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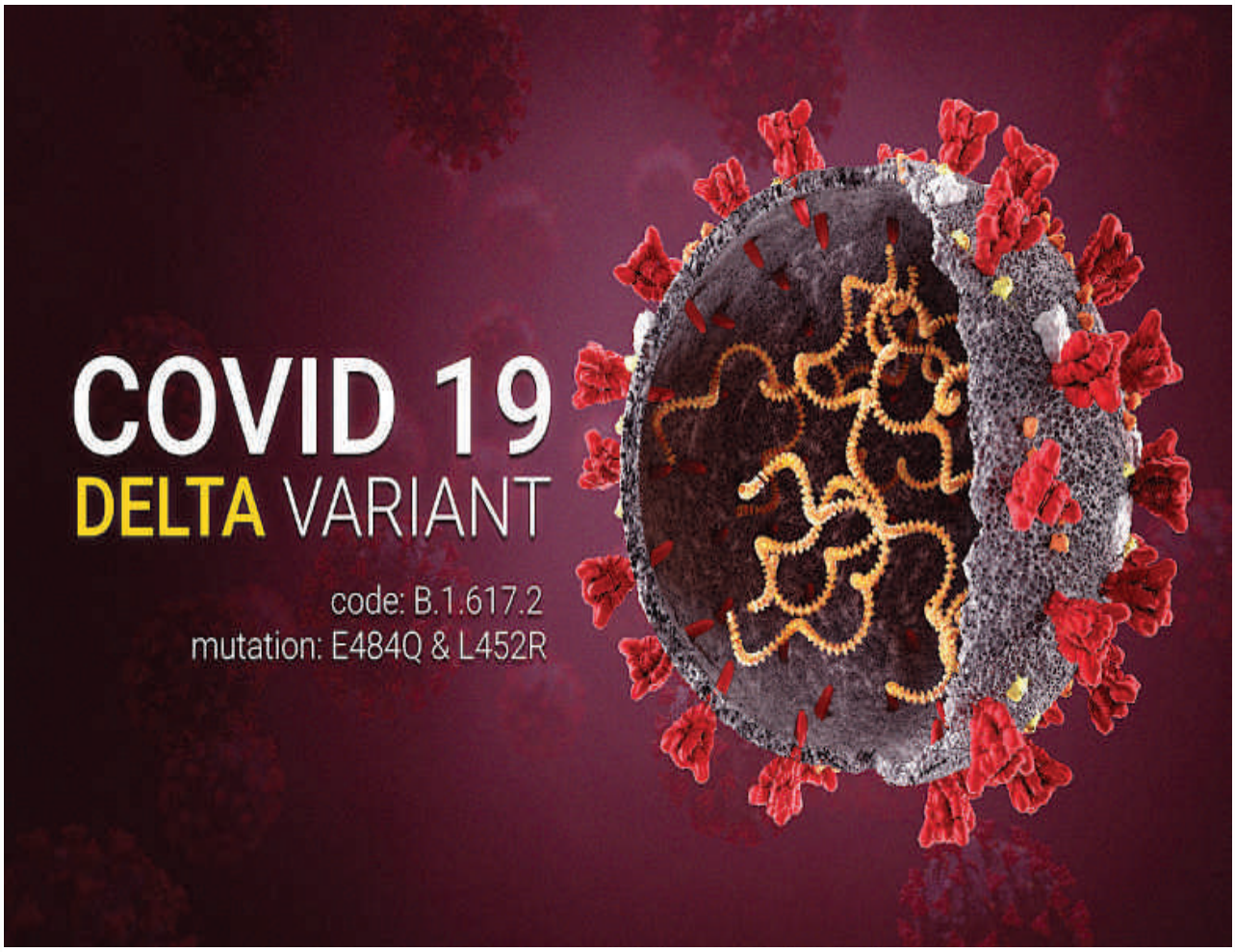

The Official Journal of the Gulf Federation For Cancer Control

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Original Article

Cytoreductive Surgery And Hyperthermic Intraperitoneal Chemotherapy For Recurrent Ovarian Cancer: The First Reported Experience From Saudi Arabia

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Abstract

Objectives: To report our pilot experience (feasibility, morbidity and postoperative outcomes) of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of patients with recurrent ovarian cancer and peritoneal carcinomatosis.

