# Chemotherapy Versus Supportive Care for Unresected Malignant Pleural Mesothelioma

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## Abstract

**Management for unresected malignant pleural mesothelioma is largely limited to palliative chemotherapy and best supportive care. From this study, chemotherapy may benefit metastatic epithelioid and non-metastatic non-epithelioid malignant pleural mesothelioma to a greater degree than metastatic non-epithelioid disease.**

**Background:** Management options for unresected malignant pleural mesothelioma (MPM) are largely limited to palliative chemotherapy and best supportive care. This study sought to delineate subgroups most likely to benefit from chemotherapy. **Patients and Methods:** The National Cancer Database was queried for newly-diagnosed unresected sarcomatoid, biphasic, and/or metastatic (M1) MPM. Statistics included Kaplan-Meier overall survival (OS) analysis with and without propensity matching, landmark Kaplan-Meier analysis to address immortal time bias, and multivariable Cox proportional hazards modeling in all patients as well as within histologic/M-classification-based subcohorts. **Results:** Of 4655 patients (48% chemotherapy, 52% best supportive care), 15%, 27%, and 40% had epithelioid, biphasic, and sarcomatoid disease, respectively; 41% had M1 disease. The median OS in the chemotherapy and BSC cohorts was 10.4 versus 4.8 months ($P < .001$). OS differences persisted following landmark analysis ($P = .038$) and propensity matching ($P < .001$). Chemotherapy was associated with higher OS in M1 cases with unknown histology and M1 epithelioid patients ($P < .001$ for both). For non-epithelioid cases, chemotherapy was associated with higher OS for M0 ($P < .001$ for sarcomatoid and biphasic) but not M1 ($P > .05$ for both) disease. **Conclusions:** Chemotherapy may benefit metastatic epithelioid and non-metastatic non-epithelioid MPM to a greater degree than metastatic non-epithelioid disease. Causation, however, is not implied, and careful patient selection in this population cannot be understated.

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## Introduction

Malignant pleural mesothelioma (MPM) is an aggressive neoplasm with a very poor prognosis. The majority of patients present with unresectable disease, for which treatment options are largely limited to palliative chemotherapy (with or without palliative radiotherapy) and best supportive care (BSC).[1] Because patients with MPM are often symptomatic, chemotherapy is considered an important palliative therapy for this population.[2] Chemotherapy affords a clinical response in up to 50% of patients[3,4] and may improve symptoms and avoid or delay quality of life deterioration[3,5,6]; modern systemic paradigms could even be associated with outcome improvements.[7] However, BSC alone is also an effective method with which to manage symptomatic burden[8,9]; additionally, concerns remain regarding possibly toxicity with palliative chemotherapy.[10]

Small retrospective studies evaluating BSC versus palliative chemotherapy have shown outcome benefits for the latter[11,12];

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however, a British randomized trial addressing this issue failed to show an overall survival (OS) advantage to chemotherapy in a study population with about 74% epithelioid histology.[13] This trial was initially designed as a 3-arm study to compare BSC versus BSC + mitomycin/vinblastine/cisplatin chemotherapy versus BSC + vinorelbine, but owing to slow accrual and the positive results from a phase III trial of pemetrexed-based chemotherapy,[3] the trial was modified to a 2-arm design by merging both chemotherapy groups. Thus, the overall analysis of BSC with or without chemotherapy was negative ($P = .29$ for OS), but the BSC + vinorelbine arm (which, following the schema re-design, became only an exploratory comparison) displayed a trend towards improved OS over BSC alone ($P = .08$).

The National Comprehensive Cancer Network (NCCN) currently recommends 3 options for metastatic, biphasic, sarcomatoid, and/or medically inoperable disease.[1] These include BSC, upfront chemotherapy, or chemotherapy at clinical progression. Because various subgroups of MPM may differentially benefit from chemotherapy, this study utilized a large, contemporary national database to evaluate the effect of chemotherapy on various histologic- and M-classification-based subgroups of MPM.

