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Bowel Complications in 203 Cases of Peritoneal Surface Malignancies Treated With Peritonectomy and Closed-Technique Intraperitoneal Hyperthermic Perfusion

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Background: Peritonectomy and intraperitoneal hyperthermic perfusion (IPHP) are increasingly used in the management of carcinomatosis of various sites of origin. We analyzed the risk factors for bowel complications with primary anastomoses and the closed technique for IPHP.

Methods: From 1995 to 2004, 203 consecutive procedures were performed at the National Cancer Institute of Milan. We retrospectively analyzed this series of patients. Treated pathologies included peritoneal mesothelioma; pseudomyxoma peritonei; colorectal, ovarian, or gastric carcinomatosis; and abdominal sarcomatosis. All digestive anastomoses were performed before the IPHP. Only one defunctioning stoma was used.

Results: We found a bowel complication rate of 10.8%. The bowel complications:anastomoses ratio was 11.3%. On univariate analysis we found a statistically significant association between bowel complications and the following variables: sex, previous systemic chemotherapy status, number of anastomoses (fewer than two vs. two or more), duration of the procedure (<8.7 vs. ≥ 8.7 hours), and extent of cytoreduction. After multivariate analysis, male sex (odds ratio [OR], 4.2), no previous systemic chemotherapy (OR, 3.5), and duration of the procedure ≥ 8.7 hours (OR, 6.3) were considered independent risk factors for bowel complications.

Conclusions: Bowel complications are not increased when primary unprotected anastomoses are performed during peritonectomy and IPHP when the closed technique is used. Male sex, duration of the procedure, and no previous systemic chemotherapy are independent unfavorable risk factors.

Key Words: Peritoneal carcinomatosis—Peritonectomy—Intraperitoneal hyperthermic perfusion—Intestinal complications.

Several prospective studies have shown promising results when cytoreductive surgery (CRS) and intraperitoneal hyperthermic perfusion (IPHP) were used to treat peritoneal carcinomatosis. Verwaal et al. [1]demonstrated a clear survival advantage for this new

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treatment strategy in the only randomized controlled trial in patients with carcinomatosis of colorectal origin. The institution of a program in peritoneal carcinomatosis requires not only highly specialized human resources, but also complex technological facilities to[2] perform the CRS plus IPHP, which minimizes treatment-related morbidity and mortality and maximizes results in terms of survival and quality of life. In this context, the identification of risk factors for postoperative complications is of major concern. Small-bowel perforations and anastomotic leaks are the most common complications associated with a surgical procedure that combines unusually lengthy operative times, numerous and complex resections, peritoneal stripping, and a heated intraperitoneal chemotherapy component.

However, there is no consensus in the literature with respect to the surgical and perfusion techniques, which differ from one center to another. Some authors promote performing a proximal diverting stoma for low rectal anastomoses, [3–5]whereas others do not.[6,7] Another difference relates to the fact that many authors advocate completing the anastomoses before the hyperthermic perfusion,[7] whereas most do so after the perfusion.[1,5,8,9]Moreover, open, closed, and semiclosed techniques are being used for the chemotherapy perfusion. In this study, we proposed to assess the bowel complication rate and the risk factors for their occurrence in locoregional procedures performed with closed-technique IPHP by using primary anastomoses after a low anterior resection and by completing all the anastomoses before the perfusion.

PATIENTS AND METHODS

Patients undergoing CRS and IPHP since 1995 at the National Cancer Institute (NCI) of Milan constitute the present study population. In accordance with the study design, patients were considered suitable for recruitment after a complete evaluation, including physical examination, biochemical and hematological tests, and chest/abdominal/pelvic computed tomography. Eligibility criteria included the following: a confirmed histological diagnosis of peritoneal mesothelioma, pseudomyxoma peritonei, colorectal, ovarian, or gastric carcinomatosis, or abdominal sarcomatosis; age <75 years; World Health Organization performance status ≤ 2; good cardiac, renal, hepatic, and bone marrow function; and informed written consent to participate in the study. One-hundred ninety-eight patients have taken part in the study since the initiation of the program at the NCI of Milan. There were 132 (67%) female and 66 (33%) male patients. The median age was 52 years (range, 22–76 years). Two hundred three procedures were performed during the study period. Five patients were treated twice: three with peritoneal mesothelioma, one with ovarian cancer, and one with pseudomyxoma peritonei.

