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ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

Predictors of Anastomotic Failure After Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Does Technique Matter?

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ABSTRACT

Background. Anastomotic failure (AF) after cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) remains a dreaded complication. Whether specific factors, including anastomotic technique, are associated with AF is poorly understood.

Methods. Patients who underwent CRS-HIPEC including at least one bowel resection between 2000 and 2017 from 12 academic institutions were reviewed to determine factors associated with AF (anastomotic leak or enteric fistula).

Results. Among 1020 patients who met the inclusion criteria, the median age was 55 years, 43.9% were male, and the most common histology was appendiceal neoplasm (62.3%). The median Peritoneal Cancer Index was 14, and 93.2% of the patients underwent CC0/1 resection. Overall, 82 of the patients (8%) experienced an AF, whereas 938 (92.0%) did not. In the multivariable analysis, the factors associated with AF included male gender (odds ratio [OR], 2.2; $p < 0.01$), left-sided colorectal resection (OR 10.0; $p = 0.03$), and preoperative albumin (OR 1.8 per g/dL; $p = 0.02$).Technical factors such as method (stapled vs hand-sewn), timing of anastomosis, and chemotherapy regimen used were not associated with AF (all $p > 0.05$). Anastomotic failure was associated with longer hospital stay (23 vs 10 days; $p < 0.01$), higher complication rate (90% vs 59%; $p < 0.01$), higher reoperation rate (41% vs 9%; $p < 0.01$), more 30-day readmissions (59% vs 22%; $p < 0.01$), greater 30-day mortality (9% vs 1%; $p < 0.01$), and greater 90-day mortality (16% vs 8%; $p = 0.02$) as well as shorter median overall survival (25.6 vs 66.0 months; $p < 0.01$).

Conclusions. Among patients undergoing CRS-HIPEC, AF is independently associated with postoperative morbidity and worse long-term outcomes. Because patient- and tumor-related, but not technical, factors are associated with AF, operative technique may be individualized based on patient considerations and surgeon preference.

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Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) has emerged as a recommended surgical approach for patients with peritoneal surface malignancies. At experienced high-volume centers, CRS-HIPEC can be performed safely with acceptable rates of morbidity and low rates of mortality comparable with the postoperative outcomes reported for other surgical oncology procedures of similar magnitude.[1,2]

A particularly dreaded complication after CRS-HIPEC is anastomotic failure (AF), reported in previous studies to occur with an incidence of 8–12%.[3–7] Given its impact on morbidity and mortality,[6] efforts to reduce the incidence of AF after CRS-HIPEC are therefore needed, but the risk factors for AF are poorly understood. Even when standard surgical principles are routinely followed during CRS-HIPEC, certain technical aspects are regularly debated, including whether to perform a hand-sewn or stapled restorative bowel anastomosis and whether to complete these maneuvers before or after HIPEC.[8–11]

Therefore this study aimed primarily to investigate technical and other perioperative factors associated with AF using a large multi-institutional database. The secondary aim was to describe the incidence of AF as well as its impact on the short- and long-term outcomes for patients undergoing CRS-HIPEC.

METHODS

Data Acquisition and Cohort Selection

A retrospective review of the US HIPEC Collaborative was performed to identify all patients who underwent CRS-HIPEC with at least one bowel resection between 2000 and 2017. The US HIPEC Collaborative is a multi-institutional effort composed of 2372 patient entries from 12 academic institutions in the United States who routinely perform CRS-HIPEC. Patients were excluded from the study if they did not undergo a bowel resection or did not have intraperitoneal chemotherapy (Fig. 1).

Study Variables and Outcomes

Patients were classified based on the development of a postoperative AF, defined as anastomotic leak, enteric fistula originating from the gastrointestinal tract, or both. Specifically, AF was defined as any anastomotic leak or enteric fistula that occurred during the postoperative period without a time limit. Anastomotic leak was defined as any postoperative disruption of the enteric anastomosis leading to leakage of enteric contents. Enteric fistula was defined as an abnormal fistulous connection between the gastrointestinal tract and the atmosphere. These definitions were not presumptuous of nor dependent on management.

