Ontario Health
Cancer Care Ontario

Guideline 7-11 Version 3

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

Surgical, Radiation, and Systemic Treatments of Patients with Thymic Epithelial Tumours

C. Falkson, E.T. Vella, P.M. Ellis, D.E. Maziak, Y.C. Ung, E. Yu and the Lung Cancer Disease Site Group

An assessment conducted in November 2023 deferred the review of Guideline 7-11 Version 3. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 7-11 Version 3 comprises 5 sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/736

Section 1:	**Recommendations Summary**
Section 2:	**Guideline**
Section 3:	**Guideline Methods Overview**
Section 4:	**Evidence Review**
Section 5:	**Internal and External Review**

Report Date: March 10, 2022

For information about this document, please contact Dr. C. Falkson, the lead author, through the PEBC at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

For information about the PEBC and the most current version of all reports, please visit the OH (CCO) website at https://www.cancercareontario.ca/en/guidelines-advice or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

PEBC Report Citation (Vancouver Style): Falkson C, Vella ET, Ellis PM, Maziak D, Ung YC, Yu E. Surgical, radiation, and systemic treatments of patients with thymic epithelial tumours. Toronto (ON): Ontario Health (Cancer Care Ontario); 2022 March 10. Program in Evidence-Based Care Guideline No.: 7-11 version 3.

Copyright

This report is copyrighted by Ontario Health (Cancer Care Ontario); the report and the illustrations herein may not be reproduced without the express written permission of Ontario Health (Cancer Care Ontario). Ontario Health (Cancer Care Ontario) reserves the right at any time, and at its sole discretion, to change or revoke this authorization.

Disclaimer

Care has been taken in the preparation of the information contained in this report. Nevertheless, any person seeking to consult the report or apply its recommendations is expected to use independent medical judgment in the context of individual clinical circumstances or to seek out the supervision of a qualified clinician. Ontario Health (Cancer Care Ontario) makes no representations or guarantees of any kind whatsoever regarding the report content or its use or application and disclaims any responsibility for its use or application in any way.

Table of Contents

Surgical, Radiation, and Systemic Treatments of Patients with Thymic Epithelial Tumours

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For the justification associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES

The objective of this guideline is to determine the most effective therapy for patients with thymic epithelial tumours.

TARGET POPULATION

The target population are adult patients with thymic epithelial tumours, including thymoma, thymic carcinoma, and thymic neuroendocrine tumours (NETs).

INTENDED USERS

The intended users of this guideline are all healthcare professionals managing patients with thymic epithelial tumours.

DEFINITIONS

Complete resection – refers to an R0 resection of the tumour 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 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), the tumour, and any involved structures

Partial resection – refers to resection of less than the entire thymus, but includes the tumour and any involved structures

RECOMMENDATIONS

The staging system for patients with thymic epithelial tumours has recently changed to a TNM staging system [1,2]. The evidence used to support these recommendations was mainly from observational studies that used the prior Masaoka and Masaoka-Koga staging systems [3,4]. Given the lack of randomized trials, the Working Group endorsed most of the consensus-based recommendations from the previous version of this guideline [5] (see Appendix 1). For patients with thymic NETS, recommendations were endorsed from the National Comprehensive Cancer Network (NCCN) Version 1.2021 Neuroendocrine and Adrenal Tumors Guideline [6].

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 multidisciplinary cancer conference (MCC) is strongly recommended, not just at local MCC but also with higher-volume centres. Presentation at the International Thymic Malignancies Interest Group tumour board should be considered.

PATIENTS WITH THYMOMA

THYMOMA TNM 8th 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 myasthenia gravis (MG).
2. Open or minimally invasive approaches (e.g., video-assisted thoracic surgery [VATS] or robot-assisted thoracoscopic surgery [RATS]) are both recommended as the standard of care.

Radiotherapy

3. Neoadjuvant radiotherapy is not recommended.
4. Postoperative radiotherapy (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.

THYMOMA TNM 8th 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. However, 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 versus 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.

THYMOMA TNM 8th 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 following neoadjuvant therapy, with the aim being total removal of the tumour 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 prior to surgery that complete resection may not be feasible, neoadjuvant chemotherapy or chemoradiotherapy should be considered prior to 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. Histological confirmation of diagnosis is recommended prior to 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 centre.
24. Where surgery is not feasible, chemotherapy concurrent with, or sequential to, radiotherapy is recommended.

THYMOMA TNM 8th 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 following neoadjuvant therapy, with the aim being total removal of all tumour 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 prior to surgery that complete resection may not be feasible, neoadjuvant chemotherapy or chemoradiotherapy should be considered prior to 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 centre.
36. Where surgery is not feasible, chemotherapy can be considered. Chemotherapy can be given concurrent with, or sequential to, radiotherapy.

THYMOMA TNM 8th 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.

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.

PATIENTS WITH THYMIC CARCINOMA

THYMIC CARCINOMA TNM 8th 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.
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.

THYMIC CARCINOMA TNM 8th 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 versus 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.

THYMIC CARCINOMA TNM 8th 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 following neoadjuvant therapy, with the aim being total removal of the tumour 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 prior to surgery that complete resection may not be feasible, neoadjuvant chemotherapy or chemoradiotherapy should be considered prior to 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. Histological confirmation of diagnosis is recommended prior to 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 centre.
26. Where surgery is not feasible, chemotherapy concurrent with, or sequential to, radiotherapy is recommended.

THYMIC CARCINOMA TNM 8th 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 following neoadjuvant therapy, with the aim being total removal of all tumour 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 prior to surgery that complete resection may not be feasible, neoadjuvant chemotherapy or chemoradiotherapy should be considered prior to surgery.
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 centre.
38. Where surgery is not feasible, chemotherapy concurrent with, or sequential to, radiotherapy is recommended.

THYMIC CARCINOMA TNM 8th 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.

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.

PATIENTS WITH THYMIC NEUROENDOCRINE TUMOURS
(endorsed from the NCCN Version 1.2021 Neuroendocrine and Adrenal Tumors Guideline [6])

THYMIC NEUROENDOCRINE TUMOURS Localized disease (Stage I-II)

Surgery

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

THYMIC NEUROENDOCRINE TUMOURS 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 tumours with atypical histology or tumours with higher mitotic and proliferative indices (e.g., Ki-67). Cytotoxic chemotherapy options include cisplatin + etoposide, or carboplatin + etoposide.

THYMIC NEUROENDOCRINE TUMOURS 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 somatostatin receptor [SSR]-positive and/or hormonal symptoms), or
   Everolimus, or
   Temozolomide ± capecitabine, or
   Radiotherapy

Intermediate grade (atypical carcinoid)

9. Observation (if asymptomatic and non-progressive), or
   Radiotherapy ± concurrent cisplatin + etoposide or carboplatin + etoposide (chemoradiation is thought to have most efficacy for tumours with atypical histology or tumours 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 non-functional tumours and continued in patients with functional tumours; 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).

THYMIC NEUROENDOCRINE TUMOURS 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 tumour burden and low grade (typical carcinoid)

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

Clinically significant tumour 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 tumours 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 tumours 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 non-functional tumours and continued in patients with functional tumours; those regimens may be used in combination with any of the subsequent options.

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 PORT treatments or treatments in

high-volume centres since they may live further away from these centres in Ontario or may have difficulty in acquiring transportation for daily treatments than patients in urban areas or patients who are less disadvantaged. Also, peptide receptor radionuclide therapy has not been approved for patients with thymic epithelial tumours in Ontario.

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.

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 prior clinical experiences with patients with thymic epithelial tumours to assume their relevant values and preferences.

Surgical, Radiation, and Systemic Treatments of Patients with Thymic Epithelial Tumours

Section 2: Guideline – Recommendations and Justification

GUIDELINE OBJECTIVES

The objective of this guideline is to determine the most effective therapy for patients with thymic epithelial tumours.

TARGET POPULATION

The target population are adult patients with thymic epithelial tumours, including thymoma, thymic carcinoma, and thymic neuroendocrine tumours (NETs).

INTENDED USERS

The intended users of this guideline are all healthcare professionals managing patients with thymic epithelial tumours.

DEFINITIONS

Complete resection – refers to an R0 resection of the tumour 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 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), the tumour, and any involved structures

Partial resection – refers to resection of less than the entire thymus, but includes the tumour and any involved structures

RECOMMENDATIONS AND JUSTIFICATION

The staging system for patients with thymic epithelial tumours has recently changed to a TNM staging system [1,2]. The evidence used to support these recommendations was mainly from observational studies that used the prior Masaoka and Masaoka-Koga (MK) staging systems [3,4]. Given the lack of randomized trials, the Working Group endorsed most of the consensus-based recommendations from the previous version of this guideline [5] (see Appendix 1). For patients with thymic NETS, recommendations were endorsed from the National Comprehensive Cancer Network (NCCN) Version 1.2021 Neuroendocrine and Adrenal Tumors Guideline [6].

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 multidisciplinary cancer conference (MCC) is strongly recommended, not just at local MCC but also with higher-volume centres. Presentation at the International Thymic Malignancies Interest Group (ITMIG) tumour board should be considered.

PATIENTS WITH THYMOMA

THYMOMA TNM 8th 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 myasthenia gravis (MG).
2. Open or minimally invasive approaches (e.g., video-assisted thoracic surgery [VATS] or robot-assisted thoracoscopic surgery [RATS]) are both recommended as the standard of care.

Radiotherapy

3. Neoadjuvant radiotherapy is not recommended.
4. Postoperative radiotherapy (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 does not favour 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 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 favouring 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 Program in Evidence-Based Care (PEBC) recommendation for patients with MK stage I thymoma.

For recommendation 4, the evidence suggested there was possibly a small difference in desirable effects favouring 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 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 MK stage III patients in the studies. The magnitude of benefit might be greater for these patients than for patients with MK stage I/II thymoma. However, the Working Group's certainty in the evidence was low. Because these patients are bordering early versus 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 demonstrate benefit with chemoradiotherapy in this population and there would be fewer adverse effects using one modality of therapy rather than two modalities.

THYMOMA TNM 8th 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. However, 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 versus 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 MK stage III patients in the studies. The magnitude of benefit might be greater for these patients than for patients with MK stage I/II thymoma. However, the Working Group's certainty in the evidence was low. Because these patients are bordering early versus 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 toxicities [7] 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 demonstrate benefit with chemoradiotherapy in this population and there would be fewer adverse effects using one modality of therapy rather than two modalities.

THYMOMA TNM 8th 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 following neoadjuvant therapy, with the aim being total removal of the tumour 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 prior to surgery that complete resection may not be feasible, neoadjuvant chemotherapy or chemoradiotherapy should be considered prior to 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. Histological confirmation of diagnosis is recommended prior to 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 centre.
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. However, 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 improve the chance of an R0 resection. However, the impact on survival is unknown. Also, 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 there was possibly a moderate difference in desirable effects favouring 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 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

For recommendation 23, since the definition of unresectable disease is debated, the Working Group believed this should be discussed at an MCC, rather then provide a definition.

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

THYMOMA TNM 8th 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 following neoadjuvant therapy, with the aim being total removal of all tumour 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 prior to surgery that complete resection may not be feasible, neoadjuvant chemotherapy or chemoradiotherapy should be considered prior to 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 centre.
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 following 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 there was possibly a moderate difference in desirable effects favouring 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 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, since the definition of unresectable disease is debated, the Working Group believed this should be discussed at an MCC, rather then provide a definition.

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

THYMOMA TNM 8th 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.

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

Since this is a heterogenous 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 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 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. Also, 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 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 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. Also, there was insufficient indirect evidence to recommend second-line agents such as pembrolizumab.

PATIENTS WITH THYMIC CARCINOMA

THYMIC CARCINOMA TNM 8th 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.
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 (T1aN0M0/T1bN0M0)

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 there was possibly a small difference in desirable effects favouring 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 the absolute overall survival effect might be larger for patients with thymic carcinoma then for patients with thymoma. Therefore, the Working Group recommended that PORT be considered for these patients.

Systemic therapy

For recommendation 5 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 this patients.

Medically Inoperable Stage I Disease

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

THYMIC CARCINOMA TNM 8th 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 versus 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 there was possibly a small difference in desirable effects favouring 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 the absolute overall survival effect might be larger for patients with thymic carcinoma then for patients with thymoma. Also, the magnitude of benefit might be larger for patients with a higher risk of mortality seen 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

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 8th 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 following neoadjuvant therapy, with the aim being total removal of the tumour 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 prior to surgery that complete resection may not be feasible, neoadjuvant chemotherapy or chemoradiotherapy should be considered prior to 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. Histological confirmation of diagnosis is recommended prior to 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 centre.
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 stage 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. However, 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 there was possibly a moderate difference in desirable effects favouring 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 the absolute overall survival effect might be larger for patients with thymic carcinoma then for patients with thymoma. Also, the magnitude of benefit might be larger for patients with a higher risk of mortality seen 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 favouring 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

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

THYMIC CARCINOMA TNM 8th 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 following neoadjuvant therapy, with the aim being total removal of all tumour 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 prior to surgery that complete resection may not be feasible, neoadjuvant chemotherapy or chemoradiotherapy should be considered prior to surgery.

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 centre.
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 stage 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. However, 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 there was possibly a moderate difference in desirable effects favouring 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 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 tumour and improve the chance of an R0 resection, rather than give chemotherapy in the adjuvant setting.

Unresectable Stage IVa Disease

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

THYMIC CARCINOMA TNM 8th 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)

Since this is a heterogenous 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 to suggest an advantage of other first-line systemic agents such as octreotide over platinum-based chemotherapy for patients with advanced or recurrent thymoma. Also, 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 to suggest an advantage of other first-line systemic agents such as octreotide over platinum-based chemotherapy for patients with advanced or recurrent thymoma. Also, there was insufficient evidence to recommend second-line agents such as pembrolizumab.

PATIENTS WITH THYMIC NEUROENDOCRINE TUMOURS

(endorsed from the NCCN Version 1.2021 Neuroendocrine and Adrenal Tumors Guideline [6])

THYMIC NEUROENDOCRINE TUMOURS Localized disease (Stage 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 NEUROENDOCRINE TUMOURS localized disease (Stage I-II)

The Working Group endorsed NCCN Version 1.2021 Neuroendocrine and Adrenal Tumors Guideline recommendation to resect patients with localized (stage I-II) thymic NETs [1]. 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 were used to inform recommendation 1.

THYMIC NEUROENDOCRINE TUMOURS 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 tumours with atypical histology or tumours with higher mitotic and proliferative indices (e.g., Ki-67). Cytotoxic chemotherapy options include cisplatin + etoposide, or carboplatin + etoposide.

Justification for recommendations for THYMIC NEUROENDOCRINE TUMOURS 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 were used to inform recommendation 3.
Recommendations 5 and 6 were endorsed from the NCCN Version 1.2021 Neuroendocrine and Adrenal Tumors Guideline [6].

THYMIC NEUROENDOCRINE TUMOURS 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 somatostatin receptor [SSR]-positive and/or hormonal symptoms), or
   Everolimus, or
   Temozolomide ± capecitabine, or
   Radiotherapy

Intermediate grade (atypical carcinoid)

9. Observation (if asymptomatic and non-progressive), or
   Radiotherapy ± concurrent cisplatin + etoposide or carboplatin + etoposide (chemoradiation is thought to have most efficacy for tumours with atypical histology or tumours 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 non-functional tumours and continued in patients with functional tumours; 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 NEUROENDOCRINE TUMOURS 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 NEUROENDOCRINE TUMOURS 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 tumour burden and low grade (typical carcinoid)

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

Clinically significant tumour 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 tumours 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 tumours 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 non-functional tumours and continued in patients with functional tumours; those regimens may be used in combination with any of the subsequent options.

Justification for recommendations for THYMIC NEUROENDOCRINE TUMOURS Metastatic disease (Stage IV)

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

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 PORT treatments or treatments in high-volume centres since they may live further away from these centres in Ontario or may have difficulty in acquiring transportation for daily treatments than patients in urban areas or patients who are less disadvantaged. Also, peptide receptor radionuclide therapy has not been approved for patients with thymic epithelial tumours in Ontario.

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.

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 prior clinical experiences with patients with thymic epithelial tumours to assume their relevant values and preferences.

Surgical, Radiation, and Systemic Treatments of Patients with Thymic Epithelial Tumours

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

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

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of OH (CCO) supported by the Ontario Ministry of Health (OMH). All work produced by the PEBC is editorially independent from the OMH.

JUSTIFICATION FOR GUIDELINE

Thymic tumours are rare. The previous 2010 PEBC document was based on a formal consensus process and provided recommendations for patients only with thymoma. More comparative studies have been published to guide clinicians in terms of treatment for patients with these tumours. The goal of this updated guideline is to provide clinicians with evidence-based guidance on how to treat patients with thymic epithelial tumours, including thymoma, thymic carcinoma, and thymic NETs.

GUIDELINE DEVELOPERS

This guideline was developed by the Treatment of Thymic Tumours GDG (Appendix 2), 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 Tumours 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. Other members of the Treatment of Thymic Tumours 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 2, 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 [8,9]. This process includes a systematic review, 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 PEBC uses the AGREE II framework [10] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development and to improve the completeness and transparency of reporting in practice guidelines. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

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. This is described in the *PEBC Document Assessment and Review Protocol*.

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 found in Section 4 were included. Guidelines older than three 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: ECRI 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, very few studies were found that could inform the recommendations for thymic NETs. Therefore, an updated search for guidelines that included recommendations for patients with thymic NETS was performed. Guidelines older than three years (published before 2018) were excluded.

The following sources were searched for guidelines on June 11, 2021 with the search terms neuroendocrine and carcinoid: ECRI 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 were found that met the inclusion criteria [6,11]. The Working Group chose to endorse the NCCN 2021 guideline because it provided recommendations for all patients with thymic NETs, whereas the ESMO 2021 provided recommendations only for patients with thymic carcinoids. Although 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.

RECOMMENDATIONS 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 key stakeholders (e.g., patients, clinicians, policy makers, etc.), and the potential impact on equity, acceptability and feasibility of implementation according to GRADE's evidence-to-decision framework [12]. The results of the questions associated with this framework can be found in Appendix 3. If insufficient evidence was found, then the Working Group considered endorsing the recommendations from the previous version of this guideline (see Appendix 1) [5]. A list of any implementation considerations (e.g., costs, human resources, and unique requirements for special or disadvantaged populations, dissemination issues, etc.) was provided along with the recommendations for information purposes.

ENDORSEMENT PROCESS

The Working Group reviewed the NCCN Version 1.2021 Neuroendocrine and Adrenal Tumors Guideline [6] 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 content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey.

DISSEMINATION AND IMPLEMENTATION

The guideline will be published on the OH (CCO) website and may be submitted for publication to a peer-reviewed journal. The Professional Consultation of the External Review is intended to facilitate the dissemination of the guideline to Ontario practitioners. Section 1 of this guideline is a summary document to support the implementation of the guideline in practice. OH (CCO)-PEBC guidelines are routinely included in several international guideline databases including the CPAC Cancer Guidelines Database, the CMA/Joule CPG Infobase database, NICE Evidence Search (UK), and the Guidelines International Network (GIN) Library.

ACKNOWLEDGEMENTS

The Treatment of Thymic Tumours GDG would like to thank the following individuals for their assistance in developing this report:

- Muriel Brackstone, Anthony Brade, Nicholas Garth, Sheila McNair, Duvaraga Sivajohanathan, Jonathan Sussman, Eric Winquist, and Xiaomei Yao for providing feedback on draft versions.
- Faith Maelzer for conducting a data audit.
- Sara Miller for copy editing.

Surgical, Radiation, and Systemic Treatments of Patients with Thymic Epithelial Tumours

Section 4: Systematic Review

INTRODUCTION

Thymic epithelial tumours are relatively rare with an incidence of 3.2 per 1,000,000 people [13]. They are classified as thymoma, thymic carcinoma, and NETs. Approximately 80% of thymic epithelial tumours are thymomas [13]. Thymic carcinomas are less abundant and more aggressive than thymomas [14] with thymic NETs being the least common type [15,16]. The five-year overall survival rates are approximately 90% for thymoma [17], 55% for thymic carcinoma [18] and 28% to 75% for thymic NETs [19,20].

Surgery is considered the standard treatment for patients with thymoma with the aim of negative surgical margins since completeness of resection is the most important prognostic factor [21-23]. Neoadjuvant therapy, typically chemotherapy, is generally given to reduce the size of the tumour to improve the chances of a complete resection [5]. PORT may be given to patients with poorer prognosis [5]. Patients who are not amenable to surgery may be offered a combination of chemotherapy and/or radiotherapy [5].

The PEBC developed a consensus guideline for patients with thymoma [5]. There was little definite evidence to support those recommendations and a consensus process was used to generate recommendations. Since then 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 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 [1,2].

The Working Group of the Treatment of Thymic Tumours GDG developed this evidentiary base to update the evidence and expand the scope to include patients with thymic epithelial tumours. This systematic review will inform the recommendations as part of a clinical practice guideline. Based on the objectives of this guideline (Section 2), the Working Group derived the research question outlined below. This systematic review has been registered on the PROSPERO website (International prospective register of systematic reviews) with the following registration number CRD42020179191 [24].

RESEARCH QUESTION

What are the benefits and harms of the treatment options for patients with thymic epithelial tumours? The interventions under consideration were systemic therapy (chemotherapy, imatinib, cixutumumab, sunitinib, saracatinib, everolimus, octreotide, pembrolizumab, nivolumab, atezolizumab), radiotherapy, surgery, or any combination of these treatments. The comparator was another treatment (systemic therapy, radiotherapy, surgery, or any combination) or no treatment.

Outcomes

The Working Group considered overall survival, toxicity rates (grade 3 or above toxicities), and progression- or recurrence-free survival to be critical outcomes and response rates, and quality of life to be important outcomes for systemic therapy. The Working Group considered overall survival, toxicity rates (pneumonia, esophagitis, dermatitis), progression- or recurrence-free survival to be critical outcomes and response rates, and quality of life to be important outcomes for radiotherapy. The Working Group considered overall survival, and

positive/negative margin rate to be critical outcomes and progression- or recurrence-free survival, short-term (30-day) mortality, response rates, local recurrence, nodal (regional) disease, metastatic disease, quality of life, length of hospital stay, chest-in-tube days, conversion to open sternotomy, intraoperative complications and postoperative complications, toxicity rates (pain), postoperative bleeding, and reoperation to be important outcomes for surgery.

METHODS

Search for Systematic Reviews and Primary Literature

Systematic reviews were included if they met the following criteria: the review addressed the research question with similar inclusion or exclusion criteria, and the review had a moderate or high overall rating as assessed with the AMSTAR 2 tool [25]. If more than one systematic review met the inclusion criteria, then one systematic review for each outcome per comparison was selected by EV based on its age, quality, and the best match with our study selection criteria stated below.

For each outcome per comparison, if no systematic review was included, then a search for primary literature was conducted. For any included systematic review, an updated search for primary literature was performed. If any included systematic review was limited in scope, then a search for primary literature to address the limitation in scope was conducted.

Literature Search Strategy

MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews were searched for systematic reviews since the time of the previous PEBC 2009 publication until April 5, 2021. MEDLINE, EMBASE, and the Cochrane Clinical Trials Registry were searched from inception for primary literature until April 5, 2021. PubMed was searched on August 26, 2021 for primary literature not indexed in MEDLINE. Clinicaltrials.gov was searched on August 26, 2021 for ongoing trials and to identify data from any existing trials (see Appendix 4 for the full search strategies).

Primary Literature Study Selection Criteria and Process

Fully published studies or published abstracts of completed studies of phase II or III randomized controlled trials (RCTs) were included. If no or low-quality RCTs were available, then fully published comparative studies were included. If no comparative studies were available, then fully published non-comparative studies with at least 25 patients were included. Studies with patients who had MG without thymoma were excluded. Studies published in a language other than English were excluded.

A review of the titles and abstracts was done by EV independently. For studies that warranted full-text review, EV reviewed each study in collaboration with CF, if uncertainty existed.

Data Extraction and Assessment of Risk of Bias

All included primary studies underwent data extraction by EV independently, with all extracted data and information audited subsequently by an independent auditor. Ratios, including hazard ratios (HRs), were expressed with a ratio of <1.0 indicating benefit for the intervention rather than the comparator.

Risk of bias (ROB) per outcome for each included study was assessed using ROBINS-I [26] for any observational comparative studies and Cochrane ROB for Interventions [27] for any RCTs.

Synthesizing the Evidence

For time-to-event outcomes, when clinically and methodologically homogeneous results from two or more studies were available, a meta-analysis was conducted using Review Manager 5.4 software provided by the Cochrane Collaboration [28]. HRs, rather than the number of events at a specific time, were the preferred statistic for meta-analysis, and were used as reported. If the HR and/or its standard error were not reported, they were derived from other information reported in the study if available, using the methods described by Parmar et al. [29]. The generic inverse variance model with random effects was used. Adjusted effect measurements were used, if available. In cases where studies reported multiple adjusted estimates, the one that best minimized the ROB due to confounding was selected. Sensitivity analyses by any variability in ROB or by the following confounders: age, stage, year of diagnosis, comorbidity, paraneoplastic syndromes (e.g., MG), socioeconomic status, use of other treatments (e.g., neoadjuvant chemotherapy or chemoradiotherapy, type of surgery), and surgical margin status (i.e., complete resection) may have been conducted. Absolute values were reported for any ratios using baseline risks extracted from included studies.

The chi-squared (X^2) test was used to test the null hypothesis of homogeneity, and a probability level less than or equal to 5% ($p \leq 0.05$) was considered indicative of statistical heterogeneity. If heterogeneity was detected, then the I^2 index was used to quantify the percentage of the variability in the effect estimates that was due to heterogeneity.

The following subgroups were considered for separate analysis: patients with thymoma or thymic carcinoma or thymic NETs (i.e., thymic carcinoids), patients with different TNM classifications or different stages, patients with resectable or unresectable tumours, and patients with recurrent disease. If no data were available from patients for each type of tumour, then studies that had pooled outcomes from patients with different types of thymic epithelial tumours may have been analyzed separately.

When only non-comparative studies were available, the risk of an event (or proportion) in each non-comparative study was calculated. With clinically and methodologically homogenous studies, the proportions from each non-comparative study weighted by the sample size were combined for each intervention. The pooled proportion for each intervention was presented, if possible, but a relative effect between any two interventions was not calculated.

Assessment of the Certainty of the Evidence

The certainty of the evidence per outcome for each comparison, taking into account ROB, inconsistency, indirectness, imprecision, and publication bias was assessed using the Grading of Recommendations, Assessment, Development and Evaluations method [30].

RESULTS

Search for Systematic Reviews

There were 29 systematic reviews that were found on this topic (see Appendix 5). However, none of the systematic reviews matched the (P)opulation, (I)ntervention, (C)ontrol, and (O)utcomes components of the research question with similar inclusion or exclusion criteria.

Search for Primary Literature

Literature Search Results and ROB

There were 10,837 results from the combined MEDLINE, EMBASE and Cochrane search of which 106 studies met the inclusion criteria. A PRISMA flow chart with the reasons for exclusion can be found in Appendix 5. The characteristics of the studies selected for inclusion can be found in Appendix 6. The assessment of the ROB of these included studies can be found in Appendix 7.

Comparisons and the Certainty of the Evidence

The number of included studies is reported in Table 4-1. All of the studies, except for one small RCT [31] and an abstract of an RCT [32], were observational with low to very low certainty in the evidence. The meta-analyses conducted can be found in Appendix 8. The comparison surgery versus no surgery was not included in the results because there would be a strong selection bias to select patients with better prognosis for surgery. Since complete resection is the most robust prognostic indicator for overall survival [21-23], it was assumed that obtaining a complete resection was the preferred treatment choice.

Table 4-1. Number of included studies per outcome per comparison

Treatment(s)	Outcomes	Number of studies
THYMOMA		
Partial thymectomy vs. total thymectomy	OS	5 [33-37]
	DFS	2 [36,38]
	Recurrence	4 [35,39-41]
	Complications	4 [34,39-41]
	Length of stay	3 [34,35,41]
	Chest drainage	3 [34,35,41]
	Blood loss	3 [34,35,41]
Minimally invasive surgery vs. open thymectomy	OS	11 [34,36,42-50]
	DFS	4 [36,46,51,52]
	Recurrence	7 [42,45,48,51,53-55]
	Complications	13 [43,46,48,51,54-62]
	Length of stay	11 [43,45,46,48,58,63-68]
	Chest drainage	8 [43,45,58,63-65,67,68]
	Blood loss	10 [43,45,54,58,63,64,66-69]
Neoadjuvant therapy vs. no neoadjuvant therapy	OS	3 [70-72]
Neoadjuvant chemotherapy vs. no chemotherapy	OS	3 [73-75]
	DFS	2 [73,75]
Neoadjuvant radiotherapy vs. no neoadjuvant therapy	OS	2 [76,77]
Neoadjuvant chemotherapy	Response	2 [78,79]
Radiotherapy and/or chemotherapy vs. no therapy	OS	1 [80]
First-line anthracycline-based therapy	Response	3 [81-83]

First-line octreotide	Response	1 [84]
Second-line cixutumumab	Response	1 [85]
Second-line everolimus	Response	1 [86]
Chemotherapy	Grade ≥3 leukopenia	2 [81,82]
	Grade ≥3 anemia	2 [81,82]
	Grade ≥3 thrombocytopenia	2 [81,82]
Adjuvant chemotherapy vs. no adjuvant chemotherapy	OS	2 [75,87]
	DFS	1 [75]
PORT vs. no PORT	OS	13 [31,36,52,75,88-96]
	DFS	5 [36,52,75,92,95]
	Grade ≥3 toxicities	9 [32,97-104]
	Long-term toxicities	1 [7]
THYMIC CARCINOMA		
Partial thymectomy vs. total thymectomy	OS	1 [105]
Minimally invasive surgery vs. open thymectomy	OS	1 [106]
	DFS	1 [106]
	Length of stay	1 [107]
	Chest drainage	1 [107]
	Blood loss	1 [107]
Neoadjuvant therapy vs. no neoadjuvant therapy	OS	1 [108]
Neoadjuvant chemotherapy vs. no chemotherapy	OS	2 [109,110]
	DFS	1 [110]
Neoadjuvant chemotherapy	Response	1 [111]
First-line chemoradiotherapy vs. chemotherapy	OS	1 [112]
First-line anthracycline-based therapy	Response	2 [113,114]
First-line non-anthracycline-based therapy	Response	6 [114-119]
Chemoradiotherapy	Response	1 [120]
Second-line anthracycline-based therapy	Response	1 [121]

Second-line non-anthracycline-based therapy	Response	1 [121]
Second-line S-1 monotherapy	Response	3 [121-123]
Second-line pembrolizumab	Response	2 [124,125]
Second-line lenvatinib	Response	1 [126]
Chemotherapy	Grade ≥3 leukopenia	2 [113,115]
	Grade ≥3 neutropenia	4 [113,115,118,123]
	Grade ≥3 febrile neutropenia	2 [113,115]
	Grade ≥3 thrombocytopenia	4 [113,118,122,123]
	Grade ≥3 anemia	3 [113,115,123]
	Grade ≥3 nausea	3 [113,118,122]
	Grade ≥3 anorexia	3 [113,115,123]
Pembrolizumab	Grade ≥3 toxicities	1 [125]
Lenvatinib	Grade ≥3 leukopenia	1 [126]
	Grade ≥3 neutropenia	1 [126]
	Grade ≥3 thrombocytopenia	1 [126]
	Grade ≥3 anemia	1 [126]
	Grade ≥3 nausea	1 [126]
Adjuvant chemotherapy vs. no adjuvant chemotherapy	OS	5 [95,106,127-129]
	DFS	7 [92,95,106,129-132]
PORT vs. no PORT	OS	7 [90,95,105,106,110,127,129]
	DFS	6 [95,106,110,127,129,131]
	Grade ≥3 toxicities	9 [32,97-104]
THYMIC NETs		
Partial thymectomy vs. total thymectomy	OS	1 [133]
Neoadjuvant therapy vs. no neoadjuvant therapy	OS	1 [134]
Neoadjuvant chemotherapy vs. no chemotherapy	OS	1 [109]
Adjuvant chemotherapy vs. no adjuvant chemotherapy	OS	2 [109,135]

PORT vs. no PORT	OS	2 [109,135]
	Grade ≥3 toxicities	9 [32,97-104]

Abbreviations: DFS, disease-free survival; NETs, neuroendocrine tumours; OS, overall survival; PORT, postoperative radiotherapy

Comparisons for patients with thymoma

Partial thymectomy versus total thymectomy for patients with thymoma

The absolute point estimates comparing partial thymectomy versus total thymectomy in patients with thymoma slightly favoured partial thymectomy for all patient outcomes, but the certainty in these estimates was low to very low (Table 4-2). The confidence intervals were wide and favoured either treatment at its limits for overall survival, recurrence, complications, and the duration of chest drainage. There was significant heterogeneity for overall survival that was not reduced substantially by removing the study with higher ROB [35] (I^2 = 69%, p=0.02). Furthermore, subgroup analysis by MG status was not significant (p=0.87). However, studies with all patients with MG were compared with studies who had some patients with MG, rather than no patients with MG. Most patients included in the studies had MK stage I or II thymoma. Patients generally received partial thymectomy using minimally invasive techniques, whereas for a total thymectomy, they usually had an open thymectomy. This may have confounded the results. Also, there was concern that patients with more favourable prognosis were selected to receive partial thymectomy and would have biased the results in favour of partial thymectomy. Furthermore, the studies may have not had adequate follow-up to detect any differences in overall survival.

Minimally invasive surgery versus open thymectomy for patients with thymoma

VATS was the main method used for minimally invasive surgery (MIS), with some studies using a combination of VATS and RATS [49,53,57] and others compared RATS versus open thymectomy [55,62]. Most of these studies included patients with stages I or II thymoma. The effects for overall survival (HR, 0.61; 95% confidence interval [CI], 0.43 to 0.85; p=0.004), but not for disease-free survival (DFS) (HR, 1.06; 95% CI, 0.58 to 1.92; p=0.85), comparing MIS versus open thymectomy in patients with thymoma favoured MIS, but the confidence in these estimates was low to very low (Table 4-3). The postoperative outcomes also tended to favour MIS, which resulted in 2.86 fewer days in the hospital, 0.95 fewer days of chest drainage, and 109.01 ml less of blood loss, but again the certainty in these outcomes was very low. There was concern that patients with more favourable prognosis were selected to receive MIS, which would bias the results in favour of MIS, especially for overall survival. Also, patients may have received less extensive surgery with MIS than with open thymectomy. This may have confounded the results.

Neoadjuvant therapy versus no neoadjuvant therapy for patients with thymoma

The point estimates indicated that fewer patients would survive with neoadjuvant therapy compared with no neoadjuvant therapy (Table 4-4). However, the certainty in these estimates was low to very low because of the wide confidence intervals. Patients selected to receive neoadjuvant therapy may have had worse prognosis than patients who did not receive neoadjuvant therapy. This is because the intention of neoadjuvant therapy is to reduce the size of the tumour before resection. There were two included studies that provided the response to neoadjuvant chemotherapy (weighted mean 71%) [78,79].

The most common chemotherapy toxicities were anemia (weighted mean 37%) and leukopenia (weighted mean 30%) [81,82]. These toxicities were reported in patients with stage III or IV thymoma and may not generalize to patients with resectable thymoma.

PORT versus no PORT for patients with thymoma

The relative effects comparing PORT with no PORT in patients with thymoma favoured PORT for overall survival (HR, 0.70; 95% CI, 0.59 to 0.82; p=0.0001) and DFS (HR, 0.60; 95% CI, 0.39 to 0.91; p=0.02) (Table 4-5). It is estimated that the absolute effect would be larger for patients at high risk for death (72 more per 1000 patients survive) than for low-risk patients (18 more per 1000 patients survive). One very small RCT [31] was combined with the observational studies because there was minimal change to the point estimate or heterogeneity with its addition. For overall survival, subgroup analysis by stage (p=0.28) or sensitivity analyses by ROB (p=0.75) or resection status (p=0.38) did not reveal significant interactions. However, for subgroup analysis by resection status, studies were grouped into patients with complete resection and patients with any resection status. There were no HRs available for patients with incomplete resections comparing PORT with no PORT.

All patients in the no PORT group had resectable tumours. Patients who were selected to receive PORT may have had worse prognosis than patients who did not receive PORT. For example, patients with more advanced stages (MK III or IV) may have received PORT more often than patients with less advanced stages. However, even though this selection bias would favour the no PORT group, survival seemed to be longer in patients who received PORT.

Nine studies provided information about toxicities [32,97-104]. Eight non-comparative studies provided information about toxicities for patients receiving PORT. Four of these studies included patients with thymoma or thymic carcinoma [98,100,102,104] and one study included patients with thymic carcinoma or thymic NETs [103]. One abstract of a small RCT reported adverse effects for patients with or without PORT [32]. There appeared to be few instances of grade 3 or greater acute toxicities. These outcomes were not always reported. There was one study that reported the number of patients with thymoma who experienced secondary malignancies and cardiac mortality following radiotherapy [7]. Patients who received radiotherapy did not have statistically higher secondary malignancies (located anywhere [11.7% versus 12.4%, p=0.70] or only in the thorax [3.4% versus 4.3%, p=0.31]) or cardiac mortality (14.3% radiation versus 12.9% no radiation, p=0.83) compared with patients who did not receive radiotherapy.

Adjuvant chemotherapy versus no adjuvant therapy for patients with thymoma

There were very few studies that reported outcomes for this comparison. It seems that patients would not benefit from adjuvant chemotherapy (HR for OS, 1.82; 95% CI, 0.56 to 5.94; p=0.32), but the certainty in these estimates was very low (Table 4-6). Patients with worse prognosis might have been selected for adjuvant chemotherapy compared with patients who did not receive adjuvant therapy, biasing the results toward the no adjuvant therapy group. The confidence intervals were wide and favoured either comparator at its end points. The chemotherapy toxicities were based on patients with advanced stages and may not apply to patients with resectable tumours.

Treatment comparisons for patients with advanced or recurrent thymoma

It appeared that patients with unresectable tumours lived longer with radiotherapy and/or chemotherapy than with no therapy (HR for OS, 0.53; 95% CI, 0.26 to 1.09; p=not reported), but the certainty in this evidence was very low (Table 4-7). Patients with advanced or recurrent thymoma tended to respond to first- or second-line systemic therapy. There seemed to be a higher response with first-line anthracycline-based chemotherapy (weighted mean 70%) than with first-line octreotide (38%), but these agents were not directly compared. There were two studies that reported the response rates to second-line cixutumumab (14%) and everolimus (9%) in patients with advanced or recurrent thymoma [7,85,86]. The chemotherapy

toxicities appeared to be low, but they were underreported with the highest rates for grade ≥ 3 anemia (weighted mean 37%) and grade ≥3 leukopenia (weighted mean 30%).

