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## RESEARCH ARTICLE

### SHORT TERM AND FOLLOW-UP RESULTS OF SECONDARY CYTOREDUCTIVE SURGERY IN PATIENTS WITH RECURRENT OVARIAN CANCER

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#### ABSTRACT

**Background:** Despite advances in medical and surgical management of ovarian cancer, recurrence is still significant issue with secondary cytoreductive surgery (SCS) being considered as treatment option for carefully selected patients. **Objective:** To assess short term and follow up outcomes of secondary cytoreductive surgery among recurrent ovarian cancer patients. **Patients and Method:** After approval of ethics committee, this study included forty four female patients who were diagnosed with recurrent ovarian cancer between 2014 and 2019. They were treated at Surgery Department, Kuwait Cancer Control Center, Kuwait and both Surgery and Gynecology Departments, Suez Canal University Hospitals, Ismailia, Egypt. All patients had undergone secondary cytoreductive surgery and were followed up for 4-40 months. **Results:** The most common site of recurrence at presentation was local pelvic recurrence (52.27%) with peritoneal disease reported among 34.09%. Ascites was found among 18.18% of patients. The most commonly reported complications included ileus (13.64%), DVT (9.09) and wound infection (9.09%). Local recurrence after SCS was reported among 34.09% of patients. Mean disease free survival (DFS) was 24.8 months. **Conclusion:** secondary cytoreductive surgery for recurrent ovarian cancer is feasible when patient selection is appropriate and it can offer the patient with a better outcome regarding the DFS.

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#### INTRODUCTION

Ovarian carcinoma is considered one of the most common causes of cancer-related deaths among all gynecologic tumors. It ranks sixth among female malignancies worldwide (Torre et al., 2015). Adding to the reliance of the disease, it is worthy to know that the newly diagnosed patients with ovarian cancers accounted for approximately 4% of all newly diagnosed female cancer patients each year (Tetsche et al., 2006; Noer et al., 2016). Five year survival has been recently improved thanks to the advances in both medical and surgical management of ovarian carcinoma (Fader, 2007). However, and for fit patients, surgery is often the initial treatment of choice for ovarian cancer. When optimal debulking is not possible, patients are considered for neoadjuvant chemotherapy then interval debulking surgery followed by chemotherapy. Patients who are not fit for surgery may be given chemotherapy and considered for later surgery, or treated essentially with chemotherapy (Saitian Zeng, 2017).

However, despite all efforts for early diagnosis and optimum management of ovarian carcinoma, recurrence is still an important disease burden among significant proportion of patients (approximately 70%) (Joslin et al., 2014). Chemotherapy remains the standard care of women with platinum-sensitive recurrent ovarian cancer (ROC) (Du Bois et al., 2017; Shanghai Gynecologic Oncology Group, 2018). Secondary cytoreductive surgery is a subsequent surgical debulking after primary treatment and a treatment-free interval (Al Rawahi, 2013). It is a treatment option for recurrent ovarian cancer when complete resection is possible, due to anticipated better prognosis (Al Rawahi et al., 2013; Bristow, 2009). In 2012, Tian et al. (2012) established a model for preoperative prediction of complete resection in SCS. The model categorized platinum-sensitive ROC patients as low and high-risk groups using 6 variables: International Federation of Gynecology and Obstetrics (FIGO) stage, macroscopic residual disease after primary cytoreduction, disease-free interval (DFI), performance status (PS) at recurrence, cancer antigen 125 (CA125) at recurrence, and ascites at recurrence. Patients in low-risk group considered good candidates for secondary cytoreductive surgery.

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The Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) model is another tool used to select candidates for secondary SCS (Harter, 2011). The current study aimed to assess short term and follow up outcome of patients with recurrent ovarian cancer undergoing secondary cytoreductive surgery.

