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Is Fecal Diversion Needed in Pelvic Anastomoses During Hyperthermic Intraperitoneal Chemotherapy (HIPEC)?

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Dr. Alessio Pigazzi was appointed the chief of Colon and Rectal Surgery at Weill Cornell Medical Center/NewYork-Presbyterian in 2020. His research focuses on minimally invasive techniques to improve recovery after cancer surgery, postoperative chemotherapy, as well as the relationship between diet and colorectal cancer.

In this article, Dr. Pigazzi and his co-authors present their findings of performing a fecal diversion before CRS and HIPEC treatment in patients who have had a prior anastomosis.

Key terms for this article:

- **Pelvic anastomosis:** Patients who have had prior colon or rectal resection have had tissue or sections of the organs removed. A pelvic anastomosis is then performed to connect and restore function.
- **CRS and HIPEC:** Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is a surgical treatment for cancer. During this procedure, tumors are surgically removed and the surrounding area is treated with heated chemotherapy.
- **Fecal diversion:** Fecal diversion is the creation of a small pouch outside of the body that collects feces temporarily.
- **Ileostomy:** To remove waste from the body, an ileostomy brings the end of the small intestine to the body and creates an opening (stoma). Feces pass out of the small intestine and the stoma into an external bag.

A past pelvic anastomosis may make HIPEC treatment more difficult because the warm chemotherapy treatment can leak at the site of the anastomosis. This article's research demonstrates that a diverting ileostomy reduces the rate of leakage during HIPEC treatment.

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ORIGINAL ARTICLE – COLORECTAL CANCER

Is Fecal Diversion Needed in Pelvic Anastomoses During Hyperthermic Intraperitoneal Chemotherapy (HIPEC)?

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ABSTRACT
Background. The role of fecal diversion with pelvic anastomosis during cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is not well defined.
Methods. A retrospective review of patients who underwent CRS and HIPEC between 2009 and 2016 was performed to identify those with a pelvic anastomosis (colorectal, ileorectal, or coloanal anastomosis).
Results. The study identified 73 patients who underwent CRS and HIPEC at three different institutions between July 2009 and June of 2016. Of these patients, 32 (44%) underwent a primary anastomosis with a diverting ileostomy, whereas 41 (56%) underwent a primary anastomosis without fecal diversion. The anastomotic leak rate for the no-diversion group was 22% compared with 0% for the group with a diverting ileostomy ($p < 0.01$). The 90-day mortality rate for the no-diversion group was 7.1%. The hospital stay was 14.1 ± 8.0 days in the diversion group compared with 17.9 ± 12.5 days in the no-diversion group ($p = 0.12$). Of those patients with a diverting ileostomy, 68% ($n = 22$) had their bowel continuity restored, 18% of which required a laparotomy for reversal. Postoperative complications occurred for 50% of those who required a laparotomy and for 44% of those who did not require a laparotomy ($p = 0.84$).
Conclusion. Diverting ileostomies in patients with a pelvic anastomosis undergoing CRS and HIPEC are associated with a significantly reduced anastomotic leak rate. Reversal of the diverting ileostomy in this patient population required a laparotomy in 18% of the cases and had an associated morbidity rate of 50%.

Anastomotic leaks are a potentially catastrophic complication of colorectal resections. Contemporary leak rates for colorectal anastomosis vary widely by study.[1] Clinically significant leak rates are reported for up to 12% of all colorectal anastomoses and up to 14% of low rectal anastomoses, and are associated with increased rates of mortality, cost, and hospital length of stay.[2–6]

Several risk factors associated with an increased risk of anastomotic leak have been identified including male gender, malnutrition, preoperative weight loss, cardiovascular disease, steroid use, perioperative blood transfusion, advanced age, obesity, previous irradiation, and a low level of anastomosis.[5,7–12] Previous studies have described an anastomotic leak rate for patients undergoing cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) as high as 10%.[13–16] However, it is not known whether HIPEC represents an independent risk factor for anastomotic leak.

