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A retrospective study of 17,995 patients investigating the location and recurrence of papillary thyroid cancer

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The incidence of papillary thyroid cancer (PTC) has recently increased. Although PTC usually has a good prognosis, patients with advanced or localized metastases experience a high rate of recurrence. Although many studies have investigated PTC recurrence, a correlation between PTC location and recurrence remains unclear. Thus, we aimed to determine whether the location of PTC affects recurrence.Data were obtained from a single thyroid surgery center with >6000 surgical cases per year. Between 2009 and 2022, 17,995 were enrolled in this study after screening. The location of the cancerous lesions was determined from ultrasound and pathology reports as well as the division of the lateral thyroid lobes into coronal and sagittal perspectives. The coronal plane was equally divided into upper, middle, and lower parts, and the sagittal plane was equally divided into anterior and dorsal aspects. Kaplan-Meier analysis and Cox proportional hazards regression models were used to analyze recurrence and risk factors. This study concluded that the upper part of the coronal plane and the dorsal part of the sagittal plane were most strongly associated with recurrence. Multifactorial analysis showed that lymph node metastatic status, multifocality, and superior and dorsal location of the tumor were significantly associated with PTC recurrence.

Thyroid cancer is currently recognized as the most common malignancy of the endocrine system[1]. Papillary thyroid cancer (PTC) accounts for the majority of differentiated thyroid cancers, accounting for nearly 90% of the total incidence of thyroid cancer, and usually has an excellent prognosis[2]. However, several recent studies have shown that despite the good prognosis of PTC, a small percentage of patients still face a high risk of recurrence or mortality, such as those with lateral cervical lymph node metastases or locally advanced PTC. In addition to the increasing incidence of PTC, identification of the factors influencing PTC recurrence needs to be addressed[3,4].

While many factors influence PTC recurrence, they may not be definitive. Previous studies have suggested that factors such as male sex, older age, multifocality, and extrathyroidal invasion may suggest a worse prognosis; however, some studies' findings have differed. The most recognized factors affecting PTC recurrence are tumor size, lymph node metastasis, and distant metastasis[5–7]. Regarding tumor size, according to the latest American Thyroid Association (ATA) guidelines published in 2015, thyroid cancers smaller than 1 cm should be managed with active surveillance owing to a favorable prognosis, while tumors larger than 4 cm usually indicate a poorer prognosis[8]. In recent years, many studies have focused on the relationship between lymph node metastasis and the prognosis of PTC. Hwangbo et al. suggested that patients with PTC and ≥2 metastatic lymph nodes had a significantly increased long-term recurrence rate[9]. However, recent studies have indicated that thyroid cancer location also influences its clinicopathological features. Heng et al. concluded that upper PTC is more prone to lateral cervical lymph node metastasis, which suggests that PTC location influences lymph node metastasis[10]. Lymph node metastasis is an important factor affecting the recurrence of PTC. Therefore, this study aimed to further investigate the relationship between thyroid tumor location and recurrence.

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Results

Patient characteristics

We reviewed the data of 23,754 patients between December 2009 and April 2022, of whom 5759 were excluded because of persistent disease, final diagnosis of non-PTC, initial distant metastases, irregular follow-up, and isthmus tumors or the presence of other confounding factors unsuitable for inclusion in this study. Figure 1 shows the patient recruitment pathway for this study. Thus, 17,995 patients were included in this study. The clinicopathological characteristics of the patients are shown in Table 1.

In the relapse group, 46 patients (38.0%) were aged ≥ 45 years, and 75 patients (62.0%) were aged < 45 years. A larger total of 95 (78.5%) patients were female, whereas only 26 (21.5%) were male. In the recurrence group, we counted a total of 159 cancerous lesions. The mean tumor size in the recurrence group was 1.25 (± 28.89) cm, and most patients had tumors smaller than 1.5 cm ($n = 80$, 66.1%). The number of cancerous lesions with extrathyroidal extension was 105 (66%), and the number of patients with multifocal cancer was 69 (57.0%). Furthermore, 80 (66.1%) patients had lymph node metastasis in the central region, and 34 (28.0%) patients had lateral cervical lymph node metastasis. In the recurrence group, 70 (57.9%) patients underwent total thyroidectomy. Of the 53 patients tested for the B-Raf gene, 47 had mutations. The follow-up time was 38.2 (± 28.89) months. In the non-recurrent group, 8921 (49.9%) patients were aged ≥ 45 years, and 8953 (50.1%) were aged < 45 years. Women also made up a larger proportion, with 14,699 (82.2%) female patients, compared with only 3175 (17.8%) male patients. The mean tumor size in the non-recurrent group was 1.08 (± 0.85) cm, and most patients had tumors smaller than 1.5 cm ($n = 13078$, 73.2%). Extrathyroidal extension was observed in 13,143 (44.2%) cancer lesions and multifocal cancer was observed in 10,338 (57.8%) patients. Additionally, 7055 (39.5%) patients had lymph node metastasis in the central region, and 1341 (7.5%) had lateral cervical lymph node metastasis. In the recurrence group, 12,441 (69.4%) patients underwent total thyroidectomy. The follow-up time was 66.3 (± 31.26) months.

