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The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: Proposals for the N and M Components for the Forthcoming (8th) Edition of the TNM Classification of Malignant Tumors

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Abstract: Stage classification is an important underpinning of management of patients with cancer, and rests on a combination of three components: T for tumor extent, N for nodal involvement, and M for more distant metastases. This article details an initiative to develop proposals for the first official stage classification system for thymic malignancies for the 8th edition of the stage classification manuals. Specifically, the results of analysis of a large database and the considerations leading to the proposed N and M components are described. Nodal involvement is divided into an anterior (N1) and a deep (N2) category. Metastases can involve pleural or pericardial nodules (M1a) or intraparenchymal pulmonary nodules or metastases to distant sites (M1b).

Key Words: Staging, Prognosis, Thymoma, Thymic carcinoma, Stage classification

(*J Thorac Oncol.* 2014;9: S81–S87)

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Disclosure: The authors declare no conflict of interest.

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ISSN: 1556-0864/14/0909-0S81

Stage classification is fundamental to management of patients with cancer because it provides a common language regarding anatomical extent of disease. Progress in thymic malignancy has been slowed by the lack of a universal, clearly defined system. Therefore, the Thymic Domain of the Staging and Prognostic Factors Committee (TD-SPFC) of the International Association for the Study of Lung Cancer (IASLC) and the International Thymic Malignancies Interest Group (ITMIG) sought to develop a TNM stage classification system that would be applicable to both thymoma and thymic carcinoma (TC).[1] This has advantages in being consistent with the general format of the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) stage classification system. Furthermore, a single system for thymoma and TC provides simplicity, which is important in a rare disease.

Five TNM stage classification systems for thymic malignancies have been previously proposed, but there is no official, widely adopted system.[2] These schemes divide the N component into two to four categories and the M component into two to three categories. Although there are similarities among the N and M categories in some of these systems, there are also differences. The TD-SPFC created specific N and M workgroups to consider what would best serve the needs of the global medical community to inform the 8th edition of the AJCC/UICC stage classification for thymic malignancy. This article reports on the deliberations and outcomes of this process.

METHODS

A general overview of the database used for this analysis and the principles guiding the development of a stage classification system have been described elsewhere.[1,3,4] In summary, a large international retrospective database including more than 10,000 patients overall was developed by the ITMIG and several other organizations (European Society of Thoracic Surgeons,

Japanese Association for Research in the Thymus [JART], Chinese Alliance for Research in Thymoma). The IASLC provided infrastructure and funding to allow an extensive analysis, which was performed by the Cancer Research And Biostatistics group to develop TNM-based, data-driven stage classification proposals to inform the 8th edition of the AJCC/UICC stage classification system. Papers describing details of the T component and the stage grouping are provided elsewhere.[3,4]

Despite the large size of the database, details regarding the N or M status were available in only a subset of the patients. This reflects the fact that advanced thymic tumors are less common, the fact that data on resected patients was more readily available for inclusion in the database, and that retrospective data was most often collected according to traditional staging systems which often did not discriminate among details of N and M involvement. The vast majority of data with sufficient detail comes from JART. This organization and the country of Japan have had a long-standing commitment to gathering detailed data regarding extent of disease of thymic and other cancers. This was invaluable to the IASLC/ITMIG stage classification project (Fig. 1). 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.

The limited amount of detailed data precluded being able to assess whether there were statistically significant differences in the outcomes of various cohorts. The analysis was based primarily on a visual assessment that suggested a difference, similarities of the N classification to a consensus-based ITMIG/IASLC mediastinal thymic node map,[5] similarities of the M classification to the Masaoka and Masaoka-Koga stage classification systems (representing the two systems in most common use), practical considerations relative to the conduct of surgery for thymic malignancies and a consensus opinion about what was worthwhile to distinguish. Details of the statistical methods that were used where possible are described elsewhere.[3]

A collaborative process was conducted by ITMIG in conjunction with the TD-SPFC to develop a node map for thymic malignancies.[5] This workgroup considered anatomical factors, surgical aspects, and existing node mapping systems (i.e., for lung, head, and neck cancers and previously proposed systems for thymic malignancy) to develop a proposed map. The product of this effort was remarkably similar to what the TD-SPFC group developed through analysis of the available data. The ITMIG node map workgroup and the TD-SPFC discussed and coordinated their efforts to produce a final node map and an N classification system that were congruent.

PROPOSED N COMPONENT CLASSIFICATION

The proposed N classification is shown in Table 1. The TD-SPFC proposes dividing nodal involvement into an anterior (perithymic, N1) and a deep (N2) category, consistent with the definitions of these regions in the ITMIG/IASLC node map (Fig. 2).[5] The anterior region extends from the hyoid bone to the diaphragm, bounded anteriorly by the sternum, posteriorly by the trachea (neck) and pericardium (chest), and

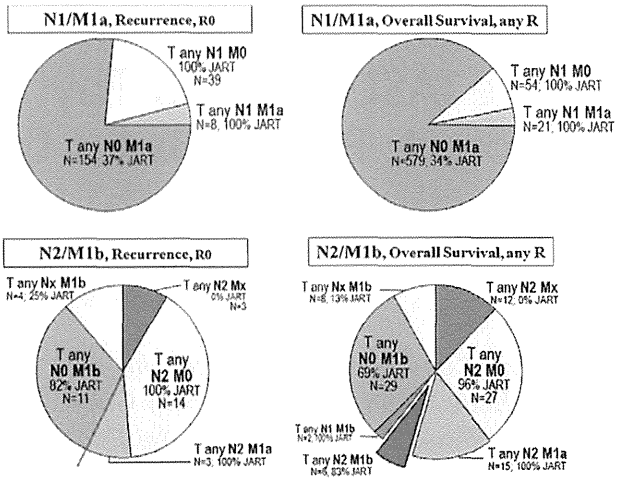


FIGURE 1. Evaluable patients for the N and M component analysis. Diagram of evaluable patients available for analysis, by N and M characteristic, with the proportion contributed by the Japanese Association for Research in the Thymus (JART).

