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EXPERT CONSENSUS DOCUMENT

The Society of Thoracic Surgeons Expert Consensus Document on the Surgical Management of Thymomas

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EXPERT CONSENSUS STATEMENTS

DIAGNOSTIC APPROACH.

1. Thymoma or suspected thymoma should be managed by members of a multidisciplinary team with clinical expertise, particularly for decision making pertaining to the need for pretreatment biopsy, surgical resectability, neoadjuvant or adjuvant therapy, and management of recurrent disease.

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2. Contrast-enhanced computed tomography imaging is recommended for evaluation of an anterior mediastinal mass. Magnetic resonance imaging may be used to distinguish between differential diagnoses and to better elucidate local invasion and involvement of the heart (cardiac magnetic resonance imaging). Fluorodeoxyglucose-positron emission tomography may also be used as an adjunct to differentiate between a thymic malignancy (mild to moderate uptake) and lymphoma (high uptake).
3. Acetylcholine receptor (AChR) antibody, α-fetoprotein (AFP), β-human chorionic gonadotropin (β-HCG), and lactate dehydrogenase (LDH) levels should be considered in the appropriate setting in the evaluation of a patient presenting with an anterior mediastinal mass.
4. The American Joint Committee on Cancer/Union for International Cancer Control TNM staging system should be used to stage thymic malignancies.
5. Biopsy before resection is not necessary for a suspected thymoma unless the tumor appears unresectable.

TREATMENT PLANNING AND SURGICAL CONSIDERATIONS.

6. A goal of R0 resection by thymothymectomy should be considered the standard for thymic malignancies for optimal disease-free survival and overall survival and to mitigate the risk of postoperative myasthenia gravis. Thymomectomy alone may be considered in patients with clinical stage I disease who are at elevated surgical risk.
7. If an R0 resection is deemed probable for a suspected thymic malignancy, primary surgery without neoadjuvant therapy is appropriate, irrespective of tumor size.
8. Neoadjuvant chemotherapy or chemoradiotherapy should be considered in patients with locally advanced thymoma in whom a complete R0 resection may be difficult to achieve with primary surgery.
9. Thymoma resection should involve complete resection of all contiguous and noncontiguous disease, including any pleural or lung nodules and grossly abnormal lymph nodes. Resection of adjacent structures, such as pericardium, phrenic nerve, pleura, lung, and major vascular structures, may be required, but bilateral phrenic nerve resection should be avoided due to severe respiratory morbidity.

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10. Minimally invasive surgery should be considered if a total thymectomy and complete R0 resection can safely be achieved.
11. Surgeons should have sufficient technical expertise and clinical experience to ensure complete resection that accomplishes all oncologic goals safely while avoiding tumor spillage, particularly for minimally invasive approaches.

ROLE OF SURGERY IN LOCALLY ADVANCED AND PLEURAL DISEASE.

12. In patients with acceptable surgical risk, multimodality therapy with macroscopic complete resection is recommended for synchronous or metachronous pleural and pericardial metastases confined to a single hemithorax. For pleural disease, pleurectomy/decortication is preferred over extrapleural pneumonectomy when feasible.
13. For pleural dissemination, selective pleurectomy of metastatic lesions may be considered if complete macroscopic resection of all disease can reasonably be expected. Radical or total pleurectomy is not necessary if complete macroscopic resection can be achieved with selective pleurectomy.
14. For TNM stage IVA thymic malignancies with pleural metastases, neoadjuvant chemotherapy should be considered prior to resection.
15. Intraoperative adjuvant treatments for microscopic residual disease, such as photodynamic therapy or heated intrathoracic chemotherapy, may be considered at experienced centers in patients undergoing resection of disseminated pleural metastases.

ADJUVANT THERAPY AND SURVEILLANCE.

16. Orientation and labeling of resected specimens by the surgeon is recommended to improve pathologic interpretation of surgical margins.
17. After R0 resection, postoperative radiotherapy is recommended for TNM stage II and III thymoma. Postoperative radiotherapy may be considered for completely resected TNM stage I disease with invasion into mediastinal fat or pleura. Postoperative radiotherapy is not recommended for completely resected TNM stage I disease without macroscopic transcapsular invasion.
18. After R0 resection for TNM stage I, II, and III thymoma, adjuvant chemotherapy is not recommended.
19. After R1 resection, postoperative radiotherapy is recommended, whereas adjuvant chemotherapy is not.
20. After R2 resection, postoperative radiotherapy is recommended, whereas selective use of adjuvant chemotherapy may be considered.
21. For TNM stage IV disease, postoperative radiotherapy should be considered on an individualized basis.
22. Surgical resection for limited local or regional recurrence after previous thymoma resection is appropriate in acceptable-risk patients if an R0 resection can be achieved.
23. Acceptable-risk patients with extensive but potentially resectable recurrent disease should be considered for multimodal therapy with neoadjuvant chemotherapy, followed by possible surgical resection.
24. After thymoma resection, surveillance imaging with chest computed tomography is recommended at 6-month intervals for 2 years, followed annually thereafter for a minimum of 10 years. For completely resected TNM stage I disease with no transcapsular invasion (T1a tumors), surveillance imaging at 12-month intervals rather than 6-month intervals can be considered.

Thymoma is a rare epithelial tumor arising from the thymus gland, with an annual incidence in the United States of 0.15 to 0.19 per 100,000.[1] Despite its rarity, thymoma is the most common anterior mediastinal tumor in adult patients. As such, thoracic surgeons will undoubtedly encounter cases in clinical practice of an anterior mediastinal mass suspected to be thymoma. There is a paucity of level 1 evidence covering all aspects of thymoma management primarily due to the low incidence of this tumor. Nevertheless, there are published guidelines focusing on various aspects of diagnosis and treatment.[2-5] The intent of this expert consensus document is to guide thoracic surgeons with the diagnostic approach and treatment considerations from a surgical perspective, including the role of surgery in metastatic and recurrent disease. Because the level of supporting literature is insufficient for an evidence-based guideline, this expert consensus document was written based on the best available evidence.

METHODOLOGY

The Society of Thoracic Surgeons (STS) Workforce on Evidence Based Surgery recruited an

expert consensus task force to evaluate existing literature pertaining to surgical considerations in the management of thymomas. Authors included general thoracic surgeons with expertise in thoracic surgical oncology, along with a medical and radiation oncologist with expertise in neoadjuvant and adjuvant therapies for thymoma. A literature search was conducted at the discretion of the authors on the following: imaging characteristics, diagnostic tests, staging, surgical approach and technique, neoadjuvant and adjuvant therapy, surgery for advanced or recurrent disease, and postoperative surveillance.

Consensus statements were drafted in accordance with the modified Delphi method. Votes for each proposed statement were tallied using a 5-point Likert scale, with the option to abstain on statements not pertaining to the specific authors' area of expertise. Statements with 75% of responding authors selecting *agree* or *strongly agree* were considered to have reached consensus. Strength and level of evidence is not presented given that the STS expert consensus process results in opinion statements rather than formal recommendations.

I. DIAGNOSTIC APPROACH

A. MULTIDISCIPLINARY TEAM APPROACH. An essential aspect of thymoma treatment, particularly for advanced disease, is the involvement of a multidisciplinary team with expertise in thymic malignancies. Subspecialties should include thoracic surgical oncology, medical oncology, radiation oncology, pathology, radiology, and neurology in patients with myasthenia gravis. The literature demonstrates not only improved survival with multimodal therapy for advanced disease[6,7] but also support from thoracic surgeons for a multidisciplinary team approach.[8] Given the heterogeneity at presentation with respect to tumor size and potential invasion, treatment strategies should be delineated in a multidisciplinary fashion before the initiation of any therapy.

A critical determination is whether the thymoma is potentially primarily resectable, necessitating evaluation by an experienced thoracic surgical oncologist. If complete resection does not appear likely with primary surgery, multimodal therapy should be discussed, although data on the efficacy of increasing resectability is mixed based on available retrospective studies.[6,9-16] After surgery, multidisciplinary discussion is important to review details of the operation that may necessitate postoperative radiotherapy (PORT) irrespective of pathologic stage, such as areas with close surgical margins or inadvertent tumor fragmentation.[17] For metastatic or recurrent disease, a multidisciplinary team is necessary for a discussion of local and systemic treatment options individualized to the patient. These aspects of thymoma treatment will be detailed throughout this expert consensus document, but such examples illustrate the importance of a multidisciplinary team approach.

Consensus statement 1: Thymoma or suspected thymoma should be managed by members of a multidisciplinary team with clinical expertise, particularly for decision making pertaining to the need for pretreatment biopsy, surgical resectability, neoadjuvant or adjuvant therapy, and management of recurrent disease.

- *Strongly agree, 78.6%*
- *Agree, 14.3%*
- *Neither agree nor disagree, 7.1%*
- *Disagree, 0%*
- *Strongly disagree, 0%*

B. IMAGING FEATURES OF THYMOMA. Thymic tumors, specifically thymoma, are often discovered incidentally. Although various methods of chest diagnostic imaging may be used to identify an anterior mediastinal mass, computed tomography (CT), magnetic resonance imaging (MRI), and fluorodeoxyglucose (FDG)-positron emission tomography (PET) scans are most frequently used to characterize thymomas and help refine the differential diagnoses to distinguish them from other anterior mediastinal masses.

Computed Tomography. A contrast-enhanced CT scan is the most popular imaging method used for the initial evaluation of thymoma.[18] Thymic tumors comprise approximately 50% of anterior mediastinal masses, with lymphoma comprising 25% and other tumors the final 25%.[19] Patient demographics aside, the presence of an anterior mediastinal mass on CT favors thymoma. CT may help establish size, shape, characteristics, and invasion of the tumor, although there is heterogeneity in the appearance of thymomas within the mediastinum.

There is no consensus about whether CT characteristics can distinguish between subtypes of

thymoma.[18,20] Tumor size is not useful in distinguishing histologic classification.[18] A contour that is less smooth and more lobulated is associated with more advanced thymomas as well as thymic carcinomas. Although these findings can demonstrate suspicion for a more advanced thymoma or thymic carcinoma, they are not diagnostic.[18,20,21] Thymomas are typically smaller in size than thymic carcinomas, but this too cannot be considered a reliable method of distinction.[20] Calcifications can be seen in thymomas, but are not only characteristic to thymomas in the anterior mediastinum.[20] Mediastinal fat and great vessel invasion are more likely to be associated with thymic carcinoma rather than thymoma, although both may be observed in either tumor.[20]

Most thymomas show enhancement similar to chest wall muscle.[18] Reports on the reliability of enhancement to predict subtypes of thymoma or thymic carcinoma are mixed.[18,20,21] Sophisticated radiomics analysis, rather than visual CT analysis, has also been used to discern thymoma from thymic carcinoma by denoting solidity and gray-level co-occurrence matrix-homogeneity, essentially examining the spatial relationship of pixels. This finding is associated more commonly with thymic carcinoma rather than thymoma.[22]

Effusions are not useful in distinguishing thymoma from other mediastinal masses, and the presence of lymph nodes may be seen in a variety of diagnoses.[20,21] CT may be unable to distinguish a thymoma from lymphoma.[19] Pleural seeding can also be noted on the CT scan, but may be present in both thymomas and thymic carcinomas.[20] No thymoma CT features reliably predict overall survival (OS) or disease-free survival.[18]

Magnetic Resonance Imaging. MRI may be useful in characterizing the appearance of the anterior mediastinal mass by delineating tumor planes as well as distinguishing between the differential diagnoses for the anterior mediastinal mass. MRI can more accurately delineate an intact capsule on thymomas than CT scan alone.[21] Thymic carcinomas are also noted to have a higher prevalence of heterogeneous signal intensity on MRI.[21] Cardiac MRI can be used to evaluate involvement of the myocardium.

