Sex Cord-Stromal Tumors of the Ovary

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Sex Cord-Stromal Tumors (SCST)

Sex cord-stroma
- Granulosa cell
- Thecoma
- Fibroma
- Sertoli cell
- Sertoli-Leydig
- Steroid

Germ cells
- Dysgerminoma
- Yolk sac
- Embryonal carcinoma
- Choriocarcinoma
- Teratoma

Surface epithelium-stroma
- Serous
- Mucinous
- Endometrioid
- Clear cell
- Transitional cell
# Incidence & Survival Rates by Subgroups

**Table A. Incidence, survival and prevalence of cancers in EU27**

<table>
<thead>
<tr>
<th>CATEGORY AND SUBCATEGORIES</th>
<th>Incidence rate</th>
<th>New cases</th>
<th>Observed 5-yr survival</th>
<th>Relative 5-yr survival</th>
<th>Complete prevalence</th>
<th>Prevalent Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EPITHELIAL TUMOURS OF CORPUS UTERI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma and variants of corpus uteri</td>
<td>0.13</td>
<td>671</td>
<td>76.1</td>
<td>82.7</td>
<td>133,11</td>
<td>665,573</td>
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<tr>
<td>Squamous cell carcinoma and variants of corpus uteri</td>
<td>0.10</td>
<td>383</td>
<td>73.7</td>
<td>80.2</td>
<td>42.6</td>
<td>460,237</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma of corpus uteri</td>
<td>0.01</td>
<td>11</td>
<td>75.7</td>
<td>81.0</td>
<td>0.95</td>
<td>4774</td>
</tr>
<tr>
<td>Transitional cell carcinoma of corpus uteri</td>
<td>0.01</td>
<td>11</td>
<td>75.7</td>
<td>81.0</td>
<td>0.95</td>
<td>4774</td>
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<tr>
<td><strong>EPITHELIAL TUMOURS OF CERVIX UTERI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Squamous cell carcinoma and variants of cervix uteri</td>
<td>0.07</td>
<td>28</td>
<td>73.4</td>
<td>78.2</td>
<td>7.8</td>
<td>43,136</td>
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<td>8</td>
<td>70.0</td>
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<td>4</td>
<td>100.0</td>
<td>100.0</td>
<td>0.01</td>
<td>31</td>
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<tr>
<td><strong>MIXED EPITHELIAL AND MESENCHYMAL TUMOURS OF UTERUS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.04</td>
<td>2</td>
<td>66.7</td>
<td>72.3</td>
<td>2.3</td>
<td>157</td>
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<tr>
<td><strong>EPITHELIAL TUMOURS OF OVARY AND FALLOPIAN TUBE</strong></td>
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<tr>
<td>Adenocarcinoma and variants of ovary</td>
<td>0.82</td>
<td>403</td>
<td>71.5</td>
<td>77.0</td>
<td>42.9</td>
<td>25,926</td>
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<td>Mucinous adenocarcinoma of ovary</td>
<td>0.07</td>
<td>4</td>
<td>52.4</td>
<td>57.9</td>
<td>9.56</td>
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<td>Clear cell adenocarcinoma of ovary</td>
<td>0.01</td>
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<td>48.1</td>
<td>52.5</td>
<td>2.55</td>
<td>12,756</td>
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<td>Adenocarcinoma and variants of fallopian tube</td>
<td>0.01</td>
<td>1</td>
<td>100.0</td>
<td>100.0</td>
<td>0.01</td>
<td>31</td>
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<tr>
<td><strong>NON EPITHELIAL TUMOURS OF OVARY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mixed epithelial-mesenchymal tumors of ovary</td>
<td>0.04</td>
<td>2</td>
<td>82.0</td>
<td>86.0</td>
<td>1.98</td>
<td>9,917</td>
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<td>Sex cord tumours of ovary</td>
<td>0.01</td>
<td>1</td>
<td>75.0</td>
<td>80.0</td>
<td>0.49</td>
<td>2,479</td>
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<tr>
<td></td>
<td>0.01</td>
<td>1</td>
<td>75.0</td>
<td>80.0</td>
<td>0.49</td>
<td>2,479</td>
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<tr>
<td>Malignant immature teratomas of ovary</td>
<td>0.07</td>
<td>338</td>
<td>80.4</td>
<td>83.2</td>
<td>1.50</td>
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<tr>
<td>Germ cell tumours of ovary</td>
<td>0.07</td>
<td>374</td>
<td>83.7</td>
<td>84.5</td>
<td>2.24</td>
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<td><strong>EPITHELIAL TUMOURS OF VULVA &amp; VAGINA</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma and variants of vulva and vagina</td>
<td>1.91</td>
<td>9,571</td>
<td>47.0</td>
<td>60.9</td>
<td>15.34</td>
<td>76,689</td>
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<tr>
<td>Adenocarcinoma and variants of vulva and vagina</td>
<td>0.10</td>
<td>7</td>
<td>78.6</td>
<td>81.6</td>
<td>0.52</td>
<td>2,623</td>
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<td>Paget disease of vulva and vagina</td>
<td>0.05</td>
<td>25</td>
<td>78.0</td>
<td>80.0</td>
<td>0.47</td>
<td>2,350</td>
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<tr>
<td>Undifferentiated carcinoma of vulva and vagina</td>
<td>0.01</td>
<td>40</td>
<td>26.3</td>
<td>31.5</td>
<td>0.05</td>
<td>236</td>
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<tr>
<td><strong>TROPHOBLASTIC TUMOURS OF PLACENTA</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choriocarcinoma of placenta</td>
<td>0.02</td>
<td>118</td>
<td>89.6</td>
<td>90.0</td>
<td>0.86</td>
<td>4,297</td>
</tr>
<tr>
<td></td>
<td>0.02</td>
<td>118</td>
<td>89.6</td>
<td>90.0</td>
<td>0.86</td>
<td>4,297</td>
</tr>
</tbody>
</table>

