Management of Early Stage Ovarian Cancer

DR. MACİT ARVAS
Ovarian Cancer - World

The number of new cases per 100,000 women: 11.7
The number of deaths per 100,000 women: 7.4

Percent Surviving 5 Years

46.5%
2007-2013
Ovarian Cancer - Turkey

Incidence in 2012: 2400 cases
Mortality in 2012: 1588 cases
Expected number of cases in 2020: 3156
Ovarian Cancer

Early Stage
- Stage IA, IB, IC

Advanced Stage
- Local
- Advanced
  - Stage II
  - Stage III-IV
FIGO’14 Ovarian Cancer Staging

**Early Stage**

**IA:** Limited to 1 ovary. Capsule intact, no tumor on surface, (-) washing

**IB:** Involving both ovaries. Capsule intact, no tumor on surface, (-) washing

**IC:** Surgical spill (IC1), preop capsule rupture or tumor on surface (IC2), (+) washing (IC3)
Stage I-II Disease

- Stage I: 20-33% of the patients with ovarian cancer
- Stage I-II: 35-40% of the patients with ovarian cancer
- Diagnosis is usually made by accidental discovery
  - Sonography
  - CT
  - LS

Maringe et al, Gynecol Oncol, 2012
The Prognostic Factors

- FIGO stage
- Histological subtype
- Age
- Residual disease

For stage I disease
- Grade
- Tumor rupture

Vergote et al, Lancet, 2001
The Factors Affecting Management

- Age
- Fertility desire
- Performance status
- Tumor histology
- Grade of tumor
- Resources
The Standard Surgical Management

- Exposure of the entire abdomen
- Total hysterectomy + BSO
- Removal of all sites of tumor
- Aspiration of washing or ascites
- Omentectomy
- Lymphadenectomy
- Biopsies
Upstaging 15-60%

Location %

Lymph node 5-35

Omentum 3-20

Random peritoneal bx 4-15
Survival is affected by the extent of surgery
Apparent Stage I Low-Grade EOC

- Multicenter retrospective study
- 2000-2016
- n=163
- The overall incidence of LN: 4.3%

Patterns of Lymph Node Metastases in Apparent Stage I Low-Grade Epithelial Ovarian Cancer: A Multicenter Study

Lucas Minig, MD, PhD, MBA¹, Florian Heitz, MD², David Cibula, MD³, Jamie N. Bakkum-G GAMEZ, MD⁴, Anna Germanova, MD⁵, Sean C. Dowdy, MD⁵, Eleftheria Kalogera, MD⁵, Ignacio Zapardiel, MD⁵, Kristina Lindemann, MD, PhD⁶, Philipp Harter, MD, PhD⁵, Giovanni Scambia, MD⁶, Marco Petrillo, MD⁶, Cristina Zorrero, MD⁷, Vanna Zanagnolo, MD⁷, José Miguel Cárdenas Rebollo, PhD⁷, Andreas du Bois, MD, PhD⁵, and Christina Fotopoulou, MD, PhD¹¹

<table>
<thead>
<tr>
<th>Histologic type</th>
<th>n</th>
<th>LN metastasis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous</td>
<td>56</td>
<td>11</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>68</td>
<td>1.5</td>
</tr>
<tr>
<td>Mucinous</td>
<td>39</td>
<td>0</td>
</tr>
</tbody>
</table>
- Detection of nodal metastasis using PET-CT
  - Sensitivity: 83%
  - Specificity: 95%
- PET-MR may be used in the evaluation of the primary tumor
Lymph node metastasis in stages I and II ovarian cancer: A review

M. Kleppe a, T. Wang a, T. Van Gorp a,b, B.F.M. Slangen a,b, A.J. Kruse a,b, R.F.P.M. Kruitwagen a,b,*

a Maastricht University Medical Centre, Department of Obstetrics and Gynecology, Maastricht, The Netherlands
b GROW, School for Oncology and Developmental Biology, Maastricht, The Netherlands

Overall incidence of lymph node metastasis in clinical FIGO stages I-II epithelial ovarian cancer and the anatomical distribution of positive lymph nodes.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Clinical FIGO stages</th>
<th>Positive pelvic and/or para-aortic lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I-II</td>
<td>Overall pelvic and/or para-aortic lymph nodes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Only para-aortic</td>
</tr>
<tr>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
</tbody>
</table>