Morphologic features between solid and cystic masses do not differ significantly on CT scans.[23] But with diffusion-weighted imaging on MRI, nonneoplastic cysts can be distinguished from solid masses.[23]

Positron Emission Tomography. Anterior mediastinal masses are often either thymoma or lymphoma.[19,24] The standardized uptake value (SUV) of the mass on a FDG-PET scan may be used to differentiate thymoma from lymphoma, with a lower SUV aligning with thymoma.[24] Lymphoma is likely when the maximum SUV is greater than 12.85, and thymoma is likely when maximum SUV volume is less than 7.50.[24] This should only be considered for a resectable anterior mediastinal mass because both locally advanced thymoma and locally advanced lymphoma would likely be best evaluated by a biopsy specimen.[24]

Consensus statement 2: Contrast-enhanced computed tomography imaging is recommended for evaluation of an anterior mediastinal mass. Magnetic resonance imaging may be used to distinguish between differential diagnoses and to better elucidate local invasion and involvement of the heart (cardiac magnetic resonance imaging). Fluorodeoxyglucose-positron emission tomography may also be used as an adjunct to differentiate between a thymic malignancy (mild to moderate uptake) and lymphoma (high uptake).

- *Strongly agree, 85.7%*
- *Agree, 14.3%*
- *Neither agree nor disagree, 0%*
- *Disagree, 0%*
- *Strongly disagree, 0%*

C. ADDITIONAL LABORATORY STUDIES. There is a strong association between thymomas and paraneoplastic syndromes, the most common of which is myasthenia gravis. As such, a careful history and examination to establish the presence of signs or symptoms of myasthenia gravis (ptosis, diplopia, dysarthria, etc), along with testing for acetylcholine receptor (AChR) antibodies should be considered in patients who present with a mediastinal mass.[25] Approximately 4 in 10 patients with a thymoma will also have myasthenia gravis.[26] In addition, testing for tumor markers, including α-fetoprotein (AFP), β-human chorionic gonadotropin (β-HCG), and lactate dehydrogenase (LDH) levels, can aid in the differential diagnosis between thymic malignancies and germ cell tumors.[27] The presence of elevated tumor markers in a patient would strongly indicate a diagnosis of a germ cell tumor rather than a thymic malignancy, where these levels are generally within normal reference ranges.

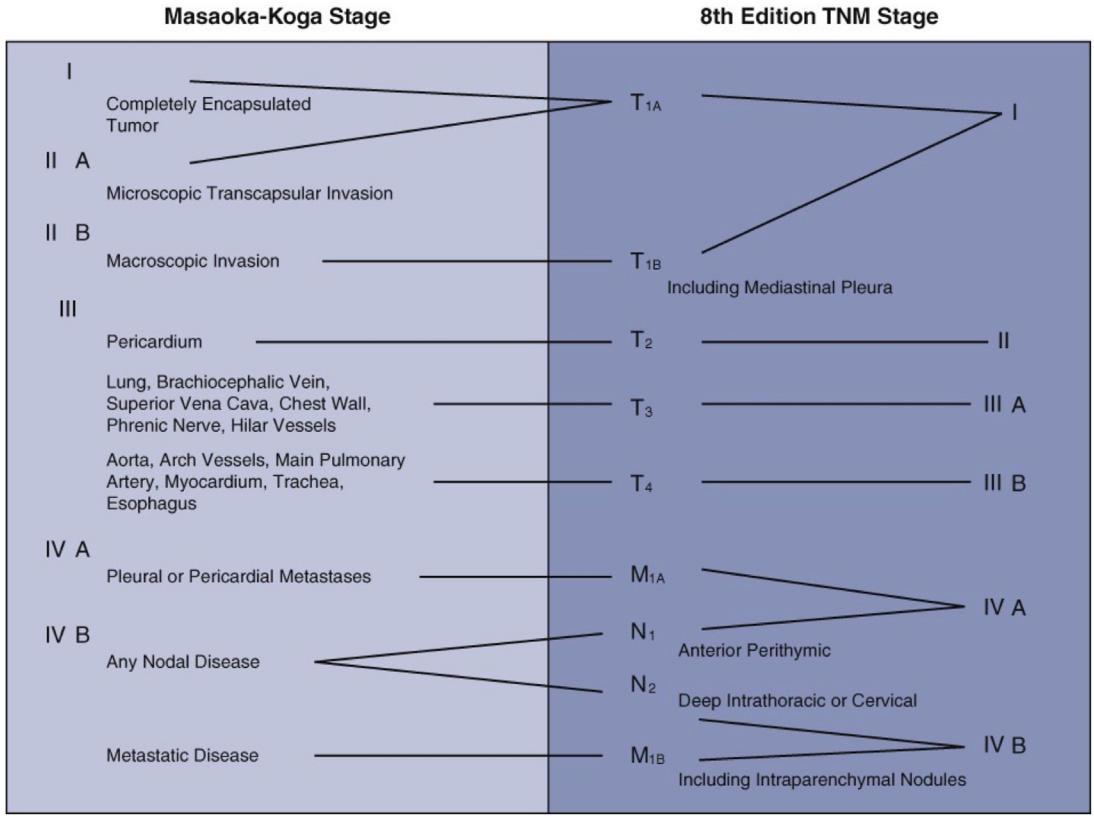

FIGURE 1 Comparison of Masaoka vs TNM staging system according to involved structures. Reproduced from Ahmad U. The eighth edition TNM stage classification for thymic tumors: What do I need to know? *J Thorac Cardiovasc Surg*. 2021 Apr;161:1524–1529, with permission from The American Association for Thoracic Surgery.

Consensus statement 3: Acetylcholine receptor (AChR) antibody, α-fetoprotein (AFP), β-human chorionic gonadotropin (β-HCG), and lactate dehydrogenase (LDH) levels should be considered in the appropriate setting in the evaluation of a patient presenting with an anterior mediastinal mass.

- *Strongly agree, 64.3%*
- *Agree, 35.7%*
- *Neither agree nor disagree, 0%*
- *Disagree, 0%*
- *Strongly disagree, 0%*

D. STAGING. The TNM staging system for thymic malignancies was adopted in the Eighth Edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) Staging Manuals in 2017 based on the results from 10,808 patients, supplanting the prior Masaoka staging system, which was a clinicopathologic system derived from 96 patients with several resultant ambiguities.[28-30] Comparison between the Masaoka and TNM staging systems is depicted in Figure 1. The TNM staging system allows for a universal common platform across malignancies and more precise comparison of patients and their prognoses; therefore, this staging system is recommended for thymic tumors over the Masaoka classification.

The TNM system defines the T category based on degree of local invasion by the tumor, the N category based on the extent of nodal involvement, and the M category based on the presence of pleural metastasis or distant metastasis[28,29] (Tables 1, 2). In this expert consensus document, the TNM staging system is used where applicable, although much of the existing literature uses the Masaoka staging system. Proposals for the Ninth Edition TNM staging have been published and are expected to become effective in 2024.[31] Changes in the Ninth Edition involve only the T component and relate to tumor size and reclassification of lung or phrenic nerve invasion (Table 3).

TABLE 1 Eighth Edition American Joint Commission on Cancer (AJCC)/Union for International Control (UICC) TNM Definitions for Thymic Malignancies

Category	Description of Involved Structures
T1	
a	Encapsulated or unencapsulated, with or without extension into mediastinal fat
b	Extension into mediastinal pleura
T2	Pericardium
T3	Lung, brachiocephalic vein, superior vena cava, chest wall, phrenic nerve, hilar (extrapericardial) pulmonary vessels
T4	Aorta, arch vessels, main pulmonary artery, myocardium, trachea, esophagus
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

Consensus statement 4: The American Joint Committee on Cancer/Union for International Cancer Control TNM staging system should be used to stage thymic malignancies.

- *Strongly agree, 64.3%*
- *Agree, 28.6%*
- *Neither agree nor disagree, 7.1%*
- *Disagree, 0%*
- *Strongly disagree, 0%*

E. PRETREATMENT BIOPSY VS PRIMARY SURGERY. After determining that intervention is warranted for an anterior mediastinal mass based on clinical, radiographic, and biochemical assessment, one must decide whether to biopsy or proceed directly to surgical resection. If the diagnosis of thymoma is highly probable based on the pretreatment evaluation and complete resection is likely based on imaging, needle biopsy is not recommended.

TABLE 2 Eighth Edition American Joint Commission on Cancer (AJCC)/Union for International Control (UICC) Edition Stage Categories for Thymic Malignancies

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IVA	Any T	N1	M0
	Any T	N0/N1	M1a
IVB	Any T	N2	M0/M1a
	Any T	Any N	M1b

Although considered a rare event, there are case reports that suggest tumor seeding of the pleural space can occur after needle biopsy,[32,33] thus converting a potentially curable tumor to metastatic pleural disease.

Several clinical features at presentation are consistent with high pretreatment probability of thymoma. Age and sex are the 2 most important initial considerations. Thymomas comprise approximately half of all anterior mediastinal tumors in men and women older than of 40 years, although this proportion decreases in men during the seventh and eighth decades of life.[4] Approximately 30% to 50% of patients with thymomas have an associated paraneoplastic syndrome, which is commonly myasthenia gravis.[4,34] Other paraneoplastic syndromes affecting virtually every physiologic system have been reported, including hematologic (eg, pure red cell aplasia, agranulocytosis, Good syndrome), neuromuscular (eg, polymyositis, Lambert-Eaton), gastrointestinal (eg, hepatitis, cholangitis, ulcerative colitis), dermatologic (eg, scleroderma, pemphigus), endocrine (eg, Cushing syndrome, Addison disease), and rheumatologic conditions (eg, rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome). Thus, in patients who present with a solitary anterior mediastinal mass along with an associated paraneoplastic syndrome or autoimmune condition, the diagnosis of thymoma should be strongly suspected.[2,3] As previously discussed, there are radiographic features on CT and MRI that are highly suggestive of thymoma.[5] Thus, imaging studies along with demographic characteristics and the presence or absence of paraneoplastic syndromes can often provide convincing clinical evidence for or against thymoma.

Clinical features suggesting an alternative diagnosis include diffuse lymphadenopathy with B-symptoms consistent with lymphoma, or patients younger than 40 years presenting with an anterior mediastinal mass. Certain radiographic findings can be pathognomonic of alternative mediastinal lesions, such as a mass contiguous with the thyroid gland in substernal goiter, a heterogenous mass containing fat and calcifications consistent with benign teratoma, or a purely cystic lesion indicative of a thymic cyst.[5] An extremely FDG-avid solitary anterior mediastinal mass on PET scan, without evidence of invasion, may represent mediastinal lymphoma; therefore, needle biopsy should be considered before deciding on resection.[24]

If clinical evaluation indicates thymoma, the next consideration pertains to resectability with primary surgery. This determination is based largely on surgeon expertise and careful review of imaging with experienced radiologists. Although no definitive tests exist, specific radiographic findings have been associated with tumor invasiveness, including tumor size, lobulated or irregular contours, or infiltration of surround tissue.[2,35-38] Evaluating for pleural or pericardial dissemination and lymph node involvement is also essential. After radiographic evaluation, a biopsy specimen should be obtained to confirm the diagnosis and guide neoadjuvant therapy if complete resection is deemed not feasible with primary surgery.[39]

Tissue diagnosis may be achieved through a percutaneous or surgical biopsy. Core needle biopsy is a safe and accurate percutaneous option[40-42] and has a higher reported yield compared to fine-needle aspiration.[43] A surgical biopsy with anterior mediastinotomy (Chamberlain procedure) is also useful when the tumor abuts the anterior chest wall,[37,44] although contemporary data series indicate comparable success rates using core needle biopsy. Transpleural biopsy with video-assisted thoracoscopic surgery (VATS) is not recommended owing to the potential risk of tumor seeding,[45] unless pleural disease is already suspected based on imaging.[37,46]

Consensus statement 5: Biopsy before resection is not necessary for a suspected thymoma unless the tumor appears unresectable.

