The Role of Neoadjuvant Chemotherapy in Ovarian Cancer

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Disclosures

• I was a man with a hammer
• I operated on all patients with suspected ovarian cancer
• Rarely did I extend incision above the umbilicus
• Often remove omentum, rarely subdiaphragm or spleen
• We debated value of bowel resection
• Achieved optimal debulking (< 2 cm) in 60% of patients
• Thought I was cool giving paclitaxel with carboplatin every 3 weeks to patients
• Knew about BRCA genes (actually worked in gene therapy), tested few if any patients
Historical Development of Primary Debulking in Advanced Stage Ovarian Cancer
How Primary Debulking Became Standard of Care

• Retrospective study of 102 stage II/III ovarian cancer patients

• Multiple linear regression of impact of multiple variables on survival

• Histologic grade and residual disease most important factors

• “Surgery provides optimal benefit when all gross tumor can be safely excised”

<table>
<thead>
<tr>
<th>Size (cm)</th>
<th>Number of patients</th>
<th>MST (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>29</td>
<td>39</td>
</tr>
<tr>
<td>0-0.5</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>0.6-1.5</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>&gt;1.5</td>
<td>29</td>
<td>11</td>
</tr>
</tbody>
</table>

Griffiths. NCI Mono, 1975
Impact of Maximum Cytoreduction of Ovarian Cancer on Survival

- Metaanalysis of 81 cohorts of stage III/IV ovarian cancer patients (6885) from articles published between 1989-98
- Linear regression models used to assess effects of several variables on survival
- Each 10% increase in maximum cytoreduction was associated with 5.5% increase in median survival

Bristow et al. JCO, 2002.
Impact of Debulking on Outcome in Advanced Ovarian Cancer

• Retrospective analysis of 3126 advanced ovarian cancer patients in 3 RCTs treated with taxane/platinum

• Median survival for R0 group 99.1 mos. vs. 36.2 and 29.6 mos. for R1-10 mm and R>10 mm (p<0.0001)

• Redefined “optimal” debulking as R0 though other studies suggest benefit with R1 resection

Incorporation of Extensive Upper Abdominal Surgery in Ovarian Cancer

- Compared outcomes in 168 ovarian cancer patients treated 96-99 to that in 210 patients treated 01-04 after EUAS implemented
- Improved optimal cytoreduction (< 1 cm) from 46% to 80%
- Improved five year PFS from 14% to 31% and OS from 35% to 47%

Morbidity Associated with Radical Debulking

- Retrospective review of 141 ovarian cancer patients who underwent primary EUAS
- 30% R0, 60% R1
- G3-5 morbidity in 31 patients (22%)
- Perioperative deaths in 2 (1.4%)

Skill of the Surgeon or Biology? – Part 1

• Review of advanced stage ovarian cancer patients enrolled on GOG 52 – CP vs. CAP in optimally debulked stage III patients
• Compared outcomes in IIIB patients to IIIC patients – all with same residual disease
• Survival better in IIIB patients despite same residual disease

Skill of the Surgeon or Biology? – Part 2

- 2655 ovarian cancer patients enrolled in GOG 182
- Examined effects of disease burden, complex surgery, and residual disease on PFS and OS
- Initial disease burden remained significant prognostic indicator despite R0

Horowitz et al. JCO, 2015.
The Development of NACT in Advanced Stage Ovarian Cancer
NACT Isn’t So Neo

• Compared 17 ovarian cancer patients treated with NACT to 59 patients treated with PDS
• Survival similar
• Postoperative hospital stay and complications less in NACT

The EORTC NACT Trial

- Noninferiority RCT randomizing ovarian cancer patients with stage III/IV to either PDS vs. NACT/IDS
- Approximately 60% HGSC and over 75% treated with paclitaxel/carboplatin
- Between 9/98 and 12/06, randomized 336 to PDS and 334 to NACT/IDS

Vergote et al. NEJM, 2010
The EORTC NACT Trial

• Optimal (< R1) 42% PDS vs. 81% in NACT/IDS; R0 19% PDS vs 51% NACT/IDS

• Median overall survival was 29 mos. in PDS vs. 30 mos. in NACT/IDS

• G3/4 postoperative toxicity/deaths higher in PDS group (2x toxicity; 2.5% vs 0.7% deaths)