14% (+) lymph node in stage I-II disease

Diameter of (+) nodes is < 6 mm in >50% of cases

Selective lymphadenectomy is not enough

Kleppe et al, Gynecol Oncol, 2011
Lymph node metastasis in stages I and II ovarian cancer: A review

M. Kleppe\textsuperscript{a}, T. Wang\textsuperscript{a}, T. Van Gorp\textsuperscript{a,b}, B.F.M. Slangen\textsuperscript{a,b}, A.J. Kruse\textsuperscript{a,b}, R.F.P.M. Kruitwagen\textsuperscript{a,b,}\textsuperscript{*}

\textsuperscript{a} Maastricht University Medical Centre, Department of Obstetrics and Gynecology, Maastricht, The Netherlands
\textsuperscript{b} GROW, School for Oncology and Developmental Biology, Maastricht, The Netherlands

<table>
<thead>
<tr>
<th>Grade</th>
<th>LN metastasis</th>
<th>Grade</th>
<th>LN metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>16.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>20%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kleppe et al, Gynecol Oncol, 2011
N=290 early stage EOC patients

LN metastasis: 14%

Independent risk factor for LN metastasis: **Serous histology**
Association of Lymphadenectomy and Survival in Stage I Ovarian Cancer Patients

John K. Chan, MD, Elizabeth G. Munro, MD, Michael K. Cheung, Amreen Husain, MD, Nelson N. Teng, MD, PhD, Jonathan S. Berek, MD, MMS, and Kathryn Osann, PhD.

OBJECTIVE: To estimate the survival impact of lymphadenectomy in women diagnosed with clinical stage I ovarian cancer.

METHODS: Demographic and clinicopathologic information from patients with stage I ovarian cancer who underwent lymphadenectomy was compared to those who did not.

CONCLUSION: Our data suggest that women with stage I non-clear cell ovarian cancers who underwent lymphadenectomy had a significant improvement in survival. (Obstet Gynecol 2007;109:12-9)

<table>
<thead>
<tr>
<th>Node Count</th>
<th>0 node</th>
<th>&lt;10 nodes</th>
<th>&gt;10 nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year OS</td>
<td>87%</td>
<td>91%</td>
<td>93%</td>
</tr>
</tbody>
</table>

\(p=0.001\)
Prognostic Significance of Lymphovascular Space Invasion in Epithelial Ovarian Cancer

✓ n=492 EOC patients
✓ LVSI (+) in 58.5% of all
✓ (+) LVSI is associated with
  ✓ High grade
  ✓ Serous histology
  ✓ LN metastasis
  ✓ Advanced stage
✓ (+) LVSI decreases DFS and OS in early stage EOC

Table 2. Multivariate analyses predicting survival in the whole cohort (N=492).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>PFS HR (95% CI)</th>
<th>P</th>
<th>OS HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>0.351</td>
<td>1</td>
<td>1.284</td>
<td>0.391</td>
</tr>
<tr>
<td>≥50</td>
<td>1.13 (0.77-1.72)</td>
<td>&lt;0.001</td>
<td>1.234 (0.75-1.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>1</td>
<td>&lt;0.001</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>III-IV</td>
<td>2.450 (1.22-4.91)</td>
<td>0.635</td>
<td>2.007 (1.58-4.76)</td>
<td>0.874</td>
</tr>
<tr>
<td>Histotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not high-grade serous</td>
<td>1</td>
<td>1</td>
<td>1.23 (0.51-1.69)</td>
<td>0.272</td>
</tr>
<tr>
<td>High-grade serous</td>
<td>1.46 (0.58-3.50)</td>
<td>0.125</td>
<td>1.29 (0.51-1.69)</td>
<td>0.272</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1.03 (0.55-1.84)</td>
<td>1.39 (0.82-2.19)</td>
</tr>
<tr>
<td>2</td>
<td>1.31 (0.73-2.04)</td>
<td>0.31</td>
<td>1.39 (0.82-2.19)</td>
<td>1.39 (0.82-2.19)</td>
</tr>
<tr>
<td>3</td>
<td>2.18 (0.86-3.72)</td>
<td>0.84</td>
<td>2.18 (0.86-3.72)</td>
<td>2.18 (0.86-3.72)</td>
</tr>
<tr>
<td>Residual</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 cm</td>
<td>1</td>
<td>&lt;0.001</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;1 cm</td>
<td>2.59 (1.61-4.73)</td>
<td>0.011</td>
<td>2.29 (1.53-3.67)</td>
<td>0.129</td>
</tr>
<tr>
<td>LVSI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
<td>1</td>
<td>1.38 (1.16-2.09)</td>
<td>1.38 (1.16-2.09)</td>
</tr>
<tr>
<td>Positive</td>
<td>1.50 (1.22-1.96)</td>
<td>0.129</td>
<td>1.50 (1.22-1.96)</td>
<td>0.129</td>
</tr>
</tbody>
</table>

