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Evidence-Based Series Report 7-11- IN REVIEW

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

The Management of Thymoma

C. Falkson, A. Bezjak, G. Darling, R. Gregg, R. Malthaner, D. Maziak, E. Yu, C.A. Smith, S. McNair, Y. Ung, W.K. Evans, and the members of the Lung Disease Site Group

Report Date: September 26, 2008

An assessment conducted in November 2013 placed Evidence-based Series (EBS) 7-11 IN REVIEW. This means that it is undergoing a review for currency and relevance. The Lung Disease Site Group has determined that it is still appropriate for this document to continue to be available while this updating process unfolds.

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Section 1: Guideline Recommendations
Section 2: Evidentiary Base and Consensus Process
Section 3: EBS Development Methods and External Review Process - The Consensus EBS Development Process

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IN REVIEW

Evidence-Based Series Report #7-11: Section 1

The Management of Thymoma: Guideline Recommendations

C. Falkson, A. Bezjak, G. Darling, R. Gregg, R. Malthaner, D. Maziak, E. Yu, C.A. Smith, S. McNair, Y. Ung, W.K. Evans and the members of the Lung Disease Site Group

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IN REVIEW

CLINICAL QUESTION

What is the optimal management of thymoma?

TARGET POPULATION

Adult patients with locally advanced, unresectable, and recurrent thymoma (excluding thymic carcinoma and carcinoids).

RECOMMENDATIONS

The following 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 by members of the Thymoma Consensus Group which includes Thymoma Working Group members, other members of the Provincial Lung Disease Site Group, and other experts from across Canada (see Section 2 for details).

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 [VATS]) 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., VATS) are not considered the standard of care and are not recommended at this time.

Radiotherapy

10. Routine adjuvant radiation is currently not recommended. Radiation should be considered in patients with high risk for local recurrence. These risk factors include invasion through the capsule, close surgical margins, WHO grade B type, and tumour adherent to pericardium.
11. Radiotherapy (RT) has risks for acute and long-term toxicity, notably a risk for the development of secondary malignancies (1) and coronary heart disease (2). 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. For stage IIIA, surgery should be considered either initially or following neoadjuvant therapy, with the aim being complete removal of the tumour with wide surgical margins. In stage IIIB, patients should be assessed for surgery following neoadjuvant chemoradiotherapy.

IN REVIEW

16. If at thoracotomy complete resection is not found to be possible, maximal debulking (with appropriate vascular reconstruction) should be undertaken. Clips should be placed to mark residual tumour for adjuvant radiation. If it is apparent prior to surgery that complete resection may not be feasible, neoadjuvant chemoradiation should be considered prior to surgery.
17. Bilateral phrenic nerve resection is not recommended because of the severe respiratory morbidity that results.

Neoadjuvant Radiotherapy and Systemic Therapy

18. Neoadjuvant chemoradiotherapy is widely used in this setting.
    - The data supporting this standard is 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.
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 tumour 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 prior to radiotherapy.
21. To establish the diagnosis of thymoma, either a computerized tomography (CT) -guided core-needle biopsy or an open surgical biopsy should be performed, prior to considering neoadjuvant therapy.

Adjuvant Radiotherapy and Systemic Therapy

22. Adjuvant radiotherapy is widely used in this setting and is recommended. Adjuvant chemotherapy may be a consideration.

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 tumour involving middle mediastinal organs such as the trachea, great arteries, and/or heart that does not respond to cisplatin-based combination chemotherapy.

Stage IVA

25. The recommendations established for stage III disease are applicable to stage IVA cases as well. 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 following neoadjuvant therapy, with the aim being complete removal of the tumour 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.

IN REVIEW

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 extensive or technically unresectable pleural or pericardial metastases, chemotherapy is commonly provided. Chemotherapy concurrent with, or sequential to, radiation therapy is also an option.
31. In stage IVA, unresectable disease may include extensive bilateral and/or pleural-based disease, pericardial metastases, or extrathoracic 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.
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 either alone or as part of combined chemoradiotherapy.
40. Octreotide, alone or in combination with a corticosteroid, may be a reasonable option.

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IN REVIEW

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IN REVIEW

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2. Adams MJ, Hardenbergh PH, Constine LS, Lipshultz SE. Radiation-associated cardiovascular disease. Crit Rev Oncol Hematol. 2003;45(1):55-75.

IN REVIEW

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Evidence-Based Series Report #7-11: Section 2

The Management of Thymoma: Evidentiary Base and Consensus Process

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CLINICAL QUESTION

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TARGET POPULATION

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INTRODUCTION

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). In Canada in 2001, there were 206 new cases of cancer of the thymus, adrenal, and other rare endocrine gland cancers (International Classification of Diseases [ICD]-10 codes 37, 74, and 75, respectively) (0.69 per 100,000 persons) and 95 deaths (0.32 per 100,000) (2). Thymomas are typically slow-growing tumours that spread by local extension. Metastases are usually confined to the pleura, pericardium, or diaphragm, while extrathoracic metastases are uncommon (3,4). Thymomas have a tendency for late recurrence, even after complete resection (5,6).

Histopathologically, thymomas are primary tumours of thymic epithelial cells. Thymic carcinoids and thymic carcinomas are also tumours of thymic epithelial cells, but thymic carcinoids are histopathologically and clinically quite different from thymomas (7-9). 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 (10,11). Studies have demonstrated a markedly decreased survival for thymic carcinoma compared to thymoma (12-17). 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 (18). 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 tumours consist of neoplastic oval or spindle-shaped epithelial cells without atypia or lymphocytes (Type AB has foci of lymphocytes). Type B tumours are characterized by plump epithelial cells, and the subtypes have increasing proportions of epithelial cells and atypia. Type C tumours are thymic carcinomas. Detterbeck conducted a systematic review of the literature and reported on the prognostic value of the WHO classification system (19). Some of the key findings from this review concerning the incidence and 10-year survival of thymoma by histological types are provided in Table 1.

Table 1. World Health Organization 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	15%	62%
C	carcinoma	15%	29%
	Thymic carcinoma		

[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 9 retrospective studies by histologic type; values are average percentages of these studies.

The TNM 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 tumour is relevant. The widely used staging classification developed by Masaoka et al in 1981 describes thymomas in terms of the local extension of the tumour (20). There are four clinical stages, as shown in Table 2. This staging system has been shown to correlate well with survival in several studies (21-28). The Masaoka staging system is a particularly useful tool in studies of thymoma, given the rarity and histopathologic heterogeneity of this tumour. Investigators have begun to describe the molecular changes that confer differing degrees of invasiveness and their relationship to the Masaoka staging system (29-31).

Table 2. Masaoka clinical staging of thymoma.

Stage	Diagnostic criteria
I	Macro-and microscopically completely encapsulated tumour invading into but not through the capsule.
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 neighbouring 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

Patients with early stage thymoma are often asymptomatic and the tumour 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

IN REVIEW

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 (32-35). Superior vena cava syndrome is not an unusual presentation for the patient with stage III or IV thymoma (36,37). In addition to myasthenia gravis, thymomas are frequently associated with other paraneoplastic phenomena, and consequently can have quite varied presentations (38-40).

The treatment of thymomas may involve surgery, radiation, and chemotherapy. These modalities may be combined; the combination largely being determined by the stage of the disease. While 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 project was undertaken using formal systematic review and consensus methodologies.

This report was developed by the Lung Cancer DSG of Cancer Care Ontario (CCO) to provide guidance to clinicians in the treatment of thymoma. The Program in Evidence-Based Care (PEBC), in conjunction with DSGs, regularly develops practice guidelines that are informed by systematic literature reviews and syntheses of published clinical evidence. For this topic, little 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. In this report, a full description of systematic review methods and results are presented first, then the methods and formal consensus process, followed by a discussion of the final recommendations.

