# Approccio chirurgico personalizzato nell'era della medicina di precisione

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# NUOVI CASI STIMATI DI NEOPLASIE IN ITALIA NEL 2020

- 377.000 NUOVE NEOPLASIE

- CORPO DELL'UTERO: 8335
- OVAIO: 5179
- CERVICE: 2365

- MAMMELLA: 65000

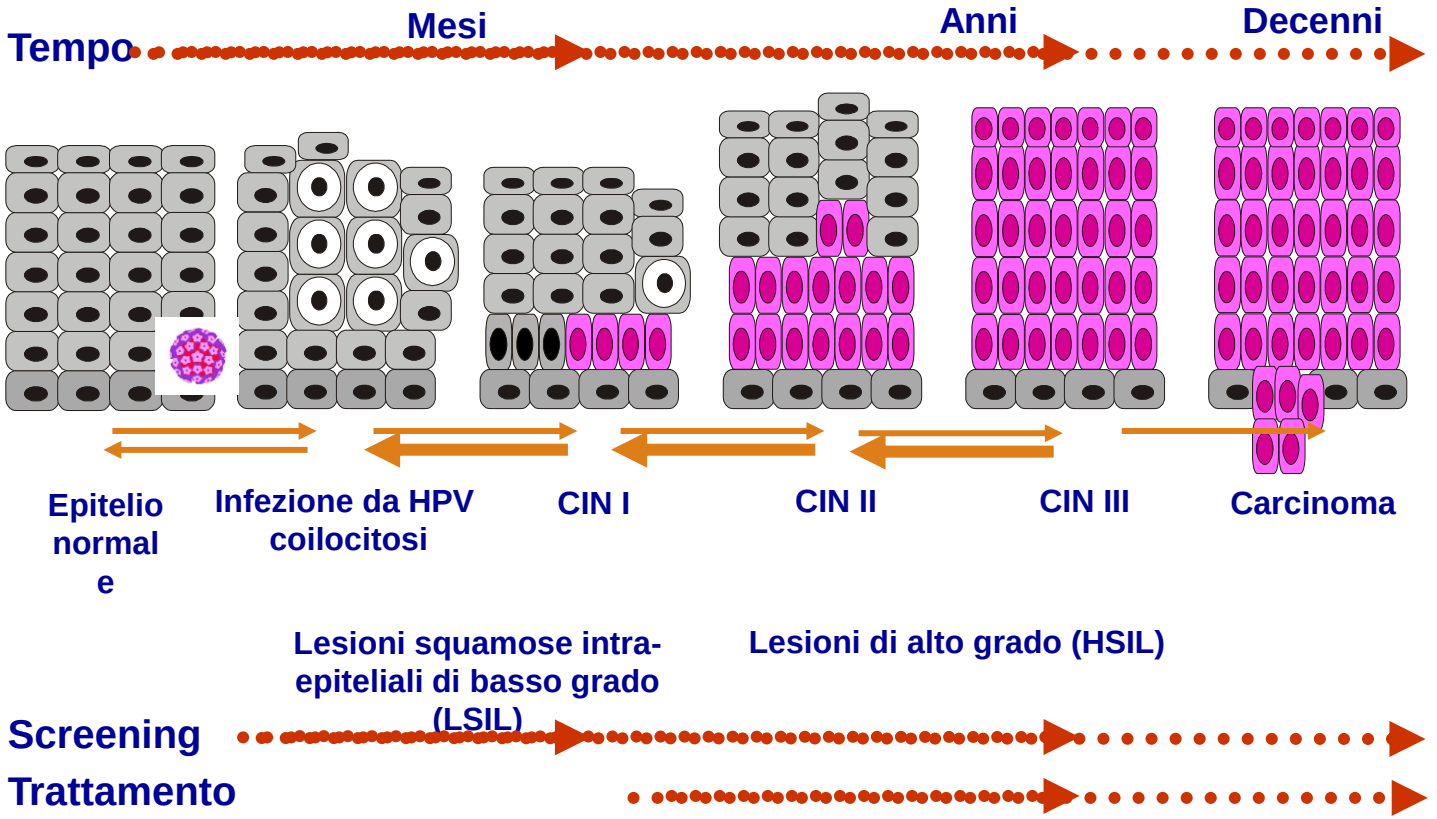
# STRATEGIA

PREVENZIONE ➡ Impedire la neoplasia

DGN PRECOCE ➡ Scoprire la neoplasia in stadi inizialissimi

NON PER TUTTE LE NEOPLASIE È POSSIBILE LA PREVENZIONE

# Progressione della malattia



# FATTORI DI RISCHIO PER IL CA MAMMARIO

## INDICATORI DEMOGRAFICI E SOCIOLOGICI

- Età
- Classi socio-cult agiate, popolazioni occidentali
- Migrazione in paesi ricchi in età prepubere

## FATTORI COSTITUZ FISIOL E RIPRODUTTIVI

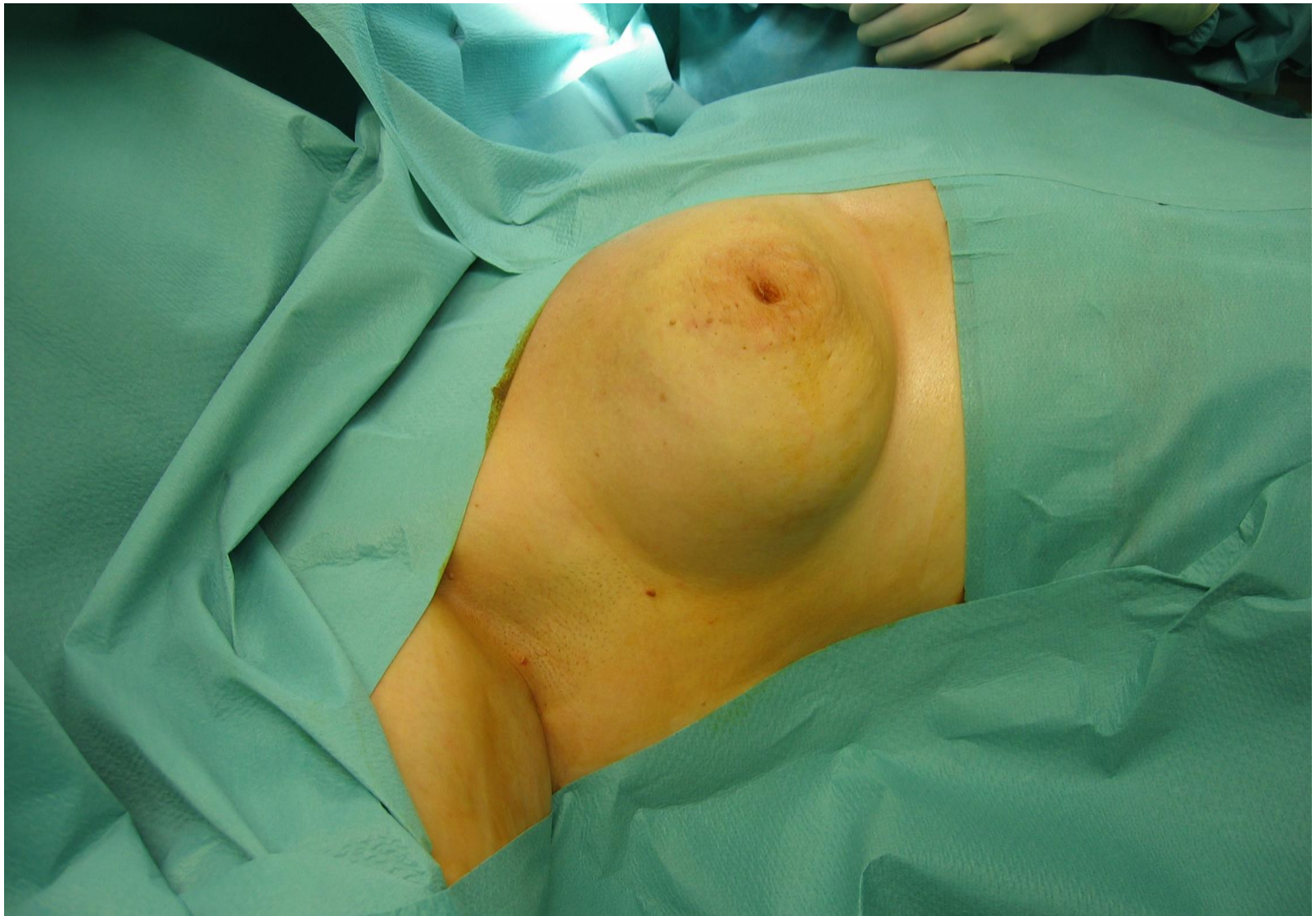
- Famiglie ad alto rischio
- Menarca precoce, nulliparità, prima grav tardiva
- Età ai figli successivi, allatt breve, età menopausa
- **Obesità e sovrappeso**

