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Original Article

Prognostic Significance of Chemotherapy Response Score in Patients Undergoing Interval Debulking Surgery and Attained Complete Cytoreduction for High-Grade Serous Tubal and Ovarian Carcinoma

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Abstract

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Objectives The chemotherapy response score (CRS) has been described to assess the pathological response to chemotherapy in patients with high-grade serous tubal and ovarian carcinoma. The main aim of this study was to assess the prognostic significance of CRS in patients who underwent interval debulking surgery and attained complete cytoreduction.

Materials and Methods A retrospective study was conducted on patients with Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage IIIC and IV high-grade serous tubal and ovarian carcinomas who had undergone surgery after three to four cycles of neoadjuvant chemotherapy and attained complete cytoreduction from January 2015 to July 2018.

Results A total of 125 patients were included in the study. The median age of the patients was 52 years. There were 21 patients (16.8%) with a CRS of 1, 53 patients (42.4%) with a CRS of 2, and 51 (40.8%) patients with a CRS of 3. The median follow-up period was 77 months. The CRS applied on the omental samples showed significant correlation with progression-free survival (PFS; CRS of 1 vs. 2: median PFS, 17 vs. 22 months; hazard ratio, 1.73; and CRS of 2 vs. 3: median PFS, 22 vs. 54 months; hazard ratio, 2.32) and overall survival (OS; CRS of 1 vs. 2: median OS, 19 vs. 40 months; hazard ratio, 2.13; CRS of 2 vs. 3: median OS, 40 months vs. not reached; hazard ratio, 2.19).

Conclusion Our study confirms that the omental CRS is significantly associated with PFS and OS in patients who attained complete cytoreduction during interval debulking surgery.

Keywords

- chemotherapy response score
- high-grade serous carcinoma
- interval debulking surgery
- neoadjuvant chemotherapy
- progression-free survival

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Introduction

Ovarian carcinoma is the most lethal gynecologic malignancy and is ranked the fifth most common cause of cancer death among females.[1] Tubo-ovarian high-grade serous carcinoma (HGSC) is the most common type, accounting for 70% of all ovarian cancers. Around 80% of these patients present with advanced disease (stages III and IV). Despite various advances in the management of ovarian cancer, HGSC remains a highly lethal malignancy with a 5-year survival of less than 30% in advanced stages. It is proposed that the tissue removed at the time of surgery after chemotherapy can be used for assessing the response to antineoplastic agents and to predict prognosis. Validated scoring systems provide prognostic information in patients with breast, esophageal, gastric, and rectal cancers following neoadjuvant treatment and are used to guide treatment after surgery.[2–4] Böhm et al[5,6] reported a simple and reproducible histopathological grading system for assessing neoadjuvant chemotherapy (NACT) response in tubo-ovarian HGSC called chemotherapy response score (CRS). It consists of a three-tier score based on omental assessment of residual disease and mainly focuses on fibroinflammatory changes, pattern of invasion, and size of the largest focus of residual tumor. They showed that the CRS predicts progression-free survival (PFS) and overall survival (OS). The International Collaboration on Cancer Reporting (ICCR) and the College of American Pathologists (CAP) have recommended the three-tier CRS system for assessing cases of advanced tubo-ovarian HGSC after NACT.[7] Currently this scoring system is yet to be adopted in routine clinical practice.

While further studies on omental CRS showed that it is reproducible and correlates with PFS, studies on OS have shown mixed results. Furthermore, various studies in the literature have included a heterogeneous group of patients with regard to the number of chemotherapy cycles,[7–9] completeness of cytoreduction,[5,10–12] chemotherapy agents,[7,9] and histology.[10,12] It has been shown that residual disease after interval debulking surgery (IDS) is the most powerful prognostic factor for PFS.[13] Therefore, to reduce the bias due to extent of cytoreduction, we have included only patients who achieved complete cytoreduction during IDS. The aim of the present study was to assess the prognostic significance of omental CRS with regard to both PFS and OS among a homogenous group of patients who had received three to four cycles of NACT with carboplatin and paclitaxel, followed by IDS and attained complete cytoreduction for the treatment of advanced tubo-ovarian HGSC.

