Original Article

Impact of hyperthermic intrathoracic chemotherapy (HITHOC) during resection of pleural mesothelioma on patient survival

Irmina A. Elliott[1,2]^, Hao He[1], Natalie S. Lui[1], Douglas Z. Liou[1], Brandon A. Guenthart[1], Joseph B. Shrager[1,2], Mark F. Berry[1,2], Leah M. Backhus[1,2]

[1]Division of Thoracic Surgery, Department of Cardiothoracic Surgery, Stanford University School of Medicine, Stanford, CA, USA; [2]Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, USA

Contributions: (I) Conception and design: IA Elliott, H He, LM Backhus; (II) Administrative support: None; (III) Provision of study materials or patients: IA Elliott, H He, DZ Liou, MF Berry, LM Backhus; (IV) Collection and assembly of data: IA Elliott, H He; (V) Data analysis and interpretation: IA Elliott, H He, LM Backhus; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Irmina A. Elliott, MD. Division of Thoracic Surgery, Department of Cardiothoracic Surgery, Stanford University School of Medicine, Falk Research Bldg., 870 Quarry Rd. Ext., Stanford, CA 94304, USA; Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, USA. Email: irmina@stanford.edu.

Background: Pleural mesothelioma (PM) is rare but portends a poor prognosis. Multimodal treatment, including aggressive surgical resection, may offer the best chance of treatment response and improved survival. Single-center studies suggest that hyperthermic intrathoracic chemotherapy (HITHOC) during surgical resection improves outcomes, but the impact of HITHOC on postoperative morbidity and survival has not been examined on a larger scale.

Methods: The National Cancer Database was queried for patients undergoing resection for PM from 2006–2017. Patients were excluded if staging or survival data was incomplete. After propensity-score matching, patients who underwent HITHOC were compared to patients who did not (case-control study). Perioperative outcomes and survival were analyzed.

Results: The final cohort consisted of 3,232 patients; of these, 365 patients underwent HITHOC. After propensity-score matching, receipt of HITHOC was associated with increased length of stay (12 *vs.* 7 days, P<0.001) and increased 30-day readmissions (9.9% *vs.* 4.9%, P=0.007), but decreased 30-day mortality (3.2% *vs.* 6.0%, P=0.017) and 90-day mortality (7.5% *vs.* 10.9%). Kaplan-Meier modeling demonstrated that HITHOC was associated with improved survival in the overall cohort (median 20.5 *vs.* 16.8 months, P=0.001). In multivariable analysis, HITHOC remained associated with improved overall survival [hazard ratio (HR) =0.80; 95% confidence interval (CI): 0.69–0.92; P=0.002], and this persisted in the propensity-matched analysis (HR =0.73; 95% CI: 0.61–0.88; P=0.001).

Conclusions: Using a large national database, we describe the impact of HITHOC on survival in patients with PM. Despite observed increased short-term morbidity, in multivariable analysis HITHOC was associated with an overall survival advantage for patients undergoing surgical resection of PM.

Keywords: Mesothelioma; pleural neoplasm; surgical margins; chemotherapy

Submitted Mar 22, 2023. Accepted for publication Aug 25, 2023. Published online Nov 03, 2023.
doi: 10.21037/jtd-23-466
View this article at: https://dx.doi.org/10.21037/jtd-23-466

^ ORCID: 0000-0002-1138-9053.

Introduction

Pleural mesothelioma (PM) is a devastating disease with poor survival (1,2). Multimodal treatment offers the best chance of long-term survival (3). Patients with Stage I–IIIa disease with preserved performance status are recommended to undergo surgical resection, accompanied by either induction chemotherapy or adjuvant chemotherapy, with or without adjuvant radiation (4). Systemic chemotherapy has traditionally been cisplatin (or carboplatin) with pemetrexed (5,6). There is increasing interest in the role of immunotherapy in mesothelioma, which has shown promise in advanced disease, especially in patients with sarcomatoid histology, and clinical trials of chemoimmunotherapy in the perioperative setting are ongoing (7,8). The best surgical approach remains controversial, with some centers and surgeons performing extended pleurectomy and decortication (eP/D), while others prefer extrapleural pneumonectomy (EPP). eP/D is associated with less perioperative mortality, and better patient-reported quality of life (9-11), but it is unclear from existing data whether one operation or the other is oncologically superior. In either approach, the goal of surgical resection is to remove all macroscopic disease, however, rarely are microscopically negative margins obtained. Local tumor recurrence is frequent, and has been reported to occur in up to 54% of cases (12,13).

Hyperthermic intraperitoneal chemotherapy (HIPEC) is increasingly used in patients with peritoneal malignancies in which complete resection is not possible, such as peritoneal mesothelioma, peritoneal dissemination of ovarian and colon cancer, and pseudomyxoma peritonei to address residual microscopic disease and reduce local tumor recurrence (14-16). Similarly, surgery for PM is cytoreductive, as an R0 resection is rarely possible, making the use of intraoperative chemotherapy attractive. Patient selection criteria vary by institution; HITHOC is usually performed after all disease has been resected and the pericardium and diaphragm have been patched, if indicated. At our institution, for example, we then place chest tubes and temporarily close the chest, and infuse cisplatin at 42 degrees for 1 hour. Single-center series have reported on the safety and tolerability of hyperthermic intrathoracic chemotherapy (HITHOC) (17-20), and one single institution cohort study of 103 patients reported that HITHOC during resection of mesothelioma improved disease-free survival (27.1 *vs.* 12.8 months) and overall survival (35.3 *vs.* 22.8 months) (17). Another single institution series of patients with epithelioid histology who underwent eP/D with HITHOC reported an overall survival of 38.1 months (21). However, there are no large-scale studies examining the impact of HITHOC during surgery for mesothelioma across multiple centers, and current treatment guidelines do not include HITHOC as part of standard of care (22). The 2022 National Comprehensive Cancer Network® (NCCN) Guidelines for the management of PM state that "*intraoperative adjuvant therapy is still under investigation but may be considered as part of a reasonable multidisciplinary approach to locally aggressive disease*" (4). The primary aim of this study was to determine whether the addition of HITHOC improves survival after surgical resection for PM using a large nationwide database. A secondary aim was to examine whether HITHOC increases short-term morbidity and mortality. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-466/rc).

