Prognostic significance of nodal metastasis in thymic malignancies: a narrative review of the current evidence

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Background and Objective: In 2016, the International Association for the Study of Lung Cancer (IASLC) in partnership with the International Thymic Malignancies Interest Group (ITMIG) published the 8th Edition of the TNM stage classification with a dedicated thymic lymph node map and recommendations for lymph node retrieval during resection to gain more uniformed data. As the prognostic significance of lymph node involvement remains controversial, we reviewed studies concerning lymph node metastasis to evaluate their prognostic importance in thymic malignancies.

Methods: Original papers available in English were selected from the date of first publication in the Medline database to June 21, 2021. Eleven retrospective cohort studies and one prospective cohort study published between 1994 and 2021 were identified for this narrative literature review, totaling 4,653 patients with a primary thymic tumor. The follow-up time of individual patients varied from 0.3 to 242 months. Eight studies reported median follow-up time data with an overall median follow-up of 51.0±42.6 months (range: 14.4–171 months). Seven studies validated prognostic factors using multivariate regression models. Propensity-matched analysis was performed in three comparative cohort studies.

Key Content and Findings: No definite conclusions can be drawn on the risk of nodal metastasis in thymic malignancies and our review validates the findings on which the N descriptor of the current 8th TNM stage classification was based.

Conclusions: This review demonstrates that patients with more locally advanced tumors, thymic neuroendocrine tumors, B3-thymomas and thymic carcinomas have a significantly higher likelihood of developing nodal metastases and that the presence of metastasis is an adverse prognostic factor for long-term outcomes in thymoma and thymic carcinoma. When performing a more rigorous lymph node dissection, higher nodal involvement rates are found which contributes to more accurate nodal staging. The studies analyzed for this review validate the findings on which the N descriptor of the current 8th TNM stage classification was based. However, more research is required to accurately evaluate the prognosis of nodal metastasis.

Keywords: Lymph node metastasis; thymic malignancies; prognosis

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Introduction

Thymic malignancies which comprise thymoma, thymic carcinoma and thymic neuroendocrine tumors are rare tumors and considered to be orphan diseases. Therefore, optimal diagnostic and therapeutic algorithms have not yet been precisely determined.

Although accounting for almost 50% of all prevascular (anterior) mediastinal masses, thymic tumors are responsible for only 0.2–1.5% of cancer cases (1-3). In the past, not only acquiring sufficient cases for analyses has been proven a challenge, but retrospective studies also lacked consistency in definition of their data. In the last decade, definite progress has been made to develop a uniform system for diagnosis, classification, staging and management of thymic malignancies. Formed in 2010, the International Thymic Malignancies Interest Group (ITMIG) first collected a large retrospective database with a standardized terminology, outcome measures and pathology (4). Since then, numerous country-based interest groups have been created and further steps in facilitating world-wide collaboration have been taken by ITMIG. Historically, various classification systems for thymic malignancies have been proposed, of which the Masaoka-Koga system was most widely used (4,5). This system proved to be a good prognostic predictor for thymoma, the most common thymic malignancy, but lacked accuracy in staging thymic carcinoma and thymic neuroendocrine tumors. Furthermore, in contrast with lung carcinoma, removal of the loco-regional lymph nodes has not been standard practice for thymic malignancies, as it was believed that lymphogenous metastases were infrequent or of little prognostic significance. The large heterogeneity in practice among institutions made it difficult to compare outcomes. However, various papers reported lower survival rates when nodal metastases were present. In 2013 the International Association for the Study of Lung Cancer (IASLC) partnered with ITMIG for an all-around data-based TNM staging system published in 2016, aimed to replace the Masaoka-Koga system which was based on the degree of local invasion of the tumor (4-7). By introducing a dedicated thymic lymph node map and precisely describing nodal assessment, the 8th Edition of the TNM stage classification for thymic malignancies has gained awareness among the scientific community and has contributed to a change in the management of thymic tumors. In the Masaoka-Koga staging system lymphatic metastasis was merely classified as a Stage IVb and no distinction was made between different nodal stations, nor between lymphogenous and hematogenous metastasis. The lymph node map outlined by ITMIG/IASLC is based on anterior and deep regions as seen during surgical dissection and the frequency and pattern of metastasis (5). Anterior mediastinal lymph nodes are presumed to be the primary drainage pathway (N1) and other intrathoracic nodes serve as a secondary drainage pathway (N2). Identifying the role of lymph node metastasis on survival and recurrence might have the potential to select patients at higher risk, allowing to guide individual therapy and follow-up. Increased interest in accurately staging nodal involvement has provided a stimulus to lymph node evaluation and dissection during interventions for thymic malignancies. With further distribution of the thymic nodal map, further advancements in thymic research are expected due to gathering of more consistent data, resulting in the most efficient treatment of patients with these rare tumors. We sought to review the current evidence surrounding lymph node metastasis in primary thymic malignancies and its prognostic relevance. What progress has the scientific community made since the adoption of the ITMIG/IASLC TNM staging system for thymic malignancies? We present the following article in accordance with the Narrative Review reporting checklist (available at https://amj.amegroups.com/article/view/10.21037/amj-21-34/rc).

