International Journal of Surgery 53 (2018) 345–349

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

Original Research

The role of postoperative radiation therapy for completely resected stage III thymoma and effect of higher heart radiation dose on risk of cardiovascular disease: A retrospective cohort study

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ARTICLE INFO

Keywords:
Cardiovascular disease
Complete resection
Higher heart dose
Radiation therapy
Stage III thymoma

ABSTRACT

Objectives: This study aimed to assess the efficacy of radiation therapy (RT) in patients with completely resected stage III thymoma and evaluate the relationship between higher heart dose and risk of cardiovascular disease (CVD).

Patients and methods: A total of 130 consecutive patients with Masaoka stage III thymoma were retrospectively reviewed from January 2003 to December 2013. Of these, 99 underwent complete tumor resection [74 received postoperative radiation therapy (S + R) and 25 received surgery alone (S alone)] and 31 patients underwent RT alone (16 due to inoperable tumors and 15 due to high surgical risk or patient refusal; R alone). Three-dimensional conformal RT/intensity-modulated RT was used for patients receiving RT.

Results: The median follow-up for all patients was 70 months. The 5- and 8-year overall survival (OS) rates were 95.6% and 93.9% for S + R, 84.0% and 67.2% for S alone, and 73.3% and 73.3% for R alone (excluding patients with inoperable tumors), respectively ($P = 0.004$). A trend of improved disease-specific survival (DSS) was also observed in the S + R group compared with the other two groups. CVD was the main nonmalignant cause of death (3/6, 50%). The median time of CVD diagnosis was 101 months after treatment. The mean heart dose was an independent risk factor for CVD.

Conclusions: Postoperative RT after complete resection improved the survival compared with surgery alone and RT alone for patients with stage III thymoma. A higher heart dose was related to increased risk of CVD in long-term survivors.

1. Introduction

Thymoma is rare, but it is the most common tumor of the anterior mediastinum (50% in adults). The incidence of thymoma is reported to be 1.5 and 1.7 per million per year in the United States [1] and Europe [2], respectively. Surgery has been the mainstay in treating thymoma. The role of postoperative radiation therapy (PORT) after complete resection remains controversial. Although PORT is widely recommended in clinical practice because of the involvement of surrounding vital structures, definitive evidence proving the efficacy of PORT in improving patient survival with completely resected stage III thymoma is scarce. Moreover, some recent studies reported that further treatment was not useful for stage III thymoma after complete resection [3–5]. Moreover, for unresectable cases, RT was usually opted as a single modality. However, the survival of these patients remains unclear.

Nonmalignant death usually occurs in long-term cancer survivors. Radiation-induced cardiovascular disease (RICVD) is the most common nonmalignant cause of death in chest-irradiated cancer survivors, such as patients with Hodgkin's lymphoma (HL) and breast cancer, and a clear association exists between high thoracic radiation dose and increased risk of cardiovascular disease (CVD) [6–10]. For patients with thymoma, advances in treatment have increased the number of long-term survivors. However, few studies have focused on RICVD and the nonmalignant causes of death in patients with thymoma.

This study aimed to assess the efficacy of PORT in completely resected stage III thymoma and evaluate the effect of higher heart radiation dose on the risk of CVD in long-term survivors.

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https://doi.org/10.1016/j.ijsu.2018.04.018
Received 9 December 2017; Received in revised form 5 April 2018; Accepted 10 April 2018
Available online 16 April 2018

2. Patients and methods

2.1. Patients

Between January 2003 and December 2013, 150 consecutive patients with Masaoka stage III thymoma were initially treated at our hospital. Patients were excluded if they underwent incomplete resection ($n = 5$), received chemotherapy alone without surgery and RT ($n = 2$), had other tumors ($n = 1$), received RT or PORT using two-dimensional RT (2D-RT) technique ($n = 8$), or had CVD ($n = 4$). Thus, 130 patients with an ECOG score of 0–2 were included in this study. Of these, 99 patients underwent complete tumor resection with (S + R, $n = 74$) or without (S alone, $n = 25$) PORT. Of these, 33 received chemotherapy after treatment (26 in the S + R group and 7 in the S-alone group). Moreover, 31 patients received RT alone without surgery (R alone) due to inoperable tumor ($n = 16$), high surgical risk ($n = 8$), or patient refusal ($n = 7$). Among them, 18 received chemotherapy after RT. All the patients receiving RT were treated with three-dimensional conformal RT/intensity-modulated RT (3D-CRT/IMRT). This retrospective study was approved by the regional ethics committee of our hospital. The study was reported in line with the STROCCS criteria [24].

2.2. Surgery

Of the 99 patients who underwent complete tumor resection, 89 underwent open thymectomy and 10 thoracoscopic thymectomy.

