Local radiotherapy for pleural dissemination of thymic tumors after initial treatment

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ABSTRACT

Pleural dissemination is a common pattern of failure after initial treatment of thymoma and thymic carcinoma, but there is no standardized treatment. As these tumors are relatively radiosensitive, we investigated the effectiveness of radiotherapy. Twenty patients underwent 33 series of local radiotherapy for 96 pleural dissemination lesions after initial treatment. Conventional radiotherapy (CRT), tomotherapy, and combination of the two were employed in 19, 13, and 1 series, respectively. The median follow-up period after the first irradiation for pleural dissemination was 46 months (range, 14–161). For all 20 patients, overall survival (OS) rates from initial radiotherapy for pleural dissemination were 100% at three years and 86% at five years. Progression-free survival (PFS) rates after 33 series of radiotherapy were 30% at three years and 16% at five years. Local control (LC) rates for 96 lesions were 98% at three years and 96% at five years. In-field recurrence was observed in only two among the 96 lesions. One patient (5%) developed grade 3 radiation pneumonitis and another (5%) developed grade 3 pericardial effusion. No other serious adverse events were observed. When disseminated nodules can be covered within localized fields, local radiotherapy may be a treatment option. Using tomotherapy, multiple lesions can be treated safely.

Keywords: thymic tumors; pleural dissemination; local radiation therapy; intensity modulated radiation therapy

INTRODUCTION

Thymic epithelial tumors are relatively rare, with an incidence of approximately 0.13 per 100 000 person–years [1], but they are the most common primary tumor of the anterior mediastinum in adults. The treatment strategy is determined based on the disease stage; when the tumor is considered resectable, surgery is generally attempted. Radiation therapy and chemotherapy may be considered for unresectable cases. Postoperative radiation therapy is also often employed. Although the recurrence rates depend on the histological subtypes, invasive thymoma and thymic carcinoma relatively frequently develop recurrence after initial treatment; the recurrence rate after initial complete resection of the primary tumor ranges between 10% and 30% [2–4]. Long-term observation is necessary because relapse develops relatively late after initial treatment [5,6]. Completeness of resection is the most significant prognostic factor [2], and incompletely resected cases have a risk of relapse. The recurrent lesions of thymoma are often located in the pleura, anterior mediastinum, and pericardium [2].

There have been few reports analyzing treatment for recurrence of thymic tumors. Several reports demonstrated good survival rates following as much surgical removal of recurrent lesions as possible [7–9], whereas chemotherapy and radiation therapy were also recommended in several reports [10–12]. However, there are only a few reports regarding treatment for pleural dissemination. Many treatments have been tried [13–15], but no standard treatment has been established. Treatment of recurrent thymoma is selected according to the individual situation due to the technical problems of repeated surgery and the relationship with surrounding organs.

As thymic tumors are known to be relatively radiosensitive neoplasms and often exhibit insidious progression, we have employed local radiation therapy for pleural disseminations of thymic tumors since more than 14 years ago. When pleural disseminations are untreated, pleural effusion, local pain, vascular invasion and spinal canal invasion may develop, which may negatively affect the prognosis [16,17]. Also, the presence of pleural dissemination may be a cause of further

dissemination. Therefore, we hypothesized that radiation therapy should play a role in controlling the lesion and preventing future occurrence of pleural effusion and other conditions and have the potential to improve the prognosis of the patients, provided that the treatment can be delivered without major complications. There have been no large studies, to our knowledge, that investigated the efficacy of local irradiation for pleural disseminations of thymic tumors; therefore, we investigated the usefulness of local radiotherapy for this condition.

