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Feasibility study of dose de-escalation in postoperative intensity-modulated radiation therapy for locally advanced thymoma

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Purpose: This study aimed to investigate retrospectively the feasibility of reducing the standard postoperative radiation therapy (PORT) dose of 45–50 Gy for locally invasive thymoma to shorten treatment duration and minimize side effects, while preserving disease-specific survival (DSS) and progression-free survival (PFS).

Materials and Methods: Between January 2016 and June 2022, 150 locally advanced thymoma patients underwent surgery followed by intensity-modulated radiation therapy, with a median follow-up of 40.8 months; the standard regimen was 45–50 Gy in 25 fractions (median biological effective dose [BED] 60 Gy), compared to a de-escalation regimen of 30–35 Gy in 10 fractions (median BED 47.25 Gy), with PFS as the primary endpoint, and overall survival (OS), DSS, and toxicity as secondary endpoints.

Results: No significant differences were found between standard and de-escalation groups in 3-year PFS ($p = 0.406$), with both groups achieving 100% 3-year DSS; two deaths in the de-escalation group were due to double primary cancers. All locoregional recurrences occurred outside the radiation field. Factors including age, initial tumor size, myasthenia gravis, and pathological type showed no correlation with PFS or OS. No grade II toxicities occurred in the de-escalation group, whereas the standard group had three cases of grade II toxicity, specifically radiation pneumonitis.

Conclusion: Radiation dose de-escalation in locally advanced thymoma patients undergoing PORT showed comparable survival outcomes with reduced toxicity and shorter treatment duration, but requires longer follow-up to confirm efficacy and safety.

Keywords: Thymoma, Adjuvant radiotherapy, Radiation dose hypofractionation, Dose-response relationship

Introduction

Thymomas are rare tumors which originated from thymic epithelial cells (TEC). While thymoma is one of the most common tumors of the anterior mediastinum neoplasm, the etiology of thymoma has not been confirmed yet [1]. The most widely used prognostic factors for thymoma are Masaoka stage and histologic types. Given the limited predictive value of the TNM stating system for individuals with thymoma, the classification relies on the Masaoka stage, which assessed the extent of tumor invasion into adjacent fatty tissue or organs. Histological subtypes of thymoma are categorized based on their morphological appearance and the ratio of lymphocytes to TEC [2,3]. Histological types A, AB, and B1 are considered to carry a lower risk, whereas types B2 and B3 are associated with

a higher risk. Consequently, the approach to treating thymoma varies according to these Masaoka stages and histological classifications. Complete surgical removal stands as the foremost treatment approach for thymoma, with the extent of resection being a critical prognostic indicator for both progression-free survival (PFS) and disease-specific survival (DSS) [4-6]. Given the high sensitivity of thymoma to radiation, radiation therapy (RT) is utilized in several therapeutic contexts, including as postoperative treatment [7], as a definitive solution for thymomas that cannot be surgically removed, and as preoperative (neoadjuvant) therapy. RT aimed at palliation is also a viable option for thymomas deemed inoperable.

However, RT can cause several side effects. Mou et al. [8] have shown that although postoperative radiation therapy (PORT) following surgery enhanced both overall survival (OS) and cancer-specific survival than surgery alone group, PORT can also increase the risk of developing secondary cancers. Additionally, Adams et al. [9] have documented various side effects following mediastinal RT, including coronary artery disease, pericarditis, lung fibrosis, and valvular disease. These side effects were even progressed after finishing RT and the severity were dependent on radiation doses [9,10]. Ratosa et al. [11] have revealed a direct correlation between the average dose of radiation absorbed by the heart (heart-D_{mean}) and the occurrence of coronary heart disease, and the incidence of death due to radiation-related cardiac disease was especially high when heart-D_{mean} exceeds 5 Gy. Okubo et al. [12] reported a case of mycotic pseudoaneurysm of the brachiocephalic artery developed long after the administration of 50 Gy to the mediastinal region, which was administered after surgical removal of an invasive thymoma.

The increase in various side effects from mediastinal irradiation, which correlate with the radiation dose, suggests that dose de-escalation could be feasible way to reduce complications while shortening treatment duration, provided that it does not diminish the efficacy of the therapy. This research explored the possibility of lowering radiation doses and shortening the number of radiation fractions to lessen side effects, all while preserving rates of PFS, OS, and DSS.

