Sentinel Lymph Node Mapping in Endometrial Cancer

Hyun Hoon Chung, M.D.

Seoul National University College of Medicine
Seoul National University Hospital

SNUH 서울대학교병원 SEOUL NATIONAL UNIVERSITY HOSPITAL

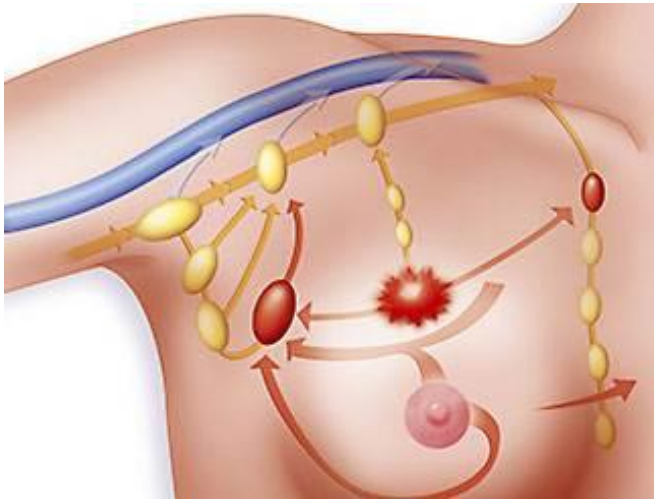
There is no potential conflict of interest.

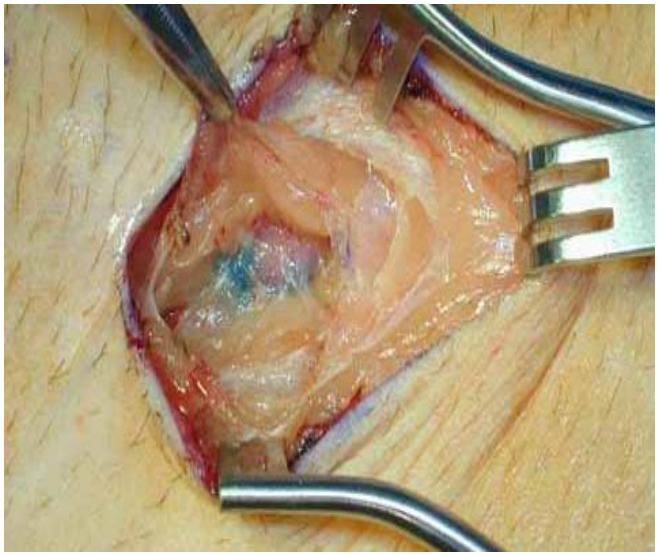
Contents

Sentinel Lymph Node (SLN)

Sentinel Lymph Node (SLN)

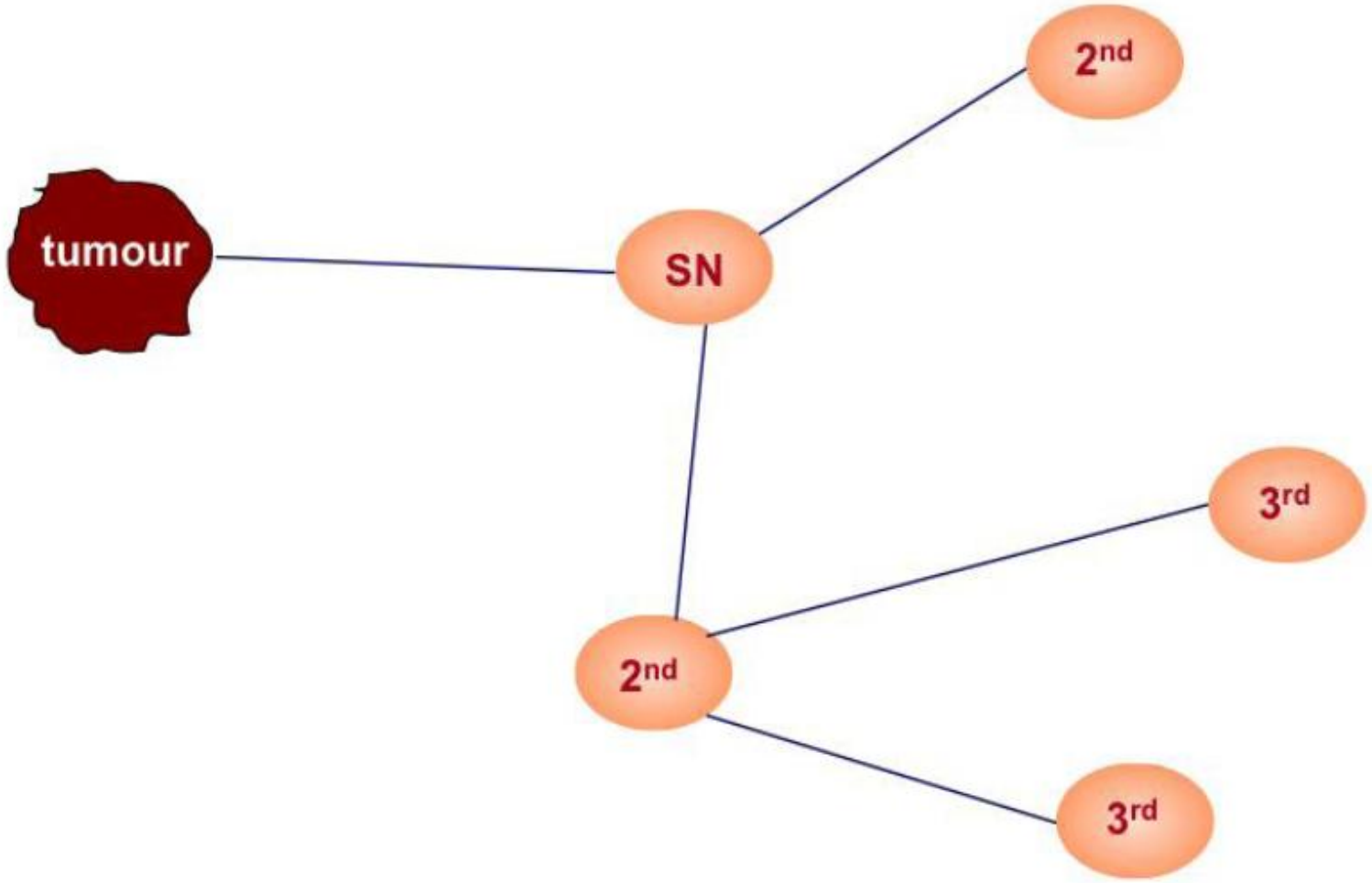
- The **first** LN in a chain of LNs from the primary tumor
- First in penile cancer (1977)
- Established in Breast cancer
  : negative predictive value of ~ 100%
- SLN in gynecologic cancers
  : controversial





Logic of SLN

- SLN 3 times more likely to harbor metastasis
- Targeting
  - The “correct” nodes
  - Most likely nodes harboring the disease
- Adequate staging
  - The end goal of SLN approach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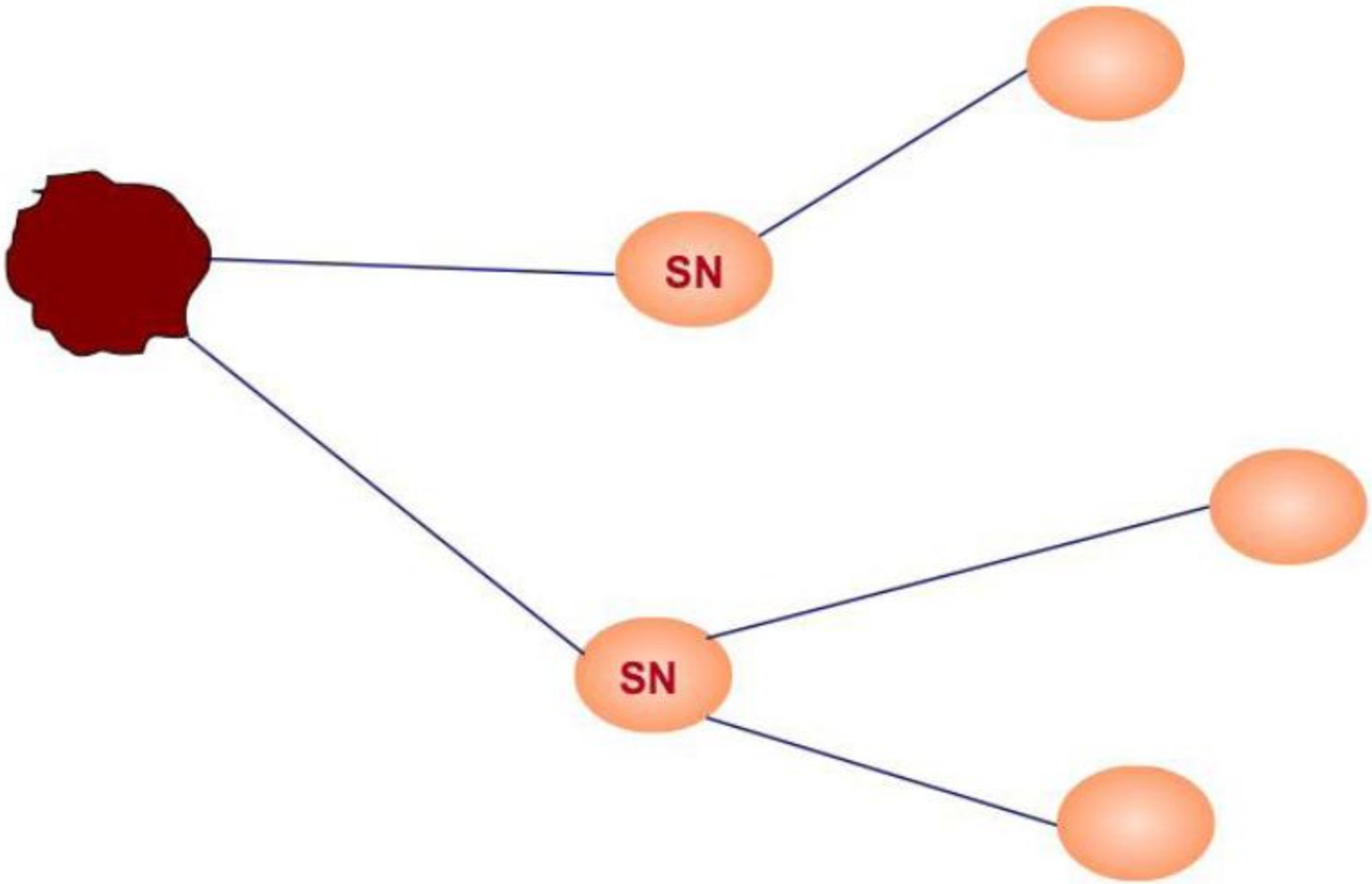
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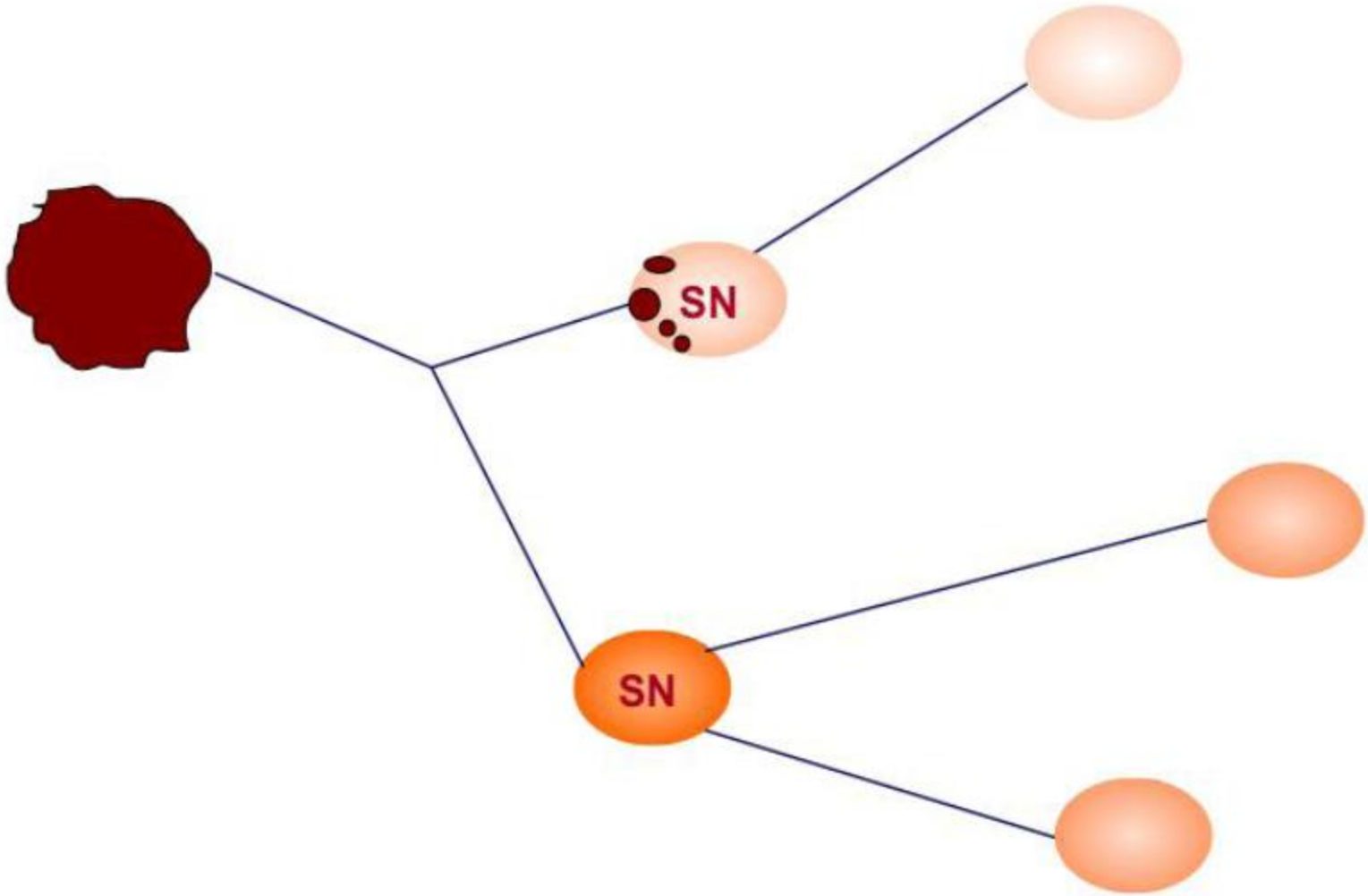
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Endometrial Cancer

