



Evaluation of Computed Tomography Scan and CA 125 Response in Predicting Operability in Advanced Ovarian Cancer and Assessing Survival Outcome in Interval Cytoreductive Surgery

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Abstract

The study aims at the prediction of optimal cytoreduction (OCR) in patients undergoing interval cytoreduction (ICR) in advanced epithelial ovarian cancer (AEOC) based on CT imaging and CA 125 values and assessing the survival pattern of these patients after ICR. This is a prospective observational study of patients with stage III C ovarian cancer who underwent ICR in our institution after neoadjuvant chemotherapy (NACT). All consecutive patients operated from April 2016 to October 2017 were included in the study. From their medical records, their demographic details and clinical variables were recorded. The CA 125 value and CT scan findings before and after chemotherapy were documented. A Bristow's predictive score (BS) was calculated based on the radiological parameters. After ICR, the outcome of the surgery was documented. Optimal cytoreduction (OCR) was defined as no gross residual disease after surgery. The surgical outcome was correlated with the CA 125 difference pre and post chemotherapy and Bristow's predictive score pre and post chemotherapy. The patients were followed up and their survival at 6 and 12 months was assessed. Univariate and multivariate analysis was done to identify factors predicting OCR. 51 patients were included in the study. Age group of the women ranged from 31 to 74 years with a mean of 52 years. Majority of the patients (70.6%) were postmenopausal. Of the 51 women, OCR could be achieved in 31 patients (60.8%). Post-chemotherapy, 36 patients had elevated CA125 above baseline of which 50% attained OCR. Forty six patients had CA 125 response post chemotherapy of which 67.4% attained OCR. Forty five patients had reduction in Bristow Score compared to the pre chemo values of which 64.4% attained OCR which was not found to be statistically significant. Overall survival was 100% survival at 6 months and 92.8% at 12 months in those who achieved OCR. Those with residual disease 0.1–1 cm had survival of 74.1% at 6 and 12 months. Those with residual disease > 1 cm had a survival of 50% at 6 and 12 months. CA125 response has a significant role in predicting OCR while CT evaluation using the BS was not useful in predicting OCR during ICR for AEOC.

Keywords Ovarian cancer · CA 125 antigen, CT scan · Cytoreduction surgical procedure · Survival analysis

Introduction

Ovarian cancer is the leading cause of death from gynaecological malignancy in women. 70–75% present in advanced stage at diagnosis. Complete surgical cytoreduction of tumour bulk to no residual disease and platinum-based chemotherapy are the mainstay of treatment. Several studies have shown that the maximum dimension of residual tumours remaining after the completion of cytoreductive surgery is an important prognostic indicator of survival [1]. Several multicentre randomised studies have investigated the role of NACT and NACT followed by ICR is an accepted treatment modality in AEOC [2, 3] Although the survival benefit of optimal surgery has been well established, patients who

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undergo suboptimal cytoreduction are exposed to significant surgical morbidity without receiving the survival benefit of surgery, so it would appear prudent to identify these patients preoperatively to offer them an alternate approach to the current standard of care.

There is no consensus as to which is the best pre-op method to assess operability. The role of CA 125 has also been extensively studied, and a pretreatment cut off of 500 U/L has been suggested by several investigators in predicting operability. Computed tomography (CT) scans are being extensively used in assessing disease response in ovarian cancer after NACT. Investigators have attempted to identify preoperative CT findings that would predict suboptimal debulking, but the predictive value of these individual parameters is controversial. Hence, various models have been devised using the CT variables, of which the most accepted one is BS [4]. The predictive index model developed by Bristow et al. demonstrated high accuracy in predicting inoperability in patients undergoing primary cytoreductive surgery in AEOC.

BS is a predictive score based on 13 radiological criteria and the performance status of the patient including performance status ≥ 2 ; peritoneal thickening, peritoneal implants ≥ 2 cm; small-bowel mesentery disease ≥ 2 cm; large-bowel mesentery disease ≥ 2 cm; omentum extension to the stomach, spleen or lesser sac, extension to the pelvic sidewall/parametria or hydroureter, ascites-large volume (which is seen on all cuts), suprarenal paraaortic lymph node ≥ 1 cm; infrarenal paraaortic lymph node ≥ 2 cm; inguinal canal disease or lymph nodes ≥ 2 cm; portahepatitis or gallbladder fossa disease ≥ 1 cm; liver lesion ≥ 2 cm on the surface or