TABLE 1. N, M Descriptors

Category	Definition (Involvement of)[a]
N0	No nodal involvement
N1	Anterior (perithymic) nodes
N2	Deep intrathoracic or cervical nodes
M0	No metastatic pleural, pericardial, or distant sites
M1	
a	Separate pleural or pericardial nodule(s)
b	Pulmonary intraparenchymal nodule or distant organ metastasis

[a]Involvement must be pathologically proven in pathologic staging.

laterally by the medial border of the carotid sheaths (neck) and the mediastinal pleura (chest). The distal boundaries of the deep region are defined by the medial edge of the trapezius muscle (neck) and the pulmonary hila (chest) laterally and the esophagus and vertebral column posteriorly. The deep region includes paratracheal, subcarinal, aortopulmonary window, hilar, jugular, and supraclavicular nodes. Involved nodes outside these regions (e.g., axillary, subdiaphragmatic) are outside the N category and considered a distant metastasis. Further details are provided elsewhere.[5]

The JART has conducted by far the best analysis of the incidence and location of node metastases from thymic malignancies.[6] Lymph node metastases were seen in 2% of 1064 thymomas, 27% of 183 TCs, and 28% of 40 thymic neuroendocrine tumors (NETT). These node metastases were seen most often in what corresponds to the region defined here as N1: of node-positive patients 89% with thymoma, 69% with TC, and 91% with NETT had involvement of N1 nodes, and 26% of thymoma, 30% of TC, and 45% of NETT had involvement of N2 nodes (most with N2 involvement also had N1 involvement).[6]

In the ITMIG/IASLC database, a limited number of patients had sufficient detail reported to allow evaluation of outcomes for the proposed anterior and deep nodal regions.

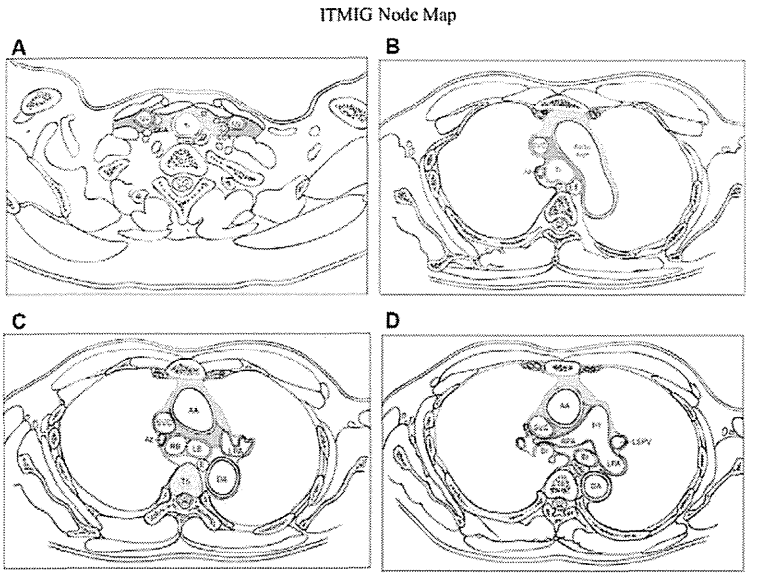


FIGURE 2. ITMIG /IASLC Lymph Node Map. Anterior and deep node regions as depicted on axial images. Anterior region (*blue*); deep region (*purple*). For further detail see Bhora et al.[5] (*A*) Thoracic inlet; (*B*) paraaortic level; (*C*) AP window level; (*D*) carina level. AA, ascending aorta; Az, azygos vein; CCA, common carotid artery; BR, bronchus; Clav, clavicle; DA, descending aorta; E, esophagus, IJV, internal jugular vein; LB, left main bronchus; LPA, left pulmonary artery; LSPV, left superior pulmonary vein; PT, pulmonary trunk; RB, right main bronchus; RPA, right pulmonary artery; SVC, superior vena cava; Tr, trachea.

Such detailed data were almost exclusively available from the patients contributed by JART. Nodes listed as N1 in JART correspond well with anterior intrathoracic (N1) nodes in the ITMIG/IASLC scheme; JART N2 nodes correspond to deep intrathoracic nodes in the ITMIG/IASLC scheme. These approximations were used to assess the outcomes of node involvement in the TD-SPFC classification proposal. There were few patients (n = 17) with involvement of neck nodes (JART N3) in the ITMIG/IASLC database. Following discussion with the curators of the JART database, these were felt in general to correspond to deep cervical nodes (N2 in the ITMIG/IASLC map). Their outcome did track with that of intrathoracic N2 nodes (5-year OS, R any was 44% for JART N2 and 40% for JART N3). Hence the JART N3 nodes were included in the Cancer Research And Biostatistics analyses together with other ITMIG/IASLC N2 nodes. A priori it was thought that data on all patients regardless of R status (i.e., R any) would be most relevant, since an R0 cohort would be more selected and less applicable to clinical staging.

Examination of the available data shows that OS among patients with any R status is better for the N1 versus the N2 category (5-year survival 69% versus 47%). This is more difficult to assess in R0 resected patients, because there are few in the N2 R0 groups; OS appears to be worse for N2 versus N1 but the rate of recurrence is similar (Fig. 3). However, none of the differences reached statistical significance (including OS in the R any cohort). The overall rates of death (Table 2) also demonstrate that N2 is worse than N1 among R any patients. Overall rates of recurrence are difficult to assess because there are few R0 patients in the N2 category, and even fewer in which recurrence information was available.

