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Elective Nodal Irradiation as Adjuvant Radiotherapy for Advanced Thymomas and Thymic Carcinomas

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Abstract

There are few reports on the field of adjuvant radiotherapy in thymic tumors. We evaluated the clinical outcomes of local radiotherapy and elective nodal irradiation in 47 patients with stage III to IV thymomas or stage II to IV thymic carcinomas. The benefit of elective nodal irradiation seemed not to be predominant over local radiotherapy, so elective nodal irradiation should not be recommended routinely.

Introduction: We evaluated the clinical outcome of patients with stage III to IV thymomas (Ts) or stage II to IV thymic carcinomas (TCs) treated with complete thymectomy and local radiation therapy (LRT, targeting the tumor bed and anterior mediastinal areas only) or elective nodal irradiation (ENI, targeting the entire mediastinal and supraclavicular regions). **Materials and Methods:** Data from 47 patients diagnosed with Ts or TCs and treated with surgery and adjuvant RT from May 2002 to May 2015 were analyzed. The standard RT dose was 50.4 Gy in 28 fractions; patients with a positive resection margin received a further 4 to 10 Gy. Survival outcomes determined at 5 years included local recurrence-free survival, regional recurrence-free survival, distant metastasis-free survival, and overall survival. **Results:** Five-year local recurrence-free survival was similar in both groups (LRT, 94.7% vs. ENI, 96.2%; $P = .849$). Significant differences were seen in 5-year regional recurrence-free survival (LRT, 55.1% vs. ENI, 83.7%; $P = .006$); however, tumor size was seen to be a significant factor (< 7 cm, 95.2% vs. ≥ 7 cm, 48.9%; $P < .001$), and the LRT group contained a greater proportion of patients with ≥ 7-cm tumors (70% vs. 33%). Multivariate analysis demonstrated that tumor size was the only significant prognostic factor ($P < .001$). No differences in 5-year overall survival were seen (LRT, 91.7% vs. ENI, 100%; $P = .106$). **Conclusion:** ENI may not be indicated in all cases, as additional benefit in reducing recurrence or improving survival was not predominant. LRT seems to be a feasible option with favorable patient outcomes.

Introduction

The role of adjuvant radiation therapy (RT) in the treatment of thymomas (Ts) and thymic carcinomas (TCs) remains controversial. Previous studies suggest that excellent long-term control of Masaoka stage I Ts can be achieved after R0 resection without the requirement for adjuvant therapy.[1,2] In addition, several retrospective

studies have found no survival benefit associated with adjuvant RT in stage II Ts.[3,4] Some benefit has, however, been shown in patients with stage III and IV Ts.[5-7] As TCs have a more aggressive pathology than Ts, adjuvant RT is considered in patients with stage II to IV tumors.[8,9]

Previous studies have focused largely on clinical outcomes, with few reports investigating outcomes related to the radiation treatment field. Studies of elective nodal irradiation (ENI) have been reported, but its efficacy is unclear owing to the low rate of lymphogenous metastasis associated with Ts. Kondo et al analyzed lymph node (LN) metastasis in Ts and TCs, reporting a rate of nodal metastasis of 1.8% and 27%, respectively.[10] Moreover, most tumors with LN disease metastasized to anterior mediastinal LNs (Ts, 90%; TCs, 69%). Elective nodal coverage is not routinely recommended in clinical practice, and there are little data available on the efficacy of

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ENI. Therefore, we evaluated the clinical outcome of patients with stage III to IV Ts/TCs or stage II TCs treated with local RT (LRT) or ENI in a single tertiary referral center.

Materials and Methods

Patients

Data from patients diagnosed with Ts or TCs and treated with surgery and adjuvant RT at our hospital between May 2002 and May 2015 were included in the analysis. Among 154 patients, 52 patients had stage III to IV Ts/TCs or stage II TCs. Patients who had no available follow-up data (n = 3) and those with gross residual disease after surgery (n = 2) were excluded from the study. Data from the remaining 47 patients were included in the analysis. The tumor stage was determined according to the Masaoka-Koga staging system.[11] Pathologic examination was performed according to the World Health Organization (WHO) classification system.[12] A waiver of informed consent was obtained from the local institutional review board prior to analysis.

