Complex Treatment of Female Genital Tract Neoplasms. Vulvar, cervical, endometrial and ovarian cancers management recommendations.

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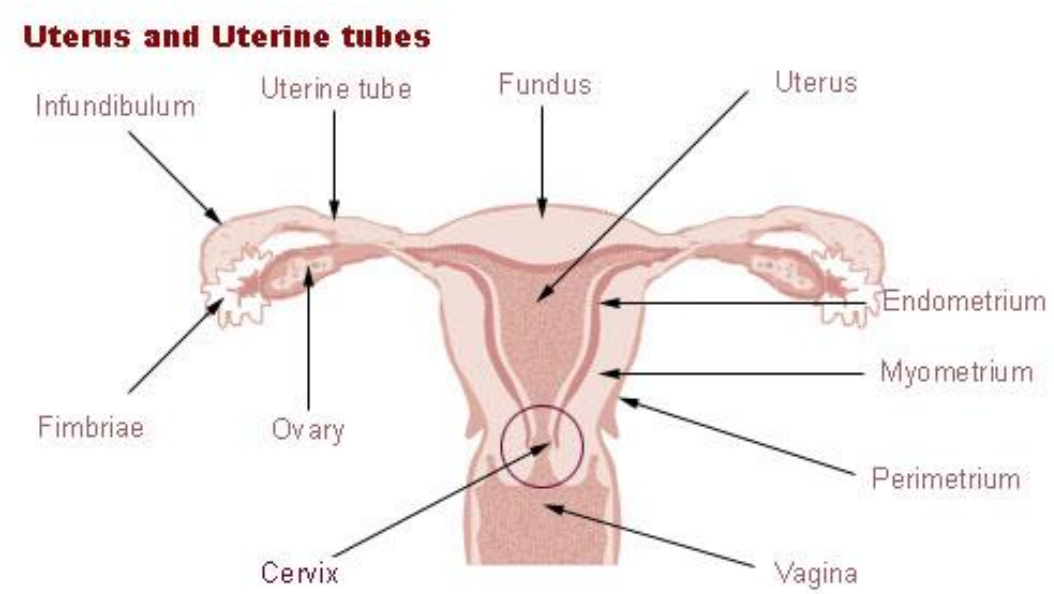
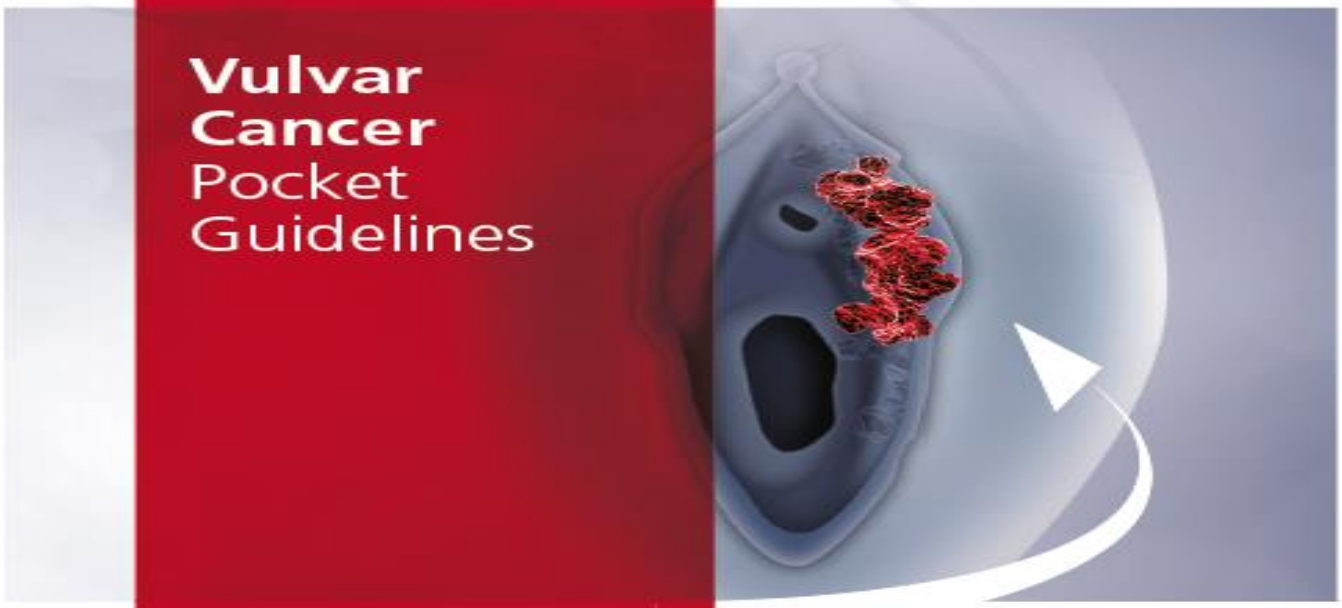
Female genital tract neoplasms:

- Corpus of the uterus: endometrial cancer; sarcoma
- Cervix: cervical cancer
- Adnexa: ovarian cancer and tubal cancer
- Vagina and vulva: vaginal cancer and vulvar cancer



ESGO Guidelines
and Quality Indicators

Vulvar Cancer Pocket Guidelines



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PREOPERATIVE INVESTIGATIONS

✓	In any patient suspected for vulvar cancer, diagnosis should be established by a punch/incision biopsy. Excision biopsy should be avoided for initial diagnosis, as this may obstruct further treatment planning.
✓	In patients with multiple vulvar lesions, all lesions should be biopsied separately (with clear documentation of mapping).
✓	All patients with vulvar cancer should be referred to a Gynaecological Oncology Centre (GOC) and treated by a multidisciplinary gynaecological oncology team.

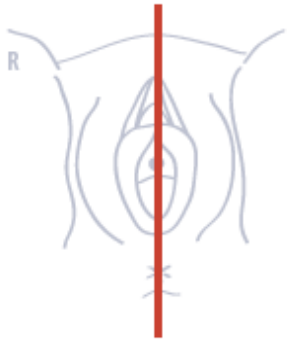
STAGING SYSTEM

✓	Vulvar cancer should be staged according to FIGO and/or TNM classification[2].

[2] Throughout these recommendations, advanced stage of disease is defined as clinical T3 and/or N3.

PREOPERATIVE INVESTIGATIONS

✓	Preoperative work-up should at least include clear documentation of the clinical exam (size of lesion, distance to the midline/clitoris/anus/vagina/urethra and palpation of lymph nodes). Picture or clinical drawing is advised (see below).

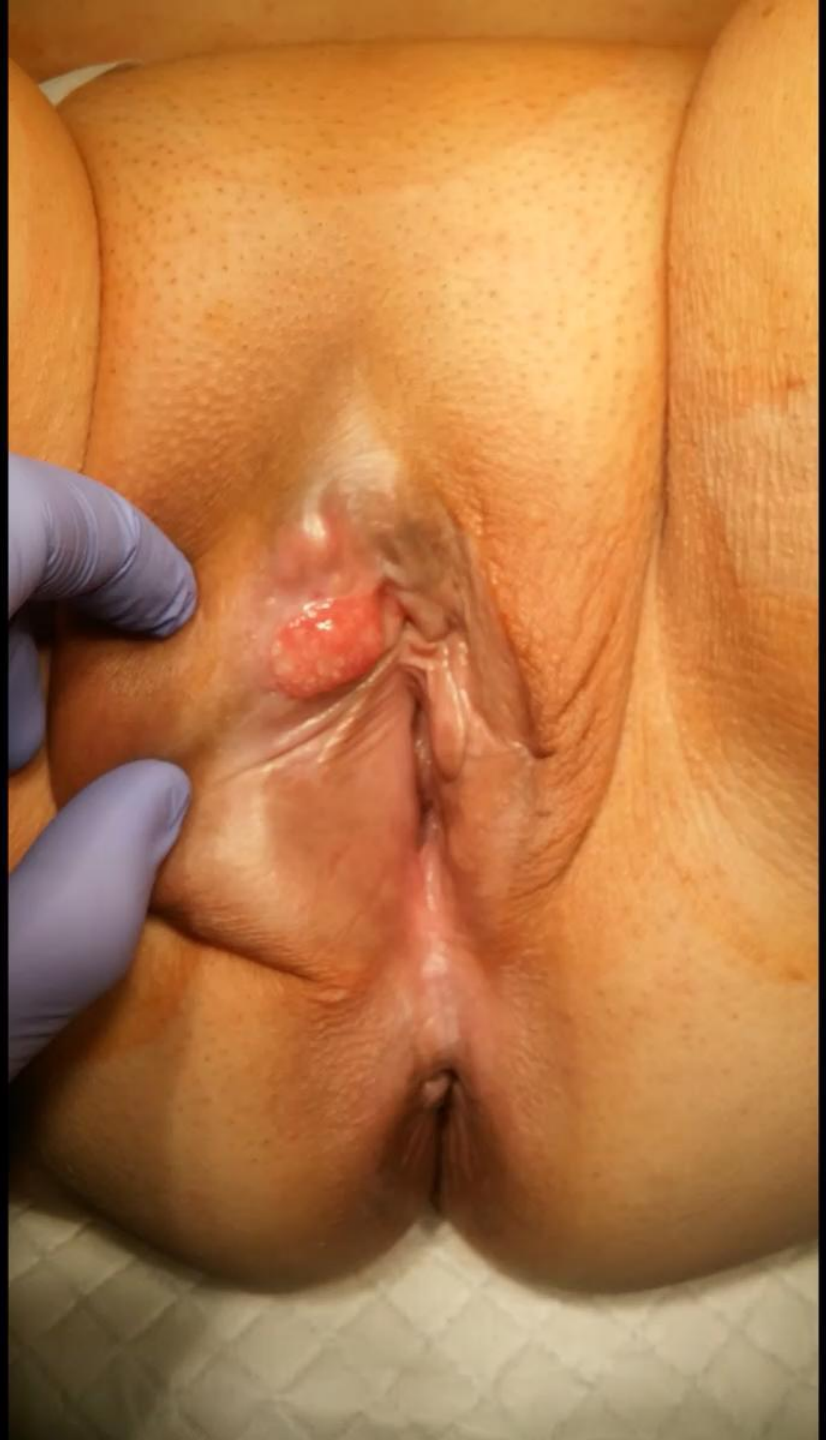


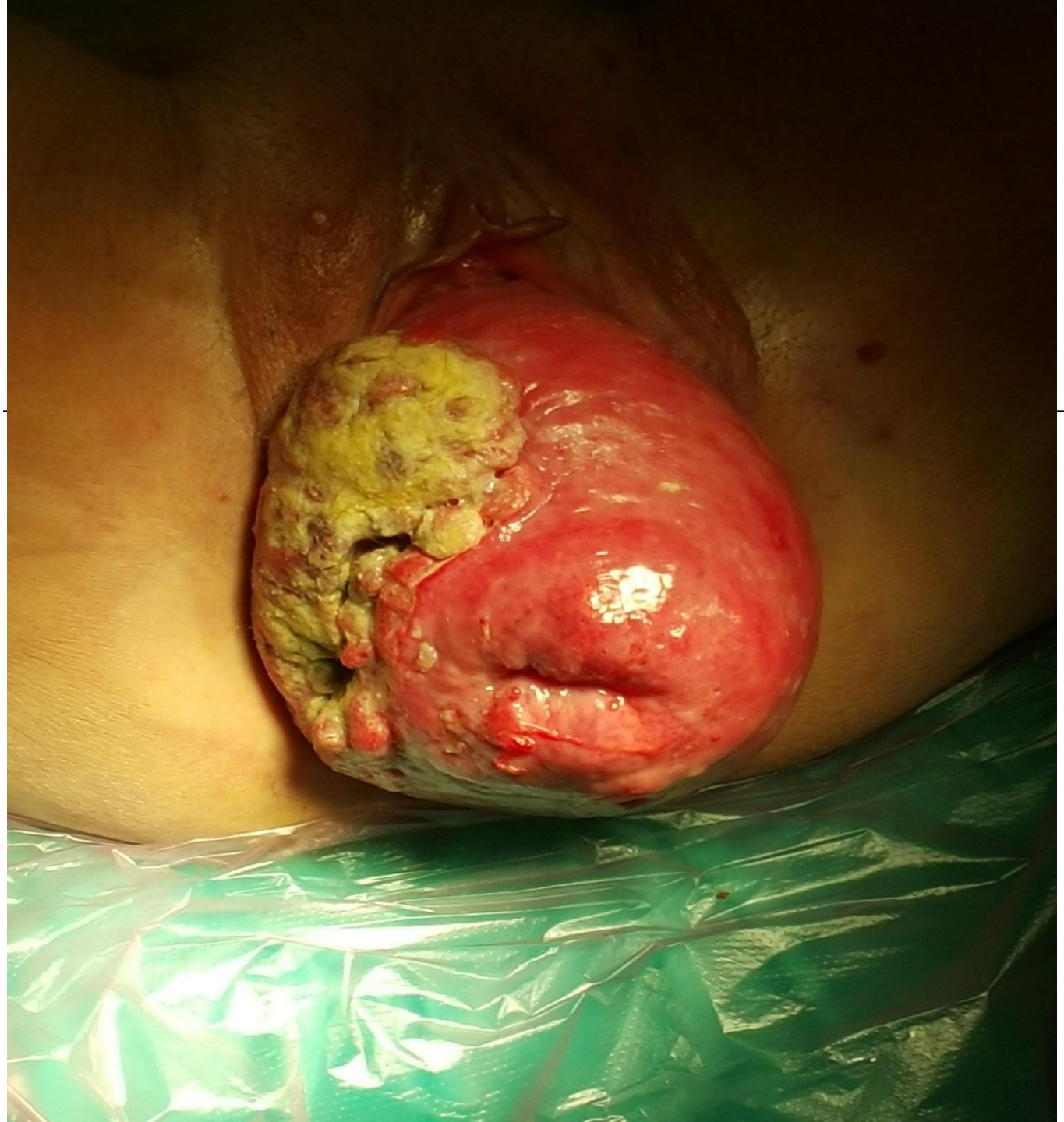
✓	Evaluation of the cervix/vagina/anus is recommended.
C	Prior to sentinel lymph node biopsy, clinical examination and imaging of the groins, (either by ultrasound, (positron emission tomography-) computed tomography ((PET-) CT), or magnetic resonance imaging (MRI)) are required to identify potential lymph node metastases.
✓	Suspicious nodes (at palpation and/or imaging) should be analysed by fine-needle aspiration (FNA), or core biopsy when this would alter primary treatment.
✓	Further staging with CT thorax/abdomen and pelvis is recommended where there is a clinical suspicion of, or proven, (nodal) metastatic disease and/or advanced stage disease.
✓	The pathology report on preoperative biopsy should at least include histological type and depth of invasion.

SURGICAL MANAGEMENT

Local treatment

C	Radical local excision is recommended.
✓	Consider additional, more superficial resection of differentiated vulvar intraepithelial neoplasia (d-VIN) in addition to radical local excision of invasive tumours.
✓	In multifocal invasive disease, radical excision of each lesion as a separate entity may be considered. Vulvectomy may be required in cases with multifocal invasion arising on a background of extensive vulvar dermatosis.
✓	The goal of excision is to obtain tumour-free pathological margins. Surgical excision margins of at least 1 cm are advised. It is acceptable to consider narrower margins where the tumour lies close to midline structures (clitoris, urethra, anus), and preservation of their function is desired.
✓	When invasive disease extends to the pathological excision margins of the primary tumour, reexcision is the treatment of choice.
✓	The optimal management of the groin (full inguinofemoral lymph-adenectomy or isolated removal only) for enlarged, proven metastatic nodes remains to be defined.





Groin treatment

C	Groin treatment should be performed for tumours > pT1a.
B	For unifocal tumours < 4 cm without suspicious groin nodes on clinical examination and imaging (any modality) the sentinel lymph node procedure is recommended.
C	For tumours ≥ 4 cm and/or in case of multifocal invasive disease, inguinofemoral lymphadenectomy by separate incisions is recommended. In lateral tumours (medial border > 1 cm from midline), ipsilateral inguinofemoral lymphadenectomy is recommended. Contralateral inguinofemoral lymphadenectomy may be performed when ipsilateral nodes show metastatic disease.
D	When lymphadenectomy is indicated, superficial and deep femoral nodes should be removed.
C	Preservation of the saphenous vein is recommended.
✓	Advanced stage patients should be evaluated in a multidisciplinary setting to determine the optimal choice and order of treatment modalities.
✓	Where enlarged (> 2 cm) pelvic nodes are identified, their removal should be considered.

Reconstructive surgery

✓	Availability of reconstructive surgical skills as part of the multidisciplinary team is required in early as well as advanced stage disease.

SENTINEL LYMPH NODE PROCEDURE

B	The sentinel lymph node procedure is recommended in patients with unifocal cancers of < 4 cm, without suspicious groin nodes.
B	Use of radioactive tracer is mandatory; use of blue dye is optional.
C	Lymphoscintigram is advised to enable the preoperative identification, location, and number of sentinel lymph nodes.
C	Intraoperative evaluation and/or frozen sectioning of the sentinel lymph node can be performed in an attempt to prevent a second surgical procedure. Caution is warranted because of an increased risk of missing micrometastases on final pathology due to the loss of tissue arising from processing for frozen section assessment.
✓	When a sentinel lymph node is not found (method failure), inguinofemoral lymphadenectomy should be performed.
C	Where metastatic disease is identified in the sentinel lymph node (any size): inguinofemoral lymphadenectomy in the groin with the metastatic sentinel lymph node.
✓	For tumours involving the midline: bilateral sentinel lymph node detection is mandatory. Where only unilateral sentinel lymph node detection is achieved, an inguinofemoral lymphadenectomy in the contralateral groin should be performed.
C	Pathological evaluation of sentinel lymph nodes should include serial sectioning at levels of at least every 200 µm. If the H&E sections are negative, immunohistochemistry should be performed.