SYSTEMATIC REVIEW

Methods

The evidence-based series (EBS) guidelines developed by CCO's PEBC use the methods of the Practice Guidelines Development Cycle1. The Lung DSG conducted a systematic review of the literature to establish an evidentiary base for the development of clinical practice recommendations for 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 the retrieved literature was filtered using these criteria. Data were extracted from the selected publications, double checked by a second reviewer for accuracy, and summarized in table format.

The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

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." Relevant articles and abstracts were selected and reviewed by a methodologist.

Study Selection Criteria

Studies were included in this systematic review if they were:

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1 Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12.

IN REVIEW

1. Primary research studies of any design type (e.g., randomized controlled trial [RCT], prospective study, retrospective chart audit).
2. Prospective reports with greater than 10 patients, or retrospective studies with 100 or more patients.
3. Published in English.
4. Reported data on patients with thymoma.
5. Reported data with both of the following features:
   (a) Single or multi-modality treatment strategies involving surgery, chemotherapy, or radiotherapy.
   (b) Clinical outcomes for treated patients, including response, survival, and toxicity rates.

Studies were excluded in this systematic review if they were:

1. Studies dealing solely with thymic carcinoids or thymic carcinoma, and trials that pooled survival data of patients with thymoma, thymic carcinoma, or other mediastinal tumours.
2. Studies focusing on myasthenia gravis.
3. Letters, reviews, and editorials reporting trial data.
4. Trials published in a language other than English.

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.

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 a group receiving surgery alone (n=13) or to a group receiving surgery followed by adjuvant radiation (n=16). All patients underwent resection through a median sternotomy. Follow-up ranged from one to 15 years. The authors found no difference in five and 10-year survival between the two groups and no recurrence or metastases in either group (41). The trial had very low statistical power because of its small size; *a priori* power calculations were not reported by the trial authors.

IN REVIEW

Three retrospective chart audits (4,27,42) and a survey (43) with greater than 100 patients reported the outcomes associated 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 in 2003 (43). Records of 1,093 thymoma patients were compiled, and the 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, rates 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 follow a decreasing survival trend for more advanced disease. Ten-year survival rates were somewhat lower and exhibited a similar trend by stage.

Table 3. Retrospective evidence of surgery as primary treatment in multimodality strategies for thymoma. [a]

			Resections		Overall Survival	
Trial		**N**	**Complete**	**Incomplete**	**5-Year**	**10-Year**
Retrospective Chart Audits						
Okumara 1999 (27)	Total	194	87%	11%		
	I	78				99%
	II	94				94%
	III	56	NR	NR		88%
	IVA	10				30%
	IVB	6				0%
Murakawa 2000 (42)	Total	140				
	I	64			91%	80%
	II	32			97%	92%
	III	28			68%	54%
	IV	16			69%	60%
Regnard 1996 (4)	Total	370	70%	8%		67%
	I	135				
	II	70	NR	NR		
	III	83				
	IV	19				
Survey						
Kondo 2003 (43)	Total	1093	88%	5%		
	I	522	100%	0%	100%	
	II	247	100%	0%	95%	
	III	204			89%	
	IVA	73	63%	16%	71%	
	IVB	35			53%	

Notes: NR = not reported.

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

Okumara 1999: Postoperative radiation to mediastinum: all patients 1957-1985; limited to patients with invasive thymoma including stage II, III, IV 1986-1996. Chemotherapy: All stage IV and stage III where resection incomplete.

Murakawa 2000: Postoperative irradiation for stage II, III, IV.

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

IN REVIEW

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 (44-46). PAC (cyclophosphamide, doxorubicin, cisplatin) was the most commonly used chemotherapy regimen, though one trial investigated ADOC (cisplatin+doxorubicin, vincristine, and cyclophosphamide). The median age of patients ranged from 47 to 55 years. Resections were performed following 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 overall survival varied considerably and ranged from 31% to 95%; progression-free survival was substantially lower and ranged from 31% to 77%.

Table 4. Prospective trials of neoadjuvant chemoradiotherapy in multimodality treatment of advanced thymoma (stage III/IV).

Trial	N [a] (%III,%IV)	Agents [b]	Surgery	RTdose Gy,	FU median	Response		Survival 5-yr, median	
			R0, R+			CR	ORR	OS	D/PFS
Kim 2004 (44)	22 (50,50)	PAC+ PDN	16,5	50-60, NR	50	14%	76%	95%	77%
Berruti 1999 (45)	16 (63,38)	ADOC	9, NR	45, NR [c]	NR	6%	81%	31%, 48	31%, 33
Loehrer 1997 (46)	23 (96,4)	PAC	0,4	54, 1.8 [d]	14,125 [e]	22%	73%	53%, 93	54%, 93[f]

Notes: 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 years, numerical values indicate median progression-free survival time in months; ECOG = Eastern Cooperative Oncology Group; FU = median duration of follow-up, in months; 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; R0 = complete resection; R+ = residual; RT = number of patients given radiotherapy; SECSG/SWOG = Southeastern Cancer Study Group/ Southwest Oncology Group; y = years.

[a] Number of evaluable patients, percentage values indicate proportion of sample with stage III and IVA or IVB disease, where reported.

[b] ADOC = cisplatin+doxorubicin, vincristine, cyclophosphamide; PAC = cyclophosphamide, doxorubicin, cisplatin; PDN = prednisone; dosage amounts and schedules varied by study.

[c] Only 13 of 16 patients received radiotherapy.

[d] RT provided concurrent with chemotherapy.

[e] 14 months for ECOG pts, and 125 months for SECSG/SWOG patients.

[f] 5-year failure-free rate, median time-to-treatment failure.

IN REVIEW

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 (47-51). Chemotherapy regimens varied among the trials, and included octreotide, cisplatin, etoposide, ifosfamide, and others. In one trial (48); all patients enrolled were refractory to at least one prior chemotherapy regimen.

Overall response rates ranged from 32 to 56%, but complete responses were much less frequent and ranged from 0 to 38%. Overall two-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%.

Table 5. Prospective trials of primary chemotherapy in single modality treatment of advanced thymoma (stage III/IV).

Trial		N (%III,%IV) [a]	Agents[b]	Age[c]	FU	Response		Survival (2-yr)	
						CR	ORR	OS	PFS
Loehrer (47)	2004	38 (5,89)	O, O+PDN	51	~50	5%	53%	76%	13%
Palmieri (48)	2002	16[d] (25,69)	O or L,+Pd	51	43	6%[d]	37%[d]	~30%	~25%
Loehrer (49)	2001	28 (21,78)	P+E+I	55	43	0%	32%	70%	NR
Highley (50)	1999	13 (27,73)	I	48	NR	38%	46%	73%	NR
Giaccone (51)	1996	16 (NR)	P+E	45	84	31%	56%	~79%	~56%

Notes: CR = number of patients achieving a complete response; FU = median duration of follow-up, in months; NR = not reported; PFS = progression-free survival, percentage values indicate proportion alive without disease progression at 2 years, 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 years; yr = year.

[a] Number of evaluable patients, percentage values indicate proportion of patients with stage III and IVA and/or IVB disease, where reported.

[b] E = etoposide; I = ifosfamide; L = lanreotide; P = cisplatin; PDN = prednisone; O = octreotide; 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.

Radiotherapy as a Single Treatment Modality

Only one prospective trial (n=25) of single modality radiotherapy in advanced thymoma was retrieved (52) (Table 6). All patients had malignant invasive stage III thymomas, and the authors did not report any other therapy being prescribed. The mean radiation dose was 46.36 Gy, and ranged from 32.4 to 58 Gy. Fraction sizes ranged from 1.8 to 2.0 Gy per day, five days per week. Five-year overall survival and progression-free survival were 72% and 81%, respectively, and recurrence at five years was 15%.

