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Treatment modalities and prognostic factors in patients with Masaoka-Koga stage III thymoma: a single center study

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► ***Original article***

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ABSTRACT

Background*:** Clinical stage and the ability to achieve comprehensive treatment were the prognostic features of thymoma. In the present study, we aimed to analyze the efficacy of different types of therapy in patients with Masaoka-Koga stage III thymoma. ***Materials and Methods: From 2001 to 2018, patients newly diagnosed with thymoma was retrospectively analyzed. The c2test was used to evaluate patient characteristics, the Kaplan-Meier method was used to calculate overall survival (OS), log-rank method was applied to examine the difference between groups, and Cox regression was used to analysis the potential prognostic factors of OS. ***Results:*** The median follow-up time was 50 months (range: 3-221 months), and median OS was 51 (range: 3-221) months. The radical surgery group had a significantly better OS than the palliative surgery group. The 5- year, 10-year OS were 88.2%, 74.4% in the radical surgery group, whereas the 5- year, 10-year OS were 51.8% and 32.4% in the palliative group. The 5-year OS in surgery followed by adjuvant radiotherapy group was higher than that of surgery alone group (82.8% vs 55.8%, P=0.033); similarly, the 10-year OS of the two groups were 64.2% and, 50.2%, respectively (P＜0.05). Multivariate analysis revealed that age < 50 years (HR [hazard ratio]: 0.264), radical resection (HR:0.134, P=0.000), and surgery combined with radiotherapy (HR:2.778, P=0.009) were independently associated with better OS. ***Conclusion:*** In Masaoka-Koga stage III thymoma, patients treated with radical surgery was capable of achieving better OS than patients treated with palliative surgery. Moreover, radical surgery was an independent factor of prognosis.

INTRODUCTION

Thymoma was a rare type of tumor that originating from the epithelial cells of the thymus [1]. Despite the high cure rates, however, thymoma has malignant potential because of its ability to invade locally and metastasize regionally [2]. Myasthenia gravis and other autoimmune paraneoplastic diseases were frequently observed in patients of thymomas [3]. The anatomic extent of thymoma at the time of surgical resection has been utilized for staging, and Masaoka staging system was widely used in this malignant tumor across the world [4].

Surgery has been considered as the definitive treatment for operable thymoma [5]. However, when tumors broken through the capsule and invaded to the surrounding organs, it was difficult to achieve completed resection [6]. Masaoka-Koga stage III thymoma refers to gross tumor invasion of extrathymic organs or tissues such as the mediastinal pleura, pericardium, lung, phrenic nerve, and great vessels [7]. Therefore, comprehensive strategies including surgery combined with postoperative adjuvant chemoradiotherapy, or neoadjuvant chemoradiotherapy followed by surgery were needed for the treatment of stage III thymoma [8].

Over the past few decades, the role of radiotherapy and chemotherapy in the treatment of stage III thymoma has been explored [9]. Indeed, thymoma was considered to be sensitivity to both radiotherapy and chemotherapy [10]. Durable responses have been observed in incompletely resected and inoperable patients after treated with radiotherapy [11]. With advances in radiation delivery techniques, high doses could be delivered to tumors while sparing normal tissue. Thus, radiotherapy and chemotherapy were often recommended in the management of stage III thymoma. There were medical data from smaller, mostly institutional series to suggest survival benefits in patients treated with radiotherapy and chemotherapy [12]. However, Prospective randomized trial assessing the efficacy of radiotherapy and chemotherapy for stage III thymoma was rare.

Given the relatively low incidence and lack of sufficient evidence in thymoma, standard treatment patterns for Masaoka-Koga stage III cancer have not been well established. A better understanding of radiotherapy and chemotherapy for thymoma will allow investigators to develop novel treatment modalities. This study explored the clinical features, treatment options and the prognosis of surgically resected stage III thymoma, and aimed to provide novel point of views for better management of this

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malignant tumor.