RADIATION THERAPY

✓	Adjuvant radiotherapy should start as soon as possible, preferably within 6 weeks of surgical treatment.
✓	When invasive disease extends to the pathological excision margins of the primary tumour, and further surgical excision is not possible, postoperative radiotherapy should be performed.
✓	In case of close but clear pathological margins, postoperative vulvar radiotherapy may be considered to reduce the frequency of local recurrences. There is no consensus for the threshold of pathological margin distance below which adjuvant radiotherapy should be advised.
B	Postoperative radiotherapy to the groin is recommended for cases with > 1 metastatic lymph node and/or the presence of extracapsular lymph node involvement.
✓	Adjuvant radiotherapy for metastatic groin nodes should include the ipsilateral groin area and where pelvic nodes are non-suspicious on imaging, the distal part of the iliac nodes with an upper limit at the level of the bifurcation of the common iliac artery.
C	Based on evidence from other squamous cell cancers such as cervical, head & neck, and anal cancer, the addition of concomitant, radiosensitising chemotherapy to adjuvant radiotherapy should be considered.

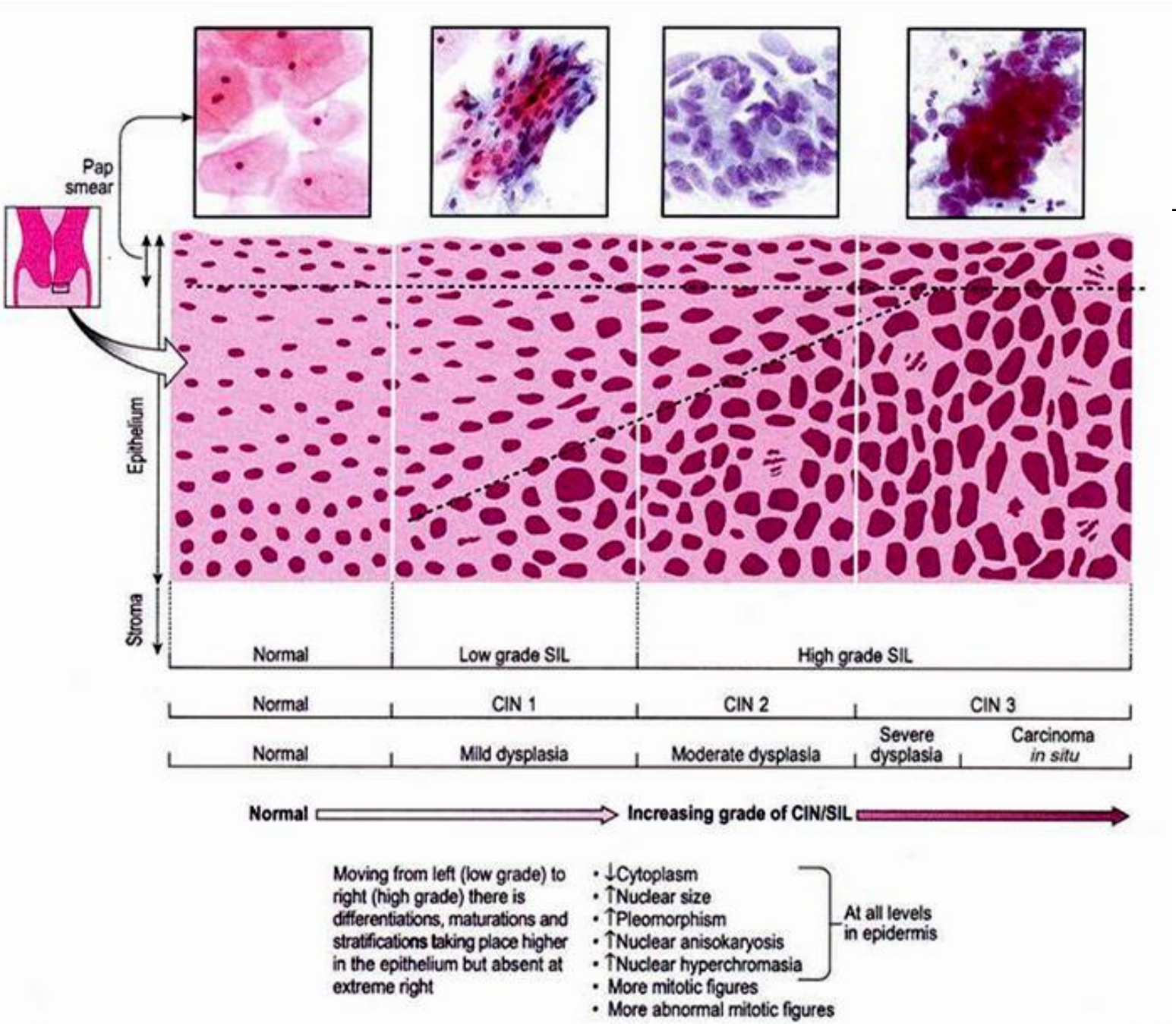
CHEMORADIATION

C	Definitive chemoradiation (with radiation dose escalation) is the treatment of choice in patients with unresectable disease.
C	In advanced stage disease, neoadjuvant chemoradiation should be considered in order to avoid exenterative surgery.
C	Radiosensitising chemotherapy, preferably with weekly cisplatin, is recommended.

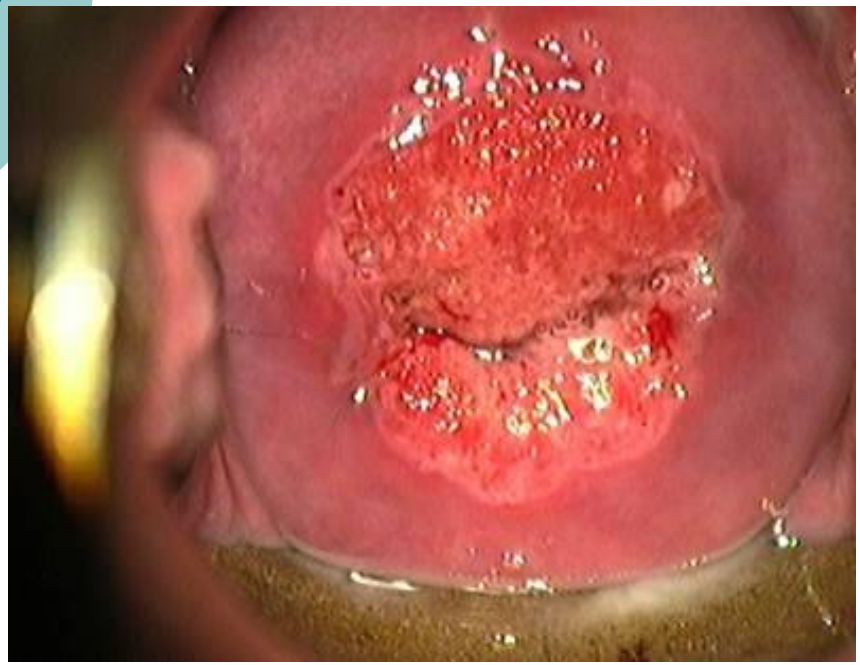
SYSTEMIC TREATMENT

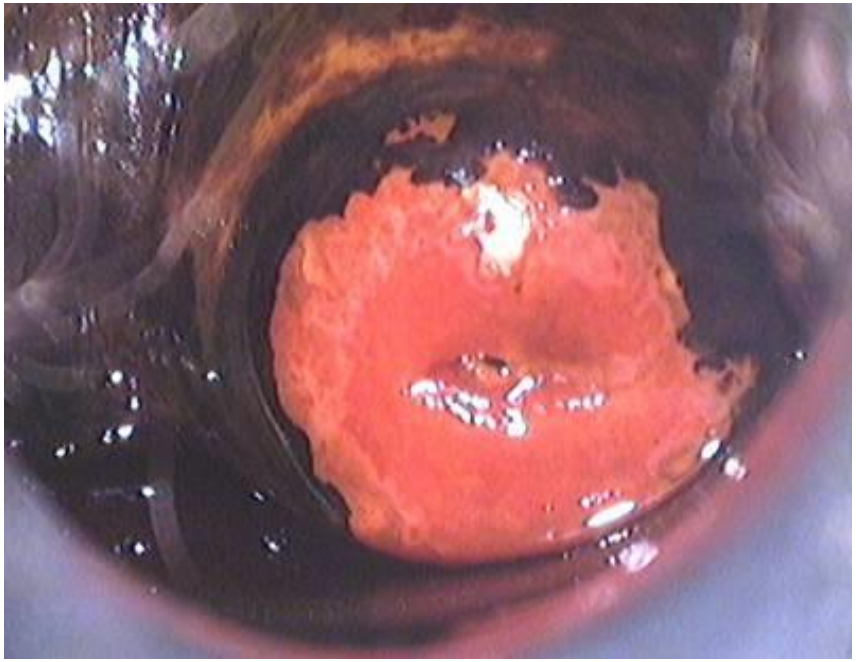
D	Data in vulvar cancer are insufficient to recommend a preferred schedule in a palliative setting.

Premalignant lesions of the cervical cancer – Cervical Intraepithelial Neoplasia (CIN)

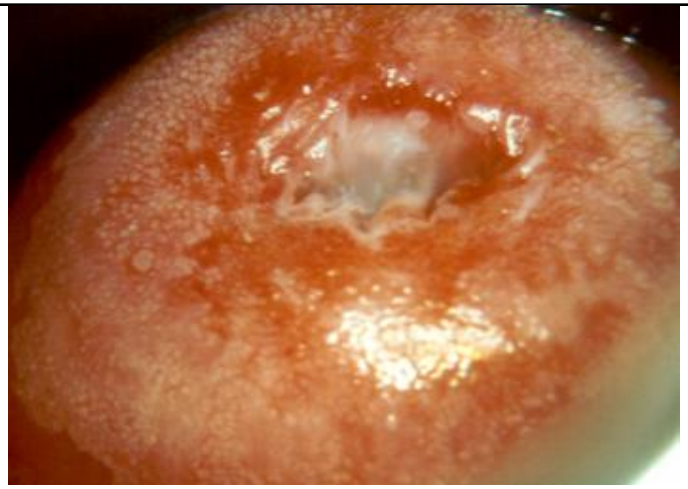

Pap smear
Epithelium
Stroma
Normal
Low grade SIL
High grade SIL
Normal
CIN 1
CIN 2
CIN 3
Normal
Mild dysplasia
Moderate dysplasia
Severe dysplasia
Carcinoma in situ
Normal
Increasing grade of CIN/SIL
Moving from left (low grade) to right (high grade) there is differentiations, maturations and stratifications taking place higher in the epithelium but absent at extreme right
• ↓Cytoplasm
• ↑Nuclear size
• ↑Pleomorphism
• ↑Nuclear anisokaryosis
• ↑Nuclear hyperchromasia
At all levels in epidermis
• More mitotic figures
• More abnormal mitotic figures

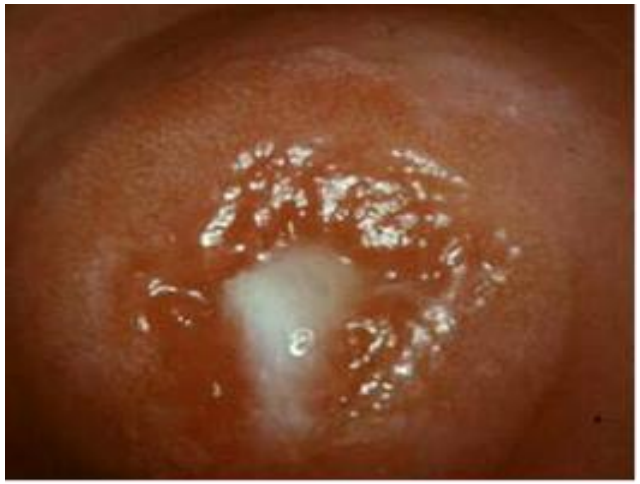
Colposcopy – ectopy after acetic acid and iodine solution

