Cervix Cancer Committee

International prospective validation trial of sentinel node biopsy in cervical cancer

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For GINECO Group

Nodal involvement is the most important prognostic factor for early cervical cancer

Low tumor burden
<25% N+ patients
1N+ in 50% cases
size 1-22mm; 22%<2mm

Complications of systematic lymphadenectomy

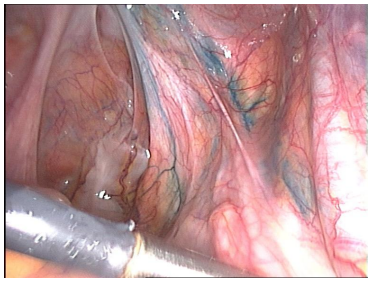
Up 10% nodal recurrences in « pN0 » patients

Inoue T & al 1990
Benedetti Panici PL & al 1996
Lee K & al 2006
Sakuragi N & al 1999
Horn L & al 2008
Gortzak Uzan L & al 2010

❖ The sentinel node concept:

- First node (group of nodes) draining a solid tumour
- The SN status is representative of downstream nodes

Targeted surgery



- Validated in breast, vulvar cancer, penile cancer, melanoma

Sentinel Node Biopsy – early cervical cancer

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

*: high NPV in case of bilateral detection and respect of the Cormier algrythm

Altgassen G & al 2008
Lécuru F & al 2011
Plante M,Roy M & al 2011
Cormier B & al 2011
Mathevet P & al 2015

What has been done ?

- Prospective Multicentre Diagnostic trials
  - Altgassen C & al 2008
  - Lécuru F & al 2011

- Randomized multicentre trial
  - Main objective : morbidity (II: quality of life, cost, etc)
  - Design : SLN vs. SLN + PLN (in N0 patients)
  - Preliminary results : better QoL with SLN alone (Mathevet P & al, ASCO 2015)

- WE NEED A VALIDATION STUDY !

2014 NCCN Guidelines

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2014
Cervical Cancer

NCCN Guidelines Index
Cervical Cancer TOC
Discussion

CLINICAL STAGE	PRIMARY TREATMENT (FERTILITY SPARING)[d]	
Stage IA1 (no lymphovascular space invasion [LVSI])	Cone biopsy[e] with negative margins (preferably a non-fragmented specimen with 3-mm negative margins) (If positive margins, repeat cone biopsy or perform trachelectomy)	See Surveillance (CERV-10)
Stage IA1 (with LVSI) and Stage IA2	Cone biopsy[e] with negative margins (preferably a non-fragmented specimen with 3-mm negative margins- if positive margins, repeat cone biopsy or perform trachelectomy) + pelvic lymph node dissection ± para-aortic lymph node sampling (category 2B) (Consider sentinel lymph node mapping [category 2B])[f] or Radical trachelectomy + pelvic lymph node dissection[f] (± para-aortic lymph node sampling [category 2B]) (Consider sentinel lymph node mapping [category 2B])[f]	See Surveillance (CERV-10)
Stage IB1[c]	Radical trachelectomy + pelvic lymph node dissection[f] ± para-aortic lymph node sampling (Consider sentinel lymph node mapping [category 2B])[f,g]	See Surveillance (CERV-10)

[c]Fertility-sparing surgery for stage IB1 has been most validated for tumors ≤2 cm. Small cell neuroendocrine histology and adenoma malignum are not considered suitable tumors for this procedure.

[d]No data support a fertility-sparing approach in small cell neuroendocrine tumors or minimal deviation adenocarcinoma (also known as adenoma malignum). Total hysterectomy after completion of childbearing is at the patient's and surgeon's discretion, but is strongly advised in women with continued abnormal pap smears or chronic persistent HPV infection.

[e]Cold knife conization (CKC) is the preferred method of diagnostic excision, but LEEP is acceptable, provided adequate margins and proper orientation are obtained.

[f]See Principles of Evaluation and Surgical Staging (CERV-A).

[g]For SLN mapping (category 2B), the best detection rates and mapping results are in tumors <2 cm.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

N Abu Rustum, Melbourne 2014

Pending questions

- Not a standard despite numerous papers
  - What is necessary to become a standard ?

- Prognosis of « Low volume disease » ?
  - Cut-off ?
  - Treatment ?

- (Translational research)

⟶ Need for a validation study

Methodology

- Randomized trial
  - SLN vs SLN + PLN (in N0 patients)
- Co-primary
  - DFS + QoL

Objectives

- Main objective: « co-primary » disease free survival and health related quality of life
  - non-inferiority of SLN biopsy vs SLN biopsy + lymphadenectomy for DFS
  - superiority of SLN biopsy for QoL
  - The hypothesis is that SLN biopsy alone provides similar survival and better quality of life.

