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ORIGINAL ARTICLE

Impact of Radicality Versus Timing of Surgery in Patients with Advanced Ovarian Cancer (Stage III C) Undergoing CRS and HIPEC—a Retrospective Study by INDEPSO

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Abstract

HIPEC in addition to interval CRS has shown a survival benefit of 12 months compared to CRS alone. However, there are many controversial issues pertaining to CRS itself which should be addressed first. To compare NACT and primary CRS approaches when CRS is categorized according to the extent of resection. To evaluate the feasibility of performing HIPEC at these two time points. A retrospective analysis of patients with stage III C ovarian cancer undergoing primary and interval CRS + HIPEC was performed. The surgical approach for interval CRS was classified as (1) resection of sites of residual disease alone or (2) resection of sites involved before NACT. The morphological response was divided into different categories, and surgeons had to state what they consider residual disease and what they do not. From January 2013 to December 2017, 54 patients were included (18-primary; 36-interval). Median PCI 11 vs 6.5 ($p = 0.07$); CC-0 was obtained in 77.7%. Three surgeons resected previously involved sites; three sites of residual disease only. All surgeons resected areas of scarring. Twenty percent patients had residual disease in "normal-looking" peritoneum. Morbidity ($p = 0.09$), median OS ($p = 0.71$), and median DFS ($p = 0.54$) were similar in the two groups. Early recurrence occurred in 50% with resection of residual disease alone compared to 16.6% when previous disease sites were resected ($p = 0.07$). Interval CRS should be performed to resect sites involved prior to NACT and not just sites of residual disease. HIPEC can be performed in both primary/interval settings with acceptable morbidity.

Keywords Ovarian cancer · Cytoreductive surgery · Interval debulking · HIPEC · Radical surgery · Interval CRS

Introduction

With cytoreductive surgery and systemic chemotherapy, the 5-year overall survival for advanced ovarian cancer is only 30–50%. [1, 2] Encouraging reports from several nonrandomized studies and case series have shown improved survival with the use of HIPEC in ovarian cancer. [3] Recently, a phase 3 randomized controlled trial has shown a 12-month survival benefit in patients undergoing HIPEC in addition to CRS after neoadjuvant chemotherapy (NACT) in stage III C ovarian cancer. [4] However, there are many controversial issues pertaining to CRS itself in ovarian cancer which should be addressed before evaluating the benefit of HIPEC.

Many investigators have stressed upon the impact of the timing of surgery in ovarian cancer. [5] When surgery is performed after few cycles of NACT, the morbidity is reduced but if the overall results are compared matching patients according to the completeness of surgery, the survival is inferior following NACT as compared to CRS

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performed upfront [6]. Ovarian cancer is a chemosensitive disease in which first-line chemotherapy produces a response rate of around 60–80% [7]. This is similar to the response rates in breast cancer [8]. However, surgery following NACT is clearly non-inferior in breast cancer and is used to downstage large tumors to allow conservation of the breast [8]. In locally advanced breast cancer, there is usually one primary tumor and a predefined nodal basin. In contrast, stage III C ovarian cancer presents as multiple small and large nodules distributed over the entire peritoneum. Imaging can determine the response to chemotherapy but it cannot accurately identify the sites of residual disease [9]. Hence, the surgeon has to rely on visual inspection performed during surgery to determine the sites of residual disease. All investigators use only the size of residual disease as a metric to evaluate the adequacy of the surgery. However, this is a very subjective evaluation. There is no consensus on what to do with sites of minimal residual disease or scarring [10]. It has been demonstrated that normal peritoneum and scar tissue following NACT can both harbor residual disease [11]. A systematic description of surgical strategy to be followed at the time of interval CRS is missing in scientific literature, and hence, the results of studies will remain questionable.

