Gynecologic Cancer InterGroup
Cervix Cancer Research Network

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

SLN mapping in cervical cancer

Dr Marie Plante
Gynecologic Oncologist
L'Hôtel-Dieu de Québec
Laval University

UNIVERSITÉ LAVAL

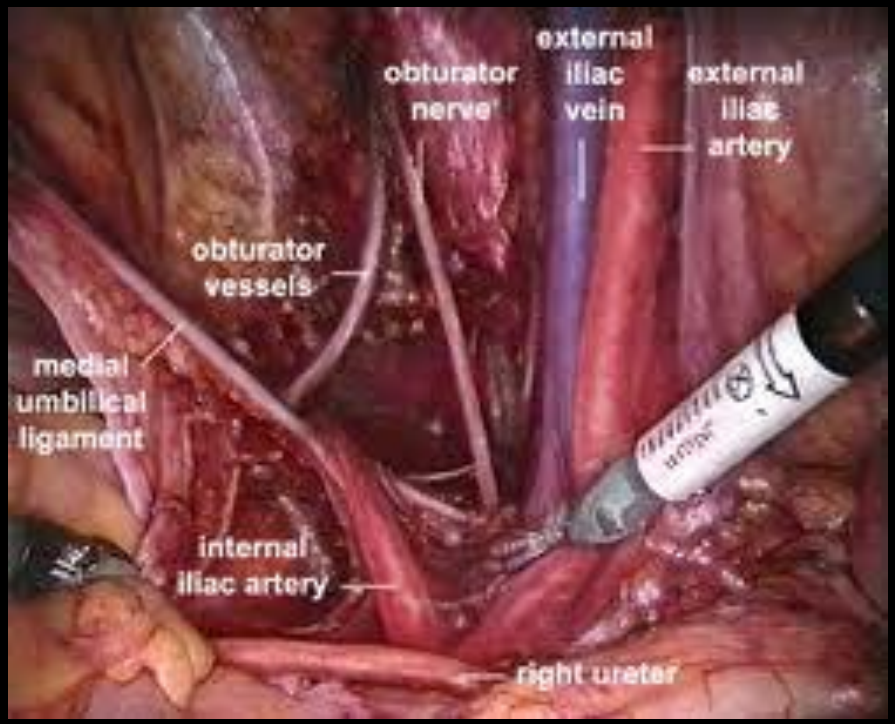
CHU de Québec

Cervix Cancer Education Symposium, January 2017, Mexico

LN status

- Part of the surgical staging of all solid tumors
- One of the most important prognostic factor
  - Predictor of outcome
  - Need for adjuvant treatment

LN dissection



Pelvic LND

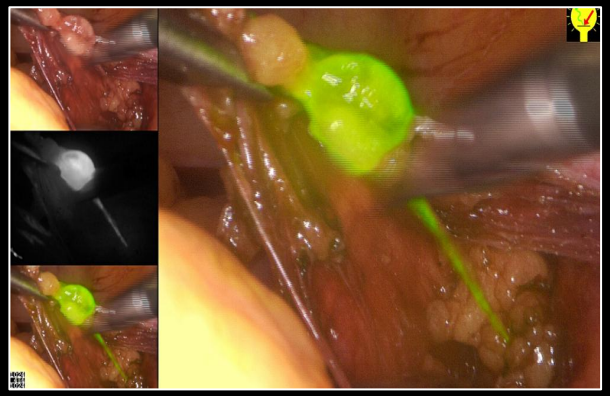
Para-aortic LND

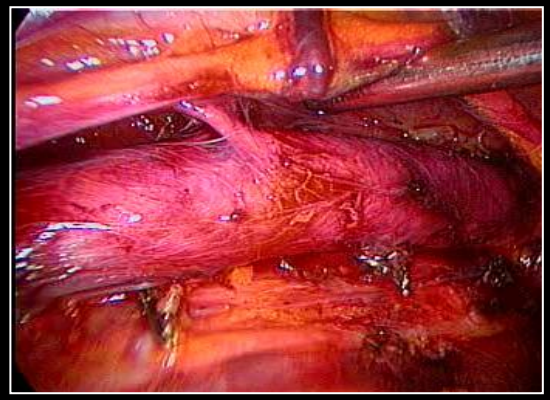
LN dissection

- **Morbidity of the LN dissection**
  - Nerve / vessels damage
  - Lymphoedema, lymphocele
  - Increased OR time
  - Obese / elderly patient population

SLN mapping

- Logical / intelligent compromise
  - Between no nodes at all and complete LND





VOLUME 29 · NUMBER 13 · MAY 1 2011

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Bilateral Negative Sentinel Nodes Accurately Predict Absence of Lymph Node Metastasis in Early Cervical Cancer: Results of the SENTICOL Study

Fabrice Lécuru, Patrice Mathevet, Denis Querleu, Eric Leblanc, Philipe Morice, Emile Daraï, Henri Marret, Laurent Magaud, Florence Gillaizeau, Gilles Chatellier, and Daniel Dargent†

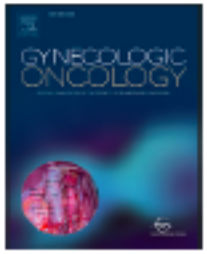
No false negative results were observed in the 104 patients (76.5%) in whom SLN were identified bilaterally

Gynecologic Oncology 139 (2015) 559–567

Contents lists available at ScienceDirect

Gynecologic Oncology

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



Review Article

The sentinel node procedure in early stage cervical cancer, taking the next step; a diagnostic review

Casper Tax [a,*], Maroeska M. Rovers [a,b], Corine de Graaf [c], Petra L.M. Zusterzeel [c], Ruud L.M. Bekkers [c]

[a] Radboud University Medical Centre, Radboudumc Institute for Health Sciences, Department of Operating Rooms, P.O. Box 9101, 6500 HB Nijmegen, the Netherlands
[b] Radboud University Medical Centre, Radboudumc Institute for Health Sciences, Department of Health Evidence, P.O. Box 9101, 6500 HB Nijmegen, the Netherlands
[c] Radboud University Medical Centre, Radboudumc Institute for Health Sciences, Department of Gynaecology, P.O. Box 9101, 6500 HB Nijmegen, the Netherlands

Conclusions. Early stage cervical cancer patients (FIGO IA2, IB1, IIA primary tumor size < 40 mm) who have no suspicious pre-, and per-operative lymph nodes, and have bilateral negative SLNs after ultra staging, have a residual risk of 0.08% (1/1257) on occult metastases. On the basis of these results we recommend not to perform a full PLND in these patients.

Gynecologic Oncology xxx (2016) xxx–xxx

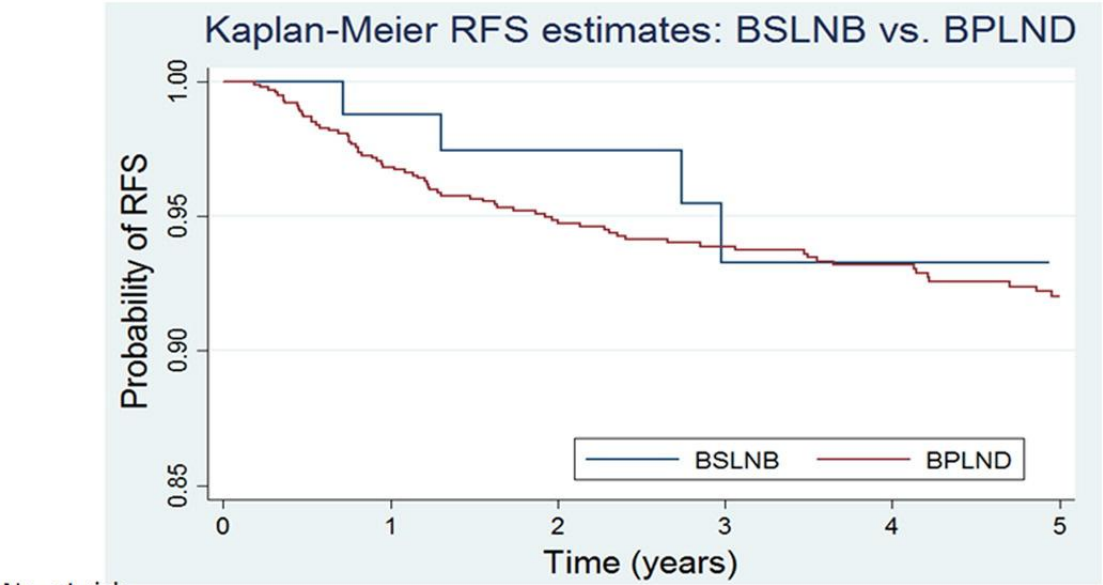
Contents lists available at ScienceDirect

Gynecologic Oncology

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

Can sentinel lymph node biopsy replace pelvic lymphadenectomy for early cervical cancer?

Genevieve K. Lennox [a], Allan Covens [a,b,*]



No. at risk						
BSLNB	110	78	64	43	34	9
BPLND	1078	917	813	715	612	485

Node negative
BPLND: 1078
BSLNB : 110

NCCN guidelines

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

CLINICAL STAGE[b]	PRIMARY TREATMENT (NON-FERTILITY SPARING)	
Stage IB1 and Stage IIA1	Radical hysterectomy + pelvic lymph node dissection[h] (category 1) ± para-aortic lymph node sampling (category 2B) (Consider SLN mapping)[n,l]	See Surgical Findings (CERV-5)
	or Pelvic EBRT[j,k] + brachytherapy (total point A dose: 80–85 Gy)[l,k] ± concurrent cisplatin-containing chemotherapy[n]	See Surveillance (CERV-10)
Stage IB2 and Stage IIA2 (also see CERV-6 for additional recommendations for non-primary surgery patients)	Definitive pelvic EBRT[k] + concurrent cisplatin-containing chemotherapy[n] + brachytherapy (total point A dose ≥85 Gy)[l,k] (category 1 for primary chemoradiation)	See Surveillance (CERV-10)
	or Radical hysterectomy + pelvic lymph node dissection[h] ± para-aortic lymph node sampling (category 2B)	See Surgical Findings (CERV-5)
	or Pelvic EBRT[k] + concurrent cisplatin-containing chemotherapy[n] + brachytherapy[l,o,k] + adjuvant hysterectomy[p] (category 3)	See Surveillance (CERV-10)

NCCN guidelines

National Comprehensive Cancer Network®

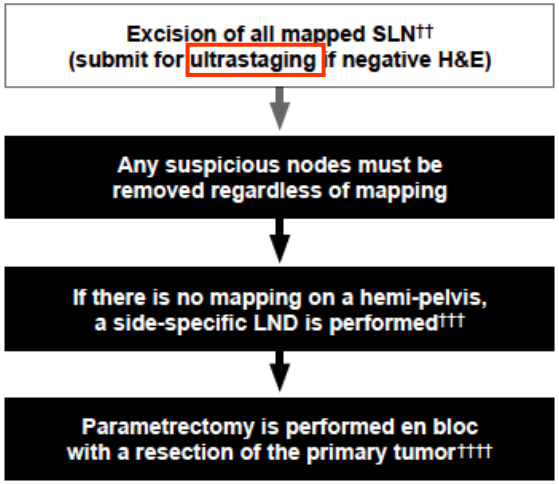
NCCN Guidelines Version 1.2017
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

The key to a successful SLN mapping is 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 3).

Figure 3: Surgical/SLN Mapping Algorithm for Early-Stage Cervical Cancer†



H&E: Hematoxylin and eosin staining
LND: Lymphadenectomy
SLN: Sentinel lymph node

NCCN guidelines

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2017
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF EVALUATION AND SURGICAL STAGING

Sentinel Lymph Node Mapping for Cervical Cancer:

- SLN mapping as part of the surgical management of select stage I cervical cancer is considered in gynecologic oncology practices worldwide. While this technique has been used in tumors up to 4 cm in size, the best detection rates and mapping results are in tumors less than 2 cm.[9-12] This simple technique utilizes a direct cervical injection with dye or radiocolloid Technetium-99 (99Tc) into the cervix, usually at 2 or 4 points as shown in Figure 1 (below). The SLNs are identified at the time of surgery with direct visualization of colored dye, a fluorescent camera if indocyanine green (ICG) was used, or a gamma probe if 99Tc was used. SLNs following a cervical injection are commonly located medial to the external iliac vessels, ventral to the hypogastric vessels, or in the superior part of the obturator space (Figure 2). SLNs usually undergo ultrastaging by pathologists, which allows for higher detection of micrometastasis that may alter postoperative management.[2,13]

Figure 1: Options of SLN Cervical Injection Sites†

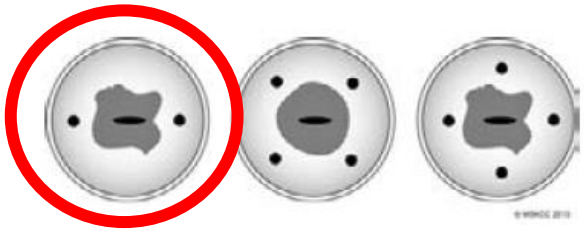
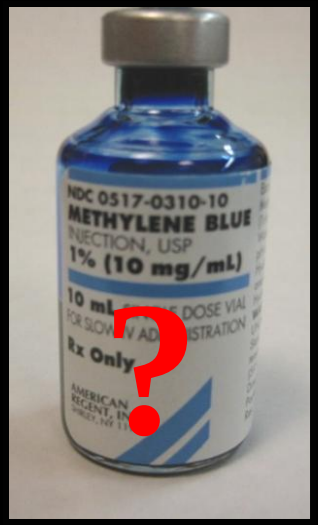


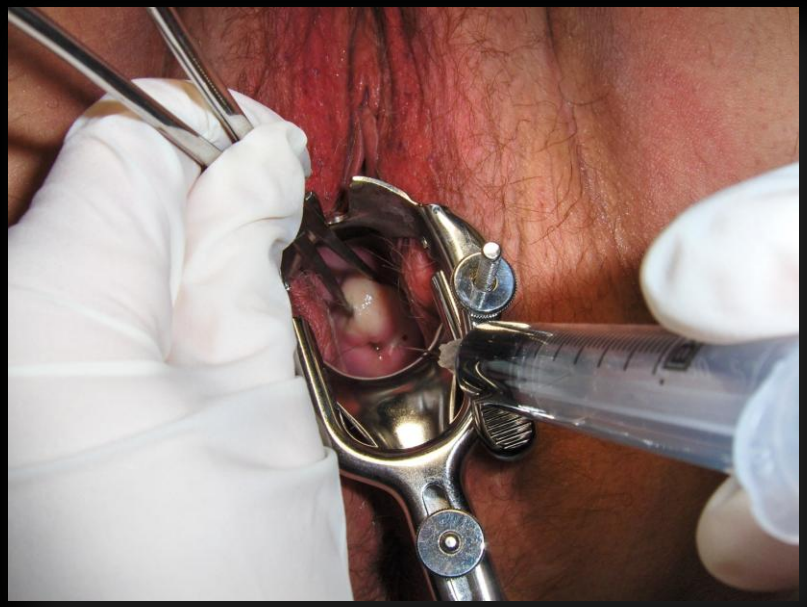
Figure 2: SLNs (blue, arrow) After Cervical Injection Are Commonly Located Medial to the External Iliac, Ventral to the Hypogastric, or in the Superior Part of the Obturator Space†

SLN mapping

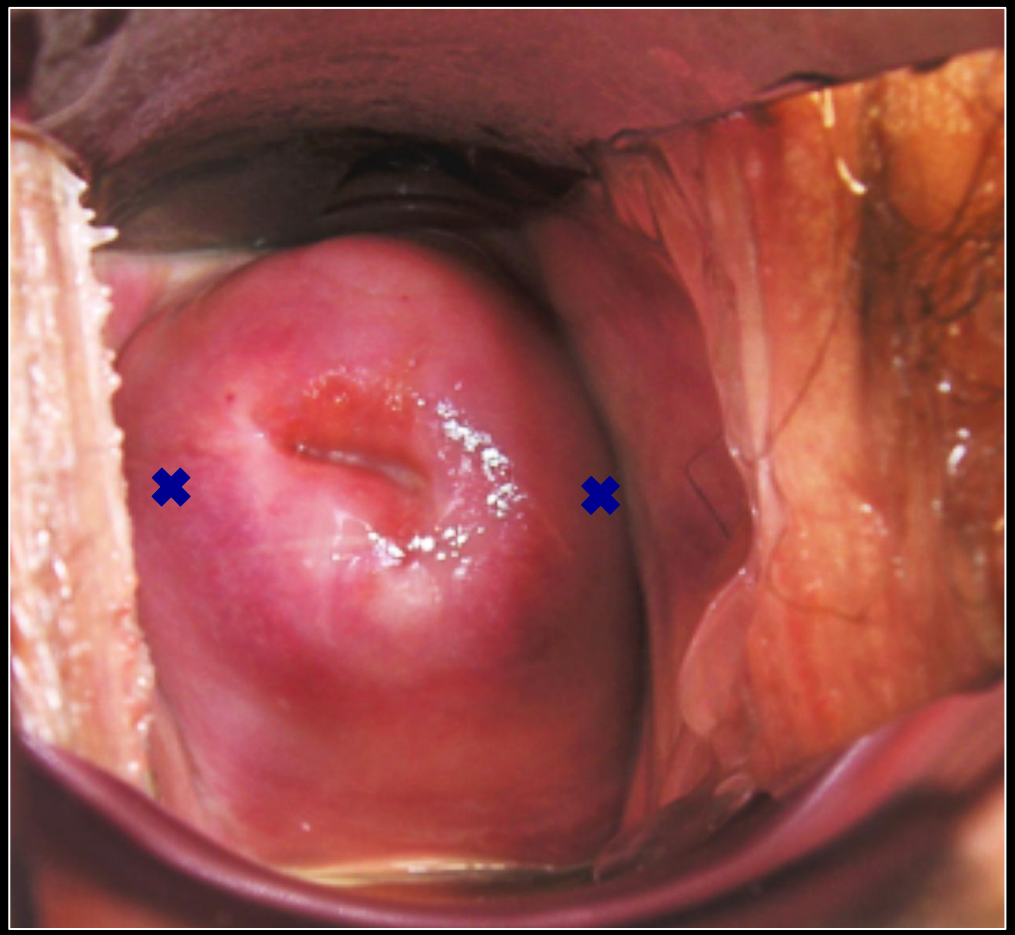
- Tracers
  - Blue dye
  - Tc-99
  - ICG

