

The Role of Radiation Therapy in Malignant Thymoma

A Surveillance, Epidemiology, and End Results Database Analysis

Annemarie T. Fernandes, BA,* Eric T. Shinohara, MD,* Mengye Guo, PhD,† Nandita Mitra, PhD,*
Lynn D. Wilson, MD, MPH,‡ Ramesh Rengan, MD, PhD,* and James M. Metz, MD*

Introduction: The potential benefits and long-term complications of radiotherapy treatment for malignant thymoma are unclear. This is a retrospective analysis of outcome in patients with malignant thymoma from the Surveillance, Epidemiology, and End Results database between 1973 and 2005.

Methods: Of the 1987 patients identified, 1334 were analyzed. Patients were categorized according to the Masaoka staging system as stage I to IIA, IIB or III to IV. The primary end points were overall survival, cardiac mortality, and the development of secondary malignancies.

Results: Patients received surgery and radiation (50%), surgery alone (26%), radiation alone (12%), or no treatment (12%). The median follow-up time for survivors was 65 months (range, 1–361 months). There was no significant increase in the 12-year cumulative incidence rate of death from heart disease (10.2% radiation versus 7.5% no radiation, $p = 0.83$) or incidence of secondary malignancies (11.7% versus 12.4%, $p = 0.70$) with radiation. Compared with surgery alone, adjuvant radiation significantly improved overall survival in patients with stage III to IV disease ($p = 0.04$) and demonstrated a nonsignificant trend in patients with stage IIB disease ($p = 0.09$). However, after excluding patients surviving less than 4 months to account for surgical mortality, the benefit with radiation was no longer significant (stage IIB: $p = 0.45$, stage III–IV: $p = 0.44$).

Conclusions: Radiation does not seem to increase the risk of cardiac mortality or secondary malignancy in patients with malignant thymoma. Although the routine use of postoperative radiotherapy in malignant thymoma does not appear warranted, high-risk patients may benefit from adjuvant radiation. This study can help to design prospective trials to further establish the role of radiotherapy in malignant thymoma.

Key Words: Thymoma, Radiation, Secondary malignancy, Cardiac toxicity.

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Although thymic tumors are the most common tumors of the anterior mediastinum, they are relatively rare with a reported incidence of 0.15 per 100,000 person-years.¹ These tumors are characterized as indolent with a lymphogenous metastasis rate of 1.8% and an even rarer hematogenous metastasis rate.² Surgical resection is considered the mainstay of treatment for malignant thymoma, and the extent of surgical resection is an important prognostic factor.³ The role of radiation therapy, however, is unclear.

The controversy regarding the use of radiation in malignant thymoma stems from the paucity of data on the topic. Given the low incidence of malignant thymoma and the excellent response to complete surgical resection, the use of radiation therapy remains suboptimally defined. Prior studies have suggested that Masaoka stage I tumors are adequately controlled after complete surgical resection, whereas stage III and IV thymomas have more of an apparent benefit from adjuvant radiation therapy.^{3–6} Data regarding the use of postoperative radiation in patients with stage II thymoma are less clear.⁷

Given the proximity of the thymus to vital mediastinal structures, there is a risk of radiation-induced cardiotoxicity in patients who receive radiation therapy for malignant thymoma. The risk of cardiotoxicity has been well documented in patients receiving thoracic irradiation for Hodgkin disease and tangential fields for breast cancer. In addition to cardiac morbidity, radiation therapy has been associated with the development of secondary malignancies.^{8–14} The development of leukemias, lymphomas, thyroid carcinomas, breast carcinomas, and sarcomas is of particular concern in patients with radiation exposure. Cardiac toxicity and the development of secondary malignancies are considered long-term complications of radiation therapy. Because patients with malignant thymoma have favorable prognoses, the long-term implications of treatment need to be evaluated.

This study was designed to examine the role of radiation in the treatment of malignant thymoma in a large group of patients from the Surveillance, Epidemiology, and End Results (SEER) database. The clinical outcomes as well as

*University of Pennsylvania, Philadelphia, Pennsylvania; †Dana Farber Cancer Institute, Boston, Massachusetts; and ‡Yale University School of Medicine, New Haven, Connecticut.

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Address for correspondence: Annemarie T. Fernandes, BA, University of Pennsylvania, 2 Donner, 3400 Spruce Street, Philadelphia, PA 19104.
E-mail: Annemarie.fernandes@gmail.com

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the long-term morbidity and mortality from radiation treatment are considered.