MATERIALS AND METHODS
Patients
This study was approved by the Institutional Review Board of Nagoya City University Graduate School of Medical Sciences (approval number: 60-19-0128) and was conducted in compliance with the guidelines of the Helsinki Declaration. As this study is a retrospective study, informed consent was obtained from all patients in the form of opt-out on the website. We reviewed medical records of patients who had been radiologically or histologically diagnosed with pleural dissemination of thymoma or thymic carcinoma between March 2005 and May 2018, and received radiation therapy for pleural dissemination at our institution. Indications for the treatment were considered as follows: (i) pleural disseminations enlarging over time, (ii) patient refusal of other treatment options including surgery and chemotherapy, and (iii) no pleural effusion. Because of the criterion (1), the largest diameter of tumors in the axial plane was usually ≥10 mm, but smaller tumors were treated simultaneously when the tumors were multiple and the largest one was ≥10 mm. Hereinafter, the tumor size is defined as the maximum thickness from the pleura (mm) × diameter orthogonal to its line in the axial plane (mm). Twenty patients were identified for inclusion in this study. Our criteria for radiological diagnosis of pleural dissemination were previously published [18]. Local pleural recurrence was defined as a new pleural (parietal, visceral, or interlobar) nodule detected on computed tomography (CT) after initial surgical or chemoradiotherapy treatment. For this analysis, two patients palliatively treated for pain relief were excluded. No patient had active double cancer. No patient received concurrent chemoradiotherapy for pleural dissemination, but three received chemotherapy after radiation. The Eastern Cooperative Oncology Group (ECOG) performance status (PS) was 0–2 in all patients. Seven of the 20 patients received irradiation twice and two received irradiation four times in total for pleural disseminations at different sites. Multiple pleural dissemination lesions were treated simultaneously in 11 patients. As a result, 33 treatment series were carried out and 96 tumors were treated in total. The patient characteristics and treatment history are shown in Table 1.

Planning and treatment
Our treatment planning method was described in detail previously [19]. Briefly, all patients underwent planning CT with a slice thickness of 2.5 or 3.2 mm under shallow free breathing. When respiratory movements of the lesions were large, CT during inspiratory and expiratory phases was added. The clinical target volume (CTV) was the visible tumor volume and that on CT during the three phases was superimposed on 3D radiation treatment planning systems. The mean planning target volume (PTV) margin was 7 mm (standard deviation, SD, 2) for the lung and chest wall sides, and 8 mm (SD, 2) for the craniocaudal

Table 1. Patient characteristics and treatment history

Patient and treatment characteristics	Number of patients
Age at diagnosis (years) Median (range)	60 (32–81)
Sex (male/female)	9 / 11
Masaoka stage at diagnosis (III/IVa/IVb/unknown)	10 / 8 / 1 / 1
WHO histology (A/AB/B1/B2/B3/TC/unknown)	1 / 2 / 1 / 8 / 4 / 3 / 1
Myasthenia gravis (yes/no)	6 / 14
Initial surgical resection (yes/no)	19 / 1
Previous radiotherapy (yes/no)	16 / 4
Mediastinum irradiation (yes/no)	12 / 8
Hemithorax irradiation (yes/no)	4 / 16
Previous chemotherapy (yes/no)	14 / 6
Steroid pulse before radiotherapy (yes/no)	6 / 14

direction. It was intended to cover 95% of the PTV with ≥95% of the prescribed dose. The maximum dose allowed within the PTV was 107%. Regarding the dose constraints of organs at risk, the volume of the lung receiving ≥20 Gy (V_{20Gy}), mean lung dose, heart V_{30Gy} and mean heart dose were set to be <35%, <20 Gy, <45% and < 26 Gy, respectively. In tomotherapy planning, lung V_{5Gy} was kept below 65%.

All radiation therapy was carried out using 6- or 10-MV X rays with fractionation every weekday. In the treatment series using conventional radiotherapy (CRT), tangential or parallel opposing fields or multiple fields whenever necessary were used to treat the lesion. More recently, tomotherapy (TomoTherapy® or Radixact® System, Accuray, Sunnyvale, CA, USA) was used in 14 series to simultaneously treat multiple lesions; the TomoHelical mode was used in 12 series and the TomoDirect mode was used in 1. In the remaining 1 series, CRT was used first and then TomoDirect radiation was used after 40 Gy. In general, CRT was used to treat one or two lesions, and tomotherapy was used to simultaneously treat three or more lesions. However, depending upon the location and shape of the tumors, tomotherapy was also used to treat one or two lesions; especially tomotherapy was considered useful when the tumors existed near the previously irradiated regions. Our method of tomotherapy for pleural disseminations was similar to those used for breast cancer as described in detail previously [20]. The details of radiation therapy and tumor characteristics are shown in Table 2. Using CRT, the median tumor number treated per series was 1 (range 1–5), whereas it was 3 (range 1–20) for tomotherapy. In cases treated by the combination of CRT and tomotherapy, the target number was 4. The median dose per fraction was 2.0 Gy (range, 1.5–3.0) and the median total dose was 50 Gy (range, 39–60).

