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Adjuvant Radiotherapy for Stages II and III Resected Thymoma: a Single Institution Experience

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Abstract

Purpose—Role of adjuvant radiation for Masaoka stage II and III thymoma remains controversial. The aim of this study was to evaluate the clinical benefits of radiation therapy for resected stages II and III thymoma.

Methods and Materials—We retrospectively reviewed the medical records of 175 thymoma patients treated from July 1996 to January 2013 at University of Washington Medical Center; 88 patients with adequate follow-up and who met histologic criteria were included. We evaluated progression-free survival (PFS) and overall survival (OS), and compared these outcomes in patients treated by surgery (S) alone versus surgery plus radiotherapy (S + RT). Cox regression models and log-rank tests were used to compare PFS and OS for S versus S + RT, and they were further assessed by margin-positive versus margin-negative subgroups using Kaplan-Meier curves.

Results—Among the 88 thymoma patients, 22 were stage II and 18 were stage III. For all stages II and III patients, adjuvant radiation was not identified as a significant predictor for PFS ($P = 0.95$) or OS ($P = 0.63$). A positive surgical margin predicted for a worse OS (hazard ratio = 7.1; $P = 0.004$). Further investigation revealed for resection margin-positive patients; S + RT had higher OS than S alone ($P = 0.006$).

Conclusions—For stages II and III thymoma, postoperative adjuvant radiation was not associated with statistically significant differences in PFS or OS in this study. Our results indicated a potential OS benefit of adjuvant RT in patients with positive resection margins, and therefore may be considered in this patient population.

Keywords

adjuvant radiotherapy; thymoma; margin status; prognosis; overall survival; progression-free survival

Introduction

Surgery constitutes the primary treatment modality for resectable thymomas. The role of radiation therapy (RT) for locally invasive but nonmetastatic (stages II and III) thymomas remains controversial. Previous studies have shown conflicting results regarding the role of adjuvant RT in resected thymoma. There are data that suggest RT can decrease the local recurrence rate and increase the 5-year overall survival (OS) from 18% to 62% in stages II to IVa thymoma.¹ In contrast, there are other studies that do not show a benefit in recurrence or survival for resected stage II thymoma.^{2–5} In current clinical practice, RT is often given in the adjuvant setting for higher Masaoka stages, incomplete resection, or positive resection margins. However, this practice remains controversial due to the conflicting clinical evidence. The goal of this study is to determine the effect of postoperative RT on the outcome of stages II and III thymoma patients treated at our institution.

Materials and Methods

Patient Population, Adjuvant Radiation, and Follow-up

We retrospectively reviewed the medical records of 175 thymoma patients who were treated and followed from July 1996 to January 2013 at our institution. Potentially resectable patients underwent pre-operative imaging, followed by surgical resection and subsequent referral for adjuvant therapy. Relapse within the surgery bed or radiation field was defined as a local recurrence. Patients with < 6 months of follow-up or without complete pathologic staging were excluded. Eighty-eight histologically confirmed thymoma patients with adequate follow-up and who met histological criteria were included in this study.

Pathological Staging and Margin Status

Staging was based on the surgical and pathological criteria described by Masaoka and colleagues^[6] in 1981 and modified in 1994: stage I - macroscopically completely encapsulated and microscopically no capsular invasion; stage II - macroscopic invasion into surrounding fatty tissue or mediastinal pleura, or microscopic invasion into capsule; stage III - macroscopic invasion into neighboring organs (pericardium, great vessels, or lung); stage IVa - pleural or pericardial dissemination; and stage IVb - lymphogenous or hematogenous metastasis. Staging was retrospectively reviewed and confirmed by dual observer review based on the pathology reports and surgeons' operative notes. Margin status (positive or negative) was retrospectively reviewed and confirmed by dual observer unblinded review based on the pathology reports.

Statistical Analysis

We used multivariate Cox regression models to examine the effect of covariates on OS and progression-free survival (PFS), including stage, margin status, and use of adjuvant radiation

for all patients. Kaplan-Meier curves with the log-rank test was used to compare surgery alone (S) versus surgery followed by radiotherapy (S + RT) on OS and PFS for stages II and III patients and after stratifying treatment groups by margin status. $P = 0.05$ was considered statistically significant. Survival time and time to recurrence were calculated from the date of surgery.

Results

Patients Characteristics

Among the 175 thymoma patients treated and followed at our institutions from July 1996 to January 2013, 88 patients with complete staging, complete pathology (including resection margin status), and adequate follow-up were included. Among the 88 thymoma patients, 26 (30%) patients had myasthenia gravis (table 1). Out of the 88 patients, 22 were stage II and 18 were stage III. Out of the 22 resected stage II patients, 10 (45%) received radiotherapy and 12 (55%) did not. The median radiation dose for stage II was 50.4 Gy (range 45–55 Gy). Among the 18 stage III patients, 13 (72%) underwent surgery and radiotherapy, 2 (11%) underwent surgery only, 2 underwent surgery and adjuvant chemotherapy, and 1 received concurrent chemoradiation. The median radiation dose for stage III was 59.4 Gy (range 45–70 Gy). In the S alone group, 20% were margin positive, while in the S+RT group, 68% were margin positive ($p < 0.001$, Fisher's exact test).

