and the indolent course of most cases, *BRAF* V600E mutation is likely insufficient on its own to explain the aggressive behavior of some tumors. Next generation sequencing (NGS) of advanced PTCs has shown that aggressive tumor behavior and recurrence are more likely when more than one oncogenic mutation is present, especially when *TERT* promoter, *TP53, PIK3CA* and/or *AKT1* mutations co-exist with *BRAF* V600E mutations (3, 12, 16, 17). Moreover, these mutations may act in concert with *BRAF* V600E mutations to induce RAI refractoriness by leading to increased signaling in the MAPK and PI3K/AKT/mTOR pathways and further reducing NIS signaling (4, 18)

Follicular thyroid carcinomas (FTCs), which represent only 2-5% of all thyroid cancers, are most often associated with mutations involving the *RAS* oncogene, and rarely, *PAX8-PPARγ* rearrangements (11, 12). Mutations in genes encoding components of the PI3K/PTEN/AKT signaling pathway are also frequent: for instance, *PTEN* mutations are encountered in up to 10% of sporadic FTCs (19, 20). *TERT* promoter mutations can also be found in FTCs and are associated with more aggressive disease (16).

Oncocytic thyroid carcinomas (OTCs, previously Hürthle cell carcinomas), now considered as a separate subtype of thyroid cancer, harbor a mutational profile distinct from those of PTCs and FTCs (21, 22). In fact, OTCs are not associated with *BRAF* mutations, and rarely harbor *RAS* mutations or oncogenic fusions (5, 21, 22), justifying that it was inappropriate to consider them as a subtype of FTC. OTCs are rather characterized by near-haploid chromosomal content in most tumors, as well as mitochondrial DNA alterations (22). Furthermore, genes found to be more frequently altered in OTCs include *DAXX, TP53, TERT* promoter and *EIF1AX*, among others (5, 21, 22).

Agents targeting some of the mutations known to contribute to thyroid cancer pathogenesis have been developed in the last two decades, significantly changing the outcome of patients with advanced DTCs. Table 1 summarizes all currently FDA-approved kinase inhibitors for RR-DTCs.

Kinase inhibitors

FDA-approved non-specific tyrosine kinase inhibitors

The first two agents that were approved by the Food and Drug Administration (FDA) for the treatment of patients with locally recurrent or metastatic, progressive, RR-DTC are sorafenib (approved in 2013) and lenvatinib (approved in 2015), both multikinase inhibitors (MKI) with anti-angiogenic action through inhibition of the vascular endothelial growth factor receptors (VEGF-R) 1,2 and 3. In fact, DTCs were shown to exhibit disorganized vasculature and cancer-cell hypoxia, leading to an increased activation and expression of VEGF-R and a dependence on its signaling for tumor survival (11). VEGF and its receptor are therefore interesting therapeutic targets. Sorafenib and lenvatinib

TABLE 1 FDA-approved Drugs in advanced RR-DTC.

Drug	Target	Number of patients with DTC in study*	Efficacy results	Reference
Cabozantinib	VEGFR2, AXL, MET, RET, C-KIT	125	ORR: 15% Median PFS: NR	Brose et al. (23)
Dabrafenib (Single agent)	*BRAF* V600E	26	ORR: 35% Median PFS: 10.7 months	Busaidy et al. (24)
Dabrafenib + trametinib	Dabrafenib: *BRAF* V600E Trametinib: MEK	27	ORR: 30% Median PFS: 15.1 months	Busaidy et al. (24)
Entrectinib	*NTRK* fusions, *ALK, ROS1*	13	ORR: 53.8% Median PFS: 19.9 months	Demetri et al. (25)
Larotrectinib	*NTRK* fusions	21	ORR: 71% 24-month PFS: 86%	Waguespack et al. (26)
Lenvatinib	VEGFR1-3, RET, FGFR1-4, PDGFR, KIT	261	ORR: 64.8% Median PFS: 18.3 months	Schlumberger et al. (27)
Pralsetinib	*RET* fusions and mutations	21	ORR: 86% Median PFS: 19.4 months	Mansfield et al. (28)
Selpercatinib	*RET* fusions and mutations	19	ORR: 79% 12-month PFS: 64%	Wirth et al. (29)
Sorafenib	VEGFR1-3, RET, RAF, PDGFR-β	207	ORR: 12.2% Median PFS: 10.8 months	Brose et al. (30)

NR, not reached; VEGFR1-3, VEGF receptors 1-3l FGFR1-4, FGF receptors 1-4.
*Data from the highest-phase trials were used. When more than one trial of the same phase was available, their data were pooled.

also have variable inhibitory actions on other kinases, including RET, fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) receptors.

Sorafenib

Efficacity of sorafenib for the treatment of advanced DTC was demonstrated in the phase 3 randomized, double-blind, placebo-controlled trial DECISION (30). This study enrolled 416 patients with locally advanced or metastatic RR-DTC that had progressed in the previous 14 months and had not been previously treated with targeted therapy or chemotherapy. Median progression-free survival (PFS) was significantly longer in the sorafenib group (10.8 months) compared to the placebo group (5.8 months; hazard ratio [HR] 0.59, 95% CI 0.45-0.76; $p < 0.0001$). Objective response rate (ORR) and disease control rate (DCR) were also significantly higher in the sorafenib group, respectively 12.2% compared with 0.5%, and 54.1% compared with 33.8%. Overall survival (OS) did not differ significantly between the treatment groups (HR 0.80; 95% CI 0.54-1.19; $p = 0.14$), but patients were allowed to cross over from the placebo to the treatment arm at disease progression.

Lenvatinib

Similarly, the phase 3 SELECT trial led to the FDA approval of lenvatinib (27). This randomized, double-blind, placebo-controlled trial included 261 patients with RR-DTC that had progression within the previous 13 months. Patients treated with up to one prior tyrosine kinase inhibitor (TKI) were included. Median progression-free survival was 14.7 months longer in the lenvatinib group (PFS 18.3 versus 3.6 months; HR 0.21, 99% CI 0.14-0.31; $p < 0.001$). This PFS benefit was independent of previous TKI therapy. ORR was 64.8% in the lenvatinib group as opposed to 1.5% in the placebo group (Odds ratio [OR] 28.87; 95% CI 12.46 – 66.86; $p < 0.001$), with four complete responses (CR). Although no significant difference in OS was observed between the two groups (HR for death 0.73, 95% CI 0.50-1.07; p=0.10), there was a significant survival benefit with the use of lenvatinib in patients over the age of 65 despite crossover from the placebo to the treatment arm at disease progression (OS not reached VS 18.4 months; HR 0.53; 95% CI 0.31-0.91; $p = 0.02$).

Although they led to significant prolongation of PFS, these agents were associated with adverse events (AEs) in virtually all patients, including grade ≥ 3 adverse events in 75.9% of patients on lenvatinib and 37.2% of patients on sorafenib. AEs led to discontinuation of lenvatinib in 14.2% of patients and sorafenib in 18.8%, while treatment interruptions and dose reductions due to toxicity occurred in well over 50% of patient with both agents (27, 30). Most common AEs include hypertension, palmar-plantar erythrodysaesthesia syndrome, fatigue, weight loss, diarrhea, and stomatitis.

Cabozantinib

In September 2021, a third MKI, cabozantinib, was approved by the FDA as a second line therapy for patients with locally advanced or metastatic RR-DTC that has progressed following prior VEGF-R targeted therapy. Cabozantinib inhibits multiple tyrosine kinases involved in tumor growth and angiogenesis including VEGF-R2, AXL, c-MET and RET (5, 23). Notably, upregulation of c-MET and AXL signaling has been shown to play a role in resistance to antiangiogenic agents (31, 32), which serves as a premise for the

use of cabozantinib in patients who have progressed on VEGF-R TKIs. Cabozantinib has been approved and widely used since 2012 for the treatment of advanced medullary thyroid carcinoma (MTC). More recent approval of this drug in DTC was based on results from COSMIC-311 (23), a double-blind, phase 3 placebo-controlled trial in which 258 patients with RR-DTC that had progressed on or following prior VEGF-R TKI treatment were randomized 2:1 to cabozantinib or placebo. Patients had to have received previous treatment with at least lenvatinib or sorafenib, and no more than two previous VEGF-R TKIs were allowed. Patients who progressed on placebo could crossover to open label cabozantinib. PFS was significantly prolonged in the group treated with cabozantinib (11.0 versus 1.9 months; HR 0.22, 96% CI 0.15-0.32; $p < 0.0001$) despite a short median follow-up of 10.1 months. PFS improvement was observed irrespective of previous treatment. ORR also favored cabozantinib (11% [95% CI 6.9%-16.9%] versus 0% [95% CI 0.0%-4.1%]; p=0.0003), with 18 confirmed partial responses (PR) in the treatment group as opposed to none in the placebo group. Overall, results of the COSMIC-311 trial were encouraging in a population of patients with aggressive disease that would have otherwise progressed rapidly, as illustrated by the very short median PFS in the placebo group, and in whom treatment options are limited.

Similar to sorafenib and lenvatinib, AEs are very frequent with cabozantinib, occurring in 94% of patients. Grade 3 or 4 AEs were observed in 57% of patients on cabozantinib, most frequently palmar-plantar erythrodysaesthesia syndrome, fatigue, hypertension, and diarrhea. These AEs were comparable to those reported in other studies and were manageable.

FDA-approved selective kinase inhibitors

Although MKIs can significantly improve PFS in patients with advanced RR-DTCs, these therapies have multiple drawbacks. Their toxicity profile can have a major impact on patients' quality of life and may limit their long-term effective use in clinical practice. For instance, real-life studies with lenvatinib describe treatment interruption and dose reduction rates as high as 79.5% (33). Moreover, as we will discuss below, many patients will eventually develop resistance to treatment and progress. For these reasons, the quest for treatments that do not target the angiogenic pathway and provide more personalized therapeutic options for patients with advanced DTCs has continued, culminating in the FDA-approval of various selective kinase inhibitors. These agents target more specifically one or a few kinases involved in tumorigenesis, which allows for better efficacy and most importantly less toxicity.

BRAF +/- MEK inhibitors

As mentioned earlier, the *BRAF* V600E mutation is the most frequent oncogenic driver in PTCs, present in 60% of cases, which makes it an attractive therapeutic target. BRAF + MEK inhibitors have been used for many years in other *BRAF*-mutated solid tumors, mainly melanoma and non-small cell lung carcinoma (NSCLC).

Dabrafenib and trametinib

The combination of dabrafenib and trametinib, a selective BRAF and MEK 1/2 inhibitor respectively, was FDA approved in 2018 for the treatment of locally advanced or metastatic *BRAF* V600E-mutant anaplastic thyroid cancer (ATC) and has significantly changed the treatment paradigm of these tumors which were previously viewed as a death sentence (34–37). Most recently, based on data from the ROAR (NCT02034110) (38) and NCI-MATCH (39) basket trials, the FDA granted in June 2022 an accelerated approval of dabrafenib in combination with trametinib for the treatment of patients with *BRAF* V600E-mutated metastatic or unresectable solid tumors who have progressed on prior treatment and have no other satisfactory treatment options, including thyroid cancers.

Dabrafenib was first shown to be promising in patients with DTC in a phase 1 basket trial (40). This led to a randomized, multicenter, open-label phase 2 trial in patients with *BRAF* mutated PTC (24). This study included 53 patients with progressive disease within 13 months before enrollment. Patients could have received up to three priors oral MKIs, excluding other selective BRAF or MEK inhibitors. Patients were randomized to dabrafenib monotherapy or dabrafenib in combination with trametinib, and primary endpoint was ORR in each group within the first 24 weeks of therapy. It was hypothesized that combination therapy would have superior clinical efficacy due to dual inhibition of the MAPK pathway as well as mitigation of potential mechanisms of resistance to dabrafenib through MEK kinase inhibition. Patients on dabrafenib alone were allowed to crossover to the combination group on disease progression. ORR, which included minor responses (defined as a 20 to 29% decrease in the sum of target lesions), was 42% (95% CI 23–63%) with dabrafenib and 48% (95% CI 29–68%) with dabrafenib + trametinib ($p = 0.67$). Median PFS was also not statistically different between the two groups (10.7 [CI 3.8-34.7] versus 15.1 [CI 12.3-37.3] months; p=0.65). The median OS was 37.9 months [CI 23.4–NR] with single-agent dabrafenib and 47.5 months [CI 27.9–57.8] with combination therapy ($p = 0.99$). Notably, of the 14 patients who crossed over at progression, 4 (29%) had an objective response, including 3 PRs and one minor response, and 8 had stable disease (SD). Grade 3 AEs occurred in about 50% of patients in both groups. Most frequent AEs associated with dabrafenib alone were skin disorders, fever, and hyperglycemia, while fever, hypophosphatemia and fatigue were most common with combination therapy. Skin disorders were strikingly less frequent with the combination compared to dabrafenib alone (33% VS 65% respectively). This trial, although not showing any superiority of combined BRAF and MEK inhibition over BRAF inhibitor therapy alone, did show prolonged PFS and OS with both treatment strategies, making dabrafenib +/- trametinib a therapeutic option for patients with advanced *BRAF*-mutated PTCs, especially when anti-angiogenic agents are contraindicated or associated with significant risk. This being said, there has been no direct comparisons between dabrafenib and MKIs such as lenvatinib in *BRAF*-mutated advanced DTCs to justify favoring one treatment over the other.

RET inhibitors

RET is a transmembrane glycoprotein receptor-tyrosine kinase (RTK). Ligand binding leads to RET homodimerization followed by trans-phosphorylation of tyrosine residues within the intracellular domains and activation of several signal transduction cascades involved in cellular proliferation, including the MAPK and PI3K pathways (41). Oncogenic activation of RET can occur through three main mechanisms: mutations leading to activation of the kinase domain by ligand-independent dimerization, mutations causing direct activation of the RET kinase domain, and chromosomal rearrangements producing chimeric proteins with constitutively active RET kinase domain (41, 42). Germline activating *RET* mutations are associated with multiple endocrine neoplasia type 2 (MEN2) syndromes, while somatic *RET* mutations are found in ~ 65% of all sporadic MTCs (41). *RET* rearrangements, on the other hand, have been identified in various solid tumors, including about 5 to 10% of PTCs, most frequently in children and in patients with prior exposure to radiation (41). *CCDC6-RET* and *NCOA4-RET* are the most frequently identified *RET* fusions in PTCs.

Involvement of *RET* alterations in tumorigenesis makes this RTK a potentially actionable therapeutic target. Moreover, tissue-specific *RET* knockout studies in mice, targeting the hematopoietic, neuronal, and lymphoid tissues, suggested that RET inhibition would most likely result in very little clinically significant AEs (43–45). This led to efforts aiming to identify selective RET inhibitors that would be used to treat *RET* mutated tumors in patients.

Selpercatinib (LOXO-292) and pralsetinib (BLU-667) are two potent and highly selective RET kinase inhibitors that have been recently FDA approved in 2020 for patients with *RET* fusion-positive DTCs and *RET*-mutant MTCs who require systemic therapy.

Selpercatinib

Efficacy of selpercatinib in *RET*-altered thyroid cancers was demonstrated in the LIBRETTO-001 trial (29). This phase 1/2 study included 19 patients with *RET* fusion-positive thyroid cancers, mainly PTCs (13/19). Most patients (79%) had had previous therapy with at least one MKI. In the *RET* fusion-positive DTC cohort, ORR was 79% (95% CI 54-94), including one CR and 14 PRs. Interestingly, 2/3 patients with poorly differentiated thyroid cancers (PDTC), 1/1 patient with OTC and 1/2 patients with ATC had PRs to therapy. Median PFS was not reached, but 64% of patients were progression-free at 1 year. Among all the patients with *RET*-altered thyroid cancers treated with selpercatinib in the trial (n=162), grade 3 or grade 4 treatment related AEs occurred in 28% and 2% respectively, most frequently hypertension (in 21% of patients) and increased cytolytic liver enzymes (increased alanine aminotransferase in 11% and asparte aminotransferase in 9%).

Pralsetinib

ARROW is a phase 1/2 trial evaluating the efficacy of pralsetinib in patients with *RET*-altered locally advanced or metastatic solid tumors, including thyroid carcinomas (46). Updated data presented at the 2022 American Society of Clinical Oncology (ASCO) meeting in 21 patients with previously treated *RET* fusion-positive thyroid cancers showed an ORR of 86% (95% CI 64-97), including 15 PRs. Duration of response was 17.5 months (95% CI 16.0 – NR) and PFS was 19.4 months (95% CI 13.0 – NR) (28). Similar to selpercatinib, pralsetinib was well tolerated, with a manageable safety profile. Most frequent grade 3 AEs were hypertension (17% of all trial patients) and cytopenia (neutropenia in 13%, lymphopenia in 11% and anaemia in 10%). One case of grade 5 pneumonia also occurred (46).

In both the LIBRETTO-001 and ARROW trials, AE-related dose reductions and treatment discontinuations were relatively low with only 2 and 4% of discontinuations of selpercatinib and pralsetinib respectively (28, 46).

NTRK inhibitors

The tropomyosin-receptor kinase (TRK) family of RTKs includes TRKA, TRKB and TRKC which are encoded respectively by the neurotrophic receptor tyrosine kinase genes *NTRK1*, *NTRK2* and *NTRK3* (47–49). Once activated, TRK RTKs signal through several downstream pathways involved in cellular proliferation, among which MAPK and PI3K/AKT. TRK receptors play an important role in the nervous system development (47). Oncogenic fusions leading to constitutive activation of the kinase domain have been described in all three *NTRK* genes, and these alterations have been identified in multiple solid tumors including colorectal cancer, lung cancer, and melanoma. In the thyroid, *NTRK*-driven malignancies are rare, found in 2-3% of thyroid cancers in adults, including PTCs, OTC, ATCs, and PDTCs (10, 48, 49). Like *RET*-fusions, *NTRK* fusions are more frequent in pediatric patients with PTCs (up to 25% of cases) as well as in patients with previous radiation exposure. Despite their rarity, *NTRK* fusion-positive thyroid cancers are important to identify as we have now two FDA-approved targeted TRK inhibitors which have demonstrated clinical safety and efficacy in patients with metastatic or unresectable solid tumors with *NTRK* gene fusion.

Larotrectinib

Larotrectinib is a highly selective and potent TRK inhibitor with central nervous system activity (CNS). A pooled analysis (26) of 28 patients with *NTRK* fusion-positive thyroid cancers treated with larotrectinib from three basket trials (50–52) showed an ORR of 71% (95% CI 51-87), including 2 CRs, 18 PRs and 4 SDs. All patients with CNS metastases at baseline had a PR. 24-month PFS and OS were respectively 69 and 76%. When excluding the 7 patients with ATC, ORR increased to 86% (95% CI 64-97) and 24-months PFS to 84%. Response to therapy was irrespective of previous systemic therapy: 13 patients with DTC who had one or more prior lines of systemic therapy had an ORR of 92%. Notably, AEs were mainly grade 1 and 2, with only two patients who experienced grade 3 treatment-related AEs (anaemia and lymphopenia). No patients required treatment discontinuation due to AEs and only 2 patients experienced AEs leading to dose reduction.

Entrectinib

Entrectinib is another potent TRK inhibitor which was specifically designed to have systemic activity and cross the blood-brain barrier (25, 53, 54). Entrectinib also exhibits inhibitory action against ALK and ROS1 tyrosine kinases, which have been involved in resistance to TKIs (5, 25, 53, 54). In April 2022, updated pooled data (25) from two phase 1 studies (ALKA-372-001 and STARTRK-1) (53) in patients with *NTRK, ROS1* or *ALK* alterations and one phase 2 basket study (STARTRK-2) (54) focusing on patients with *NTRK* fusion-positive solid tumors, were published. 13/121 patients had thyroid cancer, including 7 with CNS metastases. ORR was 53.8% (95% CI 25.1-80.8), median PFS was 19.9 months (95% CI 6.5-33.8), and OS was 19.9 months (14.5 – non evaluable [NE]). In the overall population, 11 patients had measurable CNS metastases at baseline, among which intracranial ORR was 63.6% (95%CI 30.8 – 89.1). Like larotrectinib, treatment related AEs were mostly grade 1/2, with AE-related treatment discontinuations in 8.3% of patients.

Therefore, larotrectinib and entrectinib appear as reliable and durable treatment options in *NTRK* fusion-positive thyroid cancers, including those with CNS metastases.

Other non-FDA approved kinase inhibitors studied in DTC

We are frequently faced in clinical practice with patients that progress or do not tolerate the previously described FDA-approved treatments. In these situations, we resort to the off-label use of other anti-neoplastic agents that have been or are currently being studied in advanced DTCs and have shown some efficacy.

Vemurafenib, a selective BRAF inhibitor approved for treatment of *BRAF*-mutated melanoma, was in fact the first BRAF-inhibitor studied in DTC. Its efficacy was initially demonstrated in a small case series of 3 patients with metastatic *BRAF* V600E-mutated PTC (55). This was later confirmed by a phase 2 non-randomized, open-label, multicenter trial in which patients with recurrent or metastatic RAI-refractory *BRAF* V600E-mutated PTC, who were either TKI-naïve (cohort 1, n=26) or had progressed on VEGF-R TKI (cohort 2, n=22), received single-agent vemurafenib (56). In cohort 1, DCR with vemurafenib was 73% (95% CI 52-88) with 10 (38.5%) patients who had PR and 9 (35%) who had SD as best overall response. In cohort 2, response rates were lower, with 6 (27.3%) patients who had a PR as best overall response and 6 who had SD, leading to a DCR of 55% (95% CI 32-76). Median PFS was 18.2 months (95% CI 15.5-29.3) and 8.9 months (95% CI 5.5 -NE) in cohorts 1 and 2 respectively. Median OS was not yet reached in cohort 1, while it was 14.4 months (95% CI 8.2-29.5) in cohort 2. AEs were mostly grade 1-2, including rash, fatigue, alopecia, dysgeusia, creatinine increase and weight loss. Vemurafenib seems therefore to be a valid therapeutic option for *BRAF*-mutated PTCs, although it yet has to be studied in a phase 3 trial.

Encorafenib is another BRAF inhibitor, currently approved in combination with the MEK-inhibitor binimetinib for *BRAF*-mutated metastatic melanoma and colorectal carcinoma. It has a more than 10-times longer dissociation half-life than dabrafenib or vemurafenib, allowing more sustained target inhibition and potentially a more potent antitumor activity (57). Moreover, it is associated with low rates of pyrexia and photosensitivity which are the two main dose-limiting AEs with the dabrafenib/trametinib and vemurafenib/cobimetinib combinations, respectively (57, 58). Although no clinical data is currently available for its use in thyroid cancer, there is an ongoing phase 2 trial examining encorafenib combined with binimetinib, with or without immunotherapy (nivolumab), in patients with metastatic *BRAF* V600E mutant RR-DTC (NCT04061980). In practice, this drug can be considered as an alternative when dabrafenib is not tolerated, especially due to intractable fevers.

Everolimus, an inhibitor of mammalian target of rapamycin (mTOR), has been studied in several trials for treatment of advanced RR-DTCs. In fact, as previously discussed, activation of the PI3K/PTEN/AKT signaling pathway is frequent in advanced thyroid cancers. This is often due to a mutation of the PTEN protein, a PI3K inhibitor. Parallel activation of this pathway has also been suggested as an escape mechanism to TKIs. mTOR, a serine-threonine kinase, is a downstream effector of the PI3K/AKT pathway and serves as a potential therapeutic target. The first reported trial of everolimus in thyroid cancers was a multicenter, open-label, phase 2 study in South Korea that enrolled patients with all thyroid cancer histologies, including 6 patients with ATC and 9 with MTC (59). Among the 38 patients that were evaluable for response, DCR was 81%, including 2 PRs (both in DTC patients). 45% of patients showed durable SD for 24 weeks or longer. Median PFS in patients with DTC was 43 weeks. Treatment was overall well tolerated with mostly grade 1 AEs. This study was followed by a second phase 2 trial in the Netherlands, which enrolled 28 patients with advanced DTC, 54% of whom had previous treatment with a TKI, namely sorafenib (60). Sixty five percent of patients showed SD as their best response, with 58% having SD lasting more than 24 weeks. However, there were no PRs or CRs. Median PFS was 9 months (95% CI, 4-14), and median OS was 18 months (95% CI 7-29). Hanna and colleagues further expanded on the topic with another phase 2 trial, once again in all thyroid cancer histologies (61). In the DTC cohort (n=33), in which 51% of patients had previously been treated with a TKI, best response to therapy was SD in 82% and PR in 3%. Median PFS was 12.9 months (7.3-18.6), and median OS was not reached. Interestingly, in this trial, DTC patients with only a *BRAF* mutation had the longest PFS on everolimus, while patients with alterations in the PI3K/mTOR/AKT pathway did not show better response to therapy. Thus, these three phase 2 trials demonstrate that mTOR inhibition is a viable second-line option in patients who progress on TKI therapy.

The combination of **everolimus plus sorafenib** showed improvement of PFS in comparison with sorafenib alone in a randomized phase 2 trial in patients with RAI-R oncocytic thyroid carcinoma that included 34 evaluable patients (62). PFS was significantly improved in the sorafenib plus everolimus arm (24.7 months (95% CI 6.1-no upper) compared to the sorafenib arm (10.9 months (95% CI 5.5-no upper). Response rates were similar between groups.

