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Review Article

Thymoma: A Review of Research Progression

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Abstract

Thymoma is considered a rare disease, yet it is the most common anterosuperior mediastinal neoplasm. The WHO classified six different types of thymic tumors: A, AB, B1, B2, B3, and C. Currently, the most commonly used staging schemes are the Masaoka staging system and the TNM staging system proposed by the WHO. Currently, surgery remains the primary treatment option for thymoma. Operable cases will be treated further with surgery; however, the value of postoperative radiation therapy for completely resected stage II/III thymomas remains uncertain, whereas postoperative chemotherapy or radiotherapy is important for the treatment of all stage IVa thymomas. For stage IVb thymomas, chemotherapy is an important option, although adjuvant radiation therapy may also be considered.

Keywords: Review; Research Progression; Therapy; Thymoma

Introduction

Thymoma is considered a rare disease. The overall incidence of thymoma in the United States is 0.13 per 100,000 person-years according to the Surveillance, Epidemiology, and End Results Program (SEER) database [1], and a European database yielded an incidence of 0.17 per 100,000 person-years [2]. Although specific incidence data remain lacking in China, thymoma is the most common anterosuperior mediastinal neoplasm, accounting for 30% of adult anterior mediastinal tumors and 20% of all malignant mediastinal tumors. Still, most studies of this rare cancer have been based on small numbers of clinical cases recruited at single treatment centers, and the treatment and prognosis remain controversial because of the lack of high-quality evidence-based studies. This article reviews recent advances in thymoma treatment and prognosis in an attempt to provide a reference for clinicians.

Histological Classification, Clinical Stage and Prognostic Value

The Histological Classification of Thymoma

Thymomas arise from the epithelial cells of the thymus in the presence of a variable admixture of benign lymphocytes. In the "L-B classification", the first widely adopted histological thymoma classification since its introduction in 1961, Bernatz et al. [3] classified thymomas into one of four types based on the shapes of the neoplastic epithelial cells and the ratios of lymphocytes to epithelial cells: predominantly lymphocytic, mixed lymphoepithelial, predominantly epithelial (polygonal cell), and spindle cell epithelial thymomas. However, this classification system provided no prognostic information regarding the evolution of subtype-related diseases. In 1985, Marino and Muller-Hermelink [4] reported the "M-H classification", which was based on the morphologic and functional resemblances of neoplastic epithelial cells to normal thymic cortical and medullary epithelial cells and classified tumors

as medullary, mixed, predominantly cortical, cortical, or well-differentiated thymic carcinoma. However, although this prognostically valuable system was used as a reference for the World Health Organization (WHO) classification, it was not widely adopted.

The WHO proposed a new classification system in 1999 to standardize the histodiagnosis of thymoma [5]. This system remains the most widely used, and classifies six different types of thymic tumors: A, AB, B1, B2, B3, and C. Type A tumors comprise neoplastic epithelial cells with a spindle/oval shape. Type B tumor cells have a dendritic or plump (epithelioid) appearance, and can be further subdivided into three subtypes: B1, predominantly cortical; B2, cortical thymoma; B3, well differentiated thymic carcinoma. Tumors that exhibit both of these morphologies are designated as type AB. All thymic carcinomas (e.g., squamous-cell carcinoma, mucoepidermoid carcinoma, basiloma) are classified as type C. The 2004 update to the WHO classification also defined neuroendocrine neoplasm as a type C thymoma [6].

Thymoma Stage Classification

Thymoma staging has also evolved over time. In the 1970s, thymomas were classified as either benign and malignant [7]. Several schemes were later introduced, including the system introduced in 1978 by Bergh et al. [8] and modified by Wilkins and Castleman in 1979 [9], the system reported by Verley and Hollmann in 1985 [10], and the thymic tumor classification put forth by a French study group in 1991 [11]. However, these were based on small patient samples and lacked clinical evidence, and therefore were not widely implemented. Currently, the most commonly used schemes are the Masaoka staging system (Table 1) and the TNM staging system (Table 2) proposed by the WHO. Of these, the former was determined using large cohort studies [12]. The International Thymic Malignancy Interest Group (ITMIG) further suggested the subdivision of stage II into stages IIa and IIb, which corresponded to invasion of the pleura and mediastinal pleura, respectively. Additionally, a subdivision of stage III yielded stages IIIa and IIIb, which corresponded to invasion of pericardium/lung and great vessels, respectively. Although these suggestions are reasonable, confirmatory evidence is lacking because of the rarity of this disease.

