

Perioperative outcomes in patients treated with total parietal peritonectomy and multi-visceral resections with or without HIPEC at different time points in the history of advanced ovarian cancer

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Objective: The morbidity of hyperthermic intraperitoneal chemotherapy (HIPEC) in relation to the extent of surgical resection has not been analyzed in advanced ovarian cancer. The goal was to evaluate the perioperative outcomes in patients treated with a total parietal peritonectomy (TPP) and multi-visceral resections with/without HIPEC at different time points in the history of advanced ovarian cancer. **Methods:** This is a retrospective study of 144 patients treated from 1 December 2018 to 30 June 2020. In the interval setting, a TPP was performed as part of a registered protocol (CTRI 2018/12/016789) and in the primary and recurrent setting when the extent of disease necessitated it. The analysis of the perioperative outcomes included evaluation of the 90-day grade 3–4 morbidity and mortality and time to starting adjuvant chemotherapy. **Results:** Thirty (20.8%) patients had primary cytoreductive surgery (CRS), 90 (62.5%) interval CRS and 24 (16.2%) CRS for recurrence. HIPEC was performed in 57 (39.5%) patients. 93.7% had all 7 peritonectomies, 61% had more than three visceral resections and 62.5% had at least one bowel anastomosis. Grade 3–4 morbidity was seen in 31.9% and was similar with/without HIPEC. On multi-variable logistic regression analysis, patients receiving neoadjuvant chemotherapy ($p = 0.031$) and undergoing small bowel resection ($p = 0.038$) had a higher risk of grade 3–4 morbidity and those with peritoneal cancer index (PCI) < 10 ($p = 0.001$) had a lower risk. All except two patients started chemotherapy within 6 weeks of surgery. **Conclusions:** In this study, the addition of HIPEC to TPP and multi-visceral resections had an acceptable morbidity. The morbidity was affected by the disease extent and the extent of surgery performed and not by HIPEC.

Keywords

Advanced ovarian cancer; Cytoreductive surgery; HIPEC; Total parietal peritonectomy; Major-morbidity; Post-operative morbidity

1. Introduction

Advanced ovarian cancer is an incurable disease despite the advances in surgical treatment and systemic therapies. The addition of hyperthermic intraperitoneal chemotherapy (HIPEC) to interval cytoreductive surgery (CRS) performed after neoadjuvant chemotherapy (NACT) has demonstrated a survival benefit compared to CRS alone [1]. The role of HIPEC in patients undergoing primary CRS/debulking surgery and those undergoing surgery for recurrence (NCT01376752) is being evaluated in clinical trials [2, 3]. One of the main concerns with HIPEC is the added morbidity that results from the use of heated chemotherapy [4, 5]. Several prospective and retrospective studies have shown that the morbidity of HIPEC is similar to that following CRS alone [6, 7]. A recent retrospective study showed a similar morbidity and survival with the addition of HIPEC to primary or interval cytoreductive surgery [8].

Advanced ovarian cancer comprises a heterogeneous group of patients with varying extent and volume of disease [9]. Specifically, after NACT the amount of residual disease is variable and the extent of peritoneal and adjacent visceral resection performed during CRS can vary greatly. There is no standard surgical strategy for these patients except leaving be-

hind no visible residual disease [10, 11]. Surgeons, thus, have their preferences and practices regarding the amount of peritoneum that is resected with some performing formal peritonectomies in the involved region and others resecting just focal areas of tumor bearing peritoneum. Similarly, the visceral resections also vary from one surgeon to another for the same amount of disease. And this should have a bearing on the morbidity of HIPEC since extensive CRS procedures carry their own morbidity.

The parietal peritoneum is the most common site of disease in patients undergoing primary, interval and secondary CRS for recurrent disease [12–14]. Though various guidelines recommend resecting only disease bearing areas, our group has been evaluating the role of resection of the entire parietal peritoneum (total parietal peritonectomy-TPP) irrespective of the disease extent in patients undergoing interval CRS and the early results show that such a strategy may reduce the rate of early recurrence [15, 16]. In the primary and recurrent setting, a TPP is performed only when all parietal regions have visible disease. The morbidity of CRS and HIPEC in relation to the extent of surgery has never been evaluated. In this study our goal was to evaluate the 90-day major morbidity and mortality in patients undergoing TPP as part of CRS with or without HIPEC at three different time points- primary, interval and secondary CRS (for recurrent disease).

