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Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in recurrent ovarian cancer with peritoneal metastasis: a prospective registry study on 41 patients

https://doi.org/10.1515/pp-2017-0021
Received August 7, 2017; accepted October 24, 2017;
previously published online November 8, 2017

Abstract

Background: Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal metastases from ovarian cancer have been shown to have a role in recurrent ovarian cancer, but are still not considered standard therapy.

Methods: From March 2005 to July 2013, 41 patients who underwent 44 CRS and HIPEC for peritoneal metastases in recurrent ovarian cancer were included in this study. Details were obtained from a prospectively maintained database. Our aim was to report our 5-year overall and disease-free survivals, as well as prognostic factors for survival.

Results: The median age was 50 years (range 23–73). Median duration of surgery was 510 min (range 230–840) and median peritoneal carcinomatosis index (PCI) score was 9.5 (range 0–31). About 92.7% of the patients had completeness of cytoreduction (CC) scores of 0 or 1. Median follow-up was 43.9 months (range 0.7–108.9). There were no mortalities and the high-grade morbidity rate was 31.8%. Median overall survival was 42.8 months (range 28.6–99.9) 5-year overall and disease-free survivals were 49.3% and 7.5% respectively. On multivariate analysis, histology and CC score were significantly associated with overall survival while histology and disease-free interval were associated with disease-free survival. The odds of developing a high-grade complication more than doubled for each additional surgical procedure performed ($p = 0.01$).

Conclusions: CRS and HIPEC can attain prolonged survival in selected patients with peritoneal metastasis in recurrent ovarian cancer.

Keywords: cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, peritoneal disease, peritoneal metastases, peritonectomy, recurrent ovarian cancer

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Introduction

Ovarian cancer is the second most common gynecological malignancy and the commonest cause of cancer death among women [1]. Optimal debulking followed by carboplatin-based systemic chemotherapy is established for primary advanced ovarian cancer [2–6]. However, the disease recurs in up to 70% of patients and long-term survival rates remain poor at 20–30% [7, 8]. Treatment with various chemotherapy regimes result in a median survival that varies from 9 to 35 months, depending on platinum sensitivity [9]. As recurrent disease is often peritoneal without evidence of systemic metastases, it is ideally suited for aggressive loco-regional therapy. The goal of cytoreductive surgery (CRS) is the complete removal of all macroscopic disease and its role in recurrent disease is supported by a meta-analysis that showed that residual tumor is an important determining factor in disease recurrence [10].

Chemotherapy for ovarian cancer has traditionally been given intravenously. The use of intraperitoneal chemotherapy in the adjuvant setting for ovarian cancers has been supported by several randomized studies [8, 10, 11]. However, the addition of heat to chemotherapy and the use of hyperthermic intraperitoneal chemotherapy (HIPEC), in the management of ovarian cancer, remain contentious. Conversely, CRS and HIPEC have been used

since the 1990s for various other peritoneal surface malignancies [12–18].

HIPEC combines the regional pharmacokinetic advantage of the intraperitoneal drug delivery with the enhanced cytotoxicity of the drug by heat [19, 20]. CRS and HIPEC have been evaluated in the primary, advanced and recurrent ovarian cancer settings [21]. A review by Mulier et al. suggests that the potential benefit is strongest for the salvage cases (recurrent ovarian cancer after initial complete response to CRS and chemotherapy [22]. We aim to share our experience with CRS and HIPEC for recurrent ovarian cancers.

Materials and methods

The study has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the Singapore Health Services Centralized Institutional Review Board. Informed consent was obtained from all individuals included in this study. The conducted research is not related to animals use. About 50 patients underwent 53 CRS and HIPEC procedures for peritoneal disease from known ovarian cancer at the National Cancer Centre Singapore between March 2005 and July 2013. Patients were excluded from the study if they received CRS and HIPEC for primary disease. Hence, the study included 41 patients who underwent 44 CRS and HIPEC for recurrent ovarian disease. Patients had an Eastern Cooperative Group (ECOG) performance status 0 or 1, and absence of distant metastases on imaging. All patients were discussed at multidisciplinary tumor board meetings and deemed to have disease that was likely to be amenable to complete cytoreduction (CC).

CRS was performed as described by Sugarbaker and aimed to remove all macroscopic peritoneal disease [23]. The Peritoneal Cancer Index (PCI) score was used to describe the extent of disease [23]. The completeness of resection was measured by the CC score [24, 25].