Pazopanib is an antiangiogenic MKI that inhibits VEGF, FGF, PDGF, KIT and RET receptors. It is currently FDA approved for other solid tumors including renal cell carcinoma. Pazopanib was evaluated in two phase 2 trials looking at its efficacy in patients with RR-DTC (63, 64). In 2010, Bible and colleagues conducted a first trial in 37 patients, 18 of which had confirmed PR to therapy (response rate 49%; 95%CI 35-68). Responses were seen in 8/11 (73%) patients with follicular tumors, 5/11 (45%) patients with oncocytic tumors, and 5/15 (33%) patients with papillary tumors. Therapy was well tolerated with 46% of patients taking pazopanib for 12 months or longer. The most frequent AEs were fatigue, skin and hair hypopigmentation, diarrhea, and nausea. In 2020, the same group published a larger phase 2 international study in 60 patients with advanced or progressive RR-DTC treated with pazopanib. In this second trial, response rate was slightly lower, with 36.7% of patients having a PR (CI 24.6-50.1). This is probably explained by the fact that patients were more heavily pretreated than in the prior study (91.7% VS 27%). Median PFS was 11.4 months and median OS 2.6 years. Both studies did not show any differences in response to therapy between histological subtypes of DTC, nor according to mutation profile. There is therefore substantiating evidence to support the efficacy of pazopanib in RR-DTC, and it should be considered as a therapeutic option in patients who progress or do not tolerate other FDA-approved therapies.

Other kinase inhibitors, such as **sunitinib** (65–67)**, vandetanib** (68)**, axitinib** (69–71) and **dovitinib** (72) have been tested in thyroid cancer, all showing modest efficacy.

Potential mechanisms of drug resistance

Despite promising initial results, all kinase inhibitors seem to become eventually ineffective, leading to inevitable disease progression. Current research efforts are therefore focused on identifying resistance mechanisms to kinase inhibitors and ways to overcome them. To date, a few potential mechanisms of tumor resistance to kinase inhibitors have been described (73) (Figure 2).

First, acquired resistance to tyrosine kinase inhibitors can involve escape mechanisms that activate parallel signaling pathways. For instance, upregulation of alternative angiogenic signaling factors such as FGF2, PDGF or epidermal growth factor receptor (EGFR) has been observed in tumors resistant to anti-VEGF TKIs (74–76). One possible factor underlying this phenomenon is hypoxia secondary to VEGF-R inhibition (74–76). In fact, hypoxia induces gene expression of proangiogenic factors primarily through the HIF-1α (hypoxia inducible factor-1α) transcription factor. Moreover, activation of the PI3K/AKT pathway or reactivation of the JAK-STAT pathway were also shown to be involved in acquired resistance to sorafenib (76). Similarly, several studies have demonstrated that cancer cells develop resistance to BRAF inhibitors by overexpressing growth factor receptors at their surface, including KIT, c-MET, EGFR and PDGF-receptor-β (PDFGR-β), leading to MAPK pathway reactivation despite BRAF inhibition (73, 77, 78). The treatment strategy to counteract this activation of alternate pathways is to either add a second TKI or to switch to another targeted systemic therapy. For example, in a multicenter phase 2 International Thyroid Oncology Group (ITOG) trial, cabozantinib conferred significant additional PFS and OS benefits (12.7 and 34.7 months respectively) in advanced DTC patients who had progressed on prior VEGF-R targeted therapy (79).

Factors associated to the tumor microenvironement have also been involved in resistance to kinase inhibitors. Pericytes are stromal cells that play a key role in the angiogenic microenvironement of thyroid cancers, in part by facilitating vessel maturation. PDGF growth factor-BB (PDGF-BB), which promotes pericyte proliferation through interaction with PDGFR-β, has been found to be increased in *BRAF* V600E-mutated PTCs, and pericytes have been shown to support the growth and survival of PTC cells (80, 81). Furthermore, *in vitro* studies suggest that pericytes might play a role in resistance to sorafenib and vemurafenib through secretion of thrombospondin-1 (TSP-1) and TGFβ1, which trigger rebound elevation in ERK1/2 and AKT levels allowing tumor cells to overcome inhibitory effects of these targeted therapies (82). Cancer-associated fibroblasts (CAF) have also been shown to promote cancer growth and to play a role in drug resistance (83).

Epithelial-mesenchymal transition (EMT) of tumor cells, induced by secondary mutations, hypoxia and other stimulating factors from the tumor microenvironment, was also shown to be involved in resistance to sorafenib (76) and lenvatinib (84). In fact, studies identified changes in treatment-resistant cells towards a mesenchymal morphology (76, 84, 85). Tumor cells undergoing EMT loose cell adhesion molecules such as E-cadherin and gain mesenchymal cell markers such as vimentin and N-cadherin, resulting in loss of cell-to-cell contacts and increased motility, which favor their dissemination to distant sites (84, 85). In addition, EMT makes tumor cells resistant to apoptosis and anti-tumor drugs (84, 85). Nonetheless, the exact interaction between EMT and anti-VEGFR TKIs resistance remains unknown.

Acquired wild-type copy number amplifications has also been identified as a resistance mechanism to BRAF inhibitors. For example, MCL1 copy number gain has been associated with resistance to vemurafenib treatment in PTC (86). MCL1 is an anti-apoptotic member of the BCL2 family, which might regulate parallel signaling pathways activating BRAF in PTCs resistant to anti-BRAF agents. Similarly, in another case report of a PTC which underwent ATC transformation while on dabrafenib (87), acquired triploidy of chromosome 7, which harbors the *EGFR, RAC1, MET*, and *BRAF* genes, was demonstrated in the progressive metastatic lesion. Copy number amplifications of these protooncogenes were consequently present in the dedifferentiated sample, probably contributing to tumor progression.

Finally, acquisition of secondary point mutations has also been proposed as a resistance mechanism to TKIs. For instance, a study exposing *BRAF* V600E mutated KTC1 thyroid cancer cells to long term vemurafenib showed development of secondary *KRAS* point mutations, allowing these cells to bypass BRAF inhibition (88). In addition to *RAS* point mutations, other acquired mutations that possibly confer drug resistance were found in the *RAC1, PTEN, NF1, NF2, TP53*, and *CDKN2A* genes (73, 87, 89). Moreover, it is

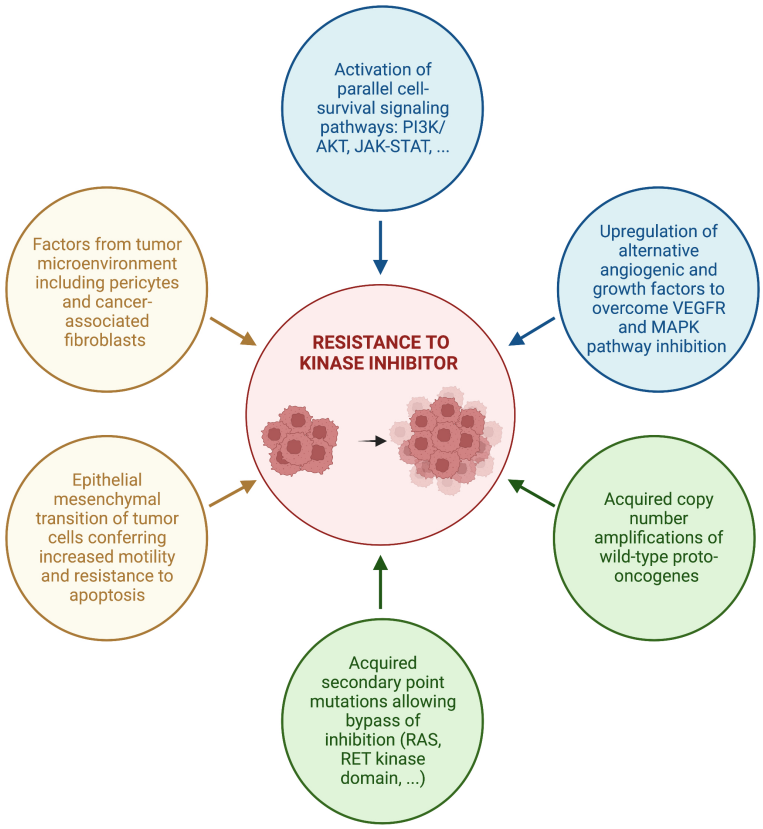

FIGURE 2
Proposed mechanisms of resistance to kinase inhibitors.

now well recognized that acquired mutations in the RET kinase domain cause resistance to selective RET-inhibitors by interfering with drug binding. These include *RET* G810 solvent-front mutations as well as non-gatekeeper mutations at hinge (Y806C/N) and β2 strand (V738A) sites within the RET kinase domain (90–93).

Identification and better understanding of these resistance mechanisms pave the way for future novel therapies including combination of kinase inhibitors, potentiation of TKIs by adding immunotherapy, and redifferentiation therapy.

Immunotherapy in DTC

In the past decade, immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy. These monoclonal antibodies reactivate T-cell response against cancer cells, by blocking either the lymphocyte inhibitory receptor CTLA4 or the interaction between T-cell receptor PD-1 with its ligands PDL-1 and PDL-2 at the surface of cancer cells. To date, seven ICIs have received FDA approval for the treatment of various neoplasms including melanoma, NSCLC, renal cell carcinoma, and many others.

Just like in other neoplasia, thyroid cancer cells also escape immune surveillance, making ICIs an interesting therapeutic avenue. Immune escape in DTCs occurs through various mechanisms. First, deficient antigen presentation and reduced T-cell activation has been shown to play a role. This can occur either by downregulation of major histocompatibility complex (MHC) class I, mutations within the T-cell receptor binding domain of MHC-I, or loss of function of β2-microglobulin which results in disruption of MHC-I folding and transport to the cell surface (94, 95). Notably, MHC-I and β2-microglobulin expression were shown to be reduced or absent in 76% of PTCs (96).

Moreover, an immunosuppressive tumor microenvironment (TME) contributes to immune tolerance. Infiltration by regulatory T cells (Treg), which facilitate self-tolerance by suppressing effector T cells, has been observed in many tumor types (94). In PTC, increased Treg has been shown to correlate with lymph node metastasis and might be indicative of more aggressive disease (95, 97, 98). Other cells of the immune system including tumor-associated macrophages, plasmacytoid dendritic cells and tumor-associated mast cells are all overexpressed in the TME of DTCs and contribute to immune escape. Conversely, aberrant tumor vasculature that impairs the infiltration of immune cells can also occur (78). Finally, exhausted $PD1^{+}CD8^{+}$ T cells with defective cytokine production also play a role in the immunosuppressive milieu of DTCs (97, 98).

Several signaling pathways that are activated by oncogenic mutations associated with thyroid cancer can contribute to the immune escape. Among those, constitutive activation of the MAPK pathway impairs recruitment and function of tumor-infiltrating lymphocytes through increased expression of VEGF and multiple

inhibitory cytokines (94, 95). Similarly, increased signaling in the PI3K pathway favors recruitment of inhibitory immune cells to the TME and reduces cytotoxic T-lymphocyte activity (94, 95).

Another major mechanism of immune escape in thyroid cancer as well as many other tumor types is up-regulation of inhibitory immune checkpoints, mainly PDL-1 but also PD-1, PDL-2 and CTLA4 (95). Notably, PDL-1 has been shown to be overexpressed in more advanced DTCs, with significant correlation between PDL-1 expression and lymph node metastasis, extrathyroidal invasion and disease-free survival (99). Interestingly, PDL-1 expression was higher in *BRAF* V600E mutant tumors, which are known to have the potential for more aggressive behavior.

Therefore, since pathogenesis of thyroid cancers includes escape of the immune system, reactivation of the anti-tumoral immune response may prove useful in the treatment of some thyroid neoplasia. This rationale led to various studies looking at ICIs in advanced DTCs.

Pembrolizmab single agent

KEYNOTE-028 is a phase Ib clinical trial of the PD-1 targeting antibody pembrolizumab in patients with PDL-1 positive, locally advanced or metastatic DTC (100). Of note, patients did not need to have radioiodine refractory disease or progression to be enrolled in the study. 22 patients were treated with pembrolizumab 10mg/kg every 2 weeks for 24 months or until confirmed progressive disease, unacceptable AEs, or investigator or patient decision to withdraw. 50% of patients had previously received an MKI. ORR was 9% (95% CI 1-29%) with only 2 PRs. Clinical benefit rate, defined as PR + SD for at least 6 months, was of 50% (95% CI 28-72%). Median PFS was 7 months (95% CI 2-14 months). At data cutoff, median OS was not reached (95% CI, 22 months to not reached), with 6- and 12-month OS rates of 100 and 90%, respectively. Treatment was overall well tolerated, the most frequent AEs being diarrhea (in 32% of patients) and fatigue (in 18%). Only one grade 3 AE occurred, namely colitis, and no grade 4 AEs or AE-related treatment discontinuations were described.

Lenvatinib and pembrolizumab combination

An ongoing phase 2 trial (NCT02973997) explores the combination of lenvatinib and pembrolizumab as a first line treatment of RR-DTCs with disease progression less than 14 month prior to enrollment (101).. In fact, VEGF has been associated with resistance to immune checkpoint blockade (94). VEGF axis promotes a hypoxic and immunosuppressive TME by decreasing T cell infiltration, impairing cytotoxic T cell activity, and promoting repressive immune cell infiltration. Thus, inhibition of VEGF signaling might represent an important strategy to enhance ICI efficacy. Inhibition of VEGF-R was correlated with improved response to ICIs in renal cell carcinoma, and the combination of lenvatinib + pembrolizumab has been approved for advanced endometrial carcinoma (102). Therefore, lenvatinib + pembrolizumab was also explored in DTC. Results reported in a poster at the 2020 ASCO meeting in 30 patients showed PR in 62% of patients and SD in 35%. Median time to tumor size nadir was 7.4 months (CI 1.6-17.8). Notably, 14/29 evaluable patients were still on therapy at data cutoff (7.6-18.9 months) and 6/19 (43%) patients had not yet reached tumor size nadir. Median PFS was not yet reached, but PFS at 12 months was 74%. Seventy percent of patients had grade 3 AEs and 10% had grade 4 AEs. The most common grade > 3 AEs were hypertension (in 47%), weight loss (in 13%) and maculopapular rash (in 13%). Therefore, the combination of lenvatinib + pembrolizumab seems promising, although it is unclear yet if addition of pembrolizumab brings any supplemental benefits to single agent lenvatinib as PR and SD rates with the combination are similar to those with lenvatinib alone (27). Updated data from the lenvatinib + pembrolizumab trial might help answer this question, especially if PFS or OS benefits are achieved.

Cabozantinib and atezolizumab combination

Another ongoing multinational phase 1b trial, COSMIC-21 (NCT03170960), is evaluating cabozantinib in combination with the anti-PDL-1 antibody atezolizumab in advanced solid tumors, including DTCs. Similar to lenvatinib, cabozantinib has immunomodulatory properties that counteract tumor-induced immunosuppression and may enhance response to ICIs. Combination of cabozantinib and nivolumab, a PD-1 inhibitor, has already shown efficacy in a phase 3 randomized trial for advanced renal cell carcinoma (103). Efficacy and safety results of cabozantinib + atezolizumab as a first line therapy in 31 patients with locally advanced, metastatic and/or progressive RR-DTCs included in the COSMIC-021 trial were presented in a highlighted poster at the 2022 American Thyroid Association (ATA) meeting (104). Patients who had received any other systemic anticancer therapy were excluded. Fifty-eight percent of patients had PTC and 61% of the tumors were harboring a *BRAF* mutation. Patients were treated with cabozantinib 40mg daily and atezolizumab 1200mg every 3 weeks. At data cutoff, with a median follow-up of 24.9 months (95% CI 14.9-33.3), ORR was 42% (95% CI 25-61) including 13 PRs and 17 SDs. Impressively, DCR was 97% (30/31) with the remaining patient having no post-baseline assessment available. Duration of response to therapy was 22 months (95% CI 1.4 -28.0), median PFS was 15.2 months (95% CI 10.4-24.3), and 28/31 patients were still alive at data cutoff. Grade 3/4 AEs occurred in 55% of patients, mainly diarrhea (13%) and cytolytic transaminase increase (10%), with 4 patients having had to stop treatment due to AEs related to one or both drugs. Overall, AEs related to the combination therapy were consistent with those of the individual agents and were manageable. Therefore, first-line combination of cabozantinib + atezolizumab in advanced RR-DTC provided durable responses and a high rate of disease control across different subtypes of DTC, which makes it an interesting therapeutic option.

Ipilimumab plus nivolumab

Combined CTLA4 and PD-1 blockade has also shown efficacy in multiple tumors including melanoma and renal cell carcinoma. In fact, combination therapy overcomes ICI resistance: CTLA4 inhibition increases T-cell priming and reduces Tregs in the TME, while PD-1 inhibition enhances T cell effector response (95). Preclinical data suggests that this combination could also be beneficial in aggressive RR-DTCs. Therefore, an ongoing phase 2 study (NCT03246958) is looking at the combination of nivolumab (an anti-PD-1) and ipilimumab (an anti-CTLA4) in RR-DTCs, including PDTCs (105). Results in 32 patients were presented in a poster at the 2020 ASCO meeting. Three (9%) patients achieved partial response, including one near-complete response, while 14/32 (44%) had stable disease. Median PFS at data cutoff was 4.9 months.

Cabozantinib and ipilimumab plus nivolumab combination

Ipilimumab/nivolumab combination has also been studied in association with cabozantinib in a multicenter phase 2 trial looking at locally advanced or metastatic RR-DTCs that have progressed on one previous anti-VEGFR therapy (NCT03914300). Interim results in 11 patients were presented at the 2022 ATA meeting (106). Interestingly, 45% (5/11) of patients included in the study had OTC and 18% (2/11) had PDTC. ORR within the first 6 months, which was the trial's primary endpoint, was 9% (1/11), while ORR at data cutoff was 18% with 6 SDs and 2 PRs. Median PFS and OS were respectively 9 months (3.0-NR) and 19.2 months (4.6-NR). Only 3 patients were still on trial treatment at data cutoff. Therefore, although this triple combination therapy was overall well tolerated, efficacy was very limited and ipilimumab+ nivolumab did not seem to offer any additional advantage to cabozantinib monotherapy.

Multiple other clinical trials looking at various ICIs in advanced DTC are currently underway, including a phase 2 trial studying encorafenib + binimetinib with or without nivolumab in patients with metastatic *BRAF* V600E mutant RR-DTC (NCT04061980), and a phase 2 trial evaluating the combination of the anti-PDL-1 durvalumab with the anti-CTLA4 tremelimumab in advanced RR-DTC (NCT03753919). Table 2 summarizes ongoing and published trials of immunotherapy in DTC.

Redifferentiation therapy

Loss of RAI sensitivity in DTCs is associated with more aggressive disease and a significantly poorer prognosis. RAI refractoriness is due to loss of thyroid differentiation features, among which the most important is Na/I symporter (NIS) function and expression. In fact, NIS allows active iodine transport into follicular cells and is responsible for RAI entry into thyroid cancer cells. Immunohistochemistry studies have shown that NIS protein expression is significantly decreased in differentiated thyroid cancer tissues (107). Decreased targeting of NIS to the plasma membrane through reduced vesicular trafficking (108) and impaired cell-cell adhesion secondary to loss of E-cadherin (109) might also play a role in loss of RAI uptake in advanced thyroid cancers.

It has now been well demonstrated that MAPK pathway activation is associated with dedifferentiation and a decreased NIS expression (110, 111). Moreover, studies have shown that the degree of tumor dedifferentiation correlates with the magnitude of activation of the MAPK pathway, and that *BRAF* V600E mutations lead to greater MAPK activation than *RAS* or RTK alterations (11, 110, 111). Conversely, suppressing the MAPK pathway with BRAF or MEK inhibitors in mice was shown to restore NIS expression and RAI uptake (15). These findings opened the floor to redifferentiation therapy, a treatment strategy in which we aim to restore RAI uptake, allowing subsequent treatment with RAI in a tumor which was previously considered as RAI-refractory.

In the first clinical study looking at redifferentiation therapy, 24 patients with RR-DTC were treated with a MEK inhibitor, selumetinib, for 4 weeks (112). Of the 20 patients who could be evaluated, 60% (12/20) had increased uptake on subsequent ^{124}I PET-CT scan, 8 of which reached the dosimetry threshold for radioiodine therapy (i.e. if one or more lesions could be treated with a dose of ≥ 2000 cGy with an ^{131}I administered activity ≤ 300 mCi) and were therefore treated with RAI. During the 6 months-follow-up period after radioiodine therapy, a reduction in the size of target lesions was observed in all patients, with confirmed PR in 5/8 patients and SD in 3/8 as the best overall response. In the study cohort, 9 patients had tumors harboring a *BRAF* V600E mutation, 5 a *NRAS* mutation, 3 a *RET* fusion and 3 had no identified mutation.

Interestingly, in the selumetinib redifferentiation trial, the 8 patients who reached the dosimetry threshold included all 5 patients with an *NRAS* mutation but only 1 patient with a *BRAF* mutation (112). This led to the hypothesis that MEK inhibitors possibly achieve an incomplete blockade of MAPK signaling in *BRAF*-mutant tumors which harbor a higher degree of pathway activation. Therefore, this was followed by four trials evaluating redifferentiation with BRAF inhibitors in *BRAF*-mutated RR-DTC.

First, Rothenberg and colleagues (113) enrolled ten patients with *BRAF* V600E mutant RAI-refractory PTCs. Each patient received dabrafenib for 25 days, followed by an ^{131}I whole body scan (WBS). 6/10 patients whose scan showed new sites of radioiodine uptake remained on dabrafenib for a total of 42 days, after which they received an empiric dose of 150 mCi of RAI. At 3 months, 2/6 patients had PR and 4/6 patients had SD.

Similarly, Dunn and colleagues (114) studied redifferentiation therapy using vemurafenib in a cohort of 12 patients with *BRAF* mutant RR-DTC, excluding OTCs. Patients were treated with vemurafenib for 4 weeks. Pre-treatment ^{124}I PET-CT lesional dosimetry was done before and 4 weeks after vemurafenib therapy. Patients in whom at least one index tumor (of ≥ 5mm in maximal diameter) was predicted to absorb ≥2000 cGy with a clinically administered ^{131}I activity of ≤ 300 mCi, identified as ^{124}I responders, were subsequently treated with RAI while still on vemurafenib. 10/12 completed the 4-week treatment course of vemurafenib, and 4 of them were ^{124}I responders, qualifying for RAI therapy. At 6 months, 2/4 patients had SD and 2/4 had a PR. Of

TABLE 2 Summary of ongoing and published trials of immunotherapy in DTC.

Drug	Trial	Number of patients	Study population	Efficacy results	Reference
Atezolizumab + cabozantinib	COSMIC-021 (NCT03170960), Phase Ib	31	Treatment-naïve, locally advanced, metastatic and/or progressive RR-DTCs	42% PR, 55% SD Median PFS: 15.2 months	Taylor et al. (104)
Durvalumab + tremelimumab	NCT03753919, phase II	N/A	Locally advanced or metastatic RR-DTC	Ongoing	N/A
Ipilimumab+ nivolumab	NCT03246958, Phase II	32	Metastatic RR-DTC with progression ≤ 13 months prior to enrollment	**Interim results:** 9% PR, 44% SD Median PFS: 4.9months	Lorch et al. (105)
Ipilimumab/ nivolumab + cabozantinib	NCT03914300, Phase II	11	Locally advanced or metastatic RR-DTCs that have progressed on one previous anti-VEGFR therapy	**Interim results:** 18% PR, 54% SD Median PFS: 9 months	Konda et al. (106)
Nivolumab + encorafenib/ binimetinib	NCT04061980, Phase II	N/A	Metastatic, *BRAF* V600E mutant RR-DTC	Ongoing	N/A
Pembrolizumab (Single agent)	KEYNOTE-028 (NCT02054806), Phase Ib	22	Locally advanced or metastatic DTC	PR+SD for at least 6 mos: 50% Median PFS: 7 months	Mehnert et al. (100)
Pembrolizumab + lenvatinib	NCT02973997, Phase II	30	Treatment-naïve, RR-DTC with progression ≤ 14 months prior to enrollment	62% PR, 35% SD Median PFS: NR 12-month PFS: 74%	Haugen et al. (101)

Mos, months; NR, not reached; N/A, not applicable.

these four patients, two required subsequent thyroid cancer treatment at 9 and 18 months, and the other two patients have not required further therapy at 22 and 33 months, suggesting prolonged benefits.

Weber and colleagues (115) performed a prospective phase II redifferentiation study in which 6 patients with *BRAF*-mutated RR-DTC were treated with dabrafenib + trametinib while 14 patients with *BRAF* wild-type tumors were treated with trametinib alone for 21 ± 3 days. Redifferentiation was achieved in 2/6 *BRAF*-mutated and 5/14 *BRAF* wild-type patients, all of which received a dosimetry-guided therapeutic dose of RAI. At one year, response to therapy per RECIST 1.1 was PR in 1/7 patient, SD in 5/7 patients and PD in 1/7 patient. Both *BRAF*-mutated patients had some decrease in tumor size following redifferentiation therapy (one PR and one SD).