Materials and Methods

This was a retrospective analysis of patients with stage IIIC and IV tubo-ovarian HGSC, who received three to four cycles of platinum-based NACT with carboplatin and paclitaxel followed by IDS and attained complete cytoreduction from January 2015 to July 2018. In order to avoid any bias, we have included all consecutive patients who fitted the above criteria during the study period. This study was performed with the approval of the Institutional Review Board (IRB No: 11/2019/05) and followed the principles of the Declaration of Helsinki. Demographic data, cancer antigen 125 (CA 125) levels, imaging, biopsy report, Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage, details of chemotherapy, surgical procedure, follow-up, and details of relapse were collected from the medical records.

NACT was given to patients with (1) medically inoperable disease, (2) preoperative imaging showing disease not amenable to complete cytoreduction (e.g., root of mesentery involvement, extra-abdominal metastasis), and (3) parenchymal liver metastasis. NACT was initiated after confirming the diagnosis by guided biopsy and immunohistochemistry. The surgery consisted of hysterectomy, bilateral salpingo-oophorectomy, and omentectomy with or without various radical surgeries (e.g., bowel resection and peritonectomy). After surgery, patients received two to three cycles of post-operative adjuvant chemotherapy to complete six cycles of chemotherapy. Follow-up data were collected till March 2024. Follow-up data were collected from the medical records. Data were analyzed using SPSS 28.0.

Pathology Review

Hematoxylin and eosin (H&E) stained slides of IDS were reviewed by a single experienced oncology pathologist. Omental slides with the most viable tumor and least chemotherapy response were selected. For cases with no residual tumor, slides with the largest area of treatment effect were selected. The slides were scored according to the three-tier system proposed by Böhm et al[6] as follows:

- CRS of 1: No or minimal tumor response. Mainly viable tumor with no or minimal regression-associated fibroinflammatory changes, limited to a few foci
- CRS of 2: Appreciable tumor response amid viable tumor that is readily identifiable. The tumor is regularly distributed, ranging from multifocal or diffuse regression-associated fibroinflammatory changes with viable tumor in sheets, streaks, or nodules to extensive regression-associated fibroinflammatory changes with multifocal residual tumor, which is easily identifiable
- CRS of 3: Complete or near-complete response with no residual tumor OR minimal irregularly scattered tumor foci seen as individual cells, cell groups, or nodules up to a maximum size of 2 mm. There are mainly regression-associated fibroinflammatory changes or, in rare cases, no or very little residual tumor in the complete absence of any inflammatory response.

Outcome Measurement

The patients were followed up till March 2024. PFS was calculated from the date of the first NACT to the first evidence of progression (radiological/Gynecologic Cancer Intergroup CA 125 criteria for biochemical progression).[14] OS was calculated from the date of the first NACT to the date of death or last follow-up.

Statistical Analysis

The data were summarized using descriptive statistics (frequency, percentage, median, range, mean, and standard

deviation). The survival probabilities were estimated using the Kaplan–Meier method, and the significance difference between survival probabilities was tested using the Log-rank test. The risk of various factors on survival was estimated using the Cox regression model. A *p*-value less than 0.05 was considered significant. The correlation of percent reduction in CA 125 with PFS was calculated by Spearman's rho test, while its correlation with CRS was assessed by the Kruskal–Wallis test.

Results

Baseline Characteristics

A total of 125 patients who received three to four cycles of NACT with carboplatin and paclitaxel and attained complete cytoreduction during IDS were included in the study. The median age of the patients was 52 years (range: 27–70 years). There were 91 patients (72.8%) with stage IIIC disease and 34 patients (27.2%) had stage IV disease. Seventy-five women (60%) had received three cycles of NACT and 50 women (40%) had received four cycles of NACT.

The median pretreatment CA 125 level was 1,014 U/mL (range: 43–51,876 U/mL). Following NACT, there was a marked response in CA 125 levels and the median CA 125 level fell to 44 U/mL (range: 2.7–2,238 U/mL). Surgical complexity was categorized into two groups according to the Aletti scoring system.[15] While 80.8% surgeries were of low complexity (Aletti score of 1–3), around 19.2% patients underwent more complex procedures including bowel resection anastomosis, splenectomy, and other upper abdominal surgeries.

The CRS was assessed by a single pathologist on omental sections. There were 21 patients (16.8%) with a CRS of 1, 53 patients (42.4%) with a CRS of 2, and 51 (40.8%) patients with a CRS of 3. Examples of histopathological features of the three CRS on H&E-stained slides are shown in ►Fig. 1. The baseline characteristics of the patients is given in ►Table 1.

