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

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Abstract

Introduction/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 MPM patients to provide data for use in the treatment selection process for elderly patients with potentially resectable disease.

Patients & Methods—Overall survival (OS) of patients younger than 70 and 70 years or older with Stage I–III MPM who underwent cancer-directed surgery or non-operative 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=0.001). Cancer-directed surgery was used much less commonly in patients 70 and older compared to patients younger than 70 (22% [109/497] versus 46% [175/382], p<0.001), but patients 70 and older had improved 1-year (59.4% versus 37.9%) and 3-year (15.4% versus 8.0%) OS compared to non-operative management. The benefit of surgery in patients 70 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 to non-operative management for both patients younger than 70 years and patients age 70 years or older.

MicroAbstract

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

Keywords

Geriatric; Survival; Operative; Non-sarcomotoid; Elderly

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] Due 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 2004–2010 to evaluate the survival of elderly MPM patients and to determine how age impacts the potential benefits of surgery for patients with MPM. Our objective 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 2004–2010 were evaluated because specific American Joint Committee on Cancer's TMN staging (6th 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 ICD-O-3 morphology codes 9050–9055. Only patients with known nonsarcomatoid histology, laterality and surgery information who had pathologically proven stage I, II and III malignant mesothelioma of pleura and lung were included. Only epithelioid and biphasic histologies are 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, including all postmortem cases; any case not confirmed microscopically; retroperitoneal, peritoneal, genital, heart, mediastinum, soft tissue, digestive, other, and unknown primary site.[13] Variables analyzed included age, sex, 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 non-operative management. Differences in patient and treatment characteristics were assessed using Pearson's chi-square test for categorical variables and 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, sex, 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, 6th ed.[12]

A propensity-matched analysis which aimed to create a cohort of non-operative 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 2 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 <0.05 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–III malignant pleural mesothelioma of non-sarcomatoid 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 non-operatively and patients who underwent surgery are detailed in Table 1. Patients treated with surgery were younger, had higher clinical 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=0.001).

Survival Analysis of Patients who underwent Non-operative management vs Cancer-directed Surgery

Surgery was associated with better survival compared to non-operative management in univariate analysis (p<0.001, Figure 1). Specifically, the improvements in survival associated with surgery over non-operative management were observed both in the short-term (1-year survival 63% [95% CI, 57–69%] vs 44% [95% CI, 39–48%]) and mid-term (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 surgery (HR 0.71; 95% CI: 0.58–0.86; p=0.001) was the strongest predictor of improved survival. Age (HR 1.03; 95%CI: 1.02–1.03; p<0.001) and biphasic histology (HR 1.51; 95% CI: 1.22–1.86; p<0.001) were associated with worse survival. These results did not significantly change in the sensitivity analysis that only included patients who were more likely have undergone curative-intent surgery (data not shown).

Outcomes stratified by age group

Baseline demographic characteristics and treatment for patients stratified by age younger than 70 years and 70 years and older are detailed in Table 3. As shown in the table, surgery was used much less often in the older group. However, cancer-directed surgery was associated with significantly better overall survival compared to non-operative management in univariate analysis for both patients younger than 70 years (p=0.01, Figure 2A) and 70 years and older (p<0.001, Figure 2B). The 30-day mortality of patients younger than 70 and those 70 and older was 4.6% and 13.0%, respectively (p<0.001). Table 4 details the short-term, mid-term, and long-term survival associated with surgery over non-operative management.

Survival Analysis of Patients who underwent Cancer-directed Surgery

Although both older and younger patient age groups obtained benefit from surgery, older age was a predictor of worse survival in survival analysis that only included patients who underwent cancer-directed surgery. Age less than 70 years was associated with superior survival when compared to age 70 and over (p=0.03) (Figure 3). In the Cox proportional hazards survival model, adjusted for available baseline characteristics (Table 5) and limited to patients who had undergone cancer-directed surgery, increasing age and biphasic histology were associated with worse survival.

Propensity analysis

Comparison of baseline patient characteristics after propensity matching between patients who underwent non-operative management and patients who underwent cancer-directed surgery, stratified by age younger than 70 or 70 years and older, is shown in Table 6. After propensity matching, there were no statistically significant differences between the operative and non-operative groups in any of the patient characteristics, and cancer-directed surgery continued to be associated with significantly better overall survival for both patients younger and older than 70 years (Figure 4A and Figure 4B). For patients younger than 70 years, the 30-day mortality was 5.7% in the non-operative group and 3.4% in the surgery group (p=0.46). For patients 70 years and older, the 30-day mortality was 12.8% in the non-operative group and 10.1% in the surgery group (p=0.60). These results did not significantly change when we focused the analysis to only patients who underwent likely curative-intent surgery.

Survival analysis of patients 80 years and older

The 1-, 3- and 5- year survival of patients 80 years and older of age was 34.1% (95% CI, 27.1–41.3%), 4.3% (95% CI, 1.5–9.4%), and 0.0% (95% CI, NA), respectively (Figure 5). Patients who are over 80 and underwent non-operative management have similar 1-, 3- and 5- year survival (34.3% [95% CI, 26.9–41.9%], 3.8% [95% CI, 1.1–9.4%] and 0.0% [95% CI, NA]), respectively, when compared with patients over 80 who underwent surgery (32.2% [95% CI, 12.2–54.3%], 6.4% [95% CI, 0.0–25.2%] and 0.0% [95% CI, NA]. In a separate Cox proportional hazards survival model limited to only patients 80 years old or greater, surgery was not associated with improved survival (HR, 0.96; 95% CI: 0.57–1.61; p=0.87).

