Abstract

OBJECTIVES: Surgery for thymic epithelial tumours (TETs) with pleural involvement is infrequently performed. Thus, the value of surgical therapy for primary or recurrent TETs with pleural involvement is not sufficiently defined yet.

METHODS: Twelve institutions contributed retrospective data on 152 patients undergoing surgery (1977–2014) on behalf of the ESTS Thymic Working group. Outcome measures included overall (OS), cause-specific (CSS) and disease-free (DFS) survival as well as freedom from recurrence (FFR).

RESULTS: In 70.4% of cases, pleural involvement was present at the time of primary intervention, whereas 29.6% had surgery for recurrent disease involving the pleura. Pleural involvement resulted from thymomas (88.8%) and thymic carcinomas (11.2%). Forty extrapleural pneumonectomies (EPPs), 23 total pleurectomies (TPs), and 88 local pleurectomies (LPs) were performed (completeness of resection in 76.8%). OS for the entire patient population at 1, 3, 5 and 10 years was 96.4%, 91.0%, 87.2% and 62.7%, respectively. There was no statistically significant difference regarding FFR and OS for patients with local or advanced disease undergoing EPP, TP or LP. Thymic carcinomas in comparison with thymomas had a negative impact on OS [hazard ratio 6.506, \( P = 0.002 \)], CSS and FFR. Incomplete resections predicted worse OS [hazard ratio 6.696, \( P = 0.003 \)].

CONCLUSIONS: Complete resection remains the mainstay of treatment for TETs with pleural involvement. Study populations treated with EPP, TP and LP had similar survival that may be factual as observed, but in the presence of selection bias, we can further conclude from the results that EPP, TP and LP are equally effective procedures. Procedural choice depends upon the extent of tumour distribution. EPPs, TPs and LPs performed within a multimodality setting seem to be efficient procedures for local control of disease, as they yield excellent results regarding OS, DFS, CSS and FFR.

Keywords: Thymoma • Thymic carcinoma • Pleural disease • Extrapleural pneumonectomy • Pleurectomy

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INTRODUCTION

Thymic epithelial tumours (TETs), namely thymomas and thymic carcinomas (TCs), are rare neoplasms of thymic epithelial origin. TETs present in different clinical stages and show a variety of histological patterns. They are being treated in small numbers in many different centres worldwide with heterogeneous diagnostic and therapeutic algorithms. Advanced-stage TETs with pleural or pericardial dissemination (Masaoka-Koga Stage IVA [1]) are encountered in only 6.8% of all patients with TETs [1–3]. The best treatment for Stage IVA TETs still has to be defined. Complete surgical resection is the mainstay of treatment for patients with TETs. For patients with metastases of TETs to the visceral or parietal pleura, different surgical techniques are employed. Surgical techniques vary from extrapleural pneumonectomy (EPP) to total pleurectomy (TP) or local pleurectomy (LP), and frequently resections are combined with chemotherapy (ChT) and/or radiotherapy (RT) [4, 5]. In general, the indication to perform EPP is the finding of numerous visceral and parietal pleural and pericardial implants (and pulmonary nodules) that cannot be locally resected [6]. TP is the removal of all parietal, mediastinal and diaphragmatic pleural surfaces and pericardium with or without resection of the diaphragm. The decision to perform TP is made when visceral pleura and lung are not affected by malignant disease. LP is metastasectomy (local resection) of pleural implants without removal of all pleural surfaces. It is performed for mono- or oligometastatic disease.

The value of surgical therapy with or without ChT and/or RT for primary or recurrent thymic tumours with pleural involvement is not sufficiently defined yet, due to limitations in the available data. In this collaborative effort, members of the European Society of Thoracic Surgeons (ESTS) Thymic Working Group retrospectively collected data on patients undergoing thoracic surgical procedures for primary and recurrent thymic tumours with pleural involvement. The current work reflects the former and current practice patterns of European and Canadian thoracic surgery institutions treating TETs with pleural and/or pericardial involvement.

MATERIALS AND METHODS

On behalf of the ESTS Thymic Working Group, emails were sent to ESTS members to ask for participation on this retrospective data collection in the treatment of patients with TETs with pleural involvement. Respondents received a detailed standardized questionnaire (Supplementary Material, Table S1). In this collaborative effort, a total of 152 patients with pleural disease of TETs were reported by 12 institutions from 8 countries. All institutions were specialized thoracic surgery centres routinely performing surgery on patients with TETs. The reported patients were diagnosed and operated between February 1977 and November 2014 (90% of patients between 1 January 2001 and 30 November 2014, Supplementary Material, Table S2).