MATERIALS AND METHODS

Patients' population

From January 2001 to November 2018, medical records of thymoma patients in the First Hospital of Lianyungang were retrospectively analyzed. Patients must have met all of the following inclusion criteria to be eligible for analyses in this study. Inclusion criteria: (1) Newly diagnosed Masaoka-Koga stage III patients, for example, these with gross tumor invasion to surrounding organs, including mediastinal pleura, pericardium, great vessels, phrenic nerve, lung, etc., without lymph node and organ metastasis; (2) Treated with surgical resection; (3) With biopsy proved thymoma; (4) Without personal history of other malignant tumors. Exclusion criteria: (1) Pathologically unclear or other thymic tumors other than thymoma, such as thymoma squamous cell carcinoma or neuroendocrine carcinoma; (2) Recurrent thymoma; (3) Those who refused to receive surgery. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. The present study was approved by the Research Ethics Committee of the First People's Hospital of Lianyungang (no. 202203189).

Surgical resection

All the patients included in the present analysis were treated with surgical resection, some of the patients received neoadjuvant radiotherapy and/or chemotherapy, and the other patients received adjuvant radiotherapy or chemotherapy. The World Health Organization classification was used for histological typing. The criteria for invasion of surrounding tissues including: intraoperative macroscopic invasion or tumor invasion were confirmed by surgical pathology. Patients were excluded from stage III when the primary tumor and the surrounding organs were tightly adhered without obvious invasion. According to the completeness of tumor resection, surgical treatment for thymomas could be divided into radical surgery (R0 resection) and palliative surgery (R1 resection refers to microscopic tumor resection, and R2 resection refers to macroscopic tumor resection). Surgery was performed with median sternotomy or video-assisted thoracoscopic tumor resection. For radical surgery, the tumor-invading tissues were completely removed, including mediastinal pleurectomy, pericardiectomy, phrenic nerve resection, partial resection of vascular wall, partial resection of lung tissues, etc. Palliative surgery means partially excised with visible residual tumors.

Radiotherapy

Radiotherapy includes preoperative radiotherapy and postoperative radiotherapy. Surgery were performed within 4-8 weeks after preoperative radiotherapy. The target volume of preoperative radiotherapy including the primary tumor of the mediastinum by imaging, and without prophylactic irradiation of the supraclavicular area. Postoperative radiotherapy started within 4-8 weeks after surgery. For patients who achieved R0 resection, the target volume including the postoperative tumor bed. For patients who achieved R1 or R2 resection, the target volume including both the tumor bed and the residual tumors. Three-dimensional conformal radiotherapy or intensity-modulated radiotherapy were conducted by using a linear accelerator (Varian VitalBeam, USA); and the mean doses to spinal cord was less than 45 Gray (Gy). The median dose was 60Gy (range: 10-70Gy, fraction: 1-35), of which the median dose of preoperative radiotherapy was 40Gy (range: 24-70Gy, fraction: 12-35), and the median dose of postoperative radiotherapy was 60Gy (range: 10-70Gy, fraction: 1-35).

Chemotherapy

Chemotherapy includes preoperative chemotherapy and postoperative chemotherapy. Chemotherapy regimens include taxane (Qilu, China) combined with platinum (Qilu, China), etoposide (Qilu, China) combined with platinum (Qilu, China), gemcitabine (Qilu, China) combined with platinum (Qilu, China), cyclophosphamide (Qilu, China) combined with anthracycline (Qilu, China) and cisplatin (Qilu, China). The median number of chemotherapy cycles was 4 (range: 1-8), of which the median number of preoperative chemotherapy cycles was 2 (range: 1-3), and the median number of postoperative chemotherapy cycles was 2 (range: 1-4).

Follow-up

After treatment, all the patients were followed up every 3 months in the first 2 years, then every 6 months for the next 3-5 years, and then annually. Patients follow up including physical examination, chest computed tomography (CT), abdominal ultrasound, and bone imaging. Tumor recurrence or progression were confirmed by imaging (enhanced CT, bone scintigraphy, or positron emission tomography–computed tomography) and histology.

