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Nomogram to predict the prognostic value of tumor deposits for patients with papillary thyroid carcinoma

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Abstract

Background: Tumor deposits (TDs), nodules in the peritumoral adipose tissue with no architectural residue of lymph node, have previously been described in colorectal adenocarcinomas with poor prognosis. However, the significance of TD has not been fully investigated in patients with papillary thyroid carcinoma (PTC).

Method: We retrospectively enrolled 541 patients undergoing surgery between 2015 and 2021. The patients were classified into two groups according to TD status (TD vs non-TD), and the clinicopathologic characteristics and disease-free survival (DFS) were compared. Associations of TD presence with other clinicopathologic factors were evaluated by logistic regression analysis. Univariate and multivariate Cox regression analyses were performed to determine the primary cohort's prognostic factors for DFS. A nomogram was constructed for clinicians as a quantitative tool for estimating DFS.

Result: In our cohort, TD were identified in 16.1% of patients and had higher rate of aggressive features, including microscopic and gross extrathyroidal extension, invasion of the recurrent laryngeal nerve and esophagus, prevertebral fascia involvement or encasement of the carotid artery/internal jugular vein, extranodal extension, advanced clinical stage, tumor recurrence and distant metastasis (all $P < 0.05$). Univariate and multivariate Cox regression analyses confirmed TD as an independent prognostic factor for DFS, with a 2.501-fold increased risk of recurrence ($P < 0.001$). The nomogram, incorporating TD and other significant factors, demonstrated good discrimination and calibration (C-index = 0.79).

Conclusion: The presence of TD was significantly associated with poor prognosis in PTC patients. TD showed promising efficacy as a potential prognostic indicator for PTC patients.

Keywords: tumor deposits; extranodal extension; papillary thyroid carcinoma; lymph node metastasis; prognosis

Introduction

Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy, with a favorable prognosis in most patients due to its indolent clinical course and a 10-year survival rate over 90% (1). However, approximately 10% of PTC patients exhibit aggressive

clinicopathological features, leading to higher rates of disease recurrence and mortality (2, 3). Clinical risk stratification and decision-making frameworks are important and should be constantly updated with the developing acquaintance of PTC.

Lymph node metastasis (LNM) as a prognostic factor has been plagued by controversy (4). In the American Thyroid Association (ATA) 2009 risk stratification system for tumor recurrence (5), the presence of LNM was classified as intermediate risk. In the revised ATA risk stratification published in 2015 (6), less than five pathologic N₁ micrometastases (smaller than 0.2 cm in largest dimension) was classified as low risk; more than five pathologic N₁ with all involved lymph nodes <3 cm in largest dimension or with any metastatic lymph node ≥3 cm in largest dimension was considered as intermediate risk or high risk, respectively. Extranodal extension (ENE), which represents an extension of lymph node metastatic cells through the nodal capsule into the perinodal fatty tissue, was also considered as high-risk factor (6). Recently, it was reported that lymph node yielded and positive lymph node ratios in the initial central neck dissection were associated with recurrent or persistent disease in PTC patients undergoing reoperations (7, 8).

Tumor deposits (TDs) were first described by Gabriel *et al.* in the 1930s in the context of colorectal cancers (9), and associated with poorer prognosis. More recently, in the 7th edition of the American Joint Committee on Cancer (AJCC) staging system (10), TDs were defined as irregular, discrete tumor masses in addition to the primary tumor that is located within the lymph drainage area of the primary tumor, without residual LN tissues. TDs were recognized as a separate entity to LNM. TD-positive tumors are classified as the new pN1c category in the absence of LNM, and consequently are considered stage III colon cancer (10). The negative prognostic value of TD has been explored in several types of malignancies, including colorectal cancer (11, 12), gastric cancer (13), esophageal cancer (14) and head and neck squamous cell carcinoma (15). Li *et al.* initially reported TD was associated with Level V LNM in PTC patients (16). Recently, Durak *et al.* reported the presence of TDs in thyroid carcinoma and suggested their association with more aggressive tumor behavior (17). However, the role of TD in PTC requires further exploration.

Aim of this study is to evaluate the prevalence of TDs in a large cohort of PTC patients, analyze their association with clinicopathological features and assess their prognostic significance. By doing so, we hope to provide new insights into risk stratification and treatment strategies for PTC.