Stage	Description
I	Macroscopically, complete encapsulation; microscopically, no capsular invasion
II	1. Macroscopic invasion of the surrounding fatty tissue or mediastinal pleura, or
	2. Microscopic invasion of the capsule
III	Macroscopic invasion of a neighboring organ (e.g., pericardium, great vessels, or lung)
IV	A. Pleural or pericardial dissemination
	B. Lymphogenous or hematogenous metastasis

Table 1: Masaoka Clinical Staging Criteria.

T descriptor			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor is completely encapsulated		
T2	Tumor invades pericapsular connective tissue		
T3	Tumor invades neighboring structures (e.g., pericardium, mediastinal pleura, thoracic wall, great vessels, and lung)		
T4	Tumor exhibits pleural or pericardial dissemination		
N descriptor			
Nx	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in anterior mediastinal lymph nodes		
N2	Metastasis in other intrathoracic lymph nodes, excluding anterior mediastinal lymph nodes		
N3	Metastasis in scalene and/or supraclavicular lymph nodes		
M descriptor			
Mx	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping			
I	T1N0M0	II	T2N0M0
III	T1N1M0	IV	T4NanyM0
	T2N1M0		TanyN2-3M0
	T3N0-1M0		TanyNanyM1

Table 2: WHO TNM Classification of Thymic Epithelial Tumors.

Prognostic Value

In most previous studies, the Masaoka stage was identified as the most important independent prognostic factor [13-17], with 5-year Overall Survival (OS) rates of 97-100%, 98-100%, 68.8-83%, and 35-57.2% for stages I, II, III, and IV, respectively. The corresponding 10-year OS rates were 90%, 70%, 55%, and 35%, respectively, and the 20-year OS rates were 89%, 91%, 49%, and 0%, respectively. The same studies also identified the WHO histological classification as a major prognostic factor [13-18]. Here, type A/AB/B1 was associated with a much better prognosis relative to type B2/B3, with 5-year OS rates of 90-100%/92-100%/81-94.4% vs. 75-94.4%/70-91.7%; however, the prognostic value of the WHO stage remained lower than that of the Masaoka stage. Because the relationship between the histological classification and prognosis is not statistically evident for Masaoka stage III/IV thymomas, some researchers suggest that only a Masaoka stage

I/II classification has prognostic value [13-16]. Other prognostic factors identified in previous studies include the tumor volume, surgical margin, and presence of Myasthenia Gravis (MG) [14-19].

Thymoma Treatment and Related Prognostic Value

Surgical Treatment

Currently, surgery remains the primary treatment option for thymoma. Several studies have identified complete resection as one of the most important prognostic factors [20-23]. Accordingly, surgical treatment must achieve a maximum complete resection; this may include an extended resection and even the partial resection of involved tissues and organ systems, such as affected sections of the pericardium, lung, and great vessels.

Surgical Value According to Thymoma Stage

For early-stage thymoma, surgery is a radical and effective therapy. Currently, 10-year OS rates as high as 90% and 84% have been reported for completely resected stage I and II thymomas, respectively [24-27]. Notably, early-stage thymoma is associated with low recurrence rates, according to the Chinese Academy of Medical Sciences (CAMS; stage I and II thymoma: 0% and 7.5%, respectively) [26-27]. Still, although Margaritora et al. [28] identified complete resection ($P < 0.001$), Masaoka stage ($P = 0.010$), and WHO histological classification ($P < 0.001$) as factors related to survival, only complete resection remained a statistically significant beneficial factor in a multivariate analysis ($P < 0.001$).

