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Second-look Surgery for Appendiceal High Grade and Colorectal Cancers Following Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

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Abstract. *Background/Aim: Up to a third of patients undergoing cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis (PC) of appendiceal or colorectal origin receive a stoma during primary surgery. Stoma reversal provides an opportunity for second-look surgery. Patients and Methods: We performed a retrospective analysis of prospectively collected data of patients with colorectal cancer (CRC) or high-grade appendiceal cancer (AC) from 2006 to 2021 from our database. A total of 34 consecutive stoma closure patients with no evidence of preoperative disease recurrence (tumor markers and CT scans) were compared with 141 consecutive re-do CRS/HIPEC patients with known recurrence. Results: Eleven patients (32.4%) were identified to have peritoneal recurrence at stoma closure. Time between first and second CRS was 12 months (4 to 64.2) in the stoma closure group vs. 24.6 months (5.8 to 119.8) in the re-do group, while median peritoneal cancer index (PCI) was 4 (3 to 6) vs. 8 (1 to 39), respectively (p=0.0143). Conclusion: Second-look laparotomy during stoma closure identified unexpected PC in 32.4% of our patients with significantly lower PCI than planned re-do operations.*

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In recent decades, cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) for select patients with peritoneal carcinomatosis (PC) has shown improved survival rates compared to systemic chemotherapy with or without palliative surgery (1-5). One meta-analysis has shown that CRS with HIPEC offers a median survival of 29 months in patients with PC, which is significantly longer than the median survival of 17.9 months for standard chemotherapy alone (6).

Despite advancements in CRS and HIPEC, peritoneal disease recurrence rates in colorectal cancer (CRC) or high-grade appendiceal cancer (AC) can be as high as 80% and 40%, respectively, within two years of surgery (7, 8). Currently, postoperative monitoring consists primarily of routine cross-sectional imaging by way of computed tomography (CT) scan, combined with serum biochemical markers to diagnose recurrence of disease (9). Patients with recurrent disease may then undergo a second CRS (hereafter, re-do CRS). However, recurrence is often difficult to detect by imaging and biochemistry alone as patients are often asymptomatic in the early stages of recurrence, and the sensitivity of CT scanning in detecting peritoneal recurrence approaches 60%, while also being influenced by factors such as size and extent of disease, location of spread, and radiologist expertise (10, 11). It has been established in the literature that the extent of peritoneal disease, as measured by the peritoneal cancer index (PCI), has a significant impact on the patient's prognosis, with a lower burden of peritoneal disease being associated with better CRS outcomes and improvements in morbidity (12). As earlier detection of disease is associated with a lower burden of peritoneal disease, better techniques should be devised to enable earlier

