Non epithelial ovarian tumors

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Rare gynecologic malignancies (R-GYN):

- Defined as <6/100,000/year\(^1\)
- Represent >50% of gynecologic cancers\(^2\)
- Involve >30 histologic subtypes\(^2\)

### Rare Epithelial Gynecologic Cancers

- Cervical adenocarcinoma
- Ovarian low grade
- Ovarian transitional cell/Brenner tumor
- Ovarian squamous
- Endometrial papillary serous/squamous
- Vulvar and Vaginal cancers
- Clear cell cancers
- Carcinosarcomas
- Mucinous cancers
- Small cell cancers

### Rare Non-epithelial Gynecologic Cancers

- All Gyn Sarcoma
- Sex cord tumors
- Germ cell tumors
- Sarcoma

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1. [http://www.rarecare.eu](http://www.rarecare.eu)
2. G Trama et al Eur J Cancer 2015

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Most important challenges

• To identify the right diagnosis
• To define the prognosis
• To define the best “standard” of care
  – Radical surgery versus FSS
  – Adjuvant therapies for who
  – The best option in relapse
• To organize national management
• To develop international collaboration
Focus on the most “frequent” rare ovarian tumors & systemic treatments

• Rare ovarian non epithelial tumors:
  – Germ cell tumors
  – Sex cords stromal tumors
  – Small cell carcinoma

• Rare epithelial carcinoma
  – LGSC
  – Mucinous carcinoma
  – Clear cell carcinoma
  – Carcinosarcoma
Ovarian Germ Cell Tumors

• 5% of all ovarian malignancies
• Usually in adolescents or young adults
• 60-70% STAGE 1 at diagnosis, despite very aggressive
• Bilateral involvement is rare (except dysgerminoma)
• Highly chemo-responsive and curable if properly treated
• No randomized trials in OGCT, extrapolation from randomized trials in testis cancer
Dysgerminomas

- Most patients Stage 1a- surveillance appropriate
- 15-20% will relapse, mostly, in 1-2 years from diagnosis
- The recurrent tumour is biologically identical to newly diagnosed cancer
- Excellent salvage rate with chemotherapy

Non-Dysgerminomas

- Accurate monitoring of tumor markers (AFP and βhCG)
- Worsen prognosis
- Adjuvant treatment with BEP x 3-4 cycles (according to stage)
Standard Treatment

Based on a combination of the principles of management of male germ cell tumours and epithelial ovarian cancer

• Surgery → **fertility sparing surgery** for majority! Also for advanced disease
• Surveillance
• Chemotherapy
• (Radiotherapy)

Prognostic factors are not well characterised

• Stage; elevation of βHCG and AFP/ poor marker decline; age >45; histology, dysgerminoma v non dysgerminoma or yolk sac

Murugaesu N. JCO October 20, 2006 vol. 24 (30)4862-4866
Primary Surgery Goals

• Definition of histology
• Fertility-sparing approach even in advanced stages

• The contralateral ovary → NO
• Adequate staging : is systematic lymphadenectomy needed → No
  – Lymphadenectomy does not affect survival even in node + patients (Madhi et al 2011)

• Complete tumor resection → think to NACT
  – Advanced disease : surgery may be limited to avoid increased morbidity or a long postoperative recovery with a subsequent delay in chemotherapy
# Germ Cell Tumors: Standard Chemotherapy

- **BEP Protocol**

<table>
<thead>
<tr>
<th>Jour</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>8</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatine 20 mg/m² IV</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etoposide 100 mg/m² IV</td>
<td>#</td>
<td>#</td>
<td>#</td>
<td>#</td>
<td>#</td>
<td></td>
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</tr>
<tr>
<td>Bléomycine 30 mg IV</td>
<td>〇</td>
<td>〇</td>
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<td></td>
</tr>
</tbody>
</table>

- Early start after surgery
- DI respect ++++
- Alternative adjuvant therapy for low risk disease
  - 2 cycles BEP or EP (dysgerminoma)
  - Dysgerminoma: Carboplatin/Etop or Carboplatin AUC 7 x 2
  - JEB (carboplatin AUC8, etoposide 500mg/m², bleomycin 15/m² D1)

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How important is Bleomycin?

