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Survival Impact of Secondary Cytoreductive Surgery for Recurrent Ovarian Cancer in an Asian Population

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ABSTRACT

Objective: The aim of this study was to evaluate the role of secondary cytoreductive surgery in Asian patients with recurrent ovarian cancer and to assess prognostic variables on overall post-recurrence survival time. ***Methods:*** We conducted a retrospective review of patients with recurrent ovarian cancer who underwent secondary cytoreduction at the Gynaecological Cancer Center at the KK Women's and Children's Hospital, Singapore, between 1999 and 2009. Eligible patients included those who had been firstly treated by primary cytoreductive surgery and followed by adjuvant chemotherapy and had a period of clinical remission of at least six months and subsequently underwent secondary cytoreductive surgery for recurrence. Univariate analysis was performed to evaluate various variables influencing the overall survival. ***Results:*** Twenty-five patients met our eligibility criteria. The median age was 52 years (range=31–78 years). The median time from completion of primary treatment to recurrence was 25.1 months (range=6.4–83.4). Secondary cytoreduction was optimal in 20 of 25 patients (80%). The median follow-up duration was 38.9 months (range=17.8–72.4) and median overall survival time was 33.1 months (95% confidence interval, 15.3–undefined.). Ten (40.0%) patients required bowel resection, but no end colostomy was performed. One (4.0%) patient had wedge resection of the liver, one (4.0%) had a distal pancreatectomy, one (4.0%) had a unilateral nephrectomy, and one (4.0%) had adrenalectomy. There were no operative deaths. The overall survival of patients who responded to secondary cytoreductive surgery and adjuvant chemotherapy was significantly longer than those patients who did not respond to the treatment. Of those patients who responded to the surgical management, patients with clear cell carcinoma fared well compared to those with the endometrioid, mucinous adenocarcinoma, and papillary serous type ($p<0.001$). Complete secondary cytoreductive surgery appeared to have some relationship to overall survival but was not statistically significant. ***Conclusion:*** In carefully selected patients with recurrent ovarian cancer, optimal cytoreductive surgery is possible and in a subgroup of patients who respond to surgery and chemotherapy survival is significantly longer.

The role of primary cytoreductive surgery in the management of ovarian cancer is well established. It is known that complete cytoreductive surgery enhances the efficacy of chemotherapy by decreasing the cell clones that are resistant. Also, chemotherapy is delivered better to a small and well-vascularised residual tumor.[1] Despite the standard treatment of primary cytoreduction and systemic chemotherapy, 70–90% of patients develop recurrent disease.[2] Patients who have recurrence after six months of primary treatment are known to be platinum sensitive and hence most often rechallenged with platinum-based chemotherapy with various response rates due to the heterogeneity of the recurrent disease.

The role of surgery in the management of recurrent ovarian cancer has not been well established. Recent literature shows that in a selected group of patients, secondary cytoreductive surgery improves the prognosis.[2-5] The two most consistent factors showing favorable outcome in patients undergoing secondary cytoreductive procedure were prolonged

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treatment-free survival (first recurrence from six months to 24 months) and postoperative residual disease, described as "<0.5mm," "microscopic," or "none."[3-6] A meta-analysis by Bristow et al,[7] supports the role of secondary cytoreductive surgery and proved that residual disease after debulking surgery is an important determinant of survival. New surgical options are emerging for selected patients with recurrent ovarian cancer, such as complete cytoreductive surgery including peritonectomy and hyperthermic intraperitoneal chemotherapy (HIPEC). These surgeries aim at achieving minimal or no residual disease and targeting the remaining residual disease with heated intraperitoneal chemotherapy. Again, this is based on the principle of using aggressive primary cytoreductive surgery with intraperitoneal chemotherapy for advanced ovarian cancer. Chi et al,[8] demonstrated that along with traditional primary cytoreductive surgery, incorporating procedures such as resection of diaphragm peritonectomy, splenectomy, distal pancreatectomy, partial hepatectomy, cholecystectomy, and portal caval dissection in order to address tumor deposits in the upper abdomen has led to improved five-year progression–free survival.