Discussion

In this population-based study, we found that age was an important determinant both for survival and for the use of cancer-directed surgery. Patients age 70 and older were much less likely to have surgery compared to younger patients. Patients 70 years and older who underwent cancer-directed surgery had a worse survival compared to patients younger than 70 years, but surgery was associated with higher survival when compared to non-operative management in both patient age groups. However, in a subset analysis of patients greater than 80 years old, we found that surgery did not confer a survival advantage after multivariable adjustment. These data suggest that while patients >70 years can still derive clear benefit from surgery, these potential advantages may not translate in patients >80 years.

This data can be used by clinicians when considering treatment for older patients with MPM, as currently available evidence generally does not include a significant amount of elderly patients or provide specific estimates of the impact of age on outcomes. While virtually every study of mesothelioma has shown that increased age is associated with worse survival,[3] the majority of these studies have a median age ranging from 57 to 63 years[10,11,15–22] and there are very few studies that report specific outcomes for elderly patients (>70 years). Spaggiari et al. reported the outcomes of 518 patients with MPM who underwent extrapleural pneumonectomy, of whom 62 patients were greater than 70 years[15] and had 1-, and 3-year survivals of 58% and 16%. In 2008, Ceresoli et al. reported the outcomes of 48 elderly patients > 70 years who had participated in two phase II trials of pemetrexed and carboplatin and were not surgical candidates; 1-year survival for these patients was 48%. In 2014, Ceresoli et al. reported the outcomes of 241 patients with MPM aged 70 years and older, of whom 18 had underwent surgery. The authors did not report the survival for patients who underwent surgery, but did note that for their entire cohort, median overall survival was 11.4 months and age > 75 years was associated with worse survival in multivariable analysis.[10] Our study, with a median age of 74 and 67 in the non-operative and surgical groups, respectively, has an older population than most studies of MPM patients,[10,11,15–22] although our survival results are comparable to those reported by Spaggiari and colleagues and Ceresoli and colleagues.

Advantages of using SEER data for this study include the large number of patients available for analysis from an unbiased population-based registry, with volume sufficient to perform subgroup analyses. The limitations of the current study are similar to as previously discussed[4,23] and these include lack of information regarding patient comorbidities, socioeconomic status, chemotherapy regimens, details regarding the operation, and details regarding clinical and pathologic staging. We would expect that most patients would have received some form of chemotherapy in addition to cancer-directed surgery to ensure complete removal of microresidual disease;[24,25] however, there are no details in the SEER database regarding the specific treatment type and duration. Another limitation of the SEER database is that it does not provide details on the type of cancer-directed surgery the patient received. Therefore, our results may have included patients who received palliative-intent surgery and may underestimate the impact of curative-intent surgery. To better evaluate whether curative-intent surgery is beneficial, 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. The results from this analysis were consistent with the results from our primary analysis of patients receiving any type of cancer-directed surgery. An additional limitation, which has been discussed in detail previously,[23] is with regards to staging data recorded in the SEER database. In SEER, the tumor stage that is recorded is based on pathological information when surgery was the initial cancer-directed therapy, and clinical information if patients had neoadjuvant therapy prior to surgery, or if surgery was not performed.[23] Thus, patients in the operative group had pathologic staging recorded, and patients in the non-operative group had clinical staging recorded. In the present study, patients in the surgery group had higher disease stage, which is consistent with previous findings from studies showing that clinical staging underestimates disease extent.[26,27]

In summary, surgical treatment of mesothelioma is associated with improved long-term outcomes, even among the elderly, in a national population-based cancer database. Although this database has inherent limitations, the analysis does suggest that appropriately selected elderly patients potentially derive benefit from surgery. While these results cannot be used to show definitive benefit to surgery in all elderly patients, the analysis does suggest that advanced age alone should not be used as an absolute contraindication to surgery and that even elderly patients should go through a multidisciplinary evaluation to decide if surgery should be part of their treatment regimen. While patients older than 70 years may potentially derive clear benefit from surgery, these potential advantages may not translate in patients older than 80 years. Future research should focus on evaluating the comorbidities and characteristics that are most important in the elderly population to optimize both perioperative outcomes and long-term survival.

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Clinical Practice Points

Malignant pleural mesothelioma (MPM) is a highly aggressive cancer associated with poor survival. It is known that increased age is associated with worse survival, but few studies report outcomes for patients with mesothelioma of advanced stage. In particular, the survival benefit of surgery for elderly patients with MPM has not been clearly established. In this study, surgery was found to be associated with improved survival compared to non-operative management for both MPM patients younger and older than 70 years, even after propensity-score matching. The analysis suggests that surgery confers potential survival benefit to appropriately selected elderly patients and that advanced age alone should not be an absolute contraindication to surgery. Based on the study findings, elderly patients with MPM should go through a multidisciplinary evaluation to decide if surgery should be part of their treatment regimen.