Methods: Thirty nine patients were retrospectively analyzed for perioperative details.

Results: The vast majority of patients had platinum–sensitive disease (69.2%). Complete (CC–0) and incomplete (CC–1/2) resections were achieved in 24 (61.5%) and 15 (38.5%) patients, respectively. The median peritoneal cancer index (PCI) was 14 (range: 2–28). Cisplatin (50 mg/m^2) and doxorubicin (15 mg/m^2) was the most frequently used HIPEC regimen (87.2%). No intraoperative morbidity/mortality happened. A total of eight patients developed III–IV postoperative complications (20.5%). Median follow–up time was 41 months (range: 3–106). No 60–day readmission/mortality happened. At the last date of follow–up, there were 13 patients who were alive without disease (33.4%); mortality occurred in 10 patients (25.6%). For all patients, the mean disease–free survival (DFS) and overall survival (OS) were 46.3 months (95% CI: 33.7–58.9) and 81 months (95% CI: 68.6–93.3), respectively. PCI >14 was correlated with statistically significant poor DFS and OS at univariate analysis (p=0.046). When compared to CC–0, CC–1/2 was correlated with poor DFS and OS, however, without statistical significance. Cox multivariate analyses of DFS and OS failed to demonstrate PCI score, CC score and platinum–sensitivity as independent prognostic factors of DFS and OS.

Conclusions: Our study demonstrated the feasibility, safety and favorable clinical outcomes of CRS and HIPEC in patients with recurrent ovarian cancer and peritoneal carcinomatosis.

Keywords: Cytoreductive surgery; hyperthermic intraperitoneal chemotherapy; peritoneal carcinomatosis; ovarian cancer; recurrent; Saudi Arabia

Introduction

Epithelial ovarian cancer remains the most frequent cause of cancer–related mortalities among patients with female reproductive system malignancies.(1) Despite the first–line treatment protocol of radical surgical cytoreduction and postoperative platinum–based chemotherapy, roughly 70% of patients develop disease relapse in the manifestation of peritoneal carcinomatosis within five years.(2)

The optimal treatment of patients with recurrent epithelial ovarian cancer with peritoneal carcinomatosis remains a focus of dispute among oncologists.(3) As recurrent ovarian cancer is largely peritoneal disease in the absence of widespread metastases, it is best suited for loco–regional regimens.(3) Recent high–quality evidence from meta–analysis revealed the improved overall survival (OS) impact of loco–regional therapy comprising combined cytoreductive surgery (CRS) and

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hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with recurrent ovarian cancer and peritoneal carcinomatosis.[4] Several international medical centers reported their single– and multi–institutional experiences of CRS and HIPEC in patients with recurrent ovarian cancer and peritoneal carcinomatosis.[5–10] Nevertheless, no parallel study to date was described from Saudi Arabia, a third–world country with a relatively growing learning experience in the management of peritoneal surface malignancies.

Hence, the primary objective of this study is to share our pilot experience (feasibility, morbidity and postoperative outcomes) of CRS and HIPEC for the treatment of patients with recurrent ovarian cancer and peritoneal carcinomatosis.

Materials and Methods

This retrospective cross–sectional study was completed at the Department of Obstetrics and Gynecology, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia. The study protocol was approved by the respective Ethical Committee.

From December 2015 to December 2019, the medical records of all patients with peritoneal carcinomatosis arising from recurrent ovarian cancer and treated with CRS and HIPEC were queried for clinical and survival data.

Inclusion criteria for considering CRS and HIPEC included: (i) age below 75 years, (ii) Eastern Cooperative Oncology Group performance status ≤2, (iii) satisfactory laboratory profiles, (iv) proven diagnosis of recurrent ovarian cancer with peritoneal carcinomatosis confirmed by imaging modality and/or intraoperative biopsy, (v) no evidence of systemic metastases, (vi) signed written informed consent and (vii) amenability of tumor to complete cytoreduction.

Preoperative data included age, body mass index, time from first initial surgery to time of CRS and HIPEC for recurrent disease, platinum sensitivity and previous treatments (surgery, radiotherapy and chemotherapy). Operative data included tumor grade, tumor histology, cytoreduction completeness (CC) score, peritoneal cancer index (PCI) score, HIPEC drug, use of ureteric stenting, operative time, estimated blood loss, intraoperative morbidity and intraoperative mortality. Postoperative data included follow–up duration, hospital stay, 60–day morbidity (Clavien–Dindo surgical complications),[11] 60–day mortality, 60–day readmission, adjuvant therapy and latest wellbeing status.

