



# Clinicopathologic Characteristics, Treatment Patterns, and Survival Outcomes in Malignant Mesothelioma: A Population-based SEER Study, 2004-2023

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## ABSTRACT

**Objective:** Treatment for malignant mesothelioma has changed over two decades. We described clinicopathologic features, treatment patterns, and survival by primary site, diagnosis era, age group, and histologic subtype.

**Material and Methods:** This population-based retrospective cohort study used the Surveillance, Epidemiology, and End Results (SEER) 17 registries and included a total of 10,873 patients diagnosed between 2004 and 2023. Overall survival (OS) and cancer-specific survival (CSS) were analyzed with Kaplan-Meier estimation, log-rank testing, Cox regression, and Fine-Gray competing-risk regression.

**Results:** Pleural mesothelioma occurred in 8,886 patients, peritoneal mesothelioma in 1,377 patients, and other or unknown sites in 610 patients. Men comprised 72.7%; 63.6% had distant-stage disease; and 43.0% lacked a specified subtype. Chemotherapy was recorded in 48.5%, surgery in 26.9%, and radiation in 9.8%. Median OS was 9 months and median CSS was 11 months; median OS was 17 months in peritoneal disease and 9 months in pleural disease. Peritoneal site was associated with lower mortality [adjusted hazard ratio (aHR): 0.81; 95% confidence interval (CI): 0.76-0.88]; diagnosis during 2016-2023 was also associated with lower mortality (aHR: 0.84; 95% CI: 0.80-0.88). Fibrous histology (aHR: 1.99; 95% CI: 1.85-2.13) and age 80 years or older (aHR: 2.00; 95% CI: 1.86-2.16) were associated with higher mortality; all  $p < 0.001$ . Fine-Gray estimates were directionally consistent (peritoneal site: subdistribution HR: 0.87).

**Conclusion:** Mesothelioma survival remained poor overall, but was better among patients diagnosed in 2016-2023. Advanced age, fibrous histology, and unspecified subtype were associated with higher adjusted mortality. More complete subtype ascertainment and reporting would strengthen prognostic interpretation and registry-based research.

**Keywords:** Mesothelioma; SEER program; survival analysis; peritoneal neoplasms; pleural neoplasms

## INTRODUCTION

Malignant mesothelioma is a rare, aggressive malignancy of mesothelial cells lining the pleura, peritoneum, pericardium, and tunica vaginalis.<sup>1</sup> Most tumors arise in the pleura, with the peritoneum the second most common primary site; other sites are rare.<sup>1</sup> Asbestos exposure is the main recognized cause, and the long interval between exposure and diagnosis means that the contemporary disease burden largely reflects historical exposure patterns.<sup>2</sup> Despite major declines in asbestos use, the annual number of mesothelioma deaths in

the United States has remained substantial.<sup>1,3</sup> Environmental fibers also contribute to disease, and erionite exposure in Cappadocia produced some of the highest mesothelioma rates recorded worldwide.<sup>4</sup> Türkiye has established a national surveillance program to monitor environmental exposure to asbestos and erionite.<sup>5</sup> Mesothelioma, therefore, remains a contemporary public health concern.

Histology shapes outcomes. Pathologists classify mesothelioma as epithelioid, sarcomatoid, or biphasic, and epithelioid tumors carry the most favorable prognosis.<sup>6</sup>

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Registries still record many cases without a specified subtype, partly because reliable classification can be difficult in limited biopsy specimens.<sup>6</sup> This gap matters because subtyping guides prognostic counseling and treatment choice. Primary site matters as well: peritoneal mesothelioma differs from pleural disease in patient demographics, clinical course, and treatment approach.<sup>7</sup> Treatment has also evolved. Cisplatin plus pemetrexed became the first-line standard of care for unresectable pleural disease early in the study period.<sup>8</sup> Nivolumab plus ipilimumab improved overall survival (OS) compared with chemotherapy.<sup>9</sup> The role of radical surgery remains unsettled; in the randomized MARS 2 trial, adding extended pleurectomy decortication to chemotherapy did not improve survival compared with chemotherapy alone.<sup>10</sup> Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy has been associated with prolonged survival in carefully selected patients with peritoneal disease.<sup>11</sup>

Whether outcomes observed in clinical trials and in specialized centers extend to the broader patient population remains uncertain. Trials enroll a more selected group than a population-based cancer registry does. Registry data, therefore, complement trial evidence and describe outcomes among patients who never enter trials. Earlier analyses of the Surveillance, Epidemiology, and End Results (SEER) database examined primary sites individually, including pleural and peritoneal cohorts.<sup>12,13</sup> Population-based evidence comparing pleural, peritoneal, and other or unknown primary sites within a single cohort using a common adjusted model remains limited. Few studies have applied competing-risk methods to mesothelioma-specific mortality in this setting.

We therefore aimed to characterize the clinicopathologic features, treatment patterns, and survival outcomes of patients diagnosed with malignant mesothelioma between 2004 and 2023 who were recorded in the SEER database. Comparisons were performed across primary site, diagnosis era, age group, and histologic subtype for both overall and cancer-specific survival (CSS). Secondary analyses used competing-risks regression to evaluate mesothelioma-specific mortality and to examine the prognostic significance of metastatic patterns in distant-stage disease.

## MATERIAL AND METHODS

### Study Design and Data Source

We conducted a population-based, retrospective cohort study using data from the SEER 17 registries, November 2025 submission (2000-2023), accessed July 3, 2026. The SEER Program compiles standardized demographic, clinicopathologic, first-course treatment, and survival data from participating population-based cancer registries in the

United States. The SEER database contains de-identified, publicly available data. Institutional review board approval was not required.

### Study Population

Malignant mesothelioma was defined by ICD-O-3 morphology codes 9050 to 9053 and 9055 with malignant behavior; only microscopically confirmed cases were included in the cohort. These criteria identified 13,200 patients who were diagnosed between 2000 and 2023 (Figure 1). The SEER Combined Summary Stage with Expanded Regional Codes variable is available from 2004 onward; therefore, we excluded 2,327 patients diagnosed between 2000 and 2003. The final analytic cohort included 10,873 patients.

Primary-site groups were derived from ICD-O-3 topography and the corresponding SEER primary-site labels. The three mutually exclusive categories were pleural, peritoneal, and other or unknown primary sites. The other/unknown group included mesotheliomas arising at non-pleural, non-peritoneal sites, and cases with unspecified primary sites.

### Variables and Definitions

Demographic variables included age at diagnosis, sex, race and ethnicity, marital status at diagnosis, and year of diagnosis. Age groups were <60, 60-69, 70-79, and ≥80 years. Years of diagnosis were grouped into three calendar periods: 2004-2009, 2010-2015, and 2016-2023. The study began in 2004 because the summary-stage variable was available that year. Two successive six-year intervals defined the early and middle periods; the final group extended through the last available diagnosis year, 2023. These groups provide broad temporal, rather than treatment-specific, comparisons. In the registry, race and ethnicity were categorized into six groups: non-Hispanic White; non-Hispanic Black; non-Hispanic American Indian or Alaska Native; non-Hispanic Asian or Pacific Islander; Hispanic (all races); and non-Hispanic unknown race. Marital status groups were classified as: married; single or never married; divorced, separated, or widowed; unmarried or domestic partner; and unknown.

County-level median household income and the rural-urban continuum were obtained from the SEER county attribute variables. Median household income, adjusted to 2024 dollars, was categorized as <\$75,000, \$75,000-\$99,999, ≥\$100,000, and unknown or missing. Rural-urban categories were metropolitan areas with ≥1 million population, metropolitan areas with <1 million population, non-metropolitan areas, and unknown or missing.

Tumor variables included primary site, histologic subtype, laterality, diagnostic confirmation, and summary stage. Histologic subtypes were derived from ICD-O-3 morphology

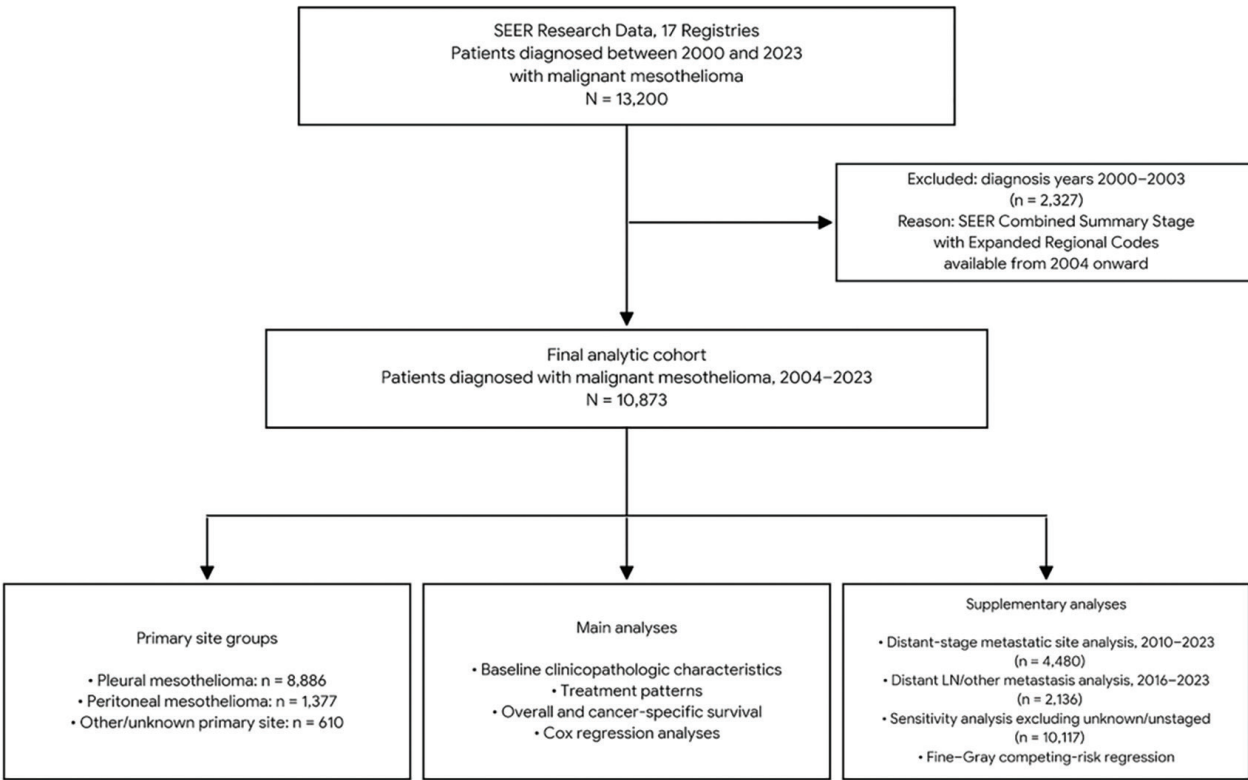


**FIGURE 1:** Flow diagram of cohort selection and analytic populations.

The initial SEER cohort included 13,200 patients diagnosed with malignant mesothelioma between 2000 and 2023. Patients diagnosed between 2000 and 2003 were excluded because the SEER Combined Summary Stage with Expanded Regional Codes variable was available from 2004 onward. The final analytic cohort included 10,873 patients diagnosed between 2004 and 2023 and was categorized by primary site as pleural, peritoneal, or other or unknown. Site-specific metastatic variables for bone, brain, liver, and lung were analyzed among distant-stage patients diagnosed from 2010 to 2023, whereas distant lymph node and other metastasis variables were analyzed in the 2016-2023 subset.