## Materials and Methods

The National Cancer Database (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons

**Figure 1** Patient Selection Diagram

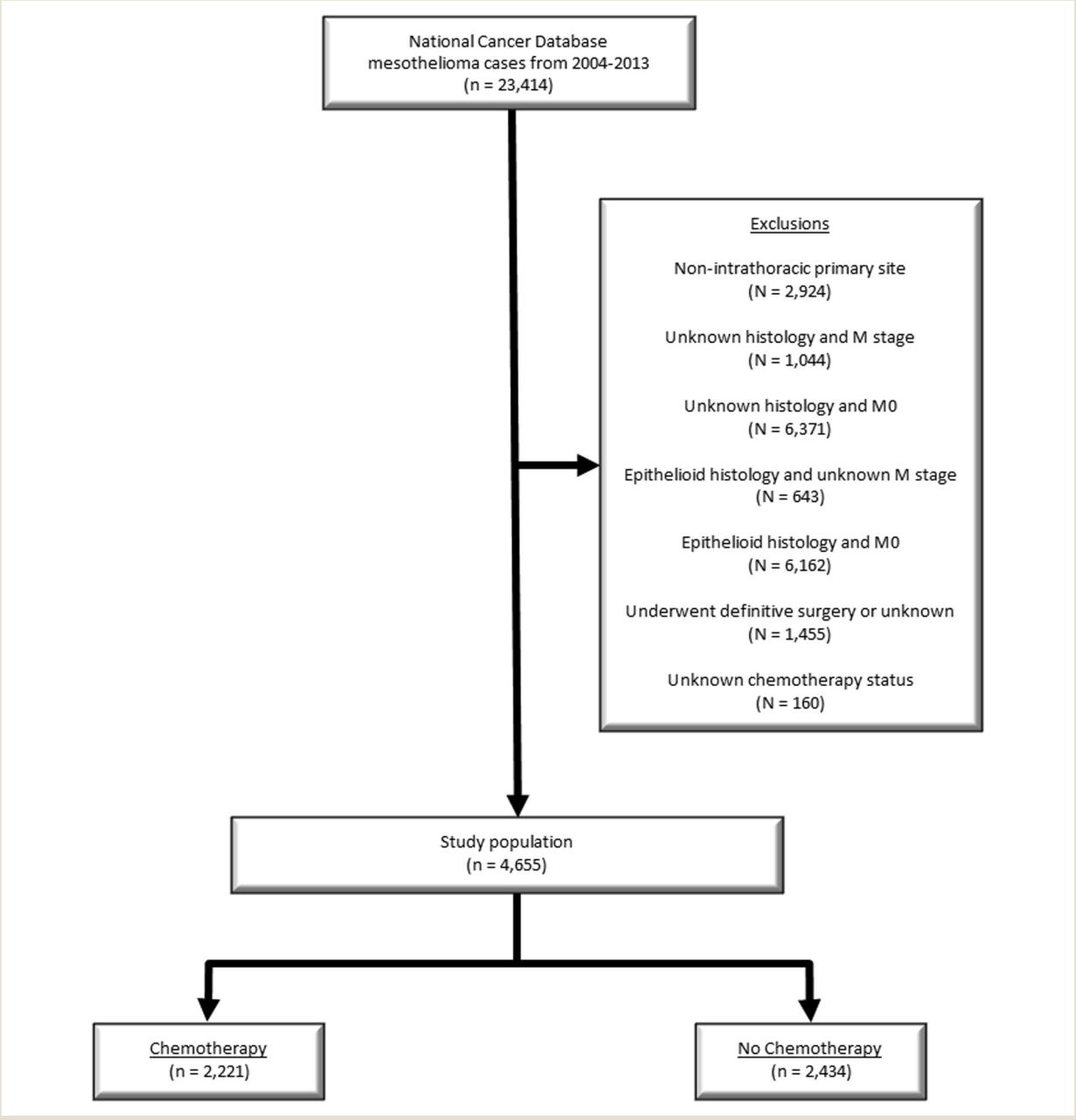


**Table 1** Clinical Characteristics of the Patient Populations

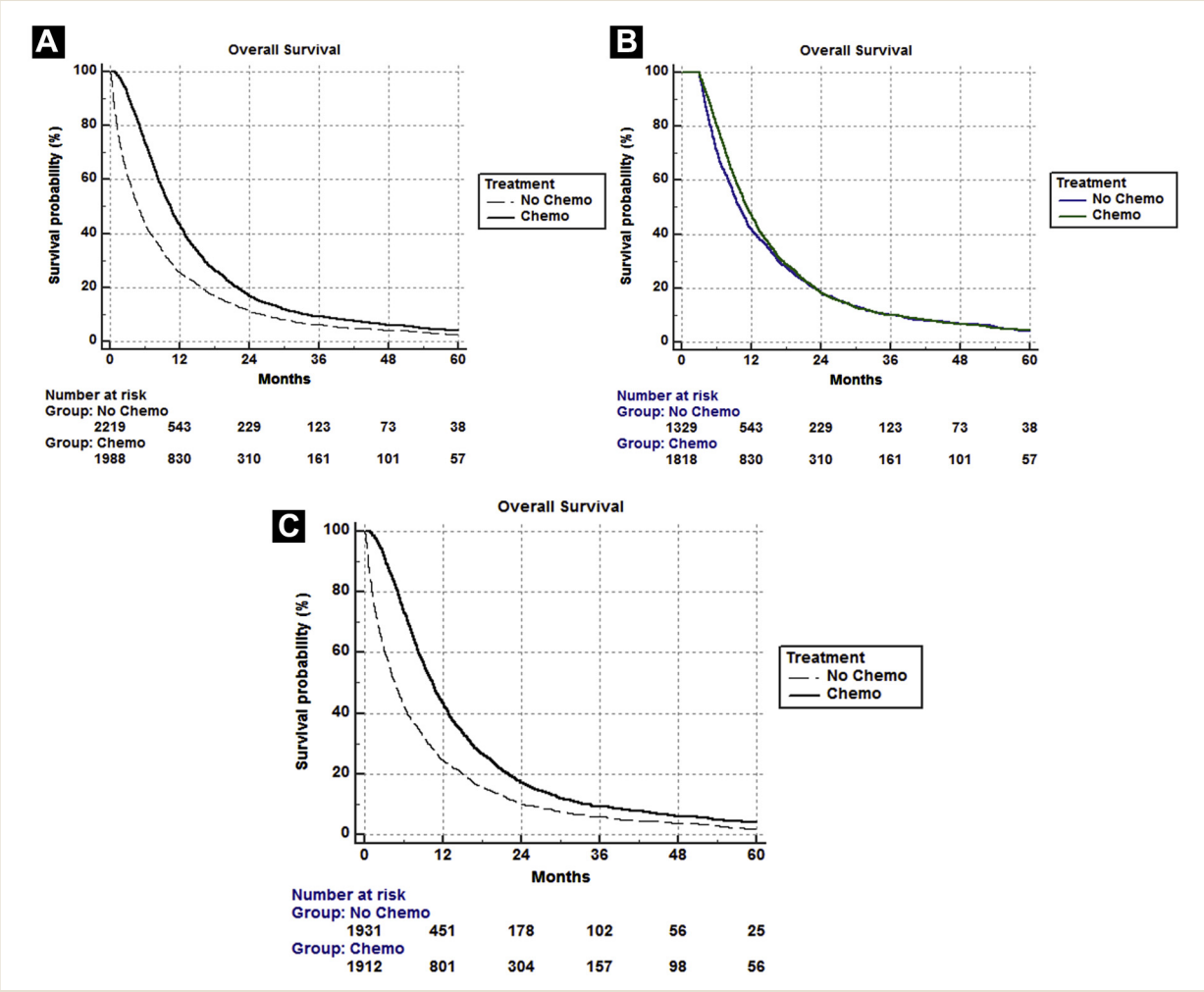
| Parameter | Chemotherapy (N = 2221), n (%) | No Chemotherapy (N = 2434), n (%) |
|---|---|---|
| **Age, y** | | |
| < 74 | 1065 (48) | 1204 (49) |
| ≥ 74 | 1156 (52) | 1230 (51) |
| **Gender** | | |
| Male | 1815 (82) | 2012 (83) |
| Female | 406 (18) | 422 (17) |
| **Race** | | |
| White | 2070 (93) | 2256 (93) |
| Black | 94 (4) | 102 (4) |
| Other | 42 (2) | 53 (2) |
| Unknown | 15 (1) | 23 (1) |
| **Charlson-Deyo comorbidity index** | | |
| 0 | 1544 (70) | 1678 (69) |
| 1 | 472 (21) | 534 (22) |
| 2 | 205 (9) | 222 (9) |
| **Income, US dollars/year** | | |
| < $30,000 | 311 (14) | 334 (14) |
| $30,000-$34,999 | 515 (23) | 550 (23) |
| $35,000-$45,999 | 615 (28) | 671 (28) |
| ≥ $46,000 | 719 (32) | 816 (34) |
| Unknown | 61 (3) | 63 (3) |
| **Percentage of adults in zip code without high school diploma** | | |
| ≥ 21% | 316 (14) | 314 (13) |
| 13%-20.9% | 543 (24) | 578 (24) |
| 7%-12.9% | 761 (34) | 862 (35) |
| < 7% | 541 (24) | 618 (25) |
| Unknown | 63 (3) | 62 (3) |
| **Patient residence** | | |