- Most common gynecologic malignancy
- Most cases, early-stage (90%)
- Metastatic nodal disease: 10-15%
- Importance of
  - Proper staging
  - Avoiding missing undetected metastatic lesions

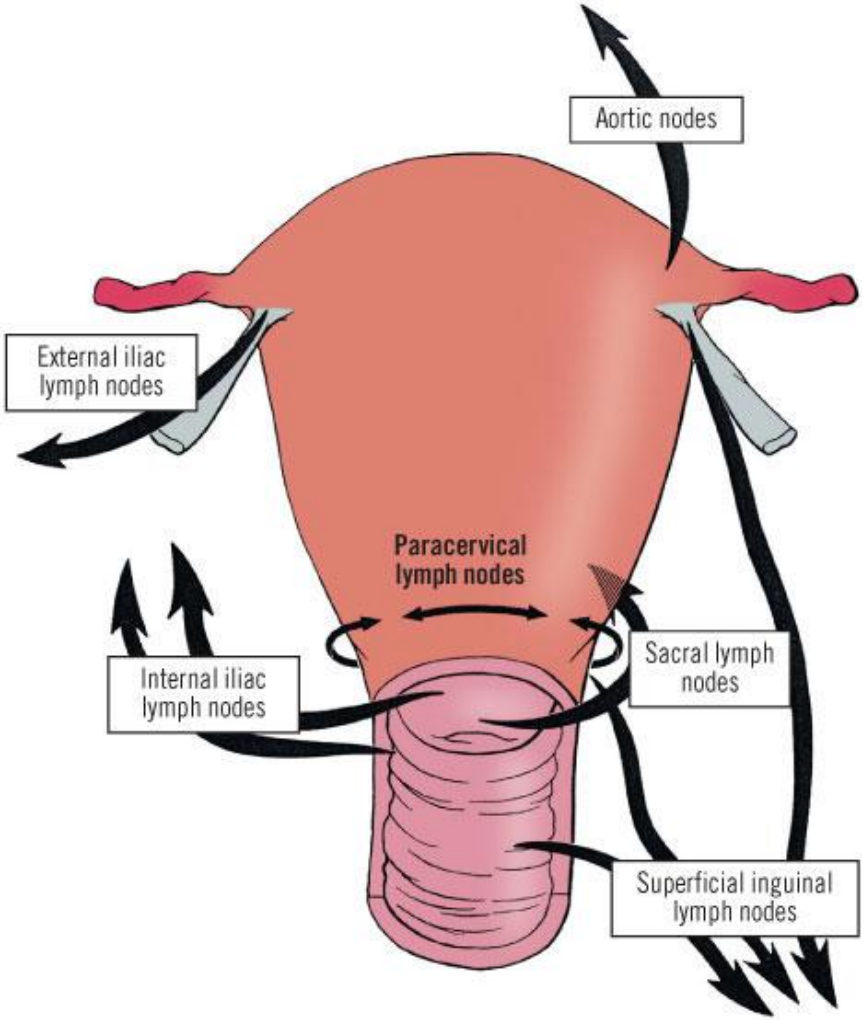
Abu-Rustum et al., Gynecol Oncol 2009;113:163-9

SLN Detection in EM Cancer

- Complexity in lymphatic drainage
- Injection tracers and methods
- Learning curve
  : < 30 *vs.* > 30 cases for SLN detection – 77% vs. 94%

Van Oostrum NH, et al. Acta Obstet Gynecol Scand 2012;91:174-81
Ballester M, et al. Ann Surg Oncol 2008;15:1523-29

Lymphatic Drainage



Distribution of SLNs

- Pelvic LN: 90%
- Common iliac: 6%
- Para-aortic: 4%

Abu-Rustum NR, et al. Gynecol Oncol 2009;113:163-9

NCCN Guidelines V 1. 2015

NCCN Evidence & Consensus

Category	Level of evidence	Consensus
1	High	Uniform consensus
2A	Low	Uniform consensus
2B	Low	Consensus
3	Any	Major disagreement

NCCN Guidelines Version 1.2015
Endometrial Carcinoma

NCCN Guidelines Index
Uterine Neoplasms TOC
Discussion

PRINCIPLES OF EVALUATION AND SURGICAL STAGING

Principles of Surgical Staging for Endometrial Cancer[1-3]

- **Total hysterectomy and bilateral salpingo-oophorectomy (TH/BSO) is the main treatment of apparent uterine confined endometrial cancer, unless patients are interested in and are candidates for fertility-sparing options (See ENDO-8). Many patients with locally advanced endometrial carcinoma are also candidates for TH/BSO. (See Hysterectomy and Pathologic Evaluation [ENDO-A])**
- **The hysterectomy and adnexectomy may be performed through laparotomy, vaginally, or via minimally invasive techniques such as laparoscopy or robotic surgery.**
- **Visual evaluation of the peritoneal, diaphragmatic, and serosal surfaces with biopsy of any suspicious lesions is important to exclude extrauterine disease.**
- **While peritoneal cytology does not affect staging, FIGO and AJCC continue to recommend that it be obtained and reported.**
- **Omental biopsy is commonly performed in tumors with serous adenocarcinoma, clear cell adenocarcinoma, or carcinosarcoma histology.**
- **Excision of suspicious or enlarged lymph nodes in the pelvic or paraaortic regions is important to exclude nodal metastasis.**
- **Pelvic nodal dissection with pathologic evaluation continues to be an important part of the surgical staging for selected uterine confined endometrial cancer as it can identify important prognostic information that may alter treatment decisions.**
- **Pelvic lymph nodes from the external iliac, internal iliac, obturator, and common iliac nodes are frequently removed for staging purposes.**
- **Para-aortic nodal evaluation from the inframesenteric and infrarenal regions may also be utilized for staging of select high-risk tumors such as deeply invasive lesions, high-grade histology, and tumors of serous adenocarcinoma, clear cell adenocarcinoma, or carcinosarcoma features.**
- **Sentinel lymph node (SLN) mapping may be considered (category 3) in selected patients. (See pages 2-4 of ENDO-B)**
- **Some patients may not be candidates for lymph node dissection.**

PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

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

- The role of SLN mapping is currently being evaluated. No prospective randomized trials have been reported that evaluate this technique in endometrial cancer. If SLN mapping is considered, the expertise of the surgeon and attention to technical detail is critical. The use of SLN mapping in high-risk histologies (serous adenocarcinoma, clear cell adenocarcinoma, or carcinosarcomas) should be undertaken with particular caution.

- SLN mapping can be considered (category 3) for the surgical staging of apparent uterine-confined malignancy when there is no metastasis demonstrated by imaging studies or no obvious extrauterine 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 (ie, SLN in patients with early-stage endometrial cancer[4-6]).

- The combination of a superficial (1-3 mm) and 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-B 3 of 5).

- 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-B 3 of 5).

- A less common location is usually seen when the lymphatic trunks do not cross over the obliterated umbilical and move cephalad following the mesoureter; in these cases, the SLN is usually seen in the common iliac presacral region (Figure 3 on ENDO-B 3 of 5).

