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Prognostic Factors and Significance of Gastrointestinal Leak After Cytoreductive Surgery (CRS) with Heated Intraperitoneal Chemotherapy (HIPEC)

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Abstract

Background—Gastrointestinal leak (GIL) after cytoreductive surgery with heated intraperitoneal chemotherapy (CRS/HIPEC) is associated with significant morbidity and mortality. This study aimed to identify GIL prognostic factors and its impact on overall survival.

Methods—A retrospective analysis of a prospectively maintained database comprising 1270 CRS/HIPEC procedures was performed. Type of GIL, functional and resection status, morbidity, mortality, and survival were reviewed.

Results—Gastrointestinal leaks were identified in 8.7% (110/1270) of CRS/HIPEC procedures, including 53 anastomotic leaks (4.2%), 53 hollow viscus perforations (4.2%), and four leaks at unknown sites. The multivariate predictors of leak were Eastern Cooperative Oncology Group (ECOG) functional status (ECOG 1 vs. 0: odds ratio [OR] 2.12, $p = 0.009$; ECOG 2 vs. 0: OR 2.90, $p = 0.004$), and number of anastomoses (OR 5.34; $p < 0.0001$). The in-hospital mortality rate for the GIL cohort was 21.8% (24/110), with a 72% (80/110) reoperation rate. The leak cohort had a higher major morbidity rate (88.3 vs. 23.3%; $p < 0.0001$), a longer hospital stay (39.0 vs. 9.9 days; $p < 0.0001$), and a longer intensive care unit (ICU) stay (7.7 vs. 1.7 days; $p = 0.0003$). After surgical mortality was excluded, the overall survival periods for the leak and no-leak patients with complete cytoreduction were respectively 1.5 and 4.98 years ($p = 0.0001$). Clinically significant decreases in survival were observed for all primary malignancies.

Conclusions—Gastrointestinal leak after CRS/HIPEC is a source of significant mortality, with a decrease in overall survival even after complete CRS. Preoperative functional status and number of anastomoses are predictors of leak for CRS/HIPEC patients.

Cytoreductive surgery with heated intraperitoneal chemotherapy (CRS/HIPEC) has emerged as the treatment method of choice for epithelial malignancies with limited intraperitoneal spread. In experienced peritoneal surface disease (PSD) centers, the operation currently is

performed with morbidity and mortality directly comparable with the morbidity and mortality reported for surgical oncology procedures of similar extent.¹

The outcome after CRS/HIPEC depends on type of primary malignancy, volume of peritoneal disease, completeness of cytoreduction, and functional status of the patient.^{2,3} However, it is unknown whether chemoperfusion contributes to the severity of common surgical complications, such as gastrointestinal leak (GIL). The impact of GIL on overall survival of PSD patients also is not well defined.

The primary aims of this study were to identify predictors of gastrointestinal leak in CRS/HIPEC patients and its impact on surgical outcomes and to determine the impact of GIL on overall survival of patients who have achieved a complete CRS.

METHODS

A retrospective analysis of a prospectively maintained database comprising 1270 CRS/HIPEC procedures from 1991 to 2015 was performed. The data abstracted included age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, type of primary malignancy, pre-HIPEC chemotherapy, intraperitoneal chemotherapy agent, comorbidities, preoperative albumin, R (completeness of resection) status, total number of organs resected, Peritoneal Cancer Index (PCI) score,⁴ estimated blood loss (EBL), and prior Surgical Score (PSS).⁵ Data specific to the occurrence of a leak were obtained through chart review and included imaging methods, operative reports, IR drain placement, diversion, timing of the leak, number of anastomoses, and performance of handsewn or stapled anastomosis.

Gastrointestinal leak (GIL) was defined as a leak from the upper or lower gastrointestinal tract and was further subdivided into anastomotic leaks and perforations. Anastomotic leak was defined as a leak from a connection site between two portions of the gastrointestinal tract. Perforation was defined as a leak from sites away from an anastomosis as a result of tumor implant resection in the form of wedge resection, cauterization, or tangential excision. Cases with bile, ureteral, bladder, or pancreatic leaks were excluded from this analysis.

