

Advances in surgical treatment

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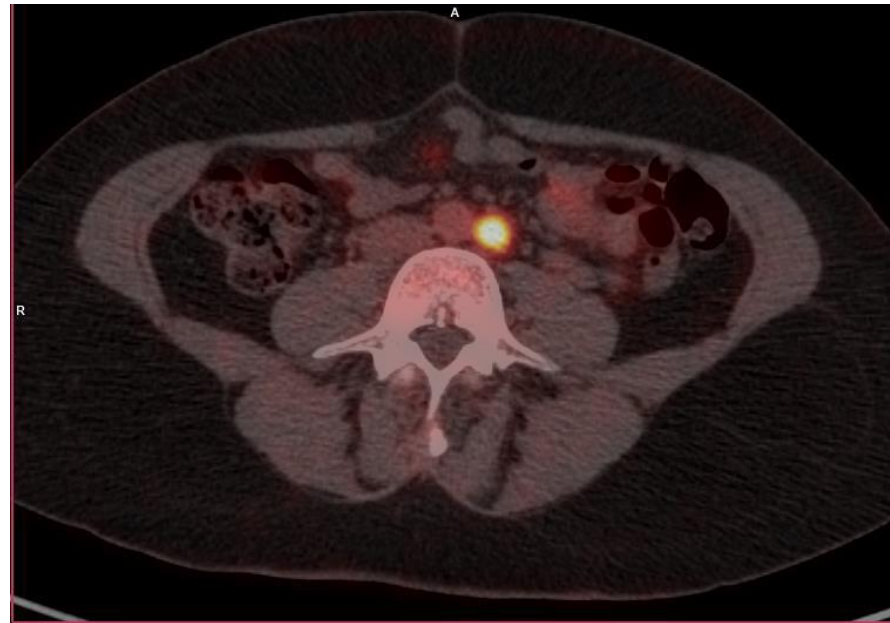
Advances in surgical treatment

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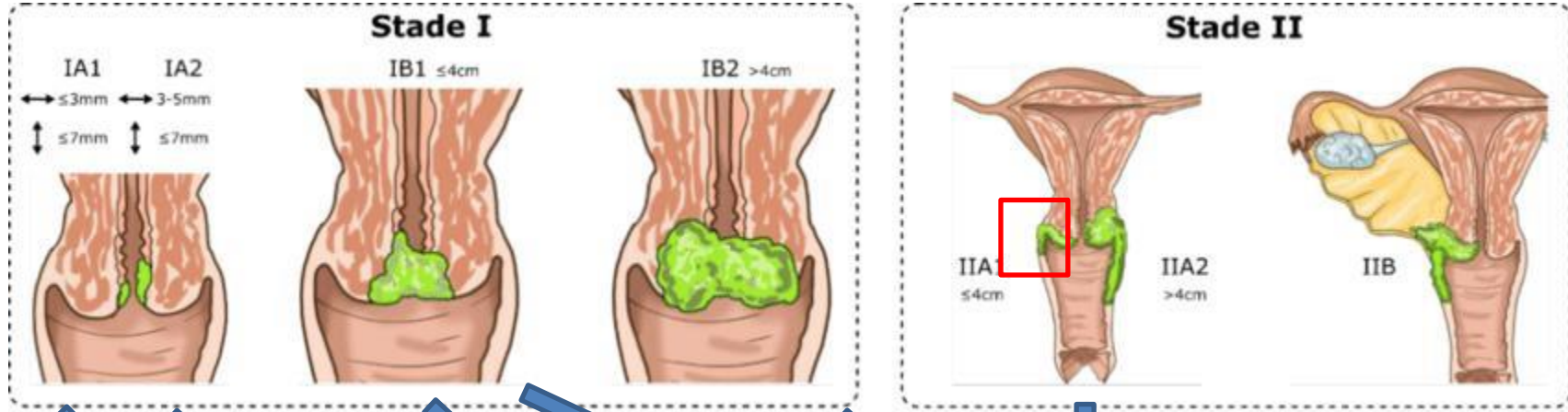
Change of landscape: small tumors with a limited nodal extension

- Selection of patients with small tumors ($\leq 4\text{cm}$), without parametrial extension and with a low risk of nodal metastasis
- HPV+ tumors
- Frequently young patients with long survival and wish to preserve fertility



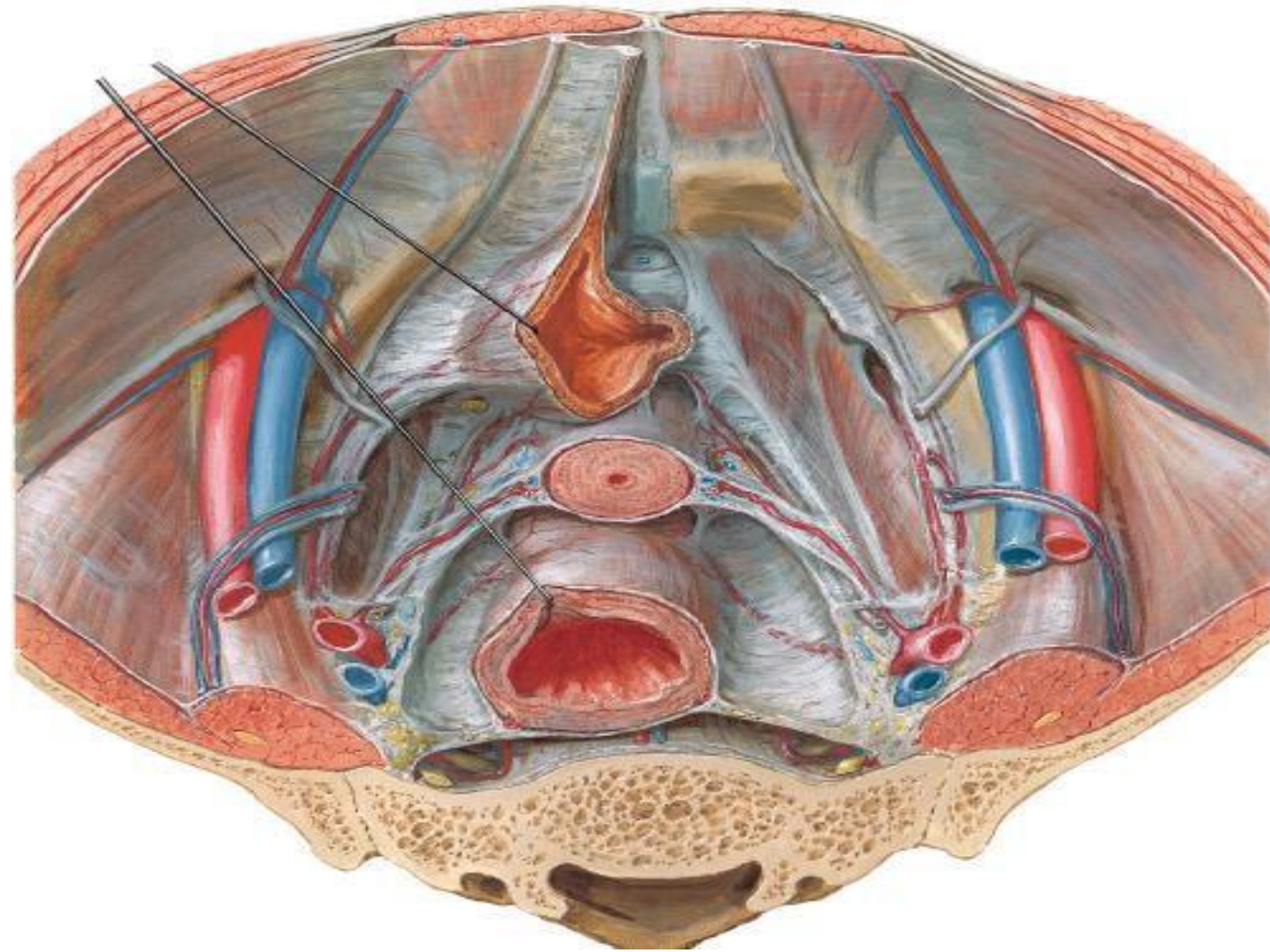
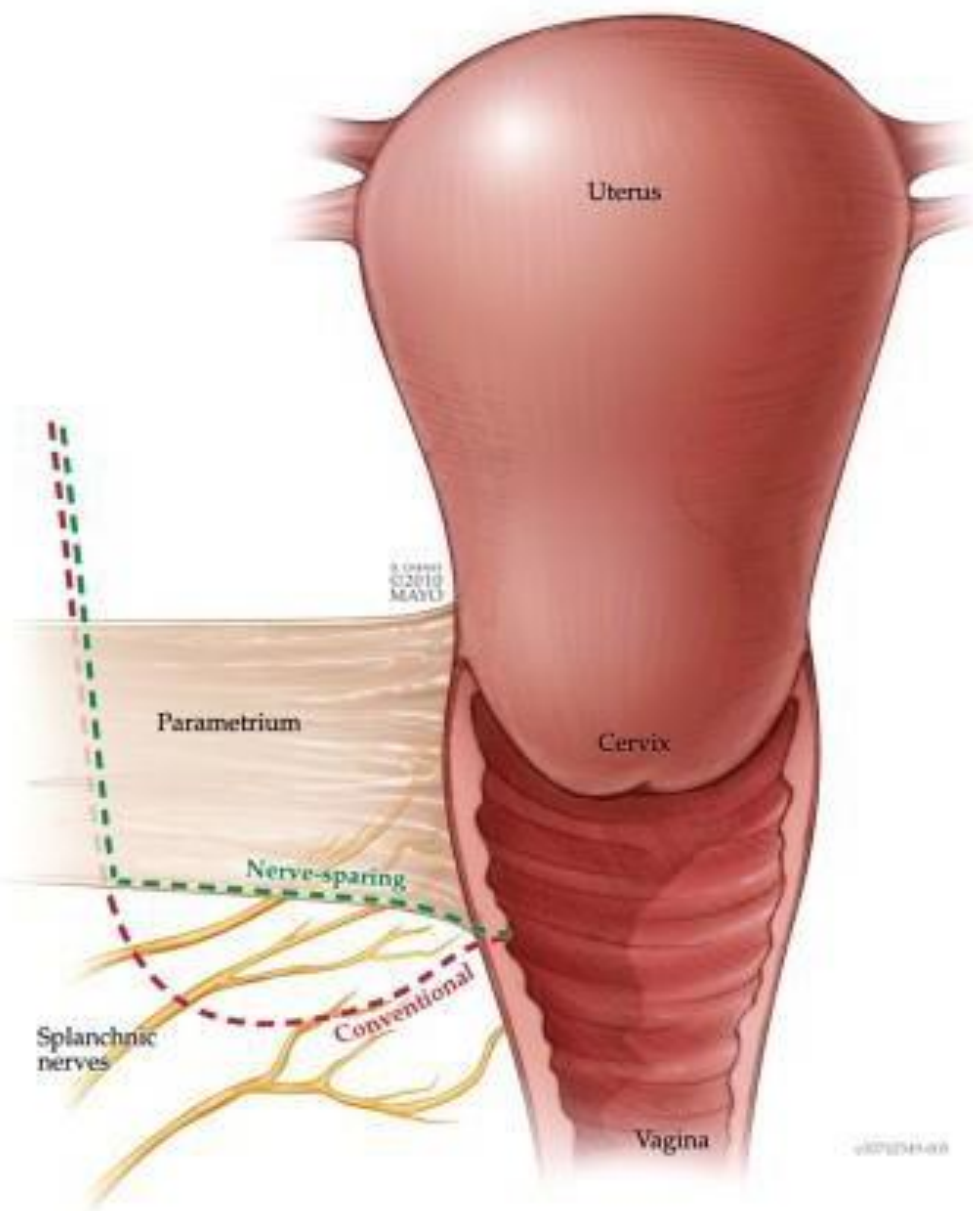
Dr C Malhaire (MRI)
Dr V Huchet (PET-CT)