Finally, Leboulleux et al. (116) recently published another prospective multicentric trial in which 21 patients with *BRAF*-mutated metastatic, progressive, RR-DTCs were treated with dabrafenib and trametinib for 42 days then received an empiric dose of RAI 150 mCi irrespective of uptake on diagnostic WBS. Only one patient had ^{131}I uptake on baseline diagnostic WBS while 20 patients demonstrated uptake on the post-therapeutic WBS. Responses at six months were SD in 52% of patients, PR in 38% and PD in 10%, which corresponds to a tumor control rate of 90%. Eleven patients with PR at 6 or 12 months were re-treated with a second course of dabrafenib + trametinib followed by RAI. Nine of the 10 evaluable patients within this group had abnormal ^{131}I uptake on the second post-treatment WBS. At 6 months, 6/10 patients had a PR and 1/10 a CR. The 12-month PFS rate was 82.0% (95% CI, 58.8-92.8). Notably, re-induction of ^{131}I uptake and response rates following redifferentiation with dabrafenib and trametinib were higher in this study compared to what was reported by Weber et al. (115). Potential explanations for these differences include longer duration of drug therapy (42 *vs* 21 days), higher dose of dabrafenib (150 mg *vs* 75 mg twice daily), more limited tumor volume (no lesion larger than 3 cm) as well as empiric treatment of all patients regardless of restoration of uptake on diagnostic WBS in the trial by Leboulleux and colleagues.

Successful redifferentiation of *RAS* mutant tumors with MEK inhibition in the selumetinib pilot study (112) also led to a phase 2 trial looking at efficacy of the MEK 1/2 inhibitor trametinib for redifferentiation of *RAS* mutant and *RAS* wild-type RR-DTCs. 15/25 patients in the *RAS*-mutant cohort met the dosimetry threshold for radioiodine therapy on ^{124}I PET, 14 of which received RAI. At 6 months, ORR was 32%, with 8 PRs (57%), 3 SDs (21%) and 2 PDs (21%). Six-month PFS in the *RAS* mutant patients was 44%. In the *RAS* wild-type cohort (n=9), 3/4 patients with *BRAF* Class II alterations and 1/4 patients with *RET* rearrangements qualified for RAI, with 3 SDs and 1 PR (in patient with a BRAF-altered tumor) (117).

Additional retrospective studies have confirmed that redifferentiation represents a promising new therapeutic approach in patients with advanced RR-DTCs. Jaber et al. (118) described 13 patients with RR-DTC in whom targeted therapy with either single-agent BRAF or MEK inhibitor, or combination of dabrafenib and trametinib (in one patient), led to increased ^{131}I uptake. 9/13

patients were treated with RAI, all of whom had durable disease control (3 PRs, 6 SDs). Interestingly, *RAS*-mutated tumors seemed to have a better response to redifferentiation therapy compared to *BRAF*-mutated tumors in this study (118). On the other hand, Iravani et al (119) described 6 patients who received redifferentiation therapy with either trametinib in tumors harboring an *NRAS* mutation, or combined BRAF and MEK inhibition (with either dabrafenib+trametinib or vemurafenib + cobimetinib) in tumors with *BRAF* V600E mutations. Only 1/3 patients with an *NRAS* mutation but all 3 patients with a *BRAF* V600E mutation demonstrated restoration of RAI uptake and underwent subsequent RAI therapy. Of these 4 patients, 3 achieved PR and 1 had SD with a median follow-up of 16.6 months.

The concept of redifferentiation might also apply to tumors harboring other than *BRAF* or *RAS* mutations. For instance, Groussin and colleagues (120) described one case of successful redifferentiation therapy with Larotrectinib in a patient with metastatic PTC harboring an *EML4-NTRK3* gene fusion. Similarly, restoration of radioiodine uptake in patients with *RET*-fusion positive RR-DTC has been reported following treatment with selective RET-inhibitors pralsetinib (121) and selpercatinib (122).

Thus, substantial data now shows that mutation-guided MAPK pathway inhibition seems to be an efficient strategy to redifferentiate RR-DTCs (Table 3). However, available trials are significantly heterogeneous with regard to multiple aspects, including definition of radioiodine-refractory disease, inclusion criteria, duration of TKI therapy prior to RAI administration, choice of imaging modality to determine restoration of RAI uptake (^{124}I PET/CT versus ^{123}I scintigraphy) and dose of RAI (dosimetry-guided versus empiric). It also remains unclear whether increase of uptake on diagnostic WBS performed after treatment with the kinase inhibitors should be used as a criterion to select candidates for RAI administration. Therefore, more studies are needed to identify the optimal choice and duration of TKI before RAI, to better determine the characteristics of patients who are most likely to benefit from redifferentiation therapy, and to clarify the long-term risks as well as the duration of response to this therapeutic approach.

Future perspectives in radioiodine refractory DTC

When tolerated, TKIs can lead to a significant decrease in tumor size and could allow surgical resection of a previously inoperable tumor: this is referred to as neoadjuvant chemotherapy. Most MKIs used in advanced DTC are anti-angiogenic and thus may lead to poor wound healing and fistula formation. Therefore, these drugs need to be discontinued several weeks before surgery, which makes them unfit for use in the neoadjuvant setting. Nevertheless, case reports have been published in which MKIs, mostly lenvatinib (123) and sorafenib (124), have been successfully used to achieve shrinkage of locally aggressive tumors invading major cervical vessels, allowing subsequent complete surgical resection. More recently, a systematic review of neoadjuvant targeted therapy in locally advanced thyroid cancer (125) reported an R0/R1 resection rate of 78.1% among 27 patients, across all thyroid cancer subtype including ATC, MTC and PDTC. This review included 18 patients with DTC, all of whom were treated with non-selective TKIs with anti-VEGFR activity (anlotinib, lenvatinib, sorafenib). Despite this, no increased hemorrhagic risk during surgery was reported. To further explore this therapeutic avenue, there is currently a phase II multicenter clinical trial examining the efficacy of neoadjuvant lenvatinib in patients with locally advanced DTC (NCT04321954).

Selective kinase inhibitors, on the other hand, have little to no anti-angiogenic properties, which makes them potentially safer in the neoadjuvant setting. A clinical trial looking at the neoadjuvant use of the selective BRAF-inhibitor vemurafenib in 17 patients with unresectable *BRAF*-mutated PTC, has been reported (126). Eleven patients who completed the 56 days of treatment with vemurafenib underwent subsequent surgery: 8 had a complete resection (R0), and 3 had a resection leaving only microscopic residual disease (R1). 3/11 patients had an incomplete resection. One patient, whose tumor was involving the carotid, had a fatal hemorrhage two weeks after surgery.

Although neoadjuvant use of targeted therapy is not standard in the management of locally advanced DTCs, this approach is promising and is being increasingly used in clinical practice, especially with the growing availability of specific kinase inhibitors. Nevertheless, more data is required to confirm the efficacy, safety, and long-term benefits of this treatment strategy. An ongoing trial looking at the use of neoadjuvant selpercatinib for locally advanced *RET*-altered thyroid cancers might help answer some of these concerns (NCT04759911).

Another major therapeutic avenue that is being explored for advanced radioiodine refractory thyroid carcinomas, resistant to existing treatments, is chimeric antigen receptor T-cell (CAR-T) therapy. CAR-T cells are genetically engineered T-cells that express a chimeric antigen receptor, which contains a single-chain variable fragment (scFv) responsible for antigen recognition, and an intracellular signaling domain which initiates T cell activation. CAR molecules can reprogram T-cells to recognize and eliminate tumor cells expressing specific antigens (127, 128). CAR-Ts have demonstrated remarkable efficacy in hematological neoplasms and are currently being studied in various solid tumors. However, use of CAR-T therapy is more challenging in solid tumors, due to an immunosuppressive tumor microenvironment that impedes the access of CAR-T cells into the tumor. Moreover, antigen selection in solid tumors can also be challenging, because many tumor antigens also have some low-level expression in normal tissues, exposing the patient to a risk of "on-target, off-tumor" toxicity (128). The TSH-receptor, a well-known thyroid specific antigen, seems to be a promising target for CAR-Ts in advanced DTCs in *in-vitro* and mouse models (129). Moreover, a study assessing the safety and tolerability of autologous CAR-T cells targeting intracellular adhesion molecular-1 (ICAM-1) in advanced refractory poorly differentiated thyroid cancers is currently ongoing (NCT04420754).

TABLE 3 Summary of redifferentiation therapy trials in DTC.

TKI	Duration of TKI prior to RAI	Evaluable patients (n)	Restoration of uptake (n)	Patients treated with RAI	Efficacy results	Reference
Selumetinib	4 weeks	20	12/20	5/5 *NRAS* MUT 1/9 *BRAF* MUT 1/3 *RET* fusion 1/3 WT	At 6 months: 5/8 PR 3/8 SD	Ho et al. (112)
Dabrafenib	6 weeks	10, all with *BRAF* V600E mutations	6/10	6	At 3 months: 2/6 PR 4/6 SD	Rothenberg et al. (113)
Vemurafenib	4 weeks	10, all with *BRAF* V600E mutations	6/10	4	At 3 months: 2/4 PR 2/4 SD	Dunn et al. (114)
Trametinib if *BRAF*-WT, dabrafenib + trametinib if *BRAF*-mutated	21 ± 3 days	20	7	5/14 *BRAF* WT 2/6 *BRAF* MUT	At 1 year: 1/7 PR 5/7 SD 1/7 PD	Weber et al. (115)
Dabrafenib + trametinib in *BRAF*-mutated RR-DTC	42 days	21	11/17 at 4 weeks 20/21 on PTWBS	21	At 6 months: 8/21 PR 11/21 SD 2/21 PD	Leboulleux et al. (116)
Trametinib	4 weeks	25 *RAS* MUT, 9 *RAS* WT	19	14/25 *RAS* MUT 3/4 *BRAF* MUT 1/4 *RET* altered	At 6 months: PR 9/18 SD 6/18 PD 3/18	Burman et al. (117)
BRAFi+/- MEKi if *BRAF*-mutated, MEKi if *RAS*-mutated, trametinib in WT patient	0.9 – 76.4 months	13	8/13	3/3 *RAS* MUT 5/9 *BRAF* MUT 1/1 WT*	3/9 PR 6/9 SD	Jaber el al (118).
Trametinib if *RAS*-mutated, dafrafenib/trametinib or vemurafenib/cobimetinib if BRAF-mutated	4 weeks	6	4/6	1/3 *RAS* MUT 3/3 *BRAF* MUT	3/4 PR 1/4 SD	Iravani et al. (119)

*Patient treated empirically with ^{131}I despite no restoration of uptake on diagnostic whole-body scan.
WT, wild type; BRAFi, BRAF inhibitor; MEKi, MEK inhibitor; PTWBS, post-therapeutic whole body scan; MUT, mutant.

Conclusion

Better understanding of the molecular mechanisms underlying thyroid cancer has revolutionized the treatment of advanced, radioiodine refractory disease. Over the past decade, we have seen an expansion in the use of kinase inhibitors for advanced thyroid cancers, with the most recent approval of six selective, less toxic, targeted agents. The increasing number of available drugs raises the question as to what is the optimal treatment sequence, which remains to be defined. Moreover, although these drugs offer a delay in disease progression and tumor size shrinkage, none have led to an improved length of survival. For many of these agents, drug related toxicity is non negligeable and can significantly alter quality of life. Furthermore, patients eventually develop resistance to these therapies and experience disease progression. Therefore, identification of the optimal timing for initiation of systemic therapy is crucial, taking into consideration disease burden and rate of progression, presence of symptoms, as well as patient comorbidities and toxicity profile of potential drugs. Given limitations of currently available therapies, the search for a curative treatment for RR-DTC, with long-term persistent efficacy, continues.

Author contributions

SH: Conceptualization; Literature review; Data curation and Writing original draft. MC, M-CH, PI, MH and NB: Review and editing of original draft. RD: Conceptualization; Review and editing of original draft. All authors contributed to the article and approved the submitted version.

Conflict of interest

RD has received grant funding from Eisai, Exelixis, AstraZeneca, and Merck and has participated in advisory boards for Exelixis and Bayer. MC has received grant funding from Genentech and Merck and has received consulting fees from

Exelixis and Bayer. MH has received grant funding from Eli Lilly & Co. and has participated in a steering committee for Eli Lilly & Co. NB has received grant funding from GSK, has received consulting fees from Eisai and Loxo and has participated in advisory board for Exelixis.

The remaining 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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Analysis of risk factors for intra-cystic hemorrhage in microwave ablation of partially cystic thyroid nodules

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Objective: The aim of this study is to identify risk factors of intra-cystic hemorrhage in microwave ablation of mixed solid and cystic microwave ablation s, and to design a preoperative nomogram to predict the risk value of intraoperative bleeding with the goal of individualizing the surgical approach toward different types of cystic and solid thyroid nodules.

Methods: A total of 241 patients with cystic-solid thyroid nodules who underwent ultrasound-guided percutaneous microwave ablation were retrospectively divided into a bleeding group and a non-bleeding group to compare the diameter, cystic proportion, cystic fluid nature, color Doppler flow imaging, Contrast-enhanced ultrasound (CEUS) findings, and operative methods. Based on univariate and multivariate analysis, the important risk factors of nodular intracapsular hemorrhage in the ablation procedure were projected to a nomogram for predicting the possibility of intraoperative hemorrhage in the thyroid cystic solid nodules.

Results: Intra-cystic hemorrhage was developed in 37 cases during the ablation of mixed thyroid nodules with a total incidence of 15% (37/241). Significant differences were found statistically between the two groups on the diameter of the lesions, CEUS findings, the cystic fluid ratio, and operative methods (P = 0.000, P = 0.001, P = 0.024, P = 0.002). The possibility of intraoperative nodular intracapsular hemorrhage was predicted by the model based on the risk factors with the accuracy of 81% and prediction consistency index (C-index) of 0.78.

Conclusion: A new and efficient prediction model was developed based on the identified risk factors for intracapsular hemorrhage during microwave ablation of mixed thyroid nodules, which will aid in the development of targeted surgical planning for different types of cystic thyroid nodules, thus reducing the risk of hemorrhage during ablation.

KEYWORDS

ultrasound-guided microwave ablation, mixed cystic and solid thyroid nodule, contrast-enhanced ultrasound, intra-cystic bleeding, intracapsular hemorrhage

Abbreviations: MWA, microwave ablation; CDFI, color Doppler flow imaging, CEUS; Ultrasonic Contrast.

Introduction

A thyroid nodule has been discovered in more than 70% of the general population with a low incidence of malignant pathology (1, 2). Most patients undergo aggressive treatments for enlarged nodules (≥4 cm) that result in symptoms secondary to local mass effect (3). Thyroidectomy, through either open or endoscopic approaches, has long been the first-line choice as a definitive measure for this disease. Nevertheless, thyroidectomy not only carries various intra- and postoperative adverse risks (4), but also cannot eliminate the need the risk of re-operation in the case of recurrence (5, 6). As a result, various minimally invasive interventions, including ethanol ablation (7), laser ablation (8), microwave ablation (MWA) (9), and radiofrequency ablation (10) have emerged for managing large symptomatic benign thyroid nodules.

Microwave ablation has emerged as a preferred treatment methods, due to its many clinical advantages. The mechanism of treatment involves destruction of tumor via thermal stress, resulting in *in-situ* inactivation of the thyroid nodules. This results in less tissue carbonation, stronger coagulation, a larger destruction range, shorter ablation time, more uniform ablation, the limited cooling effect from blood perfusion, and more cost-effectiveness, all of which, thus have made MWA outperform traditional surgery in the treatment of benign solid or solid-cystic thyroid nodules (11). A recent study showed that the ultrasound-guided ablation achieved a one-year nodule reduction rate of 82.5–90.0%. Moreover, the application of mobile ablation and water isolation technology along with the empirical accumulation of operators have gradually lowered the complication rates related to the procedure, and have increased the safety and reliability of the operation (12–16).

Common procedure-related complications of thyroid nodule ablation are hoarseness, nodule rupture, and hemorrhage (17). Among these, intraoperative hemorrhage can lead to eventual hematoma formation, thereby prolonging the operation time and delaying the postoperative recovery (18). Since only a handful reports are available on the methods regarding the management of cystic-solid thyroid nodules and prevention of intraoperative intra-capsular hemorrhage (13, 19), this study aims to analyze the risk factors for intra-capsular hemorrhage during complicated cystic-solid nodule ablation, and to design a working prediction model to help better design targeted ablation plans for different types of cystic-solid nodules.

Methods and materials

Patient selection

The present study retrospectively selected all the patients with the diagnosis of benign cystic-solid thyroid nodules who underwent ultrasound-guided microwave ablation treatment in our hospital from May 2017 to November 2022 (Figure 1). The inclusion criteria were listed as follows: (1) all patients undergoing both puncture cytology and liquid-based lamella cells for the preoperative pathological diagnosis; (2) thyroid nodule being greater than 2 cm at its longest diameter; (3) thyroid nodule being comprised of ≥20% cystic components. Moreover, patients who presented obvious symptoms as dyspnea or dysphagia or hoarseness or persistent anxiety about the possible malignant transformation were also candidates for the ablation procedure. The exclusion criteria included: (1) patients who presented any of the comorbidity of severe bleeding, coagulopathy, and poorly controlled severe cardiopulmonary diseases; (2) patients who were allergic to the ultrasound contrast medium; (3) patients who had the pathologically confirmed malignant or uncertain thyroid lesions by fine needle aspiration; (4) patients who had received any kind of

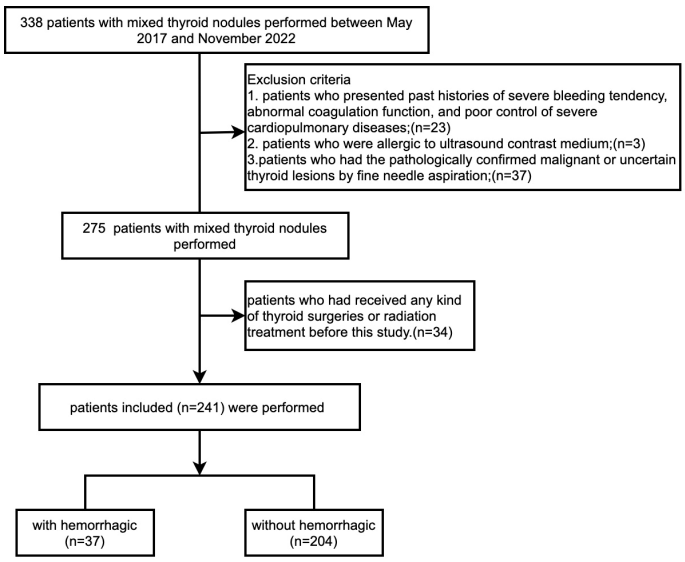

FIGURE 1
Flowchart shows study inclusion and exclusion criteria.

thyroid surgeries or radiation treatment before this study. Moreover, the institutional review board of our hospital had reviewed and approved the study, and all participants had signed informed consent of procedures.

Microwave ablation system and ultrasound guidance

All thyroid nodular lesions were ultrasonographically measured by using either MyLab™ Twice (Esaote, Italy) or Logic E9 (GE, USA) scanners equipped with LA523 and ML6-15 high-frequency linear array probes. Before the ablation, the microwave system ECO-100A1 (Yigao, China) was set at a frequency range in between 915MHz and 2450GHz for generating maximum temperatures of approximately 140°C. During the ablation, the probe was powered with 40 W to maintain the ablation temperatures above 100 °C, minimizing tissue vaporization and carbonization according to the manufacturer's recommendation. Additionally, the contrast agent used for enhancing sonographic imaging was SonoVue (Bracco Imaging SpA, Milano, Italy) dry powder, which was further made into a microbubble suspension with infusion of 5 ml of normal saline before its use (Supplementary Materials for details).

Pre-ablation evaluation

All the patients underwent thorough preoperative ultrasonographical studies to identify and analyze the nature, location, size, number, and the blood supply of the nodule, all of which helped to tailor the operating procedure for avoiding the injuries toward important blood nerves and vessels around the nodule. Specifically, the mechanical index was adjusted as 0.07, and both peripheral and internal enhancement patterns of the nodule were carefully assessed during contrast-enhanced ultrasonography.

Operative procedure

The ablation procedure was conducted in the hybrid operating room with the implementation of ultrasonographic equipment. The patients were placed in a dorsal decubitus position with the hyperextension of the neck in between the ultrasonographic device on the left side and the ablation instrument on the right side. After peripheral intravenous access was established, lines were connected for intraoperatively monitoring vital signs, and the surgical field was sterilized with iodine. The ablation procedure was initiated only under local anesthesia with the injection of lidocaine through the skin and into the deep fascial planes to the level of the anterior thyroid capsule. At this moment, the ultrasound scanning with a sterile probe was performed over the operating area to re-evaluate all critical structures (Figure 2), including the trachea and neck vessels in order to design a safe insertion path for the ablation needles so as to prevent vascular injuries from the puncture. If a thyroid nodule possesses cystic-solid nature with the cystic fluid as a jelly-like substance, the fluid can be aspirated after the injection of 0.9% normal saline to reduce the volume of the mixed lesion.

Subsequently, the microwave needle was forwarded to the targeted place to touch off real-time US-guided ablation on the lesion. Intraoperatively, patients are frequently asked to speak for monitoring any voice changes. When the nodule was small, the fixed ablation method was used. The extension of the ablation zone corresponded to the echogenic change around the antenna, and thus, if the hyperechoic zone failed to completely cover the nodule, the needle would be readjusted to achieve complete coverage of the target tissue by the ablation zone. After removing the ablation needle from the puncture site, compression was applied on the site for 2–3 minutes. In the case of multiple lesions, the ablations were performed on the unblocked nodules first, and then on the remaining nodules one by one. For nodules larger than 5 cm, in atypical locations, or located retrosternally, MWA was often performed in stages in order to avoid the development of complications. Following the ablation procedure, contrast-enhanced ultrasound can be performed again, and an additional round of ablation can be completed if the contrast is visualized to flow into the surgical bed. Afterward, all patients underwent local compression on the neck for 30 minutes with ice bag to relieve pain and reduce edema, and then were closely monitored for more than 2 hours before being discharged to home.

Intraoperative intra-cystic bleeding usually occurs from puncturing the thyroid, aspirating cystic fluid to deflate cyst cavity, and penetrating the nodule. Therefore, the puncture point should be first compressed for 3–5 minutes after the procedure to prevent bleeding. During the operation, If bleeding was not stopped after 2–3 rounds of repeated aspiration, the source of the bleeding could be ablated under ultrasound guidance to achieve hemostasis. For intracapsular hematomas that could not be aspirated, ablation will be performed on the solid component of the nodule.

Image analysis

Adler grading method was used for visualizing the blood flow signals to and around the nodules with the doppler ultrasound, and in further evaluating intracystic hemorrhage, which commonly presented after aspirating or the ablation needle being inserted into the nodule, showing high or isoechoic punctate and mass signals in the nodule, and occasionally unveiling jetting signals as the bleeding site from the cyst wall.