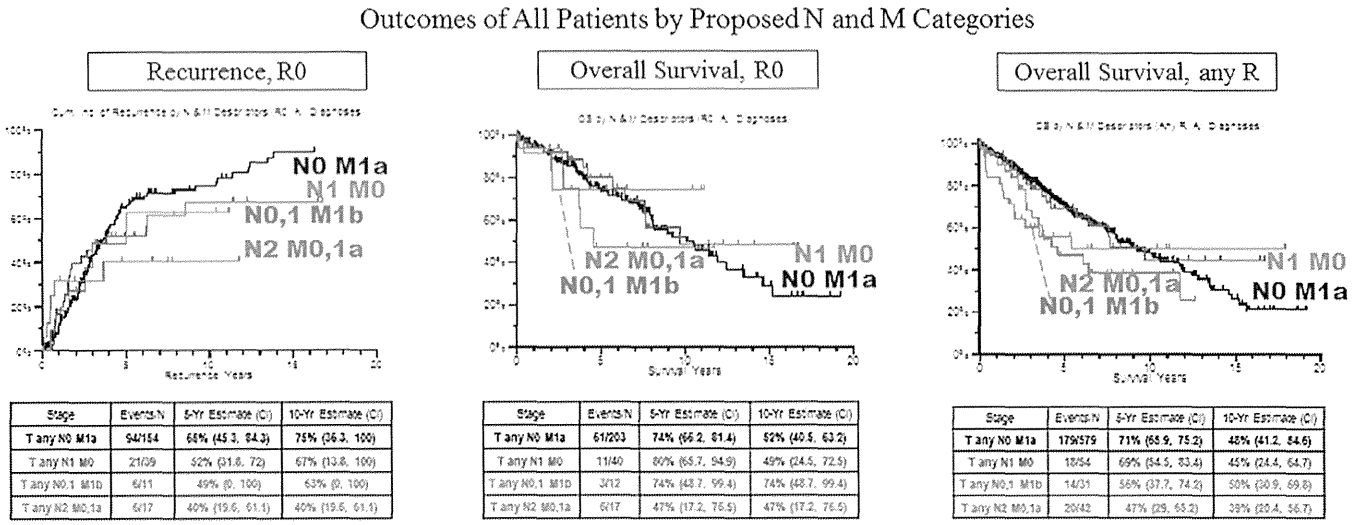
The TD-SPFC proposes to distinguish N1 from N2 nodes as outlined for several reasons. The speculation that involvement of nodes close to the thymus (N1) signifies less advanced or aggressive disease than involvement of deep (N2) nodes seems plausible. This is borne out at least qualitatively by the data in the ITMIG/IASLC database and by prior JART analyses,[6,7] although the power to detect statistical significance for the difference is limited by the amount of data available. From a practical, clinical standpoint, the separation of anterior and deep regions is appealing because the anterior region nodes would be included in an extended thymectomy, whereas access to the deep region nodes would require extra effort. Furthermore, the separation is similar to what has been used by the JART in previous analyses and corresponds to the ITMIG/IASLC consensus-based node map developed by a parallel process.[5–7] Finally, in the absence of data demonstrating that further subdivision (i.e., N3) distinguishes patients with a different prognosis, it seems that keeping it simpler is better.

Microscopic demonstration of involvement is needed to classify a node as involved by pathologic stage classification. Invasion by direct extension is counted as nodal involvement. There is no data to assess the impact of direct invasion versus a nodal deposit that is separate from the primary tumor. However, the TD-SPFC decided on this definition to be consistent with the IASLC/AJCC/UICC definition for lung cancer.

To stage nodes accurately, ITMIG has proposed that anterior mediastinal nodes be routinely removed along with the thymus and encouraged a systematic sampling of deep nodes when resecting thymomas with invasion of mediastinal structures (pericardium, lung, etc.).[8] For TC, a systematic removal of both N1 and N2 nodes is recommended during curative-intent resection.[8] A study specifically addressing the role of node dissection in TC (37 patients) also suggested that anterior and paratracheal nodes should be routinely dissected, especially when adjacent organs were invaded.[9] A minimum number of 10 dissected nodes were suggested in that study, as this appeared to correlate with better survival.[9]

PROPOSED M COMPONENT CLASSIFICATION

The M component is divided into three categories: M0 if there are no metastatic sites, M1a if there are pleural or pericardial nodules separate from the primary tumor mass, and M1b if there are distant (extrathoracic) metastases or pulmonary



Stage	Events/N	5-Yr Estimate (CI)	10-Yr Estimate (CI)
T any N0 M1a	94/154	68% (45.3, 84.3)	75% (36.3, 100)
T any N1 M0	21/39	52% (31.8, 72)	67% (13.8, 100)
T any N0,1 M1b	6/11	49% (0, 100)	63% (0, 100)
T any N2 M0,1a	6/17	40% (19.6, 61.1)	40% (19.6, 61.1)

Stage	Events/N	5-Yr Estimate (CI)	10-Yr Estimate (CI)
T any N0 M1a	61/203	74% (66.2, 81.4)	62% (49.5, 63.2)
T any N1 M0	11/40	80% (65.7, 94.9)	49% (24.5, 72.5)
T any N0,1 M1b	3/12	74% (48.7, 99.4)	74% (48.7, 99.4)
T any N2 M0,1a	6/17	47% (17.2, 76.5)	47% (17.2, 76.5)

Stage	Events/N	5-Yr Estimate (CI)	10-Yr Estimate (CI)
T any N0 M1a	179/579	71% (65.9, 75.2)	48% (41.2, 54.6)
T any N1 M0	18/54	69% (54.5, 83.4)	45% (24.4, 64.7)
T any N0,1 M1b	14/31	56% (37.7, 74.2)	50% (30.9, 69.8)
T any N2 M0,1a	20/42	47% (29, 65.2)	39% (20.4, 56.7)

FIGURE 3. Outcomes of all patients by proposed N and M categories. Outcomes of all patients with a thymic malignancy of any type. *A*, Cumulative incidence of recurrence, R0 resected patients; (*B*) overall survival, R0 resected patients; (*C*) overall survival, all patients (any R status); point estimates at 5 and 10 years are provided in the tables. There are no statistically significant differences between the curves. CI, 95% confidence interval; Cum. Inc. of Recurrence, cumulative incidence of recurrence; *N*, total number of evaluable patients; OS, overall survival; R0, complete resection; Yr, year.