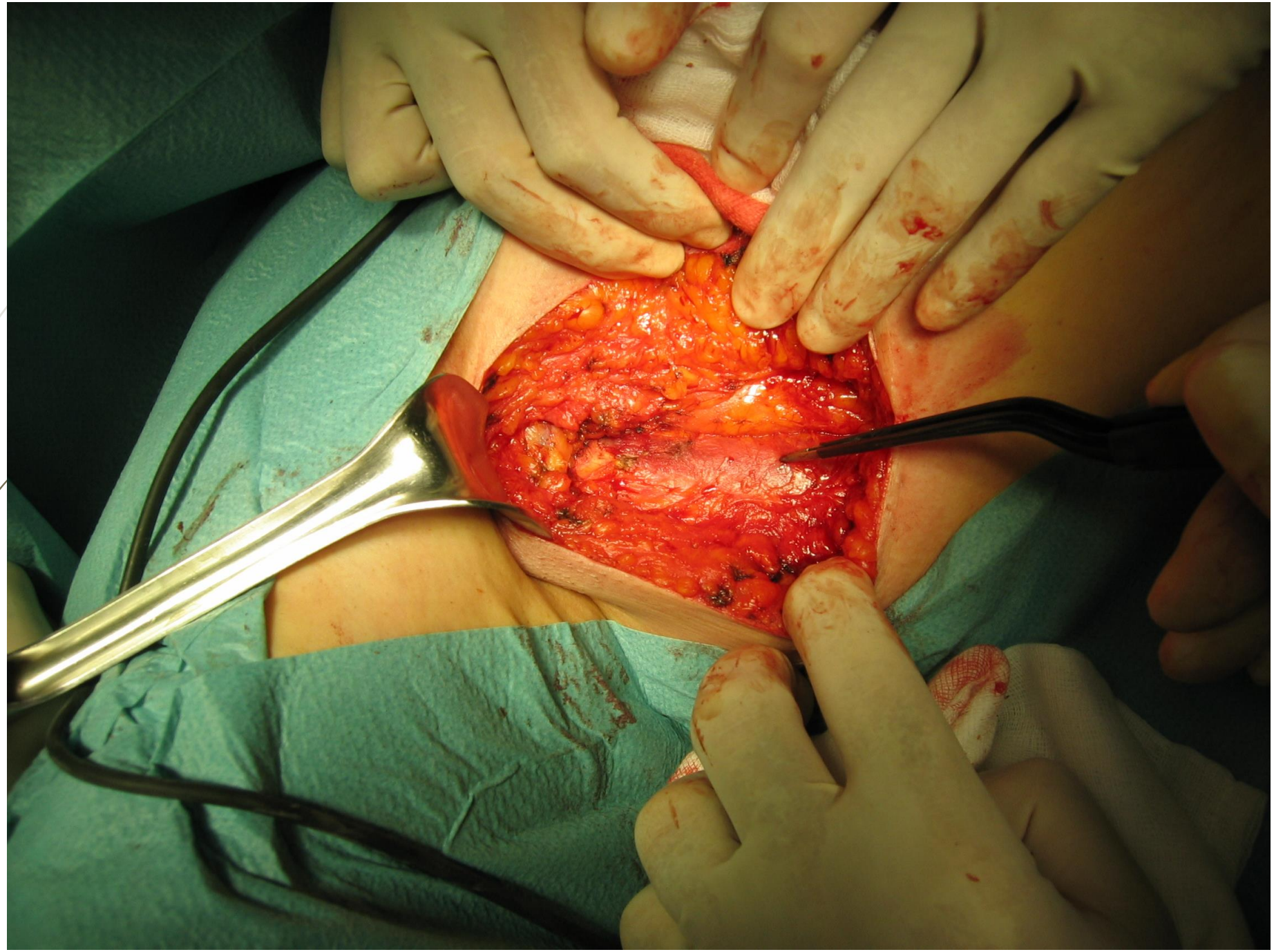
## FATTORI AMBIENTALI

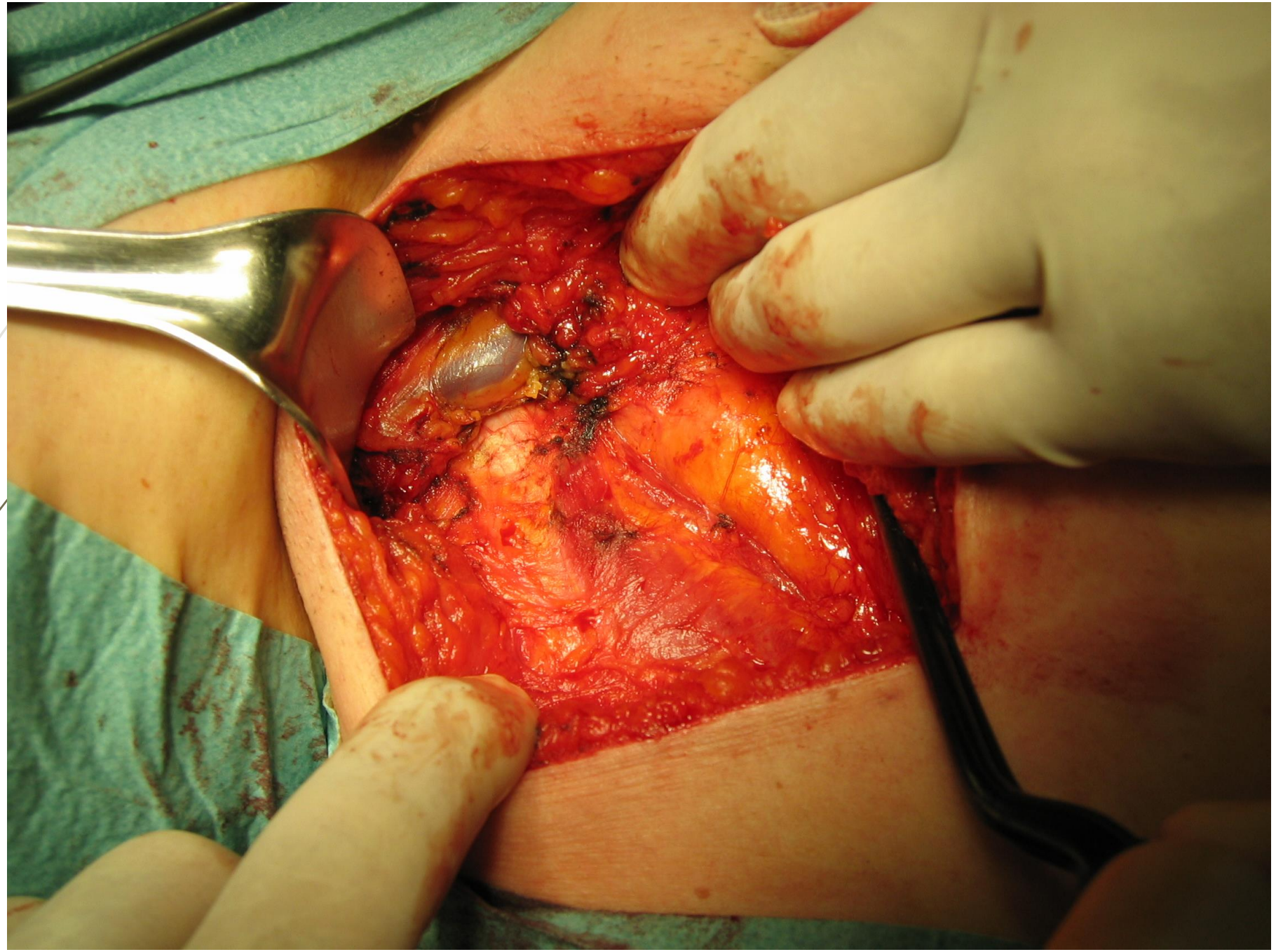
- Rad ionizz, HRT, CO, dieta ricca, **sedentarietà**, alcool, dieta povera di frutta e verdura e di fitoestrogeni

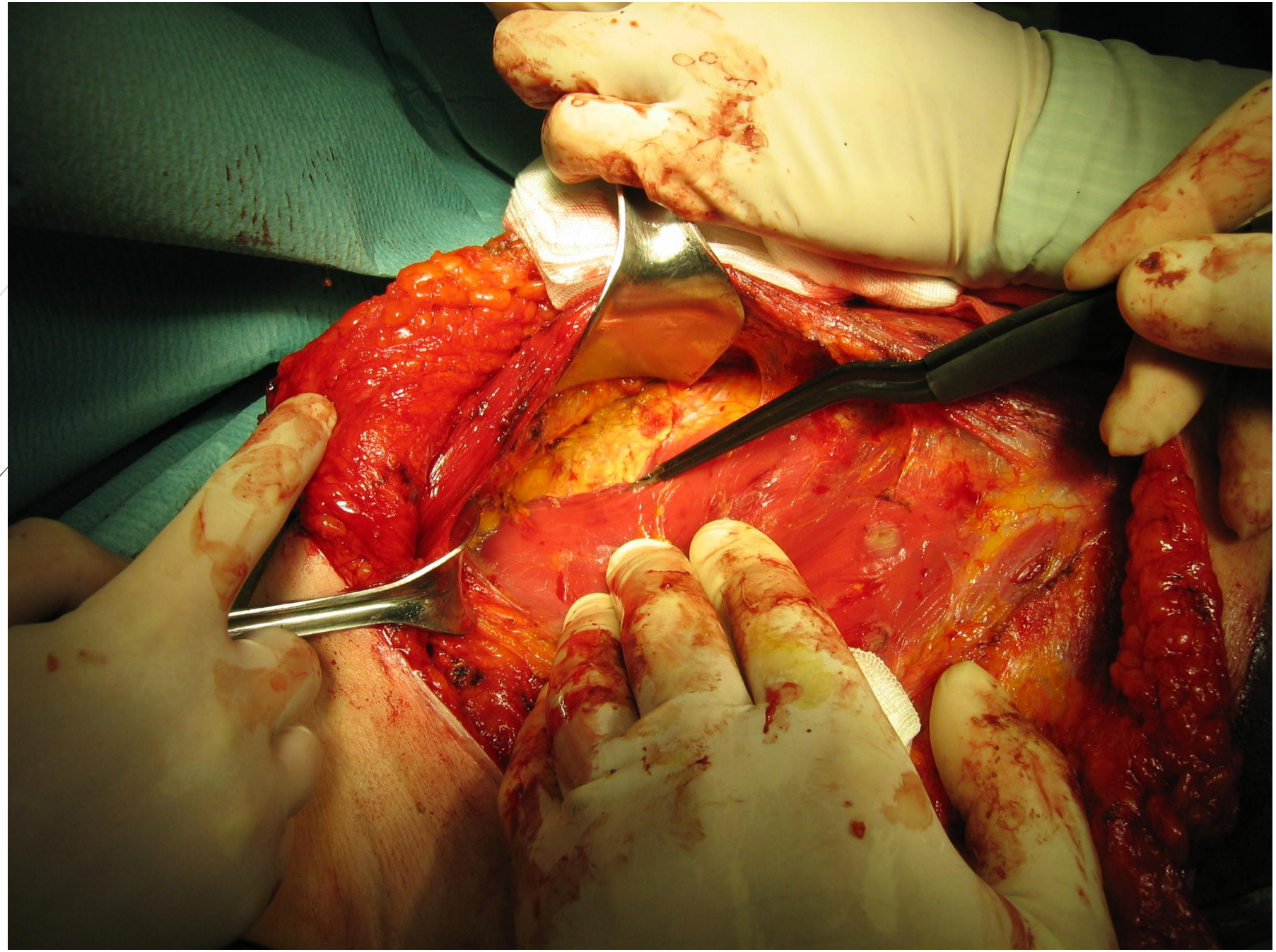
**BRCA I – BRCA II** - 50-80% ⟹ K (pop generale 10%)