Blue Dye

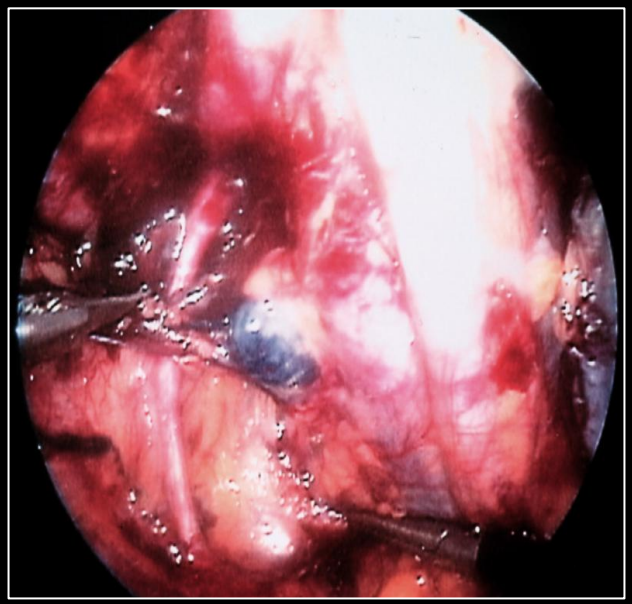


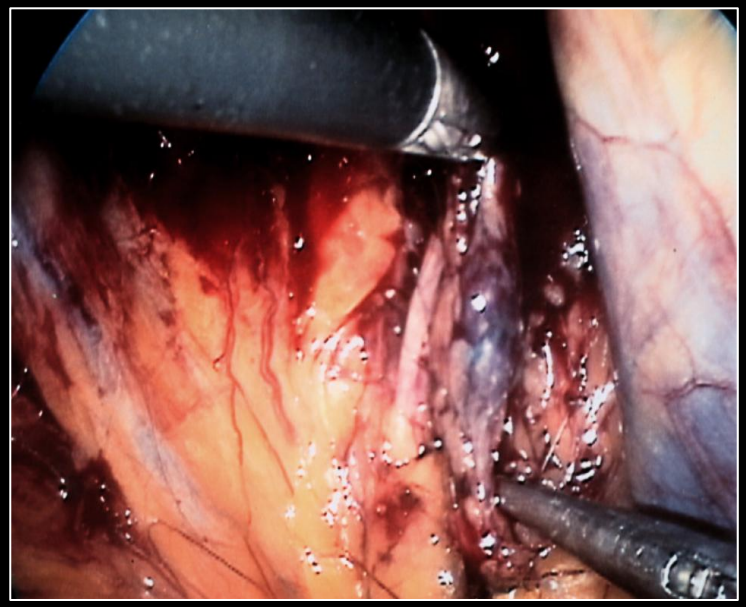


Blue Dye

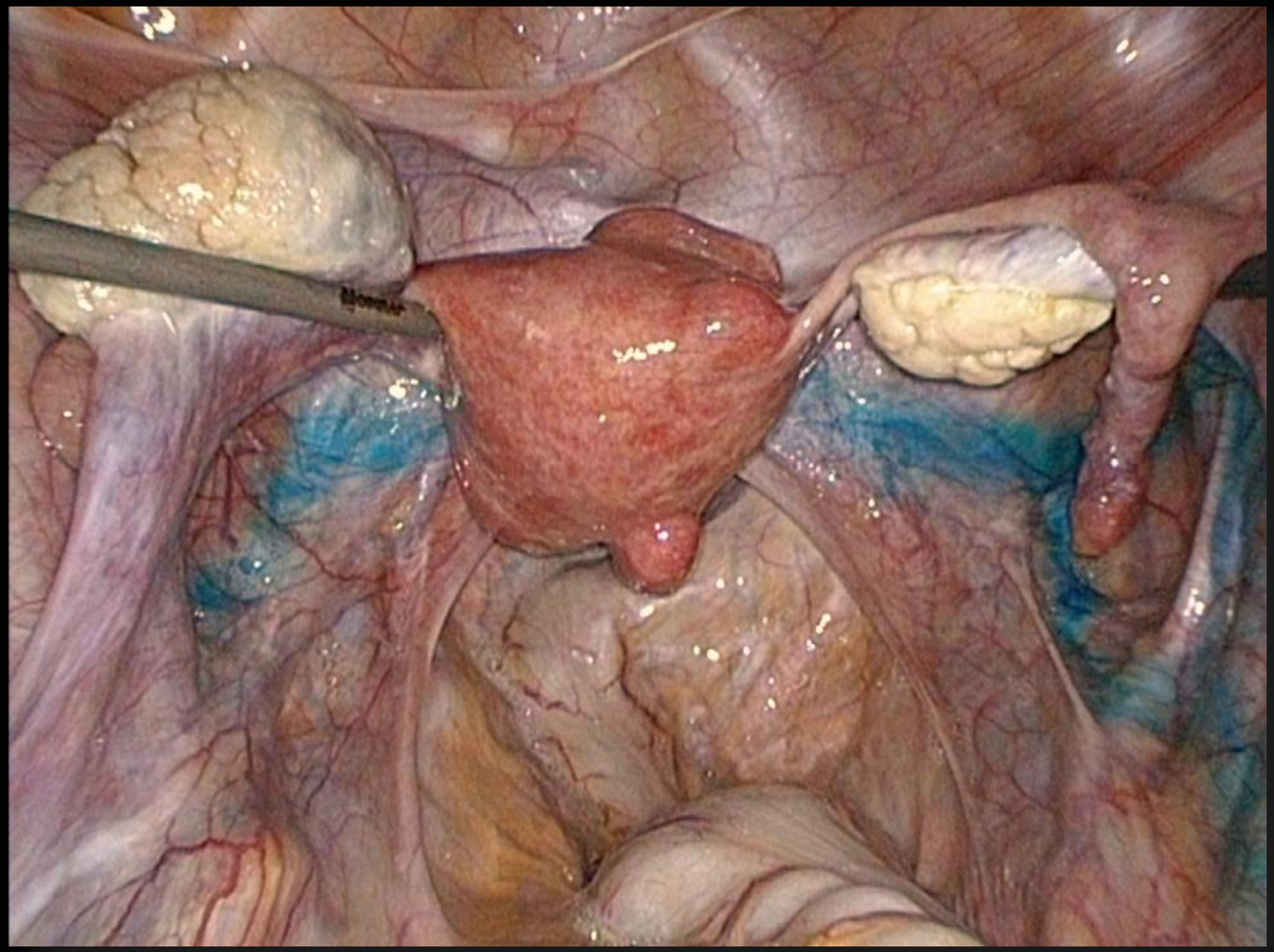


Blue Dye

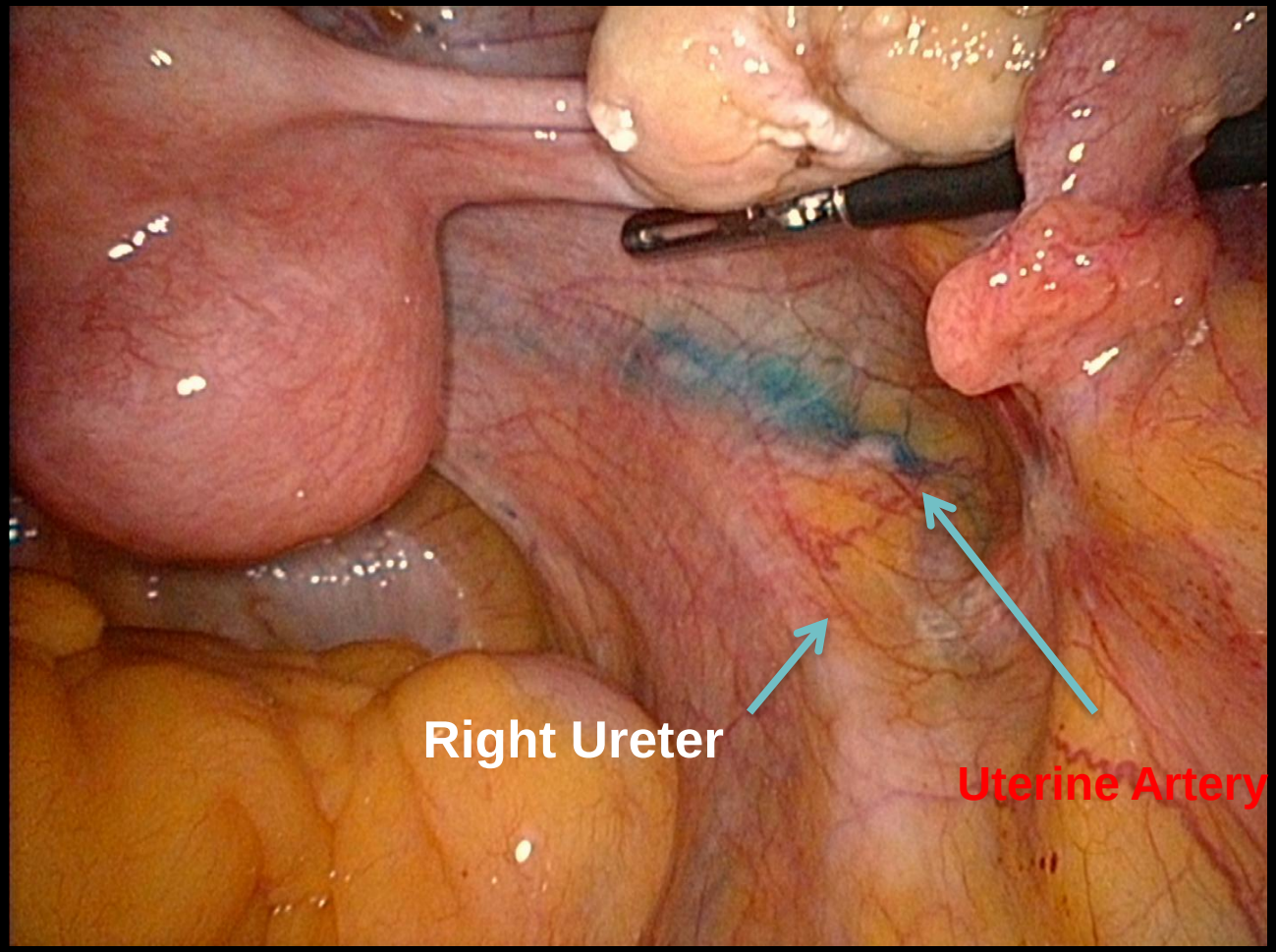




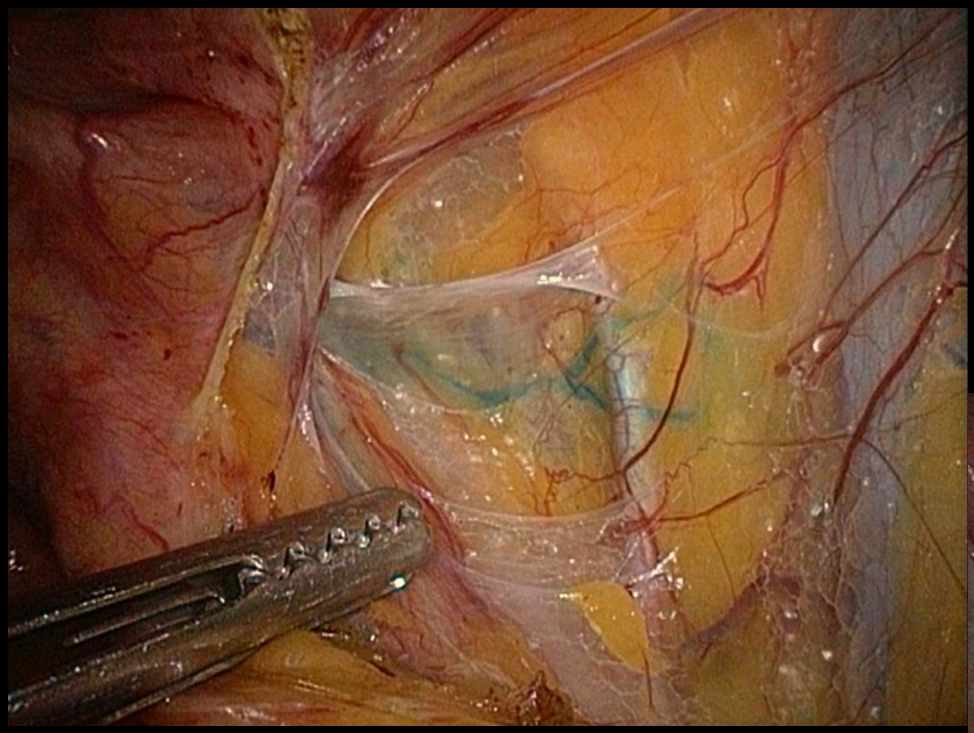
Sentinel node mapping

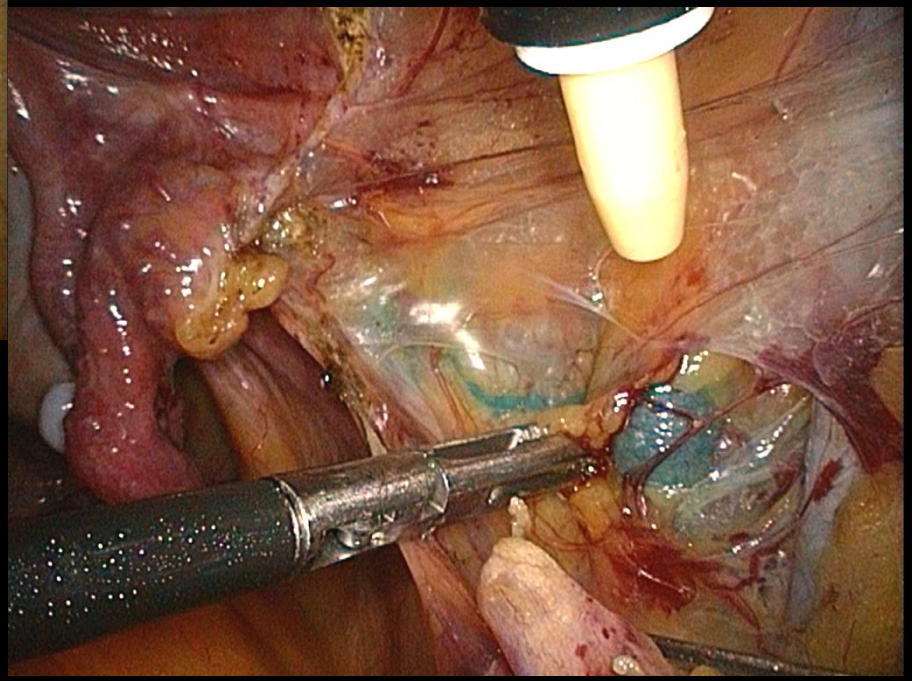


Sentinel node mapping



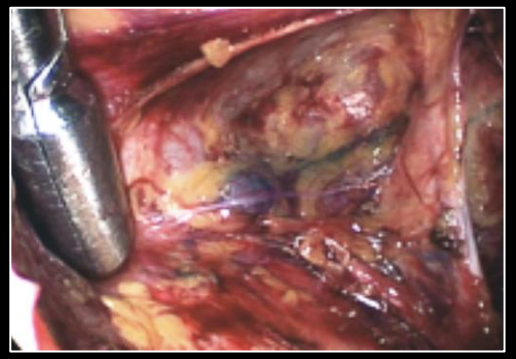
Sentinel node mapping



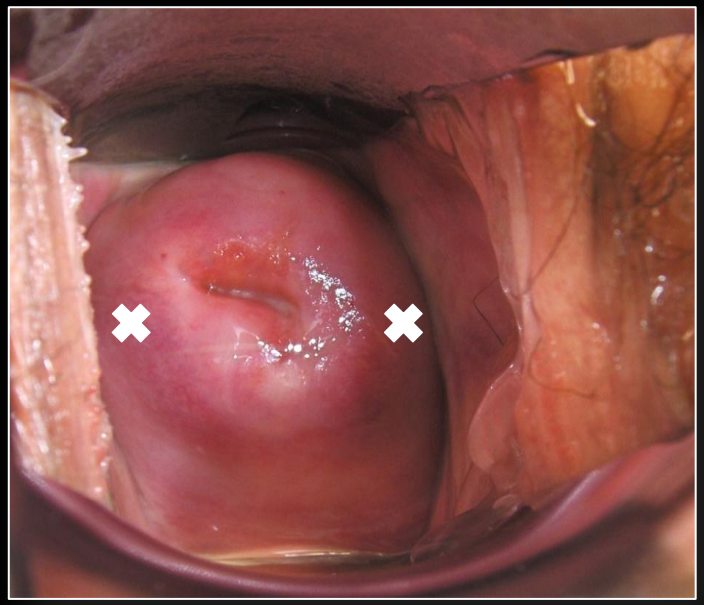


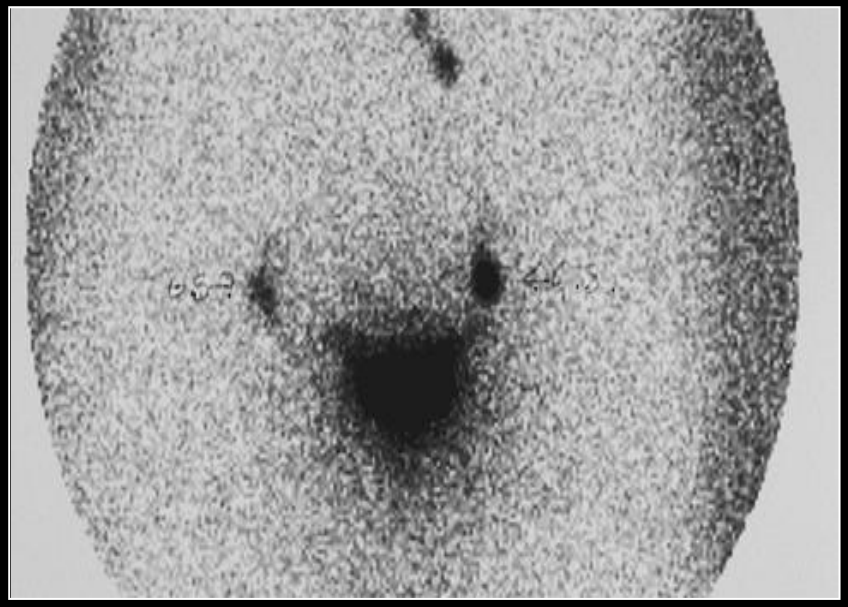
Blue Dye

- Cheap and easy to inject
- Rapid transit to nodes
- Leakage
- Blood less dissection
- Less reliable in obese patients
- Allergic reaction (1-2%)