- *Strongly agree, 53.8%*
- *Agree, 46.2%*
- *Neither agree nor disagree, 0%*
- *Disagree, 0%*
- *Strongly disagree, 0%*
- *Abstain, 1*

II. TREATMENT PLANNING AND SURGICAL CONSIDERATIONS

A. THYMOTHYMECTOMY VS THYMOMECTOMY ALONE.

Complete thymectomy through a median sternotomy was considered the standard treatment of thymic epithelial tumors without myasthenia gravis for several decades until minimally invasive techniques evolved and became universally adapted, allowing a limited resection technique. This has been described as thymomectomy, whereas a complete resection of the tumor and entire thymus gland, including the 2 horns, has been reported as thymothymectomy. Other synonymous terms include total thymectomy or complete thymectomy.

TABLE 3 Proposed T Component of Thymic Tumors for the Ninth Edition of the TNM Classification of Malignant Tumors[a]

T	Description
T1	Tumor limited to the thymus, with or without encapsulation, or directly invades into the mediastinum alone or directly invades the mediastinal pleura but does not involve any other mediastinal structure.
T1a	5 cm or less in its greatest dimension[b]
T1b	Larger than 5 cm in its greatest dimension[b]
T2	Tumor directly invades the pericardium (either partial or full-thickness), the lung, or the phrenic nerve
T3	Tumor directly invades any of the following: (1) brachiocephalic vein, (2) superior vena cava, (3) chest wall, or (4) extrapericardial pulmonary arteries or veins
T4	Tumor directly invades any of the following: (1) aorta (ascending, arch, or descending), (2) arch vessels, (3) intrapericardial pulmonary artery or veins, (4) myocardium, (5) trachea, or (6) esophagus

[a]Reproduced from Ruffini E and associates. The International Association for the Study of Lung Cancer Thymic Epithelial Tumors Staging Project: Proposal for a Stage Classification for the Forthcoming (Ninth) Edition of the TNM Classification of Malignant Tumors. *J Thorac Oncol.* 2023 Dec;18:1655–1671. https://doi.org/10.1016/j.jtho.2023.09.002. Epub 2023 Sep 9. PMID: 37689391, ©2023 International Association for the Study of Lung Cancer. Published by Elsevier Inc., licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/); [b]Irrespective of mediastinal pleura invasion. Mediastinal pleura invasion is to be recorded as an "additional histologic descriptor."

In general, a limited resection offers a shorter operative time and potentially fewer complications. However, current literature has failed to confirm a significant advantage of a limited resection in the immediate postoperative period, because length of stay and complication rates are similar compared with thymothymectomy. Conversely, a complete thymectomy, in theory, should likely reduce the risk of local recurrence and in turn OS, in addition to decreasing the risk of developing myasthenia gravis in the postoperative period.

Owing to the rarity of the disease, current practice patterns and society guidelines are based on nonrandomized, retrospective studies with heterogeneity in patient populations, duration of patient enrollment and follow-up, mixture of open and minimally invasive operations and, in certain reports, a limited number of patients. Furthermore, long-term follow-up is necessary to produce an impactful outcome from a retrospective analysis due to slow tumor growth in patients with thymoma.

In general, several studies have shown no differences in long-term outcomes between thymothymectomy and thymomectomy. One noticeable outlier is a multicenter study by the European Society of Thoracic Surgeons (ESTS) thymic

working group.[47] In this 23-center retrospective study, 32 thymomectomy patients were compared using 3:1 propensity matching with 88 thymothymectomy patients undergoing resection for cT1a-b N0 M0 lesions. Postoperative complications, 30-day mortality, and length of stay were similar. The 5-year freedom from recurrence was 98% in thymothymectomy group compared with 79% in the thymomectomy group ($P = .025$). There was a trend toward improved 5-year OS in thymothymectomy patients (80% vs 49%, $P = .144$). The VATS technique was used to perform 28.3% of the procedures during the study period of 2000 to 2017. One of the key limitations of this study is the relatively small number of patients in the thymomectomy group and higher-than-expected (6% [2 of 32]) 30-day mortality in this group. The authors also acquiesced to the influence of variation in intraoperative techniques in the assessment of intraoperative surgical margins.

In a study by the Japanese Association for Research on the Thymus (JART), Nakagawa and associates[48] evaluated 1286 patients treated at 32 institutions between 1991 and 2010 for Masaoka stage I and II thymoma. Patients who underwent VATS were excluded given that minimally invasive techniques for thymoma resection were not considered standard during the particular study period. The patients who underwent thymomectomy were older and had smaller tumors. The 5-year OS was 97.3% in thymomectomy group and 96.9% in the thymothymectomy group ($P = .487$). Higher local recurrence was observed in thymomectomy group (2.2% vs 0.4%, $P = .0613$); however, thymothymectomy patients had a higher rate of surgical complications (8.3% vs 4.3%, $P = .0397$). The authors concluded similar long-term prognosis in patients with limited resection. In an earlier report by the same authors,[49] 5- and 10-year survival rates were 96.7% and 92.2% in the thymomectomy group compared with 94% and 86.2% in the thymothymectomy group ($P = .755$), respectively. In this study of 173 patients, myasthenia gravis developed postoperatively in 3% in the thymomectomy group and in 8% in the thymothymectomy group.

In a similar retrospective study of patients between 1994 and 2012,[50] Chinese Alliance for Research in Thymomas (ChART) investigators reported outcomes of 1047 patients undergoing surgery for Masaoka stage I and II. The 10-year OS was similar between the 2 groups along with recurrence rates (3.1% vs 5.4%). However, the recurrence rate was lower after thymothymectomy (2.9%) compared with thymomectomy alone (14.5%) in Masaoka stage II patients ($P = .001$). This study had various surgical techniques, including sternotomy and VATS, and included patients with myasthenia gravis.

Narm and colleagues[51] performed a multicenter propensity-matched study, enrolling 762 patients with Masaoka stage I and II thymoma without myasthenia gravis, undergoing a thymomectomy or a thymothymectomy, and allowing VATS as well as sternotomy techniques in both cohorts. The authors identified no difference in 10-year OS and disease-free survival after propensity matching.

Voulaz and associates[52] reported similar outcomes in 255 patients undergoing limited vs complete resection between 1986 and 2019, all with Masaoka stage I and II and no myasthenia gravis. After propensity matching, there was no difference in neither disease-free ($P = .11$) nor thymoma-related survival ($P = .37$) in the 2 groups.

In patients with well-circumscribed thymoma without myasthenia gravis, thymomectomy alone leads to similar long-term outcomes compared with thymothymectomy in most studies. There are no randomized studies in this regard, and major publications have noticeable heterogeneity in surgical technique. Thus, thymothymectomy should be considered the standard for patients with acceptable surgical risk, and thymomectomy alone should be reserved for higher-risk patients. Surgeons should critically assess the tumor and surrounding tissues for adequate margins and rule out multifocal disease by their best judgment intraoperatively before deciding on the type of resection.

Consensus statement 6: A goal of R0 resection by thymothymectomy should be considered the standard for thymic malignancies for optimal disease-free survival and overall survival and to mitigate the risk of postoperative myasthenia gravis. Thymomectomy alone may be considered in patients with clinical stage I disease who are at elevated surgical risk.

- *Strongly agree, 50%*
- *Agree, 50%*
- *Neither agree nor disagree, 0%*
- *Disagree, 0%*
- *Strongly disagree, 0%*

B. NEOADJUVANT THERAPY VS PRIMARY SURGERY. Complete surgical R0 resection remains the key prognostic factor in the treatment of thymoma.[10,38,53-57] For Masaoka stage I and stage II

TABLE 4 Retrospective Neoadjuvant Chemotherapy Studies for Treatment of Advanced Thymoma

Authors	Total Patients	Neoadjuvant Chemotherapy Patients	R0 Resection Rate (NA vs Primary Surgery)	*P* Value	Overall 5-Year Survival Rate (NA vs Primary Surgery)	*P* Value	Comments
Khorfan et al,[10] 2021	1849	127 (12.6)	57.2 vs 54.2	.50	76.8 vs 73.6	NS	NA not associated with completeness of resection
Park et al,[11] 2019	1486	110 (7.4)	63.7 vs 70.6	.38	72.6 vs 73.8	.22	No benefit of NA in resectability or survival
Yamada et al,[12] 2015	310	42 (13.5)	Not available	…	Not available	…	NA was independent predictor of poor survival ($P < .001$)
Leuzzi et al,[13] 2016	370	88 (24.9)	65.4vs 79.9	.01	84.2 vs 91.4	.61	NA was associated with reduced R0 resection rates in unmatched groups

Data are shown as n (%) or as the percentage rate. NA, neoadjuvant chemotherapy; NS, not significant.

thymomas, the likelihood of achieving a complete resection approximates 100%, with 10-year survival rates greater than 80% and recurrence rates of less than 16%.[58-63] Tumor size alone does not impact the ability to achieve a complete resection based on an analysis performed for the International Association for the Study of Lung Cancer/International Thymic Malignancy Interest Group (IASLC/ITMIG) thymic epithelial tumor staging project.[64] In contrast to the high likelihood of R0 resection with early-stage thymoma, Masaoka stage III and IV thymomas are associated with less than 50% likelihood of achieving a complete resection. Because of this discrepancy in achieving complete resection with locally advanced thymomas, neoadjuvant therapy strategies have been used to increase the likelihood of an R0 resection and improve survival.

Role of Neoadjuvant Chemotherapy in the Treatment of Thymoma. Given the high likelihood of achieving a complete resection in Masaoka stage I and stage II thymomas, there is no evidence to support the role of neoadjuvant chemotherapy before surgery in early-stage disease. The focus of neoadjuvant chemotherapy has been on locally advanced disease (Masaoka stage III and IV). Although no prospective randomized studies have investigated the role of neoadjuvant chemotherapy for locally advanced thymoma, a number of multi-institutional retrospective studies have attempted to determine the efficacy of this treatment modality. The findings of these studies are summarized in Table 4.[10-13]

The most recent analysis (2021) performed in the United States using the National Cancer Database was designed to describe the current treatment strategies and associated survival for Masaoka stage III and IV thymoma.[10] A total of 1849 patients (1108 with stage III and 741 with stage IV) were identified within the database. In this cohort of patients, 12.6% (n = 127) of patients received neoadjuvant chemotherapy. Because the total number of patients that received any neoadjuvant therapy was small (n = 160 [15.6%]), all neoadjuvant modalities were combined in this analysis. Of the patients who received some form of neoadjuvant treatment, 79% received only neoadjuvant chemotherapy. In the neoadjuvant group, complete (R0) resection was achieved in 57.2% of patients compared with 54.2% in patients who were treated with primary surgery. This difference between treatment groups was not statistically significant ($P = .50$). Furthermore, on logistic regression, neoadjuvant therapy was not associated with an R0 resection (odds ratio, 1.20; 95% CI, 0.75-1.93). Neoadjuvant therapy, followed by surgery, was associated with a 5-year OS of 76.8% vs 73.6% in patients who received primary surgery, which was not statistically significant.

The Korean Association for Research on the Thymus (KART) conducted a retrospective multi-institutional study investigating the role of neoadjuvant chemotherapy in 51 patients with advanced thymoma compared with 58 patients who underwent surgery alone.[11] Complete resection was achieved in 63.7% of patients undergoing neoadjuvant chemotherapy before surgery vs 70.6% in the surgery-alone group ($P = .405$). Subgroup analysis of Masaoka stage III patients comparing 5-year survival rates between neoadjuvant/surgery and surgery alone were not different (72.6% vs 73.8%, $P = .219$). Masaoka stage IV patients also demonstrated no survival benefit with the addition of neoadjuvant chemotherapy.

Overall, neoadjuvant therapy was, nevertheless, associated with a 22.5% likelihood of downstaging.

The Japanese Association for Research on the Thymus (JART) also performed a retrospective analysis of the utility of neoadjuvant therapy on 310 patients with Masaoka stage III thymomas.[12] Within the cohort, 29 patients (9.4%) received neoadjuvant chemotherapy. Neoadjuvant chemotherapy was associated with worse OS on univariate and multivariable analysis.

