The Management of Thymoma: A Systematic Review and Practice Guideline

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Introduction: Thymoma is a rare tumor for which there is little randomized evidence to guide treatment. Because of the lack of high-quality evidence, a formal consensus-based approach was used to develop recommendations on treatment.

Methods: A systematic refview of the literature was performed. Recommendations were formed from available evidence and developed through a two-round modified Delphi consensus approach.

Results: The treatment recommendations are summarized as follows: Stage I—complete resection of the entire thymus without neoadjuvant or adjuvant therapy. Stage II—complete resection of the entire thymus with consideration of adjuvant radiation for high-risk tumors. Stage IIIA—surgery either initially or after neoadjuvant therapy, or surgery followed by adjuvant therapy. Stage IIIB—treatment may include a combination of chemotherapy, radiation, and/or surgery, or if technically possible, surgery in combination with chemoradiotherapy (concurrent cisplatin based). For bulky tumors, consideration should be given to sequential chemotherapy followed by radiation. Stage IVA—as per stage III, with surgery only if metastases can be resected. Stage IVB—treatment on an individual case basis (no generic recommendations). Recurrent disease—consider surgery, radiation, and/or chemoradiation. Chemoradiation should be considered in all medically inoperable and technically inoperable patients.

Conclusion: Consensus was achieved on these recommendations, which serve to provide practical guidance to the physician treating this rare disease.

Key Words: Thymoma, Lung, Systematic review, Consensus.

(*J Thorac Oncol.* 2009;4: 911–919)

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Disclosure: The authors declare no conflicts of interest.

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ISSN: 1556-0864/09/0407-0911

Thymoma is a neoplasm of the thymus that originates in the gland's epithelial tissue. The incidence of thymoma in the United States is approximately 0.15 per 100,000 person-years.[1] Thymomas are typically slow-growing tumors that spread by local extension. Metastases are usually confined to the pleura, pericardium, or diaphragm, whereas extrathoracic metastases are uncommon.[2,3] Thymomas have a tendency for late recurrence, even after complete resection.[4,5]

Histopathologically, thymomas are primary tumors of thymic epithelial cells. Thymic carcinoids and thymic carcinomas are also tumors of thymic epithelial cells, but thymic carcinoids are histopathologically and clinically quite different from thymomas.[6–8] The distinction between thymomas and thymic carcinomas is not as clear, because thymic carcinomas have malignant cytologic features, whereas thymomas are generally considered cytologically benign.[9,10] Studies have demonstrated a markedly decreased survival for thymic carcinoma compared with thymoma.[11–16] Thymic carcinoma may, therefore, be treated as a distinct pathologic and prognostic entity.

One of the earlier classification systems used for thymomas was based on the predominant cell type—lymphocytic, epithelial, mixed epithelial, and spindle cell types.[17] In 1999, the World Health Organization (WHO) adopted a pathologic classification system (Table 1) that takes into account both histologic and morphologic features. Type A tumors consist of neoplastic oval or spindle-shaped epithelial cells without atypia or lymphocytes (Type AB has foci of lymphocytes). Type B tumors are characterized by plump epithelial cells, and the subtypes have increasing proportions of epithelial cells and atypia. Type C tumors are thymic carcinomas. Detterbeck[18] conducted a systematic review of the literature and reported on the prognostic value of the WHO classification system. Some of the key findings from this review concerning the incidence and 10-year survival of thymoma by histologic types are provided in Table 1.

The tumor, node, metastasis staging system is not particularly useful for thymomas as most patients do not have nodal disease or metastases, and, typically, only the extent of the primary tumor is relevant. The widely used staging classification developed by Masaoka et al.[19] in 1981 describes thymomas in terms of the local extension of the tumor. There are four clinical stages, as shown in Table 2. This staging system has been shown to correlate well with survival in

TABLE 1. World Health Organization (WHO) Pathologic Classification of Thymoma

WHO Type	Histologic Description	Incidence[a] (%)	10-Year Survival[b] (%)
A	Medullary thymoma	9	97
AB	Mixed thymoma	24	95
B1	Predominantly cortical thymoma	13	92
B2	Cortical thymoma	24	81
B3	Well-differentiated thymic carcinoma	15	62
C	Thymic carcinoma	15	29

[a] The incidence of histologic classes of thymoma were reported in 11 retrospective studies contained in MEDLINE between January 1999 and April 2005; the average percentages across these studies are reported.

