

Adjuvant treatment in patients at high risk of recurrence of thymoma: efficacy and safety of a three-dimensional conformal radiation therapy regimen

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Background: The clinical benefits of postoperative radiation therapy (PORT) for patients with thymoma are still controversial. In the absence of defined guidelines, prognostic factors such as stage, status of surgical margins, and histology are often considered to guide the choice of adjuvant treatment (radiotherapy and/or chemotherapy). In this study, we describe our single-institution experience of three-dimensional conformal PORT administered as adjuvant treatment to patients with thymoma.

Methods: Twenty-two consecutive thymoma patients (eleven male and eleven female) with a median age of 52 years and treated at our institution by PORT were analyzed. The patients were considered at high risk of recurrence, having at least one of the following features: stage IIB or III, involved resection margins, or thymic carcinoma histology. Three-dimensional conformal PORT with a median total dose on clinical target volume of 50 (range 44–60) Gy was delivered to the tumor bed by 6–20 MV X-ray of the linear accelerator. Follow-up after radiotherapy was done by computed tomography scan every 6 months for 2 years and yearly thereafter.

Results: Two of the 22 patients developed local recurrence and four developed distant metastases. Median overall survival was 100 months, and the 3-year and 5-year survival rates were 83% and 74%, respectively. Median disease-free survival was 90 months, and the 5-year recurrence rate was 32%. On univariate analysis, pathologic stage III and presence of positive surgical margins had a significant impact on patient prognosis. Radiation toxicity was mild in most patients and no severe toxicity was registered.

Conclusion: Adjuvant radiotherapy achieved good local control and showed an acceptable toxicity profile in patients with high-risk thymoma.

Keywords: thymoma, adjuvant treatment, three-dimensional conformal radiotherapy, local control, toxicity

Introduction

Thymomas are neoplasms originating from the thymic gland and are the most frequent primary mediastinal malignancies. Based on their pathologic features, thymomas can be divided into several categories with a different prognosis. Thymic carcinoma and type B3 thymoma, for example, have a poorer prognosis than the type A, AB, B1, and B2 histotypes, according to the World Health Organization classification. However, the best prognostic classification for thymomas is Masaoka staging, according to which stage III and IV disease are characterized by significantly worse outcome and rate of recurrence compared with stage I and II.^{1–3} Surgical resection is the mainstay of treatment for localized disease, and is often followed by adjuvant radiotherapy.

Specifically, radiotherapy is recommended in the event of incomplete excision and/or advanced disease (stage III or IV, according to Masaoka), whereas stage II thymoma, except for thymic carcinoma, does not have a clear indication for adjuvant radiotherapy. Historically, the recurrence rate varies from 0% to 30% in stage II thymoma, and in stage III ranges from 13% to 64%.⁴ Stage IV thymomas are often unresectable, and chemotherapy is considered to be the best therapeutic option, although in selected cases debulking surgery followed by adjuvant chemoradiation can represent a valid alternative.⁴ In the presence of an indication for adjuvant radiotherapy, a dose ranging from 45 to 50 Gy is strongly recommended for totally resected lesions (R0 resection), whereas 54 Gy should be administered in the presence of microscopically positive resection margins (R1 resection). In the event of macroscopic residual disease (R2 resection), a total dose of 60 Gy is recommended.^{4,5} External beam radiotherapy should be performed using the three-dimensional conformal technique, or intensity-modulated radiation therapy. Due to the very low frequency of lymph node metastases, the treatment plan should cover only the primary site of disease, and include nodal irradiation only in the presence of clinically evident lymph node involvement. In addition to radiotherapy, adjuvant chemotherapy can be considered as a treatment option in the presence of adverse features, such as incomplete resection and/or a pathologic diagnosis of thymic carcinoma.¹ Nevertheless, to date, the role of adjuvant chemotherapy in the treatment of thymoma remains unclear.

Patients and methods

Patients

Twenty-two consecutive patients with a histologic diagnosis of thymoma or thymic carcinoma and treated at our institution (National Tumour Institute of Naples, Foundation G Pascale) with surgery followed by adjuvant radiotherapy were included in this retrospective study. Eleven of the 22 patients (50%) were male. The median age was 52 (range 32–72) years. Myasthenia was present at diagnosis in four patients (18%) and developed later during treatment in one further patient. The most frequent pathologic type was B2 thymoma, accounting for nine cases (41%), while five patients (22%) had AB type and three patients had thymic carcinoma. Eleven of the 22 patients had stage III disease and the remaining eleven had stage II disease according to the Masaoka classification. R0 resection was achieved in 14 patients (64%), but only R1 resection was achieved in the remaining eight patients (36%). All patients had at least