Technetium - 99

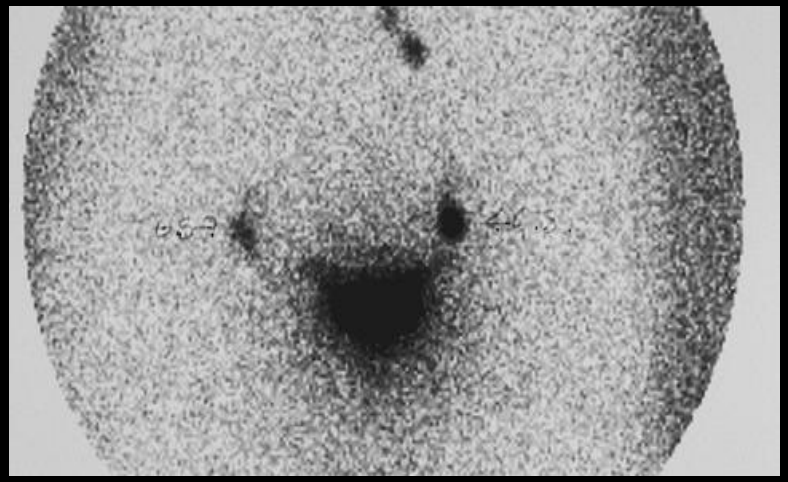


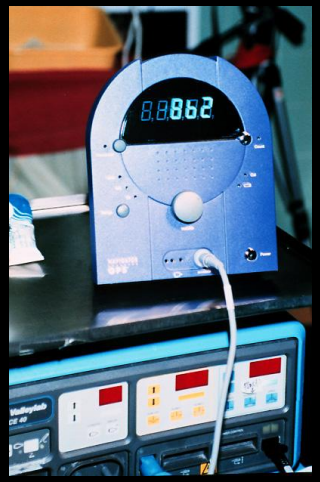


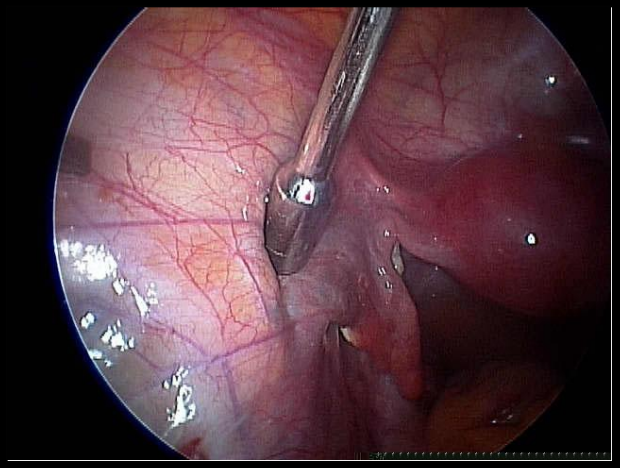
Intracervical injection
2 cc, 3 and 9 o'clock

- **In nuclear medicine**
- **The morning of surgery**
- **Lymphoscintigram**
- **20-30 min later**

Technetium - 99







Technetium - 99

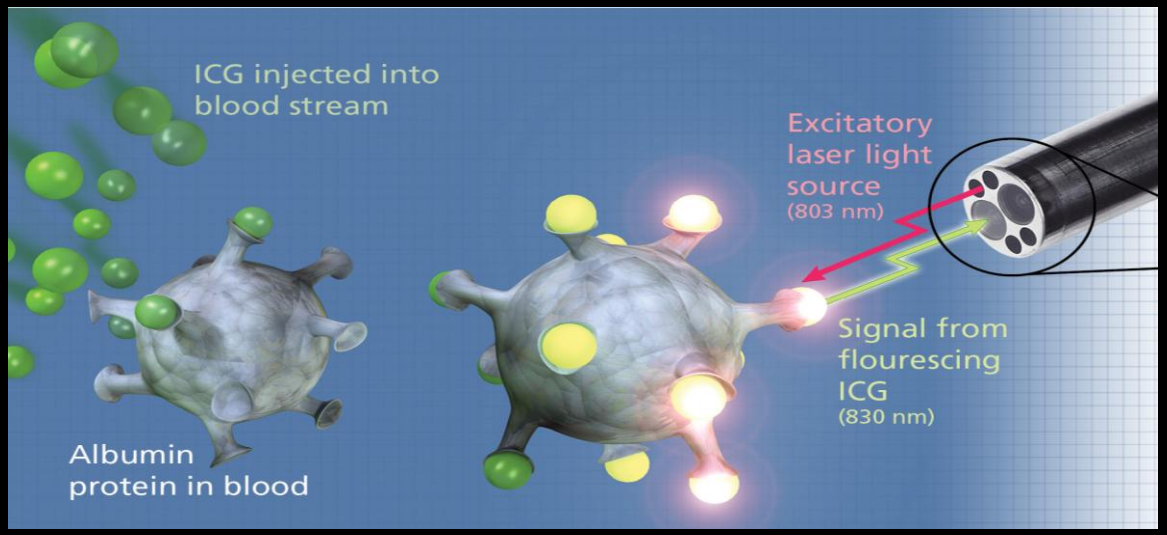
- Semi-quantitative method (count)
- Ex-vivo confirmation
- Preop LSG pictures
- Probably the “gold standard” method
- But…

Technetium - 99

- Patients' concerns vs radioactive agent
- Availability of Tc-99
- Coordinating injection times in nuclear medicine suite vs OR slate
- Wait time for the LSG
- Need for gamma probe and gamma counter
- Costly

IndoCyanine Green (ICG)

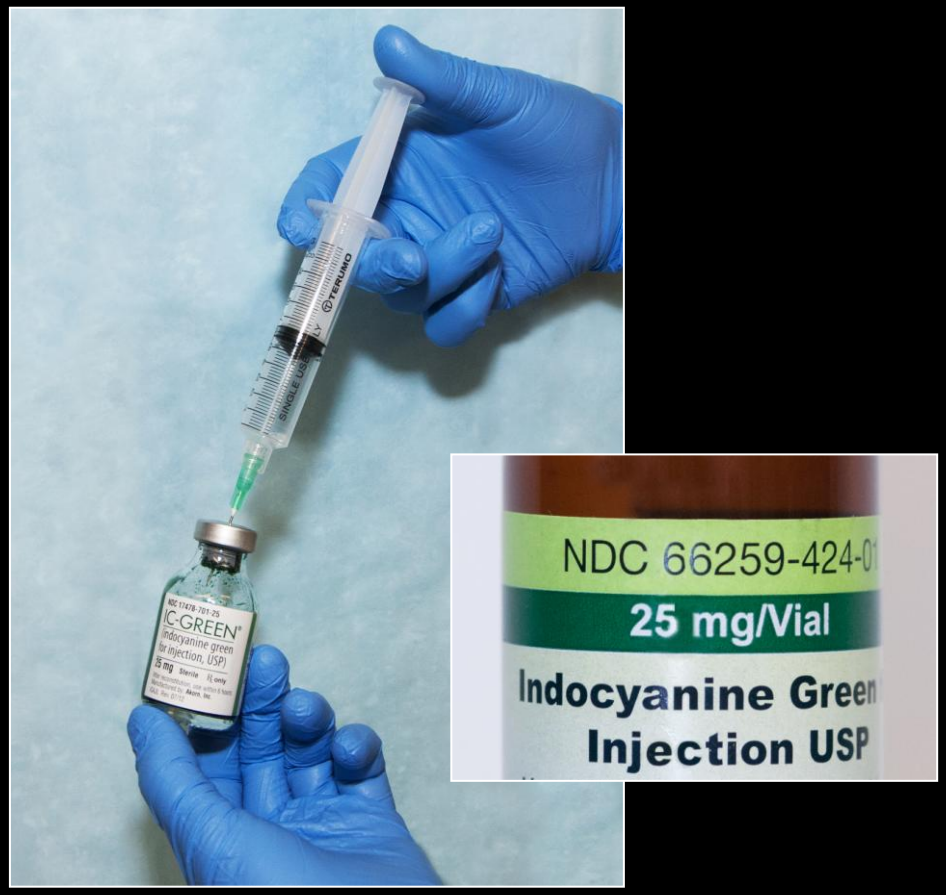
- Developed by KODAK (1950)
- Protein-bound (albumin)
- Hepato-biliary excretion
- Laser illumination (803 nm)



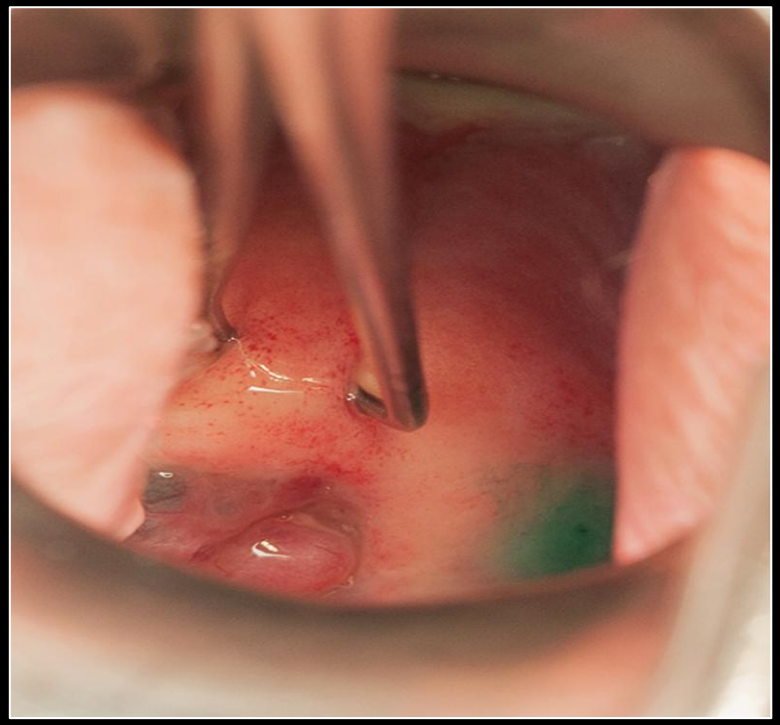
Fluorescence imaging (ICG)

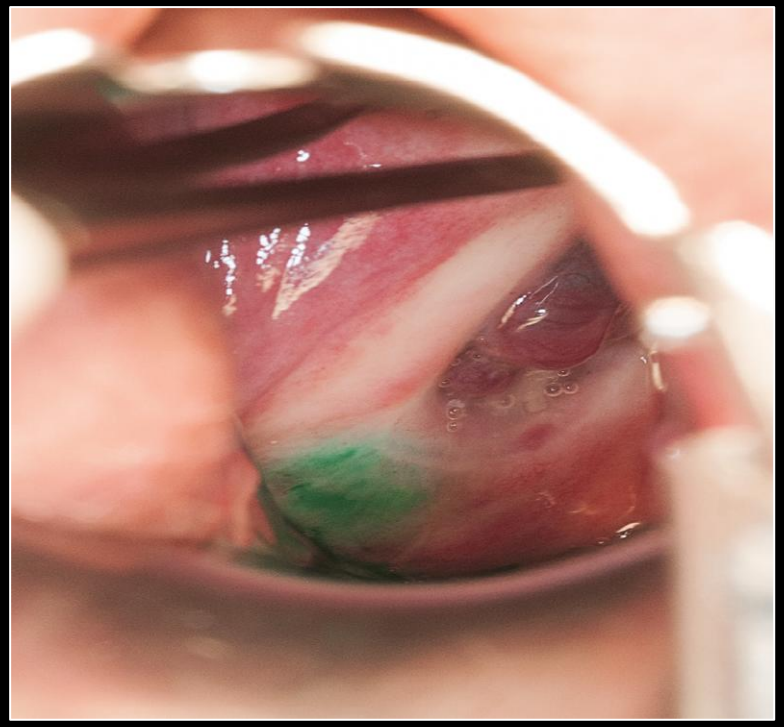
- Variety of applications
  - Vascular anatomy
  - Anastomosis integrity
  - Plastic reconstructive surgery
  - Wound care
  - Acute care surgery/trauma injuries
  - Oncology
    - SLN mapping

