Review Article



# Postoperative radiotherapy for thymic epithelial tumors: a narrative review

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**Background and Objective:** Thymic epithelial tumors (TETs), including thymomas and thymic carcinomas, are rare mediastinal tumors. Surgical resection is the treatment strategy for resectable TETs, and postoperative radiotherapy (PORT) is administered to improve local control in patients with a high risk of recurrence. The rarity of TETs has led to a lack of randomized controlled trials, and the current indications for PORT rely largely on retrospective studies. This review analyzes the literature on TETs, highlighting PORT, to guide current research and future investigations.

**Methods:** Studies that focused on TETs, addressed topics on PORT, and had English abstracts accessible online were eligible for inclusion in our review. We excluded case reports or review articles, articles written in languages other than English, articles published >30 years ago, and articles concerning thymic neuroendocrine tumors.

**Key Content and Findings:** Masaoka or Masaoka-Koga staging, World Health Organization (WHO) histological subtype, and resection status indicate PORT in resected TETs. Current literature suggests that PORT does not improve overall survival in stage I–IIA TETs, with inconsistent results for stage IIB–III TETs. Patients with a higher risk, such as carcinomas or WHO type B, might benefit from PORT if they do not develop distant metastasis. Determining which patients will benefit most from PORT requires further investigation. For recurrent TETs, the significance of applying PORT is unclear because available data are limited. Given the long-term survival of TETs, late toxicities, including radiation pneumonitis, radiation-induced cardiotoxicities, and secondary malignancies, must be addressed. Proton beam radiotherapy might reduce toxicities by sparing organs at risk compared to conventional photon beam radiotherapy. The use of high-precision radiation therapy, along with emerging immunotherapy, targeted therapy, and minimally invasive surgery, could improve TET outcomes.

**Conclusions:** This review consolidates the literature on PORT for TETs, factoring in the Masaoka-Koga staging, WHO histological subtypes, and resection status. Varying results regarding PORT efficacy have led to an undefined strategy for stage IIB–III TETs. Although advanced radiotherapy techniques promise to reduce radiation-induced toxicities, further research is needed to investigate the efficacy of PORT and combination therapy.

**Keywords:** Postoperative radiotherapy; thymic carcinoma; thymic cancer; thymic epithelial tumors (TET)

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## Introduction

### *Background*

Thymic epithelial tumors (TETs) are rare primary tumors originating from the anterior mediastinum and include thymomas and thymic carcinomas. The incidence of thymomas is 1.5 cases per million people, and that of thymic carcinoma is 0.3 cases per million people (1,2). Thymomas have a good prognosis with a 5-year overall survival (OS) rate of 90%, whereas that of thymic carcinomas is 55%, and a higher stage is associated with worse OS (3-6).

The Masaoka-Koga staging system has been commonly used for management determination and prognosis estimation of TETs (7,8). It focuses on the local invasive extent of the primary tumor (stages I–III), and pleural, pericardial, lymphogenous, or hematogenous metastases are all included in stage IV, as TETs spread locally and rarely develop lymphatic dissemination. Surgical resection is the main treatment strategy for stages I–III and IV TETs.

Pathological findings are closely associated with the prognosis of TET and are heterogeneous. According to the fifth edition of the World Health Organization (WHO) classification of the thymus and mediastinum, TETs are categorized as type A thymoma, type AB thymoma, thymoma type B1-B2-B3, several other minor thymoma subtypes, and carcinomas, including squamous cell carcinoma and adenocarcinoma (9); 10-year OS for each subtype were 100, 100, 85, 85, 65, and 40% for type A, AB, B1, B2, and B3 thymomas, and thymic carcinomas, respectively (10,11). Geographic differences exist in the frequency of WHO histological subtypes, which impact recurrence (12).

When patients with TETs undergo surgical resection, postoperative radiotherapy (PORT) is often administered to improve local control, depending on the pathological findings of the stage and the residual tumor (13).

### *Rationale and knowledge gap*

Owing to the rarity of TETs, no randomized controlled trials (RCTs) have been conducted to confirm the efficacy of PORT in TETs, and the current evidence levels are not high and are mainly based on retrospective studies. According to the National Comprehensive Cancer Network guidelines, completely resected Masaoka-Koga stage I thymomas do not require adjuvant therapy, whereas PORT is administered for TETs with microscopic (R1) or macroscopic (R2) residual tumors (13). For completely resected stage II–IV TETs, the guidelines recommend discussion by a multidisciplinary tumor board (MTB) to determine the patient's treatment strategy because the efficacy of PORT in this area remains controversial.