Total change of surgery: personalization



In sano conisation
 In sano conisation ≤2cm
 Or trachel. Radical trachel.
 Or HT Radical HT
 >2cm
 Radical HT
 NACT + cone ?

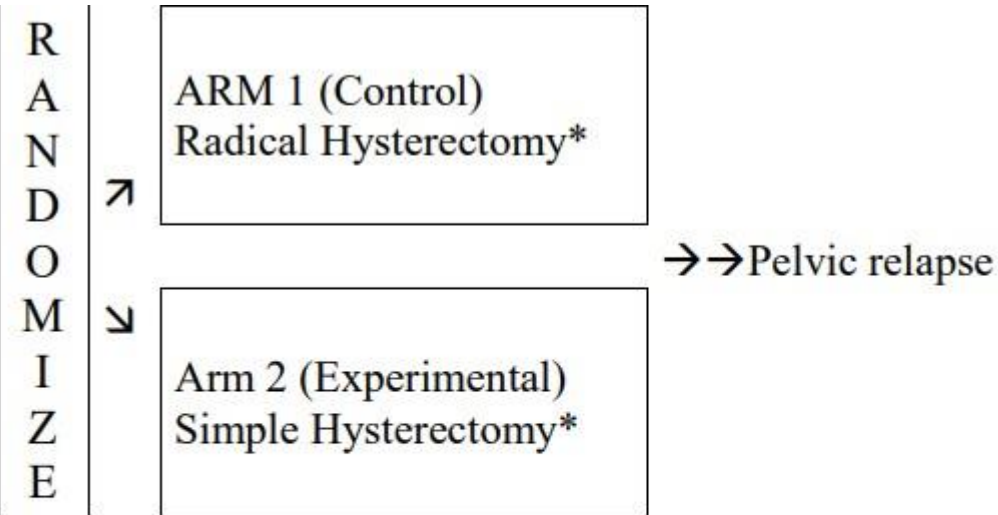




SHAPE trial

Low-risk cervical cancer as defined by:

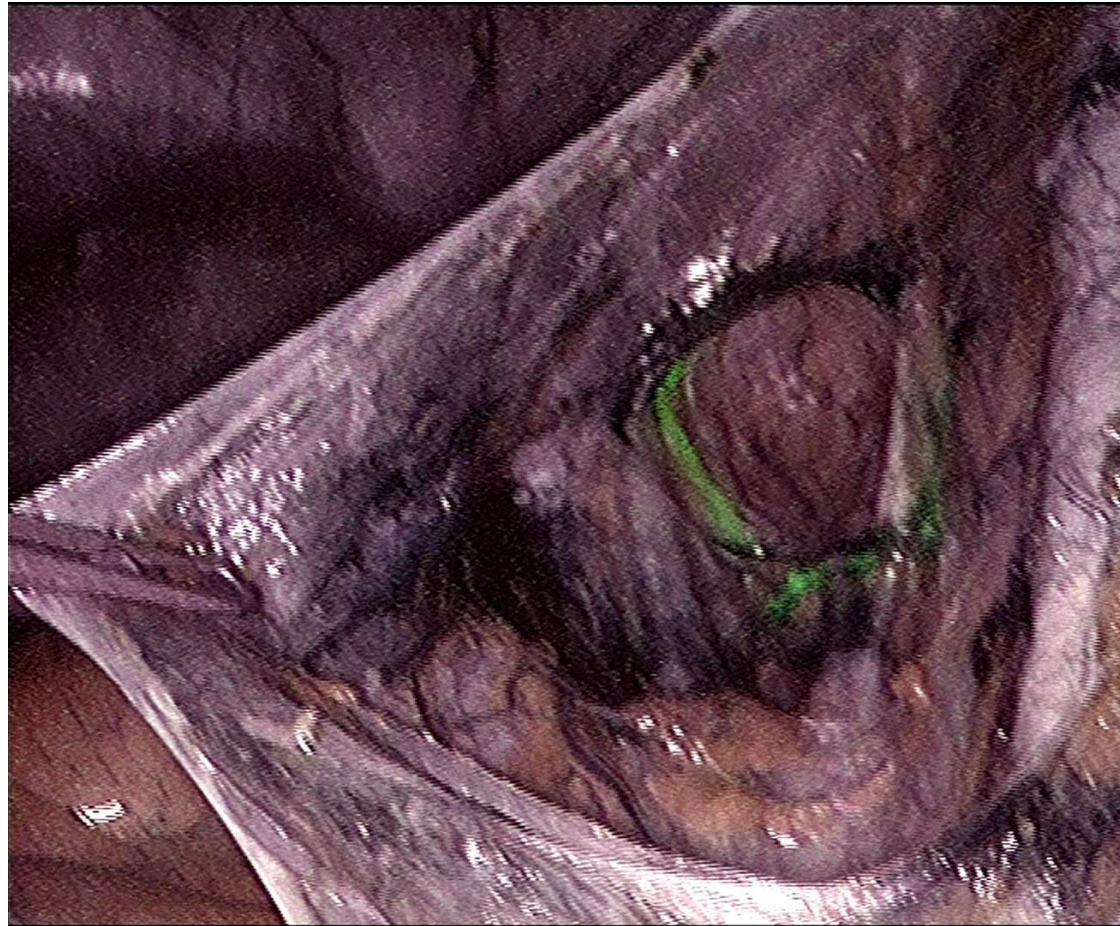
- squamous cell, adenocarcinoma, adenosquamous carcinoma
- Stage IA2 and modified IB1
- < 10mm stromal invasion on LEEP/cone
- < 50% stromal invasion on MRI
- max dimension of ≤ 20 mm
- Grade 1-3 or not assessable