Statistical analysis

Overall survival (OS) was the calculated from the date of diagnosis to the date of last follow-up or death. Local recurrence was defined as tumor proliferation in the surgical area; regional recurrence was defined as recurrence in the thoracic cavity excluded the lungs, such as the pleura, diaphragm, or mediastinal lymph nodes; distant metastases was

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defined as extra thoracic metastasis or intrapulmonary metastasis. The Statistical Package for the Social Sciences (SPSS, version 24.0, IBM, USA) software was used for statistical analysis, the $\chi 2$ test was used to evaluate clinical variables, the Kaplan-Meier analysis was used to calculate the cumulative survival rate, the Log-rank method was used to determine the difference between groups. To identify potential prognostic factors, univariate and multivariate Cox regression were analyzed. A $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

A total of 266 patients were included for analysis. The median follow-up time was 50 months (range: 3-221 months). The median age was 46 years (range: 25-76 years). According to the outcomes of surgery, the patients were divided into radical surgery group (R0 resection: 188 cases) and palliative surgery group (R1 resection: 6 cases, R2 resection: 72 cases). The Eastern Cooperative Oncology Group (ECOG) scores of all patients were between 0 and 1; approximately 25% of the individuals had myasthenia gravis; the proportion of type B thymoma was higher than other types. Mediastinal pleura and pericardium were the most common tumor organs for cancer cells to spread. Individualized comprehensive treatment was performed based on the location of primary tumors and invasion of organs. In the total patient population, 214 cases received comprehensive treatment including surgery, and 52 individuals received surgery alone; there were 188 patients received radical surgery, 78 cases treated with palliative surgery, and 174 individuals received postoperative radiotherapy. Of the 36 patients who received preoperative radiotherapy, 14 patients underwent radical surgery, 10 patients received palliative surgery, and 12 patients received palliative surgery combined with postoperative radiotherapy. The detailed data of patient characteristic were shown in table 1.

Table 1. General characteristics of patients with Masaoka-Koga stage III thymoma

Characteristic	Total (n=266)	Radical surgery n=188	Palliative surgery n=78	P	Characteristic	Total (n=266)	Radical surgery n=188	Palliative surgery n=78	P
Age					Pathological type				
≥50	114	74	40	0.249	A	16	6	10	0.023
＜50	152	114	38		AB	20	10	10	
Sex					B1	62	40	22	
Male	150	102	48	0.565	B2	92	78	14	
Female	116	86	30		B3	76	54	22	
Years					Tumor invasion				
2000-2010	144	108	36	0.256	Mediastinal pleura	230	158	72	
2011-2018	122	80	42		Vein	80	28	52	
ECOG score					Artery	32	2	30	
0	194	142	52	0.294	Pericardium	140	100	40	
1	72	46	26		Phrenic nerve	36	30	4	
Tumor diammter >8cm	90	66	24	0.691	Lung	90	56	34	
≤8cm	176	122	54		Number of organs invasived				
Myasthenia gravis					1	70	66	4	0.000
Yes	74	48	26	0.399	2	94	72	22	
No	192	140	52		≥3	102	50	52	
Radiotherapy Before surgery	36	14	22	0.005	Chemotherapy Before surgery	14	4	10	0.016
After surgery	174	134	40		After surgery	22	12	10	
No	56	40	16		No	230	172	58	

Survival analyses

The median OS of the whole group was 51 (range: 3-221) months. The 5-year and 10-year OS of the whole patient population were 76.5%, and 61.6%, respectively. The radical surgery group had better survival rates compared with the palliative surgery group (figure 1). The 5-year and 10-year OS were 88.2% and 74.4% in the radical surgery group, and 51.8%, 32.4%, respectively, in the palliative surgery group (P=0.000). Compared with surgery alone, the combination of surgery and radiotherapy was associated with higher OS. The 5-year and 10-year OS were 82.8% and 64.2% in the radical surgery group, and 55.8%, 50.2%, respectively, in the palliative surgery group (P=0.033). There was no significant difference in 5-year OS between the surgery combined with chemotherapy group and the surgery alone group (68.9% vs 77.6%, P=0.782). Compared with surgery alone, neoadjuvant therapy combined with surgery did not significantly improve OS (P=0.577). Details of patients' survival were shown in table 2).