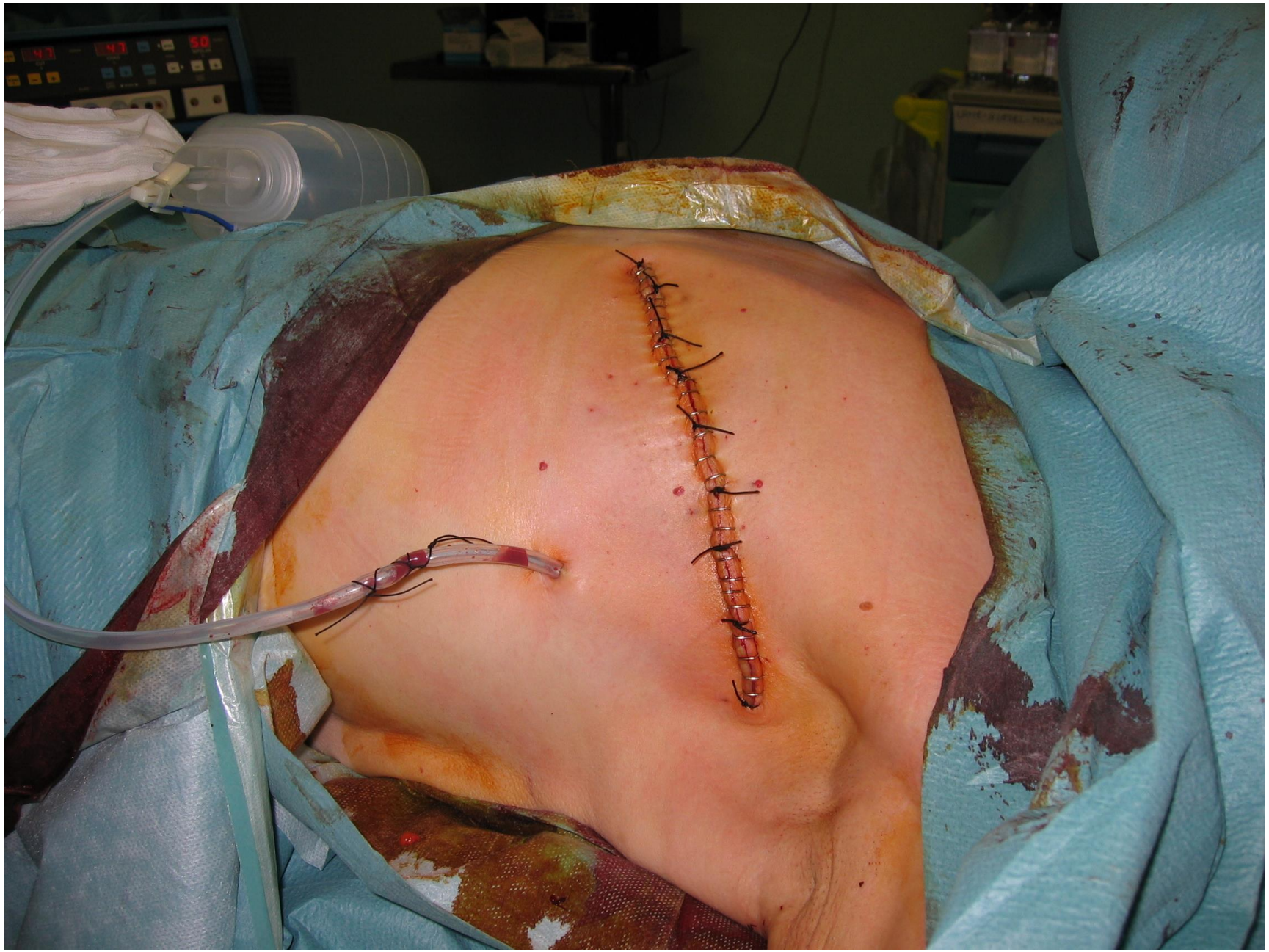
# CHIRUGIA TRADIZIONALE



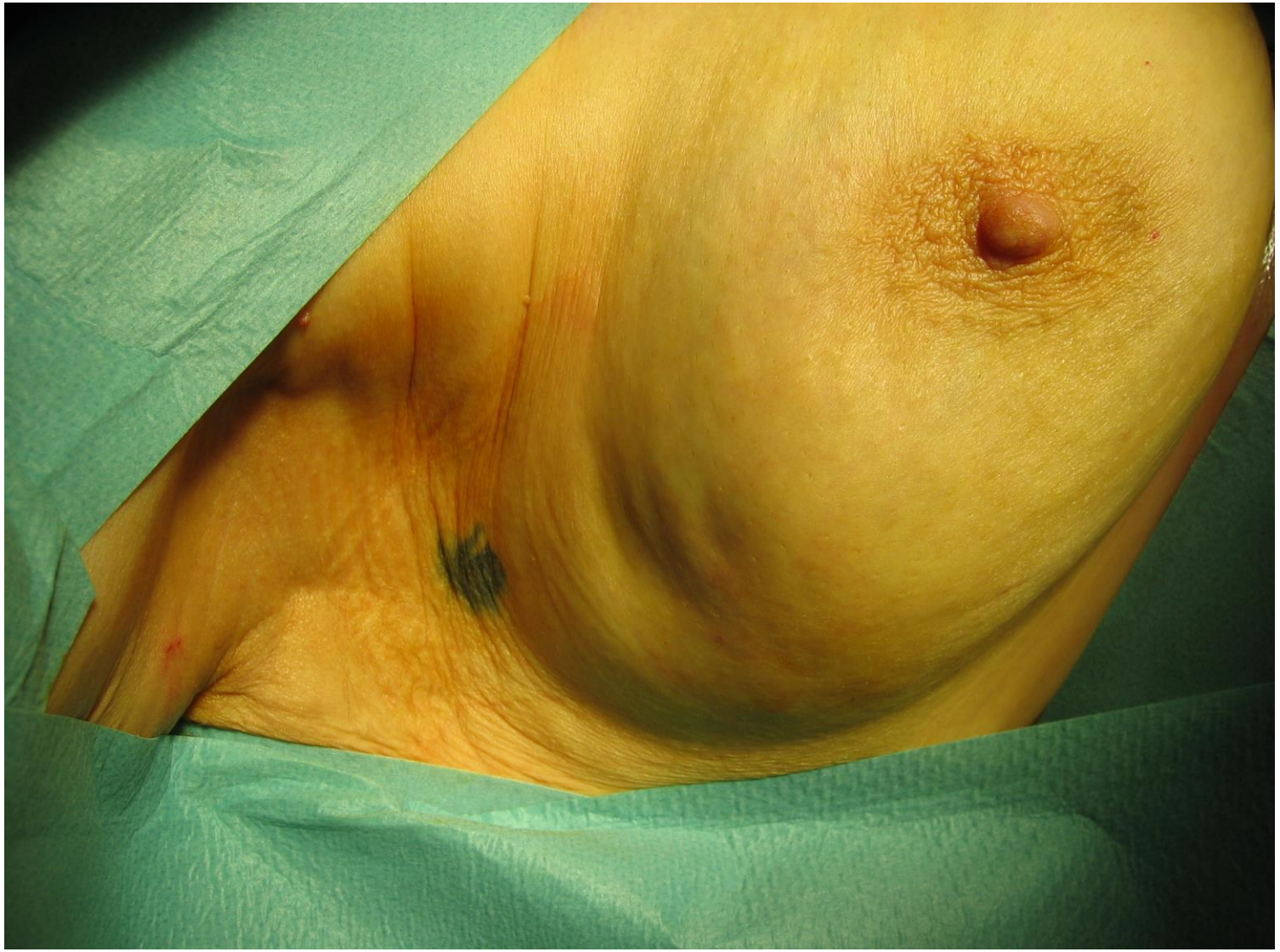


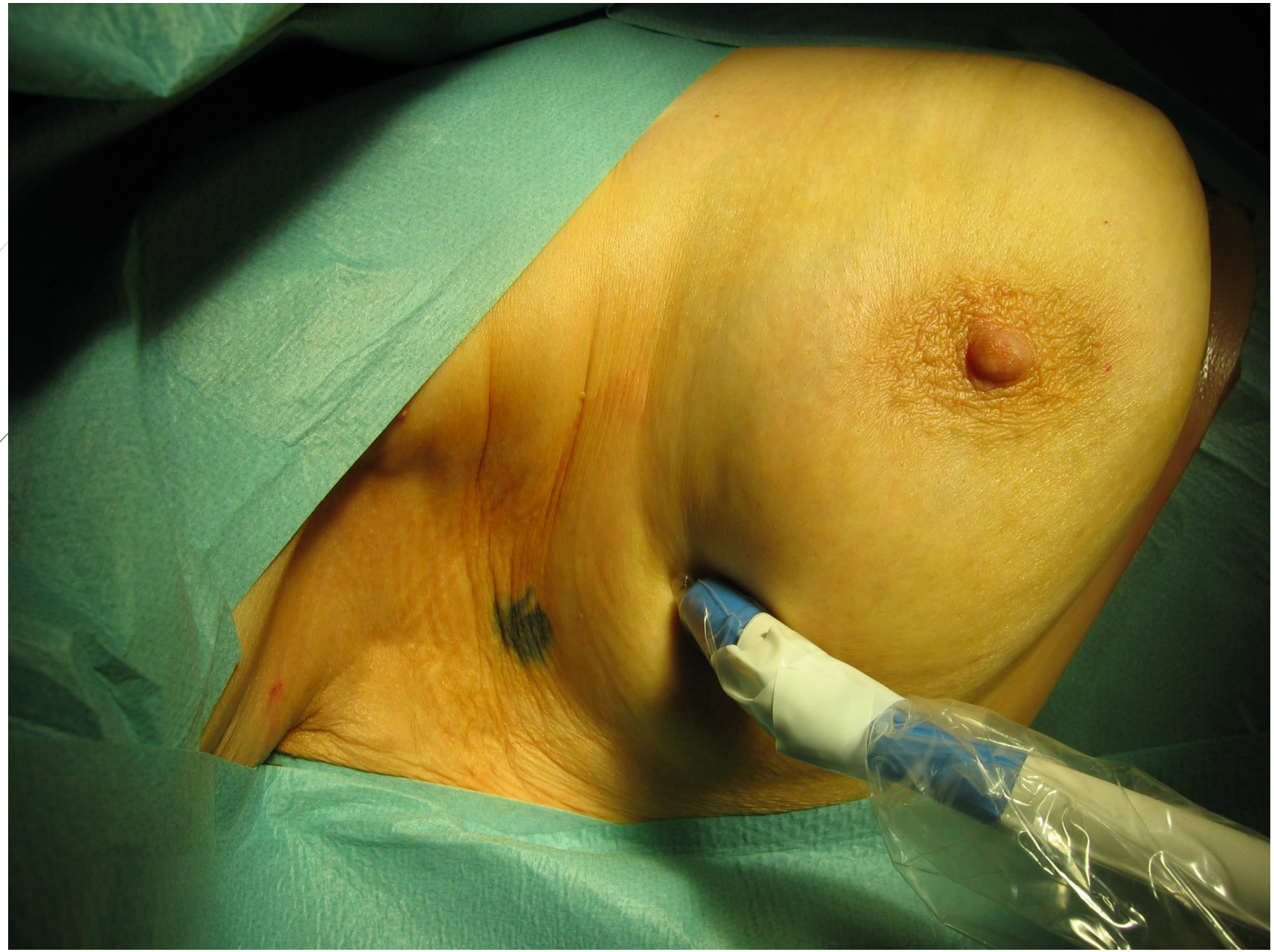


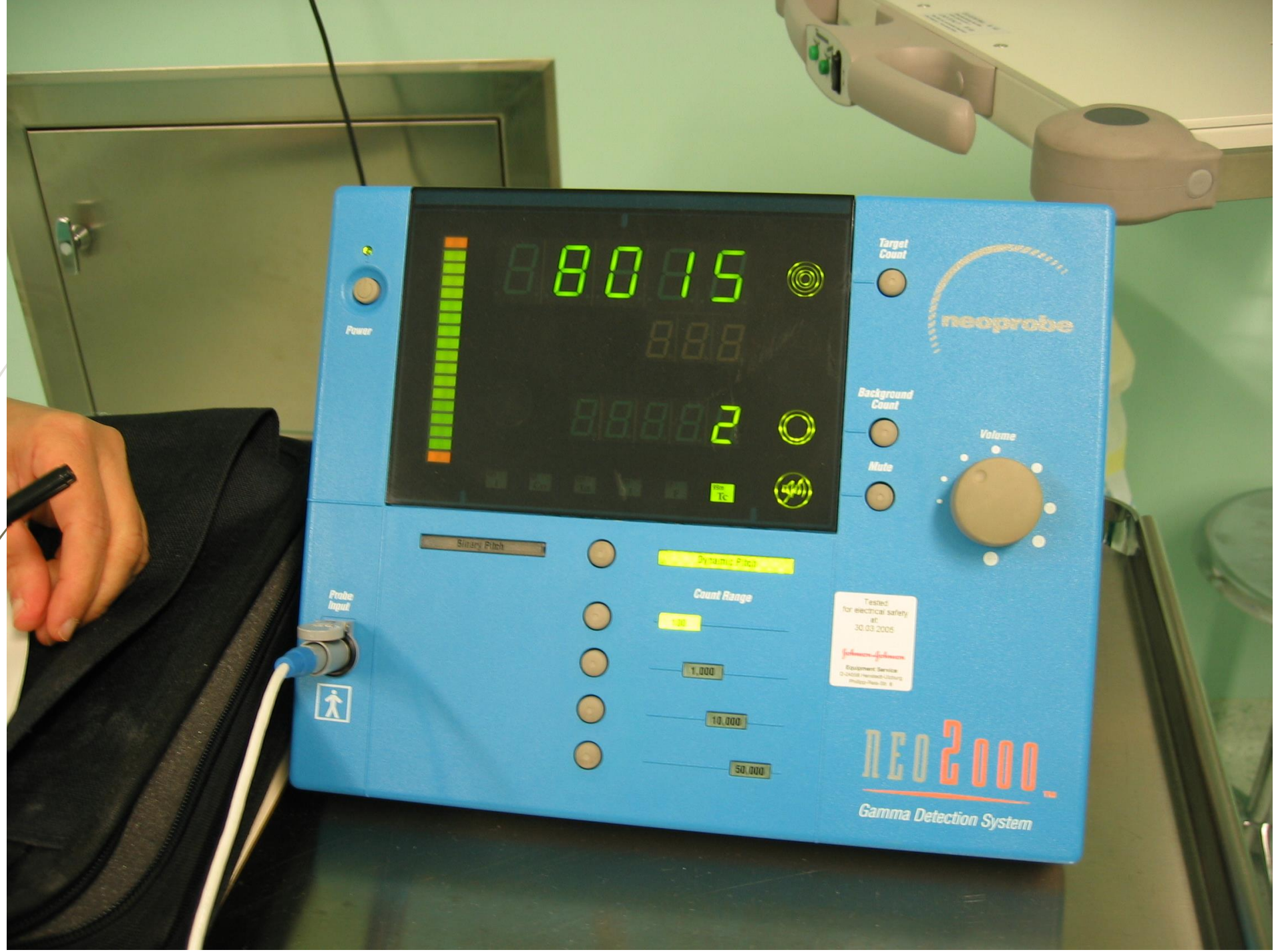




