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Long term survival and perioperative propensity score matched outcomes in diaphragmatic interventions in cytoreductive surgery + intra-peritoneal chemotherapy

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ABSTRACT

Objectives: To assess the impact of short and long term outcomes of diaphragmatic interventions in cyto-reductive surgery (CRS) and intra-peritoneal chemotherapy (IPC).
Methods: 1230 consecutive CRS/IPC procedures were preformed between 1996 and 2018 in Sydney, Australia. Redo procedures and incomplete cyto-reductions were excluded. Among these, 599 underwent diaphragmatic intervention. Preoperative heterogeneity was assessed for in 6 parameters and addressed with propensity score matching. CRS/IPC requiring diaphragmatic interventions were compared to CRS/IPC without diaphragmatic involvement. Ten perioperative outcomes were measured. Overall survival was assessed based on diagnosis type.
Results: Intraoperative results revealed a significant increase in operative hours (7.85 vs. 7.28, $p = 0.033$). Transfusion requirements were insignificantly different. Postoperatively, increased grade III and IV complications (36% vs. 26%, $p = 0.052$) were noted. There was no difference with regards to intensive care stay, hospital length of stay, hospital death and return to theatre. In terms of respiratory specific complications, an increased incidence of pneumothorax (13% vs. 3%, $p = 0.001$) and pleural effusions (24% vs. 16%, $p = 0.043$) were noted, whilst the differences in pneumonia were insignificant. Overall survival revealed diaphragm interventions; did not affect survival outcomes in colorectal cancers ($p = 0.750$, RR = 1.077, CI 0.683–1.697) and increased relative risk in low-grade appendiceal mucinous neoplasms ($p = 0.025$, RR = 2.437, CI 1.121–5.298).
Conclusion: After our three-tiered research strategy, we conclude that despite the marginal increase in short term morbidity; diaphragmatic interventions do not decrease survival in colorectal cancers and diaphragmatic disease in LAMNs maybe an independent prognosticator of disease aggression.

Introduction

Select patients with peritoneal carcinomatosis are treated with cyto-reductive surgery and intra-peritoneal chemotherapy (CRS/IPC) to increase longevity. Its efficacy is proven in low grade appendiceal mucinous neoplasms (LAMNs) [1], high grade appendiceal mucinous neoplasms (HAMNs) [1], peritoneal mesothelioma [2], ovarian cancer [3], colorectal cancer [4,5] and other rare etiologies.

The goal of cyto-reduction is to remove all macroscopic disease. It is often complex and involves multiple abdominal regions. The administration of intra-peritoneal heated chemotherapy targets residual microscopic disease. Subsequently, the combination of a technically challenging procedure with the cytotoxicity of chemotherapy [6] results in a high rate of perioperative mortality (0.37%–4.1%) and morbidity (10%–33%) [7,8].

Diaphragmatic intervention is needed in 50% of CRS/IPC procedures [9]. Retrospective single institution studies have

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demonstrated morbidity attributable to diaphragmatic interventions. This includes longer surgical times, resections and increased complication rates [9,10].

The aim of this study is to evaluate the impact of diaphragm intervention in CRS/IPC. We assess this by establishing whether the increased short-term morbidity is applicable in our population. Furthermore, by assessing overall survival we establish whether the short-term morbidity is acceptable.

Methods

This is a retrospective cohort study conducted in a single high volume center, St George Hospital, Sydney from a prospectively maintained database. Ethics approval was obtained form the local research and development committee. A database dated from September 1996 to March 2018, of all CRS/IPC for peritoneal-based malignancies, was searched. A multi-disciplinary team determines suitability for CRS/IPC. Suitability is assessed based on disease histology, extent, and ability to achieve complete cytoreduction, performance status and comorbidities. Subsequent CRS/IPC was preformed utilizing the Sugarbaker technique [11].

The extent of peritoneal disease was documented via the peritoneal carcinomatosis index (PCI) described by Jacquet and Sugarbaker [12]. Completeness of cytoreduction (CC) was recorded in a similar manner [12]. Post-operative complications were graded according to the Clavien-Dindo classification [13]. Prior surgical score was documented as described by Jacquet et al. [12]. There have been several modifications of nomenclature and pathological analysis for pseudomyxoma. We adhere to the most recent classification by Carr and colleagues [14].