Materials and methods

Patients

This study was reported according to the STROBE guideline. Patients diagnosed with PTC and treated between January 2015 and December 2021 at Nanfang Hospital, Southern Medical University, were

retrospectively identified. The study protocol was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT06051838). The inclusion criteria comprised: i) patients histopathologically diagnosed as PTC, with sections stored in the pathology department; ii) patients underwent lobectomy or total thyroidectomy and central lymph node dissection with or without lateral neck dissection; and iii) patients with detailed follow-up information after surgery. The exclusion criteria were as follows: i) patients with previous history of neck irradiation or other systematic cancers; and ii) patients who died of unrelated diseases. Among the 576 PTC cases that were included, 35 cases were excluded (Supplementary Fig. 1 (see section on [Supplementary materials](#) given at the end of the article)).

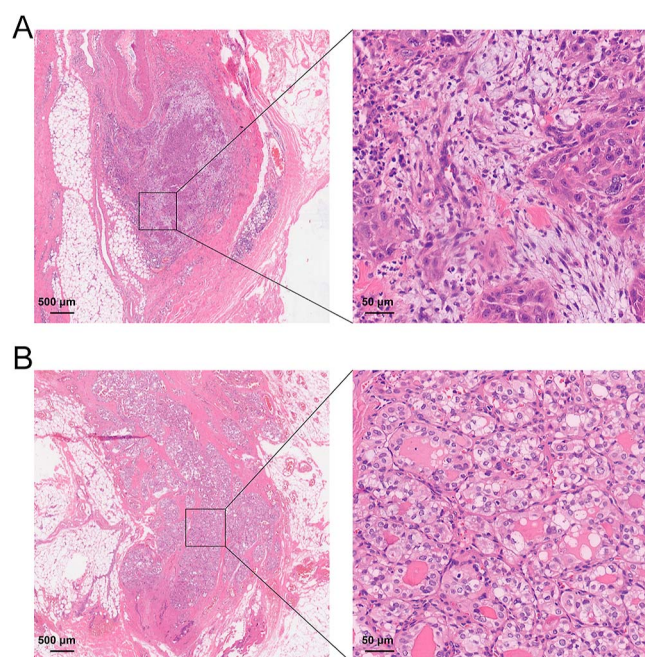
Treatment

Patients who were highly suspicious with PTC by preoperative imaging (ultrasonography (US) and computed tomography (CT)) or confirmed by fine-needle aspiration (FNA) underwent unilateral lobectomy or total thyroidectomy according to the Chinese guidelines (16). All patients underwent prophylactic central neck dissection regardless of whether LNM was reported by preoperative examination. Lateral neck dissection (Level II-Vb) was performed only in patients with pathologically proved lateral neck metastasis or suspicious imaging evidence (such as scattered calcification indicated by US) for therapeutic purposes (18). For patients who met the criteria of radioiodine (RAI) therapy, including gross invasion, metastatic lymph nodes >5 and distant metastasis, RAI was administrated. Postoperative TSH suppression therapy was established for patients according to the 2015 ATA risk stratification (6).

Pathology and definition of TD

The sections of specimens were reviewed by the pathologists at the department of pathology, and relevant information was documented in the pathology report. The pathology report and operation records were reviewed by two physicians independently, and the clinicopathological features, including age, sex, tumor size, multifocality, macro- or micro-extrathyroidal extension, ENE, invasion to recurrent laryngeal nerve/trachea/laryngeal/esophagus, invasion to prevertebral fascia or the carotid artery/internal jugular vein and TD status were retrieved from reports and then recorded. The 8th edition AJCC staging system was used to describe the pathological characteristics of PTC.

TD was identified as any tumor mass separate from the primary tumor, either circumscribed or with irregular contours, devoid of lymph node, vascular or neural architecture (Fig. 1). TD was distinguished from lymph node metastases by the absence of residual lymphoid tissue and their irregular growth patterns.

**Figure 1**

Representative presentation of TD in PTC. (A) TD with irregular contours without any residual lymph node structures. (B) TD wrapped by fibrous and adipose tissues. Scale bars, 500 µm (left panels) and 50 µm (right panels).

In our cohort, the size of TDs ranged from 0.2 to 3 cm. A minority of TDs can be seen by naked eye (Supplementary Fig. 2).

In contrast, ENE was defined as the extension of lymph node metastatic cells beyond the lymph node capsule into the perinodal adipose tissue or surrounding structures (Supplementary Fig. 3). ENE was assessed histologically by identifying tumor cells infiltrating beyond the lymph node capsule, often accompanied by stromal reaction or desmoplasia in the surrounding tissues. A comparative table (Supplementary Table 1) was provided to help distinguish between TDs and ENE.

