The ITMIG/IASLC Thymic Epithelial Tumors Staging Project: A Proposed Lymph Node Map for Thymic Epithelial Tumors in the Forthcoming 8th Edition of the TNM Classification of Malignant Tumors

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Abstract: Although the presence of nodal disease is prognostic in thymic malignancy, the significance of the extent of nodal disease has yet to be defined. Lymph node dissection has not been routinely performed, and there is currently no node map defined for thymic malignancy. To establish a universal language for reporting as well as characterize the staging of this disease more accurately, an empiric node map is proposed here. This was developed using prior classification systems, series reporting specifics of nodal involvement, anatomical studies of lymphatic drainage, and preexisting node maps of the chest as defined by the International Association for the Study of Lung Cancer and the neck as defined by the American Academy of Otolaryngology—Head and Neck Surgery and the American Society for Head and Neck Surgery. The development of this node map was a joint effort by the International Thymic Malignancy Interest Group and the Thymic Domain of the IASLC Staging and Prognostic Factors Committee. It was reviewed and subsequently approved by the members of ITMIG. This map will be used as an adjunct to define node staging as part of a universal stage classification for thymic malignancy. As more data are gathered using definitions set forth by this node map, a revision may be undertaken in the future.

Key Words: Thymic malignancy, Thymoma, Thymic carcinoma, Thymic neuroendocrine tumor, Anterior mediastinal nodes, Thymic node map, Anterior mediastinal node map, ITMIG.

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For many decades, little progress has been made in outcomes of patients with thymic malignancies. As an orphan disease, it has proven difficult to assemble a large series of patients to establish an evidence base. A further problem has been a lack of clear definitions of terms. This issue hampers communication between centers and the ability to compare and combine data.

The International Thymic Malignancies Interest Group (ITMIG) was created to provide infrastructure to overcome these hurdles. ITMIG conducted several international workshops and developed standard definitions of terms and policies that were overwhelmingly endorsed by the ITMIG membership. ITMIG has also partnered with the International Association for the Study of Lung Cancer (IASLC) to develop proposals for a validated stage classification system. To date, 15 major stage classification systems have been proposed, with most being relatively empiric based on a small number of patients. ITMIG and IASLC have brought together the global community and amassed a database of more than 10,000 patients to inform the stage classification proposals.

There is a need to develop a universally accepted definition of areas of nodal involvement from thymic malignancies. Unfortunately, the large database assembled for the stage classification project is retrospective, and details regarding which nodes were involved are vague. To gather data for a more accurate assessment, it is necessary to establish a consistent starting point, similar to the development of other standards

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Ethical adherence: The authors have declared that this study was performed in accordance to research ethical guidelines.

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that ITMIG has undertaken in this disease. Therefore, ITMIG established a workgroup to accomplish this and combined this effort with the Thymic Domain of the IASLC Staging and Prognostic Factors Committee (TD-SPFC). This article is the result of this effort.

METHODS

Process for Development of Recommendations

An initial core workgroup was assembled to review existing literature that was relevant to a node classification system for thymic malignancies (David Chen, Faiz Bhora, and Frank Detterbeck). This included in broad terms, previously proposed classification systems, series reporting specifics of nodal involvement, existing maps for other spatially related tumors (i.e., lung, laryngotracheal, and oropharyngeal cancers), and anatomical studies of the lymphatic drainage of the mediastinum. Based on this review, the core workgroup formulated preliminary recommendations, which were further discussed at a meeting of the large diverse international group of specialists at the 2013 ITMIG annual meeting (Bethesda, MD, September 2013). The ensuing proposals were further refined by the TD-SPFC, which functioned as an extended workgroup (Hisao Asamura, Conrad Falkson, Pier Luigi Filosso, Giuseppe Giaccone, James Huang, Jhingook Kim, Kazuya Kondo, Marco Lucchi, Mirella Marino, Edith Marom, Andrew Nicholson, Meinoshin Okumura, Enrico Ruffini, and Paul van Schil). Funding for the TD-SPFC was provided by IASLC. Comments were also sought from the entire ITMIG membership, which represents the vast majority of investigators active in this disease, in keeping with an ITMIG process for the development and acceptance of proposed standards. This process also included eventual formal approval by the members of ITMIG for adoption going forward as the standard to follow. Because no data was available to analyze relative to the node map beyond what the TD-SPFC performed for T, N and M components of the proposed thymic stage classification (reported elsewhere), Cancer Research And Biostatistics (CRAB) and the full IASLC SPFC committees and advisory boards encompassing all thoracic disease sites were only indirectly involved. Input was specifically sought out from the TNM committee of the Japan Lung Cancer Society (Jun Nakjima, Masaki Hara, Kazuya Kondo, Meinoshin Okumura, Yoshihiro Matsuno, Motoki Yano), because of the work that this group and others in Japan have done to investigate the impact of nodal involvement in thymic malignancies. After careful evaluation of all input, the final node classification system was defined as presented in this article.

