How successful is lung-preserving radical surgery in the mesothelioma and radical surgery-trial environment? A case-controlled analysis

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Abstract

Objective: To determine whether there is a survival benefit from open-lung-preserving surgery (radical decortication) for malignant mesothelioma, when compared with the non-radical approach in the mesothelioma and radical surgery (MARS) trial era. Methods: We compared outcomes between 13 patients with malignant mesothelioma, who underwent radical decortication (group RD, n = 13) with 13 case-matched patients, who had palliative surgery (group non-radical decortication (NRD), n = 13) over a period of 2 years from June 2006 onwards. Patients were matched for age, sex, histology, computed tomography (CT) stage, haematological indices, body mass index (BMI) and adjuvant chemotherapy. We compared perioperative and postoperative courses and long-term survival. Results: Histology was 25% biphasic and 75% epithelioid in both the groups. There was no significant difference in the proportions receiving adjuvant chemotherapy (54%, p = 1.00), but more patients in the RD group received adjuvant radiotherapy (46% vs 15%, p = 0.20). Median survival was higher for all cell types in the RD group (16.9 months vs 6.8 months, p = 0.001). Conclusion: Radical open-lung-preserving surgery may confer a survival advantage to patients with malignant mesothelioma, who are fit to undergo radical decortication followed by chemotherapy and radiotherapy. Trials of radical surgery versus no surgery should include lung-sparing operations.

Keywords: Radical decortication; Malignant pleural mesothelioma; Open-lung-preserving surgery; MARS trial

1. Introduction

The incidence of malignant mesothelioma is increasing in Great Britain. Most recent predictions suggest that the number of deaths will reach its peak between the years 2011 and 2015 with a number of deaths reaching 1950–2450 per year [1,2]. Surgical management of malignant mesothelioma is still a matter of debate. A contemporary fairly large series of selected patients with malignant mesothelioma had a survival advantage if they were treated with extrapleural pneumonectomy (EPP) (median survival of 51 months) [3]. This, and other surgical series, increased the interest in pursuing a radical surgical treatment for mesothelioma [4,5]. Recently, the mesothelioma and radical surgery (MARS) randomised trial investigated the role of EPP against no EPP surgery in the context of a trimodality therapy (neoadjuvant chemotherapy and postoperative radical hemithoracic radiotherapy) [2]. Local treatment pathways were set up so that suitable patients were identified and encouraged to enrol in the MARS trial. Patients not entering the MARS trial because they have declined to be recruited or because of being unfit, underwent either radical decortication or palliative treatment. Radical decortication is a cytoreductive debulking surgery, which aims to remove all visible diseases, including the pericardium and diaphragm in all patients.

In this study, we aimed to determine whether there is a survival benefit from open-lung-preserving surgery (radical decortication) when compared with palliative surgery or the non-radical approach (thoracoscopy and pleurodesis) in patients not having EPP.

2. Methods

Between June 2006 and June 2008, we identified 57 patients, who were diagnosed with malignant mesothelioma and were either unsuitable or declined to be recruited into the MARS trial. A total of 13 patients underwent radical decortication and 44 underwent thoracoscopy and pleurodesis. We case-matched 13 of these latter patients (group NRD) with the 13, who underwent radical decortication.
Patients were matched according to age, sex, computed tomography (CT) staging, body mass index (BMI), adjuvant chemotherapy, histology and preoperative Hb, white cell count (WCC) and platelet count.

Radical decortication was offered to all patients, who were fit enough to undergo the operation (World Health Organization (WHO): 0—1, forced expiratory volume in 1 s (FEV1) > 1.5), epithelioid or biphasic cell type, age < 70 years, refused randomisation into MARS trial, had extensive preoperative surgical staging including mediastinoscopy and lavage of opposite pleural space and peritoneum and when it was likely to remove all the disease.

3. Statistical analysis

A Statistical Package for the Social Sciences Program (SPSS) version 17 software package was used for statistical analysis. Initial analysis of data was carried out. When data showed a normal distribution, it was presented as mean and standard deviation, and the t-test was used to calculate the differences between the groups. When it showed a skewed distribution, it was presented as median and interquartile ranges, and the Mann–Whitney test was used to calculate the differences between the groups. Fisher's exact test was used for categorical data. Survival was calculated from the date of diagnosis until the date of death or the date of last follow-up. Kaplan–Meier survival function was used to calculate survival, and differences between the groups in terms of survival were calculated using the log-rank test. As the sample size was small, Cox's proportional hazards regression model was used to perform a multivariate analysis of two prognostic factors only (adjuvant radiotherapy and chemotherapy).

