Selective Targeting of Adjuvant Therapy for Endometrial Cancer: The STATEC Trial.

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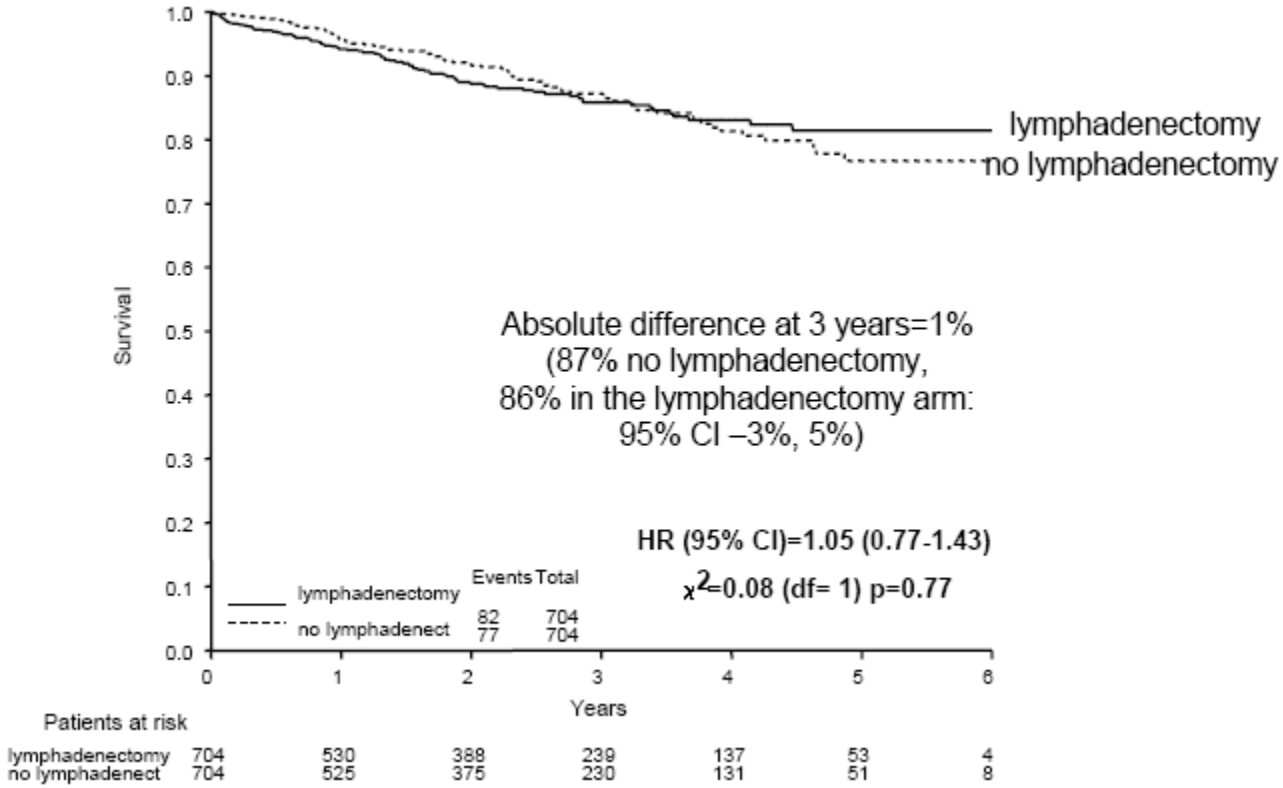
Background

- Most common gyn malignancy with rising incidence
- Ongoing debate as to value of LAD, especially in high risk patients
- Trade-off between all pts receiving adj Tx vs. only those with positive nodes
- Trials to date have failed to convince supporters of LAD despite 2 RCT showing no benefit. (Panici, 2008; Kitchener, 2009.)