*ICD-O3 code not available*
Classification of SCST

A. Granulosa-stromal cell tumors
   1. Granulosa cell tumors (GCT)
   2. Tumors in the thecoma-fibroma group
B. Sertoli-Leydig cell tumors (SLCT)
   1. Well-differentiated
   2. Of intermediated differentiation
   3. Poorly differentiated
   4. With heterologous elements
C. Gynandroblastoma
D. Sex cord with annular tubules
E. Unclassified
Sertoli-Leydig Cell Tumors (SLCT)

- 0.5% ovarian neoplasms
- Median age at diagnosis: 25 years
- 40% to 60%: Hirsutism or virilization
- Occasionally estrogen-related manifestation (isosexual pseudoprecocity)

Sex Cord Tumor (SCT) With Annular Tubules

- <1% SCST
- Median age at diagnosis: 27 years
- Sporadic or association with Peutz-Jeghers syndrome
- Germ line STK11 mutation (no somatic mutation)
SLCT: Molecular Patterns & Prognostic Factors

• **Somatic DICER-1 mutation** (gene encoding an RNase III endoribonuclease) in 60% of SLCT

• **Prognostic factors:**
  - Stage: Recurrence 12.7% stage I, 100% stage II-IV
  - Grade: Well diff OS = 100%, Poorly diff OS = 41%
  - Presence of mesenchymal heterologous elements or retiform component

OS, overall survival
Granulosa Cell Tumors

Epidemiology

• 1.5% of all ovarian tumors
• 3% to 7% of all ovarian cancer
• 70% of SCSTs
• Any age
• Perimenopausal and early postmenopausal (median age: 50-54 years)
• 5% premenarcheal
• 0.4-1.7 per 100,000 in developed countries
• 25% endometrial hyperplasia
• 5% to 10% endometrial cancer
Granulosa Cell Tumors
Diagnosis

Endocrine manifestations:

• **Childhood**: Isosexual precocious pseudopuberty

• **Reproductive age**: Menstrual irregularities/secondary amenorrhea, infertility, rarely virilization