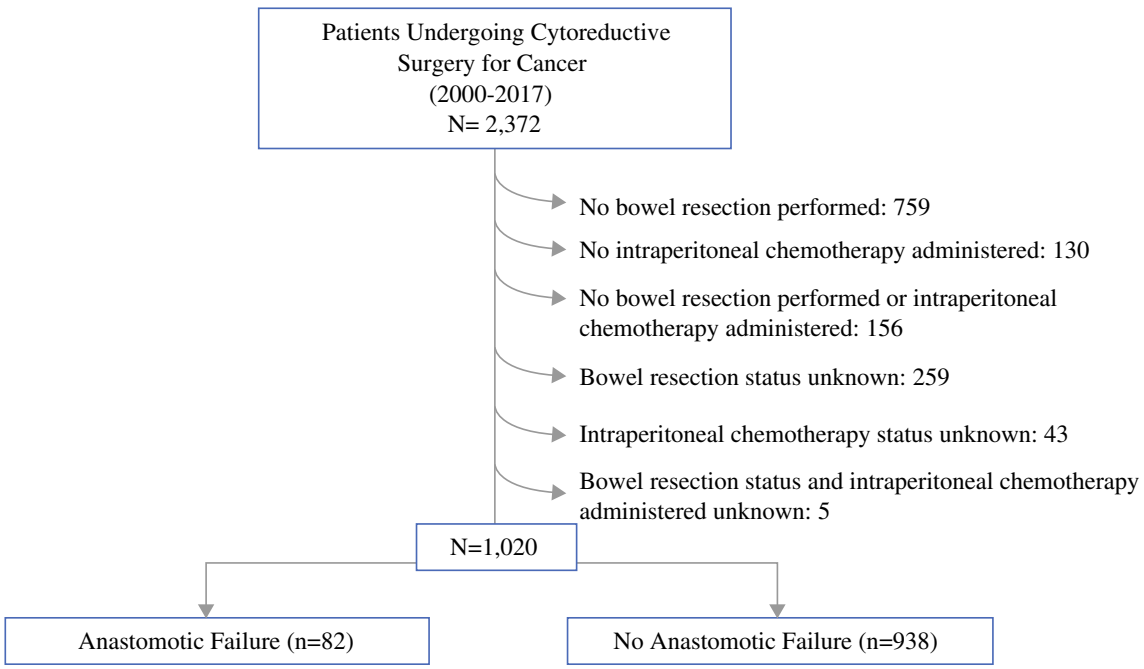

FIG. 1 Study selection of patients in the US HIPEC Collaborative

Anastomotic leaks originating from a pancreatic or biliary origin were not counted.

Operative intent was classified as curative (intent to achieve CCR 0/1 with the aim of improving patient survival), prophylactic (high-risk disease warranting respective treatment), or palliative (intervention due to bleeding, pain, obstruction, or ascites without curative intent).

Type of bowel resection was classified as small bowel, right colon, or left colon. Right colon bowel resection included resections up to the splenic flexure. Resections including the rectum were included in the left colon category. For purposes of analysis, if patients had more than one type of resection, they were classified according to the most distal anastomosis.

Method of anastomosis was classified as stapled or hand-sewn. When stapled and hand-sewn anastomoses were performed for the same patient ($n = 10$), the anastomosis was classified as stapled.

The Peritoneal Cancer Index (PCI) score defined the extent of peritoneal cancer throughout the peritoneal cavity as established by Jacquet and Sugarbaker.[12] Completeness of cytoreduction (CCR) was defined according to the following established definition: after cytoreduction, CC-0 indicated no micro- or macroscopic disease, CC-1 indicated nodules persisting less than 2.5 mm, CC-2 had nodules between 2.5 mm and 2.5 cm, and CC-3 indicated nodules larger than 2.5 cm.[13] Cardiovascular comorbidity was classified as a history of myocardial infarction, peripheral vascular disease, stroke, or congestive heart failure.

