Sentinel node mapping in gynecologic cancers

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No Disclosures
Objectives

- SLN mapping for endometrial cancer
  - Review standard staging
  - SLN method
  - SLN data
  - Current opinions / uses
- SLN mapping for cervical cancer
  - Review standard staging
  - Early stage cancer

UTERINE CANCER
Why do we surgically stage endometrial cancer?

**NCCN Guidelines Version 4.2021**

**Endometrial Carcinoma**

**INITIAL CLINICAL FINDINGS**
(Endometrioid Histology)²

**PRIMARY TREATMENT**

- **Total hysterectomy and bilateral salpingooophorectomy** (TASO) and surgical staging

- **Suitable for primary surgery**
- Disease limited to the uterus

- **Not suitable for primary surgery**
- Patient desires fertility-sparing options

- **Incomplete staging**

- **Adjuvant treatment for surgically staged:**
  - Stage IA (See ENDO-4)
  - Stage IB (See ENDO-5)
  - Stage III-IV (See ENDO-6)

- **Radiation therapy**
  - EBRT ± and/or brachytherapy
  - Consider hormone therapy in select patients

- **See Surveillance (ENDO-8)**

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**Standard Surgical Staging for Endometrial Carcinomas**

Studies on lymphadenectomy

- Creasman et al. 1997, GOG33
  - risk factors associated with LN mets: grade & depth of invasion
  - 1-3% risk of LN mets if endometrium confined, low grade

- CONSORT (Italian study) 2008
  - 541 patients with clinical stage 1 disease randomized to LND versus not.
  - No difference in adjuvant tx, no difference in DFS or OS (86% vs 90%, p=0.5)

- ASTEC 2009
  - 1400 patients with clinical stage 1 disease randomized to LND versus not.
  - No difference in OS (81% vs 80%, p=0.5)

Cochrane Review on Lymphadenectomy

No evidence that lymphadenectomy decreases the risk of death or disease recurrence in women with clinical stage 1 disease.
Risks of Lymphadenectomy

- LEG trial (GOG 244), 2020.
  - 1054 women with uterine, cervix and vulvar cancer
  - Lymphedema defined as limb volume cancer (LVC) >10%
  - Incidence of LVC >10%
    - 34% uterine
    - 35% cervical
    - 43% vulva

So why persist in lymph node assessment for uterine cancer?

National Annoyjity Day

www.AnnetteBridges.com
Sentinel Lymph Node assessment for uterine cancer


Sentinel Lymph node mapping technique

Abu Rustum et al. JNCCN 2014.
Sentinel Lymph node ultrastaging

- Each SLN
  - 2 mm interval cuts

- Each 2mm section

- 100 micron levels

- H&E
  - 5 micron sections

- IHC

FIRE trial – data on SLN detection

- Objective: estimate the sensitivity and NPV of SLN mapping using robotic assisted NIR imaging of ICG in detecting LN metastases.
  - 10 US centers, 18 surgeons
  - Clinical stage 1, any histology
  - Pelvic lymphadenectomy required (PA LN optional)
  - SLNs were examined with ultrastaging
### FIRES trial – data on SLN detection

<table>
<thead>
<tr>
<th>Patients (n=340)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic lymphadenectomy</td>
</tr>
<tr>
<td>Pelvic and para-aortic lymphadenectomy</td>
</tr>
<tr>
<td><strong>Successful mapping of sentinel lymph nodes</strong></td>
</tr>
<tr>
<td>Bilateral mapping</td>
</tr>
<tr>
<td>Para-aortic sentinel lymph node detected</td>
</tr>
<tr>
<td>Isolated para-aortic sentinel lymph node detected</td>
</tr>
<tr>
<td>Median number of sentinel lymph nodes removed</td>
</tr>
<tr>
<td>Mean number of total nodes removed</td>
</tr>
</tbody>
</table>

Data are n (%), median (range), or mean (SD; range).

**Table 2:** Surgical results in patients who had pelvic lymphadenectomy

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### FIRES trial – data on SLN detection

<table>
<thead>
<tr>
<th>Postoperative stage (n=344)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
</tr>
<tr>
<td>IB</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>IIIA</td>
</tr>
<tr>
<td>IIIIB</td>
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<tr>
<td>IIIIC</td>
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<tr>
<td>IV</td>
</tr>
</tbody>
</table>

Data are n (%). †Patients who received complete study intervention (injection of dye, attempted sentinel-lymph-node mapping, and complete surgical staging).

