Treatment of mesothelioma in Bloemfontein, South Africa

W.J. de Vries*, M.A. Long

Cardiothoracic Department, Faculty of Health Sciences, University of the Free State, Bloemfontein 9300, South Africa

Received 12 December 2002; received in revised form 24 May 2003; accepted 26 May 2003

Abstract

Objective: Two different surgical methods for treating mesothelioma (pleurectomy and pleuro pneumonectomy) were reviewed.

Methods: This was a retrospective study from 1976 to 2001. Forty-six patients, aged 35–80 years, received one of the following procedures: pleurectomy (n = 29), or pleuro pneumonectomy (n = 17). Pleurectomy was indicated in symptomatic patients with pain or pleural effusion while pleuro pneumonectomy was indicated in patients with Butchart stage I or II disease and an acceptable cardiopulmonary reserve. Patients received either chemotherapy, radiation, or in combination after surgery.

Results: The mortality rate was 3.8% for pleurectomy patients and 5.8% for pleuro pneumonectomy patients. The median survival rate for pleurectomy patients was 9 months, and 12 months for pleuro pneumonectomy patients. Pleuro pneumonectomy patients experienced less morbidity and had a shorter hospital stay than pleurectomy patients.

Conclusions: Improved survival was obtained with both procedures. Morbidity was higher in the patients who underwent pleurectomy. Important prognostic factors include tumor stage, tumor histology, duration of symptoms, and weight loss or pain as a presenting symptom. Patients with a low tumor stage, epithelial histology, absence of pain or weight loss, and a longer onset of symptoms had the best survival rate. A trend towards improved survival in patients undergoing pleuro pneumonectomy and receiving radiation as adjuvant therapy was observed.

© 2003 Elsevier B.V. All rights reserved.

Keywords: Mesothelioma; Pleurectomy; Pleuro pneumonectomy

1. Introduction

Malignant pleural mesothelioma is a heterogeneous disease with a median survival rate of 4–12 months [1]. Increase in mesothelioma cases have been reported in the United States and Europe [2]. In South Africa, the incidence of mesothelioma for white males is the highest ever reported for a national population [3]. The reason for the high incidence rates in white males is unclear (under reporting in black males suspected) with occupational exposure being the most likely reason (South Africa has a large mining component) [1,3].

Various methods are used to treat mesothelioma. Lewis [4] evaluated 62 patients on three different treatment methods. He found that patients who underwent pleurectomies had a mean survival of 6 months, while those who underwent non-operative procedures had a 9-month survival and those who received no treatment, a mean survival of greater than 9 months. Paradoxically, the shortest mean survival was seen in the pleurectomy group and in the patients who appeared to have the lowest tumor burden. Lewis suggested that the intact pleura may present a barrier to tumor growth and pleura resection may hasten tumor spread. Butchart and colleagues [5] treated 29 patients by performing pleural pneumonectomies with a complication rate of 43% and operative mortality of 31%.

Before 1985, patients diagnosed with mesothelioma in our institution underwent open biopsy or pleurectomies. After the findings of Lewis [4], an alternative method for mesothelioma treatment was considered and the patients who qualified, underwent pleuro pneumonectomy.

The aim of the study was to evaluate the two different surgical methods (pleurectomy and pleuro pneumonectomy) that were used in treating patients with mesothelioma. Various prognostic factors were also evaluated.
2. Materials and methods

This was a retrospective study of 46 patients, aged between 35 and 80 years who were admitted to Universitas and National Hospital, Bloemfontein between 1976 and 2001. Twenty-nine patients underwent pleurectomies (21 males, eight females) while 17 patients underwent pleuro pneumonectomies (12 males, five females). Two patients who underwent pleuro pneumonectomies were diagnosed post-operatively as having adenocarcinoma and were excluded from the pleuro pneumonectomy group.

Patients were classified according to the Butchart and Brigham staging systems. The structures involved in the Butchart classification are: Butchart stage I, homolateral pleura, lung and pericardium, Butchart stage II, the chest wall, mediastinal structures, opposite pleura and lymph node involvement within the chest, Butchart stage III, penetrating diaphragm to involve peritoneum directly and lymph nodes outside the chest, and Butchart stage IV, distant blood-borne metastases [5]. The structures involved in the Brigham classification are: stage I, disease confined within capsule of parietal pleura, ipsilateral pleura, lung, pericardium, diaphragm, or chest-wall disease limited to previous biopsy sites; stage II, all of stage I with positive intrathoracic (N1 or N2) lymph nodes; stage III local extension of disease into the chest wall, mediastinum, heart, or through the diaphragm, peritoneum, with or without extrathoracic or contralateral (N3) lymph node involvement; stage IV, distant metastatic disease. Note: Butchart stage II and III patients are combined into Brigham stage III [1].

