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Review

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The role of radiation therapy in the management of primary thymic epithelial neoplasms

Candice Johnstone[1], Charles B. Simone 2nd[2]

[1]Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI 53211, USA.
[2]Department of Radiation Oncology, New York Proton Center, New York, NY 10035, USA.

Correspondence to: Dr. Candice Johnstone, Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, WI 53211, USA. E-mail: cjohnstone@mcw.edu

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Abstract

Therapeutic radiation plays an important role in the management of thymoma and thymic carcinoma. These two tumor types differ substantially in their aggressiveness and prognosis. The most pressing issue in radiotherapy is which thymoma and thymic carcinoma patients need radiation. Given that these are rare cancers, few randomized trials have been published. Controversy remains regarding which patients benefit from adjuvant radiation therapy. Existing literature spans patients treated over nearly 50 years, during which time radiation therapy has evolved from rudimentary 2-dimensional based planning to conformal 3-dimensional planning to yet more conformal dose painting techniques such as intensity-modulated radiation therapy and proton therapy. If the effect of radiation is small and the natural history of a disease long, as is the case for stage I favorable histology thymoma, then differences in techniques and toxicities may have as much of an impact as whether radiation was given or not.

Keywords: Thymoma, thymic carcinoma, post-operative radiation therapy

INTRODUCTION

Therapeutic radiation plays an important role in the management of thymoma and thymic carcinoma. These two tumor types differ substantially in their aggressiveness and prognosis. Despite this, much of the existing literature investigating the use of radiation therapy in the management of these rare tumors

considers them together. To the extent that the literature separates the role of radiation in these related disease entities, it will be noted. The most pressing issues in radiotherapy are which thymoma and thymic carcinoma patients need radiation and the best technique to use to deliver radiotherapy.

Since thymoma and thymic carcinoma are rare diseases, there are few randomized trials completed to date assessing the value of any treatment modalities. Notably, however, a collaborative of French hospitals has launched RADIORYTHYMIC, a phase III randomized study investigating the role of post-operative radiation therapy in Masaoka-Koga stage IIB and III thymoma[1].

Until that data is available, controversy remains regarding which patients can benefit from adjuvant radiation therapy[2]. Currently, the existing retrospective data and population-based analyses divide radiation therapy into a dichotomous variable (yes/no). The patients included in the analyses span nearly 50 years, during which time radiation therapy has evolved from rudimentary 2-dimensional based planning to conformal 3-dimensional planning to yet more conformal dose painting techniques such as intensity-modulated radiation therapy (IMRT) and proton therapy. If the effect of radiation is small and the natural history of a disease long, as is the case for stage I favorable histology thymoma, then differences in techniques and toxicity may have as much of an impact as whether radiation was given or not.

For thymoma and thymic carcinoma, the target volume is either the post-operative tumor bed and high-risk surgical areas or the intact tumor itself. Given that thymomas and thymic carcinomas arise in the anterior mediastinum, the radiotherapy volume invariably includes critical organs at risk, such as the heart, great vessels, and lungs. In the era that was dominated by 2-dimensional radiation therapy, the fields also encompassed greater proportions of the spinal cord, trachea, and esophagus. Radiation doses to those critical organs can vary substantially depending on the technique used and the era in which radiation therapy was delivered.

LOCALIZED AND RESECTABLE THYMOMA AND THYMIC CARCINOMA

For all localized thymomas and thymic carcinomas, the standard of care is surgery. The ideal surgery is an extirpative surgery removing the entire thymus and tumor en bloc rather than removal of the tumor alone (thymomaectomy). Maximal debulking should be performed, and the high-risk areas should be marked with clips by the surgeon to serve as anatomical landmarks for the planning of adjuvant radiotherapy [Figure 1]. Ideally, negative macroscopic and microscopic margins are achieved (R0 resection). Given the rarity of thymomas, multidisciplinary coordination of care is essential, especially for patients with more advanced-stage diseases[3].

If a patient is initially unresectable, options for neoadjuvant chemotherapy or chemoradiation should be explored[4], although neoadjuvant radiation therapy is less frequently used. Surgery is performed if a patient becomes operable after induction chemotherapy; otherwise, treatment is definitive radiation therapy with or without chemotherapy. For unresectable thymic carcinomas, sequential chemotherapy followed by radiation or concurrent chemoradiation therapy are standard treatment approaches [Figure 2][5-8]. Medically inoperable patients are treated with a combination of radiation therapy and chemotherapy depending on their stage and medical comorbidities[9].

In the curative setting, there are three main scenarios for the use of radiation therapy: post-operative radiation therapy (PORT), definitive radiation therapy, and neoadjuvant radiation therapy. In the non-curative setting, radiation therapy can be used for palliation of symptoms or to treat oligoprogressive disease[10]. By far, the most common scenario is post-operative radiation therapy. Definitive radiation

