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Original Research

Predictors of treatment response in lymphogenic metastasized papillary thyroid cancer: a histopathological study

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Abstract

Background: Lymph node metastases in papillary thyroid cancer (PTC) increase the risk for persistent and recurrent disease. Data on the predictive value of histopathological features of lymph node metastases, however, are inconsistent. The aim of this study was to evaluate the prognostic significance of known and new histopathological features of lymph node metastases in a well-defined cohort of PTC patients with clinically evident lymph node metastases.

Methods: A total of 1042 lymph node metastases, derived from 129 PTC patients, were reexamined according to a predefined protocol and evaluated for diameter, extranodal extension, cystic changes, necrosis, calcifications, and the proportion of the lymph node taken up by tumor cells. Predictors for a failure to achieve a complete biochemical and structural response to treatment were determined.

Results: The presence of more than 5 lymph node metastases was the only independent predictor for a failure to achieve a complete response to treatment (odds ratio [OR] 3.39 [95% CI, 1.57-7.33], $P < .05$). Diameter nor any of the other evaluated lymph node features were significantly associated with the response to treatment.

Conclusions: Detailed reexamination of lymph nodes revealed that only the presence of more than 5 lymph node metastases was an independent predictor of failure to achieve a complete response to treatment. No predictive value was found for other histopathological features, including the diameter of the lymph node metastases. These findings have the potential to improve risk stratification in patients with PTC and clinically evident lymph node metastases.

Keywords: papillary thyroid cancer, lymph node metastases, treatment response, histopathological characteristics, risk stratification

Significance

This study aimed to quantify the prognostic implications of known histopathological features of lymph node metastases in papillary thyroid cancer and identify new predictors. A detailed reexamination of lymph node metastases was performed in a homogenous cohort of patients with clinically evident lymph node metastases that were all treated with thyroidectomy and radioactive iodine ablation. The presence of more than 5 lymph node metastases was the only independent predictor of failure to achieve a complete response to treatment. Neither size, extranodal extension, nor other examined histopathological lymph node features independently added to the risk of a failure to achieve a complete response. These findings have the potential to improve risk stratification for PTC patients with clinically evident lymph node metastases.

Introduction

Papillary thyroid cancer (PTC) is the most common histological subtype of thyroid cancer, accounting for approximately 80% of cases.[1] The disease course is generally indolent, and it has a 25-year cause-specific survival rate of 95%.[2] Lymph node metastases may occur in up to 50% of patients depending on the extent of surgery and interpretation of the pathologist.[3-6] The risk for persistent and recurrent disease is increased in patients diagnosed with lymph node metastases.[7,8] Risk factors for lymph node metastases include male sex, younger age, and higher T stage of the primary tumor.[9] Guidelines recommend to perform a therapeutic neck dissection in patients presenting with clinically evident lymph

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node metastases, defined as metastases identified on preoperative imaging or during intraoperative inspection.[4,10]

Different guidelines have incorporated histopathological features of lymph node metastases to inform clinical management.[4,10] For example, the American Thyroid Association (ATA) guideline has included size and number of lymph node metastases in their stratification system to predict the risk of structural disease recurrence.[4] There is limited information if histopathological features of lymph node metastases predict the risk of persistent or recurrent disease, and if so which features are useful in a clinical setting.[6] Studies assessing the prognostic value of number of lymph node metastases, size, cervical location, extranodal extension, or ratio between harvested and metastatic lymph nodes have yielded conflicting results.[6,11-13] This may be explained by heterogeneity in study populations (eg, prophylactic vs therapeutic neck dissection, proportion of patients treated with radioactive iodine [RAI]), the studied histopathological features, and differences in applied definitions for these features. Moreover, most studies are based on available pathology reports, which are prone to reporting bias and lack systemic evaluation, rather than histological reexamination of lymph nodes.[13-21] Furthermore, very few studies have reported on prognostic value of specific histopathological features such as calcifications, cystic appearance, and necrosis.[21,22]

The aim of this study was to define histopathological features that predicted failure to achieve a complete structural and biochemical response to treatment in a well-defined cohort of patients with PTC and clinically evident lymph node metastases. To overcome limitations of previous studies, and with the aim to identify new predictors, all individual lymph node metastases were reexamined.