Table 1 Patient characteristics

Total no. of patients	51
Age	
Mean	52
Range	31–74
Parity	
Nulliparous	6
Para 1–2	28
\geq Para 3	17
Menopausal status	
Premenopausal	15
Postmenopausal	36
Age at menopause	
< 45	7
45–52	42
≥ 53	2
Histology	
High-grade serous carcinoma	48
Low-grade serous carcinoma	2
Mucinous carcinoma	1

Table 2 Pre- and post-chemo difference in CA 125 and Bristow’s score

Pre-chemo CA 125	
≥ 500 U/L	42
< 500 U/L	9
Post-chemo CA 125	
< 35 U/L	15
≥ 35 U/L	36
Percentage reduction in CA125	
$\geq 50\%$	46
$< 50\%$	5
Pre-chemo BS	
< 4	17
≥ 4	34
Pst-chemo BS	
< 4	47
≥ 4	4
Percentage reduction in BS	
$< 40\%$	6
$\geq 40\%$	45
OCR achieved	
Yes	31
No	20

parenchymal lesion any size; and diaphragm or lung base disease ≥ 2 cm or confluent plaque. BS ≥ 4 had 100% sensitivity in predicting suboptimal cytoreduction with an accuracy of 92.7%. Bristow’s model was done and validated in primary cytoreduction and its performance in post-NACT patients have been not yet validated.

Table 3 Pre- and post-chemo CA 125 and BS significance in predicting operability

	OCR not achieved		OCR achieved		Total	P value
	No.	%	No.	%		
Pre-chemo CA 125						
< 500 U/L	3	33.3	6	66.7	9	0.7
≥ 500 U/L	17	40.5	25	59.5	42	
Post-chemo CA 125						
< 35 U/L	2	13.3	13	86.7	15	0.026
≥ 35 U/L	18	50	18	50	36	
Percentage reduction in CA 125						
$\geq 50\%$	15	32.6	31	67.4	46	0.007
$< 50\%$	5	100	0	0	5	
Absolute value of BS pre-chemo						
< 4	9	52.9	8	47.1	17	0.156
≥ 4	11	32.4	23	67.6	34	
Absolute value of BS post-chemo						
< 4	17	36.2	30	63.8	47	0.287
≥ 4	3	75	1	25	4	

It indicates significant *p* value.

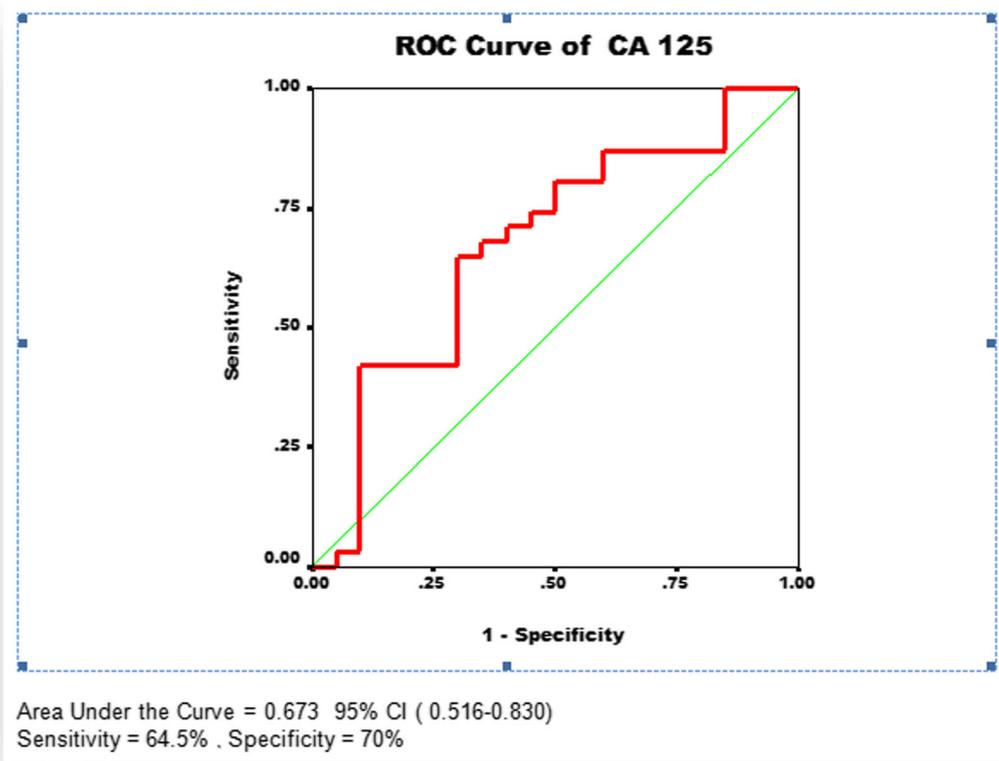


Fig. 1 ROC curve showing sensitivity and specificity of CA125 in predicting operability