The Réseau Tumeurs Thymiques et Cancer (RYTHMIC), a nationwide network for TETs in France, has prospectively gathered data to determine whether decisions on PORT made at the MTBs align with RYTHMIC guidelines and whether they are ultimately implemented in patient care (14). Among 241 patients with stage I–III disease, the MTB's decision regarding PORT was not made in accordance with the ESMO/RYTHMIC guidelines in 20 patients. When the MTB recommended PORT in cases where the guidelines would have advised against it, a clear explanation for the inconsistency with the guidelines was not found; however, the cases were stage II thymomas with WHO type B2 or stage IIA thymomas with WHO type AB thymomas. Thus, the efficacy of PORT in TETs for these subjects could be considered a gray zone in the guidelines, where different MTBs would make different decisions.

### *Objective*

This narrative review aimed to evaluate and summarize the current literature regarding PORT for TETs in terms of indications for PORT, radiotherapy techniques, and toxicities. This review sheds light on this understudied area by providing information on the current ongoing trials and recommendations for future research. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-23-38/rc).

## Methods

A summary of the search strategies is provided in *Table 1*. N.K. developed and executed the PubMed search on August 5th, 2023. The reproducible search strategies for creating a narrative review are presented in *Table 2*. The studies included in the review met the following eligibility criteria: (I) articles focusing on TETs; (II) articles that included topics on PORT; and (III) articles with English abstracts available online. The exclusion criteria were as follows: (I) case reports or review articles; (II) articles written in languages other than English; and (III) articles on thymic neuroendocrine tumors.

**Table 1** Search strategy summary

| Items | Specification |
|---|---|
| Date of search (specified to date, month and year) | August 5th, 2023 |
| Databases and other sources searched | PubMed |
| Search terms used | radiotherapy, adjuvant, postoperative, thymic, thymoma |
| Timeframe | Since August 1st, 1992, until August 5th, 2023 |
| Inclusion and exclusion criteria | Inclusion criteria |
| | (I) Articles on thymic epithelial tumors excluding thymic neuroendocrine tumor |
| | (II) Articles on postoperative radiotherapy |
| | Exclusion criteria |
| | (I) Articles written in non-English language |
| | (II) Case reports, review articles, or guidelines |
| | (III) Articles published >30 years ago |
| | (IV) Pre-clinical studies |
| Selection process | N.K. conducted the selection independently and Y.M. reviewed the process |

**Table 2** Search strategy to create a narrative review (date of search: August 5th, 2023)

| Search | Query | Items |
|---|---|---|
| #1 | Has abstract | 24,918,516 |
| | "hasabstract" (All Fields) | |
| #2 | Adjuvant radiotherapy OR Postoperative radiotherapy | 425,765 |
| | ("radiotherapy, adjuvant"(MeSH Terms) OR ("radiotherapy"(All Fields) AND "adjuvant"(All Fields)) OR "adjuvant radiotherapy"(All Fields) OR ("adjuvant"(All Fields) AND "radiotherapy"(All Fields))) OR (("postoperative period"(MeSH Terms) OR ("postoperative"(All Fields) AND "period"(All Fields)) OR "postoperative period"(All Fields) OR "postop"(All Fields) OR "postoperative"(All Fields) OR "postoperatively"(All Fields) OR "postoperatives"(All Fields)) AND ("radiotherapy"(MeSH Terms) OR "radiotherapy"(All Fields) OR "radiotherapies"(All Fields) OR "radiotherapy"(MeSH Subheading) OR "radiotherapy s"(All Fields))) | |
| #3 | Thymic (ti) OR Thymoma (ti) | 16,097 |
| | "Thymic"(Title) OR "Thymoma"(Title) | |
| #4 | #1 AND #2 AND #3 | 488 |

## Indications for PORT

One hundred eighty-four articles were identified in the search (*Figure 1*). As no RCTs have assessed the efficacy of PORT, established rationales are based on retrospective studies of large databases. Although multi- or single-institutional retrospective studies have smaller sample sizes than large database studies, they can offer more detailed results. We review both types of studies and highlight their strengths.

### *Resected TET*

Three pathological indications for PORT in resectable TETs have been discussed in the literature: pathological staging, WHO classification of histological subtypes, and resectional status (margin status).

#### Masaoka or Masaoka-Koga staging

The Masaoka or Masaoka-Koga staging system has been widely used in pathological staging to determine