Methods

Patients

Eligible for inclusion were patients with PTC and clinically evident lymph node metastases at initial presentation, who were at least 18 years old and had a neck dissection performed at the Erasmus Medical Center, a regional tertiary referral center, between January 1, 2002, and December 31, 2016. Furthermore, a minimum follow-up period of 12 months after surgery was required for eligibility, and the pathology slides of the neck dissection had to be available for reexamination. Clinically evident lymph node metastases were defined as lymph node metastases that were either preoperatively detected with palpation or imaging or identified during surgery. This study was conducted in accordance with the amended Declaration of Helsinki. This study was approved by the medical ethical board of the Erasmus University Medical Center (MEC-2018-1195). The requirement for written informed consent was waived, given the retrospective inclusion of patients.

Procedures

Data on demographic characteristics, treatment outcome, and histopathological features of the primary tumor were retrospectively retrieved from medical charts. The AJCC TNM eighth edition for postoperative staging was applied retrospectively.[7] All patients underwent total thyroidectomy and lymph node dissection (either of the central compartment, lateral compartment, or both), followed by at least 1 RAI treatment. Patients received an initial postthyroidectomy RAI dose of ~5550 MBq, except for 1 patient who was treated with 1850 MBq. In the first postoperative year, all patients received thyroid-stimulating hormone (TSH) suppressive treatment with levothyroxine and were followed up with a cervical ultrasound and regular measurements of thyroglobulin (Tg) and thyroglobulin antibodies (TgAbs), measured with *Immulite* 2000XPi (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, United States). In case of absent biochemical and radiological signs of persistent disease 12-18 months postoperative, a dynamic risk stratification was performed consisting of a recombinant TSH-stimulated Tg measurement (rh-TSH-Tg) and neck ultrasound. The response to treatment was assessed according to the classification proposed in the 2015 ATA guideline.[4] Patients were considered to have an excellent response to treatment if Tg while on levothyroxine supplementation (Tg-on) was <0.2 µg/L or rh-TSH-Tg was <1 µg/L, in combination with negative imaging and undetectable TgAb. In case of Tg-on ≥1 µg/L, rh-TSH-Tg ≥10 µg/L, or rising TgAb concentrations, the patient was classified as having a biochemical incomplete response. Patients with structural evidence of disease were classified as structural incomplete response. Finally, patients with one of the following: Tg-on detectable, but <1 µg/L or rh-TSH-Tg ≥1.0 but <10 µg/L, nonspecific findings on imaging studies, and stable or declining TgAb, were considered to have an indeterminate response. In case of progressive disease, treatment was initiated including surgery or additional RAI therapies, followed by a new response evaluation. In 2 patients who lacked a recombinant TSH-Tg measurement, negative imaging more than 10 years after initial treatment was considered a complete response. Recurrent disease was defined as new biochemical or structural disease identified more than 12 months after a complete response had been reached.

All pathology slides of cervical lymph node dissections and lymph nodes found in the thyroidectomy specimen were reevaluated by an experienced endocrine pathologist and scored according to a predefined protocol (Figure S1). We collected the following data: total number of harvested lymph nodes, number of lymph nodes with metastases, location of the lymph node metastasis (central or lateral neck), diameter of the metastasis and the presence of extranodal extension, cystic changes, calcifications (including psammoma bodies) or necrosis, and finally, the proportion of the lymph node taken up by tumor cells (100%, >50%, <50%, or subcapsular tumor localization only). Extranodal extension was defined as invasion of tumor cells beyond the lymph node capsule in the surrounding fat tissue. A cystic change was defined as a cavity within a lymph node metastasis, either looking optically empty or a space filled with papillary structures, macrophages, or colloid. Cystic changes were divided into macroscopic (>1 cm) and microscopic (<1 cm). Examples of examined histopathological features are shown in Figure 1.

Outcomes

The primary outcome was failure to achieve a complete structural and biochemical response to treatment. The secondary outcome was failure to achieve a complete response after initial treatment with surgery and RAI ablation, allowing to identify features that predicted time to achieve a complete response.

