POSTOPERATIVE RADIOTHERAPY IN THYMIC CARCINOMA: TREATMENT RESULTS AND PROGNOSTIC FACTORS

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Short running head: Postoperative radiotherapy in thymic carcinoma

ABSTRACT

Purpose: To analyze the treatment results and prognostic factors of patients with primary thymic carcinoma treated by total or subtotal tumor resection followed by radiotherapy alone.

Materials and methods: From October 1987 to October 1997, twenty-six patients with thymic carcinoma were treated with complete or incomplete surgical resection and postoperative adjuvant irradiation without chemotherapy. The radiation was delivered with 10 MV X-ray given 5 days per week at 1.8~2 Gy per fraction. Total doses ranged from 40 to 70 Gy. All patients had at least 40 months of follow-up.

Results: The 5-year overall survival rate, local control rate and distant metastasis-free rate were 77%, 91% and 57%, respectively. Several prognostic factors including sex, age, extent of resection (total resection vs subtotal resection), Masaoka staging (early stage?+?vs advanced stage?+?), pathology (low grade vs high grade) and postoperative radiation dose (?60 Gy vs?60 Gy) were evaluated in univariate analysis. The Masaoka staging system was the only statistically significant predictor in overall survival rate (p=0.0482) and distant metastasis-free rate (p=0.0193).

Conclusions: The Masaoka staging system is the most important prognostic factor in primary thymic carcinoma patients receiving postoperative radiotherapy alone. For resectable tumor, surgery and postoperative radiotherapy can get a good local control but distant metastatic rate is still high. Further investigation of more effective chemotherapy is needed.

Keywords: Thymic carcinoma, Postoperative radiotherapy, Prognostic factors.

INTRODUCTION

Thymic carcinoma is a relatively rare neoplasm, which arises from the thymic epithelium. In 1982, Snover, Levine and Rosai (1) named these tumors as thymic carcinoma and also suggested that a thymic carcinoma should fulfill the following criteria: [1] anterior mediastinal location and [2] absence of another primary tumor. Patients with thymic

carcinoma had a worse prognosis compared with thymoma because these tumors had a more aggressive histologic appearance and clinical course. (2-5) However, few studies about prognostic variables and efficacy of treatment modalities have been published because of the rarity of this tumor. Although resection of tumor is the first choice in the treatment of thymic carcinoma, the optimal adjuvant therapy is still controversial.
In this retrospective study, we reviewed the treatment results and prognostic factors of 26 patients with primary thymic carcinoma treated by total or subtotal tumor resection followed by radiotherapy alone at our radiation oncology department in 10-year period.

MATERIALS AND METHODS

Patient characteristics

From October 1987 to October 1997, twenty-eight patients with thymic carcinoma were treated with total or partial resection of tumor followed by post-operative radiotherapy at our department. Of these, two patients were excluded from our study because the radiation dose was below 40 Gy. Therefore, this retrospective study was composed of 26 patients treated with definite postoperative radiotherapy. There were 14 men and 12 women (table 1). The age ranged from 21 to 65 years, with a median of 47 years. At diagnosis, cough, chest pain and dyspnea were the most common symptoms. None of the patients exhibited any paraneoplastic syndromes such as myasthenia gravis or hematologic abnormalities.

Staging

The clinical work-up included a detailed medical history, physical examination, chest X-ray, chest computed tomography (CT) scan, bronchoscopy and bone scan. Postoperative staging was based on the criteria by Masaoka et al. (6) (table 2) and accomplished by reviewing operative findings and pathologic reports. The distribution of the 26 patients according to the staging system is as follows: 6 Stage?, 17 Stage?, 1 Stage?a(pleural seedings) and 2 Stage?b(mediastinal lymph nodes involved) (table 1).