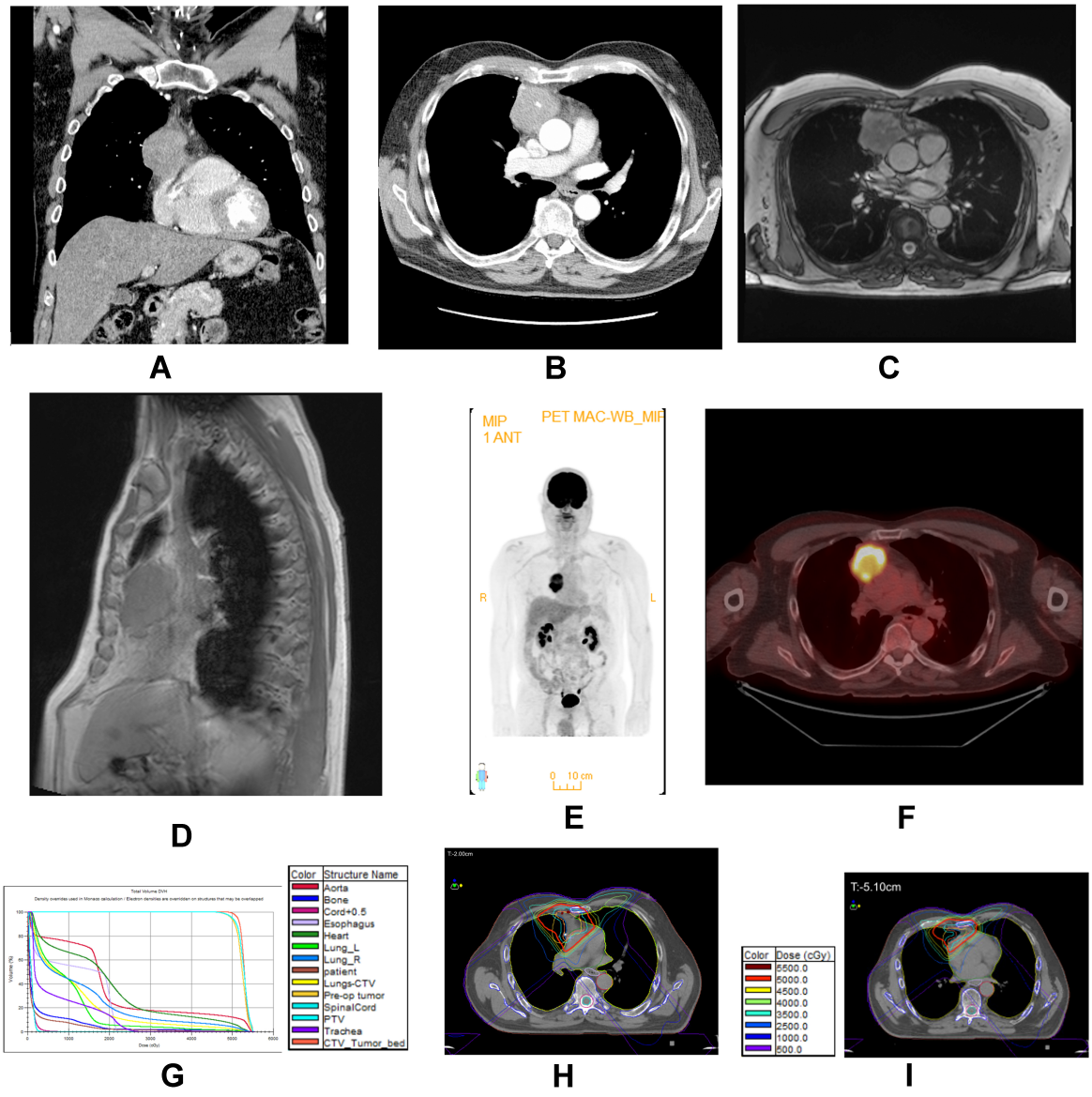


Figure 1. Depiction of the initial imaging: (A) Coronal CT image; (B) axial CT image; (C) axial MR image; (D) sagittal MR image; (E) PET-CT coronal image; (F) axial PET-CT image; (G) dose Volume Histogram and structure names for the 3D conformal RT plan; (H) dose distribution for the 3D plan axial image at the level of the pulmonary artery. One surgical clip is noted in this image; (I) dose distribution axial slice at the level of the atrium of the heart. (H and I) plan for a 75-year-old man with a stage III thymoma treated with PORT. He had an R0 resection (negative margins), then received 50 Gy in 25 fractions and is NED 2 years later.

therapy is reserved for medically inoperable patients and those patients who are unresectable despite neoadjuvant chemotherapy. A small minority of initially unresectable patients are treated with both chemotherapy and radiation therapy either sequentially or concurrently.

POST-OPERATIVE RADIATION THERAPY

Given the long natural history of thymomas with favorable 10-year survival rates, the most important question remains which patients with thymoma benefit from post-operative radiation therapy. Such a definitive answer remains unanswered and unanswerable with current data where known prognostic factors

