The Effectiveness of Postoperative Radiotherapy in Patients With Completely Resected Thymoma: A Meta-Analysis

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Background. **This meta-analysis aimed to provide a pooled analysis of clinical studies correlating postoperative radiotherapy (PORT) with survival in patients with completely resected thymoma.**

Methods. **According to the recommendations of the Cochrane Collaboration, we established a rigorous study protocol. An electronic search was conducted using online databases. Hazard ratios (HRs) and 95% confidence intervals (CIs) were used in this meta-analysis and were calculated from published survival data. A meta-analysis was conducted to assess the impact of PORT in completely resected thymoma on overall survival (OS), disease-free survival (DFS). and disease-specific survival (DSS). We also performed a subgroup analysis for OS of patients with stage II and stage III thymoma.**

Results. **Fourteen studies, which included 3,823 patients (2,096 patients who received PORT and 1,727 patients who did not receive PORT), met the selection criteria. From the available data, the thymoma patients with PORT who did not undergo resection did not have significantly improved OS (HR 0.99; 95% CI 0.87 to 1.13; $p = 0.87$), DFS (HR 1.21; 95% CI 0.97 to 1.51; $p = 0.09$), or DSS (HR 0.66; 95% CI 0.39 to 1.13; $p = 0.13$) compared with the patients who did not undergo PORT. However, our subgroup analysis showed a significant difference in OS in patients with stage II thymoma (HR 0.57; 95% CI 0.41 to 0.80; $p = 0.001$) and patients with stage III thymoma (HR 0.73; 95% CI 0.59 to 0.90; $p = 0.004$).**

Conclusion. **Our results showed that for completely resected thymoma, PORT had no advantage in the overall group of patients but increased OS in the patients with stage II and III thymoma after a complete resection. On the basis of this study, PORT is beneficial in patients with stage II and III patients after a complete resection.**

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Although thymoma is a rare tumor (0.15 cases per 100,000), it is the most common tumor in the anterior mediastinum [1]. It typically occurs in adults 40 to 70 years of age and is rare in children. Patients with thymoma have a 5-year survival rate of approximately 78% [2]. The Masaoka clinical stage is a good predictor of prognosis and is the basis for different treatments. Surgical resection is the mainstay therapy for thymoma. Radiotherapy and chemotherapy have also been widely used as adjuvant and palliative procedures [3]. Thymomas are sensitive to radiation therapy (RT), which is often used in patients with nonresectable tumors and after surgical treatment as adjuvant therapy. The impact of postoperative RT (PORT) on survival after resection of a thymoma has been evaluated in several reports, although with varying results [4–6]. All these reports used a Masaoka stage to stratify patients. The role of PORT in thymoma remains controversial. However, its use in advanced stages of the disease is well established.

Some recent studies have reported that further treatment was not useful after complete resection [7–10]. However, some have reported that PORT had potential advantages in improving survival and reducing relapse in patients with thymoma after complete resection, whereas PORT did not significantly improve survival or reduce recurrence for the cohort as a whole [7, 8]. A stage I thymoma has an excellent prognosis after complete resection. The use of adjuvant RT is currently accepted as not essential [11]. Current therapeutic indications for stage II thymoma are controversial. Although adjuvant RT has previously been considered the standard of care after a complete tumor resection for stage II thymoma [4, 12], evidence regarding its utility is insufficient because of a lack of prospective clinical trials. The criteria for administering adjuvant radiation to patients with stage II thymoma also remain controversial. The need for PORT in stage III or IV thymoma patients is less debatable, inasmuch as it has been shown to improve local control [5, 13]. Furthermore, the administration of PORT in cases of locally advanced thymoma has been shown to reduce recurrence rates [14]. Although some authors have