- Bleomycin should only be omitted if contra-indications when 4 cycles of EP can be used
- Inconsistent findings from trials of 4 EP vs 3 BEP
- De La Motte Rouge et al Gyn Oncol 2016, 2/3 relapse after BEP stopped @C1 for Yolk Sac tumours
Long-term toxicity and Late Effects

- Pulmonary toxicity 3%; decreased DLCO 20%
- AML 0.2-1%
- Neuropathy 20%
- Raynauds 20%
- Tinnitus 24%
- High tone hearing loss 70%
- Gonadal dysfunction 16-30%
- Cardiovascular disease/Hypertension

50%-60% of young women can be spared the potential morbidity of chemotherapy with successful outcome
Surveillance for all Stage I?

To avoid acute and long term toxicity

- Charing Cross Stade Ia series: 22% dysgerminomas and 36% of non-dysgerminomas relapsed. 10/11 cured with chemotherapy.
- COG (0-16 yrs & poor prognosis histology) 12/25 relapsed and 11/12 were salvaged
- MITO 9 IT (gr1-3, stade Ia-Ic): 4/19 relapsed all salvaged in surveillance vs 2/9 in CT group
- MaGIC IT (98 ped vs 81 adult) PFS & OS ≈ but diff pop (1DOD vs 6 DOD)
- French group (n= 257) Relapse YST 3/3 vs 2/22 with adj CT, IT : 3/15 vs 2/22 with Adj CT
  - No difference for OS (96,3 versus 97,8%) ESMO 2018
## Active Surveillance programme

**ESMO 2018**

### Table 5. Active surveillance programme in the management of ovarian GCTs

<table>
<thead>
<tr>
<th>Time period</th>
<th>Examination</th>
<th>Pelvic US</th>
<th>Tumour markers</th>
<th>Chest X-ray</th>
<th>CT chest abdomen pelvis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st year</td>
<td>monthly</td>
<td>2 monthly</td>
<td>every 2 weeks (first 6 months) and then monthly</td>
<td>2 monthly</td>
<td>1 month&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 months&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2nd year</td>
<td>2 monthly</td>
<td>4 monthly</td>
<td>2 monthly</td>
<td>4 monthly</td>
<td>12 months</td>
</tr>
<tr>
<td>3rd year</td>
<td>3 monthly</td>
<td>6 monthly</td>
<td>3 monthly</td>
<td>6 monthly</td>
<td></td>
</tr>
<tr>
<td>4th year</td>
<td>4 monthly</td>
<td></td>
<td>4 monthly</td>
<td>8 monthly</td>
<td></td>
</tr>
<tr>
<td>5th to 10th year</td>
<td>6 monthly</td>
<td></td>
<td>6 monthly</td>
<td>annually</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>If not carried out preoperatively.

<sup>b</sup>If clear—second look laparoscopy if inadequate staging/immatue teratoma.

CT, computed tomography; GCT, germ cell tumour; US, ultrasound.

Suggested surveillance programme based on Mount Vernon proposal. Modified from [32] with permission.
Active Surveillance requirements

- Patients should be surgically staged
- Pathology should be confirmed by a gynecologic oncology pathologist
- Normalized markers post surgery
- Counseling about recurrence risk
- Reliable patient
2\textsuperscript{nd} line Chemotherapy – Relapsed disease

Outcome very poor: 10% long term survival in Charing Cross series

1. Which salvage regimens?
   – TIP: Paclitaxel (250mg/m\textsuperscript{2} over 3 hours, d1), Ifosfamide (1.2g/m2 + mesna d1-5), Cisplatin (20mg/m\textsuperscript{2}, d1-5)
   – VeIP (Vinblastine, ifosfamide, cisplatin)
   – Platinum refractory (<6 weeks): VAC- Vincristine, Actinomycin D, Cyclophosphamide, gemcitabine oxaliplatine, oral VP16

2. What is the role of High Dose Chemotherapy?
   → For all? At relapse? As intensification of first line therapy?
   – 4/13 durable CR with tandem high dose carboplatin/etoposide
   – Sequential GemDMC/ICE + bevacizumab 55.8% RFS but 10% mortality (males)

3. What about surgery? Need to be completed

Conclusions

✓ Paradigm of a curable malignancy

✓ Focus on reduction of toxicity in low risk and improving outcomes in high risk, relapsing patients