Each institution obtained ethical approval from its ethics committee.

Study flow

There were coherent data for survival analysis on all 152 patients and on 115 patients with complete resection for analysis of freedom from recurrence (FFR; Fig. 1).

Statistics/outcome analysis

Definitions of recurrence and outcome measures were reported as recommended by the International Thymic Malignancies Interest Group [7]. Overall survival (OS) was calculated as the primary outcome from the date of surgery (first pleural surgery, Fig. 1) to the date of death of any cause. Patients without an event were censored at the last time point known to be alive. Disease-free survival was analysed from the date of surgery (first pleural surgery) to the date of recurrence or death from any cause (DFS) [8]. The end-point of interest for cause-specific survival (CSS) was defined as death from TET (censored observations: unrelated deaths and unknown cause of death) [7]. FFR was calculated only in patients after complete surgical resection (R0) from the date of surgery (first pleural surgery) to the date of recurrence and full information on recurrence status [9]. Log-rank tests were employed to compare whole Kaplan-Meier curves. Differences at 1, 3, 5 and 10 years were reported descriptively. Statistical methods are detailed further in the Supplementary Material.

RESULTS

Institutions contributed a median of 11 patient cases (range 2–38; Supplementary Material, Table S2).

The median follow-up time for the entire patient cohort was 52 months [range 0–265; 95% confidence interval: 32.0–72.0]. The study cohort consists of 2 types of patients undergoing surgery for pleural disease of TETs. Patients with pleural disease...
at primary diagnosis (70.4%) as well as patients with pleural disease who had previous surgery for a TET (without involvement of the pleura [29.6%]) were included in the study (Fig. 2). Mean age at surgery for pleural disease was 47.3 years for the cohort undergoing primary surgery for pleural disease of TETs and 54.6 years for patients with surgery for their first recurrent disease to the pleura. Forty patients (26.3%) had 1 TET resection before the first surgery of pleural disease (3 patients had 2 surgeries, 1 patient had 3 surgeries and 1 patient had 4 surgeries before pleural dissemination, respectively).

Clinical data

Basic demographic data are presented in Table 1. For initial symptoms (51.3%), diagnostic imaging, tumour location and pre-operative biopsy (68.4%), see Supplementary Material, Table S3. Myasthenia gravis (MG) was reported in 47 patients (30.9%); for other autoimmune diseases (7.2%) and other malignancies, see Supplementary Material. Seventeen patients (11.2%) were diagnosed with TC and 135 (88.8%) with thymoma. Patients were reported in pathological Masaoka-Koga Stages I (3.4%), II (6.1%), III (20.5%), IVA (65.0%) and IVB (4.8%) at their first surgery. The frequency of thymomas and TCs according to World Health Organization histology was B2 (33.6%), B3 (23.9%), B1 (13.0%), combined B2/B3 (11.6%), TC (10.3%), AB (4.1%), B1/B2 (2.0%), A (0.7%) and combined B3/TC (0.7%) (Supplementary Material, Table S4).

Surgery

Thymectomy information

Primary surgery for thymic epithelial tumours without involvement of the pleura (Scenario 1): There were 3 TET resections (thymectomies) without thymectomy, 5 thymectomies combined with basic thymectomies (removal of thymic lobes) and 22 thymectomies in conjunction with extended thymectomies (basic thymectomy plus resection of mediastinal and cervical fatty tissue). All patients had a recurrence to the pleura (Fig. 2).

Primary pleural surgery (Scenario 2): There was 6 thymectomies, 1 thymectomy combined with basic thymectomy (removal of the thymic lobes) and 64 thymectomies in conjunction with extended thymectomies. There were 3 recurrences after thymectomy only (50%), after thymectomy plus basic thymectomy 1 (100%) and thymectomy combined with extended thymectomy 26 (49.0%).