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Table 1. Demographic Data

Study	Publication Year	Source of Patients	Follow-Up (Months)		Patients		Outcomes Reported	Multivariate Analysis	Tumor Stages
			Median	Range	S Alone	S + RT			
Regnard et al	1996	France	96	1–180	24	90	DFS	Yes	I/II/III/IV
Mangi et al	2002	USA	90	1–336	35	14	DSS	Yes	II
Kondo and Monden	2003	Japan	NR	1–120	35	105	OS	Yes	III/IV
Singhal et al	2003	USA	70.3	1–120	47	23	OS	Yes	I/II
Mangi et al	2005	USA	94	2–268	7	38	DSS	Yes	III
Rena et al	2007	Italy	91	9–170	31	25	DFS	Yes	II
Vassiliou et al	2009	Greece	69	2–212	15	26	OS/DFS/DSS	Yes	I/II/III/IV
Chen et al	2009	China	63	2–303	41	66	DFS/DSS	Yes	II
Forquer et al	2010	USA	NR	1–60	315	585	OS/DSS	Yes	I/II/III
Fernandes et al	2010	USA	65	1–361	346	669	OS	Yes	I/II/III/IV
Chang et al	2011	Korea	58.5	6–231	17	59	DFS	Yes	II/III
Fan et al	2013	China	50	5–360	12	53	OS/DFS/DSS	Yes	III
Yan et al	2014	USA	49	NR	18	22	OS/DFS	Yes	II/III
Omasa et al	2014	Japan	56.8	0–258	784	321	OS/DFS	Yes	II/III

DFS = disease- free survival; DSS = disease-specific survival; NR = not reported; OS = overall survival; RT = radiation therapy; S = surgical treatment.

advocated for PORT and others have argued against its usefulness, current indications recommend PORT for all thymoma patients [5, 15].

Most of these studies were performed retrospectively with a small number of patients. However, there are a few single-institution studies demonstrating a beneficial effect of adjuvant radiation of thymoma. Further investigation into the value of PORT for thymoma is warranted. This study was designed to examine the role of PORT for completely resected thymoma in relevant trials from several electronic databases, international conference abstracts, and reference research. Clinical outcomes, overall survival (OS), disease-free survival (DFS), and disease-specific survival (DSS) from radiation treatment are considered. This meta-analysis might provide answers to surgeons' concerns with statistically greater power and better quality analyses.

Material and Methods

A systematic electronic search was independently performed by two investigators using MEDLINE, EMBASE, and the Cochrane Library database CENTRAL. These databases were searched between March 7, 2015, and March 16, 2015. The search terms "thymoma," "complete resection," "postoperative radiotherapy," and "survival" and MeSH headings "thymoma" (MeSH), "complete resection" (MeSH), "postoperative radiotherapy" (MeSH), and "survival" (MeSH) were used in combination with the Boolean operators AND or OR. Studies were selected that met all of the following inclusion criteria: reported on two cohorts of patients: complete resection alone versus complete resection with PORT. Of note, no attempt was made to search unpublished literature. Studies published solely in foreign languages were excluded. Studies that included patients with chemotherapy or metastatic disease were excluded.

Before this study was begun, a rigorous study protocol was established according to the recommendations of the Cochrane Collaboration. Abstracts of the citations identified by the search were scrutinized by two observers to determine their eligibility for inclusion in the meta-analysis. Data were extracted by the same investigators using standardized forms. Copies of full articles were obtained and reviewed independently by the same investigators against the inclusion criteria of the study. When a disagreement occurred in the trial selection, it was discussed with another investigator, and a consensus was reached. We included studies that evaluated the association of PORT with OS, DFS, or DSS of patients with a resected thymoma. Full texts of selected abstracts were obtained, and reference lists were comprehensively evaluated and cross-checked to determine whether any other data sources were available. In addition, general review articles on thymoma were examined to identify additional, potentially relevant original articles.

Table 2. Demographic Data for Subgroups II and III

Study	Publication Year	Tumor Stages	Patients	
			S Alone	S + RT
Singhal et al	2003	II	20	20
Vassiliou et al	2009	II	10	11
Fernandes et al	2010	II	62	166
		III	129	342
Fan et al	2013	III	12	53
Omasa et al	2014	II	637	199
		III	147	122

RT = radiation therapy; S = surgical treatment.