- The radiolabeled colloid most commonly injected into the cervix is technetium-99m (^{99m}Tc); colored dyes are available in a variety of forms (Isosulfan 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.[7-9]

- Key points 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-B 4 of 5).[10-12]

SLN mapping: NCCN guideline

- Apparent uterine-confined EM cancer
- Category 3 recommendation
  - Based upon any level of evidence, there is **major NCCN disagreement** that the intervention is appropriate
- Considerations
  - Surgeon's expertise
  - Technical detail

SLN mapping: NCCN guideline

- Removal of suspicious or enlarged LN
  - Regardless of SLN mapping results

- Side-specific LND if mapping fails

SLN mapping: NCCN guideline

- System-wide long-term outcome
  - yet available
- Particular caution
  - High-risk histology (serous, clear, carcinosarcoma)
- Main contraindication for SLN mapping
  - Uterine sarcoma

SLN mapping: NCCN guideline

- Category changed from 2B (V1. 2014) to 3
- Role being evaluated
- No prospective randomized trial
- Indocyanine green with NIR camera useful
- Importance of SLN algorithm

SLN Mapping

Injection Methods

- **Cervical injection only**
  : Para-aortic LNs might be missed

- **Around the tumor or into the subserosal**
  : Improved para-aortic SLN detection

- **Hysteroscopic injection**
  : Possibililty of dissemination

→ No agreement regarding the best technique

Delpech Y, et al. Surg Oncol 2008;17:237-45.

Injection Methods

- **Cervical injection vs. Endometrial injection**
  - Cervical (82%) >> Endometrial (33%)

- **ICG vs. ISB**
  - ICG (97%) >> ISB (77%)

Holloway et al., Gynecol Oncol. 2012;126:25-9.
Rossi et al.. Int J Gynecol Cancer 2013;23:1704-11.

Ultrastaging

Definition

- Serial sectioning
- Immunohistochemistry (IHC)

Additional detection: serial sectioning: 7.8%, IHC: 18.4%

Background

- "Dormant" or "occult" metastases not detected by H&E staining
- Tumor cell cluster of less than 3 cell diameters – identified in only 1%

Methods

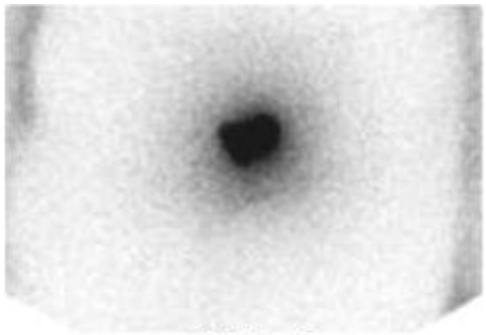
- Serial sectioning
  : 2-3 mm interval → additionally, 40-250 um interval
  : Identified 10 times in <2 mm micrometastasis
- IHC: anti-cytokeratin AE1 or AE3, anti-pancytokeratin KL1, CAM antibody

Bezu C, et al. J Experiment Clin Cancer Res 2010;29:5-8.

Imaging Modalities

Single Photon Emission Computed Tomography/Computed Tomography (SPECT/CT)

- Planar LSG + low-dose, non-contrast CT scan
- **3-D functional images** fused with anatomical data from CT



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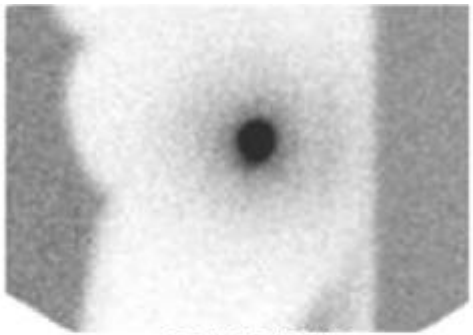

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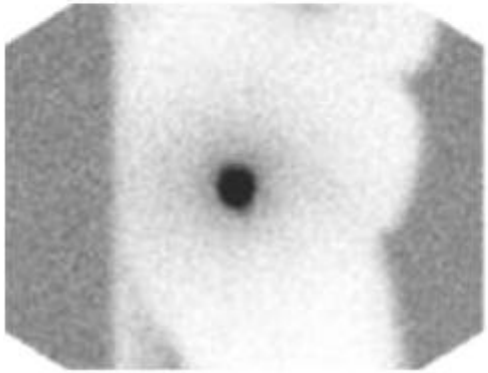

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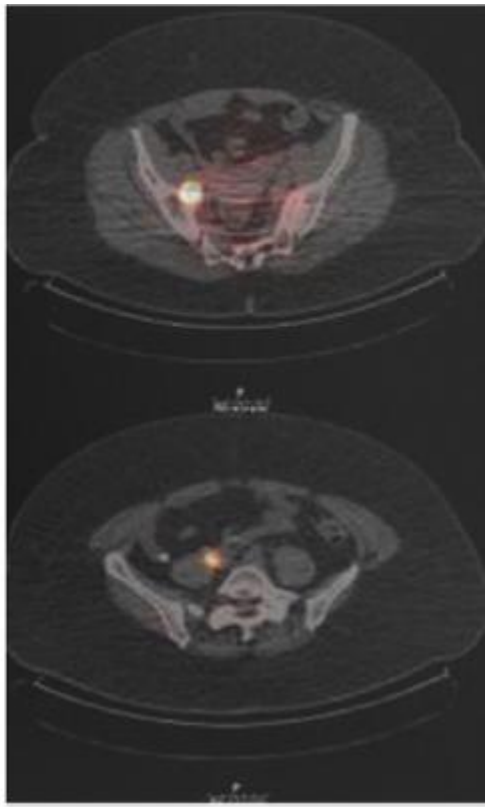
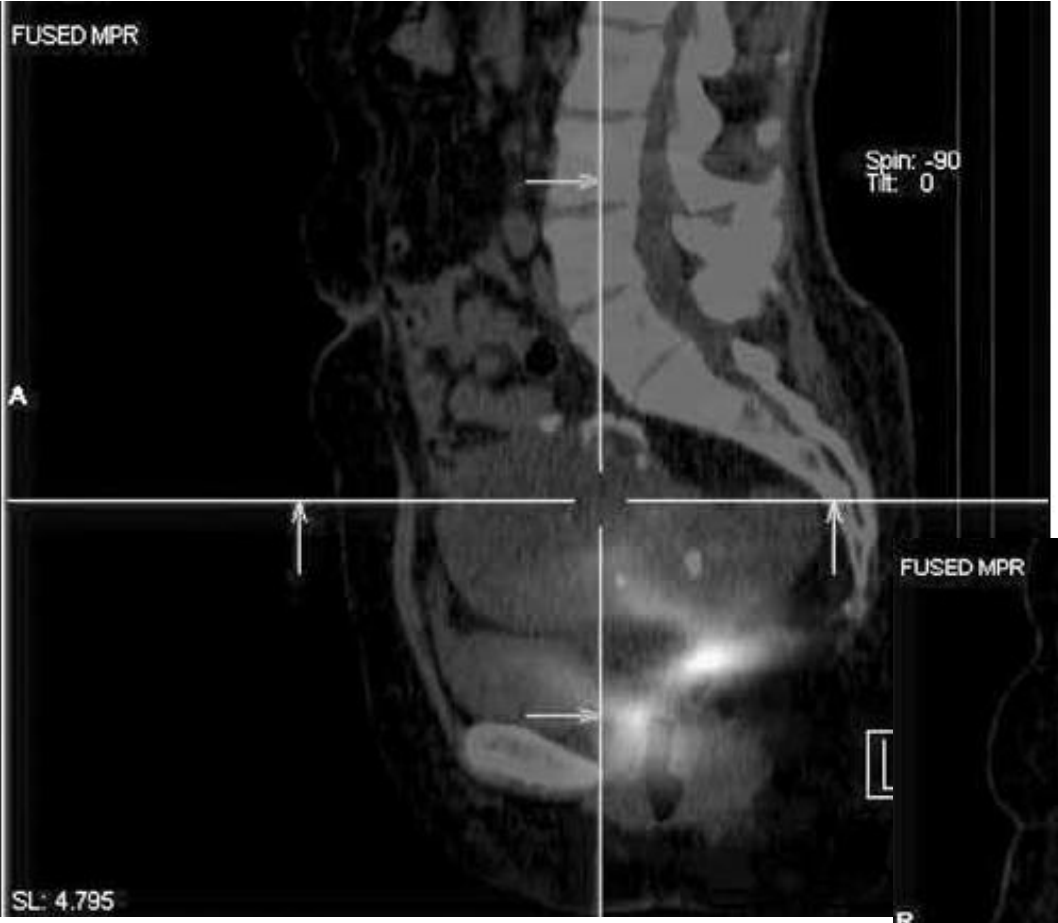


