Factors predicting poor survival after lung-sparing radical pleurectomy of IMIG stage III malignant pleural mesothelioma

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Abstract

OBJECTIVES: The role of radical pleurectomy (RP) in the management of IMIG stage III in malignant pleural mesothelioma (MPM) remains controversial. The aim of the study was to investigate the feasibility and outcome as well as to determine factors predicting poor survival.

METHODS: Patients having IMIG stage III MPM were identified within a prospective multimodality treatment study (RP followed by chemoradiation) between 2002 and 2010 at a single institution. Kaplan–Meier analyses, log-rank test and Cox regression analyses were used to estimate survival and to determine predictors of survival.

RESULTS: A total of 78 patients (66.3 ± 2.5 years, 65 males) underwent RP followed by chemoradiation. A total of 42 (54%) had IMIG stage III. Mortality and morbidity were 4.8 and 31%, respectively. Median survival and 5-year survival were 21 months and 28%, respectively, for stage III patients. Progression-free survival was 11 months. The sites of failure were predominantly locoregional (20/42, 47.6%). Pathological detection of tumour spread at the resected thoracoscopy incisions (median survival 12 vs 35 months, P = 0.01) and male gender (median survival 18 vs 68 months, P = 0.001) were significant prognostic factors (hazard ratio (HR) = 4.3; P = 0.027) in the multivariate analysis. Patients having tumour spread had survival comparable to that of patients at stage IV in the complete patient cohort (median survival 12 vs 8 months; P = 0.39).

CONCLUSIONS: Lung-sparing RP for IMIG stage III MPM is feasible and offers promising long-term survival. The tumour spread at the resected previous incisions is associated with more incomplete resections and was a negative prognosticator for long-term survival. The tumour spread at the resected previous incisions or chest tube sites should be considered as T4 or stage IV according to the IMIG staging system.

Keywords: Malignant pleural mesothelioma • Pleurectomy • Surgery • Staging • IMIG

INTRODUCTION

Malignant pleural mesothelioma (MPM) is an aggressive malignancy arising from the mesothelial surfaces of the pleura. The peak incidence of MPM is estimated to be between 2004 and 2025, depending on the country and continent [1].

Screening methods are under investigation, but there are no reliable radiological methods to detect early MPM [2]. Thus, the focus is on the treatment options in event of the diagnosis of MPM, which typically occurs at later stages of the disease. The generally disappointing results of single-modality therapies in terms of overall survival (OS) have led to multimodality treatment approaches.

Macroscopic complete resection (MCR) seems to have the greatest impact on survival in surgery-based multimodality treatment protocols [3]. Depending on the surgical ability and intraoperative findings extrapleural pneumonectomy (EPP) or radical pleurectomy (RP) might achieve MCR even at advanced stages [4]. However, the role of RP in the management of International Mesothelioma Interest Group (IMIG) stage III in MPM remains unanswered.

The aim of the present study was to investigate the feasibility and outcome as well as to determine factors predicting survival in patients undergoing RP within a multimodality treatment protocol for MPM at IMIG stage III.

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METHODS

All patients with MPM were evaluated for trimodality therapy with curative intent as described previously [5]. In brief, the multimodality therapy included RP followed by four cycles of cisplatin/pemetrexed and radiation of the chest wall. Patients having IMIG stage III MPM were identified within this prospective multimodality treatment study and analysed retrospectively between 2002 and 2010 at a single institution.

Clinical factors as well as tumour involvement for each IMIG stage III classification features were investigated as follows [6]:

(i) involvement of the endothoracic fascia,
(ii) extension into the mediastinal fat,
(iii) solitary, completely resectable focus of tumour extending into the soft tissues of the chest wall,
(iv) non-transmural involvement of the pericardium and
(v) lymph node involvement.

Institutional review board approval was obtained for this study. The trimodality treatment was registered with ClinicalTrials.gov (identifier NCT01343264). Written consent was obtained from each study patient. The study was conducted according to the revised Declaration of Helsinki and the requirements of good clinical practice.

