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Short- and Long-Term Outcomes of Patients Requiring Gastrectomy During Cytoreductive Surgery and Intraperitoneal Chemotherapy for Lower-Gastrointestinal Malignancies: A Propensity Score-Matched Analysis

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ABSTRACT

Objectives. This study was designed to assess the short- and long-term outcomes of gastric resection in cytoreductive surgery (CRS) and intraperitoneal chemotherapy (IPC) for lower gastrointestinal (GI) malignancies.

Methods. Patients with adenocarcinoma and appendiceal mucinous neoplasms were included. Redo and incomplete cytoreductions were excluded. A total of 756 patients were identified. Of these, 65 underwent gastric resection, 11 underwent wedge, 43 distal, and 11 subtotal and total gastrectomy. Preoperative differences were assessed for and addressed with matching. Perioperative outcomes, overall survival (OS), and risk-free survival (RFS) were assessed in two analyses: first all gastric resections were included and the second excluded wedge resections. Subgroup analysis according to diagnosis subtype was conducted.

Results. Demographic analysis revealed that markers of tumor aggression and poor nutrition were prevalent in the gastrectomy group. The matched analysis for gastric resections revealed higher rates of reoperation (38% vs. 22%, $p = 0.028$). After excluding wedge resections, increased rates of reoperation (40% vs. 22%, 0.019), grade 3/4 morbidity (76% vs. 59%, $p = 0.036$), and hospital stay (34 vs. 27 days, $p = 0.012$) were observed. For the unmatched cohort, OS (103 vs. 69 months, $p = 0.501$) and RFS (17 vs. 18 months, $p = 0.181$) for patients with CC = 0 were insignificantly different. In comparison for CC > 0, OS (31 vs. 83 months, $p < 0.001$) and RFS (9 vs. 20 months, $p < 0.001$) were significantly reduced in gastric resection. For the matched cohort, after excluding wedges, gastrectomy did not significantly decrease OS. However, RFS was decreased (11 vs. 20 months, $p = 0.016$).

Conclusions. Despite high postoperative morbidity, when complete cytoreduction is achieved, the need for gastric resection is not associated with inferior long-term outcomes.

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Select patients with peritoneal carcinomatosis are treated with cytoreductive surgery (CRS) and intraperitoneal chemotherapy (IPC) to increase longevity. Its efficacy has been shown in low-grade appendiceal mucinous neoplasms

(LAMNs), high-grade appendiceal mucinous neoplasms (HAMNs), peritoneal mesothelioma, ovarian cancer, adenocarcinoma, and other etiologies.[1–6]

The goal of CRS is to remove all macroscopic disease. The presence of residual disease is the most detrimental prognosticator.[1,5,7] Surgery is complex and involves resection of multiple abdominal organs and corresponding peritonectomy. Microscopic disease is targeted with heated intraperitoneal chemotherapy. The combination of a challenging procedure with the cytotoxicity of chemotherapy results in high morbidity (10–33%) and mortality (0.37–4.1%).[8–10]

Gastrectomy is required in 5–12% of CRS/IPC to achieve complete cytoreduction.[11] Studies have demonstrated significant morbidity and diminished survival.[11–14] These differences have been consistently reported and led to questioning of the role of gastrectomy during CRS. The reported morbidity needs to be interpreted with adequate clinical context. Patients requiring gastric resection have extensive disease burden and poor nutrition. Therefore, it is uncertain whether the poorer outcomes during CRS relate to gastric resection or serve as a surrogate for aggressive disease. The purpose of this study was to evaluate the impact of gastric resections on short- and long-term outcomes in a matched cohort of patients undergoing CRS/IPC.

METHODS

Treatment Setting and Patient Selection

A retrospective study from a single center—St George Hospital, Sydney, Australia—was performed. Formal ethics approval was obtained. The St George peritoneal surface malignancy database contains all procedures performed from 1996 to 2018. A multidisciplinary team determines suitability for CRS/IPC as previously described.[15]

Exclusion Criteria

During the study period, 1230 patients had undergone CRS. Patients who underwent redo surgery, incomplete cytoreduction (any completeness of cytoreduction score > 1), and had diagnoses other than adenocarcinoma, HAMNs, and LAMNs were excluded.[16] Demographic data, intraoperative details, and postoperative complications were extracted.