✓ Surveillance has not been standard of care in ovarian germ cell tumors but new evidences are coming for stage I
Sex Cord Stromal Tumours

- 7% of all ovarian cancer & Peak age 50 years
- Endocrine manifestations (oestrogen secretion 70%)
- Endometrial hyperplasia (25%) or endometrial carcinoma (5 – 10%)
- Recent findings on mutated genes: FOXL2 for adult Granulosa & DICER1 for Juvenile Granulosa & Sertoli Leydig
Sex cord tumors
Histology (WHO classification 2014)

A) Pure sex cord tumors
1. Adult Granulosa cell tumor
2. Juvenile Granulosa cell tumor
3. Sertoli cell tumors (benign)
4. Sex Cord with anular tubules

(70%)

B) Mixed sex cord stromal tumors
1. Sertoli Leydig well differentiated (androgenic, secretory in 60% of the cases)
2. Sertoli Leydig Moderately differentiated with heterologous elements
3. Sertoli Leydig Poorly differentiated with heterologous elements
4. Sertoli Leydig Retiform with heterologous elements
5. Sex cord-stromal tumors NOS

20%

C) Pure stromal tumors
1. Fibrosarcoma
2. Steroid cell
Granulosa Cell T, Clinical prognostic factors

- **Adult GCT**
  - FIGO Stage:
    - DFS at 5 years 95% (I-II) vs 59% (III-IV)
  - Age (more than **50 years old**)
    - DFS at 5 years 93% (≤ 50y) vs 84% (> 50y) (Zhang M et al. Gynecol Oncol 2007)
  - Intra peritoneal tumor rupture (Schneider, JCO 2004 & Wilson 2015)
    - IC2: 5/6 pts relapsed vs. IC1: 10/21 pts relapsed
    - Relapse stage IA 24% vs IC 43% (p<0.01)
  - Quality of the surgical staging (Clenck, ESGO 2019)

- **Juvenile GCT**
  - **Stage** is the major pronostic factor
  - Role of tandem duplication AKT1? (60% pts) (L Bessière, EBioMedecine 2015)
Adult Granulosa cell tumor
Molecular features & prognostic factors

- **FOXL2** mutation (missense mutation (402C -> G) in the FOXL2 gene (Adult form) (Shah SP, NEJM 2009)
- Utility of **FOXL2** immunostaining & mutation in all adult granulosa cell tumors but absent in other pure subtypes (D Maillet et al, 2013, McCluggage 2014, McConéchy JNCI 2016)
- More a diagnosis tool than a prognostic factor

![Diagram](image_url)
Sertoli Leidig Stromal tumours, Prognostic factors

Prognostic factors (Sigismondi C, Gynecol Oncol 2012):

• Stage: recurrence 12.7% st.I compared to 100% st. II-IV
• Grade: Well diff. OS = 100%, Poorly diff. OS = 41%
• Presence of mesenchymal heterologous elements or retiform component
• DICER1? (R Rimock, et al Histopathology 2016)

(ESMO CPG’s 2018, GCIG guidelines 2014)
Surgical therapy

- **Surgery, corner stone of treatment including**
  - Surgical staging:
    - infracolic omentectomy,
    - biopsy of the diaphragmatic peritoneum, paracolic gutters, pelvic peritoneum
    - peritoneal washings
  - Bilateral salpingo oophorectomy & total hysterectomy
  - Fertility sparing surgery (+ uterine curettage for GCT)

- **MTB: The most 4th questions**
  - Conservative – hysterectomy - re staging – lymphadenectomy

  Young age & early stage IA/IC1
Adjuvant Therapy in Stage IA?

• Chemotherapy:
  – Stage IA Granulosa cell tumor have a very low risk of recurrence (9-25%)
    • Effect on outcome not proved
    • After conservative surgery no data
  – Stage IA Sertoli Leydig stromal tumours
    • Adjuvant therapy only for Poorly differentiated or with heterologous elements

• Radiotherapy:
  – In retrospective series there was no observed benefit to adjuvant irradiation

• Hormonal therapy no data

(ESMO CPG’s 2018, GCIG guidelines 2014)
Surveillance for stage IC?

