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Institutional review – Thoracic general

Malignant pleural mesothelioma: outcome of limited surgical management

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Abstract

This study presents data on limited surgical management of malignant pleural mesothelioma. We reviewed retrospectively 70 cases of the disease managed surgically over a 10 year period. Fifteen patients received only diagnostic direct pleural biopsy, 40 had video-assisted thoracoscopic, pleural biopsy and talc pleurodesis while 15 patients underwent thoracotomy and pleurectomy for disease confined to the pleura. There were two in-hospital deaths. Actuarial survival was significantly longer in the thoracotomy group (median 14 months vs. 6 months in the other two groups, $P < 0.03$). Survival after limited surgical management of malignant mesothelioma is comparable to a previously reported more radical surgical approach.

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Keywords: Pleural malignancy; Mesothelioma; Surgery

1. Introduction

Malignant mesothelioma is the most common primary malignancy of the pleura. It arises from the mesothelial surfaces of the pleura as well as the peritoneum and the pericardium. Recognition of an association between asbestos exposure and malignant mesothelioma dates from the work of Wagner and colleagues in the 1960s [1]. The simian virus 40 (SV40) was recently identified as a significant additional carcinogen [2]. The disease shows a male preponderance, with presentation between the fifth and the seventh decades. The incidence of the disease continues to rise in the UK where annual male mesothelioma deaths are expected to reach about 3000 by the year 2020.

Diagnosis relies on histological analysis of adequate pleural biopsies. Histological subtypes include epithelioid (approximately 60% of cases), sarcomatous and biphasic (including both epithelioid and sarcomatous features). The original staging system devised by Butchart et al. [3] has been superseded by a TNM system, in line with other forms of malignancy, and updated in 1995 by the International Mesothelioma Interest Group [4]. It has previously been established that prognosis is worsened by male sex, age

greater than 65 years, short duration of symptoms to presentation, poor performance status at presentation, non-epithelioid histology, thrombocytosis, low haemoglobin and fever.

Surgical diagnosis of malignant mesothelioma can be achieved in the majority of cases without recourse to open procedure, using video-assisted thoracoscopy (VAT) [5]. Palliative techniques include talc pleurodesis (either at thoracoscopy or thoracotomy), pleurectomy with decortication, extrapleural pneumonectomy and application of intrapleural chemotherapy.

Malignant mesothelioma remains a condition of poor prognosis with a median survival of 6–18 months [5]. As life expectancy after diagnosis of the disease is short, treatment is palliative. Such prognostic figures remain poor despite attempts of multimodality treatment. We report a retrospective analysis of our experience of diagnosis and treatment of malignant mesothelioma at a regional UK cardiorespiratory centre over a 10 year period.

2. Methods

A retrospective analysis was made of all patients who were referred to a single consultant thoracic surgeon (O.M.), between January 1989 and March 1999, with pleural pathology subsequently diagnosed as malignant mesothelioma. Data were obtained from the patients' medi-

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cal notes. The referring centres and general practitioners of the patients were consulted for additional information when this was necessary. Analyzed data included age, sex, smoking history, previous asbestos exposure, degree of thrombocytosis, postoperative complications and length of survival. Patients' histological diagnoses were classified as epitheloid, sarcomatous or biphasic mesothelioma. Patients were included in the following groups based on the type of operative intervention undertaken:

Group I: open pleural biopsy in the presence of lung adhesions to the chest wall and without significant pleural effusion. In these patients, VAT was not feasible technically and pleurectomy/decortication was not considered due to tumour infiltration beyond the parietal pleura. Previous needle biopsies were negative.

Group II: this was carried out on patients with pleural effusion and tumour substantially invading the chest wall, lung parenchyma and mediastinal structures. VAT was used for diagnostic purposes and for talc pleurodesis. Groups I and II included patients at >Stage I disease and differed only in the fact that VAT was not possible in Group I patients due to the extensively invasive stage of the tumour.

Group III: pleurectomy for Stage I mesothelioma, confined to the parietal pleura in the presence of previously established histological diagnosis.

2.1. Statistical analysis

Nominal data were analyzed by means of the χ^2 test and interval data by means of the Mann–Whitney test for univariate analysis. Actuarial survival was calculated by the Kaplan–Meier method and compared with the log-rank test. Statistical significance was assumed for $P < 0.05$.

3. Results

Between January 1989 and March 1999 a total of 74 patients were diagnosed with malignant mesothelioma

following tertiary referral. Of these patients, four were treated by application of intrapleural cisplatin and have been excluded from this analysis. Demographic and clinical data of the patients are shown in Table 1. There was no predilection of histological diagnosis for either sex, smoking history or duration of symptoms. Of the 70 patients, 21% ($n = 15$) underwent diagnostic direct pleural biopsy only (Group I), 58% ($n = 40$) underwent pleural biopsy, through VAT, followed by talc pleurodesis (Group II), and 21% ($n = 15$) of patients had lateral thoracotomy and pleurectomy (Group III). In two (3.6%) of the 55 patients, thoracoscopy did not yield the diagnosis and these required a further CT guided needle biopsy.