2. Methods

This is a retrospective analysis of prospectively collected data. Written informed consent was obtained from all patients. Ethical approval is not required for retrospective analysis at the three institutions. Institutional approval was obtained for the study at all three centres. Patients undergoing CRS with or without HIPEC in the primary, interval or recurrent setting between 1 July 2018 to 30 June 2020 were included in the study. Only patients who had a total parietal peritonectomy (described below) during CRS were included in the study. For primary and secondary CRS, a TPP was performed only when the disease extent necessitated it, which means there was disease on all parietal peritoneal surfaces necessitating resection of the peritoneum. In the interval setting, it was performed irrespective of the disease extent as part of an ongoing study following a fixed surgical protocol (CTRI 2018/12/016789) [17]. At all three centres, the treatment strategy is to perform a primary CRS for all patients except those with unresectable disease or a poor performance status. Thus, NACT is only offered to patients with unresectable disease that invariably involves the entire parietal peritoneum. TPP addresses this peritoneum, that was involved prior the administration of NACT and which is known to harbor chemotherapy resistant stem cells that increase the risk of recurrence [18]. For recurrent disease, only patients with platinum sensitive recurrence were taken up for surgery. However, no predictive scores were used for patient selection. This was largely to include patients who had an in-

adequate first surgery and thus progressed or recurred early (6–12 months after completion of first line therapy) [19]. Patients who had a previous CRS were excluded as one or more of the peritonectomies had already been performed.

2.1 Surgical intervention

All surgical procedures were performed with the goal of obtaining a complete cytoreduction (no visible residual disease). Briefly, a midline incision from the xiphoid to the pubis was employed. The disease was quantified using Sugarbaker's peritoneal cancer index (PCI) [20]. Total parietal peritonectomy comprised all 5 peritonectomies-pelvic, bilateral anteroparietal, right and left upper quadrant peritonectomies and total omentectomy. For descriptive purposes, the peritonectomies were described at right and left upper quadrant, pelvic, bilateral antero parietal and mesenteric peritonectomies and greater and lesser omentectomy, that is, 7 peritonectomies in all. Mesenteric peritonectomy refers to any procedure performed on the small bowel mesentery including focal resection of tumor nodules, electroevaporation and a total or partial mesenteric peritonectomy. In patients undergoing secondary CRS, a greater omentectomy was not performed if the omentum had been removed at the first surgery or a supra-colic omentectomy was performed to remove the remnant omentum. Visceral resections were performed only for viscera involved by tumor.

For all patients, some regions like the falciform and umbilical round ligament were resected in absence of visible disease as there have a high probability of having occult disease [21]. For all patients, the completeness of cytoreduction was reported using the completeness of cytoreduction score (CC-score) [20]. A bilateral pelvic and retroperitoneal lymphadenectomy (till the level of the renal veins) was performed for all patients in whom lymph nodes were suspicious on imaging or intraoperatively.

2.2 Surgical complexity score

In addition to recording the peritonectomies and visceral resections performed, the surgical complexity score (SCS) by Aletti *et al.* was calculated for each patient and its impact on morbidity evaluated [22].

2.3 HIPEC

HIPEC was performed with cisplatin 75 mg/m² for 90 mins by the open (2 centres) or closed method (1 centre). The dose of 100 mg/m² was not used due to the non-availability of sodium thiosulfate [23].

HIPEC was offered to all patients undergoing interval CRS. HIPEC is an out-of-pocket expenditure for patients in India and was performed only for those that could afford the additional cost and consented the procedure. For patients undergoing primary CRS, it was performed only when the patient requested for the procedure. Similarly, for recurrent disease it was performed for selected patients which was at the treating surgeon's discretion. In both instances, patients and decision makers were well informed that HIPEC is not the current standard of care for that particular indication.

2.4 Evaluation of morbidity

The 90-day morbidity and mortality were recorded. The common toxicology criteria for adverse events (CTCAE) version 4.3 classification was used to record the morbidity [24]. Grades 3 and 4 were considered major morbidity.

2.5 Chemotherapy

Interval surgery was performed after 3–4 cycles of NACT. In patients who had unresectable disease after 3–4 cycles, all 6 cycles were administered before surgery. All patients undergoing primary or interval surgery received adjuvant therapy to complete a total of at least 6 cycles of chemotherapy in the first-line setting. A combination of paclitaxel and carboplatin was used for all patients. The use of bevacizumab was at the discretion of the treating physician. Adjuvant chemotherapy was administered to all patients. The choice of regimen was at the discretion of the treating physician.

For recurrent disease, NACT was administered to some patients in whom the disease was considered unresectable by the treating surgery. The choice of NACT and adjuvant therapy was again at the discretion of the treating clinician. The time from surgery to the start of adjuvant chemotherapy was recorded for all patients.