TABLE 2. Total Proportion of Recurrences or Deaths

	Recurrence, R0		Deaths, R0		Deaths, any R	
	%	Events/*n*	%	Events/*n*	%	Events/*n*
Stage IVa	**59**	**119/201**	**30**	**75/251**	**32**	**209/654**
N1 M0	54	21/39	28	11/40	33	18/54
N0 M1a	61	94/154	30	61/203	31	179/579
N1 M1a	50	4/8	38	3/8	57	12/21
Stage IVb	**49**	**17/35**	**33**	**14/43**	**43**	**43/99**
N2 M0,1a	35	6/17	35	6/17	48	20/42
N0,1 M1b	55	6/11	25	3/12	45	14/31
N2 M1b/X + NX M1b	71	5/7	36	5/14	35	9/26

The total number of recurrences or deaths observed at any time out of the total number of evaluable patients in each category.
R, resection status; R0, complete resection.

intraparenchymal nodules (Table 1). One reason for this three-way separation is that there may be a different mechanism of spread (i.e., local dissemination through the pleural or pericardial space versus hematogenous spread, although this is based on rationale and speculation). It also appears that the extent of dissemination is different, and the implications for treatment are generally viewed as different. Finally, the decision was also based on a visual impression that the outcome curves are different for M1a and M1b (Fig. 3).

The OS among N0 any R patients is better for the M1a versus the M1b category (5-year survival 71% versus 56%, Figure 3), although the differences are not statistically significant. Overall rates of death among R any patients are worse for N0,1 M1b versus N0 M1a cohorts (45% versus 31%, Table 2). The limited data available make outcomes among R0 resected patients difficult to interpret.

The ability to evaluate outcomes for statistical significance was limited given the size of the patient cohorts and by the nature of the database. The database primarily involves surgically resected patients; however, it is likely that the majority of patients diagnosed with M1a and especially M1b involvement from a thymic malignancy are managed nonsurgically. Thus, the resected M1b patients in the ITMIG/IASLC database represent a very selected subset of all M1b patients. Because of these considerations, the TD-SPFC weighed the rationale about the mechanism of spread and potential treatment implications heavily and downplayed the observed outcomes in M1b patients. A stage classification system that is applicable to all patients must take into account patients who are not resectable—at least conceptually and speculatively if data is not available for analysis.

The TD-SPFC evaluated whether there was a difference in outcomes of pleural nodules, pericardial nodules, or intraparenchymal pulmonary nodules. No difference was apparent, although the number of patients with this level of detail was limited. The TD-SPFC also discussed whether pulmonary parenchymal nodules should be classified together with pleural and pericardial nodules. The decision was made to classify pulmonary parenchymal nodules as M1b. This was based primarily on the speculation of the mechanism of spread, and the consistency this afforded with the interpretation of the Masaoka and Masaoka-Koga stage classification systems.[10] The historical classification of pleural nodules together with pericardial nodules was retained (both are considered M1a). There were too few patients to analyze and no clear difference among these groups, although there was a slight suggestion of worse OS for pericardial versus pleural nodules in R any patients).

Examination of the nature of patients included in the M1b cohort reveals that the vast majority of these had pulmonary parenchymal nodules. Those that had other distant sites

of disease but were included in the database are likely a very selected subgroup. It is also likely that many of the patients with pulmonary nodules may have been discovered incidentally at the time of resection; caution is advised in extrapolating these outcomes to patients with preoperatively identified intraparenchymal pulmonary nodules.

The recurrence and survival outcomes of patients with N1 involvement are similar to those of patients with M1a involvement. In addition, the outcomes of patients with N2 and M1b involvement (or both) are similar (Fig. 3, Table 2). The N1 and M1a cohorts were grouped into the stage group IVa and the N2 and M1b cohorts into stage group IVb, as is described elsewhere.[3] However, these similar observed outcomes do not necessarily mean that the biological behavior is the same; factors influencing a propensity for nodal involvement and pleural involvement may be different. The outcomes for thymoma and TC followed similar trends to what was observed for all patients (N1 better than N2, M1a better than M1b, Supplemental Figure 1, Supplemental Digital Content 1, http://links.lww.com/JTO/A656). Therefore, although the number of patients is limited the proposed classification appears applicable to both thymoma and TC. NETT of the thymus were not included in either of these subsets and were too few to be analyzed separately.

DISCUSSION

Development of a uniform stage classification system is a major prerequisite for progress in treatment, particularly in an uncommon malignancy. The lack of an official stage classification has been an impediment which the IASLC/ITMIG initiative set out to address. The proposals defined in this article and the companion papers pave the way for a worldwide uniform system starting with the 8th edition of the stage classification system.[3,4]

A comparison to the five previously proposed TNM classification systems reveals similarities and differences among the N classifications. The Yamakawa–Masaoka and Tsuchiya systems[11,12] defined anterior mediastinal lymph nodes around the thymus as N1, intrathoracic lymph nodes other than anterior mediastinal lymph nodes as N2, and extrathoracic lymph nodes as N3. The WHO and Bedini systems[13,14] defined N3 more specifically as scalene and/or supraclavicular lymph nodes. The Weissferdt–Moran system (for TC)[15] considers only intrathoracic nodes in the N classification. The system proposed by the TD-SPFC is similar (but more detailed and specific) in defining intrathoracic N1 and N2 nodes, but differs in classifying low cervical nodes adjacent to the upper poles of the thymus or slightly further removed (e.g., jugular or supraclavicular nodes) also as N1 and N2, respectively.

The Yamakawa–Masaoka, Tsuchiya, Weissferdt–Moran, and WHO schemes define M1 as hematogenous or distant metastases.[11,12,14,15] In these schemes, pleural or pericardial nodules are classified as T4. The Bedini scheme[13] classifies distant metastasis as M1b. Pleural nodules are designated as M1a if they are posterior to the phrenic nerve and as T4 if they are anterior to the phrenic nerve. The TD-SPFC proposal is to classify separate pleural or pericardial nodules as M1a. This fits with what appears to be a difference in outcomes, a difference in treatment approaches, and in the mechanism of spread. Furthermore, this is consistent with the classification system for lung cancer.

The TD-SPFC faced certain limitations in developing a stage classification scheme. Despite the unprecedented size of the retrospective database that was assembled, the size of subgroups rapidly becomes smaller as one tries to examine more nuances. The relative paucity of data on patients not resected compounds this issue in patients with more advanced tumors—such as those in which the N and M components are prominent. Furthermore, the advanced disease patients for whom data is available represent a skewed cohort, hampering the utility and validity of analyzing differences in outcomes. Finally, as in any retrospective database, there is missing data and lack of clarity in how details were defined at the source institutions.

