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ORIGINAL ARTICLE

Survival Outcomes for Malignant Peritoneal Mesothelioma at Academic Versus Community Hospitals

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Abstract

Background Malignant peritoneal mesothelioma is a rare disease with poor outcomes. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy is the cornerstone of therapy. We aim to compare outcomes of malignant peritoneal mesothelioma treated at academic versus community hospitals.

Methods This was a retrospective cohort study using the National Cancer Database to identify patients with malignant peritoneal mesothelioma from 2004 to 2016. Patients were divided according to treating facility type: academic or community. Outcomes were assessed using log-rank tests, Cox proportional-hazard modeling, and Kaplan-Meier survival statistics.

Results In total, 2682 patients with malignant peritoneal mesothelioma were identified. A total of 1272 (47.4%) were treated at an academic facility and 1410 (52.6%) were treated at a community facility. Five hundred forty-six (42.9%) of patients at academic facilities underwent debulking or radical surgery compared to 286 (20.2%) at community facilities. Three hundred sixty-six (28.8%) of patients at academic facilities received chemotherapy on the same day as surgery compared to 147 (10.4%) of patients at community facilities. Unadjusted 5-year survival was 29.7% (95% CI 26.7–32.7) for academic centers compared to 18.3% (95% CI 16.0–20.7) for community centers. In multivariable analysis, community facility was an independent predictor of increased risk of death (HR: 1.19, 95% CI 1.08–1.32, $p = 0.001$).

Conclusions We demonstrate better survival outcomes for malignant peritoneal mesothelioma treated at academic compared to community facilities. Patients at academic centers underwent surgery and received chemotherapy on the same day as surgery more frequently than those at community centers, suggesting that malignant peritoneal mesothelioma patients may be better served at experienced academic centers.

Keywords Malignant peritoneal mesothelioma · Survival

Introduction

Malignant peritoneal mesothelioma is a rare but aggressive disease, with an incidence of 200–400 cases per year in the USA.[1,2] Following pleural mesothelioma, the peritoneum is the second most common site for primary mesothelioma, accounting for an estimated 20–30% of mesotheliomas.[1–3] The primary risk factor for disease is asbestos exposure, although prior radiation and exposure to other minerals may also increase the risk.[2,4]

Patients with malignant peritoneal mesothelioma often present late in the course of disease, as a result of the vague and indolent nature of its symptoms, including abdominal pain, abdominal distension or swelling, weight loss, and fever.[1–3] Less commonly, patients may be diagnosed incidentally on laparoscopy, or acutely in the setting of bowel obstruction or perforation.[4–8] Typically, the disease involves locoregional spread and remains confined to the peritoneal cavity, rarely metastasizing to involve lymph nodes or distant sites.[1,2,9,10]

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Prior to the use of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in the late 1980s and early 1990s, median survival for malignant peritoneal mesothelioma was between 6 and 12 months when treated with systemic chemotherapy.[1,2,9] Given the locoregional nature of disease, the current first-line treatment approach for malignant peritoneal mesothelioma is CRS to remove macroscopic disease in combination with HIPEC.[2,3,5] This approach has been found to significantly improve survival, with a systematic review estimating survival from 34 months up to 92 months.[11] Despite these advances in therapy, and although malignant peritoneal mesothelioma has been recognized as a distinct entity from pleural mesothelioma, there are no specific National Comprehensive Cancer Network (NCCN) guidelines that exist for malignant peritoneal mesothelioma.[3,4,12] Furthermore, malignant peritoneal mesothelioma does not have an American Joint Committee on Cancer (AJCC) staging system.[13,14]

The Chicago Consensus Working Group, a panel of experts on peritoneal surface disease, published the Chicago Consensus Guidelines for the management of peritoneal mesothelioma.[15] The guidelines recommend obtaining a tissue diagnosis with core-needle biopsy to determine management approach based on histologic subtype when peritoneal mesothelioma is suspected. Though there are some nuances to treatment approach based on malignant histology subtype, when complete cytoreduction is possible and the patient is deemed a surgical candidate, treatment generally involves CRS in combination with intraperitoneal chemotherapy (typically HIPEC), with or without early postoperative intraperitoneal chemotherapy (EPIC) or neoadjuvant intraperitoneal chemotherapy (NIPC).[15] The Chicago guidelines suggest various intraperitoneal chemotherapy regimen options, the majority of which are a form of HIPEC, though they acknowledge that data is lacking to make a firm recommendation regarding a specific protocol. Furthermore, the management approach suggested by the Chicago Consensus Guidelines is occasionally dependent on stage of disease, though this is not based on an established AJCC system.[15]

With the lack of specific guidelines and expertise required to carry out CRS and HIPEC, we hypothesized that patients with malignant peritoneal mesothelioma treated at academic facilities would demonstrate superior survival outcomes compared to those treated at community facilities. In this study, we aim to compare survival outcomes of malignant peritoneal mesothelioma patients treated at academic versus community hospitals.

Materials and Methods

Data Source and Patient Selection

The National Cancer Database (NCDB) is jointly sponsored by the American College of Surgeons and the American Cancer Society. It contains demographic, disease, and treatment information for patients with a wide array of oncologic diseases treated at accredited cancer centers across the USA.[16] Using the database's participant user data files, we identified all patients diagnosed with primary malignant peritoneal mesothelioma between 2004 and 2016 (Fig. 1). Patients with benign mesothelioma histologies, notably fibrous mesothelioma and multicystic mesothelioma, were excluded.[2,3] Histologies included were mesothelioma not otherwise specified (NOS), epithelioid mesothelioma, and biphasic mesothelioma. Though sarcomatoid mesothelioma is another histologic subtype of malignant peritoneal mesothelioma, it is very rare and there were no documented cases in our patient cohort.[2,3]

Patients were divided according to treating facility type into two major groups: academic and community. The academic group included patients with a treatment facility that was categorized as academic/research. The community group included patients with a treatment facility that was categorized as one of the following: community cancer program, comprehensive community cancer program, or integrated network cancer program. Patients with a treatment facility type that was unknown were excluded. The study was deemed exempt by the Brigham and Women's Hospital institutional review board.