• Chemotherapy toxicity similar between both groups

Vergote et al. NEJM, 2010
The Impact of Residual Disease in the EORTC NACT Trial

<table>
<thead>
<tr>
<th>EORTC 55971</th>
<th>Events / Patients</th>
<th>Statistics (O-E)</th>
<th>Var.</th>
<th>HR &amp; CI</th>
<th>[1-HR]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Upfront debulking</td>
<td>Neo-adj. chemo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-49 mm</td>
<td>53 / 94</td>
<td>65 / 95</td>
<td>-12.7</td>
<td>28.6</td>
<td></td>
</tr>
<tr>
<td>50-99 mm</td>
<td>69 / 90</td>
<td>64 / 88</td>
<td>6.9</td>
<td>32.5</td>
<td></td>
</tr>
<tr>
<td>100-199 mm</td>
<td>92 / 105</td>
<td>83 / 113</td>
<td>8.4</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>&gt;200 mm</td>
<td>22 / 26</td>
<td>21 / 24</td>
<td>-0.8</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>236 / 315</strong></td>
<td><strong>233 / 320</strong></td>
<td><strong>1.8</strong></td>
<td><strong>114.4</strong></td>
<td><strong>2% ± 9</strong></td>
</tr>
</tbody>
</table>

Test for heterogeneity
Chi-square=8.8, df=3; p=0.03

Vergote et al. NEJM, 2010
The CHORUS NACT Trial

• Noninferiority RCT randomizing ovarian cancer patients with stage III/IV to either PDS vs. NACT/IDS
• Approximately 70% HGSC and 75% treated with paclitaxel/carboplatin
• Between 3/04 and 8/10, randomized 276 to PDS and 274 to NACT/IDS

The CHORUS NACT Trial

- Optimal (< R1) 41% PDS vs. 73% in NACT/IDS; R0 17% PDS vs 39% NACT/IDS
- Median overall survival was 22.6 mos. in PDS vs. 24.1 mos. in NACT/IDS
- G3/4 postoperative toxicity/deaths higher in PDS group (30% vs 15% toxicity; 6% vs 1% deaths)
- Chemotherapy toxicity similar between both groups

Other NACT Trials

- **SCORPION** (Fagotti, 2016)
  - 110 patients
  - Same R0 rates
  - Higher postop complications in PDS
  - No PFS/OS data

- **JCOC0602** (Onda, 2014)
  - 301 patients
  - Higher R0 rates with NACT
  - Higher postop complications in PDS
  - No PFS/OS data
The NCDB NACT Study

• Retrospective cohort study of approximately 23k advanced stage ovarian cancer in NCDB; 14% NACT patients
• Matched cohort of NACT to PDS
• Survival poorer in NACT group (32 vs 38 mos)
• Trial on Radical Upfront Surgery in Advanced Ovarian Cancer (TRUST) in progress

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median Overall Survival (95% CI), mo</th>
<th>HR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>All patients</td>
<td>PCS 37.3 (35.2-38.7) NACT 32.1 (30.8-34.1)</td>
<td>1.18 (1.11-1.26)</td>
</tr>
<tr>
<td>Period of diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003-2005</td>
<td>PCS 34.2 (31.5-37.1) NACT 28.7 (25.7-30.9)</td>
<td>1.19 (1.07-1.33)</td>
</tr>
<tr>
<td>2006-2009</td>
<td>PCS 37.3 (34.9-39.3) NACT 34.1 (31.2-36.7)</td>
<td>1.15 (1.05-1.27)</td>
</tr>
<tr>
<td>2010-2011</td>
<td>PCS 42.1 (41.1-44.3) NACT 33.1 (31.3-35.3)</td>
<td>1.24 (1.06-1.46)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIC</td>
<td>PCS 46.5 (41.9-51.0) NACT 37.8 (35.9-40.8)</td>
<td>1.24 (1.11-1.37)</td>
</tr>
<tr>
<td>IV</td>
<td>PCS 31.4 (29.7-33.3) NACT 28.1 (26.3-30.3)</td>
<td>1.13 (1.04-1.23)</td>
</tr>
</tbody>
</table>