HIPEC was performed using the Belmont® hyperthermia pump to deliver the intra-peritoneal chemotherapy at 42 °C for 60 min using the closed technique. The abdomen was closed temporarily during HIPEC and re-opened after, for a thorough washout and to perform any bowel anastomosis. HIPEC was performed with Cisplatin (50–80 mg/m^2 that was diluted in 2–3 L of peritoneal dialysis solution. When involvement of the subdiaphragmatic peritoneum was present and stripping of the diaphragmatic surfaces was performed, a chest tube was inserted on the corresponding side prior to initiation of HIPEC.

Prior to December 2012, we administered early post-operative intra-peritoneal chemotherapy (EPIC) with Paclitaxel as the drug of choice. All intra-operative and 30-day post-operative complications were recorded. Morbidity was evaluated using the common terminology criteria for adverse events version 3.0 of the National Institute of Health criteria.

Patients were seen at the outpatient clinic 2 weeks after discharge, and at least every 3 monthly for the first year and 6 monthly thereafter. CT scans and tumor markers were performed at each visit and when clinically indicated. Patients received adjuvant systemic chemotherapy depending on a post-operative multidisciplinary discussion and their renal function. Events of recurrent disease were recorded.

Primary end points were overall survival (OS) and disease-free survival (DFS). For patients who undergoing their second CRS and HIPEC, OS was calculated from the 1st surgery to death and DFS was calculated from the 1st surgery to relapse. Disease-free interval (DFI) was defined as the interval between the date of the surgery or treatment (from which the patient was deemed to be cleared of disease) to the date of the relapse prior to CRS-HIPEC. DFI was examined using a cut-off of 12 months as it was postulated that a recurrence occurring at less than 12 months after the previous surgery signified a worse prognosis.

Platinum sensitivity of recurrent ovarian cancers was determined based on the platinum-free interval, which was defined as the interval between the latest date on which patient received platinum-based chemotherapy treatment and the date of their recurrence. Patients with platinum-free interval ≥ 6 months were considered platinum-sensitive, while those with platinum-free interval < 6 months were deemed platinum-resistant.

Logistic regression models were fitted to estimate the association of various factors with the development of grade 3 and over post-operative complications. The differences in post-operative complications between patients who underwent CRS-HIPEC before and after 1 Nov 2012, the date on which early post-operative intra-peritoneal chemotherapy (EPIC) was ceased at NCCS, were compared using Chi-square test or Fisher's exact test as appropriate.

OS was calculated from the date of the first CRS-HIPEC to the date of death from any cause. Alive or lost to follow-up patients were censored at the date of last follow-up. DFS was calculated from the date of CRS-HIPEC to the date of first relapse after the latest CRS-HIPEC or death from any cause, whichever occurred first. Alive or lost to follow-up patients who were recurrence-free were censored at the date of last follow-up. Follow-up data was taken up to October 2015. OS and DFS distributions were estimated using Kaplan-Meier method, and the log-rank test was used to test differences between survival curves. Cox proportional hazard regression models were fitted to assess the association of various variables with survival endpoints. Proportional hazards assumption was verified for each fitted model using Schoenfeld residuals.

Multivariate model building for OS, DFS and grade 3 and over post-operative complications were performed on variables with $p < 0.05$ from the univariate analyses. Forward selection, backward elimination and stepwise selection algorithms with a selection criterion of $p < 0.05$ were applied to identify independent predictors for each endpoint.

All reported p-values were 2-sided, and a $p < 0.05$ was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Table 1 shows the clinical characteristics of the patients and the surgical details. There were 41 patients who underwent 44 surgeries. The median age was 50 years

Table 1: Patient demographics and clinical characteristics.

	n	%
Total	**41**	**100.0**
Age at CRS-HIPEC, years		
Median (range)	50.2 (23.6–73.7)	
Histology of primary ovarian cancer		
Epithelial		
Clear cell	4	9.8
Endometrioid	2	4.9
Mucinous	5	12.2
Serous	25	61.0
Undifferentiated	2	4.9
Sarcoma	1	2.4
Sex cord stromal	2	4.9
Stage of primary ovarian cancer at diagnosis[a]		
1	4	9.8
2	3	7.3
3	27	65.9
4	4	9.8
Missing	3	7.3
Disease-free interval, months		
≤ 12	11	26.8
> 12	27	65.9
Missing	3	7.3
Median (range)[a]	14.5 (2.4–69.3)	
Platinum sensitivity of recurrent ovarian cancer		
Platinum resistant	6	14.6
Platinum sensitive	26	63.4
Missing	7	17.1
Not applicable[c]	2	4.9
ECOG performance status (prior to CRS-HIPEC)		
0	36	87.8
1	4	9.8
Missing	1	2.4
Pre-op CA125, µg/L (prior to CRS-HIPEC)		
Normal (< 35)	14	34.1
Raised(≥ 35)	18	43.9
Missing	9	22.0
Median (range)[a]	51.3 (11.3–950.0)	