Bold values indicate statistically significant differences.
PFS: progression-free survival; OS: overall survival; LVSI: lymphovascular space invasion; HR: hazard ratio; CI: confidence interval.
Complete staging can be omitted in stage I mucinous tumors

Is complete surgical staging necessary in patients with stage I mucinous epithelial ovarian tumors?

Yun-Hyun Cho \textsuperscript{a}, Dae-Yeon Kim \textsuperscript{a}, Jong-Hyeok Kim \textsuperscript{a}, Yong-Man Kim \textsuperscript{a}, Kyu-Rae Kim \textsuperscript{b}, Young-Tak Kim \textsuperscript{a}, Joo-Hyun Nam \textsuperscript{a,*}

\textsuperscript{a} Department of Obstetrics and Gynecology, College of Medicine, University of Ulsan, Asan Medical Center, Seoul, Korea
\textsuperscript{b} Department of Pathology, College of Medicine, University of Ulsan, Asan Medical Center, Seoul, Korea

Received 31 March 2006
Available online 21 July 2006

Abstract

\textbf{Objective.} To evaluate the impact on prognosis of complete surgical staging in patients with stage I mucinous epithelial ovarian tumors.

\textbf{Methods.} We retrospectively reviewed the medical records of all patients with stage I mucinous epithelial tumors apparently confined to ovaries treated in the Department of Obstetrics and Gynecology, Asan Medical Center, from 1990 through 2005.

\textbf{Results.} Of 264 patients treated during this time period, 62 (23.5\%) had complete and 202 (76.5\%) had incomplete initial surgical staging. No patient with clinically apparent stage I borderline tumor was upstaged, 5 of 85 patients with invasive mucinous cancer was upstaged due to positive peritoneal cytology and there was no upstaged patient owing to occult lymph node metastasis. No recurrence was observed in the completely staged and 2 (1.4\%) in the incompletely staged group among the patients with borderline tumor developed relapse. Three (11.8\%) recurrences in the completely staged and four (6.8\%) in the incompletely staged group among the patients with invasive cancer were observed, and the difference was not statistically significant. We also observed no significant differences between two groups in progression-free survival and overall survival.

\textbf{Conclusion.} Complete surgical staging could probably be omitted in patients with stage I mucinous epithelial tumors.

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\textbf{Keywords:} Mucinous ovarian, borderline tumor, Mucinous adenocarcinoma, Surgical staging, Stage I
LS vs LT

No high quality RCT
No data to recommend LS as a routine practice

Falcetta et al., 2017
Minimally Invasive Surgical Staging in Early-stage Ovarian Carcinoma: A Systematic Review and Meta-analysis

N = 3065 early stage EOC
1450 → LS
1615 → LT

✓ Longer op time, less blood loss, less complication in LS
✓ The risk of cyst rupture is almost equivalent
✓ Survival and recurrence are almost equivalent
LS in Early Stage Ovarian Cancer

- The same intraabdominal procedure
- Specimen retrieval bags should be used
  - Prevent spillage
  - Avoid contact with port sites
- Omentum may be extracted through vagina
Is Intraoperative Frozen Section Reliable

The same final diagnosis: 94%

The same final diagnosis: 99%

Ratnavelu et al, 2016
If frozen diagnosis is borderline

The rate of cancer on final pathology

21 %

Oncological surgery may be chosen
The role of surgeon in early stage ovarian cancer