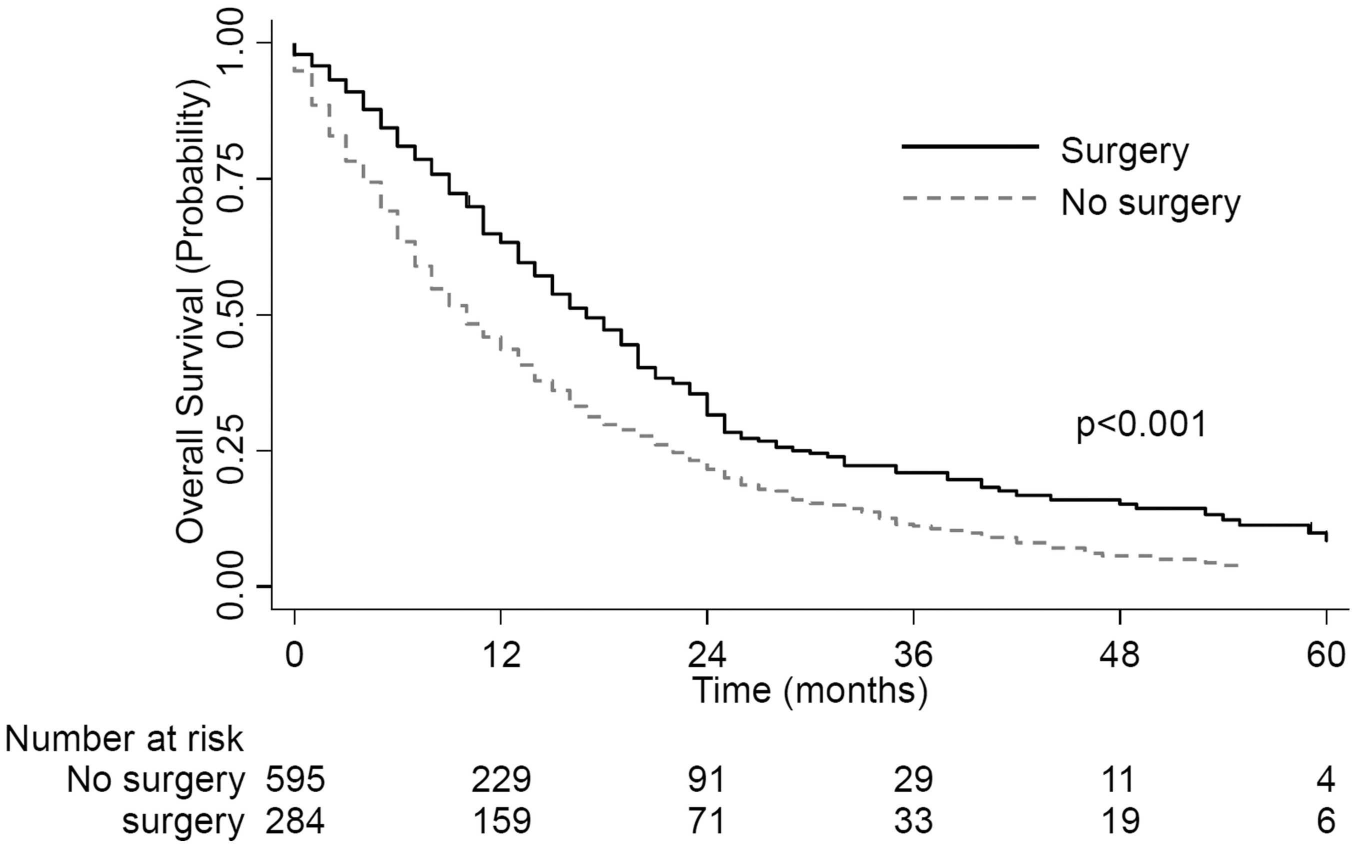
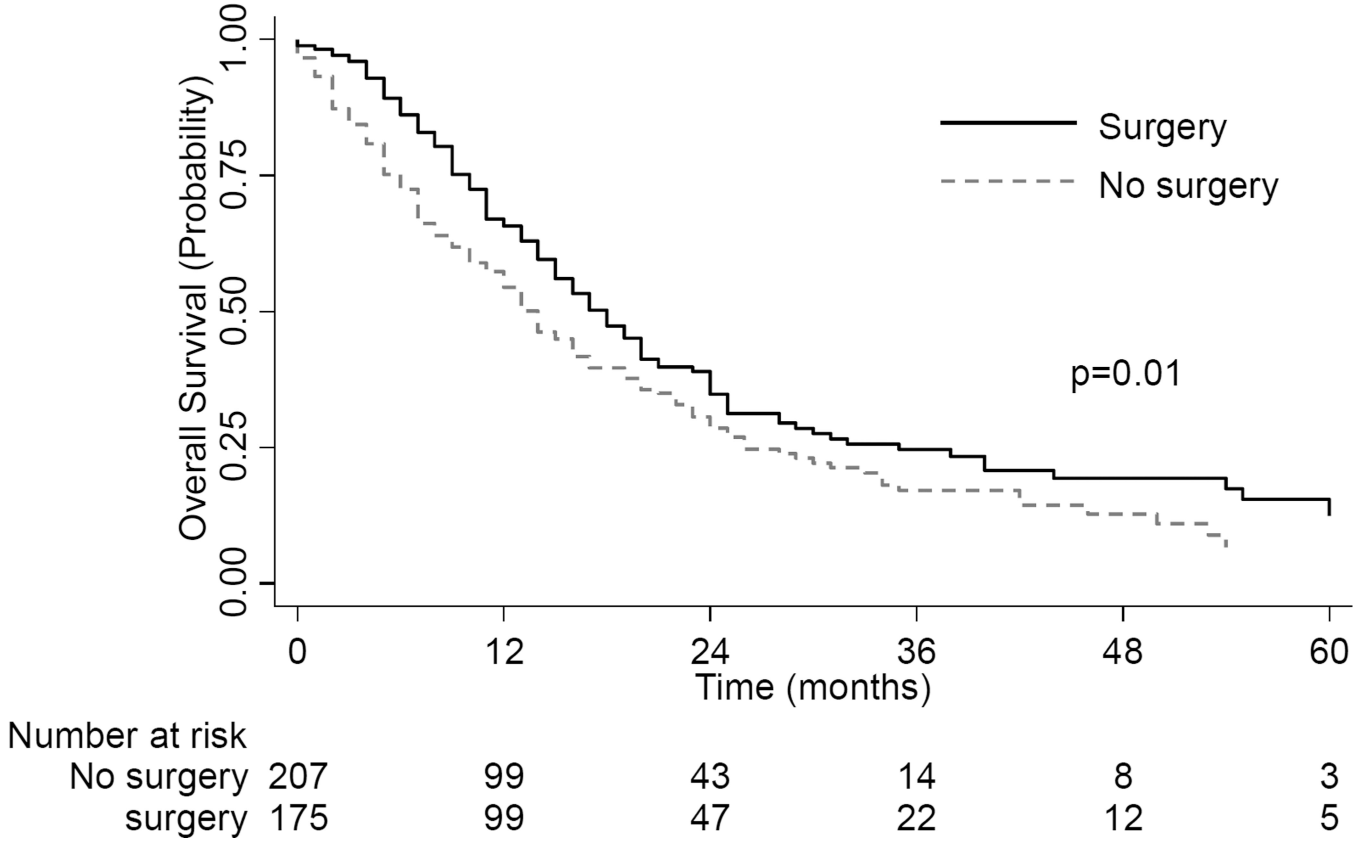


Figure 1.