The CRS/HIPEC procedure was performed with the closed technique as previously described by our group.⁶ The R0 and R1 resections were analyzed together as complete cytoreductions, whereas CRS with residual macroscopic disease was characterized as R2. Morbidity and mortality were graded on the basis of the Clavien–Dindo classification.⁷

Institutional review board approval was obtained.

Descriptive statistics including frequencies and percentages for categorical data, means, and standard deviations for continuous outcomes were calculated for all the study variables. The Kaplan–Meier method was used to estimate survival and standard errors, and the multivariate Cox model was performed for the patient who leaked. Survival of the overall population was investigated, and separate investigations were performed to obtain the survival data for the different primary malignancies. Statistical analyses were performed using SPSS 19 (SPSS, Inc., Chicago, IL, USA) and SAS 9.2 (SAS Institute) software.

RESULTS

Cohort Characteristics

During the study period, 8.7% (110/1270) of cases with GIL were identified. These cases included 53 anastomotic leaks (4.2%), 53 hollow viscus perforations (4.2%), and four leaks from a site not specified in the records. Patients with GIL were more often males ($p = 0.01$) with poorer ECOG performance status ($p < 0.0001$), incomplete cytoreduction ($p = 0.0002$), and a colorectal resection ($p < 0.0001$). The groups were similar in terms of the primary sites and agent of chemoperfusion. Appendiceal tumors were the most prevalent, with 504 identified as low grade (39.7%) and 137 identified as high grade (10.8%). “Other” included a heterogeneous group such as small bowel tumors; sarcomas; pancreatic, gallbladder, urachal, adrenal, liver tumors, gynecologic and unknown primary malignancies (Table 1).

Anastomoses

The mean number of anastomoses in the leak group was 1.14 (125 anastomoses in total), with 52 patients (47.3%) having one, 24 patients (21.8%) having two, 7 patients (6.4%) having three, 1 patient (0.9%) having four, and 26 patients (23.6%) having no anastomoses. These patients included 54 (49.1%) with stapled anastomoses, 17 (15.5%) with hand-sewn anastomoses, 13 (11.8%) with a combination of stapled and hand-sewn anastomoses, and 26 (23.6%) with no anastomoses. The anastomoses included 40 small bowel-to-colon/rectum anastomoses (36.4%), 14 small bowel-to-small bowel anastomoses (12.7%), 5 colo-colonic anastomoses (4.5%), and 22 combinations of the aforementioned anastomoses (20%).

A gastric leak occurred in 21 patients (19.1%). Of these, 3 patients (14.3%) had a Billroth I reconstruction, 3 patients (14.3%) had a Billroth II reconstruction, 3 patients (14.3%) had an esophagojejunal anastomosis, 3 patients (14.3%) had a gastrojejunal anastomosis, 1 patient (4.8%) had a stapled partial gastrectomy, 1 patient (4.8%) had a gastrostomy, and 7 patients (33.3%) had no formal gastric resection. The type of anastomosis was not found to be statistically significant in the univariate analysis.

When we dichotomized the institutional experience between the first 15 years and the last 10 years, the leak rate was found to be similar (respectively, 9.6% [41/426] and 8.2% [69/844]; $p = 0.40$).

Timing and Management of Leak

The median time for diagnosis of a leak was 10 days (interquartile range [IQR], 8 days). Nonsurgical management of a leak with imaging-guided drains was attempted in 31 cases (28.2%). This was successful in avoiding operative therapy for the leak in 19 (62.3%) of these cases. However, 12 (38.7%) of these 31 cases had to return to the operating room for definitive surgical management.

Surgical management of a leak was required in 80 (72.7%) of cases, with 27 patients (24.5%) requiring diverting stomas. Another 11 patients (10%) were medically managed with bowel rest and total parenteral nutrition (TPN) only.

Predictors of Leak

Univariate analysis identified male sex ($p = 0.01$), ECOG functional status ($p < 0.001$), extent of cytoreduction as captured by the number of resected organs ($p < 0.001$), number of anastomoses ($p < 0.001$), preoperative albumin level ($p = 0.03$), and estimated blood loss (EBL) ($p < 0.001$) to be predictors of a leak. A multivariable logistic regression analysis was performed to identify independent predictors of GIL, including the statistically significant variables from the univariate analysis. The factors that remained significant were ECOG status of 1 versus 0 (OR 2.12; $p = 0.009$), ECOG status of 2 versus 0 (OR 2.90; $p = 0.004$), and number of anastomoses (OR 5.34; $p < 0.001$) (Table 2).

