ORIGINAL ARTICLE

The risk factors for gastrointestinal anastomotic leak after cytoreduction with hyperthermic intraperitoneal chemotherapy

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ABSTRACT

BACKGROUND: Gastrointestinal anastomotic leak (GAL) is a major cause of morbidity and mortality after cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). The aim of this study is to determine the risk factors associated with GAL in peritoneal metastases (PM) surgery.

METHODS: Patients who underwent CRS and HIPEC with gastrointestinal anastomosis were included. Charlson Comorbidity Index (CCI) and Eastern Cooperative Oncology Group (ECOG) performance status were used to assess preoperative condition of the patients. GAL was recorded as gastrointestinal extralumination diagnosed clinically, radiologicaly, or during reoperation.

RESULTS: Among 362 patients who were analyzed, the median age was 54 years, 72.6% were female, and the most common histopathologies were ovarian cancer (37.8%) and colorectal (36.2%) cancer. The median Peritoneal Cancer Index was 11 and 80.1% of the patients underwent complete cytoreduction. A single anastomosis was performed in 293 (80.9%) patients, two anastomoses in 51 (14.1%) and three anastomoses in 18 (5%) patients. Diverting stoma was performed in 43 (11.8%) patients. GAL was seen in 38 (10.5%) patients. Smoking (p<0.001), ECOG performance status (p=0.014), CCI score (p=0.009), pre-operative albumin level (p=0.010), and number of resected organs (p=0.006) were significantly associated factors with GAL. Independent risk factors for GAL were smoking (Odds Radio [OR]: 6.223, confidence interval [CI]: 2.814–13.760; p<0.001), CCI score ≥7 (OR: 4.252, CI: 1.590–11.366; p=0.004), and pre-operative albumin level ≤3.5 g/dl (OR: 3.942, CI: 1.534–10.130; p=0.004).

CONCLUSION: Patient-related factors such as smoking, comorbidity, and pre-operative nutritional status had an impact on anastomotic complications. Proper patient selection and prediction of an index patient requiring a prehabilitation program with a high level of care are essential prerequisites to obtaining lower anastomotic leak rates and improving outcomes in PM surgery.

Keywords: Anastomotic leak; cytoreductive surgery; hyperthermic intraperitoneal chemotherapy; peritoneal metastasis.

INTRODUCTION

Peritoneal metastasis (PM) is often considered as an end-stage disease. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as the only potentially curative treatment of PM. Favorable survival and even cure in carefully selected patients have been reported in several studies.[1,2] CRS with HIPEC which encovers multivisceral resections and peritonectomy procedures, prolonged operative time, hemodynamic alterations, and potential toxicity of chemotherapy is a high-risk complex cancer surgery. Today, in experienced and certified peritoneal sur-

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face malignancy centers, the morbidity and mortality of CRS and HIPEC are similar to those of other major gastrointestinal operations.[3,4] Gastrointestinal anastomotic leak (GAL) is one of the most dreadful complication with reported rates of 8–12% in the literature.[5–10] The effect of HIPEC on anastomosis and the predictive factors for GAL has not been well-established yet. The aim of this study was to determine the risk factors for anastomotic leak after CRS and HIPEC in the multimodal treatment of PM.

MATERIALS AND METHODS

Study Design and Patients

All procedures performed in this study were in accordance with the ethical standards of the Institutional and National Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Local Ethics Committee. All the patients gave their written consent both for the surgery and participation to the study.

A prospectively collected database of 664 CRS and HIPEC procedures performed in a Peritoneal Surface Malignancy Center at Istanbul Medipol University Hospital between April 2007 and April 2020 was reviewed. Patients from all primary tumor origins were evaluated for eligibility. Patients older than 18 years old and who had at least one gastrointestinal anastomosis during CRS were included in the study. Patients without gastrointestinal anastomosis and with missing data were excluded from the study (Fig. 1). The interval between last chemotherapy dose and surgery was at least 4 weeks in patients who received neoadjuvant treatment. Comorbidities were assessed by the Charlson Comorbidity Index (CCI).[11] Patient performance was assessed according to the Eastern Cooperative Oncology Group (ECOG) performance scale which was prospectively recorded.

