Prognostic Score of Long-Term Survival After Surgery for Malignant Pleural Mesothelioma: A Multicenter Analysis

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Background. **Despite ongoing efforts to improve therapy in malignant pleural mesothelioma, few patients undergoing extrapleural pneumonectomy experience long-term survival (LTS). This study aims to explore predictors of LTS after extrapleural pneumonectomy and to define a prognostic score.**

Methods. **From January 2000 to December 2010, we retrospectively reviewed clinicopathologic and oncological factors in a multicenter cohort of 468 malignant pleural mesothelioma patients undergoing extrapleural pneumonectomy. LTS was defined as survival longer than 3 years. Associations were evaluated using χ^2, Student's *t*, and Mann-Whitney *U* tests. Logistic regression, Cox regression hazard model, and bootstrap analysis were applied to identify outcome predictors. Survival curves were calculated by the Kaplan-Meier method. Receiver operating characteristic analyses were used to estimate optimal cutoff and area under the curve for accuracy of the model.**

Results. **Overall, 107 patients (22.9%) survived at least 3 years. Median overall, cancer-specific, and disease-free survival times were 60 (95% confidence interval [CI], 51 to 69), 63 (95% CI, 54 to 72), and 49 months (95% CI, 39 to 58), respectively. At multivariate analysis, age (odds ratio, 0.51; 95% CI, 0.31 to 0.82), epithelioid histology (odds ratio, 7.07; 95% CI, 1.56 to 31.93), no history of asbestos exposure (odds ratio, 3.13; 95% CI, 1.13 to 8.66), and the ratio between metastatic and resected lymph nodes less than 22% (odds ratio, 4.12; 95% CI, 1.68 to 10.12) were independent predictors of LTS. According to these factors, we created a scoring system for LTS that allowed us to correctly predict overall, cancer-specific, and disease-free survival in the total sample, obtaining two different groups with favorable or poor prognosis (area under the curve, 0.74; standard error, 0.04; $p < 0.0001$).**

Conclusions. **Our prognostic model facilitates the prediction of LTS after surgery for malignant pleural mesothelioma and can help to stratify the outcome and, eventually, tailor postoperative treatment.**

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Malignant pleural mesothelioma (MPM) is a fatal asbestos-related tumor that is increasing in incidence worldwide [1]. Despite various attempts at treatment, its clinical course remains rapid and unfavorable. Surgical resection is often contraindicated as a result of cardiopulmonary comorbidities, older age, and advanced disease; in such cases, palliative therapies led to a median survival of less than 12 months [2]. In regards to which is the best surgical strategy in surgically fit patients, extrapleural pneumonectomy (EPP) represents the preferred procedure for most surgeons; however, similar to untreated patients, the prognosis after EPP alone remains poor (approximately 10 months) [3].

Despite growing evidence supporting that multimodality therapy in MPM has been associated with better survival (approximately 18 months) [4], it is still unclear

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Abbreviations and Acronyms

CI	= confidence interval
DFS	= disease-free survival
EPP	= extrapleural pneumonectomy
LN	= lymph node
LTS	= long-term survival
MPM	= malignant pleural mesothelioma
OR	= odds ratio
OS	= overall survival
RL	= ratio between metastatic and resected lymph nodes
ROC	= receiver operating characteristic
STS	= short-term survival

why a small proportion of patients (10% to 20%) obtain valid benefits from such treatment and experience long-term survival (LTS) [5, 6]. In this setting, many authors have analyzed factors mainly affecting survival in the entire cohort of patients receiving either multimodal or palliative treatment. Conversely, relatively few data are available on the subset of LTS patients undergoing surgery.

The aim of this multicenter study was to analyze the predictors of outcome in a cohort of surgically treated long-term survivors. Furthermore, on the basis of our results, we have proposed a multivariate scoring system to predict survival after EPP.

Material and Methods

Patients

With the institutional review board's approval (protocol no. 601/14), we retrospectively reviewed the clinical and surgical records of 518 patients undergoing EPP with radical intent for MPM in nine major referral centers for thoracic surgery in Italy during the period January 2000 and December 2010. To minimize the confounding bias of deaths related to comorbidity, this study excluded 50 patients who died within 90 days after surgery; thus, a total of 468 patients (median age, 61 years; range, 31 to 79 years; male/female ratio, 3.8) surviving at least 4 months were included in our analysis.

The preoperative workup included physical and physiologic examinations and imaging. Overall, clinical stage was based on total body computed tomography scan and, whenever possible, positron emission tomography findings. All patients had histologic confirmation before treatment by videothoracoscopic- or computed tomographic–guided transparietal biopsy. A talc pleurodesis was also performed in 63.2% of cases. Clinical and pathologic stages were defined according to the TNM manual (7th edition) [7].

All patients underwent EPP with en bloc excision of the parietal pleura with the entire lung, hemidiaphragm, and pericardium plus reconstruction of the diaphragm and pericardium using a synthetic or bovine prosthesis, as recommended by Wolf and colleagues [8]. The surgical access varied between a single and double thoracotomy according to the surgeon's preference. A systematic lymphadenectomy was performed according to the technique reported by Graham and associates [9]. Detailed information regarding histologic type and lymph nodes (LNs) were collected from final pathologic findings. Epithelial MPM was the most common histologic type reported (85.0%). The median number of resected LNs was 11 (range, 1 to 87), with pathologic N0, N1, N2, and N3 rates of 59.0%, 12.4%, 28.1%, and 0.5%, respectively.

In this series, oncologic treatments varied over the years according to different institutional treatment trials. Induction chemotherapy was given to 51.5% of patients, with cisplatin plus pemetrexed as the preferred regimen (65% of patients receiving neoadjuvant treatment). Adjuvant therapy was administered to 69.9% of cases (chemotherapy alone, 11.9%; radiotherapy alone, 53.5%; chemotherapy plus radiotherapy, 34.6%). Trimodal therapy (induction therapy plus EPP plus adjuvant treatment) was performed in 47.1% of patients.

Follow-up data regarding the clinical outcomes were collected from patient medical charts and from interviews with patients, their next of kin, and their general practitioners. Oncologic data were available for all patients with a median follow-up time of 18.2 months (range, 4 to 140 months). A total of 395 patients with at least 36 months' surveillance were evaluated for outcome analysis.

Statistical Analysis

LTS was defined as survival longer than two times the median overall survival (OS; 18 months) reported in our previous study [10]. Patients were stratified into two groups according to LTS: patients surviving at least 36 months (LTS group) and those surviving between 4 and 35 months (short-term survival [STS] group) after EPP.

Descriptive statistics were used to summarize study information. The correlation among variables was analyzed according to χ^2, Student's t, and Mann-Whitney U (nonparametric) tests. Univariate and multivariate regression models (forward selection, enter/remove limits, $p = 0.10$ and $p = 0.15$) were applied to identify those variables that may play a role in predicting LTS (logistic regression model) and disease-free survival (DFS) and OS (Cox proportional hazard model). The assessment of interactions between significant investigation variables was taken into account when developing the multivariate model.

The receiver operating characteristic (ROC) curve analysis was adopted for dichotomization according to outcome. The ROC analysis allowed us to assess the predictive accuracy of the prognostic model by the area under the curve determination. Cancer-specific survival, DFS, and OS were calculated by the Kaplan-Meier product-limit method from the date of surgery until relapse, cancer-related death, or death for any cause at last follow-up. The log-rank test was used to assess differences among subgroups. Significance was defined as a probability value less than 0.05. The SPSS (version 21.0; SPSS Inc., Chicago, IL) and MedCalc (version

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