Statistical analysis

All statistical analyses were performed using SPSS 26.0 version. All the numerical data were expressed as the mean ± standard deviation. An independent sample t-test was used to compare the data between the two groups, and the chi-square test was applied to compare categorical data of two groups. The spearman correlation coefficient was used to analyze the correlation between contrast enhancement mode and bleeding rate, and the univariate analysis followed by multivariate logistics regression model were performed

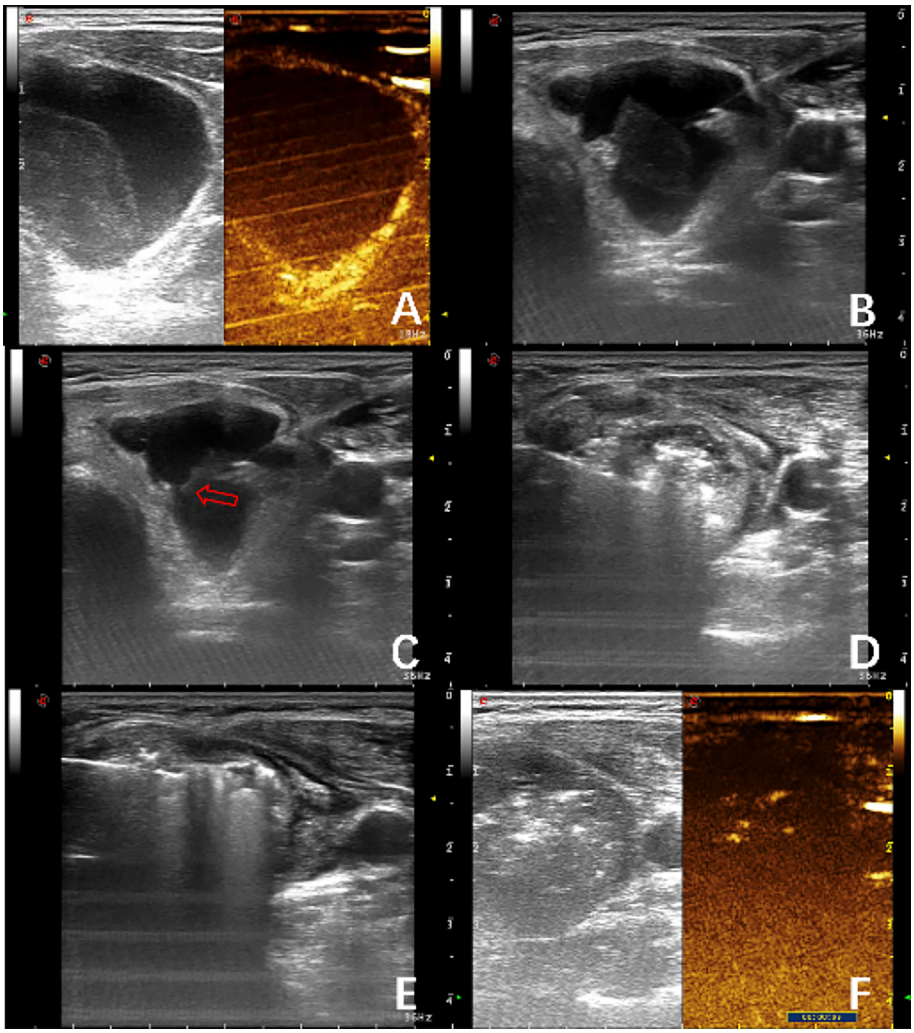

FIGURE 2
A 50-year-old woman presented with cystic solid nodules in the left lobe of the thyroid gland, about 4.1 cm × 3.7 cm × 2.8 cm in size. 70%, preoperative contrast-enhanced ultrasound showed abundant blood supply in the cyst wall and the internal solid part of the nodules and the contrast-enhanced image showed equal enhancement. **(A)** Aspiration of cyst fluid. **(B)** The nodules were bleeding in the cyst, and the bleeding spots on the cyst wall were squirted (arrows). The deflated cyst cavity was filled again, and the cavity was clouded **(C)**. Hematoma formed inside the nodules **(D)** Mobile layer-by-layer microwave ablation **(E)** was performed for solid components of nodules and hematoma. Immediate postoperative angiography, no contrast filling in and around the nodules **(F)**.

to establish a nomogram for predicting the risk factors of intraoperative bleeding by using R3.6.1 software along with the calculation of c-index. A *P*-value less or equal to 0.05 ($P < 0.05$) was considered statistically significant.

Result

General comparisons

The study collected a total of 241 patients with benign cystic-solid thyroid nodules undergoing ultrasound-guided microwave ablation in our hospital from May 2017 to November 2022. These patients had 49 males and 192 females with the age of 15–83 (50 ± 13) years old, and were further categorized into a bleeding group with intra-cystic hemorrhage (37, 15%), and a non-bleeding group (204, 85%). The further comparison did not find any significant difference in either gender, or cystic fluid properties, or CDFI grade between the two groups ($P > 0.05$), but exhibited that the length and proportion of cystic of nodules in the bleeding group were larger than those in the non-bleeding group, the operating methods of aspiration-ablation or ablation-aspiration-ablation were more common ($P < 0.05$), as shown in Table 1.

Univariate analysis

The univariate analysis did not find significant differences in age, gender nodular cystic fluid properties, and CDFI between the bleeding group and the non-bleeding group ($P > 0.05$), but unveiled the differences in nodule diameter, contrast-enhanced ultrasound findings, the proportion of cyst fluid, and the operation method

TABLE 1 Comparison of general data between the bleeding group and non-bleeding group.

Characteristics	bleeding group	non-bleeding	χ^2/t	*P value*
	n=37	n=204		
Gender, cases	9/28	40/164	0.430	>0.05
Age, years	51 ± 10	49 ± 13	0.933	>0.05
Nodules diameter	3.77 ± 0.98	3.08 ± 0.757	4.800	<0.01
Proportion of cystic fluid			7.656	<0.01
21%-50%	3 (3/37, 8%)	45 (45/204, 22%)		
51%-70%	15 (15/37, 41%)	45 (45/204, 22%)		
71%-99%	19 (19/37, 51%)	114 (114/204, 56%)		
CEUS			13.870	<0.01
No enhancement	5 (5/37, 14%)	66 (66/204, 32%)		
Low enhancement	5 (5/37, 14%)	56 (56/204, 27%)		
Equal enhancement	27 (27/37, 73%)	82 (82/204, 40%)		
Operation method			9.670	<0.05
Ablation	3 (3/37, 8%)	42 (42/204, 21%)		
infusion-ablation	30 (30/37, 81%)	159 (159/204, 78%)		
ablation-infusion-ablation	4 (4/37,11%)	3 (3/204, 1%)		
CDFI			3.254	>0.05
Grade 0	3 (3/37,8%)	36 (36/204, 18%)		
Grade 1	17 (17/37,46%)	98 (98/204, 48%)		
Grade 2	11 (11/37,30%)	47 (47/204, 23%)		
Grade 3	6 (6/37, 16%)	23 (23/204, 11%)		
Fluid properties			4.423	>0.05
Clarified yellow	4 (4/37, 11%)	16 (16/204, 8%)		
Stale bloody	25 (25/37, 68%)	129 (129/204, 63%)		
gelatinous	5 (5/37, 14%)	17 (17/204, 8%)		
None	3 (3/37, 8%)	42 (42/204, 21%)		

(CDFI was classified by Adler classification method: Grade 0: no blood flow signal; Grade 1: sparse blood flow, punctate or short line of blood flow, its long diameter does not exceed 1/2 the diameter of the nodule; Grade 2: Usually 3-4 punctate blood flow or a long vessel penetrating the lesion, the length of the diameter is equal to or greater than 1/2 of the nodule; Level 3: enriched blood flow signal).

between the two groups ($P < 0.05$). The diameter of nodules in the bleeding group ranged from 2.0 to 6.3 cm (3.77 ± 0.98), which trended higher than that in the non-bleeding group (2.0–5.7cm), with an average of (3.08 ± 0.77) cm. In the bleeding group, the proportion of cystic fluid that occupied 51% to 70% of the lesion were found in 15 patients (15/37, 41%), and more than 70% were in 19 patients (19/37, 51%). 92% of intracapsular hemorrhage occurred in the mixed cystic and solid nodules with predominantly cystic content.

In the bleeding group, there were five cases (5/37, 14%) with no enhancement in the ultrasonographic images, five cases (5/37, 14%) with low enhancement, and 27 cases (27/37, 73%) with iso-enhancement. There was a positive correlation between the enhanced pattern of nodules and the incidence of intracystic hemorrhage (spearman correlation coefficient, r = 0.258) ($P < 0.05$).

Multi-factor logistics regression analysis and nomogram risk prediction transformation

Multivariate Logistic regression analysis further identified the diameter of nodule and enhancement seen on ultrasound as independent influencing factors for bleeding ($P < 0.05$) (Table 2). Combined with previous literature (15) and clinical cases, the surgeons thought that the cystic proportion had strong clinical practical significance, and were compelled to include it in the multivariate statistical analysis. In the bleeding group, the nodules with a cystic proportion of 51%–70% accounted for 41% (15/37) of the total nodules, and the ones with cystic content of more than 70% accounted for 51% (19/37) of the total nodules. Notably,92% of intracapsular hemorrhage occurred in mixed cystic and solid

TABLE 2 Results of Logistic multivariate analysis.

Variable	Classified	β	SE	OR	95%CI	*P*
diameter		-0.8587	0.2377	0.424	0.266~0.675	0.0003
CEUS	0	0.5130	0.3731	4.376	1.453~13.181	0.1691
	1	0.4501	0.3676	4.109	1.394~12.115	0.2208
proportion of cystic fluid	1	0.9360	0.4433	2.786	0.687~11.291	0.0347
	2	-0.8474	0.3144	0.468	0.188~1.167	0.0070

nodules mainly composed of fluid. Furthermore, these three factors were ranked by the standard deviation along nomogram scales for the nomogram model as the longitudinal diameter of the lesion carrying highest risk potential (SD:0.238), the proportion of cystic fluid (SD: 0.714) being the second, and contrast-enhanced ultrasonography as the third (SD: 0.563). The total score was determined based on the individual scores calculated using the nomogram with the C-index value of 0.78 [95% confidence interval (CI) = 0.705–0.860], the accuracy of predicting intraoperative intracystic bleeding in nodules of 81%, and the area under curve of 0.782 [95% confidence interval (CI) = 0.705–0.859], altogether indicating good modeling for predicting subcapsular hemorrhage during MWA (Figures 3, 4).

Discussion

The rate of thyroid nodules detected by high-frequency ultrasound is as high as 50%–76%, and the incidence of cystic solid nodules is the highest, accounting for 15%–53.8%. According to the American Thyroid Association guidelines, the risks of malignancy in purely cystic nodules, predominantly cystic nodules and predominantly solid nodules are about 1%, 3%, and 5%, respectively; additionally, spongiform morphology is highly specific for a benign nodule (20–22). Since most of cystic and mixed thyroid nodules pathologically possess benign nature, ultrasound-guided thermal ablation has been considered as the preferred choice when the enlargement of those nodules result in clinically significant symptoms (23, 24). A comparative study on thyroid thermal ablation versus thyroidectomy in 450 patients demonstrated that the thermal ablation was superior to conventional thyroidectomy in the categories of patient satisfaction, post-operative quality of life, and length of hospital stay (25). Furthermore, another study on MWA treatment of 474 benign thyroid nodules showed that the volume reduction rate of mixed cystic nodules (95% within 12 months) by the ablation was significantly higher than that of solid nodules, suggesting a curative effect was more definite in partially cystic thyroid nodules (15).

Importantly, MWA possesses more complexities in the treatment of thyroid cystic solid nodules than that of solid nodules, especially when intraoperative hemorrhagic occurs in the cystic lesion, which not only complicates the ablation, but also creates challenges in postoperative recovery. Thus, clinicians should pay extra attention to avoid the development of intracapsular hemorrhage during preoperative planning. This study analyzed the basic conditions of patients and the characteristics of nodules, which showed that larger cystic components of nodules contributed to a higher rate of intracystic bleeding during an ablation procedure. The diameter of nodules in the bleeding group of this study was consistent with that reported by Dong et al. (26), who reported the diameters of nodules ranged from 3.1 cm to 4.8 cm (average 3.9 cm). In addition, in the present study, 92% of intracapsular bleeding occurred in the mixed nodules predominantly with the cystic component, which was also in accordance with the study by Dong et al. (26), which found that all intraoperative bleeding nodules occurred in simple cysts or mixed nodule with more than

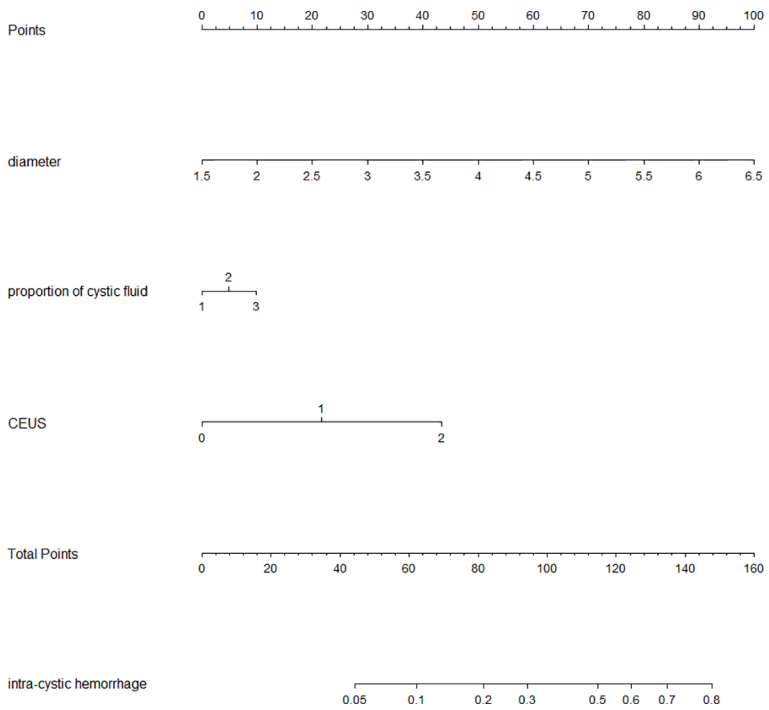

FIGURE 3
Nomogram of intraoperative intracapsular bleeding risk values. (Nodular cystic proportion 1: representing the capsule proportion of 21% to 50%; 2: representing the capsule proportion of 51% to 70%; 3: representing the capsule proportion of 71% to 99%; Contrast-enhanced ultrasound 0: no enhancement 1: low enhancement 2: equal enhancement).

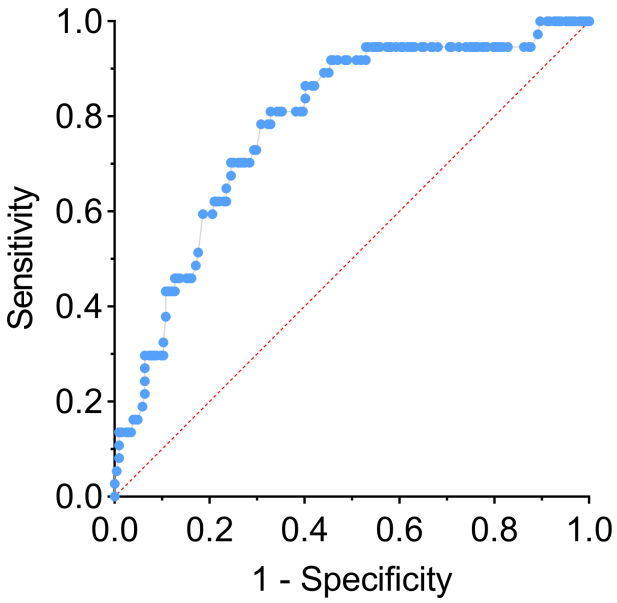

FIGURE 4
ROC curve of nomogram.

80% cystic proportion. Both our and Dong's studies indicated that a higher cystic component in the mixed nodule resulted in higher risk in developing intracystic bleeding. Moreover, we found that iso-enhancing nodules accounted for 76% (19/25) of the total cases of hemorrhage, thereby suggesting that contrast-enhanced ultrasonography can be an effective method in preoperative preparation for predicting the bleeding risk. Following an extensive literature search for other similar studies, two articles by Kim et al. (17) and Agyekum et al. (18) were found to report the intraoperative complications related to cystic nodule ablation. However, none of these articles discussed intra-ablation hemorrhage in the cystic nodules. Our study has been the first one ever to investigate contributing factors to the development of hemorrhage and propose a prediction model for the ablation team to evaluate the bleeding risk of the cystic nodule in the thyroid in the process of ablation.

A nomogram can visually represent the quantitative relationship between different predictor variables and target variables, and it can be used to predict the correlation extent of the incidence of an event and its potential risk factors. In this study, the top three contributory factors to the intra-lesion hemorrhage in the ablated mixed thyroid nodules were further ranked by their standard deviation along the nomogram scales in the nomogram model with the diameter of the nodules the cystic proportion of mixed nodules, and preoperative contrast-enhanced ultrasonography, which may more specifically direct the operators to take more strict and targeted operating procedures to prevent the intracystic bleeding from developing. Since our nomogram on these three risk factors carries the accuracy rate of 80.76%, the model can be efficiently translated into the daily practice on the MWA of mixed thyroid nodules.

Clinically, our study suggests that the ablation should be postponed in patients with a recent sudden increase in nodular volume or a history of hemorrhagic disease; technically, we emphasized that the needle tip should be placed far from the cyst wall, a small amount of fluid should be retained in the nodules with large cystic components to prevent the rupture of fragile vessels in the nodules after a sudden drop in pressure, and larger vessels should be avoided during ablation. For the nodules with rich blood flow, which are inevitably damaged during the procedure, we normally ligated the blood vessel first and drained the cyst fluid afterward. Intra-capsular hemorrhage that often occurred after the puncture and aspiration were completed or after the ablation needle entered the node presented with the expansion of the drained cyst cavity and could be managed with the compression on the puncture point for 3 to 5 minutes to prevent further extravasation, follow by aspiration of the remaining blood. If the hemorrhage continued after 2 to 3 aspiration attempts, additional ablations were performed with higher power at the suspected site of hemorrhage.

Based upon the findings in this study, the corresponding individualized ablation procedures are proposed for the nodules with different characteristics. First, for thyroid nodules with cystic component comprising 71%–90% of the total nodule volume, if the solid part or septa shows no or low enhancement by contrast-enhanced ultrasound, and the aspirated cyst fluid does not contain fresh blood, the operation can be performed with extracting cystic fluid first and then ablating the nodules thoroughly; if the above nodules are found to have jelly-like cystic material, the cystic material should be first diluted with the injection of a small amount of normal saline to alter the viscosity of the components in the cyst cavity, afterward, the mixed nodules can undergo MWA after the withdrawal of most of the cyst fluid; if a contrast-enhanced ultrasound showed solid components separated by equal enhancement with thick vessels on color Doppler imaging, the thick large vessels and the solid part of the nodules can be ablated first, then the cystic fluid in the nodule can be slowly aspirated, and finally the ablation part of the remaining nodule. For the thyroid nodules with 50%–70% cystic fluid, if the blood supply can be found in the solid part or septa by contrast-enhanced ultrasound, as much cystic fluid as possible can be aspirated prior to microwave ablation. If the solid part and septa contain a rich blood supply, the ablation needle cannot be inserted through the solid component; however, if the solid component can not be avoided, the ablation can be started once the needle tip reaches the nodal brim and continued through the solid portion of the nodules. Afterward, normal saline solution can be given to fill up the lesion, subsequently, the capsule of the lesion can finally be ablated. Third, for mixed nodules with cystic material of less than 50%, if the cyst fluid is gathered at the edge of the nodules, it can be aspirated first and then ablated the nodules,

and if the cyst is dispersed (such as with spongiform nodules) or located in the central region of the nodules, it is difficult to extract fluid so such nodules can be directly ablated. Fourth, for the nodules with abundant blood supply and inevitable injury from puncture or ablation, vascular occlusion can be first performed followed by extraction of cyst fluid and then additional ablations.

The first limitation of this study is that the proportion of cystic components that could be aspirated was accurately evaluated by the volume of fluid, but for those mixed nodules, cystic fluid could not be completely aspirated or even could not be aspirated, the proportion of cystic content was only estimated based upon ultrasonographic measurement on the cystic component region, so the inconsistence in measurement should more or fewer influence results (27). Second, the long-term follow-up on the absorption of thyroid nodules was not done in this study, so the long-term outcome of MWA in the treatment of mixed thyroid nodules could not be fully established.

In conclusion, intra-cystic hemorrhage during microwave ablation of mixed thyroid nodules is not uncommon, so a feasible predictive model using identified risk factors can be used in preoperative evaluation for assessing the risk of intra-capsular hemorrhage, adding great value to clinical work in the form of improved prevention of operative complications.

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 institutional review board of the Second Hospital of Dalian Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YF: Validation, Formal analysis, Data Curation, Writing-Original Draft. YH: Investigation, Resources. Data Curation. YL: Visualization, Writing - Review & Editing. YS: Conceptualization, Methodology, Supervision, Project administration. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

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Supplementary material

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Cost-effectiveness of active surveillance versus early surgery for thyroid micropapillary carcinoma based on diagnostic and treatment norms in China

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Objectives: In this study, we compared the cost-effectiveness comparison of the active surveillance (AS) and early surgery (ES) approaches for papillary thyroid microcarcinoma (PTMC) from the perspective of the Chinese healthcare system.

Methods: We performed a cost-effectiveness analysis using a Markov model of PTMC we developed to evaluate the incremental cost-effectiveness ratio of AS and ES. Our reference case was of a 40-year-old woman diagnosed with unifocal (<10 mm) PTMC. Relevant data were extracted after an extensive literature review, and the cost incurred in each state was determined using China Medicare data on payments for ES and AS. The willingness-to-pay threshold was set at ¥242,928/quality-adjusted life-year (QALY) gained. Sensitivity analyses were performed to account for any uncertainty in the model's variables. Additional subgroup analyses were performed to determine whether AS was cost-effective when different initial monitoring ages were used.

Results: ES exhibited an effectiveness of 5.2 QALYs, whereas AS showed an effectiveness of 25.8 QALYs. Furthermore, the incremental cost-effectiveness ratio for ES versus AS was ¥1,009/QALY. The findings of all sensitivity analyses were robust. Compared with ES, AS was found to be the cost-effective strategy at initial monitoring ages of 20 and 60 years, with an incremental cost-effectiveness ratio of ¥3,431/QALY and –¥1,316/QALY at 20 and 60 years, respectively. AS was a more cost-effective strategy in patients with PTMC aged more than 60.

Conclusions: With respect to the norms of the Chinese healthcare system, AS was more cost-effective for PTMC over lifetime surveillance than ES. Furthermore, it was cost-effective even when the initial monitoring ages were different. In addition, if AS is incorporated into the management plan for PTMC in China at the earliest possible stage, a predicted savings of ¥10 × 10^8/year could

be enabled for every 50,000 cases of PTMC, which indicates a good economic return for future management programs. The identification of such nuances can help physicians and patients determine the best and most individualized long-term management strategy for low-risk PTMC.

KEYWORDS

active surveillance (AS), early surgery, cost-effectiveness (CE), papillary thyroid microcarcinoma (PTMC), papillary thyroid cancer (PTC)

1 Background

Papillary thyroid cancer accounts for 70% to 90% of thyroid malignancies and is characterized by slow growth and low invasiveness. Globally, the incidence of thyroid cancer has increased significantly in the past three decades (1) and continues to increase in the younger population (2). Meanwhile, the mortality of thyroid cancer has remained relatively stable at low levels or has decreased, almost worldwide (3). Among the various cancer types, papillary thyroid microcarcinoma (PTMC) (PTC < 1 cm) incidence showed the most rapid growth rate and the largest proportion (4). The drastic increase observed in PTMC incidence is generally attributed to the advanced and widespread use of diagnostic technologies such as high-resolution ultrasonography and fine-needle aspiration cytology (FNAC) (5, 6). Some investigators have suggested a diagnostic epidemic rather than an disease epidemic for PTMC—an accurate diagnosis of "cancer" that does not eventually manifest as symptoms or lead to death (7). PTMC overdiagnosis is also an example of medical service overuse, which increases health service and governmental expenditure (8). China is rapidly transitioning to a higher socioeconomic status. If the current growth rate continues, the overtreatment and burden of thyroid cancer may increase further. Additionally, overtreatment is an almost inevitable product of overdiagnosis, an aspect that has attracted great attention from medical establishments and the society at large. Therefore, identifying a cost-effective and sustainable strategy is a major priority for PTMC management in China.

Initial management measures involve weighing the risks and benefits of proposed treatment strategies. Surgery was a major priority for the management of low-risk PTMC before 2010 in various countries. In 2016, the Chinese Thyroid Oncology Society reached a consensus on the issue (9), stating that immediate surgical resection is the preferred treatment for patients with PTMC. Lin et al. (10) showed that surgery has a long-term economic advantage for young Australian patients with PTMC. However, even though the incidence of complications from thyroid cancer surgery is gradually decreasing, the complications are not completely avoidable (8). A multitude of unnecessary surgeries has led to an increase in the number of patients who require additional thyroxine supplementation and suffer from related complications. This may increase the physical and psychological burden of patients. Of note, the extent of thyroid cancer overdiagnosis and overtreatment is far from its peak (11, 12). The need for active early surgery (ES) treatment in low-risk PTMC has recently garnered attention (13).

Since 2010, the understanding of surgical treatment has changed in different countries. Active surveillance (AS) is a surgical alternative for selected patients with PTMC, and there is an expanding disease spectrum in which AS could be implemented. Japan established the first edition of guidelines in 2010, which adopted AS as an option for low-risk PTMC (14). In 2020, White et al. (15) reported that no negative consequences were observed among patients who were awaiting surgery, and most patients did not exhibit significant disease progression after 10 years. AS is considered a safe and effective alternative to active ES in appropriately selected patients. The results, which have been replicated in other studies, suggest that most patients with PTMC can be treated safely with AS and do not require active ES (15–18). In the latest treatment guidelines, AS strategy has been incorporated as an acceptable alternative treatment strategy for low-risk PTMC (19–22). Although currently available Chinese guidelines recommend AS for PTMC in 2022 (22), a large body of prospective clinical work on the use of AS for PTMC and most conclusions were obtained from studies published in other countries. A cost-effectiveness analysis for low-risk PTMC in China has not been conducted to date, and evidence on PTMC management with AS is insufficient. Therefore, there remain doubts regarding whether AS should be used widely in China. Additional evidence is needed on the costs and effectiveness of AS strategy in developing countries like China.

To bridge this evidential gap, we assessed the cost-effectiveness of ES and AS strategies as management approaches for patients with PTMC. We believe our findings could facilitate decision-making for patients and surgeons.