Methods

The National Cancer Database (NCDB) contains data from all Committee-on-Cancer approved facilities in North America, and is estimated to capture over 70% of newly diagnosed cancers in the United States. All patients in the NCDB diagnosed with PM from 2006 to 2017 were identified. Patients who had incomplete survival data or unknown stage were excluded. Patients who underwent surgical resection were selected for inclusion, using procedure codes 30, 40, 50, and 60, as described previously by other authors when analyzing mesothelioma cases from the NCDB (3,23-25).

Patients were then stratified by whether or not they received HITHOC during surgical resection, defined as NCDB data item name "RX_SUMM_SYSTEMIC_SUR_SEQ" coded as 5 ("Intraoperative systemic therapy") or 6 ("Intraoperative systemic therapy with other systemic therapy administered before or after surgery"). Patient, tumor, and clinical characteristics were compared between patients who did and did not receive HITHOC using the Student's unpaired *t*-test, Wilcoxon rank-sum test, Pearson's chi-squared, or Fisher's exact test as appropriate for categorical and continuous variables.

Propensity scores were calculated through logistic regression on HITHOC status, in which age, comorbidity index, histology, stage, year of diagnosis, facility type, and county type were included as predictors. When matching

non-HITHOC patients to HITHOC patients, exact matching was done based on histology and stage. To improve imbalance among covariates between the groups, further reduce bias compared to 1:1 or fixed ratio matching, and make greater use of available information, an optimal variable ratio matching method was employed (26,27). Using the criterion of minimizing global propensity score distance through matching implementation, one or two non-HITHOC patients were matched to each HITHOC patient. A suitable match could not be identified for 53 HITHOC patients; these were excluded. Before matching, standard mean difference (SMD) and variance ratio of the global propensity score of the cohort were 0.722 and 1.481, respectively. After optimal propensity-score matching, SMD and variance ratio of the global propensity score of the weighted matched groups were 0.006 and 1.013, respectively, indicating that excellent balance between matched groups had been obtained (28,29).

Unadjusted survival was estimated with Kaplan-Meier modeling and compared with log-rank tests, and multivariable Cox proportional-hazards models were constructed using clinically relevant variables including age, sex, race, comorbidity score, histology, stage, year of diagnoses, receipt of chemotherapy, radiotherapy and HITHOC to identify factors that independently impacted survival. Subgroup analysis of only patients with epithelioid histology was undertaken in order to explore the impact of HITHOC in a more homogenous group of tumors.

A sensitivity analysis was performed in order to address the possibility of a higher proportion of patients in the non-HITHOC group undergoing less aggressive surgical resection (for example, with diagnostic or palliative intent, as opposed to curative intent) resulting in confounding. To this end, a subgroup was created and analyzed including only surgery codes 40 (total surgical removal of primary site) and 60 (radical surgery).

A P value of <0.05 was used to determine statistical significance. Analyses were performed using SAS version 9.4.1 (SAS Institute, Cary, NC, USA) and IBM SPSS Statistics 25. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Results

Patient characteristics

From 2006 to 2017, there were 3,232 patients who underwent surgical resection for PM entered in to the NCDB who met criteria for inclusion in the study (Figure S1). Of those, 365 (11.3%) received HITHOC. Baseline patient and tumor characteristics for the overall cohort and propensity-matched groups are shown in *Table 1*. Patients undergoing HITHOC were more likely to be younger, had fewer comorbidities, were more likely to be treated in an academic center, and to have been treated later in the study period. There was also variation in the distribution of histology types and final pathologic stage, and patients receiving HITHOC were less likely to receive systemic chemotherapy or radiation. After propensity-score matching, the groups were well-matched in all preoperative and tumor characteristics.

Postoperative outcomes

Postoperative outcomes for the overall cohort and propensity-matched groups are shown in *Table 1*. Patients who underwent HITHOC were more likely to have longer lengths of stay (12 *vs.* 6 days, P<0.001) and had increased rates of 30-day readmissions (9.9% *vs.* 5.2%, P<0.001), and these differences persisted after propensity matching. In the overall cohort, patients who received HITHOC had equivalent 30-day mortality (2.8% *vs.* 5.3%, P=0.059), but lower 90-day mortality (6.6% *vs.* 12.4%, P=0.002). After propensity matching, both 30- and 90-day mortality were lower in the HITHOC group (3.2% *vs.* 6.0%, P=0.017, and 7.5% *vs.* 10.9%, P=0.046, respectively).

