The role of surgery in the management of locally advanced and metastatic thymoma: a narrative review

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Abstract: Thymic epithelial tumors (TETs) are rare neoplasms. While treatment guidelines for early stage TETs are well established, treatment for advanced and locally invasive and metastatic TETs (Masaoka stage IVa/IVb) is varied. Many studies examining outcomes in this patient population are single institution, retrospective studies with small sample sizes. Further complicating study of advanced TETs is that Masaoka stage IVa/IVb describes a wide variety of disease heterogeneity, and includes both thymoma and thymic carcinoma. Thus, recommendations for treatment strategies vary widely. Surgical resection with an R0 resection is a key component of treatment for early stage TETs, however the utility of surgery and appropriate surgical approach for patients with locally invasive disease is debated and ranges from local metastasectomy to extrapleural pneumonectomy (EPP). The use of multimodal therapies, including adjuvant and neoadjuvant radiation and chemoradiation, are important for patients with locally advanced disease, however identifying patients who would most benefit from each strategy has been challenging. In this review we examined the literature to provide treatment strategies for advanced TETs. Surgery with an R0 resection should be attempted in all risk appropriate patients. Multimodal therapies are likely beneficial to patients particularly with locally advanced disease, and neoadjuvant therapies may increase likelihood of R0 resection. Further investigation is necessary to identify optimal treatment strategies for patients with locally advanced TETs.

Keywords: Pleural thymoma; thymoma; extrapleural pneumonectomy (EPP); multimodality treatment

Introduction

Thymic epithelial tumors (TET) are neoplasms originating from the epithelial cells of the thymus, and can be further classified as thymoma or thymic carcinoma. While the majority of patients present with local disease amenable to upfront complete resection with the expectation of long-term cure, certain subsets of patients are more difficult to manage and require a multidisciplinary approach. Masaoka stage III, IVa and IVb patients, who have local invasion, pleural dissemination, or distant spread respectively, are more challenging to manage (1). Indeed, while Masaoka stages I–III have established treatment guidelines, no broadly accepted treatment paradigms exist for stage IVa, and while patients with stage IVb usually are treated with combination chemoradiation, there may exist selected patients in this group who would benefit from surgical treatment as well.

Stage IVa disease in particular is rare making it a challenging disease to study (2,3). Most of the published data comes from single center, retrospective studies with

few included patients. There are many different treatment strategies for advanced TETs, including proceeding to upfront surgical resection, chemotherapy, and radiation only, or multimodal therapies incorporating surgery and chemoradiation. Complicating the study of stage IVa disease further is the heterogeneous presentation—for example 'pleural disease' may represent a single deposit, diffuse involvement amenable to extrapleural resection, or bulky unresectable disease. Furthermore, stage IVa includes both pleural and pericardial disease, the latter of which may not be considered resectable. Additionally, there is no distinction made for both recurrent disease versus those patients presenting with *de novo* pleural metastatic disease; or for thymic carcinoma and thymoma. Because of the diverse presentation of stage IVa disease, as well as the multitude of treatment options, stage IVa TETs is a challenging condition to manage.

Herein, we present a scoping review of the literature regarding treatment strategies for stage IVa disease. We provide the results of a current literature review and a summary of current data in an effort to provide recommendations when treating the infrequent patient with pleural metastatic TET. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/med-20-34).

Methods

We performed a scoping review of the literature to identify studies pertinent to the treatment of patients with Masaoka Stage IVa thymoma. PubMed was searched with terms including "advanced thymoma treatment options", "thymoma surgical resection "thymoma multimodal therapies", "stage Iva thymoma", "stage IVa thymoma resection", "stage IVa thymoma treatment", "chemotherapy advanced thymoma", and "targeted therapies thymoma". The search was limited to English language studies published in the last 20 years. The original Masaoka staging paper fell outside of this time frame but was included, as were updates to the staging system. The NCCN and ESMO guidelines for thymic masses were also included and reviewed, and the references were searched for additional publications. Additional sources were included if cited in other papers and deemed to be relevant and novel to the review below.

Stage IVa TET: considerations and heterogeneity

Stage IVa thymomas represent a wide variety of different presentations and is really a collection of different diseases. We outline three separate distinguishing characteristics that need to be considered in every patient: pleural disease burden at presentation, histology (i.e., thymoma *vs.* thymic carcinoma, and histologic subset for thymomas) and *de novo* diagnosis of stage IVa disease or recurrent disease.