Kaplan-Meier survival for patients with mesothelioma, stratified by treatment.


Overall Survival (Probability)
1.00
0.75
0.50
0.25
0.00
Surgery
No surgery
p=0.01
0
12
24
36
48
60
Time (months)
Number at risk
No surgery 207 99 43 14 8 3
surgery 175 99 47 22 12 5

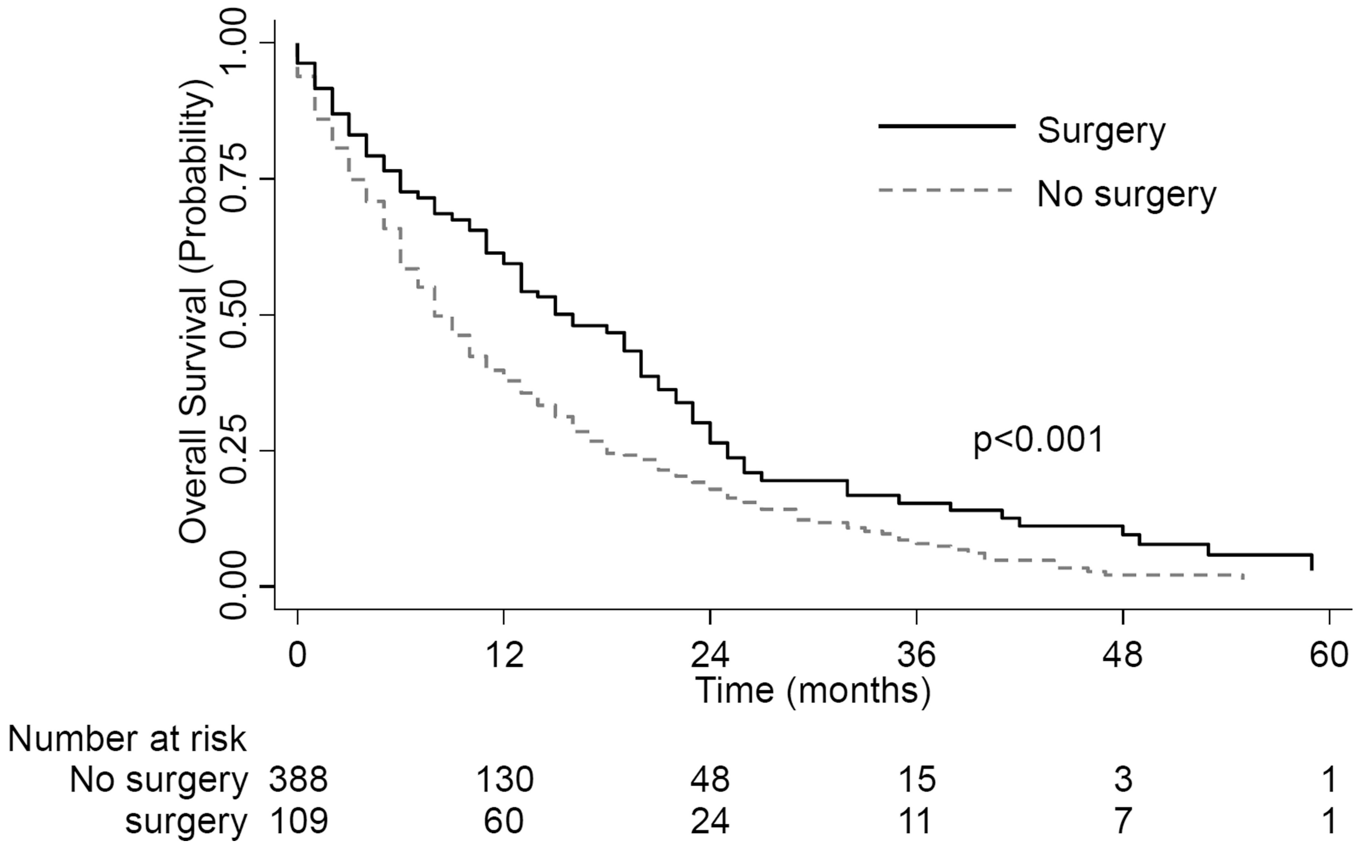


Figure 2.

Kaplan-Meier overall survival in patients younger than 70 years old, cancer-directed surgery vs no surgery (A), and patients 70 years and older, cancer-directed surgery vs no surgery (B).