LN: Lymph node; SEER: Surveillance, Epidemiology, and End Results.

codes and classified into five groups: mesothelioma not otherwise specified (NOS), epithelioid, fibrous, biphasic, and multicystic or other mesothelioma. The 2021 World Health Organization (WHO) classification recognizes three histologic subtypes of mesothelioma: epithelioid, sarcomatoid, and biphasic.<sup>14</sup> In SEER, ICD-O-3 code 9051 carries the label fibrous mesothelioma and covers sarcomatoid, spindle, and desmoplastic tumors. We kept the SEER label in the tables and used sarcomatoid when referring to the current WHO classification. The multicystic or other category contained two patients; therefore, we retained it in the descriptive table but excluded it from the subgroup survival and regression analyses. Summary stage was derived from the SEER Combined Summary Stage with Expanded Regional Codes variable and categorized as localized, regional, distant, or unknown/unstaged.

Treatment variables included primary tumor surgery, reason for no cancer-directed surgery, radiation therapy,

chemotherapy, surgery-radiation sequence, systemic therapy-surgery sequence, combined treatment modality, and time from diagnosis to treatment. Descriptive analyses classified primary tumor surgery into three categories: surgery performed, no surgery, and unknown [death certificate only (DCO) or autopsy only]. Regression models instead used a four-category variable representing the reason for no cancer-directed surgery: surgery performed; not recommended or contraindicated; recommended but not performed or status unknown; and unknown, DCO, or autopsy only. Radiation and chemotherapy were each classified into two categories: given and no or unknown. The SEER treatment recodes combine patients without recorded treatment and patients with unknown treatment status in the same category; therefore, we did not interpret these categories as confirmed absence of treatment. The combined treatment modality was derived from recorded variables for surgery, chemotherapy, and radiation; time from diagnosis to treatment was summarized as the median and interquartile range (IQR).

## Outcomes

The primary outcome was OS, measured from diagnosis to death from any cause, with patients alive at last follow-up censored. The secondary outcome was CSS, measured from diagnosis to death attributable to mesothelioma, as defined by the SEER cause-specific death classification. Follow-up was administratively limited to December 31, 2023. Deaths from other causes were censored in the Kaplan-Meier and cause-specific Cox analyses, whereas the Fine-Gray model treated them as competing events. Survival time was measured in months, and patients with a recorded survival time of zero months were assigned 0.5 months to retain them in the time-to-event analyses.

## Metastatic Subgroup Analyses

SEER records site-specific metastasis to bone, brain, liver, and lung only from 2010 onward; therefore, the metastatic analyses covered distant-stage patients diagnosed from 2010 to 2023. SEER records distant lymph node and other metastases from 2016 onward, and we examined these two variables in the 2016-2023 subset. A metastatic-site burden variable counted the sites explicitly recorded as metastatic in bone, brain, liver, and lung. The categories were: no recorded metastatic sites, a single recorded metastatic site, and multiple recorded metastatic sites. Patients with unknown or blank values for an organ-specific variable were excluded from the corresponding organ-specific comparison. For the burden count, unknown or blank values were not counted as recorded metastatic sites. The “no recorded metastatic site” category may therefore include incomplete site-specific records and does not indicate a confirmed absence of metastasis. Metastases outside these four organs were not included in the count; all patients in this subgroup had distant-stage disease.

## Statistical Analysis

Within each primary-site group, we summarized categorical variables as counts and column percentages, and continuous variables as medians and IQRs. Group comparisons were conducted using the  $\chi^2$  test or Fisher’s exact test; the latter was applied when expected cell counts were small. The Kruskal-Wallis test compared the time from diagnosis to treatment.

Follow-up was estimated using the reverse Kaplan-Meier method and is reported as median months with a 95% confidence interval (CI).<sup>15</sup> Kaplan-Meier estimation produced OS and CSS probabilities at 12, 36, and 60 months, with CIs from Greenwood standard errors and a log-log transformation. The log-rank test compared survival curves that we plotted by primary site, diagnosis era, age group, and histologic subtype.

We fitted separate univariable Cox proportional hazards models for each covariate to estimate unadjusted hazard ratios (HRs). These models served a descriptive purpose and did not guide variable selection. Multivariable Cox models for OS and CSS produced adjusted HRs (aHRs). Covariates were chosen a priori on clinical and epidemiologic grounds and based on availability in SEER: primary site, age group, diagnosis era, sex, race and ethnicity, marital status, county-level median household income, rural-urban continuum, histologic subtype, summary stage, cancer-directed surgery status, radiation therapy, and chemotherapy. Reference categories were chosen for clinical interpretability and are identified in the tables. The multicystic and other histologic categories were excluded from all regression models.

Cause-specific Cox regression was used as the primary approach for CSS. A Fine-Gray model was additionally used to evaluate mesothelioma-specific mortality, treating deaths from other causes as competing events; its estimates were reported as adjusted subdistribution HRs (sHRs).<sup>16,17</sup> A sensitivity analysis reran the multivariable Cox models after excluding patients with unknown or unstaged disease; these models included 10,117 patients. Estimates from categories with fewer than 10 patients were considered unstable and were not interpreted.

For the Cox models, we assessed the proportional hazards assumption using Schoenfeld residuals and log-minus-log survival plots. For the Fine-Gray model, we assessed the proportional sHRs assumption with a goodness-of-fit test based on modified weighted Schoenfeld residuals. No meaningful violations were identified in either assessment. Estimates are reported with 95% CIs and two-sided p-values, and  $p < 0.05$  is considered statistically significant. No adjustment for multiple comparisons was applied; secondary and supplementary analyses were considered exploratory.

Data management and preprocessing were performed in Python version 3.12. We used pandas, NumPy, and SciPy for data handling and group comparisons; lifelines for Kaplan-Meier estimation and Cox regression; and matplotlib for figure generation. Fine-Gray regression and assessment of proportional sHRs were performed in R version 4.5.2 using the cmprsk and crrSC packages, respectively.

## RESULTS

### Baseline Characteristics

The analytic cohort included 10,873 patients (Table 1). Pleural mesothelioma accounted for 8,886 patients, peritoneal mesothelioma accounted for 1,377 patients, and other or unknown sites accounted for 610 patients. Of the cohort,

**TABLE 1: Baseline clinicopathologic characteristics of patients with malignant mesothelioma according to primary site, SEER 2004-2023.**

