Brief Report

Radiotherapy for stage IVa thymoma—Shanghai Chest experience

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Abstract: To investigate the effect of two modalities, radiotherapy (RT) and surgery plus entire hemithoracic radiotherapy (EHRT), on stage IVa thymoma. Patients enrolled in this study meet the following criteria: histologically proven thymoma; primary stage IVa or pleural dissemination after initial curative treatment. One treatment modality is intensity-modulated radiotherapy (IMRT) for pleural lesions with a dose ranging from 30–50 Gy, the other is macroscopically surgical resection plus EHRT with a dose of 13 Gy in 13 fractions. From July 2012 to April 2018, there were totally 56 patients enrolled in this study. The median age was 45 years old (range, 20–75 years old). There were 35 male and 21 female patients. The histology subtype distribution was 1 AB, 8 B1, 20 B2 and 27 B3, respectively. Thirty-one patients received IMRT for pleural dissemination and the response rate (CR + PR) was 97%. The mean local control time was 40 months (95% CI, 32.6–47.3 months). The in-field and out-field recurrence were 32% and 94%, respectively. The 2-year progression free survival (PFS) was 18%. While for patients who were treated by surgery plus EHRT, the in- and out-field recurrence were 8% and 16%, respectively. The 2-year PFS was 40%. The 2-year PFS for B1, B2 and B3 were 20%, 50% and 23%, respectively (P=0.255). Major toxicity occurred in IMRT group, 5 died of radiation-induced pneumonitis. Both IMRT and surgery plus EHRT showed good local control for stage IVa thymoma. Since stage IVa thymoma has a tendency to involve the whole hemithorax, surgery plus EHRT has a potential to produce longer PFS.

Keywords: Entire hemithorax radiotherapy (EHRT); pleural dissemination; thymoma; intensity-modulated radiotherapy (IMRT)

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Introduction

Thymomas are neoplasms arising from the thymic epithelial cells. Primary stage IVa thymoma accounts for about 6.8% in all thymic tumor cases (1). Also, pleural recurrence is the most common failure type after curative treatment such as surgical resection (2,3). They are considered a disseminated disease and are usually challenging in terms of treatment approach. By far, the treatment of pleural metastasis is still controversial. Here, we reported our experience in managing stage IVa thymoma, using radiotherapy (RT) as a major modality.

Part 1: intensity modulated radiotherapy (IMRT) for pleural recurrence of thymoma

This study was started from 2012, and registered as a phase II clinical trial (ChiCTR-ONC-12002095). It was approved by the Ethical Committee of Shanghai Chest Hospital. Informed consents were collected from all the patients. The inclusion criteria includes: (I) pathologically proven thymoma; (II) measurable pleural lesion on CT image; (III) patients are intolerant of or refuse surgery; (IV) progression after chemotherapy. The target of radiation was contoured according to the following

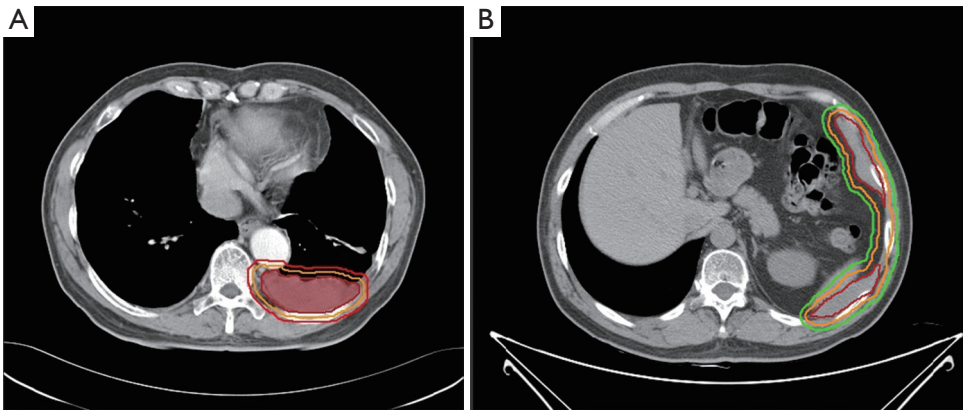

Figure 1 The target contouring. (A) The target contouring of one single pleural lesion; (B) the target contouring of multiple pleural lesions (red: GTV; orange: CTV; green: PTV). GTV, gross tumor volume; CTV, clinical tumor volume; PTV, planning tumor volume.