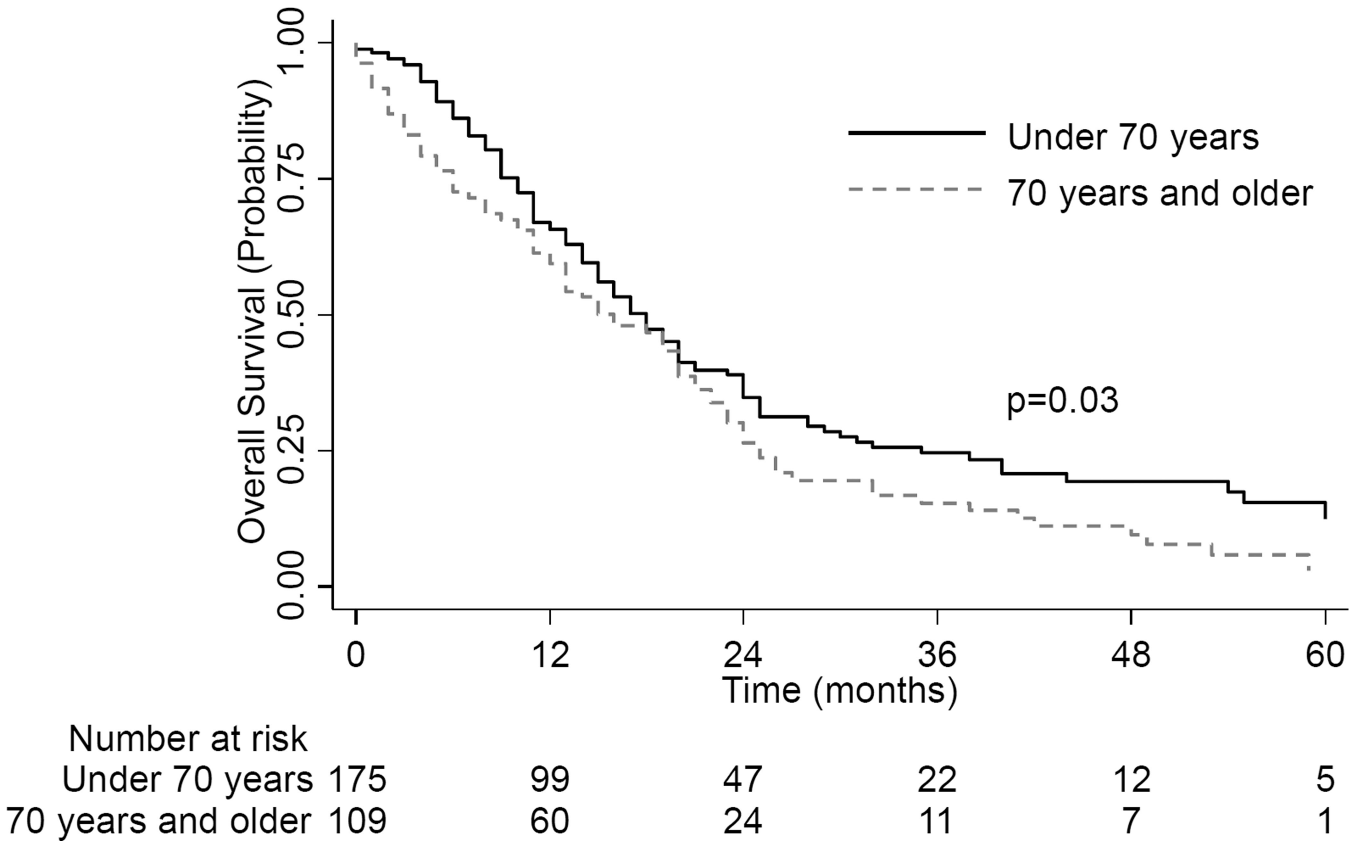
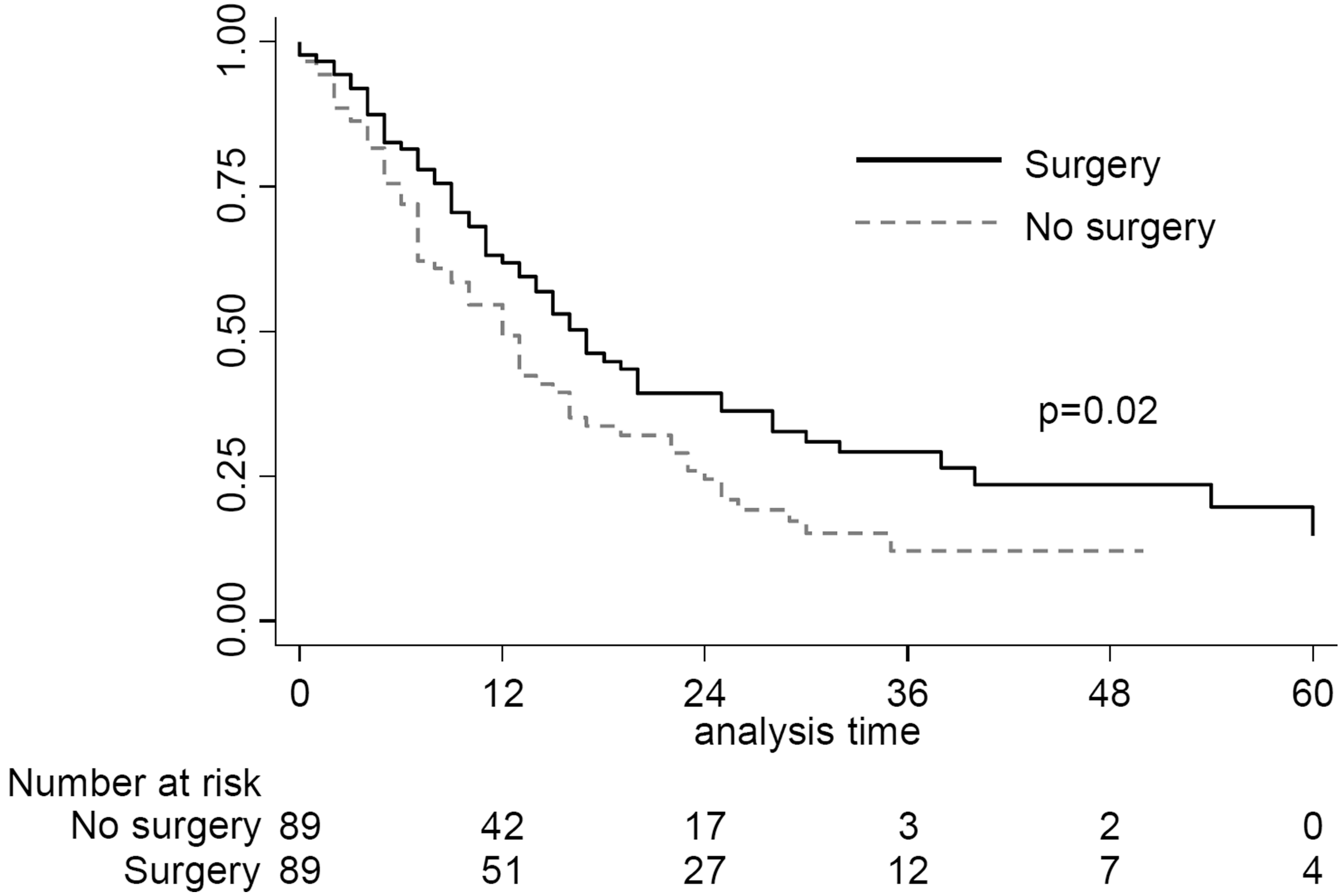