The next important issue in this regard is patient selection. Patients in stage III C ovarian cancer can have less or more extensive disease. In a large proportion, most surgeons would unanimously adopt one of the two approaches; for e.g., in a patient with massive ascites leading to breathlessness, few would prefer surgery upfront and in those with limited peritoneal disease outside the pelvis without ascites, most would prefer to perform a primary CRS. There remains a subgroup that has moderate ascites with peritoneal disease that is completely resectable and in this situation, the debate of selecting one of the two approaches arises [12]. One can quote any study published in literature and choose to believe NACT is inferior or non-inferior, but in reality, till the surgical procedures are standardized based on the extent of resection rather than a subjective evaluation of the size of residual disease, such a comparison is of questionable value.

In study, we aimed to make a comparison between the two approaches when the surgery was categorized according to the extent of resection and the type of morphological response on visual inspection during surgery was categorized. In addition, our aim was to evaluate the feasibility of performing HIPEC at these two time points.

Methods

A retrospective analysis of prospectively collected data from members of the Indian Network for Development of Peritoneal Surface Oncology (INDEPSO) was performed. All patients undergoing primary and interval CRS with HIPEC enrolled in the Indian HIPEC registry were included in the study. Patients with an initial diagnosis of serous epithelial ovarian cancer with peritoneal disease outside the pelvis (Stage III C) were included in the study. The decision to perform a primary CRS or interval CRS was based on the probability of obtaining a complete cytoreduction, and when a CC-0 resection was not possible, 3 cycles of neoadjuvant chemotherapy were administered first. Institutional permission was obtained by each surgeon to perform HIPEC in addition to CRS.

Surgical Procedures

All patients underwent systematic exploration of the abdominal cavity through a midline incision from the xiphoid to the pubis. The extent of disease was quantified according to Sugarbaker's peritoneal cancer index (PCI) [13]. The peritonectomy procedures comprised of the five peritonectomies described by Sugarbaker, i.e. pelvic, bilateral anteroparietal, right upper quadrant, left upper quadrant, and a total omentectomy [14]. In the presence of any amount of disease in a region, the peritonectomy corresponding to that region was performed. For example, in presence of a single deposit in the pouch of Douglas, a complete pelvic peritonectomy was performed. In the interval setting, the same principle was followed. The surgical approach in the interval setting was classified into two categories—resection of sites of residual disease alone and resection of sites involved before NACT plus sites of residual disease. Surgeons were asked to state if they resect areas of scarring or not. In addition, the morphological response was divided into different categories and surgeons had to state what they consider residual disease and resect and what they do not consider residual disease.

A retroperitoneal lymphadenectomy was performed till the level of the renal veins in all patients.

The completeness of cytoreduction score was used to describe the completeness of surgery. The goal of all the procedures was to obtain a CC-0 resection. [13]

HIPEC

HIPEC was performed by the open technique maintaining an intra-abdominal temperature of 41–43°C using a cisplatin-based regimen for 90 min. Cisplatin was given alone at 70–80 mg/m^2 or in combination with adriamycin (cisplatin 50 mg/m^2 and adriamycin 15 mg/m^2) in 2–4 l of peritoneal dialysis fluid [14, 15]. Bidirectional chemotherapy was given in patients in whom the combination of cisplatin, and adriamycin was used with 1300 mg/^{2} of ifosfamide infused

intravenously over 90 min of the HIPEC procedure as described by Sugarbaker. [15]

Adverse Events

Adverse events (AEs) were reported according to the National Cancer Institute Common Toxicology Criteria for Adverse Events (CTCAE) version 4.3 [16]. All patients received standard doublet chemotherapy comprising of a platinum compound and taxane. A total of 6 cycles was administered as neoadjuvant and adjuvant therapy.

Evaluation of Pathological Response to Chemotherapy

The pathological response to chemotherapy was graded based on the chemotherapy response score developed by Bohm et al. [17, 18]. The term "chemotherapy response grade" (CRG) is used here. CRG 1 stands for minimal or no tumor response, CRG 2 for appreciable tumor response amid viable tumor that is easily identifiable, and CRG 3 for complete or near-complete response with no residual tumor or minimal irregularly scattered tumor foci up to 2 mm in size [17]. The response was assessed not just in the ovaries and the omentum (as in Bohm's study) but also at the peritoneal sites.