The prognostic relationship of multimodality therapies on Masaoka stage III thymomas was investigated by a large multi-institutional group organized through the European Society of Thoracic Surgeons (ESTS).[13] The analysis included 370 patients diagnosed with Masaoka stage III thymoma, of which 88 patients (24.5%) received neoadjuvant chemotherapy before surgery. R0 resection was achieved in 65.4% of patients who underwent neoadjuvant chemotherapy compared with 79.9% in the surgery-alone group ($P = .01$). Overall, neoadjuvant chemotherapy was not associated with superior recurrence-free survival or cancer-specific survival compared with surgery alone.

In summary, using induction chemotherapy to increase the likelihood of R0 resection and improved survival in patients with Masaoka stage III and IV thymoma is not well supported in the available retrospective studies. Because of the likelihood of significant selection bias, lack of clear indication for use of neoadjuvant therapy, and lack of standardization of chemotherapeutic regimens, one should not rule out the efficacy of neoadjuvant therapy in locally advanced thymoma before investigating its effect in a prospective study. As such, use of neoadjuvant chemotherapy in the setting of locally advanced thymoma should be discussed in a multidisciplinary setting between specialties treating patients with locally advanced thymomas.

Role of Neoadjuvant Chemoradiotherapy in Thymoma. Based on the synergistic effect of combined chemotherapy and radiotherapy in lung cancer, one prospective study investigated the role of combined neoadjuvant chemoradiotherapy in advanced thymoma. This single-arm multicenter clinical trial evaluated the efficacy of neoadjuvant chemoradiotherapy in locally advanced thymic tumors.[14] The study enrolled 22 patients, with 95.4% of patients completing the neoadjuvant chemoradiotherapy regimen. Partial radiologic responses to neoadjuvant chemoradiotherapy were found in 45% of patients, with no patients having disease progression after treatment. Of the 21 patients who underwent surgery, 77% had an R0 resection. This R0 resection rate compares favorably to patients undergoing neoadjuvant chemotherapy alone, with complete resection rates as low as 43%.[18] No patients had a complete pathologic response after neoadjuvant chemoradiotherapy. One important aspect to consider in this study was the morbidity associated with the treatment modality in this patient population. Grade 3 or 4 toxicity developed in 41% of patients after neoadjuvant chemoradiotherapy, 36% of patients had a postoperative complication, and 2 of the 21 patients died after surgery.

More recently, a single institutional retrospective study compared outcomes of neoadjuvant chemotherapy or chemoradiotherapy vs surgery alone in patients with advanced thymoma.[16] The study included 45 patients, of whom 19 patients received neoadjuvant chemotherapy or chemoradiotherapy and surgery compared with 26 patients who received only surgery. There were no significant differences in the percentage of R0 resection between treatment groups. OS between treatment groups was not significantly different. However, 10-year recurrence-free survival was significantly higher at 75% in the neoadjuvant therapy group compared with 30% in the surgery alone group. Notably, patients in the neoadjuvant therapy group had a higher incidence of wound healing complications compared with surgery alone (15.8% vs 0%, $P = .036$).

Another single-institution retrospective study by Wang and associates[65] examined 81 patients with initially unresectable thymic epithelial tumors who underwent neoadjuvant chemotherapy or chemoradiotherapy, followed by surgical resection. Nearly 70% of patients had major tumor response from neoadjuvant therapy, and the R0 resection rate was 74%. Direct comparison between neoadjuvant chemotherapy vs chemoradiotherapy was not done in this study, although the authors noted that overall the adverse events were modest and well tolerated.

Evaluation of these limited studies suggests that the addition of radiotherapy to neoadjuvant chemotherapy may increase the likelihood of a complete resection. However, the downside of including radiation in the neoadjuvant therapy regimen is the higher incidence of toxicity and postoperative complications. Given the paucity of studies on the role of neoadjuvant chemoradiotherapy in advanced thymomas, the decision

to incorporate this modality into treatment plans should be considered after a multidisciplinary discussion.

Consensus statement 7: If an R0 resection is deemed probable for a suspected thymic malignancy, primary surgery without neoadjuvant therapy is appropriate, irrespective of tumor size.

- *Strongly agree, 64.3%*
- *Agree, 35.7%*
- *Neither agree nor disagree, 0%*
- *Disagree, 0%*
- *Strongly disagree, 0%*

Consensus statement 8: Neoadjuvant chemotherapy or chemoradiotherapy should be considered in patients with locally advanced thymoma in whom a complete R0 resection may be difficult to achieve with primary surgery.

- *Strongly agree, 57.1%*
- *Agree, 42.9%*
- *Neither agree nor disagree, 0%*
- *Disagree, 0%*
- *Strongly disagree, 0%*

C. SURGICAL MANAGEMENT OF THYMOMAS. Surgery is integral to the cure of thymomas, with chemotherapy and radiotherapy having a role in advanced cases.[66] Total thymectomy with complete surgical excision of the tumor is generally recommended for all resectable thymomas in patients who can tolerate the surgery.[3,19,63,45,67-69] Completeness of resection is the most important predictor of outcome,[70] with excellent 10-year survival rates of approximately 90% and 70% for resected Masaoka stage I and II thymomas, respectively.[3,59,70,71]

Thymoma resection should encompass complete excision of the lesion with complete resection of contiguous and noncontiguous disease, including any pleural or lung nodules that are present.[45,72-74] Thymomas are more likely to be locally invasive to adjacent structures, such as the lung, pericardium, or into the pleural space, rather than to spread to regional lymph nodes or extrathoracic sites.[29,75-77] Complete resection may therefore require resection of adjacent structures, including pericardium, phrenic nerve, pleura, lung, and major vascular structures. Bilateral phrenic nerve resection should be avoided due to severe respiratory morbidity.

The surgical approach to thymoma bears the risk of major morbidity or mortality, considering the location of thymoma in the anterior mediastinum adjacent to other vital structures of the chest. During the operation, the surgeon should resect any suspicious lymph nodes and send them to pathology separately.[78] For TNM stage I thymoma, resect adjacent and anterior mediastinal lymph nodes. For TNM stage II and III thymoma, an anterior mediastinal lymph node dissection and a systematic sampling of intrathoracic sites is recommended. For known or suspected thymic carcinoma, a sampling of anterior mediastinal, intrathoracic, supraclavicular, and lower cervical lymph nodes should be done.[78]

Open vs Minimally Invasive Approach. Historically, thymoma resection was approached through an open operation. Depending on the specific location and nature of the tumor, the approach might involve median sternotomy, thoracotomy, bilateral anterior thoracotomy with sternal division (clamshell incision), or hemiclamshell incision with sternothoracotomy. These approaches have benefits of optimizing surgical exposure, which can facilitate safe manipulation of the tumor and critical structures, complete resection, and reconstruction of involved adjacent mediastinal structures when necessary. Specifically, major vascular structures including the heart can be carefully manipulated to allow complete resection and avoid massive bleeding or catastrophic events such as intraoperative death.

An open approach can also permit careful manipulation and avoid violation of the tumor or its capsule and optimize the chance for cure with surgical resection. Tumor spillage can potentially convert a curable situation into an incurable scenario and increase risk of recurrence and need for further therapies.[66] Adequate exposure and visualization can also facilitate preservation of phrenic nerve function when the nerve is close but not directly involved by the tumor.

However, open approaches can be associated with both short-term and long-term disabilities in function, delay in returning to presurgery activity, and reduced quality of life. Minimally invasive surgical approaches to lung resection in the chest, when feasible, have demonstrated short-term advantages over open surgery without compromise of oncologic principles and outcomes.[79,80] Additionally, the use of minimally invasive lung surgery can reduce risk of surgery in elderly patients or those with compromised pulmonary function.[81,82] Although randomized studies allowing comparison of long-term outcomes between open and minimally invasive approaches

for mediastinal tumors have not been conducted, the short-term benefits of minimally invasive surgery (with VATS, robotic-assisted thoracoscopic surgery [RATS] surgery, or a subxiphoid approach) over open surgery are now well established. When feasible, minimally invasive surgery should be considered if a complete oncologic resection can be achieved.[83-87]

Guidelines regarding thymoma resection recognize that a minimally invasive approach is acceptable, but that randomized or long-term studies showing that these techniques do not compromise long-term outcomes are limited.[45,69,88,89] Nevertheless, several retrospective and noncontrolled studies have shown minimally invasive approaches to thymoma resection are both feasible and safe, with short-term advantages of shorter hospitalizations, shorter operative times, fewer postoperative complications, and less blood loss over open approaches.[69,71,83-87,90-96] Studies using the National Cancer Database evaluating patients with stage I to stage III thymoma reported an approximately 20% increase in the use of minimally invasive resection between 2010 and 2014 with comparable R0 rates to open resection.[71,97] Other large database studies, such as the ITMIG database, reported acceptable R0 resection rates with the use of minimally invasive approaches.[98,99] A systematic review of open, VATS, and RATS thymectomy also concluded that minimally invasive approaches offer significant morbidity advantages over open surgery.[100]

Minimally invasive approaches have not been demonstrated to compromise oncologic effectiveness.[95,101] A systematic review of 1061 patients with thymomas reported similar 5-year OS (VATS: 83%-100% vs open: 79%-98%) and 10-year recurrence-free survival (VATS: 89%-100% vs open: 80%-93%) in patients undergoing VATS compared with open thymectomy.[88] A retrospective review compared 2835 patients with thymomas undergoing VATS thymectomy or sternotomy[102] and reported a similar 5-year OS rate between the 2 approaches. Meta-analyses have also showed that VATS is safe and that patients have similar OS compared with those receiving open thymectomy.[103,104]

Importantly, a minimally invasive approach should only be undertaken when resection can be safely achieved without violating standard oncologic principles.[105] Although tumor size will influence the choice of approach, minimally invasive surgery has been demonstrated to be safe for tumors larger than 5 cm. Surgeons must carefully consider the specific appearance of larger tumors when deciding on the surgical approach.[96,105] Tumor invasiveness rather than size should be an important factor in determining whether a minimally invasive approach is feasible.[106]

Additionally, surgeons must consider their own experience and expertise to ensure a complete resection and that all oncologic goals are safely achieved. Surgeons should either not attempt a minimally invasive approach if there are concerns related to these specific goals or should have a fallback plan for conversion to an open approach should minimally invasive exploration demonstrate that minimally invasive resection is not feasible. Surgery should not persist with a minimally invasive approach if any concerns exist related to safety, violation of the tumor capsule, or completeness of resection.

Choice of Minimally Invasive Approach. Multiple minimally invasive approaches are available for thymoma resection. These include a VATS approach, a RATS approach, and a subxiphoid approach. Each is safe, feasible, and has benefits over open approaches. The most appropriate approach for a particular patient is dependent in part on the tumor location and the surgeon's expertise and experience.

VATS and RATS both use one side of the chest, generally with multiple small anterior and lateral incisions while the patient is supine with a bump under the operative side. The laterality of approach is typically determined by the tumor location. It should be noted that approach through only one side of the chest for a tumor that is in the midline does have some risk of inadvertent injury to the contralateral phrenic nerve. This risk can be reduced by placing an additional incision and camera in the contralateral chest, but there are still limitations to avoiding inadvertent manipulation or injury to the phrenic nerve when performing dissection from the contralateral side. In some cases, bilateral surgery may be appropriate so that dissection of tissue near the phrenic nerve is as safe as possible.