Surgery

CRS was performed by the same dedicated surgical team. Mechanical bowel preparation and venous thromboembolism prophylaxis were given to all of the patients. Intravenous antibiotics (cefuroxime axetil and metronidazole) were administered 30 min before incision and repeated in every 3 h. Extent of the disease was assessed by peritoneal carcinomatosis index (PCI).[12] The aim of CRS was to achieve complete eradication of the macroscopic tumor burden. Palliative interventions (stoma formation, by-pass, and/or debulking) were performed when complete cytoreduction was not anticipated and these patients were excluded from the analysis. Peritonectomy was performed on only involved surface except for peritoneal mesothelioma. Anastomosis was performed by linear or circular double-stapled technic before HIPEC. "Completeness of Cytoreduction" (CC) classification (no residual disease: CC-0, residual disease <2.5 mm: CC-1, residual disease of 2.5 mm–2.5 cm: CC-2 and residual disease >2.5 cm: CC3) was used to score residual disease.[13]

Diverting stoma was performed at surgeon's discretion as occasion requires. Unless there were no strict criteria for performing stoma, the well-known indications including neoadjuvant radiotherapy and/or chemotherapy, distal rectal anastomosis, poor nutritional status, poor ECOG performance, and prolonged operative duration were taken notice of.

HIPEC

After CRS, two inflow (one was in the pelvis and the other in the subhepatic area) and two outflow drains and two thermal probes were positioned in the abdominal cavity and HIPEC was delivered by a perfusion system device (The Belmont® Rapid Infuser RI-2, MA, USA) with the closed abdominal technique. The chemotherapeutic agents were decided on our MDT individually for every patient. Oxaliplatin (400 mg/

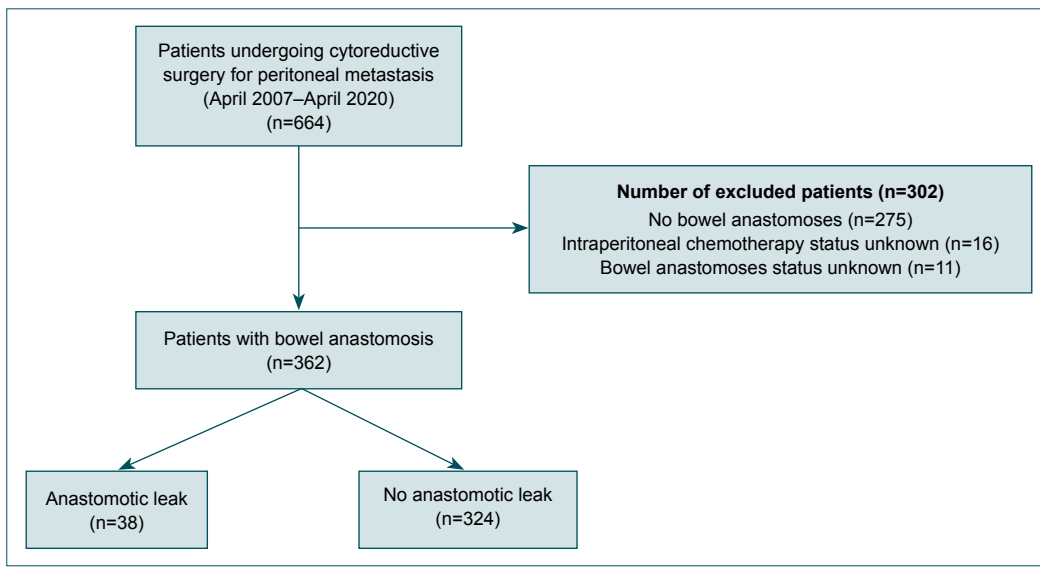

Figure 1. Flowchart of patient selection to study.

m^2, 30 min) or Mitomycin-C (10 mg/m^2, 90 min) and/or Cisplatin (75 mg/m^2, 90 min) were administered at a constant temperature of 42.5°C. Patients did not receive concurrent intravenous chemotherapy.