Postoperative complications were defined as wound-related (superficial and deep wound infections, wound disruption), cardiovascular (myocardial infarction, cardiac arrest, cerebral vascular accident), respiratory (pneumonia, unplanned intubation, ventilator support for more than 48 h, tracheostomy, pleural effusion, pneumothorax, need for chest drainage with tube thoracostomy or pleural thoracentesis), hematologic (deep vein thrombosis, pulmonary embolism, bleeding), gastrointestinal (pancreatitis, ileus, initiation of tube feeds or parenteral nutrition, replacement of a nasogastric tube), renal (progressive renal insufficiency, acute renal failure, ureteral injury), postoperative sepsis, or intraoperative death.

Anastomotic failure was not included in the complication definition given its role as a dependent variable in our study design. Incidence of intrabdominal wound infection was not included due to overlap with incidence of AF. Occurrence of death was measured from the time of surgery. Morbidity was further graded using the Clavien-Dindo classification.[14]

Statistical Analysis

Descriptive statistics were calculated using frequencies and percentages for categorical data and using medians and interquartile ranges for continuous data. Categorical variables were assessed using the Chi square test for proportions or Fisher's exact test as appropriate, whereas continuous variables were analyzed using Student's t test or the Mann–Whitney U test as appropriate.

A multivariable logistic regression model was created to determine risk factors for AF. Clinically relevant variables were chosen a priori for entrance into the model. Specifically, the backward selection method was used to evaluate which patient demographics (age, gender, race), preoperative characteristics (American Society of Anesthesiologists [ASA] class, history of abdominal surgery, serum albumin level, tumor histology), and perioperative factors (resection location, number of anastomoses, stapled or hand-sewn anastomosis, anastomosis performed before or after HIPEC, type and duration of HIPEC, estimated blood loss, operative time) were associated with postoperative AF.

The Kaplan–Meier method and the log-rank test was used to estimate overall survival (OS) differences between those with and without AF overall and for select histologic subgroups. Then a multivariable Cox proportional hazards model was used to determine factors associated with OS. The aforementioned variables used in the multivariable logistic regression model were used for model creation with the addition of AF.

All analyses were performed with two-sided p values (alpha, 0.05). Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). The institutional review board at each participating institution independently approved this study.

RESULTS

Cohort Characteristics

Of the 2372 patients who underwent CRS in the US HIPEC Collaborative, 1020 had both HIPEC and at least one bowel resection and were included in the current analysis (Fig. 1). The demographic, clinical, and operative characteristics of the overall cohort are presented in Table 1. The majority of the patients were younger than 65 years (76.3%), female (56.1%), and white (80.3%).

Patient comorbidities were present in a majority of the patients, with 81.6% having an ASA classification of 3 or higher. The predominant histology was appendiceal neoplasm (62.3%) followed by colorectal cancer (27.5%). The median PCI was 14, and 93.2% of the patients underwent CC0/1 resection.

TABLE 1 Demographic, clinical, and operative characteristics of the patients undergoing a bowel resection and heated intraperitoneal chemotherapy for cancer

