Sentinel Lymph Node Detection in Endometrial Cancer: From Pilot Studies to a Functional SLN Algorithm

New Technology Facilitating a Paradigm Shift?

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Why SLN Techiques in Endometrial Cancer

Identify node-positive low-risk patients

Avoid excessive lymphadenectomy / reduce operative time and morbidity in high-risk patients

Simplify preop risk group investigation (MI><50%)

Avoid problems preop under/overstaging risk groups

Increase the detection rate of positive nodes
(ultrasectioning, IHC + 3%-6%)

Endometrial cancer

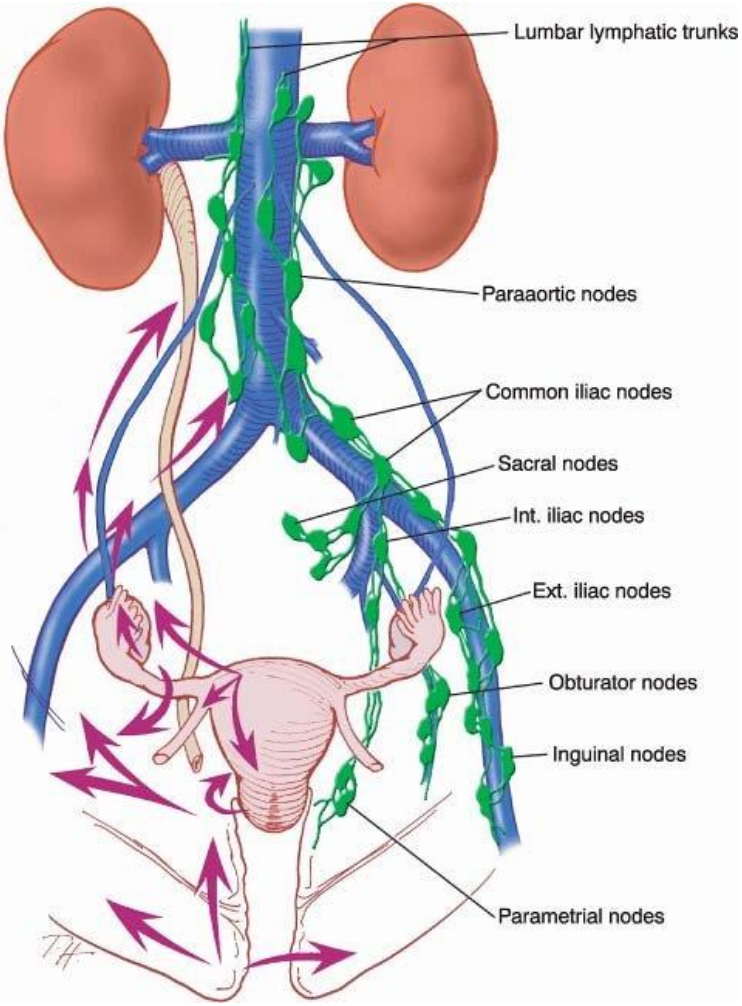
5-year disease-free survival

87% node-negative patients

71% pos pelvic nodes

36% if paraaortic nodes involved*

Needs for Optimal Use/ Development of SLN in Endometrial Cancer



Knowledge of lymphatic anatomy!

A tracer that gives a clear identification of afferent lymph vessel (to define SLN)

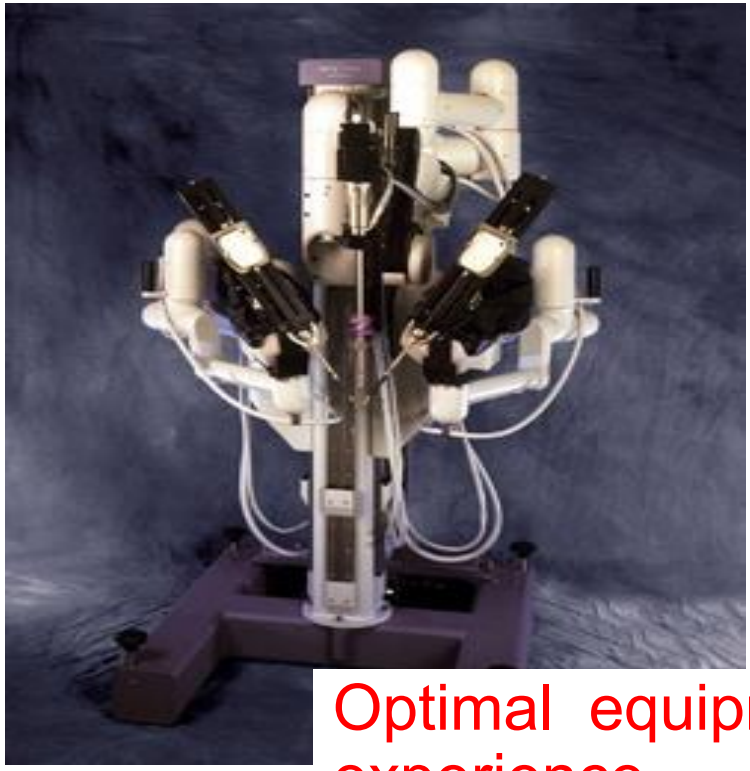
High bilateral technical success rate

Rapid uptake/ intraop injection

Reproducible injection and surgical algorithm

A good surgeon’s experience and a high success of full LND with adequate nodal yield when intended

A



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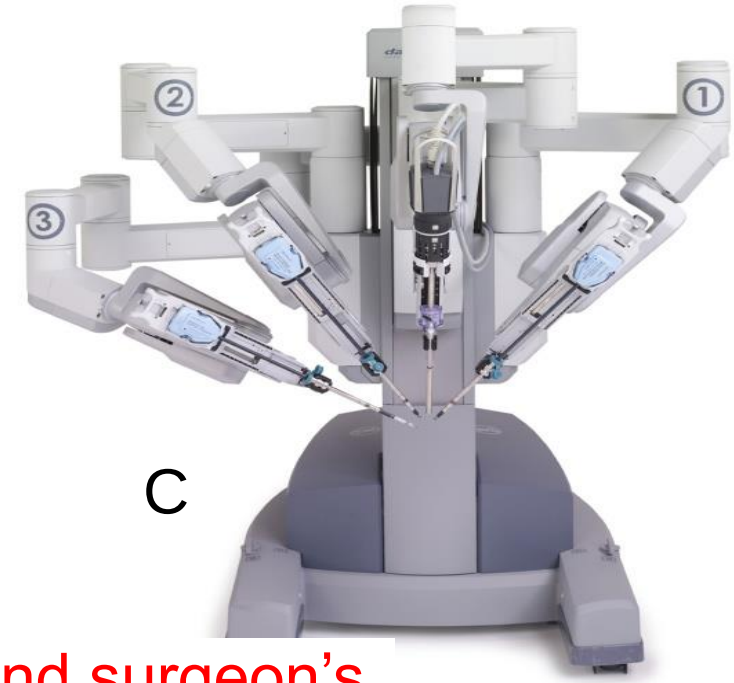


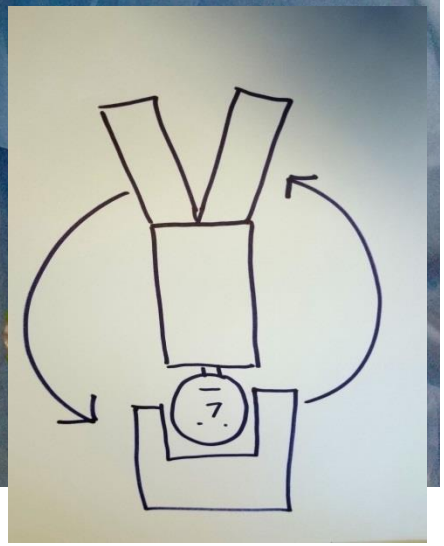
Optimal equipment and surgeon's experience…..

B

D

Image not available

Paraaortic From “Down and Up”



Double side docking or
Central head docking (rotated patient)

Time consuming
Cumbersome for anesthetist and staff

May increase % full PA LND in difficult cases
(not always identifiable upfront)

da Vinci Xi

Same surgeons' console as da Vinci Si
"roof-hung" robot arms
Optics and instrument arms interchangeable
Range of motion expanded
Longer instruments
Various options included
One docking for all procedures?
Retroperitoneal paraaortic possible?

Increase proportion of full (LRV) paraaortic LND when indicated

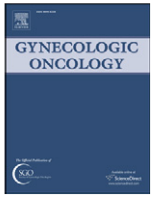
Decrease surgical time

Separate Surgeons' Learning Curve for SLN *per se*…..

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno



Improving sentinel lymph node detection rates in endometrial cancer: How many cases are needed?

Fady Khoury-Collado [a], Gretchen E. Glaser [b], Oliver Zivanovic [a], Yukio Sonoda [a], Douglas A. Levine [a], Dennis S. Chi [a], Mary L. Gemignani [c], Richard R. Barakat [a], Nadeem R. Abu-Rustum [a,*]

First half of study; 50/64 (78%) ≥ unilat SLN detection; 2 false negative

Second half of study: 48/51 (94%) ≥ unilat SLN detection; 0 false negative

Need for standardization and simplification of the surgical algorithm

Approx 20 cases/surgeons estimated to achieve proficiency for the SLN concept

Critical Issues With SLN in Endometrial Cancer?

Does injection site matter?

Does the technique allow an adequate identification / definition of SLN?

Can / should paraaortic SLN be defined?

How to achieve ≥90% bilat detection rate?