Pandit-Taskar N, et al. Gynecol Oncol 2010;117:59-64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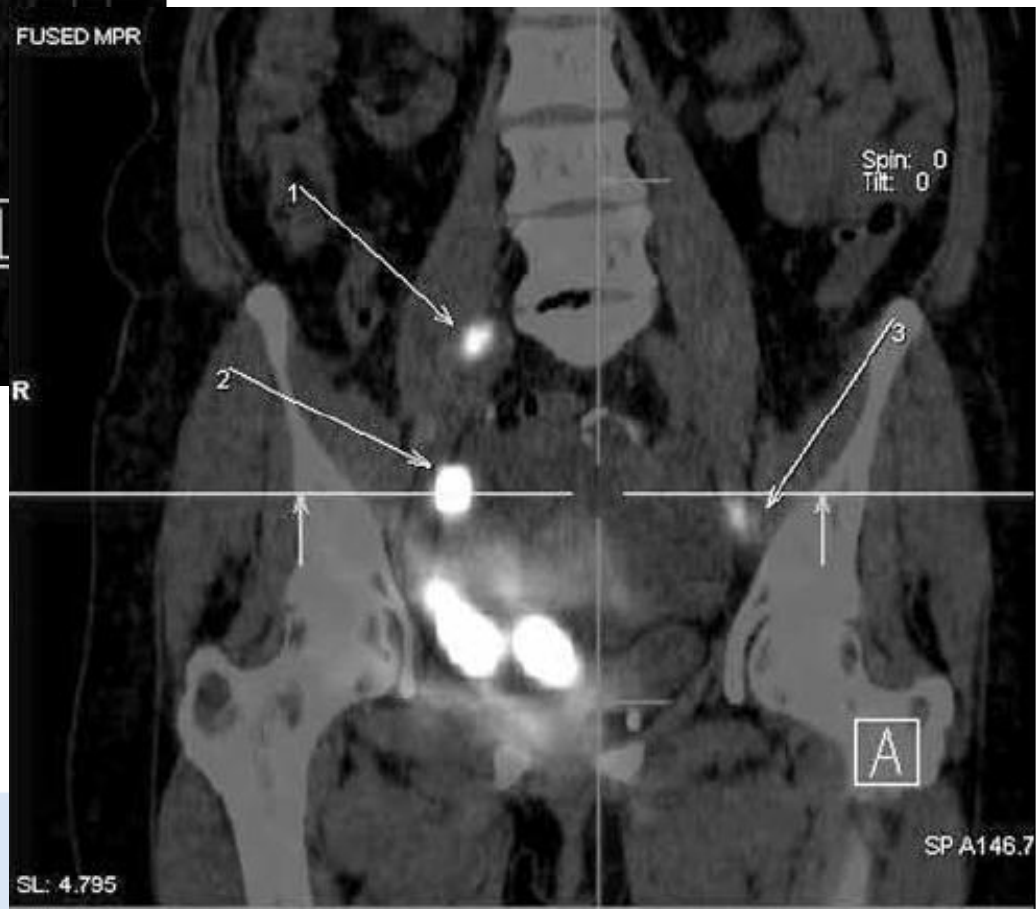
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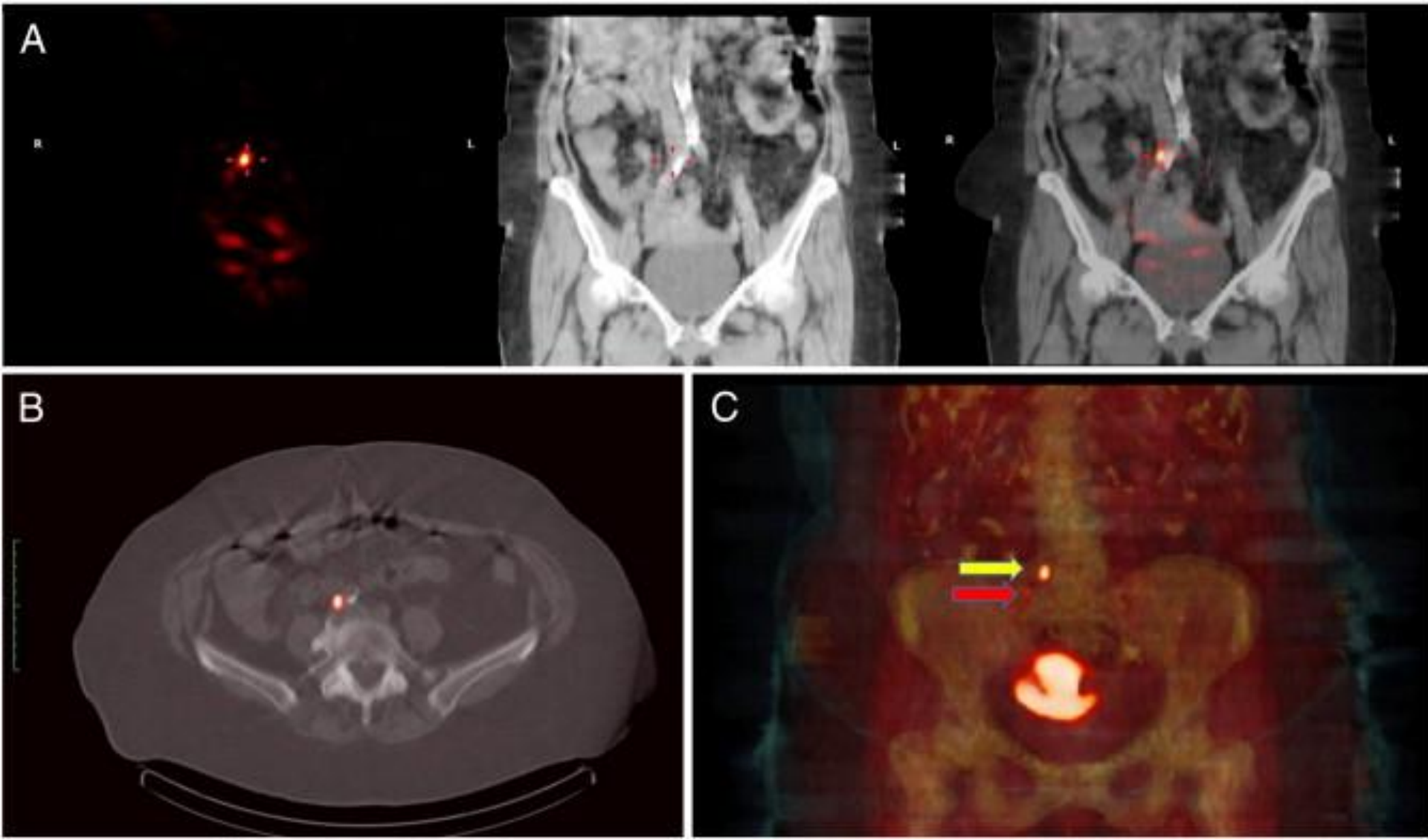
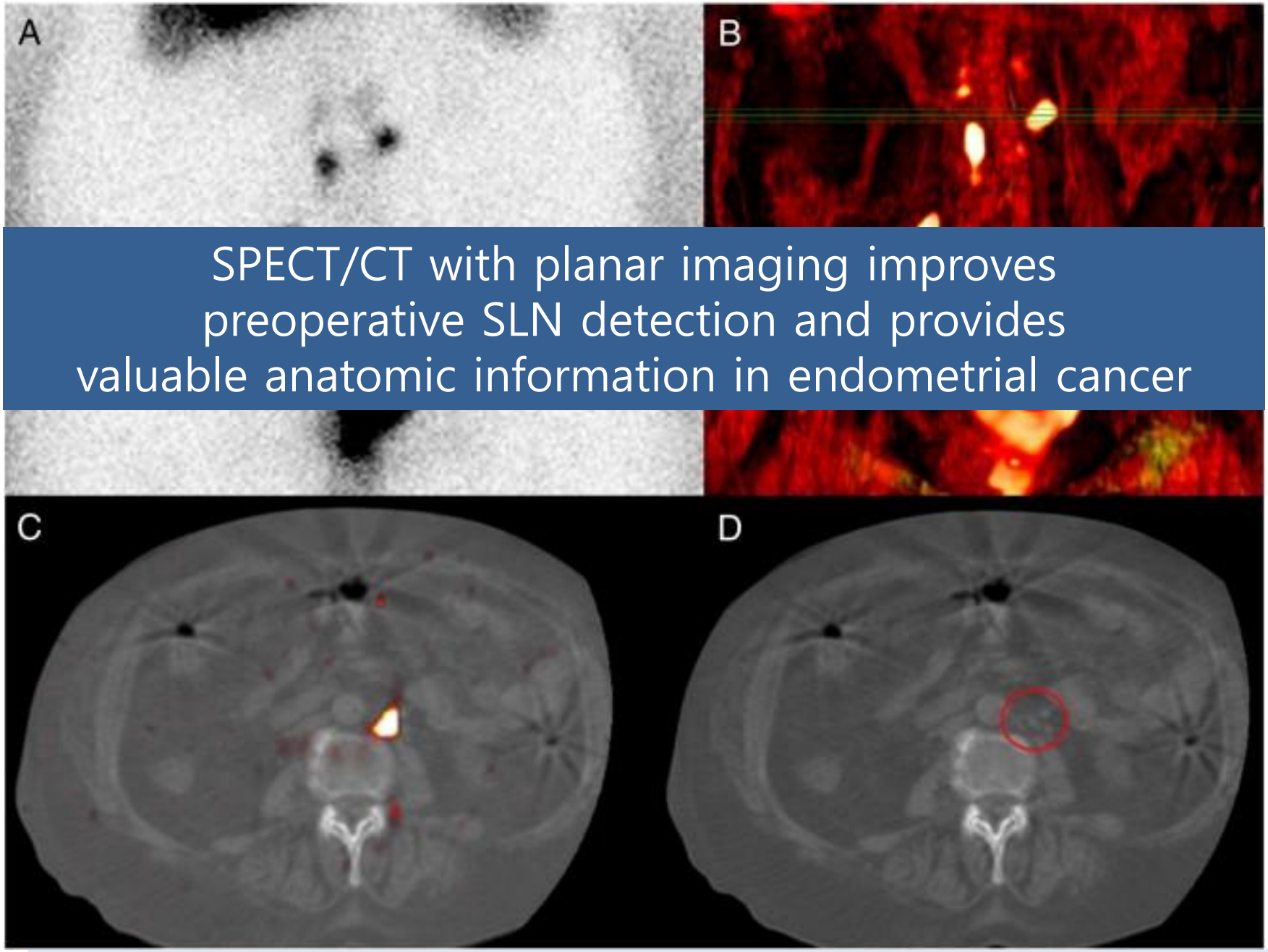


Perissinotti et al., Gynecol Oncol. 2013;129:42-8.



SPECT/CT with planar imaging improves preoperative SLN detection and provides valuable anatomic information in endometrial cancer

Perissinotti et al., Gynecol Oncol. 2013;129:42-8.

SPECT/CT

Pros

- Increased background radioactivity
- Provide an anatomic reference for SLN distribution

Cons

SPECT/CT not changed the outcome

- Scanning using gamma probe or blue dye still necessary
- SLNs are found in typical areas (external iliac or obturator)

Sawicki S, et al. Nuc Med Comm 2013;34:590-6

SLN Mapping

- Image-guided procedure
- Well-established
  - Melanoma, breast cancer, vulvar cancer
- Concept
  - Lymph drains in an orderly pattern
  - Remove the first LN in a regional lymphatics

Khoury-Collado et al., Gynecol Oncol 2011;122:251-4

Surgical Dilemma

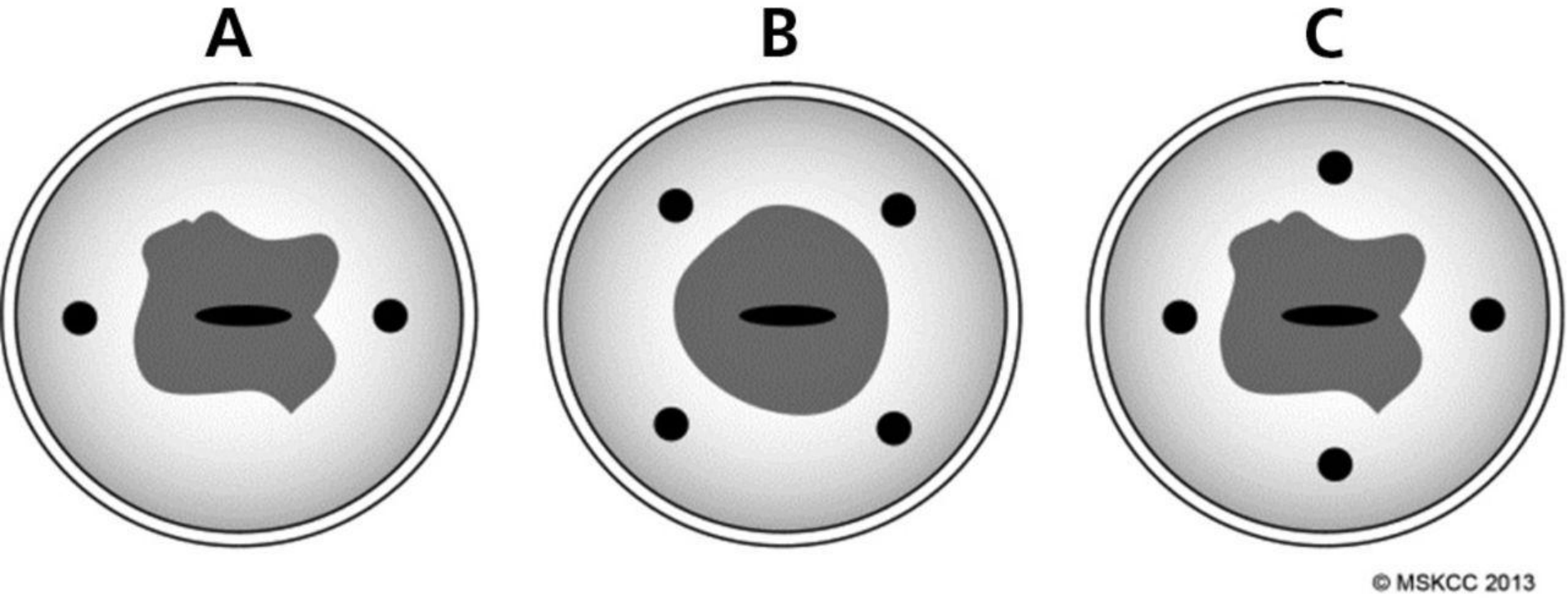
- Understaging *versus* overtreating

- Many patients with early-stage
  - Surgery with insufficient nodal evaluation
  - Inadequate surgical staging
  - Unnecessary adjuvant therapy

