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Abstract:

Outcomes of secondary cytoreduction surgery (SCS) were evaluated for morbidity, progression free survival (PFS) and overall survival (OS) and factors influencing results were explored. Retrospective analysis of all cases of SCS for epithelial ovarian cancer (EOC) was performed from October 2010 to December 2017. 62 patients were prospectively identified as candidates for SCS and 57 underwent SCS. 20(35%) patients required bowel resection/s, 24(42%) had nodal resections and 11(19%) had extensive upper abdominal surgery. 51(89%) achieved complete cytoreduction. After a median follow-up of 30 months (range 9 – 95 months), median PFS was 32 months (CI 17 – 76 months) and median OS has not reached. Seventeen patients have died and 32 have progressed. Three patients had Clavien-Dindo grade-3 and two had grade-4 morbidity. Patients who had multi-site recurrence had shorter median PFS (p=0.04) and patients who required bowel resections had lower median OS (p=0.009) compared to rest of the cohort.

Key words: Recurrent epithelial ovarian cancer; Ovarian cancer; Secondary cytoreduction surgery; Secondary debulking surgery; ovarian neoplasm

Highlights:

1. Secondary cytoreduction surgery in selected group of patients is well tolerated and has good survival outcomes.
2. Patients with multisite recurrence tend to relapse earlier compared to patients with single site recurrence.
3. Patients requiring bowel resection/s for recurrent epithelial ovarian cancer has lower overall survival.

Impact statement:

What is already known on this subject? Retrospective studies have confirmed survival advantage for recurrence in epithelial ovarian cancer and recommend SCS for carefully selected patients. This finding is being evaluated in randomised control trials currently.

What do the results of this study add? This study presents excellent results for survival outcomes after SCS and highlights importance of careful selection of patients with a goal to achieve complete cytoreduction. In addition, for the first time in literature, this study also explores various factors that may influence results and finds that there are no differences in survival outcomes whether these patients had early stage or advanced stage disease earlier. Patients who have multisite recurrence tend to have shorter PFS but no difference were noted for overall survival. Patients who have recurrence in bowels necessitating resection/s have a shorter median OS compared to rest of cohorts, however, still achieving a good survival time.

What are the implications of these findings for clinical practice and/or further research? These findings will raise awareness for the clinicians and patients while discussing surgical outcomes and would set an achievable standard to improve cancer services. The pattern of recurrence and associated outcomes also point towards difference in biological nature of recurrent disease and could provide an opportunity for scientists to study the biological makeup of these recurrent tumours.

Does sites of recurrence impact survival in secondary cytoreduction surgery for recurrent epithelial ovarian cancer?

Background:

Despite treatment with cytoreductive surgery and platinum based chemotherapy recurrence rates for epithelial ovarian cancer is approximately 70 – 90% (Armstrong, 2002). Management of recurrent disease aims to prolong survival and maintain or improve quality of life whilst minimising treatment related toxicities. The mainstay of treatment for platinum sensitive recurrent epithelial ovarian cancer is second line platinum based combination chemotherapy either with Paclitaxel, Gemcitabine and more recently Liposomal Doxorubicin as evidenced from randomised controlled trials and systematic reviews (Fung-Kee-Fung et al., 2007; Gladieff et al., 2012; Parmar et al., 2003; Pfisterer et al., 2006; Wagner et al., 2012). In selected patients, platinum based chemotherapy may be followed by maintenance Bevacizumab or PARP inhibitors which have been shown to improve progression free survival when compared to chemotherapy alone.

Recent interim reporting of AGO-OVAR DESKTOP III randomised controlled trial, informed a 5.6 months improvement in progression free survival in women undergoing secondary cytoreduction surgery followed by chemotherapy compared to women receiving 2nd line chemotherapy alone, though the overall survival outcomes are awaited (Du Bois et al., 2017). However, a similar trial GOG 213 from the United States only reported a progression free survival advantage of 1.7 months among women undergoing secondary cytoreduction surgery followed by platinum based chemotherapy and Bevacizumab when compared to combination of chemotherapy and Bevacizumab without surgery (Coleman, 2018).