Methods

We performed an online literature search in Medline using the PubMed interface and the search strategy aimed to select all papers on lymph node involvement and metastasis in thymic malignancies in patients who underwent surgery, available in English. Case reports were not eligible for selection. Original studies were selected from the date of first publication in the database to June 21, 2021.

Due to the narrative nature of this review and the absence of randomized studies, clinical relevance was the unique judgment criteria for article inclusion. PRISMA guidelines were, therefore not employed. Nodal involvement rate (NIR) is defined as the ratio of number of patients with lymph node metastasis to the total number of patients. Due to paucity of available data, overall survival or recurrence were chosen as main outcome measures. *Table 1* shows the search strategy summary.

Results

The search initially identified 23 original studies focused on primary thymic tumors. After assessment of each full-text article for eligibility, 11 studies were excluded due to

Table 1 Search strategy summary

Items	Specification
Date of search	June 21, 2021
Databases and other sources searched	Medline using PubMed interface + citation tracking
Search terms used	Free text words related to thymic epithelial tumors and lymph node metastasis (full search strategy is provided in Appendix 1)
Timeframe	Date of database inception to June 21, 2021
Inclusion and exclusion criteria	Inclusion of papers reporting on lymph node involvement and metastasis in thymic malignancies in patients who underwent surgery, available in English. Papers must provide survival information Exclusion of guidelines, editorial reviews and case reports
Selection process	Independent study selection and data extraction performed by WKH and PEVS. No discrepancies occurred
Addition consideration	Clinical relevance was the unique judgment criteria for article inclusion

providing insufficient data or including patients who did not underwent curative-intent surgery. Twelve studies were identified suitable for review and are detailed in *Table 2*. The majority of the studies were retrospective and only one prospective study was found. A total of 4,653 patients were included. Thymic malignancies were generally subdivided in thymomas, thymic carcinomas and neuroendocrine thymic tumors (NETT).

In five reviewed articles complete resection could not be achieved in the full patient population. Three of the included studies conducted before the publication of the ITMIG/IASLC lymph node map, used a classification proposed by Yamakawa (8).

Overall survival was the most commonly used endpoint. Six studies reported data on recurrence-free survival. The follow-up time of individual patients varied from 0.3 to 242 months. Eight studies reported median follow-up time data with an overall median follow-up of 51.0±42.6 months (range: 14.4–171 months). The remaining four studies did not mention follow-up time. Seven studies validated prognostic factors using multivariate regression models. Propensity-matched analysis was performed in three comparative cohort studies (12,15,17).

Presence of lymph node metastasis was found to be a significant prognostic factor for survival for thymoma (2,16) and thymic carcinoma (2,10,16). Patients with more locally advanced tumors, thymic neuroendocrine tumors (10,13,14), B3-thymomas (13) and thymic carcinomas (13,15) have a significantly higher likelihood of developing nodal metastases. Both Kondo and Weksler identified Masaoka staging for patients with thymomas (2) or carcinomas (10) and resection status in patients with thymomas and thymic carcinomas, as predictors of survival. Gu and associates came to the same conclusion on thymic carcinomas as well (13).