Background

Existing thymic classification systems.

An official, universally accepted staging system has not been available for thymic epithelial tumors. Previously proposed thymic stage classification systems have been recently summarized.[1] The most widely accepted system is the Masaoka classification, initially established in 1981 and modified in 1994 by Koga et al.[2] The four-tiered Masaoka-Koga system stratifies stages I to IVA based on tumor stage/extent of invasion, whereas stage IVB is reserved for nodal and distant metastasis combined; this was endorsed by the International Thymic Malignancy Interest Group (ITMIG) in 2011.[3,4] The Masaoka-Koga system seems to be a good predictor of prognosis for thymoma, the most common thymic epithelial tumor; however, it may not be as accurate for staging thymic carcinoma and neuroendocrine tumors of the thymus.[5,6] Despite sharing anatomical origin, thymomas are clinicopathologically distinct from thymic carcinomas and neuroendocrine tumors of the thymus; nodal metastasis is rare in the former, more common in the latter.

Four thymic classification systems have defined N subgroups, summarized in Table 1. The Yamakawa/Masaoka[7] and National Cancer Center Hospital of Japan[8] systems are the same with respect to definition of the N subgroups (they differ in the T definitions and the stage groupings). The World Health Organization Consensus Committee[9] and the Istituto Nazionale Tumori[10] systems are also almost identical to one another. Overall, the primary difference in these systems is that the more recent ones specify specific neck nodes as N3 instead of simply grouping all extrathoracic nodes together. Specific definitions of anatomic boundaries of the nodal regions were not provided in these manuscripts.

Nodal metastasis patterns of thymic malignancies.

A review of 1320 thymic epithelial tumors by Kondo[6] revealed a 3.2% incidence of lymphogenous and/or distant metastasis (stage IVB) in patients with thymoma, and a 33% incidence of such metastases in thymic carcinoma patients. He also calculated significant 5-year survival differences between stages IVA and IVB ($p = 0.019$ for overall, $p = 0.023$ tumor-specific 5-year survival).

TABLE 1. Thymic Malignancy Classification Systems

	Yamakawa	NCCHJ	WHO	INT
N0	No lymph node metastasis	No lymph node metastasis	No lymph node metastasis	No lymph node metastasis
N1	Metastasis to anterior mediastinal lymph nodes	Metastasis to anterior mediastinal lymph nodes	Metastasis to anterior mediastinal lymph nodes	Metastasis to anterior mediastinal lymph nodes
N2	Metastasis to intrathoracic lymph nodes except anterior mediastinal lymph nodes	Metastasis to intrathoracic lymph nodes excluding anterior mediastinal lymph nodes	Metastasis to other intrathoracic lymph nodes excluding anterior mediastinal lymph nodes	Metastasis to intrathoracic lymph nodes other than anterior mediastinal lymph nodes
N3	Metastasis to extrathoracic lymph nodes	Metastasis to extrathoracic lymph nodes	Metastasis to scalene and/or supraclavicular lymph nodes	Metastasis to prescalene or supraclavicular lymph nodes

NCCHJ, National Cancer Center Hospital of Japan; WHO, World Health Organization; INT, Istituto Nazionale Tumori.

This indicates that the presence of nodal or distant metastasis influences prognosis, warranting further investigation.

Anterior mediastinal lymph nodes seem to be the primary drainage basin for thymic epithelial tumors. This has been determined based on frequency and pattern of metastasis in addition to anatomical location (however, thymic carcinomas may exhibit skip metastases). If there is nodal involvement, these are located in the anterior mediastinum in approximately 90% in thymomas, 70% in thymic carcinomas, and 90% in neuroendocrine tumors of the thymus.[5]

Kondo et al also subclassified stage IVB into IVBi (Tany**N1**M0), IVBii (Tany**N2-3**M0), and IVBiii (TanyNany**M1**), but found no differences in 5-year survival ($p = 0.24$ between IVA and IVBi, $p = 0.25$ between IVBi and IVBii, and $p = 0.52$ between IVBii and IVBiii).[6] The small size of these subgroups (IVBi $n = 25$, IVBii $n = 25$, and IVBiii $n = 26$) undermines the ability to assess statistical significance; however, there was a trend toward improved survival for the N1 group compared with the N2/N3 group. In addition, there may have been unresectable stage IVB cases that were not included in the database provided by the member surgeons of the Japanese Association for Chest Surgery. Although the mere presence of nodal disease has prognostic influence, the prognostic effect of characteristics of metastasis such as location, number of nodes, number of stations, presence of angiolymphatic invasion, perineural involvement, and extracapsular involvement remains to be determined.

Anatomical studies of mediastinal lymphatics.