Cytoreductive Surgery and Intraperitoneal Chemotherapy

Cytoreductive surgery and intraperitoneal chemotherapy was performed via the Sugarbaker technique.[17] Peritoneal disease was graded utilising the peritoneal cancer index (PCI), as described by Jacquet and Sugarbaker.[16] Completeness of cytoreduction (CC) was recorded in a similar manner.[16] Postoperative complications were graded with the Clavien-Dindo classification.[18] IPC was administered as previously described by this unit.[15]

Gastric Resections: Surgical Technique

Wedge resections were performed with a linear stapling device. Reconstruction after a subtotal or partial gastrectomy was performed using the Billroth 1 technique to preserve small bowel length. Where small bowel length was not an issue, the Billroth 2 technique was used. Reconstruction after subtotal or total gastrectomy was performed using a Roux-en-Y.

Statistical Analyses

All statistical analyses were performed using SPSS and R. Only two-sided p values < 0.05 were considered significant. When appropriate, the independent samples t test was utilised for continuous variables and expressed as means. Categorical variables were assessed using Chi-squared or Fisher's exact test and reported as frequencies and proportions. The assumptions of normality were tested graphically with histograms. When the distribution is nonnormal and of similar shape, the Mann–Whitney U test is utilised and reported as medians. When the distribution is nonnormal and not of similar shape, the Wilcoxon rank-sum test is used and the units are expressed as rank.

Impact of Gastric Resections: Matching Strategy

The "matchit" package on R with the settings of nearest neighbour matching, caliper width of 0.2 and 1:2 matching was used. Based on clinical importance and significant differences on demographic analysis, age, American Society of Anaesthesia Score (ASA), preoperative albumin, carcinoembryonic antigen (CEA), carbohydrate antigen 19.9 (CA19.9), diagnosis, PCI, heated intraperitoneal chemotherapy (HIPEC), operative hours, units of blood transfused (intraoperative), signet ring cells, CC score, and early postoperative intraperitoneal chemotherapy (EPIC) were utilised as variables in the matching equation. Figure 1 depicts a jitter plot and a line plot highlighting the demographic differences before and after matching.

Perioperative Outcomes

The matched and unmatched cohort underwent univariable analysis to assess morbidity grade, hospital death,

