Cytoreductive Surgery for Advanced Ovarian Cancer
How Far Should We Go To Achieve Optimal Status?

Jonathan S. Berek, MD, MMS
Laurie Kraus Lacob Professor
Stanford University School of Medicine
Senior Scientific Advisor
Stanford Comprehensive Cancer Institute
Stanford University
Surgical Cytoreduction of Ovarian Cancer

- Optimal “debulking” (<1.5 cm)
- median survival longer than suboptimal & similar to those whose disease small prior to resection*

*Griffiths CT. Seminars Oncol 1975
Berek JS, Leventhal J, Griffiths TC, Obstet Gynecol 1979
Cytoreductive Surgery for Advanced Ovarian Cancer

Acknowledgement

Neville F. Hacker, MD
Archana Rao, MD

1st Edition of Berek and Hacker, 1985
Cytoreductive Surgery in Ovarian Cancer

Is it the act of committing cytoreduction or the manner in which the disease grows, i.e., its tumor biology, that permits optimal debulking?

Is the outcome a result of the surgery, or just the natural history of the cancer?
“Well, I guess that explains the abdominal pains.”
Cytoreductive Surgery for Advanced Ovarian Cancer

- Gold standard for most patients with stage III metastatic epithelial ovarian, fallopian tube & peritoneal (Ov-FT-P) cancers

- Requires appropriate surgical expertise

- Best performed in regional cancer centers
Cytoreductive Surgery for Advanced Ovarian Cancer

What are the factors that influence the maximal cytoreductive effort?

• Performance status of patient
• Biology of the disease
• Extent of metastatic disease
• Distribution of disease
• Aggressiveness of surgeon
Cytoreductive Surgery for Advanced Ovarian Cancer

What is the most optimal status?

- < 0.5 cm
- 0

Hoskins, et al. Gynecol Oncol 1992
Cytoreductive Surgery for Advanced Ovarian Cancer

- Stage IV disease
  - less clear how effective
How aggressive should we be?

• Pelvic viscera-colectomy
• Lymphadenectomy
• Small intestinal resection
• Splenectomy
• Diaphragm resection
• Hepatic resection
• Pulmonary-pleura resection
Resection of a bulky, positive lower precaval lymph nodes, which were causing partial obstruction of the right ureter.
Resection of Lymph Nodes During Cytoreductive Surgery

• Prospective, randomized study of patients whose tumors were optimally cytoreduced in the peritoneal cavity underwent systematic pelvic and paraaortic lymphadenectomy vs. resection of bulky nodes only.

• Well matched arms

  Systematic lymphadenectomy = 216 (189 eval) pts
  Nodal debulking = 211 (195 eval) pts

• PFS = 27.4 vs. 22.4 (5 mo +)

• 5-year OS 48.5% vs. 47 % (95% CI =8.4-10.6%)

J Natl Cancer Inst 2005;97:560
Carcinomatosis
Large omental cake densely adherent to and infiltrating into the spleen
Radical Upper Abdominal Surgery
Resection of transverse colon, omentum, spleen & distal pancreas to remove metastatic disease involving the omentum, spleen, & transverse mesocolon
PET/CT scan - ovarian cancer metastasis involving the liver & right diaphragm (L)
Involved segment of right diaphragm resected, still attached to disease in liver (R)

Hacker 2017
Resection of underlying disease in the liver.
Hemostasis secured by sutures and application of hemostatic material
“Let’s hope we never have to use it!”
Cytoreductive Surgery for Advanced Ovarian Cancer

- Primary Debulking Surgery (PDS) vs. Neoadjuvant Chemotherapy (NACT) > Interval debulking surgery (IDS)
Meta-analysis of the randomized EORTC and CHORUS Neoadjuvant versus Primary Debulking trials in advanced Ovarian Cancer

Ignace Vergote,
Corneel Coens, Matthew Nankivell, Gunnar B. Kristensen, Max Parmar, Tom Ehlen, Gordon C. Jayson, Nick Johnson, Ann Marie Swart, René Verheijen, W. Glenn McCluggage, Tim Perren, Pier-Luigi Benedetti, Gemma Kenter, Antonio Casado, Cesar Mendiola, Gavin Stuart, Nick S. Reed,
Sean Kehoe
Meta-analysis of the randomized EORTC and CHORUS Neoadjuvant versus Primary Debulking trials in advanced ovarian cancer