Variable	Overall *n* (%)	Anastomotic failure *n* (%)	No Anastomotic failure *n* (%)	*p* value
Demographics				
Age (years)				
< 65	778 (76)	59 (72)	719 (77)	0.34
≥ 65	242 (24)	23 (28)	2119 (23)	
Gender				
Male	448 (44)	49 (60)	399 (43)	< 0.01
Female	572 (56)	33 (40)	539 (57)	
Race				
White	809 (80)	70 (86)	739 (80)	0.19
Non-white	198 (20)	11 (14)	187 (20)	
Patient characteristics				
BMI				
Normal	353 (35)	30 (37)	323 (35)	0.86
Obese	308 (30)	26 (32)	282 (30)	
Overweight	330 (33)	24 (29)	306 (33)	
Underweight	21 (2)	2 (2)	19 (2)	
ASA class				
2	167 (18)	14 (18)	153 (18)	0.39
3	681 (75)	56 (72)	625 (75)	
4	60 (7)	8 (10)	52 (6)	
Functional status				
Independent	851 (98)	77 (96)	774 (98)	0.43
Not independent	21 (2)	3 (4)	18 (2)	
Cardiovascular history	92 (9)	7 (9)	85 (9)	1.00
Smoking history	316 (31)	26 (32)	290 (31)	0.10
Renal disease	15 (2)	0 (0)	15 (2)	0.62
GERD and PUD	207 (21)	15 (19)	192 (21)	0.67
Ascites	180 (18)	11 (13)	169 (18)	0.29
Albumin: median g/dl (IQR)	4.1 (3.8–4.4)	4.0 (3.7–4.3)	4.1 (3.8–4.4)	0.13
Gastrointestinal obstruction	66 (7)	7 (9)	59 (6)	0.48
History prior abdominal surgery	853 (89)	63 (82)	790 (89)	0.06
Histology				
Appendiceal	635 (62)	54 (66)	581 (62)	0.58
Colorectal	280 (28)	24 (29)	256 (27)	
Gastric	18 (2)	2 (2)	16 (2)	
Peritoneal mesothelioma	47 (5)	2 (2)	45 (5)	
Small bowel	15 (2)	0 (0)	15 (2)	
Other	25 (2)	0 (0)	25 (3)	
Neoadjuvant therapy	387 (38)	33 (41)	354 (38)	0.63
Intraoperative characteristics				
Operative intent				
Curative	959 (96)	76 (96)	883 (96)	0.75
Palliative	27 (3)	2 (3)	25 (3)	
Prophylactic	9 (0.9)	1 (1)	8 (1)	
Resection location				
Small bowel only	136 (13)	5 (6)	131 (14)	0.06
Right colon ± small bowel	501 (49)	39 (48)	462 (49)	
Left colon ± right colon ± small bowel	379 (37)	38 (46)	341 (37)	

TABLE 1 continued

Variable	Overall *n* (%)	Anastomotic failure *n* (%)	No Anastomotic failure *n* (%)	*p* value
No. of anastomoses				
0–1	719 (71)	47 (57)	672 (72)	< 0.01
≥ 2	301 (30)	35 (43)	266 (28)	
Anastomosis location(s)				
Small bowel only	139 (16)	5 (7)	134 (16)	0.09
Large bowel only	515 (57)	44 (61)	471 (57)	
Small and large bowel	244 (27)	23 (32)	221 (27)	
Intraperitoneal chemotherapy				
Mitomycin-C	958 (94)	77 (94)	880 (94)	1.00
Other	63 (6)	5 (6)	58 (6)	
Anastomosis before or after perfusion				
Before	230 (26)	14 (20)	216 (26)	0.26
After	663 (74)	57 (80)	606 (74)	
Intraperitoneal chemotherapy duration (min)				
≤ 60	53 (5)	5 (6)	48 (5)	0.80
> 60	919 (94)	75 (94)	844 (95)	
Anastomosis technique				
Hand-sewn	185 (21)	12 (17)	173 (21)	0.45
Stapled	699 (79)	60 (83)	639 (79)	
Median PCI (IQR)	14 (8–21)	16.3 (9–23)	14.8 (8–21)	0.16
CCR				
0	645 (67)	44 (56)	601 (68)	0.14
1	258 (27)	29 (37)	229 (26)	
2	54 (6)	5 (6)	49 (6)	
3	12 (1)	1 (1)	11 (1)	
Diverting loop ileostomy	96 (12)	7 (11)	89 (12)	1.00
End ileostomy or colostomy	87 (9)	10 (13)	77 (8)	0.21
IVF (ml)				
Low (0, < 5000)	131 (17)	10 (16)	121 (17)	0.46
Medium (5000, < 10,000)	459 (59)	34 (53)	425 (59)	
High (≥ 10,000)	194 (25)	20 (31)	174 (24)	
EBL (ml)				
Low (0, < 100)	50 (5)	2 (2)	48 (5)	0.04
Medium (100, < 1000)	814 (81)	61 (74)	753 (81)	
High (≥ 1000)	144 (14)	19 (23)	125 (14)	
Median operative time: h (IQR)	8.8 (7–11)	9.6 (7.4–11.9)	9.0 (6.9–10.9)	0.06

BMI body mass index, *ASA* American Society of Anesthesiology, *GERD* gastroesophageal reflux disease, *PUD* peptic ulcer disease, *g/dl* grams/deciliter, *IQR* interquartile range, *PCI* peritoneal cancer index, *CCR* completeness of cytoreduction, *ml* milliliters

The majority of the patients had one anastomosis created (58.4%). The resection locations were distributed throughout the gastrointestinal tract, with 49.3% of the patients having a right colon resection, 37.3% having a left colon resection, and 13.4% having small bowel resection alone. Anastomotic creation was most commonly performed using a stapler (79.1%) and most often after HIPEC (74.2%). A minority of patients underwent diverting loop ileostomy (11.8%) or end enterostomy (8.7%).

