ORIGINAL ARTICLE

The International Association for the Study of Lung Cancer Thymic Epithelial Tumor Staging Project: A Re-Assessment of the International Thymic Malignancy Interest Group/International Association for the Study of Lung Cancer Lymph Node Map for Thymic Epithelial Tumors for the Forthcoming Ninth Edition of the TNM Classification of Malignant Tumors

Edith M. Marom, MD,[a] Wentao Fang, MD,[b] Enrico Ruffini, MD,[c,*] Frank Detterbeck, MD,[d] Usman Ahmad, MD,[e] Sarit Appel, MD,[f] Andrea Bille, MD,[g] Souheil Boubia, MD,[h] Cecilia Brambilla, MD,[i] Vanessa Cilento, MPH,[j] Ayten Kayi Cangir, MD,[k] Conrad Falkson, MbChB., MD,[l] Pier Luigi Filosso, MD,[m] Giuseppe Giaccone, MD,[n] Nicolas Girard, MD,[o] Emily Goren, PhD, MS,[j] Francesco Guerrera, MD,[c] James Huang, MD,[p] Maurizio Infante, MD,[q] Dong-Kwan Kim, MD,[r] Marco Lucchi, MD,[s] Mirella Marino, MD,[t] Andrew G. Nicholson, MD,[i] Meinoshin Okumura, MD,[u] Ramon Rami-Porta, MD,[v] Andreas Rimner, MD,[p] Charles B. Simone II, MD,[p] Hisao Asamura, MD[w]; Members of the IASLC Staging and Prognostic Factors Committee and of the Advisory Boards and Participating Institutions[**]

[a]*Department of Diagnostic Imaging, Chaim Sheba Medical Center, Tel-Aviv University, Ramat Gan, Israel*
[b]*Shanghai Chest Hospital, Jiaotong University Medical School, Shanghai, People's Republic of China*
[c]*University of Torino, Torino, Italy*
[d]*Yale University School of Medicine, New Haven, Connecticut*
[e]*Thoracic Surgery in the Heart, Vascular & Thoracic Institute at Cleveland Clinic, Abu Dhabi, United Arab Emirates*
[f]*Sheba Medical Center, Ramat Gan, Israel*
[g]*Guy's Hospital, London, United Kingdom*
[h]*University Hospital Ibn Rochd, Casablanca, Morocco*
[i]*Royal Brompton and Harefield NHS Hospitals, Guy's and St. Thomas' NHS Foundation Trust and National Heart and Lung Institute, Imperial College, London, United Kingdom*
[j]*Cancer Research And Biostatistics (CRAB), Seattle, Washington*

*Corresponding author.

**See Appendices

Disclosure: Dr. Ruffini reports receiving personal fees from AstraZeneca, outside the submitted work. Dr. Asamura reports receiving grants and personal fees from Johnson and Johnson and Covidien Japan; grants from Taiho, Astellas, AstraZeneca, and Lily, outside the submitted work. Dr. Boubia reports receiving personal fees from Medtronic and AstraZeneca, outside the submitted work. Dr. Marom reports receiving other support from Boehringer Ingelheim and Merck Sharp & Dohme, outside the submitted work. Dr. Nicholson reports receiving personal fees from Merck, Boehringer Ingelheim, Novartis, AstraZeneca, Bristol-Myers Squibb, Roche, AbbVie, Oncologica, UpToDate, European Society of Oncology, and Liberum; grants and personal fees from Pfizer, outside the submitted work. Dr. Rimner reports receiving grants and personal fees from Boehringer Ingelheim, AstraZeneca, and Merck; grants from Pfizer and Varian Medical Systems; personal fees from Cybrexa, MoreHealth, and ResearchTo-Practice; and nonfinancial support from Philips/Elekta, outside the submitted work. Dr. Okumura reports receiving grants and personal fees from Eisai, Chugai Pharmaceutical, Alexion Pharmaceuticals, AstraZeneca, UCB Japan, Johnson and Johnson, and Canon Medical Systems, outside the submitted work. The remaining authors declare no conflict of interest.

Address for correspondence: Enrico Ruffini, MD, Thoracic Surgery, University of Torino, 14, Corso Dogliotti, 10126 Torino, Italy. E-mail: enrico.ruffini@unito.it

ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2023.09.001

[k]Ankara University Faculty of Medicine, Ankara, Turkey
[l]Queen's University in Kingston, Ontario, Canada
[m]Baggiovara Civil Hospital, University of Modena, Modena, Italy
[n]Meyer Cancer Center, Weill-Cornell Medicine, New York, New York
[o]Institut Curie, Thorax Institute Curie Montsouris, Paris, France; Paris Saclay University, UVSQ, Versailles, France
[p]Memorial Sloan Kettering Cancer Center, New York, New York
[q]University and Hospital Trust, Verona, Italy
[r]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[s]Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy
[t]IRCCS Regina Elena National Cancer Institute, Rome, Italy
[u]National Hospital Organization Osaka Toneyama Medical Center, Osaka, Japan
[v]Hospital Universitari Mutua Terrassa, Terrassa, Spain, and Network of Centers for Biomedical Research in Respiratory Diseases (CIBERES) Lung Cancer Group, Terrassa, Spain
[w]Keio University, Tokyo, Japan

Received 26 July 2023; revised 29 August 2023; accepted 1 September 2023
Available online - 9 September 2023

ABSTRACT

Introduction: A lymph node map is the pillar on which accurate assignment and documentation of nodal classification stands. The International Thymic Malignancy Interest Group created the first map for thymic epithelial malignancies in conjunction with the eighth edition of the TNM classification, representing the first official TNM classification of thymic epithelial malignancies. The map was based on clinical experience and published studies, but it was largely empirical because of limited available data. Dissemination of the map and implementation of a standard thymic stage classification across the world in 2017 have provided more consistent and granular data.

Methods: More than twice as many cases of node involvement are available for analysis in the current database compared with that of the eighth edition database, allowing validation of many aspects of the eighth edition map. This article details the process and considerations for refinement of the thymic map for the ninth TNM used by the Thymic Domain of the Staging and Prognostic Factors Committee of the International Association for the Study of Lung Cancer. The committee evaluated a large international collaborative data set, published anatomical and clinical studies pertaining to lymph node spread from thymic epithelial tumors, in conjunction with the analysis underlying refinements of the TNM components for the ninth edition TNM classification.

Results: The node map boundaries of the N1 and N2 categories remain unchanged. Visual clarifications have been added to the nomenclature of nodal stations within these regions.

Conclusions: On the basis of the recommendation to keep the N component unchanged for the ninth edition TNM classification, the lymph node map remains unchanged as well; however, clarifications have been added to facilitate clinical use.

Keywords: Thymic malignancy; Thymoma; Thymic carcinoma; Thymic neuroendocrine tumor; Thymic node map

Introduction

With the introduction of the first internationally accepted TNM stage classification for thymic epithelial tumors (TETs) in the eighth edition of TNM classification of malignant tumors, revealing that node involvement affected overall survival, a lymph node map was created for the first time by the International Thymic Malignancy Interest Group (ITMIG) and distributed in conjunction with the International Association for the Study of Lung Cancer (IASLC),[1] to serve as a worldwide standard in the collection of nodal data. The proposal for the ninth edition TNM stage classification for TET presented in this issue is the first to be on the basis of data collected using a worldwide standard TNM system, with a lymph node map to serve as guidance. This has more than doubled the number of pathologically-proven assessable node-positive data compared with that of the eighth edition database.

The objective of the present article was to consider refinements to the regional lymph node map created a decade ago,[1] while taking into account studies pertaining to lymph node spread from TET, in conjunction with the analysis used to create proposals for the ninth edition TNM classification of malignant tumors.