CRS-HIPEC, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; ECOG, Eastern Cooperative Oncology Group.[a]Among patients with non-missing data. [b]As each patient was staged according to the latest FIGO staging criteria over time, the staging data were not comparable across patients in this study if there were changes between stages across the different FIGO staging versions used. [b]These patients did not receive platinum-based chemotherapy prior to their recurrence which were treated by CRS-HIPEC.

old (range 23–73). 93% of the patients had epithelial histologies. The median follow-up was 43.9 months (range 0.7–108.9). The median duration of surgery was 510 minutes (range 230–840) and the median PCI score was 9.5 (range 0–31). 92.7% of patients had a CC score of 0 or 1. The median estimated blood loss was 1.3 L (range 0.25–5.1) and the median hospital stay was 16 days (range 8–188). There was no 30-day mortality but one patient died from complications 6 months after surgery. This patient had an eventful post-operative course with small bowel and bladder perforations requiring multiple surgeries, radiological interventions as well as a prolonged stay in ICU. The patient eventually suffered from a subarachnoid hemorrhage and passed away.

The median OS was 42.8 months (range 28.6–99.9) The 1-, 3- and 5-year OS rates were 92.0%, 61.4% and 49.3% respectively. Clear cell histology, a shorter DFI, a higher pre-operative CA125 level and CC score of 1 were associated with an inferior OS on univariate analysis (Table 2). Patients who received post-operative chemotherapy had a better OS than patients who did not, although the difference was not statistically significant. On multivariate analysis, only histology (HR = 7.75; 95% CI = 1.94–30.97; p = 0.004) and CC score (HR = 10.91; 95% CI = 2.48–47.97; p = 0.002) remained significant for OS (Table 2).

The median DFS was 21.7 months (range 31.4–25.3). The 1-, 3- and 5-year DFS rates were 78.2%, 18.8% and 7.5% respectively. On univariate analysis, clear cell histology, a shorter DFI, platinum resistance and a higher PCI score were significantly associated with DFS. On multivariate analysis, clear cell histology (HR = 3.92; 95% CI, 1.09–14.05; p = 0.036) and a shorter DFI (HR = 3.23; 95% CI, 1.39–7.50; p = 0.006) were significant (Table 3).

The overall morbidity rate was 61%. However, less than a third of the patients suffered grade 3 or above complications that required invasive interventions, with two-thirds of these complications attributed to intra-abdominal collections or pleural effusions that resolved with simple percutaneous drainage. After EPIC was stopped in our institution, the rate of high-grade morbidity dropped from 37% to 17% (p = 0.645). 4 (9.1%) patients had grade 4 complications; 2 of these were acute renal impairment that required inpatient dialysis, one of whom went on to require long-term dialysis (2.3%) whilst the other eventually recovered and did not need long term renal support. One patient had a hydrothorax that required intubation and chest tube insertion and the last patient had a small bowel and bladder perforation and was the only patient (2.3%) who required a relaparotomy for surgical repair of post-operative complications.

On univariate analysis, duration of peritonectomy of more than 8 hours (p = 0.05), a higher number of procedures (gastrectomy, colectomy, small bowel resection, splenectomy, subdiaphragmatic stripping) (p = 0.01) and cholecystectomy (p = 0.042), were associated with

Table 2: Overall survival.

