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Original Article

Pathology Section

Prognostic Role of CRS in High Grade Serous Ovarian Tumour Patients Receiving Neoadjuvant Chemotherapy in a Tertiary Care Hospital of Central India

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ABSTRACT

Introduction: Ovarian tumours are rarely diagnosed early, patients presents only when the abdominal mass is appreciable in size. The current mode of treatment involves neoadjuvant chemotherapy with interval debulking surgery, followed by completion of the chemotherapy. The pathological examination of the interval debulking specimen allows an evaluation of the extent of the response to the chemotherapy and sensitivity of the tumour to the same. The Chemotherapy Response Score (CRS) developed by Bohm S et al., is being used to predict the prognosis of these patients. The advent of molecular genetics has allowed us to categorise tumours as per the mutations they possess, the prominent in High Grade Serous Carcinoma (HGSC) being Tumour Protein 53 (TP53), Breast Carcinoma 1/2 (BRCA1/2) and Homologous Recombination Deficiency (HRD). This knowledge is used to cater to the specific therapeutic needs of the patients.

Aim: To apply the CRS to cases of high grade serous carcinomas of the ovary, presenting to the centre and association of the score with their survival.

Materials and Methods: This retrospective and prospective study was conducted in a tertiary care hospital, on 30 patients of high grade serous carcinoma of ovary who received neoadjuvant chemotherapy and had interval debulking surgery were included in the study. The histopathological examination of the resected specimen was done with special emphasis on the omental deposits and the degree of necrosis, fibrosis, inflammation, macrophages and residual tumour. Chi–square test was used to analyse the histopathological parameters with CRS. The p-value <0.05 was considered as statistically significant.

Results: The histological parameters of necrosis, chronic inflammation and residual tumour in the omental deposits were found to be the statistically significant in association to the CRS scores. Also, the CRS grading was associated with the survival of the patients.

Conclusion: The CRS was found to associate well with the survival of the patients. This study recommends that CRS score be done in all post Neoadjuvant Chemotherapy (NACT) high grade serous ovarian tumours, which will guide further treatment.

Keywords: Chemotherapy response score, Debulking surgery, Ovarian cancer

INTRODUCTION

After cervical cancer, ovarian cancer is the second most common gynaecological malignancy in western countries and is responsible for the most mortality amongst them [1]. The new 2020 World Health Organisation (WHO) classification of ovarian cancers takes into account morphology, immune-profile and molecular profiles. On the basis of this, there are five main epithelial carcinomas: high and low grade serous carcinoma, endometroid carcinoma, clear cell carcinoma and mucinous carcinoma. Majority of advanced stage ovarian cancers are represented by high grade serous carcinoma (70%) and are the most lethal [2].

The treatment protocols for advanced stage ovarian cancer have changed over the years from the initial approach of primary surgical resection followed by postoperative chemotherapy, to primary Neoadjuvant Chemotherapy (NACT) for cytoreduction followed by debulking. International Federation of Gynaecology and Obstetrics (FIGO) stage III/IV ovarian cancers are now started with platinum-based cycles of chemotherapy to reduce the tumour bulk, with interval debulking and followed by completion of cycles of chemotherapy. National Comprehensive Cancer Network (NCCN) guidelines for 2012 recommended this approach to reduce morbidity associated with surgery [3].

The tumour response to NACT is assessed on the histopathological examination of interval debulking specimens and thus guides the treatment. Bohm S et al., developed a histopathologic scoring system for measuring response to NACT in interval debulking surgery specimens of stage III C to IV tubo-ovarian high grade serous carcinoma, called CRS [4]. This scoring system has still not found its place in the routine oncology reporting in India. In this study implementation of the CRS in the Indian scenario was approached and its association with the prognosis, as measured by the disease free survival of the patients who have undergone interval debulking post NACT, at our centre.

MATERIALS AND METHODS

This was a retrospective and prospective study conducted in a tertiary care hospital, on 30 cases of high grade serous ovarian cancers, who presented over a period of three years (January 2018 to December 2020). Approval for the study was taken from the Institutional Ethics Committee (IEC) (IEC no. CMCH/EC/2022/04-12).

Inclusion criteria: Patients with ovarian malignant tumours who received initial chemotherapy and then had interval debulking surgery, and were on follow-up were included in the study.

Exclusion criteria: a) Patients with tumours other than high grade serous carcinoma of the ovary, b) Patients of serous carcinoma of the ovary who did not receive chemotherapy before surgery, c) patients who were lost to follow-up were excluded from surgery.

Sample size: All the cases during the stated study time period were included i.e. 30 cases were included as per the inclusion and criteria stated above.