Prognostic Factors for OS and PFS

Positive surgical margins predicted for worse OS (hazard ratio [HR] = 7.1, $P = 0.004$, Table 2). None of the covariates was identified as an independent prognostic factor for PFS (Table 3); the 1 possible exception was positive margin status, for which the multivariate Cox model showed a trend toward a significantly increased HR for disease progression (HR = 5.5, $P = 0.06$, Table 3).

Clinical Outcomes

Figure 1A shows the Kaplan-Meier curves for OS. Among stages II and III thymoma patients, the 5-year OS was 72.9% in S alone group and 88.4% in S + RT group. There was no statistically significant difference in OS when comparing S + RT versus S alone (log-rank test, $P = 0.95$).

Figure 1B shows the Kaplan-Meier curves for PFS. Among stages II and III thymoma patients, the 5-year PFS was 59.3% in S alone group and 75.9% in S + RT group. There was no statistically significant difference in PFS when comparing S + RT versus S alone (log-rank test, $P = 0.63$).

As shown in Figure 2A, among margin-positive stages II and III patients, OS was 81.5% at 5 years in the S + RT group, and 0% at 5 years for S alone group. Five-year OS was 100% in both S alone group and the S + RT group in margin-negative stages II and III patients (Fig. 2B). Figure 2 shows the impact of S + RT versus S alone on OS stratified by margin status. The margin-positive stages II and III thymoma patients treated with S + RT had higher OS than S alone (log-rank test, $P = 0.006$); whereas, margin-negative stages II and III thymoma

patients did not demonstrate any significant differences between S + RT versus S alone (log-rank test, $P = 0.733$). Figure 3 shows the impact of S + RT versus S alone on PFS stratified by margin status. No statically significant differences in PFS were observed between S + RT versus S alone in margin-positive (log-rank test, $P = 0.467$) or margin-negative (log-rank test, $P = 0.847$) stage II and III thymoma.

In terms of pattern of failure, among those stages II and III patients with positive margins who did undergo RT (13 patients), there were 3 patients who had local recurrence and no patient with distant failure detected by the end of the study time. Among those stages II and III patients with positive margins who did not undergo RT (8 patients), there were 2 patients who had local recurrence and 1 patient with distant failure by the end of the study time. Statistical analysis on the pattern of failure was not performed due to the limited sample size.

Discussion

Studies of thymoma are challenging due to its relatively low incidence, a prolonged disease course, and the need for extended follow-up. Several large series have shown that the Masaoka staging correlated well with survival.^{7–9} Other studies also showed that complete surgical resection is the most important prognostic factor for survival.^{9,10} There are no reported prospective studies so far to provide a definitive conclusion on the clinical benefits of adjuvant radiation in stages II and III thymoma patients, and retrospective studies so far have reported mixed results.^{11–15} Several reported series by investigators at University of Pennsylvania,^{2,5} Memorial Sloan Kettering Cancer Center,⁴ Massachusetts General Hospital,¹⁶ and University of Eastern Piedmont in Italy¹⁷ showed no local control benefit of adjuvant radiation in stage II thymoma. Studies at Massachusetts General Hospital found that adjuvant radiation was not independently associated with disease progression on a multivariable analysis of stages II and III patients.¹⁸ Similarly, this single-institutional retrospective study showed that adjuvant RT increased OS and PFS but this finding was not statistically significant. We did demonstrate improved OS in the subgroup of margin-positive patients.

Previous studies have shown that complete surgical resection is the most important prognostic factor [9–10]. Our study using Cox regression modeling showed that positive surgical margin predicted worse overall survival (hazard ratio=7.1; $P=0.004$). Given that the positive resection margin predicts Previous studies have shown that complete surgical resection is the most important prognostic factor.^{9,10} Our study using Cox regression modeling showed that positive surgical margin was an independent factor associated with worse OS (HR = 7.1, $P = 0.004$). Given that the positive resection margin predicts for worse outcome and that most (69%) patients in the S + RT group had positive margins, it is possible that the effect of radiation may have been confounded by the higher number of patients with positive margins. To test this hypothesis, we compared the OS of resected stages II and III thymoma patients with or without RT separately for the margin-positive subgroups and the margin-negative subgroups. We found that for resection marginpositive stages II and III thymoma, S + RT resulted in a higher OS than S alone ($P = 0.006$); for resection margin-negative stages II and III thymoma, no statistically significant differences

were observed between S + RT versus S alone ($P = 0.733$). The exact underlying mechanism for the difference in OS in the margin-positive patients who received and who did not receive RT is unknown. One possibility could be that RT eradicated and sterilized the positive resection margins, and thus delayed or prevented the local recurrence and/or metastasis process. This may have contributed to the improved OS in the group who received RT. For PFS, similar to OS, the Kaplan-Meier analyses showed a trend favoring the receipt of RT after surgery for both PFS and OS in margin-positive stages II and III thymoma patients. However, no statistically significant differences in PFS were observed between S + RT versus S alone in margin-positive ($P = 0.467$) stages II and III patients; again, likely owing to the limited patient numbers.