Compared with radical surgery alone (40 cases), palliative surgery combined with postoperative radiotherapy (52 cases) was associated with a better survival, the 5-year and 10-year OS of the two groups were 72%, 45% and 77.3%, 70.3%, respectively (P=0.385).

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Table 2. Cox proportional hazards regression for OS.

Variable	OS（%）			Variable	OS（%）		
	5-year	10-year	P		5-year	10-year	P
Age				Combined with chemotherapy			
≥50	63.9	43.1	0.001	Yes	68.9	--	0.782
<50	87.2	76.9		No	77.6	62.3	
Sex				Invasion of mediastinal pleura			
Male	74.2	61.9	0.573	Yes	74.6	56.9	0.024
Female	79.5	60.6		No	90	90	
Tumor diammter >8cm	72.2	52.1	0.395	Neoadjuvant therapy			
≤8cm	78.9	67.1		Yes	79.4	61.9	0.577
				No	62	62	
Years				Invasion of the lungs			
2000-2010	79.8	61.1	0.672	Yes	74	60.6	0.166
2011-2018	71.2	71.2		No	77.9	62.5	
ECOG score				Invasion of the vein			
0	79	67.5	0.224	Yes	61.9	45.1	0.024
1	70.4	44.8		No	83.2	69.2	
Myasthenia gravis				Invasion of the artery			
Yes	59	36.9	0.002	Yes	69.3	34.7	0.281
No	82.9	69.9		No	77.8	64.8	
Surgery			0.000	Invasion of great vessels			
Radical	76.5	61.6		Yes	63.8	46.5	0.036
Palliative	60.8	40.5		No	83.8	69.6	
Pathological type				Invasion of the phrenic nerve			
B2/B3	75.8	58.6	0.969	Yes	85.9	71.5	0.558
Other	77	65.6		No	75.4	60.6	
Combined with radiotherapy				Number of organs invasived			
			0.033	1	93.1	93.1	0.006
Yes	82.8	64.2		2	64.8	43	
No	55.8	50.2		≥3	76.2	55.5	

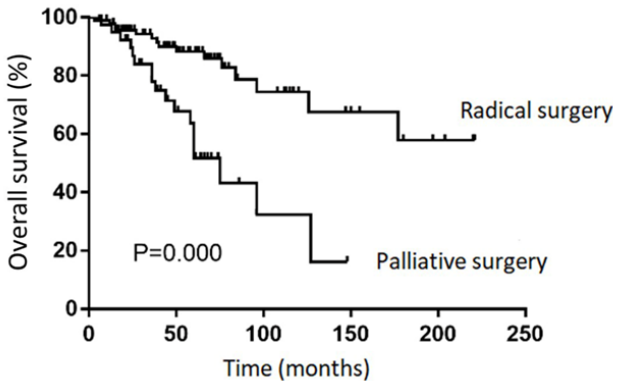

Figure 1. The overall survival of patients with Masaoka-Koga stage III thymoma in radical surgery group and palliative surgery group.

Prognostic factors of OS

Next, we performed both univariate and multivariate analyses to determine the independent prognostic factors of OS. Univariate analysis (Table 2) uncovered age <50 years (P=0.001), no myasthenia gravis (P=0.002), received radical surgery (P=0.000), combined with radiotherapy (P=0.033), no mediastinal pleural invasion (P=0.024), no venous invasion (P=0.001), no great vessel invasion (P=0.036), and single organ invasion (P=0.006) were associated with better OS. These factors were included in the multivariate analysis, and the results showed that age <50 years (HR: 0.264, P=0.001), radical surgical resection (HR: 0.134, P=0.000), surgery combined with radiotherapy (HR: 0.134, P=0.000) 2.778, P=0.009) was independently prognostic factors of favorable OS.