Increasing Rates of NACT in Management of Ovarian Cancer

- Observational study of 1,538 women with advanced stage ovarian cancer at 6 NCI CCC
- Compared NACT use between 2003 and 2012
- NACT increased from 16% during 2003-10 to 34% during 2011-12 in stage IIIC disease
- NACT increased from 41% to 62% in stage IV disease during same time periods
- PDS outcomes better in stage IIIC patients optimally debulked

Meyer LA et al. JCO, 2016.
Choosing Between PDS and NACT
Role of Preoperative Imaging and CA125 in Predicting Results of Cytoreduction in Ovarian Cancer

- Prospective trial evaluating 9 criteria associated with suboptimal cytoreduction
- From 7/01-12/12, 350 ovarian cancer patients enrolled
- RD for predictive score of 0-2 was 45%; RD for predictive score ≥3 exceeded 65%

<table>
<thead>
<tr>
<th>Criteria</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
<th>Predictive score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 60 years</td>
<td>1.49</td>
<td>1.14–1.93</td>
<td>0.003</td>
<td>1</td>
</tr>
<tr>
<td>CA-125 ≥ 600 U/mL</td>
<td>1.29</td>
<td>1.15–1.43</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>ASA ≥ 3</td>
<td>1.6</td>
<td>1.55–1.66</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Lesion in splenic hilum/ligaments</td>
<td>1.36</td>
<td>1.13–1.64</td>
<td>0.001</td>
<td>1</td>
</tr>
<tr>
<td>Gastrohepatic ligament/porta hepatitis lesion</td>
<td>1.44</td>
<td>1.24–1.67</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Retroperitoneal lymph nodes above the renal hilum</td>
<td>1.31</td>
<td>1.11–1.55</td>
<td>0.002</td>
<td>1</td>
</tr>
<tr>
<td>(including supradiaphragmatic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse small bowel</td>
<td>1.12</td>
<td>1.1–1.14</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>adhesions/thickening</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal ascites (moderate-severe)</td>
<td>2.21</td>
<td>1.72–2.83</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Gallbladder fossa/Liver intersegmental fissure lesion</td>
<td>2</td>
<td>1.72–2.33</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Lesser sac lesion &gt;1 cm</td>
<td>2.24</td>
<td>1.51–3.31</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Root of the superior mesenteric artery lesion</td>
<td>4.06</td>
<td>3.12–5.29</td>
<td>&lt;0.001</td>
<td>4</td>
</tr>
</tbody>
</table>

Suidan et al. Gynecol Oncol, 2017
Role of Laparoscopy in Predicting Results of Cytoreduction in Ovarian Cancer

• Evaluated a Predictive Index Value (PIV) in cohorts of advanced ovarian cancer patients
• Omental cake, carcinomatosis, diaphragm disease, mesentary retraction, bowel infiltration, liver metastasis all assigned score of 2
• PIV > 8 had PPV for suboptimal debulking of 100%
• Validated in several prospective trials (Olympia – MITO 13)

Fagotti et al. AJOB, 2008.
Fagotti et al. AJOG, 2013.
RCT of Laparoscopy in Predicting Results of Cytoreduction in Ovarian Cancer

- RCT of PDS vs laparoscopy in patients with suspected ovarian cancer
- Between 5/11 and 2/15, 201 patients enrolled
- 63/102 (62%) assigned to laparoscopy had PDS
- Futile laparotomy (residual > 1 cm) occurred in 10% of 102 patients undergoing laparoscopy vs. 39% of 99 patients undergoing PDS

Rutten et al. JCO, 2016
SGO/ASCO Guidelines for NACT

- All women with suspected ovarian cancer should be evaluated by gyn oncologist and at minimum CT scan should be performed
- Women with high perioperative risk profile or low probability of resection to < 1cm (preferably R0) should receive NACT
- Women fit for surgery could be offered either NACT or primary debulking provided high probability of resection to < 1cm (preferably R0)
- Before treating with NACT, histology confirmation of ovarian primary with core biopsy or cytology with CA125/CEA ratio > 25 should be performed

Wright et al. JCO, 2016
Leuven Guidelines for NACT

• **Diagnosis**
  - Biopsy consistent with advanced stage ovarian cancer
  - CA125/CEA > 25

• **Metastasis**
  - Intrahepatic metastasis
  - Diffuse carcinomatosis, particularly stomach, small bowel and mesentery
  - Nonresectable extra-abdominal metastasis