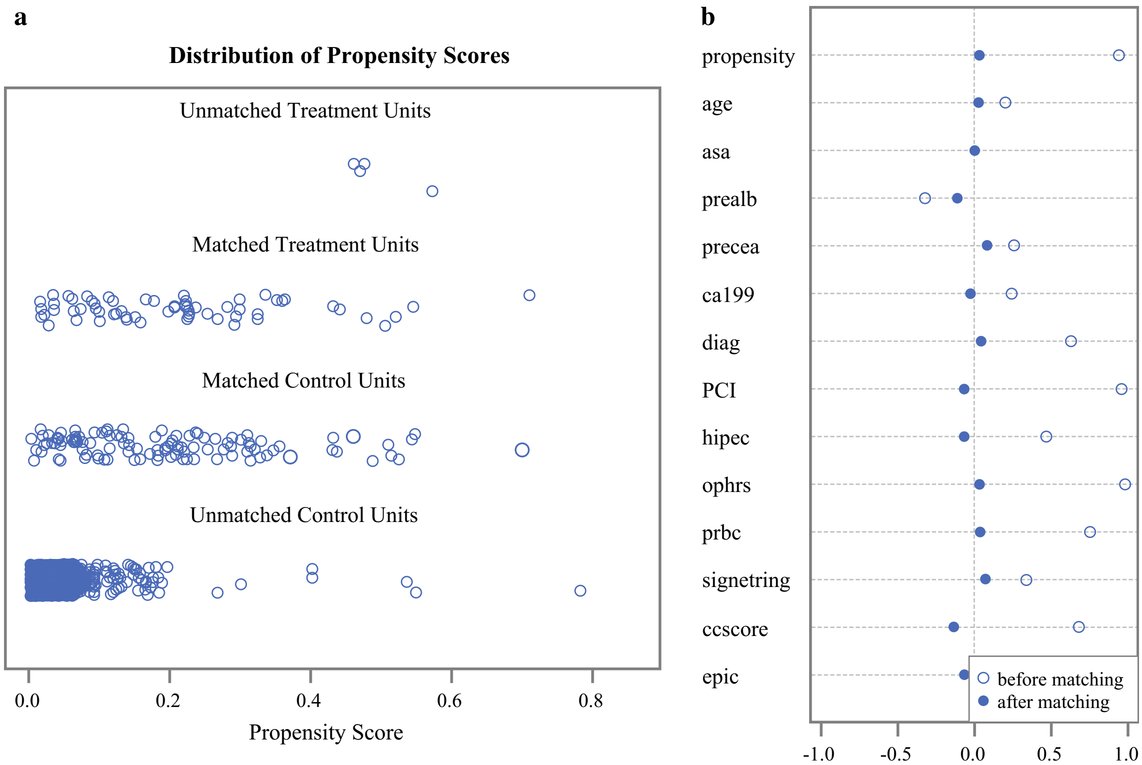

FIG. 1 Jitter plot (**a**) and line plot (**b**) highlighting the demographic differences before and after matching

reoperation rates, intensive care stay, high dependency stay, and total length of stay. This was performed separately for the combined lower gastrointestinal malignancies, adenocarcinomas, and appendiceal mucinous neoplasms.

To determine the morbidity associated with radical resections, a subgroup analysis was performed. Wedge resections were excluded from the matched data set, and univariable analysis was conducted as described above.

Survival Data

Overall survival (OS) and recurrence-free survival (RFS) times were plotted using the Kaplan–Meier method via the log-rank test. Separate analyses were conducted for the matched and un-matched data. Subgroup analyses were performed for aggressive gastric resections (partial, subtotal, and total) and for separate tumour subtypes.

RESULTS

Patient Characteristics

A total of 756 patients underwent CRS/IPC during the study period. In this cohort, 65 patients (8.6%) required gastric resections (11 wedge, 43 partial/distal, 10 subtotal, and 1 total gastrectomy). The mean age was 55 (standard deviation [SD] 13) years. There were 338 males (44.7%). The mean PCI was 17 (SD 11.7). The primary tumor was adenocarcinoma in 314 patients (41.5%), HAMNS in 209 (27.6%), and LAMNs in 233 (30.8%).

All Patients

Demographics A summary of patient characteristics is provided in Table 1. The gastrectomy group had a higher mean age, increased serum tumour markers, and decreased preoperative albumin. Increased prevalence of signet ring cells and decreased CC score 0 also were noted. Other differences were found with regards to diagnosis, PCI, operative hours, and units of blood transfused. Table 1 also summarizes how these variables are standardized after matching.

Operative Differences The gastrectomy group had increased colon (86% vs. 71%, $p = 0.011$), spleen (79% vs. 40%, $p < 0.001$), pancreas (23% vs. 3%, $p < 0.001$), and small bowel (68% vs. 45%, $p < 0.001$) resections. However, nephrectomy (1.5% vs. 2.3%, $p = 0.686$), cystectomy (4.6% vs. 3.5%, $p = 0.635$), and hepatectomy (4.6% vs. 10.1%, $p = 0.150$) rates were insignificantly different.

TABLE 1 Patient characteristics unmatched and matched

		Unmatched			Matched		
		Gastrectomy	No gastrectomy	p value	Gastrectomy	No gastrectomy	p value
Variable	Count	65	691		61	117	
Age	Mean	57	54	0.162	57	58	0.779
ASA12	Count	18 (28%)	214 (31%)	0.584	16 (26%)	31 (26%)	0.969
Diagnosis	Mean Rank	**494**	**368**	**< 0.001**	91	89	0.769
Signet ring cells	Count	**17 (26%)**	**80 (12%)**	**0.001**	16 (26%)	32 (27%)	0.873
PCI	Mean rank	**553**	**362**	**< 0.001**	92	88	0.600
CC Score 0	Count	**28 (43%)**	**533 (77%)**	**< 0.001**	27 (44%)	55 (47%)	0.727
CEA	Mean	**85**	**36**	**0.037**	75	62	0.598
CA19.9	Mean	**609**	**157**	**0.049**	386	402	0.943
Preoperative albumin	Mean	**35**	**37**	**0.001**	34	34	0.973
Operative hours	Mean	**11**	**8**	**<0.001**	11	10	0.331
PRBC	Median	**10**	**3**	**<0.001**	9	7	0.369
HIPEC	Count	64 (98%)	640 (93%)	0.117	60 (98%)	115 (98%)	1.000
EPIC	Count	27 (42%)	311 (45%)	0.570	24 (39%)	50 (43%)	0.663