Survival analysis

Kaplan-Meier survival probability estimation found that patients who received HITHOC had significantly improved survival (P<0.0001, *Figure 1A*). Median survival was improved to 20.5 months in the HITHOC group *vs.* 16.8 months (P=0.001). In multivariable Cox proportional-hazards modeling, HITHOC was independently associated with improved survival [hazard ratio (HR) =0.80, P=0.002]. Other factors independently associated with improved survival were younger age, female sex, type of treatment center, metropolitan county, epithelioid histology, earlier stage of disease, treatment later in the study period, and receipt of chemotherapy (*Table 2*). After propensity matching, Kaplan-Meier curves did not show a statistically significant improvement in survival with HITHOC (P=0.119, *Figure 1B*), median survival 18.5 *vs.* 17.9 months. However, when controlling for relevant demographic

Table 1 Baseline characteristics and outcomes of patients, stratified by receipt of HITHOC, in overall cohort and propensity-matched cohort

Characteristics and outcomes	Overall cohort			Propensity-matched cohort		
	HITHOC		P value	HITHOC		P value
	No (n=2,867)	Yes (n=365)		No (n=468)	Yes (n=312)	
Age (years)	67.85 (10.12)	65.68 (10.21)	<0.001*	66.94 (8.15)	66.34 (8.53)	0.322
Female	630 (22.0)	74 (20.3)	0.459	108 (23.1)	64 (20.5)	0.397
Race			0.592			0.933
White	2,669 (93.1)	345 (94.5)		438 (93.6)	294 (94.2)	
Black	110 (3.8)	11 (3.0)		17 (3.6)	10 (3.2)	
Others	88 (3.1)	9 (2.5)		13 (2.8)	8 (2.7)	
Charlson/Deyo comorbidity score			0.009*			0.811
0	2,078 (72.5)	292 (80.0)		371 (79.3)	252 (80.8)	
1	602 (21.0)	57 (15.6)		77 (16.5)	46 (14.7)	
≥2	187 (6.5)	16 (4.4)		20 (4.3)	14 (4.5)	
Facility type			<0.001*			0.423
Community cancer program	107 (3.8)	12 (3.4)		18 (3.9)	12 (3.9)	
Comprehensive community cancer program	774 (27.3)	56 (15.7)		103 (22.0)	56 (18.0)	
Academic/research program	1,685 (59.5)	266 (74.5)		309 (66.0)	223 (71.5)	
Integrated network cancer program	265 (9.4)	23 (6.4)		38 (8.1)	21 (6.7)	
Insurance type			0.641			0.633
Private	1,047 (36.5)	142 (38.9)		180 (38.5)	116 (37.2)	
Medicaid/Medicare/other government	1,731 (60.4)	211 (57.8)		278 (59.4)	186 (59.6)	
Uninsured/insurance status unknown	89 (3.1)	12 (3.3)		10 (2.1)	10 (3.2)	
County type			0.074			0.266
Metropolitan	2,324 (85.8)	260 (82.0)		398 (85.0)	256 (82.1)	
Urban/rural	386 (14.2)	57 (18.0)		70 (15.0)	56 (17.9)	
Year of diagnosis			<0.001*			0.308
2006–2009	853 (29.8)	50 (13.7)		79 (16.9)	50 (16.0)	
2010–2013	1,127 (39.3)	116 (31.8)		173 (37.0)	101 (32.4)	
2014–2016	887 (30.9)	199 (54.5)		216 (46.2)	161 (42.7)	
Histology			<0.001*			0.807
Epithelioid	1,664 (58.0)	249 (68.2)		330 (70.5)	210 (67.3)	
Biphasic	440 (15.4)	76 (20.8)		87 (18.6)	66 (21.2)	
Sarcomatoid	241 (8.4)	13 (3.6)		14 (3.0)	10 (3.2)	
Unknown	522 (18.2)	27 (7.4)		37 (7.9)	26 (8.3)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics and outcomes	Overall cohort			Propensity-matched cohort		
	HITHOC		P value	HITHOC		P value
	No (n=2,867)	Yes (n=365)		No (n=468)	Yes (n=312)	
Pathologic stage			<0.001*			0.893
I	470 (16.4)	34 (9.3)		41 (8.8)	26 (8.3)	
II	487 (17.0)	46 (12.6)		52 (11.1)	40 (12.8)	
III	1,155 (40.3)	200 (54.8)		266 (56.8)	172 (55.1)	
IV	755 (26.3)	85 (23.3)		109 (23.3)	74 (23.7)	
Chemotherapy			<0.001*			<0.001*
Yes	1,889 (65.9)	173 (47.4)		350 (74.8)	193 (49.0)	
No	978 (34.1)	192 (52.6)		118 (25.2)	159 (51.0)	
Radiation			<0.001*			<0.001*
Yes	676 (23.6)	31 (8.5)		131 (28.0)	28 (9.0)	
No	2191 (76.4)	334 (91.5)		337 (72.0)	284 (91.0)	
Length of stay (days)	6 [4, 10]	12 [7, 17]	<0.001*	7 [5, 11]	12 [7, 18]	<0.001*
30-day readmission	148 (5.2)	36 (9.9)	<0.001*	23 (4.9)	31 (9.9)	0.007*
30-day mortality	150 (5.3)	10 (2.8)	0.059	28 (6.0)	10 (3.2)	0.017*
90-day mortality	352 (12.4)	24 (6.6)	0.002*	51 (10.9)	23 (7.5)	0.046*

Data are presented as mean (SD), n (%), or median [IQR]. *, P<0.05. HITHOC, hyperthermic intrathoracic chemotherapy; SD, standard deviation; IQR, interquartile range.