- Secondary objectives:
- - Longitudinal and other dimensions of health related Quality of life.
- - Positive and negative predictive values of SLN biopsy.
- - Outcome of pN1 patients according to the size of metastasis and treatment.
- - Overall survival.
- - Recurrence free survival.

- Inclusion criteria :
- - Squamous or adenocarcinoma of the cervix (proven by biopsy or cone biopsy)
- - Stage Ia1 with lymphovascular emboli to IIa1 (clinical stage)
- - Maximum diameter ≤40mm on MRI
- - No suspicious node on pelvic and abdominal MRI (small axis ≥ 8-10mm and morphologic criteria)
- - Informed consent given

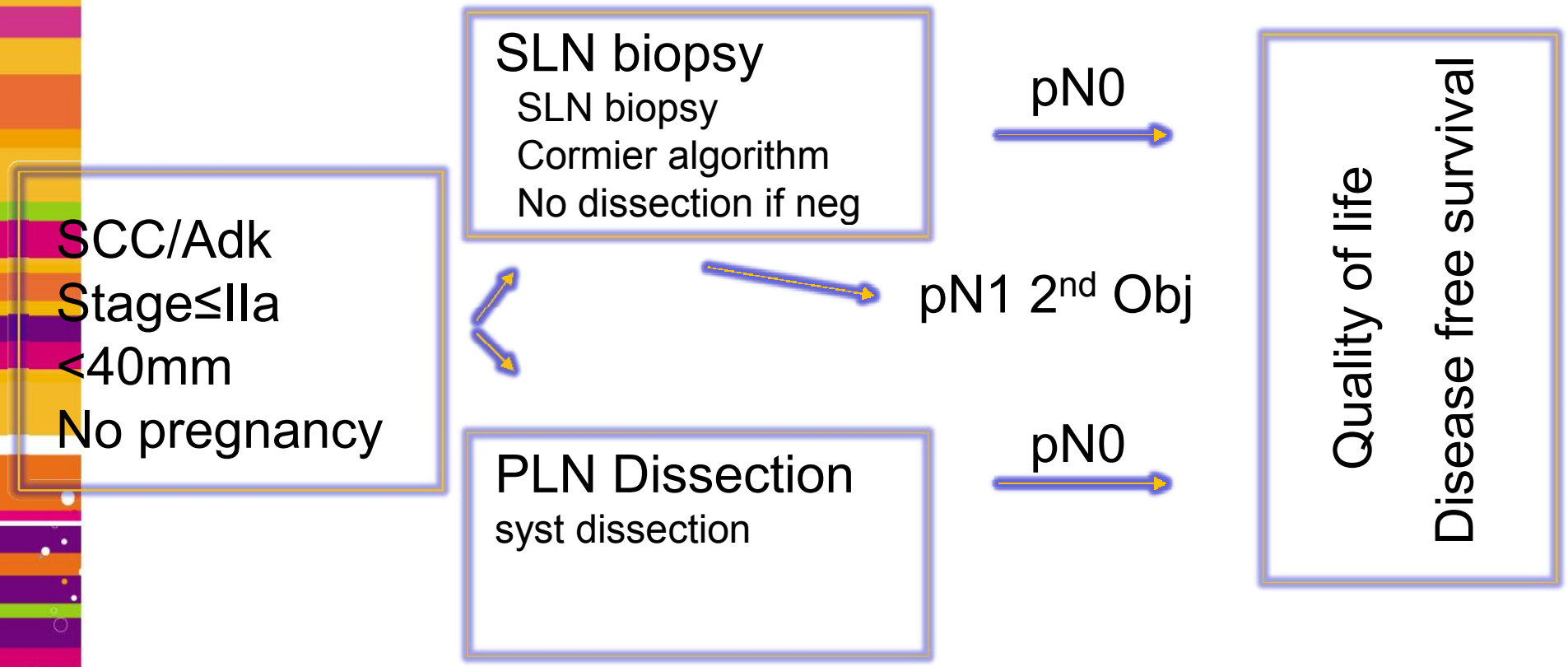
- Non inclusion criteria:
- - Age <18 years
- - Pregnancy
- - Previous pelvic of abdominal cancer
- - Previous chemo and/or radiation therapy for the cervical cancer
- - Allergy to blue dye, isotope or indocyanine green

Validation study

- Randomized trial

- Qualified centers
  - Surgeon qualification, “Cormier algorithm”, pathology, etc.
  - Comparison of SLN negative patients
  - Prospective matching 1:1 according to stage, date Dg, age, tumor diameter
  - Co-primary: DFS & QoL

Schema


SCC/Adk
Stage≤IIa
<40mm
No pregnancy
SLN biopsy
SLN biopsy
Cormier algorithm
No dissection if neg
pN0
pN1 2nd Obj
PLN Dissection
syst dissection
pN0
Quality of life
Disease free survival

Prognosis of Limited Nodal Metastases

- Patients with ≥1 metastatic SLN (ITC, micromet, macromet).