Because the RATS approach is a more recent technique, related studies with long-term follow-up are few. However, published series evaluating outcomes after RATS show promising data. Separate single-center series of 158 patients[107] and 213 patients[108] undergoing robotic resection of tumors with a median size of 4.6 to 4.7 cm had 3.5% to 4.4% major morbidity and no deaths, 1- to 2-day median length of stay, with a 98.8% R0 rate. In 1 series, there was only 1 local/regional recurrence after a median follow-up of 32 months[108] and a

94% recurrence-free survival in the other study after median follow-up of 43 months.[107] Other studies have shown similar results in the feasibility of a robotic approach for short- and medium-term outcomes.[109]

Although VATS and RATS have both been demonstrated to have advantages over open approaches, there have been limited direct comparisons between these minimally invasive approaches. Operative times have been demonstrably shorter with a RATS approach, but both approaches have yielded similar outcomes.[110] Interestingly, a systematic review and meta-analysis comparing 688 RATS and 730 VATS patients from 11 studies found no significant difference in operative time, although RATS was associated with less blood loss, lower volume of chest tube drainage, fewer postoperative pleural drainage days, shorter postoperative hospital stay, and fewer postoperative complications.[111] The RATS approach to mediastinal surgery has theoretical advantages based on improved visualization and dissection technique related to the wristed instrumentation of the robotic technology. However, how clinically significant the differences between VATS and RATS approaches are is not clear, because both can be safely used in the appropriate setting based on the surgeon's expertise.

A somewhat newer approach to anterior mediastinal surgery is through a subxiphoid approach.[112] This technique has theoretical advantages of being less painful or morbid, because the incision avoids trauma to intercostal muscles but does cause trauma to the upper abdominal fascia.[113] The technique may permit a patient to avoid single-lung ventilation, at least for the entirety of the procedure. Although VATS approaches that avoid intubation and allow spontaneous ventilation can be done and are described, a subxiphoid approach may be more conducive to allow adequate mediastinal visualization when regional anesthesia with spontaneous ventilation through a laryngeal mask is used.[114]

The subxiphoid approach improves visualization of bilateral phrenic nerves, decreases pain, and also allows a wider amount of resected tissue.[115] Meta-analyses that examined studies comparing the subxiphoid approach with other minimally invasive techniques found the subxiphoid approach had less pain, shorter length of stay, and reduced blood loss while not increasing operative time, incidence of complications, transition to thoracotomy, postoperative pleural effusion, phrenic nerve palsy, and lung infection.[116,117] Few studies have compared the oncologic outcomes of subxiphoid to other approaches. A single-institution retrospective study of 40 patients showed that the subxiphoid approach has similar rates of R0 resection compared with VATS.[118]

Consensus statement 9: Thymoma resection should involve complete resection of all contiguous and noncontiguous disease, including any pleural or lung nodules and grossly abnormal lymph nodes. Resection of adjacent structures, such as pericardium, phrenic nerve, pleura, lung, and major vascular structures, may be required, but bilateral phrenic nerve resection should be avoided due to severe respiratory morbidity.

- *Strongly agree, 84.6%*
- *Agree, 15.4%*
- *Neither agree nor disagree, 0%*
- *Disagree, 0%*
- *Strongly disagree, 0%*
- *Abstain, 1*

Consensus statement 10: Minimally invasive surgery should be considered if a total thymectomy and complete R0 resection can safely be achieved.

- *Strongly agree, 69.2%*
- *Agree, 30.8%*
- *Neither agree nor disagree, 0%*
- *Disagree, 0%*
- *Strongly disagree, 0%*
- *Abstain, 1*

Consensus statement 11: Surgeons should have sufficient technical expertise and clinical experience to ensure complete resection that accomplishes all oncologic goals safely while avoiding tumor spillage, particularly for minimally invasive approaches.

- *Strongly agree, 76.9%*
- *Agree, 23.1%*
- *Neither agree nor disagree, 0%*
- *Disagree, 0%*
- *Strongly disagree, 0%*
- *Abstain, 1*

III. ROLE OF SURGERY IN LOCALLY ADVANCED AND PLEURAL DISEASE

A. PREOPERATIVE EVALUATION: MULTIDISCIPLINARY ASSESSMENT AND APPROACH. Although treatment options vary from center to center, locally advanced thymoma should be managed by a

multidisciplinary approach. As previously described, collective evaluation by thoracic surgeons, radiologists, pathologists, medical oncologists, radiation oncologists, and neurologists when myasthenia gravis is present should be the standard of care in locally advanced thymic tumor management. Thymomas are chemosensitive tumors, and a variety of combination chemotherapy regimens have been reported with varying response rates.[19]

Two group trials have demonstrated the sensitivity of the thymomas to chemotherapy. The cisplatin, doxorubicin, and cyclophosphamide regimen led by the Eastern Cooperative Oncology Group[119] and the cisplatin and etoposide regimen led by European Organisation for Research and Treatment of Cancer[120] have been demonstrated to be effective in patients with metastatic or unresectable disease. These 2 studies encouraged the use of neoadjuvant treatment for locally advanced thymomas to decrease the size of the tumors and permit access to vital structures for complete resection. Ultimately, the decision regarding resectability should be made by an experienced thoracic surgeon in a multidisciplinary setting, and neoadjuvant therapy should be discussed as a part of multimodality treatment if this has the potential to improve the chance of complete resection. Details regarding the potential benefits of neoadjuvant therapy are described in a previous section of this document.

Operative Risk Assessment. Operative risk is defined as the potential for perioperative mortality and morbidity. Surgical resection has been the mainstay treatment of thymoma, with a mortality rate of 2% and complication rate of 20% in locally advanced cases.[3] When superior vena cava (SVC) resection is required in locally advanced thymic epithelial tumors, the mortality rate has been reported to vary between 7.4% and 10.3% at 90 days after surgery.[121,122] Additional risks in locally advanced thymic tumor surgery have been reported, such as intraoperative and postoperative bleeding, associated nerve injuries, including phrenic and recurrent laryngeal nerve, pneumonia, and additional complications due to technical failures, such as thrombosis of reconstructed vasculature. Similarly, potential injuries and the potential need for lung resections make the physiologic assessment of the patient necessary. Although there has not been an established minimum threshold for forced expiratory volume in 1 second or forced vital capacity, and diffusion of the lung for carbon monoxide levels similar to lung cancer surgery, these tests may indicate cardiopulmonary functional capacity. If lung resection is going to be involved, the patient should be evaluated as a lung resection patient.

At presentation, 40% of all mediastinal tumors are asymptomatic.[123] In locally advanced thymoma patients, mediastinal mass effects could include direct involvement or compression of mediastinal structures. All large mediastinal tumors may cause acute or chronic respiratory insufficiency.[124] In addition, large tumors can cause cough, stridor, hemoptysis, shortness of breath due to pleural effusion or phrenic nerve invasion, pain, dysphagia, hoarseness, SVC syndrome, hypotension due to pericardial effusion and cardiac compression, and Horner syndrome.

If the patient has myasthenia gravis, the preoperative management should include medical optimization in conjunction with the treating neurologists. Preoperative intravenous immunoglobulin or plasmapheresis may reduce the risk of perioperative myasthenic complications. For patients with any paraneoplastic syndrome, preoperative evaluation and treatment, when necessary, should be conducted in a multidisciplinary fashion to ensure patients are safe for surgery. Therapies may include steroid administration, plasmapheresis, intravenous immunoglobulin, or blood product transfusion. A systematic review of thymoma patients with paraneoplastic syndromes indicated that approximately 75% of patients may have partial or complete resolution of the paraneoplastic syndrome after surgical resection, and that complete resolution was associated with improved survival.[125] For myasthenia gravis patients, remission rates after thymectomy are lower in patients with thymoma compared with those without thymoma.[126,127]

Imaging Methods in Locally Advanced Thymic Cancer. Radiologic studies recommended for locally advanced disease were covered in detail earlier in this document. Examples of locally advanced thymoma with invasion of adjacent structures seen on contrast CT and MRI are depicted in Figure 2.

Certain anterior mediastinal masses, such as substernal goiters, benign teratoma, and benign cysts, can be reliably identified by imaging alone.[5] Locally advanced thymic epithelial tumors can

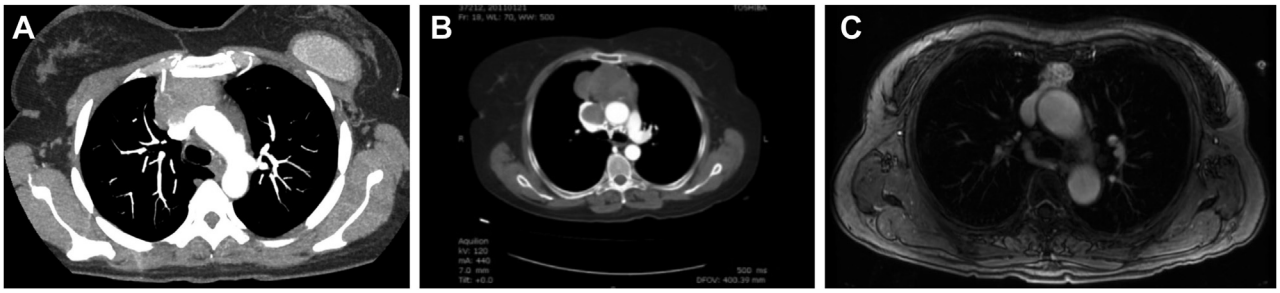

FIGURE 2 Examples of locally advanced thymoma with invasion of adjacent structures. (A) Tumor with infiltration of innominate vein and superior vena cava on contrast computed tomography (CT). (B) Tumor within the right atrium from infiltration through superior vena cava on contrast CT. (C) Tumor infiltrating innominate vein seen with magnetic resonance imaging.

similarly exhibit characteristic features. This makes communication vital between the clinician and radiologist. Contrast-enhanced CT and MRI should be used to evaluate for T3 and T4 disease. In consideration for clinical diagnosis, certain features, such as clinical presentation, age, sex, and confirmatory laboratory tests should be considered.[4]

PET scan may be used to assess the uptake of the mass as well as involvement of lymph nodes, pleural or pericardial involvement, and distant disease.[128] Studies published over the last 2 decades demonstrate that thymoma generally has a lower mean SUVmax value, whereas all thymic carcinomas and some lymphomas have higher values.[128] Data suggest that FDG-PET appears to be effective in predicting the grade of malignancy, pathologic response to induction therapy, disease stage, and long-term prognosis.[129] Several other radiotracers have been reported to have some application in thymic epithelial tumors.[129]

Angiography, including pulmonary or coronary angiograms, may be valuable to assess the vascularization of large tumors. During angiography, embolization of the vessels feeding the tumor could be identified before surgery. This can theoretically decrease blood loss during surgery and has been reported mostly for paraganglioma, although this procedure is rarely needed for thymoma given the lack of evidence demonstrating benefit of less perioperative bleeding.[130,131]

Histopathologic Examination Before Surgery for Locally Advanced Thymoma. In contrast to noninvasive thymoma, histopathologic examination is generally needed for locally advanced tumors. A CT-guided biopsy can provide sufficient tissue. Risk of tumor dissemination into the pleural cavity has been reported but is considered low risk with needle biopsy compared with VATS.[132] In patients with myasthenia gravis where neoadjuvant treatment is not indicated for a noninvasive anterior mediastinal mass, surgery without a biopsy specimen is appropriate given the presumption that the mass is a thymoma. In a T3 or T4 thymoma where complete resection is challenging, histopathologic examination and neoadjuvant treatment, followed by surgery, should be considered as described previously.[74,133]

Importance of Staging in Locally Advanced Thymoma—Masaoka vs TNM Staging System. Locally advanced thymomas are characterized by involvement of adjacent structures. In the Masaoka staging system, thymomas are considered stage III in the event of any invasion of any adjacent structure, including pericardium, great vessels (SVC, brachiocephalic veins, aorta, and pulmonary artery), lung parenchyma, chest wall, and phrenic nerve. Up to 30% of all resected thymic tumors are locally invasive.[134,135] A limitation of the Masaoka staging system is that any invasive tumor is categorized as stage III, irrespective of whether the structures involved are easily resected, such as pericardium, or require complex reconstruction, such as the SVC or hilar vessels.

