Original Study

Impact of Age on Long-Term Outcomes of Surgery for Malignant Pleural Mesothelioma

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Abstract

The impact of age on outcomes in 879 patients with malignant pleural mesothelioma was evaluated using the Surveillance, Epidemiology, and End Results database with Cox proportional hazard models and propensity score-matched analysis. Surgery was found to be associated with improved survival compared with nonoperative management for both patients younger and older than 70 years, suggesting a potential benefit of surgery to elderly patients.

Background: Although malignant pleural mesothelioma (MPM) is generally a disease associated with more advanced age, the association of age, treatment, and outcomes has not been well-characterized. We evaluated the impact of age on outcomes in patients with MPM to provide data for use in the treatment selection process for elderly patients with potentially resectable disease. **Patients and Methods:** Overall survival (OS) of patients younger than 70 and 70 years or older with Stage I to III MPM who underwent cancer-directed surgery or nonoperative management in the Surveillance, Epidemiology, and End Results database (2004-2010) was evaluated using multivariable Cox proportional hazard models and propensity score-matched analysis. **Results:** Cancer-directed surgery was used in 284 of 879 (32%) patients who met inclusion criteria, and was associated with improved OS in multivariable analysis (hazard ratio, 0.71; $P = .001$). Cancer-directed surgery was used much less commonly in patients 70 years and older compared with patients younger than 70 years (22% [109/497] vs. 46% [175/382]; $P < .001$), but patients 70 years and older had improved 1-year (59.4% vs. 37.9%) and 3-year (15.4% vs. 8.0%) OS compared with nonoperative management. The benefit of surgery in patients 70 years and older was observed even after propensity score-matched analysis was used to control for selection bias. **Conclusion:** Surgical treatment is associated with improved survival compared with nonoperative management for both patients younger than 70 years and patients aged 70 years or older.

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Introduction

Malignant pleural mesothelioma (MPM) is a highly aggressive cancer with a relatively poor prognosis and a median survival of approximately 12 months.[1-3] Owing to a long latent stage, 58% of patients diagnosed with MPM are over the age of 70 years upon presentation,[4] and the incidence of elderly patients diagnosed with MPM globally is increasing.[5-10] Although increasing age has consistently been shown to be associated with worse survival,[3] there are very few studies that report specific outcomes among elderly patients. In particular, the survival benefit of surgery for elderly patients with MPM has not been clearly established.[3,11] Quantitative data to support difficult treatment decisions about when to offer surgery for elderly MPM patients are needed, as a subset of these patients with favorable prognostic factors may experience extended survival by undergoing cancer-directed surgery. In the present study, we analyzed the Surveillance, Epidemiology, and End Results (SEER) database from 2004 to 2010 to evaluate the survival of elderly patients with MPM and to determine how age impacts the potential benefits of surgery for patients with MPM. Our objective

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is to provide clinicians with quantifiable evidence that can be used in the treatment decision process for elderly patients with MPM and to specifically test the hypothesis that surgery is associated with survival benefit in elderly patients.

Materials and Methods

This study of the SEER program database was approved by the Institutional Review Board at Duke University. Patients included in this study were those 18 years or older with epithelioid and biphasic MPM diagnosed between 2004 and 2010. Only cases identified from 2004 to 2010 were evaluated because specific American Joint Committee on Cancer's TMN staging (Sixth Edition)[12] information was available in SEER only from 2004 to 2010, as staging was categorized as "early" and "late" in earlier SEER periods.[13] Patients were selected using International Classification of Diseases for Oncology, Third Edition morphology codes 9050 to 9055. Only patients with known nonsarcomatoid histology, laterality, and surgery information who had pathologically proven stage I, II, or III malignant mesothelioma of pleura and lung were included. Only epithelioid and biphasic histologies were included, although of note, the pathologic diagnosis of biphasic may be dependent on the volume of tissue available for analysis. Patients with sarcomatoid histology and stage IV disease were excluded because these patients are generally not considered candidates for surgery under current guidelines.[3] Other exclusion criteria are similar to as previously described, and we excluded all postmortem cases, any case not confirmed microscopically, and disease described as retroperitoneal, peritoneal, genital, heart, mediastinum, soft tissue, digestive, other, and unknown.[13] Variables analyzed included age, gender, race, marital status, laterality, histology, surgery, stage, year of diagnosis, vital status, and time to last available reported survival time point. Chemotherapy information is not recorded in the SEER database.