| Metro | 1062 (48) | 1188 (49) |
| Urban | 486 (22) | 500 (21) |
| Rural | 212 (10) | 264 (11) |
| Unknown | 461 (21) | 482 (20) |
| **Facility type** | | |
| Community | 1328 (60) | 1415 (58) |
| Academic | 874 (39) | 1003 (41) |
| Unknown | 19 (1) | 16 (1) |
| **Distance to treatment facility, miles** | | |
| < 10 | 1075 (48) | 1158 (48) |
| ≥ 10 | 1088 (49) | 1216 (50) |
| Unknown | 58 (3) | 60 (2) |
| **Facility location** | | |
| Northeast | 548 (25) | 650 (27) |
| Midwest | 601 (27) | 663 (27) |
| South | 693 (31) | 742 (30) |
| West | 364 (16) | 366 (15) |
| Unknown | 15 (1) | 13 (1) |
| **Years of diagnosis** | | |
| 2004-2008 | 934 (42) | 981 (40) |
| 2009-2013 | 1287 (58) | 1453 (60) |
| **Histology** | | |
| Epithelioid | 311 (14) | 376 (15) |
| Biphasic | 532 (24) | 738 (30) |
| Sarcomatoid | 920 (41) | 952 (39) |
| Unknown | 458 (21) | 368 (15) |
| **Clinical T classification** | | |
| TX | 730 (33) | 732 (30) |
| T1 | 324 (15) | 395 (16) |
| T2 | 304 (14) | 403 (17) |
| T3 | 199 (9) | 223 (9) |
| T4 | 664 (30) | 681 (28) |
| **Clinical N classification** | | |
| NX | 763 (34) | 795 (33) |
| N0 | 959 (43) | 1124 (46) |
| N1 | 97 (4) | 89 (4) |
| N2 | 327 (15) | 349 (14) |
| N3 | 75 (3) | 77 (3) |
| **Clinical M classification** | | |
| MX | 142 (6) | 156 (6) |
| M0 | 1123 (51) | 1329 (55) |
| M1 | 956 (43) | 949 (39) |

