The Rise & Fall of Lymphadenectomy in Advanced Ovarian Cancer

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Advanced Ovarian Cancer
Advanced Ovarian Cancer
Debate Facts about Gyn Oncologists

- We are so fixated on lymphadenectomy
- It is extremely rare to find a solid tumor malignancy where the removal of normal appearing nodes improves survival
My Counterpoint

• Unless future studies confirm otherwise: the removal of clinically normal nodes should not be considered a standard procedure for women with advanced ovarian cancer

• Many would accept resection of bulky nodes as part of the surgical effort of removing all gross disease
3 Components to Primary Surgical Cytoreduction

1. Pelvic
2. Abdominal
3. Retroperitoneal
Removal of “bulky” nodes only!
Do we believe that this is the ONLY positive node in this patient?

Lymphadenectomy is Necessary for “Optimal” Cytoreduction!
How Common is the Problem? What is the Incidence of (+) LN in Advanced Ovarian Cancer?

= 66%

49% positive LN > 1 cm diameter

17% had positive LN > 1 cm not identified by palpation or inspection

Debate Questions

• Why would pelvic lymphadenectomy reduce death from a peritoneal surface malignancy that kills women due to malignant bowel obstruction?
Debate Questions

• Would pelvic lymphadenectomy reduce death from a malignant bowel obstruction?
Debate Questions

• Is it likely that para-aortic lymphadenectomy will reduce peritoneal carcinomatosis recurrence and secondary malignant bowel obstruction in the future of a women who presents with advanced peritoneal disease?
What do we know about the retroperitoneal lymph nodes in advanced ovarian cancer?

- Autopsy studies demonstrated a very high incidence of positive retroperitoneal nodes.
- Retrospective studies suggest an advantage to systematic LND when tumor was optimally resected in the peritoneal cavity.
- The only randomized prospective study revealed a 7-month benefit in progression-free survival for patients having systematic lymphadenectomy, but no benefit in terms of overall survival.

Hacker NF IJGC 2008
<table>
<thead>
<tr>
<th>Series</th>
<th>Year</th>
<th>No.</th>
<th>Survival: <strong>LND vs. No LND</strong></th>
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</thead>
<tbody>
<tr>
<td>Burghardt</td>
<td>1986</td>
<td>110</td>
<td>5-yr: 53% vs. 13%</td>
</tr>
<tr>
<td>Spirtos</td>
<td>1995</td>
<td>56</td>
<td>Removal of macro (+) LN has survival similar to micro (+) or (-) LN</td>
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<td>Scarabelli</td>
<td>1995</td>
<td>105</td>
<td>LND improved survival of untreated pts</td>
</tr>
<tr>
<td>Di Re</td>
<td>1996</td>
<td>248</td>
<td>5-yr Optimal &amp; LND=46%, no LND =30% (p=0.05)</td>
</tr>
<tr>
<td>Scarabelli</td>
<td>1997</td>
<td>142</td>
<td>LND improved survival of untreated pts</td>
</tr>
<tr>
<td>Allen</td>
<td>1999</td>
<td>130</td>
<td>5-Yr: 38% vs. 22%</td>
</tr>
</tbody>
</table>
Does systematic lymphadenectomy have a benefit on survival of suboptimally debulked patients with stage III ovarian carcinoma?


- Retrospective study n= 61 suboptimally debulked patients with stage III ovarian carcinoma.

CONCLUSIONS:
- Lymphadenectomy seems not to have an evident prognostic value and a benefit on survival in suboptimally debulked patients with stage III ovarian carcinoma.

Saygili U, et al. from Dokuz Eylul University School of Medicine, Izmir, Turkey

Fig. 1. Survival according to performance of lymphadenectomy in 51 subtotally debulked patients with stage III ovarian carcinoma. *Log-rank.
Systematic lymphadenectomy has a diagnostic value in early-stage ovarian cancer:
- Up to 22% of women are upstaged
- Rarely can help avoid postoperative chemotherapy

In advanced ovarian cancer, lymphadenectomy improves progression-free survival despite a higher incidence of postoperative complications
- No improvement of overall survival

Overall survival (OS) for patients with optimally debulked advanced ovarian carcinoma undergoing systematic aortic and pelvic lymphadenectomy compared with resection of bulky nodes only

Proposed Phase III study of the role of lymphadenectomy in advanced ovarian cancer

Management of retroperitoneal lymph nodes in advanced ovarian cancer.