Exclusion criteria

The database consisted of a total of 1230 patients. Patients that underwent redo surgery and incomplete cyto-reduction were excluded. A total of 952 patients were identified and of those 599 had diaphragmatic interventions. Demographic data, intra-operative details and postoperative complications were extracted from the database.

Surgical technique

For this case series, diaphragm interventions included patients undergoing both diaphragmatic stripping and muscle resection. Our unit routinely preforms complete diaphragmatic peritonectomy and very rarely preformed localized peritonectomy. However, if muscle involvement is present, local resection and repair is preformed primarily or with a mesh. Pleural drains are routinely inserted in all patients undergoing diaphragmatic interventions. Any extra-abdominal invasion, including tumor invading the pleural space was considered a contraindication to surgery.

Statistical analyses

Statistical analyses were preformed using R 3.1.0 and SPSS version 23: IBM corporation, New York). Univariate analysis was utilized to identify heterogeneity with regards to 6 preoperative variables; including ASA, sex, diagnosis, PSS, age and PCI. Any significant heterogeneity was adjusted for with propensity score analysis utilizing the matchit package on R. Independent samples T-Test was utilized for continuous variables and expressed as mean and SD. Categorical variables were assessed using the chi-squared test and expressed as frequencies and proportions. Where the chi-squared analysis was violated, fishers exact test was utilized.

Overall survival was estimated using the non-matched data sets from the date of CRS/IPC to the date of death or last follow-up. The log-rank test compared survival between groups on Kaplan-Meier method analysis. Cox regression was preformed and accounted for the following co-variates: ASA, PSS, PCI and HIPEC. Assumptions were tested with covariates as a function of time and graphically via log minus log plots and scatter plots.

Results

Patient characteristics

After redo and incomplete cyto-reductions had been excluded, a total of 952 patients underwent CRS/IPC. In this cohort 599 patients (63%) underwent diaphragmatic interventions. The mean age was 54 ± 13. There were 411 (43.2%) male individuals. The mean PCI was 17 ± 11. The histology of the primary tumor was colorectal 314 (33%), HAMNs 209 (22%), peritoneal mesothelioma 72 (8%), LAMNs 233 (25%), other 78 (8%), ovarian 46 (5%).

Diaphragm interventions

Of the 599 patients that underwent diaphragmatic CRS, 512 patients had diaphragmatic stripping, 72 had resection and 15 underwent localized diaphragmatic stripping.

Pre-operative heterogeneity

A summary of preoperative characteristics between the groups is provided in Table 1. Significant differences in diagnosis, PSS and PCI were noted. HAMNs (30% vs. 8%), peritoneal mesothelioma (9% vs. 5%), LAMNs (30% vs 16%) and ovarian (7% vs. 1%) cancers underwent diaphragm intervention more often then not. Conversely, colorectal (19% vs. 57%) and others (5% vs. 14%, $p < 0.001$) underwent more non-diaphragmatic CRS/IPC. Additionally, the diaphragmatic group had significantly more patients with PSS 0 (33% vs. 17%) and less with PSS 1 (32% vs. 49%). Tumor burden was considerably higher in diaphragm interventions. The data was matched for diagnosis, PSS and PCI and yielded 180 patients in each group.

Perioperative outcomes

Table 2 summarizes the perioperative outcomes between the groups with the propensity-matched data. Intraoperative results illustrated a significantly increased operative time and non-significant red blood cell transfusion requirements. Post-operatively there were increased grade III and IV complications (36% vs. 26%). No difference was noted in intensive care stay, length of stay, hospital death and return to theatre. In terms of respiratory specific complications, an increased incidence of pneumothorax (13% vs. 3%) and pleural effusions (24% vs. 16%) were noted, whilst the differences in pneumonia were insignificant.

Overall survival (OS) results

The median length of follow-up of all patients was 25 months. At the time of the study 377 (40%) patients had died from disease.

A total of 314 patients underwent CRS/IPC for Colorectal cancer; 114 underwent diaphragm intervention. At the time of the study 153 patients had died from disease. Overall survival was significantly decreased in diaphragm interventions on Kaplan Meir (43 vs. 27 months median survival $p = 0.001$). However, the trend was not supported on cox regression ($p = 0.750$, RR = 1.077, CI 0.683–1.697, Fig. 1).

Table 1
Preoperative characteristics; diaphragm vs no diaphragm.