Tumor location and recurrence

The relationship between the occurrence and recurrence of PTC in both coronal and sagittal thyroid dimensions was investigated. We first evaluated the presence or absence of significant heterogeneity between different tumor locations and clinicopathological characteristics that may influence recurrence, as shown in Table 2. In the univariate analysis, no significant differences were identified between all three positional categories (upper, middle, and lower) in the coronal plane and age, sex, tumor size, lymph node metastasis, multifocality, extrathyroidal extension, and the two positional categories (anterior and dorsal) in the sagittal plane. Similarly, the two positional categories in the sagittal plane (anterolateral and dorsal) were not significantly different from the clinicopathological characteristics.

Next, a Kaplan-Meier analysis and log-rank test were performed to investigate whether a significant difference was observed between the locations of PTC occurrence and recurrence. Of the three positional categories on the coronal surface of the thyroid (upper, middle, and lower), tumors located in the upper part showed a significant correlation with recurrence of PTC, followed by tumors located in the middle, and tumors located in the lower part showed the weakest relationship with recurrence, as shown in Fig. 2 (log-rank test $p = 0.0044$). Similarly,

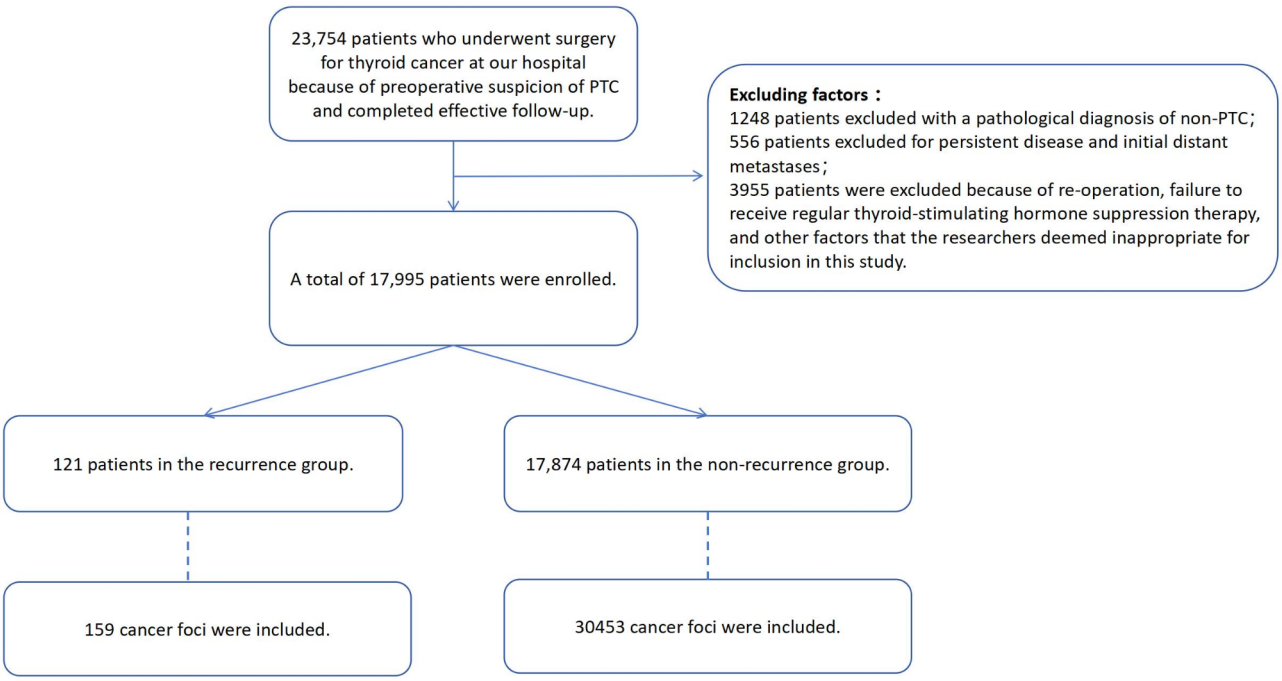

Fig. 1. Flowchart of patient selection in this study.