Disease heterogeneity

Stage IVa disease encompasses a wide range of disease extent. Patients may have a solitary small pleural implant or multiple large pleural implants, but are staged the same. When classifying disease burden by number of pleural implants and size of largest pleural implant, patients with higher disease burden (often defined as 11 or more implants) have worse outcomes including worse overall survival and recurrence free survival (4-6). In a retrospective review, Lucchi *et al.* found that patients with multiple pleural implants had significantly worse overall survival than patients with a single pleural implant (6). Kimura *et al.* similarly found that patients with 11 or more pleural implants had a 10-year overall survival of 51% compared to 79% in those with 10 or fewer implants. There was also a worse recurrence free survival, with no patients in the 11 or more group recurrence free at 10 years compared to 35% of those with 10 or fewer implants (5). Kimura *et al.* also stratified patients based on size of biggest pleural implant (greater than 2.5 cm or less than 2.5 cm) and found that there was no difference in overall survival (71% and 73%) however 44% of patients with implants <2.5 cm had 10-year recurrence free survival compared to 0% of patients with larger implants. Okuda *et al.* found the number of pleural implants (10 or fewer and 11 or more) directly correlated with resectability, and also demonstrated that patients with fewer implants tended to have better overall survival (4). It is theorized that patients with higher disease burden are less resectable and more likely to have microscopic implants than those with less disease burden, leading to their worse overall survival and recurrence free survival (4,5).

Histology: thymoma or thymic carcinoma?

Thymic carcinomas have significantly worse prognosis when compared to thymomas (2,7,8). Patients with thymic carcinomas had worse overall survival, higher rates of recurrence, and less response to chemotherapy compared to patients with thymomas (2,7-9). There is contrasting evidence regarding the survival benefit of radiation therapy

in patients with thymic carcinoma, and chemotherapy has not been shown to reliably confer a survival benefit (8). Because of this, surgical resection has been an important component of treatment (8). Ma *et al.* report upfront surgical resection was associated with better overall survival in patients with thymic carcinoma than those who underwent neoadjuvant radiation followed by delayed surgery (10). Interestingly, this survival benefit was not seen in patients with thymomas. The group reports that they controlled for unfavorable disease characteristics between those undergoing up front surgery and those with delayed surgery in multivariable analysis, but acknowledge that some survival difference may be because patients who underwent neoadjuvant therapies had more extensive disease. They concluded that upfront surgery, when compared to neoadjuvant chemo- or chemoradiation, was associated with longer overall survival in patients with thymic carcinoma, whereas this association was not observed in thymomas.

De novo disease and recurrence

The most common site of thymoma relapse is the pleura, by definition making most recurrences stage IVa. However, patients who recur and present as stage IVa are quite different than patients with *de novo* stage IVa disease. Patients with *de novo* disease are more likely to have a higher grade tumor than those with recurrent disease, with one study finding that 86% of patients with *de novo* disease had a WHO subtype B2 or higher disease, compared with 70% for recurrent disease (5). *De novo* disease also has worse overall survival and higher rates of recurrence (3,7). Thus, it has been suggested that multi-modal therapy is important for local control in *de novo* disease (5). Conversely, surgical re-resection is a mainstay of treatment for recurrent disease. Patients undergoing surgical resection for recurrent disease had significantly better outcomes than those treated with adjuvant therapy alone, and recurrent disease may have less response to adjuvant or "pseudo-neoadjuvant" therapy (4,5,11). Resection remains a hallmark of treatment in patients with both *de novo* disease and recurrence, however neoadjuvant and adjuvant therapies may have a greater role for patients' whose initial presentation is stage IVa disease.

The role of surgery in stage IVa TETs

It is well established that a mainstay of treatment in many TETs, especially for those presenting with more localized disease, is an R0 resection. Repeated studies have shown that an R0 resection was predictive of both longer overall survival and disease-free survival (2,7,12). Based on a multicenter retrospective review of TETs, The European Association of Thoracic Surgeons (ESTS) recommends that surgical resection should be attempted whenever possible (8).