[b] Ten-year thymoma-specific survival was reported in nine retrospective studies by histologic class; values are average percentages of these studies.

TABLE 2. Masaoka Clinical Staging of Thymoma

Stage	Diagnostic Criteria
I	Macro- and microscopically completely encapsulated (tumor invading into but not through the capsule is included)
II	A. Microscopic transcapsular invasion
	B. Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium
III	Macroscopic invasion into neighboring organs (i.e., pericardium, great vessels, or lung)
	A. Without invasion of great vessels
	B. With invasion of great vessels
IV	A. Pleural or pericardial dissemination
	B. Lymphogenous or hematogenous metastases

several studies.[20–27] The Masaoka staging system is a particularly useful tool in studies of thymoma, given the rarity and histopathologic heterogeneity of this tumor. Investigators have begun to describe the molecular changes that confer differing degrees of invasiveness and their relationship to the Masaoka staging system.[28–30]

Patients with early-stage thymoma are often asymptomatic, and the tumor is detected incidentally on a chest x-ray or computed tomography (CT) scan. Patients with myasthenia gravis routinely have chest CT scans as part of their workup because of the high association with thymoma. More advanced thymoma present with symptoms related to the involvement of local structures. The most common presenting symptoms for thymomas are dyspnea, chest pain, cough, and symptoms of myasthenia gravis.[31–34] Superior vena cava syndrome is not an unusual presentation for the patient with stage III or stage IV thymoma.[35,36] In addition to myasthenia gravis, thymomas are frequently associated with other paraneoplastic phenomena, and consequently can have quite varied presentations.[37–39]

The treatment of thymoma may involve surgery, radiation, and chemotherapy. These modalities may be combined; the combination largely being determined by the stage of the disease. Although there have been advances in these modalities of care in the last two decades, there is little definitive evidence to inform best clinical practice. Nonetheless, the community of clinicians in Ontario expressed the need for guidance in this area.

This report was developed by the Lung Cancer Disease Site Group (DSG) through Cancer Care Ontario's Program in Evidence-Based Care, which regularly develops practice guidelines that are informed by systematic literature reviews and syntheses of published clinical evidence. For this topic, little high-quality evidence was available, and a formal consensus-based methodology was used to supplement the available evidentiary base, thereby allowing the development of reasonable recommendations for the management of thymoma.

SYSTEMATIC REVIEW

Methods

A systematic review of the literature was conducted on the treatment of thymoma. Key research questions and clinical outcomes were established a priori by a working group of clinicians, and a systematic search strategy was developed and conducted in consultation with a research methodologist. Precise inclusion and exclusion criteria were established and applied to the retrieved literature and data were extracted from the selected publications by a methodologist. The data were double checked by a second reviewer for accuracy and summarized in table format.

Literature Search Strategy

The MEDLINE (Ovid) (1996 through June 2006) database was searched for relevant published systematic reviews and primary studies. Search terms included "thymoma" or "thymic neoplasms."

Study Selection Criteria

Primary research studies of any design type (e.g., randomized controlled trial [RCT], prospective study, retrospective chart audit) were included in this systematic review if they were prospective reports with greater than 10 patients, or retrospective studies with 100 or more patients; published in English; reported data on patients with thymoma, and reported data with single or multimodality treatment strategies involving surgery, chemotherapy, or radiotherapy and clinical outcomes for treated patients, including response, survival, and toxicity rates. Studies focusing on myasthenia gravis or dealing solely with thymic carcinoids or thymic carcinoma, and trials that pooled survival data of patients with thymoma and thymic carcinoma or other mediastinal tumors were excluded. Letters, reviews, and editorials reporting trial data were also not considered.

Synthesizing the Evidence

The relevant outcome data from the selected studies were tabulated in tables and arranged by study design and modality for analysis. Most of the included studies were retrospective chart audits of patients receiving different treatments for various stages of disease. The few available prospective trials included patients with advanced stage (III/IV) thymoma treated with chemotherapy and/or radiotherapy and

used a number of different treatment approaches. Because of this heterogeneity, the data were not appropriate for statistical pooling.