Surgical Outcomes

In the leak cohort, higher major morbidity (grades 3 and 4) (88.3 vs. 23.3%; $p < 0.0001$), longer hospital stay (39.0 vs. 9.9 days; $p < 0.0001$), and longer intensive care unit (ICU) stay (7.7 vs. 1.70 days; $p = 0.0003$) were found. The observed mortality rate in the leak cohort was 21.8% (24/110).

A multivariable Cox model of analysis was performed to identify predictors of mortality after a gastrointestinal leak. Gastric primary malignancies (OR 10.21; $p = 0.008$) and ECOG status of 2 or higher (ECOG 2: OR 3.40; $p = 0.0309$; ECOG 3: OR 36.29; $p < 0.0001$) were shown to be independent predictors of mortality for the leak group only. Sex ($p = 0.92$), colon primary malignancy ($p = 0.42$), mesothelioma ($p = 0.33$), ovarian primary malignancy ($p = 0.07$), pre-HIPEC chemotherapy ($p = 0.07$), ECOG status of 1 ($p = 0.75$), resection status ($p = 0.31$), number of anastomoses ($p = 0.40$), preoperative body mass index (BMI) ($p = 0.77$), preoperative albumin ($p = 0.48$), length of ICU stay ($p = 0.70$), and prior Surgical Score (1: $p = 0.32$; 2: $p = 0.47$; 3: $p = 0.37$) were not predictive of mortality after a leak (Table 3).

Impact of Gastrointestinal Leak on Survival

In a multivariable Cox proportional hazards regression model, the factors found to be associated with decreased survival after a gastrointestinal leak were pre-HIPEC systemic chemotherapy (hazard ratio [HR] 1.80; $p < 0.0001$), ECOG functional status higher than 0 (1: HR 1.28, $p = 0.009$; 2: HR 1.86, $p < 0.0001$), and R2 status of resection (HR 2.62; $p < 0.0001$), whereas gastric cancer exhibited the worst survival among all primary malignancies after a leak (HR 4.84; $p < 0.0001$). Lower preoperative BMI (HR 0.99; $p = 0.003$) and prior surgical score of 1 (HR 0.74; $p = 0.01$) were associated with improved survival after a leak (Table 4).

After surgical mortality was excluded, the overall survival periods for all the leak and no-leak patients were respectively 1.5 and 4.98 years ($p = 0.0001$). The patients with complete R0/R1 macroscopic CRS who experienced a leak after CRS/HIPEC, regardless of primary malignancy, showed a decreased median overall survival period of 1.63 years compared with 3.12 years in the no-leak group ($p = 0.0007$) (Fig. 1). When survival was studied on the basis of the same primary malignancy and complete R0/R1 macroscopic cytoreduction, after exclusion of surgical mortality, all primary malignancies exhibited clinically worse overall survival after a leak, including appendiceal tumor (1.58 vs. 3.06 years; $p = 0.89$), colon

tumor (1.52 vs. 2.98 years; $p = 0.19$), and gastric tumor (0.48 vs. 0.93 years; $p = 0.31$), with ovarian primary malignancies also reaching statistical significance (2.22 vs. 4.69 years; $p = 0.02$).

DISCUSSION

Resection of limited peritoneal disease has taken on increasing importance in light of impressive data for CRS/HIPEC. However, there are lingering concerns regarding the morbidity attendant to the procedure, and gastrointestinal leaks are a feared complication. Gastrointestinal leak after CRS/HIPEC often results in loss of functional status, reduces the ability to mount an immune response, and can delay systemic chemotherapy, with a potentially detrimental effect on survival.