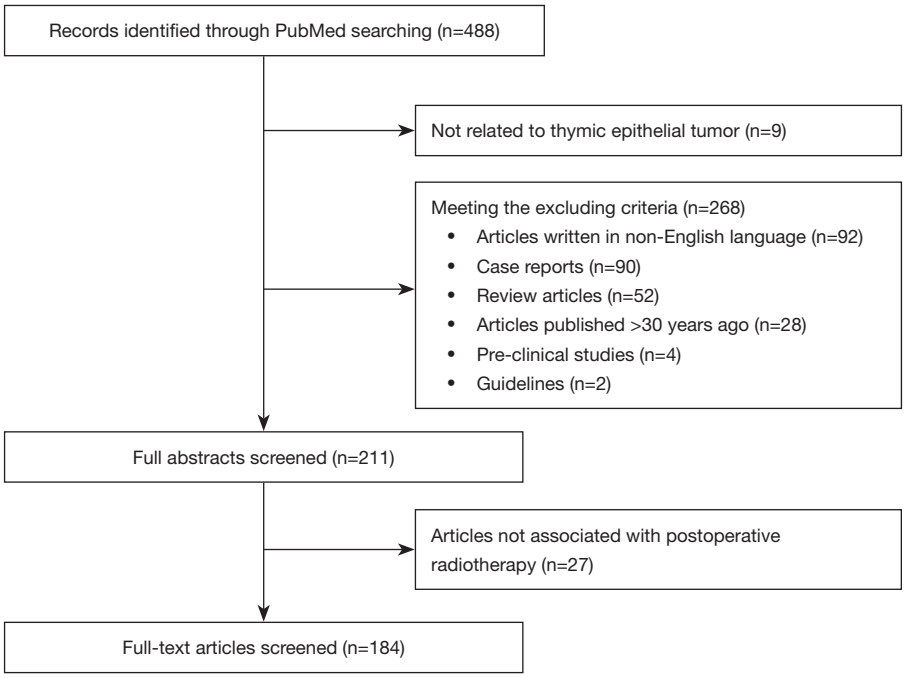


**Figure 1** Flow chart for literature search and selection.

the indications for PORT in TETs. In contrast, the International Thymic Malignancy Interest Group (ITMIG), European Society of Thoracic Surgeons, Japanese Association of Research in Thymus, and Chinese Alliance for Research on Thymomas developed an international database, which resulted in the development of the TNM stage classification. It provides information on lymphatic involvement and tumor dissemination in addition to tumor invasion extent, and is comparable or superior in grouping TETs for predicting prognosis and guiding clinical management (15-17). However, previous reports on PORT were largely based on Masaoka or Masaoka-Koga staging, and a paradigm shift is occurring from the traditional Masaoka-Koga system to a TNM system. In this section, we outline the benefits of PORT according to the Masaoka or Masaoka-Koga stages. In *Table 3*, we present previous database studies that assessed the efficacy of PORT on OS, which have yielded conflicting results.

One of the largest retrospective database analyses using the National Cancer Data Base (NCDB) investigated 4,056 patients who underwent surgery for stage I–IV TETs (30). PORT positively correlated with improved OS in patients diagnosed with either thymoma or thymic carcinoma. For patients with stage IIB or III thymoma, PORT significantly increased OS. Among the subsets with margin-negative stage IIB thymoma, PORT was still associated with better OS. In patients with thymic carcinoma, PORT was significantly correlated with increased OS across the entire cohort. When classified into stages I–IIA, IIB, and III, no significant differences were noted, although a slight increase in OS was observed in patients with stage III disease. In another study using the ITMIG database, Rimner *et al.* reported an OS benefit with PORT in patients with completely resected stage II and III thymoma (29).

In contrast, a Surveillance, Epidemiology, and End Results (SEER) database study, which focused on 1,334 patients with thymoma between 1973 and 2005, did not show an OS benefit of PORT in patients with stage IIB disease (18). Lim *et al.* used a more recent patient cohort from the same database and reported that PORT in stages III–IV was associated with improved OS; however, no corresponding efficacy was observed in stage IIB (25). The Japanese Association for Research on the Thymus Database Study, which included 1,265 patients with TETs, showed that PORT improved recurrence-free survival (RFS) for stage II–III thymic carcinoma, but did not improve OS and RFS for stage II–III thymoma (23).

Five meta-analyses reported PORT for TETs: two TETs, two thymomas, and one thymic carcinoma. Two meta-analyses on PORT for TETs concluded that