Materials and Methods

The study was conducted after the IRB approval. It was undertaken to assess whether CT scan scoring using BS and CA125 response to NACT has a role in predicting operability in patients undergoing ICR. This is a prospective observational study done in our institute over a period of 1 year. All consecutive patients undergoing ICR after 3 cycles of NACT were included. Patients were less than 75 years, had Eastern cooperative oncology group (ECOG) performance status 0/1, proven AEOC. Exclusion criteria included previous suboptimal surgeries, borderline ovarian tumour and those patients not willing for extensive surgeries. The study was done with IRB approval.

We recruited patients with CT scan suggestive of stage III C disease and histologically proven AEOC who were planned for NACT as per the institutional protocol and ICR after completion of chemotherapy. Chemotherapy given was 3 cycles of carboplatin and paclitaxel every 3 weekly. Paclitaxel is given in a dose of 175 mg/m² over 3 h and carboplatin is given AUC 5 over 1 h. The CA 125 value pre-chemo was documented. Pre-chemo BS was calculated based on the 13 radiological features. A post-chemo CA 125 and CT scan was done 2 weeks following the third chemotherapy. CT scans were performed on a 16-slice MDCT (GE Medical system) after administration of oral and iv contrast(1.5 ml/kg). Ten-millimetre axial sections were acquired and reconstructed at

1.25 mm. Multiplanar reformatting was also done as per need. All images were viewed on PACS work station. The Bristow's score calculation was done by our radiologist expert in the field of oncology. These women then underwent ICR, 3 weeks after the third cycle of chemotherapy. The definition of OCR was defined as no gross residual disease [5]. The surgeries were performed by the same gynec oncology team of the institution. The surgery was by a midline vertical incision under combined epidural and general anaesthesia. Standard surgical procedure included hysterectomy, bilateral salpingo-oophorectomy, total omentectomy, excision of peritoneal and subdiaphragmatic tumour deposits with bowel resection if needed. The amount of residual disease was documented as no gross residual disease (OCR), < 1 cm, ≥ 1 cm. Post-chemo absolute value of CA125, the percentage reduction in CA 125 and the percentage reduction in BS was also calculated and correlated with the surgical outcome.

Statistical Analysis

Continuous variables were expressed as mean and standard deviation and categorical variables as counts and percentage. The chi-square test or Fisher's exact test was used for comparison of categorical variables between the same groups. Logistic regression was used to estimate the odds ratios (OR) and 95% CI to measure the association between pre-chemo and post-chemo CA 125 and Bristow's score. Values