Co-variate		Diaphragm	No diaphragm	P value
		599	353	
ASA				0.74
	1	27	9	
	2	151	111	
	3	316	171	
	4	45	21	
Sex				0.645
	M	262	149	
	F	337	204	
Diagnosis				<0.001*
	Colorectal	114	200	
	HAMNs	181	28	
	Peritoneal Mesothelioma	55	17	
	LAMNs	178	55	
	Others	30	48	
	Ovarian	41	5	
PSS				<0.001*
	0	197	61	
	1	192	172	
	2	193	109	
	3	11	7	
Age	Mean SD	53.09 13.39	54.84 13.02	0.052
PCI	Mean SD	22.67 10.34	8.16 6.28	<0.000*

ASA; American society of anesthesiologists, HAMNs; high-grade appendiceal neoplasms, LAMNs; low-grade appendiceal neoplasms, PSS; prior surgical score, PCI; peritoneal cancer index.

Table 2
Diaphragm vs no diaphragm.

Co-variable	Unit	Diaphragm	No diaphragm	P value
PPM	Count	180	180	
Operative hours	Mean	7.85	7.28	**0.033***
	SD	2.447	2.564	
RBC	Mean	4.09	3.79	0.628
	SD	5.815	5.716	
ICU days	Mean	3.33	2.84	0.288
	SD	4.93	3.50	
Length of stay	Mean	25.42	21.96	0.175
	SD	26.134	21.87	
Pneumonia	Count	10	7	0.448
Pleural effusion	Count	44	29	**0.043***
Pneumothorax	Count	23	6	**0.001***
Return to OT	Count	25	19	0.315
Hospital Death	Count	1	2	1.000
Morbidity grade III. IV	Count	64	47	**0.052***

PPM; propensity matched, RBC; red blood cells, CC; completeness of cytoreduction, OT; operating theatre, ICU; intensive care unit.

A total of 233 patients with LAMNs underwent CRS/IPC, 178 patients underwent diaphragm intervention. Overall survival was significantly effected on Kaplan Meir (63 vs. 102 months median survival $p = 0.027$). Similarly, on cox regression, diaphragm interventions significantly effected survival ($p = 0.025$, RR = 2.437, CI 1.121–5.298, Fig. 2).

The event rates were too low to calculate survival outcomes for other diagnosis including HAMNs, mesothelioma, ovarian cancer, gastric cancer and others.

Discussion and conclusions

Diaphragmatic interventions are performed in nearly 50% of all CRS/IPC patients. There is a pervading opinion that diaphragmatic instrumentation is an independent predictor of morbidity, ICU stay and respiratory complications. With such a large cohort undergoing diaphragmatic CRS/IPC these results need to be examined and validated.

In the literature, the studies of diaphragmatic interventions are limited. There are two series that warrant discussion. The first is by Franssen [9] and colleagues who analyze the short-term perioperative morbidity of diaphragmatic interventions. Their approach is similar to our study. Univariate analysis was conducted for baseline characteristics. Significant disparity was discovered with the incidence of pseudomyxoma, number of organs operated on, PCI, estimated blood loss and length of surgery. Their matching strategy was not transparent. If all the disparate variables were matched, their data would be un-applicable to other populations.

Despite the limitations, Franssen and colleagues discovered that intra-operatively diaphragm interventions were associated with significantly increased PRBC. They comment on a mean increase in CC score, which is difficult to interpret, as CC score is not a continuous variable and should be treated as either an ordinal or nominal variable. Postoperatively, a significantly increased 30-day complication rate, ICU-stay and length of stay were observed. Their patient counts were too few to perform a histological based survival analysis.

The second study that merits citation is by Muallem and colleagues [10]. Their study is a retrospective case series limited to ovarian pathology. The authors note increased disease aggression in the diaphragmatic intervention cohort. No matched controls in terms of disease aggression and baseline comorbid state were provided. Significant postoperative complications, infections and pleural effusions were observed. Importantly, they preformed Kaplan Meier curves for diaphragmatic interventions. Encouragingly, median overall survival was insignificantly variable between the diaphragm intervention and non-intervention groups, specifically in ovarian cancer. This implies a complete cytoreduction, even in more aggressive disease confers a survival advantage.