Materials and Methods

1. Patients and treatment

In this retrospective study, we examined the data of patients from the Yonsei Cancer Center diagnosed with locally advanced thymoma who underwent RT following surgery from January 2016 to June 2022. A total of 152 patients were initially considered, all of whom received intensity-modulated radiation therapy. In all patients, the thymomas were completely resected (R0). The conventional RT regimen delivered 45–50 Gy across 25 fractions (with a median biological effective dose [BED] of 60 Gy), whereas the dose de-escalation RT cohort received 30–35 Gy over 10 fractions (with a median BED of 47.25 Gy). Two patients who underwent chemotherapy were excluded, leaving 150 patients for analysis. We collected clinical information at initial diagnosis and at the time of recurrence, including variables such as age, gender, Masaoka stage, histologic type, size of the initial tumor, presence of a secondary primary cancer, and existence of myasthenia gravis from the electronic medical records. Additionally, data on the location of thymoma recurrence, the interval to recurrence, survival time, cause of death, and types of salvage treatments for recurrence were also gathered. To compare the biological effective RT doses between the two groups, we calculated the BED using on alpha/beta ratio of 10.

Treatment results were assessed through chest computed tomography scans 1 month after the completion of PORT, followed by routine scans every 6–12 months throughout the follow-up period. Infield recurrence was classified as a recurrence within the planning target volume (PTV), outfield recurrence as an intrathoracic recurrence outside the PTV receiving 95% to 100% of the prescribed dose, and distant metastasis as recurrences occurring outside the thoracic region. The grading of adverse events (AEs) after RT was done according to the Common Terminology Criteria for Adverse Events version 4.0.

2. Statistical analysis

Statistical analyses were performed using SPSS software version 29.0 (IBM Corp., Armonk, NY, USA). The time from completion of RT to the first observed progression of thymoma defined PFS. OS was the time from the end of RT until the death of the patients, whole DSS measured the time from the conclusion of PORT to death specifically due to thymoma. The Kaplan-Meier method was employed to compute PFS, OS, and DSS, with the log-rank test assessing any significant differences between the two groups. Univariate Cox regression analysis was performed to identify significant prognostic factors, with p-values less than 0.05 considered statistically significant. In cases where no deaths occurred within certain patient groups, the Cox model yielded excessively wide confidence intervals. To mitigate this issue, Firth's bias correction method was applied.

Results

1. Patient characteristics

This study identified 152 patients with locally invasive thymoma from January 2016 to June 2022. Two patients who underwent chemotherapy both before and after surgery were omitted from

the study. Consequently, 150 patients were included in the analysis. These patients were divided into two groups based on the radiation dose they received: the standard dose group, which received 45–50 Gy over 25 fractions in 5 weeks, and the de-escalation group, which received 30–35 Gy over 10 fractions in 2 weeks (Fig. 1).

Table 1 outlines the overall demographics of the entire study cohort. Within this cohort, the de-escalation group comprised 28 male patients (62.2%), while the standard group included 53 male patients (50.5%), showing no significant gender distribution difference between the two groups (p = 0.126). Every patient underwent PORT. Among entire population, 50 patients were diagnosed at Masaoka stage IIA (33.3%), 90 at IIB (62.7%), and six at stage III (4.0%), with no notable variance in distribution between the de-escalation and standard groups (p = 0.509). The World Health Organization histologic types of AB and B2 were predominant, and this trend consistent across both treatment groups, with no significant disparity observed between them (p = 0.741). In the study,

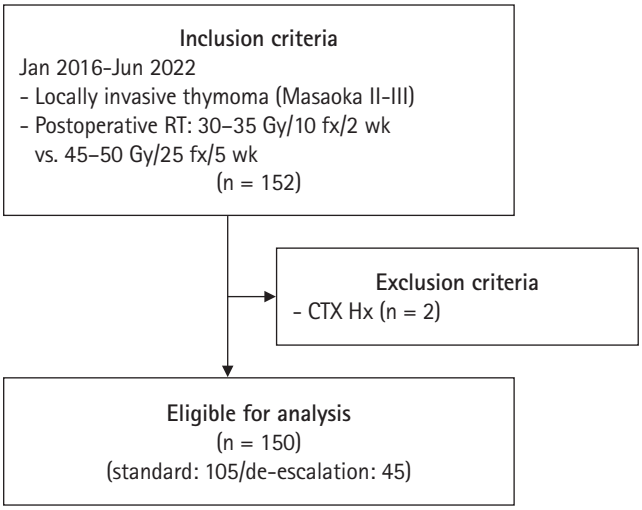

Fig. 1. Flowchart for the selection scheme of the study population. RT, radiation therapy; fx, fraction; wk, week; CTx Hx, chemotherapy history.