Complications were common. Overall, 62% of the patients experienced at least one postoperative complication, including 25% classified as Clavien-Dindo grade 3 or higher. The overall AF rate among the selected study cohort (n = 1020) was 8%. The patients with complications included 11.6% who underwent reoperation, 25% who were readmitted within 30 days, and 8.7% who died within 90 days after surgery.

TABLE 2 Multivariable analysis of anastomotic failure for patients undergoing a bowel resection and heated intraperitoneal chemotherapy for cancer

Variable	95% CI			
	OR	Lower	Upper	*p* value
Male gender	2.2	1.2	4.0	0.01
Resection location (reference = small bowel)				
Right colon	6.3	0.8	48	0.07
Left colon	10.0	1.3	75	0.03
Albumin (g/dl)	1.8	1.1	3.0	0.04

The area under the receiver operator curve of the model was 0.687

OR odds ratio, *CI* confidence interval, *g/dl* grams/deciliter

Risk Factors for Anastomotic Failure

In the univariate analysis, the factors significantly associated with AF among the patients who underwent CRS-HIPEC with at least one bowel resection included male gender (60% vs 43%; $p < 0.01$), two or more anastomoses (43% vs 28%; $p < 0.01$), and an estimated blood loss greater than 1 l (23% vs 14%; $p = 0.04$). Anastomotic failure was not significantly associated with whether the anastomosis was created using a stapled technique (83% vs 79%) or a hand-sewn technique (17% vs 21%) ($p = 0.45$). Furthermore, AF rates did not differ between anastomosis created before HIPEC (20% vs 26%) or after HIPEC (80% vs 74%) ($p = 0.26$) (Table 1). Of 379 patients treated with left-sided colon resection, 87 underwent synchronous creation of a diverting loop ileostomy, with 6 of these patients experiencing AF (6.9%). Of 66 patients treated with CCR-2 or CCR-3, 4 underwent synchronous creation of a diverting loop ileostomy, with none experiencing AF.

In the multivariable analysis, the factors associated with AF included male gender (odds ratio [OR], 2.2; $p = 0.01$), left-sided colorectal resection versus small bowel resection (OR 10.0; $p = 0.03$), and preoperative serum albumin (OR 1.8 per decrease in 1 g/dL; $p = 0.04$) (Table 2).

Impact of Anastomotic Failure on Short-Term Outcomes

The incidence of postoperative complication (separate from the AF) was higher among the patients with AF (90% vs 59%; $p < 0.01$). The most common complications associated with incidence of AF were initiation of postoperative parenteral nutrition (75.3%), systemic sepsis (37.3%), and ileus (34.1%). Furthermore, AF was associated with an overall increase in reoperation rate (41% vs 9%; $p < 0.01$), median hospital stay (23 vs 10 days; $p < 0.01$), 30-day readmission rate (59% vs 22%; $p < 0.01$), 30-day mortality rate (9% vs 1%; $p < 0.01$), and 90-day mortality rate (16% vs 8%; $p = 0.02$).

Impact of Anastomotic Failure on Survival

Anastomotic failure was associated with a decreased median OS (25.6 vs 66.0 months; $p < 0.01$) (Fig. 2a). This OS effect persisted when we examined select histologic subgroups of appendiceal (93.6 vs 60.1 months; $p < 0.01$) and colorectal (31.5 vs 11.8 months; $p < 0.01$) malignancies, and trended toward significance for gastric malignancies (12.8 vs 5.4 months; $p = 0.09$) (Fig. 2b–d). When the patients who died within 90-days were excluded, AF remained associated with a decreased median OS (33.5 vs 68.0 months; $p < 0.01$) (Fig. 2e). In multivariable modeling, the factors independently associated with worse OS were AF (hazard ratio [HR], 2.1; $p < 0.01$) and histology (colorectal cancer [HR 2.7; $p < 0.01$] and gastric cancer [HR 8.6; $p < 0.01$] vs appendiceal neoplasms) (Table 3).