Table 6. Prospective trials of radiotherapy treatment of advanced thymoma (stage III).

Trial	N	Dose	Survival		Recurrence
			OS 5-ry	DFS 5-yr	
Sur 1997 (52)	25	46.36 Gy (mean)	72%	81%	15% at 5y

Notes: DFS = disease-free survival rate; Gy = gray; N = number of evaluable patients; OS = overall survival rate; yr = year.

IN REVIEW

CONSENSUS-BASED GUIDELINE DEVELOPMENT PROCESS

Methods

The Thymoma Working Group (TWG; the authors of this report) used a modified Delphi approach to develop draft guideline recommendations through consensus. The steps in the process are outlined in Figure 1. In the first phase, the TWG drafted and confirmed a preliminary set of thirty-eight recommendations related to key treatment issues in the management of thymoma. In this phase, discussions were conducted through teleconference and email communication and were informed by the evidence presented in the systematic review above, additional evidence provided in narrative reviews of the topic (53,54), and the clinical experience of members. The objective of the second phase, Round One Consensus, was to obtain consensus on the draft recommendations by clinicians who treat thymoma. The larger group is referred to as the Consensus Group (CG; Figure 1). Prior to the first consensus round, a letter was sent to prospective members of the CG requesting their participation in the consensus process. This group consisted of members of the TWG, members of the PEBC Provincial Lung DSG (n=28), members of the PEBC Hematology DSG for whom this type of practice was thought to be relevant (n=14), and thoracic surgeons (n=27) from across Canada who were identified by the TWG as physicians involved in the management of thymoma. Subsequently, the systematic review, draft recommendations, and questionnaire were mailed to the CG. In the questionnaire, respondents were asked to provide their opinion on general questions about the report and were also asked to rate their agreement with each recommendation on a seven-point Likert scale, ranging from "strongly agree" at 1, through "neither agree or disagree" at 4, to "strongly disagree" at 7.

The first round feedback was analysed and distributed to the TWG, and the members revised the initial recommendations in response. In the second consensus round, a package was again sent to the CG, consisting of the original recommendations, the results of the first consensus round, the modified recommendations in response to the first round feedback, and a questionnaire. For revised recommendations, CG members were asked to rate their preference for both the original Round One recommendation, and a modification to that recommendation. The questionnaire used for Round Two is included as Appendix 1 of this document. The responses to the second round consultation were analyzed and reviewed by the TWG and final recommendations established.

IN REVIEW

Phase 1: ***Generate Draft Recommendations***	**Thymoma Working Group (TWG):** 1. Define Question 2. Conduct Systematic Review 3. Formulate Recommendations
Phase 2: ***Round One Consensus (Steps 4 – 7)***	**Consensus Group (CG):** 4. Evidence review, recommendations and questionnair sent to the CG. 5. Participants rate appropriateness of recommendation on a scale from 0 to 7 and provide written feedback. **Thymoma Working Group (TWG):** 6. Responses analyzed for agreement and consensus. 7. Authors modify recommendations based on feedback.
Phase 3: ***Round Two Consensus (Steps 8 – 10)***	**Consensus Group (CG):** 9. Original and modified recommendations, feedback on round one, and questionnaire sent to CG. 10. Participants rate appropriateness of recommendations on a scale from 0 to 7 and provide written feedback.
Phase 4: ***Final Consensus Meeting***	**Thymoma Working Group (TWG):** 8. TWG reviews consensus results, draft practice guideline and votes on approval of guideline recommendations.

Figure 1. Steps in the formal consensus process (a modified Delphi approach) used to develop the recommendations for the management of thymoma.

IN REVIEW

Aggregation of Responses and Interpretation of Consensus

For each recommendation, the overall response rate, the frequency of response for each point on the 7-point Likert scale, the median and inter-quartile range (IQR), and the mean and standard deviation were calculated. While there is no single acceptable method for mathematical aggregation of consensus results, the following criteria were used for this guideline (Figure 2):

Consensus - Strong agreement: If more than 75% of responses were 1 or 2 (out of 7 on the response scale), the recommendation was considered to have attained a consensus of "strong agreement" with the recommendation as stated, and was accepted.

Consensus - Agreement: If 66% to 75% of responses were a 1 or 2, with a median value of 2 or less, the consensus was considered to be "agreement" and was accepted.

Consensus - Disagreement: If more than 50% of responses were a 6 or 7, the consensus was considered to be "disagreement", and the recommendation was rejected.

No consensus: In all other cases from above, the recommendation was considered to have no clear agreement or disagreement, and the lack of consensus was stated.

Figure 2. Criteria used to determine the acceptance, rejection or lack of consensus regarding the recommendations.

	AGREEMENT	DISAGREEMENT	UNCLEAR
CRITERIA	Strong Agreement: > 75% of responses = 1 or 2 AND Median value = 1	> 50% of responses = 6 or 7	All other cases
	Agreement: 66% to 75% of responses = 1 or 2 AND Median value ≤ 2		
ACTION	↓ ACCEPT RECOMMENDATION	↓ REJECT RECOMMENDATION	↓ NEITHER ACCEPT OR REJECT
	CONSENSUS		NO CONSENSUS

Results

Participation Rates for the Consensus Group

In the first round, 69 mail surveys were sent and 25 responses were received (Table 7). The fourteen surveys sent to Hematology DSG members were not returned. Based on feedback from members of this group that they did not manage thymoma patients, these practitioners were deemed to be an inappropriate audience and were excluded from the results analyses. The Round One response rate was therefore 25/55 (45%). Of the practitioners who responded, 24 indicated the report was relevant to their clinical practice and completed the survey. These 24 respondents (medical oncologists n=4, radiation oncologists n=6, surgeons n=14) were considered the CG for the remainder of the formal consensus process. Following revisions to the recommendations in response to Round One, the second round questionnaire was sent to the 24 CG members, and a response was received by 22/24 (92%). Completed surveys were returned by mail as well as by phone, fax, and email.

IN REVIEW

Table 7: Participants in the Consensus Group.

		Total	Lung DSG Members	Hematology DSG Members	Thoracic Surgeons (Canadian)
Round One	Sent	69	28 (9)	14	27
	Returned	25	13 (9)	0	11
Round Two	Sent	24	13 (9)	0	11
	Returned	22	13 (9)	0	9

Notes: Values in brackets note responses from the Thymoma report working group members. One individual listed under Lung DSG members was an external guest reviewer.

PHASE TWO

Consensus Round One – Results and Revisions

In Round One, members of the CG were in strong agreement for 26 of the initial set of 38 recommendations developed by the TWG and, therefore, the 26 recommendations were accepted. For the remaining 12 recommendations, the level of agreement ranged between 54% and 75%, with a median value of 2, thus indicating that no consensus had been reached.

Following Round One, the recommendations were revised by the TWG on the basis of written feedback received from the CG. Two new recommendations for stage I and II for "medically inoperable" patients were added, and seven recommendations were modified, three that were not accepted (no consensus), and four that were accepted in the first round. In Round Two, both the original recommendations and the revised versions were presented to the CG members for rating, and to determine, by consensus, which version of the recommendations were most strongly supported.

Consensus Round Two – Results and Final Recommendations

The Round Two Questionnaire included the original recommendations and a visual representation of the frequency distributions of the ratings for each of the 38 recommendations considered in Round One and the two additional recommendations (n=40). For the seven revised recommendations, both the original and revised versions were presented.