# CHIRUGIA CONSERVATIVA



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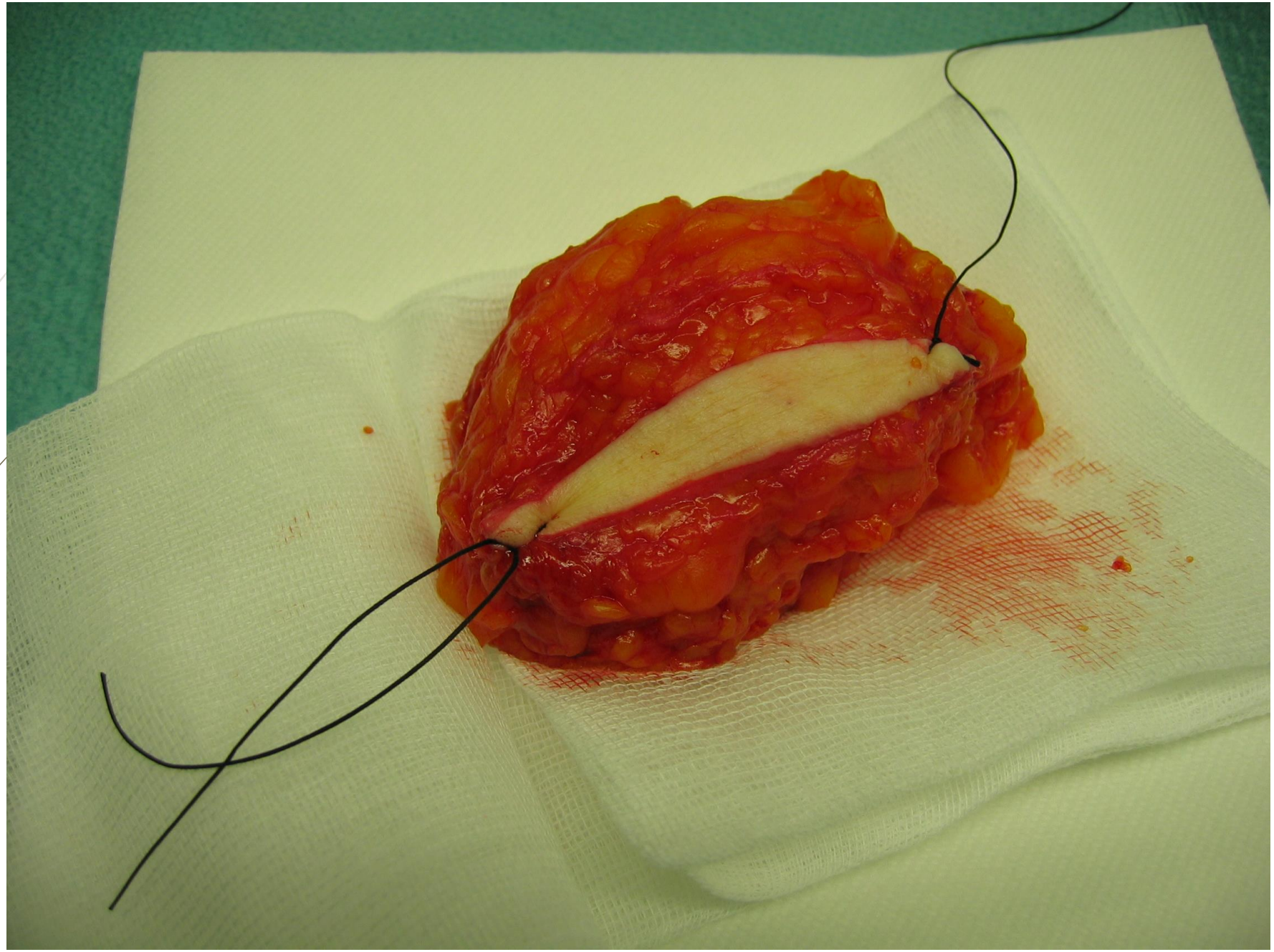
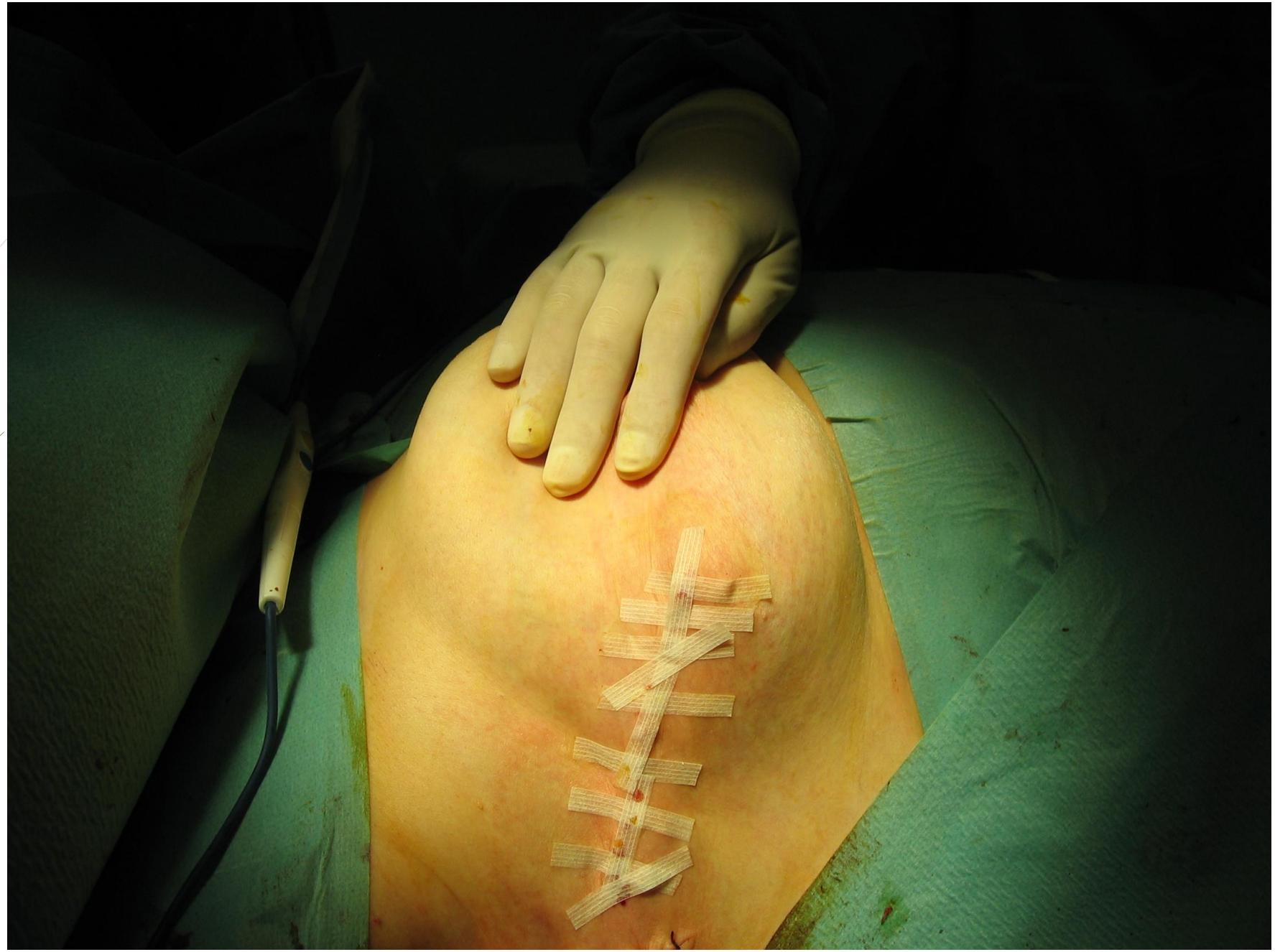
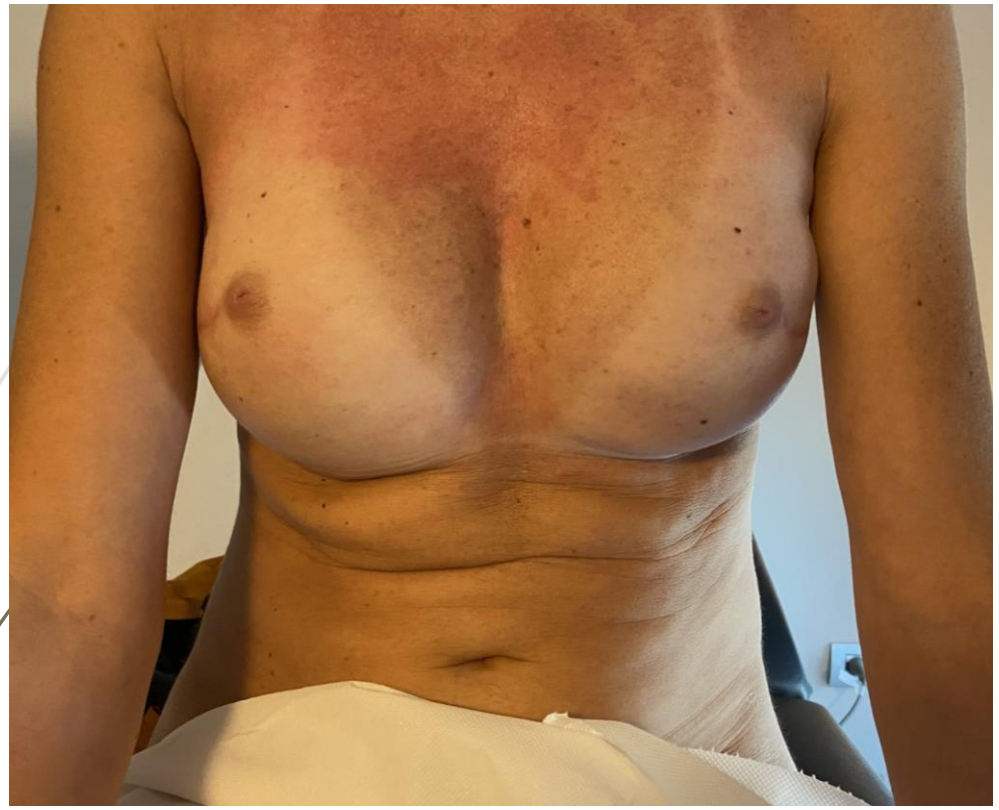
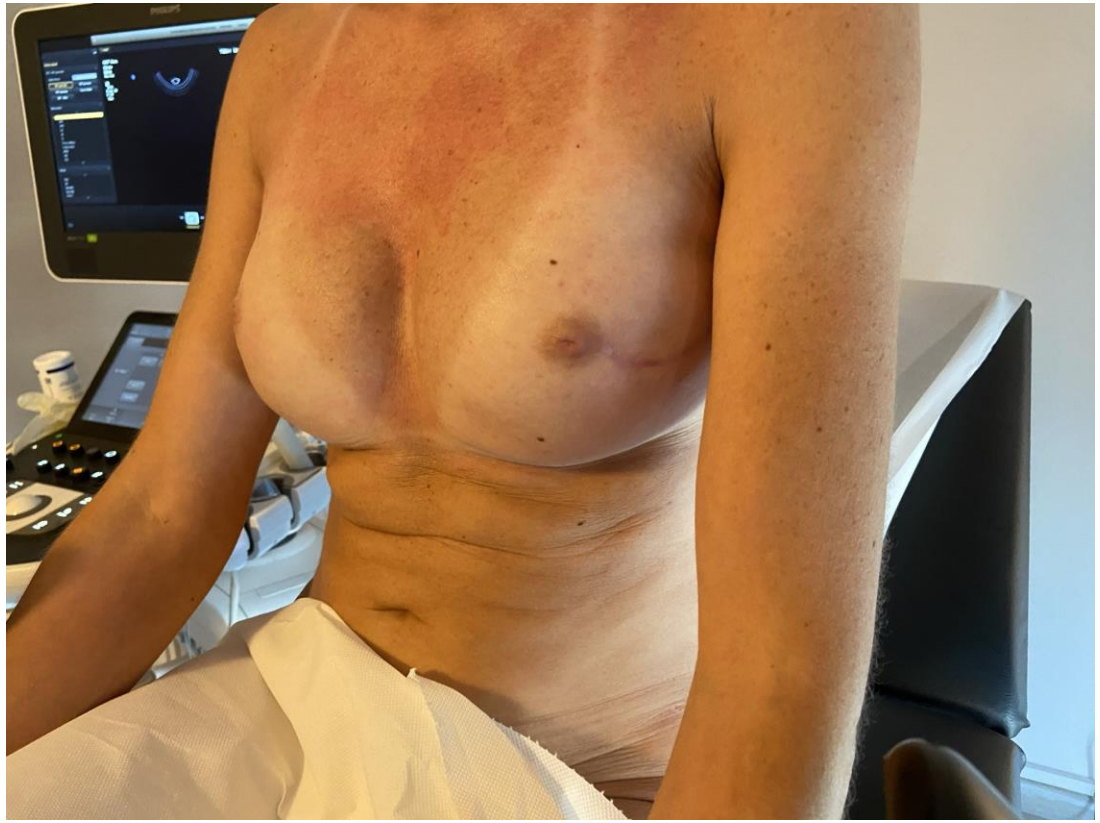




