Sentinel Lymph Node Sampling in Gynecologic Oncology: Is there a Role?

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• I have no conflict of interest
Overview

• Sentinel Lymph Node
• Intro & Rationale
• Technique
• Current Data According To Disease Sites
• Conclusions
INTRO & RATIONALE
Sentinel Lymph Node (SLN)

• Simplify the surgical procedure and decrease morbidity

• SLN biopsy can have other advantages
  1. more reliable detection of key nodes in atypical localizations
  2. detection of small metastasis
  3. intraoperative triage
SLN

- *Used in endometrial, cervical, and vulvar cancers*

Pictures from Dr T Beşe
TECHNIQUE
• *Injection sites*...
• Blue dye

• Lymphoscintigraphy

• ICG
Figure 2. Left external iliac sentinel lymph node.

Figure 3. Right external iliac sentinel lymph node.

Figure 5. Excised sentinel lymph node.
• Video..
  – 4’10-6’20
CURRENT DATA
Sentinel lymph node biopsy in the management of gynecologic cancer

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Curr Opin Obstet Gynecol 2015, 27:66–72
CERVICAL CANCER
SLN in cervical cancer...

• Intensive scientific interest

• Good evidence of a high detection rate and low false-negative rate

• SLN biopsy has not been incorporated into current recommendations for clinical management and, surprisingly, it is not widely used in routine clinical practice.
Localization

• **Most common regions: (65-85% of cases)**
  – around the external iliac vessels
  – space between the external and internal iliac vessels
    • ‘interiliac’, ‘supraobturator’, or ‘obturator fossa’ in different papers

• **10% of SLN in less-common regions**
  – presacral, paramettrial, or internal iliac nodes
  – more importantly, in **4–9% of patients**: above the aortic bifurcation in the **paraaortic region**

• **SLN biopsy can identify these nodes and increase the reliability of lymph node surgical staging**
Detection Rate

• In older studies: from 55 to 100%

• French prospective trial
  – Combined technique
    – *At least one SLN was detected*: 98%
    – *Bilateral detection*: 77%

• Evidence:
  – best detection rate is achieved if blue-dye and radioactive tracer are combined

Detection Rate

• Changes due to size of the tumor;
  – Smaller the better...

  – Small tumors:
    • Overall detection rate: 95%
    • Side-specific detection rate 84%

  – Large tumors were only 80 and 59%

ICG

• New technique based on fluorescence imaging was introduced in cervical cancer: *Indocyanine green* is injected into the cervix as a tracer and detected by *near-infrared (NIR) fluorescence* imaging in the retroperitoneum.
  – In 227 cases collected in three US institutions there was an **overall SLN detection rate of 95% and bilateral detection of 79%**
  – *Combination with conventional blue dye did not improve the success rate*
  – Interestingly, in a relatively high proportion of cases (10%) *SLN was found in the paraaortic region*

Sensitivity

• Sensitivity and the false-negative rate are the key features for SLN concept reliability, and show the risk that any other pelvic lymph nodes will be involved if SLN(s) are negative.

• Prospective multicenter study: SLN ultrastaging, the French Ganglion Sentinelle dans le Cancer du Col (SENTICOL) study,
  – 135 patients with small tumors
  – overall sensitivity of 92%
  – 100% in the subset of patients with bilateral SLN detection

• Retrospective multicenter study of 645 patients with SLN biopsy and ultrastaging
  – sensitivity of SLN ultrastaging was 91% for the whole group
  – 97% for those patients with bilateral SLN detection
Sensitivity

• Pathologic ultrastaging:
  – *allows for the detection of low-volume disease*
  – *increases sensitivity of the staging*
  – *SLN biopsy is reliable also in larger tumors if SLN are detected bilaterally and ultrastaging is performed*

• *Lymph node staging should be always performed on both sides of the pelvis separately and high sensitivity can be obtained only if SLN is detected bilaterally; the important feature in SLN*
Sensitivity

• Although the first reports of abandoning systematic lymphadenectomy have appeared it is not yet a generally accepted approach.

• Expectation:
  – Based on current evidence, SLN concept will prove noninferiority over systematic lymphadenectomy, particularly in smaller tumors.

Cibula et al. Curr Opin 2015
Intraoperative sentinel lymph node evaluation and pathologic processing

• **Allows intraoperative triage**
  
  – *If positive lymph nodes at the beginning of the surgery: abandoning radical hysterectomy or fertility sparing procedures*
  
  – *Decrease posttreatment morbidity*
Intraoperative sentinel lymph node evaluation and pathologic processing

- Studies of large series of patients with SLN biopsy unfortunately showed a low reliability of intraoperative SLN evaluation.
  - The French prospective multicenter study found 17 false-negative nodes in 15 patients out of 20 with positive lymph nodes on final pathology
    - Missed small volume disease cases of micrometastasis (four) or isolated tumor cells (nine).
    - However, four cases of macrometastasis were also missed intraoperatively.

