Does Surgery Improve Survival of Patients with Malignant Pleural Mesothelioma?

A Multicenter Retrospective Analysis of 1365 Consecutive Patients

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Background: Surgery with pleurectomy/decortication (P/D) or extrapleural pneumonectomy (EPP) can be an option for selected patients with resectable malignant pleural mesothelioma (MPM). The aim of this study was to investigate the impact of surgical treatment on the outcome of patients with MPM.

Methods: We retrospectively reviewed data from 1365 consecutive patients with histologically proven MPM, treated from 1982 to 2012 in six Institutions. Patients received chemotherapy alone (n = 172), best supportive care (n = 690), or surgical treatment (n = 503), by either P/D (n = 202) or EPP (n = 301) with or without chemotherapy.

Results: After a median follow-up of 6.7 years (range, 1.1–14.8), 230 patients (16.8%) were alive; median survival for patients who received palliative treatment or chemotherapy alone, P/D, and EPP were 11.7 (95% CI, 10.5–12.5), 20.5 (95% CI, 18.2–23.1), and 18.8 (95% CI, 17.2–20.9) months, respectively. The 30-day mortality was 2.6% after P/D and 4.1% after EPP ($p = 0.401$). According to multivariate analysis (n = 1227), age less than 70, epithelial histology, and chemotherapy were independent favorable prognostic factors. In the subset of 313 patients (25.5%) with all favorable prognostic factors, median survival was 18.6 months after medical therapy alone, 24.6 months after P/D, and 20.9 months after EPP ($p = 0.596$).

Conclusions: Our data suggest that patients with good prognostic factors had a similar survival whether they received medical therapy only, P/D, or EPP. The modest benefit observed after surgery during medical treatment requires further investigation, and a large multicenter, randomized trial, testing P/D after induction chemotherapy versus chemotherapy alone in MPM patients with good prognostic factors, is needed.

Key Words: Malignant pleural mesothelioma, Extrapleural pneumonectomy, Pleurectomy/decortication, Chemotherapy, Palliative treatment.

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Malignant pleural mesothelioma (MPM) is a rare and aggressive disease with approximately 2500 newly diagnosed cases each year in United States and approximately 5000 in Western Europe.[1,2] Median survival is 6 to 9 months from the diagnosis, and 6-month, 1-year, and 5-year overall survival are 55%, 33%, and 5%, respectively.[3]

Medical management of MPM with chemotherapy or radiotherapy has obtained only limited improvement of survival, with pemetrexed and cisplatin chemotherapy reaching a median survival of 12 versus 9 months with best supportive care.[4] Surgery can be an option for patients with good performance status and resectable disease, by either pleurectomy/decortication (P/D) or extrapleural pneumonectomy (EPP), but patient selection and optimal surgical strategy are still controversial. The aim of surgery is to remove all macroscopic disease, but a complete resection without microresidual disease (R0) is extremely difficult to obtain. Therefore, surgical treatment has been combined with chemotherapy and radiotherapy to improve local control and survival. Encouraging results have been reported for EPP combined with chemotherapy and radiotherapy, with a median survival ranging from 17 to 35 months.[5–7] Recently, several studies comparing the EPP with less invasive surgical procedures, such as P/D, showed similar results in terms of survival, with lower postoperative morbidity and mortality.[8–10] The best treatment for the individual patient remains unknown, because published series are too small and heterogeneous to demonstrate statistically significant differences in survival. In fact,

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surgical patients selected on the basis of best prognostic factors are usually compared with nonsurgical candidates with the poorest prognosis.

At present, there is only one small, prospective, randomized study, the Mesothelioma And Radical Surgery (MARS) trial, which did not show any benefit of EPP after chemotherapy compared with chemotherapy alone.[11] Moreover, the decision to perform either P/D or EPP is on the basis of surgeon's preference rather than scientific data.

The primary aim of this retrospective, multicenter study was to investigate the impact of surgical treatment on the outcome of patients with MPM, having adjusted for independent prognostic factors.

MATERIAL AND METHODS

We retrospectively reviewed data from 1365 consecutive patients with histologically proven MPM, who had undergone thoracoscopic or open pleural biopsy between September 1982 and September 2012 at six Institutions (Spedali Civili Brescia, Ospedale Maggiore della Carità Novara, San Luigi Hospital Orbassano (Torino), Policlinico hospital Milan, IRCCS San Martino Genova, and Fondazione IRCCS Istituto Nazionale dei Tumori Milan; Supplemental Table, Supplemental Digital Content 1, http://links.lww.com/JTO/A517). A common variable database was created. Clinical data were obtained from institutional databases, and variables recorded included age, sex, asbestos exposure, smoking history, histologic subtype, stage, surgical procedure, and chemotherapeutic regimens when available.

