Secondary Cytoreductive Surgery for Recurrent Ovarian Cancer

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Presentation Objectives

To address the following clinical questions regarding SCRS for recurrent ovarian cancer:

(1) What is the potential survival benefit of successful SCRS and what constitutes an optimal surgical resection?
(2) What is the feasibility of successful SCRS?
(3) What is the associated risk of morbidity?
(4) Are there clearly defined selection criteria by which to identify patients suitable for SCRS?
Recurrent Ovarian Cancer

Scope of the problem
- 25,400 new primary cases annually (U.S)
- 17,780 cases with regional / distant spread
- Recurrence risk 40-90%

Management considerations
- Therapeutic goals
  - cure / survival extension / palliation
- Timing of intervention
  - immediate vs delayed
- Treatment options
  - chemotherapy, surgery, radiation, hormonal, or investigational agents
Secondary Cytoreductive Surgery

Because the majority of patients with advanced-stage epithelial ovarian cancer will ultimately experience a recurrence of their disease, the therapeutic value of repeating the initial surgical treatment plan (secondary tumor cytoreduction) has been widely debated.
Survival After Secondary Cytoreductive Surgery for Ovarian Cancer

- UCLA 1974-79: 32 patients
- Optimal residual (<1.5cm) in 38%
- Heterogeneous population
  - operation interval 6-48 months
  - second-look laparotomy (11)
  - bowel obstruction (12)

**Terminology**

(1) **Progressive Disease**: clinical disease progression during front-line chemotherapy

(2) **Interval Debulking**: initially unresectable disease treated with abbreviated course of chemotherapy followed by repeat attempt at debulking

(3) **Second-Look Surgery**: clinically without evidence of disease after primary surgery and chemotherapy

(4) **Recurrent Disease**: complete clinical response with an extended (6-12m) disease-free interval
Secondary Cytoreductive Surgery for Non-Responders to Front-Line Therapy

- MD Anderson Cancer Center 1977-84: 33 patients
  - stable (2) / progressive disease (31)
- Optimal residual (<1.0cm) in 21.2%
- Median survival time
  - optimal residual = 19.5m
  - suboptimal residual = 8.3m
  - concluded that survival benefit ‘clinically insignificant’

*Morris et al. Gynecol Oncol 1989; 33: 1.*
# SCRS for Recurrent Ovarian Cancer

<table>
<thead>
<tr>
<th>Author / Year</th>
<th>N</th>
<th>DFI (mo)</th>
<th>Residual</th>
<th>Feasibility</th>
<th>Survival (mo)</th>
<th>p-value</th>
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<table>
<thead>
<tr>
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<td>Onda 2005</td>
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<tr>
<td>Matsumoto 2006</td>
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<td>≤2cm</td>
<td>NA</td>
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<td>&gt;1cm</td>
<td>13%</td>
<td>19</td>
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</table>

- Number of studies: 24
- Number or patients: 1,627
- Proportion of studies showing a statistically significant survival advantage for successful SCRS: 92% (22/24)
Summary of SCRS Literature

- **Feasibility**
  - optimal residual 37% to 87%
  - complete cytoreduction 9% to 83%

- **Morbidity**
  - serious complications in 9% to 44%
  - mortality 0% to 4%

- **Survival extension after successful SCRS**
  - optimal: 5 to 42 months vs suboptimal
  - complete: 10 to 58 months vs any residual
**Objective:** determine relative impact of multiple prognostic variables in patients undergoing SCRS

**Methods:**
- Medline database (1983-2007)
- 40 patient cohorts (2,019 patients)
- simple/multiple linear regression analyses
- weighted correlation calculations

<table>
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<th>Statistical Variables</th>
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<tr>
<td>Year of publication</td>
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<tr>
<td>Disease-free interval</td>
</tr>
<tr>
<td>Tumor grade/histology</td>
</tr>
<tr>
<td>Sequence of surg/chemo</td>
</tr>
<tr>
<td>Proportion with complete resection</td>
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<tr>
<td>Age</td>
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<tr>
<td>Localized disease</td>
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<tr>
<td>Bowel resection</td>
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<tr>
<td>Salvage chemo regimen</td>
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</table>

*Bristow RE et al. Gynecol Oncol 2009; 112: 265.*
Cytoreductive surgery for recurrent ovarian cancer: A meta-analysis

Robert E. Bristow \textsuperscript{a,*}, Isha Puri \textsuperscript{a}, Dennis S. Chi \textsuperscript{b}

Increasing Year of Publication
Each 1 yr increase = 1.12 m
95\%CI = 0.43 – 1.82 m (p=0.002)

Proportion Complete Cytoreduction
Each 10\% increase = 2.84 m
95\%CI = 1.29 – 4.38 m (p=0.0008)