A therapeutic role - randomised trials

ASTEC surgical results: Overall survival



Panici et al results: Overall survival

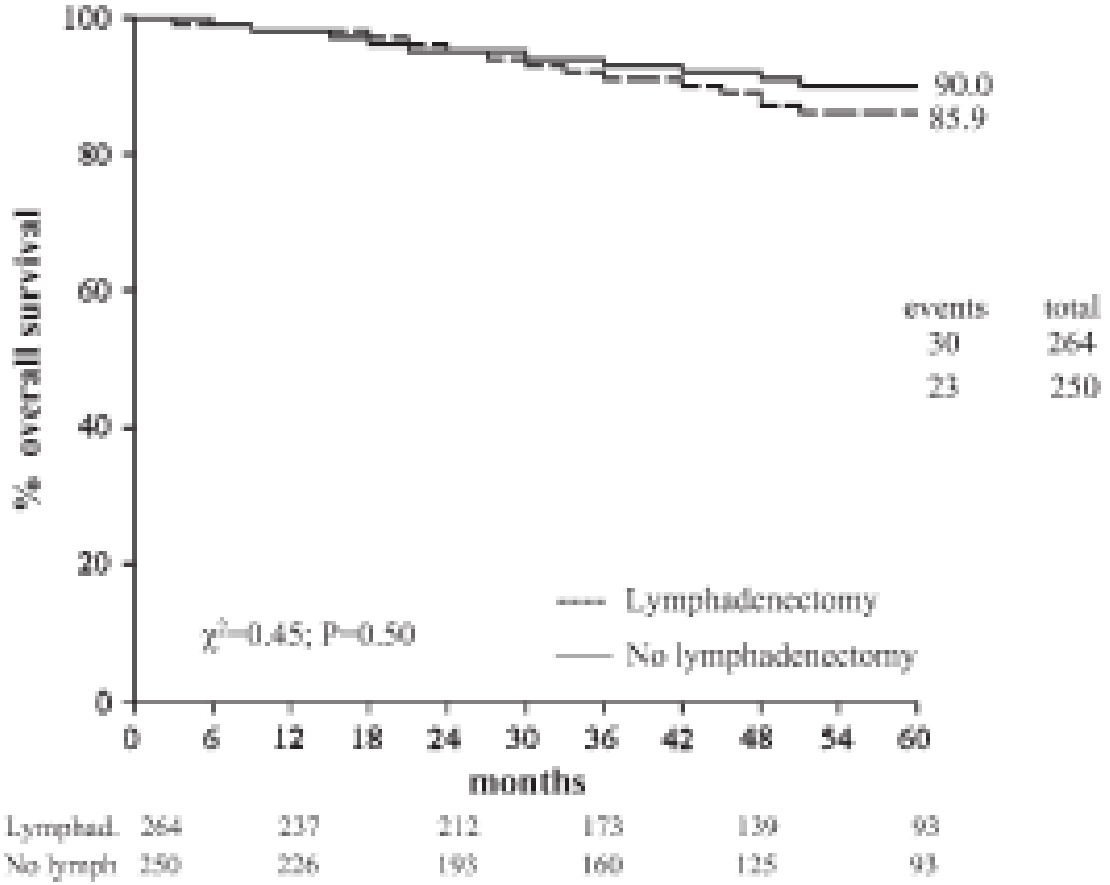


Figure 3. Overall survival for patients with clinical early-stage endometrial cancer undergoing systematic pelvic lymphadenectomy (Lymphad.) vs those undergoing resection of bulky lymph nodes only (No lymph). All statistical tests were two-sided.

Criticisms of previous RCTs

- too many low risk patients were included
- insufficient surgical effort with respect to both number of lymph nodes removed and the extent of dissection, i.e. para-aortic node dissection was not mandated
- lymph node status did not direct adjuvant therapy.

Extent of dissection

% Lymph node metastasis stratified by grade 3, myometrial invasion in endometrioid endometrial cancer; 2004-2008.

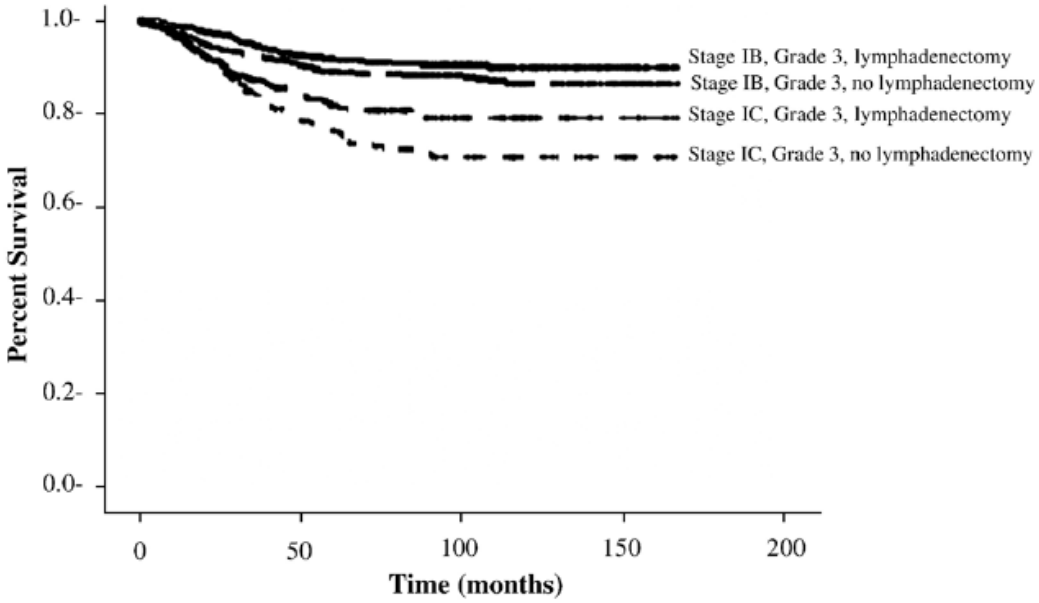
Site of LN mets	Grade	Myoinvasion	
No macro extrauteruine disease		<50%	≥50%
Pelvic alone	3	6.9%	35.3%
Para-aortic alone	3	0	25%
Para-aortic with neg pelvic	3	0	27.3%

Kumar et al, Gynecol Oncol. 2014 Jan; 132(1): 38–43.

