Correlation between the Number of Lymph Node Metastases and Lung Metastasis in Papillary Thyroid Cancer

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Context: A prognostic classification system based on aggregate numbers of lymph node metastases may better estimate the risk of distant metastasis.

Objective: This investigation sought to evaluate a papillary thyroid cancer (PTC) patient's risk of distant metastasis.

Design: This was a retrospective analysis.

Setting: The setting was a tertiary referral center.

Patients: Included were 972 PTC patients.

Intervention: The intervention was compartment-oriented surgery.

Main Outcome Measure: The main outcome measure was lung, bone, and liver metastasis.

Results: Eighty-seven (9.0%) of the 972 PTC patients had distant metastases to lung (79 patients), bone (16 patients), liver (two patients), brain and skin (one patient each). For distant metastasis, more than 20 lymph node metastases had a specificity of 90.8% and a negative predictive value of 92.7%, whereas sensitivity and positive predictive value were low (27.6 and 22.9%). On multivariate logistic regression, 1–5, 6–10, and 11–20 involved nodes denoted a moderate risk of lung metastasis [odds ratio (OR), 9.9, 10.6, and 13.8; $P \leq 0.004$], whereas more than 20 involved nodes indicated a high risk of lung metastasis (OR, 25.0; $P < 0.001$). Mediastinal lymph node metastasis carried a moderate risk of lung metastasis (OR, 7.5; $P = 0.001$). When these numeric categories of lymph node metastases were exchanged for current tumor node metastasis (TNM) N categories, the OR decreased from 25.0 (for > 20 lymph node metastases) to 16.4 (N1b), and from 9.9–13.8 (for 1–20 lymph node metastases) to 4.7 (N1a).

Conclusion: In PTC, categories of 0, 1–20, and more than 20 lymph node metastases correlate better with lung metastasis than current TNM N categories N0, N1a, and N1b. **(*J Clin Endocrinol Metab* 97: 4375–4382, 2012)**

In most solid tumors, involvement of locoregional lymph nodes represents an advanced stage of disease. Nevertheless, there are marked differences among cancer entities in how many lymph node metastases need to be grouped together in how many N categories to capture the incremental risk of cancer-specific death. For head and neck cancers, size and location of lymph node metastases have been used to build N categories of increasing risk. For gastrointestinal cancers, successive brackets of lymph node metastases have been defined as N categories regardless of size and location: 1–3 (N1) and more than 3 nodes (N2) for small bowel, appendix, and colorectal cancer; 1–2 (N1), 3–6 (N2), and more than 6 nodes (N3) for esophageal and gastric cancer; and 1–3 (N1), 4–9 (N2),

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Abbreviations: OR, Odds ratio; PTC, papillary thyroid cancer; TNM, tumor node metastasis.

and more than 9 nodes (N3) for breast cancer (1, 2). For medullary thyroid cancer, our group recently put forward N categories consisting of 1–10 (N1), 11–20 (N2), and more than 20 (N3) lymph node metastases, which derived from multivariate analyses on lung metastasis (3).

Papillary thyroid cancer (PTC), a follicular cell-derived parenchymal cancer, also commonly spreads to neck nodes. The clinical relevance of occult lymph node metastases is unclear, given the absence of natural history data. Remarkably, the same body of evidence has given rise to divergent conclusions worldwide as to whether occult lymph node metastases need to be cleared by way of prophylactic lymph node dissection as a matter of principle, and if so, how extensively. For clinically apparent lymph node metastases, there is consensus that these nodes should be removed by way of therapeutic lymph node dissection.

Greater numbers of lymph node metastases entail greater risks of locoregional tumor persistence and recurrence in PTC. For instance, the number of involved lymph nodes in the central neck (more than two to five lymph node metastases) correlates with a patient's risk of harboring lymph node metastases also in the lateral neck (4, 5). Involvement of lateral lymph nodes on either side of the neck, a condition that is associated with more involved nodes (6), was the only significant risk factor for lung metastasis in another study (7). Likewise, extranodal (extracapsular) growth of lymph node metastases, portending a worse cancer-specific survival in PTC (8–10), correlated with the number of lymph node metastases ($r = 0.78$; $P < 0.0001$) (11). PTC patients with mediastinal lymph node metastases also have more lymph node metastases (means of 14 *vs.* seven nodes; $P = 0.001$) than patients without such involvement (12). Mediastinal lymph node metastases from PTC have been linked to distant metastases (12), a recognized determinant of cancer-specific mortality (13).