Variables and Outcomes

Variables related to patient demographics and disease and treatment characteristics were collected and assessed. Demographic variables included age, sex, race, Charlson Comorbidity Index, insurance status, income, and education status. Disease and treatment variables included histologic subtype, surgical procedure, regional lymph nodes, receipt of chemotherapy (neoadjuvant, same-day as definitive surgery, adjuvant), and receipt of radiation therapy. Surgical procedure was divided into categories with peritoneum as the primary surgical site: local tumor destruction or excision, partial or total resection of the primary site (peritoneum), debulking surgery (surgery stated as "debulking"), radical surgery (partial or total resection of the primary site – peritoneum – and resection of other involved organs in continuity), surgery not otherwise specified (NOS), or unknown. Chemotherapy was categorized as neoadjuvant, same-day, or adjuvant. These categories were determined based on the timing of chemotherapy in reference to definitive surgical procedure. Since the NCDB does not specifically report the chemotherapy route of administration, as intravenous infusion for systemic chemotherapy or intraperitoneal for HIPEC, we added the category of "same-day" chemotherapy as day of definitive surgery to assume that this could be representative of receipt of HIPEC. The NCDB also does

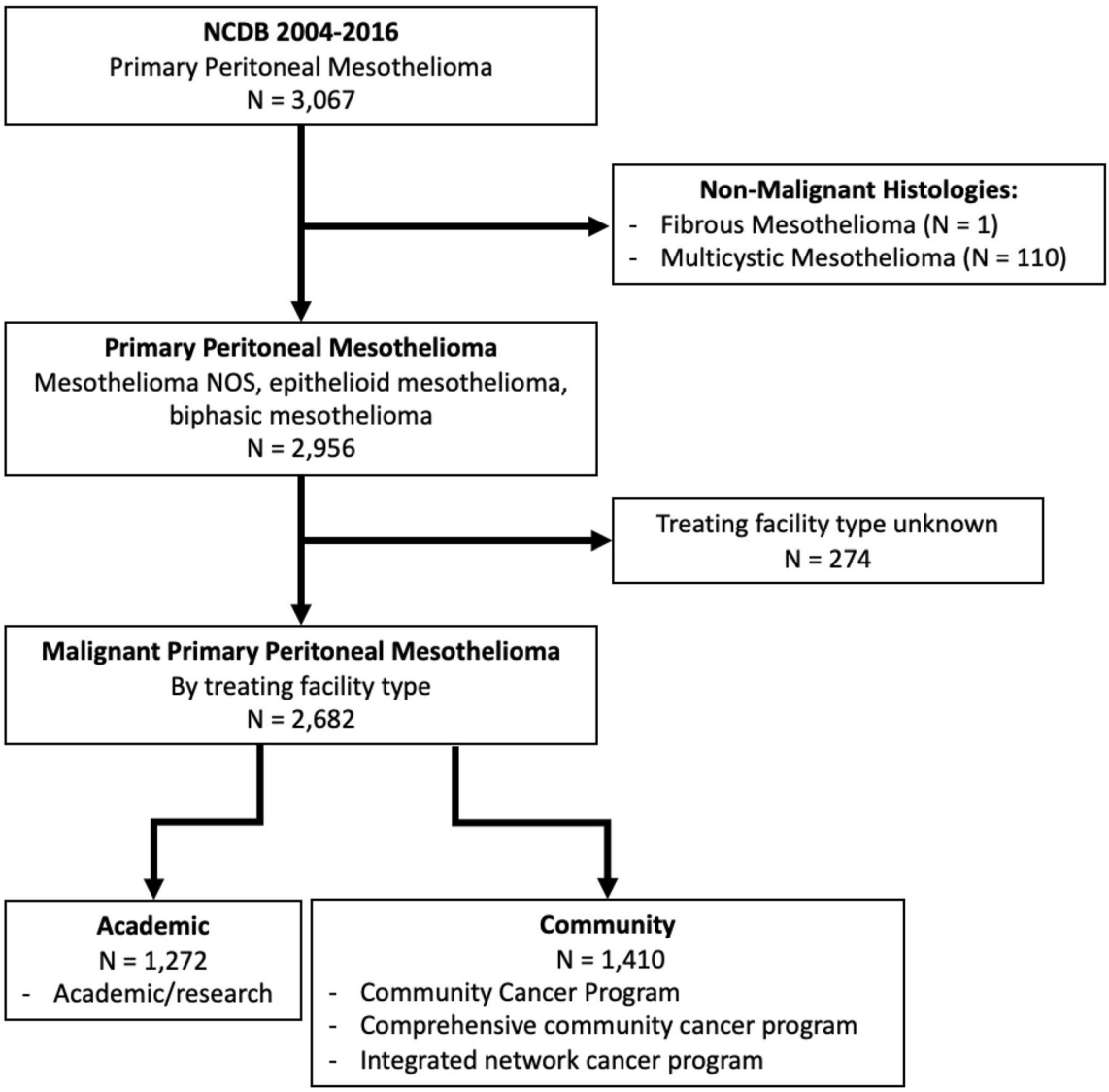

Figure 1 Flowchart of patient selection from the National Cancer Database (NCDB). NOS, not otherwise specified

not collect information on specific chemotherapy agent administered.

The primary outcomes of interest were median, 1-year, and 5-year survival by treating facility type.