Materials and Methods

The Thymic Domain of IASLC's Staging and Prognostic Factors Committee (TD-SPFC) consists of an international multidisciplinary group of experts.[2] As part

of developing a TNM classification of TET for the eighth edition of the TNM classification of malignant tumors, the Thymic Domain included a critical assessment of the ITMIG-IASLC thymic node map.[1]

The following questions were addressed: (1) How had the eighth edition map been received and how broadly was it implemented? (2) Were new insights available in the published reports that suggested potential refinements? (3) Did data from the IASLC database which was used for the ninth TNM corroborate the largely empirical N1 and N2 categories? (4) Did data suggest any changes, for example, addition of an N3 category, revision of the previously defined boundaries? (5) Did the N Subcommittee of the TD-SPFC propose revisions to the N component that required any revisions of the node map? (6) How implementable was the node map, that is, were aspects of the eighth edition map poorly understood, was there consistency in implementation in a clinical [imaging] context or a pathologic [surgical] context? These questions were considered primarily from the standpoint of the node map, although, clearly, there is overlap with clinical recommendations and norms, that is, reporting of imaging findings and extent of intraoperative sampling.

A PubMed article search was performed to assess whether new published reports suggested a revision. This involved broad search terms as follows: "thymus lymph node drainage" and "thymoma or thymic carcinoma or thymic neuroendocrine tumor and lymph node." The search was limited to English language and focused on the years 2000 to 2023, thus overlapping to some extent the search used for the eighth edition map. Of 1127 identified titles, articles were selected for full review that pertained to anatomy, prevalence, outcome, staging, and lymph node dissection with respect to node location. Most of the articles had already been reviewed during development of the eighth edition map.

The findings of the background research were discussed, and potential revisions to the node map were considered. Criteria for making changes included evidence that the node groups should be divided further (or less), evidence that different boundaries would better reflect what is known about lymphatic anatomy with respect to the thymus, regional distribution of node involvement, ease of radiologic and surgical implementation, prognostic impact of regional node involvement, and the results of the ninth edition N Subcommittee of the TD-SPFC. An important consideration in a rare tumor was simplicity, for example, minimizing change unless strongly suggested by evidence and consistency across all types of thymic malignancies.

Results

Acceptance of the TET Node Map in the Eighth Edition TNM

The acceptance of the TET TNM in the eighth edition TNM stage classification was questioned in a web-based cross-sectional survey questionnaire.[3] It was conducted between September and December 2018, only 1 year and 2 years after implementation of the eighth edition TNM classification in the United States and the rest of the world, respectively. There were 217 responses collected from 37 countries in four continents. The eighth edition TNM classification system was considered useful by 78% of responders and was used in daily clinical practice by 64% of responders. Nevertheless, although 72% of the responders were aware of the dedicated ITMIG/IASLC thymic nodal map, only 48% were using it and only 54% found it effective. According to this survey, N1 nodal dissection was performed for 50% of patients with thymoma and 66% of patients with thymic carcinoma. N2 nodal dissection was performed for 21% and 41% of patients with thymoma and thymic carcinoma, respectively. Respondents in Asia paid the greatest attention to the N category compared with those in Europe and the Americas. Nodal dissection was most often performed for T3 tumors (33%) and less often for T2 (9%) and T1 (8%) tumors. N2 dissection was prompted primarily by abnormal F-fluorodeoxyglucose uptake (40%), suspicious intraoperative appearance (42%), or an enlarged lymph node on computed tomography (CT) (30%). Routine N2 dissection was reported for thymic carcinomas and neuroendocrine thymic tumors (NETTs) and all advanced thymomas by 30% and 25% of responders, respectively. Approximately 50% performed N1 nodal dissection, but only 21% performed N2 dissection when using a minimally invasive approach to resection (approaches that typically involve early stage tumors).

We concluded that although dissemination of the lymph node map in such a short period of time was a success, its implementation into daily practice needed improvement. This could be accomplished by improving and clarifying the lymph node map and educating those dealing with clinical stage evaluation and lymph node harvesting.

Insights From the Published Reports for Potential Lymph Node Map Refinement

Historical studies have revealed that overall survival is worse for patients with TETs and any lymph node involvement,[4–11] which was also found in the eighth edition TNM analysis.[12] The decision to adopt nodal regions in the eighth edition classification—prevascular (N1) and deep intrathoracic (N2)—was based on

assumptions in the absence of statistical data. The N1 region, being closer to the thymus, was assumed to have a better prognosis. Anatomical studies[13,14] and historic data revealing a greater frequency of spread to the N1 region supported the concept that this would be the first region for nodal spread. The Japanese Association for Research in the Thymus (JART) revealed in 2003[7] that most nodal metastases involve the N1 region: 90% for thymoma, 69% for thymic carcinoma, and 91% for NETT. This study could not confirm a difference in outcomes,[7] with the exception of worse survival for patients with thymic carcinoma with N2 versus N1 involvement. The lack of a survival difference in other subsets was attributed to the small numbers of patients for evaluation.

Three studies have focused on defining nodal regions for TET. All were conducted before the implementation of the eighth edition TNM classification; no new studies have been published. The three studies were based on single institution cohorts, involving 16,[15] 123,[16] and 207[17] patients. All suggested four nodal categories, N0 to N3: N0, no nodal involvement; N1, prevascular nodal involvement; and N2, intrathoracic lymph nodes excluding the prevascular lymph nodes. The N3 category is where they differed. One[16] defined N3 as prescalene or supraclavicular lymph nodes, whereas the others[15,17] designated any extrathoracic lymph nodes as N3. Boundaries between nodal groups were not clearly defined, and a nodal map was not provided. Statistical support for the divisions could not be found due to the small sizes of the cohorts. Furthermore, the use of these four nodal categories could not be statistically validated when assessed with the 1320 patient JART database.[7] The eighth edition TNM analysis also had insufficient data to permit statistical analysis of N stations. The ITMIG/IASLC node map defined N1 and N2 categories on the basis of the tendency for survival difference in the JART database and the argument that N1 lymph nodes would routinely be included in the harvested specimen with thymectomy, whereas N2 nodal sampling would require an extra effort, and sometimes an added surgical procedure. An N3 region was omitted in favor of keeping the system simple and the rarity of the disease and nodal involvement.

The true prevalence of lymph node involvement in TET is unclear because lymph node dissection has been rarely performed in TET. Nodal involvement is common in thymic carcinoma and NETT[6,7,10]; it is also higher in patients with stage III and higher stage thymoma as compared with stage I or II disease.[11,18] The only prospective study assessing the prevalence of nodal involvement[18] suggested distinction of a high-risk group, with 70% having nodal involvement (stage T3 or higher, WHO histologic type—B3, thymic carcinoma, or NETT), and a low-risk group with only 0.5% involvement (thymoma types A–B2, clinical (c) stages I–II). This study also noted that N2 involvement was generally on the ipsilateral side of the tumor, except in NETT, which tended to be bilateral.

In conclusion, the evaluation of available reports suggested that issues needing evaluation included confirmation of a prognostic difference between N1 versus N2, whether there should be an N3 category for supraclavicular or perhaps extra thoracic lymph node involvement, and whether laterality of lymph node involvement affected survival.

Current IASLC Database Corroboration of the N1 and N2 Division

In the ninth edition database, with more than double the assessable lymph nodes involved as compared with the database used for the eighth edition TNM, we were able to confirm statistically significant worse survival for N2 versus N1 versus N0 involvement in patients with thymic carcinoma (without distant metastases).[19] In patients with thymoma (all M categories), statistically worse survival was found with N2 versus N1 involvement. Nevertheless, assessment of patients with thymoma without distant metastases (M0) was precluded, because there were only seven such patients with N2 disease. There were insufficient data to evaluate the impact of N2 involvement in patients with NETT. In addition, the current database confirms that nodal involvement predominantly occurs in the N1 region for thymoma (73%) and NETT (81%) but in only 47% for thymic carcinoma.

Possible Revision of Boundaries or Subdivision of Nodal Regions

The current IASLC database did not permit analysis of boundaries or further subdivision of node stations. Most patients with involved lymph nodes lacked granular information regarding the specific location of the nodes within the N1 or N2 stations. The extremely limited numbers of sampled cervical N2 lymph nodes or extrathoracic lymph nodes precluded assessment of an N3 category. Likewise, the limited information regarding laterality precluded evaluation of this issue. These limitations and the decision of the N Subcommittee to make no changes in the N categories led to the decision not to redefine boundaries or subdivide the node stations of the lymph node map.[19]

Implementation of the Node Map

Studies assessing the accuracy of imaging in identifying nodal spread from TET are anecdotal.[20–22] In the eighth edition TNM questionnaire,[3] CT was perceived as

being moderately accurate by a few respondents for c-N1 (43%) and c-N2 (47%) and magnetic resonance imaging was perceived as moderately accurate by even fewer respondents for cN1 (25%) and cN2 (27%). In the ninth edition database, despite having 6820 patients with pathologically confirmed assessable lymph nodes, only 1288 patients (19%) had clinical nodal categorization. Of the 1048 patients with thymoma with both clinical and pathologic data, the clinical N0, N1, or N2 category matched the pathologic N category in 98%, 9%, and 11%, respectively. Of the 221 patients with thymic carcinoma with both clinical and pathologic data, the clinical N0, N1, or N2 category matched the pathologic N category in 89%, 14%, and 61%, respectively (Fig. 1*A* and *B*).