The primary aim of this study was to identify predictors of gastrointestinal leak in CRS/HIPEC patients and its impact on surgical outcomes. The incidence of gastrointestinal leak in the studied cohort was 8.7%, with reported rates in the literature ranging widely between 5 and 34%.^{8–11} The median time for manifestation of a leak was 10 days, considerably longer than the 5 days described for non-HIPEC colorectal procedures.¹² This may have been related to an adverse effect on anastomotic healing from heated intraperitoneal chemotherapy or possibly a late chemotherapy effect on cytoreduced bowel implants. Therefore, given the late presentation of a post-HIPEC gastrointestinal leak, a high index of suspicion needs to be maintained well into the postoperative period to achieve early identification and initiation of treatment.

Predictors of leak in this analysis were found to be the functional status of the patient and the number of anastomoses.^{8,13} Therefore, during cytoreduction, it may be more advantageous to sacrifice additional short lengths of bowel than to risk more than one anastomoses. We were surprised to find that in this analysis, the PCI score was not a predictor of GIL, unlike previous reports in the literature.¹⁴ Although the number of anastomoses was predictive of a leak, 50% of the leak events in the studied cohort were not due to an anastomosis, but rather to late perforations. Therefore, patients with scattered bowel involvement who require resection of multiple bowel implants to achieve a complete CRS are equally prone to the development of a leak even without anastomosis. This should be taken into consideration and specifically looked for during any reexploration of the patient. Isolated resection of small bowel lesions should not be attempted unless a complete CRS is feasible.

Gastrointestinal leak after HIPEC is associated with a 22% mortality rate, similar to the 20% mortality rate described after leak in colorectal procedures not followed by chemoperfusion.¹⁵ In our study, gastric resection was associated with increased mortality, as previously reported by Bartlett et al.¹⁶ We currently perform CRS/HIPEC for gastric cancer only if the PCI score is lower than six, if peritoneal lavage is positive, or after extensive upfront chemotherapy is performed without progression. The 72% reoperation rate, 90% major morbidity rate, and extended hospital stay all underscore the importance of performing CRS/HIPEC procedures in tertiary facilities with multiple layers of available

resources. The importance of intensive attentive postoperative care is most clear for these patients.

Gastrointestinal leak was significant for decreased overall survival only in the univariate analysis ($p = 0.0008$) and not in the multivariate analysis ($p = 0.3$). This possibly may have been due to inclusion of different primary malignancies with markedly different biologic behaviors. More specifically, the majority were low-grade appendiceal primary tumors. Patients with these tumors demonstrate a much less aggressive biologic behavior that often allows for the effects of a leak on prognosis to be ameliorated. Therefore, the impact of gastrointestinal leak on overall survival after CRS/HIPEC was evaluated for patients with the same primary tumor who achieved a complete CRS, after exclusion of surgical mortality. Specifically, all completely cytoreduced primary tumors studied showed nearly a 50% reduction in survival compared with complete CRS patients who had no leak.

Although the current study analyzed a large cohort of patients, it was not free of the inherent limitations of a single-institution retrospective review incorporating data collected during 25 years. Selection bias has played a role in the reported outcomes due to evolution of our selection criteria as a result of accumulated institutional experience. In addition, despite the volume of available data, subgroup analysis suffered from low power. Furthermore, most of the patients with poor performance status underwent surgery early in the experience, and we no longer offer CRS/HIPEC to patients with an ECOG performance status of three or higher. Patients with an ECOG of two also should be selected cautiously on a case-by-case basis, depending on their comorbidities as well as their tumor burden and type of primary.

Determining when to perform CRS/HIPEC for patients with peritoneal dissemination requires a complex multi-disciplinary approach that considers the tolerability and efficacy of systemic chemotherapy. To minimize the risk of GIL, any preoperative chemotherapy should be delivered to decrease the PCI score and optimize the likelihood of a complete cytoreduction. However, it should not be administered to the detriment of the patient's performance status because the ECOG status is strongly linked to the risk of major morbidity and GIL. The value of open and regular communication between medical and surgical oncologists is clear in this regard. We typically suggest no more than six cycles of first-line therapy before CRS/HIPEC if the disease appears to be amenable to complete cytoreduction. It is worth noting that preoperative chemotherapy was associated with decreased survival, but likely represents a surrogate for worse tumor biology.

In conclusion, gastrointestinal leak after CRS/HIPEC is associated with significant mortality, morbidity, prolonged hospital stay, and use of resources. Survival for patients who have experienced a leak after CRS/HIPEC is inferior to that for their non-leak counterparts even when complete macroscopic cytoreduction has been achieved.