Characteristic	Recurrence ($n=121$)	Non-recur ($n=17874$)	p-value
Age (years; mean ± SD)			
< 45	75 (62.0%)	8953 (50.1%)	*0.009**
≥ 45	46 (38.0%)	8921 (49.9%)	
Gender			
Male	26 (21.5%)	3175 (17.8%)	0.286
Female	95 (78.5%)	14,699 (82.2%)	
Total cancer foci	159	30,453	–
Largest tumor diameter			
< 1.5 cm	80 (66.1%)	13,078 (73.2%)	0.081
≥ 1.5 cm	41 (33.9%)	4796 (26.8%)	
Mean (cm; mean ± SD)	1.25 (± 28.89)	1.08 (± 0.85)	
Extrathyroidal tumor extension[a]	95 (59.7%)	13,143 (44.2%)	*0.001**
Multifocality of tumor	69 (57.0%)	10,338 (57.8%)	0.857
Central LN metastasis(N1a)	80 (66.1%)	7055 (39.5%)	*0.001**
Lateral LN metastasis(N1b, CT scans)	34 (28.0%)	1341 (7.5%)	*0.001**
I-131 therapy	64 (52.9%)	-	–
B-raf	47/53	2280/2470	0.329
Total thyroidectomy	70 (57.9%)	12,441(69.4%)	*0.005**
Location[a]			
Upper/Middle/Lower	68/55/36	9998/10,158/10,297	*0.005**
Anterior/Dorsal	47/112	15,211/15,242	*0.001**
Follow time (months; mean ± SD)	38.2 (± 28.89)	66.3 (± 31.26)	–

Table 1. Demographics and clinical characteristics of the cohort. * Statistically significant [a]Comparison with all cancer foci, All patients with N1b underwent CT scans; Extrathyroidal tumor extension, the cancer lesion break through the normal boundaries of the thyroid gland. Significant values are in [Italics].

when studying the relationship between the two positional categories (anterior and dorsal) on the sagittal plane of the thyroid and recurrence, dorsally located tumors showed a significant correlation with PTC recurrence (log-rank test, $p<0.001$; hazard ratio [HR], 0.4262; 95% confidence interval [CI], 0.3098–0.5864) (Fig. 2).

Furthermore, taking into account the broad temporal scope of the study and the potential for variations in the relevant treatment protocols over time, which could influence the study's outcomes, we conducted subgroup analyses on a five-year data subset. The findings from these analyses are presented in Fig. 3. As can be observed from the results, the conclusions derived from the patient data within the five-year period are consistent with our overall findings.

Clinicopathologic factors for PTC recurrence

In addition to studying the relationship between positional factors of PTC occurrence and recurrence, other risk factors associated with recurrence were described. A multivariate Cox proportional risk regression analysis was performed, as shown in Table 3. Multifactorial analysis showed that lymph node metastasis status (N1a: HR 2.870; 95% CI 2.019–4.079; $p<0.001$) (N1b: HR 2.883; 95% CI 2.102–3.955; $p<0.001$), tumor size (≥ 1.5 cm: HR 1.330; 95% CI 1.181–1.499; $p<0.001$), multifocality (HR 2.376; 95% CI 1.774–3.180; $p<0.001$), upper location of the tumor (vs. middle: HR 0.680; 95% CI 0.501–0.925; $p=0.014$) (vs. lower: HR 0.456; 95% CI 0.323–0.643; $p<0.001$), dorsal location of the tumor (vs. anterior: HR 2.222; 95% CI 1.667–2.960; $p<0.001$) were significantly correlated with recurrence, whereas age (≥ 45 years: HR 1.002; 95% CI 0.990–1.014; $p=0.743$), sex (female: HR 0.965; 95% CI 0.703–1.323; $p=0.823$), and extrathyroidal tumor extension (HR 1.180; 95% CI 0.802–1.737; $p=0.401$) were not significantly correlated with recurrence.