Table 1. Baseline characteristics of patients with locally invasive thymoma

	Total (n = 150)	De-escalation (n = 45)	Standard dose (n = 105)	p-value
Sex				0.213
Male	81 (54.0)	28 (62.2)	53 (50.5)	
Female	69 (46.0)	17 (37.8)	52 (49.5)	
Age (year)				0.936
20–29	4 (2.7)	1 (2.2)	3 (2.9)	
30–39	18 (12.0)	5 (11.1)	13 (12.4)	
40–49	27 (18.0)	9 (20.0)	18 (17.1)	
50–59	46 (30.6)	16 (35.6)	30 (28.6)	
60–69	36 (24.0)	9 (20.0)	27 (25.7)	
Over 70	19 (12.7)	5 (11.1)	14 (13.3)	
Masaoka stage				0.526
IIA	50 (33.3)	13 (28.9)	37 (35.2)	
IIB	94 (62.7)	31 (68.9)	63 (60.0)	
IIIA	6 (4.0)	1 (2.2)	5 (4.8)	
Histology type				0.744
A	10 (6.7)	3 (6.7)	7 (6.7)	
AB	54 (36.0)	15 (33.3)	39 (37.1)	
B1	17 (11.3)	7 (15.6)	10 (9.5)	
B2	50 (33.3)	16 (35.5)	34 (32.4)	
B3	19 (12.7)	4 (8.9)	15 (14.3)	
Tumor size (cm)				0.489
0–4.9	88 (58.7)	26 (57.8)	62 (59.0)	
5–9.9	59 (39.3)	19 (42.2)	40 (38.1)	
≥ 10	3 (2.0)	0 (0)	3 (2.9)	
Double primary				> 0.999
Yes	19 (12.7)	6 (13.3)	13 (12.4)	
No	131 (87.3)	39 (86.7)	92 (87.6)	

Values are presented as number (%).

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most tumors ranged in size from 0 to 4.9 cm, with merely three individuals throughout the entire group showing tumors greater than 10cm. The distribution was uniform across both treatment groups (p = 0.319). Furthermore, 12 patients were diagnosed with a secondary primary caner, each of which was completely treated with no signs of the disease left. The comparison showed no significant variance in the incidence of secondary primary cancers between the groups receiving dose de-escalation and those on the standard dose (p = 0.593).

2. OS and PFS

Median follow-up period was 40.8 months in this study. The 3-year OS rates were significantly different between de-escalation group and standard dose group (89.7% vs. 100%, p = 0.004) (Supplementary Fig. S1). Although two patients died in de-escalation group, they were dead because of secondary cancers; One patient succumbed to lung cancer, the other to stomach cancer, both of which were pathologically confirmed as secondary primary cancer following their initial diagnosis of locally invasive thymoma and subsequent surgery and RT. The 3-year DSS was identical in both groups (100% vs. 100%), indicating no significant difference in survival related to the disease itself. The 3-year PFS rates were similarly indistinguishable between the two groups (p = 0.406) (Fig. 2). Regarding recurrence patterns, all recurrences were observed in the standard dose group, with no instances of infield recurrence reported in this study (Supplementary Fig. S2).