Statistical analysis

A logistic regression model was used to test the associations of histopathological lymph node features with the primary

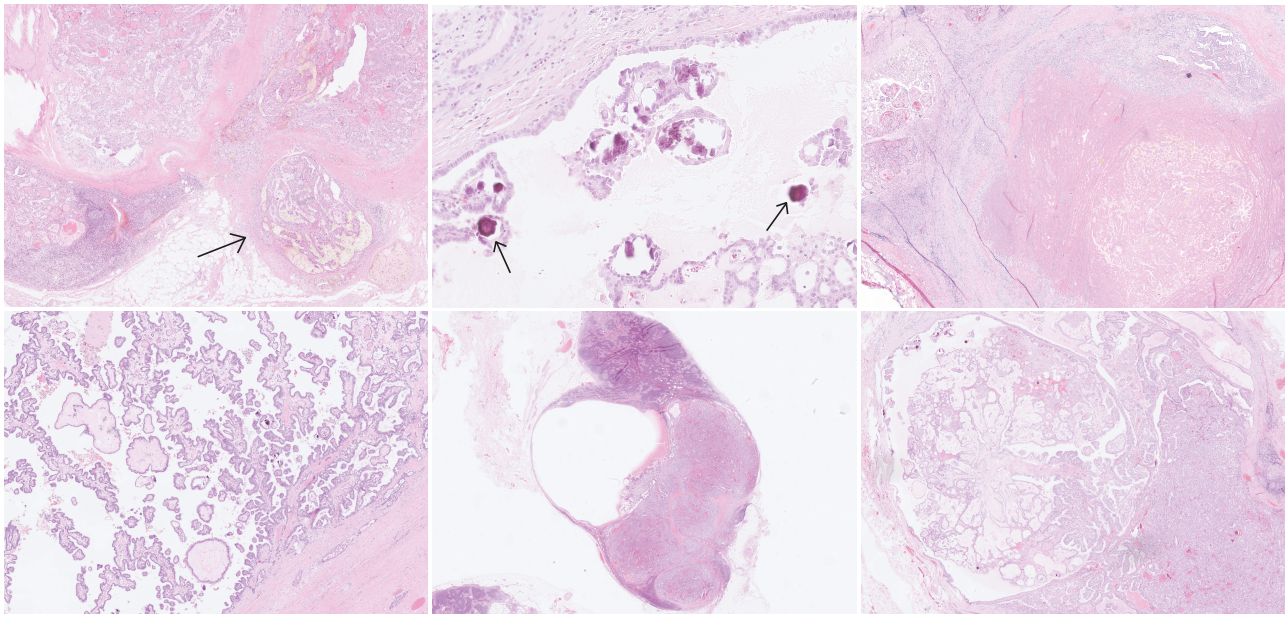

Figure 1. Upper left image: extranodal extension with extracapsular tumor extension into the extranodal fat tissue (indicated by an arrow). Upper middle image: deposits of calcification. Psammoma bodies defined by lamellated round structures are indicated with arrows. Upper right image: necrosis with pink amorphous material and debris on the mid and right side of the image. On the lower row are three examples of microcystic changes characterized by microscopic (<1 cm in diameter) optically open spaces filled with or surrounded by tumor cells.

