Wong *et al. J Cancer Metastasis Treat* 2023;9:34
DOI: 10.20517/2394-4722.2023.57

Journal of Cancer Metastasis and Treatment

Original Article

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Does delaying surgery following induction chemotherapy compromise survival in patients with mesothelioma?

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How to cite this article: Wong LY, Baiu I, Leipzig M, Titan A, Liou DZ, Lui N, Berry M, Shrager JB, Backhus L. Does delaying surgery following induction chemotherapy compromise survival in patients with mesothelioma? *J Cancer Metastasis Treat* 2023;9:34. https://dx.doi.org/10.20517/2394-4722.2023.57

Received: 13 Jun 2023 **First Decision:** 21 Aug 2023 **Revised:** 21 Aug 2023 **Accepted:** 28 Aug 2023 **Published:** 15 Sep 2023

Academic Editor: Robert Arthur Kratzke **Copy Editor:** Fangling Lan **Production Editor:** Fangling Lan

Abstract

Objective: The ideal time interval between induction chemotherapy and surgery and the impact on cancer mortality in patients with mesothelioma remains unclear.

Methods: We queried the National Cancer Database (2004-2017) for patients with favorable prognostic factors considered for surgery. *Immediate surgery* was performed within 3 months following the start of induction chemotherapy, while *delayed surgery* was defined as surgery performed later than 3 months. We compared both groups to those who did not have an operation despite being surgical candidates, as well as to those who were treated with surgery only. Overall mortality was assessed using Cox proportional hazard models adjusting for covariates.

Results: A total of 4,294 patients were included, with the majority of patients undergoing induction chemotherapy followed by no surgery (3,370, 78%). The proportion of patients undergoing both immediate and delayed surgery increased over the last decade, but delayed surgery continued to be more common. There were no significant differences in baseline characteristics between the immediate and delayed surgery groups. Higher comorbidity scores were significantly associated with an increased risk of death on multivariable analysis, but the timing of

surgery was not. This held true with a sensitivity analysis using 6 months as the definition of delayed surgery.

Conclusions: This study shows that delaying surgery following induction chemotherapy does not compromise overall survival in patients with mesothelioma.

Keywords: Malignant pleural mesothelioma, mesothelioma surgery, mesothelioma treatment

INTRODUCTION

Mesothelioma is a rare disease associated with a history of asbestos exposure[1]. Unlike other thoracic malignancies, no single treatment has been shown to be superior, with overall survival ranging from 9-24 months, depending on the stage and histology. While multimodality approaches using a combination of chemotherapy, surgery and radiation are currently recommended, treatment guidelines remain controversial. The low prevalence of disease limits the ability to perform large randomized controlled trials to guide evidence-based therapy[2]. Furthermore, the heterogeneity of surgical approaches has made comparisons among different studies difficult.

The American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines recommend surgery for patients with epithelioid histology who are surgical candidates with stages I and II disease[3]. Similarly, the National Comprehensive Cancer Network (NCCN) recommends pemetrexed/cisplatin based-chemotherapy followed by surgical resection or vice versa for patients with stages I-IIIA, but with caution in patients with sarcomatoid, mixed histology or patients with N2 disease[4]. Certain factors such as early stage, age at operation under 60, epithelioid histology, absence of lymph node involvement, and receipt of induction chemotherapy have been associated with improved survival[5]. Prior research studies report the benefits of surgery in patients with epithelioid histology but poor outcomes associated with sarcomatoid or biphasic histologies. Similarly, patients with N0 disease have improved outcomes following surgery compared to those who are node-negative[6,7]. Despite this data, surgery in mesothelioma remains a topic of contentious debate due to the high morbidity and mortality associated with the choice of radical operative intervention[8]. The two most commonly employed surgical techniques are extrapleural pneumonectomy (EPP) and extended pleurectomy/decortication (P/D). Multiple studies have evaluated the advantages and disadvantages of each, and systematic reviews suggest modest superiority of P/D with lower perioperative morbidity and mortality, with similar or superior long-term survival and improved quality of life compared to EPP[9-12]. A multicenter retrospective analysis of 1,365 patients found similar survival among patients who received medical therapy only, P/D, or EPP; the modest benefit observed after surgery could not be elucidated from this study due to limitations in the available data[13]. More recently, several studies suggested that EPP might actually increase mortality[14,15]

Together, these data suggest that surgical intervention in patients with mesothelioma should be a carefully weighed decision that considers a multitude of factors. Delaying surgical intervention could be a means to mitigate risk if it allows for better patient selection and identification of favorable tumor biology. Allowing for more time between treatment modalities may provide more time for patients to recover from the toxicity of chemotherapy, address frailty, and potentially optimize nutrition prior to a major operation. Yet, the ideal timing of surgical resection following induction chemotherapy has not been explored in the literature. Given the potential for significant morbidity associated with either one of the definitive surgical interventions for mesothelioma, we sought to investigate whether a delay in surgical resection following induction chemotherapy would be feasible and not compromise survival outcomes.