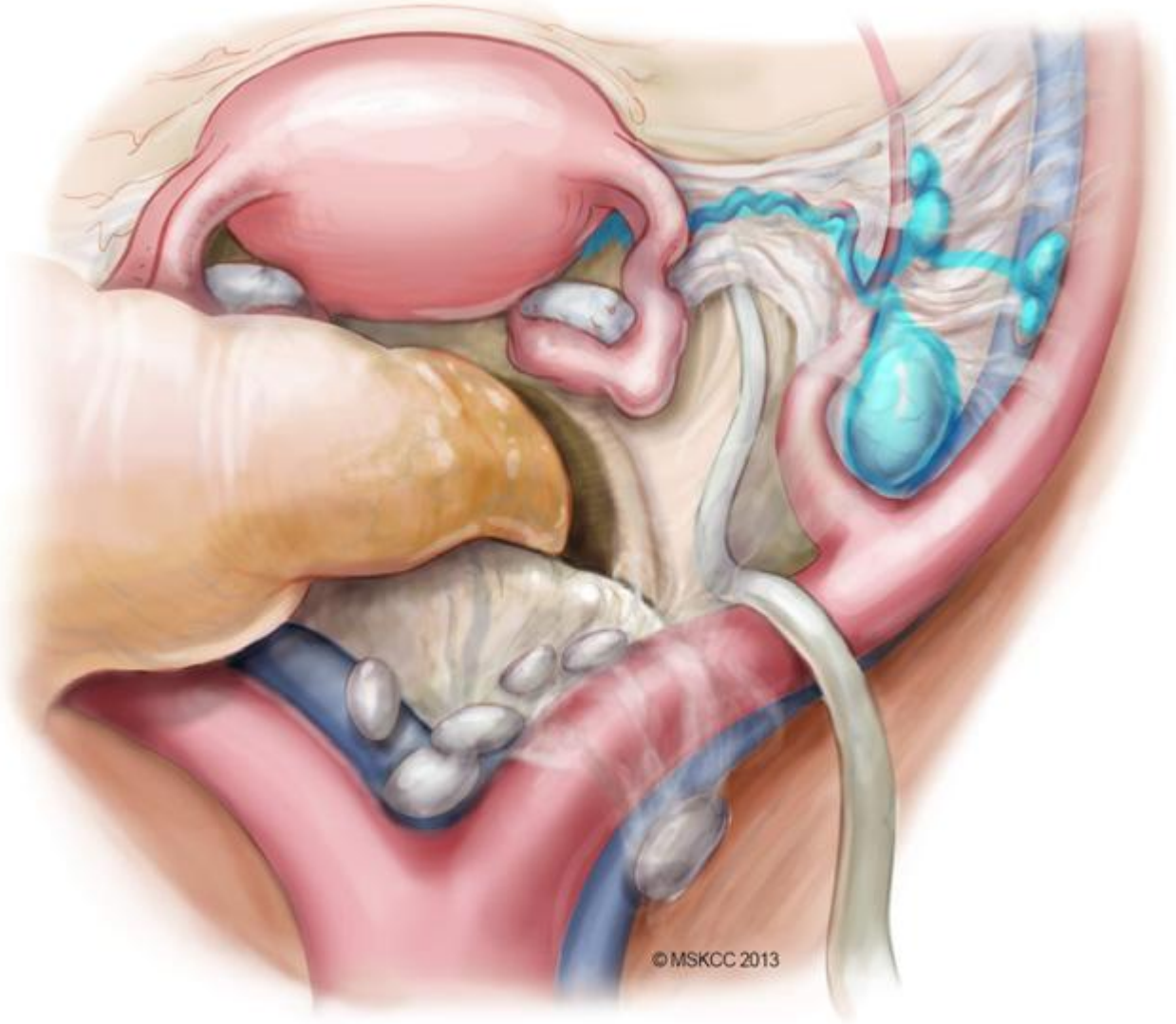
Barakat et al., Gynecol Oncol 2007;105:150-6

SLN Mapping in EM Cancer

SLN Mapping Techniques



Most Common Drainage Route



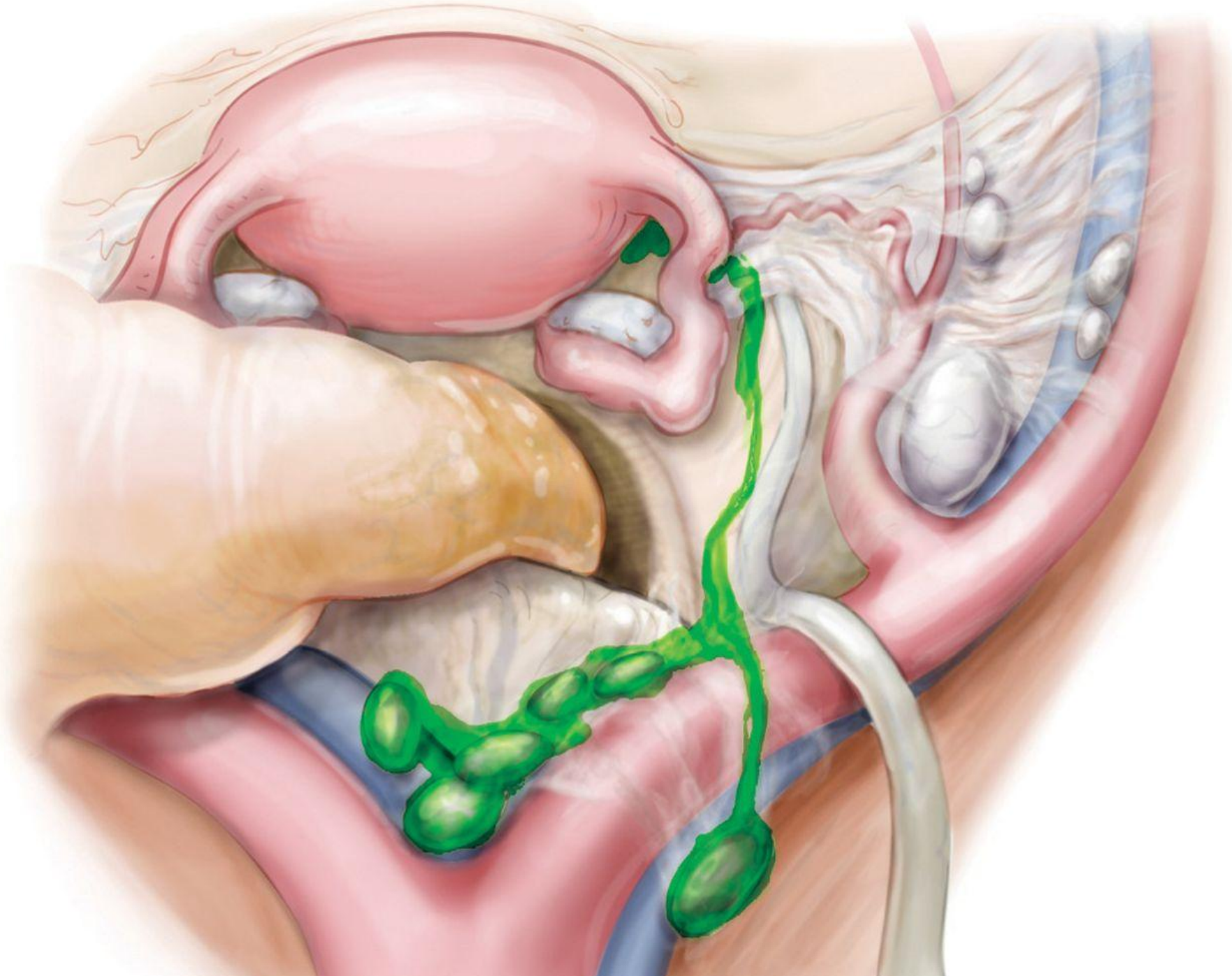
Abu-Rustum, et al. J Obstet Gynecol Res 2013;40:327-34.

Common Metastatic SLN

- **Internal iliac** **36%**
- **External iliac** **30%**
- **Obturator** **23%**
- Common iliac 8%
- Para-aortic 3%

- Isolated para-aortic LN involvement: 1 ~ 1.6%

Abu-Rustum et al., Gynecol Oncol 2009;113:163-9
Abu-Rustum et al., Gynecol Oncol 2009;115:236-8



SLN Detection

Authors	No. of patients	Injection site	Detection method	Unilateral detection percentage	Bilateral detection percentage	False-negative percentage
Burke (1996)	15	SSM	blue dye	67	NS	50
Echt (1999)	8	SSM	blue dye	0	0	0
Holub (2002)	13	SSM	blue dye	62	NS	0
	12	SSM+PC	blue dye	83	NS	0
Pelosi (2002)	16	PC	blue dye+radiocolloid	94	56	0
Gargiulo (2003)	11	PC	blue dye+radiocolloid	100	35	0
Raspagliesi (2004)	18	HS	blue dye+radiocolloid	100	NS	0
Holub (2004)	25	SSM+PC	blue dye	84	81	0
Fersis (2004)	10	HS	radiocolloid	70	20	0
Niikura (2004)	28	HS	radiocolloid	82	NS	0
Maccuro (2005)	26	HS	blue dye+radiocolloid	100	NS	0
Bats (2005)	26	PC	blue dye+radiocolloid	81	NS	0
Li (2007)	20	SSM	blue dye	75	NS	NS
Frumovitz (2007)	18	SSM	blue dye+/radiocolloid	45	39	0
Altgassen (2007)	23	SSM	blue dye	92	NS	NS
Delpech (2007)	23	PC	blue dye+radiocolloid	83	48	NS
Barranger (2009	33	PC	blue dye/ radiocolloid	82	54	0

HS, hysteroscopic; NS, non-specified; PC, paracervical; SSM, subserosal myometrium.