Follow-up

All patients received examination every 3–6 months during the 2 years after surgery, and then at least once a year thereafter. Follow-up data were obtained from outpatient and inpatient admission records or phone interviews with the patients or their family members. The last follow-up was conducted by February 28, 2023.

In this study, the disease-free survival (DFS) was set as the primary outcome, of which the endpoint was defined as tumor locoregional recurrence, distant metastasis and disease-specific death. A patient was identified as deceased, if the cause of death was confirmed by the death certificate or the hospitalization record to identify disease-specific death. Patients were defined as disease

recurrence, if recurrent or persistent PTC was observed according to standard biochemical, cytological, histological and radiographical criteria. The tumor locoregional recurrence was defined as combined biochemical (serum thyroglobulin) and structural recurrences. The structural tumor recurrence was defined as confirmed physical tumor existence of the recurrent or persistent disease, not just positive serum thyroglobulin. The distant metastasis was confirmed by radioactive iodine scan, ^{18}F FDG-PET scan or pathological examination.

Statistical analysis

Continuous variables were summarized as the mean (standard deviation, SD) or median (interquartile range, IQR), and they were compared using Student's *t* test and Wilcoxon test (or the Mann–Whitney *H* test, if appropriate). Frequencies with percentages were compared using the χ^2 test or Fisher exact probability test. Time from surgery to recurrence, metastasis or death was calculated as DFS. DFS curves were plotted using the Kaplan–Meier method and compared between the presence of TDs group and the absence of TDs group using the log-rank test. Cox proportional hazards model was performed to estimate the hazard ratio (HR), with a 95% CI for factors potentially associated with DFS. Then, factors with *P*-value <0.05 in univariable analysis were further examined in the multivariable Cox regression model, and the concordance index (C index) model was reported. Finally, a nomogram based on the multivariable Cox regression analysis was constructed for the 2-year and 3-year DFS. All statistical analyses were conducted with the R software (version 4.2.1). Differences with a two-sided *P* < 0.05 were considered statistically significant.

Results

Study population

This study enrolled 541 PTC patients, whose clinicopathological characteristics are shown in Table 1. Our cohort included 186 (34.4%) males and 355 (65.6%) females, with a median (IQR) age of 40 (31 to 50) and 13.3% older than 55 years old. The median follow-up time after surgery was 35 months (IQR, 27–42 months).

Of the 541 patients, 89 (16.5%) received postoperative RAI therapy. The proportion of patients who underwent RAI in the TD-positive cohort was higher than that in the non-TD cohort. 87 (16.1%) patients were observed with TD (TD-positive cohort), while 454 patients (83.9%) were not observed with TD (non-TD cohort). Compared with the non-TD cohort, the proportion of female was smaller (51.7 vs 68.3%; *P* = 0.009) and the proportion of age over 55 years was higher (20.7 vs 11.9%, *P* = 0.041) in the TD-positive cohort. No differences in body mass index (BMI) (23.03 vs 23.22 kg/m², *P* = 0.221) was observed between the TD and non-TD cohort (Table 1).

Table 1 Comparison of the clinicopathological characteristics between patients with TDs and non-TDs. Data are presented as the median (IQR), mean $\pm$ SD or as *n* (%). Statistically significant *P* values are present in bold.