The present evidence of secondary cytoreduction surgery is based on retrospective cohort studies (da Costa et al., 2016; Eisenkop, Friedman, & Spirtos, 2000; Joshi & Joshi, 2014; van de Laar et al., 2016). A review of such studies by Harter et al., (2005) demonstrated survival advantage for no residual disease at secondary cytoreduction surgery as well as patients with residual disease < 1cm compared to patients with residual disease > 1cm. However, the role of secondary cytoreduction surgery with an outcome of residual disease < 1 cm was not clear (Philipp Harter & du Bois, 2005). A meta-analysis of secondary cytoreduction surgery for recurrent ovarian cancer showed improvement in survival only for those patients who achieved complete cytoreduction (Bristow, Puri, & Chi, 2009). Similarly, a Cochrane review based on non-randomised studies also found significant improvement in overall survival after secondary cytoreduction surgery in women with platinum sensitive disease achieving complete cytoreduction, but progression free survival outcomes were not reported (Al Rawahi et al., 2013). In another Cochrane review, authors did not find any study which compared role of secondary cytoreduction surgery followed by chemotherapy and chemotherapy alone (Galaal et al., 2010).

The aim of this study was to evaluate the use of secondary cytoreduction surgery in women with recurrent epithelial ovarian cancer in terms of morbidity and survival at Pan Birmingham Gynaecological cancer centre, UK, as well as exploring any differences in survival outcomes based on their age, histopathology, International Federation of Gynaecology and Obstetrics (FIGO) stage at initial diagnosis, recurrence pattern, treatment free interval and types of surgical interventions.

Methods:

Pan Birmingham Gynaecological cancer centre, United Kingdom, is hub for gynaecological cancer surgery for 5 cancer units and serves a population over 2.2 million people in and around Birmingham though also receives referrals within the West Midlands (population over 5 million). Within the Centre, extensive ovarian cancer surgery is accepted as standard of care for over 10 years (Phillips et al., 2017; Phillips et al., 2018).

The prospective data base recorded by the multidisciplinary team was interrogated to identify all women undergoing secondary cytoreduction surgery for recurrent epithelial ovarian cancer between October 2010 and December 2017 after approval from the research and development department. All cases of recurrent epithelial ovarian cancer are routinely discussed at the weekly gynaecological oncology multidisciplinary team meeting following clinical, radiological or biochemical detection of recurrence. After detection, all patients are screened for their full blood count, renal function and liver function. Computed tomography scan of chest, abdomen and pelvis or Positron emission tomography–computed tomography scans are performed where considered appropriate to identify suitability for secondary cytoreduction surgery. Cases were considered for surgery if they satisfied the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) score as described in the DESKTOP I trial (P. Harter et al., 2006) and agreed by local surgical team. After surgery – the intention was that all patients would receive adjuvant chemotherapy according to protocol and adjusted to individual patients.

Data collection: Data was collected with a pre-planned proforma from the patient's electronic and personal notes which included age; performance status; FIGO staging at initial diagnosis; histopathological diagnosis; disease free interval; peritoneal

carcinomatosis index (Jacquet P., 1996) at primary surgery; Aletti's surgical complexity score (Aletti, Dowdy, Podratz, & Cliby, 2007) at primary surgery; cytoreduction outcome of primary surgery; site/s of recurrence; procedures performed during secondary debulking surgery; outcome of the surgery; post-operative complications as per Clavien-Dindo classification (Dindo, Demartines, & Clavien, 2004); follow-up duration; date of second recurrence and date of death from all causes. Site/s of recurrence was classified as per intra-operative mapping of disease to define the level of recurrences and residuals (level 1 = pelvis, level 2 = mid abdomen, omentum, both flanks below transverse colon and small bowels and mesentery, and level 3 = upper abdomen above transverse colon (Braicu et al., 2012; Sehouli et al., 2003). The follow-up details were obtained from case notes and by contacting the general practitioners, where patients appeared to be lost at follow-up as on 31st December 2018.

Statistical analysis: All statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS) version-22. Kaplan-Meir, Log rank (Mantel-cox) method was used to determine progression free survival and overall survival. Platinum free interval was calculated from the date of completion of chemotherapy treatment and first relapse (Rustin et al., 2011). Progression free survival was calculated from the date of secondary cytoreduction surgery and date of diagnosis of second recurrence. Overall survival was calculated as the time (in months) from the date of secondary cytoreduction surgery and death from all causes or it was censored at date of last follow-up.