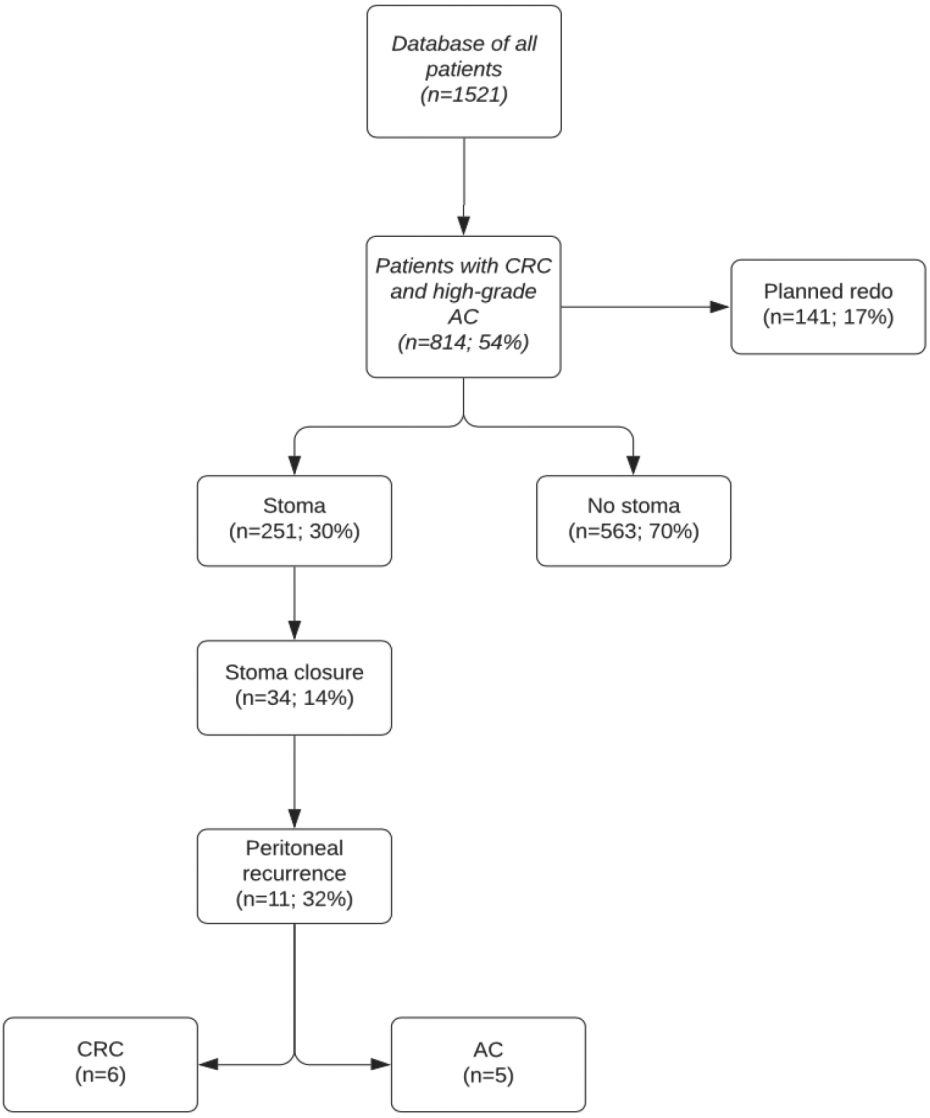

Figure 1. *Study population comparing stoma closure and planned re-do groups.*

detection of disease recurrence with subsequent improvement in patient outcomes.

To detect the disease earlier and thereby improve prognosis, a relatively new strategy has been suggested. This strategy involves "second-look" surgery, which is a complete surgical exploration of the abdomen to identify any recurrent metastatic disease from colorectal or appendiceal origin. If recurrence of disease has been detected, patients can undergo a repeat CRS with HIPEC in the same surgery. Several studies have shown that repeat CRS and HIPEC on patients with recurrence from colorectal or appendiceal origin improves long-term survival and morbidity rates (13-16). In our study, we utilised routine stoma reversal surgery as an opportunity to explore and detect disease recurrence early and compared this with results from patients undergoing a planned re-do CRS.

Patients and Methods

A prospectively maintained database of patients with CRC or high-grade AC from 2006 to 2021 was retrospectively reviewed. Thirty-four consecutive stoma closure patients with no evidence of preoperative disease recurrence (tumor markers and CT scans) were studied as well as 141 consecutive CRC and AC patients selected for re-do surgery (Figure 1).

The peritonectomy center at St George Hospital is a high-volume referral center where more than 1,500 CRS/HIPEC procedures were done for patients with PC. In our practice, second-look surgery is not routinely offered to PC patients treated with CRS/HIPEC as it

Table I. *Patient characteristics*.

Patient characteristics	Stoma closure with recurrence (n=11)	Planned re-do (n=141)	*p*-Value
Age, years	54	56.58	0.290
Sex			
Male	4	60	
Female	7	82	
Diagnosis			
Appendiceal cancer	5	54	
Colorectal cancer	6	88	
Duration from first to second CRS, months	15.9	35	0.354

CRS: Cytoreductive surgery.

Table II. *Patient outcomes after primary cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC)*.