The question of whether a change in the surgical paradigm should occur for recurrent ovarian cancer remains a topic of debate. The primary objective of this study was to evaluate our experience with secondary cytoreductive surgery for Asian patients with recurrent ovarian cancer and to evaluate various prognostic variables on overall post-recurrence survival time.

METHODS

After obtaining Institutional Review Board approval, the Gynaecological Cancer Center at KK Women's and Children's Hospital, Singapore, database was reviewed to identify patients with recurrent ovarian cancer who underwent secondary cytoreductive surgery from 1999 to 2009. Only those patients with epithelial ovarian cancer who had primary surgery followed by platinum-based adjuvant chemotherapy and who were in clinical remission for six months were included in the study. All patients with recurrent ovarian cancer were presented at multidisciplinary tumor board meeting and, based on their clinical and radiological findings, patients who were deemed to have the resectable disease were selected for secondary cytoreductive surgery. The criteria for optimal cytoreductive surgery varied during the study period, before 2002 it was taken as <2cm and after that it was <1cm. Following surgery, patients were treated with a platinum-based chemotherapy combination and were changed to second- or third-line regimens based on their response. Twenty-five patients were identified from the database that fulfilled our criteria. Data were retrieved for age, details of primary surgery, stage, histological type, grade, adjuvant chemotherapy treatment, secondary debulking surgery if optimal or sub-optimal, follow-up, and survival outcome.

Disease-free interval (DFI) was calculated as the time (in months) from the date of completion of chemotherapy following primary cytoreductive surgery to the date of recurrence. Overall survival (OS) was calculated as the time (in months) from the date of completion of chemotherapy following secondary cytoreductive surgery to the date of death from all causes or censored at the date of last follow-up. Disease-free survival (DFS) was calculated as the time (in months) from the date of completion of chemotherapy following secondary cytoreductive surgery to the date of recurrence or death from all causes, or censored at date of last follow-up. Patients who had progressive disease following secondary cytoreductive surgery were excluded from the analysis of DFS. Median follow-up duration was estimated using the reverse Kaplan-Meier method. The Kaplan-Meier method was used to determine the survival functions for DFI, OS, and DFS. Median DFI, OS, and DFS were derived, and 95% confidence intervals (CI) were calculated using the log-log method. One-, two- and three-year survival rates were also derived from the Kaplan-Meier survivor function. The log-rank test was used to determine if there was a difference in survival curves between different groups of patients. A two-sided *p*-value of less than 0.050 was taken as significant. All analyzes were performed using Stata 9.0 software (StataCorp, Texas, US).

RESULTS

During the study period, 25 patients were identified who underwent secondary cytoreductive surgery for recurrent ovarian cancer. Demographics and clinical characteristics of the patients at the time of diagnosis of recurrence are summarized in

Table 1: Demographics and clinical characteristics at recurrence.

Variables	n (%)
Age at initial diagnosis (years)	
Median (range)	52 (31–78)
Primary surgery	
Optimal	20 (80.0)
Suboptimal	5 (20.0)
Disease stage	
I	7 (28.0)
II	3 (12.0)
III	13 (52.0)
IV	0 (0)
Unstaged	2 (8.0)
Grade of the disease	
Well-differentiated	5 (20.0)
Moderately differentiated	10 (40.0)
Poorly differentiated	10 (40.0)
Histology	
Serous	11 (44.0)
Endometroid	7 (28.0)
Clear cell	5 (20.0)
Mucinous	2 (8.0)
Site of recurrence	
Solitary	19 (76.0)
Multiple	6 (24.0)
Neoadjuvant therapy before secondary cytoreduction	9 (36.0)
Secondary cytoreduction	
Optimal	20 (80.0)
Suboptimal	5 (20.0)
Surgical procedure associated with secondary debulking	
Wedge resection of liver	1
Colon resection	8
Small bowel resection	2
Distal pancreatectomy	1
Splenectomy	2
Adrenalectomy	1
Unilateral nephrectomy	1
Adjuvant therapy after secondary cytoreduction	
Yes	23 (92.0)
No	2(8.0)

Table 1. The median age at the time of recurrence was 52 years (range=31–78); 13 (52.0%) patients initially had stage III disease. At primary cytoreductive surgery, 20 patients (80.0%) had optimal, and five (20.0%) had suboptimal cytoreductive surgery. After primary surgery, all patients received platinum-based chemotherapy. The median DFI was 25.1 months (range=6.4–83.4). At the 5% significance level, only tumor grade was significantly (p<0.009) related to the disease-free interval [Table 2]. The median disease-free interval was 63.2, 16.7, and 22.4 months in disease grades one, two, and three, respectively. Patients with grade two and three tumors had shorter DFI compared to patients with grade one disease.