Before 1985, pleurectomy was indicated in symptomatic patients with pain and/or effusion. Although an attempt was made to remove all macroscopic visible tumor, the pleurectomies were usually incomplete, especially over the diaphragmatic and mediastinal surfaces. The operation was performed through a posterolateral thoracotomy, attempting to remove both the visceral and the parietal pleura. Patients were usually extubated immediately after the procedure.

Pleuro pneumonectomy was performed in patients classified as Butchart stage I or II who had an acceptable cardiopulmonary reserve. Computed tomography was used to determine tumor burden and resectability. Spirometric lung function estimation was done in all patients. The patients had a predicted post-operative forced expiratory volume in one second of at least 0.8 L/s. Pleuro pneumonectomy was performed through a posterolateral thoracotomy. The lung was mobilized and dissection was done extrapleurally. The lung and diaphragm were removed en bloc and the pericardium was excised if affected by tumor. Small pericardial defects were closed directly and bovine pericardium was used for larger defects. No synthetic mesh or any other material was used as a substitute for the diaphragm. No herniation occurred in this study. Patients were usually ventilated between 10 and 16 h.

Patients received chemotherapy, radiation or a combination of chemotherapy and radiation after surgery. According to the adjuvant therapy, the patients underwent the following treatment: chemotherapy and radiation (n = 23), chemotherapy (n = 13), radiation (n = 3), no chemotherapy or radiation (n = 5). The patients receiving no treatment included two mortalities and three patients from the pleurectomy group who refused further adjuvant therapy. Patients in the pleurectomy group received: chemotherapy and radiation (n = 19), chemotherapy (n = 6). Patients in the pleuro pneumonectomy group received: chemotherapy and radiation (n = 4), chemotherapy (n = 7) and radiation (n = 3). Chemotherapy used was platolin, adriamycin and mitomycin. Radiation was given to a total dose of 3000 cGy.

Survival rate was analyzed by the Kaplan–Meier method and differences in survival were assessed by the log-rank test and log-rank test for trend. Proportions were compared with Fisher’s exact test. Differences were considered significant with a P value <0.05.

3. Results

The median age of the pleuro pneumonectomy patients was 61 years and the pleurectomy patients 57 years (P = 0.8). The number of males and females were similar for the two groups (P = NS). All the patients were symptomatic and presented with one or more of the following: dyspnoea (58%), pain (34%), or weight loss (30%). Pain occurred in eight (53%) pleuro pneumonectomy patients and in 16 (55%) pleurectomy patients (P = 0.90). Dyspnoea was reported in 13 (86%) pleuro pneumonectomy patients and 25 (86%) pleurectomy patients (P = 0.9). Weight loss occurred in eight (46%) pleuro pneumonectomy patients and seven (24%) pleurectomy patients (P = 0.12).

Most patients (75%) reported an exposure to asbestos, while 20% reported no apparent exposure. In 5% the exposure was unknown. A similar pattern of exposure was seen in both patient groups. Less than half (43%) of the patients smoked, 36% did not smoke while the smoking status of 21% was unknown. A similar pattern was observed in both patient groups. Concurrent diseases included diabetes (n = 1), emphysema (n = 1), ischemic heart disease (n = 3), hypertension (n = 1) and previous pneumectomy (n = 1). All the concurrent diseases occurred in the pleurectomy patients except for the single patient with mild emphysema who underwent a pleuro pneumonectomy (P = 0.14).

The patients’ histology (n = 46) was as follows: epithelial (n = 38), sarcomatoid (n = 2), mixed cell type (n = 4) and adenocarcinoma (n = 2). The two adenocarcinoma patients had a median survival rate of 3.5 months. Histology for adenocarcinoma was confirmed with electron microscopy and immunochemical stains after pleuro
Pneumonectomies were performed. The histopathological diagnosis of mesothelioma can be difficult and common diagnostic dilemmas for the pathologist include the differentiation between adenocarcinoma and tubulopapillary mesothelioma.

The mortality was 3.8% in the pleurectomy patients while it was 5.8% in the pleuropneumonectomy patients. No cardiac rhythm abnormalities, infarction, pneumonia, re-operation, ventilation >72 h, or wound infection was recorded in any of the patients who underwent pleuropneumonectomy. Empyema occurred in one pleuropneumonectomy patient, but cleared on conservative treatment (antibiotics and chest tube drainage). Greater morbidity was experienced in the pleurectomy patients and included atelectasis (n = 2), more than 4 units of blood (n = 3), prolonged air-leaks (n = 3), discharge with drainage tube due to prolonged air-leak (n = 1), and ventilation for more than 72 h (n = 1, P = 0.04).

