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Minimal extrathyroid extension in papillary micro carcinoma of the thyroid is an independent risk factor for relapse through lymph node and distant metastases

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ABSTRACT

Aims

Minimal extrathyroid extension (mETE) is no longer considered in the new 8th edition of the AJCC/UICC staging system. Therefore, papillary thyroid microcarcinoma with mETE previously staged as pT3 will now be staged as pT1a and most likely not receive adjuvant radioiodine therapy. However, it remains unclear if mETE is associated with higher aggressiveness in papillary thyroid microcarcinoma. Therefore, the aim of this study was to investigate if mETE is associated with higher risk of lymph node or distant metastases.

Methods

721 patients with thyroid papillary microcarcinoma presenting at our department for postoperative counseling from 05/1983 to 8/2012 were included in this retrospective analysis (median follow-up time 9.30 years). The impact of mETE on the presence of lymph node metastases at thyroidectomy and relapse through lymph node and distant metastases was assessed by logistic regression and Fine-Gray model analyses.

Results

10.7% (n=77) of patients had mETE. mETE was an independent risk factor for lymph node metastases at thyroidectomy with an adjusted odds ratio of 4.33 (95%CI: 2.02-9.60, $p<0.001$) in multivariable analysis. Patients with mETE had significantly more relapses through lymph node (over 5 years: 13.1% vs. 1.25%; $p < 0.001$) and distant metastases (over 5 years: 7.8% vs. 1.1%; $p < 0.001$) compared to patients without mETE. mETE was an independent risk factor for relapse through lymph node and distant metastases in multivariable analysis (hazard ratio: 7.78, 95%CI: 2.87-21.16, $p< 0.001$ and 4.09, 95%CI: 1.25-13.36, $p=0.020$).

Conclusion

mETE is a statistically significant and independent risk factor for relapse through lymph node and distant metastases in papillary microcarcinoma. Therefore, future studies should evaluate, if patients with mETE and microcarcinoma might benefit from intensified surveillance and therapy.

ABBREVIATIONS

AJCC: American Joint Committee on Cancer

ATA: American thyroid association

DTC: Differentiated thyroid cancer

LNM: Lymph node metastases

METE: Minimal extrathyroid extension

PTC: Papillary thyroid cancer

PTMC: Papillary thyroid microcarcinoma

UICC: Union for International Cancer Control

INTRODUCTION

Differentiated thyroid cancer (DTC) is classified according to the AJCC/UICC TNM system and has an increasing incidence, especially of small papillary tumors ≤ 10 mm (*1*). Up to the 7th edition of the TNM system, minimal extrathyroid extension (mETE) was considered in determining the T-stage. However, several studies demonstrated mETE to have no impact on disease-related mortality, e.g. a study by Hay et al. with 3,524 patients or a meta-analysis by Diker-Cohen with 23,816 patients (*2–6*). Also, there are studies demonstrating no impact of mETE on recurrence free survival in DTC (*7–9*).

Since the TNM system strives for optimal prediction of cancer-related overall survival, the new 8th edition of the AJVV/UICC cancer staging manual no longer considers mETE (*10*). In consequence, tumors < 4 cm with mETE which would have been classified as T3 according to the 7th edition are now classified as T1 when ≤ 2 cm or T2 if > 2 and ≤ 4 cm (*11–13*).

However, patients wth mETE in the aforementioned studies had significantly more often radioiodine therapy (RAI) than those without mETE. This is not surprising since according to the 7th edition of TNM tumors with mETE were classified as at least T3, for which according to ATA and the European Society for Medical Oncology radioiodine therapy should be considered (*14,15*). Hence, tumors with mETE could represent a more aggressive subset of tumors, only showing comparable survival rates to completely intrathyroidal tumors due to higher rates of initial radioiodine therapy according to the higher T stages.