Consensus-Based Guideline Development Process

Draft recommendations were developed by a working group comprised members of the Lung DSG. The draft recommendations were constructed from the evidence contained in the systematic review above and the clinical experience of members. To obtain consensus on the draft recommendations, clinical experts (i.e., oncologists, pathologists, and thoracic surgeons) from across Canada who treat thymoma participated in a two-round modified Delphi approach.[40,41] The modified Delphi process was chosen because it provides a formal process for synthesizing expert opinion; the results are anonymous so the private opinion of each participant is incorporated; it provides for an explicit method of aggregating results; and in-person meetings are not required. The clinical experts were mailed a report consisting of the systematic review and practice guideline, along with a questionnaire. In the questionnaire, respondents were asked to rate their agreement with each recommendation on a seven-point likert scale, ranging from "strongly agree" to "strongly disagree." The draft recommendations were modified in response to the results of this first consensus round. In the second consensus round, the original and modified recommendations, and a questionnaire were mailed to respondents. Respondents were asked to rate their preference for both the original recommendation and the modified recommendation. If more than 75% of responses were rated as "strongly agree" or "agree," the recommendation was considered to have attained a consensus of "strong agreement." If 66 to 75% of responses were rated as "strongly agree," then the consensus was considered to be "agreement." If more than 50% of responses were rated as "strongly disagree" or "disagree," then the consensus was considered to be "disagreement." In all other cases, the consensus was considered to be "equivocal," with no clear endorsement or rejection of the recommendation. The complete methods of the consensus process are published elsewhere. The resulting clinical practice guideline was reviewed and approved by the Program in Evidence-Based Care Report Approval Panel.

RESULTS

Literature Search Results

The literature search retrieved 215 unique journal publications from MEDLINE. After filtering the abstracts according to the selection criteria, 13 studies met the inclusion criteria, and these publications were retrieved for data extraction. No systematic reviews or evidence-based practice guidelines were identified. Five studies of surgery as primary treatment were eligible for inclusion and included a single RCT, three retrospective case reports (with sample sizes ranging from 140 to 370), and one survey. Nine prospective studies of chemotherapy (single modality $n = 5$, multimodality $n = 3$) or radiotherapy ($n = 1$) were eligible for inclusion and had sample sizes ranging from 16 to 38 patients.

Outcomes

Surgery as Primary Treatment in Multimodality Strategies for Thymoma

One small RCT ($n = 29$) involving completely resected stage I thymoma randomized patients to surgery alone ($n = 13$) or to surgery followed by adjuvant radiation ($n = 16$). All patients underwent resection through a median sternotomy. Follow-up ranged from 1 to 15 years. The authors found no difference in 5 and 10-year survival between the two groups and no recurrence or metastases in either group.[42] The trial had very low statistical power because of its small size; a priori power calculations were not reported by the trial authors.

Three retrospective chart audits[3,26,43] and a survey[44] with greater than 100 patients reported outcomes associated

TABLE 3. Retrospective Evidence of Surgery as Primary Treatment in Multimodality Strategies for Thymoma[a]

		Resections (%)		Overall Survival (%)	
Trial	***N***	**Complete**	**Incomplete**	**5 yr**	**10 yr**
Retrospective chart audits					
Okumura et al.[26]					
Total	194	87	11		
I	78	NR	NR		99
II	94				94
III	56				88
IVA	10				30
IVB	6				0
Murakawa et al.[43]					
Total	140				
I	64			91	80
II	32			97	92
III	28			68	54
IV	16			69	60
Regnard et al.[3]					
Total	370	70	8		67
I	135	NR	NR		
II	70				
III	83				
IV	19				
Survey					
Kondo and Monden[44]					
Total	1093	88	5		
I	522	100	0	100	
II	247	100	0	95	
III	204	63	16	89	
IVA	73			71	
IVB	35			53	

[a] Multimodality therapies included postoperative adjuvant chemotherapy and radiotherapy, varying by stage and study as detailed below.

Okumara et al., 1999—postoperative radiation to mediastinum: all patients 1957–1985; limited to patients with invasive thymoma including stages II, III, IV 1986–1996. Chemotherapy: all stage IV and stage III where resection is incomplete.

Murakawa et al., 2000—postoperative irradiation for stages II, III, and IV.

Regnard et al., 1996—postoperative radiotherapy for invasive thymoma: 13% of stage I, 78% of stage II, and 83% of stage III. For stage IV, 90% had postoperative radiotherapy and/or chemotherapy.

N, number of patients; NR, not reported.

with primary surgical resection of thymoma as part of multimodality treatment strategies, including adjuvant chemotherapy and radiotherapy. A large survey of 185 institutes certified by the Japanese Association for Chest Surgery was reported by Kondo et al.[44] in 2003. Records of 1093 thymoma patients were compiled, and these data were reported by stage and treatment modality.