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References

1. Levine EA, Stewart JH, Shen P, Russell GB, Loggie BL, Votanopoulos KI. Intraperitoneal chemotherapy for peritoneal surface malignancy: experience with 1000 patients. *J Am Coll Surg.* 2014; 218:573–85. [PubMed: 24491244]
2. Glockzin G, Schlitt HJ, Piso P. Peritoneal carcinomatosis: patients selection, perioperative complications, and quality of life related to cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *World J Surg Oncol.* 2009; 8:1–8.
3. Ihemelandu CU, Mcquellon R, Shen P, Stewart JH, Votanopoulos K, Levine EA. Predicting postoperative morbidity following cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CS + HIPEC) with preoperative FACT-C (Functional Assessment of Cancer Therapy) and patient-rated performance status. *Ann Surg Oncol.* 2013; 20:3519–26. [PubMed: 23748607]
4. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. *Cancer Treat Res.* 1996; 82:359–74. [PubMed: 8849962]
5. Sugarbaker, PH. Technical Handbook for the Integration of Cytoreductive Surgery and Perioperative Intraperitoneal Chemotherapy Into the Surgical Management of Gastrointestinal and Gynecologic Malignancy. 4. Grand Rapids; The Ludann Company: 2005.
6. Levine EA, Iv JHS, Russell GB, Geisinger KR, Loggie BL, Shen P. Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy for peritoneal surface malignancy: experience with 501 procedures. *J Am Coll Surg.* 2007; 204:943–53. [PubMed: 17481516]
7. Dindo D, Demartines N, Clavien P. Classification of surgical complications. *Ann Surg.* 2004; 240:205–13. [PubMed: 15273542]
8. Younan R, Kusamura S, Baratti D, et al. Bowel complications in 203 cases of peritoneal surface malignancies treated with peritonectomy and closed-technique intraperitoneal hyperthermic perfusion. *Ann Surg Oncol.* 2005; 12:910–8. [PubMed: 16177862]
9. Sugarbaker PH. Cytoreduction including total gastrectomy for pseudomyxoma peritonei. *Br J Surg.* 2002; 89:208–12. [PubMed: 11856136]
10. Elias D, Gilly F, Boutitie F, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. *J Clin Oncol.* 2009; 28:63–8. [PubMed: 19917863]
11. Glehen O, Gilly FN, Boutitie F, et al. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. *Cancer.* 2010; 116:5608–18. [PubMed: 20737573]
12. Damrauer SM, Bordeianou L, Berger D. Contained anastomotic leaks after colorectal surgery: are we too slow to act? *Arch Surg.* 2009; 144:333–8. [PubMed: 19380646]
13. Desantis M, Bernard JL, Casanova V, et al. Morbidity, mortality, and oncological outcomes of 401 consecutive cytoreductive procedures with hyperthermic intraperitoneal chemotherapy (HIPEC). *Langenbecks Arch Surg.* 2015; 400:37–48. [PubMed: 25319432]
14. Saxena A, Yan TD, Morris DL. Critical assessment of preoperative and operative risk factors for complications after iterative peritonectomy procedures. *Eur J Surg Oncol.* 2010; 36:309–14. [PubMed: 19615849]
15. Thornton M, Joshi H, Vimalachandran C, Heath R, Carter P, Gur U, Rooney P. Management and outcome of colorectal anastomotic leaks. *Int J Colorectal Dis.* 2011; 26:313–20. [PubMed: 21107847]
16. Bartlett EK, Meise C, Roses RE, Fraker DL, Kelz RR, Karakousis GC. Morbidity and mortality of cytoreduction with intraperitoneal chemotherapy: outcomes from the ACS NSQIP database. *Ann Surg Oncol.* 2014; 21:1494–500. [PubMed: 23990289]

FIG. 1.