Evaluation
All patients were followed up by regular CT after radiation therapy. The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was used to evaluate tumor response. Toxicity was rated according

Table 2. Treatment details and tumor characteristics

Treatment / tumor details	Number
Total treatment patients / series / lesions	20 / 33 / 96
CRT[a] / tomotherapy / CRT + tomotherapy (series)	19 / 13 / 1
Total prescribed dose (Gy) Median (range)	50 (39–60)
Dose per fraction (Gy) Median (range)	2.0 (1.5–3.0)
BED_{10}[b] (Gy) Median (range)	65 (48–75)
Maximum tumor thickness from pleura (mm) Median (range)	9 (3–40)
Maximum tumor diameter (mm) Median (range)	20 (5–76)
Tumor size[c] (mm^2) Median (range)	181 (15–2240)

[a]CRT, conventional radiation therapy.
[b]BED_{10}, biologically effective dose with an α/β ratio of 10 Gy.
[c]Tumor size is defined by the maximum thickness from the pleura (mm) × diameter (mm) orthogonal to its line in the axial plane.

to the Common Terminology Criteria for Adverse Events version 5.0. Overall survival (OS) rates for 20 patients, progression-free survival (PFS) rates after 33 series of treatment, and local control (LC) rates for 96 tumors were calculated from the date of starting radiation therapy using the Kaplan–Meier method. Differences between subgroups in these curves were analyzed by the log-rank test. The data were evaluated by adopting the WHO histological classification before revision [21] that was actually used at the time of definitive diagnosis. Results were regarded as significant if the probability value was less than 5% ($p < 0.05$). All statistical analyses were carried out using the open source software EZR version 1.40. The multivariate Cox proportional hazard model was used to evaluate the variables showing associations with OS in the univariate analyses.

RESULTS
Survival, progression-free survival and local control
The median follow-up period after the first radiotherapy session for pleural dissemination was 46 months (range, 14–161). The mean ages (± SD) at the time of initial treatment and the time of irradiation for pleural dissemination were 53 ± 12 and 59 ± 12 years, respectively. The median time from initial treatment to recurrence was 36 months (range, 5–171), and that to local radiation therapy for pleural dissemination was 52 months (range, 15–221).

The OS, PFS, and LC curves for the 20 patients, 33 series of treatment, and 96 tumors are shown in Fig. 1. For all 20 patients, the OS was 100% at three years and 86% at five years. Two patients died of the disease and one died of an unknown cause. The PFS after 33 series of treatment was 30% at three years and 16% at five years. Only one patient developed distant metastases in the peritoneum, and pleural recurrence at different sites was observed after 23 series of treatment. The median time to recurrence was 18 months (range, 2–113). LC rates for the 96 lesions were 98% at three years and 96% at five years.

In-field local recurrence developed for two lesions; one was type B3 thymoma with a size of 442 mm^2 treated by 50 Gy in 25 fractions and another was type A with a size of 551 mm^2 treated by 60 Gy in 30 fractions. A scatter diagram of LC status according to the size
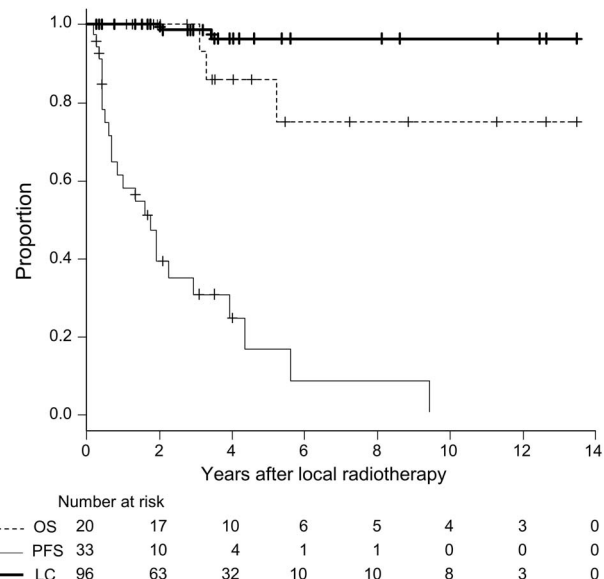