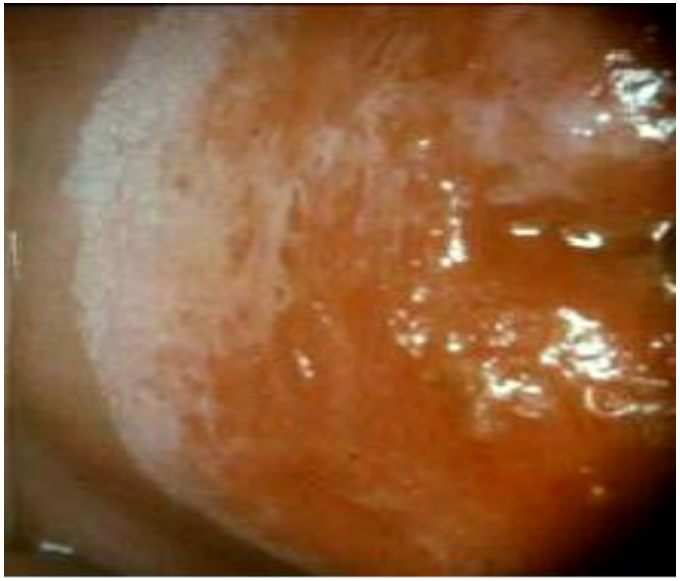


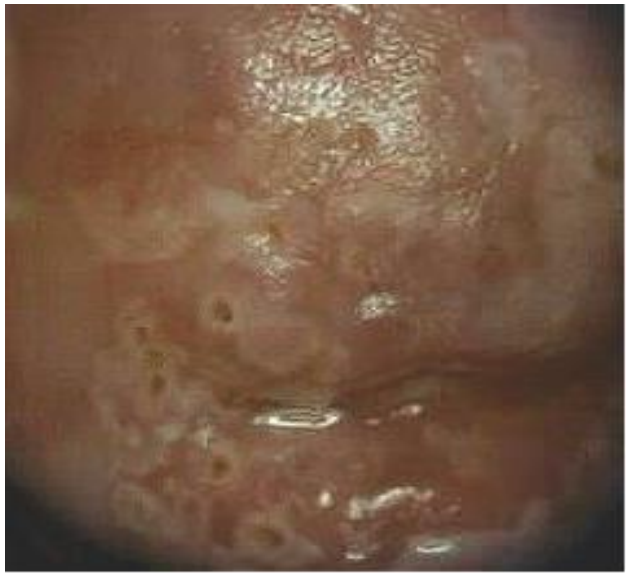


Colposcopy – HSIL images







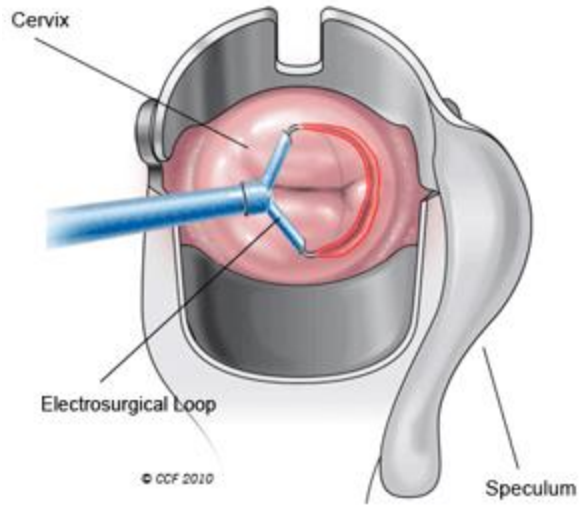


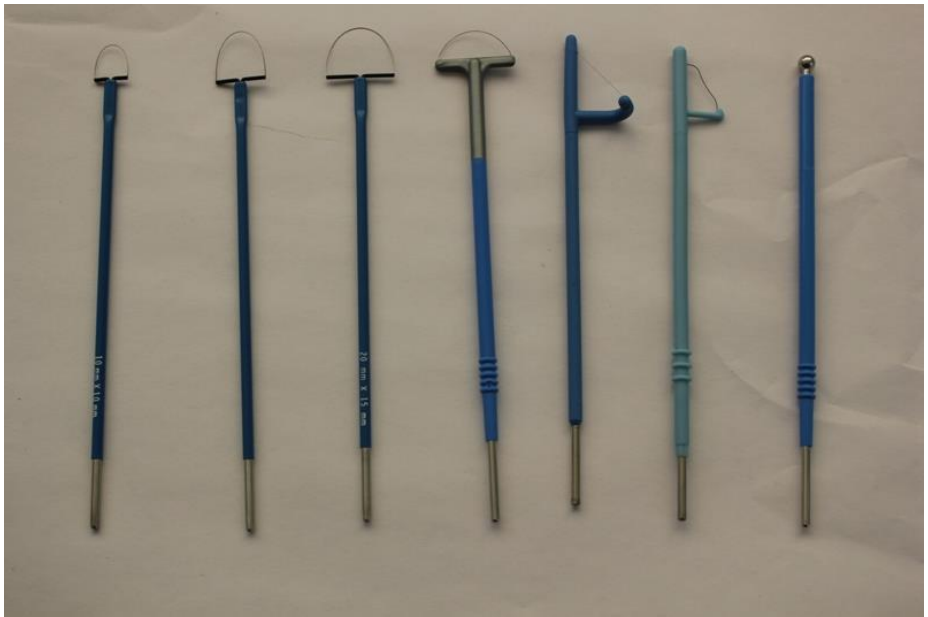
CIN treatment

CIN 1 ⟶ **OBSERVE !**

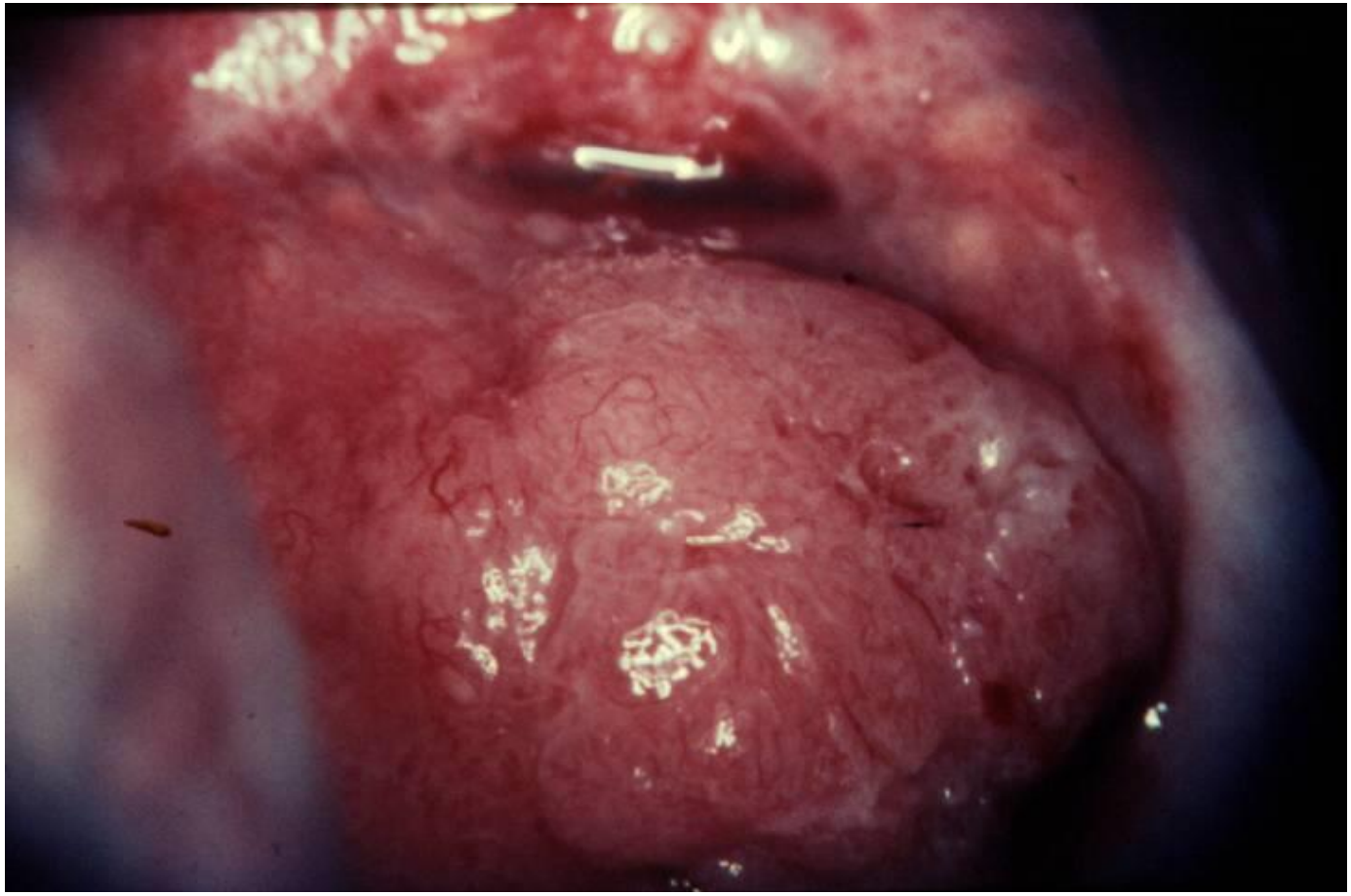
CIN 2/3 ⟶ **CONISATION !**

LEEP/LLETZ





Colposcopy – invasive cervical cancer – bulky tumor



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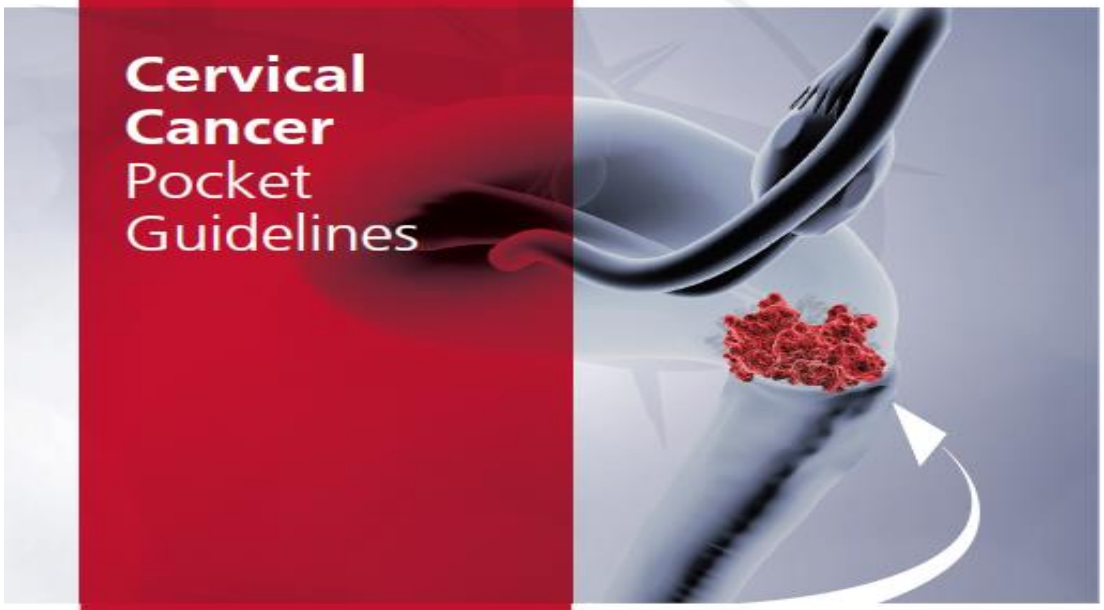
Cervical Cancer Pocket Guidelines



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GENERAL RECOMMENDATIONS

✓ Treatment planning should be made on a multidisciplinary basis (generally at a tumour board meeting) and based upon the comprehensive and precise knowledge of prognostic and predictive factors for oncological outcome, morbidity and quality of life.

✓ Patients should be carefully counseled on the suggested treatment plan, and potential alternatives, including risks and benefits of all options.

✓ Treatment should be undertaken by a dedicated team of specialists in the diagnosis and management of gynaecological cancers.

Prognostic factors

B Proper documentation of the following major tumour related prognostic factors is recommended:

- TNM and FIGO stage, including a maximum tumour size and detailed description of extracervical tumour extension and nodal involvement (number, size, location).
- Pathological tumour type.
- Depth of cervical stromal invasion and a minimum thickness of uninvolved cervical stroma.
- Presence or absence of lymphovascular space involvement (LVSI).
- Presence or absence of distant metastases.

STAGING

FIGO staging and TNM classification

✓ Patients with cervical cancer should be staged according to the TNM classification. Clinical staging (FIGO) should also be documented *(Table 1)*.

C TNM should be based on a correlation of various modalities (integrating physical examination, imaging and pathology) after discussion in a multidisciplinary forum.

✓ The method used to determine tumour status (T), lymph node status (N) and systemic status (M) i.e. clinical (c), imaging (i) and/or pathological (p) should be recorded.

✓ Lymph node metastases should be classified according to the TNM classification (see Principles of pathological evaluation).

Local clinical and radiological diagnostic work-up

✓ Pelvic examination and biopsy +/- colposcopy are mandatory components to diagnose cervical cancer.

B Pandatory initial work-up for assessment of pelvic tumour extent and to guide treatment options is pelvic magnetic resonance imaging (MRI).

✓ Endovaginal/transrectal ultrasound is an option if performed by a properly trained sonographer.

✓ Cystoscopy or rectoscopy may be considered to provide a biopsy if suspicious lesions in the urinary bladder or rectum are documented on MRI or ultrasound.

MANAGEMENT OF STAGE T1a

Diagnosis of stage T1a disease

✓ Diagnosis of T1a cancer should be based on a conisation (or excision) specimen examined by an expert pathologist. Management must be based on an expert pathology review, with accurate measurement of the maximum horizontal two dimensions, depth of invasion, margin status, coexisting pathology and reliable assessment of LVSI.

✓ Loop or laser conisation are preferable to cold-knife conisation in women desiring fertility preservation. Maximum care should be taken to provide an intact (unfragmented) specimen with minimal thermal artefact. The cone specimen should be oriented for the pathologist.

C Surgical margins of the cone specimen should be clear of both invasive and preinvasive disease (except for preinvasive disease in ectocervix).

Management of stage T1a1 disease

✓ Management of patients with stage T1a1 disease should be individualised depending on the age, the desire for fertility preservation and the presence or absence of LVSI.

✓ In case of positive margins (except for preinvasive disease in ectocervix), a repeat conisation should be performed to rule out more extensive invasive disease.

B Lymph node staging is not indicated in T1a1 LVSI-negative patients but can be considered in T1a1 LVSI-positive patients. Sentinel lymph node biopsy (without additional pelvic lymph node dissection) is an acceptable method of lymph node staging.

C Conisation can be considered a definitive treatment as hysterectomy does not improve the outcome.

C Radical surgical approaches such as radical hysterectomy or parametrectomy represent overtreatment for patients with T1a1 disease.

Management of stage T1a2 disease

C In patients with stage T1a2 disease, conisation alone or simple hysterectomyis an adequate treatment.

B Parametrial resection is not indicated.

B Lymph node staging can be considered in LVSI- patients but should be performed in LVSI+patients. Sentinel lymph node biopsy alone (without additional pelvic lymph node dissection) appears to be an acceptable method of LN staging.

✓ Routine completion of hysterectomy is not recommended after conservative management of stage T1a disease.

MANAGEMENT OF STAGES T1b1/T2a1

General recommendation

C — Treatment strategy should aim for the avoidance of combining radical surgery and radiotherapy due to the highest morbidity after combined treatment.

Negative lymph nodes on radiological staging

Surgical treatment

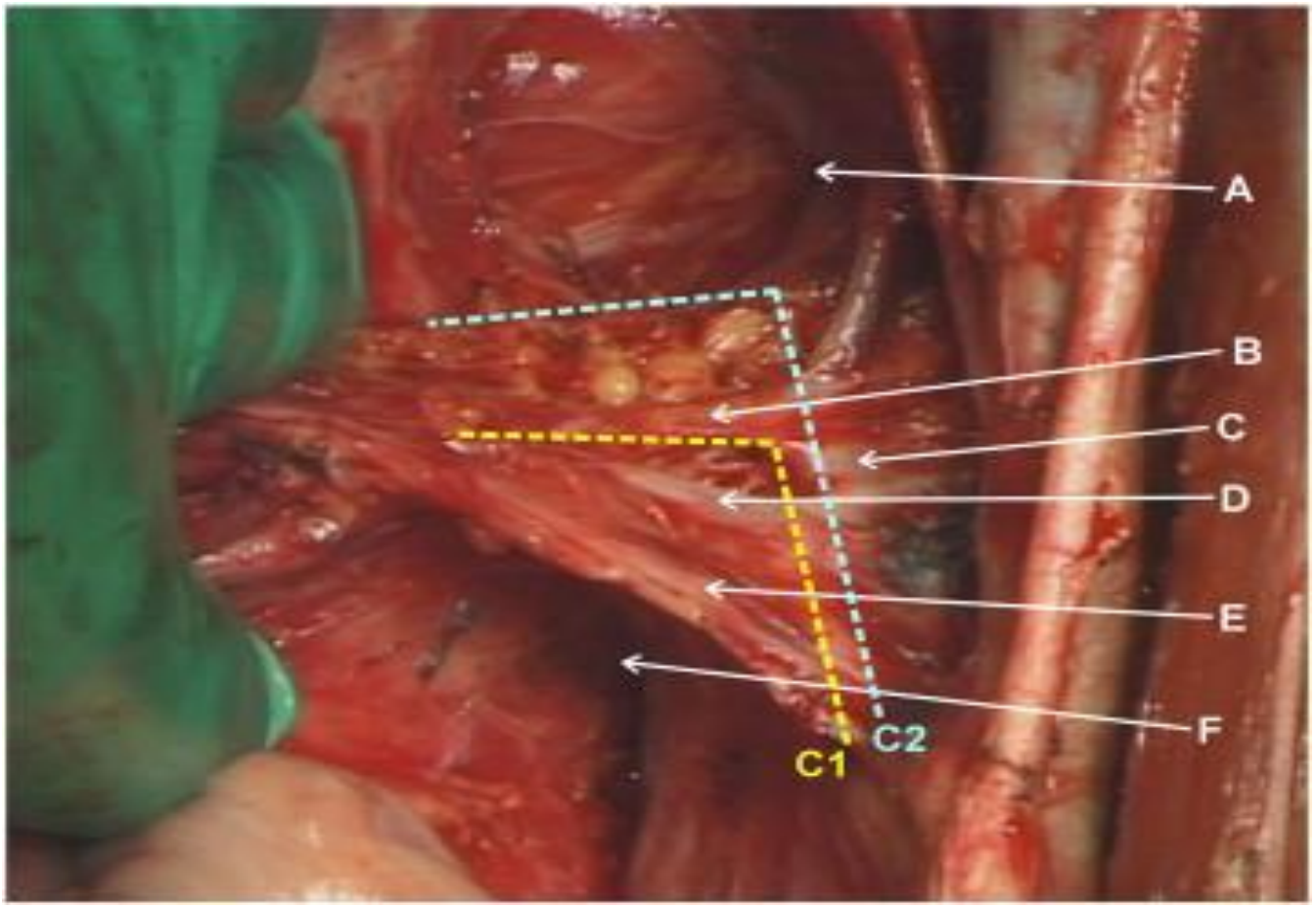
B — Radical surgery by a gynaecological oncologist is the preferred treatment modality. Minimal invasive approach is favoured. ? LACC Study ?

B — The standard lymph node staging procedure is systematic pelvic lymphadenectomy. Sentinel node biopsy before pelvic lymphadenectomy is strongly recommended. Combination of blue dye with radiocolloid or use of indocyanine green alone are the recommended techniques.

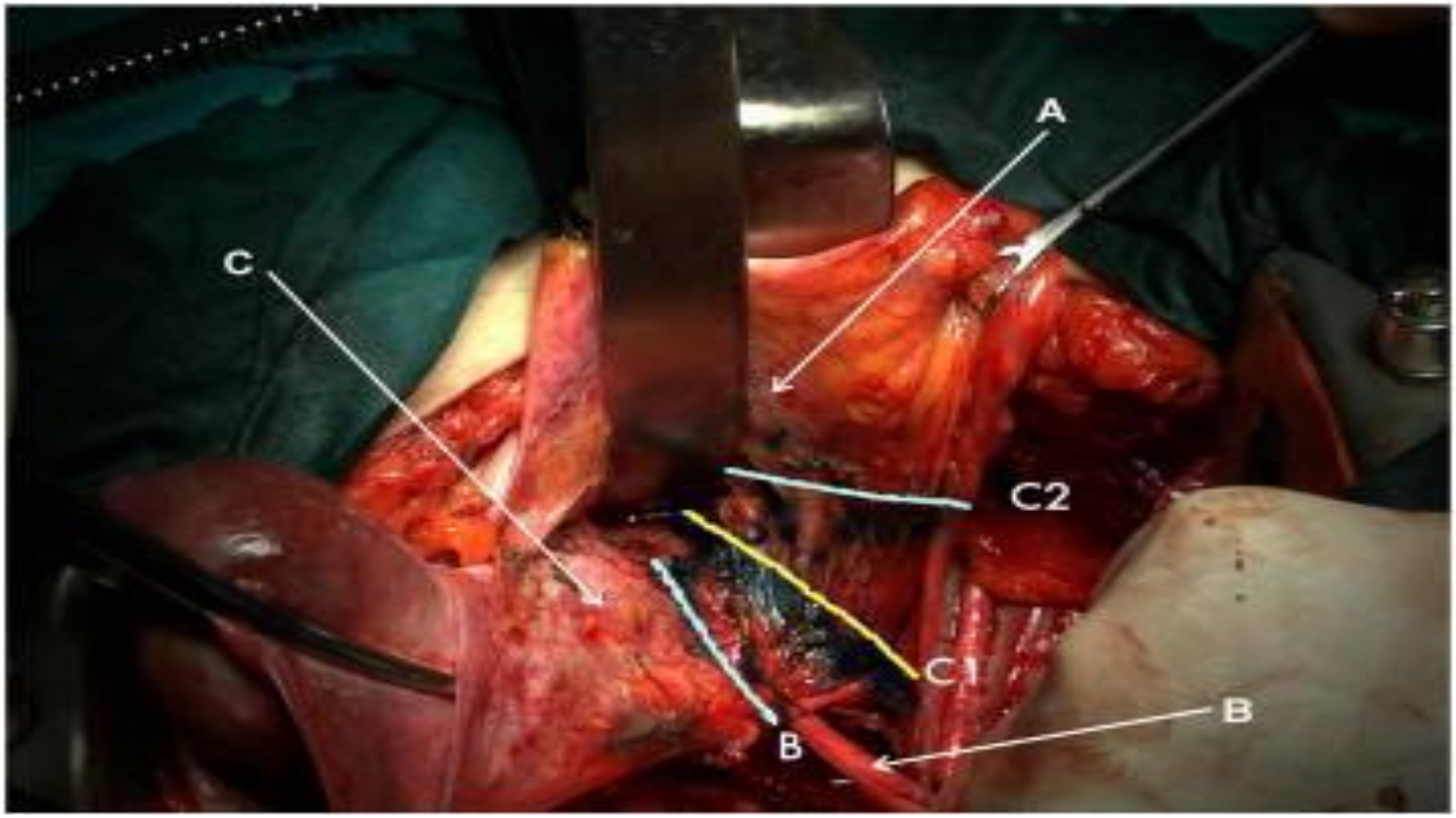
✓ — Lymph node assessment should be performed as the first step of surgical management. Intraoperative assessment of lymph node status (frozen section) is recommended. All sentinel nodes from both sides of the pelvis and/or any suspicious lymph nodes should be sent for frozen section. If sentinel node is not detected, intraoperative assessment of the pelvic lymph nodes should be considered.