Gynecologic Oncology 123 (2011) 522–527

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Sentinel lymph node biopsy in endometrial cancer: Meta-analysis of 26 studies

Sokbom Kang *, Heon Jong Yoo, Jong Ha Hwang, Myong-Cheol Lim, Sang-Soo Seo, Sang-Yoon Park

Center for Uterine Cancer, National Cancer Center, Goyang, 410-769, Republic of Korea

26 studies with 1101 women
Radiotracer, dye or combined
Various injection sites cx, hysterosc, subserosal
Significant heterogeneity between studies

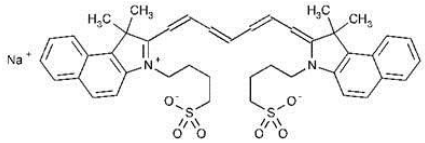
Results:

Detection rate (≥1 SLN)	78%	95% CI (73-84%)	**≥ unilateral**
Sensitivity	93%	95% CI (85-10%)	
Average n SLN	2.6	(range 1-5)	
False-negative rate	≥1% *	(Bayesian estimate)	

Cervical injection higher detection rate than hysteroscopic
Cervical injection higher sensitivy than subserosal fundal

Need for method development and standardization

Indocynanin green (ICG)



C43H47N2NaO6S2 Molecular weight 774.96

1H-Benz[e]indolium,2-[7-[1,3-dihydro-1,1-dimethyl-3-(4-sulfobutyl)-2H-benz[e]indol-2-ylidene]-1,3,5-heptatrienyl]-1,1-dimethyl-3-(4-sulfobutyl)-,hydroxide,inner salt,sodium salt.
2-[7-[1,1-Dimethyl-3-(4-sulfobutyl)benz[e]indolin-2-ylidene]-1,3,5-heptatrienyl]-1,1-dimethyl-3-(4-sulfobutyl)-1Hbenz[e]indolium hydroxide,inner salt,sodium salt [3599-32-4].
»Indocyanine Green contains not less than 94.0percent and not more than 105.0percent of C43H47N2NaO6S2,
contains up to 5.0 percent of sodium iodide

Approved for intravenous use since many years

Rapid (minutes) spread

10-15 min disapp if iv

Stays in tissue >12hours if interstitial injection

(off label use)

Contraindications:

Allergy to Iodine

Serious liver disease

Risk of allergic reaction

1/42 000 uses*

*Speich R et al. Anaphylactoid reactions after indocyanine administration. Ann Intern Med 1988;109;345-6

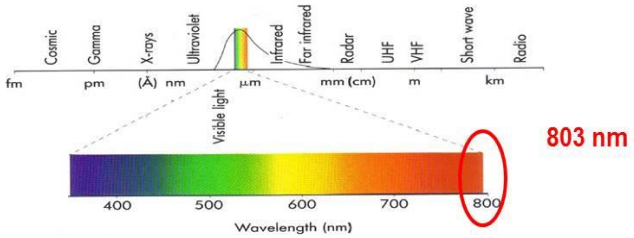
Basic equipment

Near infrared imager system

(i.e available with DVSi)

NIR 803 nm light source

Adapted optics and software



Ian Persson 2013

Injection technique for endometrial cancer

Use a 1 mL syringe with thin long needle

Injection technique

Lund:

1.25 mg ICG Slowly submucosally + 3 cm into stroma at 3 adn 9 O'clock (total dose 2,5 mg)

Chapel Hill **(Rossi*)**

0,5mg 1cm into the cervical stroma 3 and 9 clockwize

Florida **(Holloway**)**

0,6mg " each cervical quadrant" depth not stated

Optimal dose

0.65-1.25 mg per side
(0.25-0,5 mL)

*Rossi et al. Robotically assisted fluorescence-guided Lymph node mapping with ICG for gynecologic Malignancies: feasibility study. Gynecol Oncol (124);78-82

**Holloway R et al. Detection of sentinel lymph nodes in Patients with endometrial cancer undergoing robotic-assisted Staging…… Gynecol Oncol 2012(126); 25-9

Large Single-Center *Retrospective* Study With Cervical Injection of ICG or Blue Dye

Total ***bilateral*** detection rate with ICG 79%* (goal ≥90%)

Algorithm

SLN removed

Macroscopic suspect nodes removed

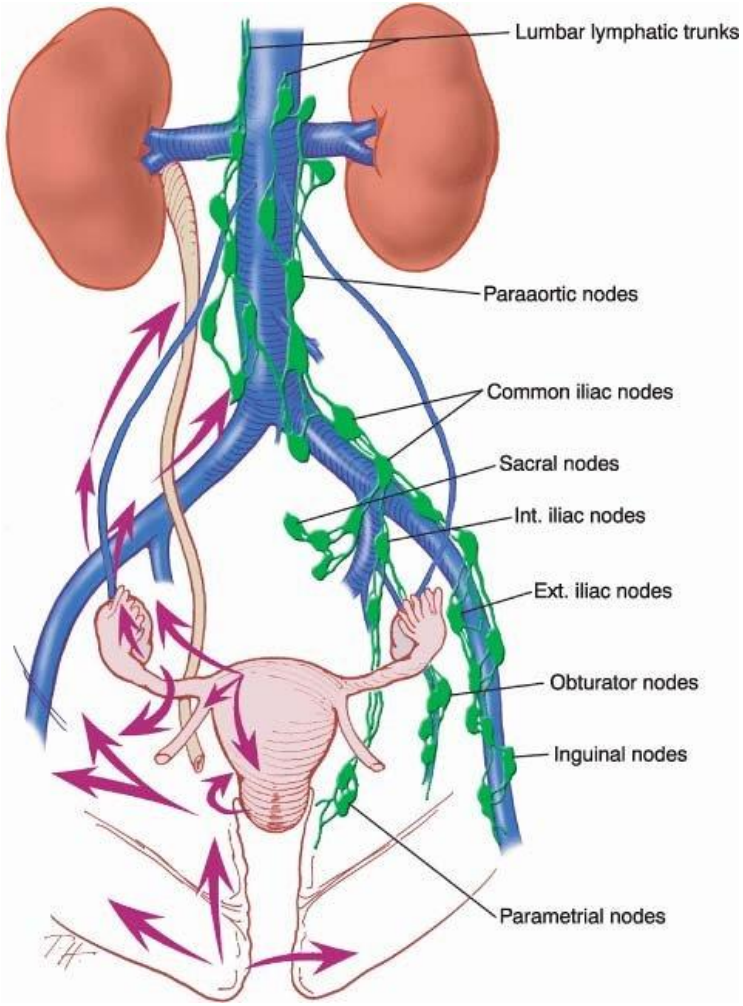
If no uptake uni/bilat full LND

Performance of SLN alone compared to the algorithm for all patients.

	LN positive	LN negative		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		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

Jewell EL, et al. *Gynecol Oncol*. 2014;133(2):274-277; Barlin JN, et al. *Gynecol Oncol.* 2012;125(3):531-535.

Needs for Optimal Use of SLN in EC



Knowledge of lymphatic anatomy!!!

A tracer that gives a clear identification of afferent lymph vessel (to define SLN)

ICG provides that

High bilateral technical success rate

Reproducible (simple) injection site

Rapid uptake/ intraop eval, **re**-injection

ICG provides that

Reproducible simple surgical algorithm

Does Injection Site Matter?

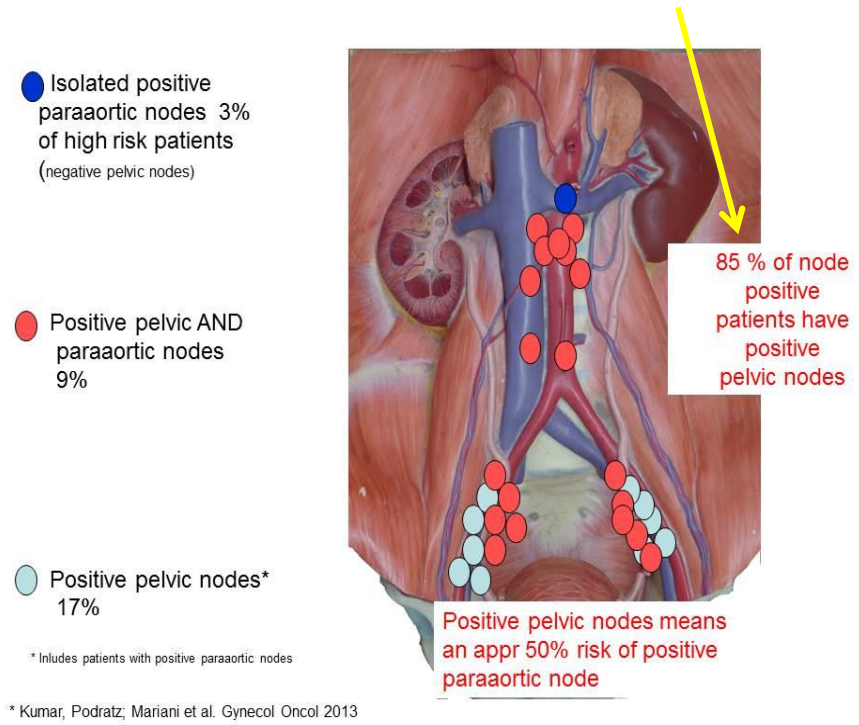
Similar anatomical distribution of SLN after cervical and fundal injection of ICG[1]

Similar anatomical distribution of pelvic SLN after subserosal and cervical injection of ICG[2]

Both studies, as well as several others show a **lower overall detection rate** with fundal / subserosal injection

Intellectual logic argument:
EC spreads primarily to the pelvic side walls.
PA skip mets are rare

A cervical injection displays pelvic lymphatic drainage…
Hence will also detect pelvic SLN in EC