Table 4-2. Summary of findings for partial thymectomy versus total thymectomy for patients with thymoma

Certainty assessment							Summary of findings					
							# of patients		Effect		Certainty	Importance
# of studies	Design	Risk of bias [a]	Inconsistency	Indirectness	Imprecision	Other considerations	partial	total	Relative (95% CI)	Absolute (95% CI)		
Overall survival (early stages) (median follow-up: range 4 years to 6 years)												
5 [b]	observational	very serious	serious [c]	not serious	not serious	none	1014	2205 95.4% at 5 years [d]	**HR 0.84** (0.44-1.57) [survival]	**7 more per 1000** (from 25 fewer to 25 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**
Disease-free survival (stages I-II) (median follow-up: range 4 years to 9 years)												
2	observational	very serious	not serious	not serious	serious [e]	none	64	97 84.3% at 5 years [f]	**HR 0.41** (0.17-0.95) [disease-free survival]	**89 more per 1000** (from 7 more to 128 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**
Recurrence (median follow-up: range 4 years to 6 years)												
4	observational	very serious	not serious	not serious	not serious	none	14/426 (3.3%)	12/430 (2.8%)	**RR 0.94** (0.34-2.63)	**2 fewer per 1000** (from 18 fewer to 45 more)	⊕⊕◯◯ **LOW**	**CRITICAL**
Complications												
4	observational	very serious	not serious	not serious	not serious	none	23/492 (4.7%)	43/529 (8.1%)	**RR 0.67** (0.40-1.13)	**27 fewer per 1000** (from 49 fewer to 11 more)	⊕⊕◯◯ **LOW**	**IMPORTANT**
Length of stay (days) (stages I-II)												
3	observational	extremely serious	serious [g]	not serious	not serious	none	269	226	-	**MD 1.11 lower** (2.21 lower to 0)	⊕◯◯◯ **VERY LOW**	**IMPORTANT**
Chest drainage (days) (stages I-II)												
3	observational	extremely serious	serious [h]	not serious	not serious	none	269	226	-	**MD 0.89 lower** (1.85 lower to 0.08 higher)	⊕◯◯◯ **VERY LOW**	**IMPORTANT**
Blood loss (ml) (stages I-II)												
3	observational	extremely serious	not serious	not serious	not serious	none	269	226	-	**MD 100.1 lower** (105.87 lower to 94.32 lower)	⊕◯◯◯ **VERY LOW**	**IMPORTANT**

Abbreviations: CI, confidence interval; HR, hazard ratio; MD, mean difference; RR, relative risk

a. According to the ROBINS-I tool

b. There were 8 studies that provided data for HR for overall survival comparing partial thymectomy versus total thymectomy in patients with thymoma. Four studies included patients from the same hospital [33,38,39,136]. Hishida 2020 was chosen for the meta-analysis because it was the largest study with a lower risk of bias.

c. I^2 was 74%, P=0.004
d. Median overall survival from included studies that provided this information
e. Small sample size
f. Reported by Sakamaki 2014 [36]
g. I^2 was 83%, P=0.003
h. I^2 was 84%, P=0.002

Table 4-3. Summary of findings for minimally invasive surgery versus open thymectomy for patients with thymoma

Certainty assessment							Summary of findings					
							# of patients		Effect		Certainty	Importance
# of studies	Design	Risk of bias [a]	Inconsistency	Indirectness	Imprecision	Other considerations	MIS	open	Relative (95% CI)	Absolute (95% CI)		
Overall survival (median follow-up: range 3 years to 12 years)												
11[b]	observational	very serious	not serious	not serious	not serious	none	1076	1760 93.8% at 5 years [c]	**HR 0.61** (0.43-0.85) [survival]	**24 more per 1000** (from 9 more to 35 more)	⊕⊕◯◯ **LOW**	**CRITICAL**
Disease-free survival (median follow-up: range 3 years to 7 years)												
4	observational	extremely serious	not serious	not serious	not serious	none	248	218 75.3 at 5 years% [d]	**HR 1.06** (0.58-1.92) [disease-free Survival]	**13 fewer per 1000** (from 173 fewer to 95 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**
Recurrence (median follow-up: range 2 years to 13 years)												
7[e]	observational	extremely serious	not serious	not serious	not serious	none	14/386 (3.6%)	36/424 (8.5%)	**RR 0.58** (0.31-1.08)	**36 fewer per 1000** (from 59 fewer to 7 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**
Complications												
13[f]	observational	extremely serious	not serious	not serious	not serious	none	49/407 (12.0%)	203/973 (20.9%)	**RR 0.53** (0.36-0.79)	**98 fewer per 1000** (from 134 fewer to 44 fewer)	⊕◯◯◯ **VERY LOW**	**IMPORTANT**
Length of stay (days) (stages I-II)												
11	observational	extremely serious	serious [g]	not serious	not serious	none	463	336	-	**MD 2.86 lower** (3.86 lower to 1.77 lower)	⊕◯◯◯ **VERY LOW**	**IMPORTANT**
Chest drainage (days) (stages I-II)												
8	observational	extremely serious	serious [g]	not serious	not serious	none	374	274	-	**MD 0.95 lower** (1.45 lower to 0.45 lower)	⊕◯◯◯ **VERY LOW**	**IMPORTANT**

Blood loss (ml) (stages I-II)												
10	observational	extremely serious	serious [g]	not serious	not serious	none	464	377	-	**MD 109.01 lower** (155.55 lower to 62.47 lower)	⊕◯◯◯ **VERY LOW**	**IMPORTANT**

Abbreviations: CI, confidence interval; HR, hazard ratio; MD, mean difference; MIS, minimally invasive surgery; RR, relative risk

a. According to the ROBINS-I tool

b. There were 13 studies that provided data for HR for overall survival comparing MIS versus open thymectomy in patients with thymoma. Three studies included patients from the same Chinese hospital [47,52,68]. Tian 2020 Surgical outcomes was chosen for the meta-analysis because it had the lowest risk of bias.

c. Median overall survival from included studies that provided this information

d. Median disease-free survival from included studies that provided this information

e. There were 9 studies that provided HR data for recurrence comparing MIS versus open thymectomy in patients with thymoma. Two studies included patients from the same Japanese hospital [51,137]. Odaka 2017 Thoracoscopic was chosen for the meta-analysis because it was the most recent. Two other studies included patients from the same Japanese hospital [42,69]. Agatsuma 2017 was chosen for the meta-analysis because it had a lower risk of bias.

f. There were 17 studies that provided HR data for complications comparing video-assisted thoracic surgery versus open thymectomy in patients with thymoma. Three studies included patients from the same Japanese hospital [51,67,137]. Odaka 2017 Thoracoscopic was chosen for the meta-analysis because it was the most recent. Three other studies included patients from the same Japanese hospital [39,42,69]. Nakajima 2016 was chosen for the meta-analysis because it was larger.

g. The effect estimates mostly favoured MIS

Table 4-4. Summary of findings for neoadjuvant therapy versus no neoadjuvant therapy for patients with thymoma

Certainty assessment							Summary of findings					
							# of patients		Effect			
# of studies	Design	Risk of bias [a]	Inconsistency	Indirectness	Imprecision	Other considerations	Neoadjuvant therapy	No neoadjuvant therapy	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
OVERALL SURVIVAL												
• **Neoadjuvant therapy vs. no neoadjuvant therapy (median follow-up: range 6 years to 8 years)**												
3[b]	observational	very serious	serious [c]	not serious	serious [d]	none	2905	79.8%[e] at 5 years	**HR 1.53** (0.70-3.33) [survival]	**90 fewer per 1000** (from 326 fewer to 56 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**
• **Neoadjuvant chemotherapy vs. no neoadjuvant therapy (median follow-up: range 3 years to 4 years)**												
3[f]	observational	extremely serious	serious [g]	not serious	serious [d]	none	39	500 79.8%[e] at 5 years	**HR 1.03** (0.20-5.44) [survival]	**5 fewer per 1000** (from 505 fewer to 158 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**

• **Neoadjuvant radiotherapy vs. no neoadjuvant therapy (median follow-up: 6 years)**												
2	observational	very serious	not serious	not serious	not serious	none	40	865 79.8%[e] at 5 years	**HR 1.51** (1.17-1.94) [survival]	**87 fewer per 1000** (from 153 fewer to 30 fewer)	⊕⊕◯◯ **LOW**	**CRITICAL**
DISEASE-FREE SURVIVAL												
• **Neoadjuvant chemotherapy vs. no neoadjuvant therapy (median follow-up: 3 years)**												
2[h]	observational	very serious	not serious	not serious	serious[d]	none	19	466 57.7%[i] at 3 years	**HR 1.90** (0.74-4.87) [disease-free survival]	**225 fewer per 1000** (from 508 fewer to 89 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**
RESPONSE (anthracycline-based)												
2[j]	observational	extremely serious	not serious	not serious	serious[k]	none	62 Weighted mean (SD) 71% (2%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**CRITICAL**
GRADE ≥3 CHEMOTHERAPY TOXICITIES (stages III-IV)												
• **Grade ≥ 3 leukopenia**												
2	observational	extremely serious	not serious	serious[l]	serious[k]	none	67 Weighted mean (SD) 30% (9%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥ 3 anemia**												
2	observational	extremely serious	serious[m]	serious[l]	serious[k]	none	67 Weighted mean (SD) 37% (42%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥ 3 thrombocytopenia**												
2	observational	extremely serious	serious[m]	serious[l]	serious[k]	none	67 Weighted mean (SD) 12% (13%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**

Abbreviations: CI, confidence interval; HR, hazard ratio

a. According to the ROBINS-I tool

b. There were 5 studies that provided data for HR for overall survival comparing neoadjuvant therapy with no neoadjuvant therapy in patients with thymoma. Two studies [70,138] included patients from the same Italian institutions. Guerrara 2015 was chosen for the meta-analyses because it was the larger study with a lower risk of bias. Also, two studies included patients from the same Japanese institution [72,139]. Yamada 2015 was chosen for the meta-analyses because it was the larger study.

c. I^2 was 84%, P=0.002

d. Wide confidence interval

e. Reported in Bian 2019 [140]

f. There were 6 studies that provided data for HR for overall survival comparing neoadjuvant chemotherapy with no neoadjuvant therapy in patients with thymoma. Two studies [73,141] were from overlapping years from the same Japanese hospital. Hakiri 2019 was chosen for the meta-analyses because it was the most recent and largest study. Two studies included patients from the same Indian centre [74,142]. Kumar 2020 Surgical was chosen because it was larger. Two studies included patients from the same Korean center [75,77]. Song 2020 was chosen because it was larger.

g. I^2 was 77%, P=0.01

h. There were 4 studies that provided data for HR for DFS comparing neoadjuvant therapy/chemotherapy with no neoadjuvant therapy in patients with thymoma. Three studies included patients from the same Japanese hospital [72,73,141]. Hakiri 2019 was selected because it had the lowest risk of bias. This study compared neoadjuvant chemotherapy with no neoadjuvant therapy in patients with thymoma.

i. Reported in Yano 2009 [141] for stage IV thymoma

j. There were 3 studies that included the response to anthracycline-based neoadjuvant chemotherapy, but one study with a response of 78% did not report the sample size and could not be included in the weighted outcome [111]

k. Small sample size

l. Studies included patients with stage III-IV thymoma. This may not generalize to resectable patients.

m. Large differences in proportions reported

Table 4-5. Summary of findings for PORT versus no PORT for patients with thymoma

Certainty assessment							Summary of findings					
							# of patients		Effect		Certainty	Importance
# of studies	Study design	Risk of bias [a]	Inconsistency	Indirectness	Imprecision	Other considerations	PORT	No PORT	Relative (95% CI)	Absolute (95% CI)		
Overall survival (resectable patients) (median follow-up: range 3 years to 7 years)												
13[b]	1 RCT 12 observational	very serious	not serious	not serious	not serious	none	3905 patients	4617 patients 94% at 5 years [c]	**HR 0.70** (0.59 to 0.82) [survival]	**18 more per 1000** (from 11 more to 24 more)	⊕⊕◯◯ **LOW**	**CRITICAL**
								73% at 5 years [c]		**72 more per 1000** (from 43 more to 101 more)		
Disease-free survival (resectable patients) (median follow-up: range 4 years to 7 years)												
5[d]	observational	very serious	not serious	not serious	not serious	none	209	256 patients 86% at 5 years [e]	**HR 0.60** (0.39-0.91) [disease-free survival]	**53 more per 1000** (from 12 more to 83 more)	⊕⊕◯◯ **LOW**	**CRITICAL**
								50% at 5 years [e]		**160 more per 1000** (from 32 more to 263 more)		
Grade ≥3 toxicities (resectable patients)												

9	1 RCT 8 case series	very serious	not serious	not serious [f]	not serious	none	10/548	0/19	Not estimable		⊕⊕◯◯ **LOW**	**CRITICAL**

Abbreviations: CI, confidence interval; HR, hazard ratio; PORT, postoperative radiotherapy; RCT, randomized controlled trial

a. According to the ROBINS-I tool

b. There were 21 studies that provided data for HR for overall survival comparing PORT with no PORT in patients with thymoma. Seven studies [37,91,140,143-146] were from overlapping years from the SEER database. Mou 2018 was chosen for the meta-analyses because it had the largest and most inclusive sample from among the studies with lower risk of bias. Two studies included patients from the same Korean database [34,75]. Song 2020 was chosen because it was more recent and larger. Also, three studies were conducted in the same Chinese institution [31,52,101]. Yuan 2017 and Zhang 1999 were chosen for the meta-analyses because the populations did not overlap and because Zhang 1999 was the only small RCT.

c. From the included studies, the second highest survival at 5 years was chosen for the low-risk population and the second lowest survival at 5 years was chosen for the high-risk population.

d. There were 8 studies that provided HR data for disease-free survival comparing PORT with no PORT in patients with thymoma. Three studies [52,99,101] were conducted in the same Chinese institution. Yuan 2017 was chosen in the meta-analyses because it had the largest and most inclusive sample with the lowest risk of bias. Two studies included patients from the same South Korean hospital [75,147]. Song 2020 was chosen for the meta-analysis because it was more recent and larger.

e. Median DFS at 5 years from Chang 2011 [147] and Song 2020 [75] for the low-risk population and from Song 2020 [75] for the high-risk population

f. Indirectness was not a concern because the number of events was consistently low across patients with different types of thymic tumours

Table 4-6. Summary of findings for adjuvant chemotherapy versus no adjuvant therapy for patients with thymoma

Certainty assessment							Summary of findings					Importance
							# of patients		Effect		Certainty	
# of studies	Design	Risk of bias [a]	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvant chemotherapy	No adjuvant therapy	Relative (95% CI)	Absolute (95% CI)		
OVERALL SURVIVAL (median follow-up: 6 years)												
2[b]	observational	very serious	serious [c]	not serious	serious [d]	none	79	566 79.8%[e] at 5 years	**HR 1.82** (0.56-5.94) [survival]	**135 fewer per 1000** (from 536 fewer to 83 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**
DISEASE-FREE SURVIVAL (median follow-up: not reported)												
1	observational	very serious	not serious	not serious	serious [f]	none	20	384 50.2%[g] at 5 years	**HR 1.83** (0.77-4.37) [disease-free survival]	**219 fewer per 1000** (from 453 fewer to 86 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**

GRADE ≥3 CHEMOTHERAPY TOXICITIES (stages III-IV)												
• **Grade ≥3 leukopenia**												
2	observational	extremely serious	not serious	serious [h]	serious [i]	none	67 Weighted mean (SD) 30% (9%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 anemia**												
2	observational	extremely serious	serious [j]	serious [h]	serious [i]	none	67 Weighted mean (SD) 37% (42%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 thrombocytopenia**												
2	observational	extremely serious	serious [j]	serious [h]	serious [i]	none	67 Weighted mean (SD) 12% (13%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**

Abbreviations: CI, confidence interval; HR, hazard ratio

a. According to the ROBINS-I tool
b. There were 3 studies that provided data for HR for overall survival comparing adjuvant chemotherapy with no adjuvant therapy in patients with thymoma. Two studies included patients from the same Korean centre [75,77]. Song 2020 was chosen because it was larger.
c. I^2 was 74%, P=0.05
d. Wide confidence interval
e. Reported in Bian 2019 [140]
f. Only one study
g. Mean of Sandri 2014 [148] and Song 2014 Treatment [149]
h. Studies included patients with stage III-IV thymoma. This may not generalize to resectable patients.
i. Small sample size
j. Large differences in proportions reported

Table 4-7. Summary of findings for first/second-line systemic therapy for patients with advanced/recurrent thymoma

Certainty assessment							Summary of findings					
							# of patients		Effect		Certainty	Importance
# of studies	Design	Risk of bias [a]	Inconsistency	Indirectness	Imprecision	Other considerations	First/second-line therapy	Control	Relative (95% CI)	Absolute (95% CI)		
OVERALL SURVIVAL												
• **Radiotherapy and/or chemotherapy vs. no therapy (median follow-up: not reported)**												

1	observational	very serious	not serious	not serious	serious [b]	none	417	32 38.1%[c] at 5 years	**HR 0.53** (0.26-1.09) [survival]	**219 more per 1000** (from 32 fewer to 397 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**
RESPONSE												
• **Advanced/recurrent (first-line)**												
3 Anthracycline-based	observational	extremely serious	not serious	not serious	serious [d]	none	93 Weighted mean (SD) 70% (17%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**CRITICAL**
1 Octreotide	observational	extremely serious	not serious	not serious	serious [e]	none	32 38%	-	Not estimable		⊕◯◯◯ **VERY LOW**	**CRITICAL**
• **Advanced/recurrent (second-line)**												
1 Cixutumumab	observational	extremely serious	not serious	not serious	serious [e]	none	37 14%	-	Not estimable		⊕◯◯◯ **VERY LOW**	**CRITICAL**
1 Everolimus	observational	extremely serious	not serious	not serious	serious [e]	none	32 9%	-	Not estimable		**VERY LOW**	**CRITICAL**
GRADE ≥3 CHEMOTHERAPY TOXICITIES (stages III-IV)												
• **Grade ≥3 leukopenia**												
2	observational	extremely serious	not serious	not serious	serious [d]	none	67 Weighted mean (SD) 30% (9%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 thrombocytopenia**												
2	observational	extremely serious	serious [f]	not serious	serious [d]	none	67 Weighted mean (SD) 12% (13%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 anemia**												
2	observational	extremely serious	serious [f]	not serious	serious [d]	none	67 Weighted mean (SD) 37% (42%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**

Abbreviations: CI, confidence interval; HR, hazard ratio

a. According to the ROBINS-I tool
b. Only one study
c. Reported by Khorfan 2021 [80]
d. Small sample size
e. Only one study
f. Large differences in proportions reported

Comparisons for patients with thymic carcinoma

Partial thymectomy versus total thymectomy for patients with thymic carcinoma

There was only one study that reported overall survival for this comparison with very low certainty in this evidence (Table 4-8). The point estimate favoured partial thymectomy, but the upper confidence interval favoured total thymectomy (HR, 0.89; 95% CI, 0.55 to 1.45; p=0.646). No studies reported other outcomes for this comparison for patients with thymic carcinoma.

MIS versus open thymectomy for patients with thymic carcinoma

There was only one included study per outcome for this comparison with very low certainty in the evidence (Table 4-9). All MISs were performed by VATS and all point estimates favoured MIS. However, for overall survival, DFS, and the duration of chest drainage, the end points of the confidence intervals favoured open thymectomy. The wide confidence intervals could be attributed to the small sample sizes and, therefore, reduce the confidence in these effects.

Neoadjuvant therapy versus no neoadjuvant therapy for patients with thymic carcinoma

There were very few studies that compared neoadjuvant therapy with no neoadjuvant therapy (Table 4-10). The evidence suggested that more patients would survive longer with neoadjuvant therapy compared with no neoadjuvant therapy (HR, 0.84; 95% CI, 0.49 to 1.42; p=0.510), but not with neoadjuvant chemotherapy compared with no chemotherapy (HR, 1.24; 95% CI, 0.89 to 1.71; p=0.20). However, the certainty in these estimates was very low with wide confidence intervals. These comparisons were not the most appropriate comparisons because neoadjuvant therapy could include chemotherapy or radiotherapy or both. Therefore, it was difficult to determine which treatment combination was the most effective. Also, patients selected to receive neoadjuvant therapy may have had worse prognosis than patients who did not receive neoadjuvant therapy. This is because the intention of neoadjuvant therapy is to reduce the size of the tumour before resection. There was only one included study that provided the response to neoadjuvant chemotherapy (78%) [111].

The most common chemotherapy toxicities were leukopenia (weighted mean 56%) and neutropenia (weighted mean 48%). These toxicities were reported in patients with stage III or IV thymic carcinoma and may not generalize to patients with resectable tumours.

PORT versus no PORT for patients with thymic carcinoma

More patients with thymic carcinoma survived longer with PORT than without PORT (Table 4-11; HR for overall survival, 0.65; 95% CI, 0.47 to 0.89; p=0.008; HR for DFS, 0.59; 95% CI, 0.41 to 0.84; p=0.004). The certainty in the evidence was low. However, the absolute effects for patients with thymic carcinoma were larger than the effects for patients with thymoma. For overall survival, subgroup analysis by stage (p=0.16) or sensitivity analyses by ROB (p=0.07) or resection status (p=0.97) did not reveal significant interactions, but overall survival for patients with complete resection was compared with patients with any resection status rather than patients with an incomplete resection.

All patients in the no PORT group had resectable tumours. Patients who were selected to receive PORT may have had worse prognosis than patients who did not receive PORT. For example, patients with more advanced stages (MK III or IV) may have received PORT more often than patients with less advanced stages. However, even though this selection bias would favour the no PORT group, survival seemed to be longer in patients who received PORT.

Since few studies reported adverse effects, toxicities were reported from the same studies as those reported in the thymoma section.

Adjuvant chemotherapy versus no adjuvant therapy for patients with thymic carcinoma

For overall survival, the absolute value favoured adjuvant chemotherapy in patients with thymic carcinoma (Table 4-12; 94 more per 1000 patients would survive). However, the certainty in the estimate was very low. The majority of studies had extremely serious ROB. Furthermore, it was unclear how many patients received PORT in the no adjuvant chemotherapy group and whether this was balanced with the adjuvant chemotherapy group. However, patients with poorer prognosis may have been selected for adjuvant chemotherapy and may have biased the results in the direction of no adjuvant chemotherapy, yet an overall survival advantage was observed.

For DFS, 13 more per 1000 patients would be disease free longer with adjuvant chemotherapy, but there was heterogeneity across studies. Sensitivity analysis revealed a subgroup effect for ROB (p=0.04), but not with resection status (p=0.14). Studies that had lower ROBs reported smaller effects that favoured no adjuvant chemotherapy (HR, 1.47; 95% CI, 0.76 to 2.82; p=0.25) compared with studies with higher ROBs (HR, 0.70; 95% CI, 0.53 to 0.92; p=0.01).

There were only five studies that reported grade 3 or higher toxicities for chemotherapy in patients with thymic carcinoma [113,115,118,122,123]. There was a wide range in proportions reported with some reporting few events to others reporting more moderate proportions. These studies included patients with MK stages III-IV thymic carcinoma and may not generalize to patients with resectable tumours.

Treatment comparisons for patients with advanced or recurrent thymic carcinoma

It appeared that patients lived longer with first-line chemoradiotherapy than with chemotherapy alone, but this was from one very small study (Table 4-13; HR, 0.42; 95% CI, 0.18 to 1.01; p=0.05) [112]. Patients with advanced or recurrent thymic carcinoma tended to respond to first- or second-line systemic therapy. There did not seem to be a great deal of difference in response to different types of systemic therapies. Ko 2018 found no statistical difference in patients' responses between first-line carboplatin plus paclitaxel (40%) versus cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC) (41%; p=0.90) [114]. Likewise, Agatsuma 2011 did not report a difference in responses between patients who received first-line ADOC (55%) compared with carboplatin-based chemotherapy (20%; p=0.33) [113]. Similarly, in the second-line setting, no differences in responses were observed between patients who received S-1 monotherapy (39%) versus carboplatin plus paclitaxel (21%; p=0.15) or ADOC (21%; p=0.29) [121]. Furthermore, studies comparing different first- or second-line chemotherapy regimens found no statistical differences in overall survival [114,121]. The toxicities appeared to be low in most outcomes, but they were underreported.

Table 4-8. Summary of findings for partial thymectomy versus total thymectomy for patients with thymic carcinoma

Certainty assessment							Summary of findings					
							# of patients		Effect		Certainty	Importance
# of studies	Design	Risk of bias [a]	Inconsistency	Indirectness	Imprecision	Other considerations	partial	total	Relative (95% CI)	Absolute (95% CI)		
Overall survival (median follow-up: unknown)												
1	observational	very serious	not serious	not serious	serious [b]	none	112	122 60% at 5 years [c]	**HR 0.89** (0.55-1.45) [survival]	**35 more per 1000** (from 123 fewer to 155 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**

Abbreviations: CI, confidence interval; HR, hazard ratio

a. According to the ROBINS-I tool

b. Only one study

c. Reported in Lim 2017 [105]

Table 4-9. Summary of findings for minimally invasive surgery versus open thymectomy for patients with thymic carcinoma

Certainty assessment							Summary of findings					
							# of patients		Effect		Certainty	Importance
# of studies	Design	Risk of bias [a]	Inconsistency	Indirectness	Imprecision	Other considerations	MIS	open	Relative (95% CI)	Absolute (95% CI)		
Overall survival (median follow-up: 3 years) (patients with complete resection)												
1	observational	extremely serious	not serious	not serious	serious [b]	none	10	69 60% at 5 years [c]	**HR 0.93** (0.12-7.05) [survival]	**22 more per 1000** (from 573 fewer to 341 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**
Disease-free survival (median follow-up: 3 years) (patients with complete resection)												
1	observational	extremely serious	not serious	not serious	serious [b]	none	10	69 58.5 at 5 years% [d]	**HR 0.45** (0.06-3.31) [disease-free survival]	**201 more per 1000** (from 415 fewer to 383 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**
Recurrence (median follow-up: range 2 years to 9 years)												
0												
Complications												
0												
Length of stay (days)												

1	observational	extremely serious	not serious	not serious	serious [e]	none	4	4		**MD 12.5 lower** (21.32 lower to 3.68 lower)	⊕◯◯◯ **VERY LOW**	**IMPORTANT**
Chest drainage (days)												
1	observational	extremely serious	not serious	not serious	serious [e]	none	4	4		**MD 5.7 lower** (12.63 lower to 1.23 higher)	⊕◯◯◯ **VERY LOW**	**IMPORTANT**
Blood loss (ml)												
1	observational	extremely serious	not serious	not serious	serious [e]	none	4	4		**MD 245.80 lower** (388.1 lower to 103.50 lower	⊕◯◯◯ **VERY LOW**	**IMPORTANT**

Abbreviations: CI, confidence interval; HR, hazard ratio; MD, mean difference; MIS, minimally invasive surgery

a. According to the ROBINS-I tool
b. Only one study with small sample size
c. Reported in Lim 2017 [105]
d. Reported in Liu 2017 [150]
e. Very small sample size

Table 4-10. Summary of findings for neoadjuvant therapy versus no neoadjuvant therapy for patients with thymic carcinoma

Certainty assessment							Summary of findings					Importance
							# of patients		Effect		Certainty	
# of studies	Design	Risk of bias [a]	Inconsistency	Indirectness	Imprecision	Other considerations	Neoadjuvant therapy	No neoadjuvant therapy	Relative (95% CI)	Absolute (95% CI)		
OVERALL SURVIVAL												
• **Neoadjuvant therapy vs. no neoadjuvant therapy (resected patients) (median follow-up: 4 years)**												
1	observational	very serious	not serious	not serious	serious [b]	none	78	137 61%[c] at 5 years	**HR 0.84** (0.49-1.42) [survival]	**50 more per 1000** (from 114 fewer to 175 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**
• **Neoadjuvant chemotherapy vs. no chemotherapy (resected patients) (median follow-up: range 3 to 9 years)**												
2[d]	observational	very serious	not serious	not serious	serious [e]	none	63	231 61%[c] at 5 years	**HR 1.24** (0.89-1.71) [survival]	**68 fewer per 1000** (from 181 fewer to 34 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**
• **Neoadjuvant radiotherapy vs. no radiotherapy**												
0												
DISEASE-FREE SURVIVAL												

Neoadjuvant chemotherapy vs. no neoadjuvant therapy (completely resected) (median follow-up: 9 years)												
1[f]	observational	very serious	not serious	not serious	serious[b]	none	169	44.1% at 5 years[g]	**HR 1.72** (0.91-3.25) [disease-free survival]	**196 fewer per 1000** (from 371 fewer to 34 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**
RESPONSE (anthracycline-based)												
1	observational	extremely serious	not serious	not serious	serious[b]	none	91 74%		Not estimable		⊕◯◯◯ **VERY LOW**	**CRITICAL**
GRADE ≥3 CHEMOTHERAPY TOXICITIES (stages III-IV)[h]												
• **Grade ≥3 leukopenia**												
2	observational	extremely serious	not serious	serious[j]	serious[k]	none	99 Weighted mean (SD) 56% (14%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 neutropenia**												
4	observational	extremely serious	serious[i]	serious[j]	serious[k]	none	180 Weighted mean (SD) 48% (34%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 febrile neutropenia**												
2	observational	extremely serious	not serious	serious[j]	serious[k]	none	99 Weighted mean (SD) 8% (3%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 thrombocytopenia**												
4	observational	extremely serious	not serious	serious[j]	serious[k]	none	144 Weighted mean (SD) 3% (3%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 anemia**												
3	observational	extremely serious	not serious	serious[j]	serious[k]	none	143 Weighted mean (SD) 7% (6%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 nausea**												
3	observational	extremely serious	not serious	serious[j]	serious[k]	none	97 Weighted mean (SD) 12% (9%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 anorexia**												
3	observational	extremely serious	not serious	serious[j]	serious[k]	none	143 Weighted mean (SD) 9% (10%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**

Abbreviations: CI, confidence interval; HR, hazard ratio

a. According to the ROBINS-I tool
b. Only one study
c. Reported in Ruffini 2014 Thymic [108]
d. There were 3 studies that provided data for HR for overall survival comparing neoadjuvant chemotherapy with no chemotherapy in patients with thymic carcinoma. Two studies included patients from the United States [109,151]. Bakhos 2020 was chosen for the meta-analysis because it was larger. Bakhos compared neoadjuvant chemotherapy vs. no chemotherapy and Hishida 2016 compared neoadjuvant chemotherapy vs. no neoadjuvant chemotherapy.
e. Small sample size
f. There were 2 studies that provided data for HR for disease-free survival comparing neoadjuvant chemotherapy with no neoadjuvant therapy in patients with thymic carcinoma. However, in one of the studies [151] it was unclear whether the direction of the effect would favour neoadjuvant chemotherapy or no neoadjuvant therapy. Therefore, only one study [110], which included patients with R0 resection, was included.
g. Reported by Mao 2015 [129] for patients with thymic carcinoma who did not receive postoperative radiotherapy and were completed resected
h. There were 5 studies that provided information about chemotherapy toxicities [113,115,118,122,123]. Hirai 2015 and Okuma 2020 included patients from the same Japanese institution. For any outcomes that reported results from both studies, Hirai 2015 was chosen over Okuma 2020 because it was larger.
i. Large differences in proportions reported
j. Studies included patients with stage III-IV thymic carcinoma. This may not generalize to resectable patients.
k. Small sample size

Table 4-11. Summary of findings for PORT versus no PORT for patients with thymic carcinoma

Certainty assessment							Summary of findings					Importance
							# of patients		Effect		Certainty	
# of studies	Design	Risk of bias [a]	Inconsistency	Indirectness	Imprecision	Other considerations	PORT	No PORT	Relative (95% CI)	Absolute (95% CI)		
Overall survival (resectable patients) (median follow-up: range 3 years to 9 years)												
7[b]	observational	very serious	not serious [c]	not serious	not serious	none	1175	1011 53.8% at 5 years [d]	**HR 0.65** (0.47-0.89) [survival]	**130 more per 1000** (from 38 more to 209 more)	⊕⊕◯◯ **LOW**	**CRITICAL**
Disease-free survival (resectable patients) (median follow-up: range 3 years to 9 years)												
6[e]	observational	very serious	not serious [c]	not serious	not serious	none	259	134 44.1% at 5 years [f]	**HR 0.59** (0.41-0.84) [disease-free survival]	**176 more per 1000** (from 62 more to 274 more)	⊕⊕◯◯ **LOW**	**CRITICAL**
Grade ≥3 toxicities (resectable patients)												

9	1 RCT 8 case series	very serious	not serious	not serious [g]	not serious	none	10/549	0/19	Not estimable		⊕⊕◯◯ **LOW**	**CRITICAL**

Abbreviations: CI, confidence interval; HR, hazard ratio; PORT, postoperative radiotherapy; RCT, randomized controlled trial

a. According to the ROBINS-I tool

b. There were 13 studies that provided data for HR for overall survival comparing PORT with no PORT in patients with thymic carcinoma. Three studies [90,109,128,152] were from overlapping years from the National Cancer Data Base. Jackson 2017 was chosen for the meta-analyses because it had the largest and most inclusive sample with the lowest risk of bias (ROB). Two studies used the SEER database [105,153]. Lim 2017 was chosen because it was larger and had a lower ROB. Four studies included patients from the same Chinese centre [127,130,132,150]. Fu 2016 was chosen because it was the largest with a lower ROB. Also, two studies were from overlapping years from the JART database [92,110]. Hishida 2016 was chosen in the meta-analyses because it had the largest and most inclusive sample.

c. Even though there was statistical heterogeneity, most point estimates favoured PORT.

d. Median overall survival at 5 years from included studies that provided this information

e. There were 9 studies that provided HR data for disease-free survival comparing PORT with no PORT in patients with thymic carcinoma. Two studies were from overlapping years from the JART database [92,110]. Hishida 2016 was chosen for the meta-analyses because it had the largest and most inclusive sample. Three studies included patients from the same Chinese centre [127,130,150]. Fu 2016 was chosen because it was the largest study.

f. Reported by Mao 2015 [129]

g. Indirectness was not a concern because the number of events was consistently low across patients with different types of thymic tumours

Table 4-12. Summary of findings for adjuvant chemotherapy versus no adjuvant chemotherapy for patients with thymic carcinoma

Certainty assessment							Summary of findings					Importance
							# of patients		Effect		Certainty	
# of studies	Design	Risk of bias [a]	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvant chemotherapy	No adjuvant therapy	Relative (95% CI)	Absolute (95% CI)		
Overall survival (median follow-up: range 3 years to 6 years)												
5[b]	observational	extremely serious	not serious	not serious	not serious	none	402	502 56.8%[c] at 5 years	**HR 0.73** (0.55-0.98) [survival]	**94 more per 1000** (from 6 more to 165 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**
Disease-free survival (median follow-up: range 3 years to 6 years)												
7[d]	observational	very serious	serious [e]	not serious	not serious	none	242	427 54.8%[c] at 5 years	**HR 0.96** (0.64-1.44) [disease-free survival]	**13 more per 1000** (from 127 fewer to 132 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**
Grade ≥3 toxicities (stages III-IV) [f]												
• **Grade ≥3 leukopenia**												

2	observational	extremely serious	not serious	serious [h]	serious [i]	none	99 Weighted mean (SD) 56% (14%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 neutropenia**												
4	observational	extremely serious	serious [g]	serious [h]	serious [i]	none	180 Weighted mean (SD) 48% (34%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 febrile neutropenia**												
2	observational	extremely serious	not serious	serious [h]	serious [i]	none	99 Weighted mean (SD) 8% (3%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 thrombocytopenia**												
4	observational	extremely serious	not serious	serious [h]	serious [i]	none	144 Weighted mean (SD) 3% (3%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 anemia**												
3	observational	extremely serious	not serious	serious [h]	serious [i]	none	143 Weighted mean (SD) 7% (6%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 nausea**												
3	observational	extremely serious	not serious	serious [h]	serious [i]	none	97 Weighted mean (SD) 12% (9%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 anorexia**												
3	observational	extremely serious	not serious	serious [h]	serious [i]	none	143 Weighted mean (SD) 9% (10%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**

Abbreviations: CI, confidence interval; HR, hazard ratio

a. According to the ROBINS-I tool

b. There were 7 studies that provided data for HR for overall survival comparing adjuvant chemotherapy with no adjuvant chemotherapy in patients with thymic carcinoma. Four studies included patients from the same Chinese institution [127,130,132,154]. Fu 2016 was chosen for the meta-analysis because it was the largest study. Two studies were from the National Cancer Database [109,128]. Kim 2019 was chosen for the meta-analysis because all patients were resected in the control group, unlike patients in the Bakhos 2020 study. The reference group in the Kim 2019 study were patients who had surgery only. The reference group for the Bakhos 2020 study were patients who did not receive chemotherapy.

c. Reported in Song 2014 Outcome [130]

d. There were 8 studies that provided data for HR for disease-free survival comparing adjuvant chemotherapy with no adjuvant chemotherapy in patients with thymic carcinoma. Two studies included patients from the same Chinese institution [130,154]. Song 2014 was chosen for the meta-analysis because it was the larger study. Zhao 2013 only included patients with squamous cell thymic carcinoma. Omasa 2015 included patients with stage II or III thymic carcinoma. Tang 2021 included patients with T3 N0 M0 thymic carcinoma.

e. I^2 was 57%, P=0.03
f. There were 5 studies that provided information about chemotherapy toxicities [113,115,118,122,123]. Hirai 2015 and Okuma 2020 included patients from the same Japanese institution. For any outcomes that reported results from both studies, Hirai 2015 was chosen over Okuma 2020 because it was larger.
g. Large differences in proportions reported
h. Studies included patients with stage III-IV thymic carcinoma. This may not generalize to patients with resectable tumours.
i. Small sample size

Table 4-13. Summary of findings for first/second-line systemic therapy for patients with advanced/recurrent thymic carcinoma

Certainty assessment							Summary of findings					
							# of patients		Effect		Certainty	Importance
# of studies	Design	Risk of bias [a]	Inconsistency	Indirectness	Imprecision	Other considerations	First/second-line therapy	Control	Relative (95% CI)	Absolute (95% CI)		
OVERALL SURVIVAL												
• **First-line chemoradiotherapy vs. chemotherapy (median follow-up: 2 years)**												
1	observational	extremely serious	not serious	not serious	serious [b]	none	13	21 36%[c] at 5 years	**HR 0.42** (0.18-1.01) [survival]	**291 more per 1000** (from 4 fewer to 472 more)	⨁◯◯◯ **VERY LOW**	**CRITICAL**
RESPONSE												
• **Advanced/recurrent (first-line)**												
2[d] Anthracycline-based	observational	extremely serious	not serious	not serious	serious [e]	none	108 Weighted mean (SD) 45% (8%)	-	Not estimable		⨁◯◯◯ **VERY LOW**	**CRITICAL**
6 Non-anthracycline-based	observational	extremely serious	not serious	not serious	not serious	none	318 Weighted mean (SD) 41% (13%)	-	Not estimable		⨁◯◯◯ **VERY LOW**	**CRITICAL**
1 Chemoradiotherapy	observational	extremely serious	not serious	not serious	serious [e]	none	34 88%	-	Not estimable		⨁◯◯◯ **VERY LOW**	**CRITICAL**
• **Advanced/recurrent (second-line)**												
1 Anthracycline-based	observational	extremely serious	not serious	not serious	serious [e]	none	17 21%	-	Not estimable		⨁◯◯◯ **VERY LOW**	**CRITICAL**
1 Non-anthracycline-based	observational	extremely serious	not serious	not serious	serious [e]	none	60 21%	-	Not estimable		**VERY LOW**	**CRITICAL**

3 S-1 monotherapy	observational	extremely serious	not serious	not serious	serious [e]	none	104 Weighted mean (SD) 35% (4%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**CRITICAL**
2 Pembrolizumab	observational	extremely serious	not serious	not serious	serious [e]	none	66 Weighted mean (SD) 21% (2%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**CRITICAL**
1 Lenvatinib	observational	extremely serious	not serious	not serious	serious [e]	none	42 38%	-	Not estimable		⊕◯◯◯ **VERY LOW**	**CRITICAL**
GRADE ≥3 TOXICITIES												
• **Grade ≥3 toxicities**												
1 Pembrolizumab	observational	extremely serious	not serious	not serious	serious [e]	none	40 15%	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 leukopenia**												
2 Chemotherapy (stage III-IV)	observational	extremely serious	not serious	not serious	serious [e]	none	99 Weighted mean (SD) 56% (14%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
1 Lenvatinib	observational	extremely serious	not serious	not serious	serious [e]	none	42 5%	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 neutropenia**												
4 Chemotherapy (stage III-IV)	observational	extremely serious	serious [f]	not serious	serious [e]	none	180 Weighted mean (SD) 48% (34%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
1 Lenvatinib	observational	extremely serious	not serious	not serious	serious [e]	none	42 5%	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 febrile neutropenia**												
2 Chemotherapy (stage III-IV)	observational	extremely serious	not serious	not serious	serious [e]	none	99 Weighted mean (SD) 8% (3%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 thrombocytopenia**												
4 Chemotherapy (stage III-IV)	observational	extremely serious	not serious	not serious	serious [e]	none	144 Weighted mean (SD) 3% (3%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
1 Lenvatinib	observational	extremely serious	not serious	not serious	serious [e]	none	42 5%	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 anemia**												

3 Chemotherapy (stage III-IV)	observational	extremely serious	not serious	not serious	serious [e]	none	143 Weighted mean (SD) 7% (6%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
1 Lenvatinib	observational	extremely serious	not serious	not serious	serious [e]	none	42 0%	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 nausea**												
3 Chemotherapy (stage III-IV)	observational	extremely serious	not serious	not serious	serious [e]	none	97 Weighted mean (SD) 12% (9%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
1 Lenvatinib	observational	extremely serious	not serious	not serious	serious [e]	none	42 0%	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**
• **Grade ≥3 anorexia**												
3 Chemotherapy (stage III-IV)	observational	extremely serious	not serious	not serious	serious [e]	none	143 Weighted mean (SD) 9% (10%)	-	Not estimable		⊕◯◯◯ **VERY LOW**	**IMPORTANT**

Abbreviations: CI, confidence interval; HR, hazard ratio

a. According to the ROBINS-I tool
b. Only one study
c. Median overall survival reported in Ogawa 2002 [155] and Zhai 2017 [156] for the chemotherapy group
d. There were 3 studies that provided responses for first-line anthracycline-based chemotherapy. Two studies may have included patients from the same Japanese institutions [114,157]. Ko 2018 was chosen because it was larger.
e. Small sample size
f. Large differences in proportions reported

Comparisons for patients with thymic NETs

Partial thymectomy versus total thymectomy for patients with thymic NETs

There was only one study that provided data for HR for overall survival comparing partial thymectomy versus total thymectomy in patients with thymic NETs (Table 4-14; HR, 1.54; 95% CI, 0.93 to 2.56; p=0.09) [133]. The certainty in the evidence was very low.