# CHIRURGIA PROFILATTICA DI RIDUZIONE DEL RISCHIO

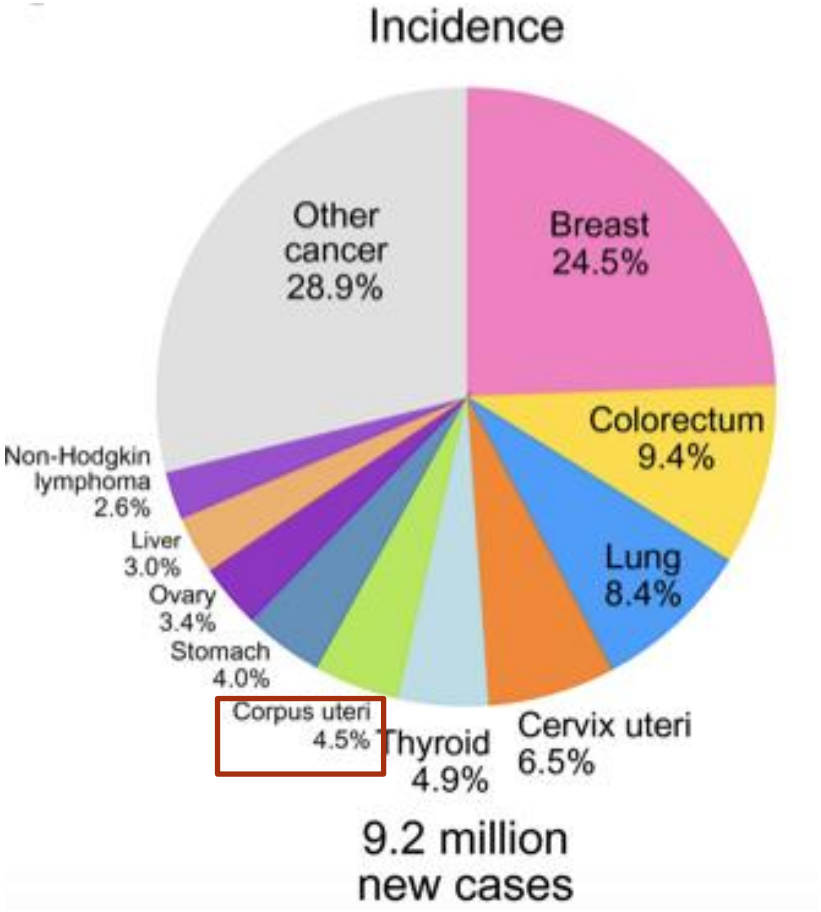


BRCA 1-2



# CARCINOMA DELL'ENDOMETRIO

- E' il tumore ginecologico più frequente in Europa
- Nel mondo è il sesto tumore per incidenza nelle donne
- La fascia di età media in Italia è 50-69 anni
- La sopravvivenza globale a 5 anni è dell'76% (EUROCARE-5 study).



# Fattori di rischio

- Obesità (BMI >30)
- Iperestrogenismo (ovaio polistico, DM, tamoxifene)
- Predisposizione genetica o familiare (Sindrome di Lynch tipo II: endometrio, mammella, colon, ovaio)

❑ I contraccettivi orali combinati RIDUCONO il rischio di carcinoma dell'endometrio

# Vecchia classificazione

- Due varianti:

- **Tipo I:** **carcinoma endometrioide,** estrogeno dipendente, 80 %, prognosi più favorevole

- **Tipo II:** **istotipi speciali** (sieroso papillare, cellule chiare, mucinoso, squamoso, inidfferenziato, misto), NON estrogeno dipendenti, 20%

# Nuova classificazione molecolare

- Quattro sottogruppi:

1. **POLE ultramutated**, prognosi favorevole

1. **MSI hypermutated**, instabilità dei microsatelliti

1. **Copy number low** (endometrioidi)

1. **Copy number high** (serous-like), prognosi sfavorevole

# Definition of prognostic risk groups integrating molecular markers

ESGO European Society of Gynaecological Oncology

ESTRO

European Society of Pathology

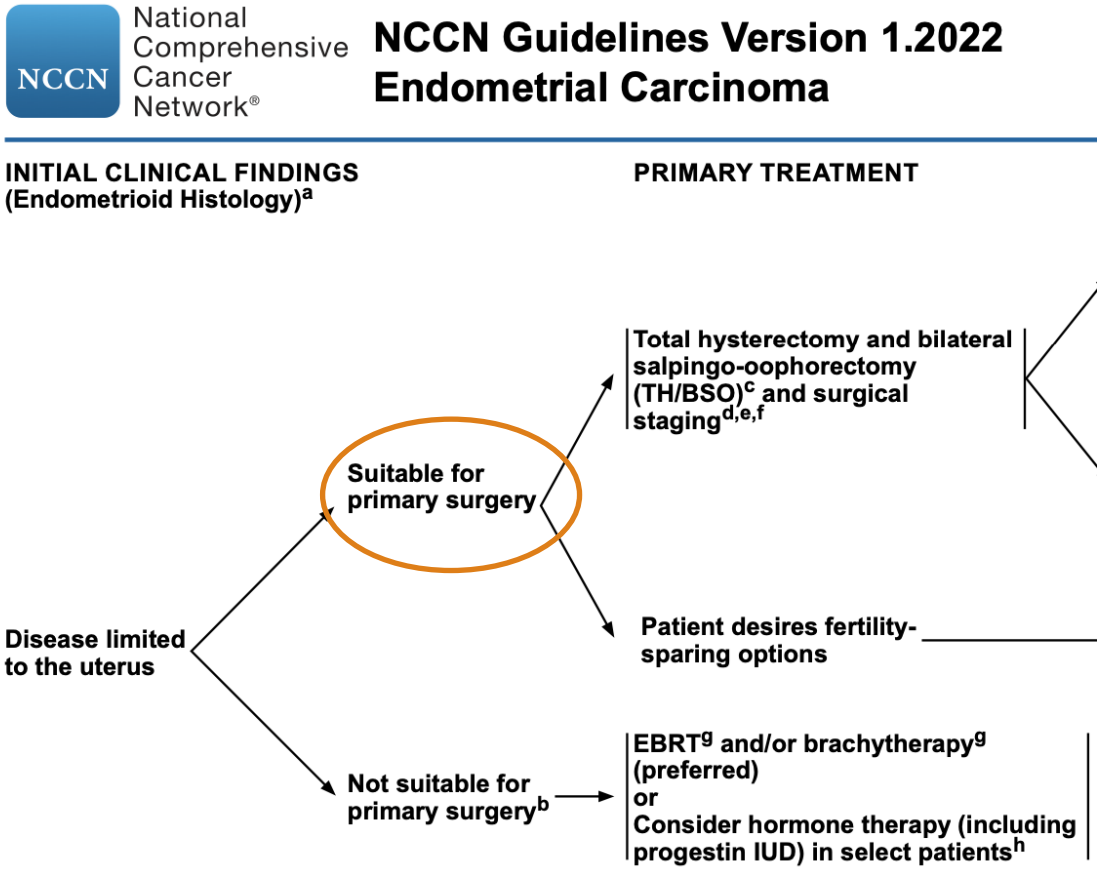
***GUIDELINE 2020***

**Table 2** Definition of prognostic risk groups

| Risk group | Molecular classification unknown | Molecular classification known*† |
|---|---|---|
| **Low** | ► Stage IA endometrioid + low-grade‡ + LVSI negative or focal | ► Stage I–II ***POLEmut*** endometrial carcinoma, no residual disease<br>► Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal |
| **Intermediate** | ► Stage IB endometrioid + low-grade‡ + LVSI negative or focal<br>► Stage IA endometrioid + high-grade‡ + LVSI negative or focal<br>► Stage IA non-endometrioid (serous, clear cell, undifferentiared carcinoma, carcinosarcoma, mixed) without myometrial invasion | ► Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal<br>► Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade‡ + LVSI negative or focal<br>► Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion |
| **High–intermediate** | ► Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion<br>► Stage IB endometrioid high-grade‡ regardless of LVSI status<br>► Stage II | ► Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion<br>► Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade‡ regardless of LVSI status<br>► Stage II **MMRd/NSMP** endometrioid carcinoma |
| **High** | ► Stage III–IVA with no residual disease<br>► Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease | ► Stage III–IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease<br>► Stage I–IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease<br>► Stage I–IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease |
| **Advanced metastatic** | ► Stage III–IVA with residual disease<br>► Stage IVB | ► Stage III–IVA with residual disease of any molecular type<br>► Stage IVB of any molecular type |

# Surgical treatment

## SURGERY IS THE INITIAL TREATMENT FOR ENDOMETRIAL CANCER



# Surgical management of apparent stage I/II endometrial carcinomas

- **Minimally invasive surgery** is the preferred surgical approach, including patients with high-risk endometrial carcinoma.
- Any intra-peritoneal tumor spillage, including tumor rupture or morcellation (including in a bag), should be avoided.
- Tumors with metastases outside the uterus and cervix (excluding lymph node metastases) are relative contra-indications for minimally invasive surgery.

