Original Article

Secondary debulking for ovarian carcinoma relapse: The R-R dilemma – is the prognosis different for residual or recurrent disease?

Spiliotis et al. Residual or recurrent ovarian cancer: Difference in prognosis?

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Abstract
Objective: To analyse the kind of ovarian cancer relapse by separating residual from recurrent disease and correlating them with patients' survival.
Material and methods: Retrospective study of 200 women with ovarian carcinoma relapse during the period 2005-2017.
Results: The main sites of residual disease included great omentum, epiploic appendices, liver round ligament, gallbladder, cervical/vaginal stump. Median survival for women with residual disease treated with cytoreductive surgery (CRS) + hyperthermic intraperitoneal chemotherapy (HIPEC)+ systemic chemotherapy was 38 months compared to the control group which reached 23,8 months. The morbidity rates were 18% versus 7% respectively while the mortality rates were 2.5% versus 1.3%. The main sites of recurrent disease included mesenterium, pelvic floor, diaphragm, and Glisson's capsule. Women with recurrent disease treated with CRS +HIPEC+ systemic chemotherapy had median survival rates of 26 months versus 16 months in the control group. The morbidity rates were 22% versus 15% respectively while the mortality rates were 3.3% versus 0%.
Conclusion: Patients undergoing secondary debulking plus HIPEC for ovarian carcinoma relapse have a different prognosis when comparing cases with residual to those with recurrent disease. A different prognosis is presented in women undergoing secondary debulking plus HIPEC for ovarian carcinoma relapse when comparing cases with residual to those with recurrent disease.
Keywords: HIPEC, ovarian carcinoma, relapse, residual, recurrence, management, survival, prognosis

Introduction

Epithelial ovarian carcinoma (EOC) accounts for 2% of female cancer cases with high mortality rates and a five-year survival falling at 46%. Although, the use of bevacizumab and poly ADP ribose polymerase (PARP) inhibitors as well as the ultraradical surgical approach to achieve zero residual disease were recently added in the current management, no satisfactory results can be achieved regarding progression free and overall survival. However, ultraradical debulking in combination with HIPEC revealed to be an alternative safe and effective approach. Around 70% of all women with ovarian carcinoma relapse after primary debulking and first-line chemotherapy.

The objective of our study is to discuss the possible differences in survival between residual and recurrent disease in ovarian cancer patients presenting with disease relapse.

Patients and Methods

Two hundred patients with EOC relapse were retrospectively studied using our database. All the patients with ovarian carcinoma relapse were operated in three different hospitals by the same surgical group from 2005 to 2017.

During secondary cytoreduction, remaining abdominal disease after suboptimal or optimal primary or interval debulking was characterized as residual disease while new disease found in patients who had primary or interval complete cytoreduction was considered as a recurrence. 140/200 patients were detected with residual disease compared to 50/200 with recurrent disease and 10/200 with splachnic metastases (Fig.1).

Both groups of patients with recurrent and residual disease were divided in two subgroups: the one receiving CRS and HIPEC followed by systemic chemotherapy, and a second subgroup receiving CRS and systemic chemotherapy alone. The ten patients with splachnic metastases received systemic chemotherapy (Fig. 2,3).

Results

The mean age of the patients was 69 years old ranging from 42 to 83 years old. The mean BMI was 31 (range 24 to 43) and 34 patients had family history of ovarian cancer. No information was available regarding their BRCA status. All patients had initially received 6 cycles of carboplatin and taxol. Platinum free interval was more than 6 months in all the cases ranging from 10 months to 22 months. A difference was found between the sites of recurrent and residual disease. The main sites of residual disease included great omentum (67%), epiploic appendices (33%), liver round ligament (55%), gallbladder (33%), cervical/vaginal stump (30%). The recurrent disease sites in the residual disease group were the same with the sites in primary surgery. The median preoperative peritoneal cancer index (PCI) was 18 and we achieved complete cytoreduction in 75% while 20% of the women faced grade 3,4 complications. Median overall survival for women with residual disease treated with CRS +HIPEC+ systemic chemotherapy was 38 months compared to the control group which reached 23,8 months. (Fig. 4). In this group of patients, the morbidity rates were 18% versus 7% respectively while the mortality rates were 2.5% versus 1.3%. The main sites of recurrent disease included mesenterium (50%), pelvic floor (40%), diaphragm (60%), and Glisson's capsule (40%). The median preoperative PCI was 22 and we achieved complete cytoreduction in 64% while 14% of the patients faced grade 3,4 complications. In the recurrent disease group, the median overall survival rates reached 26 and 16 months respectively (Fig. 5). In this group of patients, the morbidity rates were 22% versus 15% respectively while the mortality rates were 3.3% versus 0%.