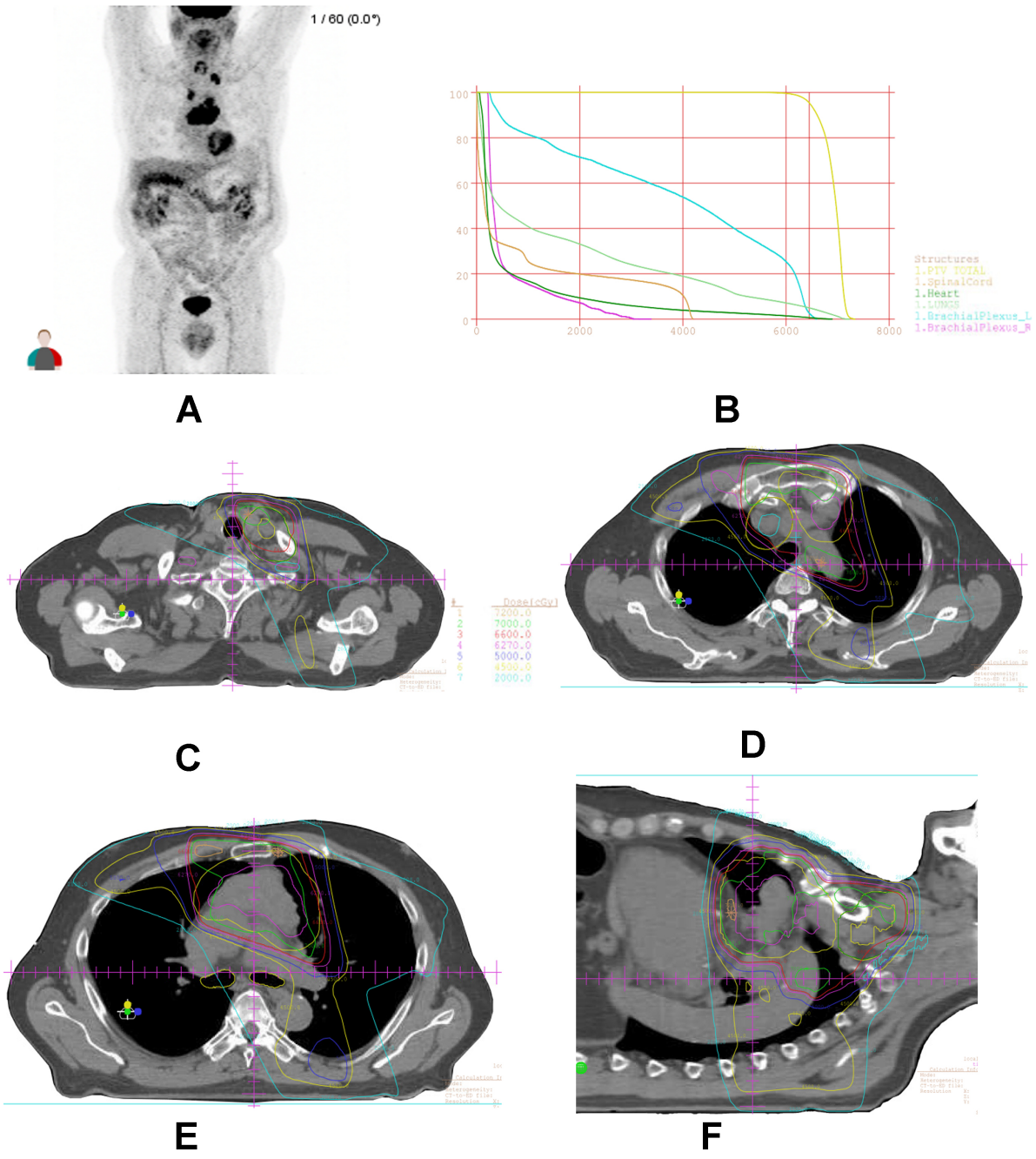


Figure 2. Patient who presented at age 74 with an unresectable thymic squamous cell carcinoma with disease in his left supraclavicular lymph nodes, his right level 2 and 4 lymph nodes and in the thymus [(A) PET-CT at diagnosis]. He was treated with definitive chemoradiation to a dose of 66 Gy in 33 fractions [(B) dose-volume histogram with structure set for D plan; (C) axial image of dose distribution at the level of the supraclavicular lymph nodes; (D) axial image of dose distribution at the level of the sternomanubrial joint; (E) axial image of dose distribution at the level of the pulmonary artery; (F) sagittal image of dose distribution] with weekly carboplatin and Taxol, followed by 2 additional cycles of carboplatin and Taxol.

such as WHO histologic subtype and margin status (RO *vs.* R1 *vs.* R2) are not always accounted for in the larger databases that span generations, and there are inherent limitations of large databases and retrospective analysis in a rare disease, as well as inherent biases in who is referred to receive adjuvant

radiotherapy in nonrandomized reports. Only one small underpowered randomized trial of 29 total patients with the very early-stage disease has been reported in the literature[11].

One retrospective analysis stands out from the rest, as the database and publication were developed by the International Thymic Malignancy Interest Group (ITMIG). ITMIG strives to coordinate the world's efforts in the investigation and treatment of thymic epithelial tumors. They have published standardized radiation therapy definitions and reporting guidelines as well as standardized outcome measures[12,13]. The use of these resources in the creation of databases and the collection of data could address many of the limitations in the currently available datasets. The analysis assessed patients with Masaoka stage II and III thymomas who underwent a complete R0 resection. Sixty-nine percent of patients had stage II disease, and seventy percent of tumors were WHO B1, B2, or B3. Fifty-five percent of patients received PORT. PORT was associated with improved 5- and 10- year overall survival (OS) whether the group was analyzed together or separated by stage (OS benefit $P = 0.021$ for stage II and $P = 0.0005$ for stage III), with 5-year OS 95% with PORT *vs.* 90% without and 10-year OS 86% with PORT *vs.* 79% without, $P = 0.002$[14].

In the last decade, there have been at least six analyses of the Surveillance, Epidemiology, and End Results (SEER) database[15-20]. SEER databases are limited in their ability to definitively answer the question of PORT in thymomas for many reasons. Most important among them are the fact that the stage is not clearly captured in the SEER database and must be inferred from other variables and the reason that PORT was chosen to be or not be administered is also not captured. Table 1 describes results from SEER analyses completed since 2010. These analyses provide conflicting data regarding which patients with thymoma and thymic carcinoma benefit from PORT.

Similar analyses have been performed using the American College of Surgeons National Cancer Data Base, shown in Table 2[21-23]. These databases have the advantage of capturing the first course of treatment, including chemotherapy, surgery, radiation, and more detailed pathologic characteristics including margin status. These studies show a benefit to PORT in various populations, but like the SEER analyses, they provide conflicting evidence on the benefits of PORT.

For completeness, Table 3 details the conclusions of systematic reviews and meta-analyses performed in the last 5 years[24-28]. These are of more limited help in answering which patients can benefit most from PORT given the heterogeneity of the data included, different populations, and conflicting results. One systematic review used the data collected to inform the formal expert consensus using a modified Delphi approach and is not included in the table[9]. Several larger multi-institutional databases have been compiled to determine the benefit of PORT [Table 4][14,29,30]. The patient populations in each study varied, and taken together, there is no clear consensus on the benefit of PORT. Similarly, several single institutional trials have demonstrated a benefit to PORT in sub-populations of thymoma patients [Table 5][31-35].

Taken together, several general themes emerge. Patients benefit from PORT with positive margins, more advanced stage, and more aggressive histologic subtypes, especially when multiple adverse features are present. These findings are seen in most, but not all, of the series.

NOMOGRAMS TO PREDICT RECURRENCE RISK AND BENEFIT OF POST-OPERATIVE RADIATION THERAPY

Given the heterogeneity of the existing data, two nomograms have been developed to aid decision making for the use of PORT. Neither is particularly easy to use, as both require the use of a specific chart with varying points assigned to different prognostic factors[36,37]. One from Korea incorporates age, sex, T stage, N

Table 1. Results of the benefit of PORT from analyses of the SEER database

	T/TC/TNET	Years	Stages	Number of patients	Effect of PORT
Weksler *et al.*[19]	T	NS	III	476	Improved disease-specific survival but not overall survival
Forquer *et al.*[15]	T/TC	1973-2005	NS	901	No benefit for stage I; possible benefit for stage II-III, especially if non-extirpative surgery
Patel *et al.*[18]	T	1973-2003	I-III	1254	Improves overall survival
Wen *et al.*[20]	TNET	1988-2015	I-IV	293	Improved overall survival for stage IIB-IV; Improved cause-specific survival for stage III-IV
Muslim *et al.*[17]	T	1988-2015	IB-IV	1,120	Stage III most likely to benefit
Lim *et al.*[16]	TC	2004-2013	I-IV	312	Improved overall survival

NS: Not stated; T: thymoma; TC: thymic carcinoma; TNET: thoracic neuroendocrine carcinoma; PORT: post-operative radiation therapy.

Table 2. Results of the benefit of PORT from analyses of the National Cancer Database (NCDB)

	T/TC	Years	Stages	Number of patients	Effect of PORT
Boothe *et al.*[21]	T/TC	2004-2012	I-IV	1156	Increased OS with WHO A, AB, and C
Jackson *et al.*[22]	T/TC	2004-2012	II-III	4056	Increased OS, especially for stage IIB-III and positive margins
Kim *et al.*[23]	TC	2004-2013	IIB-III	632	Increased OS for stage IIB with positive margins and for stage III

T: Thymoma; TC: thymic carcinoma; PORT: post-operative radiation therapy; OS: overall survival.