- In the Canadian study of 211 patients,
  - 10 false-negative cases
    - Including seven micrometastasis, two isolated tumor cells, and one macrometastasis of the size of 2.9 mm

- Cibula et al.
  - 225 patients,
    - Correct in 39 out 73 cases with positive lymph nodes,
    - Missing eight cases with macrometastasis, 18 with micrometastasis and eight with isolated tumor cells
    - The false-negative rate was higher in bigger tumors (>2cm largest diameter) (P 1/4 0.042) and in the presence of LVSI (P 1/4 0.004).
Low-volume disease

• If the SLN on both sides of the pelvis are negative, the risk that any other pelvic lymph node is positive is as low as 0–3%
  – usually two to four in one patient, allows for their extensive pathologic processing.

• SLN evaluation are not standardized:
  – Sections, which should not be larger than 150–200mm in order to guarantee the reliable detection of small metastasis between 1 and 3 mm

• Pathologic ultrastaging increases the detection rate of small metastasis around 2mm and smaller
  – macrometastasis (>2mm),
  – low-volume disease:
    • micrometastasis (<2mm and >0.2mm) & isolated tumor cells (<0.2mm)
Low-volume disease

• Largest retrospective series
  – 645 patients with SLN biopsy
  – overall survival was significantly and equally reduced in patients with macrometastasis (hazard ratio 6.85; 95% confidence interval, 2.59–18.05) and micrometastasis (hazard ratio 6.86; 95% confidence interval, 2.09–22.61).

• The presence of micrometastasis was an independent prognostic factor for survival in a multivariate model.

• No prognostic significance was found for isolated tumor cells.

Sentinel Lymph Node Evaluation in Women with Cervical Cancer

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Conclusions

Sentinel lymph node biopsy is currently the standard of care for certain malignancies, including melanoma and breast cancer. For women with early-stage cervical cancer, multiple studies confirm that the evaluation of sentinel lymph nodes is feasible with excellent detection rates and sensitivity. These findings have important implications as they suggest that less radical surgery is safe for selected patients. Ongoing studies seek to validate these findings and determine the impact of sentinel node biopsy on quality of life in these women.
ENDOMETRIAL CANCER
Lymphadenectomy

• Low rate of metastases
  – the standard of therapy still includes a complete or selective pelvic and paraaortic lymphadenectomy for adequate staging, which is the most important prognostic factor

• Lymphadenectomy is not without complications:
  – particularly lower leg lymphedema
• Early stage disease:
  – two large randomized, prospective studies
  – *no survival benefit with comprehensive lymphadenectomy*
  – Possible role of SLN mapping
  – *Currently, MSKCC uses a combined superficial (1 – 3 mm) and deep (1 – 2 cm) cervical injection for SLN mapping in patients with endometrial cancer, although others have argued for uterine subserosal injections or endometrial injections via hysteroscopy*
Barlin et al. institutional SLN mapping algorithm 498 pts
- blue dye cervical injections
- significantly reduced the false-negative rate (14.9 to 1.9%)
- increased sensitivity (85.1 to 98.1%) and the negative predictive value (98.1 to 99.8%)

**FIGURE 1.** Sentinel lymph node mapping algorithm. LND, lymph node dissection; SLN, sentinel lymph node.
*Ultrastaging described below.*
MSKCC Experience

- Began algorithm in 2008
- *Rate of complete lymphadenectomy has decreased from 65 to 23% at the institution*
  - Parallel decreases in median operation room time (1 h) and median operative time (40 min)
  - Median number of lymph nodes removed has also decreased (20 to seven lymph nodes)
  - *This change in surgical practice has not compromised the rate of detection of nodal metastases*
• **Ultrastaging:**
  – If H&E assessment negative then two 5mm sections
  – At each level, one side is stained with H&E and the other with immunohistochemistry using the anti-cytokeratin AE1:AE3, totaling four slides per block
  – **Immunohistochemistry ultrastaging** was able to detect up to an additional 4.5% of low-volume metastases to SLNs (four of 508 patients with micrometastases, and 19 of 508 patients with isolated tumor cells), which could possibly have been missed by routine H&E staining
  – Importance of myoinvasion:
    • Twenty (87%) of the 23 patients with ultrastage-detected low-volume metastases also had some degree of myoinvasion as opposed to only 0.8% in those with no myoinvasion,
    • If validated suggests: ultrastaging in patients with no myoinvasion is unnecessary

• **ICG**
  – 277 patients with uterine or cervical cancer
  – **improved bilateral detection rate**
    • 156 (79%) of 197 ICG-only cases and 23 (77%) of 30 ICG and blue dye case
    • :blue dye unnecessary
    • Furthermore, the bilateral SLN mapping rate using blue dye alone is 61%; it is 75% when using blue dye and technetium (99mTC), likely rendering **99mTC unnecessary** as well
Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis

Anna Jo Bodurtha Smith, MD, MPH, MSc; Amanda Nickles Fader, MD; Edward J. Tanner, MD

- 55 studies
- 4915 women
- SLN detection of metastasis is 96%

CONCLUSION: Sentinel lymph node mapping is feasible and accurately predicts nodal status in women with endometrial cancer. The current data favors the use of cervical injection techniques with indocyanine green. Sentinel lymph mapping may be considered an alternative standard of care in the staging of women with endometrial cancer.
Review Article

Sentinel lymph node mapping and staging in endometrial cancer: A Society of Gynecologic Oncology literature review with consensus recommendations

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9. Consensus recommendations

Based on the current literature, we recommend that:

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.
VULVAR CANCER
VULVAR CANCER

• Surgical treatment has changed dramatically over the last 5 years.
• Since in 2008 the results of the Groningen International Study on Sentinel nodes in Vulvar cancer (GROINSS-V) were published, the SLN procedure has been incorporated in the standard of care for patients with early-stage vulvar cancer in many countries.
GROINSS-V

- Multicenter observational study
- Patients with a negative SLN no longer underwent inguinofemoral lymphadenectomy
- The eligibility criteria of this study were unifocal squamous cell cancers, less than 4 cm, without suspicious nodes at clinical examination.
  - Groin recurrence in 2.3% (6/259)
  - Recurrences are at least comparable to that treated with formal lymphadenectomy of any type.

  - Safe to omit inguinofemoral lymphadenectomy in patients with a negative SLN

- The accuracy of the SLN procedure was confirmed by Levenback et al. GOG
  - the SLN biopsy was routinely followed by inguinofemoral lymphadenectomy
  - tumors less than 4 cm and a negative SLN, 2% was false negative

SLN

• Combined technique
  – the combination of a radioactive tracer and blue dye
  – *SLN detection rate with a radioactive tracer is much higher compared with blue dye alone*

• *SLN biopsy using 99mTc and blue dye with ultrastaging* may be considered the most cost-effective strategy based on the outcome of survival free of morbidity for 2 years

• The performance of a lymphoscintigram preoperatively is thought to be useful, as it identifies the site (unilateral or bilateral) and number of SLNs that should be removed.
  – Coleman et al. showed that in lateral ambiguous lesions (lesions within 2cm of the midline, but not involving the midline), unilateral SLN identification is safe when the lymphoscintigram shows only unilateral lymphodrainage.
Pitfalls

1. *Patients with multifocal disease not suitable*

2. *Patients who underwent radio(chemo)therapy on the vulva and/or groin*
   - damage to the lymph vessels

- **Preoperative imaging advised in patients eligible for SLN detection, to rule out gross nodal involvement**

- **Surgical assessment is still mandatory** to accurately determine lymph node status, especially because missing metastases is often fatal
• Clinical significance of micrometastases is currently unclear

• Groin recurrences with only micrometastases in the SLN
  – *GROINSS-V data in patients with SLN micrometastases (<2 mm), the chance on nonsentinel node involvement was approximately 7%*
  – Therefore, every patient with metastases in the SLN, regardless of size, requires adjuvant treatment (inguinofemoral lymphadenectomy)
• Intraoperative transcutaneous imaging of an injected fluorescent tracer may lead to a one-step procedure, while maintaining the high sensitivity.
  – technically feasible
  – identification rate comparable to radioactive tracer
  – Depth of penetration is very limited. Only feasible in lean patients.

• **GROINSS-V-II** is now ongoing and investigates whether patients with a positive sentinel node could be spared the morbidity of an inguinofemoral lymphadenectomy or double modality treatment by treating their groins with primary radiotherapy.
  – Results of this study are expected in 2017
  – Ongoing but not recruiting patients
CONCLUSIONS
There are multiple reasons for using SLN ultrastaging followed by standard pelvic lymphadenectomy in the current management of patients with cervical cancer, such as more reliable detection of key nodes, the detection of micrometastasis and, although with limited reliability, intraoperative triage of patients for further management.

A replacement of systematic lymphadenectomy by sole SLN biopsy will need to wait for the results of ongoing controlled studies.
• The use of SLN mapping in patients with endometrial cancer can help the vast majority of these patients avoid a standard lymphadenectomy, which is associated with debilitating, long-term side-effects, such as lower extremity lymphedema.
Near-infrared fluorescence imaging with the use of the fluorophobe indocyanine green alone in endometrial and cervical cancer has shown high bilateral detection rates, likely rendering the use of 99mTC and blue dye unnecessary.
The application of the SLN procedure in vulvar cancer patients is safe, when performed by an experienced multidisciplinary team in well selected patients (primary squamous cell cancers, unifocal disease, tumors less than 4 cm, no enlarged/suspicious nodes at clinical examination and/or imaging).
Gyn Onco Multidisciplinary Team

- Prof Dr Sinan Berkman
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- Asist Prof Esat Namal

- Thank you...