**Table 1:** Clinical-pathological features

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FIRES trial – data on SLN detection

<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

SLN mapping increases the detection of LN metastases compared to routine lymphadenectomy


SLN mapping – high risk histologies?

- Senti-Endo (France, Lancet 2011)
  - Sensitivity of 84%, NPV of 97%
  - All 3 false negatives had high-grade histologies

- Touhami et al (Tunisia, GynOnc 2017)
  - High-risk histologies had SLN and full pelvic LND.
  - Sensitivity remained high at 96%

- Ehrisman et al (Duke, Gyn Onc Rep 2016)
  - High-risk histologies had SLN and full pelvic LND.
  - Negative predictive value was 92%
  - Employing the SLN algorithm decreases false negative rate to 0%.
SLN mapping – atypical hyperplasia (EIN)?

- Touhami et al (Gyn Onc 2018)
  - Patients divided into atypical hyperplasia (“AH-only”) and atypical hyperplasia, cannot rule out malignancy (“AH-cannot rule out cancer”).
  - 53% patients had cancer on final pathology – 61 patients with stage 1 and 3 with stage 3C
  - Conclusion: Risk of LN involvement in “AH-only” is null.

- Opinion (expert opinion, not data driven)
  - SLN are performed for DCIS which has ~25% risk of invasion
  - If 50% of EIN are cancer and if ~15% of these could have occult stage 3 disease then SLN dissection is a reasonable approach to decrease the risk of full lymphadenectomy.

Lymph node assessment risk for EIN

- **43%** with EIN will have cancer on hysterectomy specimen.
- **12%** of cancers diagnosed pre-op as EIN will have deeply invasive, high-grade tumors
- **7%** of patients staged at the time of hysterectomy with a pre-operative diagnosis of EIN have nodal metastatic disease

PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

Figure 4: The SLN algorithm for surgical staging of endometrial cancer

1. Peritoneal & serosal evaluation & washings
2. Retroperitoneal evaluation
   - Excision of all mapped SLN with ultrastaging
   - Any suspicious nodes must be removed regardless of mapping
3. If there is no mapping on a hemi-pelvis, a side-specific LND is performed
   - Para-aortic LND—done at attending discretion

CERVICAL CANCER
Role of LN evaluation in cervical cancer

Don’t use two radical treatments when one will be potentially curative

Sentinel Lymph Node Mapping with ICG

Abu-Rustum. Sentinel Lymph node mapping. https://doi.org/10.6004/jnccn.2014.0026
Risks associated with lymphadenectomy

SLN Algorithm

Peritoneal and serosal evaluations and washings

Retroperitoneal evaluation
- Excision of all mapped SLNs with ultrastaging
- Any suspicious nodes must be removed regardless of mapping

If there is no mapping on a hemi-pelvis, a side-specific LND is performed
- Para-aortic LND is performed at the attending's discretion

Gynecol Oncol 2012;125:534.
SLN mapping – cervical cancer

- **Tax et al (Gyn Onc 2015)**
  - Review article of 47 studies with 4130 patients
  - Pooled data – sensitivity of 94% and negative predictive value ranging from 91-100%
  - If early stage disease (1A-2A), tumor <4cm and negative SLNs after ultrastaging the false negative rate was 1/1257.

- **Salvo et al (2017 MD Anderson)**
  - Retrospective study of 188 patients who underwent both LND & SLN
  - Only one patient had a false-negative result, yielding a sensitivity of 96.4% and negative predictive value of 99.3%
  - Ultrastaging of SLNs found an additional 22% of node positive patients that would have been missed with H&E staining alone

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SLN mapping – cervical cancer

- **SENTIX (EJC 2020)**
  - 47 sites, 18 countries
  - Stage 1A1 – 1B2, 4cm or smaller, no suspicious LNs on pre-op imaging
  - SLNs were sent for FROZEN section diagnosis
  - Ultrastaging mandatory
  - No restrictions on dye used for SLN detection or surgical approach (MIS vs. open)
  - Patients registered in the trial if SLNs were negative on FROZEN section. Patients with cancer identified on FROZEN section were “managed according to institutional guidelines”
SLN mapping – cervical cancer

Conclusions

- SLN evaluation for uterine and cervical cancer is a preferable treatment for LN assessment assuming surgeons have expertise and training in the technique.
- SLN can be considered for surgical evaluation of EIN
- Pathology collaboration for ultrastaging is a crucial part of the evaluation of SLNs