Treatment

Complete thymectomy was performed in all patients. Partial lung resection or great vessel resection was performed if required. ENI was conducted according to the protocols of individual radiation oncologists. For LRT, computed tomography (CT) images with a slide thickness of 2.5 mm were acquired. The tumor bed was delineated according to the first diagnostic and postoperative images. The clinical target volume (CTV) was contoured radially along the anterior perithymic nodal areas with 2-cm longitudinal extension. The planning target volume (PTV) involved a 7-mm expansion of the CTV (Figure 1A). The radiation field was reduced after irradiating 41.4 Gy (fraction size of 1.8 Gy) for some patients. In these cases, reduced volume was defined as a 7- to 10-mm expansion of the tumor bed. The standard RT dose was 50.4 Gy in 28 fractions in cases with a clear resection. Patients with a positive resection margin (RM) received a further 4 to 10 Gy (fraction size of 1.8-2 Gy).

ENI covered not only the anterior mediastinal nodal area, but also the deep mediastinal and supraclavicular regions (Figure 1B). Prior to August 2008, a 2-dimensional planning technique using 2 anterior and posterior parallel pairs (AP/PA) was utilized for ENI. After 41.4 Gy irradiation, CT images were acquired for reducing the radiation field. The reduced volume of ENI was the same as the initial volume of LRT. After August 2008, CT simulation was also adopted for the initial planning of ENI (Figure 1C). Treatment verification was performed via weekly kV imaging guidance using set-up correction based on bony anatomy.

Some patients received neoadjuvant chemotherapy to reduce tumor volume and facilitate R0 resection. The regimens included 2 to 4 cycles of the following: (1) ADOC: doxorubicin (40 mg/m^2) and cisplatin (50 mg/m^2) on day 1, vincristine (0.6 mg/m^2) on day 3, and cyclophosphamide (700 mg/m^2) on day 4 every 4 weeks; (2) IP: ifosfamide (1500 mg/m^2) and cisplatin (20 mg/m^2) on days 1 to 5 with mesna uroprotection on days 1 to 6, every 4 weeks; (3) ICE: ifosfamide (1500 mg/m^2) and etoposide (60 mg/m^2) on days 1 to 3 with mesna uroprotection on days 1 to 4 and carboplatin (300 mg/m^2) on day 1, every 3 weeks. No adjuvant chemotherapy was administered.

Complete blood count tests and chest x-rays (CXRs) were performed weekly in all patients during RT. Patients were routinely followed up by a radiation oncologist and/or medical oncologist; chest CT and chest x-ray was performed 1 month after treatment, every 3 months during the first 2 years, and every 6 months thereafter until the 5-year timepoint.

Evaluation of Survival and Statistical Analysis

The survival outcomes included 5-year local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), distant metastasis-free survival (DMFS), and overall survival (OS). Outcome measures were defined according to the International Thymic Malignancy Interest Group (ITMIG) guidelines.[13] Local recurrence was defined as in-field failures; regional recurrence was defined as any intrathoracic failure including pleural, pericardial nodules, and LN adjacent to the primary lesion. Distant metastases included extrathoracic and intraparenchymal pulmonary nodules. Toxicities were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Adverse events occurring during treatment and within 3 months of CRT were defined as acute toxicities.

All survival parameters were evaluated from the start of treatment. Survival was calculated using the Kaplan-Meier method from the date of treatment discontinuation until death. The log-rank test was used for univariate analysis; the Cox proportional hazard model was used for multivariate analysis. All statistical tests were performed using SPSS version 21.0.