Surgery for pleural disease of thymic epithelial tumours: surgical approach, type and completeness of resection

Different surgical approaches were chosen to resect TETs with pleural involvement (Table 2). For the resection of pleural disease, EPP was performed in 26.5%, TP in 15.2% and LP in 58.3% of
patients. EPP, TP and LP were performed in 32 cases (29.9%), 13 cases (12.1%, including 1 case of pleurectomy/decortication [P/D]) and 62 cases (57.9%) for primary pleural surgery (Scenario 2), respectively. In patients with pleural surgery for recurrence (Scenario 1, first pleural surgery) EPP, TP and LP were carried out in 8 patients (18.2%) and 10 patients (22.7%, including 3 patients with P/D) and 26 patients (59.1%, respectively (missing information: 1 patient). Completeness of resection was pathologically confirmed in 76 (71%, R0), incomplete resection in 16 (15%, R1) and 15 (14%, R2) for primary pleural surgery. Completeness of resection for recurrent pleural surgery was reported as: 40 (90.9%, R0), 1 (2.3%, R1) and 2 (4.5%, R2), respectively (missing information: 2 patients).

The mean number of resected pleural nodules was 7.7 [range 1–90]. Tumour invasion/adherence (Table 2).

**Treatment of the diaphragm in patients with thymic epithelial tumours and pleural involvement**

In non-EPP patients, there were 52 patients with metastasis of TETs to the diaphragm. Diaphragmatic resection was performed in 34 cases: 6 complete and 28 partial resections of the diaphragm (missing information on extent of resection in 2 cases). There were 16 pleurectomies of the diaphragm without resection of the diaphragm.

Diaphragmatic plication was performed in 5 patients due to paralysis of the diaphragm as a result of oncologic phrenic nerve resection.

**Multimodal therapy**

Neoadjuvant therapy was administered in 67 patients (62.2%), pseudo-neoadjuvant therapy before surgery for recurrence in 15 patients (33.3%), adjuvant therapy in 68 patients (63.6%) and pseudo-adjuvant therapy after surgery for recurrence in 10 patients (22.2%), respectively (Table 2). Neo- and pseudo-neoadjuvant PAC ChT (planned protocol: cisplatin 50 mg/m², doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m²) was administered in 45 patients of the 76 (59.2%) patients who received ChT. For induction therapy (n = 65), the mean number of administered ChT cycles was 4.15 (median 4, range 2–8).

Radiotherapy was administered in a neoadjuvant (8 patients), pseudo-neoadjuvant (1 patient), adjuvant (63 patients) or pseudo-adjuvant (5 patients) setting. The administered mean radiation dose was 40.9 G [median 45 G, range 20–56 G] for neoadjuvant therapy and 50.3 G [median 50 G, range 24–60 G] for adjuvant therapy.

**Recurrence after surgery with or without chemo- and radiotherapy for pleural disease of thymic epithelial tumours**

The median time from primary surgery for a TET without involvement of the pleura to surgery for recurrence of disease to the pleura (first pleural surgery, Scenario 1) was 55.0 months.

The median time to recurrence after the first pleural surgery (second recurrence in Scenario 1 and first recurrence in Scenario 2, see Fig. 2) was 46 months. Recurrence after complete resection (R0) with or without ChT and/or RT for TETs with pleural involvement occurred in 59 patients (51.3%). See Table 2 for type of recurrence. The mean total number of recurrences after surgery for pleural disease was 1.47 (median 1, range 1–9).