Postoperative complications included two deaths (one each in Groups II and III) within 48 h of surgery relating to respiratory failure, one case of acute renal failure (recovered) and two persistent air leaks (resolving with chemical pleurodesis and a Meredith bag, respectively) (Table 1). All patients received radiotherapy to the chest drain sites to prevent tumour recurrence.

Actuarial survival, including the two in-hospital deaths, is presented in Fig. 1. Median survival was 6 months for Groups I and II and 14 months ($P = 0.03$) for Group III (Fig. 1). One year survival was 20%, 17.5% and 53.5% in Groups I, II and III, respectively. Two year survival was 6.7%, 10% and 40% and 5 year survival was 0%, 0% and 27%, respectively.

From a histological point of view, 48 (68.5%) patients had epitheloid tumours, six (8.5%) had sarcomatous, while 16 (23%) mesotheliomas were biphasic. Survival was longer with epitheloid histological subtype (median of 9.5 months, $P = 0.04$) compared to biphasic (5.5 months) or sarcomatous subtype (4 months). Patients in Group III were significantly ($P = 0.008$) more likely to have epitheloid tumours than those in Groups I and II. At the time of retrospective analysis (July 2000), four patients in our series were still alive. One patient from Group I was alive at 14 months, two from Group II at 16 months and one from

Table 1
Patients' characteristics

	Total ($n = 70$)	Group I ($n = 15$)	Group II ($n = 40$)	Group III ($n = 15$)
Age (years) (range)	66.1 (45–89)	66.6 (48–82)	68.4 (50–89)	62.2 (45–82)
Sex (n)				
Male	51 (73%)	10	28	13
Female	19 (27%)	5	12	2
Asbestos exposure (n)	19 (27%)	7	10	2
Smoking history (n)	33 (47%)	6	17	10
Histology (n)				
Epitheloid	48 (68%)	9	27	12
Sarcomatous	6 (8%)	2	3	1
Biphasic	16 (23%)	4	10	2
Complications (n)				
Acute renal failure	1 (1.4%)	–	–	1
Persistent air leak	2 (2.8%)	–	–	2
Hospital death	2 (2.8%)	–	1	1

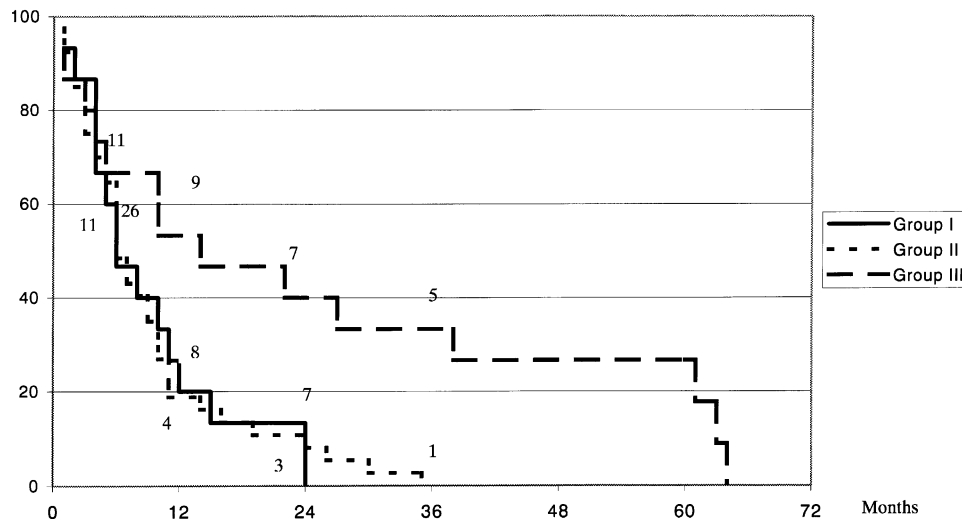


Fig. 1. This figure presents the actuarial survival in the three groups of patients with malignant pleural mesothelioma, calculated with the Kaplan–Meier method. The y-axis shows % of survival while the x-axis presents survival in months. Numbers within the figure represent patients remaining at risk.

Group III at 54 months. Analysis of survival statistics showed a weak inverse correlation between age at presentation and prognosis ($r = -0.43$, $P \leq 0.05$). The prognosis showed moderate correlation with the degree of initial thrombocytosis ($r = -0.19$, $P \leq 0.05$).