In 2005, Leboulleux *et al.* (11) introduced a risk classification system based on the number of involved lymph nodes, with less than 5, 6–10, and more than 10 nodes signifying low, intermediate, and high risks of tumor persistence and recurrence, respectively. The uptake of this risk stratification scheme has been poor in an environment eschewing routine lymph node dissections because of concerns regarding surgical morbidity and clinical benefit (14, 15).

The present evidence suggests that a classification system based on aggregate numbers of lymph node metastases may also be clinically useful to estimate the risk of distant metastasis. This study of 972 PTC patients with complete histopathological information from a single institution aimed at evaluating a PTC patient's individual risk for: 1) lung metastasis; 2) bone metastasis; and 3) other distant metastasis considering an array of clinical and pathological risk factors including the number of lymph node metastases.

Patients and Methods

Study population

A total of 1188 consecutive patients underwent initial cervical operations (461 patients) and/or reoperations (727 patients) for PTC between November 1994 and June 2012 at the Department of General, Visceral, and Vascular Surgery in Halle (Saale), Germany. No systematic lymph node dissection was carried out in 206 patients, 190 of whom had no lymph node dissection because PTC was an incidental finding (none had distant metastasis). A further 16 patients underwent resection of a target lesion only (two of whom had distant metastasis). For 10 additional patients who were reoperated on in the neck (three of whom had distant metastasis), the number of previously involved and removed nodes was unavailable. Included in this retrospective clinical-pathological study were all those 972 patients (82%) who had lymph node dissections at this institution [282 patients referred for initial operations, 19 of whom (6.7%) had distant metastasis] or elsewhere [690 patients referred for reoperations, 68 of whom (9.9%) had distant metastasis] and had histopathological information for each lymph node removed. For retrospective analysis of existing data sets from routine patient care, no institutional review board approval is required under German law and applicable institutional regulations.

Total thyroidectomy and compartment-oriented surgery

All 972 patients had total thyroidectomy with systematic lymph node dissection of the central neck compartment using the compartment-oriented approach (16). The lateral neck compartments had been dissected systematically in 484 patients (50%) ipsilateral to, and in 186 patients (19%) contralateral to the largest primary thyroid tumor. Systematic lymph node dissections of the mediastinal compartment, extending between the brachiocephalic vein and tracheal bifurcation, had been carried out in 40 patients (4%) by way of complete median sternotomy. All operations were conducted using optical magnification and bipolar coagulation, as described previously (17). Lateral and/or mediastinal neck dissections were performed when clinical or ultrasonographic criteria (initial dissections) or other positive imaging studies (subsequent dissections) suggested lymph node metastases. Informed consent was obtained before each operation that represented standard practice of care in accordance with the practice guidelines of the German Cancer Association (18). Distant metastases *per se* were not an exclusion criterion because of the recognized longevity of patients with metastatic PTC.

Pathological examination of surgical specimens

All specimens were subjected to histopathological examination and embedded in paraffin. Conventional staining (hematoxylin and eosin) and thyroglobulin immunohistochemistry, respectively, were performed on every surgical specimen as appropriate. PTC was diagnosed according to the World Health

