Original Article

Impact of location and size of minimal extrathyroidal extension on lymph node metastasis in papillary thyroid cancer: a retrospective analysis

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Background: The 8th edition of the American Joint Committee on Cancer (AJCC)'s T-stage for differentiated thyroid cancer (DTC) removes minimal extrathyroidal extension (mETE), while ignoring the risk of mETE would lead to overtreatment or inadequate treatment. The aim of this study was to investigate the impact of location and size of mETE on lymph node metastasis in papillary thyroid cancer (PTC).

Methods: A retrospective analysis of 267 patients who underwent unilateral radical surgery for PTC was conducted. According to the postoperative pathology, they were divided into mETE group (121 patients) and non-mETE group (146 patients). The number of lymph nodes dissected and the number of lymph nodes metastasized were compared between the two groups. The linear regression analysis and the receiver operating characteristic (ROC) curves were performed to evaluate the impact of the locations and sizes on lymph node metastasis.

Results: There was no significant difference in the number of lymph node dissected between the mETE group and the non-mETE group. The tumor located at the upper part and the size <1.0 cm in mETE group showed a higher number of lymph node metastasis (0.78±0.88 *vs.* 0.25±0.45, P=0.03). Meanwhile, in the mETE group, the number of patients with lymph node metastasis was higher than that in the non-mETE group. Further subgroup analysis revealed that for PTC patients with tumors at the upper part and size <1.0 cm, the number of those with lymph node metastasis in the mETE group was also greater than that in the non-mETE group. Furthermore, the Spearman correlation analysis showed a positive correlation between tumors located at the upper part with a size <1.0 cm and lymph node metastasis rate (R=0.647, P=0.004). Additionally, if the upper part tumor was within 1 cm, the tumor's size was able to identify the lymph node metastasis, with the optimal cut-off point of 0.45 cm (Youden index =0.650).

Conclusions: When tumors combine with mETE, the probability of lymph node metastasis increases in tumors located at the upper part with a size <1.0 cm. Especially, when the upper part tumor is within 1 cm, the tumors of size ≥0.45 cm are more likely to have lymph node metastasis.

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Keywords: Minimal extrathyroidal extension (mETE); papillary thyroid cancer (PTC); lymph node; metastasis

Submitted Jul 03, 2024. Accepted for publication Sep 05, 2024. Published online Sep 27, 2024.
doi: 10.21037/gs-24-273
View this article at: https://dx.doi.org/10.21037/gs-24-273

Introduction

In recent years, the incidence of thyroid cancer has rapidly increased (1). Papillary thyroid cancer (PTC) is the main pathological type (2), so the main focus of thyroid cancer treatment is the treatment of PTC. The 8th edition of the American Joint Committee on Cancer (AJCC) staging system for differentiated thyroid cancer (DTC) divides T3 staging into T3a and T3b (3), compared to the 7th edition staging, minimal extrathyroidal extension (mETE) has been removed from the T staging and replaced with gross extrathyroidal extension (gETE). According to the two editions of the staging system, extrathyroidal extension (ETE) can be divided into the following two categories: (I) microscopic ETE (histology): the tumor only extends through the capsule, or the tumor extends to any anterior cervical strap muscles; (II) naked eye ETE (gETE): with obvious anterior cervical strap muscles invasion, more severe external invasion (subcutaneous tissue, major organs, nerves and blood vessels, etc.). Based on this, most researchers classify microscopic invasion as mETE. According to the latest version of the National Comprehensive Cancer Network (NCCN) guidelines (4), ETE is an indication for total thyroidectomy, and it can also affect postoperative endocrine therapy and iodine therapy for DTC. So, if the risk level of ETE is not distinguished, it would lead to overtreatment or inadequate treatment (5).