In an effort to overcome the heterogeneity in this Masaoka stage group, the new TNM staging system separates T stage into the following 3 categories based on the structures involved: pericardium (T2 or stage II), neighboring organs that can be resected and reconstructed if necessary (T3 or stage IIIA), and potentially unresectable structures (T4 or

stage IIIB). Patients with TNM stage IIIA tumors are characterized by invasion of the lung, phrenic nerve, brachiocephalic vein, SVC, extrapericardial hilar vessel, or chest wall, whereas TNM stage IIIB tumors are characterized by infiltration of aorta, arch vessels, myocardium, intrapericardial pulmonary artery, trachea, or esophagus.[64]

Notably, the Ninth Edition TNM stage classification is scheduled to take effect in 2024 with several changes to the T component.[31] T1 tumors will be stratified by size, with tumors 5 cm or smaller categorized as T1a and tumors greater than 5 cm categorized as T1b. Additionally, invasion of the lung or phrenic nerve will be reclassified from T3 to T2 (Table 3).

TNM stage IVA and IVB thymomas are similarly distinguished in part by resectability of metastatic lymph nodes and noncontiguous disease. TNM stage IVA disease includes potentially resectable anterior (perithymic) lymph nodes along with pleural or pericardial nodules, whereas TNM stage IVB disease involves deep intrathoracic or cervical nodes, pulmonary intraparenchymal nodules, and distant organs. As such, the TNM staging system is more appropriate in the context of determining the need for multimodality treatment of locally advanced thymic tumors. Surgery for locally advanced disease is more challenging when, for instance, resection and reconstruction of the SVC is necessary, compared with the direct resection of involved pericardium. Thus, TNM staging is a more precise method to characterize the extent of disease and can help facilitate communication and collaboration for multimodal therapy.[13]

B. ANESTHESIA CONSIDERATIONS. Physiologic changes that occur during the induction of anesthesia may potentiate compressive effects of the mass. The effects of supine position, anesthetic agents on muscle tone, positive pressure ventilation, and minor surgical trauma can cause a decrease in lung and thoracic volume. Mediastinal mass syndrome (MMS), characterized as cardiopulmonary compromise resulting from compression of mediastinal structures by a mass, may be seen during the induction of anesthesia, depending on the size of the tumor.[136] The exact incidence of MMS remains unknown, and only isolated cases have been presented.[136] Inadequate evaluation and preparations in the perioperative period could lead to life-threatening problems. Therefore, preoperative workup and detailed imaging are essential to assess the extent of invasion to mediastinal structures and the potential for cardiopulmonary compromise upon anesthesia induction.[123]

The clinical presentation may range from absence of symptoms to acute intraoperative or postoperative cardiorespiratory decompensation. The anesthesiologist should adhere to precautionary measures, and further discussions should be made with the surgeon to ensure safe perioperative anesthesia. Several studies have attempted to standardize the anesthesiology approach to prevent MMS.[136,137]

Anesthesia Risk Assessment. Preoperative assessment should be done to delineate low-risk, intermediate-risk, and high-risk patients. Intermediate-risk patients have either tracheobronchial only or tracheobronchial plus associated hemodynamic compression symptoms.[136] If there is involvement of the SVC, large-bore venous access should be obtained in the lower extremity, preferably the femoral vein. This should be performed regardless of the risk category. Double-lumen endobronchial intubation should be discussed between the anesthesiologist and surgeon. The preferred approach for airway management in a high-risk patient is maintenance of spontaneous ventilation and awake fiberoptic intubation. The use of short-acting medications is strongly recommended for precise control of depth of anesthesia.[136,138]

Intravenous Access and Airway Management. There are 2 reasons for lower extremity venous access in locally advanced large tumors. A change in intrathoracic pressure might increase the effects of SVC syndrome, cardiac tamponade, or pulmonary artery compression, leading to sudden cardiac arrest. Dynamic hyperinflation and auto-positive end-expiratory pressure can also decrease venous return to heart.[136] A secondary advantage of lower extremity venous access is the continuity of the intravenous access during clamping of the SVC when necessary for reconstruction.

In a major airway collapse or obstruction, rigid bronchoscopy may be necessary to secure the airway. The basic principles of cardiac tamponade treatment should be followed, such as the administration of intravenous fluids, followed by vasopressor and inotropic medications in the case of ongoing hemodynamic compromise. The surgeon should act promptly to physically elevate the mass away from the heart or trachea after sudden collapse after sternotomy or thoracotomy. Given the potential for sudden decompensation before or after anesthesia induction, the surgeon, operating room staff, and anesthesiologist must be

prepared to respond to any acute events. When MMS occurs, definitive rescue depends on extracorporeal support, which can maintain oxygenation and circulation.[137] Depending on the level of risk, obtaining stand-by extracorporeal support before anesthesia induction may be appropriate.[139,140]

C. SURGICAL CONSIDERATIONS FOR TNM STAGE III DISEASE. Median sternotomy has been the standard approach for TNM stage III thymoma surgery. This approach provides excellent exposure if the tumor invades the neighboring organs. A clamshell incision may be preferred when the tumor is more extensive and invades both pleural cavities. In general, structures that can potentially be resected and reconstructed include the left brachiocephalic vein, SVC, right atrium, lung, and diaphragm. Resection and reconstruction of the ascending aorta and pulmonary vessels may rarely be indicated in very select cases.[141]

Rarely, thoracotomy or hemiclamshell approaches may be required. A hemiclamshell approach provides excellent exposure to mediastinum, arch vessels, and involved pleural space. For this exposure, an anterior thoracotomy through the fourth or fifth intercostal space is performed, which is then combined with a partial median sternotomy. This technique has been reported to provide the best approach to ipsilateral brachiocephalic veins.

In some centers, minimally invasive surgery with RATS or VATS has been used successfully to resect Masaoka stage III thymomas when the invasion of thymoma is limited to the pericardium and brachiocephalic vein.[142] It should be emphasized that a minimally invasive approach for any invasive thymoma should be carefully evaluated and attempted only if the surgeon has the experience and expertise to achieve a complete resection safely in this fashion.

Direct Invasion to the Lung. The infiltrated portion of the lung should be resected en bloc with the thymoma, which may entail wedge resection, segmentectomy, or lobectomy, depending on the extension of the tumor. Pneumonectomy or extrapleural pneumonectomy may be necessary in some cases for complete resection; however, the risks and benefits of the operation and expected outcomes must be evaluated carefully.[143-146] Extrapleural pneumonectomy and outcomes will be discussed in the next part of this document.

Phrenic Nerve Resection. Phrenic nerve resection may be necessary for complete resection, particularly if there is invasion of the SVC or specific portions of the pericardium. In patients with appropriate pulmonary reserve, resection of 1 phrenic nerve is acceptable. Consideration of simultaneous ipsilateral diaphragmatic plication at the time of surgery is appropriate.

The need for phrenic nerve preservation has been debated as well as the utility of radiotherapy on the spared nerve area.[147] Nerve-sparing surgery is performed with the intention to treat all patients with advanced-stage thymomas without preoperative evidence of hemidiaphragm palsy but with macroscopic evidence of phrenic nerve involvement. Providing adjuvant radiotherapy (45 to 60 Gy), with or without chemotherapy, has been recommended. This technique may be used in patients with infiltration to the phrenic nerve but without paralysis of the diaphragm, especially in those affected by severe comorbidities, poor performance status,[148] or patients with myasthenia gravis.

SVC, Aorta, and Intracardiac Thymic Tumor Resection. SVC, aorta, and intracardiac thymic cancer surgery are technically challenging operations, even for high-volume centers. Few surgeons have reported experiences with such aggressive operations. This limitation is mostly due to the concerns for high morbidity and mortality rates. The survival after SVC resection has been studied in several articles.[122,149-151] The 5-year OS with SVC resection was reported between 45% and 58.1%, with a complication rate of 11.1% to 65%.[149-154]

Infiltration of the SVC is a common occurrence in TNM stage III to IVA thymic tumors. The extent of SVC resection may range from partial resection with primary repair to patch reconstruction and tube interposition graft. The safety, techniques, and long-term outcomes of SVC resection for thymic tumors have long been a contentious topic of discussion. Most of the experiences are retrospective reviews describing progression-free survival and OS. Two series reported a total of 14 and 29 patients who underwent surgery for Masaoka stages III-IVA.[122,152] Presence of a thymic carcinoma and SVC resection were reported to be adverse prognostic factors.[152] The median OS and progression-free survival of all SVC-resected patients were 50 months (range, 5-207 months) and 31 months (range, 5-151 months), respectively, in 1 study.[152] Another study reported median OS and disease-free survival to be 39 and 30 months, respectively.[122] The 30- and 90-day mortality rates were 3.4% and 10.3% in that study.[122]

Both studies confirmed that SVC resection and reconstruction in Masaoka stage III and IVA thymic cancers could be performed with acceptable morbidity and mortality. Stage IVA patients with SVC involvement can be treated with similar results as stage III patients. As discussed previously, multimodality treatment should be discussed before resection.[122]

Locally advanced thymic tumors invading the heart or great vessels are generally not considered for surgery.[153] Limited presentations identified in the literature with cardiopulmonary bypass support include only case reports or case series.[154-157] Locally advanced thymic cancers involving the aorta, arch vessels, or intracardiac extension should only be considered at experienced thoracic surgery centers. Neoadjuvant treatment should also be considered in these circumstances.[158]

D. SURGICAL CONSIDERATIONS FOR TNM STAGE IVA DISEASE. Because complete resection is the most important prognostic factor for thymic malignancies, surgical resection remains the mainstay of treatment for thymoma, even in the setting of pleural metastases at presentation.[159] Despite the presence of metastatic disease, thymoma with pleural dissemination remains primarily a surgical disease, unless the patient is otherwise unfit for surgery from a medical standpoint. The metastatic pattern of thymoma preferentially results in disease that remains confined to the chest, most commonly as pleural metastases, which presents an opportunity for local control with surgical resection. Nodal metastases in thymoma are rare, but when present, can also potentially be resected through a lymphadenectomy.[160] Pleural metastases frequently present as individual deposits, and pleurectomy is often feasible, allowing for resection of all the lesions. Metastases on the visceral pleura may be excised sharply with visceral pleurectomy or by wedge resection, depending on the extent of the disease.

Although all gross disease should be completely resected, whether total or complete pleurectomy of the entire pleura (including normal unaffected pleura) is beneficial is unclear, and no data exist to support that strategy. In situations where the disease burden is greater, with bulky, confluent pleural disease encasing the lung, extrapleural pneumonectomy may be considered in the appropriate patient.[74]

The presence of metastatic disease along with the extent of the primary tumor may raise consideration for a multimodality approach incorporating neoadjuvant therapy to decrease the tumor burden, potentially improve resectability, and reduce the risk of recurrence. Because thymomas tend to be fairly chemosensitive, response rates of up to 100% have been observed.[161,162] There are no randomized trials to validate this strategy; however, several series have demonstrated the feasibility and safety of this approach, with good long-term outcomes.[7,74,161-164] Although causation cannot be proven, long-term outcomes collectively suggesting that more than half of all patients with pleural disease undergoing multimodality therapy may live more than 10 years is encouraging.[7,74,161-164]

The extent of pleural disease may make anterior approach a challenge if the primary tumor in the mediastinum mandates a transsternal approach, either through a median sternotomy or a hemiclamshell incision. In these settings, it may be helpful to consider approaching the pleural disease separately from a lateral approach through a separate thoracotomy, particularly if there is extensive disease around the diaphragm or a major diaphragm resection and reconstruction is required.[74] This may facilitate a thorough exploration of the entire pleural space and provide appropriate exposure to the deep recesses of the costophrenic sulcus. This is particularly relevant in situations where extrapleural pneumonectomy is required.