Organization's International Histological Classification of Tumors (19, 20), subsuming poorly differentiated follicular cell-derived tumors under the category of PTC rather than treating them as a disease entity in its own right (21). A diagnosis of poor tumor differentiation required histological evidence of insular, trabecular, and solid patterns, usually together with infiltrative growth, necrosis, and obvious vascular invasion (20). Pathological reports from other facilities were examined, and outside specimens were reviewed to resolve discrepancies between previous and current histopathology. Primary tumor diameter was measured directly on the surgical thyroid specimens. When multiple tumors were present, only the size of the largest thyroid cancer was taken. All lymph node metastases were diagnosed on histopathological analysis using conventional methodology. Aggregate numbers of lymph node metastases were calculated by summing up the respective numbers of histopathologically confirmed lymph node metastases documented for each operation at this institution or elsewhere. Not considered for the study were those patients for whom the quantity of the reported lymph node metastases was not specified in the histology report or whose histopathology reports were unavailable. Extranodal growth was diagnosed in the presence of perinodal tumor extension or a soft tissue infiltrate bordered by an incomplete residual lymph node capsule. Only histopathologically involved nodes were counted as mediastinal lymph node metastases. This conservative approach yields minimum estimates of mediastinal lymph node involvement. The diagnosis of distant metastasis was based on histopathological demonstration of tumor at distant organs or, in the absence thereof, on unequivocal evidence on ultrasonography, computed tomography, magnetic resonance imaging, radioiodine scan, 18-fluorodeoxyglucose positron emission tomography, or any combination of these imaging modalities, irrespective of when it was noted.

Statistical analysis

Categorical and continuous data were tested on univariate analysis with the two-tailed Fisher's exact test and one-way ANOVA, respectively. Multiple testing was adjusted for by using the Bonferroni correction. To ensure sufficiently large numbers of patients and events in each group, continuous data were categorized as appropriate: primary tumor diameter in bands of 20 or less, 21–40, and more than 40 mm, and aggregate lymph node metastases in bands of 0, 1–5, 6–10, 11–20, and more than 20 nodes. Stratification by these incremental categories was used, in addition to multivariate analyses, to reduce the potential effects of referral bias (implying the preferential referral of patients with more advanced tumors to a tertiary center). Multivariate logistic regression models on lung metastasis were built to quantify the independent contributions of relevant clinical-pathological variables. Kaplan-Meier analysis (22) and the log-rank test were employed to explore the relationship between the number of involved nodes and lung, bone, and liver metastasis. The level of statistical significance (all values were two-tailed) was set at <0.05.

Results

Spectrum of distant metastasis

Among all 972 PTC patients, 87 patients (9.0%) had distant metastases (Table 1). Specifically, 79 patients revealed lung metastases (8.1%); 16 patients, bone metastases (1.6%); two patients, liver metastases; and one patient each, brain and skin metastases, alone or concomitantly. Among the 87 patients with distant metastases, eight patients (9%) had node-negative PTC: two patients with lung metastases only, four patients with bone metastases only, and two patients with combined lung and liver metastases.

TABLE 1. Spectrum of distant metastasis among the 87 affected PTC patients

Distant metastasis, involved organ systems	Patients n	Patients %
Lung only	69	90
Bone only	7	9
Brain only	1	1
Liver only	0	0
Lung and bone	8[a]	80
Lung and liver	1	10
Lung and liver and bone	1	10

A total of 77 patients (89%) had metastasis involving only one organ system, whereas 10 patients (11%) had metastases involving more than one organ system.

[a] One patient also revealed histologically confirmed skin metastasis.

Patients by number of organ systems with distant metastasis

The 77 patients with distant metastasis confined to one distant organ system differed significantly, after correction for multiple testing, from the 885 patients without distant organ involvement in largest primary tumor diameter, extrathyroidal tumor extension, extranodal tumor growth, lymph node metastasis, number of involved lymph nodes, and mediastinal lymph node metastasis (Table 2).

The 10 patients with involvement of more than one distant organ system were 18–20 yr older than the 885 patients with no distant metastasis and the 77 patients with involvement of one distant organ system only (Table 2). These 10 patients also displayed significantly larger primary tumors and more frequently mediastinal lymph node metastasis than the former 885 patients.

For distant metastatic disease, the presence of more than 20 lymph node metastases had a high specificity of 90.8% and a large negative predictive value of 92.7%. The corresponding sensitivity of 27.6% and positive predictive value of 22.9% were much lower, consistent with the infrequency of distant metastasis among PTC patients.