VATS versus open thymectomy for patients with thymic NETs

There were no included studies.

Neoadjuvant therapy versus no neoadjuvant therapy for patients with thymic NETs

There was one study that provided data for HR for overall survival comparing neoadjuvant therapy versus no neoadjuvant therapy in patients with thymic NETs (Table 4-15; HR, 1.32; 95% CI, 0.61 to 2.84; p=0.48) [134]. Also, one study reported overall survival for neoadjuvant chemotherapy versus no chemotherapy (HR, 0.50; 95% CI, 0.10 to 2.20; p=0.35) [109]. The certainty in the evidence was very low.

PORT versus no PORT for patients with thymic NETs

There were very few studies that reported on outcomes for patients with thymic NETs (Table 4-16). It seems that more patients would survive longer with PORT than without PORT (HR, 0.62; 95% CI, 0.39 to 0.97; p=0.04), but the certainty in the evidence was very low. Since few studies reported adverse effects, toxicities were reported from the same studies as those reported for the thymoma section.

Adjuvant therapy versus no adjuvant therapy for patients with thymic NETs

There were two studies that provided data for HR for overall survival comparing adjuvant therapy versus no adjuvant therapy in patients with thymic NETs (Table 4-17; HR, 1.03; 95% CI, 0.48 to 2.22; p=0.93) [109,135]. The certainty in the evidence was very low.

Treatment comparisons for patients with advanced or recurrent thymic NETs

There were no included studies.

Table 4-14. Summary of findings for partial thymectomy versus total thymectomy for patients with thymic NETs

Certainty assessment							Summary of findings					Importance
							# of patients		Effect		Certainty	
# of studies	Design	Risk of bias [a]	Inconsistency	Indirectness	Imprecision	Other considerations	partial	total	Relative (95% CI)	Absolute (95% CI)		
Overall survival (median follow-up: 3 years)												
1	observational	very serious	not serious	not serious	serious [b]	none	74	106 60% at 5 years [c]	**HR 1.54** (0.93-2.56) [survival]	**145 fewer per 1000** (from 330 fewer to 22 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**

Abbreviations: CI, confidence interval; HR, hazard ratio; NETs, neuroendocrine tumours

a. According to the ROBINS-I tool

b. Only one study

c. Reported in Lim 2017 [105] for patients with thymic carcinoma

Table 4-15. Summary of findings for neoadjuvant therapy versus no neoadjuvant therapy for patients with thymic NETs

Certainty assessment							Summary of findings					Importance
							# of patients		Effect		Certainty	
# of studies	Design	Risk of bias [a]	Inconsistency	Indirectness	Imprecision	Other considerations	Neoadjuvant therapy	No neoadjuvant therapy	Relative (95% CI)	Absolute (95% CI)		
OVERALL SURVIVAL												
• **Neoadjuvant therapy vs. no neoadjuvant therapy (median follow-up: 4 years)**												
1	observational	extremely serious	not serious	not serious	serious [b]	none	21	146 61%[c] at 5 years	**HR 1.32** (0.61-2.84) [survival]	**89 fewer per 1000** (from 364 fewer to 130 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**
• **Neoadjuvant chemotherapy vs. no chemotherapy (resected patients) (median follow-up: range 3 years)**												
1	observational	extremely serious	not serious	not serious	serious [b]	none	295	61%[c] at 5 years	**HR 0.50** (0.10-2.20) [survival]	**171 more per 1000** (from 273 fewer to 342 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**

Abbreviations: CI, confidence interval; HR, hazard ratio; NETs, neuroendocrine tumours

a. According to the ROBINS-I tool

b. Only one study
c. Reported in Ruffini 2014 Thymic [108] for patients with thymic carcinoma

Table 4-16. Summary of findings for PORT versus no PORT for patients with thymic NETs

Certainty assessment							Summary of findings					Importance
							# of patients		Effect		Certainty	
# of studies	Design	Risk of bias [a]	Inconsistency	Indirectness	Imprecision	Other considerations	PORT	No PORT	Relative (95% CI)	Absolute (95% CI)		
Overall survival (resectable patients) (median follow-up: 3 to 4 years)												
2[b]	observational	extremely serious	not serious	not serious	not serious	none	468	53.8% at 5 years [c]	**HR 0.62** (0.39-0.97) [survival]	**143 more per 1000** (from 10 more to 247 more)	⊕◯◯◯ **VERY LOW**	**CRITICAL**
Grade ≥3 toxicities (resectable patients)												
9[d]	1 RCT 8 case series	very serious	not serious	not serious [e]	not serious	none	10/549	0/19	Not estimable		⊕⊕◯◯ **LOW**	**CRITICAL**

Abbreviations: CI, confidence interval; HR, hazard ratio; NETs, neuroendocrine tumours PORT, postoperative radiotherapy; RCT, randomized controlled trial

a. According to the ROBINS-I tool
b. There were 4 studies that provided data for HR for overall survival comparing PORT with no PORT in patients with thymic NETs. Three studies [133,135,158] were from overlapping years from the SEER database. Bian 2018 was chosen for the meta-analyses because it had the lowest risk of bias.
c. Median overall survival at 5 years was taken from included studies that provided this information for patients with thymic carcinoma.
d. Nine studies provided information about toxicities [32,97-104]. Eight non-comparative studies provided information about toxicities for patients receiving PORT. Four of these studies included patients with thymoma or thymic carcinoma [98,100,102,104] and one study included patients with thymic carcinoma or thymic NETs [103]. One abstract of a small RCT reported adverse effects for patients with or without PORT [32].
e. Indirectness was not a concern because the number of events was consistently low across patients with different types of thymic tumours

Table 4-17. Summary of findings for adjuvant chemotherapy versus no adjuvant chemotherapy for patients with thymic NETs

Certainty assessment							Summary of findings					Importance
							# of patients		Effect		Certainty	
# of studies	Design	Risk of bias [a]	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvant therapy	No adjuvant therapy	Relative (95% CI)	Absolute (95% CI)		
Overall survival (median follow-up: range 3 years)												
2	observational	extremely	not serious	not serious	not serious	none	420		**HR 1.03**			**CRITICAL**

		serious						56.8%[b] at 5 years	(0.48-2.22) [survival]	**10 fewer per 1000** (from 283 fewer to 194 more)	⊕◯◯◯ **VERY LOW**	

Abbreviations: CI, confidence interval; HR, hazard ratio

a. According to the ROBINS-I tool

b. Reported in Song 2014 Outcome [130] for patients with thymic carcinoma

Ongoing or Unpublished Studies

See Appendix 9.

DISCUSSION

This systematic review examined the outcomes of surgical, radiotherapy, and systemic treatment options available to patients with thymic epithelial tumours, specifically thymoma, thymic carcinoma, and thymic NETs. Most of the evidence was derived from retrospective studies and, therefore, strong conclusions could not be made. Furthermore, there was very little evidence to inform recommendations for patients with thymic NETs.

For patients with thymoma, although the point estimates favoured partial thymectomy over total thymectomy, the certainty in these effects were low to very low. The confidence intervals were wide, favouring either treatment at its ends for overall survival and recurrence. The complications and perioperative outcomes were better for patients who had partial thymectomy. However, patients with better prognosis may have been selected to receive partial thymectomy, skewing the results in favour of this treatment. Therefore, the evidence was not strong enough to replace the standard treatment of total thymectomy. This was consistent with the conclusions of Fiorelli et al.'s 2019 systematic review of patients with non-myasthenic early-stage thymoma comparing partial versus total thymectomy for recurrence and survival [159].

A similar situation was found for outcomes comparing MIS with open thymectomy for patients with thymoma. All outcomes, except for DFS, were better when patients had MIS compared with open thymectomy. Patients tended to live longer and had fewer complications with MIS. Yang et al.'s 2016 systematic review also found that patients experienced beneficial perioperative outcomes with MIS, but found no statistical differences in the odds ratios for five-year overall survival or DFS between patients who received MIS versus open thymectomy [160]. Again, however, patients with poorer prognosis may have been selected for open thymectomy, biasing the results to favour patients who had MIS in our systematic review. This coupled with low to very low certainty in the evidence led to recommendations for either treatment.

The largest magnitude of survival benefits was found for patients who received PORT compared with no PORT, especially for patients with thymic carcinoma and patients with thymoma at high risk of mortality. Lim et al.'s 2016 systematic review also found that patients with stage III or IV MK stage thymoma had improved overall survival with PORT, but not for patients with stage II MK stage thymoma [161]. Furthermore, Hamaji et al.'s 2017 systematic review also observed improved overall survival in patients with thymic carcinoma given PORT [162]. The evidence for our review was still derived from observational studies with low certainty in the overall effects, but patients with poorer status may have been selected for PORT, which would work against its benefit. Acute radiotherapy toxicities did not appear to be frequent, but long-term effects could not be adequately determined. Therefore, the strongest evidence for survival benefit in this review supported the use of PORT.

The results were mixed for adjuvant chemotherapy for patients with thymoma and thymic carcinoma; there was an overall survival advantage for patients with thymic carcinoma, but not for patients with thymoma. There was very low certainty in this evidence, and it was unclear whether patients who received PORT were matched across groups. However, cases with poorer prognosis may have been selected for adjuvant chemotherapy, biasing the results against this treatment; however, an overall survival benefit was observed in patients with thymic carcinoma. Grade 3 or above chemotherapy toxicities, reported in patients with MK stages III-IV, ranged from 3% to 56% and may not necessarily apply to patients with resectable tumours.

Survival seemed to be worse for patients who received neoadjuvant chemotherapy. This is to be expected since patients with poorer prognosis were selected to receive neoadjuvant

chemotherapy. The intention of this treatment is to reduce the tumour size to improve the chances of obtaining negative surgical margins. Therefore, responses to neoadjuvant chemotherapy were extracted and found to be greater than 70% in patients with thymoma or thymic carcinoma; however, few included studies reported on this outcome. Hamaji et al.'s 2015 meta-analysis found response rates of 59% following induction therapy with chemotherapy or chemoradiotherapy in patients with advanced thymic epithelial tumours [163].

Additional evidence for response rates was found in patients with upfront unresectable advanced or recurrent tumours. Anthracycline-based chemotherapy achieved average response rates of 70% in patients with thymoma and approximately 40% in patients with thymic carcinoma in the first-line setting, while octreotide resulted in a 38% response rate in patients with thymoma. Rates were lower in the second-line setting and ranged from 9% to 14% for patients with thymoma and 21% to 38% in patients with thymic carcinoma. There did not appear to be a great deal of difference in response rates with different types of systemic therapy. This was also found in Berghmans et al.'s 2018 systematic review with response rates mostly above 50% regardless of the line of treatment [164]. The toxicities for these systemic treatments were mainly low, but they were underreported.

There were several limitations in the evidence mainly because this is a rare disease. There was a lack of RCTs, and the evidence was based on observational studies that did not always control for confounders. The studies were small, retrospective and suffered from selection biases that were dependent on the surgeon's or physician's treatment preferences. Patients were categorized according to the previous MK staging system and this evidence may not directly apply to recommendations using the new staging system. Furthermore, there was very little evidence on adverse events, especially long-term effects.

CONCLUSIONS

The strongest support for a survival benefit was found for PORT in patients with thymic carcinoma and for patients with thymoma, especially those with a high risk for mortality. There was some suggestion for a survival benefit for adjuvant chemotherapy in patients with thymic carcinoma, but it was unclear whether PORT confounded the results. However, it does appear that patients with thymic carcinoma or thymoma respond to chemotherapy. It was difficult to discern a difference between different surgical techniques because patients with better prognosis were selected for MIS and partial thymectomy and these patients generally displayed better outcomes than comparative strategies. Future collaborative efforts are needed to gather larger data from prospective studies.

Surgical, Radiation, and Systemic Treatments of Patients with Thymic Epithelial Tumours

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC Report Approval Panel (RAP) (Appendix 2). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the 23 members of the GDG Expert Panel, 19 members voted, for a total of 83% response in October 2021. Of those who voted, 17 approved the document (89%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. I do not agree with VATS or RATS resection for advanced-stage tumours. I realize that the literature suggests that these are acceptable approaches and I agree with that for stage I and II tumours. I may be wrong but my reading is that the papers suggesting that VATS and RATs are equivalent include smaller tumours. Stage III tumours are invasive tumours and require resection of structures such as the superior vena cava, innominate vein, lung, chest wall, etc. It is conceivable that such structures could be resected by RATS but I do not believe we are at that stage of expertise. I think it is irresponsible to include statements indicating that VATS or RATS are acceptable alternatives for the surgical management of stage III or IV tumours. I would posit that an R0 resection is unlikely and a non-R0 resection has done the patient a disservice.	The Working Group agreed with this and changed the following recommendations: For TNM stage III and IVa thymoma "Open thymectomy is recommended as the standard of care. Minimally invasive approaches are not recommended as the standard of care." and for thymic carcinoma and thymic NETs "Open thymectomy is recommended as the standard of care.".
2. For recommendation, "Bilateral phrenic nerve resection is not recommended because of the severe respiratory morbidity that results", I suggest this be reworded to "unilateral only phrenic nerve resection is acceptable".	This recommendation has been reworded.
3. The evidence provided does not support neoadjuvant chemotherapy in thymoma or thymic carcinoma. With HR >1 for overall survival, the contrary could be argued. More nuanced language could indicate that responses might allow surgery, but the benefit to survival is unclear.	We have modified the justification to indicate that patients who respond to neoadjuvant chemotherapy could potentially improve their chances of an R0 resection. However, the impact on survival is unknown.

4. In the neoadjuvant therapy versus no neoadjuvant therapy section, for patients with thymoma the wording '90 fewer per 1000 patients would survive longer' is odd and confusing. This sounds like the treatment is harmful.	This has been reworded for clarity.

RAP Review and Approval

Three RAP members reviewed this document in October 2021. The RAP conditionally approved the document on October 18, 2021. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from RAP

Comments	Responses
1. The methods for formulating the recommendations are clearly described in section 3; however, it is not clear which prior guidelines were used when 'adopting' or 'endorsing' prior recommendations as is stated throughout the recommendations in section 2.	This statement was added prior to the recommendation section. "When insufficient evidence was found, the Working Group endorsed the recommendations from the previous version of this guideline (see Appendix 1) or for patients with thymic NETS, recommendations were endorsed from the NCCN Version 1.2021 Neuroendocrine and Adrenal Tumors Guideline.".
2. Thymic NET is the only of the three diseases where 'Evaluation' has its own recommendation box. Is there a reason that diagnostic modalities, imaging, etc., are not required for thymoma or thymic carcinoma?	We have deleted the 'Evaluation' recommendations from thymic NETs because this guideline focuses on treatment.
3. One suggestion is to develop and support international clinical trials as the best mechanism to improve treatment for these rare tumours.	We have added international studies under further research priorities.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Three targeted peer reviewers from Ontario who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Two responses were received (Appendix 2). Results of the feedback survey are summarized in Table 5-3. The main comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=2)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.	0	1	0	0	1
2. Rate the guideline presentation.	0	0	0	0	2
3. Rate the guideline recommendations.	0	1	0	0	1

4. Rate the completeness of reporting.	0	0	0	0	2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	0	1	1	0
6. Rate the overall quality of the guideline report.	0	0	1	0	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	0	1	0	0	1
8. I would recommend this guideline for use in practice.	1	0	0	0	1
9. What are the barriers or enablers to the implementation of this guideline report?	None reported				

Table 5-4. Summary of the Working Group's responses to comments from targeted peer reviewers.

Comments	Responses
1. I am not enthusiastic about any of the statements that adjuvant chemotherapy could be "Considered". I think that requires an RCT. If there is very poor evidence or no evidence for adjuvant chemotherapy then I think the default should be to say that it is not recommended.	These recommendations were reviewed again and a more conservative approach was taken.
2. Some guidance on dose ranges and volume for radiotherapy in various circumstances would be helpful.	This is beyond the scope of this document and would need to be addressed in a radiation specific document.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. Eighty-six clinicians in Ontario with an interest in lung cancer in the PEBC database were contacted by email to inform them of the survey. Twenty-four (28%) responses were received. Fifteen stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from nine people are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

	Reviewer Ratings (N=9)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	0	3	2	4
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	0	0	3	0	6
3. I would recommend this guideline for use in practice.	0	0	2	2	5
4. What are the barriers or enablers to the implementation of this guideline report?	There may be variable access across the province to the following: high-volume				

	thoracic referral centres; thoracic MCCs; peptide receptor radionuclide therapy with 177Lu-dotatate, octreotide or lanreotide (for neuroendocrine tumours); and post-operative radiation therapy.

Table 5-6. Summary of the Working Group's responses to comments from professional consultants.

Comments	Responses
1. I think the intended users of this guideline are oncologists and thoracic surgeons involved in the treatment of patients with thymic epithelial tumours.	This has been changed to include all healthcare professionals managing patients with thymic epithelial tumours.
2. The definition of complete resection should include the tumour.	The definitions have been clarified to include whether the thymus, tumour, or involved structures should be resected.
3. I would recommend discussion of cases not just at local MCC but also discussion with colleagues/centres with higher volume/experience with thymic carcinoma. It would also be appropriate to mention the ITMIG tumour board as an opportunity to discuss challenging cases.	The third general principle was added in response to this comment.
4. There is variable access across the province to high-volume thoracic referral centres, PORT, and peptide receptor radionuclide therapy with 177Lu-dotatate, octreotide or lanreotide (for NETs).	Access to high-volume referral centres and peptide receptor radionucleotide therapy were added to the implementation considerations.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

References

1. Huang J, Ahmad U, Antonicelli A, Catlin AC, Fang W, Gomez D, et al. Development of the international thymic malignancy interest group international database: an unprecedented resource for the study of a rare group of tumors. J Thorac Oncol. 2014;9(10):1573-8.
2. Nicholson AG, Detterbeck FC, Marino M, Kim J, Stratton K, Giroux D, et al. The IASLC/ITMIG Thymic Epithelial Tumors Staging Project: proposals for the T Component for the forthcoming (8th) edition of the TNM classification of malignant tumors. J Thorac Oncol. 2014;9(9 Suppl 2):S73-80.
3. Koga K, Matsuno Y, Noguchi M, Mukai K, Asamura H, Goya T, et al. A review of 79 thymomas: modification of staging system and reappraisal of conventional division into invasive and non-invasive thymoma. Pathol Int. 1994;44(5):359-67.
4. Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up study of thymomas with special reference to their clinical stages. Cancer. 1981;48(11):2485-92.
5. 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;4(7):911-9.
6. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Neuroendocrine and Adrenal Tumors Guideline Version 1.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed [July 28, 2021]. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
7. Fernandes AT, Shinohara ET, Guo M, Mitra N, Wilson LD, Rengan R, et al. The role of radiation therapy in malignant thymoma: A surveillance, epidemiology, and end results database analysis. J Thorac Oncol. 2010;5(9):1454-60.
8. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the Practice Guidelines Development Cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.
9. Browman GP, Levine MN, Mohide EA, Hayward RS, 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(2):502-12.
10. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ. 2010;182(18):E839-42.
11. Baudin E, Caplin M, Garcia-Carbonero R, Fazio N, Ferolla P, Filosso PL, et al. Lung and thymic carcinoids: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up(☆). Ann Oncol. 2021;32(4):439-51.
12. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. BMJ. 2016;353:i2016.
13. de Jong WK, Blaauwgeers JL, Schaapveld M, Timens W, Klinkenberg TJ, Groen HJ. Thymic epithelial tumours: a population-based study of the incidence, diagnostic procedures and therapy. Eur J Cancer. 2008;44(1):123-30.
14. Ahmad U, Yao X, Detterbeck F, Huang J, Antonicelli A, Filosso PL, et al. Thymic carcinoma outcomes and prognosis: Results of an international analysis. J Thorac Cardiovasc Surg. 2015;149(1):95-101.e2.
15. Gaur P, Leary C, Yao JC. Thymic neuroendocrine tumors: a SEER database analysis of 160 patients. Ann Surg. 2010;251(6):1117-21.

16. Travis WD, Brambilla E, Muller-Hermelink HK, Harris C. Pathology and Genetics of Tumors of the Lung, Pleura, Thymus and Heart. World Health Organization Classification of Tumours. 2004.
17. Masaoka A. Staging system of thymoma. J Thorac Oncol. 2010;5(10 Suppl 4):S304-12.
18. Weksler B, Dhupar R, Parikh V, Nason KS, Pennathur A, Ferson PF. Thymic carcinoma: a multivariate analysis of factors predictive of survival in 290 patients. Ann Thorac Surg. 2013;95(1):299-303.
19. Gal AA, Kornstein MJ, Cohen C, Duarte IG, Miller JI, Mansour KA. Neuroendocrine tumors of the thymus: a clinicopathological and prognostic study. Ann Thorac Surg. 2001;72(4):1179-82.
20. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. Ann Thorac Surg. 2003;76(3):878-84; discussion 84-5.
21. Nakagawa K, Asamura H, Matsuno Y, Suzuki K, Kondo H, Maeshima A, et al. Thymoma: a clinicopathologic study based on the new World Health Organization classification. J Thorac Cardiovasc Surg. 2003;126(4):1134-40.
22. Rea F, Marulli G, Girardi R, Bortolotti L, Favaretto A, Galligioni A, et al. Long-term survival and prognostic factors in thymic epithelial tumours. Eur J Cardiothorac Surg. 2004;26(2):412-8.
23. Regnard JF, Magdeleinat P, Dromer C, Dulmet E, de Montpreville V, Levi JF, et al. Prognostic factors and long-term results after thymoma resection: a series of 307 patients. J Thorac Cardiovasc Surg. 1996;112(2):376-84.
24. Conrad Falkson, Emily Vella, Peter Ellis, Donna Maziak, Yee Ung, Edward Yu. Surgical, radiation, and systemic treatments of patients with thymic epithelial tumours. PROSPERO 2020 CRD42020179191 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020179191.
25. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.
26. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.
27. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
28. Review Manager (RevMan) [Computer program]. Version 5.4. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020.
29. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. [erratum appears in Stat Med. 2004;3(11):1817]. Stat Med. 1998;17(24):2815-34.
30. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94.
31. Zhang H, Lu N, Wang M, Gu X, Zhang D. Postoperative radiotherapy for stage I thymoma: a prospective randomized trial in 29 cases. Chin Med J. 1999;112(2):136-8.
32. Zhai YR, Feng Q, Gao Y, Hui Z, Zhou Z, Xiao Z, et al. THYPORT: Postoperative Radiotherapy Versus Surgery Alone in Masaoka Stage II Thymoma: Mid-Term Result of a Prospective Randomized Study from a Single Center(NCT 02014805). Int J Radiat Oncol Biol Phys. 2019;105 (1 Supplement):E492-E3.
33. Hishida T, Asamura H, Yoshida K, Tsuboi M, Yokoi K, Toyooka S, et al. Clinical features and prognostic impact of coexisting autoimmune disease other than myasthenia gravis in

resected thymomas: analysis of a Japanese multi-institutional retrospective database. Eur J Cardiothorac Surg. 2020;14:14.
34. Narm KS, Lee CY, Do YW, Jung HS, Byun GE, Lee JG, et al. Limited thymectomy as a potential alternative treatment option for early-stage thymoma: A multi-institutional propensity-matched study. Lung Cancer. 2016;101:22-7.
35. Rusidanmu A, Huang S, Lv X. Is thymomectomy sufficient for non-myasthenic early stage thymoma patients? A retrospective, single center experience. Thorac Cancer. 2018;9(1):88-93.
36. Sakamaki Y, Oda T, Kanazawa G, Shimokawa T, Kido T, Shiono H. Intermediate-term oncologic outcomes after video-assisted thoracoscopic thymectomy for early-stage thymoma. J Thorac Cardiovasc Surg. 2014;148(4):1230-7.e1.
37. Zhao M, Yin J, Yang X, Jiang T, Lu T, Huang Y, et al. Nomogram to predict thymoma prognosis: A population-based study of 1312 cases. Thoracic Cancer. 2019;10(5):1167-75.
38. Onuki T, Ishikawa S, Iguchi K, Goto Y, Sakai M, Inagaki M, et al. Limited thymectomy for stage I or II thymomas. Lung Cancer. 2010;68(3):460-5.
39. Nakagawa K, Yokoi K, Nakajima J, Tanaka F, Maniwa Y, Suzuki M, et al. Is thymomectomy alone appropriate for stage I (T1N0M0) thymoma? Results of a propensity-score analysis. Ann Thorac Surg. 2016;101(2):520-6.
40. Tassi V, Ceccarelli S, Zannori C, Gili A, Daddi N, Bellezza G, et al. Could thymomectomy be a reasonable option for non-myasthenic thymoma patients? J Thorac Dis. 2017;9(10):3817-24.
41. Tseng YC, Hsieh CC, Huang HY, Huang CS, Hsu WH, Huang BS, et al. Is thymectomy necessary in nonmyasthenic patients with early thymoma? J Thorac Oncol. 2013;8(7):952-8.
42. Agatsuma H, Yoshida K, Yoshino I, Okumura M, Higashiyama M, Suzuki K, et al. Video-assisted thoracic surgery thymectomy versus sternotomy thymectomy in patients with thymoma. Ann Thorac Surg. 2017;104(3):1047-53.
43. He ZF, Wu YB, Lu D, Ni HZ. Efficacy and safety of video-assisted thoracic surgery and median sternotomy in the treatment of thymoma-associated myasthenia gravis. Int J Clin Exp Med. 2016;9(11):21922-31.
44. Kocer B, Kaplan T, Gunal N, Kocer BG, Akkas Y, Yazkan R, et al. Long-term survival after R0 resection of thymoma. Asian Cardiovasc Thorac Ann. 2018;26(6):461-6.
45. Liu TJ, Lin MW, Hsieh MS, Kao MW, Chen KC, Chang CC, et al. Video-assisted thoracoscopic surgical thymectomy to treat early thymoma: A comparison with the conventional transsternal approach. Ann Surg Oncol. 2014;21(1):322-8.
46. Manoly I, Whistance RN, Sreekumar R, Khawaja S, Horton JM, Khan AZ, et al. Early and mid-term outcomes of trans-sternal and video-assisted thoracoscopic surgery for thymoma. Eur J Cardiothorac Surg. 2014;45(6):e187-e93.
47. Tian W, Sun Y, Wu Q, Jiao P, Ma C, Yu H, et al. Surgical outcomes of 215 patients with thymic epithelial tumors: A single-center experience. Thorac Cancer. 2020;11(7):1840-7.
48. Trivino A, Congregado M, Loscertales J, Cozar F, Pinos N, Carmona P, et al. Comparative analysis of video-assisted thoracoscopic thymectomy versus open resection for early-stage thymoma. Cir Esp. 2015;93(7):466-71.
49. Yang CJ, Hurd J, Shah SA, Liou D, Wang H, Backhus LM, et al. A national analysis of open versus minimally invasive thymectomy for stage I to III thymoma. J Thorac Cardiovasc Surg. 2020;160(2):555-67.e15.
50. Zhang X, Li B, Zou J, Su C, Zhu H, Chen T, et al. Perioperative risk factors for occurrence of myasthenia gravis after thymectomy in patients with thymoma. Interact Cardiovasc Thorac Surg. 2020;31(4):519-26.

51. Odaka M, Tsukamoto Y, Shibasaki T, Katou D, Mori S, Asano H, et al. Thoracoscopic thymectomy is a feasible and less invasive alternative for the surgical treatment of large thymomas. Interact Cardiovasc Thorac Surg. 2017;25(1):103-7.
52. Yuan ZY, Gao SG, Mu JW, Xue Q, Mao YS, Wang DL, et al. Long-term outcomes of 307 patients after complete thymoma resection. Chin J Cancer. 2017;36 (1) (no pagination)(46).
53. Jurado J, Javidfar J, Newmark A, Lavelle M, Bacchetta M, Gorenstein L, et al. Minimally invasive thymectomy and open thymectomy: Outcome analysis of 263 patients. Ann Thorac Surg. 2012;94(3):974-82.
54. Lin Q, Zhang Y, Yang L. Single-center retrospective analysis of 162 cases with thymoma complicating myasthenia gravis. J BUON. 2017;22(3):741-5.
55. Marulli G, Comacchio GM, Schiavon M, Rebusso A, Mammana M, Zampieri D, et al. Comparing robotic and trans-sternal thymectomy for early-stage thymoma: A propensity score-matching study. Eur J Cardiothorac Surg. 2018;54(3):579-84.
56. Allakhverdiev A, Davydov M, Allakhverdieva G, Akhmedov P. Thoracoscopic thymectomy - The method of choise in surgical treatment of non-invasive thymomas. Ann Med Surg. 2019;42:29-34.
57. Fadayomi AB, Iniguez CEB, Chowdhury R, Coppolino A, Jacobson F, Jaklitsch M, et al. Propensity score adjusted comparison of minimally invasive versus open thymectomy in the management of early stage thymoma. Thorac Cardiovasc Surg. 2018;66(4):352-8.
58. He Z, Zhu Q, Wen W, Chen L, Xu H, Li H. Surgical approaches for stage I and II thymoma-associated myasthenia gravis: Feasibility of complete video-assisted thoracoscopic surgery (VATS) thymectomy in comparison with trans-sternal resection. J Biomed Res. 2013;27(1):62-70.
59. Maniscalco P, Tamburini N, Quarantotto F, Grossi W, Garelli E, Cavallesco G. Long-term outcome for early stage thymoma: Comparison between thoracoscopic and open approaches. Thorac Cardiovasc Surg. 2015;63(3 Supplement 04):201-5.
60. Mu JW, Chen GY, Sun KL, Wang DW, Zhang BH, Li N, et al. Application of video-assisted thoracic surgery in the standard operation for thoracic tumors. Cancer Biol Med. 2013;10(1):28-35.
61. Nakajima J, Okumura M, Yano M, Date H, Haniuda M, Sano Y, et al. Myasthenia gravis with thymic epithelial tumour: A retrospective analysis of a Japanese database. Eur J Cardiothorac Surg. 2016;49(5):1510-5.
62. Ye B, Li W, Ge XX, Feng J, Ji CY, Cheng M, et al. Surgical treatment of early-stage thymomas: Robot-assisted thoracoscopic surgery versus transsternal thymectomy. Surg Endosc. 2014;28(1):122-6.
63. Chao YK, Liu YH, Hsieh MJ, Wu YC, Chen TP, Lu MS, et al. Long-term outcomes after thoracoscopic resection of stage I and II thymoma: A propensity-matched study. Ann Surg Oncol. 2015;22(4):1371-6.
64. Cheng YJ, Kao EL, Chou SH. Videothoracoscopic resection of stage II thymoma: Prospective comparison of the results between thoracoscopy and open methods. Chest. 2005;128(4):3010-2.
65. Chung JW, Kim HR, Kim DK, Chun MS, Kim YH, Park SI, et al. Long-term results of thoracoscopic thymectomy for thymoma without myasthenia gravis. J Int Med Res. 2012;40(5):1973-81.
66. Kimura T, Inoue M, Kadota Y, Shiono H, Shintani Y, Nakagiri T, et al. The oncological feasibility and limitations of video-assisted thoracoscopic thymectomy for early-stage thymomas. Eur J Cardiothorac Surg. 2013;44(3):e214-e8.
67. Odaka M, Akiba T, Yabe M, Hiramatsu M, Matsudaira H, Hirano J, et al. Unilateral thoracoscopic subtotal thymectomy for the treatment of stage I and II thymoma. Eur J Cardiothorac Surg. 2010;37(4):824-6.

68. Tian W, Li X, Tong H, Weng W, Yang F, Jiang G, et al. Surgical effect and prognostic factors of myasthenia gravis with thymomas. Thorac Cancer. 2020;11(5):1288-96.
69. Tagawa T, Yamasaki N, Tsuchiya T, Miyazaki T, Morino S, Akamine S, et al. Thoracoscopic versus transsternal resection for early stage thymoma: long-term outcomes. Surg Today. 2014:1-6.
70. Guerrera F, Rendina EA, Venuta F, Margaritora S, Ciccone AM, Novellis P, et al. Does the world health organization histological classification predict outcomes after thymomectomy? results of a multicentre study on 750 patients. Eur J Cardiothorac Surg. 2015;48(1):48-54.
71. Liou DZ, Ramakrishnan D, Lui NS, Shrager JB, Backhus LM, Berry MF. Does size matter? A national analysis of the utility of induction therapy for large thymomas. J Thorac Dis. 2020;12(4):1329-41.
72. Yamada Y, Yoshino I, Nakajima J, Miyoshi S, Ohnuki T, Suzuki M, et al. Surgical outcomes of patients with stage III thymoma in the Japanese nationwide database. Ann Thorac Surg. 2015;100(3):961-7.
73. Hakiri S, Fukui T, Mori S, Kawaguchi K, Nakamura S, Ozeki N, et al. Clinicopathologic features of thymoma with the expression of programmed death ligand 1. Ann Thorac Surg. 2019;107(2):418-24.
74. Kumar A, Pulle MV, Asaf BB, Shivnani G, Maheshwari A, Puri HV, et al. Surgical and oncological outcomes in locally advanced thymoma. Ind J Surg Oncol. 2020.
75. Song SH, Suh JW, Yu WS, Byun GE, Park SY, Lee CY, et al. The role of postoperative radiotherapy in stage II and III thymoma: a Korean multicenter database study. J Thorac Dis. 2020;12(11):6680-9.
76. Bian D, Zhou F, Yang W, Zhang K, Chen L, Jiang G, et al. Thymoma size significantly affects the survival, metastasis and effectiveness of adjuvant therapies: A population based study. Oncotarget. 2018;9(15):12273-83.
77. Song JS, Kim D, Kwon JH, Kim HR, Choi CM, Jang SJ. Clinicopathologic significance and immunogenomic analysis of programmed death-ligand 1 (PD-L1) and programmed death 1 (PD-1) expression in thymic epithelial tumors. Front Oncol. 2019;9 (no pagination)(1055).
78. Lucchi M, Melfi F, Dini P, Basolo F, Viti A, Givigliano F, et al. Neoadjuvant chemotherapy for stage III and IVA thymomas: A single-institution experience with a long follow-up. J Thorac Oncol. 2006;1(4):308-13.
79. Rea F, Marulli G, Di Chiara F, Schiavon M, Perissinotto E, Breda C, et al. Multidisciplinary approach for advanced stage thymic tumors: Long-term outcome. Lung Cancer. 2011;72(1):68-72.
80. Khorfan R, Bharat A, Odell DD. Management and Long-Term Outcomes of Advanced Stage Thymoma in the United States. Ann Thorac Surg. 2021;111(1):223-30.
81. Fornasiero A, Daniele O, Ghiotto C, Piazza M, Fiore-Donati L, Calabro F, et al. Chemotherapy for invasive thymoma: A 13-year experience. Cancer. 1991;68(1):30-3.
82. Kunitoh H, Tamura T, Shibata T, Nakagawa K, Takeda K, Nishiwaki Y, et al. A phase-II trial of dose-dense chemotherapy in patients with disseminated thymoma: Report of a Japan Clinical Oncology Group trial (JCOG 9605). Br J Cancer. 2009;101(9):1549-54.
83. Loehrer Sr PJ, Kim K, Aisner SC, Livingston R, Einhorn LH, Johnson D, et al. Cisplatin plus doxorubicin plus cyclophosphamide in metastatic or recurrent thymoma: Final results of an intergroup trial. J Clin Oncol. 1994;12(6):1164-8.
84. Loehrer Sr PJ, Wang W, Johnson DH, Ettinger DS. Octreotide alone or with prednisone in patients with advanced thymoma and thymic carcinoma: An Eastern Cooperative Oncology Group phase II trial. J Clin Oncol. 2004;22(2):293-9.
85. Rajan A, Carter CA, Berman A, Cao L, Kelly RJ, Thomas A, et al. Cixutumumab for patients with recurrent or refractory advanced thymic epithelial tumours: A multicentre, open-label, phase 2 trial. Lancet Oncol. 2014;15(2):191-200.