HACKER, N. JGIC 2008
The role of pelvic & aortic lymphadenectomy at second-look surgery in apparent early stage ovarian cancer after inadequate surgical staging followed by adjuvant chemotherapy

Signorelli M, Landoni F, Mangioni C. Gynecol Oncol. 2014

1991-2013, 66 patients stage IA-IIA epithelial ovarian carcinoma suboptimal surgically staged and treated with adjuvant chemotherapy, underwent second look surgery including SAPL.
The role of pelvic & aortic lymphadenectomy at second-look surgery in apparent early stage ovarian cancer after inadequate surgical staging followed by adjuvant chemotherapy

Signorelli M, Landoni F, Mangioni C. Gynecol Oncol. 2014

RESULTS:
Only one woman had nodal metastasis (1.5%)

After a median follow-up of 78 months, 5 (7.6%) died of progressive disease

The 5-year disease-free survival and overall survival are 92% and 96%
The role of pelvic & aortic lymphadenectomy at second-look surgery in apparent stage I-IIA ovarian cancer after inadequate surgical staging followed by adjuvant chemotherapy

Signorelli M, Landoni F, Mangioni C. Gynecol Oncol. 2014

The risk of nodal metastases in stage I-IIA Unstaged ovarian cancer after adjuvant chemotherapy is negligible

Lymphadenectomy at second-look is not indicated in this subset of women
Systematic pelvic and aortic lymphadenectomy in advanced ovarian cancer patients at the time of interval debulking surgery: a double-institution case-control study.


- Retrospective 2005 -2010, 151 patients with AOC
- **RESULTS:**
  - 2-year PFS 36% vs. 25% (p = ns)
  - 2-year overall survival 69 vs. 88% (p = ns), in the case and controls, respectively.
- **Cost** = longer operating time, transfusions.

**CONCLUSIONS:**

- Lymphadenectomy at the time of IDS could be omitted, at least in high-risk patients
Kaplan–Meier curves for ovarian cancer patients submitted to IDS lymphadenectomy vs. no lymphadenectomy $p = 0.834$, log-rank test. PFS is expressed in months on the x axis.
Overall Survival

Kaplan–Meier curves for ovarian cancer patients submitted to IDS lymphadenectomy vs. no lymphadenectomy; p = 0.777, log-rank test. OS is expressed in months on the x axis.
Prognostic significance of systematic lymphadenectomy at primary debulking surgery in advanced ovarian cancer

- Retrospective 189 stage IIIC ovarian cancer (2000-2011)
- No gross residual (NGR) or residual 0.1-1cm: OS of LND 86 vs. 46 months, p=0.02
- If residual >1cm: No difference in OS (39 vs. 40 months)

CONCLUSION:

- Systematic lymphadenectomy may have a therapeutic value and be significantly associated with improved survival in stage IIIC ovarian cancer patients with no visible residual disease.

Suk-Joon Chang, Robert Bristow, Hee-Sug Ryu. Gynecologic Oncology, 2012
Prognostic significance of systematic lymphadenectomy as part of primary debulking surgery in patients with advanced ovarian cancer

Overall survival by lymphadenectomy in all patients (n = 189)

Suk-Joon Chang, Robert Bristow, Hee-Sug Ryu. Gynecologic Oncology, 2012
Overall survival by lymphadenectomy in patients with NGR (n = 61)

Controversies in the management of ovarian cancer: pros and cons for lymphadenectomy

- The effect of lymphadenectomy on survival in advanced ovarian cancer is still unknown.
- Patients with residual peritoneal tumor are unlikely to benefit from lymphadenectomy.
- The German AGO has initiated the first study in advanced ovarian cancer (LION) which compares lymphadenectomy with no LND in patients without any visible tumor residual.
- Until these data are available, no subgroup of patients has been shown to benefit from LND.

Camara O, Sehouli J. Anticancer Res. 2009
Published Randomized Trials
Randomized study of systematic lymphadenectomy in ovarian cancer macroscopically confined to the pelvis

- 268 pts randomized to RPLND vs. control

- ORT longer, more transfusions in RPLND (240 vs. 150 min, & 36 vs. 22%)

- More pts with (+) nodes in RPLND (22% vs. 9%, \(P=0.007\))

- Better upstaging which may impact postop treatment regimen

- “This trial may have lacked power”.

5-year progression-free survival
71% (No LAD) vs. 78% (LAD)

5-year overall survival

81% (No LAD) vs. 84% (LAD)

Randomized Trials

Systematic Aortic and Pelvic Lymphadenectomy Versus Resection of Bulky Nodes Only in Optimally Debulked Advanced Ovarian Cancer: A Randomized Clinical Trial

Pierluigi Benedetti Panici, Angelo Maggioni, Neville Hacker, Fabio Landoni, Sven Ackermann, Elio Campagnutta, Karl Tamussino, Raimund Winter, Antonio Pellegrino, Stefano Greggi, Roberto Angioli, Natalina Manci, Giovanni Scambia, Tiziana Dell’Anna, Roldano Fossati, Irene Floriani, Rita S. Rossi, Roberto Grassi, Giuseppe Favalli, Francesco Raspagliesi, Diana Giannarelli, Luca Martella, Costantino Mangioni

Journal of the National Cancer Institute, Vol. 97, No. 8, April 20, 2005
INTERNATIONAL RANDOMIZED TRIAL


• All should have intraperitoneal residual tumors ≤ 1 cm.