• **Postmenopausal**: Abnormal vaginal bleeding
  – Endometrial hyperplasia 25%
  – Endometrial adenocarcinoma 5% to 10%
Diagnosis

• **Initial symptoms:** Pelvic pain, and menstrual irregularities

• **Imaging:** Pelvic ultrasound, and/or abdomino-pelvic computed tomography (CT-scan)

• **Tumor markers:** CA-125, inhibin B (secreted by GCTs) & antimüllerian hormone (AMH) specific for GCT in postmenopausal

• **The staging system** for ovarian SCTs is defined by the International Federation of Gynecology and Obstetrics (FIGO)
GCT Treatment

Surgery as primary treatment
• TAH/BSO + surgical staging
• Role of fertility-sparing surgery

Adjuvant treatment (?)
• Chemotherapy (CT)
• Radiotherapy (RT)
• Hormonal therapy (HT)

TAH/BSO, total abdominal hysterectomy bilateral salpingo oophorectomy
Conservative Surgery?

SEER database of 339 patients (01/1992 to 12/2001)¹
• 265 young patients (<50 years) with stage I-II
• 110 patients (54%) had conservative uterine-sparing surgery
• No outcome difference between women undergoing standard vs conservative surgery (95%)

Lauszus (Denmark) n = 181 (1962 to 2003)²
• 51 (33%) received conservative surgery
• Recurrences rate: 20% standard surg vs 31% conservative surg
• Death rate: 12% standard surg vs 19% conservative surg

Lymphadenectomy?

- MD Anderson:
  - N = 257 patients with SCST; relapse 45%; 2% N+

<table>
<thead>
<tr>
<th>Histology</th>
<th>N</th>
<th>No of Relapse</th>
<th>Positive Nodes at Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult GCT</td>
<td>178</td>
<td>85 (48%)</td>
<td>5</td>
</tr>
<tr>
<td>Juvenile GCT</td>
<td>27</td>
<td>14 (52%)</td>
<td></td>
</tr>
<tr>
<td>SLCT</td>
<td>31</td>
<td>9 (28%)</td>
<td>0</td>
</tr>
<tr>
<td>SCTAT*</td>
<td>6</td>
<td>4 (67%)</td>
<td>0</td>
</tr>
<tr>
<td>Mixed SCST</td>
<td>13</td>
<td>4 (31%)</td>
<td>1</td>
</tr>
<tr>
<td>Undifferentiated SCST</td>
<td>2</td>
<td>1 (50%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Disease-Specific Survival by Stage

Survival According to Residual Disease and Stage

Kaplan-Meier curve comparing overall survival for patients with presence or absence of residual disease.

26 patients
- 18 patients: Stage I
- 3 patients: Stage II
- 4 patients: Stage III
- 1 patient: Stage IV

Residual tumor was present in 5 patients.

Adjuvant Therapy in Stage I GCT

• Patients with stage I GST have a very low risk of recurrence (9%)
• No prognostic factors clearly identified beside stage
• No data that adjuvant treatment can improve disease-free survival (DFS) or OS
Adjuvant Therapy in Stage I GCT

• Patients with stage I GST have a very low risk of recurrence (9%)

1. Chemotherapy plays no role in the adjuvant setting. No data that adjuvant treatment can improve disease-free survival (DFS) or OS
Tumor Rupture

Preop rupture: 3/12 patients received CT
Intraop rupture: 4/9 patients received CT

Treatment of Advanced, Recurrent GCT
Recurrent GCT

• How frequent is relapse?
  – Rare (10%)

• When does it occur?
  – Median time 4-6 years; late recurrences 10-30 years post diagnosis can occur

• Where?
  – Upper abdomen (55% to 70%) and the pelvis (30% to 45%)

• Is it curable?
  – Long-term salvage rate <20%
  – Surgery plays the main role
Recurrent Disease Management