DISCUSSION

As in other abdominal operations, AF has long been a feared complication of CRS-HIPEC given its known impact on postoperative mortality,[6,15] resource utilization,[6,16] patient quality of life,[17] and long-term oncologic outcomes.[18] The findings from this large multi-institutional analysis of CRS-HIPEC performed at high-volume U.S. institutions are largely consistent with the findings of these prior studies. First, the incidence of AF is relatively low at experienced centers.[6] This finding is comparable with that for patients who did not undergo HIPEC.[19] Second, patients who experience AF have significantly higher rates of postoperative morbidity including death within 90 days or the need for reoperation, and this effect persists for long-term OS as well. Finally, although several independent risk factors for AF were identified, technical factors including anastomotic technique, timing of the anastomosis, and HIPEC regimen were notably not associated with AF.

Previous literature has raised awareness of the risks for AF when a bowel resection is performed during CRS-HIPEC. During HIPEC, a carrier solution is heated higher than 40 °C, then instilled with a chemotherapy agent such as mitomycin-C, followed by continued perfusion in circuit to the abdominal cavity, typically for 90 min, often with physical agitation of the abdomen. In the setting of intraperitoneal chemotherapy, there is ongoing concern for proper healing postoperatively.[20]

Animal models have previously demonstrated that HIPEC results in lower bursting pressure and altered collagen deposition, leading to impaired anastomotic healing;[20,21] However, recent trials examining the association of HIPEC with leak rate have not demonstrated any difference.