Bristow RE et al. Gynecol Oncol 2009; 112: 265.
## Multiple Linear Regression Analysis

### Median Cohort Survival

<table>
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<tr>
<th>Variable</th>
<th>Δ Median Survival</th>
<th>Significance</th>
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<tr>
<td>Year of publication (+1 yr)</td>
<td>+1.00m</td>
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<tr>
<td>Median cohort age</td>
<td>-0.55m</td>
<td>0.39</td>
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<tr>
<td>Proportion surgery/chemo (+10%)</td>
<td>+0.43m</td>
<td>0.66</td>
</tr>
<tr>
<td>Proportion serous histology (+10%)</td>
<td>+1.09m</td>
<td>0.68</td>
</tr>
<tr>
<td>Proportion grade 3 tumor (+10%)</td>
<td>+0.43m</td>
<td>0.79</td>
</tr>
<tr>
<td>Proportion localized disease (+10%)</td>
<td>-1.16m</td>
<td>0.28</td>
</tr>
<tr>
<td>Proportion bowel resection (+10%)</td>
<td>+0.83m</td>
<td>0.56</td>
</tr>
</tbody>
</table>

*Bristow RE et al. Gynecol Oncol 2009; 112: 265.*
Women’s Cancer Center

- Recurrent epithelial ovarian cancer
  - 106 consecutive patients
  - DFI ≥ 6 months
- Complete cytoreduction in 82.1%
  - largest size of recurrent tumor (≤10cm)
  - surgery prior to salvage chemotherapy
  - performance status
- Median post-recurrence survival = 36 mos

Women’s Cancer Center
Disease-Free Interval

Women’s Cancer Center
Largest Size of Recurrence

Women’s Cancer Center
Residual Disease

Criteria for Consideration of SCRS

(1) Complete clinical response with a disease-free interval ≥6 months

(2) Rising CA125 level and/or radiographic or physical findings suggestive of recurrence

(3) Absence of unresectable extra-abdominal or hepatic metastases

(4) Patient acceptance of post-SCRS adjuvant therapy

(5) Absence of medical contraindications to SCRS

(6) GOG performance status score ≤3
• Recurrent epithelial ovarian cancer
  - 46 patients
  - Median DFI = 26 months
  - DFI \geq 12 \text{ months} – 89%
  - Localized disease – 54%
• Complete secondary cytoreduction - 41%
• Median overall survival = 22.5 months

Royal Hospital for Women
Disease-Free Interval

Survival Benefit - Risk Ratio Analysis

- No prior platinum: p-value = 0.58
- Residual disease:
  - Nil: p-value = 0.01
  - < 1 cm: p-value = 0.30
- Disease-free interval:
  - 12-24 months: p-value = 0.43
  - > 24 months: p-value = 0.01

Guidelines and Selection Criteria for SCRS in Recurrent, Platinum-Sensitive Ovarian Cancer

- Retrospective review MSKCC 1987-2001
  - 153 evaluable patients
  - Complete clinical remission + DFI ≥6 months
  - Stage III/IV disease – 65%; grade 2/3 tumor – 84%

- Operative findings / procedures

<table>
<thead>
<tr>
<th>Ascites</th>
<th>19%</th>
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<tbody>
<tr>
<td>One site</td>
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<tr>
<td>Multiple sites</td>
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<tr>
<td>Carcinomatosis</td>
<td>29%</td>
</tr>
<tr>
<td>Large bowel resection</td>
<td>31%</td>
</tr>
<tr>
<td>Small bowel resection</td>
<td>21%</td>
</tr>
<tr>
<td>Lymphadenectomy</td>
<td>15%</td>
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<tr>
<td>Omentectomy</td>
<td>12%</td>
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</table>

Central Pelvic Recurrence
Gastrocolic Ligament Recurrence
Guidelines and Selection Criteria for SCRS in Recurrent, Platinum-Sensitive Ovarian Cancer

● Residual disease after SCRS
  - no macroscopic 41%
  - 0.1 to 0.5cm 11%
  - 0.6 to 1.0cm 14%
  - 1.1 to 2.0cm 7%
  - ≥2.1cm 27%

● Median post-SCRS follow-up = 36.9 months
● Median overall post-SCRS survival = 41.7 months

Guidelines and Selection Criteria for SCRS in Recurrent, Platinum-Sensitive Ovarian Cancer

Survival as a function of Residual Disease

Guidelines and Selection Criteria for SCRS in Recurrent, Platinum-Sensitive Ovarian Cancer

Survival as a function of Disease-Free Interval

- Little change @ DFI 6-12 m
- Significant change @ 13-30 m
- Benefit plateaus after 30 m
- 30 m DFI most prognostic

