The role of lymphadenectomy in gynecologic oncology (GO)

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The role of lymphadenectomy in GO

* General considerations
* Vulvar cancer
* Vaginal cancer
* Cervical cancer
* Endometrial cancer
* Cancer of the fallopian tube (PCFT)
* Ovarian cancer
General considerations (1)

* Conclusions according to EBM, if possible
  - meta-analysis/syst. review of RCTs
  - RCTs
  - nRCTs (present, historical)
  - CCS
  - cross sectional studies
  - follow-up studies
  - case series / reports
  - expert opinion
In all (almost) cancers

- lymph node status is included to the staging system (TNM, FIGO)
- lymphadenectomy is a basic procedure in primary surgery
- the presence of lymph node metastases (LNMs) is a highly significant prognostic factor
The presence of LNMs cannot be profoundly judged by:
- ultrasound, CT or MRI
- inspection or palpation
- sampling of “suspicious” or enlarged nodes
* More than 50% of the pelvic nodes are < 1 cm in size (endometrial cancer)

Girardi 1993, Benedetti 1998
* The size and shape of LNs do not correlate with the presence of LNMss
- only 10% of the metastatic LNs are enlarged

Wu et al. 1984, Petru et al. 1994
Lymphadenectomies in gyn ca
- N=126, LNM were found in 5%
- in 64% palpation = histology
- in 34% palp normal, histo = LNM
- in 3% palp = LNM, histo normal
- sens 72%, spec 81%, PPV 56%, NPV 89%

Arango et al. Gynecol Oncol 2000;95:553-
Quality control of LND
- what is that - is there any?
- different handling of specimens, pathologist-dependent (?)
- groin: 5-10 LNs per side
- pelvis: biopsy < 10, sampling 10-15, LND > 20 LNs
- para-aortic: 10-15 LNs
* We can not base our decisions on RCTs

- mainly because there are not any
- some is going on, some are planned to begin

  vulvar cancer /sentinel node

  endometrial cancer / LND (MRC-ASTEC-trial)
* Decision maker’s burden

- enourmous amount of data / studies / opinions with limited value
- still you have make a decision how to perform surgery
- ”on the other hand on the other hand” is not enough
- decision´s validity = benefit of the patient
Slogans to remember

1. There is no cure for the bad surgery - especially in primary phase
2. There are many roads to Rome
3. Seeking the truth is endless, but not hopeless
4. The bigger head, the bigger headache!
Staging is based on surgical findings (FIGO)

** Groin LNMs are frequent: 21-59 %

** Clinical examination overestimates the presence of LNMs by 15 %

* Ultrasound: sens 82 %, spec 87 %

Iversen et al. 1981

Mäkela, Leminen, Kärkkäinen, Lehtovirta 1993
<table>
<thead>
<tr>
<th>Size of the tumor</th>
<th>Groin LNM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 cm</td>
<td>18.0</td>
</tr>
<tr>
<td>1-2</td>
<td>19.4</td>
</tr>
<tr>
<td>2-3</td>
<td>31.4</td>
</tr>
<tr>
<td>3-4</td>
<td>54.3</td>
</tr>
<tr>
<td>4-5</td>
<td>39.6</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>51.8</td>
</tr>
</tbody>
</table>

Homesley et al. Gynecol Oncol 1993
* Groin LNMs (%) by tumor thickness

<table>
<thead>
<tr>
<th>Tumor Thickness</th>
<th>Ipsilat</th>
<th>Contralat</th>
<th>Bilat</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2 mm</td>
<td>6.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3-5</td>
<td>20.4</td>
<td>1.9</td>
<td>2.8</td>
</tr>
<tr>
<td>6-10</td>
<td>28.8</td>
<td>3.8</td>
<td>11.3</td>
</tr>
<tr>
<td>11-</td>
<td>36.7</td>
<td>6.7</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Homesley et al. 1993
Vulvar cancer (4)

