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Management of Malignant Pleural Mesothelioma in the Elderly Population

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ABSTRACT

Background. The median age at diagnosis for malignant pleural mesothelioma (MPM) is approximately 72 years. Elderly patients pose unique management challenges because of the increased risk of therapy-related toxicities and mortality. Because there are no high-volume retrospective studies, prospective trials, or dedicated treatment recommendations for this population, this investigation addresses a major knowledge gap by examining national practice patterns and postoperative/survival outcomes in elderly MPM patients.

Methods. The National Cancer Database was queried for patients aged ≥ 80 years with newly diagnosed nonmetastatic MPM. Multivariable logistic regression ascertained factors associated with observation and surgery. Kaplan–Meier analysis assessed overall survival (OS), and multivariable Cox proportional hazards modeling examined factors associated with OS. Survival was also calculated following propensity matching. Additionally, postoperative outcomes were evaluated in surgical patients.

Results. Of 4526 patients, 2% received surgery and chemotherapy, 22% underwent chemotherapy alone, and 63% were observed. Respective median OS was 12.2, 9.5,

and 4.1 months ($p < 0.001$). Differences between all groups persisted following propensity matching (all comparisons $p < 0.05$). For the 8% of patients who underwent specified definitive surgery (95% of whom received pleurectomy/decortication), 30- and 90-day mortality rates were 11.0% and 28.5%, respectively. The median length of postoperative hospitalization was 6 days, with 30-day readmission occurring in 7.5% of patients.

Conclusions. The majority of elderly MPM patients in the US are observed, which was associated with poorer OS than chemotherapy and/or surgery. Although highly selected surgery/chemotherapy patients were associated with the longest OS, given the high biases in database studies and high perioperative mortality rates, careful patient selection for combined modality approaches in this population is imperative.

Malignant pleural mesothelioma (MPM) is commonly treated with a multidisciplinary approach involving gross macroscopic resection (with or without intraoperative therapy) if resectable; chemotherapy is also recommended, as well as radiotherapy in select cases.[1–6] However, based on the particular clinical circumstance, recommendations by the National Comprehensive Cancer Network (NCCN) also list chemotherapy alone and best supportive care as viable options.[1]

In addition to resectability status, age is a major determinant of oncologic management. In part owing to the long latency from asbestos exposure to diagnosis, MPM is diagnosed at a median age of approximately 72 years.[1] As a result, many patients cannot tolerate aggressive multimodality therapy.[7] Exacerbating this issue is the fact that

elderly patients are highly underrepresented in MPM clinical trials, as the median age of patients in three major randomized studies was 61–62 years.[8–10] In two of these three trials, no patients over the age of 74 years were enrolled.[9,10]

It is critical to study the elderly MPM population for multiple reasons. First, their incidence as a proportion of all MPM diagnoses is rising.[11] Second, although overall MPM-related mortality is slightly declining in many countries, it is *increasing* for elderly patients across the world.[12] Third, elderly patients are more prone to treatment-related death, which is notable in light of the relatively high mortality rates of MPM surgical procedures.[9] Taken together, compared with younger patients, it is arguably even more important to carefully weigh the notions of overtreatment versus undertreatment in elderly patients. This is essential to practicing judicious oncologic management, namely by pitting the potential for oncologic gain against the risk of treatment-related toxicities.

Unfortunately, evidence-based management for elderly MPM patients remains extremely limited, including a complete lack of prospective trials in this population to date. As such, there are no specific treatment guidelines for elderly patients with MPM (including by the NCCN[1]), and management is thus determined largely on an individualized basis. To address this knowledge gap, this study is the largest known investigation of MPM in this challenging population. The goals of this study include evaluation of how these elderly patients are managed in the US, as well as outcomes [overall survival (OS) and postoperative events] across multiple treatment approaches.