## PATIENTS AND METHODS

After approval of our ethics committee, the present descriptive cross-sectional study performed between October 2014 and March 2019 and included 44 female patients diagnosed with recurrent ovarian cancer presented to Surgery Department, Kuwait Cancer Control Center, Kuwait and both Surgery and Gynecology Departments, Faculty of Medicine, Suez Canal University Hospitals, Ismailia, Egypt. All patients were diagnosed as having evidence of recurrence as found by mean of clinical examination and imaging studies including CT abdomen and pelvis and PET-CT scan with or without raised tumor marker CA125 levels. Those patient completed their primary treatment including surgery and chemotherapy at either of both institutions where the study was carried out, and were assigned as platinum sensitive or responders with disease free survival (DFS) for at least six months. Patients showed advanced or deemed irresectable by imaging studies or those with distant metastasis were excluded. Also patients showed ECOG performance status of more than 3 or any absolute medical contraindications to extensive surgical procedures were excluded. Demographic data and medical history were obtained from the patients including age, comorbid medical conditions and data regarding the initial diagnosis of the tumor, both radiologically and pathologically, were documented. Data regarding the initial therapy (surgical with-or-without chemotherapy) and disease-free interval were also recorded. CT and/or PET-CT scan of the abdomen and pelvis was performed to determine the resectability of the tumors. Decision to implement a plan for management was taken on case by case basis through a MDT meeting including medical, surgical oncologist and radiologist to reach a consensus regarding the treatment of each patient. Some patient went to surgery and others allocated to chemotherapy first followed by reassessment then surgery. Preoperative routine investigations were performed to determine fitness for anesthesia and eligibility for surgery and informed consent was taken after explaining the cost and benefits that could be encountered after surgery.

**Surgical management:** All patients had midline exploratory incision and the extent of the disease recurrence was assessed and every effort was done to reach maximum optimal debulking. All data regarding operative steps, extent of resection, surgical morbidity, complications or any untoward events were recorded. The resected tumor tissues were sent for histopathological examination, for confirmation of the initial pathological diagnosis.

**Postoperative management:** All patients sent for ICU for overnight monitoring and discharged early morning unless there was an indication to be kept in ICU. Early postoperative complications including; wound infection, chest infection and thromboembolism and any operative mortality were documented

**Postoperative short term and follow up assessment:** All patients were put under follow up program with medical and surgical oncologists and disease free survival was assessed

through the period that follow the surgical procedure without any symptoms or signs of disease recurrence. Follow up PET-CT scan done to assess optimal cytoreduction as it was defined as either no residual disease or residual disease less than 1cm in maximal dimension. Serial postoperative measurements of tumor marker CA125 were performed to assess the response to treatment. Follow up period ranged between 4 to 40 months. Main outcome measures are short term complications, local recurrence, and disease free survival.

**Statistical analysis:** Gathered information was processed using SPSS version 25 (SPSS Inc., Chicago, IL, USA.). Quantitative data was expressed as means  $\pm$  SD while qualitative data was expressed as number and percentages (%). Kaplan Meier survival analysis graph was produced to describe disease free survival among studied patients. A probability value (p-value)  $<0.05$  was considered statistically significant.

## RESULTS

Mean age of the studied patients was 55.64 years old with 31.82% of patients age  $> 60$  years old. The most common original pathology was serous ovarian carcinoma (70.45%). Only one patient showed different pathology on recurrence where original pathology was borderline and new pathology was found to be serous. Mean disease free survival period after the primary surgery was 19.23 months. The most common site of recurrence was local pelvic recurrence (52.27%) with peritoneal disease reported among 34.09%. Ascites was found among 18.18% of patients (Table 1). Initial secondary cytoreductive surgery followed by chemotherapy was the plan of management among 75% of patients while chemotherapy preceded surgery among 25% of patients. Most of patients stayed in ICU for 1 day only (68.18%). However, 22.73% of the studied patients remained in ICU for more than 2 days (Table 2). Regarding early complications, more than half of the patients didn't report any early complications (56.82%). The most commonly reported complications included ileus (13.64%), DVT (9.09) and wound infection (9.09%). Chest infection was reported among 2.27% of patients. One patient had fatal pulmonary embolism. Over follow up period up to 40 months with mean of 17.3 month, 50% of patient didn't show any late complications. Local recurrence was reported among 34.09% of patients while one patient showed evidence of distant metastasis. Other commonly reported late complications included reoperation for obstruction (6.82%) and incisional hernia (4.55%) (Table 3).