A therapeutic role – retrospective cohort study

Chan et al 2007

No effect in low risk disease, improved in high risk
Depends on numbers of nodes (more is better)
Depends on extent of nodal dissection (more is better)



5-year disease-specific survival:

	Lymphadenectomy	No Lymphadenectomy	p-value
Stage IB grade3	91.7% (n=1,070)	89.1% (n=852)	p=0.048
Stage IC grade3	81.7% (n=483)	76.3% (n=401)	p=0.058

Fig. 1. Kaplan–Meier disease-specific survival of stage I grade 3 endometrioid uterine cancer patients based on lymphadenectomy.

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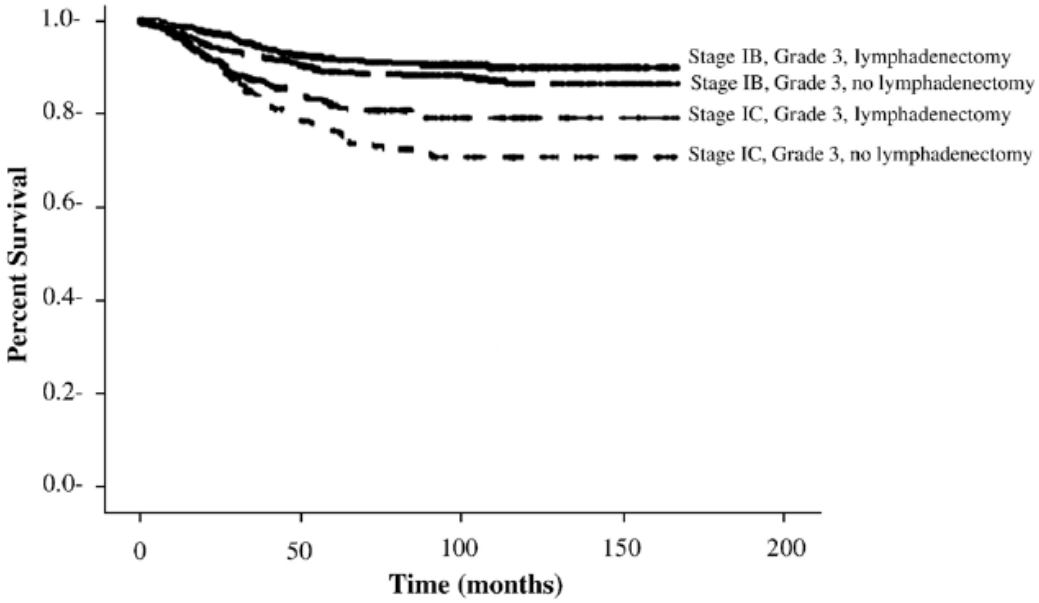

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GCIG endometrial meeting, 2012

- only high risk patients to be included
- mandate para aortic and pelvic node LAD
- ensure strict surgical quality assurance
- utilise lymph node status to direct adjuvant therapy
- include quality of life and toxicity outcomes
- quality assurance training and external pathology review
- inclusion of a sentinel node study within the node dissection arm