We speculate that clinical assessment of N2 involvement seems to be more accurate in thymic carcinoma than thymoma because thymic carcinoma typically has much higher F-fluorodeoxyglucose uptake[21,23–28] and N2 nodal dissection is heavily influenced by positron emission tomography findings.[3] The poor performance of imaging in correctly identifying N1 disease may be due to difficulty in differentiating N1 nodes from the primary tumor which they may abut and also because these nodes are often smaller than 1 cm, not meeting the CT definition used for lymphadenopathy.[22]

In conclusion, the analysis of the available data regarding clinical and pathologic N categorization revealed challenges in clinical implementation that need to be addressed. Better definition of imaging features that accurately predict the actual N status is needed. Such research is hampered if clinical stage is recorded infrequently. Furthermore, granular data on node location are needed. Addressing this likely requires inclusion of such details in prospective databases, including better clarity on boundaries of the N regions and how to define node stations within them. This is necessary to achieve a common language between radiologists, surgeons, and pathologists, so that future iterations of the TNM staging will be more accurate.

Current Lymph Node Map Recommendations

The ITMIG/IASLC node map remains the same as that suggested for the eighth edition TNM classification. The nodal map takes into account the current N Subcommittee decision for no change in the N component, suggesting for practicality, both at operation and imaging, to divide into two nodal regions: anterior and deep. The anterior region is the thymic bed compartment in the anterior lower neck and the thymic bed in the chest, which is the prevascular compartment[29] (Table 1). Lymph nodes in the anterior compartment are considered the primary drainage pathway for the thymus. This is based on the anatomical and TET lymph node involvement studies described previously. Anatomical studies reveal that this anterior compartment has well-established nodal groups[13] and lymphatic trunks.[14] Nevertheless, it would be impractical to further divide this compartment. Boundaries between these node groups cannot be found by imaging, and lymph nodes in this region should be routinely removed during en-bloc resection of the entire thymus with surrounding fat, even with stages I and II disease.[30]

Nevertheless, recording aspects of node location within the N1 region is needed to foster better definition of imaging characteristics and surgical management going forward. The description of nodes within this compartment takes into account the nomenclature and

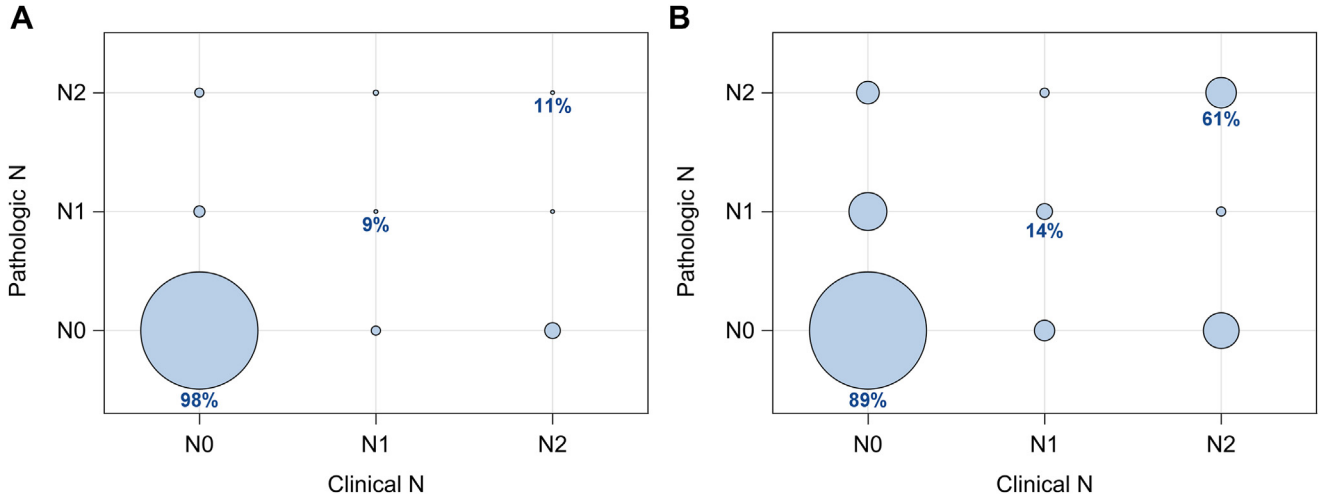

Figure 1. Bubble depiction of the clinical and pathologic concordance of N. The size of the bubble corresponds with the percent of pathologic N patients correctly identified clinically (by imaging). (*A*) Thymoma. (*B*) Thymic carcinoma.

Table 1. Anterior Region (N1)—Prevascular Mediastinum and Anterior Cervical Lymph Nodes

Region Boundaries	Node Groups[a]	Node Group Boundaries
Superior: lower border of cricoid cartilage Lateral (neck): medial border of the carotid sheath/jugular vein Lateral (chest): mediastinal pleura Anterior: sternum Posterior (medially): great vessels, pericardium Posterior (laterally): phrenic nerve Inferior: xiphoid, diaphragm	Low anterior cervical: peritracheal, perithyroid, (AAO-HNS/ASHNS level 6/IASLC level 1)	Superior: lower border of the cricoid cartilage Lateral: common carotid arteries Inferior: superior border of the manubrium
	Peri-thymic	Proximity to the thymus
	Prevascular (IASLC level 3a)	Superior: apex of chest Anterior: posterior sternum Posterior: anterior SVC Inferior: carina
	Para-aortic, ascending aorta, superior phrenic (IASLC level 6)	Superior: line tangential to sup border of aortic arch Inferior: inferior border of aortic arch
	Supradiaphragmatic/inferior phrenic/pericardial (along inferior poles of thymus)	Superior: inferior border of aortic arch Anterior: post sternum Posterior: phrenic nerve (laterally) or pericardium (medially) Inferior: diaphragm

[a]Region and node group boundaries adapted directly from definitions established by IASLC[31] and AAO-HNS and ASHNS.[32]
AAO-HNS, American Academy of Otolaryngology—Head and Neck Surgery; ASHNS, American Society for Head and Neck Surgery; IASLC, International Association for the Study of Lung Cancer; SVC, superior vena cava.

some of the boundaries used for the intrathoracic lymph nodes described by the IASLC for lung cancer[31] and for the neck by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS)/American Society for Head and Neck Surgery (ASHNS) lymph node maps[32] (Table 1). The N1 region includes the thymus, surrounding fat, and lymph nodes within the boundaries described in Table 1. Note is made that dissection of this region includes removal of the AAO-HNS/ASHNS level 6 lymph nodes in the neck, lymph nodes immediately abutting the thymus, right and left, where the mediastinal pleura abuts the mediastinal fat, including resection of this fat with lymph nodes to the diaphragm and lymph nodes just lateral to the transverse aorta (IASLC station 6). This does not include the level inferior to that, the aortopulmonary lymph node group (IASLC station 5), which lies posterior and medial to the left phrenic nerve, which is considered a deep node and does not belong to this anterior compartment. Likewise, the lymph nodes along the internal mammary vessels are not part of this anterior compartment.

The deep region contains N2 lymph nodes. It appears from anatomical studies[13,14] and from studies of the prevalence of nodal involvement by TET[4–11,18,33,34] that the path of spread from N1 lymph nodes is variable and depends on the location of specific N2 nodes. The boundaries of the deep region are described in Table 2. This deep region includes tracheobronchial (IASLC stations 2 and 4), aortopulmonary window (IASLC station 5), subcarinal (IASLC station 7), hilar (IASLC station 10 only) lymph nodes, internal mammary lymph nodes, and the deep cervical lymph nodes. These deep cervical lymph nodes include the lower jugular (AAO-HNS/ASHNS station 4a) and supraclavicular lymph nodes (AAO-HNS/ASHNS station 5b) (Fig. 2*A–I*).