The 5-year freedom from recurrence (FFR) rate in Kaplan-Meier analysis varied from 25% (carcinoma with lymph node involvement) to 92.5% (thymoma) among the included studies. For thymic carcinomas the 5-year FFR rate varied from 67.6% to 74.6% in N0 patients compared to 25% to 33.3% in patients with lymph node metastasis (9,11). Two studies reported a significant difference in 5-year FFR rate of patients with and without lymph nodal involvement (9,11). In 2018, Hwang and colleagues concluded that lymph node metastasis was a significant negative prognostic factor for FFR in patients with thymomas and carcinomas, and they observed a statistical difference in FFR rate as N stage progressed (15). Park and associates too identified separate FFR rates for nodal subgroups (9). The FFR rate of the group with pathologic N0 by extensive dissection was significantly better than N1 subgroup. However, in remaining subgroups (Nx: no node dissection; N0a: pathologic N0 by limited dissection) no statistically significant difference was observed.

Overall 5-year survival rates among all thymic malignancies varied from 43% (carcinoma) to 84.5% (thymic malignancy), whereas 10-year survival varied from 34.4% (carcinoma) to 73.3% (thymic malignancy). Significant differences in survival rates were observed when nodal involvement was present (2,9,13,16,17). Moreover, prognosis tends to worsen according progression of the

Table 2 Characteristics and findings of included studies

Author, year, journal and country	Study type	Patient group	Nodal involvement rate (% patients)	Used classification N descriptor	pN stage (% patients)	Median follow-up (months, range)	Free from recurrence rate (%)	Survival outcomes	Key results
Tsuchiya *et al.* (8) (1994), *Pathol Int*, Japan	Retrospective	16 patients with carcinomas; 3 patients (18.8%) received neoadjuvant therapy; Complete resection was achieved in 7 cases (43.8%) Single center	5/16 (31.3)	Yamakawa	N1: 3/16 (18.8) N2: 1/16 (6.3) N3: 1/16 (6.3)	28 (0.3–242)	NR	5-year SR: 43% 10-year SR: 34.4%	Clear separation of survival curves between stages I and III or IV and between III and IV suggesting possible role of lymph node involvement on prognosis
Kondo *et al.* (2) (2003), *Ann Thorac Surg*, Japan	Retrospective	1,320 patients (1,064 thymomas, 183 carcinomas, 40 carcinoids). No standardized LND	Thymoma: 19/1,064 (1.8)	Yamakawa	Thymoma: N1: 14/1,064 (1.3) N2: 5/1,064 (0.5)	NR	NR	5-year SR: Thymoma: N0: 95.6% N1: 61.5% N2: 20%	N factor was one of the predictors of survival in thymoma and thymic carcinoma
			Carcinoma: 49/183 (26.8)		Carcinoma: N1: 19/183 (10.4) N2: 15/183 (8.2) N3: 15/183 (8.2)			Carcinoma + carcinoid: N0: 56% N1: 42.1% N2: 29.3% N3: 18.8%	High rate of skip metastases in thymic carcinomas
		Multicenter (115 institutions)	Carcinoid: 11/40 (27.5)		Carcinoid: N1: 3/40 (7.5) N2: 5/40 (12.5) N3: 3/40 (7.5)				

Table 2 (*continued*)

Table 2 (*continued*)