Variable	Categories		Univariate analysis		Final multivariate model	
		E/N	HR, 95 % CI	p[a]	HR, 95 % CI	p[a]
Age at CRS-HIPEC	Per year increase		19/41 0.97 (0.93–1.01)	0.174[b]		
Histology	Non-clear cell	16/37	1	0.001	1	0.004
	Clear cell	3/4	6.45 (1.76–23.66)		7.75 (1.94–30.97)	
Stage[c]	1–2	2/7	1	0.516		
	3–4		15/31 1.63 (0.37–7.26)			
Disease-free interval	Per month increase		19/38 0.92 (0.86–0.99)	0.027[b]		
	>12 months	11/27	1	0.020		
	≤12 months		8/11 2.91 (1.13–7.47)			
Platinum sensitivity	Sensitive	11/26	1	0.085		
	Resistant	3/6	3.04 (0.80–11.49)			
ECOG status	0	17/36	1	0.612		
	1		1/4 0.59 (0.08–4.55)			
Pre-op CA125	Per µg/L increase		15/32 1.002 (1.000–1.004)	0.026[b]		
	<35 µg/L	7/14	1	0.538		
	≥35 µg/L		8/18 1.40 (0.48–4.07)			
PCI score	Per unit increase	14/34	1.06 (0.99–1.14)[d]	0.113[b]		
Subdiaphragmatic stripping	No	6/12	1	0.678		
	Yes		13/29 1.23 (0.47–3.24)			
Colectomy	No	9/17	1	0.405		
	Yes		10/24 1.47 (0.59–3.65)			
Small bowel resection	No	14/32	1	0.291		
	Yes		5/9 1.75 (0.61–4.98)			
Splenectomy	No	14/29	1	0.383		
	Yes		5/12 0.63 (0.22–1.79)			
Cholecystectomy	No	13/29	1	0.687		
	Yes		6/12 1.22 (0.46–3.28)			
No. of CRS procedures	Per unit increase	19/41	1.14 (0.76–1.71)[d]	0.535[b]		
Duration of peritonectomy	Per min increase	19/41	1.00 (0.99–1.01)[d]	0.128[b]		
CC score	0	14/34	1	<0.001	1	0.002
	1	3/4	9.39 (2.29–38.53)		10.91 (2.48–47.97)	
Post-op chemo	No	4/8	1	0.533		
	Yes		15/32 0.70 (0.22–2.19)			
Pre- or post-op bevacizumab	No	16/34	1	0.855		
	Yes		3/6 0.89 (0.25–3.14)			

E, deaths; N, patients; HR, hazard rratio; CRS-HIPEC, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; ECOG, Eastern Cooperative Oncology Group; PCI, peritoneal cancer index; CC, completeness of cytoreduction. [a]Based on Log-rank test, unless otherwise specified. [b]Based on Wald test. [c]As each patient was staged according to the latest FIGO staging criteria over time, the staging data were not comparable across patients in this study if there were changes between stages across the different FIGO staging versions used. [d]Violated proportional hazards assumption. Note: Did not include pre-op chemotherapy in this table as most of the patients in the study received pre-op chemotherapy.

development of a high-grade complication (Table 4). In the multivariate model, only the number of procedures remained associated with developing a high-grade complication (p = 0.01). The odds ratio of developing a high-grade complication was 2.68 for each additional procedure performed (95 % CI = 1.27–5.67; p = 0.010).

After surgery, disease recurred in 27 out of 44 patients (61.4 %), at a median of 13 months (range 2–62 months). 11 patients recurred in a single site while 16 patients recurred in multiple sites. The most common site of recurrence was in the peritoneum (52 %), followed by the liver (41 %) and lymph nodes (33 %). Among the 11 patients who had disease at only a single site, 6 had their recurrences in the peritoneum, 2 in the liver, 1 in the lymph nodes and 1 in the pelvis. Of the 6 with recurrent peritoneal-only disease, 1 progressed while on chemotherapy. 2 required emergency surgeries and extensive disease was found intra-operatively in both that

Table 3: Disease-free survival.