Overall survival after cytoreductive surgery with heated intraperitoneal chemotherapy (CRS/HIPEC) stratified by the presence or absence of leak (R0/R1 resections only). $p = 0.0008$

TABLE 1

Clinicopathologic characteristics of study groups

	Overall <i>n</i> (%)	No leak (<i>n</i> = 1160) <i>n</i> (%)	Leak (<i>n</i> = 110) <i>n</i> (%)	<i>P</i> value
Sex				
Female	689 (54.3)	642 (55.4)	47 (42.7)	0.01
Male	579 (45.7)	516 (44.6)	63 (57.3)	
Primary tumor				
Appendiceal	641 (50.7)	579 (50.2)	62 (56.4)	0.73
Colon	289 (22.9)	267 (23.1)	22 (20)	
Gastric	49 (3.9)	44 (3.8)	5 (4.6)	
Mesothelioma	93 (7.4)	85 (7.4)	8 (7.3)	
Ovarian	80 (6.3)	76 (6.6)	4 (3.6)	
Other	112 (8.9)	103 (8.9)	9 (8.2)	
ECOG status				
0	607 (47.8)	578 (49.8)	29 (26.4)	<0.0001
1	487 (38.4)	436 (37.6)	51 (46.4)	
2	138 (10.9)	112 (9.7)	26 (23.6)	
Resection status				
0 or 1	622 (48.9)	587 (50.6)	35 (31.8)	0.0002
2	648 (51)	573 (49.4)	75 (68.2)	
Colon/rectum resection	651 (51.3)	569 (49)	82 (74.6)	<0.0001
Small bowel resection	437 (34.4)	385 (33.2)	52 (47.3)	0.003
Mitomycin	1015 (79.9)	929 (80.1)	86 (78.2)	0.63
Mitoxantrane	27 (2.1)	24 (2.1)	3 (2.7)	0.65
Carboplatin	45 (3.5)	41 (3.5)	4(3.6)	0.96
Oxaliplatin	150 (11.8)	132 (11.4)	18 (16.4)	0.12
Cisplatin	64 (5)	60 (5.2)	4 (3.6)	0.48

ECOG Eastern Cooperative Oncology Group

TABLE 2

Predictive factors of leak: uni- and multivariate analyses

	Univariate			Multivariate (based on univariate)		
	OR	95% CI	P value	OR	95% CI	P value
Male sex	1.67	1.12–2.48	0.01	0.98	0.6–1.59	0.93
Primary tumor						
Appendiceal	Ref					
Colon	0.77	0.46–1.28	0.31			
Gastric	1.06	0.41–2.78	0.90			
Mesothelioma	0.88	0.41–1.9	0.74			
Ovarian	0.49	0.17–1.39	0.18			
Other	0.82	0.39–1.69	0.59			
Pre-HIPEC chemotherapy	1.24	0.84–1.83	0.29			
ECOG status						
0	Ref					
1	2.33	1.45–3.74	<0.001	2.12	1.21–3.74	0.009
2	4.63	2.63–8.16	<0.001	2.90	1.42–5.91	0.004
Resection status						
0 or 1	Ref					
2	2.20	1.45–3.33	<0.001	1.28	0.76–2.16	0.35
No. of resected organs	1.29	1.18–1.4	<0.001	1.10	0.99–1.22	0.06
PCI	0.99	0.97–1.01	0.33			
EBL	1.44	1.18–1.75	<0.001	1.007	0.76–1.34	0.96
No. of anastomoses	6.32	4.73–8.46	<0.001	5.34	3.92–7.29	<0.001
Preoperative albumin	1.21	1.02–1.43	0.03	0.85	0.66–1.09	0.19
HIPEC age	1.01	0.99–1.02	0.39			
Prior surgical score						
0	Ref					
1	1.11	0.64–1.94	0.71			
2	1.44	0.87–2.38	0.16			
3	1.52	0.66–3.51	0.33			

	Univariate			Multivariate (based on univariate)		
	OR	95% CI	P value	OR	95% CI	P value
No of comorbidities	0.91	0.60–1.37	0.65			
Smoking	1.46	0.97–2.21	0.07	1.58	0.97–2.60	0.07

OR odds ratio, CI confidence interval, HIPEC hyperthermic intraperitoneal chemotherapy, ECOG Eastern Cooperative Oncology Group, PCI peritoneal carcinomatosis index, EBL estimated blood loss

TABLE 3

Predictors of surgical mortality after a leak multivariable Cox model for the leak group