2 Methods

2.1 Patient reference case scenario

To indicate the range of individuals most representative of the patient cohort with thyroid nodules detected, the reference case selected was of an otherwise healthy, 40-year-old woman with a biopsied unifocal PTMC without characteristics that would warrant hemithyroidectomy (such as an unfavorable location near the trachea or recurrent laryngeal nerve, or lymph node metastases)

or risk factors that would require a more aggressive surgical approach by resection (such as a family history of thyroid cancer, neck irradiation, other tumors, or uncontrolled chronic disease). The patient, who was initially in the AS or ES state, underwent various changes and eventually entered a state corresponding to death (life expectancy: 80 years). The model cycle was of 1 year with 40 cycles. The reasons for selecting this as the base case were as follows: (1) This was similar to the base case used in previous cost-effectiveness analyses of thyroid cancer to simulate the cost-effectiveness of different treatment methods. (2) We aimed to focus on AS with respect to the duration of follow-up and assess whether AS is cost-effective based on the need for lifetime surveillance. In addition, the incidence of thyroid cancer is higher in women. Thus, we selected a 40-year-old female patient for the base case.

2.2 Model overview

We provided evidence-based policy recommendations by developing a comprehensive and dynamic decision-analytic Markov model. The model was constructed using Tree Age Pro 2011 (Figure 1). A Markov decision tree provides a logical structure of decisions and potential events as they unfold over time. The Markov nodes for AS and ES represent a potential transition to new health states and include the following:

- Stable disease
- Disease progression (including primary tumor growth increase ≥3 mm, FNAC-confirmed lymph node metastasis in the new area)
- Lateral lymph node metastases
- Death

Quality-adjusted life-year (QALY) is a metric that reflects the length and health-related quality of life. It is calculated using the number of years lived and the utility score of a particular state of health. It is a dimensionless number between 1 (perfect health) and 0 (death).

2.3 Treatment characteristics and strategies

Patients undergoing AS were monitored when they still had cancer, whereas patients undergoing ES were monitored after cancer removal. If patients in the AS group developed a primary tumor growth, they underwent hemithyroidectomy + isthmectomy + unilateral central neck dissection. If patients in the ES group developed a new tumor in the remaining glandular lobes after surgery, they underwent total thyroidectomy + unilateral central neck dissection. If patients in either group developed central (group VI) lymph node metastases or lateral lymph node metastases, they underwent total thyroidectomy + central neck dissection or lateral lymph node dissection, respectively. In contrast, patients who did not develop metastases in the lymph node or other areas were monitored indefinitely (Figure 2).

Next, patients in both groups were subjected to a 40-year follow-up, which commenced when the patients were 40 and was conducted twice a year. Patients in both groups were monitored annually with a surveillance regimen comprising physician office visits, thyroid function and blood tests, neck/supraclavicular lymph node ultrasonography examinations, laryngoscopy, and other related tests. The tests were conducted every 6 months. Chest computed tomography scans and computed tomography neck enhancement scans were conducted once a year.

Permanent complications from hemithyroidectomy included permanent vocal cord palsy and hypothyroidism. Short-term complications included temporary vocal cord palsy. Complications from total thyroidectomy included permanent hypothyroidism, hypoparathyroidism, and unilateral/bilateral recurrent laryngeal nerve injury.

2.4 Sensitivity and scenario analyses

A series of sensitivity analyses were performed to explore how the results varied across a plausible range. The results of a deterministic sensitivity analysis are presented as tornado figures (Figure 3). One-way sensitivity analyses were performed to assess the impact of individual parameters in the model. In the univariable sensitivity analysis, transformation probability, health utility value, and cost change range were set to ±10%, and the discount rate range was set to 1% to 5% (23) (Table 1; Supplementary Tables 2, 3).

Probabilistic sensitivity analyses were conducted to explore uncertainties around model inputs by varying them simultaneously. Probabilistic sensitivity analyses were performed using Monte Carlo simulations with 1,000 iterations with different distributions, where the transition probabilities and utilities followed a beta distribution pattern and the cost followed a normal distribution pattern. The ranges and distribution patterns of the parameters used in the sensitivity analyses are shown in Supplementary Table 3. The results of the probabilistic sensitivity analyses are presented as scatter plots and cost-effectiveness acceptability curves (Supplementary Figures 2, 3)

3 Model inputs

3.1 Probabilities

Estimates on the prevalence of complications from initial operations (total thyroidectomy and hemithyroidectomy) and reoperations (lymph node dissection) were derived from separate literature searches using specific terms like “recurrent laryngeal nerve,” “hypothyroidism,” “thyroidectomy,” “permanent complication,” and “temporary complication.” However, limited data are available on the transition probabilities from one stage to the next stage for Chinese patients with PTMC. Therefore, the probabilities of annual transition were inferred from published literature from other Asian countries, with a preference for data from countries with Chinese or associated populations (e.g., individuals from Hong Kong or Japan). If data for Asian

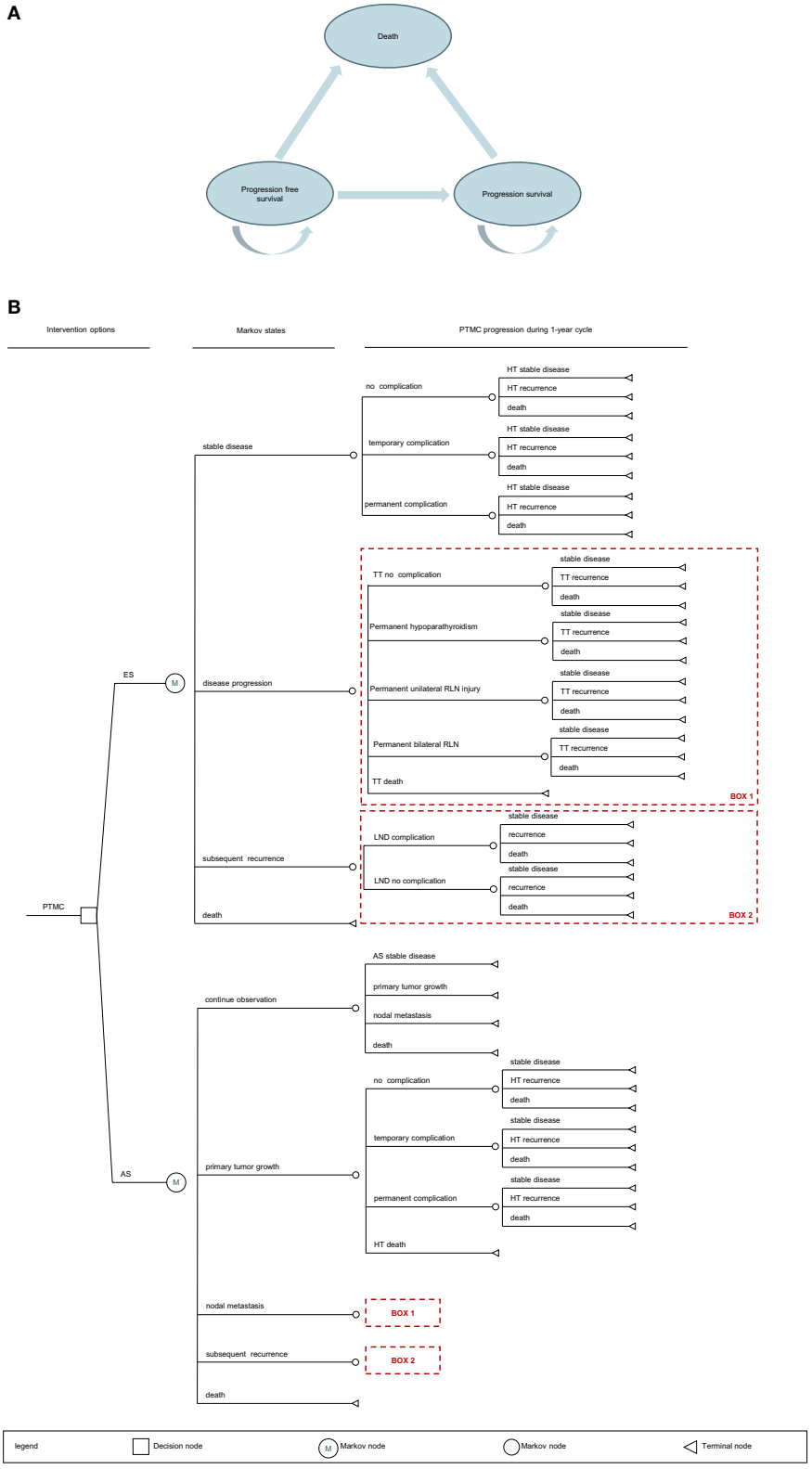

FIGURE 1
(A) Bubble plot. PTMC, papillary thyroid microcarcinoma; AS, active surveillance; ES, early surgery; HT, hemithyroidectomy; TT, total thyroidectomy; LND, lymph node dissection. **(B)** Markov model structure. PTMC, papillary thyroid microcarcinoma; AS, active surveillance; ES, early surgery; LND, lymph node dissection.

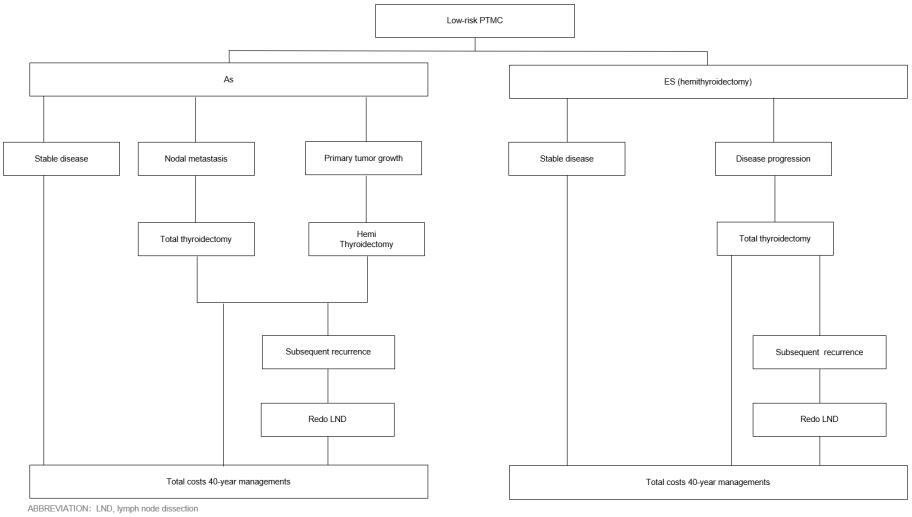

FIGURE 2
PTMC is based on ES and AS management processes. ICER, incremental cost-effectiveness ratio; AS, active surveillance; ES, early surgery; HT, hemithyroidectomy; TT, total thyroidectomy.

individuals were unavailable, we used probabilities obtained for individuals from other regions. In studies where multi-year incidence was reported instead of the 1-year PTMC incidence, the 1-year incidence was calculated using the formula $r = -\log(1-p)/t$, where r denotes the 1-year incidence and p represents the cumulative incidence over the length of the interval t. All transition probabilities from one health state to another took place in a 1-year cycle. For example, Miyauchi et al. (27) reported that the 10-year rates of primary tumor growth and regional lymph node metastases were 3.7% and 3.7%, respectively, for patients aged 40–59 years. These were converted to annual rates of 0.38% and 0.38%, respectively, for a Markov model with a 1-year cycle. Once the patients' ages were changed, their probabilities for developing nodular growth and regional lymph node metastases were altered. Other transformation probability values were the same in all age groups (Table 1).

3.2 Utilities

The health utility value inputs used to calculate QALYs were obtained from the published literature. Table 1 lists the utilities used in the model. Of note, the quality of life of patients undergoing AS for PTMC in a Chinese setting is unclear. Although PTMC is

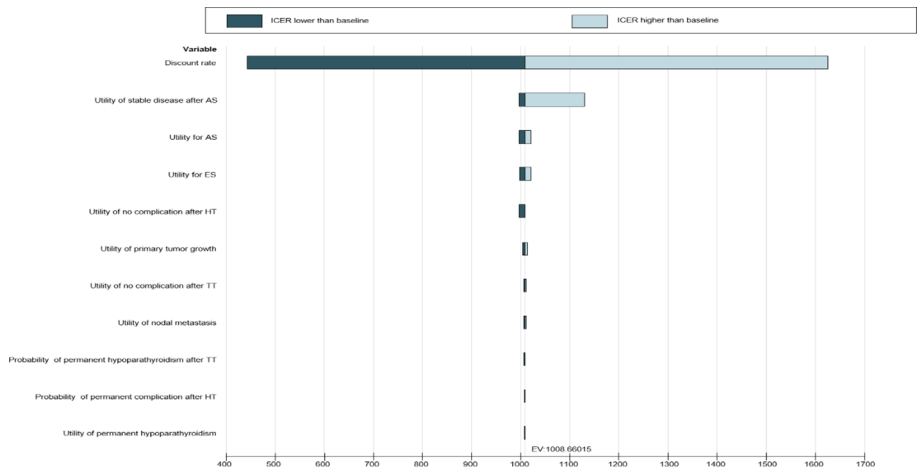

FIGURE 3
Tornado diagram–ICER–patients.

TABLE 1 Inputs of the Markov model.

Input	Value	Distribution	Analysis range	Mean	Standard deviation	Country	Reference
Probability							
Permanent complication from HT	0.015	Beta	0.014-0.017	0.016	0.0008	Hong Kong, America	17, 24
Temporary complication from HT	0.015	Beta	0.014-0.017	0.016	0.0008	America	15
Recurrence after HT	0.004	Beta	0.0036-0.0044	0.004	0.0002	America	25
Recurrence after TT	0.008	Beta	0.007-0.009	0.008	0.0005	America	15
Stable disease after HT	0.684	Beta	0.616-0.752	0.684	0.035	America	26
Permanent unilateral RLN injury after TT	0.015	Beta	0.014-0.017	0.016	0.0008	America	15
Hypoparathyroidism after TT	0.089	Beta	0.080-0.098	0.09	0.005	America	15
Permanent bilateral RLN injury after TT	0.003	Beta	0.0027-0.0033	0.003	0.0002	America	15
Death after HT	0.002	Beta	0.0018-0.0022	0.002	0.0001	America	15
Death after TT	0.002	Beta	0.0018-0.0022	0.002	0.0001	America	15
Complication from redo LND	0.32	Beta	0.288-0.352	0.32	0.16	Hong Kong, America	17, 24
Probability nodule growth							
20-29	0.22	–	–			Japan	27
30-39	0.084	–	–			Japan	27
40-49	0.0380	–	–			Japan	27
50-59	0.0240	–	–			Japan	27
60-69	0.0003	–	–			Japan	27
70-79	0.0006	–	–			Japan	27
Probability nodal metastasis							
20-29	0.165	–	–			Japan	27
30-39	0.061	–	–			Japan	27
40-49	0.0380	–	–			Japan	27
50-59	0.0240	–	–			Japan	27
60-69	0.0068	–	–			Japan	27
70-79	0.0036	–	–			Japan	27
Health utilities							
AS stable disease	0.99	Beta	0.89-1	0.99	0.05	America	28
No complication after HT	0.99	Beta	0.89-1	0.99	0.05	America	25
Permanent complication after HT	0.63	Beta	0.57-0.69	0.63	0.032	America	29
Temporary complication after HT	0.627	Beta	0.56-0.69	0.627	0.032	America	15
Permanent bilateral RLN injury after TT	0.21	Beta	0.19-0.23	0.21	0.01	America	30
Utilities of Permanent hypoparathyroidism after TT	0.778	Beta	0.7-0.86	0.778	0.039	America	30
Permanent unilateral RLN injury after TT	0.6729	Beta	0.57-0.69	0.6279	0.032	America	30
Redo LND	0.56	Beta	0.5-0.62	0.56	0.029	America	29
LND complication	0.41	Beta	0.37-0.45	0.41	0.02	America	29
No complication after TT	0.83	Beta	0.75-0.91	0.83	0.042	America	15

(Continued)

TABLE 1 Continued

Input	Value	Distribution	Analysis range	Mean	Standard deviation	Country	Reference
Active surveillance	0.11	Beta	0.1-0.12	0.11	0.006	America	25
Disease progression	0.54	Beta	0.49-0.59	0.54	0.028	America	25
Early surgery	0.74	Beta	0.67-0.81	0.74	0.038	America	29
Nodal metastasis	0.25	Beta	0.23-0.28	0.25	0.013	America	15
Primary tumor growth	0.54	Beta	0.49-0.59	0.54	0.028	America	29
Recurrence	0.54	Beta	0.49-0.59	0.54	0.028	America	29
Discount rate	0.03		0-0.05			China	
Start age	20						

HT, hemithyroidectomy; TT, total thyroidectomy; RLN, recurrent laryngeal nerve; LND, lymph node dissection.

usually asymptomatic, several patients associate the idea of "living with cancer" with some degree of anxiety and experience a progressive decline in the quality of life.

3.3 Costs

Direct medical cost information was collected from a tertiary Chinese general hospital (Supplementary Table 1). These costs are controlled by the Chinese Government and show limited variation between institutions positioned parallelly in the healthcare system. Based on the Chinese treatment plan, monitoring costs were calculated by referring to real-world patient treatment cost data and consulting with clinical experts. All figures are provided in Chinese yuan (¥) (Supplementary Table 2).

4 Analysis

In agreement with the China Guidelines for Pharmacoeconomic Evaluations, we conducted the analysis using data from China's healthcare system. According to these guidelines, we added a discount of 3% on future costs and benefits (23). We estimated the lifetime costs of two strategies and their effects in terms of QALYs (31). We calculated the incremental cost-effectiveness ratio, defined as the cost difference divided by the change in QALYs. The willingness-to-pay threshold (¥242,928) was estimated to be three times the gross domestic product per capita in China in 2021 (¥80,976). An incremental cost-effectiveness ratio of less than ¥242,928/QALY indicated that AS is cost-effective in China (32).

5 Results

5.1 Base case

In the base case scenario of a 40-year follow-up for both ES and AS (for patients diagnosed at 40 years of age), ES was costlier at ¥53,461, but it also had a greater effectiveness of 5.2 QALYs. In contrast, AS was more expensive at ¥74,198 and had an effectiveness of 25.8 QALYs. The effectiveness of treating patients with PTMC with AS was 20.6 QALYs, whereas the incremental cost per capita was ¥20,737. The corresponding incremental cost-effectiveness ratio was ¥1,009/QALY, which implied that for each additional QALY obtained, the incremental cost-effectiveness ratio was ¥1,009/

TABLE 2 Cost-effectiveness of PTMC at different ages.

Follow-up time period	Age at diagnosis	Strategy	Cost, ¥	ΔCost	Effectiveness, QALY	ΔQALY	CER	ICER, ¥ per QALY
60-year HT vs 60-year AS	20	ES	53,450	N/A	5.2	N/A	10,261	N/A
		AS	137,744	84,294	29.8	24.5	4,626	3,431
40-year HT vs 40-year AS	40	ES	53,461	N/A	5.2	N/A	10,281	N/A
		AS	74,198	20,737	25.8	20.6	2,879	1,009
20-year HT vs 20-year AS	60	ES	53,449	N/A	5.2	N/A	10,279	N/A
		AS	38127	-15321	16.9	11.6	2256	-1316

HT, hemithyroidectomy; AS, active surveillance; ES, early surgery; QALY, quality-adjusted life-year; CER, cost-effectiveness ratio; ICER, incremental cost-effectiveness ratio; N/A, not applicable.

QALY, which was lower than the willingness-to-pay threshold set for this study and lower than the per-capita gross domestic product in 2021. Therefore, even though AS was consistently more expensive than ES, it was also more effective (Supplementary Figure 1; Table 2).

In the base case scenario of 20 years of follow-up for patients diagnosed at 60 years or more, even though AS was consistently more expensive at ¥137,744, it also had a higher effectiveness at 29.8 QALYs. The incremental cost-effectiveness ratio for AS was ¥3,431/QALY, which was lower than the willingness-to-pay limit. Owing to the difference in the initial monitoring age of patients, the net costs would be positive at 20 years and 40 years when AS was adopted. Meanwhile, from 60 years onwards, the annual net costs would be negative. At 60 years, AS was less costly than ES, at ¥38,127, and was more effective, with 16.9 QALYs achieved in older patients. ES was more expensive at ¥53,449 and was associated with 5.2 QALYs. The resulting incremental cost-effectiveness ratio for AS was −¥1316/QALY, which made AS cost-effective. We concluded that AS remained cost-effective regardless of the age at which patients were initially monitored (Supplementary Figure 1; Table 2).

5.2 Sensitivity analysis

Supplemental Table 3 summarizes the results of the univariate sensitivity analysis for inputs that have limited effect on the incremental cost-effectiveness ratio in the reference case when the incremental cost-effectiveness ratio is lower than the threshold. These variables had the widest range in the incremental cost-effectiveness ratio when they varied from their greatest to their least range values. Two-way sensitivity analysis showed that varying the parameters did not substantially alter the cost-effectiveness of AS strategies (Figure 3).

Supplemental Figure 2 depicts the results of the probabilistic sensitivity analyses. One hundred percent of the scatters were present in the first quadrant and were less than three times the gross domestic product per capita. This indicated that ES did not show cost-effectiveness in any of the 1,000 iterations. Supplemental Figure 3 depicts the results of the cost-effectiveness acceptability curves. If the willingness-to-pay threshold increased to ¥24,292/QALY, AS would be cost-effective at a probability of 50%. If the willingness-to-pay threshold increased to ¥48,565.8/QALY, the probability of AS being cost-effective would increase to 100%.

6 Discussion

To our knowledge, this is the first study to examine the cost-effectiveness of AS in the management of incidental PTMC in China. In our reference case, AS was more cost-effective than ES throughout the lifetime of a patient with PTMC. However, findings from a prospective cohort study in Australia indicated that surgery may have a long-term economic advantage for younger Australian patients with PTMC (10); the study did not use a decision tree, Markov model, or utility score. Therefore, the validity of the model was low. This may explain the inconsistency with our findings. Additionally, one of the most frequently asked questions about AS is how long follow-up should continue and whether most of the processes are cost-effective over lifetime surveillance (33). Previous studies have estimated the cost-effectiveness based on 10-year or 20-year follow-ups, but patients with PTMC with a good prognosis usually survive for more than 20 or 30 years (17, 25). Therefore, even though our findings show that longer periods of follow-up may lead to higher costs for young patients, the incremental cost-effectiveness ratio (¥3,431/QALY) remains lower than the willingness-to-pay threshold over a 60-year follow-up period. Thus, we propose monitoring for patients with PTMC until the primary tumor size increases to 3 mm or more.

Particularly, when patients are selected for AS, their age should be considered. The findings of a multicenter cohort study in Korea indicated that the risk of an increase in the tumor volume in patients aged less than 45 years was twice greater than that of older patients who underwent AS for low-risk PTMC (34). Moreover, Lang et al. (17) showed in a subgroup analysis that patients aged less than 40 years prefer ES over AS. This suggests that an AS strategy according to age would be necessary in terms of not only cost but also effectiveness. Our research findings showed that AS always remained cost-effective at different initial monitoring ages. AS was found to be less cost-effective in younger patients and more cost-effective in patients with PTMC aged over 60 years. This result is concordant with the findings of a study conducted by Youssef et al. (35). The reason may be explained by the findings reported by Ito et al., showing that a greater age is associated with a lower risk of disease progression, tumor enlargement, and novel lymph node metastasis. In such cases, AS may limit the need for ES and thereby decrease surgical complications (36). Another reason may be that PTMC occurs at an earlier age than other cancers (37), and younger patients tend to exhibit a greater risk of disease progression than elderly patients (27).

When the patient was younger than 60 years, the AS strategy was more expensive, and the total cost increased more rapidly than that of ES. Therefore, when only cost was considered, AS was preferable for patients at an advanced age or with a reduced (20 years) life expectancy, whereas ES was preferable for younger and healthier patients (with a longer life expectancy). This could be attributed to the continuance of half-yearly examinations and the cumulative possibility of more costly "late" surgery and the associated complications over time. In a similar study, Kim et al. (38) reported that the initial cost of AS is estimated to be 5.6 times lower than that of lobectomy, whereas the 10-year cumulative costs of AS ($2,545) and lobectomy, regardless of LT4 ($3,045), are similar at a discount rate of 3%. However, in the long-term follow-up period, immediate surgery is estimated to be more economical than AS. The costs of the two management approaches are similar in Hong Kong (17), wherein adopting the non-surgical approach not only ensured cost-effectiveness in the initial 16 years but also ensured that the method remained cost-effective thereafter. This finding was substantially different from that in the United States and Japan, implying that the outcome

could be affected by each country's national health insurance coverage and the thyroid ultrasound interval during follow-up.

However, in terms of effectiveness, as measured by QALY gained, AS was more effective than ES, regardless of the length of observation. This was because the former resulted in fewer permanent procedure-related complications. In fact, in the sensitivity analysis, incremental QALYs were always positive, implying that AS was always more effective than ES, regardless of surgical complications, the rate of recurrence, or the discount rate. Furthermore, the range of the incremental cost-effectiveness ratio was far lesser than the willingness-to-pay threshold. Therefore, consistent with the findings from our initial hypothesis, AS is always a cost-saving or cost-effective strategy in PTMC management. In addition, patient preference and willingness to participate in AS may be difficult to predict, and some patients may abandon AS owing to anxiety associated with the burden of living with cancer. Patient compliance may be reduced during the years of follow-up. Additionally, the convenience of the clinical consultation environment is often not convincing for Chinese patients. Furthermore, the medical billing value for AS management cannot match that of a physician (usually ¥7 per outpatient visit), which makes follow-up during AS challenging. To promote the implementation of AS in China, it may be necessary for an authoritative thyroid surgeon to provide reasonable communication and follow-up and to tailor AS strategies for patients with low-risk PTMC. Additionally, reforming the medical billing system for diagnosis and treatment is essential to fully encourage doctors.