In all patients, tissue sampling was achieved by means of thoracoscopy (n = 1282) or open pleural biopsy (n = 83) under general anesthesia. In the absence of pleural effusion, patients underwent open pleural biopsy by lateral minithoracotomy. Three tumor cell types were identified: epithelial, biphasic, and sarcomatous.

Eight hundred sixty-two patients received medical treatment alone, consisting in either chemotherapy (n = 172) or best supportive care (n = 690); 503 patients received surgical treatment with or without chemotherapy, consisting in either P/D (n = 202, 6 patients underwent only pleurectomy) or EPP (n = 301) according to their performance status, histology, and clinical staging of the disease. Before 2004, chemotherapy consisted of cisplatin and/or gemcitabine and after that date a combination of cisplatin and pemetrexed. Patients with histologically confirmed nonsarcomatous MPM, younger than 75 years, with a Eastern Cooperative Oncology Group performance status of 0 to 1, and normal liver and renal function tests were evaluated for surgery with pulmonary function testing, quantitative ventilation–perfusion scanning, echocardiography, and computed tomographic (CT) scanning of the chest and abdomen. Additional imaging studies were performed as clinically indicated.

Patients were considered suitable candidates for multimodality therapy with EPP if the predicted postoperative forced expiratory volume in 1 second was at least 1 liter, and echocardiography showed a grossly normal cardiac function and an ejection fraction of more than 45%, with an estimated normal pulmonary artery pressure. Surgical resectability was defined by tumor confined to one hemithorax without any evidence of metastatic disease, or invasion of the chest wall (preservation of extrapleural fat planes, absence of extrapleural soft-tissue masses, and absence of rib displacement or infiltration) or mediastinum (normal CT attenuation values of mediastinal content), or transdiaphragmatic extension (smooth diaphragmatic undersurface). The decision to perform EPP or P/D was based on the extent of the disease, with locally advanced MPM patients being treated mainly with EPP. EPP was defined as an en bloc resection of the pleura, lung, ipsilateral diaphragm, and pericardium; P/D was defined as an extrapleural dissection from the apex to the diaphragm; decortication of the lung was performed where the visceral pleura was macroscopically involved including the pulmonary fissures down to the pulmonary artery and pleural reflections if involved. The aim of surgery was to obtain a radical macroscopic resection. Postoperatively, patients treated with P/D received adjuvant chemotherapy and/or radiotherapy. Since 1999, after EPP, adjuvant chemo-radiation was carried out according to the scheme by Sugarbaker et al.[5]

Sixty-eight patients (19 in nonsurgical group, 46 in P/D group, and 3 in EPP group) were lost at follow-up. The remaining 1297 patients were followed up until death or for a minimum period of 1 year. Survival was measured from the date of surgical diagnosis; in the surgical groups (P/D and EPP groups), the survival was also analyzed from the data of surgery. In the surgical group, the median interval between diagnosis and surgery was 2.8 months (range, 0.5–4 months).

Patients were followed up with a chest CT arranged every 6 months to monitor response to treatment or disease progression. Those relapsing after multimodality therapy were offered second-line treatment: combination chemotherapy with pemetrexed and cisplatin or single-agent vinorelbine. Radiotherapy was offered as a palliative measure when patients were diagnosed with relapse.

The following characteristics were analyzed: age, sex, asbestos exposure, smoking history, performance status, histology, and treatment options (palliative treatment, chemotherapy, or surgery), dividing patients undergone EPP or PD and chemotherapeutic regimens with or without pemetrexed.

Univariate and multivariate analyses were performed, using the Cox regression model. A two-sided test was used at 5% level of significance. The univariate and multivariate analyses were limited to patients (n = 1227) in whom information on overall survival (OS) was available. Survival functions were estimated using the Kaplan–Meier technique. The subgroup of covariates that best discriminated the prognosis was obtained by means of the classification and regression tree (CART) method. Statistical analysis was performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC); the CART method was applied using R version 2.15.1; the survival plots were performed using STATA version 12.1.

RESULTS

A total of 1365 consecutive patients were enrolled in the study. Most of the patients were male (68.1%) and the most frequent tumor cell type was the epithelial (57.9%); patient characteristics were summarized in Table 1. Clinical and pathological staging were reported in Table 1; the data showed that