Table 2: Median disease-free interval for all patients by prognostic factors.

Variables	No. of events/ No. of patients	Disease-free interval* (months)	p-value
All patients	25/25	25.1 (12.8–35.2)	
Cancer stage			
One	7/7	33.7 (5.8–52.4)	0.630
Two	3/3	23.0 (9.8–undefined)	
Three	13/13	16.8 (10.7–33.6)	
Tumor grade			
One	5/5	63.2 (5.8–undefined)	0.009
Two	10/10	16.7 (8.0–38.0)	
Three	10/10	22.4 (5.4–26.6)	
Histopathology			
Serous	11/11	26.6 (10.7–46.2)	0.705
Endometroid	7/7	12.8 (8.0–51.4)	
Clear cell	5/5	25.1 (12.6–undefined)	
Mucinous	2/2	5.8 (5.8–undefined)	
Primary cytoreduction			
Optimal	20/20	25.1 (9.8–46.2)	0.313
Suboptimal	5/5	22.4 (10.7–undefined)	

***Median (95% CI).*

Patients with optimal versus suboptimal primary cytoreductive surgery also appeared to have some relationship with the DFI [Table 3]; however, this was not statistically significant (p<0.348). This could be because the criteria for optimal cytoreduction varied in the study group.

Optimal secondary cytoreduction was achieved in 20 (80.0%) patients, five (20.0%) had suboptimal debulking. Of those five patients, three had nodal metastasis adherent to a major vessel, and the other two patients had a frozen pelvis with the disease extending up to the pelvic sidewall. Ten (40.0%) patients required bowel resection, but no end colostomy was performed. One (4.0%) patient had wedge resection of the liver, one (4.0%) had distal pancreatectomy, one (4.0%) had a unilateral nephrectomy, and one (4.0%) had adrenalectomy. There was no operative mortality. Following secondary cytoreductive surgery, 23 (85.2%) patients had adjuvant platinum-based chemotherapy and two patients refused chemotherapy. Patients who did not respond to platinum-based chemotherapy were treated with second- and third-line chemotherapeutic agents.

The median follow-up duration for all patients was 38.9 months (95% CI, 17.8–72.4 months). Median overall survival was not reached for many groups, and 95% confidence intervals were not fully

Table 3: Median overall survival for all patients by prognostic factors.

Variables	No. of events/ No. of patients	Median disease-free interval (months)**	*p*-value
All patients	11/25	33.1 (15.3–undefined)	
Stage			
One	2/7	NR(1.3–undefined)	0.024
Two	3/3	8.1 (8.0–undefined)	
Three	5/13	33.1 (11.6–undefined)	
Tumor grade			
One	2/5	NR (8.1–undefined)	0.981
Two	5/10	33.1 (8.0–undefined)	
Three	4/10	21.8 (1.3–undefined)	
Histopathology			
Serous	4/11	33.1 (9.7–undefined)	0.089
Endometroid	2/7	NR(8.0–undefined)	
Mucinous	2/2	8.1 (8.1–undefined)	
Clear cell	3/5	21.8 (1.3–undefined)	
Secondary cytoreduction			
Optimal	7/20	NR (15.3–undefined)	0.348
Suboptimal	4/5	21.8 (9.7–undefined)	
Disease-free interval			
<12 months	2/6	NR (8.0–undefined)	0.761
≥12 months	9/19	30.6 (11.6–undefined)	
Response to secondary cytoreductive surgery			
No*	4/7	11.6 (1.3–undefined)	0.007
Yes	7/18	NR (18.5–undefined)	

***Median (95% CI); NR: Not reached.*
**These patients had the progressive disease even after secondary surgery and chemotherapy.*

defined due to a small number of events (11 deaths out of 25 patients in total). Of the 25 patients, 12 (48.0%) developed a second recurrence and of these five patients underwent a third cytoreductive surgery, and seven patients received palliative chemotherapy.