Variable	Total	Non-TD	TD	<i>P</i> value
Total cases, <i>n</i>	541	454	87	
Age at diagnosis, years	40.00 (31.00–50.00)	40.00 (31.00–49.00)	42.00 (31.00–53.00)	0.182
≥55 years	72 (13.3)	54 (11.9)	18 (20.7)	0.041
Sex				
Male	186 (34.4)	144 (31.7)	42 (48.3)	0.004
Female	355 (65.6)	310 (68.3)	45 (51.7)	
BMI	23.03 (20.58–25.39)	23.03 (20.51–25.25)	23.22 (20.98–26.36)	0.221
Multifocality				<0.001
No	361 (66.7)	322 (70.9)	39 (44.8)	
Yes	180 (33.3)	132 (29.1)	48 (55.2)	
Tumor size, cm	1.28 $\pm$ 0.88	1.20 $\pm$ 0.83	1.72 $\pm$ 0.98	<0.001
TD size, cm	---	---	0.91 $\pm$ 0.49	---
I131 treatment				<0.001
No	452 (83.5)	419 (92.3)	33 (37.9)	
Yes	89 (16.5)	35 (7.7)	54 (62.1)	
Microscopic ETE	47 (8.7)	25 (5.5)	22 (25.3)	<0.001
Gross ETE invading strap muscle	53 (9.8)	27 (5.9)	26 (29.9)	<0.001
Recurrent laryngeal nerve invasion	52 (9.6)	21 (4.6)	31 (35.6)	<0.001
Trachea/laryngeal invasion	3 (0.6)	2 (0.4)	1 (1.1)	0.978
Esophagus invasion	8 (1.5)	4 (0.9)	4 (4.6)	0.032
PVF invasion*	9 (1.7)	4 (0.9)	5 (5.7)	0.005
ENE	27 (7.0)	9 (2.0)	18 (20.7)	<0.001
Lymphovascular invasion	38 (6.6)	16 (3.5)	22 (25.3)	<0.001
T Stage				<0.001
I–II	450 (83.2)	409 (90.1)	41 (47.1)	
III–IV	91 (16.8)	45 (9.9)	46 (52.9)	
N stage				<0.001
N0	194 (35.9)	189 (41.6)	5 (5.7)	
N1a	217 (40.1)	197 (43.4)	20 (23.0)	
N1b	130 (24.0)	68 (15.0)	62 (71.3)	
Clinical stage				<0.001
I	488 (90.2)	423 (93.2)	65 (74.7)	
II	41 (7.6)	28 (6.2)	13 (14.9)	
III	8 (1.5)	2 (0.4)	6 (6.9)	
IV	4 (0.7)	1 (0.2)	3 (3.4)	
Recurrence	43 (7.9)	30 (6.6)	13 (14.9)	0.016
Distant metastasis	9 (1.7)	4 (0.9)	5 (5.2)	0.005

ETE, extrathyroidal extension; PVF, prevertebral fascia; TDs, tumor deposits; ENE, extranodal extension.

*Prevertebral fascia invasion or encasing the carotid artery/internal jugular vein.

Clinicopathological characteristics

In our cohort, the size of TDs ranged from 0.2 to 3 cm, with a mean size of 0.91 cm (SD 0.49). Regarding the location of TDs, they were identified in the central neck compartment (Level VI) in 81.4% of patients, consistent with the known lymphatic drainage pattern of PTC. In addition, TDs were found in the lateral neck compartments (Levels II–V) in 41.5% of patients, typically in cases with more advanced disease. In 4% of patients, TDs were located outside traditional lymph node chains, such as within the carotid sheath. Notably, some patients exhibited TDs in multiple regions, including both central and lateral compartments and non-lymphatic areas. Compared with patients in the non-TD cohort, patients in the TD cohort were more commonly accompanied by multifocality (55.2 vs 29.1%, $P < 0.001$). The mean diameter of

primary tumor was larger in the TD cohort (1.72 ± 0.98 vs 1.20 ± 0.83 , $P < 0.001$). Microscopic extrathyroidal extension and gross extrathyroidal extension invading strap muscle were present more frequently in the TD cohort (25.3 vs 5.5%, $P < 0.001$; 29.9 vs 5.9%, $P < 0.001$). Invasion to recurrent laryngeal nerve (35.6% vs 4.6%, $P < 0.001$), esophagus (4.6 vs 0.9%, $P < 0.001$), prevertebral fascia invasion or encasing the carotid artery/internal jugular vein (5.7 vs 0.9%, $P < 0.001$), ENE (20.7 vs 2.0%, $P < 0.001$) and lymphovascular invasion (LVI, 25.3 vs 3.5%, $P < 0.001$) were highly likely to happen in the TD cohort compared to the non-TD cohort. There was a higher rate of more advanced T stage, N stage and clinical stage among patients with TD than those without TD ($P < 0.001$). TD was also associated with higher rate of tumor recurrence (14.9 vs 6.6%, $P = 0.016$) and distant metastasis (5.2 vs 0.9%, $P = 0.005$) than patients without TD.

Disease-free survival

Kaplan–Meier estimated curves for the presence or absence of TD are displayed in Fig. 2. DFS rates at 12, 24 and 36 months were 96.7, 94.0 and 92.6% for cases without TD. In cases with TD, the 12-, 24- and 36-month DFS were 92.5, 85.8 and 69.2%. Significant decrease in was observed in DFS in patients with TD when compared with those without TD ($P < 0.0001$).