Percentages may not add to 100% because of rounding.

and the American Cancer Society that consists of information regarding tumor characteristics, patient demographics, and patient survival for approximately 70% of the United States population.[14] The NCDB contains information not included in the Surveillance, Epidemiology, and End Results database, including details regarding the use of systemic therapy. The American College of Surgeons and the CoC have not verified and are neither responsible for the analytic or statistical methodology employed nor the conclusions drawn from these data. As all patient information in the NCDB is de-identified, this study was exempt from institutional review board evaluation.

The NCDB Participant User File corresponding to mesothelioma (2004-2013) was utilized for this study. Inclusion criteria for this investigation corresponded to current NCCN guidelines, which state that resection should be reserved only for nonmetastatic epithelioid MPM; M1 (stage IV), sarcomatoid, biphasic, or medically inoperable cases should be considered for BSC or palliative chemotherapy. As a result, patients were included if M1 disease was present (even if histology was unknown, because NCCN recommends the same management for M1 cases regardless of histology[1]) but excluded if M0/MX patients also had unknown histology. Of the epithelioid patients, only M1 epithelioid cases were included because (1) resection is recommended for M0 epithelioid MPM[1] and (2) although the NCCN states that medically inoperable M0 epithelioid patients should not

**Figure 2** Comparison of Overall Survival Between Treatment Paradigms in the Overall Population (A), on Landmark Analysis of ≥ 3-Month Survivors (B), and Following Propensity Matching (C)




Abbreviation: Chemo = chemotherapy.