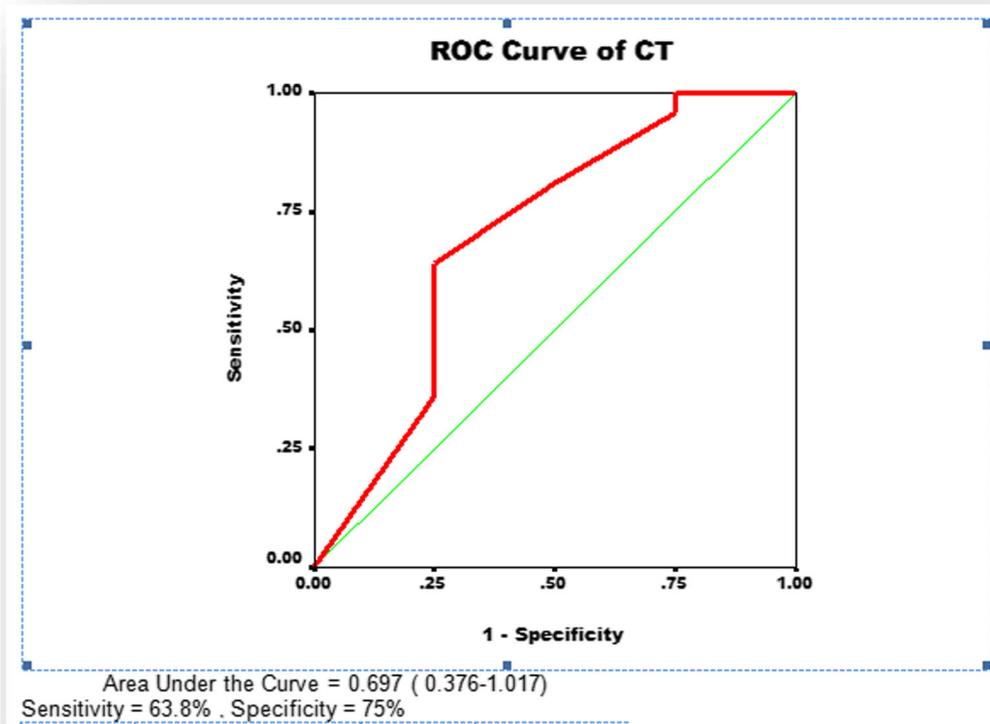


Fig. 2 ROC curve showing sensitivity and specificity of CT scan in predicting operability

of individual parameters of BS in predicting operability was also evaluated. Missing values of the variables with incomplete data were excluded from the analysis. Statistical software SPSS 11.5 for Windows (SPSS Inc., Chicago, IL, USA) was used for conducting the statistical analysis and all statistical tests were performed at the two-tailed significance level of 0.05.

Results

In the study period from April 2016 to October 2017, we studied 51 patients fulfilling the above criteria. The patient details are shown in Table 1. Age group of the women ranged from 31 to 74 years with a mean of 52. 70.6% were postmenopausal, 11.7% were nulliparous, 31.4% were para 1, 23.4% were para 2, 21.6% were para 3 and 11.7% were para 4 or above. 13.7% attained menopause before 44 years, 82.4% attained menopause between ages of 45–52 years and 3.9% attained menopause after 52 years. 94.2% were high-grade serous carcinoma, 3.9% were low-grade serous carcinoma and 1.9% was of mucinous carcinoma.

Of the 51 patients, OCR was attained in 31 patients (60.8%). The pre- and post-chemo CA 125 values and

Bristow's score are given in Table 2. Pre-chemo, 9 patients had a CA 125 < 500 U/L, of which 66.7% achieved OCR and 33.3% did not achieve OCR. 42 patients had CA 125 > 500 U/L, of which 59.5% achieved OCR and 40.5% did not achieve OCR (p value 0.7). On logistic regression analysis, pre-chemo CA 125 of > 500 U/L had a RR of 1.36 (95% CI 0.30–6.20). Post-chemo, 15 patients had CA 125 < 35 U/L, of which 86.7% achieved OCR and 13.3% did not achieve OCR. Thirty-six patients had a CA 125 of > 35 U/L, of which 50% achieved OCR and 50% did not achieve OCR. On logistic regression analysis, post-chemo CA 125 of > 35 U/L had a RR of 6.49 (95% CI 1.28–32.99). Forty-six patients had > 50% reduction in CA 125 post-chemotherapy, of which 67.4% achieved OCR and 32.6% did not achieve OCR. 5 patients had < 50% reduction in CA 125, of which 100% did not achieve OCR (Table 3). The ROC curves for CA 125 showed a sensitivity of 64.5% and specificity of 70% in predicting operability (Fig. 1).

Pre-chemo, 34 patients had BS ≥ 4 , of which 67.6% achieved OCR and 32.4% did not achieve OCR. Seventeen patients had BS < 4, of which 47.1% achieved OCR and 52.9% did not achieve OCR (p value 0.156). Post-chemo, 47 patients had a BS < 4, of which 63.8% achieved OCR and 36.2% did not. Four patients had BS > 4 of which only