86.Zucali PA, De Pas T, Palmieri G, Favaretto A, Chella A, Tiseo M, et al. Phase II study of everolimus in patients with thymoma and thymic carcinoma previously treated with cisplatin-based chemotherapy. J Clin Oncol. 2018;36(4):342-9.
87.Wu KL, Mao JF, Chen GY, Fu XL, Qian H, Jiang GL. Prognostic predictors and long-term outcome of postoperative irradiation in thymoma: A study of 241 patients. Cancer Invest. 2009;27(10):1008-15.
88.Bian D, Zhao L, Zhang X, Lv F, Zhu Z, Qiu H, et al. Immunohistochemistry biomarker TP53 expression predicts the survival of thymomas. Gland Surg. 2020;9(2):291-9.
89.Eralp Y, Aydiner A, Kizir A, Kaytan E, Oral EN, Topuz E. Resectable thymoma: Treatment outcome and prognostic factors in the late adolescent and adult age group. Cancer Invest. 2003;21(5):737-43.
90.Jackson MW, Palma DA, Camidge DR, Jones BL, Robin TP, Sher DJ, et al. The Impact of Postoperative Radiotherapy for Thymoma and Thymic Carcinoma. J Thorac Oncol. 2017;12(4):734-44.
91.Mou H, Liao Q, Hou X, Chen T, Zhu Y. Clinical characteristics, risk factors, and outcomes after adjuvant radiotherapy for patients with thymoma in the United States: analysis of the Surveillance, Epidemiology, and End Results (SEER) Registry (1988-2013). Int J Radiat Biol. 2018;94(5):495-502.
92.Omasa M, Date H, Sozu T, Sato T, Nagai K, Yokoi K, et al. Postoperative radiotherapy is effective for thymic carcinoma but not for thymoma in stage II and III thymic epithelial tumors: The Japanese Association for Research on the Thymus Database Study. Cancer. 2015;121(7):1008-16.
93.Rimner A, Yao X, Huang J, Antonicelli A, Ahmad U, Korst RJ, et al. Postoperative radiation therapy is associated with longer overall survival in completely resected stage II and III thymoma-an analysis of the international thymic malignancies interest group retrospective database. J Thorac Oncol. 2016;11(10):1785-92.
94.Singhal S, Shrager JB, Rosenthal DI, Livolsi VA, Kaiser LR, Wright CD, et al. Comparison of stages I-II thymoma treated by complete resection with or without adjuvant radiation. Ann Thorac Surg. 2003;76(5):1635-42.
95.Tang EK, Chang JM, Chang CC, Wu SY, Huang WL, Chen YY, et al. Prognostic Factor of Completely Resected and Pathologic T3 N0 M0 Thymic Epithelial Tumor. Ann Thorac Surg. 2021;111(4):1164-73.
96.Yan J, Liu Q, Moseley JN, Baik CS, Chow LQM, Goulart BHM, et al. Adjuvant radiotherapy for stages II and III resected thymoma: A single-institutional experience. Am J Clin Oncol. 2016;39(3):223-7.
97.Berman AT, Litzky L, Livolsi V, Singhal S, Kucharczuk JC, Cooper JD, et al. Adjuvant radiotherapy for completely resected stage 2 thymoma. Cancer. 2011;117(15):3502-8.
98.Bruni A, Stefani A, Perna M, Borghetti P, Giaj Levra N, D'Angelo E, et al. The role of postoperative radiotherapy for thymomas: a multicentric retrospective evaluation from three Italian centers and review of the literature. J Thorac Dis. 2020;12(12):7518-30.
99.Chen YD, Feng QF, Lu HZ, Mao YS, Zhou ZM, Ou GF, et al. Role of adjuvant radiotherapy for stage II thymoma after complete tumor resection. Int J Radiat Oncol Biol Phys. 2010;78(5):1400-6.
100.D'Angelillo RM, Trodella L, Ramella S, Cellini N, Balducci M, Mantini G, et al. Novel Prognostic Groups in Thymic Epithelial Tumors: Assessment of Risk and Therapeutic Strategy Selection. Int J Radiat Oncol Biol Phys. 2008;71(2):420-7.
101.Fan C, Feng Q, Chen Y, Zhai Y, Zhou Z, Chen D, et al. Postoperative radiotherapy for completely resected Masaoka stage III thymoma: A retrospective study of 65 cases from a single institution. Radiat Oncol. 2013;8 (1) (no pagination)(199).

102.Hafner MF, Roeder F, Sterzing F, Krug D, Koerber SA, Kappes J, et al. Postoperative radiotherapy of patients with thymic epithelial tumors (TET): A retrospective analysis of outcome and toxicity. Strahlenther Onkol. 2014;191(2):133-40.
103.Lee KH, Noh JM, Ahn YC, Oh D, Kim J, Shim YM, et al. Patterns of failure following postoperative radiation therapy based on "tumor bed with margin" for stage II to IV Type C thymic epithelial tumor. Int J Radiat Oncol Biol Phys. 2018;102(5):1505-13.
104.Tomita N, Okuda K, Ogawa Y, Iida M, Eguchi Y, Kitagawa Y, et al. Relationship between radiation doses to heart substructures and radiation pneumonitis in patients with thymic epithelial tumors. Sci Rep. 2020;10(1):11191.
105.Lim YJ, Song C, Kim JS. Improved survival with postoperative radiotherapy in thymic carcinoma: A propensity-matched analysis of Surveillance, Epidemiology, and End Results (SEER) database. Lung Cancer. 2017;108:161-7.
106.Yuan ZY, Gao SG, Mu JW, Xue Q, Mao YS, Wang DL, et al. Prognostic value of preoperative neutrophil-lymphocyte ratio is superior to platelet-lymphocyte ratio for survival in patients who underwent complete resection of thymic carcinoma. J Thorac Dis. 2016;8(7):1487-96.
107.Cheng YJ. Videothoracoscopic resection of encapsulated thymic carcinoma: Retrospective comparison of the results between thoracoscopy and open methods. Ann Surg Oncol. 2008;15(8):2235-8.
108.Ruffini E, Detterbeck F, van Raemdonck D, Rocco G, Thomas P, Weder W, et al. Thymic carcinoma: A cohort study of patients from the European Society of Thoracic Surgeons database. J Thorac Oncol. 2014;9(4):541-8.
109.Bakhos CT, Salami AC, Kaiser LR, Petrov RV, Abbas AE. Thymic neuroendocrine tumors and thymic carcinoma: demographics, treatment, and survival. Innovations (Phila). 2020;15(5):468-74.
110.Hishida T, Nomura S, Yano M, Asamura H, Yamashita M, Ohde Y, et al. Long-term outcome and prognostic factors of surgically treated thymic carcinoma: Results of 306 cases from a Japanese nationwide database study. Eur J Cardiothorac Surg. 2016;49(3):835-41.
111.Merveilleux du Vignaux C, Dansin E, Mhanna L, Greillier L, Pichon E, Kerjouan M, et al. Systemic therapy in advanced thymic epithelial tumors: insights from the RYTHMIC prospective cohort. J Thorac Oncol. 2018;13(11):1762-70.
112.Miura Y, Kaira K, Sakurai R, Imai H, Tomizawa Y, Sunaga N, et al. Prognostic effect of class III beta-tubulin and topoisomerase-II in patients with advanced thymic carcinoma who received combination chemotherapy, including taxanes or topoisomerase-ii inhibitors. Oncol Lett. 2017;14(2):2369-78.
113.Agatsuma T, Koizumi T, Kanda S, Ito M, Urushihata K, Yamamoto H, et al. Combination chemotherapy with doxorubicin, vincristine, cyclophosphamide, and platinum compounds for advanced thymic carcinoma. J Thorac Oncol. 2011;6(12):2130-4.
114.Ko R, Shukuya T, Okuma Y, Tateishi K, Imai H, Iwasawa S, et al. Prognostic factors and efficacy of first-line chemotherapy in patients with advanced thymic carcinoma: A retrospective analysis of 286 patients from NEJ023 study. Oncologist. 2018;23(10):1210-7.
115.Hirai F, Yamanaka T, Taguchi K, Daga H, Ono A, Tanaka K, et al. A multicenter phase II study of carboplatin and paclitaxel for advanced thymic carcinoma: WJOG4207L. Ann Oncol. 2015;26(2):363-8.
116.Kim HS, Lee JY, Lim SH, Sun JM, Lee SH, Ahn JS, et al. A prospective phase II study of cisplatin and Cremophor EL-free paclitaxel (Genexol-PM) in patients with unresectable thymic epithelial tumors. J Thorac Oncol. 2015;10(12):1800-6.
117.Song Z, Yu X, Zhang Y. Chemotherapy and prognosis in advanced thymic carcinoma patients. Clinics (Sao Paulo, Brazil). 2015;70(12):775-80.
118.Xu JP, Hao XZ, Zhang XR, Yang S, Shi YK. Efficacy and safety of the combination of paclitaxel and platinum in advanced thymic carcinoma. Thorac Cancer. 2016;7(2):222-5.

119.Yang X, Zhuo M, Shi A, Yang S, Wang Z, Wu M, et al. Optimal first-line treatment for advanced thymic carcinoma. Thorac Cancer. 2019;10(11):2081-7.
120.Fan XW, Yang Y, Wang HB, Xu Y, Kang M, Xie LY, et al. Intensity modulated radiation therapy plus etoposide/cisplatin for patients with limited advanced unresectable thymic epithelial tumors: A prospective phase 2 study. Int J Radiat Oncol Biol Phys. 2020.
121.Tateishi K, Ko R, Shukuya T, Okuma Y, Watanabe S, Kuyama S, et al. Clinical outcomes of second-line chemotherapy in patients with previously treated advanced thymic carcinoma: A retrospective analysis of 191 patients from the NEJ023 study. Oncologist. 2019.
122.Okuma Y, Goto Y, Ohyanagi F, Sunami K, Nakahara Y, Kitazono S, et al. Phase II trial of S-1 treatment as palliative-intent chemotherapy for previously treated advanced thymic carcinoma. Cancer Med. 2020;9(20):7418-27.
123.Wang CL, Gao LT, Lu CX. S-1 salvage chemotherapy for stage IV thymic carcinoma: A study of 44 cases. J Thorac Dis. 2019;11(7):2816-21.
124.Cho J, Kim HS, Ku BM, Choi YL, Cristescu R, Han J, et al. Pembrolizumab for patients with refractory or relapsed thymic epithelial tumor: An open-label phase II trial. J Clin Oncol. 2019;37(24):2162-70.
125.Giaccone G, Kim C, Thompson J, McGuire C, Kallakury B, Chahine JJ, et al. Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study. Lancet Oncol. 2018;19(3):347-55.
126.Sato J, Satouchi M, Itoh S, Okuma Y, Niho S, Mizugaki H, et al. Lenvatinib in patients with advanced or metastatic thymic carcinoma (REMORA): a multicentre, phase 2 trial. Lancet Oncol. 2020;21(6):843-50.
127.Fu H, Gu ZT, Fang WT, Fu JH, Shen Y, Han YT, et al. Long-term survival after Surgical treatment of thymic carcinoma: A retrospective analysis from the Chinese Alliance for Research of Thymoma database. Ann Surg Oncol. 2016;23(2):619-25.
128.Kim S, Bull DA, Hsu CH, Hsu CC. The Role of Adjuvant Therapy in Advanced Thymic Carcinoma: A National Cancer Database Analysis. Ann Thorac Surg. 2019;23.
129.Mao Y, Wu S. Treatment and survival analyses of completely resected thymic carcinoma patients. Onco Targets Ther. 2015;8:2503-7.
130.Song Z, Zhang Y. Outcomes after surgical resection of thymic carcinoma: A study from a single tertiary referral centre. Eur J Surg Oncol. 2014;40(11):1523-7.
131.Wang Y, Xu L, Du T, Gao Y, Wu Z, Luo D. A nomogram predicting recurrence and guiding adjuvant radiation for thymic carcinoma after resection. Ann Thorac Surg. 2018;106(1):257-63.
132.Zhao Y, Zhao H, Hu D, Fan L, Shi J, Fang W. Surgical treatment and prognosis of thymic squamous cell carcinoma: A retrospective analysis of 105 cases. Ann Thorac Surg. 2013;96(3):1019-24.
133.Wen J, Chen J, Chen D, Liu D, Xu X, Huang L, et al. Evaluation of the prognostic value of surgery and postoperative radiotherapy for patients with thymic neuroendocrine tumors: A propensity-matched study based on the SEER database. Thorac Cancer. 2018;9(12):1603-13.
134.Fang W, Filosso PL, Roden AC, Gu Z, Liu Y, Agzarian J, et al. Clinicopathological features and current treatment outcomes of neuroendocrine thymic tumours. Eur J Cardiothorac Surg. 2020;25:25.
135.Bian D, Qi M, Hu J, Ning Y, Zhou F, Fei K, et al. The comparison of predictive factors regarding prognoses and invasion of thymic neuroendocrine tumors preoperatively and postoperatively. J Thorac Dis. 2018;10(3):1657-69.
136.Nakagawa K, Asamura H, Sakurai H, Watanabe SI, Tsuta K. Does the mode of surgical resection affect the prognosis/recurrence in patients with thymoma? J Surg Oncol. 2014;109(3):179-83.

137.Odaka M, Shibasaki T, Asano H, Marushima H, Yamashita M, Morikawa T. Feasibility of thoracoscopic thymectomy for treatment of early-stage thymoma. Asian J Endosc Surg. 2015;8(4):439-44.
138.Leuzzi G, Rocco G, Ruffini E, Sperduti I, Detterbeck F, Weder W, et al. Multimodality therapy for locally advanced thymomas: A propensity score-matched cohort study from the European Society of Thoracic Surgeons Database. J Thorac Cardiovasc Surg. 2016;151(1):47-57.e1.
139.Tian D, Shiiya H, Sato M, Sun CB, Anraku M, Nakajima J. Tumor location may affect the clinicopathological features and prognosis of thymomas. Thorac Cancer. 2019;10(11):2096-105.
140.Bian D, Ge T, Song N, Zhang P, Zhang H, Fei K. The secondary surgery provides significant benefits to recurrent thymoma: A retrospective analysis based on surveillance, epidemiology and end results database. Transl Cancer Res. 2019;8(3):840-7.
141.Yano M, Sasaki H, Yukiue H, Kawano O, Okuda K, Hikosaka Y, et al. Thymoma with dissemination: Efficacy of macroscopic total resection of disseminated nodules. World J Surg. 2009;33(7):1425-31.
142.Kumar A, Pulle MV, Asaf BB, Shivnani G, Maheshwari A, Kodaganur SG, et al. Superior vena cava resection in locally advanced thymoma-surgical and survival outcomes. Ind J Surg Oncol. 2020;11(4):711-9.
143.Lim YJ, Kim HJ, Wu HG. Role of postoperative radiotherapy in nonlocalized thymoma: Propensity-matched analysis of Surveillance, Epidemiology, and End Results database. J Thorac Oncol. 2015;10(9):1357-63.
144.Mou H, Kong Y, Wu Y, Wu Y, Yu L. Effect of Postoperative Radiotherapy in Thymoma Patients: A SEER-Based Study. Oncol Res Treat. 2021;44(1-2):28-35.
145.Weksler B, Pennathur A, Sullivan JL, Nason KS. Resection of thymoma should include nodal sampling. J Thorac Cardiovasc Surg. 2015;149(3):737-42.
146.Weksler B, Shende M, Nason KS, Gallagher A, Ferson PF, Pennathur A. The role of adjuvant radiation therapy for resected stage III thymoma: A population-based study. Ann Thorac Surg. 2012;93(6):1822-9.
147.Chang JH, Kim HJ, Wu HG, Kim JH, Kim YT. Postoperative radiotherapy for completely resected stage II or III thymoma. J Thorac Oncol. 2011;6(7):1282-6.
148.Sandri A, Cusumano G, Lococo F, Alifano M, Granone P, Margaritora S, et al. Long-term results after treatment for recurrent thymoma a multicenter analysis. J Thorac Oncol. 2014;9(12):1796-804.
149.Song Z, Jin X, Zhang Y. Treatment and prognosis of type B2 thymoma. World J Surg Oncol. 2014;12:291.
150.Liu Q, Fu X, Su X, Wang X, Zhang Y, Yang H, et al. Elevated pretreatment serum lactate dehydrogenase level predicts inferior overall survival and disease-free survival after resection of thymic carcinoma. J Thorac Dis. 2017;9(11):4550-60.
151.Okereke IC, Kesler KA, Freeman RK, Rieger KM, Birdas TJ, Ascioti AJ, et al. Thymic carcinoma: Outcomes after surgical resection. Ann Thorac Surg. 2012;93(5):1668-73.
152.Boothe D, Orton A, Thorpe C, Kokeny K, Hitchcock YJ. Postoperative radiotherapy in locally invasive malignancies of the thymus: Patterns of care and survival. J Thorac Oncol. 2016;11(12):2218-26.
153.Ye C, Bao M, Li H, Liu X, Jiang G, Wang W. Surgery in Masaoka stage IV thymic carcinoma: a propensity-matched study based on the SEER database. J Thorac Dis. 2020;12(3):659-71.
154.Sun Y, Liu J, Yu X. Treatment and prognosis of Masaoka stage 3 thymic carcinoma: A retrospective study of 32 cases. Onco Targets Ther. 2015;8:699-702.
155.Ogawa K, Toita T, Uno T, Fuwa N, Kakinohana Y, Kamata M, et al. Treatment and prognosis of thymic carcinoma a retrospective: Analysis of 40 cases. Cancer. 2002;94(12):3115-9.

156.Zhai Y, Hui Z, Ji W, Wang X, Liang J, Mao Y, et al. A Single-Center Analysis of the Treatment and Prognosis of Patients With Thymic Carcinoma. Ann Thorac Surg. 2017;104(5):1718-24.
157.Inoue A, Sugawara S, Harada M, Kobayashi K, Kozuki T, Kuyama S, et al. Phase II study of amrubicin combined with carboplatin for thymic carcinoma and invasive thymoma North Japan Lung Cancer Group study 0803. J Thorac Oncol. 2014;9(12):1805-9.
158.Sullivan JL, Weksler B. Neuroendocrine tumors of the thymus: Analysis of factors affecting survival in 254 patients. Ann Thorac Surg. 2017;103(3):935-9.
159.Fiorelli A, Natale G, Freda C, Santini M. Is thymomectomy equivalent to complete thymectomy in non-myasthenic patients with early-stage thymoma? Interact Cardiovasc Thorac Surg. 2019;28(3):399-403.
160.Yang Y, Dong J, Huang Y. Thoracoscopic thymectomy versus open thymectomy for the treatment of thymoma: A meta-analysis. Eur J Surg Oncol. 2016;42(11):1720-8.
161.Lim YJ, Kim E, Kim HJ, Wu HG, Yan J, Liu Q, et al. Survival impact of adjuvant radiation therapy in Masaoka stage II to IV thymomas: A systematic review and meta-analysis. Int J Radiat Oncol Biol Phys. 2016;94(5):1129-36.
162.Hamaji M, Shah RM, Ali SO, Bettenhausen A, Lee HS, Burt BM. A meta-analysis of postoperative radiotherapy for thymic carcinoma. Ann Thorac Surg. 2017;103(5):1668-75.
163.Hamaji M, Ali SO, Burt BM. A meta-analysis of induction therapy for advanced thymic epithelial tumors. Ann Thorac Surg. 2015;99(5):1848-56.
164.Berghmans T, Durieux V, Holbrechts S, Jungels C, Lafitte JJ, Meert AP, et al. Systemic treatments for thymoma and thymic carcinoma: A systematic review. Lung Cancer. 2018;126:25-31.

Appendix 1: PEBC'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 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 has risks for acute and long-term toxicity, notably a risk for the development of secondary malignancies (4) 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 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. 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 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 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-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.
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.

Appendix 2: Affiliations and Conflict of Interest Declarations

In accordance with the PEBC Conflict of Interest Policy, the Members of the Treatment of Thymic Tumours GDG Working Group, Expert Panel, Report Approval Panel, and Targeted Peer Reviewers were asked to disclose potential conflicts of interest.

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 Leighl Medical Oncologist Lung Cancer Disease Site Group	Received institutional support from: Amgen, Array, Astra Zeneca, Bristol-Myers Squibb, MSD, Roche, Pfizer, Takeda, Novartis, Lilly, Bayer, Guardant Health, Inivata
Robert MacRae Radiation Oncologist Lung Cancer Disease Site Group	Received $500 or more in a single year from Astra Zeneca 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	• 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	
Muriel Brackstone Surgical Oncologist, London Regional Cancer Program Medical Director, London Breast Care Clinic Director, London Tumour Biobank Professor of Surgery & Oncology, Western University	None declared
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	• Received $500 or more in a single year from Amgen, Bayer, Eisai, Ipsen, Merck, and Roche • Received an unrestricted educational grant 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

Appendix 3: Responses to GRADE's evidence-to-decision framework

Type of tumour	Comparison	Desirable effects	Undesirable effects	Certainty of evidence	Values	Balance of effects	Equity	Acceptability	Feasibility	Generalizable
Thymoma	Partial vs. total thymectomy	Trivial	Trivial	Very low	No uncertainty or variability	Does not favour 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 favours 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 favours 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 favours 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

Type of tumour	Comparison	Desirable effects	Undesirable effects	Certainty of evidence	Values	Balance of effects	Equity	Acceptability	Feasibility	Generalizable
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 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
Thymoma	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
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

Type of tumour	Comparison	Desirable effects	Undesirable effects	Certainty of evidence	Values	Balance of effects	Equity	Acceptability	Feasibility	Generalizable
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	Favours adjuvant chemotherapy	Probably no impact	Yes	Yes	Yes, based on stage

MG, Myasthenia gravis; MIS, Minimally invasive surgery; NETs, Neuroendocrine tumours; OS, Overall survival; PORT, Postoperative radiotherapy

The data for the surgical comparisons were very limited for patients with thymic carcinoma. Therefore, indirect evidence from patients with thymoma were used as indirect evidence for these comparisons.

Appendix 4: Literature Search Strategy

Databases: **Embase** 1996 to 2021 April 05**, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials** February 2021**, EBM Reviews - Cochrane Database of Systematic Reviews** 2005 to March 31, 2021

Search Strategy:

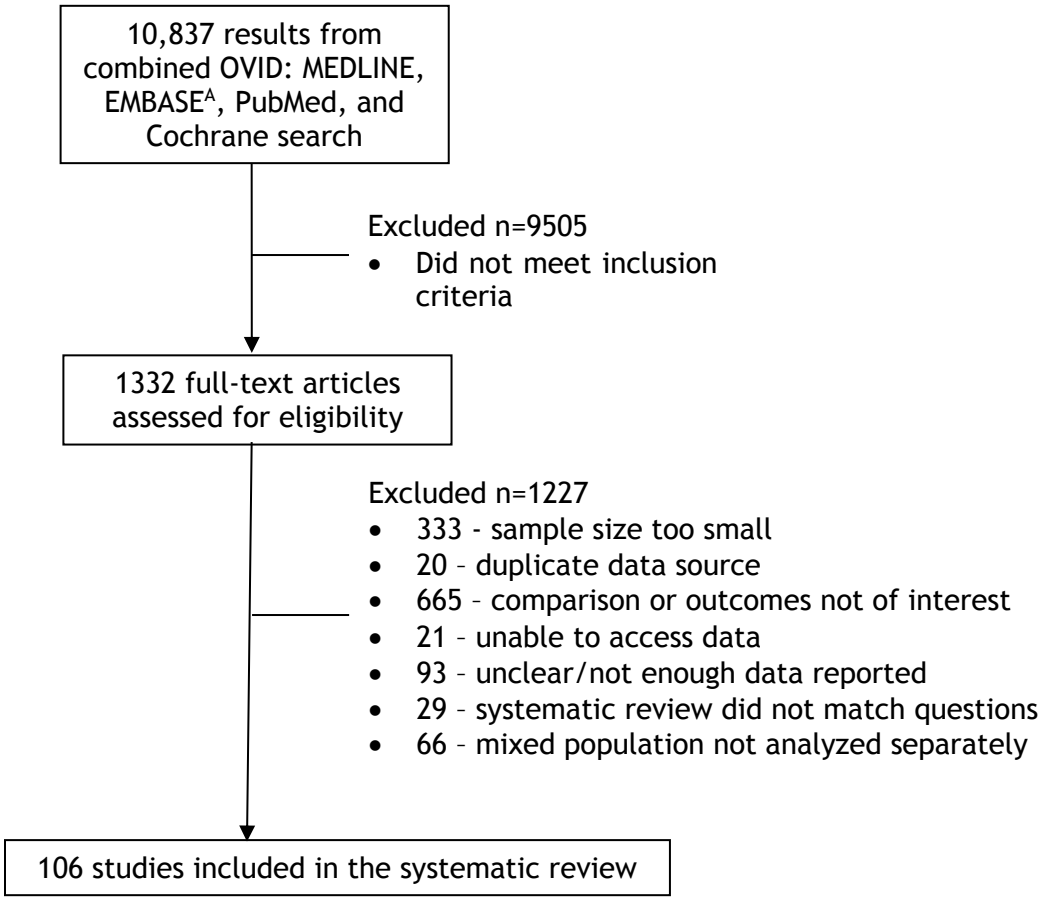
exp thymoma/ or exp thymus cancer/ or exp thymus neoplasms/
(thymoma$ or (thym$ adj2 (cancer$ or neoplas$ or adenocarcinom$ or carcino$ or malignan$ or tumo?r$))).mp.
1 or 2
exp Antineoplastic Agent/ or exp drug therapy/ or exp chemotherapy, adjuvant/ or exp adjuvant chemotherapy/ or exp cancer adjuvant therapy/ or exp chemotherapy/ or exp cancer chemotherapy/ or exp cancer combination chemotherapy/ or exp combination chemotherapy/ or exp multimodality cancer therapy/ or exp Antineoplastic Agents/ or exp Antineoplastic combined chemotherapy protocols/ or exp surgery/ or exp thoracic surgery/ or exp thymectomy/ or exp sternotomy/ or exp radiotherapy/ or cancer radiotherapy/ or exp preoperative radiotherapy/ or exp radiotherapy, adjuvant/ or exp systemic therapy/ or exp imatinib mesylate/ or exp imatinib/ or exp cixutumumab/ or exp sunitinib/ or exp saracatinib/ or exp everolimus/ or exp octreotide/ or exp pembrolizumab/ or exp nivolumab/ or exp atezolizumab/ or exp cisplatin/ or exp carboplatin/ or exp platinum/
(chemotherap: or surger: or surgical or operativ: or resect: or radiotherap: or chemoradi: or radiochemo: or systemic therap: or systemic treatment: or thymectom: or sternotom: or imatinib or cixutumumab or sunitinib or saracatinib or everolimus or octreotide or pembrolizumab or nivolumab or atezolizumab or cisplatin or carboplatin or platinum or Gleevec or Glivec or Sutent or Zortress or Certican or Afinitor or Votubia or Evertor or Sandostatin or Bynfezia Pen or Keytruda or lambrolizumab or Opdivo or MDX1106 or Tecentriq or MPDL3280A or platin$ or cisplatin$ or platamin$ or neoplatin$ or cismaplat$ or CDDP or CBDCA or carboplatin$ or paraplatin$).mp.
STI-571.mp.
ONO-4538.mp.
MK-3475.mp.
BMS-936558.mp.
4 or 5 or 6 or 7 or 8 or 9
3 and 10
animal/ not (exp human/ or humans/)
11 not 12

(comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
(editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
14 or 15
13 not 16
limit 17 to english language [Limit not valid in CDSR; records were retained]

PubMed was searched on August 26, 2021 with the following search strategy:
((thymoma[Title]) OR (thymic[Title])) OR (thymus[Title]) Filters: in the last 1 year, Humans, English

Appendix 5: PRISMA Flow Diagram

Figure 1: Flow diagram of results from literature search strategies



[A] Online search strategy available in Appendix 4
Abbreviations: EMBASE, Excerpta Medica; MEDLINE, Medical Literature Analysis and Retrieval System Online

Appendix 6: Characteristics of included studies

Study Database / Location Design Study period	Population Follow-up	Intervention (n)	Control (n)	Outcome(s) of interest	Adjusted factor(s)
Agatsuma 2017 [42] JART database, Japan Retrospective 1991-2010	Thymoma Inclusion: median sternotomy or VATS Exclusion: lateral thoracotomy, sternotomy with VATS, not curative resection, partial thymectomy, stage III & IV, treated before 1994 Median VATS 3.7 years, sternotomy 5.2 years	VATS (140) propensity-matched	Median sternotomy (140) propensity-matched	OS, Recurrence	None
Agatsuma 2011 [113] Respiratory Division of Shinshu University hospital, Japan Retrospective 1996-2010	Thymic carcinoma (3% NETs) Inclusion: previously untreated, Masaoka stage IVa or IVb, and received first-line chemotherapy Median 35.5 months (range 6.2–96.5 months)	ADOC chemotherapy (29)	Carboplatin-based chemotherapy (5)	Response	None
		First-line platinum-based chemotherapy (34)		Grade ≥3 hematologic toxicities	
		First-line platinum-based chemotherapy (34)		Grade ≥3 non-hematologic toxicities	
Allahkverdiev 2019 [56] N. N. Blokhin Russian Cancer Research Center Retrospective 2008-?	Thymoma	Thoracoscopic thymectomy (33)	Open thymectomy (26) sternotomy	Postoperative complications	None
Bakhos 2020 [109] National Cancer Database, USA Retrospective 2004-2015	Thymic carcinoma (n=1194) & thymic NETs (n=295) Exclusion: age <18 years, unstaged tumours Median thymic carcinoma: 3.2 years thymic NETs: 3.8 years	Neoadjuvant chemotherapy (?) for thymic carcinoma	No chemotherapy (?) for thymic carcinoma	OS (?)	None
		Neoadjuvant chemotherapy (?) for thymic NETs	No chemotherapy (?) for thymic NETs	OS (?)	
		Adjuvant chemotherapy (?) for thymic NETs	No chemotherapy (?) for thymic NETs	OS (?)	
		PORT (?)	No PORT (?)	OS (?)	

		for thymic NETs	for thymic NETs		
Berman 2011 [97] University of Pennsylvania Medical Center, USA Retrospective 1990-2008	Thymoma Inclusion: completely resected, Masaoka stage II, minimum six month follow-up	PORT (37) median dose 5040 cGy		Grade ≥3 toxicities	None
Bian 2020 [88] Fudan University Affiliated Huadong Hospital, China Retrospective 2001-2016	Thymoma Inclusion: complete resection Exclusion: malignant oncologic history, palliative surgery, neoadjuvant therapies, did not abide by the prescriptions from surgeons postoperatively Median 54 months (range 0-195 months)	PORT (41)	No PORT (57)	OS	None
Bian 2018 [76] SEER database, USA Retrospective 1973-2014	Thymoma Inclusion: resection, complete data Exclusion: tumour history, <12 years old, carcinoma	Neoadjuvant radiotherapy (37)	No radiotherapy (576)	OS	Age, stage, tumour size
Bian 2018 The comparison [135] SEER database, USA Retrospective 1998-2014	Thymic NETs Exclusion: history of other tumours or incomplete data	PORT (?) for resected	No PORT (?) for resected	OS (n=125)	Age, gender, histology, stage
		Adjuvant chemotherapy (?) for resected	No adjuvant chemotherapy (?) for resected	OS (n=125)	
Bruni 2020 [98] Three Italian hospitals Retrospective 1981-2015	Thymoma or thymic carcinoma Inclusion: resection Mean 130 months (range 3–417 months)	PORT (113)		Grade ≥3 toxicities	None
Chao 2015 [63] Chang Gung Memorial Hospital, China Retrospective 1991-2007	Thymoma Inclusion: resection with curative intent, stage I or II Median 53 months	VATS (48) propensity-matched on age, MG, stage, tumour size 1 conversion	Median sternotomy (48) propensity-matched on age, MG, stage, tumour size	Blood loss, Chest tube drainage duration, Hospital duration	None

Chen 2010 [99] Cancer Hospital of Peking Union Medical College, China Retrospective 1964-2006	Thymoma Inclusion: complete resection, Masaoka stage II Exclusion: incomplete data, thymic carcinoma Median 63 months (range 2-303 months)	PORT (66) median dose 60 Gy (range 22-60 Gy)		Grade ≥3 lung fibrosis	None
Cheng 2008 [107] Three hospitals in Southern Taiwan Retrospective 2002-2007	Thymic carcinoma Inclusion: Masaoka stage I and II encapsulated, curative-intent resection Mean 3.76 ± 1.43 years	VATS (4) no conversions	Open median sternotomy (4)	Intraoperative blood loss, Pleural drainage time, Postoperative hospital stay	None
Cheng 2005 [64] Kaohsiung Medical University Hospital, Taiwan Prospective 1999-2004	Thymoma Inclusion: resection with curative intent, stage II Mean 33.9 ± 19.7 months	Videothoracoscopic (12) no conversions	Open median sternotomy (10)	Intraoperative blood loss, Pleural drainage duration, Postoperative hospital stay duration	None
Cho 2019 [124] Samsung Medical Center, Korea Prospective 2016	Thymoma & thymic carcinoma Inclusion: disease progressed after at least one line of platinum-based chemotherapy, ≥18 years, PS ≤ 2, adequate organ and bone marrow function Exclusion: systemic treatment for autoimmune disease within the past year, severe autoimmune disease, interstitial lung disease, active infection requiring systemic therapy, history of HIV infection, active hepatitis B/C virus infection, radiation therapy within 2 weeks of first pembrolizumab dose, or previous treatment with any other anti-PD-1/L1 therapy Median 14.9 months (interquartile range, 6.25-20.7)	Pembrolizumab (26) only thymic carcinoma		Response	None
Chung 2012 [65]	Thymoma Inclusion: tumours in anterior mediastinum and under	Thoracoscopic thymectomy (25)	Sternotomy thymectomy (45)	Chest intubation duration, Hospital stay duration	None

Asan Medical Centre database, South Korea Retrospective 2002-2008	innominate vein, tumours <5 cm in diameter at the widest point, distinctive fat plane between tumour and surrounding tissue Exclusion: neoadjuvant chemotherapy, MG, type B3 or C thymomas, open thoracotomy, pleural metastasis, conversion Mean 78.0 ± 21.9 months (thoracoscopic thymectomy) 70.0 ± 23.6 months (sternotomy thymectomy)				
D'Angelillo 2008 [100] Italy Retrospective 1974-2004	Thymoma & thymic carcinoma Inclusion: resection Mean 13.8 years	PORT (98)		Grade ≥3 toxicities	None
Eralp 2003 [89] University of Istanbul, Turkey Retrospective 1990-2000	Thymoma Inclusion: resection, invasive, complete data Median 39 months (range 1.3–111 months)	PORT (24) total dose of 5040 cGy-60 Gy	No PORT (7)	OS	None
Fadayomi 2018 [57] Brigham and Women's Hospital, USA Retrospective 2005-2015	Thymoma Inclusion: stage I and II, thymectomy Exclusion: thymic carcinoma, hyperplasia, atrophy, lymphomas, benign thymic pathologies, concurrent extrapleural pneumonectomy, stage III and IV thymoma Median 52.5 months (interquartile range 48 months) (open thymectomy) and 27 months (interquartile range 37 months) (minimally invasive thymectomy)	Minimally invasive thymectomy (19) VATS or robotic thymectomy propensity-matched on comorbidity index, stage, tumour size	Open thymectomy (34) sternotomy, hemi-clamshell, or thoracotomy propensity-matched on comorbidity index, stage, tumour size	90-day postoperative morbidity	None

Fan 2020 Intensity [120] Fudan University Shanghai Cancer Center, China Prospective (NCT02636556) 2011-2018	Thymoma & thymic carcinoma Inclusion: age 18 to 75, previously untreated and unresectable limited advanced disease, lesions could be encompassed within radiation fields, PS 0 to 2, adequate bone marrow reserve, hepatic function and renal function Exclusion: distant metastases not included in the radiation field, history of malignancy excluding carcinoma in situ of the cervix in the last 5 years; previous chemotherapy, radiation therapy, or thoracic surgery, active pulmonary infection, being pregnant or lactating Median 46 months (range 7-101 months)	Concurrent intensity modulated radiation therapy plus etoposide/cisplatin (34) only thymic carcinoma		Response	None
Fan 2013 [101] Cancer Hospital of the Peking Union Medical College, China Retrospective 1982-2010	Thymoma Inclusion: complete resection, Masaoka stage III Exclusion: incomplete data, neoadjuvant radiotherapy, thymic carcinoma or carcinoid Median 50 months (range 5–360 months)	PORT (53) median dose 56 Gy (range 28–60 Gy)	No PORT (12)	OS	None
		PORT (53) median dose 56 Gy (range 28–60 Gy)		Grade ≥3 pneumonitis, Grade ≥3 agranulocytosis	
Fang 2020 [134] 21 centres in China, Europe and North America Retrospective 1989-2016	Thymic NETs Median 45 months (range 1–270) months	Neoadjuvant therapy (21)	No neoadjuvant therapy (146)	OS	None
Fernandes 2010 [7] SEER, USA Retrospective 1973-2005	Thymoma Exclusion: <18 years, incomplete data, thymic carcinoma, diagnosed in 2004 or 2005	Radiotherapy (1334)		Cardiac mortality, Secondary malignancies	None