Moreover, in the aforementioned studies, the impact of mETE was not studied in a microcarcinoma (PTMC) only group, but for tumors with various sizes. In the case of a large 4-cm-sized tumor, it seems plausible that mETE might not additionally influence survival. Yet, in small tumors with a diameter ≤ 1 cm, mETE might still be clinically relevant. The impact of

removing mETE from T-staging in the 8th edition of the TNM system is especially pronounced for papillary carcinoma ≤ 10 mm with mETE, which will now be attributed the lowest possible T-stage pT1a instead of T3.

Therefore, the aim of the present study was to investigate, if mETE is an independent risk factor for tumor relapse in a large cohort of patients with PTMC and should be accounted for.

MATERIALS AND METHODS

Patients, Postoperative Management and Follow-up

For this retrospective analysis, 721 consecutive patients with PTMC initially presenting in our department for postoperative counseling from 05/1983 to 08/2012 were enrolled. The median follow-up time was 9.30 years, with the last follow-up data recorded in 12/2020.

Extent of thyroidectomy and lymph node resection are detailed in Table 1. Histological and TNM classifications were present for all patients. To ensure consistent TNM classification, all patients were (re-)classified according to the AJCC/UICC 6th edition (1997). Patients were divided into two groups: Tumors confined to the thyroid and those with mETE as previously published (*16,17*). Tumors were designated as mETE when the pathology report of the thyroidectomy sample stated minimal extrathyroid extension (*12,18*). 74.9% of patients received adjuvant RAI treatment with consecutive ^{131}I-whole-body scintigraphy after initial presentation. Between surgery and ^{131}I-treatment, L-thyroxine treatment was withheld or stopped for 4 – 6 weeks (*19*). In those patients that received RAI-therapy, stimulated thyroglobulin measurement, cervical ultrasound and diagnostic whole-body scintigraphy with ^{131}I were performed 3 to 6 months and 1 year after initial adjuvant RAI in accordance with national and international standards prevailing at the time (*20,21*). If one or more of these diagnostic tests were positive, further courses of ^{131}I were given as needed (*19*). Long-term follow-up consisted of Tg measurement on LT4 therapy, serum thyrotropin and neck ultrasound yearly.

Table 1 describes the patients' characteristics in detail. The study protocol was approved by the local ethics committee (2019-459-f-S) and performed in accordance with the 1964 Declaration of Helsinki and its later amendments.

Endpoints

Primary endpoints were cumulative incidence of lymph node metastases (1) and distant metastases relapse (2). Secondary endpoint was the presence of lymph node metastases in the thyroidectomy sample. Analyses were adjusted for extent of thyroidectomy and lymph node dissection if numerically feasable.

Distant metastases were diagnosed based on surgery with histologic workup or on a composite score requiring positive RAI imaging findings and elevated thyroglobulin (Tg) levels. Relapse through distant metastases was considered present when distant metastases were diagnosed after thyroidectomy, including recurrence in non-regional lymph nodes or visceral sites. Table 2 provides details on the detection of distant metastases. LNM-relapse was considered in two cases: 1) When LNM were diagnosed in patients without LNM in the thyroidectomy sample after thyroidectomy. 2) When LNM became apparent in patients who had LNM in the thyroidectomy sample in the course of follow-up after initial adjuvant RAI-treatment. In both cases diagnoss were based on a composite score consisting of RAI imaging and elevated thyroglobulin levels or surgery with histological work up. Presence of LNM in the thyroidectomy sample was histologically ascertained in all patients that underwent lymph node resection.

Statistical Analysis

Normally-distributed data are described using mean and standard deviation, non-normally-distributed using median and interquartile range. Normality was assessed by histograms and skewness statistics. Univariable and multivariable logistic regression analyses were carried out to evaluate the effect of age, sex, tumor size, multifocality, extent of lymph node resection and mETE on the presence of LNM at thyroidectomy, in the subgroup of patients that had lymph node

resection (i.e. known nodal status at thyroidectomy). Results are reported as odds ratios (OR), corresponding 95% confidence intervals (95%CI) and p-values of the Wald test.