Pleuropneumonectomy patients had a shorter hospital stay with 80% leaving the hospital within 5–10 days and only 20% staying longer. Forty-eight percent of the pleurectomy patients left the hospital within 5–10 days and 40% stayed in hospital longer than 10 days (p = 0.03, odds ratio 4.8). The median hospital stay for pleuropneumonectomy patients was 8 days while it was 9 days for the patients who underwent pleurectomy (P = 0.32).

Follow-up was complete in 28 pleurectomy patients (excluding one death) and 14 pleuropneumonectomy patients (excluding one death and two adenocarcinoma patients). The longest survival in the pleuropneumonectomy group was more than 15 years while two patients survived >7 years. The remainder in the group had a median survival of 12 months. In the pleurectomy group one patient survived 12 years while three survived more than 5 years. The remainder had a median survival of 9 months.

There was no significant difference in the survival rates between the two groups (Fig. 1).

The median survival rate of the patients, in relation to certain prognostic factors is given in Table 1. The duration of symptoms was significant (P = 0.004) and patients who presented with symptoms for more than 6 months had a better median survival (26 months) than the patients who presented with symptoms for less than 6 months (median survival 8 months). A history of weight loss was significant (P < 0.0001, Fig. 2) and in those with no weight loss the median survival was 14 months, while if patients lost more than 5 kg during the preceding 6 months, the median survival was only 7 months. Weight loss in the pleuropneumonectomy patients was associated with an 8.5 months median survival while those with no weight loss had a median survival of 48 months (P = 0.012). Similarly, weight loss in the pleurectomy patients was associated with a median survival of 6 months and those with no weight loss a median survival of 12 months (P = 0.001). Pain as a presenting symptom was also significant (Fig. 3). Patients undergoing pleuropneumonectomy who presented with no pain survived a median of 37 months. This differed...
significantly from patients undergoing pleurectomy who presented with no pain (median survival 11 months, $P = 0.02$). Pleuro pneumonectomy patients presenting with no pain did not differ significantly from pleuro pneumonectomy patients presenting with pain (median survival 12 months, $P = 0.08$) or pleurectomy patients with pain (median survival 12 months, $P = 0.06$). When comparing the pneumonectomy patients presenting with no pain to pleurectomy patients with and without pain the survival curves showed a significant trend toward increased survival in pleuro pneumonectomy patients without pain (log-rank test for trend, $P = 0.03$).

The histology type significantly influenced the median survival of the patients ($P < 0.0001$, Table 1). The most favorable appeared to be the epithelial cell type (median survival 12 months). The mixed cell type and sarcomatoid cell type had a median survival of 5 and 6.5 months, respectively. Histology for the pleuro pneumonectomy patients was: epithelial ($n = 14$) and sarcomatoid ($n = 1$) and for the pleurectomy patients: epithelial ($n = 24$), mixed cell type ($n = 4$) and sarcomatoid ($n = 1$). The median survival rate for epithelial type was 9 months in the pleurectomy patients and 13 months in the pleuro pneumonectomy patients ($P = 0.11$). The mixed cell type occurred only in the pleurectomy patients ($n = 4$) and had a median survival of 5.5 months. One sarcomatoid type occurred in a pleuro pneumonectomy patient (mortality), and one in a pleurectomy patient who survived 13 months (median survival rate for sarcomatoid cell type was 6.5 months).

The Butchart stage classification data was available for 43 patients and were as follows: Butchart stage I ($n = 14$), Butchart stage II ($n = 24$), and Butchart stage III ($n = 5$). The number of patients undergoing pleuro pneumonectomy or pleurectomy in Butchart stage I was similar ($P = 0.34$). Butchart stage II differed between the two groups ($P = 0.04$, odds ratio 3.46) with more patients undergoing pleurectomy ($n = 19$) than undergoing pleuro pneumonectomy ($n = 5$). As expected, the Butchart stage had a significant influence on median survival (Fig. 4). Butchart I patients had a median survival of 49 months, Butchart II 11 months, and Butchart III 6 months.