Table 1 Patients' characteristics (n=31)

Characteristic	N (%)
Age	49 [22–70] y
Gender	
Male	21 (68%)
Female	10 (32%)
WHO histology	
AB	1 (3%)
B1	5 (16%)
B2	6 (19%)
B3	19 (61%)
Myasthenia gravis+	10 (32%)
Surgery	
One time	23 (74%)
Two times	6 (19%)
No	2 (6%)
Time to recurrence	25 [9–132] m
PORT dose	50 [40–66] Gy

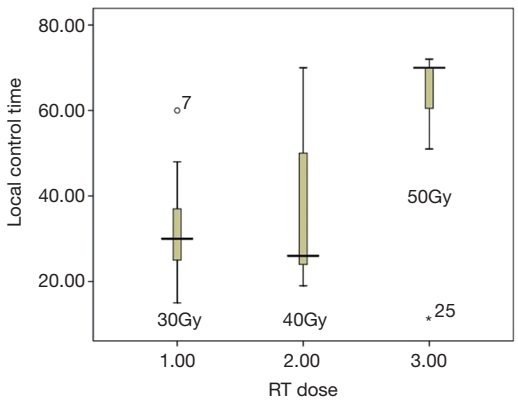

Figure 2 Local control time of different radiation dose.

principles: the gross tumor volume (GTV) included all visible tumors; a margin of 4–5 mm was added to GTV to form the clinical tumor volume (CTV). Considering the movement of organs and set-up error, we expanded another 5 mm margin beyond CTV to form the planning tumor volume (PTV). When the pleural lesion was single, it was countered as *Figure 1A*, whereas for multiple pleural lesions, the target was countered as *Figure 1B*. There were three dose categories of 30, 40 and 50 Gy. Since all patients had received previous RT to mediastinal area, the total dose of previous RT and current RT was restricted under V20 <35% and MLD <16 Gy.

From February 2012 to August 2016, there were totally 31 patients enrolled in this study. The patients' information was summarized in *Table 1*. In the median follow-up of 48 [24–70] months, the overall response rate was 97% (CR 45% + PR 52%). The median local control time was 40 (95% CI: 32.6–47.3) months. There were 10 (32%) patients who developed in-field recurrence, while 29 (93.5%) patients developed out-field recurrence.

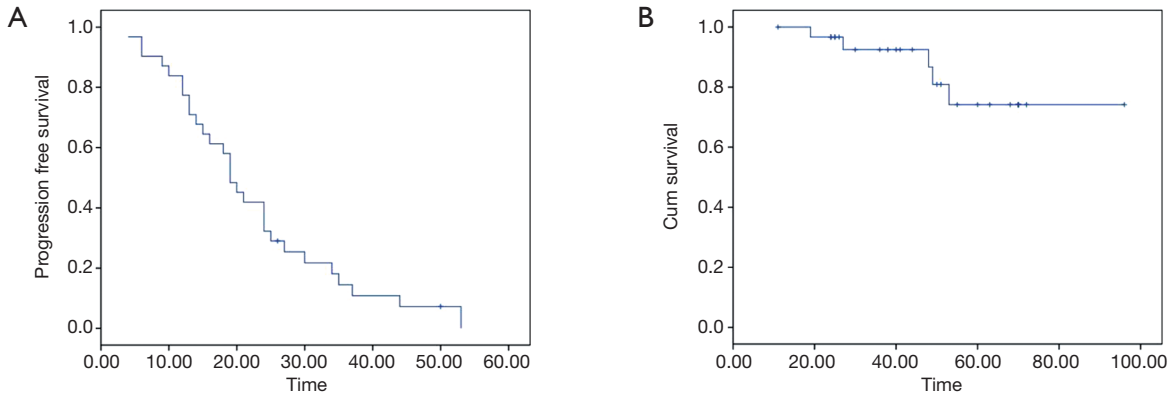

Figure 3 The survival of patients treated with IMRT. (A) The progression free survival of all patients; (B) the overall survival of all patients. IMRT, intensity-modulated radiotherapy.