Post-operative Period and Evaluation of Complications

Patients who had pre-operative nutritional deficiency and/or post-operative delayed oral feeding due to prolonged ileus or complications received parenteral and/or enteral nutritional support. Intravenous antibiotics have been administered until post-operative day 3 in patients with enterotomy.

"Common Terminology Criteria for Adverse Events" criteria were used to classify complications and HIPEC toxicity.[14] GAL was defined as the clinical, radiological, or surgical detection of extralumination of intestinal contents from anastomotic sites into the abdominal cavity. Clinically, the presence of intestinal contents in surgical drains, percutaneous drains or at the suture line; radiologically, the fluid collection and/or presence of extraluminal air around anastomosis, and extralumination of contrast material into the abdominal cavity were recorded as anastomotic leakage. The detection of intestinal contents in the peritoneal cavity from anastomotic defects during reoperation was accepted as the surgical diagnosis of anastomotic leakage. Perforations from gastrointestinal tract away from an anastomosis and biliary, urinary, or pancreatic leaks were not considered as GAL. Death within 90 days after surgery and in-hospital mortality was recorded as perioperative mortality.

Statistical Analysis

Continuous variables were expressed as means and range and categorical variables as frequency and percentages. Association between categorical variables and GAL was determined with the Chi-square. Association between continuous variables and GAL was tested by independent samples t test. Association between non-parametric variables and GAL was tested by Mann–Whitney U test. P<0.05 was defined as statistically significant. Logistic regression analysis was used to identify risk factors in multivariate analysis.

Table 1. Clinical and demographic characteristics of the patients

	n=362 (%)	GAL		p*
		(-) n=324 (%)	(+) n=38 (%)	
Gender				0.880
Female	263 (72.6)	235 (89.4)	28 (10.6)	
Male	99 (27.3)	89 (89.9)	10 (10.1)	
Age (year, mean±SD)	54.3±13.7	54.1±13.8	56.2±12.1	0.357
BMI (kg/m^2, mean±SD)	28.4±14.2	28.4±14.8	28.3±5.3	0.966
Smoking (+)	89 (24.6)	68 (76.4)	21 (23.6)	<0.001
Origin				0.935
Ovarian	173 (37.8)	121 (88.3)	16 (11.7)	
Colorectal	131 (36.2)	117 (89.3)	14 (10.6)	
Appendix	43 (11.9)	39 (90.7)	4 (9.3)	
Gastric	21 (5.8)	19 (90.5)	2 (9.5)	
Peritoneal Malign Mesothelioma	15 (4.1)	14 (93.3)	1 (6.7)	
Other	15 (4.1)	14 (93.4)	1 (6.6)	
CCI				0.009
<7	137 (37.8)	130 (94.9)	7 (5.1)	
≥7	225 (62.2)	194 (86.2)	31 (13.8)	
ECOG score				0.014
0	172 (47.5)	160 (93)	12 (7)	
1	156 (43.1)	138 888.5)	18 (11.5)	
2	34 (9.4)	26 (76.5)	8 (23.5)	
Preoperative albumin (g/dl, mean±SD)	3.7±0.6	3.8±0.6	3.5±0.6	0.010
Neoadjuvant chemotherapy (+)	223 (61.6)	196 (87.9)	27 (12.1)	0.205
Previous surgical intervention (+)	241 (66.6)	217 (90)	24 (10)	0.637

GAL: Gastrointestinal anastomotic leak; BMI: Body mass index; CCI: Charlson co-morbidity index; SD: Standard deviation. *Pearson χ^2 test, independent samples t-test and Mann-Whitney U test.

RESULTS

A total of 362 patients with gastrointestinal anastomosis were included in the study and 263 (72.6%) of the patients were female. The mean age was 54.3±13.7 years. Eighty-nine (24.6%) patients were active smokers. The origin of PM was ovarian in 173 (37.8%), colorectal in 131 (36.2%), appendix in 43 (11.9%), peritoneal malign mesothelioma in 15 (4.1%), stomach in 21 (5.8%), and other origins in 15 (4.1%) patients. Detailed clinical and demographic characteristics of the patients are given in Table 1.