For locally advanced thymomas (Masaoka stage III/IV), complete resection is more difficult and the success rates range from 60% to 89% [20-22,25,29-31]. As with early-stage disease, patients with locally advanced thymomas can achieve better long-term survival after a complete resection. Kondo et al. reported 5-year OS rates as high as 90% among patients with completely resected stage III/IV thymomas [12], and Fan et al. [32] of CAMS showed that, among stage III thymoma cases, radical resection was significantly superior to palliative resection and biopsy in terms of 5-year OS (88% vs. 59% and 57%, respectively, $P = 0.002$), disease-free survival (DFS; $P = 0.003$), and tumor-specific survival rate ($P = 0.004$). However, local recurrence and distant metastasis frequently occur, even after radical resection. According to Fan et al. [31], the local recurrence rate of stage III thymoma after surgery alone was 16.7%. In the same report, however, the addition of radiation therapy to surgery reduced the recurrence rate to 3.8%. Accordingly, most clinicians favor multimodal therapies, such as surgery followed by adjuvant chemoradiotherapy, or neoadjuvant chemoradiotherapy followed by surgery. For example, Marulli et al. [25] reported that 5- and 10-year OS rates of 82% and 64% among patients with stage III thymoma who were treated with a combination of surgery and chemoradiotherapy. However, despite the trend toward improved survival with radiotherapy, as reported by Fan and colleagues, and advances in radiotherapy techniques, no standard concurrent treatment has been established.

Among patients with pleural metastasis (stage IVa), lack of cases and high selectivity have hindered consensus regarding treatment modes and prognosis. In an earlier clinical study, Fabre et al. [33] treated 17 stage IVa thymoma patients with combined pleuropulmonary resection and chemoradiotherapy and observed respective 5- and 10-year OS rates of 60% and 30% respectively. However, postoperative complications and mortality rates as high as 47% and 29.4%, respectively, were reported from that study. In a retrospective study, Ishikawa et al. [34] reported a good local control rate, and even a radical curative effect, after pleuropulmonary resection for stage IVa thymoma. Wright et al. [35] found that pleuropulmonary resection was safe (one postoperative complication) and improved survival (5- and 10-year OS: 75% and 50%, respectively) when performed for five patients with locally advanced thymoma (two cases of recurrence, three cases of stage IVa disease). However, despite the good survival prognoses indicated by the above studies, chemoradiotherapy was recommended after pleuropulmonary resection for stage IVa thymoma. However, this treatment regimen is associated with high rates of postoperative complications and mortality; accordingly, decisions regarding surgery should be made carefully, or surgery should be performed after chemotherapy for tumor volume reduction.

Prognostic Effects of Advances in Surgical Technology

Continuous advances in surgical technology, such as the evolution of Video-Assisted Thoracoscopic Surgery (VATS) and the recent introduction of robotic surgery, have further diversified the therapeutic approaches to thymoma. According to previous reports [36-38], patients treated using VATS had a reduced Mean Operating Time (MOT), ICU observational time, and average hospitalization period, as well as fewer postoperative complications, when compared to those subjected to traditional surgery. Although the two surgical modalities did not yield significant differences in 5-year OS and DFS in those studies, a Japanese investigation observed a higher 5-year OS rate among patients with stage I/II thymoma who underwent VATS (97.0% vs. 79.5%, $P = 0.041$) [39].

Radiation Therapy

Thymomas are relatively radiation-sensitive; accordingly, radiation therapy can be used as an adjuvant treatment in cases involving incomplete resection or poor pathologic classification, or as the major therapeutic option for inoperable thymomas. However, the administration of postoperative adjuvant radiation therapy to all patients, especially those with early-stage and completely resected thymomas, remains controversial, with a majority of researchers considering this decision to be dependent on the stage and completeness of excision.

For stage I thymomas, the complete resection rate nearly reaches 100%, with postoperative recurrence rates below 3% [27,40]

and 10-year postoperative OS rates as high as 92.3%. For such cases, postoperative radiotherapy is generally unnecessary. Recently, a SEER database analysis [41] found that postoperative radiotherapy did not yield benefit for patients with local disease (Masaoka stage I), and appeared to decrease the 5-year Cause-Specific Survival (CSS) (91% vs. 98%, P = 0.03). Therefore, adjuvant treatment is not recommended after a complete resection of stage I thymoma.

In contrast, the role of postoperative radiotherapy for Masaoka stage II/III tumors remains controversial. SEER database analyses [23,41] demonstrated a survival advantage of postoperative radiotherapy, with respective 5- and 10-year OS rates of 64% and 41% for stage II and 53% and 35% for stage III tumors (P = 0.002). In contrast, many other reports [30,42-45] demonstrated that postoperative radiotherapy did not improve survival rates among patients with completely resected tumors. In an analysis of 107 radical excision cases of stage II thymoma at the Cancer Hospital, CAMS, Chen et al. [26] found that adjuvant radiotherapy after complete tumor resection did not significantly reduce recurrence rates or improve survival rates. Although the univariate analysis identified a large tumor volume, stage IIb disease, and a type B3 classification as prognostic factors, only type B3 remained an independent prognostic factor in the multivariate analysis. Furthermore, patients who underwent Three-Dimensional Conformational Radiotherapy (3D-CRT) or Intensity Modulated Radiotherapy (IMRT) had a 5-year local control rate of 100%, vs. the rate of 90% with conventional RT; however, this difference was not statistically significant (p = 0.201).