Cytoreductive Surgery

The surgical technique was described in detail previously and is based on the Sugarbaker principles of peritonectomy,[10] with a few modifications. In brief, CRS was performed on the basis of disease extension by the following steps: (1) greater omentectomy and right parietal peritonectomy, with or without right colon resection; (2) pelvic peritonectomy, with or without sigmoid colon resection and with or without hysterectomy and bilateral salpingo-oophorectomy; (3) lesser omentectomy and dissection of the duodenal-hepatic ligament, with or without antrectomy and cholecystectomy; (4) right upper quadrant peritonectomy and glissonian capsule resection; (5) left upper quadrant peritonectomy and left parietal peritonectomy, with or without splenectomy; and (6) other intestinal resection and/or abdominal mass resection. All operations were performed by the same surgical team.

Peritoneal carcinomatosis was classified as follows: P1, dissemination into primary tumor; P2, slight dissemination into remote peritoneum; and P3, marked dissemination into remote peritoneum.[11] Cytoreduction was classified into three levels according to the number of procedures performed: level I, one or two procedures; level II, three or four procedures; and level III, five or more procedures. Residual disease after surgery was classified according to Sugarbaker criteria: completeness of cytoreduction (cc)-0, no residual disease; cc-1, minimal residual disease (up to 2.5 mm); cc-2, residual disease of 2.6 to 2.5 cm; and cc-3, residual disease >2.5 cm.

Anastomotic Techniques

Stomach

Whether a partial or total gastrectomy is performed, we always use a Roux-en-Y reconstruction. In cases of partial gastrectomy, the stomach and proximal duodenum are transected by using a gastrointestinal anastomosis (GIA) stapler. The lower part of the GIA-stapled line of the gastric remnant is then cut with scissors, and the ensuing end-to-side

gastrojejunal anastomosis is hand-sewn with one layer of continuous Maxon 4-0 stitches (United States Surgical Corporation, Norwalk, CT). The distal end-to-side jejunojejunal anastomosis is also hand-sewn in the same fashion. When a total gastrectomy is completed, an end-to-side esophagojejunal anastomosis is performed with a circular stapler, usually of size 25-mm. A GIA stapler is applied to the remaining proximal end of the jejunal limb. The distal anastomosis is similar to the one described previously.

Small Intestine and Colon

Small-bowel and colic anastomoses are always hand-sewn in an end-to-end fashion by using single-layer extramucosal continuous Maxon 4-0 or 3-0 stitches. For all anastomoses, we start a running stitch on the antimesenteric border for the anterior layer and then start a second running stitch at the mesenteric side for the posterior layer. This allows to complete the anastomoses on the free antimesenteric border, thus avoiding the mesentery and better visualizing the bowel wall.

Rectum

Most of the time, we and other investigators have found that the cul-de-sac area is filled with coalescing tumor implants that also include much of the sigmoid colon. A complete pelvic peritonectomy with a low anterior resection is frequently needed to completely remove these tumor implants. In a few selected cases, however, we have been able to preserve the rectum and resect only the overlying visceral peritoneum, including the peritoneal reflection. In case of low anterior resection, the lower margin of bowel transection is usually below the level of the peritoneal reflection. The low colorectal anastomosis is performed with an intraluminal stapler of 29- to 33-mm diameter after a distal washout of the rectal remnant with a diluted iodine solution. We then test the integrity of the anastomoses with air insufflation from below.

Intraperitoneal Hyperthermic Perfusion

IPHP follows completion of the anastomoses. The closed-abdomen technique is used for all our patients. Two inflow catheters are inserted, one in the right subphrenic space and one deep in the pelvic cavity, as are two outflow catheters, one in the left subphrenic space and the second more superficially in the pelvic cavity. Six thermocouples are used to continuously monitor the inflow, outflow, and intraperitoneal cavity temperatures. Temporary abdominal skin closure follows with a tight continuous nylon stitch. The catheters are then connected to an extracorporeal perfusion circuit (Performer LRT; Rand, Medolla, Italy). The intraperitoneal temperature is maintained at 42.5°C during the perfusion. Different chemotherapeutic agents are used, depending on the tumor histological characteristics. Intraperitoneal chemotherapy regimens are as follows: (1) cisplatin (CDDP; 25 mg/m^2/L) and mitomycin C (MMC; 3.3 mg/m^2/L)[12] for pseudomyxoma peritonei and colorectal and gastric carcinomatosis and (2) CDDP (43 mg/L of perfusate) and doxorubicin (15.25 mg/L of perfusate)[13] for mesothelioma, ovarian carcinomatosis, and sarcomatosis. The perfusate is then instilled into the peritoneal cavity at a mean flow of 600 ml/min.