Note is made that lymph nodes within the chest, abdomen, neck, or elsewhere, not mentioned in these regions, are not considered locoregional spread and constitute M1b disease (Fig. 3*A–C*).

Discussion

The node map boundaries of the N1 and N2 categories remain unchanged. Nevertheless, visual clarifications have been added to the nomenclature of nodal stations within these regions for better documentation with the ninth edition TNM classification (Tables 1 and 2 and Fig. 2).

There has been a major shift in the approach to nodal classification of TET since the initiative by ITMIG and IASLC that led to sharing of databases of the thymic societies at that time (ITMIG, JART, European Society of Thoracic Surgeons, and Chinese Alliance for Research in Thymoma) and the development of the first official TNM-based stage classification system. This ushered in many research studies and greater understanding. Studies have revealed that the prevalence of lymph node involvement is much higher when intentional lymph node dissection is performed and that nodal involvement is associated with a worse survival. This prognostic impact is confirmed in the ninth edition analysis; details and recommendations for the N component for the ninth TNM stage classification are reported in a separate article. A survival difference for N2 versus N1 versus N0 was confirmed for patients with thymic carcinoma, and

Table 2. Deep Region (N2) (Visceral Mediastinum and Deep Cervical Nodes)

Region Boundaries	Node Groups[a]	Node Group Boundaries
Superior: level of lower border of cricoid cartilage Anteromedial (neck): lateral border of sternohyoid, medial border of carotid sheath/jugular vein Posterolateral (neck): anterior border of trapezius Anterior (chest): aortic arch, aortopulmonary window-anterior border of the SVC Posterior (chest): esophagus Lateral (chest): pulmonary hila Inferior: diaphragm	Perijugular (AAO-HNS/ASHNS level 4)	Superior: level of lower border of cricoid cartilage Anteromedial: medial border of the jugular vein and carotid artery Posterolateral: lateral border of sternocleidomastoid Inferior: clavicle
	Supraclavicular (AAO-HNS/ASHNS level 5b)	Superior: level of lower border of cricoid cartilage Anteromedial: posterior border of sternocleidomastoid Posterolateral: anterior border of trapezius Inferior: clavicle
	Internal mammary arteries	Proximity to internal mammary arteries
	Upper paratracheal (IASLC level 2)	Superior: superior border of manubrium, apices of lungs Inferior: intersection of lower border of innominate vein with trachea; superior border of aortic arch
	Lower paratracheal (IASLC level 4)	Superior: intersection of lower border of innominate vein with trachea; superior border of aortic arch Inferior: lower border of azygos vein, superior border of left main pulmonary artery
	Subaortic/aortopulmonary window (IASLC level 5)	Superior: inferior border of aortic arch Inferior: superior border of left main pulmonary artery
	Subcarinal (IASLC level 7)	Superior: carina Inferior: upper border of lower lobe bronchus on the left; lower border of bronchus intermedium on the right
	Hilar (IASLC level 10)	Superior: lower rim of azygos vein on right, upper rim of pulmonary artery on left Inferior: interlobar region bilaterally

[a]Region and node group boundaries adapted directly from definitions established by IASLC[31] and AAO-HNS and ASHNS.[32]
AAO-HNS, American Academy of Otolaryngology—Head and Neck Surgery; ASHNS, American Society for Head and Neck Surgery; IASLC, International Association for the Study of Lung Cancer; SVC, superior vena cava.

partially also for patients with thymoma. For patients with thymoma, we did prove that overall survival was significantly worse for patients with N1 disease as compared with N0 disease. Nevertheless, although survival was numerically worse for patients with thymoma with N2 as compared with N1 involvement, the limited number of cases with N2 node assessment precluded a robust statistical analysis.

Unfortunately, despite awareness of the existence of the TET nodal map[1] and an impressive increase in nodal dissection during surgical treatment in patients with TET, many cases lacked details regarding node involvement (both specific node location and documentation of the region of involvement). Questions that remain unanswered include whether N2 involvement portends a worse prognosis in patients with thymoma as compared with N1 disease, whether laterality affects survival, or whether a possible N3 category is justified. Whether subcarinal (IASLC station 7) or supraclavicular (AAO-HNS/ASHNS station 5b) node involvement carries a worse prognosis has clinical and technical implications: dissection of these nodes often requires a separate procedure, especially when using a minimally invasive approach. The lack of detailed reporting during clinical (imaging) stage evaluation hampers research—although the poor concordance of clinical and pathologic N classification clearly identifies this as a major knowledge gap.

In 2011, ITMIG proposed standards for surgeons and pathologists during the course of resection of TET.[30] Studies since then have supported these standards. The complete resection of N1 lymph nodes at thymectomy adds prognostic information, and careful inspection of this prevascular fat and documentation by the handling pathologist/technician should be emphasized. The increase in nodal involvement for greater than or equal to T3 thymoma, including any thymic carcinoma or NETT tumor, requires N2 lymph node sampling; this is confirmed in the analysis of the current TNM database.