In an analysis and summary of the treatment outcomes of patients with stage III thymoma, Fan, et al. [32] found that postoperative radiotherapy could significantly improve survival among incompletely resected and inoperable cases; in contrast, completely resected cases did not achieve a significant survival benefit from postoperative radiotherapy. However, a stratified analysis [31] found that cases treated with 3D-CRT or IMRT fared better than did those treated with conventional RT or surgery alone. However, those studies selected patients over a relatively longtime span and were complicated by considerably heterogeneity of the clinical data. Furthermore, Weksler et al. [46] reported that although postoperative radiotherapy improved the DFS (P = 0.049) of stage III thymoma, it had no effect on OS. In summary, no strong evidence exists to confirm the benefits of postoperative radiotherapy for thymoma, and adjuvant postoperative radiotherapy appears to have a limited effect in cases of completely resected stage II thymoma. For stage III cases, other factors should be considered, including the suitability of follow-up for cases of completely resected type A/AB thymoma, which has good prognosis, the use of adjuvant radiation therapy for type B thymomas, and the superiority of 3D-CRT or IMRT.

For completely resected thymomas, postoperative radiotherapy is often recommended to reduce the risk of local recurrence and thereby improve the survival prognosis [41,47-51]. Thymomas, particularly those classified as stage III, often involve the surrounding tissues and organs and thereby leave microscopic and macroscopic residues, despite successful resection rates of up to 80%. Furthermore, even completely resected stage III thymomas are associated with higher recurrence rates relative to stage I/II tumors. Because the survival rate after R1 resection is similar to that after R0 resection [25], adjuvant treatment may sufficiently control minimal postoperative residual disease. According to some reports [42,52], however, postoperative radiotherapy does not decrease local recurrence rates because most recurrent tumors occur in the pleura, beyond the radiotherapy target volume. In 2009, Korst et al. [53] conducted a meta-analysis of data from 592 patients in 13 of 22 previously reported retrospective studies and found that postoperative radiotherapy did not decrease the recurrence rate among cases of completely resected stage II/III thymoma. However, the role of postoperative radiotherapy remained uncertain because of the heterogeneity of the clinical data.

In the past 20 years, significant progress has been observed in radiotherapy technologies and theories, including more precise positioning, smaller radiation fields and irradiation doses, and fewer side effects to organs at risk. These changes may clarify the role of radiation therapy. Furthermore, the prognosis varies among thymoma cases according to the extent of disease and excision and the histologic type. This variability reduces inter-study comparability and increases the heterogeneity of results from single populations, given the rarity of the condition, long patient selection period, and technical/theoretical improvement, leading to the poor assessment of postoperative radiation. Of note, although postoperative radiotherapy did not improve survival or recurrence rates among patients of completely resected stage II/III thymoma, it may have beneficial effects for high-risk patients. Current recommendations include the use of a prospective controlled multicenter study to address the large number of confounding elements associated with postoperative radiotherapy.

Chemotherapy

Thymomas are also relatively sensitive to chemotherapy and respond at rates exceeding 50% (80% in some reports). Locally advanced thymomas (Masaoka stage III/IVa) are associated with a low complete resection rate, high recurrence rate, and low 5-year OS rate. Accordingly, treatment regimens comprising induction chemotherapy followed by surgery or radiation therapy or surgery with adjuvant chemoradiotherapy have been widely in attempts to reduce local recurrence rates. Giaccone et al. [54] and Macchiarini et al. [55] respectively reported the necessity of induction chemotherapy for thymoma in 1985 and 1991, and more recent studies have reported response rates of 70% following induction chemotherapy. In a retrospective study, Cardillo et al. [30] analyzed 61 cases of stage III/IV thymoma (including thymic carcinoma) that were classified into groups treated with induction chemotherapy followed by surgery (31 cases) or surgery alone (30 cases). The 10-year OS rates of those treated and not treated with induction