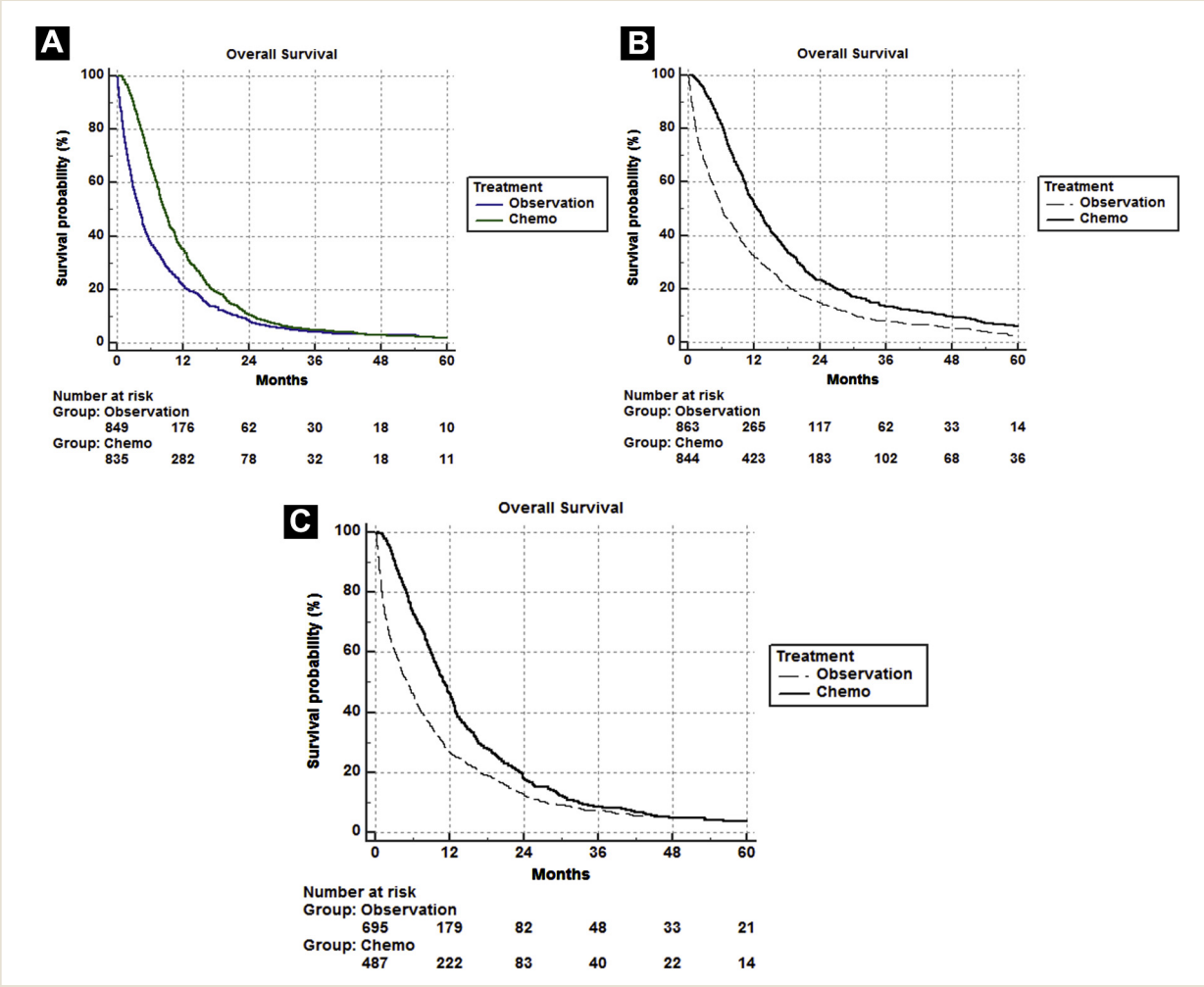
undergo resection, the NCDB does not give specific reasons for medical inoperability, and thus M0 epithelioid patients who did not undergo surgery were obligatorily removed to minimize bias. Lastly, additional exclusion criteria were receipt of definitive surgery, and unknown surgery or chemotherapy status.

