Cancer stem cells and EMT in high grade serous epithelial ovarian cancer: Correlation with chemotherapy response at neo-adjuvant chemotherapy and DNA damage response (PROVAT2 Study), proof of concept.

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Introduction

• Debate continues whether primary surgery (PDS) followed by adjuvant platinum-based chemotherapy or neo-adjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) should be the preferred option of treatment in stage 3/ 4 epithelial ovarian cancer (EOC). At Tata Medical Center (TMC), Kolkata

• FIGO stage 3/4 EOCs, disease recurrence at 12 months including platinum resistant recurrence was significantly higher in the NACT group compared to primary surgery group (38% vs. 7%) despite the fact that NACT patients underwent > 90% optimal abdominal cytoreduction.
• This would indicate possible tumor-related factors/ chemo-therapy induced factors in the NACT group despite being adequately removed during cytoreductive surgery contributing to chemo-resistance.
• The biological factors leading to poorer chemoresponse after NACT therefore needs to be addressed as in many institutions, NACT is being projected as an alternative to primary surgery with reduced morbidity.

Aim and Objectives :

1. To compare the status of different populations of CSCs andtheir EMT markers, between patients undergoing primary surgery (chemo-naive) vis-à-visatand interval surgery after receiving neo-adjuvant chemotherapy (NACT) and correlate the findings with i. chemotherapy response score (CRS) ii. platinum resistance iii. rdisease recurrence ecurrence free and survival,and iv. DNA repair status
2. To delineate the mechanisms underlying NACT induced changes on these different CSC populations and EMT and the effects of the same on drug-resistance and
3. To explore the possibility of repurposing of drugs used in other diseases for sensitizing CSCs towards conventional chemotherapeutic regimen.

Generation of spheres from human ovarian cancer cell lines.