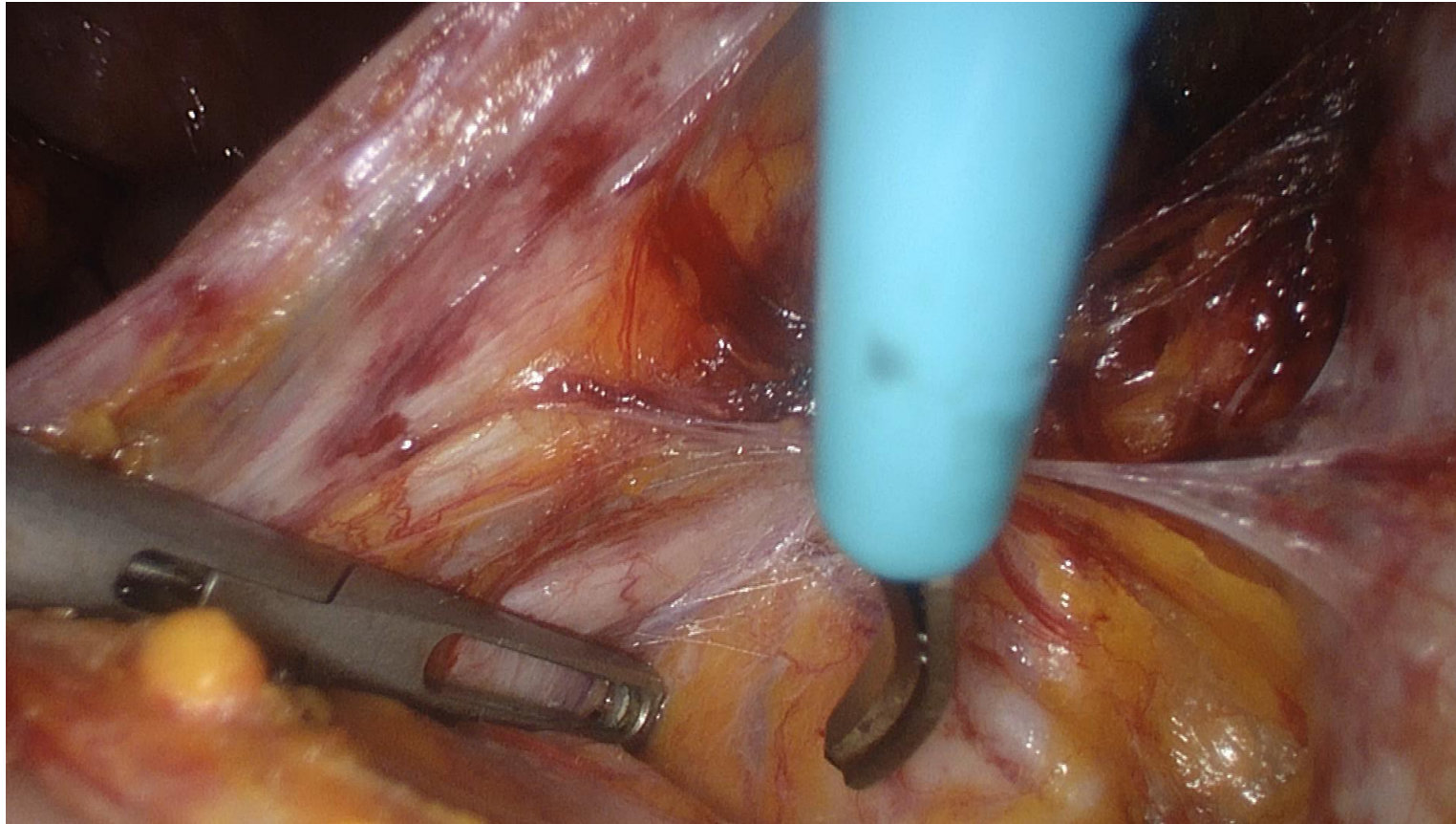
* Regardless of treatment assignment, surgery will include pelvic lymph node dissection with optional sentinel lymph node (SN) mapping. If SN mapping is to be done, the mode is optional, but the laparoscopic approach is preferred.

Planned sample size: 700 (non-inferiority at 0.05 level with 80% power)

Nodes: sentinel node biopsy



Nodes: sentinel node biopsy



Sensibility and negative predictive value

Table 2
Diagnostic accuracy per technique.

| | Studies | TP | FN | TN | Total | Pooled sensitivity (95% CI) | Range NPV |
|-------------------|---------|-----|-----|------|-------|-----------------------------|-----------|
| Overall | 43 | 544 | 156 | 2620 | 3320 | 81% (47–95%) | 59–100% |
| FS or H&E | 18 | 176 | 94 | 1005 | 1275 | 68% (38–88%) | 59–100% |
| Ultra staging | | 251 | 19 | 1005 | 1275 | 94% (80–99%) | 91–100% |
| Proposed criteria | | 251 | 1 | 1005 | 1257 | 99% (98–100%) ^a | 97–100% |

CI; confidence interval.

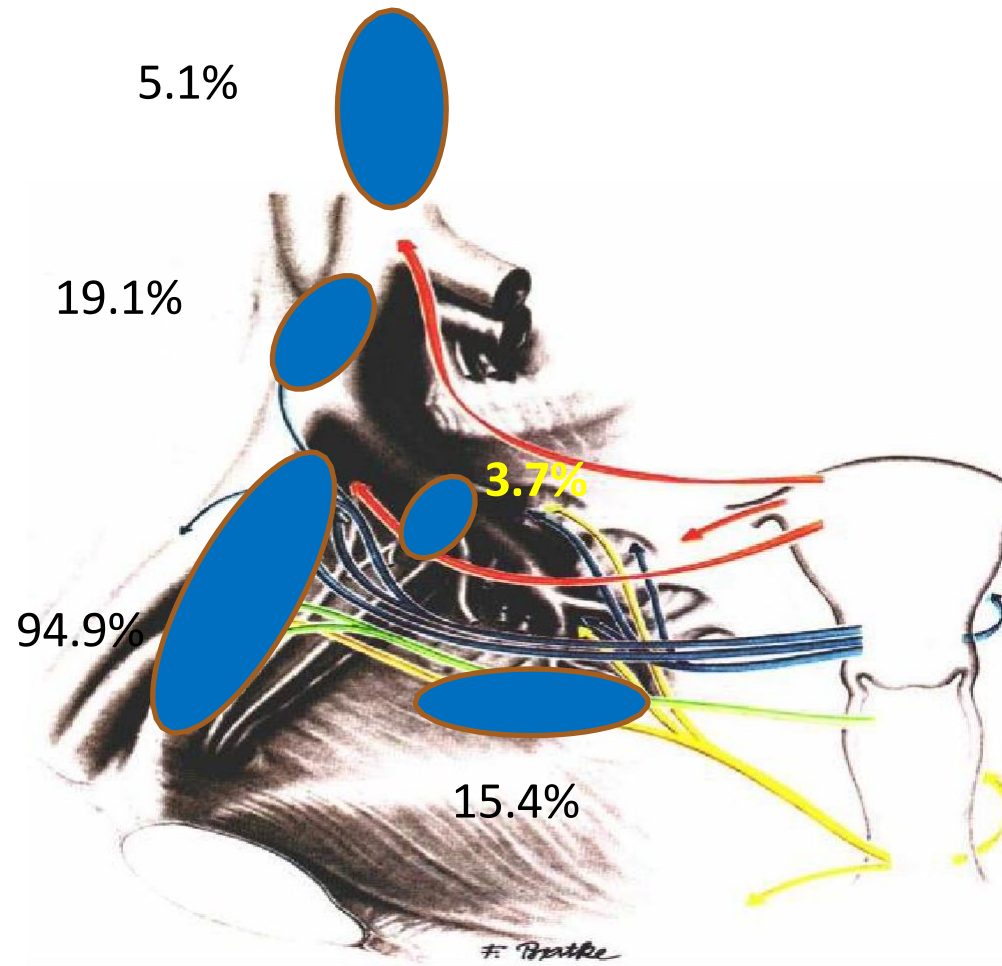
TP; true positive i.e. a tumor positive SLN regardless of remaining pelvic lymph nodes status.

FN; false negative i.e. a tumor negative SLN with metastasis present in remaining pelvic lymph nodes.

TN; true negative i.e. a tumor negative SLN and no metastasis present in remaining pelvic lymph nodes.

^a Assessed if it were a single study.

Anatomical information



≥ 1 SLN in an unexpected area in 38.2% patients.

SLN **ONLY** in an unexpected area in 5.1%

Metastatic SLN in an unexpected area in 4/23 (17%) of pos. patients.

