BRCA AND OVARIAN CANCER: A MORPHOLOGICAL, IMMUNOHISTOCHEMICAL AND GENETIC STUDY OF HIGH GRADE SEROUS CARCINOMA AND TUBAL PRECURSORS


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Disclosure Information

I hereby declare that I have had business or personal interests in the following industrial enterprises since 1 September 2017:

**Name of the enterprise / Nature of the interest**

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INTRODUCTION: HIGH GRADE SEROUS CARCINOMA

- Ovarian cancer: 250,000 cases/year, 140,000 deaths/year
- HGSC: 70% of all ovarian cancers
- 20% STAGE I/II: 80% STAGE III/IV
- **Classic morphology:** papillary and solid growth patterns, intermediate grade nuclei, prominent nucleoli, scattered bizarre giant cells, high mitotic rate
• **Solid-Pseudoendometrioid-Transitional (SET)** variant of high grade serous carcinomas (HGSC) has been recently described in **BRCA 1/2** mutated patients

• Characterized by high mitotic activity, frequent bizarre mitoses, abundant TILs, is seen typically, but not exclusively, in cases with germline or somatic BRCA-related abnormalities

• The association between SET-HGSC and tubal precursor lesion (SCOUT-STIL-STIC) is still controversial

**INTRODUCTION: BRCA AND HGSC**

**Morphologic patterns associated with BRCA1 and BRCA2 genotype in ovarian carcinoma**

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AIM OF THE STUDY

To investigate the correlation between BRCA mutational status and:

- HGSC morphology
- Tubal putative precursor lesions
- Immunohistochemical (IHC) profile
- Tumor infiltrating lymphocytes (TILs)
MATERIALS & METHODS

• 27 consecutive patients with HGSC (patient mean age 52.5 years) from 2015 to 2017
• BRCA Germline and Somatic test (FFPE & fresh frozen tissue)
• Tumour percentage of histological patterns was evaluated on H&E sections
• HGSC diagnosis was confirmed by p53/WT1/PAX8 IHC status
• Assessment of SCOUT (Secretory Cell Outgrowth), STIL (Serous Tubal Intraepithelial Lesion) and STIC (Serous Tubal Intraepithelial Carcinoma) was performed using a double staining for Bcl2/p53 together with Ki-67
MATERIALS & METHODS

- Intratumoral TILs (iTILs) were counted semi-quantitatively
- CD8+ Lymphocytes/10 HPF
RESULTS: MORPHOLGY AND IHC ANALYSIS

- 18/27 (66.7%) HGSC-SET vs 9/27 (33.3%) HGSC Classic Morphology
- Pseudo-Endometrioid pattern most common in HGSC-SET
- 27/27 (100%) WT1 strong positivity
- 27/27 (100%) PAX8 positivity focal to diffuse
- 27/27 (100%) p53 mutational patterns: 16/27 (60%) p53 hyperexpression, 11/27 (40%) p53 complete loss
RESULTS: TUBAL PRECURSOR LESIONS

- **SET-HGSC** showed a lower association with **STIC** (p=0.02)
- **SCOUT** and **STIL** → no statistically significant difference
RESULTS: iTILs

- 40 CD8+ / 10 HPF cut-off
- SET morphology $\rightarrow$ strong association with increased iTILs ($p=0.0005$)
RESULTS: BRCA MUTATION AND HISTOLOGY

- 9/27 (33.3%) patients carried a BRCA mutation
- 2/9 (22.2%) variants of uncertain significance (VUS)

- Molecular BRCA test: FFPE & Fresh frozen tissue \(\rightarrow\) identical results

- SET morphology \textit{statistically tended} towards BRCA+ patients compared to BRCA- group (p=0.06)

- BRCA status became statistically irrelevant when VUS patients were excluded from BRCA mutated group.

- 7/9 (77.8%) pathogenic variants (P)
CONCLUSIONS

- **SET-HGSC** showed a statistically significant association with **increased iTILs**
- **STIC** was significantly more frequent in HGSC with **classic morphology**
- **SET morphology** tended towards **BRCA+** patients