# Editorial: pleural recurrence of thymoma — what is the value of intra-thoracic chemo-hyperthermia?

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Thymomas are malignant neoplasms that can recur and/or metastasize and in some cases patients might die from the disease (1). However, most patients with thymoma have a favorable outcome and are disease-free after complete resection of the tumor. The overall 5-year disease-free survival of thymomas has been shown to be between 71% and 91.7% and depends largely on stage and completeness of resection (2-5). Overall, recurrences are infrequent and occur in 11 to 14.8% of patients with thymic epithelial tumors (TET) in a median or mean time of 83 or 86 months, respectively (6-9). For instance data from the retrospective Japanese nationwide registry of TET encompassing 2,835 patients who underwent surgical resection of TET found recurrences in 14.8% of patients after 2.7 (±2.3) years after initial treatment. Most recurrences (54.1% to 58.1%) occur in the pleura (6,9).

TET are rare neoplasms with an incidence of only 1–5/ million population/year (10,11). The paucity of thymomas together with their favorable outcome in most patients hampers the study of these tumors, in particular the analysis of subsets of patients such as patients with pleural recurrences. Only small, mostly single-institution case series currently provide data on a variety of treatments for these patients; results of prospective randomized trials are not available. Therefore, there is no standardized treatment of patients with recurrent thymomas and specifically pleural recurrences. The guidelines of the National Comprehensive Cancer Network (NCCN) suggest that patients with TET should be managed by a multidisciplinary team with experience in the treatment of TET (12). In general, such a multidisciplinary team includes medical and radiation oncologists, pathologists, radiologists, thoracic surgeons, and possibly neurologists (as many thymomas are associated with myasthenia gravis). Moreover, complete resection has been widely accepted as the mainstay treatment of thymomas with curative intent with or without neoadjuvant and/or adjuvant radiation therapy and/or chemotherapy, depending on stage and resection status of the tumor (12,13). Furthermore, chemotherapy or surgery has been recommended for ipsilateral pleural metastases by the NCCN (12). After chemotherapy, the possibility of resection should be re-evaluated. Also, post-surgical chemotherapy or radiation therapy might be considered. The European Society for Medical Oncology (ESMO) recommends that recurrences should be managed similarly to newly diagnosed stage IVA TET which includes tumors with pleural implant (13). Similarly to NCCN, ESMO recommends surgery if the recurrent tumor appears resectable (13). This is supported for instance by a study by Hamaji et al. in which multivariate analysis showed that surgical management led to a prolonged survival of patients with recurrent thymoma with a 5-year survival of 54% (7). In that study, 97 of the 219 (44.3%) patients with pleural recurrence were treated surgically. Amongst all patients with recurrence (also including patients with recurrences outside of the pleura) who were treated with surgery, R0 and R1-resected patients had a significant longer overall survival than R2-resected patients or patients who did not

undergo resection.

However, a selection bias cannot be denied in such studies as patients who are considered for surgical treatment in general have less extensive disease and therefore might already are predestined for a better outcome. Furthermore, while pleural recurrences can sometimes present as single lesions, more frequently they occur as multiple lesions and can be quite extensive and/or infiltrate the lung and diaphragm. Therefore, in some cases, debulking surgery instead of R0 resection is the only surgical option which may be considered as part of a multidisciplinary protocol (14). In other cases extended pleuropneumonectomy might be attempted (14). However, specifically pleuropneumonectomy is in general associated with a high morbidity and mortality rate. Fabre D et al reviewed retrospectively 17 patients with Masaoka stage IVA disease, 8 of which had recurrent thymoma (15). All patients were surgically treated with pleuropneumonectomy. Of the 8 patients with recurrent thymoma, 6 underwent R0 resection, 2 had a R1 resection. One patient received postoperative chemotherapy. Three patients developed a bronchopleural fistula. Three patients were alive after 48-108 months; 5 died after 2 to 149 months. In the entire study population of 17 patients, 8 (47%) patients had a major complication including bronchopleural fistulas, acute respiratory distress syndrome and atrial fibrillation amongst others. Although there were no operative deaths, the 30-day mortality was 17.6% with 2 additional deaths 2 and 3 months post-surgery. Overall, the authors concluded that although pleuropneumonectomy might be part of a multimodality approach and performed in highly selected patients in whom it might provide good long-term survival, the procedure is associated with a high morbidity and mortality rate.