ICG preparation



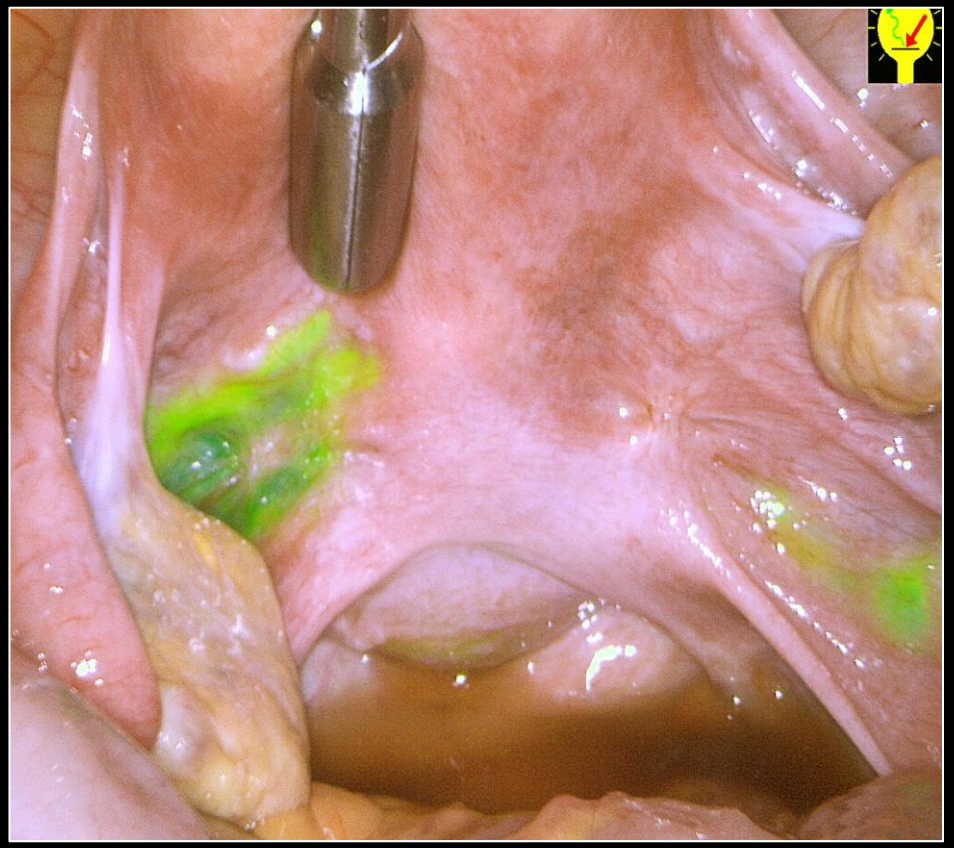
ICG injection





Intraoperative cervical injection
2cc, at 3 and 9 o'clock
25-gauge spinal needle

ICG SLN mapping

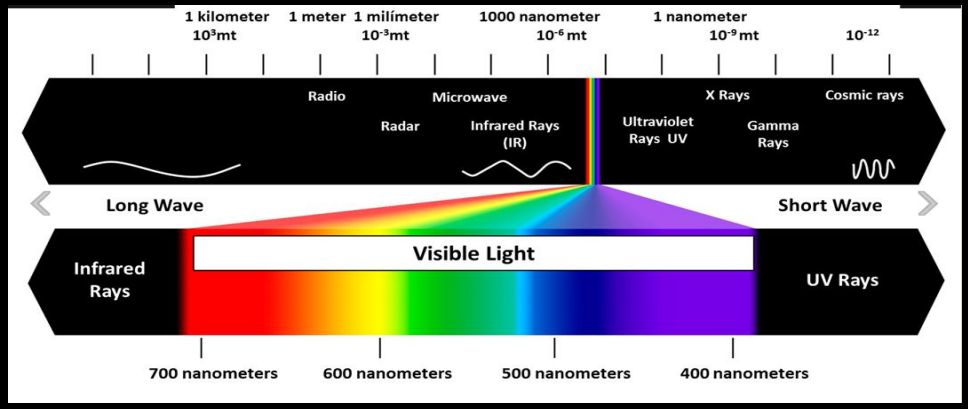


Endoscopy Unit

Endoscopy Unit

0 or 30º scope

“pinpoint” button



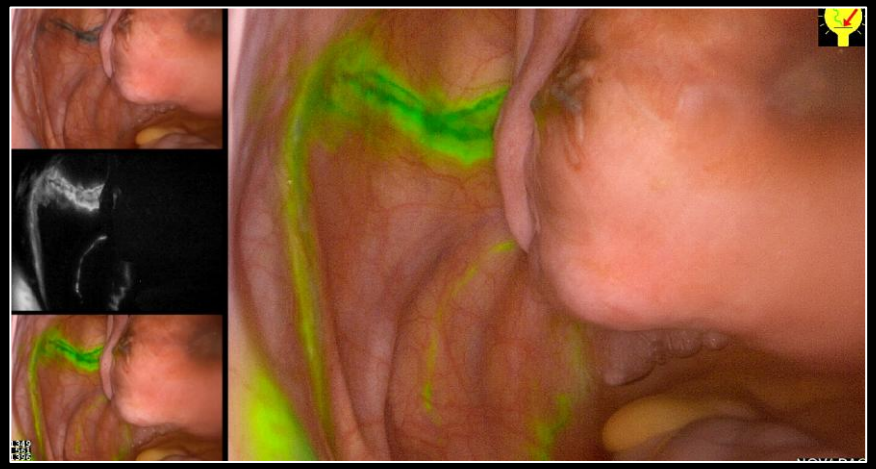
activates NIR mode

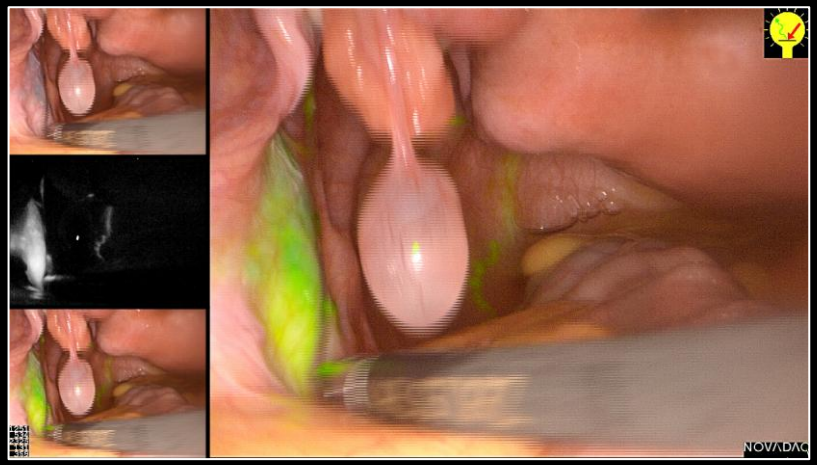
ICG SLN mapping

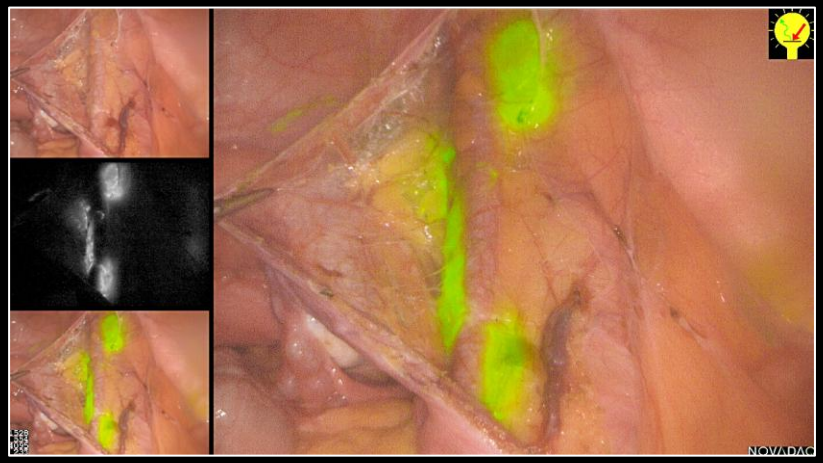
Normal mode

Spy mode

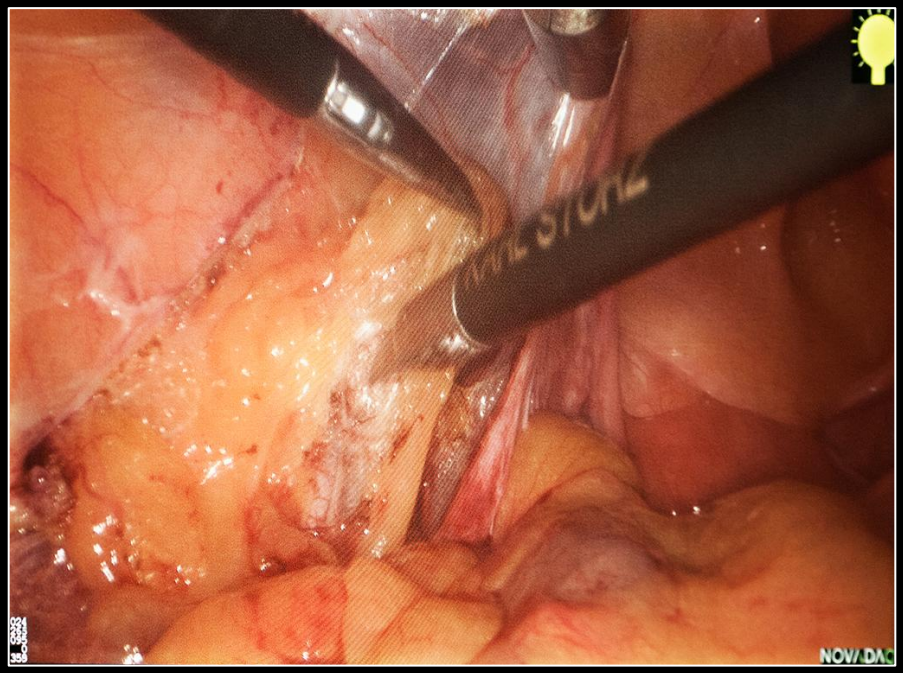
NIR mode

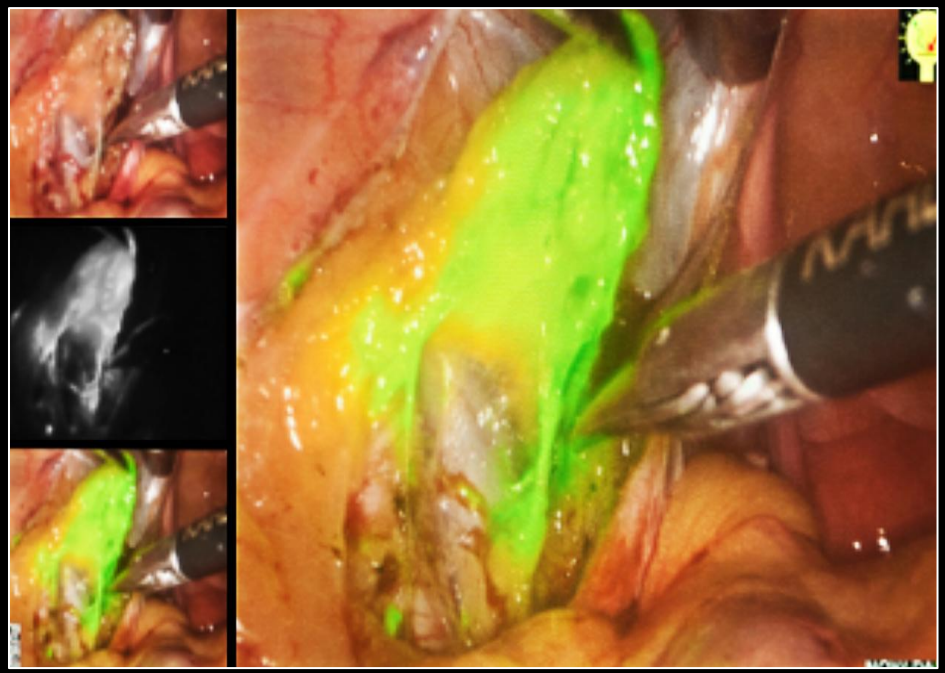






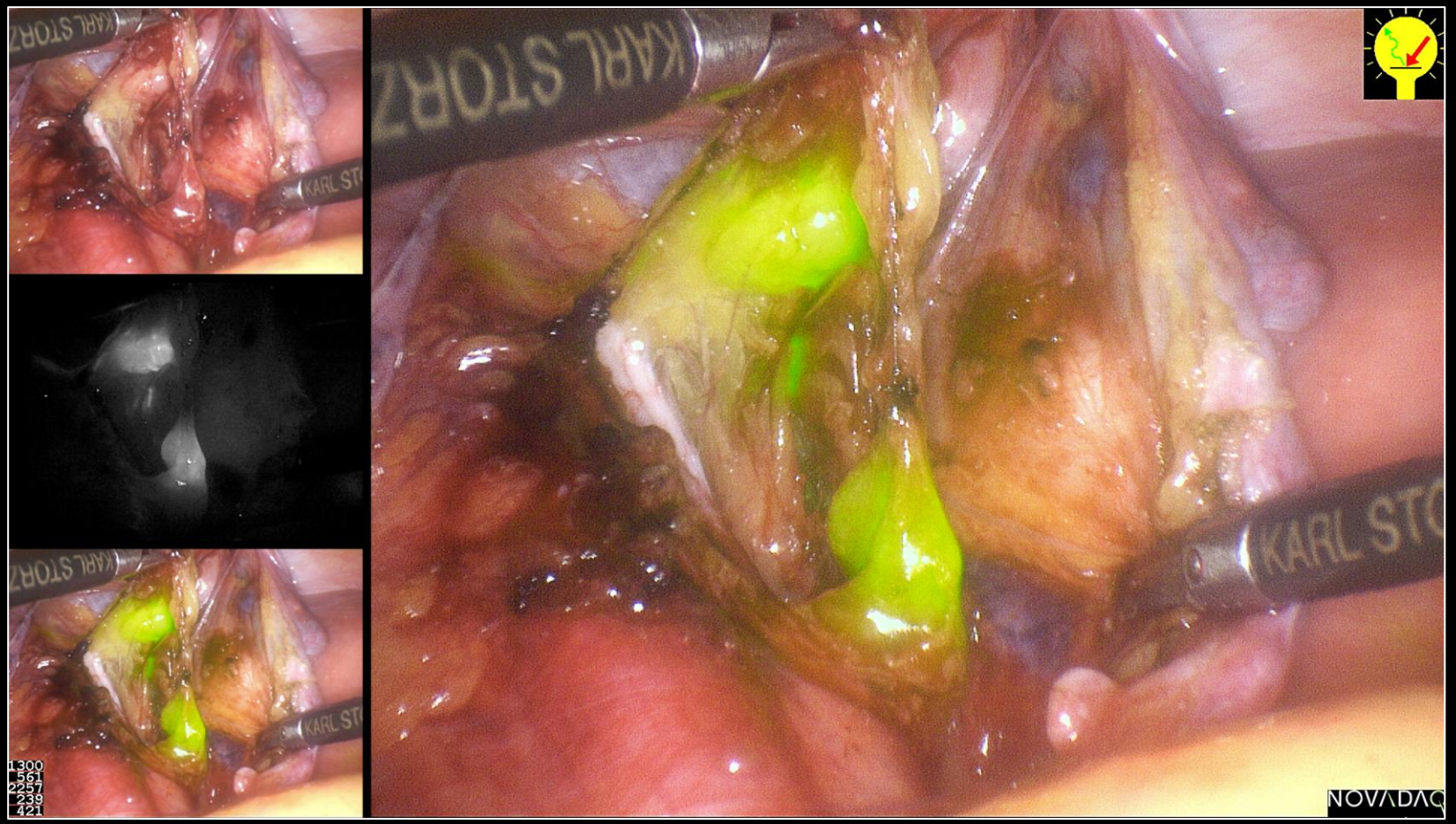
ICG SLN mapping



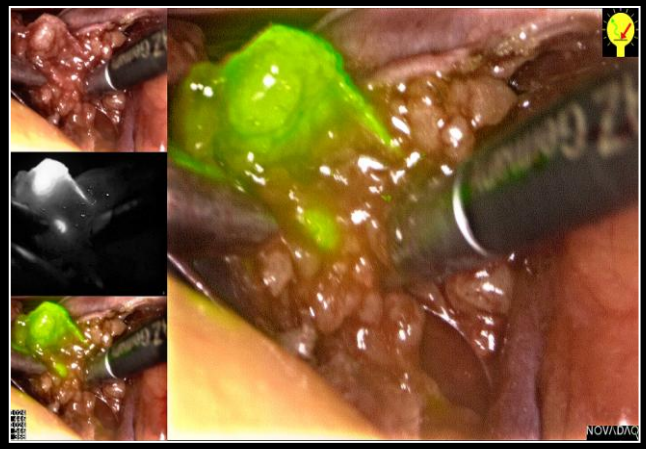


Maintains normal tissue color
Can switch mode as often as needed

ICG SLN mapping

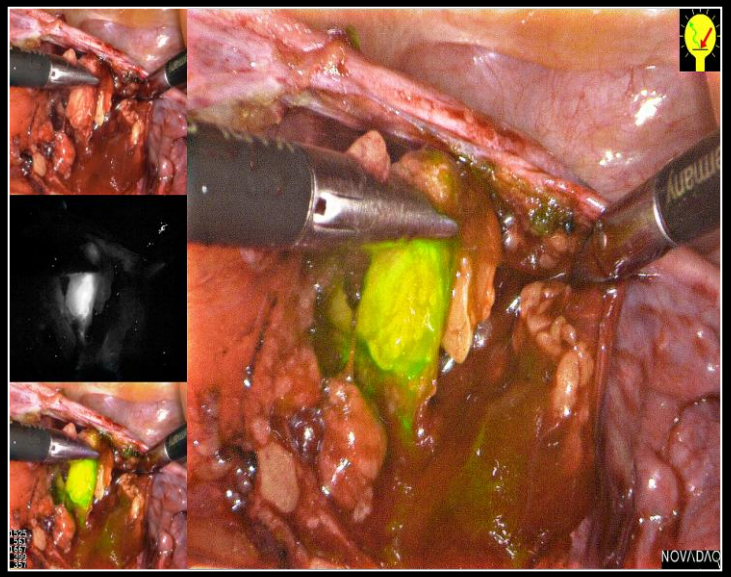


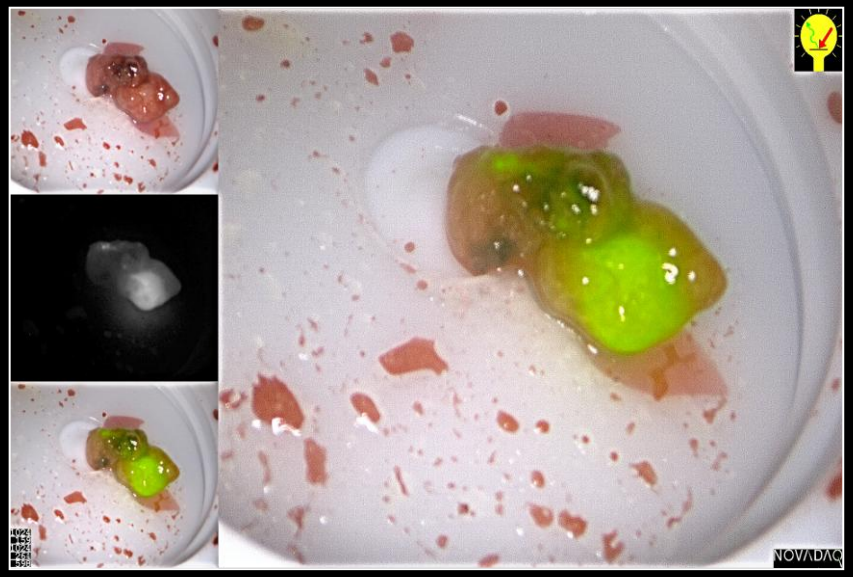