The definition of pleurectomy/decortication (P/D) or RP remains inconsistent. According to our definition, RP is a surgical procedure with resection of the visceral and parietal pleura while preserving the lung. Wedge resections are carried out in the event of deep infiltration of the lung parenchyma. Phrenic nerve, pericardium and diaphragm are preserved if possible from the oncological point of view. Partial or total resection and reconstruction of the diaphragm and pericardium can be carried out depending on the intraoperative findings. On the contrary, the International Association for the Study of Lung Cancer International Staging (IASLC) Committee and the IMIG defined P/D as a surgical procedure to remove all macroscopic tumour involving the parietal and visceral pleura. The term ‘extended’ P/D is proposed if the diaphragm or pericardium is resected [7].

Operative mortality was defined as death within 30 days after surgery or during the same hospital admission. All patients were seen at our department 4 weeks after surgery, at the end of the treatment and then at 6-months intervals. All patients were followed up until death or the date of last follow-up (31 January 2012) if still alive. Physical examination included a detailed assessment of the chest wall at every visit. The course of the disease was monitored by computed tomography (CT) scan of the chest. Additional diagnostic evaluation, particularly Positron emission tomography/CT, was performed in the event of a presumptive diagnosis of recurrence.

Means and standard deviations are used for description of continuous measures. Descriptive statistics for discrete variables are presented as frequencies and percentages. Survival and prognostic factors were analysed by the Kaplan–Meier method. Survival was calculated from the date of resection to the date of death or the date of last follow-up. The log-rank test was used to assess statistical significance. Cox proportional hazard analysis was applied to evaluate the influences of predictors on survival. Probability value of <0.05 was considered statistically significant. Confidence intervals (CI 95%) were used to quantify the extent of the observed differences. Data were stored using Excel (Microsoft, Seattle, WA, USA). SPSS 15.0 software (SPSS, Inc., Chicago, IL, USA) was used to analyse the data.

RESULTS

A total of 78 patients (66.3 ± 2.5 years, 65 males) underwent RP followed by chemoradiation. Thirty-nine out of 42 patients (93%) proceeded to adjuvant chemotherapy. Thirty-six patients (86%) completed the trimodality therapy. For the complete patient cohort, the median survival and the 5-year survival were 32 months and 25%, respectively. Out of 78 patients (54%), 42 had IMIG stage III. Mortality and morbidity were 4.8 and 31%, respectively. median survival was 21 months (CI 95% 5.6–36.7) at stage III. One-, 3- and 5-year survival rates were 86, 37 and 28% (Fig. 1), respectively.

Incomplete resections (median survival 13 vs 35 months, \( P = 0.01 \), Fig. 2), pathological detection of tumour spread at the resected previous incisions (median survival 12 vs 35 months,
However, the tumour spread was associated with more incom-pletions, laterality and age had no signifi-cant impact on survival. Tumour spread at the resected previous incisions (spaced m-dash, median survival 12 months; IMIG stage IV (dashed line, median survival 8 months); P < 0.001.

Figure 3: Survival depending on tumour spread at the resected previous incisions. No tumour spread at the resected previous incisions (spaced m-dash, median survival 35 months); the tumour spread at the resected previous incisions (continuous line, median survival 12 months; IMIG stage IV (dashed line, median survival 8 months); P < 0.001.

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P < 0.001, Fig. 3) and male gender (median survival 12 vs 35 months, P < 0.001) were associated with significantly inferior survival in the univariate analyses (Table 1). Patients having tumour spread at the resected thoracoscopy incisions had comparable survival as patients at stage IV in the complete patient cohort (median survival 12 vs 8 months, P = 0.39, Fig. 3).

Histology (epithelial vs non-epithelial), lymph node metastases (N0 vs N1–2), T classification (involvement of the endothoracic fascia, extension into the mediastinal fat and non-transmural involvement of the pericardium), type of additional surgical resections, laterality and age had no significant impact on survival. Tumour spread at the resected previous incisions remained the only significant prognostic factor (HR = 4.3; P = 0.027) in the multivariate analysis for IMIG stage III patients (Table 1). However, the tumour spread was associated with more in-complete resections (P = 0.047).

Progression-free survival (PFS) was 11 months (CI 95% 9.8–12.5). Male gender (11 vs 16 months, P = 0.076) and R2-resections (9 vs 15 months, P < 0.001) and tumour spread at resected previous incisions (9 vs 14 months, P = 0.009) were associated with inferior PFS.

The sites of failure were loco-regional (20/42, 47.6%), distant (6/42, 14.3%) and both (6/42, 14.3%).