Statistically significant values ($p \leq 0.05$) are given in bold

ASA12 American Society of Anesthesia Score 1 or 2, *CEA* carcinoembryonic antigen, *CA* carbohydrate antigen, *PCI* peritoneal cancer index, *HIPEC* heated intraperitoneal chemotherapy, *PRBC* packed red blood cells transfused intraoperatively, *CC* completeness of cytoreduction, *EPIC* early postoperative intraperitoneal chemotherapy

Perioperative Outcomes (Unmatched) The unmatched gastric resection cohort had increased grade 3/4 morbidity (66% vs. 38%, $p < 0.001$), reoperation (37% vs. 14%, $p < 0.001$), and in-hospital death (6% vs. 1%, $p = 0.001$). Correspondingly, there was a significant increase in median ICU (3 vs. 2, $p < 0.001$), HDU (4 vs. 2, $p = 0.004$), and total hospital stay (30 vs. 20, $p < 0.001$).

Perioperative Outcomes (Matched) A summary of the perioperative outcomes following propensity score matching is provided in Table 2. Patients who required gastric resections had increased rates of reoperation. There were no differences in grade 3/4 morbidity, hospital death, ICU or HDU stay, and LOS. Subgroup analysis for appendiceal mucinous neoplasms revealed increased rates of reoperation. No differences were found in perioperative outcomes for adenocarcinoma.

Subgroup Analysis following Exclusion of Wedge Resections

Perioperative Outcomes (Matched) Summaries of the matched perioperative outcomes are found in Table 2. The gastrectomy cohort had increased rates of reoperation, grade 3/4 morbidity, and length of stay. There were no differences in hospital death or ICU and HDU stay. Subgroup analysis for appendiceal mucinous neoplasms revealed increased rates of reoperation. Analysis for adenocarcinoma revealed a weak trend for increased hospital stay.

Overall Survival and Recurrence-Free Survival (Unmatched)

A total of 561 patients in lower gastrointestinal malignancies underwent CRS/IPC and achieved CC = 0. At the time of the study there were 195 deaths. Gastrectomy did not affect OS (103 vs. 69 months, $p = 0.501$; Fig. 2a).

A total of 561 patients in lower gastrointestinal malignancies underwent CRS/IPC and achieved CC = 0. At the time of the study, there were 337 recurrences. Gastrectomy did not affect RFS (17 vs. 18 months, $p = 0.181$; Fig. 2b).

A total of 226 patients in lower gastrointestinal malignancies underwent CRS/IPC and achieved CC > 0. At the time of the study, there were 96 deaths. Gastrectomy significantly affected OS (31 vs. 83 months, $p < 0.001$; Fig. 2c).

A total of 226 patients with lower gastrointestinal malignancies underwent CRS/IPC and achieved CC > 0. At the time of the study, there were 154 recurrences. Gastrectomy significantly affected RFS (9 vs. 20 months, $p < 0.001$; Fig. 2d).

TABLE 2 Matched perioperative outcomes

		Perioperative outcomes—wedges included			Perioperative outcomes—no wedges		
		Gastrectomy	No gastrectomy	*p* value	Gastrectomy	No gastrectomy	*p* value
Lower gastrointestinal							
Number		61	117		50	117	
Return to theatre	Count	**23 (38%)**	**26 (22%)**	**0.028**	**20 (40%)**	**26 (22%)**	**0.019**
In-hospital death	Count	3 (5%)	3 (3%)	0.414	2 (4%)	3 (0.8%)	0.636
Morbidity grade 3, 4	Count	42 (69%)	69 (59%)	0.197	**38 (76%)**	**69 (59%)**	**0.036**
ICU stay	Median	3	3	0.101	4	3	0.121
HDU stay	Median	3	2	0.312	4	2	0.090
LOS	Median	30	27	0.102	**34**	**27**	**0.012**
Appendiceal mucinous neoplasms							
Number		50	92		44	92	
Return to theatre	Count	**19 (38%)**	**19 (21%)**	**0.026**	**16 (36%)**	**19 (21%)**	**0.050**
In-hospital death	Count	3 (6%)	2 (2%)	0.345	2 (5%)	2 (2%)	0.595
Morbidity grade 3, 4	Count	36 (72%)	57 (62%)	0.270	33 (75%)	57 (62%)	0.133
ICU stay	Median	4	3	0.100	4	3	0.141
HDU stay	Median	4	4	0.543	4	2	0.472
LOS	Median	34	29	0.156	34	27	0.079
Adenocarcinoma							
Number		11	25		6	25	
Return to theatre	Count	4 (36%)	7 (28%)	0.703	4 (66%)	7 (28%)	0.151
In-hospital death	Count	0 (0%)	1 (4%)	1.000	0 (0%)	1 (0.04%)	0.618
Morbidity grade 3, 4	Count	6 (55%)	12 (48%)	1.000	5 (83%)	12 (48%)	0.185
ICU stay	Median	3	3	0.735	3	3	0.575
HDU stay	Median	0	0	0.636	5	0	0.130
LOS	Median	26	20	0.342	31	20	0.060