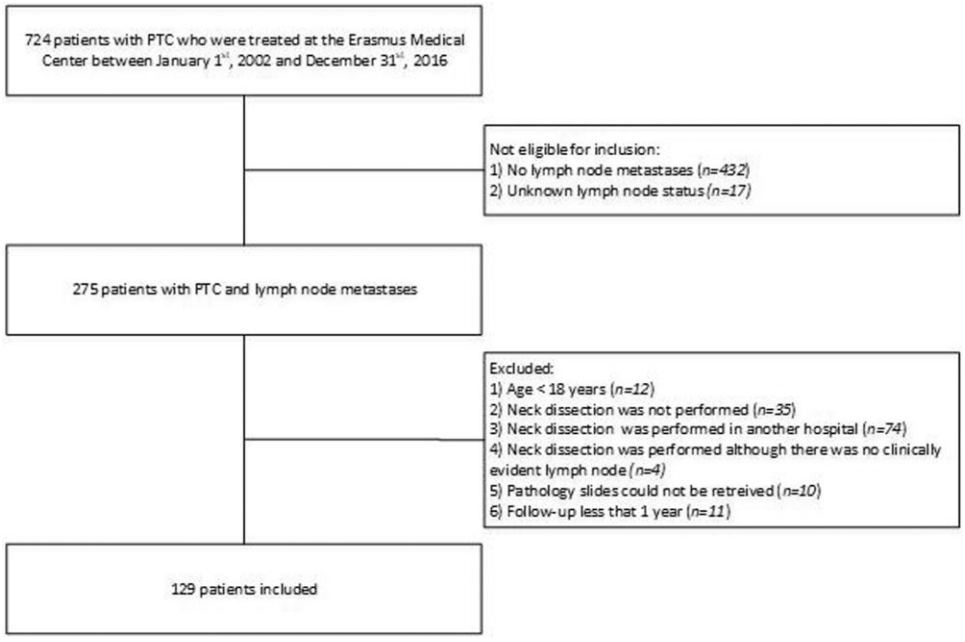

Figure 2. Study participants. Reasons that patients with lymph node metastases did not undergo a neck dissection include the absence of clinically evident lymph node metastases ($n = 12$), the surgery was not possible from a technical point of view (eg, encasement of vital structures; $n = 5$), patient preference ($n = 1$), and unknown due to incomplete data ($n = 17$). PTC, papillary thyroid cancer.

and secondary outcomes. Variables with a $P < .10$ in univariable analysis were selected for the multivariable model. Variables that created collinearity were excluded. A P-value of .05 was considered statistically significant. Differences in the proportion of patients that reached a complete response, stratified by lymph node features, were estimated with the Kaplan–Meier method. Correlations between histopathological features were assessed with a Mann–Whitney U test or Spearman correlation test when appropriate. Receiver operating characteristic (ROC) curve analysis was used to extract sensitivity and specificity values for specific cutoffs of the number of lymph node metastases for the endpoint of a complete response to treatment. A generalized linear mixed model was used to estimate differences between lymph node metastases located in the central vs the lateral neck department. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 25.0.

Results

Patient characteristics

A total of 276 patients with PTC and lymph node metastases were assessed for eligibility, and 129 patients were included for the final analysis (Figure 2). Median follow-up was 76 months (range 15-224). A complete response to treatment was identified in 50.4% (65 out of 129) patients of whom 70.8% (46 out of 65) achieved a complete response after initial treatment with surgery and RAI ablation therapy. Recurrence after a complete response occurred in 4.5% (6 out of 133) patients, and disease-specific mortality was 7.0% (9 out of 133 patients). Baseline characteristics are summarized in Table 1.

Lymph node features: correlations and differences between the central and lateral compartment

In 62.0% (80 out of 129) of patients, more than 5 lymph node metastases were present, while 20.9% (27 out of 129) of patients had a lymph node larger than 3 cm, and 73.6% (95 out of 129) of patients had ≥1 lymph node with extranodal extension. Cystic changes <1 cm were present in 84.5% (109 out of 129) of patients, and cystic changes ≥1 cm were present in 42.6% (55 out of 129) of patients. Necrosis was present in 14.0% (18 out of 133) of patients.

The number of lymph node metastases was correlated with the number of lymph nodes in the lateral compartment (Spearman correlation coefficient [rho] 0.748, $P < .001$), the number of lymph nodes with extranodal extension (rho = 0.501, $P < .001$), and the number of lymph nodes with cystic changes (rho = 0.590, $P < .001$). Compared with lymph node metastases in the central neck compartment, lymph node metastases in the lateral compartment were larger (median diameter 9.0 mm [IQR 3.0-16.8] vs 5.0 mm [IQR 2.5-10], $P < .001$) and had more often cystic changes (OR 1.84 [95% CI, 1.32-2.67], $P < .001$; Table 2).

Predictors for a failure to achieve a complete structural and biochemical response to treatment

The presence of more than 5 lymph node metastases was the only independent predictor for the primary, as well as the secondary outcome (OR 4.17 [1.40-12.4], $P < .05$ and OR 4.14 [1.70-10.0], $P < .01$, respectively; Table 3). Sensitivity and specificity for different cutoffs for the number of lymph node metastases on the outcome of response to treatment are shown in Table S1.