2.6 Statistical analysis

Categorical data were described as number (%). Abnormally distributed continuous data were expressed as the median and range. Categorical data were compared with the χ^2 test. For comparison of median values, the independent sample *t* test was used and for means, the Mann-Whitney *U* test. A *p*-value of <0.05 was considered statistically significant. The impact of various prognostic factors on major morbidity was evaluated using the logistic regression analysis.

3. Results

Thirty (20.8%) patients underwent primary CRS, 90 (62.5%) underwent interval CRS and 24 (16.2%) patients underwent secondary CRS. Fifty-seven (39.5%) patients were treated with HIPEC and 87 (60.5%) did not undergo the procedure. The median surgical PCI was 17 [range 1–37]. 94 (65.2%) patients had a CC-0 resection, 42 (29.1%) CC-1 and 8 (5.5%) had a CC-2 resection. The median hospital stay was 12 days [range 7–38 d] and the median ICU stay 3 days [range 0–14 d]. Major complications were seen in 46 (31.9%) patients and 5 (3.4%) died within 90 days of surgery. Twelve patients (8.3%) required re-operation for complications. The median time to starting adjuvant chemotherapy was 38 [32–77] days and all except two patients started chemotherapy within 6 weeks of surgery (Table 1).

3.1 Surgical procedures

135 (93.7%) patients had all seven peritonectomies and 88 (61%) had resection of more than three viscera (Table 2). Ninety (62.5%) patients had at least one bowel anastomosis; 75 (52%) patients had a rectosigmoid resection and 19 (13.1%) patients had a diverting stoma. Resection of the diaphragm was performed in 21 (14.5%) patients, a splenec-

tomy in 55 (38.1%), total colectomy in 12 (8.3%) and regional lymphadenectomy in 102 (70.8%) patients. 79.9% of all procedures were 'complex' according to the SCS, 20.1% of intermediate complexity and none of low complexity.

3.2 Grade 3–4 morbidity and mortality

The 90-day major morbidity was 31.9% (46 patients) and 5 patients died within 90 days of surgery. Respiratory complications seen in 11 (7.6%) patients, post-operative ascites/fluid collections requiring drainage in 10 (6.9%) patients, hemorrhage in 5 (3.4%) patients and bowel fistulas in 4 (2.7%) patients were the most common post-operative complications (Table 3). More hemorrhagic complications were seen in 4 (7.0%) patients undergoing HIPEC. Of the 5 post-operative deaths, 1 was due to hemorrhagic shock, 3 due to systemic sepsis and 1 due to myocardial infarction that occurred after discharge from the hospital within 90-days of surgery. On univariate logistic regression analysis, a PCI <10 was associated with a lower risk of major complications ($p = 0.030$). Patients undergoing NACT ($p = 0.032$), those undergoing small bowel resection ($p = 0.022$), those with operative time more than 480 mins ($p = 0.014$) and having more than 1 bowel anastomosis ($p = 0.025$) were at a higher risk of complications (Table 4). On multivariable analysis, patients with a PCI <10 had a lower risk of complications ($p = 0.001$) where as those receiving NACT ($p = 0.031$) and having small bowel resection ($p = 0.038$) had a higher risk of developing major complications.

3.3 Time to adjuvant chemotherapy

The median time to adjuvant chemotherapy was 38 days [range 32–77 days]. All except 2 patients started chemotherapy within 6 weeks of surgery. One of these two patients had a complex urological fistula and started chemotherapy at 11 weeks. The other patient had urosepsis due to which adjuvant chemotherapy was started at 8 weeks but could not be completed due to persistent infection.

3.4 HIPEC versus no HIPEC

There were more patients undergoing primary CRS in the no-HIPEC group ($p = 0.062$). The surgical PCI was higher in the HIPEC group though the difference was not statistically significant. The operative time was longer in the HIPEC group but the average blood loss was similar (Table 1). More patients in the HIPEC group had all 7 peritonectomies ($p = 0.008$) and a splenectomy ($p = 0.066$) (Table 2). A significantly higher proportion of patients in the HIPEC group had a complex SCS ($p = 0.019$). Other clinical and surgical parameters were similar between the two groups. The major morbidity and post-operative mortality did not differ significantly between the HIPEC (35.0%) and non-HIPEC (29.8%) groups ($p = 0.278$). More patients required reoperation in the HIPEC group for which, the most common indication being post-operative hemorrhage.

