

Surgical, Radiation, and Systemic Treatments of Patients With Thymic Epithelial Tumors: A Clinical Practice Guideline



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ABSTRACT

Introduction: The aim of this guideline was to provide recommendations for the most effective therapy for patients with thymic epithelial tumors, including thymoma, thymic carcinoma, and thymic neuroendocrine tumors (NETs). This guideline is intended to be used by all health care professionals managing patients with thymic epithelial tumors.

Methods: The guideline was developed by Ontario Health (Cancer Care Ontario)'s Program in Evidence-Based Care and by the Lung Cancer Disease Site Group through a systematic review of the evidence, expert consensus, and formal internal and external reviews.

Results: Evidence-based recommendations were developed to improve the management of patients with thymic epithelial tumors. The guideline includes recommendations for surgical, radiation, and systemic treatments for patients with thymoma, thymic carcinoma, and thymic NETs separated by stage of disease using the TNM staging system. Recommendations for patients with thymic NETs were endorsed from the 2021 National Comprehensive Cancer Network Neuroendocrine and Adrenal Tumors Guideline.

Conclusions: This guideline reflects the new staging system for patients with thymoma and thymic carcinoma and includes supporting evidence from the best available studies.

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Keywords: Thymic epithelial tumors; Systemic therapy; Chemotherapy; Radiotherapy; Surgery; Guideline

Introduction

A previous 2010 Program in Evidence-Based Care (PEBC) guideline was based on a formal consensus process and provided recommendations for patients only with thymoma.¹ More comparative studies have been published to guide clinicians in terms of treatment for patients with these tumors. Furthermore, the International Association for the Study of Lung Cancer and the International Thymic Malignancy Interest Group introduced a newer staging system that was approved by the Union for the International Cancer

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Control and the American Joint Committee on Cancer in the eighth edition of the TNM classification to replace the previous Masaoka and Masaoka-Koga (MK) staging systems.^{2,3}

Therefore, Ontario Health (Cancer Care Ontario)'s Lung Disease Site Group (DSG) has collaborated with the PEBC to develop this multidisciplinary, evidence-based guideline. The goal of this guideline is to provide clinicians with guidance on how to treat patients with thymic epithelial tumors, including thymoma, thymic carcinoma, and thymic neuroendocrine tumors (NETs).

Materials and Methods

Guideline Developers

This guideline was developed by the Treatment of Thymic Tumors Guideline Development Group (GDG) (Appendix A), which was convened at the request of the Lung Cancer Disease Site Group and the Thoracic Cancers Advisory Committee.

The project was led by a small Working Group of the Treatment of Thymic Tumors GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in radiation oncology, surgical oncology, medical oncology, and health research methodology. The Lung DSG members of the Treatment of Thymic Tumors GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix A and were managed in accordance with the PEBC Conflict of Interest Policy.

Guideline Development Methods

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle.^{4,5} This process includes a systematic review (Falkson et al.¹), interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base.

Search for Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine whether any guideline could be endorsed. Evidence-based guidelines with systematic reviews that

addressed the research question “What are the benefits and harms of the treatment options for patients with thymic epithelial tumours?” were included. Guidelines older than 3 years (published before 2017) were excluded.

The following sources were searched for guidelines on January 9, 2020, with the search terms thymic, thymus, and thymoma: Emergency Care Research Institute Guidelines Trust, National Institute for Health and Care Excellence Evidence Search, Canadian Partnership Against Cancer Guidelines Database, Canadian Medical Association Journal Infobase, Scottish Intercollegiate Guidelines Network, American Society of Clinical Oncology, National Health and Medical Research Council—Australia Clinical Practice Guidelines Portal, and Cancer Council Australia—Cancer Guidelines Wiki. No guideline met the inclusion criteria.

Following the results of the systematic review (Falkson et al.¹), very few studies that could inform the recommendations for thymic NETs were found. Therefore, an updated search for guidelines that included recommendations for patients with thymic NETs was performed. Guidelines older than 3 years (published before 2018) were excluded.

The following sources were searched for guidelines on June 11, 2021, with the search terms neuroendocrine and carcinoid: Emergency Care Research Institute Guidelines Trust, National Institute for Health and Care Excellence Evidence Search, Canadian Partnership Against Cancer Guidelines Database, Canadian Medical Association Journal Infobase, Scottish Intercollegiate Guidelines Network, American Society of Clinical Oncology, National Health and Medical Research Council—Australia Clinical Practice Guidelines Portal, and Cancer Council Australia—Cancer Guidelines Wiki. Two guidelines that met the inclusion criteria were found.^{6,7} The Working Group chose to endorse the National Comprehensive Cancer Network (NCCN) 2021 guideline because it provided recommendations for all patients with thymic NETs, whereas the European Society for Medical Oncology 2021 provided recommendations only for patients with thymic carcinoids. Although the NCCN guidelines are not based on systematic reviews, this NCCN 2021 guideline included a description of the evidence that was used to support their recommendations.

Recommendation Development Methods

PEBC guideline recommendations are based on evidence of the magnitude of the desirable and undesirable effects of an intervention or accuracy of a test and take into account the certainty of the evidence, the values of

Table 1. General Principles

1. The aim of surgery in all cases is to achieve a complete resection.
2. The TNM staging system should be used for all patients.
3. Discussion of all patients at a MCC is strongly recommended, not just at local MCC but also with higher-volume centers. Presentation at the ITMIG tumor board should be considered.

ITMIG, International Thymic Malignancy Interest Group; MCC, multidisciplinary cancer conference.

key stakeholders (e.g., patients, clinicians, and policy makers), and the potential impact on equity, acceptability, and feasibility of implementation according to the evidence-to-decision framework of the Grading of Recommendations, Assessment, Development, and Evaluations.⁸ The results of the questions associated with this framework can be found in [Appendix B](#). If insufficient evidence was found, then the Working Group considered endorsing the recommendations from the previous version of this guideline (see [Appendix C](#)).¹ A list of any implementation considerations (e.g., costs, human resources, and unique requirements for special or disadvantaged populations and dissemination issues) was provided along with the recommendations for information purposes.

Endorsement Process

The Working Group reviewed the NCCN Version 1.2021 Neuroendocrine and Adrenal Tumors Guideline⁶ in detail and reviewed each recommendation of that guideline to determine whether it could be endorsed, endorsed with changes, or rejected. This determination was based on the agreement of the Working Group with the interpretation of the available evidence presented in the guideline, whether the recommendation was applicable and acceptable to the Ontario context, whether it was feasible for implementation, and whether new evidence reported since the guideline was developed might change any of the recommendations.

Guideline Review and Approval

Internal Review. For the guideline document to be approved, 75% of the Lung DSG had to vote indicating whether they approved the document or abstained from voting for a specified reason, and of those who voted, 75% had to approve the document. On September 16, 2021, the draft guideline was sent to the Lung DSG members for approval. Of the 23 members, 19 (83%) voted. Of those who voted, 17 (89%) approved the document.

In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must approve the document. On October 18, 2021, three

RAP members reviewed and conditionally approved the draft guideline. Any comments were addressed with the Working Group before being sent to external reviewers.