Table 1 Baseline characteristics of 125 patients

Characteristic	No. of patients
Median age, y (range)	52 (27–70)
Histology	
High-grade serous	125 (100%)
FIGO stage	
IIIC	91 (72.8%)
IV	34 (27.2%)
No. of cycles of NACT	
3	75 (60%)
4	50 (40%
Complete cytoreduction	125 (100%)

Abbreviations: FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; NACT, neoadjuvant chemotherapy.

Follow-Up and Survival

The median follow-up period was 77 months. During this time period, 94 (75.2%) patients had relapses. While 54% (28/51) patients with a CRS of 3 had disease relapse, 86.79% (46/53) patients with a CRS of 2 and 95.2% patients (20/21) with a CRS of relapsed. The median PFS for the entire cohort was 26 months (95% confidence interval [CI]: 22.13–29.86). The median PFS for patients with a CRS of 1 was 17 months (95% CI: 14.30–19.69), that for patients with a CRS of 2 was 22 months (95% CI: 16.90–27.09), and that for patients with a CRS of was 54 months (95% CI: 21.71–109.11). The CRS applied on the omental samples showed a significant correlation with PFS (CRS of 1 vs. 2: median PFS, 17 vs. 22 months; hazard ratio, 1.73; 95% CI: 1.01–2.96; $p = 0.04$ and CRS of 2 vs 3: median PFS, 22 vs. 54 months; hazard ratio, 2.32; 95% CI: 1.44–3.72; $p < 0.001$). The Kaplan–Meier survival curves for PFS by individual scores is shown in ►Fig. 2.

The total mortality was 82 (65.6%), which included 19 (90.47%) patients with a CRS of 1, 39 (73.58%) patients with a

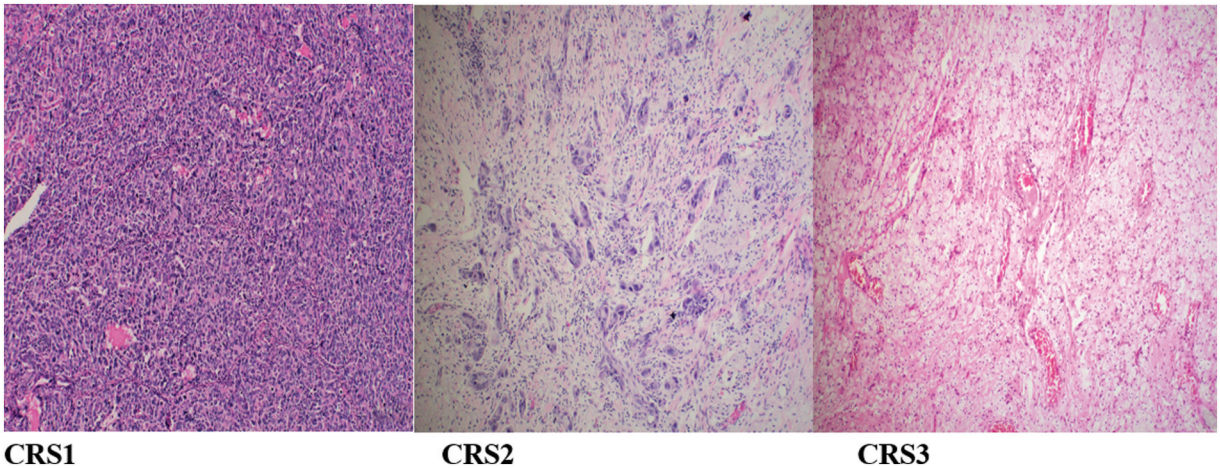

Fig. 1 Examples of histopathological features of the three chemotherapy response scores (CRS) on hematoxylin and eosin (H&E) stained slides. CRS of 1: mainly viable tumor with no or minimal regression associated fibroinflammatory changes. CRS of 2: appreciable tumor response along with identifiable viable tumor. CRS of 3: mainly regression-associated fibroinflammatory changes and no residual tumor.

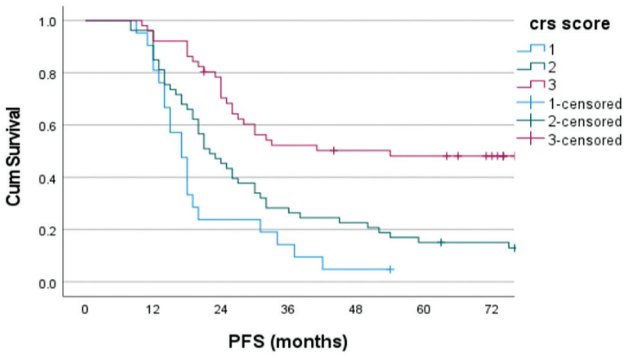

Fig. 2 Progression-free survival (PFS) stratified by omental chemotherapy response score (CRS). Cum, cumulative.