Assumptions

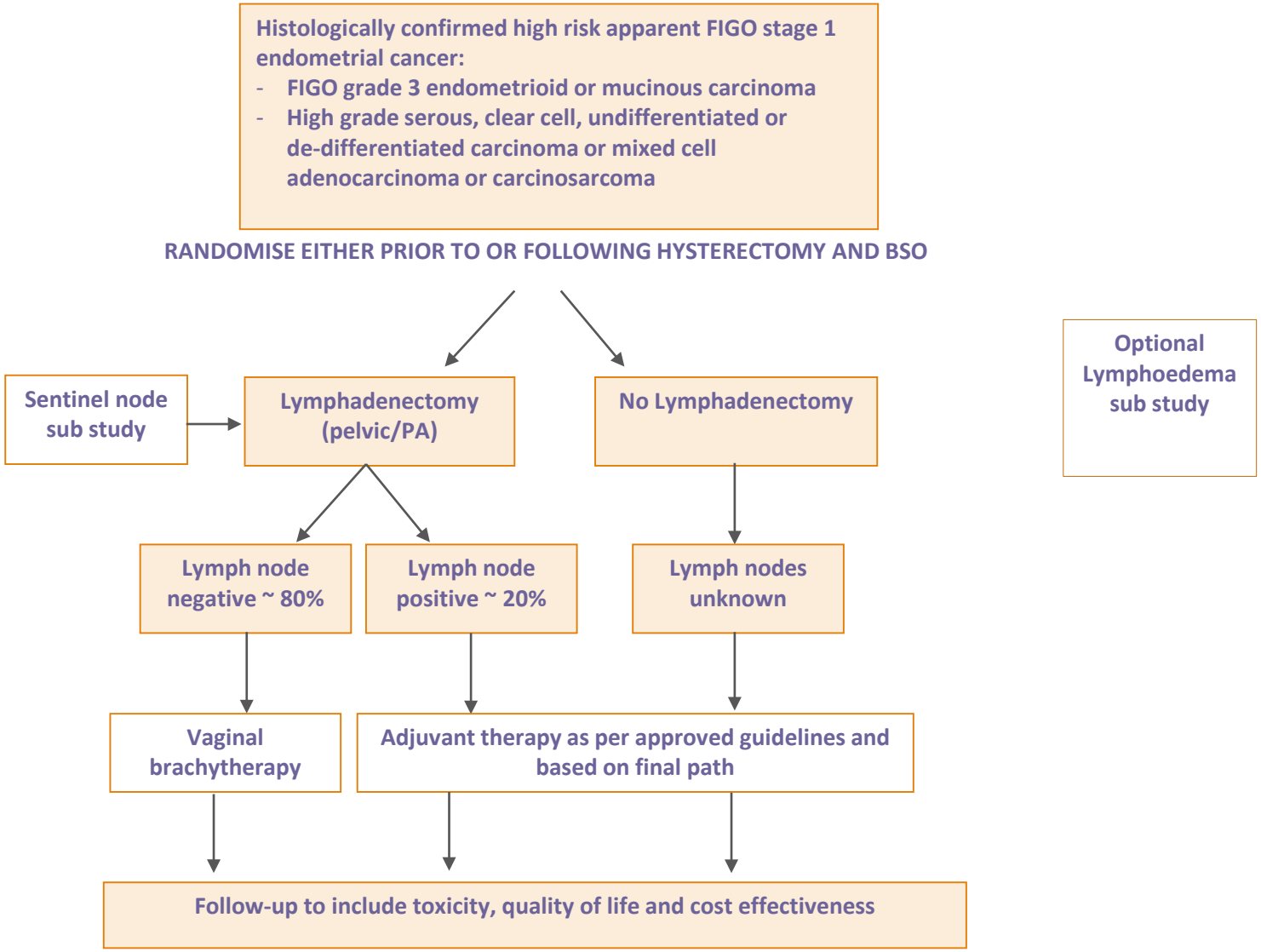
- Tailoring adjuvant therapy based on node status may limit toxicity with equal survival
- Improvement in survival may require systemic therapy
- Lymphadenectomy is **not** independently therapeutic
- Sentinel node biopsy may be as effective as full lymphadenectomy to triage patients to adjuvant therapy

Primary Aim

- to determine whether staging LAD, used to restrict adjuvant therapy to node positive women only, is non-inferior to adjuvant therapy given routinely to all women in this patient population (as determined by uterine risk factors).
- Primary outcome measure: overall survival at 5 years.

Secondary Aims

- DFS, endometrial cancer event free and endometrial cancer specific survival.
- Distribution of pelvic and distant relapse
- treatment side effects, including quality of life measures;
- cost effectiveness of each intervention;
- the accuracy rates of sentinel node biopsy compared to complete node dissection, including whether it is prognostic in terms of survival (substudy);


Histologically confirmed high risk apparent FIGO stage 1 endometrial cancer:
- FIGO grade 3 endometrioid or mucinous carcinoma
- High grade serous, clear cell, undifferentiated or de-differentiated carcinoma or mixed cell adenocarcinoma or carcinosarcoma
RANDOMISE EITHER PRIOR TO OR FOLLOWING HYSTERECTOMY AND BSO
Sentinel node sub study
Lymphadenectomy (pelvic/PA)
No Lymphadenectomy
Optional Lymphoedema sub study
Lymph node negative ~ 80%
Lymph node positive ~ 20%
Lymph nodes unknown
Vaginal brachytherapy
Adjuvant therapy as per approved guidelines and based on final path
Follow-up to include toxicity, quality of life and cost effectiveness