### Table 2: Treatment modalities

| n (%) | n = 152 |
|-------|---------|
| Preoperative treatment | Neoadjuvant 67/107 (62.6) |
| Chemotherapy 59/67 (88.1) |
| Radiotherapy 5/67 (7.5) |
| Radiotherapy and chemotherapy 3/67 (4.4) |
| Neo-neoadjuvant 15/45 (33.3) |
| Chemotherapy 14/15 (93.3) |
| Radiotherapy 1/15 (6.7) |
| Radiotherapy and chemotherapy 0/15 (0.0) |
| Response to preoperative therapy | Stable disease 5 (7.5) |
| Partial response 48 (71.6) |
| Progression 3 (3.9) |
| No information 11 (16.4) |
| Pseudo-neoadjuvant Stable disease 1 (6.6) |
| Partial response 7 (46.6) |
| Progression 0 (0.0) |
| No information 7 (46.6) |
| Postoperative treatment | Adjvant 68/107 (63.6) |
| Chemotherapy 5/68 (7.3) |
| Radiotherapy 49/68 (72.1) |
| Radiotherapy and chemotherapy 14/68 (20.6) |
| Pseudo-adjuvant Chemotherapy 5/10 (50.0) |
| Radiotherapy 4/10 (40.0) |
| Radiotherapy and chemotherapy 1/10 (10.0) |
| Surgical approach | Thoracotomy 61 (40.4) |
| Sternotomy 65 (43.0) |
| Clamshell 6 (4.0) |
| Hemi-clamshell 16 (10.6) |
| Video-assisted thoracic surgery 3 (2.0) |
| Type of pleural surgery | Extrapleural pneumonectomy 40 (26.5) |
| Local pleurectomy 88 (51.2) |
| Total pleurectomy 23 (53.8) |
| Invasion | Lung 91 (65.9) |
| Pericardium 76 (53.9) |
| Pleura | Parietalis 40 (28.2) |
| Visceralis 6 (4.2) |
| Diaphragmatic 11 (7.7) |
| Parietal/visceral/diaphragmatic 67 (47.2) |
| Diaphragm muscle 39 (27.7) |
| Superior vena cava 10 (7.1) |
| Thoracic wall 9 (6.4) |
| Phrenic nerve 33 (23.4) |
| Adherence | Lung 68 (47.6) |
| Pencardium 56 (39.2) |
| Diaphragmatic musculature 41 (28.7) |
| Aorta 8 (5.6) |
| Great vessels other than aorta 12 (8.4) |
| Residual tumour | R0 116 (77.3) |
| R1 17 (11.3) |
| R2 17 (11.3) |
| Recurrence Yes 15/100 (48.7) |
| No information 59 (51.3) |
| Recurrence type Local 15/59 (25.4) |
| Regional 30/59 (50.8) |
| Distant 9/59 (15.3) |
| Regional and distant 5/59 (8.5) |

*Recurrences only after R0 resection were included in the analysis.*
Mortality during the first postoperative year

Two patients died during the first 30 days (perioperative mortality) after pleural surgery for TETs (patients with TC suffered from pneumonia and acute respiratory distress syndrome after EPP; patient with TC undergoing total pleurectomy died due to acute pulmonary embolism and prolonged air leak). One patient with B2 thymoma undergoing EPP died between 30 and 90 days postoperatively (cause of death not tumour related). Two more patients died between 90 days and 1 year. A patient with TC after EPP died related to progression of metastatic disease at 8 months, and another patient with B2 thymoma after EPP died from pneumonia resulting in acute respiratory distress syndrome 10 months after surgery.

Complications

There were documented data on 103 patients on complications or follow-up without complications. Of these, 59 patients had no surgical complications. Complications allocated to their respective type of surgery (Supplementary Material, Table S5).

Survival analysis

Outcome: overall survival, cause-specific survival, disease-free survival and freedom from recurrence

The number of events for survival analyses (n = 152) and analyses of FFR (n = 115) is indicated in Fig. 1 (number of events for the respective subgroup analyses is indicated in Figs 2 and 3). OS of the entire patient cohort at 1, 3, 5 and 10 years was 96.4%, 91.0%, 87.2% and 62.7%, respectively. Accordingly, DFS, CSS and FFR were calculated: DFS: 84.3%, 60.9%, 44.9% and 15.2%; CSS: 97.8%, 94.9%, 92.3% and 79.7%; FFR (n = 115) at 1, 3, 5 and 10 years was 83.1%, 57.9%, 43.0% and 22.2%, respectively (Fig. 3).

Analysis of OS at 3, 5 and 10 years revealed statistically significant differences between primary pleural surgery and surgery for pleural recurrence (P = 0.028, P = 0.023, P = 0.027, respectively). Comparably, the analysis of OS at 3, 5 and 10 years revealed statistically significant differences between complete and incomplete resections: R0 vs R1/R2 (P = 0.032, P = 0.003, P = 0.001, respectively). While there were no statistically significant differences in FFR for the type of surgery: EPP vs TP vs LP, there were differences in OS [1-year: P = 0.010], DFS [3-year: P = 0.021 and 5-year: P = 0.037] and CSS [1-year: P = 0.012 and 3-year: P = 0.041]. The calculation of OS, DFS, CSS and FFR for thymomas versus TCs at 1, 3, 5 and 10 years revealed statistical significance for all analysis. Analysis of OS and CSS revealed a statistically significant survival advantage for patients with MG (10-year OS: P = 0.010; the 5 and 10-year CSS: P = 0.047 and P = 0.014, respectively; Fig. 4 and Supplementary Material, Table S6). In non-EPP patients with pericardial resection (n = 52), there was significantly worse survival at 10 years (OS at 1, 3, 5 and 10 years for pericardial resection yes (n = 52) vs no (n = 52): 98.0% vs 100.0% (P = 0.322), 93.3% vs 100.0% (P = 0.082), 86.7% vs 97.0% (P = 0.082), and 55.1% vs 87.2% (P = 0.010), respectively.