CRS procedures were carried out as previously described by Sugarbaker.[12] PCI and CC scores were assessed intraoperatively by the operating surgeons.[13] The score of PCI was used to assess the extent of peritoneal carcinomatosis. The score of CC was used to assess the extent of residual tumor after completion of CRS. In this study, CC–0 score (no gross residual disease) was regarded as complete cytoreduction. On the other hand, CC–1 (up to 2.5 mm gross residual disease), CC–2 (2.5 mm to 2.5 cm gross residual disease) and CC–3 (more than 2.5 cm gross residual disease) scores were regarded as incomplete cytoreduction.

Our HIPEC protocol had been previously described.[14–16] Briefly, open–abdomen HIPEC technique was carried out at the completion of CRS. Options of HIPEC drugs included either single–agent cisplatin (100 mg/m^2), single–agent melphalan (60 mg/m^2), single–agent mitomycin c (30 mg/m^2) or combination cisplatin (50 mg/m^2) plus doxorubicin (15 mg/m^2) as per the endorsements of the multidisciplinary gynecologic oncology and medical oncology team. HIPEC drugs were circulated in the abdominopelvic cavity for 90 min at 42 °C. Some patients received bilateral ureteric stenting as previously reported by our center.[17]

Postoperatively, several patients received adjuvant chemotherapy of paclitaxel plus carboplatin as deemed appropriate by the multidisciplinary gynecologic oncology and medical oncology team.

Data were reported as numbers and percentages (%) or means/medians and standard deviations (SDs). Wherever applicable, ranges (minimum–maximum) were reported. DFS was calculated from the day of CRS and HIPEC to the time of local/distant disease progression or last date of follow–up, whichever comes first. OS was calculated from the day of CRS and HIPEC to the time of death or last date of follow–up, whichever comes first. DFS and OS rates were reported as means with 95% confidence intervals (95% CIs) and calculated according to the Kaplan–Meier method and compared by using two–tailed log–rank test. Univariate and multivariate Cox proportional hazards model was used to evaluate the significance of several prognostic variables (PCI score, CC score and platinum sensitivity) in predicting DFS and OS. All statistical analyses were completed using the Statistical Package for Social Sciences (SPSS) software version 27 for Windows (SPSS Inc., Chicago, IL, USA). For all results, p values less than 0.05 were determined to be statistically significant.

Results

A sum of 39 patients was included in the analysis. Table 1 portrays the demographic and clinical characteristics of patients. The median time from first staging surgery to HIPEC operation for recurrent ovarian disease was 25

± 30.9 months (range: 4.4–136.9). The vast majority of patients had platinum–sensitive disease (69.2%) and received adjuvant chemotherapy (56.4%).

Variable	n (%)
Median age ± SD (range)	50 ± 12.2 years (24–72)
Median BMI ± SD (range)	28 ± 8 kg/m^2 (16–56)
Age	
<50 years	20 (51.3)
≥50 years	19 (48.7)
Median time from first surgery to HIPEC ± SD (range)	25 ± 30.9 months (4.4–136.9)
Platinum–sensitivity	
Sensitive	27 (69.2)
Resistant	12 (30.8)
Adjuvant chemotherapy	
None	17 (43.6)
Carboplatin	1 (2.6)
Paclitaxel + Carboplatin	12 (30.8)
Doxorubicin + Carboplatin	2 (5.1)
Gemcitabine + Carboplatin	4 (10.3)
Paclitaxel + Carboplatin + Doxorubicin	2 (5.1)

Table 1: Demographic and clinical characteristics of patients.

BMI: body mass index; HIPEC: hyperthermic intraperitoneal chemotherapy; SD: standard deviation

Table 2 shows the patients' operative details. Complete (CC–0) and incomplete (CC–1/2) resections were achieved in 24 (61.5%) and 15 (38.5%) patients, respectively. The median PCI score ± SD was 14 ± 8 (range: 2–28). Three (7.7%) and 33 (84.6%) patients received intraoperative radiotherapy and bilateral ureteral stenting, respectively. Combination cisplatin (50 mg/m^2) and doxorubicin (15 mg/m^2) was the most frequently used HIPEC regimen (87.2%). No intraoperative morbidity or mortality was encountered.