PATIENTS AND METHODS

This is a retrospective review of data from the National Cancer Institute's SEER program. Patients from 1973 to 2005 provided by 17 registries (San Francisco-Oakland, Connecticut, metropolitan Detroit, metropolitan Atlanta, Hawaii, Iowa, New Mexico, Seattle, Utah, San Jose-Monterey, Los Angeles, Alaska Natives, Rural Georgia, California excluding San Francisco/San Jose-Monterey/Los Angeles, Kentucky, Louisiana, and New Jersey) were identified.

Malignant thymoma cases were identified by histology (thymus = 8580), primary site (thymus = 379), and International Classification for Childhood Cancer site recode extended ICD-0-3 (XI [f.5] carcinomas of thymus). SEER only collects data on "malignant" thymomas.¹ Thymomas can be classified as "malignant" or "benign" based on evidence for capsular invasion. All cases reported to SEER after January 1, 2001, were coded for "ICD-0-3 histology and behavior" to identify tumors by the World Health Organization (WHO) histology classification system. Before January 1, 2001, however, thymic carcinoma cases (WHO histology type C) were unable to be distinguished from malignant thymoma cases and were therefore unable to be excluded from analysis. Data on WHO histology were unavailable for more than 78% of patients. Patients younger than 18 years, patients with missing surgery or radiation data, and patients with distinguishable thymic carcinoma histology were excluded from analysis. Patients diagnosed in 2004 or 2005 were also excluded to ensure an adequate follow-up time. Information about patient demographics and tumor factors that could be associated with overall survival (OS) was collected (age at diagnosis, sex, race, marital status, SEER registry, and year of diagnosis). The SEER database does not report chemotherapy use or margin status.

Patients were staged according to the Masaoka staging system for malignant thymoma. Patients were categorized into three groups: I to IIA ("Invasive carcinoma confined to gland of origin" or "Localized, NOS"), IIB ("Adjacent connective tissue"), or III to IV ("Adjacent organs/structures in mediastinum," "further contiguous extension," or "metastasis"). Because the SEER database does not code for microscopic capsular invasion, stage IIA patients were unable to be distinguished from stage I patients. The category, "Adjacent organs/structure in the mediastinum" probably included patients with pericardial or pleural dissemination. Therefore, stage III patients were unable to be distinguished from stage IV patients.

Patients were also divided into four groups according to treatment: (1) surgery and radiation, (2) surgery alone, (3) radiation alone, and (4) no treatment. Patients treated with all types of surgery were included in the analysis. However, patients coded as "Incisional, needle, or aspiration biopsy," "exploratory only," or "surgery of regional and/or distant sites/nodes only" were not considered to have undergone a surgical resection. Radiation treatment consisted of "Beam Radiation" or "Radiation, NOS." The majority of patients

received radiation treatment after surgery; however, 36 patients received preoperative radiation and 6 patients received radiation before and after surgery. The primary end points were OS, cardiac mortality (cause of death, "COD to site recode" = "Disease of the Heart"), and the development of secondary malignancies. An additional OS analysis excluding patients surviving less than 4 months was performed to account for possible bias that would favor the adjuvant radiation group.^{15,16}

Statistical Analysis

Associations between the type of treatment and clinical factors, demographic factors, and secondary malignancy development were assessed using the χ^2 test, analysis of variance, and the Kruskal-Wallis test. Survival time was calculated as the number of months from the malignant thymoma diagnosis date to the SEER date of death. Survival was censored as of the last month when patients were known to be alive. OS was investigated using survival curves generated by the Kaplan-Meier approach and log-rank tests. Cox proportional hazards models were used to analyze the association of treatment type and covariates. Cardiac mortality was determined using the χ^2 test and cumulative incidence rate of death.

All statistical analyses were carried out using SAS version 9.1 (SAS Institute, Cary, NC), STATA/IC (Version 10.0 for Windows, College Station, TX), or R version 1.1.1 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Patient Characteristics

From 1973 to 2005, a total of 1986 patients with malignant thymoma were identified. There were 167 patients with thymic carcinoma histology, 14 patients younger than 18 years, 212 patients with missing surgery or radiation data, and 331 patients diagnosed in 2004 or 2005. Seventy-two patients met multiple exclusion criteria. After applying the exclusion criteria, a total of 1334 patients were available for analysis. The median follow-up time was 52 months (range, 0–361 months) for all patients and 65 months (range, 1–361 months) for survivors.