CTI and micrometastases

| Size of metastases | | | |
|--------------------|-----------------|--------|----------|
| Study | SENTICOL I – II | SENTIX | SENTIREC |
| N | 321 | 391 | 245 |
| Macromet. | 16 | 29 | 28 |
| Micromet. | 11 | 21 | 10 |
| ITC | 13 | 12 | ? |

Guani B & al Cancers 2020

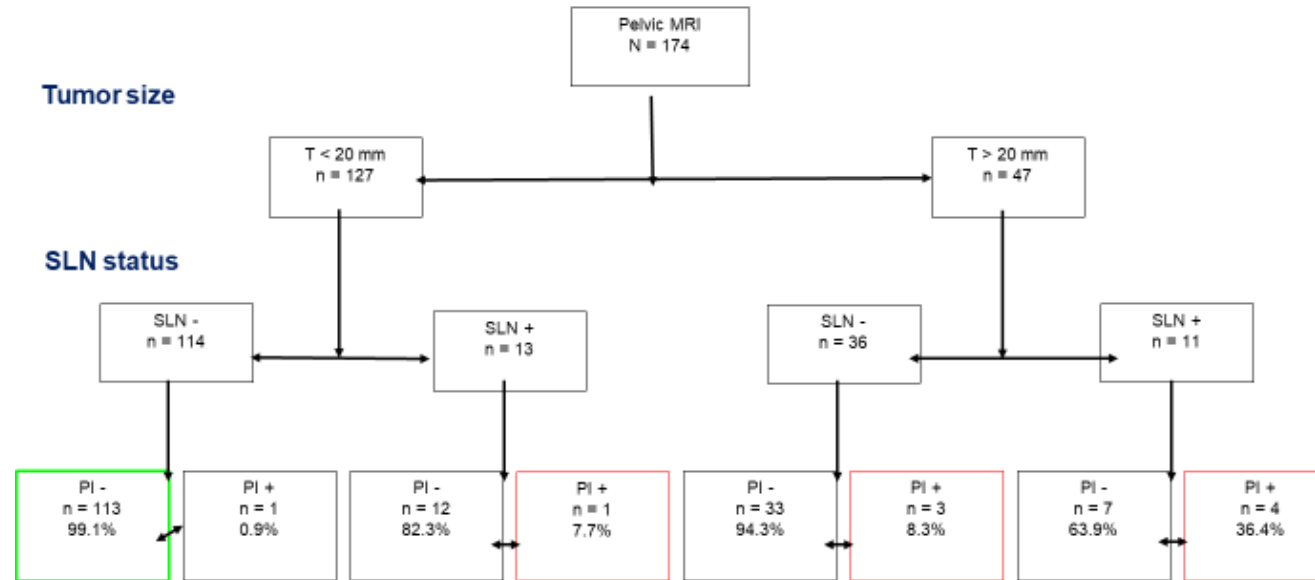
Cibula D & al Eur J Cancer 2020

Sponholtz A & al Gynecol Oncol 2021

Added value

Parametrial information

SLN and parametrial involvement



Balaya V & al 2019

Morbidity

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

| | Arm A (TEST) | | Arm B (CONTROL) | | P VALUE |
|-----------------------------|--------------|-------|-----------------|-------|---------------|
| | 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 2017

Quality of life

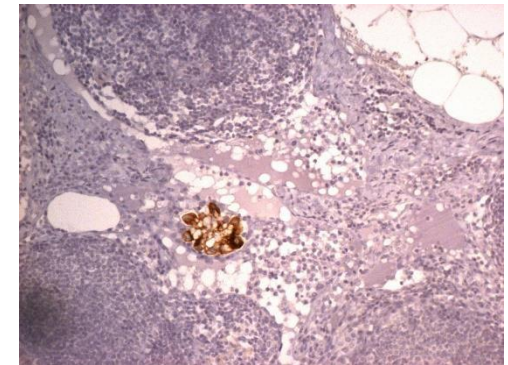
TABLE 3 | Percentage of increase of the circumferences of mid-thigh and top thigh between the two groups (SLN alone vs. standard).

| Mean differential (%) | SLN group | Standard group |
|-------------------------|-----------|----------------|
| Mid-thigh, right | 3.92 | |
| Mid-thigh, left (%) | 3.53 | |
| Top of thigh, right (%) | 2.25 | |
| Top of thigh, left (%) | | |

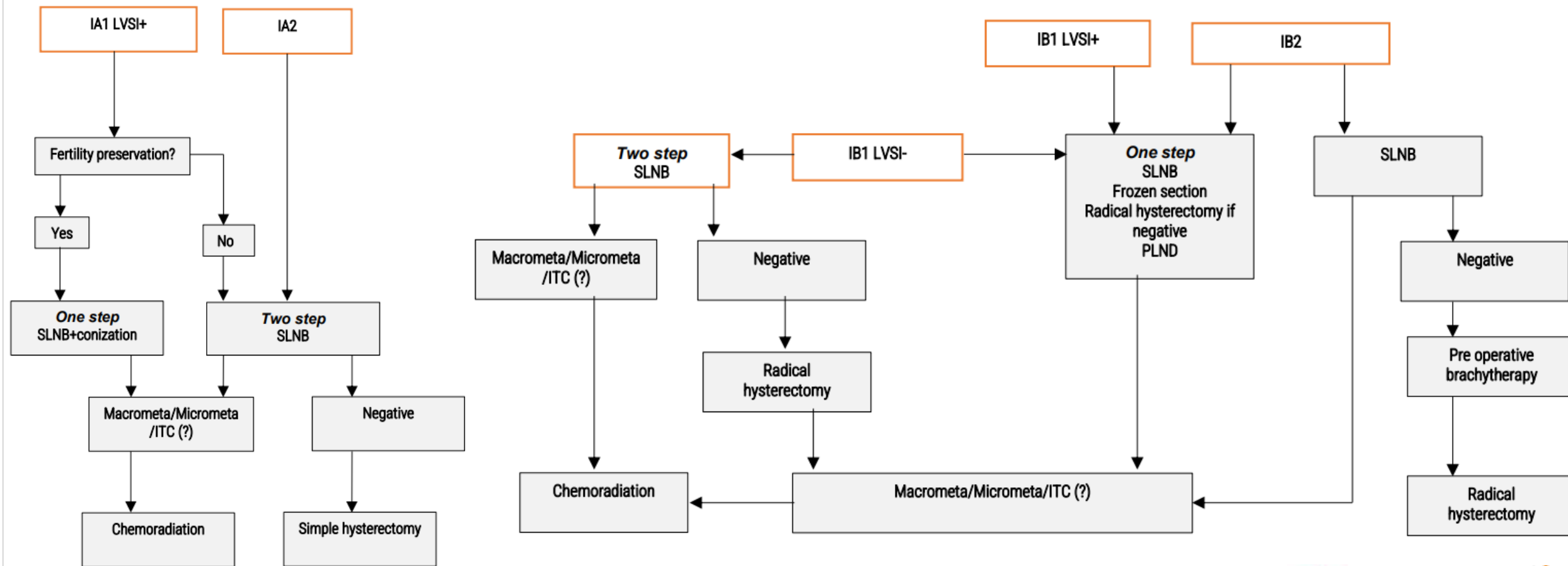
The difference is calculated between the measurements at the first and last visits and the mean of the measurements at the first and last visits of thigh.

Ultrastaging.

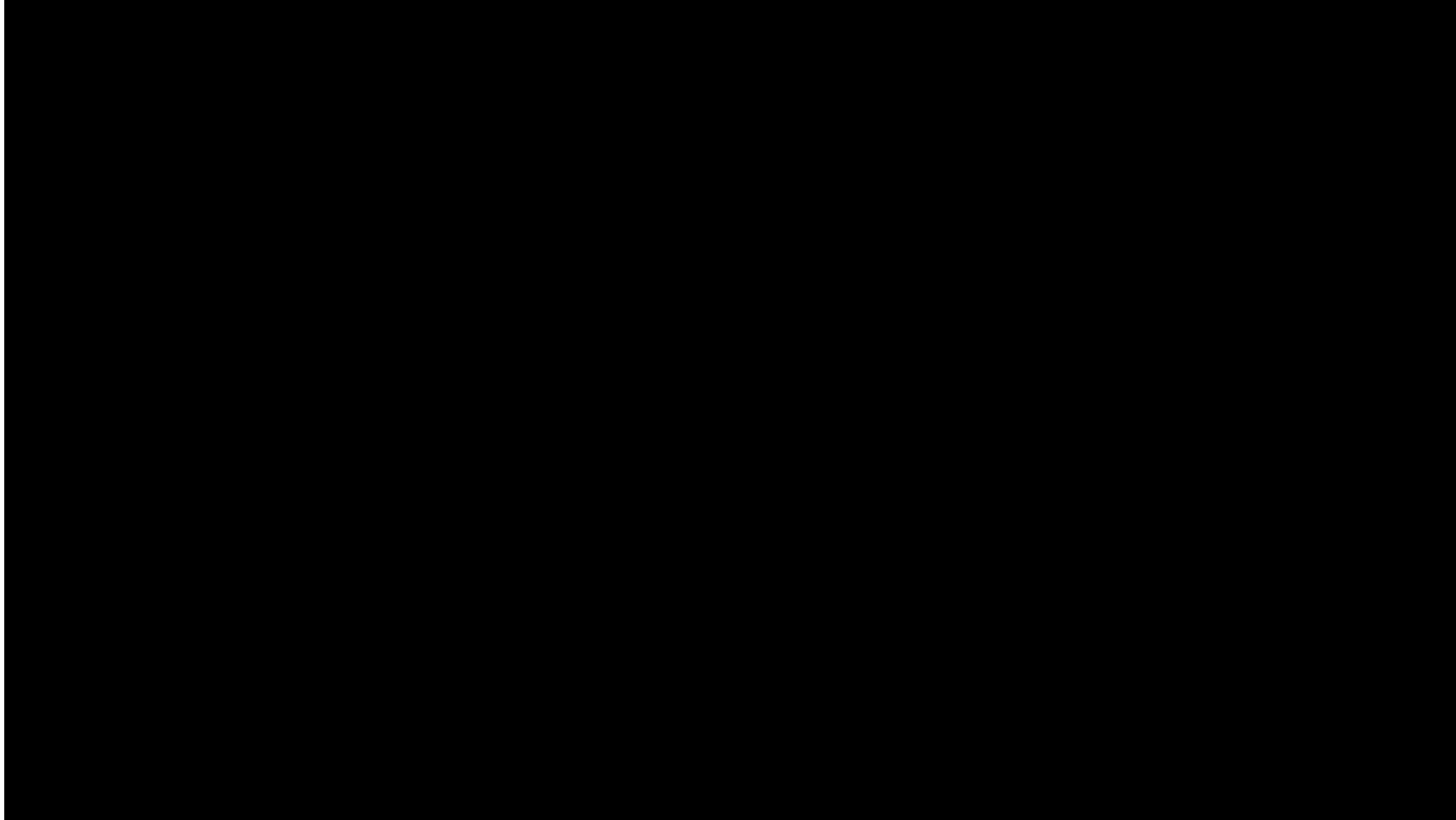
- Diagnosis of Isolated Tumor Cells (<0.2mm), or micrometastases (0.2 – 2mm)
- ESGO/ESTRO/ESP: pN1 & pN1(mi) vs pN0(i+)
- FIGO The presence of micrometastases or isolated tumor cells may be recorded. But their presence does not change the stage.
- Discussed prognostic value
 - Cibula D & al 2012. Micromet. and macromet. share the same OS
 - Colturato L & al 2016. mic significant in Xivariate analysis (recurrence)
 - Cibula D & al 2020. poorer prognosis for mic
 - Diaz J & al 2011. Similar prognosis for pN0 and pN1
 - Guani B & al 2018. Similar prognosis for pN0, ITC, mic
 - Nica A & al 2020. similar prognosis
 - Guani B & al 2020. Similar prognosis pN0, ITC, mic
 - Guani B & al 2021. Impact of micromet on PFS & OS
 - No impact in breast, etc.