MATERIALS AND METHODS

The National Cancer Database (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons (ACS) and the American Cancer Society that consists of information regarding tumor characteristics, patient demographics, and patient survival for approximately 70% of the US population.[13] The data used in this study were derived from a de-identified NCDB file. The ACS 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 database 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 were patients ≥80 years of age with newly diagnosed nonmetastatic MPM. The definition of 80 years was utilized because the median age at diagnosis is over 70 years.[1] Patients were excluded for metastatic disease (or unknown M classification) and/or if the primary disease was located in a non-intrathoracic site. Of note, the minority of patients who received surgery without chemotherapy (which is not a recognized treatment option for MPM[1]) or had unknown surgery/chemotherapy status, were still included in this study so that national patterns of care could be evaluated since indiscriminately excluding patients can heighten biases when assessing patterns of care. However, they were excluded from further analyses following multivariable logistic regression.

In accordance with the variables in NCDB files, information collected on each patient broadly included demographic, clinical, and treatment data. Statistical analysis was performed using MedCalc version 18 (MedCalc Software, Ostend, Belgium). Tests were two-sided, with a threshold of $p < 0.05$ for statistical significance. First, clinical characteristics of the overall cohort were tabulated. Second, two sets of multivariable logistic regression analyses were performed to ascertain factors independently associated with (1) receipt of surgical therapy (regardless of chemotherapy status) and (2) observation (defined as the lack of both surgery and 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. Multivariable Cox proportional hazards modeling (backward stepwise selection) was utilized to evaluate predictors of OS. Although addressing immortal time bias was a consideration, owing to the very short life expectancy of the cohorts herein, exploratory landmark analysis resulted in excluding too many patients for that analysis to be statistically reliable. 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 the particular treatment group was assessed using a simple logistic regression model. Covariates that were significantly associated with treatment type ($p < 0.05$) 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.[14, 15] Kaplan–Meier curves were then generated on the propensity-matched patients.

RESULTS

A patient selection diagram is illustrated in Fig. 1. Overall, 4526 patients met the study criteria (Table 1). The vast majority of patients were Caucasian, male, and had Medicare insurance, and the median age was 84 years

[interquartile range (IQR) 82–86]. In total, 3960 (87%) patients did not undergo surgery (regardless of chemotherapy status). Of the 344 (8%) patients who underwent surgery using a defined surgical technique, 18 (5%) underwent extrapleural pneumonectomy (EPP) and the remainder ($n = 326$, 95%) underwent pleurectomy/decortication (P/D). Chemotherapy was delivered (regardless of surgical status) in 1142 (25%) patients. When evaluating management in a combined manner, 993 (22%) patients received chemotherapy alone, 566 (13%) received surgery alone, 97 (2%) underwent both surgery and chemotherapy, and 2853 (63%) patients were observed.

Multivariable logistic regression analyses were performed to evaluate independent predictors of receiving surgery (regardless of chemotherapy, largely because so few patients were in the surgery/chemotherapy cohort) and observation (Table 2). Patients undergoing surgery were more likely to be younger and had biphasic histology ($p < 0.05$ for both). Observation was more often performed in older patients, females, community facilities, and sarcomatoid disease ($p < 0.05$ for all). There were also differences based on comorbidity status and geographic location ($p < 0.05$ for both).

Median follow-up using the reverse Kaplan–Meier method was 63 months (IQR 34–90). Kaplan–Meier estimates comparing OS in patients having received surgery/chemotherapy, chemotherapy alone, and observation are illustrated in Fig. 2a (the surgery alone cohort was not further addressed because it is a nonstandard treatment as recognized by the NCCN[1]). Respective median survival figures were 12.2 months [95% confidence interval (CI) 10.2–16.9], 9.5 months (95% CI 8.6–10.2), and 4.1 months (95% CI 3.8–4.4) ($p < 0.001$; $p = 0.06$ for pairwise comparison for surgery/chemotherapy vs. chemotherapy alone). Exploratory analysis of surgery/chemotherapy versus chemotherapy alone for the epithelioid population suffered from low sample sizes in the combined modality group, but was not significantly different (median 15.0 vs. 12.1 months, $p = 0.68$) (Fig. 2b).