The stage-specific survival, operative morbidity and mortality, and overall survival for surgical resection from the four studies are shown in Table 3. The studies involve a wide range of treatment approaches, making it difficult to correlate specific multimodality treatment regimens with survival. Five-year overall survival rates were reported by stage. For stage I, 5-year survival ranged from 89 to 100%; for stage II 71 to 97%; for stage III 68 to 89%, and for stage IV, 47 to 69%. Overall, survival rates were quite high for early-stage disease but followed a decreasing survival trend for more advanced disease. Despite reduced survival in advanced disease, maximal debulking surgery seems beneficial, facilitating radiotherapy and thereby improving survival.[45] Ten-year survival rates were somewhat lower and exhibited a similar trend by stage.

Chemotherapy and Radiotherapy in Single and Multimodality Treatment for Advanced Thymoma

Data from the prospective studies of chemotherapy or radiotherapy in the management of advanced thymoma were compiled. Advanced thymoma, as described in these trials, refers to later stage disease, typically stages III and IVA or B. Trials included patients with disease characterized as being locally advanced, invasive, malignant, recurrent, and unresectable.

Neoadjuvant Chemoradiotherapy in Multimodality Treatment

Limited data on the outcomes associated with neoadjuvant chemoradiotherapy in advanced thymoma are available (Table 4). In most studies, sample sizes were too small to permit meaningful statistical comparisons. The three available prospective studies included a total of 61 patients and ranged in sample size from 16 to 23 patients.[46–48] PAC (cyclophosphamide, doxorubicin, cisplatin) was the most commonly used chemotherapy regimen, although one trial investigated ADOC (cisplatin + doxorubicin, vincristine, and cyclophosphamide). The median age of patients ranged from 47 to 55 years. Resections were performed after chemotherapy, with varying degrees of success. Radiotherapy was sequential to chemotherapy in all trials. Follow-up ranged from 14 to 50 months.

Overall response rates ranged from 70 to 81%; complete responses were much less frequent and ranged from 6 to 22%. Five-year survival varied considerably and ranged from 31 to 95%; progression-free survival was substantially lower and ranged from 31 to 77%.

Chemotherapy as a Single Treatment Modality

Limited data on outcomes associated with chemotherapy as the primary therapy in advanced thymoma are available (Table 5). In most studies, there were too few patients enrolled to permit meaningful statistical comparisons. The five available prospective studies included a total of 111 patients, and ranged in sample size from 13 to 38 patients.[49–53] Chemotherapy regimens varied among the trials, and included octreotide, cisplatin, etoposide, ifosfamide, and others. In one trial,[50] all patients enrolled were refractory to at least one prior chemotherapy regimen.

Overall response rates ranged from 32 to 56%, but complete responses were less frequent and ranged from 0 to 38%. Overall 2-year survival varied considerably and ranged from 30 to 79%; progression-free survival was reported less frequently but was generally lower, with rates ranging from 13 to 56%.

Radiotherapy as a Single Treatment Modality

Only one prospective trial ($n = 25$) of single modality radiotherapy in advanced thymoma was retrieved[54] (Table 6). All patients had malignant invasive stage III thymoma, and the authors did not report any other therapy being prescribed. The mean radiation dose was 46.36 Gy (range, 32.4–58 Gy). Fraction sizes ranged from 1.8 to 2.0 Gy per day, 5 days per week. Five-year overall survival and progression-free sur-

TABLE 4. Prospective Trials of Neoadjuvant Chemoradiotherapy in Multimodality Treatment of Advanced Thymoma (Stages III/IV)

Trial	*N* (%III, %IV)[a]	Agents[b]	Surgery R0, R+	RT Dose Gy	FU Median	Response (%) CR	Response (%) ORR	Survival 5-yr, Median OS	Survival 5-yr, Median DFS	Survival 5-yr, Median PFS
Kim et al.[46]	22 (50, 50)	PAC + PDN	16, 5	50–60	50	14	76	95%	NR	77%, NR
Berruti et al.[47]	16 (63, 38)	ADOC	9, NR	45[c]	NR	6	81	31%, 48	31%, 33	NR
Loehrer et al.[48]	23 (96, 4)	PAC	0, 4	54[d]	14, 125[e]	22	70	53%, 93	54%, 93[f]	

[a] Percentage values indicate proportion of sample with stages III and IV disease.
[b] Dosage amounts and schedules varied by study.
[c] Only 13 of 16 patients received radiotherapy.
[d] Radiation provided concurrent with chemotherapy.
[e] Minimum follow-up was 14 mo for ECOG patients and 125 mo for SECSG/SWOG patients.
[f] Five-year failure-free rate, median time-to-treatment failure.