The considerably low cost of outpatient services in China made the differences between the costs of ES and AS seem obvious. The ES cost-effectiveness ratio is twofold greater than the AS cost-effectiveness ratio at 20 years of age. Among individuals and families, 21% of cancer patients met the WHO standard of poverty owing to illness (healthcare costs >30% of the household income) in China. For the government, treating a disease with an excellent prognosis may require the use of financial resources in large amounts owing to overdiagnosis and overtreatment. If approximately 50,000 patients are over-diagnosed with PTMC in China in 2022, with each patient aged 40 years or more and opting for AS, the government can save ¥10×10^8 (8). Notably, the actual circumstances may be more severe than this. Therefore, real-world investigations on the cost-effectiveness of PTMC based on data from the Chinese population and the incorporation of AS into the management plan for PTMC in China should be implemented as soon as possible.

The differences between the findings of this study and previous studies may be partly attributed to the differences in the treatment styles adopted in different countries. First, owing to insufficient radiofrequency ablation, the challenges of radiofrequency ablation after surgery have increased. The treatment method used in our study did not involve radiofrequency ablation; instead, we used methods recommended in the standard clinical process for PTMC treatment in China. Additional prospective studies and high-level evidence-based medical data for long-term follow-up observations are needed to demonstrate the safety and efficacy of AS in clinical settings. In addition, because PTMC is mostly an early tumor, the unilateral resection of the glandular lobe and isthmus is sufficient to remove malignant tissue. Thus, postoperative radioiodine remnant ablation is unnecessary. Current consensus also does not recommend radiofrequency ablation and radioiodine remnant ablation in low-risk patients. Second, because only a small number of patients with PTMC develop lymph node metastasis, lymph node dissection in zone VI on the side of the lesion should be performed during hemithyroidectomy + central neck dissection and total thyroidectomy + central neck dissection, with careful dissection and effective preservation of the parathyroid gland and recurrent laryngeal nerve (9). Owing to the rarity of lateral lymph node metastasis with PTMC, lateral lymph node dissection was not performed in the hemithyroidectomy + central neck dissection and total thyroidectomy + central neck dissection procedures. Third, in the United States, the follow-up interval for thyroid ultrasound is 1 year, whereas, in Hong Kong, it is 6 months. In this study, the frequency of follow-up was decided according to the diagnosis and treatment norms in the consensus. The follow-up interval in the two groups of patients with ES and AS was 6 months, which may have affected the results of the cost-effectiveness analysis and the generalizability of findings. The best imaging method for regular follow-up was thyroid ultrasound, which is usually performed by a specialized radiologist using standard specialization (17, 25). The use of ultrasound for measuring thyroid tumor size and lymph node metastases may be challenging. However, ultrasound and pathology have been used successfully to measure tumors only a few millimeters apart in length with precision. The accuracy of an ultrasound diagnosis depends on the experience of the technician, and considerable differences may exist between the results obtained by ultrasound technicians with different levels of expertise (11).

Our study had several limitations. First, insurance policies and medical costs vary in different countries, and the costs in this study are likely to differ from those in other countries. In our study, we only considered direct medical costs but excluded direct non-medical costs and indirect costs (unavailable). Hence, we could not determine cost-effectiveness from a societal perspective, which is the most appropriate and comprehensive perspective. Additionally, because the cost of adverse reactions was included in hospital costs in the base case scenario, we only considered the most important complications (such as hypothyroidism, hypoparathyroidism, and unilateral/bilateral recurrent laryngeal nerve injury) but not the total cost of adverse reactions. Undoubtedly, a part of the cost of adverse reactions may have been excluded. However, if these adverse effects are considered in the study, the difference in cost-effectiveness between AS and ES may be even greater, suggesting that AS is more cost-effective for PTMC. Furthermore, the cost-effectiveness of AS versus ES in the context of the Chinese healthcare system has not been considered in other studies. Therefore, the transformation probability and health utility refer to those in similar foreign studies. This also suggests the need for further prospective studies, including assessments of the QALY scores of patients with PTMC, to ensure that the right measures are taken while preparing patient-tailored treatment plans. Additionally, because these parameters change as patients age, fixed inputs, such as the probability of recurrence after HT and total thyroidectomy, were limitations of this study. However, the results of the sensitivity analysis showed that the value was robust over a relatively wide range of inputs. Finally, because this study was only based on a mathematical model, we should have considered

various local factors in China (e.g., surgical modality, regular monitoring programs, and the national healthcare system) when selecting the best management strategy for Chinese patients with PTMC. The results are applicable only to the Chinese healthcare system and should be interpreted cautiously in other countries.

7 Conclusions

AS was a more cost-effective strategy for patients with PTMC than ES and remained cost-effective at different initial monitoring ages. The findings of this study provide essential evidence for China's PTMC management policy. In China, the overtreatment of PTMC leads to unfavorable changes in the balance between patient benefits and the economy, which is an early warning sign for this emerging economy and other countries at similar stages of development.

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

ML, MZ, QQ, YA, and YL collected data. ML, MZ, QQ, and WY analyzed the data. ML, MZ and QQ wrote the manuscript. WY approved the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1166433/full#supplementary-material

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Development of a novel clinical support tool for active surveillance of low risk papillary thyroid cancer

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Background: Active surveillance (AS) is an alternative to surgery in select patients with very low risk papillary thyroid cancer (PTC). Many clinicians feel ill-equipped in selecting appropriate patients. We aimed to 1) Develop an evidence-based web delivered decision support tool to assist clinicians in identifying patients appropriate for AS; and 2) Evaluate the prevalence of patients suitable for AS in a tertiary high volume thyroid cancer centre.

Method: A REDCap web based clinical support tool was developed utilising evidence-based characteristics for AS suitability available to clinicals during initial assessment. A retrospective database was interrogated for patients who underwent hemithyroidectomy between 2012 – 2021 with final histopathology demonstrating PTC. Patients with PTCs>2cm, missing data, benign disease on surgical histopathology or incidental PTC were excluded.

Results: Between 2012 - 2021, 763 patients underwent hemithyroidectomy with final histopathology confirming PTC. Of these, 316 patients were excluded (missing data, incidental PTC, concomitant hyperparathyroidism were most common reasons for exclusion) and 114/447 remaining patients had a pre-operative fine needle aspirate (FNA) of Bethesda V or VI (high likelihood of malignancy). Using the tool, 59/114 (52%) met criteria for AS. The majority of patients were female (85% *vs* 15% male); median age 36 years (range 19 – 78). Following initial surgery, 10/59 patients had a completion thyroidectomy, with 4/10 demonstrating malignancy in contralateral lobe and eight of those patients undergoing I^{131} ablation. During a median follow up of over 3 years, 49/59 (83%) did not require further surgery or intervention with no patients developing recurrence. A subgroup analysis with second radiology assessment excluded 4/59 patients as meeting criteria for AS based on presence of ETE on preoperative ultrasound. None of these 4 patients had completion thyroidectomy.

Conclusion: Our clinical support tool identifies patients with PTC potentially suitable for AS which could be utilised during initial patient assessment. In a

retrospective cohort of patients who had hemithyroidectomy for PTC with a pre-operative FNA diagnosis of Bethesda V or VI, 55/114 (48%) patients may have been suitable for AS. Prospective validation studies are required for implementation of the tool in clinical practice.

KEYWORDS

active surveillance, low risk thyroid cancer, clinical support tool, papillary thyroid cancer, watchful waiting, de-escalation treatment

Introduction

Incidence of thyroid cancer has increased over past decades, largely attributed to improvement in imaging techniques and identification of incidental thyroid nodules (1). Most of these nodules will be benign; however, a small percentage will harbour malignancy (1). Papillary thyroid cancer (PTC) is the most common type of thyroid malignancy, with excellent prognosis and 5 year survival rates over 97% (2, 3). Despite increased diagnosis of incidental thyroid cancers, mortality rates remain largely unchanged and are overall low, suggesting over-diagnosis of low risk cancers (4). In addition to the psychological impact of a cancer diagnosis, there are financial implications on the health care industry for overdiagnosis which need to be considered. In South Korea the economic burden of thyroid cancer increased from $257 million in 2000 to $1.7 billion by 2010, with no change in thyroid cancer mortality (5). These figures are similarly seen in other countries and highlight the need to balance the risk and cost of treatment against the risk of disease progression (6).

Thyroid cancer can be classified into low, intermediate or high risk based on tumour stage, presence of lymphovascular invasion (LVI), extrathyroidal extension (ETE) and tumour location in relation to the capsule (7). Low risk papillary thyroid cancer are smaller tumours, typically less than 1cm (microcarcinoma), without LVI, ETE or presence of nodal or distant metastasis (8). Certain histological subtypes of papillary thyroid cancer or presence of molecular mutations such as *BRAF V600E* can behave more aggressively, and this information is typically identified in the final histopathology report (2).

The natural history of low risk PTC is indolent and slow growing, with low rates of locoregional or distant metastasis (9). Historically the management of these cancers has been surgical, with either total thyroidectomy or lobectomy. Following the updated American Thyroid Association (ATA) guidelines in 2015, hemithyroidectomy is now an accepted surgical option for low risk differentiated cancer (7). Potential surgical complications of hemithyroidectomy such as wound infection, vocal cord or recurrent laryngeal nerve palsy, temporary or permanent hypoparathyroidism, or hypothyroidism may still occur and while these rates are low in experienced centres, these should be considered in treatment decisions (10, 11).

Due to this epidemic of overdiagnosis, the role of active surveillance (AS) as an alternative to thyroid surgery in the management of low risk PTC has gained traction in the past decade and is included in the most recent ATA guidelines (7). Evidence for active surveillance dates back to 1993, through a prospective study in Kuma Hospital where patients with low risk PTC either underwent active surveillance or immediate surgery (12). Patients in the AS arm had low rates of tumour growth or development of nodal disease over 10 years. Those who had tumour growth or nodal disease underwent rescue surgery with no difference in mortality between groups (12). This safety data has now been replicated by many other centres (13–15). The bulk of studies for AS are in papillary microcarcinomas (PMC) however there is now evidence for inclusion of tumours up to 2cm. Sakai et al. included patients with tumours up to 2cm in their prospective active surveillance trial, demonstrating low rates of tumour growth and lymph node metastases in patients who underwent active surveillance, at 7% and 3% respectively (13). Even patients who underwent subsequent surgery from the AS arm did not demonstrate any disease recurrence in the follow up period, reflecting that the size criteria can be safely extended (13). This data has also been replicated by Ho et al. (2022) (14).

While there is robust evidence for AS for low risk PTC <2cm, not every patient with a low risk PTC should undergo AS. Characterising both the tumour and patient features that make patients ideal candidates has become clearer in the recent years. Tuttle et al. have described tumour and patient characteristics that help risk stratify patients into ideal, appropriate, or inappropriate for active surveillance (15). Presence of nodal or distant metastases, extrathyroidal extension (ETE) or lymphovascular invasion (LVI), or unfavourable tumour location (e.g. adjacent to a critical structure with potential for tumour invasion) exclude active surveillance as a suitable option (15). Lohia et al. recommended there should be >2mm of normal parenchyma between the thyroid nodule and the capsule to avoid potential tumour growth to nearby critical structures and this has been adopted by some centres (15).

Despite the continuously growing body of evidence for active surveillance, many clinicians do not feel comfortable in identifying appropriate patients (16). Wei et al. performed a scoping review to explore factors that influenced clinician and patients decision in selecting either active surveillance, hemi- or total thyroidectomy for low risk thyroid cancer (17). Patients were more likely to consider conservative therapy if provided with adequate information (17). Key barriers identified that prevented patients or physicians from selecting AS included lack of published surveillance protocol/ guidelines and physician comfortability in recommending AS to

patients (17, 18). This highlights the potential role for a clinical decision support tool to help clinicians identify if their patient is suitable for active surveillance, which to our knowledge is not available in the literature.

Methods

This study was performed at the Department of Diabetes and Endocrinology, the Department of Endocrine Surgery and the Department of Radiology at Royal North Shore Hospital. Ethics approval was by the local Northern Sydney Health District Ethics Committee (2020/ETH02787).

Clinical support tool development

A web based clinical support tool was developed and built on REDCap software (Supplementary Appendix 1). It utilised evidence based characteristics for AS suitability and generated a result indicating whether a patient was suitable for active surveillance. The tool was designed to apply the pre-operative ultrasound findings and patient data such as presence of local or distant metastasis, age, calcitonin level, comorbidities that would preclude them from surgery (15).

Patients were deemed suitable for active surveillance by the tool if they were aged ≥18 years, tumour size ≤2cm, no evidence of ETE or LVI on ultrasound, had no nodal or distant metastases and >2mm normal gland parenchyma (Figure 1). Tumour size was determined by the maximum tumour diameter and tumours up to 2cm were included.

Retrospective analysis

A retrospective thyroid cancer surgery database was interrogated for patients who underwent hemithyroidectomy between 2012-2021 with final histopathology demonstrating PTC. This database captures information about thyroid cancer surgery performed by endocrine surgeons at our institution and their affiliated operating sites.

Patients were excluded from analysis if; there was missing histopathology or pre-operative ultrasound data, the histopathology demonstrated a cancer other than PTC, the final histopathology

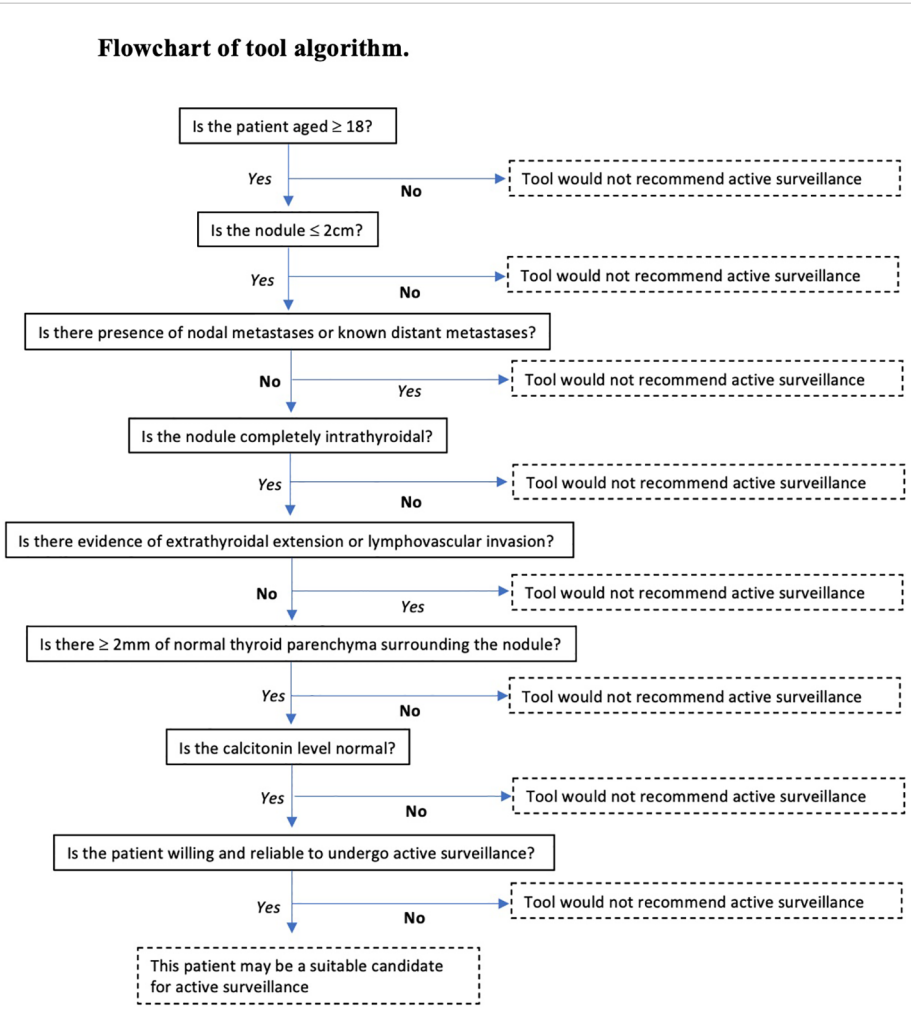

FIGURE 1
The flowchart outlines the algorithm of the clinical support tool.

showed an incidental PTC, they had hemithyroidectomy and contralateral nodulectomy, or if they had concomitant hyperparathyroidism and underwent parathyroidectomy.

Remaining patients were stratified according to pre-operative Bethesda category. Our cohort of interest were patients with a high risk of malignancy on biopsy or with a pre-operative biopsy result of either Bethesda V (BV, suspicious for malignancy) or Bethesda VI (BVI, malignancy). The tool was applied utilising pre-operative ultrasound reports and information from surgical database forms. Information was also extracted from surgical consultation letters, histopathology and imaging results, referral letters and electronic medical records where available. Given the retrospective nature of this study, we were unable to ascertain patient willingness to participate in active surveillance, however for the purpose of our prevalence assessment we assumed all patients would be amenable.

Subgroup analysis with sonologist

A sonologist and imaging trainee reviewed the ultrasound images in a subgroup of 22 patients to determine if AS features were easily identified on pre-operative ultrasound. The preoperative ultrasound images were unavailable for the remaining 37 patients deemed suitable for AS. The nodule of interest was assessed for presence of LVI, ETE, proximity to critical structures and presence of 2mm normal gland surrounding the nodule, and the tool was applied.

Statistical analysis

Statistics were performed in Microsoft Excel. Sample T tests were used to analyse differences in age, and median tumour size between the group had completion surgery versus those who had no completion surgery as well as between the subgroup who had evidence of malignancy on completion surgery versus those who had no malignancy. A p value of <0.05 was considered significant.

Results

Prevalence of AS suitability

During 2012 – 2021, 763 patients underwent hemithyroidectomy with final histopathology demonstrating PTC. Excluded from analysis were 316 patients (see Figure 2), leaving a cohort of 447 potentially eligible patients. We analysed the cohort of 447 patients by Bethesda category and found 114 patients (26%) had a pre-operative Bethesda result of BV or BVI. The tool was applied to the potentially suitable 114 patients with BV/BVI FNA and 59/114 (52%) were found to meet criteria for active surveillance. Of the 55/114 (48%) who were deemed unsuitable, all patients had nodule size >2cm. Assessment of all Bethesda results yielded: 353/447; 79% were unsuitable (>2cm tumour) and 95/447 (21%) potentially suitable for AS. 63% of those 95 patients were BV/VI reflecting that a majority would have a high risk of malignancy from the FNA.

Characteristics of patients suitable for AS

Most patients with BV/BVI results who were deemed suitable for active surveillance were young females, with median age 36 years (Table 1). Median size of nodules in this group was 10mm, with size ranging 4mm – 19mm and majority of patients had T1a tumours (tumour ≤1cm).

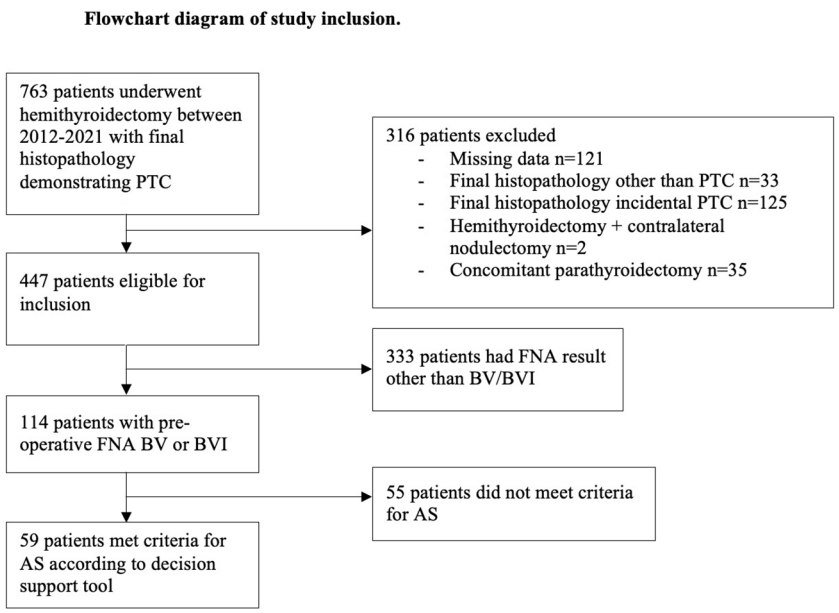

FIGURE 2
The PRISMA diagram outlines the selection process for our study. PTC, papillary thyroid cancer; FNA, fine needle aspirate; AS, active surveillance; BV, Bethesda V; BVI, Bethesda VI.

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TABLE 1 Baseline characteristics of patients suitable for active surveillance.

Characteristic	Value
Age range	19 – 78 years
Median age	36 years
Male	9/59 (15%)
Female	50/59 (85%)
Bethesda V	29 (49%)
Bethesda VI	30 (51%)
Nodule size range	4-19mm
Nodule size	T1aN0M0 – 37/59 (63%) T1bN0M0 – 22/59 (37%)
Median nodule size	10mm

TNM refers to American Joint Committee on Cancer (AJCC) staging tumour (T), nodes (N), metastes (M).

Patients who had further surgical intervention

We next analysed the characteristics of the cohort who went on to have further surgical intervention to ascertain if we could predict the need for further treatment. Most patients (49/59) did not require any further surgical or medical intervention for a median of 3.25 years (ranging from 0.2 – 7.35 years) follow up. After MDT and patient discussion, ten patients went on to have completion hemithyroidectomy. Evaluation of their initial histopathology demonstrated higher rates of lymphovascular invasion (80% versus 18%, p<0.01) and lymph node involvement (90% versus 27%, p<0.01) compared to patients who did not undergo completion hemithyroidectomy. There was a trend for patients who underwent completion surgery to be younger (median age 34 *vs.* 39 years, p=0.05) with bigger nodules (median nodule size 12mm *vs.* 10mm, p=0.05) however these were of borderline statistical significance. Rates of tumour multifocality or presence of ETE did not differ significantly between groups (Table 2).

Patients with malignancy on completion thyroidectomy

We next examined the characteristics of patients who were found to have malignancy in the contralateral lobe and this was seen in 4/10 (40%) of patients who underwent completion thyroidectomy. In these patients the average age was 36 years and median tumour size was 11mm. All four followed up with I-^{131} therapy, and four patients with benign histopathology in contralateral lobe also received I-^{131} (Table S1). No patients in the study cohort had evidence of disease recurrence at median 3.25 years follow up (0.2 – 7.35 years). Evaluation of the initial hemithyroidectomy histopathology of the four patients with contralateral lobe malignancy demonstrated that all had classical papillary architectures subtype. All four had lymph node involvement on initial histopathology (Table 3). Two of the four patients with malignancy in contralateral lobe had multifocal tumours in initial histopathology, compared with one out of the six patients with benign histopathology on completion. No patients with malignancy in contralateral lobe had an aggressive histological subtype (such as poorly differentiated features, tall cell variant, diffuse sclerosing etc).

TABLE 2 Comparison of patients who had no completion surgery vs. completion surgery.

Characteristic	No completion surgery (n=49)	Completion surgery (n=10)	P value
Age range	19 – 78	20 – 52	
Median age	39 years	34 years	0.05
Male Female	8/49 (16%) 41/49 (84%)	1/10 (10%) 9/10 (90%)	0.619
Pre-operative FNA Bethesda V Bethesda VI	 23/49 (47%) 26/49 (53%)	 6/10 (60%) 4/10 (40%)	
Median nodule size (range)	10mm (4-19)	12mm (8-18)	0.058
Tumour focality Unifocal Multifocal	 41/49 (84%) 8/49 (16%)	 7/10 (70%) 3/10 (30%)	0.319
Presence of ETE	9/49 (18%)	2/10 (20%)	0.905
Presence of LVI	9/49 (18%)	8/10 (80%)	<0.01
Presence of LN involvement	13/49 (27%)	9/10 (90%)	<0.01
BRAF V600E positivity	27/49 (55%)	8/10 (80%)	0.149

FNA, fine needle aspirate; ETE, extrathyroidal extension; LVI, lymphovascular invasion; LN, lymph node.

Histopathology from initial hemithyroidectomy showed similar lesion size between patients who had malignancy *vs.* benign pathology on completion hemithyroidectomy, with median size 11mm *vs.* 12mm respectively. Patients who went on to have malignancy in contralateral lobe were slightly younger, with median age 32.5 years versus 35.5 years. There were similar rates of ETE in each group however higher rates of LVI in the group who did not have evidence of malignancy in contralateral lobe (Table 3).