The mean PCI was 11.6 (±5.6). A single anastomosis was performed in 293 (80.9%) patients. Fifty-one (14.1%) patients had two and 18 (5%) had three anastomoses. Type of the anastomosis was entero-colic in 117 (26%), colo-rectal in 102 (22.7%), entero-enteric in 96 (21.3%), entero-rectal in 87 (19.3%), esophago-jejunostomy in 19 (4.2%), colo-colic 17 (3.7%), and gastro-jejunostomy in 11 (2.4%) patients. Eighty-eight patients had stoma, 43 of them had diverting stoma, and 45 had end-stoma. Complete cytoreduction (CC-0) was achieved in 290 (80.1%) patients. Toxicity associated with HIPEC occurred in 26 (7.2%) patients. The most common toxicity was nephro-

Table 2. Comparison of surgical characteristics between GAL and non-GAL groups

	n=362 (%)	GAL		p*
		(-) n=324 (89.5%)	(+) n=38 (%) (10.5%)	
PCI (mean±SD)	11.6±5.6	11.5±5.5	13±6.1	0.130
Number of resected organs (mean±SD)	3.2±1.7	3.1±1.7	3.9±1.9	0.006
Number of anastomosis	1.24±0.5	1.24±0.5	1.24±0.6	0.966
1	293 (80.9)	262 (89.4)	31 (10.6)	
2	51 (14.1)	46 (90.2)	5 (9.8)	
3	18 (5)	16 (88.9)	2 (11.1)	
Type of the anastomosis				0.363
Esophago-jejunostomy	19 (4.2)	18 (94.7)	1 (5.3)	
Gastro-jejunostomy	11 (2.4)	8 (72.7)	3 (27.3)	
Entero-enteric	96 (21.3)	91 (94.7)	5 (5.3)	
Entero-colic	117 (26)	107 (91.4)	10 (8.6)	
Colo-colic	17 (3.7)	13 (76.4)	4 (23.6)	
Entero-rectal	87 (19.3)	78 (89.6)	9 (10.4)	
Colorectal	102 (22.7)	96 (94.1)	6 (5.9)	
Ostomy (+)	88 (24.3)	77 (87.5)	11 (12.5)	0.508
Diverting ostomy	43 (11.8)	38 (88.3)	5 (11.6)	0.841
End-ostomy	45 (12.4)	39 (86.6)	6 (13.3)	0.507
Intraoperative blood transfusion (+)	158 (43.6)	138 (87.3)	20 (12.7)	0.238
Completeness of cytoreduction				0.139
CC-0	290 (80.1)	263 (90.7)	27 (9.3)	
CC-1&2	72 (19.9)	61 (84.7)	11 (15.3)	
HIPEC agent				0.250
Cisplatin + Mitomycin	108 (29.8)	101 (93.5)	7 (6.5)	
Oxaliplatin	102 (28.2)	88 (86.3)	14 (13.7)	
Cisplatin	96 (26.5)	88 (91.7)	8 (8.3)	
5-Fluorouracil	39 (10.8)	33 (84.6)	6 (15.4)	
Others	17 (4.7)	14 (82.4)	3 (17.6)	
Operative time (min, mean±SD)	354.2±118.9	375.3±122.6	0.302	
HIPEC toxicity (+)	26 (7.2)	23 (88.5)	3 (11.5)	0.857
Hospital stay (days, mean±SD)	18.9±13.8	17.9±12.7	27.7±18.6	0.003
Peri-operative mortality	29 (8)	19 (65.5)	10 (34.5)	<0.001

GAL: Gastrointestinal anastomotic leak; PCI: Peritoneal carcinomatosis index; HIPEC: Hyperthermic intraperitoneal chemotherapy; SD: Standard deviation. *Pearson χ^2 test, independent samples t-test and Mann-Whitney U test.

toxicity and occurred in 21 (80.7%) of the patients. Perioperative mortality was seen in 29 (8%) patients (Table 2).