## Guidelines and Selection Criteria for SCRS in Recurrent, Platinum-Sensitive Ovarian Cancer

### Significant Variables on Multivariate Survival Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter</th>
<th>Median Survival</th>
<th>Significance</th>
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<td>≥0.6cm</td>
<td>26.7 months</td>
<td>p&lt;0.001</td>
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<td>Disease-free interval</td>
<td>6-12 months</td>
<td>30.0 months</td>
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<td></td>
<td>12-30 months</td>
<td>39.0 months</td>
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<td>≥30 months</td>
<td>51.0 months</td>
<td>p=0.004</td>
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<td>Extent of disease</td>
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</tr>
<tr>
<td></td>
<td>multiple</td>
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<tr>
<td></td>
<td>carcinomatosis</td>
<td>28.0 months</td>
<td>p=0.01</td>
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# Guidelines and Selection Criteria for SCRS in Recurrent, Platinum-Sensitive Ovarian Cancer

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<th>Solitary</th>
<th>Multiple</th>
<th>Carcinomatosis</th>
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<td>Equivocal</td>
<td>No SCRS</td>
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<tr>
<td>12-30 mo</td>
<td>SCRS</td>
<td>SCRS</td>
<td>Equivocal</td>
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<td>&gt;30 mo</td>
<td>SCRS</td>
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</tbody>
</table>

*Chi DS et al. Cancer 2006; 106: 1933.*
Prognostic Factors Associated with Prolonged Survival After SCRS other than Residual Disease

(1) Age <55 years
(2) Disease-free interval (>12m, >17.5m, >24m, >36m)
(3) Optimal PCRS
(4) Complete clinical response to initial platinum therapy
(5) GOG performance status ≤3
(6) Ascites
(7) Size of largest tumor >10cm
(8) Number of recurrence sites >1
(9) SCRS prior to salvage chemotherapy
(10) ≥6 cycles of salvage chemotherapy
Characteristics Associated with a Higher Likelihood of Optimal SCRS

(1) Age <55 years
(2) Disease-free interval (>12m, >17.5m)
(3) Optimal PCRS
(4) Complete clinical response to initial platinum therapy
(5) GOG performance status ≤3
(6) Size of largest tumor >10cm
(7) Number of recurrence sites >1
(8) SCRS prior to salvage chemotherapy
Surgery in Recurrent Ovarian Cancer: The Arbeitsgemeinschaft Gynaekologische Onkologie (AGO)
DESKTOP OVAR Trial

- Exploratory study to develop selection criteria
- Retrospective review – 267 patients
- Complete resection (CR) – significant survival advantage
  - 45.2m vs 19.7m (HR = 3.71, 95%CI=2.27-6.05)
  - CR achieved in 49.8% of cases
- Factors associated with CR
  - ECOG – 0
  - initial FIGO Stage I/II disease
  - NGR at primary surgery
  - absence of ascites

Influence of Residual Disease on Overall Survival

Multivariate Analysis of Factors Affecting Complete Resection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR</th>
<th>95%CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG PS</td>
<td>2.65</td>
<td>1.56-4.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NGR @ primary op</td>
<td>2.46</td>
<td>1.45-4.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ascites</td>
<td>5.08</td>
<td>1.97-13.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Localized disease</td>
<td>1.55</td>
<td>0.85-2.82</td>
<td>0.155</td>
</tr>
</tbody>
</table>

Subgroup analysis of carcinomatosis group (n=125)

- Impact of probability of complete resection
  - no carcinomatosis = 74%
  - carcinomatosis = 26%

- Univariate analysis
  - no carcinomatosis = 45.3m
  - carcinomatosis = 19.9m
  - p<0.0001

**DESKTOP I - Carcinomatosis**

**Surgery for Recurrent Ovarian Cancer: Role of Peritoneal Carcinomatosis: Exploratory Analysis of the DESKTOP I Trial About Risk Factors, Surgical Implications, and Prognostic Value of Peritoneal Carcinomatosis**

- Subgroup undergoing complete resection (n=125, 50%)
- Impact of carcinomatosis is mitigated
  - no carcinomatosis 2yr = 81%
  - carcinomatosis 2yr = 77%
  - p = 0.96
- Carcinomatosis is *not* an independent predictor of worse survival *if* complete resection can be achieved

Prospective Validation Study of a Predictive Score for Operability of Recurrent Ovarian Cancer

The Multicenter Intergroup Study DESKTOP II. A Project of the AGO Kommission OVAR, AGO Study Group, NOGGO, AGO-Austria, and MITO

• Prospective validation study of DESKTOP-II criteria
  1) good performance status (ECOG-0)
  2) no gross residual at primary surgery
  3) absence of ascites >500cc
     - ‘AGO score’ positive if all 3 criteria satisfied

• Primary endpoint: prediction of CR in score-positive cases
  - selection of patients for high probability of NGR disease

Prospective Validation Study of a Predictive Score for Operability of Recurrent Ovarian Cancer