✓ — If intraoperative lymph node assessment is negative or it is not done, systematic pelvic lymph node dissection should be performed. At present, sentinel node biopsy alone cannot be recommended outside prospective clinical trials. Systematic lymph node dissection should include the removal of lymphatic tissue from regions with the most frequent occurrence of positive lymph nodes (sentinel nodes) including obturator fossa, external iliac regions, common iliac regions bilaterally, and presacral region. Distal external iliac lymph nodes (so called circumflex iliac lymph nodes) should be spared if they are not macroscopically suspicious.

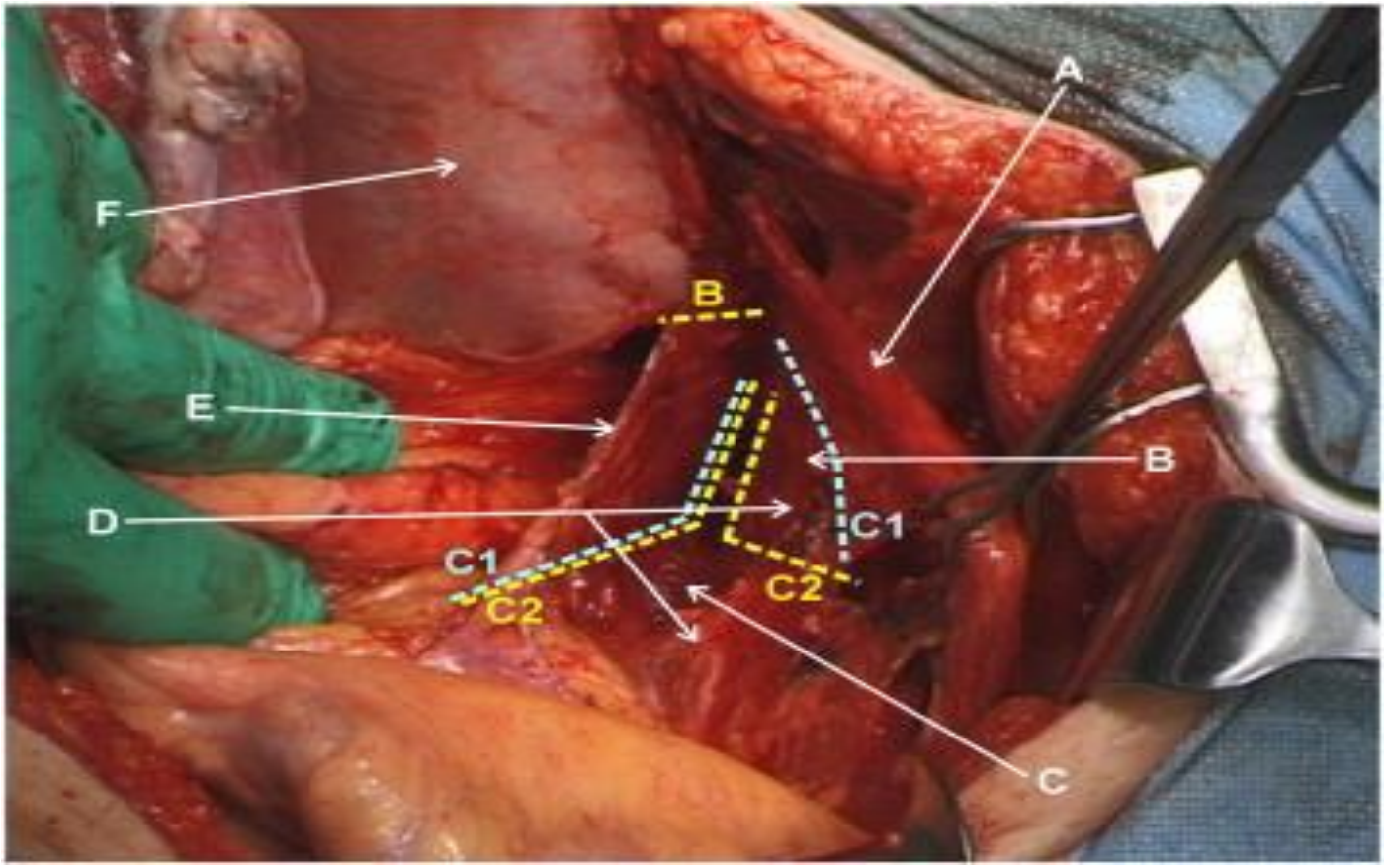
Radical hysterectomy – lateral parametria

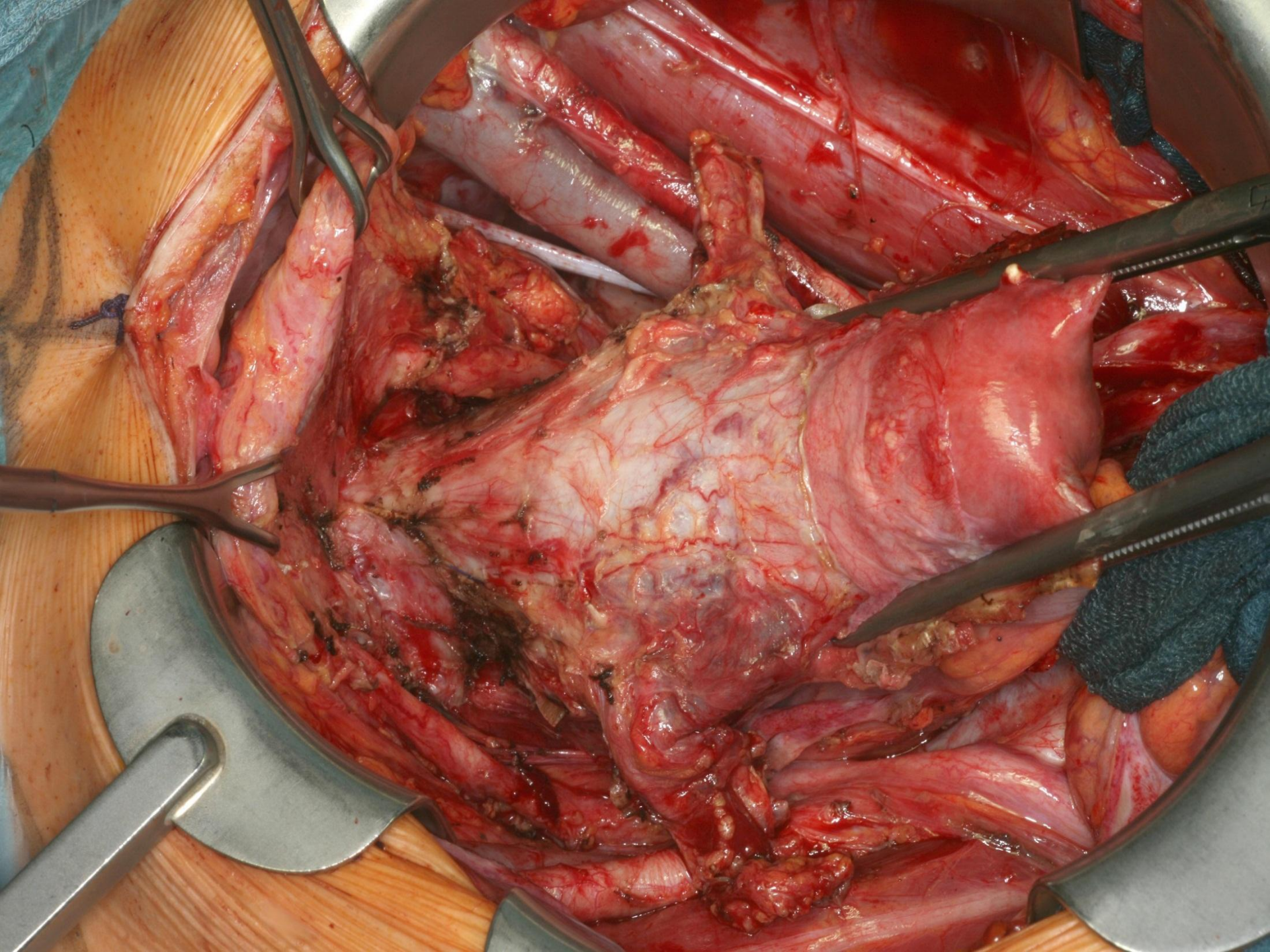


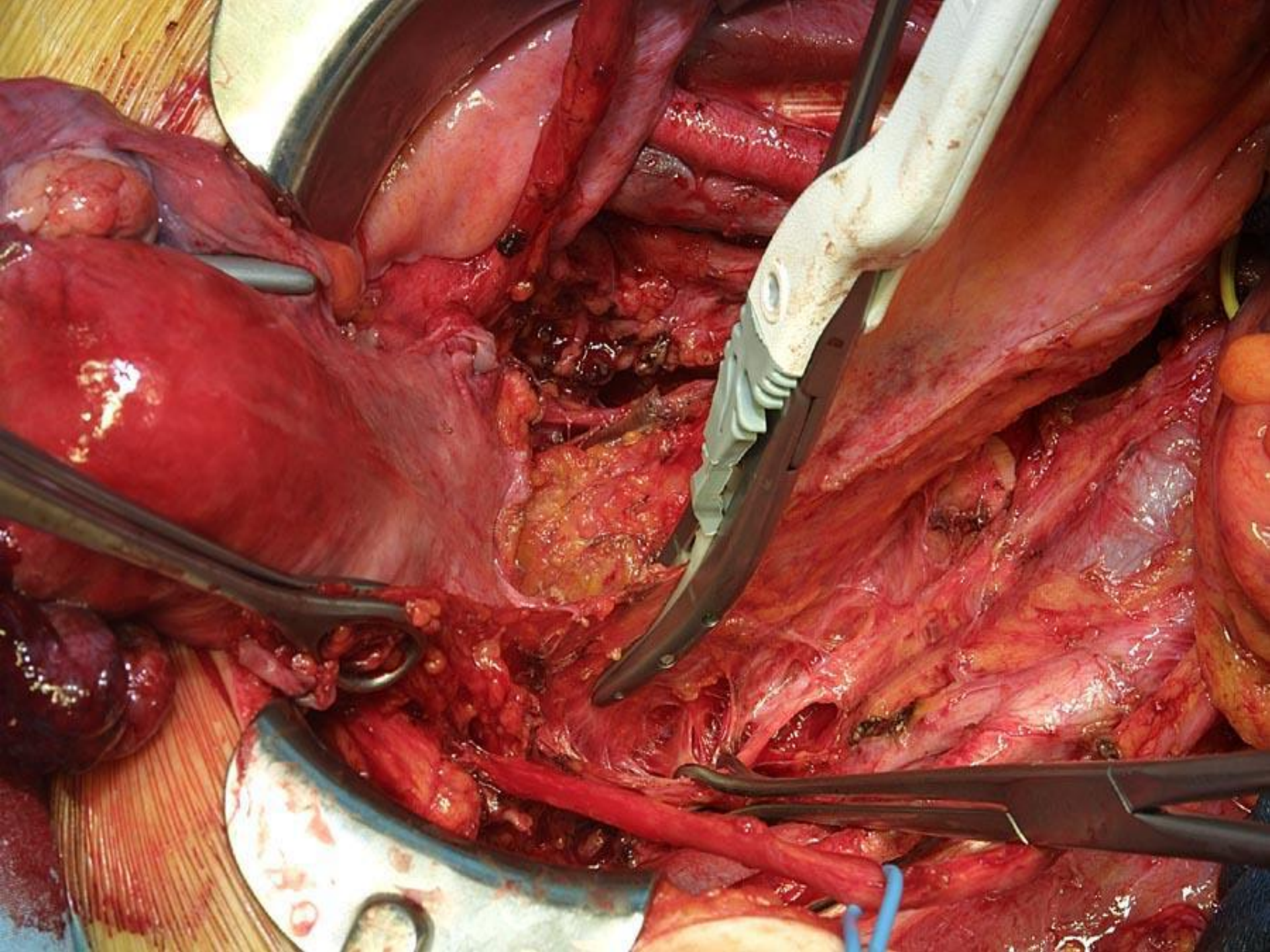
Radical hysterectomy – anterior parametria

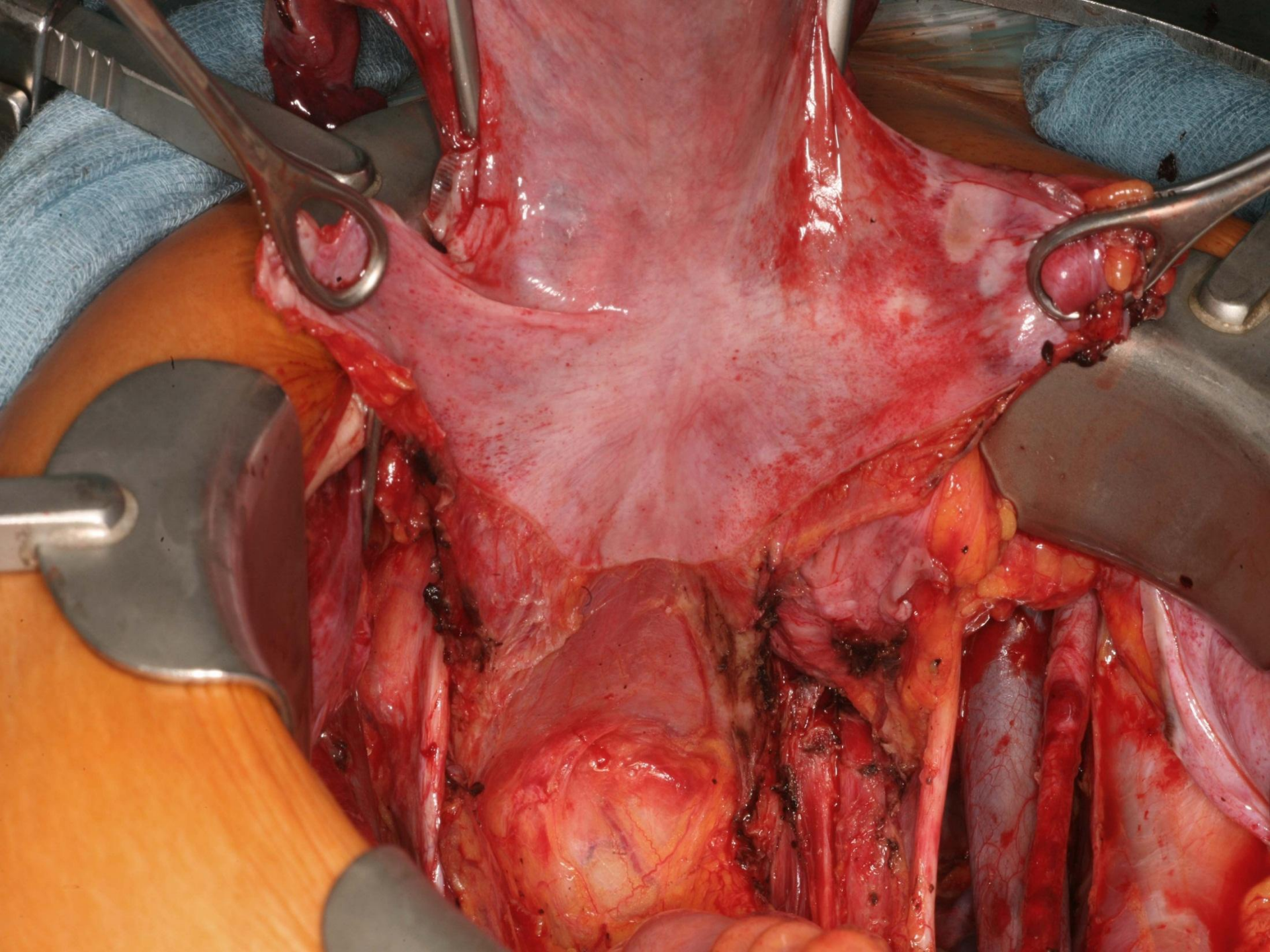


Radical hysterectomy – posterior parametria









Adjuvant treatment

B

Adjuvant radiotherapy should be considered in the presence of combination of risk factors at final pathology such as tumour size, LVSI, and depth of stromal invasion.

✓

When in these situations an adequate type of radical hysterectomy has been performed *(Table 3)*, observation is an alternative option, especially in teams experienced in this approach.

B

After primary radical surgery, adjuvant chemoradiotherapy is indicated in the following groups of patients (see Principles of radiotherapy):

- metastatic involvement of pelvic lymph nodes, including the presence of macrometastases pN1 or micrometastases pN1(mi) in either sentinel node or any other pelvic lymph nodes detected by intraoperative or final pathologic assessment ⇨ chemoradiotherapy;
- positive surgical margins (vagina/parametria) ⇨ chemoradiotherapy brachytherapy boost may be considered
- parametrial involvement ⇨ chemoradiotherapy

MANAGEMENT OF LOCALLY ADVANCED CERVICAL CANCER

Stage T1b2/T2a2 and negative lymph nodes on radiological staging

B	Treatment strategy should aim for avoiding the combination of radical surgery and postoperative external radiotherapy, due to the significant increase of morbidity and no evident impact on survival.
A	Definitive platinum-based chemoradiotherapy and brachytherapy is the preferred treatment (see Principles of radiotherapy).
C	Paraaortic lymph node dissection, at least up to inferior mesenteric artery, may be considered before chemoradiotherapy and brachytherapy. Pelvic lymph node dissection is not required.
✓	Radical surgery is an alternative option, in particular in patients without negative risk factors (combinations of tumour size, LVSI, and/or depth of stromal invasion). Quality of surgery, both parametrectomy and lymph node dissection is, however, of key importance in the management of large tumours. Intraoperative assessment of lymph node status (frozen section) is recommended as the first step. If lymph node involvement is detected intraoperatively, including macrometastases or micrometastases, further pelvic lymph node dissection and radical hysterectomy should be avoided and patients should be referred for definitive chemoradiotherapy and brachytherapy. Paraaortic lymph node dissection, at least up to inferior mesenteric artery, may be considered for staging purposes. If intraoperative lymph node assessment is negative or it is not done, systematic pelvic lymph node dissection should be performed. Type C2 radical hysterectomy is recommended.
C	Neoadjuvant chemotherapy followed by radical surgery is a controversial alternative. The benefit of tumour downsizing with regards to prognosis has not been proven.