Figure 1 Irradiated Field of Local Radiotherapy (A) and Elective Nodal Irradiation (B, C)
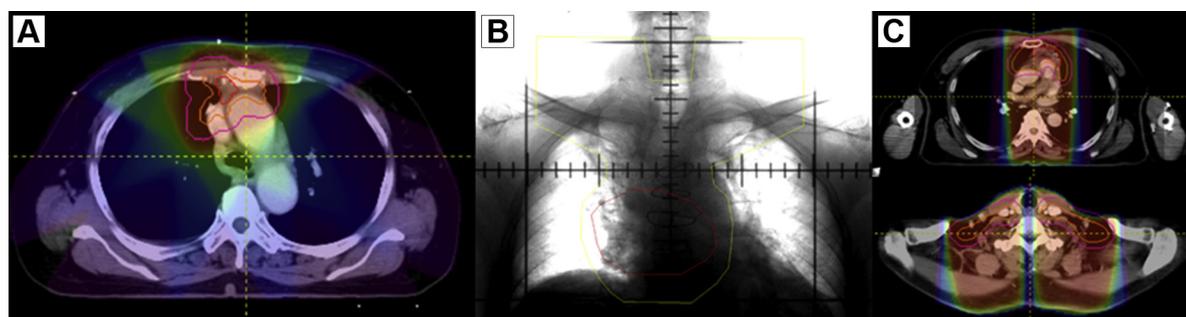
Table 1	Patient Characteristics		
	LRT (n = 20), n (%)	ENI (n = 27), n (%)	*P*
Gender			.960
Male	12 (60.0)	16 (59.3)	
Female	8 (40.0)	11 (40.7)	
Median age, y (range)	53.5 (30-72)	52 (36-75)	.595
ECOG performance status			.104
0	7 (35.0)	16 (59.3)	
1	13 (65.0)	11 (40.7)	
Pathologic classification			.987
A-B1	5 (25.0)	2 (7.4)	
B2-3	4 (20.0)	15 (55.6)	
C	11 (55.0)	10 (37.0)	
Masaoka stage			.493
IIA	3 (15.0)	3 (11.1)	
IIB	1 (5.0)	2 (7.4)	
III	14 (70.0)	17 (63.0)	
IVB	2 (10.0)	5 (18.5)	
Combined MG			.986
No	17 (85.0)	23 (85.2)	
Yes	3 (15.0)	4 (14.8)	
Median tumor size, cm (range)	7.5 (3.7-16.0)	6.0 (2.7-11.0)	.020
<7	6 (30.0)	18 (66.7)	.012
≥7	14 (70.0)	9 (33.3)	

Abbreviations: ECOG = Eastern Cooperative Oncology Group; ENI = elective nodal irradiation; LRT = local radiotherapy; MG = myasthenia gravis.

Table 2	Treatment Characteristics		
	LRT (n = 20), n (%)	ENI (n = 27), n (%)	*P*
Type of surgery			.588
Thymectomy	8 (40.0)	13 (48.1)	
Thymectomy + partial lung resection	12 (60.0)	14 (51.9)	
VATS			.112
No	8 (40.0)	13 (48.1)	
Yes	12 (60.0)	14 (51.9)	
RM			.829
Negative	15 (75.0)	21 (77.8)	
Positive	5 (25.0)	6 (22.2)	
Number of positive LN(s)			.240
0	18 (90.0)	22 (81.5)	
1	2 (10.0)	3 (11.1)	
2	0 (0.0)	2 (7.4)	
Neoadjuvant chemotherapy			.601
No	15 (75.0)	22 (81.5)	
Yes	5 (25.0)	5 (18.5)	
Median radiation dose, Gy (range)	50.4 (48.6-62)	50.4 (50.4-59.4)	.863

Abbreviations: ENI = Elective nodal irradiation; LN = lymph node; LRT = local radiotherapy; RM = resection margin; VATS = video-assisted thoracoscopic surgery.

48.6-62 Gy). All treatment variables were identical between the 2 groups (Table 2).
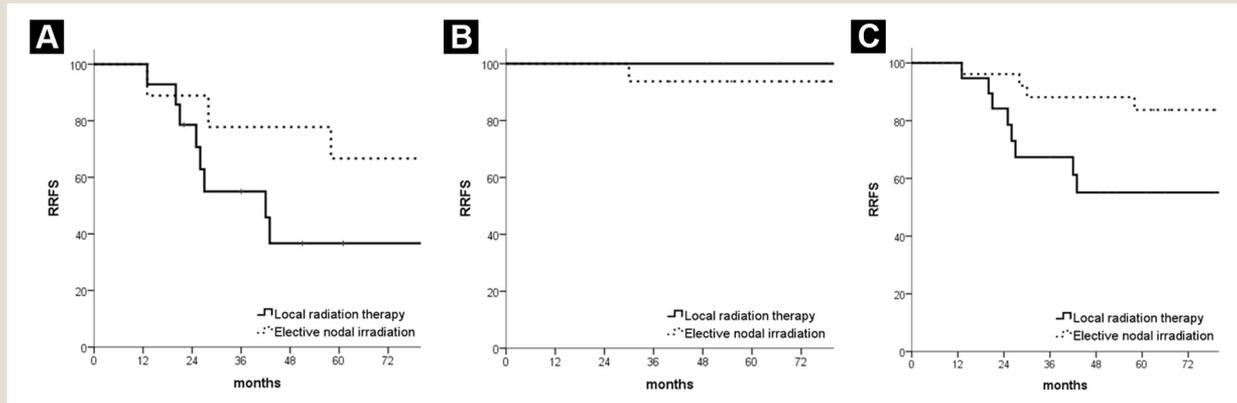
Assessment of Recurrence and Survival

With a median follow-up time of 68 months (range, 8-162 months), 5-year LRFS, RRFS, DMFS, and OS were 95.6%, 71.6%, 76.7%, and 97.4%, respectively.