The median age of the patient population was 58 years (range, 18–94 years), 53% were male, 69% were Caucasian, and 65.2% were married. Among the four treatment groups, there was a significant difference in age, stage, and year of diagnosis ($p < 0.001$, Table 1) but no significant difference in sex ($p = 0.70$), race ($p = 0.21$), marital status ($p = 0.15$), or WHO histology ($p = 0.82$).

Analysis of OS

Figure 1 and Table 2 demonstrate OS rates for patients with malignant thymoma by treatment group and stage. At each stage, patients had improved OS with surgery and radiation or surgery alone compared with radiation alone or no treatment ($p < 0.001$). Compared with surgery alone, adjuvant radiation did not improve OS in patients with stage I to IIA disease ($p = 0.43$) but did significantly improve OS in patients with stage III to IV disease ($p = 0.04$). There was a nonsignificant trend toward improved OS in stage IIB

TABLE 1. Characteristics of Study Patients

Variable (N)	Surgery and Radiation (N = 669, 50.2%)	Surgery Alone (N = 346, 25.9%)	Radiation Alone (N = 155, 11.6%)	No Treatment (N = 164, 12.3%)	p
Median age, yrs (SD)	55 (14.1)	60 (16.5)	64 (16.4)	64.5 (16.7)	<0.001
Stage					
I–IIA (278)	138 (49.6%)	114 (41.0%)	12 (4.3%)	14 (5.0%)	
IIB (245)	166 (67.8%)	62 (25.3%)	8 (3.3%)	9 (3.7%)	
III–IV (682)	342 (50.2%)	129 (18.9%)	107 (15.7%)	104 (15.3%)	<0.001
Year of diagnosis					
1973–1983 (158)	102 (64.6%)	49 (31.0%)	0 (0%)	7 (4.4%)	
1984–1993 (320)	155 (48.4%)	82 (25.6%)	44 (13.8%)	39 (12.2%)	
1994–2003 (856)	412 (48.1%)	215 (25.1%)	111 (13.0%)	118 (13.8%)	<0.001