Figure 3.

Kaplan-Meier overall survival in patients with cancer-directed surgery, stratified by age less than 70 and age 70 years and older.


1.00
0.75
0.50
0.25
0.00
Surgery
No surgery
p=0.02
0
12
24
36
48
60
analysis time
Number at risk
No surgery 89 42 17 3 2 0
Surgery 89 51 27 12 7 4

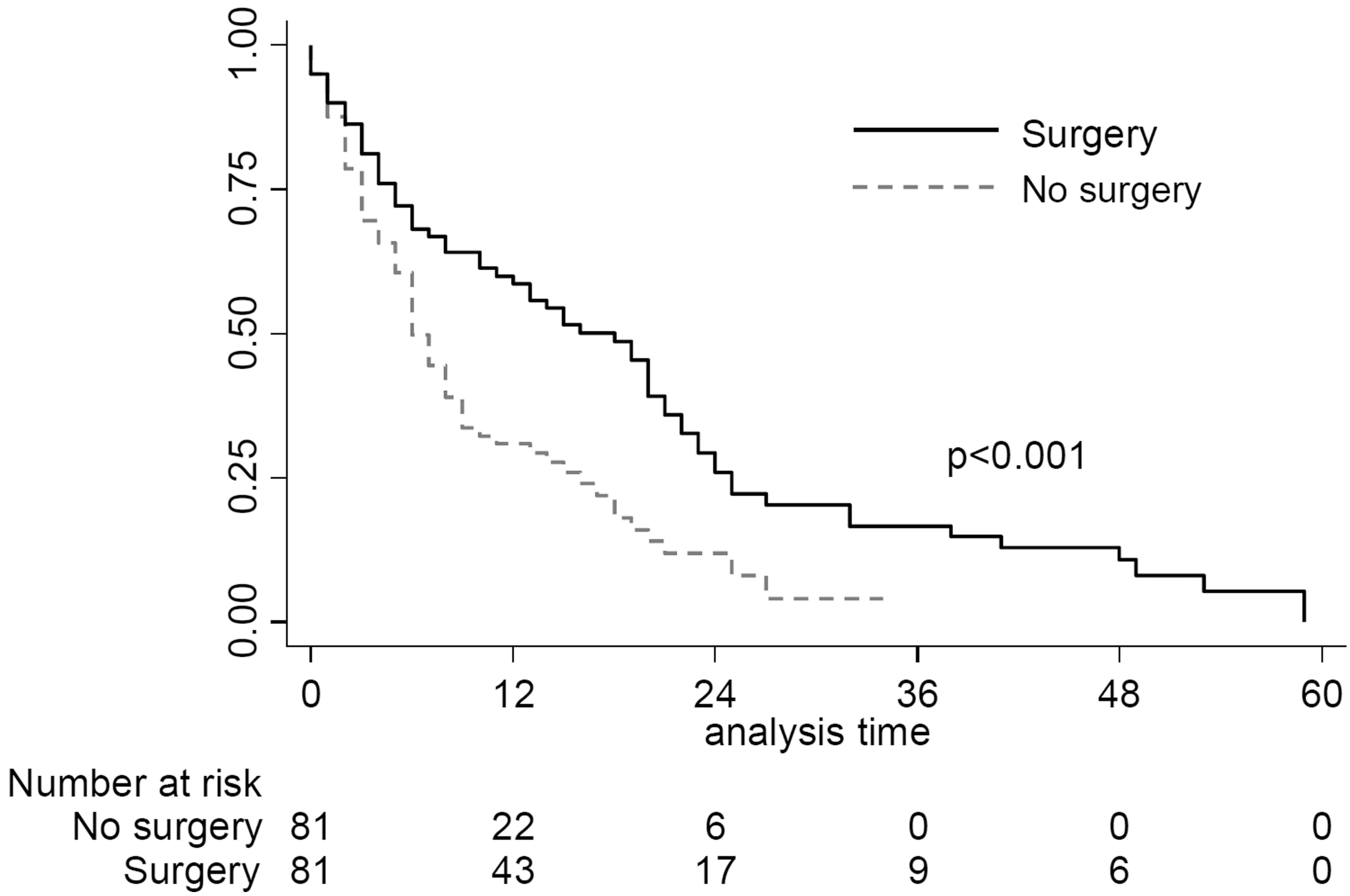


Figure 4.

Kaplan-Meier overall survival in matched patients younger than 70 years old, cancer-directed surgery vs no surgery (A), and matched patients 70 years and older, cancer-directed surgery vs no surgery (B).