MATERIAL AND METHODS

Administered by the American Cancer Society and the American College of Surgeons (ACS) Commission on Cancer (CoC), the National Cancer Database (NCDB) comprises data from over 1,500 cancer centers in the United States[16]. The NCDB uses the American Joint Committee on Cancer (AJCC) 7th edition TNM classifications for the years of study inclusion (2004-2017)[17].

We queried the NCDB for all diagnoses of mesothelioma during the thirteen-year period mentioned above and limited the data to patients with epithelioid histology and clinical stages I, II and III. We excluded patients with metastatic disease, unknown stage, or any missing datapoints [Figure 1]. We specifically analyzed only patients who were deemed to be surgical candidates for *definitive surgery* per the NCDB, which is defined as an operation targeted towards disease treatment. Similarly, *induction chemotherapy* refers to treatment intended to cure. Patients who received palliative surgery and/or palliative chemotherapy were excluded from the analysis. The NCDB includes start times for chemotherapy and surgery but does not provide end dates for these therapies. Thus, time intervals between treatments were based on available treatment start dates. We divided the study cohort of surgical candidates who met the above criteria into 4 groups: (1) patients who received induction chemotherapy followed by surgery within 3 months from the start of chemotherapy (*Immediate Surgery, IS*); (2) patients who received induction chemotherapy followed by surgery at a time interval that was longer than 3 months from the start of chemotherapy (*Delayed Surgery, DS*); (3) patients who received chemotherapy with the intent to treat as induction, but did not undergo a definitive operation (*No Surgery, NS*); and (4) patients who did not receive chemotherapy and were treated only with definitive surgery (*Surgery Only, SO*) [Supplementary Figure 1]. Logistic regression models were performed to determine mortality as a function of the timing of definitive surgery. A propensity-matched analysis was conducted to compare the IS and DS groups to assess 5-year overall survival using Kaplan-Meier curves. A secondary analysis using a 6-month delay, instead of 3-months as above, was performed to evaluate the effect on mortality with increased delay from the start of chemotherapy to surgery. Length of stay and 30-day readmission rates were analyzed as proxies for morbidity.

The primary outcomes were vital status and median survival, and the primary predictor variables were timing and receipt of surgery. Age, gender, race, Charlson Comorbidity Score, and cancer stage were independent variables. Categorical variables were reported as frequencies and proportions, and continuous variables were reported as medians and interquartile ranges (IQR). Either Chi-square or Fisher's exact statistical test was used to compare the association of timing of treatment and vital status with other categorical variables. For continuous variables, Kolmogorov-Smirnov test was performed to test the normality of the data. Kruskal-Wallis test was used to compare mean age and definitive surgical procedure from the day of diagnosis, time from diagnosis to treatment among different treatment modalities. Mann-Whitney test was applied to compare continuous variables with the vital status. Time-to-event analysis was performed using Kaplan-Meier method and the differences were tested using log-rank test. Independent predictors of death risk were estimated using Cox proportional hazard model. A probability value of < 0.05 was considered to be statistically significant. All statistical analyses were performed using SAS, Version 9.4 (SAS Institute INC), IBM SPSS Statistics, Version 25 & 26 (IBM).