Study Procedure

Patients were diagnosed on the basis of ultrasonography findings of enlarged ovaries with solid and cystic component, raised Cancer

(CA) 125 and/or positive effusion cytology. These patients were given initial four cycles of platinum-based chemotherapy, comprising paclitaxel and carboplatin. This was followed by interval debulking surgery after which the histopathological examination was done and the rest of the chemotherapy cycles were completed.

Surgical specimens received included total hysterectomy with regional lymph node dissection and omentum for staging. Specimens were grossed, and sections were stained with Haematoxylin and Eosin (H&E). Two experienced pathologists reviewed the sections, with emphasis on residual tumour, fibrosis, necrosis, inflammation, calcification, macrophages and omental and extraovarian deposits. These histological parameters have been graded as <50% and ≥50% of entire tissue on the most representative H&E section for that parameter. Calcification and metastatic deposits were graded as present or absent. The chemotherapy response scoring was done as per the three-tier CRS system proposed by Bohm S et al., in 2015, and incorporated in the dataset of Royal College of Pathologists [Table/Fig-1] [4,5]. An association between the CRS scores and the postoperative period follow-up of the patients was done, including the recurrences, death and disease-free survival of the patients.

CRS	Histopathological criteria for CRS
CRS 1	Largely viable tumour with minimal or no regression.
CRS 2	Identifiable tumour response, with areas of regression related fibro-inflammatory changes and multiple foci of residual tumour.
CRS 3	No evidence of residual tumour or minimal tumour as represented by singly dispersed tumour cells or groups <2 mm in size. Entire tumour replaced by regression related fibroinflammatory changes.

[Table/Fig-1]: Criteria for CRS as adapted from Bohm S et al., [4].

STATISTICAL ANALYSIS

The statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) software version 23.0. Pearson Chi-square test was used to analyse the histopathological parameters with chemotherapy response score. The p-value <0.05 was considered as statistically significant.

RESULTS

Total 30 cases of advanced stage ovarian cancers who underwent interval debulking surgery post NACT included in the study ranged in age from 41-70 years, with a mean age of 51 years and 8 months. The median age was 51 yrs, 20% of the cases belonged to 41-45 years of age, 16.67% cases belonged to 46-50 years of age, 23.33% were in the age range between 51-55 years, 26.67% in the age range between 56-60 years and 6.66% were in the age range between 61-65 years and 66-70 years each. Total 66.6% of the patients had disease involving bilateral ovaries, and of the rest, 26.8% involved only the left and 6.6% involved the right ovary. Eight patients had positive ascitic fluid cytology; these patients had bilateral disease with capsular breech of the ovaries. These cases also had high grade residual tumour post NACT thus showing minimal response to the chemotherapy regimen.

The degree of fibrosis was inversely proportional to the residual tumour burden. Patients with the highest degree of fibrosis, were the ones with lesser or no residual viable tumour. However, the p-value was 0.9 and was not statistically significant when compared with the CRS scoring [Table/Fig-2].

The cases with the greater tumour burden also showed more extensive necrosis. Necrosis was noted in the ovaries, lymph nodes and omentum. Patients with moderate necrosis of the omental deposits had a better CRS scoring and prognosis; as compared to those with greater necrosis with a p-value of 0.0368 [Table/Fig-2]. Thus, the necrosis bears a significant association with the CRS and hence with prognosis.

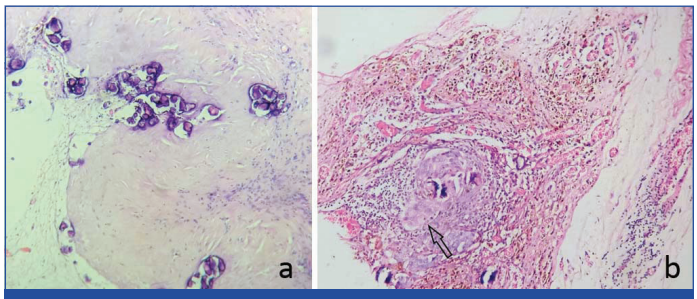
Foamy macrophages were seen when the tumour burden was more, and were less with less viable tumour. However, on comparison

Pathological reponses	CRS Grading	1	2	3	Total	p-value calculated by Pearson Chi-square test
Necrosis	≥50%	8	4	3	15	0.0368
	<50%	2	4	9	15	
	Total	10	8	12	30	
Fibrosis	≥50%	7	4	4	15	0.91
	<50%	6	5	4	15	
	Total	13	9	8	30	
Inflammation	≥50%	7	6	2	15	0.02
	<50%	2	4	9	15	
	Total	9	10	11	30	
Macrophages	≥50%	7	4	3	14	0.067
	<50%	3	3	10	16	
	Total	10	7	13	30	
Residual tumour	≥50%	5	6	3	14	0.034
	<50%	2	3	11	16	
	Total	7	9	14	30	