Proposition of algorithm



RH + protective maneuvers



Laparoscopy ? Or laparotomy ?

A thunderbolt

A

| Population | Disease-free Survival Rate at 4.5 Yr (95% CI) | | Difference (95% CI) |
|-------------------------------|---|-------------------|---------------------|
| | Minimally Invasive Surgery | Open Surgery | |
| Intention-to-treat population | 86.0 (79.7–90.4) | 96.5 (92.7–100.0) | 10.5 (3.8–17.2) |
| Per-protocol population | 87.1 (81.0–91.3) | 96.5 (92.7–100.0) | 9.4 (2.7–16.1) |

percent

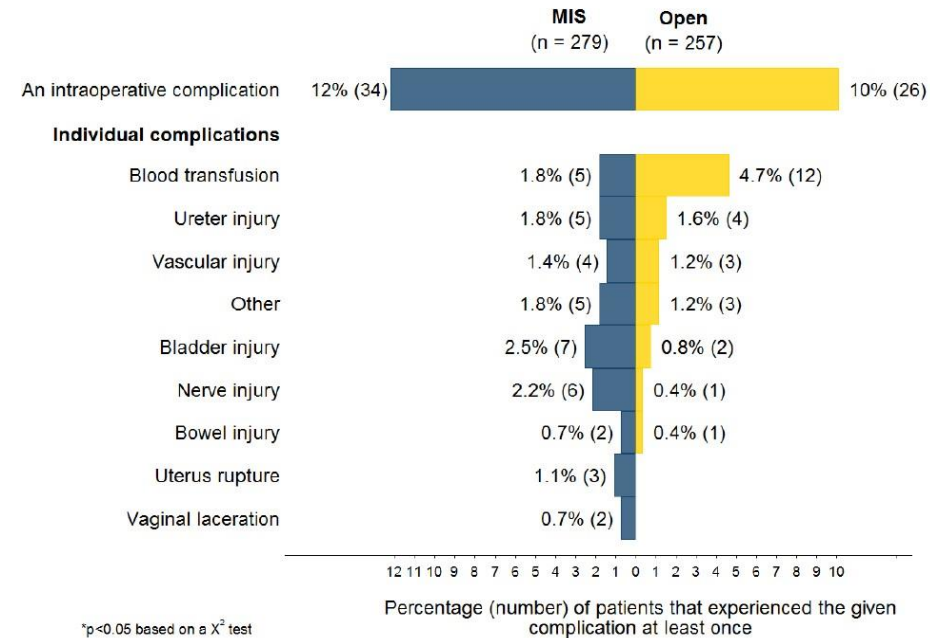
Table S4. Adjudicated sites of recurrence by randomized treatment

| Site of recurrence | No. (%) | |
|--------------------|---------|----------|
| | Open | MIS |
| Vault | 3 (43) | 4 (15) |
| Pelvis | 0 (0) | 7 (26) |
| Abdomen | 0 (0) | 1 (4) |
| Distant | 1 (14) | 2 (7) |
| Multiple | 2 (29) | 10 (37) |
| Other | 1 (14) | 3 (11) |
| Total | 7 (100) | 27 (100) |

MIS denotes minimally invasive surgery (laparoscopic/robotic) and Open total abdominal radical hysterectomy.

And the second layer

| | MIS (n = 279) | Open (n = 257) | Difference (95% CI) | P-value |
|---|------------------|-------------------|------------------------|---------|
| INTRA-OPERATIVE COMPLICATIONS (FIGURE 2) | | | | |
| At least one intra-operative event | 34 (12.2%) | 26 (10.1%) | 2.1% (-3.3%, 7.4%) | 0.45 |
| Blood transfusion | 5 (1.8%) | 12 (4.7%) | -2.9% (-5.9%, 0.1%) | 0.06 |
| Ureter injury | 5 (1.8%) | 4 (1.6%) | 0.2% (-1.9%, 2.4%) | 0.83 |
| Vascular injury | 4 (1.4%) | 3 (1.2%) | 0.3% (-1.6%, 2.2%) | 0.79 |
| Other | 5 (1.8%) | 3 (1.2%) | 0.6% (-1.4%, 2.7%) | 0.55 |
| Bladder injury | 7 (2.5%) | 2 (0.8%) | 1.7% (-0.4%, 3.9%) | 0.11 |
| Nerve injury | 6 (2.2%) | 1 (0.4%) | 1.8% (-0.1%, 3.6%) | 0.06 |
| Bowel injury | 2 (0.7%) | 1 (0.4%) | 0.3% (-0.9%, 1.6%) | 0.61 |
| Uterus rupture | 3 (1.1%) | 0 (0.0%) | 1.1% (-0.7%, 2.9%) | 0.24 |
| Vaginal laceration | 2 (0.7%) | 0 (0.0%) | 0.7% (-0.9%, 2.4%) | 0.39 |
| POST-OPERATIVE COMPLICATIONS (FIGURE 3) | | | | |
| At least one post-operative event | 164 (59%) | 136 (53%) | 5.9% (-2.5%, 14.3%) | 0.17 |
| Adverse events by organ system | | | | |
| Any urinary complications | 63 (22.6%) | 46 (17.9%) | 4.7% (-2.1%, 11.5%) | 0.18 |
| Any GI complications | 44 (15.8%) | 36 (14.0%) | 1.8% (-4.3%, 7.8%) | 0.57 |
| Any pulmonary complications | 5 (1.8%) | 3 (1.2%) | 0.6% (-1.4%, 2.7%) | 0.55 |
| Any cardiac complications | 2 (0.7%) | 10 (3.9%) | -3.2% (-5.7%, -0.6%) | 0.02 |
| Any sepsis complications | 2 (0.7%) | 2 (0.8%) | -0.1% (-1.5%, 1.4%) | 0.93 |
| Any other AE | 95 (34.1%) | 86 (33.5%) | 0.6% (-7.4%, 8.6%) | 0.89 |
| Individual Adverse Events | | | | |
| Pain | 19 (6.8%) | 24 (9.3%) | -2.5% (-7.2%, 2.1%) | 0.28 |
| Anaemia | 16 (5.7%) | 16 (6.2%) | -0.5% (-4.5%, 3.5%) | 0.81 |
| Delay in bladder function | 13 (4.7%) | 13 (5.0%) | -0.3% (-3.9%, 3.3%) | 0.87 |
| Vaginal vault complications | 11 (3.9%) | 2 (0.8%) | 3.2% (0.6%, 5.7%) | 0.01 |
| Genitourinary fistula or stricture | 10 (3.6%) | 7 (2.7%) | 0.9% (-2.1%, 3.8%) | 0.57 |
| Nausea | 8 (2.9%) | 9 (3.5%) | -0.6% (-3.6%, 2.3%) | 0.68 |
| Neuropathy | 7 (2.5%) | 2 (0.8%) | 1.7% (-0.4%, 3.9%) | 0.11 |
| Febrile morbidity | 6 (2.2%) | 2 (0.8%) | 1.4% (-0.6%, 3.4%) | 0.18 |
| Surgical site infection | 5 (1.8%) | 4 (1.6%) | 0.2% (-1.9%, 2.4%) | 0.83 |
| Wound complications | 4 (1.4%) | 16 (6.2%) | -4.8% (-8.1%, -1.5%) | 0.004 |
| Gastrointestinal obstruction | 3 (1.1%) | 1 (0.4%) | 0.7% (-0.7%, 2.1%) | 0.35 |
| Anxiety | 2 (0.7%) | 3 (1.2%) | -0.5% (-2.1%, 1.2%) | 0.59 |
| Acute renal injury | 1 (0.4%) | 1 (0.4%) | -0.0% (-1.1%, 1.0%) | 0.95 |
| Gastrointestinal fistula | 1 (0.4%) | 0 (0.0%) | 0.4% (-1.1%, 1.8%) | 0.64 |
| DVT/PE | 1 (0.4%) | 0 (0.0%) | 0.4% (-1.1%, 1.8%) | 0.64 |



Laparoscopy ? Or laparotomy ?