- **Detection rate: unilateral: 45~100%, bilateral: 20~56%**
- **False-negative rate: 0~50%**

Van Oostrum NH, et al. Acta Obstet Gynecol Scand 2012;91:174-81

SLN Mapping

- **Lymphoscintigraphy**
  - ^{99m}Tc
  - Gamma probe
  - SPECT
- **Colored-dye injection**
  - Isosulfan blue 1 / methylen blue 1%
  - 1 mL for each quadrant, 5 – 10 sec
- **Fluorescent SLN imaging**
  - Indocyanine green (ICG)
  - Near-infrared fluorescent imaging

Injection Tracers

Blue dye

- **Isosulfan blue**
- Blue violet
- Methylene blue

  : stain observed 5-15 min after the injection

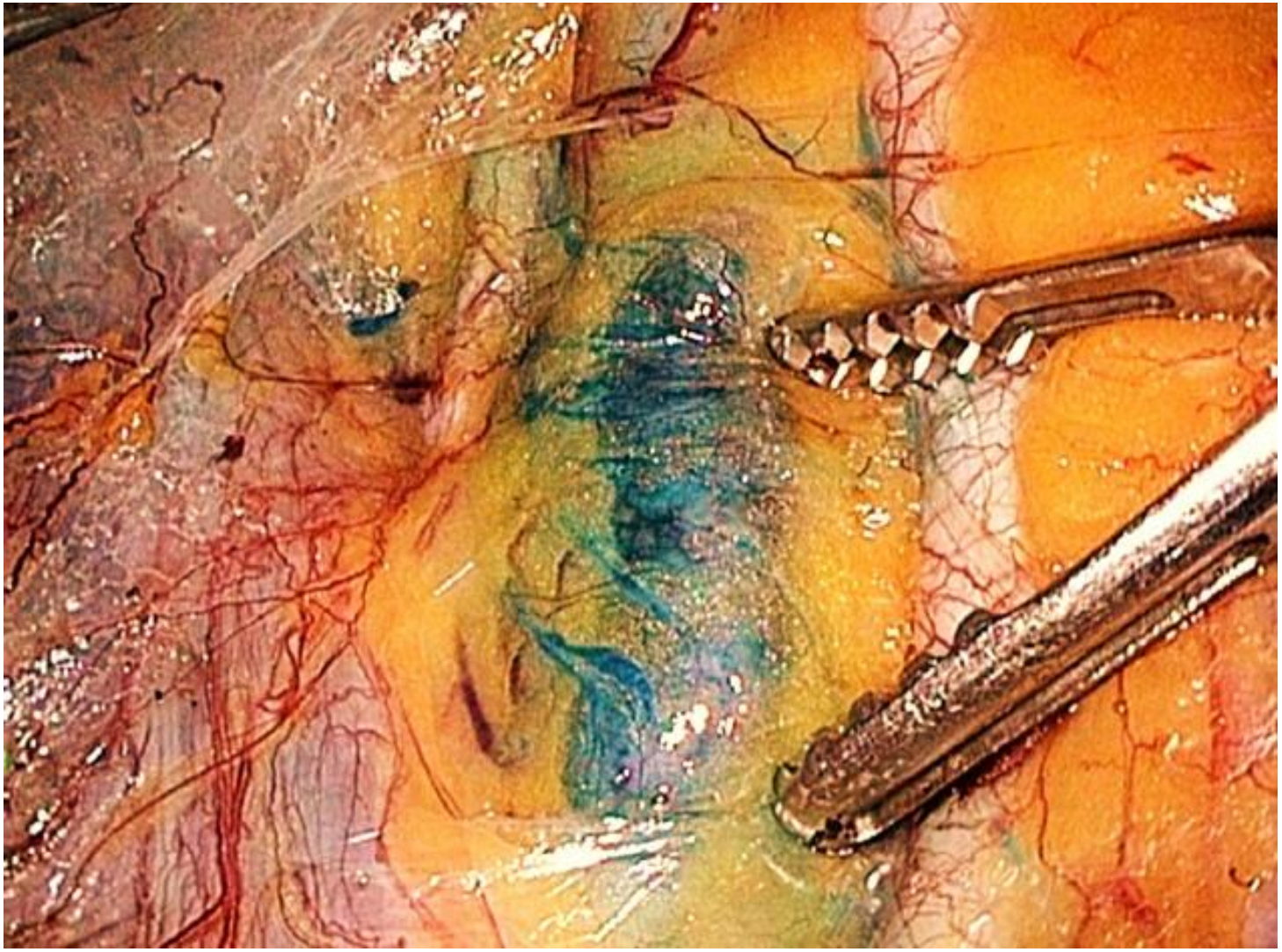
  colored for up to 60 min

Radioactive tracer

- ^{99m}Tc-sulfur colloid
- ^{99m}Tc-nanocolloid human serum albumin

El-Ghobashy et al. EJSO 2009;35:675-85

Isosulfan Blue

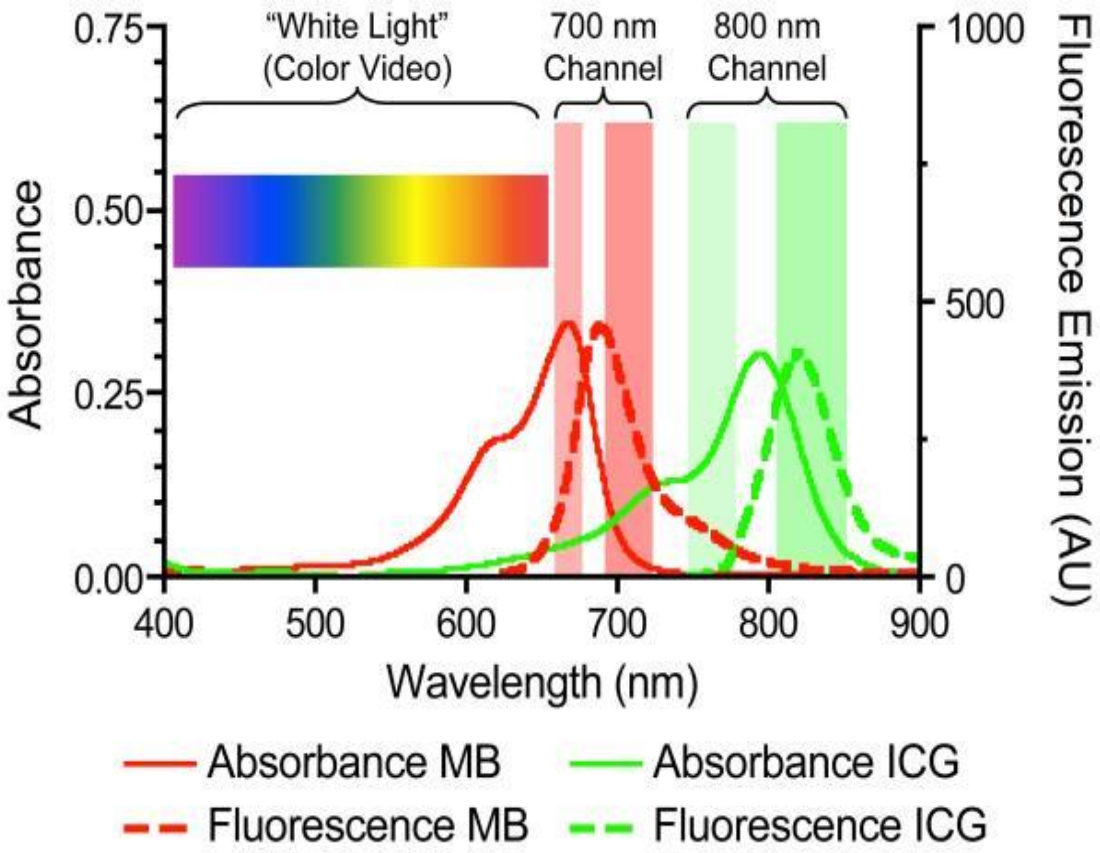


Abu-Rustum, et al. J Obstet Gynecol Res 2013;40:327-34.

Injection Tracers

Indocyanine green

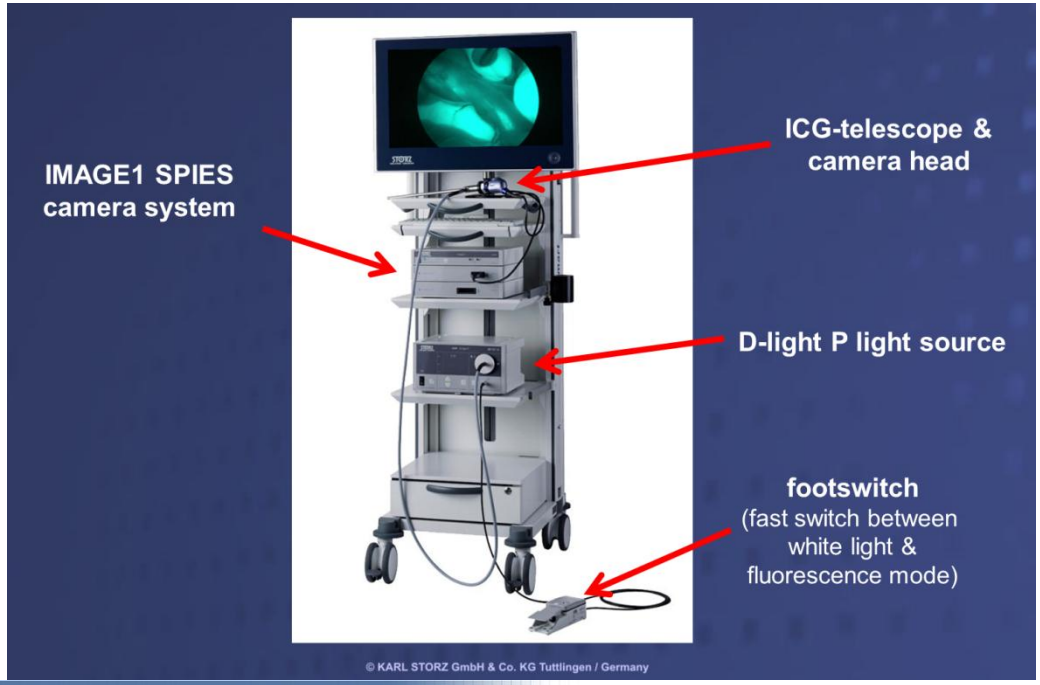
- $C_{43}H_{47}N_2O_6S_2Na$



Devices for ICG Detection

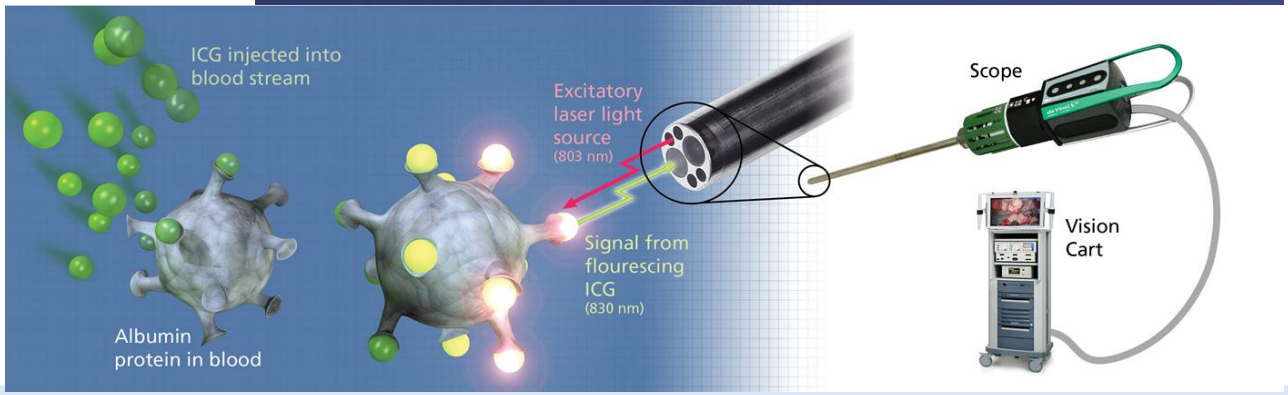
IMAGE1 SPEIS

(Karl Storz)