3.5 Primary, interval and secondary CRS

More patients received HIPEC in the interval and secondary CRS groups compared to the primary CRS group.

Table 1. Clinical characteristics of 144 patients undergoing TPP with or without HIPEC.

Clinical parameter	All patients	TPP and HIPEC	TPP	<i>p</i> -value
		N = 57 (%)	N = 87 (%)	
Age				
<50	40 (27.7)	16 (28.0)	24 (27.5)	0.949
>50	104 (72.3)	41 (72.0)	63 (72.5)	
Indication				
Primary	30 (20.8)	7 (12.2)	23 (26.4)	0.062
Interval	90 (62.5)	37 (64.9)	53 (60.9)	
Recurrence	24 (16.6)	13 (22.8)	11 (12.6)	
No of lines of previous chemotherapy				
0	120 (83.3)	44 (77.1)	75 (86.2)	0.245
1	16 (11.1)	8 (14.0)	8 (9.1)	
>1	8 (5.5)	5 (8.7)	3 (3.4)	
Neoadjuvant chemotherapy				
Yes	97 (67.3)	39 (68.4)	58 (66.6)	0.826
No	47 (32.7)	18 (31.9)	29 (33.4)	
No of NACT cycles				
3–4	75 (52.0)	33 (57.8)	42 (44.8)	0.159
>4	22 (15.2)	6 (10.5)	16 (55.2)	
Type of recurrence				
Partially platinum sensitive	3 (2.0)	1 (1.7)	2 (2.2)	0.537
Platinum sensitive	21 (14.5)	11 (19.2)	10 (11.4)	
ECOG				
0–1	142 (98.7)	57 (100.0)	85 (97.7)	0.811
>1	2 (1.3)	0 (0.0)	2 (2.3)	
ASA Score				
1	120 (83.3)	50 (87.8)	70 (80.4)	0.330
2–3	24 (16.7)	7 (12.2)	17 (19.6)	
Median surgical PCI [range]	17 [1–37]	19 [1–37]	15 [1–31]	0.005
Surgical PCI				
0–9	29 (20.1)	8 (14.0)	21 (24.1)	0.097
10–19	60 (41.6)	22 (38.5)	38 (43.6)	
20–29	47 (32.6)	25 (43.8)	22 (25.2)	
30–39	8 (5.5)	2 (3.5)	6 (6.8)	
CC-score				
CC-0	94 (65.2)	37 (64.9)	57 (65.5)	0.637
CC-1	42 (29.1)	18 (31.5)	24 (87.5)	
CC-2/3	8 (5.5)	2 (3.5)	6 (6.8)	
Mean operating time (mins)	430 ± 141	480 ± 114	340 ± 127	<0.001
Blood loss (mL)	800 ± 590	730 ± 503	975 ± 602	0.114
Median ICU stay	3 [0–14]	3 [1–14]	3 [0–11]	0.273
Median hospital stay	12 [7–38]	12 [7–38]	13 [8–37]	0.880
90-day grade 3–4 morbidity	46 (31.9)	20 (35.0)	26 (29.8)	0.278
90-day post-operative mortality	5 (3.4)	3 (5.2)	2 (2.2)	0.342
Return to operating room	12 (8.3)	8 (14.0)	4 (4.5)	0.053
Median time to adjuvant chemotherapy	38 [32–77]	39 [38–50]	35 [32–77]	0.871

Abbreviations: NACT, neoadjuvant chemotherapy; ECOG, Eastern cooperative oncology group; PCI, peritoneal cancer index; ASA, American Society of Anesthesiologists; TPP, total parietal peritonectomy; HIPEC, hyperthermic intraperitoneal chemotherapy; CC-score, completeness of cytoreduction score; ICU, intensive care unit.

Table 2. Surgical procedures performed in 144 patients undergoing TPP with or without HIPEC.