**Table 3** Previous database studies assessing the efficacy of postoperative radiotherapy on overall survival

| Authors | N | Primary | Stage | Database | Masaoka or Masaoka-Koga staging | | | | | 5-year OS in PORT *vs.* no PORT in stage II–IV |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | I | IIA | IIB | III | IV | |
| Fernandes *et al.* (18) | 1,334 | Car | I–IV | SEER | NS (I–IIA) | | NS | S (III–IV) | | Median, 134 *vs.* 115 months (IIB) |
| Patel *et al.* (19) | 1,464 | Thy | I–IV | SEER | NS | | S (II–III) | | NA | 64% *vs.* 53% (II–III) |
| Weksler *et al.* (20) | 476 | Thy | III | SEER | – | – | – | NS | – | Median, 127 *vs.*105 months |
| Mariano *et al.* (21) | 171 | Thy | I–IV | BCCAR | NA | | NS (II) | NA | NA | NA |
| Ruffini *et al.* (22) | 2,265 | Car | I–IV | ESTS | | | S | | | 69% *vs.* 61% |
| Omasa *et al.* (23) | 1,265 | TET | II–III | JART | – | | NS (II) | NS | – | 97% *vs*. 96% (II, Thy)<br>93% *vs*. 90% (III, Thy)<br>91% *vs*. 87% (II, Car)<br>65% *vs*. 64% (III, Car) |
| Hishida *et al.* (24) | 306 | Car | I–IV | JART | | | NS (I–IV) | | | 78% *vs.* 74% |
| Lim *et al.* (25) | 529 | Thy | IIB–IV | SEER | – | – | NS | S | S | NA |
| Fu *et al.* (26) | 329 | Car | I–IV | ChART | | NS (R0, I–II) | | S (R0) | S (R0) | NA |
| | | | | | | | S (R1–2, I–IV) | | | |
| Wang *et al.* (27) | 1,850 | Thy | I–IV | ChART | | | NS (I–IV) | | | NA |
| Liu *et al.* (28) | 1,546 | TET | I–III | ChART | NS | | NS (II) | NS | – | 90% *vs.* 96% |
| Rimner *et al.* (29) | 1,263 | Thy | II–III | ITMIG | – | | S (R0) | S (R0) | – | 97% *vs*. 93% (II)<br>92% *vs*. 76% (III) |
| Jackson *et al.* (30) | 4,056 | TET | I–IV | NCDB | NS (I–IIA) | | S (Thy), NS (Car) | S (Thy), NS (Car) | NA | NA |
| Lim *et al.* (31) | 312 | Car | I–IV | SEER | | NS (I–II) | | S | NS | NA |
| Mou *et al.* (32) | 2,234 | Thy | I–IV | SEER | NS (I–IIA) | | NS | S (III–IV) | | 75.4% *vs.* 62.9% (III–IV) |
| Bian *et al.* (33) | 1,272 | Thy | I–IV | SEER | NS | | S (IIA–III) | | S | NA |
| Gu *et al.* (34) | 1,087 | TET | I–II* | ChART | | NS (I–II) | | – | – | NA |
| Kim *et al.* (35) | 632 | Car | IIB–III | NCDB | – | – | S<br>NS (R0) | S | – | NA |
| Mou *et al.* (36) | 2,236 | Thy | I–IV | SEER | NS (I–IIA) | | NS | S (III–IV) | | NA |
| Wu *et al.* (37) | 216 | Car | I–IV | SEER | | | NS (I–IV) | | | NA |
| Muslim *et al.* (38) | 1,120 | Thy | IIB–IV | SEER | – | – | NS† | S† | NS† | NA |
| Lococo *et al.* (39) | 203 | Car | I–IV | ESTS | | | S | | | 74% *vs.* 55% |
| Zhang *et al.* (40) | 2,558 | TET | I–IV | SEER | NS (I–IIA) | | S | S (Thy), NS (Car) | | 82% *vs*. 75% (IIB, Thy)<br>66% *vs*. 46% (III–IV, Thy)<br>72% *vs*. 61% (IIB, Car)<br>38% *vs*. 23% (III–IV, Car) |
| Lin *et al.* (41) | 700 | Thy | IIB–III | SEER | – | – | NS | S | – | NA |

*, UICC stage I (equal to Masaoka stages I and II); †, disease-specific survival, not OS. OS, overall survival; PORT, postoperative radiotherapy; Car, thymic carcinoma; SEER, Surveillance, Epidemiology, and End Results; NS, not significant; S, significant; Thy, thymoma; BCCAR, British Columbia Cancer Agency Registry; NA, not available; ESTS, European Society of Thoracic Surgeons; TET, thymic epithelial tumor; JART, Japanese Association for Research on the Thymus; ChART, Chinese Alliance for Research of Thymoma database; ITMIG, International Thymic Malignancies Interest Group ; NCDB, National Cancer Database.

**Table 4** Summary table of advantages and disadvantages of large-database studies

| Database | Pros | Cons |
|---|---|---|
| All | Large series of patients | Retrospective studies contain bias; no detailed records of failure patterns, chemotherapy, and radiotherapy |
| SEER | Propensity score-matched studies were performed; cause of death and second malignancy were available; can be focused on specific histological type | Surgical margin status, comorbidities, patient performance status, and Masaoka-Koga staging were unavailable; WHO histology classification was unavailable for the majority; no central review of histological classification was performed; the ethnic characteristics were diverse |
| ChART | Propensity score-matched studies were performed; TNM staging was utilized | Missing patient information caused the majority to excluded from the analysis; Masaoka-Koga staging was unavailable |
| JART | The number of patients with missing data (including OS) was very small; Masaoka staging was utilized | No central review of histological classification was performed |
| ESTS | Clinico-pathological variables affecting long-term survival were investigated; Masaoka staging was utilized; neuroendocrine thymic tumors were excluded from the analysis | Only surgical cases in high-volume centers were included; no central review of histological classification was performed; nodal status and the site of distant metastases were unavailable |
| NCDB | Margin status was incorporated into the analysis | Masaoka-Koga staging was unavailable; no central review of histological classification was performed |
| BCCAR | Variability in clinical behavior and practice variations were focused; Masaoka-Koga staging was utilized; pathology review and reclassification were performed | 10% of the data were unavailable for analysis; the number of patients with stage I was limited |
| ITMIG | Completely resected stage II and III thymoma were the focus; Masaoka or Masaoka-Koga staging was utilized | Stages IIA, IIB, and II were all categorized as stage II. |