Anastomotic leaks were seen in 38 (10.5%) patients: Ten entero-colic, nine entero-rectal, six colo-rectal, five entero-enteric, four colo-colic, three gastro-jejunostomy, and one esophago-jejunostomy anastomoses. Type of the anastomosis did not have an impact on the leak rate (p=0.36). The median day-to-leak was 21.3 (±13.42). Perioperative mortality was seen in 10 of 38 (26.3%) patients with GAL, with a 76.3% reoperation rate.

The overall morbidity rate among all patients was 30.7% (n=111), whereas the mortality rate was 8% (n=29).

Details of the GAL and management (Table 3):

Esophago-jejunostomy

Anastomotic leak was seen in one of 19 anastomoses which was detected on post-operative day 10th. Relaparotomy, lavage and endoscopic stenting were performed.

Gastro-jejunostomy

Anastomotic leak was seen in 3 of 11 anastomoses, on mean 19 (±15) days. One successfully treated with percutaneous drainage, other two patients underwent reoperation and one patient died.

Entero-enterostomy

Anastomotic leak was seen in five of 96 anastomoses on mean 17 (±15.2) days. Anastomosis was resected and terminal stoma was created in three patients. Percutaneous drainage was performed in one patient. One patient died after reoperation and primary repair.

Entero-colic Anastomosis

Anastomotic leak was seen in 10 of 117 anastomoses on mean 26 (±13.1) days which was the latest observed one among other types of anastomoses. One of them was treated medically, and the other was treated with percutaneous drainage. Four of eight patients who were re-operated died.

Colo-colic Anastomosis

Anastomotic leak was seen in four of 17 anastomoses on mean 14 (±6.7) days. Anastomosis was resected and terminal stoma was created in three patients and other one successfully treated with percutaneous drainage. No post-operative mortality was observed.

Entero-rectal Anastomosis

Anastomotic leakage was seen in 9 out of 87 anastomoses on mean 25.8 (±12.7) days. One of them was treated medically, one with percutaneous drainage, and the remaining seven were treated by resection and terminal stoma – two patients died.

Colo-rectal Anastomosis

Anastomotic leak was seen in 6 of 102 anastomoses on mean 17.8 (±14.9) days. One of the two patients who underwent percutaneous drainage and one of four patients who underwent resection and terminal stoma were dead.

Risk Factors for GAL

Smoking (p<0.001), high ECOG performance score (p=0.014), high CCI score (p=0.009), low preoperative albumin (p=0.010), and high number of resected organs (p=0.006) were significantly associated with increased GAL rate. Hospital stay (p=0.003) was longer and perioperative mortality rate (p<0.001) was higher in patients with GAL. Gender, age, tumor origin, PCI score, CC score, blood loss, operative time, number of anastomoses, diverting stoma, and intraperitoneal chemotherapeutic agent had no effect (Tables 1 and 2).

Multivariate analysis showed that smoking history (Odds Radio [OR]: 6.223, confidence interval [CI]: 2.814–13.760;

Table 3. Management of GAL according to anastomosis types

Type of the anastomosis	Total (n=362)	GAL			Management of GAL		
		(-) n=324	(+) n=38	GAL day (mean)	Medical/ Conservative (n=2)	Percutaneous drainage (n=7)	Re-operation (n=29)
Esophago-jejunostomy	19 (4.2)	18 (94.7)	1 (5.3)	10	–	–	1
Gastro-jejunostomy	11 (2.4)	8 (72.7)	3 (27.3)	19	–	1	2
Entero-enteric	96 (21.3)	91 (94.7)	5 (5.3)	17	–	1	4
Entero-colic	117 (26)	107 (91.4)	10 (8.6)	26	1	1	8
Colo-colic	17 (3.7)	13 (76.4)	4 (23.6)	14	–	1	3
Entero-rectal	87 (19.3)	78 (89.6)	9 (10.4)	25.8	1	1	7
Colorectal	102 (22.7)	96 (94.1)	6 (5.9)	17.8	–	2	4

GAL: Gastrointestinal anastomotic leak.