Agreement with Recommendations

Following Round Two, there was a consensus of "strong agreement" for 34 and "agreement" for four of the 40 Round Two recommendations; these 38 recommendations were accepted. The summary of the responses for both Round One and Two are compiled in Appendix 2. For the final two recommendations for stage IVB and recurrent disease respectively, there was no consensus to accept or reject, according to the criteria established for this process (Figure 2). Agreement for one recommendation was 65% and for the second 58%, disagreement was 5% for both, and 30% and 37% neither agreed nor disagreed (Table 9). The majority of respondents were surgeons (R1 n=14, R2 n=12); a separate subanalysis of this group did not show any substantial deviation from the overall results.

Preference for Original versus Revised Versions of Recommendations:

Seven recommendations were targeted for revision after Round One and they are presented in Table 8 with the frequency and median scores from the CG in Round Two. There was a clear preference for the original version of two revised recommendation (items #22a and 37a), and in both cases the DSG agreed to adopt the original version in light of feedback. There was "agreement" for both original and revised options of the recommendation concerning incomplete resection in stage III thymoma (item #16), though a slight preference for the revised option. The revised item was an expansion of the original, and the DSG

IN REVIEW

adopted the revised version in this guideline. For items #10 and #15, there was strong agreement with both the original and revised option, and no preference for one over the other. Specifically, for item #10 concerning radiotherapy in stage II thymoma, the DSG felt the sentiment of the recommendations was the same in both instances (i.e., that adjuvant radiotherapy be reserved for high-risk cases), and adopted the revised wording for its guideline. For item #15, the revised recommendation was a more detailed expansion of the original. Given the strong agreement for both, the DSG adopted the revised recommendation for this guideline. With no clear preference between the two versions for stage III thymoma, where surgery is inappropriate (item #23), the DSG adopted the original recommendation of chemotherapy concurrent with, or sequential to, radiation alone. Regarding surgery in stage IVA thymoma (item #26), there was "agreement" with both the original and revised recommendation. The original recommendation advised resecting pleural and pericardial metastases when surgery was performed, and the revised recommendation emphasized performing surgery only if pleural and pericardial metastases could be resected. For this guideline, the DSG adopted the revised version, noting comparable agreement but fewer respondents indicating disagreement for this item.

Table 8. Score frequencies for the original recommendations from Round One (a) and the revised recommendations (b) presented to the consensus group for Round Two. (The recommendation adopted by the TWG is indicated by a check mark in the left column (✓). Scores range from 1 to 7 where: 1 = strongly agree, 2 = agree, 3 = somewhat agree, 4 = neither agree or disagree, 5 = somewhat disagree, 6 = disagree, 7 = strongly disagree. Mdn = median.)

Recommendation		Score Frequency							Mdn
		1	2	3	4	5	6	7	
	Stage II Thymoma								
10	(a) Postoperative radiotherapy is recommended only if the risk of local recurrence is felt to be high. Risk factors include evidence of gross invasion through the capsule, close surgical margins, all WHO grade B-type thymomas, and tumour adherent to the pericardium.	8	12	1	1	0	0	0	2
10 ✓	(b) Routine adjuvant radiation is currently not recommended. Radiation should be considered in patients with high risk for local recurrence. These risk factors include: invasion through the capsule, close surgical margins, WHO grade B type, and tumour adherent to pericardium.	12	8	0	2	0	0	0	1
	Stage III Thymoma								
15	(a) Surgery should be considered either initially or following neoadjuvant therapy, with the aim being complete removal of the tumour with wide surgical margins.	15	6	1	0	0	0	0	1
15 ✓	(b) In stage IIIA, surgery should be considered either initially or following neoadjuvant therapy, with the aim being complete removal of the tumour with wide surgical margins. In stage IIIB, patients should be assessed for surgery following neoadjuvant chemoradiotherapy.	15	4	2	1	0	0	0	1

IN REVIEW

Recommendation		Score Frequency							Mdn
		1	2	3	4	5	6	7	
16	(a) For patients in whom complete resection is not feasible, maximal debulking of the tumour should take place, including vascular reconstruction where necessary. Any residual tumour should be marked with surgical clips.	3	11	0	4	2	2	0	2
16 ✓	(b) If at thoracotomy complete resection is found to not be possible, maximal debulking (with appropriate vascular reconstruction) should be undertaken. Clips should be placed to mark residual tumour for adjuvant radiation. If it is apparent prior to surgery that complete resection may not be feasible, neoadjuvant chemoradiation should be considered prior to surgery.	10	5	3	2	2	0	0	2
22 ✓	(a) Adjuvant radiotherapy is widely used in this setting and is recommended. Adjuvant chemotherapy may be a consideration.	13	9	0	0	0	0	0	1
22	(b) Adjuvant radiotherapy is widely used in patients with resectable or potentially resectable stage III disease and is recommended. Adjuvant chemotherapy may also be offered.	10	10	0	1	0	0	1	2
23 ✓	(a) Where surgery is inappropriate, chemotherapy concurrent with, or sequential to, radiation therapy is recommended.	15	7	0	0	0	0	0	1
23	(b) Where surgery is inappropriate, chemoradiation (concurrent or sequential) or radiation alone is recommended.	15	5	1	0	1	0	0	1
	Stage IVA Thymoma								
	Resectable or Potentially Resectable Stage IVA Disease								
26	(a) Surgery should be considered either initially or following neoadjuvant therapy, with the aim being complete removal of the tumour with wide surgical margins. It is recommended that pleural and pericardial metastases be resected.	4	13	1	2	0	2	0	2
26 ✓	(b) Surgery should be considered either initially or following neoadjuvant therapy, with the aim being complete removal of the tumour with wide surgical margins. Surgery is recommended only if pleural and pericardial metastases can be resected.	9	7	1	3	2	0	0	2
	Recurrent Disease								
37 ✓	(a) 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.	6	12	2	0	0	2	0	2

IN REVIEW

Recommendation		Score Frequency							Mdn
		1	2	3	4	5	6	7	
37	(b) 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 and extrapleural metastases is an appropriate initial approach. For cases with multiple pleural metastases, chemotherapy, followed by total pleurectomy or extrapleural pneumonectomy if possible, is often appropriate.	3	8	4	3	0	3	1	2.5

Summary of Written Comments

Thirteen out of twenty-four respondents (54%) provided written comments in Round One, and 4/22 provided written feedback in Round Two. Many of the comments were suggestions for revisions to individual recommendations. Based on the agreement of the CG and the rationale for the revisions, the TWG modified the recommendation in response to feedback. The written feedback from Round One and Two is detailed in Appendix 3; points of contention concerning the recommendations are addressed in the Discussion.

Table 9. Recommendations without consensus following Round 2.

Stage IVB
32. These types of thymoma are extremely rare, and generic recommendations are not possible. Agreement [Round One/Round Two]: 61%/65%; Disagreement (Round One/Round Two): 0/5%; Neither agree nor disagree [Round One/Round Two]: 39%/30%)
Stage IVB: Systemic Therapy
36. Octreotide, alone or in combination with a corticosteroid, may be a reasonable option for recurrent cases. Agreement [Round One/Round Two]: 54%/58%; Disagreement: 0/5%; Neither agree nor disagree: 38%/29%)

DISCUSSION

The Lung DSG places particular emphasis on results from published RCTs, in making its clinical recommendations. Data from studies of lesser quality design are considered in the absence of RCT evidence, particularly where such studies provide strong and consistent information. The systematic review on the topic of thymoma revealed very little high quality evidence; the rarity of the disease makes it difficult to conduct large-sized trials. In light of the paucity of high-quality evidence on this topic, and the interest expressed by clinicians for guidance in this area, the Lung DSG undertook a consensus-based approach in developing its recommendations for the management of thymoma.