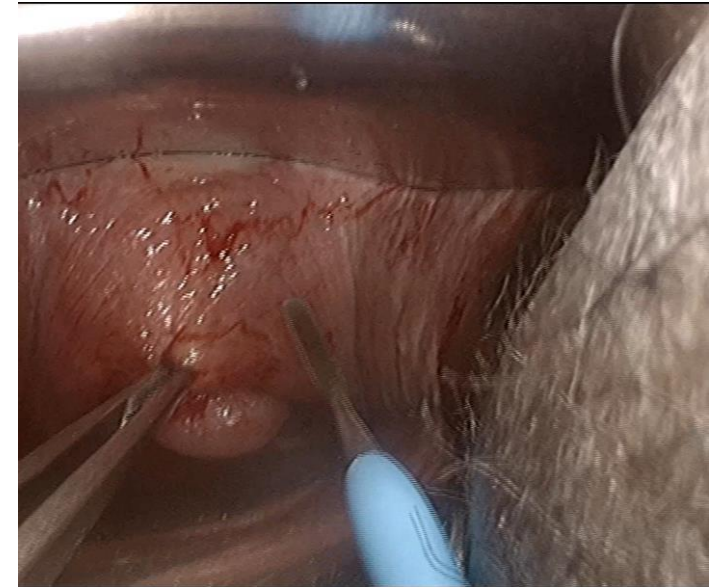
Table 2 Recurrence rates by surgical approach

| | Open surgery (n=3860) | Minimally invasive surgery (n=3766) | Total (n=7626) |
|--------------------------------------|----------------------------------|--|---------------------------|
| Total number of recurrences | 433 (11.2%) | 432 (11.5%) | 865 (11.3%) |
| Number of carcinomatosis recurrences | 38 (1%) | 96 (2.6%) | 134 (1.8%) |
| Rate of carcinomatosis* | 8.8% | 22.2% | 15.5% |

*Among patients with recurrence.

Laparoscopy ? Or laparotomy ?

- SUCCOR trial: real life data in europe
- Overall, HR for recurrence is 2.31 for MIS when compared to open (tumors>2cm). Similar findings for OS.
- But:
 - NS between open surgery and MIS without uterine manipulator
 - NS between open surgery and MIS with vaginal closure
 - NS between open surgery and MIS with preoperative conisation



CONCLUSION

For T>2cm radical hysterectomy by laparotomy provides the best results in terms of DFS and OS.

The « laparotomy » arm of the LACC trial should be considered as the present gold standard.

A laparoscopic – vaginal access, without uterine manipulator, with tumor exclusion, can be an option in a trained team, with an informed consent.
Place of preoperative brachytherapy.

Who should operate CC? And where ?

How to train surgeons for CC surgery ?

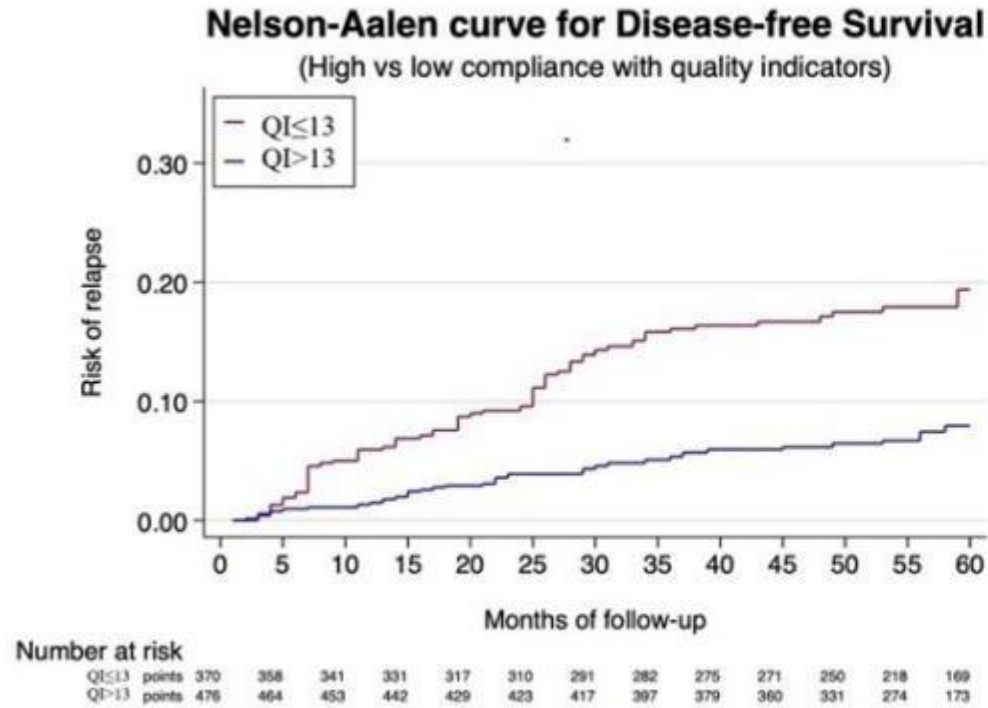


Figure 1 Nelson-Aalen cumulative hazard estimates for relapse. QI, quality indicator.

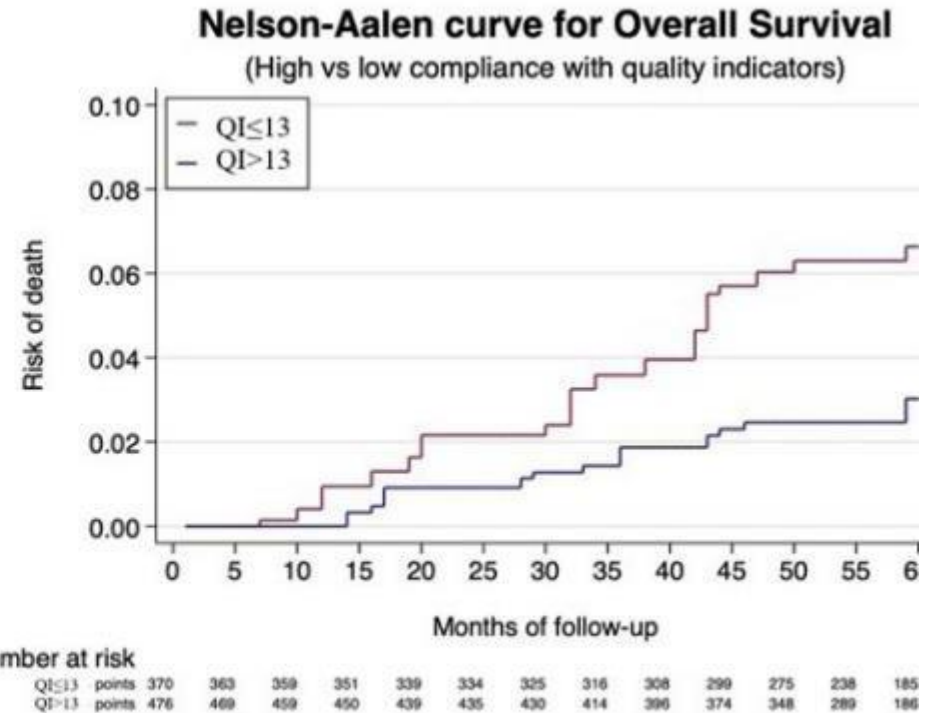
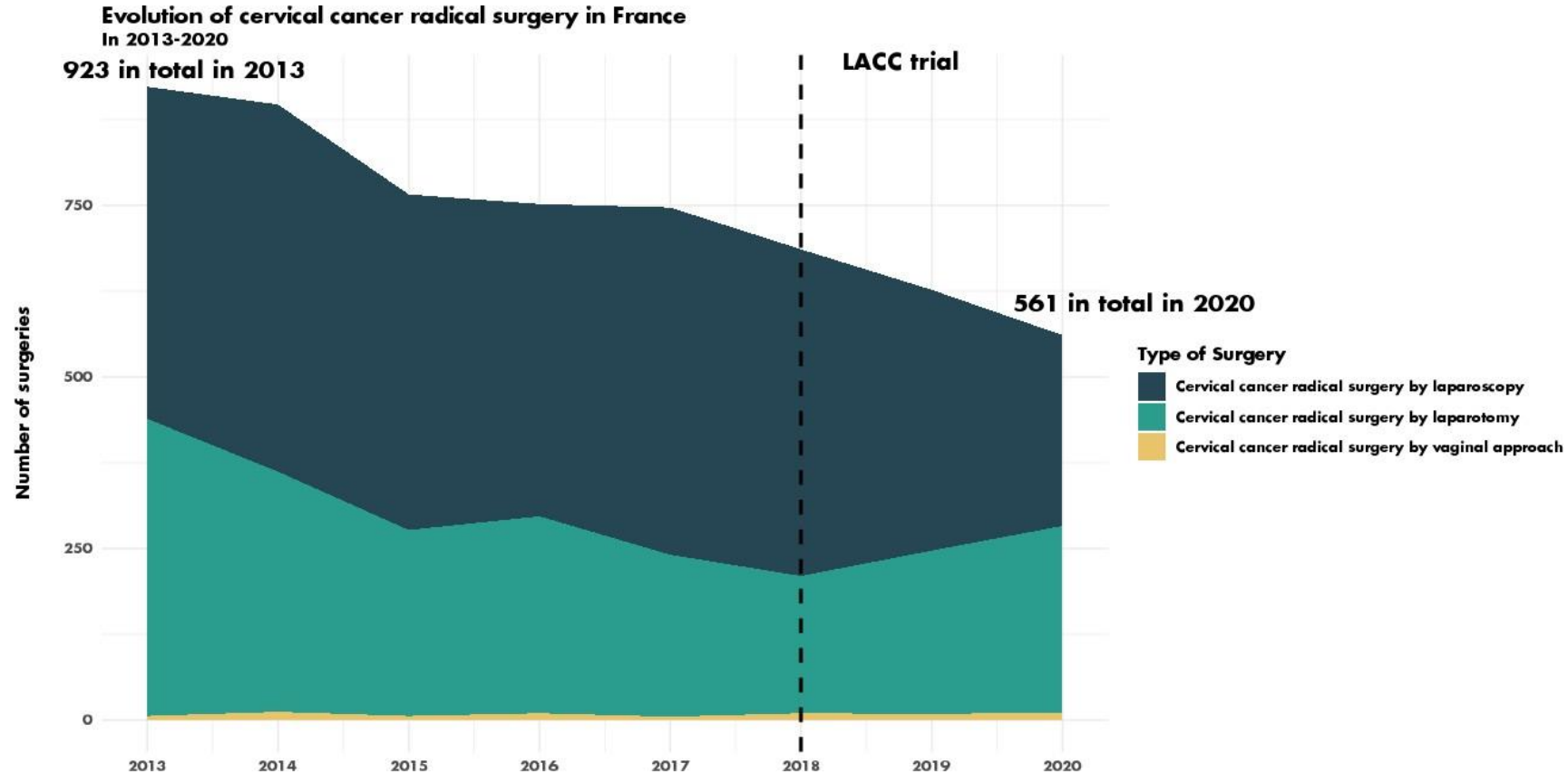