External Review. Feedback on the approved draft guideline was obtained from content experts and the target users through two processes. Through the Targeted Peer Review, three individuals with content expertise were identified by the Working Group and asked to review and provide feedback on the guideline document. Two responses were received and reviewed. Through Professional Consultation, 86 clinicians in Ontario with an interest in lung cancer in the PEBC database were contacted by e-mail to inform them of the survey. A total of 24 (28%) responses were received and reviewed. Professional Consultation of the External Review process was intended to facilitate the dissemination of the guideline to Ontario practitioners.

Results

The final guideline recommendations reflect the integration of feedback obtained through the external review processes with the document as drafted by the Working Group and approved by the Lung DSG and the PEBC RAP ([Tables 1-4](#)).

Clinical Practice Guideline

Guideline Objective. The objective of this guideline is to provide recommendations for the most effective therapy for patients with thymic epithelial tumors.

Target Population. The target population is adult patients with thymic epithelial tumors, including thymoma, thymic carcinoma, and thymic NETs.

Intended Users. The intended users of this guideline are all health care professionals managing patients with thymic epithelial tumors.

Definitions. Complete resection refers to an R0 resection of the tumor or resection with negative margins.

Total resection refers to resection of the entire thymus (including all mediastinal tissues anterior to the pericardium, aorta, and superior vena cava from the phrenic nerve to the phrenic nerve laterally and from the diaphragm inferiorly to the level of the thyroid gland superiorly, including the upper poles of the thymus), the tumor, and any involved structures.

Partial resection refers to resection of less than the entire thymus but includes the tumor and any involved structures.

Table 2. Recommendations for Patients With Thymoma

Thymoma TNM Eighth Edition Stage I (T1aN0M0/T1bN0M0) (Encapsulated or unencapsulated, with or without extension into mediastinal fat/Extension into mediastinal pleura)

Surgery

1. Total resection is preferred over partial resection, especially for patients with MG.
2. Open or minimally invasive approaches (e.g., VATS or RATS) are both recommended as the standard of care.

Radiotherapy

3. Neoadjuvant radiotherapy is not recommended.
4. PORT is not routinely recommended.

Systemic therapy

5. Neither neoadjuvant nor adjuvant systemic therapy is recommended.

Medically inoperable stage I disease

6. Radiotherapy could be considered for patients who are medically unfit for surgery.

Justification for recommendations for Thymoma TNM Stage I (T1aN0M0/T1bN0M0)

Surgery

The evidence suggested that the balance between the desirable and undesirable effects did not favor either partial or total thymectomy for patients with early MK stage I/II thymoma; however, the working group's certainty in the evidence was very low. The working group preferred to recommend total thymectomy because the evidence was not strong enough to change standard practice of total thymectomy, especially for patients with MG.

The evidence suggested that there was no clear difference in desirable effects, but there was a reduction in undesirable effects, such as complications, length of hospital stay, and blood loss, favoring minimally invasive approaches compared with open median sternotomy for patients with early MK stage I/II thymoma. The working group recommended either technique because their certainty in the evidence was very low.

The working group believed that patients with T1bN0M0 should be treated in the same manner as patients with T1aN0M0 thymoma. They used the indirect evidence from studies that included patients with MK stage I/II thymoma to inform these recommendations.

Radiotherapy

Recommendation 3 was endorsed from the previous PEBC recommendation for patients with MK stage I thymoma.

For recommendation 4, the evidence suggested that there was possibly a small difference in desirable effects favoring PORT compared with no PORT, with trivial differences in acute harmful effects for patients with MK stage I/II thymoma. The long-term adverse effects were not well documented for patients with thymoma. The evidence suggested that the magnitude of benefit might be less for patients with earlier MK stage I/II thymoma compared with later MK stage III/IV thymoma. Therefore, the working group agreed to not routinely recommend PORT for patients with T1aN0M0 disease.

Patients with T1bN0M0 thymoma would have been categorized as patients with MK stage III in the studies. The magnitude of benefit might be greater for these patients than for patients with MK stage I/II thymoma. Nevertheless, the working group's certainty in the evidence was low. Because these patients are bordering early vs. late MK stage thymoma and negative surgical margins can generally be achieved, the working group agreed to not routinely recommend PORT for patients with T1bN0M0 disease.

Systemic therapy

Recommendation 5 was endorsed from the previous PEBC guideline for patients with MK stage I thymoma.

Medically inoperable stage I disease

Recommendation 6 was adapted from the previous PEBC recommendation for patients with MK stage I thymoma, which recommended chemoradiotherapy or radiotherapy alone. Chemoradiotherapy was removed from this recommendation because there was a lack of evidence to reveal benefit with chemoradiotherapy in this population and there would be fewer adverse effects using one modality of therapy rather than two modalities.

Thymoma TNM Eighth Edition Stage II (T2N0M0) (Invasion of pericardium)

Surgery

7. Total resection is preferred over partial resection, especially for patients with MG.
8. Open or minimally invasive approaches (e.g., VATS or RATS) are both recommended as the standard of care.

Radiotherapy

9. Neoadjuvant radiotherapy is not recommended.
10. Routine PORT is currently not recommended. Nevertheless, PORT should be considered in patients with incomplete resection or positive margins. Radiotherapy has risks for acute and late toxicities. Late toxicities such as cardiac disease and secondary malignancies may be more relevant in younger patients. Possible harms vs. benefits need to be discussed with patients.

Systemic therapy

11. Neither neoadjuvant nor adjuvant systemic therapy is recommended.

Medically inoperable stage II disease

12. Radiotherapy could be considered for patients who are medically unfit for surgery.

Justification for recommendations for Thymoma TNM Stage II (T2N0M0)

Surgery

The working group believed that these patients should be treated in the same manner as patients with TNM stage I thymoma. They used the indirect evidence from studies that included patients with MK stage I/II thymoma to inform these recommendations.

Radiotherapy

For recommendation 9, the working group believed that these patients should be treated in the same manner as patients with TNM stage I thymoma.

For recommendation 10, patients with TNM stage II (T2N0M0) thymoma would have been categorized as patients with MK stage III in the studies. The magnitude of benefit might be greater for these patients than for patients with MK stage I/II thymoma. Nevertheless,

Table 2. Continued

the working group's certainty in the evidence was low. Because these patients are bordering early vs. late MK stage thymoma, the working group conditionally recommended port for patients with poorer prognosis who have incomplete resection or positive margins. The importance of considering radiotherapy toxicities¹¹ was endorsed from the previous PEBC recommendation.

Systemic therapy

Recommendation 11 was endorsed from the previous PEBC recommendation for patients with MK stage II thymoma.

Medically inoperable stage II disease

Recommendation 12 was adapted from the previous PEBC recommendation for patients with MK stage II thymoma, which recommended chemoradiotherapy or radiotherapy alone. Chemoradiotherapy was removed from this recommendation because there was a lack of evidence to reveal benefit with chemoradiotherapy in this population and there would be fewer adverse effects using one modality of therapy rather than two modalities.