| Characteristic                       | Category                                      | Total<br>(n=10,873) | Pleural<br>(n=8,886) | Peritoneal<br>(n=1,377) | Other or unknown<br>(n=610) | p-value |
|--------------------------------------|-----------------------------------------------|---------------------|----------------------|-------------------------|-----------------------------|---------|
| Age group, years                     | <60                                           | 1,844 (17.0)        | 1,108 (12.5)         | 598 (43.4)              | 138 (22.6)                  | <0.001  |
|                                      | 60-69                                         | 2,618 (24.1)        | 2,149 (24.2)         | 336 (24.4)              | 133 (21.8)                  |         |
|                                      | 70-79                                         | 3,609 (33.2)        | 3,123 (35.1)         | 306 (22.2)              | 180 (29.5)                  |         |
|                                      | ≥80                                           | 2,802 (25.8)        | 2,506 (28.2)         | 137 (9.9)               | 159 (26.1)                  |         |
| Year of diagnosis                    | 2004-2009                                     | 3,490 (32.1)        | 2,934 (33.0)         | 385 (28.0)              | 171 (28.0)                  | <0.001  |
|                                      | 2010-2015                                     | 3,417 (31.4)        | 2,836 (31.9)         | 385 (28.0)              | 196 (32.1)                  |         |
|                                      | 2016-2023                                     | 3,966 (36.5)        | 3,116 (35.1)         | 607 (44.1)              | 243 (39.8)                  |         |
| Sex                                  | Male                                          | 7,909 (72.7)        | 6,747 (75.9)         | 745 (54.1)              | 417 (68.4)                  | <0.001  |
|                                      | Female                                        | 2,964 (27.3)        | 2,139 (24.1)         | 632 (45.9)              | 193 (31.6)                  |         |
| Race and ethnicity                   | Non-Hispanic White                            | 8,251 (75.9)        | 6,853 (77.1)         | 956 (69.4)              | 442 (72.5)                  | <0.001  |
|                                      | Non-Hispanic Black                            | 557 (5.1)           | 447 (5.0)            | 75 (5.4)                | 35 (5.7)                    |         |
|                                      | Non-Hispanic American Indian or Alaska Native | 57 (0.5)            | 47 (0.5)             | 9 (0.7)                 | 1 (0.2)                     |         |
|                                      | Non-Hispanic Asian or Pacific Islander        | 470 (4.3)           | 354 (4.0)            | 79 (5.7)                | 37 (6.1)                    |         |
|                                      | Hispanic, all races                           | 1,516 (13.9)        | 1,169 (13.2)         | 255 (18.5)              | 92 (15.1)                   |         |
|                                      | Non-Hispanic unknown race                     | 22 (0.2)            | 16 (0.2)             | 3 (0.2)                 | 3 (0.5)                     |         |
| Marital status                       | Married                                       | 6,806 (62.6)        | 5,649 (63.6)         | 817 (59.3)              | 340 (55.7)                  | <0.001  |
|                                      | Single or never married                       | 1,214 (11.2)        | 874 (9.8)            | 244 (17.7)              | 96 (15.7)                   |         |
|                                      | Divorced, separated, or widowed               | 2,418 (22.2)        | 2,004 (22.6)         | 275 (20.0)              | 139 (22.8)                  |         |
|                                      | Unmarried or domestic partner                 | 34 (0.3)            | 26 (0.3)             | 4 (0.3)                 | 4 (0.7)                     |         |
|                                      | Unknown                                       | 401 (3.7)           | 333 (3.7)            | 37 (2.7)                | 31 (5.1)                    |         |
| County-level median household income | <\$75,000                                     | 3,138 (28.9)        | 2,501 (28.1)         | 397 (28.8)              | 240 (39.3)                  | <0.001  |
|                                      | \$75,000-\$99,999                             | 4,856 (44.7)        | 4,014 (45.2)         | 594 (43.1)              | 248 (40.7)                  |         |
|                                      | ≥\$100,000                                    | 2,878 (26.5)        | 2,370 (26.7)         | 386 (28.0)              | 122 (20.0)                  |         |
|                                      | Unknown or missing                            | 1 (0.0)             | 1 (0.0)              | 0 (0.0)                 | 0 (0.0)                     |         |
| Rural-urban continuum                | Metropolitan ≥1 million                       | 6,551 (60.3)        | 5,437 (61.2)         | 805 (58.5)              | 309 (50.7)                  | <0.001  |
|                                      | Metropolitan <1 million                       | 3,145 (28.9)        | 2,532 (28.5)         | 422 (30.6)              | 191 (31.3)                  |         |
|                                      | Non-metropolitan                              | 1,172 (10.8)        | 913 (10.3)           | 149 (10.8)              | 110 (18.0)                  |         |
|                                      | Unknown or missing                            | 5 (0.0)             | 4 (0.0)              | 1 (0.1)                 | 0 (0.0)                     |         |
| Histologic subtype                   | Mesothelioma, NOS                             | 4,675 (43.0)        | 3,637 (40.9)         | 672 (48.8)              | 366 (60.0)                  | <0.001  |
|                                      | Epithelioid mesothelioma                      | 4,239 (39.0)        | 3,460 (38.9)         | 613 (44.5)              | 166 (27.2)                  |         |
|                                      | Fibrous mesothelioma                          | 1,139 (10.5)        | 1,037 (11.7)         | 44 (3.2)                | 58 (9.5)                    |         |
|                                      | Biphasic mesothelioma                         | 818 (7.5)           | 752 (8.5)            | 47 (3.4)                | 19 (3.1)                    |         |
|                                      | Multicystic or other mesothelioma             | 2 (0.0)             | 0 (0.0)              | 1 (0.1)                 | 1 (0.2)                     |         |
| Laterality                           | Right                                         | 5,215 (48.0)        | 5,000 (56.3)         | 4 (0.3)                 | 211 (34.6)                  | <0.001  |
|                                      | Left                                          | 3,525 (32.4)        | 3,367 (37.9)         | 0 (0.0)                 | 158 (25.9)                  |         |
|                                      | Bilateral                                     | 147 (1.4)           | 137 (1.5)            | 1 (0.1)                 | 9 (1.5)                     |         |
|                                      | Not a paired site                             | 1,544 (14.2)        | 0 (0.0)              | 1,359 (98.7)            | 185 (30.3)                  |         |
|                                      | Unknown or unspecified                        | 442 (4.1)           | 382 (4.3)            | 13 (0.9)                | 47 (7.7)                    |         |
| Diagnostic confirmation              | Positive histology                            | 10,864 (99.9)       | 8,879 (99.9)         | 1,376 (99.9)            | 609 (99.8)                  |         |
|                                      | Positive cytology                             | 0 (0.0)             | 0 (0.0)              | 0 (0.0)                 | 0 (0.0)                     |         |
|                                      | Positive microscopic confirmation, NOS        | 9 (0.1)             | 7 (0.1)              | 1 (0.1)                 | 1 (0.2)                     |         |
| Summary stage                        | Localized                                     | 1,218 (11.2)        | 951 (10.7)           | 158 (11.5)              | 109 (17.9)                  | <0.001  |
|                                      | Regional                                      | 1,985 (18.3)        | 1,692 (19.0)         | 200 (14.5)              | 93 (15.2)                   |         |
|                                      | Distant                                       | 6,916 (63.6)        | 5,797 (65.2)         | 841 (61.1)              | 278 (45.6)                  |         |
|                                      | Unknown or unstaged                           | 754 (6.9)           | 446 (5.0)            | 178 (12.9)              | 130 (21.3)                  |         |

Values are presented as number (%). Percentages are column percentages within each primary-site group unless otherwise indicated. The study cohort included patients diagnosed with malignant mesothelioma between 2004 and 2023 in the SEER database. Primary site groups were categorized as pleural, peritoneal, and other or unknown based on ICD-O-3 topography codes. Histologic subtypes were grouped using ICD-O-3 morphology codes. Summary stage was based on the SEER Combined Summary Stage with Expanded Regional Codes variable. County-level median household income and rural-urban continuum were derived from SEER county attributes. p values were calculated using the  $\chi^2$  test or Fisher exact test, as appropriate.

NOS: Not otherwise specified; SEER: Surveillance, Epidemiology, and End Results.

7,909 patients (72.7%) were men. Most patients were aged 70 years or older: 3,609 (33.2%) were aged 70-79 years and 2,802 (25.8%) were aged 80 years or older. Non-Hispanic White patients numbered 8,251 (75.9%). The three diagnostic eras included 3,490 patients (32.1%) in 2004-2009, 3,417 (31.4%) in 2010-2015, and 3,966 (36.5%) in 2016-2023.

Age and sex distributions differed between the peritoneal and pleural groups. Patients younger than 60 years made up 43.4% of the peritoneal group and 12.5% of the pleural group. Women made up 45.9% and 24.1% of the two groups, respectively.

Mesothelioma NOS was the largest histologic category, with 4,675 patients (43.0%). Epithelioid mesothelioma was observed in 4,239 patients (39.0%), followed by fibrous mesothelioma in 1,139 (10.5%) and biphasic mesothelioma in 818 (7.5%). Two patients had multicystic or other forms of mesothelioma. Among the microscopically confirmed cohort, 10,864 patients (99.9%) were coded as positive histology and 9 patients as positive microscopic confirmation, NOS. Distant-stage disease was recorded in 6,916 patients (63.6%), regional disease in 1,985 (18.3%), and localized disease in 1,218 (11.2%). Stage was unknown or unstaged in 754 patients (6.9%). Among characteristics for which comparisons were reported, all differed across primary-site groups (all  $p < 0.001$ ).

### Treatment Patterns

Primary tumor surgery was recorded in 2,924 patients (26.9%) (Table 2). Recorded surgery was more frequent in peritoneal disease (595 patients; 43.2%) than in pleural disease (2,140 patients; 24.1%). Chemotherapy was recorded for 5,275 patients (48.5%) overall; for 853 (61.9%) with peritoneal disease and for 4,229 (47.6%) with pleural disease. Radiation was recorded in 1,061 patients (9.8%) overall and was rare in peritoneal disease, where it occurred in 13 patients (0.9%). For chemotherapy and radiation, the complementary categories combine patients with no recorded treatment and those with unknown treatment status.

No surgery, chemotherapy, or radiation was recorded for 4,223 patients (38.8%). This proportion was higher in pleural disease at 3,584 patients (40.3%) than in peritoneal disease at 365 patients (26.5%). Surgery plus chemotherapy was the most common multimodality pattern in both groups, but it was far more frequent in peritoneal disease (435 patients; 31.6%) than in pleural disease (935 patients; 10.5%). Trimodality treatment was uncommon overall, occurring in 340 patients (3.1%). The median time from diagnosis to treatment was 32 days (IQR: 10-55). All treatment comparisons differed across primary-site groups (all  $p < 0.001$ ).

### Survival According to Primary Site

Median reverse Kaplan-Meier follow-up time was 103 months (95% CI: 99-111) (Table 3). All-cause mortality was observed in 9,622 patients (88.5%); 8,686 (79.9%) died of mesothelioma. Median OS was 9 months (95% CI: 9-10), with 1-year OS of 41.7% (95% CI: 40.8-42.6) and 3-year OS of 16.0% (95% CI: 15.3-16.7). Median CSS was 11 months (95% CI: 10-11).

Both OS and CSS differed by primary site (log-rank  $p < 0.001$  for both; Figure 2A and 2B). Median OS was 9 months (95% CI: 9-9) for pleural disease, 17 months (95% CI: 15-20) for peritoneal disease, and 7 months (95% CI: 6-9) for the other or unknown group. Five-year OS was 6.1% (95% CI: 5.6-6.6), 28.7% (95% CI: 26.1-31.3), and 21.4% (95% CI: 18.0-24.9), respectively. The other/unknown group had the shortest median OS but a higher 5-year OS than the pleural group. The median CSS followed the same order: 10, 20, and 9 months. Five-year CSS was 8.0% (95% CI: 7.4-8.7) in pleural disease and 32.1% (95% CI: 29.3-34.9) in peritoneal disease.

### Survival According to Era, Age, and Histology

Both OS and CSS differed across diagnostic eras (log-rank  $p < 0.001$  for each; Supplementary Table 1; Figure 3A and 3B). Median OS was 8 months in 2004-2009, 9 months in 2010-2015, and 11 months in 2016-2023; 3-year OS rose from 12.8% to 14.9% and then to 20.5%. The median CSS followed the same order at 9, 10, and 13 months.

Survival declined with increasing age (log-rank test  $p < 0.001$  for both OS and CSS; Figure 4A and 4B). Median OS was 19 months in patients younger than 60 years, 11 months in those aged 60-69 years, 8 months in those aged 70-79 years, and 5 months in those aged 80 years or older. Five-year OS declined from 26.5% in patients younger than 60 years to 2.6% in those aged 80 years or older.

Survival differed by histologic subtype (log-rank  $p < 0.001$  for OS and CSS; Figure 5A and 5B). Median OS was 14 months for epithelioid mesothelioma; 8 months for mesothelioma NOS; 8 months for biphasic mesothelioma; and 4 months for fibrous mesothelioma.

### Univariable and Multivariable Regression

In univariable analyses, a peritoneal primary site was associated with lower mortality than a pleural primary site (HR: 0.52; 95% CI: 0.49-0.56) (Table 4). Recorded chemotherapy was associated with an HR of 0.63 (95% CI: 0.61-0.66), and recorded radiation was associated with an HR of 0.88 (95% CI: 0.82-0.94;  $p < 0.001$ ).