Study Parameters

We defined bowel complications as bowel perforation or anastomotic leak. A bowel perforation occurs at a site away from an anastomosis. An anastomotic leak is a breach and/or complete dehiscence at the suture line. For the assessment of factors predictive of bowel complications, the following clinical variables were evaluated: tumor histological characteristics (gastrointestinal vs. nongastrointestinal), sex, performance status (World Health Organization), age (<52 vs. ≥ 52 years), body mass index (<25 vs. ≥ 25 kg/m^2), no previous systemic chemotherapy, previous radiotherapy, carcinomatosis extent (P1 or P2 vs. P3), number of anastomoses (fewer than two vs. two or more), duration of the procedure (<8.7 vs. ≥ 8.7 hours), extent of the cytoreduction (level I or II vs. level III), completeness of cytoreduction (cc-0/1 vs. cc-2/3), IPHP drug schedule (CDDP and doxorubicin vs. CDDP and MMC), and CDDP IPHP dose (<240 vs. ≥ 240 mg).

Statistics

A univariate analysis of each clinical variable was performed by Fisher's exact test or χ^2 test to determine the probability of association with bowel complications. A logistic regression model was used in a multivariate analysis to determine the correlation between clinical variables and bowel complications. All clinical variables with a P value $\leq .05$ were included in the model. The backward-elimination method was used to determine which clinical variables best predict bowel complications. All sta-

tistical analysis were conducted by using SPSS software version 8.0.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

From 1995 to 2004, 198 consecutive patients underwent 203 cytoreductive and IPHP procedures at the NCI of Milan. They constitute the study population. The most frequent neoplasm treated was mesothelioma, with 50 cases (25%). Other treated neoplasms included 48 cases (24%) of pseudomyxoma peritonei, 40 cases (20%) of ovarian carcinomatosis, 32 cases (15%) of abdominal sarcomatosis, 13 cases (6%) of colorectal carcinomatosis, 12 cases (6%) of gastric carcinomatosis, and 8 cases (4%) of other origins. Mean and median durations of operation were 527 and 490 minutes, respectively (range, 240–1320 minutes). Eighty-nine percent of patients received optimal cytoreduction (cc-0 and −1). Mean organ resections were 2.4 per patient. Overall, 480 various organ resections were performed. We excluded the peritonectomy procedures from this number. A total of 194 anastomoses were performed, with a mean of .96 anastomoses per patient (range, 0–4). Ninety-four patients (46%) had none performed. Conversely, 53 patients (26%) had a single anastomotic site, 34 patients (17%) had 2, 15 patients (8%) had 3, and 7 additional patients (3%) had 4 anastomoses performed. Details on the extent of the peritoneal disease, on the extent of the operation performed, and on the residual disease at the end of the operation are listed in Table 1. Only one patient (.5%) had a terminal ostomy during the study period: this was a female patient who underwent a total colectomy with small-bowel resection and whose ileorectal anastomoses could not be fashioned because of undue tension. After 203 consecutive procedures, 22 patients (10.8%) had bowel complications. We designated a bowel complications:anastomoses (BC/A) ratio, which is the total number of bowel complications divided by the total number of anastomoses performed. We found a BC/A ratio of 11.3%. Two patients (1%) died overall.

TABLE 1. *Clinical and surgical peritoneal disease features*

Variable	No. of patients	%
Histological type distribution		
Peritoneal mesothelioma	50	25
Pseudomyxoma peritonei	48	24
Ovarian carcinomatosis	40	20
Abdominal sarcomatosis	32	15
Colorectal carcinomatosis	13	6
Gastric carcinomatosis	12	6
Other origins	8	4
Peritoneal disease extent		
1	20	9.9
2	58	28.6
3	121	59.6
N/A	3	1.5
Extent of cytoreduction		
I	37	18.2
II	84	41.4
III	82	40.4
Completeness of cytoreduction (cc) score		
cc-0	139	68.5
cc-1	41	20.2
cc-2	14	6.9
cc-3	9	4.4

N/A, not available.