Stage T1b2/T2a2 and involved lymph nodes on radiological staging

A	Definitive chemoradiotherapy and brachytherapy is recommended in patients with unequivocally involved pelvic lymph nodes on imaging (see Principles of radiotherapy).
C	An additional radiation boost to the involved lymph nodes should be applied (see Principles of radiotherapy).
C	Paraaortic lymph node dissection, at least up to inferior mesenteric artery, may be considered before treatment for staging purposes in patients with negative paraaortic lymph node on imaging.
✓	Debulking of suspicious pelvic lymph nodes may be considered.

Stages T2b, T3a/b, T4a

A	Definitive platinum based chemoradiotherapy and brachytherapy is recommended (see Principles of radiotherapy).
C	An additional radiation boost to the involved lymph nodes should be applied (see Principles of radiotherapy).
C	Paraaortic lymph node dissection, at least up to inferior mesenteric artery, may be considered before treatment in patients with negative paraaortic lymph nodes on imaging.
✓	Debulking of suspicious pelvic lymph nodes may be considered. Pelvic exenteration is an option in selected cases with stage T4N0M0 disease.

Palliative treatment

✓	Recommendations for palliative treatment should only be made after a thorough review of the case by a specialist multidisciplinary team and taking into account the performance status, co-morbidities, patient's symptoms and wishes of the patient. The palliative care specialist should be actively involved.
B	Palliative taxane/ platinum combination chemotherapy with /without bevacizumab is the preferred option.
✓	There is currently no standard second line chemotherapy and such patients should be considered for clinical trials.
✓	In symptomatic patients, palliative treatment should be tailored according to clinical situations.
D	In patients with disseminated disease at presentation, radiotherapy (usually a fractionated course) should be considered for effective palliation.
D	Palliative radiotherapy (single fraction / short course) to control bleeding, discharge and pain due to pelvic disease or bone metastases should be considered.
✓	For spinal cord compression due to bone metastases, neuro-surgical intervention or short course fractionated radiotherapy schedule should be considered.
✓	Surgical interventions including diversion stoma and / or stenting should be considered as appropriate e.g. in case of obstructive symptomatic disease.

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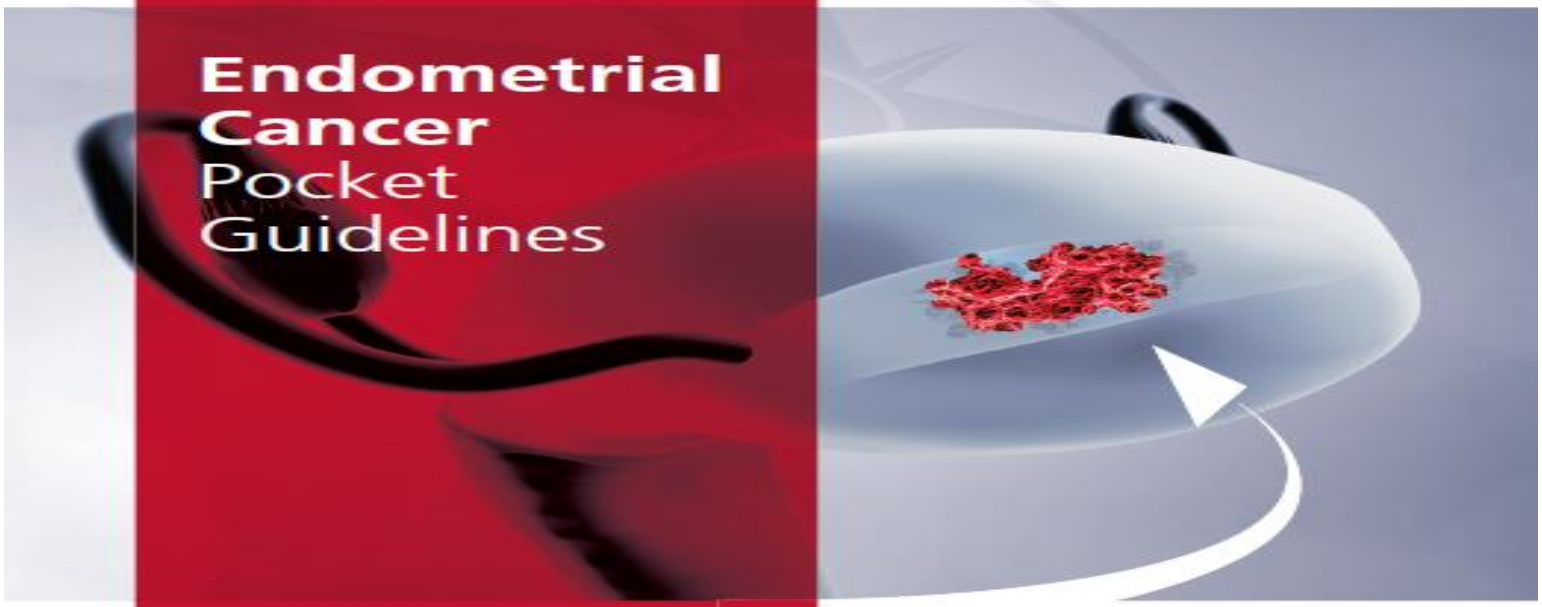
Endometrial Cancer Pocket Guidelines



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Endometrial cancer.
Prognostic factors

- Histologic type
- Grading (G)
- Staging (FIGO, TNM)
- Age (> 60 yo)
- Myometrium infiltration
- Lymph vessels infiltration (LVSI)
- Cervix infiltration
- Lymph node metastases
- Receptors expression (*ER, PR*)
- Molecular biology and gene expression of *p53, HER2, MSI, MMR, PTEN, KRAS*

Methods of endometrial cancer treatment

- Surgery only
- Radiotherapy alone: tele + brachy
- Surgery + radiotherapy
- Surgery + radiotherapy and adjuvant systemic treatment (chemotherapy, hormonotherapy, immunotherapy)

SURGERY

4. How does the medical condition influence surgical treatment?

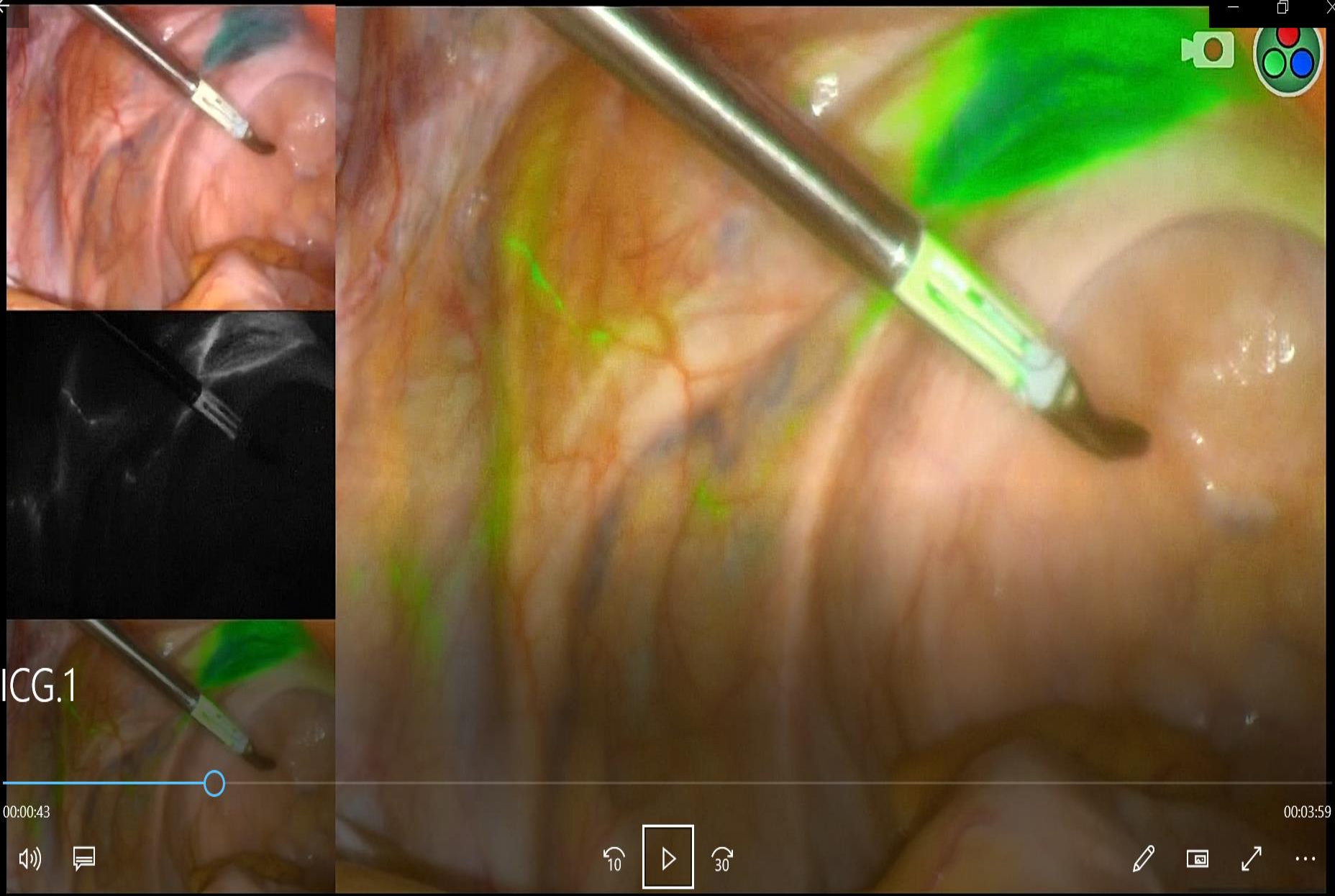
A	Mandatory work-up must include: Family history; general assessment and inventory of comorbidities; geriatric assessment, if appropriate; clinical examination, including pelvic examination; transvaginal or transrectal ultrasound; and complete pathology assessment (histotype and grade) of an endometrial biopsy or curettage specimen *(LoE V)*
A	Extent of surgery should be adapted to the medical condition of the patient *(LoE V)*
A	In clinical stage I, grade 1 and 2: At least one of the three following tools should be used to assess myometrial invasion if LND is considered: Expert ultrasound and/or MRI and/or intra-operative pathological examination *(LoE IV)*
C	Other imaging methods (thoracic, abdominal and pelvic CT scan, MRI, PET scan or ultrasound) should be considered to assess ovarian, nodal, peritoneal or metastatic disease *(LoE IV)*
B	There is no evidence for the clinical usefulness of serum tumour markers, including CA 125 *(LoE IV)*
A	Standard surgery is total hysterectomy with bilateral salpingo-oophorectomy without vaginal cuff *(LoE IV)*
B	Ovarian preservation can be considered in patients younger than 45 years old with grade 1 EEC with myometrial invasion <50% and no obvious ovarian or other extra-uterine disease *(LoE IV)*
B	In cases of ovarian preservation, salpingectomy is recommended *(LoE IV)*
B	Ovarian preservation is not recommended for patients with cancer family history involving ovarian cancer risk (e.g. BRCA mutation, LS etc.). Genetic counselling/testing should be offered *(LoE IV)*
A	Minimally invasive surgery is recommended in the surgical management of low- and intermediate risk endometrial cancer *(LoE I)*

6. How radical should the surgery be in different stages and pathological subtypes of endometrial cancer?

B	Radical hysterectomy is not recommended for the management of stage II endometrial cancer *(LoE IV)*
B	Modified (type B) or type A radical hysterectomy should be considered only if required for obtaining free margins *(LoE IV)*
B	Lymphadenectomy is recommended for clinical or intra-operative stage II endometrial cancer *(LoE IV)*
A	Complete macroscopic cytoreduction and comprehensive staging is recommended in advanced endometrial cancer *(LoE IV)*
B	Multimodality management should be considered for the treatment of advanced endometrial cancer when surgery may significantly impair vaginal function *(LoE IV)*
B	In non-EEC (apparent stage I), lymphadenectomy is recommended *(LoE IV)*
C	Staging omentectomy is not mandatory in clear-cell or undifferentiated endometrial carcinoma and carcinosarcoma *(LoE IV)*
C	Staging omentectomy should be considered in serous carcinoma *(LoE IV)*

5. What are the indications for and to what extent is lymphadenectomy indicated in the surgical management of endometrial cancer?

A	Peritoneal cytology is no longer considered mandatory for staging *(LoE IV)*
B	If a lymphadenectomy is performed, systematic removal of pelvic and para-aortic nodes up to the level of the renal veins should be considered *(LoE IV)*
D	SLND is still experimental, but large series suggest that it is feasible. SLND increases the detection of lymph nodes with small metastases and isolated tumour cells; however, the importance of these findings is unclear *(LoE IV)*
B	Lymphadenectomy is a staging procedure and allows tailoring of adjuvant therapy *(LoE III)*
A	Patients with low-risk endometrioid carcinoma (grade 1 or 2 and superficial myometrial invasion <50%) have a low risk of lymph node involvement, and two RCTs did not show a survival benefit. Therefore, lymphadenectomy is not recommended for these patients *(LoE II)*
C	For patients with intermediate risk (deep myometrial invasion >50% or grade 3 superficial myometrial invasion <50%), data have not shown a survival benefit. Lymphadenectomy can be considered for staging purposes in these patients *(LoE II)*
B	For patients with high risk (grade 3 with deep myometrial invasion >50%), lymphadenectomy should be recommended *(LoE IV)*
C	Lymphadenectomy to complete staging could be considered in previously incompletely operated high-risk patients to tailor adjuvant therapy *(LoE V)*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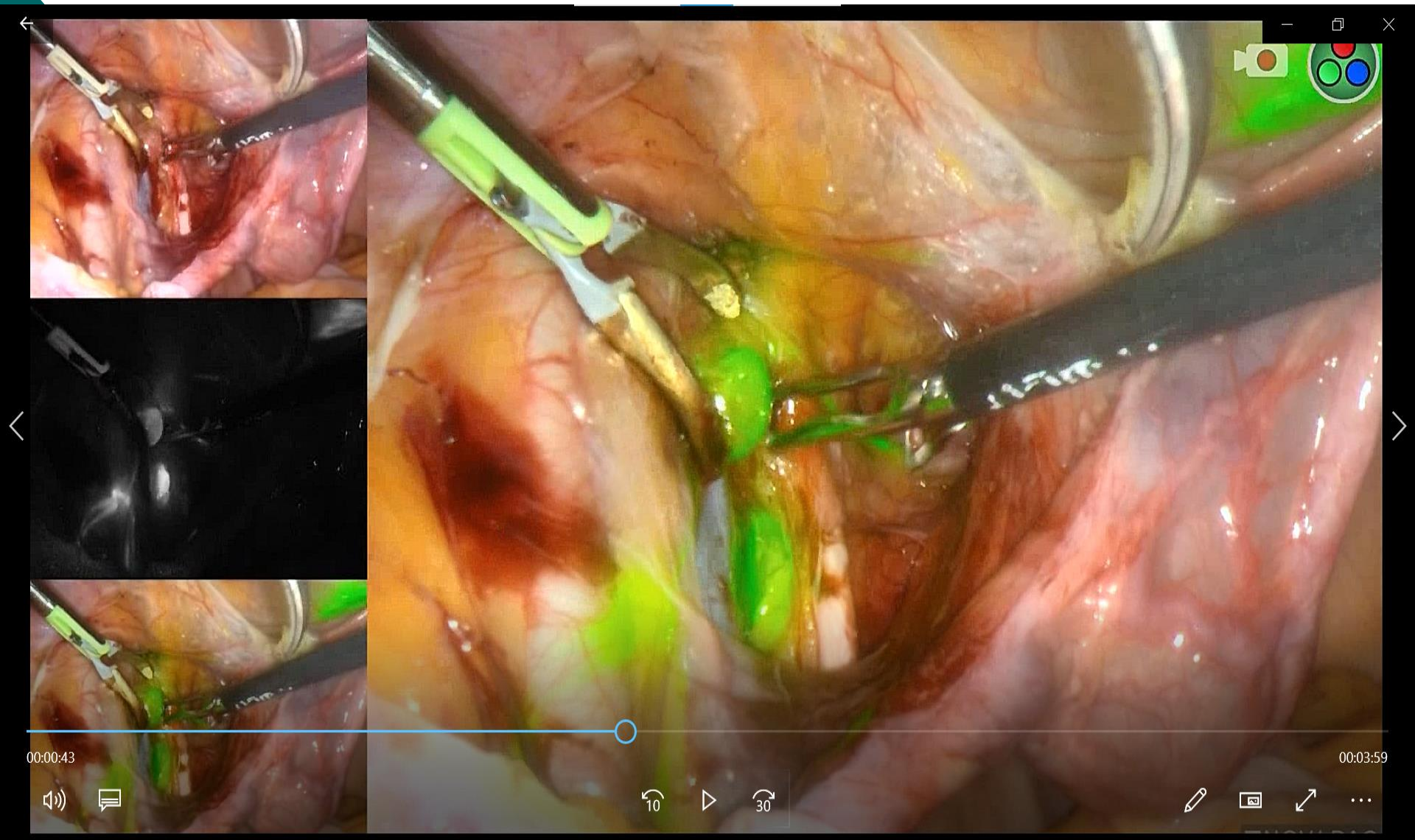
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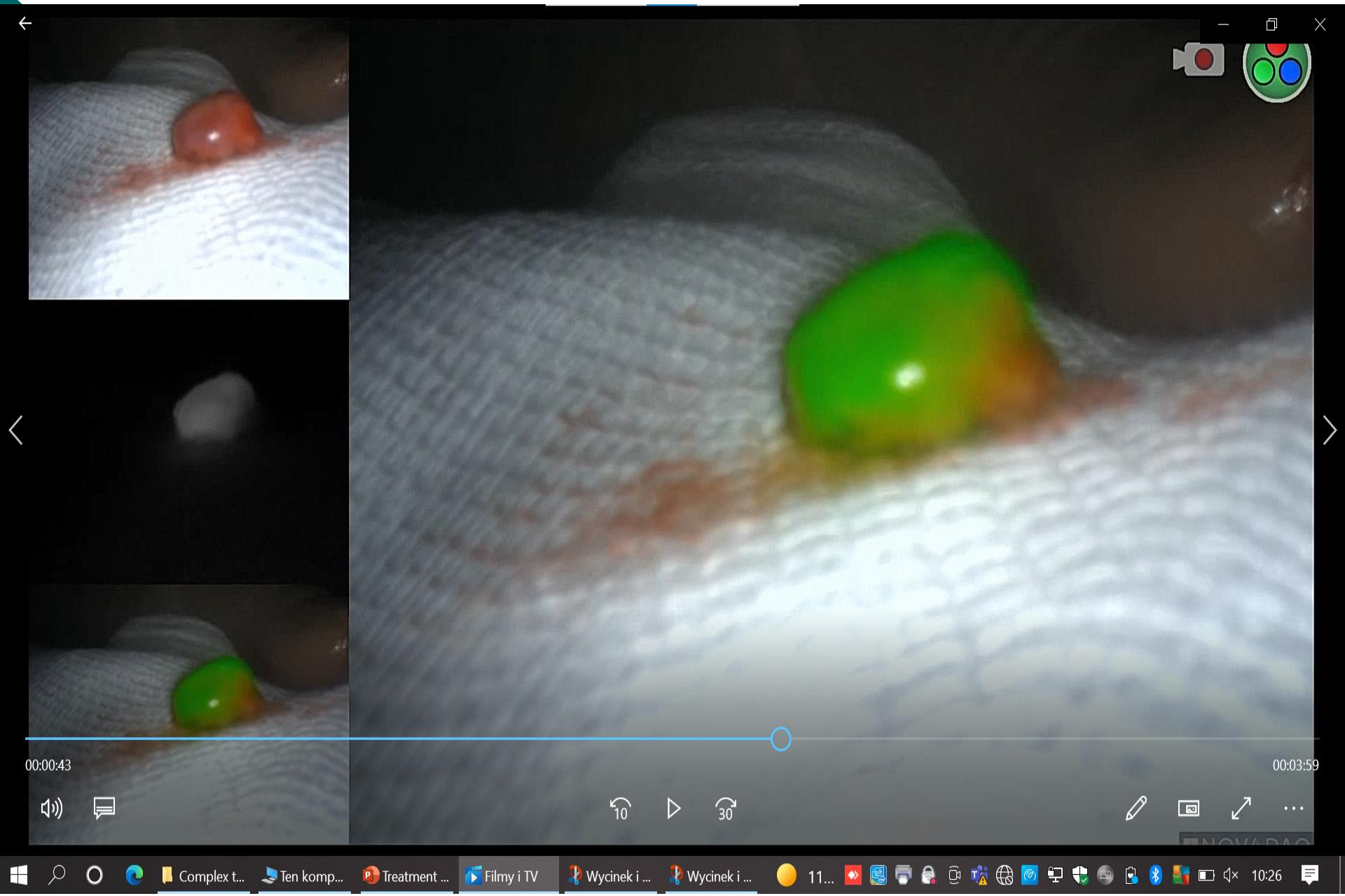
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ADJUVANT TREATMENT