Statistically significant values ($p \leq 0.05$) are given in bold

ICU intensive care unit, *HDU* high dependency unit, *LOS* length of stay, *HAMNs* high-grade appendiceal mucinous neoplasms, *LAMNs* low-grade appendiceal mucinous neoplasms

Overall Survival and Recurrence-Free Survival (Matched)

A total of 178 patients in lower gastrointestinal malignancies underwent CRS/IPC. At the time of the study, there were 82 deaths. Gastrectomy insignificantly affected OS (37 vs. 58 months median survival, $p = 0.213$; Fig. 3a).

A total of 178 patients in lower gastrointestinal malignancies underwent CRS/IPC. At the time of the study, there were 134 recurrences. Gastrectomy significantly affected RFS (11 vs. 20 months median survival, $p = 0.035$; Fig. 3b).

Overall survival following the exclusion of wedges comprised 167 patients in lower gastrointestinal malignancies. At the time of the study, there were 77 deaths. Gastrectomy insignificantly affected OS (31 vs. 58 months median survival, $p = 0.181$; Fig. 3c).

Recurrence-free survival following the exclusion of wedges included 167 patients in lower gastrointestinal malignancies. At the time of the study, there were 126 recurrences. Gastrectomy significantly affected RFS (11 vs. 20 months median survival, $p = 0.016$; Fig. 3d).

A total of 142 patients underwent CRS/IPC for appendiceal mucinous neoplasms. At the time of the study, there were 63 deaths. Gastrectomy insignificantly affected OS (51 vs. 64 months median survival, $p = 0.168$).

In total, 142 patients were included for RFS of appendiceal mucinous neoplasms. At the time of the study, there were 108 recurrences. Gastrectomy significantly affected RFS (11 vs. 20 months median survival, $p = 0.050$).

A total of 36 patients underwent CRS/IPC for adenocarcinoma. At the time of the study, there were 19 deaths. Overall survival was insignificantly effected on Kaplan–Meier (21 vs. 35 months median survival, $p = 0.892$).

Thirty-six patients were included for RFS of adenocarcinoma. At the time of the study, there were 26 recurrences. Gastrectomy insignificantly effected RFS (8 vs. 15 months median survival, $p = 0.264$).

