Surgery for early (stage I-II) ovarian cancer

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Charite, Berlin
Diagnosis

Surgery for early (stage I-II) invasive epithelial ovarian cancer. ESGO recommendations

• Clinical examination including abdominal, vaginal and rectal examinations, assessment of the groin, axilla, and supraclavicular areas, lung and breast should be performed
• Routine pelvic (transvaginal) ultrasound and if needed suprapubic must be used as a primary workup tool in any adnexal mass
• Specialized pelvic and abdominal complementary imaging (ultrasound and/or MRI and/or CT scan and/or PET-CT) should be performed in case of undetermined or suspicious masses at routine ultrasound examination
Preoperative workup

Surgery for early (stage I-II) invasive epithelial ovarian cancer. ESGO recommendations

- Recommendation: a thoraco-abdomino-pelvic imaging must be performed in patients with non emergency clinical presentation and suspected carcinoma of the ovary; a blood sampling must be taken for blood markers assessment, at least Ca-125 levels.

- Possible additional markers, including AFP, hCG, LDH, CEA, Ca 19-9, inhibin B or AMH, estradiol, testosterone, must be taken in specific circumstances: young patient, or imaging suggesting a mucinous, or non epithelial, or extra-adnexal tumor.
Specialized multidisciplinary decision making

Surgery for early (stage I-II) invasive epithelial ovarian cancer. ESGO recommendations

Patients with non emergency clinical presentation and suspected malignancy of the adnexa should be referred to a specialist in gynecologic oncology (certified gynaecological oncologist or specialist surgeon as defined for advanced ovarian cancer surgery) and discussed preoperatively in a multidisciplinary meeting

All patients must be reviewed postoperatively at a gynaecological oncology multidisciplinary meeting
Early ovarian cancer

- 30% of the patients present in FIGO stage I or II.
- The most important prognostic factor is stage (5YOS: 60-90%). Further prognostic factors: grading, histological subtype and quality of management (iatrogenic rupture, incomplete staging).
Surgical management (1)

- Midline laparotomy is required to manage early ovarian cancers, with the exception of apparent stage I which can be managed laparoscopically by a gynaecological oncologist with specific expertise in laparoscopy, without rupture and without contamination of the abdominal cavity and wall.

- Intraoperative rupture of a yet unruptured adnexal mass must be avoided.
Staging-Operation im Stadium FIGO I-IIA*

(AGO)

**Definition:**

*early ovarian cancer:*

- FIGO I A G > 1 or unknown
- FIGO I B/C - IIA all G

**Standard-Staging:**

Laparotomy

(9 Items) TAH + BSO (unless in fertility sparing surgery)

- Omentectomy
- Peritoneal-biopsies(all 4 quadrants)
- cytology
- pelvic and paraaortic LND
- (appendectomy)
+ tumorfree!!
<table>
<thead>
<tr>
<th>Step</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Vertical incision</td>
</tr>
<tr>
<td>2.</td>
<td>Send peritoneal fluid. If none, send peritoneal washings</td>
</tr>
<tr>
<td>3.</td>
<td>Inspect and palpate all peritoneal surfaces</td>
</tr>
<tr>
<td>4.</td>
<td>Omentectomy</td>
</tr>
<tr>
<td>5.</td>
<td>TAH-BSO</td>
</tr>
<tr>
<td>6.</td>
<td>Resect gross disease within the abdominal cavity</td>
</tr>
<tr>
<td>7.</td>
<td>In absence of disease beyond the pelvis, peritoneal biopsies</td>
</tr>
<tr>
<td>8.</td>
<td>Pelvic and para-aortic nodes for:</td>
</tr>
<tr>
<td></td>
<td>- Stage IIIB disease (microscopic disease in omentum 2 cm)</td>
</tr>
<tr>
<td></td>
<td>- Not required for stage 3C or 4 disease, unless only disease is a palpable node</td>
</tr>
</tbody>
</table>
Why staging in apparently early ovarian cancer?