Recurrence and metastases

Tumor recurrence occurred in 88 patients (33%), the median recurrence time was 30 months (range: 2-115 months). Among these patients, there were 32 cases of local recurrence, 48 cases of regional recurrence, and 46 cases of distant metastasis. Local recurrence was mostly observed in the primary tumor bed or the residual tumors. Regional recurrence was frequently detected in the pleura (36 cases), diaphragm (4 cases), and pericardium (8 cases). Distant metastases were usually seen in bone (10 cases), extrathoracic lymph nodes (6 cases), liver (4 cases), brain (4 cases), and the lungs (22 cases).

DISCUSSION

Thymoma was an indolent tumor that occurs in the anterior mediastinum, and surgery was the main treatment for cure [13]. Masaoka-Koga stage III tumors invaded to the surrounding tissues and adjacent organs; due to the complicated anatomy of the diseased tissue, it was difficult to perform complete surgical resection [14]. In this study, the complete resection rate of the 266 stage III patients was 70.7%.

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Since not all thymic tumors can be completely removed, surgery based comprehensive treatments have been conducted to increase the radical resection rate and survival. The current results suggested that radical surgery and age were independent prognostic factors of OS; on the contrary, neoadjuvant therapy and chemotherapy had no significant effect on prognosis.

To date, whether the extent tumor resection had a significantly impact on patient survival remains controversial in thymomas. Although most of the studies concluded by improved survival [15-18], however, there were several analyses demonstrated the extent of primary tumor resection had insignificant impact on the outcomes of thymoma patients [19, 20]. Unsatisfactory surgical resection was the main reasons of this contradictory conclusion. Therefore, The European Association of Thoracic Surgeons (ESTS) Thymic Working Group emphasized the importance to achieve complete resection for Masaoka-Koga stage III tumors, eventhough extensive vascular reconstruction were indispensable [21]. The present analysis suggested that the extent of surgical resection was an independent prognostic factor for OS, radical surgery was associated with favorable survival compared to palliative surgery. Notably, there was insignificant difference in survival between the radical surgery group and palliative surgery combined with radiotherapy group. Our results suggested palliative surgery followed by local radiotherapy was capable of eradicating residual cancer cells in tumor bed.

The effect of postoperative radiotherapy in invasive thymoma has been investigated, however, researchers have not reached a consensus. For completely resected stage III thymoma, previous studies showed that the survival and prognosis were not significantly improved after postoperative radiotherapy [18, 22]. In contrast, multicenter retrospective studies demonstrated that postoperative radiotherapy was effective in improving OS in stage III thymoma [23-25]. Variables including patients characteristics, chemotherapy regime, surgery, and radiotherapy scheme may have impacts on treatment outcomes [26]. Indeed, recent studies showed high doses of postoperative radiotherapy was associated with improved survival compared with palliative surgery alone or palliative surgery combined with low doses radiotherapy [27]. These results suggested postoperative radiotherapy may be considered for patients who received palliative surgery alone. The current study depicted postoperative radiotherapy was an independent factor of OS. Therefore, postoperative radiotherapy should be considered according to the extent of surgery and the purpose of treatment for stage III thymoma. For patients received radical surgery, low doses of postoperative radiotherapy were efficient to improve outcomes, and for patients treated with palliative surgery, radical radiation doses were recommended. For incomplete resected thymoma. In recent years, stereotactic body radiation therapy (SBRT), a type of radiotherapy that can deliver high dose radiation more precisely and quickly than conventional radiotherapy, was under investigation in thymoma [28]. SBRT not only shortens the total radiation treatment and reduces the damage to the surrounding normal tissues, but also increases the total dose of equivalent biological effects [29]. There was a prospective study focused on the feasibility, efficacy and toxicity of SBRT in the treatment of thymoma (NCT03078699).