In accordance with the variables in the NCDB files, information collected on each patient broadly included demographic, clinical, and treatment data. Statistical analysis was performed with MedCalc version 18 (Ostend, Belgium). Tests were 2-sided, with a threshold of $P < .05$ for statistical significance. First, clinical characteristics of the overall cohort were tabulated. Second, multivariable logistic regression analysis was performed to ascertain factors independently associated with receipt of chemotherapy. Third, Kaplan-Meier curves were calculated to evaluate OS, defined as the interval between the date of diagnosis and the date of death, or censored at last contact. Landmark Kaplan-Meier analysis of ≥ 3-month survivors was additionally performed to address immortal time bias. Multivariable Cox proportional hazards modeling was utilized to evaluate predictors of OS. Fourth, in an attempt to minimize selection and indication biases, patients underwent 1:1 propensity matching. To estimate the propensity score for each patient, the univariate association of each covariate with treatment type was assessed using a simple logistic regression model. Covariates that were significantly associated with treatment type ($P < .05$) were included in a multivariable logistic regression model, and backwards stepwise selection was performed with $\alpha = 0.20$; matching was performed with a caliper 0.2 times the standard deviation of the logit propensity score.[15,16] Kaplan-Meier curves were then generated on the propensity-matched patients.

## Results

A patient selection diagram is illustrated in Figure 1. Overall, 4655 patients met study criteria (Table 1). Of these, 2221 (48%) received chemotherapy, and 2434 (52%) did not. Of note, 15% of the overall cohort had epithelioid disease, along with 27% biphasic and 40% sarcomatoid histology, with the remainder having

**Figure 3** Comparison of Overall Survival Between Treatment Paradigms in the M1 (Metastatic) (A), Sarcomatoid (B), and Biphasic (C) Subsets




Abbreviation: Chemo = chemotherapy.

unknown histology. Irrespective of histology, 41% of the population had metastatic disease. Groups were well-balanced; no single factor independently predicted for administration of chemotherapy on multivariable logistic regression analysis ($P > .05$ for all variables). However, there were nonsignificant trends for chemotherapy being more often delivered to sarcomatoid disease ($P = .107$) and less often to biphasic cases ($P = .085$).

The median follow-up for all patients was 7.4 months (interquartile range, 3.0-15.5 months). Kaplan-Meier estimates comparing OS in patients having received chemotherapy versus BSC are illustrated in Figure 2A. Respective median survival figures were 10.4 months (95% confidence interval [CI], 9.9-10.8 months) and 4.8 months (95% CI, 4.5-5.2 months) ($P < .001$). A landmark analysis of $\geq$ 3-month survivors confirmed significant findings between both cohorts (median 11.2 vs. 10.0 months; $P = .038$) (Figure 2B). Following propensity matching, the chemotherapy cohort remained associated with higher OS than BSC (10.4 months; 95% CI, 9.9-10.8 months vs. 4.6 months; 95% CI, 4.2-5.0 months; $P < .001$) (Figure 2C). In all patients, there were 2 significant factors associated with OS on Cox multivariate analysis: receipt of chemotherapy (hazard ratio [HR], 0.640; 95% CI, 0.601-0.681; $P < .001$) and epithelioid histology (relative to biphasic: HR, 0.627; 95% CI, 0.568-0.693; relative to sarcomatoid: HR, 0.551; 95% CI, 0.501-0.606; $P < .001$ for both).

Further analysis of chemotherapy versus BSC was performed in the M1 subpopulation (regardless of histology), which showed a median OS of 8.6 months (95% CI, 8.1-9.3 months) for chemotherapy versus 4.1 months (95% CI, 3.7-4.6 months) with BSC ($P < .001$) (Figure 3A). Additionally, regardless of M classification, this sub-analysis was repeated separately with the sarcomatoid (12.6 months; 95% CI, 11.8-13.6 months vs. 6.1 months; 95% CI, 5.6-6.9 months; $P < .001$) (Figure 3B) and biphasic subsets (11.1 months; 95% CI, 10.2-12.2 months vs. 5.3 months; 95% CI, 4.2-6.0 months; $P < .001$) (Figure 3C).

