Sentinel lymph node mapping in endometrial cancer...

and cervix cancer?

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No disclosures or conflicts of interest
Sentinel lymph nodes in GYN: The Outline...

• Endometrial cancer
  • Lymphadenectomy review
  • SLN method
  • SLN data
  • Current opinions/uses

• Cervical cancer (brief)
  • SLN data
  • Current opinions/uses
Endometrial cancer

Figure 2. Average annual percent change in age-standardised endometrial cancer incidence rates for (A) all ages and (B) age 25 to 49 years and age 50+ years and older, over the last 10 years available, and 95% confidence intervals. The last 10 years vary by population from 2001–2011 to 2004–2013. The average annual percent change was not computed for South Africa for age 25 to 49 years due to several years with no new cases. Confidence intervals have been truncated on the plots for Costa Rica and South Africa for all ages, and age 50 years and older. Twelve regional registries.
Endometrial cancer

<table>
<thead>
<tr>
<th>Table 1: 2009 FIGO staging system for carcinoma of the endometrium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I*</td>
</tr>
<tr>
<td>IA</td>
</tr>
<tr>
<td>IB</td>
</tr>
</tbody>
</table>
| Stage II | Tumor invades the cervical stroma but does not extend beyond the uterus*
| Stage III* | Local and/or regional spread of tumor*
| IIIA    | Tumor invades the serosa of the corpus uteri and/or adnexas |
| IIIB    | Vaginal and/or parametrial involvement |
| IIIC    | Metastases to pelvis and/or para-aortic lymph nodes |
| IIIC1   | Positive pelvic nodes |
| IIIC2   | Positive para-aortic lymph nodes with or without positive pelvic lymph nodes |
| Stage IV* | Tumor invades bladder and/or bowel mucosa and/or distant metastases |
| IVA     | Tumor invasion of bladder and/or bowel mucosa |
| IVB     | Disant metastases, including intra-abdominal metastases and or inguinal lymph nodes |

FIGO = International Federation of Gynecology and Obstetrics
* Includes grades 1, 2, or 3
* Endocervical glandular involvement only should be considered as stage I and no longer as stage II.
* Positive cytology has to be reported separately without changing the stage.
Pelvic and paraaortic lymph node dissection
- Always?
- Sentinel?
- Complete?
- Why?
Who gets a lymphadenectomy?

1. Everyone (old school)
2. No one (Europe)
3. Some people
   1. High-risk histologies
   2. Frozen section criteria (Mayo Clinic)
4. Sentinel lymph nodes
Endometrial cancer:
Studies on lymphadenectomy

- **Creasman** et al 1987, **GOG 33**
  - Clinicopathologic assessment of 933 evaluable patients
  - Low rate of positive nodes in low grade, endometrial only disease (1-3%)

- **CONSORT** (Italian study) 2008
  - 541 women with clinical stage I randomized to LND vs. not.
  - No difference in adjuvant treatment (69% vs 65%, $P=0.07$ PLND vs no PLND)
  - No difference in 5 yr DFS (81% vs 82%, $P=0.68$), PLND vs no PLND
  - No difference in 5 yr OS (86% vs 90%, $P=0.50$), PLND vs no PLND

- **ASTEC/EN.5** 2009
  - 1408 women with clinical stage I endometrial cancer
  - Randomized to Hyst/BSO vs. Hyst BSO +LND
  - In PLND arm, 9% had involved nodes (median 12 nodes removed). 5-year OS no PLND 81% vs PLND 80% (NS)
# GOG-33: Risk of LN involvement

<table>
<thead>
<tr>
<th>PELVIC NODES</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrium only</td>
<td>0%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Inner 1/3</td>
<td>3%</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>Middle 1/3</td>
<td>0%</td>
<td>9%</td>
<td>4%</td>
</tr>
<tr>
<td>Outer 1/3</td>
<td>11%</td>
<td>19%</td>
<td>34%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PARA-AORTIC NODES</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrium only</td>
<td>0%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Inner 1/3</td>
<td>1%</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Middle 1/3</td>
<td>5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Outer 1/3</td>
<td>6%</td>
<td>14%</td>
<td>23%</td>
</tr>
</tbody>
</table>

Endometrial cancer: Studies on lymphadenectomy

Cochran Review

- All randomized trials comparing lymphadenectomy with no lymphadenectomy reviewed
- No evidence that lymphadenectomy decreases the risk of death or disease recurrence compared with no lymphadenectomy in women with presumed stage I disease
  - More surgical morbidity
    - Lymphedema
    - Lymphocyst formation

May K et al Cochrane Database Syst Rev. 2010 Jan 20;(1).
Morbidity of Lymphadenectomy
So WHY do we do it?