Following propensity matching, the surgery/chemotherapy cohort was associated with higher OS than those undergoing chemotherapy alone [13.4 (95% CI 10.9–19.3) months vs. 6.5 (95% CI 5.5–7.8) months, $p = 0.002$] (Fig. 2c). Similarly, a statistical difference remained between the chemotherapy alone and observation
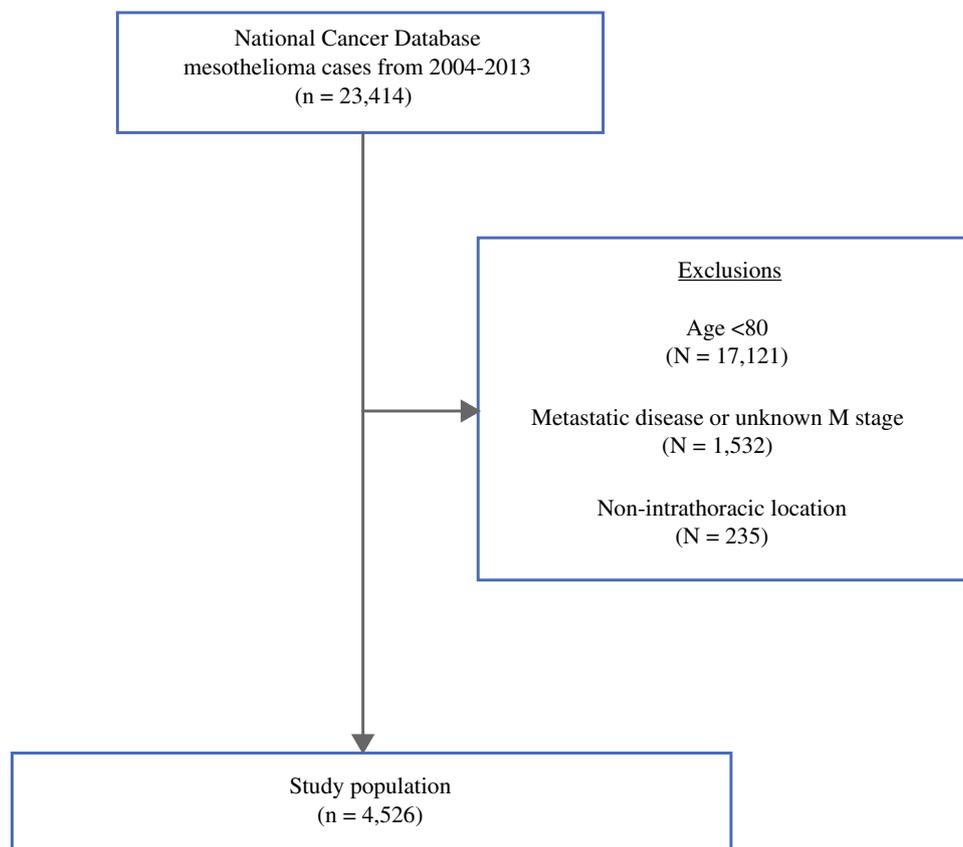