20-30% incidence of occult metastases:

- positive cytology: 20%
- omentum: 6%
- diaphragm: 15%
- peritoneal biopsies: 13%
- para-aortal LN: 14%
- pelvic LN: 8%
• 122 patients of mainly IA (33%) and IC (41%) stage → 19 patients had positive peritoneal biopsies (16%) at surgical staging.

• Even though only 6 (5%) of those were from normal-appearing tissue, comprehensive staging resulted in upstaging of 4% of all patients by the random peritoneal biopsies alone.

• 5 (4%) of the patients had even microscopic metastases to the omentum, 4 (3%) of whom were upstaged by this finding alone

Treatment quality in early ovarian cancer
FIGO I-IIA
(„max. 1 nissing item fehlt“ and adequate chemotherapy)

**QS-OVAR 2001**
- Standard mit OP "optimal": 19%
- kein Standard: 81%

**QS-OVAR 2004**
- Standard mit OP "optimal": 33%
- kein Standard: 67%

**QS-OVAR 2008**
- Standard mit OP "optimal": 55%
- kein Standard: 45%

*p < 0.001*

2001-2008: 53/ 488 (10.9pts died, of them 47/ 53 (88.7%) without any standart treatment"
Surgical management (2)

- Total hysterectomy and bilateral salpingo-oophorectomy is standard
  - Fertility preserving surgery (unilateral salpingo-oophorectomy) should be offered to selected premenopausal patients with apparent stage IA*
    - Discussion on fertility must be mentioned in the patient record
    - Final decision based on final stage and grade: fertility preservation is accepted in case of stage IA or IC1, low-grade serous or endometrioid carcinoma, or expansile type mucinous tumors
    - Other stage I substages or pathologic subtypes, subject to individualized decision
    - Uterine preservation with bilateral salpingo-oophorectomy, can be considered in selected young patients with apparent stage IB low risk invasive carcinoma and normal endometrial biopsy finding. However, there is very few data to support this policy.
Role of frozen section

- The availability of frozen section may allow the necessary surgical staging to be done at the time of initial surgery. It is understood that frozen section may not be conclusive and that definitive pathology is the gold standard of diagnosis.

- In the absence of frozen section or in case of inconclusive frozen section, a two-step procedure should be preferred.
Surgical staging

Surgery for early (stage I-II) invasive epithelial ovarian cancer. ESGO recommendations

- Staging of patients with early ovarian cancer defines the indication for adjuvant treatment and also provides valuable prognostic information
- Up to 30% of patients are upstaged as a result of comprehensive staging
- Proper staging is an independent prognostic factor
- When early carcinoma is incidentally found at surgery for a suspected ‘benign’ condition, a second surgical procedure will be required. When the patient has not been comprehensively staged, a second surgical procedure must be considered routinely
- Laparoscopic surgery is an acceptable approach if performed by a gynecologic oncologist with adequate expertise to perform a comprehensive staging. Further studies are needed to definitively confirm the safety of the approach.
Surgical staging

Surgery for early (stage I-II) invasive epithelial ovarian cancer. ESGO recommendations

- Visual assessment of the entire peritoneal cavity
- Peritoneal washings or cytology, taken prior to manipulation of the tumour
- Blind peritoneal biopsies from the pelvis, paracolic spaces, and the subdiaphragmatic spaces bilaterally
- At least infracolic omentectomy
- Bilateral pelvic and para-aortic lymph node dissection up to the level of the left renal vein (with the exception of stage I expansile type mucinous adenocarcinomas)

- Restaging for the only purpose of performing appendectomy is not mandatory even in case of mucinous histology if the appendix has been examined and found normal
Quality indicators for early (stage I-II) ovarian cancer

A system of 7 quality indicators has been defined in relation to the recommendations elaborated by the International Development Group. A new system of assessment of the quality of staging has been designed.
Preoperative workup

• Recommendation: a thoraco-abdomino-pelvic imaging must be performed in patients with non-emergency clinical presentation and suspected carcinoma of the ovary; a blood sampling must be taken for blood markers assessment, at least Ca-125 levels.