Bowel Complications: Anatomical Location

The ileocolic anastomosis was the most common site of bowel complications (Table 2). Seven patients had postoperative morbidity at this site. The small bowel was the next most common site, with five patients experiencing intestinal morbidity. Four patients had a surgical complication related to the colon. Only two patients had complications at the level of the colorectal anastomosis. Finally, two complications occurred at the level of the duodenum, and one occurred at the level of the stomach. One patient had both a small-bowel and a colorectal anastomotic complication. No information was available for the remaining two patients.

Complication Types and Management

Bowel complications (Table 2) occurred at a mean duration of 11.5 postoperative days and a median duration of 10 days (range, 3–28 days). In 17 patients, the complication occurred at an anastomotic site or suture line. Six complications were demonstrated to be at a site away from the anastomoses or suture line. Five patients with ileocolic anastomotic leaks underwent reoperation and bowel resection with reanastomosis. Two patients of this group had a protective ileostomy. The remaining two patients, with ileocolic fistulas, were conservatively treated with total parenteral nutrition and had spontaneous resolution of their fistula. One small-bowel anastomotic leak was surgically treated, and another was conservatively managed. Three small-bowel perforations occurred at random sites not related to a suture line and were all surgically treated. One patient with a colorectal anastomotic dehiscence was surgically treated and given a colostomy, whereas the other was

TABLE 2. *Anatomical location, description, and management of bowel complications*

Anatomical location	No. of patients	Bowel perforations	Anastomotic leaks	Surgical treatment	Conservative management
Ileocolic anastomosis	7	0	7	5	2
Small bowel	5	3	2	4	1
Colon	4	1	3		
Colorectal anastomosis	2	0	2	1	1
Duodenum	2	1	1	2	0
Stomach	1	1	0	1	0
Not available	2	0	2		
Total[a]	23				

[a] One patient had two simultaneous bowel complications.

TABLE 3. *Univariate and multivariate analysis of clinical risk factors for bowel complications*

Independent variable	OR (crude)	*P* value (χ^2)	Adjusted OR (95% CI)[a]	*P* value
Tumor histology GI	1.6	NS		
Male sex	4.1	.002	4.2 (1.5–12.1)	.01
Performance status 0	.6	NS		
Age ≥ 52 y	.9	NS		
BMI > 25 kg/m^2	.5	.1		
No previous systemic CHT	3.9	.005	3.5 (1.1–11.6)	.04
Previous RT	1.7	NS		
Carcinomatosis extent 3	2.4	.07		
Number of anastomoses ≥ 2	4.3	.002		
Procedure duration ≥ 8.7 h	6.4	.0003	6.3 (1.7–23.2)	.01
Extent of cytoreduction level III	3.1	.01		
Completeness of cytoreduction score cc-2/3	.8	NS		
IPHP drug schedule CDDP + MMC	1.6	NS		
CDDP IPHP dose ≥ 240 mg (no)	1.7	NS		

OR, odds ratio; CI, confidence interval; GI, gastrointestinal; NS, not significant; BMI, body mass index; CHT, chemotherapy; RT, radiotherapy; IPHP, intraperitoneal hyperthermic perfusion; CDDP, cisplatin; MMC, mitomycin C.
[a] Logistic regression model with backward-elimination method.

conservatively treated with drainage and total parenteral nutrition. Overall, six patients (27%) received a stoma as part of their final management, including one performed to gain access to a major presacral bleed.

Risk Factors

After univariate analysis, we found a statistically significant association between bowel complications and the following variables: sex, no previous systemic chemotherapy, number of anastomoses (fewer than two vs. two or more), duration of the procedure (< 8.7 vs. ≥8.7 hours), and extent of cytoreduction (level III vs. levels I and II; Table 3). After multivariate analysis, the following variables remained in the model and were considered independent risk factors for the occurrence of bowel complications: male sex (odds ratio [OR], 4.2; 95% confidence interval, 1.5–12.1), no previous systemic chemotherapy (OR, 3.5; 95% confidence interval, 1.1–11.6), and duration of the procedure ≥8.7 hours (OR, 6.3; 95% confidence interval, 1.7–23.2).