**DISCUSSION**

The role of surgery in the management of MPM at stage III remains a matter of debate. EPP has historically been considered the standard surgical approach for advanced stage MPM. The rationale for EPP was based on the philosophy of achieving ‘wider negative’ margins. However, this study demonstrated that RP is feasible at IMIG stage III with acceptable mortality and morbidity rates. Based on a 5-year survival rate of 28%, long-term survival could be observed. The tumour spread at the resected thoracoscopy was identified as a negative prognosticator for long-term survival at IMIG stage III, with a survival similar to that of IMIG stage IV patients.

Our study showed that RP can achieve MCR in 62% of the cases and prolong survival in patients with MPM at stage III. Similarly, patients undergoing EPP have MCR between 60 and 68% of the cases at all stages [8, 9]. Routine diagnostic evaluation is based on CT and MR imaging [10]. Nevertheless, both approaches rely primarily on morphological criteria and have grey zones in distinguishing between tumour invasion and inflammatory attachments. Both techniques certainly do not allow the detection of unresectable tumour invasion for sure. Moreover, both operative procedures share the similar benefit of achieving MCR and the risk of doubtful negative margins at all stages. Lung tissue, mediastinal organs and vessels, parietal and visceral pleura, as well as chest wall line-up next to each other within few millimetres. In this context, the superiority of EPP over the lung-sparing procedures remains unconfirmed. There were no survival differences comparing EPP and P/D at advanced IMIG stage III (10 vs 13 months) [11]. Importantly, Lang-Lazdunski et al. [12] showed that patients undergoing P/D and having incomplete resection (R2) had a survival comparable with that of patients having MCR with EPP. Thus, extension of the surgical procedure at advanced IMIG stages might not lead to superior survival.

Stage III according to the IMIG staging system is heterogeneous. Any T3 tumour as well as any lymph node metastases in the ipsilateral chest (T1–3 N1–2) is grouped to stage III [13]. We observed no statistically significant survival differences with regard to the stage III-descriptors lymph node metastases (N0 vs N1–2), involvement of the endothoracic fascia, extension into the mediastinal fat and non-transmural involvement of the pericardium, respectively. This observation with regard to lymph node metastases might be only true at stage III, but might not be applicable to all stages. Systematic lymphadenectomy is done routinely according to IASLC lung cancer surgery guidelines [14]. We do not dissect the lymph nodes along the internal mammary artery or the intercostal lymph nodes routinely but only in the event of macroscopic lymph node metastases. There might be the possibility of incomplete lymph node sampling, which affected the analyses. However, tumour spread at the resected previous incisions remained the only significant prognostic factor for stage III MPM patients. Patients having tumour spread at the resected previous incisions had survival similar to that of patients at stage IV in the complete patient cohort. Richards et al. [15] examined the pathological characteristics of...
354 MPM patients undergoing EPP. According to their analysis, 10% of patients had tumour spread at the previous chest tube sites which was associated with the median survival of 12 months like the median survival of our patients. These findings suggest that solitary, completely resectable focus of the tumour extending into the soft tissues of the chest wall as tumour spread at the resected previous incisions or chest tube sites should be considered as T4 or stage IV according to the IMIG staging system. Importantly, tumour spread was associated with more incomplete resections in the present study. Thus, detecting tumour spread at the resected previous incisions or chest tube sites at frozen section during surgery might affect decision making with regard to avoiding futile complex surgical procedures. However, a frozen section of pleural tissue during surgery to decide on intraoperative therapy might be challenging. The possibilities of differentiating between benign conditions (inflammation, infection) and neoplasms (primary pleural malignancy, pleuritis carcinomatosis from metastastic disease) are limited during a frozen section [16]. Unambiguous detection of malignancy in biopsy site tissue during a frozen section might be helpful only if there are no known other pre-existing malign diseases other than MPM in the patients’ medical history.

The association of female gender and survival advantage has been reported consistently [17-19]. In the present study, very long-term survivors beyond 5 years at IMIG stage III were exclusively women. This phenomenon was also described by Wolf et al. [20]. In our patient cohort, women survived a median of 35 months compared with 12 months for men. We could not detect any difference in the distribution of the possible other prognostic factors between men and women. Oestrogen receptor-beta might play an important role since its expression has been identified as a positive prognostic factor for malignant mesothelioma in women. Pinton et al. [21] showed, in an in vitro study, that treatment with 17β-estradiol results in an oestrogen receptor-beta-mediated inhibition of malignant mesothelioma cell proliferation. However, the hormonal status of the women is not available in this study. Furthermore, different gene expressions as well as gene expression ratios might result in a better response to systemic chemotherapy. Gordon et al. [22] demonstrated that a four-gene expression ratio test could statistically significantly predict the treatment-related patient outcome in mesothelioma, irrespective of the histological subtypes of the tumour.