7. What is the current best definition of risk groups for adjuvant therapy?

A definition of risk groups to identify patients at risk of recurrence who may benefit from adjuvant therapy has been devised by the consensus panel and is shown in table 2.

Table 2. New risk groups to guide adjuvant therapy use

Risk group	Description	LoE
Low	Stage I endometrioid, grade 1-2, <50% myometrial invasion, LVSI negative	I
Intermediate	Stage I endometrioid, grade 1-2, ≥50% myometrial invasion, LVSI negative	I
High-intermediate	Stage I endometrioid, grade 3, <50% myometrial invasion, regardless of LVSI status	I
	Stage I endometrioid, grade 1-2, LVSI unequivocally positive, regardless of depth of invasion	II
High	Stage I endometrioid, grade 3, ≥50% myometrial invasion, regardless of LVSI status	I
	Stage II	I
	Stage III endometrioid, no residual disease	I
	Non-endometrioid (serous or clear-cell or undifferentiated carcinoma, or carcinosarcoma)	I
Advanced	Stage III residual disease and stage IVA	I
Metastatic	Stage IVB	I

FIGO 2009 staging used; molecular factors were considered but not included; tumour size was considered but not included; nodal status may be considered for treatment recommendations

8. What are the best evidence-based adjuvant treatment strategies for patients with low- and intermediate-risk endometrial cancer?

A	In patients with low-risk endometrial cancer (stage I endometrioid, grade 1–2, <50% myometrial invasion, LVSI negative), no adjuvant treatment is recommended *(LoE I)*
B	In patients with intermediate-riskendometrial cancer (stage I endometrioid, grade 1–2, ≥50% myometrial invasion, LVSI negative), adjuvant brachytherapy is recommended to decrease vaginal recurrence *(LoE I)*
C	In patients with intermediate-risk endometrial cancer (stage I endometrioid, grade 1–2, ≥50% myometrial invasion, LVSI negative), no adjuvant treatment is an option, especially for patients aged <60 years *(LoE II)*
	In patients with high-intermediate risk endometrial cancer (stage I endometrioid, grade 3, <50% myometrial invasion, regardless of LVSI status; or stage I endometrioid, grade 1–2, LVSI unequivocally positive, regardless of depth of invasion):
	1. Surgical nodal staging performed, node negative:
B	a. Adjuvant brachytherapy is recommended to decrease vaginal recurrence *(LoE III)*
C	b. No adjuvant therapy is an option *(LoE III)*
	2. No surgical nodal staging:
B	a. Adjuvant EBRT recommended for LVSI unequivocally positive to decrease pelvic recurrence *(LoE III)*
B	b. Adjuvant brachytherapy alone is recommended for grade 3 and LVSI negative to decrease vaginal recurrence *(LoE III)*
C	3. Systemic therapy is of uncertain benefit; clinical studies are encouraged *(LoE III)*

9. What are the best evidence-based adjuvant treatment strategies for patients with high-risk endometrial cancer?

In patients with high-risk endometrial cancer (stage I endometrioid, grade 3, ≥50% myometrial invasion, regardless of LVSI status):

1. Surgical nodal staging performed, node negative:

B a. Adjuvant EBRT with limited fields should be considered to decrease locoregional recurrence *(LoE I)*

B b. Adjuvant brachytherapy may be considered as an alternative to decrease vaginal recurrence *(LoE III)*

C c. Adjuvant systemic therapy is under investigation *(LoE II)*

2. No surgical nodal staging:

B a. Adjuvant EBRT is generally recommended for pelvic control and relapse-free survival *(LoE III)*

C b. Sequential adjuvant chemotherapy may be considered to improve PFS and cancer-specific survival (CSS) *(LoE II)*

B c. There is more evidence to support giving chemotherapy and EBRT in combination rather than either treatment modality alone *(LoE II)*

In patients with high-risk, stage II endometrial cancer:

1. Simple hysterectomy, surgical nodal staging performed, node negative:

B a. Grade 1–2, LVSI negative: Recommend vaginal brachytherapy to improve local control *(LoE III)*

B b. Grade 3 or LVSI unequivocally positive:

i. Recommend limited field EBRT *(LoE III)*

C ii. Consider brachytherapy boost *(LoE IV)*

C iii. Chemotherapy is under investigation *(LoE III)*

2. Simple hysterectomy, no surgical nodal staging:

B a. EBRT is recommended *(LoE III)*

C b. Consider brachytherapy boost *(LoE IV)*

B c. Grade 3 or LVSI unequivocally positive: Sequential adjuvant chemotherapy should be considered *(LoE III)*

In patients with high-risk, stage III endometrial cancer and no residual disease:

1. EBRT is recommended to:

B a. Decrease pelvic recurrence *(LoE I)*

B b. Improve PFS *(LoE I)*

B c. Improve survival *(LoE IV)*

B 2. Chemotherapy is recommended to improve PFS and CSS *(LoE II)*

3. There is more evidence to give chemotherapy and EBRT in combination than either alone in stage III disease:

B a. IIIA: Chemotherapy AND EBRT to be considered *(LoE II)*

B b. IIIB: Chemotherapy AND EBRT to be considered *(LoE II)*

B c. IIIC1: Chemotherapy AND EBRT to be considered *(LoE II)*

B d. IIIC2: Chemotherapy AND extended field EBRT to be considered *(LoE II)*

In patients with high-risk, non-endometrioid cancers:

1. Serous and clear cell after comprehensive staging:

B a. Consider chemotherapy; clinical trials are encouraged *(LoE III)*

C b. Stage IA, LVSI negative: Consider vaginal brachytherapy only without chemotherapy *(LoE IV)*

C c. Stage ≥IB: EBRT may be considered in addition to chemotherapy, especially for node-positive disease *(LoE III)*

2. Carcinosarcoma and undifferentiated tumours:

B a. Chemotherapy is recommended *(LoE II)*

C b. Consider EBRT; clinical trials are encouraged *(LoE III)*

11. What are the optimal systemic therapies for advanced/recurrent disease?

C	Hormone therapy is indicated in advanced or recurrent EEC *(LoE II)*
B	Hormone therapy is more likely to be effective in grade 1 or 2 endometrioid tumours *(LoE IV)*
B	Hormone receptor status should be determined before hormone therapy is initiated, as it is more likely to be effective in patients with positive PgR and ER status *(LoE III)*
C	Biopsy of recurrent disease could be considered as there may be differences in hormone receptor status in the primary and metastatic tumour *(LoE III)*
A	Hormone therapy is the preferred front-line systemic therapy for patients with hormone receptorpositive tumours—grade 1 or 2 and without rapidly progressive disease *(LoE V)*
A	Progestogens (e.g. MPA 200 mg or MA 160 mg) are generally recommended *(LoE III)*
C	Other hormonal agents to consider after progestins include tamoxifen, fulvestrant and aromatase inhibitors *(LoE III)*
A	The standard of care is six cycles of 3- weekly carboplatin and paclitaxel. This is based on the preliminary communication of a randomised trial showing similar efficacy and less toxicity compared with cisplatin/ doxorubicin/paclitaxel *(LoE I)*
C	There is no standard of care for second-line chemotherapy *(LoE V)*

Ovarian cancer

- Surgical treatment is the primary choice in ovarian cancer patients
- Real assessment of disease spread often cannot be done earlier then during the operation

Difficult surgery: many procedures in one surgery

Resection of pericardic nodes

Celiax axis

Diaphragm Stripping/
Resection/
I[ver mobilization
Liver resection

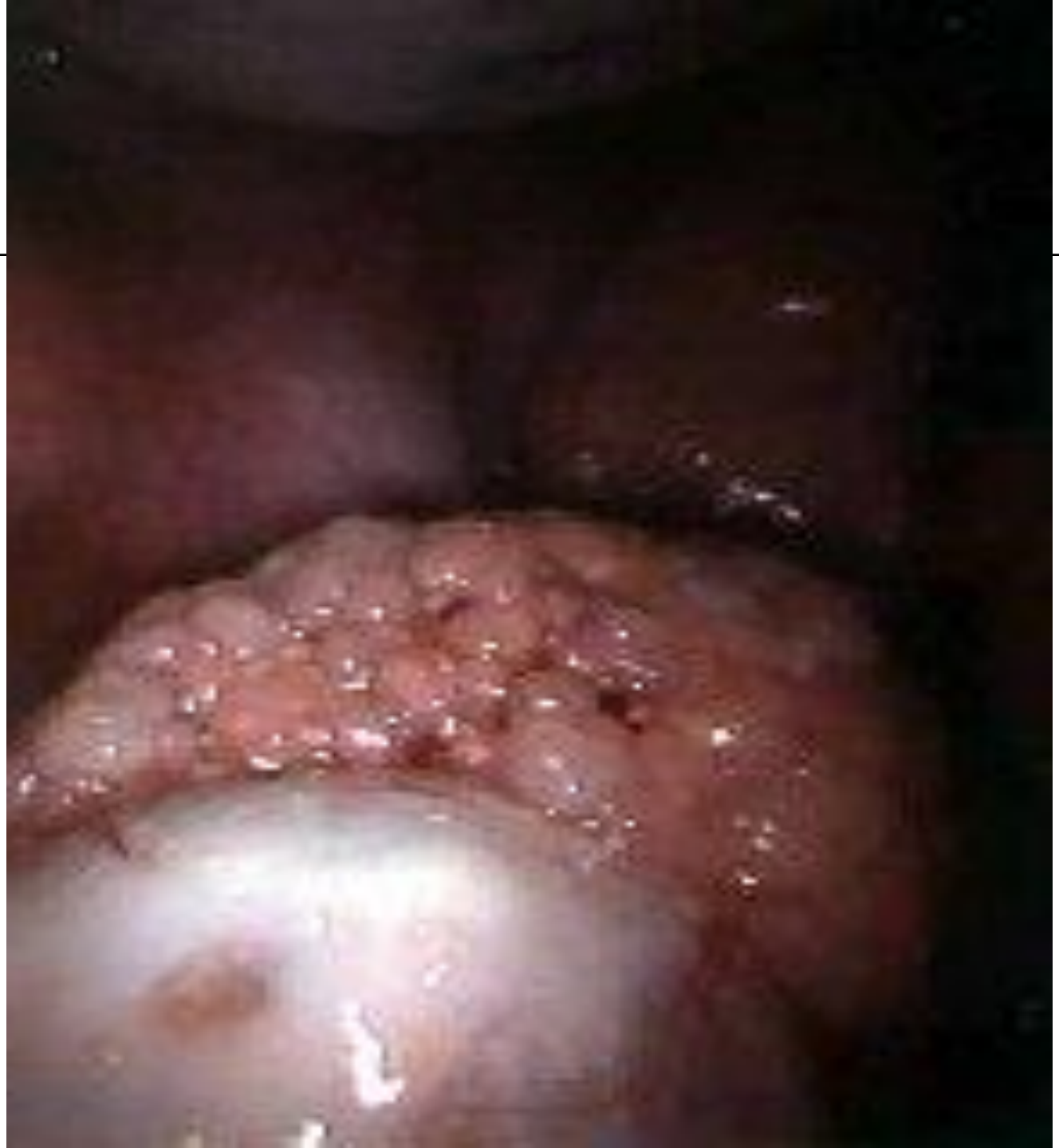
Splenectomy/tail of pancreas

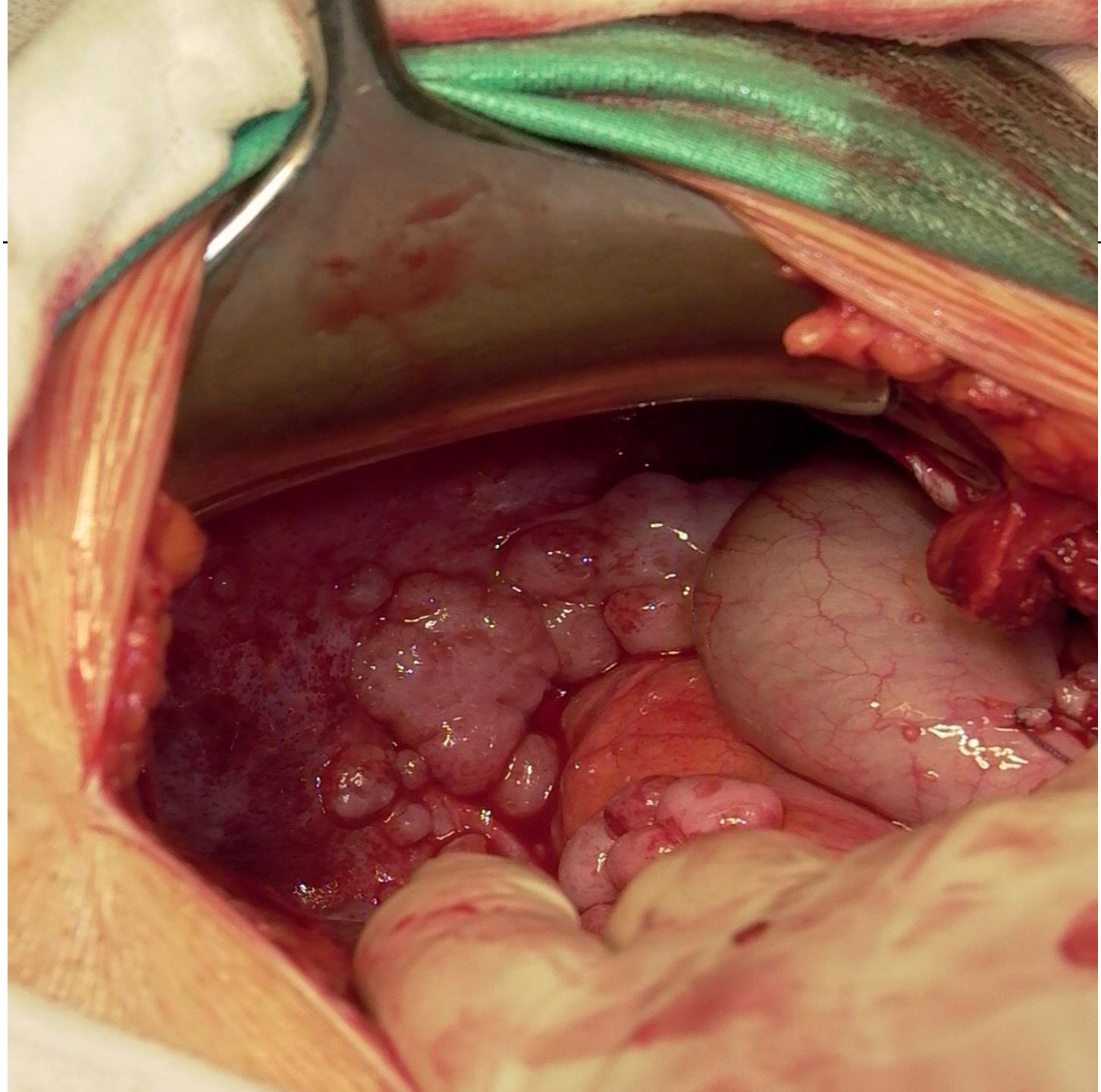
Retroperitoneal dissection limphoadenectomy