In the multivariable model, peritoneal primary site remained associated with lower mortality (aHR: 0.81; 95%

**TABLE 2: Treatment patterns of patients with malignant mesothelioma according to primary site, SEER 2004-2023.**

| Characteristic                         | Category                                        | Total (n=10,873) | Pleural (n=8,886) | Peritoneal (n=1,377) | Other or unknown (n=610) | p-value |
|----------------------------------------|-------------------------------------------------|------------------|-------------------|----------------------|--------------------------|---------|
| Primary tumor surgery                  | Surgery performed                               | 2,924 (26.9)     | 2,140 (24.1)      | 595 (43.2)           | 189 (31.0)               | <0.001  |
|                                        | No surgery                                      | 7,867 (72.4)     | 6,682 (75.2)      | 775 (56.3)           | 410 (67.2)               |         |
|                                        | Unknown, DCO, or autopsy only                   | 82 (0.8)         | 64 (0.7)          | 7 (0.5)              | 11 (1.8)                 |         |
| Reason no cancer-directed surgery      | Surgery performed                               | 2,924 (26.9)     | 2,140 (24.1)      | 595 (43.2)           | 189 (31.0)               | <0.001  |
|                                        | Not recommended                                 | 6,987 (64.3)     | 5,931 (66.7)      | 691 (50.2)           | 365 (59.8)               |         |
|                                        | Not recommended or contraindicated              | 484 (4.5)        | 433 (4.9)         | 38 (2.8)             | 13 (2.1)                 |         |
|                                        | Recommended but not performed, unknown reason   | 193 (1.8)        | 157 (1.8)         | 13 (0.9)             | 23 (3.8)                 |         |
|                                        | Recommended but refused                         | 130 (1.2)        | 115 (1.3)         | 11 (0.8)             | 4 (0.7)                  |         |
|                                        | Recommended, unknown if performed               | 47 (0.4)         | 31 (0.3)          | 14 (1.0)             | 2 (0.3)                  |         |
|                                        | Patient died before surgery                     | 26 (0.2)         | 15 (0.2)          | 8 (0.6)              | 3 (0.5)                  |         |
|                                        | Unknown, DCO, or autopsy only                   | 82 (0.8)         | 64 (0.7)          | 7 (0.5)              | 11 (1.8)                 |         |
| Radiation therapy                      | Radiation given                                 | 1,061 (9.8)      | 994 (11.2)        | 13 (0.9)             | 54 (8.9)                 | <0.001  |
|                                        | No or unknown radiation                         | 9,812 (90.2)     | 7,892 (88.8)      | 1,364 (99.1)         | 556 (91.1)               |         |
| Chemotherapy                           | Chemotherapy yes                                | 5,275 (48.5)     | 4,229 (47.6)      | 853 (61.9)           | 193 (31.6)               | <0.001  |
|                                        | No or unknown chemotherapy                      | 5,598 (51.5)     | 4,657 (52.4)      | 524 (38.1)           | 417 (68.4)               |         |
| Surgery-radiation sequence             | No radiation and/or no surgery                  | 10,318 (94.9)    | 8,357 (94.0)      | 1,369 (99.4)         | 592 (97.0)               | <0.001  |
|                                        | Radiation after surgery                         | 536 (4.9)        | 511 (5.8)         | 8 (0.6)              | 17 (2.8)                 |         |
|                                        | Radiation before surgery                        | 11 (0.1)         | 11 (0.1)          | 0 (0.0)              | 0 (0.0)                  |         |
|                                        | Radiation before and after surgery              | 4 (0.0)          | 3 (0.0)           | 0 (0.0)              | 1 (0.2)                  |         |
|                                        | Other or unknown sequence                       | 4 (0.0)          | 4 (0.0)           | 0 (0.0)              | 0 (0.0)                  |         |
| Systemic therapy-surgery sequence      | No systemic therapy and/or surgery              | 7,328 (67.4)     | 6,109 (68.7)      | 754 (54.8)           | 465 (76.2)               | <0.001  |
|                                        | Systemic therapy after surgery                  | 1,201 (11.0)     | 953 (10.7)        | 188 (13.7)           | 60 (9.8)                 |         |
|                                        | Systemic therapy before surgery                 | 249 (2.3)        | 216 (2.4)         | 33 (2.4)             | 0 (0.0)                  |         |
|                                        | Systemic therapy both before and after surgery  | 114 (1.0)        | 73 (0.8)          | 37 (2.7)             | 4 (0.7)                  |         |
|                                        | Intraoperative or other systemic sequence       | 253 (2.3)        | 78 (0.9)          | 174 (12.6)           | 1 (0.2)                  |         |
|                                        | Unknown sequence                                | 3 (0.0)          | 3 (0.0)           | 0 (0.0)              | 0 (0.0)                  |         |
|                                        | Unavailable or blank                            | 1,725 (15.9)     | 1,454 (16.4)      | 191 (13.9)           | 80 (13.1)                |         |
| Combined treatment modality            | No recorded surgery, chemotherapy, or radiation | 4,223 (38.8)     | 3,584 (40.3)      | 365 (26.5)           | 274 (44.9)               | <0.001  |
|                                        | Surgery alone                                   | 975 (9.0)        | 703 (7.9)         | 155 (11.3)           | 117 (19.2)               |         |
|                                        | Chemotherapy alone                              | 3,187 (29.3)     | 2,670 (30.0)      | 409 (29.7)           | 108 (17.7)               |         |
|                                        | Radiation alone                                 | 218 (2.0)        | 195 (2.2)         | 4 (0.3)              | 19 (3.1)                 |         |
|                                        | Surgery + chemotherapy                          | 1,427 (13.1)     | 935 (10.5)        | 435 (31.6)           | 57 (9.3)                 |         |
|                                        | Surgery + radiation                             | 182 (1.7)        | 175 (2.0)         | 0 (0.0)              | 7 (1.1)                  |         |
|                                        | Chemotherapy + radiation                        | 321 (3.0)        | 297 (3.3)         | 4 (0.3)              | 20 (3.3)                 |         |
|                                        | Surgery + chemotherapy + radiation              | 340 (3.1)        | 327 (3.7)         | 5 (0.4)              | 8 (1.3)                  |         |
| Time from diagnosis to treatment, days | Median (IQR)                                    | 32 (10-55)       | 33 (13-56)        | 28 (1-55)            | 13 (0-38)                | <0.001  |

Values are presented as number (%) unless otherwise indicated. Percentages are column percentages within each primary-site group. p-values were calculated using the  $\chi^2$  test or Fisher's exact test for categorical variables and the Kruskal-Wallis test for time from diagnosis to treatment. "No or unknown chemotherapy" and "no or unknown radiation" reflect SEER treatment recode categories and should not be interpreted as confirmed absence of treatment in every case. "Unavailable or blank" for systemic therapy-surgery sequence primarily reflects years or records in which sequence information was not available or not coded.

DCO: Death certificate only; IQR: Interquartile range; SEER: Surveillance, Epidemiology, and End Results.

CI: 0.76-0.88;  $p < 0.001$ ) (Table 5). Diagnosis in 2016-2023 was associated with an aHR of 0.84 (95% CI: 0.80-0.88;  $p < 0.001$ ) compared with 2004-2009, whereas 2010-2015 did not differ significantly (aHR: 0.96; 95% CI: 0.92-1.01;  $p = 0.126$ ). Patients aged 80 years or older had an aHR of 2.00 (95% CI: 1.86-2.16) compared with patients younger than 60 years. Among histologic subtypes, fibrous histology had the highest aHR (aHR: 1.99; 95% CI: 1.85-2.13), followed by biphasic (aHR: 1.57;

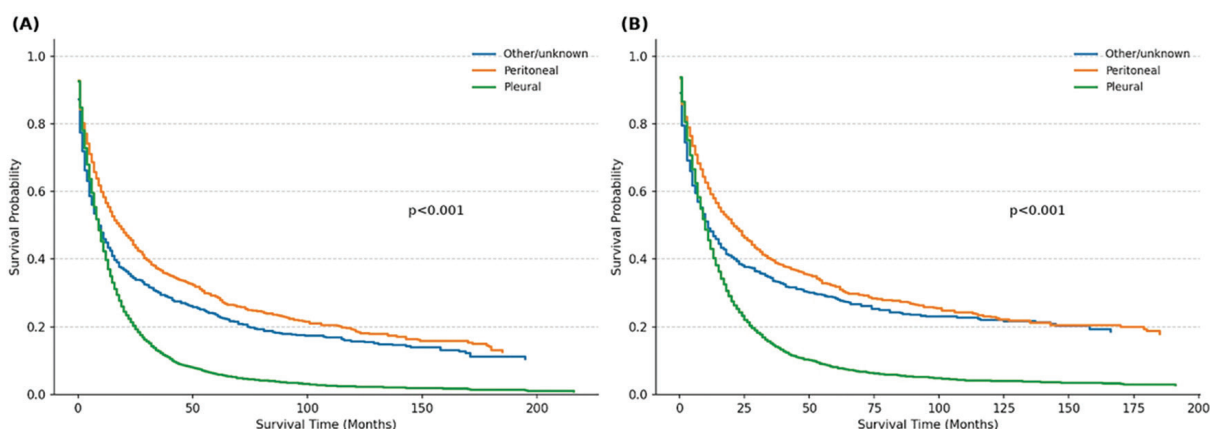
95% CI: 1.45-1.70) and NOS mesothelioma (aHR: 1.20; 95% CI: 1.14-1.26), compared with epithelioid histology. Distant-stage disease was associated with an aHR of 1.53 (95% CI: 1.43-1.64) compared with localized disease. Men had higher mortality than women (aHR: 1.27; 95% CI: 1.21-1.33). Non-metropolitan residence was associated with higher mortality than residence in metropolitan areas with a population of at least 1 million (aHR: 1.11; 95% CI: 1.03-1.20;  $p = 0.008$ ).