For the primary outcome, there was a positive association of the number of lymph nodes with extranodal extension (OR 1.23 [1.03-1.45], $P = .019$) and the presence of necrosis (OR 3.00 [0.99-9.11], $P = .052$) with failure to achieve a complete response to treatment in univariable, but not in multivariable analysis. For the secondary outcome, there was a positive association of the number of lymph nodes in the lateral compartment (OR 1.20 [1.06-1.35], $P < .01$) with failure to achieve a complete response after initial treatment in univariable, but not in multivariable analysis (Table S2). No prognostic statistical significance was present for the diameter of the lymph node metastasis (neither mean diameter nor the presence of a lymph node metastasis ≥3 cm), the presence of cystic changes, calcification, necrosis, or the proportion of the lymph node taken up by tumor cells (Figure 3).

Table 1. Clinicopathological characteristics of PTC patients with lymph node metastases ($n = 129$).

	n	%
Age (years), mean (SD)	48.5 (16.4)	
Sex, female	71	55.0
T-stage		
T0	5	3.9
T1	24	41.9
T2	29	22.5
T3	27	20.9
T4	14	10.9
Extrathyroidal extension	20	15.5
Incomplete tumor resection[a]	31	24.0
Vascular invasion present	32	24.8
N-stage		
N1a	13	10.1
N1b	116	89.9
Distant metastases at presentation	19	14.7
2015 ATA risk stratification		
Low	0	0.0
Intermediate	56	43.4
High	73	56.6
Neck dissection		
Central compartment	15	11.6
Lateral compartment	12	9.3
Central and lateral compartments	102	79.1
Response to treatment		
Complete response	65	50.4
Complete response after prior treatment	46	36.0
Recurrence after complete response	6	4.7
Disease status end of follow-up		
Excellent response	59	45.7
Biochemical incomplete response	11	8.5
Structural incomplete response	34	26.4
Indeterminate response	19	14.7
Not stratified	5	3.9
Disease-specific mortality	9	7.0

Data are presented as *n* (%) or as mean (SD). T-stage and N-stage according to the AJCC TNM staging system, eighth edition.
Abbreviations: ATA, American Thyroid Association; IQR, interquartile range; N, number; PTC, papillary thyroid cancer; SD, standard deviation.
[a]Incomplete tumor resection is defined as any microscopically positive surgical margin.

Discussion

Following the reexamination of 1042 lymph node metastases, we showed that the presence of more than 5 lymph node metastases is an independent predictor of failure to achieve a complete biochemical and structural response to treatment, whereas there was no association of other histopathological features, including diameter of the lymph node metastasis and extranodal extension with response to treatment.

Multiple studies have shown that a higher number of lymph node metastases is associated with worse prognosis.[13,14,16,19,23,24] According to the ATA risk stratification tool, patients are upstaged from low to intermediate risk for disease recurrence if more than 5 lymph node metastases are present at pathology examination.[4,6,25] We were able to show that within the subgroup of patients with clinically evident lymph node metastases, by definition classified as intermediate risk for disease recurrence according to the ATA guideline, the number of lymph node metastases further discriminates the risk for persistent disease. We were unable to confirm the other histopathological feature, that is, diameter (≥3 cm) of the lymph node metastases, which is included in the ATA risk stratification tool, to be associated with a failure

Table 2. Histopathological characteristics of lymph node metastases ($n = 878$) stratified by neck compartment in 102 patients that underwent both central and lateral neck dissections.

	Central neck compartment ($n = 381$)		Lateral neck compartment ($n = 497$)		OR (95% CI)	*P*-value
LNM diameter in mm, median (IQR)	5.0 (2.5-10.0)		9.0 (3.0-16.8)			<.001
LNM ≥ 3 cm	3	0.8%	37	7.4%	2.55 (1.33-4.89)	.005
Extranodal extension	95	24.9%	143	28.8%	1.19 (0.85-1.65)	.308
Cystic changes						
<1 cm	160	42.0%	271	54.5%	1.84 (1.32-2.67)	<.001
≥1 cm	14	3.7%	83	16.7%	8.86 (4.53-17.3)	<.001
Necrosis	5	1.3%	17	3.4%	1.39 (0.70-2.74)	.343
Calcification	198	52.0%	281	56.5%	1.21 (0.92-1.58)	.172
Proportion of LN taken up by metastatic cells						
100% involvement	136	35.7%	202	40.6%	1.00 (0.58-1.72)	.987
>50% involvement	114	29.9%	138	27.8%	1.25 (0.72-2.17)	.429
<50% involvement	102	26.8%	111	22.3%	1.40 (0.80-2.45)	.244
Subcapsular tumor deposition	28	7.3%	41	8.2%	Reference	

Data are presented as median (IQR) or *n* (%).
Abbreviations: CI, confidence interval; cm, centimeter; IQR, interquartile range; LN, lymph node; LNM, lymph node metastasis; mm, millimeter; OR, odds ratio.