• **Patient characteristics**
  - Impaired PS
  - Multiple co-morbidities
  - Poor nutrition
  - Not accepting of supportive care i.e. transfusion

Vergote et al. JCO, 2016
# Categorizing Ovarian Cancer

<table>
<thead>
<tr>
<th>Category</th>
<th>Tumor location</th>
<th>Massive ascites</th>
<th>Intestinal resection</th>
<th>PDS vs NACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pelvis</td>
<td>No</td>
<td>No</td>
<td>PDS</td>
</tr>
<tr>
<td>2</td>
<td>Pelvis</td>
<td>No</td>
<td>Yes</td>
<td>PDS</td>
</tr>
<tr>
<td>3</td>
<td>Upper abdomen</td>
<td>No</td>
<td>No</td>
<td>PDS</td>
</tr>
<tr>
<td>4</td>
<td>Upper abdomen</td>
<td>No</td>
<td>Yes</td>
<td>PDS</td>
</tr>
<tr>
<td>5</td>
<td>Upper abdomen/ miliary spread</td>
<td>Yes</td>
<td>Multiple</td>
<td>NACT</td>
</tr>
</tbody>
</table>

Markar et al. The Oncol, 2016
Issues in the Management of Ovarian Cancer Patients Treated with NACT
Evolving Treatment Paradigms for Advanced Stage Ovarian Cancer

- Surgery
  - PDS vs NACT/IDS
- Chemotherapy
  - Paclitaxel/carbo
  - Paclitaxel/carbo with bevacizumab
  - Dose dense regimens
  - IV vs IP
  - Other platinum combinations
- Novel therapeutics
  - Antiangiogenics
  - PARP inhibitors
  - Immuno-oncology
  - NGS/HRD guided treatments
NACT Chemotherapy and Timing of IDS

• Chemotherapy
  • Most studies utilized paclitaxel/carboplatin q 3wk combination therapy
  • In retrospective study, DD paclitaxel with carboplatin associated with higher pCR and R0 rates but also with higher toxicity
  • In phase 4 study, bevacizumab added to chemotherapy did not significantly enhance complication rates
  • Limited role for IP chemotherapy prior to IDS
  • Great platform to study novel agents and effect on tumor biology

• IDS
  • IDS done in most studies after 3-4 cycles
  • Surgery after 6 cycles is really a second look laparotomy
  • Generally done by laparotomy with less morbidity

Wright et al. JCO, 2016.
Feasibility of MIS for Interval Debulking

• MISSION trial evaluated MIS in ovarian cancer patients with complete response after treated by median of 4 cycles of NACT
• Applied to 30 (58%) of 52 eligible patients
• Procedures included TLHBSO, omentectomy, appendectomy, peritoneal resection
• R0 reached in 29/30 patients

Alletti et al. AJPG, 2016.
Surgical Specialty Matters!

• When compared to gynecologists or surgeons, gynecologic oncologists more likely to:
  • Appropriately stage
  • Achieve optimal debulking
  • Less likely to have colostomy
  • Utilize chemotherapy
  • Have improved outcomes (in some studies)

IP Chemotherapy after NACT and IDS

• Several studies have demonstrated feasibility

• OV21/PETROC – Randomized phase II trial of IV vs two IP regimens
  • From 2009-15, 275 patients enrolled
  • PD9 rates improved with IP carbo regimen (23.3% vs 42.2% in IV arm)
  • PFS and OS not statistically different

Take Home Points

• Ovarian cancer is not one disease – Read IOM report
• Get a gynecologic oncologist involved at time of diagnosis
• Useful ways to stratify patients – tumor markers, imaging, laparoscopy
• PDS best when can optimally debulk (R0-R1)
• NACT proven to be non-inferior and less morbid
• Various chemotherapy options pre and post IDS
• Thought the timing may not affect OS, IDS should be after 3-4 cycles
• Patients selected for NACT generally have the worse prognosis as a function of the disease not the treatment
The Next Trial for Advanced Ovarian Cancer

- Selected HGSC ovarian cancer patients randomized between:
  - Arm 1 – NACT with IDS
  - Arm 2 – NACT with IDS and maintenance therapy
  - Arm 3 – NACT alone
  - Arm 4 – NACT alone with maintenance therapy