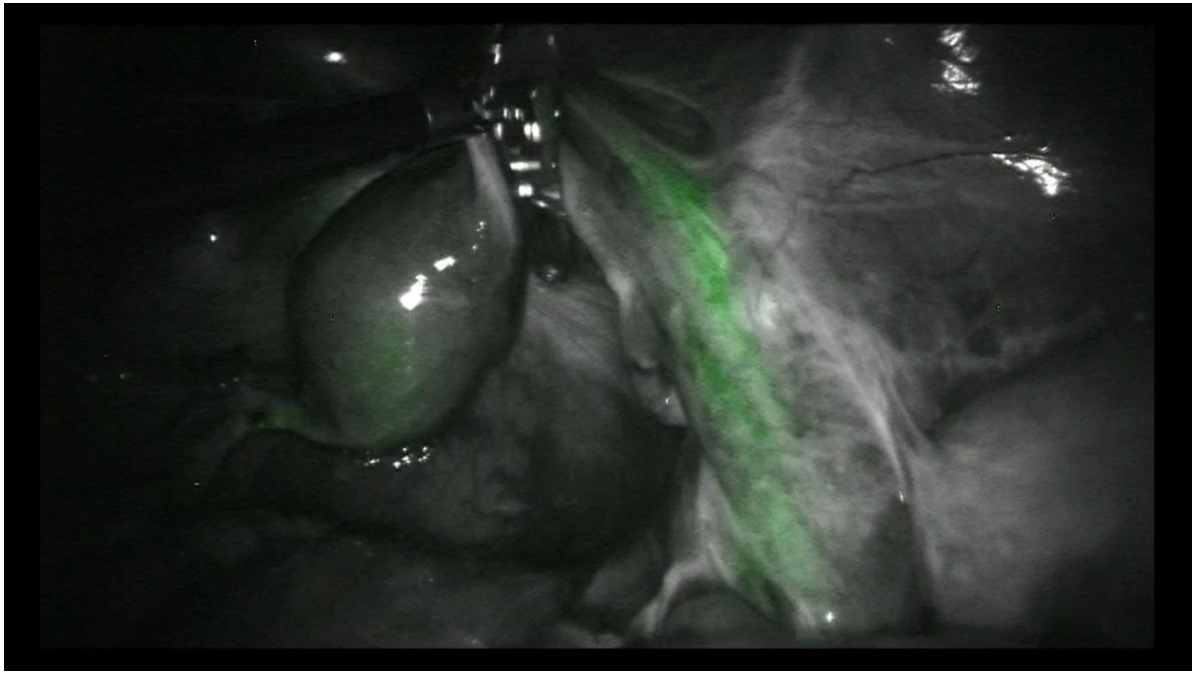


1. Rossi EC, et al. *Int J Gynecol Cancer.* 2013;23(9):1704-1711. 2. Pilot study of 10+20 EC. Persson J, unpublished data.

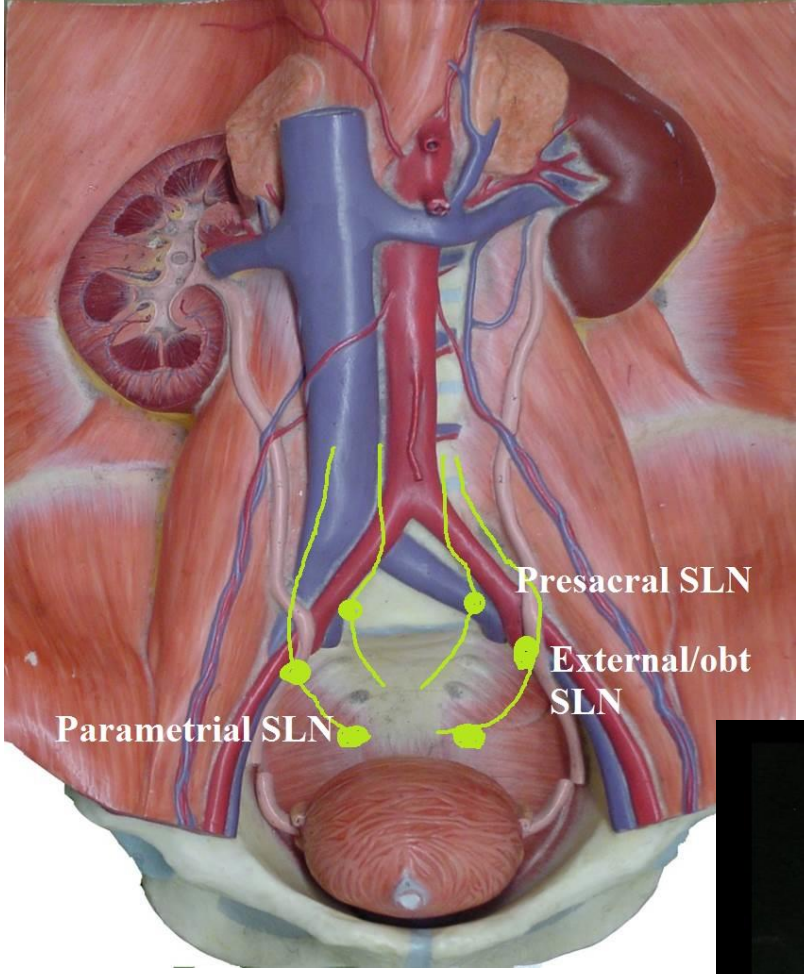
Does Injection Site Matter?

There is no lymphatic connection between
the IP ligament and pelvic lymph nodes.

A fundal/ subserosal injection potentially
giving a higher uptake in the IP-ligaments does not
add to the detection of pelvic SLN.



Conclusion:
A cervical injection of
tracer is the way to go

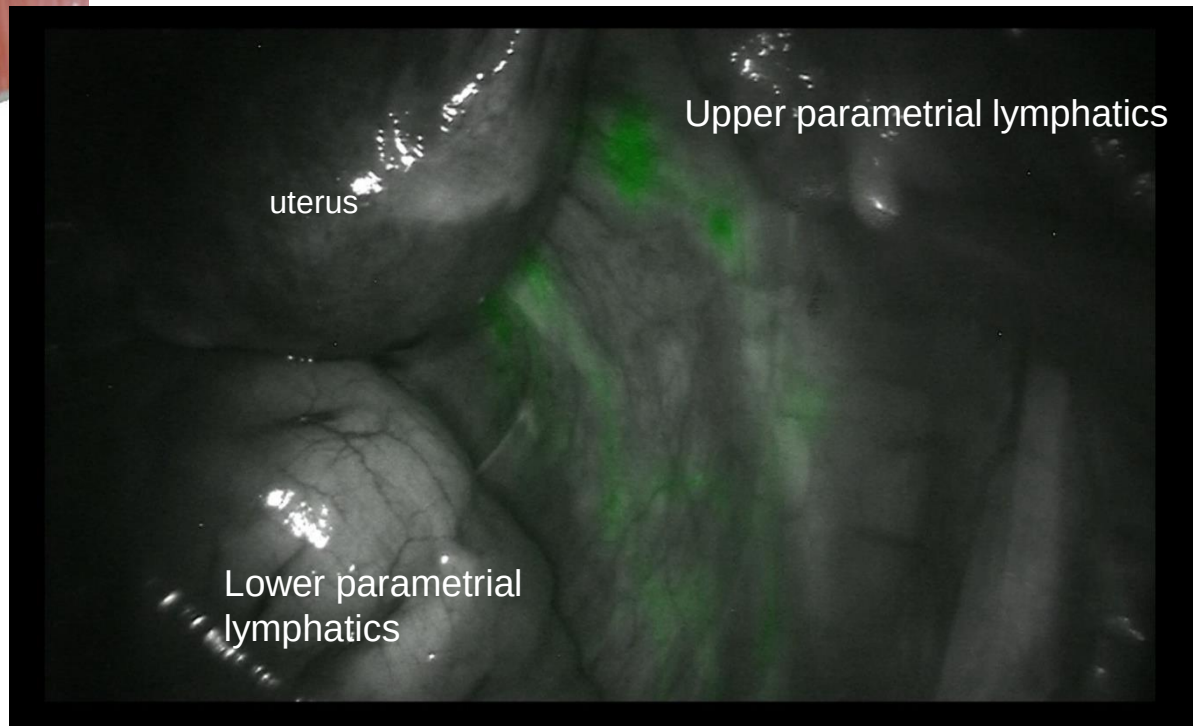


Two well defined separate pelvic lymphatics deriving from the uterus

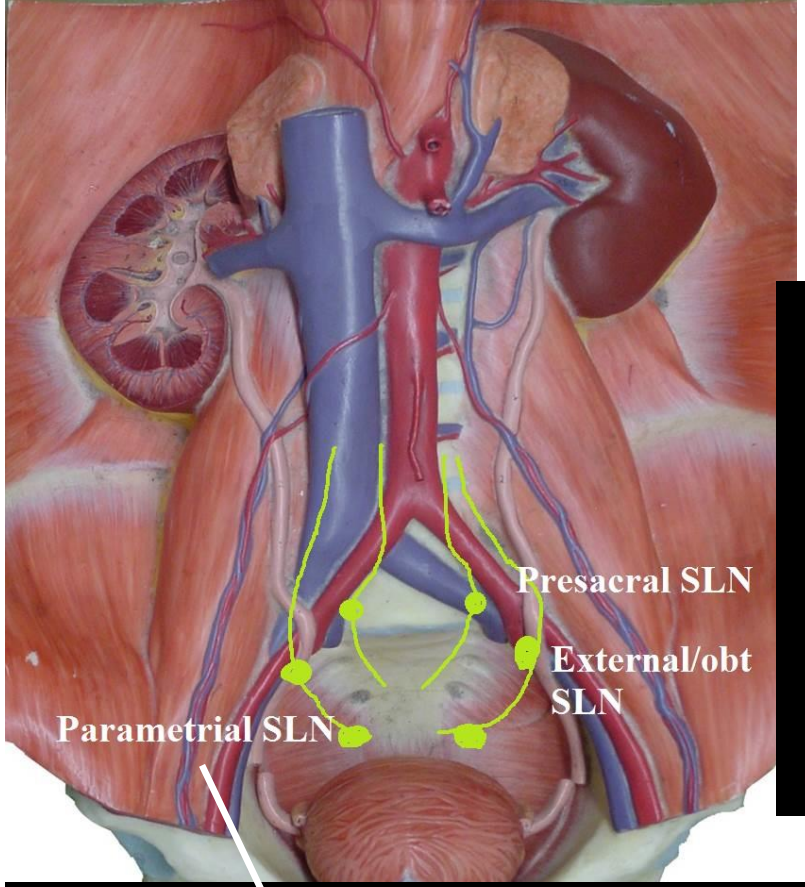
Upper parametrial!

