Borderline Tumor of the Ovary

= BOT = LMP Tumors

Taylor, 1929: "semi-malignant tumors of the ovary"

UICC, 1964: separate entity

FIGO, 1971: serous cystadenoma with proliferating activity but with no infiltrative destructive growth (low potential malignancy)

WHO, 1973/1999: "borderline malignancy" (low malignant potential)

Should not be used anymore: Borderline Carcinoma, Carcinoma of low malignant potential


Epidemiology BOT vs. Ovarian Cancer

Pts. with BOT are younger (and fitter !?)
Epidemiology BOT vs. Ovarian Cancer

FIGO I in BOT:
6,362 pts. in serie
unselected for FIGO stage

FIGO I in invasive OC:
6,362 pts. in serie
FIGO World Report 26

Survival BOT and invasive Ovarian Carcinoma
FIGO World Report Vol. 26

Pts. with BOT have a much better prognosis!
**Mucinous Histology in BOT vs. Ovarian Cancer**

S-BOT and M-BOT: 5,808 pts. in series unselected for histology

Mucinous and serous histo-type in invasive OC: metaanalysis of 8 GCIG studies including 9,791 pts.

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**“Two-Pathways-Hypothese”**

**High-grade Pathway**

- Tube (via TIC)
- Surface epithelium of the ovary
- Mullerian epithelium peritoneum

**Low-grade Pathway**

- Tube (via TIC)
- Mullerian epithelium peritoneum

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K. Levanon et al. JCO 2008

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Inactivation of tumor-suppressors
Like protein phosphatase 2a (PP2A), p53, or pRb in vitro induce invasiveness of BOT
MM Woo et al., Gynecol Oncol 2008

Still under debate:
• malignant transformation or
• coincidence (susceptibility) of de novo carcinoma

Prognostic Factors
Prognostic factors: FIGO stage / Implants

Implants in BOT
- non invasive
- epithelial
- desmoplastic
- invasive

Literatur review*:
- 75 series including 7,268 pts.; 80% FIGO I
- Recurrences
  - all histo-types:
    - FIGO I: 5.8%
    - FIGO > I: 25.4%
  - S-BOT only:
    - “ 6.3%”
    - “ 30.2%”


Prognostic factor: invasiveness of implants

Metaanalysis (23 series)
Median observation period: 89 months
FIGO stage II/III: 467 pts.

non-invasive implants: 363 (78%)
recurrence: n.a.
died: 17 (4.7%)
Survival rate: 95%

invasive implants: 104 (22%)
recurrence: n.a.
died: 35 (34%)
Survival rate: 66%

905 pts.
839
19.6%
n.a.
237
40.7%
n.a.
Prognostic factors in S-BOT

Literature review*:

• Microinvasion:
  • 17 series, 265 pts.
  • in 12.3% of S-BOT
  • recurrence rate 23.2%
  • prognosis independent of FIGO (?)

• micropapillary growth:
  • 17 series, 305 pts.
  • in 9.5% of S-BOT
  • recurrence rate 36.1%
  • prognosis independent of FIGO (?)


Clinics
Clinical, pre-OP diagnosis in BOT
= the majority of pts. are primarily operated inadequately
(at least 25% each understaged and or overtreated –> frozen section?)