• Repeat debulking surgery should be considered in all patients

• Localized recurrence—consider radiation

  • Hormonal therapy

  • Chemotherapy
Hormonal Therapy in Ovarian GSTs: A Systematic Review

<table>
<thead>
<tr>
<th>Response</th>
<th>N = 31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>8 (25.8%)</td>
</tr>
<tr>
<td>Partial</td>
<td>14 (45.2%)</td>
</tr>
<tr>
<td>Stable</td>
<td>4 (12.9%)</td>
</tr>
<tr>
<td>Progressive</td>
<td>5 (16.1%)</td>
</tr>
</tbody>
</table>

Median PFS: 18 months (treatment period 1970-2013)

CR, complete response; DES, diethylstilboestrol; MPA, medroxyprogesterone acetate; PR, partial response
Anastrozole and letrozole, MPA, megestrol acetate alternating with tamoxifen and DES yielded most CR and PR

Median PFS: 18 months (treatment period 1970-2013)

CR, complete response; DES, diethylstilboestrol; MPA, medroxyprogesterone acetate; PR, partial response

Clinical Outcomes of Recurrent Ovarian GCTs Treated With Letrozole: A 10-Year Retrospective Case-Series of the Royal Marsden Hospital

- 47 patients
- 29 (63%) recurrent disease
- 16 patients received letrozole
- 50% received letrozole at 4° relapse
- Previous treatment: Platinum-based chemotherapy (50%), at least one surgery (75%) and HT (62.5%) with tamoxifen and/or goserelin
- RR (radiologic) 56.3% (n = 9); clinical benefit rate 100%; median PFS 21.3 months

HT, hormone therapy; RR, response rate
Is Chemotherapy Effective in GCTs?
# Chemotherapy in Advanced/Recurrent SCST

<table>
<thead>
<tr>
<th>Author</th>
<th>Chemo</th>
<th>No. Patients</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gershenson (1987)</td>
<td>CAP</td>
<td>8</td>
<td>63%</td>
</tr>
<tr>
<td>Pectasides (1992)</td>
<td>CAP</td>
<td>10</td>
<td>60%</td>
</tr>
<tr>
<td>Uygun (2003)</td>
<td>CAP</td>
<td>9</td>
<td>44%</td>
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## Chemotherapy in Advanced/Recurrent SCST

<table>
<thead>
<tr>
<th>Author</th>
<th>Chemo</th>
<th>No. Patients</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colombo (1986)</td>
<td>PVB</td>
<td>11</td>
<td>82%</td>
</tr>
<tr>
<td>Zambetti (1990)</td>
<td>PVB</td>
<td>7</td>
<td>66%</td>
</tr>
<tr>
<td>Pecorelli (1999)</td>
<td>PVB</td>
<td>38</td>
<td>61%</td>
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</table>

## Chemotherapy in Advanced/Recurrent SCST

<table>
<thead>
<tr>
<th>Author</th>
<th>Chemo</th>
<th>No. Patients</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gershenson (1996)</td>
<td>BEP</td>
<td>6</td>
<td>83%</td>
</tr>
<tr>
<td>Homesley (1999)</td>
<td>BEP</td>
<td>II look 38</td>
<td>37% CR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Measurable 25</td>
<td>40%</td>
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<tr>
<td>Pautier (2008)</td>
<td>BEP</td>
<td>20</td>
<td>90%</td>
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<tr>
<td>Van Meurs (2014)</td>
<td>BEP</td>
<td>9</td>
<td>22%</td>
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The Activity of Taxanes Compared With BEP in the Treatment of Sex Cord-Stromal Ovarian Tumors

<table>
<thead>
<tr>
<th>Newly diagnosed</th>
<th>Taxane Group</th>
<th>BEP Group</th>
<th>P</th>
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<tbody>
<tr>
<td>RR</td>
<td>82%</td>
<td>82%</td>
<td>NS</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>97.2</td>
<td>52+</td>
<td>.994</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>52+</td>
<td>46.1</td>
<td>.213</td>
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<table>
<thead>
<tr>
<th>Recurrent disease</th>
<th>Taxane Group</th>
<th>BEP Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>37%</td>
<td>71%</td>
<td>NS</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>7.2</td>
<td>11.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Phase II: Carbo-Paclitaxel or BEP in Advanced or Recurrent SCST