Author, year, journal and country	Study type	Patient group	Nodal involvement rate (% patients)	Used classification N descriptor	pN stage (% patients)	Median follow-up (months, range)	Free from recurrence rate (%)	Survival outcomes	Key results
Park *et al.* (9) (2013), *Ann Thorac Surg*, Korea	Retrospective	37 patients with carcinomas; 4 patients (10.8%) received neoadjuvant therapy; LND was performed in 29 cases (78.4%) Single center	6/37 (16.2)	Yamakawa	N1: 3/37 (8.1) N2: 3/37 (8.1)	60	5-year overall: 68.2% LN–: 74.6% LN+: 33.3%	5-year SR: overall: 65.5% 5-year DFS rate: overall: 60.9%	Significant higher rate of nodal involvement in case of invasion of neighboring organs Significant difference in DFS and FFR if lymph node involvement present
Weksler *et al.* (10) (2015), *J Thorac Oncol*, USA	Retrospective	229 patients (176 carcinomas, 53 carcinoids), selected from SEER database 14 patients (6.1%) received neoadjuvant therapy Complete resection was achieved in 93% No standardized LND Inclusion if at least one lymph node was analyzed. Exclusion if death within 30 days after surgery	Carcinoma: 59/176 (33.5) Carcinoid: 33/53 (62.3)	NR	NR	103 (73.6–132.4)	NR	Median survival: LN-: 124 m LN+: 47 m	Significant difference in survival if lymph node involvement is present Lymph node involvement more likely in NETT and more advanced tumors Nodal sampling lead to an upstaging in 84% of patients
Hwang *et al.* (11) (2016), *J Thorac Oncol*, Korea	Retrospective	201 patients whom 131 underwent LND (99 thymomas, 32 carcinoids) Single center	Thymoma: 5/99 (5.1) Carcinoma: 8/32 (25)	IASLC/ITMIG	Thymoma: N1: 2/99 (2.0) N2: 3/99 (3.0) Carcinoma: N1: 4/32 (12.5) N2: 4/32 (12.5)	60	5-year: Thymoma: N0: 92.5% N1/2: 60% Carcinoma: N0: 67.6% N1/2: 25%	Entire cohort 10-year SR: 73.3%	Tumor size is a significant factor for lymph node metastases with an optimal cutoff for prediction of node metastasis of 6 cm (sensitivity of 77% and specificity of 62%)

Table 2 (*continued*)

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Author, year, journal and country	Study type	Patient group	Nodal involvement rate (% patients)	Used classification N descriptor	pN stage (% patients)	Median follow-up (months, range)	Free from recurrence rate (%)	Survival outcomes	Key results
Zhao *et al.* (12) (2017), *Eur J Cardiothorac Surg*, China	Retrospective comparative	343 patients (287 carcinomas, 56 carcinoids)	Carcinoma: 48/287 (16.0)	IASLC/ITMIG	Carcinoma: N1: 21/287 (7.3) N2: 17/287 (5.9)	Carcinoma: 47 (1–173)	Carcinoma: 5-year: 41.1% 10-year: 32.4%	Carcinoma: 5-year SR: 63.7% 10-year SR: 48.4%	
		40 patients (11.7%) received neoadjuvant therapy	Carcinoid: 16/56 (28.6)		Carcinoid: N1: 10/56 (17.9) N2: 5/56 (8.9)	Carcinoid: 55 (2–152)	Carcinoid: 5-year: 37.5%	Carcinoid: 5-year SR: 80.7% 10-year SR: 51.9%	
		No standard LNR							
		Single center							
Gu *et al.* (13) (2017), *Interact Cardiovasc Thorac Surg*, China	Retrospective	1,617 patients (1,310 thymomas, 265 carcinomas, 42 carcinoids), selected from ChART database	Thymoma: 7/1,310 (0.5)	IASLC/ITMIG	NR	NR	NR	Overall SR: LN-: 92.5%	Tumor histology and pT stage are independent risk factors for predicting lymph node metastases
		Complete resection was achieved in 90.3%	Carcinoma: 21/265 (7.9)					LN+: 51.9%	Significant difference in DFS and OS if lymph node involvement is present
		Multicenter (18 institutions)	Carcinoid: 7/42 (16.7)						
Fang *et al.* (14) (2018), *J Thorac CardioVasc Surg*, China	Prospective	275 patients (243 thymomas, 24 carcinomas, 8 carcinoids)	Thymoma: 5/243 (2.1)	IASLC/ITMIG	Thymoma: N1: 2/243 (0.8) N2: 4/243 (1.6)	NR	NR	NR	N2 dissection is an independent risk factor for N disease
		No standardized LND, minimum harvest of at least one N1-station	Carcinoma: 6/24 (25.0)		Carcinoma: N1: 4/24 (16.7) N2: 2/24 (8.3)				
		Multicenter (15 institutions)	Carcinoid: 4/8 (50)		Carcinoid: N1: 1/8 (12.5) N2: 4/8 (50.0)				

Table 2 (*continued*)

