Institutional report - Thoracic general

Radical surgery for malignant pleural mesothelioma: results and prognosis

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Abstract

The role of surgical treatment for malignant pleural mesothelioma (MPM) continues to be controversial. We carried out a retrospective review of the prognosis in patients who had radical surgery for MPM. Of 87 consecutive patients on whom surgical exploration for biopsy-proven MPM was performed, 31 patients underwent extrapleural pneumonectomy (EPP) and 34 patients underwent pleurectomy/decortication (P/D). Sixty-five patients having EPP or P/D included 58 men (89%). The median age was 60 years (range 35–78) and the histologic type was epithelial in 48 patients (74%). IMIG staging classification was p-stage I disease in eight patients (12%), p-stage II in 13 (20%), p-stage III in 40 (62%) and p-stage IV in 4 (6%). Operative mortality was 3.2% for EPP and none for P/D. The median and 3-year survivals after EPP were 14 months and 21% whereas those after P/D were 17 months and 24%, respectively. A multivariate analysis demonstrated that older patient age \((P=0.0467)\), non-epithelial histology \((P=0.0057)\) and p-stage III–IV disease \((P=0.0019)\), but not gender, side, surgical procedure, were significant independent negative prognostic factors. Although P/D appears to be acceptable in early stages, we encourage EPP, en bloc resection without entering the pleural cavity with intent for curability, which provides oncologically complete resection of all disease.

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Keywords: Malignant mesothelioma; Extrapleural pneumonectomy; Pleurectomy/decortication; Survival

1. Introduction

Not anything frustrates thoracic surgeons more than to be faced with a malignant pleural mesothelioma (MPM), which is a rare tumor, characterized by locally aggressive behavior, is an unvaryingly fatal disease and has been recalcitrant to various treatments. In general, the median survivals after diagnosis were 8–18 months for the majority because of chemotherapeutic resistance and of the difficulty in performing complete resection; thus specific curative treatments were not offered with a sense of nihilism, and the therapeutic strategies actually performed were not often uniform even in all-inclusive cancer centers [1]. However, ideal therapeutic options should be investigated because the incidence has been continuing to rise in most countries.

The significance of surgery continues to be a matter of debate. Sugarbaker and colleagues [2] conducted a major series in surgical treatment by extrapleural pneumonectomy (EPP) for MPM, demonstrating that patients with microscopic negative resection margins, negative lymph nodes and epithelial histology had an excellent long-term survival (median and 5-year survivals: 51 months and 46%, respectively). Although EPP has been eagerly adopted for MPM in some medical centers, the superiority over a lung-sparing procedure pleurectomy/decortication (P/D) remains unverified.

In addition to the USA and Europe, MPM concerns us seriously in Japan since we are facing an epidemic, which will peak around the year 2020 due to the prevalence of occupational exposure to asbestos and the long latency period. In the present study, we analyzed the surgical results of patients radically performing EPP or P/D for MPM, and evaluated the prognostic factors. This analysis, although small, is an instructive representation of all that is controversial in the management of the patient with the potentially resectable mesothelioma. In addition, we reported our results of recent multimodality treatment including EPP with adjuvant hemithorax conformal radiation for the purpose of clinical trials.

2. Patients and methods

Between November 1986 and December 2006, 87 consecutive patients underwent surgical exploration for possi-
Pleurectomy had known asbestos exposure. Forty-one patients (a right-sided lesion and 24 (37%) had a left-sided lesion. The histologic type of the tumor was epithelial in 48 (69%) women and 58 (74%) men. According to the IMIG staging system, pathological examination demonstrated that 8 patients had stage I disease (12%), 13 patients had stage II disease (20%), 40 patients had stage III disease (62%) and 4 patients had stage IV disease (6%). In the four patients with pathologic stage IV lesion, postoperative pathological examination showed microscopically residual tumors in the chest wall (T4 disease) although intraoperative findings had macroscopically revealed complete resection of the tumor.