◆ **Primary objectives:**
  - To assess the activity of paclitaxel and carboplatin 3 weekly with respect to PFS (using BEP as a reference) in newly diagnosed advanced or recurrent chemonaive ovarian SCST

◆ **Secondary objectives:**
  - Toxicity
  - OS
  - ORR

NCT104522 ClinicalTrials.gov
## Compilation of Results of Chemotherapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No.</th>
<th>RR, %</th>
<th>Duration, Months</th>
<th>Toxic Death</th>
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<tbody>
<tr>
<td>CAP</td>
<td>30</td>
<td>73</td>
<td>5-162</td>
<td>0</td>
</tr>
<tr>
<td>BEP</td>
<td>92</td>
<td>72</td>
<td>5-165</td>
<td>2</td>
</tr>
<tr>
<td>PVB</td>
<td>56</td>
<td>70</td>
<td>2-99</td>
<td>3</td>
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</table>
## Compilation of Results of Chemotherapy

<table>
<thead>
<tr>
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</tr>
<tr>
<td>PVB</td>
<td>56</td>
<td>70</td>
<td>2-99</td>
<td>3</td>
</tr>
</tbody>
</table>

2. Chemotherapy is effective in the treatment of advanced/recurrent GCT
Surveillance (GCIG Recommendations)

- **Physical examination and tumor markers** every 4 months for the first 2 years, every 6 months during year 3rd, 4th, and 5th or until progression.
- **Pelvic ultrasound** need to be performed every 6 months in those patients who have undergone fertility sparing surgery.
- **CT-scan** of the abdomen and pelvis if clinically indicated.
- The use of PET-scan for follow up is not well established yet.
- Due to very late relapse, some experts recommend prolonged follow up until 10 or 15 years.
Inhibin
AIMS:

1) To Investigate the role of Inhibin B as GCTs recurrence marker

2) To study the relationship between Inhibin B levels and relapse dimension to planning imaging and eventually surgery approach.

SAMPLE

52 patients followed at the European Institute of Oncology of Milan from January 1996 to December 2015

we selected only patients that have performed a serial Inhibin B dosage, during their follow-up

39 patients
RESULTS...

Role of Inhibin B as marker to detect recurrence:

Post-menopausal patients

Patient status (0= disease free; 1= with relapse)
RESULTS …

CT scan & Inhibin B dosage…

Post-menopausal patients
Targeted Therapy
Response after 11 months of treatment. Prior treatment included bleomycin with cisplatin and etoposide, doxorubicin, tamoxifen, carboplatin, leuprolide, topotecan, paclitaxel, and an experimental medication.

Efficacy and Safety of Bevacizumab in Recurrent SCST
Results of a Phase II Trial of the Gynecologic Oncology Group

- Bevacizumab 15 mg/kg every 3 weeks
- 36 patients:
  - 6 PR (16.7%)
  - 28 SD (77.8%)
  - 2 PD (5.6%)
- Median PFS: 9.3 months
- Median OS not reached with a median follow-up of 32.5 months
- G4 toxicities: Hypertension and proteinuria
- Lower inhibin A and B values predictive of response

ALIENOR DESIGN: 60 Patients

Population:
Patients with a histologically confirmed diagnosis of ovarian SCST in relapse after a platinum-based chemotherapy.
Mutation of *FOXL2* in GCTs of the Ovary

- Adult-type GCTs 97% (86/89)
- Thecomas 21% (3/14)
- Juvenile-type GCTs 10% (1/10)
- No mutation in 49 SCSTs of other types and 329 unrelated ovarian or breast tumors

**Mutant *FOXL2* is a potential driver in the pathogenesis of adult-type GCTs**

FOXL2 IHC and Mutational Analysis as a Standard Diagnostic (Kommoss et al. *Mod Pathol*. 2013)