Patients were stratified into subgroups based on age and SEER-recorded TNM stage. The primary analysis examined the effects of patient age strata and stage on overall survival of patients undergoing cancer-directed surgery and nonoperative management. Differences in patient and treatment characteristics were assessed using the Pearson chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. Overall survival analyses for patients, stratified by age and treatment, were performed by Kaplan-Meier analysis. For the entire cohort, predictors of survival were calculated using a multivariable Cox proportional hazards model. In an attempt to better identify patients who were likely to benefit from surgery, separate multivariable Cox proportional hazards models were performed to estimate predictors of survival for patients who had undergone cancer-directed surgery, and for patients age 80 years and older. Covariates included in both Cox models were known age, gender, race, marital status, laterality, radiation use, histology, and disease stage (I, II, III), according to the American Joint Committee on Cancer's Cancer Staging Manual, Sixth Edition.[12]

A propensity-matched analysis, which aimed to create a cohort of nonoperative patients who, based on known and possible confounders, would have a similar propensity to receive a cancer-directed operation as the patients undergoing cancer-directed surgery, was performed as previously described to attempt to control for nonrandom differences between patients who did and did not have cancer-directed surgery.[14] Briefly, to assess the potential impact of age on the survival of cancer-directed surgery, patients were stratified into two groups: patients younger than 70 years old and patients 70 years or older. The patient- and disease-related variables chosen for the matching algorithm were felt to most likely act as confounders and were entered into a logistic regression model to calculate propensity scores; a radius-matching algorithm was used to find the most appropriate matched pairs. After propensity score-matching, differences between groups were assessed using standard summary statistics. The Kaplan-Meier method was used to assess overall survival across groups.

Cancer-directed surgery was defined from the SEER "surgery of the primary site" code and included codes 30 (simple partial surgical removal of primary site), 40 (total surgical removal of primary site), 50 (surgery stated to be "debulking"), and 60 (radical surgery). Because it is possible that some of these surgical procedures were palliative and not curative in intent, a sensitivity analysis was performed analyzing only patients who received surgery coded as "total surgical removal of primary site" and "radical surgery" in the SEER database to better estimate the true impact of curative-intent surgery.

Model diagnostics were assessed, no major model assumptions were violated, an affirmative decision was made to control for type I error at the level of the comparison, and a P value $< .05$ was used to indicate statistical significance for all comparisons and analyses. All statistical analyses were performed using Stata Statistical Software: Release 12.0 (StataCorp LP, College Station, TX).

Results

Baseline Characteristics

A total of 879 patients with stage I to III MPM of nonsarcomatoid histology from 2004 through 2010 were identified for inclusion in this study. Cancer-directed surgery was used in 32% (n = 284) of these patients. Baseline demographic, treatment, and tumor characteristics of patients who were managed nonoperatively and patients who underwent surgery are detailed in Table 1. Patients treated with surgery were younger, had higher stage disease, slightly higher frequency of biphasic disease, and were more likely to be married than patients who did not have surgery. Radiation therapy overall was used in the minority of patients, but was more likely to be used in patients who were also treated with surgery. The 30-day mortality of patients who did not receive surgery was 11.7% versus 4.3% for patients who underwent surgery ($P = .001$).

Survival Analysis of Patients Who Underwent Nonoperative Management Versus Cancer-Directed Surgery

Surgery was associated with better survival compared with nonoperative management in univariable analysis ($P < .001$; Figure 1). Specifically, the improvements in survival associated with surgery over nonoperative management were observed both in the short term (1-year survival 63% [95% confidence interval (CI), 57%-69%] versus 44% [95% CI, 39%-48%]) and midterm (3-year survival 21% [95% CI, 16%-27%] vs. 11% [95% CI, 8%-15%]). However, long-term survival was poor for both groups (5-year survival 8% [95% CI, 4%-14%] vs. 3% [95% CI, 1%-6%]) (Figure 1). In the Cox proportional hazards survival model, adjusted for available baseline characteristics (Table 2), use of cancer-directed