SEER, Surveillance, Epidemiology, and End Results database; WHO, World Health Organization; ChART, Chinese Alliance for Research of Thymoma database; JART, Japanese Association for Research on the Thymus Database; OS, overall survival; ESTS, European Society of Thoracic Surgeons database; NCDB, National Cancer Database; BCCAR, British Columbia Cancer Agency Registry; ITMIG, International Thymic Malignancies Interest Group Retrospective Database.

current evidence did not support any benefit of PORT on recurrence in patients with complete resection of stage II or III TETs (42,43). Two meta-analyses, one with 3,823 patients from fourteen studies and the other with 4,746 patients from five studies, showed that increased OS was observed in the subgroup analysis of completely resected stage II or III thymoma (44,45). Hamaji *et al.* also showed that PORT improves the long-term survival outcomes of patients with thymic carcinoma, although stage-specific or resectional status-specific recommendations were not available in the meta-analysis (46).

These discrepancies among large database studies or meta-analyses can be attributed to the rarity of TETs and the inherent bias in studies, such as patient eligibility, lack of or missing covariates derived from the database, adjuvant radiotherapy, including concurrent use of chemotherapy, or the covariates utilized for propensity score matching analysis. Furthermore, information from Masaoka or Masaoka-Koga staging is not specifically recorded in the NCDB or the SEER database and is inferred and subjectively classified based on recorded information as far as possible. This could be a limitation of large database analysis (*Table 4*).

The incompleteness of the traditional Masaoka-Koga staging is also a limitation, as it provides no information on the number of involved organs or tumor size, both of which appear to be promising factors for prognostic stratification (17,47). Therefore, an optimal staging system to identify patients with poor prognosis who are at high risk for recurrence is necessary. Such patients could be ideal candidates for PORT or less-invasive surgery combined with PORT. For example, in patients with phrenic nerve involvement (Masaoka-Koga stage III or higher), *en bloc* resection can lead to diaphragmatic impairment and pulmonary function deterioration. Phrenic nerve-sparing surgery combined with PORT is feasible with an acceptable

local control rate of 92.9% (48). The ninth edition of the TNM stage classification, which is based on a large international database, is expected to contribute significantly to this field.

**WHO histological subtypes**

The patterns of metastasis and recurrence significantly differ across the WHO classification histological subtypes; the time to metastasis is shortest in thymic carcinoma, followed by high-risk thymoma (WHO types B2 and B3), and longest in low-risk thymoma (A, AB, and B1) (9,12,49,50). According to an analysis of the ITMIG retrospective database, PORT was associated with a trend toward better OS in all subgroups of stage II and III thymoma, and the greatest and most statistically significant survival advantage with PORT was observed in the subgroup of patients with stage III WHO types B1, B2, or B3 thymoma (29). In contrast, Muslim *et al.* reported that SEER database analysis did not reveal a significant disease-specific survival advantage of PORT in any of the WHO histological subtypes among patients with stage IIB–IV thymoma (38). This could be mainly due to differences in the stages of the eligible patient cohorts. For thymic carcinoma, we did not find any reports examining the differences between squamous cell carcinoma and adenocarcinoma.

**Resectional status**

Complete resection was associated with improved OS in patients with TETs. Resectional status is a well-known factor for indicating PORT in TETs because PORT is associated with improved OS in patients with incomplete resections or positive margins (28,30,35).

When total resection is not possible, subtotal resection, or debulking surgery, may yield a higher survival rate than that for inoperable thymoma but not for thymic carcinoma (5). Zhai *et al.* conducted a retrospective study on debulking surgery plus PORT versus radiotherapy in 47 patients with unresectable stage III thymic carcinoma (51). The results revealed 5-year OS rates of 54.4% and 0%, respectively. Thus, there may be merit in the so-called "debulking procedures" followed by PORT, but only in highly selected cases. Mastromarino *et al.* investigated 79 patients with types B2 and B3 thymomas, including R1 or R2 residual tumors (52). Regardless of whether residual tumors existed in the primary tumor or pleural space, PORT significantly improved progression-free survival in patients with R1 residual tumors, whereas postoperative chemotherapy or chemoradiotherapy improved cancer-specific survival in patients with R2 residual tumors.