Regarding 21 patients with nodal involvement, only three patients (14%) had metastasis confined to N1 sites while 18 patients (86%) had N2 disease. The characteristics of the patients according to surgical procedure are shown in Table 1. There were trends toward more epithelial type and more early stage lesion in the P/D group rather than in the EPP group. Major postoperative complications occurred in 15 patients (48%) in EPP group and five patients (15%) in P/D group. One in-hospital operative death secondary to lung infarction occurred in the EPP group. Other complications included supraventricular arrhythmias (eight patients in EPP group and three patients in P/D group), respiratory failure (four patients in EPP group), respiratory infection (one patient in EPP group and two patients in P/D group), bleeding, heart hernia, bronchial stump insufficiency, chylothorax (two patients each in EPP group) as well as heart failure, laryngeal nerve palsy (one patient each in EPP group). Thirty-day operative mortality was 1.5% (1/65 patients) for the entire patient group and was 3.2% (1/31) for the patients who had an EPP. No patients undergoing P/D had operative mortality.

Because follow-up length reflected the inclusion of patients who had a poor life expectancy and of patients who died postoperatively, the median follow-up time for all 65 patients was nine months. When overall survival of the 31 patients who had an EPP was compared with that of the 34 patients who had a P/D (Fig. 1), the difference was not statistically significant (P=0.9220). The median and 3-year survivals after EPP were 13 months and 33%, whereas those after P/D were 17 months and 24%, respectively. Because of the small number of patients with mixed histology or sarcomatoid histology, they were classified together for survival analysis and compared to patients with pure epithelial histology (Fig. 2). The median and 3-year survivals with epithelial histology were 18 months and 33% while those with non-epithelial histology were 8 months and 8%, respectively. There was a greatly significant difference in survival in favor of patients who had a pure epithelial histology (P=0.0048).

The overall survivals in accordance with pathologic stage are shown in Fig. 3. When individually compared between four stage categories, there was no difference in survival.

### Table 1

<table>
<thead>
<tr>
<th>Characteristics of the patients according to the type of surgical procedure performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrapleural pneumonectomy</td>
</tr>
<tr>
<td>Number</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Side</td>
</tr>
<tr>
<td>Histology</td>
</tr>
<tr>
<td>Epi</td>
</tr>
<tr>
<td>mix</td>
</tr>
<tr>
<td>sar</td>
</tr>
</tbody>
</table>

Epi, epithelial type; mix, mixed; sar, sarcomatoid; IMIG, International Meso-thelioma Interest Group.
Fig. 1. Overall survival analyzed according to surgical procedure. There was no significant difference between patients with extrapleural pneumonectomy vs. pleurectomy/decortication ($P=0.9220$).

Fig. 2. Overall survival analyzed according to histologic type. Patients who had epithelial histology had a significantly better prognosis ($P=0.0048$).

Fig. 3. Overall survival analyzed according to pathologic stage. Stage had a high impact on prognosis (stage I vs. II, $P=0.8927$; stage II vs. III, $P=0.0615$; stage III vs. IV, $P=0.0012$).

for stage I vs. stage II ($P=0.8927$), but a marginal difference for stage II vs. stage III ($P=0.0615$) and a significant difference for stage III vs. stage IV ($P=0.0012$). The small numbers of patients with stage I ($n=8$) or stage II ($n=13$) could make the comparison less trustworthy. When overall survivals according to T status were examined, there was significant difference from the median survival of 23 months for T1-2 tumors and of eight months for T3–4 tumors ($P=0.0037$). Regarding overall survival classified by N status, the median survival for N0 tumors was 17 months while that for N1-2 tumors was 12 months ($P=0.2016$).

In a multivariate analysis with various prognostic factors which included gender, age, tumor side, histology, pathologic stage, and surgical procedure, older age ($P=0.0467$), non-epithelial histology ($P=0.0057$) and pathologic stage III–IV disease ($P=0.0019$) had a significantly negative impact on survival. Thus, a younger patient with a stage I–II epithelial tumor should be a good candidate for radical surgery (Table 2).