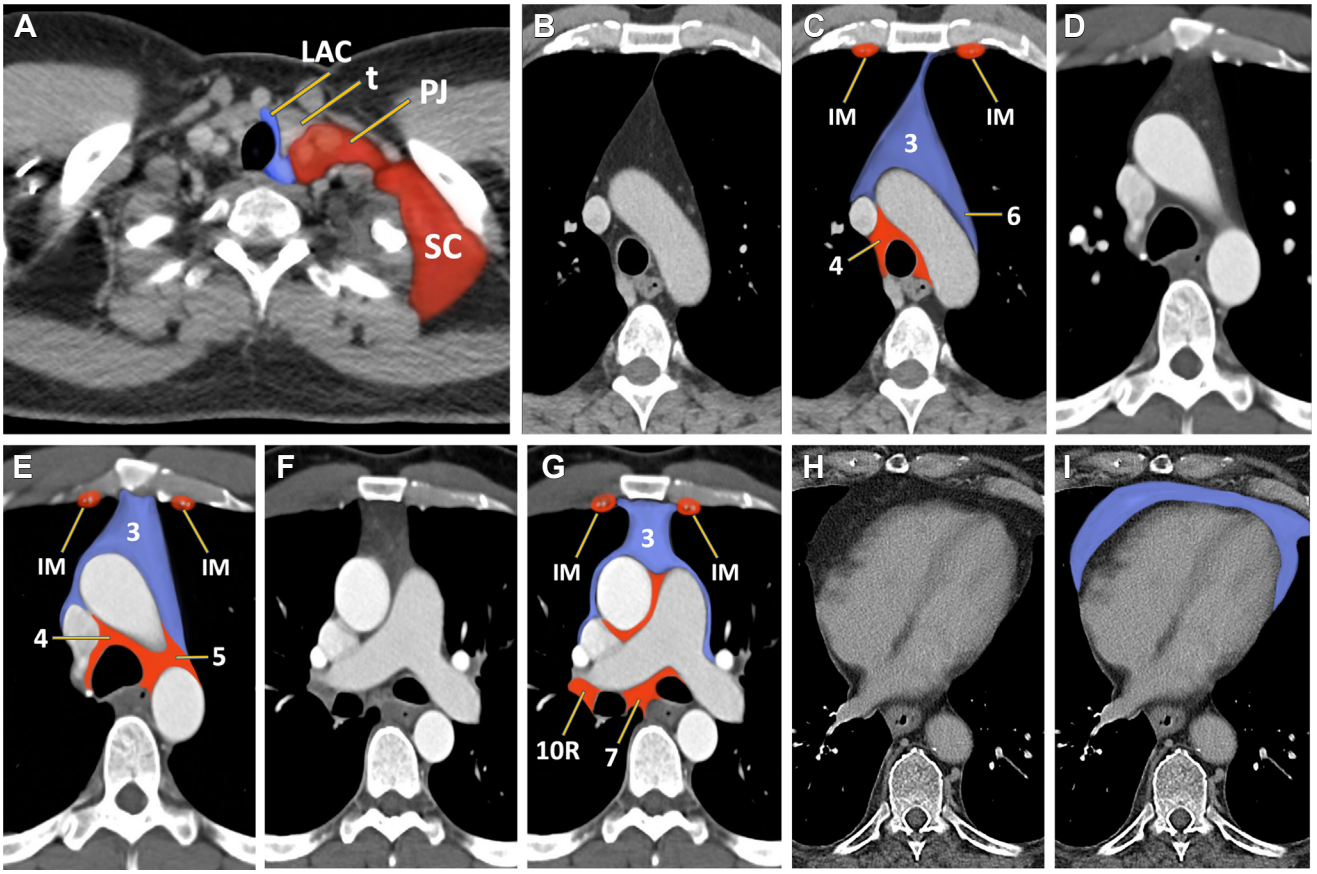

Figure 2. Native and annotated axial computed tomography images revealing the node groups, marking the boundaries of the anterior (N1) and deep (N2) lymph node levels at the levels of the (*A*) lower neck, (*B*, *C*) aortic arch, (*D*, *E*) aorto-pulmonary window, (*F*, *G*) main pulmonary artery, (*H*, *I*) and base of the heart. Boundaries of the anterior (N1) and deep (N2) level are shaded in blue and red, respectively. IASLC, International Association for the Study of Lung Cancer; IM, internal mammary; LAC, low anterior cervical; PJ, perijugular; SC, supraclavicular; t, thyroid gland. Numbers refer to IASLC node map used for lung cancer.[31] Courtesy of the International Association for the Study of Lung Cancer. Copyright 2023, Aletta Ann Frazier.

As treatment is decided before resection and pathologic final staging, diagnostic radiologists should scrutinize imaging of newly diagnosed patients with TET, emphasizing lymph nodes that seem suspicious even when smaller than 1 cm; some retrospective studies[6,20–22] have revealed that involved lymph nodes are often smaller than 1 cm. It is no surprise that imaging seemed to fare better in detection of N2 disease as compared with N1 disease. We speculate that the lack of systematic N2 evaluation by most centers means that most N2 nodes assessed in the database were due to imaging suspicion of involvement. The low rate of pathologic N2 assessment in general means we know little about the false-negative rate of N2 involvement by imaging. The use of the nodal map, together with labeling of all lymph nodes by name, number, and side (right or left) for radiologists at initial stage evaluation and for surgeons and pathologists at resection would markedly enhance our knowledge and likely our management of patients. Currently, available data suggest that systematic nodal sampling is required, as imaging performance is poor. A collaborative prospective study is needed to assess the true performance of imaging in nodal evaluation because all studies including the ninth edition database are skewed.

In conclusions, analysis of the data available for the ninth edition stage classification proposals confirmed the fundamental structure of the ITMIG/IASLC node map. The assessment of published reports, implementation of the eighth edition node map and the data accumulated since then did not justify making any changes. Nevertheless, the assessment did reveal knowledge gaps and opportunities for progress. We have added details regarding nodes within the N1 and N2 stations and sought to clarify definition of boundaries. We call for recording of greater detail and more thorough clinical and pathologic evaluation of the N status. We believe that the updated node map and greater detail in databases will markedly enhance our knowledge and improve our management of patients in the future.

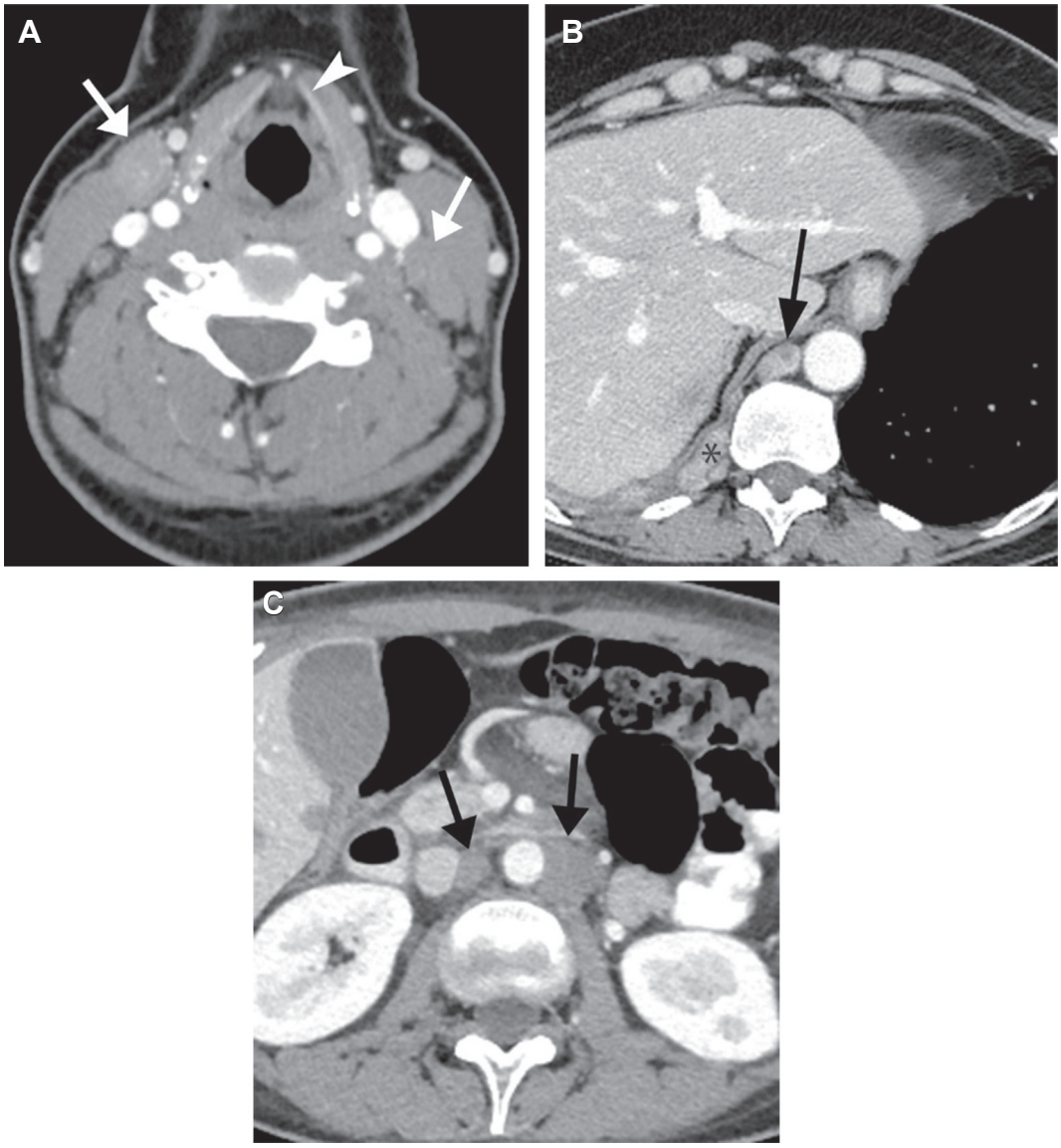

Figure 3. Examples of patients with TET and lymph node metastases considered nonregional (M disease). (*A*) Axial contrast-enhanced neck CT at the superior margin of the thyroid cartilage (arrowhead) reveals bilateral neck lymphadenopathy (arrows). Locoregional spread in the neck is limited to lymph nodes below the cricoid cartilage level. Involved lymph nodes superior to this are considered M disease. (*B*) Axial contrast-enhanced CT of the lower chest reveals right retro-crural lymphadenopathy (arrow). Note this lymph node is surrounded by fat and separate from the right pleural metastatic disease (*). Retro-crural lymph nodes are outside of the TET nodal map, and their involvement is considered M disease. (*C*) Axial contrast-enhanced CT of the upper abdomen at the level of the lower kidney poles reveals bilateral para-aortic lymphadenopathy (arrows). Abdominal and retroperitoneal lymph node involvement is outside of the TET nodal map and is considered M disease. One should carefully insure that soft tissue in this region is separate from contiguous pleural involvement, as in this case. CT, computed tomography; TET, thymic epithelial tumor.

CRediT Authorship Contribution Statement

Edith M. Marom: Conceptualization, Methodology, Writing—Original draft preparation.

Wentao Fang: Conceptualization, Methodology, Writing—Original draft preparation.

Frank Detterbeck: Supervision, Reviewing and editing.