While the role of surgery in stage IVa disease is less clear, several studies show that select patients with stage IVa disease go on to have excellent overall and disease free survival after surgical resection. In a multicenter retrospective review studying patients who underwent surgery for stage IVa disease, Okuda *et al.* reported a 5-year overall survival greater than 80%, which is much higher than the previously reported 50% 5-year overall survival of stage IVa disease after surgery (4). In a review from Sloan Kettering, Bott *et al.* compared outcomes between patients with stage IVa disease who were treated surgically or medically, and found that surgical patients trended towards better overall survival compared to the medically treated patients, with a median survival of 156 months compared to 50 months (11). Kimura *et al.* retrospectively studied nearly 300 patients who underwent surgical resection for stage IVa disease, and reported a 5 and 10-year overall survival of 91% and 82%. They concluded that surgical resection is safe and can lead to good long-term prognosis (5).

However, as Lucchi *et al.* note, these studies include highly selected patients both in terms of physical fitness for surgery but also in terms of disease burden and tumor characteristics, and these differences become especially important when comparing surgery to definitive chemoradiation (12). These studies are almost entirely retrospective and patients in the surgical arm often have resectable tumors and are in better condition than patients in the medical arm (12). Even in patients with an R0 resection, the ESTS working group found that over 50% of patients had recurrence, demonstrating that while complete resection may prolong survival, the disease often recurs (7). In breaking down the kind of recurrence, the group reports 25% had local recurrence, 50% had regional recurrence, 15% had distant recurrence, and approximately 10% had both regional and distant recurrence (7).

Surgical approaches

The main surgical approaches are local resection of pleural metastasis, total pleurectomy/decortication, or extrapleural pneumonectomy (EPP). Debulking is generally not advisable for unresectable patients, but could be considered in select circumstances. One surgical approach has not

been consistently shown to lead to improved survival over the others; thus, many advocate for selecting the surgical approach based on patient specific factors including extent of disease, invasiveness of tumor, and other multimodal therapies that may play a role in treatment course (3,13).

Pleurectomy, either complete or local, is most commonly performed if the lung parenchyma does not have measurable disease involvement. The efficacy of pleurectomy compared to the more invasive EPP is debated, with some claiming it leads to worse overall and progression free survival (13) while others finding these differences are not significant and allows for a less morbid procedure and lung preservation (14). Nakamura *et al.* found that pleurectomy had significantly worse outcomes than EPP, with 5-year progression free survival of 26.9% compared to 83.3%, which the authors attributed to the inability to resect clinically invisible nodules with pleurectomy (14).

In unresectable disease, some groups have advocated for debulking. A large review of over 1,300 patients by Kondo *et al.*, found that patients who underwent subtotal resection had improved overall survival as compared to patients who did not undergo any kind of resection, although this may be in part due to selection bias in who is selected for attempted surgical resection (15). Many others show that only an R0 resection has been consistently shown to be associated with survival.

The most extensive surgical resection is EPP, where the lung, a portion of the diaphragm, and visceral and parietal pleura of the lungs and pericardium are removed (16). EPP is primarily used for mesothelioma, however has also been performed for patients with locally advanced thymomas, particularly those with multiple pulmonary nodules and diffuse or bulky pleural implants (7). Theoretically, EPP improves local control by resecting disseminated invisible tumor cells (17). Patients undergoing EPP have been shown to have longer progression free survival, overall survival, and disease-free recurrence when compared to other surgical approaches (18,19). In a retrospective review of the role of EPP in patients with stage IVa thymoma, Ishikawa *et al.* found that patients who underwent other surgical approaches had a 100% recurrence rate, whereas patients undergoing EPP had a 25% recurrence rate (18). The authors went so far as to state it is "impossible to obtain an R0 resection in patients with multiple pleural tumors without EPP" (18). One important consideration is whether the high morbidity associated with EPP outweighs the potential benefit of improved local control (3). One group in Paris reported a 90-day postoperative mortality of nearly 30% in patients undergoing EPP, and a postoperative complication rate of approximately 50% (20)—while this study was an outlier, and most report far better complication and mortality rates, this study illustrates the potential issues associated with this morbid operation. Moser *et al.* found patients undergoing EPP had worse overall survival than patients undergoing the less invasive pleurectomy, although this was not significant in multivariate analysis (7). Many acknowledge the potential benefit of EPP, however emphasize the importance of patient selection to identify who would tolerate and benefit from major surgery (16,18).