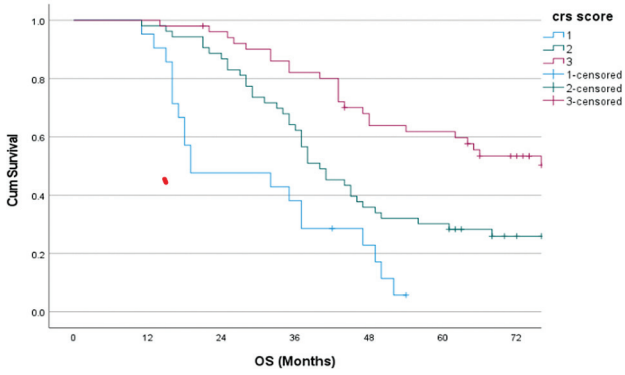

Fig. 3 Overall survival (OS) stratified by omental chemotherapy response score (CRS). Cum, cumulative.

CRS of 2, and 24 (47.05%) patients with a CRS of 3. The median OS for the entire cohort was 45 months (95% CI: 39.66–50.33). The median OS for patients with a CRS of 1 was 19 months (95% CI: 0.00–39.93), that for patients with a CRS of 2 was 40 months (95% CI: 32.86–47.13), and that for patients with a CRS of 3 was not reached. The CRS applied on the omental samples showed a significant correlation with OS (CRS of 1 vs. 2: median OS, 19 vs. 40 months; hazard ratio, 2.13; 95% CI, 1.22–3.73; $p = 0.008$ and CRS of 2 vs. 3: median PFS, 40 months vs. not reached; hazard ratio, 2.19; 95% CI, 1.31–3.67; $p = 0.003$). The Kaplan–Meier survival curves for OS by individual scores are shown in ►**Fig. 3**.

The percent reduction in CA 125 after NACT ranged from 7.7 to 99.9%, with a mean reduction of 88.27%. The reduction in CA 125 after NACT did not correlate with the CRS ($p = 0.377$). It was also seen that the percent reduction in CA 125 did not correlate with PFS (Spearman's rho test score of 0.048, $p = 0.602$).

Discussion

The present study confirms that the omental CRS is significantly associated with PFS and OS. All our patients had high-grade serous tubo-ovarian carcinoma, received three to four cycles of NACT with carboplatin and paclitaxel, and achieved complete cytoreduction, making it a homogeneous group. Various studies in literature have included patients with other histologies, [12,16] given more than four cycles of NACT[8,9] or other agents along with carboplatin and paclitaxel.[9] The distribution of CRS in our study (CRS of 1: 16.8%; CRS of 2: 42.4%; and CRS of 3: 40.8%) was quite different to that of Böhm et al's[5] validation cohort (CRS1: 7%; CRS of 2: 66.2%; and CRS of 3: 26.8%) but similar to the study by Rajkumar et al[8] (CRS of 1: 19.8%; CRS of 2: 37.8%, and CRS of 3: 42.4%). We had a higher proportion of patients with a CRS of 1 (16.8%) as compared with Böhm et al's validation cohort (7.0%) even though we included only patients who had attained complete cytoreduction.

Following the study by Böhm et al,[5] few other studies[8,17] also showed that CRS assessed in omental samples predicted PFS and OS. On the contrary, according to some other studies, CRS predicted PFS but not OS.[13,18] Currently, evidence on correlation between CRS and OS is conflicting. In our study, the omental CRS had a statistically significant correlation with PFS and OS and adds further information to the current literature that omental assessment of CRS helps in predicting OS after IDS. Thus, IDS specimens that show visible treatment effects in the form of minimal residual tumor and more profound stromal fibrosis (CRS of 3) are more chemosensitive tumors with better prognosis as compared with those with absent visible treatment effect in the form of large tumor deposits and viable tumor cells (CRS of 1) indicating poor chemotherapy response.