• **Background and aims.**
  – Pre-planned meta-analysis of 2 randomized trials (EORTC 55971-NEJM 2010;363:943 - and MRC CHORUS- Lancet 2015;6763: 62223) comparing neoadjuvant chemotherapy (NACT) with primary debulking surgery (PDS) in advanced ovarian-fallopian tube cancer

• **Methods.**
  – The patient data of both trials were updated and merged in one data base (data base lock EORTC June 6, 2015 and CHORUS May 20, 2015)

• **Median follow-up: 7.6 years:**
  – EORTC: 9.2 y
  – Chorus: 5.9 y
Randomized EORTC-GCG/NCIC-CTG Trial
NACT + IDS vs PDS

Ovarian, fallopian tube, or peritoneal cancer
FIGO stage IIIc-IV (n = 718)

Randomization

Primary debulking surgery
- 3 x platinum-based CT
- Interval debulking (not obligatory)
- ≥3 x platinum-based CT

Neoadjuvant chemotherapy
- 3 x platinum-based CT
- Interval debulking if no PD
- ≥3 x platinum-based CT

48 patients excluded from 1 center → N = 670

Primary endpoint: Overall survival
Secondary endpoints: Progression-free survival, quality of life, complications

EORTC: NACT + IDS vs PDS: ITT
Overall Survival

Median survival
PDS: 29 months
IDS: 30 months
HR for IDS 0.98 (0.84, 1.13)

CHORUS trial (Kehoe S et al)

Randomized
N=552

PS
N=276
Primary surgery
N=248
Post-op chemo
N=210

NACT
N=274
Neoadjuvant chemo
N=252
Surgery
N=214
Post-op chemo
N=199

Randomized in error 2
Ineligible at disease conf 10
Progression/unfit/died 9
Patient withdrew 3

Progression/unfit/died 18
Patient withdrew 3
Physician choice 4
No malignancy 2
Incomplete data 1

No post-op chemo 35
Incomplete data 3

Complete response 5
Insufficient response 1
Ineligible 2
Patient choice 1

No post-op chemo 15

Kehoe S, Lancet 2015;6763: 62223
Overall survival
CHORUS TRIAL

Overall survival
intention-to-treat population

<table>
<thead>
<tr>
<th>Time from randomisation (months)</th>
<th>PS (N=276)</th>
<th>NACT (N=274)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Events</td>
</tr>
<tr>
<td></td>
<td>211</td>
<td>199</td>
</tr>
<tr>
<td>Median (months)</td>
<td>22.8</td>
<td>24.5</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(19.1, 26.0)</td>
<td>(21.3, 29.1)</td>
</tr>
<tr>
<td>HR* (95% CI)</td>
<td>0.87</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>(0.71, 1.05)</td>
<td>(1.05)</td>
</tr>
<tr>
<td>1-year OS rate</td>
<td>70%</td>
<td>76%</td>
</tr>
<tr>
<td>3-year OS rate</td>
<td>32%</td>
<td>34%</td>
</tr>
</tbody>
</table>

9% IIA-IIIB in PDS with R0 rate of 16%

Kehoe S, Lancet 2015, 386:249

* HR adjusted for baseline stratification factors.
## Meta-analysis

### EORTC & Chorus trials (n = 1220)

<table>
<thead>
<tr>
<th></th>
<th>EORTC (n= 670)</th>
<th>Chorus (n=550)</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (y)</td>
<td>62</td>
<td>65</td>
<td>63</td>
</tr>
<tr>
<td>Largest metastatic tumor size (mm)</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>CA125 at entry (KU/L)</td>
<td>1161</td>
<td>1016</td>
<td>1089</td>
</tr>
<tr>
<td>WHO performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>44.8%</td>
<td>31.1%</td>
<td>38.6%</td>
</tr>
<tr>
<td>1</td>
<td>42.4%</td>
<td>49.3%</td>
<td>45.5%</td>
</tr>
<tr>
<td>2</td>
<td>12.5%</td>
<td>18.5%</td>
<td>15.2%</td>
</tr>
<tr>
<td>3</td>
<td>0%</td>
<td>0.9%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Missing</td>
<td>0.3%</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>FIGO stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>0%</td>
<td>3.5%</td>
<td>1.6%</td>
</tr>
<tr>
<td>IIIA</td>
<td>0%</td>
<td>2.5%</td>
<td>1.1%</td>
</tr>
<tr>
<td>IIIB</td>
<td>0.1%</td>
<td>3.8%</td>
<td>1.8%</td>
</tr>
<tr>
<td>IIIC</td>
<td>76.1%</td>
<td>58.4%</td>
<td>68.1%</td>
</tr>
<tr>
<td>IV</td>
<td>23.6%</td>
<td>13.1%</td>
<td>18.9%</td>
</tr>
<tr>
<td>Missing</td>
<td>0.1%</td>
<td>18.7%</td>
<td>8.5%</td>
</tr>
</tbody>
</table>
Meta-analysis
EORTC and Chorus trials (n = 1220)