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Author, year, journal and country	Study type	Patient group	Nodal involvement rate (% patients)	Used classification N descriptor	pN stage (% patients)	Median follow-up (months, range)	Free from recurrence rate (%)	Survival outcomes	Key results
Hwang *et al.* (15) (2018), *J Thorac Oncol*, Korea	Retrospective comparative	1587 patients whom 446 underwent LND (after propensity score matching: 297 thymomas, 91 carcinomas and carcinoids)	Thymoma: 20/297 (6.7)	IASLC/ITMIG	Thymoma: N1: 7/297 (2.4) N2: 6/297 (2.0)	171	10-year: Thymoma: 82.5%	Overall SR: 5-year: 84.5%	Conclusions on improvement of long-term oncological outcomes could not be made by enforcing standard lymph node dissection
		No standard N2-dissection	Carcinoma/ carcinoid: 47/91 (51.6)		Carcinoma/ carcinoid: N1: 16/91 (17.6) N2: 15/91 (16.5)		Carcinoma/ carcinoid: 45.7%	10-year: 68.7%	Significant difference in FFR-rate if lymph node involvement is present
		Complete resection was achieved in 89.2%							
		Multicenter (4 institutions)							
Cheufou *et al.* (16) (2019), *Ann Thorac Surg*, Germany	Retrospective	53 patients (43 thymomas and carcinomas, 10 carcinoid)	Thymoma/ carcinoma: 13/43 (30.2)	IASLC/ITMIG	N1: 11/53 (20.8) N2: 5/53 (9.4)	NR	NR	Overall SR: 5-year: 79%	
		15 patients (28.3%) received neoadjuvant therapy	Carcinoid: 3/10 (30.0)						
		Macroscopic complete resection was achieved in 88.7%							
		Single center							
Hamaji *et al.* (17) (2021), *Interact CardioVasc Thorac Surg*, Japan	Retrospective comparative	75 patients (71 carcinomas, 4 carcinoids)	Carcinoma: 17/71 (23.9)	IASLC/ITMIG	N1: 12/75 (16) N2: 8/75 (10.7)	38.4 (0.4–162)	5-year: 50.5%	5-year SR: 49.8%	
		11 patients (14.7%) received neoadjuvant therapy	Carcinoid: 3/4 (75.0)						
		No standardized LND							
		Single center							

Table 2 (*continued*)

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Author, year, journal and country	Study type	Patient group	Nodal involvement rate (% patients)	Used classification N descriptor	pN stage (% patients)	Median follow-up (months, range)	Free from recurrence rate (%)	Survival outcomes	Key results
Clermidy *et al.* (18) (2021), *Lung Cancer*, France	Retrospective	99 patients with thymomas (study group with standardized LND *vs.* historical control group) 10 patients (10.1%) received neoadjuvant therapy Single center	3/99 (3.0)	IASLC/ITMIG	N1: 0 N2: 3/99 (3.0)	Study group: 14.4 (1.0–30.8) Control group: 43.4 (14.3–67.3)	NR	NR	Significant higher rate of nodal involvement in case of more advanced stages (≥T2)

NR, not reported; SR, survival rate; LND, lymph node dissection; LN−, no lymph node involvement; LN+, lymph node involvement present; DFS, disease-free survival; FFR, Free from recurrence; SEER, Surveillance Epidemiology and End Results; m, months; NETT, neuroendocrine thymic tumor; IASLC, International Association for the Study of Lung Cancer; ITMIG, International Thymic Malignancies Interest Group; cm, centimeter; LNR, lymph node retrieval; ChART, Chinese Alliance for Research in Thymomas; OS, overall survival.

N stage (2,11,17) albeit statistical significance was only reached in one study by Kondo *et al.* (2).

When comparing thymic carcinomas and NETT in a propensity-matched analysis, Zhao and associates did not find a significant difference in overall survival and disease-free survival (12).

Discussion

Historically, several reasons have been responsible for the lack of sufficient data to analyze long-term oncological outcomes for thymic malignancies. First of all, the difficulty to obtain sufficient numbers of patients to examine, despite long study periods, is due to the rarity of thymic malignancies and their relatively long recurrence free periods. Moreover, thymomas, thymic carcinomas and thymic neuroendocrine tumors each have their own biological and clinical characteristics and cannot be equated. Even within thymomas, histopathologic subtypes (A/AB/B1 *vs.* B2/B3) possibly warrant a different approach in clinical management (19,20). As Weksler *et al.* addressed in their study, type B3 thymomas can be misdiagnosed as a thymic carcinoma (10). Study interpretation therefore relies on accurate pathological evaluation. In our review four studies identified histotypes B2 and B3 of thymomas as a risk factor for lymph node metastasis, based on the notion that B-type thymomas act more aggressively (11,13-15).