Time-to-event data were analyzed within a competing risk framework accounting for the competing risk of death. As distant metastases at thyroidectomy were considered a terminal event, the corresponding endpoint was analysed in the subgroup of patients without distant metastases at thyroidectomy. Cumulative incidences of distant metastases and LNM relapse after thyroidectomy were estimated based on the Fine-Gray model and compared between mETE positive and negative patients using Gray's test (*22,23*). To adjust for further factors, a multivariable Fine-Gray subdistribution hazard regression was conducted. Results are presented as subdistribution hazard ratios (HR), corresponding 95% CIs and p-values. Follow-up times were calculated by reverse Kaplan-Meier. All inferential statistics were intended to be exploratory and were interpreted accordingly. The reported two-sided p-values were used only to generate new hypotheses. p-values ≤ 0.05 were considered statistically significant. Analyses were performed using R statistical software version 3.6.1 (The R Foundation, r-project.org).

RESULTS

Patient Characteristics

Between 05/1983 and 28/2012, 721 patients with PTMC presented for postoperative counseling in our department. Patients were followed up on a yearly basis (median follow up time 9.30 years). No patient died due to thyroid cancer. mETE was present in 77 (10.7%) of patients Patient characteristics are summarized in Table 1. Comparative characteristics between patients with confined tumors and mETE are presented in Table 3.

Differences between Patients with and without mETE

The proportion of patients with LNM in the thyroidectomy sample (subcohort of patients with lymph nodes resected at the thyroidectomy, N=216) was higher in patients with mETE (27/44, 61.4%) compared to those without mETE (49/172, 28.5%, $p < 0.001$). LNM-relapse occurred in 11 out of 77 patients (14.3%) with mETE in the course of follow-up and 10 out of 644 patients without mETE (1.6%). Relapse through distant metastases (subcohort of patients without known distant metastases at thyroidectomy, N=719) occurred in 7 out of 77 patients in the subgroup of patients with mETE (9.1%), and in 8 out of 642 patients with confined tumors (1.2%). See Table 3 for additional differences between patients with mETE and confined tumors. To adjust for interfering effects and loss to follow-up, multivariate regressions and survival analysis were performed in the next section.

Risk Factors Associated with Lymph Node Metastases Detected at Thyroidectomy

Risk factors associated with LNM detected at thyroidectomy where analyzed in the subset of patients that had lymph nodes removed at thyroidectomy (n=216). In 140 out of those 216

patients (64.8%), no LNM were found, 55 (25.5%) had central LNM and 21 (9.7%) LNM in the lateral compartment.

The proportion of patients with LNM was higher in patients with mETE (27/44, 61.4%) compared to those without mETE (49/172, 30,2%, p <0.001).

Results of the multivariable analysis using logistic regression are summarized in Table 4 and visualized in Figure 1. Sex, extent of lymph node resection (neck dissection vs. node picking) and mETE were significant risk factors for LNM, while tumor size was not. Adjusted odds ratio for LNM in regard to mETE was found to be 4.33 (95%CI: 2.02-9.60, p<0.001).

Risk Factors Associated with Lymph Node Metastases Relapse

LNM relapse occurred in 21 out of 721 patients during the course of follow up (11/77 of patients with mETE, 10/644 without mETE). The five-year cumulative incidences were given by 13.12% (95% CI: 6.69– 21.77) and 1.25% (95% CI: 0.59– 2.37, p<0.001), for patients with mETE and those with confined tumors, respectively (Figure 2).

In the multivariable competing risk regression (Table 5), mETE (HR: 7.80, 95%CI: 2.87-21.16, p<0.001), male sex (HR: 4.17, 95%CI: 1.63-10.67, p=0.003), and tumor size (HR: 1.15, 95%CI: 1.02-1.30, p=0.022) were found to be independent risk factors for LNM relapse while age and multifocality were not.

Risk Factors Associated with Distant Metastasis Relapse

Distant metastases occurred in 15 out of 719 patients without distant metastases at thyroidectomy during the course of follow-up (mETE: 7/77, confined: 8/642). The five-year cumulative incidences were given by 7.79% (95% CI: 3.16-15.19) and 1.11% (95% CI: 0.50-2.19, p<0.001), for patients with mETE and those with confined tumors respectively (Figure 3).