QI 1: recommendation is met in over 95% of patients.
Specialized multidisciplinary decision making

Patients with non emergency clinical presentation and suspected carcinoma of the ovary should be referred to a specialist in gynecologic oncology (certified gynecologic oncologist or specialist surgeon as defined in QI 3 for advanced ovarian cancer surgery)

• All patients must be reviewed postoperatively at a gynaecologic oncology multidisciplinary meeting

QI 2: requirement is met in 100 % of patients
Midline laparotomy is required to manage early ovarian cancers, with the exception of a few apparent stage I which can be managed laparoscopically without rupture and without contamination of the abdominal wall. **QI 3: 100% of patients with early ovarian cancer meet the requirement**

Intraoperative rupture of a yet unruptured adnexal mass should be avoided. **QI 4: 90% of early ovarian cancers are removed unruptured (pT IC1/pT IA+IB<0.1)**
Surgical management (2)

- Total hysterectomy and bilateral salpingo-oophorectomy is standard
  - Discussion on fertility must be mentioned in the patient record wherever applicable

*QI 5: requirement is met in 100% of patients*
Role of frozen section

• The availability of frozen section may allow the necessary surgical staging to be done at the time of initial surgery. It is understood that frozen section may not be conclusive and that definitive pathology is the gold standard of diagnosis.

• In the absence of frozen section or in case of inconclusive frozen section, a two-step procedure must be considered.

QI 6: frozen section is available in the institution
Quality assurance for surgical staging

ESGO modified Trimbos 2003* classification:

- **optimal**: all components of staging are present (inspection and palpation of all peritoneal surfaces; biopsies of any suspect lesions for metastases; peritoneal washing and routine peritoneal biopsies**; infracolic omentectomy; pelvic and paraaortic lymph node dissection)

- **suboptimal**: everything between inadequate and optimal

- **inadequate**: not performed, or information is not available

QI 7: 100% of patients have optimal staging

* JNCI, 2003;95:113-25

** Suggested procedure for blind biopsies: right and left hemidiaphragm, right and left paracolic gutter, pelvic sidewalls, bladder peritoneum, and pouch of Douglas
Lymph node metastases in ovarian cancer

- LN involvement
  Stage I: 15-25%
  Stage II: 20-40%
  Stage III: 50-75%

Paraaortal more often involved (75%) than pelvic (15%), solely contralateral 11%

*Negishi et al. Gynecol Oncol 2004*
ASCO 2002, Sakurai et al., 
VALIDITY OF COMPLETE PARAAORTIC AND PELVIC LYMPHADENECTOMY IN APPARENT STAGE I (PT1) OVARIAN CARCINOMA 1989-2000

• pT1a = N1: 10,6% (7/66)
• pT1b = N1: 55,6% (5/9)
• pT1c = N1: 18,1% (24/141)
• pelv. N1 + paraa. N0: 0 Pts.
Rate of patients with apparently early EOC that had positive pelvic and/or paraaortic lymph nodes after systematic lymph node dissection