On univariable Cox regression analysis (Table 2), age at diagnosis, sex, BMI and multifocality were not associated with DFS. Larger tumor size (HR = 1.977, 95% CI = 1.628–2.401), gross extrathyroidal extension invading strap muscle (HR = 4.961, 95% CI = 2.714–9.068), recurrent laryngeal nerve invasion (HR = 4.481, 95% CI = 2.381–8.431), prevertebral fascia invasion or encasing the carotid artery/internal jugular vein (HR = 9.548, 95% CI = 3.406–26.764) and advanced N1 stage (HR = 1.660, 95% CI = 1.158–2.381) were significantly associated with worse DFS. Presence of ENE (HR = 3.222, 95% CI = 1.278–8.125) or LVI (HR = 4.656, 95% CI = 2.315–9.364) conferred a risk of worse DFS compared with those who does not present. Presence of TD (HR = 4.071, 95% CI = 2.289–7.242) showed statistically significant link to worse DFS. The multivariate Cox regression analysis indicated that the larger tumor size (HR = 1.804, 95% CI = 1.482–2.196), presence of LVI (HR = 2.498, 95% CI = 1.168–5.344) and presence of TD (HR = 2.501, 95% CI = 1.353–4.624) remained associated with worse DFS (Table 2).

Based on the multivariable model, a nomogram prediction model was generated by incorporating the

aforementioned three independent predictors (tumor size, LVI and TD) to provide clinician with a quantitative tool for estimating DFS (Fig. 3A). The C index for the model was 0.79 (95% CI = 0.73–0.85). The AUROC values for the 2-year and 3-year DFS of the nomogram were 0.840 (0.779–0.900) and 0.830 (0.762–0.899), respectively (Fig. 3B). The calibration curves showed that the nomogram-predicted DFS probability was in good agreement with the actual observations (Fig. 3C).

Discussion

TD is believed to reflect tumor aggressiveness. However, the pathogenesis of TD is still unelucidated, and several hypotheses have been raised. TD may originate from tumor cells directly released into extranodal spaces, overgrowth of cancer cells after lymphovascular or perineural infiltration or after LN involvement via ENE or total LN replacement (13, 19). In melanomas, TD may indicate ‘in-transit metastases’ nodules of cancer cells in intermediate locations before they reach the nearest LN (20). For colorectal cancer, TD is a site-specific prognostic factor correlating with vascular invasion, perineural invasion and lymphatic invasion (10, 21).

The definition of ENE, which refers to cancer cells infiltrating the extranodal adipose tissue beyond the capsule of the lymph node, can often be confusing to the TD (22). The major difference between TD and ENE is that TD has no histological evidence of residual lymph node or identifiable vascular or neural structures (23). Some experts have suggested that ENE and TD share similar characteristics in terms of originality and tumor biology, leading to the hypothesis that TD could potentially be an advanced stage of ENE (24). In the 8th AJCC manual for head and neck squamous cell carcinoma, TD should be recorded as a positive lymph node with ENE (23). However, many physicians hold an opposite opinion, since the pathogenesis of ENE and TDs in tumors may not be the same (25). For colorectal cancer, TD has been in the tumor node metastasis (TNM) staging system since 5th edition (26), while ENE was only recommended as a registry data collection variable in the latest 8th edition (23). For gastric cancer, in the latest 8th edition, both TD and ENE were recommended as registry data collection variables (23). These evidences suggest that there are significant differences between these two variables in tumor staging and prognosis. Given the facts that PTCs are prone to spread through lymphatic pathways, and the absence of TD as a collection variable in both the 8th AJCC manual on thyroid cancer and the 2015 ATA guideline, we wondered if this particular pathological change would exist in PTCs; if the answer is yes, we further wanted to demonstrate TD's characteristics and clinical implications in PTC patients.