Several limitations apply to this single-institutional retrospective study. Because of its observational design, inherent selection bias could have confounded the results. There may be selection biases depending on referral patterns. More specifically, patients referred for RT could have been more likely to have tumors with characteristics associated with prognosis other than involved margins, including, for example, World Health Organization Classification of Thymoma and tumor size. Our study did not account for the potential impact of these other characteristics on survival outcomes. Patients were referred for adjuvant radiation at the discretion of the treating surgeons. Some patients with positive margins were not referred for RT due to surgeons' preference and variations in practice patterns. Because of the small sample size, limitations to reach statistically significant differences were also possible and our study was likely powered to only detect very large differences in survival outcomes. Furthermore, it is possible that some patients with positive resection margins did not receive postoperative RT due to poorer ECOG performance status, and variations in practice patterns among different institutions may limit the application of the single-institution results to other institutions. Despite these limitations, the observed impact of adjuvant RT on OS outcomes deserves further investigation in future prospective trials for stages II and III thymoma.

Conclusions

For stage II and III thymoma, adjuvant radiation after surgery did not lead to statistically significant differences in progression-free or overall survival, but our results are limited by the sample size. Postoperative radiation seemed to improve the OS in the subset of patients with positive resection margins, and therefore may be considered in this patient population.

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Fig 1. Kaplan-Meier curves for overall survival (OS) (A) and progression-free survival (PFS) (B) in stage II and III thymoma patients. Kaplan-Meier curves demonstrate no statistically significant difference in OS ($P = 0.95$, log-rank test) or PFS ($P = 0.63$, log-rank test) between stage II and III patients undergoing surgery alone versus surgery plus radiation (solid line: S alone; dotted line: S + RT).

Fig 2.

Kaplan-Meier curves for overall survival (OS) in resection margin-positive (A) and resection margin-negative (B) stage II and III thymoma patients. For resection margin-positive stage II and III thymoma, S + RT had higher OS than S alone ($P=0.006$). For margin-negative stage II and III thymoma, no significant differences were observed between S + RT versus S alone ($P=0.733$) (solid line: S alone; dotted line: S + RT).

Fig 3.

Kaplan-Meier curves for progression-free survival (PFS) in resection margin-positive (A) and resection margin-negative (B) stage II and III thymoma patients. For margin-positive stage II and III thymoma, no significant differences were observed between S + RT versus S alone ($P = 0.467$). For margin-negative stage II and III thymoma, no significant differences were observed between S + RT versus S alone ($P = 0.847$) (solid line: S alone; dotted line: S + RT).

Table 1

Patients Characteristics

	Total : 88 thymoma patients
Mean Age	57
Men: Women (No., %)	42: 46 (49%: 52%)
Associated Myasthenia Gravis (No., %)	26 (30%)
Stage I (No., %)	33 (37.5%)
Stage II (No., %)	22 (25%)
Stage III (No., %)	18 (20.5)
Stage IV (No., %)	15 (17%)
Margin positive patients (No., %)	37 (42%)
Recurrence (No., %)	20 (22.7%)
Mortality from the disease (No., %)	13 (15%)
Stage I patients who received both S & RT	2 (6.2% of 33 stage I patients)
Stage II patients who received both S & RT	9 (40.9% of 22 stage I patients)
Stage III patients who received both S & RT	13 (72.2% of 18 stage I patients)
Stage IV patients who received both S & RT	7 (46.7% of 15 stage I patients)

Table 2

Cox regression models to examine the prognostic factors for overall survival

Covariate	Hazard Ratio	P	95% confidence interval
Stage			
1	1.00		
2	3.78	0.10	0.78–18.34
3	2.65	0.32	0.38–18.32
4	2.05	0.47	0.29–14.60
Surgery + Radiation			
With Radiation *	1.00		
Without Radiation	0.49	0.36	0.11–2.26
Surgical margin			
Negative *	1.00		
Positive	7.13	0.004	1.87–27.10

* Reference category

Cox regression modeling showed that positive surgical margin predicted worse overall survival, (hazard ratio=7.1; P=0.004). Adjuvant radiation was not identified as a significant predictor for overall survival (p=0.36).

Table 3

Cox regression models to examine the prognostic factors for progression-free survival

Covariate	Hazard Ratio	P	95% confidence interval
Stage			
1 *	1.00		
2	8.38	0.07	0.83–84.92
3	9.16	0.11	0.63–133.20
4	9.61	0.10	0.67–137.20
Surgery + Radiation			
With Radiation *	1.00		
Without Radiation	0.41	0.41	0.05–3.44
Surgical margin			
Negative *	1.00		
Positive	5.47	0.06	<u>0.93–32.08</u>

* Reference category.

There was no statistically significant factor identified as an independent prognostic factor for disease progression; the hazard ratio of resection margin- positive patients approached significance at 5.47 ($P = 0.06$). Adjuvant radiation was not identified as a significant predictor for progression-free survival ($P = 0.41$).