In summary, the current literature suggests that PORT does not improve OS in stage I–IIA TETs, with inconsistent results for stage IIB–III TETs. The currently available data suggest that stage II–III TETs are a heterogeneous population; at least stages IIA and IIB need to be considered separately as indications for PORT, not considered together as stage II. PORT for stage III TETs can contribute to improved OS in patients with higher-risk grades, such as carcinoma or WHO type B2–B3, and may benefit from PORT in terms of improved OS when they do not develop distant metastasis. Identifying patients less likely to develop early distant metastases and can genuinely benefit from PORT remains a gray zone that requires further exploration.

***Recurrent TET***

After definitive radiotherapy or PORT, the 5-year cumulative incidence of all intrathoracic failures was 24% (53). The most common site of failure was the out-of-field pleural space, followed by the 5-year incidence of in-field failure of 7%. Although radiotherapy is critical in the multimodal treatment of intrathoracic recurrent TETs (54,55), several aspects warrant careful consideration.

First, the prognostic significance of PORT in patients with recurrent TETs remains unclear. Several studies with a limited sample size have indicated that adjuvant therapies, including PORT, do not effectively reduce recurrence or improve survival outcomes (56,57). Second, when considering PORT for recurrent TETs, examining the overlap between the field irradiated during initial PORT and the target volume at the time of recurrence is imperative. Furthermore, it is essential to ensure that the cumulative dose to the organs at risk is within the established dose constraints, as described in "Radiotherapy techniques". Recently, phase II trials have demonstrated that targeted therapies, including everolimus, lenvatinib, and sunitinib, may induce durable disease control in patients with recurrent TETs as second-line treatment (58-60). However, there is no evidence supporting the concurrent use of systemic therapies and radiotherapy. Therefore, when administering PORT for recurrent TETs, pausing targeted therapy before and after PORT based on its half-life should be considered.

## Radiotherapy techniques

### *Photon beam radiotherapy*

Photon beam radiotherapy is commonly used in PORT. In this section, we outline the standard procedures and techniques for photon beam radiotherapy based on previous literature and guidelines (13,61,62). Three-dimensional conformal radiotherapy (3D-CRT) is conventionally used as a common delivery technique. Recently, intensity-modulated radiotherapy (IMRT), which enables the delivery of conformal radiation doses to irregularly shaped target volumes with high-precision fitted dose distribution, could be expected to decrease the dose delivered to organs at risk, sparing over 3D-CRT and has been applied to PORT (63).

Before initiating PORT, physicians should ensure the absence of infection or wound dehiscence. While there is no definitive maximum period from surgery to PORT, it has been reported that a delay of more than 3 months post-surgery often leads physicians to decide to skip PORT (14). Given that the respiratory motion of the upper mediastinum is typically minimal, respiratory-gated radiotherapy or breath-hold radiotherapy techniques to reduce motion are not mandatory.

Postoperative changes should be considered when delineating target volumes. As expert agreement for delineating postoperative cases is low compared with that of definitive cases, a contouring atlas for TETs with expert consensus is urgently needed (64). The utilization of four-dimensional-CT and positron emission tomography-CT fusion should be implemented for contour delineation, if available (64). It is also recommended to fuse preoperative CT with treatment-planning CT and deform preoperative CT to fit the treatment-planning CT. Gross tumor volume was defined as incomplete resection. In cases of complete resection, the clinical target volume (CTV) should encompass the tumor bed, surgical clips, and potential sites of residual disease. In cases of incomplete resection, the entire thymus should be included in the CTV. In instances where the margins are close or positive, surgical clips are useful for identifying the site of boost irradiation. The rates of lymphogenous metastasis in thymoma and thymic carcinoma are 1.8 and 27%, respectively (65). There was no significant difference in 5-year OS between local radiation therapy (targeting the tumor bed and anterior mediastinal areas only) and elective nodal irradiation (targeting the entire mediastinal and supraclavicular regions) in patients with TETs (65,66). Therefore, elective nodal irradiation is not recommended for TETs. The prescribed doses range from 45–50 Gy for negative or close margins, 54 Gy for microscopically positive resection margins, and 60–70 Gy for gross residual disease, administered in 1.8–2.0 Gy fractions.

As the dose constraints of organs at risk, normal tissue dose-volume constraints for conventionally fractionated radiotherapy for lung cancer could be applied to PORT in TETs; spinal cord max dose ≤50 Gy; lung $V_{20Gy}$ ≤35–40% ($V_{xGy}$: percentage of the volume receiving at least X Gy), mean dose ≤20 Gy; heart $V_{50Gy}$ ≤25%, mean dose ≤20 Gy; esophagus mean dose ≤34 Gy, $V_{60Gy}$ ≤17% (67).