Multimodality treatment

Multimodal therapy is standard of care for locally advanced or disseminated disease. Multimodal treatment describes a combined treatment approach including neoadjuvant and adjuvant therapies, and surgical resection. There is no standard chemotherapy regimen. The NCCN guidelines recommend CAP (cisplatin, doxorubicin, cyclophosphamide) and estimate response rates of approximately 40%; however, CAMP (cisplatin, doxorubicin, cyclophosphamide, and methyl prednisone) is also used (2,14,21). ESMO recommends either CAP or cisplatin and etoposide (22). Other regimens include ADOC (Adriamycin, vincristine, cyclophosphamide, cisplatin), IP (irinotecan, cisplatin) and cisplatin doublets, however these are less commonly used (23). Radiation regimens are similarly not standardized, and varies if the disease is *de novo* or recurrent (2); furthermore, the role that histology should play in these decisions is unclear, as the guidelines are similar for thymomas of any subtype, as well as thymic carcinomas.

Multimodal regimens consisting of surgery, radiation and chemotherapy are attractive, as strategies are needed to address the high local and systemic recurrence rates when surgery is used in isolation. Many studies have shown good survival with stage IVa disease with trimodal therapy, including a nearly 60% 9-year survival in certain series (24). Despite this, Moser *et al.* found no survival benefit of multimodal therapy when comparing outcomes between patients who underwent surgery only versus a multimodal approach (7). Examining this issue is complicated by the fact that heterogeneous treatment regimens are difficult to compare across different studies, however, most clinicians will recommend some form of combination treatment with surgery for Masaoka stage IVa disease (3,9).

Neoadjuvant treatment

Currently, neoadjuvant chemotherapy is recommended by the NCCN and ESMO guidelines for "potentially resectable" locally advanced tumors (2). Neoadjuvant radiotherapy, in combination with chemotherapy, has also been examined in a phase 2, multi-institutional clinical trial for patients with locally advanced thymic tumors (25). Radiologic criteria were used to define locally advanced tumors and included patients with Masaoka stages I-IVa. 20 patients completed the trial, and 15 were stage III or IVa. 11 had at least a partial response to neoadjuvant therapy. Following neoadjuvant therapy, 17/20 patients went on to have a complete R0 resection, and the remaining 3 had an R1 resection (25). The surgical approach was varied during attempted resection. All patients who underwent complete R0 resection were recurrence free at 27 months follow up. This rate of R0 resection is among the highest published, suggesting that neoadjuvant chemoradiotherapy may improve rate of R0 resection in patients with locally advanced disease. However, a comparative trial between chemotherapy alone and chemoradiation before surgery has not been carried out thus either neoadjuvant regimen is currently acceptable (2). The optimal sequence of therapy is still debated, with some retrospective evidence casting doubt on the superiority of neoadjuvant treatment (2,4,7). Even in studies that did not find worse outcomes, many found that neoadjuvant treatment was not associated with superior outcomes (4,7,13). However, there are several biases inherent to retrospectively comparing outcomes between patients who received neoadjuvant therapies and those who did not, including selection bias and immortal time bias. Further research is needed to clarify if neoadjuvant therapy has benefit and if so, what patient populations will have the greatest benefit.

Adjuvant treatment

The NCCN guidelines recommend adjuvant treatment for R1 and R2 resections, and recommend considering adjuvant radiation for R0 resections for stage II–IV thymoma and thymic carcinoma with capsular invasion (2). ESMO guidelines recommend adjuvant radiotherapy for stage III–IVa thymoma, stage II–IVa thymic carcinoma, and state it "may be considered" for thymoma patients with histologic subtypes B2 and B3, or if there is capsular invasion (stage II) (22). ESMO does not recommend adjuvant chemotherapy for R0 or R1 thymomas, and state chemotherapy "may be considered" for stage III–IVa thymic carcinomas (22). Data regarding survival benefit of adjuvant therapy after R0 resection is mixed, with some citing improved overall survival (8,26) and others demonstrating no benefit after a complete resection (7,15). Kim *et al.* retrospectively studied patients with stage IIb and III thymoma and compared outcomes for those who received adjuvant radiotherapy and those who only underwent surgery only (27). For patients with IIb thymoma with an R0 resection there was no survival benefit with radiotherapy. For patients with stage III thymoma, or those with stage IIb thymoma with a positive margin, patients who received adjuvant radiotherapy had improved overall survival compared to those who underwent surgical resection alone (17).

Adjuvant hemi-thoracic low dose radiation may enable control of pleural dissemination and prevent recurrence (28). Sugie *et al.* compared recurrence rates in patients with stage IVa thymoma who underwent routine post-operative mediastinal radiation therapy (OMRT) to those who underwent low dose entire hemi-thorax radiation (EHTR) therapy. At 3 years, 51% of OMRT patients had recurred while 29% of EHTR patients had recurred, however this difference was not significant (28). Targeted adjuvant radiation shows promise to improve local control while decreasing systemic side effects of therapies.