In multivariable competing risk regression (Table 6) both mETE and the presence of LNM at thyroidectomy (N1 vs. N0) were found to be independent risk factors for distant metastases occurrence after thyroidectomy (HR: 4.09, 95%CI: 1.25-13.36, p=0.020 and HR: 8.76, 95%CI: 1.16-66.17, p=0.035).

DISCUSSION

The risk of lymph node metastases at thyroidectomy and relapse through LNM and distant metastases in patients with PTMC was analyzed with regard to mETE by the present study. mETE was found to be an independent risk factor for the presence of LNM at thyroidectomy and an independent risk factor for relapse through both distant and LNM.

The implications of mETE in papillary thyroid cancer are highly controversial. Multiple studies have reported that mETE is not associated with higher rates of LNM, distant metastases, or mortality in differentiated thyroid cancer (*3,4,24*). Therefore, mETE was removed from the new 8th edition of the TNM staging system. However, it seems unjustified to compare the outcome of patients with mETE to those without, as both groups have been treated with different intensity: patients with mETE significantly more often received RAI, compared to patients without mETE (*2*). Therefore, the not observed difference in outcome between the groups might have been caused by confounding factors.

The impact of removing mETE from T staging is especially pronounced for papillary carcinoma ≤ 10 mm with mETE, which would have previously been staged as T3. With the new 8th edition of TNM, these tumors are now attributed to the lowest possible stage pT1a. Very recent studies including differentiated thyroid cancer of all sizes indicate that not only gross, but also minimal extrathyroid extension is associated with increased mortality and recurrence (*25,26*). To further corroborate these findings, the implications of mETE was assessed in a large, homogenous group of patients with PTMC by the present study.

Increased odds for LNM presence at surgery in patients with mETE were observed in the present study. This indicates that mETE tumors show a more aggressive phenotype. The finding is

well in line with the results of Zhi et al. and others, finding mETE to be a risk factor for LNM in patients with PTMC (*25–31*).

Castagna et al. reported that mETE is a risk factor for LNM only in patients with a tumor size greater than 1.5 cm (*32*). This in contrast to our findings, which showed that mETE positive patients are more frequently affected by LNM at thyroidectomy than mETE negative patients, irrespective of tumor size (Figure 1).

The role of mETE for relapse through distant metastases in PTMC is likewise controversial. Six previous studies with PTMC-only cohorts could not find an impact of mETE on any cancer recurrence (*5,26,29,31,33,34*). However, the cohorts in those studies were rather small, ranging from 144 to 288 patients. Three studies with larger PTMC-only cohorts, ranging from 287 to 531 patients, were able to demonstrated an impact of mETE on relapse in univariable analysis (*17,27,35*). However, these studies did not investigate distant metastsases relapse, but any cancer recurrence. To date, there was no evidence for a higher rate of relapse for distant metastases associated with mETE. Our study in contrast, employing a cohort of 721 patients, could show for the first time that mETE is a statistically significant independent risk factor both for LNM and distant metastases relapse. As distant metastases are associated with a significantly worsened prognosis, this finding is of great clinical relevance (*15*).

The presence of LNM at thyroidectomy was identified as a further independent risk factor for relapse through distant metastases. Therefore, patients with LNM and mETE seem to have a particularly high risk of distant metastases after thyroidectomy compared to patients without both characteristics. Due to the delayed effects associated with mETE (i.e. relapse through distant metastases) it seems advisable to still integrate mETE in the T stage as proposed by Schmid et al. (*12*).

Given the higher cumulative incidence of LNM and distant metastases relapse in patients with PTMC and mETE compared to those without, adjuvant RAI might be advisable. A study by Rosario et al. investigated disease recurrence rates of patients with mETE who did not receive adjuvant RAI (*36*). Only 2% of their patients had recurrent disease, leading to their conclusion that RAI can be omitted in patients with mETE. However, only patients without LNM at diagnosis and only 20 patients with PTMC have been enrolled, which hampers their results' transferability. As mETE is a risk factor for lymph node and especially distant metastases, mETE-positive tumors might be biologically more aggressive and could deserve an intensified treatment. Especially patients with both LNM in the thyroidectomy sample and mETE might benefit from an initial RAI. Until further studies explicitly investigate the benefit of RAI in patients with PTMC and mETE, the clinician has to carefully review the pathological report after thyroidectomy and discuss the option of adjuvant RAI when mETE is present.