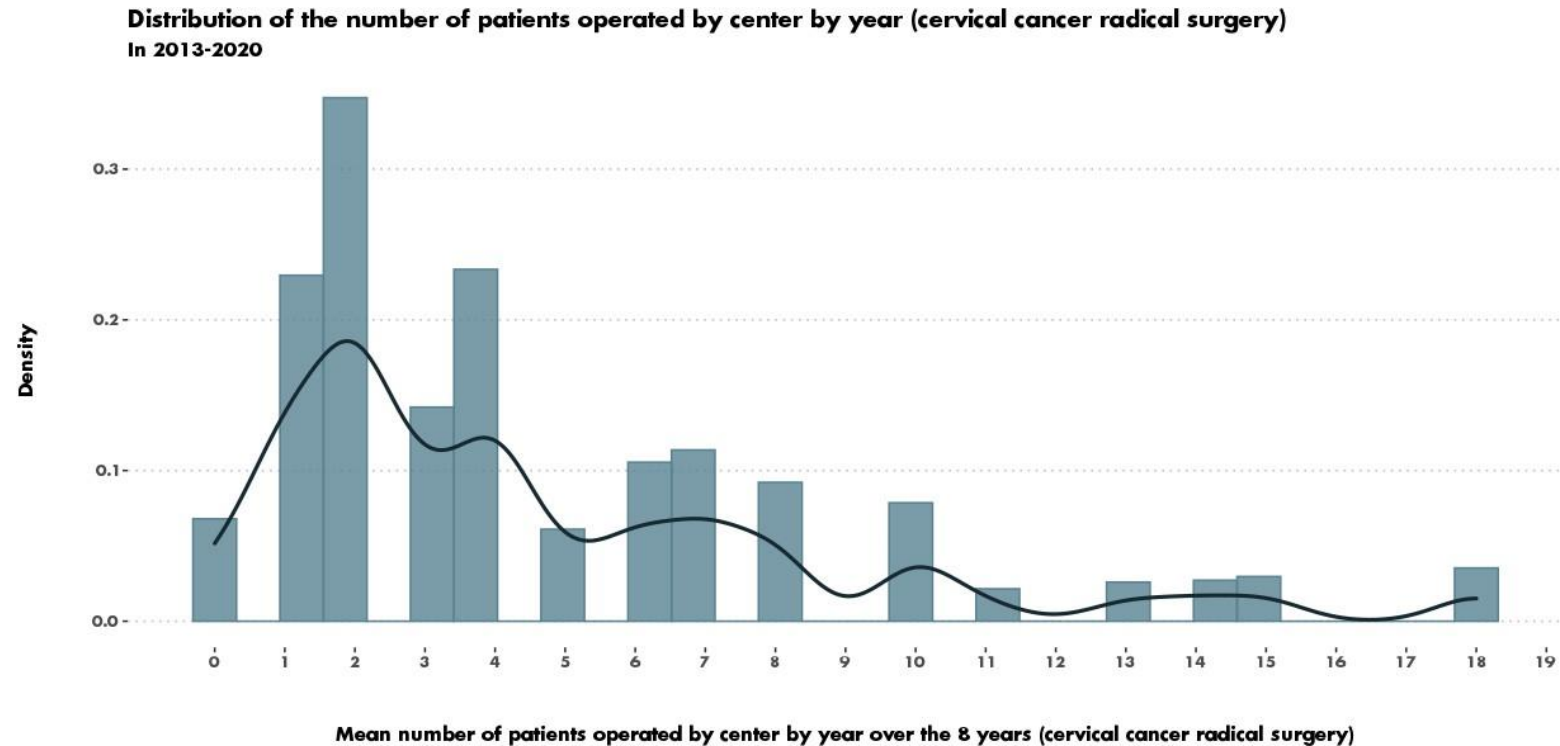
Figure 2 Nelson-Aalen cumulative hazard estimates for death. QI, quality indicator.

Who should operate CC? And where ?

How to train surgeons for CC surgery ?



Who should operate CC? And where ? How to train surgeons for CC surgery ?



Centralisation

Décision complexe/gestes complexes

- Stade Ia1 sans emboles : pas de p/ HT
- Stade Ia1 avec emboles :
 - Préservation de fertilité : GS + curage, e. ultrastadification, conisation in sano
 - Pas de préservation de fertilité : GS + cu
- Stade Ia2
 - Préservation de fertilité : GS + curage, e. ultrastadification, conisation in sano ou tr
 - Pas de préservation de fertilité : GS + cur
- Stade Ib1 sans emboles
 - Préservation de fertilité : GS + curage, e. ultrastadification, conisation in sano ou tr
 - Pas de préservation de fertilité : GS + Ct
- Stade Ib1 avec emboles
 - Préservation de fertilité : GS + curage, e.
 - Pas de préservation de fertilité : Curiethé
- Stade Ib2 sans emboles
 - Préservation de fertilité : non ou inclusior curage, examen extemporané et conisati
 - Pas de préservation de fertilité : Curiethé
- Stade Ib2 avec emboles
 - Préservation de fertilité : non ou inclusior curage, examen extemporané et conisati
 - Pas de préservation de fertilité : Curiethé
- Stade IIa1
 - Préservation de fertilité : non
 - Pas de préservation de fertilité : Curiethé

Role of Centralization of Surgery in Stage IB Carcinoma of the Cervix: A Review of 498 Cases

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Received May 19, 1989

A review was undertaken of 498 patients with stage IB carcinoma of the cervix managed over a 15-year period in the Regional Gynaecological Oncology Centre, Gateshead. All but 4 were treated by radical hysterectomy, with adjuvant radiotherapy and/or chemotherapy for those with involved pelvic nodes. The overall 5-year survival in those with negative nodes was 91.4% compared with 50.5% in those with positive nodes ($P < 0.05$). Of those dying from the disease, 7 patients only (1.4%) developed central recurrence, the remainder experiencing pelvic side-wall or distant recurrence. There was no difference in survival related to patient age. There were three deaths related to surgery and a fistula rate of only 1.2%. Bladder hypotonia and lymphocyst affected a minority of patients in the long term. The data support the case for radical surgery in stage IB carcinoma of the cervix, managed on a centralized referral basis. © 1990 Academic Press, Inc.