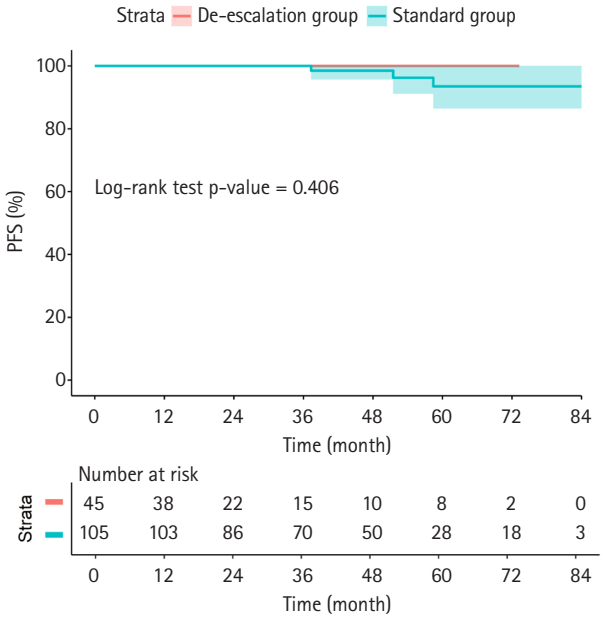

Fig. 2. Kaplan-Meier curves of progression-free survival (PFS) in de-escalation group versus standard dose group. Three-year PFS was 100% and 100% respectively (p = 0.406).

Three patients experienced distant metastases, all of whom underwent additional salvage pleurectomy to manage disease progression, including one patient undergoing third pleurectomy, another second, and a third also undergoing third pleurectomy. Following the repeated pleurectomies, these patients were still alive at the study's follow-up endpoint. There were no instances of salvage RT being used to manage disease progression or recurrence. Moreover, no instances of outfield recurrences were recorded in any patient throughout the study up to the final follow-up point.

Univariate analysis revealed that factors such as age, sex, the occurrence of a second primary cancer, the size of the tumor, the presence of myasthenia gravis, and the Masaoka stage did not significantly impact OS and PFS. Given the lack of significant predictors for OS and PFS identified in this study, a multivariate analysis was not conducted (Table 2).

3. Toxicity

Among total 45 patients in de-escalation group, just one manifested a grade 1 toxicity, presenting as slight chest pain, with none experiencing AEs beyond grade 2. Those in the standard dose population encountered higher level of toxicities. Within the 105 patients in this group, three suffered from grade 1 toxicities (one instance of chest pain and two of dyspnea on exertion), and another three displayed grade 2 (comprising one case of tachycardia and two of radiation-induced pneumonitis). The study did not report any toxicities exceeding grade 3. Despite these findings, the difference in the frequency of AEs across the two cohorts was not statistically significant. When analyzing the severity of all toxicities, the p-value for the comparison between the groups stood at 0.676, and was specifically 0.517 for grade 2 toxicities, as outlined in Supplementary Table S1.

Discussion and Conclusion

Previous research has shown that patients with locally advanced thymoma benefit from PORT [13-15]. The recommended adjuvant RT dose ranges from 45 to 50 Gy (1.8–2.0 Gy per daily fraction) for clear or close surgical margins, is largely based on retrospective analyses and empirical observations rather than phase I/II dose-finding studies [15-17] Our institutional experience with this 45–50 Gy regimen has historically shown low recurrence rates. However, considering the continuous debate regarding the clinical utility of PORT, particularly for Masaoka stage II thymoma, and the well-documented risk of dose-dependent AEs such as coronary artery disease, pericarditis, lung fibrosis, and valvular disease [8-12], the rationale for the de-escalated dose regimen was explored. This

Table 2. Prognostic factors for overall survival and progression-free survival (univariate analysis)

Variable	Overall survival		Progression-free survival	
	p-value	3-Year (%)	p-value	3-Year (%)
Sex				
Male (reference)	-	96.0	-	100
Female	0.257[a]	100	0.096[a]	100
Age (year)				
≥ 60 (reference)	-	97.1	-	100
< 60	0.763	98.5	0.343[a]	100
Double primary cancer				
No (reference)	-	100	-	100
Yes	0.006[a]	85.1	0.350	100
Tumor size (cm)				
< 5 (reference)	-	98.4	-	100
≥ 5	0.873	97.5	0.118	100
Myasthenia gravis				
No (reference)	-	98.4	-	100
Yes	0.508	96.8	0.762	100
Masaoka stage				
IIA (reference)	-	97.5	-	100
IIB	0.704[a]	98.0	0.718	100
IIIA	N/E	100	0.186	100

N/E, not evaluable.
[a]Firth's bias correction.

approach aimed to mitigate potential long-term toxicities and shorten treatment duration without compromising efficacy, referencing the outcomes of studies where PORT might be omitted entirely. The de-escalation protocol was implemented based on the treating physician's clinical judgment, balancing the known benefits of PORT with the potential to reduce treatment burden and side effects in a disease with often indolent behavior.