FIG. 1 Patient selection process

TABLE 1 Clinical characteristics of the overall cohort

Parameter	All patients (N = 4526)
Median age, years (IQR)	84 (82–86)
Sex	
Male	3570 (79)
Female	956 (21)
Race	
White	4308 (95)
Black	124 (3)
Other	59 (1)
Unknown	35 (1)
Charlson–Deyo comorbidity index	
0	2885 (64)
1	1141 (25)
2	500 (11)
Insurance type	
Private	419 (9)
Medicaid	24 (1)
Medicare	3973 (88)
Other government	24 (1)
Uninsured	10 (0)
Unknown	76 (2)
Income (US$/year)	
< 30,000	546 (12)
30,000–34,999	963 (21)
35,000–45,999	1309 (29)
≥ 46,000	1586 (35)
Unknown	122 (3)
Percentage of adults in zip code area without a high-school diploma	
≥ 21	460 (10)
13–20.9	1013 (22)
7–12.9	1656 (37)
< 7	1276 (28)
Unknown	121 (3)
Patient residence	
Metro	3731 (82)
Urban	510 (11)
Rural	62 (1)
Unknown	223 (5)
Facility location	
Northeast	1211 (27)
Midwest	1261 (28)
South	1252 (28)
West	802 (18)
Facility type	
Community	3042 (67)
Academic	1478 (33)
Unknown	6 (0)

TABLE 1 continued

Parameter	All patients (N = 4526)
Median distance to the treating facility, miles (IQR)	7 (3–17)
Year of diagnosis	
2004–2008	2712 (60)
2009–2013	1814 (40)
Clinical T classification	
T1	1211 (27)
T2	731 (16)
T3	327 (7)
T4	850 (19)
Unknown	1407 (31)
Clinical N classification	
N0	2393 (53)
N1	109 (2)
N2	446 (10)
N3	56 (1)
Unknown	1522 (34)
Histology	
Epithelioid	1438 (32)
Biphasic	267 (6)
Sarcomatoid	644 (14)
Unknown	2177 (48)
Surgery	
None	3960 (87)
Extrapleural pneumonectomy	18 (0)
Pleurectomy/decortication	326 (7)
Unknown	222 (5)
Chemotherapy	
Yes	1142 (25)
No	3243 (72)
Unknown	141 (3)
Radiation therapy	
Yes	230 (5)
No	4262 (95)
Unknown	34 (0)

Data are expressed as n (%) unless otherwise specified

Percentages may not add to 100% because of rounding

IQR interquartile range

groups following propensity matching [9.8 (95% CI 8.8–10.4) months vs. 4.6 (95% CI 4.1–5.1) months; $p < 0.001$] (Fig. 2d).

In the overall (pre-matched) cohort, when adjusting for potential confounders, there were several predictors of OS on multivariable analysis (Table 3). These included advancing age, male sex, increasing comorbidities, low income, treatment at community facilities, advancing nodal disease, and non-epithelioid histology ($p < 0.05$ for all). Of

TABLE 2 Factors associated with receiving surgery or observation on multivariable logistic regression analysis