one of the following risk factors: stage III disease, stage IIb (macroscopic extracapsular involvement), thymic carcinoma, or positive resection margins (R1 surgery). External beam radiotherapy was administered using 6–20 MV X-ray of the linear accelerator. The patients underwent computed tomography (CT) and a three-dimensional treatment plan simulation. In all patients, the clinical target volume encompassed the entire mediastinal space in which the tumor was located. Elective nodal irradiation was not performed. The planning target volume was calculated by adding a margin to the clinical target volume that ranged from 0.5 to 1 cm. The total dose delivered varied from a minimum of 44 Gy to a maximum of 60 Gy, according to stage and margin status. The dose fraction was either 2.0 or 1.8 Gy per day. In addition to radiotherapy, adjuvant chemotherapy was administered for three stage III patients (13%); in all three cases, a polychemotherapy regimen containing cyclophosphamide, cisplatin, and doxorubicin was administered prior to radiation therapy. The patient and treatment characteristics are described in detail in Table 1.

Follow-up

A CT scan was performed before and after surgery, and 30–45 days after completion of adjuvant radiotherapy. In addition, follow-up was performed with periodic clinical

Table 1 Patients and treatment characteristics

Median (range) age, years	52 (32–72)
Sex	
Male	50% (11/22)
Female	50% (11/22)
Histology	
A	5% (1/22)
AB	22% (5/22)
B1	10% (2/22)
B2	41% (9/22)
B3	10% (2/22)
C	12% (3/22)
Stage	
IIA	10% (2/22)
IIB	40% (9/22)
III	50% (11/22)
Surgery	
R0	66% (14/22)
R1	34% (8/22)
Radiotherapy, Gy	
44–50	32% (6/22)
50–54	34% (8/22)
60	34% (8/22)
Chemotherapy	
No	85% (18/22)
Yes	15% (4/22)

visits consisting of anamnesis, physical examination, and a CT scan. Follow-up visits were at 6-monthly intervals during the first 2 years following the end of radiotherapy. After 2 years, follow-up was yearly.

Disease-free survival was calculated starting from the end of radiotherapy through to recurrence or death. Overall survival was considered as the time elapsing from the end of radiotherapy to patient death. In the absence of either recurrence or death, patients were censored to the date of the last follow-up visit. Acute toxicity was determined by analyzing the side effects occurring within 3 months from the beginning of radiotherapy. Late toxicity was determined by evaluating the side effects occurring after 3 months from the beginning of radiotherapy.

Statistical analysis

Actuarial overall survival and disease-free survival were estimated at 3 and 5 years using the Kaplan–Meier method. Univariate analysis and the log-rank test were used to investigate the influence of the demographic and clinical variables on relapse rate and survival. All statistical tests were two-sided and a *P*-value of 0.05 was considered to be statistically significant.

Results

Twenty-two patients were treated from March 2003 to March 2013. Median overall survival was 100 months, while the 3-year and 5-year overall survival rates were 83% and 74%, respectively. Median disease-free survival was 90 months, while the 3-year and 5-year relapse rates were 16% and 32%, respectively (Figure 1). On univariate analysis, only stage and margin status had a significant impact on the outcome. With regard to stage, the median overall survival was 100 months for stage IIA/IIB patients and 60 months for stage III patients (*P*=0.032). In addition, disease-free survival was 90 months for stage IIA/IIB versus 48 months for stage III patients (*P*=0.035). With regard to margin status, the median overall survival and disease-free survival for the R0 subgroup versus the R1 subgroup were 100 months versus 36 months (*P*=0.009) and 90 months versus 32 months (*P*=0.029), respectively. Age did not have any effect on prognosis. Survival and relapse rates in relation to all the aforementioned variables are shown in Table 2. Seven patients experienced disease relapse, two of which were locoregional and five were distant recurrences. Two patients had their radiotherapy interrupted at 44 Gy because of the occurrence of grade 3 dysphagia, which was the most frequent acute toxicity, and was observed in a total of eight patients (40%), four being

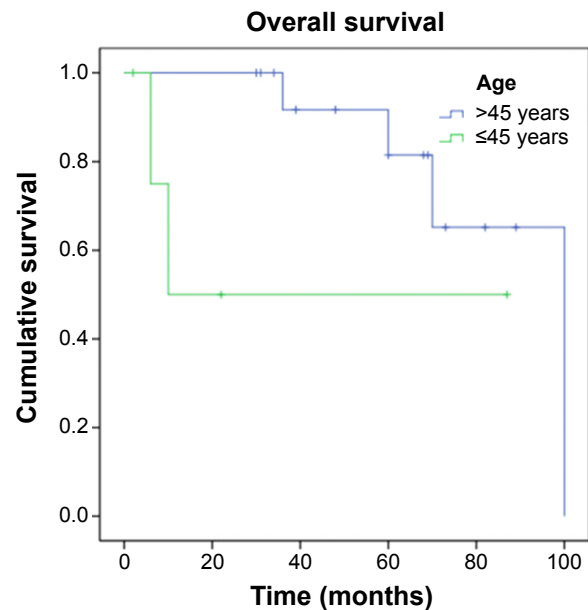


Figure 1 Kaplan–Meier curves for overall survival.

grade 2 and two being grade 1. All the patients recovered from dysphagia during treatment or within a maximum of 2 weeks after the end of radiotherapy, and no chronic swallowing dysfunction was observed. Dyspnea was reported in three patients, accompanied by chest pain in two cases. In all three patients, the symptoms resolved on antibiotic and symptomatic therapy. A list of the acute side effects observed in this study is provided in Table 3.