ICG SLN mapping



ICG does not tend to “leak out”
Detection rate much better in obese patients

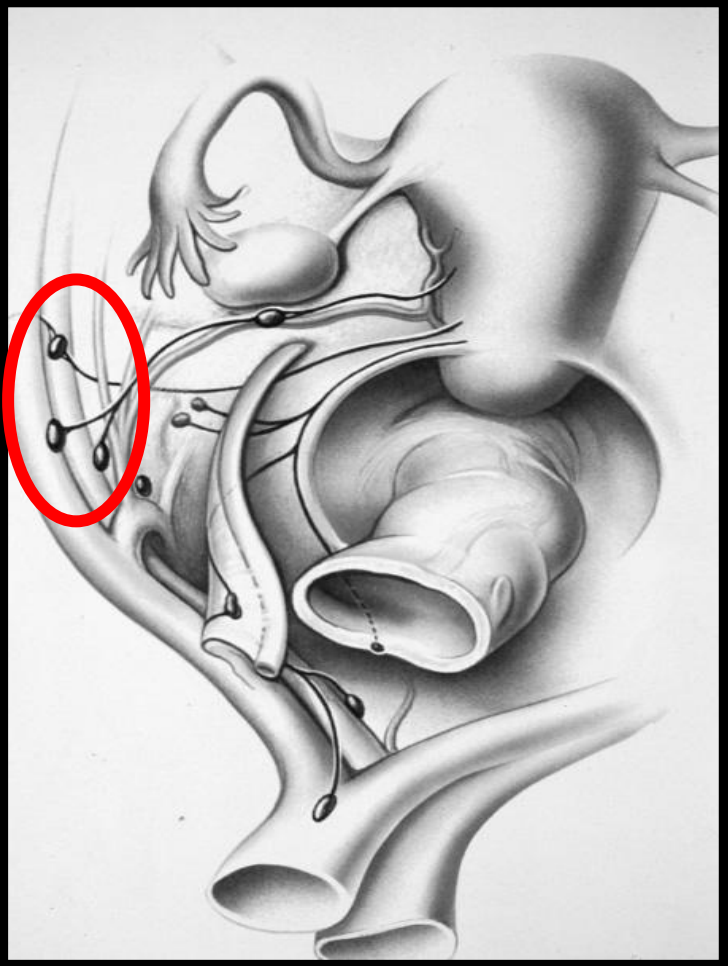
ICG SLN mapping



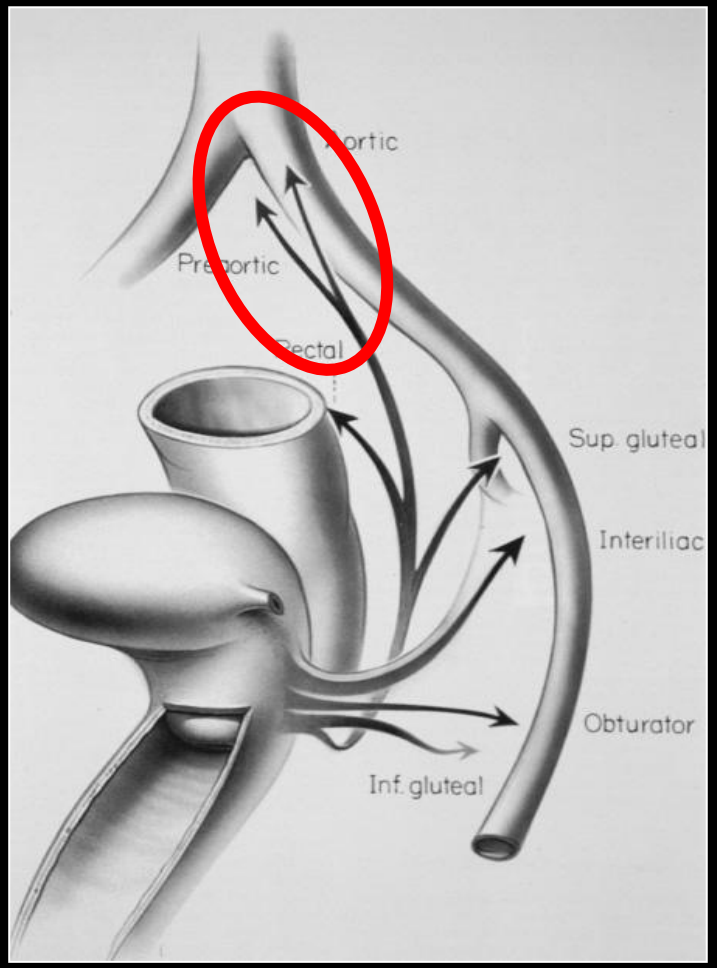


Detection rate much better in bloody surgical field

Lymphatic drainage



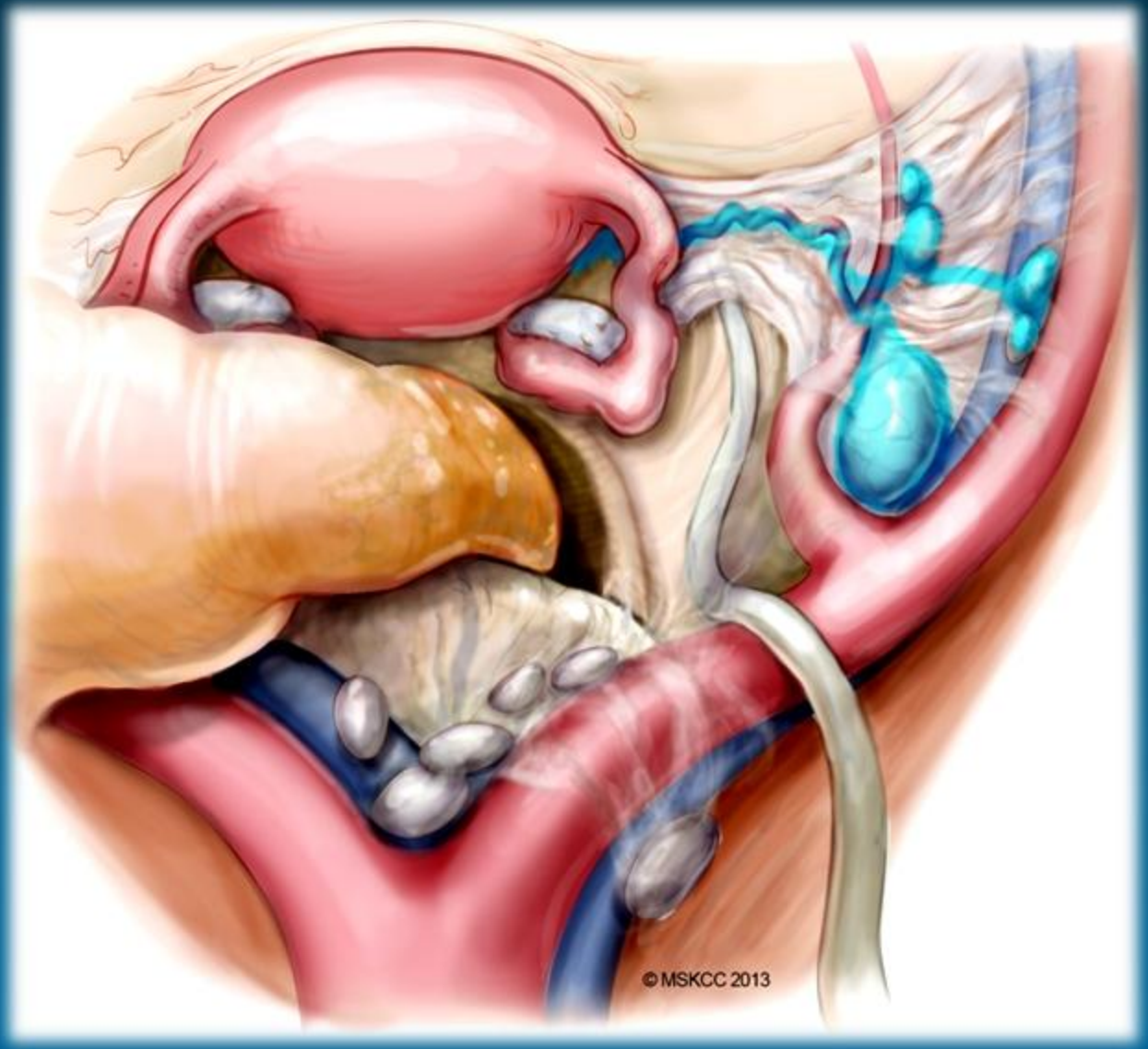
Pelvic nodes



Paraaortic nodes

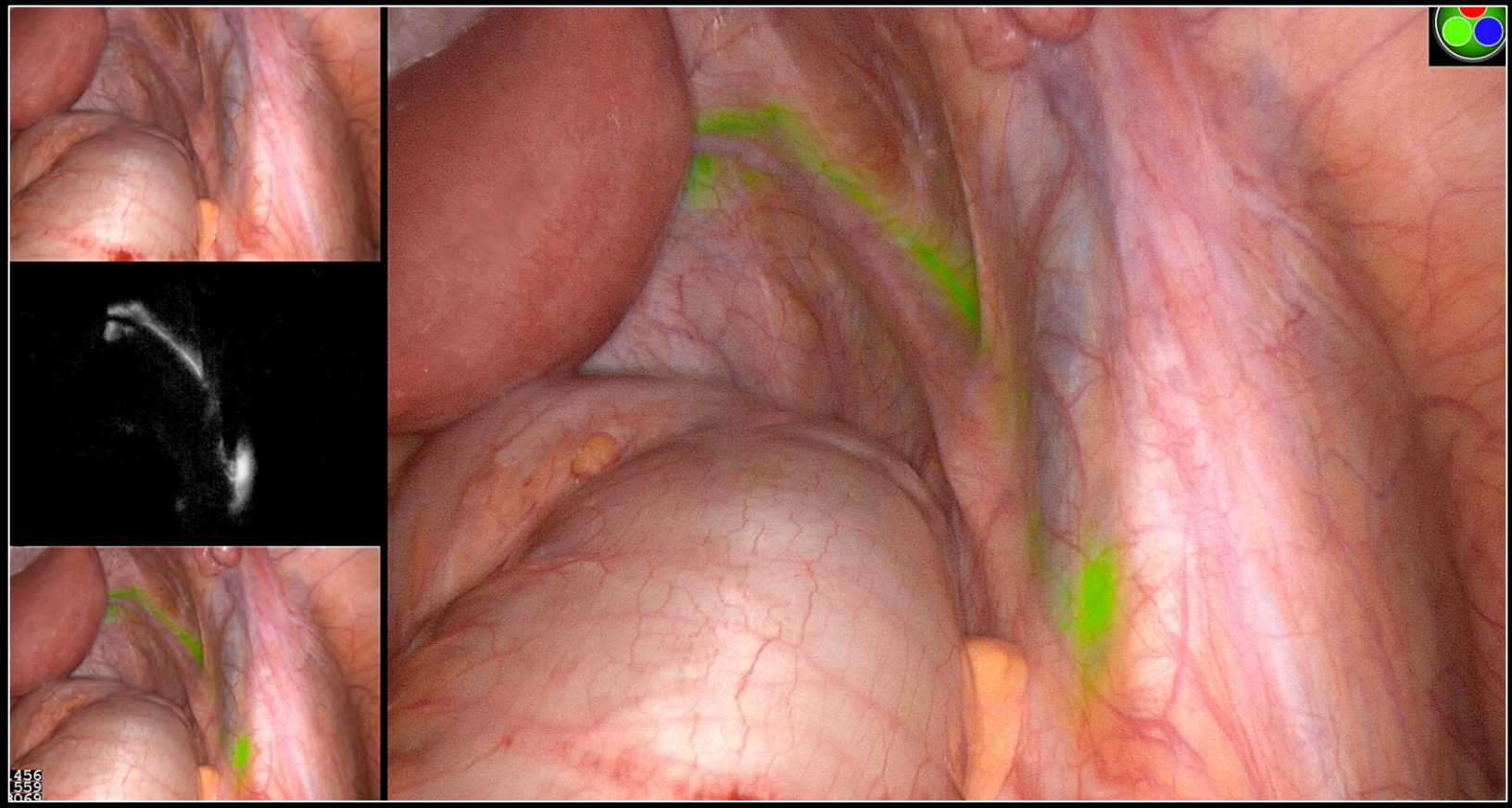
Plentl and Friedman, 1971

Hints to Drainage

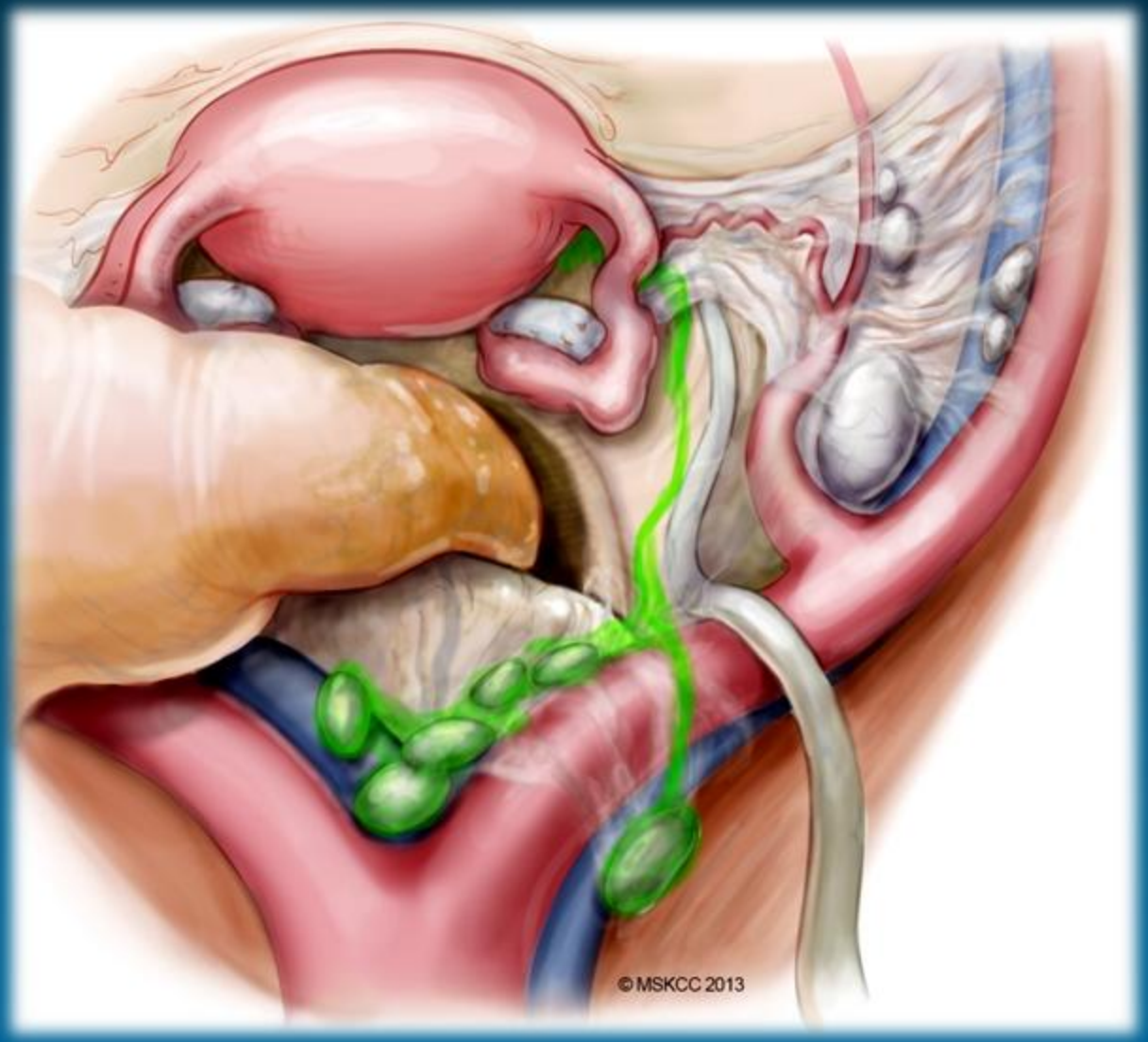


Abu-Rustum NR. MSKCC 2013

ICG SLN localisation

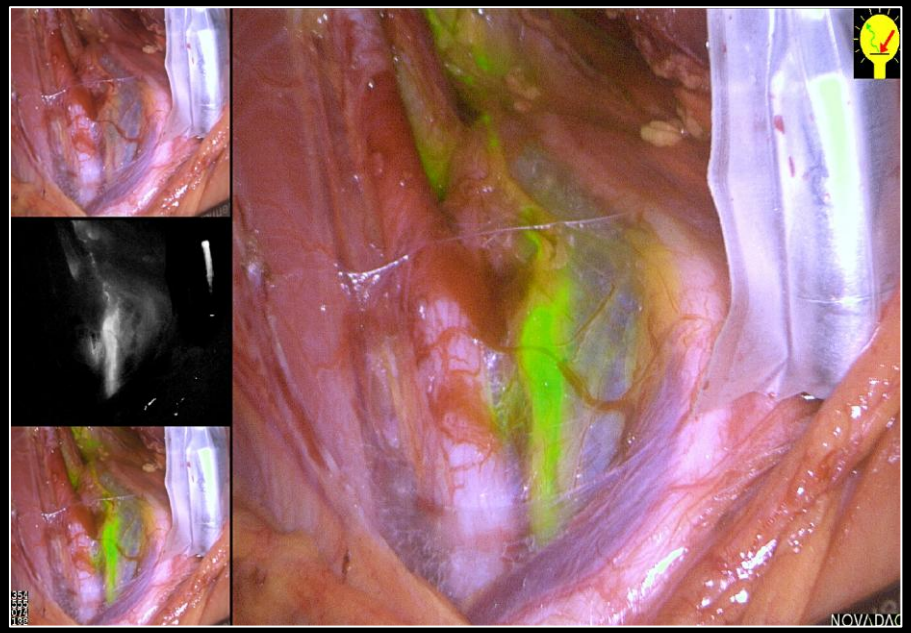


Hints to Drainage



Abu-Rustum NR. MSKCC 2013

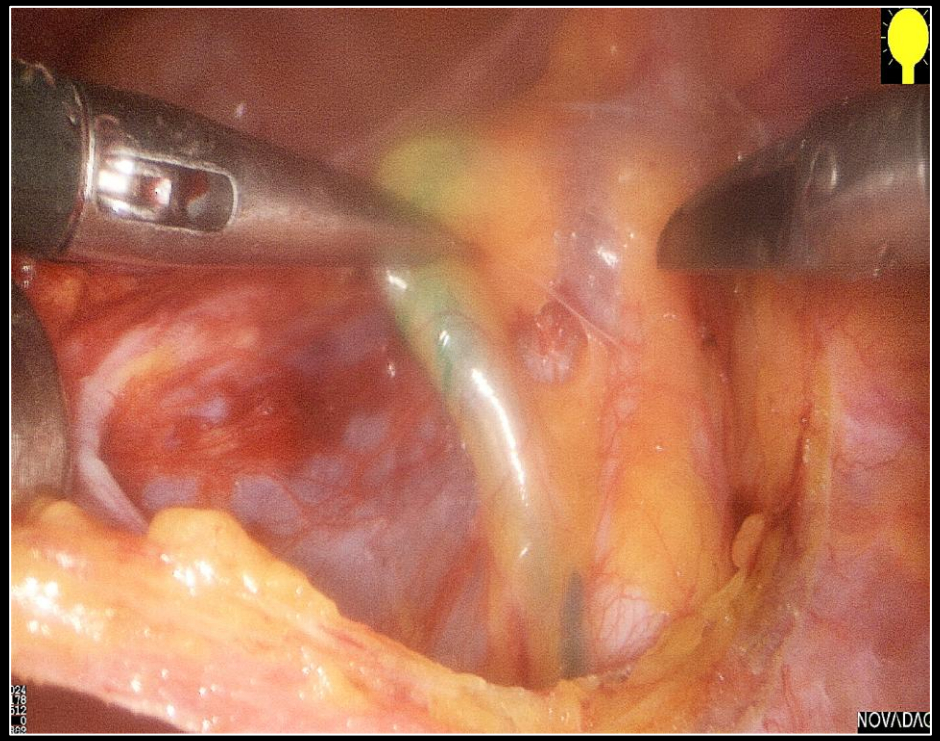
ICG SLN localisation

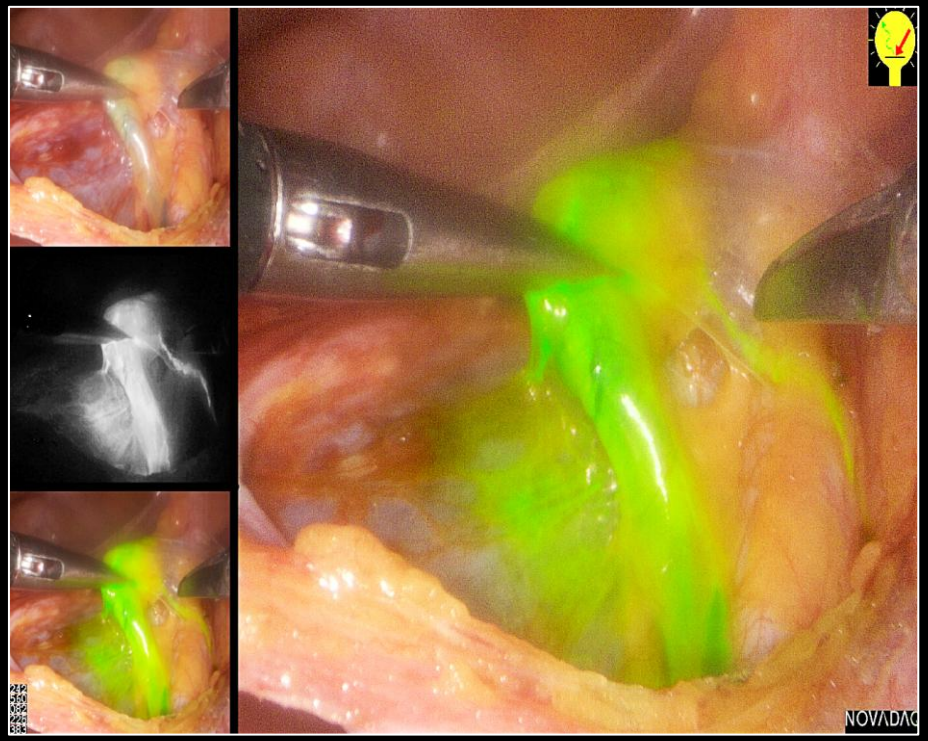


ICG SLN mapping: pitfalls

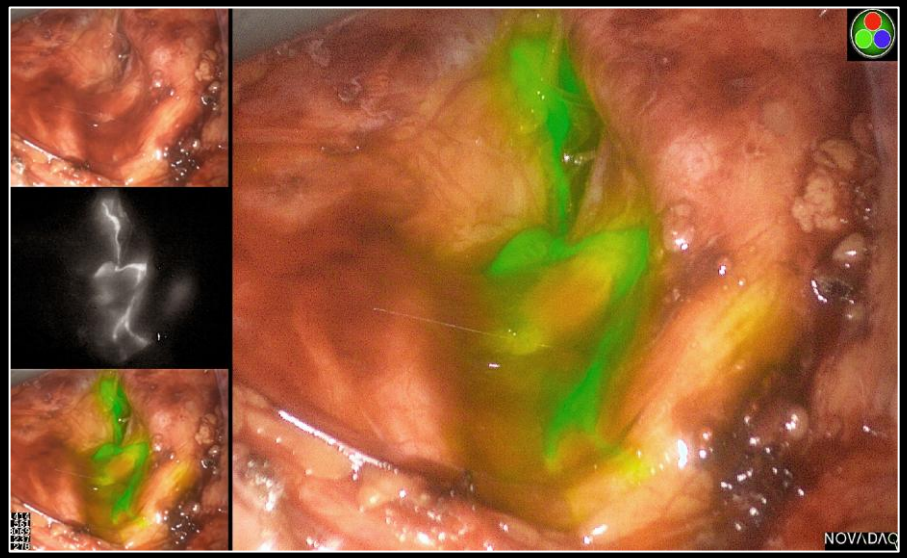
- Lymph nodes or swollen lymphatics ??
- Smear effect