However, we must remember that the purpose of stage classification is to develop a useful nomenclature. Considering outcomes is only a tool to accomplish this; furthermore, the observations must be interpreted with clinical insight into the entire spectrum of factors that affect outcomes—the anatomical extent of disease being only one factor that in some situations may contribute relatively little. The TD-SPFC sought to consider all factors not only the analysis of outcomes.

The proposed stage classification is only a step in an ongoing process. ITMIG has initiated prospective data collection which is much more detailed. Furthermore, the TD-SPFC will begin development of a prognostic prediction model. These initiatives should foster further progress in the future. In the meantime, the TD-SPFC hopes that the proposed classification will be found to be useful in providing a consistent language that facilitates collaboration around the world.

CONCLUSION

The proposals for the N and M components of stage classification in thymic malignancies described in this article represent the output of an initiative conducted by IASLC and ITMIG to develop a uniform official classification system that facilitates communication and collaboration around the world. This work was conducted over the course of 4 years, and involved extensive analysis of a large worldwide database, as well as consideration of clinical and practical factors. Together with proposals for T classification and stage grouping, this provides a solid basis for stage classification of thymic malignancies.

ACKNOWLEDGMENTS

A.G.N. was supported by the National Institute of Health Research Respiratory Disease Biomedical Research Unit at the Royal Brompton and Harefield NHS Foundation Trust and Imperial College London.

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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.

(*J Thorac Oncol.* 2014;9: S88–S96)

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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Disclosure: The authors declare no conflict of interest.

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

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ISSN: 1556-0864/14/0909-0S88

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.

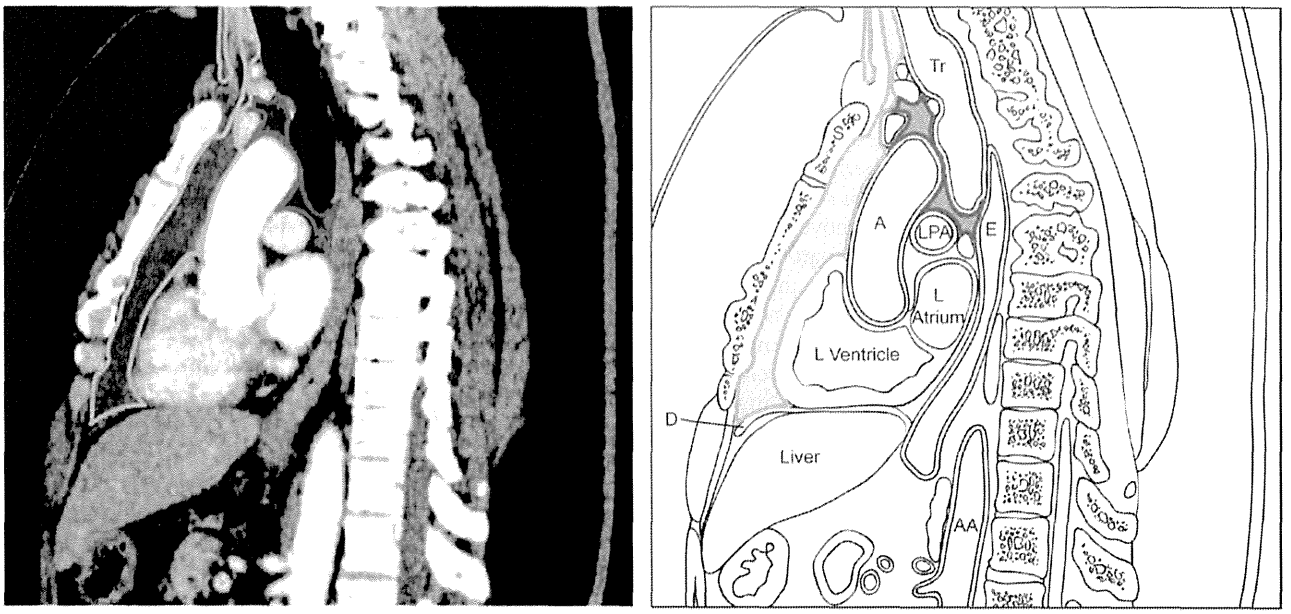

FIGURE 1. Mediastinum, sagittal section. Anterior region (*blue*) and deep region (*purple*). Tr, trachea; E, esophagus; LPA, left pulmonary artery; A, aorta; D, diaphragm.

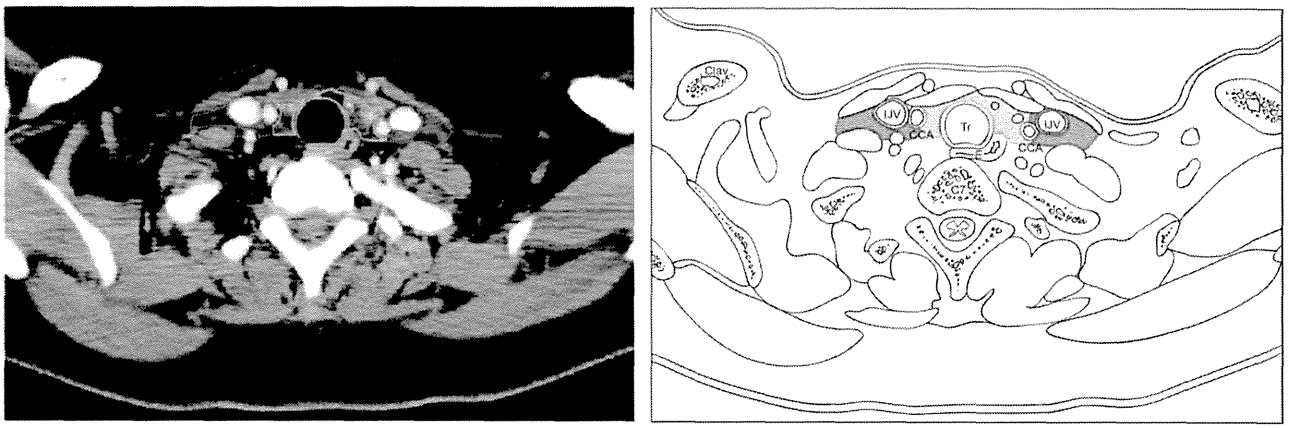

FIGURE 2. Thoracic inlet, axial section. Anterior region (*blue*) and deep region (*purple*). CCA, common carotid artery; IJV, internal jugular vein; Tr, trachea; Clav, clavicle; E, esophagus.