The most common mode of metastasis in PTC is lymph node metastasis (6). In the investigation of the impact of ETE on lymph node metastasis and recurrence in PTC, diverse scholars have obtained varying research outcomes. There is a study indicating that the presence and infiltration degree of ETE might result in different prognoses of PTC in cases with different primary tumor sizes (7). Another research result showed that regardless of the patient's age, the risk of recurrence with endoscopic ETE increases by 2.24 times (8). A latest study revealed that mETE is the only risk factor for recurrence in PTC patients (9). Some studies suggest that gETE is the predictive factor for lymph node metastasis and increases the risk of tumor recurrence, affecting survival rate (10,11). Generally speaking, there is less controversy over the relationship between gETE and tumor staging and lymph node metastasis, with controversy mainly focused on mETE.

However, lymph node metastasis in PTC is closely related to the location and size of the tumor. Research suggests that tumors located in the lower part with a diameter ≥1.0 cm can be a high-risk factor for central lymph node metastasis (12,13); the tumor located at the upper part with a diameter ≥2.0 cm is a high-risk factor for cervical lymph node metastasis (14); so special attention should be paid to the relationship between tumor location and size and lymph node metastasis. At present, research on mETE has not analyzed the location and the size of tumors in combination, making it difficult to explain the impact of mETE on lymph node metastasis. The results all have a certain degree of bias. Based on this, this study analyzed the impact of different locations and sizes of mETE on lymph node metastasis in PTC. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-24-273/rc).

Highlight box

Key findings

- When papillary thyroid cancer (PTC) tumors combine with minimal extrathyroidal extension (mETE), the probability of lymph node metastasis increases in tumors located at the upper part with a size <1.0 cm. Especially when the upper part tumor is within 1 cm, tumors of size ≥0.45 cm are more likely to have lymph node metastasis.

What is known and what is new?

- The 8th edition of the American Joint Committee on Cancer's T-stage for differentiated thyroid cancer removes mETE, while ignoring the risk of mETE would lead to overtreatment or inadequate treatment. We for the first time combined the location and size of tumors in PTC patients to analyze their impact on lymph node metastasis.

What is the implication, and what should change now?

- The PTC patients with mETE are recommended to be stratified with individualized stage based on their tumor location and size. That would better guide clinical treatment and provide prognostic information.

Methods

Clinical data

From July 1, 2022, to February 1, 2024, 267 patients with thyroid cancer who underwent surgery at The First Affiliated Hospital of Xiamen University were randomly selected. The operations were all performed by the same experienced group of surgeons. The clinical records of the patients were reviewed retrospectively. The inclusion criteria were as follows: (I) diagnosed with unilateral thyroid cancer before the operation and underwent unilateral radical thyroid cancer resection, (II) underwent radical thyroid cancer resection for the first time, (III) no cervical lymph node metastasis or suspected distant metastasis was found before and after surgery, (IV) postoperative pathology confirmed the tumor was classic variants of PTC, rather than other high-risk subtypes such as high cell subtypes, (V) postoperative pathology confirmed no other characteristics of aggressiveness like the presence of vascular infiltration, (VI) the patients signed an informed consent form for the operation. The exclusion criteria were as follows: (I) patients with incomplete clinical data, (II) patients who had other tumour-related diseases, (III) patients with serious diseases of other systems. According to the postoperative pathology, we divided the patients into a mETE group and non-mETE group, with 121 cases in the mETE group and 146 cases in the non-mETE group.

Definitions

We divided the thyroid gland lobes into the upper part, the middle part (at the same level as the isthmus), and the lower part based on the isthmus (15). The range of lymph nodes dissected was the lymph nodes in the unilateral cervical central lymph nodes.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The First Affiliated Hospital of Xiamen University (No. XMYY-20022KYSB144) and individual consent for this retrospective analysis was waived.

Statistical analysis

Statistical analyses were performed using SPSS for Windows statistical software (ver. 22.0; SPSS Inc, Chicago, IL, USA). Measurement data are expressed as mean ± standard deviation (mean ± SD), count data are expressed as percentages. The *t* test was used for intergroup comparisons of measurement data, and the χ^2 test was used for intergroup comparisons of count data. Spearman correlation analysis was used to analyze the correlation between two variables. The receiver operating characteristic (ROC) curve was plotted and the area under the curves (AUCs) were calculated to assess the predictive accuracy. P<0.05 was considered statistically significant.