An extensive literature search reveals that there is no established lymph node nomenclature delineating the anterior mediastinal nodes other than the N staging systems presented in Table 1.[7–10] There were, however, several sources that were helpful in identifying mediastinal nodes and drainage patterns:

1. *Caplan*[11]: Classification of the human mediastinum based upon a longitudinal series of 984 autopsies over 17 years. Injection of hydrogen peroxide was used to delineate lymphatic drainage in cadaveric subjects. Of particular note, the anterior mediastinum was determined to contain five major node groups on the right and six major node groups on the left: right and left superior internal thoracic, right and left brachiocephalic, right superior phrenic (superior precaval), left superior phrenic (preaortic), right inferior phrenic (inferior precaval), left inferior phrenic (prepericardial), azygos arch, aortic arch/pulmonary artery, and left superior vagal/preaortic subclavian-carotid chain.
2. *Murakami et al*[12]: Classification of bronchomediastinal collecting vessels based on cadaveric dissection of eight subjects. The authors observed consistent lymphatic trunks, or large collecting vessels, on the right in an anterior and posterior pathway, and variable trunks on the left in a superior and inferior pathway with three consistent contributory node groups. In particular, the divisions on the right included the right brachiocephalic and anterior/posterior mediastinal trunks, whereas the divisions on the left included the uppermost paratracheal nodes, anterior mediastinal nodes (surrounding the phrenic nerve anterior and inferior to the aortic arch), and the left tracheobronchial nodes. They also observed a prominent communicating vessel between the right and left systems situated anterior to the trachea and above the aortic arch; it was often associated with the brachiocephalic angle nodes. Altogether, the results suggested prominence of the following nodal groups: brachiocephalic angle, right/left venous angles (jugulo-subclavian junction), phrenic, paratracheal, and tracheobronchial.
3. *Gregoire et al*[13]: Description of anatomic and functional mediastinal drainage pathways as it relates to clinical target volumes for radiation therapy in cancer treatment. The thorax is divided into four major compartments: parasternal, brachiocephalic, intertracheobronchial, and posterior mediastinal. The parasternal area is defined craniocaudally by the sternoclavicular joints and the xiphoid, and in an anterior/posterior plane by the deep surface of the sternum to the transversus thoracis, respectively. The brachiocephalic area includes the anterior mediastinal fat and the area anterior to the great vessels; craniocaudally, its boundaries are the clavicle and T6, and its lateral boundaries are the right and left mediastinal pleura. In addition, the entire thorax was functionally classified into an anterior, central, and posterior stream. The anterior stream includes the parasternal and brachiocephalic compartments and unites with the central (primarily tracheobronchial) stream in the superior mediastinum to form the common bronchomediastinal trunks.

Related classifications.

In the IASLC lung cancer node map proposal,[14] the workgroup notably identified that lymph node drainage in the superior mediastinum converges over the right paratracheal area and extends across the midline toward the left. Appropriately, the demarcation between right and left in terms of levels 2 and 4 needed not lie over the midline trachea, but instead to the left lateral border of the trachea. A recent retrospective review by Park et al[15] corroborates this—metastasis was mainly found in the right paratracheal nodes, and they recommended dissection of 10 or more lymph nodes in the anterior mediastinum and the right paratracheal area in thymic carcinoma.

The American Academy of Otolaryngology—Head and Neck Surgery/American Society for Head and Neck Surgery (AAO-HNS/ASHNS) node map[16] (established in 1991, updated in 2002) provides a correlate for neck lymph nodes as it relates to superior mediastinal tumors. The anterior lower neck is of particular interest as selective neck dissection of this region is indicated for thyroid cancer and cervical esophageal/tracheal cancer. These lymph nodes consist of paratracheal, precricoid (Delphian), and perithyroidal/recurrent laryngeal nodes.

RESULTS

The node map that was developed is a functional demarcation of mediastinal regions that incorporates retrospective data, preexisting node classifications in the IASLC map and the AAO-HNS/ASHNS map, and prominent nodes defined by prior studies.[11–13] Retrospective data and current N staging

systems[7–10] describe anterior mediastinal nodes as the primary drainage pathway and intrathoracic nodes excluding the anterior mediastinum as the secondary drainage pathway.

Two major regions are defined by the map: anterior and deep. The most logical method of describing regions is based on the boundaries that define the peripheral extent of dissection in all axes; this reflects the method used for thymic dissection in which the specimen is removed en bloc. It is sometimes challenging to orient visceral anatomical landmarks relative to the thymus during dissection in vivo, and it is even more difficult to do so once the specimen has been explanted from the patient. Given that prognostic importance to particular regions has not been demonstrated, it seems more practical not to complicate the system by subdividing nodes beyond what is encompassed by an extensive en bloc resection as described. There may be more evidence to perform dedicated lymph node dissections[15] in thymic carcinoma, but such nodes can be defined within these proposed regions. Similarly, the issue of laterality in node metastasis is not well defined. As aforementioned, there is data that suggest prominence of right paratracheal nodes in node-positive cases. Aside from that, however, there is no evidence to support the significance of laterality in other node stations.