Recurrence of disease occurs locally and distantly irrespective of the aggressiveness of surgery. PFS after multimodality treatment for MPM using EPP varies in prospective studies between 13.5 and 18.3 months [9, 23]. PFS was 11 months in the present study. Co-founding factors for inferior PFS were male gender, incomplete resections and tumour spread at resected previous incisions in this study when compared with prognosticators of OS in general. The predominant site of failure was loco-regional in 47.6% of the cases. This is an unacceptably high rate of loco-regional failure per se. Nonetheless, according to Nakas et al. [24] lung-preserving total pleurectomy does no seem to increase the risk of local failure. The local failure rate was 44% after total pleurectomy compared with 41% after EPP. In summary, MPM tends to remain in the ipsilateral thoracic cavity, irrespective of the type of surgery. Further investigations to establish effective additive intracavitary therapy is warranted for the treatment of microscopic residual disease and for loco-regional control of the disease in the long-term. One possible direction could be intraoperative photodynamic therapy [25].

We acknowledge the limitations of this study. The relatively small number of patients enrolled at a single institution in this study protocol limits the interpretation and the drawing of strong conclusions. OS might be further affected by still undefined molecular and genetic factors as well as non-surgical best supportive care modalities. There is a lack of control groups in the present study. Conclusions may be strengthened or weakened with more patients and longer follow-up. Furthermore, these promising OS after RP at IMIG stage III could be attributed to the patient selection. These facts should be taken into consideration when the results of the present study are interpreted.

CONCLUSIONS

Lung-sparing RP for IMIG stage III MPM is feasible and offers promising long-term survival. The tumour spread at the resected previous incisions is associated with more incomplete resections and was a negative prognosticator of long-term survival. The tumour spread at the resected previous incisions or chest tube sites should be considered as T4 or stage IV according to the IMIG staging system. The high rate of loco-regional failure warrants further investigation of the loco-regional control of the disease.

Conflict of interest: none declared.

REFERENCES


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**Lung-sparing total pleurectomy: the surgical option of choice in malignant pleural mesothelioma?**

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**Keywords:** Malignant pleural mesothelioma • Pleurectomy • Surgery • Staging • IMIG

The incidence of malignant pleural mesothelioma (MPM) in Western Europe is increasing significantly [1]. Increased patient awareness of potential therapy and results from North American centres have stimulated specialist European surgical centres to expand their programs. There has been a shift in specialist surgical opinion away from extrapleural pneumonectomy (EPP) towards lung-sparing surgery in MPM. This may be attributed to an increasing age at presentation with consequent increasing co-morbidity, particularly COPD. There is also an increasing appreciation that lung-sparing surgery can prolong survival from MPM.

This finding is confirmed by Bolukbas et al. [2] in this issue, who report 28% 5-year survival in 42 patients with IMIG Stage III MPM. In their series, survival was even greater (median survival 38 months) in those who underwent a complete resection. Unfortunately, macroscopic complete resection was not achieved in 16 of the 42 patients and one wonders whether EPP may have been preferable in these cases. These authors highlight other important prognostic factors, particularly tumour infiltration of previous diagnostic biopsy sites. While also noted by the Boston group [3], this finding may in itself be a surrogate marker for increased tumour volume, thus leading to incomplete R2 resection, or for unfavourable tumour biology. The clinical implication of this is that core biopsy of suspicious biopsy sites should be performed prior to radical surgery. Positive results could then prompt induction chemotherapy to exclude those who may progress inexorably despite therapy. The time interval between diagnosis and major surgery is not clear in the Wiesbaden experience, but this should be kept as short as possible.

Apart from involvement of previous incisions and completeness of excision, Bolukbas did not identify nodal status or cell type as significant prognostic factors. These findings do not correlate with the largest series of survival data for mesothelioma surgery reported by the IASLC staging group [4] and probably reflect the small sample. It is imperative that radical surgery should only be considered in patients whose prognosis would...