	Median 52 months (range 0–361 months)				
Fornasiero 1991 [81] Padova Medical Oncology Department, Italy Retrospective 1997-1990	Thymoma Inclusion: stage III or IV	ADOC (37)		Grade ≥3 anemia, Grade ≥3 leukopenia, Grade ≥3 thrombocytopenia, response	None
Fu 2016 [127] ChART database, China Retrospective 1996-2013	Thymic carcinoma (4% NETs) Inclusion: radical resection Median 35.8 months (interquartile range 20.1-66.9 months)	PORT (224)	No PORT (105)	OS	Resection status, stage
		PORT (138) for completely resected	No PORT (73) for completely resected	DFS	
		Adjuvant chemotherapy (148)	No adjuvant chemotherapy (181)	OS	None
Giaccone 2018 [125] Lombardi Comprehensive Cancer Center, USA Prospective NCT02364076 2015-2016	Thymic carcinoma Inclusion: recurrent, progressed after at least one line of chemotherapy, PS 0-2, no history of autoimmune disease or other malignancy, adequate organ function Exclusion: HIV or hepatitis infections, immunodeficiency, interstitial pneumonitis, previous treatment with an immune checkpoint inhibitor Median 20 months (interquartile range 14–26 months)	Pembrolizumab (40)		Grade ≥3 toxicities, Response	None
Guerrara 2015 [70] Six Italian Thoracic Surgery Institutions Retrospective 1990-2011	Thymoma Inclusion: resection Exclusion: thymic carcinoma & NETs Mean 90 months (range 3–274 months)	Neoadjuvant therapy (?)	No neoadjuvant therapy (?)	OS (n=746)	Age, gender, histology, MG, resection status, stage, year of intervention
Hafner 2014 [102] University Hospital of Heidelberg or the	Thymoma & thymic carcinoma Inclusion: resection, PORT Exclusion: incomplete records, follow-up <6 months	PORT (41) mean dose 51.7 Gy (range 49–60 Gy)		Grade ≥3 toxicities	None

German Cancer Research Center Retrospective 1995-2012	Median 61 months (range 15–174 months)				
Hakiri 2019 [73] Nagoya University Hospital, Japan Retrospective 2004-2015	Thymoma Inclusion: resection Median 37 months (range 1-137 months)	Neoadjuvant chemotherapy (8)	No neoadjuvant chemotherapy (73)	OS	None
		Neoadjuvant chemotherapy (8)	No neoadjuvant chemotherapy (73)	DFS	Age, gender, histology, PD-L1 expression, stage
He 2016 [43] First Affiliated Hospital of Wenzhou Medical University, China Retrospective 2004-2010	Thymoma with MG Inclusion: imaging confirmation, no pre-operative MG crisis, complete data Exclusion: refusal for follow-up, hormones or immunosuppressive agents or suffered from other autoimmune diseases in first 3 months of treatment, unclear MG 6-60 months after operation, 5-year follow-up rate 74.0%	VATS (39)	Median sternotomy (34)	Complications, Blood loss, Overall survival, Pleural drainage, Postoperative hospital duration,	None
He 2013 [58] Nanjing Medical University, China Retrospective 2006-2011	Thymoma or thymic carcinoma with MG Inclusion: stage I or II Range 12-61 months	VATS (15) no conversions	Trans-sternal thymectomy (18)	Blood loss, Complications, Hospital stay, Pleural drainage	None
Hirai 2015 [115] West Japan Oncology Group Prospective WJOG4207L 2008-2010	Thymic carcinoma Inclusion: chemotherapy-naïve, >20 years, unresectable, stage III or IV, PS 0-1, adequate bone marrow reserve, renal and hepatic function Exclusion: uncontrolled pleural or pericardial effusion, brain tumour with symptoms, superior vena cava syndrome, interstitial pneumonitis, other active malignancy, serious allergy to medical drugs, and MG	Carboplatin + paclitaxel (39)		Grade ≥3 leukopenia, Grade ≥3 neutropenia, Grade ≥3 anemia, Grade ≥3 febrile neutropenia, Grade ≥3 anorexia, Response	None
Hishida 2020 [33] JART database, Japan Retrospective 1991-2010	Thymoma Exclusion: thymic carcinoma, thymic NETs, other/unclassified thymic tumour, MG	Partial thymectomy (349)	Total thymectomy (1432)	OS	Age, gender, histology, history of malignant disease, pre-/postoperative

					therapy, presence of non-MG autoimmune disease, resection status, stage, tumour size
Hishida 2016 [110] JART database, Japan Retrospective 1991-2010	Thymic carcinoma Inclusion: resection Exclusion: Type B3 thymomas and thymic NETs Median 8.7 years	PORT (145) Median dose 50 Gy	No PORT (249)	OS	Resection status, stage
		Neoadjuvant cisplatin/carboplatin-chemotherapy (63)	No neoadjuvant chemotherapy (231)	OS	
		PORT (?) for completely resected	No PORT (?) for completely resected	RFS (n=169)	Stage
		Neoadjuvant cisplatin/carboplatin-chemotherapy (?) for completely resected	No neoadjuvant chemotherapy (?) for completely resected	RFS (n=169)	
Jackson 2017 [90] National Cancer Data Base, USA Retrospective 2004-2012	Thymoma or thymic carcinoma Inclusion: resection Exclusion: neoadjuvant radiotherapy, death occurred within 1 month of diagnosis Median 57.2 months (range 1.08-129.15 months) for thymoma Median 59.5 months (range 1.15-130.23 months) for thymic carcinoma	PORT (1444) only thymoma	No PORT (1587) only thymoma	OS	Age, comorbidity score, distance to facility, facility type, gender, histology, income, insurance status, race, resection status, stage, year of diagnosis
		PORT (557) only thymic carcinoma	No PORT (468) only thymic carcinoma	OS	Age, comorbidity score, distance to facility, facility type, gender, income, insurance status, race, resection status, stage, year of diagnosis
		PORT (431) only stage I-IIA thymoma	No PORT (813) only stage I-IIA thymoma	OS	Histology, resection status, stage
		PORT (359) only stage IIB thymoma	No PORT (274) only stage IIB thymoma	OS	
		PORT (451) only stage III thymoma	No PORT (317) only stage III thymoma	OS	
		PORT (165) only stage IV thymoma	No PORT (136) only stage IV thymoma	OS	

Jurado 2012 [53] Columbia University Medical Center, USA Retrospective 2000-2011	Thymoma Median 24.2 months (minimally invasive thymectomy) and 81 months (open thymectomy)	Minimally invasive thymectomy (10)	Open thymectomy (62)	Recurrence rate	None
Khorfan 2021 [80] National Cancer Database, USA Retrospective 2004-2016	Thymoma Inclusion: stages III & IV Exclusion: thymic carcinoma	Radiotherapy and/or chemotherapy (417)	No treatment (32)	OS	Age, Charlson score, gender, histology, hospital type, income, insurance, metastases, metropolitan area, race, stage, tumour size
Kim 2019 [128] National Cancer Database, USA Retrospective 2004-2013	Thymic carcinoma Inclusion: stage IIB & III, curative resection Exclusion: neoadjuvant therapy, unknown stage, treatment or survival information, treated with palliative intent	Adjuvant chemotherapy alone (63) only stage IIB	Surgery alone (58) only stage IIB	OS	None
		PORT only (6) only stage IIB	Surgery alone (58) only stage IIB	OS	
		Adjuvant chemotherapy alone (129) only stage III	Surgery alone (143) only stage III	OS	
		PORT only (56) only stage III	Surgery alone (143) only stage III	OS	
Kim 2015 [116] Samsung Medical Center, Korea Prospective 2012-2014	Thymoma & thymic carcinoma Inclusion: unresectable, 18 years or older, PS 0 or 1, adequate bone marrow reserve, renal function, and hepatic function Exclusion: prior malignancies, unless curatively treated with no evidence of recurrence within previous 5 years, no prior palliative chemotherapy Median 15.5 months	Cisplatin and Cremophor EL-free paclitaxel (Genexol-PM) (27) with thymic carcinoma		Response	None
Kimura 2013 [66] Osaka University Hospital, Japan Retrospective 2002-2009	Thymoma Inclusion: stage I and II Mean 53.7 months ± standard deviation 24.5 months (VATS) and	VATS (45)	Open sternotomy (29)	Blood loss, Hospital duration	None

	49.6 months ± standard deviation 25.3 months (open sternotomy)				
Ko 2018 [114] North East Japan Study Group (NEJ023) Retrospective 1995-2014	Thymic carcinoma (13% NETs) Inclusion: advanced stage or recurrent treated with palliative-intent chemotherapy without any indication of curative treatment Median 55.5 months	Single-agent chemotherapy (10)	Platinum doublet chemotherapy (178)	OS	Age, gender, histology, performance status, stage (Masaoka & WHO)
		Other multidrug chemotherapies (98)	Platinum doublet chemotherapy (178)	OS	
		Single-agent chemotherapy (2) only stage IVb	Other multidrug chemotherapies (53) only stage IVb	OS	Age, gender, histology, lymph node metastasis, performance status
		Platinum doublet chemotherapy (89) only stage IVb	Other multidrug chemotherapies (53) only stage IVb	OS	
		Carboplatin plus paclitaxel (70)	ADOC (79)	RR	None
		Cisplatin plus etoposide (35)		RR	
Kocer 2018 [44] Turkey Retrospective 2004-2016	Thymoma Inclusion: complete resection Mean 128.67±7.95 months	VATS (8)	Transsternal extended thymectomy (54)	OS	None
Kumar 2020 Surgical [74] Tertiary referral center New Delhi, India Retrospective 2012-2019	Thymoma Inclusion: stages III-IVA Median 58 months	Neoadjuvant chemotherapy (20)	No neoadjuvant chemotherapy (34)	OS	None
Kunitoh 2009 [82] JCOG 9605, Japan Prospective 1997-2004	Thymoma Inclusion: stage IV, chemotherapy-naïve, 15–70 years, PS 0–2, adequate organ function Exclusion: thymic carcinoma, thymic NETs, uncontrolled heart disease, diabetes or hypertension, pulmonary fibrosis or active pneumonitis, infections necessitating systemic use of antibiotics, disease necessitating emergency radiotherapy, active concomitant malignancy, pregnancy, grave complications of thymoma	Chemotherapy (30) cisplatin, vincristine, doxorubicin, etoposide, granulocyte colony-stimulating factor		RR, Grade ≥3 leukopenia, Grade ≥3 anemia, Grade ≥3 thrombocytopenia	None

Lee 2018 [103] Samsung Medical Center, Korea Retrospective 2002-2014	Thymic carcinoma & thymic NETs Inclusion: stages II to IV, PORT Median 69 months (range 6-160 months)	PORT (53)		Toxicity	None
Lim 2017 [105] SEER database, USA Retrospective 2004-2013	Thymic carcinoma Inclusion: resection Exclusion: survival time <1 month	PORT (128) propensity-matched	No PORT (128) propensity-matched	OS	Age, stage
		Local/partial resection (112)	Total/radical resection (122)	OS	
		PORT (50) only stage I-II propensity-matched	No PORT (45) only stage I-II propensity-matched	OS	None
		PORT (39) only stage III propensity-matched	No PORT (43) only stage III propensity-matched	OS	
		PORT (29) only stage IV propensity-matched	No PORT (28) only stage IV propensity-matched	OS	
Lin 2017 [54] Jiangxi Provincial People's Hospital Nanchang, China Retrospective 1993-2015	Thymoma with MG Median 12.6 years	VATS (55)	Conventional thymectomy (107)	Blood loss, Complications, Recurrence rate	None
Liou 2020 [71] National Cancer Database, USA Retrospective 2006-2013	Thymoma Inclusion: stages I-III, resection, complete data Exclusion: previous malignancies	Neoadjuvant therapy (166)	No neoadjuvant therapy (1683)	OS	Age, Charlson comorbidity index, gender, resection status, stage, tumour size
Liu 2014 [45] National Taiwan University Hospital Retrospective 1991-2010	Thymoma Inclusion: stage I and II, resection Mean 61.9 months (VATS) 69.7 months (sternotomy)	VATS (76) one conversion	Sternotomy (44) transsternal thymectomy	OS, Blood loss, Drainage duration, Hospital duration, Recurrence rate	None
Loehrer 2004 [84] Eastern Cooperative Oncology Group, USA Prospective 1998-2000	Thymoma & thymic carcinoma Inclusion: unresectable, invasive, recurrent, or metastatic, >18 years, prior radiotherapy were eligible if tumour grew in an area of prior radiation or in a metastatic site before study	Octreotide with or without prednisone (32) only thymoma		Response	None

	entry, adequate hepatic function, PS 0 or 1 Exclusion: acute intracurrent complications or other contraindications to high-dose corticosteroid therapy				
Loehrer 1994 [83] Southeastern Cancer Study Group or Eastern Cooperative Oncology Group, USA Retrospective 1983-1992	Thymoma & thymic carcinoma Inclusion: metastatic or locally progressive recurrent disease following radiotherapy, Karnofsky performance score ≥50, adequate renal, hepatic function and bone marrow reserve Exclusion: prior chemotherapy, prior malignancy within the previous 5 years, or history of congestive heart failure	Cisplatin, doxorubicin, and cyclophosphamide (29) only thymoma		Response	None
Lucchi 2006 [78] University of Pisa, Italy Prospective 1989-2004	Thymoma Inclusion: stages III-IVa, neoadjuvant chemotherapy, surgery, and PORT Exclusion: thymic carcinoma	Cisplatin, epirubicin, and etoposide (30)		Response	None
Maniscalco 2015 [59] Sant'Anna Hospital of Ferrara, Italy Retrospective 1995-2007	Thymoma Inclusion: stage I and II Exclusion: thymic carcinoma Median 123 months	VATS (13) No conversions	Open thymectomy (14) median sternotomy	Complications	None
Manoly 2014 [46] United Kingdom Retrospective 2004-2010	Thymoma Inclusion: thymectomy Exclusion: non-thymomatous MG or other mediastinal mass, aged <18 years at time of surgery, unresectable Mean 33 ± 17.8 months	VATS (17) two conversions	Trans-sternal thymectomy (22)	5-year OS, DFS, Complications, Hospital duration	None
Mao 2015 [129] Hangzhou Cancer Hospital, China Retrospective 2001-2013	Thymic carcinoma (7% NETs) Inclusion: complete resection Median 72 months (range 25-168 months)	PORT (25) Median dose 54.2 Gy	No PORT (29)	OS, DFS	Gender, histology, stage
		Adjuvant cisplatin-based chemotherapy (16)	No adjuvant chemotherapy (38)	OS, DFS	
Marulli 2018 [55] University of Padova, Italy	Thymoma	RATS (41) one conversion	Median sternotomy (41)	Postoperative complications, Recurrence	None

Retrospective 1982-2017	Inclusion: stage I and II, complete resection with trans-sternal or robotic approach Exclusion: thymic neoplasms other than thymoma Median 28.3 months (interquartile range 18.2-61.4 months) 88.3 months (interquartile range 61.6-116.4 months)	propensity-matched on age, histology, MG, stage, tumour size	propensity-matched on age, histology, MG, stage, tumour size		
Merveilleux du Vignaux 2018 [111] Réseau tumeurs THYMIques et Cancer, France Prospective 2012-2015	Thymoma & thymic carcinoma Inclusion: received at least one cycle of systemic therapy	Cyclophosphamide, adriamycin (doxorubicin), and cisplatin (?) only thymoma		Response	None
		Cyclophosphamide, adriamycin (doxorubicin), and cisplatin (?) only thymic carcinoma		Response	
Miura 2017 Prognostic [112] Three Japanese Institutions Retrospective 1998-2014	Thymic carcinoma (12% NETs) Inclusion: advanced or recurrent, combination chemotherapy Median 27.5 months (range 1.3-119.7 months)	Chemoradiotherapy (13)	Chemotherapy (21)	OS	None
Mou 2018 [91] SEER database, USA Retrospective 1988-2013	Thymoma Inclusion: resection, demographic, stage and postoperative data	PORT (1121)	No PORT (1113)	OS	Age, marital status, previous primary malignancy, stage
Mu 2013 [60] Chinese Academy of Medical Sciences Retrospective 2009-2012	Thymoma	VATS (41)	Open thymectomy (41)	Morbidity	None
Nakagawa 2016 [39] JART database, Japan Retrospective 1991-2010	Thymoma Inclusion: stage I or II Exclusion: MG, VATS Median 53 months (both groups) 48 months (thymomectomy) 59 months (thymothymomectomy)	Thymomectomy (276) propensity-matched on adjuvant radiotherapy, age, histology, sex, stage, tumour size	Thymothymomectomy (276) propensity-matched on adjuvant radiotherapy, age, histology, sex, stage, tumour size	Postoperative complications, Recurrence rate	None

Nakajima 2016 [61] JART database, Japan Retrospective 1991-2010	Thymoma with MG	Thoracoscopic resection (46)	Open resection (549)	Postoperative complications	None
Narm 2016 [34] KART database, Korea Retrospective 2000-2013	Thymoma Inclusion: stage I or II, thymectomy Exclusion: MG, thymic carcinoma, rare histologic thymoma type (such as metaplastic and microscopic), incomplete data Median 49 months (range 0.2–189 months)	Limited thymectomy (141) propensity-matched on age, gender, histology, PORT, stage, surgical approach, tumour size	Complete thymectomy (141) propensity-matched on age, gender, histology, PORT, stage, surgical approach, tumour size	OS	Age, gender, histology, PORT, resection status, surgical type, stage, tumour size
		VATS (297)	Sternotomy (393)	OS	
		Limited thymectomy (141) propensity-matched on adjuvant radiotherapy, age, gender, histology, stage, surgical approach, tumour size	Complete thymectomy (141) propensity-matched on adjuvant radiotherapy, age, gender, histology, stage, surgical approach, tumour size	Blood loss, Chest tube duration, Complications, Postoperative hospital duration	None
Odaka 2017 Thoracoscopic [51] Jikei University School of Medicine, Japan Retrospective 1996-2014	Thymoma Inclusion: >50 mm, stage I–IVa, thymectomy Exclusion: thymic carcinoma, recurrent, biopsy Median 49 months (range 5–112) (thoracoscopic thymectomy) and 109 months (range 16–168) (open thymectomy)	Thoracoscopic thymectomy (90)	Open thymectomy (45)	DFS	Histology, stage, thymoma >50 mm
		Thoracoscopic thymectomy (38)	Open thymectomy (25)	Complications, Recurrence rate	None
Odaka 2010 [67] Jikei University School of Medicine, Japan Retrospective 2000-2008	Thymoma Inclusion: stage I or II, resection with curative intent Exclusion: MG 21.6 months (range 5-40 months) (unilateral thoracoscopic subtotal thymectomy) 58.6 months (range 18—99 months) (trans-sternal thymectomy)	Unilateral thoracoscopic subtotal thymectomy (22) no conversions	Trans-sternal thymectomy (18)	Blood loss, Postoperative hospital duration, Postoperative pleural drainage	None
Okuma 2020 [122] Three Japanese centers Retrospective	Thymic carcinoma Inclusion: received first-line platinum-based chemotherapy, recurrent or stage IVa/b, >20	S-1 (26)		Response rate, Grade ≥3 thrombocytopenia Grade ≥3 nausea	None

2013-2016	years, PS 0-2, adequate bone marrow reserve, aspartate aminotransferase/alanine aminotransferase equal to or less than 2.5 times of the upper limit of each hospital, serum bilirubin ≤1.5 mg/dL, creatinine level equal to or less than 1.5 mg/dL, SpO2 ≥92%. Median 27.0 months				
Omasa 2015 [92] JART database, Japan Retrospective 1991-2010	Thymoma or thymic carcinoma Inclusion: Masaoka stage II or III, resection Exclusion: thymic NETs, macroscopic gross residual tumour and lack of PORT information Median 1704 days (range 0-7741 days)	PORT (321) only thymoma	No PORT (784) only thymoma	OS	Resection status, stage
		PORT (315) only thymoma	No PORT (758) only thymoma	RFS	
		Adjuvant chemotherapy (22) only thymic carcinoma	No adjuvant chemotherapy (132) only thymic carcinoma	RFS	Resection status, stage
Onuki 2010 [38] Tsukuba University Hospital and Tsuchiura Kyodo General Hospital, Japan Retrospective 1982-2007	Thymoma Inclusion: stage I or II Mean 104.2 standard deviation ± 58.1 months (limited thymectomy) 67.3±54.8 months (total thymectomy)	Limited thymectomy (18)	Total thymectomy (61)	DFS	None
Rajan 2014 [85] USA Prospective NCT00965250 2009-2012	Thymoma & thymic carcinoma Inclusion: recurrent, failure of previous chemotherapy, PS 0-1, adequate organ function Median 24.0 months (interquartile range 17.3–36.9)	Cixutumumab (37) only thymoma		Response	None
Rea 2011 [79] University Hospital of Padova, Italy Retrospective 1980-2005	Thymoma & thymic carcinoma Inclusion: stages III, IVa and IVb without extrathoracic metastases, resection	Induction ADOC (32) only thymoma		Response	None

Rimner 2016 [93] ITMIG database Retrospective 1990-2012	Thymoma Inclusion: complete resection, stage II or III Exclusion: thymic carcinoma or NETs, neoadjuvant or palliative radiotherapy Median no PORT 2.66 years. Median PORT 4.05 years	PORT (689)	No PORT (574)	OS	Age, gender, histology, paraneoplastic syndrome, stage, tumour size
Ruffini 2014 Thymic [108] ESTS database, Europe Retrospective 1990-2010	Thymic carcinoma Inclusion: resection Median 44 months (range 2-214 months)	Neoadjuvant therapy (78)	No neoadjuvant therapy (137)	OS	Age, gender, histology, MG, resection status, stage, tumour size
Rusidanmu 2018 [35] First Affiliated Hospital of Zhejiang University, China Retrospective 2003-2013	Thymoma Inclusion: resection with curative intent Exclusion: thymic carcinoma, hyperplasia, cysts, or non-epithelial tumours, stages III and IV, MG, unknown histology, biopsied intraoperatively, neoadjuvant therapy	Thymomectomy (75)	Thymectomy (43)	OS, Blood loss, Postoperative drainage, Postoperative hospital duration, Recurrence rate	None
Sakamaki 2014 [36] Osaka Police Hospital, Japan Retrospective 1998-2011	Thymoma Inclusion: complete resection, stage I or II Exclusion: thymic carcinoma or carcinoids, advanced stage Median 49 months (range 2-154)	PORT (8)	No PORT (74)	OS, RFS	Age, histology, MG, stage
		Total thymectomy (36)	Partial thymectomy (46)	OS, RFS	
		VATS (71)	Open thymectomy (11)	OS, RFS	None
Sato 2020 [126] Eight Japanese centers Retrospective 2017-2018	Thymic carcinoma Inclusion: progressed following at least one platinum-based chemotherapy, unresectable advanced (stage IIIa, IIIb, IVa, and IVb) or metastatic, 20 years or older, PS 0 or 1, adequate organ function Exclusion: multiple primary malignancies with disease-free period within 5 years, interstitial lung diseases, thrombotic or	Lenvatinib (42)		Response rate, Grade ≥3 leukopenia Grade ≥3 neutropenia Grade ≥3 thrombocytopenia Grade ≥3 anemia Grade ≥3 nausea	None

	cardiac events within 6 months before trial, proteinuria greater than or equal to 1 g per 24 h, infections requiring systemic treatment, fever of 38°C or higher, active hemoptysis, or HIV positive Median 15.5 months (interquartile range 13.1–17.5)				
Singhal 2003 [94] University of Pennsylvania Medical Center, USA Retrospective 1992-2002	Thymoma Inclusion: complete resection, stage I or II Median 70.3 months	PORT (23) 45 to 55 Gy	No PORT (47)	OS	None
Song 2020 [75] KART Retrospective 2000-2013	Thymoma Inclusion: stages II, III Exclusion: benign diseases, stages I and IV, thymic carcinomas or NETs, missing data	Neoadjuvant chemotherapy (11)	No neoadjuvant chemotherapy (393)	OS	Age, extent of surgery, gender, histology, MG, postoperative complications, recurrence, resection status, stage
		Adjuvant chemotherapy (20)	No adjuvant chemotherapy (384)	OS	
		PORT (202) matched for adjuvant chemotherapy, age, extent of surgery, gender, histology, MG, postoperative complications, resection status, stage, tumour size	No PORT (202) matched for adjuvant chemotherapy, age, extent of surgery, gender, histology, MG, postoperative complications, resection status, stage, tumour size	OS	
		PORT (172) stage II only	No PORT (174) stage II only	OS	
		PORT (30) stage III only	No PORT (28) stage III only	OS	
		Neoadjuvant chemotherapy (11)	No neoadjuvant chemotherapy (393)	RFS	Age, extent of surgery, gender, histology, MG, postoperative complications, resection status, stage
		Adjuvant chemotherapy (20)	No adjuvant chemotherapy (384)	RFS	
		PORT (202)	No PORT (202)	RFS	

Song 2019 [77] Asan Medical Center, South Korea Retrospective 1996-2014	Thymoma Inclusion: resection, neoadjuvant and/or adjuvant therapy Exclusion: no clinical data Median 73 months (range 2-237 months)	Neoadjuvant radiotherapy (3) 4,500 cGY in 25 fractions or 6,000 cGY in 30 fractions	No neoadjuvant therapy (289)	OS	Histology, PD-L1 expression, stage
Song 2015 [117] Zhejiang Cancer Hospital, China Retrospective 2000-2012	Thymic carcinoma Inclusion: stage IV	Carboplatin or cisplatin-based doublet chemotherapy (including paclitaxel, gemcitabine, vinorelbine, cyclophosphamide and docetaxel) (43)		Response	None
Song 2014 Outcomes [130] Zhejiang Cancer Hospital, China Retrospective 1996-2011	Thymic carcinoma Inclusion: resection Exclusion: lost to follow-up and death from other disease not related to thymic carcinoma Median 68 months (range 20-189 months)	Adjuvant chemotherapy (38)	No adjuvant chemotherapy (38)	DFS	Age, gender, histology, resection status, stage
Tagawa 2014 [69] Nagasaki University Hospital and Oita Prefectural Hospital, Japan Retrospective 1995-2007	Thymoma Inclusion: resection Mean 109.0 months (range 37–145 months) (VATS) and 102.0 months (range 44–175 months) (trans-sternal thymectomy)	VATS (15)	Trans-sternal thymectomy (12)	Blood loss	None
Tang 2021 [95] Chia-Yi Christian Hospital, Kaohsiung Veterans General Hospital, National Cheng-Kung University Hospital, Taiwan Retrospective 1988-2017	Thymoma or thymic carcinoma Inclusion: complete resection, T3 N0 M0 (pT3 N0 M0) Median thymoma: 60 months (range 10-189 months) thymic carcinoma: 48 months (range 6-219 months)	PORT (34) thymoma only matched for age, cardiopulmonary disorder extrathymic malignancy, gender, histology, locoregional invasion, MG, performance status, perioperative complications, systemic or metabolic disease	No PORT (7) thymoma only matched for age, cardiopulmonary disorder extrathymic malignancy, gender, histology, locoregional invasion, MG, performance status, perioperative complications, systemic or metabolic disease	OS	Age, gender, histology, lung invasion, superior vena cava or innominate vein invasion
		PORT (34) thymoma only	No PORT (7) thymoma only	DFS	Cardiopulmonary disorder, lung invasion, MG,

		matched for age, cardiopulmonary disorder extrathymic malignancy, gender, histology, locoregional invasion, MG, performance status, perioperative complications, systemic or metabolic disease	matched for age, cardiopulmonary disorder extrathymic malignancy, gender, histology, locoregional invasion, MG, performance status, perioperative complications, systemic or metabolic disease		phrenic nerve invasion, systemic metabolic disease
		PORT (40) thymic carcinoma only matched for age, cardiopulmonary disorder extrathymic malignancy, gender, histology, locoregional invasion, MG, performance status, perioperative complications, systemic or metabolic disease	No PORT (9) thymic carcinoma only matched for age, cardiopulmonary disorder extrathymic malignancy, gender, histology, locoregional invasion, MG, performance status, perioperative complications, systemic or metabolic disease	OS	Age
		PORT (40) thymic carcinoma only matched for age, cardiopulmonary disorder extrathymic malignancy, gender, histology, locoregional invasion, MG, performance status, perioperative complications, systemic or metabolic disease	No PORT (9) thymic carcinoma only matched for age, cardiopulmonary disorder extrathymic malignancy, gender, histology, locoregional invasion, MG, performance status, perioperative complications, systemic or metabolic disease	DFS	Cardiopulmonary disorder, systemic metabolic disease
		Adjuvant chemotherapy (13) thymic carcinoma only	No adjuvant chemotherapy (36) thymic carcinoma only	OS, DFS	None
Tassi 2017 [40] Thoracic Surgery Units of Santa Maria della Misericordia Hospital and Santa Maria Hospital, Italy Retrospective 1996-2015	Thymoma Inclusion: complete resection Exclusion: MG, thymic carcinoma, biopsy, R2 resection Median 77.4 months (range 1–255 months)	Extended thymectomy (70)	Thymomectomy (22)	Complications, Recurrence rate	None

Tateishi 2019 [121] North East Japan Study Group (NEJ023) Retrospective 1995-2014	Thymic carcinoma (12% NETs) Inclusion: previously treated advanced stage or recurrent, treated with palliative-intent second-line chemotherapy, complete data Median 50.5 months (95% confidence interval 36.5-76.0 months)	Other second-line multidrug chemotherapy (26)	Second-line platinum doublets (110)	OS	None
		Second-line monotherapy (55)	Second-line platinum doublets (110)	OS	
		ADOC (17)		Response	
		Carboplatin plus paclitaxel (60)		Response	
		S-1 monotherapy (18)		Response	
Tian 2020 [68] Peking University People's Hospital and Beijing Hospital, China Retrospective 2010-2018	Thymoma Inclusion: resection, MG Median 45 months (range 2–114 months)	VATS (137) two conversions	Transsternal thymectomy (57)	Blood loss, Chest drainage, Length of stay	None
Tian 2020 Surgical outcomes [47] Beijing Hospital, China Retrospective 2011-2018	Thymoma Inclusion: resection Median 42 months	VATS (?)	Open thymectomy (?)	OS (?)	Complication, resection status, stage
Tomita 2020 [104] Nagoya City University Graduate School of Medical Sciences, Japan Retrospective 2004-2017	Thymoma or thymic carcinoma Inclusion: definitive radiotherapy or PORT Median 68 months (range 8–182 months)	Radiotherapy (70)		Grade ≥3 toxicities	None
Trivino 2015 [48] Spain Retrospective 1993-2011	Thymoma Inclusion: stage I-II, resection Median 147 months (sternotomy) 107 months (VATS)	VATS (27)	Sternotomy (11)	OS, Recurrence rate, Hospital duration, Postoperative complications	None
Tseng 2013 [41] Taipei Veterans General Hospital, Taiwan Retrospective 2002-2011	Thymoma Inclusion: complete resection, stage I or II Exclusion: thymic carcinoma, MG, neoadjuvant therapy Median 57 months (6–121 months)	Thymomectomy without thymectomy (53) thoracotomy or VATS one conversion	Thymomectomy with extended thymectomy (42) median sternotomy	Blood loss, Postoperative complications, Postoperative drainage, Postoperative hospital duration, Recurrence rate	None

Wang 2019 [123] Shanghai Chest Hospital, China Retrospective 2013-2017	Thymic carcinoma Inclusion: stage IV, relapsed, previously treated by front-line chemotherapy, <80 years PS 0-2, adequate bone marrow, hepatic, and renal function Median 14 months	Chemotherapy (44) S-1		Grade ≥3 anorexia, Grade ≥3 thrombocytopenia, Grade ≥3 neutropenia, Grade ≥3 anemia, Response	None
Wang 2018 [131] Xinjiang Medical University Affiliated Tumor Hospital, China Retrospective 2009-2013	Thymic carcinoma Inclusion: resection	PORT (108)	No PORT (44)	RFS	None
		Adjuvant chemotherapy (49)	No adjuvant chemotherapy (103)	RFS	
Wen 2018 [133] SEER database, USA Retrospective 1998-2015	Thymic NETs Inclusion: survival duration ≥1 month Exclusion: cases with a death certificate or autopsy Median 38 months (range 1-174 months)	Local/partial resection (74) for resected	Total/radical resection (106) for resected	OS	Gender, geographic location, histology, stage
Wu 2009 [87] Fudan University Cancer Hospital, China Retrospective 1970-2000	Thymoma Inclusion: resection & PORT, complete stage data, no other tumours Exclusion: thymic carcinoma, neoadjuvant radiotherapy Median 72 months (range 6–336 months)	Adjuvant chemotherapy (59)	No adjuvant chemotherapy (182)	OS	Age, gender, histology, interval between resection and PORT, MG, resection type, stage
Xu 2016 [118] Chinese Academy of Medical Sciences Retrospective ?	Thymic carcinoma Inclusion: stage IV	Paclitaxel and platinum (37)		Grade ≥3 neutropenia, Grade ≥3 nausea/emesis, Grade ≥3 thrombocytopenia, Response	None

Yamada 2015 [72] JART database, Japan Retrospective 1991-2010	Thymoma Inclusion: stage III, resection Exclusion: thymic carcinoma & NETs Mean 2240 days (range 10-7741 days)	Neoadjuvant therapy (42)	No neoadjuvant therapy (268)	OS	Age, chest wall invasion, gender, histology, number of involved sites, performance status
Yan 2016 [96] Washington Medical Center, USA Retrospective 1996-2013	Thymoma Inclusion: resection Exclusion: ≤6 months of follow-up, incomplete pathologic staging	PORT (31)	No PORT (57)	OS	Resection status, stage
Yang 2019 Optimal [119] Beijing Cancer Hospital, China Retrospective 2006-2015	Thymic carcinoma (1% NETs) Inclusion: stage IV with complete follow-up data Median 27.8 months (range 4.5-88.7 months)	First-line paclitaxel-platinum (36)	First-line gemcitabine-platinum (31)	Response	None
Yang 2020 [49] National Cancer Data Base, USA Retrospective 2010-2014	Thymoma Inclusion: stage I-III, thymectomy Exclusion: nonmalignant pathology, history of unrelated malignancy, age <18 years Median minimally-invasive thymectomy: 35.9 months (interquartile range 24.9-52.2) open: 40.7 months (interquartile range 27.3-56.8)	Minimally-invasive thymectomy (317) 34 conversions	Open thymectomy (906)	OS	Age, comorbidity score, distance from facility, education, facility type, gender, histology, insurance, race, stage, tumour size
Ye 2014 [62] Shanghai Chest Hospital, China Retrospective 2009-2012	Thymoma Inclusion: stage I or II, trans-sternal thymectomy or RATS Exclusion: MG	RATS (23) no conversions	Trans-sternal thymectomy (51)	Postoperative complications	None
Yuan 2017 [52] Chinese Academy of Medical Sciences and Peking Union Medical College Retrospective 2003-2014	Thymoma Inclusion: complete resection Exclusion: neoadjuvant therapy Median 86 months (range 24-160 months)	PORT (142)	No PORT (165)	DFS	Histology, stage
		PORT (142)	No PORT (165)	OS	None
		VATS (70)	Transthoracic resection (140)	DFS	
Yuan 2016 [106]	Thymic carcinoma (11% NETs)	PORT (56)	No PORT (23)	OS, DFS	None

Department of Thoracic Surgery of the National Cancer Center/Cancer Hospital Chinese Academy of Medical Sciences and Peking Union Medical College, China Retrospective 2005-2015	Inclusion: complete resection Exclusion: preoperative radiotherapy or chemotherapy, coexistent hematologic disorders, or active infection at time of surgery Median 40 months (range 1-130 months)	Adjuvant chemotherapy (33)	No adjuvant chemotherapy (46)	OS, DFS	
		VATS (10)	Open resection (69)	OS, DFS	
Zhai 2019 [32] abstract Chinese Academy of Medical Sciences, China RCT NCT 02014805 2014-2018	Thymoma Inclusion: PS 0-2, interval of surgery to radiotherapy <2 months, stage II-III, WHO B type Exclusion: Second primary tumour, serious comorbidity, neoadjuvant therapy, adjuvant chemotherapy Median 31.6 months	PORT (17) dose 50 Gy (25 fraction)	No PORT (19)	Grade ≥3 toxicity	None
Zhang 2020 [50] First Affiliated Hospital of Sun Yat-sen University, China Retrospective 2004-2016	Thymoma Inclusion: resection Exclusion: diagnosis of MG depending on symptoms, antibody levels and electromyography results before surgery, complications of other autoimmune diseases, age at surgery >80 years old or <16 years old, stage IV disease, exploratory operation	VATS (84)	Median sternotomy (145)	OS	None
Zhang 1999 [31] Chinese Academy of Medical Sciences and Peking Union Medical College, China RCT 1981-1996	Thymoma Inclusion: stage I, <65 years, complete resection, complete capsule 1-15 years	PORT (16) 50-60 Gy	No PORT (13)	OS	None

Zhao 2019 [37] SEER database, USA Retrospective 1983-2014	Thymoma Inclusion: resection Exclusion: primary reporting source was an autopsy, death certificate, nursing home, or hospice, survival duration of ≤3 months, neoadjuvant radiotherapy, unknown treatment sequence with surgery Median 68 (range 4–304 months)	Simple/partial surgical removal (403)	Total surgical removal (553)	OS	Age, histology, marital status, stage, tumour size
Zhao 2013 [132] Shanghai Chest Hospital, China Retrospective 2003-2010	Thymic carcinoma Inclusion: squamous cell, curative intent resection, no history of squamous tumour elsewhere, had follow-up information Median 52.2 months (range 20-112 months)	Adjuvant chemotherapy (71)	No adjuvant chemotherapy (34)	DFS	Differentiation, presenting symptoms, resection status, tumour size, vessel invasion
Zucali 2018 [86] Italy Prospective NCT02049047 2011-2013	Thymic & thymic carcinoma Inclusion: failure of at least one previous line of platinum-based chemotherapy	Everolimus (32) only thymoma		Response	None