Prominent nodes defined uniformly by Caplan,[11] Murakami et al,[12] and Gregoire et al[13] are included and distributed to the appropriate regions in this map ([1] low cervical/sternal notch, [2] venous angle: left and right, [3] brachiocephalic angle, [4] tracheobronchial: left and right, [5] paraaortic, [6] subaortic, [7] superior phrenic: left and right (preaortic/precaval), and [8] inferior phrenic: left and right).

The *anterior region (N1)* (Table 2, Figures 1–6) encompasses the space surrounding the thymus that is anterior to the pericardium and great vessels, extending from the hyoid bone superiorly to the diaphragm inferiorly and between the mediastinal pleura. The anterior region extends from the back of the sternum anteriorly; the posterior border is the pericardium in the middle and the level of the phrenic nerves in the lateral aspects of the mediastinum. These boundaries reflect the conventional dissection performed in extended thymectomy (dissection of contiguous left and right mediastinal pleura, mediastinal, and pericardiophrenic fatty tissues and dissection of paraaortic [IASLC level 6] nodes in addition to complete removal of thymus).[17] The computed tomography images in the figures demonstrate the posterior floor of the anterior region in several representative sections. In those anatomical sections not represented by these figures, radiologists should follow the guideline of demarcating the regions by the peripheral extent of conventional surgical dissection as previously mentioned.

This region includes anterior mediastinal nodes (perithymic, prevascular, paraaortic, and supradiaphragmatic nodes) and anterior cervical nodes (as conventionally defined by level 6 of the AAO-HNS/ASHNS classification). The term perithymic nodes is meant for lymph nodes immediately adjacent to the thymus that are not captured in one of the other categories (which were developed with lung cancer in mind). In the area of the great vessels, the posterior boundary of this region includes paraaortic nodes (IASLC level 6) but not aortopulmonary window nodes (IASLC level 5). Therefore, the posterior border of the anterior region is defined as the anterior border of the aortopulmonary window (Figures 4 and 5). The internal mammary nodes are excluded from this region (and allocated instead to the deep region) because they are rarely dissected in practice and there is no

TABLE 2. Anterior Region (N1) (Anterior Mediastinal and Anterior Cervical Nodes)

Region Boundaries	Node Groups[14, 16]	Node Group Boundaries
Sup: Hyoid Bone Lat (Neck): Medial Border of Carotid Sheaths Lat (Chest): Mediastinal Pleura Ant: Sternum Post (Medially): Great Vessels, Pericardium Post (Laterally): Phrenic Nerve Inf: Xiphoid, diaphragm	Low Ant Cervical: Pretracheal, Paratracheal, Peri-thyroid, Precricoid/Delphian (AAO-HNS / ASHNS Level 6 / IASLC Level 1)	Sup: inferior border of cricoid Lat: common carotid arteries Inf: superior border of manubrium
	Peri-Thymic	Proximity to thymus
	Prevascular (IASLC Level 3a)	Sup: apex of chest Ant: posterior sternum Post: anterior SVC Inf: carina
	Paraaortic, Ascending Aorta, Superior Phrenics (IASLC Level 6)	Sup: line tangential to sup border of aortic arch Inf: inf border of aortic arch
	Supradiaphragmatic / Inferior Phrenics / Pericardial (along inferior poles of thymus)	Sup: inf border of aortic arch Ant: post sternum Post: phrenic nerve (laterally) or pericardium (medially) Inf: diaphragm

Region and node group boundaries adapted directly from definitions established by AAO-HNS, ASHNS, and IASLC.

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; sup, superior; ant, anterior; inf, inferior; lat, lateral; post, posterior; SVC, superior vena cava.