Study population

Key inclusion criteria

- Histologically confirmed G3 endometroid adenocarcinoma, clear cell, serous, undifferentiated or dedifferentiated carcinoma or mixed or carcinosarcoma
- Surgery performed within 5 weeks of randomisation
- Able to undergo adj Tx (incl chemotherapy) within 8 weeks of surgery

Key exclusion criteria

- Grossly enlarged nodes on MR scan or CT scan
- Invasion of cervical stroma
- Macroscopic disease outside uterus on MRI /CT scan/CXR.
- Separate malignancy in last 5 years
- Small cell carcinoma with neuroendocrine differentiation

Statistics

- **Primary endpoint is overall survival**
  - Secondary: disease-free, endometrial cancer-event free & endometrial cancer-specific survival, pelvic and extra-pelvic relapse-free survival, surgical adverse events, quality of life and cost effectivenes
  - Diagnostic performance of sentinel node procedure

- Non-inferiority trial: 5% margin of survival difference
  2000 patients required (85% power, minimum of 1720 at 80% power).

Considerations

- Surgical
- Adjuvant therapy
- Sentinel nodes
- Lymphoedema substudy

Surgical

Major surgical trial -

- Pre randomisation CT / MRI abdo pelvis + CXR / CT chest – disease outside uterus is excluded
- If randomised to no LAD arm but disease found in abdomen at operation , can remove disease at surgeon's discretion
- Laparoscopic, robotic, or open - Can be randomised after simple hysterectomy BSO if no LAD done
- Quality assurance – photographs of lymph node bed required
    - PA areas –to IMA or renal vein
    - QA failure – explanation, possibility of on-site monitoring, training, withdrawal

Adjuvant therapy (biggest headache!)

- NOT A TRIAL OF ADJ TREATMENT!
- Try to minimise variety of adj Tx to avoid criticisms that study results are due to differing adj Tx rather than study intervention
- Comprehensive guidance document setting out dosing and dose adjustment to minimise possibility of overdosing or under dosing
- Will have several approved adj Tx (evidence based), but with either chemo alone or chemo and XRT. Adj Tx must be prespecified by centre and consistent across all histologies

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Arm 1 – Lymphadenectomy

- Node negative: vaginal brachytherapy alone
- Node negative but otherwise stage III (e.g. ovarian involvement, growth beyond serosa: treat as ‘stage 3’ below)

Node positive

- external beam radiotherapy (EBRT) and chemotherapy

Arm 2 – No Lymphadenectomy

Stage	Grade	LVSI	Treatment	Reference
1A	3/serous	No	Vag brachy	PORTEC2
1A	3/serous	Yes	EBRT	GOG249/PORTEC3
1B	3	ANY	EBRT	GOG249/PORTEC3
1B	Serous	ANY	EBRT & chemo	PORTEC3
II (after surgery)	3/serous	ANY	EBRT & chemo	PORTEC3

