Optimal Cytoreduction

On who to operate
By whom to operate
When to operate
When not to operate
Which order to operate

Simon Hyde – Mercy Hospital for Women
Heidelberg – Australia
THERE ARE 3 KINDS OF LIES

Lies

Damned Lies

and

STATISTICS

Benjamin Disraeli
British Prime Minister 1874-80
In principle advanced ovarian cancer is incurable – pragmatic not nihilistic

We aim for maximising overall survival whilst minimising morbidity from the disease and treatment

Bias: the majority of evidence continually compares apples with a grocer shop variety of different fruit

“Just because you can doesn’t mean you should” & “Just because you can’t doesn’t mean it shouldn’t be considered”
No Screening Test!
Survival Trends in Ovarian Cancer

Trends in death rates for Ovary (ICD10 C56), Australia, 1968–2006

Australian Institute of Health and Welfare and Australasian Association of Cancer Registries, Cancer survival and prevalence in Australia, Canberra, 2008
Cytoreductive Surgery for Advanced Ovarian Cancer

- Meigs 1934
  - Suggested aggressive surgery may be of benefit in advanced ovarian cancer
  - Then nothing really happened until
- Munnell (1968) and Elcos & Quinlan (1969)
  - Marked survival advantage with no residual disease
- Griffiths (1975)
  - Quantified survival advantage against residual tumour volume. No resid, <1.5cm, >1.5 cm.

Ellis L, Quinlan EJ. Malignant tumors of the ovary managed with postoperative megavoltage irradiation. Radiology. 1969 Sep;93(3):659-63
Theoretical benefits of surgical cytoreduction

- Removing large necrotic masses promotes drug delivery to smaller tumors with good blood supply
- Removing resistant clones decreases the likelihood of early onset drug resistance
- Tiny implants have a higher growth fraction that should be more chemosensitive
- Removing cancer in specific locations, such as tumors causing a bowel obstruction, improves the patient’s nutritional and immunologic status
- Log Kill Hypothesis
## Tumour Volume and Survival

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Optimal*</th>
<th>Suboptimal*</th>
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<tbody>
<tr>
<td>Pohl</td>
<td>1984</td>
<td>45</td>
<td>16</td>
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<tr>
<td>Conte</td>
<td>1985</td>
<td>25+</td>
<td>14</td>
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<tr>
<td>Posada</td>
<td>1985</td>
<td>30+</td>
<td>18</td>
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<td>Louie</td>
<td>1986</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>Redman</td>
<td>1986</td>
<td>37</td>
<td>26</td>
</tr>
<tr>
<td>Neijt</td>
<td>1987</td>
<td>40</td>
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<td>Hainsworth</td>
<td>1988</td>
<td>72</td>
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<tr>
<td>Piver</td>
<td>1988</td>
<td>48</td>
<td>21</td>
</tr>
<tr>
<td>Sutton</td>
<td>1989</td>
<td>45</td>
<td>23</td>
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</table>

**Mean**

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Optimal*</td>
<td>Suboptimal*</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>41</td>
<td>18</td>
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</table>

*As defined by each author.