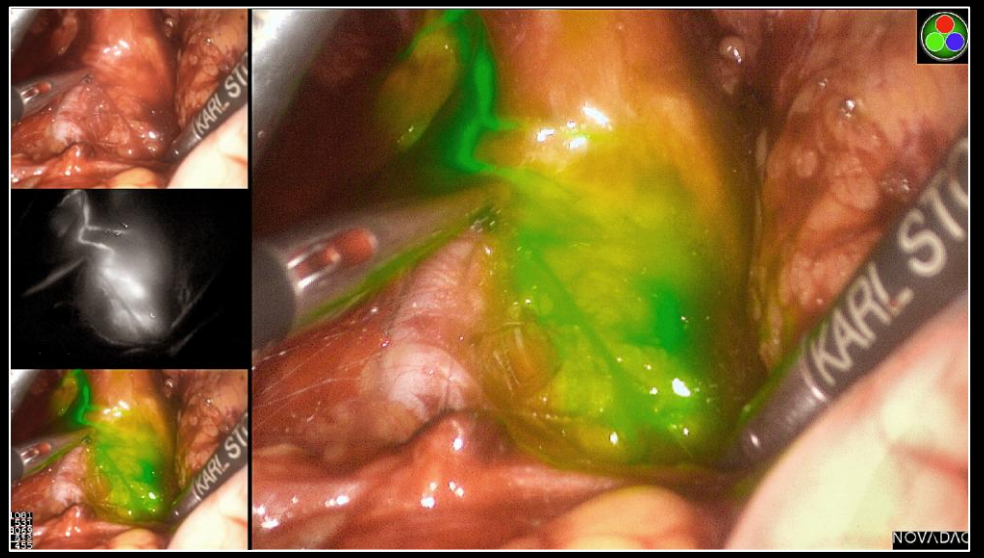
Lymph nodes vs. swollen lymphatics





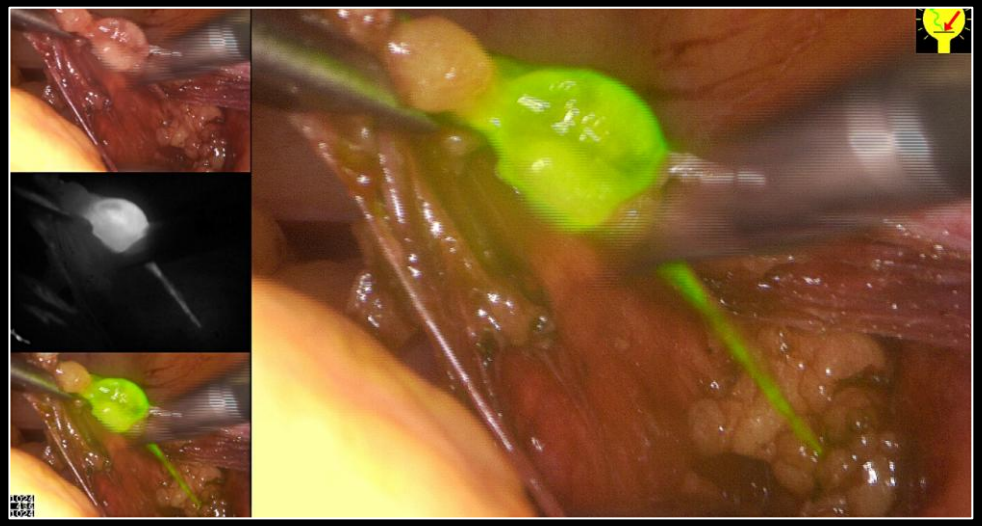
Lymph nodes vs. swollen lymphatics

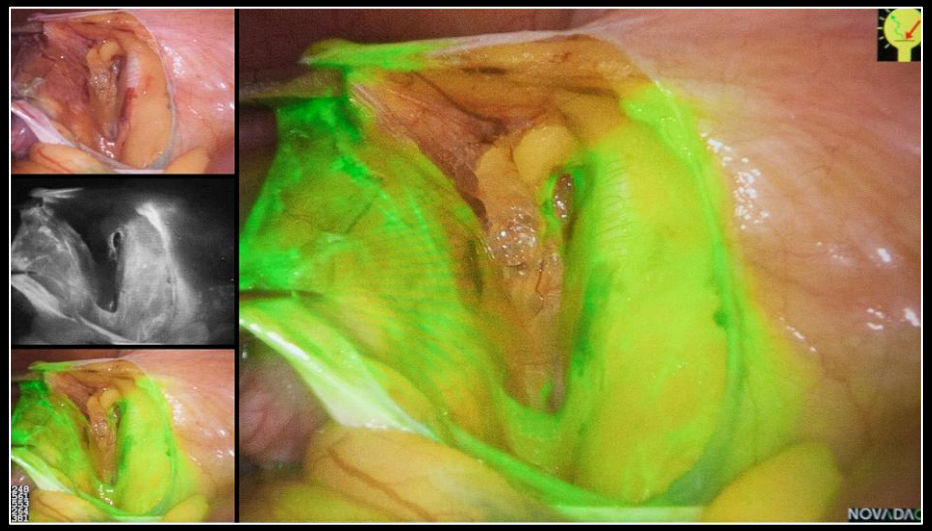




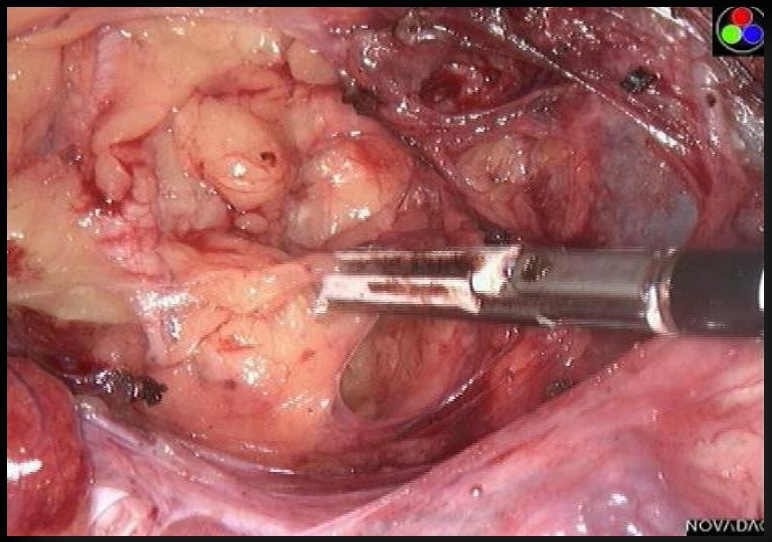
SPY mode - NIR mode

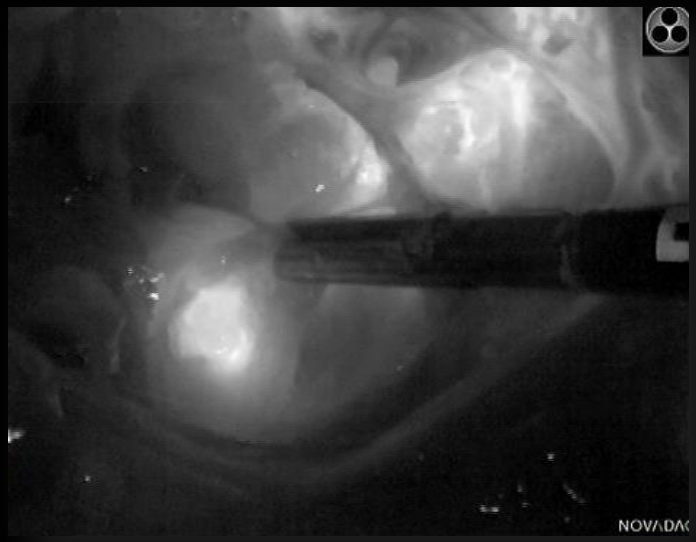
Smear effect

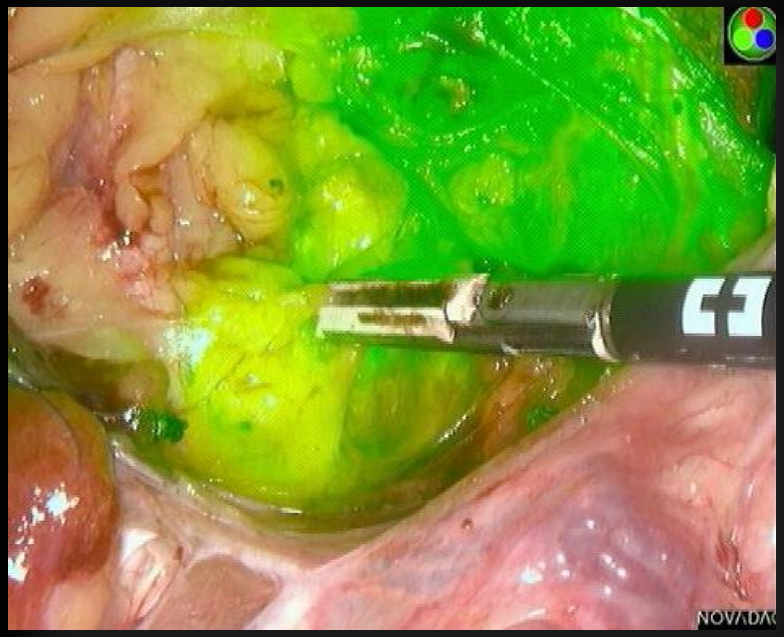


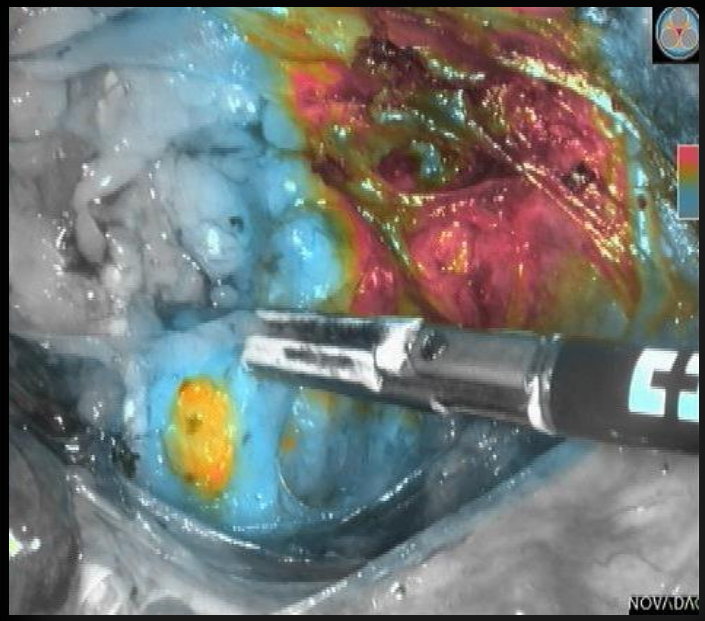


ICG – Color Segmented Fluorescence

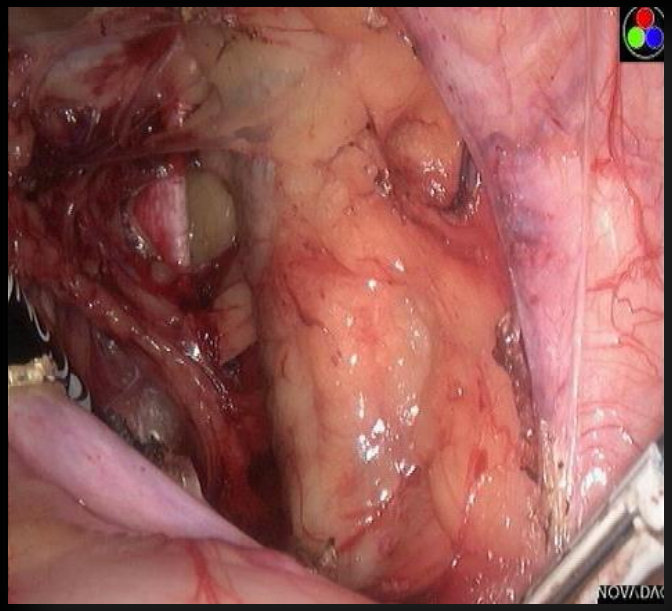


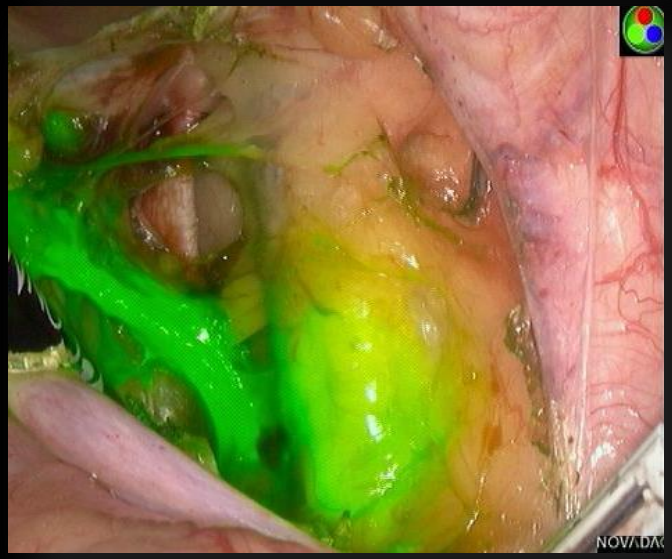


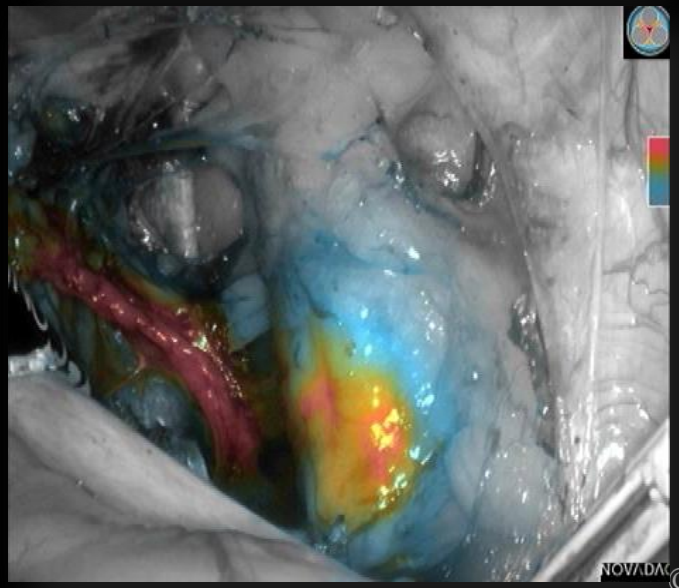




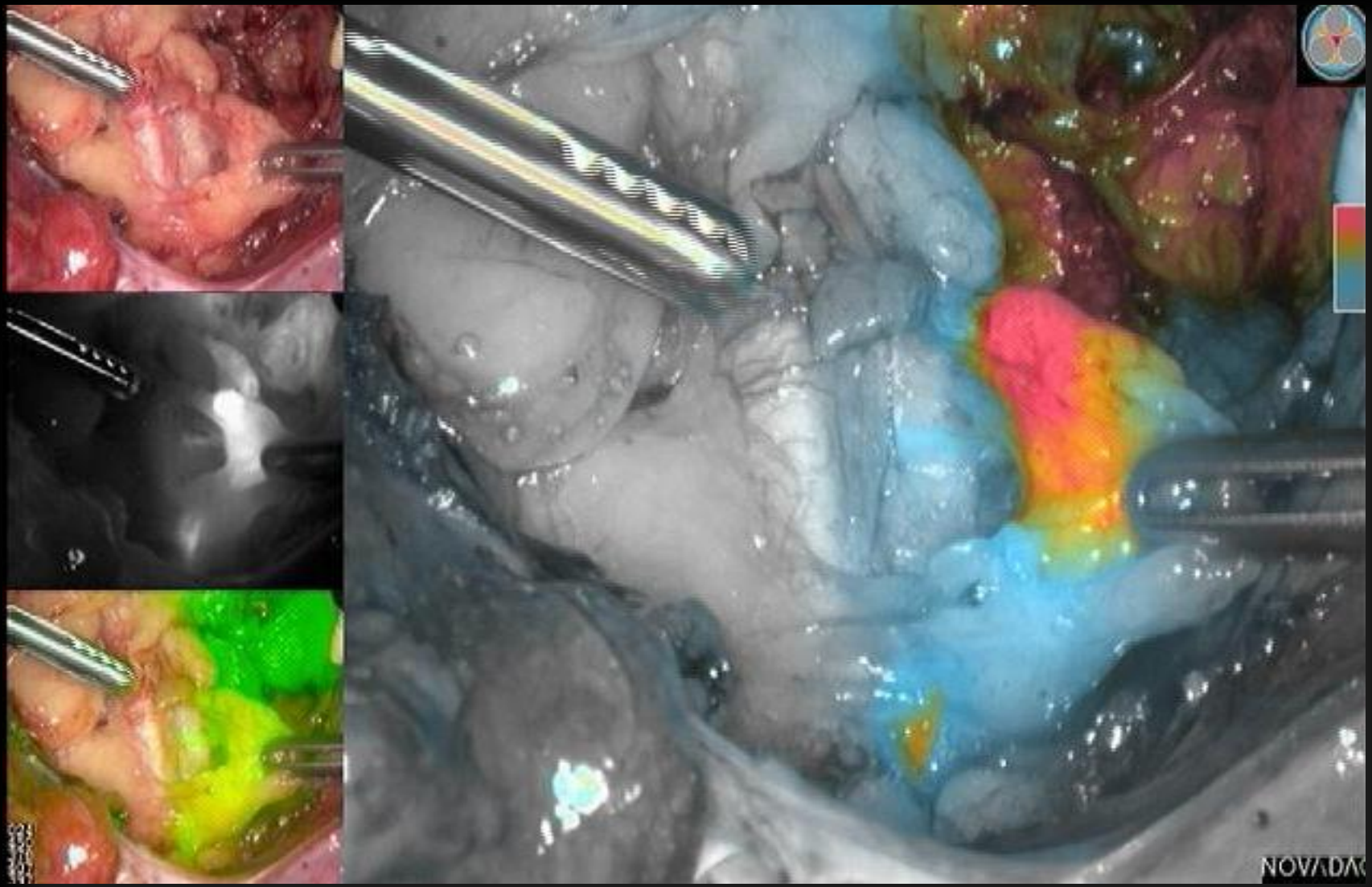
ICG – Color Segmented Fluorescence