Clinical parameter	All patients	TPP and HIPEC	TPP	p-value
	N = 144 (%)	N = 57 (%)	N = 87 (%)	
Surgical complexity score				
Low	0 (0.0)	0 (0.0)	0 (0.0)	0.019
Intermediate	29 (20.1)	6 (10.5)	23 (26.4)	
Complex	115 (79.9)	51 (89.5)	64 (73.6)	
Peritonectomies				
5	6 (4.1)	1 (1.7)	5 (5.7)	0.008
6	3 (2.0)	1 (1.7)	2 (2.2)	
7	135 (93.7)	55 (96.4)	80 (91.9)	
Visceral resections				
0	7 (4.8)	1 (1.7)	6 (6.8)	0.276
0–3	56 (38.8)	26 (45.6)	30 (34.4)	
4–5	57 (39.5)	19 (33.3)	38 (43.6)	
>5	31 (21.5)	12 (21.2)	19 (21.8)	
Bowel anastomosis				
0	54 (37.5)	16 (28.0)	38 (43.6)	0.203
1	68 (47.2)	29 (50.8)	39 (44.8)	
2	18 (12.5)	10 (17.5)	8 (9.1)	
>2	4 (2.7)	2 (3.5)	2 (2.2)	
Diverting o'stomy				
Yes	19 (13.1)	6 (10.5)	13 (14.9)	0.443
No	125 (86.9)	51 (89.5)	74 (85.1)	
Diaphragm resection	21 (14.5)	7 (12.2)	14 (16.0)	0.526
Pancreatic resection	3 (2.0)	1 (1.7)	2 (2.2)	0.882
Splenectomy	55 (38.1)	27 (47.3)	28 (32.1)	0.066
Rectosigmoid resection	75 (52.0)	32 (56.1)	43 (75.4)	0.972
Total colectomy	12 (8.3)	6 (10.2)	6 (6.8)	0.440
Small bowel resection	10 (6.9)	3 (5.2)	7 (8.0)	0.520
Lymph node dissection	102 (70.8)	44 (77.1)	58 (66.6)	0.174

Abbreviations: TPP, total parietal peritonectomy; HIPEC, hyperthermic intraperitoneal chemotherapy.

The major morbidity and mortality were similar in the three groups (Table 5). 100% of the patients in the interval CRS group had all 7 peritonectomies since the formal protocol required it. The number of visceral resections (>3 viscera resected) and lymphadenectomy were significantly higher in the primary and interval groups compared to the secondary CRS group (Table 6). 70% of the patients in the primary and secondary CRS groups and 56% in the interval group had at least one bowel anastomosis.

4. Discussion

This study shows that extensive cytoreductive surgery comprising of TPP and multi-visceral resection can be performed with an acceptable morbidity (31.9%) at different time points in the history of advanced ovarian cancer. The use of HIPEC did not add to the morbidity which was influenced by the extent of disease and the extent of surgery. All except two patients were able to start adjuvant chemotherapy within 6 weeks of surgery.

Patients receiving NACT had a significantly higher risk

of morbidity. These were the patients undergoing interval or secondary CRS. Some patients with recurrent disease received neoadjuvant chemotherapy to downstage the disease. These were the patients who did not have a complete cytoreduction during the first surgery that was performed by non-specialists and were considered for a secondary cytoreduction [19]. Currently there is no study evaluating the role of secondary CRS in such patients. Some of these patients who are asymptomatic with a good performance status could benefit from a secondary CRS. And this is the reason why we have not used any of the scores for selecting patients for secondary CRS. Regarding patients undergoing interval CRS, the PCI and extent of surgical resection did not differ compared to the two other groups. There are several reasons for this. First, a fixed surgical protocol that necessitated performing all seven peritonectomies was followed as part of an ongoing study. A total small bowel mesenteric peritonectomy is not part of the protocol and in absence of visible disease representative biopsies were taken from each of the regions 9–12. Second, all surgeons resected areas of scarring post NACT as these areas are known to harbor chemotherapy resistant stem cells [25]. Therefore, certain viscera like the rectum prone to harboring residual disease were resected even if the tumor nodules had been replaced by scar tissue. Third, being referral centers, patients with more advanced disease and a poor response to chemotherapy were referred for surgery.

4.1 Extent of surgery and the surgical complexity score (SCS)

The complexity of surgery is difficult to define. According to the surgical complexity score by Aletti *et al.*, all the procedures in this study were intermediate or complex with nearly 80% being complex. This is probably the reason why it had no impact on the morbidity. The HIPEC group had a significantly higher proportion of complex procedures compared to the non-HIPEC group. Though this score has been validated, it does not take into account some complex procedures that are often part of such surgeries like clearance of region 2 that includes the lesser omentum, periportal region and the superior recess of the lesser sac [26–28].

The number of peritonectomies and viscera resected did not have an impact on morbidity probably because a large proportion of patients had all 7 peritonectomies (93.7%) and more than 3 visceral resections (61.0%). The number of bowel anastomoses was more than 1 in 15.2% and one or more in 62.3%. Though this factor was significant on univariate analysis, it was not significant on multivariate analysis. Small bowel resection was performed in 10 patients of which 9/10 had a PCI >10 and 8/10 patients had both 2 or more bowel anastomoses and resection of more than 3 viscera. Thus, small bowel resection could be considered a surrogate for more extensive surgery in this study and it was an independent predictor of an increased major morbidity. In a retrospective study of 130 patients, the volume of disease on the small bowel as determined by the small bowel PCI was one of the independent predictors of a poorer overall survival [29].