Table 3. Results of the benefit of PORT from systematic reviews and meta-analysis

	T/TC	Years	Stages	Number of patients/number of studies	Effect of PORT
Ma *et al.*[26]	T/TC	1984-2014	II-III	1280/19	No survival benefit in completely resected patients
Zhou *et al.*[28]	T	1996-2015	I-IV	3823/14	OS benefit only in stage II-III
Lim *et al.*[25]	T	2003-2014	II-IV	1724/7	OS benefit in stage III-IV
Tateishi *et al.*[27]	T	2009-2016	II-III	4746/5	OS benefit in stage II and III, no DFS benefit
Hamaji *et al.*[24]	TC	2012-2016	I-IV	973/7	OS benefit in all stages

T: Thymoma; TC: thymic carcinoma; OS: overall survival; PORT: post-operative radiation therapy; DFS: disease free survival.

Table 4. Results of the benefit of PORT from analyses of larger multi-center experiences

	T/TC/TNET	Years	Stages	Number of patients	Effect of PORT
Rimner *et al.*[14] ITMIG	T	1990-2012	II-III	1263	Increased OS in both stage II and stage III
Liu *et al.*[29] China	T/TC/TNET	1994-2012	I-III	1546	No benefit if complete resection; Improved OS and DFS with incomplete resection
Song *et al.*[30] Korea	T	2000-2013	II-III	404	Improved OS and DFS in stage III; No benefit in stage II

ITMIG: International thymic malignancy interest group; T: thymoma; TC: thymic carcinoma; TNET: thoracic neuroendocrine carcinoma; OS: overall survival; PORT: post-operative radiation therapy; DSS: disease specific survival; DFS: recurrence free survival.

stage, M stage, and histologic subtype. The second one, developed for thymic carcinomas, incorporates serum lactose dehydrogenase (LDH), dichotomous variables of complete resection and great vessel invasion, T stage (T1/2 *vs.* T3/4), Masaoka stage (I/II *vs.* III/IV), and histologic grade (Low/intermediate *vs.* high).

Table 5. Results of the benefit of PORT from analyses of single-institution experiences

	T/TC	Years	Stages	Number of patients	Effect of PORT
Bruni *et al.*[31]	T	1981-2015	I-IV	183	Improved DSS and OS in patients with positive margins
Tang *et al.*[33]	T/TC	1988-2017	pT3N0	607	Improved OS
Leuzzi *et al.*[32]	T	1990-2010	III	370	Improved OS with PORT +/- chemotherapy
Yan *et al.*[35]	T	1996-2013	II-III	88	No PFS or PS benefit in R0 resection; potential OS benefit for positive margins
Tseng *et al.*[34]	TC	2004-2014	I-IV	78	Improved PFS after R0 resection with PORT

T: Thymoma; TC: thymic carcinoma; OS: overall survival; PORT: post-operative radiation therapy; DSS: disease specific survival; PFS: progression free survival.

RECURRENCE PATTERNS

Recurrences after initial treatment have been described. In a study of 53 patients with Masaoka stage II-IV thymic carcinoma and thymic neuroendocrine carcinoma patients, 25 recurrences were noted[38]. Forty-four of these had initial R0 resections. The vast majority were in the pleura, out of the radiation field, followed by the lung parenchyma and lymph nodes. Radiation therapy for isolated pleural metastases has been described with limited toxicity and excellent local control and survival benefits. Higher radiation doses (50-52 Gy at 2 Gy per fraction) were correlated with better results[39,40]. Lower doses tended to be used with larger recurrences to respect normal tissue constraints. More recently, a report using stereotactic body radiation therapy (SBRT) to treat thymoma has been reported and was associated with excellent rates of local control [Figure 3][41]. Extrapolating from other diseases that originate or metastasize to the pleural, SBRT could be a promising emerging modality for managing pleural disease in thymic patients with oligoprogression[42].

GUIDELINES

Given the contradictory evidence presented above, several large medical societies have developed guidelines for the treatment of resectable thymoma [Table 6] and thymic carcinoma [Table 7] by stage[5-9]. Given the relatively recent introduction of the TNM staging, both Masaoka and AJCC staging are included in the tables[43].

RADIATION THERAPY SIMULATION AND PLANNING

Once it has been determined that a patient needs radiation therapy, a radiation simulation or planning session should be performed. Radiation should be started within 3 months of completion of surgery, although it can be later if a patient is receiving adjuvant chemotherapy. Clearance from the thoracic surgeon before starting adjuvant radiation therapy, especially if a patient has had a median sternotomy, is essential.

If possible, patients should be immobilized in the supine position with their arms above their head. This position allows for multiple beam angles or arc radiotherapy with the intent of achieving a highly conformal radiation treatment plan. Once the position is established, a CT scan should be performed. If needed, intravenous contrast can be used to accentuate vascular anatomy and identify the area of residual disease or better define gross disease in patients who undergo an R2 rection or are inoperable, respectively. Tumor motion or tumor bed (depending on treatment indication) should be assessed with a 4-dimensional CT scan. If that technology is not available or if a patient's breathing pattern is not reproducible, a slow helical CT or CT scan performed at end inspiration and end-expiration can determine target motion.

Table 6. Comparison of guideline recommendations for resectable thymoma. Columns list the guideline issuing organization. Abbreviations are explained below the table

Stage MK (TNM)	ESMO[6]	CCO[9]	GOECP-SEOR[8]	AIOM[5]	TYME[6]
I (T1a)	R0 - no PORT R1 - PORT	No PORT	R0 - none R1 - PORT	Consider for WHO B3 with ECE or massive ECE	R0 - none R1 - PORT
IIA (T1a)	R0 - no PORT for WHO A, AB, B1-2 PORT for WHO B3 R1 - PORT	No routine PORT; consider close margin, or WHO B	R0 - none for WBO A-B2, consider for WBO B3 R1 - PORT	PORT	R0 - none R1 - PORT
IIB (T1b)	R0 - no PORT for WHO A, AB, B1 PORT for WBO B2-3 R1 - PORT	PORT	R0 - PORT for WBO B2-B3 or pericardium+ R1 - PORT	PORT	R0, WHO A-B1 - no PORT R0, WHO B2-3 - PORT R1 - PORT
IIIA (T2, T3, T4)	PORT	Neoadjuvant RT *vs.* PORT	PORT	PORT	PORT
IIIB (T2, T3, T4)	PORT	Neoadjuvant RT *vs.* PORT	PORT	PORT	PORT
IVA (M1a)	PORT	Neoadjuvant RT *vs.* PORT	PORT	PORT for pN1 with R0 resection	PORT

ECE: Extracapsular extension; R0: complete macroscopic resection; negative margins; R1: microscopic residual disease pN1: IVB not included as typically unresectable; ESMO: European Society of Medical Oncology; GOECP/SEOR: Oncology Group for the Study of Lung Cancer/Spanish Society of Radiation Oncology; AIOM: Italian Association of Medical Oncology; TYME: Italian Collaborative Group for Thymic Malignancies; CCO: Cancer Care Ontario. A, AB, B1, B2, B3 refer to the WHO classification of thymomas.