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (IC)</th>
<th>Relapse rate</th>
<th>Adj CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>MITO9</td>
<td>IC, n = 40, (45% incomplete staging)</td>
<td>35%</td>
<td>mixed</td>
</tr>
<tr>
<td>Schneider</td>
<td>IC1, n = 12</td>
<td>0%</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>IC2-3, n = 9</td>
<td>44%</td>
<td>50%</td>
</tr>
<tr>
<td>Sun</td>
<td>IC, n = 45</td>
<td>29%</td>
<td>n = 2</td>
</tr>
<tr>
<td>Meisel</td>
<td>IC, n = 22</td>
<td>5%</td>
<td>no</td>
</tr>
<tr>
<td>Wilson</td>
<td>IC, n = 46</td>
<td>IC1 43%, IC2 80%</td>
<td>no</td>
</tr>
<tr>
<td>Wang 2018</td>
<td>IC1, n = 34</td>
<td>27%</td>
<td>9/28 relapsed without Adj CT</td>
</tr>
<tr>
<td></td>
<td>IC2-3, n = 26</td>
<td></td>
<td>7/32 with Adj CT</td>
</tr>
</tbody>
</table>

- Must be rigorous, only after complete staging by an experienced team
- For an extended period
- Real benefit of Adj CT stage IC2-3 need to be confirmed
Chemotherapy for Stage II to IV disease

- Platinum based chemotherapy should be proposed
- Response rate for chemotherapy in the literature 44%-83% (advanced and recurrent disease)
  - Most frequent platinum based regimen: BEP (3 to 4 cycles)
  - Options: carboplatin-paclitaxel X 6

(Brown J., JCO 2004), (ESMO guidelines 2012)
ESMO guidelines 2018
## Sex Cord Stromal tumors, Risk of relapse

<table>
<thead>
<tr>
<th>AUTHORS</th>
<th>Nb cases</th>
<th>Nb rec.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz</td>
<td>37</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Stenwig</td>
<td>118</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>Evans</td>
<td>118</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>Ray-Coquard</td>
<td>70</td>
<td>19</td>
<td>27</td>
</tr>
<tr>
<td>Chan</td>
<td>83</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>Wilson</td>
<td>160</td>
<td>51</td>
<td>32</td>
</tr>
<tr>
<td>Mc Conechy</td>
<td>336</td>
<td>140</td>
<td>41</td>
</tr>
<tr>
<td><em>mtFOXL2</em>+</td>
<td>256</td>
<td>90</td>
<td>35</td>
</tr>
<tr>
<td><em>No GCT</em></td>
<td>63</td>
<td>43</td>
<td>71</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>780</strong></td>
<td><strong>280</strong></td>
<td><strong>36%</strong></td>
</tr>
</tbody>
</table>

*Survival after relapse: 13 to 27% (interval 2 to 23 years)*

**Options**
- Surgery
- Chemotherapy
- Hormonal therapy
- Targeted therapies
Relapse

Relapse after initial treatment without CT:
- Debulking surgery & repeated cytoreductive surgeries whenever possible
- Platinum based chemotherapy

Additional treatment after CT failure:
- Debulking surgery & repeated cytoreductive surgeries whenever possible
  - Median PFS1 (7 years!) median PFS2 (10 years!)
  - No place for CC1 or CC2 surgery nor HIPEC!
- Chemotherapy (CAP, wPaclitaxel, VAC, etoposide, bevacizumab, etc. ...)
- Radiation therapy in selected cases
- Hormonal therapy for AGCT (anti aromatase, LH-RH inh, tamoxifen, progestin)

(ESMO CPG’s 2018, GCIG guidelines 2014)
New data from ASCO 2018

- Banerjee et al, PARAGON trial Anastrozol for metastatic aGCT (n = 41 pts)

Clinical Benefit Rate at 3 months (RECIST/Inhibin) = 80.0% (95% CI 65.2% - 89.5%)

Response at 3 months (RECIST/Inhibin):
- Partial Response = 1 (2.5%)
- Stable Disease = 31 (77.5%)
- Progressive Disease = 8 (20.0%)
- Median PFS was 8.6 m (95% CI 5.5 – 13.5m)
- Best response (RECIST) partial response (10% n=4)
- 25 (63%) patients were progression free at 6 months
- 2 patients remain on treatment at 14.8 and 53.5 months
Rational for Angiogenesis