Results

General information

The general information of the two groups of patients was compared in terms of age, gender, body mass index (BMI), the tumor size, the location of the tumor, the surgical approach, and the stage, etc. There was no statistically significant difference, and they were comparable (*Table 1*).

The situations of lymph nodes dissected and lymph node metastasis between the two groups

There was no statistically significant difference in the number of lymph nodes dissected between the two groups (*Table 2*). In terms of lymph node metastasis, there was no statistically significant difference between the two groups with the size of tumor ≥1.0 cm and the tumor located in the middle and lower parts with their size <1.0 cm (*Table 3*). However, the mETE group had significantly more metastatic lymph nodes than the non-mETE group when the tumor was located at the upper part and the size <1.0 cm (0.78±0.88 *vs.* 0.25±0.45, P=0.03) (*Table 3*).

The number of patients showing lymph node metastasis was compared between the two groups

The number of patients with lymph node metastasis in the mETE group was significantly higher than that in the non-mETE group (P=0.04) (*Table 4*). When the subgroup analysis was conducted, in the subgroup where the tumor was located at the upper part and the size <1.0 cm, the number of patients with lymph node metastasis in the mETE group was significantly higher than that in the non-mETE group (P=0.03). In the remaining subgroup analyses, there was no statistical significance between the two groups (*Table 4*).

Table 1 Clinical characteristics of the two groups

Group	mETE (n=121)	Non-mETE (n=146)	χ^2/t	P
Age (years), mean ± SD	42.98±11.33	42.21±11.05	–0.555	0.91
BMI (kg/m^2), mean ± SD	24.14±3.35	23.57±3.49	–1.340	0.45
Gender, n (%)			0.934	0.33
Woman	91 (34.1)	117 (43.8)		
Man	30 (11.2)	29 (10.9		
Tumor size, n (%)			2.048	0.15
<1.0 cm	59 (22.1)	84 (31.5)		
≥1.0 cm	62 (23.2)	62 (23.2)		
The location of the tumor, n (%)			3.522	0.17
The upper part	36 (13.5)	29 (10.9)		
The middle part	43 (16.1)	60 (22.5)		
The lower part	42 (15.7)	57 (21.3)		
Surgical approach, n (%)			0.005	0.95
Endoscope	36 (13.5)	44 (16.5)		
Open surgery	85 (31.8)	102 (38.2)		
Stage, n (%)			1.881	0.17
I	109 (40.8)	138 (51.7)		
II	12 (4.5)	8 (3.0)		
Tumor location and size, n (%)			5.903	0.32
The upper part <1.0 cm	18 (6.7)	16 (6)		
The middle part <1.0 cm	21 (7.9)	33 (12.4)		
The lower part <1.0 cm	20 (7.5)	35 (13.1)		
The upper part ≥1.0 cm	18 (6.7)	13 (4.9)		
The middle part ≥1.0 cm	22 (8.2)	27 (10.1)		
The lower part ≥1.0 cm	22 (8.2)	22 (8.2)		

mETE, minimal extrathyroidal extension; SD, standard deviation; BMI, body mass index.

Table 2 Comparison of the number of lymph nodes dissected in PTC of different location and size

Group	Number of LNs dissected		*t*	P
	mETE	Non-mETE		
The upper part <1.0 cm	4.39±2.59	5.13±3.86	0.659	0.41
The middle part <1.0 cm	5.48±4.16	7.67±4.82	1.715	0.74
The lower part <1.0 cm	5.95±3.03	5.57±4.18	–0.354	0.13
The upper part ≥1.0 cm	5.72±4.31	7.54±4.93	1.091	0.71
The middle part ≥1.0 cm	8.55±4.65	6.04±4.42	–1.930	0.81
The lower part ≥1.0 cm	4.55±3.47	6.50±3.49	1.862	0.63

Data are presented as mean ± SD. LNs, lymph nodes; mETE, minimal extrathyroidal extension; SD, standard deviation.