Lymph node dissection (LND); three-incision technique; modified vulvectomy
**Vulvar cancer (5)**

* Ipilateral groin LND in all stages when resectable except:
  - stage 0 - Ia (size < 2 cm, inv < 1 mm)
* Bilateral groin LND when central lesion
* Pelvic LND when groin LNMs found (frozen section)
* Sentinel lymph node technique (SND)

* Published studies over 250, ongoing RCTs

* Accrediation / learning curve
  - ”30 procedures, 27 successful, 1 FN allowed”

* ”Gyn oncologist who perform SND procedure in vulvar cancer patients should perform the technique by following strict protocol and within the protection of a clinical trial”

de Hullu JA et al. Gynecol Oncol 2004;94:10-
* Sentinel lymph node technique (SND)
  - systemic review, 29 studies 1979-2004
  - SND by Tc is the best: sensitivity 97%
  - studies were small, often poor design
  - efficacy (reducing the radicality and patient morbidity without reducing survival demands) RCT to be done

Selman et al. Gynecol Oncol 2005 Aug
Vulvar cancer (8)

* Vulvectomy (modified) + LNDs complications (%)

Wound infection  39 - 47
Wound breakdown  17 - 20
Lymphocysts       7 - 40
Lymphedema        12 - 28

Leimenen et al. EJOOG 2000: N=149
Vergote et al. IJGC 2003: N=172
Vaginal cancer

* Staging is based on clinical findings (FIGO)
* All pelvic lymph nodes are prone to LNMs; frequency?
* Treatment is highly individualized
  - RT, CRT, surgery, combination
  - the role of LND?
Staging is based on *clinical* findings (FIGO); TNM if operation +

Pelvic +- para-aortic LNMs are frequent:
st I 2-43 %, st II 40-71 %

Pelvic LND is a crucial part of the primary surgery of stage Ib-IIa patients
- Wertheim, Schauta, Meigs, Rutledge II-IV, LRH, trachelectomy
- para-aortic - mostly when pelv LNMs
Cervical cancer (2)

* Pelvic LND is not needed
  - stage 0 (carcinoma in situ)
  - stage Ia1 (small microinvasive cancer)

* Trachelectomy
  - st. Ia2-b1, no fertility problems
  - size < 20-25 mm, G1-2, no LNM

- prior pelvic LND (laparoscopy)
- if LNM -> radical operation
Staging is based on surgical findings (FIGO)

Presence of LNMs is associated with stage, grade, invasion, histology

LN status most powerful prognostic factor

Morrow et al. 1991

Still -the role of LND is not yet defined, no consensus has been found
## Endometrial cancer (2)

<table>
<thead>
<tr>
<th>LNMs (%) by st Ia-b and grade</th>
<th>Pelvic</th>
<th>Para-aortic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia G 1</td>
<td>0-2</td>
<td>0</td>
</tr>
<tr>
<td>G 2</td>
<td>2.7-4</td>
<td>2.7-4</td>
</tr>
<tr>
<td>G 3</td>
<td>11-15</td>
<td>7-15</td>
</tr>
<tr>
<td>Ib G 1</td>
<td>3.6-4</td>
<td>0-4</td>
</tr>
<tr>
<td>G 2</td>
<td>8.1-10</td>
<td>2.7-7</td>
</tr>
<tr>
<td>G 3</td>
<td>26-40</td>
<td>16-26.7</td>
</tr>
</tbody>
</table>

*Boronow et al. 1984, Creasman et al. Cancer 1987*
* LNMs (%) by G1-3 and stage I

<table>
<thead>
<tr>
<th></th>
<th>Pelvic</th>
<th>Para-aortic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>G 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ia</td>
<td>3.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Ib</td>
<td>7.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Ic</td>
<td>7.8</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>G 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ia</td>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td>Ib</td>
<td>10.2</td>
<td>6.1</td>
</tr>
<tr>
<td>Ic</td>
<td>21.7</td>
<td>8.9</td>
</tr>
</tbody>
</table>