Variable	Categories		Univariate analysis		Final multivariate model	
		E/N	HR, 95 % CI	p[a]	HR, 95 % CI	p[a]
Age at CRS-HIPEC	Per year increase	32/41	0.98 (0.95–1.02)	0.319		
Histology	Non-clear cell	29/37	1	0.065	1	0.036
	Clear cell	3/4	2.99 (0.88–10.11)		3.92 (1.09–14.05)	
Stage[c]	1–2	6/7	1	0.590		
	3–4	24/31	0.78 (0.31–1.94)			
Disease-free	Per month increase	31/38	0.97 (0.94–1.01)	0.098		
interval	>12 months	21/27	1	0.010	1	0.006
	≤12 months	10/11	2.79 (1.24–6.28)		3.23 (1.39–7.50)	
Platinum	Sensitive	19/26	1	0.046		
sensitivity	Resistant	5/6	2.74 (0.98–7.65)			
ECOG status	0	28/36	1	0.448		
	1	3/4	0.63 (0.19–2.10)			
Pre-op CA125	Per µg/L increase	26/32	1.00 (0.99–1.00)	0.871		
	<35 µg/L	12/14	1	0.349		
	≥35 µg/L	14/18	1.48 (0.65–3.36)			
PCI score	Per unit increase	26/34	1.06 (1.00–1.12)	0.040		
Subdiaphragmatic	No	9/12	1	0.236		
stripping	Yes	23/29	1.63 (0.72–3.66)			
Colectomy	No	15/17	1	0.613		
	Yes	17/24	1.20 (0.59–2.44)[d]			
Small bowel	No	25/32	1	0.503		
resection	Yes	7/9	1.34 (0.57–3.13)			
Splenectomy	No	22/29	1	0.796		
	Yes	10/12	0.90 (0.42–1.94)			
Cholecystectomy	No	22/29	1	0.787		
	Yes	10/12	0.90 (0.42–1.94)			
No. of CRS procedures	Per unit increase	32/41	1.03 (0.74–1.42)	0.874		
Duration of peritonectomy	Per min increase	32/41	1.00 (0.99–1.00)	0.652		
CC score	0	26/34	1	0.111		
	1	3/4	2.61 (0.77–8.91)			
Post-op chemo	No	5/8	1	0.707		
	Yes	27/32	1.23 (0.42–3.61)			
Pre- or post-op	No	27/34	1	0.488		
bevacizumab	Yes	5/6	0.71 (0.27–1.88)			

E, relapse or deaths; N, patients; HR, hazard ratio; CRS-HIPEC, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; ECOG, Eastern Cooperative Oncology Group; PCI, peritoneal cancer index; CC, completeness of cytoreduction. [a]Based on Log-rank test, unless otherwise specified. [b]Based on Wald test. [c]As each patient was staged according to the latest FIGO staging criteria over time, the staging data were not comparable across patients in this study if there were changes between stages across the different FIGO staging versions used. [d]Violated proportional hazards assumption. Note: Did not include pre-op chemotherapy in this table as most of the patients in the study received pre-op chemotherapy.

precluded a redo CRS-HIPEC. Three patients were planned for and underwent repeat CRS and HIPEC successfully. Among these 3 patients, 1 passed away 9 months after the repeat CRS and HIPEC from recurrent disease. 1 patient was alive 12 months after the second CRS-HIPEC, with no evidence of recurrence but was subsequently lost to follow-up. The last patient remains alive 42 months after the second surgery but she recurred after 24 months. She was treated with systemic chemotherapy and a third CRS was planned but was abandoned due to extensive disease. Those that recurred in multiple sites were planned for palliative treatment. On analysis of the differences between patients who recurred at a single site versus multiple sites, those who recurred at multiple sites had a shorter DFI compared to those who recurred at a single site (11.8 months vs. 16.7 months; p = 0.061). There

Table 4: Development of grade 3 and over post-op complications.

Variable	Categories		Univariate analysis		Final multivariate model	
		E/N	OR, 95 % CI	p[a]	OR, 95 % CI	p[a]
Age at CRS-HIPEC	Per year increase	14/41	0.99 (0.93–1.06)	0.780		
Histology	Non-clear cell	12/37	1	0.489		
	Clear cell	2/4	2.08 (0.26–16.63)			
Stage	1–2	2/7	1	0.850		
	3–4	10/31	1.19 (0.20–7.23)			
Disease-free	Per month increase	12/38	0.98 (0.93–1.03)	0.371		
interval	> 12 months	9/27	1	0.716		
	≤ 12 months	3/11	0.75 (0.16–3.53)			
Platinum	Sensitive	6/26	1	0.603		
sensitivity	Resistant	2/6	1.67 (0.24–11.45)			
ECOG status	0	13/36	1	0.662		
	1	1/4	0.59 (0.06–6.27)			
Pre-op CA125	Per µg/L increase	9/32	1.00 (0.99–1.01)	0.186		
	< 35 µg/L	4/14	1	0.961		
	≥ 35 µg/L	5/18	0.96 (0.20–4.54)			
PCI score	Per unit increase	10/34	1.03 (0.94–1.13)	0.515		
Subdiaphragmatic	No	2/12	1	0.143		
stripping	Yes	12/29	3.53 (0.65–19.10)			
Colectomy	No	5/17	1	0.591		
	Yes	9/24	1.44 (0.38–5.45)			
Small bowel	No	9/32	1	0.135		
resection	Yes	5/9	3.19 (0.70–14.66)			
Splenectomy	No	8/29	1	0.175		
	Yes	6/12	2.63 (0.65–10.58)			
Cholecystectomy	No	7/29	1	0.042		
	Yes	7/12	4.40 (1.06–18.36)			
No. of CRS procedures	Per unit increase	14/41	2.68 (1.27–5.67)	0.010	2.68 (1.27–5.67)	0.010
Duration of peritonectomy	Per min increase	14/41	1.005(1.000–1.010)	0.050		
CC score	0	12/34	1	0.684		
	1	1/4	0.61 (0.06–6.54)			