The Lung DSG TWG met through a number of teleconferences to review the most recent evidence available on thymoma and to establish draft recommendations that form the basis for this consensus development process. The Working Group acknowledges that the available evidence did not directly establish optimal strategies in thymoma management. Some key issues addressed in the discussions concerned (a) the applicability of radiotherapy in early stage disease and (b) the role and appropriate sequencing of chemotherapy in relation to radiotherapy in more advanced disease. Based on their clinical experience, the members of the Working Group proposed thirty-eight draft recommendations.

IN REVIEW

A two-round formal consensus process elicited clinicians' agreement with the proposed draft recommendations. Two additional recommendations were added following the first round of the consensus process. After revisions and two rounds of feedback, there was no disagreement with 38 recommendations and a lack of consensus for two recommendations (Table 9). Variance in clinical opinion on some issues is anticipated, and in some cases it may be unreasonable to expect to reach complete agreement. The DSG presents a set of consensus recommendations in the following section that have been shaped by a group of experienced clinicians from across Canada but predominantly from Ontario.

Less consensus agreement was evident for the recommendations related to surgery in stage III/IV disease, and treatment for advanced or recurrent disease than for other stages of the disease or modality of care. For surgery in stage III disease, complete resection or maximal debulking was recommended (item #16), with a consideration for neoadjuvant chemoradiation depending on tumour extent added as a revision following Round One. Less agreement on this recommendation likely reflects clinician preferences regarding treatment aggressiveness, as was indicated in written feedback and perhaps the predominance of surgeons in the respondent group.

There was no consensus on the use of octreotide in stage IVB (item #36) or recurrent disease (item #40) by the criteria used in this process (i.e. agreement > 65%). The DSG has chosen to adopt these two recommendations as presented in Round Two, acknowledging the lack of consensus among clinicians on these issues.

Finally, the DSG notes the response rate to the consensus survey was sub-optimal. We hope this project will help to illustrate to clinicians the importance of formal consensus methods in developing clinical practice guidance, particularly for topics where there is a paucity of quality clinical evidence,and encourage their participation in future consensus projects.

FINAL CONSENSUS RECOMMENDATIONS FOR THE MANAGEMENT OF THYMOMA

Table 10 presents the final recommendations for the management of thymoma that were reviewed in the second consensus round. The frequencies of scores for each response option are presented as well as the median score. Scores range from 1 to 7 where: 1 = strongly agree, 2 = agree, 3 = somewhat agree, 4 = neither agree or disagree, 5 = somewhat disagree, 6 = disagree, 7 = strongly disagree. Mdn = median.

Table 10. Final consensus recommendations for the management of thymoma.

	Recommendation	Score Frequency							Mdn
		1	2	3	4	5	6	7	
	Stage I Thymoma								
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.	19	3	0	0	0	0	0	1
2	For resection of thymoma, an open median sternotomy surgical approach is recommended.	20	2	0	0	0	0	0	1
3	Minimally invasive approaches (e.g., video-assisted thoracic surgery [VATS]) are not considered the standard of care and are not recommended at this time.	14	16	0	2	0	0	0	1
4	Neither postoperative nor neoadjuvant radiotherapy is recommended for stage I disease.	22	0	0	0	0	0	0	1
5	Neither postoperative nor neoadjuvant systemic therapy is recommended for stage I disease.	22	0	0	0	0	0	0	1

IN PREVIEW

	Recommendation	Score Frequency 1	2	3	4	5	6	7	Mdn
6	Chemoradiation or radiation alone should be considered for patients who are medically unfit for surgery.	8	7	3	3	1	0	0	2
	Stage II Thymoma								
7	Complete surgical resection (as outlined for stage I) is the usual practice and is the recommended standard of care.	20	2	0	0	0	0	0	1
8	For resection of thymoma, an open median sternotomy surgical approach is recommended.	20	2	0	0	0	0	0	1
9	Minimally invasive approaches (e.g., VATS) are not considered the standard of care and are not recommended at this time.	16	4	0	2	0	0	0	1
10	Routine adjuvant radiation is currently not recommended. Radiation should be considered in patients with high risk for local recurrence. These risk factors include: invasion through the capsule, close surgical margins, WHO grade B type, and tumour adherent to pericardium.	12	8	0	2	0	0	0	1
11	Radiotherapy (RT) has risks for acute and long-term toxicity, notably a risk for the development of secondary malignancies (8), and coronary heart disease (9). Possible risks and benefits need to be discussed with patients, particularly in younger individuals.	22	0	0	0	0	0	0	1
12	Neither postoperative nor neoadjuvant systemic therapy is recommended for stage II disease.	20	2	0	0	0	0	0	1
13	Chemoradiation or radiation alone should be considered for patients who are medically unfit for surgery.	20	6	2	2	0	0	0	1
	Stage III Thymoma								
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.	18	4	0	0	0	0	0	1
15	In stage IIIA, surgery should be considered either initially or following neoadjuvant therapy, with the aim being complete removal of the tumour with wide surgical margins. In stage IIIB, patients should be assessed for surgery following neoadjuvant chemoradiotherapy.	15	4	2	1	0	0	0	1
16	If at thoracotomy complete resection is found to not be possible, maximal debulking (with appropriate vascular reconstruction) should be undertaken. Clips should be placed to mark residual tumour for adjuvant radiation. If it is apparent prior to surgery that complete resection may not be feasible, neoadjuvant chemoradiation should be considered prior to surgery.	10	5	3	2	2	0	0	2
17	Bilateral phrenic nerve resection is not recommended because of the severe respiratory morbidity that results.	22	0	0	0	0	0	0	1
18	Neoadjuvant chemoradiotherapy is widely used in this setting. The data supporting this standard is not yet established.	7	13	2	0	0	0	0	2
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.	8	13	1	0	0	0	0	2

IN REVIEW

	Recommendation	Score Frequency 1	2	3	4	5	6	7	Mdn
20	If treatment volumes are small, concurrent chemoradiotherapy is recommended as a reasonable option. If the initial tumour volume is considered to be too bulky, sequential therapy, with chemotherapy followed by radiation therapy, is recommended as a reasonable option. Resections may be performed prior to radiotherapy.	4	15	1	1	0	0	1	2
21	To establish the diagnosis of thymoma, either a computerized tomography (CT)-guided core-needle biopsy or an open surgical biopsy should be performed, prior to considering neoadjuvant therapy.	22	0	0	0	0	0	0	1
22	Adjuvant radiotherapy is widely used in this setting and is recommended. Adjuvant chemotherapy may be a consideration.	13	9	0	0	0	0	0	1
23	Where surgery is inappropriate, chemotherapy concurrent with, or sequential to, radiation therapy is recommended.	15	7	0	0	0	0	0	1
24	The definition of unresectable disease is debated, and may vary with surgical expertise, but is generally defined by extensive tumour involving middle mediastinal organs such as the trachea, great arteries, and/or heart that does not respond to cisplatin-based combination chemotherapy.	11	8	2	1	0	0	0	1.5
	Stage IVA Thymoma								
	Resectable or Potentially Resectable Stage IVA Disease								
25	The recommendations established for stage III disease are applicable to stage IVA cases as well. The following are notable modifications or exceptions to this:	8	13	1	0	0	0	0	2
26	Surgery should be considered either initially or following neoadjuvant therapy, with the aim being complete removal of the tumour with wide surgical margins. Surgery is recommended only if pleural and pericardial metastases can be resected.	9	7	1	3	2	0	0	2
27	Neoadjuvant chemoradiotherapy is an option in this setting.	9	11	2	0	0	0	0	2
28	Cisplatin-based combination chemotherapy regimens are reasonable options.	11	10	1	0	0	0	0	1.5
29	Adjuvant chemoradiotherapy is an option.	10	11	1	0	0	0	0	2
	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.	11	10	1					1.5
31	In stage IVA, unresectable disease may include extensive bilateral and/or pleural-based disease, pericardial metastases, or extrathoracic metastases.	20	1	0	0	0	0	1	1
	Stage IVB								
32	These types of thymoma are extremely rare, and generic recommendations are not possible.	9	6	4	2	0	1	0	2
33	Surgical interventions are not applicable	16	5	1	0	0	0	0	1
34	Radiotherapy may be appropriate, particularly for life-threatening situations.	17	5	0	0	0	0	0	1
35	Cisplatin-based combination chemotherapy is an appropriate option.	16	6	0	0	0	0	0	1
36	Octreotide, alone or in combination with a corticosteroid, may be a reasonable option for recurrent cases.	5	9	2	5	0	0	1	2