Results:

Between October 2010 and December 2017, 782 patients underwent surgery for ovarian cancer. Of these, 62 (7.9%) patients were identified as candidates for secondary cytoreduction surgery and 57 (7.2%) patients underwent secondary cytoreduction surgery for epithelial ovarian cancer. Among those, who did not have surgery, two patients were not considered suitable for surgery at subsequent team meeting due to disseminated disease on imaging. One patient had examination under anaesthesia and considered to be inoperable due to tumour adherence to sacrum. One patient declined surgery and other moved out of the area. The Median age of women undergoing secondary cytoreduction surgery was 58.5 years (Range 18 – 80 years). Forty eight (84%) patients were classified as Eastern Cooperative Oncology Group (ECOG) performance status 0 and 7 (12%) had performance status of 1. Mean serum albumin level for these patients was 43 g/L (Range 35 – 52 g/L).

Primary disease and treatment: At initial surgery for epithelial ovarian cancer, 20 (35%) patients had early stage disease (FIGO 1 – 2) and 37 (65%) had advanced stage disease (FIGO 3 – 4). Forty five (79%) patients received primary debulking surgery and 12 (21%) had neoadjuvant chemotherapy followed by debulking surgery. Most (90%) patients had a peritoneal carcinomatosis index (PCI) up to 6 and 42 (74%) had histological diagnosis of serous carcinoma, of whom 4 (7%) were low grade. Aletti's surgical complexity scores (Aletti et al., 2007) were low (0 - 3) for 45 (79%) patients, and the remaining 12 (21%) scoring 4 or more (range 4 - 9). Following the surgery 53 (93%) patients had complete cytoreduction (CC-0), 2 patients had residual disease < 1cm and 2 patients had residual disease > 1cm. Among the patients with residual disease > 2cm patients, one patient had received fertility sparing surgery for a mucinous carcinoma, but soon progressed at 3 months

post-surgery and was considered for secondary cytoreduction surgery. Another patient had residual disease in pelvis. The clinical characteristics and details of primary treatment are given in table 1. The diagnosis of recurrence was made clinically and with rising CA125 in 80% of patients. All patients had cross-sectional imaging to identify the site of recurrence. Most (n=44, 77%) had a disease free period of more than 12 months.

Secondary cytoreduction surgery: Of the 57 patients, who underwent secondary cytoreduction surgery, the sites of recurrences were: single site recurrence either at level 1, 2 or 3 (n=24, 42%) and multisite recurrences (n=33, 58%) (Sehouli et al., 2003). Overall, levels of recurrences were: level 1 (n=41, 72%), level 2 (n=39, 68%) and level 3 (n=15, 26%). Required surgical procedures were variable: 20 (35%) patients required gastrointestinal surgery. One patient underwent right hemicolectomy and recto-sigmoid resection. Nodal surgery to remove bulky lymph nodes from pelvis and para-aortic region were carried out for 24 (42%) of the patients and 2 (4%) patients required coeliac axis nodes resection. Pelvic or parietal peritonectomy were required for 11 (19%) patients and omentectomy was performed for 16 (28%) patients. Upper abdominal surgeries performed in 11 (19%) patients. Details of these procedures are given in table 2.

Complete cytoreduction was achieved in 51 (89%) patients, 1 patient had residual disease < 1cm in the upper abdomen and 5 (9%) patients had residual disease > 1cm: 3 had disseminated carcinomatosis, 1 had diaphragmatic disease and 1 had a central hepatic parenchymal lesion.

Post-operatively, 5 (9%) patients experienced Clavien-Dindo grade 3 or grade 4 morbidity. Among patients who developed grade 3 morbidity, one patient had

lymphorrhoea requiring radiological drainage and 2 patients returned to theatre (one for stoma site hematoma and another for drainage of pelvic collection). Among patients who had grade 4 morbidity, one patient had faecal peritonitis requiring return to theatre and critical care admission. A further patient needed critical care admission due to sepsis and compromised renal function. No prolonged morbidity or mortality was observed. Fifty five (96.5%) patients received adjuvant platinum based chemotherapy following surgery and 4 of these patients underwent further surgery for isolated recurrence. Two (3.5%) patients declined adjuvant chemotherapy.

