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Impact of mesothelioma histologic subtype on outcomes in the Surveillance, Epidemiology, and End Results database

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ABSTRACT

Background: This study was conducted to determine how malignant pleural mesothelioma (MPM) histology was associated with the use of surgery and survival.

Methods: Overall survival of patients with stage I–III epithelioid, sarcomatoid, and biphasic MPM in the Surveillance, Epidemiology, and End Results database from 2004–2010 was evaluated using multivariate Cox proportional hazards models.

Results: Of 1183 patients who met inclusion criteria, histologic subtype was epithelioid in 811 patients (69%), biphasic in 148 patients (12%), and sarcomatoid in 224 patients (19%). Median survival was 14 mo in the epithelioid group, 10 mo in the biphasic group, and 4 mo in the sarcomatoid group ($P < 0.01$). Cancer-directed surgery was used more often in patients with epithelioid (37%, 299/811) and biphasic (44%, 65/148) histologies as compared with patients with sarcomatoid histology (26%, 58/224; $P < 0.01$). Among patients who underwent surgery, median survival was 19 mo in the epithelioid group, 12 mo in the biphasic group, and 4 mo in the sarcomatoid group ($P < 0.01$). In multivariate analysis, surgery was associated with improved survival in the epithelioid group (hazard ratio [HR] 0.72; $P < 0.01$) but not in biphasic (HR 0.73; $P = 0.19$) or sarcomatoid (HR 0.79; $P = 0.18$) groups.

Conclusions: Cancer-directed surgery is associated with significantly improved survival for MPM patients with epithelioid histology, but patients with sarcomatoid and biphasic histologies have poor prognoses that may not be favored by operative treatment. The specific histology should be identified before treatment, so that surgery can be offered to patients with epithelioid histology, as these patients are most likely to benefit.

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1. Introduction

Malignant pleural mesothelioma (MPM) is a rare but aggressive and often fatal malignancy [1]. Most patients present with advanced disease, and the median overall survival is approximately 1 y [1]. The recommended treatment for mesothelioma is dependent on both stage and histology. Previous studies have found epithelioid MPM to portend a better prognosis than sarcomatoid or biphasic histologic subtypes [2–12]. Therefore, it is recommended that patients with medically operable clinical stage I–III epithelioid or mixed histology disease undergo multimodality therapy including surgery [1]. Current National Comprehensive Cancer Network (NCCN) guidelines [13] recommend chemotherapy alone for all patients who have sarcomatoid histology, as well as for medically inoperable or clinical stage IV patients.

Despite these guidelines, the relative benefit of surgery for mesothelioma compared with nonsurgical therapy has not been well quantified, and different opinions exist with regards to benefit of surgery when applied alone or in conjunction with chemotherapy [14–17]. Furthermore, there is a lack of data to establish the relative efficacy of extrapleural pneumonectomy (EPP) compared with pleurectomy and decortication (P/D), leading to further controversy [15,18–22]. A randomized feasibility study did not find that EPP improved outcomes compared with chemotherapy alone for patients with mesothelioma [23–25]. In addition, several studies have shown that a small but significant number of patients with nonepithelioid MPM undergo surgery as the initial cancer-directed therapy [2,8,10,11,14]. This study was undertaken to improve the level of evidence available to clinicians who are considering offering surgery to patients with mesothelioma using a population-based database to better quantify the survival benefits of surgery. Specifically, the purpose of this study was to assess outcomes of patients who did or did not receive cancer-directed surgery for epithelioid, sarcomatoid, and biphasic subtypes of MPM stratified by stage using population-based data from the United States National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program database that has captured a geographically diverse cohort of patients diagnosed with MPM.

2. Methods

We reviewed the SEER database from 2004–2010 for patients with stage I–III MPM by International Classification of Diseases for Oncology, 3rd Edition morphology codes 9050–9053 and 9055. Cases before 2004 were not included for analysis because specific American Joint Committee on Cancer's TNM staging (sixth edition) [26] information was not recorded in the SEER database until 2004. Only patients whose histologic subtype was known were included in the study. For this study, we used the more commonly used term "sarcomatoid" when describing the mesotheliomas recorded as "fibrous" in SEER because fibrous mesothelioma in SEER refers to sarcomatoid mesothelioma as well as the different subtypes of sarcomatoid mesothelioma (including spindled, sarcomatoid and desmoplastic mesothelioma, and fibrous mesothelioma not otherwise specified) [8,27]. The SEER database records whether cancer-directed surgery was performed, where cancer-directed surgery includes both curative and palliative surgery [8,28]. Frequency of EPP and P/D is not recorded. Patients were further excluded if laterality (right or left) was unknown or if race was unknown. Patients with stage IV disease were excluded, as surgery is usually not indicated as a treatment option for this group regardless of histology. In addition, one patient identified as having T stage = 0 was also excluded from analysis because of concerns over discordancy in staging. Extracted variables include age, sex, race, marital status, laterality, histology, surgery, stage, reasons for not performing surgery, year of diagnosis, vital status, and time to last available reported survival time point.

Patients were stratified into subgroups based on histology and SEER-recorded overall stage. Our primary analysis was to examine the effects of cancer-directed surgery according to histologic MPM subtype and stage on overall survival. We assessed for predictors of receiving cancer-directed surgery using univariate and multivariate logistic regression analysis including age at diagnosis, sex, race, histology, marital status, stage, radiation use, and laterality in the model. Kaplan–Meier analysis was performed to determine the association of histologic subtype and tumor stage on survival. Surgery as a predictor of survival was assessed using multivariate Cox proportional hazards model for each histologic subtype. The following covariates were used: age at diagnosis, sex, known race, known histology, marital status (known married or unmarried), radiation use, laterality (known right or left-sided primary disease), and disease stage (I–III) according to the American Joint Committee on Cancer's TNM staging (sixth edition) [26].

Cancer-directed surgery in the SEER database does not include details regarding the specific type of surgery. To assess the potential impact of including palliative procedures in the surgical group, a sensitivity analysis was performed where only patients who received likely curative-intent surgery (SEER codes of "total surgical removal of primary site" and "radical surgery") were considered to have undergone surgical resection. To assess the potential selection bias of surgery being more likely used in patients with less extensive local disease or smaller tumor burdens, we also performed a sensitivity analysis where we included T and N statuses into our Cox proportional hazard models.

All statistical analyses were performed using Stata Statistical Software: Release 12.0, StataCorp LP, College Station, TX. A P value of 0.05 was used to define statistical significance. Exemption from institutional review board approval was obtained before data analysis.

3. Results

Of 4935 patients with MPM identified in the SEER database between 2004 and 2010, 1183 patients met study criteria (Fig. 1). The majority of patients were white, male, and aged ≥70 y, with a right-sided disease (Table 1). A total of 69% of patients had epithelioid histology (n = 811), whereas 19% had sarcomatoid histology (n = 244) and 12% had biphasic histology (n = 148).