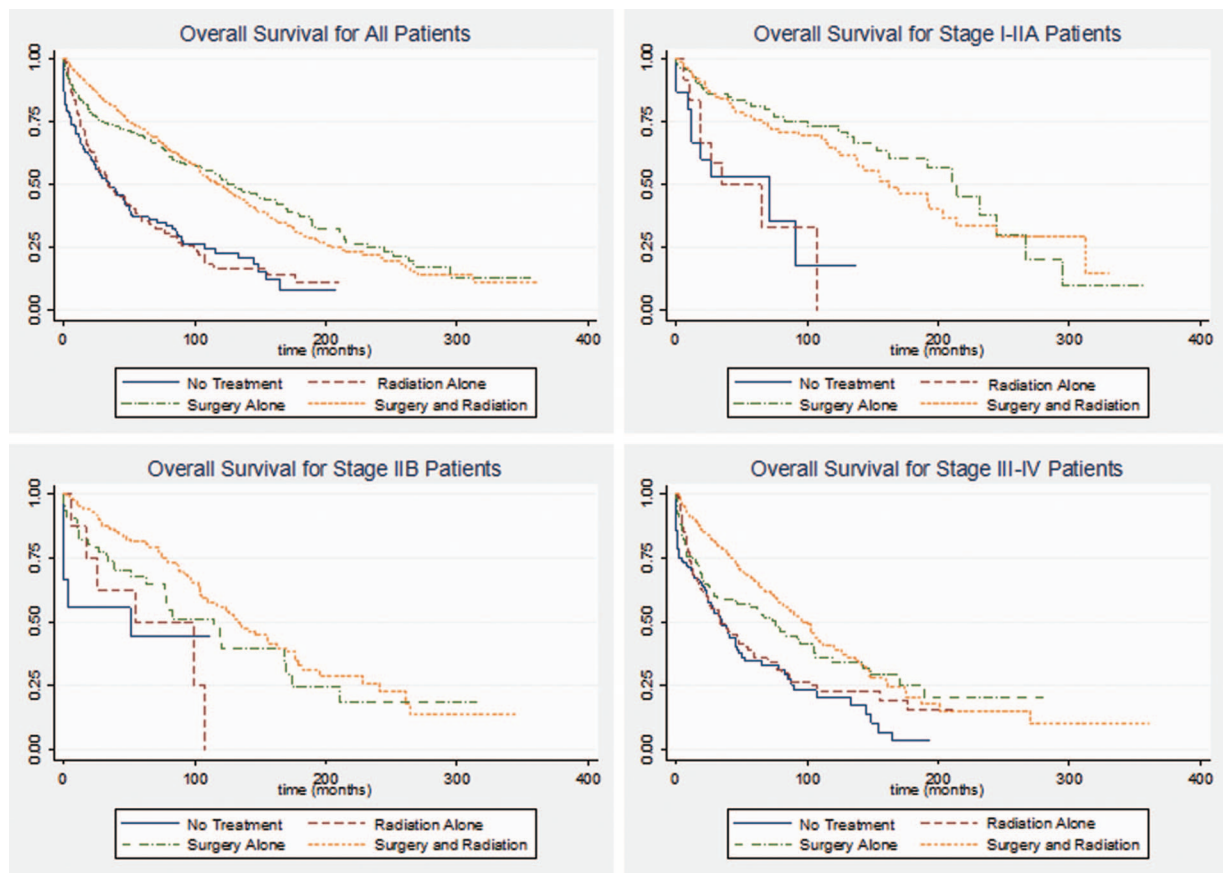


FIGURE 1. Kaplan-Meier curves of overall survival for the four treatment groups by stage.

TABLE 2. Median Overall Survival by Stage, in Months (95% CI)

	Surgery and Radiation	Surgery Alone	Radiation Alone	No Treatment
All patients	117 (104–133)	130 (105–162)	34 (26–48)	35 (24–48)
Stage I–IIA	163 (138–214)	214 (153–267)	50 (10–108)	71 (p = 0.76) ^a
Stage IIB	134 (110–162)	115 (77–170)	77 (6–108)	51 (p = 0.95) ^a
Stage III–IV	97 (82–107)	76 (43–105)	34 (23–53)	35 (24–46)

^ap value computed from log-rank test comparing no treatment vs. radiation alone.
CI, confidence interval.

patients treated with adjuvant radiation ($p = 0.09$). Radiation alone did not improve OS at any stage when compared with no treatment.

To control for surgical deaths and patients with significant morbidity, we excluded 75 patients surviving less than 4 months and performed the analysis for OS. The 4-month mortality among patients treated with surgery alone was 3.5% (4 of 114), 9.7% (6 of 62), and 11.6% (15 of 129) for stage I to IIA, IIB, and III to IV, respectively. The mortality among patients treated with surgery and radiation was 1.4% (2 of 138), 0.6% (1 of 166), and 2.0% (7 of 342) for stage I to IIA, IIB, and III to IV, respectively. A total of 40 patients treated with radiation alone or no treatment survived less than 4 months. After excluding patients surviving less than 4 months, the difference between patients treated with surgery alone and surgery and radiation, assessed by the log-rank test, was not statistically significant ($p = 0.24$), even among stage I to IIA ($p = 0.22$), IIB ($p = 0.45$), or III to IV ($p = 0.44$) patients.

A multivariable analysis of patients treated with surgery and radiation or surgery alone was performed to determine associations between various patient factors and OS. In the multivariable analysis, race, sex, and adjuvant radiation were not associated with OS, whereas increasing age (hazard ratio [HR] = 1.03 [95% confidence interval [CI]: 1.02–1.04]) and increasing stage (stage I–IIA: HR = 1, stage IIB: HR = 1.45 [95% CI: 1.09–1.93], stage III–IV: HR = 2.3 [95% CI: 1.79–2.95]) were negative prognostic factors. Compared with married patients, patients who were not married (HR = 1.25 [95% CI: 1.02–1.53]) had poorer OS. Increasing year of diagnosis was associated with improved OS. Patients diagnosed between 1984–1993 (HR = 0.62 [95% CI: 0.48–0.80]) and 1994–2003 (HR = 0.50 [95% CI: 0.39–0.65]) had improved OS compared with patients diagnosed between 1973 and 1983 (HR = 1).