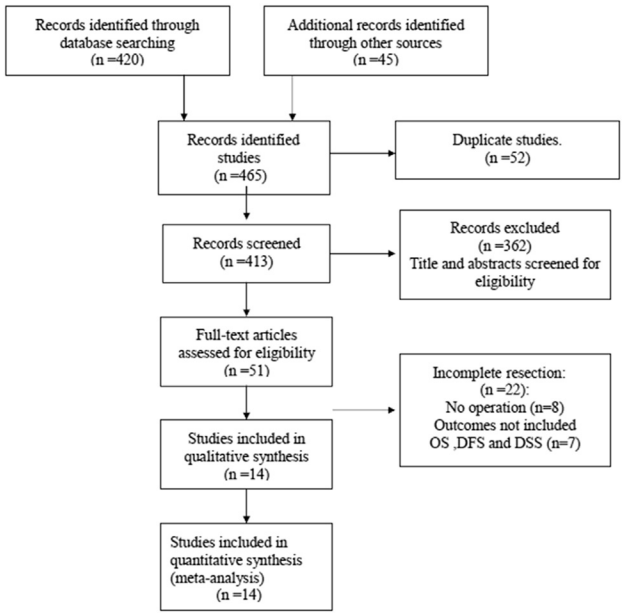

Fig 1. Flow chart of literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

Statistical Analysis

Synchronized extraction results were pooled statistically as effect estimates in meta-analyses. We estimated hazard ratios (HRs) with corresponding standard errors (SEs) for dichotomous outcomes and the weighted mean difference (WMD) with corresponding SEs for continuous outcomes. For each study, HRs and corresponding SEs were estimated from publications. Some studies directly stated HRs and corresponding SEs. In other studies they were calculated according to the following parameters: total number of events, number of patients at risk in each group, and log-rank statistic or its p value. Then, we calculated the log (HR) and SE (log (HR)) according to the methods described by Tierney and colleagues [16]. Level of heterogeneity (Level of variance) across studies was evaluated with the I^2 statistic. I^2 of 40%, 70%, and 100% was used to represent low, moderate, and high variance, respectively. A fixed effect model was used for calculating pooled HR. A random-effects model was used if clinical characteristics and methodology did not differ greatly and I^2 >40%. A pooled HR >1 implied a worse survival for the group with PORT. All statistical analyses were performed with Review manager 5.3 (http://www.cochrane.org).

Results

Characteristics of Included Trials

After screening, 14 studies comprising 3,823 patients (2,096 with PORT vs 1,727 without PORT) were included. All eligible studies were published between 1996 and 2015 [7–11, 17–25]. Table 1 shows the details for each trial, including baseline characteristics, publication year of the study, and tumor stage for each trial. Table 2 shows the details for the subgroup of stage II and stage III patients. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart (Fig 1) describes the details of the literature search for this systematic review.

Impact of PORT on OS

The impact of PORT on OS after thymoma resection in the eight studies was evaluated with Review Manager software. There was no statistical difference between the groups with respect to OS (HR 0.99; 95% CI 0.87 to 1.13; $p = 0.87$). There was no evidence of statistical heterogeneity ($I^2 = 1\%$, $\chi^2 = 7.05$, df = 7, $p = 0.42$) (Fig 2). However, the subgroup analysis of studies indicated a significant difference and a positive correlation between PORT and duration of OS in enrolled patients with stage II resected thymoma (HR 0.57; 95% CI 0.41 to 0.80; $p = 0.001$) (Fig 3) and those with stage III resected thymoma (HR 0.73; 95% CI 0.59 to 0.90; $p = 0.004$) (Fig 4). There was no evidence of statistical heterogeneity ($I^2 = 0\%$, $\chi^2 = 2.52$, df = 3, $p = 0.47$).

Impact of PORT on DFS

The impact of PORT on DFS in patients with resected thymoma in eight studies was evaluated with Review Manager software. PORT did not improve DFS (HR 1.21; 95% CI 0.97 to 1.51; $p = 0.09$) in all the patients with resected thymoma compared with operation alone (Fig 5). There was no evidence of statistical heterogeneity ($I^2 = 9\%$, $\chi^2 = 7.69$, df = 7, $p = 0.36$).

Impact of PORT on DSS

Three studies reported the incidence of disease-specific survival. There was no statistical difference in the DSS rate between those treated with and without PORT (HR 0.66; 95% CI 0.39 to 1.13; $p = 0.13$) (Fig 6). Statistical heterogeneity was not detected ($I^2 = 0\%$, $\chi^2 = 1.08$, df = 5, $p = 0.96$).

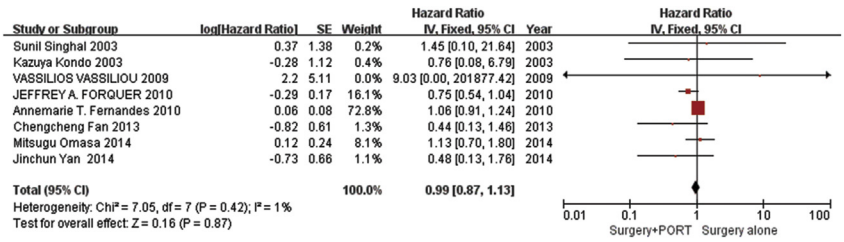

Fig 2. Forest plot for impact of postoperative radiotherapy on overall survival.