IN REVIEW

	Recommendation	Score Frequency 1	2	3	4	5	6	7	Mdn
	Recurrent Disease								
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.	6	12	2	0	0	2	0	2
38	Radiotherapy may be appropriate either alone or in combination with chemotherapy.	7	13	1	1	0	0	0	2
39	Cisplatin-based chemotherapy may be an appropriate therapy either alone or as part of combined chemoradiotherapy.	9	11	2	0	0	0	0	2
40	Octreotide, alone or in combination with a corticosteroid, may be a reasonable option.	3	12	1	5	0	0	1	2

***Note:** Recommendations 36 and 40 did not achieve consensus but did receive a rating of AGREE from 65% and 58% of respondents, respectively.

CONCLUSION

This report reflects the integration of feedback obtained through the formal consensus guideline development process with final approval given by the Lung DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

JOURNAL REFERENCE

The following systematic review and practice guideline article was published in the *Journal of Thoracic Oncology* (http://journals.lww.com/jto/):

- Falkson CB, Bezjak A, Darling G, Gregg R, Malthaner R, Maziak DE, et al. The management of thymoma: a systematic review and practice guideline. J Thorac Oncol. 2009 Jul;4(7):911-9. doi: 10.1097/JTO.0b013e3181a4b8e0.

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IN REVIEW

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IN REVIEW

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IN REVIEW

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Evidence-Based Series #7-11: Section 3

The Management of Thymoma: EBS Development Methods and External Review Process – The Consensus EBS Development Process

C. Falkson, A. Bezjak, G. Darling, R. Gregg, R. Malthaner, D. Maziak, E. Yu, C.A. Smith, S. McNair, Y. Ung, W.K. Evans and the members of the Lung Disease Site Group

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: September 26, 2008

IN REVIEW

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical decisions about cancer care and to support cancer system planning and policy development.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series: A New Look to the PEBC Practice Guidelines

Each Evidence-Based Series is comprised of three sections.

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its

interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.

- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process*. Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Lung Disease Site Group of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on the management of thymoma, developed through systematic review, evidence synthesis, and a formal consensus process with practitioners in Ontario.

For this topic, a systematic review yielded little quality evidence upon which to base recommendations. A formal consensus-based methodology was employed to obtain the expert opinion of clinicians who treat thymoma to make practice recommendations for the treatment and management of thymoma in Ontario.

Report Approval Panel

Prior to the publication of this evidence-based series report, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. The key issue raised by the Panel was a need to better explain the consensus method. The Panel noted confusion particularly around what is meant by consensus versus agreement. The Lung DSG agreed that the section outlining the consensus process could use clarification and the section was revised. Additional editorial changes suggested by the panel were also made.

Methods

Following the review and discussion of Sections 1 and 2 of this evidence-based series and the review and approval of the report by the PEBC Report Approval Panel and the Thymoma Working Group, the Lung Cancer DSG decided the report was ready for publication. Having engaged all the clinicians who treat thymoma through the consensus process, the DSG felt there was no additional benefit to recirculating the document for further review and feedback.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Lung DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

IN REVIEW

Funding
The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

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For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
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IN REVIEW

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IN REVIEW

Appendix 1: Round Two questionnaire and information materials. (Note: The numbering of the items in the original questionnaire has been changed to align with the final recommendations.)

CANCER CARE ONTARIO'S PROGRAM IN EVIDENCE-BASED CARE

CONSENSUS RECOMMENDATIONS DEVELOPMENT PROCESS

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EVIDENCE-BASED SERIES #7-11: THE MANAGEMENT OF THYMOMA

ROUND TWO

As part of the consensus process, we ask that you review the guideline recommendations a second time, in light of the results from Round One that are provided in this questionnaire.

1. For some recommendations (e.g., #1, #2), >75% of Round One respondents were in agreement. Please rescore these items if you wish, but no response will be interpreted as "strongly agree".

2. Recommendations for which ≤ 75% of respondents were in agreement have been highlighted in grey. Please rescore all of these recommendations (see Example 1 below).

3. Revisions were suggested for seven recommendations. These are highlighted in grey, and marked with a curved arrow in the left margin. Please rescore both a) and b) options (see Example 2 below).

4. Two new recommendations have been added (i.e., 6, and 13). Please score your agreement with these items.

A data table of the complete results from Round One is provided in the Appendix.

***Example 1**

► For each item, please indicate the extent to which you agree or disagree with the recommendations as stated. ◄	strongly agree			neither agree or disagree			strongly disagree
1. (a) Surgery should be considered either initially or following neoadjuvant therapy, with the aim being complete removal of the tumour with wide surgical margins.	6	4	6	1		1	
	☐	☐	☐	☐	☐	☐	☐

Frequency of Round One responses by agreement category (1 to 7)

Please indicate your agreement score in the appropriate box

***Example 2**

1. (a) Surgery should be considered either initially or following neoadjuvant therapy, with the aim being complete removal of the tumour with wide surgical margins.	6	4	6	1		1	
	☐	☐	☐	☐	☐	☐	☐
? 1. (b) In stage IIIA, surgery should be considered either initially or following neoadjuvant therapy, with the aim being complete removal of the tumour with wide surgical margins. **In stage IIIB, patients should be assessed for surgery following neoadjuvant chemoradiotherapy.**	☐	☐	☐	☐	☐	☐	☐

Please score your agreement rating for **both** option (a) and (b).

For some items there will be an option (a) and (b). Option (a) is the recommendation that was circulated in Round One, with a response frequency chart. Option (b) is a revision of option (a) that incorporates written feedback.

See Over

► For each item, please indicate the extent to which you agree or disagree with the recommendations as stated. ◄

	strongly agree			neither agree or disagree			strongly disagree
Stage I	**Frequency Charts**						
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.	16	6	2				
2. For resection of thymoma, an open median sternotomy surgical approach is recommended.	15	6	2	1			
3. Minimally invasive approaches (e.g., video-assisted thoracic surgery [VATS]) are not considered the standard of care and are not recommended at this time.	10	8	2	2	1	1	
Radiotherapy							
4. Neither postoperative nor neoadjuvant radiotherapy is recommended for stage I disease.	20	3	1				
Systemic Therapy							
5. Neither postoperative nor neoadjuvant systemic therapy is recommended for stage I disease.	21	2	1				
• ***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.	18	6					
8. For resection of thymoma, an open median sternotomy surgical approach is recommended.	17	5	2				
9. Minimally invasive approaches (e.g., VATS) are not considered the standard of care and are not recommended at this time.	12	10		1			
Radiotherapy							
10(a) Postoperative radiotherapy is recommended only if the risk of local recurrence is felt to be high. Risk factors include evidence of gross invasion through the capsule, close surgical margins, all WHO grade B-type thymomas, and tumour adherent to the pericardium.	10	10	1	2		1	