Confirmation of FOXL2 aGCT specific c.402C>G mutation by Sanger Sequencing


TaqMan-based digital mutation assay for FOXL2 aGCT specific c.402C>G mutation
FOXL2 Mutations in Adult-Type GCT

- Present in 95% of cases usually heterozygous
- Not seen in juvenile type GCT
- If mutation can be targeted that approach will potentially work for most aGCT

- It may also be useful as a monitoring tool

Case 3 – 7 months post primary diagnosis
1.4% (75/5463)
Mutant FOXL2
275 non-epithelial ovarian tumors (Germ cell = 35, SCST = 212)

- Comprehensive tumor profiling using IHC, ISH, and gene sequencing detected mutations in 99.6% of patients.
- SCSTs appears to be a disease associated with frequent loss of PTEN, RRM1, and TUBB3 tumor suppressors, as well as endocrine receptor over expression.
- OGCTs may have a higher percentage of TP53 mutations than SCSTs, suggesting that genomic chaos is an important mechanism in the pathogenesis of these tumors; this interesting hypothesis will require further validation.

IHC, immunohistochemistry; ISH, in situ fluorescence; OGCT, ovarian germ cell tumors
275 non-epithelial ovarian tumors (Germ cell = 35, SCST = 212)

- Comprehensive tumor profiling using IHC, ISH, and gene sequencing detected mutations in 99.6% of patients.

Identification of these changes can provide a rationale for treatment options not routinely considered or those associated with targeted therapies and warrant future clinical trials in this cancer type.

OGCTs may have a higher percentage of TP53 mutations than SCSTs, suggesting that genomic chaos is an important mechanism in the pathogenesis of these tumors; this interesting hypothesis will require further validation.

IHC, immunohistochemistry; ISH, in situ fluorescence; OGCT, ovarian germ cell tumors
Chemotherapy and GCT?

• Is it effective? YES
• When? In metastatic/recurrent GCT, not as adjuvant
• Which? Platinum-based: BEP or Carboplatin/paclitaxel
• Targeted agents? Bevacizumab, PTEN, FOXL2
Stage I SCST: Standard Treatment

- **Surgery**
  - TAH/BSO + staging is the standard treatment, lymphadenectomy can be omitted in the absence of enlarged nodes
  - Fertility-sparing surgery is recommended in young women
  - Surgery may be performed through a mini-invasive approach

- **Adjuvant treatment**
  - There is no evidence that adjuvant treatment improves survival in stage I
  - Consider platinum-based chemotherapy for patients with GCTs stage IC or SLCTs poorly differentiated or with heterologous elements
Stage II-IV SCST: Standard Treatment

- **Surgery**
  - Maximal debulking surgery must be attempted in order to remove all macroscopic tumor in case of extensive disease

- **Adjuvant chemotherapy**
  - Platinum-based chemotherapy
  - Possible regimens include PEB or carboplatin-paclitaxel
Relapsed SCST: Standard Treatment

• **Surgery**
  - Surgery is a critical component of successful management. Surgical resection should be attempted whenever feasible. Repeated cytoreductive surgeries are often needed in case of multiple relapses

• **Adjuvant chemotherapy**
  - Platinum-based chemotherapy with BEP or carboplatin/paclitaxel should be considered if not previously administered or after a platinum-free interval >1 year
  - Possible alternative regimens include: Weekly paclitaxel, VAC, paclitaxel-ifosfamide
  - Consider clinical trials
  - Consider no treatment or hormonal treatment in case of isolated lesions, radically resected
SCST: Future Research

• **Stage I**
  – How to identify patients at high risk for relapse?
    Since relapses are almost incurable, this question represents a priority

• **Advanced/recurrent**
  – Observation vs adjuvant therapy in case of complete resection
  – Hormonal therapy if no residual tumor?
  – Which chemotherapy: BEP or carboplatin/paclitaxel? (Phase II ongoing) Single agent?
  – Targeted therapy? Which? Alone or with chemotherapy?
  – Role of radiotherapy?