Lastly, we showed our results of multimodality treatment prospectively performed in recent times (Table 3). Since September 2004, EPP with adjuvant conformal radiotherapy of 54 Gy to ipsilateral hemi-thorax was performed in four patients. The difficulty in providing adjuvant chemotherapy following EPP led us to carry out trimodality therapeutic strategy with neo-adjuvant setting of chemotherapy. Therefore, since May 2006, five patients were treated with two cycles of cisplatin (80 mg/m$^2$) and gemcitabine (1000 mg/m$^2$) followed by EPP and adjuvant conformal hemithorax radiation of 54 Gy. All the patients underwent surgery within six weeks of completion of neo-adjuvant chemotherapy and radiotherapy was initiated within 11 weeks postoperatively. All patients but one were male, and age range was 51–71 years. There were six epithelial type and three mixed type. Interestingly, although all the patients had been preoperatively diagnosed as clinical stage I–II disease (N0 disease), pathologic examination post-operatively demonstrated N2 disease in five patients (56%).

### Table 2

Multivariate analysis of prognostic factors ($n=65$)

<table>
<thead>
<tr>
<th>Factors</th>
<th>Unfavorable</th>
<th>Favorable</th>
<th>Risk ratio</th>
<th>95% CI</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female</td>
<td>Male</td>
<td>1.849</td>
<td>0.752–4.546</td>
<td>0.1892</td>
</tr>
<tr>
<td>Age (years)</td>
<td>&gt; 60</td>
<td>≤60</td>
<td>1.907</td>
<td>1.009–3.601</td>
<td>0.0467</td>
</tr>
<tr>
<td>Side</td>
<td>Right</td>
<td>Left</td>
<td>1.382</td>
<td>0.688–2.775</td>
<td>0.3626</td>
</tr>
<tr>
<td>Histology</td>
<td>Non-epi</td>
<td>Epi</td>
<td>2.922</td>
<td>1.366–6.249</td>
<td>0.0057</td>
</tr>
<tr>
<td>Pathologic stage</td>
<td>III–IV</td>
<td>I–II</td>
<td>2.792</td>
<td>1.459–5.343</td>
<td>0.0019</td>
</tr>
<tr>
<td>Procedure</td>
<td>P/L</td>
<td>EPP</td>
<td>1.498</td>
<td>0.806–2.786</td>
<td>0.2011</td>
</tr>
</tbody>
</table>

CI, confidence interval; Epi, epithelial type; P/L, pleurectomy/decortication; EPP, extrapleural pneumonectomy.
All patients have completed the prescribed chemotherapy, surgery, and radiotherapy without grade four toxicity or treatment-related fetal complication. All patients but one who received EPP with adjuvant hemi-thorax radiotherapy and died from the tumor 13 months after treatment, are alive without any recurrence. This multimodality therapy is feasible although our result has to be translated judiciously due to the relatively short follow-up length and small number of patients.

4. Discussion

The multivariate analysis of this study showed that stage I and II disease had a much more favorable survival than more advanced disease. The results including other series [2, 5] implied a survival advantage for patients with early stage disease undergoing radically surgical resection although a lead time must be always considered. Thus, our data would dismiss our despair over treatment of MPM and support early diagnosis and radical surgery. We, however, must exercise a caution for the potential of confusion between improving prognosis by treatment and by beginning the clock sooner. Our analysis also suggested that epithelial histology had a better prognosis than a non-epithelial one. As the same outcomes were shown in other reports [2, 5], it should be appropriate to employ the factor as a stratification in clinical trials.