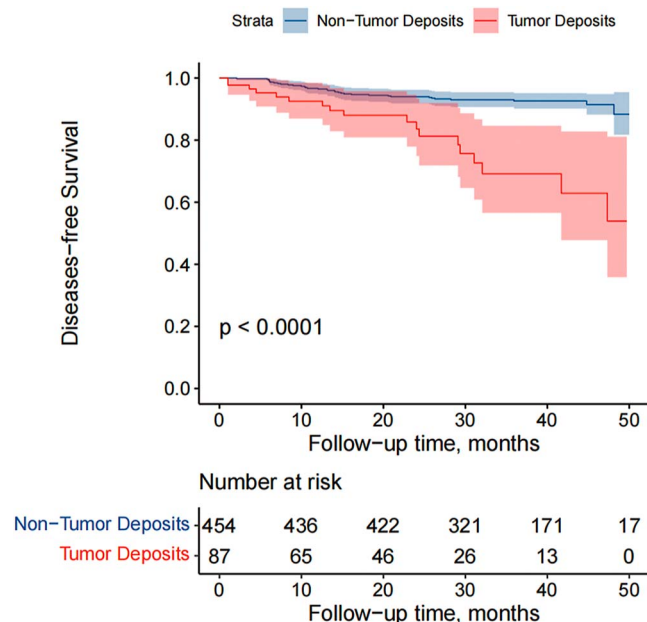


Figure 2

Kaplan–Meier survival curves showing DFS according to the effect of TDs on patients with PTC.

Table 2 Univariate and multivariate Cox regression analysis for disease-free survival of patients with PTC.

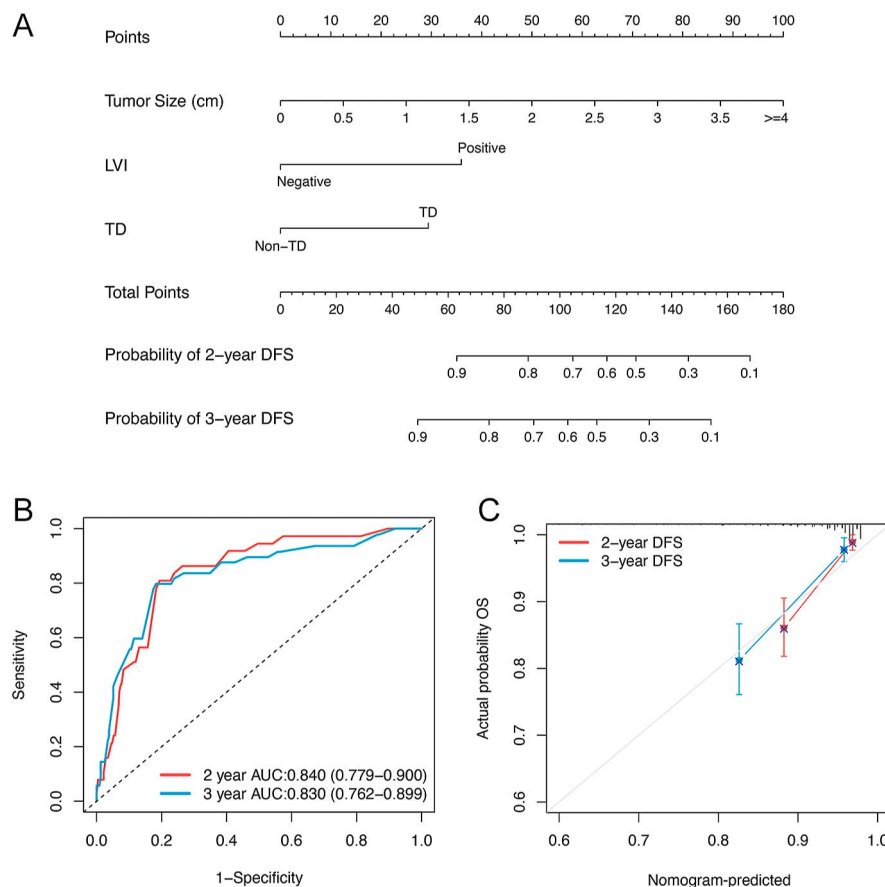
Variable	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age at diagnosis	1.000 (0.978–1.022)	0.995	NA	
Sex	0.609 (0.352–1.054)	0.076	NA	
BMI	1.062 (0.988–1.140)	0.102	NA	
Multifocality	1.460 (0.839–2.541)	0.181	NA	
Tumor size	1.977 (1.628–2.401)	<0.001	1.804 (1.482–2.196)	<0.001
Microscopic ETE	0.721 (0.225–2.314)	0.582	NA	
Gross ETE invading strap muscle	4.961 (2.714–9.068)	<0.001	NA	
Recurrent laryngeal nerve invasion	4.481 (2.381–8.431)	<0.001	NA	
Trachea/laryngeal invasion	4.534 (0.625–32.876)	0.135	NA	
Esophagus invasion	1.941 (0.267–14.095)	0.512	NA	
PVF invasion*	9.548 (3.406–26.764)	<0.001	NA	
ENE	3.222 (1.278–8.125)	0.013	NA	
Lymphovascular invasion	4.656 (2.315–9.364)	<0.001	2.498 (1.168–5.344)	0.018
N stage	1.660 (1.158–2.381)	0.006	NA	
TD vs non-TD	4.071 (2.289–7.242)	<0.001	2.501 (1.353–4.624)	0.003

ETE, extrathyroidal extension; PVF, prevertebral fascia; TDs, tumor deposits; PTC, papillary thyroid carcinoma; ENE, extranodal extension.