Pre-OP diagnosis
Number of hospitals: 323
Multiple answers were allowed

<table>
<thead>
<tr>
<th></th>
<th>100%</th>
<th>54,2%</th>
<th>28,2%</th>
<th>19,5%</th>
<th>8,4%</th>
<th>3,4%</th>
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<td></td>
<td>48,4%</td>
<td>22,2%</td>
<td>27,3%</td>
<td>2%</td>
<td></td>
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<td>(n=175)</td>
<td>(n=91)</td>
<td>(n=63)</td>
<td>(n=27)</td>
<td>(n=11)</td>
<td></td>
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<tr>
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<td>0%</td>
<td>50%</td>
<td>100%</td>
<td>50%</td>
<td>100%</td>
<td>50%</td>
</tr>
<tr>
<td>suspect cancer</td>
<td>100%</td>
<td>50%</td>
<td>100%</td>
<td>50%</td>
<td>100%</td>
<td>50%</td>
</tr>
<tr>
<td>probably benign</td>
<td>100%</td>
<td>50%</td>
<td>100%</td>
<td>50%</td>
<td>100%</td>
<td>50%</td>
</tr>
<tr>
<td>suspect BOT</td>
<td>100%</td>
<td>50%</td>
<td>100%</td>
<td>50%</td>
<td>100%</td>
<td>50%</td>
</tr>
<tr>
<td>n.a.</td>
<td>100%</td>
<td>50%</td>
<td>100%</td>
<td>50%</td>
<td>100%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Spain: Cusido M et al. Gynecol Oncol 2007

Re-Staging after incomplete staging initially?

<table>
<thead>
<tr>
<th>Author</th>
<th>Pts.</th>
<th>Pts. with up-staging = pts. with residuals detected during Re-staging</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Fauvet 2005</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>Maneo</td>
<td>30</td>
<td>11</td>
</tr>
<tr>
<td>Odegaard</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>T.-Colomer</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Hopkins</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>Darai</td>
<td>42</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>28 x FIGO IA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 x FIGO IC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 x FIGO IIA</td>
</tr>
<tr>
<td>Fauvet 2004</td>
<td>54</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35 x FIGO IA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 x IIIB, 1 x IIIA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 x FIGO IIC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>41 x FIGO I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13 x FIGO II/III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27 x FIGO I</td>
</tr>
<tr>
<td>Snider</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>Querieu</td>
<td>30</td>
<td>8</td>
</tr>
<tr>
<td>Camatte</td>
<td>28</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>28 x FIGO I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33 x FIGO I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 x FIGO IA</td>
</tr>
<tr>
<td>all</td>
<td>284</td>
<td>70</td>
</tr>
</tbody>
</table>

Impact of re-staging on recurrence rate (possible) – on survival (probably low)?

© AdB 2010
Therapy guidelines in BOT - HSK-Standard 
(adapted from German AGO-Guidelines)

- **vertical laparotomy** (or: informed consent for endoscopy)
- inspection and palpation of whole abdominal cavity
- Cytology and blind peritoneal biopsies
- resection of all adhesions or suspect lesions
- omentectomy
- bilateral salpingoophorectomy and hysterectomy 
  (or: informed consent for fertility sparing surgery)
- **omentumectomy in M-BOT or unknown histo-type**
  *(intra-OP frozen section ?)* and **post-OP central pathology review in all cases**
- **no lymphadenectomy** (without any prognostic impact)
- **no post-OP chemotherapy**

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When do you give adjuvant chemotherapy to BOT pts. ?
(survey in 323 hospitals treating BOT)

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J Sehouli et al, BMC 2009
Why do we not give adjuvante chemotherapy?

C Trope et al., Gynecol Oncol 1993
Metaanalysis of 4 prospective studies in Norway including BOT FIGO I/II
- survival without adjuvant therapy: 99%
- with adjuvant therapy (radio-/chemotherapy): 94%

276 pts. with BOT and at least 5 years follow-up
- 113 pts. with FIGO II-III
  - 52 pts. with adjuvant therapy (34 Chemo, 8 Rad, 10 Chemo+Rad)
    - > 71% survived after 126,5 months median follow-up (60-516 mos.)
  - 61 pts. without adjuvant therapy
    - > 87% survived after 93 months median follow-up (60-270 mos.)

Why do we not give adjuvante chemotherapy?