**TABLE 3: Survival outcomes of patients with malignant mesothelioma according to primary site, SEER 2004-2023.**

| Characteristic    | Category                                  | Total (n=10,873)  | Pleural (n=8,886) | Peritoneal (n=1,377) | Other or unknown (n=610) | p-value |
|-------------------|-------------------------------------------|-------------------|-------------------|----------------------|--------------------------|---------|
| Follow-up, months | Median, reverse Kaplan-Meier (95% CI)     | 103 (99-111)      | 101 (93-115)      | 100 (84-106)         | 113 (94-123)             | NA      |
| OS event          | Death from any cause, n (%)               | 9,622 (88.5)      | 8,134 (91.5)      | 996 (72.3)           | 492 (80.7)               | <0.001  |
| OS                | Median, months (95% CI)                   | 9 (9-10)          | 9 (9-9)           | 17 (15-20)           | 7 (6-9)                  | <0.001  |
| OS                | 1-year OS (95% CI)                        | 41.7% (40.8-42.6) | 39.6% (38.6-40.6) | 55.8% (53.1-58.4)    | 41.1% (37.1-45.0)        |         |
| OS                | 3-year OS (95% CI)                        | 16.0% (15.3-16.7) | 12.2% (11.5-13.0) | 36.4% (33.7-39.1)    | 26.6% (23.0-30.2)        |         |
| OS                | 5-year OS (95% CI)                        | 9.7% (9.1-10.3)   | 6.1% (5.6-6.6)    | 28.7% (26.1-31.3)    | 21.4% (18.0-24.9)        |         |
| CSS event         | Death attributable to mesothelioma, n (%) | 8,686 (79.9)      | 7,370 (82.9)      | 895 (65.0)           | 421 (69.0)               | <0.001  |
| CSS               | Median, months (95% CI)                   | 11 (10-11)        | 10 (10-10)        | 20 (17-24)           | 9 (7-11)                 | <0.001  |
| CSS               | 1-year CSS (95% CI)                       | 45.0% (44.1-46.0) | 43.0% (41.9-44.1) | 58.4% (55.7-61.1)    | 44.8% (40.7-48.9)        |         |
| CSS               | 3-year CSS (95% CI)                       | 18.8% (18.0-19.6) | 14.7% (13.9-15.5) | 39.4% (36.7-42.2)    | 31.2% (27.3-35.2)        |         |
| CSS               | 5-year CSS (95% CI)                       | 12.2% (11.5-12.9) | 8.0% (7.4-8.7)    | 32.1% (29.3-34.9)    | 26.3% (22.5-30.3)        |         |

Values are presented as number (%) or Kaplan-Meier estimates with 95% CIs unless otherwise indicated. Follow-up was estimated using the reverse Kaplan-Meier method and is presented as median months with 95% CI. OS was defined from diagnosis to death from any cause. CSS was defined from diagnosis to death attributable to mesothelioma, with deaths from other causes censored. Survival probabilities are Kaplan-Meier estimates at 12, 36, and 60 months. CIs for Kaplan-Meier estimates were calculated using Greenwood standard errors with log-log transformation. p-values for event distributions were calculated using the  $\chi^2$  test; p-values for survival comparisons were based on the log-rank test across primary-site groups. Zero-month survival was recorded as 0.5 months for time-to-event analyses.

CI: Confidence interval; CSS: Cancer-specific survival; NA: Not applicable; OS: Overall survival; SEER: Surveillance, Epidemiology, and End Results.

**FIGURE 2: Kaplan-Meier survival curves according to primary site among patients with malignant mesothelioma, SEER 2004-2023.**

(A) Overall survival (OS) and (B) cancer-specific survival (CSS) according to pleural, peritoneal, and other or unknown primary site groups. Survival differences were compared using the log-rank test. OS was defined as time from diagnosis to death from any cause. CSS was defined as time from diagnosis to death attributable to mesothelioma, with deaths from other causes censored. Group sizes were 8,886 for pleural, 1,377 for peritoneal, and 610 for other or unknown primary sites. Table 3 reports total events, median survival, and 1-, 3-, and 5-year estimates with 95% confidence intervals. Time-specific numbers at risk are not shown; late curve tails should be interpreted cautiously.

SEER: Surveillance, Epidemiology, and End Results.

Cancer-directed surgery status was also associated with mortality. Compared with patients who underwent surgery, those for whom surgery was not recommended or was contraindicated had an aHR of 1.59 (95% CI: 1.51-1.68;  $p<0.001$ ), those for whom surgery was recommended but not performed, or whose status was unknown had an aHR of 1.22 (95% CI: 1.09-1.37;  $p<0.001$ ), and those in the unknown, death-certificate-only, or autopsy-only category had an aHR of 1.76 (95% CI: 1.39-2.23;  $p<0.001$ ).

Recorded chemotherapy was associated with lower mortality (aHR: 0.72; 95% CI: 0.69-0.75;  $p<0.001$ ). Treatment-selection bias and immortal-time bias may influence this association.

Chemotherapy was modeled as a fixed baseline variable, with the reference category combining patients with no recorded chemotherapy and those with unknown treatment status; this estimate is not evidence of a causal treatment effect. Recorded radiation was not associated with mortality after adjustment (aHR: 1.01; 95% CI: 0.94-1.08;  $p=0.831$ ). CSS estimates were similar in direction and magnitude to the OS estimates (Table 5).

### Sensitivity and Competing-risk Analyses

A sensitivity analysis that excluded patients with unknown or unstaged disease gave similar estimates (Supplementary

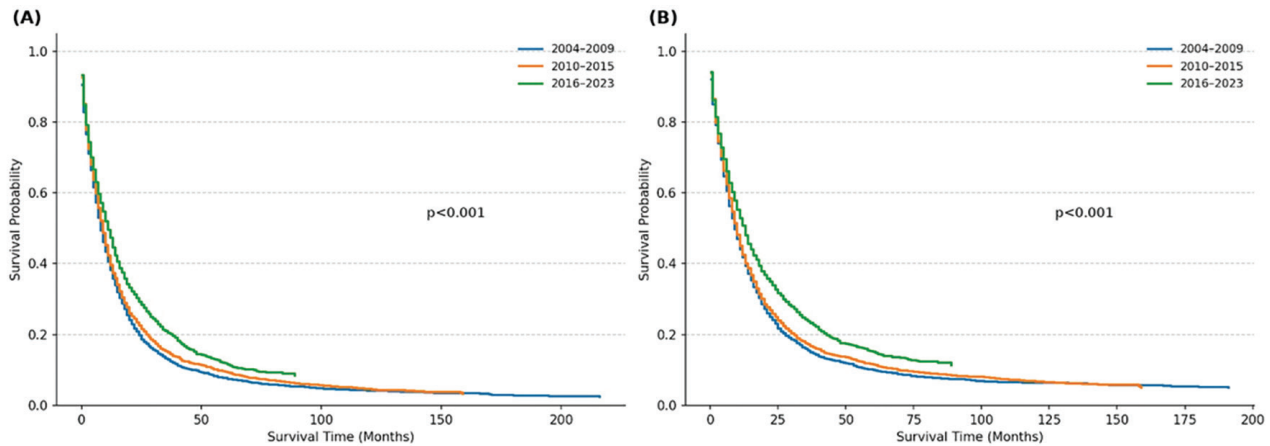


**FIGURE 3:** Kaplan-Meier survival curves according to diagnosis era among patients with malignant mesothelioma, SEER 2004-2023.

(A) Overall survival (OS) and (B) cancer-specific survival (CSS) stratified by diagnosis era: 2004-2009, 2010-2015, and 2016-2023. Survival differences were compared using the log-rank test. OS was defined as time from diagnosis to death from any cause. CSS was defined as time from diagnosis to death attributable to mesothelioma, with deaths from other causes censored. Group sizes were 3,490 for 2004-2009, 3,417 for 2010-2015, and 3,966 for 2016-2023. Supplementary Table 1 reports total events, median survival, and 1-, 3-, and 5-year estimates with 95% confidence intervals. Time-specific numbers at risk are not shown; late curve tails should be interpreted cautiously.

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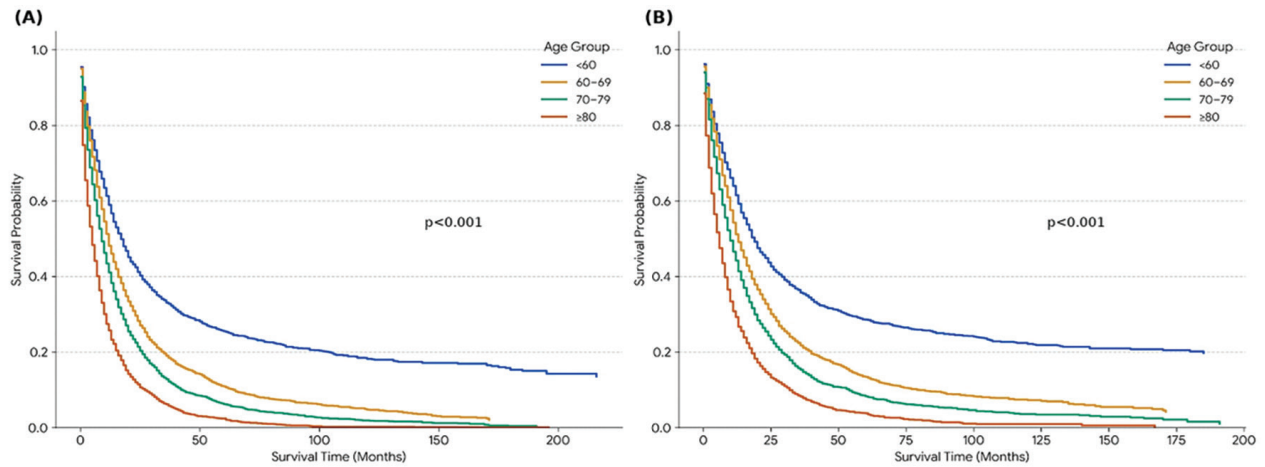


**FIGURE 4:** Kaplan-Meier survival curves according to age group among patients with malignant mesothelioma, SEER 2004-2023.

(A) Overall survival (OS) and (B) cancer-specific survival (CSS) stratified by age group: <60, 60-69, 70-79, and ≥80 years. Survival differences were compared using the log-rank test. OS was defined as time from diagnosis to death from any cause. CSS was defined as time from diagnosis to death attributable to mesothelioma, with deaths from other causes censored. Group sizes were 1,844 for <60 years, 2,618 for 60-69 years, 3,609 for 70-79 years, and 2,802 for ≥80 years. Supplementary Table 1 reports total events, median survival, and 1-, 3-, and 5-year estimates with 95% confidence intervals. Time-specific numbers at risk are not shown; late curve tails should be interpreted cautiously.

SEER: Surveillance, Epidemiology, and End Results.

Table 2). Peritoneal site had an aHR of 0.84 (95% CI: 0.78-0.91), diagnosis in 2016-2023 had an aHR of 0.85 (95% CI: 0.80-0.89), and recorded chemotherapy had an aHR of 0.70 (95% CI: 0.67-0.74).

The Fine-Gray model agreed with the cause-specific Cox model in the direction of effects, although several sHR estimates were numerically closer to 1.0 (Supplementary

Table 3). The peritoneal site had an sHR of 0.87 (95% CI: 0.81-0.94), and a diagnosis in 2016-2023 had an sHR of 0.84 (95% CI: 0.80-0.89). Fibrous histology had an sHR of 1.62 (95% CI: 1.50-1.74) and a cause-specific aHR of 2.02; and recorded chemotherapy had an sHR of 0.85 (95% CI: 0.82-0.89) and a cause-specific aHR of 0.75. Recorded radiation again showed no association (sHR: 1.06; 95% CI: 0.99-1.14;  $p=0.116$ ).