- disease free survival and overall survival
- according to
  - size of metastasis
  - Treatment (local practice, defined before the beginning of the study).

Number of subjects

- 1-DFS
- With a 3 years-disease free survival of 85% to demonstrate a non-inferiority of SLN biopsy vs SLN biopsy + lymphadenectomy with a non-inferiority margin of 5% (80 vs 85%, HR = 1.373). With a unilateral alpha error of 5%, and a power of 80%, **900 patients** in 3 years, with 4 years of follow-up should be included to observe the required 219 events. An interim analysis is planned when at least 110 events will be observed to reject H0 or H1 using O Brien Fleming and alpha spending function.

- 2-HRQoL
- We target 3 HRQoL dimensions global health, pain and physical functioning of EORTC QLQC 30.
- To demonstrate a superiority of at least one of the 3 targeted dimensions without significant deterioration in at least one with a minimal important difference in mean score of at least 5 points (SD: 20), and a bilateral alpha type one error of 0.015 (Bonferroni adjustment) it would be required to have **815 patients** with available HRQoL scores to reach 85% statistical power.

- 200 patients will be recruited in France (39 centers).
- 780 000€
- International collaboration requested

Thank you

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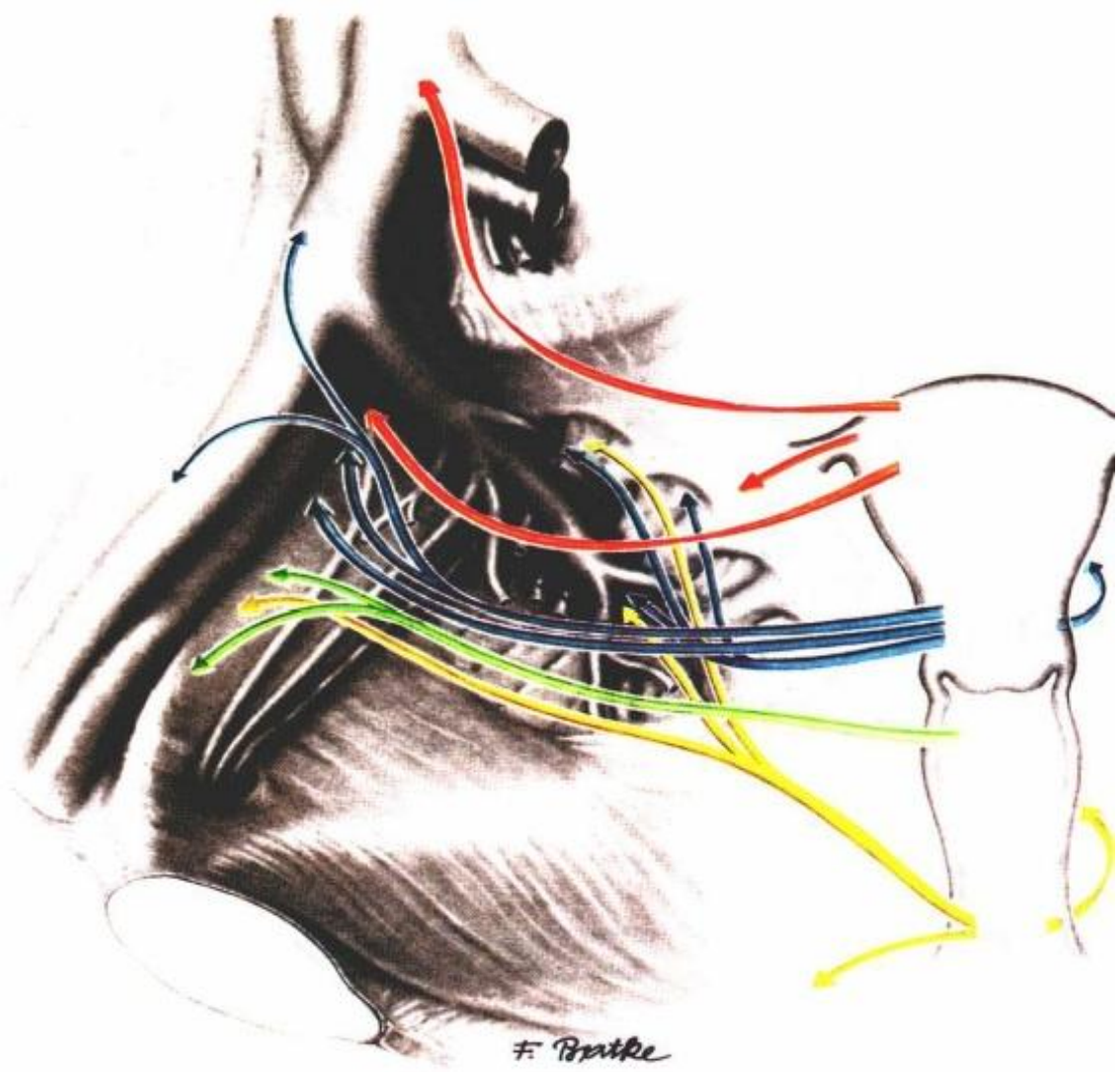