A p-value of < 0.05 was taken as the level of significance.

4. Results

4.1. Preoperative variables

Matching between the two groups was ensured. There was no difference in the age and gender distribution between the two groups. Male to female ratio was 12:1 in both groups (p = 1.00). Median age was 60 (57—66 years) years in the RD group and 64 (56—69 years) years in the NRD group (p = 0.59). Other variables are presented in Table 1. A difference in FEV1 was apparent, but not significant.

There was no difference between the two groups in the cell type of mesothelioma. Patients who underwent radical decortication were staged according to the pathological tumour-node-metastasis (TNM) staging system, but this was not possible for the NRD group as this relies on postoperative results. TNM clinical stages of the two groups and pathological stages of the RD group are summarised in Tables 2 and 3. Resection margins could only be assessed in the RD group and they were negative in seven (54%) patients and microscopically involved (R1) in six (46%) patients.

4.2. Surgical technique

4.2.1. RD group

Those patients who underwent radical decortication had the operation that has been previously described [4]. Patients are placed in lateral decubitus position, the oesophagus intubated with a dilator to aid identification and the thoracotomy placed to include excision of any biopsy tract down to pleura. The decortication is labelled radical as it entailed a complete macroscopic removal of all the pleura, which means removal of the diaphragm and pericardium. Both were replaced with Marlex mesh. Fibrin and synthetic sealants were used on occasion but not routinely (Tisseal and Pleuraseal).

The plane between the parietal pleura and the endothoracic fascia is developed. This dissection is carried out with
a combination of pledgeted instruments, where the tissue is too hard for fingers and swabs. The dissection is carried round the apex onto the pericardium. Care is needed to protect the subclavian vessels, which did not disrupt. The internal mammary vessels were ligated as they were universally avulsed; the azygos was intentionally preserved, where possible, in case it helped reduce postoperative pleural-fluid accumulation. The visceral pleurectomy is an important and challenging part of the operation. The aim is complete removal of the visceral pleura. Perhaps, counterintuitively; the pleurectomy is quite straightforward after a talc pleurodesis. Peeling beneath the visceral layer produces a ‘raw’ surface. Careful haemostasis and closure of the larger air leaks is felt to be more important by the senior author than a liberal application of sealant. Two or sometimes three drains are placed and postoperative suction is maintained until postoperative bleeding is no longer a problem. Suction is then replaced for ambulatory drainage. No special details were discussed with the pathologist regarding the assessment of resection margins.

4.2.2. NRD group
These patients underwent a video-assisted drainage of the pleural space. Once completely dry, 8 g of dry talc is insufflated and a chest drain inserted. Benefit of doubt was given to trapped lungs and drains were managed with postoperative suction until drainage had subsided.

4.3. Postoperative course of the RD group
All patients in the RD group underwent open radical decortication. Median length of hospital stay was 13 (10.5–19) days. Median length of intensive therapy unit (ITU) stay was 2.7 (0–3.5 days) days.
Three (23%) patients developed prolonged air leak, two (15%) patients had type I respiratory failure, two (15%) patients developed pneumothorax, four (31%) patients developed lower respiratory-tract infection, four (31%) patients suffered from atrial fibrillation and two (15%) patients from pleural effusion. Median duration of chest drainage was 18 (7–23 days) days.

4.4. Adjuvant chemotherapy and radiotherapy
The same proportion of patients in both groups received adjuvant chemotherapy (54%, \( p = 1.00 \)). Four (31%) patients in the RD group and five (38%) patients in the NRD group received combination chemotherapy of Premetrexed and Cisplatin. Gemcitabine and Cisplatin were given to two (15%) patients in the RD group and one (8%) patient in the NRD group. One (8%) patient in each group received Vinonelbine.
Prophylactic radiotherapy to wound site and/or chest drain site was offered to patients in both the groups. Six (46%) patients in the RD group and two (15%) patients in the NRD group received a prophylactic radiotherapy dose of 20 Gy (\( p = 0.20 \)).