Literature (no randomized trials!):
- 34 series with 693 pts. with adjuvant chemotherapy and 1.253 pts. without adjuvant chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>FIGO II-IV</th>
<th>FIGO I</th>
<th>FIGO II-IV</th>
<th>FIGO I</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>relapse</td>
<td>relapse</td>
<td>relapse</td>
<td>relapse</td>
</tr>
<tr>
<td>546</td>
<td>185</td>
<td>133</td>
<td>550</td>
<td>42</td>
</tr>
<tr>
<td>(33,9%)</td>
<td>(14,3%)</td>
<td>(11,3%)</td>
<td>(7,6%)</td>
<td></td>
</tr>
</tbody>
</table>
Prognostic factor: surgery of BOT

• Cystectomy vs. salpingoophorectomy

<table>
<thead>
<tr>
<th>Risk for recurrence:</th>
<th>Histological type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conservative surgery</td>
<td>Malignant</td>
</tr>
<tr>
<td>Cystectomy</td>
<td>1:1</td>
</tr>
<tr>
<td>Salpingoophorectomy</td>
<td>1:10</td>
</tr>
</tbody>
</table>

Yokoyama Y et al. BJU 2006

Literature:

• 27 series: 435 pts. with cystectomy and 1.718 pts. with USO/BSO
• recurrence rate: 31.4% after cystectomy
  7.7% after USO/BSO
• Prognosis: PFS +++, quo ad vitam (+/?) → informed consent!


Laparoscopy (LSK) „versus“ Laparotomy

<table>
<thead>
<tr>
<th>Author</th>
<th>Pts.</th>
<th>FIGO II/III</th>
<th>Laparotomy</th>
<th>Laparoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liapis</td>
<td>93</td>
<td>22.6%</td>
<td>86</td>
<td>7</td>
</tr>
<tr>
<td>Lackmann</td>
<td>16</td>
<td>100%</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Desfus</td>
<td>118</td>
<td>-</td>
<td>54</td>
<td>48</td>
</tr>
<tr>
<td>Poncelet</td>
<td>313</td>
<td>-</td>
<td>218</td>
<td>95</td>
</tr>
<tr>
<td>Maneo</td>
<td>92</td>
<td>1.6%</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>Romagnolo</td>
<td>113</td>
<td>11.5%</td>
<td>51</td>
<td>52</td>
</tr>
<tr>
<td>De la Cruz</td>
<td>186</td>
<td>14.9%</td>
<td>112</td>
<td>57</td>
</tr>
<tr>
<td>Ren</td>
<td>224</td>
<td>31.2%</td>
<td>182</td>
<td>45</td>
</tr>
<tr>
<td>Fauvel</td>
<td>558</td>
<td>6.4%</td>
<td>209</td>
<td>149</td>
</tr>
<tr>
<td>Odegaard</td>
<td>107</td>
<td>-</td>
<td>69</td>
<td>38</td>
</tr>
<tr>
<td>Nutall</td>
<td>11</td>
<td>18.2%</td>
<td>-</td>
<td>11</td>
</tr>
<tr>
<td>Palomba</td>
<td>32</td>
<td>5.4%</td>
<td>-</td>
<td>32</td>
</tr>
<tr>
<td>Darai</td>
<td>25</td>
<td>4.0%</td>
<td>-</td>
<td>25</td>
</tr>
<tr>
<td>Saracchioli</td>
<td>19</td>
<td>-</td>
<td>-</td>
<td>19</td>
</tr>
<tr>
<td>Tsonetti</td>
<td>43</td>
<td>-</td>
<td>-</td>
<td>43</td>
</tr>
</tbody>
</table>

alle: 1.038 137 95 652 185 97
Rupture in pts. with information: 137 of 771 (17.8%)
185 of 588 (31.6%)

Relapse in pts. with information: 95 of 1.038 (9.2%)
97 of 652 (14.9%)

Less adverse events vs higher risk → informed consent!


