Radiotherapy and Oncology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original article

Patterns and predictors of recurrence after radical resection of thymoma ☆

Cai Xu [a], Qin-Fu Feng [a,*], Cheng-Cheng Fan [c], Yi-Rui Zhai [a], Yi-Dong Chen [d], Hong-Xing Zhang [a], Ze-Fen Xiao [a], Jun Liang [a], Dong-Fu Chen [a], Zong-Mei Zhou [a], Lu-Hua Wang [a], Jie He [b]

[a] Department of Radiation Oncology; [b] Department of Thorax Surgery, Cancer Hospital/Institute, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing; [c] Department of Radiation Oncology, Cancer Hospital, Zhengzhou University; and [d] Department of Radiation Oncology, Beijing Shijitan Hospital, China

ARTICLE INFO

Article history:
Received 1 August 2014
Received in revised form 2 March 2015
Accepted 2 March 2015
Available online xxxx

Keywords:
Thymoma
Recurrence pattern
Recurrence predictors
Complete resection

ABSTRACT

Background: Recurrence of thymomas even after complete resection is common, but the relapse patterns remain controversial. This study aimed to define the patterns and predictors of relapse after complete resection of thymoma.

Methods: A single-institution retrospective study was performed with 331 patients who underwent radical resection of thymoma between 1991 and 2012.

Results: After a median follow-up of 59 months, the recurrence rate was 6.9% (23/331). Relapse occurred in 23 patients with the pleura (14) and tumor bed (6) as the most common sites of recurrence. According to the definitions of the International Thymic Malignancy Interest Group, 10 (43.5%) patients had local relapse, 15 (65.2%) had regional relapse, 10 (43.5%) had distant relapse. The difference in survival following relapse between lung and regional relapse was statistically significant ($P = 0.027$) but that between lung and distant relapse was not ($P = 0.808$). The recurrence rates correlated with the initial Masaoka stage. Further, recurrence also correlated with World Health Organization (WHO) tumor type. The recurrence-free survival rates in patients with tumor size $\geqslant 8$ cm were worse than those of patients with tumor size <8 cm ($P = 0.007$). Tumor size was also correlated with stage ($r = 0.110$). As tumor becomes larger, the stage is more advanced ($P = 0.023$). Multivariate analysis showed that Masaoka stage ($P = 0.005$), tumor size ($P = 0.033$), and WHO histological type ($P = 0.046$) were predictive factors of relapse.

Conclusion: Regional recurrence is the most common relapse pattern but local and distant relapse are also common. Advanced Masaoka stage, larger tumor size, and type B3 are risk factors of recurrence. Lung relapse should be considered distant relapse. Further, tumor size was correlated with Masaoka stage and therefore should be considered in the staging system.

Thymic epithelial tumors (TETs) are rare epithelial neoplasms of the thymus, with an annual incidence of only 0.15 cases per 100,000 in the United States [1]. Yet, they represent the most frequently diagnosed tumor of the anterior mediastinum. Although TETs include a series of neoplasms that differ morphologically as well as biologically, the most common histological type is thymoma. Complete resection is still the mainstay of treatment and significantly improves long-term survival [2]. However, the relapse of thymoma is not uncommon, and the recurrence rate is related to the stage of the disease at detection; for instance, recurrence after complete resection of a stage I TET is rare [3], but even after complete resection, the recurrence rates for stage II or III lesions can be as high as 62% and 80%, respectively [4].

Because of the rarity of thymomas, almost all previously published studies on this neoplasm were retrospective single-institution series, which often cover multiple decades in order to include a reasonable number of patients. Further, a standardized, uniform set of definitions for thymoma recurrence and relapse patterns are lacking. To solve this problem, the International Thymic Malignancy Interest Group (ITMIG) listed standard outcome measures and definitions for thymoma recurrence and relapse patterns in 2010 [5]. As mentioned above, the incidence of recurrence is generally very low, and the outcome of retreatment after recurrence is good. However, the patient's quality of life might be poor

☆ This paper was received as poster at the 4th international Thymic Malignancy Interest Group Annual Meeting (ITMIG 2013), September 6–7, 2013, Bethesda, Maryland, USA.

* Corresponding author.
E-mail addresses: xchdls@126.com (C. Xu), 13811300221@163.com (Q.-F. Feng).

http://dx.doi.org/10.1016/j.radonc.2015.03.001
0167-8140/

after multiple treatments for multiple recurrences. Thus, freedom from recurrence is a better measure than survival in the case of patients who have successfully undergone radical resection. In the present retrospective observational analysis based on ITMIG definitions, we explored the relapse patterns and factors that might bolster strategies for the prevention, surveillance, and treatment of recurrent thymoma.

Methods

We retrospectively reviewed the medical records of 331 patients with thymoma initially treated with complete resection at our hospital from 1991 through 2012. Patients with prior resection at other hospitals, R1/R2 or biopsy resection, thymic carcinoma, or incomplete data were excluded. Masaoka-Koga staging systems [6] were adopted, and pathologic results were classified according to World health organization (WHO) histological classification [7].