Table 4. Preoperative factors independently associated with GAL in multivariate analysis

	OR	95% CI	p
Smoking	6.223	2.814–13.760	<0 .001
CCI score ≥7	4.252	1.590–11.366	0 .004
Preoperative albumin ≤3.5 g/dl	3.942	1.534–10.130	0 .004

GAL: Gastrointestinal anastomotic leak; CCI score: Charlson Co-morbidity Index score; OR: Odds ratio.

p<0.001), CCI score ≥7 (OR: 4.252, CI: 1.590–11.366; p=0.004), and low pre-operative albumin level ≤3.5 g/dl (OR: 3.942, CI: 1.534–10.130; p=0.004) were independent risk factors for GAL (Table 4).

DISCUSSION

The anastomotic leak rate found in this series is 10.5% and approximately one-third of the patients with leak have died. These results confirmed that CRS with HIPEC is yet a high-risk surgery even in experienced centers. On the other hand, independent risk factors were smoking (OR: 6.223), high CCI score (OR: 4.252), and low serum albumin (OR: 3.942) which might be somewhat ameliorated pre-operative variables. Intraoperative factors and disease-related variables seemed to have less impact on anastomotic complications with a standardized surgical technic in a high-volume center.

GAL after CRS and HIPEC reported in the literature ranges between 8 and 12%.[5–9] Male sex, number of the anastomoses and resected organs, left-sided colorectal resection, operative time, nutritional status, ECOG status, intraoperative blood loss, previous systemic chemotherapy, smoking, and CC had all been found to be associated with increased risk for intestinal leak in several studies. Details of large series focusing on GAL and enteric fistulae are given in Table 5.[5–8] Most of these studies have given the rates for GAL of entire series including patients with no anastomoses. The methods for intraperitoneal chemotherapy (open/closed, early post-operative intraperitoneal chemotherapy/HIPEC, and before/after anastomosis) were not homogenous. Moreover, the definition of anastomotic leak was conflicting that some of the studies did not report the anastomotic leak separately, but all the bowel complications and fistulas instead. The present study analyzed a relatively homogenous series including closed-HIPEC technique with one or more gastrointestinal anastomoses performed before HIPEC. The GAL definition did not involve hollow viscus perforations and/or fistulas unassociated with the anastomosis. Therefore, our results reflect a pure morbidity analysis focused on GAL.

In a cohort of 1270 patients, Chouliaras et al.,[6] reported 8.7% gastrointestinal leak rate: 4.2% viscus perforation and 4.2% GAL. Approximately 1/5 of the patients who included in the study had no anastomoses. Number of the anastomoses (OR: 5.34, p<0.001) and ECOG status (ECOG 1 vs. 0, OR: 2.12, p=0.009; ECOG 2 vs. 0, OR: 2.90, p=0.004) were independent risk factors for gastrointestinal leaks including perforations. In contrast with the literature, the number of the anastomoses was not associated with GALs in our study, possibly because most of our patients had a single anastomosis. In a series of 918 patients, gastrointestinal leak rate including hollow viscus perforations and intestinal fistulas was 5.8%.[7] Pre-operative serum albumin <3.5 g/dl and operation time >8.6 h were independent risk factors for GAL. Another study of 185 patients revealed 8.6% of GAL and determined the operative time, the number of the anastomoses, previous systemic chemotherapy, and the nutritional status as important risk factors to predict the anastomotic leak.[5] In another series of 1020 patients, anastomotic leak rate including enteric fistulas was 8%.[8] The majority of the patients had one or more anastomosis (84%). Male gender (OR: 2.2; p<0.01), left-sided colorectal resection (OR: 10.0; p=0.03), and pre-operative albumin (OR: 1.8/g/dl; p=0.02) were independent risk factors for anastomotic failure. Consistent with the literature smoking, low ECOG performance score, increased CCI, decreased pre-operative albumin level, and high number of resected organs were associated with significantly increased GAL in our series. Serum albumin is the most important indicator of nutritional status, and therefore, low albumin levels are associated with an increased risk of post-operative complications. In addition, albumin functions as a negative acute phase protein, and its concentration decreases in response to surgical stress. It has been shown that low pre-operative albumin levels are closely associated with increased post-operative mortality and morbidity,[15,16] as well as pulmonary, urological, wound-healing complications, and anastomotic leakage.[16] As the albumin level is the only potentially modifiable factor identified, it is likely that prehabilitation with optimization of comorbidities and nutritional depletion by an intense pre-operative care to reduce GAL can improve outcome in high-risk patients.

