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SLN & Lymphadenectomy in early stage cervical cancer

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ECC: Risk factors of recurrence

–Lymph node metastases

- Large cervical tumor (>4cm)
- Parametrial extension
- Non squamous histology
- Deep (>75%) stromal invasion
- LVSI

Fuller A & al 1989
Schorge J & al 1997
Landoni F & al 1997
Lennox G & al 2017

Prognosis = Nodes

- Prognosis is different between N0 et N1 patients (macrometastases)*
- Better prognosis in “occult” metastases vs macroscopic
- Poorer prognosis with increasing number of nodes, if ≥ 2 (10% 5-year DFS / node)
- Prognosis linked to location of nodes (the highest the worst)
- Prognosis of N+ depends of parametrial invasion

- Ib – IIa (IIb), RH + PLN + RT(CT)

van Bommel P & al 1987
Delgado G & al 1990
Inoue T & al 1990
Suprasert P & al 2013
Tinga D & al 1990
Tsai C & al 1999

Prognosis = nodes

- 5 to 20% patients from Ia1 to IIa have metastatic lymph nodes.
- Only **ONE** node is invaded in 35-54.8% of patients pN1
- Small size of the metastasis
  - ➢ Median size of metastasis is 1.5 mm
  - ➢ 22 to 38% measure less than 2mm
  - ➢ 100% of metastases measure less than 8 mm

Inoue 1990 Cancer
Benedetti Panici 1996 GynOncol
Lee K 2006 JOGR
Horn 2008 GynOncol
Gortzak Uzan 2010 GynOncol
Achouri 2013 EJSO

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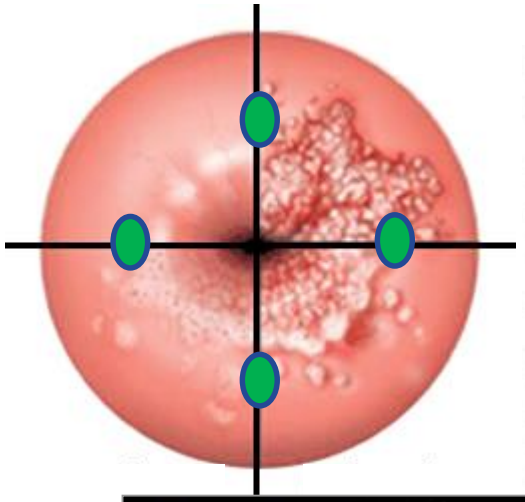
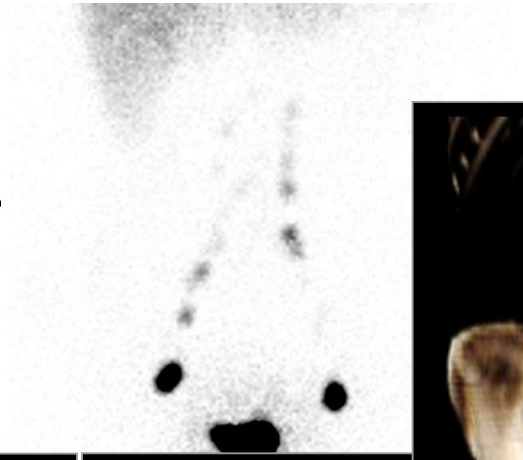
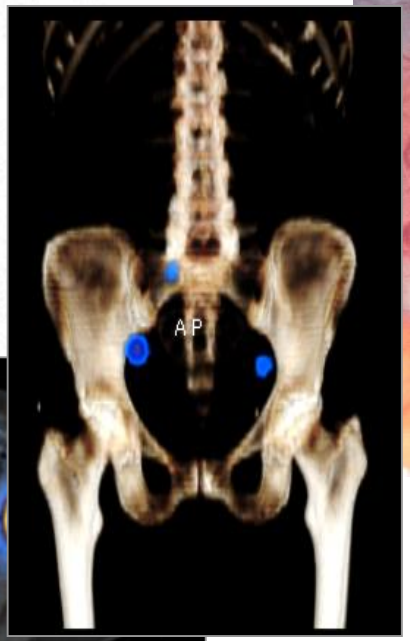
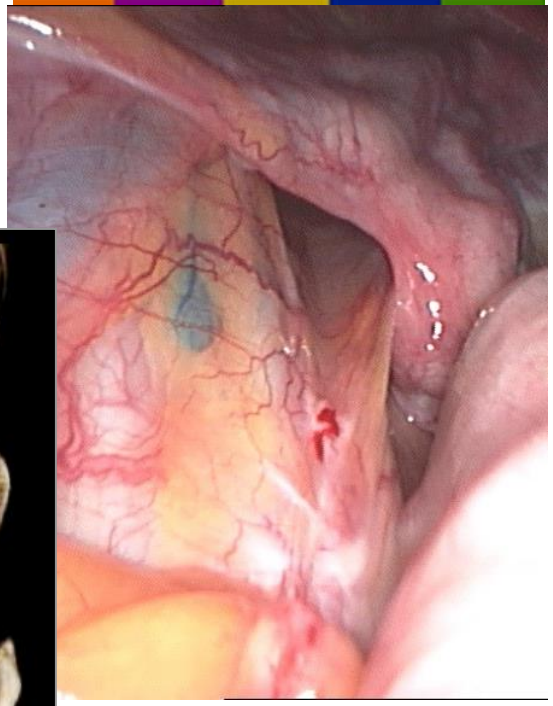
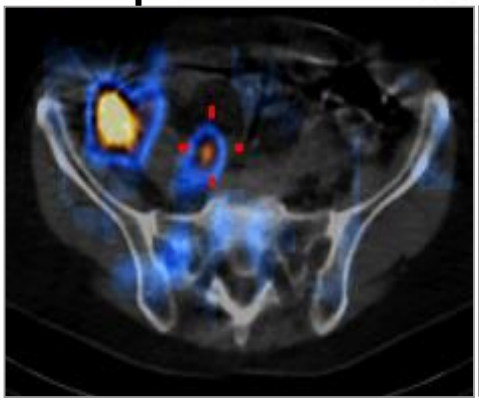
The SLN concept