• After the completion of cytoreductive surgery, randomized to resection of bulky nodes only vs. systematic LND

Table 1. Clinical and tumor characteristics by treatment arm

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No lymphadenectomy (n = 211)</th>
<th>Lymphadenectomy (n = 216)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Median age (25th–75th percentiles)</td>
<td>56.0 (47–62)</td>
<td>53.0 (45–61)</td>
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<tr>
<td>FIGO* stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIb</td>
<td>37</td>
<td>17.5</td>
</tr>
<tr>
<td>IIIc</td>
<td>162</td>
<td>76.8</td>
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<tr>
<td>IV</td>
<td>12</td>
<td>5.7</td>
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<td>Missing data</td>
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<td>-</td>
</tr>
<tr>
<td>Residual tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>79</td>
<td>37.4</td>
</tr>
<tr>
<td>≤1 cm</td>
<td>118</td>
<td>55.9</td>
</tr>
<tr>
<td>1–2 cm</td>
<td>12</td>
<td>5.7</td>
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<td>2</td>
<td>0.9</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (well differentiated)</td>
<td>11</td>
<td>5.2</td>
</tr>
<tr>
<td>2 (moderately well differentiated)</td>
<td>37</td>
<td>17.5</td>
</tr>
<tr>
<td>3 (poorly differentiated)</td>
<td>160</td>
<td>75.8</td>
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<td>1.4</td>
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<tr>
<td>Serous</td>
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<td>62.6</td>
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<tr>
<td>Endometrioid</td>
<td>28</td>
<td>13.3</td>
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<tr>
<td>Mucinous</td>
<td>6</td>
<td>2.8</td>
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<tr>
<td>Clear-cell</td>
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<td>5.7</td>
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<tr>
<td>Undifferentiated</td>
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<td>10.9</td>
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<td>Other</td>
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<td>3.8</td>
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<td>2</td>
<td>0.9</td>
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</table>

*International Federation of Gynecology and Obstetrics.

Journal of the National Cancer Institute, Vol. 97, No. 8, April 20, 2005
Table 2. Median number (25th–75th percentiles) of resected nodes by treatment arm

<table>
<thead>
<tr>
<th>Nodal site</th>
<th>No lymphadenectomy (n = 211)</th>
<th>Lymphadenectomy (n = 216)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Pelvic</td>
<td>1 (0–6)</td>
<td>28.5 (22–41)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lumbo-aortic</td>
<td>1 (0–5)</td>
<td>23 (16–32)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pelvic and lumbo-aortic</td>
<td>4 (0–11)</td>
<td>51.5 (41–70)</td>
<td>&lt;.001</td>
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<td>Missing data</td>
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<td>2</td>
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</table>
Systematic lymphadenectomy detected a higher number of patients with nodal metastases compared with the removal of bulky nodes only, thus increasing the amount of disease removed.
Additional 1.5 hrs, 350 ml EBL, and 12% higher transfusion rate

<table>
<thead>
<tr>
<th>Surgical outcome</th>
<th>No lymphadenectomy (n = 211)</th>
<th>Lymphadenectomy (n = 216)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median operating time (min)</td>
<td>210 (170–280)</td>
<td>300 (250–360)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>(25th–75th percentiles)</td>
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<td></td>
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<tr>
<td>Missing data</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Median blood loss (mL)</td>
<td>650 (400–1200)</td>
<td>1000 (600–1500)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>(25th–75th percentiles)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>14</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Patients transfused (%)</td>
<td>59.2</td>
<td>71.7</td>
<td>.006</td>
</tr>
<tr>
<td>Median hospital stay (days)</td>
<td>9 (7–12)</td>
<td>9 (7–13)</td>
<td>.21</td>
</tr>
<tr>
<td>(25th–75th percentiles)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>9</td>
<td>10</td>
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</table>
# POST-OPERATIVE COMPLICATIONS

<table>
<thead>
<tr>
<th>COMPLICATION</th>
<th>LYMPHADENECTOMY</th>
<th></th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO 211</td>
<td>YES 216</td>
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<tr>
<td>THROMBOEMBOLIC EVENTS</td>
<td>3</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>INTESTINAL FISTULA</td>
<td>4</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>URETERAL FISTULA</td>
<td>2</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>ANASTOMOTIC DEHISCENCE</td>
<td>2</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>PROLOGED ILEUS</td>
<td>5</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>INFECTION</td>
<td>14</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>INTESTINAL PERFORATION</td>
<td>5</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td><strong>LYMPHOCYST/LYMPHEDEMA</strong></td>
<td>--</td>
<td>14</td>
<td><strong>0.0001</strong></td>
</tr>
<tr>
<td>HEMOPERITONEUM</td>
<td>1</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>OTHER</td>
<td>3</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>39 (18%)</strong></td>
<td><strong>60 (28%)</strong></td>
<td><strong>0.014</strong></td>
</tr>
</tbody>
</table>
Watch for the Renal Artery
Preop Adenopathy
42 yof IIIC HG serous ov ca s/p debulking an RPLND Right Renal Infarct
Left Infrarenal Adenopathy