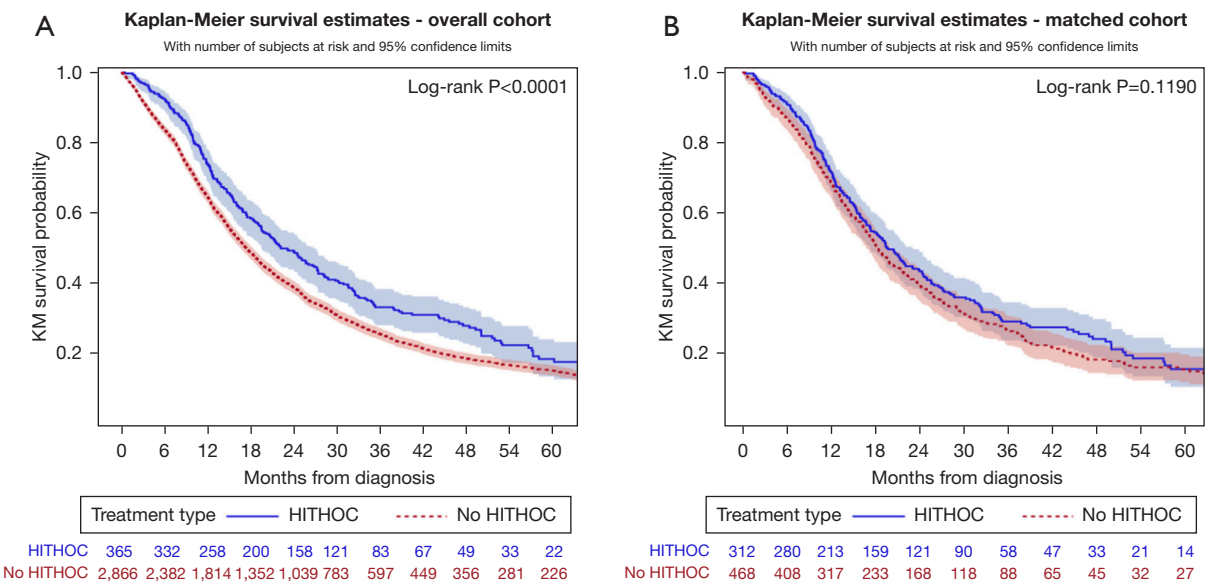

Figure 1 Patient survival after resection of PM, stratified by receipt of HITHOC in overall cohort (A) and in propensity-matched cohort (B). KM, Kaplan-Meier; HITHOC, hyperthermic intrathoracic chemotherapy; PM, pleural mesothelioma.

Table 2 Cox proportional-hazards model of factors associated with survival in overall cohort and propensity-matched cohort

Factors	Overall cohort		Propensity-matched cohort	
	HR (95% CI)	P value	HR (95% CI)	P value
Age per 5 years	1.11 (1.09–1.14)	<0.001*	1.09 (1.04–1.15)	0.001*
Sex (ref = female)				
Male	1.51 (1.36–1.67)	<0.001*	1.62 (1.31–2.01)	<0.001*
Race (ref = White)				
Black	1.12 (0.91–1.38)	0.293	0.91 (0.59–1.41)	0.674
Asian/others	1.06 (0.83–1.35)	0.629	1.53 (0.92–2.54)	0.102
Charlson/Deyo comorbidity score (ref=0)				
1	1.07 (0.97–1.19)	0.157	0.93 (0.74–1.16)	0.500
≥2	1.16 (0.99–1.36)	0.073	0.97 (0.65–1.44)	0.866
Facility (ref = academic/research)				
Community cancer program	1.05 (0.85–1.29)	0.673	1.17 (0.75–1.80)	0.492
Comprehensive community cancer program	1.17 (1.06–1.28)	0.001*	1.33 (1.08–1.63)	0.006*
Integrated network cancer program	1.08 (0.94–1.24)	0.303	1.50 (1.11–2.03)	0.009*
County (ref = metropolitan)				
Urban/rural	1.14 (1.02–1.28)	0.020*	0.91 (0.72–1.15)	0.413
Histology (ref = epithelioid)				
Biphasic	1.79 (1.60–2.00)	<0.001*	1.99 (1.62–2.44)	<0.001*
Sarcomatoid	2.21 (1.91–2.55)	<0.001*	2.75 (1.74–4.32)	<0.001*
Unknown	1.09 (0.98–1.22)	0.130	1.03 (0.76–1.40)	0.847
Stage (ref = stage I)				
II	0.96 (0.84–1.11)	0.584	1.40 (0.95–2.05)	0.085
III	1.24 (1.10–1.40)	<0.001*	1.65 (1.21–2.26)	0.002*
IV	1.53 (1.35–1.74)	<0.001*	2.38 (1.71–3.32)	<0.001*
Year of diagnosis (ref =2006–2009)				
2010–2013	0.87 (0.79–0.95)	0.003*	0.90 (0.71–1.14)	0.379
2014–2016	0.78 (0.70–0.87)	<0.001*	0.76 (0.60–0.96)	0.024*
Chemotherapy	0.71 (0.65–0.77)	<0.001*	0.61 (0.50–0.73)	<0.001*
Radiation	0.93 (0.84–1.02)	0.130	0.98 (0.79–1.21)	0.838
HITHOC	0.80 (0.69–0.92)	0.002*	0.73 (0.61–0.88)	0.001*

*, P<0.05. HR, hazard ratio; CI, confidence interval; HITHOC, hyperthermic intrathoracic chemotherapy.

and clinical factors in multivariable Cox proportional-hazards modeling among the propensity-matched groups, HITHOC was associated with a significantly decreased relative risk of death (HR =0.73; P=0.001), as shown in *Table 2*.