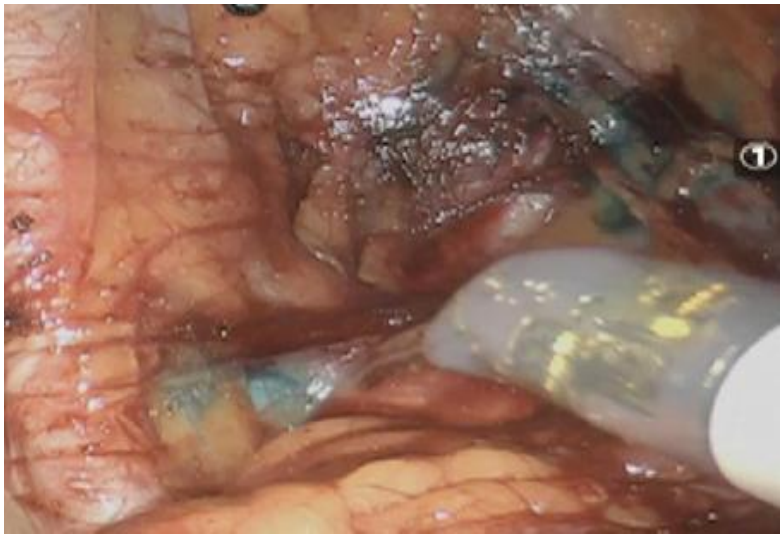
Firefly

(Da Vinci)

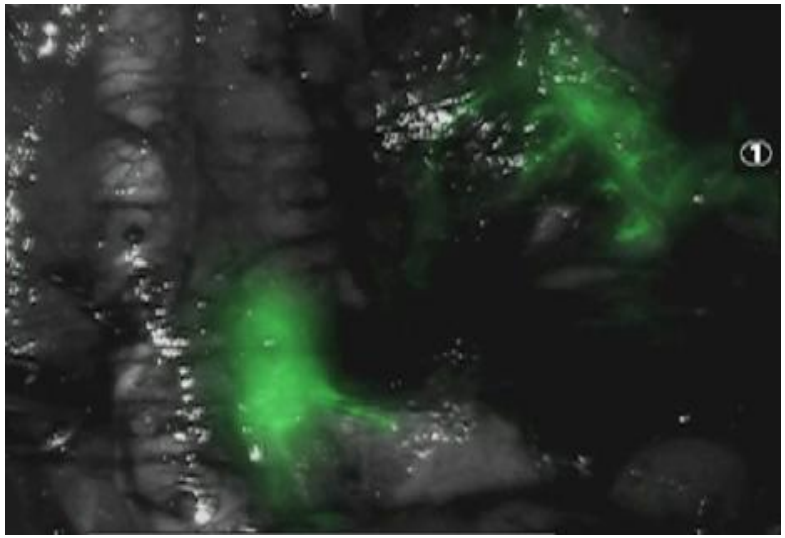


Injection Tracers

Near-infrared (NIR) imaging



Colorimetric Detection of Isosulfan Blue

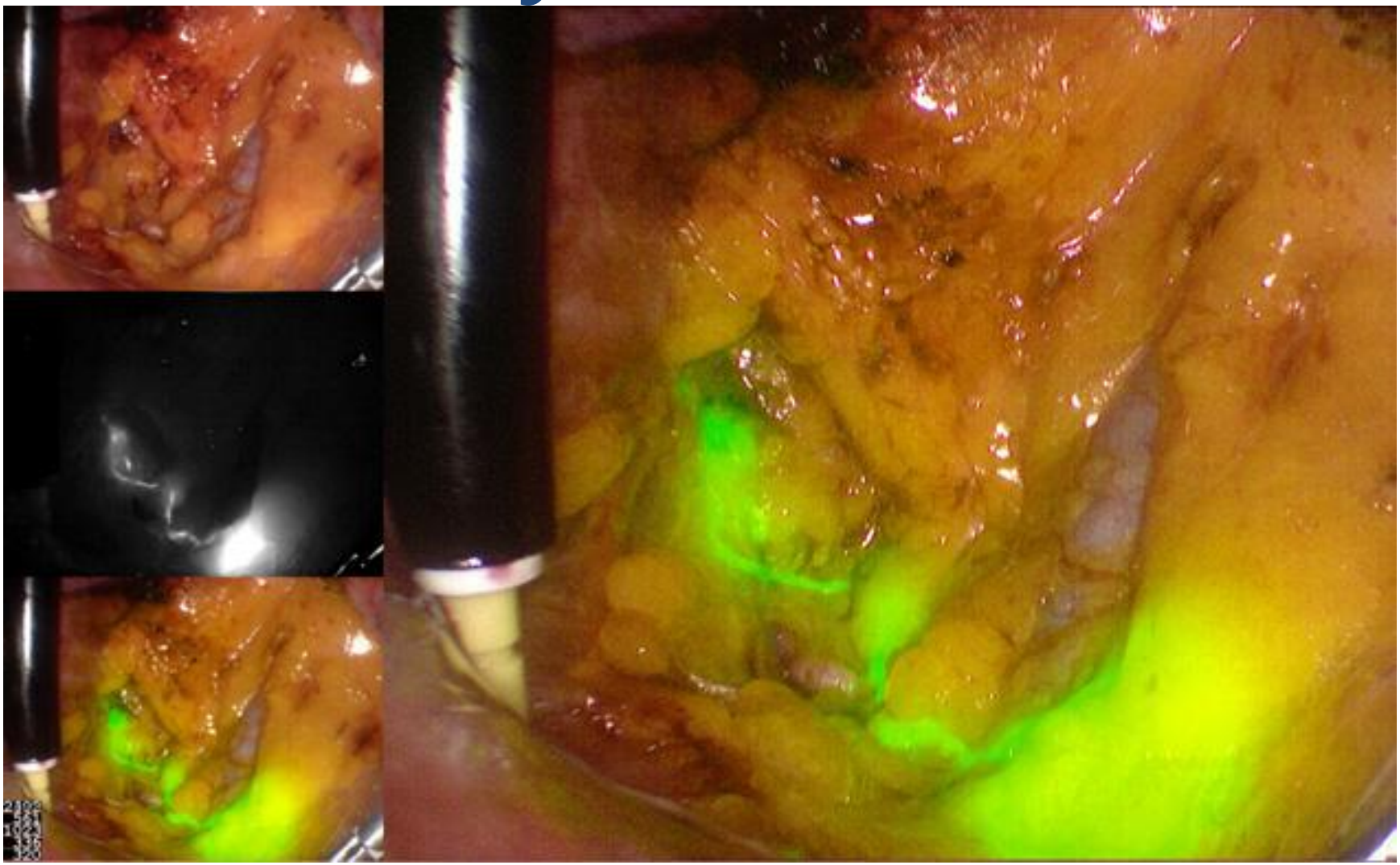


NIR imaging of indocyanine green

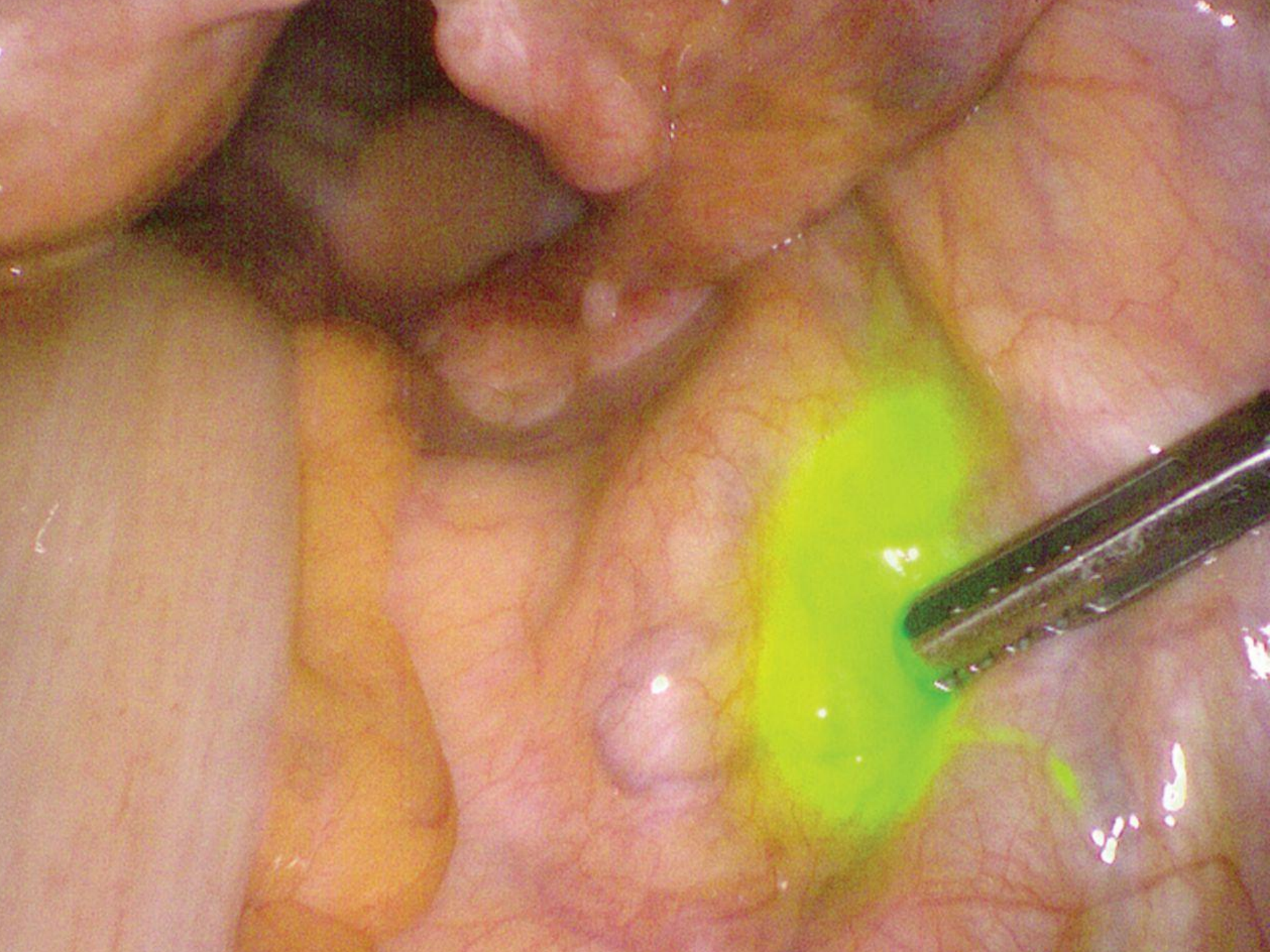
High tissue penetration
Low autofluorescence
Lack of radiation exposure