Table 3 Comparison of the number of lymph nodes metastasized in PTC of different location and size

Group	Number of LNs metastasized		*t*	P
	mETE	Non-mETE		
The upper part <1.0 cm	0.78±0.88	0.25±0.45	–2.313	0.03*
The middle part <1.0 cm	0.86±1.53	0.70±1.08	–0.453	0.36
The lower part <1.0 cm	0.45±0.83	0.74±1.69	0.726	0.28
The upper part ≥1.0 cm	2.06±2.16	1.23±1.59	–1.167	0.32
The middle part ≥1.0 cm	2.82±2.42	1.11±2.04	–2.676	0.06
The lower part ≥1.0 cm	2.14±2.38	2.55±2.46	0.561	0.97

Data are presented as mean ± SD. *, P<0.05. LNs, lymph nodes; mETE, minimal extrathyroidal extension; SD, standard deviation.

Table 4 Comparison of the number of patients showing lymph node metastasis between the two groups

Group	The number of patients with lymph node metastasis, n (%)	The number of patients without lymph node metastasis, n (%)	χ^2	P
Total			4.138	0.04*
mETE group	69 (25.84)	52 (19.48)		
Non-mETE group	65 (24.34)	81 (30.34)		
The upper part <1.0 cm			4.480	0.03*
mETE group	11 (32.35)	7 (20.59)		
Non-mETE group	4 (11.76)	12 (35.29)		
The middle part <1.0 cm			0.009	0.92
mETE group	8 (14.81)	13 (24.07)		
Non-mETE group	13 (24.07)	20 (37.04)		
The lower part <1.0 cm			0.106	0.75
mETE group	6 (10.91)	14 (25.45)		
Non-mETE group	12 (21.82)	23 (41.82)		
The upper part ≥1.0 cm			1.304	0.25
mETE group	12 (38.71)	6 (19.35)		
Non-mETE group	6 (19.35)	7 (22.58)		
The middle part ≥1.0 cm			2.225	0.14
mETE group	16 (32.65)	6 (12.24)		
Non-mETE group	14 (28.57)	13 (26.53)		
The lower part ≥1.0 cm				
mETE group	16 (36.36)	6 (13.64)	–	–
Non-mETE group	16 (36.36)	6 (13.64)		

*, P<0.05. mETE, minimal extrathyroidal extension.

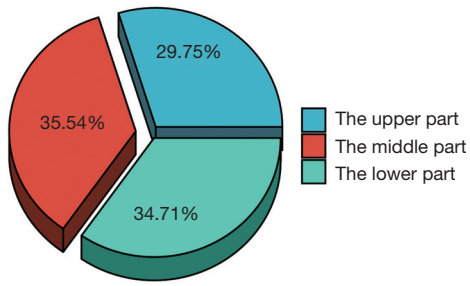

Figure 1 The distribution of mETE in the upper part, middle part, and lower part of the thyroid. mETE, minimal extrathyroidal extension.

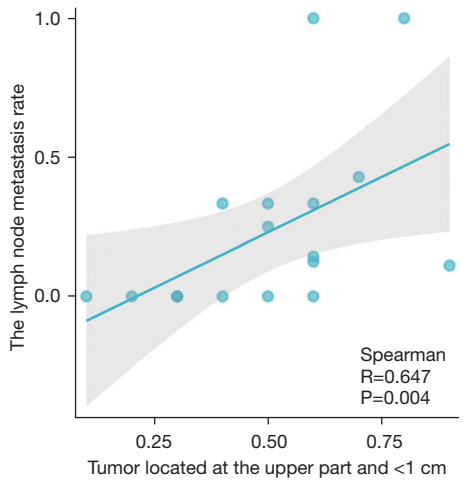

Figure 2 The correlation between the tumors located at the upper part with a size <1.0 cm and lymph node metastasis rate.