Discussion

The incidence of PTC has increased in recent years. Some studies have suggested that continuous advances in ultrasound technology and ultrasound-guided fine-needle aspiration cytology contribute to the increase; however, the reasons behind this phenomenon have not yet been fully established[11,12]. Although most patients with PTC have a good prognosis, a significant number of people still suffer from recurrence owing to the increasing population base of incidence[13,14]. Because treatment strategies continue to evolve based on geographical factors and treatment guidelines, factors that may predict the prognosis of patients with PTC have not been clearly defined[15,16]. Given the relatively low mortality rate of PTC, several studies have been recently conducted to address the factors of recurrence. However, the results of these studies were inconsistent[16,17]. Our study aimed to further investigate the factors affecting PTC recurrence by examining 13 years of clinical data from our department.

Several factors are known to potentially influence the prognosis of PTC. Tumor size, lymph node metastasis, older age, male sex, and multifocal tumors have been shown to influence recurrence[13–17]. However, some recent

Characteristic	Upper	Middle	Lower	*p*-value		Anterior	Dorsal	*p*-value
Age, years								
< 45	5079	5092	5190	0.69		7707	7646	0.221
≥ 45	4987	5121	5143			7549	7702	
Mean (± SD)	44.4(± 10.7)	44.2(± 10.8)	44.1(± 10.6)			44.2(± 10.8)	44.2(± 10.6)	
Gender								
Male	1842	1836	1823	0.474		2754	2744	0.693
Female	8224	8377	8510			12,502	12,604	
Tumor size(± SD)								
< 1.5 cm	7279	7367	7477	0.632		11,004	11,108	0.882
1.5–3 cm	2636	2692	2722			4033	4019	
> 3 cm	151	154	132			218	221	
Mean	1.09(± 0.87)	1.10(± 0.85)	1.09(± 0.86)			1.09(± 0.85)	1.10(± 0.86)	
LNM								
Nx-N0	6071	6243	6244	0.435		9195	9360	0.201
N1a	3995	3970	4089			6061	5988	
N1b	761	774	805	0.788		1176	1165	0.698
Multifocality								
Sngle	5811	5843	5920	0.725		8777	8792	0.662
Multiple	4255	4370	4413			6479	6556	
Extrathyroidal extension								
No	2878	2825	2861	0.244		4328	4236	0.127
Yes	7188	7388	7472			10,928	11,120	
Location								
Anterior	5066	5053	5131	0.551	Up…	5066	5015	0.551
Dorsal	5015	5150	5197		Mid…	5053	5150	
					Low…	5131	5197	

Table 2. The clinicopathological characteristics are stratified by tumor location. Extrathyroidal extension, the cancer lesion break through the normal boundaries of the thyroid gland.

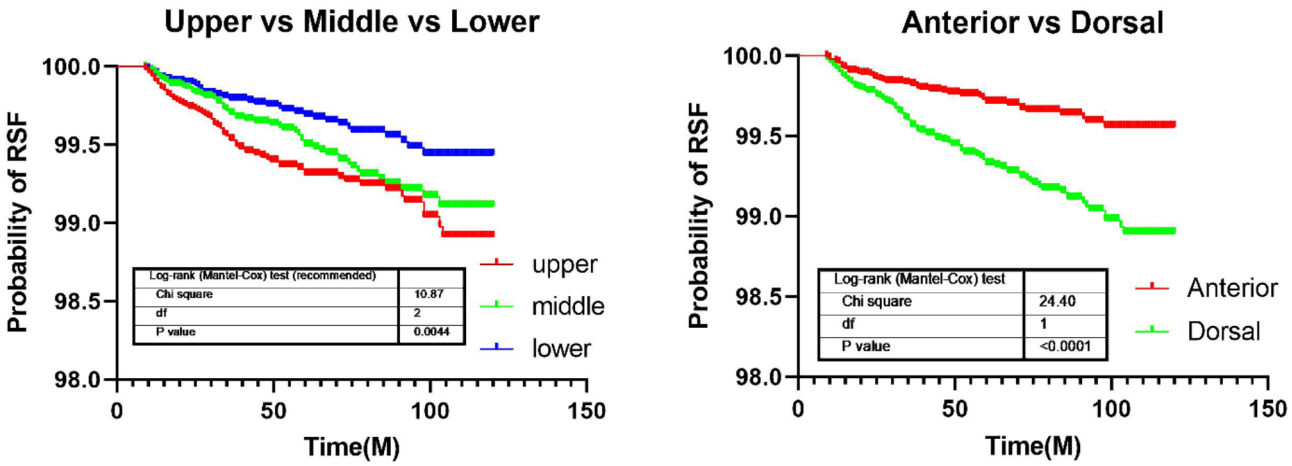

Fig. 2. RFS curves of patients with PTC stratified by tumor location (upper/middle/lower, anterior/dorsal). RFS, recurrence-free survival, $p < 0.01$. Recurrence was calculated using the Kaplan-Meier method, and p values were calculated using log-rank tests.