Fecal diversion via diverting ileostomy or colostomy is a technique frequently used to protect a high-risk anastomosis. Several studies have shown that fecal diversion does not necessarily decrease the overall leak rate, but rather decreases the clinical significance of the leaks.[17,18] However, risks associated with diverting stomas are not

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negligible. Complications such as skin irritation, acute renal failure due to high output, bowel obstruction, prolapse, and retraction and can occur in up to 70% of cases.[19–21] Additionally, stoma reversal adds another operation and its associated risks. The use of diverting stomas in low anastomoses is a source of contention, with some authors endorsing the standard use of stoma with any low anastomosis[22] and others suggesting a more selective approach.[23–26] In addition, a recent study found that stoma reversal in patients who underwent CRS and HIPEC occurred in only 26% of eligible cases and was associated with high rates of morbidity, mortality, and anastomotic leaks (9% for ileostomy).[27] Furthermore, a novel two-layered anastomosis may reduce the need for diverting ileostomy in patients who undergo CRS and HIPEC.[28] Currently, the role of fecal diversion with pelvic anastomoses in patients undergoing CRS and HIPEC is not well defined.

METHODS

We performed a retrospective review of patients who underwent CRS and HIPEC between July of 2009 and June 2016 at three different institutions (University of California Irvine, Loma Linda University, and City of Hope National Medical Center). Patients who underwent colorectal resection with pelvic anastomosis (colorectal, coloanal, or ileorectal anastomosis) were identified. The patients were stratified by whether they had primary anastomosis with fecal diversion via diverting loop-ileostomy or primary anastomosis without fecal diversion. The primary study outcome was the development of an anastomotic leak. The secondary outcomes included 90-day mortality, rate of ileostomy reversal, need for laparotomy at the time of ileostomy reversal, and postoperative complications related to ileostomy reversal.

Quantitative data were given as means with standard deviations. The results for the two surgery groups were compared using the independent sample t test for continuous variables and the cross-table Pearson chi-square test for categorical variables. All p values lower than 0.05 were considered statistically significant. Approval was obtained from each individual institution's own institutional review board.

Similar procedural techniques were used at all three institutions. Patients initially underwent laparotomy with CRS and tumor debulking. The abdomen then was closed, and HIPEC was performed. After completion of HIPEC, the abdomen was reopened, and the anastomoses were created. The use of fecal diversion by diverting ileostomy or colostomy was performed at the discretion of the operating surgeon.

RESULTS

We identified 73 patients who underwent CRS and HIPEC with pelvic anastomoses between July 2009 and June of 2016. At the time of CRS and HIPEC, 32 patients (44%) had undergone a primary anastomosis with diverting ileostomy, and the remaining 41 patients (56%) had undergone a primary anastomosis without the use of fecal diversion. The diverted group had significantly more patients with colorectal cancer (69 vs. 41%; $p = 0.01$). Conversely, the no-diversion group had more patients with appendiceal cancer (22 vs. 51%; $p = 0.01$). All the other patient and operative characteristics were similar between the two groups (Table 1).

The operative outcomes are listed in Table 2. The no-diversion group had a significantly higher rate of anastomotic leak than the diversion group (22 vs. 0%; $p < 0.01$). The reoperation rates also were higher in the no-diversion group (22 vs. 0%; $p < 0.01$). The operative times and hospital lengths of stay were similar between the two groups. The 90-day mortality rate for the no-diversion group was 7.1% ($n = 3$), with one in-hospital death. However, the death was not directly related to an anastomotic leak.