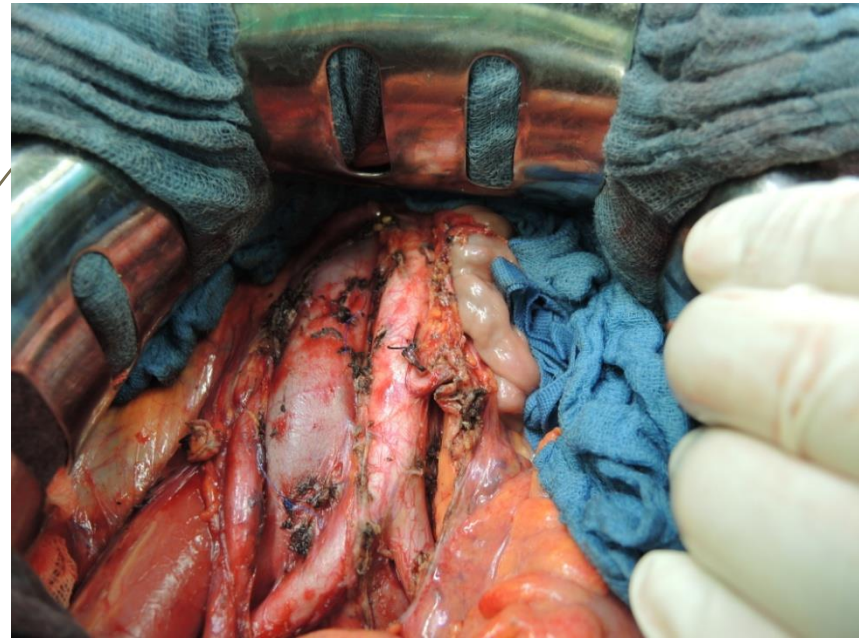
**Standard surgical procedures**

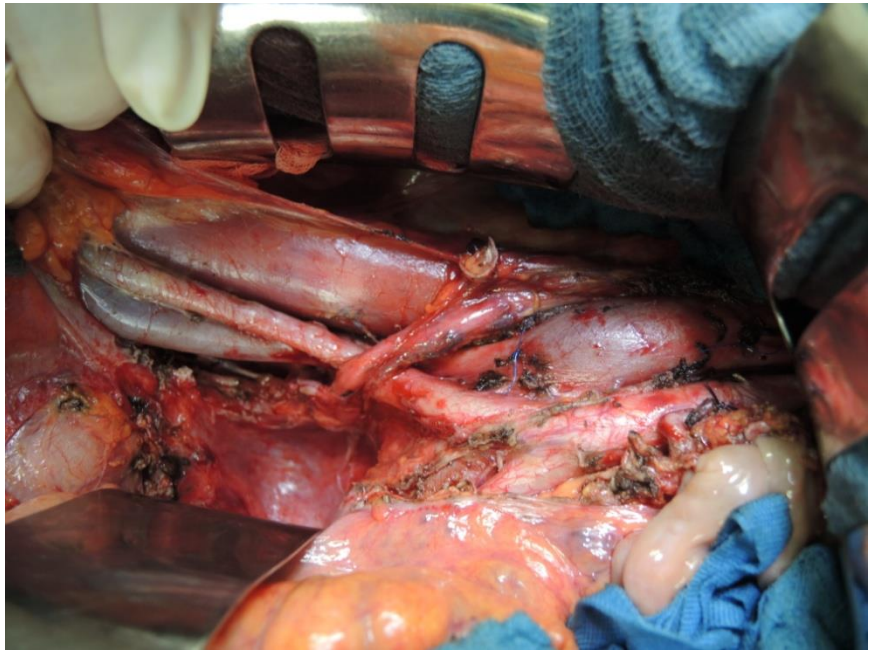
**Total hysterectomy with bilateral salpingo-oophorectomy without vaginal cuff resection.**

**Staging infracolic omentectomy** should be performed **in clinical stage I serous endometrial carcinoma, carcinosarcoma, and undifferentiated** carcinoma. It can be omitted in clear cell and endometrioid carcinoma in stage I disease.

# LYMPH NODE STAGING

- The lymph node assessment includes evaluation of the nodal basins that drain the uterus, and often comprises a pelvic nodal dissection with or without para-aortic nodal dissection. This continues to be an important aspect of surgical staging in patients with uterine-confined endometrial carcinoma, as the procedure provides important prognostic information that may alter treatment decisions.
- Pelvic lymph nodes from the external iliac, internal iliac, obturator, and common iliac nodes are frequently removed for staging purposes.
- Para-aortic nodal evaluation from the inframesenteric and infrarenal regions may also be utilized for staging in patients with high-risk tumors such as deeply invasive lesions, high-grade histology, and tumors of serous carcinoma, clear cell carcinoma, or carcinosarcoma.





# Sentinel lymph node biopsy is an acceptable alternative to systematic lymphadenectomy for lymph node staging in stage I/II.

PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

Figure 1: Common cervical injection sites for mapping uterine cancer[a]

Figure 2: Most common location of SLNs (blue, arrow) following a cervical injection[a]

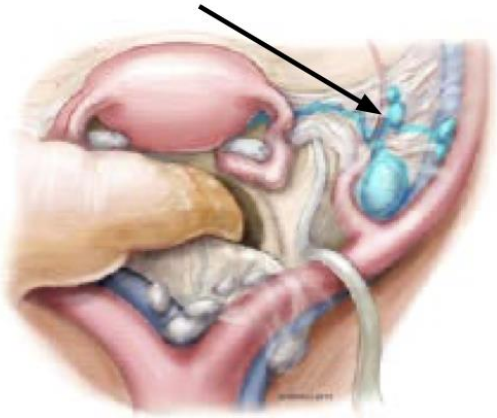
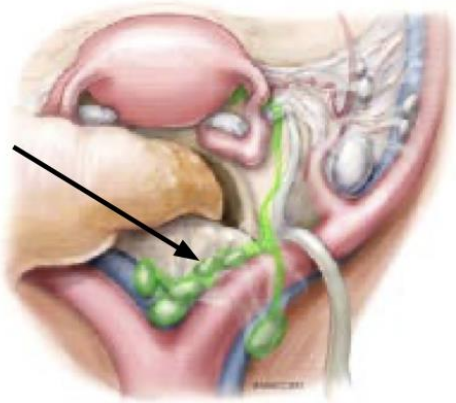


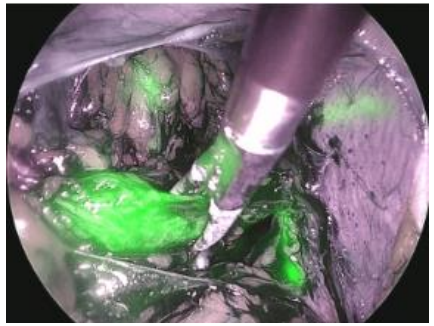
Figure 3: Less common location of SLNs (green, arrow) usually seen when lymphatic trunks are not crossing over the umbilical ligament but following the mesoureter cephalad to common iliac and presacral region[a]



# Sentinel lymph node biopsy

Indocyanine green with cervical injection

Pathologic ultrastaging



Macrometastases and micrometastases (<2 mm, pN1(mi)) = metastatic involvement

Side-specific systematic lymphadenectomy in high-intermediate-risk/high-risk patients if sentinel lymph node is not detected

Debulking of enlarged lymph nodes and para-aortic staging can be considered.

If pelvic lymph node involvement is found intra-operatively, further systematic pelvic lymph node dissection should be omitted

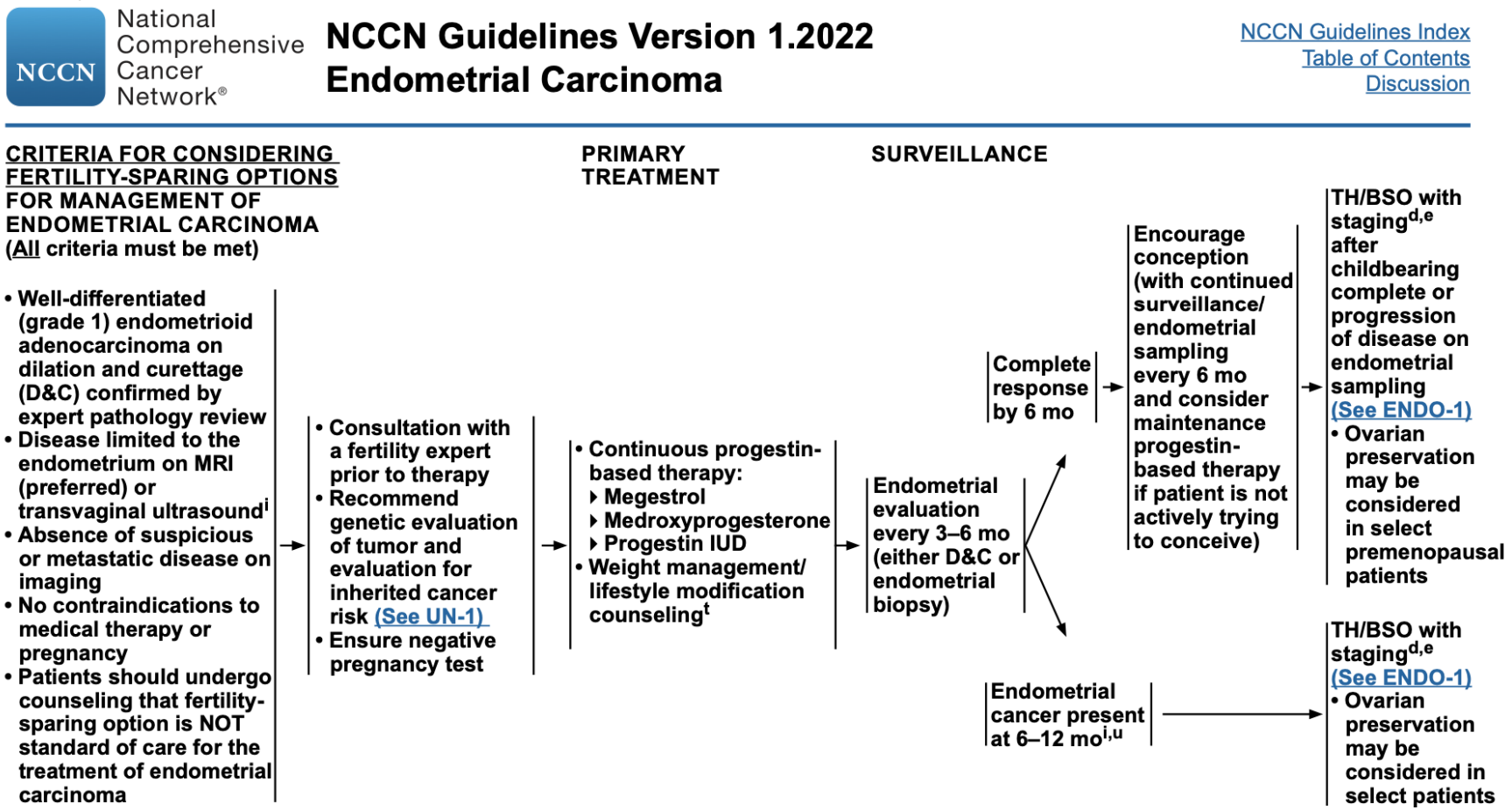
# Fertility-sparing treatment

Young women with endometrial atypical hyperplasia and endometrial cancer, which are frequently nulligravid, may have a **strong desire to preserve fertility.**

✓ 25% of endometrial cancer occur in premenopausal women

…. and about 5% in women under 40.

# FERTILITY SPARING OPTIONS



# Fertility-sparing treatment

**Work-up examination:**

✓ TV and abdominal US

✓Abdominal MRI (absence of syncronous ovarian tumour, absence of suspicious pelvic or para-aortic LN, evaluation of myometrial invasion)

Use of laparoscopy ??

**Treatment schedule:**

MPA 200-800 mg/d,  MA 160 mg/d, DHG 20 mg/d

Median duration 3-6 months

FERTILITY SPARING

## Fertility-Preserving Treatment in Young Women With Grade 1 Presumed Stage IA Endometrial Adenocarcinoma

*A Meta-Analysis*

*Zunpan Fan, MD,* Hui Li, MD,† Rui Hu, MD,* Yuling Liu, MD,* Xinyu Liu, MD,* and Liping Gu, MD**

- 28 ARTICLES
- 619 patients with EEC or ACH:
  - 456 oral progestins
  - 73 HSC resection + Progestins
  - 90 LNG-IUD

| | ORAL PROGESTINS | HSC RESECTION + PROGESTINS | LNG-IUD |
|---|---|---|---|
| COMPLETE RESPONSE RATE | 76.3% | 95.3% | 72.9% |
| RECURRENCE RATE | 30.7% | 14.1% | 11% |
| PREGNANCY RATE | 52.1% | 47.8% | 56% |

# Microinvasive cervical carcinoma: FIGO Stage IA

### Stage IA1

- Conization can be considered a definitive treatment as hysterectomy does not improve the outcome

- Lymph node staging is not indicated in LVSI-negative patients, but can be considered in T1a1 LVSI-positive patients.