The present study faces some limitations. It was conducted retrospectively and might therefore be influenced by selection biases. To counteract this effect, all patients from a period larger than 30 years have been included. However, the accuracy of diagnostic procedures has increased, which could influence the detection of metastases. Despite the long recruitment period, the number of included patients is relatively small. The presence of LNM at thyroidectomy could only be evaluated in patients that underwent lymph node resection. These patients might not represent a random subset of PTMC patients, which could limit our findings regarding this endpoint. The extent of thyroidectomy could not be included into the competing risk models of lymph node and distant metastases recurrence due to numerical reasons (nearly all patients had total thyroidectomy). Given the low incidence of mETE, multicentric analyses have to corroborate the present initial findings. Another limitation arises from the controversy among pathologists about what constitutes mETE, with currently no standardized histopathologic criteria (*18,37*). The

pathology reports from which the presence of mETE was derived for this study were issued by numerous pathologists from different institutions, possibly applying varying criteria for the diagnosis of mETE.

CONCLUSION

Minimal extrathyroid extension is an independent risk factor for cancer relapse through lymph node and distant metastases in papillary microcarcinoma of the thyroid. Therefore, future studies should evaluate, if patients with mETE and microcarcinoma might benefit from intensified surveillance and/- or therapy.

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The graphical absctract was created with BioRender.com

KEY POINTS

QUESTION: Is minimal extrathyroid extension an independent risk factor for cancer relapse in papillary microcarcinoma of the thyroid?

PERTINENT FINDINGS: This retrospective cohort study included 721 patients with thyroid papillary microcarcinoma presenting for postoperative counseling in a single institution with a median follow-up time of 9.30 years. Minimal extrathyroid extension was found to be a statistically significant and independent risk factor of cancer relapse through both lymph node and distant metastases.

IMPLICATIONS FOR PATIENT CARE: Papillary microcarcinoma patients with minimal extrathyroid extension might benefit from intensified surveillance and/ or therapy.

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TABLES

Table 1: Patient characteristics of the included cohort.

Patient characteristics	Total cohort	Confined	mETE	Uni-variate Analysis p*
Number of patients(%)	721	644 (89.3)	77 (10.7)	
Sex=male(number(%))	154 (21.4)	145 (22.5)	9 (11.7)	0.041
Age in years (mean(SD))	47.95 (12.83)	48.02 (12.77)	47.38 (13.42)	0.678
Median follow-up in years (95%CI)**	9.30 (8.89-9.94)	8.94 (8.40-9.43)	12.85 (10.76-14.38)	0.002
Extent of thyroidectomy(%)				<0.001
Hemithyroidectomy	18 (2.5)	18 (2.8)	0 (0.0)	
Subtotal thyroidectomy	126 (17.5)	125 (19.4)	1 (1.3)	
Total thyroidectomy	577 (80.0)	501 (77.8)	76 (98.7)	
Lymph node dissection(%)				<0.001
No lymph nodes resected	505 (70.0)	472 (73.3)	33 (42.9)	
Node picking	51 (7.1)	46 (7.1)	5 (6.5)	
Central compartment node dissection	120 (16.6)	93 (14.4)	27 (35.1)	
Central and lateral neck node dissection	45 (6.2)	33 (5.1)	12 (15.6)	
Number of removed lymph nodes (median[IQR])	0 [0,1]	0 [0,0]	2 [0,10]	<0.001
Adjuvant RAI treatment(%)	540 (74.9)	463 (71.9)	77 (100.0)	<0.001
Cumulative RAI activity in GBq (median[IQR])	3.00 [0.00,6.00]	3.00 [0.00,4.00]	6.00 [3.00,10.00]	<0.001
Number of RAI treatments (median[IQR])	1.00 [0.00,2.00]	1.00 [0.00,1.00]	1.00 [1.00,2.00]	<0.001
Pre RAI treatment TSH in µU/ml (median[IQR])	43.06 [15.62,77.26]	39.17 [13.24,76.89]	59.36 [42.20,77.72]	0.001
Pre RAI treatment thyreoglobulin in ng/ml (median[IQR])	2.30 [0.62,8.45]	2.50 [0.60,8.67]	2.20 [0.80,7.00]	0.935