Pathology

The criterion for diagnosis of thymic carcinoma was a thymic epithelial neoplasm displaying cytologically malignant features. Squamous cell carcinoma (11 cases) was the most common subtypes; the others were lymphoepithelioma-like carcinoma (5 cases), small cell carcinoma (1 case) and undifferentiated carcinoma (9 cases) (table 1). They were also classified as low or high-grade histology. Low-grade tumors included squamous cell carcinoma, mucoepidermoid carcinoma and basaloid carcinoma. High-grade tumors included lymphoepithelioma-like carcinoma, small cell carcinoma, undifferentiated carcinoma, sarcomatoid carcinoma and clear cell carcinoma (1, 3-5, 7-12).

Surgery

All patients underwent thoracotomy. Seventeen patients underwent total resection and nine patients underwent subtotal resection (table 1).

Radiotherapy

Twenty-six cases were treated with 10 MV X-ray by a linear accelerator combined with surgery. Initially, patients were treated with parallel-opposed anteroposterior fields up to

40-44 Gy. Afterward, offcord oblique or lateral fields were used to deliver higher doses to the mediastinum. The irradiated fields encompassed the tumor bed with 1.5 to 2 cm margin. The radiation dose ranged from 40 to 70 Gy, 1.8-2 Gy per fraction, with a median dose of 60 Gy. No patient received chemotherapy before or after operation.

Follow-up

Patients had follow-up in the Radiation Oncology Department at 1 to 3 months intervals during the first 2 years and every 4 to 6 months between the second and fifth post-treatment years; after 5 years, patients were seen annually. All patients had at least 40 months of follow-up

Statistics

We retrospectively evaluated overall survival rate, local control rate and distant metastasis-free rate (including pleural seedings, lung metastases and distant organ metastases) that were determined by the Kaplan-Meier method (13). Several prognostic factors including sex, age, extent of resection (total resection vs subtotal resection), Masaoka staging (early stage?+?vs advanced stage?+?), pathology (low grade vs high grade) and radiation dose (?60 Gy vs?60 Gy) were also evaluated in univariate analysis. The differences between curves were assessed by using the log rank test (14).

RESULTS

Overall survival rate

The 5-year overall survival rate for all patients was 77% (Fig. 1). In univariate analysis, only staging (early stage?+?vs advanced stage?+?) was found to significantly influence overall survival rate. Patients in early stage?+? had a 5-year overall survival rate of 100%, 70% for stage?+? (p=0.0482) (table 3). The 5-year overall survival rates for patients undergoing complete resection and incomplete resection were 82% and 66%, respectively (p=0.4888) (table 3). The 5-year overall survival rates for patients in low-grade thymic carcinoma and high-grade thymic carcinoma were 80% and 73%, respectively (p=0.2444) (table 3). The other prognostic factors including sex, age and radiation dose also did not significantly impact on overall survival rates (table 3).

Local control rate

For these twenty-six patients, the 5-year local control rate was 91% (Fig. 2). Patients in early stage?+? had a 5-year local control rate of 100%, 87% for advanced stage?+?. The differences were not significant (p=0.3731) (table 3). The 5-year local control rates for patients undergoing complete resection and incomplete resection were 92% and 88%, respectively (p=0.5961) (table 3). The 5-year local control rates of patients in low-grade thymic carcinoma were also no different from those of patients in high-grade tumors (p=0.2299) (table 3). No prognostic factors were found to significantly influence local control rates.

Distant metastasis-free rate

All patients had the 5-year distant metastasis-free rate of 57% (fig. 3). The 5-year distant metastasis-free rates for patients in early stage?+?and advanced stage?+? were 100% and 42%, respectively (p=0.0193) (table 3). The 5-year distant metastasis-free rates for

patients undergoing complete resection and incomplete resection were 73% and 28%, respectively (p=0.1069) (table 3) . The 5-year distant metastasis-free rates for patients in low-grade thymic carcinoma and high-grade thymic carcinoma were 61% and 53%, respectively (p=0.7198) (table 3). Staging is the only significantly prognostic factor in distant metastasis-free rate. Until now, total 11 patients had distant metastatic disease. With regard to the metastatic sites, there were 3 liver metastases, 3 lymph node metastases, 3 bony metastases, 4 lung metastases and 4 pleural seedings. Four of these eleven patients had multiple distant metastatic sites.