At the 5% significant level, only cancer stage was significantly related to overall survival. Stage two and three patients were shown to do have a worse overall survival than stage one cancer patients [Table 3]. From the Kaplan-Meier

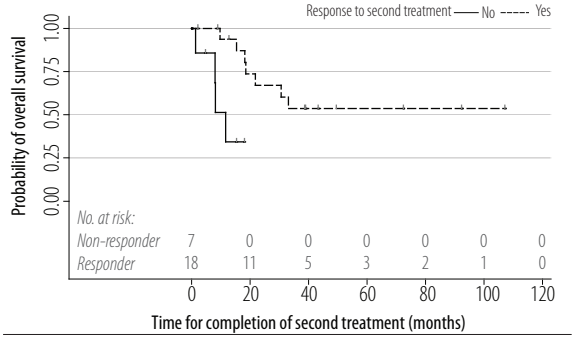

Figure 1: Kaplan-Meier plot of overall survival for all patients by their response to secondary treatment.

Table 4: Median disease-free survival by prognostic factors for patients who responded to secondary treatment.

Variables	No. of events/ No. of patients	Median disease-free survival (months)**	*p*-value
All patients	14/18	21.5 (8.2–30.6)	
Cancer stage			
One	4/6	16.6 (3.5–undefined)	0.433
Two	1/1	12.3 (only one patient)	
Three	7/9	21.5 (8.0–30.6)	
Tumor grade			
One	3/4	3.7 (3.5–undefined)	0.268
Two	7/8	16.6 (8.0–24.9)	
Three	4/6	52.9 (12.3–undefined)	
Histopathology			
Serous	6/8	22.0 (8.2–52.9)	<0.001
Endometroid	5/6	8.9 (3.7–undefined)	
Mucinous	1/1	3.5 (only one patient)	
Clear cell	2/3	87.0 (12.3–undefined)	
Secondary cytoreduction			
Optimal	10/13	22.0 (3.7–52.9)	0.803
Sub-optimal	4/5	12.3 (8.9–undefined)	
Disease-free interval (months)			
<12	3/4	22.0 (3.5–undefined)	0.727
≥12	11/14	16.6 (8.2–52.9)	

***Median (95% CI).*

plots, secondary cytoreduction being optimal or suboptimal also appeared to have some relationship with overall survival, but was not statistically significant. Additionally, patients responding to secondary treatment (i.e. secondary cytoreductive surgery plus chemotherapy) were analyzed, and those patients who had progressive disease after completion of secondary treatment were termed non-responders. Non-responders had a significantly shorter OS compared to responders (p=0.002) [Figure 1].

The DFS of those 18 patients who responded to secondary cytoreductive surgery was analyzed. Only histopathology was significantly related to disease-free survival at the 5% significance level [Table 4]. Of the histopathology types, patients with clear-cell carcinoma showed better survival (p=0.002). Overall, after a median follow-up time of 38.9 months, eight patients (32.0%) were alive with no evidence of disease, six (24.0%) were alive with disease, and eleven (44.0%) had died. Figure 1 shows the overall survival following secondary cytoreductive surgery. The overall one-, two- and three-year survival rate following secondary cytoreductive surgery was 78.1%, 56.1%, and 44.9%, respectively.

Table 5: Clinical series of cytoreductive surgery for recurrent ovarian cancer.