Butchart I differed significantly from Butchart III ($P = 0.0002$), but not from II ($P = 0.07$). Butchart II differed significantly from Butchart III ($P = 0.002$). The Butchart staging for the pleuro pneumonectomy patients were: Butchart I ($n = 10$) and Butchart II ($n = 5$). Pleurectomy patients were classified as follows: Butchart I ($n = 4$), Butchart II ($n = 19$), Butchart III ($n = 5$). Butchart I pleurectomy and pleuro pneumonectomy patients had a median survival of 62 and 15 months, respectively ($P = 0.9$). Butchart II pleurectomy and pleuro pneumonectomy patients had a median survival of 9 and 11.5 months, respectively ($P = 0.21$).

The pleuro pneumonectomy patients Brigham classification was: Brigham I + II ($n = 10$) and Brigham III ($n = 5$). The pleurectomy patients’ Brigham classification was: Brigham I + II ($n = 4$) and Brigham III ($n = 24$).
Brigham I and II patients \((n = 14)\) had a median survival of 49 months and Brigham III \((n = 29)\) 9 months \((P = 0.001)\). Brigham I + II pleurectomy patients \((n = 4)\) had a median survival of 62 months while Brigham I + II pleuro pneumonectomy patients \((n = 10)\) had a median survival of only 15 months \((P = 0.92)\). Brigham III pneumonectomy patients had a median survival of 11 months, and this was not significantly different from the former group \((P = 0.16)\). The 2-, 5- and 10-year survival rates for Brigham stage I + II were 40, 25 and 10%, respectively. The 2- and 5-year survival rate for Brigham stage III was 8 and 4%, respectively, and there were no 10-year survivors.

Adjuvant therapy had a significant influence on the survival curves (Fig. 6). Patients receiving chemotherapy only survived a median of 12 months and this differed significantly from patients receiving chemotherapy and radiation who had a median survival of 9 months \((P = 0.02)\).

Three pleuro pneumonectomy patients received only radiation with a median survival of 49 months. This did not differ significantly from the chemotherapy group, but differed significantly from the chemotherapy and radiation therapy group \((P = 0.02)\). The patients receiving chemotherapy and radiation, however, included 23 pleurectomy patients and the dose of radiation delivered to the pleural cavity is limited when there is still lung in situ, for fear of radiation pneumonitis [1]. This might explain the better survival in the radiation group consisting only of pleuro pneumonectomy patients.

The median survival (Fig. 7) for patients receiving chemotherapy and radiation was 9 months for pleurectomy patients \((n = 19)\) and 10 months for pleuro pneumonectomy patients \((n = 4, P = 0.78)\). The median survival for patients receiving chemotherapy was 14 months in those who underwent pleurectomy \((n = 6)\) and 12 months for those who underwent pleuro pneumonectomy \((n = 7, P = 0.99)\). The median survival for pleurectomy patients receiving chemotherapy and those receiving chemotherapy and radiation were similar \((P = 0.06)\).

The median survival for pleuro pneumonectomy patients receiving chemotherapy \((n = 7,\) median survival 12 months), and those receiving chemotherapy and radiation \((n = 4,\) median survival 10 months) were similar \((P = 0.45)\). The median survival for pleuro pneumonectomy patients receiving only radiation \((n = 3,\) median survival 49 months) differed significantly from pleuro pneumonectomy patients who received chemotherapy and radiation \((median\ survival\ 10\ months,\ P = 0.03), but\ not\ from\ those\ who\ received\ only chemotherapy\ (median\ survival\ 12\ months,\ P = 0.82). Comparing pleuro pneumonectomy patients who had radiation to pleuro pneumonectomy patients who had chemotherapy or the combination of chemotherapy and radiation, no significant trend in the survival curves were observed. Comparing pleuro pneumonectomy patients receiving radiation with pleurectomy patients receiving chemotherapy or the combination of chemotherapy and radiation, there was a significant trend towards a better survival in those pleuro pneumonectomy patients who received radiation \((P = 0.03,\ log-rank\ test\ for\ trend)\).

4. Discussion

In this study the median survival of the pleuro pneumonectomy and pleurectomy patients were similar. Due to shorter hospital stay, low morbidity and acceptable mortality, pleuro pneumonectomy is considered in those
patients with Brigham stage I + II disease and an acceptable cardiopulmonary reserve. Pleurectomy is performed in those patients who are not able to withstand the rigors of pleuro pneumonectomy, or as a palliative procedure in advanced disease (Butchart stage III or Brigham stage III) to control pleural effusions or severe pain when more conservative measures have failed. Most of the pleuro pneumonectomy patients left the hospital within 5–10 days. Patients who underwent pleuro pneumonectomy and did well, had symptoms for longer than 6 months, had no weight loss or pain, and were in a good physical condition. A short history associated with pain and weight loss was associated with a worse prognosis.