Imaging subgroup

To investigate the real world application of this tool, we conducted a subgroup analysis of patients in whom we were able to obtain their pre-operative ultrasound. Of the 59 patients who met criteria for active surveillance, the preoperative ultrasound images were available for 22 patients. None of the patients in this subgroup analysis were patients who had completion thyroidectomy. In 21/22 patients (95%), the sonologist was unable to identify >2mm of normal gland parenchyma between the nodule and the capsule in the saved images, identifying a real world limitation of this tool. Nodule size ranged from 5-14mm, with median nodule size of 9mm. ETE on pre-operative ultrasound

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TABLE 3 Characteristics of initial nodule size, histopathology, further treatment and recurrence in patients who had completion thyroidectomy.

Pt	Age	Sex	Nodule size	Initial histopathology	Completion Histopathology	I^{131} therapy	Recurrence
1	20	F	12mm	Unifocal 12mm tumour, classical, ETE, LVI, 11/17 LN involved, BRAF V600E positive	Benign	No	No
2	35	F	13mm	Unifocal 14mm tumour, classical, no LVI, ETE, 3/4 LN involved, tracheal invasion, BRAF V600E positive	0.4mm deposit in contralateral lobe, no LN	Yes – 224MBq	No
3	52	F	18mm	Unifocal 19mm tumour, classical, no LVI, no ETE, 0/6 LN involved, BRAF not done	Benign	Yes – 1.8 GBq	No
4	30	F	12mm	Unifocal 12mm tumour, classical, LVI, no ETE, 2/4 LN involved, BRAF V600E positive	Benign	Yes – 4 GBq	No
5	33	F	8mm	Unifocal 12mm tumour, classical, LVI, no ETE, 1/7 LN involved, BRAF V600E positive	Benign	Yes – 1 GBq	No
6	36	M	12mm	Multifocal 13mm tumour, classical, LVI, no ETE, 2/3 LN involved, BRAFV600E positive	2mm papillary thyroid cancer, no LN involved	Yes – 1 GBq	No
7	37	F	14mm	Unifocal 15mm tumour, mixed papillary/follicular, LVI, no ETE, 1/2 LN involved, BRAF V600E positive	Benign	Yes – 1 GBq	No
8	32	F	14mm	Multifocal 11mm tumour, mixed papillary/follicular, LVI, no ETE, 5/14 LN involved, BRAF V600E positive	Benign	No	No
9	32	F	11mm	Unifocal 8mm tumour, classical, no LVI, no ETE, 3/5 LN involved, BRAF V600E negative	Multifocal PTC, largest deposit 9mm, no LVI, no ETE, 3/5 LN involved	Yes – 4 GBq	No
10	41	F	9mm	Multifocal 9mm tumour, classical, LVI, no ETE, 1/4 LN involved, BRAF V600E positive	6mm PTC, no LN	Yes – 4 GBq	No

ETE, extrathyroidal extension; LVI, lymphovascular invasion; LN, lymph node; PTC, papillary thyroid cancer; MBq, megabecquerel; GBq, gigabecquerel.

was defined as extension of the nodule beyond the normal capsule line. The sonologists identified 4/22 patients with evidence of ETE which had not been identified on initial ultrasound report. Of these 4 patients, 1 was identified as definite ETE and 3 were deemed to have features suggestive of ETE, rendering them unsuitable for AS according to our protocol.

Discussion

In this retrospective analysis of patients treated by hemithyroidectomy for nodules with pre-operative cytology BV or BVI FNA, we have shown a substantial proportion of patients may have been suitable for active surveillance rather than surgery. The strongest evidence for active surveillance is for patients with high risk of malignancy (BV or BVI cytology) and as there is limited data for active surveillance in other Bethesda categories, we focused our analysis on patients with pre-operative FNA of BV or BVI. To our knowledge, there are no decision support tools available to help clinicians identify patients suitable for AS. We present a novel tool with real world application, outlining the experiences of using this tool in a cohort from a tertiary centre.

The demographic results for our appropriate AS cohort were unsurprising. Most patients in our suitable active surveillance cohort were young females which reflects known epidemiological data (19). A strength of this analysis is that it includes patients with tumours up to 2 cm. 37% of patients who were suitable for active surveillance had tumours >1 cm, and therefore would have been excluded without the extended 2 cm tumour diameter. There was no control group for comparison as very few patients in our cohort have AS thus far and the database only captures patients post surgery.

It is reasonable to propose that patients who required further surgery or medical intervention had progressive disease either distant metastases or further lymph node disease. While we do not know if these patients would have progressed without the initial surgery, our tool correctly identified characteristics meeting criteria for AS with the majority (49/59) having no further surgery. Patients who had completion surgery were generally younger, with lymph node involvement and presence of lymphovascular invasion on initial histopathology. In the group who did not have completion, we are unable to ascertain whether there was malignancy in the remaining lobe however it is reassuring that there has been no evidence of disease recurrence or development of nodal or distant metastases in this cohort (as evidenced by lack of further interventions and available progress imaging reports). Of the patients who had completion thyroidectomy, the majority (7/10 patients) had tumour size >1cm. No patients who had evidence of malignancy on completion thyroidectomy had evidence of disease recurrence on available follow up data, however we are unable to ascertain if any these

patients went on to have further treatment at another treatment location. Tumour size, multifocality, presence of ETE or LVI, presence lymph node involvement and BRAFV600E positivity did not predict malignancy in contralateral lobe. As hemithyroidectomy as a first line operation for low risk cancer gains further evidence, there is a trend away from completion thyroidectomy unless initial histopathology has concerning features. This study was not able to identify any factors in this cohort that predicted risk of malignancy in contralateral lobe, though a key limitation is the small sample size. The higher rates of LVI in the group who had completion thyroidectomy who did not have malignancy in contralateral lobe is of doubtful relevance and likely due to small sample size.

We next attempted to understand how the tool could work in clinical practice, and the feasibility of interpreting findings from the ultrasound report and original images and incorporating these into this tool. Our subgroup analysis with our imaging specialists highlighted some of the challenges of the real world application of this tool. Firstly, there is inter-observer variability in detecting the presence of ETE on ultrasound. Of the 4 patients in whom our imaging specialists deemed there to be ETE present, there was no comment on ETE in the original ultrasound report in three patients and in one patient it was documented as not present. Final histopathology for these patients demonstrated two of four had no ETE and two had presence of ETE, reflecting ultrasound and pathological disparity. The sonologist reviewing the subgroup analysis had 40 years of experience. We conclude that ETE is not feasible to be routinely analysed in a pre-operative ultrasound due to significant heterogeneity, and in further refinement of this tool we would focus more on tumour location in relation to critical structures. Several features we have used to assess feasibility for active surveillance on preoperative ultrasound (ETE, LVI, presence of 2 mm normal gland around nodule) are not routinely reported and a training and reporting template when looking at these ultrasounds may be beneficial.

Furthermore in our subgroup analysis, 21/22 patients did not have ≥2 mm between the nodule and capsule on the ultrasound. However, nodule position is inconsistently reported in ultrasound results, making it difficult to interpret from the report alone whether a nodule would meet this criteria and thus this represents a limitation to the application of this tool. Collaboration with our imaging colleagues would be necessary to develop more relevant reporting schema. Absence of 2mm of normal gland parenchyma does not preclude suitability for active surveillance, and future refinement of this tool would likely eliminate this specification and focus on more discriminatory markers such as tumour location in relation to critical structures and tumour volume kinetics (20).

This study has several key strengths. Firstly, it demonstrates a novel idea of creating a clinical decision support tool designed to empower clinicians in identifying patients who are potential candidates for active surveillance as a lack of physician knowledge has been identified as a barrier to AS implementation (19). Secondly, it demonstrates likely numbers of patients who would be potentially suitable for active surveillance based on the experience of a tertiary centre. In our cohort, 59/114 (52%) of patients with Bethesda V or VI were suitable for active surveillance based on our clinical support tool, with 55/114 (48%) deemed suitable following imaging review. The main factor that excluded patients from suitability for active surveillance was tumour size >2 cm.

Limitations of this study are that it is retrospective single centre data. There is selection bias given we analysed a low risk population by selecting patients who had been managed with hemithyroidectomy. Our follow up data was limited to information available through our thyroid cancer database and electronic medical record. We were unable to ascertain whether patients have gone on to receive further treatment through other centres, which may underestimate the risk of recurrence in our population. Thirdly, our imaging review of the 59 patients identified as being suitable for AS was incomplete as we only had access to the images of 22 patients. It is likely that further patients would have been excluded had we been able to review the entire cohort. Acknowledging this limitation, we have attempted to estimate prevalence of patients suitable for AS based on our available data.

Lastly, in the application of our clinical support tool, patient willingness to undertake active surveillance and engage with follow up is a key component of suitability. In applying our tool to this retrospective data, we were unable to ascertain patient willingness to undergo AS. Prospective studies are required to further evaluate the effectiveness of our clinical support tool in patients who are suitable for AS.

Conclusion

Our clinical decision support tool is a novel method of assisting clinicians in selecting patients that are suitable for active surveillance. Utilising this tool in our single centre cohort, almost half (48%) of patients with BV/BVI FNA and PTC on final histopathology would have been suitable for active surveillance. No patients had evidence of disease recurrence throughout our follow up period. Further prospective studies are required to evaluate this tool.

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 humans were approved by Northern Sydney Health District Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/ next of kin in accordance with the national legislation and institutional requirements.

Author contributions

EW: Methodology, data collection, formal analysis, writing -original draft, writing - reviewing and editing. BA: data analysis,

writing -reviewing and editing. GS: data analysis, writing - reviewing and editing. AG: methodology, writing - reviewing and editing. MG: Supervision, conceptualisation, formal analysis, methodology, writing - reviewing and editing. RC-B: supervision, conceptualisation, methodology, writing - reviewing and editing. 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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1160249/full#supplementary-material

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Socioeconomic disparities and regional environment are associated with cervical lymph node metastases in children and adolescents with differentiated thyroid cancer: developing a web-based predictive model

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Purpose: To establish an online predictive model for the prediction of cervical lymph node metastasis (CLNM) in children and adolescents with differentiated thyroid cancer (caDTC). And analyze the impact between socioeconomic disparities, regional environment and CLNM.

Methods: We retrospectively analyzed clinicopathological and sociodemographic data of caDTC from the Surveillance, Epidemiology, and End Results (SEER) database from 2000 to 2019. Risk factors for CLNM in caDTC were analyzed using univariate and multivariate logistic regression (LR). And use the extreme gradient boosting (XGBoost) algorithm and other commonly used ML algorithms to build CLNM prediction models. Model performance assessment and visualization were performed using the area under the receiver operating characteristic (AUROC) curve and SHapley Additive exPlanations (SHAP).

Results: In addition to common risk factors, our study found that median household income and living regional were strongly associated with CLNM. Whether in the training set or the validation set, among the ML models constructed based on these variables, the XGBoost model has the best predictive performance. After 10-fold cross-validation, the prediction performance of the model can reach the best, and its best AUROC value is 0.766 (95%CI: 0.745-0.786) in the training set, 0.736 (95%CI: 0.670-0.802) in the validation set, and 0.733 (95%CI: 0.683-0.783) in the test set. Based on this XGBoost model combined with SHAP method, we constructed a web-base predictive system.

Conclusion: The online prediction model based on the XGBoost algorithm can dynamically estimate the risk probability of CLNM in caDTC, so as to provide patients with personalized treatment advice.

KEYWORDS

cervical lymph node metastasis, children and adolescents with differentiated thyroid cancer, regional environment, socioeconomic disparities, web-based predictive model

Background

Thyroid cancer (TC) is the most common malignancy of the endocrine system, and its incidence is increasing worldwide (1, 2). Among them, differentiated thyroid carcinoma (DTC) is the most common subtype of TC, including papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), accounting for the vast majority of thyroid malignancies (3). DTC patients are prone to cervical lymph node metastasis (CLNM) and have a higher mortality rate (4). Studies have shown that the presence of cancerous nodules in the lymph node in PTC patients is a new indicator of distant metastasis and poor survival (5). However, considering that lymph node resection can cause laryngeal nerve palsy, hypocalcemia and other surgical complications, it is still controversial whether lymph node dissection should be performed in all patients (6).

Childhood and adolescent DTC (caDTC) is relatively uncommon in the population (7), but its incidence has also been increasing in recent years (8, 9). In a recent study, using data from the Surveillance, Epidemiology, and End Results (SEER) program, reported a gradual increase in the incidence of DTC in children from 1973 to 2006 [annual percentage change (APC), 1.11%; 95% CI, 0.56%-1.67%], of which, increased significantly from 2006 to 2013 (APC, 9.56%; 95%CI, 5.09%-14.22%) (8). Unfortunately, the clinical attention to caDTC is far from enough. The clinical, pathological and molecular features of caDTC differ from adult DTC. Therefore, treatment modalities that work for adults may not necessarily work for children or adolescents (10). Despite the favorable long-term prognosis of caDTC, the risk of recurrence increases significantly once CLNM develops.

TC has increased rapidly over the past 30 years, in addition to being associated with increased rates of diagnosis due to advances in imaging (11–13). Other possible causes are obesity (13)or environmental influences (12). In recent years, ethnicity and socioeconomic status have also been identified as potential reasons for the rapid rise in TC. A recent registry of review results from SEER showed different trends in TC incidence by race/ethnicity, with an increase in TC incidence among those with higher levels of care (2, 14). However, most of these studies focus on adult TC and prognosis, and there is still a lack of reports on the impact of socioeconomic disparities and regional environmental health on caDTC. At present, the research data on the occurrence of CLNM in caDTC is small and not comprehensive enough, and further studies with larger samples are needed for further confirmation.

The current methods for evaluating preoperative lymphatic status mainly include ultrasonography (US), computed tomography (CT) and invasive fine needle aspiration (FNA), but their sensitivity is limited (15, 16). There is currently a lack of more accurate methods to identify the risk of CLNM. Therefore, it is necessary to develop new diagnostic tools to assess the status of cervical lymph nodes. Machine learning (ML) is a new computer-based data analysis method that has been widely used in clinical medicine (17–19). By learning from datasets, ML can discover more interactions between variables and outcomes with better accuracy than traditional statistical methods. Since few studies have established ML prediction models based on caDTC. This study aimed to construct an online computational model for network visualization based on the extreme gradient boosting (XGBoost) algorithm and SHapley Additive exPlanations (SHAP) method to assess the risk of CLNM in caDTC patients. And analyze the impact between socioeconomic disparities, regional environment and CLNM.

Materials and methods

Data source and study population

We extracted data from the National Cancer Institute SEER database. The database collects and publishes relevant cancer outcomes for the U.S. population, including demographic characteristics, histological types, TNM stages, and treatment, etc. By registering online, we obtained an access license to the SEER database, access number 11573-Nov2021. We obtained patient information from SEER database through SEER*Stat 8.4.0.1 software (Data source: Incidence-SEER Research Plus Data, 17 Registries, Nov 2021 Sub (2000–2019)), and generated a list of patient information for analysis.

All study subjects met the following inclusion and exclusion criteria: ① Patients with a definite diagnosis of DTC. ② Children and adolescents aged ≤ 18 years old. The following subjects were excluded: ① Data were missing. ② DTC is not the only tumor (ie, combined with other tumors). Since the data used in this study were all publicly available, formal review by the relevant ethics committee was waived. Tumor histological confirmation was performed

according to histological codes and topography code C73 in the International Classification of Diseases for Oncology, Third Edition (ICD-O-3). The coding is based on the nomenclature adopted by the World Health Organization (WHO) International Histological Classification of Tumors (Blue Book). The codes for diagnosing PTC include 8050/3, 8260/3, 8340/3, 8341/3, 8342/3, 8343/3, 8344/3 and 8350/3; the codes for diagnosing FTC include 8330/3, 8331/3, 8332/3 and 8335/3. According to the latest definition and classification criteria of WHO (2017), hurthle cell carcinoma (HCC, 8290/3) is considered to have different biological characteristics from FTC, so in this research, we excluded HCC from the study outside.

Variable screening and classification

Based on extensive literature reading and expert knowledge, we extract the following features from the SEER database. Patients' socioeconomic demographic information, including age at diagnosis, sex, race, region where the tumor registry is located, median household income, and living conditions. We divided the age of diagnosis into two categories: ≤10 years and 10~18 years. Gender was divided into male and female. Race was divided into white, black and other. Among them, other including American Indian, Alaska Native, Asian or Pacific Islander. According to the region in which the patient's tumor was registered, it was divided into Pacific Coast (California, Hawaii and Seattle), Eastern (Connecticut、Georgia、Kentucky、Louisiana and New Jersey), Northern Plains (Iowa), and Southwest (New Mexico and Utah). According to the median household income, the family income of patients was divided into 4 categories, namely<5500$, 5500-6500$, 6500-7500$ and>7500$. This is based on 2019 inflation-adjusted U.S. dollars. According to the size of the population and the level of economic development, living conditions can be divided into the following four categories: living in a metropolitan area with a population of 1 million or more, living in a metropolitan area with a population of about 250,000 to 1 million, live in a metropolitan area with a population of less than 250,000, living in non-metropolitan areas.

Detailed variable definitions and classification criteria can be found in Supplementary Table 1.

Model construction and development

We used univariate and multivariate LR analysis to screen for risk factors for developing CLNM in caDTC patients. LR analysis is currently the gold standard for analyzing binary medical data. It can not only assess the risk factors for the occurrence of disease, but also provide the OR value and 95% confidence interval (CI) of the risk factors. We used the feature variables with $P<0.05$ in multivariate LR as modeling variables for ML. Use the XGBoost algorithm for predictive model building and compare with 7 other commonly used ML algorithms. Machine learning methods can be divided into generative methods and discriminant methods. Among the 8 algorithms selected, Gaussian and Bayesian models are generative methods, and the rest are discriminant methods, which makes the comparison benchmark method more comprehensive and the conclusion more convincing. In addition, through a large number of literature reading, we found that the above eight methods are the current common methods of chronic disease prediction model construction. The XGBoost algorithm belongs to the gradient tree boosting framework, which can evaluate a group of weak learners and aggregate them into a strong learner, which is a popular ML method. Model building uses 10-fold cross-validation, which is currently the technique of choice in computer science (20). All samples in the dataset were randomly divided into 10 subsets of similar size with approximately the same and mutually exclusive outcome events. In each round of training, 9 subsets are selected in turn to form the training set, and the remaining 1 subset form the validation set. Each ML model is trained and validated 10 times, each time using a different training and validation set, and the average of the 10 validation results is accepted as the final result.

We assessed model performance by area under the receiver operating characteristic curve (AUROC), sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV), and F1 score. F1 score is an index used to measure the accuracy of the binary classification model in statistics. It takes into account both the accuracy rate and recall rate of the classification model. If the accuracy rate and recall rate are both high, the model will obtain a higher F1 score. We take the ML algorithm with the largest AUROC value as the best model, and further optimize and visualize the best model. Model visualization is mainly done through the Shapley Additive exPlanations (SHAP). SHAP is a framework theory based on additive feature attribution method, first proposed by Lloyd Shapley in game theory (21). For an ensemble tree model, when doing a classification task, the model outputs a probability value. Therefore, SHAP actually attributes the output value to the shapely value of each feature, in other words, calculates the shapely value of each feature, and then measures the impact of the feature on the final output value. In order to determine the importance of each feature to the prediction model, we construct a summary plot based on the XGBoost model. The summary plot plots the SHAP values of all its features for each sample, which provides a better understanding of the overall pattern and allows the discovery of prediction outliers. Each row represents a feature, and the abscissa is the SHAP value.

Based on the XGBoost algorithm and SHAP method, we built a web-based application for identifying caDTC patients at risk for CLNM.

Statistical analysis

We divided patients into those without lymph node metastasis (LNM) and those with LNM based on whether or not they had CLNM. However, whether CLNM occurs or not is reported according to postoperative pathological findings.

Categorical variables were expressed as frequencies and percentages, and differences in distribution between the two groups were assessed using the chi-square test. We used univariate and multivariate LR analyses to identify risk factors for CLNM and

calculate their ORs and 95% Cis, and two-sided $P<0.05$ indicated that the difference was statistically significant. All Statistical analyses were performed using SPSS software (version 25.0 for windows; SPSS Inc., Chicago, IL, USA), R version 4.2.3 and python version 3.11.4. Acknowledgments:This work is supported by Extreme Smart Analysis platform (https://www.xsmartanalysis.com/).

Results

Baseline characteristics

A total of 2519 patients with caDTC aged ≤ 18 years were included in this study. There were 445 male subjects and 2074 female subjects, and a total of 1279 patients developed CLNM. In this cohort, 32.31% of patients had a median household income of more than 7,500$, 24.18% had a median household income of 6,500-7,500$, and 23.82% had a median household income of 5,500-6,500$, 19.69% of patients had a median household income of less than 5,500$. Most of these patients live in metropolitan areas with a population of 1 million (see Supplementary Table 2 for details).

Risk factors associated with cervical lymph node metastasis

The results of univariate LR analysis showed that in addition to living conditions, age, multifocality, race, sex, histological type, extrathyroidal extension (ETE), tumor size, region and median household income were closely related to the risk of CLNM in caDTC. We included risk factors with $P<0.05$ in the univariate LR analysis into the multivariate LR analysis (see Table 1 for details).

In the multivariate LR analysis (Table 1), there were significant statistical differences in all variables except sex (all $P<0.05$). The OR value of the adolescent group (10-18years) was lower than that of the children group (≤10years; OR=0.441, 95%CI: 0.297-0.654, $P<0.001$). The FTC group had a lower OR value compared with that of the PTC group (OR=0.015, 95%CI: 0.006-0.042, $P<0.001$).

TABLE 1 Univariate and multivariate LR analyses of CLNM.

Characteristics	Univariate Analysis		Multivariate Analysis	
	OR, 95%CI	*P* Value	OR, 95%CI	*P* Value
Age (years)				
≤10	1 [Reference]		1 [Reference]	
10-18	0.465 (0.332-0.651)	<0.001*	0.441 (0.297-0.654)	<0.001*
Race				
White	1 [Reference]		1 [Reference]	
Black	0.566 (0.379-0.845)	0.005*	0.617 (0.388-0.982)	0.042*
Other[a]	1.011 (0.788-1.298)	0.931	0.796 (0.597-1.060)	0.118
Sex				
Female	1 [Reference]		1 [Reference]	
Male	1.346 (1.095-1.655)	0.005*	1.224 (0.968-1.549)	0.092
Histological type				
PTC	1 [Reference]		1 [Reference]	
FTC	0.017 (0.006-0.046)	<0.001*	0.015 (0.006-0.042)	<0.001*
ETE				
Intrathyroidal extension/mETE[b]	1 [Reference]		1 [Reference]	
gETE	9.993 (5.725-17.441)	<0.001*	6.477 (3.571-11.747)	<0.001*
Tumor size (cm)				
≤1	1 [Reference]		1 [Reference]	
1-2	2.186 (1.711-2.793)	<0.001*	2.451 (1.894-3.172)	<0.001*
2-4	2.414 (1.906-3.057)	<0.001*	2.822 (2.190-3.637)	<0.001*
>4	3.389 (2.572-4.464)	<0.001*	4.152 (3.032-5.685)	<0.001*

(Continued)

TABLE 1 Continued

Characteristics	Univariate Analysis		Multivariate Analysis	
	OR, 95%CI	*P* Value	OR, 95%CI	*P* Value
Mulifocality				
Solitary tumor	1 [Reference]		1 [Reference]	
Multifocal tumor	3.052 (2.505-3.719)	<0.001*	2.477 (2.005-3.060)	<0.001*
Unknown	1.760 (1.452-2.132)	<0.001*	1.450 (1.167-1.802)	0.001*
Region[c]				
Pacific Coast	1 [Reference]		1 [Reference]	
East	0.611 (0.516-0.724)	<0.001*	0.662 (0.543-0.805)	<0.001*
Northern Plains	0.705 (0.474-1.049)	0.085	0.828 (0.530-1.293)	0.406
Southwest	0.978 (0.719-1.331)	0.888	1.063 (0.749-1.508)	0.734
Median household income				
<55,000$	1 [Reference]		1 [Reference]	
55,000-64,999$	1.351 (1.064-1.715)	0.013*	1.133 (0.861-1.491)	0.372
65,000-74,999$	1.202 (0.948-1.525)	0.129	1.105 (0.844-1.449)	0.467
≥75,000$	1.401 (1.119-1.753)	0.003*	1.331 (1.025-1.728)	0.032*
Living conditions				
Metropolitan areas (1 million or more)	1 [Reference]			
Metropolitan areas (250,000 to 1 million)	0.915 (0.753-1.112)	0.372		
Metropolitan areas (less than 250,000)	0.780 (0.585-1.041)	0.092		
Nonmetropolitan counties[d]	0.933 (0.712-1.222)	0.612		

[a]Other including American Indian, Alaska Native, Asian or Pacific Islander;
[b]Intrathyroidal extension/mETE including limited to the thyroid, or any tumor with minimal extrathyroid extension;
[c]Region: Pacific coast including California, Hawaii and Seattle; East including Connecticut、Georgia、Kentucky、Louisiana and New Jersey; Northern plains including Iowa; Southwest including New Mexico and Utah;
[d]Nonmetropolitan counties including nonmetropolitan adjacent to a metropolitan area and nonmetropolitan counties not adjacent to a metropolitan area.
CLNM, Cervical lymph node metastasis; PTC, Papillary thyroid carcinoma; FTC, Follicular thyroid carcinoma; ETE, Extrathyroid extension; mETE, Minimal extrathyroidal extension; gETE, Gross extrathyroidal extension.
The symbol * indicates $P < 0.05$.