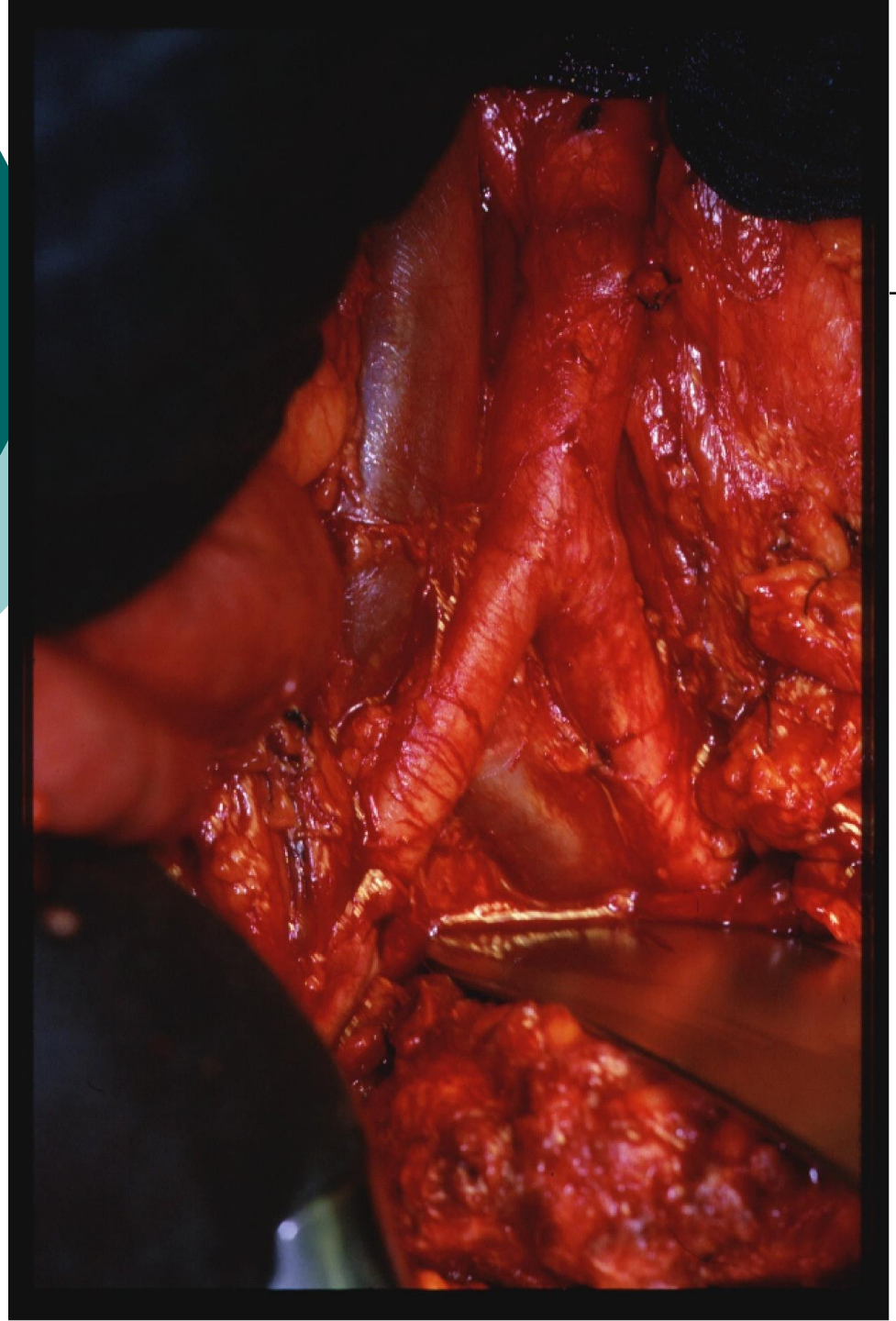
Right /Left- paracolic,
Parietal and pelvic
Peritonectomy/

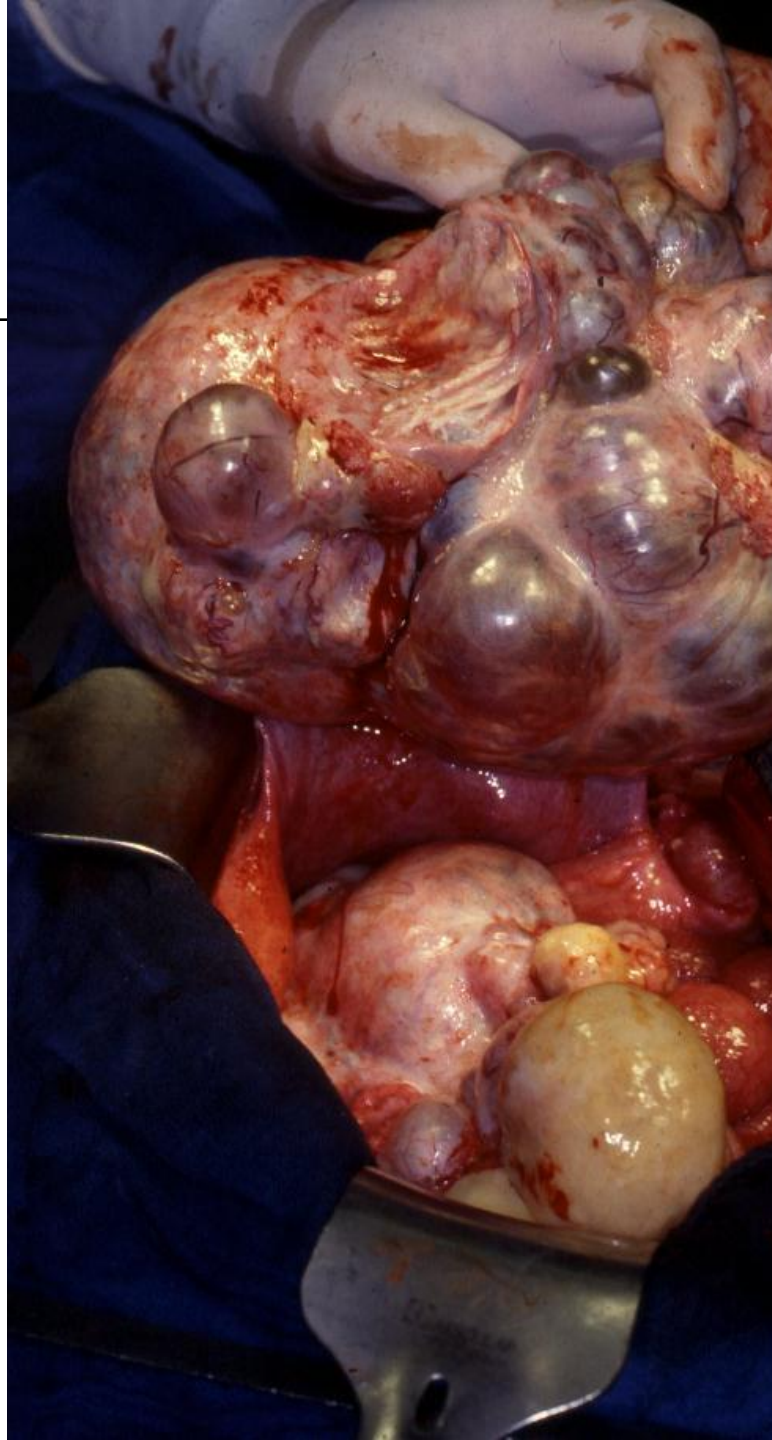
Small and large
Bowel resction

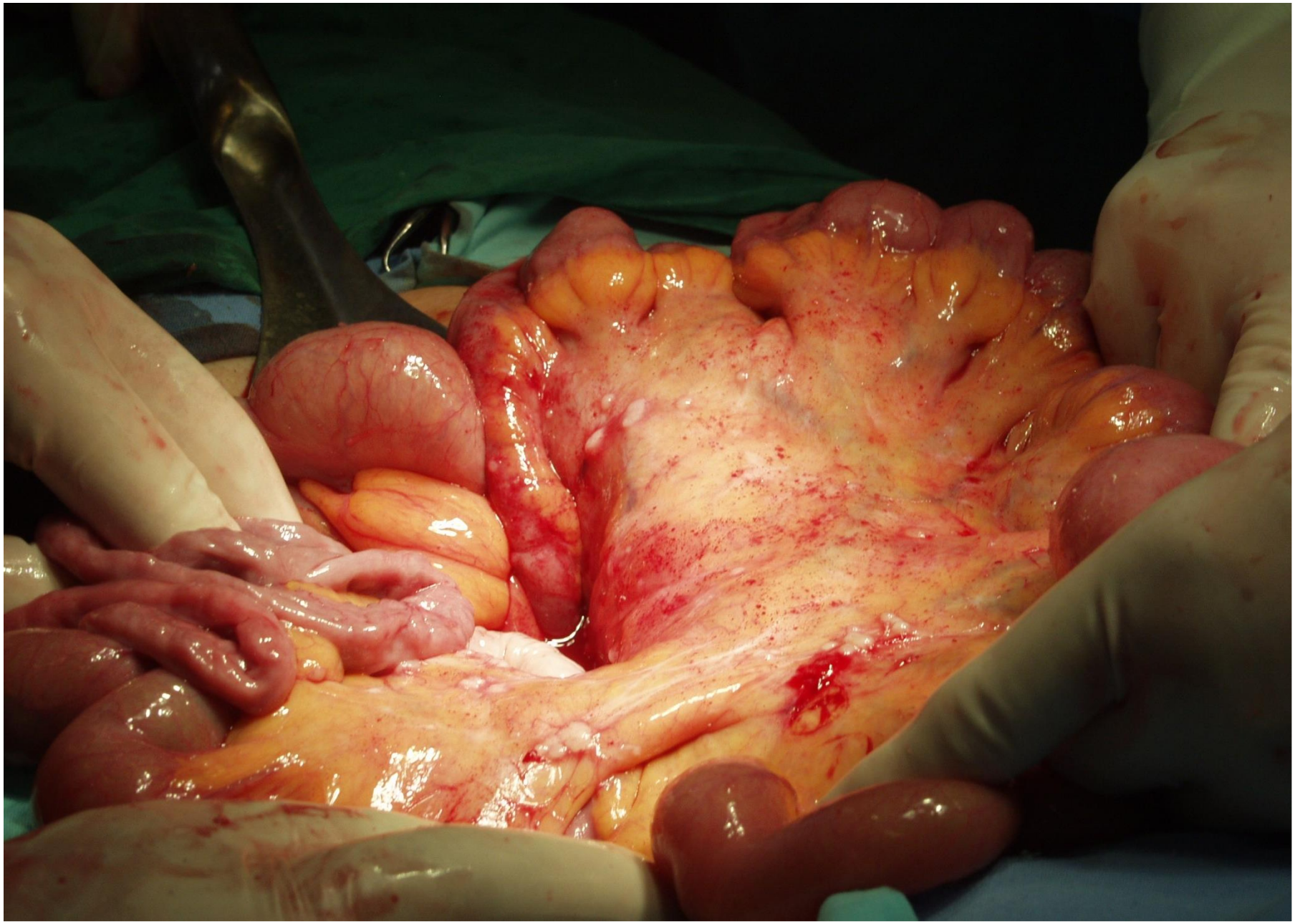
Rectosigmoid resection



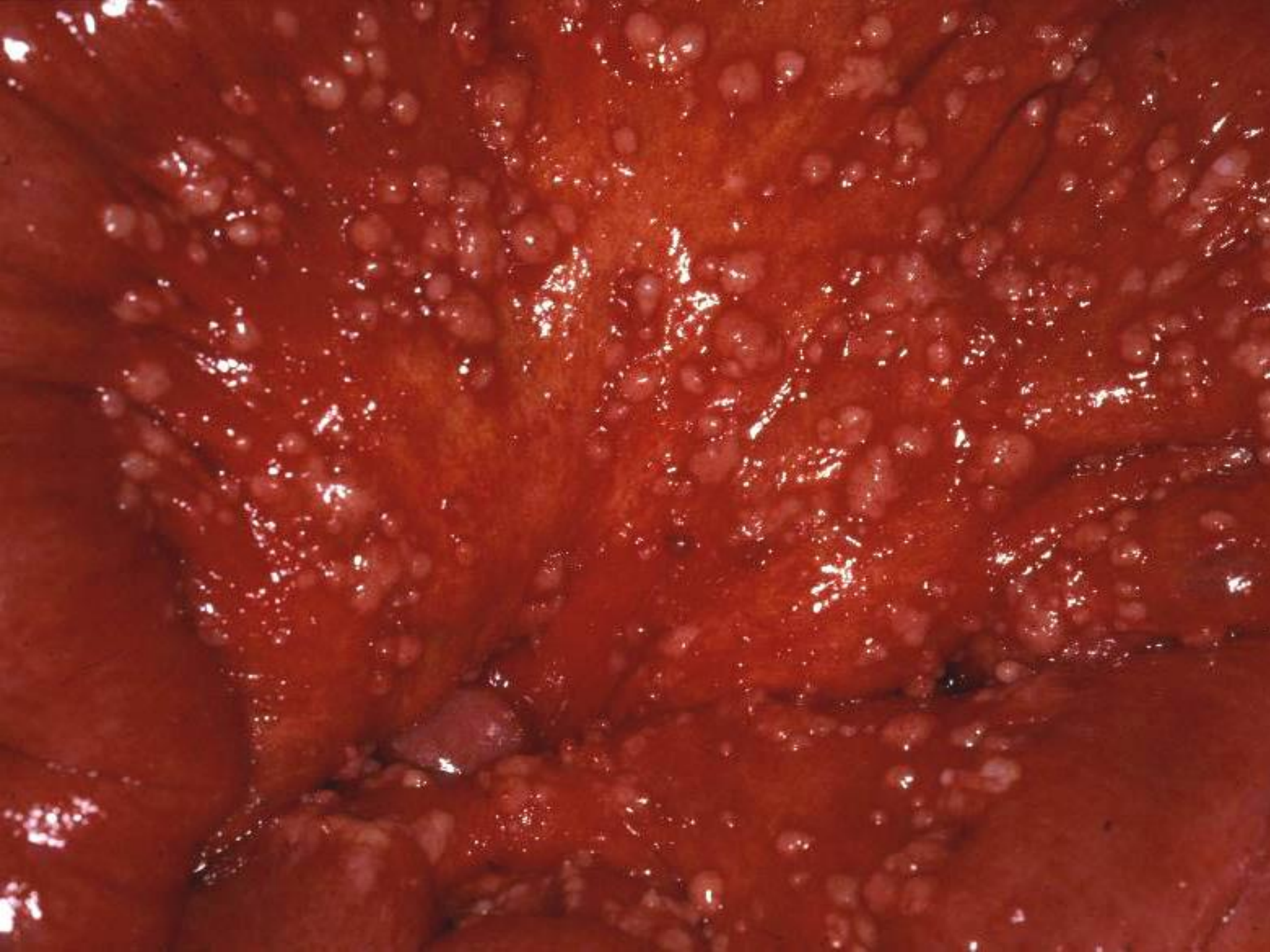








guzki otrzewnej krezki jelita cienkiego (materiał własny)



Ovarian cancer surgery target

- IA G1

the only situation when reproductive possibilities can be preserved (adnexectomy, staging procedure including lymph nodes sampling) and no adiuvant chemo is demanded