## Rates of Optimal Cytoreduction

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>(N)</th>
<th>Number</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Smith</td>
<td>1979</td>
<td>792</td>
<td>190</td>
<td>24</td>
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<tr>
<td>Delgado</td>
<td>1984</td>
<td>75</td>
<td>13</td>
<td>17</td>
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<tr>
<td>Neijt</td>
<td>1984</td>
<td>186</td>
<td>76</td>
<td>41</td>
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<td>Wharton</td>
<td>1984</td>
<td>395</td>
<td>154</td>
<td>39</td>
</tr>
<tr>
<td>Redman</td>
<td>1986</td>
<td>86</td>
<td>34</td>
<td>40</td>
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<tr>
<td>Heintz</td>
<td>1986</td>
<td>70</td>
<td>49</td>
<td>70</td>
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<td>Neijt</td>
<td>1987</td>
<td>191</td>
<td>94</td>
<td>49</td>
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<tr>
<td>Piver</td>
<td>1988</td>
<td>40</td>
<td>35</td>
<td>87</td>
</tr>
<tr>
<td>Potter</td>
<td>1991</td>
<td>185</td>
<td>119</td>
<td>64</td>
</tr>
<tr>
<td>Eisenkop</td>
<td>1992</td>
<td>126</td>
<td>103</td>
<td>82</td>
</tr>
<tr>
<td>Baker</td>
<td>1994</td>
<td>136</td>
<td>113</td>
<td>83</td>
</tr>
<tr>
<td>Bolis</td>
<td>1997</td>
<td>306</td>
<td>141</td>
<td>46.1</td>
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<tr>
<td>Eisenkop</td>
<td>1998</td>
<td>163</td>
<td>161</td>
<td>98.8</td>
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</tbody>
</table>
Survival Effect of Cytoreductive Surgery

Optimal Cytoreduction

Chi DS. Gynecol Oncol. 2006 Nov;103(2):559-64.
Prognostic Factors in Advanced Ovarian Cancer

Winter 2007

- 1895 patients. (GOG 111, 114, 132, 152, 158, 172)
- Stage 3 epithelial ovarian cancer
- All received paclitaxel/platinum combination

<table>
<thead>
<tr>
<th>Residual tumour</th>
<th>% of patients</th>
<th>PFS months</th>
<th>OS months</th>
</tr>
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<tbody>
<tr>
<td>Microscopic</td>
<td>23</td>
<td>33</td>
<td>71.7</td>
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<tr>
<td>&lt; 1 cm</td>
<td>42</td>
<td>16.8</td>
<td>42.4</td>
</tr>
<tr>
<td>&gt; 1 cm</td>
<td>35</td>
<td>14.1</td>
<td>35</td>
</tr>
</tbody>
</table>

- PFS and OS significantly related to
  - Residual tumour volume
  - Age, Performance status, Histology
Morbidity and Mortality of Cytoreductive Surgery

- Age,
- Performance status,
- Operative time
- Extent of surgery.

Post-operative mortality (30 days) (28 Publications)

- Population based studies 3.7%
- Single centre studies 2.5%
- Mean post operative mortality 2.8%.

Gerestein CG. Postoperative mortality after primary cytoreductive surgery for advanced stage epithelial ovarian cancer: a systematic review. Gynecol Oncol. 2009 Sep;114(3):523-7
Morbidity of Ultraradical Cytoreductive Surgery

   - **29% grade 3-4 complications** (invasive radiologic intervention, reoperation, unplanned ICU admission, chronic disability)

2. EORTC/NCIC study

<table>
<thead>
<tr>
<th></th>
<th>ICR</th>
<th>PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>2%</td>
<td>8%</td>
</tr>
<tr>
<td>Haemorrhage G3/4</td>
<td>4%</td>
<td>7%</td>
</tr>
</tbody>
</table>
Neoadjuvant Chemotherapy & Interval Cytoreduction (ICR)

AFTER SUB-OPTIMAL PRIMARY SURGERY

- 3 randomised controlled trials. 857 patients
- 6 non randomised studies. 369 patients
Interval Cytoreduction
Redman 1994

- A prospective multicentre randomised study
- 79 patients - bulky residual disease after primary surg
- 37 randomised to intervention debulking surgery,
  - 25 (67%) underwent intervention debulking surgery
- median survival
  - intervention debulking group 15 months
  - chemotherapy alone 12 months
- hazard ratio = 0.71; 95% CI 0.44-1.13
- No significant difference in median survival

Interval Cytoreduction
van der Burg 1995

- 319 patients randomised
- > 1 cm residual tumour after initial surgery
- Cisplatin/cyclophosphamide +/- Interval cytoreduction
- 278 evaluated

Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median survival</th>
<th>Alive at 2 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval cytoreduction</td>
<td>26 mths</td>
<td>56%</td>
</tr>
<tr>
<td>Chemotherapy only</td>
<td>20 mths</td>
<td>46%</td>
</tr>
</tbody>
</table>