Enrico Ruffini: Supervision, Reviewing and editing, Final check.

Usman Ahmad: Reviewing and editing.

Sarit Appel: Reviewing and editing.

Andrea Bille: Reviewing and editing.

Souheil Boubia: Reviewing and editing.

Cecilia Brambilla: Reviewing and editing.

Vanessa Cilentro: Data collection and harmonization.

Ayten Kayi Cangir: Reviewing and editing.
Conrad Falkson: Reviewing and editing.
Pier Luigi Filosso: Reviewing and editing.
Giuseppe Giaccone: Reviewing and editing.
Nicolas Girard: Reviewing and editing.
Emily Goren: Data collection and harmonization.
Francesco Guerrera: Reviewing and editing.
James Huang: Reviewing and editing.
Maurizio Infante: Reviewing and editing.
Dong-Kwan Kim: Reviewing and editing.
Marco Lucchi: Reviewing and editing.
Mirella Marino: Reviewing and editing.
Andrew G. Nicholson: Reviewing and editing.
Meinoshin Okumura: Reviewing and editing.
Ramon Rami-Porta: Reviewing and editing.
Andreas Rimner: Reviewing and editing.
Charles B. Simone II: Reviewing and editing.
Hisao Asamura: Reviewing and editing.

Acknowledgments

The authors thank the expert and professional secretarial support provided by Patricia Vigués-Frantzen Hospital Universitari Mútua Terrassa, Terrassa, Barcelona, Spain.

Appendix 1

IASLC Staging and Prognostic Factors Committee

Hisao Asamura (chair), Keio University, Tokyo, Japan; Valerie Rusch (chair elect), Memorial Sloan Kettering Cancer Center, New York, New York; Ramón Rami-Porta (past chair), Hospital Universitari Mutua Terrassa, Terrassa, Spain; Luiz Henrique Araujo, Brazilian National Cancer Institute, Rio de Janeiro, Brazil; David Beer, University of Michigan, Ann Arbor, Michigan; Pietro Bertoglio, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; Ricardo Beyruti, University of São Paulo Medical School, Sao Paolo, Brazil; Andrea Billè, Guy's Hospital, London, United Kingdom; Souheil Boubia, University Hospital Ibn Rochd, Laboratoire de Pathologie Cellulaire et Moléculaire Hassan II University of Casablanca, Casablanca, Morocco; Elisabeth Brambilla, Centre Hospitalier Universitaire, Grenoble, France, University of Grenoble Alpes, Grenoble, France; A. K. Cangir, Ankara University Faculty of Medicine, Ankara, Turkey; David Carbone, The Ohio State University, Columbus, Ohio; Vanessa Cilento, Cancer Research And Biostatistics, Seattle, Washington; Casey Connolly, IASLC, Denver, Colorado; Gail Darling, Dalhousie University, Nova Scotia Health, Halifax, Nova Scotia, Canada; Frank Detterbeck, Yale University School of Medicine, New Haven, Connecticut; Daniel Dibaba, Cancer Research And Biostatistics, Seattle, Washington; Xavier Benoit D'Journo, Aix-Marseille University, Marseille, France; Jessica Donington, University of Chicago, Chicago, Illinois; Wilfried Eberhardt, West German Cancer Centre, University Hospital Essen, Essen, Germany; John Edwards, Northern General Hospital, Sheffield, United Kingdom; Jeremy Erasmus, M. D. Anderson Cancer Center, Houston, Texas; Wentao Fang, Shanghai Chest Hospital, Jiaotong University Medical School, Shanghai, People's Republic of China; Dean Fennell, Leicester Cancer Research Centre, University of Leicester and University Hospital of Leicester National Health Service Trust, Leicester, United Kingdom; Kwun Fong, University of Queensland Thoracic Research Centre, Brisbane, Australia; Françoise Galateau-Salle, Centre Hospitalier Universitaire, Caen, France; Oliver Gautschi, Cancer Center, Cantonal Hospital Lucerne, Lucerne, Switzerland; Ritu R. Gill, Beth Israel Lahey Health, Boston, Massachusetts; Dorothy Giroux, Cancer Research And Biostatistics, Seattle, Washington; Meredith Giuliani, The Princess Margaret Cancer Centre/University Health Network, Toronto, ON, Canada; Jin Mo Goo, Seoul National University, Seoul, Republic of Korea; Seiki Hasegawa, Hyogo College of Medicine, Nishinomiya, Japan; Fred Hirsch, Center for Thoracic Oncology, Tisch Cancer Institute, Mount Sinai Health System, New York, New York; Hans Hoffman, Technical University of Munich, Munich, Germany; Wayne Hofstetter, M. D. Anderson Cancer Center, Houston, Texas; James Huang, Memorial Sloan Kettering Cancer Center, New York, New York; Philippe Joubert, Quebec Heart and Lung Institute, Quebec, Canada; Kemp Kernstine, The University of Texas Southwestern Medical Center, Dallas, Texas; Keith Kerr, University of Aberdeen, School of Medicine and Dentistry, Aberdeen, United Kingdom; Young Tae Kim, Seoul National University, Seoul, Republic of Korea; Dong-Kwan Kim, Samsung Medical Center, Seoul, Republic of Korea; Hedy Kindler, The University of Chicago Medical Center, Chicago, Illinois; Yolande Lievens, Ghent University Hospital, Ghent, Belgium; Hui Liu, Sun Yat-Sen University Cancer Center, Guangdong Sheng, People's Republic of China; Donald E. Low, Virginia Mason Medical Center, Seattle, Washington; Gustavo Lyons, Buenos Aires British Hospital, Buenos Aires, Argentina; Heber MacMahon, University of Chicago, Chicago, Illinois; Alyson Mahar, University of Manitoba, Manitoba, Canada; Mirella Marino, IRCCS Regina Elena National Cancer Institute, Rome, Italy; Edith M. Marom, M.D. Anderson Cancer Center, Houston, Texas, and University of Tel-Aviv, the Chaim Sheba Medical Center, Tel-Aviv, Israel; José-María Matilla, Valladolid University Hospital, Valladolid, Spain; Jan van Meerbeeck, Antwerp University and Antwerp University Hospital, Antwerp, Belgium; Luis M. Montuenga, Center of Applied Medical Research, University of Navarra, Pamplona, Spain and Centro de Investigación Biomédica en Red de Cáncer, Madrid, Spain; Andrew Nicholson, Royal Brompton and Harefield

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Advisory Board to the Mesothelioma Domain

Jennifer Sauter, Memorial Sloan Kettering Cancer Center, New York, New York; Andrea Wolf, Icahn School of Medicine at Mount Sinai, New York, New York.

Appendix 2

Chairpersons and Members of the Subcommittees of the Lung Cancer, Epithelial Thymic Tumors and Malignant Pleural Mesothelioma Domains of the IASLC Staging and Prognostic Factors Committee

IASLC Staging and Prognostic Factors Committee Chair: Hisao Asamura.

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Lung Cancer Domain Vice Chair: Kemp Kernstine.

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Lung Cancer Domain Stage. Hisao Asamura (chair), Giuseppe Cardillo, Frank Detterbeck, John Edwards, Kwun Fong, Meredith Giuliani, James Huang, Kemp Kernstine, Edith M. Marom, Andrew G. Nicholson, Ramón Rami-Porta, William Travis, Ming Tsao, Paul Van Schil, Shun-ichi Watanabe.

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Lung Cancer Domain Prognostic Factors Subcommittee. Frank Detterbeck (chair), Raymond U. Osarogiagbon (co-chair), Alex Brunelli, Kwun Fong, James Huang, Young Tae Kim, Mark Krasnik, Hiu Liu, Jan van Meerbeeck, Luis M. Montuenga, Andrew G. Nicholson, Valerie Rusch, Robert Samstein, Navneet Singh, Martin Tammemägi, Ricardo Terra, Ming Tsao, Akif Turna, Terence Williams.

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Thymic Domain T descriptor Subcommittee: Andrew Nicholson (chair), Cecilia Brambilla, A. K. Cangir, Maurizio Infante, Mirella Marino, Edith M. Marom, Meinoshin Okumura.

Thymic Domain N descriptor Subcommittee: Wentao Fang (chair), Frank Detterbeck, Pier Luigi Filosso, Marco Lucchi, Edith M. Marom, Charles B. Simone II.