studies have shown that location may affect the clinicopathological features of PTC and its prognosis[3,18–21]. Xiang et al. concluded that PTC located in the middle part of the middle third of the thyroid gland were associated with both central and lateral neck metastases[20]. Interestingly, studies have suggested that PTC located in the upper thyroid is more likely to have metastases in the lateral cervical lymph nodes, and PTC located in the lower thyroid is more likely to have metastases in the central lymph nodes; metastases in the lateral cervical lymph nodes usually suggest a worse prognosis[18,19]. For example, Heng et al. concluded that upper PTC is more likely to metastasize, and their study showed that upper PTC indicated a worse prognosis[10]. Based on the variability of

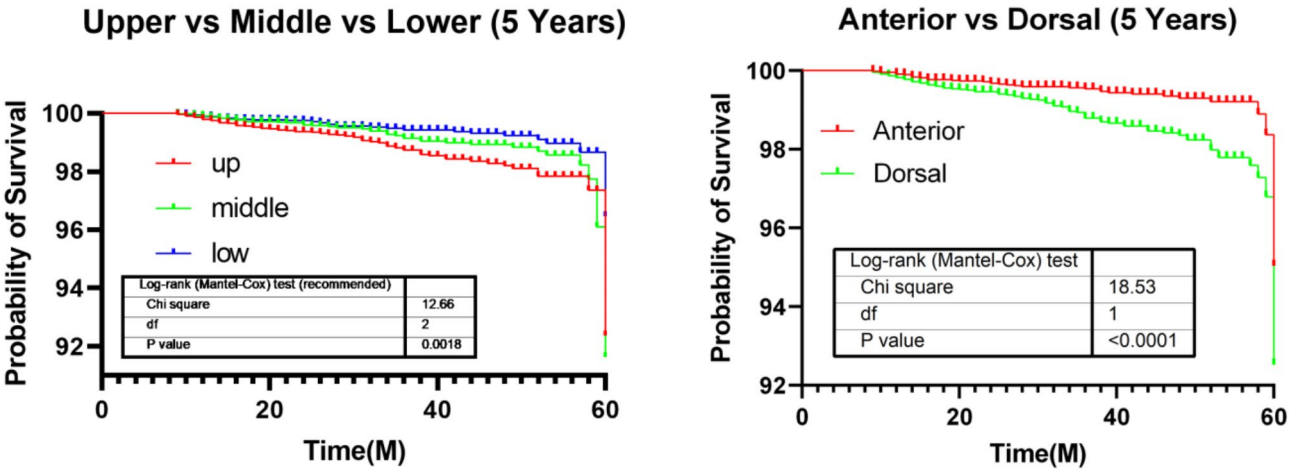

Fig. 3. RFS curves of PTC patients at 5 years stratified by tumor location (upper/middle/lower, anterior/dorsal). RFS, recurrence-free survival, $p < 0.01$. Recurrence was calculated using the Kaplan-Meier method, and p values were calculated using log-rank tests.

Characteristic	Hazard ratio (95% CI)	*P*-value
Gender (Female vs. male)	0.965 (0.703–1.323)	0.823
Age, years (≥ 45 vs. < 45)	1.002 (0.990–1.014)	0.743
Lymph node metastasis status		
N1a (N0-Nx vs. N1a)	2.870 (2.019–4.079)	*< 0.001**
N1b (N0-N1a vs. N1b)	2.883 (2.102–3.955)	*< 0.001**
Tumor size, cm (< 1.5 vs. ≥ 1.5)	1.330 (1.181–1.499)	*< 0.001**
Multifocality (+)	2.376 (1.774–3.180)	*< 0.001**
Extrathyroidal extension (+)	1.180 (0.802–1.737)	0.401
Upper (vs. Middle and Lower)		
Middle	0.680 (0.501–0.925)	0.014
Lower	0.456 (0.323–0.643)	*< 0.001**
Anterior (vs. Dorsal)	2.222 (1.667–2.960)	*< 0.001**

Table 3. Multivariate Cox proportional risk regression of risk factors for recurrence of PTC. *Statistically significant; Extrathyroidal extension, the cancer lesion break through the normal boundaries of the thyroid gland. Significant values are in [Italics].

these studies, whether the location of PTC affects prognosis remains unknown. However, in a study published in the journal *Thyroid*, Jasim et al. showed that the location of thyroid nodules was an independent risk factor for predicting the risk of thyroid cancer, with isthmic nodules having the highest risk of cancer diagnosis and inferior lobe nodules having the lowest risk[21]. Although these findings suggest that the location of PTC is a factor that can influence prognosis, this consideration has not been well elucidated. Therefore, the present study was conducted.