Table 3. Multivariable analysis for the primary endpoint of complete response and secondary endpoint of complete response after prior treatment with thyroidectomy and RAI ablation therapy ($n = 129$).

	Primary endpoint		Secondary endpoint	
	OR (CI)	*P*-value	OR (CI)	*P*-value
Age	1.04 (1.00-1.07)	.034	1.00 (0.98-1.03)	.789
Sex (female)	0.76 (0.30-1.90)	.554	0.92 (0.39-2.16)	.841
High-risk feature(s) of the primary tumor	7.14 (2.31-22.0)	<.001	8.32 (2.12-32.7)	.002
Distant metastases	5.97 (1.10-32.5)	.039	5.87 (0.68-51.0)	.109
Lymph node features				
LNM ≥ 5	4.17 (1.40-12.4)	.010	4.13 (1.70-10.0)	.002
LNM with ENE, number	1.14 (0.93-1.40)	.218		
Presence of at least 1 LNM with necrosis	1.59 (0.41-6.16)	.502		

High-risk feature(s) of the primary tumor included gross extrathyroidal extension, vascular invasion, and incomplete tumor resection.
Abbreviations: CI, confidence interval; ENE, extranodal extension; LN, lymph node; LNM, lymph node metastases; OR, odds ratio.

to achieve a complete response to therapy. The 3-cm cutoff was derived from 2 studies that differed from our study in a number of aspects.[16,26] In these studies, prophylactic central neck dissections were routinely performed, likely driving the association between larger lymph nodes and risk of recurrence as prophylactic neck dissections also yield nonclinically relevant micrometastases. Indeed, prophylactic central neck dissections are not routinely recommended anymore, but may be considered only in advanced primary tumors (stage T3 or T4).[4] Furthermore, only 3.8% (23 out of 604) of patients in 1 study and none in the other study received treatment with RAI ablation and TSH suppressive therapy. In multiple studies in patients who received RAI treatment, size had no prognostic significance.[19,26-30] Only 1 study with a comparable cohort of 347 RAI-treated patients found a marginal association between the maximum diameter of lymph node metastases and distant metastasis-free survival (hazard ratio [HR] 1.1, $P = .026$), but not for local recurrence or disease-free survival.[24] Combining our data with those in the preexisting literature, the diameter of the lymph node metastasis does not seem to incorporate any meaningful predictive properties for the response to treatment in RAI-treated populations. Consequently, upstaging such patients to the ATA high-risk group does not seem to be justified.

We failed to demonstrate that the mere presence of extranodal extension has any prognostic value for predicting the response to treatment, which is in agreement with other studies in patients with clinically evident lymph node metastases.[31,32] The number of lymph nodes with extranodal extension was associated with the response to treatment in univariable, but not in multivariable analysis. The number of lymph nodes with extranodal extension was, however, correlated with the total number of metastases. The absence of a predictive value of the ratio of number of lymph node metastases with extranodal extension to total number of lymph node metastases supports the lack of an independent association. Studies that found extranodal extension to be an independent predictor for disease recurrence often included a control group of patients without lymph node metastases or with pathological lymph node metastases, as opposed to clinically evident metastases, or did not adjust for the total number of lymph node metastases in multivariable analysis.[14,17,33] Different definitions for extranodal extension, ranging from microscopically extracapsular invasion to invasion into adjacent organs, and low concordance between pathologists pertaining this feature introduce heterogeneity in literature.[17,34,35] There is a need for consensus on histological criteria for extranodal extension, and future studies are needed to assess the association

