CHEMOTHERAPY RESPONSE SCORING (CRS) FROM MULTIPLE SITES DURING INTERVAL DEBULKING SURGERY IN OVARIAN CANCER: EXPERIENCE FROM A TERTIARY REFERRAL CENTER IN EASTERN INDIA

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INTRODUCTION and AIMS

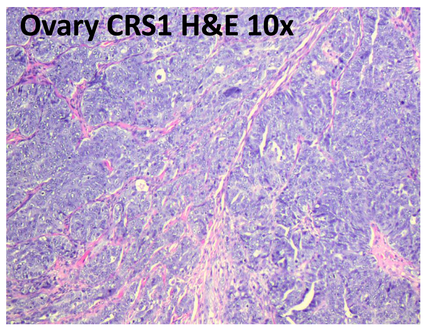
- In our institution, the principle mode of treatment for advanced (stage IIB-IVB) stage epithelial ovarian cancer till December 2014 has been IDS (interval debulking surgery) with optimal (<1cm residual diease); however, we have noticed significant clinical and biochemical recurrence during follow up. Using a subjective pathological response criteria, 94 women (2011-2014) were categorised in to good (n=47) and poor responders (n=47); no difference was noted in recurrence patterns with approximately 50% recurrence rate and 25% platinum resistance.(Lucksom et al, ESGO 2015)
- Since 2015, we adopted a policy where PDS (primary debulking surgery) was the primary modality (60-70% cases) and CC0/ CC1(<2.5mm residual) was the standard for optimal cytoreduction (PCI scoring was used). Also we adopted a 3 tier system for grading pathological response at NACT using the CRS scoring criteria and the CAP guidelines.
- In this study, we aim to validate the 3 tier CRS and correlate with clinical parameters and recurrence.

METHODS

Criteria for the Chemotherapy Response Score

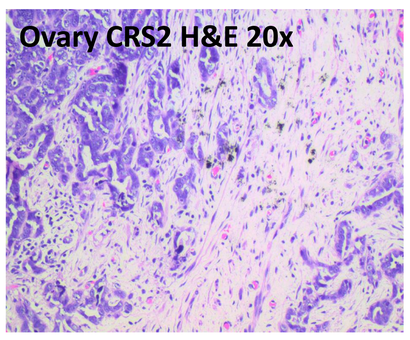
Boehm S, Faruqi A, Said I, et al. Chemotherapy Response Score: Development and Validation of a System to Quantify Histopathologic Response to Neoadjuvant Chemotherapy in Tubo-Ovarian High-Grade Serous Carcinoma. DOI: 10.1200/JCO.2014.60.5212

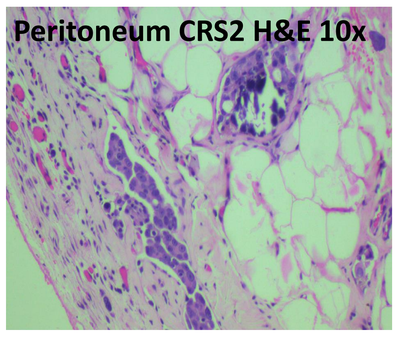
CRS 1	No or minimal tumor response. Mainly viable tumor with no or minimal regression-associated fibro-inflammatory changes, limited to a few foci.
CRS 2	Appreciable tumor response amid viable tumor that is readily identifiable. Tumor is regularly distributed, ranging from multifocal or diffuse regression-associated fibro-inflammatory changes with viable tumor in sheets, streaks, or nodules to extensive regression-associated Fibro-inflammatory changes with multifocal residual tumor, which is easily identifiable.
CRS 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 2 mm maximum size. Mainly regression-associated fibro-inflammatory changes or, in rare cases no or very little residual tumor in the complete absence of any inflammatory response.



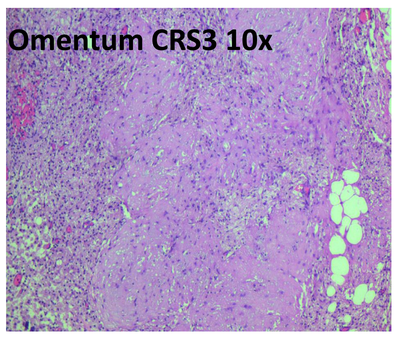
Ovary - CRS1 (No response)

Mainly viable tumour with no regression associated fibro-inflammatory changes

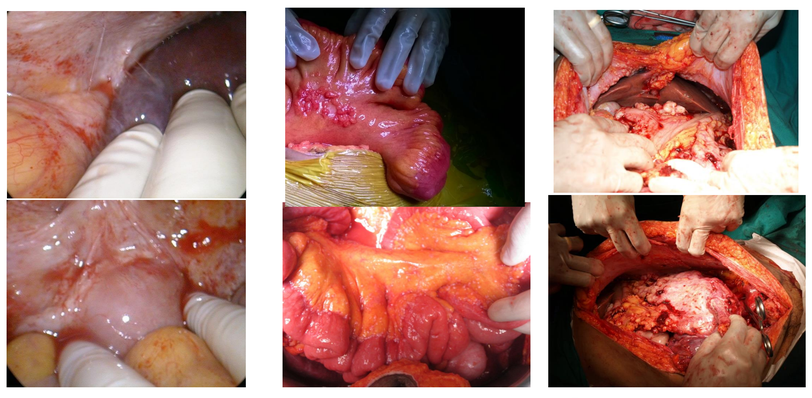




Ovary - CRS2 (Partial response)
Multifocal tumour with regression-associated fibro-inflammatory changes



Omentum - CRS3 (Complete response)
No residual viable tumour in a case of Primary peritoneal carcinoma. Sheets of foamy macrophages and regression associated fibro-inflammatory changes seen.