Patients residing in the Eastern United States had a lower risk of developing cervical LNM than those residing in the Pacific Coast (OR=0.662, 95%CI: 0.543-0.805, *P*<0.001). Multifocality, larger tumors, and more extracapsular invasion of the thyroid are associated with a higher risk of developing CLNM. Among racial types, blacks had a reduced risk of developing CLNM compared with whites.

More importantly, we found that people with higher median household income (≥75,000$) had a higher risk of developing CLNM than those with lower median household income (35,000-54,999$) (OR=1.331, 95%CI: 1.025-1.728, *P*=0.032*). To further understand the reasons for this distributional difference, we analyzed the impact of region, ethnicity, and living conditions on caDTC household income (see Table 2 for details). We can see that patients with a median household income>7,500$ mainly live in metropolitan areas with a population of about 1 million. Among them, 98.16% of the population lives in the economically developed areas of the Pacific Coast and East. The proportions of minority (American Indian, Alaska Native, Asian or Pacific Islander) are relatively higher in these regions.

Machine learning model construction and screening

We used variables with *P*<0.05 in multivariate LR analysis for 8 different ML model constructions. The predictive model was constructed using a 10-fold cross-validation method. The parameter settings of each model are shown in Supplementary Table 3. Whether in the training set or the validation set, the XGBoost algorithm has the highest AUROC value and is the best predictive model (see Table 3 for details, Figures 1A, B). Its AUROC value is 0.762 (95%CI: 0.743-0.781) in the training set and 0.736 (95%CI: 0.676-0.797) in the validation set. Figure 1C shows calibration curves for different ML models. It can be

TABLE 2 Effect of region、race and living conditions on median household income in caDTC.

Category	Median household income				X^2	P
	<5500$	5500-6500$	6500-7500$	>7500$		
Living conditions						
Metropolitan areas (1 million or more)	45(9.073)	376(62.667)	429(70.443)	663(81.450)	1051.926	<0.001*
Metropolitan areas (250,000 to 1 million)	148(29.839)	113(18.833)	150(24.631)	138(16.953)		
Metropolitan areas (less than 250,000)	116(23.387)	76(12.667)	17(2.791)	3(0.369)		
Nonmetropolitan counties	187(37.702)	35(5.833)	13(2.135)	10(1.229)		
Region[a]						
Pacific Coast	127(25.605)	367(61.167)	316(51.888)	452(55.528)	290.07	<0.001*
East	273(55.040)	147(24.500)	196(32.184)	347(42.629)		
Northern Plains	37(7.460)	47(7.833)	21(3.448)	1(0.123)		
Southwest	59(11.895)	39(6.500)	76(12.479)	14(1.720)		
Race						
White	450(90.726)	507(84.500)	533(87.521)	643(78.993)	89.209	<0.001*
Black	30(6.048)	34(5.667)	22(3.612)	21(2.580)		
Other[b]	16(3.226)	59(9.833)	54(8.867)	150(18.428)		

[a]Region: Pacific coast including California, Hawaii and Seattle; East including Connecticut、Georgia、Kentucky、Louisiana and New Jersey; Northern plains including Iowa; Southwest including New Mexico and Utah.
[b]Other including Asian or Pacific Islander, American Indian/Alaska Native.
The symbol * indicates $P < 0.05$.

seen from the figure that the calibration curves of these ML models are in good agreement with the reference line, that is, the diagonal line, indicating that the predicted values estimated by these models are in the best agreement with the actual values. Figure 1D shows the decision curve analysis of each model, and the results show that the population estimated using these models has a good benefit.

Web-based application system development

We used the XGBoost algorithm with the best predictive performance for the visualization of the predictive model and the development of the web application system (Figure 2). We randomly selected 15% of the data in the total sample as the test set (N=377). The remaining samples were used as training set and validation set for 10-fold cross-validation. The model has AUC=0.766 (95%CI: 0.745-0.786) in the training set, AUC=0.736 (95%CI: 0.670-0.802) in the validation set, and AUC=0.733 (95%CI: 0.683-0.783) in the test set. Figure 2F shows SHAP based on XGBoost algorithm.

This application has a friendly interface (Figure 3). The user only needs to enter 8 variables in the web browser, and the specific values of these variables are selected from the drop-down list. Once the doctor submits the data, the app provides probabilistic information about the risk of LNM and provides advice. The web link of the web application system is https://www.xsmartanalysis.com/model/predict/?mid=1171&symbol=3rOeoUn1660006924zB6.

Discussion

In response to the current elevated incidence of TC, adding reliable and easy-to-use CLNM prediction models will allow clinicians and intelligent systems to better make evidence-based patient care decisions. This study has developed and internally validated a web-based model to predict the risk of developing CLNM in patients with caDTC. The study population was obtained from patients registered with multiple cancer centers in the US SEER database. In this study, we constructed an online computational model of risk for the caDTC network visualization, using the XGBoost algorithm and the SHAP method, based on a large cohort (2,519 cases). The model consisted of eight main risk factors, including age, race, histological type, tumor size, ETE, multiple foci, area of residence, and median household income. Compared with other large studies, in addition to having similar CLNM-related risk factors in this study, we found that socioeconomic factors and regional environment had a significant effect on the performance of caDTC patients. To the best of our knowledge, this is a larger comprehensive study and intelligent model construction on caDTC patients and socioeconomic differences.

A growing number of studies have shown that socioeconomic status has a critical impact on TC prognosis. A study from Almubarak et al (22)found that living in a rural area (P<0.001) and low literacy (P=0.021) were significantly associated with the onset of late stage TC. This study suggests that even in a country like

TABLE 3 Comparison of prediction performance of 8 different machine learning models.

ML	AUROC (95%CI)	Accuracy (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	F1-score (95%CI)
Training set							
XGBoost*	0.762 (0.743-0.781)	0.686 (0.683-0.688)	0.695 (0.661-0.729)	0.678 (0.645-0.712)	0.692 (0.680-0.705)	0.683 (0.670-0.696)	0.692 (0.681-0.703)
SVM	0.748 (0.728-0.768)	0.683 (0.681-0.686)	0.759 (0.749-0.769)	0.608 (0.597-0.619)	0.666 (0.663-0.670)	0.707 (0.702-0.713)	0.710 (0.706-0.713)
RF	0.727 (0.707-0.748)	0.659 (0.656-0.662)	0.657 (0.617-0.698)	0.663 (0.626-0.700)	0.673 (0.663-0.682)	0.649 (0.637-0.661)	0.663 (0.646-0.679)
MLP	0.748 (0.728-0.768)	0.674 (0.669-0.678)	0.654 (0.627-0.681)	0.697 (0.676-0.717)	0.690 (0.683-0.696)	0.661 (0.650-0.672)	0.670 (0.658-0.682)
LR	0.718 (0.697-0.738)	0.649 (0.647-0.651)	0.741 (0.696-0.785)	0.557 (0.512-0.601)	0.635 (0.624-0.645)	0.677 (0.659-0.695)	0.681 (0.667-0.695)
KNN	0.748 (0.728-0.767)	0.669 (0.666-0.672)	0.653 (0.646-0.660)	0.710 (0.701-0.718)	0.731 (0.724-0.738)	0.631 (0.626-0.636)	0.690 (0.686-0.693)
GNB	0.726 (0.706-0.746)	0.663 (0.660-0.666)	0.706 (0.691-0.721)	0.623 (0.609-0.636)	0.659 (0.655-0.663)	0.669 (0.662-0.676)	0.682 (0.676-0.687)
AdaBoost	0.737 (0.717-0.757)	0.665 (0.663-0.666)	0.665 (0.642-0.688)	0.670 (0.649-0.691)	0.679 (0.677-0.682)	0.651 (0.647-0.655)	0.672 (0.661-0.682)
Validation set							
XGBoost*	0.736 (0.676-0.797)	0.667 (0.652-0.682)	0.709 (0.641-0.777)	0.660 (0.588-0.731)	0.674 (0.654-0.694)	0.663 (0.648-0.679)	0.686 (0.655-0.717)
SVM	0.719 (0.656-0.781)	0.660 (0.643-0.677)	0.738 (0.665-0.811)	0.623 (0.550-0.695)	0.646 (0.631-0.661)	0.682 (0.657-0.706)	0.685 (0.648-0.721)
RF	0.724 (0.663-0.786)	0.651 (0.636-0.666)	0.678 (0.586-0.769)	0.658 (0.572-0.744)	0.666 (0.644-0.687)	0.641 (0.624-0.659)	0.664 (0.623-0.706)
MLP	0.731 (0.671-0.792)	0.653 (0.629-0.678)	0.708 (0.629-0.788)	0.655 (0.566-0.744)	0.665 (0.643-0.687)	0.643 (0.616-0.670)	0.680 (0.641-0.720)
LR	0.715 (0.652-0.777)	0.630 (0.606-0.655)	0.769 (0.690-0.849)	0.565 (0.473-0.656)	0.616 (0.596-0.637)	0.658 (0.621-0.695)	0.680 (0.644-0.717)
KNN	0.684 (0.619-0.748)	0.626 (0.602-0.651)	0.675 (0.572-0.779)	0.610 (0.492-0.729)	0.678 (0.642-0.714)	0.596 (0.577-0.615)	0.664 (0.611-0.716)
GNB	0.720 (0.658-0.782)	0.661 (0.638-0.684)	0.777 (0.718-0.835)	0.576 (0.501-0.651)	0.656 (0.637-0.675)	0.667 (0.639-0.696)	0.708 (0.685-0.731)
AdaBoost	0.735 (0.674-0.795)	0.663 (0.650-0.675)	0.650 (0.588-0.712)	0.707 (0.655-0.759)	0.678 (0.663-0.692)	0.649 (0.637-0.661)	0.660 (0.624-0.697)

*indicated that the best performance of the ML classifier in the training set and validation sets was XGBoost (Ranked according to AUC).
ML, Machine learning; XGBoost, Extreme gradient boosting; RF, Random forest; AdaBoost, Adaptive boosting; GNB, Gaussian naive bayes; MLP, Multilayer perceptron; SVM, Support vector machine; KNN, k-nearest neighbor; LR, Logistic regression; AUROC, Area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, Negative predictive value; CI, Confidence interval.

Saudi Arabia, which has a strong government-funded healthcare system, there are health disparities among people struggling with TC, with patients in the low socioeconomic status group often being diagnosed at a more advanced stage at the time of presentation. Swegal et al (23)also showed that in addition to the effect on incidence, low socioeconomic status was associated with poorer survival in highly differentiated thyroid cancer (WDTC). A study by Harari et al (24)also confirmed that TC patients of black and low socioeconomic status had worse outcomes. The effect of socioeconomic status on the incidence and prognosis of WDTC has been well studied. However, the relationship between socioeconomic level and CLNM has not been described. Our findings seem to lead to the opposite conclusion that patients with caDTC with higher household income (≥75,000$) are more likely to develop CLNM. to further understand the reasons for this distributional difference, we analyzed the effects of region, race and living conditions on household income in caDTC. We could see that patients with median household income >75,000$ lived mainly in metropolitan areas with a population of about 1 million. Of this group, 98.16% live in economically developed areas such as the Pacific Coast and East. The percentage of minorities (American Indian, Alaska Native, Asian or Pacific Islander) was relatively higher in these areas. The reasons for these factors may be related to the following factors: ① Higher socioeconomic status is more likely

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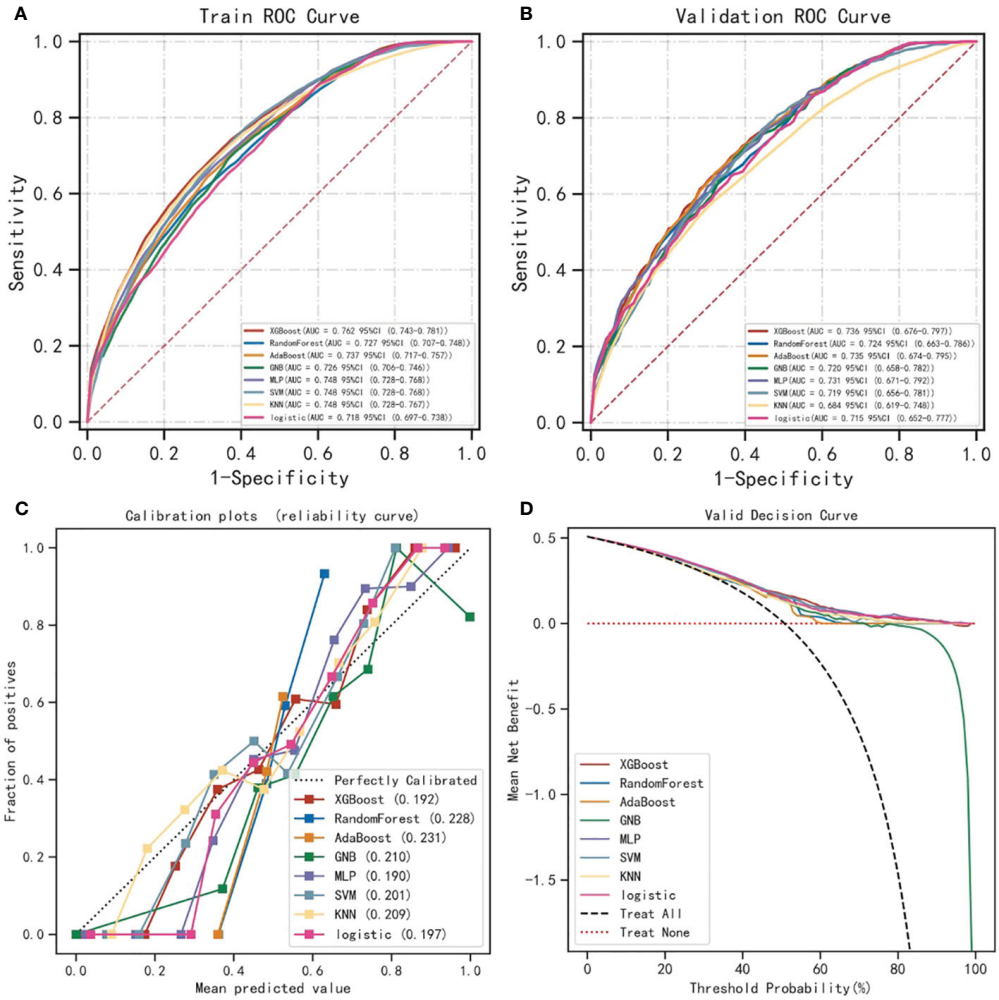

FIGURE 1
Performance comparison of XGBoost algorithm and other ML algorithms in predicting lymph node metastasis. **(A, B)** compare the performance of 8 different ML algorithms in building predictive models. Whether in the training set or the validation set, the XGBoost algorithm has the highest AUROC value and is the best predictive model. **(C)** is the calibration curve of the prediction model. The abscissa of the graph is the predicted probability, that is, the probability of the event occurrence is predicted by the prediction model. The ordinate is the actual probability, that is, the patient's actual event rate. Each colored solid line is a fitted line, representing the actual value corresponding to the predicted value. If the predicted value is equal to the actual value, the solid line exactly coincides with the diagonal dashed line. **(D)** shows the decision curve analysis of each model. The results of the study showed that the population using the ML model benefited well. ML, Machine learning; XGBoost, Extreme gradient boosting; AUROC, Area under the receiver operating characteristic.

to have access to good medical resources and relatively higher levels of CLNM detection. ② Our study also found that patients with higher average income levels tend to live closer to large cities. These places, in turn, may have more environmental pollution compared to remote rural areas, and TC is a class of diseases related to environmental health. This may also explain to some extent why the prevalence of TC is much higher in areas with developed economic levels compared to less developed areas. ③ In recent years, it has also been shown that obesity and high body mass index (BMI) are strongly associated with the occurrence of TC (25, 26), and obesity is also more prevalent in areas with high economic income. This may, to some extent, explain the greater risk of CLNM among those with median income>75,000$ in this study. The multifactorial LR analysis in this study showed a lower risk of CLNM in blacks compared to whites, which may also be related to the higher economic level and BMI possessed by whites. This is one of the limitations of this study as we were unable to assess the BMI of the patients in this study.

With the continuous development of science and technology, ML has brought great convenience to our life. However, there is limited research using ML algorithms to predict the occurrence of cervical LNM in TC, especially in the application to patients with caDTC. ML uses algorithms to process and reveal patterns in large amounts of data to develop predictive models that automatically improve over time. A growing number of studies are predicting the risk of disease by constructing Web-based models. Such Web-based health care content has become a primary source of health information for patients without direct guidance from health care providers (27).

In this study, we combined the XGBoost algorithm and SHAP method to construct an online computational model of the network

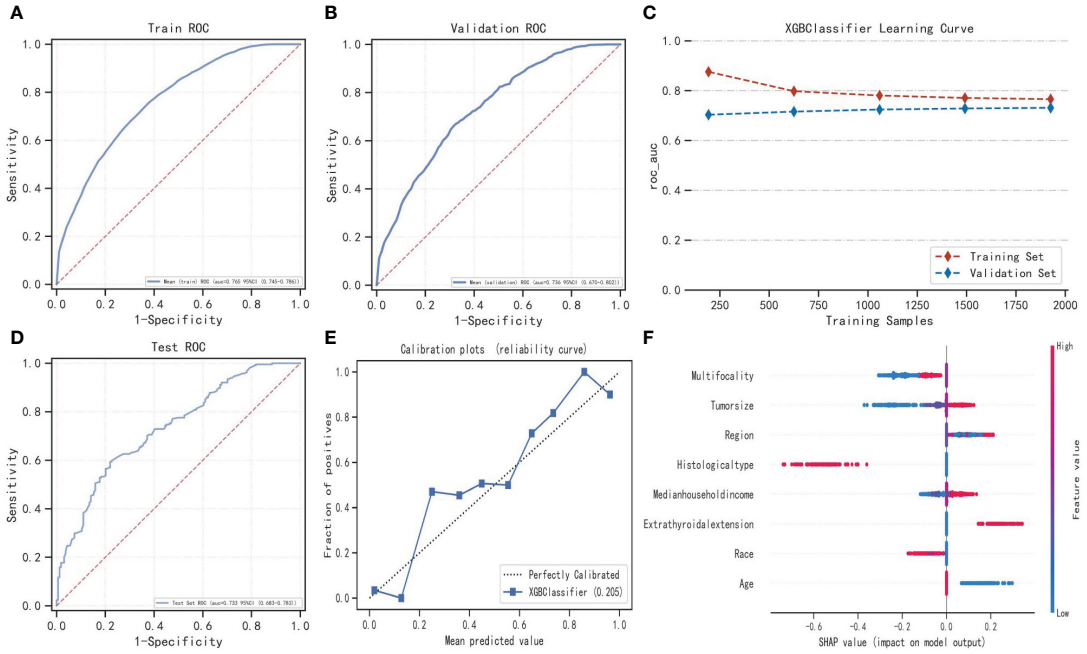

FIGURE 2
Construction of LNM prediction model based on XGBoost algorithm and SHAP method. **(A–D)** show the optimization process of the XGBoost model based on 10-fold cross-validation. When the learning curves of the training set and validation set converge **(C)**, the prediction performance of the XGBoost model is the best at this time. **(E)** is the calibration curve based on the XGBoost model. **(F)** shows SHAP based on the XGBoost model. XGBoost, Extreme gradient boosting; ROC, Receiver operating characteristic; SHAP, Shapley Additive exPlanations.

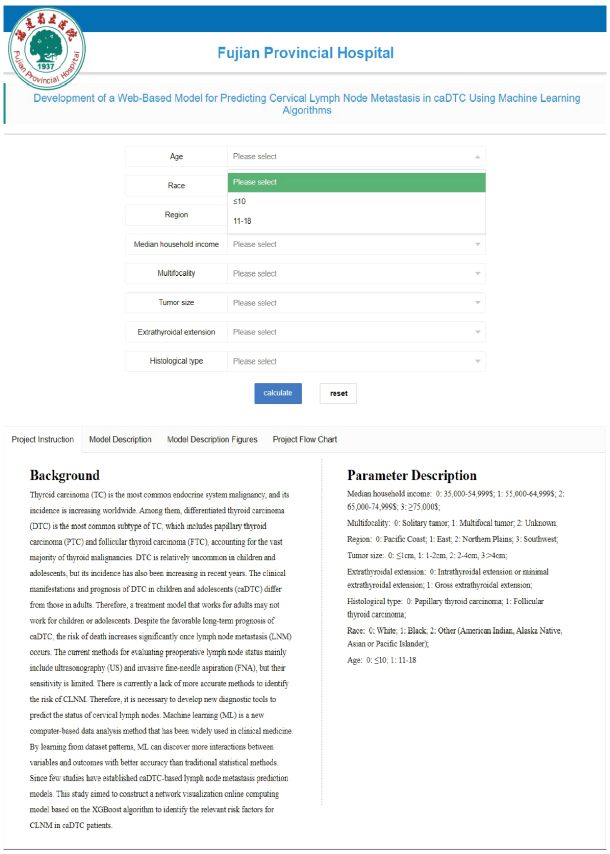

FIGURE 3
Web-based visual risk prediction model page for CLNM in caDTC.

for the occurrence of CLNM in caDTC. By integrating eight risk factors, we can estimate the risk of developing CLNM in a particular caDTC patient and provide treatment advice. By entering personalized information, patients can share this information with family members, and this approach can reduce the anxiety level of patients' families to some extent. It is well known that different patients require different healthcare content and that it changes over time. In addition, another advantage of personalized healthcare content is its potential to improve health-related choices, i.e., shared responsibility for clinical decisions with patients (shared decision making) (28). Such Web-based personalized predictive models and decision support have been shown to improve patient knowledge and facilitate decisions that are more aligned with patient values and preferences (29, 30).

This study has the following advantages: ① This is the first study of ML algorithm-based models to predict the occurrence of CLNM in patients with caDTC. It shows that these ML-based models have good predictive performance and clinical application, among which the XGBoost model has the best predictive performance. ② We constructed an online application model for the risk of developing CLNM in patients with caDTC based on the XGBoost algorithm and the SHAP method, which compensates for the unexplainable limitations of ML black-box operation. ③ There are few studies on caDTC. In addition to the known risk factors, we found that socioeconomic factors and regional environment have a significant impact on the performance of patients with caDTC. In addition there are some limitations of this study: ① This study is a retrospective cohort study and data bias cannot be avoided. It needs to be validated in future studies through rigorously designed prospective studies. ② In a study of this size, false positive results may occur by statistical chance alone. However, our shorter confidence intervals imply a higher precision and accuracy in estimating the effect. ③ Our regression analysis of risk factors that may explain CLNM also has some limitations, such as obesity, family history, exposure to radiation/carcinogens, and lifestyle. Unfortunately, we did not obtain this information from the registry, so we were unable to assess whether these factors had an impact on the adjusted analysis.

Conclusions

An online prediction model constructed based on the XGBoost algorithm can dynamically estimate the risk probability of developing CLNM in caDTC thus providing personalized treatment advice for patients. Socioeconomic disparities and regional environment have a significant impact on the performance and outcome of caDTC.

Data availability statement

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

Ethics statement

Since the data used in this study were all publicly available, formal review by the relevant ethics committee was waived. The studies were conducted in accordance with the local legislation and institutional requirements.

Author contributions

GC has 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 and GC. Acquisition, analysis, or interpretation of data: JWW, YL, and YM. Drafting of the manuscript: YM, WL, JY, JPW, and GC. Critical revision of the manuscript for important intellectual content: YM, JWW, and YL. Statistical analysis: YM, JWW, and YL. Supervision: GC. 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/fendo.2024.1128711/full#supplementary-material

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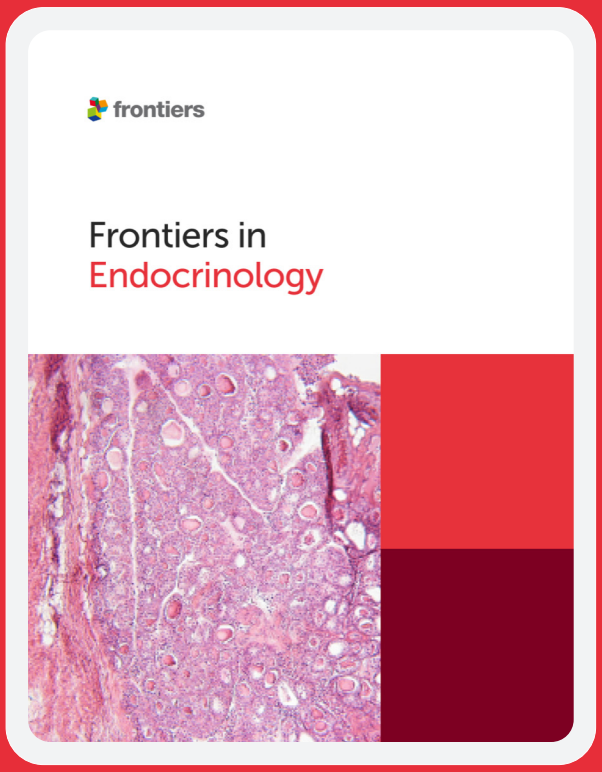

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