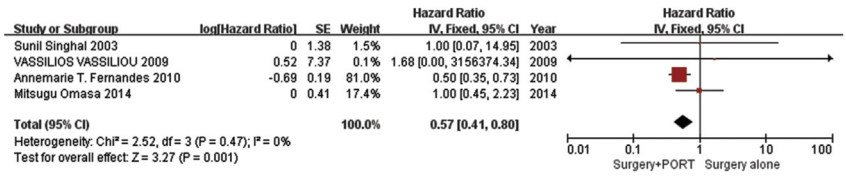

Fig 3. Forest plot for impact of postoperative radiotherapy on overall survival in stage II disease.

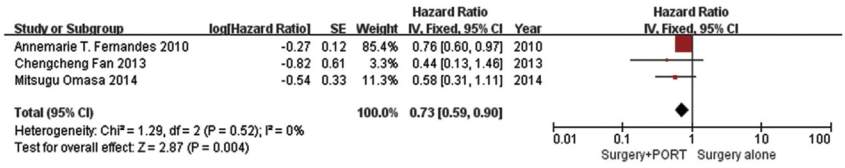

Fig 4. Forest plot for impact of postoperative radiotherapy on overall survival in stage III disease.

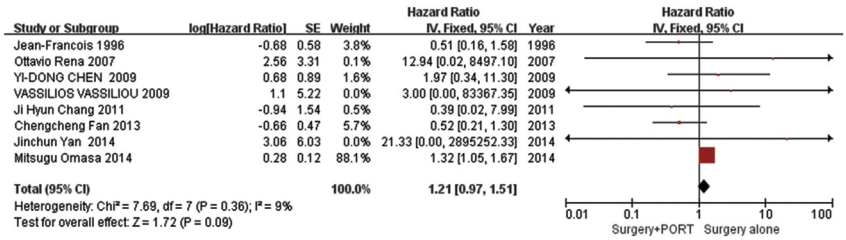

Fig 5. Forest plot for impact of postoperative radiotherapy on disease-free survival.

Assessment for Publication Bias

The funnel plot is a graphic representation of the log of the HRs plotted against the SEs of the log of the HRs for all of the studies used in the meta-analysis. No significant publication bias was observed in the funnel plots and Begg's test ($p = 0.412$) (Fig 7).

Comment

Thymoma is a rare disease of the thymic epithelium. Unlike thymic carcinoma, thymoma generally has a good prognosis. In large studies, OS has been reported at 67% after 5 years and 53% after 10 years [26]. Surgical resection is the mainstay treatment of thymoma. Complete resection of a thymoma results in a 50% increase in 5-year survival [27]. Additionally, RT and chemotherapy are given as adjuvant treatment modalities. However, according to observations from several researchers, PORT is controversial even after complete resection in every stage of thymoma.

In the current study [10, 18, 25], no significant improvement in survival was noted in patients with stage I thymoma who were treated with PORT compared with those not treated with PORT, which is consistent with previously reported results. The efficacies of PORT for stages II and III thymoma have historically been discussed separately because the former is considered an early-stage tumor with a low risk of recurrence and the latter is an advanced-stage tumor with a relatively high risk of recurrence. Current therapeutic indications concerning Masaoka stage II thymoma are controversial. The results of the current study [7, 9, 10] can be explained in part by the finding that the long-term outcomes in the thymoma patients who did not undergo PORT were satisfactory, which made it difficult to demonstrate that PORT had a further benefit on survival. This suggests that complete resection alone was sufficient to achieve a good prognosis in this population. However, some other authors remain in favor of RT after operation in stage II thymoma. The beneficial role of PORT in patients with

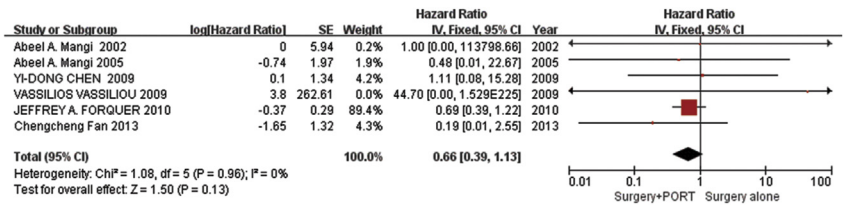

Fig 6. Forest plot for impact of postoperative radiotherapy on disease-specific survival.