DISCUSSION

Peritonectomy and IPHP is a complex and time-consuming procedure that was initially described by Sugarbaker.[14] It has yielded very encouraging results according to many phase II studies in selected patients affected by peritoneal carcinomatosis from pseudomyxoma peritonei and peritoneal mesothelioma and in patients with colorectal cancer, according to one phase III study. These promising results have prompted many centers worldwide to initiate peritoneal surface malignancy programs.

To our knowledge, this is the first series to thoroughly analyze the intestinal complications associated with peritonectomy and IPHP. The results of this study indicate that locoregional therapy—when performed with primary anastomoses, without liberal indications for protective ostomies, and with the

closed abdomen technique for IPHP—is viable option in terms of procedure-related bowel complications. We had a total of 22 (10.8%) bowel complications in 203 procedures. Our results seem in line with those reported by other authors, which range from 3.9% to 34% (Table 4).[3,5–9,15–22] However, such a comparison should be made cautiously for several reasons. First, throughout the published literature, we found great variability in the definition of bowel-related complications. Some authors report digestive fistulas,[5,6,7,9] others differentiate fistulas from anastomotic leaks,[16] and still others define bowel leaks as the presence of either an anastomotic leak or a bowel perforation.[21] Second, the series are heterogeneous in terms of the distributions of potential risk factors for bowel complications. Third, intuitively, the more anastomoses performed, the higher the risk of complications. In the overview of published series (Table 4), the mean number of anastomoses per patient varies widely from .4 to 2.8 anastomoses per patient. This is a severalfold difference and could account for major differences with regard to bowel complications. The total number of anastomoses performed would thus be a confounding factor for the complication rate when comparing different series and relating them to the different techniques used. Therefore, we suggest that the bowel complication rate should also be correlated with the total number of anastomoses performed. Thus, to render the comparison between the various series less biased, we designated a BC/A ratio, which is the total number of bowel complications divided by the total number of anastomoses performed for the entire series of patients a center is reporting. We therefore recommend separate reporting of the BC/A ratio as an adjunct to the fistula rate. Accordingly, we found that the BC/A ratio in our study was 11.3%, which is in agreement with the figures found in the literature, which range from 7.2% to 17.4% (Table 4).

After univariate analysis, we identified the following variables as possible risk factors for bowel complications: sex, previous systemic chemotherapy status, number of anastomoses (fewer than two vs. two or more), duration of the procedure (< 8.7 vs. ≥ 8.7 hours), and extent of cytoreduction. After the multivariate analysis, only male sex, no previous systemic chemotherapy, and duration of surgery were shown to be independent risk factors for the occurrence of bowel complications.

Four comprehensive studies on the morbidity associated with peritonectomy and IPHP have been published.[5,7,15,16] Glehen et al.,[7] in the biggest series (216 procedures), found on univariate analysis that carcinomatosis extent, duration of surgery, and number of anastomoses were significantly associated with the occurrence of digestive fistulas. However, only 73 procedures combined both CRS and IPHP; the remaining 143 patients received only IPHP. Jacquet et al.[15] conducted a study on 60 patients by using CRS and IPHP with MMC followed by 1 cycle of early postoperative intraperitoneal 5-fluorouracil. They used the closed-abdomen technique and performed the anastomoses after perfusion. They found on univariate analysis that bowel leakage was related to the duration of surgery and the number of peritonectomy procedures. In another comprehensive series analyzing all the morbidities associated with 200 cytoreductive operations combined with IPHP, Stephens et al.[16] found that intraoperative blood loss was the only associated risk factor for anastomotic leaks. In the last comprehensive series, bowel complications were not separately analyzed.[5]

Our data are in line with those reported by other authors[7,15] concerning the duration of the procedure as a risk factor for bowel complications. However, we found that male sex and no previous systemic chemotherapy were unfavorable risk factors. Several reasons could explain these new findings, such as differences between cohorts concerning the distribution of several potential risk factors (e.g., sex, duration of the operation, number of anastomoses, and IPHP techniques), thus rendering comparison of the results somewhat problematic. Moreover, not all the studies used the same statistical method (multivariate analysis). In addition, the analysis performed in our study included only clinical and surgical variables related to the preoperative and intraoperative phases of the procedure. One can raise the hypothesis that by including preoperative, intraoperative anesthesia, and immediate postoperative parameters, reflecting, for example, the nutritional, hemodynamic, and/or respiratory status, new independent risk factors for bowel complications could emerge.