Table 4 Significance of individual BS parameters post-chemotherapy

	OCR not achieved(n)	OCR achieved(n)	Total(n)	P value
Peritoneal thickening absent	1	25	26	0.35
Peritoneal thickening present	3	22	25	
Peritoneal implants ≥ 2 cm absent	2	40	42	0.139
Peritoneal implants ≥ 2 cm present	2	7	9	
Ascitis on all cuts absent	3	44	47	0.286
Ascitis on all cuts present	1	3	4	
Small bowel mesentery disease ≥ 2 cm absent	4	45	49	1
Small bowel mesentery disease ≥ 2 cm present	0	2	2	
Large bowel mesentery disease ≥ 2 cm absent	3	45	48	0.221
Large bowel mesentery disease ≥ 2 cm present	1	2	3	
Omental extension to stomach, spleen or lesser sac absent	3	41	44	0.457
Omental extension to stomach, spleen or lesser sac present	1	6	7	
Extension to pelvic side wall, hydroureter, inguinal canal absent	2	45	47	0.027
Extension to pelvic side wall, hydroureter, inguinal canal present	2	2	4	
Suprarenal para aortic lymph node ≥ 1 cm absent	3	46	49	0.152
Suprarenal para aortic lymph node ≥ 1 cm present	1	1	2	
Infrarenal para aortic lymph node ≥ 2 cm absent	3	47	50	0.078
Infrarenal para aortic lymph node ≥ 2 cm present	1	0	1	
Liver lesion absent	3	40	43	0.506
Liver lesion present	1	7	8	
Portahepatis/gall bladder fossa disease ≥ 1 cm absent	3	44	47	0.286
Portahepatis/gall bladder fossa disease ≥ 1 cm present	1	3	4	
Inguinal canal disease ≥ 2 cm or Inguinal Lymph Node absent	4	45	49	1
Inguinal canal disease ≥ 2 cm or Inguinal Lymph Node present	0	2	2	
Diaphragm or lung base disease absent	3	45	48	0.221
Diaphragm or lung base disease present	1	2	3	

It indicates significant *p* value.

25% achieved OCR; 75% did not achieve OCR (*p* value 0.287). On logistic regression analysis, BS of > 4 had a RR of 5.29.(95% CI 0.51–54.96) (Table 3). To find the significant difference between pre- and post-chemo BS, chi-square test was used but it did not show any statistical significance.

Post-chemo, 45 patients had a $> 40\%$ reduction in BS, of which 64.4% achieved OCR and 6 patients had $< 40\%$ reduction in BS of which 33.3% achieved OCR (*p* value 0.145) which was not statistically significant. The ROC curves for CT scan showed a sensitivity of 63.8% and a specificity of 75% in predicting operability. (Fig. 2).

On multivariate analysis, post-chemo CA 125 value and $> 50\%$ reduction in CA 125 were significant in predicting operability. Post-chemotherapy, of all the individual parameters of BS, only one parameter that is disease extension to the pelvic side wall and hydroureter had individual statistical significance in predicting operability during ICR. Post-chemo, it was present in 4 patients, of which only 50% achieved OCR (*p* value 0.027) (Table 4).

The survival data in our study was last updated on June 2018 which was 6 months after the last patient completed her treatment. Using the Kaplan-Meier survival curves, we found that those who achieved OCR had 100% survival at

6 months and 92.8% at 12 months. Those with residual disease 0.1–1 cm had survival of 74.1% at 6 and 12 months. Those with residual disease > 1 cm had a survival of 50% at 6 and 12 months (Fig. 3).

At 6 months, the OS was 100% and the DFS was 94.1%. The OS and DFS at 1 year was 89.8% and 65.2% respectively, whereas the OS and DFS at 2 years were 70.2% and 16.4% respectively. (Figs. 4 and 5).

Of the 51 patients, 12 had died due to disease recurrence, intestinal obstruction in 10 patients and brain metastases in 2 patients.

Discussion

Ovarian cancer is the leading cause of cancer-related mortality in women. Most of the women will be asymptomatic at presentation or will be having nonspecific symptoms. Majority present with advanced cancer and are managed by chemotherapy and cytoreductive surgery.

The concept of ovarian tumour debulking was initially put by Dr. Joe Meigs in 1934. But it was only after a few decades that its importance in ovarian cancer treatment was established