Statistical Analysis

Patients were divided according to treating facility type: academic or community. Demographic, disease, and treatment characteristics were assessed using descriptive statistics. Log-rank testing and Kaplan-Meier survival statistics were used to compare overall survival between groups. Unadjusted median, 1-, and 5-year survival were calculated. Adjusted overall survival for the entire patient cohort and for 3 subgroups was calculated and compared between academic and community facilities utilizing Kaplan-Meier plots. The 3 subgroups were patients treated with chemotherapy, patients treated with surgery, and patients treated with both chemotherapy and surgery. Cox proportional-hazard modeling was used to conduct a multivariable analysis and calculate hazard ratios (HRs). For adjusted analyses, we controlled for the following variables: age, sex, race, Charlson Comorbidity Index, insurance, income, education, histologic subtype, surgical procedure, regional lymph nodes, receipt of chemotherapy (neoadjuvant, same-day as definitive surgery, adjuvant), and receipt of radiation. Statistical significance was defined as p value < 0.05 for a two-sided test. Statistical analyses were performed using STATA statistical software, edition 16.1 (StataCorp, College Station, TX).

Results

Patient Characteristics

A total of 2682 patients with primary malignant peritoneal mesothelioma were identified. In total, 1272 (47.4%) of patients were treated at academic facilities and 1410 (52.6%) of patients were treated at community facilities. Demographic variables for each group are presented in Table 1. All demographic variables demonstrated an association with facility type (all p-values < 0.05) with the exception of sex (p = 0.935). In both groups, the majority of patients were male (56.4% in the academic group and 56.6% in the community group), and the majority of patients were non-Hispanic White (83.3% in the academic group and 87.6% in the community group). Fifty percent of patients treated at academic facilities

Table 1 Demographic characteristics of malignant peritoneal mesothelioma patients by treating facility type

Variable	Facility Type		All	p value
	Academic	Community	N (%)	
	N (%)	N (%)	(N total = 2682)	
	(N total = 1272)	(N total = 1410)		
Age				
≤ 50	230 (18.1)	149 (10.6)	379 (14.1)	< 0.001
51 – 60	344 (27.0)	306 (21.7)	650 (24.2)	
61 – 70	355 (27.9)	418 (29.7)	773 (28.8)	
71 – 80	260 (20.4)	342 (24.3)	601 (22.5)	
81 – 90	83 (6.5)	195 (13.8)	278 (10.4)	
Sex				
Male	717 (56.4)	797 (56.6)	1,514 (56.5)	0.935
Female	555 (43.6)	613 (43.5)	1168 (43.6)	
Race				
Non-Hispanic White	1,060 (83.3)	1,235 (87.6)	2,295 (85.6)	< 0.001
Non-Hispanic Black	75 (5.9)	65 (4.6)	140 (5.2)	
Hispanic	76 (6.0)	74 (5.3)	150 (5.6)	
Asian	21 (1.7)	23(1.6)	44 (1.6)	
Other	11 (0.9)	7 (0.5)	18 (0.7)	
Charlson Comorbidity Index				
0	980 (77.0)	1,025 (72.7)	2,005 (74.8)	0.001
1	226 (17.8)	263 (18.7)	489 (18.2)	
≥ 2	66 (5.2)	122 (8.7)	188 (7.0)	
Insurance				
Private	636 (50.0)	559 (39.7)	1,195 (44.5)	< 0.001
Medicaid	91 (7.2)	72 (5.1)	163 (6.1)	
Medicare	473 (37.2)	722 (51.2)	1,195 (44.6)	
Uninsured	35 (2.8)	40 (2.8)	75 (2.8)	
Unknown	37 (2.9)	17 (1.2)	54 (2.0)	
Income				
< $38,000	172 (13.5)	192 (13.6)	364 (13.6)	< 0.001
$38,000 – 47,999	273 (21.5)	345 (24.5)	618 (23.0)	
$48,000 – 62,999	293 (23.0)	409 (29.0)	702 (26.2)	
> $63,000	529 (41.6)	457 (32.4)	989 (36.8)	
Unknown	5 (0.39)	7 (0.5)	12 (0.5)	
Education (% no high school degree)				
< 7%	394 (31.0)	373 (26.5)	767 (28.6)	0.046
7 – 12.9%	391 (30.7)	474 (33.6)	865 (32.3)	
13 – 20.9%	299 (23.5)	373 (26.5)	672 (25.1)	
> 21%	183 (14.4)	184 (13.1)	367 (13.7)	
Unknown	5 (0.4)	6 (0.4)	11 (0.4)	

were privately insured, while 51.2% of patients treated at community facilities were insured with Medicare. Patients treated at academic facilities tended to be younger, have higher incomes, and have higher levels of education compared to patients treated at community hospitals.

Disease and Treatment Characteristics

Table 2 presents disease and treatment characteristics by treating facility type. All variables were associated with facility type (all p values < 0.001), with the exception of radiation therapy (p = 1.00).

For histologic subtype, epithelioid mesothelioma was more common in the academic group (52.1%) compared to the community group (40.3%). The majority of patients in the community group were categorized as mesothelioma NOS (55.8%). Few patients in both groups had biphasic mesothelioma, and no patients had sarcomatoid mesothelioma.

With regard to surgical treatment, patients in the academic group were more likely to have undergone surgery than those in the community group. In particular, patients treated at academic facilities were more likely to have undergone surgical debulking (32.2% for the academic group, 15.2% for the community group) or radical surgery (10.7% for the academic group, 5.0% for the community group) as part of their treatment, compared to those treated at community facilities.