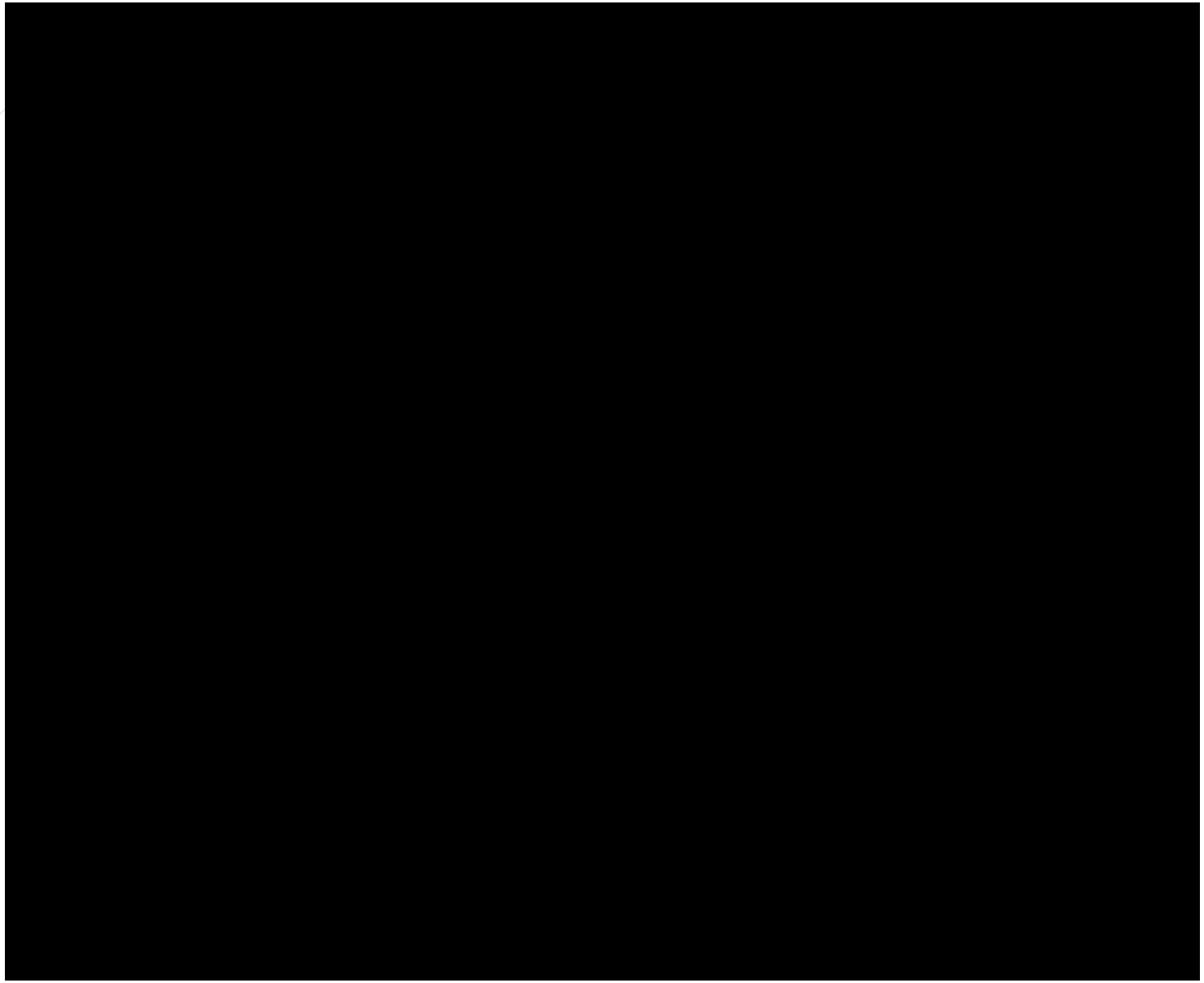
### Stage IA2

- Conization alone or simple hysterectomy.

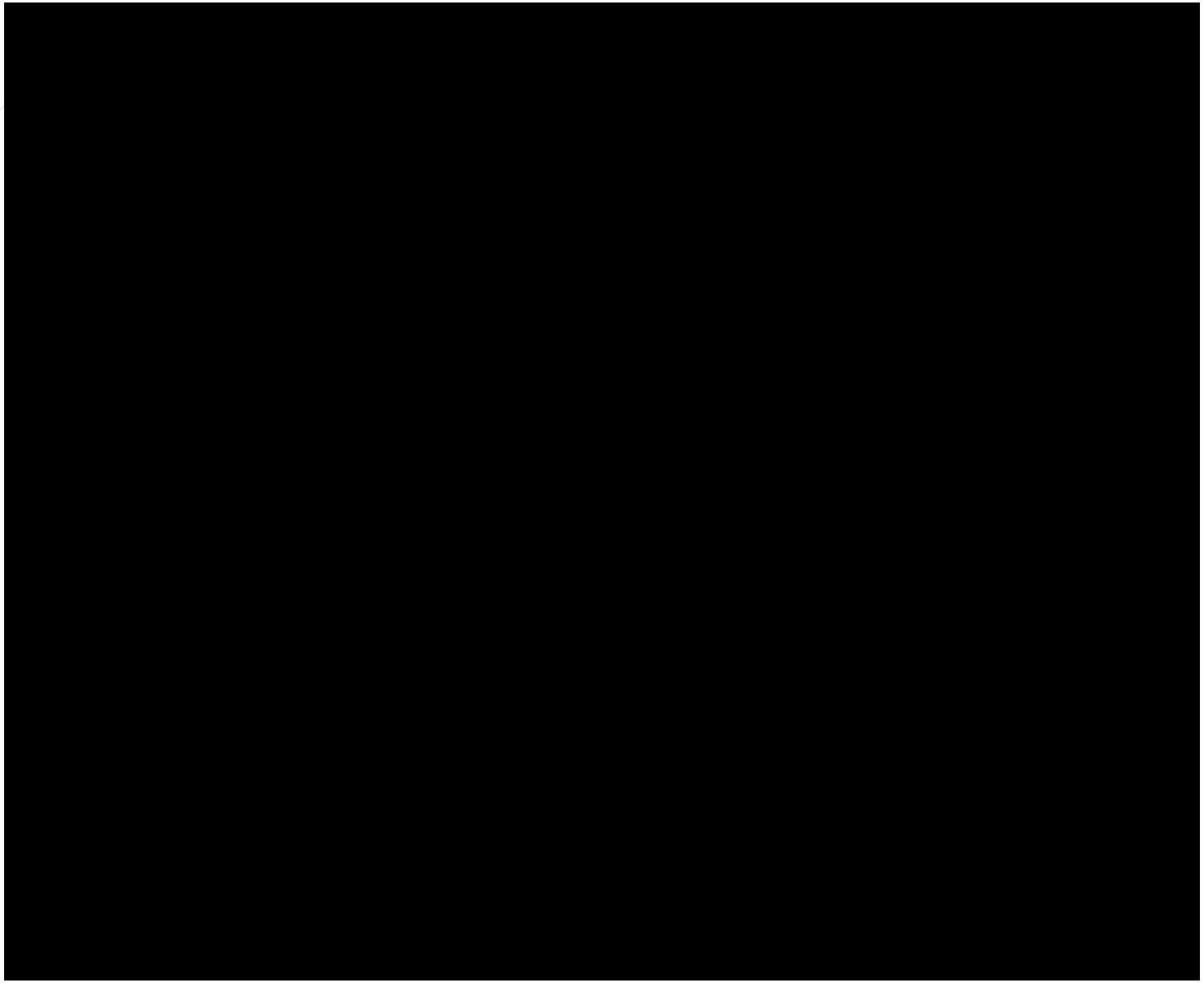
- Lymph node staging should be performed in LVSI-positive patients.

Sentinel lymph node biopsy alone (without additional pelvic lymph node dissection) appears to be an acceptable method of LN staging.

# ENDOCERVICOSCOPIA



# ESCISSIONE CON AGO



# Invasive cervical carcinoma: FIGO Stage IB1,IB2, IIA1

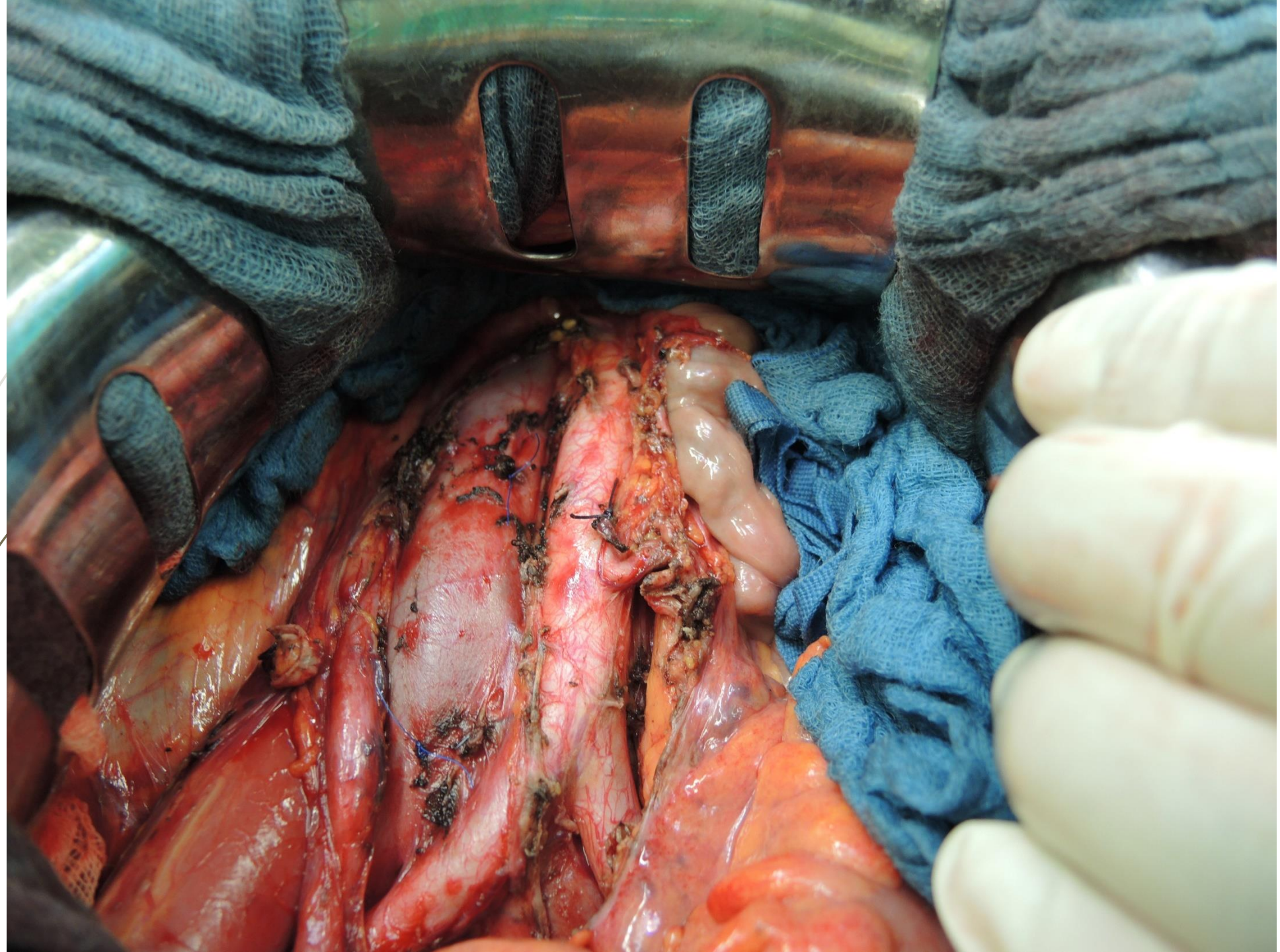
- The standard lymph node staging procedure is systematic pelvic lymphadenectomy.
- **Sentinel node biopsy** before pelvic lymphadenectomy **is strongly recommended**