Abbreviations: ADOC - cisplatin, doxorubicin, vincristine, and cyclophosphamide; cGY – centigrays; ChART - Chinese Alliance for Research of Thymoma; CSS – cancer/cause-specific survival; 3D-CRT - Three-dimensional conformal radiotherapy; DFS – disease-free survival; DSS – disease-specific survival; EHRT - low-dose entire hemithorax radiotherapy; ESTS - European Society of Thoracic Surgeons; FFLF - freedom from locoregional failure; FFDM - freedom from distant metastasis; FFR – freedom from recurrence; Gy – grays; HIV – human immunodeficiency virus; IMRT – intensity modulated radiotherapy; ITMIG - International Thymic Malignancies Interest Group; JART - Japanese Association for Research on the Thymus; JCOG – Japanese Clinical Oncology Group; KART - Korea Association for Research on the Thymoma; LRFS - Local-regional relapse free survival; MG – myasthenia gravis; MRT – mediastinal radiotherapy; N – number; NET – neuroendocrine tumours; NOS – not otherwise specified; ORR – objective response rate; OS – overall survival; PD-L1 - Programmed death-ligand 1; PORT – postoperative radiotherapy; PRS – post-recurrence survival; PS – performance status; RATS - robot-assisted thoracoscopic surgery; RCT – randomized controlled trial; RFS – relapse/recurrence-free survival; RMFS - recurrence and metastasis–free survival; RR – response/recurrence rate; SEER - Surveillance, Epidemiology, and End Results; USA – United States of America; VATS - Video-assisted thoracoscopic surgery; WHO – World Health Organization

Appendix 7: Risk of bias of included studies

ROBINS-I

Study	Type of tumour	Comparison(s)	Confounding	Selection of participants	Classification of interventions	Deviation from intended interventions	Missing data	Measurement of outcomes	Selection of reported result	Overall bias
Agatsuma 2017 [42]	Thymoma	VATS vs. median sternotomy	Serious	Low	Low	Low	Low	Low (OS) Mod (Others)	Serious	Serious
Agatsuma 2011 [113]	Thymic carcinoma	ADOC chemotherapy vs. carboplatin-based chemotherapy	Critical	Low	Low	Low	Low	Mod	Serious	Critical
Allahkverdiev 2019 [56]	Thymoma	Thoracoscopic thymectomy vs. open thymectomy	Critical	Low	Low	Low	Low	Mod	Serious	Critical
Bakhos 2020 [109]	Thymic carcinoma or thymic NETs	Neoadjuvant chemotherapy vs. no chemotherapy Adjuvant chemotherapy vs. no chemotherapy PORT vs. no PORT	Critical	Low	Low	Low	Low	Low	Serious	Critical
Bian 2020 [88]	Thymoma	PORT vs. no PORT	Critical	Low	Low	Low	Low	Low	Serious	Critical
Bian 2018 [76]	Thymoma	Neoadjuvant radiotherapy vs. no radiotherapy	Serious	Low	Low	Low	Low	Low	Serious	Serious
Bian 2018 The comparison [135]	Thymic NETs	PORT vs. no PORT Adjuvant chemotherapy vs. no adjuvant chemotherapy	Serious	Low	Low	Low	Low	Low	Serious	Serious
Chao 2015 [63]	Thymoma	VATS vs. median sternotomy	Serious	Low	Low	Low	Low	Mod	Serious	Serious
Cheng 2008 [107]	Thymic carcinoma	VATS vs. open median sternotomy	Critical	Low	Low	Low	Low	Mod	Serious	Critical
Cheng 2005 [64]	Thymoma	Videothoracoscopic vs. open median sternotomy	Critical	Low	Low	Low	Low	Mod	Serious	Critical
Chung 2012 [65]	Thymoma	Thoracoscopic thymectomy vs. sternotomy thymectomy	Critical	Low	Low	Low	Low	Mod	Serious	Critical
Eralp 2003 [89]	Thymoma	PORT vs. no PORT	Critical	Low	Low	Low	Low	Low	Serious	Critical
Fadayomi 2018 [57]	Thymoma	Minimally invasive thymectomy vs. open thymectomy	Serious	Low	Low	Low	Low	Mod	Serious	Serious
Fan 2013 [101]	Thymoma	PORT vs. no PORT	Critical	Low	Low	Low	Low	Low	Serious	Critical

Fang 2020 [134]	Thymic NETs	Neoadjuvant therapy vs. no neoadjuvant therapy	Critical	Low	Low	Low	Low	Low	Serious	Critical
Fu 2016 [127]	Thymic carcinoma	PORT vs. no PORT	Serious	Low	Low	Low	Low	Low (OS) Mod (Others)	Serious	Serious
		Adjuvant chemotherapy vs. no adjuvant chemotherapy	Critical	Low	Low	Low	Low	Low	Serious	Critical
Guerrara 2015 [70]	Thymoma	Neoadjuvant therapy vs. no neoadjuvant therapy	Serious	Low	Low	Low	Low	Low	Serious	Serious
Hakiri 2019 [73]	Thymoma	Neoadjuvant chemotherapy vs. no neoadjuvant chemotherapy	Critical (OS) Serious (DFS)	Low	Low	Low	Low	Low (OS) Mod (DFS)	Serious	Critical (OS) Serious (DFS)
He 2016 [43]	Thymoma with MG	VATS vs. median sternotomy	Critical	Low	Low	Low	Low	Low (OS) Mod (Others)	Serious	Critical
He 2013 [58]	Thymoma or thymic carcinoma with MG	VATS vs. trans-sternal thymectomy	Critical	Low	Low	Low	Low	Mod	Serious	Critical
Hishida 2020 [33]	Thymoma	Total vs. partial thymectomy	Serious	Low	Low	Low	Low	Low	Serious	Serious
Hishida 2016 [110]	Thymic carcinoma	PORT vs. no PORT Neoadjuvant chemotherapy vs. no neoadjuvant chemotherapy	Serious	Low	Low	Low	Low	Low (OS) Mod (Others)	Serious	Serious
Jackson 2017 [90]	Thymoma or thymic carcinoma	PORT vs. no PORT	Serious	Low	Low	Low	Low	Low	Serious	Serious
Jurado 2012 [53]	Thymoma	Minimally invasive thymectomy vs. open thymectomy	Critical	Low	Low	Low	Low	Mod	Serious	Critical
Khorfan 2021 [80]	Thymoma	Radiotherapy and/or chemotherapy vs. no treatment	Serious	Low	Low	Low	Low	Low	Serious	Serious
Kim 2019 [128]	Thymic carcinoma	PORT vs. surgery alone Adjuvant chemotherapy vs. surgery alone	Critical	Low	Low	Low	Low	Low	Serious	Critical
Kimura 2013 [66]	Thymoma	VATS vs. open sternotomy	Critical	Low	Low	Low	Low	Mod	Serious	Critical
Ko 2018 [114]	Thymic carcinoma	Different chemotherapy regimens	Serious	Low	Low	Low	Low	Low Mod (others)	Serious	Serious
Kocer 2018 [44]	Thymoma	VATS vs. extended thymectomy	Critical	Low	Low	Low	Low	Low	Serious	Critical
Kumar 2020 Surgical [74]	Thymoma	Neoadjuvant chemotherapy vs. no neoadjuvant chemotherapy	Critical	Low	Low	Low	Low	Low	Serious	Critical
Lim 2017 [105]		PORT vs. no PORT	Serious	Low	Low	Low	Low	Low	Serious	Serious

	Thymic carcinoma	Total/radical resection vs. local/partial resection								
		Subgroup analyses	Critical	Low	Low	Low	Low	Low	Serious	Critical
Lin 2017 [54]	Thymoma with MG	VATS vs. conventional thymectomy	Critical	Low	Low	Low	Low	Mod	Serious	Critical
Liou 2020 [71]	Thymoma	Neoadjuvant therapy vs. no neoadjuvant therapy	Serious	Low	Low	Low	Low	Low	Serious	Serious
Liu 2014 [45]	Thymoma	VATS vs. sternotomy	Critical	Low	Low	Low	Low	Low (OS) Mod (Others)	Serious	Critical
Maniscalco 2015 [59]	Thymoma	VATS vs. open thymectomy	Critical	Low	Low	Low	Low	Mod	Serious	Critical
Manoly 2014 [46]	Thymoma	VATS vs. trans-sternal thymectomy	Critical	Low	Low	Low	Low	Low (OS) Mod (Others)	Serious	Critical
Mao 2015 [129]	Thymic carcinoma	PORT vs. no PORT Adjuvant chemotherapy vs. no adjuvant chemotherapy	Serious	Low	Low	Low	Low	Low (OS) Mod (Others)	Serious	Serious
Marulli 2018 [55]	Thymoma	RATS vs. median sternotomy	Serious	Low	Low	Low	Low	Mod	Serious	Serious
Miura 2017 Prognostic [112]	Thymic carcinoma	Chemoradiotherapy vs. chemotherapy	Critical	Low	Low	Low	Low	Low	Serious	Critical
Mou 2018 [91]	Thymoma	PORT vs. no PORT	Serious	Low	Low	Low	Low	Low	Serious	Serious
Mu 2013 [60]	Thymoma	VATS vs. open thymectomy	Critical	Low	Low	Low	Low	Mod	Serious	Critical
Nakagawa 2016 [39]	Thymoma	Thymomectomy vs. thymothymomectomy	Serious	Low	Low	Low	Low	Mod	Serious	Serious
Nakajima 2016 [61]	Thymoma with MG	Thoracoscopic resection vs. open resection	Critical	Low	Low	Low	Low	Mod	Serious	Critical
Narm 2016 [34]	Thymoma	Limited thymectomy vs. complete thymectomy VATS vs. sternotomy	Serious	Low	Low	Low	Serious	Low (OS) Mod (Others)	Serious	Serious
Odaka 2017 Thoracoscopic [51]	Thymoma	Thoracoscopic thymectomy vs. open thymectomy	Critical (Others) Serious (DFS)	Low	Low	Low	Serious	Mod	Serious	Critical (Others) Serious (DFS)
Odaka 2010 [67]	Thymoma	Unilateral thoracoscopic subtotal thymectomy vs. trans-sternal thymectomy	Critical	Low	Low	Low	Low	Mod	Serious	Critical
Omasa 2015 [92]	Thymoma or thymic carcinoma	PORT vs. no PORT Adjuvant chemotherapy vs. no adjuvant chemotherapy	Serious	Low	Low	Low	Serious	Low (OS) Mod (Others)	Serious	Serious
Onuki 2010 [38]	Thymoma	Limited thymectomy vs. total thymectomy	Critical	Low	Low	Low	Low	Mod	Serious	Critical
Rimner 2016 [93]	Thymoma	PORT vs. no PORT	Serious	Low	Low	Low	Low	Low	Serious	Serious
Ruffini 2014 Thymic [108]	Thymic carcinoma	Neoadjuvant therapy vs. no neoadjuvant therapy	Serious	Low	Low	Low	Low	Low	Serious	Serious

Rusidanmu 2018 [35]	Thymoma	Thymomectomy vs. thymectomy	Critical	Low	Low	Low	Serious	Low (OS) Mod (Others)	Serious	Critical
Sakamaki 2014 [36]	Thymoma	PORT vs. no PORT Total thymectomy vs. partial thymectomy	Serious	Low	Low	Low	Low	Low (OS) Mod (Others)	Serious	Serious
		VATS vs. open thymectomy	Critical	Low	Low	Low	Low	Low (OS) Mod (Others)	Serious	Critical
Singhal 2003 [94]	Thymoma	PORT vs. no PORT	Critical	Low	Low	Low	Low	Low	Serious	Critical
Song 2020 [75]	Thymoma	Neoadjuvant chemotherapy vs. no neoadjuvant chemotherapy Adjuvant chemotherapy vs. no adjuvant chemotherapy PORT vs. no PORT	Serious	Low	Low	Low	Low	Low (OS) Mod (Others)	Serious	Serious
Song 2019 [77]	Thymoma	Neoadjuvant radiotherapy vs. no neoadjuvant therapy	Serious	Low	Low	Low	Low	Low	Serious	Serious
Song 2014 Outcomes [130]	Thymic carcinoma	Adjuvant chemotherapy vs. no adjuvant chemotherapy	Serious	Low	Low	Low	Low	Mod	Serious	Serious
Tagawa 2014 [69]	Thymoma	VATS vs. trans-sternal thymectomy	Critical	Low	Low	Low	Serious	Mod	Serious	Critical
Tang 2021 [95]	Thymoma	PORT vs. no PORT	Serious	Low	Low	Low	Low	Low (OS) Mod (Others)	Serious	Serious
	Thymic carcinoma	PORT vs. no PORT	Serious	Low	Low	Low	Low	Low (OS) Mod (Others)	Serious	Serious
		Adjuvant chemotherapy vs. no adjuvant chemotherapy	Critical	Low	Low	Low	Low	Low (OS) Mod (Others)	Serious	Critical
Tassi 2017 [40]	Thymoma	Extended thymectomy vs. thymomectomy	Critical	Low	Serious	Low	Serious	Low	Serious	Critical
Tateishi 2019 [121]	Thymic carcinoma	Second-line platinum doublets vs. other second-line multidrug chemotherapy or second-line monotherapy	Critical	Low	Low	Low	Low	Low	Serious	Critical
Tian 2020 [68]	Thymoma	VATS vs. trans-sternal thymectomy	Critical	Low	Low	Low	Low	Mod	Serious	Critical
Tian 2020 Surgical outcomes [47]	Thymoma	VATS vs. open thymectomy	Serious	Low	Low	Low	Low	Low	Serious	Serious
Trivino 2015 [48]	Thymoma	VATS vs. sternotomy	Critical	Low	Low	Low	Low	Low (OS) Mod (Others)	Serious	Critical
Tseng 2013 [41]	Thymoma	Thymomectomy without thymectomy vs.	Critical	Low	Low	Low	Low	Mod	Serious	Critical

		thymomectomy with extended thymectomy								
Wang 2018 [131]	Thymic carcinoma	PORT vs. no PORT Adjuvant chemotherapy vs. no adjuvant chemotherapy	Critical	Low	Low	Low	Low	Mod	Serious	Critical
Wen 2018 [133]	Thymic NETs	Local/partial resection vs. total/radical resection	Serious	Low	Low	Low	Low	Low	Serious	Serious
Wu 2009 [87]	Thymoma	Adjuvant chemotherapy vs. no adjuvant chemotherapy	Serious	Low	Low	Low	Low	Low	Serious	Serious
Yamada 2015 [72]	Thymoma	Neoadjuvant therapy vs. no neoadjuvant therapy	Serious	Low	Low	Low	Low	Low	Serious	Serious
Yan 2016 [96]	Thymoma	PORT vs. no PORT	Serious	Low	Low	Low	Low	Low	Serious	Serious
Yang 2020 [49]	Thymoma	Minimally-invasive thymectomy vs. open thymectomy	Serious	Low	Low	Low	Low	Low	Serious	Serious
Yang 2019 Optimal [119]	Thymic carcinoma	First-line paclitaxel-platinum vs. first-line gemcitabine-platinum	Critical	Low	Low	Low	Low	Mod	Serious	Critical
Ye 2014 [62]	Thymoma	RATS vs. trans-sternal thymectomy	Critical	Low	Low	Low	Low	Mod	Serious	Critical
Yuan 2017 [52]	Thymoma	PORT vs. no PORT	Critical (OS) Serious (DFS)	Low	Low	Low	Serious	Low (OS) Mod (DFS)	Serious	Critical (OS) Serious (DFS)
		VATS vs. transthoracic resection	Critical	Low	Low	Low	Low	Mod	Serious	Critical
Yuan 2016 [106]	Thymic carcinoma	PORT vs. no PORT Adjuvant chemotherapy vs. no adjuvant chemotherapy VATS vs. open resection	Critical	Low	Low	Low	Low	Low (OS) Mod (Others)	Serious	Critical
Zhang 2020 [50]	Thymoma	VATS vs. median sternotomy	Critical	Low	Low	Low	Low	Low	Serious	Critical
Zhao 2019 [37]	Thymoma	Simple/partial surgical removal vs. total surgical removal	Serious	Low	Low	Low	Low	Low	Serious	Serious
Zhao 2013 [132]	Thymic carcinoma	Chemotherapy vs. no chemotherapy	Serious	Low	Low	Low	Low	Mod	Serious	Serious

Abbreviations: ADOC – cisplatin, doxorubicin, vincristine, and cyclophosphamide; DFS – disease-free survival; OS – overall survival; NETs – neuroendocrine tumours; MG – myasthenia gravis; Mod – moderate; PORT – postoperative radiotherapy; VATS – video-assisted thoracoscopic surgery

Cochrane ROB for Interventions

Study	Type of tumour	Comparison(s)	Randomization Process	Deviation from intended interventions	Missing data	Measurement of outcomes	Selection of reported result	Overall bias
Zhai 2019 [32] abstract	Thymoma	PORT vs. no PORT	Some	Some	Low	Some	Some	Some
Zhang 1999 [31]	Thymoma	PORT vs. no PORT	Low	Low	Low	Low	Low	Low

Abbreviation: PORT – postoperative radiotherapy; ROB – risk of bias

Appendix 8: Meta-analyses

Figure 1 **Partial thymectomy versus total thymectomy for OS for patients with thymoma**

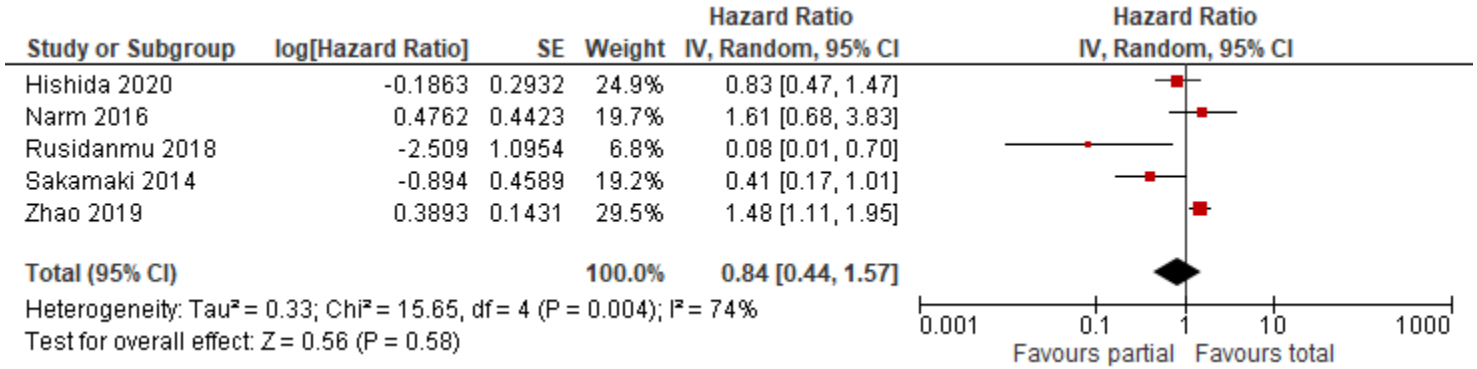


Figure 2 **Partial thymectomy versus total thymectomy for OS for patients with thymoma by MG status**

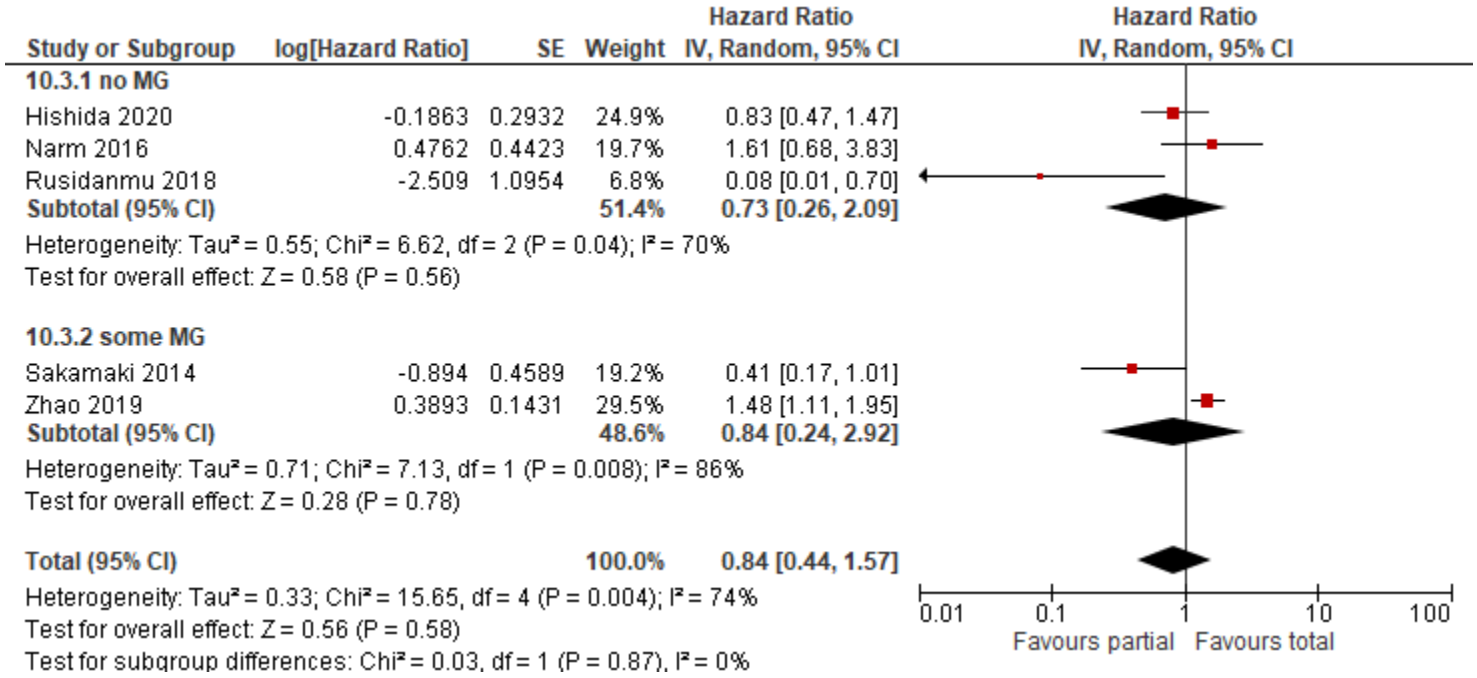


Figure 3 **Partial thymectomy versus total thymectomy for OS for patients with thymoma by risk of bias**

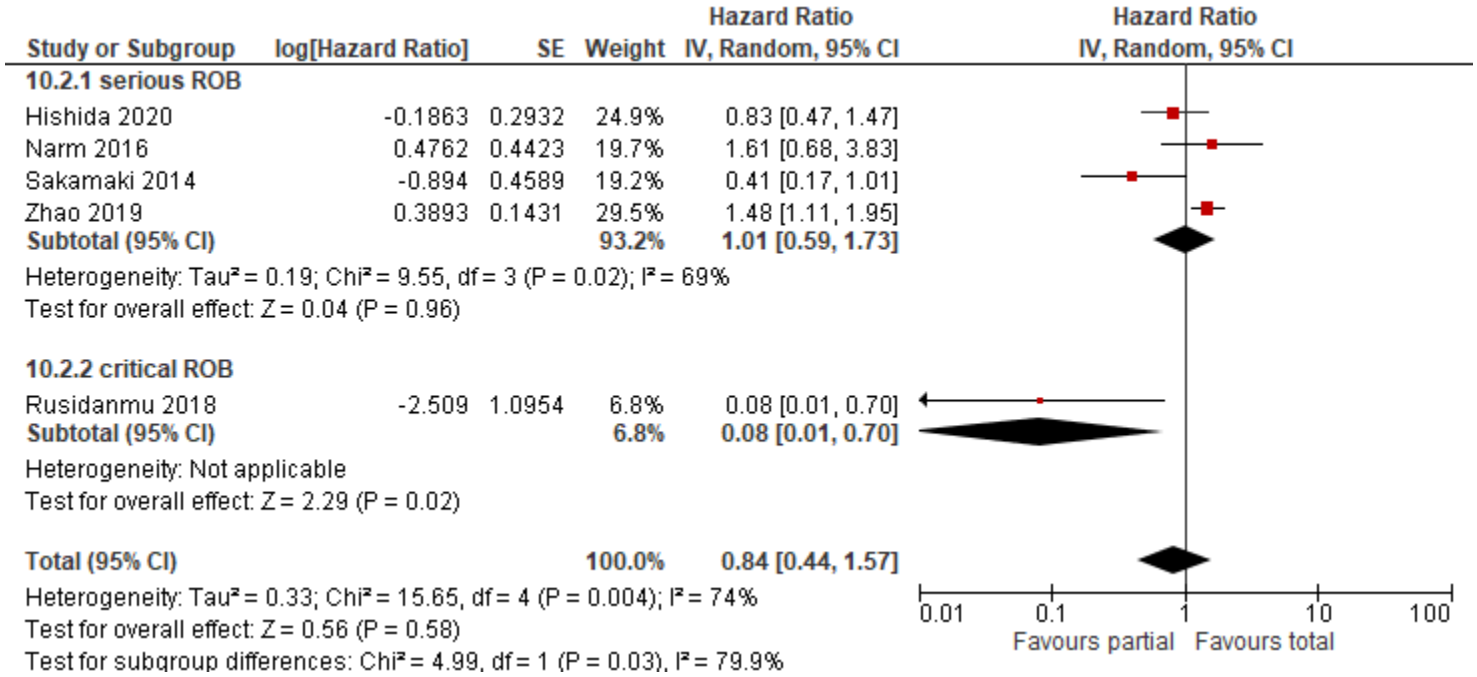


Figure 4 **Partial thymectomy versus total thymectomy for DFS for patients with thymoma (stages I-II)**

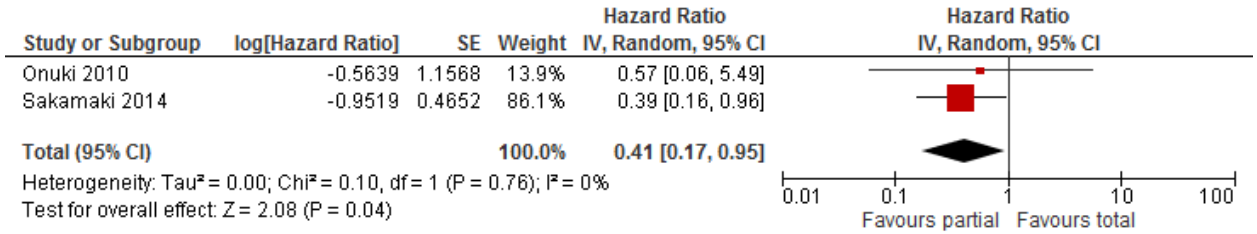


Figure 5 **Partial thymectomy versus total thymectomy for recurrence for patients with thymoma**

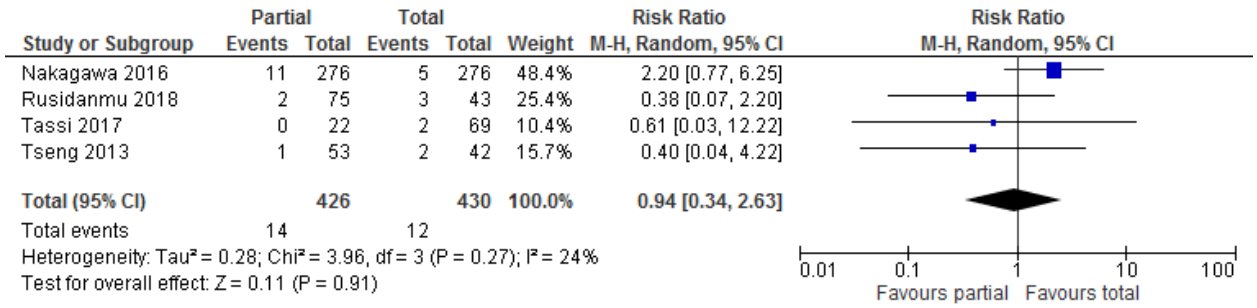


Figure 6 **Partial thymectomy versus total thymectomy for complications for patients with thymoma**

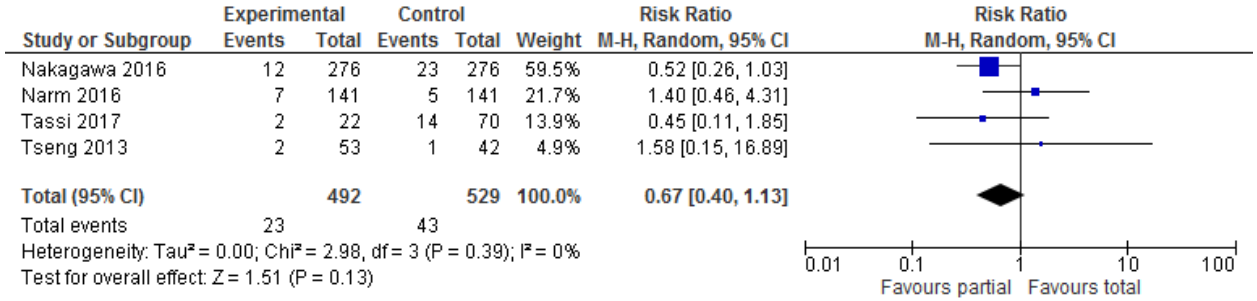


Figure 7 **Partial thymectomy versus total thymectomy for length of stay for patients with thymoma (stages I-II)**

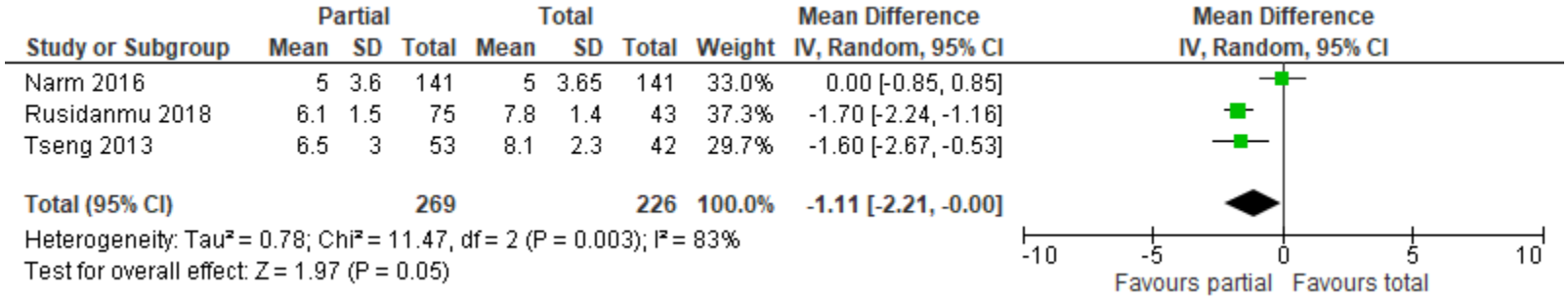


Figure 8 **Partial thymectomy versus total thymectomy for chest drainage for patients with thymoma (stages I-II)**

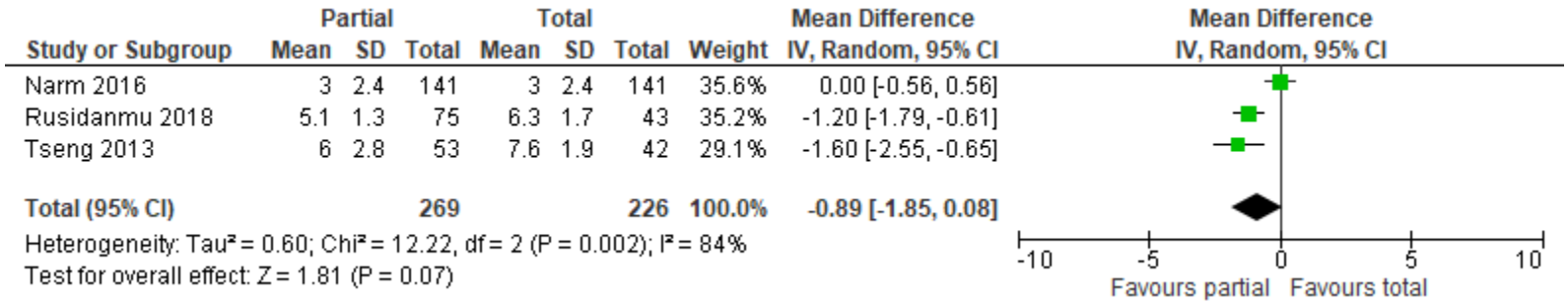


Figure 9 **Partial thymectomy versus total thymectomy for blood loss for patients with thymoma (stages I-II)**

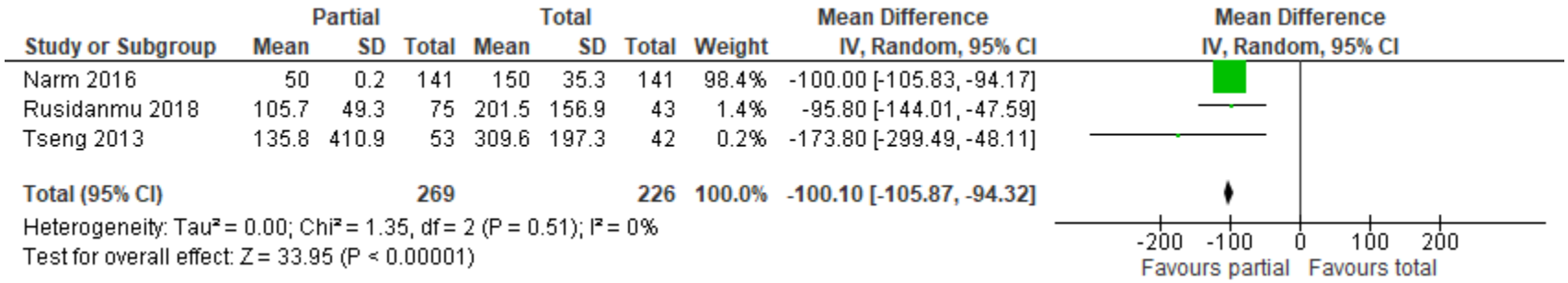


Figure 10 **MIS versus open thymectomy for OS for patients with thymoma**

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Agatsuma 2017	-0.2776	0.8367	4.4%	0.76 [0.15, 3.91]
He 2016	-2.2302	1.1574	2.3%	0.11 [0.01, 1.04]
Kocer 2018	-0.6033	0.505	11.9%	0.55 [0.20, 1.47]
Liu 2014	-1.1479	0.866	4.1%	0.32 [0.06, 1.73]
Manoly 2014	0.9771	1.2247	2.0%	2.66 [0.24, 29.30]
Narm 2016	-0.755	0.5533	9.9%	0.47 [0.16, 1.39]
Sakamaki 2014	-2.9981	1.4671	1.4%	0.05 [0.00, 0.88]
Tian 2020 Surgical outcomes	0.2311	0.6307	7.7%	1.26 [0.37, 4.34]
Trivino 2015	0.6491	1.1025	2.5%	1.91 [0.22, 16.61]
Yang 2020	-0.5621	0.316	29.9%	0.57 [0.31, 1.06]
Zhang 2020	-0.3711	0.3536	24.0%	0.69 [0.35, 1.38]
Total (95% CI)			**100.0%**	**0.61 [0.43, 0.85]**

Heterogeneity: Tau² = 0.00; Chi² = 10.07, df = 10 (P = 0.43); I² = 1%
Test for overall effect: Z = 2.87 (P = 0.004)

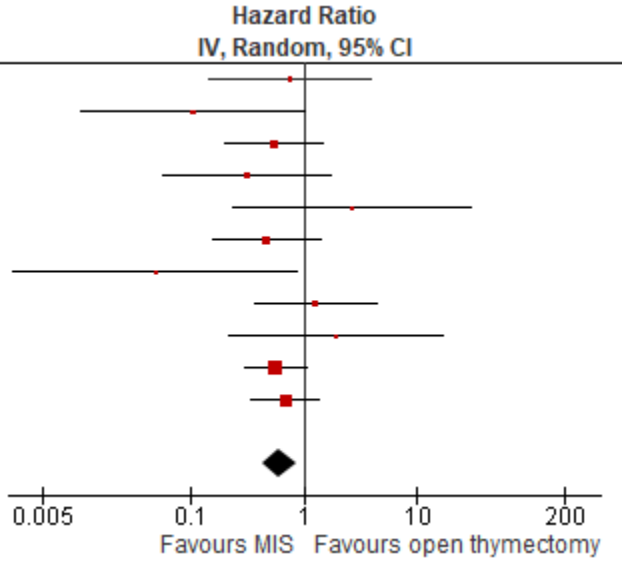


Figure 11 **MIS versus open thymectomy for DFS for patients with thymoma**

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Manoly 2014	-0.1995	0.9129	11.0%	0.82 [0.14, 4.90]
Odaka 2017 Thoracoscopic	-0.0024	0.8032	14.3%	1.00 [0.21, 4.82]
Sakamaki 2014	-1.5699	1.1979	6.4%	0.21 [0.02, 2.18]
Yuan 2017	0.2654	0.367	68.3%	1.30 [0.64, 2.68]
Total (95% CI)			**100.0%**	**1.06 [0.58, 1.92]**

Heterogeneity: Tau² = 0.00; Chi² = 2.25, df = 3 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.19 (P = 0.85)

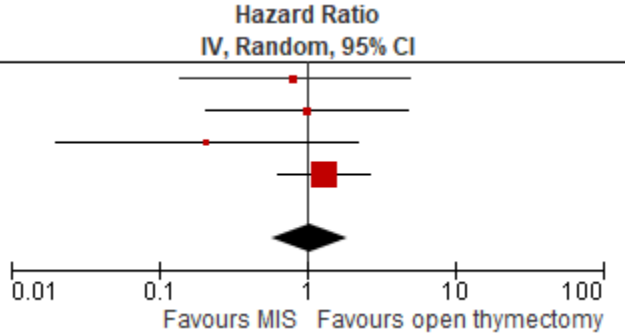


Figure 12 **MIS versus open thymectomy for recurrence for patients with thymoma**

Study or Subgroup	MIS Events	MIS Total	Open thymectomy Events	Open thymectomy Total	Weight	Risk Ratio M-H, Random, 95% CI
Agatsuma 2017	3	139	4	134	18.3%	0.72 [0.16, 3.17]
Jurado 2012	0	10	5	62	5.0%	0.52 [0.03, 8.76]
Lin 2017	5	55	23	107	48.1%	0.42 [0.17, 1.05]
Liu 2014	2	76	1	44	7.1%	1.16 [0.11, 12.41]
Marulli 2018	1	41	0	41	4.0%	3.00 [0.13, 71.56]
Odaka 2017 Thoracoscopic	2	38	3	25	13.5%	0.44 [0.08, 2.44]
Trivino 2015	1	27	0	11	4.1%	1.29 [0.06, 29.36]
Total (95% CI)		**386**		**424**	**100.0%**	**0.58 [0.31, 1.08]**
Total events	14		36			