This study aimed to investigate the relationship between PTC location and recurrence. Thyroid cancer foci were located using ultrasound. Most previous studies investigating the location of PTC used ultrasound to localize tumor centroids or primary tumors. However, the use of ultrasound has several limitations. PTCs tend to exhibit multiple foci; therefore, this approach is relatively one-sided when a multifocal PTC is located using only one location. Moreover, the thyroid gland volume is relatively small, and this localization method is even less applicable when tumors are large and invade multiple sites or when tumors are located on the division line of two sites. In cases of recurrence, the part of the tumor responsible for poor prognosis cannot be determined. To solve this problem in the present study, a method based on tumor location was employed. The advantage of this method is that each area is viewed independently, and when ultrasound and pathologic examination reveal the presence of a cancerous lesion, its location is recorded. With this method, the relationship between each site and recurrence can be analyzed independently without considering the aforementioned confounding factors. As our sample size was adequate, this method was effective.

We concluded that tumors located superiorly on the coronal side of the thyroid and those located dorsally on the sagittal side were more likely to recur. These findings are consistent with those of previous studies[22]. Our conclusions may help guide clinicians to treat tumors in the upper part or dorsal side more thoroughly and to target any necessary treatment, such as I-131 therapy, to minimize the possibility of recurrence. In addition,

we found that in the coronal plane of the thyroid, tumors with closer proximity to the upper part indicated a poorer prognosis. This research indicated that the recurrence rate of malignant lesions in the upper portion of the thyroid gland seems to surpass that of lesions in the middle and lower regions. Furthermore, lesions in the middle thyroid are more prone to recurrence compared to those in the lower thyroid. Consequently, we posited that the nearer the cancerous foci are to the upper thyroid, the higher the risk of recurrence becomes. This observation could be associated with the upper thyroid's proximity to the lateral neck. Additionally, since all patients in our study underwent central neck lymph node dissection, this might explain the lower recurrence rate of tumors situated in the lower part of the thyroid gland. Moreover, our study revealed that tumors located on the dorsal side were more susceptible to recurrence, a result that aligns with several recent studies. This finding may be linked to the dorsal side's closeness to the thyroid bed. Additionally, we attempted to identify other risk factors associated with recurrence. Multivariate Cox proportional hazard regression revealed that the degree of lymph node metastasis, tumor size, multifocality, and tumor location were significantly associated with recurrence, whereas age, sex, and extrathyroidal tumor extension were not significantly associated with recurrence. This heterogeneity may be related to geography or population groups[23–25]. Upon examining the data presented in Table 3, it becomes evident that tumors situated in the upper region exhibit a higher recurrence rate compared to those in the middle and lower regions. Since we analyzed subgroups of patients from the last five years and the conclusions obtained were consistent with the overall findings, we believe that the conclusions are trustworthy despite the time span of our study.

The present study had some limitations. First, thyroid cancer is strongly associated with genetic mutations. We attempted to perform mutation analysis (e.g. B-Raf gene) based on our sample[26,27] However, limited by the large time period and inconsistent testing, only a fraction of patients were tested for the B-Raf gene, and the interpretation in the molecular genetic field was not perfect. Furthermore, the B-raf test at our institution is typically employed as a supplementary diagnostic tool in instances where the pathological diagnosis is inconclusive. Consequently, there exists a potential bias when the B-raf-positive cohort is examined as an independent subgroup based on our data. Additionally, as indicated in Table 1, our findings did not reveal a significant correlation between B-raf status and recurrence. Hence, we refrained from analyzing the B-raf-positive group as a distinct subgroup. Finally, although we had a long follow-up period, relapse may have occurred later in the non-relapse group. Therefore, we will continue to follow the patients in this study and keep the data updated.

In conclusion, PTC location affects prognosis, and tumors located in the upper and dorsal areas should receive greater attention, as they are more prone to recurrence.