While adjuvant radiation is commonly used, the role of adjuvant chemotherapy remains unclear. Attaran *et al.* performed a "Best Evidence" review of adjuvant chemotherapy indications for patients with advanced thymomas (29). They concluded that adjuvant radiation and chemoradiation should be considered for all patients with stage III–IV thymomas, however found that chemotherapy alone, without radiation, does not improve overall survival. The group stated that chemotherapy theoretically could improve disease control in areas not treated by radiation, however no evidence shows a definitive survival benefit (29).

Investigational therapy

Novel, investigational therapies are also being studied to improve treatment options for advanced TETs. Intrathoracic heated chemotherapy (ITHC) is a recent treatment option where heated chemotherapy is given to the pleural space after resection is complete, and has been used in patients with diffuse pleural disease (30). Maury *et al.* retrospectively studied patients who underwent surgical resection of advanced thymoma and ITHC and reported a median 1- and 5-year overall survival of 92% and 86%.

Three patients had complications from chemotherapy including bone marrow aplasia, and spontaneous, reversible grade 2 kidney failure (31). Of the 14 patients alive through follow up, 12 remained disease free (31). Refaely *et al.* performed ITHC and reported similar patient tolerance of the ITHC with no ipsilateral relapse, and only one patient with a suspected contralateral relapse (32).

Targeted therapies are a novel but growing treatment option for malignancies. Molecules targeting signaling pathways such as c-KIT and EGFR have had disappointing results in thymomas and thymic carcinomas, with no reports of complete response and rare reports of partial response (33). Sorafenib and sunitinib, both multi-target tyrosine kinase inhibitors, have had slightly improved, but not robust, response rates in thymomas and thymic carcinomas that are refractory to chemotherapy (33). Sunitinib recently was studied in a phase 2 open label trial by Thomas *et al.*, and maximally achieved a "partial response" (34). Interestingly, more patients with thymic carcinoma achieved a partial response (25%) as compared to patients with thymoma (6%) (34). A case study published in NEJM of a metastatic thymic carcinoma responding to imatinib was initially promising, however when studied further in a phase 2 clinical trial imatinib maximally achieved "stable disease", with more than 70% of patients having progressive disease (17). Greater understanding of the signaling pathways and identification of tumor markers to indicate which patients may benefit from targeted therapies is needed (34).

Immunotherapy markers, particularly the programmed death ligand (PD-L1) have been increasingly studied in TETs as a potential target for additional therapy. Yokoyama *et al.* reviewed PD-L1 expression in a group of 82 patients with thymoma and associated gene expression with clinical factors (35). 54% of patients had high expression of PD-L1. High expression was associated with higher grade tumors (B2-B3) and more advanced stage (stage III–IV). On multivariable analysis, high expressors were significantly more likely to recur with shorter disease-free survival, however there was no difference in overall survival. Katsuya *et al.* also studied PD-L1 expression, and reported that 70% of thymic carcinomas and 23% of thymomas stained positive for PD-L1 (36). To date, there are no studies reporting outcomes with response rate to PD-L1 therapies, but this is a promising option to explore for patients with persistent, recurrent disease.

Conclusions

Stage IVa TET describes a wide range of disease severity and presentation. While guideline recommendations for all Stage IVa TETs are complex given the heterogeneity of the disease, in general several principles can be gleaned from the literature to guide clinical decisions making. Surgery with a goal of R0 resection should be attempted in patients who are appropriate operative candidates. In young patients with good cardiopulmonary status, a more aggressive approach such as EPP may be considered to increase likelihood of an R0 resection. In older patients, the surgical approach should be determined based on extent of disease, patient fitness, and use of neo/adjuvant therapies. Multimodal therapies are likely useful in prolonging overall survival, and may facilitate an R0 resection in some cases. This is particularly important for patients with extensive disease and/or *de novo* disease, however multimodal therapies should be explored further and with greater standardization to assess efficacy. Adjuvant radiation to the affected hemithorax may help improve local control. Patients with thymic carcinoma have been shown to have greater benefit with early surgery, and if patients are resectable, surgical intervention should not be delayed for neoadjuvant therapy. We are excited by possibilities in future research, such as exploring targeted molecular therapies, to continue to identify treatment options for patients with advanced and locally invasive thymomas.

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Footnote

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