The first independent risk factor on multivariate analysis was male sex, which had an OR of 4.2 favoring complications. It is well known that the male pelvis is more difficult to dissect than its female counterpart for anatomical reasons. Nevertheless, this cannot totally account for our results for two reasons: first, we encountered only two colorectal anastomotic fistulas in our series, and, second, one of these was in a man and the other in a woman.

Receiving previous systemic chemotherapy was a protective factor in our series. Patients not receiving chemotherapy had an OR of 3.8 for presenting

TABLE 4. *Overview of bowel complications associated with CRS and IPHP (series with more than 35 patients)*

Author	No. proc	% Male patients	Predom histol	Mean no. anast/pt	Protect. ostomy (%)
Jacquet et al.[15]	60	62	Appendix, colon	1.8	None
Stephens et al.[16]	200	53	PMP, colon	NA	NA
Witkamp et al.[8]	46	41	PMP	2	39
	64	42	Colon	2.6	NA
Elias et al.[6,17]	36	39	PMP	2.8	NA
Moran and Cecil[3] and Parvaiz et al.[18]	43	NA	PMP	NA	NA
	56		Colon, PMP, ovarian	.6	
Glehen et al.[7,19,20]	73	37			NA
	56	48	Colon	.4 ≤2 (69)	NA
Verwaal et al.[5]	102	56	Colon	>2 (33)	42
Shen et al.[21]	77	58	Colon	NA	13
Elias et al.[9]	39	33	Colon, PMP	Median 2	None
Present series	203	33	PM, PMP, ovarian	1	.5

complications. This could be explained by the fact that patients eligible to receive chemotherapy have a better performance status and a more favorable prognosis. A selection bias could have occurred in that setting.

The multivariate analysis confirmed that the longer the procedure, the higher the risk of intestinal complications. We found an OR of 6.9 when the procedure lasted longer than 8.7 hours. Patients who underwent a procedure longer than 8.7 hours had almost a 7-fold increase in bowel complications. This does not imply that CRS and IPHP should be completed in less than 8.7 hours, but rather that that duration of operation simply reflects the extent of the operation, the carcinomatosis extent, the total number of anastomoses performed, or all of these. It is a surrogate-like measure of these three variables. The number of anastomoses was not shown in our series to be an independent risk factor. Theoretically, more anastomoses should increase bowel complications. In our opinion, this unexpected finding can be explained only by the small number of events (a total of 22).

Variations exist regarding surgical and IPHP techniques. At the NCI of Milan, we have used the closed technique for perfusion of the abdomen since 1995. Some authors have postulated that the closed technique is associated with a higher bowel complication rate and thus have changed to the open perfusion technique.[15,16] However, the main reason behind the use of the open technique at many centers is to improve drug and heat distribution. Sarnaik et al.,[23] comparing the different techniques, postulated that the inadequate circulation of the perfusate with the closed technique could contribute to more bowel complications. The reason for this would be focal hyperthermic and chemotherapeutic injuries. This is based on the observation by Elias et al.[24] that uneven distribution throughout the abdomen was shown when methylene blue was instilled into the abdomen during a closed IPHP procedure.

We found six bowel perforations in our series. They all occurred away from suture lines. Possible explanations could be the overlooking of partial-thickness damage to intestinal surfaces. This, in turn, could have been aggravated by the subsequent heated chemotherapy. These injuries to intestinal surfaces could be the result of either the extensive surgical dissection per se or the thermal damage from direct use of the ball-tip electrocautery on the cancerous implants on the serosal surfaces. Another possible explanation is the focal heat injury at the tip of the inflow catheter. However, we always place the latter away from intestinal surfaces.

