



Optimal therapy for thymic epithelial tumors with pleural involvement

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Comment on: Moser B, Fadel E, Fabre D, *et al.* Surgical therapy of thymic tumours with pleural involvement: an ESTS Thymic Working Group Project. *Eur J Cardiothorac Surg* 2017;52:346-55.

Received: 27 September 2017; Accepted: 23 October 2017; Published: 17 November 2017.

doi: 10.21037/med.2017.10.09

View this article at: <http://dx.doi.org/10.21037/med.2017.10.09>

Thymic epithelial tumors (TETs) are rare neoplasms that include thymomas and thymic carcinomas. It has been widely accepted that surgery remains the mainstay of treatment, with radiation and chemotherapy also being applied as adjuvant and palliative procedures. Complete resection represents the best treatment strategy for early stage tumors (Masaoka stages I and II); however, it currently remains unclear whether median sternotomy or a thoracoscopic approach is the most appropriate. The optimal treatment for thymomas and thymic carcinomas with the advanced stages (III and IV) of the Masaoka classification has long been debated (1,2). Multimodality therapy (surgery, chemotherapy, and radiation) has been used for TET cases with pleural dissemination (stage IVA). However, there is a lack of consensus on treatment strategies because of the rarity of these cases. Although there are some reports on surgery for the pleural involvement of thymoma, the number of cases is low (5–21 cases) (3).

A recent article entitled “Surgical therapy of thymic tumours with pleural involvement: an ESTS Thymic Working Group Project.” was published in the *European Journal of Cardio-Thoracic Surgery* (4). The European Society of Thoracic Surgeons (ESTS) Thymic Working Group collected 152 patients with the pleural disease of TETs from 12 institutions in 8 countries in Europe and Canada. This report showed that all patients with pleural involvement treated by surgery had relatively good survival (5-year survival rate: 87%), and that there was no significant difference in survival between patients who underwent extrapleural pneumonectomy (EPP), total pleurectomy (TP), or local pleurectomy (LP) as the surgical approach for

pleural involvement. Thymic carcinomas and incomplete resection had a negative impact on survival. The cases in this study consisted of 2 groups: 107 (70%) cases in surgery for primary tumors with pleural involvement (Masaoka stage IVA) and 45 (30%) cases in surgery for tumor recurrence with pleural involvement after the first surgery.

Primary tumors with pleural involvement (stage IVA tumors) are initially discussed. The Japanese Association for Research on the Thymus (JART) reported 118 Masaoka stage IVA thymomas in 2014 (5). The ESTS report included thymomas (135 cases) and thymic carcinomas (17 cases), while JART included only thymomas. Although the ESTS report included thymic carcinomas (11%), the 5-year overall survival (OS) rates in both reports were similar [approximately 80% (ESTS) and 87% (JART)] (4,5). Both reports found that B2 (ESTS; 34%, JART; 46%) and B3 thymomas (ESTS; 24%, JART; 32%) were the main types of thymomas with pleural involvement (4,5). The ESTS report showed that thymic carcinoma had a worse prognostic impact on OS, cause-specific survival (CSS), and freedom from recurrence (FFR) than thymoma in a multivariable analysis. The 5- and 10-year OS rates of patients with thymic carcinoma were 56% and 0%, respectively (4).

Both reports demonstrated that the complete resection of tumors was a significantly favorable prognostic factor for OS in stage IVA tumors, although the ESTS report statistically calculated between completely resected (R0) and macroscopically residual tumors (R1) + microscopically residual tumors (R2), while the JART report calculated between R0 + R1 and R2 (4,5). The number of complete resection cases in the ESTS report was higher than that

in the JART report (89% *vs.* 45%) (4,5). Several studies supported this. Yano *et al.* (21 stage IVA thymomas) reported that patients who underwent resection showed a better prognosis than those who did not, and the RFS of patients who underwent total resection was better than those with subtotal resection (6). Rena *et al.* (18 stage IVA thymomas) showed that 5- and 10-year disease-related survival rates of complete and incomplete resection were 100% and 52% and 72% and 0%, respectively (7). These values for stage IVA thymomas coincide with the important finding that the completeness of resection was one of the independent prognostic factors identified using a multivariate analysis on thymomas, as supported by several large studies (8,9). Most of the studies published to date have reported that patients who underwent surgical resection for stage IVA TET had no operative mortality (10). Surgery for stage IVA thymomas appears to be safe and is associated with low operative mortality. Patients who underwent surgery had a better prognosis than those who did not. Furthermore, patients who underwent complete resection showed better survival than those with incomplete resection.