*Prevertebral fascia invasion or encasing the carotid artery/internal jugular vein.

Li *et al.* initially reported that TD was associated with Level V LNM in PTC patients (16); however, the authors did not strictly distinguish ENE and TD. Durak *et al.* demonstrated the existence of TDs in thyroid carcinoma cases (PTC and medullary thyroid carcinoma), and indicated a more aggressive behavior

pattern of TDs in these patients (17). The present study revealed the presence of TD and ENE by reviewing a group of 541 PTC specimens and explored its prognostic value by constructing a nomogram to accurately predict DFS in PTC patients. We found that TD did exist in PTC patients and distinguished from ENE.

**Figure 3**

Nomogram for 2-year and 3-year DFS for patients with PTC. (A) Nomogram for predicting DFS. (B) Two-year and 3-year time-dependent ROC curves. 2 years AUC: the area under the curve (AUC) of the receiver operating characteristic (ROC) analysis for 2-year DFS prediction. 3 years AUC: The area under the curve (AUC) of the ROC analysis for 3-year DFS prediction. (C) Two-year and 3-year calibration curves.

The incidence of TD and ENE in this study population was 16.1 and 5.0%, respectively. The tumor characteristics related to aggressive behavior of PTC, including larger tumor diameter, higher rate of micro- or macro-extrathyroidal extension and more advanced T/N/clinical stage, were significantly associated with the presence of TD. Univariate Cox regression analysis showed that both ENE and TD were associated with poor prognosis. In multivariate analysis, TD, not ENE, was an independent prognostic factor for DFS in PTC patients. We speculated that two reasons may explain this result: first, TD may show a superior role to ENE for a worse prognosis, which is similar to ENE grade system used in head and neck cancer (27). According to this grading system, deposits of cancer cells in sub-serosal fat without a recognizable lymph node were directly upgraded to ENE grade 4. Second, the number of patients with ENE was relatively small (5%) compared with previous studies, ranging from 10.5 to 64.3% (28, 29, 30, 31, 32). In this study, there were several patients both presented with TD and ENE; this confounding factor may exclude ENE from multivariate analysis. In the future study, we will include more patients with ENE to further validate this finding. In our opinion, ENE should be analyzed separately from TDs, at least for research purposes.

We also established a nomogram model to predict the prognosis of PTC patients. Previous studies have found that TD presented several kinds of solid malignancies (14, 15, 33, 34, 35). The incidence of TD in colorectal cancer varied from 12.3 to 43.85% in colorectal cancer (36, 37, 38). TDs were found in 20.9% in 7,445 patients, 23.21% in 1,034 patients and 22.0% in 369 patients in different studies on gastric cancer and all associated with poor survival (34, 39, 40). One study on head and neck squamous cell carcinoma has established the inferior survival outcomes in TD-positive patients compared with TD-negative cases, with reported 24-month DFS 37.9% in TD-positive cohort versus 85.2% in TD-negative cohort (15). Durak *et al.* (17) found that patients who are TD-positive have significantly worse relapse-free survival (RFS) and overall survival (OS), which is consistent with the results of our study. However, it seems that few pathologists have realized the value of TD in PTC patients. Therefore, the presence of TD has not been routinely included in the pathological reports or has been classified as ENE. We suggest that pathologists carefully inspect perithyroid adipose/muscular/soft tissues and lymph node chains, and be aware of and be alert on the characteristics of TD as follow: i) peritumoral discrete tumor nodules, either circumscribed or with irregular contours; ii) no identifiable lymph node architecture (no subcapsular sinuses, lymphoid follicles, or afferent/efferent lymphatic channels); and iii) no identifiable vascular or neural architecture. For surgeons, when suspicious TD is encountered during surgery, they should be carefully isolated by removing surrounding excess tissue and