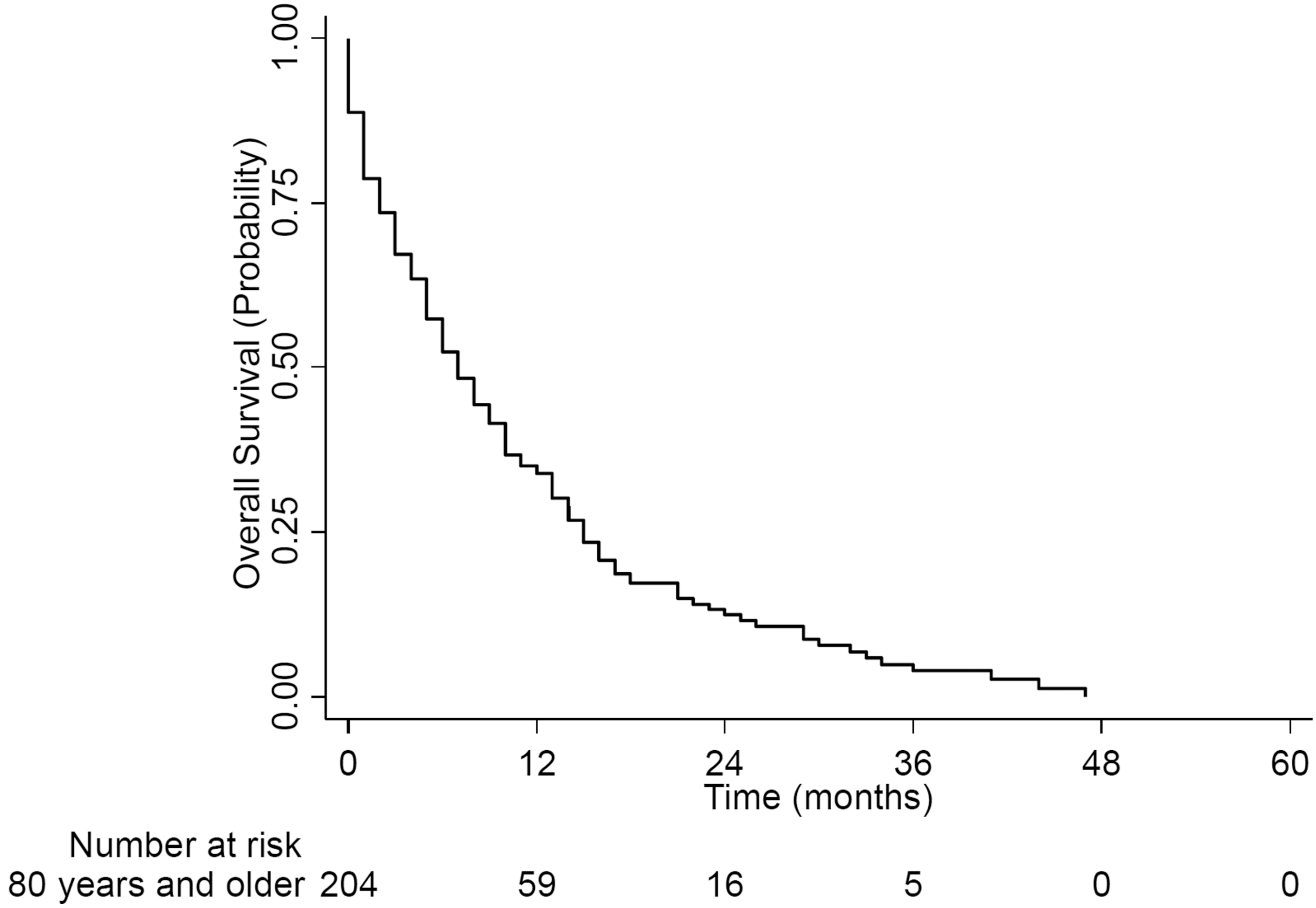


Figure 5.
Kaplan-Meier overall survival of patients 80 years and older.

Table 1

Preoperative Characteristics of Patients (n = 879)

Characteristics	No Surgery (n=595)	Surgery (n=284)	p Value
Age, y, median	74	67	<0.001
Age groups, n (%)			<0.001
<70 y	207 (35)	175 (62)	
70–79 y	216 (36)	89 (31)	
80+ y	172 (29)	20 (7)	
Sex, n (%)			0.52
Male	464 (78)	216 (76)	
Female	131 (22)	68 (24)	
Race, n (%)			0.36
White	551 (93)	268 (94)	
Black	29 (5)	8 (3)	
Other	15 (3)	8 (3)	
Marital status, n (%)			0.01
Married	385 (65)	210 (74)	
Not Married	200 (34)	73 (26)	
Other	10 (2)	1 (0)	
Laterality, n (%)			0.77
Right	352 (59)	165 (58)	
Left	243 (41)	119 (42)	
Histology, n (%)			0.04
Epithelioid	512 (86)	229 (81)	
Biphasic	83 (14)	55 (19)	
Disease Stage, n (%)			<0.001
Stage 1	260 (44)	46 (16)	
Stage 2	171 (29)	70 (25)	
Stage 3	164 (28)	168 (59)	
Radiotherapy, n (%)			<0.001
No radiotherapy	568 (95)	184 (65)	
Radiotherapy	27 (5)	100 (35)	

Table 2

Risk of Death for Patients with Mesothelioma from 2004 to 2010.