Table 3. Major complications in 144 patients undergoing TPP with or without HIPEC.

Complication	All patients	TPP and HIPEC	TPP	<i>p</i> -value
	N = 144 (%)	N = 57 (%)	N = 87 (%)	
Total number of patients with major complications	46 (31.9)	20 (35.0)	26 (29.8)	
Hemorrhage	5 (3.4)	4 (7.0)	1 (1.1)	
Bowel fistula/anastomotic leaks	4 (2.7)	2 (3.5)	2 (2.2)	
Intestinal perforation	0 (0.0)	0 (0.0)	0 (0.0)	
Other GI complications	4 (2.7)	1 (1.7)	3 (3.4)	
Respiratory complications	11 (7.6)	3 (5.2)	8 (9.1)	0.384
Cardiac complications	2 (1.3)	1 (1.7)	1 (1.1)	
Urologic complications	2 (1.3)	1 (1.7)	1 (1.1)	
Nephrotoxicity	0 (0.0)	0 (0.0)	0 (0.0)	
Hematologic toxicity	3 (2.0)	2 (3.5)	1 (1.1)	
Neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	
Systemic sepsis	4 (2.7)	2 (3.5)	2 (2.2)	
Surgical site infection	2 (1.3)	1 (1.7)	1 (1.1)	
Wound dehiscence	3 (2.0)	0 (0.0)	3 (3.4)	
Intrabdominal abscess	3 (2.0)	0 (0.0)	3 (3.4)	
Post op ascites/fluid collection	10 (6.9)	3 (5.2)	7 (8.0)	0.520
90-day post-operative mortality	5 (3.4)	3 (5.2)	2 (2.2)	

Abbreviations: GI, gastrointestinal; TPP, total parietal peritonectomy; HIPEC, hyperthermic intraperitoneal chemotherapy.

Table 4. Factors affecting major morbidity.

Clinical parameter	Univariate analysis	Multivariate analysis	95% confidence interval	
	<i>p</i> -value	<i>p</i> -value	Lower bound	Upper bound
Age >40	0.476			
HIPEC drug	0.499			
Timing of intervention	0.541			
NACT	0.032	0.031	0.017	0.592
Rectosigmoid resection	0.065			
Colonic resection	0.092			
Splenectomy	0.447			
Small bowel resection	0.022	0.038	0.016	0.339
Glissonectomy	0.354			
Diaphragmatic resection	0.940			
Lymphadenectomy	0.271			
PCI <10	0.030	0.001	-0.117 -0.117	-0.414
Stoma	0.842			
HIPEC	0.379			
CC-0 versus CC-1-3	0.886			
Bowel anastomosis	0.025	NS		
Peritonectomies	0.174			
Surgical Complexity Score (SCS)	0.732			
Duration of surgery >480 mins	0.014	NS		

Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; NACT, neoadjuvant chemotherapy; PCI, peritoneal cancer index.

4.2 Type of complications

Considering that all patients had diaphragmatic surgery, the incidence of respiratory complications (7.6%) is low [30]. There are two practices that have reduced the incidence of these complications in our experience. All patients start incentive spirometry from the day they are first seen by the sur-

geon. The other is the use of non-invasive ventilation after extubation in the post-operative period. Though many surgeons do not advocate it, we used thoracic drainage tubes for all patients undergoing diaphragmatic stripping which may be responsible for the fewer complications.

Table 5. Comparison of clinical parameters of patients undergoing primary, interval and secondary CRS.