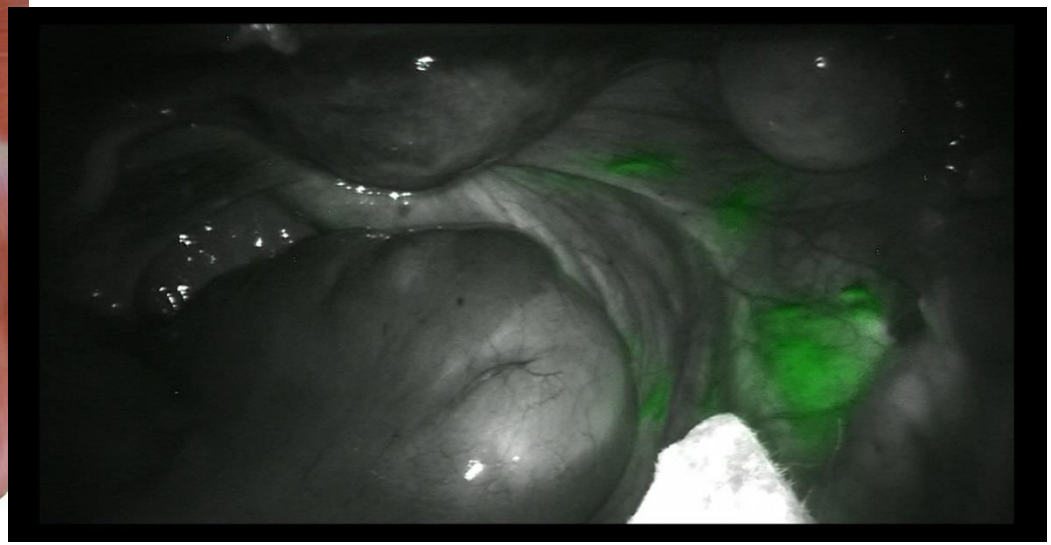
Lower parametrial!

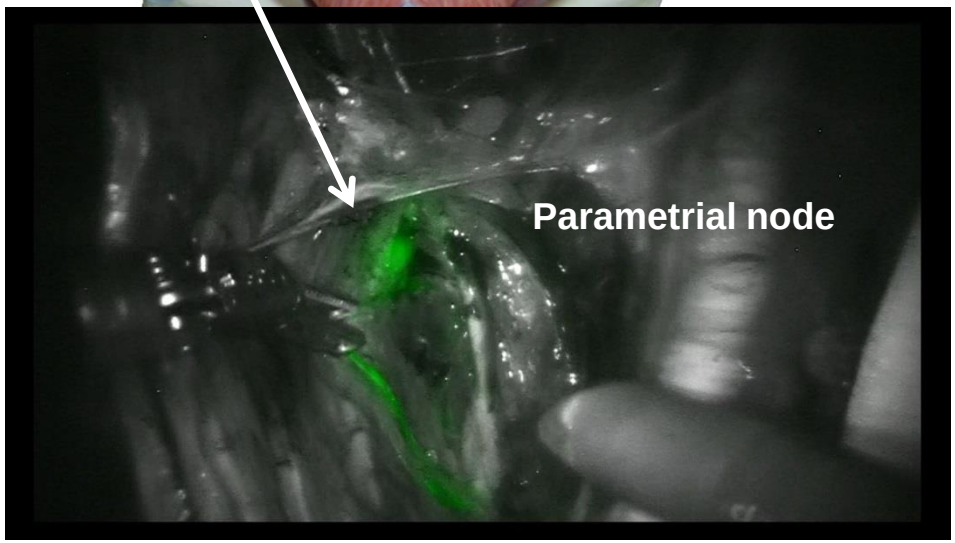
Exploring and learning the lymphatic anatomy

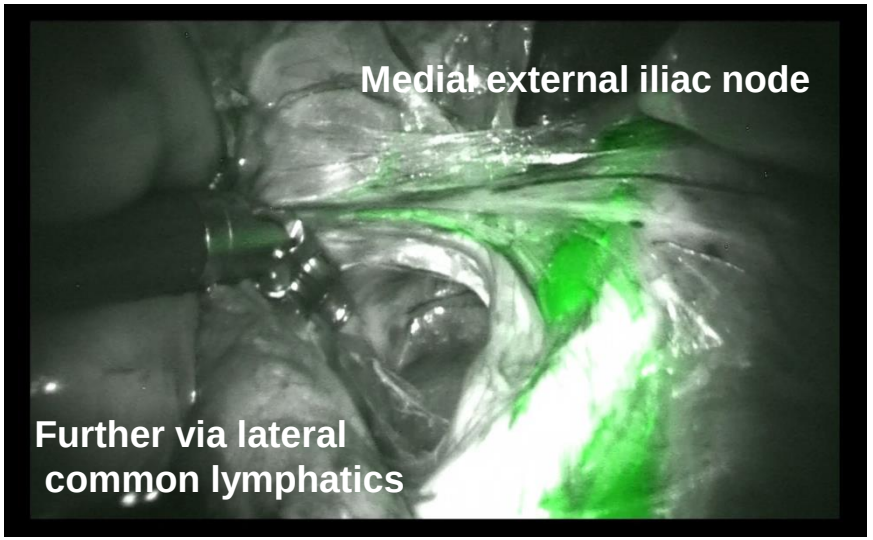


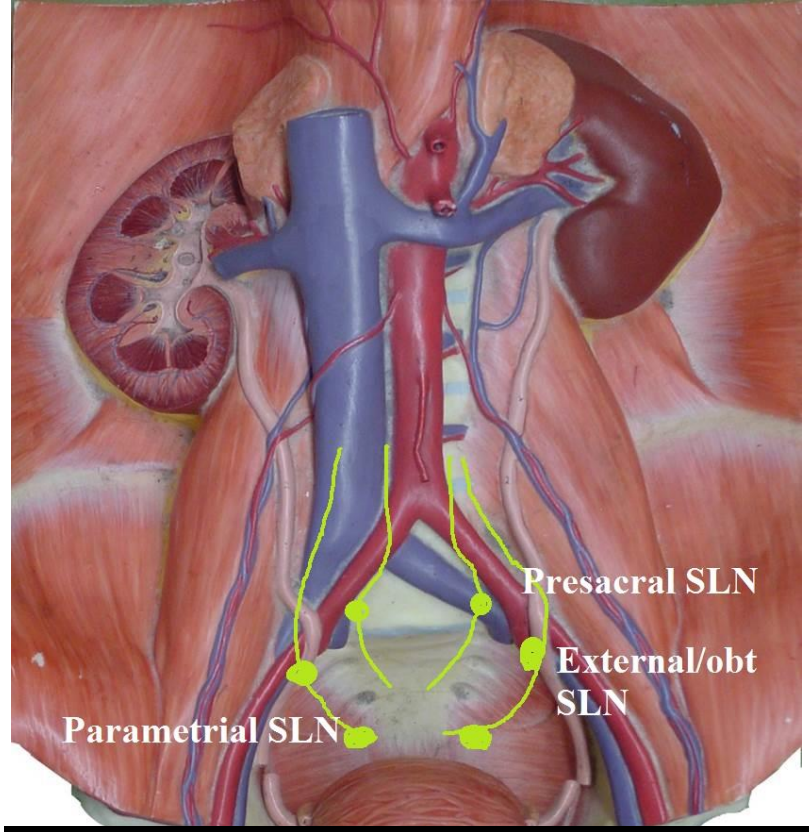
Upper parametrial: following the uterine artery to the medial external/proximal obturator nodes