Even now, the criteria for selecting patients for radical surgery remain a matter of debate. In this series, we included patients if the thoracic surgeon deemed a macroscopically complete resection possible. Historically EPP had met with a high operative mortality in the order of 10–20%, although it has been reported to be approximately 5% in highly specialized centers [2, 5]. Another surgical procedure P/D, which allows radical resection of the early-stage tumor while preserving the lung parenchyma, is technically difficult but it is generally less morbid and better tolerated than EPP [6–8]. In the present study, the operative mortality was 3.2% for the patients who had an EPP while none of the patients who had a P/D died perioperatively. This series demonstrated that the type of surgery between EPP and P/D never affects the postoperative prognosis with long follow-up, supporting data of the Sloan-Kettering Cancer Center [5]. In our series, it should be noted that relatively early stage disease and epithelial histology were somewhat predominant in patients having P/D. In general, the surgical procedure is inherently stage dependent and potentially driven by surgeon bias. The most crucial matter is which procedure the surgeon should choose if he/she is confronted with a patient of equal cardiopulmonary demographics that tolerate either EPP or P/D. We favor an en bloc resection of the tumor without entering the pleural cavity by EPP. The surgeon should do what is required to achieve the purpose of the surgery, which is the grade of curability for us, while considering the evaluation of the patient’s cardiopulmonary function.

As a single modality, surgery or radiation for MPM has individually been disappointing. Addition of aggressive radiotherapy following removal of the whole lung by EPP can be effective for local control of pathology because inadequate local control has been the main cause of death. A phase II trial from Sloan-Kettering of postoperative radiation in high doses indicated a reduction in the local failure rate to 6% without apparent impact on prognosis [9]. Caution should be taken for high doses of radiotherapy after EPP because of severe complications such as pneumonitis, pericarditis and mediastinitis. Whether high doses of conformal or intensity-modulated radiotherapy are feasible and effective for local control following EPP is unknown, but promising. The difficulty in providing aggressive adjuvant chemotherapy after EPP led us to perform a pilot study with neo-adjuvant setting of chemotherapy. While phase II studies showed that the response rate of MPM to cisplatin and gemcitabine has been reported to range between 16% and 47% [10, 11], a phase III study showed that the response to cisplatin and pemetrexed has been reported to be 41% in advanced MPM [12]. We are now using the latter combination in a neo-adjuvant approach. Our experience in the nine patients having multimodality therapy showed no in-hospital mortality and perioperative severe complications, providing the basis of a prospective clinical trial which will start in Japan. Radical surgery and hemi-thorax radiotherapy in high doses following neo-adjuvant systemic chemotherapy including cisplatin is a demanding therapeutic strategy and should be reserved...
for dedicated centers with an acceptable mortality and morbidity.

References


eComment: Crucial Japanese evidence of surgery for malignant pleural mesothelioma

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doi:10.1510/icvts.2007.166322A

Recently, the number of patients with malignant pleural mesothelioma (MPM) has been increasing in Japan. Thus, it is crucial to establish an effective modality for MPM. A phase II trial of multi-modality for MPM will start using Japanese patients. The paper in this journal [1] is the first report showing the feasibility of surgery for MPM using a large number of Japanese patients, offering a referral evidence of the Japanese prospective study.

Reference


eComment: EPP and P/D: which to choose?

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doi:10.1510/icvts.2007.166322B

I read with great interest the article by Okada and others [1]. I believe that this article represents the state of the art of surgical treatment for malignant plural mesothelioma (MPM) in Japan, not only because this is Japan’s largest series from a single center, but also the above team is famous for close collaboration of MPM experts.

In the present study, the authors, however, also showed no significant difference of survival between extrapleural pneumonectomy (EPP) and pleurectomy/decortication (P/D). Okada interprets that the result reflects relatively early stage disease and predominant epithelial histology in P/D group. However, a similar result has been reported from Memorial Sloan-Kettering Cancer Center Group [2], where more than half of the patients were belonging to unclassified histology and staging information was missing in almost half of the patients. The above facts lead to a hypothesis that EPP and P/D might be equal in view of postoperative median survival. The possible mechanism is that severity of EPP may offset its curative power. If so, EPP should be indicated only for patients who seek for cure, not for extending survival with MPM. It is still unsolved whether P/D is just a limited surgery for patients with poor surgical durability or not. I am interested in the authors’ current policy for P/D.

References