The lymph node metastasis in the mETE group

We calculated the distribution of mETE in the upper part, middle part, and lower part of the thyroid. The mETE in the upper part accounted for 29.75%, the middle part and the lower part account for 35.54% and 34.71%, respectively (*Figure 1*). To further analyze, the Spearman correlation analysis was performed to explore the correlation between the tumors located at the upper part with a size <1.0 cm and lymph node metastasis rate (*Figure 2*). The lymph node metastasis rate was shown to be correlated positively with the tumors located at the upper part with a size <1.0 cm (R=0.647; P=0.004). The lymph node metastasis rate is the number of lymph nodes metastasized divided by the total number of lymph nodes dissected in each case.

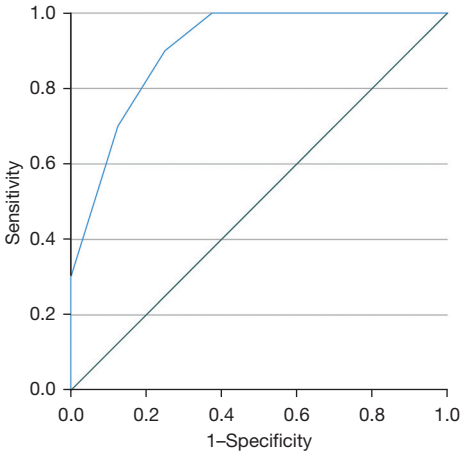

Figure 3 Receiver operating characteristic curves and area under receiver operating characteristic curves for the lymph node metastasis using the size of the tumor located at the upper part with a size <1.0 cm.

The ROC curve for the predictive analysis in the mETE group was plotted

ROC analysis was used to determine the suggested cut-off values for the lymph node metastasis for the size of the tumor located at the upper part with a size <1.0 cm. *Figure 3* shows that the size of the tumor located at the upper part with a size <1.0 cm performed relatively well in the lymph node metastasis. The AUC [95% confidence interval (CI)] for the size of the tumor located at the upper part was 0.906 (0.763–1.000). The best cut-off point for the size of the tumor located at the upper part with a size <1.0 cm in mETE was 0.45 cm (Youden index =0.650).

Discussion

Given that lymph node metastasis is associated with prognosis and recurrence (16), investigating the pattern of lymph node metastasis in PTC holds great significance for guiding the treatment of patients. Currently, there is a widespread consensus that mETE still has a remarkable impact on lymph node metastasis (17-19). However, the limitation of these studies lies in that they fail to distinguish between tumor size and location, and are unable to effectively integrate mETE with the biological behavior of PTC. How mETE should be reflected in Tumor-Node-Metastasis (TNM) staging remains a controversial issue. In an attempt to address those problems, we combined the

location and the size of the tumor to study the pattern of lymph node metastasis in PTC patients with mETE.