In this study, we compared OS, DSS, and PFS between two groups: a de-escalation group, which received 30–35 Gy over 10 fractions in 2 weeks, and a standard treatment group, which received 45–50 Gy over 25 fractions in 5 weeks. With a median follow-up of 40.8 months, there were no significant differences in PFS and DSS between the groups. Although there was a notable difference in OS, this was attributed to the occurrence of second primary cancers.

Upon examining potential prognostic variables, we found that none of the factors considered—age, sex, presence of myasthenia gravis and double primary cancer, tumor size, and Masaoka stage—had an impact on OS and PFS. Regarding local control, there were no infield recurrences in either group, defined as a relapse within the PTV volume. This indicates that the de-escalation group did not compromise progression rates compared to the standard group. Therefore, the dose de-escalation strategy is a viable method that does not impair survival or progression rates. However, while tumor size was not a significant factor in PFS, three patients in the standard group with tumors measuring 5 to 10 cm in diameter experienced distant metastases. This discrepancy might be due to the small sample size, suggesting that with a larger population, tumor size could become a more meaningful factor in predicting prognosis.

The study observed no toxicity greater than grade 3, and particularly in the de-escalation group, only grade 1 toxicity was noted. Since the de-escalation group experienced no more than grade 2 toxicity, dose de-escalation might be safer than the standard radiation dose.

It is crucial to address the ongoing debate regarding the necessity of PORT for Masaoka stage II thymoma, which is classified as a T1 tumor in the TNM staging system. While some studies suggest that PORT may be omitted in this stage, our findings, coupled with evidence from the International Thymic Malignancies Interest Group retrospective database by Rimner et al. [15], indicate that PORT is associated with a significant OS benefit even in completely resected stage II thymoma. Given that the majority (96%) of our cohort comprised patients with stage II disease, reducing the PORT dose, even if PORT might be omitted in some cases, could still be beneficial by mitigating toxicity while potentially retaining the survival advantages observed. Although the number of stage III pa-

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tients in our cohort was small, dose de-escalation did not appear to compromise recurrence or survival outcomes. A future study with a larger patient population will be necessary to draw more definitive conclusions, and we acknowledge that this is a limitation inherent to the retrospective design of our analysis.

After all, we would conclude that de-escalated dose hypofractionated PORT shows the same treatment effect as standard dose treatment, while reducing radiation toxicity and shortening the treatment period for patients with locally advanced thymoma.

However, there are several limitations in this study. First, the population size might be insufficient. As mentioned earlier, distant metastasis only occurred when the tumor size exceeded 5 cm. Therefore, if the sample size were larger, the results of the univariate analysis might differ, as other studies have shown that the Masaoka stage is a predictive factor for OS and PFS in thymoma patients [13,14]. Second, the follow-up duration should have been longer than in this research. We could only obtain 3-year OS, DSS, and PFS, as the median follow-up period was 40.8 months, showing no difference in DSS and PFS. With a longer duration, we might have been able to obtain 5-year and 10-year OS, DSS, and PFS, potentially altering the study results. Lastly, to thoroughly assess the feasibility of dose de-escalation in patients with thymic tumors, further studies are needed to include a broader range of thymic cancer patients. Since we only investigated the practicability of dose de-escalation in locally advanced thymoma patients, we could not determine whether this strategy applies to all patients with malignant thymic tumors. Therefore, further studies with larger populations, longer follow-ups, and including all Masaoka stages are needed to verify the feasibility of dose de-escalation in thymic tumor patients. Specifically, the results of this retrospective study highlight the critical need for future prospective randomized controlled trials to definitively establish the optimal and appropriate radiation dose for PORT in thymoma, moving beyond empirical selections.

Statement of Ethics

The protocol of this study was approved by the Yonsei University College of Medicine, Severance Hospital, Institutional Review Board (4-2024-0278). Written informed consent was not required, which is decided by the Yonsei University College of Medicine, Severance Hospital, Institutional Review Board committee.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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None.

Author Contributions

Conceptualization, YJH, CGL; Data curation, YJH, HC, JL, SHM; Investigation, YJH, HC, JL, SHM; Statistical analysis, YJH; Validation, EHK; Project administration, CGL; Supervision, CGL; Writing of the original draft, YJH; Writing of the review and editing, EHK.

Data Availability Statement

The data supporting this study's findings are not publicly available as they contain information that could potentially compromise participant privacy but are available from the corresponding author.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.3857/roj.2025.00255.

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