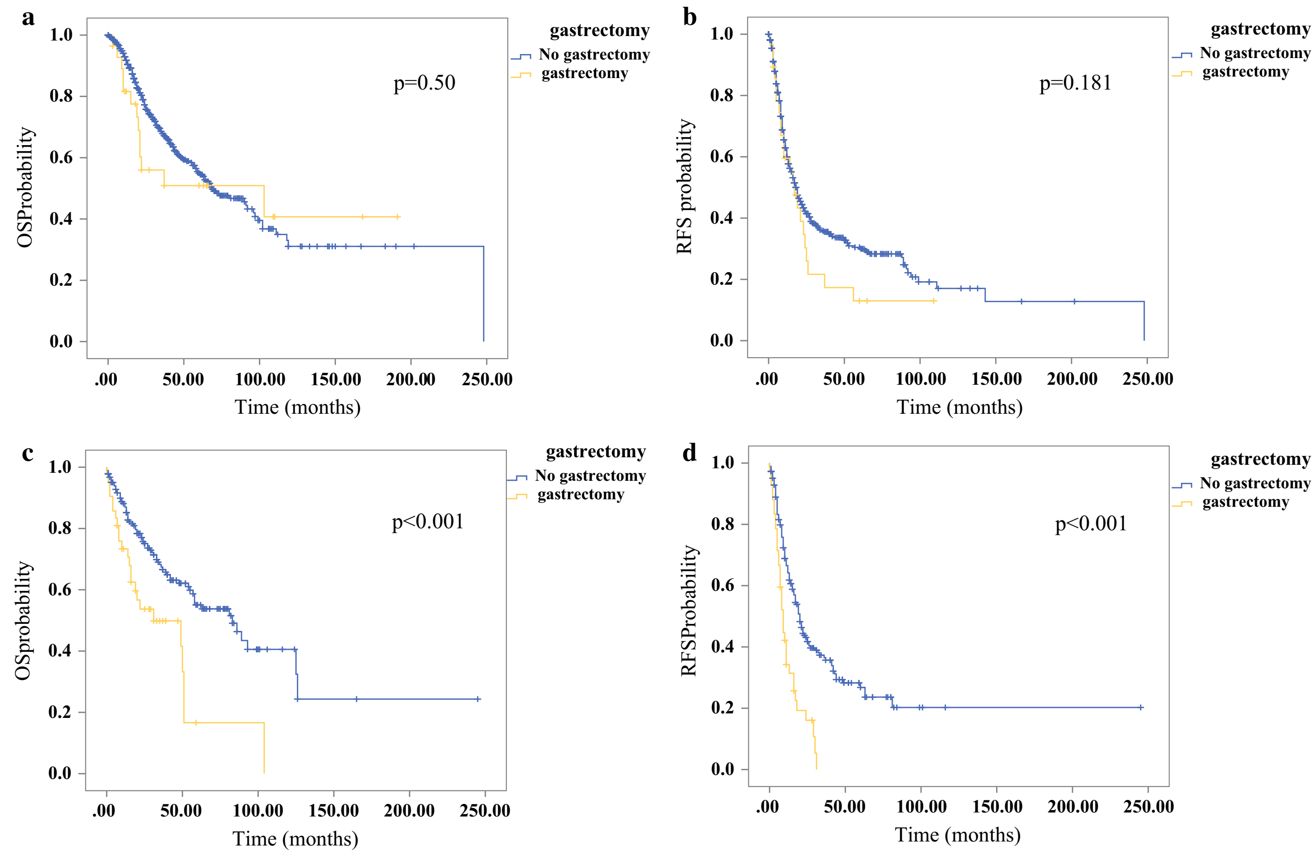

FIG. 2 Overall and recurrence-free survival for the unmatched cohort: for the patients with a completeness of cytoreduction score (CC) of 0 (**a**, **b**) and then for a separate analysis with a completeness of cytoreduction score greater than 0 (**c**, **d**)

DISCUSSION

The role of gastric resections in CRS/IPC is debated. The controversy centers on the reported high morbidity, mortality, and decreased survival. Previous studies have failed to account for differences in tumor aggression and poor nutrition. To test existing views, we utilize matching to adjust for tumor aggression and perform subgroup analysis based on histology and gastrectomy type.

Four studies have assessed the role of gastrectomy in CRS/IPC. Sugarbaker describes a two-stage total gastrectomy technique in a series of 45 CRS for LAMNs.[11] Importantly, 18 of these patients required total colectomy and 5 were severely malnourished. The mortality rate was 2.2%, esophago-jejunal leakage 4.4%, reoperation rate was 15.6%, and fistula rate 17.8%. This series has no control group or survival analysis.

Piso and colleagues describe gastrectomy as a one-stage procedure.[12] Their cohort consisted of 37 patients with various diagnoses. The treatment group consisted of 7 wedge, 15 distal, and 15 total gastric resections. No hospital mortality was observed, and surgical complications included: 16% pancreatitis, 10.8% abdominal collections, 5.4% biliary leak, 2.7% bleeding, and no anastomotic leaks. Weaknesses in their study include the absence of a control group, survival analysis, stratification for tumor histology, and gastrectomy type.