Less adverse events vs higher risk → informed consent!
### Fertility sparing versus radical surgery

**Literature: 67 series**  
* % of those cohorts with complete information available

<table>
<thead>
<tr>
<th>FIGO Stages</th>
<th>Fertility sparing OP</th>
<th></th>
<th>Radical OP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pts.</td>
<td>Relapse</td>
<td></td>
<td>Pts.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>all</td>
<td>Ovary only</td>
<td></td>
</tr>
<tr>
<td>all FIGO</td>
<td>2.868</td>
<td>439</td>
<td>303</td>
<td>3.735</td>
</tr>
<tr>
<td>(%)*</td>
<td></td>
<td>15.7%</td>
<td>74.5%</td>
<td></td>
</tr>
<tr>
<td>FIGO I</td>
<td>1.810</td>
<td>223</td>
<td>168</td>
<td>2.076</td>
</tr>
<tr>
<td>(%)*</td>
<td></td>
<td>12.6%</td>
<td>84.8%</td>
<td></td>
</tr>
<tr>
<td>FIGO II-III</td>
<td>256</td>
<td>97</td>
<td>53</td>
<td>437</td>
</tr>
<tr>
<td>(%)*</td>
<td></td>
<td>44.8%</td>
<td>54.0%</td>
<td></td>
</tr>
</tbody>
</table>

*higher recurrence risk outside ovary in FIGO II-III*  
*informed consent*

---

**Outcome BOT**  
- Recurrence
- need for Re-OP
- death?

**Outcome**  
- children
- Endocrinum
- cosmesis (LSK)
- Morbidity (LSK)
### Outcome relapsed BOT -> invasives (low grade) carcinoma?

**Literature:** 89 series

<table>
<thead>
<tr>
<th></th>
<th>Pts.</th>
<th>Recurrence</th>
<th>deceased</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pts</td>
<td>invasive recurrence</td>
<td>of disease (DoD)</td>
<td>DID</td>
</tr>
<tr>
<td>all:</td>
<td>8.234 pts.</td>
<td>919</td>
<td>201</td>
<td>269</td>
</tr>
<tr>
<td>Recurrence rate:</td>
<td>11,0%</td>
<td>27,5% of all recurrences</td>
<td>26,2% of all recurrences</td>
<td></td>
</tr>
<tr>
<td>All with &gt;5 yrs. follow-up:</td>
<td>4.903 pts.</td>
<td>616</td>
<td>167</td>
<td>191</td>
</tr>
<tr>
<td>recurrence rate:</td>
<td>11,7%</td>
<td>33,3% of all recurrences</td>
<td>30,4% of all recurrences</td>
<td></td>
</tr>
</tbody>
</table>

Relation DoD : DID = 1 : 1,7

---

**Graph:** Pts. Deceased due to relapsed BOT

- Silva 06
- Sykes 97
- Crispens 02
- Longacre 05
- McKenney 06
- Nakashima 90
- Winter 02
- Desfeux 05
- Morice 03
- Bell 88
- Bostwick 86
- Ji 96
- Julian 72
- Buttin 02
- Trope 93
- Pratt 02
- Laurent 08
- Suh-Burgmann 06
- Casey 93
- Kennedy 96
- Hogg 06
Recommendation HSK: Treatment of BOT

Child bearing desire

- yes
  - fertility sparing OP
    - yes
      - Cytology, Omentectomy, Peritoneal biopsies, Appendectomy (in M-BOT)
    - no
      - microinvasion
        - yes
          - Consider re-OP after completion of family planning
        - no
          - Follow-up for at least 15 years including anamnesis, gynec exam., VUS
  - no
    - Radical surgery
      - yes
        - Hysterectomy and Adnexectomy bilaterally (BSO)
      - no
        - non-invasive
          - Adnexectomy unilaterally (USO) or Cystectomy unilaterally (CE - after USO) or USO+CE if Natural/BOT
        - yes
          - Follow-up for at least 15 years including anamnesis, gynec exam., VUS