The role of neoadjuvant chemotherapy in the management of advanced ovarian cancer

Sang-Yoon Park
Center for Uterine Cancer
National Cancer Center Korea
Treatment strategy in ovarian cancer

Maximum debulking surgery

Minimum residual tumor without morbidity interrupting post-op chemotherapy

Increase survival with improved QOL
How to minimize residual tumor?

Maximum debulking surgery

- Conventional surgery
  - TAH, BSO
  - LAR
  - Omentectomy
  - PLND, PALND
  - Multiple biopsy
  - Cytology

- Extensive surgery
  - Pelvic peritonectomy
  - Splenectomy
  - Distal pancreatectomy
  - Diaphragmatic stripping and/or resection
  - Liver resection
  - Resection of tumor from porta hepatis
  - Cholecystectomy
  - Total colectomy
Extensive surgical procedures

Pelvic peritonectomy with modified post. exenteration

Splenectomy with distal pancreatectomy

Diaphragmatic stripping and resection

Liver resection

Resection of tumor from porta hepatis

Total coloectomy with splenectomy
Can we always perform these extensive procedures in all patients?

No, we can’t.
Factors influencing surgery

**Patient’s factor**
- Too extensive
- Severe medical disease
- PS > 3

**Institution’s factor**
- Non-cooperative surgical oncology
- Insufficient operation room
Factors influencing surgery

**Social factor**
- Lack of confidence
- Poor rapport

**Surgeon’s factor**
- Inadequate technique
- Shortage of experience
- Insufficient conviction

신념!!!!!
When we cannot perform all those extensive procedures, what should we do?

Transfer?

Neoadjuvant chemotherapy!!!
History of NAC

1979: Schwartz PE (Yale university)
- Poor medical condition

1993: Nelson BE (Yale university)
- Advanced ovarian cancer
- CT evaluation may be helpful to make decision of NAC
  
  *JCO* 1993; 11:166–172

**CT scan criteria**
- Disease in the thorax
- Porta hepatis metastases
- Suprarenal para-aortic lymph nodes
- Disease >2 cm in diameter involving the diaphragm
- Confluence with implants in the liver serosa
- Omentum reaching the hilum of the spleen
Terminology

Surgery

- **Primary debulking surgery (PDS)**
  - Primary cytoreductive surgery

- **Interval debulking surgery (IDS)**
  - Chemotherapy – surgery – chemotherapy

Chemotherapy

- **Induction chemotherapy**
  - General description
  - Chemotherapy to reduce tumor size for further surgery.

- **Neoadjuvant chemotherapy (NAC)**
  - More specific
  - Only biopsy is done for histologic diagnosis.
Advantage of NAC

- Less morbidity
  - Retrospective: (Lawton 1989; Morice 2003)
  - Prospective cohort studies: (Giannopoulos 2006)

- Increase optimal resection rate
  - (Lawton 1989; Jacob 1991; Surwit 1996; Ansquer 2001; Kuhn 2001; Chan 2003; Morice 2003; Giannopoulos 2006; Lee 2006)

- Better QOL
  - (Chan 2003)

What about survival with NAC?
Survival reports of NAC

Conflicting results
- Due to various characteristics of the patients and their disease
  - Chemosensitivity
  - Post-op residual tumor size
Non-randomized and retrospective

**Superior**
(Vergote 1998; Kuhn 2001)

**Similar**
(Jacob 1991; Surwit 1996; Schwartz 1999; Kayikciog 2001; Morice 2003; Shibata 2003; Loizzi 2005;)

**Inferior**
(Fanfani 2003, Steed 2006)
Meta-analysis and systemic review

**Superior**

(Elit 1995)

OR, 0.5 ($p = 0.02$), included 33 studies

**Similar**

(Bristow 2007)

3 major RCTs concerning suboptimal surgery, 6 non-randomized studies, 26 retrospective and phase I/II studies.