According to ITMIG definitions, the relapse of thymoma is defined as a strong clinical suspicion of thymoma recurrence, without a specific requirement of pathological proof. The time of recurrence should be recorded as the time when a strong suspicion first exists. Further, recurrence is divided into three categories. Local recurrence is defined as disease appearing in the bed of the thymus (i.e., the anterior mediastinum) or tissues immediately contiguous with the normal thymus or the thymoma (i.e., pleural recurrence in the area of a previously resected stage IVa tumor, or cervical lymph node recurrence adjacent to a previously resected thymoma). Regional recurrence is defined as intrathoracic recurrence in an area not immediately contiguous with the thymus gland or the previous thymic neoplasm (i.e., pleural and pericardial nodules). Lastly, distant recurrence includes extrathoracic recurrence or recurrence in the lower neck or intraparenchymal pulmonary nodules [5]. One oncologist and two radiologists diagnosed patients with recurrence according to clinical symptoms and the results of CT scan and MRI when needed. Biopsy is not mandatory.

The rates of overall survival (OS), cancer-specific survival (CSS), and recurrence-free survival (RFS) and OS rates following recurrence were calculated actuarially according to the Kaplan–Meier method. OS was measured from the date of operation until the day of death or last follow-up visit. RFS was measured from the date of operation until the date of recurrence, death or last follow-up visit. OS rates following recurrence was measured from the date of recurrence until the day of death or last follow-up visit. Univariate analysis was performed by the Kaplan–Meier method to assess recurrence factors for RFS, with comparison using a log-rank test for initial analysis. Subsequently, multivariate analysis was performed using the Cox regression model to identify predictive recurrence factors. Differences in categorical variables were statistically examined using the χ^2 test. The correlation between the tumor size and Masaoka stage was determined using Spearman's correlation test. A *P*-value less than 0.05 indicated statistical significance. Statistical analysis was performed using SPSS software version 19.0.

Results

Patient characteristics are summarized in Table 1. Of the 331 patients, 126 received adjuvant radiotherapy and 117 of these 126 patients completed postoperative radiotherapy. Of these 117 patients, 2 received postoperative whole pleural radiotherapy, at a target dose of 3000 cGy and 4000 cGy, respectively, and tumor bed radiotherapy at dose of 5000 cGy. The remaining 115 patients received tumor bed radiation with a median target dose of 5800 cGy (range, 4000–6200 cGy) in 180–200 cGy fractions over 5–6 weeks. 0f 331, only 4 patients received cisplatin/doxorubicin-based chemotherapy for 2–4 cycles.

Table 1
Characteristics of the 331 patients and results of recurrence factor analysis.

Variables	Patients	Recurrence (%)	5-year RFS rates (%)	10-year RFS rates (%)	*P*
Age (years)					0.906
⩾50	174	12 (6.9)	92.4	88.5	
<50	157	11 (7.0)	96.0	86.3	
Sex					0.515
Male	171	13 (7.6)	94.8	84.2	
Female	160	10 (6.3)	92.5	90.4	
MG					0.197
Presence	57	7 (12.3)	93.9	87.8	
Absence	269	16 (5.9)	93.4	89.5	
UN	5	0			
Tumor size (cm)				0.007	
⩾8	121	15 (12.4)	89.2	77.1	
<8	204	8 (3.9)	96.1	93.7	
UN	6	0			
Masaoka stage				0.000	
I	196	2 (1.0)	99.4	97.9	
II	93	9 (9.7)	88.3	76.5	
III	33	8 (24.2)	81.5	57.4	
IV	8	4 (50)	57.1	57.1	
UN	1	0			
WHO type					0.000
A + AB	154	5 (3.2)	96.6	94.6	
B1	67	4 (6)	96.2	88.0	
B2	50	3 (6)	93.4	83.0	
B3	44	10 (22.7)	76.8	58.3	
UN	16	1 (6.3)			
Initial symptoms					0.643
Presence	173	13 (7.5)	93.2	86.8	
Absence	157	9 (5.7)	95.1	88.7	
UN	1	1 (100)			
PORT					0.170
Yes	117	10 (8.5)	91.6	87.0	
No	192	8 (4.2)	96.6	91.7	

Abbreviations: RFS, Recurrence-free survival; PORT, postoperative radiotherapy; MG, myasthenia gravis; UN, unknown.

The median follow-up duration was 59 months (range, 3–256 months), and recurrence was observed in 23 of the 331 patients (6.9%) during follow-up. The median recurrence time was 33 months (range, 5–98 months). The 5- and 10-year OS, CSS, and RFS rates for the entire group after initial treatment were 92.3%, 95%, 93.6% and 84.9%, 89.4%, 87.2%, respectively. The outcome of patients with relapse was much worse than those without relapse; the 5- and 10-year OS rates were 77.4% and 52.4% in the former, respectively, while they were 94% and 89.2%, respectively, in the latter ($P = 0.000$).

Table 2 in the Supplementary Material shows the recurrence sites and patterns in the 23 patients with relapse. Relapses were found at the following sites: pleura (14 patients), tumor bed (6), lung (6), chest wall (4), lymph node metastasis (2), abdominal node metastasis (1), liver (1). The most common recurrence site was the pleura, accounting for 60.9% of the cases, followed by the tumor bed (26.1%) and lung (26.1%). According to the ITMIG classification, 10 patients (43.5%) had local recurrence, 15 (65.2%) had regional recurrence, 10 (43.5%) had distant recurrence.

There were 4 patients with local recurrences alone, 6 with regional recurrences alone, and 4 with distant recurrences alone. The OS curves following recurrence in the local, regional, and distant relapse patterns are shown in Fig. 1 and show that the OS rates differed significantly between local and distant relapse and between regional and distant relapse ($P = 0.014$ and $P = 0.009$, respectively), but were similar between local and regional relapse ($P = 0.662$).

Please cite this article in press as: Xu C et al. Patterns and predictors of recurrence after radical resection of thymoma. Radiother Oncol (2015), http://dx.doi.org/10.1016/j.radonc.2015.03.001