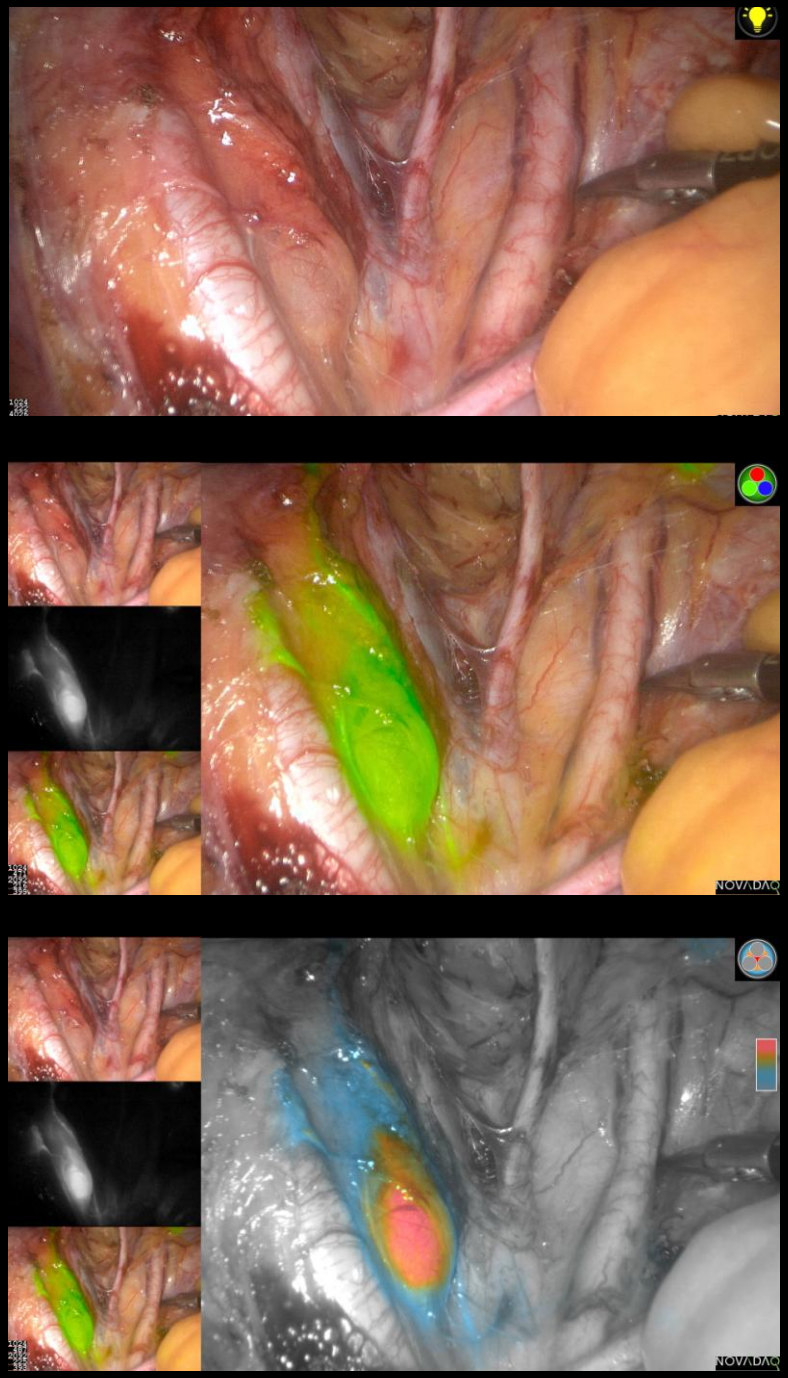




ICG – Color Segmented Fluorescence



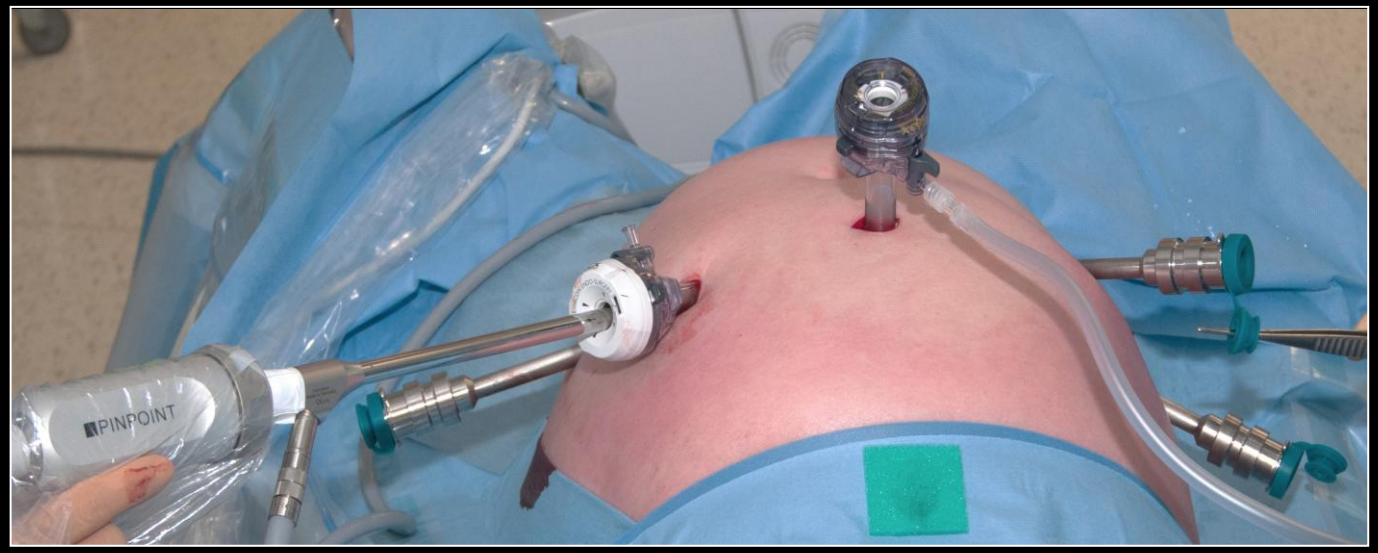
CSF mode

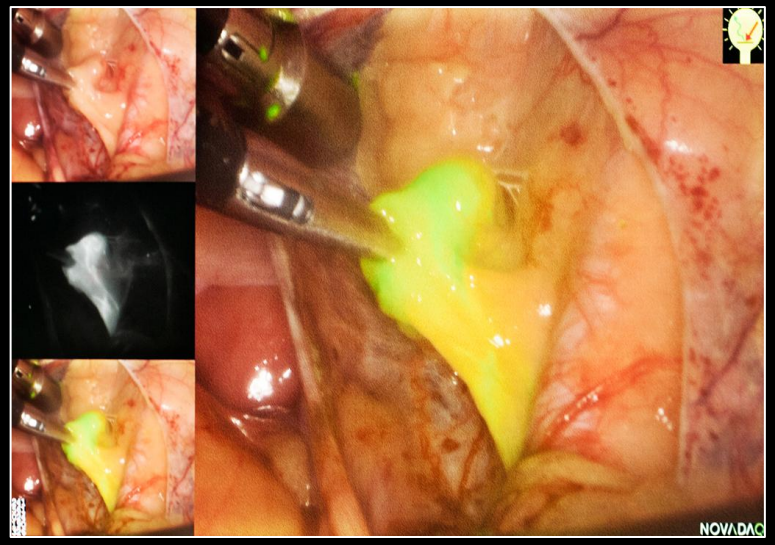


ICG SLN mapping

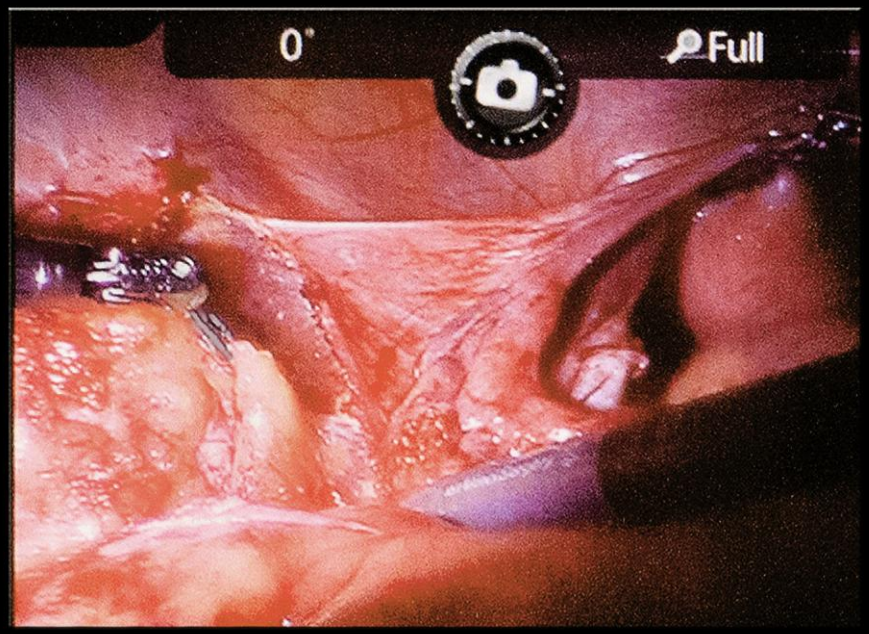
- Different applications of the endoscopic pinpoint system
  - Laparoscopy
  - Prior to robotic surgery
  - Combined with robotic surgery
  - Laparotomy

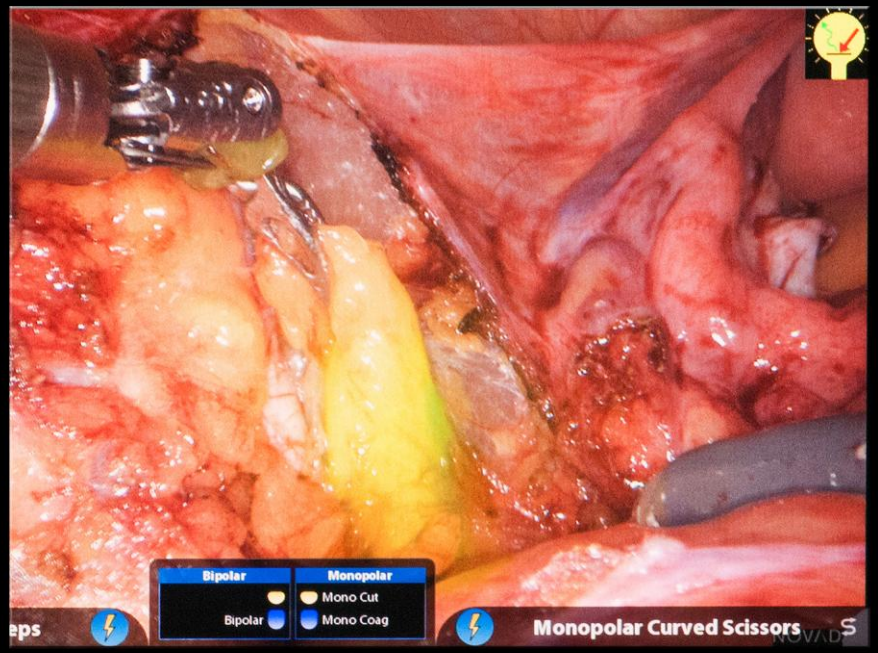
Pinpoint combined with robotic sx



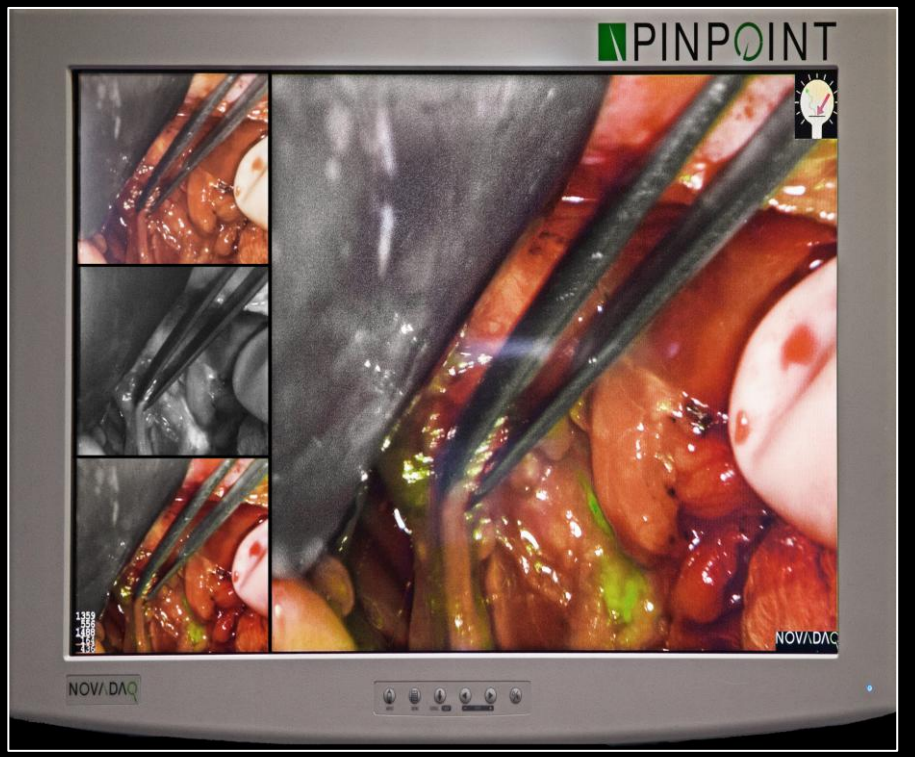


Pinpoint combined with robotic sx





Pinpoint and laparotomy



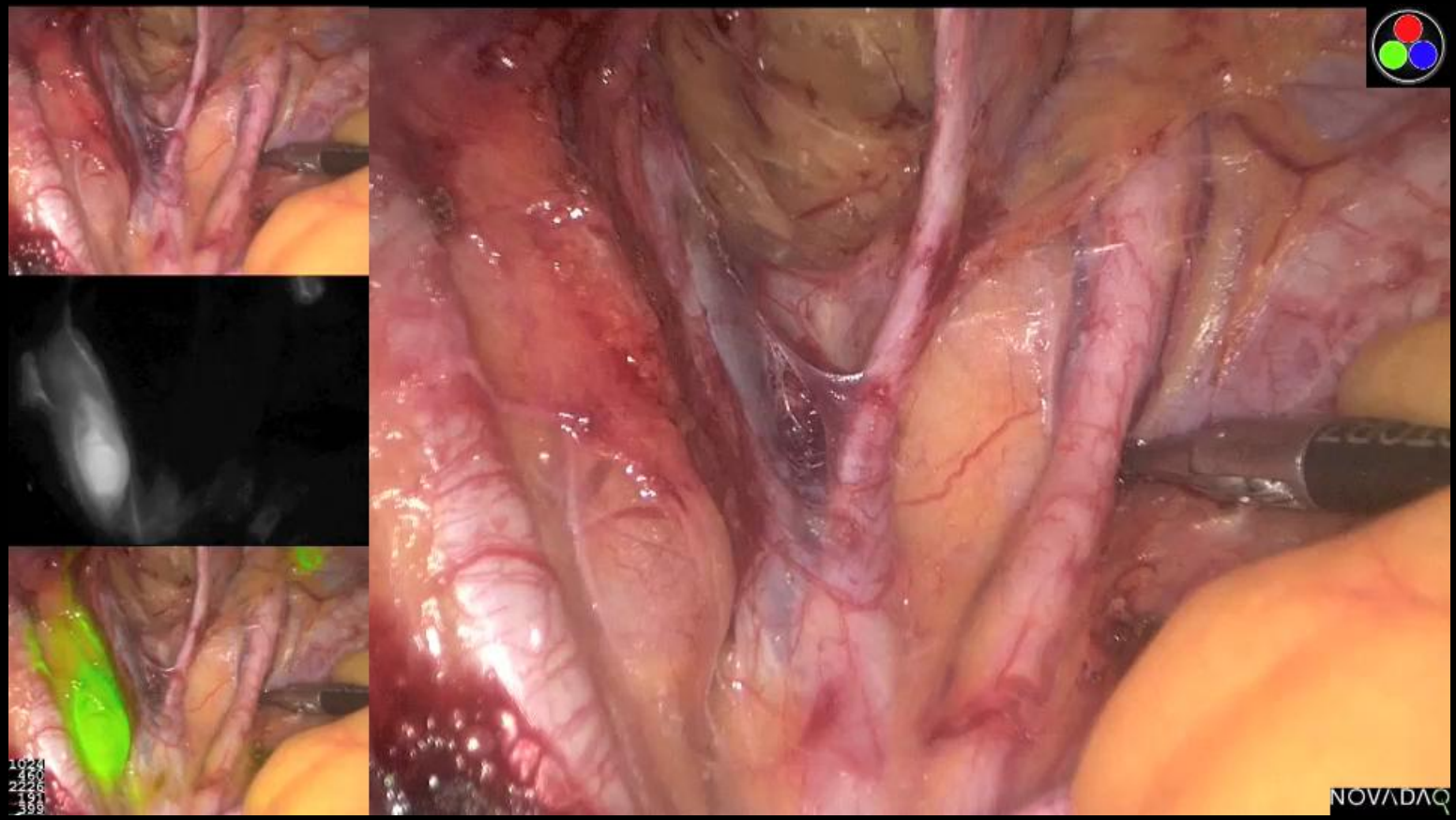
Pinpoint and laparotomy

IndoCyanine Green (ICG)