DISCUSSION

In 1978, Levine and Rosai (7) proposed a classification for malignant thymoma as follows: [1] Category?malignant thymoma: with no or minimal cytologic atypia, i.e., invasive thymoma [2] Category?malignant thymoma : thymic epithelial tumors with obvious malignant cytologic appearance, i.e., thymic carcinoma. Several previous studies have showed that patients with thymic carcinoma had a worse prognosis than with invasive thymoma. The 5-year overall survival rate of thymic carcinoma was about 30% (8, 15), however, it was about 50-70% (6, 16-18) for invasive thymoma. The incidence of distant metastases in patients with invasive thymoma was about 3-8% (7, 16, 18), but as high as 50-70% (3, 5, 8, 19) in patients with thymic carcinoma. Therefore, the term "malignant thymoma" is not optimal because it is easily confused. Morinaga et al. (20), Carlson et al. (21) and Chang et al. (15) suggested to divide primary thymic epithelial tumors into three groups: non-invasive thymoma, invasive thymoma and thymic carcinoma. We also prefer this classification for primary thymic epithelial tumors.

Thymic carcinoma is a relatively rare disease. The standard treatment modalities are still under investigation. Although resection of tumor is the first choice in the treatment of thymic carcinoma, the optimal adjuvant therapy is still controversial. In our retrospective study, twenty-six patients underwent total or subtotal resection of tumor followed by postoperative radiotherapy alone. No patients received chemotherapy. The 5-year overall survival rate, local control rate and distant metastasis-free rate were 77%, 91% and 57%, respectively. The data showed that the surgical resection followed by postoperative irradiation could get good local control, but distant metastatic rate was still high. Postoperative irradiation was recommended for invasive thymoma (17, 22, 23, 24, 25). However, the role of irradiation in the treatment of thymic carcinoma was unclear because of limited experience. In Hsu et al. study (2), there was a tendency that favors postoperative radiotherapy although the difference in survival time between the radiotherapy group and non-radiotherapy group was not statistically significant. How to decrease distant metastatic rate and further improve overall survival rate is our main strategy in the future. Therefore, systemic chemotherapy is needed to control remote metastatic lesions. In previous studies, few reports can be cited on the efficacy of chemotherapy for thymic carcinoma. In 1993, Yano T et al. reported eight cases of thymic carcinoma (26). A complete resection of the primary tumor could be done in only 3 patients; the others had diagnostic biopsy and then radiation treatment. All patients received systemic chemotherapy with different regimens to counter either metastatic or locally recurrent lesions. Only two patients (with a regimen including cyclophosphamide, doxorubicin and vincristine) obtained a partial response. In 1993, Weide LG et al. reported five patients with thymic carcinoma treated with cisplatin based combination chemotherapy (27). Three patients responded (two completely) to cisplatin-based

chemotherapy. In 2000, Nakamura Y et al. reported that ten patients with unresectable thymic carcinoma were treated with platinum-based chemotherapy with or without radiotherapy (28). Four of the 10 patients responded to chemotherapy and both the median progression-free survival period and the median response duration were 6 months. Because of the rarity of this tumor, the precise role of chemotherapy is unclear. More effective chemotherapy with new agents is necessary for prospective trials in the treatment of thymic carcinoma.

In our study, twenty-six patients with primary thymic carcinoma were treated by surgery and postoperative radiotherapy. The treatment modalities were identical. Several prognostic factors including sex, age, extent of resection (total resection vs subtotal resection), staging (early stage?+?vs advanced stage?+?), histology grade (low grade vs high grade) and post-operative radiation dose (? 60 Gy vs ?60 Gy) were evaluated. In univariate analysis, Masaoka staging was the only statistically significant prognostic factor in overall survival rate and distant metastasis-free rate, but insignificant in local control rate. The other prognostic factors were all insignificant in overall survival rates, local control rate and distant metastasis-free rate. In previous studies, David Blumberg et al. (29) reviewed 43 patients with thymic carcinoma who underwent complete resection (n=29) or partial resection (n=14) of tumor. Patients having complete resection received adjuvant chemotherapy (n=3), radiation (n=8), and combined chemotherapy and radiation (n=13). Patients having incomplete resection were treated postoperatively with chemotherapy (n=1), radiation (n=6), and combined chemotherapy and radiation (n=7). There were wide variations in treatment modalities. On univariate analysis, survival was not dependent on the extent of tumor resection (p=0.18) and Masaoka stage (p=0.29). About the extent of tumor resection, the 5-year overall survival rates for patients undergoing complete resection and incomplete resection in our study were 82% and 66%, respectively (p=0.4888). The true reason for the absence of impact of complete/incomplete resection on disease outcome was not clear. But we think that postoperative radiotherapy may be the main cause of getting good local control and improving treatment outcome in patients receiving incomplete tumor resection.