### *Proton beam therapy*

A dosimetric comparison study has shown that both proton beam radiotherapy and carbon-ion radiotherapy excel in sparing organs at risk, such as the heart, lungs, left ventricle, esophagus, and spinal cord, and in improving target volume coverage when compared to photon IMRT (63,68-72). This is anticipated to reduce toxicity, potentially decreasing major cardiac events and the occurrence of secondary malignant neoplasms. Previous studies on proton beam radiotherapy for TETs are presented in *Table 5*. No toxicities more severe than grade 3 were observed following proton beam radiotherapy, and the OS and locoregional control rates were comparable with those achieved with photon beam radiotherapy. It should be noted that the sample sizes in these studies were small and included both PORT and definitive RT. Future clinical trials with larger cohorts and direct comparisons between proton and photon beam radiotherapies are essential.

## Toxicity

Common acute toxicities associated with PORT for TETs include fatigue, dermatitis, esophagitis, pneumonitis, and myelosuppression. Given the location of the anterior mediastinum, the severity of esophagitis is typically milder than in other intrathoracic tumors such as esophageal or lung cancers. Consequently, this study focused on detailing the more significant late toxicities that require special consideration, including pneumonitis, cardiotoxicities, and secondary malignancies.

### *Radiation pneumonitis*

Previous studies have reported that the irradiated dose to the normal lung is one of the common risk factors for

**Table 5** Literature on proton beam radiotherapy in TETs for PORT

| Authors | Year | N [N of PORT] | Primary | Prescribed dose, median (range) | Efficacy | Toxicity ≥ grade 3 |
|---|---|---|---|---|---|---|
| Vogel *et al.* (73) | 2016 | 27 [17] | TET | 61.2 CGE (50.4–70.0 CGE) | 3-year OS: 94%<br>3-year regional control: 96% | No |
| Parikh *et al.* (71) | 2016 | 4 [4] | Thymoma | 57.0 CGE (50.4–66.6 CGE) | No death and no recurrences occurred | No |
| Zhu *et al.* (70) | 2018 | 6 [5] | Thymoma | 60 GyE (54–70 GyE) | 3 patients experienced recurrences (0 local recurrence) | No |
| Mercado *et al.* (74) | 2019 | 30 [26] | TET | 54 GyE (45–70 GyE) | 5 patients experienced recurrence (1 local recurrence)<br>4 died (3 died of TETs) | No |

TET, thymic epithelial tumor; PORT, postoperative radiotherapy; CGE, cobalt-gray equivalent; OS, overall survival; GyE, gray equivalent.

developing radiation pneumonitis in patients with lung cancer: lung $V_{20Gy}$, mean lung dose, and absolute lung volume spared from a 5 Gy dose (75,76). In PORT for TETs, the irradiated dose to the normal lung is usually lower than that in definitive radiotherapy for lung cancer because the tumor bed is located in the mediastinum. The incidence of grade 2 or higher radiation pneumonitis in PORT for TETs is reported to be <10%, which is lower than that in definitive radiotherapy for lung cancer. Therefore, only a few studies have reported the risk factors for radiation pneumonitis in TETs. Moiseenko *et al.* quantified the influence of irradiated lung volume and dose on the lung response and showed that the mean lung dose was strongly correlated with lung complications, including pneumonitis and fibrosis (77). Tomita *et al.* reported that pulmonary artery $V_{35Gy}$ was significantly associated with radiation pneumonitis in patients with TET (78). In summary, efforts should be made to reduce the irradiation dose to the normal lung as much as possible during PORT for TETs, even though the risk of radiation pneumonitis is very low.

### *Radiation-induced cardiotoxicities*

The onset of radiation-induced cardiotoxicities occurs years or decades after PORT, and the typical symptoms are acute pericarditis, pericardial effusion, coronary artery disease, stenosis and regurgitation of valves, arrhythmia, and heart failure. Radiation-induced cardiotoxicities are a concern in long-term survivors of thoracic irradiation, such as patients with breast cancer or lymphoma. It is well known that after PORT in patients with breast cancer, the rates of major coronary events increase linearly with the mean dose to the heart by 7.4% per gray (79). Meanwhile, a SEER database analysis showed that radiotherapy does not increase the risk of cardiac mortality (12-year cumulative incidence or death, 10.2% radiation *vs.* 7.5% no radiation) in patients with thymoma (18). Given the prolonged survival of patients undergoing TETs, cardiotoxicity remains a critical concern following mediastinal irradiation via PORT. There is a pressing need for prospective studies that screen for cardiac event risks and consistently monitor radiation-induced cardiotoxicity.

### *Second malignancies*

Thymomas are associated with an increased risk of secondary malignancies. Patients face a higher risk of death from this second type of cancer than from recurrence (80). The lifetime attributable risk of secondary fatal cancer in patients receiving PORT (50 Gy in 25 fractions) for thymoma has been reported to be approximately 1–3% (81). Mou *et al.* reported that patients with thymoma who underwent surgery with PORT had a higher rate of secondary cancers than those who underwent surgery without PORT, based on the SEER database (32). In contrast, two studies concluded that radiotherapy did not increase the risk of secondary malignancy in patients with thymoma (18,82).