Thymoma TNM Eighth Edition Stage III (T3N0M0/T4N0M0) (involvement of lung, brachiocephalic vein, superior vena cava, chest wall, phrenic nerve, hilar [extrapericardial] pulmonary vessels/Involvement of aorta, arch vessels, main pulmonary artery, myocardium, trachea, or esophagus)

13. Patients presenting with locally advanced disease should be carefully evaluated for multimodality therapy.

Resectable or potentially resectable stage IIIa disease

Surgery

14. Surgery should be considered either initially or after neoadjuvant therapy, with the aim being total removal of the tumor with clear surgical margins.

15. Total resection is preferred over partial resection, especially for patients with MG.

16. Open thymectomy is recommended as the standard of care. Minimally invasive approaches are not recommended as the standard of care.

17. If at initial surgery there are concerns about clear resection margins, clips should be placed to mark areas at risk to guide PORT. If it is apparent before surgery that complete resection may not be feasible, neoadjuvant chemotherapy or chemoradiotherapy should be considered before surgery.

18. Unilateral phrenic nerve resection is acceptable. Bilateral phrenic nerve resection is contraindicated because of the severe respiratory morbidity that results.

Neoadjuvant systemic therapy and radiotherapy

19. The decision to give neoadjuvant therapy should be discussed at an MCC. Options include neoadjuvant chemotherapy (with possible PORT) or concurrent chemoradiotherapy. Histologic confirmation of diagnosis is recommended before any therapy.

20. 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 is a reasonable option.

PORT and Adjuvant Systemic Therapy

21. PORT could be offered if the patient has not received neoadjuvant radiotherapy.

22. Adjuvant chemotherapy is not routinely recommended and should not be offered without discussion at MCC.

Unresectable Stage III Disease

23. The distinction between resectable and unresectable disease is controversial and patients with suspected unresectable stage III disease should be discussed at an MCC for consideration for referral to a high-volume tertiary thoracic surgical center.

24. Where surgery is not feasible, chemotherapy concurrent with, or sequential to, radiotherapy is recommended.

Justification for recommendations for Thymoma TNM Stage III (T3N0M0/T4N0M0)

Recommendation 13 was endorsed from the previous PEBC recommendation for patients with MK stage III thymoma.

Surgery

Recommendation 14 was endorsed from the previous PEBC recommendation for patients with MK stage III thymoma.

For recommendation 15, the working group used the indirect evidence from studies that included patients with MK stage I/II thymoma to inform these recommendations.

For recommendation 16, the working group chose to recommend only open thymectomy because the studies for minimally invasive approaches included patients with MK stage I/II thymoma and the ability to obtain a complete resection with beneficial outcomes in more advanced patients has not yet been determined.

Recommendation 17 was endorsed from the previous PEBC guideline. Nevertheless, debulking was removed from recommendation 17 because it is no longer a standard of practice.

Recommendation 18 was endorsed from the previous PEBC guideline for patients with MK stage III thymoma.

Neoadjuvant systemic therapy and radiotherapy

For recommendation 19, neoadjuvant chemotherapy was added to neoadjuvant chemoradiotherapy because there was evidence to suggest that patients respond to chemotherapy, and either of these modalities potentially improves the chance of an R0 resection. However, the impact on survival is unknown. In addition, there may be an increase in toxicity with combination therapy.

Furthermore, if radiotherapy is given in the neoadjuvant setting, then PORT is not recommended. The working group believed that the sequencing of chemoradiotherapy is complicated and should be discussed at an MCC.

Recommendation 20 was endorsed from the previous PEBC recommendation for patients with MK stage III thymoma.

PORT and adjuvant systemic therapy

The evidence suggested that there was possibly a moderate difference in desirable effects favoring PORT compared with no PORT, with trivial differences in acute harmful effects. The long-term adverse effects were not well documented for thymoma. The working group believed that PORT's benefits outweighed the potential harm in these patients.

There was insufficient evidence to recommend for or against the use of adjuvant chemotherapy.

Unresectable stage III disease

Table 2. Continued

For recommendation 23, because the definition of unresectable disease is debated, the working group believed that this should be discussed at an MCC, rather than provide a definition.

Recommendation 24 was endorsed from the previous PEBC recommendation for patients with MK stage III thymoma.

Thymoma TNM Eighth Edition Stage IVa (TanyN1M0/TanyN0M1a/TanyN1M1a) (Involvement of anterior [perithymic] nodes/separate pleural or pericardial nodule(s)/Anterior [perithymic] nodes, Separate pleural or pericardial nodule(s))

25. Patients should all be discussed at an MCC and be evaluated for multimodality therapy.

Resectable or potentially resectable stage IVa disease

Surgery

26. Surgery should be considered either initially or after neoadjuvant therapy, with the aim being total removal of all tumors with clear surgical margins. Surgery is recommended only if pleural and pericardial metastases can be resected.

27. Total resection is preferred over partial resection, especially for patients with MG.

28. Open thymectomy is recommended as the standard of care. Minimally invasive approaches are not recommended as the standard of care.

29. If at initial surgery there are concerns about clear resection margins, clips should be placed to mark areas at risk to guide PORT. If it is apparent before surgery that complete resection may not be feasible, neoadjuvant chemotherapy or chemoradiotherapy should be considered before surgery.

30. Unilateral phrenic nerve resection is acceptable. Bilateral phrenic nerve resection is contraindicated because of the severe respiratory morbidity that results.

Neoadjuvant systemic therapy

31. Neoadjuvant chemotherapy is an option in this setting.

32. 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 is a reasonable option.

PORT and adjuvant systemic therapy

33. PORT should be offered if the patient has not received neoadjuvant radiotherapy.

34. Adjuvant chemotherapy is not routinely recommended and should not be offered without discussion at an MCC.

Unresectable stage IVa disease

35. The distinction between resectable and unresectable disease is controversial and patients with suspected unresectable stage IVa disease should be discussed at an MCC for consideration for referral to a high-volume tertiary thoracic surgical center.

36. Where surgery is not feasible, chemotherapy can be considered. Chemotherapy can be given concurrent with, or sequential to, radiotherapy.

Justification for recommendations for Thymoma TNM Stage IVa (TanyN1M0/TanyN0M1a/TanyN1M1a)

Recommendation 25 was added to emphasize that multimodality therapy should be considered.

Surgery

Recommendation 26 was endorsed from the previous PEBC recommendation for patients with MK stage IVa thymoma.

For recommendation 27, the working group used the indirect evidence from studies that included patients with MK stage I/II thymoma to inform these recommendations.

For recommendation 28, the working group chose to recommend only open thymectomy because the studies for minimally invasive approaches included patients with MK stage I/II thymoma and the ability to obtain a complete resection with beneficial outcomes in more advanced patients has not yet been determined.

Recommendation 29 was endorsed from the previous PEBC guideline for patients with MK stage III thymoma. However, debulking was removed from recommendation 29 because it is no longer a standard of practice.

Recommendation 30 was endorsed from the previous PEBC guideline for patients with MK stage III thymoma.