Chan et al, Obstet Gynecol, 2007
ESGO Guideline for Ovarian Cancer Surgery

Recommendations

✓ Midline LT
✓ Two-step surgery
  ✓ If frozen is not available
✓ At least infracolic omentectomy
✓ Pelvic-paraaortic LA
  ✓ Up to the left renal vein
  ✓ Exception: mucinous tumor

Acceptable

✓ LS

Querleu et al, Int J Gynecol Cancer, 2017
Fertility-Sparing Surgery (FSS) in EOC

USO + Surgical Staging

- Stage IA, IC
- Histologic type
  - Clear cell
- Grade 1, 2
  - 3
- Age < 40 years
Fertility-sparing surgery in epithelial ovarian cancer: a systematic review of oncological issues

E. Bentivegna¹, S. Gouy¹, A. Maulard¹, P. Pautier², A. Leary²,³, N. Colombo⁴ & P. Morice¹,⁵,⁶*

n= 1100

<table>
<thead>
<tr>
<th>Stage</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA, grade 1</td>
<td>7%</td>
</tr>
<tr>
<td>IA, grade 2</td>
<td>11%</td>
</tr>
<tr>
<td>IA, grade 3</td>
<td>29%</td>
</tr>
<tr>
<td>IC, grade 1-2</td>
<td>11%</td>
</tr>
<tr>
<td>IC, grade 3</td>
<td>23%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage IC</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC1</td>
<td>12%</td>
</tr>
<tr>
<td>IC2</td>
<td>22%</td>
</tr>
<tr>
<td>IC3</td>
<td>19%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histology</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell (n=115)</td>
<td>17%</td>
</tr>
</tbody>
</table>
Fertility-sparing surgery in epithelial ovarian cancer: a systematic review of oncological issues

E. Bentivegna¹, S. Gouy¹, A. Maulard¹, P. Pautier², A. Leary²,³, N. Colombo⁴ & P. Morice¹,⁵,⁶*

- FSS is safe in stage IA, G 1-2 and IC1 disease
- Safety is questionable for G 3 or stage IC3 disease
- FSS can be considered in stage I clear cell tumors
Adjuvant Therapy
Well-known RCTs on Adjuvant Therapy

- **EORTC-ACTION Trial**
  - n= 448
  - Stage IA-B, G2-3; stage IC-IIA; stage I-IIA with clear cell histology
  - Randomization: CT (min. 4 cycles platinum based) vs observation

- **ICON-1 Trial**
  - n= 477
  - Stage I-II EOC
  - Randomization: CT (6 cycles platinum based) vs observation

Trimbos et al, J Nati Cancer Inst, 2003
Colombo et al, J Nati Cancer Inst, 2003
Optimal staging is associated with longer survival

Overall survival and type of surgery

No difference between CT and observation in optimally staged patients

Overall survival and adjuvant therapy in optimally staged patients

CT is associated with longer survival in inadequately staged patients.

Overall survival and adjuvant therapy in inadequately staged patients.
No difference between optimal and suboptimal staging in CT arm

**Overall survival in adjuvant CT arm:** optimally and non-optimally staged patients
10-year Follow-up Data of ACTION and ICON-1

Surgical Staging and Treatment of Early Ovarian Cancer: Long-term Analysis From a Randomized Trial

Baptist Trimbos, Petra Timmers, Sergio Pecorelli, Corneel Coens, Koen Ven, Maria van der Burg, Antonio Casado

Optimal treatment of early-stage ovarian cancer

F. Collinson\textsuperscript{1}, W. Qian\textsuperscript{2}, R. Fossati\textsuperscript{3}, A. Lissoni\textsuperscript{4}, C. Williams\textsuperscript{5}, M. Parmar\textsuperscript{6*}, J. Ledermann\textsuperscript{7}, N. Colombo\textsuperscript{8} & A. Swart\textsuperscript{9} on behalf of the ICON1 collaborators
### Clinical advantage of adjuvant chemo- in stage I/II disease