Prognostic factors

Table 3 illustrates the analysis of predictors (univariable and multivariable analysis) using 3 end-points: OS, CSS and FFR.
Figure 4: Survival analysis: comparison of primary pleural surgery and pleural surgery for recurrence: OS (A), FFR (B), type of surgery: EPP vs TP vs LP: OS (C), FFR (D), thymoma vs TC: OS (E), FFR (F), and completeness of resection: OS (G), FFR (H). EPP: extrapleural pneumonectomy; TP: total pleurectomy; LP: local pleurectomy; TC: thymic carcinoma.
At univariable analysis, the presence of MG was beneficial at increasing OS [hazard ratio (HR) 0.234; \( P = 0.019 \)], while TC, incomplete resection, TC vs thymomas, primary pleural surgery vs surgery for pleural recurrence, type of pleural surgery (EPP vs TP/LP), preoperative and postoperative therapy had a negative impact on OS.

TCs in comparison with thymomas at multivariable analysis had a negative impact on OS [HR 6.506; \( P = 0.002 \)], CSS [HR 13.144; \( P = 0.001 \)] and FFR [HR 1.491; \( P = 0.025 \)]. TC vs thymomas, primary pleural surgery compared with surgery for pleural recurrence [HR 4.132; \( P = 0.040 \)] at multivariable analysis. In order to eliminate the potential strong bias of incomplete resection on other predictors, we also performed multivariable analysis only on patients after complete resection (R0): negative impact of OS male sex [HR 3.176; \( P = 0.025 \)], TC [HR 3.988; \( P = 0.013 \)], primary pleural surgery compared with surgery for pleural recurrence [HR 4.132; \( P = 0.040 \)], and no effect was found for MG, age, type of surgery, preoperative or postoperative treatments. Analysis of multimodality therapy (all patients with [pseudo]-neo- and [pseudo]-adjuvant therapy combined: \( n = 126 \)) vs surgery alone (\( n = 26 \)) revealed no statistically significant differences.

Univariable analysis for the number of resected nodules (\( n = 122 \)) with a cut-off value of 4 (median number of resected nodules) for dichotomizing groups revealed no statistically significant differences.

**DISCUSSION**

TETs are a rare and heterogeneous entity. Whereas for the lower stages of disease, complete surgical resection has become the accepted standard and mainstay of treatment, little data exist about the value of surgical resection in advanced stages. Especially for Masaoka–Koga Stage IVA, which is defined by the presence of pleural spread and metastasis, the value of surgical resection
remains in question. The reason for this lies in the low number of cases that are usually seen in single institutions as well as in the heterogeneity of the clinical presentation. Whereas some patients present with only one or few well-defined and localized pleural lesions, others have a diffuse pattern of pleural involvement and few patients have the combination of pleural and intraparenchymal tumour spread in the lung. Accordingly, surgical attempts for radical resection vary from LP over TP to EPP (complete en bloc removal of pleura, diaphragm and lungs).

The intention of this retrospective study among members of the ESTS Thymic Working Group was therefore to accumulate a sufficiently large cohort of patients that would allow for meaningful statistical analysis and provide better insight and understanding of the role of surgical resection for TETs in Stage IVA.

The most important finding of this study was that complete surgical R0 resection, regardless of which surgical method was applied, as well as the histology of thymomas compared with TCs, was predictive for improved OS at multivariable analysis.

Certainly the choice of the surgical procedure is dependent from the underlying situation and extent of spread of disease. It therefore appears evident that patients undergoing EPP were in an even more advanced tumour situation, compared with patients in whom complete resection was achieved by TP or simple LP. It is therefore even more remarkable that with the extended surgical procedure of EPP, a similar positive effect on OS was achieved in more advanced tumour situations, as with the somewhat more limited procedures in less advanced situations.

Better survival was evident in patients with surgery for recurrent disease to the pleura (first pleural surgery/Scenario 1). In this patient cohort, 18.2% EPPs, 2.2% TCs and 6.8% incomplete resections were performed in contrast to 29.9% EPPs, 15.0% TCs and 29.9% incomplete resections in patients with primary pleural surgery (Scenario 2). There is an obvious bias in disease severity and the resulting invasiveness of the necessary surgical procedure that may not allow a fair comparison of these patient cohorts. Nevertheless, it demonstrates again the excellent outcome of surgery for recurrent disease to the pleura [10]. One might also speculate about different biology of TETs presenting with pleural involvement at first diagnosis or that patients in institutional follow-up programmes after thymic surgery (tertiary prevention) are diagnosed earlier with recurrence than patients with TETs with pleural involvement without prior thymic surgery (no primary prevention).