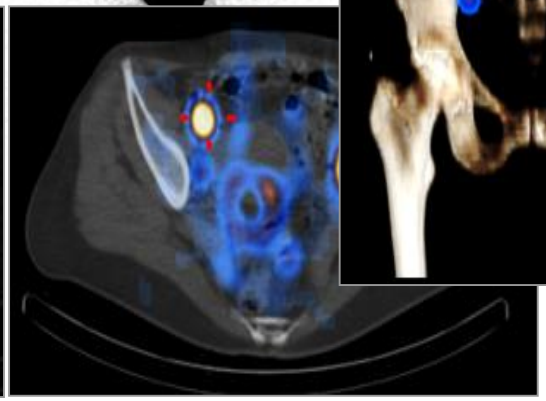












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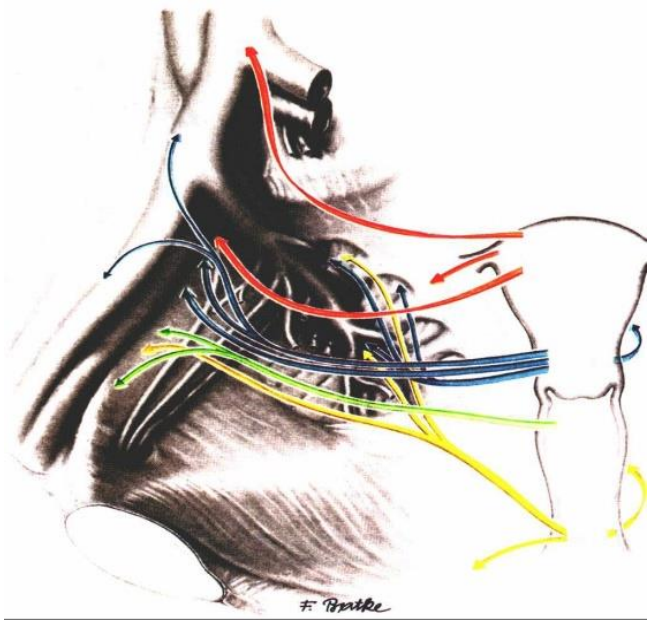
Check list

- Lymphatic drainage ?
- Main pathway + variations ?
- Accessible tumor ?
- Tracer ?
- Nodes accessible ?
- Impact on patients treatment ?



Reiffenstuhl G & al

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Assessment

❖ Feasibility	☑
❖ Reproducibility	☑
❖ Diagnostic accuracy	☑ *
❖ Anatomical information	☑
❖ Histological information (prognosis?)	☑
❖ Reduced morbidity	☑
❖ Similar prognosis	?
❖ Useful data	?