RESULTS

During the 2004-2017 NCDB study period, 33,123 patients with mesothelioma were identified. The majority of patients were excluded on the basis of sarcomatoid histology, leaving 4,294 epithelioid mesothelioma cases with stage I, II or III and complete data points regarding treatment options as the final study cohort. The overall cohort had a median age of 71, with the majority being in the 50-80 year age group. The group

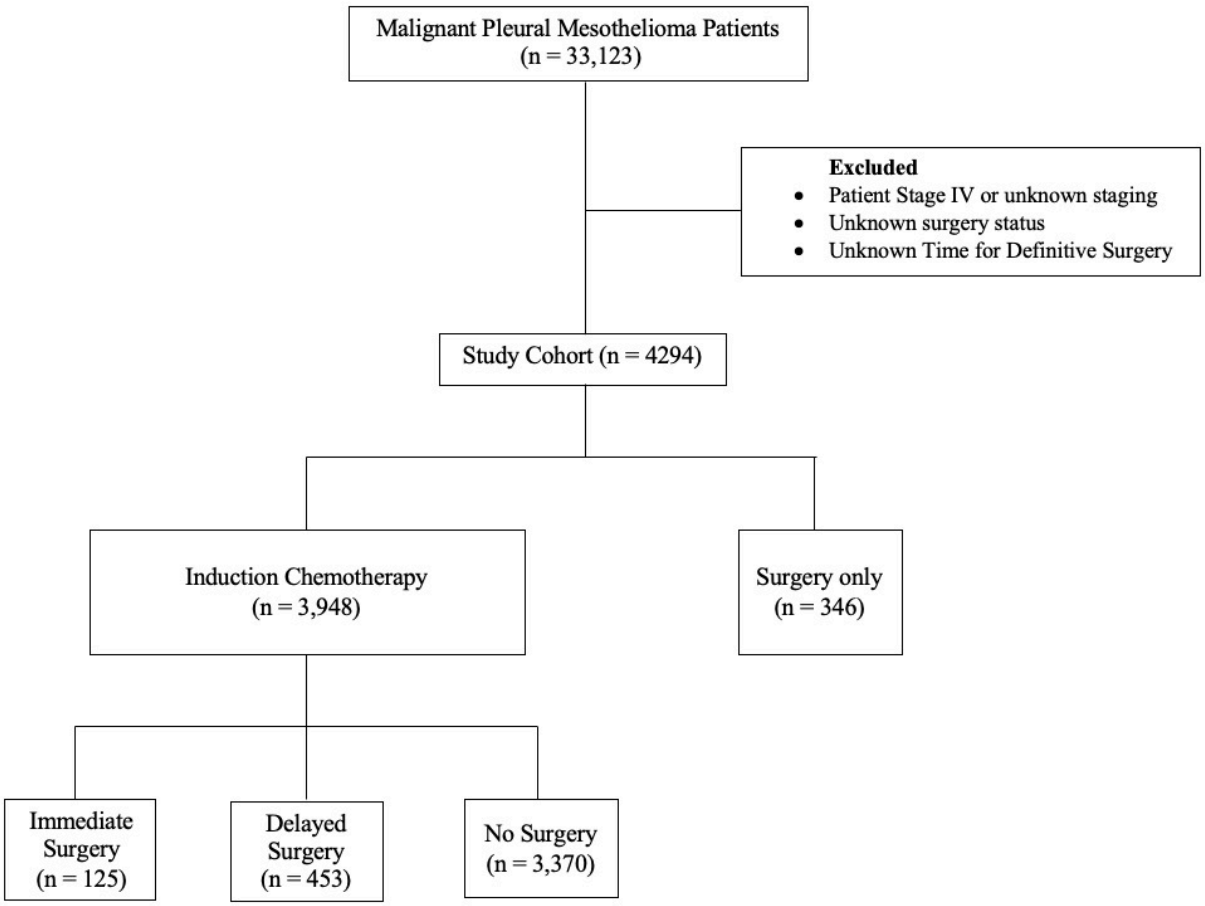

Figure 1. CONSORT diagram.

consisted of mostly white males with a Charlson comorbidity score of 0, with a relatively equal distribution of stage 1, 2, and 3 diseases [Table 1]. The median time from diagnosis to chemotherapy was 40 days and from diagnosis to definitive surgery was 123 days. Only 14% were alive at the end of the thirteen-year study period.

Of the 4,294 patients, the majority (3,948, 92%) received induction chemotherapy and the remaining 346 (8%) only had surgery as treatment without induction treatment. For patients who underwent induction chemotherapy, 125 (3%) had IS, 453 (11%) had DS, and 3,370 (85%) had NS [Table 1]. Over the study period, NS as a treatment option became less favorable, while IS, DS, and SO increased with time [Figure 2]. Of the 924 patients who underwent surgery, 408 (44.2%) patients received extrapleural pneumonectomy and 516 (55.8%) received pleurectomy and decortication. DS continued to be more common than IS for mesothelioma treatment. When comparing the IS and DS groups, patients seemed to be well matched on all baseline characteristics, including sex, race, comorbidity score, stage, vital status, and time from diagnosis to chemotherapy [Table 1]. On Cox proportional hazards modeling, only a higher comorbidity score was associated with worse outcomes [Table 2]. Specifically, the timing of surgery did not have a significant association with increased mortality. The 5-year survival function in Supplementary Figure 2 shows that both IS and DS have similar survival trajectories over time.