For operable thymoma, surgical resection was the standard treatment. Importantly, neoadjuvant was associated with the benefits of shrink tumors, increase complete resection rates, and eradicate occult metastases [30, 31]. Retrospective studies reported that the response rate of neoadjuvant chemotherapy was over 50%, and there was a role for downstaging by neoadjuvant chemotherapy [32, 33]. Thus, if preoperative imaging or intraoperative exploration revealed that the tumor could not be completely resected, neoadjuvant chemotherapy or radiotherapy should be considered. In this study, neoadjuvant therapy combined with surgery was inefficient in improving OS compared with radical surgery alone. The patients who received neoadjuvant therapy usually had larger tumor volumes and more severe invasion of surrounding tissues and organs, these factors make it difficult to completely remove the primary tumor even after neoadjuvant therapy. Therefore, rigorous prospective studies are necessary to confirm the role of neoadjuvant therapy in operable thymoma. A group from US performed a phase II study of neoadjuvant treatment use in trimodality therapy for patients with high risk thymoma (NCT00387868).

Consistent with previous reports, our study indicated that age was an important factor affecting survival, and patients diagnosed younger than 50 had better OS [34]. In addition, pathological type and tumor size had also been reported as prognostic factors [33-35]. Yamada et al showed that chest wall invasion was associated with poorer survival, while the number of organs invaded has no effect on survival [36]. In the current study, there were no cases of chest wall invasion. Furthermore, our results also demonstrated that the number of organs invaded was not an independent factor of OS.

Since the durable clinical activity and favorable tolerability, immunotherapy has a rapidly expanding role for the treatment of malignant tumors [37]. Thymoma was a programmed cell death 1 ligand 1 (PD-L1) expressing tumor, and the expression frequencies was about 23–92% [38]. Several evidences showed immunotherapy might influence future development of immunotherapeutic modalities for the treatment of thymoma [39-41]. Avelumab, a PD-L1

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inhibitor, was evaluated in a Phase I dose-escalation study in patients with recurrent thymoma, and was associated with an objective response rate of 29% [41]. Nivolumab, a programmed death-1 antibody, was evaluated in a phase II study in Patients with type B3 thymoma that previously treated with chemotherapy (NCT03134118). More clinical trials are needed to discover additional immunotherapy drugs to improve clinical outcomes.

There were several clinical trials focused on the comprehensive treatment modalities in thymoma. The safety of concurrent chemoradiotherapy for limited advanced unresectable thymoma was explored by a group from China (NCT02636556). In addition, a Randomized Phase III Study was conducted to analyze whether adjuvant radiochemotherapy has a better survival than adjuvant radiotherapy in patients of incomplete resection thymoma (NCT02633514). Instead of using high energy X-rays (convention radiotherapy) to destroy tumor cells, proton therapy is another type of radiotherapy that use protons rather than X-rays. Proton radiotherapy has been shown to reduce normal tissue toxicity compared to convention radiotherapy [42]. A multicenter non-randomized phase II study of proton beam radiotherapy in patients with thymoma was conducted (NCT04822077).

Although the results are fascinating, several limitations existed in this study. First, the retrospective nature of the study. Second, the cases in subgroup analyses were relatively small. Additionally, over the past decades, the continuous improvement of surgical techniques and radiotherapy techniques may influence the outcomes of included patients. Therefore, further investigation is needed to confirm our analyses.

CONCLUSION

In conclusion, radical surgery is the most important treatment for Masaoka-Koga stage III thymoma. The OS of radical resection group were significantly higher than those of palliative resection cohort, radical surgery was the most important factor affecting prognosis. In addition, age and postoperative radiotherapy were also independent factors of OS.

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