RAI = radioactive iodine; SD = standard deviation; IQR = inter quartile range. *Determined with Fisher's exact test for categorical variables and Wilcoxon test for continuous variables;** calculated by reverse Kaplan-Meier

Table 2: Detailed report on patients with distant metastases.

mETE	Age at initial presentation	Type of distant metastasis	Initial LNM	Tumor diameter in mm	Days between postoperative counseling and confirmation of metastasis
No	65	Mediastinal LNM	No	4	119
Yes	68	Bone	No	5	4213
No	69	Bone	No	1	-25*
No	30	Pulmonary	No	7	454
No	26	Pulmonary	No	10	830
No	48	Bone	No	4	7
No	25	Bone	No	9	0
No	44	Pulmonary	No	7	40
Yes	54	Bone and Pulmonary	Yes	9	50
Yes	58	Pulmonary	No	9	121
Yes	55	Pulmonary	Yes	5	61
No	48	Pulmonary	Yes	4	4309
No	15	Pulmonary	Yes	10	14
Yes	15	Pulmonary	Yes	8	28
Yes	37	Pulmonary	Yes	3	256
Yes	23	Pulmonary	Yes	5	442
No	6	Pulmonary	Yes	10	22

* Initial diagnosis of thyroid cancer was made after bone metastasis confirmation.

Table 3: Characteristics of patients with and without mETE.

Patient characteristics	Total cohort	Confined	mETE	Univariable Analysis p*
Number of patients(%)	721	644 (89.3)	77 (10.7)	
Number of metastasized lymph nodes (median[IQR])	0 [0,0]	0 [0,0]	0 [0,1]	<0.001
Nodal stage given by histopathologic examination of the surgical specimen(%)				<0.001
pN0	137 (19.0)	120 (18.6)	17 (22.1)	
pN1a	57 (7.9)	39 (6.1)	18 (23.4)	
pN1b	22 (3.1)	13 (2.0)	9 (11.7)	
pNx	505 (70.0)	472 (73.3)	33 (42.9)	
Five-year cumulative incidence of lymph node metastases relapse in % (95%CI)	2.54 (1.57-3.91)	1.25 (0.59-2.37)	13.12 (6.69-21.77)	<0.001
Five-year cumulative incidence distant metastases relapse in % (95%CI)**	1.83 (1.03-3.03)	1.11 (0.50-2.19)	7.79 (3.16-15.19)	<0.001
Tumor size in mm (median[IQR]	5.00 [3.00,8.00]	5.00 [3.00,8.00]	8.00 [6.00,10.00]	<0.001
Multifocal disease(%)	135 (18.7)	118 (18.3)	17 (22.1)	0.520

RAI=radioactive iodine; SD=standard deviation; IQR=inter quartile range. *Determined with Fisher's exact test for categorical variables and Wilcoxon test for continuous variables; ** assessed in the subset of patients without distant metastases at thyroidectomy (N=719)

Table 4: Univariable and multivariable logistic regression analysis of risk factors for lymph node metastasis diagnosed in histologic workup of thyroidectomy sample adjusted for lymph node and thyroidectomy extent. Only the subgroup of patients that had lymph nodes resected are included (N=216).