4. Discussion

This retrospective study reports data on the management of patients who were referred with radiologically suspicious pleural lesions to one tertiary referral thoracic surgical centre and were subsequently found to have malignant mesothelioma. VAT is widely recognized as a procedure of diagnostic and therapeutic value. It has been established that thoracoscopy results in obtaining an adequate amount of tissue for histological diagnosis in the vast majority of patients [5]. In our series, 53 (96.4%) of the 55 mesotheliomas that received VAT biopsy were diagnosed successfully.

VAT talc pleurodesis has been used successfully in the palliation of malignant pleural effusions, including patients with mesothelioma [5]. VAT talc pleurodesis is carried out, in preference to bedside talc slurry, in particular when the diagnosis is not established preoperatively and VAT is performed primarily for diagnostic purposes. In our institution, we treated 40 patients with thoracoscopic talc pleurodesis for malignant mesothelioma causing debilitating pleural effusion and stage higher than I. Significant recurrence of the effusion did not occur in any of these patients. Their survival did not differ from patients who only had direct pleural biopsy but it was significantly shorter than Stage I patients receiving pleurectomy.

Tumours confined to parietal pleura (Stage I according to Butchart and TNM classification) were treated with pleurectomy. In these patients, postoperative morbidity was low (Table 1). In the pleurectomy group, postoperative survival

was significantly longer in comparison to patients with mesothelioma invading the chest wall who received diagnostic direct pleural biopsy or VAT pleural biopsy and talc pleurodesis. Furthermore, there was an association between age and survival as well as between thrombocytosis and survival. It has previously been demonstrated that age, duration of symptoms, degree of thrombocytosis and histological subtype [6] have prognostic implications for malignant mesothelioma.

Current treatment strategies for malignant mesothelioma vary according to the referral centre, and include combinations of surgery, radiotherapy, chemotherapy, immunotherapy, photodynamic therapy and medical palliation. There is little general consensus with regard to treatment modalities and the role of clinical staging in the management of malignant mesothelioma.

The surgical approach to malignant mesothelioma has included attempts of palliation with cytoreduction with the hope of disease modification. Pleurectomy has proven successful in reducing the recurrence of pleural effusion and dyspnoea in patients with the disease [7]. The procedure carries a low operative mortality (1–2%) and is the preferred palliative treatment for Stage I malignant mesothelioma in our institution. In our experience, one (6.6%) of the 15 patients died in hospital. Previously reported median survivals range from 6.7 to 21 months [8,9]. This compares with our own figure for median survival irrespective of histology of 14 months. Pleurectomy per se has not been shown to improve prognosis. However, there have been reports that the combination of pleurectomy with irradiation achieved a mean survival of 22.5 months, with a 2 year survival of 41%, in a select group of patients with epithelioid mesothelioma [9]. Our patients received radiotherapy to the chest drain sites but no other form of combination therapy.

Extrapleural pneumonectomy, in which the ipsilateral parietal and visceral pleura, the contained lung, pericardium

and diaphragm are resected en bloc, has been used for mesothelioma in some thoracic surgical centres. The procedure was originally related to high morbidity and mortality [10] and was, therefore, not practised by our institution during the period covered in this report. Indeed, large series of patients undergoing extrapleural pneumonectomy over the previous two decades report morbidity rates of 50% and overall median survival of 10–19 months [10]. These survival rates are similar to the ones achieved at our centre in patients undergoing pleurectomy which carries a low complication rate. There have been, however, recent encouraging reports of patients undergoing extrapleural pneumonectomy in combination with photodynamic therapy, radiation or chemotherapy [11–13]. Median survival for Stage I tumours was 33–35 months. Larger experience will be necessary but, provided complication rates are low, multimodality treatment for Stage I mesothelioma is promising.

With regard to non-surgical treatment, trials of systemic chemotherapy have been disappointing both for single agent and combined agent therapy. Response rates have ranged from 0 to 20% [14]. Intrapleural therapy has been attempted for malignant mesothelioma in the form of intracavitary chemotherapy with radionuclides or biological agents [9]. Intrapleural chemotherapy with cisplatin is currently being used at our institution. The four patients treated so far were excluded from this analysis and will be reported separately.

In our practice, the decision to carry out thoracotomy and decortication is based on histological findings obtained at thoracoscopy and includes patients that belong mostly to Stage I, according to the Butchart and TNM classification. In our practice, the choice of surgical procedure is largely based on macroscopic findings at thoracoscopy or thoracotomy. Thus, patients with tumour confined ostensibly within the capsule of the ipsilateral parietal pleura proceed to pleurectomy with decortication. In addition to their early stage of disease, these patients were more likely to have tumours of epithelial histology. The improved survival, therefore, may be attributable to the combined factors of the early stage of the disease, the histological type and not necessarily to the cytoreductive effect of decortication. Furthermore, Group III patients were probably not comparable with Groups I and II, due to the different stage of the disease. It is important to emphasize that, in view of the poor prognosis of malignant mesothelioma, we decided our operative strategy in order to achieve the best possible palliation with low complication rate but without curative intent.