Table 1. Baseline demographics and disease characteristics

Characteristic	Overall *n* = 4,294	Immediate surgery *n* = 125[1]	Delayed surgery *n* = 453[1]	NO surgery *n* = 3,370[1]	Surgery only *n* = 346[1]	*P* value comparing IS *vs.* DS
Age	71 (64, 77)	67 (60, 71)	66 (59, 70)	73 (66, 78)	66 (57, 72)	0.4
Age category						0.6
< 50 years	157 (3.7%)	9 (7.2%)	28 (6.2%)	76 (2.3%)	44 (13%)	
50-80 years	3,552 (83%)	116 (93%)	420 (93%)	2,722 (81%)	294 (85%)	
> 80 years	585 (14%)	0 (0%)	5 (1.1%)	572 (17%)	8 (2.3%)	
Gender						0.7
Female	970 (23%)	32 (26%)	124 (27%)	709 (21%)	105 (30%)	
Male	3,324 (77%)	93 (74%)	329 (73%)	2,661 (79%)	241 (70%)	
Race						0.13
Black	182 (4.3%)	3 (2.4%)	18 (4.0%)	148 (4.4%)	13 (3.8%)	
Other	71 (1.7%)	0 (0%)	12 (2.7%)	55 (1.6%)	4 (1.2%)	
White	4,005 (94%)	120 (98%)	419 (93%)	3,141 (94%)	325 (95%)	
Unknown	36	2	4	26	4	
Charlson comorbidity score						0.4
0	3,094 (72%)	106 (85%)	354 (78%)	2,357 (70%)	277 (80%)	
1	850 (20%)	16 (13%)	82 (18%)	705 (21%)	47 (14%)	
2	250 (5.8%)	3 (2.4%)	13 (2.9%)	216 (6.4%)	18 (5.2%)	
3	100 (2.3%)	0 (0%)	4 (0.9%)	92 (2.7%)	4 (1.2%)	
Stage						0.6
1	1,400 (33%)	22 (18%)	89 (20%)	1,242 (37%)	47 (14%)	
2	849 (20%)	26 (21%)	77 (17%)	689 (20%)	57 (16%)	
3	2,045 (48%)	77 (62%)	287 (63%)	1,439 (43%)	242 (70%)	
Diagnosis						0.7
Cytology	243 (5.7%)	3 (2.4%)	8 (1.8%)	226 (6.7%)	6 (1.7%)	
Histology	4,051 (94%)	122 (98%)	445 (98%)	3,144 (93%)	340 (98%)	
Vital status	571 (14%)	22 (20%)	99 (25%)	351 (11%)	99 (33%)	0.3
Unknown	328	17	52	213	46	
Time from diagnosis to chemotherapy	40 (26, 61)	38 (22, 51)	39 (26, 55)	38 (25, 59)	58 (41, 79)	0.5
Time from diagnosis to definitive surgery	123 (68, 169)	108 (91, 122)	166 (141, 199)	NA (NA, NA)	58 (41, 79)	< 0.001

[1]Median (IQR); *n* (%).

Table 2. Adjusted cox proportional hazard model for risk of death for immediate *vs.* delayed surgery, with delayed surgery defined as > 3 months after start of chemotherapy

Characteristic	HR	95%CI	*P*-value
Age	1.00	0.98, 1.02	0.9
Gender			
Female	Ref	-	
Male	1.01	0.69, 1.49	> 0.9
Race			
Black	Ref	-	
Other	1.44	0.24, 8.73	0.7
White	1.17	0.37, 3.74	0.8
Comorbidity score	1.50	1.10, 2.05	0.011
Staging	1.00	0.79, 1.27	> 0.9
Timing of surgery			
Delayed surgery	Ref	-	
Immediate surgery	0.98	0.61, 1.59	> 0.9

HR: Hazard ratio; CI: confidence interval.