Discussion

Recurrent ovarian cancer is treatable but rarely curable. The recurrence rates depend on the stage at diagnosis reaching 10%, 30%, 70-90% and 90-95% for stages I to IV respectively (1). One of the main factors affecting the patient's risk of recurrence is the completeness of primary/interval debulking. The majority of the ovarian cancer women present recurrences in the peritoneal cavity independently of the primary/interval debulking extend and/or type of chemotherapy (2). Rose et al proposed a nomogram for predicting individual survival after ovarian cancer recurrence which included time to recurrence after initial chemotherapy, clear cell or mucinous histology, performance status, stage IV disease and age (3). A recent retrospective study revealed that peritoneal recurrences are found in 75% of patients with advanced-disease group, and the relapse is found at both treated and untreated sites. Nodal relapses were found in 38% of all cases while isolated distant metastases were identified in 8% of patients (4). According to Ushiyama et al around 55% of women recur at the primary site and the rest present with distant metastases including retroperitoneal nodes, liver or spleen, brain, and bone (1). In our study the main areas of relapse included great omentum, epiploic appendices, liver round ligament, gallbladder, cervical/vaginal stump in the residual disease group compared to mesenterium, pelvic floor, diaphragm, and Glisson's capsule in the recurrent disease group.Women with recurrent ovarian cancer may be eligible for secondary cytoreduction (1).

DESKTOP trial suggested the main selection criteria of operability for patients with recurrent ovarian cancer including good performance status, absence or small volume of ascites at recurrence, and completeness of primary surgery (5). Recently, DESKTOP III revealed that secondary cytoreduction compared to second line chemotherapy in 407 relapsed patients after a progression free interval period of more than 6 months as well as a positive AGO-Score performance status Eastern Cooperative Oncology Group (ECOG) 0, ascetic volume of less than 500 ml, and zero residual at initial debulking leads to improved progression free survival (19.6 months versus 14 months) (6). Regarding overall survival rates, the results remain still immature and are not published yet (6). Another study proposed that the main predictors for complete cytoreduction in women undergoing secondary cytoreduction include stage of disease, complete primary/interval debulking surgery, progression free interval, CA125 value and presence of ascites at recurrence (7). Based on the above, Zang et al suggested a prognostic model to predict survival benefit from secondary debulking including four parameters (progression free interval, presence of ascitic fluid at recurrence, extent of recurrent disease and completeness of secondary cytoreduction based on the residual disease (8). More specifically, the median survival after secondary debulking for women with progression free interval >23.1 months was 45.0 months compared to 21.0 months in women with progression free interval of < 23.1 months. The cut-off level of CA 125 at recurrence was found to be 251.0 U ml^{-1}. Median survival was found to be 43.9 months in women with local disease compared to 20.0 months in patients with multiple areas of recurrence (8). Zero residual disease after secondary cytoreduction was the strongest prognostic factor. More specifically, the median survival was 57.7 months in women achieving R0 during secondary cytoreduction compared to 27.0 months in R1 group, and 15.6 months in R2 group (8,9). Furthermore, Laga et al confirmed that DESKTOP score and Tian model are the main predictors of candidates' selection for complete secondary cytoreduction (10). However, in their study 61% and 70% of the patients were debulked to R0 independently of the negative

preoperative scores. For this reason, they suggested that other anatomic and metabolic imaging criteria should be evaluated to recognise eligible patients patients for HIPEC plus secondary cytoreduction. (10)
HIPEC following secondary cytoreduction is an alternative approach for patients with recurrent ovarian disease. Harter et al concluded that "HIPEC remains experimental in ovarian cancer patients but it can be used inside prospective controlled trials." (5). A recent metaanalysis showed better overall survival rates for recurrent ovarian cancer patients when adding HIPEC to secondary cytoreduction and traditional chemotherapy. Additionally, a positive correlation between completeness of debulking and survival was found. In the same analysis, morbidity and mortality rates were similar. (11) It should be highlighted that in high-volume centers with HIPEC specialists, morbidity and mortality has drastically improved (12,13). The published results from our center showed that women with advanced ovarian carcinoma recurrence had a mean survival benefit of around 13.3 months when HIPEC is offered (26.7 months) versus 13.4 months in the non HIPEC group (14). Hotouras et al showed that in women with ovarian carcinoma recurrence undergoing debulking plus HIPEC administration, the overall survival ranged between 26.7 and 35 months, with progression free survival varying between 8.5 and 48 months. (15). The role of HIPEC in ovarian cancer patients was recently confirmed in a randomised controlled trial which highlighted a better progression free survival (15 versus 11 months) as well as overall survival (46 versus 34 months) in patients with stage III epithelial ovarian cancer undergoing interval cytoreduction plus HIPEC administration (16). Results of other randomized trials in the field are awaited.
The question raised by our study is whether disease recurrence refers to relapse or residual disease post initial surgery and whether secondary cytoreduction followed by HIPEC have different effect in progression free and overall survival in the two different groups. This was actually confirmed from our results as median survival for women with residual disease treated with CRS +HIPEC+ systemic chemotherapy was 38 months compared to the control group which reached 23,8 months. In addition, patients presented with recurrent disease, had median survival rates of 26 and 16 months respectively. To summarise addition of HIPEC improves survival rates in both patients with residual as well as recurrent disease while such rates are obviously better in the residual compared to recurrent disease group. Such findings also highlight the need of major cytoreductive effort/ultraradical surgery at the moment of primary/interval cytoreduction.
This study has some limitations which have to be pointed out including the small patient population and the retrospective nature of the study. It is well known fact that maximal and optimal cytoreduction have better prognosis than suboptimal debulking. A hundred and forty patients had residual disease in our study. This number could be considered quite high but we should clarify that all these patients were referred to our group for further management in our tertiary centres after being operated either by not subspecialists or in cases where neoadjuvant chemotherapy had not been considered an option prior to primary debulking. Unfortunately, as the majority of the patients were initially treated by not subspecialists, we are unable to subdivide optimal and suboptimal cytoreduction categories in the residual disease group.