Discussion

To date, the role of adjuvant radiotherapy in the treatment of thymoma has not been clearly defined. Several controversial clinical studies have investigated the effect of adjuvant radiotherapy in patients at high risk of recurrence due to either locally advanced stage or presence of positive margins after surgery.^{5–10} Ruffini et al highlighted the inconsistency of the results of these studies, showing both negative and positive results of radiotherapy in prolonging survival in totally resected stage III thymomas.^{10,11} Much less controversial is the role of radiotherapy in completely resected stage II disease, where increasing evidence suggests an absence of additional benefit provided by adjuvant radiotherapy.^{11–13} Nevertheless, some authors have underscored the importance of certain “risk factors”, such as pleural invasion, margin status, and pathology in the indication of adjuvant radiotherapy for stage II thymoma.^{13,14} According to these authors, thymic carcinoma indeed represents a different disease and, consequently, it is advisable to manage it differently from other thymomas. The US and European guidelines recommend

Table 2 Univariate analysis

	OS rate at 3 years (%)	OS rate at 5 years (%)	P-value	RR at 3 years	RR at 5 years	P-value
Age, years						
≤45	50	50	NS	50	50	0.066
>45	91.7	81.5		6.7	26.5	
Sex						
Male	83.3	66.7	NS	11.1	46.7	NS
Female	80	80		20	20	
Histology						
A/AB/BI	83.3	83.3	NS	16.7	16.7	NS
B2/B3/C	82.1	68.4		16.1	42.5	
Stage						
IIA/IIIB	100	100	0.032	0	14.3	0.035
III	62.2	41.5		35.2	56.8	
Surgery						
R0	100	90	0.009	0	20	0.029
R1	47.6	0		42.9	100	

Abbreviations: OS, overall survival; NS, not statistically significant; RR, relapse rate.

use of adjuvant radiotherapy in thymic carcinoma, starting from stage II disease.¹ Our report entails use of adjuvant radiotherapy in patients with at least one of the following risk factors: stage IIb (macroscopic extracapsular extension), stage III, not totally microscopically resected thymoma (R1 resection), and thymic carcinoma (starting from stage II). We observed a remarkable median overall survival of 100 months and 3-year and 5-year actuarial survival rates of 83% and 74%, respectively. These data are particularly impressive if we consider that 35% of our patients had not undergone radical surgery (R1 resection). At univariate analysis, the margin status (R0 versus R1) and pathologic staging had a significant impact on prognosis, with the patients undergoing R1 resection and those having stage III disease being at higher risk of developing recurrence. Five of the eight R1 patients relapsed within 5 years; three of these patients had distant relapses (two lung and one bone) and two had local recurrences (pleural metastases). These results are completely in line with previously published data.¹⁵ On the other hand, histology did not affect the prognosis, although this finding may be due to the small sample size. Moreover, four of six recurrences were

distant, highlighting the fairly good local control reached by adjuvant radiotherapy. Treatment-related toxicity was generally mild, with grade 2 dysphagia being the worse side effect encountered. Neutropenia occurred only in CT-treated patients and did not affect subsequent administration of radiotherapy. Late toxicity was not observed. Of note, in previously published clinical trials, grade 1 and 2 pneumonitis were reported, especially when a large clinical target volume was encompassed,¹⁶ but we did not observe this side effect in our study. Moreover, we did not find cardiovascular toxicity (pericarditis and pericardial effusion), which is sometimes described in the literature,¹⁷ although this could be due to the relatively short follow-up period (10 years) and the small number of patients examined.

Conclusion

We can conclude that adjuvant radiotherapy, using a three-dimensional conformal technique and administering a total dose ranging from 45 to 60 Gy, has the potential to be well tolerated and to achieve good disease control in patients with a diagnosis of thymoma at high risk of recurrence.

The main limitations of our study are the small sample size and the lack of a control arm treated by conventional surgery alone with or without adjuvant intensity-modulated radiation therapy or chemoradiation. Therefore, any potential conclusions regarding the efficacy and safety of this treatment need to be confirmed in larger randomized trials.

Disclosure

The authors report no conflicts of interest in this work.

Table 3 Acute toxicity reported as percentages

	G1	G2	G3
Dysphagia	27%	4%	
Chest pain	14%		
Dyspnea	9%		
Leukopenia*		14%	

Note: *Only for chemotherapy-treated patients.

Abbreviation: G, grade of toxicity.

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