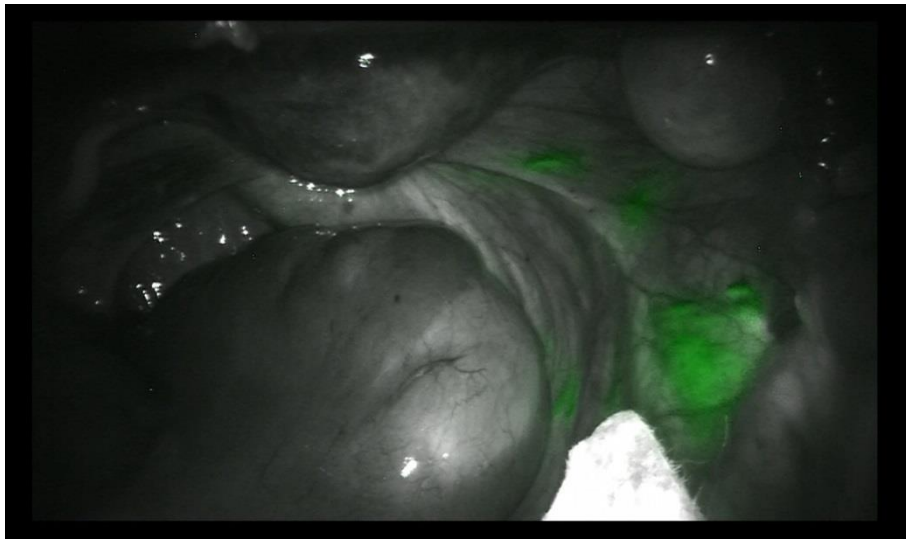


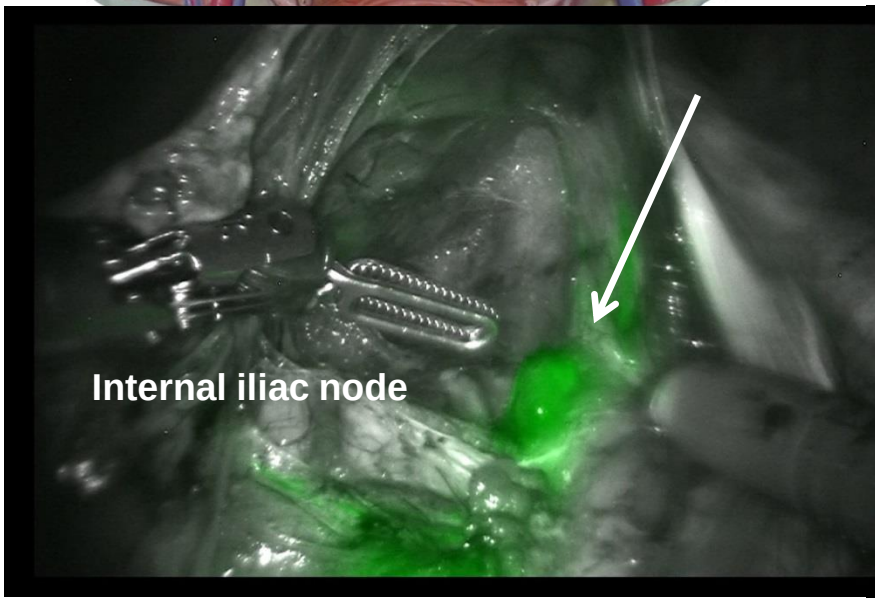


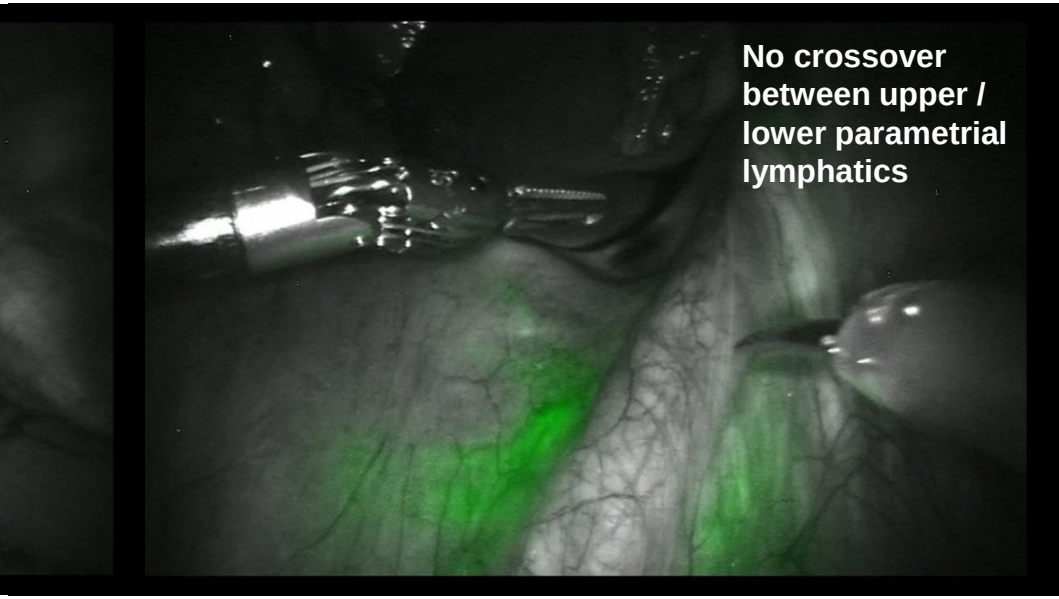




Lower parametrial: following the ventral rim of the sacrouterine lig to internal iliac and presacral nodes







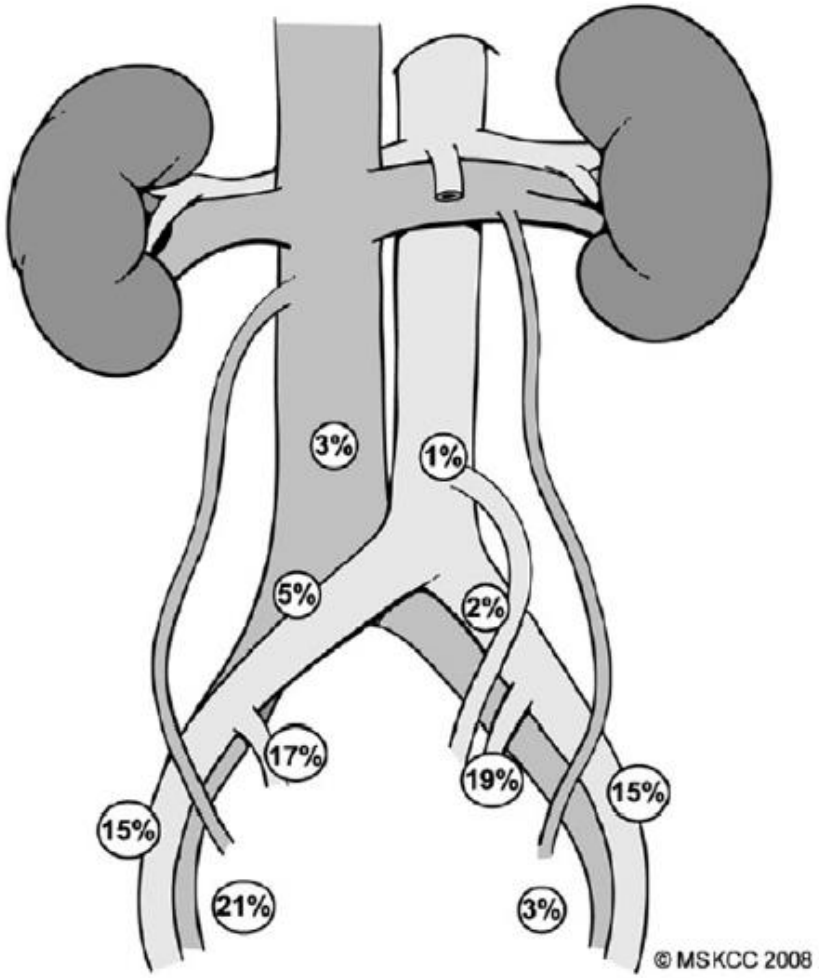


Figure 2 Schematic representation of the location and approximate frequency of sentinel lymph nodes in grade 1 endometrial cancer. The proximal obturator nodes and the internal iliac nodes are anatomically difficult to distinguish and frequently overlap.