Patients by type of distant metastasis

The 69 patients with lung metastasis differed significantly, after correction for multiple testing, from the 885 patients without distant metastasis in largest primary tumor diameter, extrathyroidal tumor extension, extranodal tumor

TABLE 2. PTC patients by number of organ systems with distant metastasis

Variable	Total (n = 972)	No. of organ systems with distant metastasis: 0 (n = 885)	1 (n = 77)	2 (n = 10)	P (0 *vs.* 1)
Age at tissue diagnosis (yr), mean [95% confidence interval]	43.0 [41.9; 44.2]	43.0 [41.9; 44.2]	40.9 [36.1; 45.8]	60.7[d,e] [53.4; 68.0]	0.32
Male gender	311 (32)	271 (31)	35 (45)	5 (50)	0.010
Diameter of largest primary tumor (mm), mean [95% confidence interval][a]	22.7 [21.6; 23.8]	21.8 [20.7; 22.9]	31.9 [26.9; 37.0]	40.5[d] [22.2; 58.8]	<0.001[c]
Extrathyroidal tumor extension[b]	398 (42)	340 (39)	51 (66)	7 (70)	<0.001[c]
Extranodal tumor growth	78 (8)	59 (7)	17 (22)	2 (10)	<0.001[c]
Lymph node metastasis	587 (60)	508 (57)	71 (92)	8 (80)	<0.001[c]
No. of involved lymph nodes, mean [95% confidence interval]	6.9 [6.2; 7.5]	6.2 [5.5; 6.8]	15.1 [11.1; 19.1]	8.0 [2.3; 13.7]	<0.001[c]
0	385 (40)	377 (43)	6 (8)	2 (20)	
1–5	231 (24)	206 (23)	22 (29)	3 (30)	
6–10	128 (13)	114 (13)	13 (17)	1 (10)	
11–20	123 (13)	107 (12)	13 (17)	3 (30)	
>20	105 (11)	81 (9)	23 (30)	1 (10)	
Mediastinal lymph node metastasis	24 (2)	12 (1)	9 (12)	3 (30)[d]	<0.001[c]
Poor tumor differentiation	30 (3)	24 (3)	4 (5)	2 (20)	0.27

Data are expressed as number (percentage) unless specified otherwise.

[a] Excluding 89, 73, 16, and 0 patients with no information on primary tumor diameter, respectively.

[b] Excluding 15, 15, 0, and 0 patients with no information on extrathyroidal tumor extension, respectively.

[c] Statistically significant after Bonferroni correction for multiple testing within each type of comparison.

[d] Statistically significant ($P \leq 0.002$) after Bonferroni correction for multiple testing within each type of comparison (0 *vs.* 2).

[e] Statistically significant ($P = 0.005$) after Bonferroni correction for multiple testing within each type of comparison (1 *vs.* 2).

growth, lymph node metastasis, number of involved lymph nodes, and mediastinal lymph node metastasis (Table 3). Conversely, the seven patients with bone metastasis, after correction for multiple testing, had significantly larger primary tumors and tended to be 16–20 yr older than the 885 patients without distant metastasis and the 69 patients with lung metastasis only (Table 3). Remarkably, none of the seven patients with bone metastasis only, but more than half of the 69 patients with lung metastasis only had more than 10 lymph node metastases.

For lung metastasis in the absence of any other distant metastasis, more than 20 lymph node metastases had a