Survival: As of 31st December 2018, with a median follow up duration of 30 months (Range 9 – 95 months), 32 (56%) patients were diagnosed with recurrence and 17 (30%) patients have died. Overall median progression free survival after secondary cytoreduction surgery was 32 months (95% confidence interval (CI) 17.5 – 46.5 months) and the median overall survival is yet to be reached (Figure 1). At univariate analysis the survival outcome among different comparative characteristics including age, FIGO stage at initial surgery, histopathology and platinum free interval were not statistically different (Table 3). It was observed that multisite recurrence relapsed earlier compared to single site recurrence (22 months, 95% CI 18.9 – 25 vs 38 months, 95% CI 27.9 – 48, p=0.04), however the overall survival were not statistically different.

Further analyses of required surgical procedures in secondary cytoreduction surgery were carried out to understand disease distribution and probably its biological behaviour. Patients who needed bowel resections had a lower progression free survival (22 months vs 32 months, p=0.311) and overall survival compared to the others (38 months, 95% CI 31.5 – 44.4 months vs median overall survival not

reached, p=0.009) (Figure 2). Retroperitoneal recurrences requiring nodal resections were associated with longer, though not statistically significant progression free survival (32 months vs 22 months, P=0.329) and overall survival (Median overall survival not yet reached vs 54 months, 95% CI 14 – 93.4 months).

Discussion:

Recurrent epithelial ovarian cancer is usually a terminal condition, but as shown in this study, with careful patient selection, surgery can possibly prolong survival. Of course, this is a single centre study, retrospective in nature with all the associated inherent biases. Such biases should be reduced with the full report on the Desktop III trial, but an interim analysis reported a median progression free survival of 19.6 months in surgical intervention arm, indicating surgery has a positive impact when used for selected patients with relapsed disease. A total of 54 patients had cytoreductive surgery for recurrent ovarian cancer in OCEANS trial and reported a progression free survival of 7.5 months in Pegylated Liposomal Doxorubicin arm and 16.7 months in Bevacizumab arm (Aghajanian et al., 2012). However, the proportion of these patients achieving complete cytoreduction is not reported. Our study showed a higher progression free survival of 32 months (95% CI 17.5 - 44.4 months). This likely reflects the non-randomised nature of our series but nevertheless indicates the importance of patient selection in achieving complete cytoreduction in a high proportion of these patients.

The strength of our study is that all cases of secondary cytoreduction surgery were included in a prospective database. An inevitable criticism is how the decisions regarding patient selection were arrived at during the multidisciplinary team meeting.

However, all attempts were made to select patients in accordance with DESKTOP I criteria.

A novel element in this study is the information relating outcomes to the recurrence patterns and types of surgical procedures performed. We have not found this within similar articles. An intraperitoneal recurrence involving the bowel probably reflects an inherent tumour biology differing from those with retroperitoneal relapse, or indeed some host factors. Similarly, a single site recurrence may have different tumour biology or host factors compared to multi-site recurrence. In this series, subgroup analysis of different variables that may affect survival showed statistical significance: a lower progression free survival for patients with multisite recurrence ($p=0.04$) and a lower overall survival for patients with bowel resections ($p=0.009$) (Table 3). These findings can be useful in aiding decision making and of course, counselling patients. We are unable to draw any conclusion due to smaller number of cases in our study; nevertheless, it may well be pointing towards a new area to be explored in a multicentre setting and convincing evidence may be valuable to patients and clinicians.

In an attempt to further improve the survival for this group of patients, use of heated intraperitoneal chemotherapy (HIPEC) is not well established yet. A systematic review (Hotouras et al., 2016) found 16 studies, most of them were single centre, case control, prospective or retrospective studies. These studies have previously explored the option of use of HIPEC in recurrent ovarian cancer surgery and due to wide variation in the practice; a mixed results have been reported regarding survival and morbidities associated to HIPEC. A randomised control trial with small number of cases (Spiliotis et al., 2015) demonstrated a survival advantage of 13.3 months ($p=0.006$). However, this advantage was again applicable to those patients who

achieved complete cytoreduction (CC-0). We still await a clear consensus regarding the use of HIPEC in relapse cases for advanced ovarian cancer. At our centre, HIPEC is not being utilized and our aim remains to provide complete cytoreduction with maximal surgical efforts.

This study adds to the literature on secondary cytoreduction surgery for relapsed epithelial ovarian cancer, and seems to support this approach for carefully selected patients. Of importance is the ability to achieve complete cytoreduction in as many patients as possible. The outcome of DESKTOP III will, of course, give the more definitive answer to this important question.