The Multicenter Intergroup Study DESKTOP II. A Project of the AGO Kommission OVAR, AGO Study Group, NOGGO, AGO-Austria, and MITO

- 46 international centers
- 516 patients enrolled
  - 8/06 – 3/08
- Secondary objectives
  - feasibility
  - morbidity

Prospective Validation Study of a Predictive Score for Operability of Recurrent Ovarian Cancer

The Multicenter Intergroup Study DESKTOP II. A Project of the AGO Kommission OVAR, AGO Study Group, NOGGO, AGO-Austria, and MITO

**Operative Findings**
- Carcinomatosis:
  - None: 48%
  - Localized: 20%
  - Diffuse: 31%

**Surgical Results**
- Residual disease:
  - NGR: 76%
  - 1-10mm: 10%
  - >10mm: 14%

**Number of lesions**
- 1-3: 47%
- 4-5: 11%
- >5: 41%

**Morbidity**
- Any complication: 33%
- Transfusion: 44%
- Re-operation: 11%

Prospective Validation Study of a Predictive Score for Operability of Recurrent Ovarian Cancer

The Multicenter Intergroup Study DESKTOP II. A Project of the AGO Kommission OVAR, AGO Study Group, NOGGO, AGO-Austria, and MITO

- First prospectively evaluated instrument to positively predict secondary cytoreductive surgical outcome
- Useful in identifying patients likely to benefit
- May be too restrictive compared to MSKCC “Chi-criteria”
- Approach should be individualized

<table>
<thead>
<tr>
<th>Performance status</th>
<th>Disease-free interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequacy of PCS</td>
<td>Extent of recurrent disease</td>
</tr>
<tr>
<td>Treatment options</td>
<td></td>
</tr>
</tbody>
</table>

Selection Criteria - Summary

Predictors of Surgical Outcome
- disease-free interval
- largest tumor size
- 'localized' disease
- surgery prior to chemo
- performance status

Predictors of Survival
- disease-free interval
- largest tumor size
- surgery prior to chemo
- complete cytoreduction
Secondary Cytoreductive Surgery

‘The Matrix’ of Prognostic Variables

- Chemosensitive disease
- Surgery before salvage chemo
- Prolonged disease-free interval
- Completeness of cytoreduction
- Higher performance status
- Smaller tumor size & ‘localized’ disease
- EARLY DETECTION
**Recurrent Ovarian Cancer**

**Surveillance Techniques**

- Clinical exam
- Serum CA125
  
  Sensitivity = 79-95%, PPV 95-100%
  
  Precedes clinically detectable disease

- Imaging modalities
  - Computed tomography
    
    Sensitivity = 40-93%
  
  - Magnetic resonance imaging
  
  - Radioimmunoscintigraphy
  
  - Positron emission tomography ± CT

- Value of routine surveillance for recurrence?
Tertiary CRS

- Retrospective review MSKCC 1990-2002 TCRS
- Significant and independent predictors of survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter</th>
<th>Post-TCRS Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual disease</td>
<td>≤0.5cm</td>
<td>36.3 months</td>
</tr>
<tr>
<td></td>
<td>&gt;0.5cm</td>
<td>10.6 months</td>
</tr>
<tr>
<td>TFI</td>
<td>≤12 months</td>
<td>15.0 months</td>
</tr>
<tr>
<td></td>
<td>&gt;12 months</td>
<td>60.4 months</td>
</tr>
</tbody>
</table>
Critical Evaluation of SCRS in Recurrent Ovarian Cancer

- Retrospective review of existing published data on salvage surgery for recurrent ovarian cancer
- Analysis of the impact of SCRS on survival is limited by:
  1. Inter-investigator differences in defining optimal cytoreduction
  2. Heterogeneity of patients included
  3. Lack of information on post-operative therapy
  4. Absence of robust prospective randomized data

Cytoreductive Surgery for Recurrent Ovarian Cancer

- Heterogeneous patient population
  - survival determinants are multifactorial

- Individualize therapeutic approach:
  - patient life goals
  - performance status
  - operative risk
  - available adjuvant therapeutic options
Cytoreductive Surgery for Recurrent Ovarian Cancer

- Guiding principles
  - Selection criteria
    - disease-free interval
    - performance status
    - tumor burden (size / number of lesions)
  - Consistent survival advantage
    - completeness of resection
  - Early detection of recurrent disease
Thank You!
Treatment Preferences in Recurrent Ovarian Cancer

- Decision board analysis: 81 ovarian cancer pts and 75 noncancer controls
- Desire aggressive salvage therapy: cancer pts 86%, controls 57%
- Med surv of therapy to switch to palliation: cancer pts 5 mos, controls 8 mos
- Majority of women desire continued aggressive treatment, even if outcome could be poor

Donovan KA et al. Gynecol Oncol 2002