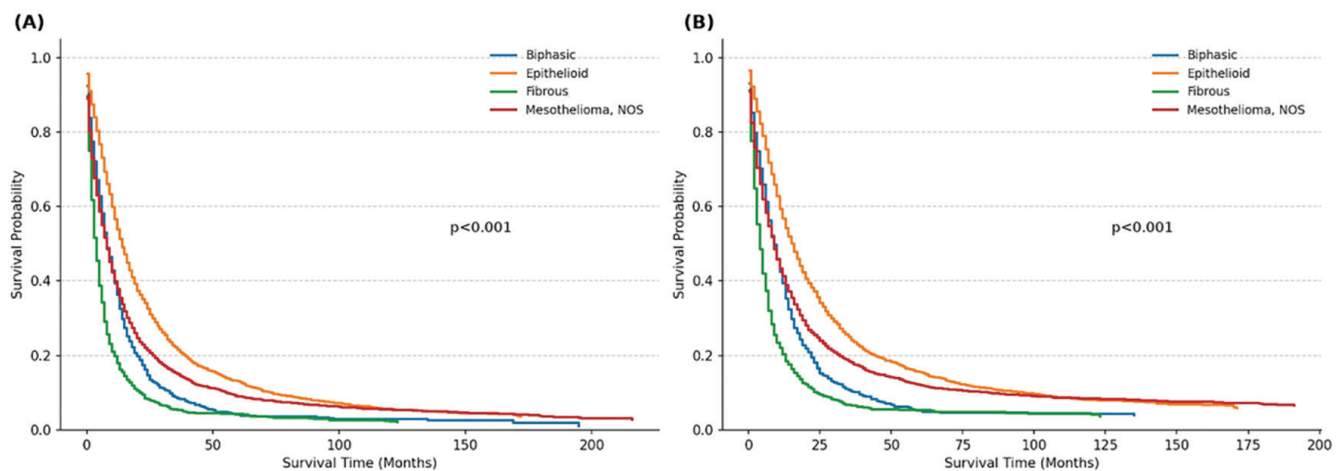


**FIGURE 5:** Kaplan-Meier survival curves according to histologic subtype among patients with malignant mesothelioma, SEER 2004-2023.

(A) Overall survival (OS) and (B) cancer-specific survival (CSS) stratified by histologic subtype. Survival differences were compared using the log-rank test. OS was defined as time from diagnosis to death from any cause. CSS was defined as time from diagnosis to death attributable to mesothelioma, with deaths from other causes censored. The multicystic or other mesothelioma category was not plotted because it included only two patients. Group sizes were 4,675 for mesothelioma not otherwise specified (NOS), 4,239 for epithelioid, 1,139 for fibrous, and 818 for biphasic mesothelioma. Supplementary Table 1 reports total events, median survival, and 1-, 3-, and 5-year estimates with 95% confidence intervals. Time-specific numbers at risk are not shown; late curve tails should be interpreted cautiously.

SEER: Surveillance, Epidemiology, and End Results.

### Metastatic Subgroup

Among the 4,480 distant-stage patients diagnosed from 2010 to 2023, the lung was the most commonly recorded metastatic site, occurring in 512 patients (11.4%) (Supplementary Table 4). Bone involvement was observed in 350 patients (7.8%), liver involvement in 276 (6.2%), and brain involvement in 49

(1.1%). Among patients assessed for these four organ-specific variables, 3,512 (78.4%) had no recorded metastatic site, 782 (17.5%) had a single recorded metastatic site, and 186 (4.2%) had multiple recorded metastatic sites. The “no recorded metastatic site” category does not establish the absence of metastasis because incomplete records or disease at other sites may account for cases in this group. In the 2016-2023

**TABLE 4:** Univariable Cox regression analysis for OS and CSS among patients with malignant mesothelioma, SEER 2004-2023.

| Variable           | Category                                      | OS HR (95% CI)   | p-value | CSS HR (95% CI)  | p-value |
|--------------------|-----------------------------------------------|------------------|---------|------------------|---------|
| Primary site       | Pleural                                       | 1 [Reference]    |         | 1 [Reference]    |         |
|                    | Peritoneal                                    | 0.52 (0.49-0.56) | <0.001  | 0.53 (0.49-0.57) | <0.001  |
|                    | Other or unknown                              | 0.74 (0.68-0.81) | <0.001  | 0.72 (0.65-0.79) | <0.001  |
| Age group, years   | <60                                           | 1 [Reference]    |         | 1 [Reference]    |         |
|                    | 60-69                                         | 1.55 (1.45-1.66) | <0.001  | 1.51 (1.41-1.62) | <0.001  |
|                    | 70-79                                         | 1.92 (1.80-2.05) | <0.001  | 1.87 (1.74-2.00) | <0.001  |
|                    | ≥80                                           | 2.86 (2.67-3.06) | <0.001  | 2.74 (2.56-2.94) | <0.001  |
| Diagnosis era      | 2004-2009                                     | 1 [Reference]    |         | 1 [Reference]    |         |
|                    | 2010-2015                                     | 0.93 (0.89-0.98) | 0.005   | 0.95 (0.90-1.00) | 0.055   |
|                    | 2016-2023                                     | 0.80 (0.76-0.84) | <0.001  | 0.80 (0.76-0.84) | <0.001  |
| Sex                | Female                                        | 1 [Reference]    |         | 1 [Reference]    |         |
|                    | Male                                          | 1.41 (1.35-1.48) | <0.001  | 1.42 (1.35-1.49) | <0.001  |
| Race and ethnicity | Non-Hispanic White                            | 1 [Reference]    |         | 1 [Reference]    |         |
|                    | Non-Hispanic Black                            | 0.90 (0.82-0.99) | 0.028   | 0.85 (0.77-0.94) | 0.002   |
|                    | Non-Hispanic American Indian or Alaska Native | 0.90 (0.68-1.18) | 0.434   | 0.90 (0.67-1.19) | 0.454   |
|                    | Non-Hispanic Asian or Pacific Islander        | 0.98 (0.89-1.09) | 0.723   | 0.99 (0.89-1.10) | 0.798   |
|                    | Hispanic, all races                           | 0.87 (0.82-0.93) | <0.001  | 0.84 (0.79-0.90) | <0.001  |
|                    | Non-Hispanic unknown race                     | 0.32 (0.15-0.67) | 0.002   | 0.25 (0.10-0.60) | 0.002   |

TABLE 4: Continued.

| Variable                             | Category                                 | OS HR (95% CI)    | p-value | CSS HR (95% CI)   | p-value |
|--------------------------------------|------------------------------------------|-------------------|---------|-------------------|---------|
| Marital status                       | Married                                  | 1 [Reference]     |         | 1 [Reference]     |         |
|                                      | Single or never married                  | 0.97 (0.90-1.03)  | 0.318   | 0.93 (0.87-1.00)  | 0.062   |
|                                      | Divorced, separated, or widowed          | 1.21 (1.15-1.27)  | <0.001  | 1.18 (1.12-1.24)  | <0.001  |
|                                      | Unmarried or domestic partner            | 1.18 (0.82-1.71)  | 0.362   | 1.11 (0.75-1.64)  | 0.616   |
|                                      | Unknown                                  | 0.94 (0.84-1.05)  | 0.277   | 0.89 (0.79-1.01)  | 0.062   |
| County-level median household income | ≥\$100,000                               | 1 [Reference]     |         | 1 [Reference]     |         |
|                                      | \$75,000-\$99,999                        | 1.08 (1.03-1.14)  | 0.002   | 1.06 (1.01-1.12)  | 0.020   |
|                                      | <\$75,000                                | 1.08 (1.02-1.14)  | 0.006   | 1.08 (1.02-1.14)  | 0.010   |
|                                      | Unknown or missing                       | 4.96 (0.70-35.23) | 0.109   | 5.59 (0.79-39.75) | 0.085   |
| Rural-urban continuum                | Metropolitan ≥1 million                  | 1 [Reference]     |         | 1 [Reference]     |         |
|                                      | Metropolitan <1 million                  | 1.02 (0.97-1.07)  | 0.433   | 1.03 (0.98-1.08)  | 0.310   |
|                                      | Non-metropolitan                         | 1.12 (1.05-1.20)  | <0.001  | 1.17 (1.10-1.26)  | <0.001  |
|                                      | Unknown or missing                       | 2.20 (0.92-5.29)  | 0.078   | 1.93 (0.72-5.15)  | 0.188   |
| Histologic subtype                   | Epithelioid mesothelioma                 | 1 [Reference]     |         | 1 [Reference]     |         |
|                                      | Mesothelioma, NOS                        | 1.37 (1.31-1.43)  | <0.001  | 1.34 (1.28-1.41)  | <0.001  |
|                                      | Fibrous mesothelioma                     | 2.32 (2.16-2.48)  | <0.001  | 2.34 (2.18-2.52)  | <0.001  |
|                                      | Biphasic mesothelioma                    | 1.54 (1.42-1.66)  | <0.001  | 1.55 (1.43-1.68)  | <0.001  |
| Summary stage                        | Localized                                | 1 [Reference]     |         | 1 [Reference]     |         |
|                                      | Regional                                 | 1.15 (1.07-1.25)  | <0.001  | 1.18 (1.08-1.28)  | <0.001  |
|                                      | Distant                                  | 1.53 (1.43-1.64)  | <0.001  | 1.58 (1.47-1.70)  | <0.001  |
|                                      | Unknown or unstaged                      | 1.16 (1.05-1.28)  | 0.004   | 1.14 (1.02-1.27)  | 0.017   |
| Cancer-directed surgery status       | Surgery performed                        | 1 [Reference]     |         | 1 [Reference]     |         |
|                                      | Not recommended or contraindicated       | 2.02 (1.93-2.12)  | <0.001  | 2.04 (1.94-2.15)  | <0.001  |
|                                      | Recommended but not performed or unknown | 1.63 (1.45-1.82)  | <0.001  | 1.61 (1.43-1.81)  | <0.001  |
|                                      | Unknown, DCO, or autopsy only            | 2.26 (1.79-2.84)  | <0.001  | 1.82 (1.39-2.38)  | <0.001  |
| Radiation therapy                    | No or unknown radiation                  | 1 [Reference]     |         | 1 [Reference]     |         |
|                                      | Radiation given                          | 0.88 (0.82-0.94)  | <0.001  | 0.90 (0.84-0.97)  | 0.005   |
| Chemotherapy                         | No or unknown chemotherapy               | 1 [Reference]     |         | 1 [Reference]     |         |
|                                      | Chemotherapy yes                         | 0.63 (0.61-0.66)  | <0.001  | 0.66 (0.63-0.69)  | <0.001  |

Univariable Cox proportional hazards models were fitted separately for each covariate. These analyses were intended to describe unadjusted associations with OS and CSS and were not used as a variable-selection procedure for the multivariable models. OS was defined as death from any cause. CSS was defined as death attributable to mesothelioma, with deaths from other causes censored. Estimates for categories with fewer than 10 patients are unstable and are not interpreted. The multicystic or other mesothelioma category included only two patients and was not included in Cox regression models because of sparse data and unstable hazard ratio estimation. Zero-month survival was recoded as 0.5 months for time-to-event modeling.