Parameter	Endpoint: surgery		Endpoint: observation	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Age, years				
≤ 84	Ref	Ref	Ref	Ref
> 84	0.527 (0.372–0.748)	**< 0.001**	2.512 (2.108–2.993)	**< 0.001**
Sex				
Male	Ref	Ref	Ref	Ref
Female	0.913 (0.612–1.361)	0.655	1.469 (1.187–1.817)	**< 0.001**
Race				
White	Ref	Ref	Ref	Ref
Black	0.612 (0.184–2.038)	0.424	1.389 (0.812–2.375)	0.230
Other	1.049 (0.308–3.579)	0.939	0.890 (0.442–1.793)	0.745
Charlson–Deyo comorbidity index				
0	Ref	Ref	Ref	Ref
1	0.969 (0.666–1.401)	0.868	1.477 (1.206–1.808)	**< 0.001**
2	0.708 (0.394–1.274)	0.249	1.670 (1.254–2.223)	**< 0.001**
Income (US$/year)				
< 30,000	Ref	Ref	Ref	Ref
30,000–34,999	1.110 (0.580–2.125)	0.752	0.961 (0.695–1.330)	0.811
35,000-45,999	1.317 (0.692–2.501)	0.401	0.859 (0.617–1.195)	0.366
≥ 46,000	1.458 (0.726–2.929)	0.290	0.819 (0.570–1.179)	0.283
Percentage of adults in zip code area without a high-school diploma				
≥ 21	Ref	Ref	Ref	Ref
13–20.9	1.347 (0.691–2.627)	0.382	0.697 (0.496–0.980)	**0.038**
7–12.9	0.848 (0.422–1.701)	0.644	0.780 (0.551–1.104)	0.161
< 7	1.376 (0.655–2.894)	0.400	0.711 (0.484–1.045)	0.083
Patient residence				
Metro	Ref	Ref	Ref	Ref
Urban	0.881 (0.501–1.550)	0.661	1.021 (0.769–1.355)	0.887
Rural	[a]	[a]	1.148 (0.535–2.461)	0.724
Facility location				
Northeast	Ref	Ref	Ref	Ref
Midwest	0.880 (0.574–1.348)	0.556	1.259 (0.999–1.589)	0.051
South	1.083 (0.704–1.666)	0.716	1.136 (0.896–1.441)	0.293
Pacific	0.726 (0.428–1.232)	0.236	1.631 (1.242–2.141)	**< 0.001**
Facility type				
Community	Ref	Ref	Ref	Ref
Academic	1.117 (0.797–1.565)	0.521	0.812 (0.676–0.975)	**0.026**
Distance to the treating facility, miles				
≤ 7	Ref	Ref	Ref	Ref
> 7	1.052 (0.755–1.466)	0.766	1.029 (0.861–1.231)	0.751
Year of diagnosis				
2004–2008	Ref	Ref	Ref	Ref
2009–2012	0.959 (0.695–1.325)	0.801	0.934 (0.787–1.100)	0.438
Clinical T classification				
T1	Ref	Ref	Ref	Ref
T2	2.014 (1.392–2.914)	**< 0.001**	0.706 (0.569–0.876)	**0.002**
T3	0.986 (0.559–1.739)	0.961	0.901 (0.672–1.208)	0.485

TABLE 2 continued

Parameter	Endpoint: surgery		Endpoint: observation	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value
T4	0.679 (0.428–1.080)	0.102	0.834 (0.673–1.033)	0.097
Clinical N classification				
N0	Ref	Ref	Ref	Ref
N1	0.830 (0.347–1.989)	0.677	0.812 (0.522–1.262)	0.354
N2	0.731 (0.445–1.199)	0.214	0.793 (0.626–1.005)	0.055
N3	1.111 (0.380–3.246)	0.848	0.938 (0.518–1.700)	0.834
Histology				
Epithelioid	Ref	Ref	Ref	Ref
Biphasic	2.038 (1.237–3.357)	**0.005**	0.936 (0.662–1.323)	0.708
Sarcomatoid	1.031 (0.660–1.612)	0.893	1.425 (1.096–1.852)	**0.008**
Unknown[b]	0.441 (0.298–0.654)	**< 0.001**	1.506 (1.241–1.828)	**< 0.001**

Statistically significant p-values are shown in bold

[a]There were no pertinent events, as no rural patients underwent surgery

[b]Because histology is known to be a powerful predictor of management and outcomes, persons with unknown histology were deliberately analyzed as part of an exploratory sensitivity analysis herein

OR odds ratio, *CI* confidence interval

note, with reference to the combined modality cohort, receipt of either chemotherapy alone or observation was associated with poorer OS ($p = 0.019$ and $p < 0.001$, respectively).

Next, all four postoperative outcomes coded in the NCDB were evaluated in the surgical population. The 30- and 90-day mortality rates were 11.0% and 28.5%, respectively, and the median length of postoperative hospitalization was 6 days (IQR 4–9). Readmission within 30 days occurred in 7.5% of patients. Of note, because so few surgical patients received EPP, statistical comparison of postoperative outcomes by resection technique was not statistically feasible.