Clinical parameter	All patients N = 144(%)	Primary CRS N = 30 (%)	Interval CRS N = 90 (%)	Secondary CRS N = 24 (%)	p-value
Age					
<50	40 (27.7)	9 (30.0)	20 (22.3)	11 (45.8)	0.068
>50	104 (72.3)	21 (70.0)	70 (77.7)	13 (54.2)	
No of lines of previous chemotherapy					
0	120 (83.3)	30 (100.0)	90 (100.0)	0 (0.0)	<0.001
1	16 (11.1)	0 (0.0)	0 (0.0)	16 (66.6)	
>1	8 (5.5)	0 (0.0)	0 (0.0)	8 (33.3)	
Neoadjuvant chemotherapy					
Yes	97 (67.3)	0 (0.0)	90 (100.0)	7 (29.1)	<0.001
No	47 (32.7)	30 (100.0)	0 (0.0)	17 (70.9)	
No of NACT cycles					
3–4	75 (52.0)	-	70 (77.7)	5 (20.8)	0.699
>4	22 (15.2)	-	20 (22.3)	2 (8.3)	
ECOG					
0–1	144 (100.0)	30 (100.0)	90 (100.0)	24 (100.0)	-
>1		0 (0.0)	0 (0.0)	0 (0.0)	
ASA					
1	120 (83.3)	23 (76.6)	79 (87.7)	18 (75.0)	0.19
2–3	24 (16.7)	7 (23.4)	11 (12.3)	6 (25.0)	
Median surgical PCI [range]	17 [1–37]	18 [6–35]	16 [1–37]	18 [5–31]	0.523
Surgical PCI					
0–9	29 (20.1)	7 (23.3)	17 (18.8)	5 (20.8)	0.191
10–19	60 (41.6)	9 (30.0)	44 (48.8)	7 (29.1)	
20–29	47 (32.6)	11 (36.6)	27 (30.0)	9 (37.5)	
30–39	8 (5.5)	3 (10.0)	2 (2.2)	3 (12.5)	
CC-score					
CC-0	94 (65.2)	21 (70.0)	64 (71.1)	9 (37.5)	0.039
CC-1	42 (29.1)	9 (30.0)	21 (23.3)	12 (50.0)	
CC-2/3	8 (5.5)	0 (0.0)	5 (5.5)	3 (12.5)	
HIPEC					
Yes	57 (39.5)	5 (16.6)	38 (42.2)	14 (58.3)	0.005
No	87 (60.5)	25 (83.4)	52 (51.8)	10 (41.7)	
Mean operating time (mins)	430 ± 141	321.9	409.8	534.31	0.006
Blood loss (mL)	990 ± 590	1002.5	1046.5	850	0.088
Median ICU stay (days)	3 [0–14]	2 [0–5]	2 [0–12]	3 [2–14]	0.347
Median hospital stay (days)	12 [7–38]	12 [8–20]	13 [7–38]	14 [7–36]	0.377
90-day grade 3–4 morbidity	46 (31.9)	8 (26.6)	30 (33.3)	8 (33.3)	0.784
90-day post-operative mortality	5 (3.4)	2 (6.6)	4 (4.4)	1 (4.1)	0.873
Return to operating room	12 (8.3)	1 (3.3)	9 (10.0)	2 (8.3)	0.519

Abbreviations: NACT, neoadjuvant chemotherapy; ECOG, Eastern cooperative oncology group; PCI, peritoneal cancer index; ASA, American Society of Anesthesiologists; CRS, cytoreductive surgery; CC-score, completeness of cytoreduction score; HIPEC, hyperthermic intraperitoneal chemotherapy.

The second most common complication was post-operative fluid collections and ascites that are common after such extensive resections especially when a para-aortic lymphadenectomy is performed. Since the publication of the LION trial, only enlarged or suspicious nodes are removed during surgery [31].

Though nearly 65% of the patients had at least one bowel resection and only 13.1% had a diverting o'stomy, the incidence of bowel fistulas (2.7%) could be considered low.

All surgeons routinely apply a protective layer of sutures around the rectal anastomosis as described by Sugarbaker which helps avoiding a stoma [32]. However, when more than two anastomoses were performed all patients had a diverting stoma. All patients with an anastomotic leak or fistula were salvaged and were able to start chemotherapy on time.

4.3 Mortality

There were 5 (3.4%) post-operative deaths which may be a concern in this patient population. One patient died due to

Table 6. Comparison of surgical procedures performed in patients undergoing primary, interval and secondary CRS.