FIGO 1993-95
Endometrial cancer (4)

- Low risk (< 4 %)
  - st Ia G1-2
  - inv. < 1/3 + G 1-2
  - inv. 1/3-2/3 + G 1
  - LVI -
  - histology = pure adeno

- High risk (20-45 %)
  - G 3
  - inv. 1/3-2/3 + G 2
  - inv. > 2/3 + G 1-3
  - LVI +
  - histology = other than pure adeno

Boronow 1984, -87, -97
Problems of risk evaluation
- 81-88 % of the cases represent stage I-II (FIGO statistics, Faught et al. 1994)
- reliable method (besides histologic specimen) to evaluate invasion is missing
  - ultrasound, peroperative inspection or frozen section; accuracy 80-85 %
The effect of LND on survival

Improves


No effect

- Trimle, Kosary and Park. Gynecol Oncol 1998
  N=9185; st Ia G 3 better, st I-II improved
The effect of para-aortic LND on survival (Mariani et al. Gynecol Oncol 2000;76:348-)

Criteria: at least 5 removed LNs

N=188

- 1) N=137: high risk, not st IV
  - 5-YSR 85 % P-ALND +, 71 % P-ALND -

- 2) N=51: pelvic LNMs, not st IV
  - 5-YSR 77 % P-ALND +, 42 % P-ALND -
The effect of LND on survival

**FIGO 1993-95 (N=5694); 5-YSR (%)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>53.8</td>
<td>87.4 (+ 33.6)</td>
</tr>
<tr>
<td>II</td>
<td>41.4</td>
<td>76.3 (+ 34.9)</td>
</tr>
<tr>
<td>III</td>
<td>23.1</td>
<td>56.6 (+ 33.5)</td>
</tr>
<tr>
<td>IV</td>
<td>12.0</td>
<td>17.8 (+ 5.8)</td>
</tr>
</tbody>
</table>
Complete surgical procedure gives significant information considering postoperative treatment modalities
- brachy instead of pelvic RT
- CT instead of RT
- less complications, better survival (?)

Goudge et al. Gynecol Oncol 2004
**Impact of proper surgical staging**

<table>
<thead>
<tr>
<th>Performer</th>
<th>PSS in</th>
<th>The use of adj. RT</th>
<th>Adj. RT St I (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gynecol.</td>
<td>96</td>
<td>8.6</td>
<td>0</td>
</tr>
<tr>
<td>General gynecol.</td>
<td>19</td>
<td>21.7</td>
<td>18</td>
</tr>
</tbody>
</table>

Roland et al. Gynecol Oncol 2004
### Endometrial cancer (10)

<table>
<thead>
<tr>
<th></th>
<th>LND -</th>
<th>LND +</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BTFs (%)</strong></td>
<td>6</td>
<td>14</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Febr. morb (%)</strong></td>
<td>20</td>
<td>26</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Op. time (min)</strong></td>
<td>117</td>
<td>139</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Blood loss (ml)</strong></td>
<td>322</td>
<td>442</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>1. bowel mov.</strong></td>
<td>4.8</td>
<td>6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Hosp. stay</strong></td>
<td>6.0</td>
<td>7.6</td>
<td>ns</td>
</tr>
</tbody>
</table>

*Mariana et al. AJOG 2000*
Endometrial cancer (11)

* **AH + BSO + LND complications**

<table>
<thead>
<tr>
<th>Complication</th>
<th>%</th>
<th>Related to LND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocysts</td>
<td>1.2 - 3</td>
<td>+</td>
</tr>
<tr>
<td>Bladder damage</td>
<td>0.45</td>
<td>+ -</td>
</tr>
<tr>
<td>Bowel damage</td>
<td>1.9</td>
<td>+ -</td>
</tr>
<tr>
<td>PE</td>
<td>1.1</td>
<td>+ -</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>2.3</td>
<td>+ -</td>
</tr>
<tr>
<td>Wound abcess</td>
<td>3.2</td>
<td>-</td>
</tr>
</tbody>
</table>