Conclusion

Our retrospective study shows that HIPEC improves survival rates in both patients with residual as well as recurrent disease. Better survival rates were found in women with residual disease treated with HIPEC – rates which are actually longer compared to the recurrent group. Prospective randomized multicentre studies are essential to further empower our findings.

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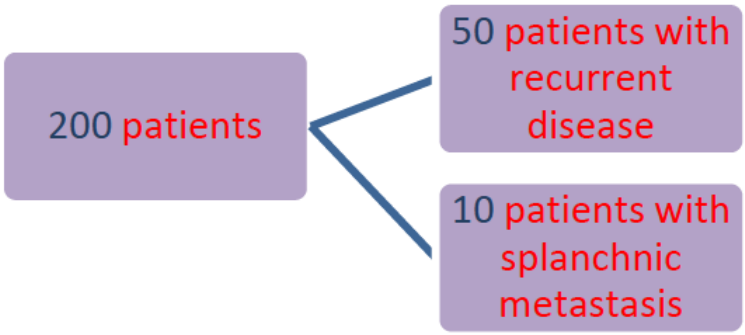

Figure 1. Flow chart of the patients' cohort

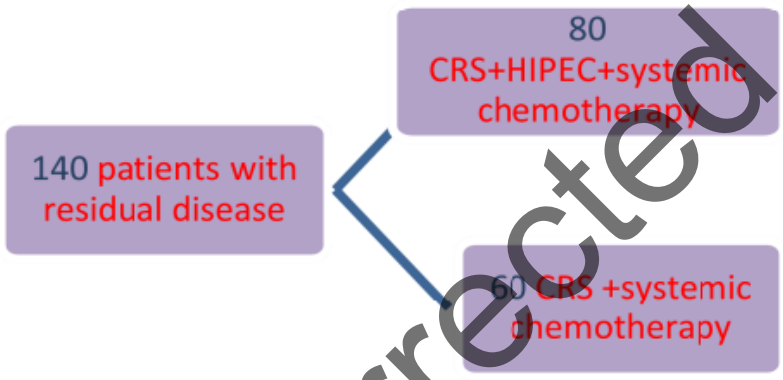

Figure 2. Division of patients with residual disease

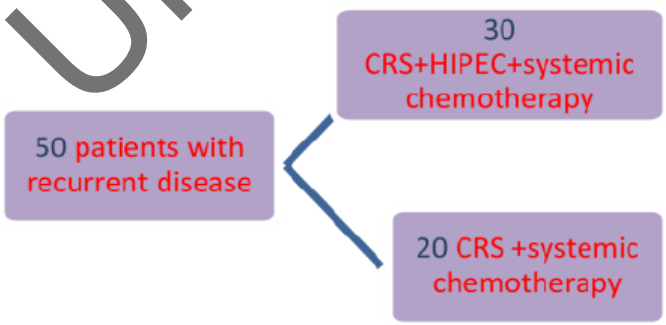

Figure 3. Division of patients with recurrent disease

Residual disease group	Median survival	Morbidity/Mortality
CRS+HIPEC+System chem	38 months	18%/2.5%
CRS+System chem	23.8 months	7%/1.3%

Figure 4. Survival, morbidity and mortality rates in patients with residual disease

Recurrent disease group	Median survival	Morbidity/Mortality
CRS+HIPEC+System chem	26 months	22%/3.3%
CRS+System chem	16 months	15%/0%

Figure 5. Survival, morbidity and mortality rates in patients with recurrent disease