• Nodal status is highly prognostic
• Nodal status allows tailoring or avoidance of adjuvant therapy
Rationale for Sentinel Lymph Nodes:

• Nodal status is highly prognostic
• Nodal status allows tailoring or avoidance of adjuvant therapy
• Lymphadenectomy has long term side effects and can increase peri-operative complications
• Previous studies in endometrioid cancer do not demonstrate a therapeutic effect of lymphadenectomy
Sentinel lymphadenectomy: The Method

**Figures 1, 2, and 3** are reproduced with permission from Memorial Sloan Kettering Cancer Center. © 2013, Memorial Sloan Kettering Cancer Center.
Figure 4 Sentinel lymph node (SLN) mapping after cervical indocyanine green (ICG) injection in endometrial cancer. The right lymphatic trunks and an SLN located between the external iliac and internal iliac artery is shown.
**Figure 5** Indocyanine green injected into the cervix, leading into a right external iliac sentinel lymph node.

**Figure 6** Left pelvic lymphatic trunks with indocyanine green fluorescence imaging after a cervical injection to map endometrial cancer. The sentinel lymph node is located in the medial aspect of the iliac vessels, with a secondary node just lateral to the external iliac artery.

From Abu-Rastrom 2014 JNCCN
Sentinel lymphadenectomy: The Method

SLN Protocol
LN cut in 3 mm sections

Each section cut to 4 levels

H&E
AE1/AE3 IHC
H&E
H&E
Sentinel lymphadenectomy for endometrial cancer: The Data

- Holloway et al. *Gynecol Oncol.* 2016 May;141(2):206-210

Sentinel Lymph Nodes: The Data

• Holloway et al. *Gynecol Oncol.* 2016 May;141(2):206-210
  • Retrospective comparison of SLN vs. standard LND n=781, (SLN=119)
  • More lymph node mets seen in mapped nodes (30.3% vs. 14.7%)
  • No data on recurrence or survival
OBJECTIVE:
Estimate sensitivity and negative predictive value (NPV) of SLN mapping using ROBOTIC assisted fluorescence imaging of ICG in detecting lymphatic metastases in patients with endometrial cancer.
FIRES Trial

- Multicenter, prospective cohort study, 10 US centers, 18 surgeons
- Clinical Stage I, any histology
- No prior therapy, retroperitoneal surgery, or extra uterine disease
- 0.5mg/mL ICG tracer, cervical injection 1cm deep at 3 & 9 o’clock
- Pelvic lymphadenectomy required, para-aortics optional
- Ultra-staging of SLN (3mm cuts)
- Primary endpoints: Sensitivity & NPV

**FIRES Trial**

<table>
<thead>
<tr>
<th>Final pathology (postoperative grade) (n=356)*</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrioid grade</td>
<td>292 (82%)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>152 (43%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>102 (29%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>38 (11%)</td>
</tr>
<tr>
<td>Serous</td>
<td>41 (12%)</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>Clear cell</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (1%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postoperative stage (n=344)+</th>
<th>Patients (n=340)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>228 (66%)</td>
</tr>
<tr>
<td>IB</td>
<td>47 (14%)</td>
</tr>
<tr>
<td>II</td>
<td>15 (4%)</td>
</tr>
<tr>
<td>IIIA</td>
<td>10 (3%)</td>
</tr>
<tr>
<td>IIIB</td>
<td>0</td>
</tr>
<tr>
<td>III†</td>
<td>41 (12%)</td>
</tr>
<tr>
<td>IV</td>
<td>3 (1%)</td>
</tr>
</tbody>
</table>

- Median age 63 yrs (29-83)
- Median BMI 33.4 kg/m² (18-60)
- 9% adverse events
- One ureteral injury

FIRES Trial

- 97.2% sensitivity of detecting nodal metastasis
  - 3% false negative rate
- 99.6% negative predictive value
- 60% (21/35) with metastatic disease only in SLN
- 54% (19/35) metastasis only identified on ultra staging

<table>
<thead>
<tr>
<th></th>
<th>True positive nodes</th>
<th>True negative nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive sentinel lymph node</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>Negative sentinel lymph node</td>
<td>1</td>
<td>257</td>
</tr>
</tbody>
</table>

*Table 3: Sensitivity and specificity data*

Sentinel Lymph Nodes: The Data

FIRES TRIAL
CONCLUSION:
In women with endometrial cancer SLN Bx using ICG and near infrared imaging on a robotic platform accurately identifies nodal metastatic disease.