In terms of chemotherapy, a slightly larger proportion of patients in the community group received neoadjuvant chemotherapy (34.0% in the community group, compared to 28.3% in the academic group). However, same-day chemotherapy was received by a much larger proportion of patients treated at academic facilities (28.8%) compared to community facilities (10.4%). Adjuvant chemotherapy was similar

Table 2 Disease and treatment characteristics of malignant peritoneal mesothelioma patients by treating facility type

Variable	Facility type		All	p value
	Academic	Community		
	N (%)	*N* (%)	*N* (%)	
	(*N* total = 1272)	(*N* total = 1410)	(*N* total = 2682)	
Histology				
Mesothelioma NOS	543 (42.7)	787 (55.8)	1,330 (49.6)	< 0.001
Epithelioid mesothelioma	663 (52.1)	568 (40.3)	1,231 (45.9)	
Biphasic mesothelioma	66 (5.2)	55 (3.9)	121 (4.5)	
surgery				
None	478 (37.6)	872 (61.8)	1,350 (50.3)	< 0.001
Local tumor destruction/excision	68 (5.4)	89 (6.3)	157 (5.9)	
Partial or total peritoneal resection	147 (11.6)	119 (8.4)	266 (9.9)	
Debulking	410 (32.2)	214 (15.2)	624 (23.3)	
Radical surgery	136 (10.7)	71 (5.0)	207 (7.7)	
Surgery NOS	28 (2.2)	36 (2.6)	64 (2.4)	
Unknown	5 (0.4)	9 (0.6)	14 (0.5)	
Regional lymph nodes				
Negative	177 (13.9)	92 (6.5)	269 (10.0)	< 0.001
Positive	69 (5.4)	56 (4.0)	125 (4.7)	
None examined or unknown	1026 (80.7)	1262 (89.5)	2288 (85.3)	
Chemotherapy				
None	334 (26.3)	548 (38.9)	882 (32.9)	< 0.001
Neoadjuvant	360 (28.3)	480 (34.0)	840 (31.3)	
Same-day	366 (28.8)	147 (10.4)	513 (19.1)	
Adjuvant	179 (14.1)	184 (13.1)	363 (13.5)	
Unknown	33 (2.6)	51 (3.6)	84 (3.1)	
Radiation				
None	1253 (98.5)	1385 (98.2)	2638 (98.4)	1.00
Radiation	7 (0.6)	10 (0.7)	17(0.6)	
Unknown	12 (0.9)	15 (1.1)	27 (1.0)	

*Debulking = surgery stated as "debulking." Radical surgery = partial or total peritoneal resection with resection in continuity of other involved organs. *NOS*, not otherwise specified

between the two groups, with 14.1% receiving adjuvant chemotherapy at academic facilities compared to 13.1% at community facilities.

Survival Outcomes

In unadjusted survival analysis, treatment at an academic center was associated with statistically significant improved survival ($p < 0.001$). Table 3 presents unadjusted survival data. Median survival for patients treated at academic centers was 24.8 months (95% CI 22.2–27.9), while median survival for patients treated at community centers was 11.6 months (95% CI 10.2–13.0). One-year survival was 66.2% (95% CI 63.3–68.9) and 48.9% (95% CI 46.1–51.7) for academic and community facilities, respectively. Five-year survival for patients in the academic group was 29.7% (95% CI 26.7–32.7), compared to 18.3% (95% CI 16.0–20.7) for patients in the community group.

In adjusted survival analyses, academic facility demonstrated improved overall survival compared to community facility across the entire study period. This was true for the entire patient cohort, and for the 3 subgroups: patients treated with chemotherapy, patients treated with surgery, and patients treated with both chemotherapy and surgery (Fig. 2 A–D). The survival difference observed between groups widened in the subgroup analysis, with the largest difference seen among patients who were treated with both chemotherapy and surgery.

Results from multivariable analysis are presented in Table 4. Treatment at a community facility was a statistically significant independent predictor of a higher risk of death (HR: 1.19, 95% CI 1.08–1.32, $p = 0.001$). Increasing age was associated with an incremental increase in the risk of death. Patients in the highest age group of 81–90 had an HR of 2.86 (95% CI 2.27–3.61, $p < 0.001$). Female sex was an independent predictor of improved survival (HR 0.65, 95% CI 0.58–0.72, $p < 0.001$). Compared to mesothelioma NOS, epithelioid mesothelioma was independently associated with a lower risk of death (HR 0.88, 95% CI 0.80–0.97, $p = 0.013$), while biphasic mesothelioma was independently associated with a higher risk of death (HR 1.94, 95% CI 1.55–2.43, $p < 0.001$). With regard to surgical procedures, local tumor destruction or tumor excision (HR 0.53, 95% CI 0.43–0.66, $p < 0.001$), partial or total peritoneal resection (HR 0.49, 95% CI 0.40–0.59), $p < 0.001$), debulking surgery (HR 0.62, 95% CI 0.52–0.73, $p < 0.001$), radical surgery (HR 0.69, 95% CI 0.55–0.86, $p = 0.001$), and unspecified surgery (HR 0.66, 95% CI 0.47–0.92, $p = 0.014$) were all associated with better survival compared to no surgery. Receipt of neoadjuvant, same-day, and adjuvant chemotherapy were all independently associated with lower risk of death compared to no chemotherapy. Specifically, receipt of same-day chemotherapy was associated with the lowest risk of death with an HR of 0.55 (95% CI 0.46–0.65, $p < 0.001$) compared to neoadjuvant chemotherapy with an HR 0.70 (95% CI 0.62–0.79, $p < 0.001$) and adjuvant therapy with an HR of 0.78 (95% CI 0.66–0.94, $p = 0.007$). Conversely, receipt of radiation was not a statistically significant predictor of survival (HR 0.76, 95% 0.44–1.30, $p = 0.278$).

Discussion

In this retrospective national database study of malignant peritoneal mesothelioma, we found significantly improved median, 1-, and 5-year survival for patients treated at academic facilities compared to community facilities. Community facility was an independent predictor of higher risk of death compared to academic facility, and patients at academic facilities were more likely to undergo debulking or radical surgery and receive same-day chemotherapy compared to those at community facilities.