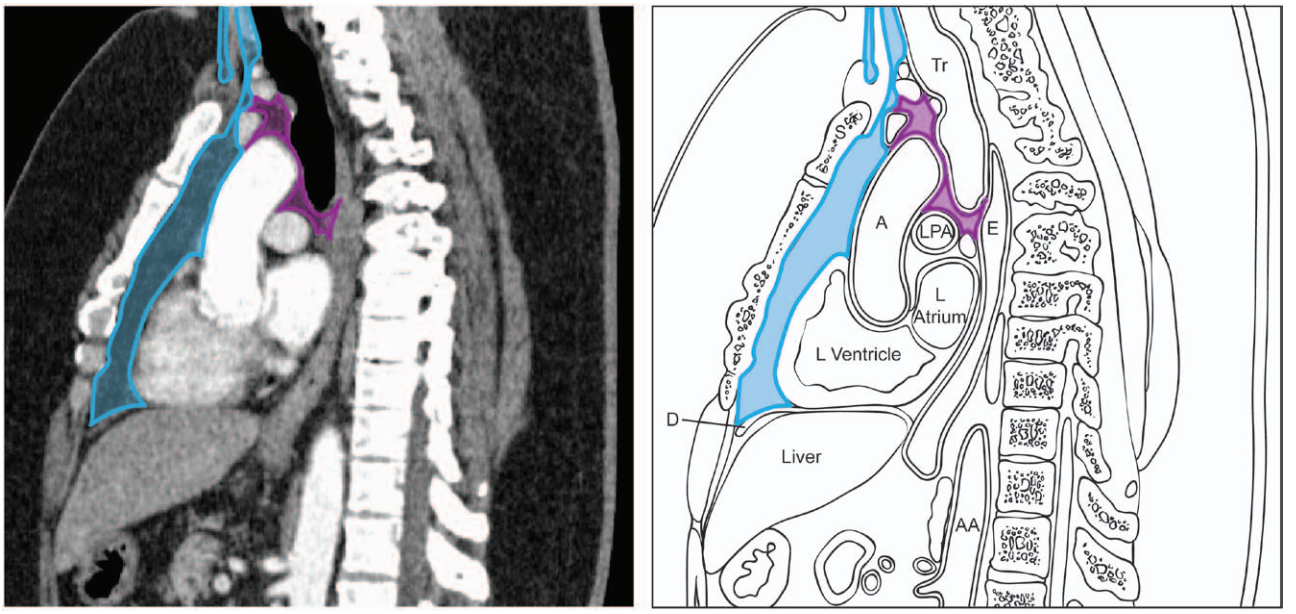

FIGURE 1. Mediastinum, sagittal section. Anterior region (*blue*) and deep region (*purple*). Tr, trachea; E, esophagus; LPA, left pulmonary artery; A, aorta; D, diaphragm.

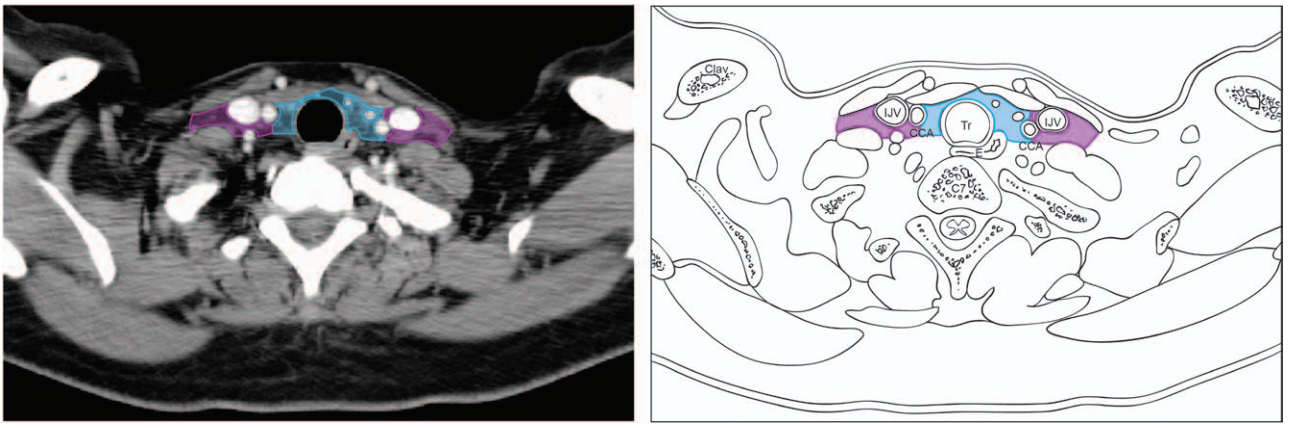

FIGURE 2. Thoracic inlet, axial section. Anterior region (*blue*) and deep region (*purple*). CCA, common carotid artery; IJV, internal jugular vein; Tr, trachea; Clav, clavicle; E, esophagus.

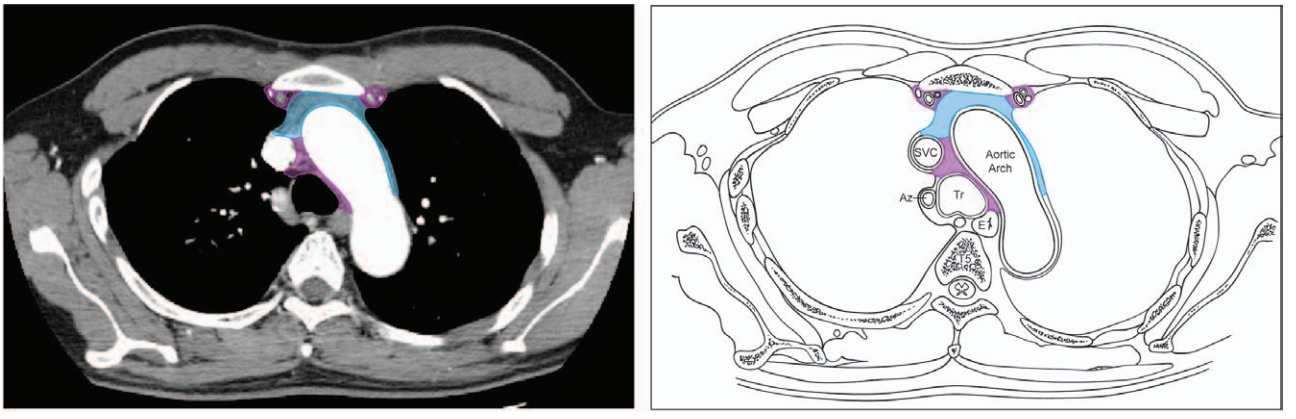

FIGURE 3. Paraaortic level, axial section. Anterior region (*blue*) and deep region (*purple*). SVC, superior vena cava; E, esophagus; Tr, trachea.