	LNM -	LNM +	Odds ratios univariable analysis (95% CI)	*p univariable analysis*	Odds ratios multivariable analysis (95% CI)	*p multivariable analysis*
N	140	76				
Sex = male (%)	24 (17.1)	25 (32.9)	2.37 (1.24-4.56)	0.009	2.83 (1.36-5.98)	0.006
Age (mean (SD))	44.79 (12.50)	41.54 (13.92)	0.98 (0.96-1.00)	0.082	0.98 (0.96-1.01)	0.183
Tumor size in mm (median [IQR])	7.00 [4.00,9.00]	7.00 [5.00,9.00]	1.05 (0.94-1.18)	0.378	1.04 (0.91-1.18)	0.579
Multifocality (%)	27 (19.3)	16 (21.1)	1.12 (0.55-2.21)	0.756	1.09 (0.49-2.39)	0.834
Neck dissection vs. node picking (%)	93 (66.4)	72 (94.7)	9.10 (3.50-31.17)	<0.001	6.55 (2.41-23.05)	<0.001
Total thyroidectomy vs. subtotal/hemthyroidectomy (%)	131 (93.6)	74 (97.4)	2.54 (0.63-16.96)	0.241	1.28 (0.25-9.94)	0.782
mETE (%)	17 (12.1)	27 (35.5)	3.99 (2.02-8.09)	<0.001	4.33 (2.02-9.60)	<0.001

mETE=minimal extrathyroid extension, LNM=lymph node metastases, SD=standard deviation; IQR=inter quartile range, CI=confidence interval.

Table 5: Multivariable competing risk regression analysis for lymph node metastasis relapse after thyroidectomy based on Fine-Gray proportional subdistribution hazards model.

Variable	HR	95% CI	p-value
Sex (male-female)	4.17	1.63-10.67	0.003
Age	1.00	0.98-1.03	0.690
Tumor size	1.15	1.02-1.30	0.022
Multifocality (yes-no)	2.44	0.97-6.17	0.060
Lymph nodes resected at thyroidectomy (yes vs. no)	3.23	1.33-7.86	0.010
mETE (yes-no)	7.80	2.87-21.16	<0.001

HR = hazard ratio, CI = confidence interval

Table 6: Multivariable competing risk regression analysis for distant metastasis relapse after thyroidectomy based on Fine-Gray proportional subdistribution hazards model.

Variable	HR	95% CI	p-value
Sex (male-female)	1.52	0.48-4.82	0.470
Age	0.96	0.91-1.01	0.140
Tumor size	1.06	0.85-1.32	0.610
Multifocality (yes-no)	2.25	0.73-6.90	0.160
N status at thyroidectomy (Nx vs. N0)	2.60	0.30-22.51	0.390
N status at thyroidectomy (N1 vs. N0)	8.76	1.16-66.17	0.035
mETE (yes-no)	4.09	1.25-13.36	0.020

HR = hazard ratio, CI = confidence interval

FIGURES

Figure 1: Addjusted odds rations for lymph node metastases at thyroidectomy (evaluated in the subgroup of patients that had lymph nodes resected at thyroidectomy, N=216). Odds ratios in tabularly form are found in Table 4.