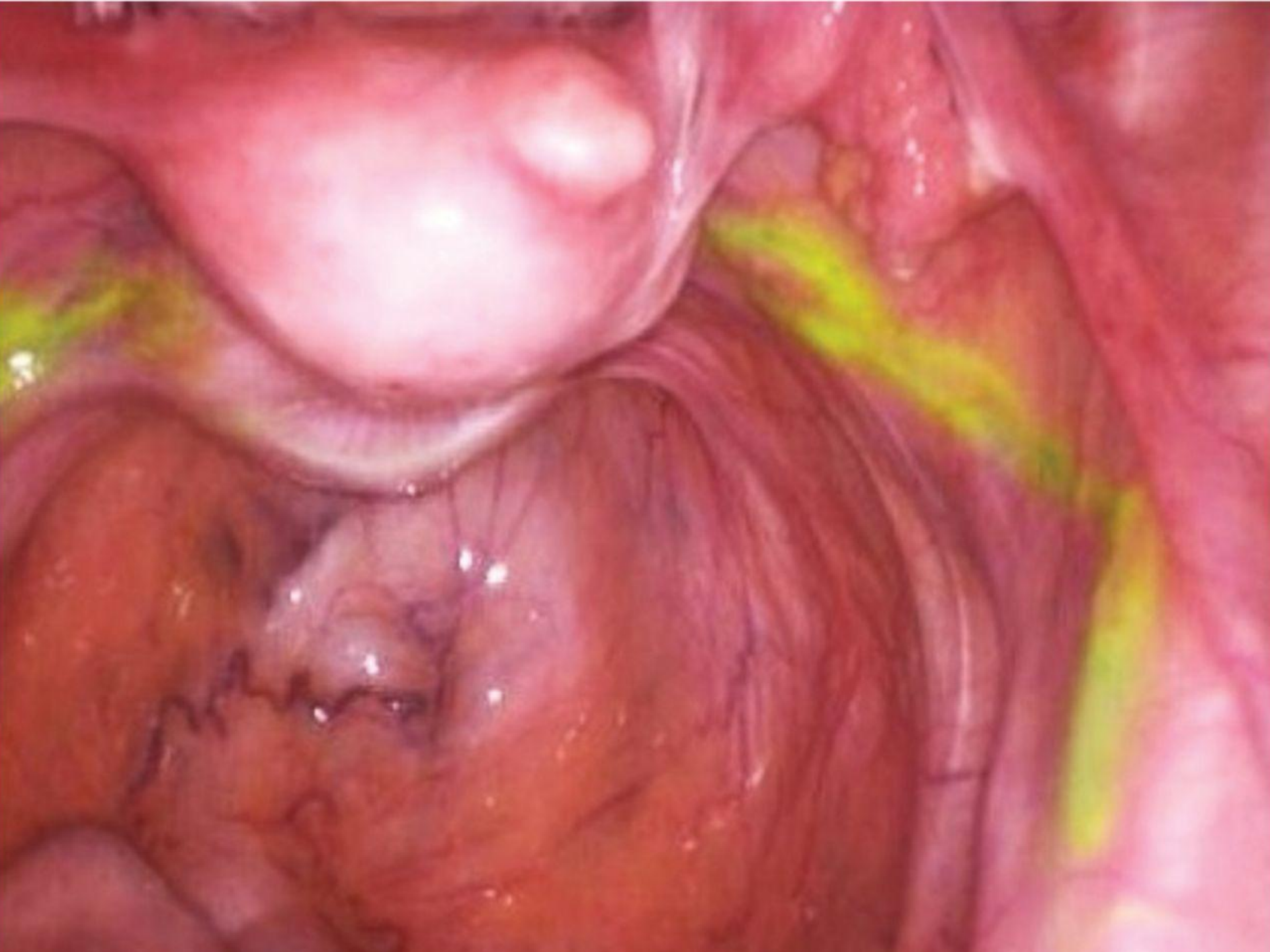
Holloway RW, et al. Gynecol Oncol 2012;126:25-9

Indocyanine Green



Abu-Rustum, et al. J Obstet Gynecol Res 2013;40:327-34.





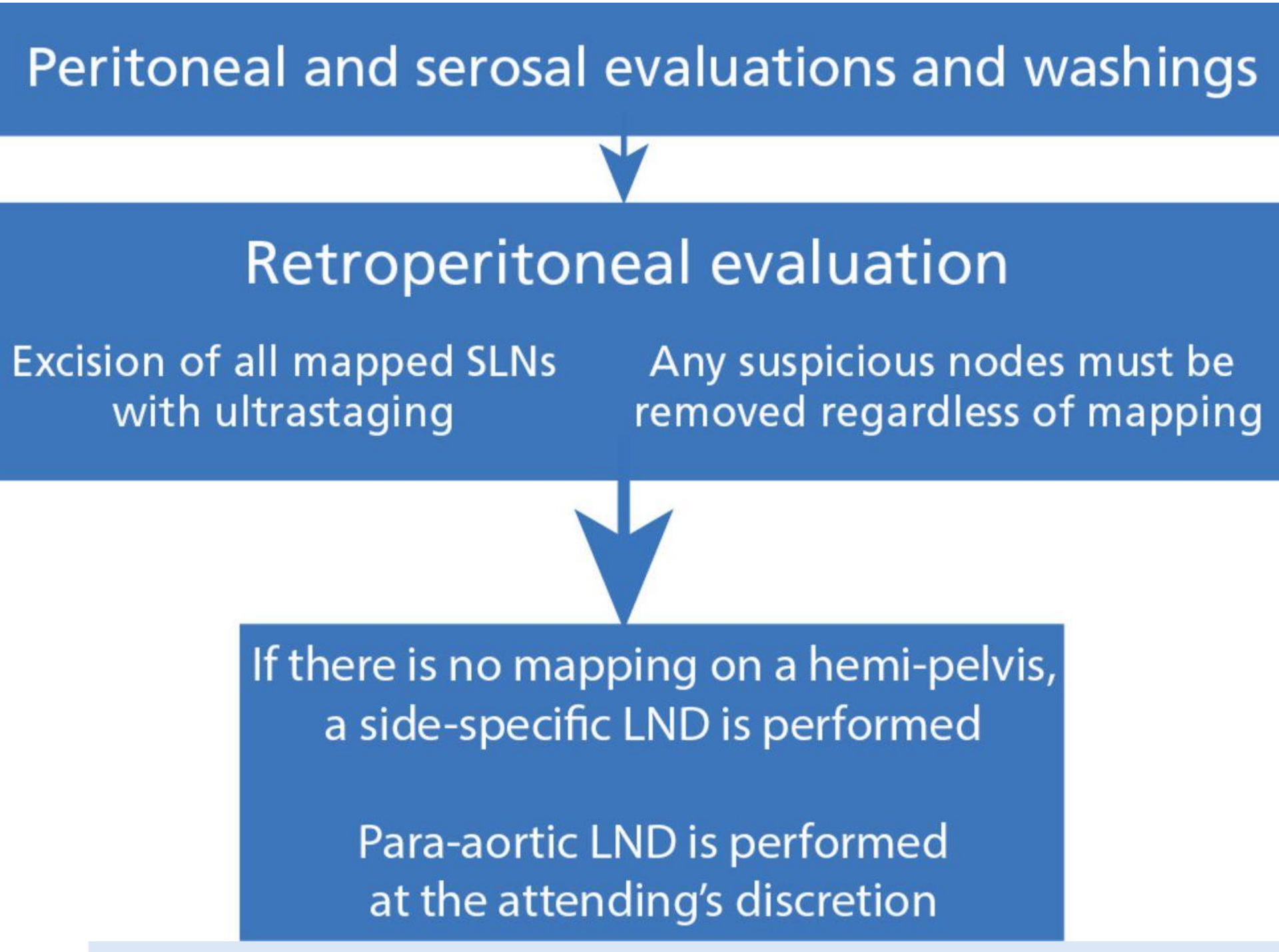
Sinno et al., Gynecol Oncol 2014;134:281-6

SLN Mapping Algorithm

- Major priority of SLN: Low false-negativity
- **MSKCC algorithm: NCCN guideline**
  - Grossly enlarged suspicious LN
  - Side-specific LND for non-mapping hemipelvis
  - Decreasing the false-negativity

    (14.9 % → 1.9 %)

Barlin et al., Gynecol Oncol 2012;123:531-5


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

SLN Metastasis

Table 3 Performance of SLN Mapping Alone Compared With the Algorithm for All Patients

	LN Positive	LN Negative	Total	SLN Alone	Calculation	Result
SLN positive	40	0	40	Sensitivity	40/47	85.1
SLN negative	7	354	361	Negative predictive value	354/361	98.1
	47	354	401	False-negative rate	7/47	14.9
	LN Positive	**LN Negative**	**Total**	**Algorithm**	**Calculation**	**Result**
Algorithm positive	53	0	53	Sensitivity	53/54	98.1
Algorithm negative	1	420	421	Negative predictive value	420/421	99.8
	54	420	474	False-negative rate	1/54	1.9

Abbreviations: LN, lymph node; SLN, sentinel lymph node.

From Barlin JN, Khoury-Collado F, Kim CH, et al. The importance of applying a sentinel lymph node mapping algorithm in endometrial cancer staging: beyond removal of blue nodes. Gynecol Oncol 2012;125:533; with permission.

Therapeutic Effect of LND?

- ASTEC
  - No benefit
  - Half had ≤ 9 nodes removed
  - Many treated with RT irrespective of LN status
- Panici et al.
  - No benefit
- SEPAL
  - Improved OS
  - LND vs. adjuvant chemotherapy

Kitchner et al., Lancet 2009;373:125-36.
Panici et al., J Natl Cancer Inst 2008;100:1707-16.
Todo et al., Lancet 2010;375:1165-72

Conclusions

- SLN mapping may be considered in selected pts
- Surgeon experience and pathologic support
- Prospective studies warranted for validation

Thank you for your attention.