We do not routinely protect low colorectal anastomoses on the basis of the complexity and long duration of the procedure. Because of these last two factors, indications for proximal diverting stomas seem to be more liberal than for common surgical procedures. Some authors recommend, for example, performing a colostomy for all rectal resections.[5]

TABLE 4. *Continued*

IPHP techn.	Timing of anastomoses	BC/A ratio (%)	Duration	Bowel complication rate (%)	Risk factors for bowel complications
Closed	After	9.3	Mean 10.9	17	Duration of operation, number of peritonectomy procedures[a]
Open	After	NA	NA	7.5	Intraoperative blood loss[a]
Open	After	17.4	Mean 10	34	
Multiple	Before and after	8	Median 7.3	18.8	
Open	NA	7.2	Median 10	22.2	
NA	NA	NA	Median 10.5	5	
					Carcinomatosis extent, duration of operation, number of anastomoses[a]
Closed	Before	NA	Mean 6.1	10.7	
Closed	Before	17.3	Mean 5.3	8	
Open	After	NA	Median 7.5	17.6	
Closed	After	NA	Median 9	NA	
Open	After	NA	Median 8	10.3	Duration of surgery, sex, no previous chemotherapy[b]
Closed	Before	11.3	Median 8.2	10.8	Extent of cytoreduction, number of anastomoses[a]

CRS, cytoreductive surgery; IPHP, intraperitoneal hyperthermic perfusion; No. proc, number of procedures; Predom histol, predominant histology; Mean no. anast/pt, mean anastomoses per patient; Protect., protective; techn., technique, BC/A, bowel complications/anastomoses; PMP, pseudomyxoma peritonei; NA, not available, PM, peritoneal mesothelioma.

[a] On univariate analysis.

[b] On multivariate analysis.

Others have found unacceptably high risks of anastomotic leaks when performing low anterior resections and emphasize the importance of preserving the rectum and, if this is not possible, having a proximal defunctioning stoma.[3] Others have found a significant association between the performance of a bowel anastomosis and the occurrence of sepsis. Therefore, they suggest being more cautious about completing an anastomosis and being more open to performing a stoma.[21] During the entire study period, we performed only 1 diverting ostomy, despite a total of 58 low colorectal anastomoses fashioned. We found that only two patients had an anastomotic leak at this site. Therefore, in our opinion, to primarily complete unprotected colorectal anastomoses seems to be a viable alternative. The decision to perform a diverting stoma should not be guided by the type of operation, but rather should be based on the established risk factors for a leak in the surgical practice. An interesting finding in this study was that most patients had bowel complications at or distal to the ileocolic anastomoses (13 patients; 60%). On the basis of these data, it is now our policy in case of the need for a protecting stoma to perform a temporary ileostomy rather than a colostomy.

Another technical variation of CRS and IPHP is the optimal timing for bowel anastomoses. They can be performed either after the completion of the IPHP or just before the IPHP component. Proponents of the first alternative argue that delaying the anastomosis permits a better distribution of heat and drugs inside the peritoneal cavity during the IPHP. In addition, they state that the risk of postoperative bowel complications can be diminished as a result of the avoidance of the potential adverse effects of heat and chemotherapy on the suture line healing. However, others have proposed the second alternative, which is supported by experimental and clinical evidence. In fact, the influence of chemotherapy on suture healing depends on the type of drug. In animal studies, anastomotic healing can be impaired by intraperitoneal MMC, but not by 5-fluorouracil at a normal temperature[25,26] or by paclitaxel.[27] Local hyperthermia alone has no adverse effect on rat anastomotic healing.[28] Moreover, there seems to be no increased morbidity due to postoperative bowel fistula or anastomotic leak when anastomoses are constructed before IPHP.[29–31]

In conclusion, our acceptable bowel complication rate, in the context of locoregional therapy, suggests that CRS and IPHP could be performed by using primary anastomoses and the closed-abdomen technique for the IPHP and by fashioning the intestinal anastomoses before the perfusion. This study was conducted in a large cohort of patients but suffers from a methodological limitation regarding the retrospective design and absence of a control group. Obviously, our intent was not to defend the superiority of one technique for locoregional therapy over the others; this could be done only on the basis of a

prospective randomized study. The search for risk factors for complications should be further continued by analyzing new aspects related not only to the locoregional therapy.

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