Reiffenstuhl G & al

Cervical cancer = good candidate for SLN biopsy

Table 4. Negative Predictive Value of Pelvic SLN Detection According to Labeling Substance, Tumor Size, Preceding Conization, and Unilateral/Bilateral Detection

Subgroup	Total No. of Patients	No. of Patients		Negative Predictive Value (%)	95% CI	*P**
		True Negative	SLN Negative			
Total†	504	398	422	94.3	91.6 to 96.4	—
Marker						
Technetium	45	38	40	95.0	83.0 to 99.4	.808
Patent blue	157	124	133	93.2	87.5 to 96.8	
Combined	302	236	249	94.8	91.2 to 97.1	
Tumor size						
≤ 20 mm	232	210	212	99.1	96.6 to 100	< .001
> 20 mm	239	162	183	88.5	82.9 to 92.8	
Inconclusive	18					
SLN detection						
Unilateral	188	142	156	91.0	85.4 to 95.1	.062
Bilateral	213	166	172	96.5	92.5 to 98.8	
Inconclusive	103					
Patients with tumor size ≤ 20 mm						
Preceding conization						
Yes	177	166	167	99.4	96.7 to 100	.380
No	55	44	45	97.8	88.2 to 100	
SLN detection						
Unilateral	69	60	61	98.4	91.2 to 100	.999
Bilateral	113	101	102	99.0	94.6 to 100	

Abbreviation: SLN, sentinel lymph node.
*P value of χ^2 test or Fisher's exact test as appropriate.
†Three patients with inconclusive SLN status were excluded from analysis.

Altgassen G & al 2008

ARCAGY - GINECO

Diagnostic value

	Lymphadenectomy		
	pN1	pN0	total
SLN biopsy			
SLN +	23	ND	23
SLN -	2	111	113
total	25	111	136

FN rate / patient : 2 / 25 (8%)

sensitivity: 92% (95% IC: 74% - 99%) VPN : 98.2% (95%IC : 93.2% –99.8%)

NO FALSE NEGATIVE IN PATIENTS WITH BILATERAL DETECTION

Lécuru F & al. 2011

Table 5
Sensitivity of the sentinel lymph node to detect node metastases on final pathology.

Patients group	Sensitivity (SLN with metastasis)
Over all (N = 211)	87.9% (29/33)
At least 1 SLN identified (N = 209)	90.6% (29/32)
Bilateral SLNs identified N = 181	100% (25/25)

Plante M & Roy M 2011

SNB algorithm

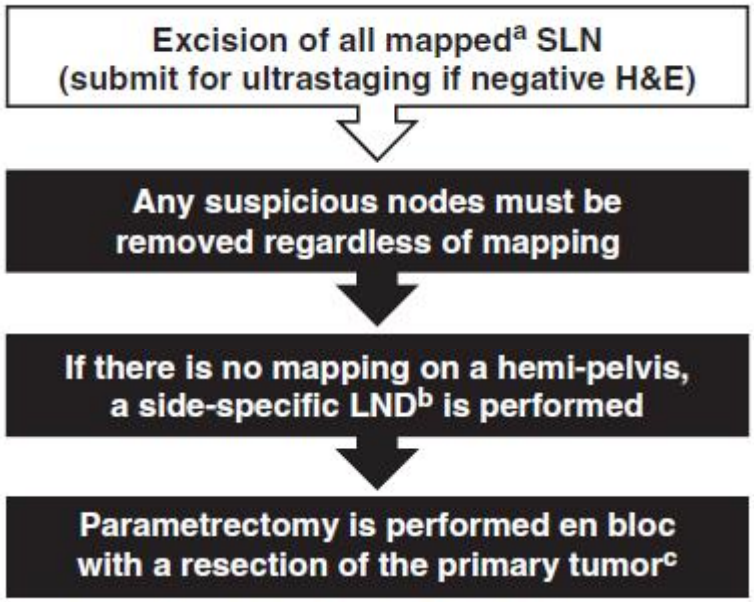

Fig. 1. Surgical algorithm for early cervical cancer. "SLN", sentinel lymph node; "H&E", hematoxylin and eosin staining; "LND", lymphadenectomy. [a]Intracervical injection with isosulfan blue dye, 99m technetium, or both; [b]including interiliac/subaortic nodes; [c]exceptions made for select cases, see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