After understanding the literature, our series attempts to build on the existing analysis by providing more rigorous analytical methodology to re-affirm or reject current paradigms. This is approached by a three-tiered strategy. Firstly, univariate analysis was conducted to quantify preoperative heterogeneity, which built the basis of our propensity scoring method. Secondly, the matched data set was then utilized to measure intraoperative, postoperative

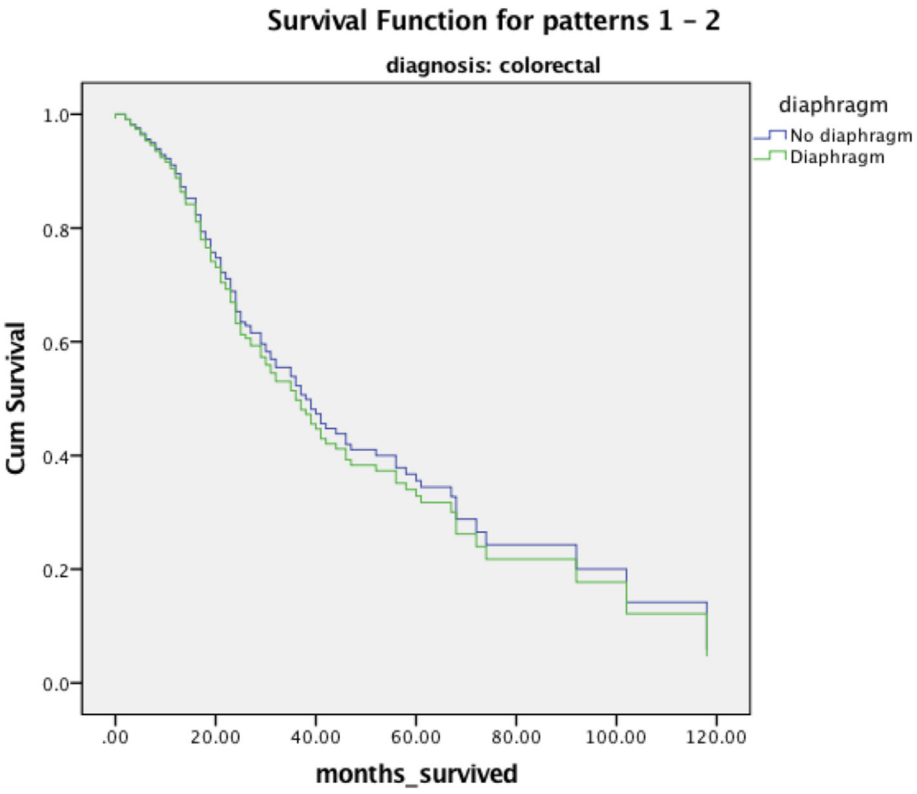

Fig. 1. Cox regression survival curve for diaphragmatic interventions in CRS/IPC for colorectal cancer.