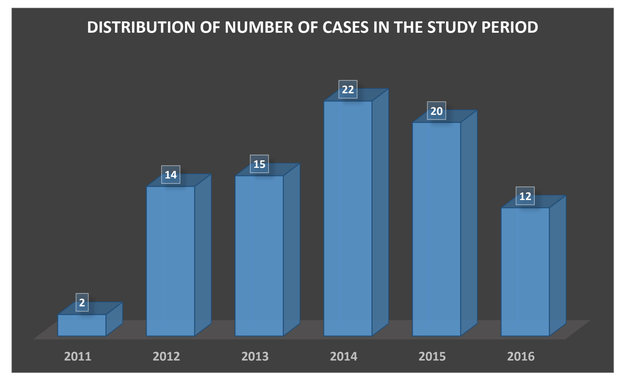


Good response **Some response** **Poor response**

- Observational study.
- Study period 1 (2011-2015): data on CRS vs PFS and PFI. At least 6 month PFI data available (n=73)
- Study period 2: (2015-2016 July): Data on CRS vs radiological and intra-operative response, Peritoneal carcinomatosis Index (PCI), CC score (cytoreduction status)(n=32)
- CRS scoring was done on 3 sites: both ovaries, both fallopian tubes and omentum on single H &E stained section
- Scoring was done by 2 independent reviewers (DM & KG). Training for CRS was obtained after personal communication with Dr N Singh and the website http://www.gpecimage.ubc.ca/aperio/images/crs
- Only high grade serous histology and stage IIB-IVB cases where all 3 sites were sampled were included
- Individual site scores as well as the worst CRS of all sites was recorded
- Data was collected from hospital electronic medical records system and Redcap database.
- Follow up status was updated till July 2016
- PFS (progression free survival) was calculate from date of diagnosis
- GCIG criteria for biochemical/radiological/ clinical recurrence
- PFI (platinum free interval) was calculated from the date of C6 chemotherapy

RESULTS

CHARACTERISTICS	N (%) n=73
Median age, years (range)	52 (35-71)
Origin of HGSC	
• Ovary	• 44 (60)
• Fallopian tube	• 25 (34)
• Peritoneal	• 04 (06)
Clinical stage	
• IIIC	• 54 (74)
• IV	• 17 (24)
• NA	• 02 (02)
Cycles of NACT	
• 3 or 4	• 68 (93)
• > 4	• 05 (07)
Regimen of NACT	
• Carboplatin + Paclitaxel	• 70 (96)
• Carboplatin	• 03 (04)
Outcome of debulking surgery : Residual disease	
• No macroscopic disease	• 61 (84)
• > 0 but < 1.0 cm	• 05 (07)
• > 1.0 cm	• 03 (04)
• NA	• 04 (05)



N=32 (2015,2016)	CC0 N (%)	CC1 N (%)	CC2 N (%)	CC3 N (%)	Median PCI
CRS1	1 (50%)	0	0	1 (50%)	14
CRS2	12 (66%)	5 (27%)	1 (6%)	0	10
CRS3	8 (80%)	1 (10%)	1 (10%)	0	08

	Median Initial CA125	Median Post NACT CA125
CRS1	564	50
CRS2	1390	52
CRS3	1240	13

CRS score correlated with CC score, PCI, intra-op findings and Ca125. Lower Ca125 seen in CRS1 may be indicative of poor tumour biology

CRS score vs disease recurrence (PFS)

SITE	CRS1	CRS2	CRS3
OVARY	72%	65%	40%
FALLOPIAN TUBE	66%	63%	58%
OMENTUM	83%	66%	48%

3 sites; worst CRS	CRS1	CRS2	CRS3
	75%	60.5	37.5

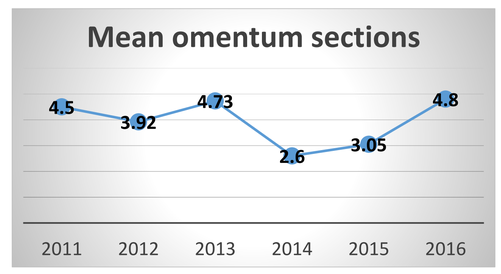
✓CRS3 in the ovary is the best predictor for a good outcome followed by omentum

✓CRS1 in omentum is the best predictor for poor outcome followed by CRS1 in ovary.

✓ ? Sampling error- lesser representative sections obtained from omentum could explain the low predictive value for CRS3

OMENTUM PFS	≤ 12 months	> 12 and ≤ 24 months
CRS1	43%	43%
CRS2	55%	26%
CRS1+2	53%	29%
CRS3	21%	57%

OMENTUM PFI	< 6 months	> 6 and ≤ 12 months
CRS1	43%	43%
CRS2	34%	21%
CRS3	07%	32%



Bohm et al : At less than 6 months after last adjuvant chemotherapy, 6% of patients with CRS 3, 43% with CRS 2, and 40% with CRS 1 showed progression (ie, primary platinum-resistant disease). Our data was comparable

CRS 3 Identifies Patients With Low Probability of Primary Platinum-Resistant Disease

SUMMARY / CONCLUSION

- **The CRS system is a potential step toward individualized treatment modification in patients with HGSC after NACT and IDS. The system is easy to apply, reproducible and seems to be prognostically relevant**.

Future work:

- Explore the possibility whether these CRS subgroups represent distinct biologic subsets. Translational studies to look into the molecular subtypes are in the horizon.
- To explore whether CRS can be applied to different treatment regimens and in combination with new prognostic and/or predictive factors.

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