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)

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
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 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                   |                     |
| A B                             | 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.
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 125I 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.

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**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.
Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors Mirella Marino and Brett W. Carter for the series “Dedicated to the 9th International Thymic Malignancy Interest Group Annual Meeting (ITMIG 2018)” published in Mediastinum. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/med.2019.02.01). The series “Dedicated to the 9th International Thymic Malignancy Interest Group Annual Meeting (ITMIG 2018)” was commissioned by the editorial office without any funding or sponsorship. WF serves as an unpaid Editor-in-Chief of Mediastinum. The
authors have no other conflicts of interest to declare.

**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.

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doi: 10.21037/med.2019.02.01

**Cite this article as:** Wang C, Gao L, Fang W. Radiotherapy for stage IVA thymoma—Shanghai Chest experience. Mediastinum 2019;3:7.