PA1   SKOV3   OVCAR3
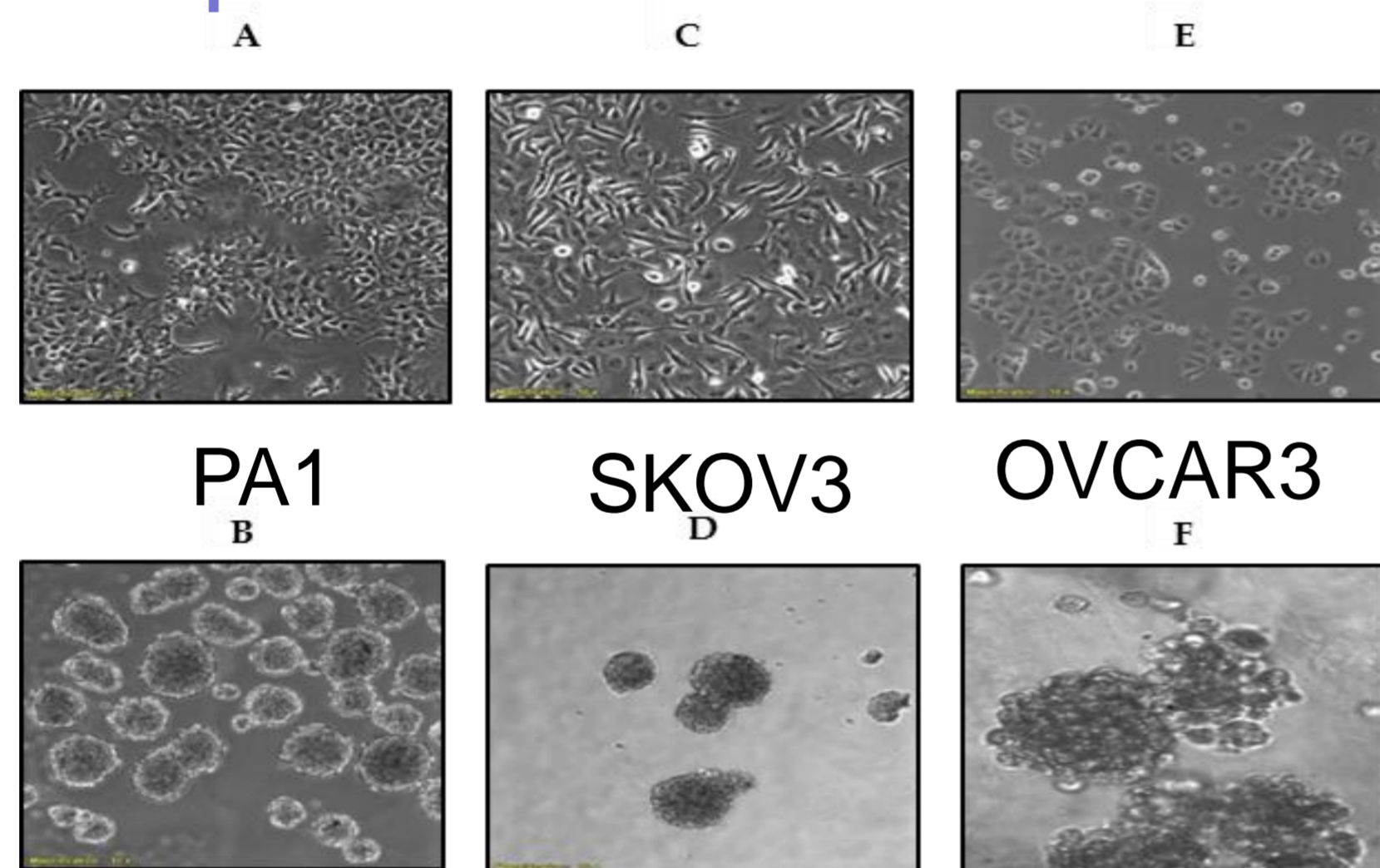
Increase CSCs in Ovcar3 cell and sphere with cisplatin treatment
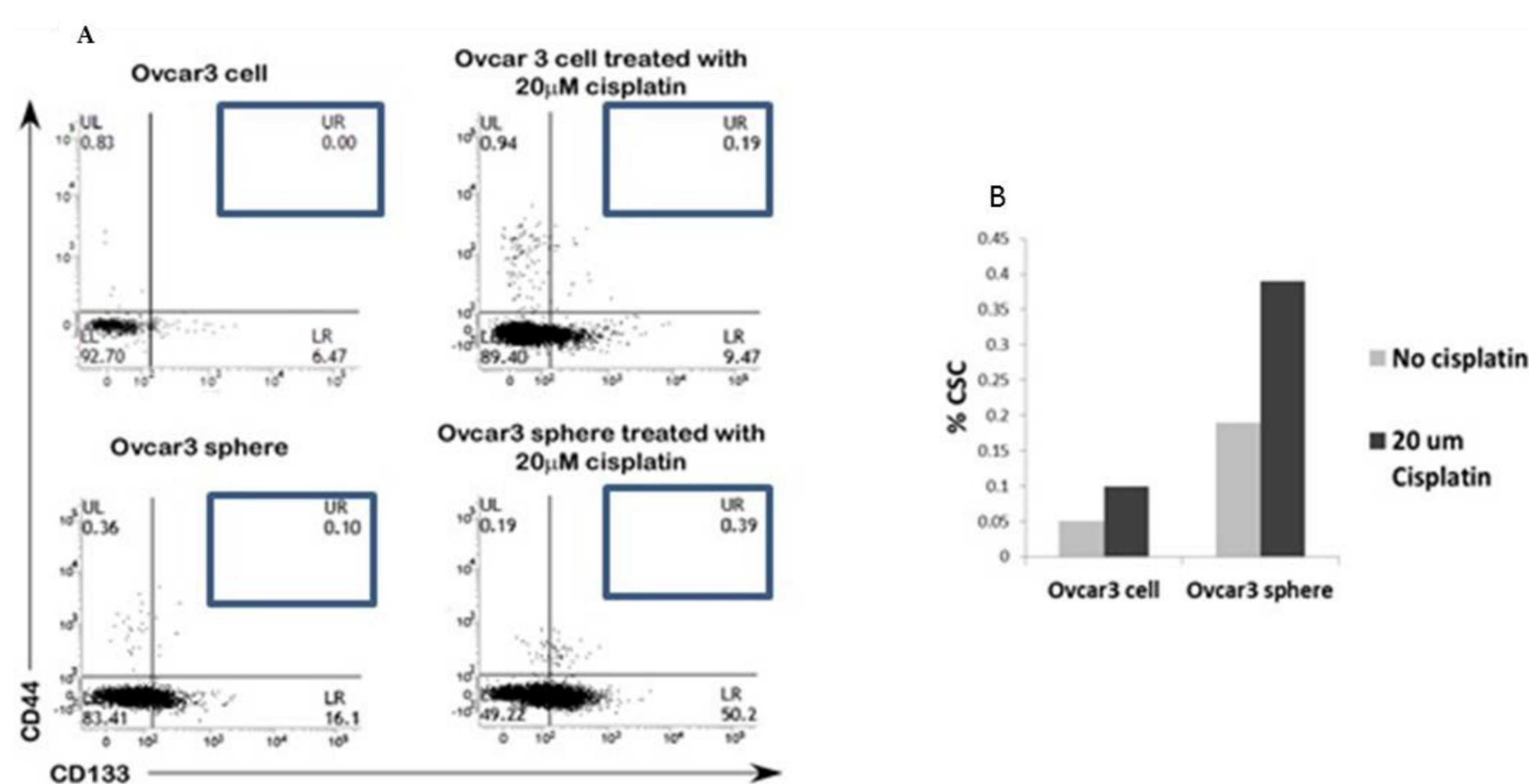
Methodology