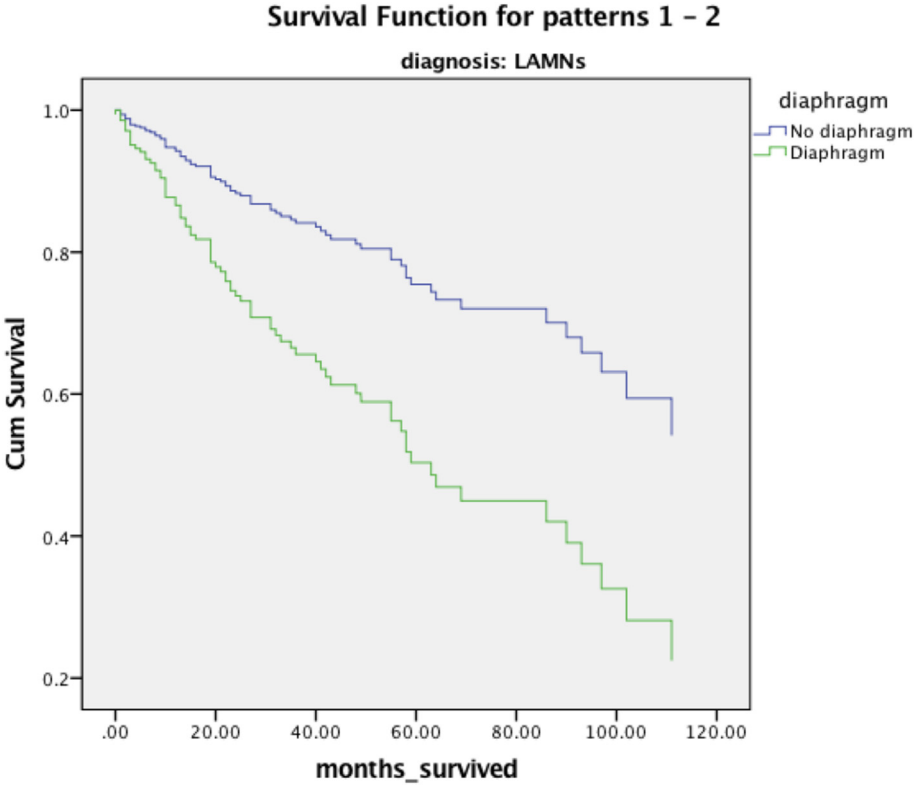

Fig. 2. Cox regression survival curve for diaphragmatic interventions in CRS/IPC for LAMNs.

and respiratory outcomes. Thirdly, an overall survival analysis based on tumor type was conducted. In essence, by comparing the long-term survival we can evaluate weather the short-term perioperative morbidity justifies the interventions.

The preoperative markers that determined heterogeneity between the diaphragm and non-diaphragm groups were carefully considered. These included ASA, sex, diagnosis, PSS, Age and PCI. Other categories such as intraoperative time and number of organs were intentionally not included because it was felt that they would be derivatives of the categories above. This would make the data of our study too specific and run the risk of not being applicable to other study populations.

Interestingly, in our analysis significant heterogeneity was found in diagnosis, PSS and PCI. Certain histological subtypes were more likely to undergo diaphragmatic CRS/IPC: HAMNs, peritoneal mesothelioma, LAMNs and ovarian cancers. Additionally, the diaphragmatic group had significantly more patients with PSS 0. Tumor burden was considerably higher in cytoreductive surgery requiring diaphragm intervention. These three variables were utilized as co-variates to formulate our propensity matched data sets.

Univariate analysis was then conducted on the matched data. Similar to Franssen and colleagues, our results revealed increased grade III and IV morbidity. Additionally, despite the routine use of pleural drains higher incidences of pleural effusions and pneumothorax were observed. This is likely a result from early pleural drain removal or complications whilst inserting or removing drains.

Lastly, survival analysis was preformed on an unmatched data, to have the requisite number of events. The survival curves and hazard ratio for each tumor type was examined. The differences on Kaplan Meier need to be cautiously interpreted, as they do not control for disease aggression, comorbid state and intraoperative management. To address this issue, a cox regression model with ASA, PSS, PCI and HIPEC as covariates was developed.

The cox regression model for colorectal cancer illustrated no difference in the overall survival between diaphragmatic CRS and non-diaphragmatic CRS. In fact the survival curves almost lay superimposed.

The cox regression model for LAMNs revealed an increased mortality for diaphragmatic CRS. The reason for this disparity can be explained by the fact that an adequate control group is not available. Patients with non-diaphragmatic disease have limited disease and this is reflected in their lower PCI. In contrast patients with unresectable diaphragm disease have higher disease aggression. These groups are clinically and prognostically different from the setting of resectable diaphragmatic disease. Our cox regression model attempts to rectify this by utilizing PCI as a covariate. However, diaphragmatic disease could be an independent marker of disease aggression and thus our model covariates maybe an inadequate surrogate as a control group. The most appropriate way to assess survival would be to compare survival in patients with resectable disease and refused treatment to those that have resectable disease and undergone complete cytoreduction.

Our study has several limitations. It is a retrospective, observational study with limitations inherent to this design. Firstly, unidentified confounding factors could influence results. Secondly, our data did not contain extubation times, which would be an important end-point to measure in terms of respiratory failure related to diaphragmatic instrumentation. Thirdly, our sample size may be too low to detect complications, which have low event rates. Fourthly, subtypes of diaphragmatic interventions were not compared. Lastly, this is a single institution study and the results may not be applicable to all institutions.

After our three-tiered research strategy, we conclude that despite the marginal increase in short term morbidity; diaphragmatic interventions do not decrease survival in colorectal cancers and diaphragmatic disease in LAMNs maybe an independent prognosticator of disease aggression.

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