The incidence of secondary malignancies and deaths from secondary malignancies are lower in thymic carcinoma than in thymoma (83).

The association between TETs and secondary malignancies cannot be attributed solely to radiotherapy. Further investigations with long-term follow-ups and large

sample sizes are needed because of the rare incidence of TETs and secondary malignancies.

## Future indications

Radiotherapy has undergone significant advancements in recent decades. Research supporting the use of IMRT or particle therapy is ongoing, and accumulated data are expected to be published in the near future, contributing to the establishment of new evidence. Adopting these innovative radiotherapy techniques for TETs is expected to enhance patient outcomes (84). For definitive treatment or PORT, we have highlighted the radiotherapy techniques projected to be utilized for TETs in the coming years.

RADIORHYTHMIC, a phase III randomized study of PORT in stage IIB/III thymomas after complete surgical resection, was conducted by the RYTHMIC and is currently ongoing (85). Three hundred and fourteen patients will be randomized to either the PORT group (50–54 Gy to the mediastinum using IMRT or proton beam therapy) or the surveillance group. The results will be expected in 2028. Hemithoracic intensity-modulated pleural radiation therapy (IMPRINT) for malignant pleural mesothelioma has been developed as part of a multimodality treatment for patients receiving pleurectomy/decortication to spare the affected side of the lung (86). As recurrent TETs often develop pleural dissemination, IMPRINT can be applied to control pleural dissemination (53,87). SABR-COMET, a randomized phase II study aimed at determining the effect of stereotactic body radiotherapy (SBRT) in patients with a controlled primary tumor and 1–5 oligometastatic lesions, demonstrated that SBRT was associated with improved OS (88). Yano *et al.* reported 24 patients with recurrent thymoma, revealing that patients with a limited number of recurrent lesions had a better prognosis regardless of treatment (89). Based on these findings, SBRT may be an effective treatment option for patients with oligometastatic TETs. Adaptive radiotherapy, which aims to decrease the dose to normal tissues and allow for dose escalation to the target volume by changing the radiation treatment plan delivered to a patient during the course of radiotherapy to account for either temporal changes in anatomy (e.g., tumor size, internal motion, variations in respiratory patterns, weight loss) or changes in tumor biology/function (e.g., hypoxia) (90), is promising for application in TETs (91,92). Intraoperative radiotherapy has been used for intractable cancers such as pancreatic cancer and osteosarcoma (93,94). Cui *et al.* applied intraoperative radiotherapy (8–10 Gy) to TETs and reported its safety and efficacy in 14 patients with invasive thymomas as a less time-consuming and less invasive radiotherapy technique for improving locoregional control (95). The mean time for installation and operation of the radiation equipment 57.6 minutes (range, 48–72 minutes). During a median follow-up period of 41 months, no recurrence, death, or severe toxicity were observed.

As part of the multimodal treatment, surgical approaches, systemic therapy, and radiotherapy techniques are drastically evolving. Salfity *et al.* reported on minimally invasive surgery in managing resectable thymomas based on the NCDB and showed that PORT was less frequent in thoracoscopic thymectomies than in traditional open sternotomy (96). As the efficacy of PORT in different surgical approaches remains unknown, future investigations may reveal the different indications and irradiation fields for PORT depending on the surgical approach. Several studies have reported abscopal and bystander effects after radiotherapy in thymic carcinoma (97,98). A combination of immunotherapy and radiotherapy is expected to enhance these effects and improve patient outcomes. The abscopal effect was proposed in 1953, and it is hypothesized that the immune system plays a role in mediating this phenomenon, leading to therapeutic effects on lesions located outside the irradiated field (99,100). Currently, a clinical investigation on the abscopal effect of radiotherapy in combination with recombinant human granulocyte-macrophage colony-stimulating factor for advanced TETs is ongoing in China (ClinicalTrials.gov; NCT05407649).

Advancements in radiotherapy techniques combined with other novel surgical or systematic approaches can further improve the outcomes. Therefore, an optimal treatment strategy combined with PORT should be identified using prospective data.

## Conclusions

This narrative review presents a synthesis of the existing literature on the efficacy and toxicities of PORT in relation to OS. Considering the Masaoka-Koga staging, WHO histological subtypes, and resection status, indications for PORT have been determined for stage IIB–III TETs, although inconsistent results have been observed. Identifying patients who benefit from PORT for locoregional control can refine treatment strategies for TETs. Given that TETs typically result in long-term survival, late toxicities, such as radiation pneumonitis,

radiation-induced cardiac toxicities, and secondary malignancies, are significant. However, a decrease in these toxicities has been anticipated with the introduction of advanced radiotherapy techniques. Further studies are required to evaluate the value of PORT based on patient characteristics and combination therapy.

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