ADOC, cisplatin + doxorubicin, vincristine, cyclophosphamide; CR, number of patients achieving a complete response; dose, refers to the total radiation dose given patients; D/PFS, disease or progression-free survival, percentage values indicate proportion alive without disease progression at 5 yr; numerical values indicate median progression-free survival time in months; ECOG, Eastern Cooperative Oncology Group; FU, follow-up in months; Gy, Gray; *N*, number of evaluable patients; NR, not reported; ORR, CR plus number of patients achieving a partial response; OS, overall survival rate, percentage values indicate proportion alive at follow-up period; numerical values indicate median survival time in months; PAC, cyclophosphamide, doxorubicin, cisplatin; PDN, prednisone; R0, complete resection; R+, residual; RT, radiotherapy; SECSG/SWOG, Southeastern Cancer Study Group/Southwest Oncology Group.

TABLE 5. Prospective Trials of Primary Chemotherapy in Single Modality Treatment of Advanced Thymoma (Stages III/IV)

Trial	*N* (%III, %IV)[a]	Agents[b]	Age[c]	FU	Response (%)		Survival, 2 yr (%)	
					CR	ORR	OS	PFS
Loehrer et al.[49]	38 (5, 89)	O, O + PDN	51	~50	5	53	76	13
Palmieri et al.[50]	16[d] (25, 69)	O or L, +PDN	51	43	6[d]	37[d]	~30	~25
Loehrer et al.[51]	28 (21, 78)	*P* + E + I	55	43	0	32	70	NR
Highley et al.[52]	13 (27, 73)	I	48	NR	38	46	73	NR
Giaccone et al.[53]	16 (NR)	*P* + E	45	84	31	56	~79	~56

[a] Percentage values indicate proportion of sample with stages III and IVA and/or IVB disease, where reported.
[b] Dosage amounts and schedules varied by study.
[c] Median age of patients at start of therapy.
[d] This study included only previously treated patients refractory to chemotherapy, nine of which had received prior surgery.
CR, number of patients achieving a complete response; E, etoposide; FU, median duration of follow-up in months; I, ifosfamide; L, lanreotide; *N*, number of evaluable patients; NR, not reported; O, octreotide; *P*, cisplatin; PDN, prednisone; PFS, progression-free survival, percentage values indicate proportion alive without disease progression at 2 yr, numerical values indicate median progression-free survival time in months; ORR, CR plus number of patients achieving a partial response; OS, overall survival rate, percentage values indicate proportion alive at 2 yr.

TABLE 6. Prospective Trials of Primary Radiotherapy Treatment of Advanced Thymoma (Stage III)

Trial	*N*	Dose	Survival (%)		
			OS 5 yr	DFS 5 yr	15% at 5 yr
Sur et al.[54]	25	46.36 Gy (mean)	72	81	15% at 5 yr

DFS, disease-free survival rate; Gy, gray; *N*, number of evaluable patients; OS, overall survival rate.

vival were 72 and 81%, respectively, and recurrence at 5 years was 15%.

DISCUSSION

Over the past 12 years, the Lung DSG has produced 25 evidence-based guidelines on various aspects of lung cancer.[55] The Lung DSG has always placed great emphasis on the results from published RCTs (level 1 evidence) in making its clinical recommendations. This systematic review on thymoma management revealed very little high-quality evidence. The rarity of the disease makes it difficult to conduct randomized trials with adequate sample sizes to detect clinically significant differences in outcome. Because of the interest expressed by clinicians for guidance in this area, the Lung DSG undertook to produce a guideline despite the paucity of high-quality evidence on this topic. For the first time, the Lung DSG used a different approach and employed a formal consensus method. A description of the consensus methods used (a two-round modified Delphi process), the results obtained, and a discussion of the consensus process are presented in a separate manuscript.