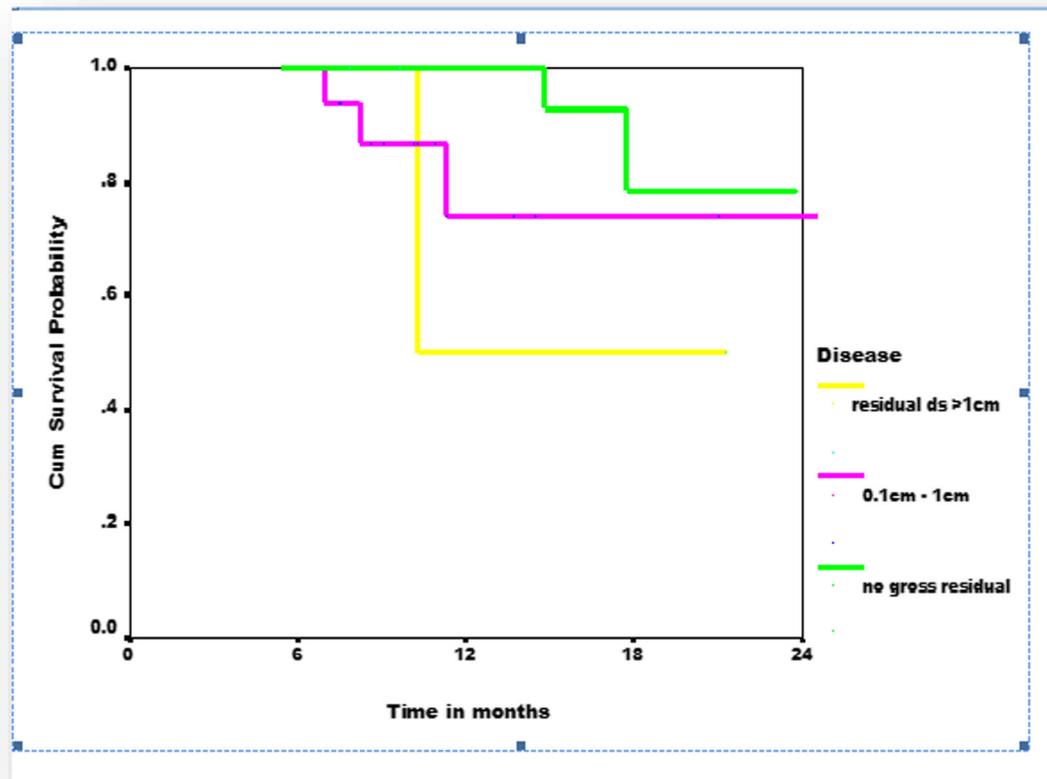


Fig. 3 Survival at 6 months and 1 year

by Dr. C Thomas Griffiths in the 1970s. The amount of residual disease is the most important factor affecting the survival and the recurrence probability. The success of the surgery depends on proper patient selection, extent of disease and surgeon expertise. The definition of the optimal cytoreduction has changed over several years, and now, it is defined as “No gross residual disease”. Extensive upper abdominal disease is an indicator of aggressive disease, but that does not rule out operability. For tertiary centres with expertise for radical procedures like splenectomy, diaphragmatic resection will have a higher OCR rate and increased chance of survival.

An idea regarding the disease load can be obtained by imaging and by serum tumour markers. CA 125 is the most widely studied ovarian tumour marker. It was identified by Bast, Knapp and colleagues in 1981. It is considered as the gold standard. CA 125 is raised in approximately 90% of women with advanced ovarian cancers and in as many as 50% of early ovarian cancers. It has a diagnostic and prognostic role, as well as it is used to detect recurrences. There are various studies which showed that women with high levels of CA 125 have a decreased possibility of operability. Studies have been conducted to define a cutoff level of CA 125, above which the chances of OCR reduces. In a study Chi et al., CA 125 had a sensitivity of 78% and a specificity of 73% in

assessing the operability [6]. Some authors believe that CA125 is just a predictor of high tumour volume and not of low resectability [7, 8]. In our study, CA 125 had a significant role in predicting operability. The post-chemo CA 125 value (< 35U/L) as well as the percentage reduction in CA 125 (> 50% reduction) post-chemotherapy was found to be statistically significant in predicting operability with a sensitivity of 64.5% and specificity of 70%. The sensitivity of CA 125 in our study was lesser as compared to the other studies, because even though 46/51 patients achieved $\geq 50\%$ reduction in CA 125, only 31 (67.4%) of them could achieve OCR.