Fabio and colleagues are the first to provide a control group.[13] A total of 747 patients with LAMNs were included. Of these, 86 patients (11.5%) underwent partial or total gastric resections. Increased grade III–IV complications (31% vs. 13%, $p = 0.001$) were noted. On Kaplan–Meier analysis, 3-year (87% vs. 96%), 5-year (77% vs. 88%), and 10-year (64% vs. 81%) OS was significantly reduced. These results have led to controversy regarding the role of gastrectomy in CRS. However, their control group was not appropriately selected. Fabio et al. demonstrate increased serum tumor markers and total colectomy rates in the gastrectomy cohort. These are associated with aggressive disease, and no attempt was made to assess for this.[19–23] Also, baseline comorbidities were not assessed.

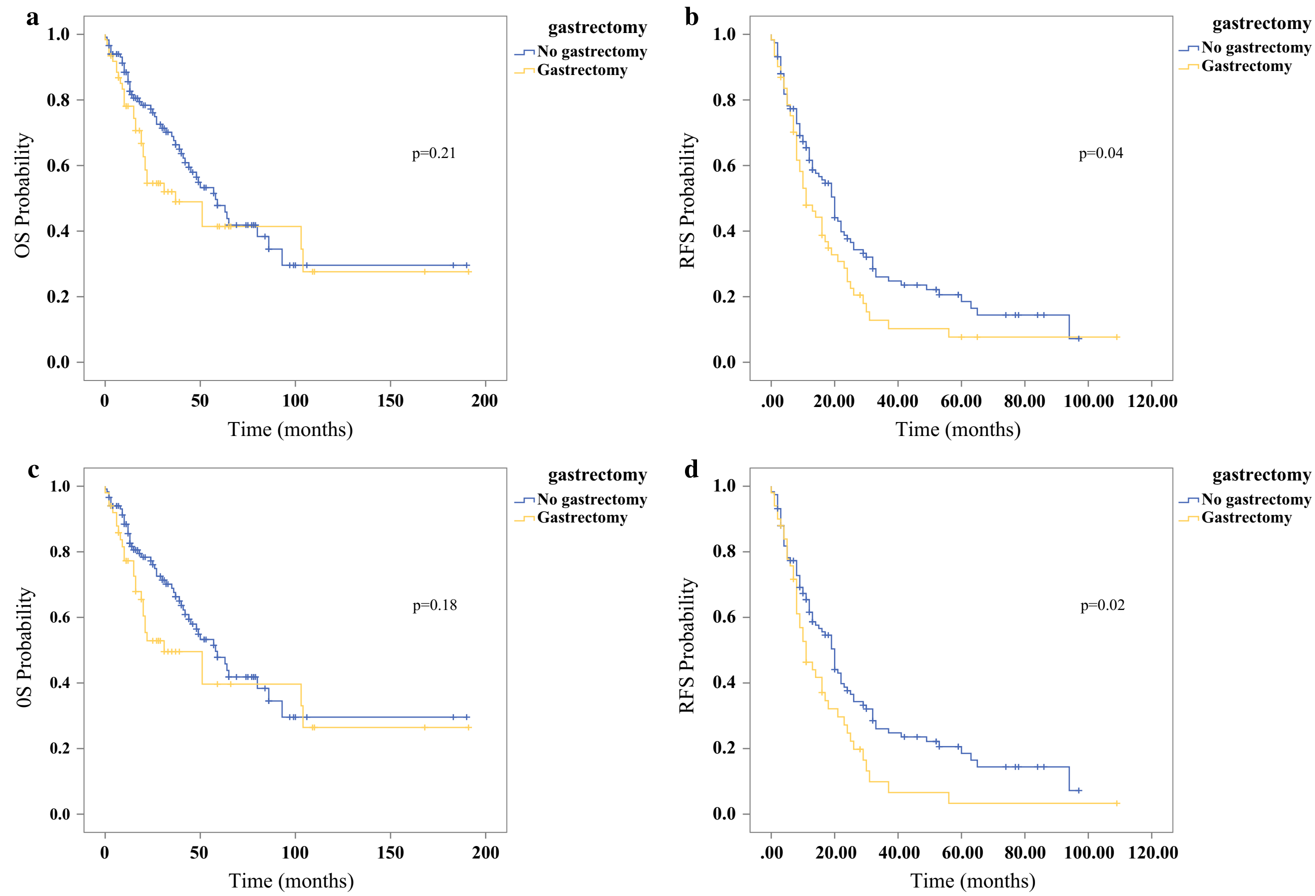

FIG. 3 Overall and recurrence-free survival for the matched cohort: for the whole cohort (**a**, **b**) and then for a separate analysis excluding wedge resections (**c**, **d**)