SLN mapping *increases* the detection of metastasis overall compared to routine lymphadenectomy
Sentinel lymph nodes: The Data

- Zahl Eriksson et al: Mayo Clinic v. MSK
  - Complete LND versus SLN
  - Retrospective
  - Oncologic outcomes

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Recurrences.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SLN cohort N=642</td>
</tr>
<tr>
<td>Disease progression/recurrence within 3 years, N (%)</td>
<td>19 (3.0)</td>
</tr>
<tr>
<td>3-year disease-free survival, % (95% CI)</td>
<td>94.9 (92.4–97.5)</td>
</tr>
<tr>
<td>Route of first recurrence, N</td>
<td></td>
</tr>
<tr>
<td>Hematogenous only</td>
<td>4</td>
</tr>
<tr>
<td>Hematogenous and lymphatic</td>
<td>–</td>
</tr>
<tr>
<td>Hematogenous and peritoneal</td>
<td>1</td>
</tr>
<tr>
<td>Hematogenous, lymphatic and peritoneal</td>
<td>1</td>
</tr>
<tr>
<td>Lymphatic only</td>
<td>2</td>
</tr>
<tr>
<td>Lymphatic and peritoneal</td>
<td>1</td>
</tr>
<tr>
<td>Vaginal only</td>
<td>9</td>
</tr>
<tr>
<td>Vaginal and peritoneal</td>
<td>–</td>
</tr>
<tr>
<td>Peritoneal only</td>
<td>1</td>
</tr>
</tbody>
</table>

SLN, sentinel lymph node; LND, lymph node dissection.

Gynecol. Oncol., 140 (2016), pp. 394-399
Sentinel Lymph Node - High Risk Histologies?!

- **SENTI-ENDO (France, Lancet 2011)**
  - NPV of 97% (95% CI 91-99) and sensitivity of 84% (62-95).
  - All three false negatives had type 2 endometrial cancer.

- **Touhami et al (Tunisia, Gyn Onc 2017)**
  - High risk EC $\rightarrow$ SLN f/b lymphadenectomy
  - Sensitivity of 95.8% (23/24) and a negative predictive value of 98.2%(57/58).

- **Ehrisman et al (Duke, Gyn Onc Rep 2016)**
  - High risk EC $\rightarrow$ SLN f/b LND
  - The false negative rate of SLN mapping *alone* was 2/26 (7.7%); the NPV was 92.3%.
**Sentinel lymph nodes: The Guidelines**

**NCCN Guidelines Version 2.2019**

**Endometrial Carcinoma**

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**PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED**

**Principles of Sentinel Lymph Node(s) Mapping for Endometrial Cancer Staging**

- Prospective and retrospective studies demonstrate that compared to systematic lymphadenectomy, SLN mapping with ultrastaging may increase the detection of lymph node metastasis with low false-negative rates in women with apparent uterine-confined disease. If SLN mapping is considered, the expertise of the surgeon and attention to technical detail is critical. Recent evidence indicates that sentinel node mapping may also be used in high-risk histologies (serous carcinoma, clear cell carcinoma, carcinosarcoma).
- SLN mapping can be considered for the surgical staging of apparent uterine-confined malignancy when there is no metastasis demonstrated by imaging studies or no obvious extraterine disease at exploration.
- A cervical injection with dye has emerged as a useful and validated technique for identification of lymph nodes that are at high risk for metastases (i.e., SLN in patients with early-stage endometrial cancer).
- Superficial (1-3 mm) and optional deep (1-2 cm) cervical injection leads to dye delivery to the main layers of lymphatic channel origins in the cervix and corpus, namely the superficial subserosal, intermediate stromal, and deep submucosal lymphatic sites of origin (Figure 1 on **ENDO-C 3 of 6**).
- Injection into the uterine cervix provides excellent dye penetration to the region of the uterine vessels and main uterine lymphatic trunks that condense in the parametria and appear in the broad ligament leading to pelvic and occasionally paraaortic sentinel nodes.
- The uterine body lymphatic trunks commonly cross over the obliterated umbilical artery with the most common location of pelvic SLN being medial to the external iliac, ventral to the hypogastric, or in the superior part of the obturator region (Figure 2 on **ENDO-C 3 of 6**).
- A less common location is usually seen when the lymphatic trunks do not cross over the obliterated umbilical and move cephalad following the mesenteric; in these cases, the SLN is usually seen in the common iliac presacral region (Figure 3 on **ENDO-C 3 of 6**).
- The radiolabeled colloid most commonly injected into the cervix is technetium-99m (99mTc); colored dyes are available in a variety of forms (Isoflurane Blue 1% and Methylene Blue 1%, Patent Blue 2.5% sodium).
- Indocyanine green (ICG) recently emerged as a useful imaging dye that requires near-infrared camera for localization, provides a very high SLN detection rate, and is commonly used in many practices at the present time.
- Low-volume nodal metastasis to SLN detected only by enhanced pathologic ultrastaging is another potential value to staging with SLN.
- The key point to a successful SLN mapping is the adherence to the SLN algorithm, which requires the performance of a side-specific nodal dissection in cases of failed mapping and removal of any suspicious or grossly enlarged nodes regardless of mapping (Figure 4 on **ENDO-C 4 of 6**).
- For cases of failed SLN mapping, intraoperative assessment may be used to guide treatment.
Sentinel lymph nodes:
The Guidelines