Fig. 1. Curves of overall survival (dotted line) for all 20 patients, progression-free survival after 33 treatment series (thin line) and local control for 96 lesions of pleural dissemination (bold line).
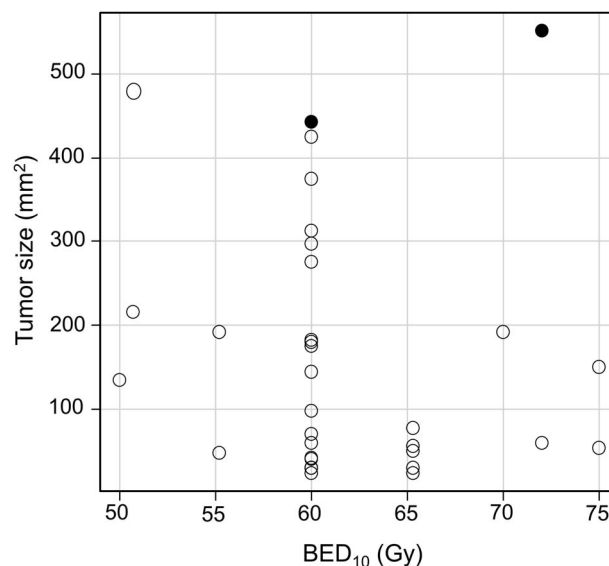

Fig. 2. Tumor size (maximum thickness from the pleura × diameter orthogonal to its line in the axial plane) and BED_{10} in 32 cases with no local recurrence within four years (○) and in two cases with local recurrence (●).

and biologically effective dose with an α/β ratio of 10 Gy (BED_{10}), excluding 62 lesions without local recurrence within four years, are shown in Fig. 2. The two recurrent lesions were located at the upper middle to right areas. Tumors with a size <400 mm^2 did not develop in-field local recurrence with a BED_{10} of 60 Gy or less.

Table 3. Adverse events

	Grade 1	Grade 2	Grade 3	Total
Pneumonitis	18 (90%)	1 (5%)	1 (5%)	20 (100%)
Nausea	3 (15%)	1 (5%)	0	4 (20%)
Dysphagia	1 (5%)	1 (5%)	0	2 (10%)
Pericardial effusion	0	0	1 (5%)	1 (5%)
Pleural effusion	3 (15%)	1 (5%)	0	4 (20%)
Dermatitis radiation	5 (25%)	1 (5%)	0	6 (30%)

Adverse events

Complications of treatment are summarized in Table 3. One patient developed grade 3 radiation pneumonitis (5%) and another developed grade 2 (5%) pneumonitis. All other pneumonitis was grade 1. The patient developing grade 3 pneumonitis received treatment for two relatively large tumors (tumor size: 418 and 312 mm^2, respectively) simultaneously. One patient had grade 3 pericardial effusion (5%); the patient received local radiotherapy twice for relatively large tumors (size: 2240 and 480 mm^2, respectively). In addition, she had received steroid-pulse therapy and systemic chemotherapy before the local radiation treatments. Among the nine patients who underwent two or more series of treatment, only one developed grade ≥ 2 toxicity. As local pleural irradiation usually does not produce myelosuppression, hematological toxicities were not evaluated.

Statistical analysis

We analyzed age ($<$ vs ≥ 65 years), gender, WHO PS (0 vs ≥ 1), Masaoka stage [22] (III vs IVA/B), WHO histological classification (A/AB/B1/B2 vs B3/C), presence of myasthenia gravis (MG), chemotherapy history, history of postoperative radiation, radiation method (CRT vs tomotherapy), tumor size ($<$ vs ≥ 400 mm^2), number of irradiated lesions (1 vs ≥ 2), number of radiation series (1 vs ≥ 2), and total radiation doses in BED_{10} ($<$ vs ≥ 65 Gy) as potential prognostic factors. Regarding OS, PS 0 was associated with better OS ($P < 0.001$), and patients who underwent two or more series of radiation for pleural dissemination had a better OS than those undergoing only one series (five-year OS, 100% vs 67%; seven-year OS, 100% vs 33%; $P = 0.018$). The former patients had a five-year OS of 100% after the second treatment for pleural dissemination. Regarding PFS, younger age was associated with better rates ($P = 0.024$). Regarding LC, smaller tumor size was associated with better rates ($P = 0.00021$). In multivariate analyses, no factor was associated with OS.