First CRS and HIPEC	Stoma closure with recurrence (n=11)	Planned re-do (n=141)	*p*-Value
PCI	16 (11-25)	19 (2-39)	0.398
CC0	7	98	0.552
>CC0	4	38	
HIPEC			
MMC	7	60	
Oxaliplatin	4	58	
EPIC	1	63	

CC0: Complete cytoreduction; >CC0: residual tumor; MMC: mitomycin C; EPIC: early postoperative intraperitoneal chemotherapy.

remains controversial and carries a risk of morbidity and mortality. However, we adopted the practice of second-look surgery during routine stoma closure in PC patients who had primary CRS/HIPEC during which a stoma was created.

These patients are followed up by clinical exam, serial imaging (CT scan every three months and a PET scan every six months), tumor markers and multi-disciplinary team (MDT) discussions. Appropriate discussions and decisions were made during MDT meetings if any surveillance results raised suspicion for peritoneal recurrence. Otherwise, patients were routinely scheduled for a stoma closure and second-look surgery in approximately 12 months from their primary CRS/HIPEC.

The surgeon who performed the initial CRS/HIPEC procedure attended the stoma closure and second-look surgery. During the second-look surgery, the patient's PCI was scored, and decisions regarding the approach to treatment with CRS were made based on the intraoperative findings and discussions with our MDT. If the recurrence was resectable, complete cytoreduction was attempted, followed by the appropriate choice of HIPEC and early postoperative intraperitoneal chemotherapy in some cases. Patient consent was obtained and included a laparotomy, complete division of adhesions, reversal of stoma, thorough abdominal exploration, and intra-operative liver ultrasound.

Statistics. Categorical data were expressed as frequency distributions and compared using the χ^2 or Fisher's exact test, whereas normally distributed continuous data were expressed as means and compared using the student's *t*-test. PCI was evaluated using non-parametric independent samples median tests. Complete cytoreduction (CC) score was evaluated using Fisher's exact tests.

Results

Out of the 34 patients who underwent a stoma closure, 11 patients (32.4%) were identified to have peritoneal recurrence (6 CRC and 5 AC) (Figure 1). Time from the first to the second CRS was 12 (4 to 64.2) months in the stoma closure group and 24.6 (5.8 to 119.8) months for the re-do CRS group (Table I). There was no significant difference between both groups concerning the PCI and completeness of resection at the first CRS (Table II). However, in the second CRS, the median PCI was 4 (3 to 6) in the stoma closure group compared with 8 (1 to 39) for planned re-do CRS (p=0.0143) (Table III) (Figure 2). All patients in the stoma closure group (11/11) achieved complete cytoreduction (CC0) compared to 73.8% (104/141) for planned re-do (Table III) (Figure 3).

Table III. *Patient outcomes after second cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC)*.

Second CRS and HIPEC	Stoma closure with recurrence (n=11)	Planned re-do (n=141)	*p*-Value
PCI	4 (3-6)	8 (1-39)	0.0143
CC0	11	104	0.050
>CC0	0	37	
HIPEC			
MMC	7	84	
Oxaliplatin	4	39	
EPIC	1	34	

CC0: Complete cytoreduction; >CC0: residual tumor; MMC: mitomycin C; PCI: peritoneal cancer index; EPIC: early postoperative intraperitoneal chemotherapy.

Discussion

In appendiceal cancer, the PCI has been shown to directly correlate with the ability to achieve complete cytoreduction (CC0) of metastatic disease, where there is a linear relationship between PCI score and CC0. Thus, as complete CRS is directly related to survival, the PCI score can indirectly predict survival through its ability to anticipate the completeness of the cytoreductive resection (17, 18). For this reason, PCI and CC0 are predictors of long-term survival outcomes in patients with PC secondary to high-grade appendiceal cancer (19-25). In addition, there is no PCI limit above which a complete CRS/HIPEC cannot yield survival benefit (18). Similarly, the PCI and CC0 are two important