(Morrison 2007)

No conclusion

**Inferior**

(Bristow 2006)

Included 835 patients from 51 studies

Included only phase I to II and retrospective studies
RANDOMISED TRIAL COMPARING PRIMARY DEBULKING SURGERY (PDS) WITH NEOADJUVANT CHEMOTHERAPY (NACT) FOLLOWED BY INTERVAL DEBULKING (IDS) IN STAGE IIIC-IV OVARIAN, FALLOPIAN TUBE AND PERITONEAL CANCER.
RANDOMISED EORTC-GCG/NCIC-CTG TRIAL ON NACT + IDS VERSUS PDS

Ovarian, tuba or peritonal cancer
FIGO stage IIIc-IV (n = 718)

Randomisation

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

Primary Endpoint: Overall survival
Secondary endpoints: Progression Free Survival, Quality of Life, Complications
Randomised EORTC-GCG/NCIC-CTG trial on NACT + IDS versus PDS
Surgical findings and results (PP1)

<table>
<thead>
<tr>
<th></th>
<th>PDS (n = 329)</th>
<th>NACT -&gt; IDS (n = 339)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastases before &gt; 2 cm</td>
<td>95%</td>
<td>68%</td>
</tr>
<tr>
<td>Metastases before &gt; 10 cm</td>
<td>62%</td>
<td>27%</td>
</tr>
<tr>
<td>No residual after surgery</td>
<td>21%</td>
<td>53%</td>
</tr>
<tr>
<td>≤ 1 cm after surgery</td>
<td>46%</td>
<td>82%</td>
</tr>
</tbody>
</table>

* % calculated on the 306 patients who underwent IDS.
Randomised EORTC-GCG/NCIC-CTG trial on NACT + IDS versus PDS
Surgical characteristics (PP1)

<table>
<thead>
<tr>
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<th>PDS (n = 329)</th>
<th>NACT -&gt; IDS (n = 339)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative mortality (&lt; 28 days)</td>
<td>2.7%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Postoperative sepsis</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Fistula (bowel/GU)</td>
<td>1.2% / 0.3%</td>
<td>0.3% / 0.6%</td>
</tr>
<tr>
<td>Operative time (minutes)</td>
<td>180</td>
<td>180</td>
</tr>
<tr>
<td>Red blood cell transfusion</td>
<td>51%</td>
<td>53%</td>
</tr>
<tr>
<td>Hemorrhage Grade 3/4</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>Venous Gr 3/4</td>
<td>2.4%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>
NACT + IDS versus PDS: ITT

Progression-free survival

Median PFS
PDS: 12 months
IDS: 12 months
HR for IDS: 0.99 (0.87, 1.13)
NACT + IDS versus PDS: ITT

Overall survival

Median survival
PDS: 29 months
IDS: 30 months

HR for IDS: 0.98 (0.85, 1.14)

<table>
<thead>
<tr>
<th>O</th>
<th>N</th>
<th>Number of patients at risk</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>259</td>
<td>361</td>
<td>183 68 16 2</td>
<td>Upfront debulking</td>
</tr>
<tr>
<td>251</td>
<td>357</td>
<td>191 56 11 1</td>
<td>Neoadjuvant chemio</td>
</tr>
</tbody>
</table>
The essential point of EORTC study

- NAC followed by IDS produces similar OS and PFS outcomes compare to standard PDS followed by chemotherapy in FIGO stage IIIc–IV ovarian cancer.
- NAC can be considered as the preferred treatment due to the lower morbidity in stage IIIc–IV.

Should NAC be administered in all patients with stage IIIc–IV?
How about if we try NAC only in case with the patients predicted to be optimal unresectability?
Personal experiences

1991.9–1992.8:
- Post-doc fellow at Yale University

1994. 6:
- Visit Prof. Schwartz at Yale University
- Protocol endorsement
# Differences between protocols of Yale & KCCH

**Yale University (1993)**
- Disease in the thorax
- Porta hepatis metastasis
- Suprarenal lymph node metastasis
- Disease >2 cm in diameter involving the diaphragm
- Confluence with implants in the liver serosa
- Omentum reaching the hilum of the spleen

**KCCH (1994)**
- Stage IIIc disease
  - Dense tumor involvement in
    - Mesenteric root
    - Suprarenal PALN
    - Diaphragm
    - Abdominal wall
- Stage IV disease
  - Parenchymal metastasis in
    - Liver
    - Lung
    - Pancreas
  - Distant LN metastasis
Results (KSOG, 1997)