- Pre clinic data
  - GCT are highly vascularized
  - Expression of VEGF & VEGFr
  - VEGF signaling is required for survival of aGCT in vitro
  - VEGF induces tumor progression in vivo model

- GOG 251: Phase II Trial of Bevacizumab for Recurrent Sex Cord-Stromal Tumors of the Ovary
  - Bevacizumab 15 mg/kg IV Q. 21d for pts. with measurable disease
  - N = 36, previous line of CT = 2
  - RR 17%, SD 78%, PD 6%
  - Median PFS 9.3 months
  - Median OS not reached
  - Safe regimen

A Farkkila, JECM 2011, Tsoi et al, Trans Oncol 2013
J Brown et al, Cancer 2013
**ALIENOR trial**  A randomized, open label, phase II trial of bevacizumab plus weekly paclitaxel followed by maintenance with bevacizumab monotherapy versus weekly paclitaxel followed by observation in patients with relapsed ovarian sex-cord stromal tumors

**Population**
Patients in relapse with an ovarian sex-cord stromal tumor, histologically confirmed, previously treated by platinum-based chemotherapy.

**Main Objective**
Clinical benefit (non progression after 6 months)

**Arm A**
- Paclitaxel 80mg/m², IV, at J1, J8 and J15 every 4 weeks
- Bevacizumab 10mg/kg, IV, D1 and D15

**Arm B**
- Observation
- Bevacizumab 15mg/Kg, Every 3 weeks
- Paclitaxel 80mg/m², IV, at J1, J8 and J15 every 4 weeks

**N = 60 pts**

Ray-Coquard et al, ESMO 2018
## Response and duration of response

<table>
<thead>
<tr>
<th></th>
<th>Control Arm&lt;br&gt;N=32</th>
<th>Experimental Arm&lt;br&gt;N=27</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective Response rate</strong></td>
<td>25.0% (8 / 32)</td>
<td>44.4% (12 / 27)</td>
</tr>
<tr>
<td><strong>95% confidence interval</strong></td>
<td>[11.5% ; 43.4%]</td>
<td>[25.5% ; 64.7%]</td>
</tr>
<tr>
<td><strong>Best overall response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0 / 32 (0.0%)</td>
<td>2 / 27 (7.4%)</td>
</tr>
<tr>
<td>PR</td>
<td>8 / 32 (25.0%)</td>
<td>10 / 27 (37.0%)</td>
</tr>
<tr>
<td>SD</td>
<td>17 / 32 (53.1%)</td>
<td>12 / 27 (44.4%)</td>
</tr>
<tr>
<td>PD</td>
<td>7 / 32 (21.9%)</td>
<td>3 / 27 (11.1%)</td>
</tr>
<tr>
<td><strong>Median Response duration</strong></td>
<td>18 months (7.1 – 22.6)</td>
<td>15.2 months (6.6 – 22.5)</td>
</tr>
</tbody>
</table>
Progression free survival & Conclusions

- This is the 1st randomized clinical trial in relapsed SCTs run at the worldwide level demonstrating that randomized trials are feasible in rare ovarian tumors with the help of a strong international collaboration (GCIG & ENGOT)

- Addition of bevacizumab to weekly paclitaxel regimen increases ORR from 25.0% to 44.4% with manageable toxicity, but does not improve PFS, and TSST of relapsed STCs in this trial

- wPaclitaxel performed very well compared to historical data with paclitaxel 3W, bevacizumab alone, other CT regimens, or anastrozol (PARAGON trial)
Summary SCT

• **1st line therapy**
  - Fertility sparing surgery for early stage
  - Radical surgery for advanced disease & IC2-3
  - Postoperative chemotherapy should be discussed for
    - aGCT st. II-IV & residual disease
    - Sertoli Leydig undifferentiated or heterologous elements
  - Expert review & molecular biology → yes !
  - Expert Multidisciplinary Tumor Board → yes!

• **Relapse**
  - Repeat surgical resections whenever feasible
  - Hormonal therapy in selected cases (AGCT), which one?
  - Chemotherapy options: weekly paclitaxel is the standard post platine ...
  - Clinical trial & translational research!