CT scans are routinely done in the evaluation of AEOC to find out the extent of disease and to plan surgical management. One of the fallacy of CT scan is its inability to detect disease < 1 cm in size [9, 10]. In a study by Aliya Qayyum et al., in the role of CT scan and MRI in predicting suboptimal cytoreduction, CT scan had a sensitivity of 79% and specificity of 99%. MRI was also found to be equally effective with a sensitivity of 71% and specificity of 100% [11]. This study was however limited in that it was a retrospective study and included patients with all stages of disease, which could have been the reason for the higher sensitivity and specificity. Over the years, several studies have been done to assess the utility of CT scan in prediction of operability; significant of these

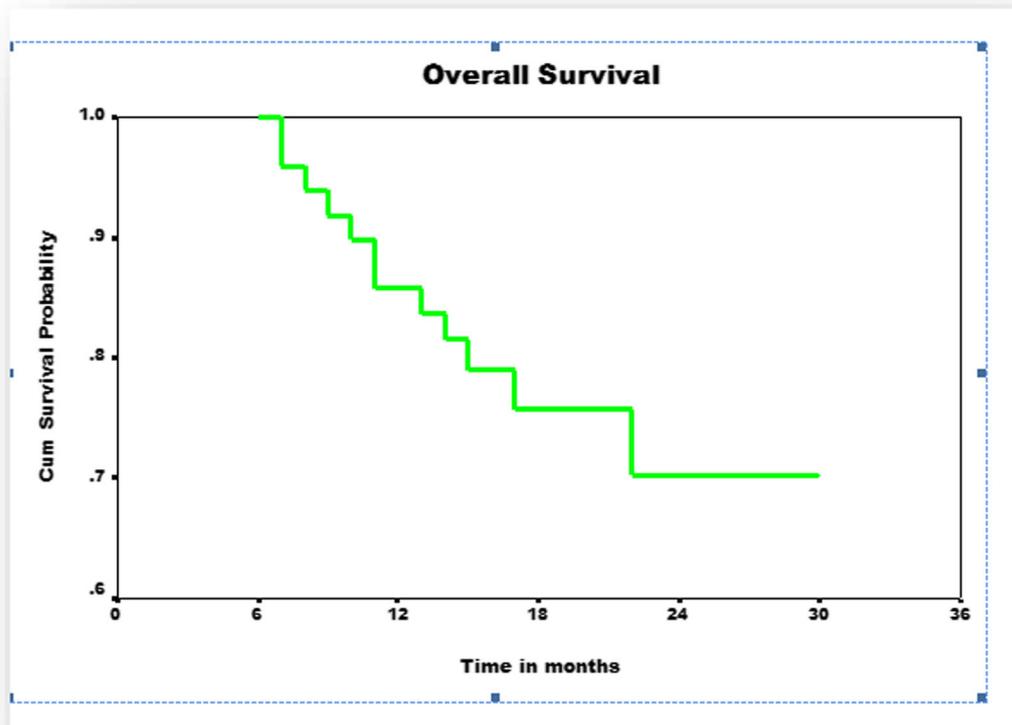


Fig. 4 Overall survival at 1 and 2 years

include the Nelson's CT score and Bristow's predictive score [12–14]. Studies by Bristow et al. showed a sensitivity of 100%, Nelson et al. showed a sensitivity of 92% and PPV of 67% in predicting operability. The sensitivity of CT scan in predicting operability in our study is 63.8% which is low as compared to other studies. This was because, in spite of 47/51 patients having a good response to chemotherapy with a post-chemo BS < 4, only 63.8% could achieve OCR. This was because of the subcentimetric diseases which were missed out during a CT scan. The results were similar to another study by FV Coakley et al. where the overall sensitivity of CT scan in detecting disease was 85–93%, whereas its sensitivity in detecting peritoneal disease < 1 cm was 25–50% [10]. More large-scale studies should be carried out to assess the role of CT scan in predicting cytoreduction.

As the original study by Bristow et al. in 2000 was done by taking the definition of OCR as < 1 cm, we implemented the same in our study to find out if there was any statistical significance. Pre-chemo, of the 34 patients with BS \geq 4, 94.1% ($n = 32$) achieved OCR and 5.9% ($n = 2$) did not achieve OCR. Post-chemo, of the 47 patients with BS < 4, 95.7% ($n = 45$) achieved OCR; 4.3% ($n = 2$) did not attain OCR. Percentage reduction in BS was calculated to look for its statistical significance in predicting operability. Here, 40% reduction in BS post-chemo had a significant role in predicting

residual disease to < 1 cm. Forty-five patients had a BS reduction of \geq 40%, of which 95.6% ($n = 43$) achieved OCR. A cutoff of 40% reduction in our study showed that it could predict OCR with a sensitivity of 89.8% and specificity of 93%.