CI: Confidence interval; CSS: Cancer-specific survival; DCO: Death certificate only; HR: Hazard ratio; NOS: Not otherwise specified; OS: Overall survival; SEER: Surveillance, Epidemiology, and End Results.

TABLE 5: Multivariable Cox regression analysis for OS and CSS among patients with malignant mesothelioma, SEER 2004-2023.

| Variable         | Category         | OS aHR (95% CI)  | p-value | CSS aHR (95% CI) | p-value |
|------------------|------------------|------------------|---------|------------------|---------|
| Primary site     | Pleural          | 1 [Reference]    |         | 1 [Reference]    |         |
|                  | Peritoneal       | 0.81 (0.76-0.88) | <0.001  | 0.83 (0.77-0.89) | <0.001  |
|                  | Other or unknown | 0.89 (0.81-0.98) | 0.022   | 0.88 (0.79-0.97) | 0.011   |
| Age group, years | <60              | 1 [Reference]    |         | 1 [Reference]    |         |
|                  | 60-69            | 1.35 (1.26-1.44) | <0.001  | 1.30 (1.21-1.40) | <0.001  |
|                  | 70-79            | 1.58 (1.47-1.69) | <0.001  | 1.51 (1.41-1.62) | <0.001  |
|                  | ≥80              | 2.00 (1.86-2.16) | <0.001  | 1.92 (1.78-2.08) | <0.001  |
| Diagnosis era    | 2004-2009        | 1 [Reference]    |         | 1 [Reference]    |         |
|                  | 2010-2015        | 0.96 (0.92-1.01) | 0.126   | 0.98 (0.93-1.03) | 0.467   |
|                  | 2016-2023        | 0.84 (0.80-0.88) | <0.001  | 0.84 (0.79-0.89) | <0.001  |
| Sex              | Female           | 1 [Reference]    |         | 1 [Reference]    |         |
|                  | Male             | 1.27 (1.21-1.33) | <0.001  | 1.27 (1.20-1.33) | <0.001  |

TABLE 5: Continued.

| Variable                             | Category                                      | OS aHR (95% CI)   | p-value | CSS aHR (95% CI)  | p-value |
|--------------------------------------|-----------------------------------------------|-------------------|---------|-------------------|---------|
| Race and ethnicity                   | Non-Hispanic White                            | 1 [Reference]     |         | 1 [Reference]     |         |
|                                      | Non-Hispanic Black                            | 1.04 (0.94-1.14)  | 0.467   | 0.98 (0.89-1.09)  | 0.760   |
|                                      | Non-Hispanic American Indian or Alaska Native | 0.86 (0.65-1.14)  | 0.294   | 0.87 (0.65-1.17)  | 0.362   |
|                                      | Non-Hispanic Asian or Pacific Islander        | 1.17 (1.06-1.29)  | 0.003   | 1.17 (1.05-1.30)  | 0.005   |
|                                      | Hispanic, all races                           | 1.04 (0.97-1.10)  | 0.259   | 1.00 (0.93-1.06)  | 0.917   |
|                                      | Non-Hispanic unknown race                     | 0.34 (0.16-0.71)  | 0.004   | 0.28 (0.12-0.67)  | 0.004   |
| Marital status                       | Married                                       | 1 [Reference]     |         | 1 [Reference]     |         |
|                                      | Single or never married                       | 1.19 (1.11-1.28)  | <0.001  | 1.16 (1.08-1.24)  | <0.001  |
|                                      | Divorced, separated, or widowed               | 1.13 (1.08-1.19)  | <0.001  | 1.11 (1.05-1.17)  | <0.001  |
|                                      | Unmarried or domestic partner                 | 1.44 (1.00-2.08)  | 0.049   | 1.36 (0.92-2.02)  | 0.125   |
|                                      | Unknown                                       | 0.94 (0.84-1.05)  | 0.276   | 0.91 (0.80-1.02)  | 0.105   |
| County-level median household income | ≥\$100,000                                    | 1 [Reference]     |         | 1 [Reference]     |         |
|                                      | \$75,000-\$99,999                             | 1.05 (1.00-1.10)  | 0.062   | 1.03 (0.98-1.08)  | 0.300   |
|                                      | <\$75,000                                     | 1.06 (0.99-1.13)  | 0.077   | 1.04 (0.97-1.11)  | 0.293   |
|                                      | Unknown or missing                            | 4.42 (0.48-40.49) | 0.189   | 6.56 (0.66-64.70) | 0.107   |
| Rural-urban continuum                | Metropolitan ≥1 million                       | 1 [Reference]     |         | 1 [Reference]     |         |
|                                      | Metropolitan <1 million                       | 1.05 (1.00-1.10)  | 0.066   | 1.06 (1.00-1.11)  | 0.033   |
|                                      | Non-metropolitan                              | 1.11 (1.03-1.20)  | 0.008   | 1.17 (1.08-1.27)  | <0.001  |
|                                      | Unknown or missing                            | 1.15 (0.41-3.20)  | 0.788   | 0.94 (0.29-3.05)  | 0.924   |
| Histologic subtype                   | Epithelioid mesothelioma                      | 1 [Reference]     |         | 1 [Reference]     |         |
|                                      | Mesothelioma, NOS                             | 1.20 (1.14-1.26)  | <0.001  | 1.19 (1.13-1.25)  | <0.001  |
|                                      | Fibrous mesothelioma                          | 1.99 (1.85-2.13)  | <0.001  | 2.02 (1.87-2.17)  | <0.001  |
|                                      | Biphasic mesothelioma                         | 1.57 (1.45-1.70)  | <0.001  | 1.58 (1.46-1.72)  | <0.001  |
| Summary stage                        | Localized                                     | 1 [Reference]     |         | 1 [Reference]     |         |
|                                      | Regional                                      | 1.24 (1.15-1.35)  | <0.001  | 1.25 (1.15-1.37)  | <0.001  |
|                                      | Distant                                       | 1.53 (1.43-1.64)  | <0.001  | 1.57 (1.46-1.69)  | <0.001  |
|                                      | Unknown or unstaged                           | 1.12 (1.01-1.25)  | 0.028   | 1.12 (1.00-1.25)  | 0.043   |
| Cancer-directed surgery status       | Surgery performed                             | 1 [Reference]     |         | 1 [Reference]     |         |
|                                      | Not recommended or contraindicated            | 1.59 (1.51-1.68)  | <0.001  | 1.63 (1.55-1.73)  | <0.001  |
|                                      | Recommended but not performed or unknown      | 1.22 (1.09-1.37)  | <0.001  | 1.23 (1.09-1.39)  | <0.001  |
|                                      | Unknown, DCO, or autopsy only                 | 1.76 (1.39-2.23)  | <0.001  | 1.46 (1.11-1.93)  | 0.007   |
| Radiation therapy                    | No or unknown radiation                       | 1 [Reference]     |         | 1 [Reference]     |         |
|                                      | Radiation given                               | 1.01 (0.94-1.08)  | 0.831   | 1.03 (0.96-1.10)  | 0.464   |
| Chemotherapy                         | No or unknown chemotherapy                    | 1 [Reference]     |         | 1 [Reference]     |         |
|                                      | Chemotherapy yes                              | 0.72 (0.69-0.75)  | <0.001  | 0.75 (0.71-0.78)  | <0.001  |

The multivariable Cox proportional hazards models were adjusted for all variables shown in the table, including primary site, age group, diagnosis era, sex, race and ethnicity, marital status, county-level median household income, rural-urban continuum, histologic subtype, summary stage, cancer-directed surgery status, radiation therapy, and chemotherapy. Variables were selected a priori based on clinical relevance, epidemiologic importance, and availability in the SEER database rather than statistical significance in univariable analyses. Univariable analyses were presented for descriptive purposes only and were not used to determine variable inclusion in the multivariable models. OS was defined as death from any cause. CSS was defined as death attributable to mesothelioma, with deaths from other causes censored. Estimates for categories with fewer than 10 patients are unstable and are not interpreted. This applies to the unknown or missing income category (n=1) and the unknown or missing rural-urban category (n=5). The multicystic or other mesothelioma category included only two patients and was not included in Cox regression models because of sparse data and unstable HR estimation. Zero-month survival was recoded as 0.5 months for time-to-event modeling.

aHR: Adjusted hazard ratio; CI: Confidence interval; CSS: Cancer-specific survival; DCO: Death certificate only; NOS: Not otherwise specified; OS: Overall survival; SEER: Surveillance, Epidemiology, and End Results.

subset of 2,136 patients, distant lymph node metastasis was recorded in 249 (11.7%), and other metastases were recorded in 847 (39.7%).

Each of the four organ-specific metastases was associated with shorter OS (all log-rank  $p < 0.001$ ; Supplementary Table 5). Median OS was 3 months in patients with bone metastasis versus 9 months in those without, and 2 months in patients with brain metastasis versus 9 months in those without. Median OS was 4 months in patients with either liver or lung metastasis, compared with 9 months in patients without the respective metastasis. Median OS decreased from 10 months with no recorded metastatic site, to 5 months with a single recorded metastatic site, and to 2 months with multiple recorded metastatic sites. In the 2016-2023 subset, distant lymph node metastasis was not associated with OS (log-rank  $p = 0.333$ ). Patients with recorded other metastases had higher 3-year CSS than those without (21.9% versus 17.7%; log-rank  $p = 0.043$ ). This exploratory comparison was not adjusted for multiple testing.

## DISCUSSION

We analyzed two decades of population-level data on malignant mesothelioma. Survival remained poor across the cohort, but it was not uniform. Peritoneal disease was associated with longer survival than pleural disease, and part of that difference persisted after adjustment. Patients diagnosed in the most recent era had better survival, while the middle era did not differ from the earliest era. Fibrous histology was among the factors with the largest aHRs. Recorded chemotherapy was associated with lower mortality, whereas recorded radiation showed no association after adjustment.

Peritoneal mesothelioma behaved as a distinct disease entity. Patients were younger and more often female, which match earlier descriptions of this entity.<sup>7</sup> An earlier SEER analysis characterized the peritoneal group separately, but did not compare it with pleural disease.<sup>13</sup> Median OS was 17 months, compared with 9 months in pleural disease. The unadjusted HR of 0.52 increased to 0.81 after multivariable adjustment; however, a more modest adjusted association with the primary site remained. Specialized centers report substantially longer survival with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. A multi-institutional series of 405 patients reported a median survival of 53 months, whereas a single-center series of 108 patients reported a median survival of 63.2 months.<sup>11,18</sup> Our median peritoneal value was 17 months, but these figures are not directly comparable. The surgical series enrolled patients

selected to undergo cytoreduction, whereas our population-based cohort included a broader spectrum of peritoneal cases meeting the study criteria. No surgery, chemotherapy, or radiation was recorded for 26.5% of the peritoneal cohort. The difference may reflect patient selection, disease characteristics, treatment intensity, and referral to specialized centers.