1. For patients with endometrial cancer, SLN mapping by cervical injection of tracers accurately predicts the presence of pelvic lymph node metastasis and has a low (<5%) false-negative rate when the NCCN surgical algorithm is closely followed. It is recommended that completion lymphadenectomy be performed as an “add on” until an individual surgeon’s experience documents literature-comparable success of SLN detection and a <5% false-negative rate.

2. Use of ICG dye with NIR fluorescent imaging has similar rates of mapping success to those of radiocolloid Tc-99 combined with blue dye. Radiocolloid Tc-99 combined with dye remains an acceptable approach. When available, cervical injection of ICG dye with infrared imaging is preferable because of technical ease, high success, and reliability.

3. Patients with low-grade endometrioid adenocarcinoma (grade 1 or 2) are appropriately staged following the NCCN SLN algorithm guidelines (version 1.2017); SLN mapping can be performed in lieu of routine pelvic lymphadenectomy for patients with apparent uterine-confined grade 1 and 2 endometrioid cancers.

4. SLN mapping increases the overall detection of metastasis compared to routine lymphadenectomy. As with all cancers, however, patients should be counseled regarding the potential risk for missed occult disease using SLN biopsy for staging endometrial cancer.

5. SLN mapping is accurate for detecting pelvic nodal metastasis and some aortic SLNs. Decisions about completion para-aortic dissection should be at the attending surgeon’s discretion based on individualized patient characteristics and tumor-based risk criteria (depth of invasion, histology, and pelvic node status).

6. Pathologic processing of each SLN should include serial sectioning along the longitudinal plane of the node at 2-mm intervals and microscopic examination of all slices with at least 1 representative H&E level. Pathologic ultrastaging (deeper level sections and/or immunohistochemical studies) increases the detection of ITCs and micrometastasis. The clinical significance of increased detection of ITCs in this setting is currently uncertain and deserves study in well-designed clinical trials.

7. Incorporating the NCCN SLN mapping algorithm into the staging of high-grade endometrial cancer (grade 3 endometrioid, serous, clear cell, or carcinosarcoma) is feasible and currently utilized by several institutions, with encouraging early results. Completion lymphadenectomy with para-aortic assessment is reasonable in patients with high-grade disease until more data regarding the safety and efficacy of SLN biopsies alone become available.
Who Gets Sentinel Lymph Nodes?

• All FIGO1/FIGO2 endometrial adenocarcinomas

• Endometrial intraepithelial neoplasia/Complex atypical hyperplasia?
  • When biopsy/curettings concerning for at least FIGO1
  • When frozen section not reliable or feasible
  • When concerned about the morbidity of frozen-section indicated lymphadenectomy

• High grade histologies?
  “Retrospective data support that when high-grade cancers such as carcinosarcoma and uterine papillary serous carcinoma are staged with SLN biopsy, oncologic outcomes appear similar to historical cohorts”
What do we not know?

• Uncertainty about the disease status of normal-appearing non-sentinel lymph nodes, and the potential for residual metastatic disease.