Table 3 displays the patients' postoperative details. A total of eight patients developed III–IV postoperative complications (20.5%). Grade III complications included gastropleural fistula (n=1), vesicovaginal fistula (n=1), hemoperitoneum (n=1), intraabdominal abscess (n=1) and anastomotic leak (n=2); all of which were managed with surgical intervention. Grade IV complications included deep vein thrombosis with resultant pulmonary embolism in two patients (n=2) who required intensive care unit surveillance. Median follow–up time was 41 ± 27.6 months (range: 3–106). No 60–day readmission or mortality was encountered. At the last date of follow–up, there were 13 patients who were alive without disease (33.4%); mortality occurred in 10 patients (25.6%).

Parameter	n (%)
Tumor histology	
Endometrioid adenocarcinoma	5 (12.8)
Serous carcinoma	33 (84.6)
Mucinous carcinoma	1 (2.6)
Tumor grade	
Low	1 (2.6)
High	38 (97.4)
CC score	
CC–0	24 (61.5)
CC–1	11 (28.2)
CC–2	4 (10.3)
Median PCI ± SD (range)	14 ± 8 (2–28)
PCI score	
≤14	21 (53.8)
>14	18 (46.2)
HIPEC chemotherapeutic	
Cisplatin (100 mg/m^2)	1 (2.6)
Melphalan (60 mg/m^2)	1 (2.6)
Mitomycin C (30 mg/m^2)	3 (7.7)
Cisplatin (50 mg/m^2) + Doxorubicin (15 mg/m^2)	34 (87.2)
Intraoperative radiation therapy (IORT)	
No	36 (92.3)
Yes	3 (7.7)
Ureteral stenting	
No	33 (84.6)
Yes	6 (15.4)
Median operative time ± SD (range)	8 ± 0.9 hr (6–10)
Median EBL ± SD (range)	600 ± 500 ml (300–2000)
Intra–operative morbidity	0
Intra–operative mortality	0

Table 2: Operative details of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).

CC: cytoreduction completeness; EBL: estimated blood loss; HIPEC: hyperthermic intraperitoneal chemotherapy; PCI: peritoneal cancer index; SD: standard deviation

Median hospital stay ± SD (range)	19 ± 26 days (8–130)
Postoperative Clavien–Dindo complications	
Grade III	6 (15.4)
Grade IV	2 (5.1)
Median follow–up in months ± SD (range)	41 ± 27.6 (3–106)
60–day readmission	0
60–day mortality	0
Postoperative radiotherapy	0
Postoperative chemotherapy	35 (89.7)
Current status	
Alive, no disease	13 (33.4)
Alive, with disease	16 (41)
Dead	10 (25.6)

Table 3: Postoperative details after cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC).
SD: standard deviation

Kaplan–Meier survival curves for DFS and OS of the entire cohort are portrayed in Figure 1 and Figure 2, respectively. For all patients, the mean DFS and OS were 46.3 months (95% CI: 33.7–58.9) and 81 months (95% CI: 68.6–93.3), respectively.

With respect to univariate analysis of parameters related to DFS and OS, our findings demonstrated that PCI >14 was correlated with statistically significant poor DFS and OS (p=0.046) (Table 4). When compared to CC–0 (complete cytoreduction), CC–1/2 (incomplete cytoreduction) was correlated with poor DFS and OS, however, without reaching statistical significance (Table 4).

Kaplan–Meier survival curves for DFS according to PCI score, CC score and platinum–sensitivity are shown in Figure 3, Figure 4 and Figure 5, respectively. Kaplan–Meier survival curves for OS according to PCI score, CC score and platinum–sensitivity are shown in Figure 6, Figure 7 and Figure 8, respectively.

Cox multivariate analyses of DFS and OS failed to demonstrate PCI score, CC score and platinum–sensitivity as independent prognostic factors of DFS and OS (Table 5).