*It is not feasible to just “pluck” this one out*
5-Year PFS Improved from 21% to 31%
Median PFS Improved by 7 months

X^2 (LOG-RANK): 5.8055 (P=0.016)

EVENTS | TOTALS
--- | ---
153 | 211
138 | 215
OVERALL SURVIVAL

Systematic lymphadenectomy in ovarian cancer at second-look surgery: a randomized clinical trial

T Dell' Anna, & F. Landoni
British Journal of Cancer 2012

The role of systematic aortic and pelvic lymphadenectomy at second-look surgery in early-stage or optimally debulked advanced ovarian cancer
The role of systematic aortic & pelvic lymphadenectomy at second-look surgery in early-stage or optimally debulked advanced ovarian ca

- 1991-2001, 308 patients stage IA–IV epithelial ovarian carcinoma were randomly assigned to undergo SAPL \( n=158 \) or resection of bulky nodes only \( n=150 \)

- Primary end point was overall survival (OS)

T Dell' Anna, & F. Landoni
British Journal of Cancer 2012
Design

322 Patients randomly assigned

159 Allocated no lymphadenectomy
- 9 Patients not eligible:
  - Other synchronous cancer = 2
  - Over 12 months since the end of first-line chemotherapy = 4
  - Residual tumour > 1 cm at II surgery = 1
  - FIGO stage IV, not pleural = 2

163 allocated lymphadenectomy
- 5 Patients not eligible:
  - Other synchronous cancer = 1
  - Primary fallopian cancer = 1
  - Residual tumour > 1 cm at II surgery = 1
  - Lymphadenectomy at I surgery = 1
  - Residual tumour > 1 cm at I surgery and no first-line chemotherapy = 1

150 Available for intention to treat analysis

158 Available for intention to treat analysis

T Dell' Anna, & F. Landoni
British Journal of Cancer 2012
The role of systematic aortic & pelvic lymphadenectomy at second-look surgery in early-stage or optimally debulked advanced ovarian ca

Results:

• Operating time, blood loss, blood transfusions and hospital stay were higher in the SAPL

• Number of resected nodes and the % of women with nodal metastases were higher in the SAPL
The role of systematic aortic & pelvic lymphadenectomy at second-look surgery in early-stage or optimally debulked advanced ovarian ca

Results:

• Sites of first recurrences were similar in both arms
• Risk for progression and death were not different
• 5-year PFS = 40.9% and 53.8%
• 5-year OS = 63.5% and 67.4%, in the SAPL and in the control arm, respectively

Conclusion:

• SAPL in second-look surgery for advanced ovarian cancer did not improve PFS and OS.
Overall survival

Events | Totals
--- | ---
58 | 150
66 | 158

χ² (log-rank): 0.0565 (P=0.8122)

Patients at risk

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>Radical lymphadenectomy</th>
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<tbody>
<tr>
<td>150</td>
<td>158</td>
</tr>
<tr>
<td>138</td>
<td>145</td>
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<td>123</td>
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<td>37</td>
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</table>
Summary
LYMPHADENECTOMY IN OVARIAN CANCER

• SYSTEMATIC LYMPHADENECTOMY DETECTS A HIGHER NUMBER OF PATIENTS WITH NODAL METASTASES

• SYSTEMATIC LYMPHADENECTOMY IS FEASIBLE BUT INCREASES EBL, LYMPHOCYST & LYMPHEDEMA

• IN ADVANCED OVARIAN CANCER LYMPHADENECTOMY IMPROVES PROGRESSION FREE SURVIVAL IN PATIENTS WHO ACHIEVED OPTIMAL PERITONEAL CYTOREDUCTION
Future Directions in Surgery

- When surgery is undertaken - Requirement for maximal attempt at primary peritoneal cytoreduction and to limit morbidity.

- AGO-LION (lymphadenectomy in ovarian neoplasm) trial
The CARACO trial  
F Lecuru 2011

Further randomized trials are needed to balance risks and benefits of systematic lymphadenectomy in advanced-stage disease

CARACO is a French ongoing trial, built to bring a reply to this important question
Bottom Line
we need better drugs for this disease
Newer Biologic Agent

“Pedrosizumab previously known as PTR 2012”
Thank You