Cause of Death Analysis

A cause-specific mortality analysis was performed on the 706 patients (52.9%) who died by the time of data collection. The analysis demonstrated that 36.7% of patients died of malignant thymoma, 13.7% died of diseases of the heart, and 49.6% died of all other causes. Patients receiving radiation treatment did not have an increased rate of cardiac mortality compared with patients not receiving radiation (14.3% radiation versus 12.9% no radiation, $p = 0.68$). A separate analysis evaluating only patients with stage I to IIA thymoma was performed. Patients with stage I to IIA thymoma have longer survival compared with patients with advanced disease and seem to have a worse prognosis with adjuvant radiation (Figure 1 and Table 2). The analysis with early-stage patients did not reveal a significant increase in cardiac mortality with radiation treatment (15.2% radiation versus 14.5% no radiation, $p = 0.92$). In addition, a separate analysis excluding patients surviving less than 4 months was performed because cardiac complications often account for postoperative deaths. In this analysis, there was no increased rate of cardiac mortality in the patients treated receiving radiation (14.4% radiation versus 12.0% no radiation, $p = 0.40$).

TABLE 3. Cumulative Incidence Rate of Death

Treatment, Cause of Death (N)	3 yr	6 yr	12 yr	24 yr	Gray Test p Value
No radiation, heart (36)	0.048	0.059	0.075	0.118	0.83
Radiation, heart (61)	0.021	0.034	0.102	0.174	
No radiation, other cause of death (243)	0.293	0.379	0.541	0.745	0.06
Radiation, other cause of death (366)	0.225	0.355	0.532	0.699	

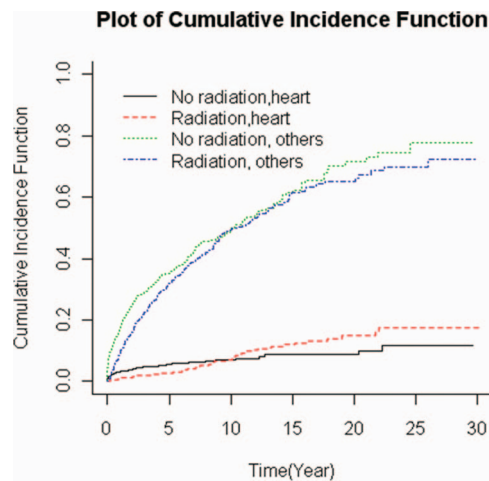


FIGURE 2. Cumulative incidence rate (CIR) of death. The graph depicts the CIR of death from heart disease in patients treated with (dashed) and without (solid) radiation therapy. The plot also compares the CIR of death from all other causes of death in patients treated with (dot-dash) or without (dot) radiation therapy.

The cumulative incidence rate of cardiac mortality for patients receiving radiation versus those not receiving radiation was 3.4% versus 5.9% at 6 years and 17.4% versus 11.8% at 24 years (Table 3 and Figure 2). The difference was not statistically significant ($p = 0.83$). Interestingly, there was a nonsignificant decrease in the cumulative incidence rate of death from all other causes of death in the radiation group ($p = 0.06$).

Secondary Malignancy Analysis

The incidence of secondary malignancy development after treatment for malignant thymoma was analyzed. There were a total of 159 patients (11.9%) who developed any secondary malignancy and 56 patients (4.2%) who developed a thoracic secondary malignancy. Thoracic malignancies were cancers limited to the thyroid, breast, esophagus, and lung. Comparing patients who received radiation ($N = 824$) and those who did not ($N = 510$), there was no difference in the development of all secondary malignancies (11.7% versus 12.4%, $p = 0.70$) or thoracic secondary malignancies (3.4% versus 4.3%, $p = 0.31$). Table 4 summarizes the breakdown of thoracic secondary malignancies by site as well as the incidence of leukemia and lymphoma.

TABLE 4. Secondary Malignancies Among Patients with Thymoma After Treatment with or without Radiation (N = 1334)

	Radiation (n = 824)	No Radiation (n = 510)
Thyroid	1 (0.12%)	4 (0.78%)
Breast	12 (1.46%)	7 (1.37%)
Esophagus	3 (0.36%)	2 (0.39%)
Lung and bronchus	12 (1.46%)	9 (1.76%)
Lymphoma	10 (1.21%)	1 (0.20%)
Leukemia	7 (0.85%)	2 (0.39%)
All other malignancies	51 (6.19%)	38 (7.45%)
All sites	96 (11.65%)	63 (12.35%)

Overall *p* value = 0.22

DISCUSSION

To our knowledge, this is the largest study to address the long-term implications of radiation therapy in patients with malignant thymoma. Because of the indolent nature of malignant thymoma, patients with the disease tend to have relatively good prognoses. With patients living for years after treatment, the adverse effects related to radiation therapy are of concern.