Different from those studies, we also analyzed the effect of HIPEC toxicity and diverting stoma. Unfortunately, we did not have a control group which underwent only CRS without HIPEC to observe the clear effect of HIPEC alone. Even so, HIPEC toxicity had no any adverse effect on anastomotic complications. Diverting ostomies are often used to protect high-risk anastomoses located in the lower pelvis. Several studies have shown that fecal diversion does not reduce the rate of anastomotic leaks, but, on the contrary, it reduces the clinical significance of leaks.[17,18] Two studies analyzed the effects of fecal diversion in CRS and HIPEC showed that diversion significantly reduced the rate of anastomotic leak, but increased readmission rate and increased the risk of anastomotic leak following reversal surgery.[19,20] In our series, only 24.3% of the patients had a stoma and 11.8% of them were diverting type. Unlike the two studies mentioned above, no reducing effect of stoma on GAL was observed.

Table 5. Literature review of anastomotic leak after CRS and HIPEC

Authors, year	n	Patients with GAL, n (%)	Origin of PC in patients with GAL (n)	HIPEC technique	Risk factors for GAL	Independent risk factors for GAL
Halkia, 2015[5]	185	16 (8.6)	PMP (2) Ovarian (8) Gastric (1) Colorectal (3) Mesothelioma (1) Appendix (1)	Open and closed abdominal technic	Operative time Number of anastomoses Previous systemic CT Nutritional status	–
Chouliaras, 2016[6]	1270	116* (8.7)	Appendix (62) Colon (22) Gastric (5) Mesothelioma (8) Ovarian (4) Other (9)	Closed abdominal technic	Male sex ECOG status Numbers of resected organs Number of anastomoses Pre-operative albumin level Estimated blood loss	ECOG status Number of anastomoses
Valle, 2016[7]	918	53* (5.8)	Colorectal (10) Appendix (12) PMP (21) Ovarian (3) Mesothelioma (7)	Open abdominal technic	CC-2 cytoreduction NPWT Smoking	Preoperative albumin Operative time
Wiseman, 2020[8]	1020	82* (8)	Appendix (54) Colorectal (24) Gastric (2) Mesothelioma (2)	Open and closed abdominal technic	Male gender History prior abdominal surgery Left-sided colorectal resection Number of anastomosis Operative time Estimate blood loss	Male gender Preoperative albumin Left-sided colorectal resection
Present study, 2022	362	38 (10.5)	Ovarian (16) Colorectal (14) Appendix (4) Gastric (2) Other (2)	Closed abdominal technic	Smoking ECOG status CCI score Preoperative albumin level	Smoking CCI score ≥7 Preoperavie albumin level ≤3.5 g/dl

GAL: Gastrointestinal anastomotic leak; PC: Peritoneal carcinomatosis; HIPEC: Hyperthermic intraperitoneal chemotherapy; PMP: Pseudomyxoma peritonei; CT: Chemotherapy; NPWT: Negative pressure wound therapy; PCI: Peritoneal carcinomatosis index; ECOG: Eastern Cooperative Oncology Group; CCI: Charlson Co-morbidity Index; CRS: Cytoreductive surgery. *Including hollow viscus perforations and intestinal fistulas.

Another remarkable aspect was that the median time to appearance of GAL was 18 days, which is significantly longer than the 5 days described for non-HIPEC colorectal procedures.[21] This may be due to the negative effect of HIPEC on anastomotic healing, or even the absence of obvious signs of anastomotic leakage in the non-peritonealized ("denuded") abdominal cavity. Considering that anastomotic leakage may present in relatively later postoperative days and the clinical symptomatology is subtle, a high index of suspicion is mandatory in the post-operative period for early diagnosis and initiation of treatment.

Our study had several limitations, most notably were its retrospective design and single institutional structure. Another limitation was lack of an objective defined pre-operative nutritional status assessment. Subgroup analysis in terms of anastomosis type was not performed due to small number of cases in the groups. However, our results presented a clear review of GAL in a relatively large consecutive series.