Overall survival
By study

Overall Score test: p=0.004

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (N)</th>
<th>Observed Events (O)</th>
<th>Median (95% CI, Years)</th>
<th>% at 5 Year(s) (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P.Value (Score test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC 55971</td>
<td>670</td>
<td>602</td>
<td>2.62 (2.32, 2.69)</td>
<td>21.3 (18.3, 24.5)</td>
<td>1.00</td>
<td>0.004</td>
</tr>
<tr>
<td>MRC CHORUS</td>
<td>550</td>
<td>451</td>
<td>1.95 (1.71, 2.18)</td>
<td>16.5 (13.2, 20.1)</td>
<td>1.20 (1.06, 1.36)</td>
<td>0.004</td>
</tr>
</tbody>
</table>
Meta-analysis
EORTC and Chorus trials (n = 1220)

Overall survival
By treatment arm

Overall Score test stratified for Study: p=0.577

<table>
<thead>
<tr>
<th></th>
<th>Patients (N)</th>
<th>Observed Events (O)</th>
<th>Median (95% CI) (Years)</th>
<th>% at 5 Year(s) (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-Value (Score test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upfront debulking surgery</td>
<td>612</td>
<td>528</td>
<td>2.24 (1.97, 2.40)</td>
<td>19.3 (16.2, 22.7)</td>
<td>1.00</td>
<td>0.577</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>608</td>
<td>525</td>
<td>2.30 (2.12, 2.56)</td>
<td>19.3 (16.1, 22.6)</td>
<td>0.97 (0.86, 1.09)</td>
<td>0.577</td>
</tr>
</tbody>
</table>

Log-rank test: p-value=0.577
Meta-analysis
EORTC and Chorus trials (n = 1220)

Overall survival
FIGO IIIc

By treatment arm (n= 831)

Overall Score test stratified for Study: p=0.583

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (N)</th>
<th>Observed Events (O)</th>
<th>Median (95% CI) [Years]</th>
<th>% at 5 Year(s) (95% CI)</th>
<th>Treatment Hazard Ratio (95% CI)</th>
<th>P Value (Score test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upfront debulking surgery</td>
<td>433</td>
<td>366</td>
<td>2.37 (2.11, 2.66)</td>
<td>22.5 (18.6, 26.7)</td>
<td>1.00</td>
<td>0.583</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>398</td>
<td>347</td>
<td>2.56 (2.30, 2.72)</td>
<td>19.4 (15.5, 23.6)</td>
<td>1.04 (0.90, 1.21)</td>
<td></td>
</tr>
</tbody>
</table>

Log-rank test: p-value=0.583
Meta-analysis
EORTC and Chorus trials (n = 1220)

Overall survival
By treatment arm (n = 230)

Overall Score test stratified for Study: p=0.048

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (N)</th>
<th>Observed Events (O)</th>
<th>Median (95% CI) (Years)</th>
<th>% at 5 Year(s) (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-Value (Score test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upfront debulking surgery</td>
<td>118</td>
<td>112</td>
<td>1.77 (1.30, 2.21)</td>
<td>9.0 (4.6, 15.1)</td>
<td>1.00</td>
<td>0.048</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>112</td>
<td>104</td>
<td>2.02 (1.80, 2.55)</td>
<td>14.4 (8.6, 21.8)</td>
<td>0.76 (0.58, 1.00)</td>
<td>0.048</td>
</tr>
</tbody>
</table>