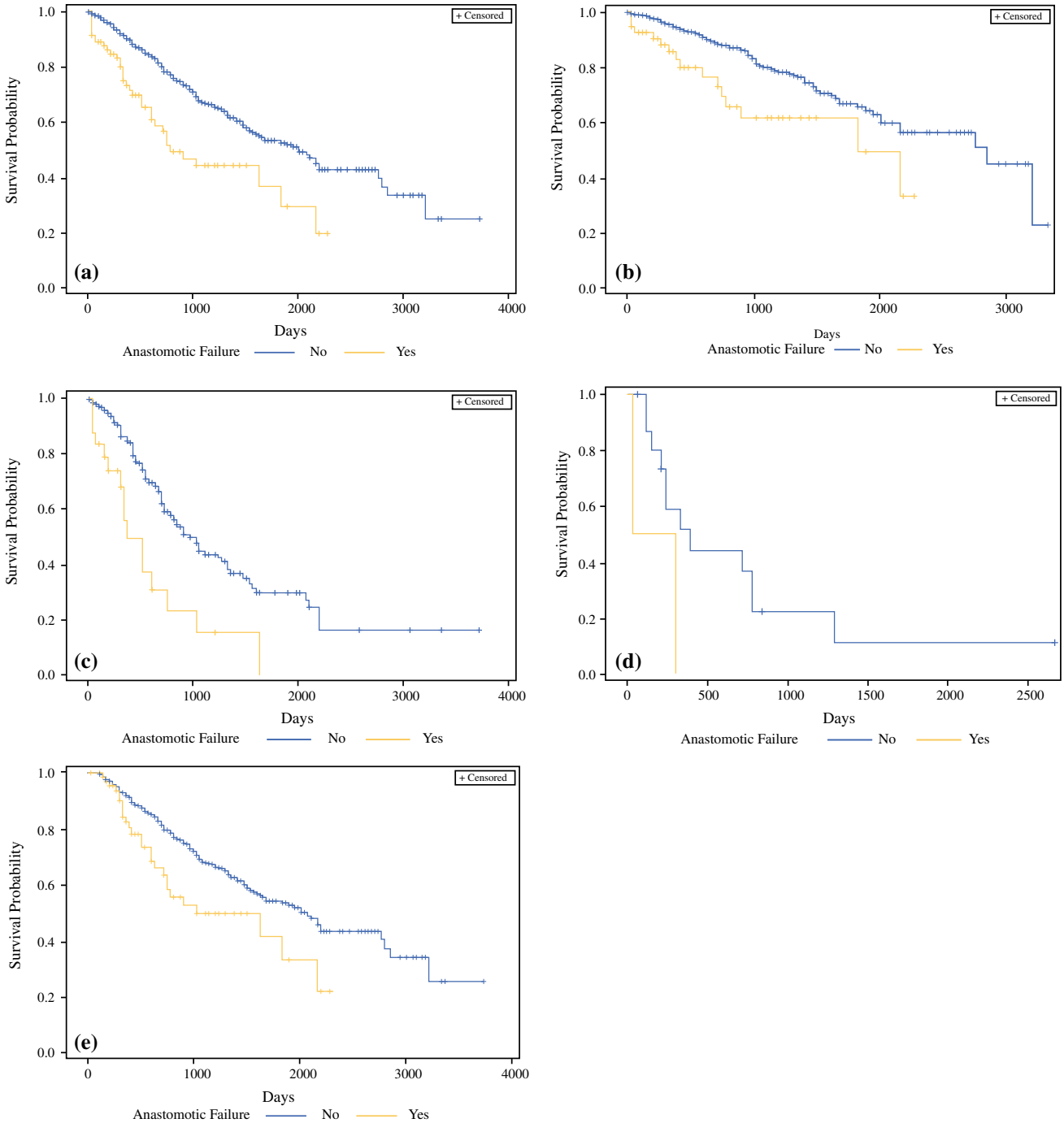

FIG. 2 a Overall survival of patients undergoing bowel resection and cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) stratified by incidence of anastomotic failure. ($p < 0.01$). **b** Overall survival of patients with appendiceal malignancies undergoing bowel resection and cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) stratified by incidence of anastomotic failure ($p < 0.01$). **c** Overall survival of patients with colorectal malignancies undergoing bowel resection and cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) stratified by incidence of anastomotic failure ($p < 0.01$). **d** Overall survival of patients with gastric malignancies undergoing bowel resection and cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) stratified by incidence of anastomotic failure ($p = 0.09$). **e** Overall survival of patients undergoing bowel resection and cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) stratified by incidence of anastomotic failure after exclusion of the patients who died within the first 90 days after surgery ($p < 0.01$)

TABLE 3 Multivariable Cox proportional hazards model of overall survival for patients undergoing a bowel resection and heated intraperitoneal chemotherapy for cancer

Variable	95% CI			
	HR	Lower	Upper	*p* value
Anastomotic failure	2.1	1.3	3.4	< 0.01
Histology (reference = appendiceal)				
Colorectal	2.7	1.9	3.9	< 0.01
Gastric	8.6	3.6	20.2	< 0.01
Small bowel	2.5	0.6	11.0	0.2
Peritoneal mesothelioma	1.2	0.6	2.8	0.6
Other	1.5	0.4	5.1	0.5

HR hazard ratio, *CI* confidence interval

During the American Society of Clinical Oncology meeting in 2018, Quenet et al.[7,22] presented preliminary findings of the Prodige 7–ACCORD 15 trial, which examined patients with peritoneal carcinomatosis of colorectal origin randomized to CRS with or without HIPEC. A comparison of digestive fistula between the HIPEC and non-HIPEC groups showed no difference in rates (10.5 vs 6.1%, nonsignificant difference). Driel et al.[23] studied HIPEC for ovarian cancer, in which 24% of the patients underwent a concomitant bowel resection. They found similar rates of gastrointestinal anastomotic leaks between the HIPEC and non-HIPEC groups (3% vs 2%).

The rate of AF in the current cohort was 8%, within the range reported in the literature (8% to 12%)[3–7] and reflective of contemporary outcomes across multiple institutions.[6,7] The three variables that were significant in the multivariable analysis for prediction of AF were male gender, left-sided colorectal resection, and preoperative serum albumin. Demonstration of male gender as a risk factor in anastomotic leak is not novel because prior studies have found an independent effect of male gender on anastomotic leak after colectomy.[24,25] Similar findings have been found among patients undergoing CRS-HIPEC.[3,6] The rationale for this phenomenon has been attributed to anatomic differences (more intraabdominal obesity, narrower pelvis),[3,24,25] hormonal differences that influence the intestinal microcirculation,[26] and possibly a higher rate of undiagnosed comorbidities.