Local recurrence occurred in only 2 cases, 1 in each of the RT field groups. The recurrence site of the case in the LRT group was the left anterior pleura, and the multiple pleural recurrences were combined. The site of recurrence in the ENI group was the left hilar LN, and lung metastasis was occurred before the hilar LN recurrence in this case. No mediastinal or supraclavicular recurrences were seen. No differences in 5-year LRFS were seen between the 2 treatment groups (LRT, 94.7% vs. ENI, 96.2%; *P* = .849).

A statistically significant difference was seen in 5-year RRFS between the 2 groups (LRT, 55.1% vs. ENI, 83.7%; *P* = .006) (Figure 2A). Variables analyzed in the univariate analysis included gender, age (< 65 vs. ≥ 65 years), Eastern Cooperative Oncology Group performance status, WHO pathologic classification (A-B1 vs. B2-3 vs. TCs), Masaoka stage, combined myasthenia gravis, and tumor size (< 7 cm vs. ≥ 7 cm). Of these, tumor size was seen to be a significant prognostic factor for RRFS (< 7 cm, 95.2% vs. ≥ 7 cm, 48.9%; *P* < .001). In addition, multivariate analysis showed tumor size to be the only statistically significant prognostic factor (*P* < .001), whereas RT field was not a significant indicator (*P* = .095). As the LRT group contained more patients with tumor size ≥ 7 cm, patients were grouped into small (< 7 cm) and bulky (≥ 7 cm) tumor subgroups to determine the effect of radiation field

Results

Patient Characteristics

The characteristics of the LRT and ENI groups are summarized in Table 1. Data from 47 patients were included in the analysis (28 male, 19 female; median age, 53 years; range, 30-75 years). Twenty-six patients were diagnosed with Ts, and 21 patients had TCs. The most common subtype of TC was squamous cell carcinoma (n = 15; 71%), followed by unknown subtype (n = 3; 14%), and single cases of neuroendocrine, basaloid, and epidermoid carcinoma. Nine patients had stage II disease, and 31 patients had stage III disease. Seven patients had stage IVB disease owing to nodal metastases alone, which were all removed after surgery. Most (5/7) of the metastatic LNs were located in anterior mediastinum and the rest of the patients had diaphragmatic LN and right cervical LN, respectively. Twenty patients were treated with LRT, and 27 received ENI. The LRT group contained more patients with large tumors (≥ 7 cm) than the ENI group. Otherwise, there were no significant differences between the 2 groups.

Treatment Characteristics

In addition to thymectomy, partial lung resection was performed in 26 patients. Video-assisted thoracoscopic surgery (VATS) was used in 5 patients. A positive RM was seen in 11 patients, and 7 patients had positive LN(s). Ten patients received neoadjuvant chemotherapy. The median radiation dose was 50.4 Gy (range,

Abbreviation: RRFS = Regional Recurrence-free survival.

according to tumor size. In the small tumor group, 5-year RRFS was 100.0% in the LRT arm and 93.8% in the ENI arm (*P* = .576) (Figure 2B). In the bulky tumor group, 5-year RRFS was 36.7% in the LRT group and 66.7% in the ENI group (*P* = .061) (Figure 2C). Among the 8 patients with TCs in the bulky tumor group, 6 patients were included in the LRT arm, whereas only 2 patients were included in the ENI arm.

The major pattern of failure was regional metastasis, with all 15 cases being pleura metastasis. Among them, only 3 cases were presented as a solitary recurrence. The locations were all middle and lower posterior pleura. In 1 patient, a salvage operation was performed with adjuvant RT; no further recurrence was seen thereafter for 137 months until death. The remaining 12 patients showed multiple pleural metastases, and most (10/12) had ipsilateral pleural

dissemination where the initial tumor was located. One case involved both sides of the pleura, and the other patient had contralateral pleural recurrence. No cases involved the cervical or mediastinal pleura covered by the ENI field. Concomitant distant metastasis was found in 6 cases, and distant metastasis occurred in 2 cases as a first relapse.