Competing interests: The authors (SK, AS, AP, RM, NM, JP, JN, AE, JB, SS, and KS) declare that they have no competing interests. STK reports other payments for lectures from Roche, other from Astra Zeneca, outside the submitted work.

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List of tables and figures:

Table 1: Clinical characteristics of patients and details of primary surgery

Clinical measures [n=57]	**Values - n [%]**
Median age in years	58.5 [18 – 80]
Less than 65 years	37 [65%]
More than 65 years	20 [35%]
ECOG Performance status	
0	48 [84%]
1	7 [12%]
2	2 [4%]
FIGO stage at initial diagnosis	
1	12 [21%]
2	8 [14%]
3	33 [58%]
4	4 [7%]
Primary diagnosis	
High grade serous carcinoma	38 [67%]
Low grade serous carcinoma	4 [7%]
Endometrioid carcinoma	3 [5%]
Mucinous carcinoma	2 [3.5%]
Clear cell carcinoma	8 [14%]
Carcinosarcoma	2 [3.5%]
Platinum free interval	
Up to 12 months	13 [23%]
More than 12 months	44 [77%]
Peritoneal carcinomatosis index at primary surgery	
Up to 6	51 [90%]
More than 6	6 [10%]
Aletti's surgical complexity score at primary surgery	
1 – 3	45 [79%]
4 – 7	10 [17.5%]
8 or more	2 [3.5%]
Outcome of primary debulking surgery	
No residual disease	53 [93%]
Residual disease less than 1 cm	2 [3.5%]
Residual disease more than 1 cm	2 [3.5%]

ECOG: Eastern Cooperative Oncology Group, FIGO: International Federation of Gynecology and Obstetrics

Table 2: Details of secondary cytoreduction surgery

Clinical measures	Values - n [%]
Level of involvement for recurrence (Sehouli et al., 2003). N =57	
Pelvis (Level 1)	41 [72%]
Mid abdomen (Level 2)	39 [68%]
Upper abdomen (Level 3)	15 [26%]
Multi-site recurrence	33 [58%]
Procedures	
Pelvic clearance	32 [56%]
Lymphadenectomy	24 [42%]
Bowel resections	20 [35%]
Peritonectomy	11 [19%]
Total omentectomy	16 [28%]
Upper abdominal surgery	11 [19%]
• Liver mobilisation / Glisson's capsule resection	3 [5%]
• Diaphragmatic stripping / resection	5 [9%]
• Splenectomy	4 [7%]
• Coeliac axis node / lesser sac nodule excision	2 [4%]
Outcome	
No residual disease (R0)	51 [89%]
Residual disease less than 1 cm (R1)	1 [2%]
Residual disease more than 1 cm (R2)	5 [9%]
Site of residual after SCS	
Upper abdomen only (Level 3)	3 [5.5%]
Peritoneal carcinomatosis (open/close)	3 [5.5%]
Post-operative complications	
Clavien Dindo Grade 3	3 [5.5%]
Clavien Dindo Grade 4	2 [4%]

SCS: Secondary cytoreduction surgery

Table 3: Surgical specifics and survival outcomes

Disease / surgical specifics	Number of patients	Median Progression free survival, months (95% Confidence interval), p-value	Median overall survival, months (95% Confidence interval), p-value
Age at SCS			
Less than 65 years	37	35 (18.1 – 51.8)	81 (41.9 – 120)
65 or more	20	22 (8.6 – 35.3)	Not reached
		p=0.190	p=0.540
FIGO stage at primary disease			
Stage 1 – 2	20	37 (12.8 – 61.1)	Not reached
Stage 3 – 4	37	32 (21.1 – 42.8)	81 (34.7 – 127)
		p=0.751	p=0.673
Histopathology			
High grade serous	38	32 (21.1 – 42.8)	Not reached
Low grade serous and Non-serous	19	35 (17.3 – 52.7)	59 (11.7 – 106.2)
		p=0.789	p=0.251
Platinum free interval			
Less than 12 months	15	37 (12.2 – 61.8)	Not reached
More than 12 months	42	32 (18.7 – 45.3)	81 (44.4 – 117.6)
		p=0.777	p=0.376
Level of involvement at recurrence			
Single site recurrence	24	38 (27.9 – 48)	Not reached
Multisite recurrence	33	22 (18.9 – 25)	81 (44.9 – 117)
		p=0.04	p=0.830
Bowel resections at surgery			
No	37	32 (19.4 – 44.6)	Not reached
Yes	20	22 (0.00 – 48.3)	38 (31.5 – 44.4)
		p=0.311	**p=0.009**
Nodal resections at surgery			
No	33	22 (15.7 – 28.2)	54 (14 – 93.4)
Yes	24	32 (20.3 – 43.6)	Not reached
		p=0.329	p=0.161
Outcome			
Overall cohort survival	57	32 (95% CI: 17.5 – 46.5)	Not reached
No macroscopic residual	51	35 (95% CI: 20.1 – 49.8)	Not reached