Survival was better for patients diagnosed in 2016-2023, with an aHR of 0.84 compared with 2004-2009; whereas the 2010-2015 era did not differ from 2004-2009. The association observed for the 2016-2023 period remained similar after excluding patients with unknown or unstaged disease and when analyzed using the Fine-Gray competing-risk model. The era boundary is an analytic division rather than a treatment landmark. Dual immune checkpoint blockade became available in the final years of the 2016-2023 study period, and chemoimmunotherapy combinations were reported near its end.<sup>9,19</sup> We did not examine survival by individual year of diagnosis and, therefore, cannot determine when within this era the change emerged. Immunotherapy use and specific systemic regimens could not be assessed in this analysis. Therefore, the observed era association cannot be attributed to any specific agent. Earlier referral, better imaging, and improved supportive care may also have contributed. The temporal pattern is worth reporting, but it is not evidence of a causal treatment effect.

The histologic subtype showed the expected prognostic ordering. Fibrous mesothelioma, the SEER label corresponding to sarcomatoid and related variants, was associated with roughly twice the hazard of epithelioid mesothelioma, with biphasic disease intermediate between these estimates. This ordering agrees with the current WHO classification and earlier prognostic work.<sup>6,14</sup> A more concerning finding was the frequency of unspecified histology. Mesothelioma NOS accounted for 43.0% of the cohort and was the largest histologic category. Its aHR of 1.20 was closer to the epithelioid estimate than to the biphasic or fibrous estimates. The NOS category is likely heterogeneous, but its underlying subtype composition cannot be recovered from registry data. Reliable subtyping can be difficult with limited biopsy specimens, and ancillary immunohistochemical or molecular assessments may not always be available. Changes in tissue sampling, ancillary testing, and pathologic classification over the study period may have influenced the recorded subtype distribution.<sup>6,14</sup> Changes in imaging and clinicopathologic attribution may also have affected assignment to pleural, peritoneal, other, or unknown primary sites. The available registry data do not allow these contributions to be quantified. Subtype informs

prognostic counseling and treatment planning. A registry in which 43.0% of cases lack a specified subtype therefore limits both clinical interpretation and epidemiologic research.

Recorded metastatic spread showed a further prognostic gradient. Survival decreased as the number of recorded metastatic sites increased. Distant lymph node involvement, however, was not associated with OS in the 2016–2023 subset. A recent registry analysis of metastatic pleural mesothelioma reported better outcomes for nodal spread than for visceral spread, whereas our analysis did not identify a survival difference with respect to recorded distant lymph node involvement.<sup>20</sup> The nominally higher CSS among patients with recorded other metastases was counterintuitive and should therefore be interpreted with caution, because these subgroup comparisons were exploratory and not adjusted for multiple testing.

Our treatment findings should be interpreted with caution. Recorded chemotherapy was associated with lower mortality, with an aHR of 0.72, but this association should not be interpreted as a causal treatment effect. Unmeasured differences in fitness, comorbidity, and treatment eligibility may contribute to treatment-selection bias. SEER recodes for chemotherapy and radiation undercount therapy and combine untreated patients with those of unknown status.<sup>21</sup> We modeled treatment as a fixed baseline characteristic rather than a time-dependent exposure. Survival between diagnosis and chemotherapy initiation could, therefore, be attributed to the treated group, thereby introducing potential immortal-time bias.<sup>22</sup> Radiation presents a second problem. It appeared protective in univariable analysis (HR: 0.88), but the association disappeared after adjustment (aHR: 1.01). Confounding by indication is a plausible explanation, since radiation therapy in mesothelioma serves both palliative and multimodality treatment purposes. Surgery elicits the greatest tension. Compared with patients who underwent surgery, those for whom surgery was not recommended or was contraindicated had an aHR of 1.59. That category inherently reflects clinical selection for surgery and may capture prognostic factors that are incompletely measured in SEER; therefore, this comparison cannot isolate a surgical treatment effect. A SEER analysis using propensity score matching reported a median survival of 15 months with surgery, compared with 8 months without it.<sup>23</sup> Propensity matching balances only recorded variables; SEER does not include performance status or a comorbidity index, so the groups can remain unequal with respect to factors that drive the surgical decision. In the randomized MARS 2 trial in patients with pleural mesothelioma, adding extended pleurectomy decortication to chemotherapy did not improve

survival.<sup>10</sup> We therefore interpret our surgical contrast as selection rather than support for radical surgery. No surgery, chemotherapy, or radiation were recorded for 38.8% of the cohort; this should not be interpreted as confirmation of absence of treatment, because the SEER variables include patients with unknown treatment status.

Sociodemographic factors were also associated with the outcome. Patients living in non-metropolitan counties had higher mortality (aHR: 1.11), and those who were single or never married had higher mortality than married patients (aHR: 1.19). Marital status may partly reflect social support and access to care. Men also had higher mortality than women did, with an aHR of 1.27. This difference persisted after multivariable adjustment for primary site, age, stage, histologic subtype, and recorded treatment. SEER does not contain the clinical, biological, or treatment-related information needed to explain it. A recent registry analysis reported a similar metropolitan and non-metropolitan gap in pleural mesothelioma, and we observed a comparable pattern across all primary sites.<sup>24</sup> Because county-level measures describe areas rather than individuals, the mechanisms behind these associations remain undetermined.

Our treatment proportions were similar to those reported in a large hospital-based registry series of pleural mesothelioma, although the two registries overlap in coverage and share similar limitations in treatment ascertainment.<sup>25</sup> Environmental exposure to asbestos and erionite keeps mesothelioma a current problem in Türkiye, where a national surveillance program remains in place.<sup>5</sup> Population-based registry data, therefore, provide complementary context to clinical trial evidence in settings where mesothelioma remains an ongoing public health concern. Taken together, our findings provide a contemporary population-level description of treatment patterns, prognostic heterogeneity, and survival differences across primary sites and diagnostic eras.

### Study Limitations

Our study has several limitations. First, SEER treatment variables may underascertain receipt of therapy. The chemotherapy and radiation recodes combine patients who received no treatment with those whose treatment status is unknown, and validation work shows limited sensitivity for both modalities.<sup>21,26</sup> We also modeled treatment at baseline rather than as a time-dependent covariate; therefore, the treatment estimates are susceptible to immortal time bias.<sup>22</sup> The dataset used for this study lacked information on performance status, comorbidity, smoking history, asbestos exposure, chemotherapy regimen, dose, and line of therapy.

Immunotherapy use could not be assessed in this analysis. The design is observational; therefore, residual confounding remains possible despite adjustment.

Second, pathologic details are limited. Molecular markers such as BAP1, CDKN2A, and MTAP are absent, as is nuclear grading for epithelioid tumors.<sup>14,27</sup> Histologic subtype was unspecified in 43.0% of cases, limiting the interpretation of histology-specific comparisons. Changes in biopsy sampling, ancillary testing, imaging, and diagnostic classification may have influenced the recorded primary-site and histologic-subtype distributions. Detailed diagnostic data were unavailable, so differences in ascertainment could not be separated from differences in disease characteristics. The other or unknown primary-site category was inherently heterogeneous. Its short median OS, contrasted with a relatively high 5-year OS, may reflect this mixed composition, which also limits interpretation of site-specific estimates for that group.

Third, several measures describe areas rather than individuals. County-level median household income and the rural-urban continuum are area-level characteristics and should not be interpreted as individual socioeconomic status. SEER 17 also covers only a subset of the United States population, which may limit generalizability to the wider national population.

Fourth, site-specific metastases and surgical details are incompletely recorded. Only sites explicitly recorded as metastatic contributed to the burden count; therefore, this variable reflects recorded, rather than necessarily complete, metastatic burden. The “no recorded metastatic site” category may include incomplete records or metastases outside the four counted organs, and does not denote the absence of metastatic disease. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy is not coded separately, which limits the inferences that we can draw about peritoneal surgery.

Fifth, the analysis has limited temporal resolution. Patients diagnosed in the most recent era had shorter potential follow-up periods, reducing the precision of longer-term survival estimates for this group. In addition, the use of broad diagnosis eras without year-specific analyses prevents identification of when, within 2016-2023, the observed survival difference emerged. Several categories contained very few patients, and estimates from categories with fewer than 10 patients were not interpreted. Time-specific numbers at risk are not displayed in Figures 2-5, which limits assessment of the patients contributing to the late portions of the curves. Late curve tails should therefore be interpreted cautiously and not as evidence of stable long-term survival plateaus. The fixed-time estimates with 95% CIs in Table 3 and

Supplementary Table 1 provide complementary information, but do not replace time-specific risk counts.

Finally, CSS relied on the SEER cause-specific death classification. Misclassification between mesothelioma-related and competing causes of death, including cardiovascular disease, is possible and is particularly relevant when interpreting outcomes in older patients. The Fine-Gray analysis accounted for competing risks but could not correct for misclassification of recorded causes of death. OS does not require attribution of a specific cause of death.

## CONCLUSION

Across two decades of population-level data, malignant mesothelioma remained a lethal disease, with a median OS of 9 months and a median CSS of 11 months. Survival was better for patients diagnosed in 2016-2023, with median OS of 11 months and 3-year OS of 20.5%. Advanced age, fibrous histology, unspecified histologic subtype, and non-metropolitan residence were each associated with higher adjusted mortality across the study period. More complete ascertainment and reporting of histologic subtype would strengthen prognostic interpretation and registry-based research.

## Ethics

**Ethics Committee Approval:** The Surveillance, Epidemiology, and End Results database contains de-identified, publicly available data. Institutional review board approval was not required.

**Informed Consent:** Not required for this study.

## Footnotes

### Authorship Contributions

Concept: E.Y., G.C.U., M.A., Design: E.Y., G.C.U., Data Collection or Processing: E.Y., G.C.U., K.B., G.A., I.D., M.A., Analysis or Interpretation: E.Y., G.C.U., M.A., Literature Search: E.Y., K.B., G.A., I.D., Writing: E.Y., G.C.U., K.B., G.A., I.D., M.A.

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**Supplementary Tables 1-5:** <https://d2v96fxpocvxx.cloudfront.net/f942abf9-a73b-4057-b48b-c3a4b7d0c2a5/content-images/0063131f-0a2d-40e6-b1b9-6d4b3d6cdb75.pdf>

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