		95% Confidence Interval		
Predictor	**Hazard Ratio**	**Lower**	**Upper**	**p Value**
Age	1.03	1.02	1.03	<0.001
Female Sex	0.88	0.72	1.07	0.21
Race				
White	Ref	Ref	Ref	Ref
Black	1.20	0.83	1.74	0.33
Other	1.15	0.70	1.87	0.58
Marital Status				
Unmarried	Ref	Ref	Ref	Ref
Married	0.88	0.74	1.05	0.16
Laterality				
Right	Ref	Ref	Ref	Ref
Left	0.91	0.78	1.07	0.24
Histology				
Epithelioid	Ref	Ref	Ref	Ref
Biphasic	1.51	1.22	1.86	<0.001
Stage				
1	Ref	Ref	Ref	Ref
2	0.88	0.72	1.08	0.21
3	1.18	0.97	1.44	0.10
Surgery	0.71	0.58	0.86	0.001
Radiotherapy	0.96	0.75	1.25	0.78

Cox proportional hazards model adjusting for age, sex, race, marital status, laterality, histology, disease stage, surgery, and radiation therapy.

Table 3

Baseline Characteristics of Patients Stratified by Age Group

Characteristic	Patients under 70 (n=382)	Patients 70 and older (n=497)	p Value
Age, y, median	63	78	<0.001
Sex, n (%)			0.37
Male	290 (76)	390 (78)	
Female	92 (24)	107 (22)	
Race, n (%)			0.42
White	354 (93)	465 (94)	
Black	15 (4)	22 (4)	
Other	13 (3)	10 (2)	
Marital Status, n (%)			0.04
Married	276 (72)	319 (64)	
Unmarried	101 (26)	172 (35)	
Other	5 (1)	6 (1)	
Laterality, n (%)			0.82
Right	223 (58)	294 (59)	
Left	159 (42)	203 (41)	
Histology, n (%)			0.26
Epithelioid	316 (83)	425 (86)	
Biphasic	66 (17)	72 (14)	
Stage, n (%)			<0.001
Stage 1	104 (27)	202 (41)	
Stage 2	97 (25)	144 (29)	
Stage 3	181 (47)	151 (30)	
Surgery, n (%)			<0.001
No surgery	207 (54)	388 (78)	
Surgery	175 (46)	109 (22)	
Radiotherapy, n (%)			<0.001
No radiotherapy	297 (78)	455 (92)	
Radiotherapy	85 (22)	42 (8)	

Table 4

Survival estimates by age and intervention

	Non-operative management, % [95% CI]	Surgery, % [95% CI]
Age <70		
1-year	54 [47–61])	66 [58–73]
3-year	17 [11–24]	25 [17–32]
5-year	7[2–14]	12 [6–22]
Age ≥70		
1-year	38 [33–43]	59 [49–68]
3-year	8 [5–12]	15 [8–24]
5-year	1 [0–4]	3 [0–11]

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Table 5

Risk of Death for Patients with Mesothelioma Undergoing Cancer-directed Surgery from 2004 to 2010.

		95% Confidence Interval		
Predictor	**Hazard Ratio**	**Lower**	**Upper**	**p Value**
Age	1.02	1.01	1.04	0.004
Female Sex	0.98	0.70	1.39	0.92
Race				
White	Ref	Ref	Ref	Ref
Black	1.08	0.47	2.53	0.85
Other	1.32	0.57	3.03	0.52
Marital Status				
Unmarried	Ref	Ref	Ref	Ref
Married	1.12	0.79	1.58	0.53
Laterality				
Right	Ref	Ref	Ref	Ref
Left	0.85	0.63	1.14	0.28
Histology				
Epithelioid	Ref	Ref	Ref	Ref
Biphasic	1.57	1.09	2.26	0.02
Stage				
1	Ref	Ref	Ref	Ref
2	1.04	0.66	1.65	0.87
3	1.25	0.82	1.91	0.29
Radiotherapy	0.79	0.58	1.08	0.14

Cox proportional hazards model adjusting for age, sex, race, marital status, laterality, histology, disease stage, and radiation therapy.

Table 6

Baseline Characteristics of Patients after Propensity Matching, Stratified by Age Group and Intervention

	Patients younger than age 70			Patients age 70 and older		
Characteristic	**No surgery (n=89)**	**Surgery (n=89)**	**p Value**	**No surgery (n=81)**	**Surgery (n=81)**	**p Value**
Age, y, median	63	63	0.67	76	77	0.45
Sex, n (%)			0.59			0.34
Male	67 (75)	70 (79)		66 (81)	61 (75)	
Female	22 (25)	19 (21)		15 (19)	20 (25)	
Race, n (%)			0.60			1.00
White	82 (92)	84 (94)		77 (95)	77 (95)	
Black	3 (3)	1 (1)		3 (4)	3 (4)	
Other	4 (4)	4 (4)		1 (1)	1 (1)	
Marital Status, n (%)			0.84			0.42
Married	74 (83)	75 (84)		55 (68)	47 (58)	
Unmarried	8 (9)	6 (7)		6 (7)	4 (5)	
Other	7 (8)	8 (9)		20 (25)	30 (37)	
Laterality, n (%)			0.65			0.75
Right	53 (60)	50 (56)		50 (62)	48 (59)	
Left	36 (40)	39 (44)		31 (38)	33 (41)	
Histology, n (%)			0.40			0.67
Epithelioid	78 (88)	74 (83)		69 (85)	67 (83)	
Biphasic	11 (12)	15 (17)		12 (15)	14 (17)	
Stage, n (%)			0.97			0.95
Stage 1	18 (20)	17 (19)		24 (30)	23 (28)	
Stage 2	19 (21)	20 (22)		22 (27)	21 (26)	
Stage 3	52 (58)	52 (58)		35 (43)	37 (46)	
Radiotherapy, n (%)			1.00			0.81
No Radiotherapy	80 (90)	80 (90)		71 (88)	72 (89)	
Radiotherapy	9 (10)	9 (10)		10 (12)	9 (11)	