chemotherapy were 57.9% and 38.1%, respectively, and a multivariate analysis identified induced chemotherapy an independent prognostic factor in this population (P = 0.003). Venuta et al. [29] conducted a prospective, non-randomized study of 45 cases and demonstrated that the combination of induction chemotherapy and postoperative radiotherapy improved the survival of patients with stage III thymoma, with complete resection rates improving to 87%. In a phase II clinical study of 22 patients with stage III–IV thymoma, Kim et al. [56] reported a 5-year OS rate of 95% after induction chemotherapy followed by surgery and adjuvant chemoradiotherapy. Furthermore, Lucchi et al. [57] compared 36 cases of stage III/IV that received neoadjuvant chemotherapy and 20 treated with surgery alone and found that induction chemotherapy effectively decreased the tumor stage and increased the resection rate. In that study, induction chemotherapy was also identified as an independent, statistically significant prognostic factor (P <0.05).

Taken together, the above results suggest that relative to surgery alone, induction chemotherapy followed by surgery and adjuvant chemoradiotherapy increased both the successful resection and survival rates. However, the sample sizes were small, and retrospective studies with larger samples and randomized controlled studies are needed. However, the use of comprehensive therapy principles is recommended when planning induction chemotherapy before surgery for a local advanced thymoma.

Treatment of Unresectable stage III/IVa and Stage IVb Thymomas

The feasible surgical options for thymomas that cannot be completely or sub totally resected include biopsy and varying degrees of cytoreductive surgery, followed by chemoradiotherapy. According to some studies, patients who underwent cytoreductive surgery achieved better survival outcomes, compared to those who underwent biopsy alone; however, other studies observed no significant difference between these procedures. Cytoreductive surgery for a thymoma is not expected to increase survival rate, despite reducing the postoperative radiation target volume and improving protection to the surrounding normal organs. Therefore, Fine Needle Aspiration Cytology (FNAC) or biopsy is recommended for a definite pathologic diagnosis of unresectable thymoma.

A combination of chemotherapy and radiation therapy can yield good survival outcomes for patients with unresectable stage III/IVa and stage IVb thymomas. The NCCN2016 study recommended chemotherapy alone or in combination with radiotherapy for these tumors, and a phase II prospective study [58] found that two to four cycles of chemotherapy (cisplatin, docetaxel, and cyclophosphamide) combined with 54 Gy of radiation to the primary tumor and metastatic lymph nodes could increase the DFS. In that study, patients who received chemoradiotherapy had a median survival time of 93 months and a 5-year OS rate of 52.5%. Currently, adjuvant and radical radiotherapy are used widely; in contrast, neoadjuvant radiotherapy represents a new treatment option for thymoma. In a study of 21 cases of stage III thymoma, Onuki et al. [59] evaluated a new comprehensive model comprising 12-20 Gy of conventional fractionated neoadjuvant radiotherapy, followed by surgery after a 1-3-week interval and postoperative adjuvant radiotherapy at a median dose of 40 Gy (range: 22–66.8 Gy). Although the sample size was small, this study indicated a significant survival benefit, with 5- and 10-year OS rates of 91% and 78%, respectively, and a 10-year DFS rate of 84% completely resection. In other words, this comprehensive model yielded good results for unresectable stage III/IVa and stage IVb thymomas and merits further use. However, the small sample size and lack of randomized controlled studies and strong evidence suggest the need for additional randomized controlled studies and accumulated cases.

Summary

To date, the histological classification, Masaoka stage, surgical margin, tumor volume, and MG have been identified as prognostic factors for thymoma. At present, thymoma treatment remains controversial. Postoperative adjuvant therapy is not needed for Masaoka stage I tumors. Surgery remains the treatment of choice for stage II and operative locally advanced thymomas. Decisions regarding postoperative radiotherapy and chemotherapy depend on the tumor stage, risk of microscopic/macroscopic residual disease, and completeness of resection. For unresectable thymomas, neoadjuvant chemotherapy is recommended to reduce the tumor volume, followed by a reassessment to determine operability. Operable cases will be treated further with surgery; however, the value of postoperative radiation therapy for completely resected stage II/III thymomas remains uncertain, whereas postoperative chemotherapy or radiotherapy is important for the treatment of all stage IVa thymomas. For stage IVb thymomas, chemotherapy is an important option, although adjuvant radiation therapy may also be considered.

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