Heterogeneity: Tau² = 0.00; Chi² = 2.26, df = 6 (P = 0.89); I² = 0%
Test for overall effect: Z = 1.72 (P = 0.09)

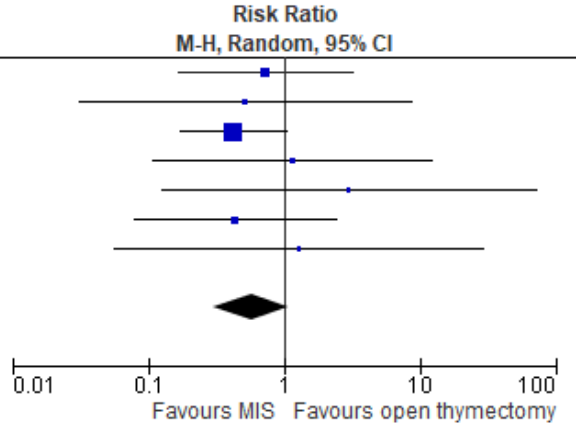


Figure 13 **MIS versus open thymectomy for complications for patients with thymoma**

Study or Subgroup	MIS Events	MIS Total	Open thymectomy Events	Open thymectomy Total	Weight	Risk Ratio M-H, Random, 95% CI
Allahkverdiev 2019	0	33	7	26	1.8%	0.05 [0.00, 0.89]
Fadayomi 2018	9	19	20	34	17.4%	0.81 [0.46, 1.40]
He 2013	4	15	6	18	9.0%	0.80 [0.28, 2.32]
He 2016	2	39	12	34	5.9%	0.15 [0.03, 0.60]
Lin 2017	14	55	28	107	17.3%	0.97 [0.56, 1.69]
Maniscalco 2015	2	13	3	14	4.8%	0.72 [0.14, 3.64]
Manoly 2014	3	17	10	22	8.4%	0.39 [0.13, 1.20]
Marulli 2018	2	41	3	41	4.3%	0.67 [0.12, 3.78]
Mu 2013	0	41	4	41	1.7%	0.11 [0.01, 2.00]
Nakajima 2016	5	46	92	549	11.8%	0.65 [0.28, 1.51]
Odaka 2017 Thoracoscopic	6	38	14	25	12.4%	0.28 [0.13, 0.64]
Trivino 2015	1	27	2	11	2.6%	0.20 [0.02, 2.02]
Ye 2014	1	23	2	51	2.5%	1.11 [0.11, 11.62]
Total (95% CI)		**407**		**973**	**100.0%**	**0.53 [0.36, 0.79]**
Total events	49		203			

Heterogeneity: Tau² = 0.15; Chi² = 18.35, df = 12 (P = 0.11); I² = 35%
Test for overall effect: Z = 3.13 (P = 0.002)

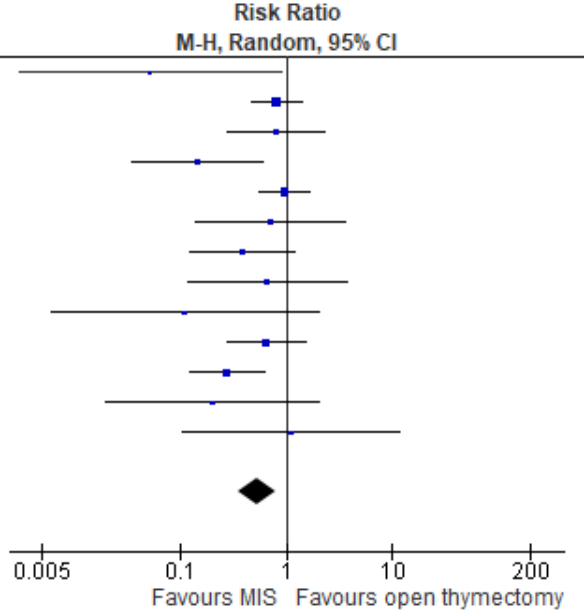


Figure 14 **MIS versus open thymectomy for length of stay for patients with thymoma**

Study or Subgroup	MIS Mean	MIS SD	MIS Total	Open thyectomy Mean	Open thyectomy SD	Open thyectomy Total	Weight	Mean Difference IV, Random, 95% CI
Chao 2015	5.8	2	48	7	2.2	48	13.5%	-1.20 [-2.04, -0.36]
Cheng 2005	6.8	2.3	12	8.9	4.4	10	6.6%	-2.10 [-5.12, 0.92]
Chung 2012	3.4	1.3	25	6.4	2.5	45	13.3%	-3.00 [-3.89, -2.11]
He 2013	10.6	5.11	15	12.22	3.64	18	6.5%	-1.62 [-4.70, 1.46]
He 2016	7.4	2.3	39	8.7	2.6	34	12.6%	-1.30 [-2.43, -0.17]
Kimura 2013	14	9	45	19	13	29	3.0%	-5.00 [-10.41, 0.41]
Liu 2014	7.13	3.62	76	9.14	3.84	44	11.7%	-2.01 [-3.41, -0.61]
Manoly 2014	4.4	1.8	17	6.4	4.6	22	9.3%	-2.00 [-4.10, 0.10]
Odaka 2010	4.6	1.7	22	11.2	3.6	18	10.3%	-6.60 [-8.41, -4.79]
Tian 2020	6.7	3.6	137	12.2	11.7	57	6.4%	-5.50 [-8.60, -2.40]
Trivino 2015	3.6	1.1	27	7.2	4.9	11	6.9%	-3.60 [-6.53, -0.67]
Total (95% CI)			**463**			**336**	**100.0%**	**-2.82 [-3.86, -1.77]**

Heterogeneity: Tau² = 1.93; Chi² = 39.90, df = 10 (P < 0.0001); I² = 75%
Test for overall effect: Z = 5.27 (P < 0.00001)

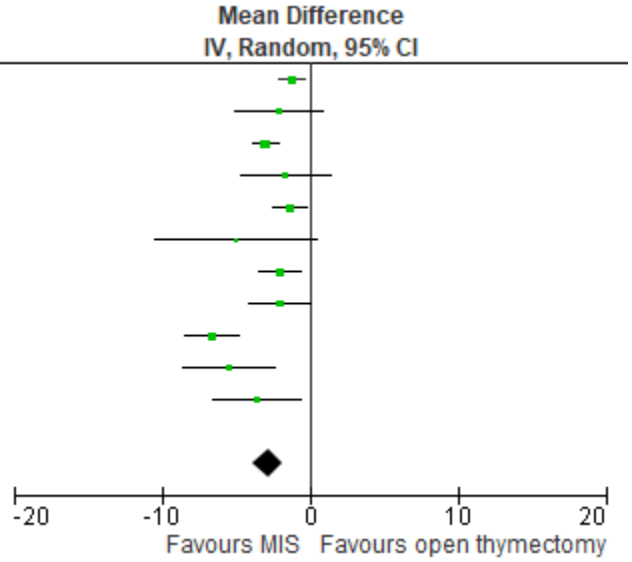


Figure 15 **MIS versus open thymectomy for chest drainage for patients with thymoma**

Study or Subgroup	MIS Mean	MIS SD	MIS Total	Open thymectomy Mean	Open thymectomy SD	Open thymectomy Total	Weight	Mean Difference IV, Random, 95% CI
Chao 2015	4.4	1.5	48	4.9	1.9	48	13.8%	-0.50 [-1.18, 0.18]
Cheng 2005	4.2	2.1	12	4.6	2.1	10	5.6%	-0.40 [-2.16, 1.36]
Chung 2012	1.84	0.94	25	3.62	2.04	45	13.6%	-1.78 [-2.48, -1.08]
He 2013	3.47	0.92	15	3.56	1.15	18	13.5%	-0.09 [-0.80, 0.62]
He 2016	2.7	1.2	39	3.5	1.6	34	14.1%	-0.80 [-1.46, -0.14]
Liu 2014	4.13	2.47	76	5.21	2.64	44	11.0%	-1.08 [-2.04, -0.12]
Odaka 2010	2	1	22	4.1	1.3	18	13.3%	-2.10 [-2.83, -1.37]
Tian 2020	3.1	1.5	137	3.7	1.9	57	15.1%	-0.60 [-1.15, -0.05]
Total (95% CI)			**374**			**274**	**100.0%**	**-0.95 [-1.45, -0.45]**

Heterogeneity: Tau² = 0.35; Chi² = 24.38, df = 7 (P = 0.0010); I² = 71%
Test for overall effect: Z = 3.70 (P = 0.0002)

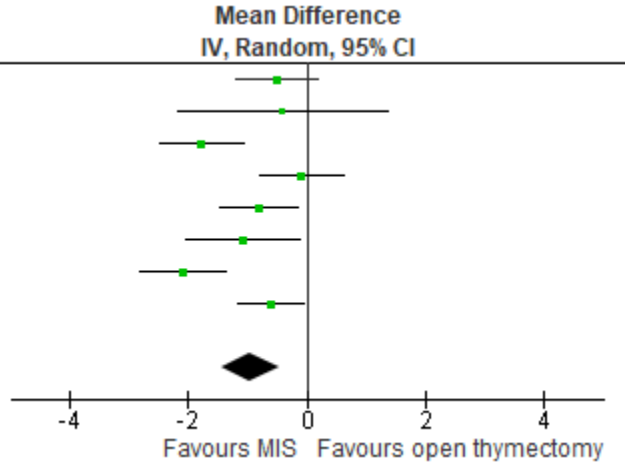


Figure 16 **MIS versus open thymectomy for blood loss for patients with thymoma**

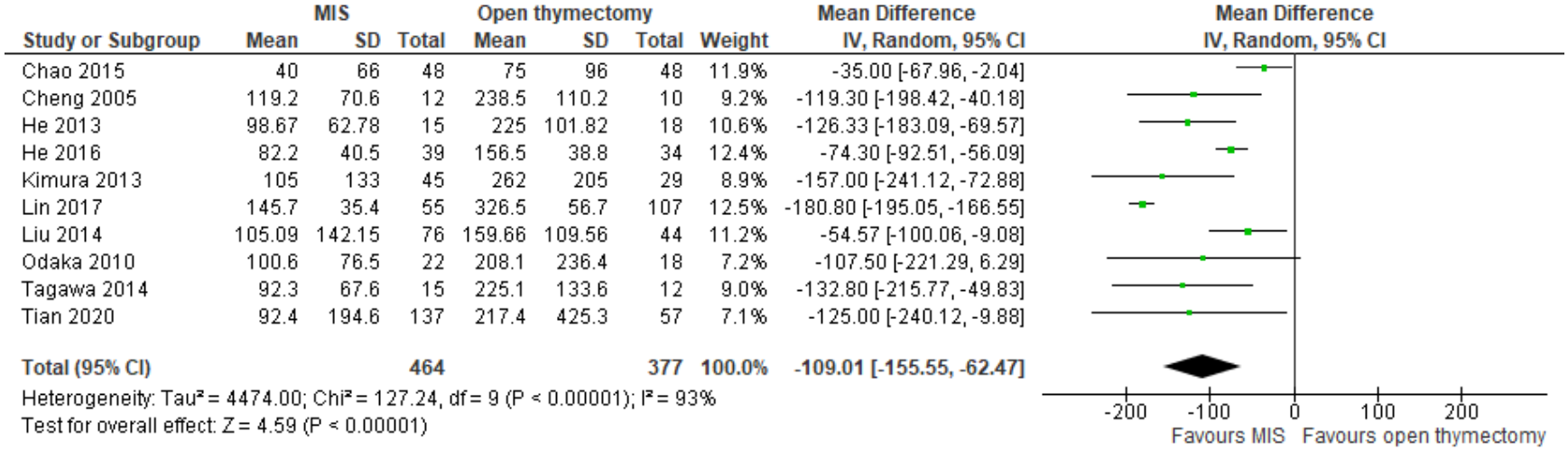


Figure 17 **Neoadjuvant therapy versus no neoadjuvant therapy for OS for patients with thymoma**

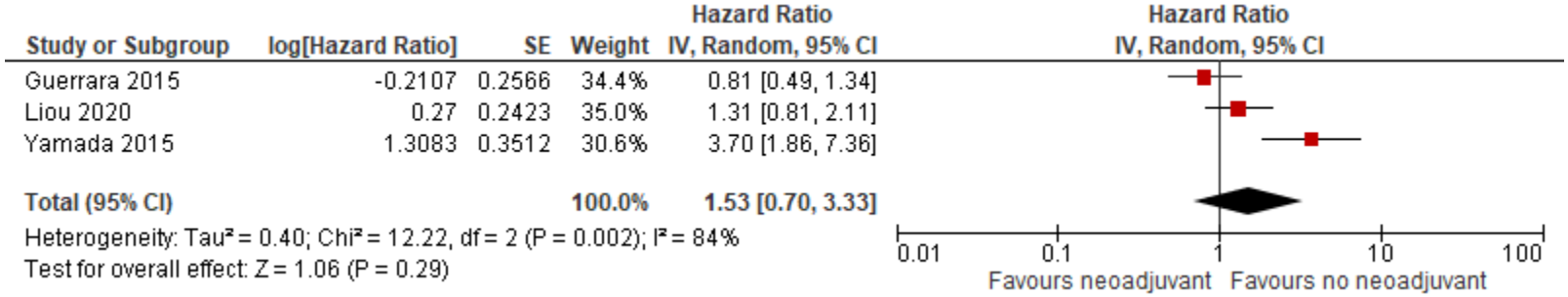


Figure 18 **Neoadjuvant chemotherapy versus no neoadjuvant therapy for OS for patients with thymoma**

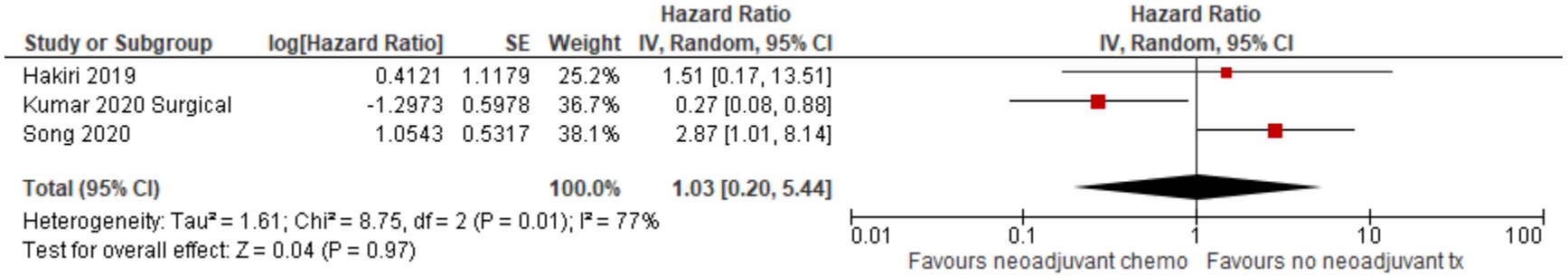


Figure 19 **Neoadjuvant radiotherapy versus no neoadjuvant therapy for OS for patients with thymoma**

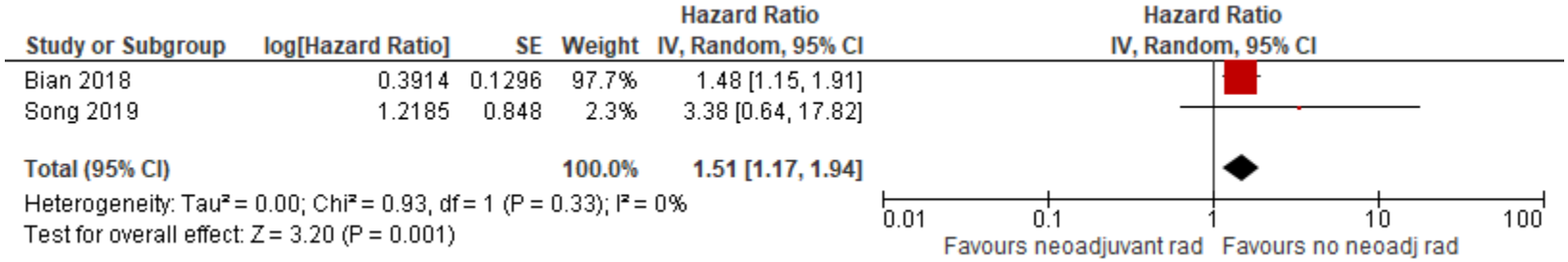


Figure 20 **Neoadjuvant chemotherapy versus no neoadjuvant therapy for DFS for patients with thymoma**

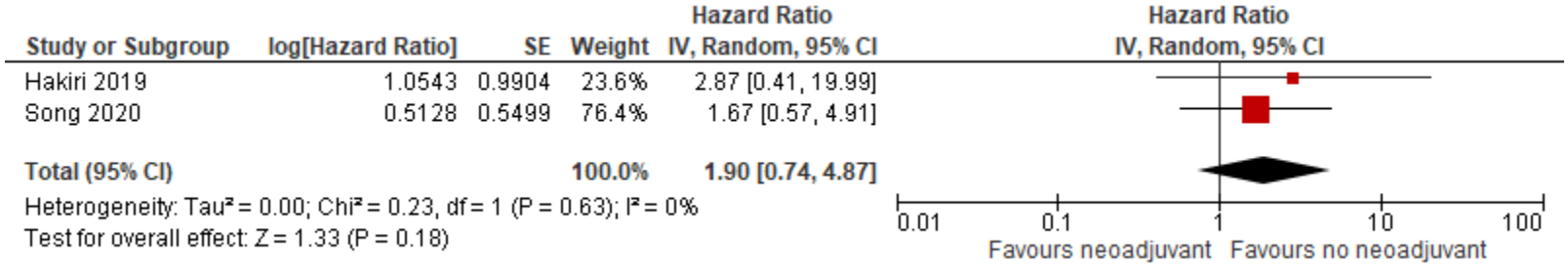


Figure 21 **PORT versus no PORT for OS for patients with thymoma**

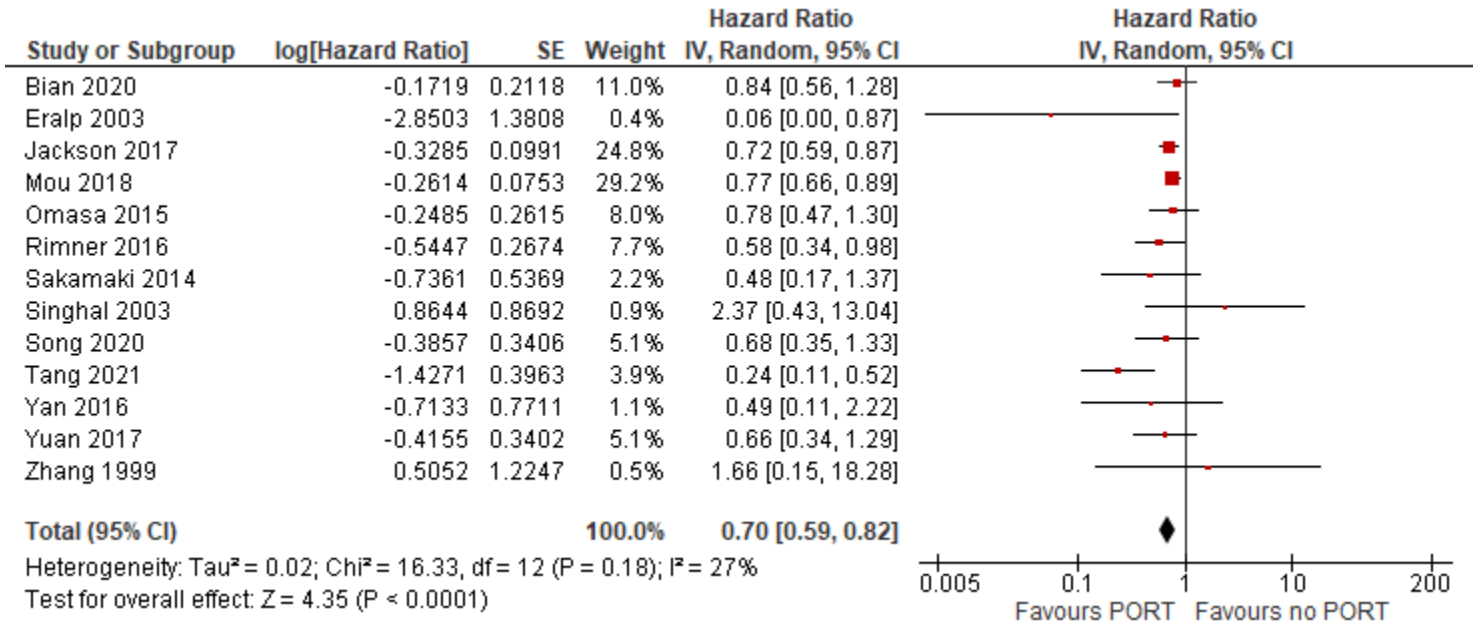


Figure 22 **PORT versus no PORT for OS for patients with thymoma by stage**

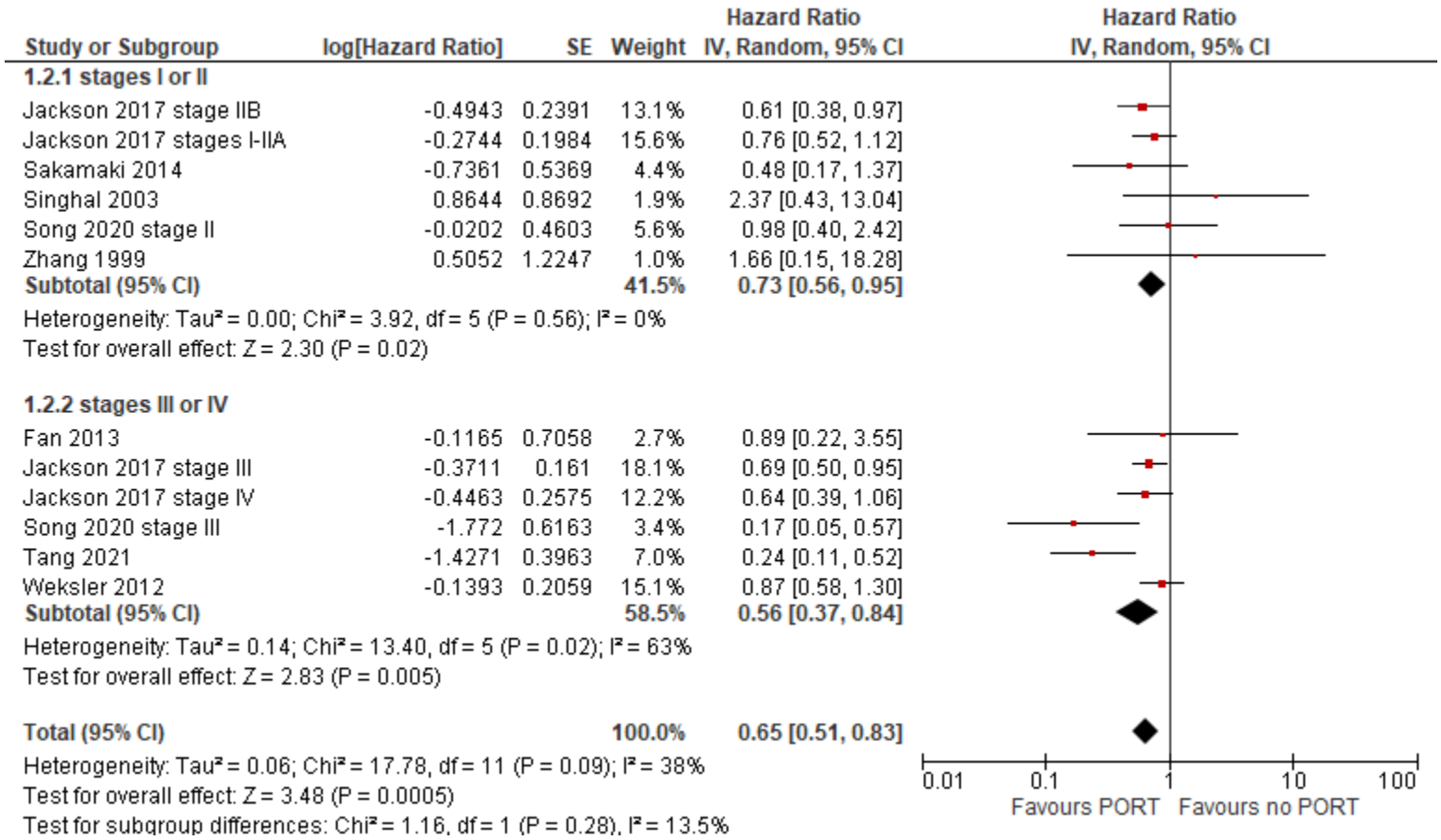


Figure 23 **PORT versus no PORT for OS for patients with thymoma by resection status**

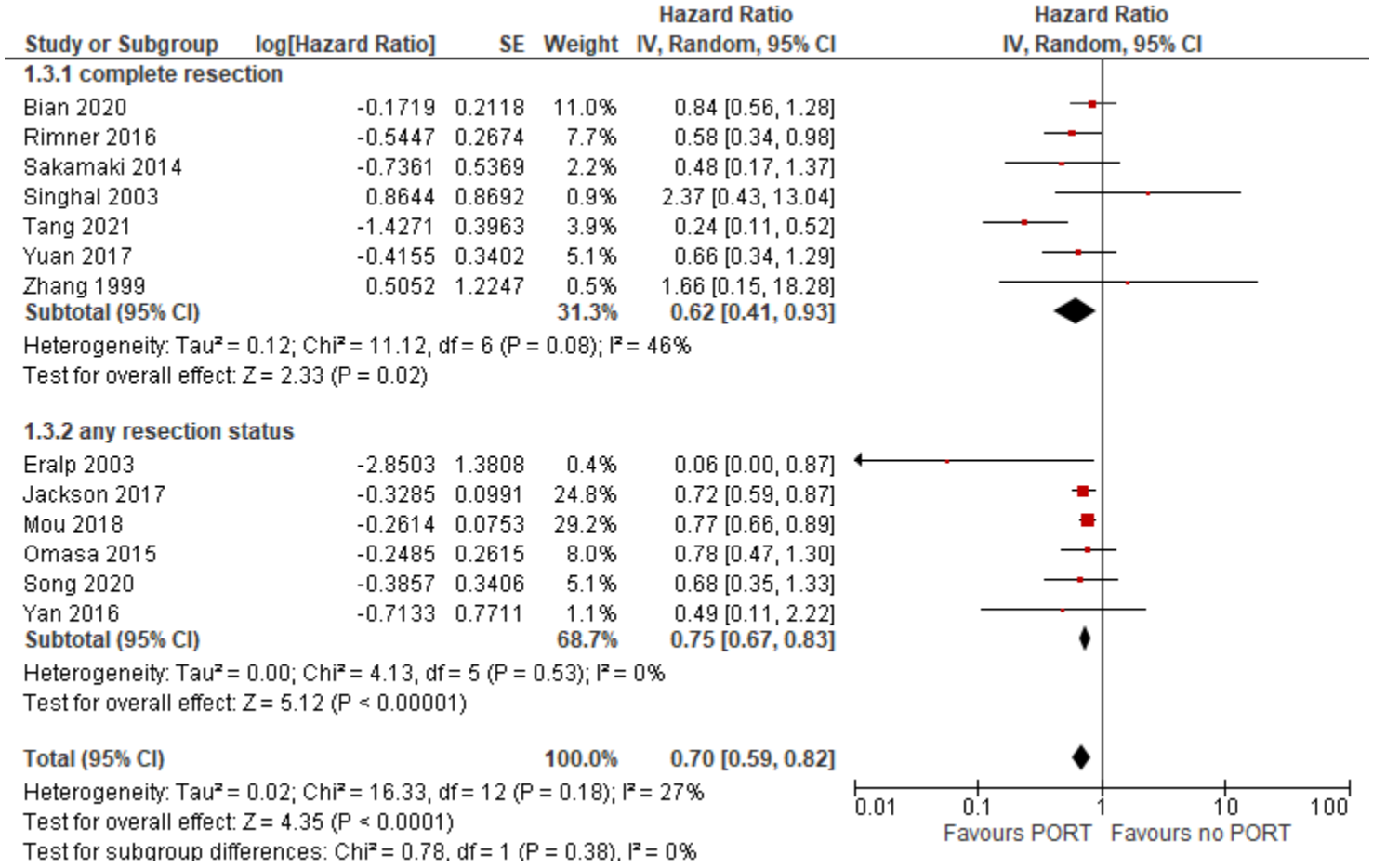


Figure 24 **PORT versus no PORT for OS for patients with thymoma by resection status (stages I/II)**

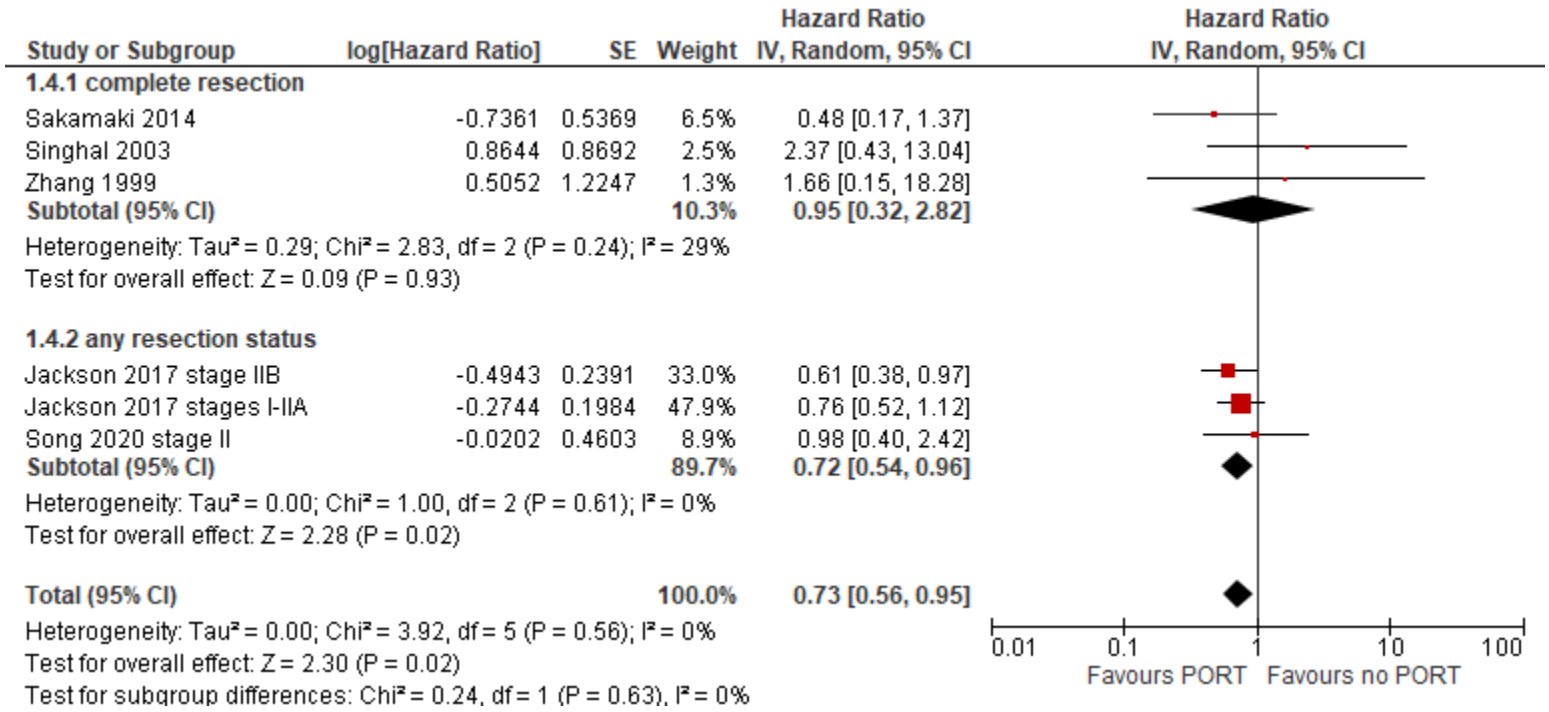


Figure 25 **PORT versus no PORT for OS for patients with thymoma by resection status (stages III/IV)**

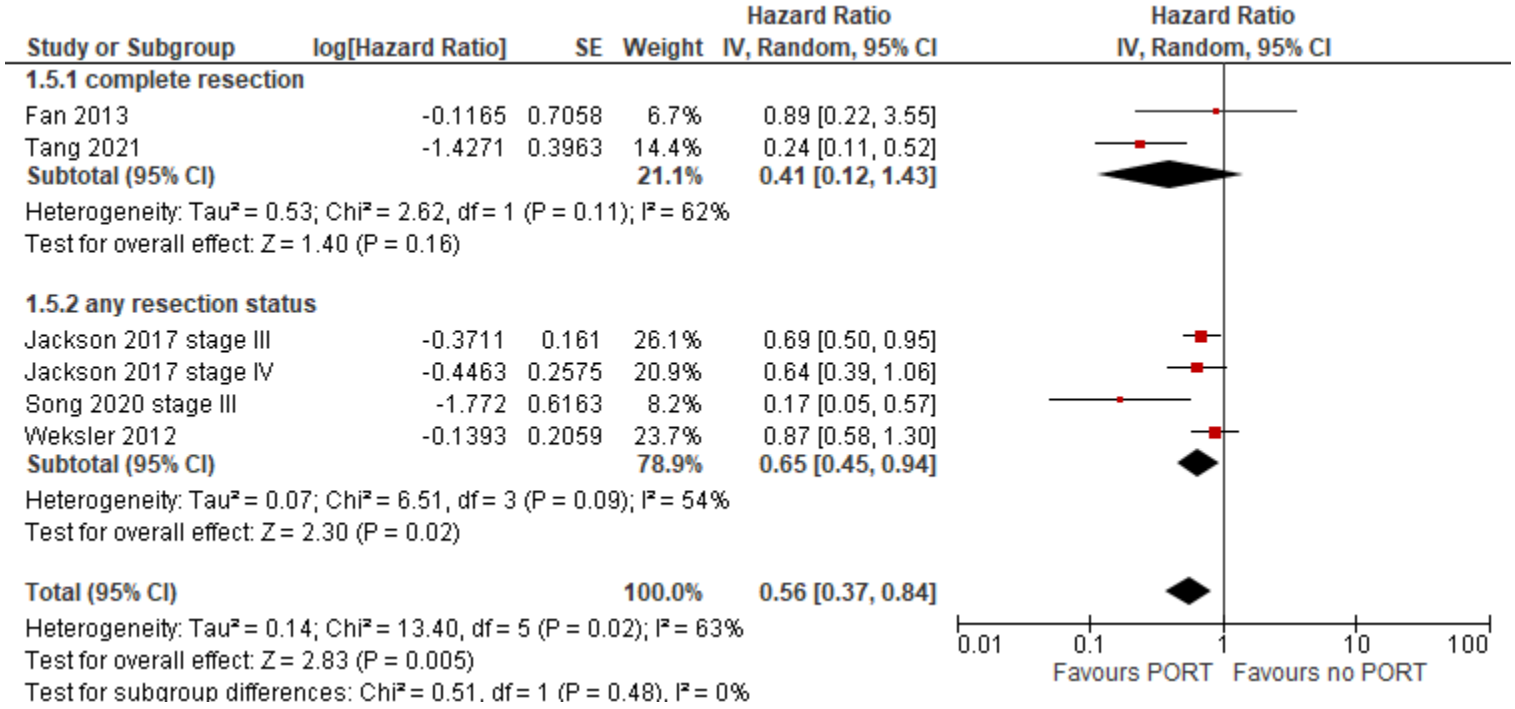


Figure 26 **PORT versus no PORT for OS for patients with thymoma by risk of bias**

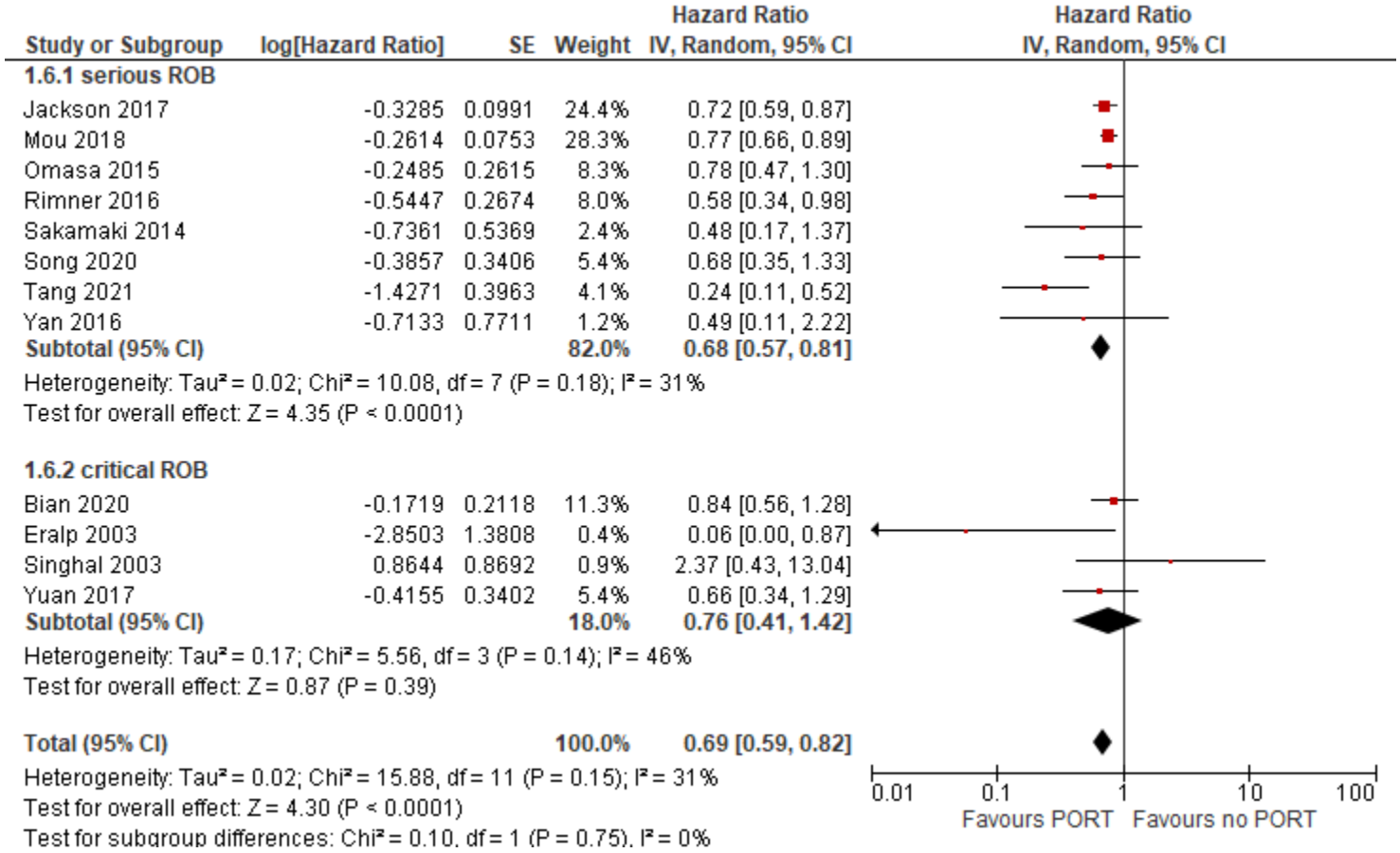


Figure 27 **PORT versus no PORT for DFS for patients with thymoma**

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Omasa 2015	-0.0202	0.1713	30.1%	0.98 [0.70, 1.37]
Sakamaki 2014	-0.7809	0.5393	11.1%	0.46 [0.16, 1.32]
Song 2020	-0.5621	0.3648	17.9%	0.57 [0.28, 1.17]
Tang 2021	-0.9163	0.2803	22.8%	0.40 [0.23, 0.69]
Yuan 2017	-0.6349	0.3609	18.1%	0.53 [0.26, 1.08]
Total (95% CI)			**100.0%**	**0.60 [0.39, 0.91]**