Level of Evidence IIIC or D!
Small Cell Ovarian Carcinoma HT

- Extremely rare (6 to 12 per year in France)
- Inactive mutation SMARCA4 (*Nat genetics* 2014): SCCO Hypercalcemic type = rhabdoid tumor family
  - Key role for SWI/SNF chromatin-remodeling complex.
- Young adult (median age 24 years)
- Hypercalcemia in 2/3 of pts & stage > IA for more 50% of patients
  - Prognostic factors: stage (st I, 55% 5y OS, st IV 0%) age > 30 y, calcium level
- **Treatment**
  - Radical surgery, platinum based chemotherapy & pelvic radiation
- **Questions**
  - HDCT impact
  - Impact of pelvic RT
  - New drugs to target SMARCA4 deficiency

*N Chiannikulchai, Annals Oncol 2017; Reed, Pautier et al, GCIG guidelines 2015*
**scco Hypercalcemic Type (SccOht)**

**Influence of treatment modality on outcome**

*In Stage I*

- Surgery alone is not adequate in stage I
- Addition of RT to CT did not improve OS
- 100% OS when High-dose chemo (HDC) is added to surgery + chemo/RT (only 9 patients)

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L. Witkowski et al. Gynecologic Oncology 2016; 141: 454–460
**SCCO Hypercalcemic Type (SCCOHT)**

**Stage I management**

- **ADJUVANT CHEMOTHERAPY**

<table>
<thead>
<tr>
<th>16 patients</th>
<th>N</th>
<th>Relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPCBAE</td>
<td>6</td>
<td>1/6</td>
</tr>
<tr>
<td>EP</td>
<td>5</td>
<td>5/5</td>
</tr>
<tr>
<td>TC</td>
<td>1</td>
<td>0/1</td>
</tr>
<tr>
<td>No adjuvant</td>
<td>2</td>
<td>2/2</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>2/2</td>
</tr>
<tr>
<td>Total</td>
<td>10/16 (62.5%)</td>
<td></td>
</tr>
</tbody>
</table>

VPCBAE: Vinblastine, cisplatin, cyclophosphamide, bleomycin, doxorubicin, and etoposide

scco hypercalcemic type (sccoht)

influence of treatment modality on outcome

in stage ii-iv

• 71% os when hdc is added to surgery + chemo/rt (only 19 patients; cr required)
• only 25% who received chemo alone are alive at 5 years
• addition of rt to chemo did not improve os (p 0.19)?

l. witkowski et al. gynecologic oncology 2016; 141: 454–460
Stage I-II

- TAH/BSO /staging [IV, A]
- Adjuvant ChT (cisplatin/etoposide based) [III, B]
- High-dose ChT + ASCT [II, C]
- Pelvic RT [IV, C]

Stage III-IV

- TAH/BSO /staging [IV, A]
  - Debulking feasible
    - yes: Debulking
    - no: Neoadjuvant ChT [IV, C]
- Adjuvant ChT (cisplatin/etoposide based) [III, B]
- High-dose ChT + ASCT [II, C]
- Pelvic RT [IV, C]

RELAPSE: Cyclophosphamide/doxorubicin/vincristine [V, B] Topotecan [V, C]
Phase I trial
SCCOHT
Clinical trials
Future directions based on Molecular Analyses

• SMARCA4 loss in SCCOHT is associated with cyclin D1 deficiency and reduced CDK4 expression - Xue YB et al Nat Commun 2019
  • CDK4/6 inhibitor trials in planning stages
  • EZH2 inhibitor trials – results of trials pending
• Immunotherapy trials
  Anti-PDL1 Ab - 4 responses (relapsed dis) 1x PR 6mo, 3 x CR> 1.5 yr Immunogenic environment
  • SCCOHT is a monogenic disease and consequently displays low TMB
  • 4 Cases of response to anti-PD-1 immune-therapy have been reported
  • A study of 11 SCCOHT tumors has shown PD-L1 expression, T cell and TAM infiltration

Jelinic et al JNCI 2018
Negative spiral for rare cancers

Rare Gynecological cancers

- No financial supports
- No interests from Agencies & Pharma
- No improvements for survival over time
- No innovations
- Few knowledge
- No evidence based Medicine → no Standard of Care
- No clinical trials

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How to change the future?