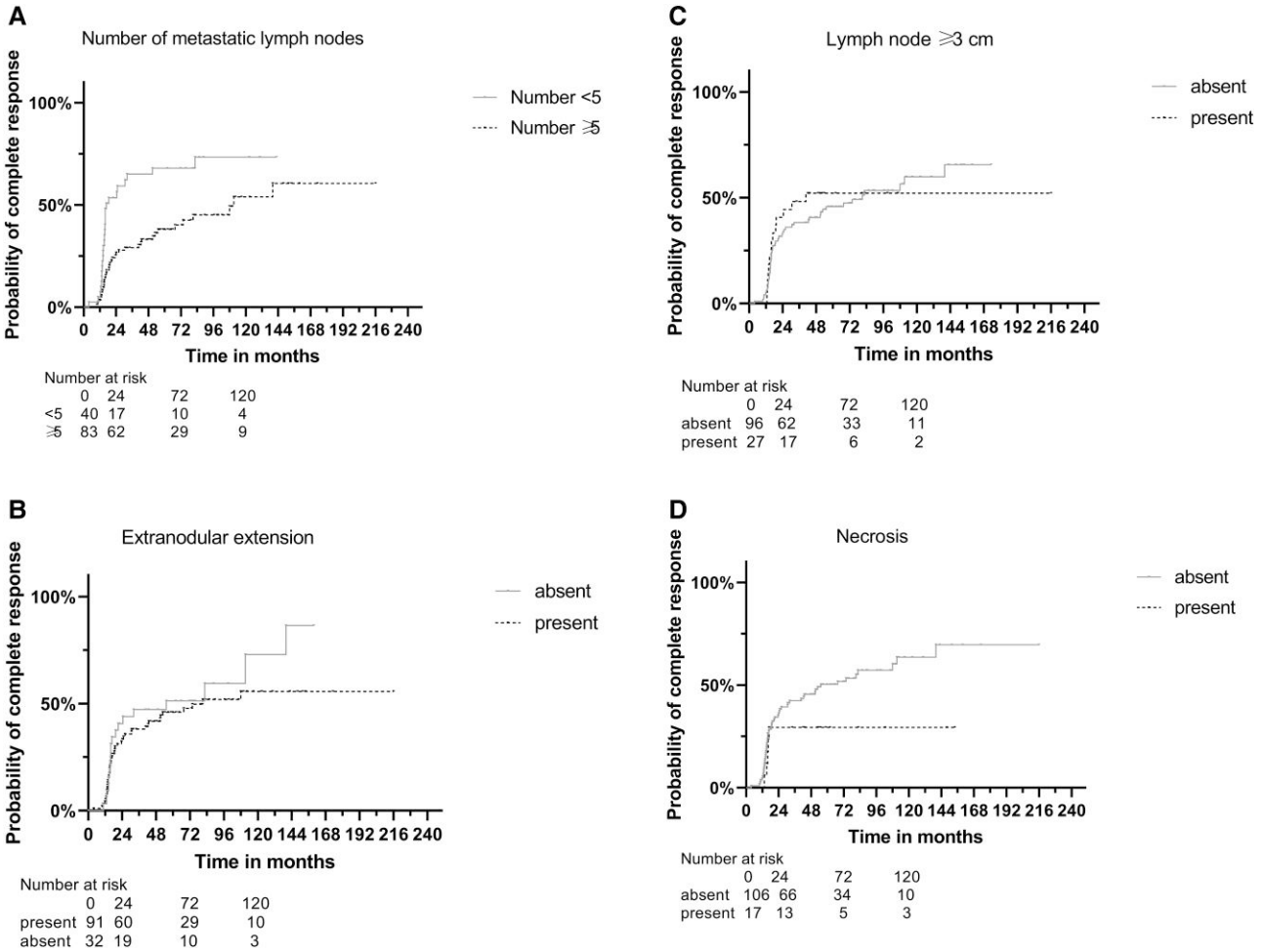

Figure 3. Kaplan–Meier estimates of time to a complete response to therapy stratified by the number of lymph node metastases (A), the presence of extranodal extension (B), the presence of a lymph node ≥ 3 cm (C), and the presence of necrosis (D).

between the extend of extranodal extension and response to treatment in patients with clinically evident lymph node metastases.

We did not identify an association between the ratio of lymph node metastases to total number of lymph nodes harvested and the response to treatment, whereas other studies identified this ratio as a predictor of recurrence and survival.[13,20,36,37] This ratio is, however, influenced by the indication and extent of neck dissections and variation in case-mix impair comparability between studies, questioning the relevance of such a variable.