Follow-Up

Disease progression was defined based on the recommendations by the Gynecologic Cancer Inter Group (GCIG) and was either radiological evidence of progression or an increase in tumor marker level [19]. Recurrence within 18 months of surgery was defined as early recurrence.

Statistical Calculations

Clinicopathological details, morbidity profile, and survival were compared between the two groups. Overall survival (OS) was calculated from the date of CRS + HIPEC to the date of death or last follow up, and progression-free survival (PFS) was determined from the date of CRS + HIPEC to the date of first recurrence. Survival curves were calculated using the Kaplan–Meier method and compared using the two-tailed log-rank test. Descriptive variables were analyzed using nonparametric tests, χ^2-test/Fischer exact test for categorical variables and Mann-Whitney U test for continuous variables. All statistical tests were two sided, with the significance level established at p value of < 0.05. All statistical analyses were conducted using SPSS version 22.0.0 (IBM Corporation, Armonk, NY, USA).

Results

Patient characteristics and treatment

From January 2013 to December 2017, 54 patients underwent CRS and HIPEC (18 in the primary and 36 in the interval setting) at 6 Indian centers (Table 1).

The median age of the entire cohort was 53 years (range 20–70). The median PCI was higher in patients undergoing interval CRS + HIPEC as compared to primary CRS + HIPEC 11 vs 6.5 ($p = 0.07$). Of all patients, 36.1% had positive retroperitoneal lymph nodes in the interval group compared to 5.5% in the primary group ($p = 0.014$). A CC-0 resection was obtained in 28 (77.7%) patients and CC-1 in 8 (22.3%) in the interval CRS group. In patients undergoing primary CRS, 14 (77.7%) had a CC-0 resection and 4 (22.3%) had a CC-1 resection.

Surgical Procedures

Three surgeons resected sites involved prior to administration of NACT and three resected sites of residual disease alone. The categorization of morphological response during surgery by six surgeons is described in Table 2. All surgeons resected areas of scarring considering them to be positive for residual disease. Upper quadrant procedures (including a right/left upper quadrant peritonectomy) were performed in 13 (72.2%) patients in the primary CRS group and 30 (83.3%) in the interval group (Table 3). Overall, previously involved sites as well as sites of residual disease were resected in 30 (83.3%) patients and only sites of residual disease were resected in 6 (16.7%). In 30 patients with resection of previously involved sites, 6 (20%) had microscopic disease in normal-looking peritoneum at one or more sites. Eleven (30.5%) patients in the interval group had resection and/or electroevaporation of mesenteric disease.

Pathology Findings

Four (11.1%) patients had a near complete response (CRG 3; 1 complete responder), 19 (52.7%) had a moderate response (CRG 2), and 13 (36.1%) had a poor response (CRG 1). The surgical PCI was the same as the pathological PCI in 17 patients, less in 6 and more in 7 in the previous site resection group (Table 4). In the other group, the surgical PCI was more in four patients and the same in two patients.

Morbidity and Mortality

The median hospital stay was longer in patients undergoing interval CRS (13.5 days) vs (10 days) following primary CRS (p-0.02). Overall, grade III–IV surgical complications were seen in 33.3% in the primary group and 13.8% in the interval

Table 1 Comparison of clinical features, disease characteristics and perioperative outcomes in patients undergoing primary versus interval cytoreduction