Table 3 lists the characteristics and outcomes of the patients undergoing ileostomy closure. Of the 32 patients who underwent initial fecal diversion, 22 (68%) had an operation to restore bowel continuity. One patient had a repeat HIPEC at the time of ileostomy closure and was excluded from any of the secondary analyses. The majority of the patients (82 vs. 18%) did not require a laparotomy at the time of reversal. The patients requiring laparotomy had a significantly longer hospital stay than those who did not require a laparotomy (9.8 ± 5.6 vs. 4.8 ± 2.6; $p = 0.01$). The two groups did not differ in terms of time from index operation to ileostomy closure, number of major CRS (resection of ≥5 organs or >3 anastomoses), or Peritoneal Cancer Index (PCI). The postoperative complication rates and severity were similar between those who required laparotomy and those who did not at the time of reversal. The postoperative complications and their frequencies are listed in Table 4.

DISCUSSION

Pelvic anastomoses are frequently required for patients undergoing CRS and HIPEC. Whether due to the location of a primary malignancy or to carcinomatous in the pelvis, an extensive resection and a low anastomosis are frequently required.

In our study, we identified an overall anastomotic leak rate of 12.3% ($n = 9$). All the leaks occurred in patients

TABLE 1 Characteristics of patients undergoing CRS and HIPEC who had a pelvic colorectal anastomosis with and without fecal diversion

	Diverted ($n = 32$) n (%)	No-diversion ($n = 41$) n (%)	p Value
Mean age (years)	56.5 ± 11.4	54.9 ± 13.7	NS
Female	16 (50.0)	23 (56)	NS
Primary malignancy			
Appendiceal	7 (21.9)	21 (51.0)	0.01
Colorectal	22 (68.8)	16 (39)	0.01
Gastric	0 (0.0)	1 (2.4)	NS
Mesothelioma	1 (3.1)	1 (2.4)	NS
Ovarian	1 (3.1)	1 (2.4)	NS
Small bowel	1 (3.1)	1 (2.4)	NS
Major CRS	10 (31.3)	10 (24)	NS
PCI	15 ± 7.9	16 ± 8.5	NS
No. of anastomoses	1.6 ± 0.7	1.9 ± 0.8	NS
Distal anastomosis type			
Coloanal	1 (3.1)	0 (0.0)	NS
Colorectal	24 (75.0)	32 (78)	NS
Ileorectal/ileocolic	6 (18.8)	9 (22)	NS
ASA class*			
2	7 (21.9)	13 (31)	NS
3	19 (59.4)	22 (54)	NS
4	5 (15.6)	5 (12)	NS
HIPEC type			
Cisplatin	1 (3.1)	1 (2.4)	NS
Cisplatin/doxorubicin	1 (3.1)	0 (0.0)	NS
Cisplatin/mitomycin C	0 (0.0)	1 (2.4)	NS
Mitomycin C	21 (65.6)	22 (54)	NS
Melphalan	0 (0.0)	1 (2.4)	NS
Oxaliplatin	9 (28.1)	16 (39)	NS
BMI	28.1 ± 4.9	26.5 ± 4.4	NS
Smoker within 6 months	4 (13)	4 (10)	NS
Prior radiation therapy	3 (9)	1 (2.4)	NS
Preoperative weight loss >10 lb	8 (25)	5 (12)	NS
Immunosuppression	19 (59)	18 (43)	NS

CRS cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *NS* not significant ($p > 0.05$), *PCI* peritoneal cancer index, *ASA* American Society of Anesthesiology, *BMI* body mass index

* ASA class data missing for one case in the no-diversion group

without a diverting ileostomy, resulting in an anastomotic leak rate of 22% for the patients without proximal fecal diversion.

In a 2015 prospective study by Akio et al.,[29] the leak rate for the patients who had a low pelvic anastomosis without a diverting ileostomy was 12.7%. Within the body of CRS and HIPEC literature, the anastomotic leak rate is reported to be as high as 10%,[13–16] but most of the studies included all intestinal anastomoses and did not focus on high-risk pelvic anastomosis.