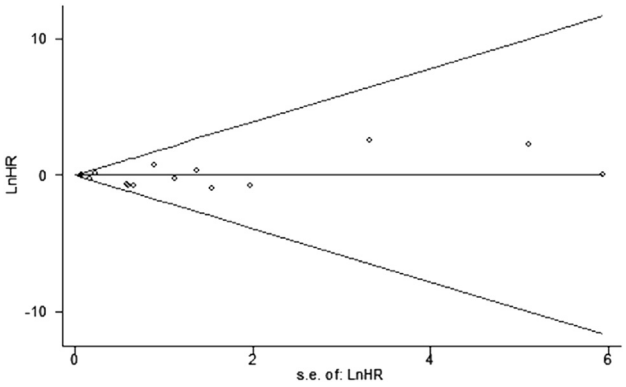

Fig 7. Begg's funnel plot with pseudo 95% confidence limits for publication bias. (LnHR = log of the hazard ratio; S.E. = standard error.)

resected stage III thymoma is less debatable, mainly because during the past 20 years, the 5-year survival rate of patients with stage III disease has not improved because of high recurrence rates despite the addition of RT to surgical treatments. The use of routine adjuvant radiation after complete resection of stage III thymoma needs to be addressed again.

As the present review details, the vast majority of studies have been small, retrospective case series that lack the statistical power to enable a clear statement to be made regarding the utility of PORT. Additionally, PORT remains controversial in the literature. A meta-analysis, such as that performed in this study, is a potentially useful tool in this situation because pooling data can result in a very powerful study, as opposed to the results obtained from smaller, individual studies. The basic purpose of this meta-analysis was to obtain a large enough sample from different studies to reveal a possible significant difference between operation alone and operation followed by PORT in terms of OS, DFS, and DSS. In this meta-analysis, we selected all well-controlled retrospective cohort studies published until March 2015.

Surprisingly, despite the theoretic benefits of PORT already outlined, pooling data from a large number of patients in this meta-analysis suggests that the addition of PORT does not affect OS, DFS, and DSS in all the patients grouped together regardless of stage after complete resection. However, OS was significantly better for the patients with stage II and III thymoma who received PORT after a complete resection compared with the patients who underwent complete resection alone. Our data demonstrate that PORT does not seem to increase long-term survival in all stages of thymoma when given after complete resection, which led us to consider that this treatment should not be routine. Utsumi and colleagues [14] reported that factors related to the ineffectiveness of PORT in studies include poor patient accrual and older RT techniques. Strobel and colleagues [3] reported that another factor is that thymoma has an indolent natural history. Many patients likely die of unrelated causes after treatment. Therefore, overall survival data reported in older studies may be falsely lowered, especially the long-term survival data. However, our data also demonstrate that PORT increased the OS rate in patients with stage II and III disease. Therefore, PORT should be taken into account in thymoma treatment, especially in patients with stage II and III disease. Our study provides good evidence for the clinical application of RT for thymoma. In general, although benefits of PORT for all stages of thymoma were not demonstrated in our study, we believe that the long-term survival of thymoma patients is increasing partly because of the clinical application of modern imaging and RT.

This meta-analysis has several potential limitations that should be taken into account. One limitation is the quality of the supporting literature. No randomized trials exist that address the efficacy of PORT. All the published data were obtained from retrospective cohort studies. We clearly understand that it would be ideal for a sufficient number of patients to be recruited within a short time to form a prospective study. However, the relative rareness of the disease makes it quite difficult to perform a prospective study in these patients. In addition, confirming the effects of treatments require a long time because the clinical course of a thymoma is slow, making it difficult to perform prospective randomized clinical studies of affected individuals. Second, only articles in the English language were considered for our analysis. If the search had been extended to include literature published in other languages, it is possible that additional relevant trials may have been identified. Additionally, only few trials met the subgroup analysis criteria, thus reducing the power of the analyses. These factors may have a potential impact on our results.

In conclusion, surgical resection is the cornerstone of treatment for patients with thymoma, regardless of invasiveness. Our results showed that PORT for completely resected thymoma had no advantage in all stages of disease, but PORT definitely increased the rate of OS in stage II and III thymoma after complete resection. On the basis of this study, PORT will be beneficial in this clinical setting, especially in patients with stage II and III thymoma after complete resection. Our results give physicians a partial guideline for thymoma treatment. A multiinstitutional and randomized controlled trial needs to be performed to explain the mechanisms of the effects of PORT in this study and to enable understanding of the additional benefits of PORT regarding DFS and OS instead of relying on the lack of results of PORT from past negative cohort studies.

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