Figure 1: Survival outcomes of patients having secondary cytoreduction surgery

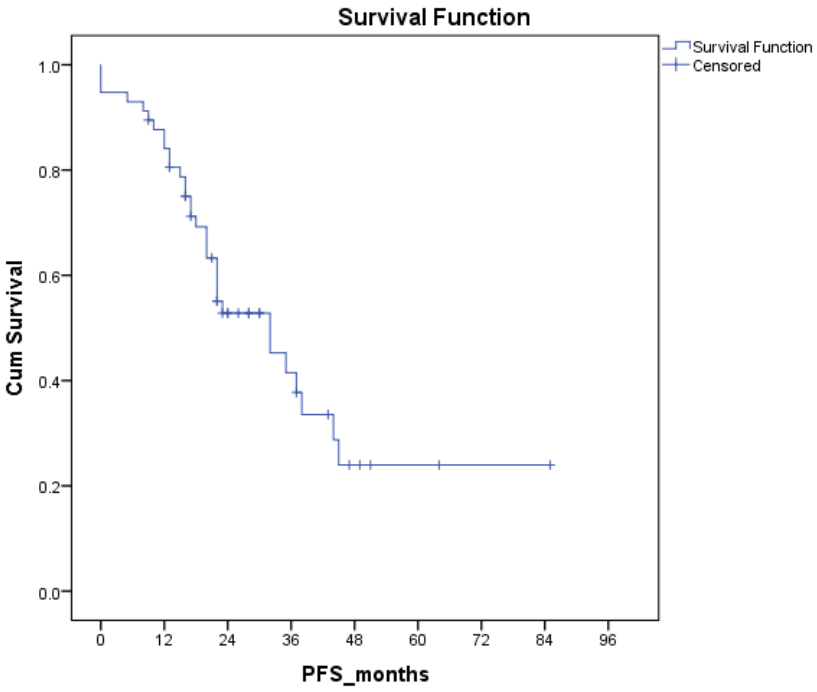

Figure 1A: Progression free survival in all patients with secondary cytoreduction surgery

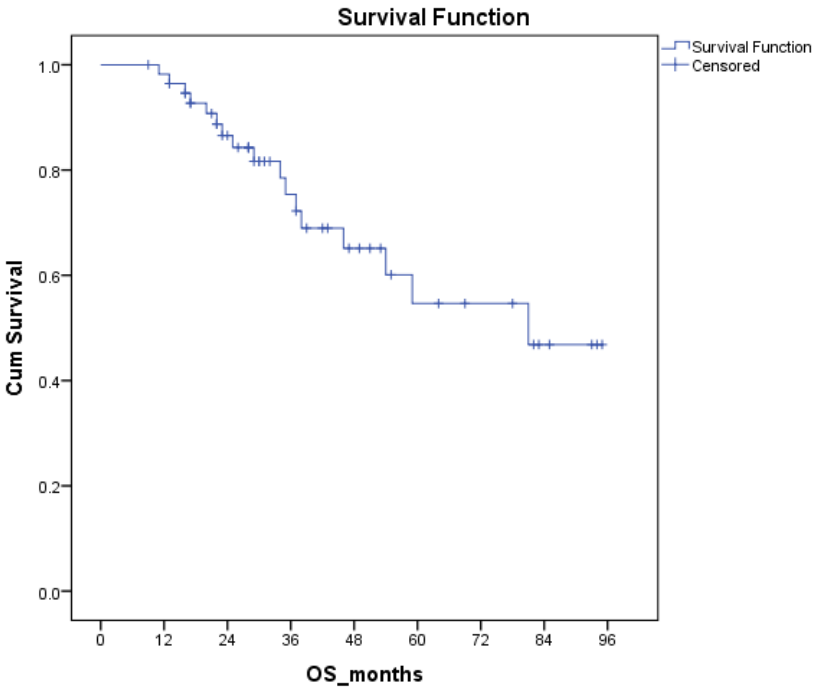

Figure 1B: Overall survival of patients having secondary cytoreduction surgery

Figure 2: Survival outcomes of patients requiring bowel resection during secondary cytoreduction surgery