Left-sided colon resection had the highest incidence of AF. The finding of distance from the anal verge is a recognized risk factor for the development of anastomotic dehiscence.[27,28] Decreases in serum albumin, a marker well described in the surgery literature for its association with postoperative morbidity,[29,30] and CRS-HIPEC[31] were found to be independently associated with AF. Because this marker was the only potentially modifiable factor identified, emphasizing preoperative nutrition and optimizing albumin levels may be an effective method of reducing AF.

Prior studies have had mixed reporting on the influence of number and location of anastomoses on associated morbidity. Franko et al.[32] investigated patients with carcinomatosis from a colorectal primary tumor treated with CRS-HIPEC and found that an increased risk of complications was associated with the number of intestinal anastomoses created. Chouliaras et al.[6] analyzed gastrointestinal leak after CRS-HIPEC and found that an increased number of anastomoses was associated with a higher rate of leak after surgery.

On the other hand, Roviello et al.[33] investigated the treatment of peritoneal carcinomatosis by CRS-HIPEC and did not find an association of visceral anastomosis with postoperative complications. Younan et al.[3] analyzed the risk factors for bowel complications with bowel anastomoses after peritonectomy and HIPEC and found that an increased number of anastomoses was not associated with postoperative bowel complications.

The results of the current study demonstrated that two or more anastomoses were associated with AF. However, this factor was no longer significant in the multivariable model. Further analysis in a prospective setting likely will provide better evidence on this interaction.

Although general guidelines exist for intraoperative strategies during of CRS-HIPEC, consensus is lacking on when to perform restorative anastomosis and which method to use.[8–11] Proponents for restorative anastomosis before perfusion rationalize that this provides ability to allow the viability of the anastomosis to be assessed after it has withstood perfusion. Others argue that exposure to chemotherapy and agitation may promote ultimate anastomotic breakdown.

Interestingly, operative technique did not influence rates of AF in the current study. For the decision whether to hand-sew or staple a restorative bowel anastomosis or whether to complete these maneuvers before or after HIPEC, the current data suggest no difference in the rates of AF. Given that adequately powered randomized controlled trials to investigate specific technical factors are unlikely, these data therefore help to assuage surgeon concern that anastomotic technique, when meticulous surgical principles are followed, can be left to surgeon preference and individual patient considerations.

The previously noted deleterious impact of AF on short- and long-term outcomes was confirmed in the current analysis. It is striking that AF was associated with a 90-day mortality rate of 16% and a median OS of just longer than

2 years. Perioperative care that emphasizes early identification, intervention, and avoidance of failure to rescue is critical to improving these outcomes.

The current study should be interpreted within the context of its limitations, most notably its retrospective design. In addition, although the multi-institutional nature of the study improved its statistical power and generalizability, the diagnosis and perioperative management of AF was not standardized. However, for the purposes of chart review, strict definitions of anastomotic leak and enteric fistula were uniformly used. Nevertheless, the classification of anastomotic leak and fistula still was subject to the retrospective interpretation of each individual institution. Similarly, given the inherent challenges of retrospective chart review in determining with certainty whether a gastrointestinal leak is secondary to an anastomotic breakdown versus unassociated bowel perforation, we elected to combine anastomotic leak and enteric fistula into a single composite outcome because these diagnoses likely represent the same clinical insult. Finally, several important variables and outcomes including preoperative practice patterns such as bowel preparation,[34] postoperative practices such as use of enhanced recovery pathways,[35] and timing of AF were not available, which limits the power of the current analysis.

CONCLUSIONS

In conclusion, among patients undergoing CRS-HIPEC for peritoneal surface malignancies, AF is independently associated with postoperative morbidity and worse long-term outcomes. Because patient- and tumor-related, but not technical, factors are associated with AF, operative technique may be individualized based on patient considerations and surgeon preference.

DISCLOSURE There are no conflicts of interest.

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