Lastly, in order to provide an approximate comparison with younger patients, an exploratory analysis between treatment groups was performed in patients <80 years of age by applying the same exclusion criteria. Of those patients with available follow-up information, 17% received surgery/chemotherapy, 47% received chemotherapy alone, and 36% received observation. Similar differences between cohorts were observed [median OS 17.7 (95% CI 16.7–18.6) months vs. 12.2 (95% CI 11.8–12.7) months vs. 6.6 (95% CI 6.1–7.1) months, respectively; $p < 0.001$] (electronic supplementary Fig. 1).

DISCUSSION

It is essential to provide evidence-based justification regarding the efficacy and safety of aggressive management in elderly MPM patients, a clinically challenging population for whom there are currently no high-volume retrospective studies, no prospective trials, and thus no dedicated standard treatment recommendations. The largest study of its kind to date, this investigation of a large, contemporary national database addresses a major knowledge gap by evaluating national practice patterns and outcomes of elderly persons with MPM. The majority of this population is observed without receiving cancer-directed therapy, which is associated with poorer OS than chemotherapy alone. Although receipt of both surgery and chemotherapy was associated with the longest OS, given the high degree of bias in NCDB studies and high postoperative mortality rates, careful patient selection for combined modality approaches in this population is imperative.

The aforementioned notions are supported by our data, which highlight the highly selected nature of the surgical cohort in this study. This implies that patients were carefully assessed for surgical tolerance, and only the most well-selected subjects received surgery. Additionally, surgical patients 'fit' enough to tolerate chemotherapy were included in the combined modality group. However, these findings may also imply that the higher observed OS herein could have been at least in part due to favorable patient selection, and not necessarily resection itself. This is particularly relevant given that no randomized evidence currently exists supporting the use of surgery (EPP), even in younger MPM patients.[9] That the surgery/chemotherapy patients were a more favorable cohort is supported by the findings on multivariable logistic regression that surgical patients were younger, and those that underwent observation had more comorbidities. Additionally, although the
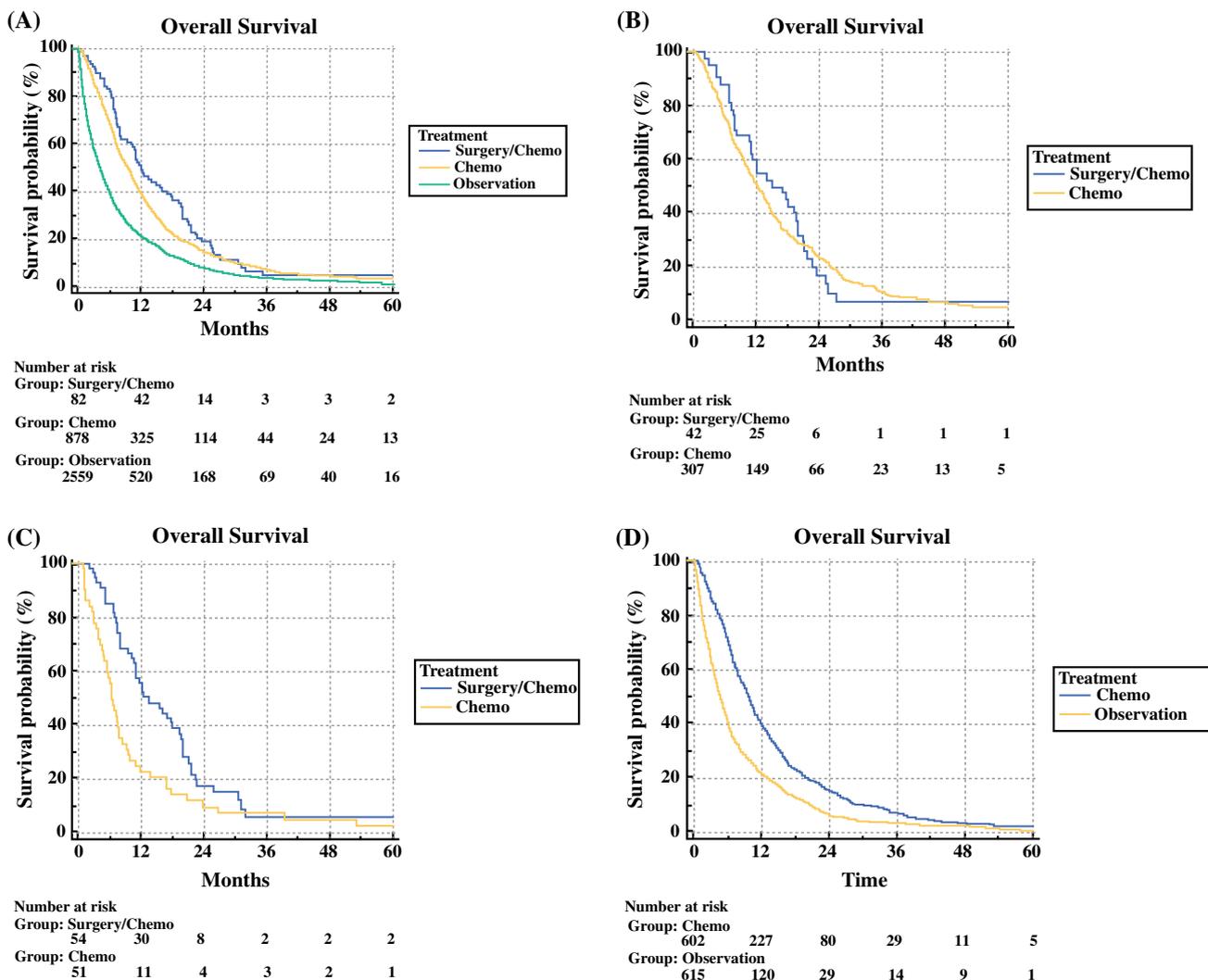
FIG. 2 Comparison of overall survival between treatment paradigms in the **a** overall population, **b** epithelioid subpopulation, and **c, d** following propensity matching. *Chemo* chemotherapy