Neoadjuvant systemic therapy

Recommendation 31 was adapted from the previous PEBC recommendation for patients with MK stage IVa thymoma, which recommended neoadjuvant chemoradiotherapy. Neoadjuvant radiotherapy was removed because any pleural plaques should be identified after surgery to treat those areas with PORT specifically.

Recommendation 32 was endorsed from the previous PEBC recommendation for patients with MK stage IVa thymoma.

PORT and adjuvant systemic therapy

The evidence suggested that there was possibly a moderate difference in desirable effects favoring PORT compared with no PORT, with trivial differences in acute harmful effects. The long-term adverse effects were not well documented for thymoma. The working group believed that PORT's benefits outweighed the potential harm in these patients.

There was insufficient evidence to recommend for or against the use of adjuvant chemotherapy.

Unresectable stage IVa disease

For recommendation 35, because the definition of unresectable disease is debated, the working group believed that this should be discussed at an MCC, rather than provide a definition.

Recommendation 36 was endorsed from the previous PEBC recommendation for patients with MK stage IVa thymoma.

Thymoma TNM Eighth Edition Stage IVb (TanyN2M0/TanyN2M1a/TanyNanyM1b) (Involvement of deep intrathoracic or cervical nodes/Deep intrathoracic or cervical nodes, separate pleural or pericardial nodule(s)/Pulmonary intraparenchymal nodule or distant organ metastasis)

37. This is a heterogeneous group of patients and treatment decisions should reflect the extent and location of metastatic disease. Generic recommendations are not possible. These patients should be discussed at an MCC, and treatment goals reviewed. Treatment options include chemotherapy (platinum-based recommended; there is insufficient evidence to recommend the routine use of other systemic agents), radiotherapy, and potential surgery.

Table 2. Continued

Justification for recommendations for Thymoma TNM Stage IVb (TanyN2M0/TanyN2M1a/TanyNanyM1b)

Because this is a heterogeneous group of patients, generic recommendations were not possible. Therefore, treatment options were provided that need to be discussed at an MCC. There was indirect evidence from patients with advanced or recurrent thymic carcinoma to suggest that there was no clear advantage in response between anthracycline and non-anthracycline platinum-based chemotherapy. Furthermore, there was insufficient evidence to suggest an advantage of other first-line systemic agents such as octreotide over platinum-based chemotherapy for patients with advanced or recurrent thymoma. Moreover, there was insufficient indirect evidence to recommend second-line agents such as pembrolizumab.

Thymoma Recurrent Disease

38. These patients should be discussed at an MCC, and multimodality therapy should be considered.

Surgery

39. Resection should be considered in patients with intrathoracic disease. This should be considered as part of multimodality care.

Radiotherapy

40. Radiotherapy may be appropriate either alone or as part of multimodality care.

Systemic therapy

41. Cisplatin-based chemotherapy may be an appropriate therapy either alone or as part of multimodality care. There is insufficient evidence to recommend the routine use of other systemic agents.

Justification for recommendations for Thymoma recurrent disease

Recommendation 38 was added to emphasize that multimodality therapy should be considered.

Surgery

Recommendation 39 was endorsed from the previous PEBC recommendation but was reworded to reflect that multimodality care should be considered.

Radiotherapy

Recommendation 40 was endorsed from the previous PEBC recommendation but was reworded to reflect that multimodality care should be considered.

Systemic therapy

For recommendation 41, there was indirect evidence from patients with advanced or recurrent thymic carcinoma to suggest that there was no clear advantage in response between anthracycline and non-anthracycline platinum-based chemotherapy. Furthermore, there was insufficient evidence to suggest an advantage of other first-line systemic agents such as octreotide over platinum-based chemotherapy for patients with advanced or recurrent thymoma. Moreover, there was insufficient indirect evidence to recommend second-line agents such as pembrolizumab.

MCC, multidisciplinary cancer conference; MG, myasthenia gravis; MK, Masaoka-Koga; PEBC, Program in Evidence-Based Care; PORT, postoperative radiotherapy; RATS, robot-assisted thoracoscopic surgery; VATS, video-assisted thoracic surgery.

Recommendations and Justification. The staging system for patients with thymic epithelial tumors has recently changed to a TNM staging system.^{2,3} The evidence used to support these recommendations was mainly from observational studies that used the previous MK staging systems.^{9,10} Given the lack of randomized trials, the Working Group endorsed many of the consensus-based recommendations for patients with thymoma from the previous PEBC version of this guideline¹ (see [Appendix C](#)). For patients with thymic NETs, recommendations were endorsed from the NCCN version 1.2021 Neuroendocrine and Adrenal Tumors Guideline.⁶

Discussion

Implementation Considerations

The Working Group members believed that patients in rural areas or patients who are disadvantaged may find it more challenging to attend daily postoperative radiotherapy treatments or treatments in high-volume centers because they may live further away from these centers in Ontario or may have difficulty in acquiring

transportation for daily treatments than patients in urban areas or patients who are less disadvantaged. Furthermore, peptide receptor radionuclide therapy has not been approved for patients with thymic epithelial tumors in Ontario, Canada.

Guideline Limitations

The Working Group for this guideline did not include patient representatives. Thus, when developing recommendations, input from patients about their values and preferences was not sought and a systematic review for this information was not performed. Working Group members used their previous clinical experiences with patients with thymic epithelial tumors to assume their relevant values and preferences.

Further Research

Larger, collaborative, international prospective trials that control for confounders are needed to provide a greater degree of certainty in the evidence to inform recommendations.

Table 3. Recommendations for Patients With Thymic Carcinoma

Thymic Carcinoma TNM Eighth Edition Stage I (T1a0m0/T1b0m0) (Encapsulated or unencapsulated, with or without extension into mediastinal fat/Extension into mediastinal pleura)

Surgery

1. Total resection is preferred over partial resection.
2. Open thymectomy is recommended as the standard of care.

Radiotherapy

3. Neoadjuvant radiotherapy is not recommended.
4. PORT may be considered.

Systemic therapy

5. Neoadjuvant chemotherapy is not recommended.
6. Adjuvant chemotherapy is not routinely recommended.

Medically inoperable stage I disease

7. Radiotherapy could be considered for patients who are medically unfit for surgery. There is insufficient evidence regarding the role of chemotherapy.

Justification for recommendations for Thymic Carcinoma TNM Stage I (T1a0m0/T1b0m0)

Surgery

For recommendation 1, the working group used the indirect evidence from studies that included patients with MK stage I/II thymoma to inform these recommendations.

For recommendation 2, the working group chose to recommend only open thymectomy because the studies for minimally invasive approaches included patients with MK stage I/II thymoma and the ability to obtain a complete resection with beneficial outcomes in patients with thymic carcinoma has not yet been determined.

Radiotherapy

Recommendation 3 remained consistent with the current recommendation for patients with TNM stage I thymoma.

For recommendation 4, the evidence suggested that there was possibly a small difference in desirable effects favoring PORT compared with no PORT, with trivial differences in acute harmful effects for patients with thymic carcinoma. The long-term adverse effects were not well documented for patients with thymic carcinoma. The evidence suggested that the absolute overall survival effect might be larger for patients with thymic carcinoma than for patients with thymoma. Therefore, the working group recommended that PORT be considered for these patients.