Surrogate end points should be used cautiously. The three prospective trials of neoadjuvant chemoradiotherapy in multimodality treatment of advanced thymoma considered tumor response as an outcome. Complete response in these trials was low, but overall survival was relatively high demonstrating a lack of a consistent relationship with survival. Response rates are typically lower in disseminated disease versus locally advanced disease.[56] One trial,[48] which included patients with limited stage disease only, did show a higher response rate.

Although advances in the last two decades have occurred in the treatment of thymoma, there is little definitive evidence to inform best clinical practice. Given the rare nature of these tumors and the multiple acceptable approaches to treatment, it was difficult for the Lung DSG to make definitive recommendations. The current data do not adequately address certain controversial topics, which include: the role of adjuvant treatment in stage II disease; the choice, timing, and sequencing of combined modality therapy (i.e., surgery, radiotherapy, and chemotherapy) in stage III disease; identifying for whom surgery is appropriate, and whether debulking surgery is appropriate in unresectable or disseminated disease as there is limited evidence to refute or support it; and determining the best treatment approach to recurrent disease. At present, there is individual and institutional variation in the timing and sequencing of treatment and what extent of disease is regarded as being resectable. Adjuvant radiation in the treatment of stage II disease remains controversial and some experts may feel that modern evidence may not support the use of radiation in completely resected disease. It is because of such controversies the authors used a consensus approach, and the recommendations are thus those of the majority opinion.

Practice Guideline

The following 40 recommendations for the management of thymoma by surgery, radiotherapy, and systemic therapy were developed through a combination of systematic review of the medical literature and a formal consensus process and are based on the Masaoka staging system.

Consensus Recommendations for the Management of Thymoma

Stage I

Surgery

1. Complete surgical resection of the entire thymus gland, including all mediastinal tissues anterior to the

pericardium, aorta, and superior vena cava from phrenic nerve to phrenic nerve laterally and from the diaphragm inferiorly to the level of the thyroid gland superiorly, including the upper poles of the thymus, is recommended as the standard of care.
2. For resection of thymoma, an open median sternotomy surgical approach is recommended.
3. Minimally invasive approaches (e.g., video-assisted thoracic surgery) are not considered the standard of care and are not recommended at this time.

Radiotherapy

4. Neither postoperative nor neoadjuvant radiotherapy is recommended for stage I disease.

Systemic Therapy

5. Neither postoperative nor neoadjuvant systemic therapy is recommended for stage I disease.

Medically Inoperable Stage I Disease

6. Chemoradiation or radiation alone should be considered for patients who are medically unfit for surgery.

Stage II

Surgery

7. Complete surgical resection (as outlined for stage I) is the usual practice and is the recommended standard of care.
8. For resection of thymoma, an open median sternotomy surgical approach is recommended.
9. Minimally invasive approaches (e.g., video-assisted thoracic surgery) are not considered the standard of care and are not recommended at this time.

Radiotherapy

10. Routine adjuvant radiation is currently not recommended for stage IIA disease. Radiation should be considered in patients with high risk for local recurrence. These risk factors include: invasion through the capsule (stage IIB), close surgical margins, WHO grade B type, and tumor adherent to pericardium.
11. Radiotherapy has risks for acute and long-term toxicity, notably a risk for the development of secondary malignancies[57] and coronary artery disease.[58] Possible risks and benefits need to be discussed with patients, particularly in younger individuals.

Systemic Therapy

12. Neither postoperative nor neoadjuvant systemic therapy is recommended for stage II disease.

Medically Inoperable Stage II Disease

13. Chemoradiation or radiation alone should be considered for patients who are medically unfit for surgery.

Stage III

14. Patients presenting with locally advanced or metastatic disease should be carefully evaluated for multimodality therapy that includes neoadjuvant chemotherapy, surgical resection, or adjuvant postoperative chemoradiotherapy.

Resectable or Potentially Resectable Stage III Disease

Surgery

15. Surgery should be considered for stage IIIA disease either initially or after neoadjuvant therapy, with the aim being complete removal of the tumor with wide surgical margins. Patients with stage IIIB disease should be assessed for surgery after neoadjuvant chemoradiotherapy.
16. If at thoracotomy complete resection is not possible, maximal debulking (with appropriate vascular reconstruction) should be undertaken. Clips should be placed to mark residual tumor to facilitate adjuvant radiation. Neoadjuvant chemoradiation should be considered before surgery if preoperative assessment indicates that complete resection may not be feasible.
17. Bilateral phrenic nerve resection is not recommended because of the severe respiratory morbidity it causes.