Endometrial cancer (12)

* LH + LND as good as AH + LND
* Certain limitations exists
  - severely obese patient
  - complicated heart or lung disease
  - previous surgery -> adhesions
  - if para-aortic procedure is not possible

∀ G 3, st. Ic, pelvic LNMs, serous ca

Malur et al. Gynecol Oncol 2001
Ovarian cancer and PCFT (1)

* Staging is based on surgical findings (FIGO)

* Presence of LNMs is associated with
  - stage, grade, histology (ser and clear cell)
  - stage I-II: 12-45 %, III-IV: 55-75 %

  di Re and Baiocchi. IJGC 2000

* LN status is a prognostic factor

* Still - the role of LND is not yet defined, no consensus has been found
* Macroscopic st Ia - b

- LNMs are limited to ipsilateral side in 73 %

- still in 15 % contralateral and in 11 % bilateral LNMs are found

- when LND -> 10-18 % up-staging

Petru et al. AJOG 1994, Ferraris et al EJGO 1888
Gershenson ASCO 2000, Di Re et al. Gynecol Oncol 1996
Ovarian cancer and PCFT (3)

* Primary surgery - recommendations for lymph node sampling (LNS) or LND
  - no residual tumor (RT) despite of stage
  - RT limited to the pelvis
  - RT outside the pelvis < 1 cm

Hoskins. Gynecol Oncol 1994
Trimbos and Bolis. Obstet Gynecol 1994
Restaging
- operation after incomplete primary surgery
- in 30% up-staging

Young et al. JAMA 1983
van der Burg et al. NEJM 1995
* Cytoreduction; interval or secondary
- if optimal result (RT < 1 cm, LND included) -> survival is better

van der Burg et al. NEJM 1995
Williams et al. 1997
Vergote et al. 2001
Second look operation

- after primary CT LNMs to be found in 25 - 77 %

- false -ve CPR in 17 - 40 % if retroperitoneum is not assessed in second look

di Re and Baiocchi. IJGC 2000
Systemic LND - effect on survival: no RCTs (and will not be)
- historic series: 5-YSR 13 vs. 53 %
- comparative series: 4-YSR 0 vs 22 %
and 5-YSR 30 vs 46 %

### LND complications (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel damage</td>
<td>3.9</td>
</tr>
<tr>
<td>Lymphocysts</td>
<td>13.5</td>
</tr>
<tr>
<td>DVT</td>
<td>5.0</td>
</tr>
<tr>
<td>PE</td>
<td>2.8</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>2.7</td>
</tr>
</tbody>
</table>

*Di Re and Baiocchi. IJGC 2000*
Summary - role of LND

* Vulvar and cervical cancers
  - well defined and accepted
  - no major arguments
  - SND to be confirmed

* Endometrial and ovarian cancers
  - lots of suggestive data for the benefit
  - major arguments, no consensus
* There is no other accurate method for proper staging and evidence of LNMs
* Doctors should not be "wrong" in such a amount of cancers cases -
  - wrong stage -> wrong treatment -> wrong results -> non-comparable studies
* Optimal cytoreduction is more often reached, courages to "action"
Why systemic LND (2)

* Right stage - adjuvant treatment not needed
  - early (macroscopic) stage - precise staging
  - reducing the use of radiotherapy
* Data for survival benefit exists
* Complication rate acceptable
  - intention to curative treatment in serious disease
  - doing accomplish learning
Systemic LND

- ovarian cancer since 1986/87
  - when restrictions - LNS
  - NOT if RT is carcinosis or far more than 1 (2) cm
- endometrial cancer since 1990
  - LNS or AH/LH + BSO if serious medical conditions, age "enough", high BMI