TABLE 3. PTC patients by type of distant metastasis

Variable	Total (n = 972)	Type of distant metastasis[a]: None (n = 885)	Lung only (n = 69)	P (*vs.* none)	Bone only (n = 7)	P (*vs.* none)
Age at tissue diagnosis (yr), mean [95% confidence interval]	43.0 [41.9; 44.2]	43.0 [41.9; 44.2]	38.9 [33.9; 43.0]	0.07	59.0 [42.9; 75.1]	0.016
Male gender	311 (32)	271 (31)	31 (45)	0.016	4 (57)	0.21
Largest primary tumor diameter (mm), mean [95% confidence interval][b]	22.7 [21.6; 23.8]	21.8 [20.7; 22.9]	29.6 [24.9; 34.4]	0.001[d]	57.6[e] [25.7; 89.5]	<0.001[d]
Extrathyroidal tumor extension[c]	398 (42)	340 (39)	45 (65)	<0.001[d]	5 (71)	0.12
Extranodal tumor growth	78 (8)	59 (7)	15 (22)	<0.001[d]	2 (29)	0.08
Lymph node metastasis	587 (60)	508 (57)	66 (96)	<0.001[d]	4 (57)	>0.99
No. of involved lymph nodes, mean [95% confidence interval]	6.9 [6.2; 7.5]	6.2 [5.5; 6.8]	16.5 [12.1; 20.8]	<0.001[d]	3.6 [0.2; 7.0]	0.48
0	385 (40)	377 (43)	3 (4)		3 (43)	
1–5	231 (24)	206 (23)	19 (28)		2 (29)	
6–10	128 (13)	114 (13)	11 (16)		2 (29)	
11–20	123 (13)	107 (12)	13 (19)		0	
>20	105 (11)	81 (9)	23 (33)		0	
Mediastinal lymph node metastasis	24 (2)	12 (1)	8 (12)	<0.001[d]	1 (14)	0.10
Poor tumor differentiation	30 (3)	24 (3)	2 (3)	0.71	2 (29)	0.016

Data are expressed as number (percentage) unless specified otherwise.

[a] Exclusive of patients with distant metastasis to other major organ systems (lung, liver, bone, or brain).

[b] Excluding 89, 73, 13, and 2 patients with no information on primary tumor diameter, respectively.

[c] Excluding 15, 15, 0, and 0 patients with no information on extrathyroidal tumor extension, respectively.

[d] Statistically significant after Bonferroni correction for multiple testing within each type of comparison.

[e] Statistically significant ($P = 0.002$) after Bonferroni correction for multiple testing within each type of comparison (lung *vs.* bone only).

high specificity of 90.8% and a large negative predictive value of 94.6%. The corresponding sensitivity of 33.3% and positive predictive value of 22.1% were much lower, reflecting the rarity of lung metastasis among PTC patients.

Multivariate analysis on lung metastasis

Because metastasis limited to one distant organ system predominantly involved the lung (Table 1), the multivariate analysis focused on lung metastasis without involvement of any other distant organ system to avoid confounding by other distant metastasis (Table 4).

Herein, the number of lymph node metastases was by far the strongest determinant of lung metastasis, with 1–5, 6–10, and 11–20 involved nodes denoting moderate risks [odds ratio (OR), 9.9, 10.6, and 13.8] and more than 20 involved nodes indicating high risk (OR, 25.0; Table 4, analysis 1). Primary tumor diameter greater than 20 mm entailed a weak risk (OR, 2.2–2.3) and mediastinal lymph node metastasis a moderate risk (OR, 7.5) of lung metastasis. When the numeric lymph node categories (0, 1–5, 6–10, 11–20, and >20; analysis 1) were exchanged for current tumor node metastasis (TNM) N categories (N0, N1a, and N1b; analysis 2), the ORs decreased from 25.0 (for >20 lymph node metastases) to 16.4 (N1b), and from 9.9–13.8 (for 1–20 lymph node metastases) to 4.7 (N1a), whereas the size effects (ORs) of the other variables remained constant (Table 4).

In separate multivariate logistic regression analyses using the same set of independent variables, but excluding the 352 patients with node-negative PTC and using 1–5 (instead of 0) lymph node metastases as the reference base, more than 20 lymph node metastases (unlike 6–10 or 11–20 lymph node metastases) retained statistical significance with an OR of 2.5 (95% confidence interval, 1.2–4.3; $P = 0.021$; modified analysis 1) and 3.5 (95% confidence interval, 1.3–22.8; $P = 0.012$; modified analysis 2), respectively.