*: high NPV in case of bilateral detection

Altgassen G & al 2008
Lécuru F & al 2011
Plante M,Roy M & al 2011
Cormier B & al 2011

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To maximize the Detection Rate

- Selection of patients
- Training cervical injection
- Combined technique
- SPECT-CT if isotope
- Use of ICG
- Training operative detection

- ≤4cm diameter
- 20 cases***
- No blue dye only
- No planar LS

- Be precise and patient

→ ≥95% detection rate

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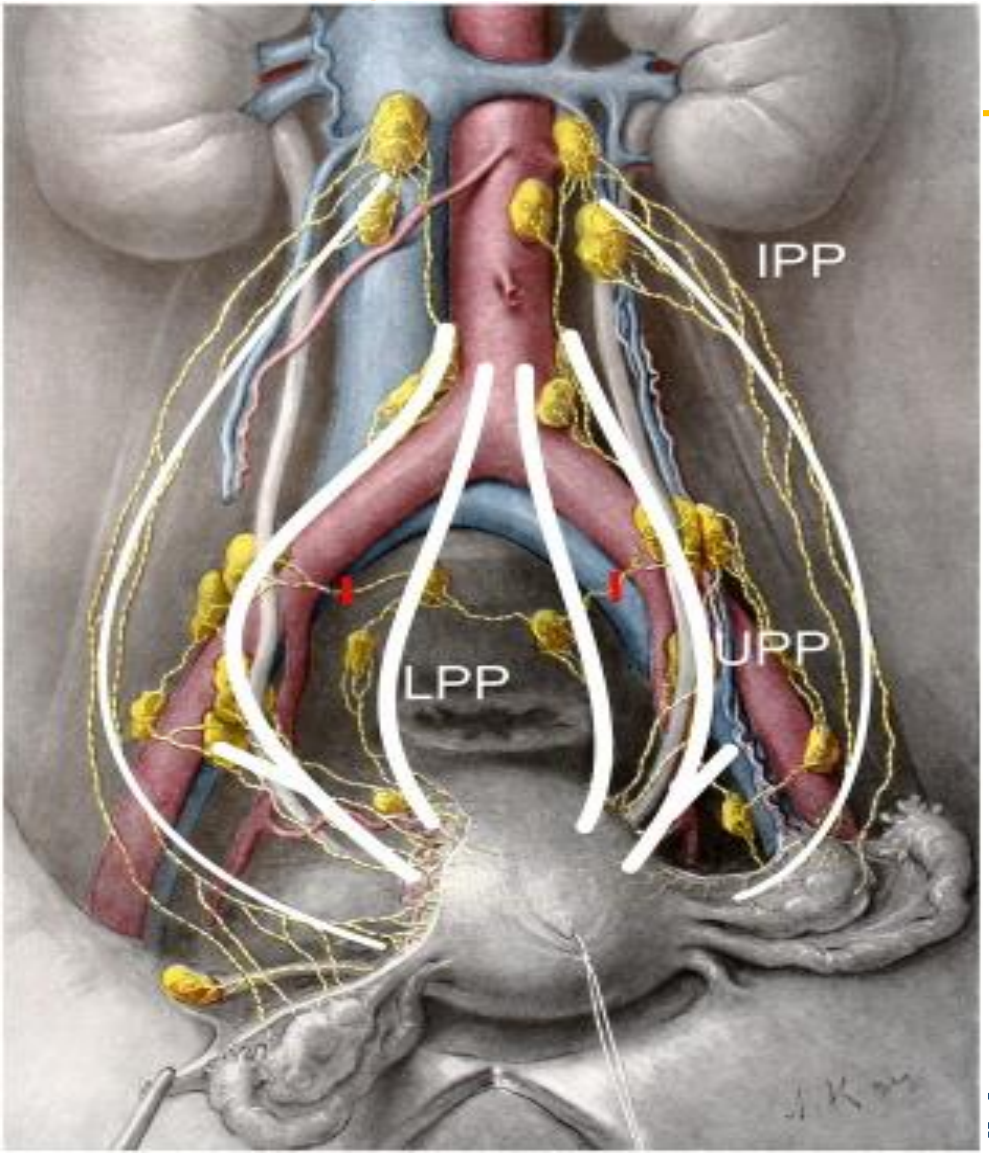

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Senticol1	Senticol2
83,5%	85,8%
5,1%	2,6%
8,5%	9,5%
2,7%	1,1%