Different treatments and different reasons to treat the diaphragm in patients with TETs and pleural involvement can be distinguished. For metastases to the diaphragm, partial or complete resection of the diaphragm or just pleurectomy of the diaphragm can be performed. The reason to perform diaphragmatic surgery is purely oncologic: metastasis to the diaphragmatic pleura with our without involvement of diaphragmatic musculature. Despite the respectable number of patients with this rare disease entity and the multicentre nature of this work, no recommendation can be given on whether just pleurectomy or full-thickness resections will result in different outcomes concerning recurrence rates or survival. Since patients with diaphragmatic involvement had concurrent nodules on other pleural sites, the isolated analysis of the issue of diaphragmatic resection or pleurectomy cannot be selectively answered (46.1% recurrences [12 of 26 R0 resections] after complete or partial diaphragmatic resections vs 44.4% recurrences [4 of 9 R0 resections] after diaphragmatic pleurectomy only). Another indication for treatment of the diaphragm in this patient cohort is in patients with tumour infiltration or inseparable tumour adherence to the phrenic nerve. In cases with obligatory demand for oncologic resection of the phrenic nerve, diaphragmatic plication is performed to flatten the paralyzed dome of the diaphragm and thus provide sufficient space for the lung to expand (functional reason).

Five-year OS of patients undergoing resection for pleural dissemination of TETs in studies with 5 to 21 patients was recently reviewed and ranges from 43.1 to 92.3% [3]. In a recent retrospective study on behalf of the Japanese Association for Research on the Thymus on 136 patients who underwent surgical resection for TETs with pleural dissemination, Masaoka Stage IVA (n = 118) and IVB (n = 18), 5-year OS was 83.5% [11]. OS of the entire patient cohort in the current study compares favourably with 87.2%.

A study of 229 patients with TC (Masaoka Stage I–IV, ESTS database) identified 5- and 10-year OS rates of 0.61 and 0.37 and 5- and 10-year FFR rates of 0.60 and 0.43. At multivariate analysis, incomplete resections and advanced stage (Masaoka–Koga Stage III–IV) had a negative impact on OS, P < 0.0001 and P = 0.02, respectively. The authors concluded that surgical resection of TC should be undertaken whenever possible [9]. Five- and 10-year OS of patients with TC (n = 17) with pleural involvement in the current study was comparable, 56.0% and 0% (6 deaths by the end of 10 years), respectively.

Masaoka–Koga Stage III–IV, incomplete resection and non-thymoma histology were identified to have a significant impact on increasing recurrences and worsening survival in an ESTS cohort study (2030 patients). Administration of adjuvant therapy after complete resection was associated with improved survival [8]. Conversely, in a Japanese study on 1320 patients the value of adjuvant therapy after complete resection was in doubt [2]. Masaoka Stage IVA patients (n = 118) with 10 or fewer pleural nodules and macroscopic complete resection were reported to have better prognosis (Japanese Association for Research on the Thymus). In Stage IVA patients with complete resection, there were no supportive data on the efficacy of ChT and/or RT [11].

Better OS and CSS of patients with MG may be explained by looking at diagnosis, resection status and type of surgery (MG*: 2.1% TCs, 17.4% incomplete resections and 10.6% EPPs in comparison with MG: 15.2% TCs, 25.0% incomplete resections and 33.7% EPPs). There was an obvious difference in disease severity between the 2 study groups. In a study on 797 thymoma patients, a slight protective effect of MG on OS was observed that was not confirmed by multivariate analysis [12]. In patients with thymoma (Masaoka–Koga Stage I–IV), MG had an influence on histology and stage presentation, but only stage had a prognostic significance on OS and DFS [13]. Reasons for these observations may be associated with earlier diagnosis of TETs in MG patients (because of closer follow-up) or improvements in MG management [13].

Ninety percent of patients (64 of 71) underwent extended thymectomy at the time of primary pleural surgery (recurrence rate: 49.0%). Six patients had thymectomy only (50% recurrences). Only 20.6% of patients undergoing extended thymectomy at primary pleural surgery had MG. Thus, general practice among thymic surgeons in primary surgery of TETs with pleural involvement is to add extended thymectomy. No conclusions on the value of added basic or extended thymectomy to thymectomy at primary surgery for pleural disease of TETs for FFR can be drawn from this study.