TABLE 4. Multivariate logistic regression analyses on lung metastasis from PTC[a]

Independent variable	No. of patients	Multivariate logistic regression analysis on lung metastasis only[a] (inclusion model) (867 patients with complete data sets)[b]			
		Analysis 1		Analysis 2	
		OR [95% CI]	*P*	OR [95% CI]	*P*
Age at tissue diagnosis (yr)					
>45 *vs.* ≤45	382 *vs.* 485	1.0 [0.5; 2.0]	0.94	1.0 [0.5; 1.8]	0.93
Gender (n)					
Male *vs.* female	281 *vs.* 586	1.3 [0.7; 2.4]	0.35	1.3 [0.7; 2.4]	0.36
Largest primary tumor diameter (mm)					
≤20	498	1		1	
20.1–40	263	2.2 [1.1; 4.3]	0.021	2.2 [1.1; 4.3]	0.018
>40	106	2.3 [1.0; 5.2]	0.05	2.2 [1.0; 5.2]	0.06
Poor tumor differentiation					
Present *vs.* absent	18 *vs.* 849	0.5 [0.1; 3.0]	0.42	0.5 [0.1; 3.4]	0.51
Extrathyroidal tumor extension					
Present *vs.* absent	377 *vs.* 530	1.1 [0.6; 2.0]	0.79	1.1 [0.6; 2.1]	0.66
Extranodal tumor growth					
Present *vs.* absent	68 *vs.* 799	2.0 [1.0; 4.2]	0.07	2.0 [1.0; 4.0]	0.07
Mediastinal lymph node metastasis					
Present *vs.* absent	16 *vs.* 851	7.5 [2.4; 23.7]	0.001	7.4 [2.4; 23.1]	0.001
No. of aggregate lymph node metastases, n (analysis 1 only)					
0	352	1		N/A	N/A
1–5	201	9.9 [2.2; 44.8]	0.003	N/A	N/A
6–10	115	10.6 [2.2; 52.0]	0.004	N/A	N/A
11–20	109	13.8 [2.8; 67.3]	0.001	N/A	N/A
>20	90	25.0 [5.2; 120.5]	<0.001	N/A	N/A
Current TNM N category (analysis 2 only)					
N0	352	N/A	N/A	1	
N1a	145	N/A	N/A	4.7 [0.9; 25.2]	0.07
N1b	370	N/A	N/A	16.4 [3.8; 71.6]	<0.001

N0, No lymph node metastasis; N1a, central lymph node metastasis; N1b, lateral/mediastinal lymph node metastasis; CI, confidence interval; N/A, not assessed.

[a] Based on 56 events (56 patients with lung metastasis in the absence of any other type of distant metastasis).

[b] Exclusive of patients with distant metastasis to other major organ systems (lung, bone, liver, or brain).