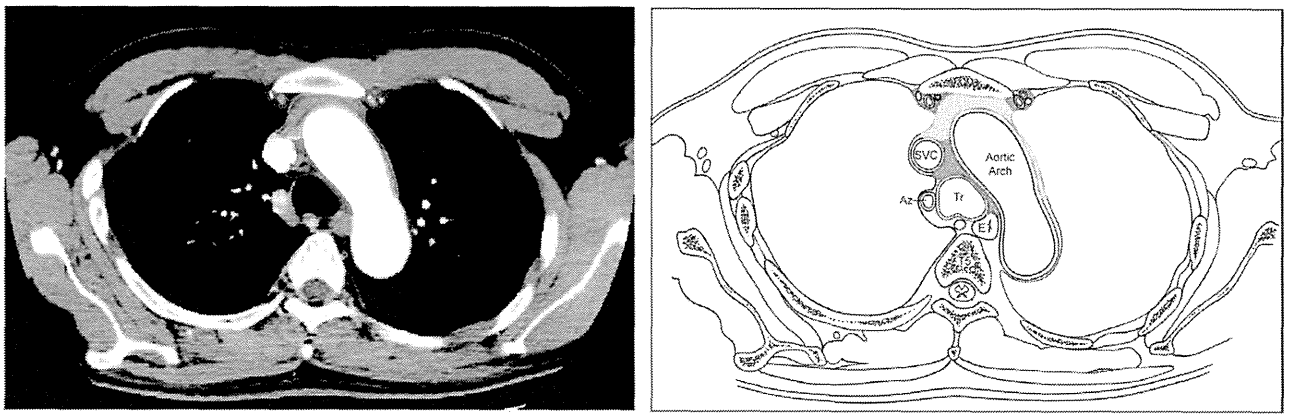

FIGURE 3. Paraaortic level, axial section. Anterior region (*blue*) and deep region (*purple*). SVC, superior vena cava; E, esophagus; Tr, trachea.

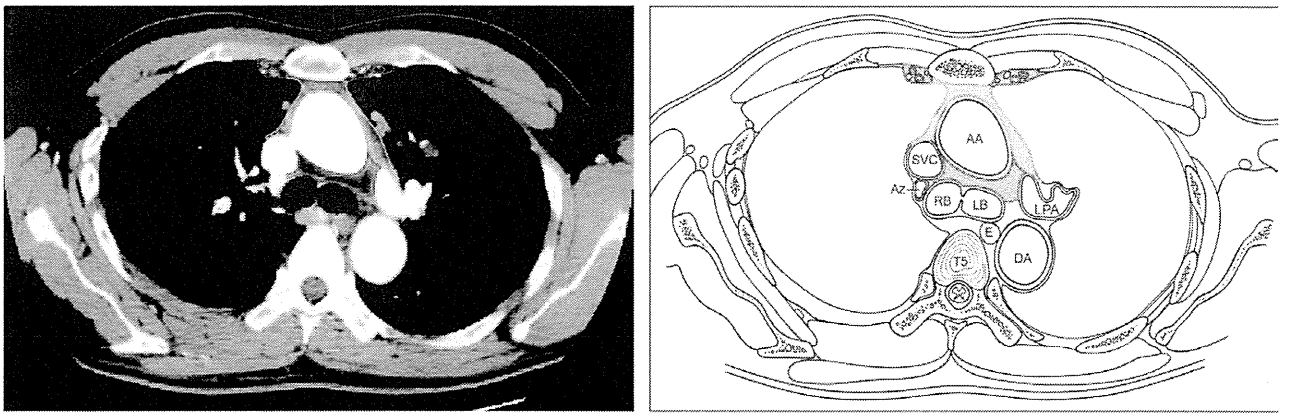

FIGURE 4. Aortopulmonary window level, axial section. Anterior region (*blue*) and deep region (*purple*). Note: deep region includes aortopulmonary window nodes. AA, ascending aorta; DA, descending aorta; LPA, left pulmonary artery; SVC, superior vena cava; Az, azygos vein; RB, right main bronchus;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

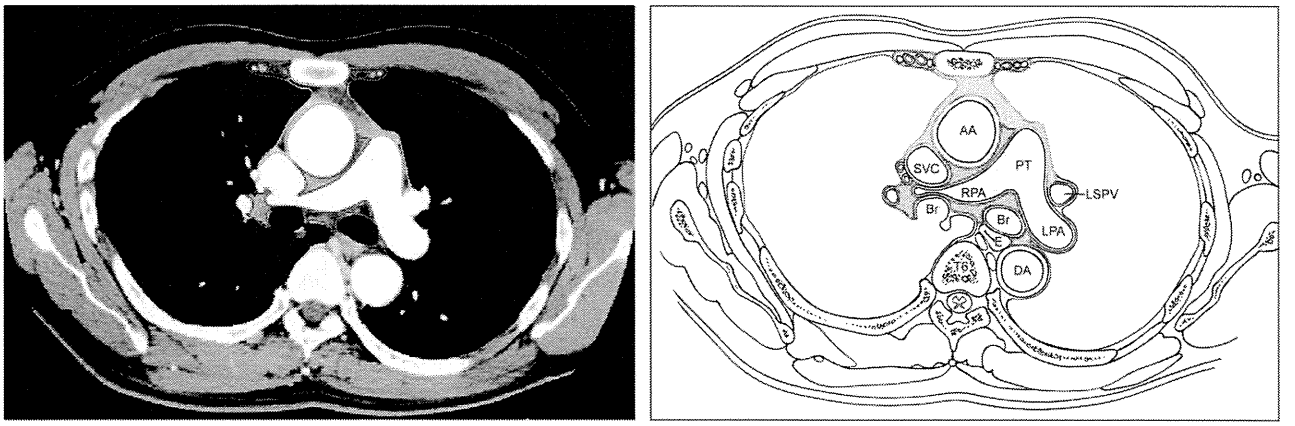

FIGURE 5. Carina level, axial section. Anterior region (*blue*) and deep region (*purple*). Note: deep region includes aortopulmonary window nodes. AA, ascending aorta; DA, descending aorta; PT, pulmonary trunk; LPA, left pulmonary artery; RPA, right pulmonary artery; SVC, superior vena cava; LSPV, left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