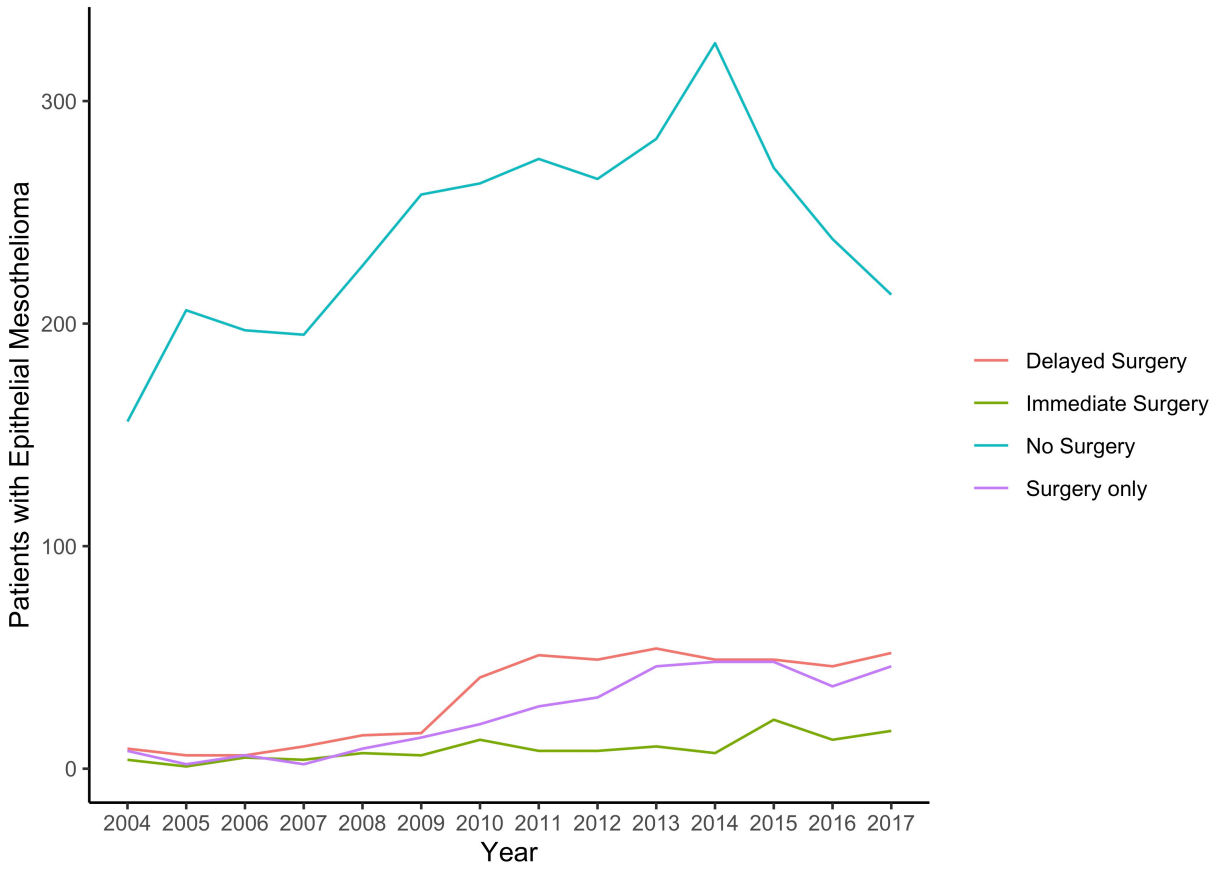

Figure 2. Trends in mesothelioma management during study duration.

A propensity-matched analysis was performed and showed that the IS and DS groups were well-matched based on age, sex, race, comorbidity score, clinical stage, and distance to treatment facility.

Supplementary Figure 3 shows the love plot of the matched groups and all variables listed were below the absolute standardized mean differences. A Kaplan-Meier curve was created to assess 5-year overall survival of the IS and DS matched groups, and there was no statistically significant difference between the two groups [Figure 3].

A sensitivity analysis was performed using 6 months as the marker to define DS to test our initial results. On preoperative characteristics, the DS group was more likely to be non-white, but otherwise, the groups were not significantly different [Table 3]. On Cox modeling, a higher comorbidity score was again associated with an increased risk of death, but the timing of surgery was not [Supplementary Table 1]. We also performed a multivariable model using continuous time as the variable, instead of a chosen length of time between diagnosis and surgery, which reflected our prior analyses [Supplementary Table 2]. Increasing the number of days from diagnosis to surgery had a HR of 1 (95%CI 1-1, $P = 0.5$), demonstrating the timing of surgery does not impact survival.