Heterogeneity: Tau² = 0.12; Chi² = 9.36, df = 4 (P = 0.05); I² = 57%
Test for overall effect: Z = 2.41 (P = 0.02)

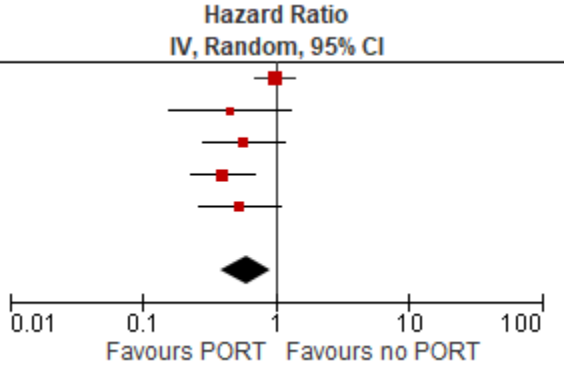


Figure 28 **Adjuvant chemotherapy versus no chemotherapy for OS for patients with thymoma**

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Song 2020	1.2837	0.5362	43.7%	3.61 [1.26, 10.33]
Wu 2009	0.0686	0.3195	56.3%	1.07 [0.57, 2.00]
Total (95% CI)			**100.0%**	**1.82 [0.56, 5.94]**

Heterogeneity: Tau² = 0.54; Chi² = 3.79, df = 1 (P = 0.05); I² = 74%
Test for overall effect: Z = 1.00 (P = 0.32)

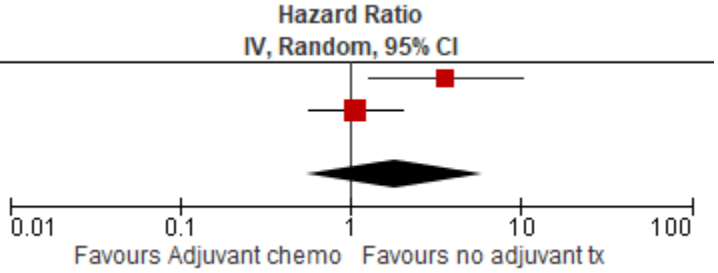


Figure 29 **Neoadjuvant chemotherapy versus no chemotherapy for OS for patients with thymic carcinoma**

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Bakhos 2020	0.1823	0.244	46.6%	1.20 [0.74, 1.94]
Hishida 2016	0.239	0.228	53.4%	1.27 [0.81, 1.99]
Total (95% CI)			**100.0%**	**1.24 [0.89, 1.71]**

Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 1.28 (P = 0.20)

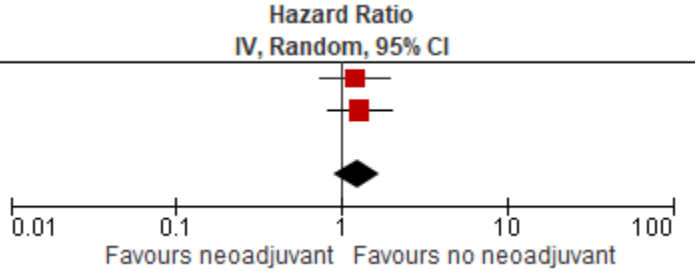


Figure 30 **PORT versus no PORT for OS for patients with thymic carcinoma**

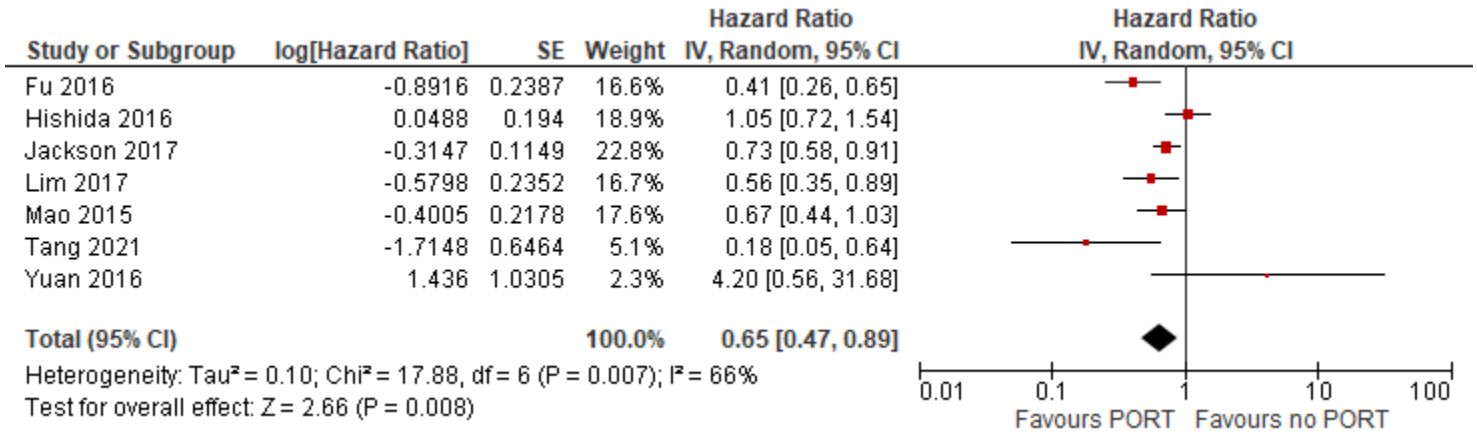


Figure 31 **PORT versus no PORT for OS for patients with thymic carcinoma by stage**

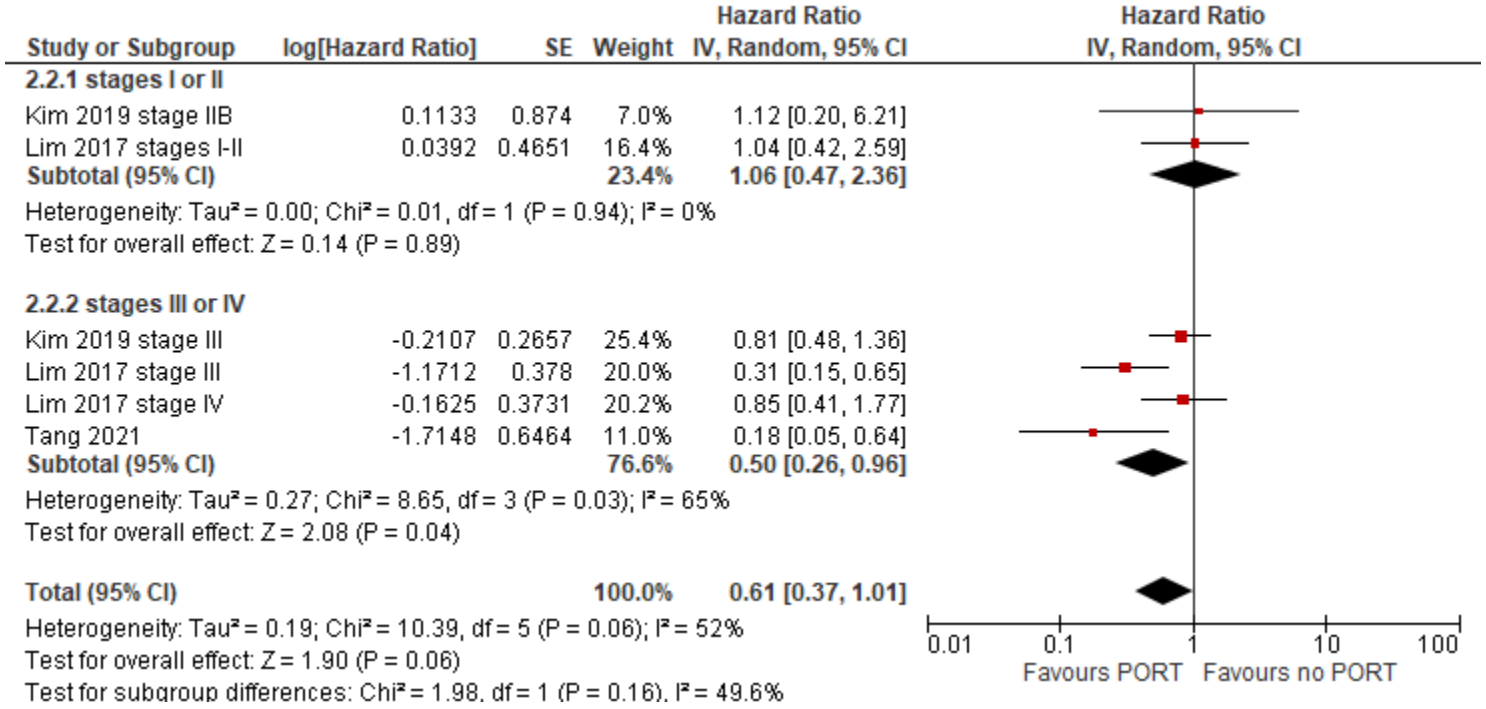


Figure 32 **PORT versus no PORT for OS for patients with thymic carcinoma by resection status**

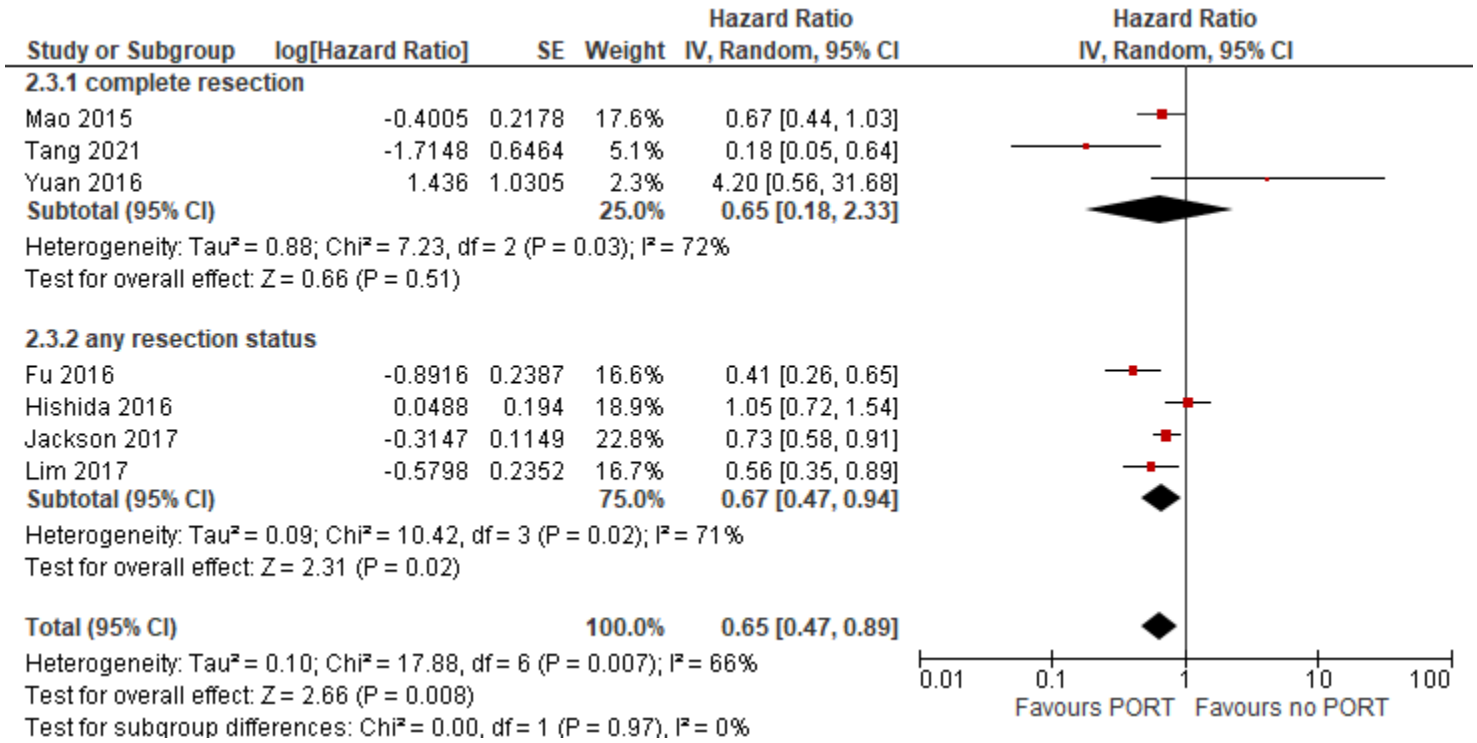


Figure 33 **PORT versus no PORT for OS for patients with thymic carcinoma by risk of bias**

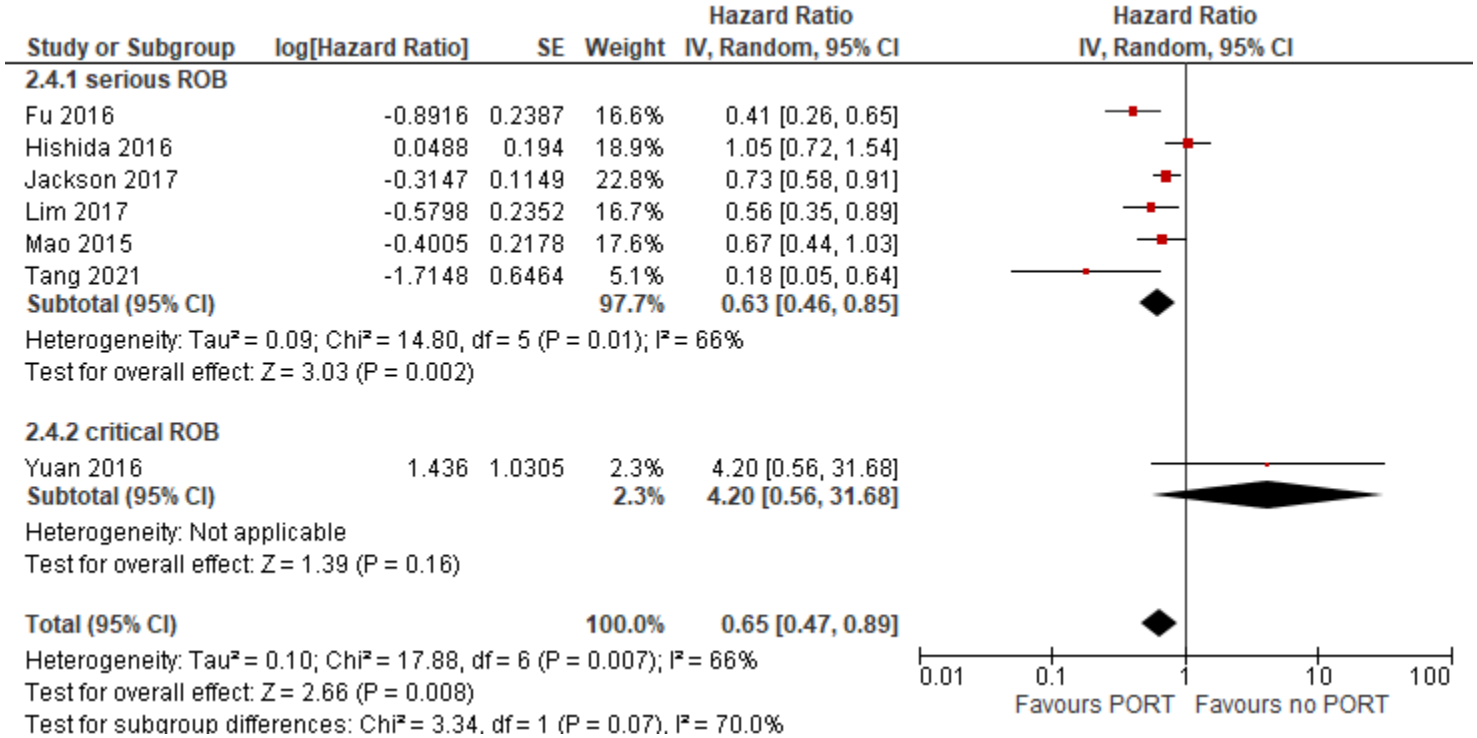


Figure 34 **PORT versus no PORT for DFS for patients with thymic carcinoma**

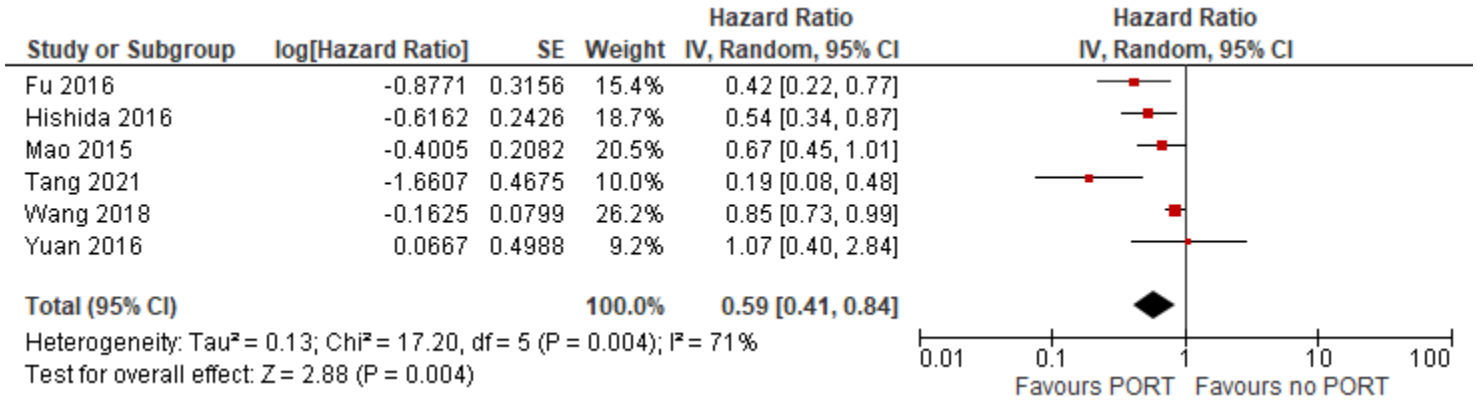


Figure 35 **Adjuvant chemotherapy versus no chemotherapy for OS for patients with thymic carcinoma**

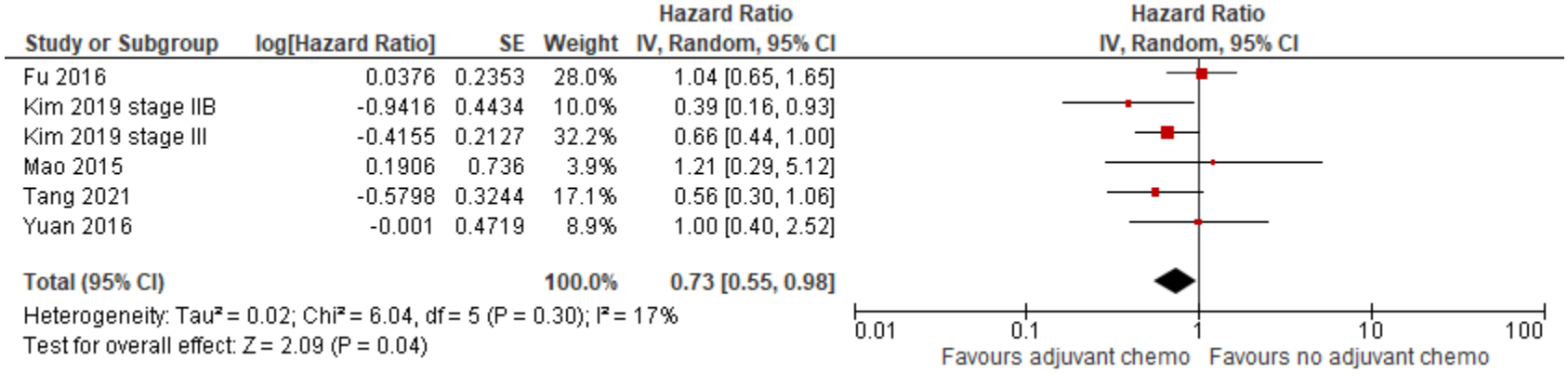


Figure 36 **Adjuvant chemotherapy versus no adjuvant chemotherapy for DFS for patients with thymic carcinoma**

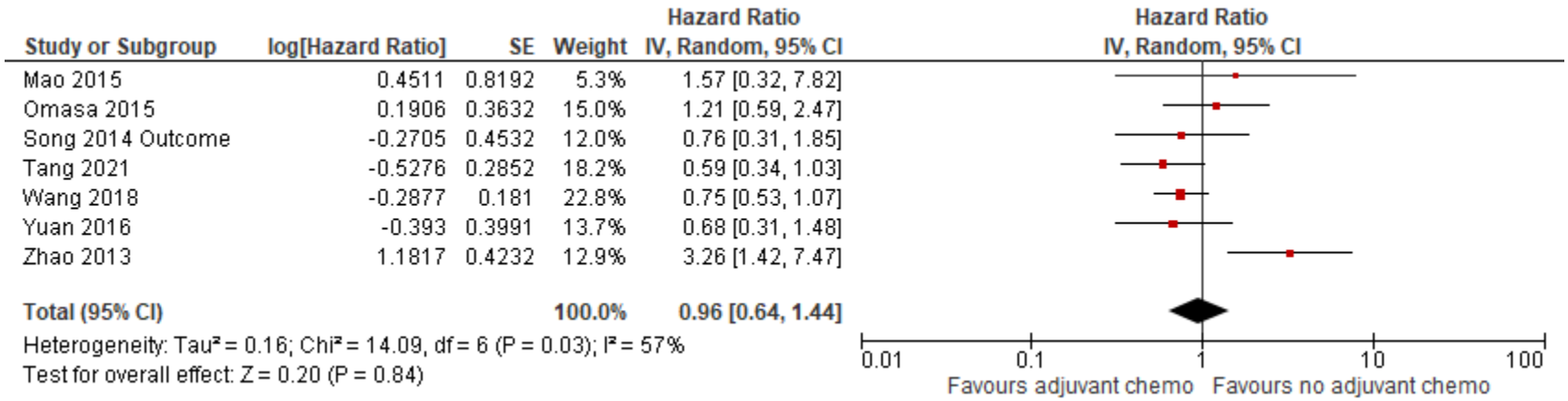


Figure 37 **Adjuvant chemotherapy versus no adjuvant chemotherapy for DFS for patients with thymic carcinoma by risk of bias**

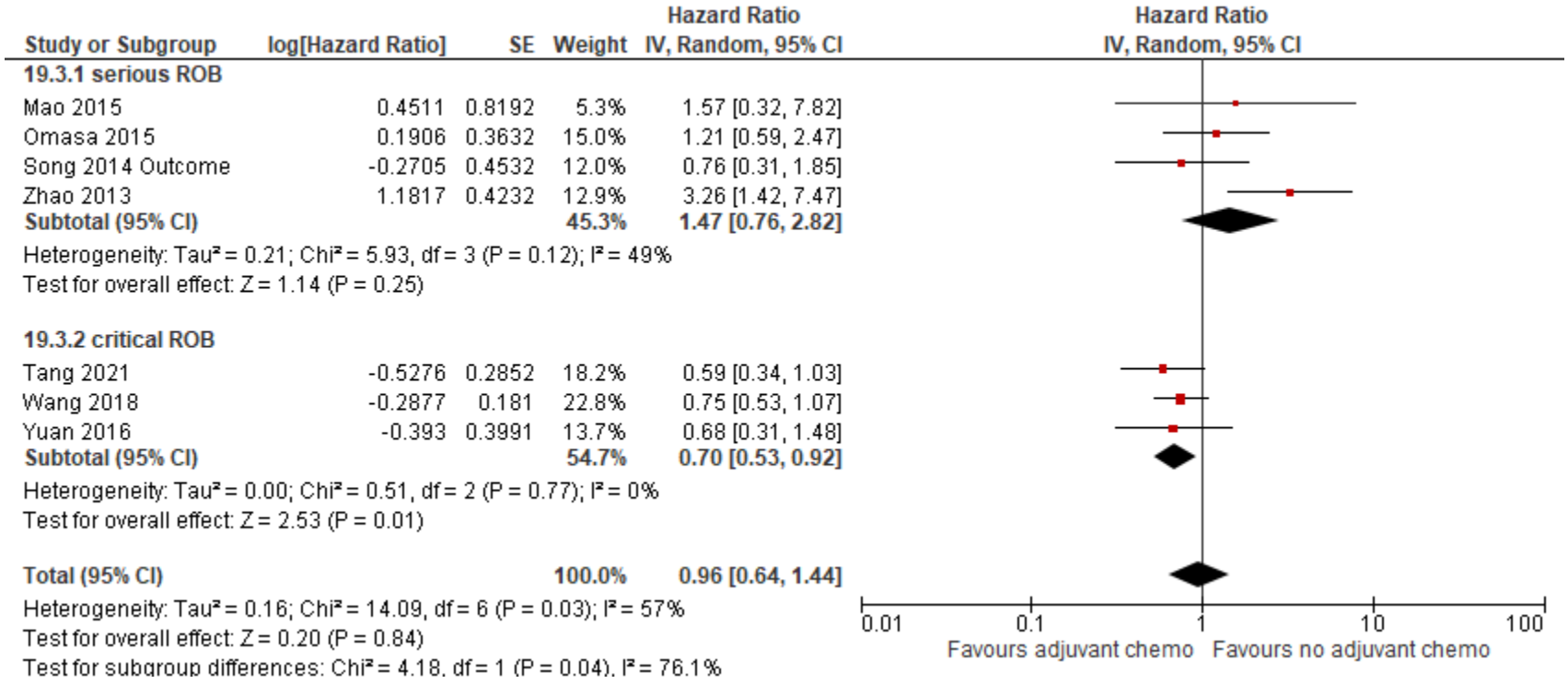


Figure 38 **Adjuvant chemotherapy versus no adjuvant chemotherapy for DFS for patients with thymic carcinoma by resection status**

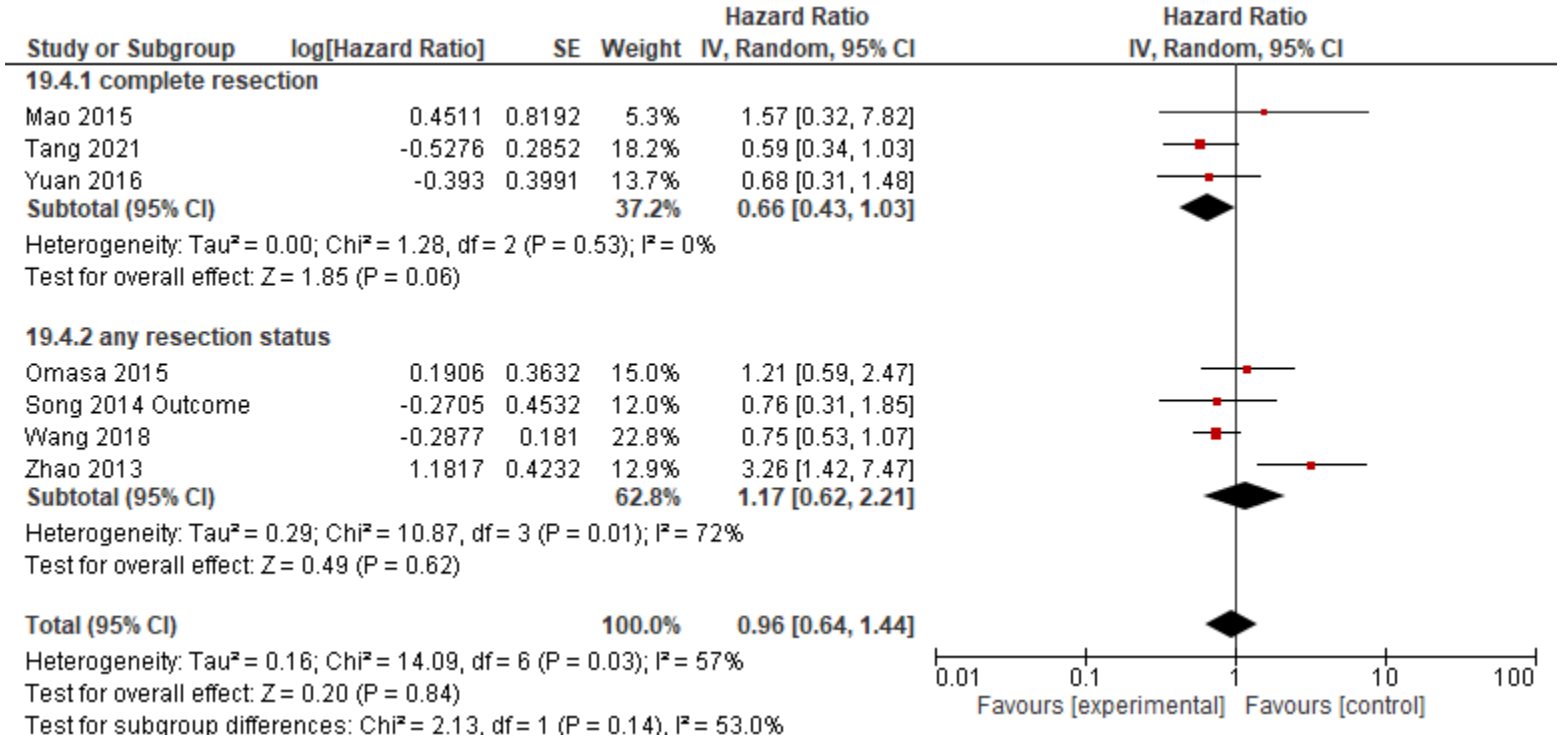


Figure 39 **PORT versus no PORT for OS for patients with thymic NETs**

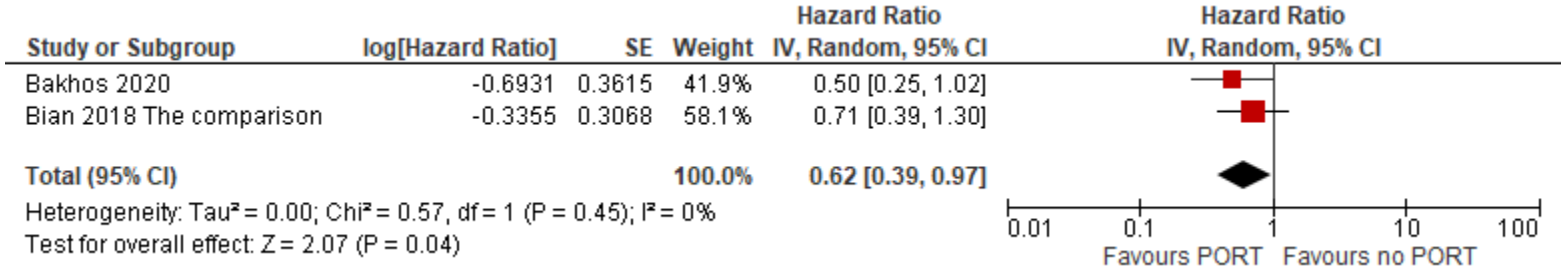
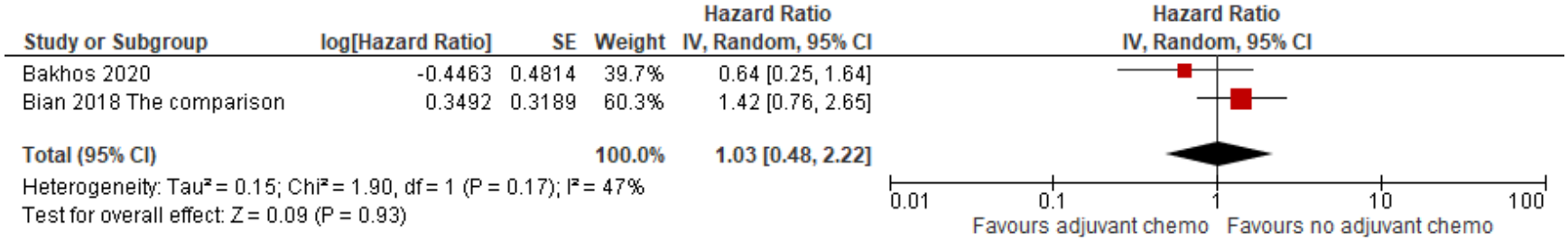


Figure 40 **Adjuvant chemotherapy versus no chemotherapy for OS for patients with thymic NETs**



Appendix 9: Ongoing or Unpublished Trials

Searched clinicaltrials.gov on August 26, 2021 with the following keywords: thymic carcinoma, thymoma, thymic cancer, thymus neoplasms, thymic epithelial tumor, thymic carcinoid, and thymoma type B3

Study Title ID
Chemotherapy Combined With Pembrolizumab in Treating Patients With Thymoma and Thymic Carcinoma NCT04554524
Bintrafusp Alfa (M7824) in Subjects With Thymoma and Thymic Carcinoma NCT04417660
Study of Thymosin a1 During Chemoradiotherapy For Unresectable Thymoma and Thymic Carcinoma NCT03663764
Nivolumab in Patients With Type B3 Thymoma and Thymic Carcinoma (NIVOTHYM) NCT03134118
Trial of Sunitinib in Patients With Type B3 Thymoma or Thymic Carcinoma in Second and Further Lines NCT03449173
A Pilot Study to Investigate the Safety and Clinical Activity of Avelumab (MSB0010718C) in Thymoma and Thymic Carcinoma After Progression on Platinum-Based Chemotherapy NCT03076554
Combination of Pembrolizumab and Lenvatinib, in Pre-treated Thymic CArcinoma paTIents (PECATI) NCT04710628
Adjuvant Treatment for Incomplete Resection Thymoma or Thymic Carcinoma NCT02633514
Ramucirumab and Carbo-Paclitaxel for Untreated Thymic Carcinoma / B3 Thymoma With Carcinoma (RELEVENT) NCT03921671
Chemoradiotherapy for Limited Advanced Unresectable Thymic Epithelial Tumors NCT02636556
Adjuvant Radiotherapy for Stage II/III Thymoma After Complete Resection NCT02633553
Randomized, Multicenter, Phase III Trial to Assess Conformal Post-operative Radiotherapy vs. Surveillance After Complete Resection of Stage II/III Thymoma (RADIO-RYTHMIC) NCT04731610
Postoperative Conformal Radiotherapy for Stage II-III B Type Thymoma NCT02014805
A Study to Test the Safety and Efficacy of Erlotinib Plus Bevacizumab to Treat Advanced Thymoma and Thymic Cancer NCT00369889
Selinexor in Patients With Advanced Thymic Epithelial Tumor Progressing After Primary Chemotherapy (SELECT) NCT03193437
Efficacy of Medical Treatment With SOM230 LAR in Patients With Primary Inoperable Thymoma and/or With Local Recurrent Thymoma to Reduce Tumor Size NCT02021942
Chemotherapy Plus Cetuximab Followed by Surgical Resection in Patients With Locally Advanced or Recurrent Thymoma or Thymic Carcinoma NCT01025089
Surgery for Masaoka-Koga I-II Thymoma NCT05001113
neoadjuvant_thymic Epithelial Tumor NCT03858582

Study Title ID
Clinical Study of Neoadjuvant PD-1 Antibody (Toripalimab) Plus Chemotherapy for Locally Advanced Thymic Epithelial Tumor NCT04667793
Abscopal Effect of SBRT in Combination With rhGM-CSF and INF-α 2b for Metastatic Thymic Epithelial Tumors NCT04517539
A Study of KN046 in Patients With Thymic Carcinoma Who Failed Immune Checkpoint Inhibitors NCT04925947
KN046 (a Humanized PD-L1/CTLA4 Bispecific Single Domain Fc Fusion Protein Antibody) in Subjects With Thymic Carcinoma NCT04469725
A Study of Sunitinib in Patients With Metastatic or Recurrent Thymic Carcinoma (KOSMIC) NCT02623127
Pembrolizumab and Sunitinib Malate in Treating Participants With Refractory Metastatic or Unresectable Thymic Cancer NCT03463460
Neoadjuvant Chemotherapy for Locally Advanced Thymic Cancer NCT01312324
Pilot Study of Imatinib (Gleevec) as Treatment for Advanced Thymic Carcinoma NCT00314873
A Phase 2 Study of Amrubicin in Relapsed or Refractory Thymic Malignancies NCT01364727
A Phase 2 Clinical Study of YY-20394 in Patients With Relapsed/Refractory Thymic Cancer NCT04975061
Carboplatin and Paclitaxel With or Without Ramucirumab in Treating Patients With Locally Advanced, Recurrent, or Metastatic Thymic Cancer That Cannot Be Removed by Surgery NCT03694002
Study on Proton Radiotherapy of Thymic Malignancies (PROTHYM) NCT04822077
A Study to Investigate the Efficacy and Safety of Atezolizumab (Tecentriq) in Previously-Treated Patients With Advanced Thymic Carcinoma NCT04321330
The Curative Effect of Extended Thymectomy Performed Through Subxiphoid-right VATS Approach With Elevation of Sternum NCT03613272
Molecular Profiling and Targeted Therapy for Advanced Non-Small Cell Lung Cancer, Small Cell Lung Cancer, and Thymic Malignancies NCT01306045
Phase-II Study of Lu177DOTATOC in Adults With STTR(+)Pulmonary, Pheochromocytoma, Paraganglioma, Unknown Primary, Thymus NETs (PUTNET), or Any Other Non-.GEP-NET. NCT04276597
Testing Cabozantinib in Patients With Advanced Pancreatic Neuroendocrine and Carcinoid Tumors NCT03375320