Thymoma can demonstrate an indolent behavior that makes aggressive local therapy relevant oncologically. Extrapleural pneumonectomy (EPP) has been used for selected thymoma patients since the 1990s generally as part of a multimodality treatment scheme for de novo or disease recurrence patients.[74] The operative technique of EPP for this disease and perioperative management have been described.[72,73,165] A cisplatin-based induction therapy approach (cisplatin, doxorubicin, and methylprednisolone [CAMP]) and adjuvant hemithoracic radiotherapy have been described in small series (4-10 patients), which have achieved 60% to 83% medium-term disease-free survivals with low operative mortality rates.[74,145,166-168]

To achieve a larger sample of patients, a European consortium accumulated 40 patients (of which approximately two-thirds were de novo cases) who achieved a 60% 10-year survival after EPP.[169] A recent review analyzed that consortium trial and others to conclude aggressive operations improve survival; however, they also noted that

long-term recurrences will develop in half of the patients and that 25% of these will be distant.[170]

Intraoperative Adjuvant Therapies. In 2001, 4 of 15 patients were reported alive without disease after pleural cytoreductive surgery (including 1 EPP), followed by hyperthermic pleural perfusion of cisplatin.[171] Since that time, investigators have reported series (ranging from 4-40 hyperthermic perfusion cases) using cisplatin alone, cisplatin with agents such as mitomycin, and at 1 center povidone-iodine.[57,172-176] Like EPP, medium-term 5-year survival results were influenced by presentation and histology (81% de novo, 67% recurrence, and 0% thymic carcinoma).[177] Pleural photodynamic therapy also achieved a 50% survival without recurrence in 8 patients.[177] Authors of a 2021 review noted their own 10-year 77% OS rate using cisplatin/epirubicin.[148] However, 40 cases published the following year showed 5-year survival of 86%, falling to 40% at 10 years, possibly because only 1 of 3 were de novo presentations.[178] Like EPP, cytoreduction surgery plus intraoperative adjuvant therapy seems to improve disease-free survival, although recurrent disease is common. A recent collective review cites a 31% recurrence rate after hyperthermic intrathoracic chemotherapy (HITHOC) occurring at 68 months on average.[179] Given the potential for better local control, centers continue to refine the regional perfusion methods.[180]

Consensus statement 12: In patients with acceptable surgical risk, multimodality therapy with macroscopic complete resection is recommended for synchronous or metachronous pleural and pericardial metastases confined to a single hemithorax. For pleural disease, pleurectomy/decortication is preferred over extrapleural pneumonectomy when feasible.

- *Strongly agree, 35.7%*
- *Agree, 57.1%*
- *Neither agree nor disagree, 7.1%*
- *Disagree, 0%*
- *Strongly disagree, 0%*

Consensus statement 13: For pleural dissemination, selective pleurectomy of metastatic lesions may be considered if complete macroscopic resection of all disease can reasonably be expected. Radical or total pleurectomy is not necessary if complete macroscopic resection can be achieved with selective pleurectomy.

- *Strongly agree, 53.8%*
- *Agree, 46.2%*
- *Neither agree nor disagree, 0%*
- *Disagree, 0%*
- *Strongly disagree, 0%*
- *Abstain, 1*

Consensus statement 14: For TNM stage IVA thymic malignancies with pleural metastases, neoadjuvant chemotherapy should be considered prior to resection.

- *Strongly agree, 50%*
- *Agree, 42.9%*
- *Neither agree nor disagree, 7.1%*
- *Disagree, 0%*
- *Strongly disagree, 0%*

Consensus statement 15: Intraoperative adjuvant treatments for microscopic residual disease, such as photodynamic therapy or heated intrathoracic chemotherapy, may be considered at experienced centers in patients undergoing resection of disseminated pleural metastases.

- *Strongly agree, 38.5%*
- *Agree, 46.2%*
- *Neither agree nor disagree, 15.4%*
- *Disagree, 0%*
- *Strongly disagree, 0%*
- *Abstain, 1*

IV. ADJUVANT THERAPY AND SURVEILLANCE

A. SURGEON'S ROLE IN PATHOLOGIC EVALUATION AND INTERPRETATION. In 2011, the ITMIG published policies and procedures for surgeons and pathologists on processing and evaluating thymic malignancy specimens.[78,181] Intraoperative specimen handling, marking, and orientation, along with lymph node evaluation and frozen section analysis, were included. A "no touch" technique should be used during dissection because direct manipulation of the tumor may cause a capsular tear leading to a potential increased risk of pleural dissemination.[181] The thymoma should be resected en bloc with the thymus gland, and any areas of surgical tissue disruption should be communicated to the pathologist as areas of nonconcern. The specimen should be extracted in a plastic bag to minimize the risk of tumor seeding and through an incision large enough to avoid disrupting the capsule.[181]

Throughout the operation, the surgeon is advised to mark margins of concern on both the specimen (suture) and the patient (clip).[78] It is advisable to place an adequately deep suture at these areas on

the specimen such that it will not be dislodged during specimen handling. These areas are best assessed on thorough pathologic evaluation because frozen section analysis for thymoma is fraught with inaccuracy given the frequency of false-positive and false-negative results.[78] Accordingly, surgeons must rely on their clinical judgment. It is recommended that surgeons mark standard areas of the specimen, including the surface adjacent to the pericardium and innominate vein, and for larger tumors also include the SVC as well as the right and left pleural surfaces.[78]

The surgeon is responsible for accurate orientation of the specimen. It is advisable to orient the specimen on a mediastinal board, which is simply a diagram of the mediastinum.[78] This allows for the demonstration of anatomic relationships between the thymus and the remaining structures. The specimen is handed off to the pathologist, who can use this strategy to understand the orientation of the specimen in vivo and identify the margins of concern marked with sutures. The surgeon and pathologist should discuss completeness of resection and review any margins of concern.[182]

Lastly, detailed documentation by the surgeon is important.[78] The operative note should include the extent of resection, lymph node assessment, and whether the pleural and pericardial spaces were examined for metastases. It should include whether gross tumor was left behind (R2 resection) and if so, to accurately document the location. It should also document any additional mediastinal structures resected, margins of concern, and how they were marked on the specimen and in the patient.

Consensus statement 16: Orientation and labeling of resected specimens by the surgeon is recommended to improve pathologic interpretation of surgical margins.

- *Strongly agree, 71.4%*
- *Agree, 28.6%*
- *Neither agree nor disagree, 0%*
- *Disagree, 0%*
- *Strongly disagree, 0%*

B. PORT FOR THYMOMA. PORT is important in the management of patients diagnosed with thymoma. The level of evidence for PORT has been low due to low thymoma incidence and the lack of randomized trials. Indications for PORT have been based on retrospective analyses including large national and international databases that cover long time spans and are affected by the use of different thymoma staging systems and selection bias, lack of detail in recorded pathology and treatment information, and ongoing technical developments in treatment modalities, including radiation oncology.

Although PORT has typically been recommended for incompletely resected thymomas and has been considered for completely resected higher-stage thymomas (https://www.nccn.org/; https://www.cancer.gov/types/thymoma),[2] the role of PORT, particularly for early stages of completely resected thymomas, has not been clear. Several large retrospective analyses have recently focused on PORT after R0 resection.

A meta-analysis by Tateishi and associates[183] evaluated 5 studies that compared surgery alone with surgery plus PORT for completely resected Masaoka/modified Masaoka stage II and III thymoma treated between 1982 and 2012. A total of 4746 patients were included, of which 2408 (50.7%) received PORT.[134,184-187] PORT resulted in significantly longer OS compared with surgery alone (hazard ratio [HR], 0.68; 95% CI, 0.57-0.83; $P < .001$). Subgroup analyses for stage II disease (HR, 0.63; 95% CI, 0.44-0.91; $P = .01$) and stage III disease (HR, 0.72; 95% CI, 0.55-0.95; $P = .02$) also showed improved OS with PORT. Although this meta-analysis suggests the use of PORT in resected stage II and III thymoma, not all studies included in this meta-analysis support a role for PORT. For example, the analysis of 1110 patients from the Japanese Association for Research on the Thymus (JART) database observed that PORT was not associated with improved recurrence-free survival or OS ($P = .35$).[186]

An analysis of the National Cancer Database studied 3031 patients diagnosed between 2004 and 2012 with modified Masaoka stage I/IIA, IIB, III, and IV thymoma.[185] There were 1880 patients (62%) with negative resection margins. After propensity score matching, PORT compared with surgery alone resulted in improved OS (HR, 0.64; 95% CI, 0.52-0.79; $P < .001$) and significantly longer survival in patients with histologic subtypes A and B, stage IIB or III disease, and positive margins, but not in stage I/IIA disease (HR, 0.76; 95% CI, 0.51-1.11; $P = 0.156$). PORT had a borderline significant effect for stage IV disease (HR, 0.64; 95% CI, 0.39-1.07; $P = 0.089$). No differentiation was made between complete and incomplete thymoma resection. However, in a subgroup analysis for stage IIB, PORT improved OS after complete resection (HR, 0.52; 95% CI, 0.28-0.96; $P = .037$).[185]

A retrospective analysis of the Surveillance, Epidemiology, and End Results (SEER) database included 2138 thymoma patients diagnosed between 2010 and 2019.[188] Of these, 909 (35.5%), 1181 (46.2%), 394 (15.4%), and 74 patients (2.9%) were classified as modified Masaoka stage I-IIA, IIB, III-IV and unknown, respectively. Total or radical resection was performed in 1247 (58.3%), 798 (37.3%) underwent local excision/partial resection, and 93 (4.4%) underwent debulking or other not further specified surgical procedures. PORT was delivered in 963 patients (45.0%). The average follow-up was 94.1 months.

Propensity score matching was performed to adjust for potential selection bias between the PORT and non-PORT groups. Multivariate analysis documented PORT as an independent prognostic factor for OS ($P < .001$) and cancer-specific survival (CSS; $P = .001$). Subgroup analysis showed that for modified Masaoka stage IIB and III/IV, PORT was a favorable factor for OS (IIB, $P < .001$; III-IV, $P = .005$) and CSS (IIB, $P = .015$; III-IV, $P = .002$). However, for patients with stage I/IIA thymoma, PORT had no benefit on OS ($P = .415$) and was an unfavorable factor for CSS ($P = .042$).[188] Whether the observed outcomes in this study pertain in the same way to completely and incompletely resected thymomas is unclear.

From the these studies, PORT is recommended for incompletely resected thymomas and for completely resected modified Masaoka stage IIB, III, and IV disease (AJCC/UICC TNM stage I with invasion into the mediastinal fat or pleura, stage II, III and IV). The benefit of PORT for completely resected modified Masaoka stage IIA disease (microscopic transcapsular invasion, AJCC/UICC TNM stage I) is less clear. Studies combining Masaoka and modified Masaoka staging report a survival benefit for PORT in completely resected stage II thymoma but did not differentiate between IIA and IIB disease.[183,187] Newer data using the modified Masaoka staging did not identify a benefit[185] or observed that PORT was even detrimental.[188]

Typical recommendations for radiation doses range between 45 and 50.4 Gy for R0, ≥54 Gy for R1, and 60 to 70 Gy for R2 resected tumors delivered in daily doses of 1.8 to 2.0 Gy over 5 to 7 weeks. Although these dose recommendations are based on older data and simple treatment methods, a limited number of recent reports that included modern PORT techniques support the these recommendations.[184,189,190] Given the longevity after a thymoma diagnosis, PORT-related adverse effects are a concern. Modern treatment techniques are recommended to reduce adverse effects, including pneumonitis, esophagitis, and cardiovascular toxicities.[184,191-193] Proton therapy can be considered to reduce sequelae of PORT, including the risk for development of secondary malignancies.[194-196]

C. ROLE OF ADJUVANT SYSTEMIC THERAPY AFTER RESECTION. Thymoma is known to be a chemotherapy-sensitive disease, with high response rates[197] and evidence of downstaging in the neoadjuvant setting.[198,199] A theoretical goal of chemotherapy in the adjuvant setting is to address micrometastatic disease. A single-institution study showed that perioperative chemotherapy was associated with lower incidence of distant metastases on univariate analysis.[200] However, there are no results from randomized control trials of adjuvant chemotherapy vs no adjuvant chemotherapy for patients who have undergone resection for thymoma. Data available on adjuvant chemotherapy are from analyses of single- and multi-institution retrospective databases.[63,69,201-205] These studies have several limitations, including selection bias and heterogeneity of known prognostic factors for thymoma, particularly resection status, stage, and histologic subtype. Rather than defining an indication for use of adjuvant chemotherapy in these studies, the decision to proceed with adjuvant chemotherapy was determined on an individual basis and varied by institutional practice.