** Carcinosarcoma, clear cell: same as for serous cancer
# No details yet on serous and stage II grade 3 from GOG-249

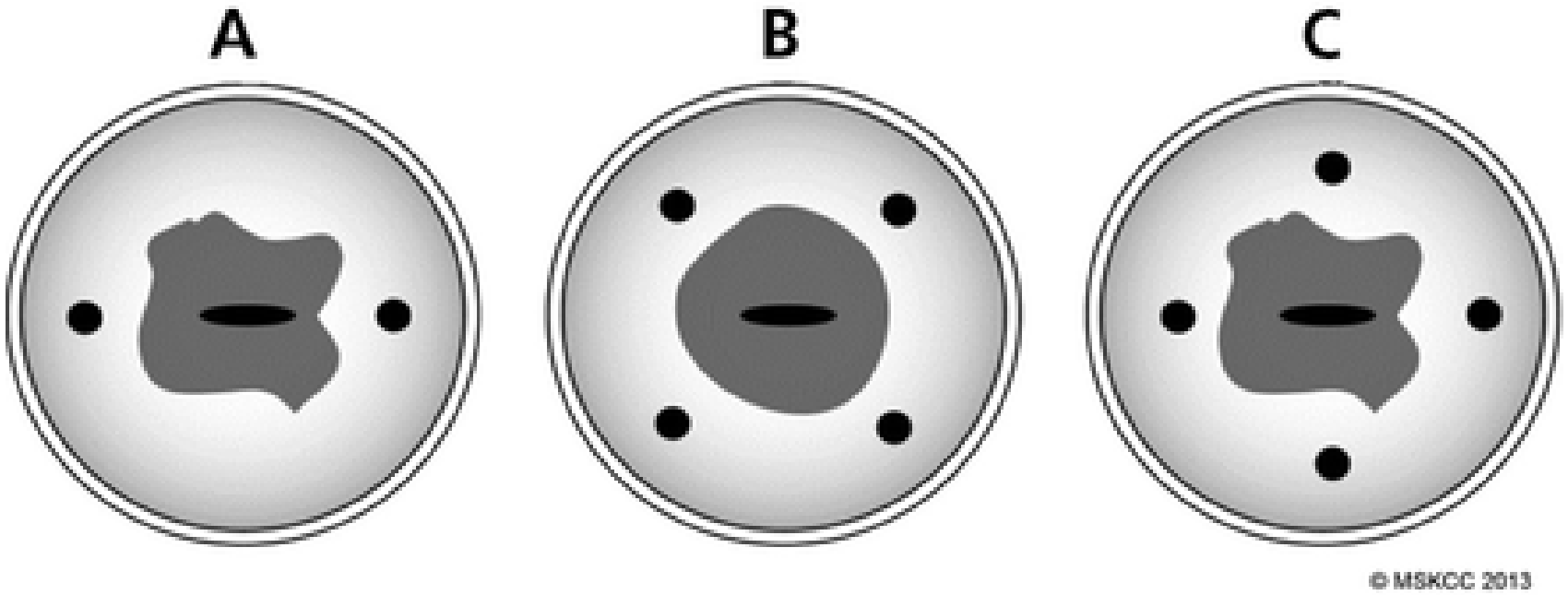
STATEC SLN Sub Study

- Optional substudy. Will allow for training in this technique.
- To determine SLN sensitivity /specificity across multiple institutions internationally
- To investigate SLN as a triage substitute for full LND
- To understand the significance of LVM (ITC or micromets) in EC and its impact on outcome
- Findings on SLN , unless also seen on routine H&E staining, will not direct treatment