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td>Benedetti-Panici, 1993</td>
<td>35</td>
<td>14</td>
</tr>
<tr>
<td>Petru, 1994</td>
<td>40</td>
<td>23</td>
</tr>
<tr>
<td>Onda, 1996</td>
<td>33</td>
<td>21</td>
</tr>
<tr>
<td>Baiocchi, 1998</td>
<td>242</td>
<td>13</td>
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<tr>
<td>Suzuki, 2000</td>
<td>47</td>
<td>11</td>
</tr>
<tr>
<td>Nomura, 2010</td>
<td>79</td>
<td>13</td>
</tr>
<tr>
<td>Harter, 2007</td>
<td>70</td>
<td>11</td>
</tr>
</tbody>
</table>
Conservative surgery for ovarian cancer in Europe: outcome by stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of patients</th>
<th>Relapse (N)</th>
<th>Relapse ovary (N)</th>
<th>Deaths</th>
</tr>
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<tbody>
<tr>
<td>IA</td>
<td>88</td>
<td>10</td>
<td>6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4</td>
</tr>
<tr>
<td>IB</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC</td>
<td>51</td>
<td>5</td>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>2</td>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td>IIIA</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIC</td>
<td>6</td>
<td>1</td>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>152</td>
<td>18 (11.8%)</td>
<td>11 (7%)</td>
<td>9 (5.9%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> One of six patients had ovarian and distant metastases.

<sup>b</sup> All patients had ovarian + peritoneal and/or retroperitoneal metastases.

*Colombo et.al. Int J Gyn Canc 2006*
Oncologic outcome after fertility sparing treatment in early ovarian cancer (FIGO I-II)

- Relapse rates: 4-17%
- Relapsed free intevall: 7-63 Monate
- 5-YOS: 80-94%
- High conception rates; no higher risk of abortions, prematurity, congenital malformation

Fotopoulou et.al. Review Obstet Gynecol Int. 2012
....but what about?