The local control time of different RT dose was shown as *Figure 2*. The progression free survival (PFS) and overall survival of all patients are shown as *Figure 3A,B*.

There were 29 patients who developed out-field recurrence. Twenty-six of them received re-RT; 2 of them received I^{125} seeds implantation and one received palliative chemotherapy. The toxicity included radiation-induced pneumonitis (7 of grade 3 and 5 of grade 5) and thoracic cavity contracture.

In summary, IMRT is highly effective for pleural recurrence of thymoma, and the ORR is more than 90%. With the increasing dose, the local control rate is improved, however, the incidence of out-field recurrence is still very high. Main toxicity is pneumonitis, and repeated IMRT is associated with higher risk.

Part 2: surgery plus hemithoracic RT

Pleural lesions are often resectable and with postoperative hemithoracic RT, high survival rates are also achievable (4-6). The rationale of using post-operative hemithoracic irradiation is based on three main points: the known sensitivity of such tumors to radiation; the known application of this RT technique in mesotheliomas after extra-pleural pneumonectomy and the fact that the risk of recurrence of the disease is much higher loco-regionally than distantly (7-9).

We started our study of surgery plus entire hemithoracic radiotherapy (EHRT) from November 2014. The protocols include: (I) complete resection of all visible tumors; (II) EHRT is started 4–6 weeks after surgery and delivered via IMRT; (III) RT dose is 13 Gy in 13 fractions; (IV) if the T stage is beyond T2, then 30 Gy radiation will be given to mediastinal tumor bed. The target contouring is shown in *Figure 4A* (above diaphragm level) and *Figure 4B* (below diaphragm level). By October 2017, we had totally 26 patients enrolled in this study, and patients' characteristics were summarized in *Table 2*.

During a median follow-up time of 19 [12–44] months, 6 (23%) patients developed recurrence. Two of them were in-field and 4 were out-field. The median time to recurrence was 20 [12–26] months. The PFS of the whole group was shown as *Figure 5*.

Fatigue, nausea and vomiting were the most common side effects, but most of them were mild and easy to relieve. There were also two cases of pyothorax and two cases of myasthenia gravis deterioration, which were recovered by proper management.

In summary, surgery plus EHRT shows good local control with mild toxicity. Since there appeared in-field and out-field recurrence, a more proper radiation field and dose need to be further explored, and the outcome may improve sequentially. Long-term follow-up is needed to check if the advantage of PFS can turn into a longer OS.