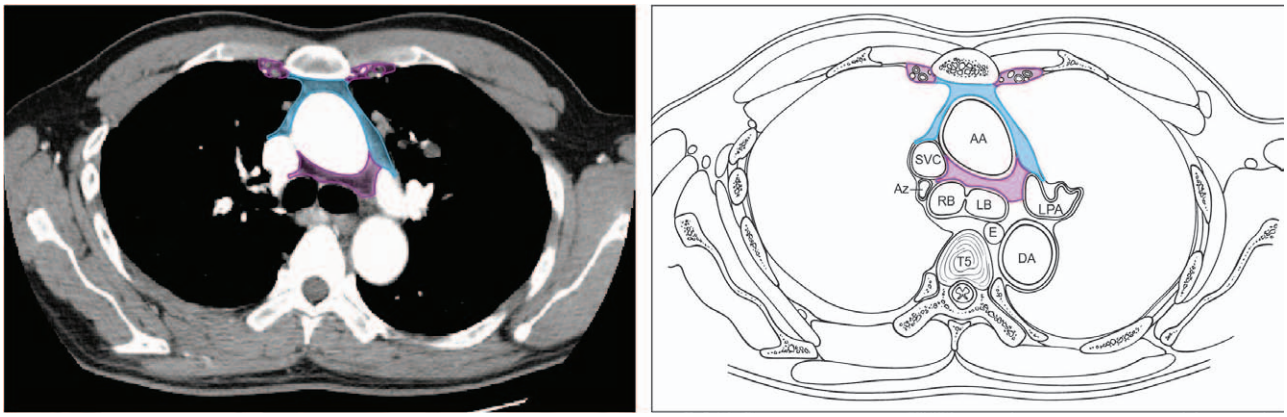

FIGURE 4. Aortopulmonary window level, axial section. Anterior region (*blue*) and deep region (*purple*). Note: deep region includes aortopulmonary window nodes. AA, ascending aorta; DA, descending aorta; LPA, left pulmonary artery; SVC, superior vena cava; Az, azygos vein; RB, right main bronchus; LB, left main bronchus.

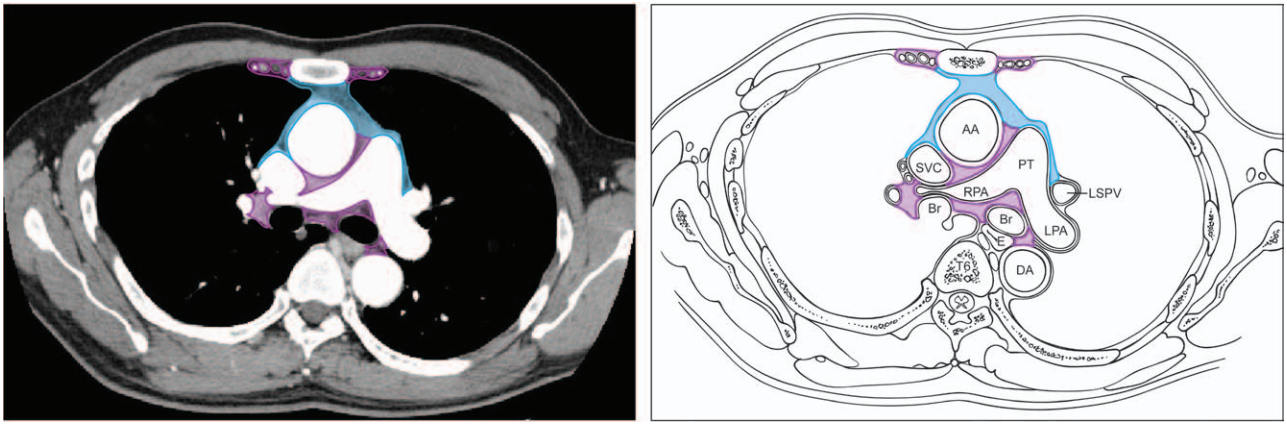

FIGURE 5. Carina level, axial section. Anterior region (*blue*) and deep region (*purple*). Note: deep region includes aortopulmonary window nodes. AA, ascending aorta; DA, descending aorta; PT, pulmonary trunk; LPA, left pulmonary artery; RPA, right pulmonary artery; SVC, superior vena cava; LSPV, left superior pulmonary vein; BR, bronchus; E, esophagus.