The large number of patients that could be collected on this rare disease entity is one of the strengths of this study. Its
retrospective nature is one of the weaknesses. The long study period necessary for collecting this large cohort of patients with this rare presentation of TETs is another limitation of this study. Innovations in diagnostic and therapeutic modalities may change institutional treatment practices influencing outcomes. Prospectively collected data on all patients with TETs and pleural involvement by ESTS/International Thymic Malignancies Interest Group and Japanese Association for Research on the Thymus are warranted. Nevertheless, this collaborative effort gives detailed insights into current diagnostic and therapeutic practices of European and Canadian thoracic surgery and underlines again the incontestable importance of surgery for patients with primary and recurrent TETs with pleural involvement. We recommend close follow-up after surgery for pleural disease of TETs.

In summary, complete surgical resection is the mainstay for treatment of patients with TETs even in Masaoka–Koga Stage IVA. The type of resection, i.e. EPP, TP, LP, is dependent from the extent and distribution of tumour. However, even in more advanced tumour situations with the combination of pleural and intraparenchymal tumour spread, EPP provides equally as good results as the less complex procedures (TP or LP) for pleural metastasis only.

**SUPPLEMENTARY MATERIAL**

Supplementary material is available at EJCTS online.

**Conflict of interest:** none declared.

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**APPENDIX. CONFERENCE DISCUSSION**

Dr M. Okumura (Osaka, Japan): I congratulate Dr Moser and colleagues for creating this large database of 152 patients undergoing surgical treatment for pleural dissemination of thymic epithelial tumours. I also agree with the indication of surgery for Stage IVA thymomas and resectable recurrent thymomas. I hope that the authors’ tremendous efforts will lead to an adequate treatment strategy for dissemination of thymic epithelial tumours. But I have 3 points that I need to clarify.

The first question is on the indication of surgery for thymic carcinoma. Thymic carcinoma was shown to be an independent significant factor for poor outcome in overall survival, cause-specific survival and freedom from recurrence in this study. The hazard ratio was 6.5, 13.1 and 2.4, respectively, in each of the analyses. Five-year freedom from recurrence is approximately 10%. These results might suggest that surgery is not indicated for pleural dissemination of thymic carcinoma.

I would like to know the authors’ opinion about the indication of pleural dissemination of thymic carcinoma. If you think that operative indication is still justified, then please let us know the condition in which surgery for dissemination of thymic carcinoma can be chosen.

The next question concerns completeness of resection. In the present study, patients undergoing R0 resection were shown to have better survival compared with R1/R2 resection. In resection of pleural lesions, it is sometimes difficult to discriminate R0 resection from R1 resection and to predict whether R0 resection can be obtained before surgery. I would like to know whether even R1 resection shows a significant difference compared with R2 resection or not.

The final question relates to operative procedures to resect pleural dissemination. There was no significant difference in either overall survival or freedom from recurrence among extrapleural pneumonectomy, total pleurectomy and local pleurectomy. If so, the least invasive procedure, local pleurectomy, should be chosen for any patient. As you mentioned, I guess that this result was obtained depending on the surgeon’s adequate selection of patients and operative procedures. If the present study is able to suggest the choice of operative procedure in specific situations, please let me know.

Dr Moser: You have read the study very closely. The first question was about thymic carcinoma. It is correct. We found (and this is not surprising as we saw this in other studies) that in thymic carcinoma, overall survival, cause-specific survival and freedom from recurrence are also worse in this study.

I am not giving guidelines: all the data are here, and I cannot give a recommendation for individual patients. But as a surgeon, I still treat patients, not statistics. I have this data in my mind, and my goal in every patient with thymic carcinoma is to achieve an R0, a complete resection, preferring surgery, because the data show that these people will have prolonged survival. So I would go for surgery also in thymic carcinoma patients with the goal of achieving a complete resection. If this is not possible, incompletely resected patients do much worse.

The second question concerned the resection status. To make this feasible for the study, we did it like others before. We only took patients with pathologically confirmed complete resections. So when the pathologist stated in one of the multiple centres, in Canada, Italy, Austria, that this was a complete resection, then we took this for the analysis of freedom from recurrence. We did not include patients who had incomplete resection after R1 resection, and who may have had a complete remission after postoperative therapy, in the analysis of freedom from recurrence. We wanted to have this as clean as possible, so we only took the pathologically confirmed complete resections in this study. We thought this would be the cleanest approach.