observation group had more sarcomatoid disease, in accordance with NCCN recommendations,[1] those who underwent resection were more often biphasic. Although the latter is contrary to current NCCN guidelines, previous versions had indeed supported resection for biphasic disease. Moreover, data show that well-selected (younger) patients with biphasic histology achieve similar outcomes following surgery as epithelioid cases.[16]

Despite the resected patients being highly selected and associated with higher OS, it should also be noted that even those highly-selected patients experienced high rates of 30- and 90-day mortality. The 30-day mortality of 11.0% herein is higher than rates of 4–7% in younger patients.[10,17–19] Similarly, the 90-day mortality herein (28.5%) is substantially higher than established rates of ≤10 to 11% in younger cohorts.[19–24] Taken together, surgical approaches could benefit highly selected older

patients with MPM, but this sobering rate of postoperative mortality (even in this well-selected elderly population) should warrant more stringent perioperative evaluation of surgical candidacy.

There are several strategies to potentially reduce postoperative mortality in elderly patients. Investigators at the University of Leicester have described the institutional evolution of an EPP-based approach with a P/D-based one, which expanded the availability of resection in elderly patients and further sharpened patient selection.[25,26] These results are in keeping with national data showing a widespread increase in P/D utilization,[27] along with the fact that very few patients herein received EPP (thus, a comparison of postoperative outcomes by surgical technique could not be performed). Other data[28] have also demonstrated that older patients achieve similar survival as younger patients, provided that the former are well-selected (analogous data