Our Preliminary Conclusion

Ideally 2 SLN on each pelvic side wall

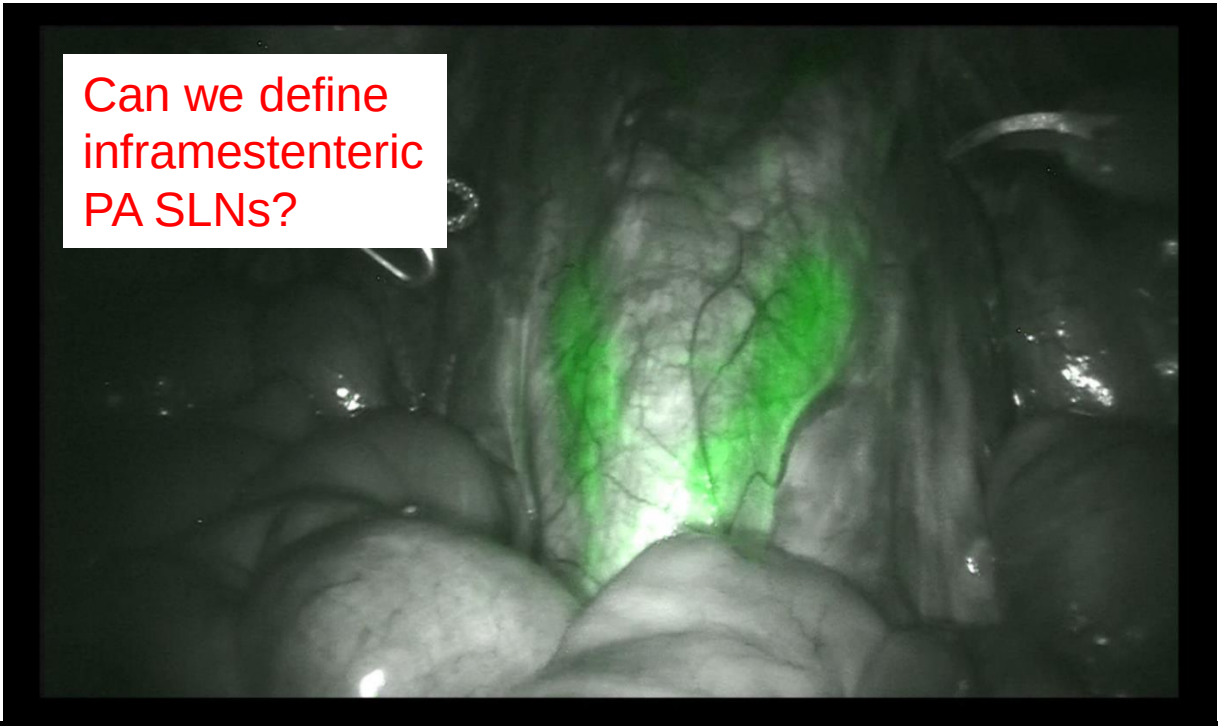
-medial external/prox obturator

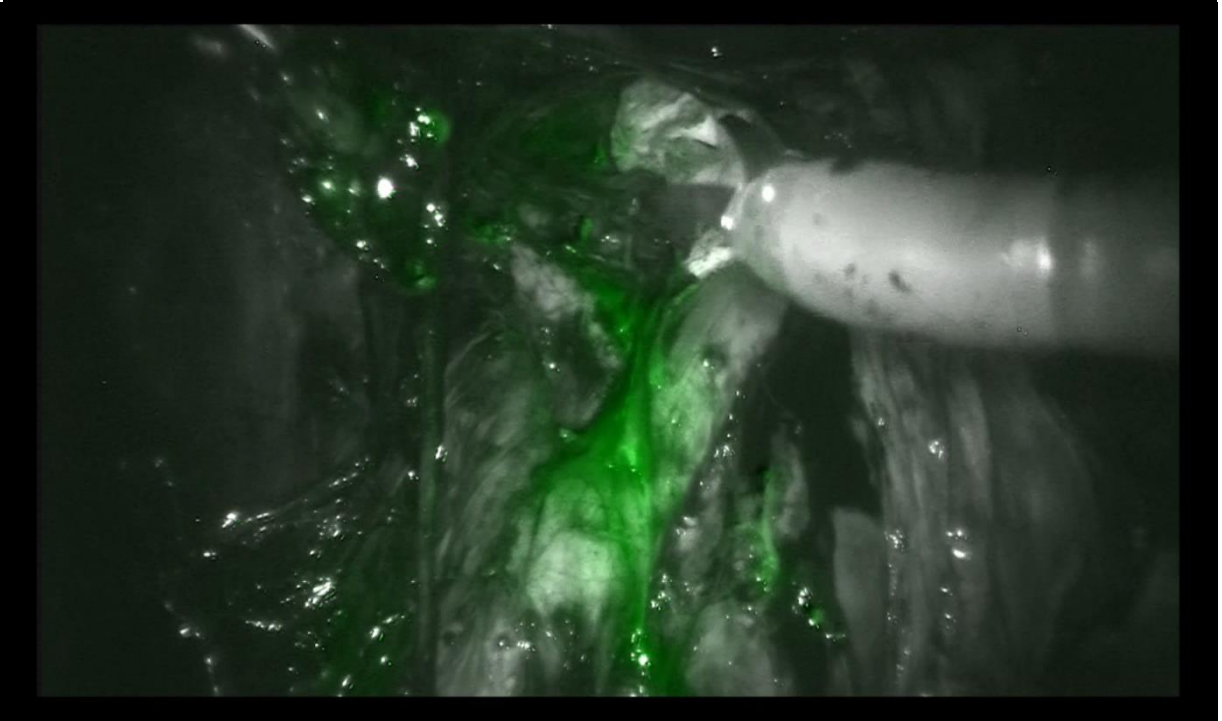
-internal iliac/presacral

Upper parametria should be removed and regarded as "sentinel tissue"

Corresponds to previous findings (exept paraaortic SLN… disc t b c)

Jewell EL, et al. *Gynecol Oncol*. 2014;133(2):274-277; Abu-Rustum NR. *J Obstet Gynaecol Res.* 2014;40(2):327-334.



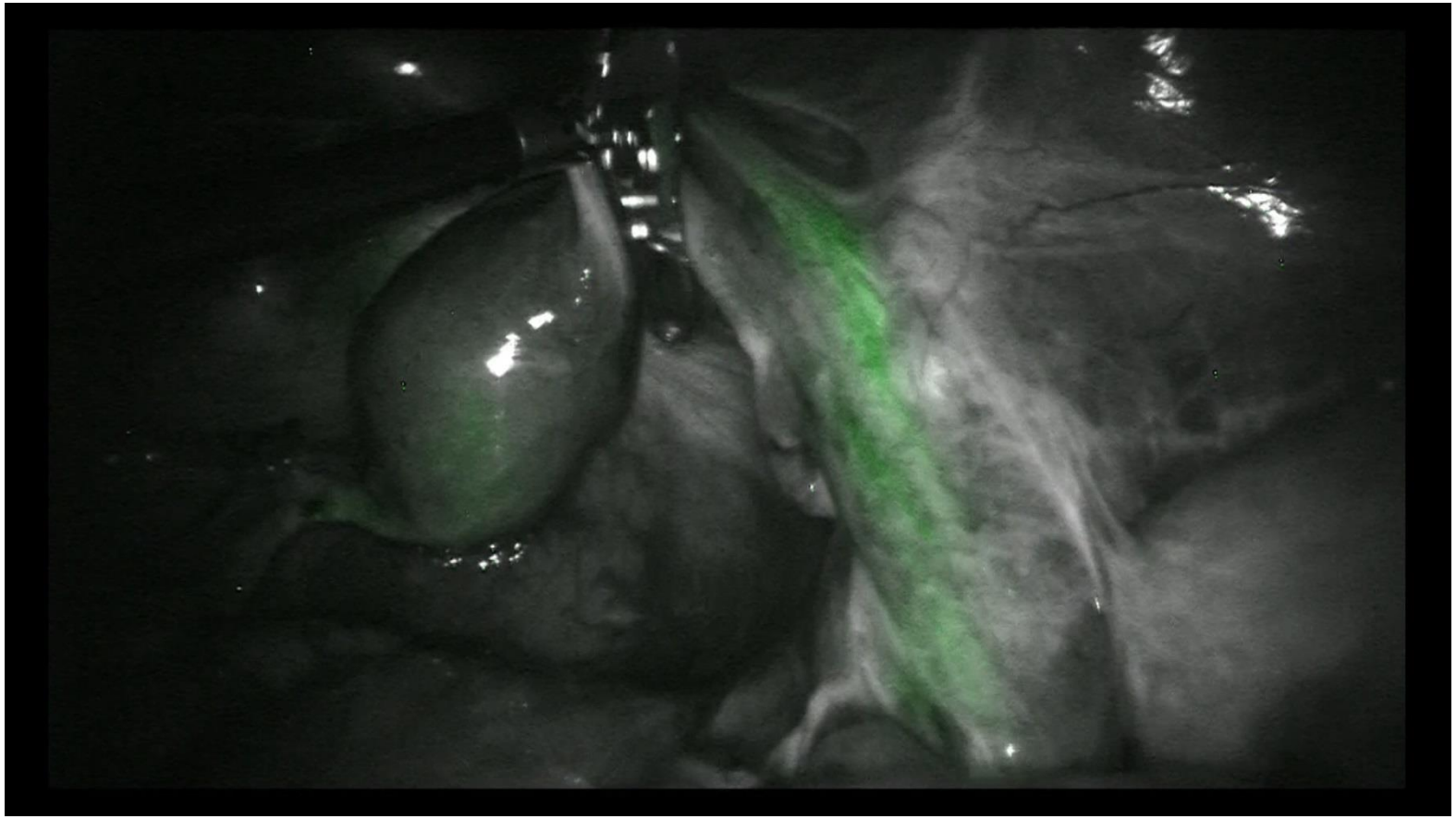


Medial inframesenteric paraaortic nodes are fed via presacral lymphatics deriving from the lower parametrial lymphatics and secondary to internal / presacral SLN

Lateral inframesenteric paraaortic nodes are fed via the lateral common iliac lymphatics deriving from from the upper parametrial lymph chain and secondary to medial ext iliac nodes

Can we define inframestenteric PA SLNs?

Separate Lymphatics via the IP-Ligaments With no Detectable Lymph Vessels to the Inframesenteric Paraaortic Area



Can we define inframestenteric PA SLNs?

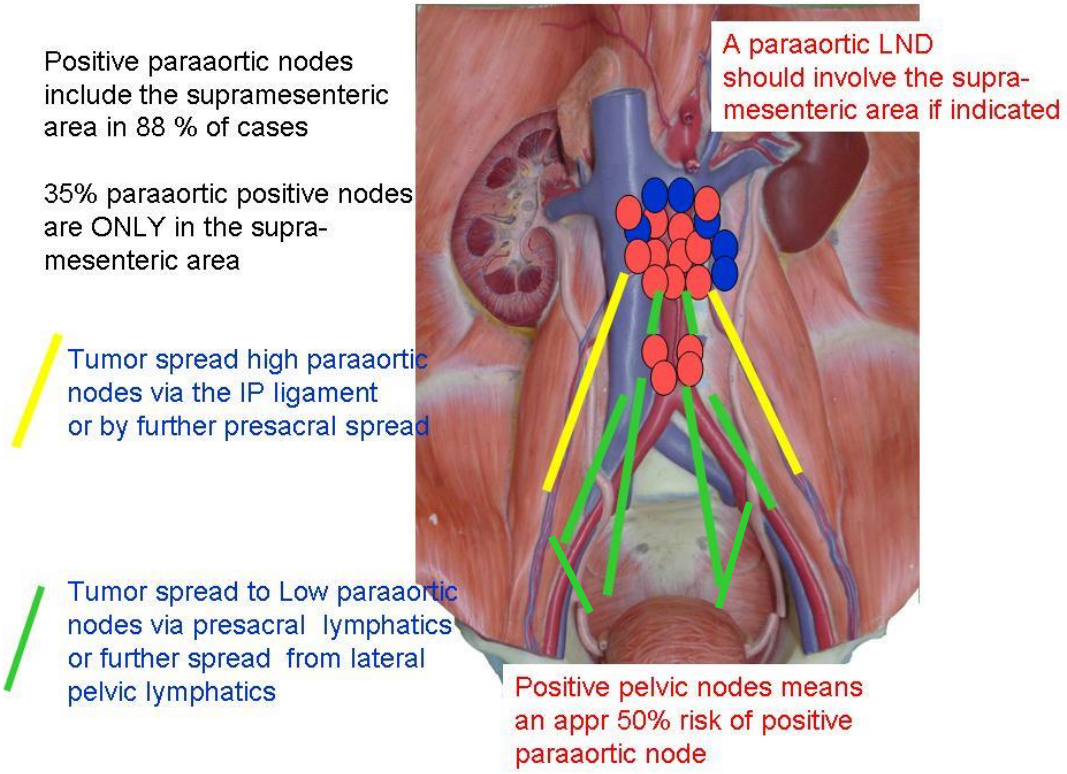
Plausible Conclusion

Inframesenteric paraaortic SLN by definition does not exist.