Systemic therapy

For recommendation 5, it remained consistent with the current recommendation for patients with TNM stage I thymoma.

For recommendation 6, there was insufficient evidence to recommend for or against the use of adjuvant chemotherapy in these patients.

Medically inoperable stage I disease

Recommendation 7 remained consistent with the current recommendation for patients with TNM stage I thymoma.

Thymic Carcinoma TNM Eighth Edition Stage II (T2N0M0) (Invasion of pericardium)

Surgery

8. Total resection is preferred over partial resection.
9. Open thymectomy is recommended as the standard of care.

Radiotherapy

10. Neoadjuvant radiotherapy is not recommended.
11. PORT should be considered. Possible harms vs. benefits need to be discussed with patients.

Systemic therapy

12. Neoadjuvant chemotherapy is not recommended.
13. Adjuvant chemotherapy is not routinely recommended.

Medically inoperable stage II disease

14. Radiotherapy could be considered for patients who are medically unfit for surgery. There is insufficient evidence regarding the role of chemotherapy.

Justification for recommendations for Thymic Carcinoma TNM Stage II (T2N0M0)

Surgery

For recommendations 8 and 9, the working group believed that these patients should be treated in the same manner as patients with TNM stage I thymic carcinoma.

Radiotherapy

For recommendation 10, the working group believed that these patients should be treated in the same manner as patients with TNM stage I thymic carcinoma.

For recommendation 11, the evidence suggested that there was possibly a small difference in desirable effects favoring PORT compared with no PORT, with trivial differences in acute harmful effects for patients with thymic carcinoma. The long-term adverse effects were not well documented for patients with thymic carcinoma. The evidence suggested that the absolute overall survival effect might be larger for patients with thymic carcinoma than for patients with thymoma. Furthermore, the magnitude of benefit might be larger for patients with a higher risk of mortality found in patients with more advanced stages. Therefore, the working group recommended that PORT should be considered for these patients.

Systemic therapy

For recommendations 12 and 13, the working group believed that these patients should be treated in the same manner as patients with TNM stage I thymic carcinoma.

Medically inoperable stage II disease

Table 3. Continued

For recommendation 14, the working group believed that these patients should be treated in the same manner as patients with TNM stage I thymic carcinoma.

Thymic Carcinoma TNM Eighth Edition Stage III (T3N0M0/T4N0M0) (Involvement of lung, brachiocephalic vein, superior vena cava, chest wall, phrenic nerve, hilar [extrapericardial] pulmonary vessels/Involvement of aorta, arch vessels, main pulmonary artery, myocardium, trachea, or esophagus)

15. Patients presenting with locally advanced disease should be carefully evaluated for multimodality therapy.

Resectable or potentially resectable stage IIIa disease Surgery

16. Surgery should be considered either initially or after neoadjuvant therapy, with the aim being total removal of the tumor with clear surgical margins.

17. Total resection is preferred over partial resection.

18. Open thymectomy is recommended as the standard of care.

19. If at initial surgery there are concerns about clear resection margins, clips should be placed to mark areas at risk to guide PORT. If it is apparent before surgery that complete resection may not be feasible, neoadjuvant chemotherapy or chemoradiotherapy should be considered before surgery.

20. Unilateral phrenic nerve resection is acceptable. Bilateral phrenic nerve resection is contraindicated because of the severe respiratory morbidity that results.

Neoadjuvant systemic therapy and radiotherapy

21. The decision to give neoadjuvant therapy should be discussed at an MCC. Options include neoadjuvant chemotherapy (with possible PORT) or concurrent chemoradiotherapy. Histologic confirmation of diagnosis is recommended before any therapy.

22. 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 is a reasonable option.

PORT and adjuvant systemic therapy

23. PORT should be offered if the patient has not received neoadjuvant radiotherapy.

24. Adjuvant chemotherapy should be considered based on representation at MCC if the patient did not have neoadjuvant chemotherapy.

Unresectable stage III disease

25. The distinction between resectable and unresectable disease is controversial and patients with suspected unresectable stage III disease should be discussed at an MCC for consideration for referral to a high-volume tertiary thoracic surgical center.

26. Where surgery is not feasible, chemotherapy concurrent with, or sequential to, radiotherapy is recommended.

Justification for recommendations for Thymic Carcinoma TNM Stage III (T3N0M0/T4N0M0)

Recommendation 15 remained consistent with the current recommendation for patients with TNM stage III thymoma.

Surgery

Recommendation 16 remained consistent with the current recommendation for patients with TNM stage III thymoma.

Recommendations 17 and 18 remained consistent with the recommendations for patients with TNM stages I and II thymic carcinoma.

Recommendations 19 and 20 remained consistent with the current recommendation for patients with TNM stage III thymoma.

Neoadjuvant systemic therapy and radiotherapy

For recommendation 21, there was evidence to suggest that patients respond to chemotherapy and potentially improve the chance of an R0 resection. Nevertheless, the impact on survival is unknown. This recommendation remained consistent with the current recommendation for patients with TNM stage III thymoma.

Recommendation 22 remained consistent with the current recommendation for patients with TNM stage III thymoma.

PORT and adjuvant systemic therapy

The evidence suggested that there was possibly a moderate difference in desirable effects favoring PORT compared with no PORT, with trivial differences in acute harmful effects. The long-term adverse effects were not well documented for patients with thymic carcinoma. The evidence suggested that the absolute overall survival effect might be larger for patients with thymic carcinoma than for patients with thymoma. Furthermore, the magnitude of benefit might be larger for patients with a higher risk of mortality found in patients with more advanced stages. Therefore, the working group recommended that PORT should be offered for these patients.

For recommendation 24, evidence with very low certainty suggested a small benefit in overall survival favoring adjuvant chemotherapy, with moderate differences in acute harmful effects for patients with thymic carcinoma. The long-term adverse effects were not well documented but are likely trivial for patients with thymic carcinoma. Because the certainty in the evidence was very low, the working group recommended adjuvant chemotherapy after discussion at an MCC for patients with advanced stages who have poorer prognosis and may benefit from this therapy.

Unresectable stage III disease

Recommendations 25 and 26 remained consistent with the current recommendation for patients with TNM stage III thymoma.

Thymic Carcinoma TNM Eighth Edition Stage IVa (TanyN1M0/TanyN0M1a/TanyN1M1a) (involvement of anterior [perithymic] nodes/separate pleural or pericardial nodule(s)/anterior [perithymic] nodes, separate pleural or pericardial nodule(s))

27. Patients should all be discussed at an MCC and be evaluated for multimodality therapy. *Resectable or potentially resectable stage IVa disease*

Surgery

28. Surgery should be considered either initially or after neoadjuvant therapy, with the aim being total removal of all tumors with clear surgical margins. Surgery is recommended only if pleural and pericardial metastases can be resected.

29. Total resection is preferred over partial resection.

30. Open thymectomy is recommended as the standard of care.

31. If at initial surgery there are concerns about clear resection margins, clips should be placed to mark areas at risk to guide PORT. If it is apparent before surgery that complete resection may not be feasible, neoadjuvant chemotherapy or chemoradiotherapy should be considered before surgery.