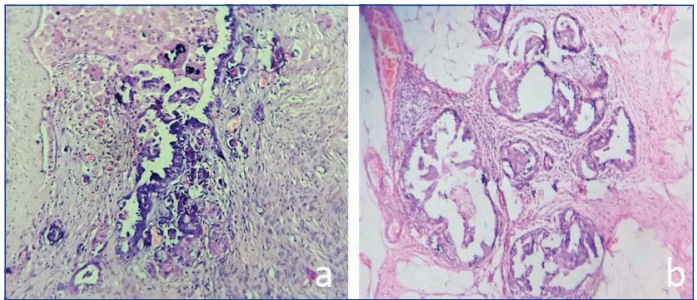
[Table/Fig-2]: Association between pathological parameters and the chemotherapy response score.
*A p-value <0.05 is considered to be statistically significant

with the CRS, the p-value was 0.067, which was statistically not significant [Table/Fig-2]. The inflammatory response was represented by the lymphocytic infiltrate. More infiltrate was seen when there was greater tumour burden, and decreased with response to the chemotherapy. The amount of infiltrate was compared to the CRS and the corresponding p-value was 0.022 and thus found to be significant [Table/Fig-2].

The patients with the maximum residual tumours in the omental deposits were representative of those having least response to the chemotherapy and were thus given the score of CRS 1 [Table/Fig-3]. Absence of viable residual tumour in omentum was CRS3 and those with identifiable tumour response was CRS 2 [Table/Fig-4]. On statistical analysis, the p-value comes to be 0.03415 and was hence significant [Table/Fig-2].



[Table/Fig-3]: a) Shows total absence of viable tumour with fibrosis and calcification; b) Shows minimum viable tumour <2 mm in size (arrow) with adjacent fibroinflammatory infiltrate, corresponding to CRS 1 (100X, H&E).



[Table/Fig-4]: a, b): Foci of viable tumour with fibroinflammatory changes, foamy macrophages and psammoma bodies, corresponding to CRS 2 (100X, H&E).

Calcification represented by psammoma bodies was more in the patients showing a better response and having a lesser tumour burden and coincided with a longer disease free interval.

The patients were followed-up for two months to 42 months postsurgery. There were deaths in three cases, all of whom were CRS 1 [Table/Fig-5]. The first had bilateral disease and >50% residual tumour, she presented within three months of surgery with metastasis in liver and expired in six months. The second case was also of bilateral disease with capsular breech, deposits in omentum and mesentery, she presented with pleural effusion and lung metastasis within eight months of surgery and died five months later. The third patient presented at 11 months with massive ascitic effusion and multiple omental metastasis, and did not survive another month.

Four cases relapsed within 12 months of surgery, of these two were CRS 1 and two were CRS 2; they presented with malignant ascites and raised CA125. Four cases relapsed after a year, two cases were CRS 2 and a single case each of CRS 1 and CRS 3. Other cases were free of disease, for a period upto 42 months.

In our study the CRS corresponded well with the disease-free survival period. CRS 3 cases showed a single recurrence i.e., 7.1% (1/14) in their follow-ups and 92.9% were disease free in the follow-up period [Table/Fig-5]. Only one CRS 1 patient had no recurrence till follow-up. The intermediate CRS 2 cases 55.6% (5/9) had no recurrence and 44.4% (4/9) came back with recurrence, but there were no deaths reported [Table/Fig-5].

CRS	Recurrence and death	Recurrence	Disease free	Total
CRS 1	3	3	1	7
CRS 2	0	4	5	9
CRS 3	0	1	13	14

[Table/Fig-5]: Association between CRS and patient survival.

DISCUSSION

The post chemotherapy changes in breast cancers, colon, osteosarcomas etc, have been documented and used as prognostic indicators. In 2015 Bohm S et al., introduced CRS for post NACT morphological changes in the omentum in high grade ovarian cancers, and proved its reproducibility and prognostic significance [4]. The International Collaboration on Cancer Reporting (ICCR) had recommended the implementation of the CRS and this has been incorporated in the dataset for reporting of tumours of ovaries, fallopian tubes and peritoneum, by the Royal College of Pathologists in 2019 [5].

The diagnosis of ovarian tumours is still indirect and based on radiology, raised CA125 levels and malignant cells in ascitic fluid. The absence of primary biopsy sampling comprises the primary categorisation and grading of tumours. Thus, the interpretation of response to the drug regimen and further treatment plan is almost entirely dependent on the post NACT histopathology report.