≥95% detection rate

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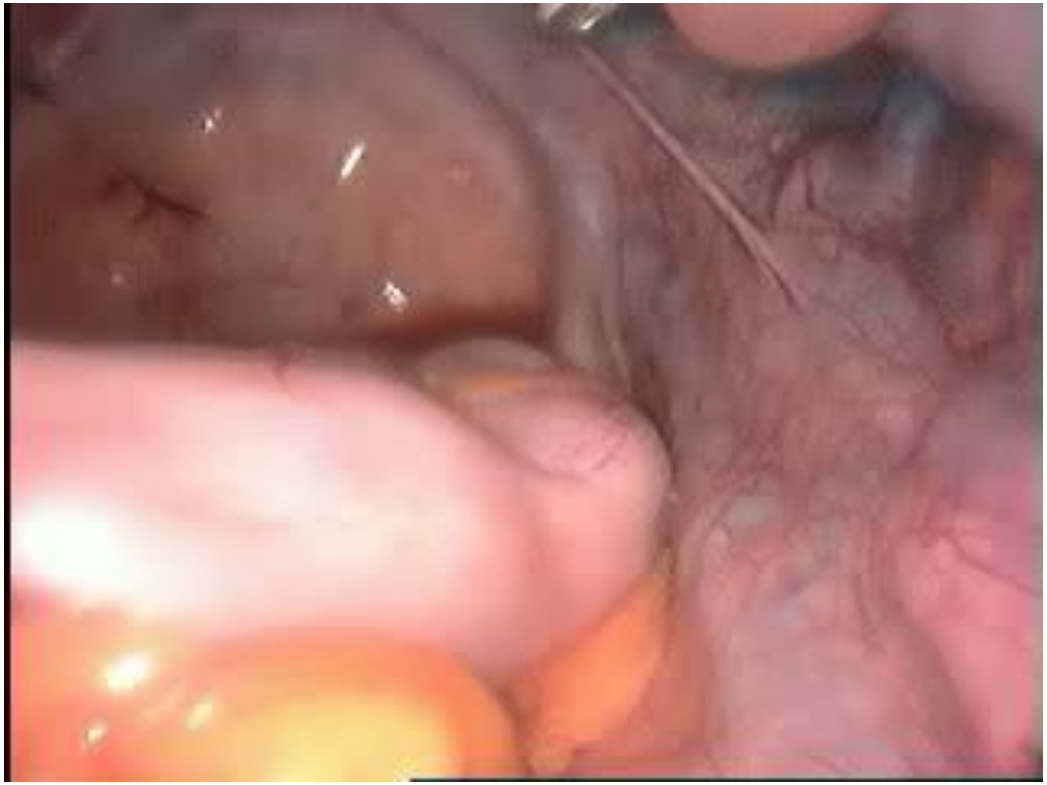

→ ≥95% detection rate

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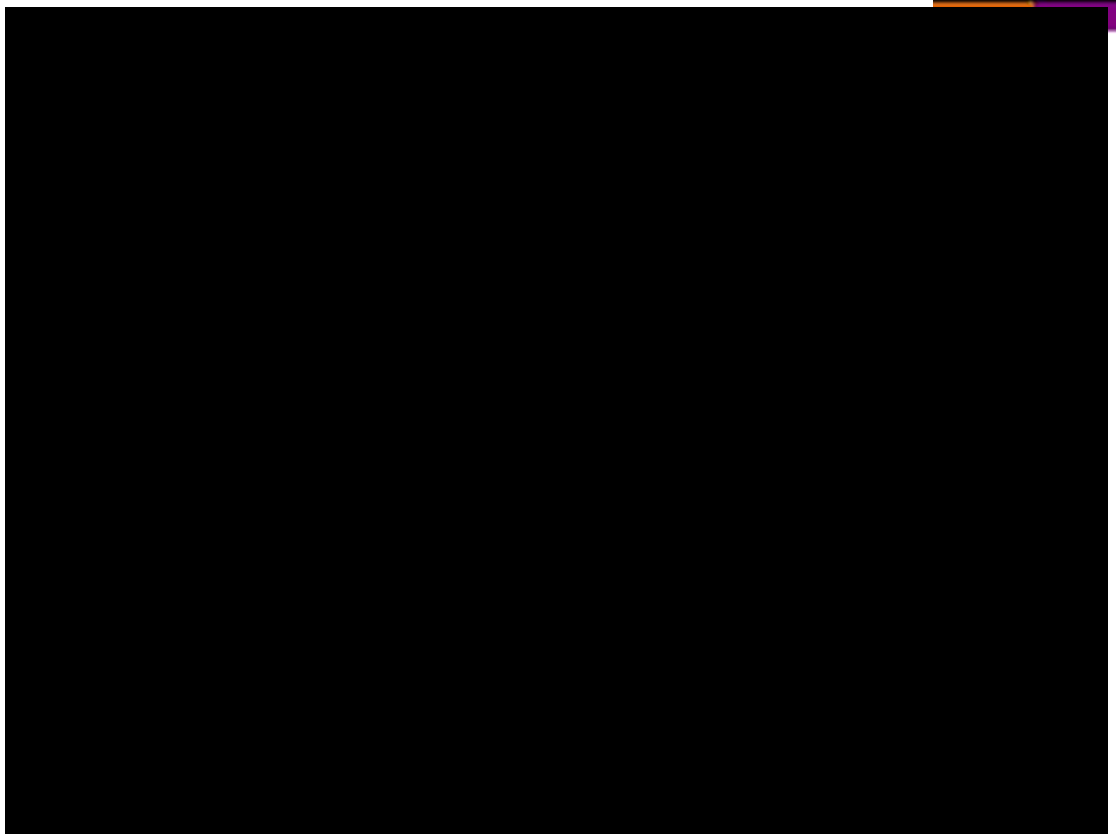