Log-rank test: p-value=0.048
## EORTC: NACT + IDS vs PDS: ITT

Survival Time: FIGO Stage

<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>EORTC 55971</th>
<th>Upfront debulking</th>
<th>Neo-adj. Chemo</th>
<th>Statistics</th>
<th>HR &amp; CI*</th>
<th>1-HR</th>
<th>% ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>185/258</td>
<td>188/253</td>
<td>-6.4</td>
<td>92.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>67/76</td>
<td>57/81</td>
<td>10.1</td>
<td>30.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>252/334</td>
<td>245/334</td>
<td>3.8</td>
<td>123.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(75.4 %) (73.4 %)

Test for heterogeneity

Chi-square=3.7, df=1: p=0.05

*90% CI everywhere

**Treatment effect:** p > 0.1

**Chi-square=3.7, df=1: p=0.05**

EORTC: NACT + IDS vs PDS: PP1
Overall Survival: Largest Metastatic Tumor Size

- <5 cm: HR, 0.64; 95% CI: 0.45-0.93

Meta-analysis
EORTC and Chorus trials (n = 1220)

Stage IIIC with metastases at diagnosis ≤ 5 cm (N=266)

Overall survival

<table>
<thead>
<tr>
<th>Trtm arm</th>
<th>Patients (N)</th>
<th>Observed Events (O)</th>
<th>Median (95% CI) (Years)</th>
<th>% at 5 Year(s) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UDS</td>
<td>136</td>
<td>108</td>
<td>2.75 (2.37, 3.20)</td>
<td>31.1 (23.4, 39.1)</td>
</tr>
<tr>
<td>NACT</td>
<td>130</td>
<td>110</td>
<td>2.51 (2.14, 2.77)</td>
<td>19.9 (13.2, 27.6)</td>
</tr>
</tbody>
</table>

Cox model

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI)</th>
<th>P-Value (Score test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>0.092</td>
</tr>
<tr>
<td>1.26 (0.96, 1.65)</td>
<td>Log-rank test: p-value=0.092</td>
</tr>
</tbody>
</table>
Conclusions
EORTC-CHORUS meta-analysis

1. 1220 patients with this group of Stage IIIc-IV ovarian cancer with long-term follow-up (7 years) - NACT results in similar survival compared with PDS

2. Only patients with biopsy proven stage IIIc or IV are candidates for neoadjuvant chemotherapy

3. Interval debulking should be planned after 3 courses of chemotherapy
Conclusions

EORTC-CHORUS meta-analysis

4. Patients with stage IIIc and metastases ≤ 5 cm are generally better treated with primary debulking, depending on good general medical condition and no extensive spread on the bowel, or tumor on inoperable sites, e.g. around superior mesenteric artery

5. Patients with Stage IV disease are generally better treated with neoadjuvant chemotherapy, except for those with pleural effusions only and easily resectable Stage IV, e.g., inguinal nodes, spleen
How to Select Patients?
Laparoscopy to predict the result of primary cytoreductive surgery in patients with advanced ovarian cancer: randomized controlled trial

<table>
<thead>
<tr>
<th>Arm</th>
<th>n</th>
<th>“futile”</th>
<th>PDS+ IDS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laprosc</td>
<td>102</td>
<td>10 (10%)</td>
<td>3 (3%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PDS</td>
<td>99</td>
<td>39 (39%)</td>
<td>28 (28%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total</td>
<td>201</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NACT- IDS vs. PDS

Criticisms of Studies

• Low percentage of patients had optimal (no residual) resection of disease
  16-40% (4-10%)

• Poorer performance status than in most upfront randomized prospective studies
  (high of 19-20% PS 2-3)
## Discussion: PDS vs. NACT-IDS

### Performance Status

<table>
<thead>
<tr>
<th>Study</th>
<th>Status 0</th>
<th>Status 2-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC</td>
<td>44-45%</td>
<td>12-13%</td>
</tr>
<tr>
<td>CHORUS</td>
<td>30-32%</td>
<td>19-20%</td>
</tr>
<tr>
<td>Mito7</td>
<td>74-75%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Presented by: Jonathan S. Berek
## Discussion: PDS vs. NACT-IDS

### Age years median (Range)

<table>
<thead>
<tr>
<th>Study</th>
<th>PDS</th>
<th>NCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHORUS</td>
<td>276 pts</td>
<td>274 pts</td>
</tr>
<tr>
<td></td>
<td>66 yrs (26-87)</td>
<td>65 yrs (34-88)</td>
</tr>
<tr>
<td>EORTC</td>
<td>336 pts</td>
<td>334 pts</td>
</tr>
<tr>
<td></td>
<td>62 yrs (25-86)</td>
<td>63 yrs (33-81)</td>
</tr>
<tr>
<td>JGOG 3016</td>
<td>57 yrs (25-87), MITO7</td>
<td>59 yrs (23-87)</td>
</tr>
</tbody>
</table>
Deaths within 28 days Postop