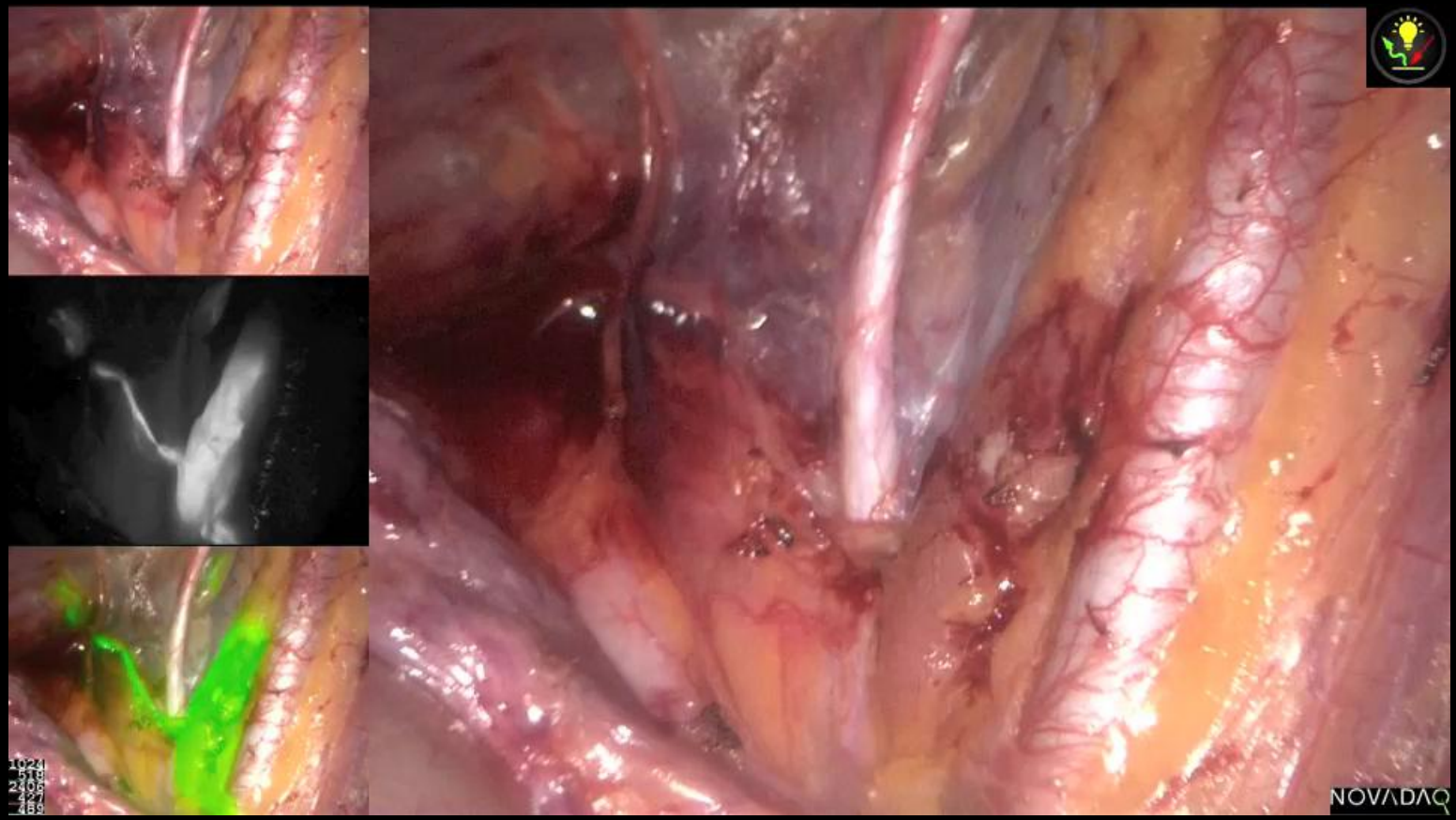
- **Safety**
  - **Allergy to iodides**
  - **May contain < 5% iodides**
  - **Risk of anaphylactic reaction VERY low**

VIDEOs

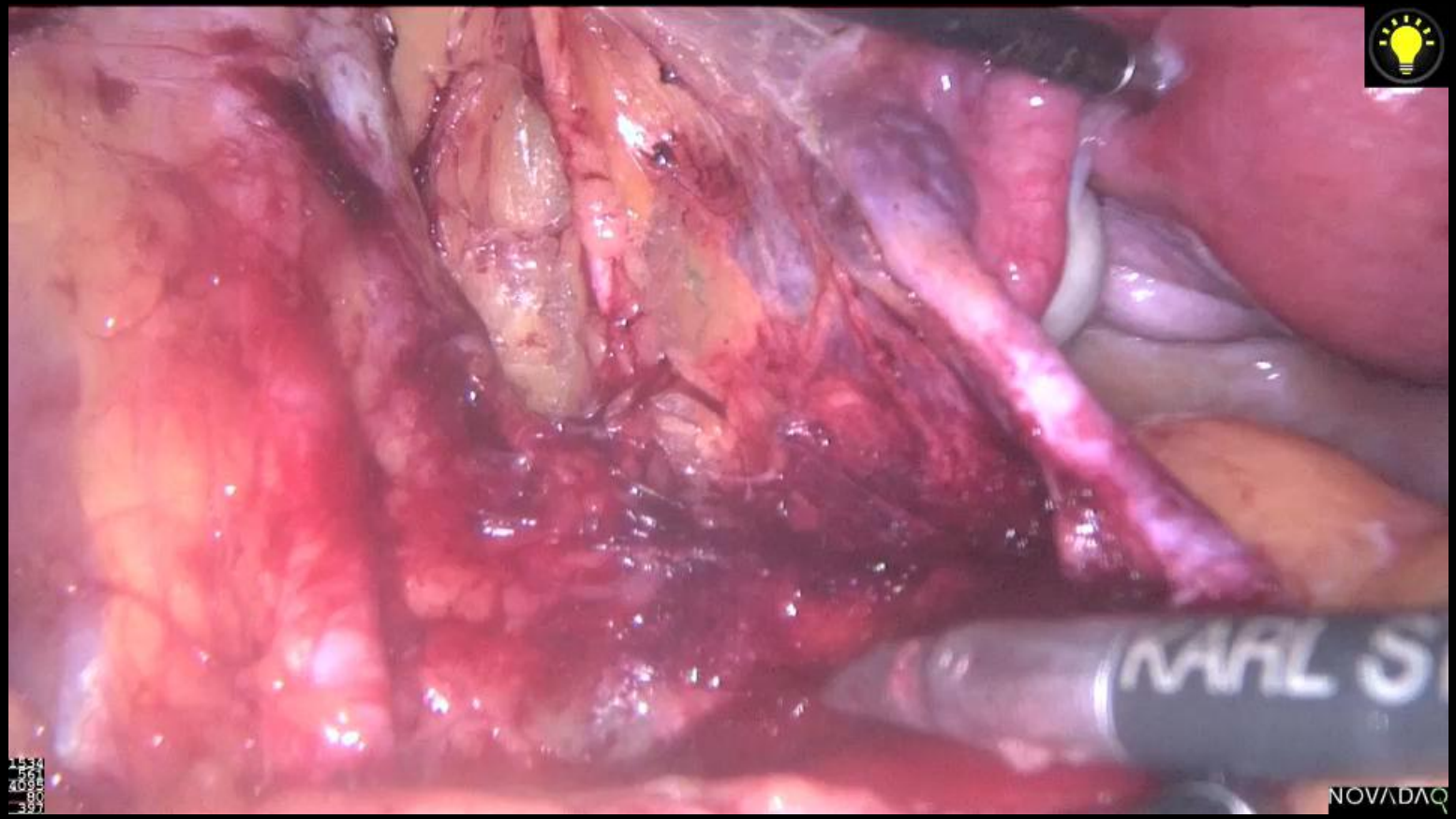
Left side



Right side



Left side - bloody

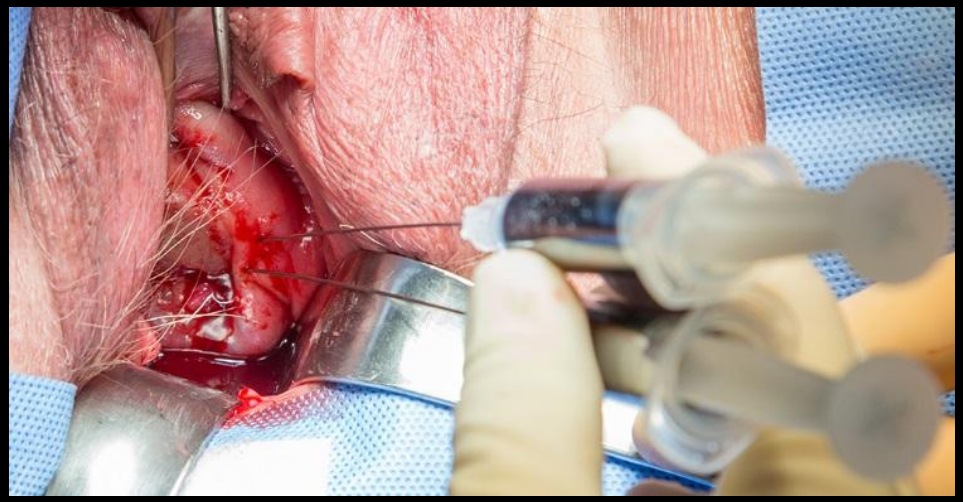


SLN mapping

- ICG currently not FDA approved for interstitial injection
  - Lymphatic mapping

FILM Study

A Randomized, Prospective, Open Label, Multicenter Study Assessing the Safety and Utility of PINPOINT® Near Infrared Fluorescence Imaging in the Identification of Lymph Nodes in Subjects with Uterine and Cervical Malignancies who are Undergoing Lymph Node Mapping

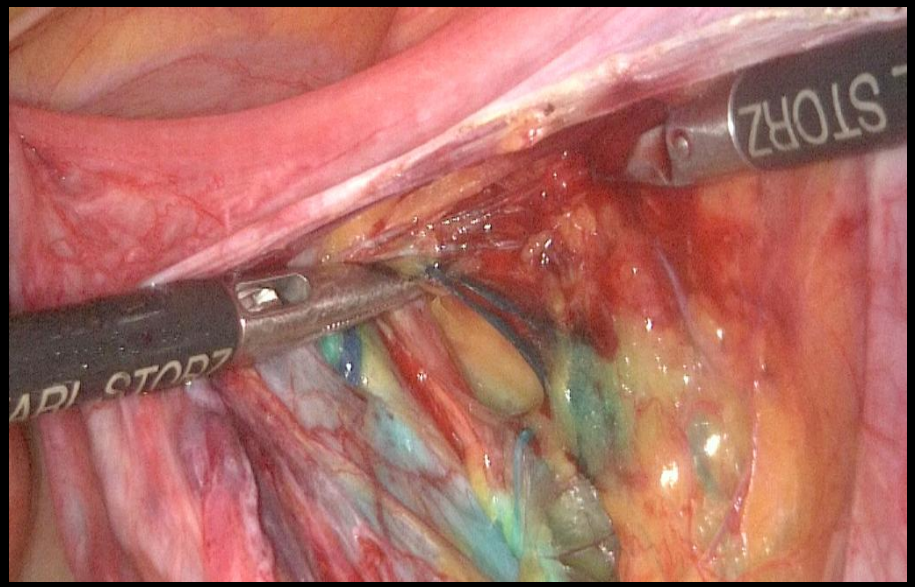


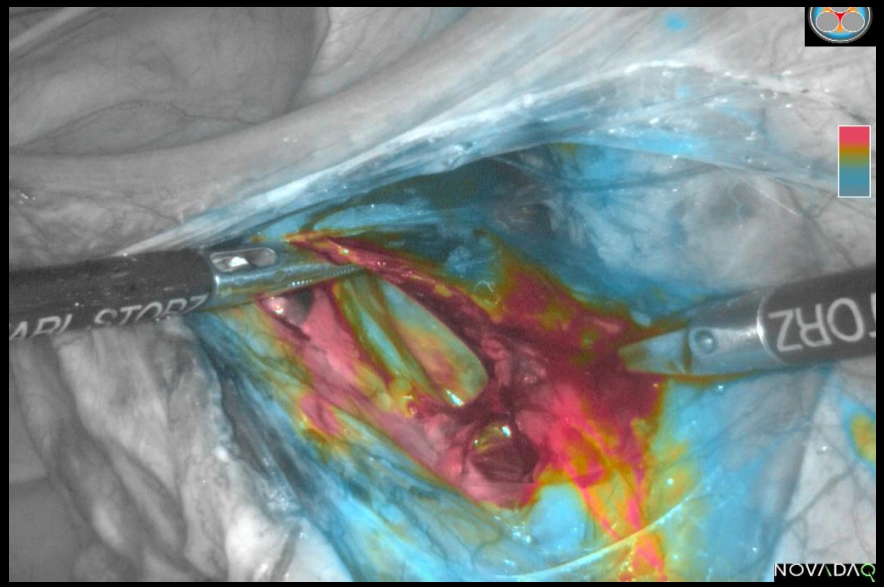
Blue Dye
ICG

The FILM study

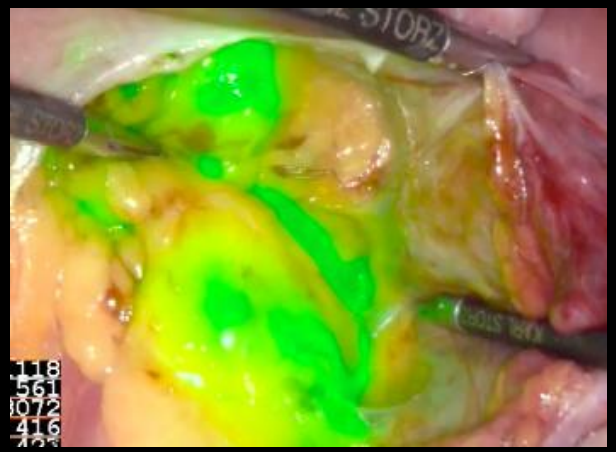
- Study design
  - randomized prospective, open label, multicenter study
  - a **non-inferiority within-patient comparison** study to determine the effectiveness of **ICG** in the identification of LNs compared to LNs identified with **Blue dye**
  - Approximately **150 subjects**

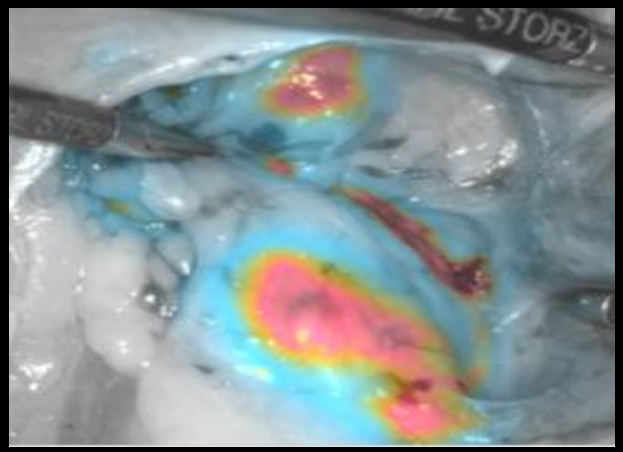
FILM study





FILM study





ELSEVIER

Review Article

JMIG The Journal of Minimally Invasive Gynecology

Role of Indocyanine Green in Sentinel Node Mapping in Gynecologic Cancers: Is Fluorescence Imaging the New Standard?

María Cecilia Darin, MD, Natalia Rodriguez Gómez-Hidalgo, MD, Shannon N. Westin, MD, Pamela T. Soliman, MD, Pedro F. Escobar, MD, Michael Frumovitz, MD, and Pedro T. Ramirez, MD*

J Minim Invasive Gynecol. 2016 Feb 1;23(2):186-93.

Available online at www.sciencedirect.com

ScienceDirect

ELSEVIER

EJSO
the Journal of Cancer Surgery

EJSO xx (2014) 1–7

www.ejso.com

Indocyanine green fluorescence-guided sentinel node biopsy: A meta-analysis on detection rate and diagnostic performance

L. Xiong [a], E. Gazyakan [a], W. Yang [b], H. Engel [a], M. Hünerbein [c], U. Kneser [a], C. Hirche [a,*]

[a] *Department of Hand, Plastic and Reconstructive Surgery, Burn Center, BG Trauma Center Ludwigshafen, University of Heidelberg, Ludwig Guttmann Str. 13, 67071 Ludwigshafen, Germany*

[b] *Eberhard-Karls-University Tübingen, BG Trauma Center Tübingen, Siegfried Weller Institut, Schnarrenbergstr. 95, 72076 Tübingen, Germany*

[c] *Department of General, Visceral and Oncological Surgery, Helios Hospital Berlin-Buch, Berlin, Germany*

Table 1
Patient characteristics and qualities of included studies.

Author	Year	Country	Sample size	Mean age	Tumor	Stage	QUADAS
T. Kitai	2005	Japan	18	56.9	Breast cancer	12 T1, 6 T2	9
K. Nagata	2006	Japan	48	–	Colorectal cancer	25 pT1, 4 pT2	11
K. Ishikawa	2007	Japan	16	57.0	Gastric cancer	14 pT1, 2 pT2.	11
N. Furukawa	2010	Japan	12	–	Cervical cancer	–	11
Y. Tajima	2010	Japan	77	57.2	Gastric cancer	52 pT1, 21 pT2, 4 pT3	11
S. Yamashita	2011	Japan	31	63.0	Lung cancer	27 pT1, 4 pT2	9
I. Miyashiro	2011	Japan	10	68.0	Gastric cancer	10 pT1	11
K. Yano	2012	Japan	130	–	Gastric cancer	109 pT1, 21 pT2	11
S. Jeschke	2012	Austria	26	62.0	Prostate cancer	13 pT2, 13 pT3	11
E. Rossi	2012	USA	20	61.0	4 cervical cancer 16 endometrial cancer	–	12
R. Holloway	2012	USA	35	63.4	Endometrial cancer	13I,4II,8III	11
C. Hirche	2012	Germany	34	–	Breast cancer	21 pT1, 24 pT2, 2 pT3/4	9
C. Hirche	2012	Germany	26	–	Colon cancer	6 pT1, 5 pT2, 15 pT3/4	11
Y. Yuasa	2012	Japan	20	65.3	Esophageal cancer	20 T1	9
J. Van der Vorst	2013	Netherlands	10	60.5	Oral cancer	–	11

QUADAS: Quality Assessment tool for Diagnostic Accuracy in Systemic reviews.

N=513 (pooled data)

Detection rate: 96%
Sensitivity: 87%
Specificity: 100%

Eur J Surg Oncol. 2014 Jul;40(7):843-9

ICG - Pinpoint system

- **Advantages**
  - **Excellent safety profile**
  - **Maintains normal colored anatomy**
  - **Switch on/off NIR mode easily**
  - **CSF mode very useful**
  - **System is versatile**
    - **Laparoscopic, robotic and open surgery**

Conclusion

- SLN mapping using endoscopic NIR fluorescence imaging with **ICG**
  - Simple, easy to learn
  - High overall / bilateral detection rate
  - **Cervical** injection works well
  - Most **practical approach** for large scale **worldwide** implementation