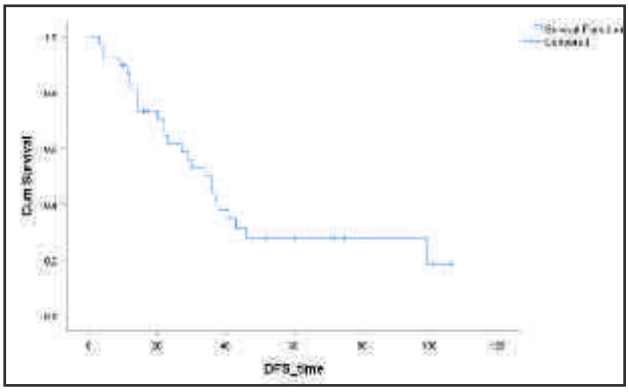

Figure 1: Kaplan–Meier survival curve for disease–free survival (DFS) for all patients.

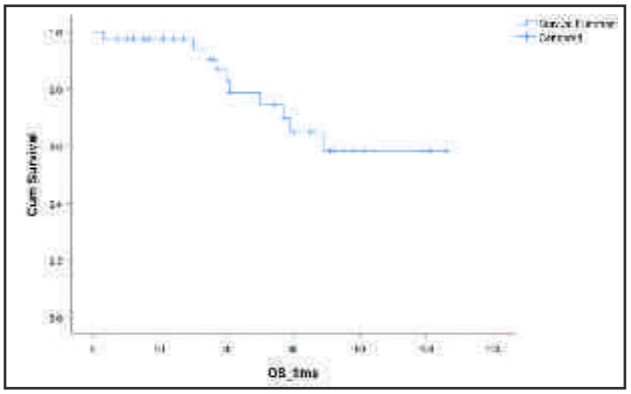

Figure 2: Kaplan–Meier survival curve for overall survival (OS) for all patients.

Variable	DFS in years Mean (95% CI)	p value*	OS in years Mean (95% CI)	p value*
Peritoneal Cancer Index (PCI) score		0.046		0.046
≤14	58.3 (38.9–77.7)		91.7 (77.8–105.6)	
>14	34.7 (20–49.4)		64.4 (46.8–82.1)	
Cytoreduction Completeness (CC) score		0.142		0.247
CC–0	53 (35.7–70.3)		87 (72.6–101.4)	
CC–1/2	36.7 (20.1–53.3)		68.6 (50.2–86.9)	
Platinum sensitivity		0.752		0.662
Sensitive	44.1 (29.9–58.4)		76.4 (61.8–91)	
Resistant	50 (26.1–73.9)		84.6 (65.8–103.3)	

Table 4: Univariate analysis of parameters related to disease–free survival (DFS) and overall survival (OS).
95% CI: 95% confidence interval; DFS: disease–free survival; HR: hazard ratio; OS: overall survival
* Two–tailed log–rank test

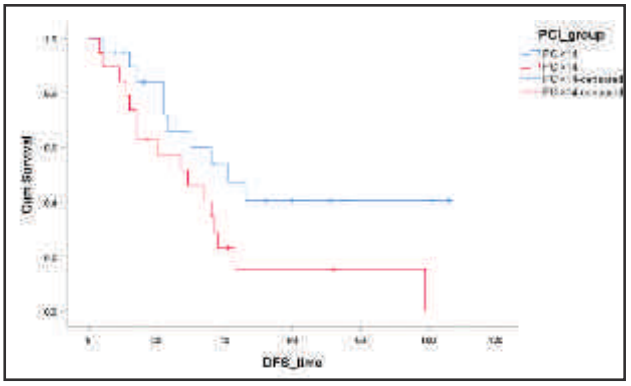

Figure 3: Kaplan–Meier survival curve for disease–free survival (DFS) according to peritoneal cancer index (PCI) score.

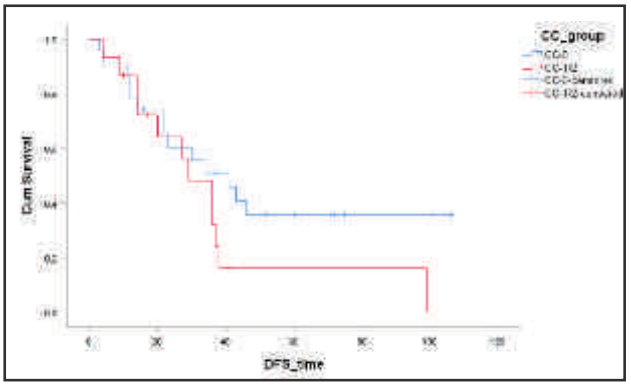

Figure 4: Kaplan–Meier survival curve for disease–free survival (DFS) according to cytoreduction completeness (CC) score.