Supramesenteric paraaortic nodes are fed via inframesenteric nodes *as well as* via the IP-ligaments

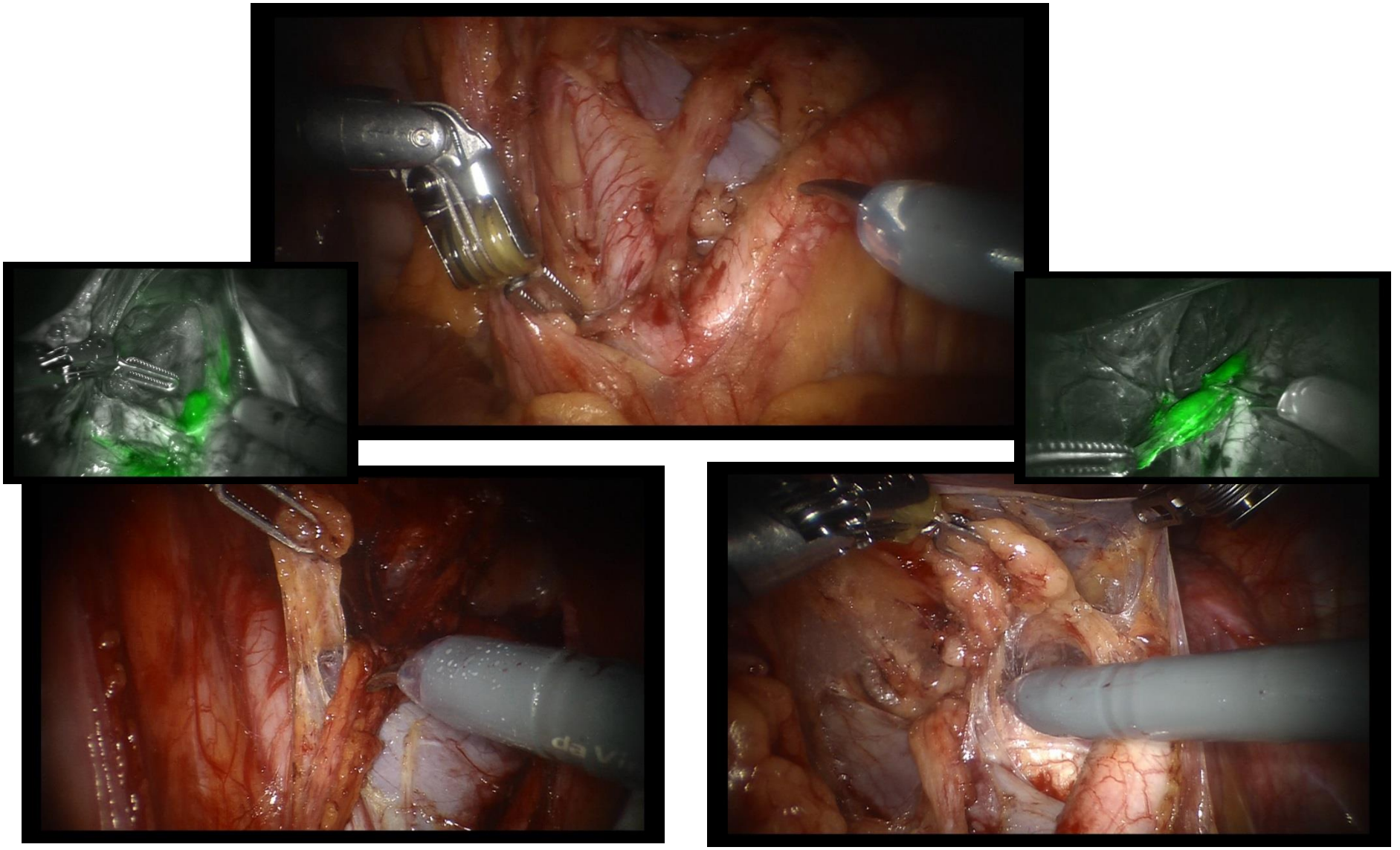
Hence, supramesenteric SLN can only be defined in the absence of inframesenteric traced nodes

Low technical succes rate for dye in IP ligaments even with fundal injection



Developing a Structured and Reproducible Surgical Algorithm

Step 1: Presacral/Internal Iliac

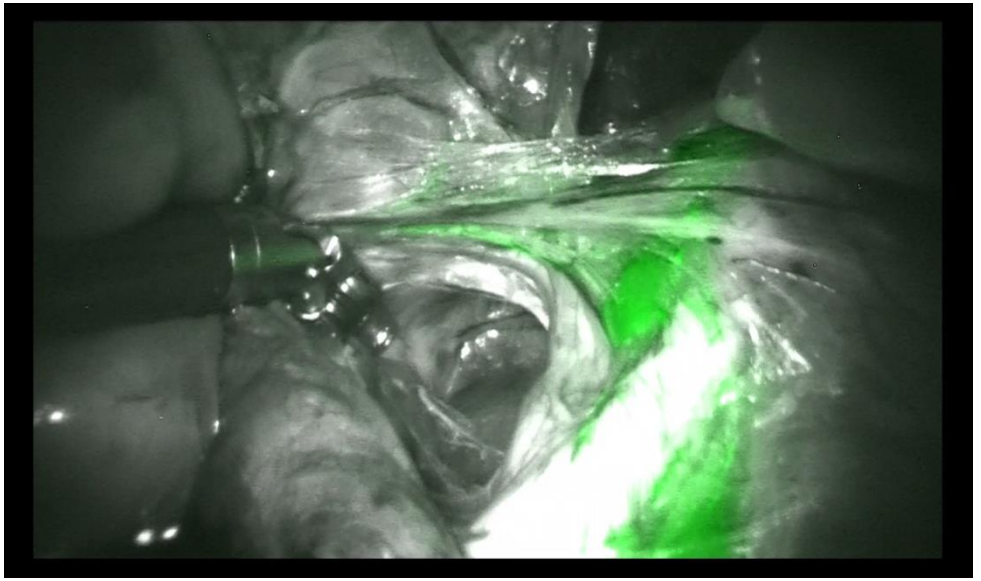


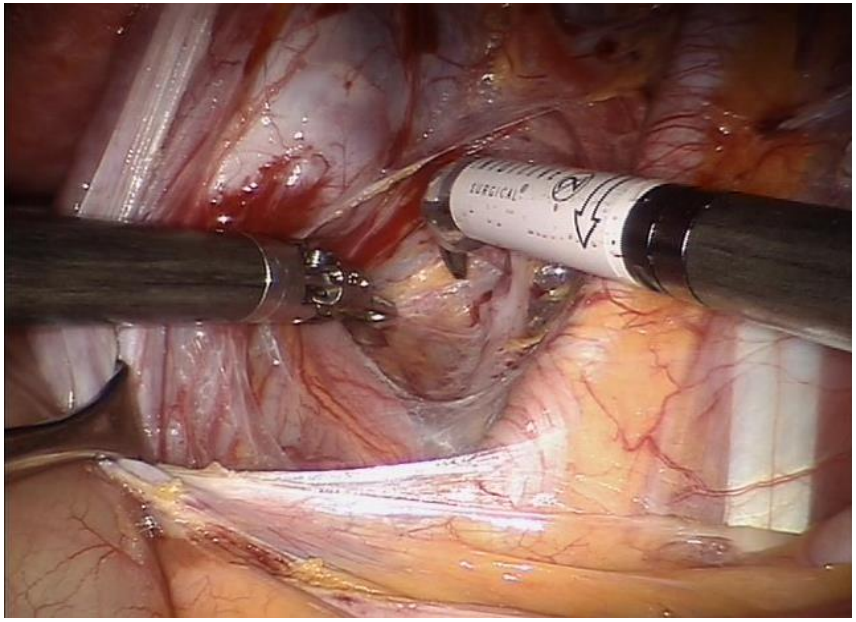
Left internal/presacral SLN

Right internal/presacral SLN

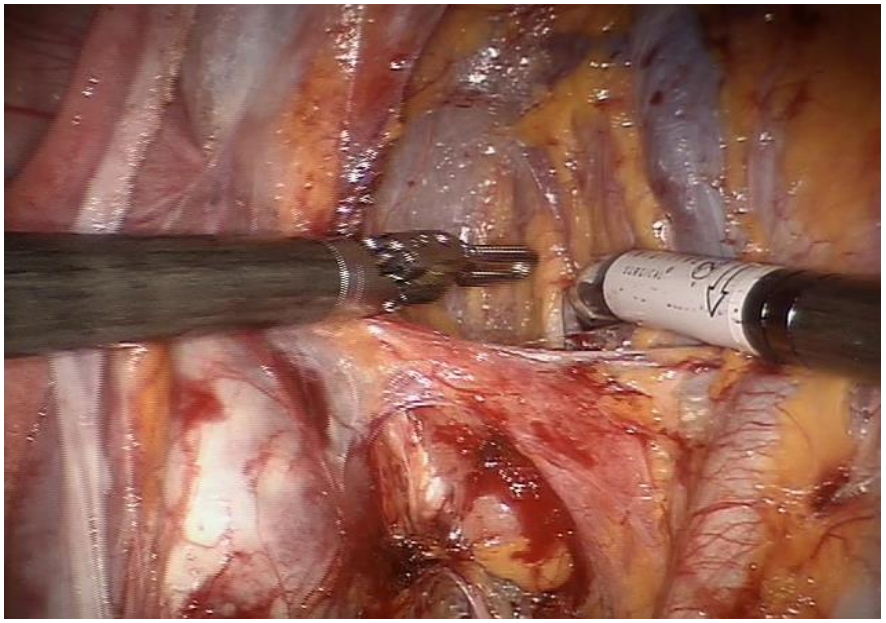
Developing a Structured and Reproducible Surgical Algorithm