Table 7. Comparison of guideline recommendations for resectable thymic carcinoma. Columns list the guideline issuing organization. Abbreviations are explained below the table

Stage MK (TNM)	ESMO	GOECP-SEOR[8]	AIOM[5]	TYME[6]
I (T1a)	PORT	R0 - no PORT R1/2 - PORT	Consider PORT	R0 - No PORT R1 - PORT
IIA (T1a)	PORT	R0 - consider PORT R1/2 - PORT	Consider PORT	R0 - No PORT R1 - PORT
IIB (T1b)	PORT	R0 - consider PORT R1/2 - PORT	PORT	PORT
IIIA (T2, T3, T4)	PORT	PORT	PORT	PORT
IIIB (T2, T3, T4)	PORT	PORT	PORT	PORT
IVA	PORT		PORT for pN1	PORT for N1-2 or R1-2 resection

ESMO: European Society of Medical Oncology; GOECP/SEOR: Oncology Group for the Study of Lung Cancer/Spanish Society of Radiation Oncology; AIOM: Italian Association of Medical Oncology; TYME: Italian Collaborative Group for Thymic Malignancies.

Once the CT simulation is complete, adjunct images may be fused to the treatment planning CT, such as 18-FDG PET-CT, diagnostic CT, and/or MR images. This is true whether patients are being simulated in the pre-operative, definitive, post-operative, or palliative settings. If a patient is treated in the pre-operative, definitive, or palliative setting, the gross disease should be contoured and labeled as the gross tumor volume (GTV). The clinical target volume (CTV) represents an expansion of the GTV to include microscopic extension of disease. In the post-operative setting, the CTV includes the pre-operative tumor volume, the tumor bed (including resected involved lymph node areas and pleural deposits if relevant), and any surgical clips. The internal target volume (ITV) encompasses the CTV and adds a margin derived from the motion analysis from the 4-D scan (or other methods). The planning target volume (PTV) adds a margin to account for set-up uncertainty. No benefit has been derived from elective nodal irradiation[44], and its use is not recommended.

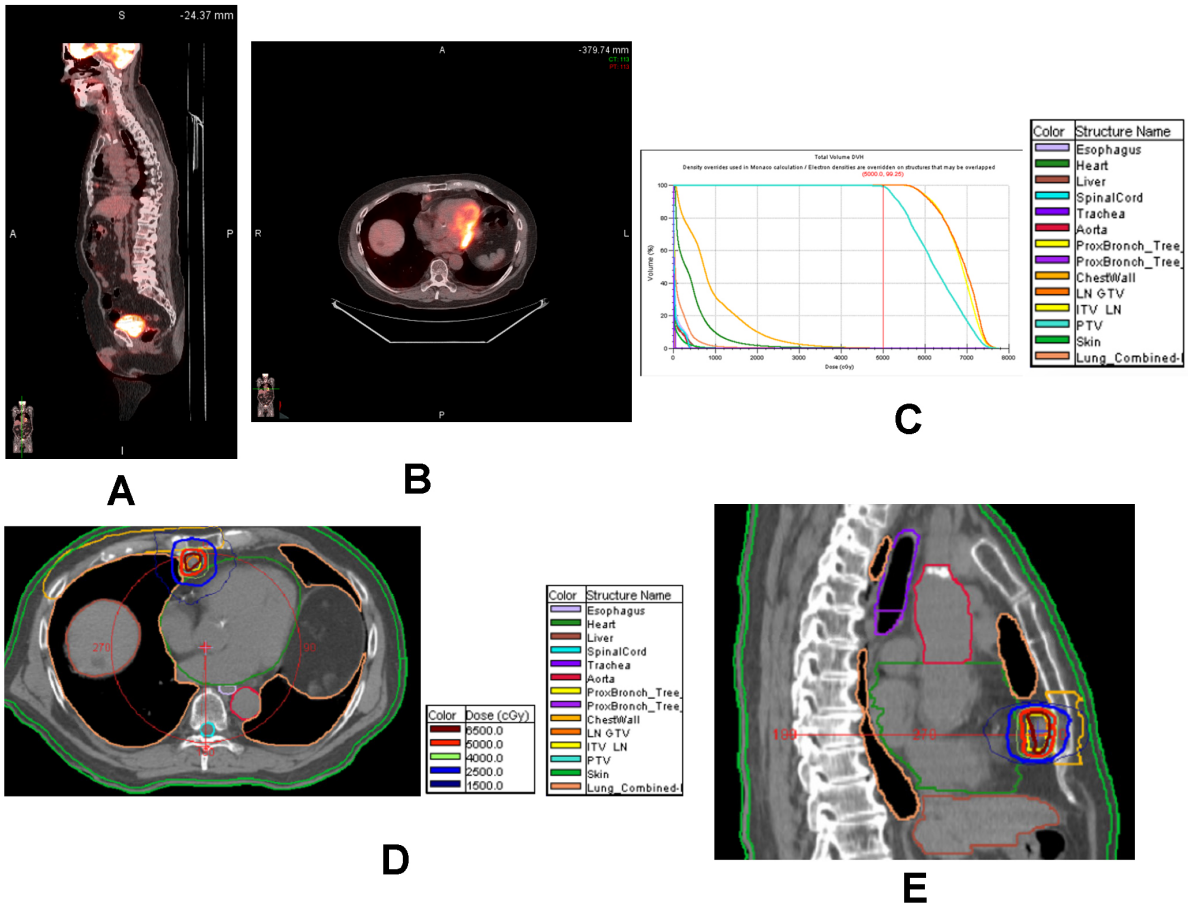
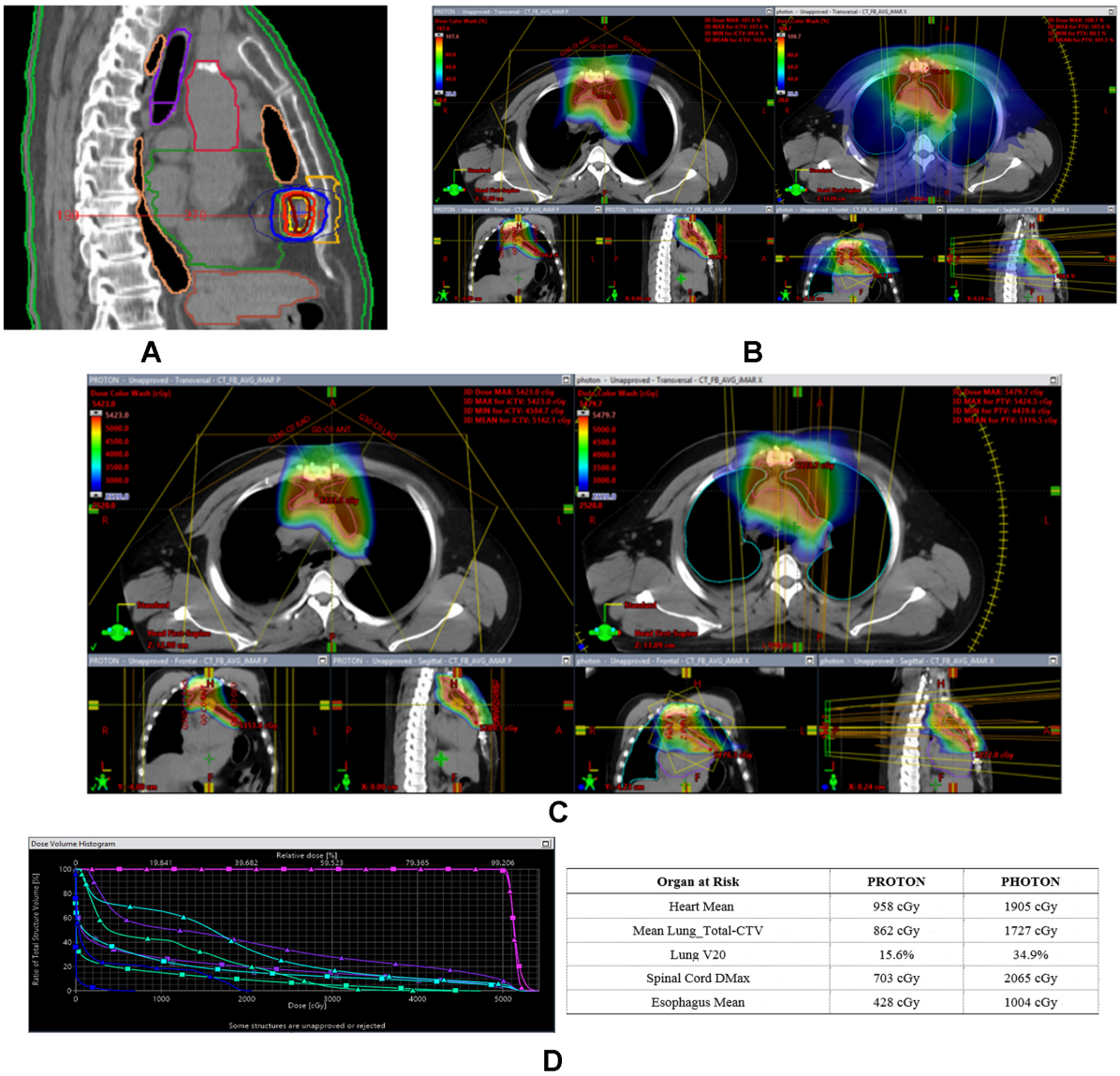