One possible explanation for the higher leak rates observed in our study population than in the general colorectal literature may be the increased intestinal edema. The CRS and HIPEC procedures can take up to 12 h and frequently require large-volume resuscitation during and after the operation. After CRS and HIPEC, patients often have significant fluid shifts, development of pleural effusions, and requirement of peritoneal drains. Previous studies have associated large-volume administration during colorectal resections with an increased risk of anastomotic

TABLE 2 Outcomes for patients undergoing CRS and HIPEC who had a pelvic anastomosis with fecal diversion versus those without fecal diversion

	Diverted ($n = 32$) n (%)	No-diversion ($n = 41$) n (%)	p Value
Surgery time (min)	666.1 ± 206.8	606 ± 189.5	NS
Hospital stay (days)	14.1 ± 8.0	17.9 ± 12.5	NS
Anastomotic leak	0 (0.0)	9 (21.9)	<0.01
Reoperation	0 (0.0)	9 (21.9)	<0.01
90-Day mortality	0 (0.0)	3 (7.14)	NS
Clavien-Dindo grade			
1	6 (18.8)	5 (12)	NS
2	11 (34.4)	10 (24)	NS
3	4 (12.5)	7 (17)	NS
4	0 (0)	4 (10)	NS
5	0 (0)	3 (7)	NS
Intestinal discontinuity at 26 weeks	13 (40)	3 (7)	<0.01
Intestinal discontinuity at 52 weeks	9 (28)	0 (0.0)	<0.01

CRS cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *NS* not significant ($p > 0.05$)

TABLE 3 Outcomes and characteristics of patients requiring laparotomy and no laparotomy for ileostomy reversal

	Laparotomy ($n = 4$) n (%)	No laparotomy ($n = 18$) n (%)	p Value
Hospital stay (days)	9.8 ± 5.6	4.8 ± 2.6	<0.01
Time to closure from index operation (weeks)	22.2 ± 11.4	18.7 ± 8.4	NS
Postoperative complications	2 (50.0)	10 (44.4)	NS
90-Day mortality	0 (0.0)	0 (0.0)	NS
HIPEC type			
Cisplatin	1 (25.0)	0 (0.0)	0.03
Cisplatin/doxorubicin	0 (0.0)	1 (5.6)	NS
Mitomycin C	0 (0.0)	15 (83.3)	<0.01
Oxaliplatin	3 (75.0)	2 (11.1)	<0.01
Major CRS	2 (50.0)	2 (11.1)	NS
PCI	16 ± 8.2	13 ± 7.2	NS
Clavien-Dindo grade			
1/2	2 (50)	8 (44)	NS
3/4	0 (0.0)	0 (0.0)	NS
5	0 (0.0)	0 (0.0)	NS

NS not significant ($p > 0.05$), *HIPEC* hyperthermic intraperitoneal chemotherapy, *CRS* cytoreductive surgery, *PCI* peritoneal cancer index

leak.[30,31] Although HIPEC has not been identified as an independent risk factor for anastomotic leak, it is reasonable to consider that the large-volume resuscitation and fluid shifts with resulting edema in these cases may be a potential cause of the higher leak rate observed.

Of the 32 patients in our study who had fecal diversion at the time of their index CRS and HIPEC operation, 68% ($n = 22$) ultimately had the continuity of their intestine restored. The mean time to closure was 19.3 ± 8.8 weeks, which is on par with previous studies reporting stoma closure rates of approximately 70% after colorectal surgery.[32,33] However, studies of CRS and HIPEC patients have reported much lower rates of stoma reversal.[16,27] These studies grouped both loop and end stomas

TABLE 4 Postoperative complications after ileostomy closure in patients undergoing CRS and HIPEC who had a diverting ileostomy created at the index operation

Complication[a]	No. of occurrences
Ileus	5
Surgical-site infection	3
Bleeding	1
Enterocutaneous fistula	1
Urinary tract infection	1

CRS cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy

[a] All complications were Clavien-Dindo grade 1 or 2

(colostomy and ileostomy) together, which likely explains the low reported closure rates.