And your third question was about the procedures. I showed you a comparison of extrapleural pneumonectomy with the procedures of total pleurectomy and local pleurectomy. There is an obvious bias in the choice of these procedures. EPP is only chosen by the surgeon if there is metastasis to the lung, to the pleural surfaces, the pericardium, the diaphragm. Then, the patient needs an EPP. And a local pleurectomy is only chosen if there is smaller metastatic or oligometastatic disease.

This is not a randomized comparison of surgical procedures. This is not the message. But the message for me is that even with this invasive surgery, EPP, you can achieve as good a result if you do a complete resection as after such a local pleurectomy where you just resect one or two nodules from the pleura. That is...
really surprising to me. So it is really worth going for radical surgery in advanced disease. This is the message that I get out of it. I don't want to say that patients who have local pleurectomy get the same result as EPP. This is not what this figure tells us. This tells us patients had the right operation and it had a good outcome.

Dr. A. Oliaro (Torino, Italy): You have reported 5 plications of the diaphragm for phrenic nerve involvement. In the Torino experience, we never suture the phrenic nerve after resection, because we don't believe in suture of the phrenic nerve. But last month, we resected the nerve and we sutured the nerve, and the phrenic nerve now functions; the diaphragm is functional. What do you think about that? Is it necessary to have a study if we must suture the nerve or we cut the nerve and we plicate the diaphragm?

Dr. Moser: This is very interesting. You are talking about phrenic nerve reconstruction, as I understand it. I never did a phrenic nerve reconstruction. In these patients with extensive disease, the phrenic nerve was obviously involved. I don't know the length of the phrenic nerve that was resected or whether there was a possibility for phrenic nerve reconstruction, but in non-EPP patients it is maybe worth following this concept.

Dr. J. Schirren (Wiesbaden, Germany): It would be interesting for me to know how many patients you looked at in the beginning of the '70s. I think the surgical technique in the '70s was not the same as in the '90s or in the 2000s. Therefore, it would be interesting to know how many patients were from this era.

Dr. Moser: As I showed on one of the introductory slides, 90% of the patients had their pleural surgery between 2001 and 2014. There were just a few patients from back then.

Dr. Schirren: But how many had an EPP in the beginning of the '70s?

Dr. Moser: I cannot tell you, but, as I said, most patients, 90% of them, were from between 2001 and 2014. So it is just a couple of patients, maybe 1 or 2 EPPs, from the period you mention.

Dr. Schirren: The chemotherapy that patients get for this extended disease is different between the '70s and the '80s and the '90s and nowadays, and, therefore, I can't believe that there is no difference between an EPP and a pleurectomy, and the patients get carboplatin and etoposide. This is very aggressive chemotherapy. I think we all know from mesothelioma that there are differences.

Dr. Moser: Of course the chemotherapy changes, but I have to say that the most predominant chemotherapy scheme was the PAC scheme, so the cisplatin-based scheme. This was more than 80%. There is not much change over the years in this. You saw that about 60% had neoadjuvant therapy, so multimodality therapy was quite frequent here.

But this is not a study on chemotherapy. This is a surgical study. This is just data that we collected to have a detailed picture. There was no complete remission. There were partial remissions for the neoadjuvant therapy in about half of the patients, but not one complete remission. We have all this data, but I can't show it. You just gave me 8 mins here.

Dr. A. Toker (Istanbul, Turkey): We have pleural involvement with thymoma, around 40 cases, and according to our experience, which we reviewed very recently, it is not uncommon that lymph node metastases occurred in these patients. I would like to know the number of obtained lymph node metastases in these patients and your attitude towards the lymph node in pleurectomy situations. Do you also do lymph node dissections in those patients who have recurred?

Dr. Moser: I think in open surgery you always do lymph node dissection. I cannot tell you the extent of lymph node dissection in this multicentre retrospective collection of data, but just a handful of lymph node metastases were reported. As you would expect in thymomas, there are not many lymph node metastases.

Dr. S. Bölükbas (Wuppertal, Germany): I have a comment. If you have lymph node metastases, then it is upstaging to IVB, not IVA, therefore you have to exclude those patients.

Dr. Moser: Absolutely, but this is not a study just on IVA. This is a study on all patients with pleural disease and their recurrences.