Thymic Domain M descriptor Subcommittee: Nicholas Girard (chair), Sarit Appel, Conrad Falkson, Wentao Fang, Giuseppe Giaccone, Hong Kwuan Kim, Edith M. Marom, Andreas Rimner.

Thymic Domain Database Subcommittee: Pier Luigi Filosso (chair), Usman Ahmad, Andrea Billè, Souheil Boubia, Frank Detterbeck, Wentao Fang, Nicholas Girard, Francesco Guerrera, James Huang, Hong Kwan Kim, Meinoshin Okumura, Enrico Ruffini.

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Esophageal Cancer Domain

Wentao Fang (chair), Xavier D'Journo (co-chair), Gail Darling, Jeremy Erasmus, Mark Ferguson, Wayne Hofstetter, Hong Kwan Kim, Donald Low, Paula Ugalde.

Appendix 3. Participating Institutions in the Third Phase of the IASLC Thymic Tumor Staging Project

Participating institutions ordered by number of eligible cases submitted

JART (2659 cases), M. Yano, Aichi Medical University, Nagakute, Japan; I. Yoshino, Chiba University, Chiba, Japan; Y. Sano, Ehime University, Matsuyama, Japan; A. Iwasaki, Fukuoka University, Fukuoka, Japan; H. Adachi, Hokkaido Cancer Center, Sapporo, Japan; K. Suzuki, Juntendo University Hospital, Tokyo, Japan; H. Asamura, Keio University, Tokyo, Japan; H. Yoon, Kinki-Chuo Chest Medical Center, Sakai, Japan; Y. Maniwa, Kobe University, Kobe, Japan; M. Suzuki, Kumamoto University, Kumamoto, Japan; H. Date, Kyoto University, Kyoto, Japan; T. Tagawa, Kyusyu University, Fukuoka, Japan; T. Nagayasu, Nagasaki University, Nagasaki, Japan; K. Okuda, Nagoya City University, Nagoya, Japan; T. F Chen-Yoshikawa, Nagoya University, Nagoya, Japan; M. Tsuboi, National Cancer Center Hospital East, Kashiwa, Japan; S. Watanabe, National Cancer Center Hospital, Tokyo, Japan; M. Tsuchida, Niigata University, Niigata, Japan; J. Usuda, Nippon Medical School, Tokyo, Japan; S. Toyooka, Okayama University, Okayama, Japan; J. Okami, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan; M. Tanahashi, Seirei Mikatahara General Hospital, Hamamatsu, Japan; M. Yamashita, Shikoku Cancer Center, Matsuyama, Japan; K. Shimizu, Shinshu University, Matsumoto, Japan; Y. Ohde, Shizuoka Cancer Center, Shizuoka, Japan; J. Nakajima, The University of Tokyo, Tokyo, Japan; K. Kondo, Tokushima University, Tokushima, Japan; N. Ikeda, Tokyo Medical University, Tokyo, Japan; H. Horio, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo,

Japan; M. Kanzaki, Tokyo Women's Medical University, Tokyo, Japan; T. Onuki, Tsuchiura Kyodo Hospital, Tsuchiura, Japan; F. Tanaka, University of Occupational and Environmental Health, Kitakyushu, Japan; M. Okumura, Y. Shintani, Osaka University, Suita, Japan; **ChART (1515 cases),** W. Xing, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, People' Republic of China; Y. Wei, Affiliated Hospital of Qingdao University, Qingdao, People's Republic of China; W. Sun, Cancer Hospital Affiliated to Xinjiang Medical School, Wulumuqi, People's Republic of China; Q. Tan, Daping Hospital, Chongqing, People's Republic of China; R. Zhang, First Affiliated Hospital of Anhui Medical University, Hefei, People's Republic of China; K. Wu, Fudan University Shanghai Cancer Center, Shanghai, People's Republic of China; C. Chen, Fujian Medical University Union Hospital, Fuzhou, People's Republic of China; X. Pan, Fujian Provincial Hospital, Fuzhou, China; C. Yang, Haian Hospital, Nantong, China; J. Ma, Harbin Cancer Hospital, Harbin, China; Y. He, Henan Provincial People's Hospital, Zhengzhou, China; L. Pang, Huashan Hospital, Fudan University, Shanghai, China; Q. Xu, Jiangxi Provincial People's Hospital, Nanchang, China; K. Zhang, Jining No. 1 People's Hospital, Jining, China; H. Liu, Liaoning Cancer Hospital, Shenyang, China; K. Chen, Peking University Cancer Hospital, Beijing, China; J. Li, Peking University People's Hospital, Beijing, China; W. Fang, Shanghai Chest Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; Y. Han, Sichuan Cancer Hospital, Chengdu, China; J. Fu, Sun Yat-sen University Cancer Center, Guangzhou, China; M. Ye, Taizhou Hospital of Zhejiang Province, Taizhou, China; X. Zhao, The Affiliated Hospital of Medical School of Ningbo University, Ningbo, China; H. Zhang, The Affiliated Hospital of Xuzhou Medical School, Xuzhou, China; Q. Wu, The First Affiliated Hospital of Chongqing Medical School, Chongqing, China; M. Chen, The First Affiliated Hospital of Guangxi Medical School, Nanning, China; D. Xie, The First Affiliated Hospital of Wenzhou Medical School, Wenzhou, China; S. Xu, The First Hospital of China Medical University, Liaoning, China; H. Wang, The Fourth Affiliated Hospital of Hebei Medical School, Shijiazhuang, China; L. Xian, The Second Affiliated Hospital of Guangxi Medical University, Nanning, China; J. Fan, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China; Q. Pang, Tianjin Medical University Cancer Hospital, Tianjin, China; P. Zhang, Tianjin Medical University General Hospital, Tianjin, China; M. Zheng, Tongren Hospital, Shanghai, China; Y. Wang, West China Hospital, Sichuan University, Chengdu, China; Y. Liao, Wuhan Union Hospital of China, Wuhan, China; X. Zhou, Zhejiang Cancer Hospital, Hangzhou, China; Z. Ren, Zhejiang Provincial Hospital of Chinese Medicine, Hangzhou, China; J. Ding, Zhongshan Hospital, Fudan University, Shanghai, China; **ESTS Thymic Registry (1411 cases):** B. Moser, University of Vienna, Austria, C. N. Foroulis, AHEPA University Hospital, Thessaloniki, Greece; A. Podobed, Alexandrov National Cancer Center, Minsk, Belarus; P. Van Schil, Antwerp University Hospital and Antwerp University, Department of Thoracic and Vascular Surgery, Edegem (Antwerp), Belgium; H. Elkhayat, Assiut University, Assiut Governorate, Egypt; ASST Santi Paolo e Carlo, Ospedale San Paolo, Thoracic Surgery, Milano, Italy; K. Kovacs, Bács-Kiskun County Teaching Hospital, Department of General Surgery, Kecskemét, Hungary; Bajcsy-Zsilinszky Hospital, Thoracic Surgery, Budapest, Hungary; Central Chest Institute of Thailand, Muang District, Nonthaburi, Thailand; Clinic University Hospital Valencia, Thoracic Surgery, Valencia, Spain; Z. Szanto, Clinical Center, Medical School, University of Pécs, Department of Surgery, Pécs, Hungary; S. Cafarotti, Ente Ospedaliero Cantonale, University of Southern Switzerland, Thoracic Surgery Department, Bellinzona, Switzerland; Erasme University Hospital, Thoracic surgery, Bruxelles, Belgium; C. Zisis, Evangelismos Hospital, Thoracic Surgery Department, Athens, Greece; S. Margaritora, Fondazione Policlinico "A. Gemelli" IRCCS, Department of Thoracic Surgery, Largo A. Gemelli, Rome, Italy; P. Mendogni, Foundation IRCCS Cà Granda Ospedale Maggiore Policlinico, Department of Cardio-Thoracic-Vascular diseases, Milan, Italy; J. Possoz, Grand Hopital de Charleroi site Gilly, Department of Cardiothoracic and Vascular Surgery, Charleroi, Belgium; A. Bille, Guys Hospital, Thoracic Surgery Department, London, UK; A. Guirao, Hospital Clinic, Thoracic Surgery, Barcelona, Spain; C. Fraile Olivero, Hospital Clínico San Carlos, Servicio Cirugía Torácica, Madrid, Spain; F. Palma Martelo, Hospital da Luz, Lisbon, Portugal; Hospital Sancta Maggiore, Sao Paulo, Brazil; G. Fortunato, Hospital Santa Isabel - Santa Casa de Misericordia da Bahia, Salvador, Brazil; M.T. Ruiz Tsukazan, Hospital São Lucas da PUCRS, Porto Allegre, Brazil; Hospital Universitari Sagrat Cor, Barcelona, Spain; Hyogo Prefectural Amagasaki Hospital, Department of Respiratory Medicine, Amagasaki, Japan; M. Casiraghi, IEO, European Institute of Oncology, IRCCS, Division of Thoracic Surgery, Milan, Italy, University of Milan, Department of Oncology and Hemato-oncology, Milan, Italy; M. Scarci, Imperial College NHS Healthcare Trust, London, UK; K. Tsakiridis, Interbalkan Medical Center, CardioThoracic Dept., Thessaloniki, Greece; C. Lequaglie, IRCCS CROB Centro Riferimento Oncologico Basilicata, Rionero in Vulture, Italy; P. Novellis, IRCCS San Raffaele Scientific Institute, Division of Thoracic Surgery, Milan, Italy; B. Ozkan, Istanbul Medical School Department of Thoracic Surgery, Istanbul University, Istanbul, Turkey; A. Turna, Istanbul University-Cerrahpaşa Cerrahpaşa Medical School Department of Thoracic Surgery, Istanbul, Turkey; E.