Our study examined only those with a diverting ileostomy used to protect a distal pelvic anastomosis. Despite the high rates of stoma closure seen in our study, ileostomy reversal in this patient population can be challenging.

A 2016 study by Doud et al.[27] evaluated the complications associated with stoma reversal in patients who had undergone CRS and HIPEC. They reported that 28% of the patients experienced a Clavien-Dindo 1 or 2 complication, whereas another 28% experienced a Clavien-Dindo 3 or 4 complication. Additionally, the authors reported a 30-day mortality rate of 4.7% and an anastomotic leak rate of 9% after ileostomy closure.

In our study, we identified an overall morbidity rate of 50%, with complications ranging from ileus to development of an enterocutaneous fistula (Table 4). All the complications were either a Clavien-Dindo grade 1 or 2. Of the 22 patients who had their stoma reversed, 18% ($n = 4$) required a laparotomy due to dense adhesions. Despite similar postoperative complication rates, these patients had significantly, longer hospital stays than those that did not require a laparotomy (19.3 ± 8.8 vs. 4.8 ± 2.6 days; $p = 0.01$). For non-CRS and HIPEC patients, ileostomy closure is associated with a complication rate of 21%.[26] The higher complication rate for the CRS and HIPEC patients may be related to intraabdominal adhesions that developed after their initial surgery.

Laparotomy was required for 18% ($n = 4$) of the patients who had their diverting ileostomy reversed. For these patients, laparotomy was required due to dense adhesion formation that prevented fewer invasive ileostomy closure techniques. The two groups did not differ in terms of major/minor CRS or PCI. However, the types of intraperitoneal chemotherapy used during HIPEC differed significantly (Table 3). The patients requiring a laparotomy underwent HIPEC with either an oxaliplatin-based ($p < 0.01$) or a cisplatin-based ($p = 0.03$) regimen. None of the patients requiring a laparotomy underwent HIPEC with mitomycin C ($p < 0.01$).

Although data on the association of chemotherapeutic agents and their effect on intraabdominal adhesion formation are mixed and limited, this could explain the significant reduction in the need for laparotomy among patients undergoing HIPEC with mitomycin C. The literature contains evidence that intraperitoneal administration of mitomycin C may reduce postoperative adhesion formation.[34–36] Reduced adhesion formation with mitomycin C also has been demonstrated in endoscopic sinus surgery and cardiac surgery animal models.[37,38] Conversely, a 1995 study by Jacquet and Sugarbaker[39] showed increased intraabdominal adhesions after intraperitoneal chemotherapy with mitomycin C. In other studies, oxaliplatin and cisplatin have been shown to increase intraabdominal adhesion formation.[40,41] Additional studies are needed to evaluate fully the role of different HIPEC chemotherapeutic agents and their effect on intraabdominal adhesion formation.

Our study had several limitations. First, it was a retrospective review and thus subject to the limitations of retrospective chart reviews. Our study included data from three centers and several different surgeons with varying levels of experience performing CRS and HIPEC. Given the duration of the study period, it is possible that practice patterns had changed with regard to creating a diverting stoma. Furthermore, the exact reason for the creation of the diverting ileostomy was not always available. Despite these limitations, this study is the first to evaluate the role of diverting ileostomy in patients with a pelvic anastomosis who underwent CRS and HIPEC.

CONCLUSION

For patients undergoing CRS and HIPEC with high-risk anastomosis, fecal diversion is associated with a significant reduction in the anastomotic leak rate. The majority of the patients with a diverting ileostomy in this study had bowel continuity restored within 6 months after their index operation. However, diverting ileostomy reversal required a laparotomy in 18% of the cases due to dense adhesions and had an associated overall morbidity rate of 50%. The use of a diverting ileostomy should be considered for patients undergoing CRS and HIPEC with a pelvic anastomosis. Additional studies are needed to evaluate risk factors for anastomotic leak in patients undergoing CRS and HIPEC.

CONFLICT OF INTEREST There are no conflicts of interest.

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