- Iatrogenic Ic disease
- Nonserous or non-endometrioid histologic subtypes
- G3
- IIIc due to „only“ LN involvement
<table>
<thead>
<tr>
<th>Author [reference]</th>
<th>Pts N</th>
<th>Median Age (y)</th>
<th>FIGO stage N (%)</th>
<th>Grade N (%)</th>
<th>Histology N (%)</th>
<th>Relapse rate N (%)</th>
<th>Mean PFS (mo) or 5y DFS</th>
<th>Characteristics of pts who relapsed</th>
<th>5y OS</th>
<th>Death</th>
<th>LND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kwon et al. 2009 [18]</td>
<td>21</td>
<td>26.7</td>
<td>17 (81%) IA 4 (19%) IC</td>
<td>16 (76%) G1 3 (14%) G2 2 (9.5%) G3</td>
<td>16 (76%) muc 2 (9.5%) endo 2 (9.5%) clear cell 1 (4.7%) serous</td>
<td>1 (4.7%)</td>
<td>34</td>
<td>IG, muc</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Kajiyama et al. 2008 [19]</td>
<td>10</td>
<td>35.9</td>
<td>4 (40%) IA 6 (60%) IC</td>
<td>NR</td>
<td>10 (100%) clear cell</td>
<td>1 (10%)</td>
<td>33</td>
<td>IC, G2, clear cell</td>
<td>NR</td>
<td>1 (10%)</td>
<td>Optional</td>
</tr>
<tr>
<td>Schlaerth et al. 2009 [3]</td>
<td>20</td>
<td>27</td>
<td>11 (55%) IA 9 (45%) IC</td>
<td>14 (70%) G1 5 (25%) G2 1 (5%) G3</td>
<td>11 (55%) muc 1 (5%) serous 6 (30%) endo 1 (5%) clear cell</td>
<td>3 (15%)</td>
<td>4.3 (9–22)</td>
<td>21C, 1 IA</td>
<td>84%</td>
<td>3 (15%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Borgfeldt et al. 2007 [20]</td>
<td>11</td>
<td>10</td>
<td>IA 1 IC</td>
<td>G1 G3</td>
<td>NR</td>
<td>1 (9%)</td>
<td>14 (8–78)</td>
<td>IC, G3</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>Schilder et al. 2002 [11]</td>
<td>52</td>
<td>26</td>
<td>42 (81%) IA 10 (19%) IC</td>
<td>38 (73%) G1 9 (17%) G2 5 (9.6%) G3</td>
<td>25 (48%) muc 10 (19%) serous 5 (9.6%) clear cell 2 (4%) mixed</td>
<td>5 (9.6%)</td>
<td>14 (8–78)</td>
<td>4 IA, G1 1 IC, G2 2 muc 2 serous 1 endo</td>
<td>98%</td>
<td>2 (4%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Kajiyama et al. 2011 [21]</td>
<td>74</td>
<td>&lt;40</td>
<td>36 (48%) IA 1 l (1.3%) Ib 37 (50%) IC</td>
<td>57 (77%) G1/G2 4 (5.4%) G3</td>
<td>4 (5.4%) serous 43 (58%) muc 13 (18%) clear cell 4 (5.4%) endo</td>
<td>NR</td>
<td>87.9% 5y DFS</td>
<td>NR</td>
<td>90.8%</td>
<td>2 (2.7%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Zanetta et al. 1997 [12]</td>
<td>56</td>
<td>29</td>
<td>32 (57%) IA 2 (3.5%) IB 22 (39%) IC</td>
<td>35 (62%) G1 14 (25%) G2 7 (12%) G3</td>
<td>18 (32%) serous 23 (41%) muc 13 (23%) endo</td>
<td>5 (9%)</td>
<td>NR</td>
<td>Mostlly 1c, G3 1a, G3 IC 3 clear cell</td>
<td>NR</td>
<td>4 (7%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Satoh et al. 2010 [16]</td>
<td>211</td>
<td>29</td>
<td>126 (66%) IA 85 (40%) IC</td>
<td>G1: 160 (76%) G2: 15 (7%) G3: 6 (2.8%) clear cell 30 (14.2%)</td>
<td>126 (60%) muc 27 (13%) serous 27 (13%) endo 30 (14.2%) Clear cell</td>
<td>18 (8.5%)</td>
<td>33.3–100% 5y DFS</td>
<td>Mostly 1c, G3 1a, G3 IC, clear cell</td>
<td>66.7–100%</td>
<td>5 (2.4%)</td>
<td>Yes</td>
</tr>
<tr>
<td>Kajiyama et al. 2011 [13]</td>
<td>41</td>
<td>&lt;40</td>
<td>27 (66%): IA 14 (34%): IC</td>
<td>NR</td>
<td>100% muc</td>
<td>3 (7.3%)</td>
<td>90.5%</td>
<td>97.3%</td>
<td>1 (2.5%)</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Kajiyama et al. 2011 [22]</td>
<td>80</td>
<td>35</td>
<td>40 (50%): IA 40 (50%): IC</td>
<td>—</td>
<td>45 (56%) muc 3 (3.7%) serous 15 (19%) endo 16 (20%) clear cell</td>
<td>10 (12.5%)</td>
<td>85.5%–92.9% 5y DFS</td>
<td>2: IA &amp; IC 16: IC</td>
<td>89.3%–90.5%</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>Kajiyama et al. 2010 [23]</td>
<td>60</td>
<td>30</td>
<td>IA 30 (50%) IB 1 (1.7%) IC 29 (48%)</td>
<td>41 (68%) G1 7 (12%) G2 2 (3.3%) G3</td>
<td>Serous 5 (8.3%) Muc. 34 (56.7%) Endo 11 (18%)</td>
<td>8 (13%)</td>
<td>89.8%</td>
<td>2 IA, 1 IB 5 IC</td>
<td>89.8%</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>Total</td>
<td>580</td>
<td>26–35.9</td>
<td>333 (57%): IA 4 (0.7%): IB 234 (40%): IC</td>
<td>334 (57%): G1 39 (6.7%): G2 20 (3.4%): G3</td>
<td>300 (52%): muc 51 (9%): serous 128 (22%): clear cell 65 (11%): endo</td>
<td>50 (8.6%)</td>
<td>33.3–100% 5y DFS</td>
<td>66.7–100%</td>
<td>18 (3.1%)</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>
Points of attention in clinical practice