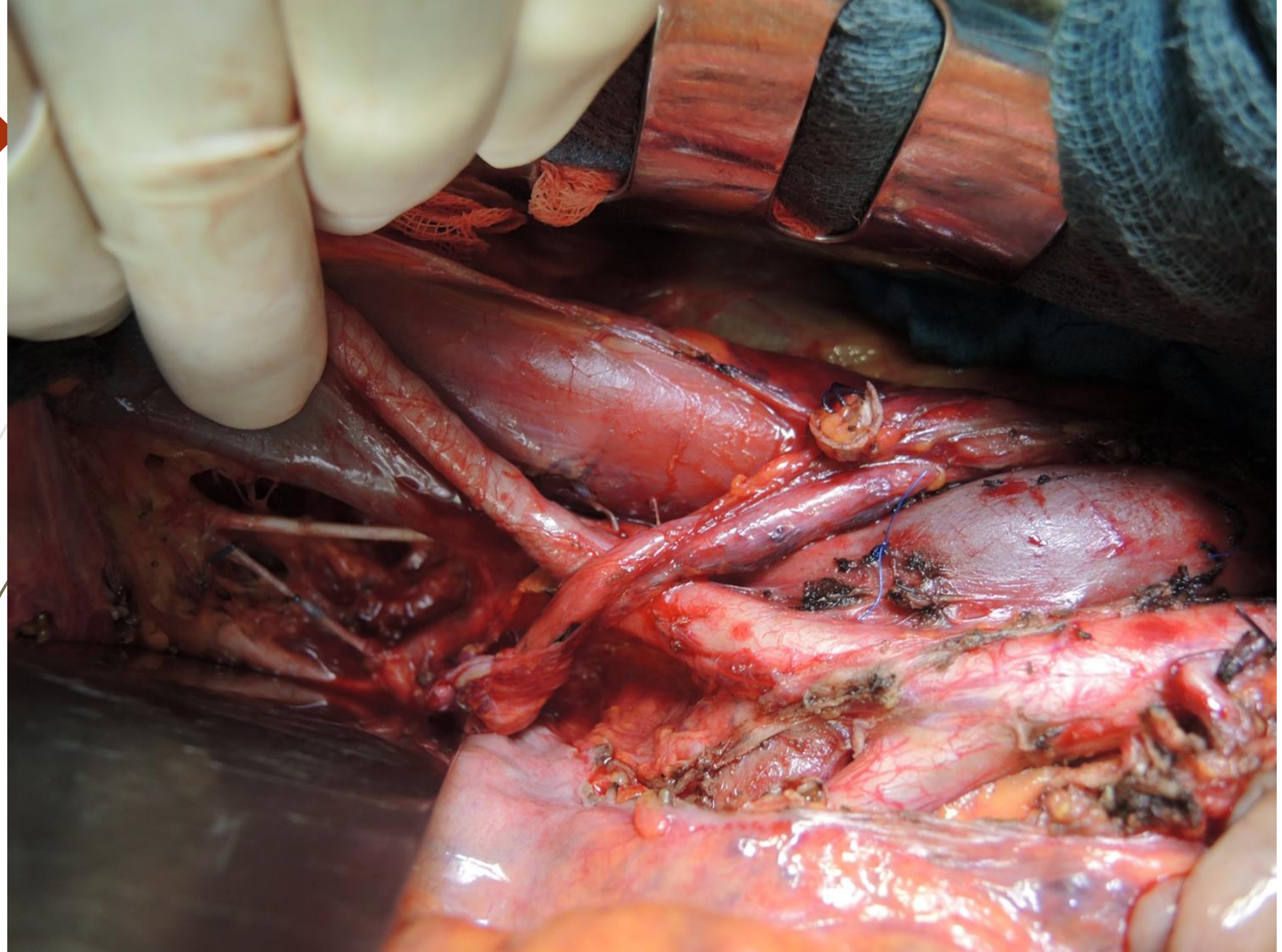
**NEGATIVE**

- Systematic pelvic lymph node dissection should be performed.
- Radical hysterectomy

**POSITIVE**

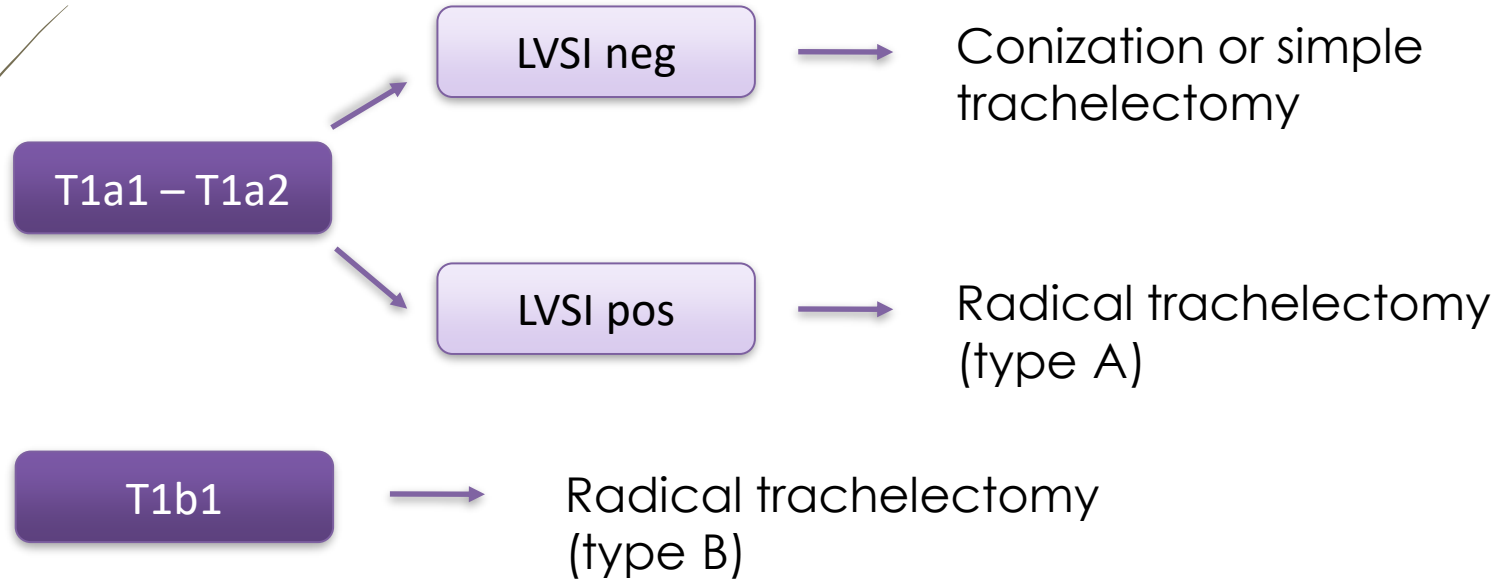
- Avoid pelvic lymph node dissection and hysterectomy
- Refer patients to definitive chemoradiotherapy
- Para-aortic lymph node dissection may be considered for staging purposes





# Fertility sparing treatment

- Squamous cell carcinoma or usual-type (HPV-related) adenocarcinoma
- Tumor size **≤ 2 cm**
- Negative pelvic lymph node status (lymph node staging should always be the first step)




Routine hysterectomy after finishing fertility plans is not necessary.

cancers

MDPI

*Review*

# Neoadjuvant Chemotherapy Prior Fertility-Sparing Surgery in Women with FIGO 2018 Stage IB2 Cervical Cancer: A Systematic Review

Alessandro Buda [1,*], Martina Borghese [2], Andrea Puppo [2], Stefania Perotto [1], Antonia Novelli [2], Chiara Borghi [1], Elena Olearo [2], Elisa Tripodi [1], Alessandra Surace [1], Enrica Bar [1], Giovanni Scambia [3,4] and Francesco Fanfani [3,4]

- 20 studies including 114 patients with 1B2 disease
- Uterine conservation achieved in only 76.7%
- Optimal pathological response to NACT in 60.9%
- Pregnancy occured spontaneously in 85.7% of women who tried to conceive

**STUDY ONGOING**:

- **IRTA study → t**rachelectomy with the open versus the minimally invasive approach

- **CONTESSA trial → s**afety of neoadjuvant chemotherapy followed by fertility-sparing surgery in young women with stage IB2 cervical cancer

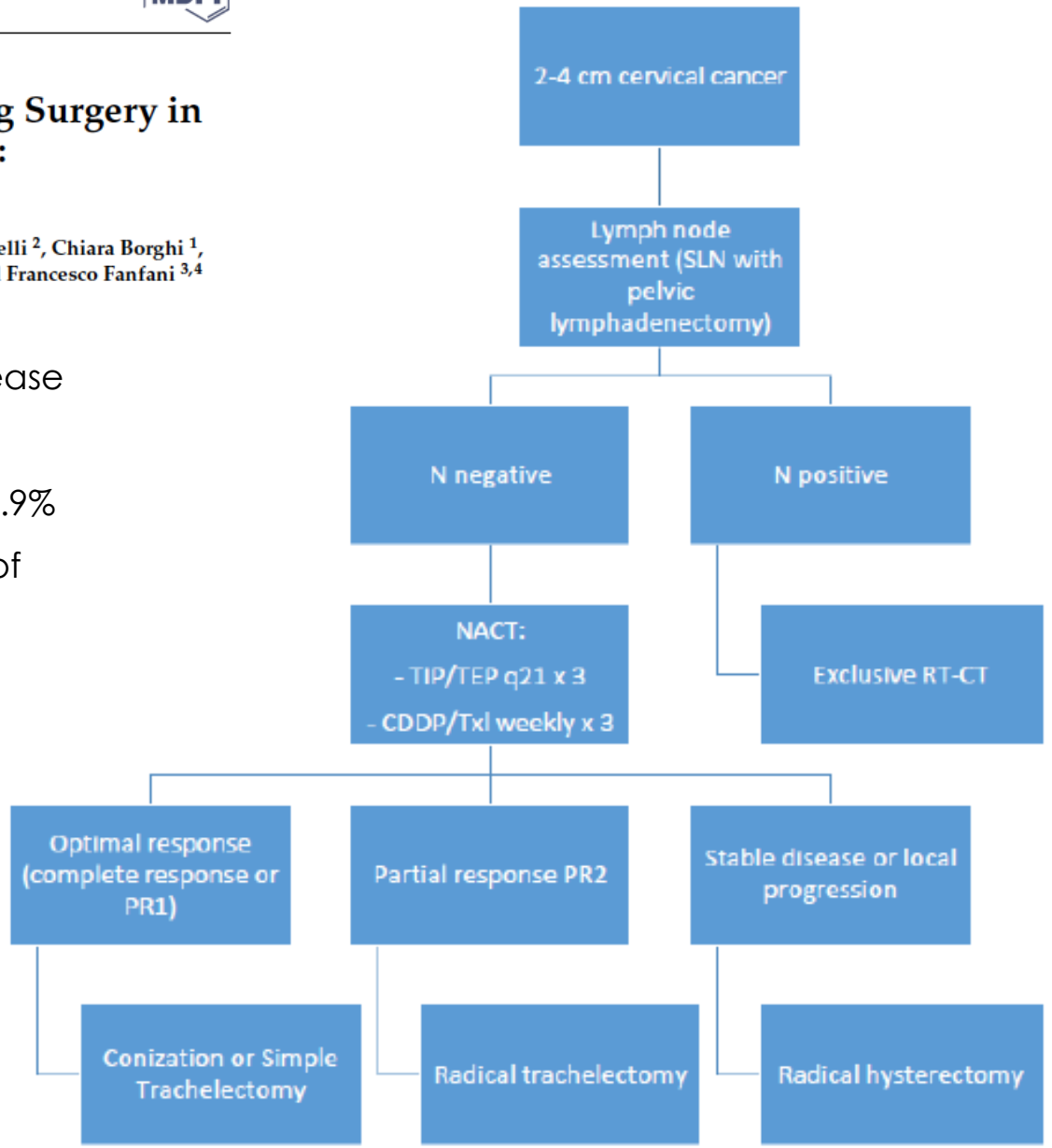
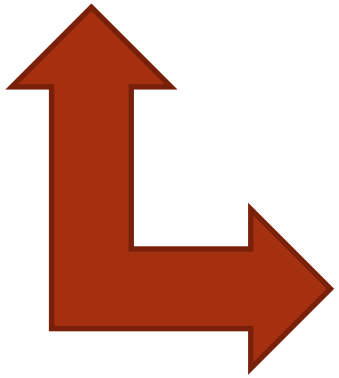



**Figure 2.** Decision-making process algorithm for women with IB2 cervical cancer.

# Conclusioni

- Progressiva de-escalation dei trattamenti
- Introduzione di tecniche mini-invasive
- Miglior selezione delle pazienti
- Miglior caratterizzazione delle neoplasie
- Introduzione di nuovi farmaci target



**- Migliori outcome oncologici**
**- Minori comorbidità**