As of yet no standardized treatment nor surveillance protocols exist. In the past, there was limited possibility to include lymph node involvement in multivariate analysis for prognosis as most institutions did not routinely assess lymph nodes during resection. Strategies in lymphadenectomy have changed during the last decades. Systematic lymph node sampling had not been standard practice with the exception of Japanese surgeons who are since long familiar with routine lymphadenectomy during resection, also for lung cancer. They used nodal stage classification systems such as those proposed by Yamakawa and colleagues (6,21,22). Historically, N1-descriptor entailed metastasis to anterior mediastinal lymph nodes (perithymic) and metastasis to the remaining intrathoracic lymph nodes as N2 (5,22). In the proposed lymph node map by ITMIG/IASLC, the N1-decriptor redefines anterior mediastinal lymph nodes by including prevascular, paraaortic and supradiaphragmatic nodes and incorporate anterior cervical nodes as well. The N2-descriptor is defined by metastasis to middle mediastinal and deep cervical lymph nodes (the "deep region") including paratracheal, subaortic, subcarinal and

hilar lymph nodes. Additionally, a N3 stage is not described in the lymph node classification of ITMIG/IASLC and metastasis to nodes that are not defined by N1 or N2 are classified as M1 (5). N0 remains unchanged and denotes absence of lymph node metastasis.

ITMIG recommends routine removal of the anterior mediastinal and cervical lymph nodes (N1) in all thymic tumors. This correlates with an extended thymectomy. In contrast, only perithymic lymph nodes are usually removed during *en-bloc* thymectomy. Systematic sampling of other intrathoracic sites (depending on tumor location: paratracheal, aortopulmonary window and subcarinal) is strongly encouraged in case of thymomas with adjacent organ involvement (stage III–IV) whereas systematic lymphadenectomy (N1+N2) is strongly recommended in all thymic carcinomas and NETT due to the high rate of lymphatic spread (5). Obviously, any suspicious node either noticed preoperatively on imaging studies or during intraoperative evaluation, should be retrieved for examination by the pathologist. A global survey conducted in 2018 by Ruffini revealed that the majority of participants (72%) were aware of the existence of a lymph node map dedicated for thymic malignancies, but only half of the participants were actually implementing it in their daily practice (23). It seems that hesitation to adopt new proposals and recommendations exists among the members of the scientific community and will take time for these practices to be universally accepted.

Whether patients with lymph node metastasis have worse outcomes than those without nodal involvement remains controversial. Establishing the presence of positive lymph nodes as an adverse prognostic factor suggests that lymph node retrieval should be recommended as it holds weight in staging and prognosis of thymic malignancies. Most studies have shown their prognostic value (2,24-28), although others (29) did not show a significant difference in survival. Especially in low-grade tumors such as thymoma with histotype A/AB/B1, lymphatic involvement is a rare occurrence (11,13). This review confirms the notion that rates of lymph node involvement are higher in thymic carcinomas and NETT compared to thymoma. Research on NETT as a single entity and its nodal involvement is scarce. Due to its rarity, majority of the reviewed studies conjoined data on thymic carcinoma and NETT. The study by Zhao *et al.* published the largest series of NETT and its incidence of nodal metastasis did not significantly differ from thymic carcinoma (12). Nevertheless, both are associated with an ill prognosis and are considered high risk for N disease as they are typically diagnosed at a more advanced stage.