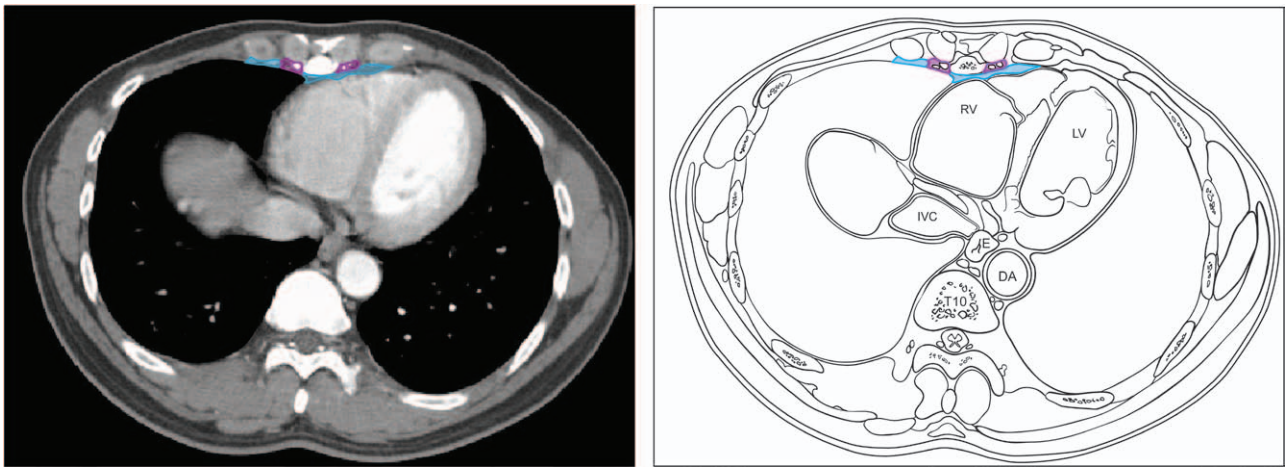

FIGURE 6. Diaphragm level, axial section. Anterior region (*blue*) and deep region (*purple*). RV, right ventricle; LV, left ventricle; IVC, inferior vena cava; DA, descending aorta; E, esophagus.

evidence to support the significance of disease in this area in thymic malignancy.

The *deep region (N2)* (Table 3, Figures 1–6) describes the space *distant* to the anterior region within the mediastinum. It is situated posterior to the anterior mediastinum, anterior to the esophagus, and among the pulmonary hila; it extends into the neck on either side of the anterior cervical nodes.

This region includes tracheobronchial and aortopulmonary window nodes (as defined by the IASLC node map), internal mammary nodes, deep cervical nodes, and supraclavicular nodes (as defined by the AAO-HNS map). The aortopulmonary window nodes are included in the deep region. These nodes are posterior to the phrenic nerve and not always included in the field of dissection; also, there is no data to support specific prognostic significance of nodal disease in this area. Also, although internal mammary nodes are anatomically separate from the rest of the deep region, they are rarely positive for nodal disease and thus, they can be regarded as pathologically "distant."

All nodes not defined by the anterior and deep regions are considered to be extrathoracic metastases (M1). These may include nodal disease in the axillary, retroperitoneal, or inguinal lymph node regions.

DISCUSSION

Lymph node involvement carries prognostic significance. However, definition of the importance of the location or extent of nodal involvement is not possible at this time. There is insufficient data; moreover, there are numerous proposed TNM staging systems that describe N1, N2, and N3 in generic terms that are open to interpretation. The development of worldwide standards through the efforts of ITMIG, the collection of prospective data in the ITMIG database, and the anticipated implementation of an official uniform stage classification system provides an opportunity to gather the data needed to assess the impact of details of node involvement. A prerequisite is the availability of a method to classify nodes in a consistent manner. We can only advance our knowledge as much as our existing framework allows.

The division of the mediastinum into an anterior and deep region is an empiric method of organizing these named nodes into a logical construct given our current data. It satisfies the need for a simple system to facilitate widespread adoption, and it builds on node classifications that are familiar to the community (namely, the IASLC and AAO-HNS/ASHNS node classifications) and anatomical patterns of mediastinal drainage. Consideration was given to defining the map based on discrete node stations, but a region-based system seems to be more appropriate to reflect the method of en bloc dissection in current practice and make this map globally applicable. By defining node areas both anatomically and on CT images, we may improve both clinical and pathological staging. Involved nodes should be classified as in either the "anterior region" or "deep region" according to the boundaries described; if possible, the specific location of the node should be recorded as well. Any invasion of nodes via direct extension should be considered nodal disease; this is similarly practiced with regard to N staging in lung cancer.[18]

The ITMIG standard policies for surgeons encourage removal of anterior mediastinal nodes at the time of resection for tumors that seem localized to the thymus.[19] The classification outlined here fits this policy, because the generally accepted definition of an extended thymectomy includes nodes of the anterior region. Pathologists should examine all submitted lymph nodes and record whether they are positive or negative for tumor. In addition, the total number of nodes sampled from each region should be recorded and included in the prospective database. For thymomas with adjacent organ involvement (Masaoka stage III or IVA undergoing curative-intent resection), it is recommended that anterior mediastinal lymph nodes be routinely removed and submitted, and a systematic sampling of intrathoracic sites is encouraged (i.e., nodes corresponding to the deep region). For thymic carcinoma, a routine systematic removal and submission of nodes in both the anterior and deep regions are recommended.