Malignant thymoma is associated with an increased risk of secondary malignancy development independent of radiation (OR = 3.8, *p* = 0.04).¹⁷ One analysis of 136 patients with malignant thymoma concluded that the increased incidence of secondary malignancies was not attributable to radiation-induced malignancies.¹⁸ The effect of radiation on the risk of secondary malignancy development after the treatment of malignant thymoma is not well documented in large cohorts of patients. Patients receiving mediastinal irradiation for various malignancies such as Hodgkin disease and breast cancers are at an increased risk for secondary malignancy.^{8,10,11,13} Solid tumor malignancies are found 9 to 60 years after radiation treatment, whereas leukemia and lymphomas are found between 5 and more than 15 years after treatment.^{9,12,14} In our study, we did not demonstrate an increased risk of secondary malignancy after radiotherapy. The rates of all secondary malignancies and thoracic secondary malignancies were similar between patients receiving radiation and patients receiving surgery alone or no treatment.

In addition to increasing the risk of secondary malignancies, radiation therapy to the chest increases a patient's risk for cardiotoxicity. Radiation-induced cardiotoxicity seems to manifest more than 5 years after radiation treatment.¹⁹ In particular, coronary artery disease seems to occur greater than 10 years after treatment, and valvular diseases tend to occur greater than 20 years after treatment.²⁰ Patients receiving radiotherapy for Hodgkin disease have a relative risk of fatal cardiac complications ranging from 2 to 6.¹³ Patients receiving radiation treatment for left-sided breast cancers have a relative risk of cardiac complications of 1.5 to 2.0.⁸⁻¹¹ Even with the long-term survival rates in patients with malignant thymoma, our analysis did not demonstrate a significant difference in cardiac mortality between patients who received radiotherapy and those who did not. However,

the cumulative incidence rate of death in Figure 2 demonstrates a gradual increase in cardiac deaths after 10 years among patients receiving radiation therapy. Although this difference is not large enough to demonstrate a statistically significant difference in cardiac mortality, the delayed increase is a concern, and studies with longer follow-up are needed.

Younger age and extensive fields of radiation are risk factors for both cardiotoxicity and secondary malignancy. In general, patients with malignant thymoma are older than patients with Hodgkin disease. Also, the radiation treatment fields for malignant thymoma are generally smaller than mantle fields and tangent fields used to treat Hodgkin disease and breast cancers, respectively. Therefore, age and radiation field may have influenced the development of long-term morbidities in patients with malignant thymoma.

In addition, combined modality treatment with chemotherapy and radiotherapy may have a synergistic effect on long-term adverse events. In breast cancer, systemic agents such as anthracyclines and trastuzumab are associated with cardiac toxicity.^{9,21} In a study of 19,046 patients with Hodgkin disease, treatment with alkylating agents without radiotherapy was associated with an increased lung cancer risk (RR = 4.5 [2.1–8.8]). The risk increased with both increasing numbers of cycles of alkylating agents and increasing radiation dose.²² Patients with malignant thymoma do not regularly receive adjuvant chemotherapy. Therefore, the infrequent use of chemotherapy may have also contributed to the similar rates of cardiac toxicity and secondary malignancy development in our study. Unfortunately, because of the limitations of the SEER database, we were unable to gather information regarding the use of chemotherapy in our patient population.

Although the long-term effects of radiation therapy do not adversely affect patients with malignant thymoma, there does not seem to be a benefit of radiation therapy in most patients. Our study demonstrates that patients with stage I to IIA thymoma do not benefit from adjuvant radiation, which is consistent with the literature.³⁻⁶ The role of radiation in stage II disease has been controversial. In our analysis, there was initially a nonsignificant trend toward improved OS in stage IIB patients treated with surgery and radiation (*p* = 0.09). After accounting for surgical mortality, the difference in survival was not significant. Two recent SEER database analyses have demonstrated improved survival in patients with stage II or stage II to III thymoma.^{23,24} The differences in staging and exclusion criteria, as described in Table 5, may explain the discrepancies in survival among the various analyses.