IN REVIEW

► For each item, please indicate the extent to which you agree or disagree with the recommendations as stated. ◄	strongly agree			neither agree or disagree			strongly disagree
(b) **Routine adjuvant radiation is currently not recommended. Radiation should be considered in patients with high risk for local recurrence. Theses risk factors include: invasion through the capsule, close surgical margins, WHO grade B type, and tumour adherent to pericardium.**	☐	☐	☐	☐	☐	☐	☐
Stage II (continued)							
Radiotherapy (continued)							
11. Radiotherapy (RT) has risks for acute and long-term toxicity, notably a risk for the development of secondary malignancies, and coronary heart disease. Possible risks and benefits need to be discussed with patients, particularly in younger individuals.	16	3	4	1			
	☐	☐	☐	☐	☐	☐	☐
Systemic Therapy							
12. Neither postoperative nor neoadjuvant systemic therapy is recommended for stage II disease.	15	7	1	1			
	☐	☐	☐	☐	☐	☐	☐
• ***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.	14	8	1	1			
	☐	☐	☐	☐	☐	☐	☐
• ***Resectable or Potentially Resectable Stage III Disease***							
Surgery							
15(a) Surgery should be considered either initially or following neoadjuvant therapy, with the aim being complete removal of the tumour with wide surgical margins.	16	5	1	1			1
	☐	☐	☐	☐	☐	☐	☐
? 15. (b) In stage IIIA, surgery should be considered either initially or following neoadjuvant therapy, with the aim being complete removal of the tumour with wide surgical margins. **In stage IIIB, patients should be assessed for surgery following neoadjuvant chemoradiotherapy.**	☐	☐	☐	☐	☐	☐	☐
16(a) For patients in whom complete resection is not feasible, maximal debulking of the tumour should take place, including vascular reconstruction where necessary. Any residual tumour should be marked with surgical clips.	6	10		4	1	2	1
	☐	☐	☐	☐	☐	☐	☐
? 16. (b) **If at thoracotomy complete resection is found to not be possible, maximal debulking (with appropriate vascular reconstruction) should be undertaken. Clips should be placed to mark residual tumour for adjuvant radiation. If it is apparent prior to surgery that complete resection may not be feasible, neoadjuvant chemoradiation should be considered prior to surgery.**	☐	☐	☐	☐	☐	☐	☐
17. Bilateral phrenic nerve resection is not recommended because of the severe respiratory morbidity that results.	18	5		1			
	☐	☐	☐	☐	☐	☐	☐
Neoadjuvant Radiotherapy and Systemic Therapy							

PREVIEW

► For each item, please indicate the extent to which you agree or disagree with the recommendations as stated. ◄	strongly agree			neither agree or disagree			strongly disagree
18. Neoadjuvant chemoradiotherapy is widely used in this setting. ► The data supporting this standard is not yet established.	7	7	7	2		1	
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.	7	12	5				
Stage III (continued)							
• ***Resectable or Potentially Resectable Stage III Disease (continued)***							
Neoadjuvant Radiotherapy and Systemic Therapy (continued)							
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 tumour volume is considered to be too bulky, sequential therapy, with chemotherapy followed by radiation therapy, is recommended as a reasonable option. Resections may be performed prior to radiotherapy.	7	10	4	3			
21. To establish the diagnosis of thymoma, either a computerized tomography (CT)-guided core-needle biopsy or an open surgical biopsy should be performed, prior to considering neoadjuvant therapy.	16	7		1			
Adjuvant Radiotherapy and Systemic Therapy							
22(a) Adjuvant radiotherapy is widely used in this setting and is recommended. Adjuvant chemotherapy may be a consideration.	8	13	1	1	1		
? 22. (b) Adjuvant radiotherapy is widely used in **patients with resectable or potentially resectable stage III disease** and is recommended. Adjuvant chemotherapy may **also be offered**.							
• ***Unresectable Stage III Disease***							
23(a) Where surgery is inappropriate, chemotherapy concurrent with, or sequential to, radiation therapy is recommended.	14	7	3				
? 23. (b) Where surgery is inappropriate, **chemoradiation (concurrent or sequential) or radiation alone is recommended**.							
24. The definition of unresectable disease is debated, and may vary with surgical expertise, but is generally defined by extensive tumour involving middle mediastinal organs such as the trachea, great arteries, and/or heart that does not respond to cisplatinum-based combination chemotherapy.	8	10	4	2			
Stage IVA							
25. The recommendations established for stage III disease are applicable to stage IVA cases as well. The following recommendations are notable modifications or exceptions to this:	4	9	6	1		3	
• ***Resectable or Potentially Resectable Stage IVA Disease***							

► For each item, please indicate the extent to which you agree or disagree with the recommendations as stated. ◄	strongly agree			neither agree or disagree			strongly disagree
Surgery							
26(a) Surgery should be considered either initially or following neoadjuvant therapy, with the aim being complete removal of the tumour with wide surgical margins. It is recommended that pleural and pericardial metastases be resected.	2	13	1	5		1	2
26. (b) Surgery should be considered either initially or following neoadjuvant therapy, with the aim being complete removal of the tumour with wide surgical margins. **Surgery is recommended only if pleural and pericardial metastases can be resected.**							
Stage IVA (continued)							
• ***Resectable or Potentially Resectable Stage IVA Disease (continued)***							
Neoadjuvant Radiotherapy and Systemic Therapy							
27. Neoadjuvant chemoradiotherapy is an option in this setting.	6	11	5		1	1	
28. Cisplatin-based combination chemotherapy regimens are reasonable options.	10	12	2				
Adjuvant Radiotherapy and Systemic Therapy							
29. Adjuvant chemoradiotherapy is an option.	7	14	2	1			
• ***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.	9	13	2				
31. In stage IVA, unresectable disease may include extensive bilateral and/or pleural-based disease, pericardial metastases, or extrathoracic metastases.	14	8	1	1			
Stage IVB							
32. These types of thymoma are extremely rare, and generic recommendations are not possible.	7	7	6	2	1		
Surgery							
33. Not applicable.	11	10	1	2			
Radiotherapy							

IN REVIEW

34. Radiotherapy may be appropriate, particularly for life-threatening situations.	11	12	1				
Systemic Therapy							
35. Cisplatin-based combination chemotherapy is an appropriate option.	11	13					
36. Octreotide, alone or in combination with a corticosteroid, may be a reasonable option for recurrent cases.	5	8	6	5			
► For each item, please indicate the extent to which you agree or disagree with the recommendations as stated. ◄	strongly agree		neither agree or disagree			strongly disagree	
Recurrent Disease							
Surgery							
37(a) 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.	4	13	6			1	
37. (b) 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 **and extrapleural metastases** is an appropriate initial approach. For cases with multiple pleural metastases, chemotherapy, **followed by total pleurectomy or extrapleural pneumonectomy if possible**, is often appropriate.							
Radiotherapy							
38. Radiotherapy may be appropriate either alone or in combination with chemotherapy.	8	13	2	1			
Systemic Therapy							
39. Cisplatin-based chemotherapy may be an appropriate therapy either alone or as part of combined chemoradiotherapy therapy.	9	15					
40. Octreotide, alone or in combination with a corticosteroid, may be a reasonable option.	5	10	3	6			

IN REVIEW

COMMENTS ABOUT THE DRAFT CONSENSUS RECOMMENDATIONS FOR THE MANAGEMENT OF THYMOMA

Please return this completed form by **FAX: 905-522-7681**, or by **MAIL to:**
Program in Evidence-Based Care, Cancer Care Ontario,
McMaster University DTC 3rd Floor, 1280 Main St W, Hamilton ON, L8S 4L8

Please feel free to email us at lacchet@mcmaster.ca in you have any questions,
or visit our Web site http://www.cancercare.on.ca/ for more information.

IN REVIEW

Appendix 2. Summary of Round One and Two Questionnaire Responses for each recommendation (item).

R1/R2 = Round One/Round Two. Recommendations with "no consensus" following Round Two are highlighted. SD = standard deviation.