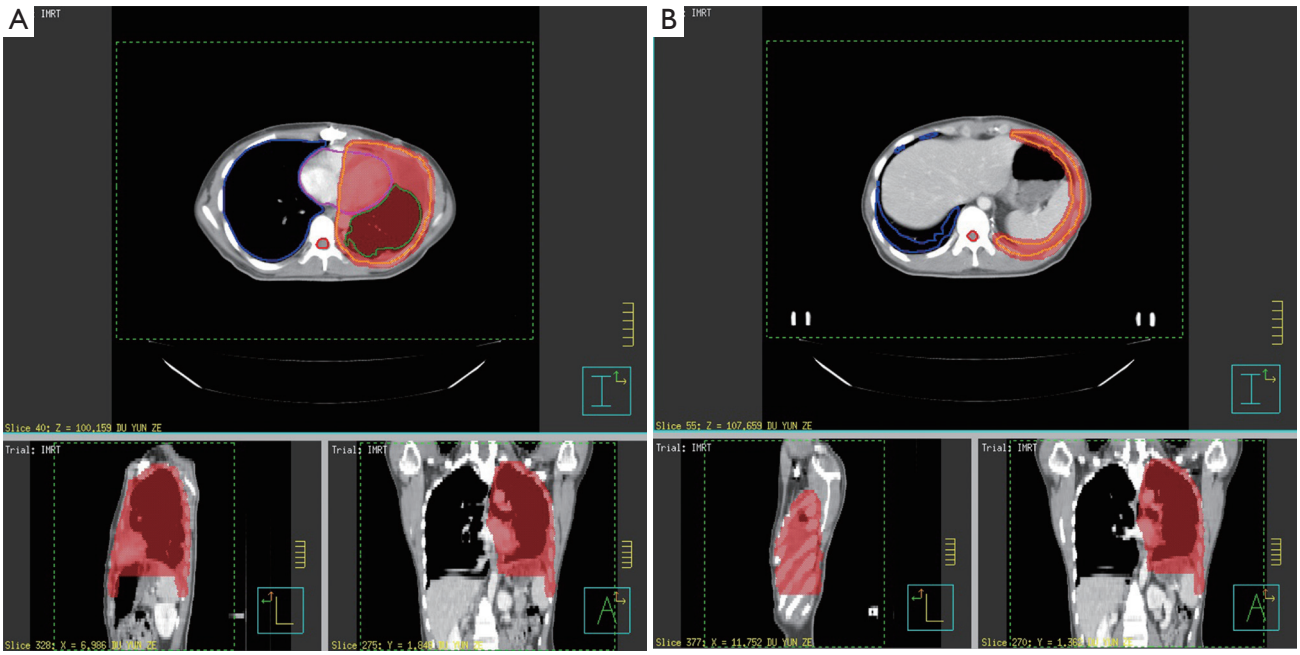

Figure 4 The target contouring of EHRT. (A) The target contouring of hemithorax (above diaphragm level); (B) the target contouring of hemithorax (below diaphragm level). EHRT, entire hemithoracic radiotherapy.

Table 2 Patients' characteristics (n=26)

Characteristic	N
Age	43 [20–70] y
Gender	
Male	14
Female	12
WHO histology	
B1	3
B2	15
B3	8
Myasthenia gravis+	6
Neoadjuvant chemo	11

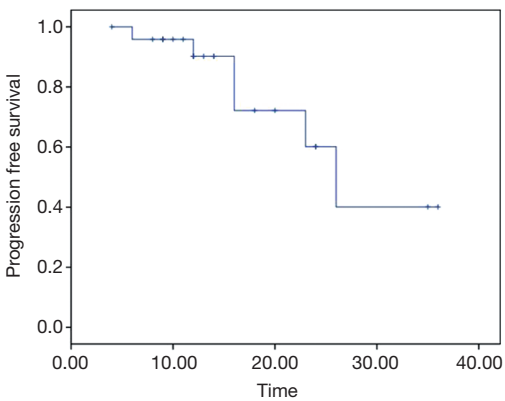

Figure 5 The progression free survival of all patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethical Committee of Shanghai Chest Hospital. Informed consents were collected from all the patients.

References

1. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. Ann Thorac Surg 2003;76:878-84.
2. Kondo K, Monden Y. Lymphogenous and hematogenous metastasis of thymic epithelial tumors. Ann Thorac Surg 2003;76:1859-64.
3. Rimner A, Gomez DR, Wu AJ, et al. Failure patterns relative to radiation treatment fields for stage II-IV thymoma. J Thorac Oncol 2014;9:403-9.
4. Tagawa T, Kometani T, Yamazaki K, et al. Prognosis and therapeutic response according to the World Health Organization histological classification in advanced thymoma. Surg Today 2011;41:1599-604.
5. Sugie C, Shibamoto Y, Ikeya-Hashizume C, et al. Invasive thymoma: postoperative mediastinal irradiation, low-dose entire hemithorax irradiation in patients with pleural dissemination. J Thorac Oncol 2008;3:75-81.
6. Huang J, Rizk NP, Travis WD, et al. Feasibility of multimodality therapy including extended resections in stage IVA thymoma. J Thorac Cardiovasc Surg 2007;134:1477-84.
7. Hung AY, Eng TY, Scarbrough TJ, et al. CRT. Mediastinum and trachea. In: Halperin EC, Perez CA, Brady LW. editors. Perez and Brady's principles and practice of radiation oncology. 5th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2008:1109-17.
8. Sovak MA, Aisner SC, Aisner J. Tumors of the pleura and mediastinum. In: Abeloff MD, Armitage J, Niederhuber J, et al. editors. Abeloff's clinical oncology. 4th ed. Philadelphia: Churchill Livingstone/Elsevier, 2008:1367-98.
9. Korst RJ, Kansler AL, Christos PJ, et al. Adjuvant radiotherapy for thymic epithelial tumors: a systematic review and meta-analysis. Ann Thorac Surg 2009;87:1641-7.

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