Our study identified important discrepancies in treatment of malignant peritoneal mesothelioma between the two groups that may help explain the differences in survival observed. Though CRS and HIPEC are the mainstay of therapy for this disease, 61.8% of patients at community centers did not undergo surgery as part of their disease treatment, compared to only 37.6% treated at academic centers. At academic facilities, 42.9% underwent debulking or radical surgery, while only 20.2% of patients at community facilities underwent these procedures. All categories of surgeries demonstrated an independent survival benefit compared to no surgery. There were also discrepancies in receipt of chemotherapy between the two groups. Though patients treated at community facilities received neoadjuvant therapy more frequently, those treated at academic facilities were more likely to receive same-day chemotherapy (28.8% at academic facilities vs. 10.4% at community facilities) which we estimate could represent receipt of

Table 3 Unadjusted survival data for malignant peritoneal mesothelioma patients by treating facility type

Facility type	Median survival Months (95% CI)	1-year survival % (95% CI)	5-year survival % (95% CI)	*p* value for log rank test
Academic	24.8 (22.2 – 27.9)	66.2 (63.3 – 68.9)	29.7 (26.7 – 32.7)	< 0.001
Community	11.6 (10.2 – 13.0)	48.9 (46.1 – 51.7)	18.3 (16.0 – 20.7)	

*95% CI, 95% confidence interval

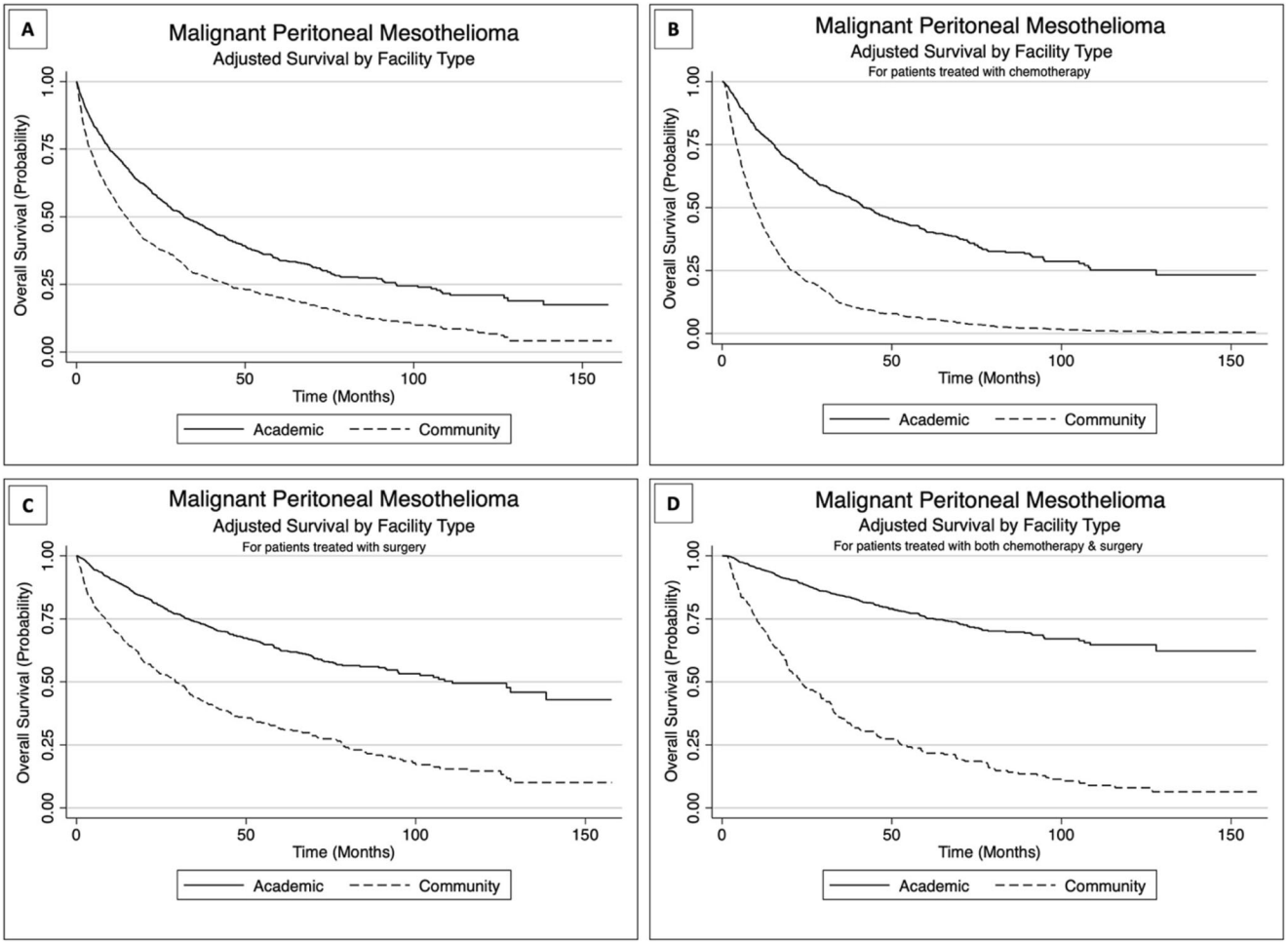

Figure 2 Overall survival by facility type for malignant peritoneal mesothelioma. Panel **A**—Adjusted* survival for all patients. Panel **B**—Adjusted* survival by facility type for patients treated with chemotherapy. Panel **C**—Adjusted* survival by facility type for patients treated with surgery. Panel **D**—Adjusted* survival by facility type for patients treated with both chemotherapy and surgery. *Variables adjusted for: age, sex, race, Charlson Comorbidity Index, insurance, income, education, histology, surgery, regional lymph nodes, chemotherapy, and radiation

intraperitoneal chemotherapy with HIPEC. Furthermore, same-day chemotherapy was independently associated with the lowest risk of death in reference to no chemotherapy, compared to either neoadjuvant or adjuvant chemotherapy.

A retrospective database study by Miura et al. of nearly 1600 patients from 1973 to 2010 assessing treatment trends of malignant peritoneal mesothelioma with CRS and HIPEC found that 61.6% of patients in the cohort did not receive surgery as part of their disease treatment.[1] Though our study analyzed data from much more recent years, the no-surgery rate in this study was similar to our community cohort. This study also found that limited surgery (defined as partial or total resection of the primary site) and radical resection (defined as partial or total removal of the primary site with resection in continuity with other organs) were both independent predictors of improved survival.[1] In our study, similarly defined surgical procedures were also independently associated with improved survival.