4.5. Survival
Median survival was higher for all cell types in the RD group (16.9 months) than the NRD group (6.8 months, \( p = 0.001 \)) (Fig. 1). Median survival for the epithelioid cell type in the RD group was also higher (16.9 months) than the NRD group (5.3 months, \( p = 0.014 \)) (Fig. 2).

5. Discussion
Patients with malignant pleural mesothelioma, who are not treated surgically, may survive nearly 12 months if they have been offered the best palliative treatment [6]. Radical decortication, as shown in our study, was associated with a significantly prolonged survival. Median survival in the 13 patients who underwent radical decortication for all cell types was 16.9 months, while it was 6.8 months in patients, who underwent palliative treatment (thoracoscopy and pleurodesis), (\( p = 0.001 \)). Radical decortication has also shown survival advantage over palliative treatment in the epithelioid cell type (16.9 months vs 5.3 months), (\( p = 0.014 \)). The median survival of the NRD group in our study was low for all cell types and for the epithelioid cell type: 6.8 months and 5.3 months, respectively, when compared with the median survival of other cohorts in the literature, who received palliative treatment (12 months) [6]. This can be attributed to the increased co-morbidity in this group of patients when compared with the RD group.
Patients’ characteristics preoperatively were nearly similar, though a nearly significant difference in FEV1 and WCC was observed. We do not believe that in this cohort the survival difference can be attributed to an FEV1 difference of 6%.

More patients received adjuvant radiotherapy in the RD group. Adjuvant chemo- and radiotherapy effect on survival was assessed using Cox’s proportional hazard regression model (hazard ratio (HR) 0.92, 95% confidence interval (CI) 0.28–2.95 and HR 0.37, 95% CI 0.09–1.52, respectively). The wide CI shows that the sample size is too small to draw any conclusions. All patients were referred to the oncologists through the multidisciplinary team and the decision to give adjuvant chemotherapy and/or radiotherapy was left to them.

The surgical role in the management of malignant pleural mesothelioma remains a matter of debate. The outcome of extrapleural pneumonectomy in the context of trimodality therapy was good in some centres [4]. However, EPP surgery is associated with a high mortality and morbidity rate (3.4–5%) and (22–50%), respectively, even in the fittest of patients [3,7–9]. In a study, which included 663 patients with malignant pleural mesothelioma, the operative mortality for EPP was 7% and 4% for radical decortication and a multivariate analysis demonstrated a HR of 1.4 for EPP (p < 0.001) controlling for stage, histology, gender and multimodality therapy. In a univariate analysis of the same group of patients, EPP was associated with a significantly worse survival when compared with radical decortication, p < 0.001, even after the operative deaths were excluded [5]. This confirms the results of our study in terms of a lower mortality in patients treated with radical decortication. However, this study concluded that the reasons behind the better survival in radical decortication group when compared with EPP surgery are multifactorial and due to selection bias and that the extent of disease, patient co-morbidities and the type of planned multimodality therapy should determine the choice of resection. In patients unfit to undergo EPP, radical decortication can be offered as a surgical alternative to EPP or as an alternative in patients uncertain about spending their remaining life in and out of hospital.

In our study, none of the 13 patients who underwent radical decortication had macroscopically positive resection margins. Six (46%) patients had microscopically involved resection margins (R1) and seven (54%) patients had complete microscopic clearance with no involvement of resection margins (R0), which contradicts what has been reported in a number of studies about the benefit of radical decortication as a palliative treatment, but not in prolonging survival [10]. The suggestion behind this is that radical decortication was unsuccessful in achieving a complete macroscopic clearance, which, as a result, will increase the rate of recurrence [10,11–13]. Our study showed that radical decortication can achieve a complete macroscopic clearance and prolong survival in patients with malignant mesothelioma, who are unfit to undergo EPP surgery.

In the era of the MARS trial, radical decortication can be offered to patients, who do not want the morbidity associated with EPP, adjuvant chemotherapy and adjuvant radiotherapy and to patients whose clinicians are worried about the results of EPP not being satisfactory. The retrospective nature of our study, the small number of cases and the possibility of selection bias might limit our conclusion; however, radical open-lung-surgery may confer a survival advantage in patients who are fit enough to undergo radical decortication followed by chemotherapy and radiotherapy. Trials of surgery versus no surgery should include lung-sparing operations.

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References