## DISCUSSION

Numerous studies have shown improved survival with secondary cytoreductive surgery, but still there is no evidence-based protocol for management of these patients. This is somewhat due to the nature of most work on this subject that usually included non-randomized, retrospective studies. As with development of resistance to platinum-based chemotherapy, and due to the varied behavior of these recurrent tumors, the role of aggressive SCS has always been questioned (Bhat et al., 2015). Our study evaluated the short-term outcomes of SCS in 44 patients with recurrent ovarian cancer. Optimal cytoreduction is now defined to be  $<1$ cm or no gross disease. The earliest report of impact of secondary cytoreductive surgery was demonstrated by Berek in 1983 (Berek et al., 1983).

**Table 1. Baseline patients' characteristics**

		Number	Percentage
Age (years)	≤ 60 years old	30	68.18%
	> 60 years old	14	31.82%
	Mean ± SD	56.64 ± 7.39	
Original pathology	Range	39 – 71	
	Borderline	3	6.82%
	Clear cell	2	4.55%
	Endometrioid	3	6.82%
	Mucinous	5	11.36%
Performance status	Serous	31	70.45%
	0	4	9.1%
	1	29	65.9%
	2	7	15.9%
Disease free survival (months)	3	4	9.1%
	Mean ± SD	19.23 ± 6.64	
Site of recurrence	Range	9 – 33	
	Local pelvic	23	52.27%
	Nodal recurrence	6	13.64%
Ascites on recurrence	Peritoneal disease	15	34.09%
	No	36	81.82%
New pathology	Yes	8	18.18%
	Same	43	97.73%
	Different	1	2.27%

**Table 2. Management plan characteristics**

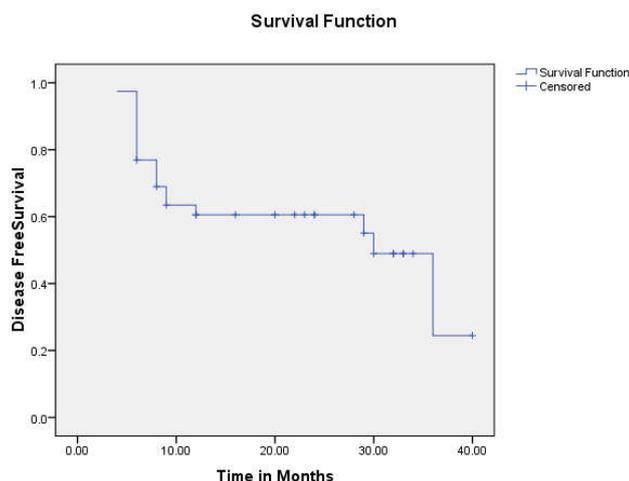
		Number	Percentage
Management plan	Chemotherapy then surgery	11	25%
	Surgery then chemotherapy	33	75%
R resection status	R0	26	59.09%
	R1	16	36.36%
	R2	2	4.55%
Postoperative ICU stay (days)	1 day	30	68.18%
	2 days	4	9.09%
	> 2 days	10	22.73%
	Mean ± SD	1.7 ± 1.2	
	Range	1 – 7	

**Table 3. Early and late postoperative complications**

		Number	Percentage
Early postoperative complications	None	25	56.82%
	Wound infection	4	9.09%
	Chest infection	1	2.27%
	Reoperation for bleeding	1	2.27%
	Ileus	6	13.64%
	Intestinal fistula	1	2.27%
	Ureteric injury	1	2.27%
	DVT	4	9.09%
	Fatal pulmonary embolism	1	2.27%
	Late postoperative complications	None	22
Local recurrence		15	34.09%
Reoperation for obstruction		3	6.82%
Incisional hernia		2	4.55%
Distant metastasis		1	2.27%
Adhesive obstruction		1	2.27%
Follow up period (months)	Mean ± SD	24.25 ± 11.68	
	Range	4 – 40	