We accept that development of this mediastinal node map is essentially empiric. However, the process of establishing this lymph node map was similar to that utilized for the IASLC lung cancer lymph node map.[14] They reconciled discrepancies in the definitions among various node classifications and established a universal map for application in future investigations. Cadaveric studies (as described above) delineating anatomical and functional lymph node drainage pathways via injection were referenced. Endorsement was achieved using a multidisciplinary workgroup within an international committee. It should be pointed out that in most tumor types, an initial node classification was developed empirically, and data accumulated later regarding the prognostic impact.

Much work remains to be done to clarify and improve thymic epithelial tumor staging. A universally adopted nodal map is needed to collect data in a consistent manner. Through the process of building on existing maps, knowledge of mediastinal drainage, broad input from all major groups and organizations active in this area, and involvement of ITMIG and the IASLC Staging and Prognostics Factors Committee, consensus has been developed for a simple two-region node map. This will set the stage to gather more consistent information and potentially contribute to future stage classification systems.

APPENDICES

Appendix 1: IASLC Staging and Prognostic Factors Committee

Peter Goldstraw, Past Chair, Royal Brompton Hospital and Imperial College, London, United Kingdom; Ramón Rami-Porta, Chair, Hospital UniversitariMutuaTerrassa, Terrassa, Spain; Hisao Asamura, Chair Elect, National Cancer Center, Tokyo, Japan; David Ball, Peter MacCallum Cancer Centre, Melbourne, Australia; David Beer, University of Michigan, Ann Arbor, MI, United States of America (USA); Ricardo Beyruti, University of Sao Paulo, Brazil; Vanessa Bolejack, Cancer Research And Biostatistics, Seattle, WA, USA; Kari Chansky, Cancer Research And Biostatistics, Seattle, WA, USA; John Crowley, Cancer Research And Biostatistics, Seattle, WA, USA; Frank Detterbeck, Yale University, New Haven, CT, USA; Wilfried Ernst Erich Eberhardt, Department of Medical Oncology, West German Cancer Centre, University Hospital, Ruhrlandklinik, University Duisburg-Essen, Essen, Germany; John Edwards, Northern

TABLE 3. Deep Region (N2) (Middle Mediastinal and Deep Cervical Nodes)

Region Boundaries	Node Groups[14, 16]	Node Group Boundaries
Sup: Level of lower border of cricoid cartilage Anteromedial (Neck): Lateral Border of Sternohyoid, Medial Border of Carotid Sheath Posterolateral (Neck): Anterior Border of Trapezius Ant (Chest): Aortic Arch, Aortopulmonary Window – Ant Border of SVC Post (Chest): Esophagus Lat (Chest): Pulmonary Hila Inf: Diaphragm	Lower Jugular (AAO-HNS / ASHNS Level 4)	Sup: Level of lower border of cricoid cartilage Anteromedial: lat border of sternohyoid Posterolateral: lat border of sternocleidomastoid Inf: clavicle
	Supraclavicular/Venous Angle: Confluence of Internal Jugular & Subclavian Vein (AAO-HNS / ASHNS Level 5b)	Sup: Level of lower border of cricoid cartilage Anteromedial: post border of sternocleidomastoid Posterolateral: ant border of trapezius Inf: clavicle
	Internal Mammary nodes	Proximity to internal mammary arteries
	Upper Paratracheal (IASLC Level 2)	Sup: sup border of manubrium, apices of lungs Inf: intersection of lower border of innominate vein with trachea; sup border of aortic arch
	Lower Paratracheal (IASLC Level 4)	Sup: intersection of lower border of innominate vein with trachea; sup border of aortic arch Inf: lower border of azygos vein, sup border of left main pulmonary artery
	Subaortic / Aortopulmonary Window (IASLC Level 5)	Sup: inf border of aortic arch Inf: sup border of left main pulmonary artery
	Subcarinal (IASLC Level 7)	Sup: carina Inf: upper border of lower lobe bronchus on the left; lower border of the bronchus intermedius on the right
	Hilar (IASLC Level 10)	Sup: lower rim of azygos vein on right, upper rim of pulmonary artery on left Inf: interlobar region bilaterally

Region and node group boundaries adapted directly from definitions established by AAO-HNS, ASHNS, and IASLC.

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; sup, superior; ant, anterior; inf, inferior; lat, lateral; post, posterior; SVC, superior vena cava.

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Appendix 2: Advisory Board of the IASLC Thymic Malignancies Domain

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Appendix 3: Advisory Board of the IASLC Mesothelioma Domain

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Appendix 4: Advisory Board of the IASLC Esophageal Cancer Domain

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