Neoadjuvant Radiotherapy and Systemic Therapy

18. Neoadjuvant chemoradiotherapy is commonly used in this setting.
    - The data supporting this standard are not yet established.

19. The optimal neoadjuvant therapy regimen for minimizing operative morbidity and mortality, and maximizing resectability and survival rates is not yet established.
    - Cisplatin-based combination chemotherapy regimens are recommended as reasonable options. Most of the clinical experience with combined modality therapy is with cisplatin and anthracycline combinations.

20. The optimal sequencing of radiotherapy and chemotherapy is not yet established.
    - If treatment volumes are small, concurrent chemoradiotherapy is recommended as a reasonable option.

If the initial tumor volume is considered to be too bulky, sequential therapy, with chemotherapy followed by radiation therapy, is recommended as a reasonable option. Resection may be performed before radiotherapy.

21. The diagnosis of thymoma should be established by either a CT-guided core-needle biopsy or an open surgical biopsy before considering neoadjuvant therapy.

Adjuvant Radiotherapy and Systemic Therapy

22. Adjuvant radiotherapy is commonly used in this setting and is recommended. Adjuvant chemotherapy may be a consideration; however, there is not enough data to routinely recommend adjuvant chemotherapy after complete resection.

Unresectable Stage III Disease

23. Where surgery is inappropriate, chemotherapy concurrent with, or sequential to, radiation therapy is recommended.

24. The definition of unresectable disease is debated, and may vary with surgical expertise, but is generally defined as extensive tumor involving middle mediastinal organs such as the trachea, great arteries, and/or heart that has not responded to cisplatin-based combination chemotherapy. The role of debulking surgery in such situations is controversial.

Stage IVA

25. The recommendations established for stage III disease are applicable to stage IVA disease. The following are notable modifications or exceptions to this:

Resectable or Potentially Resectable Stage IVA Disease

Surgery

26. Surgery should be considered either initially or after neoadjuvant therapy, with the aim being complete resection of the tumor with wide surgical margins. Surgery is recommended only if pleural and pericardial metastases can be resected.

Neoadjuvant Radiotherapy and Systemic Therapy

27. Neoadjuvant chemoradiotherapy is an option in this setting.
28. Cisplatin-based combination chemotherapy regimens are reasonable options.

Adjuvant Radiotherapy and Systemic Therapy

29. Adjuvant chemoradiotherapy is an option.

Unresectable Stage IVA Disease

30. Where surgery is not feasible because of very extensive or technically unresectable pleural or pericardial metastases, chemotherapy is commonly provided. Chemotherapy concurrent with, or sequential to, radiation therapy is also an option. Cisplatin plus anthracycline-containing regimens are the most commonly used first-line chemotherapy. Patients may often respond to multiple sequential therapies with single agents after progression on first-line therapy.
31. In stage IVA, unresectable disease may include extensive bilateral and/or pleural-based disease and pericardial metastases.

Stage IVB

32. These types of thymoma are extremely rare, and generic recommendations are not possible.

Surgery

33. Not applicable.

Radiotherapy

34. Radiotherapy may be appropriate, particularly for life-threatening situations.

Systemic Therapy

35. Cisplatin-based combination chemotherapy is an appropriate option. Cisplatin plus anthracycline-containing regimens are the most commonly used first-line chemotherapy. Patients may often respond to multiple sequential therapies with single agents after progression on first-line therapy.
36. Octreotide, alone, or in combination with a corticosteroid may be a reasonable option for recurrent cases.

Recurrent Disease

Surgery

37. Surgical resection should be considered in patients with a localized recurrence after apparently successful initial therapy. In some patients with stage IV disease, the resection of isolated pleural metastases is an appropriate initial approach. For cases with multiple pleural metastases, chemotherapy, with or without subsequent surgery, is often appropriate.

Radiotherapy

38. Radiotherapy may be appropriate either alone or in combination with chemotherapy.

Systemic Therapy

39. Cisplatin-based chemotherapy may be an appropriate therapy as part of combined chemoradiotherapy.
40. Octreotide, alone, or in combination with a corticosteroid, may be a reasonable option.

ACKNOWLEDGMENTS

The Program in Evidence-Based Care is sponsored by, but editorially independent of, Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care. Please see the Program in Evidence-based Care section of Cancer Care Ontario's Web site for a list of current Disease Site Group members (http://www.cancercare.on.ca/).

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