INTRODUCTION

Treatment of stage IB carcinoma of the cervix has resulted in 5-year survival figures of 80 to 90% in most series, whether management is by surgery alone, radiotherapy alone, or a combination of the two modalities [1,2]. Various factors have been found to influence prognosis adversely, including pelvic node metastases [3,4], vascular channel involvement [5], tumor size [6], and histological grade of tumor [7].

The purpose of this paper was to study the surgical management of stage IB cancer of the cervix in a regional center over a 15-year period. Those factors which influenced prognosis in this large series of consecutive patients were reviewed. An analysis was made of changes in mortality, and the patterns of recurrence in those dying from the disease were noted.

PATIENTS AND METHODS

The Regional Department of Gynaecological Oncology, Gateshead, provides a regional referral service for the Northern Region (population 3.4 million). A total of 498 patients with stage IB carcinoma of the cervix have been managed in the years between 1974 and 1988. The increasing referral pattern is shown in Fig. 1. Four hundred and ninety-four patients were managed by radical hysterectomy with pelvic node dissection [8]. Four were found to be unsuitable for surgery because the disease at laparotomy proved to be more advanced than the clinical staging suggested. The study population was arbitrarily divided into two groups pre- and post-January 1981 to provide a comparative temporal analysis.

MANAGEMENT CHANGES

In the initial years, 12 patients had preoperative radium; thereafter primary surgery was the standard management. Patients with negative pelvic lymph nodes had no further treatment, whereas patients with positive pelvic lymph nodes had radical whole-pelvis irradiation, except since 1985 when 35 patients have had chemotherapy (cisplatin) instead of irradiation. Since October 1988 all patients with positive pelvic nodes have been randomized into a prospective trial of irradiation versus chemotherapy/irradiation (CRC Trial 1988).

The surgical technique has evolved from a relatively limited Meigs type of radical hysterectomy to a more radical procedure involving a wide dissection of the parametrium and pelvic ligaments. The pelvic lymph node dissection is also now comprehensive using an en bloc

asion

ietria);

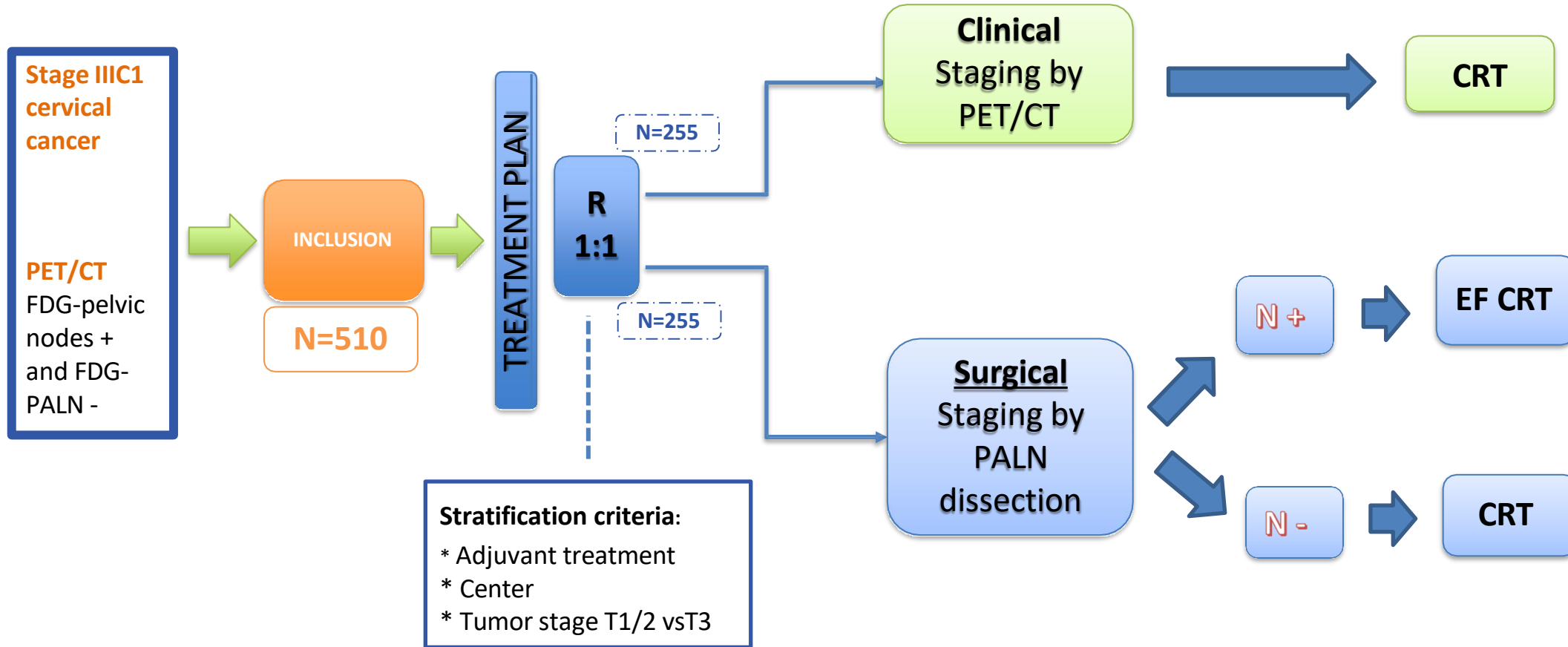
(si SHAPE+),
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'rachelectomy

1S,

of
HRT,

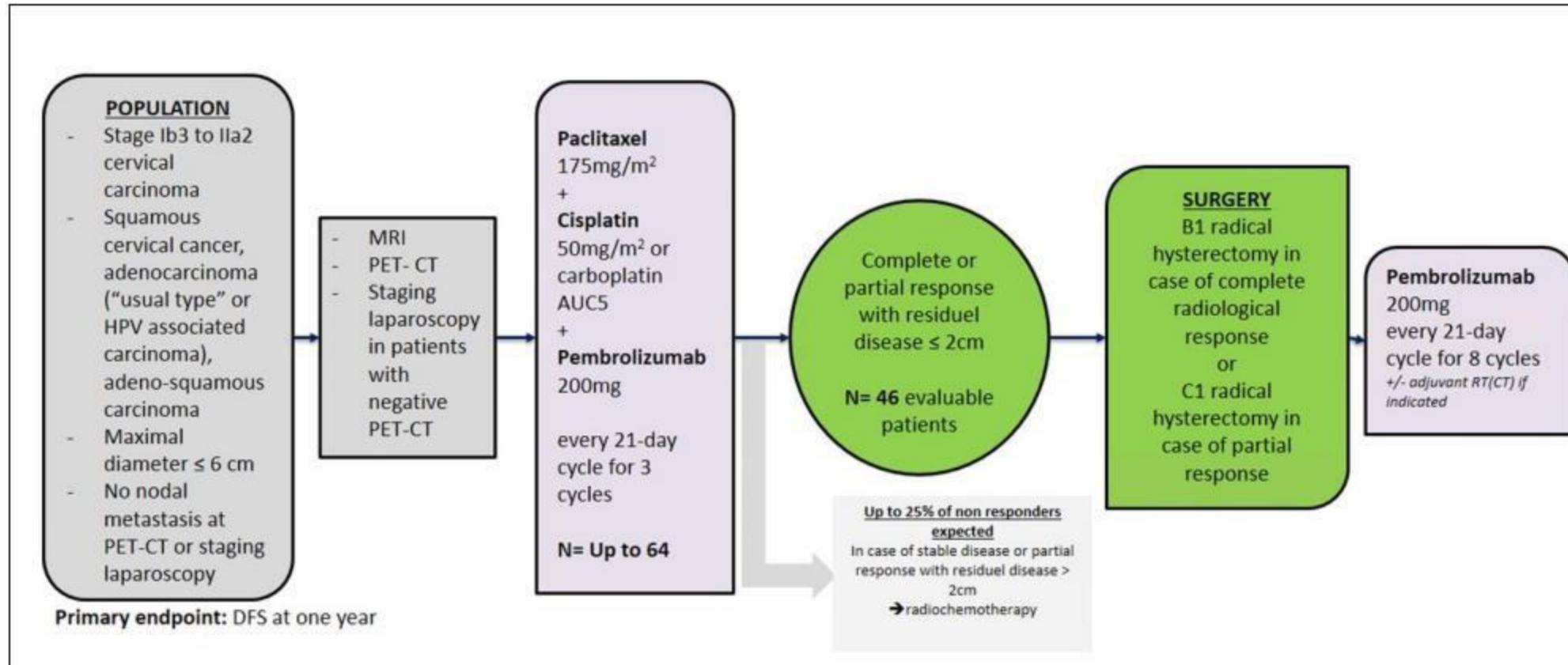
Advanced stages: laparoscopic paraaortic dissection ?

Randomization



No place for NACT – surgery.

A place for NACT+IO in selected patients ?



Conclusion

- This disease should not exist anymore. Vaccination !!!!!
- Hopefully it is becoming a rare disease in developed countries. But still a public health issue in LMIC.
- De-escalation and personalization of surgery.
- Issue of who will be trained and how ?