Author	Study type	Publication year	n (total)	Age (median)	Median overall survival (months)	Disease-free interval (months)	Optimal criteria (cm)	Optimal cytoreduction (%)	Complete cytoreduction (%)
Berek et al[9]	A	1983	32	54.5	10	6	<1.5	37.5	NA
Morris et al[10]	A	1989	30	50	16.3	36	<2.0	56.7	30.0
Janicke et al[11]	A	1992	30	53	18	16	<2.0	86.7	46.7
Segna et al[12]	A	1993	100	55	16.6	NA	<2.0	61.0	NA
Eisenkop et al[13]	B	1995	36	60.6	43	22	≤1.0	91.7	83.3
Vaccarello et al[14]	A	1995	57	57	18	20	<0.5	36.8	17.5
Landoni et al[15]	A	1998	38	51[C] (mean)	29	22	No gross	100.0	100.0
Cormio et al[16]	A	1999	21	58	29	25	<2.0	90.5	71.4
Gadducci et al[17]	A	2000	30	58.5	21	17.5	<2.0	83.3	56.7
Zang et al[18]	A	2000	60	50	11	12	≤1.0	38.3	NA
Chen et al[19]	A	2000	22	56.5	41	26	<1.0	86.4	63.6
Eisenkop et al[20]	B	2000	106	60.5	35.9	16.8	No gross	82.1	82.1
Munkarah, et al[21]	A	2001	25	55	25.1	37.6	≤2.0	72	48
Tay et al[22]	A	2002	46	50.3	22.5	26	≤1.0	71.7	41.3
Bristow et al[23]	A	2002	21	46	56.2	15.7	≤1.0	71.4	61.9**
Yoon et al[24]	B	2003	24	47.5	62	36.5	≤1.0	100.0	87.5
Zang et al[25]	A	2003	60	52	17	NA	≤1.0	38.3	NA
Meredith et al[26]	A	2003	26	62	26.3	23.4	≤1.0	80.8	69.2
Look et al[27]	A	2003	24	54	45.8	NA	<2.5	87.5	20.8
Loizzi et al[28]	D	2003	31	57	38	34	<2.0	90.3	NA
Leitao et al[29]	A	2004	26	55.5	33.4	13.4	≤0.5	73.1	53.8
Zang et al[30]	B	2004	117	53	22	15.4	≤1.0	61.5	9.4
Zanon et al[31]	B	2004	30	60	28.1	NA	≤0.25	76.7	NA
Uzan et al[32]	A	2004	12	51	50	21	No gross	100.0	100.0
Gronlund et al[33]	B	2005	38	59[C]	27.4[E]	16.3	No gross	42.1	42.1
Gungor et al[34]	A	2005	44	54.3	16	27.1	<1.0	77.3	NA
Yap et al[35]	A	2005	22	57.4	26	48.2	<0.5	100.0	NA
Onda et al[36]	B	2005	44	52	32	18.5	<1.0	84.1	59.1
Ayhan et al[37]	A	2006	64	50.6	18.6	15.5	≤1.0	82.8	43.8
Matsumoto et al[38]	A	2006	23	55.7	41.7	22.5	<2.0	43.4	30.4
Manci et al[39]	A	2006	24	54	56	26	≤0.5	100.0	66.7
Chi et al[40]	A	2006	153	56.5	41.7	NA	≤0.5	51.6	40.5
Harter et al[41]	B	2006	267	60	29.2	NA	≤1.0	75.7	49.8
Rufian et al[42]	B	2006	14	55	57	NA	≤1.0	85.0	52.0
Helm et al[43]	A	2007	18	64	31	24.6	≤0.5	94.4	61.1
Salani et al[44]	A	2007	55	57.7	48	26	≤1.0	89.1	74.5
Santillan et al[45]	A	2007	25	59	37	16	≤1.0	100.0	96.0
Benedetti Panici et al[46]	B	2007	40	51	60[C]	14	No gross	72.5	72.5
Benedetti Panici et al[47]	B	2007	47	52	49	15	≤1.0	87.2	78.7
Cotte et al[48]	B	2007	81	54.3	28.4	NA	≤0.5	80.2	55.6
Tebes et al[49]	A	2007	85	61 (mean)	30	39 (mean)	<1.0	86	NA
Fotiou et al[50]	A	2009	21	50	47	21	≤1.0	90.5	81
Bae et al[51]	A	2009	54	54	42	24	≤0.5	87	59.3

Table 5 continued...