<table>
<thead>
<tr>
<th>Surgery</th>
<th>PDS</th>
<th>NACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHORUS</td>
<td>14 (5.6%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>EORTC</td>
<td>(2.5%)</td>
<td>(0.7%)</td>
</tr>
</tbody>
</table>

PDS
- Disease progression = 4
- Pulmonary embolism = 2; infection = 3; problems with fluid balance or renal failure = 2; hemorrhage = 1; intra-operative problems = 1
- *Still under review* = 1

NACT
- Pulmonary embolism = 1
Primary Debulking vs. Neoadjuvant chemoRx + Interval Debulking

• **Controversial Points**
  – Extent of debulking surgery/surgical expertise
  – High mortality in PDS

• **Median survivals much shorter than in most upfront RCT in stage III ovarian cancer**

Presented by: Jonathan S Berek
Primary Debulking vs. Neoadjuvant chemoRx + Interval Debulking

Compared to most up-front RCT in Ov-FT-P patients-

- **Poorer than expected patient characteristics**
  - Highly selected- older, sicker, larger mets!

- **Higher tumor burden of recruited patients**
  - 62% pts in EORTC mets > 10 cm
  - 20% pts in CHORUS  PS > 2
Discussion: PDS vs. NACT-IDS

Comparison of JGOG Dose-dense vs. CHORUS/EORTC NACT

- Overall median survivals much shorter in these two studies than in JGOG
  - PFS 10-11 months vs. 28+ months
  - OS 22-24 months vs. 62+ months
- Differences in performance status & age
- Good prognosis vs. poor prognosis patients—study populations in are very different!

Presented by: Jonathan S Berek
JOGG3016: Updated Overall Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Deaths, n (%)</th>
<th>Median OS</th>
<th>5-yr survival</th>
<th>P value</th>
<th>HR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>dd-TC</td>
<td>312</td>
<td>139 (45)</td>
<td>not reached</td>
<td>58.7%</td>
<td>0.039</td>
<td>0.79</td>
<td>0.63-0.99</td>
</tr>
<tr>
<td>c-TC</td>
<td>319</td>
<td>168 (53)</td>
<td>62.2 mos.</td>
<td>51.1%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Primary Debulking vs. Neoadjuvant chemoRx
+ Interval Debulking

• Therefore

“the generalization of results from such highly selected adverse subgroups risks extrapolation to patients who are fit and present with potentially resectable disease.”

Discussion: PDS vs. NACT-IDS

How do we best select patients who should undergo PDS?

- Patient selection is key
- Need to minimize operative mortality–gynecologic oncologic surgeons in major centers
- Can we select patients by ‘Gestalt’ e.g., a ‘clinical scoring algorithm’?
- Can we develop a molecular assay that can help us predict?
TRUST

Trial on Radical Upfront Surgical Therapy

Upfront radical debulking surgery versus interval radical debulking surgery in advanced ovarian cancer
Design-proposal neoadjuvant chemotherapy
International phase III

Pts. With ovarian-, fallopian-tube or peritoneal-cancer FIGO stage IIIB, IIIC and resectable stage IV (VATS or open assessment if pleural effusion recommended/mandatory)

Primary Endpoint OS ITT population; co primary Endpoint „per Protocol“=50% resec.
Secondary Endpoints PFS, resection rates, M\'nM after 6 months, QoL, „fragility Index“
Strata: FIGO stage (III / IV), group/country, ECOG 0 vs 1/2
Defined qualification process for participating centers to ensure highest surgical quality (>50% complete resection rate, >25 procedures/year)

Surgery
Carboplatin AUC5 Paclitaxel 175 mg/sq
Bev. 15mg 15 mon
suggested therapy, also weekly paclitaxel possible if preferred or omission of Bev
Discussion: PDS vs. NACT-IDS
Take-Home Message!

• Because this is by definition a poorer prognosis group, the findings of the 2 RCTs cannot be generalized to all patients with stage III ovarian cancer!

• **Standard of care should still be primary debulking surgery followed by chemotherapy for most patients.**