• Uncertainly about whether nodal metastases are exclusively pelvic or co-exist with para-aortic disease

• Possible failure to diagnose isolated positive para-aortic disease.
# Cervical Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Extent of disease</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Carcinoma in situ (CIN)</td>
<td>~100%</td>
</tr>
<tr>
<td>I</td>
<td>Limited to cervix</td>
<td></td>
</tr>
<tr>
<td>Ia1</td>
<td>Microscopic disease: stromal invasion &lt;3mm, lateral spread &lt;7mm</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Ia2</td>
<td>Microscopic disease: stromal invasion &lt;3mm and &gt;5mm, lateral spread &lt;7mm</td>
<td></td>
</tr>
<tr>
<td>Ib1</td>
<td>Macroscopic lesion &lt;4cm in greatest dimension</td>
<td>~80%</td>
</tr>
<tr>
<td>Ib2</td>
<td>Macroscopic lesion &gt;4cm in greatest dimension</td>
<td>80-85%</td>
</tr>
<tr>
<td>II</td>
<td>Extension to uterus/parametria/vagina</td>
<td>~75-78%</td>
</tr>
<tr>
<td>IIa1</td>
<td>Involvement of upper two thirds of vagina without parametral invasion, &lt;4cm greatest diameter</td>
<td></td>
</tr>
<tr>
<td>IIa2</td>
<td>Involvement of upper two thirds of vagina without parametral invasion, &gt;4cm greatest diameter</td>
<td></td>
</tr>
<tr>
<td>IIb1</td>
<td>Involvement of upper two thirds of vagina with parametrial invasion</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Extension to pelvic side wall and/or lower third of vagina</td>
<td>~47-50%</td>
</tr>
<tr>
<td>IIIa</td>
<td>Involvement of lower third of vagina</td>
<td></td>
</tr>
<tr>
<td>IIIlb</td>
<td>Extension to pelvic side wall and/or hydrenephrosis</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Extension to adjacent organs or beyond true pelvis</td>
<td>~20-30%</td>
</tr>
<tr>
<td>IVa</td>
<td>Extension to adjacent organs e.g. bladder, bowel</td>
<td></td>
</tr>
<tr>
<td>IVb</td>
<td>Distant metastases</td>
<td></td>
</tr>
</tbody>
</table>
Cervical Cancer Sentinel Lymph Nodes: The Data

• Tax et al. Gyn Onc 2015
  • Review article
  • 47 studies with 4130 patients
  • Pooled data of diagnostic accuracy on ultra staging (18 studies; 1275 patients) showed a sensitivity of 94% (95% CI 80-99%) and negative predictive values ranging between 91 and 100%
  • Prerequisites such as early FIGO stage (IA2, IB1, IIA primary tumor size <40mm), no suspicious pre-, and peri-operative lymph nodes, and bilateral negative SLNs after ultra staging resulted in 1 remaining false negative result among 1257 patients (0.08%).
Cervical Cancer Sentinel Lymph Nodes: The Data

• Salvo et al. 2017 MD Anderson
  • Retrospective study of all patients diagnosed with early-stage cervical cancer (stages IA1-IB1 and IIA1) who underwent lymphatic mapping and SLN biopsy followed by complete pelvic lymphadenectomy as part of primary treatment August 1997 through October 2015
  • Detect at least one SLN in 90% of the patients and bilateral SLNs in 62% of the patients
  • Sensitivity of SLN biopsy was 96.4% (95% CI 79.8%–99.8%) and the negative predictive value was 99.3% (95% CI 95.6%–100.0%)
    • One false negative
  • Ultrastaging of SLNs found an additional 22% of node positive patients that would have been missed with H and E staining alone
Cervical Cancer Sentinel Lymph Nodes: The Data

**SENTIX**
- Prospective non-inferiority multicenter trial on sentinel lymph node biopsy
- Eligibility: IA1/+LVI, IA2, IB1 cervix cancer with negative LN on pre-op imagining
- 300 patients per arm
- Primary endpoint: recurrence rate
- Secondary endpoint: prevalence lower-leg lymphedema and pelvic lymphocele
- Started enrollment June 2016
- Currently 340 patients
- Oncologic outcomes 2021

A prospective multicenter trial on sentinel lymph node biopsy in patients with early-stage cervical cancer (SENTIX).
Cibula D¹, Dusek J², Jarkovsky J², Dundr P³, Querleu D⁴, van der Zee A⁵, Kucukmetin A⁶, Kocian R⁷.
Who with cervical cancer get SLND?
Questions?