Disease Stage	Item No.	R1/R2 N	Agree [1-2] %	No Consensus [3-5] %	Disagree [6-7] %	Median	Interquartile Range (IQR)	Mean	SD
I	1	24 / 20	92 / 100	8 / 0	0 / 0	1 / 1	1 / 0	1.4 / 1.0	.65 / 0
	2	24 / 20	88 / 100	13 / 0	0 / 0	1 / 1	1 / 0	1.5 / 1.0	.83 / 0
	3	24 / 20	75 / 91	21 / 9	4 / 0	2 / 1	1.75 / 0	2.1 / 1.3	1.4 / .88
	4	24 / 19	96 / 100	4 / 0	0 / 0	1 / 1	0 / 0	1.2 / 1.0	.51 / 0
	5	24 / 20	96 / 100	4 / 0	0 / 0	1 / 1	0 / 0	1.2 / 1.0	.48 / 0
	6	- / 15	- / 68	- / 32	- / 0	- / 2	- / 3	- / 2.0	- / 1.4
II	7	24 / 20	100 / 100	0 / 0	0 / 0	1 / 1	0.75 / 0	1.3 / 1.0	.44 / 0
	8	24 / 20	92 / 100	8 / 0	0 / 0	1 / 1	1 / 0	1.4 / 1.0	.65 / 0
	9	23 / 18	96 / 90	4 / 10	0 / 0	1 / 1	1 / 0	1.6 / 1.3	.73 / .92
	10	- / 20	- / 91	- / 9	- / 0	- / 1	- / 0	- / 1.3	- / .88
	11	24 / 20	79 / 100	21 / 0	0 / 0	1 / 1	1 / 0	1.6 / 1.0	.93 / 0
	12	24 / 20	92 / 100	8 / 0	0 / 0	1 / 1	1 / 0	1.5 / 1.0	.78 / 0
	13	- / 17	- / 81	- / 19	- / 0	- / 1	- / 0	- / 1.6	- / 1.2
III	14	24 / 20	92 / 100	8 / 0	0 / 0	1 / 1	1 / 0	1.5 / 1.0	.78 / 0
	15	- / 19	- / 86	- / 14	- / 0	- / 1	- / 0	- / 1.4	- / 1.1
	16	- / 15	- / 68	- / 32	- / 0	- / 2	- / 3	- / 2.0	- / 1.4
	17	24 / 18	96 / 100	4 / 0	0 / 0	1 / 1	0.75 / 0	1.3 / 1.0	.70 / 0
	18	24 / 19	58 / 91	38 / 10	4 / 0	2 / 2	2 / 0	2.3 / 1.3	1.2 / .90
	19	24 / 19	79 / 95	21 / 5	0 / 0	2 / 2	1 / 0	1.9 / 1.2	.72 / .67
	20	24 / 18	71 / 86	29 / 10	0 / 5	2 / 2	2 / 0	2.1 / 1.6	.99 / 1.5
	21	24 / 19	96 / 100	4 / 0	0 / 0	1 / 1	1 / 0	1.4 / 1.0	.72 / 0
	22	24 / 19	88 / 100	13 / 0	0 / 0	2 / 1	1 / 0	1.9 / 1.0	.97 / 0
	23	24 / 20	88 / 100	13 / 0	0 / 0	1 / 1	1 / 0	1.5 / 1.0	0.72 / 0
	24	24 / 15	75 / 83	25 / 17	0 / 0	2 / 1.5	1.75 / 0	2.0 / 1.5	.93 / 1.2
IV A	25	23 / 18	57 / 95	30 / 5	13 / 0	2 / 2	1 / 0	2.7 / 1.2	1.5 / .69
	26	24 / 16	- / 73	- / 27	- / 0	- / 2	- / 3	- / 1.8	- / 1.4
	27	24 / 18	71 / 90	25 / 10	4 / 0	2 / 2	1.75 / 0	2.3 / 1.3	1.22 / .92
	28	24 / 18	92 / 95	8 / 5	0 / 0	2 / 1.5	1 / 0	1.7 / 1.2	.64 / .69
	29	24 / 17	88 / 94	13 / 6	0 / 0	2 / 2	1 / 0	1.9 / 1.2	.74 / .71
	30	24 / 16	92 / 94	8 / 6	0 / 0	2 / 1.5	1 / 0	1.7 / 1.2	.62 / .73
	31	24 / 16	92 / 94	8 / 0	0 / 6	1 / 1	1 / 0	1.5 / 1.4	.78 / 1.5
IV B	**32**	**23 / 13**	**61 / 65**	**39 / 30**	**0 / 5**	**2 / 2**	**2 / 3**	**2.3 / 2.2**	**1.1 / 1.8**
	33	24 / 17	88 / 94	13 / 6	0 / 0	2 / 1	1 / 0	1.8 / 1.2	.90 / .71
	34	24 / 18	96 / 100	4 / 0	0 / 0	2 / 1	1 / 0	1.6 / 1.0	.58 / 0
	35	24 / 18	100 / 100	0 / 0	0 / 0	2 / 1	1 / 0	1.5 / 1.0	.51 / 0
	36	**24 / 11**	**54 / 58**	**46 / 37**	**0 / 5**	**2 / 2**	**1 / 3**	**2.5 / 2.4**	**1.1 / 1.8**
Recurrent	37	24 / 15	71 / 79	25 / 11	4 / 11	2 / 2	1 / 0	2.3 / 2.0	1.0 / 2.0
	38	24 / 18	88 / 90	13 / 10	0 / 0	2 / 2	1 / 0	1.8 / 1.3	.76 / .92
	39	24 / 18	100 / 90	0 / 10	0 / 0	2 / 2	1 / 0	1.6 / 1.3	.49 / .92
	40	24 / 14	63 / 67	38 / 29	0 / 5	2 / 2	1.75 / 3	2.4 / 2.1	1.1 / 1.8

IN REVIEW

Appendix 3: Written feedback suggestions for modifications from Round One and Two.

Round One

Additional Recommendations Requested:

- Recommendations for Stage I and II "medically inoperable" patients would be helpful.

Recommendation #9: RT in Stage II Thymoma
- We offer adjuvant RT for microscopic capsular invasion, and other recommendations [not referenced] consider this an option. The recommendation should be revised so that RT is an option where there is microscopic capsular invasion.
- Recent evidence challenges the value of radiotherapy for Stage II disease.

Recommendation #13: Surgery for Resectable or Potentially Resectable Stage III Disease
- This recommendation should be split into Stage IIIA and IIIB. The recommendation for Stage IIIB patients should be to receive upfront chemo/RT and then reassess for surgery.

Recommendation #14: Surgery for Resectable or Potentially Resectable Stage III Disease
- Debulking should not be recommended. The recommendation should be to use chemo/RT and re-explore if a good response is obtained.

Recommendation #20: Adjuvant Radiotherapy and Systematic Therapy for Resectable or Potentially Resectable Stage III Disease
- Clarify what "in this setting" refers to.

Recommendation #21: Stage III Unresectable Disease
- Should justify why this is not a stronger recommendation for RT. Single modality data supports benefit of RT alone.

Recommendation #24: Surgery for Stage IVA
- Resection should be recommended in Stage IVA only if a complete pleurectomy for pleural implants or pericardiectomy for pericardial implants is planned.
- It is unclear if there is evidence for a survival benefit of tumour debulking. The recommendation for debulking should be reconsidered.

Recommendation #35: Surgery for Recurrent Disease
- Resection should be recommended for recurrent cases only if an extrapleural pleurectomy to resect all potential pleural implants is planned.

Round Two
- Some surgical recommendations for advanced disease are quite aggressive.
- There is no data to support extrapleural pneumonectomy.

IN REVIEW