Finally, Paredes et al. surmised the American experience.[14] Their cohort consisted of 63 patients: 43 partial and 20 total gastrectomies. Gastrectomy resulted in increased morbidity (61% vs. 28%, $p < 0.001$) and hospital stay (19 vs. 11, $p < 0.001$). However, there are significant limitations in their study; all histological subtypes are included, redo surgeries were not excluded, disease burden was not assessed, and no long-term analysis was performed. Lastly, although they attempt to utilize a logistic regression model to adjust for demographic variables, there are 37 variables for 63 patients. This overfits their model and makes their results unreliable.

Our series attempted to assess the role of gastrectomy in CRS through a thorough analytical methodology. Patient demographics and operative differences were analysed. Based on this, the data was matched. Perioperative outcomes were then analysed for unmatched and matched data. Subgroup analyses to determine the outcomes based on histology and type of gastrectomy was conducted. Finally, OS and RFS were conducted in a similar manner.

The demographic markers that determine differences between the gastric resection and control groups are included in Table 1. They were limited to prevent overfitting and co-linearity during the matching process. Markers of preoperative tumor aggression and poor nutrition were prevalent in the gastrectomy group.

Perioperative analysis on matched data revealed significant rates of reoperation. The outcomes in the control group were also poor: grade 3/4 morbidity was 59%, LOS of 27 days, and reoperation rate of 27%. One may believe that the poor outcomes are inflating the morbidity associated with gastric resections. However, when the unmatched outcomes are observed, the control group outcomes of grade 3/4 morbidity are 38%, LOS of 20 days, and reoperation rate of 14%. This illustrates that when the two groups are adequately matched on disease aggression, the control group has comparable morbidity. Therefore, the poorer outcomes are partly due to tumor biology. However, even after matching, with exclusion of wedge resections, the differences in morbidity become significant.

OS and RFS for the unmatched analysis was divided into CC = 0 and CC > 0. For patients who achieved CC = 0, OS and RFS were insignificantly different. Conversely, when CC > 0, OS and RFS are significantly decreased. This implies that when complete cytoreduction can be facilitated, recurrence risk is similar to patients that undergo CRS/IPC and do not undergo gastric resection. A similar statement cannot be made about the OS. The low event rates in the CC = 0 make it uninterpretable. This is reflected in the crossing survival curve (2a). Despite this, the lack of significant difference is reassuring.

OS and RFS, for the matched analysis, were divided according to histology. Our results illustrate that there was no significant association with gastrectomy and OS. However, a reduced median survival of a year for appendiceal and adenocarcinoma was observed. It is possible that the low event rates have prevented it from reaching significance. In contrast, the RFS analysis revealed a significant association with gastrectomy and a 9-month earlier recurrence.

These results need to be interpreted with caution. The matched model attempts to adjust for tumor aggression by utilizing serum markers and PCI as covariates, but gastric disease might be an independent prognosticator. The most appropriate control would be patients with resectable disease who have refused treatment. While the matched cohort illustrates early recurrence, when a CC = 0 is achieved, RFS in the unmatched cohort is insignificant. Further studies should assess the value of performing gastric resections when CC score > 0. Other long-term endpoints, such as the rate of local gastric recurrence and symptomatic gastric progression, would further clarify the role of gastrectomy in CRS.

Our study has several limitations. It is a retrospective study with limitations inherent to its design. Unidentified confounding factors could influence results.[24] Our sample size might be too small to detect significant differences. This is a single-institution study, and the results may not be applicable to all institutions. While matching, there is a potential to overmatch. Specific perioperative complications pertaining to gastric resections, i.e., anastomotic leaks, fistula, and TPN were not available. Lastly, OS would be best assessed with the relevant histological subtype and type of gastric resection, while being compared with a cohort that has resectable gastric disease and elected not to undergo CRS.

CONCLUSIONS

We conclude that the previously reported morbidity and mortality with gastrectomy is in part attributable to inadequate comparison control groups. Despite the high postoperative morbidity, when complete cytoreduction is achieved, the need for gastric resection is not associated with inferior long-term outcomes. Further studies should be performed to determine the rate of local recurrence and value of symptomatic control.

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DISCLOSURE Nothing to disclose.

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