E, no. of patients with grade 3 and over for worst grade of post-op complications; N, patients; OR, odds ratio; CRS-HIPEC, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; ECOG, Eastern Cooperative Oncology Group; PCI, peritoneal cancer index; CC, completeness of cytoreduction. [a]Based on Wald test. [b]As each patient was staged according to the latest FIGO staging criteria over time, the staging data were not comparable across patients in this study if there were changes between stages across the different FIGO staging versions used. Note: Did not include chemotherapy variables in this table as most of the patients in the study received pre-op chemotherapy and the timing of development of post-op complications and receipt of post-op chemotherapy could be overlapped.

were no differences between the 2 groups in terms of initial stage of disease, neoadjuvant and adjuvant treatment.

Discussion

The standard of care for recurrent ovarian cancer remains debatable. Patients with platinum-resistant disease are being treated with single agent non platinum-based chemotherapy agents while patients with platinum-sensitive disease are receiving platinum-based combination chemotherapy. Secondary CRS can be considered and this view is supported by a meta-analysis that suggests that survival is improved for patients who have CC [10]. However, the duration of the DFI has not been established, although the consensus is that it should be at least 6 months [26, 27].

The review of Mulier et al. studied the evidence of HIPEC in addition to CRS at various time points for ovarian cancer [22]. In his paper, there was no evidence for HIPEC at the primary diagnosis, either before or after

chemotherapy. A potential survival benefit of adding HIPEC after a complete CRS was seen in patients who had initial incomplete CRS and were administered chemotherapy and now presented for surgery, although the survival differences were not statistically significant.

In the recurrent setting, there were 17 papers that looked at patients who underwent CRS and HIPEC as a salvage procedure [22]. The median and 5-year OSs were 15.5–57 months and 18–57 % respectively. This was compared to 3 papers published in the same time frame on comparable patients who underwent CRS without HIPEC. The median and 5-year OSs were 16–29.2 months and 11.5 % respectively [28–30]. Hence, Mulier et al. concluded that there may be a benefit to adding HIPEC to CRS in the recurrent setting.

One of the largest retrospective multicenter studies was published in 2012 by Bakrin et al. who looked at 566 patients from 13 French institutions [31]. Four-hundred and seventy four of these patients received CRS and HIPEC for recurrent disease. Median OS was 45.7 months and the 5-year OS was 37 %. Multivariate analysis showed that patients who had a performance status of more than 0 and a PCI score of more than 8 (HR 2.55, $p < 0.001$) had poorer OSs. However, as this was a multicenter study, there were variations in the HIPEC method as well as chemotherapeutic drugs used.

A recent randomized trial by Spiliotis et al. compared CRS and HIPEC to CRS alone for recurrent ovarian cancer [32]. They showed improved median survival (26.7 vs. 13.4 months, $p < 0.0006$) and improved OS at 3 years (75 % vs. 18 %, $p < 0.01$) for the group that received HIPEC. Improved survival was also shown in those with a PCI score of less than 15 and a lower CC score.

Our study reports 3-year and 5-year OS rates of 61.4 % and 49.3 % respectively, that is comparable to the literature. Many of our patients have achieved long-term survival, albeit in the presence of recurrent disease. Up to 81.2 % of them had recurred by 3 years.