Figure 3. The patient in Figure 2 recurred with an isolated deposit anterior to the heart 1.5. years after initial therapy that was just outside of the previously irradiated field. This recurrence is depicted on PET/CT in (A) sagittal and (B) axial. He was treated with 50 Gy in 5 fractions using a stereotactic body radiation therapy approach in (C) dose-volume histogram; (D) dose distribution in the axial plane; and (E) dose distribution in the sagittal plane, and he remains disease-free 5 years after his initial presentation and 3.5 years after treatment of his recurrence.

Margins are added from one tumor volume to another depending on whether motion assessment has been performed and whether daily imaging will be performed. Typical margins range from 0.3 to 1.5 cm depending on the technology used and the volume being expanded.

Conformal planning techniques are considered standard and include 3-D conformal radiation therapy (3DCRT) and intensity-modulated radiation therapy (IMRT). IMRT is more conformal and more complicated than 3DCRT and requires rigorous quality assurance mechanisms for safe delivery. There is the potential for advanced technologies, such as proton therapy, especially when delivered with pencil beam scanning, to further improve the therapeutic ratio and reduce the risks of late radiation-induced cardiac events and secondary malignancies [Figure 4][45-51]. Careful motion management and daily image guidance should be employed when delivering advanced modalities like IMRT and proton therapy[52].

Given the rarity of thymomas and thymic carcinomas, no randomized radiation dose-finding studies have been performed. Generally accepted radiation doses vary by margin status and the presence of gross residual disease. In the curative setting, radiation is delivered 5 days per week, with fraction sizes of 1.8-2 Gy per day. For completely resected, macroscopic and macroscopic margin negative (R0) patients, adjuvant radiation



Organ at Risk	PROTON	PHOTON
Heart Mean	958 cGy	1905 cGy
Mean Lung_Total-CTV	862 cGy	1727 cGy
Lung V20	15.6%	34.9%
Spinal Cord DMax	703 cGy	2065 cGy
Esophagus Mean	428 cGy	1004 cGy

Figure 4. Advanced Radiotherapy Modality Comparison. IMRT and proton therapy plans for a 32-year-old with stage IIA thymoma, WHO type B2 s/p thymectomy showing an 11.2 cm tumor with close margins (< 1 mm) and invasion into the mediastinal fat treated with adjuvant radiation therapy to 50.4/1.8 Gy. Radiation dose distribution and beam arrangements for proton (left) and VMAT IMRT (right) comparison plans depicting dose above 20% of the prescription (A) and 50% of the prescription (B). Dose-volume histogram (C) and key organ at risk tabular summary (D) between proton and photon plans.

dose is 45-50.4 Gy. In patients with a microscopic positive margin (R1), the dose ranges from 50-54 Gy. In patients treated without surgery or with gross residual disease (R2), the dose ranges from 60-70 Gy. Typical dose constraints for critical organs at risk are enumerated in Table 8. Given that patients with thymomas have favorable long-term survival rates, keeping doses to critical structures as low as possible is essential.