Interestingly, our results do not demonstrate a statistically significant benefit in OS with adjuvant radiotherapy in patients with stage III to IV disease. Although a statistically significant benefit was seen in an initial analysis, after accounting for surgical mortality, the data were no longer significant. Some studies have reported worse outcomes with adjuvant radiation therapy;²⁵ however, the majority of studies support the role of radiation therapy in advanced-stage patients.^{4-6,26} From our secondary malignancy and cardiac

TABLE 5. Comparison of SEER Database Analyses

Analysis	Inclusion and Exclusion Criteria	Definition of Stages	Outcomes	Additional Analyses
Fernandes et al.	Excluded patients with thymic carcinoma Performed an additional analysis excluding patients surviving 3 mo or less	Patients were categorized into 3 groups according to the Masaoka staging system: I-IIA, IIB, and III-IV. See Methods section.	After accounting for postoperative mortality, the data did not show a clear overall survival benefit to adjuvant radiation.	A secondary analysis demonstrated no increased risk of cardiac mortality or secondary malignancy development with radiation.
Forquer et al.	Included patients with thymic carcinoma Excluded patients surviving 3 mo or less	Patients were categorized into "localized" (stage I) and "regional" (stage II-III). The "regional" group likely included patients coded as "invasion into adjacent organs or structures." This may represent stage IVa patients with invasion into the pleura and pericardium. This analysis also excluded patients with "further contiguous extension," which may represent some stage III patients.	A possible benefit of adjuvant radiation in patients with "regional" stage II-III disease was seen.	A secondary analysis was performed in patients who received extirpative surgery. No benefit was noted for adjuvant radiation in the stage II-III patients after extirpative surgery.
Housman et al.	Excluded patients with thymic carcinoma Did not exclude patients surviving 3 mo or less	Patients were categorized into stages I, II, III, and IV. Patients defined as stage I in this analysis were coded as stage I-IIA in our analysis. This analysis's definition of stage II was the same as our definition of stage IIB.	Adjuvant radiation improved overall survival in stage II patients.	No additional analysis was performed.

mortality analyses, the difference in survival between the analyses is probably not the result of long-term radiation-induced toxicity. Instead, the unexpected survival rates may be explained by the heterogeneity of the patients in the stage III to IV group. Patients with stage IV disease likely receive only palliative radiation. In addition, patients with high-risk features such as positive margins and residual disease are more likely to have inherently poor prognoses but are also more likely to receive adjuvant radiation. Moreover, these are the patients who benefit from radiation therapy. Finally, the high 4-month mortality rate of 11.6% in stage III to IV patients treated with surgery alone potentially affected our results.

On multivariable analysis of patients treated with surgery and radiation or surgery alone, increasing age, increasing stage, and earlier year of diagnosis were poor prognostic factors. The improved survival observed in patients treated during later years may be due to advances in surgical and radiation techniques and technology as well as improved patient selection.

At each disease stage, patients had improved OS with surgery and radiation or surgery alone compared with radiation alone or no treatment. Radiation alone did not improve OS at any stage when compared with no treatment. The few studies reporting data on patients treated with radiation alone demonstrate modest disease control in patients with unresectable disease.²⁷⁻²⁹ When feasible, surgery is the primary treatment for malignant thymoma.

Our results present important information regarding the role of radiation therapy in malignant thymoma. As mentioned previously, this study is restricted by the inherent limitations of the SEER registries. In addition to data regarding chemotherapy, prognostic factors such as margin status and performance status and information about radiation treatment (dose, technique, completion rates, and type of technology) were not available in the SEER database. WHO histology classification was unavailable for the majority of patients and was unable to be applied to this analysis. Also, patients were unable to be classified further into distinct Masaoka staging groups. Finally, although there does not seem to be a significant risk of secondary malignancy development or cardiac mortality with radiation treatment for malignant thymoma in this study population, longer follow-up is needed.

CONCLUSIONS

Because these data do not demonstrate a clear OS benefit in patients treated with adjuvant radiation, this form of treatment may not be appropriate for uniform use in all patients. Radiation treatment should instead be considered for patients on an individual basis with consideration of high-risk features. Importantly, in our study, radiation therapy did not increase the risk of death from heart disease or the incidence of secondary malignancies. However, studies with longer follow-up, adjuvant chemotherapy, WHO histology classification, performance status, and margin status are needed to further elucidate the role of radiation treatment in malignant thymoma.

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