Characteristic		All patients ($n = 54$)	Primary Cytoreduction ($n = 18$)	Interval Cytoreduction ($n = 36$)	*P* value
Age	<50	22 (40.7)	9	13	0.24
	>50	32 (59.3)	9	23	
ECOG performance status	0-1	52 (96.2)	18	34	0.44
	2/3	2 (3.8)	0	2	
PCI	<10	27 (50.0)	11	16	0.68
	>10	27 (50.0)	7	20	
Median PCI			6.5	11	0.07
Average number of resected organs			2.5	3.5	
Regional nodes	Involved	14 (26.0)	1	13	0.014
	Not involved	40 (74.0)	17	23	
Average duration of surgery			428	510 mins	
Median ICU stay			1 [0-17]	2 [1-19]	
Median Hospital Stay			10	13.5	0.02
Adjuvant Chemo completion	Yes	46 (85.1)	16	30	0.001
	No	8 (14.9)	2	6	
Grade 3-4 Morbidity	Yes	2 (3.8)	0	2	0.44
	No	52 (96.2)	18	34	
90-day grade 3-4 morbidity	Yes	3 (5.6)	2	1	0.25
	No	51 (94.4)	16	35	
90 Day mortality	Yes	51(94.4)	18	33	0.28
	No	3 (5.6)	0	3	
Failure to rescue	Yes	2 (3.8)	0	2	0.44
	no	52 (96.2)	18	34	
Median Follow Up		24 months	15 months	24 months	
Median OS		NR	NR	NR	0.71
3-year OS			93.8%	84%	0.71
Median DFS		NR	NR	37months	0.59
3-year DFS			61%	56%	0.54

group ($p = 0.09$). One (2.7%) patient died within 30 days of surgery in the interval group and one in the primary CRS group. The commonest grade 3–4 complications were pulmonary complications (16.6%), systemic sepsis (7.4%), neutropenia (3.7%), and wound dehiscence (3.7%).

Survival

At a median follow up of 24 months, the 3-year overall survival (OS) was 93.8% in the primary CRS + HIPEC group as compared to 84% in the interval group ($p = 0.71$) (Fig. 1). The

Table 2 Categorization of morphological response to chemotherapy by six surgeons

Morphological finding	Potential site of residual disease	No residual disease
Tumor nodule	6	0
Confluent deposits	6	0
Omental cake	6	0
Plaque	6	0
Thickening	6	0
Scarring	6	0
Tissue adhesion	6	0
Normal peritoneum	3	3

Table 3 Surgical procedures performed in patients undergoing primary versus interval CRS and HIPEC

Characteristic		All patients ($n = 54$) (%)	Primary cytoreduction ($n = 18$)	Interval cytoreduction ($n = 36$)	P value
No. of organs resected	< 3	30 (55.5)	12	18	0.19
	> 3	24 (44.5)	6	18	
Bowel resection		23 (42.5)	9	14	0.43
Right/left subphrenic peritonectomy		44 (81.4)	14	30	0.62
Diaphragm resection		9 (16.6)	3	6	1.00
Splenectomy		13 (24.0)	5	8	0.32
Hepatic resection		2 (3.8)	2	0	
Cholecystectomy		44 (81.4)	8	36	
Distal pancreatectomy		4 (7.4)	2	2	0.46
Pelvic lymphadenectomy		54 (100)	18	36	1.00
Retroperitoneal lymphadenectomy		54 (100)	18	36	1.00

median OS was not reached in both groups. Median PFS was 37 months in the interval CRS + HIPEC group whereas the median PFS was not reached in the primary CRS + HIPEC group. The PFS at 3 years in the primary vs interval CRS + HIPEC group was 61 vs 56% respectively ($p = 0.59$). We did not find any factor that had a significant impact on either the OS or PFS.

Early recurrence, 3 (50%) out of 6 patients who had resection of only residual disease developed early recurrence and 5 (16.6%) out of 30 patients who had resection of previous, and residual disease sites developed recurrence ($p = 0.07$). Early recurrence developed in 1 (5.5%) patient in the primary CRS group compared to 8 (22%) in the interval group ($p = 0.13$).