≥95% detection rate

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To Lower the FN rate

- Stage Ia1 – IIa
- No suspicious lymph node on pre-operative imaging and per-operative assessment
- Tumour size <40mm
- **Bilateral detection**

→ FN rate: 1/1257 (0.08%)

Tax C & al 2015

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MSKCC SLN algorithm

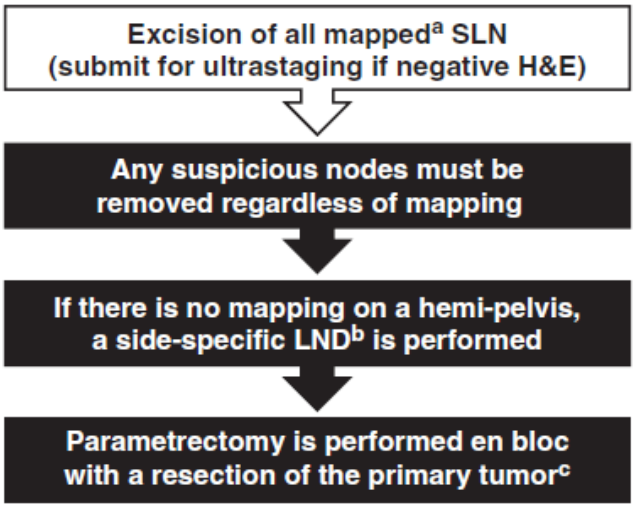

Fig. 1. Surgical algorithm for early cervical cancer. "SLN", sentinel lymph node; "H&E", hematoxylin and eosin staining; "LND", lymphadenectomy. [a]Intracervical injection with isosulfan blue dye, 99m technetium, or both; [b]including interiliac/subaortic nodes; [c]exceptions made for select cases, see text.

- 8/122 (6.6%) : failed detection = bilat LND
- 23/122 (18.9%) : unilat detection = unilat LND

- 91/122 (94.6%) : bilat detection.
- NPV 100%

Cormier B & al 2011

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Quality assurance (SENTICOL)

Preoperative

- Clinical stage ≤ IIa 1
- Abdomino-pelvic MRI : Cervical tumour <30mm, with intact parametria
- No suspicious pelvic or aorto-caval adenopathies (small axis ≥ 10mm and morphologic criteria)
- Training on the cervical isotopic injections
- Performance of lymphoscintigraphy (or SPECT) and adequate training for the interpretation of these imaging modalities.

Intervention

- Clinical exam under general anesthesia : clinical stage ≤ IIa1
- Training for the intra cervical injection of the colorimetric dye.
- Training in the exploration and dissection of sentinel lymph nodes using the laparoscopic technique.
- Bilateral sentinel lymph node detection (otherwise hemipelvic lymphadenectomy of the side with absent detection).

Pathology

- Training on the performance of frozen section of sentinel lymph nodes.
- Training on the performance of ultrastaging of sentinel lymph nodes. Sentinel nodes should be sectioned every 200 µm and stained with hematoxylin-eosin-saffron (HES). When staining is negative, a section from the same level should examined using IHC with the pan-cytokeratin antibody AE1-AE3.