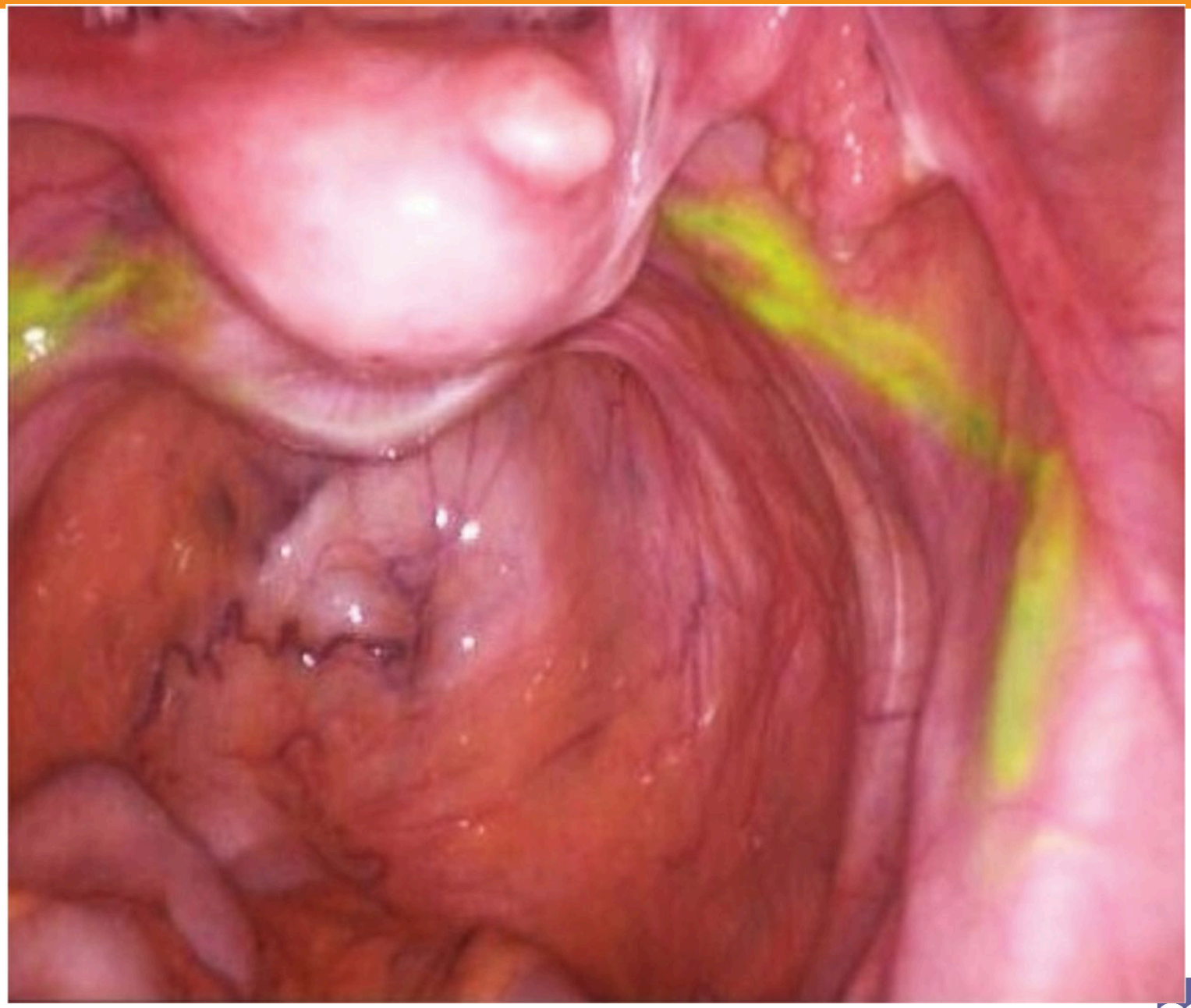
SN Protocol

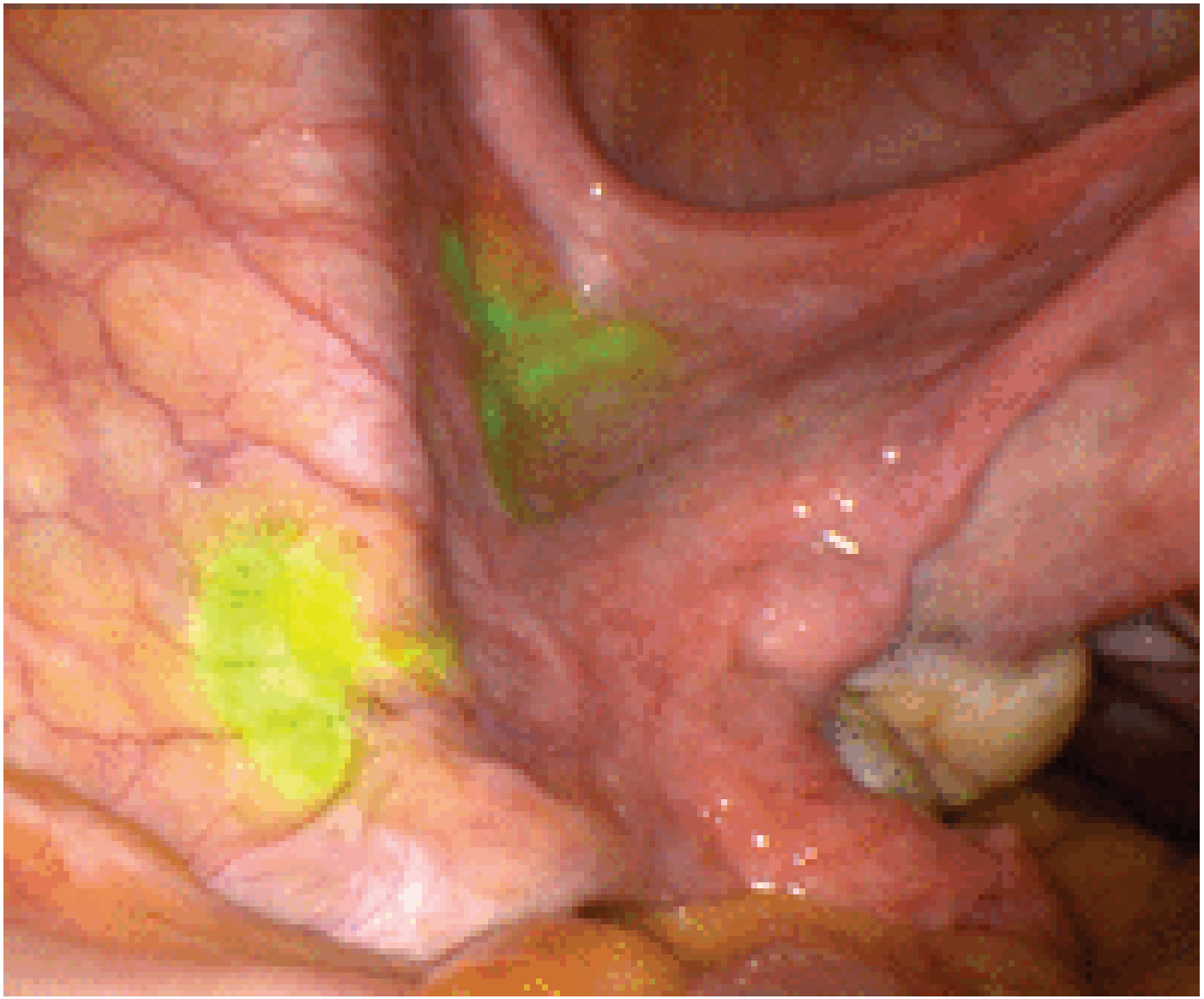
- Any Blue Dye
  - Patent Blue
  - Isosulphan
  - Methylene blue
- ICG
- Cervical injection +/- fundal