Discussion

This study demonstrates the benefit of systematic radical surgery in ovarian cancer and the feasibility of HIPEC in addition to such procedures. The median DFS of 37 months in the interval CRS arm is high compared to most published results though the follow up is short [20, 21]. Nearly 80% of our patients had upper abdominal surgery comprising of diaphragmatic peritonectomy. The abdomen was systematically explored with division of all the adhesions and adequate exposure of the peritoneal surfaces. The pattern of response to chemotherapy has not been documented for ovarian cancer; hence, one does not know which sites will respond in which manner. It is impossible to determine the disease status in certain areas without adequate exposure; for example, mere palpation of the liver surface and right diaphragm may miss disease on the lower part of the dome and the tendinous portion of the diaphragm which can be demonstrated only after complete division of the falciform and the right coronary ligament. Sometimes, there are adhesions between the peritoneum and the liver and these need to be divided to demonstrate presence or absence of residual disease. Similarly, disease in lesser sac and over the pancreatic capsule will be missed if the same is not looked for and can be present in absence of gross

Table 4 Comparison of outcomes between patients with resection of previous disease sites and resection of only residual disease sites

		Resection of previous disease sites ($n = 30$)	Resection of residual disease sites only ($n = 6$)
PCI	< 10	10	6
	> 10	20	0
CC-score	CC-0	22	6
	CC-1	8	0
Mean no of organs resected		3.2	3.1
Bowel resection		9	3
Grade 3–4 complications		5	0
Chemotherapy response grade	CRG 1	11	2
	CRG 2	16	3
	CRG 3	3	1

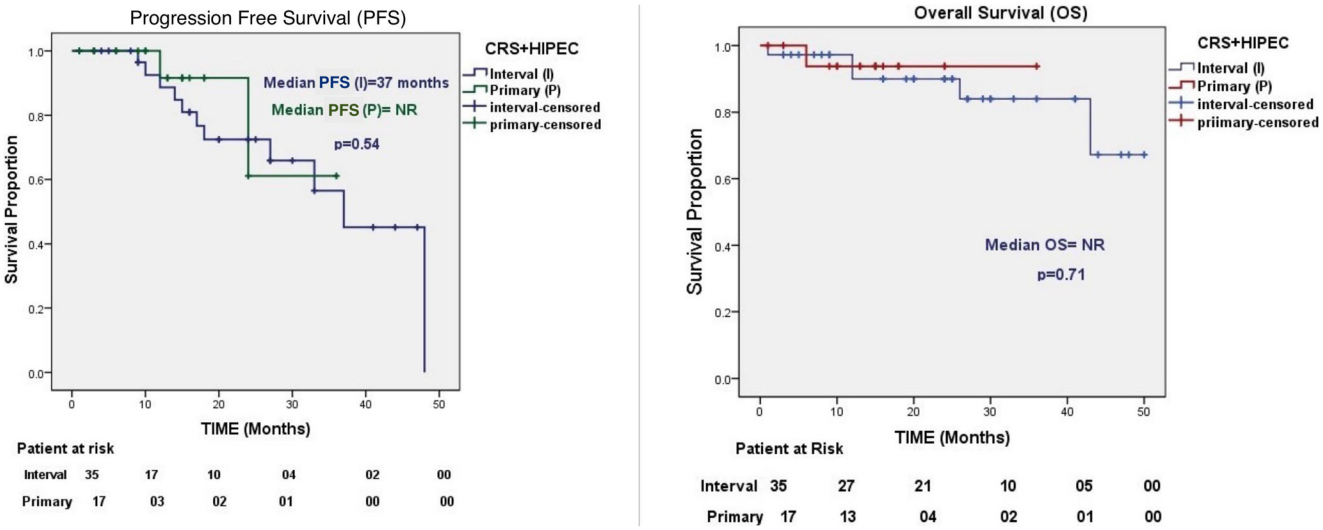

Fig. 1 Progression-free and overall survival in patients undergoing primary and interval CRS and HIPEC

omental disease. Secondly, formal peritonectomies were performed in regions harboring disease and thirdly, a uniform objective assessment of the morphological response has been made. All surgeons classified areas of scarring as residual disease and resected those areas. Our decision to resect areas of scarring and previous disease sites is supported by the fact that 20% of the patients had residual disease in normal-looking peritoneum.