- New drugs/innovations for rare ovarian patients (1st line or relapse)

- GCIG & new collaborations with ESGO, Euracan for Guidelines & clinical research
  - To fix standard of care in 1st line & relapse
  - To highlight the need for investigational treatments
  - New prognostic factors including molecular factors

- New organizations for ‘routine’ management
  - Dedicated national rare cancer network (eg French model)
    - Education for physicians, care givers and public
    - Motivate Patients advocacy group
  - European network for rare cancer (ENGOT, ESMO, ESGO, ESO, EURACAN)
  - International collaboration (GCIG)
Alienor is the first international multicentric prospective randomized trial achieved in SCTs

The French National Network dedicated to Rare gynecologic Malignant Tumors (www.ovaire-rare.org)

Rare Tumor committee engagement
Executive Committee support
Annual satellite meetings

ALIENOR trial
A randomized, open label, phase II trial of bevacizumab plus weekly paclitaxel followed by maintenance with bevacizumab monotherapy versus weekly paclitaxel followed by observation in patients with relapsed ovarian sex-cord stromal tumors

Arm A
Arm B
Observation
Standard treatment
PD

N = 60 pts

Make it possible!
Updated GCIG/ESGO guidelines

- 2 chairs + 8/12 experts from each group (designed by each group)
- 1 pathologist from different groups for each guidelines
- 1 methodologist from ESGO (François Planchamp for bibliography research and design)

### Coordinator Group

<table>
<thead>
<tr>
<th>Condition</th>
<th>Coordinator</th>
<th>Group</th>
<th>Co-Coordinator</th>
<th>Group</th>
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<tbody>
<tr>
<td>Uterine carcinosarcoma</td>
<td>Ketta Lorusso</td>
<td>MITO</td>
<td>Ronnie Shapira-Frommer</td>
<td>ISGO</td>
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<td>Uterine LMS</td>
<td>Jae-Weon Kim</td>
<td>KGOG</td>
<td>Ana Oaknin</td>
<td>GEICO</td>
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<td>Sex cord tumour</td>
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<td>GINECO</td>
<td>Philipp Harter</td>
<td>A GO</td>
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<td>Germ Cell tumour</td>
<td>Nicoletta Colombo</td>
<td>MaNGO</td>
<td>Oleysa Solheim</td>
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<td>Cancened teratoma</td>
<td>Ros Glasspool</td>
<td>SGCTG</td>
<td>Christian Marth</td>
<td>A-AGO</td>
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<td>Ovarian small cell carcinoma</td>
<td>Clare Scott</td>
<td>ANZGOG</td>
<td>Patricia Pautier</td>
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<td>Mucinous carcinoma</td>
<td>Jonathan Ledermann</td>
<td>NCRI</td>
<td>Jubilee Brown</td>
<td>GOG-F</td>
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<td>Ovarian clear cell carcinoma</td>
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<td>GEICO</td>
<td>Keiichi Fujiwara</td>
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<td>Trophoblastic diseases</td>
<td>Michael Seckl</td>
<td>ISSTD</td>
<td>Leon Massuger</td>
<td>EORTC</td>
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<td>Low grade serous carcinoma</td>
<td>David Gershenson</td>
<td>GOG-F</td>
<td>Charlie Gourley</td>
<td>SGCTG</td>
</tr>
</tbody>
</table>

### Adjuvant therapy

**Stage I**

- Sertoli Leydig tumors (except stage I with poorly differentiated or with heterologous elements)

**Stage IA/B - C1**

- Complete initial staging

**Stage IC2 - C3**

- Yes

- Chemotherapy
  - BEP* or
  - 6 carboplatin - paclitaxel

**Residual disease?**

- Properly staged with normal tumor markers post surgery?
  - No
  - Yes

- Surveillance

**Chemotherapy**

- BEP* or
- Carboplatin - paclitaxel

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* no bleomycin after 40 years old

BEP = Cisplatin 20 mg/m² /d D1 to D5 + Etoposide 100 mg/m² /d D1 to D5 + Bleomycin 30 mg D1, D8, D15

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Rare Gyn tumors are frequent!
  - Prognosis & clinical presentation really different
  - Thinking to rarity before surgery!
  - Radical surgery & of adjuvant treatment → Not for all!

Management decision making:
  - Expert Pathologists
  - Expert Multidisciplinary Tumor Board
  - Dedicated Rare Cancer Network → French experience

Education for physicians & patients
Tumoral minority is the future of the oncology
European/International Cooperation (ESMO, ESGO, Euracan, GCIG)