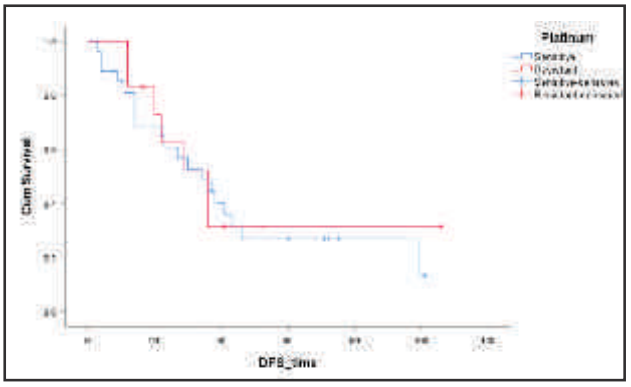

Figure 5: Kaplan–Meier survival curve for disease–free survival (DFS) according to platinum–free interval (PFI).

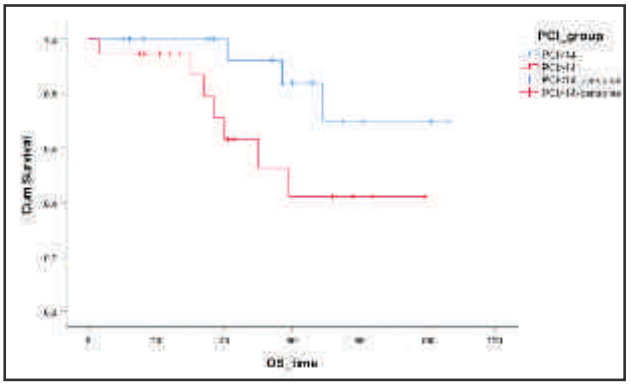

Figure 6: Kaplan–Meier survival curve for overall survival (OS) according to peritoneal cancer index (PCI) score.

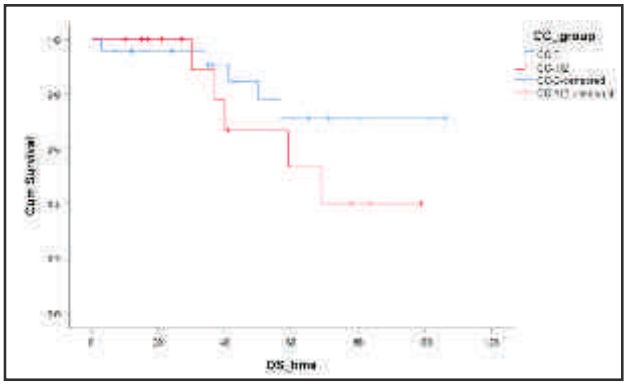

Figure 7: Kaplan–Meier survival curve for overall survival (OS) according to cytoreduction completeness (CC) score.

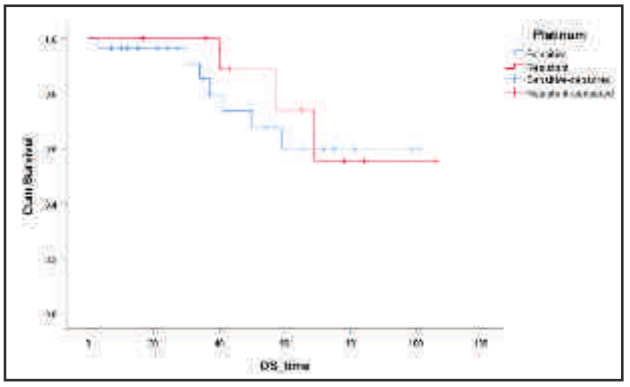

Figure 8: Kaplan–Meier survival curve for overall survival (OS) according to platinum–free interval (PFI).