Hemi-thoracic radiation for advanced thymoma or thymic carcinoma, or tumor spillage has been reported[53]. Pleural control rates would be expected to be higher with hemi-thoracic radiation, but this has not been shown to be statistically significant in the limited data employing its use to date. Overall survival and local control rates are no better than for those not receiving hemi-thoracic RT. Hemi-thoracic RT is associated with increased high-grade toxicity and is technically challenging, and it should only be

Table 8. Dose constraints for treatments of the upper mediastinum. adapted from Gomez *et al.*[12]

	RT alone	Chemo-RT	Pre-op Chemo-RT	Outcome
Spinal cord	D_{max} < 45 Gy	D_{max} < 45 Gy	D_{max} < 45 Gy	Transverse myelitis
Lung	Mean < 20 Gy	Mean < 20 Gy	Mean < 20 Gy	Symptomatic pneumonitis
	*V_{20} ≤ 40%	V_{20} ≤ 35%	V_{20} ≤ 30%	
		V_{10} ≤ 45%	V_{10} ≤ 40%	
		V_5 ≤ 65%	V_5 ≤ 55%	
Heart/pericardium	Mean < 26	Mean < 26	Mean < 26	Pericarditis Cardiac mortality
	V_{30} ≤ 45%	V_{30} ≤ 45%	V_{30} ≤ 45%	
Esophagus	Mean < 34	Mean < 34	Mean < 34	Acute esophagitis, perforation and stricture
	D_{max} ≤ 80	D_{max} ≤ 80	D_{max} ≤ 80	
	V_{70} < 20%	V_{70} < 20%	V_{70} < 20%	
	V_{50} < 50%	V_{50} < 40%	V_{50} < 40%	

*$V_{(dose)}$ < percentage represents the percentage of an organ that should receive no more than the specified dose. For example, a V20 < 40% means that no more than 40% of that organ should receive 20 Gy. D_{max} represents the maximal dose. Doses to critical organs should be as low as achievable and certainly below organ tolerance. RT: radiation therapy; chemo: chemotherapy; Pre-op: before surgery. Additional dose constraints can be found in the reference.

considered in very limited scenarios for well-select patients and in centers with experience using this technique.

CONCLUSION

Radiation therapy can be used to treat thymic epithelial cancers in the pre-operative, definitive, and post-operative settings. By far, the most common indication for radiation therapy is in the post-operative setting (PORT). There are limited randomized data to date guiding decision making and radiation recommendations. Several themes emerge from the review of the existing literature. First, it is likely that radiation therapy is most beneficial in terms of improved overall survival for patients with positive margins after surgery, more advanced stage, and more aggressive histologic subtypes. Second, advances in radiation therapy delivery may make the benefit of PORT more dramatic, as techniques like 3D-conformal radiation therapy, IMRT, and proton therapy delivered with motion management and daily image guidance can be associated with less long-term morbidity and mortality, thus improving the therapeutic ratio of radiotherapy delivery. Third, it is clear that multidisciplinary management should be employed for all patients with thymic neoplasms, and that further studies on the optimal multi-modality approach to these rare tumors are warranted.

DECLARATIONS

Authors' contributions

Did the literature review and created the data tables: Johnstone C

Contributed to the writing and editing of the manuscript, and contributed figures and images: Johnstone C, Simone CB 2nd

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Conflicts of interest

All authors declare that there are no financial conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

No identifiable information is used in the images.

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REFERENCES

1. Basse C, Botticella A, Molina TJ, et al. Radiorythmic: phase III, opened, randomized study of postoperative radiotherapy versus surveillance in stage IIb/III of masaoka koga thymoma after complete surgical resection. *Clin Lung Cancer* 2021;22:469-72. DOI PubMed
2. Shepherd A, Riely G, Detterbeck F, et al. Thymic carcinoma management patterns among international thymic malignancy interest group (ITMIG) physicians with consensus from the thymic carcinoma working group. *J Thorac Oncol* 2017;12:745-51. DOI PubMed PMC
3. Basse C, Thureau S, Bota S, et al. Multidisciplinary tumor board decision making for postoperative radiotherapy in thymic epithelial tumors: insights from the rythmic prospective cohort. *J Thorac Oncol* 2017;12:1715-22. DOI PubMed
4. Kao TN, Yang PW, Lin MW, Lee JM. Induction therapy followed by surgery for advanced thymic tumors. *Asian J Surg* 2020;43:707-8. DOI PubMed
5. Conforti F, Marino M, Vitolo V, et al. Clinical management of patients with thymic epithelial tumors: the recommendations endorsed by the Italian Association of Medical Oncology (AIOM). *ESMO Open* 2021;6:100188. DOI PubMed PMC
6. Girard N, Ruffini E, Marx A, Faivre-Finn C, Peters S; ESMO guidelines committee. thymic epithelial tumours: esmo clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015;26 Suppl 5:v40-55. DOI PubMed
7. Imbimbo M, Ottaviano M, Vitali M, et al. Best practices for the management of thymic epithelial tumors: a position paper by the Italian collaborative group for ThYmic MalignanciEs (TYME). *Cancer Treat Rev* 2018;71:76-87. DOI PubMed
8. Rico M, Flamarique S, Casares C, et al. GOECP/SEOR radiotherapy guidelines for thymic epithelial tumours. *World J Clin Oncol* 2021;12:195-216. DOI PubMed PMC
9. Falkson CB, Bezjak A, Darling G, et al. The management of thymoma: a systematic review and practice guideline. *J Thorac Oncol* 2009;4:911-9. DOI PubMed
10. Kumar N, Kumar R, Bera A, et al. Thymoma: clinical experience from a tertiary care institute from North India. *J Cancer Res Ther* 2013;9:235-9. DOI PubMed
11. 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;112:136-8. PubMed
12. Gomez D, Komaki R, Yu J, Ikushima H, Bezjak A. Radiation therapy definitions and reporting guidelines for thymic malignancies. *J Thorac Oncol* 2011;6:S1743-8. DOI PubMed
13. Huang J, Detterbeck FC, Wang Z, Loehrer PJ Sr. Standard outcome measures for thymic malignancies. *J Thorac Oncol* 2010;5:2017-23. DOI PubMed
14. Rimner A, Yao X, Huang J, 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;11:1785-92. DOI PubMed PMC
15. Forquer JA, Rong N, Fakiris AJ, Loehrer PJ Sr, Johnstone PA. Postoperative radiotherapy after surgical resection of thymoma: differing roles in localized and regional disease. *Int J Radiat Oncol Biol Phys* 2010;76:440-5. DOI PubMed
16. 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. DOI PubMed
17. Muslim Z, Baig MZ, Weber JF, et al. Invasive thymoma - which patients benefit from post-operative radiotherapy? *Asian Cardiovasc Thorac Ann* 2021;29:935-42. DOI PubMed
18. Patel S, Macdonald OK, Nagda S, Bittner N, Suntharalingam M. Evaluation of the role of radiation therapy in the management of malignant thymoma. *Int J Radiat Oncol Biol Phys* 2012;82:1797-801. DOI PubMed
19. 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;93:1822-8; discussion 1828. DOI PubMed
20. Wen J, Chen J, Chen D, 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;9:1603-13. DOI PubMed