DISCUSSION

This study sought to determine whether definitive surgical intervention can be safely delayed following induction chemotherapy in patients with mesothelioma without compromising overall survival. Over the study period, there was a trend towards performing less surgery in patients with mesothelioma, which correlates with results from the MARS trial showing a HR of 2.75 for extrapleural pneumonectomy patients versus non-surgical mesothelioma patients[14]. On the other hand, various other retrospective and prospective studies have suggested that surgery is associated with a survival advantage, indicating that selection bias likely plays a significant role in contextualizing currently available evidence[18,19]. One motivation for our study was the recognition that there are few studies investigating the clinical outcomes associated with a watchful waiting strategy and the implications of delaying surgery. We intentionally identified a cohort of clinical stage I-III mesothelioma patients with epithelioid histology to exclude known factors that have been shown to negate the potential benefit from surgery. Given the morbidity and mortality associated with current surgical options, the ability to push back an operation following medical treatment without compromising outcomes could potentially provide a beneficial time window for patients to recover from the side effects of chemotherapy and be optimized prior to a radical operation.

The survival benefit between adjuvant and neoadjuvant chemotherapy in patients with mesothelioma is clinically insignificant[20]. However, literature in non-small-cell lung carcinoma has repeatedly found that although there may be no significant disease-free survival benefit between the timing of chemotherapy, more patients are reported to complete the full course of chemotherapy if given in the neoadjuvant than the adjuvant setting, and that over 90% of patients receiving chemotherapy as induction are able to continue to surgical resection as planned[21-23]. Assessment of frailty is a growing area of interest in surgery as a means to predict surgical outcomes and select patients who might benefit from pre-surgical optimization. Among patients with thoracic malignancies, 69% of surgical candidates are deemed to be frail or prefrail on frailty assessment scores[24]. Although studies on frailty in patients with mesothelioma are lacking, frailty has been associated with increased mortality and morbidity in patients undergoing major operative procedures[25-27]. Extrapolating from these findings to patients with mesothelioma, we infer that, with an intention to treat, completing neoadjuvant chemotherapy is important, and that allowing for adequate time prior to undergoing a major surgical intervention may allow patients to recover from post-chemotherapy toxicities and improve frailty scores towards improving their surgical outcomes. Our results show that in a contemporary cohort, the majority of patients are offered induction chemotherapy rather than upfront surgery alone. This signals that surgeons treating mesothelioma are already aware of the importance of neoadjuvant treatment and are currently prioritizing this oncologic principle. A current trial in Europe

Table 3. Patient characteristics and outcomes with delayed surgery defined as 6 months post-induction therapy

Characteristic	Delayed surgery *n* = 55[1]	Immediate surgery *n* = 523[1]	*P*-value[2]
Age	65 (57, 70)	66 (59, 70)	0.4
Age category			0.3
< 50 years	6 (11%)	31 (5.9%)	
50-80 years	49 (89%)	487 (93%)	
> 80 years	0 (0%)	5 (1.0%)	
Gender			0.8
Female	14 (25%)	142 (27%)	
Male	41 (75%)	381 (73%)	
Race			0.023
Black	3 (5.5%)	18 (3.5%)	
Other	4 (7.3%)	8 (1.5%)	
White	48 (87%)	491 (95%)	
Unknown	0	6	
Charlson comorbidity score			0.2
0	40 (73%)	420 (80%)	
1	11 (20%)	87 (17%)	
2	3 (5.5%)	13 (2.5%)	
3	1 (1.8%)	3 (0.6%)	
Stage			0.4
1	8 (15%)	103 (20%)	
2	8 (15%)	95 (18%)	
3	39 (71%)	325 (62%)	
Diagnosis			> 0.9
Cytology	1 (1.8%)	10 (1.9%)	
Histology	54 (98%)	513 (98%)	
Time from diagnosis to chemotherapy	32 (21, 52)	39 (26, 55)	0.10
Time from diagnosis to definitive surgery	239 (224, 294)	148 (122, 178)	< 0.001

[1]Median (IQR); *n* (%); [2]Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test.

(NCT02436733) is testing this theory by randomizing a cohort of patients with early-stage mesothelioma into two groups: pleurectomy and decortication before and after three cycles of chemotherapy[28]. The results of this phase II trial will shed further light on the importance of treatment timing.