Mercadante, Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Thoracic Surgery, Naples, Italy; Jordanovac, University Hospital Centre Zagreb, Department of Thoracic Surgery Zagreb, Croatia; M. Esch, Klinik für Thoraxchirurgie, Delme Klinikum Delmenhorst, Delmenhorst, Germany; Klinik für Thoraxchirurgie, Kantonsspital St. Gallen, Rorschacher, Switzerland; J. Bauer, Medical University of Vienna, Department of Thoracic Surgery, Vienna, Austria; A. Ghimessy, National Institute of Oncology, Department of Thoracic Surgery, Budapest, Hungary; A. Kocsis, National Korányi Institute of Pulmonology, Department of Thoracic Surgery, Budapest, Hungary; P. Thomas, North University Hospital, Aix-Marseille University & Assistance Publique – Hôpitaux de Marseille, France; V. Barmin, P. Hertsen Moscow Oncology Research Institute - Branch of the National Medical Research Radiological Centre of the Ministry of Health of the Russian Federation, Moscow, Russia; T. Molnár, Petz Aladár Teaching Hospital, Department of General Surgery, Győr, Hungary; F. Venuta, Policlinico Umberto I, University of Rome Sapienza, Roma, Italy; I. Bravio, Portuguese Institute of Oncology Francisco Gentil, Lisbon; N. Moreno-Mata, Ramón y Cajal University Hospital, Madrid, Spain; F. Londero, S. Maria della Misericordia University Hospital, Udine, Italy; A. C. Agrafiotis, Saint-Pierre University Hospital, Brussels, Belgium; T. Gómez-Hernández, Salamanca University Hospital, Thoracic Surgery Service, Salamanca, Spain; S. Marcantonio Camargo, Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, Brazil; F. Rényi-Vámos, Semmelweis University, Department of Thoracic Surgery, Budapest, Hungary; C. Atinkaya Baytemir, Süreyyapaşa Training and Research Hospital, Thoracic Surgery, Istanbul, Turkey; S. Boubia, Universitary Hospital Ibn Rochd, Cellular and Molecular Pathology Laboratory, University Hassan II, Department of Thoracic Surgery, Casablanca, Morocco; L. Voltolini, University Hospital Careggi, Thoracic Surgery Unit, Florence, Italy; L. Ampollini, University Hospital of Parma, Thoracic Surgery, Department of Medicine and Surgery, Parma, Italy; I. Schmitt-Opitz, University Hospital Zurich, Department of Thoracic Surgery, Zurich, Switzerland; D. Van Raemdonck, University Hospitals KU Leuven, Leuven, Belgium; C. Aigner, University Medicine Essen, Ruhrlandklinik, Dept. of Thoracic Surgery, Essen, Germany; D. Loizzi, University of Foggia, Department of Medical and Surgical Sciences, Foggia, Italy; K. Marcinkowski, University of Medical Sciences, Thoracic Surgery Department, Poznan, Poland; M. Liberman, University of Montreal, Montreal, Canada; R. Mingarini Terra, University of Sao Paulo Medical School, Sao Paulo, Brazil; J. Furák, University of Szeged, Department of Surgery, Szeged, Hungary; P. Lyberis, University of Torino, Thoracic Surgery, Torino, Italy; T. Krajc, Vienna Healthcare Group – Clinic Floridsdorf, Dept. of Thoracic Surgery, Vienna, Austria; M. Congregado, Virgen del Rocío University Hospital, Sevilla, Spain; ZOL Hospital Genk, Department of Thoracic and Vascular Surgery, Genk, Belgium; **KART (1357 cases),** DK. Kim, Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, Ulsan University College of Medicine, Seoul, Korea; YS. Choi, Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; CH. Kang, Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea; JG. Lee, Department of Thoracic and Cardiovascular Surgery, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; **ITMIG (813 cases),** A. Toker, Istanbul University Medical School, Istanbul, Turkey; N. Girard, Louis Pradel Hospital, Lyon, France; J. Shrager, Stanford University, Stanford, CA, USA; B. Louie, Swedish Cancer Institute, Seattle, WA, USA; S. Keshavjee, UHN (University Health Network), Toronto, Canada; M. Ferguson, University of Chicago, Chicago, IL, USA; F. Rea, University of Padua, Padua, Italy; M. Lucchi, University of Pisa, Pisa, Italy; **RYTHMIC (383 cases),** PA. Thomas, APHM, Marseille, France; R. Gervais, Centre François Baclesse, Caen, France; E. Dansin, Centre Oscar Lambret, Lille, France; V. Westeel, CHU Besançon, Besançon, France; H. Lena, CHU Rennes, Rennes, France; L. Thiberville, CHU Rouen, Rouen, France; G. Massard, CHU Strasbourg, Strasbourg, France; J. Mazieres, CHU Toulouse, Toulouse, France; E. Pichon, CHU Tours, Tours, France; JM. Maury, Hospices Civils de Lyon, Lyon, France; N. Girard, Institut Curie, Paris, France; C. Clement-Duchene, Institut de Cancérologie de Lorraine, Nancy, France; X. Quantin, Institut de Cancérologie de Montpellier, Montpellier, France; L. Doucet, Institut de Cancérologie de l'Ouest, Nantes, France; B. Besse, Gustave Roussy, Villejuif, France; **Spanish Thymic Tumors Database (86 cases),** P. León, Complejo Hospitalario Universitario de Albacete, Albacete, Spain; C. García-Rico, Hospital Clínico Universitario de Valladolid, Valladolid, Spain; I. Martínez-Serna, Hospital Universitario 12 de Octubre, Madrid, Spain; M. Lorenzo, Hospital Universitario de Cruces, Vizcaya, Spain; L. Sánchez, Hospital Universitario Marqués de Valdecilla, Santander, Spain; JL Del Campo-Cañaveral, Hospital Universitario Puerta de Hierro, Madrid, Spain; N. Moreno, Hospital Universitario Ramon y Cajal, Madrid, Spain; E. Martínez, JC Trujillo, Hospital Universitario Santa Creu i Sant Pau, Barcelona, Spain; **Single-institution contributors:** A. Rimner, Memorial Sloan Kettering Cancer Hospital, New York, NY, US (288 cases); A. Bille, Guy's Hospital, Thoracic Surgery Department, London, UK (262 cases); A. K. Cangir, Ankara University, Faculty of Medicine, Department of Thoracic Surgery, Turkey (166 cases); B. McCaughan, C.

Kennedy, University of Sydney, Australia (97 cases); E. Pescarmona, IRCCS Regina Elena National Cancer Institute, Rome, Italy (63 cases); A. Turna, Istanbul University, Cerrahpasa Medical Faculty, Department of Thoracic Surgery, Turkey (47 cases).

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