PMC

21. 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;11:2218-26. DOI PubMed
22. Jackson MW, Palma DA, Camidge DR, et al. The impact of postoperative radiotherapy for thymoma and thymic carcinoma. *J Thorac Oncol* 2017;12:734-44. DOI PubMed
23. 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* 2020;109:1095-103. DOI PubMed
24. 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;103:1668-75. DOI PubMed
25. Lim YJ, Kim E, Kim HJ, 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;94:1129-36. DOI PubMed
26. Ma J, Sun X, Huang L, et al. Postoperative radiotherapy and tumor recurrence after complete resection of stage II/III thymic tumor: a meta-analysis of cohort studies. *Onco Targets Ther* 2016;9:4517-26. DOI PubMed PMC
27. Tateishi Y, Horita N, Namkoong H, Enomoto T, Takeda A, Kaneko T. Postoperative radiotherapy for completely resected masaoka/masaoka-koga stage II/III thymoma improves overall survival: an updated meta-analysis of 4746 patients. *J Thorac Oncol* 2021;16:677-85. DOI PubMed
28. Zhou D, Deng XF, Liu QX, Zheng H, Min JX, Dai JG. The effectiveness of postoperative radiotherapy in patients with completely resected thymoma: a meta-analysis. *Ann Thorac Surg* 2016;101:305-10. DOI PubMed
29. Liu Q, Gu Z, Yang F, et al. The role of postoperative radiotherapy for stage I/II/III thymic tumor-results of the ChART retrospective database. *J Thorac Dis* 2016;8:687-95. DOI
30. Song SH, Suh JW, Yu WS, et al. The role of postoperative radiotherapy in stage II and III thymoma: a Korean multicenter database study. *J Thorac Dis* 2020;12:6680-9. DOI PubMed PMC
31. Bruni A, Stefani A, Perna M, 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;12:7518-30. DOI PubMed PMC
32. Leuzzi G, Rocco G, Ruffini E, 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;151:47-57.e1. DOI PubMed
33. Tang EK, Chang JM, Chang CC, et al. Prognostic factor of completely resected and pathologic T3 N0 M0 thymic epithelial tumor. *Ann Thorac Surg* 2021;111:1164-73. DOI PubMed
34. Tseng YH, Lin YH, Tseng YC, et al. Adjuvant therapy for thymic carcinoma-a decade of experience in a taiwan national teaching hospital. *PLoS One* 2016;11:e0146609. DOI PubMed PMC
35. Yan J, Liu Q, Moseley JN, et al. Adjuvant radiotherapy for stages II and III resected thymoma: a single-institutional experience. *Am J Clin Oncol* 2016;39:223-7. DOI PubMed PMC
36. 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;106:257-63. DOI PubMed
37. Yun JK, Lee GD, Kim HR, et al. A nomogram for predicting recurrence after complete resection for thymic epithelial tumors based on the TNM classification: a multi-institutional retrospective analysis. *J Surg Oncol* 2019;119:1161-9. DOI PubMed
38. Lee KH, Noh JM, Ahn YC, 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;102:1505-13. DOI PubMed
39. Wang CL, Gao LT, Lyu CX, et al. Intensity modulated radiation therapy for pleural recurrence of thymoma: a prospective phase 2 study. *Int J Radiat Oncol Biol Phys* 2021;109:775-82. DOI PubMed
40. Yang AJ, Choi SH, Byun HK, Kim HJ, Lee CG, Cho J. The role of salvage radiotherapy in recurrent thymoma. *Radiat Oncol J* 2019;37:193-200. DOI PubMed PMC
41. Hao XJ, Peng B, Zhou Z, Yang XQ. Prospective study of stereotactic body radiation therapy for thymoma and thymic carcinoma: therapeutic effect and toxicity assessment. *Sci Rep* 2017;7:13549. DOI PubMed PMC
42. Barsky AR, Yegya-Raman N, Katz SI, Simone CB 2nd, Cengel KA. Managing oligoprogressive malignant pleural mesothelioma with stereotactic body radiation therapy. *Lung Cancer* 2021;157:163-4. DOI PubMed
43. Kashima J, Okuma Y. New histological classification and staging of thymic malignancies: ITMIG consensus statements and the 8th TNM staging system. *J Thorac Dis* 2017;9:3656-8. DOI PubMed PMC
44. Kim YJ, Kim SS, Song SY, et al. Elective nodal irradiation as adjuvant radiotherapy for advanced thymomas and thymic carcinomas. *Clin Lung Cancer* 2019;20:e91-6. DOI PubMed
45. Chevli N, Bland RE, Farach AM, et al. Adaptive radiation therapy for intact thymoma: an illustrative report. *Anticancer Res* 2021;41:2467-71. DOI PubMed
46. Gomez D, Komaki R. Technical advances of radiation therapy for thymic malignancies. *J Thorac Oncol* 2010;5:S336-43. DOI PubMed
47. Mercado CE, Hartsell WF, Simone CB 2nd, et al. Proton therapy for thymic malignancies: multi-institutional patterns-of-care and early clinical outcomes from the proton collaborative group and the university of Florida prospective registries. *Acta Oncol* 2019;58:1036-40. DOI PubMed
48. Vogel J, Berman AT, Lin L, et al. Prospective study of proton beam radiation therapy for adjuvant and definitive treatment of thymoma and thymic carcinoma: early response and toxicity assessment. *Radiother Oncol* 2016;118:504-9. DOI PubMed

49. Vogel J, Lin L, Litzky LA, Berman AT, Simone CB 2nd. Predicted rate of secondary malignancies following adjuvant proton versus photon radiation therapy for thymoma. *Int J Radiat Oncol Biol Phys* 2017;99:427-33. DOI PubMed
50. Vogel J, Lin L, Simone CB 2nd, Berman AT. Risk of major cardiac events following adjuvant proton versus photon radiation therapy for patients with thymic malignancies. *Acta Oncol* 2017;56:1060-4. DOI PubMed
51. Haefner MF, Verma V, Bougatf N, et al. Dosimetric comparison of advanced radiotherapy approaches using photon techniques and particle therapy in the postoperative management of thymoma. *Acta Oncol* 2018;57:1713-20. DOI PubMed
52. Molitoris JK, Diwanji T, Snider JW 3rd, et al. Advances in the use of motion management and image guidance in radiation therapy treatment for lung cancer. *J Thorac Dis* 2018;10:S2437-50. DOI PubMed PMC
53. Schild SE. Defining the role of hemithorax irradiation for thymomas is difficult. *J Thorac Oncol* 2008;3:1-2. DOI PubMed