TABLE 3 Multivariate Cox proportional hazards model for overall survival

Parameter (comparator vs. reference)	HR	95% CI	p-Value
Age (> 84 years vs. ≤ 84 years)	1.200	1.118–1.289	**< 0.001**
Sex (female vs. male)	0.838	0.770–0.913	**< 0.001**
Charlson–Deyo score (reference: 0)			
1	1.179	1.087–1.279	**< 0.001**
2	1.305	1.170–1.455	**< 0.001**
Income [reference: first (bottom) quartile]			
Second quartile	0.972	0.860–1.099	0.653
Third quartile	0.930	0.855–1.013	0.095
Fourth quartile	0.876	0.808–0.951	**0.002**
Facility type (academic vs. community)	0.918	0.852–0.988	**0.023**
Clinical N classification (reference: N0)			
N1	1.367	1.093–1.711	**0.006**
N2	1.187	1.053–1.339	**0.005**
N3	1.341	0.987–1.823	0.061
Histology (reference: epithelioid)			
Biphasic	1.519	1.297–1.778	**< 0.001**
Sarcomatoid	2.331	2.082–2.611	**< 0.001**
Unknown[a]	1.215	1.121–1.317	**< 0.001**
Treatment (reference: surgery/chemotherapy)			
Chemotherapy alone	1.172	1.451–2.313	**0.019**
Observation	1.584	1.461–1.717	**< 0.001**

Statistically significant p-values are shown in bold

Only variables included in the final multivariate model are shown

[a] Because histology is known to be a powerful predictor of management and outcomes, persons with unknown histology were deliberately analyzed as part of an exploratory sensitivity analysis herein

HR hazard ratio, *CI* confidence interval

in patients receiving first-line carboplatin/pemetrexed have also been reported[29]). Additional strategies to reduce the rate of postoperative mortality include treatment by experienced surgeons[30–32] and limiting the use of induction chemotherapy.[33] Because comparatively few elderly patients in this study received surgery, further subanalyses based on these parameters would have sharply limited sample sizes, and were thus not amenable to detailed inferential statistical evaluation.

Likewise, there are also strategies with which more careful patient selection can be achieved. Namely, when deciding on a treatment approach, clinicians should consider which patients are at higher risk of surgical complications and/or mortality. This can be accomplished by evaluating the patient as a whole, encompassing factors such as age, performance status, weight/body mass index, nutritional status, cognitive or other comorbidities, toxicities of prior therapy (if any), degree and location of disease, expected time under anesthesia, pulmonary function tests, and technical expertise. There are numerous tools to evaluate whether geriatric patients are 'functionally

elderly' or 'functionally younger', such as the Comprehensive Geriatric Assessment; the ACS has also published numerous guidelines on how to best evaluate geriatric patients for surgical interventions.[34,35]

The strengths of this analysis include relatively few exclusion criteria, so as to understand the true degree of practice patterns in the US. Additionally, the NCDB provides information on chemotherapy, which allowed for a more realistic assessment of combined modality therapy versus chemotherapy alone; it is difficult to gauge this notion in analyses that did not account for chemotherapy-related information.[36] However, NCDB studies also have several noteworthy shortcomings.[27,32,33,37] In addition to retrospective selection biases, the NCDB does not contain information on chemotherapy agents, performance status, pulmonary function tests, and salvage therapies, all of which could affect OS and confound conclusions of the current study. It also does not record other endpoints, such as specific postoperative complications, tolerance of therapy (including premature cessation of chemotherapy), and cancer-specific survival. Next, although the NCDB

includes data for 70% of the US population, only CoC-accredited facilities contribute data, and, as such, these findings may not necessarily be representative of the entire US population.

CONCLUSIONS

As the largest study of its kind to date, this investigation of a large, contemporary national database addresses a major knowledge gap by evaluating national practice patterns and outcomes of elderly patients with MPM. The majority of this population is observed without definitive anticancer therapy, which is associated with poorer OS than chemotherapy alone. Although combination treatment with surgery and chemotherapy was associated with the longest OS, given the high degree of bias in NCDB studies and high postoperative mortality rates, careful patient selection for combined modality approaches in this population is imperative.

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