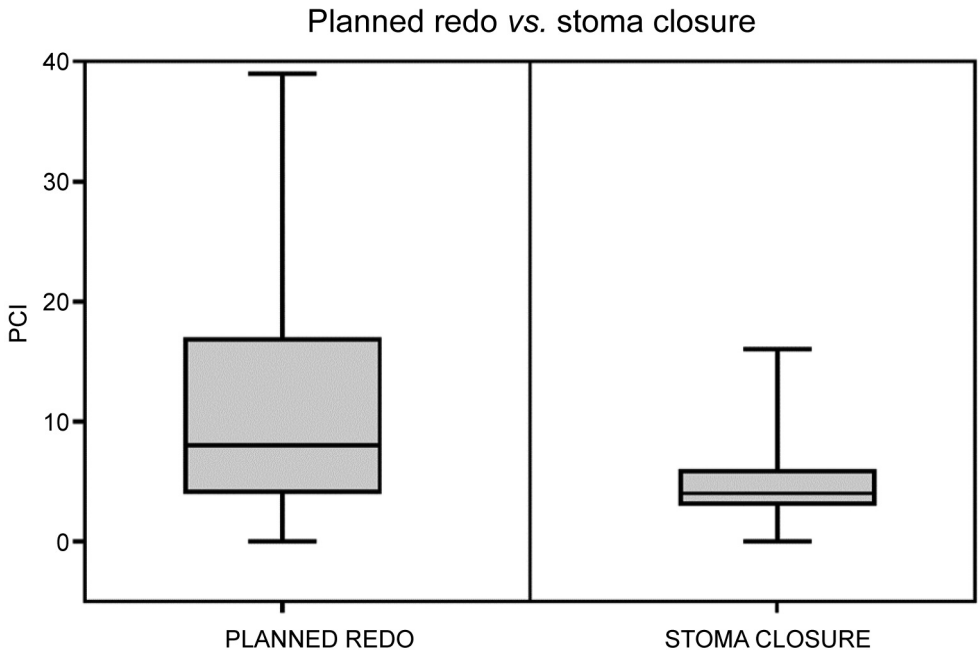

Figure 2. *Box Plot of peritoneal cancer index (PCI) for second cytoreductive surgery.*

prognostic factors in patients with peritoneal metastases secondary to colorectal cancer. Unlike the PCI in appendiceal cancer, PCI in colorectal cancer has a perfect linear correlation with overall survival (26-29). Thus, given that second-look surgery detects disease at a lower PCI score, it may be a more accurate diagnostic therapeutic procedure and provide better outcomes in select groups of patients.

Current literature is marred by conflicting results, with some studies reporting benefits for second-look surgery while others reporting the contrary (Table IV). Delhorme *et al*. found in their prospective cohort study of 14 patients undergoing a second-look laparotomy that 71% of patients had evidence of PC with median PCI of 10 (30). Complete cytoreduction was able to be achieved in all patients. Cloutier *et al*.'s retrospective analyses of patients undergoing second-look surgery for PC of colorectal origin also report similar results (31). They found that 58% (23/40) of their patients had macroscopic evidence of peritoneal disease at the time of second-look surgery, with a mean PCI of 3. Additionally, they highlighted that second-look surgery provides an opportunity to revise bowel anastomoses, a common site for recurrence, should there be evidence of disease re-growth overlying it. Likewise, Elias *et al*.'s prospective study of patients with no radiological evidence of recurrent PC undergoing second-look surgery found that 56% (23/41) of patients had recurrence at second-look (32). They concluded that second-look surgery allowed for detection of recurrent peritoneal disease at a lower PCI score and thus improved morbidity and survival rates in such patients. The results from these studies are in line with

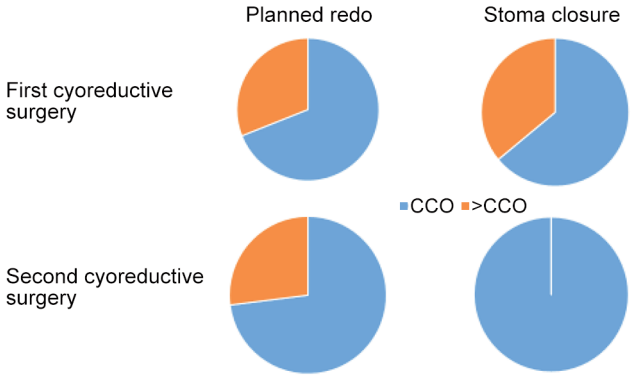

Figure 3. *Pie chart percentage of completeness of resection at first and second cytoreductive surgery.*

our conclusion that the routine second-look surgery allows for an earlier and more accurate diagnosis of PC.