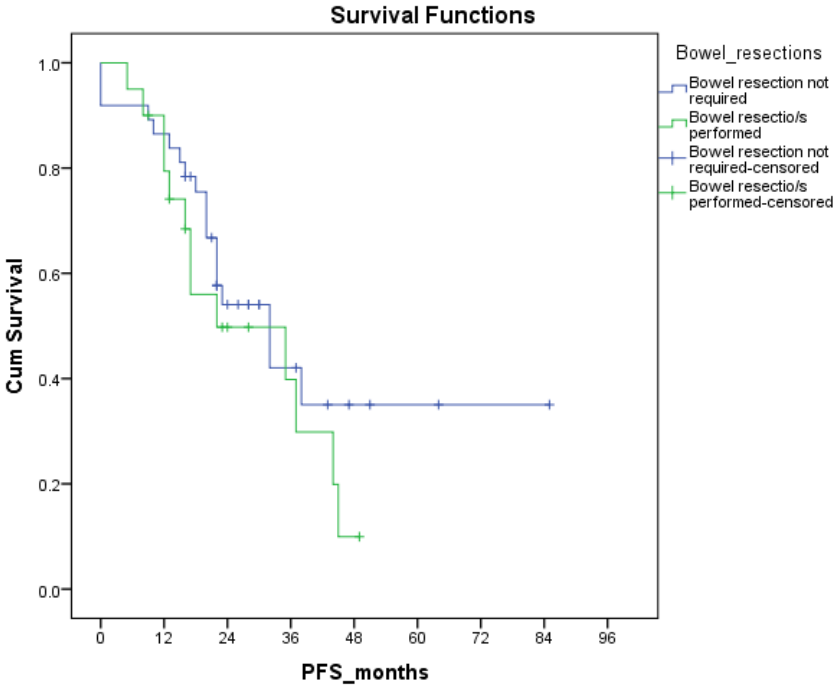

Figure 2a: Median progression free survival of patients requiring bowel resection during secondary cytoreduction surgery

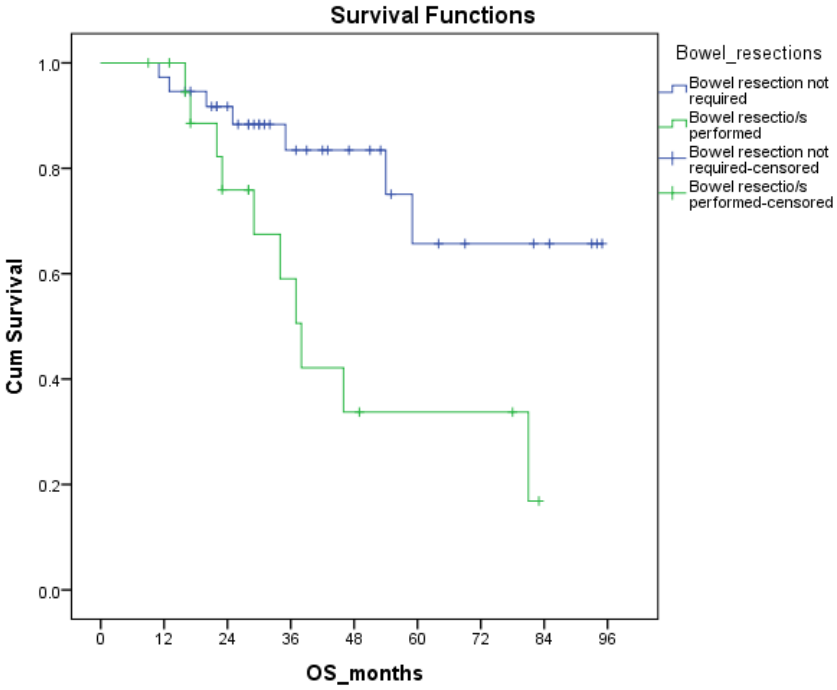

Figure 2b: Median overall survival of patients requiring bowel resection during secondary cytoreduction surgery