Clearly, the most important prognostic factor for OS and DFS was the histology. Amongst the patients with epithelial cancers, those with a clear cell histology had the poorest outcome. However, this is true of the prognosis of patients with clear cell histology even when treated with systemic chemotherapy alone. Perhaps in these patients, more stringent selection criteria should be used, such as a lower PCI score cut-off. One another factor that should be considered is the CC. It was significant for OS but only significant on univariate analysis for DFS. Ideally, a CCO should be the goal of surgery.

The finding that the DFI is not a significant factor in OS presents an interesting point. It is assumed by many that a shorter DFI indicates a poorer prognosis and if so, many of these patients may not even be considered for CRS and HIPEC. In our study, we have shown that patients with a shorter DFI do not necessarily do worse, especially if CC can be achieved, although this may be as a result of the small number of patients in this group. As a higher PCI score is associated with a poorer outcome, these patients should also be referred earlier rather than later, with CRS and HIPEC as a distinct consideration if the inclusion criteria are met.

Another interesting factor that was not associated with survival is platinum sensitivity or resistance. It is known that patients with platinum-resistant disease have a poorer survival, however, our results show that there is no difference between the 2 groups after CRS and HIPEC. A similar finding was seen in the study by Bakrin et al. It has been suggested that the administration of the chemotherapy intraperitoneally provides a higher concentration of the drug and the hyperthermia augments the cytotoxicity and penetration of the drug. Hence the platinum status of the patient should not preclude the patient from being considered for CRS and HIPEC.

There was no 30-day but we did have one patient who had complications and a prolonged stay that died 6 months after surgery. Our morbidity rate of 61 % is relatively high. Twenty-five percent were intra-abdominal collections that required percutaneous drainage and intravenous antibiotics. 88 % of these occurred before 2012, when administration of EPIC remained in our protocol. We postulated that the post-operative intra-peritoneal chemotherapy was not being drained well. We have since ceased the administration of EPIC as there was no definitive evidence to support it, and it appeared to increase the complication rate. With the change in treatment policy, our rate of intra-abdominal collections has markedly reduced [33]. The rate of high-grade complications dropped from 37 % to 17 %.

Quality of life after a major surgery such as CRS and HIPEC is a major concern. We have done retrospective and prospective studies looking at the quality of life of our patients after CRS and HIPEC. Our studies, as well as other quality of life studies, have shown that while the quality of life drops immediately after CRS and HIPEC, the patients return to baseline by 6 months [34–36].

Recent randomized trials looking at combination therapy with bevacizumab for recurrent ovarian cancer showed DFS of 6.7–12.4 months and OS of 16.6–33.6 months [37, 38]. Studies looking at a PARP(poly-ADP-ribose polymerase) inhibitor – olaparib – showed DFS of 6.3–11.2 months depending on the BRCA mutation

status [39, 40]. Given these survival rates and that of traditional chemotherapeutic agents(9–35 months), our OS rate and DFS rate of 48.2 months and 21.7 months respectively, as well as the rates found in other trials, seem to suggest a benefit to CRS and HIPEC. This should however be corroborated in future prospective randomized trials.

The main limitation of our study is that it is a retrospective one with its inherent weaknesses. Also, as the effect of EPIC on survival data is unknown, our results may be affected as only 55.8% of them had EPIC. We studied the effect of EPIC on survival and showed that there was no difference in survival between patients who received EPIC and those who did not [33]. With the evidence for CRS and HIPEC in recurrent cases mounting and acceptable mortality and morbidity demonstrated, more trials are being conducted to solidify the evidence. There are two other trials in progress. The French study (CHIPOR trial; ClinicalTrials.gov identifier NCT01376752) started in April 2011 and is currently ongoing. The second randomized trial is being conducted in Rome, Italy [41].

Conclusions

A review of our institution's experience shows that long-term survival for patients with recurrent ovarian cancer is possible. The 5-year OS of 49.3% is comparable to the results from other experienced centers and better than the results obtained with CRS and systemic chemotherapy alone, while a 5-year DFS of 7.5% indicate that many of our patients are surviving but with disease. The quoted mortality rate for CRS-HIPEC is now negligible and zero in our series, and whilst our reported morbidity is high, it has reduced with experience and changes in our protocol. The evidence for CRS and HIPEC in recurrent ovarian cancer cases is impressive in the available literature, especially when compared to CRS or chemotherapy alone. In view of the available evidence, CRS and HIPEC should be considered a viable alternative, and if proven by the ongoing randomized trials, the standard of care for patients with recurrent ovarian cancer.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.
Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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