In the current study, we found a median survival of 24.8 months for patients with malignant peritoneal mesothelioma treated at academic facilities, compared to only 11.6 months for those treated at community facilities. The median survival of less than 1 year for those treated at community facilities is comparable to median survival prior to the introduction of CRS and HIPEC as a treatment approach for this disease.[1,17] Furthermore, treatment at a community facility was associated with an independently increased risk of death. A recent study of patients who underwent radical surgery as part of their treatment demonstrated an overall survival of 38.4 months compared to 7.1 months for patients treated without surgery, while patients who were treated with both radical surgery and systemic chemotherapy demonstrated a survival of 41.8 months.[18] In this same study, treatment at an academic facility was associated with a nearly three times higher likelihood of radical surgery compared to treatment at a community cancer program.[18] A study of 62 patients with malignant peritoneal

Table 4 Cox proportional-hazards model for malignant peritoneal mesothelioma

Variable	HR	95% CI	*p* value
Facility (ref. academic)			
Community	1.19	1.08 – 1.32	0.001
Age (ref. ≤ 50)			
51 – 60	1.47	1.23 – 1.76	< 0.001
61 – 70	1.74	1.45 – 2.10	< 0.001
71 – 80	2.21	1.81 – 2.71	< 0.001
81 – 90	2.86	2.27 – 3.61	< 0.001
Sex (ref. male)			
Female	0.65	0.58 – 0.72	< 0.001
Race (ref. non-Hispanic White)			
Non-Hispanic Black	0.78	0.62 – 0.98	0.031
Hispanic	0.83	0.66 – 1.04	0.101
Asian	1.00	0.68 – 1.49	0.993
Other	0.65	0.33 – 1.26	0.198
Unknown	1.18	0.76 – 1.84	0.465
Charlson Comorbidity Index (ref. 0)			
1	1.19	1.06 – 1.35	0.004
≥ 2	1.11	0.92 – 1.34	0.280
Insurance (ref. private)			
Medicaid	1.24	0.99 - 1.55	0.061
Medicare	0.98	0.86 – 1.12	0.778
Uninsured	1.64	1.23 – 2.19	0.001
Unknown	1.22	0.85 – 1.74	0.278
Income (ref. < $38,000)			
$38,000 - 47,999	0.92	0.77 – 1.08	0.307
$48,000 – 62,999	0.99	0.83 – 1.17	0.872
> $63,000	0.88	0.73 – 1.06	0.178
Unknown	1.89	0.26 – 13.81	0.529
Education —% no high school degree (ref. < 7%)			
7 – 12.9%	1.04	0.91 – 1.19	0.538
13 – 20.9%	0.97	0.83 – 1.14	0.708
> 21%	1.01	0.83 – 1.23	0.927
Unknown	0.62	0.07 – 5.22	0.657
Histology (ref. mesothelioma NOS)			
Epithelioid Mesothelioma	0.88	0.80 – 0.97	0.013
Biphasic Mesothelioma	1.94	1.55 – 2.43	< 0.001
Surgery (ref. none)			
Local tumor destruction/excision	0.53	0.43 – 0.66	< 0.001
Partial or total peritoneal resection	0.49	0.40 – 0.59	< 0.001
Debulking	0.62	0.52 – 0.73	< 0.001
Radical surgery	0.69	0.55 – 0.86	0.001
Surgery NOS	0.66	0.47 – 0.92	0.014
Unknown	0.43	0.19 – 0.99	0.048
Regional lymph nodes (ref. negative)			
Positive	1.37	1.04 – 1.81	0.024
None examined or unknown	1.14	0.95 – 1.37	0.149
Chemotherapy (ref. none)			
Neoadjuvant	0.70	0.62 – 0.79	< 0.001
Same-day	0.55	0.46 – 0.65	< 0.001
Adjuvant	0.78	0.66 – 0.94	0.007
Unknown	0.85	0.64 – 1.14	0.281
Radiation (ref. none)			
Radiation	0.76	0.44 – 1.30	0.310
Unknown	0.75	0.45 – 1.26	0.278

*Debulking = surgery stated as "debulking." Radical surgery = Partial or total peritoneal resection with resection in continuity of other involved organs. *NOS*, not otherwise specified; *HR*, hazard ratio; *95% CI*, 95% confidence interval

mesothelioma treated with CRS and HIPEC found an overall survival of 79 months and 1- and 5-year survival rates of 84% and 50% respectively,[17] which were much higher than the survival estimates for either group in our study. A systematic review of studies conducted prior to 2006 of malignant peritoneal mesothelioma found median survival estimates between 34 and 92 months, 1-year survival rates between 60 and 88%, and 5-year survival rates between 29 and 59%.[11] Most of these estimates were higher than the current studies' survival results, though our 1- and 5-year results for patients treated at academic facilities were similar to the lower range estimates. A small prospective study of 65 patients undergoing CRS and HIPEC for malignant peritoneal mesothelioma between 2001 and 2010 found a median survival of 46.2 months and 1- and 5-year survival rates of 77% and 39%, respectively.[10] Result differences may also reflect different proportions of histologic subtypes of mesothelioma, with the epithelioid histology having a better prognosis than other subtypes.[2,3] It is important to note that in our study, epithelioid subtype was more common in the academic group and was associated with a lower risk of death in multivariable analysis. However, results are difficult to interpret given a large number of patients with mesothelioma NOS in our cohort, particularly in the community group. Furthermore, in our study, more patients in the academic group demonstrated biphasic histology, which was an independent predictor of a higher risk of death in multivariable analysis.