The European Society of Thoracic Surgeons (ESTS) organized a multicenter study to evaluate the value of surgery for TET with pleural involvement (16). Of 152 patients 45 (29.6%) had recurrent pleural disease; 135 (88.8%) had thymoma and 17 (11.2%) patients had thymic carcinoma. Surgical procedures included extrapleural pneumonectomy (n=40, 26.3%), total pleurectomy (n=23, 15.1%) and local pleurectomy (n=88, 57.9%) with complete resection achieved in 76.8%. The majority of patients in that study received neoadjuvant and/or adjuvant therapy in addition to surgery. In patients with recurrent pleural disease, complete resection was reported in 40 (90.9%) patients. Overall, incomplete resection had a worse prognosis. Complications occurred in 63.3% of extrapleural pneumonectomy patients, 50% of total pleurectomies and 28.3% of local pleurectomy

procedures. Two patients died during the first 30 days due to either acute pulmonary embolism (total pleurectomy) or acute respiratory distress syndrome (extrapleural pneumonectomy). In addition a patient who underwent extrapleural pneumonectomy died between 30 and 90 days post-surgery (tumor-unrelated) and 2 died between 90 days and 1 year due to progressive metastatic disease (extrapleural pneumonectomy) or acute respiratory distress syndrome (extrapleural pneumonectomy). Fifty-nine (51.3%) patients had a recurrence. The study confirmed that complete resection should be the mainstay of treatment for TET with pleural involvement and that all 3 techniques are equally effective procedures. However, the data also emphasize that the complication rates are relatively high specifically for extrapleural pneumonectomy and total pleurectomy procedures.