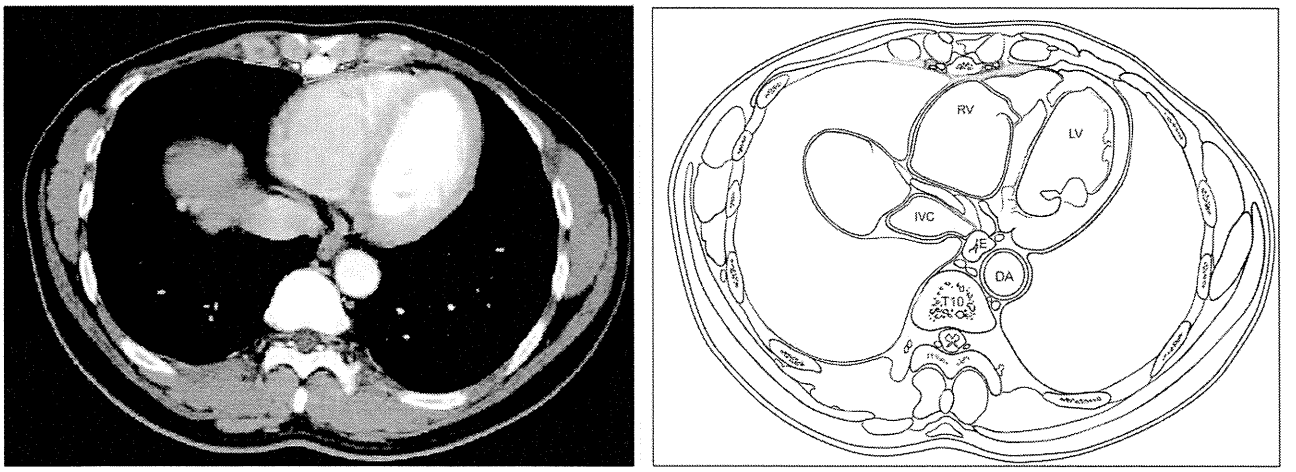

FIGURE 6. Diaphragm level, axial section. Anterior region (*blue*) and deep region (*purple*). RV, right ventricle; LV, left ventricle; IVC, inferior vena cava; DA, descending aorta; E, esophagus.

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

Conrad Falkson, Queen's University, Ontario, Canada; Pier Luigi Filosso, University of Torino, Italy; Giuseppe Giaccone, Georgetown University, Washington, DC, USA; Kazuya Kondo, University of Tokushima, Tokushima, Japan; Marco Lucchi, University of Pisa, Pisa, Italy; Meinoshin Okumura, Osaka University, Osaka, Japan.

Appendix 3: Advisory Board of the IASLC Mesothelioma Domain

Paul Baas, The Netherlands Cancer Institute, Amsterdam, The Netherlands; Jeremy Erasmus, MD Anderson Cancer Center, Houston, TX, USA; Seiki

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Appendix 4: Advisory Board of the IASLC Esophageal Cancer Domain

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Approaching the Patient with an Anterior Mediastinal Mass: A Guide for Radiologists

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Abstract: Mediastinal masses are relatively uncommon, yet include a large variety of entities. Some tumors can be diagnosed with confidence based on imaging alone; others when a typical appearance is combined with the right clinical presentation. A structured approach for radiologists is presented to facilitate evaluation of patients with anterior mediastinal tumors. The approach focuses first on the more common tumors and on imaging features that strongly suggest a particular diagnosis. Discussion with the clinician can be very helpful in formulating a presumptive diagnosis. This article also discusses that confirmatory imaging or biopsy tests are most beneficial in particular situations.

Key Words: Mediastinum, Anterior, CT, MRI, PET.

(*J Thorac Oncol.* 2014;9: S110–S118)

Mediastinal masses are relatively uncommon. Furthermore, because there is such a wide variety of pathologic entities that can occur in this region, the average radiologist or clinician will encounter many of these specific lesions only infrequently. Imaging is a critical part of establishing a presumptive diagnosis, which will guide whether and what type of confirmatory testing is needed. When classic features are present, a presumptive diagnosis can be made with a high degree of confidence based on imaging alone. However, the appearance of anterior mediastinal lesions is often less specific. Nevertheless, when combined with a typical clinical presentation, a particular entity can be strongly suggested.

Developing an appropriate differential diagnosis for a particular patient can be very useful in avoiding unnecessary and sometimes misleading biopsies or additional tests. A framework to guide the image interpretation and additional testing improves the efficiency of the evaluation. This is particularly pertinent since incidental anterior mediastinal abnormalities are discovered with increasing frequency due to increased imaging of asymptomatic patients, either for screening or staging of extrathoracic primary malignancies.[1] To address this need, the International Thymic Malignancy Interest Group (ITMIG) began an initiative to develop such a structured approach. This article represents the output of this project primarily addressed to radiologists; a companion paper focused on the clinician has also been produced.[2]

METHODS

The algorithm outlined in this document represents a consensus among radiologists and clinicians with a particular interest in anterior mediastinal diseases. The ITMIG Education Committee assembled a core workgroup (E.M.M., B.W.C., F.D., and M.O.) to review the existing literature as well as standards for imaging and clinical investigation of patients with an anterior mediastinal mass. This group drafted a proposed approach to the patient presenting with an anterior mediastinal mass. The document was then refined by an extended workgroup (Ami Rubinowitz, Wentao Fang, Jeanne B. Ackman, and Stephen Cassivi).