The presence of cystic changes, calcifications, and the proportion of the lymph node taken up by tumor cells were not predictive of a complete response to therapy. Cystic changes were observed in 81.2% of patients. This feature was more abundant in the lateral compartment and was associated with the presence of extranodal extension, both observations being in line with previous studies.[21,38] Two studies reporting on cystic lymph nodes in relation to prognosis yielded contradictory results.[21,22] In the first study, cystic lymph nodes were identified on preoperative imaging as well as intraoperatively and were associated with reduced disease-free survival.[21] The second study, in which a histological reexamination was performed, did not find an impact on disease recurrence and progression.[22] As for extranodal extension, the use of different definitions and mode of detection of cystic changes hampers comparison between studies.

One other study examined the prognostic significance of calcifications, specifically psammoma bodies, and found no association with disease recurrence, in agreement with our study.[22] The presence of necrosis was associated with a higher risk of failure to achieve a complete response in univariable, but not in multivariable analysis. To the best of our knowledge, this is the first study examining whether necrosis in lymph node metastases holds prognostic potential for recurrent or persistent disease.

We were able to study histopathological features of lymph node metastases in a homogenous cohort of patients with clinically evident lymph node metastases who all received RAI treatment. A systematic histopathological reexamination of lymph node metastases was performed according to a predefined protocol. Histological lymph node features, which were not, or marginally, studied before, such as cystic changes, calcifications, and necrosis, were also systematically studied, in addition to known features that are incorporated in guideline risk stratification tools. The inclusion of patients with clinically evident lymph node metastases may limit the generalizability of the results to any patient with pathological lymph node metastases. Current guidelines, however, advise against prophylactic neck dissections, which are prompted

by the trend toward deescalating treatment and preventing overtreatment of thyroid cancer. Therefore, the patients included in this study likely reflect current practice and, hence, provide insights into risk factors for recurrence in this specific patient population aiding clinical care. Patients in this study received a relatively high-dose of RAI. A potential dose-related response to therapy should be taken into account when interpreting the results of this study.[39] A limitation of the present study is the limited follow-up time of a median of 76 months, although ~80% of reoperations for recurrent or persistent disease occur within 5 years after initial treatment.[40] Another limitation is that data on pathological subtypes of the primary tumor were not available. This study was initiated before the publication of the 2022 World Health Organization classification of thyroid neoplasms, which recommends histological subtyping of PTC.[41] Also, information on genetic alterations of both the primary tumor and lymph node metastases were not available. The presence of a *BRAF* p.V600E mutation was found to have an additive effect on mortality risk in patients with lymph node metastases, but had no effect on the risk for local progression or disease recurrence.[42,43] In the multivariable analysis, we adjusted for invasive characteristics of the primary tumor, which have been linked to commonly seen genetic alterations in PTC that are associated with aggressive biological behaviour of the tumor.[44]

In conclusion, our study indicates that only the number of lymph node metastases is an independent predictor of a failure to achieve a complete response to treatment in PTC patients with clinically evident lymph node metastases. The diameter of the lymph node metastases does not seem to have any meaningful predictive properties for the response to treatment in RAI-treated populations. Neither extranodal extension nor other examined histopathological features of lymph node metastases independently added to the risk of a failure to achieve a complete response. Our findings may inform further optimization of risk stratification systems.

Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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Authors' contributions

Caroline M.J. van Kinschot (Conceptualization [lead], Data curation [lead], Formal analysis [lead], Investigation [lead], Methodology [lead], Project administration [lead], Resources [lead], Validation [lead], Visualization [equal], Writing—original draft [lead], Writing—review & editing [lead]), Francien H. van Nederveen (Methodology [supporting], Writing—review & editing [equal]), Lindsey Oudijk (Conceptualization [equal], Investigation [equal], Methodology [equal], Writing—review & editing [equal]), Charlotte van Noord (Writing—review & editing [equal]), Tim I.M. Korevaar (Formal analysis [supporting], Writing—review & editing [equal]), Robin Peeters (Conceptualization [equal], Writing—review & editing [equal]), Folkert J. van Kemenade (Conceptualization [equal], Methodology [equal], Writing—review & editing [equal]), and W. Edward Visser (Conceptualization [equal], Methodology [equal], Supervision [equal], Writing—review & editing [equal])

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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