That early report was followed by many retrospective studies and few prospective but non-randomized trials were reported (Chi et al., 2006; Zang, 2011; Gockley, 2019; Bickell, 2018). The present study has shown that the most common site of recurrence was local pelvic recurrence (52.27%) with peritoneal disease reported among 34.09%. Similar results have been reported by previous studies and pelvis was found to be site of highest prevalence of recurrence (Chi et al., 2006). Current study revealed that ascites was found among 18.18% of patients. In accordance with current findings, ascites was present in 19% of the patients (Chi et al., 2006). Similarly, Eisenkop et al. (2000) found that 33.0% of the patients had pelvic recurrence and about 17.0% of them had recurrence at

gastrocolic ligament/omentum. The presence of ascites was 17.0% among the studied patients (Eisenkop et al., 2000). We have shown that Mean disease free survival period was 19.23 months following primary treatment with range 9 – 33 months. Various authors indicated that one important factor that notably influences the overall survival after secondary cytoreduction was the disease free interval: a longer disease free interval was associated with more prolonged survival (Jänicke, 1992; Gadducci, 2000; Zang et al., 2000; Tay, 2002; Scarabelli, 2001). However, some studies have shown that disease free interval was not an exceptional parameter (Segna, 1993; Chi, 2009; Berek, 1983; Salani, 2007; Tebes, 2007). It is usually stated that complete resection at secondary cytoreduction surgery correlates with better prognosis.



**Graph 1. Kaplan Meier analysis survival for disease free survival after secondary cytoreductive surgery**

Previous research has asserted that, after SCS, the disease-free survival and overall survival of the patients without gross residual were notably prolonged, by 57.4 and 92.9 months, respectively. Postoperative quality of life was remarkably better than preoperative; suggesting that SCS significantly improved the quality of life of patients and reduced the symptoms and pain of patients (Saitian Zeng et al., 2017). Retrospective studies results revealed that, secondary cytoreductive surgery could help prolong patient's survival time, and half of these patients were identified with recurrent epithelial cancer by pathological examination; furthermore, these patients had better sensitivity to platinum drug chemotherapy (Al Rawahi, 2013; Bristow, 2009). Current study has shown that the most commonly reported complications included ileus (13.64%), DVT (9.09) and wound infection (9.09%). Chest infection was reported among 2.27% of patients. Lower rates of complications have been reported with previous studies (Chi et al., 2006; Pavlov et al., 2017 and Gockley et al., 2018). Pavlov et al. (30) reported that only 9.5% of their patients developed postoperative complications; including anemia, thrombocytopenia, transient metabolic acidosis, wound infection, gastrointestinal upset, prolonged bowel obstruction, and one anastomotic leak requiring reoperation. They also reported that one patient died of cerebrovascular insult (Pavlov et al., 2017).

With an average follow up of 17.3 months (range 4-40) 28 patients (63.63 %) did not show any evidence of recurrence after their secondary surgery while local recurrence was reported in 15 patients (34.09%) and One patient showed evidence of distant metastasis after 4 months. Other commonly reported late complications included reoperation for obstruction (6.82%) and incisional hernia (4.55%). Fagotti et al. (2012) reported that 66.6% of patients treated with secondary SCS and HIPEC had recurrent disease (Fagotti, 2012). Also, Szczesny et al. (33) reported that only 28 patients (37%) patients, who received SCS and chemotherapy, were alive without second recurrence (Szczesny, 2018) The discordance between current and previous findings can be attributed to longer periods of follow up in these studies compared to ours. Following SCS, our patients had a mean disease free survival of 24.8 months. This finding going with previous studies that have reported a comparable disease free survival after secondary cytoreductive surgery.

Chi et al. (2006) found that the mean DFS was 17 months after secondary cytoreductive surgery in patients with recurrent ovarian cancer (Chi et al., 2006). Also, in a more recent study, Szczesny et al. (Szczesny, 2008) reported a mean DFS of 24 months in patients treated with SCS and platinum-based chemotherapy (Szczesny, 2008). Discrepancy in periods of follow up and sample size between different studies could explain any differences in periods of disease free survival.

**Conclusion and recommendations:** In conclusion, secondary cytoreductive surgery for recurrent ovarian cancer is feasible when patient selection is appropriate and it can offer the patient with a better outcome regarding the DFS. Further randomized studies including larger sample size are still required to implement standardized management protocol for recurrent ovarian cancer patients.

**Conflicts of interest:** None of authors have any conflict of interests

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