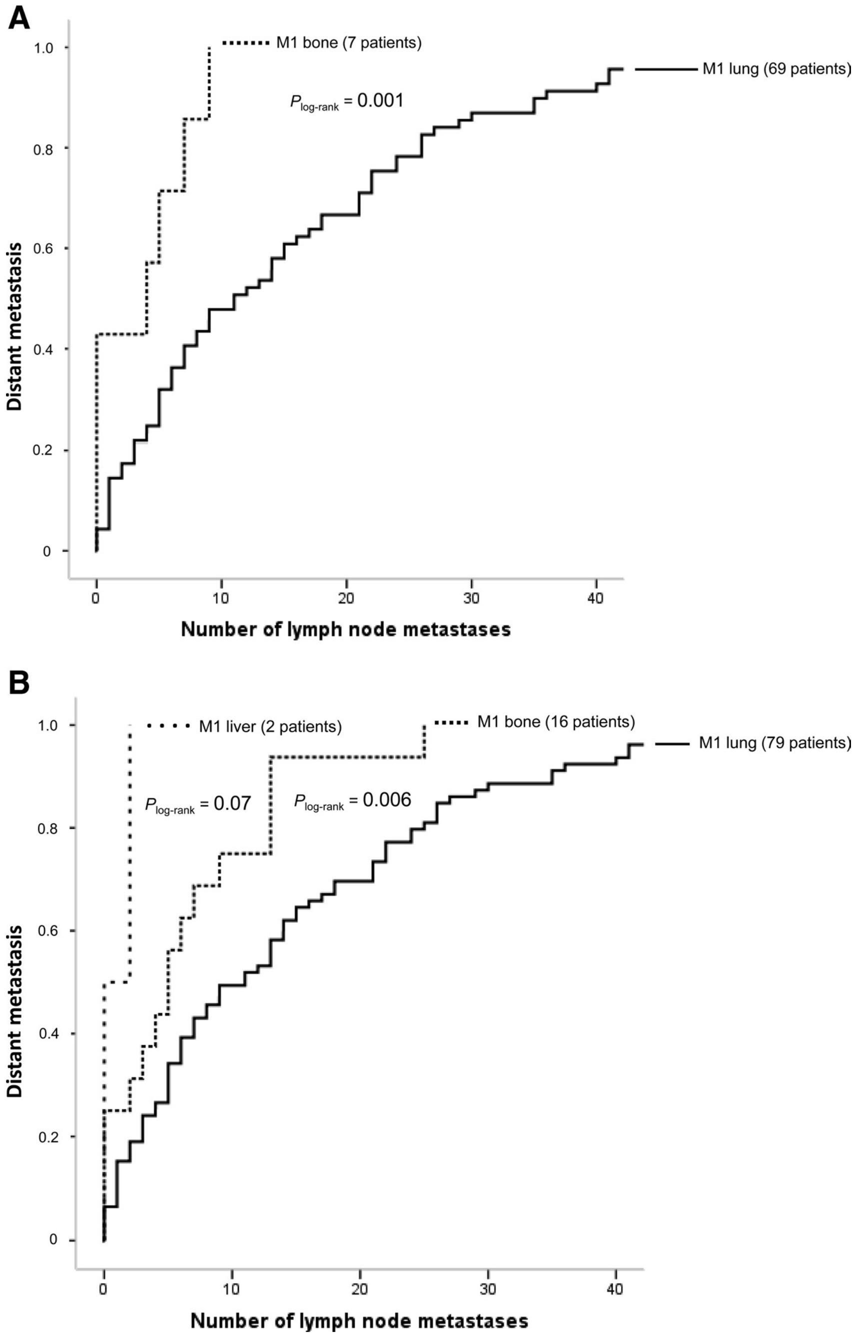

FIG. 1. Cumulative rates of distant metastasis. A, Only patients with involvement of one distant organ system. B, All affected patients (counting each involved distant organ system separately). M1, Distant metastasis.

Rates of lung, bone, and liver metastasis by number of involved lymph nodes

The cumulative risks of lung, bone, and liver metastasis were plotted against the number of lymph node metastases alone (Fig. 1A) and with or without concurrent metastasis to other distant organs (Fig. 1B) to assess the robustness of these estimates. Irrespective of whether patients with involvement of one or more than one distant organ system were studied, the number of lymph node metastases reflected fairly well the cumulative risk of lung metastasis, but less so the cumulative risks of bone or liver metastasis (Fig. 1). At variance, a recent analysis for medullary thyroid cancer, plotting the cumulative risks of lung, liver, and bone metastasis against the number of lymph node metastasis in a like manner, furnished surprisingly congruent curves for all three types of distant metastasis (3).

Discussion

The present investigation is the first to quantify the independent contributions of incremental categories of lymph node metastases to distant metastasis in a multivariate logistic regression model. Our findings suggest that the number of involved nodes is a good indicator of overall tumor burden. The latter idea underlies the current American Joint Committee on Cancer (AJCC)/Union Internationale Contre Le Cancer (UICC) TNM categories N1a *vs.* N1b (central *vs.* lateral/mediastinal lymph node metastases) for PTC.

Limitations of the study

The present clinical-histopathological investigation of 972 PTC patients shared many limitations inherent in retrospective studies. It was not designed to estimate time to recurrence or distant metastasis, which would necessitate standardization of the initial operation and follow-up investigations as to frequency and type of imaging. Arguably, some limited lymph node dissections, leaving nodes behind in undissected areas, may have caused underestimation of the number of lymph node metastases, such that inherent differences in risk, which may exist among various brackets of lymph node metastases, may have been leveled. Some of these residual nodes may become clinically apparent later on, raising the patient's risk estimate by pushing up the total number of lymph node metastases. The actual lifetime risk of lung, bone, and liver metastasis may even be higher if: 1) the observation period was prolonged; and 2) endoscopic procedures (thoracoscopy and laparoscopy), invasive imaging modalities (arterial hepatic angiography), and advanced imaging technologies had been employed more widely. Although the extent of disease was controlled for fairly well on multivariate analysis (Table 4), the predominance of patients referred for reoperation (690 of 972 patients), revealing more advanced tumors with higher rates of distant metastasis (9.9 *vs.* 6.7%), may have raised our size effect estimates (ORs).