Notably, while second-look surgery may offer earlier detection of recurrent disease at a lower PCI and better chances at complete cytoreduction, Goéré *et al*.'s randomised controlled trial found that second-look surgery did not improve patient survival compared to routine surveillance (33). Additionally, recurrence was detected in 48% (36/75) and 47% (35/75) of patients in the surveillance and second-look laparotomy groups, respectively. These results suggest that there was no additional survival benefit of second-look surgery compared to radiological surveillance in the early detection of PC. The authors also reported discordance

Table IV. *Summary of literature*.

Study	Year	Study design	Number of subjects	PCI (median)	CC	Main finding
Our study	2021	Retrospective cohort	34	4	0	Stoma closure by laparotomy identified unexpected PC in 32.4% of our patients with significantly lower PCI compared with planned re-do operations
Goéré *et al*. (33)	2020	Randomised controlled	150	4	0	Systematic second-look surgery plus oxaliplatin-HIPEC did not improve disease-free survival compared with standard surveillance.
Delhorme *et al*. (30)	2015	Prospective cohort	14	10	0-1	Routine second-look surgery with HIPEC results in increased survival rates
Cloutier *et al*. (31)	2015	Retrospective cohort	40	3	0-1	In second-look surgery and HIPEC for colorectal cancer at high-risk of peritoneal carcinomatosis, anastomosis should be resected when overlying peritoneal carcinomatosis nodules are found
Elias *et al*. (37)	2011	Prospective cohort	41	9	0-1	Second-look surgery early on allows for earlier detection and treatment for peritoneal metastases and provides good survival rates.

HIPEC: Hyperthermic intraperitoneal chemotherapy; PCI: peritoneal cancer index; CC: complete cytoreduction.

between surgical and histological diagnosis of recurrent peritoneal disease, with 11/35 (31%) patients having macroscopic lesions that were not reported as PC on histology. However, the study found a mean PCI of 4 in the second-look group, indicating that second-look surgery was in fact able to achieve its objective of detecting early-stage peritoneal recurrence. The authors concluded that while second-look surgery allows for earlier detection of disease, macroscopic surgical diagnosis has a high false-positive rate and is comparable with routine radiological surveillance, ultimately yielding no benefit in survival outcomes. A notable difference between previous studies and Goéré *et al*.'s randomised controlled trial is the non-randomised nature, where previous authors were able to set inclusion criteria that accepted patients whom they believed to be at high risk of recurrent peritoneal disease, despite radiological evidence suggesting otherwise. Thus, a comparison of studies may suggest that appropriate patient selection and a carefully considered criterion for stratifying risk of peritoneal recurrence is an essential component in perpetuating the utility of second-look laparotomy in detecting early recurrent PC.

Conclusion

While several studies have found improvements in survival outcomes with second-look surgery (30, 34, 35), other studies have shown that there is no benefit to disease-free survival or overall survival in second-look surgery compared to routine follow-up (33, 36). In our study, stoma closure surgery identified unexpected PC recurrence in 32.4% of patients, with significantly lower PCI than planned re-do operations. Although the literature remains divided on the survival benefits of second-look surgery, our study demonstrates that second-look laparotomy allows for earlier detection of disease recurrence at a lower PCI, likely translating to improved overall survival.

Conflicts of Interest

The Authors certify that they have no affiliations with or involvement in any organisation or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

Authors' Contributions

All Authors contributed to the writing of this article. Prof Morris and Dr. Alzahrani were the principal surgeons and supervisors in this study and contributed to the study design. Drs. Breakeit, Liu, and Cheng prepared the manuscript, while Shoma Barat and Dr. Suh collected and assembled the data. The statistics were performed by Dr. Breakeit. Dr. Matar edited and submitted the manuscript.

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