Epithelioid histology sub-analysis

Subgroup analysis in 1,912 patients with epithelioid histology was performed. In this subgroup, HITHOC was also associated with improved survival (P=0.0116, *Figure 2*),

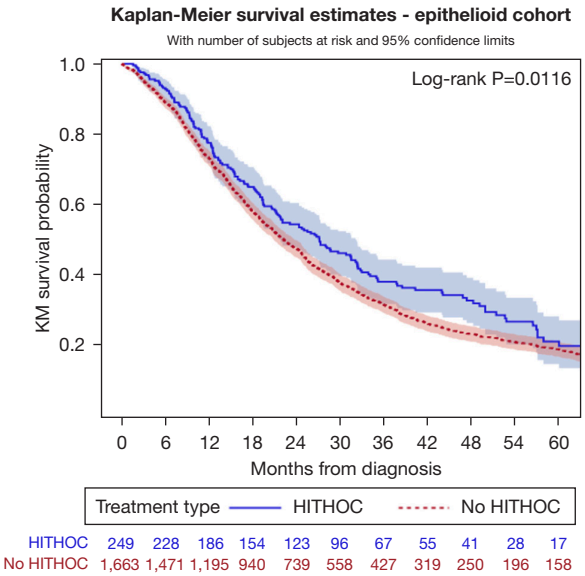

Figure 2 Patient survival of subset of patients with epithelioid histology after resection of PM, stratified by receipt of HITHOC. KM, Kaplan-Meier; HITHOC, hyperthermic intrathoracic chemotherapy; PM, pleural mesothelioma.

with a median survival of 23.1 *vs.* 20.9 months. In multivariable analysis of patients with epithelioid histology, HITHOC was again independently associated with improved survival (HR =0.84; P=0.050), as were younger age, female sex, lower comorbidity score, earlier stage of disease, treatment later in the study period, and receipt of chemotherapy (*Table 3*).

Radical surgery sub-analysis

Subgroup analysis was performed in 1,632 patients coded as having undergone "total surgical removal of the primary site" or "radical surgery". In multivariable analysis of patients undergoing radical surgery, HITHOC was again independently associated with improved survival (HR =0.76; P=0.001), as were younger age, female sex, epithelioid histology, earlier stage of disease, treatment later in the study period, and receipt of chemotherapy (*Table 4*). After propensity matching in this radical surgery subgroup, HITHOC remained independently associated with improved survival (HR =0.72; P=0.004).

Discussion

In this analysis of patients within the NCDB undergoing resection of PM, we examine the impact of intraoperative HITHOC on patient outcomes. We find that the receipt of HITHOC is independently associated with improved survival, as demonstrated by multivariable analysis of the overall patient cohort, propensity-matched groups, subset analysis of patients with epithelioid histology, and subset analysis of patients who underwent radical surgery. Our data does suggest that use of HITHOC may increase short-term morbidity, as suggested by increased length of stay and 30-day readmissions among patients receiving HITHOC, however, this did not translate into an increase in short-term mortality. This, taken with the improvement in long-term survival observed in our study, suggests there may be an acceptable trade-off of increased short-term morbidity without increased short-term mortality and improved overall survival.

There are several limitations of our study. It is a retrospective analysis of a large-scale database, subject to

Table 3 Cox proportional-hazards model of factors associated with survival in 1,912 patients with epithelioid histology

Factors	HR (95% CI)	P value
Age per 5 years	1.11 (1.07–1.14)	<0.001*
Sex (ref = female)		
Male	1.66 (1.45–1.89)	<0.001*
Charlson/Deyo comorbidity score (ref =0)		
1	1.06 (0.93–1.21)	0.362
≥2	1.46 (1.18–1.81)	0.001*
County (ref = metropolitan)		
Urban/rural	1.16 (1.00–1.35)	0.057
Stage (ref = stage I)		
II	0.98 (0.81–1.19)	0.842
III	1.35 (1.15–1.59)	<0.001*
IV	1.54 (1.30–1.84)	<0.001*
Year of diagnosis (ref =2006–2009)		
2010–2013	0.89 (0.78–1.01)	0.070
2014–2016	0.73 (0.64–0.81)	<0.001*
Chemotherapy	0.72 (0.64–0.85)	<0.001*
Radiation	0.95 (0.83–1.08)	0.4
HITHOC	0.84 (0.70–1.00)	0.050

*, P<0.05. HR, hazard ratio; CI, confidence interval; HITHOC, hyperthermic intrathoracic chemotherapy.