Regarding the staging system of thymic carcinoma, no studies have definitely confirmed the prognostic usefulness of Masaoka staging for patients with thymic carcinoma. The data of David Blumberg et al. (29) even showed that Masaoka staging system could not predict prognosis of 43 patients with thymic carcinoma under wide variations of therapeutic modalities. However, in our study, the Masaoka staging system is the most important prognostic factor in primary thymic carcinoma patients receiving postoperative radiotherapy alone. Because the characteristics of patients between our study and their group were very different, we could not make any conclusion about Masaoka staging system in such few cases. It needed to be further investigated.

With regard to the postoperative radiation dose, we could not get the dose-effect relationship on local control. Further analyzing our data, we found that most of the patients receiving higher radiation dose (?60 Gy) had the advanced stage disease or unclear resection margin. A randomized trial is necessary in the future.

Tumors in the low-grade histological group are characterized by relatively favorable clinical courses, while tumors in the high-grade histological group are characterized by aggressive clinical courses. (4, 5, 8, 10) In our series, there were no statistically significant differences in overall survival rate, local control rate and distant metastasis-

free rate between these two histological groups. The reason for this discrepancy is not clear. The small case number may be the main cause.

CONCLUSION

Masaoka staging system is the most important prognostic factor in primary thymic carcinoma patients receiving postoperative radiotherapy alone.

Thymic carcinoma is characterized by extensive local invasion and high distant metastatic rate. The clinical course is aggressive and the prognosis is poor. For resectable tumor, surgery and postoperative radiotherapy can get a good local control but distant metastatic rate is still high. Therefore, systemic chemotherapy is needed to control metastatic lesions. Until now, the precise role of chemotherapy in the treatment of thymic carcinoma is still controversial. More effective chemotherapy in multi-institutional trials is necessary.

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Table 1. Patient Characteristics
Characteristics

No. of cases
Total Cases

26
Sex

male

14

female

12
Age (years)

(47

15

< 47

11
Stage

stage?

6

stage?

17

stage?a

1

stage?b

2
Histology subtype

low-grade

squamous cell carcinoma

11

high-grade

lymphoepithelioma

5

small cell carcinoma

1

undifferentiated carcinoma

9
Surgery

total resection

17

subtotal resection

9
Radiation dose

(60 Gy

17

< 60 Gy

9

Table 2. Masaoka Staging System
Stage?
Completely encapsulated tumor without microscopic capsular invasion.
Stage?

1. Macroscopic invasion into the surrounding fatty tissue or mediastinal pleura.

2. Microscopic invasion into the capsule.
Stage?
Macroscopic invasion into the neighboring organ (ie, pericardium, great vessels, or lung).
Stage?
A. Pleural or pericardial dissemination of thymoma.

B. Lymphogenous or hematogenous metastases.

Table 3. The results of univariate analysis in different prognostic factors

End point

Variables
Overall survival
(p-value)
Local control
(p-value)
Distant metastasis free
(p-value)
Sex (male vs female)
0.4257
0.7554
0.7797
Age ((47 vs <47)
0.5217
0.1101
0.5164
Total resection vs subtotal resection
0.4888
0.5961
0.1069
Stage (?+?) vs (?+?)
0.0482*
0.3731
0.0193*
Pathology (low grade vs high grade)
0.2444
0.2299
0.7198
Dose ((60 Gy vs <60 Gy)
0.5794
0.3268
0.6002
* Statistically significant.