Table 3. Continued

32. Unilateral phrenic nerve resection is acceptable. Bilateral phrenic nerve resection is contraindicated because of the severe respiratory morbidity that results.

Neoadjuvant systemic therapy

33. Neoadjuvant chemotherapy is recommended in this setting.

34. 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 is a reasonable option.

PORT and adjuvant systemic therapy

35. PORT should be offered if the patient has not received neoadjuvant radiotherapy.

36. Neoadjuvant chemotherapy is the preferred option.

Unresectable stage IVa disease

37. The distinction between resectable and unresectable disease is controversial and patients with suspected unresectable stage IVa disease should be discussed at an MCC for consideration for referral to a high-volume tertiary thoracic surgical center.

38. Where surgery is not feasible, chemotherapy concurrent with, or sequential to, radiotherapy is recommended.

Justification for recommendations for Thymic Carcinoma TNM Stage IVa (TanyN1M0/TanyN0M1a/TanyN1M1a)

Recommendation 27 was added to emphasize that multimodality therapy should be considered.

Surgery

Recommendation 28 remained consistent with the current recommendation for patients with TNM stage IVa thymoma.

Recommendations 29 and 30 remained consistent with the recommendations for patients with TNM stages I to III thymic carcinoma.

Recommendations 31 and 32 remained consistent with the current recommendation for patients with TNM stage IVa thymoma.

Neoadjuvant systemic therapy

For recommendation 33, there was evidence to suggest that patients respond to chemotherapy and potentially improve the chance of an R0 resection. Nevertheless, the impact on survival is unknown. This recommendation remained consistent with the current recommendation for patients with TNM stage IVa thymoma.

Recommendation 34 remained consistent with the current recommendation for patients with TNM stage IVa thymoma.

PORT and adjuvant systemic therapy

The evidence suggested that there was possibly a moderate difference in desirable effects favoring PORT compared with no PORT, with trivial differences in acute harmful effects. The long-term adverse effects were not well documented for patients with thymic carcinoma. The working group believed that PORT's benefits outweighed the potential harm in these patients.

For recommendation 36, the working group preferred to give chemotherapy in the neoadjuvant setting to try to reduce the size of the tumor and improve the chance of an R0 resection, rather than give chemotherapy in the adjuvant setting.

Unresectable stage IVa disease

Recommendations 37 and 38 remained consistent with the current recommendation for patients with TNM stage IVa thymoma.

Thymic Carcinoma TNM Eighth Edition Stage IVb (TanyN2M0/TanyN2M1a/TanyNanyM1b) (Involvement of deep intrathoracic or cervical nodes/Deep intrathoracic or cervical nodes, separate pleural or pericardial nodule(s)/Pulmonary intraparenchymal nodule or distant organ metastasis)

39. This is a heterogeneous group of patients and treatment decisions should reflect the extent and location of metastatic disease. Generic recommendations are not possible. These patients should be discussed at an MCC, and treatment goals reviewed. Treatment options include chemotherapy (platinum-based recommended; there is insufficient evidence to recommend the routine use of other systemic agents), radiotherapy, and potential surgery.

Justification for recommendations for Thymic Carcinoma TNM Stage IVb (TanyN2M0/TanyN2M1a/TanyNanyM1b)

Because this is a heterogeneous group of patients, generic recommendations were not possible. Therefore, treatment options were provided that need to be discussed at an MCC. There was evidence to suggest that there was no clear advantage in response between anthracycline and non-anthracycline platinum-based chemotherapy in patients with advanced or recurrent thymic carcinoma.

Furthermore, there was insufficient indirect evidence from patients with advanced or recurrent thymoma to suggest an advantage of other first-line systemic agents such as octreotide over platinum-based chemotherapy. Moreover, there was insufficient evidence to recommend second-line agents such as pembrolizumab.

Thymic Carcinoma Recurrent Disease

40. These patients should be discussed at an MCC, and multimodality therapy should be considered.

Surgery

41. Resection should be considered in patients with intrathoracic disease. This should be considered as part of multimodality care.

Radiotherapy

42. Radiotherapy may be appropriate either alone or as part of multimodality care.

Systemic therapy

43. Cisplatin-based chemotherapy may be an appropriate therapy either alone or as part of multimodality care. There is insufficient evidence to recommend the routine use of other systemic agents.

Justification for recommendations for Thymic Carcinoma recurrent disease

Recommendation 40 was added to emphasize that multimodality therapy should be considered.

Surgery

Recommendation 41 remained consistent with the current recommendation for patients with recurrent thymoma.

Radiotherapy

Recommendation 42 remained consistent with the current recommendation for patients with recurrent thymoma.

Systemic therapy

For recommendation 43, there was evidence to suggest that there was no clear advantage in response between anthracycline and non-anthracycline platinum-based chemotherapy in patients with advanced or recurrent thymic carcinoma. Furthermore, there was insufficient indirect evidence from patients with advanced or recurrent thymoma to suggest an advantage of other first-line systemic agents such as octreotide over platinum-based chemotherapy. Moreover, there was insufficient evidence to recommend second-line agents such as pembrolizumab.

Table 4. Recommendations for Patients With Thymic NETs (Endorsed from the NCCN Version 1.2021 Neuroendocrine and Adrenal Tumors Guideline⁶)

Thymic NETs Localized disease (Stages I-II)

Surgery

1. Total resection is preferred over partial resection.
2. Open thymectomy is recommended as the standard of care.

Justification for recommendations for Thymic NETs localized disease (Stages I-II)

The working group endorsed NCCN Version 1.2021 Neuroendocrine and Adrenal Tumors Guideline recommendation to resect patients with localized (stages I-II) thymic NETs.⁷ The specific technical surgical recommendations 1 and 2 remained consistent with the PEBC recommendations for patients with TNM stage I thymic carcinoma. Indirect evidence from studies that included patients with MK stage I/II thymoma was used to inform recommendation 1.

Thymic NETs Resectable Locoregional Disease (Stage IIIA/B)

Surgery

3. Total resection is preferred over partial resection.
 4. Open thymectomy is recommended as the standard of care.
- Incomplete resection and/or positive margins with low grade (typical carcinoid)*

5. Consider observation, or Consider radiotherapy

Incomplete resection and/or positive margins with intermediate grade (atypical carcinoid)

6. Consider observation, or Consider radiotherapy ± cytotoxic chemotherapy. Chemoradiation is thought to have most efficacy for tumors with atypical histology or tumors with higher mitotic and proliferative indices (e.g., Ki-67). Cytotoxic chemotherapy options include cisplatin + etoposide or carboplatin + etoposide.

Justification for Recommendations for Thymic NETs Resectable Locoregional Disease (Stage IIIA/B)

The working group endorsed NCCN version 1.2021 Neuroendocrine and Adrenal Tumors guideline recommendation to completely resect patients with resectable locoregional (stage IIIa/b) thymic NETs.⁶ The specific technical surgical recommendations 3 and 4 remained consistent with the PEBC recommendations for patients with TNM stage I thymic carcinoma. Indirect evidence from studies that included patients with MK stage I/II thymoma was used to inform recommendation 3.