Figure 5. Check list "quality assurance"

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	Blue Dye	Isotope	ICG
Learning curve	10 - 15	10 - 15	<10
DR, bilat DR	+	++	+++
Cost	25€	373€	45€
Regulatory	No	Complex	No
Risk	++ (<2%)	0	+ (<2/1000)
Easy handling	Yes	Moderate	Yes *
Detection ergonomy	Yes §	Moderate $	Yes £
Delay inj-detection	Short (15 min)	Long	Short (<10min)
Obese patients	+	+++	+++
Control	Ex vivo	Imaging, ex vivo	Ex vivo
Leakage	Yes	No	No
Parametrium	Risk FN	Risk FN	Good

- * Possibility of re-injection
- $ coordination with nuclear medicine
- § Blue on the cervix and surrounding tissue
- £ non visible without IR light

ICG enhances DR and bilateral DR

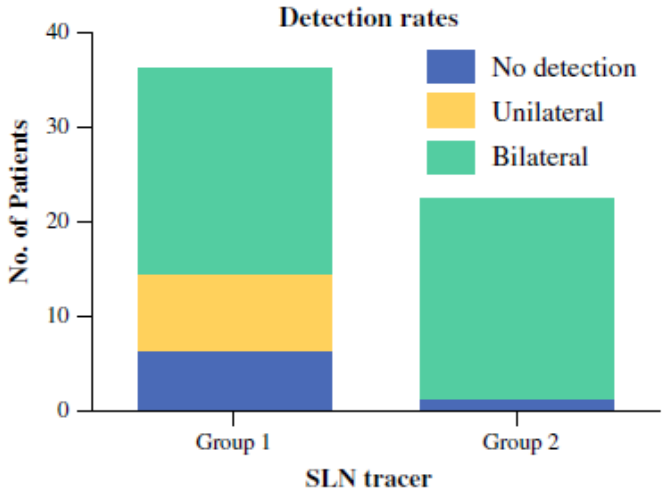

FIG. 2 Overall SLN detection rates were 83 and 95.5 % for Groups 1 and 2, respectively (p = NS). Bilateral SLN detection rates were 61 and 95.5 % for Groups 1 and 2, respectively ($p = 0.0201$). *SLN* sentinel lymph node

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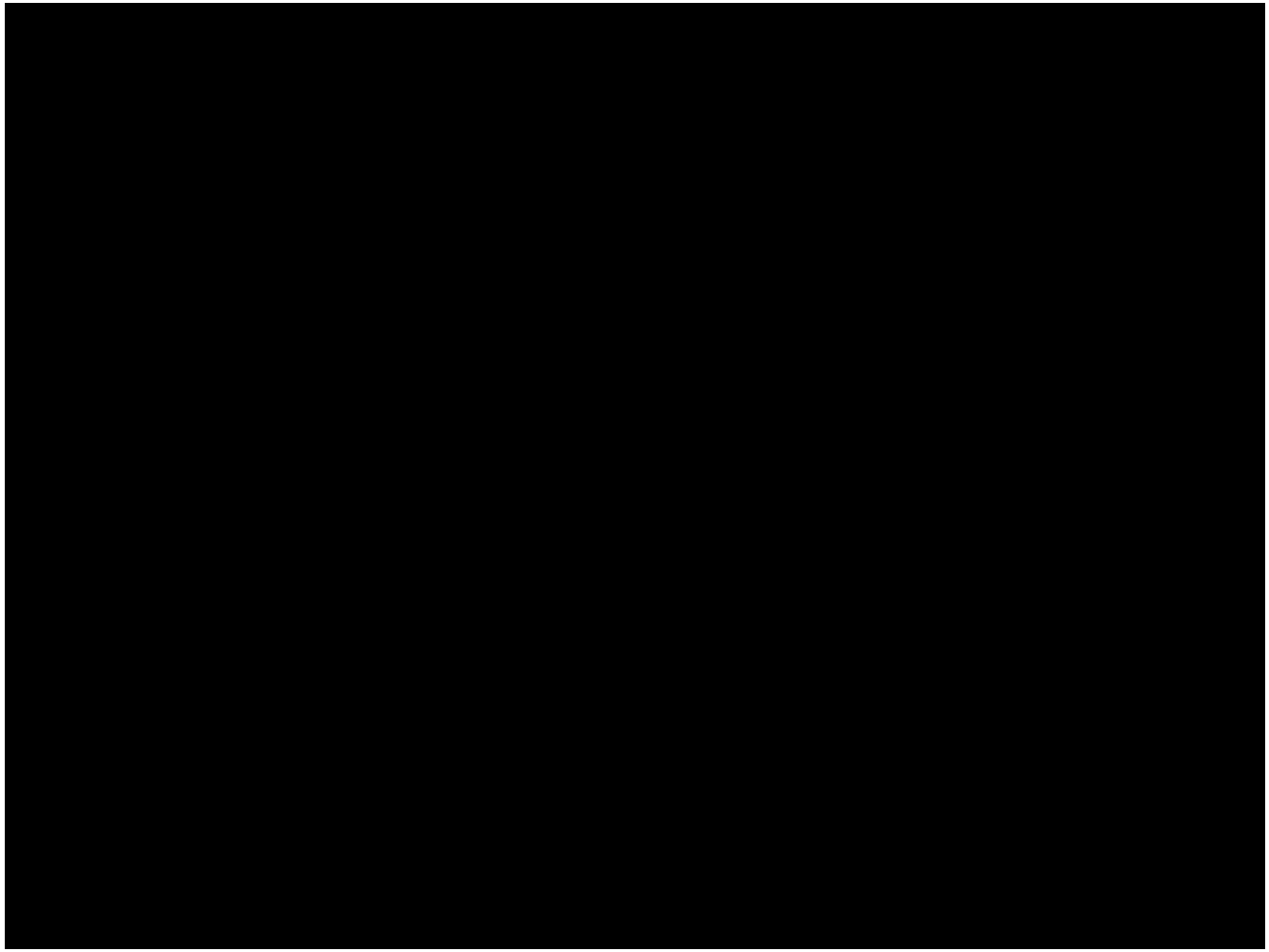
Imboden S & al 2015