1. Putative cancer stem cells from ovarian cancer cell line form spheres under non-differentiating serum free
2. Identification of Tumorigenicity/Cancer stem cell Markers in spheres using FACS and confocal microscopy
3. Analysis of distribution pattern of cell cycle phases of the sphere forming cells
4. Sphere forming cells can differentiate into multiple lineages when grown in differentiating conditions
5. Sphere forming cells express higher levels of proteins which are markers for "stemness" as compared to their non-tumorigenic counterparts
6. Cells and spheres treated with chemotherapeutic drugs will express higher percentage of CSC as compared to untreated cells/spheres

Results

Chemotherapy response scoring (CRS) during interval debulking surgery in ovarian cancer from multiple sites. CRS1 is best predictor for unfavorable outcome while CRS3 is best predictor for favorable outcome

CHEMOTHERAPY RESPONSE SCORING (CRS) FROM MULTIPLE SITES DURING INTERVAL DEBULKING SURGERY IN OVARIAN CANCER: EXPERIENCE FROM A TERTIARY REFERRAL CENTER IN EASTERN INDIA
D Midha [1], K Gupta [1], PG Lucksom, A Ghosh, B Chakraborti, J Bhaumik, A Mukhopadhyay
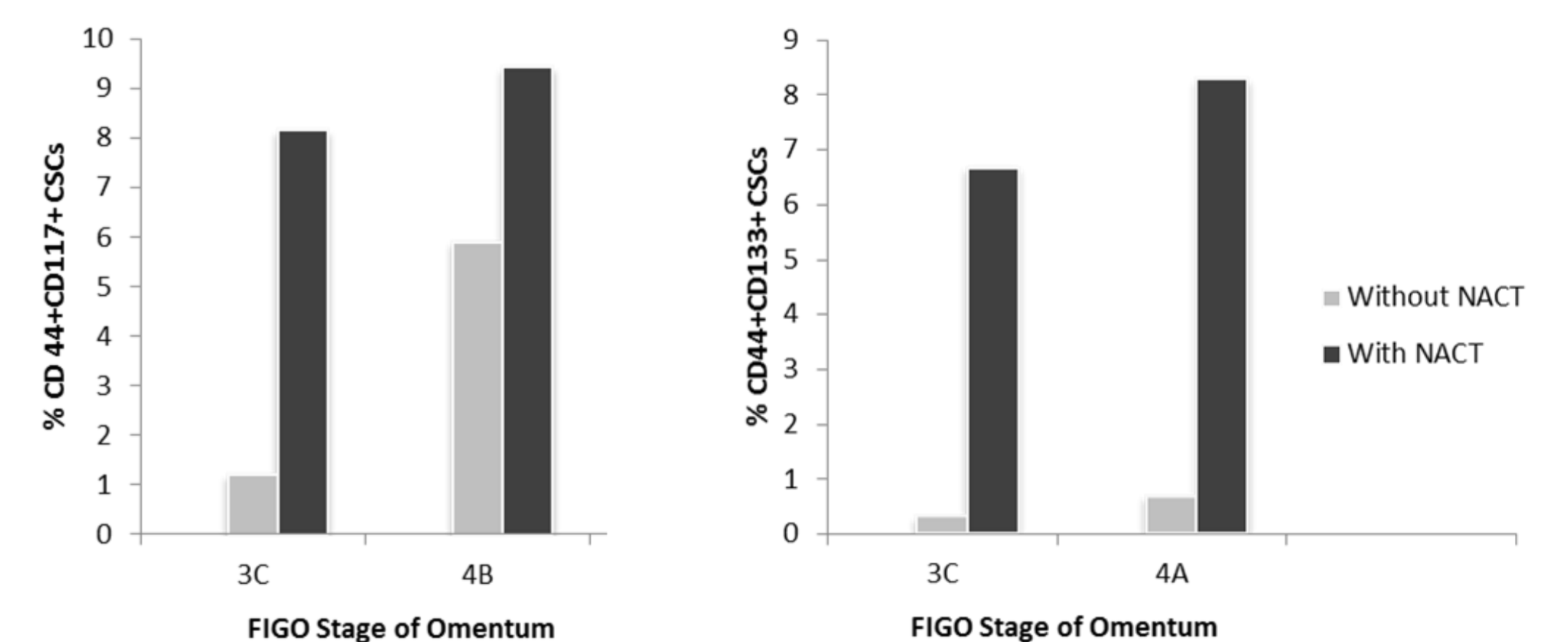
SITE	CRS1	CRS2	CRS3
OVARY	72%	65%	40%
FALLOPIAN TUBE	66%	63%	58%
OMENTUM	83%	66%	48%

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

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

✓ 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.