Recommendations 5 and 6 were endorsed from the NCCN version 1.2021 Neuroendocrine and Adrenal Tumors guideline.⁶

Thymic NETs Locally Unresectable Locoregional Disease (Stage IIIA/B)

7. For symptom control, consider addition of focal therapy (i.e., endobronchial therapy debulking, ablation).

*Primary therapy**Low grade (typical carcinoid)*

8. Observation (if asymptomatic), or Octreotide or lanreotide (if SSR positive and/or hormonal symptoms), or Everolimus, or Temozolomide ± capecitabine, or Radiotherapy

Intermediate grade (atypical carcinoid)

9. Observation (if asymptomatic and nonprogressive), or Radiotherapy ± concurrent cisplatin + etoposide or carboplatin + etoposide (chemoradiation is thought to have most efficacy for tumors with atypical histology or tumors with higher mitotic and proliferative indices [e.g., Ki-67]), or Cytotoxic chemotherapy with cisplatin + etoposide or temozolomide ± capecitabine, or Octreotide or lanreotide (if SSR positive and/or hormonal symptoms), or Everolimus

Subsequent therapy

10. If disease progression, treatment with octreotide or lanreotide should be discontinued for nonfunctional tumors and continued in patients with functional tumors; those regimens may be used in combination with any of the subsequent options.
11. Clinical trial (preferred), or Consider changing therapy if progression on first-line therapy, or Consider peptide receptor radionuclide therapy with ¹⁷⁷Lu-dotatate (if SSR positive and progression on octreotide/lanreotide).

Justification for Recommendations for Thymic NETs Locally Unresectable Locoregional Disease (Stage IIIA/B)

Recommendations 7 to 11 were endorsed from the NCCN Version 1.2021 Neuroendocrine and Adrenal Tumors Guideline.⁶

Thymic NETs Metastatic Disease (Stage IV)

12. For symptom control, consider addition of focal therapy (i.e., endobronchial therapy debulking, ablation).

13. NETs are highly heterogeneous, and all elements need to be considered (e.g., burden of disease, symptoms, histopathology, rate of growth) when determining the best course of treatment.

Asymptomatic, low tumor burden, and low grade (typical carcinoid)

14. Observe (chest CT with contrast and abdominal/pelvic multiphasic CT or magnetic resonance imaging every 3-6 mo) or octreotide or lanreotide (if SSR positive and/or hormonal symptoms).

Clinically significant tumor burden and low grade (typical carcinoid) or evidence of disease progression or intermediate grade (atypical carcinoid) or symptomatic disease

15. Clinical trial (preferred), or Observation, in select patients (observation can be considered if asymptomatic or for tumors on the lower end of the spectrum), or Octreotide or lanreotide (if SSR positive and/or hormonal symptoms), or Everolimus, or Peptide receptor radionuclide therapy with ¹⁷⁷Lu-dotatate (if SSR positive and progression on octreotide or lanreotide), or Cisplatin + etoposide or carboplatin + etoposide or temozolomide ± capecitabine (can be considered for intermediate grade/atypical tumors with Ki-67 proliferative index and mitotic index in the higher end of the defined spectrum), or Liver-directed therapy for liver-predominant disease

16. Consider changing therapy if progression on first-line therapy. If disease progression, treatment with octreotide or lanreotide should be discontinued for nonfunctional tumors and continued in patients with functional tumors; those regimens may be used in combination with any of the subsequent options.

Justification for Recommendations for Thymic NETs Metastatic Disease (Stage IV)

Recommendations 12 to 16 were endorsed from the NCCN Version 1.2021 Neuroendocrine and Adrenal Tumors Guideline.⁶

CRedit Authorship Contribution Statement

Conrad B. Falkson: Supervision, Conceptualization, Methodology, Writing—review and editing.

Emily T. Vella: Conceptualization, Methodology, Validation, Writing—original draft, Visualization, Project administration.

Peter M. Ellis, Donna E. Maziak, Yee C. Ung, Edward Yu: Conceptualization, Methodology, Writing—review and editing.

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Supplementary Data

To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at <https://doi.org/10.1016/j.jtho.2022.08.007>

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Appendix A. Affiliations and Conflict of Interest Declarations

Name and Affiliation	Declarations of Interest
Working Group	
Conrad Falkson (lead) Radiation Oncologist Lung Cancer Disease Site Group	None declared
Peter Ellis Medical Oncologist Lung Cancer Disease Site Group	Received \$500 or more in a single year from honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck, Jazz, Jansen, and Novartis and on an advisory board or as a speaker from Pfizer and Takeda
Donna Maziak Surgeon Lung Cancer Disease Site Group	None declared
Yee Ung Radiation Oncologist Lung Cancer Disease Site Group	None declared
Emily Vella Health Research Methodologist Program in Evidence-Based Care	None declared
Edward Yu Radiation Oncologist Lung Cancer Disease Site Group	None declared
Lung Cancer Disease Site Group Expert Panel	
Abdollah Behzadi Surgeon Lung Cancer Disease Site Group	None declared
Penelope Bradbury Medical Oncologist Lung Cancer Disease Site Group	Received \$500 or more in a single year in a consulting capacity from AbbVie, Boehringer Ingelheim, Merck, and Eli Lilly
Adrien Chan Medical Oncologist Lung Cancer Disease Site Group	None declared
Susanna Cheng Medical Oncologist Lung Cancer Disease Site Group	Received \$500 or more in a single year from advisory boards from Merck, AstraZeneca, and Amgen
Gail Darling Surgeon Ontario Thoracic Cancers Lead	None declared
Medhat El-Mallah Radiation Oncologist Lung Cancer Disease Site Group	None declared
John Goffin Medical Oncologist Lung Cancer Disease Site Group	Received \$500 or more in a single year from an honorarium from Eisai (2020), Bristol-Myers Squibb (2020), and Merck (2018), from a speaking fee from Amgen (2018), and as conference travel support from AstraZeneca (2017)
Richard Gregg Medical Oncologist Lung Cancer Disease Site Group	None declared
Donald Jones Surgeon Lung Cancer Disease Site Group	None declared
Jaro Kotalik Bioethicist Lung Cancer Disease Site Group	None declared
Swati Kulkarni Medical Oncologist Lung Cancer Disease Site Group	None declared
Sara Kuruvilla Medical Oncologist Lung Cancer Disease Site Group	None declared
Natasha Leigh Medical Oncologist Lung Cancer Disease Site Group	Received institutional support from Amgen, Array, AstraZeneca, Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Pfizer, Takeda, Novartis, Lilly, Bayer, Guardant Health, Inivata

(continued)