- Duration: 93.9 - 97.3
- Chemotherapy: CAP, CAP-ETI
- No. of pts: IIIC(15), IV(4)
- No. of IDS: 18 (94.7%)
- Response: CR, 0; PR ,15(78.9%)
- Post-op residual tumor:
  - none, 4(22.2%), ≤1cm, 5 (27.8%)
  - Optimal op. rate: 50%
- Median survival: 16 month
  - 3 patients with good response expired due to sepsis during adjuvant chemotherapy.
Experiences at NCC (from 2001)

Treatment principle of advanced ovarian cancer

Evaluation of optimal resectability with radiologist

- PDS
- NAC → IDS

Maximum debulking surgery both PDS and IDS
Indication for NAC

- Extraperitoneal disease (except malignant pleural effusion)
- Involvement of the mesenteric root
- Involvement of the porta hepatis
- Multiple liver metastases requiring total resection of liver
- Suprarenal lymph node metastasis
- Dense infiltrative diaphragm mass > 2cm
- Poor performance status > ECOG 3
  - Modified according to experiences
# Results

## Duration: 2001 – 2006

<table>
<thead>
<tr>
<th>No. of pts</th>
<th>Surgical extensiveness</th>
<th>Optimal op. rate (%)</th>
<th>Median PFS(^3) (M)*</th>
<th>Median OS(^4) (M)*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PDS(^1)</td>
<td>IDS(^2)</td>
<td>P-value</td>
<td></td>
</tr>
<tr>
<td>63</td>
<td></td>
<td>63</td>
<td>60</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>No difference</td>
<td>100</td>
<td>0.197</td>
<td></td>
</tr>
<tr>
<td>84</td>
<td></td>
<td>20</td>
<td>18</td>
<td>0.187</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not reached</td>
<td>55</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*: PFS was better in PDS arm in subgroup of patients with > 24 month F/U..

1; primary debulking surgery, 2; interval debulking surgery, 3; progression free survival, 4; overall survival
### Comparison

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Tx</th>
<th>N</th>
<th>Optimal op. Rate (%)</th>
<th>Median F/U (m)</th>
<th>Median PFS (m)</th>
<th>Median OS (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC, 2008</td>
<td>PDS</td>
<td>329</td>
<td>46</td>
<td>58</td>
<td>12</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>IDS</td>
<td>339</td>
<td>82</td>
<td>12</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>NCC, 2009</td>
<td>PDS</td>
<td>63</td>
<td>84</td>
<td>35</td>
<td>20</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>IDS</td>
<td>60</td>
<td>100</td>
<td>18</td>
<td>18</td>
<td>55</td>
</tr>
</tbody>
</table>

- **NCC results comparing to EORTC study**
  - More advanced disease and poor PS in IDS arm
  - Better optimal op. rate
  - Increased survival
Summary

- **Maximum debulking surgery** should be the goal of every surgical effort (PDS and IDS).
- NAC/IDS can be used as strategy for *selective patients* such as optimal unresectable anticipated and poor performance status preoperatively.
- Trial to improve **image predictibility** be needed.
- **PDS vs NAC/IDS random study** would be needed in selective patients such as optimal unresectable anticipated preoperatively.
Acknowledgement

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Gynecologic Oncology Staff

Head Radiation Oncology
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Research Nurse

Gynecologic Oncology Fellow
경청해 주셔서 감사합니다.
Japanese study (JCOGO206)

Background:
- To assess the safety and efficacy of neoadjuvant chemotherapy (NAC)
- To determine whether we can omit diagnostic laparoscopy before treatment initiation

Methods:
- diagnostic laparoscopy to confirm the clinical diagnosis.
- Four cycles of paclitaxel and carboplatin were administered as NAC, followed by interval debulking surgery and an additional 4 cycles of chemotherapy.

The end point
- The primary: clinical complete remission (cCR) rate
- secondary end point: the positive predictive value (PPV) of laparoscopy
Japanese study (JCOGO602)

**PURPOSE**
- to prove the non-inferiority of the efficacy
- to show the decrease in adverse effects

**STUDY SETTING**
- A multi-institutional (30 centers) randomized Phase III trial

**RESOURCES**
- Grants (Nos. h16-035, h19-028, Nos. 17S-1, 17S-5, 17-12) from the Ministry of Health, Labor and Welfare, Japan

**ENDPOINTS**
- The primary endpoint: overall survival
- Secondary endpoints: the efficacy of the treatments (CCR, PFSR, RR)
- 2006. 12 start
- the target sample size of 300 patients (150 patients per regimen)