Table 4 Cox proportional-hazards model of factors associated with survival in 1,632 patients who underwent radical surgery

Factors	Radical subgroup		PSM radical cohort	
	HR (95% CI)	P value	HR (95% CI)	P value
Age per 5 years	1.06 (1.02–1.09)	0.002*	1.07 (0.99–1.14)	0.061
Sex (ref = female)				
Male	1.57 (1.36–1.82)	<0.001*	1.65 (1.26–2.17)	<0.001*
Race (ref = White)				
Black	1.14 (0.81–1.60)	0.445	1.11 (0.59–2.07)	0.750
Asian/others	1.01 (0.70–1.46)	0.946	1.32 (0.61–2.87)	0.483
Charlson/Deyo comorbidity score (ref =0)				
1	0.97 (0.84–1.12)	0.688	1.04 (0.78–1.40)	0.778
2	1.25 (0.97–1.61)	0.085	1.15 (0.68–1.95)	0.612
Facility (ref = academic/research)				
Community cancer program	1.13 (0.82–1.55)	0.454	1.27 (0.73–2.21)	0.394
Comprehensive community cancer program	1.11 (0.96–1.29)	0.156	1.19 (0.90–1.58)	0.219
Integrated network cancer program	0.97 (0.79–1.20)	0.795	1.30 (0.89–1.91)	0.181
County (ref = metropolitan)				
Urban/rural	1.04 (0.87–1.23)	0.674	0.90 (0.66–1.22)	0.499
Histology (ref = epithelioid)				
Biphasic	1.72 (1.49–2.00)	<0.001*	2.36 (1.46–3.81)	<0.001*
Sarcomatoid	1.88 (1.46–2.40)	<0.001*	1.67 (1.05–2.65)	0.008*
Unknown	1.04 (0.88–1.24)	0.638	1.19 (0.79–1.78)	0.409
Stage (ref = stage I)				
II	1.07 (0.85–1.34)	0.575	1.21 (0.70–2.09)	0.493
III	1.42 (1.17–1.73)	<0.001*	1.65 (1.21–2.26)	0.002*
IV	1.64 (1.33–2.02)	<0.001*	2.38 (1.71–3.32)	<0.001*
Year of diagnosis (ref =2006–2009)				
2010–2013	0.95 (0.83–1.09)	0.475	0.96 (0.71–1.31)	0.814
2014–2016	0.84 (0.72–0.98)	0.023*	0.76 (0.55–1.03)	0.078
Chemotherapy	0.59 (0.52–0.67)	<0.001*	0.61 (0.49–0.77)	<0.001*
Radiation	0.94 (0.82–1.07)	0.313	0.91 (0.70–1.18)	0.484
HITHOC	0.76 (0.64–0.90)	0.001*	0.72 (0.58–0.90)	0.004*

*, P<0.05. PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; HITHOC, hyperthermic intrathoracic chemotherapy.

errors in coding/data collection, selection bias in treatment groups, and confounding by variables that are not controlled for in multivariable analysis. Our study design assumes that patients coded as having "intraoperative chemotherapy" received HITHOC, however, the specific type and manner of chemotherapy being administered cannot be determined. Also of note, a significant limitation of using the NCDB to analyze mesothelioma cases specifically is that the NCDB does not directly differentiate the common resections performed for mesothelioma, namely EPP and extended

pleurectomy/decortication (30). We used selection criteria in line with that used by other authors when utilizing the NCDB to assess outcomes of patients undergoing operations for mesothelioma (3,23-25), but it is not possible to know and control for the exact type of surgery the patients underwent. Given that we observed a shorter length of stay in the group not undergoing HITHOC, it is possible that the HITHOC group is biased towards patients receiving more aggressive surgery, thereby confounding the possible benefit observed with HITHOC. In an attempt to control for this possible confounding, we performed a sensitivity analysis of patients whose surgeries were coded as "total surgical removal of primary site" (surgery code 40) and "radical surgery" (code 60). In this subgroup of patients who very likely underwent aggressive, curative-intent surgery, the use of HITHOC remained independently associated with improved survival, both before and after propensity matching.

Despite these limitations, our survival data are in line with prior observations in the literature regarding survival after resection of PM. Prior studies examining HITHOC during resection have reported median survivals ranging from 18–35 months, with variation depending on specific study inclusion criteria (slightly better survival for studies including only epithelioid or early-stage patients, and slightly worse survival for more inclusive studies) (17,19,22). In terms of survival among non-HITHOC patients, our data is also consistent with previously reported median survival data from both database and single-institution studies (3,10).

The result that HITHOC is associated with decreased short-term mortality is somewhat unexpected. This may indicate a higher proportion of patients undergoing pleurectomy/decortication *vs.* EPP in the HITHOC group compared to the non-HITHOC group (9,10), although it is not possible to discern this from NCDB data. Alternatively, this could be a reflection of selection bias of overall healthier patients in the HITHOC group that is not controlled for by matching.

Additionally, while Kaplan-Meier survival estimates showed a statistically significant survival advantage with HITHOC in the overall cohort and epithelioid subgroup, this was not statistically significant in the propensity-matched group. However, HITHOC was associated with improved survival when multivariable Cox proportional-hazards models were analyzed, and this effect was consistent in all groups: the overall cohort, the propensity-matched cohort, the epithelioid only cohort, and the radical surgery subgroup. This discrepancy could be due to the combination of smaller power in the matched group and the fact that the Kaplan-Meier model does not control for confounding covariates (specifically, there was a higher use of systemic chemotherapy in the non-HITHOC group, and both chemotherapy and HITHOC were independently associated with improved survival in multivariable models). However, the consistency across all multivariable Cox models showing a decreased risk of death with HITHOC supports that a survival benefit does in fact exist.