GENERAL CONSIDERATIONS

Slightly more than half of all mediastinal masses are located in the anterior mediastinum. One-fourth of mediastinal masses are discovered in the middle mediastinum, and another one-fourth of masses are found in the posterior mediastinum.[3–11] Assignment of lesions to particular mediastinal compartments has been quite useful in narrowing the differential diagnosis. In the past, this classification was based on varying definitions based on the lateral chest radiograph. A modern, computed tomography (CT)-based definition of mediastinal compartments has been developed by ITMIG[12] building upon work done by radiologists associated with the Japanese Association for Research in the Thymus.[13]

INCIDENCE

The most common tumors of the anterior mediastinum include thymic malignancies and lymphoma, but the prevalence of the different abnormalities varies markedly according to both age and gender. Thymoma is the most common anterior mediastinal mass and primary tumor of the anterior mediastinum, with the highest incidence in middle aged patients. Other tumors of the anterior mediastinum include benign teratomas and malignant germ cell tumors such as seminomas and nonseminomatous germ cell tumors (NSGCTs).

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Disclosure: The authors declare no conflict of interest.

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ISSN: 1556-0864/14/0909-S110

Malignant teratomas, which are residual lesions after treatment of NSGCTs, are typically grouped in the same category as NSGCTs. Thymic cysts and benign cystic lesions (usually acquired, often related to surgery and radiation therapy) are among the most common nonneoplastic lesions of the anterior mediastinum. Additional nonneoplastic masses include vascular abnormalities, substernal extension of thyroid goiters, other cystic lesions such as pericardial or bronchogenic cysts, and lesions related to infection such as tuberculosis.

The true incidence of anterior mediastinal masses is difficult to ascertain from the existing literature for numerous reasons. One of the most important of these is that different clinical and/or radiologic classification schemes have been used to define the mediastinal compartments. Additionally, the inclusion of nonneoplastic lesions such as thymic and pericardial cysts differs between series. Finally, there is variability in the inclusion of lymphomas in different series. More detail on the relative incidence of anterior mediastinal tumors is provided elsewhere.[2]

ROLE OF IMAGING

A large anterior mediastinal mass is readily identified by chest radiography as it typically manifests as an extra soft tissue mass or opacity. The use of the *silhouette sign*, which describes the loss of normal borders of intrathoracic structures, increases the sensitivity of detecting mediastinal abnormalities. The borders of the anterior mediastinum, that is, the ascending aorta, right and left heart border, are visualized by radiography because they are delineated by natural contrast: the air containing lung (Figure 1*A*). The density of soft tissue masses is similar to the anterior mediastinal structures and the image produced by the X-rays cannot differentiate between the abnormal mass and the normal mediastinal structure. However, since the mass displaces the air-containing lung from the normal mediastinal structure, the border of the normal mediastinal structure is lost. This loss of normal border is termed the *silhouette sign* (Figure 1*B*). However, the identification of a small mediastinal mass requires a more methodical approach. The presence of the anterior junction line, representing the point of contact between the anterior lungs and their pleural surfaces anterior to the cardiovascular structures, can help exclude the presence of an anterior mediastinal mass. This line is seen in 20% of normal chest radiographs (Figure 2*A*). Thickening of this line indicates an anterior mediastinal mass (Figure 2*B*).

Once an abnormality is identified by chest radiography, cross-sectional imaging is used to characterize the lesion, generate a differential diagnosis, assess for other abnormalities, and guide further management. CT with intravenous (IV) contrast has traditionally been the imaging modality of choice in the evaluation and characterization of an anterior mediastinal mass. One study analyzing 127 anterior mediastinal masses of various etiologies demonstrated that CT was equal or superior to magnetic resonance imaging (MRI) in the diagnosis of anterior mediastinal masses except for thymic cysts.[14] Indeed, when a cystic mass is suspected or is to be investigated, MRI is the most useful imaging modality, because MRI is superior to CT in distinguishing cystic from solid masses (e.g., thymic cysts from thymic neoplasms), discerning cystic/necrotic components within solid masses, and discerning thymic hyperplasia from thymic tumors.[15] For patients unable to undergo contrast-enhanced CT due to renal failure or allergy to IV contrast, non-contrast MRI may be performed to characterize the lesion and evaluate for involvement of vascular structures. Chemical shift techniques used in MRI can also be used to differentiate thymic hyperplasia from thymoma in adult patients.[16,17] ^{18}F-FDG positron emission tomography (PET)/CT is not routinely performed to evaluate or characterize an anterior mediastinal mass, but may be used to stage patients with specific malignant lesions and monitor response

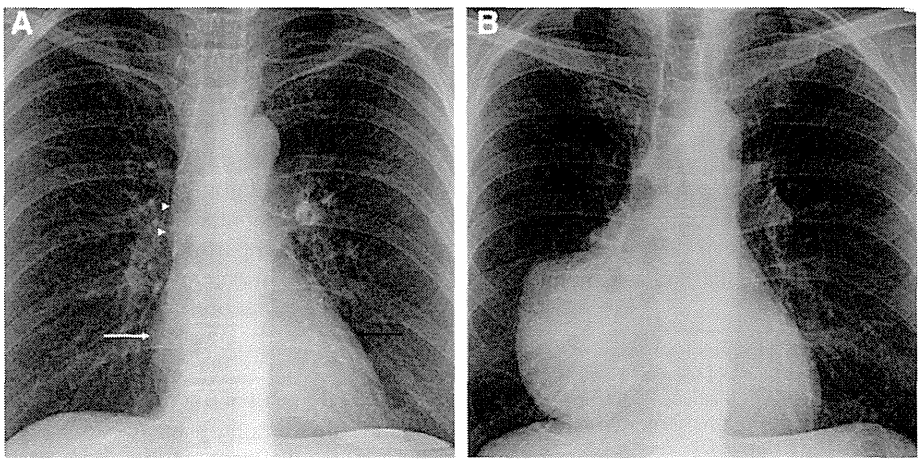

FIGURE 1. Normal anatomy and the silhouette sign. *A*, Coned-down posteroanterior chest radiograph demonstrates the normal boundaries of the anterior mediastinum: the right heart border (white arrow), left heart border (black arrow), and ascending aorta (arrowheads). These structures are normally visible on chest radiography because they are delineated by air-filled lung. *B*, Coned-down posteroanterior chest radiograph of a different patient demonstrates obscuration of the right heart border and ascending aorta by a large right anterior mediastinal mass found to represent lymphoma at the time of surgery. This loss of normal boundaries and structures, known as the silhouette sign, may be used to localize an abnormality to a specific mediastinal compartment such as the anterior mediastinum in this case.