Author	Study type	Publication year	n (total)	Age (median)	Median overall survival (months)	Disease-free interval (months)	Optimal criteria (cm)	Optimal cytoreduction (%)	Complete cytoreduction (%)
Cheng et al[52]	A	2009	21	53	27	14	≤1.0	33	NA
Bristow et al[53]	A	2009	56	56	38.4	NA	≤1.0	92.9	85.7
Fagotti et al[54]	B	2009	25	52	C	25	<0.25	NA	92
Harter et al[55]	A	2009	250	60	29.5	NA	≤1.0	NA	50
Park et al[56]	A	2010	67			20			55.2
Tian et al[57]	A	2010	125	51	31.7	16.1	≤1.0	78.9	41.5
Sehouli et al[58]	B	2010	240	57	29	NA	≤1.0	77.9	53.8
Woelber et al[59]	A	2010	48	60	26	18	<1.0	47.9	33.3
Schorge et al[1]	A	2010	40	55.4	54	28	<0.5	80	55
Fagotti et al[60]	B	2011	41	52.6	38	19	<0.25	100.0	100.0
Frederick et al[61]	A	2011	62	52.7		28.2	<1.0	40.3	36
Burton et al[62]	A	2011	20	59	22.5	18	No gross	NA	55
Königsrainer et al[63]	A	2011	31	60	1150 days	762 days	No gross	90.3	65
Classe et al[64]	A	2011	35	58.5	35	40	<1.0	60	34.3
Ceelen et al[65]	B	2012	42	52	37	3	No gross	NA	50

NA:data not available; A: retrospective review; B: prospective, non-randomized; C: median not yet reached; D: retrospective case-control; E: personal communication.

Univariate analysis was performed on various clinical variables such as DFI (fewer than vs. more than 12 months), disease stage, tumor grade, and optimal versus suboptimal surgery. There was no significant difference in any of these variables, but those patients who responded to secondary cytoreductive surgery had a longer survival period than not responders.

DISCUSSION

The role of primary cytoreductive surgery is well established in the management of epithelial ovarian cancer. Numerous investigators have documented improved survival after secondary cytoreductive surgery, but still lack evidence-based protocols for managing such patients. This is partly because most of the literature on this subject are non-randomized, retrospective studies. As these recurrent tumors develop resistance to platinum-based chemotherapy, and due to their heterogeneous behavior, the role of aggressive secondary cytoreductive surgery has always been questioned. Factors that affect survival following secondary cytoreductive surgery are disease-free interval following primary cytoreductive surgery and volume of residual disease following secondary cytoreductive surgery. Several studies, including ours, showed that the volume of residual disease after secondary cytoreduction had some effect on OS. We looked into the studies published on this subject over the last three decades. Since these studies were published between 1983 to 2012, the criteria for optimal cytoreduction varied from <2.5cm to no gross disease, we tabulated them according to the criteria used to see the rate of optimal secondary cytoreduction and their OS [Table 5]. During the period where the optimal cytoreduction was defined as <2.5 to >1.0cm, optimal cytoreduction was achieved in 37.5%–90.5% of cases and overall survival in these patients ranged from 10.0–45.8 months. When it was defined as less than <1.0cm optimal cytoreduction was achieved in 33.0%–100% of cases and the OS ranged from 11–48 months. With current definition of optimal cytoreduction being <0.25cm to no gross disease, optimal cytoreduction was achieved in 22.2%–100.0% of cases and OS in these patients was 22.5–60 months.

Various authors have shown that one important factor to have a significant influence on OS following secondary cytoreduction was the DFI (recurrence-free interval): a longer DFI was associated with more prolonged survival.[3,17,18,22,66] However, some studies have shown that DFI was not a significant variable.[4,8,9,44,49] In our study, the univariate analysis did not reveal any factors that affected the duration of OS. Our analysis was inherently limited by the

potential for selection bias as, being a retrospective study, it covered a time during which concepts of optimal cytoreductive surgery and available adjuvant therapies evolved. This could have influenced the prognostic impact of individual variables on survival.

CONCLUSION

Our experience confirms that in a selected group of patients secondary cytoreduction improves survival of patients with ovarian cancer whose disease recurs at least six months after the primary treatment. Whether this is due to the surgical procedure itself or tumor biology remains unclear. There is urgent need for a large multi-institutional prospective randomized trial to analyze various variables and selection criteria for secondary cytoreductive surgery.

Disclosure

The authors declared no conflicts of interest. No funding was received for this study.

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