Chemotherapy as a solitary adjuvant approach comprises a small proportion of the adjuvant approaches examined in many studies.[13,63,134,201-204,206] When adjuvant chemotherapy was administered, it was most often in conjunction with PORT, although the sequence of these therapies was not always clear. In addition, some studies include a proportion of patients who have also undergone neoadjuvant chemotherapy.[13,134,201] The details of the adjuvant chemotherapy regimen and number of cycles was also not consistently reported. When reported, regimens used were platinum-based, with or without anthracycline.[13,134,202,204] Given the multiple treatment variables in perioperative management, the direct contribution of adjuvant chemotherapy to patient outcomes is not clear.

In a recent updated systematic review and meta-analysis of the Program in Evidence-Based Care, the literature search spanned from 2009 to 2021, and 2 studies comparing adjuvant

chemotherapy vs no adjuvant chemotherapy for thymoma were included.[69,201,202] This analysis did not support use of adjuvant chemotherapy (HR for OS, 1.82; 95% CI, 0.56-5.94; $P = .32$), and the certainty of the estimate was low.[207] The lack of demonstrable clinical benefit may be related to selection bias, where only patients with poor prognostic factors were offered adjuvant chemotherapy.[69,201,202,206,208,209] More limited series have shown OS benefit with adjuvant therapy; however, the impact from adjuvant chemotherapy cannot necessarily be separated from adjuvant radiotherapy.[13,134]

Given the good survival of patients with resected thymoma,[210] insufficient data on the efficacy of adjuvant chemotherapy, and toxicities of chemotherapy,[69] adjuvant chemotherapy is not recommended after R0 or microscopic R1 resection. Adjuvant chemotherapy may have a role after macroscopic R2 resection, although this is based on data pertaining to the efficacy of definitive chemotherapy and radiotherapy for unresectable thymoma.[14,211-214] There is an ongoing randomized phase III study comparing adjuvant radiotherapy with or without chemotherapy in patients with incompletely resected thymic epithelial tumors (Adjuvant Treatment for Incomplete Resection Thymoma or Thymic Carcinoma, NCT02633514). Despite novel therapies emerging in the advanced setting, there are no data to support use of small molecule agents[215,216] or immunotherapy[217,218] in the adjuvant setting, with the latter being hazardous in this population due to the high rate of severe immune-related adverse events.

Consensus statement 17: After R0 resection, postoperative radiotherapy is recommended for TNM stage II and III thymoma. Postoperative radiotherapy may be considered for completely resected TNM stage I disease with invasion into mediastinal fat or pleura. Postoperative radiotherapy is not recommended for completely resected TNM stage I disease without macroscopic transcapsular invasion.

- *Strongly agree, 50%*
- *Agree, 50%*
- *Neither agree nor disagree, 0%*
- *Disagree, 0%*
- *Strongly disagree, 0%*

Consensus statement 18: After R0 resection for TNM stage I, II, and III thymoma, adjuvant chemotherapy is not recommended.

- *Strongly agree, 64.3%*
- *Agree, 35.7%*
- *Neither agree nor disagree, 0%*
- *Disagree, 0%*
- *Strongly disagree, 0%*

Consensus statement 19: After R1 resection, postoperative radiotherapy is recommended, whereas adjuvant chemotherapy is not.

- *Strongly agree, 50%*
- *Agree, 50%*
- *Neither agree nor disagree, 0%*
- *Disagree, 0%*
- *Strongly disagree, 0%*

Consensus statement 20: After R2 resection, postoperative radiotherapy is recommended, whereas selective use of adjuvant chemotherapy may be considered.

- *Strongly agree, 50%*
- *Agree, 50%*
- *Neither agree nor disagree, 0%*
- *Disagree, 0%*
- *Strongly disagree, 0%*

Consensus statement 21: For TNM stage IV disease, postoperative radiotherapy should be considered on an individualized basis.

- *Strongly agree, 42.9%*
- *Agree, 50%*
- *Neither agree nor disagree, 7.1%*
- *Disagree, 0%*
- *Strongly disagree, 0%*

D. ROLE OF SURGERY IN RECURRENT DISEASE. Thymoma recurrence after curative treatment is uncommon. However, this is highly dependent on histologic subtype and stage, with recurrence rates ranging from 10% to 29%.[219] Disease-free survival rates have been reported as low as 28% for World Health Organization (WHO) type C thymoma.[220] Treatment of recurrent disease is dependent on the site of recurrence and extent of disease. Several case series have reported results of surgical resection for recurrent disease with acceptable results and 10-year survival rates ranging from 24% to 70%.[219]

Recurrence patterns have been previously classified by ITMIG as local (mediastinum), regional (pleural cavity), or distant.[221] For local or regional recurrences, surgical resection may be reasonable in appropriately selected cases. There are no randomized controlled trials comparing surgical and nonsurgical therapies for recurrent disease. All available studies consist of

retrospective case series with relatively low sample sizes, consistent with level III evidence. A meta-analysis from 2014 identified 11 studies retrospectively comparing surgical with nonsurgical therapies. Of these, 8 reported 5-year OS results. When pooled, 5-year OS after recurrence was 70.9% ± 16.2% in patients treated with repeat resection and only 29.6% ± 21.9% when treated nonsurgically. The 10-year OS was reported in 5 studies and was 49.6% ± 27.4% when treated surgically and 18.4% ± 26.0% when treated nonsurgically.[219] The combined 5-year OS risk difference for survival after recurrence was 0.44 in favor of surgically managed disease. Similar results were seen when comparing 5- and 10-year OS results after the initial thymectomy. Overall, complete resection was achieved in 67.2% ± 20.4% of patients (ranging from 45% to 91%), and open resection was performed in 94.4% to 100% of the cases reported. Rates of adjuvant and neoadjuvant therapy were quite variable.

In the largest series to date, Chiappetta and associates[222] reported a series of 135 patients undergoing surgery for recurrent thymoma. Of these patients, 80.7% had a complete resection at the second operation. A second recurrence developed in 55% of these repeat resected patients, of whom approximately half were treated with a third surgery. Myasthenia gravis (HR, 0.45; $P = .046$) and longer disease-free interval from initial thymectomy of >36 months (HR, 0.97; $P = .006$) were independently associated with better survival. The 5- and 10-year OS rates in this study were 79.6% and 64.6%, despite more than half of the patients requiring iterative resections. A statistically significant difference was not identified in patients who underwent complete vs incomplete resection ($P = .086$). The authors of this study concluded that iterative surgical resection is a viable option for recurrent disease.

In another retrospective series of 53 patients over 20 years who developed recurrent thymoma after initial resection, Fiorelli and associates[223] reported overall 5- and 10-year survival rates of 52% and 32%, respectively. Of these 53 patients, 38 underwent surgical resection, with R0 resection achieved in 32, and gross debulking only in the remaining 6 due to extent of disease found at the time of surgery. On multivariate analysis, only R0 resection was associated with improved survival (HR, 0.058; $P = .0003$). Similar results were seen from Marulli and associates[224] in a series of 52 patients undergoing repeat resection. This study identified R0 resection, number of metastases, Masaoka stage of the primary tumor, and site of relapse to be independent predictors of survival.

Lucchi and associates[225] reported a series of 20 patients specifically with pleural recurrence after thymectomy who underwent surgical resection. They documented a 5-year survival rate of 43%, with improved survival noted in patients with a single pleural implant compared with multiple implants ($P = .03$). This, again, likely points to the ability to achieve an R0 resection. Of patients treated with surgical resection, 80% received adjuvant chemotherapy. Although this was not associated with improved survival, conclusions are limited by low sample size. Interestingly, 3 patients received HITHOC in this series. A few other series have reported the use of HITHOC for pleural recurrence of thymoma.[171,226] However, the sample sizes in these few series are quite limited, and formal conclusions are not possible at this time.

In summary, there are no prospective or randomized trials that compare surgical with nonsurgical therapy for thymoma recurrence. The existing literature consists of retrospective series with level III evidence. Surgical series show improved disease-free survival and OS in the setting of recurrent thymoma if a complete R0 resection can be achieved. There is scant literature regarding HITHOC, adjuvant, and neoadjuvant therapies in the setting of recurrent disease. Finally, it is reasonable to consider iterative surgical resection for local and regional recurrence, particularly if complete resection can be achieved.

Consensus statement 22: Surgical resection for limited local or regional recurrence after previous thymoma resection is appropriate in acceptable-risk patients if an R0 resection can be achieved.

- *Strongly agree, 50%*
- *Agree, 42.9%*
- *Neither agree nor disagree, 7.1%*
- *Disagree, 0%*
- *Strongly disagree, 0%*

Consensus statement 23: Acceptable-risk patients with extensive but potentially resectable recurrent disease should be considered for multimodal therapy with neoadjuvant chemotherapy, followed by possible surgical resection.

- *Strongly agree, 50%*
- *Agree, 35.7%*
- *Neither agree nor disagree, 14.3%*
- *Disagree, 0%*
- *Strongly disagree, 0%*

E. SURVEILLANCE IMAGING AFTER SURGICAL RESECTION. Excellent long-term survival rates are observed after complete thymoma resection. However, late recurrences have also been reported, with stage and histologic subtype identified as the most significant risk factors for recurrence. Studies examining the optimal interval for surveillance imaging are scant. However, several studies have shown risk of recurrence extends to at least 10 years after resection, depending on the stage. The 10-year disease-free survival rates have been reported as high as 90% to 100% for WHO type A-AB and Masaoka stage I thymoma.[220,227] However, a study from Kondo and associates[220] showed 20-year disease-free survival for type AB thymoma to be 84%. The 10-year disease-free survival rates steadily decreases with advancing stages, and is reported as low as 28% of WHO type C thymoma. Okereke and associates,[163] in a case series of 83 patients who underwent surgical resection of thymoma, reported the 5-year disease-free survival rate of all patients was 97%; however, 10-year disease-free survival was 89%. These studies suggest late thymoma recurrence after 5 years, although not common, is possible at all stages. As a result, National Comprehensive Cancer Network guidelines recommend surveillance imaging and long-term follow-up for at least 10 years for all patients with thymoma undergoing surgical resection.[45] Although the interval for surveillance has not been definitively established, National Comprehensive Cancer Network guidelines recommend imaging at 6-month intervals for the first 2 years, followed by annual scans for the remaining surveillance period. For complete resection of a noninvasive thymoma, 12-month surveillance imaging is considered acceptable during the first 2 years. Although most studies have used WHO and Masaoka staging, these results can be extrapolated to AJCC/UICC staging as well.

The most used methods for surveillance imaging are CT and MRI. Unfortunately, there are no prospective studies of CT imaging compared with MRI after thymoma resection. Kerpel and associates[228] have reported a retrospective series of 22 patients who received both CT and MRI for surveillance imaging after surgical resection of all thymic epithelial malignancy. Of those, 6 patients had recurrent disease. CT and MRI performed equally well in identifying pleural spread, lymphadenopathy, and pulmonary metastases. MRI identified invasion of the bone and thecal sac earlier. MRI was more effective in distinguishing between benign cysts and fluid compared with CT.[228] Therefore, due to lower costs and greater access, CT with intravenous contrast is recommended for surveillance purposes. For patients who cannot receive intravenous contrast or young patients who wish to avoid radiation, MRI provides a reasonable alternative.

Consensus statement 24: After thymoma resection, surveillance imaging with chest computed tomography is recommended at 6-month intervals for 2 years, followed annually thereafter for a minimum of 10 years. For completely resected TNM stage I disease with no transcapsular invasion (T1a tumors), surveillance imaging at 12-month intervals rather than 6-month intervals can be considered.

- *Strongly agree, 64.3%*
- *Agree, 35.7%*
- *Neither agree nor disagree, 0%*
- *Disagree, 0%*
- *Strongly disagree, 0%*

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