PDS/Chemo-naive patient tissue samples showing increase percentage of CD44+CD117+ and CD44+CD133+ CSCs in ovary and omentum samples of different FIGO stages.
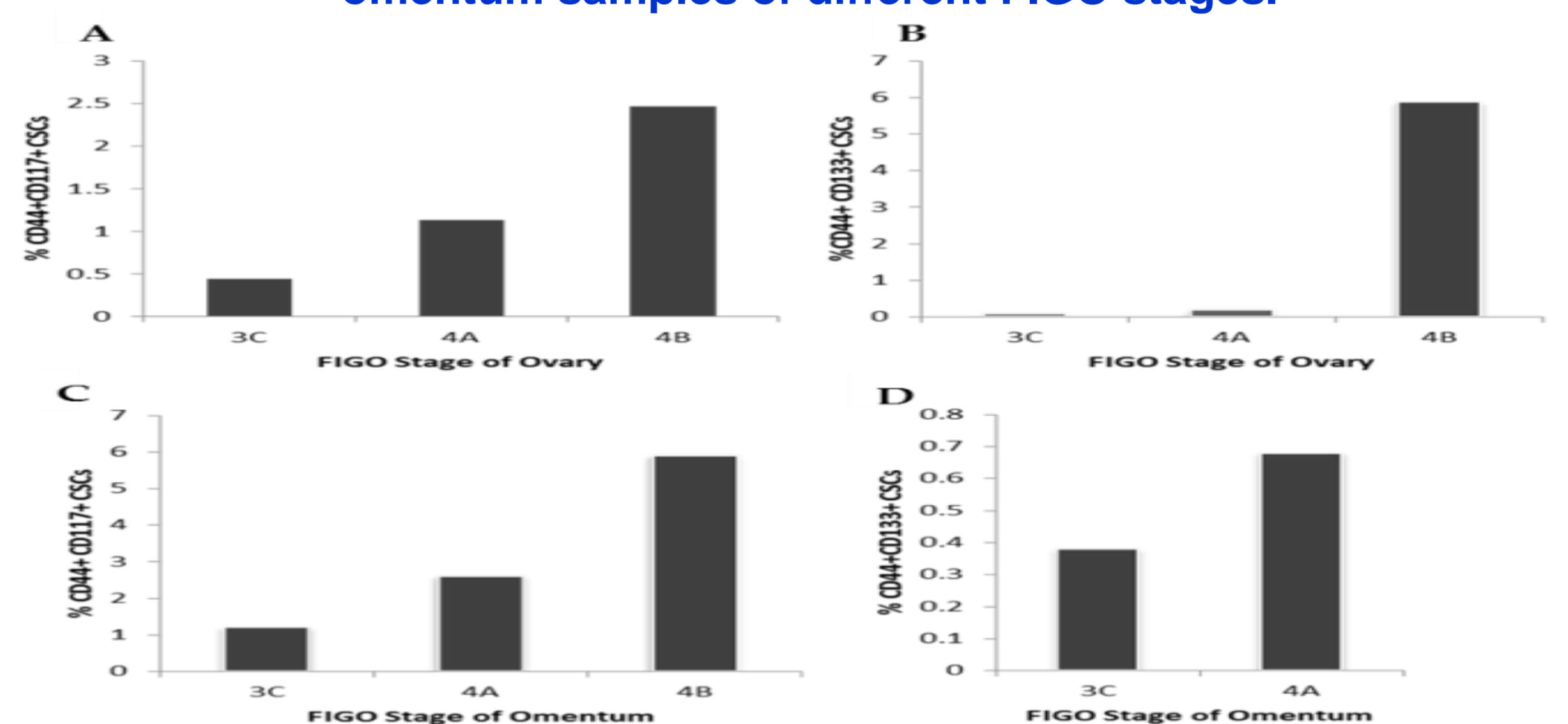
➢ Increase percentage of CD44+CD117+ and CD44+CD133+ CSCs in NACT treated compaired to untreated Omentum samples of different FIGO stages.

Conclusion:

1. CRS3 in ovary is the best predictor of good outcome
2. CRS1 is ovary is the best predictor of poor outcome
3. Increase percentage of CSC in spheroid with platinum treatment
4. With increase stage there is increase percentage of CSC in HGSEOC
5. NACT treatment enrich CSC in HGSEOC patients

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