Of the 8 distant failures, the most common sites were lung (n = 4), bone (n = 3), and liver (n = 1). Five-year DMFS was not significantly different between the 2 groups (LRT, 65.7% vs. ENI, 84.4%; *P* = .203) (Figure 3A). WHO pathologic classification was the only meaningful prognostic factor in DMFS (A-B1, 100% vs. B2-3, 88.9% vs. TCs, 55.9%; *P* = .017). Five-year OS also showed no differences between the LRT and ENI groups (LRT, 91.7% vs. ENI, 100%; *P* = .106) (Figure 3B). No significant prognostic factors were identified for OS.
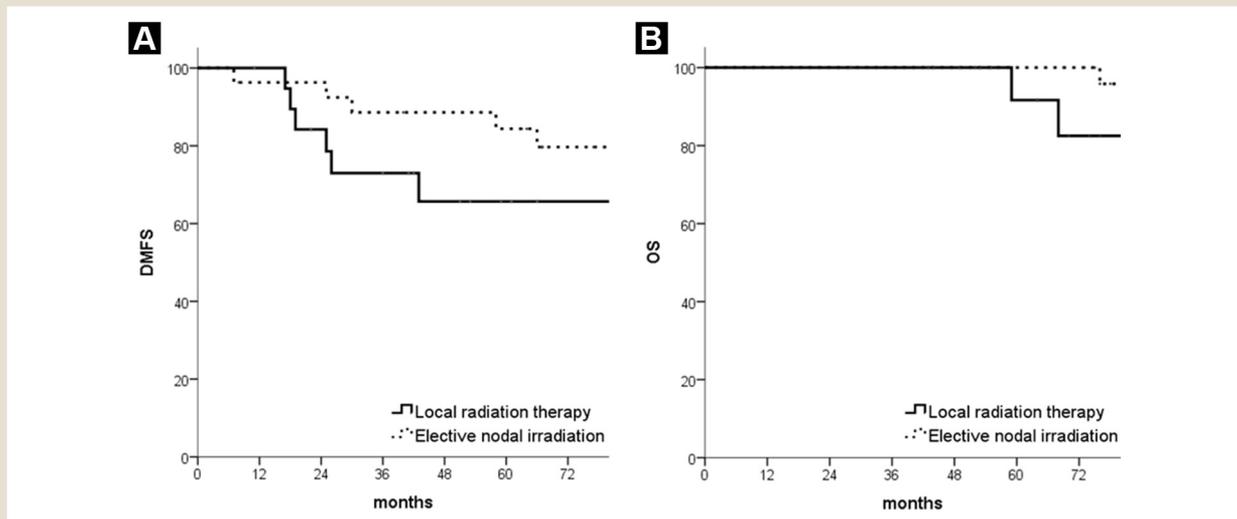
Abbreviations: DMFS = Distant metastasis-free survival; OS = overall survival.

Table 3	Acute Toxicities Associated With Adjuvant Radiotherapy		
Grade	**LRT (n = 20), n (%)**	**ENI (n = 27), n (%)**	**P**
Dermatitis			.469
0	19 (95.0)	24 (88.9)	
1	1 (5.0)	3 (11.1)	
Dysphagia			.011
0	17 (85.0)	14 (51.9)	
1	3 (15.0)	12 (44.4)	
2	0 (0.0)	1 (3.7)	
Chest pain			.759
0	18 (90.0)	25 (92.6)	
1	2 (10.0)	2 (7.4)	
Cough			.224
0	13 (65.0)	22 (81.5)	
1	7 (35.0)	5 (18.5)	
Dyspnea			.690
0	17 (85.0)	23 (85.2)	
1	2 (10.0)	4 (14.8)	
2	1 (5.0)	0 (0.0)	

Abbreviations: ENI = Elective nodal irradiation; LRT = local radiotherapy.

Toxicities

Acute toxicities associated with adjuvant RT are listed in Table 3. The incidence of grade 1 dysphagia was significantly higher in the ENI group owing to the AP/PA technique increasing the radiation dose to the esophagus. However, no late complications were seen.