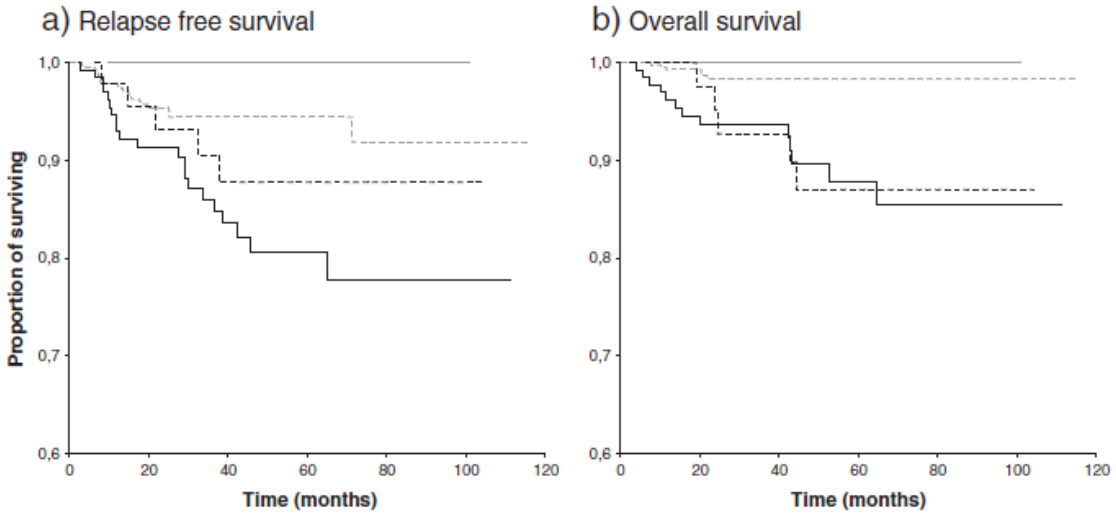


SLN better than PLN

	pN1	pN0
≤ 20mm	10%	90%
> 20mm	12%	88%

Fagotti A & al 2016
Ferrandina G & al 2017

ITC and micrometastases



Mutual comparison of categories (p values):

	Negative	ITC	Micro-met.
Macro-met	0.001*	<0.001*	0.258
Micro-met.	0.128	0.008*	
ITC	0.201		

Mutual comparison of categories (p values):

	Negative	ITC	Micro-met.
Macro-met.	<0.001*	0.009	0.886
Micro-met.	<0.001*	0.036	
ITC	0.549		

* Mark of statistical significance: p values lower than Bonferroni –corrected threshold p = 0.008

Fig. 2. Survival endpoints stratified according to final lymph node status (based on SN ultrastaging and pelvic nSN evaluation).