• Overseing „occult“ advanced stage patients through inadequate staging
• Discuss and offer fertility sparing options in young patients with ov ca
• Special attention to rare histologies with limited experience
• PREOPERATIVE Decision making process after discussion with the patient about 1-stage / 2-stage procedure
Backup Folien
### Molekularbiologische und klinikopathologische Charakteristika verschiedener histologischer Typen des Ovarialkarzinoms (WHO-Klassifikation 2014)

<table>
<thead>
<tr>
<th></th>
<th>High grade serös</th>
<th>Low grade serös</th>
<th>Muzinös / seromucinös</th>
<th>Endometrioid</th>
<th>Klarzellig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Häufigkeit (%)</td>
<td>40–70</td>
<td>5–10</td>
<td>~ 5</td>
<td>~ 10</td>
<td>~ 10</td>
</tr>
<tr>
<td>Risikokonstellation</td>
<td>BRCA1/2</td>
<td></td>
<td>HNPCC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vorläuferläsion</td>
<td>STIC (p53-Mutation)</td>
<td>SBOT</td>
<td>MBOT</td>
<td>Endometriose</td>
<td>Endometriose</td>
</tr>
<tr>
<td>Ausbreitungsmuster</td>
<td>Diffus abdominal</td>
<td>Abdomen</td>
<td>Ovar</td>
<td>Kleines Becken</td>
<td>Kleines Becken</td>
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<tr>
<td>Molekularpathologie</td>
<td>BRCA, p53-Mutation</td>
<td>B-raf-, K-ras-Mutation</td>
<td>B-raf-, K-ras-Mutation (mucinös)</td>
<td>ARID-1A-Expression/-Mutation</td>
<td>ARID-1A-Expression/-Mutation</td>
</tr>
<tr>
<td>Chemotherapie-Response</td>
<td>Hoch</td>
<td>Eher niedrig</td>
<td>mucinös: niedrig</td>
<td>Hoch</td>
<td>Niedrig</td>
</tr>
<tr>
<td>Prognose</td>
<td>Schlecht</td>
<td>Intermediär</td>
<td>Gut</td>
<td>Gut</td>
<td>Intermediär</td>
</tr>
<tr>
<td><strong>Neue Therapieansätze</strong></td>
<td>PARP-Inhibitoren WEE-1-Inhibitor (p53-Mutation - CDK 1)</td>
<td>MEK-Inhibitoren? Endokrine Therapie?</td>
<td>?</td>
<td>PARP-Inhibitoren ?</td>
<td>?</td>
</tr>
</tbody>
</table>

Undifferenzierte Karzinome und Karzinosarkome mit schlechter Prognose.
Ovarian cancer – the end of empiricism?

Cancer Volume 121, Issue 18, pages 3203-3211, 10 JUN 2015 DOI: 10.1002/cncr.29481

Green circles: Indicate data evidence for treatment use.
Orange circles: Lack of validation to support treatment use.
Red circles: No evidence for treatment use.
Ovarian carcinoma diagnosis: the clinical impact of 15 years of change - S.Kommoss et al; B J Cancer 2016
Low value of archival ovarian carcinoma histotypes - n = 286 samples – AGO OVAR 3 trial

- Clear Cell: n=35 (12%)
- Endometrioid: n=52 (18%)
- Mucinous: n=23 (8%)
- Serous: n=131 (46%)
- Transitional: n=14 (5%)
- Undifferentiated: n=31 (11%)

- Clear Cell: n=13 (5%)
- Endometrioid: n=14 (5%)
- HGSC: n=229 (80%)
- LGSC: n=21 (7%)
- Mucinous: n=9 (3%)

Nur in 54% der Fälle stellte derselbe Pathologe aus dem gleichen Material die gleiche Histologie-Subtyp-Diagnose 2014 wie zuvor 2002

Pathologe A- 2002
Pathologe A- 2014
Pathologe B- 2014