Discussion

The present study demonstrates good control of advanced stage Ts and TCs treated with complete thymectomy combined with adjuvant RT (5-year OS, 97.4%). Although the 5-year OS of stage III and IV Ts is considered to be 50% to 87% and 46% to 50%, respectively, OS seen in the present study was notably higher.[14-16] This is likely owing to the fact that the present study enrolled patients who received R0 or R1 resections, which are associated with excellent survival rates. Indeed, a large study of 1320 patients reported similar OS rates in patients with totally resected stage III to IV Ts (5-year OS, 92.9%) and TCs (5-year OS, 66.9%).[17] The study also reported the recurrence rate of stage III Ts to be 28.4%, stage IV Ts to be 64.3%, and TCs to be 51%, which is comparable to our results.

Regardless of RT field, the use of adjuvant RT in patients with Ts and TCs remains controversial. Although there are studies supporting adjuvant RT in terms of disease-free survival and OS,[5-7] several reports also show that adjuvant RT has no role in preventing recurrence and improving survival.[17-19] Nevertheless, good local control has been achieved through the use of adjuvant RT,[20,21] and it is recommended in the treatment of advanced stage Ts and TCs.

In the present study, ENI provided no additional benefit over LRT in terms of loco-regional control and survival. Although there was a trend towards inferior RRFS in the LRT subgroup of patients

with bulky tumors (Figure 2C), we attributed this to a higher level of enrollment of TCs in the LRT arm. Assessment of the failure pattern also did not support the use of ENI over LRT as the site of local recurrence in the LRT group was the irradiated pleura. All regional recurrences occurred in the distant pleura but not the cervical or mediastinal pleura. These findings are consistent with the results of a previous study investigating the failure patterns of stage II to IV Ts.[21] Using LRT only, the 5-year local recurrence and regional recurrence rate was 7% and 24%, respectively. Most regional recurrences occurred in the pleura (29/34), particularly in the costal and diaphragmatic pleura. In an attempt to reduce pleura recurrence, prophylactic entire hemithorax irradiation (EHI) has been used.[22] In this study, of 43 patients diagnosed with stage II to III Ts, only 1 of the 23 patients who received EHI relapsed, whereas 8 of the 20 patients treated with LRT relapsed. Five-year RRFS was 100% in the EHI group and 66% in the LRT group (P = .03). Significant radiation pneumonitis requiring treatment occurred in 1 patient in the LRT group and 3 patients in the EHI group. As ipsilateral pleural seeding was dominant, prophylactic EHI may have a future role with the advent of conformal techniques such as intensity-modulated RT.

We acknowledge that this study is limited by the small patient number and retrospective design, which is inherently susceptible to selection bias. As the tumor types investigated are rare, the patient population was heterogeneous with a variety of prognostic factors, and not all variables were balanced between the 2 groups. There was also the possibility of underestimation of acute and late toxicities. Nevertheless, all patients were diagnosed and treated in a single tertiary medical center, which minimized heterogeneity in diagnosis and treatment.

Conclusions

As ENI does not seem to provide predominant benefit over LRT in terms of reducing local-regional recurrence and improving survival, ENI should not be indicated in all thymic tumors. LRT might be a reasonable treatment option to achieve favorable local control. Because ipsilateral pleural recurrence was seen to be the main pattern of failure, strategies to prevent pleural metastasis, such as EHI, warrant further investigation.

Clinical Practice Points

- ENI targeting the entire mediastinal and supraclavicular regions is not routinely recommended as adjuvant treatment for Ts owing to the low rate of lymphogenous metastasis. Also, it is not widely used for TCs because the majority of nodal disease metastasized to anterior mediastinal LNs. However, there are little clinical data directly comparing the LRT targeting the tumor bed and anterior mediastinal areas only and ENI for thymic tumors.
- In this retrospective study recruiting 47 patients with stage III to IV Ts and stage II to IV TCs, we evaluated the efficacies of LRT and ENI. Five-year LRFS was similar in both groups with excellent local control (LRT, 94.7% vs. ENI, 96.2%; P = .849). Although there was significant differences in 5-year RRFS (LRT, 55.1% vs. ENI, 83.7%; P = .006), the LRT group contained a greater proportion of patients with ≥ 7 cm tumors (70% vs.

33%) which is a bad prognostic factor. There was no difference in 5-year OS (LRT, 91.7% vs. ENI, 100%; *P* = .106).

- In the present study, ENI does not demonstrate evident benefit in reducing recurrence or improving survival. The results do not support the routine use of ENI, and LRT might be sufficient in the majority of thymic tumors.

Disclosure

The authors have stated that they have no conflicts of interest.

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