Methods

Participants and follow-up

The data of patients with thyroid cancer who underwent surgery in our department (Thyroid Surgery Department, General Surgery Center, First Hospital of Jilin University, Jilin University, Changchun, Jilin Province, China) from December 2009 to April 2022 were retrospectively analyzed. This thyroid surgery center encounters > 6000 patients per year. The study was conducted in accordance with the protocol approved by the Review Board of the First Hospital of Jilin University, and informed consent was granted to be waived. Clinical data related to the location of their tumors and whether they experienced cancer recurrence were used to further analyze the relationship between the location of PTC occurrence and its prognosis. In total, 23,754 patients were effectively followed. Patients were defined as having persistent disease if the structural disease was identified by ultrasound and pathology within nine months after surgery, and recurrence was defined as the identification of structural abnormalities after the third ultrasound examination (one year postoperatively). The nine-month time point was selected because patients who underwent surgery in our department also underwent two post-operative ultrasound examinations within nine months. Patients with no significant structural abnormalities on postoperative ultrasound examinations at six and nine months were considered to have no disease recurrence. The inclusion and exclusion process is shown in Fig. 1. Exclusion factors included pathologic diagnosis of non-PTC, persistence of disease, first occurrence of distant metastasis, irregular or missed follow-up, re-operation, cancerous lesions located in the isthmus of the thyroid gland, and other factors considered by the investigators to have the potential to introduce bias into the results of the study. In addition, because fewer tumors occurred in the isthmus in the recurrence group, all patients with PTC in the isthmus were excluded to avoid bias. A total of 5759 patients were ultimately excluded, and 17,995 patients were included, 121 of whom were defined as having recurrence. All patients with PTC received thyroid-stimulating hormone suppressive therapy for at least 1 year after surgery. Finally, medical records of these eligible patients, summarizing information on age, sex, tumor size, multifocality, extrathyroidal tumor extension, lymph node metastasis, extent of surgery, and I-131 treatment, as well as information on relevant examination tests, such as neck ultrasound and neck CT, were collected for data analysis.

Study design and procedures

All enrolled patients with PTC underwent total thyroidectomy with bilateral central cervical lymph node dissection or unilateral thyroidectomy with unilateral central cervical lymph node dissection. All patients with suspected lateral cervical lymph node metastases (N1b) detected by ultrasound also underwent ct scan, and lateral cervical multifunctional preserving cervical lymph node dissection was performed in those patients in whom both ultrasound and ct scanning supported the possibility of lateral cervical lymph node metastases. The final diagnosis of whether a patient has developed lateral cervical lymph node metastasis is dependent on postoperative pathology, and neither ultrasound nor ct scans can categorize such patients as having lateral cervical lymph node metastasis. Six experienced surgeons in our department performed all the surgeries.

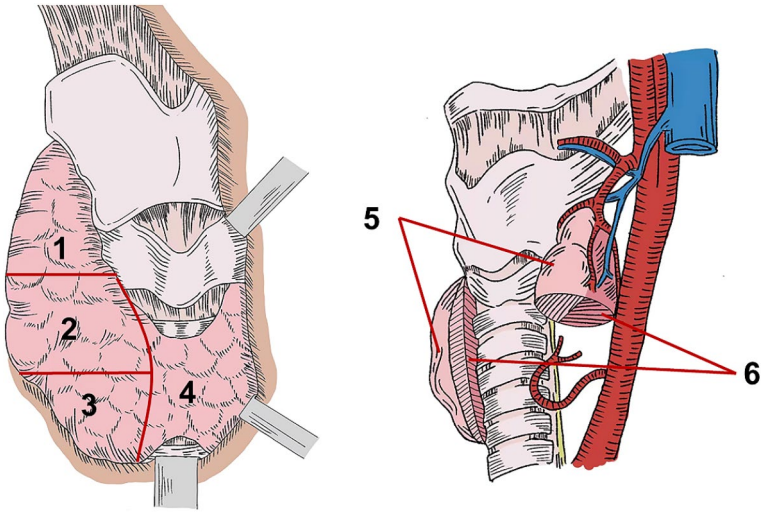

Fig. 4. Locations of thyroid. (1) Upper; (2) middle; (3) lower; (4) isthmus; (5) anterior; (6) dorsal.