Table 2 illustrates Cox multivariate analysis when stratifying for both M classification and histology. Chemotherapy seemed to

**Table 2** Effect of Chemotherapy on Overall Survival by Means of Cox Multivariate Analysis on Specific Subpopulations

| Group | Sample Size | Hazard Ratio | 95% Confidence Interval | *P* Value |
|---|---|---|---|---|
| Unknown histology, metastatic disease | 826 | 0.622 | 0.534-0.726 | **< .001** |
| Epithelioid, metastatic disease | 687 | 0.578 | 0.489-0.677 | **< .001** |
| Sarcomatoid, metastatic disease | 270 | 0.842 | 0.640-1.110 | .222 |
| Sarcomatoid, no metastases | 1402 | 0.570 | 0.508-0.639 | **< .001** |
| Biphasic, metastatic disease | 122 | 0.712 | 0.443-1.142 | .158 |
| Biphasic, no metastases | 1050 | 0.646 | 0.567-0.736 | **< .001** |

Statistically significant *P* values are in bold.

impact M1 non-epithelioid disease to a lesser degree ($P = .222$ for sarcomatoid, $P = .158$ for biphasic) than M0 non-epithelioid, M1 epithelioid, and M1 unknown histology ($P < .001$ for all).

## Discussion

This investigation, the largest study of its kind to date, implies that chemotherapy may benefit metastatic epithelioid and non-metastatic non-epithelioid MPM to a greater degree than metastatic non-epithelioid disease. Despite these findings, causation is not implied, and careful patient selection in this population cannot be understated.

Although a strength of this study is that both cohorts were notably well-balanced, these findings must still be interpreted with caution because retrospective comparisons of chemotherapy versus lack thereof may be hampered by possible imbalances in uncoded variables as well as indication biases. With respect to these data, it is known that the chemotherapy cohort was "fit" enough to receive chemotherapy, whereas it may be assumed that some proportion of the BSC group had poor functional status, which impaired chemotherapy receipt and potentially hastened mortality. In other words, the "true" effect size of chemotherapy on OS may be less than that described in this (and any other retrospective) study. As a result, our conclusions have been deliberately interpreted conservatively, namely that the relative effect size of chemotherapy is less for metastatic non-epithelioid disease.

Based on the observed interaction between M1 status and histology, few interventions (if any) may be able to overcome the extremely poor OS of non-epithelioid M1 disease. This interaction is also supported by the nearly identical HRs in Table 2 for M0 sarcomatoid and M1 epithelioid disease, which is important because the former was greatly under-represented (in favor of the latter) in the randomized trial by Muers and colleagues.[13]

Taken together, these results suggest that M classification and histology should both be utilized as major determinants of management. However, individualized judgment is still warranted because the effect size of chemotherapy also depends on important factors such as age and performance status. It is also possible that genomic analyses may better delineate which tumors are more likely to respond to chemotherapy.[17] Additionally, given the poor prognosis of unresected MPM, judicious patient counseling regarding the risks and benefits of palliative chemotherapy is paramount, and, as always, wishes of the patient and/or family should carry substantial weight.

In addition to an ongoing randomized trial evaluating early palliative interventions for this population,[18] other efforts to better address management of this population have come in the form of delivering less toxic compounds such as thalidomide[19] or lurbinectedin[20] in addition to, or in lieu of, chemotherapy. Additionally, multiple phase I and II trials of immune checkpoint inhibitors for similar clinical settings have been published over the past 1 to 2 years.[21-24] Although tolerability profiles are much improved over conventional chemotherapy, immune checkpoint inhibitors are financially cumbersome,[25,26] and overall response rates do not exceed 28%.[21-24]

NCDB studies do not substitute for randomized evidence and have several limitations.[27-32] In addition to retrospective selection and indication biases as mentioned above, the NCDB does not carry information on chemotherapy agents, dose, cycles, or tolerance. Additional information not captured by the NCDB includes disease bulk/symptomatology, performance status, pulmonary function, and salvage therapies, all which could affect OS and confound conclusions of the current study. Lastly, although the NCDB includes data for 70% of the United States population, only CoC-accredited facilities contribute data; as such, these findings may not necessarily be representative of the entire United States population.

## Conclusions

This investigation, the largest study of its kind to date, implies that chemotherapy may benefit metastatic epithelioid and non-metastatic non-epithelioid MPM to a greater degree than metastatic non-epithelioid disease. Despite these findings, causation is not implied, and careful patient selection in this population cannot be understated.

### *Clinical Practice Points*

- Management of unresected MPM includes palliative chemotherapy and BSC.
- Comparative outcomes of both approaches are under-studied.
- The effect size for chemotherapy was higher for M1 epithelioid and M0 non-epithelioid MPM than M1 non-epithelioid disease.
- Careful patient selection in this population cannot be understated.

## Disclosure

The authors have stated that they have no conflicts of interest.

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