DISCUSSION

Only a few groups have evaluated radiotherapy for pleural dissemination of thymic epithelial tumors [23–25]. Ichinose *et al.* [23] reported good LC of pleural dissemination in 8 patients treated by radiation therapy. Other groups focused on hemithoracic irradiation rather than local treatment of pleural dissemination [24,25]. Therefore, our report may be the largest series evaluating the efficacy of local radiotherapy for pleural dissemination of thymoma and thymic carcinoma. LC rates were good. Although PFS was poor because patients developed other

pleural dissemination lesions with a median interval of 18 months, OS was favorable (86% at five years). We consider that the favorable OS was due to debulking of tumors and prevention of the conditions associated with enlargement of pleural disseminations, also reflecting the insidious course of thymic tumors. Patients undergoing retreatment for pleural dissemination had a better OS than those undergoing only one series in univariate analysis, although it was not significant in multivariate analysis. Therefore, we consider this treatment, including repeat treatment, to be a useful option for this disease.

Several groups reported outcomes of surgery for recurrence [5,6,8,9,26,27]. The five- and 10-year OS rates were 37–91% and 16–82%, respectively, with some differences among the studies. Our OS results are consistent with these results. PFS rates after surgery for pleural dissemination were 13–29% at five years and 19% at 10 years [28,29]. Therefore, the PFS rates are also similar between our study and others evaluating surgical results. In a small series, the OS did not differ between patients receiving surgery plus radiation and those receiving radiation alone for intrathoracic recurrence of thymoma [30]. These tumors often cause pleural recurrence at different sites, but repeat treatment of the recurrences was generally tolerable and retreated patients had favorable OS. Only one patient undergoing repeat radiation therapy had grade 2 pulmonary toxicity in the present study.

This study demonstrated that stable LC can be achieved for most tumors. Only two developed local recurrence. Both were relatively large, and despite the relatively high doses delivered ($BED_{10} > 60$ Gy, corresponding to 50 Gy in 25 fractions), they developed recurrence within four years. On the other hand, lesions of 400 mm^2 (tumor size) or less have not yet developed recurrence with a BED_{10} of 60 Gy or less within four years, as shown in Fig. 2. Therefore, doses corresponding to 50 Gy in 25 fractions may be recommended for tumors of 400 mm^2 or less. As there are no data regarding the α/β ratio of thymic tumors, employing a ratio lower than 10 Gy may also be considered when using a more hypofractionated schedule [31].

Some reports stated the WHO histological classification as a prognostic factor [16,26], but no significant effects on OS or LCR were noted in our study with a small sample size. MG is the autoimmune disease most frequently ($> 30\%$) associated with thymoma [32,33]; these reports suggested a good prognosis of MG patients. Although 30% of our patients also had MG, we found no difference in OS and LC rates between the MG and non-MG groups. The small sample size may be related to this, and it is the largest limitation of this study.

Before installation of tomotherapy at our institution, we used CRT to treat this disease. Using localized tangential radiation, the normal lung can be effectively spared and lung damage may be

minimized. However, only a few (up to five in our study) lesions were able to be treated simultaneously, and treating multiple sites was time-consuming. The advent of tomotherapy solved this problem; multiple lesions can be effectively and safely treated. We successfully treated a patient with 20 disseminated lesions with mild toxicity (grade 2 pneumonitis). It was previously reported that the rate of grade 2 or higher radiation pneumonitis was less than 20% after whole pleural intensity-modulated radiotherapy for mesothelioma [34,35]. Therefore, the indication of local radiotherapy for pleural disseminations of thymic tumors may be expanded to include more than five lesions per treatment series.

In conclusion, our study revealed that local radiotherapy with a BED_{10} of 60 Gy may result in LC for tumors with a size smaller than 400 mm^2. Although these patients may develop pleural recurrence at different sites, they can again be treated using the same technique. As a result, a relatively long OS can be expected with this approach.

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CONFLICT OF INTEREST
The authors declare no conflicts of interest associated with this manuscript.

PRESENTATION AT A CONFERENCE
Part of this work was presented at 2016 annual meeting of ASTRO, Boston, USA

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