The survival differences observed between academic and community facilities may in part be explained by the lower rates of surgery and chemotherapy among patients treated at community hospitals. These treatment discrepancies may themselves result from a lack of standardized guidelines for malignant peritoneal mesothelioma, as well as a lack of expertise at community centers.[4] Though not specific to peritoneal mesothelioma, studies have demonstrated improved outcomes over time with CRS and HIPEC with increasing center case volume and expertise.[19] Currently, there are no dedicated

NCCN guidelines for malignant peritoneal mesothelioma, even though the peritoneum accounts for nearly a third of malignant mesothelioma, and even though specific guidelines exist for pleural mesothelioma.[12] In 2017, a set of management recommendations for peritoneal mesothelioma were published following the annual Peritoneal Surface Oncology Group International (PSOGI) meeting.[4] Among these recommendations, the expert group suggested that all patients with peritoneal mesothelioma be evaluated at a peritoneal malignancy specialty center with experience in CRS techniques, that patients with malignant peritoneal mesothelioma histologies be offered or considered for CRS with HIPEC, and that burden of peritoneal disease and completeness of cytoreduction be clearly documented.[4] The Chicago Consensus Guidelines for the management of peritoneal mesothelioma provide an algorithmic treatment approach based on histologic subtype and stage of disease.[15] These recommendations are a step forward, though little guidance is given with regard to specific regimens for HIPEC or other intraperitoneal chemotherapy. Furthermore, as there is no formal staging system developed for malignant peritoneal mesothelioma, suggested stage-specific approaches are difficult to interpret.[13] Yan et al. proposed a TNM staging system for malignant peritoneal mesothelioma, wherein the T-stage was based on the peritoneal cancer index (PCI), which quantifies peritoneal disease burden using lesion size within 12 abdominoperitoneal regions.[14] This study found important stage-specific differences in survival ranging from 29% for the highest stage of disease to 87% for the lowest stage of disease.[14] Establishing a uniform staging approach could allow for more standardized treatment guidelines. Furthermore, though the Chicago Consensus Guidelines suggest core-needle biopsy to determine treatment approach, this may be impractical in some cases where presentation is acute or diagnosis is suggested on diagnostic laparoscopy.

Our study has a few important limitations. The study utilized the NCDB as its data source, therefore requiring a retrospective design. Though the NCDB contains a vast array of treatment information, it is not possible to differentiate between systemic intravenous and intraperitoneal chemotherapy at this time, and therefore, it was not possible to specify whether part or all of chemotherapy used to treat patients was intraperitoneal (HIPEC or otherwise) or not. To try to mitigate this limitation, we categorized chemotherapy as "same-day" if the day of chemotherapy was equal to the day of definitive surgery and assumed that those who received same-day chemotherapy as the day of definitive surgery received intraperitoneal chemotherapy in the form of HIPEC. This is a significant assumption to make and we cannot rely on this being an accurate assumption to compare utilization of HIPEC between academic and community facilities. Moreover, the NCDB does not specify specific chemotherapeutic agent used, so even assuming that same-day chemotherapy consisted of HIPEC, it would not be possible to compare specific regimens provided. Regardless, specific HIPEC agent and protocol remain important points of debate.

Furthermore, as we now know that CRS is a key component of treatment for malignant peritoneal mesothelioma, it would be ideal to obtain specific surgical information for outcomes assessment. In this case, using the NCDB, the types of surgery to the peritoneum as the primary site were defined according to the following categories: no surgery, local tumor destruction or excision, partial or total resection of the primary site, debulking surgery (stated as "debulking" surgery), radical resection (partial or total resection of the peritoneum with resection in continuity of other involved organs), and surgery NOS. Given the nature of malignant peritoneal mesothelioma, it can be difficult to interpret the extent of surgery involved in any particular category without knowing the extent of peritoneal disease. That said, the NCDB does not allow quantifying the extent of disease for malignant peritoneal mesothelioma, as it does not contain information on PCI, or on the completeness of cytoreduction, for example with the completeness of cytoreduction score (CC score), which assesses the amount of residual disease remaining following surgical resection.[10,17] These variables would certainly allow a better assessment of therapeutic approach for patients with malignant peritoneal mesothelioma. In the absence of these variables, it is not possible to compare surgical outcomes by facility volume, as we would be unable to specifically define the volume of CRS and HIPEC cases at a given facility. As such, it is not possible to conduct a true volume-outcome analysis utilizing the data available in the NCDB. In light of this limitation, the current study sought to characterize and compare outcomes between academic and community facilities. However, it is important to note that academic facilities do not all necessarily have greater expertise in mesothelioma with a higher volume of CRS and HIPEC than all community facilities, with a couple single-institution studies reporting their success with CRS and HIPEC at a community center.[20,21] While acknowledging the importance of multidisciplinary care, it has been estimated that between 140 and 220 cases are needed to reach technical proficiency in CRS and HIPEC.[19]

Furthermore, as previously mentioned, histology was classified as mesothelioma NOS for the majority of patients, which is a limitation because histologic subtype has important prognostic implications for this disease.[3,4,10] Additionally, the NCDB does not provide information on pertinent risk factors for malignant peritoneal mesothelioma, particularly exposure to asbestos, which would have been interesting to assess and include in multivariable analysis. Finally, though the NCDB allows calculating overall survival, it does not provide information on disease-specific survival such that disease-free survival is unable to be estimated. Disease-specific recurrence is not reported, and therefore, we could not compare recurrence following surgery between facility types.

Conclusion

In conclusion, our study found that patients with primary malignant peritoneal mesothelioma demonstrated significantly improved survival outcomes when treated at academic facilities compared to community facilities. Patients with this disease may therefore be better served at experienced academic centers, given that CRS with HIPEC has become the mainstay of therapy and remains a fairly novel approach. There are significant gaps in treatment guidelines available for malignant peritoneal mesothelioma, and databases do not currently collect complete information on variables pertinent to the disease. As treatment with CRS and HIPEC becomes more widespread, experienced centers can collect and publish data on peritoneal mesothelioma outcomes and allow for the elaboration of treatment guidelines in a widely accessible source. Further guidelines could potentially facilitate standardization of the procedure and more widespread use, including outside of academic centers.