Our study has several strengths. While prior studies have reported outcomes of HITHOC from single centers, our study is unique in that it uses a large database, and may be more generalizable to mesothelioma patients overall. Survival data for patients undergoing surgical resection without HITHOC are in line with prior published reports (3,23-25), and survival data for patients undergoing HITHOC are consistent with prior single-institution series (17,19). Randomized trials of patients with PM are difficult to conduct due to the rarity of the diagnosis, and this is compounded by the fact that most patients are not surgical candidates, either due to extent of disease and/or lack of medical fitness for surgical resection. For this reason, analyses of large-scale databases like the NCDB, such as the one presented in this study, are an important means to understanding how to best treat patients with mesothelioma.

As has been shown with HIPEC (15), the benefits of HITHOC are likely associated with better local disease control (17). However, in this study we are not able to directly analyze the impact of HITHOC on recurrence and disease-free survival, as this data is not reported in the NCDB. Thus, the potential impact of HITHOC on local recurrence as an important intermediary outcome, and need for interventions to address local recurrence, cannot be assessed, but this is likely an essential aspect of the benefit of HITHOC that merits further study.

While HITHOC may represent an improvement in local therapy for PM, promising advances in systemic therapy are also emerging (2,8). Immunotherapy was approved in 2022 for use as first-line therapy for patients with unresectable PM after a randomized trial demonstrated a survival benefit of 18.1 compared to 14.1 months with traditional cytotoxic chemotherapy (7). In the future, combinations of these novel local and systemic treatments may offer hope for improved survival for patients diagnosed with mesothelioma.

Conclusions

This study provides support for further investigation of the use of HITHOC during surgical resection of PM, as this retrospective large database review finds that HITHOC is independently associated with improved patient survival in this devastating and rapidly progressive disease.

Acknowledgments

This work was presented as an oral presentation at the annual meeting of the Western Thoracic Surgical Association held in Kauai, HI, USA on June 23, 2022.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-466/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-466/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-466/coif). N.S.L. serves as an unpaid editorial board member of *Journal of Thoracic Disease* from September 2021 to August 2023. M.F.B. serves as an unpaid editorial board member of *Journal of Thoracic Disease* from October 2022 to September 2024. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

References

1. Rusch VW, Chansky K, Kindler HL, et al. The IASLC Mesothelioma Staging Project: Proposals for the M Descriptors and for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Mesothelioma. J Thorac Oncol 2016;11:2112-9.
2. Janes SM, Alrifai D, Fennell DA. Perspectives on the Treatment of Malignant Pleural Mesothelioma. N Engl J Med 2021;385:1207-18.
3. Nelson DB, Rice DC, Niu J, et al. Long-Term Survival Outcomes of Cancer-Directed Surgery for Malignant Pleural Mesothelioma: Propensity Score Matching Analysis. J Clin Oncol 2017;35:3354-62.
4. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Malignant Pleural Mesothelioma. 2022. Available online: https://www.nccn.org/professionals/physician_gls/pdf/meso_pleural.pdf
5. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003;21:2636-44.
6. Nowak AK, Jackson A, Sidhu C. Management of Advanced Pleural Mesothelioma-At the Crossroads. JCO Oncol Pract 2022;18:116-24.
7. Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet 2021;397:375-86.
8. Nowak AK, Lesterhuis WJ, Kok PS, et al. Durvalumab with first-line chemotherapy in previously untreated malignant pleural mesothelioma (DREAM): a multicentre, single-arm, phase 2 trial with a safety run-in. Lancet Oncol 2020;21:1213-23.
9. van Gerwen M, Wolf A, Liu B, et al. Short-term outcomes of pleurectomy decortication and extrapleural pneumonectomy in mesothelioma. J Surg Oncol 2018;118:1178-87.
10. Flores RM, Pass HI, Seshan VE, et al. Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. J Thorac Cardiovasc Surg 2008;135:620-6, 626.e1-3.
11. Schwartz RM, Lieberman-Cribbin W, Wolf A, et al. Systematic review of quality of life following pleurectomy decortication and extrapleural pneumonectomy for malignant pleural mesothelioma. BMC Cancer