Lymph node metastases as a summary measure of systemic tumor spread

The rationale behind the construction of aggregate numbers of lymph node metastases was the premise that all tumor foci in the body had been planted by the time of thyroidectomy and that there would be no subsequent tumor dissemination after removal of the primary tumor during thyroidectomy. This supposition, although reasonable in itself, may not extend to the unusual patient in whom gross residual tumor was allowed to stay in the neck for quite some time. This situation is occasionally encountered in patients with large extrathyroidal tumors that were not cleared at the very beginning. A more complete initial operation may lessen, if not take away, the load of tumor cells able to acquire additional somatic mutations that confer more aggressive growth in the presence or absence of poor tumor differentiation. Older patients and larger tumors, harboring more tumor cells, may have had greater opportunity to acquire aggressive somatic mutations. This may explain why bone metastases, being rare in the absence of distant metastasis to other organ systems (seven patients *vs.* 69 patients with lung metastasis), predominated in older patients and were significantly associated with 2-fold larger primary tumors than lung metastases (Table 3).

Systemic lymph node dissection for improved locoregional control and staging

None of our current staging systems, primarily designed to predict cancer-specific mortality and not risk of recurrence, are significantly superior to the other or account for more than a small proportion of the variance explained. Yet the AJCC/UICC TNM classification remains the most applicable and consistent staging system for PTC (23). These staging systems, founded on retrospective studies, are fairly static and hard to modify as more information is coming forward. Not long ago, Tuttle *et al.* (24) proposed a dynamic risk assessment system for recurrent differentiated thyroid cancer whereby initial American Thyroid Association (ATA) risk estimates of recurrence (low, intermediate, or high) are revised based on response to therapy. In a similar vein, the AJCC/UICC tumor classification system may need to be updated to capture incremental risks as more pathological results become known.

The absolute number of nodes removed is a critical measure of the adequacy of staging (25). Initial "understaging" may be preventable if more adequate initial lymph node dissections are conducted, obviating the need for subsequent "upstaging." For certain cancer types, the AJCC/UICC TNM classification calls for a minimum number of dissected nodes: for instance, 12–14 nodes for colorectal cancer, and 16 nodes for gastric cancer (1, 2). In the absence of clinical neck disease, adequate first operations for PTC may need to include a "prophylactic" central lymph node dissection to enable correct allocation of node-positive patients to postoperative radioiodine therapy (26). Naturally, these benefits must be balanced against the morbidity from these dissections, which is low in experienced hands (27, 28).

Future perspectives

Continual calibration of the extent of therapy, founded on up-to-date risk stratification, is the centerpiece of personalized surgery. Aggregate lymph node metastases, providing summary measures of the risks of locoregional recurrence and cancer-specific mortality, can easily be updated should more lymph node metastases surface in the process. By analogy to the AJCC/UICC N categories for other parenchymal cancers, it may be prudent to devise N categories for PTC according to the size effects (ORs) for various increments of lymph node metastases (Table 4): 0 (N0), 1–20 (N1), and more than 20 (N2) lymph node metastases. Especially the risk of locoregional recurrence depends on the number of lymph node metastases cleared at the initial operation (11, 29). Systematic lymph node dissection at the time of thyroidectomy may represent "one stitch at a time" by: 1) reducing the risk of locoregional recurrence (30); 2) avoiding the excess surgical morbidity attendant to reoperations in the neck; and 3) serving as a prognostic staging tool for a risk-adapted personalized follow-up of those thyroid cancer patients harboring incremental numbers of lymph node metastases.

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