Author Contribution All authors had substantial contributions to the conception or design of the work; or to the acquisition, analysis, or interpretation of the work; to drafting or revising of the work; made final approval; and agreed to be accountable for all aspects of the work.

Declarations

Conflict of Interest The authors declare no competing interests.

References

1. Miura JT, Johnston FM, Gamblin TC, Turaga KK. Current Trends in the Management of Malignant Peritoneal Mesothelioma. Annals of Surgical Oncology. 2014;21(12):3947-53. doi:https://doi.org/10.1245/s10434-014-3803-6.
2. Bridda A, Padoan I, Mencarelli R, Frego M. Peritoneal mesothelioma: a review. MedGenMed. 2007;9(2):32.
3. Kim J, Bhagwandin S, Labow DM. Malignant peritoneal mesothelioma: a review. Ann Transl Med. 2017;5(11):236. doi:https://doi.org/10.21037/atm.2017.03.96.
4. Turaga KK, Deraco M, Alexander HR. Current management strategies for peritoneal mesothelioma. International Journal of Hyperthermia. 2017;33(5):579-81. doi:https://doi.org/10.1080/02656736.2017.1320591.
5. Sugarbaker PH, Yan H, Grazi RV, Shmookler BM. Early localized peritoneal mesothelioma as an incidental finding at laparoscopy. Report of a case and implications regarding natural history of the disease. Cancer. 2000;89(6):1279-84. https://doi.org/10.1002/1097-0142(20000915)89:6<1279::aid-cncr12>3.0.co;2-8.
6. de Pangher Manzini V. Malignant peritoneal mesothelioma. Tumori. 2005;91(1):1-5.
7. Salemis NS, Tsiambas E, Gourgiotis S, Mela A, Karameris A, Tsohataridis E. Peritoneal mesothelioma presenting as an acute surgical abdomen due to jejunal perforation. J Dig Dis. 2007;8(4):216-21. doi:https://doi.org/10.1111/j.1751-2980.2007.00309.x.
8. Sethna K, Sugarbaker PH. Localized visceral invasion of peritoneal mesothelioma causing intestinal obstruction: a new clinical presentation. Hepatogastroenterology. 2005;52(64):1087-9.
9. Mohamed F, Sugarbaker PH. Peritoneal mesothelioma. Curr Treat Options Oncol. 2002;3(5):375-86. doi:https://doi.org/10.1007/s11864-002-0003-6.
10. Magge D, Zenati MS, Austin F, Mavanur A, Sathaiah M, Ramalingam L et al. Malignant Peritoneal Mesothelioma: Prognostic Factors and Oncologic Outcome Analysis. Annals of Surgical Oncology. 2014;21(4):1159-65. doi:https://doi.org/10.1245/s10434-013-3358-y.
11. Yan TD, Welch L, Black D, Sugarbaker PH. A systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for diffuse malignancy peritoneal mesothelioma. Ann Oncol. 2007;18(5):827-34. doi:https://doi.org/10.1093/annonc/mdl428.
12. NCCN. NCCN Guidelines for Treatment of Cancer By Site. In: NCCN Guidelines. National Comprehensive Cancer Network (NCCN), National Comprehensive Cancer Network (NCCN). 2019. https://www.nccn.org/professionals/physician_gls/default.aspx#ovarian. Accessed November 30 2020.
13. ACS. Malignant Mesothelioma Stages. American Cancer Society. 2018. https://www.cancer.org/cancer/malignant-mesothelioma/detection-diagnosis-staging/staging.html#references. Accessed November 23 2020.
14. Yan TD, Deraco M, Elias D, Glehen O, Levine EA, Moran BJ et al. A novel tumor-node-metastasis (TNM) staging system of diffuse malignant peritoneal mesothelioma using outcome analysis of a multi-institutional database*. Cancer. 2011;117(9):1855-63. doi:https://doi.org/10.1002/cncr.25640.
15. Chicago Consensus Working G. The Chicago Consensus on Peritoneal Surface Malignancies: Management of Peritoneal Mesothelioma. Ann Surg Oncol. 2020;27(6):1774-9. doi:https://doi.org/10.1245/s10434-020-08324-w.
16. ACS. National Cancer Database. American College of Surgeons. https://www.facs.org/quality-programs/cancer/ncdb. Accessed November 17 2020.
17. Yan TD, Brun EA, Cerruto CA, Haveric N, Chang D, Sugarbaker PH. Prognostic Indicators for Patients Undergoing Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy for Diffuse Malignant Peritoneal Mesothelioma†. Annals of Surgical Oncology. 2007;14(1):41-9. doi:https://doi.org/10.1245/s10434-006-9169-7.
18. Bijelic L, Darcy K, Stodghill J, Tian C, Cannon T. Predictors and Outcomes of Surgery in Peritoneal Mesothelioma: an Analysis of 2000 Patients from the National Cancer Database. Ann Surg Oncol. 2020;27(8):2974-82. doi:https://doi.org/10.1245/s10434-019-08138-5.
19. Rajeev R, Klooster B, Turaga KK. Impact of surgical volume of centers on post-operative outcomes from cytoreductive surgery and hyperthermic intra-peritoneal chemoperfusion. Journal of Gastrointestinal Oncology. 2015;7(1):122-8.
20. Kerscher AG, Mallalieu J, Pitroff A, Kerscher F, Esquivel J. Morbidity and mortality of 109 consecutive cytoreductive procedures with hyperthermic intraperitoneal chemotherapy (HIPEC) performed at a community hospital. World J Surg. 2010;34(1):62-9. doi:https://doi.org/10.1007/s00268-009-0281-2.
21. Goslin B, Sevak S, Siripong A, Onesti J, Wright GP, Melnik M et al. Outcomes of cytoreduction with hyperthermic intraperitoneal chemotherapy: our experience at a midwest community hospital. Am J Surg. 2012;203(3):383-6; discussion 7. doi:https://doi.org/10.1016/j.amjsurg.2011.09.009.