Significant survival (PFS and OS) advantage for interval debulking after induction chemotherapy (initial op often not done by gynae oncs = ? Less aggressive)
Interval Cytoreduction

Secondary cytoreductive surgery if residual > 1 cm

550 enrolled
- 448 randomised after 3 cycles of CTT
  - Interval debulking -201; no further surgery - 201

Results

<table>
<thead>
<tr>
<th></th>
<th>Median PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval surgery</td>
<td>10.5 mths</td>
<td>33.9 mths</td>
</tr>
<tr>
<td>Chemotherapy only</td>
<td>10.7 mths</td>
<td>33.7 mths</td>
</tr>
</tbody>
</table>

Interval cytoreduction for residual disease after maximal cytoreduction does not improve PFS or OS (initial op done by Gynaeconcs)
EORTC – NCIC: role of neoadjuvant chemotherapy and interval cytoreduction

- Randomised 718 pts - non inferiority design.
- Interval data – median f/u 4.8yrs
- Median OS: 29 (ICR) vs 30 (PCR) months
- Postop deaths: 2.7% (ICR) vs 6.0 (PCR)%
- Grade 3/4 fever: 2% vs 8%
- Grade 3/4 haemorrhage: 1% vs 7%
- DVT/PE: 0.3% vs 2.4%
- Optimal cytoreduction(<1cm): 82% vs 46%
Neoadjuvant Chemotherapy & Interval Cytoreduction (ICR)

No Primary Cytoreduction Procedure

2 meta analyses of same studies – different conclusions

1. Neoadjuvant CT followed by ICR does not seem to worsen the prognosis for women with advanced disease (Vergote I)

2. Survival outcome achieved with initial CT is inferior to successful up-front cytoreductive surgery (Bristow RE.)

1. Vergote I. Int J Gynecol Cancer. 2008
2. Bristow RE. Gyn Oncol. 2007
JCO 3/2015 – does aggressive surgery improve outcomes GOG 182

- Multiple arms – carbo/taxol as good as any! And less morbidity than triplets
- Analysis of surgical cytoreductivity – upfront surgical cytoreduction
- Allocated disease burden - low/mod/high volume of disease
- Cytoreductive outcomes
- Ro – optimally cytoreduced MR (microscopic residual disease) still “optimal” cytoreduced
Time Since Enrollment (months)

C

Progression-Free Survival (proportion)

- Blue: R0, DS-moderate/low (n = 661; median, 33.2)
- Yellow: R0, DS-high (n = 199; median, 18.3)
- Gray: MR, DS-moderate/low (n = 357; median, 18.1)
- Red: MR, DS-high (n = 1,438; median, 14.8)

Log-rank P < .001
The graph shows the overall survival proportion over time since enrollment for different groups:

- R0, DS-moderate/low (n = 661; median, 82.8)
- R0, DS-high (n = 199; median, 50.1)
- MR, DS-moderate/low (n = 357; median, 52.5)
- MR, DS-high (n = 1,438; median, 39.4)

The Log-rank test shows a significant difference among the groups with a P-value < .001.
Neoadjuvant Chemotherapy or Radical Surgery for Advanced Ovarian Cancer

- Individualisation of management – maximise outcome whilst minimising morbidity.
- Primary thought process: optimal surgical cytoreduction, all patients should have a gynaecologic consultation – ideally pretreatment.
- If the pts comorbidities, stage of disease, predictive volume of disease preclude the possibility of safely obtaining initial optimal surgical cytoreduction.
- Then neoadjuvant chemotherapy with view to interval cytoreduction (if responding).
In Summary:

- Optimal surgical cytoreduction and the chemosensitivity of the disease appear to be the most important prognostic factors in overall outcome.
- The timing and order of treatment remains open for debate.
- Future of pretreatment molecular profiling – identify subsets of those who may benefit from initial surgical debulking.