Conclusion

Patients with PM often have previous abdominal surgeries and many cycles of neoadjuvant treatments which conduce to altered immunity, poor performance, and nutritional deficiency. Inherent unfavorable effects of HIPEC in accompany with extensive surgery make PM patients a high-risk popu-

lation vulnerable to post-operative complications.[22] Severe complications and post-operative mortality can be decreased by experience in dedicated centers.[3,4,23] In addition to tumor-related factors, patient-related factors also affect surgical outcomes. Pre-operative nutritional status may increase post-operative complications. Prehabilitation of fragile, exhausted, and nutritionally impaired patients and proper selection of medically-fit patients may reduce GAL in PM surgery.

Ethics Committee Approval: This study was approved by the Istanbul Medipol University Non-interventional Clinical Research Ethics Committee (Date: 13.09.2022, Decision No: 799).

Peer-review: Externally peer-reviewed.

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ORİJİNAL ÇALIŞMA - *ÖZ*

Hipertermik intraperitoneal kemoterapi ile sitoredüksiyon sonrası gastrointestinal anastomoz kaçağı için risk faktörleri

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AMAÇ: Gastrointestinal anastomoz kaçağı (GAK), sitoredüktif cerrahi (SRC) ve hipertermik intraperitoneal kemoterapi (HİPEC) sonrası önemli bir morbidite ve mortalite nedenidir. Bu çalışmanın amacı peritoneal metastaz (PM) cerrahisinde GAK ile ilişkili risk faktörlerini belirlemektir.

GEREÇ VE YÖNTEM: Çalışmaya gastrointestinal anastomozlu SRC ve HİPEK uygulanan hastalar dahil edildi. Hastaların ameliyat öncesi durumunu değerlendirmek için Charlson Komorbidite İndeksi (CCI) ve Eastern Cooperative Oncology Group (ECOG) performans durumu kullanıldı. GAK klinik, radyolojik veya yeniden ameliyat sırasında teşhis edilen gastrointestinal ekstra-lüminasyon olarak kaydedildi.

BULGULAR: Analiz edilen 362 hastanın ortanca yaşı 54 idi. Hastaların %72.6'sı kadın ve en sık görülen histopatolojiler over kanseri (%37.8) ve kolorektal kanser (%36.2) idi. Medyan Periton Kanser İndeksi 11 idi ve hastaların %80.1'ine tam sitoredüksiyon uygulandı. İki yüz doksan üç (%80.9) hastada tek anastomoz, 51 (%14.1) hastada iki anastomoz ve 18 (%5) hastada üç anastomoz yapıldı. Kırk üç (%11.8) hastaya saptırıcı stoma uygulandı. Otuz sekiz (%10.5) hastada GAK görüldü. Sigara kullanımı ($p<0.001$), ECOG performans durumu ($p=0.014$), CCI skoru ($p=0.009$), preoperatif albümin düzeyi ($p=0.010$) ve rezeke edilen organ sayısı ($p=0.006$) GAK ile anlamlı ilişkili faktörlerdi. GAK için bağımsız risk faktörleri sigara (OR: 6.223, CI: 2.814–13.760; $p<0.001$), CCI skoru ≥7 (OR: 4.252, CI: 1.590–11.366; $p=0.004$) ve preoperatif albümin seviyesi ≤3.5 g/dl (OR: 3.942, CI: 1.534–10.130; $p=0.004$) idi.

TARTIŞMA: Sigara kullanımı, komorbidite ve ameliyat öncesi beslenme durumu gibi hasta ile ilişkili faktörlerin anastomoz komplikasyonları üzerinde etkisi vardı. Uygun hasta seçimi ve yüksek düzeyde bakım gerektiren prehabilitasyon programı ihtiyacı olan indeks hastanın tahmini, daha düşük anastomoz kaçak oranları elde etmek ve PM cerrahisinde sonuçları iyileştirmek için temel ön koşullardır.

Anahtar sözcükler: Anastomoz kaçağı; hipertermik intraperitoneal kemoterapi; peritoneal metastaz; sitoredüktif cerrahi.

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