2018;18:1188.
12. Baldini EH, Recht A, Strauss GM, et al. Patterns of failure after trimodality therapy for malignant pleural mesothelioma. Ann Thorac Surg 1997;63:334-8.
13. Baldini EH, Richards WG, Gill RR, et al. Updated patterns of failure after multimodality therapy for malignant pleural mesothelioma. J Thorac Cardiovasc Surg 2015;149:1374-81.
14. Auer RC, Sivajohanathan D, Biagi J, et al. Indications for hyperthermic intraperitoneal chemotherapy with cytoreductive surgery: a systematic review. Eur J Cancer 2020;127:76-95.
15. van Driel WJ, Koole SN, Sikorska K, et al. Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer. N Engl J Med 2018;378:230-40.
16. van Stein RM, Aalbers AGJ, Sonke GS, et al. Hyperthermic Intraperitoneal Chemotherapy for Ovarian and Colorectal Cancer: A Review. JAMA Oncol 2021;7:1231-8.
17. Sugarbaker DJ, Gill RR, Yeap BY, et al. Hyperthermic intraoperative pleural cisplatin chemotherapy extends interval to recurrence and survival among low-risk patients with malignant pleural mesothelioma undergoing surgical macroscopic complete resection. J Thorac Cardiovasc Surg 2013;145:955-63.
18. Burt BM, Richards WG, Lee HS, et al. A Phase I Trial of Surgical Resection and Intraoperative Hyperthermic Cisplatin and Gemcitabine for Pleural Mesothelioma. J Thorac Oncol 2018;13:1400-9.
19. Bongiolatti S, Mazzoni F, Salimbene O, et al. Induction Chemotherapy Followed by Pleurectomy Decortication and Hyperthermic Intraoperative Chemotherapy (HITHOC) for Early-Stage Epitheliod Malignant Pleural Mesothelioma-A Prospective Report. J Clin Med 2021;10:5542.
20. Ambrogi MC, Bertoglio P, Aprile V, et al. Diaphragm and lung-preserving surgery with hyperthermic chemotherapy for malignant pleural mesothelioma: A 10-year experience. J Thorac Cardiovasc Surg 2018;155:1857-1866.e2.
21. Klotz LV, Hoffmann H, Shah R, et al. Multimodal therapy of epithelioid pleural mesothelioma: improved survival by changing the surgical treatment approach. Transl Lung Cancer Res 2022;11:2230-42.
22. Migliore M, Ried M, Molins L, et al. Hyperthermic intrathoracic chemotherapy (HITHOC) should be included in the guidelines for malignant pleural mesothelioma. Ann Transl Med 2021;9:960.
23. Nelson DB, Rice DC, Mitchell KG, et al. Defining the role of adjuvant radiotherapy for malignant pleural mesothelioma: a propensity-matched landmark analysis of the National Cancer Database. J Thorac Dis 2019;11:1269-78.
24. Verma V, Ahern CA, Berlind CG, et al. National Cancer Database Report on Pneumonectomy Versus Lung-Sparing Surgery for Malignant Pleural Mesothelioma. J Thorac Oncol 2017;12:1704-14.
25. Voigt SL, Raman V, Jawitz OK, et al. The Role of Neoadjuvant Chemotherapy in Patients With Resectable Malignant Pleural Mesothelioma-An Institutional and National Analysis. J Natl Cancer Inst 2020;112:1118-27.
26. Ming K, Rosenbaum PR. Substantial gains in bias reduction from matching with a variable number of controls. Biometrics 2000;56:118-24.
27. Ming K, Rosenbaum PR. A note on optimal matching with variable controls using the assignment algorithm. J Comput Graph Stat 2001;10:455-63.
28. Rubin DB. Using propensity scores to help design observational studies: application to the tobacco litigation. Health Serv Outcomes Res Methodol 2001;2:169-88.
29. Stuart EA. Matching methods for causal inference: A review and a look forward. Stat Sci 2010;25:1-21.
30. Abdelsattar ZM, Saddoughi SA, Blackmon SH. National Cancer Database Report on Pneumonectomy Versus Lung-Sparing Surgery for Malignant Pleural Mesothelioma. J Thorac Oncol 2018;13:e64-5.

Cite this article as: Elliott IA, He H, Lui NS, Liou DZ, Guenthart BA, Shrager JB, Berry MF, Backhus LM. Impact of hyperthermic intrathoracic chemotherapy (HITHOC) during resection of pleural mesothelioma on patient survival. J Thorac Dis 2023;15(11):6140-6150. doi: 10.21037/jtd-23-466

SUPPLEMENTAL FIGURE 1

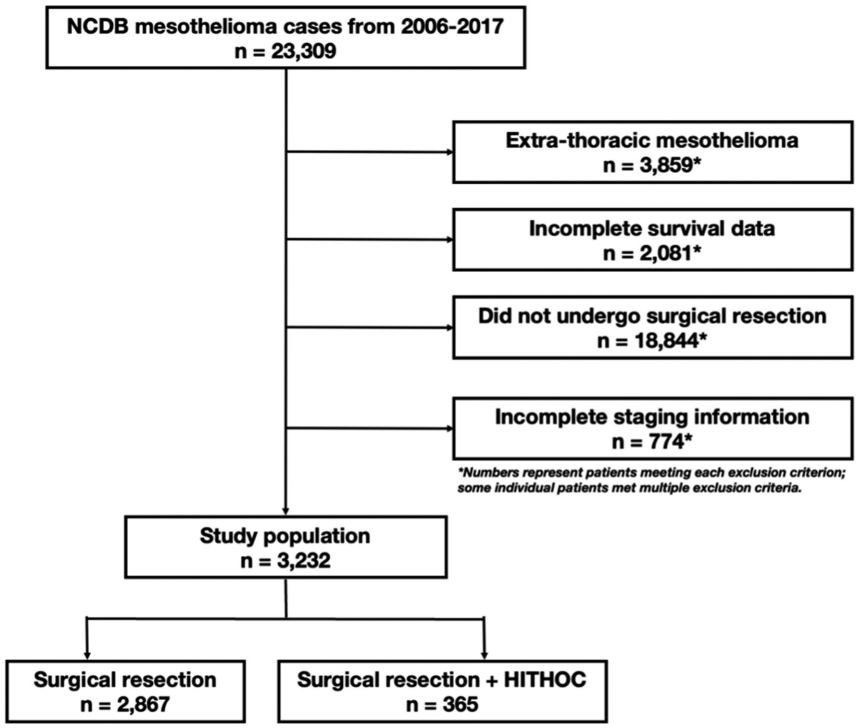

Figure S1 Diagram of selection of patients undergoing resection of PM. NCDB, National Cancer Database; HITHOC, hyperthermic intrathoracic chemotherapy; PM, pleural mesothelioma.

https://dx.doi.org/10.21037/jtd-23-466