In many TNM staging systems for other cancers, a minimum number of harvested lymph nodes is well defined. In thymic malignancies a minimal number of retrieved lymph nodes has yet to be determined. So far, very few studies have published recommendations regarding a minimal number of lymph nodes needed to be harvested. Park *et al.* advocate extensive lymph node dissection with a minimal of ten lymph nodes to accurately predict prognosis (9). It seems evident that performing systematic nodal retrieval leads to an increase in lymph node involvement rates, thus more extensive lymph node resection might be beneficial. Weksler and associates noticed a nodal upstaging in 84% of patients with thymic carcinomas and NETT if consistent lymph node sampling was performed (10). Hwang and associates extended this notion to all thymic malignancies by showing a higher nodal involvement rate with extensive lymph node dissection in their retrospective cohort studies of 2015 and 2018 (11,15). In the latter a significant upstaging of their patients was reported. Furthermore, Fang and associates compared a prospective cohort to a retrospective cohort with patients selected from the ChART database and reported N2 dissection as an independent predictor for detecting nodal involvement (14).

Studies focusing on thymic malignancies tend to favor survival as an endpoint rather than recurrence. However, many patients do not die because of tumor-related causes making recurrence the preferred long-term outcome measure.

In a recently published study, Clermidy and associates looked at the short-term outcomes and reported a higher rate of postoperative complications when performing a more rigorous lymph node dissection on thymomas, although it did not reach statistical difference (18). A higher rate of nerve injuries (recurrent laryngeal nerve) was reported in their study group. The authors remained critical of provoking possible harm by performing more invasive lymph node harvesting, especially in low-risk tumors such as thymomas where lymph node metastasis remains rare. The same study reported a low incidence of lymph node metastasis and all were located in a N2-location. Skip metastasis are predominantly associated with thymic carcinoma (2,27). This was first reported by Kondo and colleagues using the nodal map of Yamakawa and no study has been published to indicate otherwise (2,22). It may be possible that the rate of skip metastasis is still underestimated.

Reports on the location of positive lymph nodes are

scarce; so, its relevance has yet to be evaluated. Hwang *et al.* emphasized node retrieval of the paratracheal site during sampling (11). In various other studies this N2-site has been predominantly positive when harvested (9,14,17). N2-dissection hasn't been standard practice for a sufficient period of time to draw any firm conclusions.

We encountered various limitations in our review. The majority of the included studies were retrospective, noncomparative cohort studies, three were comparative with propensity-matched analysis and only one featured study was prospective. Selection bias is inherently associated with retrospective studies. In addition, heterogeneity among the included study population was observed due to different inclusion or exclusion criteria in the studies. Variables such as resection status, extent of lymph node harvesting, presence of extrathoracic metastasis and additional (neo-) adjuvant therapy all exert a prognostic influence in need for further investigation. Lastly, five studies retrospectively selected their patients from the same database (9,11-13,15). This makes it likely that there was overlap of patients among these studies. As thymic malignancies are rare, setting up large-scale prospective trials continues to be challenging and requires international cooperation as initiated by ITMIG and IASLC.

Conclusions

The studies analyzed for this review do not allow us to draw definite conclusions and our review validates the findings on which the N descriptor of the current 8th TNM stage classification was based. We found no arguments to justify a revision of the N descriptor in the upcoming 9th edition of the TNM stage classification of thymic epithelial tumors due in 2024. We acknowledge that there are still many unanswered questions and unsettled issues to be unraveled on thymic nodal involvement. Pattern of nodal metastasis and dissimilarity in location, number of involved nodes or stations and histopathologic extent of invasion are to be further investigated before definite conclusions can be made regarding its prognostic influence. Until more mature data is available, diligence on standardized node retrieval as described by the recommendations of IASLC/ITMIG is necessary. This includes N1 as well as N2 lymph nodes. The International Thymic Malignancy Interest Group (www.itmig.org) has laid out an online prospective database for thymic malignancies. We encourage all institutions to participate and aid in the collection of uniform data suitable for meaningful comparative analysis in order to provide a solid basis for the preparation of the 10th TNM classification for which a specific subcommittee has been created.

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Footnote

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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.

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Supplementary

Appendix 1

((((((thymic epithelial tum*[Text Word]) OR (thymoma[Text Word])) OR (Thymus neoplasm*[Text Word])) OR (thymic carcinoma[Text Word])) OR (thymic malignan*[Text Word])) AND ((((staging[Text Word]) OR (lymph node*[Text Word])) OR (nodal metastas*[Text Word])) OR (lymphatic metastas*[Text Word]))) AND (((surgical*[Text Word]) OR (survival[Text Word])) OR (prognosis[Text Word]))

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