Before Bohm S et al., gave their CRS on the study of omental deposits of ovarian tumours, McCluggage WG et al., and Sassen S et al., tried to assess the tumour regression in ovaries post NACT [6,7]. In 2012 Samrao D et al., in their study attempted to use the histological findings in ovaries in post NACT cases as indicators of predictive outcome of the disease [8]. Singh P et al., [9] and Ditzel HM et al., [10] carried forward the studies on omental CRS and both agreed with the longer disease-free survival of CRS 3 patients as stated by Bohm S et al., [4]. However, Singh P et al., noted that this association was not significant after controlling for debulking status [9].

All the cases of CRS 3, except one had no evidence of recurrence of disease till the follow-up period. Cases of CRS 1 score representing almost no or minimal response to treatment, came back with recurrence of disease [Table/Fig-5]. These findings collaborate the seminal paper of Bohm S et al., [4] and are in tandem with those of Singh P et al., [9] and Ditzel HM et al., [10].

Present study shows a significant statistical association with residual tumour, degree of necrosis and lymphocytic infiltrate and the CRS [Table/Fig-2]. The dystrophic calcification seen as psammomatous bodies was also associated with longer disease free survival, this concurs with the study of McCluggage WG et al., [6]. A comparison of the findings of the present study in the Indian scenario with that of Cohen PA et al., [11], Singh P et al., [9] and Ditzel HM et al., [10] support and reiterate the findings of Bohm S et al., [4], with respect to the prognosis of patients as per the CRS. The CRS 3 patients in all the above studies with minimal tumour or a complete response have fared well with longer disease-free periods as compared to the CRS 1 and 2 patients [Table/Fig-6].

Study	Findings
Cohen PA et al., [11]	The pooled Hazard Ratio (HR) for PFS (CRS3 compared to CRS1/CRS2) was 0.55 (95% CI, 0.45-0.66; p<0.001). The meta-analysis showed that CRS3 is a biomarker for survival.
Singh P et al., [9]	CRS 3 patients had a longer progression free survival (18 months) as compared CRS1/2 patients (16 months)
Ditzel HM et al., [10]	In their study also the progression free survival of CRS 3 cases was better than CRS1/2 cases (18.9 vs 10.9 months)
Present study	92.9% of CRS3 cases (13/14) were entirely disease free for the follow-up period, as compared to only 37.5% of the CRS 1 and CRS 2 cases (06/16). These results concur with the above studies.

[Table/Fig-6]: Comparison of studies done using the Chemotherapy Response Score with present study [9-11].

All high grade serous ovarian carcinomas do not necessarily respond to the current regimens, hence, the importance of interval debulking and histopathological examination. This mid-therapy evaluation is extremely helpful for guiding further treatment. The non responders can then be offered other chemotherapeutic agents to which their tumour may be sensitive. This was done by Masuda N et al., when they offered capecitabine to breast carcinoma patients, who had NACT resistant tumours; and they then had better outcomes [12]. Ivantsov AO has pointed out that tumors may change their molecular properties during treatment, thus, making an initially chemosensitive tumour a chemoresistant one [13]. High-Grade Serous Carcinoma (HGSC) are known to arise from Serous Tubal Intraepithelial Carcinoma (STIC) at the fimbrial end of the fallopian tube, and hence have now been called tubo-ovarian high grade serous carcinomas in the fifth edition of the WHO Classification of Female Genital Tumours [14]. HGSCs are associated with TP53 mutations (more than 97%) and HRD including BRCA mutations, while LGSCs are characterised by BRAF or KRAS mutations.[2] BRCA1 or BRCA2 mutations have a 30-70% higher risk of the women developing HGSC by age of 70 [15,16]. PARP inhibitors have been included as a standard of care for HGSC [17]. However non HRD tumours do not respond to PARP inhibitors, testifying to the heterologous nature of HGSCs [18]. Cohen PA et al., in their systemic review and meta-analysis also make a point towards personalised treatment on the basis of CRS stratification [11]. This makes the examination and accessibility to tissue for further cytogenetic studies most important.

Limitation(s)

This study was limited to the small sample size, as patients were lost to follow-up, and not all agree to NACT and opt for direct surgery citing monetary reasons.

CONCLUSION(S)

This study supports the findings of the paper by Bohm S et al., that the CRS from the omental grading corresponds with the disease-free survival of the patients. All the patients with CRS 3 score were disease-free, postsurgery and NACT, except one. The CRS 1 and 2 patients had shorter disease-free interval and poor prognosis. The wider implementation in the Indian scenario of the CRS score will help in prognosis of patients. Also, the molecular analysis of the CRS 1 and CRS 2 tumours will give the patients and clinicians the

option to change their chemotherapy regime based on the profile of their tumours, and hence the means to a better outcome.

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