Discussion

Ovarian cancer has a natural propensity to relapse intraperitoneally without distant metastases. Thus, this biological phenomenon of recurrent ovarian cancer with peritoneal carcinomatosis confers suitability for loco–regional therapy.[3] Despite being arguable among oncologists, a multimodal therapy encompassing CRS and HIPEC has been scrutinized as a rational management scheme for recurrent ovarian cancer with peritoneal carcinomatosis.[5–10,18] The major aim of CRS is to wipe out all technically feasible macroscopic residual foci.[7] The role of CRS in recurrent ovarian cancer is buttressed by several lines of studies in which the residual tumor volume to no macroscopic disease is the most influential factor in disease recurrence and survival.[19] On the other hand, the major aim of HIPEC is to get rid of all microscopic residual foci not amenable to gross cytoreduction.[7] Administration of HIPEC exploits the pharmacokinetic benefit of delivering loco–regional intraperitoneal drugs with intensified cytotoxicity mediated through hyperthermia.[20]

The HIPEC drug choices, doses and schedules are heterogeneous across the published studies in ovarian cancer. Thus, the standard of care HIPEC regimen in patients with recurrent ovarian cancer with peritoneal

Variable	DFS HR (95% CI)	p value*	OS in years Mean (95% CI)	p value*
Peritoneal Cancer Index (PCI) score ≤14 >14	1.991 (0.696–5.690)	0.199	3.627 (0.695–18.920)	0.126
Cytoreduction completeness (CC) score CC–0 CC–1/2	1.159 (0.401–3.349)	0.786	1.102 (0.225–5.409)	0.905
Platinum sensitivity Sensitive (platinum–free interval >12 months) Resistant (platinum–free interval <12 months)	0.856 (0.342–2.139)	0.739	0.611 (0.144–2.587)	0.503

Table 5: Cox multivariate analysis of parameters related to disease–free survival (DFS) and overall survival (OS).
95% CI: 95% confidence interval; DFS: disease–free survival; HR: hazard ratio; OS: overall survival
* Two–tailed log–rank test

carcinomatosis remains a question under investigation.[21] The characteristics of drugs favorable for HIPEC administration are summarized elsewhere.[22] Generally, the most frequently used drugs in ovarian cancer comprise platinum (cisplatin or oxaliplatin), taxane (paclitaxel), doxorubicin and mitomycin c.[10,21] All these drugs have been shown to exhibit heat stability and cytotoxicity according to in vitro and in vivo studies.[23] These drugs can be used as monotherapies or in combinations. A recent review showed that cisplatin (50 to 100 mg/m^2) is the most commonly employed drug and almost all combinations included cisplatin.[24] In our study, the HIPEC regimen of combination cisplatin (50 mg/m^2) and doxorubicin (15 mg/m^2) is in line with previous studies.[6,9] In some patients, we elected to use intensive monotherapy cisplatin (100 mg/m^2) in line with previous studies.[24] In other patients, we elected to use mitomycin c which is derived from the beneficial anticancer effects in peritoneal surface malignancies of gastrointestinal origins.[25] At our institution, treatment with a platinum–containing agent is favored for patients with platinum–sensitive ovarian cancer. In patients with platinum–resistant ovarian cancer, combination of reduced cisplatin and doxorubicin or monotherapy mitomycin c regimens are favored.

Our study depicted mean OS and DFS of 81 and 46.3 months, respectively, in patients who received CRS and HIPEC. Our study design did not take into consideration the inclusion of a control group (that is, CRS without HIPEC). Nonetheless, accruing body of evidence from meta–analyses disclosed the survival advantages of CRS and HIPEC in patients with recurrent ovarian cancer.[4] For instance, in a subgroup analysis of patients with recurrent ovarian cancer (n=5 studies), Wang and colleagues[4] reported only significantly enhanced OS (HR=0.48, 95% CI=0.24–0.96, p<0.01) but not DFS (HR=0.59, 95% CI=0.33–1.08, p=0.09) in patients who received CRS and HIPEC when contrasted to patients who received CRS only without HIPEC. So far, there is only one phase III randomized clinical trial that investigated the therapeutic efficacy of CRS and HIPEC versus CRS only in 120 patients with recurrent ovarian cancer.[10] When compared to patients who received only CRS (n=60), patients who received CRS and HIPEC (n=60) achieved significantly higher mean OS (26.7 versus 13.4 months, respectively; p<0.006) and 3–year OS rate (75 versus 18%, respectively; p<0.01); DFS was not evaluated. In a case–control study (CRS and HIPEC versus only CRS) by Le Brun et al.,[6] administration of HIPEC was demonstrated as an independent prognostic factor of OS in a multivariate analysis.