In our study, mETE was mainly based upon postoperative pathological reports, typically being described as the tumor's breakthrough of the capsule, the tumor's invasion of the surrounding adipose tissue, or the tumor's invasion of the surrounding striated muscle tissue. In order to eliminate the impact of bilateral thyroid cancer and cervical lymph node metastasis on the analysis, we particularly selected patients who had undergone radical thyroid cancer resection. Our study discovered that there was no statistically significant difference in the number of lymph node dissected between the two groups. However, in comparison with the non-mETE group, for the tumors located in the upper part of the thyroid gland with a size less than 1.0 cm, there was a greater number of lymph node metastasis in the mETE group. At the same time, within the mETE group, the number of patients with lymph node metastasis was greater than that in the non-mETE group. Further subgroup analysis showed that, for PTC patients whose tumors were located at the upper part and whose size was less than 1 cm, the number of people with lymph node metastasis in the mETE group was also more than that in the non-mETE group. These results all demonstrate that mETE indeed increases the risk of lymph node metastasis, and this risk is even more prominent when the tumor is located at the upper pole and its size is less than 1 cm. We further conducted an analysis of the correlation between the size of the tumor located at the upper part with a size <1.0 cm and the lymph node metastasis rate in the mETE group, and the results indicated that the lymph node metastasis rate was shown to be positively correlated with the size of the tumor located at the upper part with a size <1.0 cm (R=0.647; P=0.004).To further analyze, we performed the ROC curve, the AUC (95% CI) for lymph node metastasis was 0.906 (0.763–1.000). The best cut-off point for lymph node metastasis in mETE group was 0.45 cm (Youden index =0.650). The ROC analysis demonstrated that tumors within 1 cm and located at the upper part have a high ability to serve as markers of lymph node metastasis in mETE patients when the tumor size is ≥0.45 cm. To sum up, the present study showed that the tumor located at the upper part with the size <1.0 cm was independently associated with lymph node metastasis in patients with mETE. We speculate that it is related to several factors: it is generally believed that the lymphatic drainage pathway in the thyroid gland is: follicular wall lymphatic network—interlobular lymphatic vessel—subcapsular lymphatic vessel—capsular lymphatic vessel (20). Some studies suggest that the upper part thyroid cancer has a lymphatic pathway that directly drains into the lateral neck, but this has not been anatomically confirmed (21). The newly formed lymphatic vessels are mainly located around the cancer and provide channels for lymphatic metastasis (22). Relatively speaking, the upper part of the thyroid gland has a small volume and is more prone to lymph node metastasis itself. mETE appears when the tumor volume is very small, indicating that the tumor has strong invasive behavior and is more likely to produce lymph node metastasis. Moreover, with the passage of time and the increase of tumor size, the probability of such metastasis is higher. However, when the tumor volume is large and no mETE is present, it indicates a milder tumor location and biological behavior. From a molecular biology perspective, it may be related to Podoplanin, vascular endothelial growth factor C (VEGF-C) and vascular endothelial growth factor D (VEGF-D) etc. (23-25). Further research is needed on the specific molecular mechanisms.

The TNM staging system is the benchmark for preoperative and postoperative staging of cancer patients, predicting patient survival, and selecting treatment options. It is the most widely used tumor staging system in the world today. Many factors, such as tumor size, surrounding tissue infiltration, histological differentiation, and vascular infiltration, have been reported as important prognostic factors for most solid tumors after surgery. The staging of DTC in the previous 8th edition of the AJCC has made certain improvements in comparison with the staging in the 7th edition, yet it still exhibits some limitations (26). Therefore, we hope that the new staging system of PTC can incorporate tumor location, size, and whether it is combined with mETE into the T staging to better guide postoperative treatment and provide prognostic information.

There are some limitations in this study. Firstly, the research type is retrospective study, and there is a selection bias. Secondly, being restricted by the incidence rate of mETE, the number of individuals in the experimental group was small, and the data could not fully represent the actual situation. The results still require further validation by large research centers. Finally, we have not yet been able to explain the reasons for this outcome from a molecular mechanism perspective.

Conclusions

Although the latest edition of the DTC AJCC staging

system suggests that mETE is no longer quite important for tumor staging, while the probability of lymph node metastasis increases in tumors located at the upper part with a size <1.0 cm. Especially when the upper part tumor is within 1 cm, the tumor's size ≥0.45 cm is more likely to have lymph node metastasis. Therefore, we suggest that the PTC patients with mETE should be individualized T-staging based on their tumor location and size in the new AJCC T-staging edition. That would better guide clinical treatment and provide prognostic information.

Acknowledgments

We thank all the members for their generous participation. We would like to thank YUSSFF for his help in polishing our paper.
Funding: This study was funded by the 2024 Xiamen Medical and Industrial Integration Guidance Project (No. 3502Z20244ZD2011) and the 2022 Xiamen Medical and Health Guidance Project (No. 3502Z20224ZD1002).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-24-273/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-273/dss

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-273/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-24-273/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The First Affiliated Hospital of Xiamen University (No. XMYY-20022KYSB144) and individual consent for this retrospective analysis was waived.

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Cite this article as: Zhan H, Hong Y, Zhang L, Huang K, Zheng M, Zhang F. Impact of location and size of minimal extrathyroidal extension on lymph node metastasis in papillary thyroid cancer: a retrospective analysis. Gland Surg 2024;13(9):1619-1627. doi: 10.21037/gs-24-273