In conclusion, our series has confirmed certain of the accepted demographic features of malignant mesothelioma. Unlike a number of studies reporting aggressive multimodality regimes the current series represents a relatively unselected group of patients, undergoing cost-effective, minimally invasive preoperative assessment. When accompanied by appropriate intraoperative findings, cytoreductive pleurectomy was performed. This proved well tolerated and with potential survival advantage over advanced and possi-

bly more aggressive tumours. Pleurectomy remains an important and widely applicable surgical tool in cases of malignant mesothelioma. Its complication rate is low and is associated with comparable median postoperative survival to that reported in most series of patients undergoing more radical surgical resection. The combination of this procedure with developing modalities, affording improved local control, may well prove to have prognostic impact in this challenging condition.

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mitomycin or doxorubicin for malignant mesothelioma. *J Clin Oncol* 1993;11:1559–1565.

Appendix A. ICVTS on-line discussion

Author: *Alon Yellin, Chief, Sheba Medical Center, General Thoracic Surgery, Sheba Medical Center, Tel Hashomer 52621, Israel*

Date: 01-Jan-2003 01:41

Message: This study retrospectively compares three groups of patients with malignant pleural mesothelioma. Group III underwent cytoreductive surgery (pleurectomy), whereas groups I & II had biopsy with or without pleurectomy. The groups differ considerably: all patients in groups I&II were in IMIG stage III by definition, while patients in group III were in clinical stage I (LN status not reported). In addition 87% of the patients in group III had epithelial mesothelioma compared to 65% in the other two groups combined. Therefore group III is a highly selected group with expected favorable outcome. Indeed, the authors showed a significantly superior survival in this group.

To show survival benefit for pleurectomy, similar groups should be compared, and this is not the case in the present study. The authors presented no proof that pleurectomy prolongs survival. Their claim that pleurectomy offers results comparable to those of radical surgery is incorrect, as reports by Sugarbaker, Rusch and others show a median survival of more than 30 months for patients in stage I undergoing extrapleural pneumonectomy as part of an aggressive multimodality approach.

Author: *Dr. Enrico Ruffini, Thoracic Surgeon, University of Torino, Thoracic Surgery, 3, Via Genova, Torino 10126, Italy*

Date: 10-Jan-2003 07:00

Message: The article of Phillips and associates outlines different outcomes of patients with malignant pleural mesothelioma (MPM)

submitted to limited surgical management. The patients were stratified into three groups according to the Stage: Groups I and II who received palliative therapy and who presumably included patients at Stage II or higher, and group III who received only pleurectomy and who included patients at Stage I (only parietal pleura involvement). It is not clear what is the real objective of the study, since the three groups are not comparable in terms of histology, stage (and presumably T and N status) and received treatment. Any conclusion in terms of survival differences is therefore to be considered cautiously due to the major selection bias. Further, important information about the surgical technique is not detailed which would be otherwise interesting to know: how was pleurectomy performed and to what extent (complete, or incomplete); in particular, did the authors resect the diaphragm and pericardium if involved? Did the authors perform mediastinal lymphadenectomy to correctly stage the patients postoperatively for the N factor? In addition, what was the pathologic Stage in the 15 patients submitted to pleurectomy? Unfortunately, the authors did not mention it. Were all these patients really at Stage I; in other words, didn't they find any higher stage at thoracotomy? Indeed, true Stage I mesothelioma are exceedingly rare at surgery (only 2 out of 88 patients in the series of Rusch in 2001 were at pathologic Stage I) Also, which was the cause of recurrence in the group III patients? Was it local or distant; that is, did the authors have any recurrence on the visceral pleura following pleurectomy? As for survival, the reported median survival of 14 months for Stage I mesothelioma is well below the figures reported by the two larger series recently published after extrapleural pneumonectomy (EPP) from the Boston and the Memorial Sloan-Kettering Cancer Centre groups, and not greatly different from median survival following most chemotherapy regimens. I therefore do not agree with the conclusion of the authors that "pleurectomy remains an important and widely applicable surgical tool in cases of MPM". I agree even less when the authors say that "pleurectomy is associated with a comparable median postoperative survival to that reported following EPP". It is my impression that an aggressive attitude in early stage (I and II) mesotheliomas with a trimodality approach including chemotherapy, EPP and radiotherapy is worth being attempted: this approach is to date the best active symptom control with curative intent. The ongoing trials which recently have been proposed in the European Community evaluating the role of EPP and induction chemotherapy hopefully will provide an answer and a ray of hope to these patients. I would like to congratulate the authors for their valuable contribution to this extremely controversial issue.

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