	HR	95% CI	P value
Sex			
Female	Ref		
Male	1.046	0.42–2.63	0.92
Primary tumor			
Appendiceal	Ref		
Colon	1.47	0.58–3.75	0.42
Gastric	10.21	1.83–56.87	0.008
Mesothelioma	1.85	0.54–6.36	0.33
Ovarian	3.81	0.89–16.32	0.07
Other	16.41	3.20–84.09	<0.001
Pre-HIPEC Chemotherapy			
No	Ref		
Yes	1.97	0.95–4.09	0.07
ECOG status			
0	Ref		
1	1.14	0.51–2.56	0.75
2	3.40	1.12–10.30	0.03
Resection status			
0 or 1	Ref		
2	1.67	0.69–4.06	0.31
No. of anastomoses	0.84	0.59–1.18	0.40
Preoperative BMI	1.01	0.97–1.05	0.77
Preoperative albumin	0.84	0.52–1.37	0.48
Length of ICU Stay	1.01	0.98–1.03	0.70
Prior surgical score			
0	Ref		
1	1.58	0.64–3.93	0.32
2	1.43	0.54–3.83	0.47
3	0.40	0.05–3.01	0.37

HR hazard ratio, *CI* confidence interval, *HIPEC* hyperthermic intraperitoneal chemotherapy, *ECOG* Eastern Cooperative Oncology Group, *BMI* body mass index, *ICU* intensive care unit

TABLE 4

Predictors of overall survival

	Univariate models			Multivariate models ^a		
	HR	95% CI	P value	HR	95% CI	P value
Male sex	1.24	1.06–1.45	0.008	1.11	0.93–1.33	0.236
Primary tumor						
Appendiceal	Ref					
Colon	2.42	1.99–2.95	<0.0001	2.35	1.87–2.95	<0.0001
Gastric	5.16	3.68–7.24	<0.0001	4.84	3.41–6.88	<0.0001
Mesothelioma	1.67	1.22–2.29	0.001	1.51	1.09–2.08	0.013
Ovarian	1.83	1.35–2.49	<0.0001	1.83	1.31–2.55	0.0004
Other	2.46	1.89–3.2	<0.0001	2.98	2.26–3.93	<0.0001
Pre-HIPEC chemo	2.10	1.78–2.47	<0.0001	1.80	1.49–2.18	<0.0001
ECOG status						
0	Ref					
1	1.78	1.49–2.13	<0.0001	1.28	1.06–1.54	0.009
2	2.70	2.12–3.44	<0.0001	1.86	1.44–2.4	<0.0001
Resection status						
0 or 1	Ref					
2	2.38	2.01–2.81	<0.0001	2.62	2.18–3.14	<0.0001
No. of resected organs	1.03	0.99–1.07	0.082			
PCI	1.00	0.99–1.01	0.898			
EBL	1.10	0.99–1.20	0.062			
No. of anastomoses	1.28	1.14–1.44	<0.0001	1.13	0.97–1.31	0.113
Preoperative BMI	0.98	0.98–0.99	<0.0001	0.99	0.98–1.00	0.003
Preoperative albumin	0.86	0.81–0.92	<0.0001	0.95	0.89–1.02	0.157
Length of ICU stay	1.02	1.01–1.03	0.003	1.00	0.99–1.02	0.650
HIPEC age	1.00	0.99–1.01	0.3			
Leak	1.61	1.22–2.11	0.0008	1.20	0.85–1.71	0.306
Prior surgical score						
0	Ref					

Univariate models			Multivariate models ^a		
	HR	95% CI	P value	HR	95% CI
1	0.62	0.49–0.77	<0.0001	0.74	0.59–0.93
2	0.71	0.57–0.87	0.001	0.81	0.64–1.02
3	0.85	0.6–1.19	0.336	1.02	0.71–1.46
No. of comorbidities	1.04	0.88–1.23	0.663		

HR hazard ratio, CI confidence interval, HIPEC/hyperthermic intraperitoneal chemotherapy, ECOG Eastern Cooperative Oncology Group, PCI peritoneal carcinomatosis index, EBL estimated blood loss, BMI body mass index. ICU/intensive care unit

^aSelected variables with *p* values less than 0.1 for model