Delaying surgery to improve physiologic function following induction therapy can also have unintended consequences of compromising cancer outcomes. Yet, we found no significant differences in survival associated with receipt of delayed surgery beyond 3 months following chemotherapy. This suggests that waiting longer than 3 months and up to 6 months from the time of diagnosis to complete induction chemotherapy may not increase cancer mortality. One plausible explanation for this could be that patients are allowed to recover from the toxicity of chemotherapy, have their frailty addressed, and have other medical problems resolved prior to engaging in a morbid operation. Another possible explanation is that delays simply allow for better patient selection in terms of tumor biology that extends beyond physiologic recovery after chemotherapy. The latter is difficult to determine definitively. We further sought to determine the ideal window for surgical intervention by examining the upper limit of surgical delay. Nevertheless, even using an extended 6-month cutoff in our sensitivity analysis did not change outcomes on

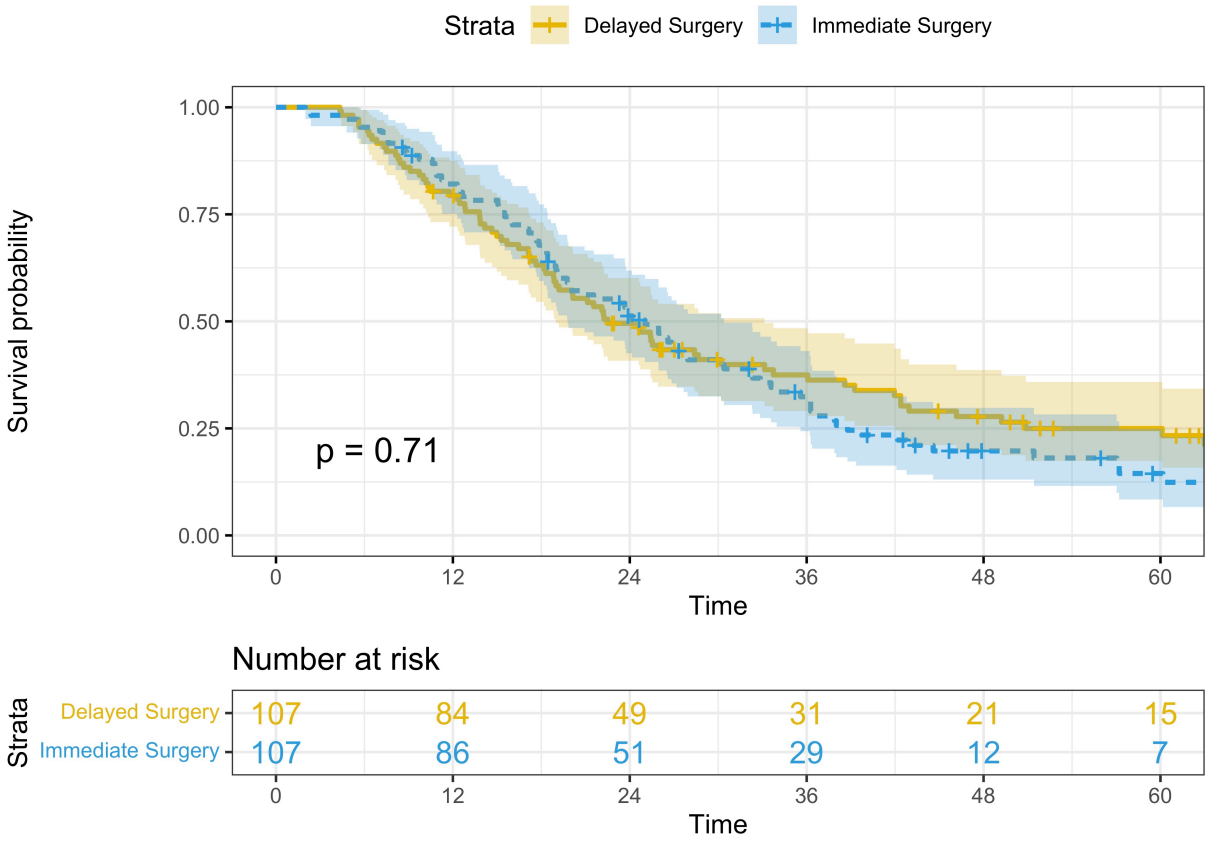

Figure 3. Kaplan Meier curve showing 5-year Overall Survival between the matched IS and DS groups.

univariate and multivariable analysis. This suggests that patients may self-select as surgical candidates early in their disease process based on their response to induction therapy and their ability to stay disease-free in the initial post-induction therapy period. The use of continuous days as a marker of increased risk of death from diagnosis to surgery further proved our results that timing may not be the most important contributor towards long-term outcomes of mesothelioma. Although the study was not powered to show a statistically significant benefit of surgery, it does suggest that the combination of induction chemotherapy and complete resection is beneficial as the primary treatment for mesothelioma.