It may be assumed from these results that systematic radical surgery following NACT targeted at resecting previously involved peritoneal sites can lead to a prolonged PFS and OS. There was no difference in the 3-year OS or PFS between the two groups. This is despite the fact that patients undergoing primary CRS and HIPEC had less extensive disease.

Of the patients in both the primary and interval groups, 77.7% had a CC-0 resection. In the remaining patients, the residual disease size was < 2.5 mm and this can be dealt with HIPEC.

The importance of a complete cytoreduction in ovarian cancer had already been demonstrated [22]. And in selecting patients for surgery upfront or chemotherapy, the possibility of a CC-0 resection should be considered. If there is even < 1 cm residual disease on the bowel as opposed to no residual disease, the approach in which no residual disease is left behind should be preferred. When primary CRS is performed leaving behind residual tumor < 1 cm, there is no way to determine if the chemotherapy completely eradicated the disease.

There was a higher incidence of complications in the primary CRS group which failed to reach statistical significance ($p = 0.09$). There was one death due to complications in the interval group (due to systemic sepsis) and one in the primary group. This is similar to the major morbidity reported in patients undergoing CRS with/without HIPEC [4, 23].

We have defined early recurrence/progression as recurrence within 18 months as the average PFS reported in most studies is 15–18 months [4, 19]. It has been shown patients who recur after 12 months of frontline therapy fare better than those that recur early, even if the disease is platinum sensitive. Early recurrence/progression was seen in 22.2% in the interval arm and only 5.5% patient in the primary CRS arm. The proportion of early recurrence was higher (50 versus 16.6%; $p = 0.07$) in patients who did not undergo resection of previous disease sites following NACT. Many times patients are not optimally cytoreduced and develop progressive disease within 6 months thus being classified as platinum resistant. This is, however, growth of residual disease. Truly platinum refractory/resistant disease is not optimally cytoreduced despite a maximal surgical effort. The question remains regarding the timing of surgery after NACT—whether disease that was not optimally cytoreduced after 3 cycles could be cytoreduced after 6 cycles.

The survival benefit of retroperitoneal lymphadenectomy in complete cytoreduced stage III C patients was challenged by the results of a recent randomized trial that did not show a benefit in patients with negative nodes on imaging in stages II–IV though 56% had microscopic disease in lymph nodes in absence of disease on imaging [24–26]. In this study, 43.3% of the patients undergoing interval CRS had positive retroperitoneal nodes and 25.9% overall. Once again, we propose that the role of lymphadenectomy in these patients should be prospectively evaluated and till some conclusive evidence is available, a systematic retroperitoneal lymphadenectomy should be performed in all patients undergoing CRS for stage III C ovarian cancer and having a CC-0 resection of the peritoneal disease.

The two groups in the study may not be strictly comparable since the median PCI is higher in the interval group. PCI is an important tool in patients with ovarian cancer. Some studies

have demonstrated its prognostic impact on survival; others have not [27, 28]. Nevertheless, it remains important for comparing the disease extent and distribution between the treatment groups.

This study has many limitations. It is retrospective with a small number of patients in each group. The groups are not balanced in terms of disease extent, and the median follow up is short. Nevertheless, it shows that at both time points, HIPEC can be added to CRS with an acceptable morbidity and mortality. To the best of our knowledge, this is the first study to categorize the morphological response to NACT on visual inspection in advanced ovarian cancer and report the surgical procedure according to the extent of resection.

Conclusions

Radical surgery following neoadjuvant chemotherapy can lead to a prolonged survival in patients with advanced ovarian cancer that cannot undergo primary CRS. Surgery following NACT needs to be standardized both in terms of categorizing the morphological response on visual inspection and the extent and should target disease sites involved prior to starting chemotherapy. Further prospective evaluation in larger series should be performed to confirm these findings. The morbidity and mortality of adding HIPEC to CRS in the primary and interval setting is acceptable.

Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflict of interest.

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