In the ESTS report, most patients (64 cases, 90%) underwent thymectomy in conjunction with extended thymectomy for the main tumors (6 thymectomies and 1 thymectomy combined with basic thymectomy) (4). The most common surgical approach for pleural involvement was the localized resection of all visible tumors—LP or TP in the ESTS (70%) and JART reports (94%) (4,5). The reported findings with this approach were a perioperative mortality of 0% and morbidity up to 39% (10). The number of EPP cases in the ESTS report was higher than that in the JART report (ESTS; 30%, JART; 6%) (4,5). Thirteen cases (12%) underwent TP in the ESTS report (4). No significant differences were observed in survival (OS, CSS, and FFR) between EPP cases and other cases (TP and LP cases) (4). The findings of the JART report supported this. The 5- and 10-year OS rates of patients with EPP in the ESTS report were approximately 80% and 40 %, respectively (4). The ESTS report showed there were four cases who underwent EPP passed away in the total number of five deaths during the first postoperative year (4). Fabre *et al.* reported eight patients with recurrent thymoma and nine patients with stage IVA disease. Complete resection was performed on 11 patients (65%), and 5- and 10-year OS rates were 60% and 30%, respectively. Thirty-day mortality was 18%, and 8 patients (47%) developed major postoperative complications, including 4 with broncho-pleural fistulae (11). Wright *et al.* also reported 5 stage IVA cases that underwent EPP

and demonstrated no operative mortality and one major complication, with 5- and 10-year OS rates of 75% and 50%, respectively (12). These reports showed that EPP cases had high operative mortality and a low postoperative quality of life. Since EPP cases had numerous visceral and parietal pleural disseminations that were not possible to locally resect, it was very difficult to assess surgical procedures based only on survival. Surgeons need to consider the choice of the surgical procedure for pleural involvement according to the number, size, and location of implant lesions, patient conditions, and operative mortality and morbidity.

Since thymomas are relatively sensitive to chemotherapy and/or radiotherapy, and complete resection is a strong prognostic factor, neoadjuvant and/or adjuvant chemotherapy and radiotherapy are expected to be effective for patients with stage IVA thymomas. In the ESTS report, neoadjuvant therapy was administered to 67 patients (62%), with most (88%) receiving chemotherapy only. Adjuvant therapy was administered to 68 patients (64%), with most (72%) receiving radiotherapy only. However, a significantly favorable effect was not observed for pre- and post-operative chemotherapy and/or radiotherapy in a multivariable analysis in all patients with pleural involvement (4). The JART report also showed no significant improvement in OS or disease-free survival (DFS) among patients treated with postoperative radiation, chemotherapy, or both over that in patients without adjuvant therapy (5). Since both studies were multicenter studies, there were various nonsurgical therapies, multimodalities—only preoperative chemotherapies, postoperative chemoradiotherapies, postoperative radiotherapies, chemotherapy regimens and radiotherapy doses. Shapiro and Korst reviewed the outcomes of patients with stage IVA TET treated with neoadjuvant therapy followed by surgical resection in 11 studies (10). Stage IVA TETs showed high radiographic response rates to neoadjuvant therapy (67–100%). The rate of R0 resection in patients with stage IVA TETs following neoadjuvant therapy ranged between 58% and 100%. Five- and 10-year OS rates were in the ranges of 70–95% and 38–79%, respectively. These values compared favorably to reports on resection without the use of neoadjuvant therapy in patients with stage IVA TETs (10). Neoadjuvant chemotherapy followed by complete resection for stage IVA thymomas may be a good treatment option that is associated with long-term survival. Large-scale and prospective studies with a constant regimen of chemotherapy are needed in order to elucidate the true effects of chemotherapy for thymic tumors with pleural involvement.

Patients with tumor recurrence of pleura involvement

after the first surgery will now be discussed. Surgery showed a good prognosis for these tumors (5- and 10-year OS rates: 100% and 90%) (4). EPP, TP, and LP were performed on 8 (18%), 10 (23%), and 26 patients (59%), respectively. Most patients underwent complete resection (91%: R0). Neoadjuvant therapy was administered to 15 patients (33%), with most (93%) receiving chemotherapy only. Adjuvant therapy was administered to 10 patients (22%) (4). The JART reported described the surgical management of recurrent TETs including pleural metastases in 2015 (13). Among 2,835 patients who underwent surgery, 420 (15%) developed recurrence. More than half of the patients who underwent resection (219 cases, 54%) developed recurrence in the pleura, which was also the most frequent metastatic site. When limited to cases of single-site recurrence, this site accounted for 58% of cases (85 out of 147 patients), with survival being favorable among resected cases (5- and 10-year OS rates: 91% and 67%) (13). The ESTS and JART reports suggested repeated resection for pleural recurrence as an acceptable option.

Surgery for patients with pleural involvement (stage IVA thymomas and recurrence thymomas) is the mainstay of treatment and complete resection is one of the most important prognostic factors. Surgeons need to consider the choice of the surgical procedure for pleural involvement according to the number, size, and location of the implant lesions, patient conditions, and operative mortality and morbidity. Multimodalities including chemotherapy and radiotherapy, particularly neoadjuvant chemotherapy, have the potential to improve the prognosis of patients with pleural involvement.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by Section Editor Dr. Zhuoqi Jia (Thoracic Department, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China).

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/med.2017.10.09>). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/med.2017.10.09

Cite this article as: Kondo K. Optimal therapy for thymic epithelial tumors with pleural involvement. Mediastinum 2017;1:17.