Appendix A. Continued

Name and Affiliation	Declarations of Interest
Robert MacRae Radiation Oncologist Lung Cancer Disease Site Group	Received \$500 or more in a single year from AstraZeneca as an advisory board member in 2019
Richard Malthaner Surgeon Lung Cancer Disease Site Group	None declared
Andrew Pearce Radiation Oncologist Lung Cancer Disease Site Group	None declared
Andrew Robinson Medical Oncologist Lung Cancer Disease Site Group	None declared
Alexander Sun Radiation Oncologist Lung Cancer Disease Site Group	None declared
Anand Swaminath Radiation Oncologist Lung Cancer Disease Site Group	None declared
Julius Toth Surgeon Lung Cancer Disease Site Group	None declared
Mark Vincent Medical Oncologist Lung Cancer Disease Site Group	<ul style="list-style-type: none"> Received \$500 or more in a single year from advisory boards from AstraZeneca, Roche, Bristol-Myers Squibb, Amgen, and Apobiologix Was a principal investigator for AstraZeneca for an osimertinib trial
Kazuhiro Yasufuku Surgeon Lung Cancer Disease Site Group	None declared
Robert Zeldin Surgeon Lung Cancer Disease Site Group	None declared
Report Approval Panel	
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Jonathan Sussman Scientific Director, Program in Evidence-Based Care Chair, Department of Oncology Juravinski Cancer Centre, Hamilton	None declared
Eric Winquist Professor, Department of Oncology University of Western Ontario Chair, Genitourinary Disease Site Team London Health Sciences Centre	<ul style="list-style-type: none"> Received \$500 or more in a single year from Amgen, Bayer, Eisai, Ipsen, Merck, and Roche Received an unrestricted educational grant from Eisai
Targeted Peer Reviewers	
Anthony Brade Trillium Health Partners, Credit Valley Hospital, Peel Regional Cancer Centre, Department of Radiation Oncology Mississauga, Ontario	None declared
Nicholas Garth The Ottawa Hospital Cancer Centre Ottawa, Ontario	None declared

Note: In accordance with the PEBC Conflict of Interest Policy, the Members of the Treatment of Thymic Tumors GDG Working Group, Expert Panel, Report Approval Panel, and Targeted Peer Reviewers were asked to disclose potential conflict of interest. PEBC, Program in Evidence-Based Care.

Appendix B. Responses to GRADE's Evidence-to-Decision Framework

Type of Tumor	Comparison	Desirable Effects	Undesirable Effects	Certainty of Evidence	Balance of Values	Balance of Effects	Equity	Acceptability	Feasibility	Generalizable
Thymoma	Partial vs. total thymectomy	Trivial	Trivial	Very low	No uncertainty or variability	Does not favor either	Probably no impact	Probably yes	Probably yes	Probably yes, not for patients with MG
Thymoma	MIS vs. open thymectomy	Small	Trivial	Very low	No uncertainty or variability	Probably favors MIS	Probably no impact	Yes	Yes	Yes, for early stage thymoma
Thymoma	PORT vs. no PORT	Varies small for early stage, moderate for late state	Trivial for acute effects. Do not know for long-term effects	Low	Possibly important uncertainty or variability	Probably favors PORT	Probably reduced	Yes	Yes	Yes, based on stage
Thymic carcinoma	PORT vs. no PORT	Varies small for early stage, moderate for late state	Trivial for acute effects. Do not know for long-term effects	Low	Possibly important uncertainty or variability	Probably favors PORT	Probably reduced	Yes	Yes	Yes, based on stage
Thymoma	Neoadjuvant chemotherapy vs. no neoadjuvant chemotherapy	Do not know, but potentially small	Moderate for acute effects. Do not know, but likely trivial for long-term effects.	Very low	No uncertainty or variability. Most people would value resectability and OS.	Do not know	Probably no impact	Yes	Yes	Do not know
Thymic carcinoma	Neoadjuvant chemotherapy vs. no neoadjuvant chemotherapy	Do not know, but potentially small	Moderate for acute effects. Do not know, but likely trivial for long-term effects.	Very low	No uncertainty or variability. Most people would value resectability and OS.	Do not know	Probably no impact	Yes	Yes	Do not know
Thymoma	First-line systemic therapy vs. no first-line systemic therapy	Do not know, but potentially small	Moderate for acute effects. Do not know, but likely trivial for long-term effects.	Very low	No uncertainty or variability. Most people would value resectability and OS.	Do not know	Probably no impact	Yes	Yes	Do not know
Thymic carcinoma	First-line systemic therapy vs. no first-line	Do not know, but potentially small	Moderate for acute effects. Do not know, but likely trivial for	Very low	No uncertainty or variability. Most people would value	Do not know	Probably no impact	Yes	Yes	Do not know

(continued)

Appendix B. Continued										
Type of Tumor	Comparison	Desirable Effects	Undesirable Effects	Certainty of Evidence	Values	Balance of Effects	Equity	Acceptability	Feasibility	Generalizable
Thymoma	systemic therapy vs. no second-line therapy	Do not know, but potentially small	long-term effects. Moderate for acute effects. Do not know, but likely trivial for long-term effects.	Very low	resectability and OS. No uncertainty or variability. Most people would value resectability and OS.	Do not know	Probably no impact	Yes	Yes	Do not know
Thymic carcinoma	Second-line systemic therapy vs. no second-line therapy	Do not know, but potentially small	Moderate for acute effects. Do not know, but likely trivial for long-term effects.	Very low	No uncertainty or variability. Most people would value resectability and OS.	Do not know	Probably no impact	Yes	Yes	Do not know
Thymoma	Adjuvant chemotherapy vs. no adjuvant therapy	Do not know, but potentially small	Moderate for acute effects. Do not know, but likely trivial for long-term effects.	Very low	No uncertainty or variability	Do not know	Probably no impact	Yes	Yes	Do not know
Thymic carcinoma	Adjuvant chemotherapy vs. no chemotherapy	Small	Moderate for acute effects. Do not know, but likely trivial for long-term effects.	Very low	No uncertainty or variability	Favors adjuvant chemotherapy	Probably no impact	Yes	Yes	Yes, based on stage

Note: The data for the surgical comparisons were very limited for patients with thymic carcinoma. Therefore, indirect evidence from patients with thymoma was used as indirect evidence for these comparisons. GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; MG, myasthenia gravis; MIS, minimally invasive surgery; OS, overall survival; PORT, postoperative radiotherapy.

Appendix C. Program in Evidence-Based Care's Previous Recommendations for Patients With 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 the phrenic nerve to the 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. 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 tumor adherent to the pericardium.

11. Radiotherapy has risks for acute- and long-term toxicity, notably a risk for the development of secondary malignancies⁴ and coronary heart disease.⁵ 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 after neoadjuvant therapy, with the aim being complete removal of the tumor with wide surgical margins. In stage IIIB, patients should be assessed for surgery after neoadjuvant chemoradiotherapy.
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 tumor for adjuvant radiation. If it is apparent before surgery that complete resection may not be feasible, neoadjuvant chemoradiation should be considered before 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 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.

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. To establish the diagnosis of thymoma, either a computerized tomography-guided core-needle biopsy or an open surgical biopsy should be performed, before 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 it is generally defined as extensive tumor 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 after neoadjuvant therapy, with the aim being complete removal 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 extensive or technically unresectable pleural or pericardial metastases, chemotherapy is most often 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.