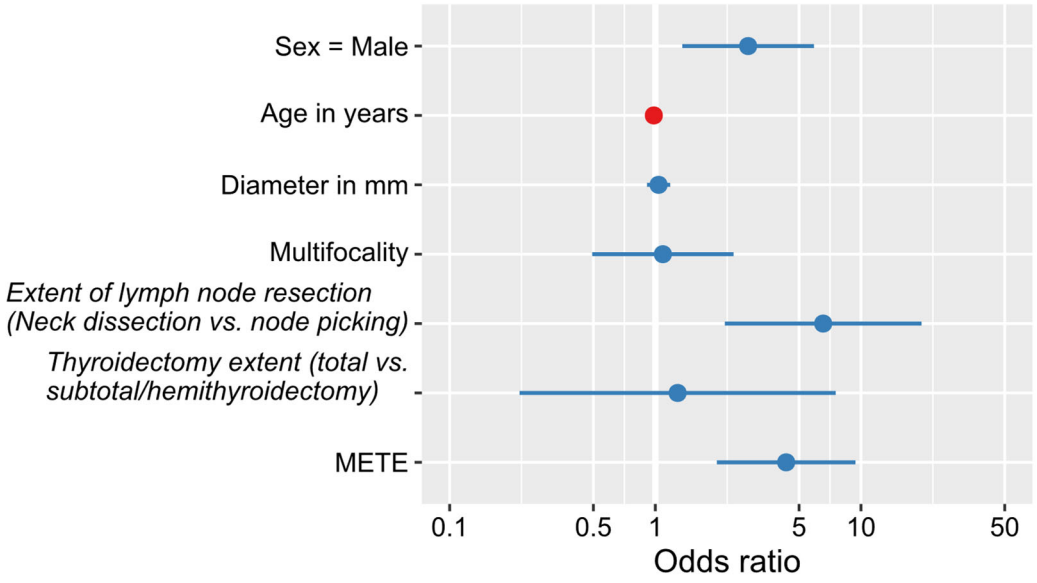


Figure 2: Cumulative incidence function of LNM-relapse after thyroidectomy stratified by mETE. Curves were compared using Gray's test (N=721).

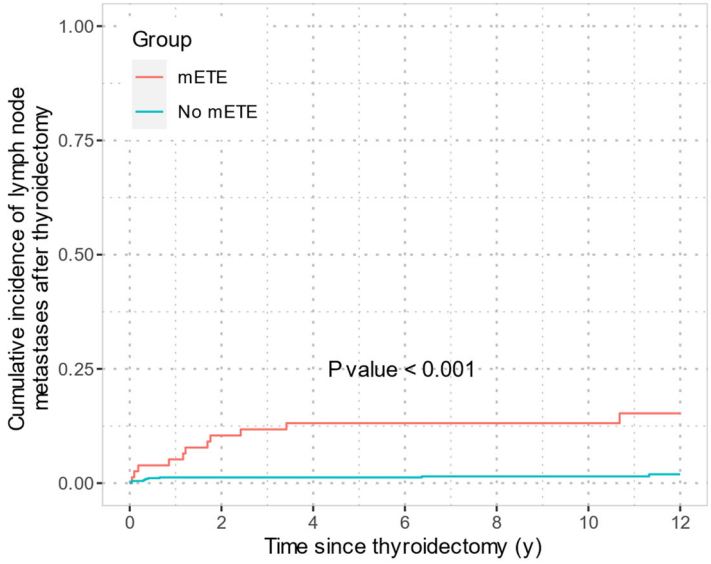
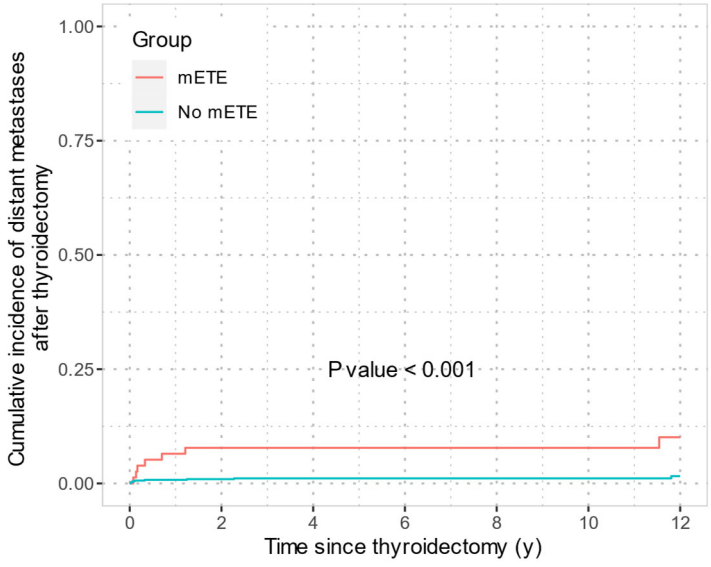


Figure 3: Cumulative incidence function of distant metastases relapse after thyroidectomy in the group of patients without distant metastases at thyroidectomy (N=719) stratified by mETE. Curves were compared using Gray's test.



GRAPHICAL ABSTRACT