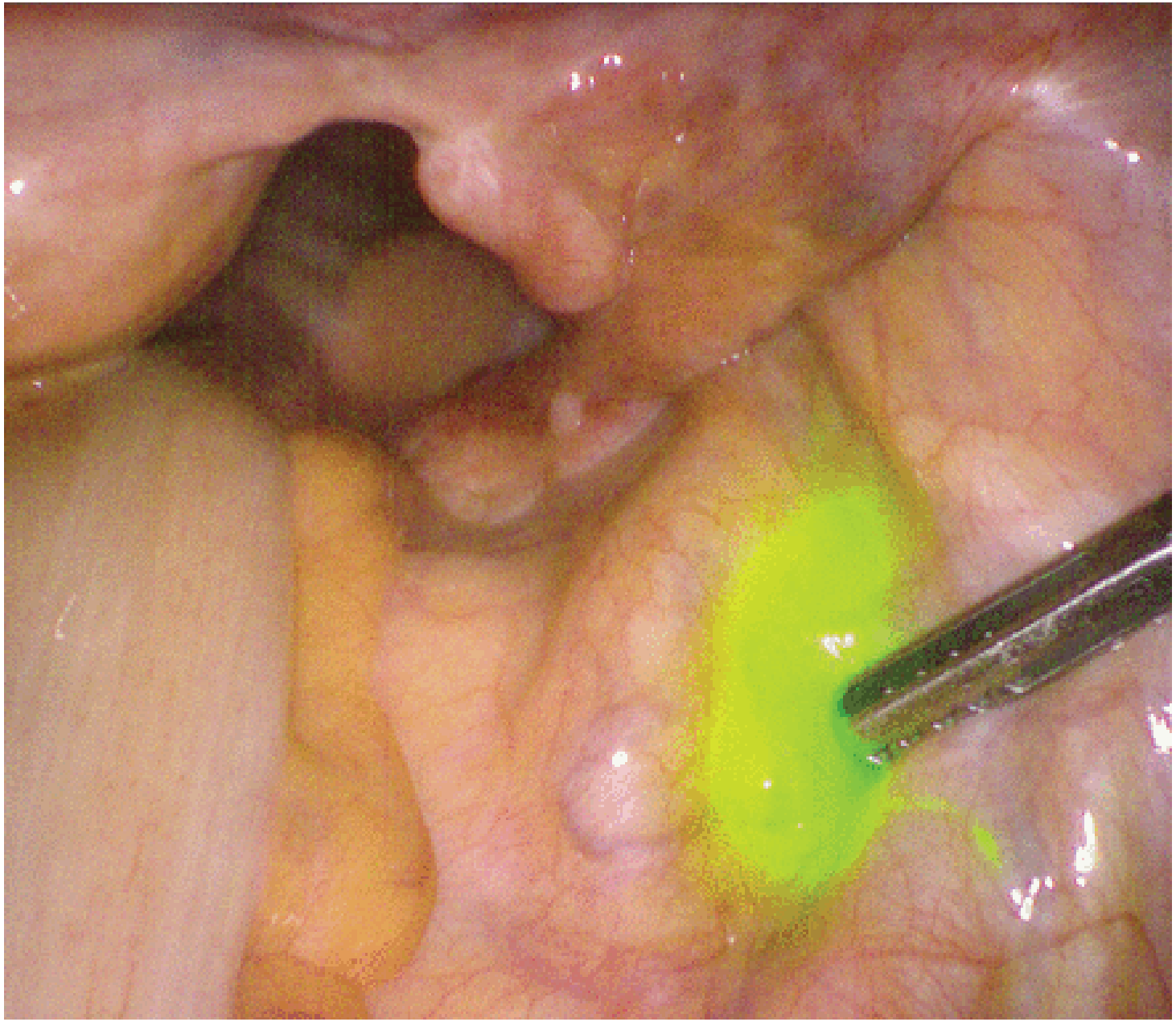
Cervical injection



Abu-Rustum NR, Levine DA, Barakat RR, eds. Atlas of Procedures in Gynecologic Oncology, 3rd ed. London: Informa Healthcare; 2013.







ANZGOG lymphoedema substudy

- Acknowledgement that self report or physician report is subjective
- Optional substudy in which patients will have objective measures of lymphoedema (BIS) which then can be compared to self report (mandatory in main study)
- Planned for 5 sites in Australia

Current status

- UK recruiting
- First ANZGOG site (Westmead) opened Dec 2017
- 2 ANZGOG pts recruited
- 3 further sites opened this month, 3 pending
- NZ had provisional ethics approval

- 4 sites yet to start ethics (investigator absence (1), TC issues (1), NZ sites awaiting NZ lead site approval (2).)