Surgical Procedure	All patients N = 144 (%)	Primary CRS N = 30 (%)	Interval CRS N = 90 (%)	Secondary CRS N = 24 (%)	p-value
Surgical complexity score					
Low	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.137
Intermediate	29 (20.1)	7 (23.3)	14 (15.5)	8 (33.3)	
Complex	115 (79.9)	23 (76.7)	76 (84.5)	16 (66.7)	
Peritonectomies					
5	6 (4.1)	2 (6.6)	0 (0.0)	4 (16.6)	0.003
6	3 (2.0)	3 (10.0)	0 (0.0)	0 (0.0)	
7	135 (93.7)	25 (83.3)	90 (100.0)	20 (83.4)	
Visceral resections					
0–3	56 (38.8)	6 (20.0)	31 (34.4)	19 (79.1)	<0.001
4–5	57 (39.5)	14 (46.6)	39 (43.3)	3 (12.5)	
>5	31 (21.5)	10 (3.3)	20 (22.2)	1 (4.1)	
Bowel anastomosis					
0	54 (37.5)	9 (30.0)	39 (43.3)	7 (29.1)	0.021
1	68 (47.2)	20 (66.6)	39 (43.3)	8 (33.3)	
2	18 (12.5)	1 (3.3)	10 (11.1)	7 (29.1)	
>2	4 (2.7)	0 (0.0)	2 (2.2)	2 (8.3)	
Diverting o'stomy					
Yes	19 (13.1)	3 (10.0)	11 (12.2)	5 (20.8)	0.457
No	125 (86.9)	27 (90.0)	79 (87.8)	19 (79.2)	
Diaphragm resection	21 (14.5)	7 (23.3)	14 (15.5)	0 (0.0)	0.149
Pancreatic resection	3 (2.0)	1 (3.3)	2 (2.2)	0 (0.0)	0.917
Splenectomy	55 (34.7)	11 (36.6)	36 (40.0)	8 (33.3)	0.821
Rectosigmoid resection	75 (52.0)	19 (63.3)	41 (45.5)	15 (62.5)	0.128
Small bowel resection	10 (6.9)	3 (10.0)	5 (5.5)	2 (8.3)	0.679
Total colectomy	12 (7.6)	4 (13.3)	8 (8.8)	0 (0.0)	0.504
Lymph node dissection	102 (70.8)	20 (66.6)	71 (78.8)	11 (45.9)	0.005

Abbreviations: CRS, cytoreductive surgery.

myocardial infarction after discharge from the hospital but was included as it may be assumed that the same was precipitated by the surgical stress. All patients undergo optimization of comorbidities before surgery. A screening echocardiogram is performed for all patients undergoing surgery, irrespective of the history of ischemic heart disease or age. All patients had a performance status of 0–1 and very few patients belonged to ASA category III. The other factor leading to post-operative mortality was systemic sepsis which has been a problem in our set-up [33]. As we have pointed out previously, the injudicious use of antibiotics in the community and hospitals both may be responsible for the emergence of multidrug resistant strains that could not be controlled with the highest antibiotics available [33]. Cultures of abdominal fluid during surgery and preoperative blood cultures are performed in patients undergoing surgery to screen out those already harboring infection and treat it early.

4.4 Time to adjuvant chemotherapy

The usual time to chemotherapy is 3–4 weeks in patients undergoing debulking surgery for ovarian cancer. Following such extensive procedures a minimum of 4 weeks is needed. The normal postoperative course of patients undergoing CRS and HIPEC is different from other surgical pro-

cedures [34]. The loss of appetite and generalized weakness persist for at least a month and starting adjuvant therapy by 6 weeks seems to be a plausible goal. In a prospective non-randomized trial evaluating the feasibility of HIPEC in patients undergoing primary CRS, the median time to starting adjuvant chemotherapy from surgery was 42 days [32].

This study is retrospective in nature and the study population was defined on the basis of the surgical procedure performed which excludes patients that were eligible for the procedure but did not undergo it due to other reasons. Similarly, except for interval CRS where all the patients were included in a prospective study with a fixed surgical protocol, selection criteria and surgical strategies were based on each of the surgeons' preferences which is the main limitation of this study. To evaluate the impact of HIPEC, more uniform criteria for performing or excluding it would yield more impactful data. Nevertheless, this study is the first to perform a correlation between the extent of CRS and morbidity in patients undergoing HIPEC. The disease extent (PCI) and the extent of surgery performed have both been meticulously documented. Future studies with a larger and more homogenous patient population should be carried out to confirm these findings.

5. Conclusions

The addition of HIPEC to TPP and multi-visceral resections had an acceptable morbidity in patients undergoing primary, interval and secondary CRS. The morbidity was affected by the disease extent and the extent of surgery performed and not by HIPEC. Further research should be performed to confirm these findings in more homogeneous patient cohorts.

Author contributions

AB and PK designed this study. AB, PK, SSin, SM, BM, SB, SSha and LP were responsible for data acquisition. SM, NB, DA, SB, MB and BM were responsible for quality control of data. The resources for the study were managed by SM, NB, DA and GG. The data analysis was performed by PK, SSin, GG, SSha and AB. The statistical calculations were performed by PK and AB. Interpretation of the results was performed by AB, PK, SSin, SM, LP and NB. The manuscript was prepared by AB, SSin and PK. All authors contributed to the editing of the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

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