More recently, a few case studies reported on their results of complete resection or cytoreduction surgery of pleural recurrences of thymoma in combination with local therapy using Intra-Thoracic Chemo-Hyperthermia (ITCH) (17-20). Compared to conventional systemic therapy ITCH may have the advantage of directly exposing the tumor to a higher concentration of the chemotherapeutic drug with less toxic systemic effects. Moreover, the combination of hyperthermia with the chemotherapeutic agent may produce an additive effect. Hyperthermia supposedly increases the effectiveness and penetration depth of the chemotherapeutic agent with additional antineoplastic effects by activating apoptosis (21). This combination therapy had been previously performed in patients with primary thymoma or thymic carcinoma with pleural spread and also malignant pleural mesothelioma (20,22). For instance in 2002 de Bree et al. enrolled patients with pleural thymoma metastases (n=3) or early-stage malignant pleural mesothelioma (n=11) in a feasibility study. These patients underwent cytoreductive surgery including 5 pneumonectomies and ITCH with Cisplatin  $(50-80 \text{ mg/m}^2)$  and Adriamycin  $(15-25 \text{ mg/m}^2)$ . The patients with mesothelioma also received adjuvant radiation therapy on the thoracotomy wound and drainage tracts. In this study morbidity and mortality was 47% and 0%, respectively. Four patients had to undergo reoperation for either rupture of the diaphragm, chylous effusion or wound dehiscence. One patient with thymoma developed grade 2 nephrotoxicity. A solitary mediastinal and a contralateral pleural thymoma recurrence occurred. In a retrospective, single institution study, Maury et al. reviewed 19 patients with pleural recurrences of thymoma (17). These patients underwent surgical cytoreduction of the pleural recurrences by pleurectomy (n=4, 22%), pleurectomy and lung wedge resection (n=14, 74%) or pleuropneumonectomy (n=1, 5%) followed by ITCH that included Mitomycin (25  $mg/m^2$ ), and Cisplatin (50  $mg/m^2$ ). There were no perioperative deaths; 5 (of 19, 26%) patients had postoperative complications, including complications related to chemotherapy (n=3; reversible grade 2 bone marrow aplasia, reversible acute kidney failure) and surgery (n=2). The treatment provided a relative long local control with a median disease-free survival after the procedure of 42 months and a median 5-year survival of 86%. Five (of 29, 26%) patients died during follow-up due to tumor progression (n=1), infection (n=3) or pulmonary embolism (n=1). Seven (of 19, 37%) had a recurrence to the ipsilateral lymph node, pericardium or ipsilateral or contralateral pleura. Ambrogi et al. also studied resection of pleural recurrences of thymomas followed by ITCH using Doxorubicin (25 mg/m<sup>2</sup>) and Cisplatin (80 mg/m<sup>2</sup>) in a prospective study of 13 consecutive patients who had developed pleural recurrence/metastasis (18). Two patients received pre-operative radiation. Complete resection with an "adequate margin around the pleural implant" was achieved in 12 (of 13, 92.3%) patients; 1 patient had an R2 resection. No toxicities were noted in the perioperative period. One patient died with disease (R2 resection) due to toxicity following systemic chemotherapy, another patient died disease free; 4 patients developed pleural relapses (ipsilateral or contralateral) and 1 patient had mediastinal and abdominal nodal metastasis. The mean survival was 58 months and 5-year survival was 92% following treatment of pleural recurrences. Yellin et al. also reported on ITCH in 14 patients with thymoma that had pleural relapse as part of a case series that included 35 patients with stage IVA thymoma or thymic carcinoma (19). Four (of 4) patients with thymic carcinoma and 13 (of 31) patients with thymoma received preoperative chemotherapy. Some patients also received adjuvant chemotherapy or radiation therapy. Patients with recurrent thymoma underwent local resection (n=5), pleurectomy (n=6), wedge/lobectomy (n=1) or chest wall resection (n=2). Six of these patients had an R0 resection. Resection was followed by ITCH with Cisplatin (100 mg/m<sup>2</sup>) and Doxorubicin (50–60 mg/m<sup>2</sup>). Five-year overall survival and progression-free survival of the 14 patients with recurrent thymoma was 67% and 48%, respectively. At the end of the follow up 8 of 14 patients were alive; 6 of whom had no evidence of disease. For the entire study population, R0 resection had better progression-free survival than R1-2 resections.

Overall, these studies show that resection or cytoreduction of pleural recurrences/metastases of thymomas followed by ITCH are feasible and relatively safe and might lead to a prolonged disease-free and overall survival. However, none of these case series were controlled by patients who did not receive ITCH or no treatment. Therefore, it is difficult to discern whether the addition of ITCH indeed has added value to surgery alone or observation. Moreover, the ITCH doses and the application of additional therapy such as radiation therapy and/or chemotherapy differed between these studies. In addition, a selection bias has to be considered as studies had different criteria for inclusion of patients. Therefore, these studies are difficult to compare amongst each other and to studies that use different treatment strategies for thymomas with pleural metastases/ recurrences. Furthermore, longer follow up would be advantageous to compare different techniques.

In conclusion, while resection or cytoreduction of recurrent/metastatic pleural disease followed by ITCH appears to be promising in the management of patients with recurrent pleural thymoma, this should be taken as hypothesis generating as many questions remain unanswered. Given the lack of prospective randomized trials it is not clear whether the addition of ITCH adds prognostic value to surgery alone as most of these patients will receive post-operative chemotherapy. Furthermore, with the available data it is not known whether the addition of ITCH would allow for less extensive pleural surgery with possibly less surgical complications and how this treatment strategy compares to other conventional systemic and/or local therapies. Larger, randomized, prospective studies which would have to be conducted globally to recruit a sufficient number of patients, are needed to answer some of these challenges.

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#### Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

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