Cibula D et al. 2012

Unexpected locations of the SN in the Senticol studies (139 and 206 patients)

Location of the SN:	Senticol1	Senticol2
– External iliac/ obturator:	83,5%	85,8%
– Para-aortic + presacral:	5,1%	2,6%
– Common iliac:	8,5%	9,5%
– Parametrium :	2,7%	1,1%

- **Unxecpected location = 16-18% patients**
- **Senticol 1: 2 patients had a metastatic aberrant SN with all pelvic nodes negative including after serial-sectioning and immunohistochemistry**

Senticol 2: PRIMARY END-POINT = MORBIDITY related to the LYMPHATIC DISSECTION

	Arm A (SLN)		Arm B (CONTROL)		P
	Nb	%	Nb	%	
Total Patients	**105**	100,0	**101**	100,0	
Global lymphatic morbidity	**33**	31,4	**52**	51,5	**0,0046**
Major morbidity (grade 3 – 4)	**1**	1	**6**	5,9	0,061
Minor morbidity (grade 1 – 2)	**32**	30,5	**50**	49,5	**0.0068**

Mathevet P & al

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Senticol 2: neurological symptoms

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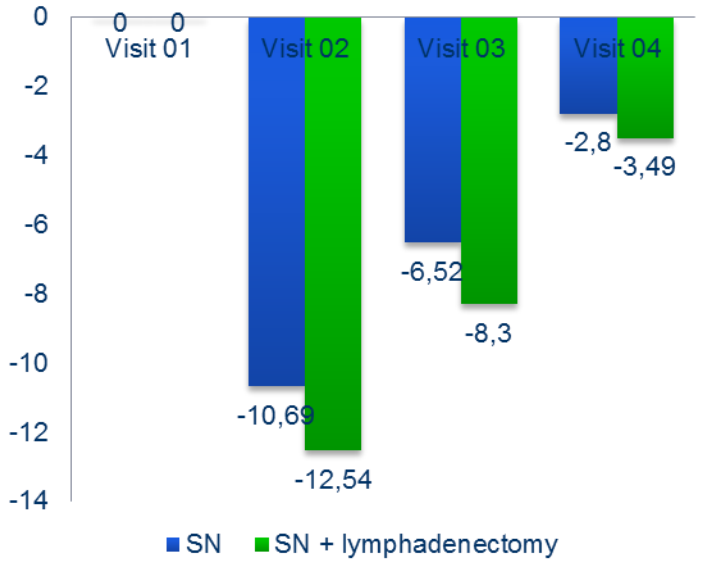
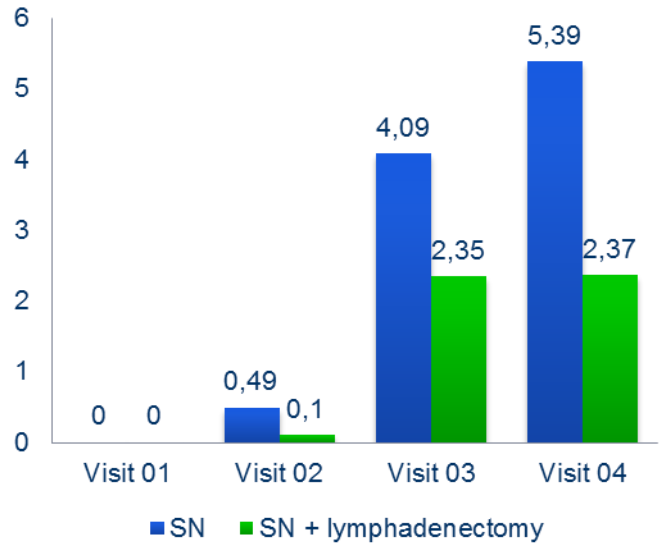
Senticol2: quality of life (SF36)



Physical score



Psychic score

Mathevet P & al

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Survival ?

- SENTIX:
  - Prospective observational study
  - on going

- SENTICOL III
  - International randomized controlled trial
  - starting

Still indications for lymphadenectomy ?

- Is there a place for patients with Ib2 or IIb stages ?
- Is there a place after neo-adjuvant chemotherapy ?
- Patients with pos SLN

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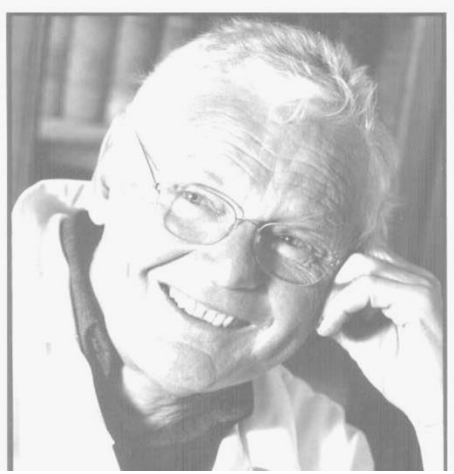
De-escalation in ECC

- Laparoscopy, Trachelectomy, Radicality, Neoadjuvant chemo, NSRH, SLN

- N0 patients
  - Maintain a good prognosis
  - Improve long term QoL
- N1 patients
  - More accurate information for a personalized treatment



Thank you

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