Step 2: Pelvic Side Wall





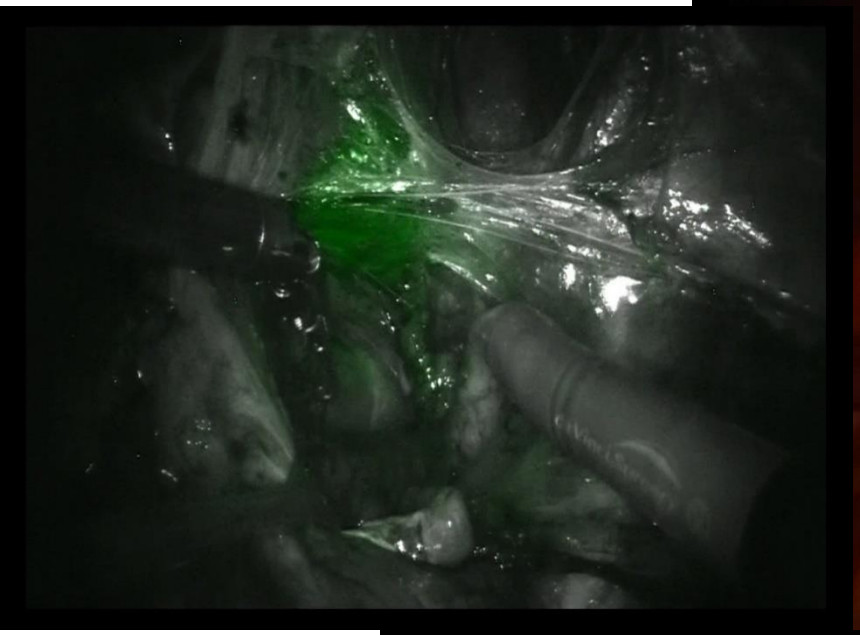
Pararectal Space

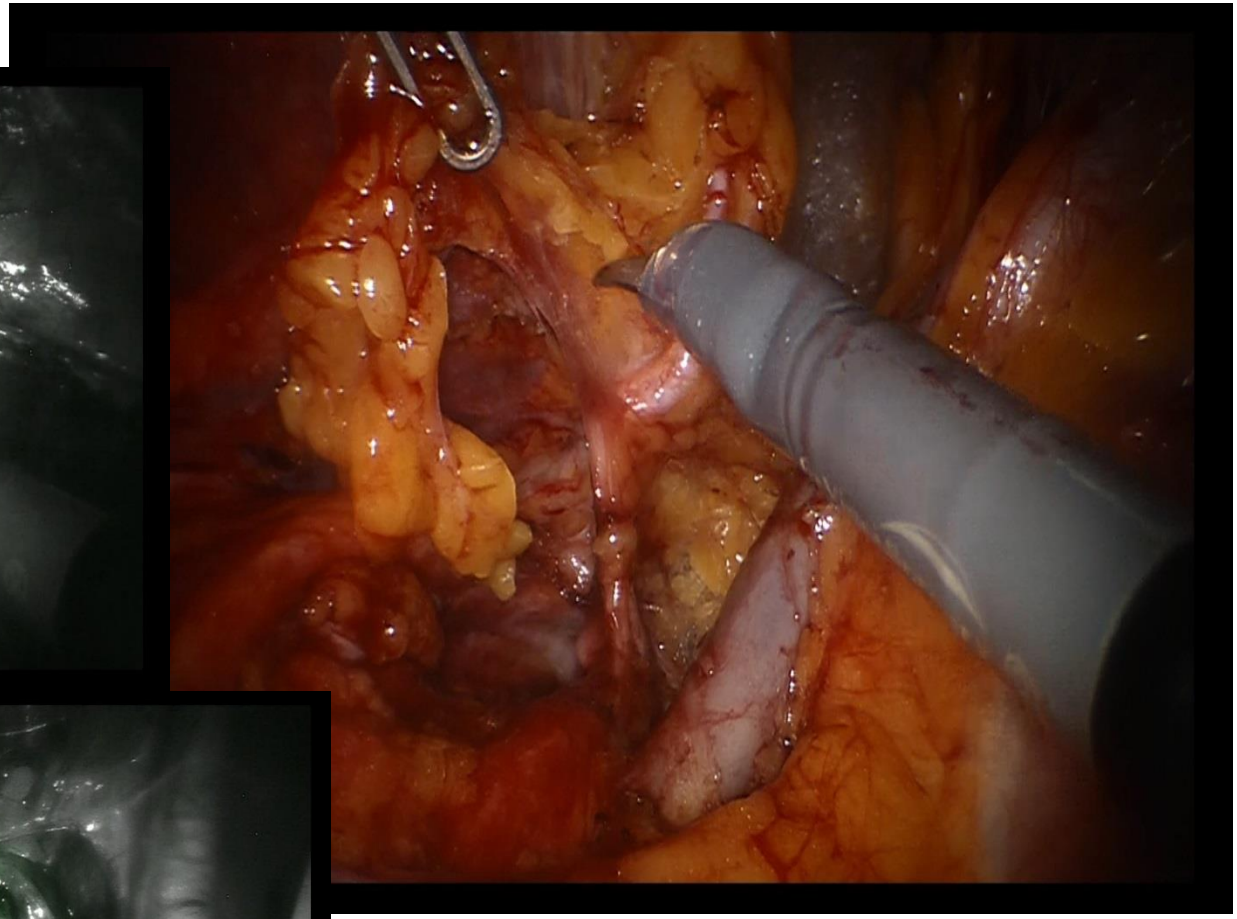


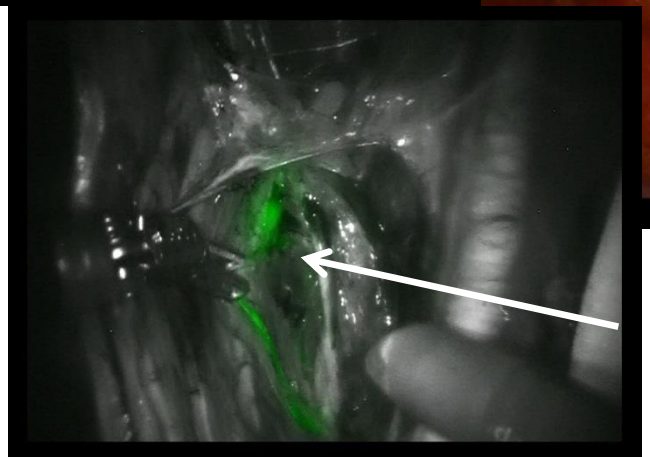
Paravesical Space

Developing a Structured and Reproducible Surgical Algorithm

Step 3: Upper Vascular Parametrium







SLN in upper parametrial tissue

Our Preparatory Work to Optimize and Standardize the SLN Concept With ICG in Endometrial Cancer

Pilot studies on lymphatic anatomy (review of recordings)

Pilot studies on injection sites, dosing, and timing

Pilot studies on bilateral detection rate with and w/o reinjection

Development of a practical reproducible surgical algorithm

Clear definition of what is a SLN + use of SLN algorithm

Prospective study on all endometrial cancers

Low risk: only SLN and upper parametria are removed

High risk: SLN, upper parametrial + full P+PA LND

Standardized Technique for SLN Endometrial Cancer

Cervical (sm+stroma) injection followed by laparoscopic visualization

Repeated cx injection ½ dose if no display of lymphatics
Uni/bilat (all op saved on video)

Fundal injection if no uptake (no need yet)

Defined surgical algorithm / surgical steps

Clear definition of SLN + suspect nodes + potent full LND if no SLN/susp nodes

Clear protocol fo nodal reports and display of local of SLN

Ultrasectioning and IHC of SLN

Detailed follow-up protocol grading of lymphedema,
lymphocysts, etc, etc

Biobanking of tumor, nodes, and serum

Particular Questions We Want to Address

The obvious ones; false neg sens spec detect rate, generalizability, etc

Do we need to visualize SLN from both upper/ lower parametrial lymphatics?

Strict definition of SLN ------ more uniform spread pattern?

Does removal of upper parametrium increase diagnosis of metastatic disease?

Confirm theory; no inframesenteric PA SLN?

Does PA LND increase lymphedema (comp with parallel study on cx ca)?

Does a sharp SLN on low-risk EC give lymphatic morbidity?

Will % pos SLN on low-risk EC correspond to what's expected?

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Thank You for Your attention

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