In our study the median PCI score was 14, reflecting the relative extensive peritoneal tumor involvement in our cohort patients with recurrent ovarian cancer. High PCI score emerged as a substantial poor prognostic marker of OS and DFS in the univariate analysis. This observation was echoed in previous studies. For example, Spiliotis et al.[10] communicated significantly worse OS in recurrent ovarian cancer patients with high PCI score ≥15 when compared to patients with low PCI score <15 (21.5 versus 30.4 months). Interestingly, Königsrainer

et al.[7] noted PCI score did not influence OS as long as complete cytoreduction (CC–0/CC–1) could be attained, suggesting the substantial prognostic impact of complete cytoreduction as a major determinant of OS.

Residual tumor volume is the most substantial prognostic factor of survival in patients with recurrent ovarian cancer in the presence[5,7,9] and absence[19,26] of HIPEC administration. Therefore, surgical radicality to eliminate all gross residual disease, as far as practically feasible, should be endeavored in all patients with recurrent ovarian cancer. Our study showed CC–0 was achieved in 61.5% of all patients and this fraction paralleled earlier studies ranging from 52% to 100%.[10,27] Spiliotis et al.[10] narrated significantly higher median OS in recurrent ovarian cancer patients with CC–0 versus CC–1 (23.9 versus 12.1 months, respectively). Konigsrainer et al.[7] defined complete and incomplete cytoreduction as patients with CC–0/CC–1 and CC–2/CC–3 scores, respectively. The median overall survival was significantly higher in the complete than incomplete cytoreduction patient groups (35 versus 14 months, respectively). In our study, CC score did not emerge as a considerable independent prognostic factor of OS in the multivariate analysis. This finding is in contrast to other studies which reported CC score as an independent prognostic factor of OS in multivariate analyses.[10,28]

Platinum–sensitivity was not a substantial prognostic factor of survival in patients with recurrent ovarian cancer treated with CRS and HIPEC. Our result was in agreement with two earlier studies.[9,10]

Our experience depicted CRS and HIPEC to be practically feasible with relatively high safety profile. No surgery–related mortality was encountered, defined as death occurring within 30 days post CRS and HIPEC. This zero mortality figure matched several earlier studies[7,18,27,28] and differed with the study by Deraco et al.[9] which reported an intraoperative mortality rate of 5.3%, defined as death taking place during the in–hospital stay post CRS and HIPEC. Pertaining to surgery–related morbidity, the rate of high–grade ≥3 adverse events was 20.5% in our study, which is largely comparable to published literature ranging from 20% to 35%.[9,27–29]. Conversely, Deraco et al.[9] communicated that the number of peritonectomy procedures and CC score correlated positively with the occurrence of grade ≥3 adverse events.

Peritoneal surface oncology is an emerging field in Saudi Arabia. So far, from our healthcare center, we previously reported our experience in the management of peritoneal carcinomatosis arising from recurrent ovarian granulosa cell tumor,[14] endometrial cancer,[15] and primary ovarian cancer.[30] In addition, we described our experience in the management of peritoneal sarcomatosis.[16] Herein, we communicated the first experience of CRS and HIPEC in the management of peritoneal carcinomatosis originating from recurrent ovarian cancer in Saudi Arabia, specifically, and the gulf region, generally. Our current study feeds the existing pool of literature with original CRS and HIPEC data from developing research teams in the field of peritoneal surface malignancy. One strength of our study is the detailed sub–group analyses to characterize the most important determinants of survival. In addition, our study highlights CRS and HIPEC as an attractive multimodal therapy with improved survival benefits in patients with recurrent ovarian cancer. Our study has several limitations that ought to be acknowledged. Such limitations comprise small sample size, retrospective design and lack of control group to scrutinize the superiority of CRS and HIPEC over CRS only. These limitations are projected to be overcome in the future by establishing peritoneal surface oncology registries and encouraging multi–centric research collaborations.

Conclusion

Our study demonstrated the feasibility, safety and favorable clinical outcomes of CRS and HIPEC in patients with recurrent ovarian cancer and peritoneal carcinomatosis. Survival was enhanced in patients with PCI score ≤14. Large–scale, randomized, controlled phase III clinical trials are needed to better consolidate the efficacy and safety of CRS and HIPEC in patients with recurrent ovarian cancer and peritoneal carcinomatosis.

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