2.3. Radiotherapy

For patients receiving PORT, the clinical target volume (CTV) was defined mainly based on the preoperative CT images. For patients receiving RT alone, the gross tumor volume (GTV) was defined as the total volume of the primary and nodal tumor masses visualized on planning CT images, and CTV was defined as the GTV plus a 0.5-cm margin. The planning target volume was defined as CTV plus a 0.5-cm margin. The prescribed dose was 60–66 Gy in 2.0-Gy daily fractions for patients who received RT alone and 50–56 Gy in 2.0-Gy daily fractions for patients who underwent PORT. Five fractions in 1 week and 3–5 fields were usually included in the treatment plan. Moreover, the mean heart dose (MHD) was calculated and extracted from the dose–volume histogram.

2.4. Chemotherapy

A total of 51 patients received chemotherapy after treatment (26 in S + R group, 18 in the R-alone group, and 7 in the S-alone group). Most of the chemotherapy regimens consisted of docetaxel (75 mg/m^2 on day 1) or vinorelbine (20 mg/m^2 on days 1 and 5), plus cisplatin (20–25 mg/m^2 on days 1–3), every 3 week a cycle, and total 2–4 cycles.

2.5. Follow-up

The last follow-up date was December 1, 2016. Most of the patients were followed up every 3–6 months for the first year, every 6 months for the next 2 years, and then annually until death. Survival and recurrence information were collected via telephone if the patient could not visit the clinic on schedule. Data regarding CVD were collected from medical records, postal questionnaires, or telephonic follow-up. CVD was graded according to the Common Terminology Criteria for Adverse Events version 4.0. Grade ≥2 CVD was counted as an event.

2.6. Statistical analysis

Statistical analysis was performed using SPSS software version 21.0 (SPSS, Inc., IL, USA). The overall survival (OS) was defined as the time from the start of treatment to death from any cause. Disease-specific survival (DSS) was defined as the time from the start of treatment to tumor-induced death. Disease-free survival (DFS) was defined as the time from the start of treatment to the first relapse. Analysis of OS, DSS, and DFS was carried out using the Kaplan–Meier method, and the difference between survival curves was tested using the log-rank test. Variables with $P < 0.05$, histologic classification, chemotherapy, and myasthenia gravis were included for a multivariate analysis using the Cox regression model. Analysis of factors related to the risk of CVD was carried out using the logistic regression. Variables with $P < 0.05$ in the univariate analysis, and MHD, chemotherapy, and age were included in the multivariate analysis. For all analyses, $P < 0.05$ was considered statistically significant.

3. Results

Radiation doses were 50–56 Gy in the PORT group and 60–66 Gy in the R-alone group. The median follow-up for all patients was 70 months (range, 3–155 months), 70 months (range, 40–155 months) for the S + R group, 70 months (range, 27–134 months) for the S-alone group, and 63 months (range, 3–126 months) for the R-alone group. Of the 130 patients, 20 (15.4%) were diagnosed with grade ≥2 CVD during follow-up [12 coronary heart disease (CHD), 4 pericardial disease, 3 myocardial disease, and 1 severe arrhythmia], including 16 with grade 2–3, 1 with grade 4, and 3 with grade 5 CVD. The median time of CVD diagnosis was 101 months (range, 45–155 months) after treatment.

3.1. Survival

By the last follow-up date, 20 (15.4%) patients had died. Among them, 14 died from tumor relapse or metastasis and the other 6 from nonmalignant causes. The details of nonmalignant deaths are shown in Table 1.

Of the 31 patients, 16 in the R-alone group were excluded from survival comparison between groups and analysis of factors related to OS due to inoperable tumors. The 5- and 8-year OS rates of the 16 patients were 75.0% and 64.3%, respectively; the 5- and 8-year DFS rates were 55.5% and 41.3%, respectively; and the 5- and 8-year DSS rates were 80.8% and 69.2%, respectively.

3.1.1. Survival comparison between groups

Patient characteristics ($n = 114$) are shown in Table 2. The 5- and 8-year OS rates were 90.1% and 84.6% for the entire group, 95.6% and 93.9% for the S + R group, 84.0% and 67.2% for the S-alone group, and 73.3% and 73.3% for the R-alone group ($P = 0.004$; Fig. 1), respectively. The 5- and 8-year DFS rates were 82.0% and 77.1% for the

Table 1
Patterns of nonmalignant death between groups.

Treatment	Total ($n = 6$)	Cardiovascular disease ($n = 3$)	Myasthenia gravis ($n = 1$)	Thrombocytopenia ($n = 1$)	Pulmonary fibrosis ($n = 1$)
S + R	1 (16.7%)	1 (33.3%)	0 (0%)	0 (0%)	0 (0%)
S alone	2 (33.3%)	0 (0%)	1 (100%)	1 (100%)	0 (0%)
R alone	3 (50.0%)	2 (66.7%)	0 (0%)	0 (0%)	1 (100%)

R, Radiotherapy; S, surgery.