The localization of thyroid cancer foci was determined using ultrasound, and preoperative and postoperative ultrasound examinations were performed by four experienced sonographers in our department. To independently analyze the relationship between each location and recurrence, this study was conducted from the perspective of each individual tumor. The location of the thyroid gland was categorized in two dimensions: coronal and sagittal planes. It was divided equally into upper, middle, and lower sites in the coronal plane and into anterior and dorsal sites in the sagittal plane (Fig. 4). The two planes were analyzed independently to exclude confounding factors of regional overlap. The locations of the cancer lesions were localized to the above five regions by applying ultrasound and pathology reports. Since PTC is often multifocal, the nodules can be located in multiple locations in the thyroid gland or on the demarcation lines between these regions; additionally, tumors may invade multiple regions if they are too large. All of these factors present challenges in accurately determining which site of cancer is responsible for PTC recurrence. Finally, we observed each region independently on a tumor-by-tumor basis. For multifocal tumors, we considered the largest cancer focus by volume as the primary lesion and the smaller ones as secondary lesions. When a secondary lesion was larger than half the size of the primary lesion, it was also documented. For cancerous lesions located on the dividing line that delineated the regions or invaded multiple regions, the location of the tumor's center point was recorded as a positive region, and the volume of the tumor and its center point were used as an additional reference. If the volume of invasion into an adjacent area exceeded 1/3 of the total tumor volume, the invaded area was recorded as the positive area, and the tumor volume and its center point were estimated using the transverse and longitudinal axes of the tumor on the ultrasound and pathology reports. Using this method, the relationship between each site and recurrence was analyzed independently of the aforementioned confounding factors. This method can be effectively applied with an adequate number of patients. Two surgeons (P.Q. & Z.W.) and a thyroid ultrasonographer (K.L.), combining ultrasound and pathology, independently reviewed cancer locations in the ultrasound reports of the enrolled patients. In the event of a discrepancy between the opinions of these two reviewers, an additional opinion of a more experienced professor (Q.Z.) of thyroid surgery was sought to ensure that the results were credible. This study was approved by the institutional ethics committee and relevant authorities.

Statistical analysis

Categorical variables are presented as frequencies and percentages, while continuous variables are presented as means and standard deviations (mean ± SD). Differences between groups were tested using the chi-square test or Fisher's exact test. The association between tumor location and recurrence was estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazard regression models were used to assess the association between clinical characteristics including age, sex, lymph node metastasis status, tumor size, multifocality, invasive thyroid, tumor location, and recurrence. Statistical analyses were performed using IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 9 (GraphPad Software Inc., San Diego, CA, USA).

Data availability

Data supporting the findings of this study are available from the corresponding author.

Received: 27 June 2024; Accepted: 24 March 2025
Published online: 27 March 2025

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Acknowledgements

The authors would like to thank the Department of Thyroid Surgery, General Surgery Center of the First Hospital of Jilin University, the Department of Clinical Research of the First Hospital of Jilin University, and the Department of Medical Records and Archives of the First Hospital of Jilin University for their support in study design (Yanhua Wu), manuscript preparation (Xianying Meng), and data management (Changyan Xu). We also thank the Natural Science Foundation of Jilin Province for financial support and thank Zhen Wu (School of Foreign Languages, Tianjin University) for English language editing.

Author contributions

Q.Z., P.Q., and Z.W. designed the study; Q.Z., P.Q., Z.W., X.H., B.Z., X.O., K.L., X.L., and Q.S. collected the clinical data and provided clinical research design suggestions; Q.Z., P.Q., and Z.W. analyzed the clinical data; P.Q. drafted the manuscript; Zh.W. edited the English language; Q.Z., P.Q., and Z.W. reviewed all data and critically revised the manuscript for intellectual content; S.L. undertaken extensive revision work, and all authors have given their approval to the final version of the manuscript.

Funding

This work was supported by grants from the Natural Science Foundation of Jilin Province (Grant no.

20200201330JC). This is a retrospective data analysis of the clinicopathologic characteristics of existing patients with thyroid cancer. All data sources were obtained from the Medical Records and Archives Administration of the First Hospital of Jilin University. Approval for this analysis was granted by The First Hospital of Jilin University Review Board.

Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
The study was conducted following the protocol approved by The First Hospital of Jilin University Review Board (Ethical approval no. AF-IRB-032-06).

Informed consent
Since data were evaluated retrospectively, pseudonymously and were solely obtained for treatment purposes, a requirement of informed consent was waived by the Ethics Committee of the First Hospital of Jilin University, China (Ethical approval no. AF-IRB-032-06).

Additional information
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