Studies have proven beyond doubt that the amount of residual disease is the most important factor affecting survival. Metanalysis by Bristow et al. showed that those with \leq 25% maximal cytoreduction had a mean weighted median survival time of 22.7 months and those with > 75% maximal cytoreduction had a mean weighted survival time of 33.9 months, an increase of 50% [15]. Another retrospective study by Suk Joon Chang and Bristow et al. showed that those with no gross residual disease after cytoreductive surgery had the longest survival [16]. They showed that those with no gross residual disease had an OS of 86 months, with residual disease 0.1 cm to 1 cm, the OS was 46 months and those with residual disease > 1 cm had the least survival of 37 months. In our study, those who achieved OCR had 100% survival at 6 months and 92.8% at 1 year. When the residual disease was 0.1 cm–1 cm, the survival was 74% at 6 months and 12 months. When the residual disease was > 1 cm, the survival at 6 and 12 months was 50%. Seventy-five to 80% of advanced ovarian malignancies will ultimately recur. As many as 20% may develop recurrence within the first 6 months

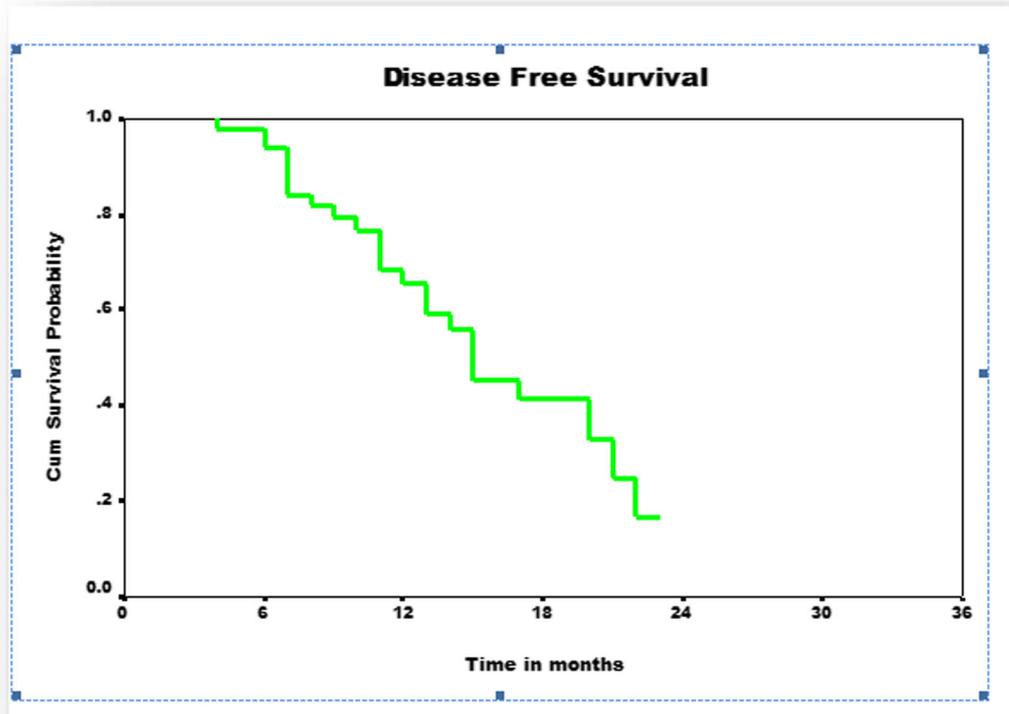


Fig. 5 Disease-free survival at 1 and 2 years

following treatment. At 6 months, the OS in our study was 100% with a DFS of 94.1%. But with time, there was a decline in the survival with the OS and DFS at 1 year of 89.8% and 65.2%, respectively, whereas at 2 years, it was 70.2% and 16.4% respectively. It was similar to a study by Lauren A Baldwin et al. where the overall relative survival in AEOC at 2 years was 65% [17].

Strengths of our study include that it is a prospective design study, homogenous sample, BS was calculated by a single expert radiologist hence reducing the bias, surgery done by the same gynec oncology team. Drawbacks of our study include a small sample size ($n = 51$) and strict inclusion criteria, as we studied only stage III C disease and those who took 3 cycles of chemotherapy pre-surgery. Although we considered no residual disease for OCR, there may be a potential survival benefit in patients left with < 1-cm residual disease.

Conclusion

CA 125 has a significant role in predicting operability in patients undergoing ICR with a post-chemo value of < 35 U/L and > 50% reduction. CT scan using the Bristow's predictive

score was not found to have a significant role in predicting optimal cytoreduction.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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