There are several limitations to this study. First, the NCDB data provides only the start dates of treatments and not the end dates, so certain assumptions were necessarily implied about the duration of chemotherapy and the interval between completion of treatment and surgical intervention. We are not able to infer from the dataset whether a patient underwent one or six cycles of chemotherapy, just as we are not able to identify disease progression or nuances of restaging following chemotherapy. Secondly, the data is lacking in granularity regarding certain aspects of the treatment plan; for example, the multiple and specific reasons behind the decision not to pursue surgery cannot be ascertained beyond knowing that a subset of patients refused an operation. Additionally, the data does not allow us to identify specific chemotherapeutic treatments and associated toxicities or, more importantly, which of the common surgical techniques were used, thus limiting our ability to fully analyze patients on an intention-to-treat basis. Furthermore, the NCDB does not provide details regarding complications from chemotherapy, interruptions in treatment due to increased frailty or deconditioning, variability in quality of life during treatment progression, or speed or extent of disease progression once treatment is initiated. Along the same lines, it is not possible to

ascertain whether the chemotherapy given was intended to be given as induction therapy versus definitive chemotherapy treatment. Mesothelioma is a rare disease, and in order to minimize confounders, we chose to only include patients with favorable prognostic factors, and this significantly limited the number of patients in the study. Lastly, the time period analyzed was wide, which, on one hand, provides us with historical context for the treatment of mesothelioma, but also may not take into consideration recent improvements made in mesothelioma treatment protocols. The current study focuses on the timing of surgery in relation to neoadjuvant chemotherapy, and future studies are warranted to investigate modern advancements such as the role and timing of immunotherapy associated with operative intervention. We surmise that trials such as Checkmate 743 showing the promise of nivolumab and ipilimumab for late-stage mesothelioma will pave the way for further trials on resectable disease and not only expand immunotherapy use to earlier-stage mesothelioma, but also to traditionally worse histologies such as sarcomatoid disease[29].

CONCLUSIONS

The current study suggests that delaying surgery following induction chemotherapy is not inferior to immediate surgery in select patients and could even offer a potential survival benefit for those requiring more time to recover following their induction treatment. In alignment with the 2022 ESMO clinical practice guidelines, we highlight that intentional patient selection and a multidisciplinary approach are key to optimizing the benefit obtained from surgical treatment[1]. In addition, given the noteworthy morbidity of currently available surgical options, the decision to proceed to surgery should not be rushed despite the grim prognosis of mesothelioma. With newer research showing that pleurectomy and decortication may be the only remaining radical operation that significantly improves survival, results from the ongoing MARS2 trial will more definitively answer the question we posed in our study[30]. From the physician's perspective, understanding the complexities of surgical treatment for mesothelioma and the nuances of various active trials will aid preoperative decision making and improve patient confidence in enrolling into future trials[31]. Additional research should also continue to focus on systemic agents and the timing, the patient's condition and disease progression prior to initiation of a specific surgical intervention in order to determine the optimal timing in light of the complexity of disease evolution.

DECLARATIONS

Authors' contributions

Formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; roles/writing - original draft; writing - review & editing: Wong LY

Conceptualization; data curation; formal analysis; methodology; project administration; resources; software; supervision; validation; visualization; roles/writing - original draft: Baiu I

Data curation; formal analysis; software; supervision; validation; visualization; roles/writing - original draft; writing - review & editing: Leipzig M

Investigation; visualization; roles/writing - original draft: Titan A

Project administration; resources; software; supervision: Liou DZ

Funding acquisition; investigation; methodology; software; supervision: Lui N

Resources; software; supervision; writing - review & editing: Berry M

Resources; visualization; writing - review & editing: Shrager JB

Conceptualization; data curation; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing - review & editing: Backhus L

Availability of data and materials
Data is available upon request.

Financial support and sponsorship
None.

Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Institutional review board.

Consent for publication
Consent for publication provided.

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