submitted separately for pathological examination. This approach facilitates more accurate identification and evaluation of TD by pathologists. TD has not been taken into account for the risk stratification. Results from our study indicated TD as a potential marker for inferior prognosis after surgery. The rate of recurrence and distant metastasis was significantly higher for cases with TD in our study cohort. The Kaplan–Meier curves showed significant lower DFS in patients with TD. According to the univariable and multivariable Cox regression analysis, larger tumor size (HR = 1.804, 95% CI = 1.482–2.196), LVI (HR = 2.498, 95% CI = 1.168–5.344) and presence of TD (HR = 2.501, 95% CI = 1.353–4.624) remained associated with worse DFS. Although the nodal disease (N1 stage), prevertebral fascia invasion or encasing the carotid artery/internal jugular vein, gross extrathyroidal extension invading strap muscle, recurrent laryngeal nerve invasion and ENE were statistically significantly associated with DFS, they were excluded after backward stepwise multivariate analysis. Previous studies have suggested that LVI, occurring in 9–20% of PTC cases, may be associated with poorer prognosis (41, 42). In our study, the incidence of LVI was 6.6% overall, while it was significantly higher at 25.3% in TD-positive patients. These findings suggest that TD, LVI and tumor size may play a significant role in risk-stratification systems to guide clinical decision-making. Surprisingly, ENE was excluded. This exclusion may be due to the reason that there were a number of patients both exhibited ENE and TD in their specimens. The lack of independent prognostic significance for nodal disease (N1 stage) may be due to its strong correlation with other aggressive features, such as TD, ENE and LVI. These factors may collectively contribute to the overall risk of recurrence, reducing the independent impact of nodal disease in the multivariate model.

Tumor size, LVI and presence of TD were incorporated into a nomogram to predict the probability of 2-year and 3-year DFS. For example, a patient with 1.5 cm tumor diameter (37 points), positive LVI (35 point) and negative TD (0 points) would have a total score of 72 points, which corresponds to an 86% probability of DFS at 2 years and 81% probability of DFS at 3 years. A patient with 2 cm tumor diameter (50 points), negative LVI (0 point) and positive TDs (30 point) would have a total of 80 points, and the probability of DFS would be 84% at 2 years and 75% at 3 years. This nomogram has good discrimination and calibration with C index of 0.79, and may assist personalized prognostication and help with identifying patients who would benefit from more aggressive surveillance and treatment. This study cohort provided comprehensive data about clinical significance of TD in PTC and displayed its prognostic value in DFS. Therefore, it may serve as a robust evidence to recommend the use of TD as an additional, novel, site-specific prognostic factor in PTC. To our knowledge, this is the first study to systematically investigate the prognostic significance of TD in a large East Asian cohort and to develop a

nomogram for predicting DFS. This nomogram provides a practical tool, which may help clinicians stratify risk and guide treatment decisions. Despite its advantages, the study had several limitations. First, it was conducted in a single center, with a selection bias. We are planning to carry out a multicenter prospective study to confirm our findings. Second, the nomogram model was limited by the number of patients with the outcomes of interest. Thus, further external validation is needed to generalize our findings and explore how to integrate TD into current risk stratification systems. Third, the follow-up period is relatively short. We will perform continuous surveillance over time on these patients.

Conclusion

This retrospective cohort study of 541 PTC patients discovered the existence of TD and found its prognostic value in PTC. TD could serve as a novel independent risk factor for inferior DFS. The TD-incorporated prognostic nomogram model was constructed to predict 2-year and 3-year DFS. The model may assist personalized risk assessment and help with decision-making on postoperative management. Further multicenter cohort studies are needed to generalize the concept of TD in PTC and explore how to integrate TD into current risk stratification systems.

Supplementary materials

This is linked to the online version of the paper at
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Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported.

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Author contribution statement

S Lei and S-T Yu had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. J Tan, S Lei and S-T Yu helped with concept and design. Acquisition, analysis and interpretation of data were done by S-T Yu, J Ge, Z Wei, B Sun, T Li and J Zou. Drafting of the manuscript was done by J Tan and S-T Yu. Critical revision of the manuscript for important intellectual content was done by Z Zhang, W Chen, S Lei and S-T Yu. Statistical analysis was performed by J Tan, J Zheng and T Wang. S-T Yu and S Lei obtained funding. Administrative, technical and material support was provided by J Zou and J Zheng. Supervision was done by S Lei and S-T Yu.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Informed consent was obtained from each patient, and the Ethics Committee of Nanfang Hospital, Southern Medical University, approved this study (NFEC-2023-326). All methods were carried out in accordance with the Declaration of Helsinki.

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