According to Rajkumar et al,[8] there was no significant difference in PFS between CRS of 1 and 2 and they suggested that the CRS functions better as a binary system (CRS of 3 vs. 1/2) than as a three-tier system. Similarly in the validation cohort of Böhm et al,[5] there was no significant difference in PFS between a CRS of 1 and 2. But Lee et al[13] could show significant differences in PFS between patients with CRS of 1 and 2 tumors ($p < 0.001$) and between those with CRS of 2 and 3 tumors ($p = 0.046$). In our study, there was a significant difference in PFS and OS between CRS of 1 and 2 and between CRS of 2 and 3. As suggested by Lee et al, no gross residual disease after surgery might have improved the survival of patients with a CRS of 2 as compared with a CRS of 1 and shows that CRS can be continued as a three-tier system.

The majority of the studies in the literature on CRS have included patients with and without gross residual disease after surgery. In the study by Lee et al,[13] it was seen that residual disease after IDS was the most powerful prognostic factor for PFS (no gross residual vs. any gross residual; adjusted HR = 0.49; 95% CI = 0.28–0.87). They suggested that no gross residual disease after IDS overcomes the partial response (CRS of 2) after NACT. According to Böhm et al,[5] CRS correlated with PFS even after adjusting for debulking status. However, Singh et al[11] did not find any significant correlation between CRS and PFS after controlling for debulking status. Barrington et al[10] failed to show a correlation between CRS and survival and suggested that the high rate of optimal debulking achieved across all CRS groups may have mitigated the prognostic significance of the scoring system. Unlike these studies, to reduce the bias due to extent of cytoreduction, our study included only patients who achieved complete cytoreduction

and showed that CRS had prognostic significance in patients who attained complete cytoreduction.

CA 125 levels are routinely used in clinical practice to assess response to treatment in ovarian cancer. Currently there is lack of data on the correlation between CRS and CA 125 response to chemotherapy. According to our study, the CA 125 response to NACT does not correlate with histological regression as assessed by the CRS nor with PFS. This is similar to the study by Böhm et al[5] who found that the CA 125 response to NACT did not discriminate between the different pathological scores. But in the study by Singh et al,[11] the percent reduction in CA 125 levels correlated with the grades of pathological response as well as with PFS. They had calculated percent reduction in CA 125 levels measured after the debulking surgery, while in our study and in the study by Böhm et al, it was measured prior to debulking surgery.

As carcinoma ovary is a highly lethal malignancy, there is an urgent need for further research on novel treatment modalities for curing this deadly disease. The CRS being a predictor of prognosis might be used for personalized treatment. Patients with a CRS of 1 who have the lowest survival should be included in clinical trials on newer modalities of treatment like Poly (ADP-ribose) polymerase (PARP) inhibitors, folate receptor inhibitors, and immune checkpoint inhibitors.

The limitation of the study was the retrospective nature of the study and absence of data on BReast CAncer gene (BRCA) status, which was not routinely done at our institute during the recruitment period. Some of the patients with better survival and CRS of 3 might be having BRCA mutations, which cannot be assessed due to lack of data on BRCA status. The strength of our study includes comparable sample size to other studies, a more homogenous group of patients, inclusion of patients who had all attained complete cytoreduction, and a very long follow-up period. Furthermore, all the slides were examined by a single experienced pathologist.

In conclusion, our study confirms that omental CRS is significantly associated with PFS and OS in patients who attained complete cytoreduction during IDS. It is a reliable prognostic tool that helps in identifying patients at high risk of early relapse who may benefit from biological agents and experimental therapies. The CRS system should be included in clinical trials assessing response to newer modalities of treatment like PARP inhibitors, folate receptor inhibitors, and immune checkpoint inhibitors. Thus, omental CRS should be incorporated into routine practice and clinical trial design as an early end point.

Previous Presentation

A part of this study with a smaller sample size was presented as poster at the 22nd European Congress of Gynecological Oncology held in Turkey. This study was conducted with the approval of the Institutional Review Board.

Authors' Contributions

A.J.S. contributed to the conception and design of the study, acquisition of data, analysis and interpretation of data, and drafting the manuscript. S.S. contributed to the conception and design of the study, critical revision of the manuscript for important intellectual content, and supervision of the study. S.C.M. contributed to critical revision of the manuscript for important intellectual content and supervision of the study. R.P. contributed to the conception and design of the study and supervision of the study. S.R.J. contributed to the conception and design of the study and supervision of the study. F.V.J. contributed to the conception and design of the study, critical revision of the manuscript for important intellectual content, and supervision of the study. R.A.Z. contributed to acquisition of data. J.K.K.M. contributed to statistical analysis and supervision of the study.

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Conflict of Interest

None declared.

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