The most common histological type encountered was epithelial and this was associated with a median survival of 12 months. This differed significantly from the median survival of the mixed and sarcomatoid cell types \( (P = 0.001) \). The median survival for both groups of patients according to histological type did not differ significantly for the epithelial type, namely 13 months, for pleuro pneumonectomy patients and 9 months for pleurectomy patients \( (P = 0.11) \). The survival for mixed and sarcomatoid cell types in both groups could not be evaluated due to the small numbers.

Our perioperative mortality of 5.8% compares well with other studies in the literature \[1,2\]. Mortality in the pleuro pneumonectomy group occurred early in our experience and was a result of technical factors (slipped ligature on the azygos vein). We did not find it necessary to replace the diaphragm with mesh or pericardium as other authors \[1,2\]. This did not affect our patients adversely (the peritoneum was left intact). The pericardium was, however, closed with bovine pericardium or directly sutured if necessary, to prevent heart herniation, especially on the right side.

Tumor stage is important in the median survival of the patients. The main advantage of the Butchart staging system is its simplicity, although it does not take tumor burden into account, as does the Brigham staging system \[1\]. Due to the retrospective nature of the study it was not possible to differentiate between Brigham stages I and II, as the nodal status was not known. All gross macroscopic visible tumor was excised in the pleuro pneumonectomy patients. Median survival for pleurectomy and pleuro pneumonectomy patients classified as Butchart I was not significant. In Butchart II patients there was no significant difference in the median survival in either group. In the current study the Butchart staging was done preoperatively by means of computed tomography and intraoperatively by estimating the local extent of the tumor. This was done by three surgeons and there could have been bias in judging the extent of the tumor. In future the Brigham staging system will be used with an increased use of magnetic resonance imaging, 2D ECHO (for pericardial involvement) and mediastinoscopy to stage the tumor more accurately. More attention will be paid to lymph node involvement as advocated by Sugarbaker et al. \[1\].

Patients receiving adjuvant chemotherapy did better than the group receiving chemotherapy and radiation. Although the dosage of radiation could have played a role, the latter group, consisting of 19 pleurectomy patients, may have represented a more severe Butchart stage with 14 patients being classified as Butchart stage II, two Butchart stage I, and three Butchart stage III. The three pleuro pneumonectomy patients who received only radiation had a median survival of 49 months, with a trend towards an increased survival \( (P = 0.03) \). The results appear promising but the numbers are too small to draw any conclusions and these findings suggest that further investigation into this group of patients is needed. Although photodynamic therapy is considered a new adjuvant treatment type, traditional therapies will still be offered. Reported median survival with photodynamic therapy was similar to this series, but associated with increased morbidity \[6\].

Duration of symptoms, weight loss and pain seem to be important prognostic indicators. The increased survival in some of the patients may be due to a ‘less aggressive’ form of mesothelioma, rather than the specific therapy applied. If one selects patients with favorable prognostic indicators i.e. no weight loss and pain, relatively long duration of symptoms, epithelial type and low Butchart or Brigham stage (without lymph node disease), increased survival may be obtained with both pleurectomy and pleuro pneumonectomy.

It is the opinion of the authors that pleurectomy has certain limitations in treating patients with mesothelioma. In performing pleurectomy it is difficult to remove all tumor completely, especially in the hilus, mediastinum and over the diaphragm. It is also difficult to remove tumor that has infiltrated the lung. The radiation dosage has to be decreased to avoid possible danger of radiation pneumonitis. In both our opinion, pleuro pneumonectomy is a more effective cytoreductive procedure than pleurectomy. Pleuro pneumonectomy will be offered to patients with Brigham stages I and II with an acceptable cardiopulmonary reserve. This will be followed post-operatively by chemotherapy and/or radiation therapy. Talc poudrage (via the thoracoscope) or pleurectomy is suggested for the symptomatic patient who does not qualify for pleuro pneumonectomy (unresectable tumor or impaired cardiopulmonary reserve). For the patient with advanced disease supportive measures will be considered.

Although no difference in survival was demonstrated between pleurectomy and pleuro pneumonectomy patients the latter can be done at our institution with an acceptable mortality while the length of hospital stay and morbidity is less than those of the pleurectomy patients. As demonstrated in this series, a 10-year survival can be obtained with either pleuro pneumonectomy or pleurectomy.

An important result of this study was that few patients with Brigham I + II, and probably favorable prognostic
factors, had a 2, 5 and 10 year survival of 40, 25 and 10%, respectively.

Acknowledgements

The authors thank Prof. G. Joubert, Prof. D. Stones and Prof. B. Diedericks for constructive comments and Mrs L. van der Westhuizen for preparing the manuscript.

References