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks</th>
<th>HR (95% CI)</th>
<th>Chemotherapy versus observation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall 5-year survival</strong></td>
<td></td>
<td><strong>HR 0.71 (0.53 to 0.93)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22 deaths out of 100 women</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>16 out of 100 women (12 to 20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Progression-free 5-year survival</strong></td>
<td></td>
<td><strong>HR 0.67 (0.53 to 0.84)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>32 women with progressive disease out of 100 women</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22 women with progressive disease out of 100 women (18 to 27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overall 10-year survival</strong></td>
<td></td>
<td><strong>HR 0.72 (0.57 to 0.92)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>33 deaths out of 100 women</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25 deaths out of 100 women (20 to 31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Progression-free 10-year survival</strong></td>
<td></td>
<td><strong>HR 0.67 (0.53 to 0.83)</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>39 women with progressive disease out of 100 women</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>28 women with progressive disease out of 100 women (23 to 34)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Included studies:**

1. ACTION 2003
2. Bolis 1995
3. ICON1 2003
4. Trope 2000
### Based on ACTION and ICON1 10-year follow-up data

<table>
<thead>
<tr>
<th>10-year survival</th>
<th>Adjuvant CT, %</th>
<th>Observation, %</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (low intermediate risk)</td>
<td>81</td>
<td>78</td>
<td>NS</td>
</tr>
<tr>
<td>DFS (low intermediate risk)</td>
<td>78</td>
<td>75</td>
<td>NS</td>
</tr>
<tr>
<td>OS (high risk)</td>
<td>71</td>
<td>56</td>
<td>0.03</td>
</tr>
<tr>
<td>DFS (high risk)</td>
<td>68</td>
<td>50</td>
<td>0.009</td>
</tr>
</tbody>
</table>

### Clinical advantage of adjuvant chemo- in stage I disease

Risk groups:
- **Low**: Stage IA, G1
- **Intermediate**: Stage IA, G2 / Stage IB or IC, G1
- **High**: Stage IA, G3 / Ib or IC G2-3 / clear cell

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**Cochrane Library**

Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer (Review)

Lawrie TA, Winter-Roche BA, Heus P, Kitchener HC
According to 10-year follow-up data of ACTION Trial:

No difference between CT and observation in optimally staged patients

CT prolongs the survival in non-optimally staged patients

Trimbos et al, J Natl Cancer Inst, 2010
Epithelial Ovarian Cancer/Fallopian Tube Cancer/
Primary Peritoneal Cancer

Stage IA or IB
- Grade 1\textsuperscript{1} (low-grade) serous/endometrioid
- Grade 2\textsuperscript{1} serous/endometrioid
- Grade 3\textsuperscript{1} or high-grade

Stage IC (Grade 1, 2, or 3)

- See LCOH-5
- Observe or Intravenous (IV) taxane/carboplatin\textsuperscript{k} x 3–6 cycles\textsuperscript{o,p}
- IV taxane/carboplatin\textsuperscript{k} x 3–6 cycles\textsuperscript{o,p}
Epithelial Ovarian Cancer/Fallopian Tube Cancer/
Primary Peritoneal Cancer

Stage IA-IB → Observe

Stage IC-II → Observe (category 2B)
or
IV taxane/carboplatin\textsuperscript{e} x 3–6 cycles
or
Hormone therapy (category 2B)
(i.e., aromatase inhibitors [anastrozole, letrozole], leuprolide acetate, tamoxifen)

Grade 1 (Low-Grade)
Serous/Endometrioid
Epithelial Carcinoma
Mucinous carcinoma

Mucinous carcinoma of the ovary

If not previously done:
- GI evaluation
- Carcinoembryonic antigen (CEA)

Consider surgical staging

Stage IA-IB → Observe

Stage IC

Observe or
IV taxane/carboplatin<br>5-FU + leucovorin + oxaliplatin<br>or<br>Capecitabine + oxaliplatin
Similar recommendations to NCCN and ESGO guidelines

*Exception: Stage IC, G1: Adjuvant CT is recommended.*

*No option for observation*
Surveillance

- **Visits**
  - Every 2-4 months for first 2 years
  - Then 3-6 months for 3 years
  - Then annually

- **Physical examination**

- **CA 125**

- **Imaging performed with contrast as clinically indicated**
  - Chest/abdominal/pelvic CT, MRI, PET-CT or PET
Thank you for your attention