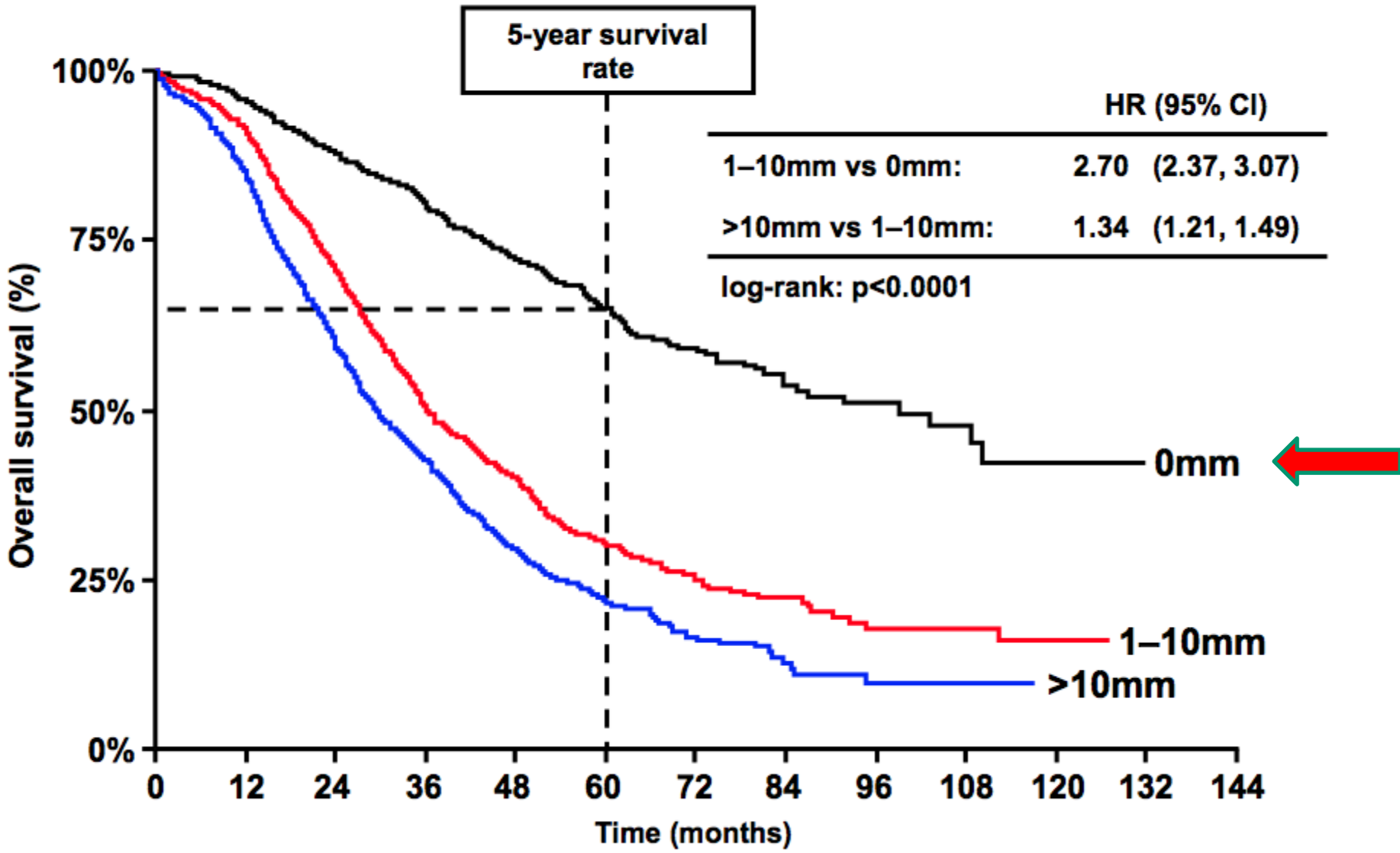
In all other cases (almost all of the patients) :

- Optimal, primary cytoreduction =

No residual (macroscopic) tumor masses after primary debulking surgery

The impact of residual tumour on outcome in advanced ovarian cancer

Data from an individual patient meta-analysis of three randomised phase III trials with 3,126 patients

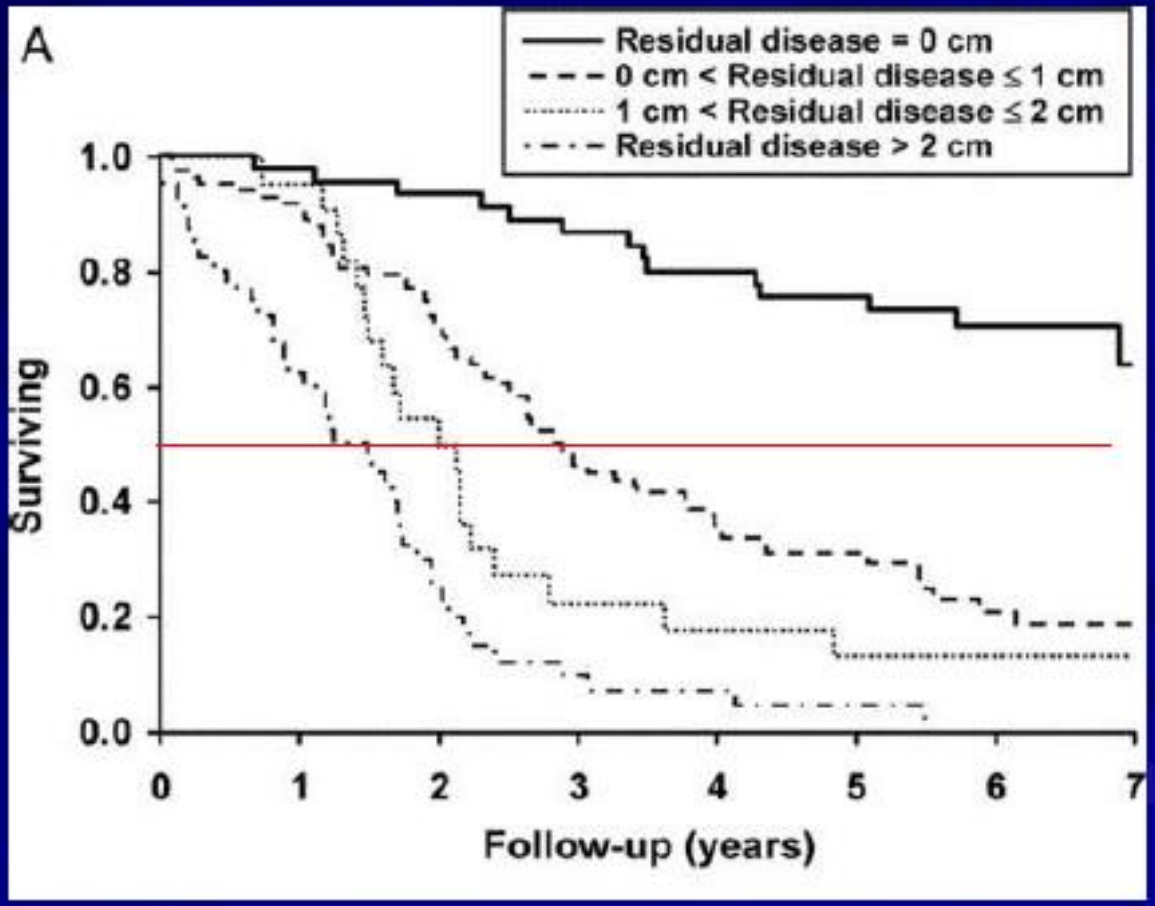


du Bois A, Reuss A, Pujade-Lauraine E, et al. Cancer 2009;15:1234–44

Surgical Effort impacts Survival in AOC

Stage IIIC (n=194) P<0.001

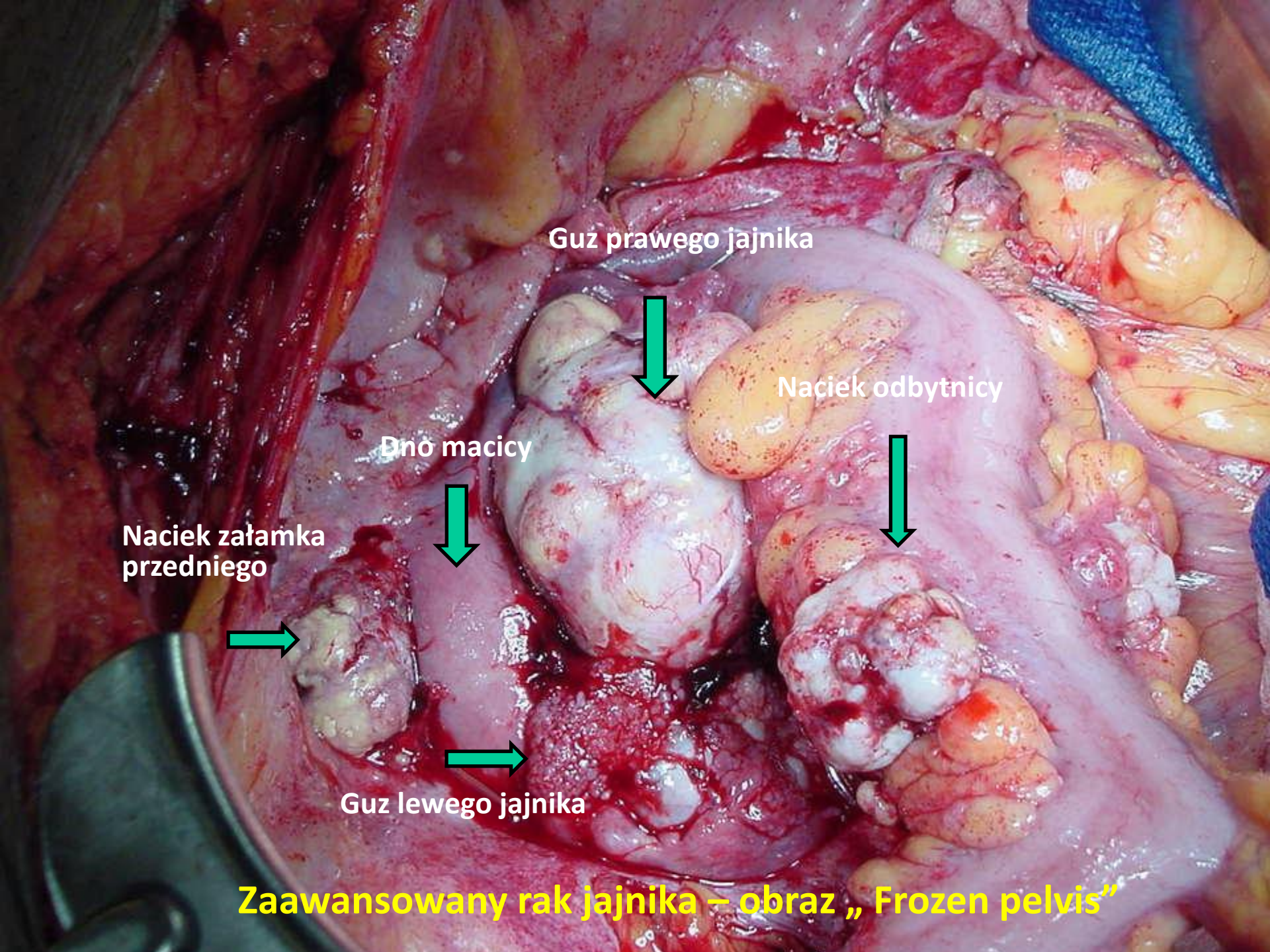
Mayo Experience*



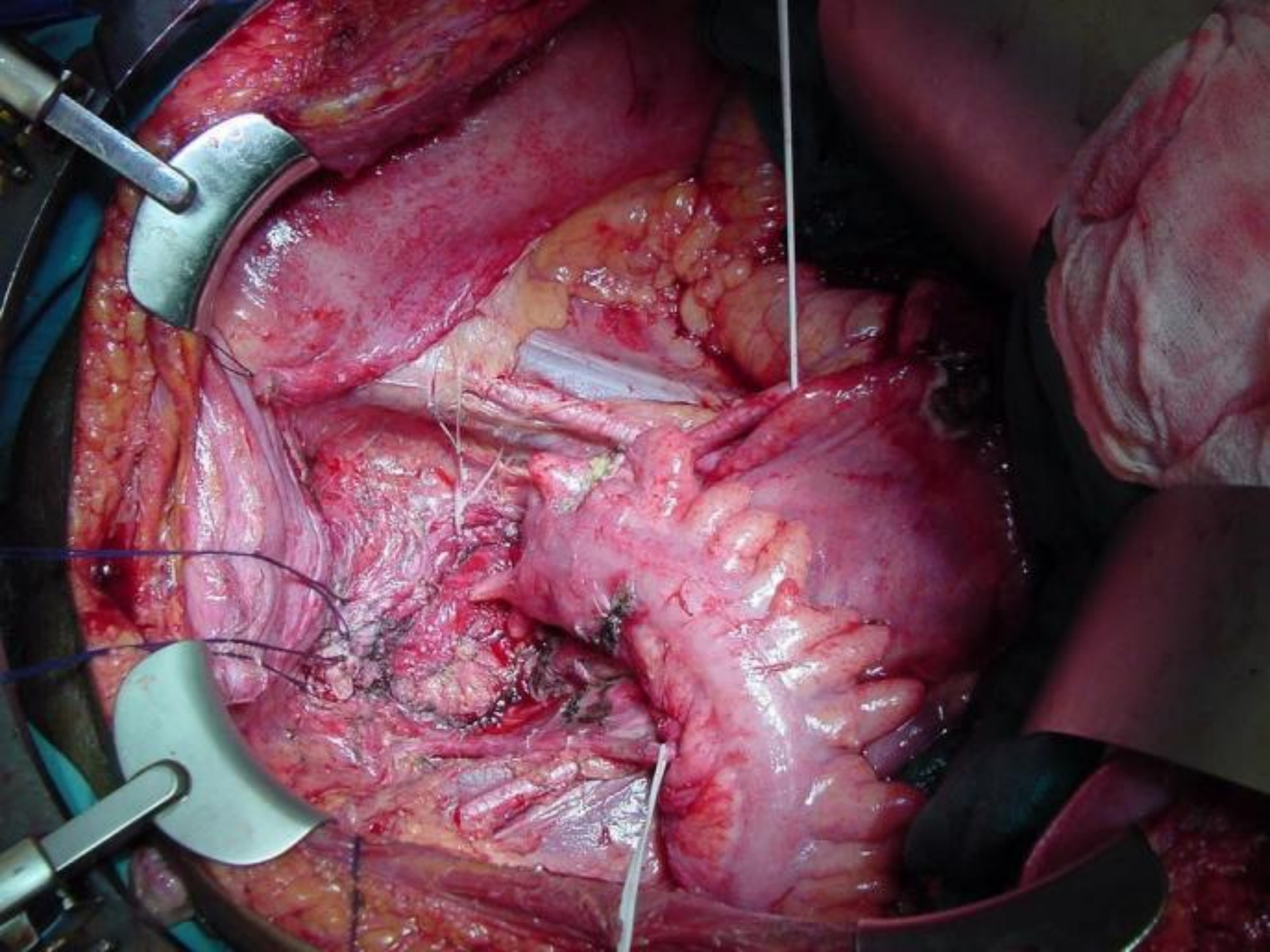
*Aletti G, et al. Obstet Gynecol 2006;107(1):77-85

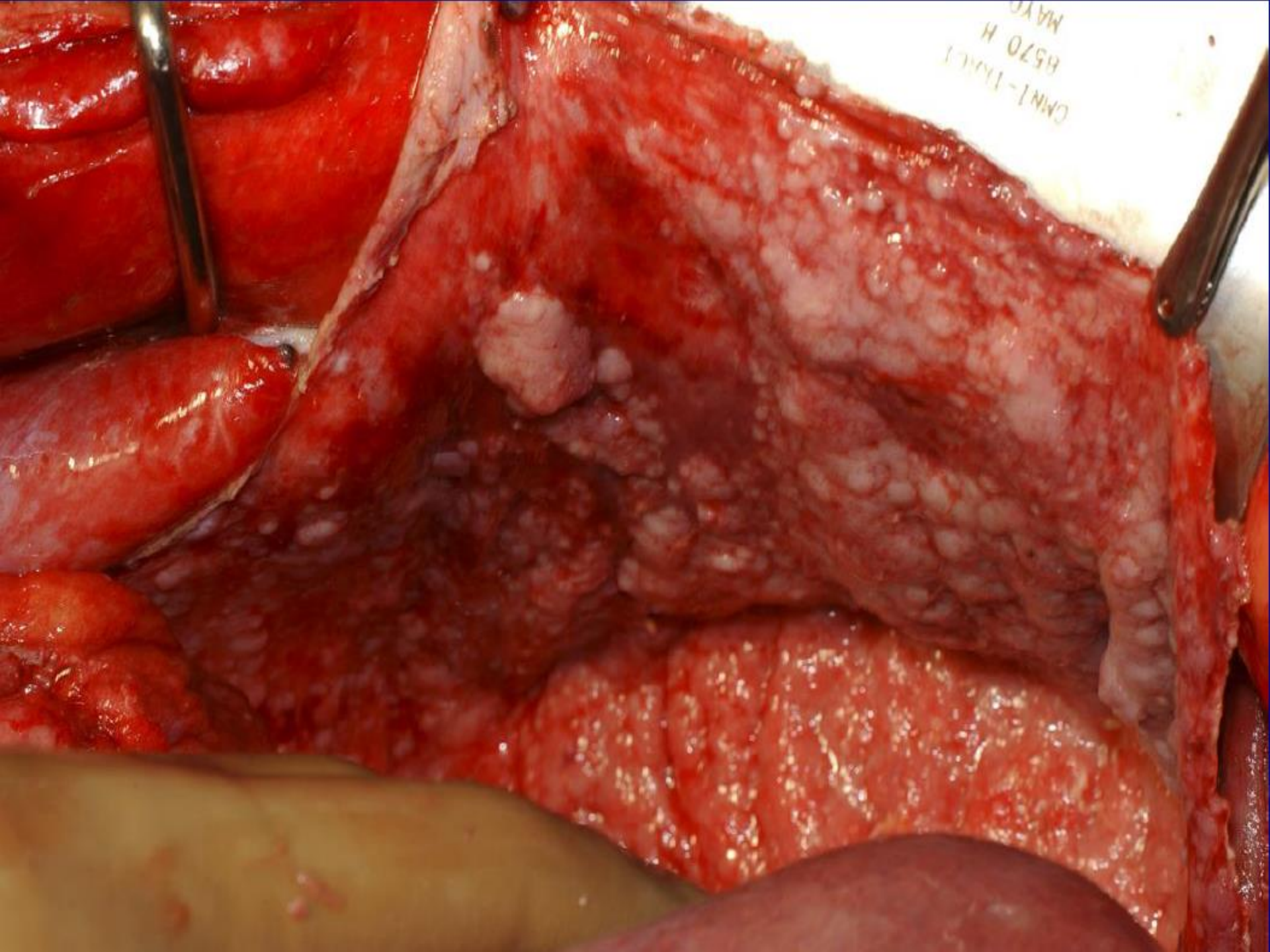
Ovarian Cancer
Cytoreduction

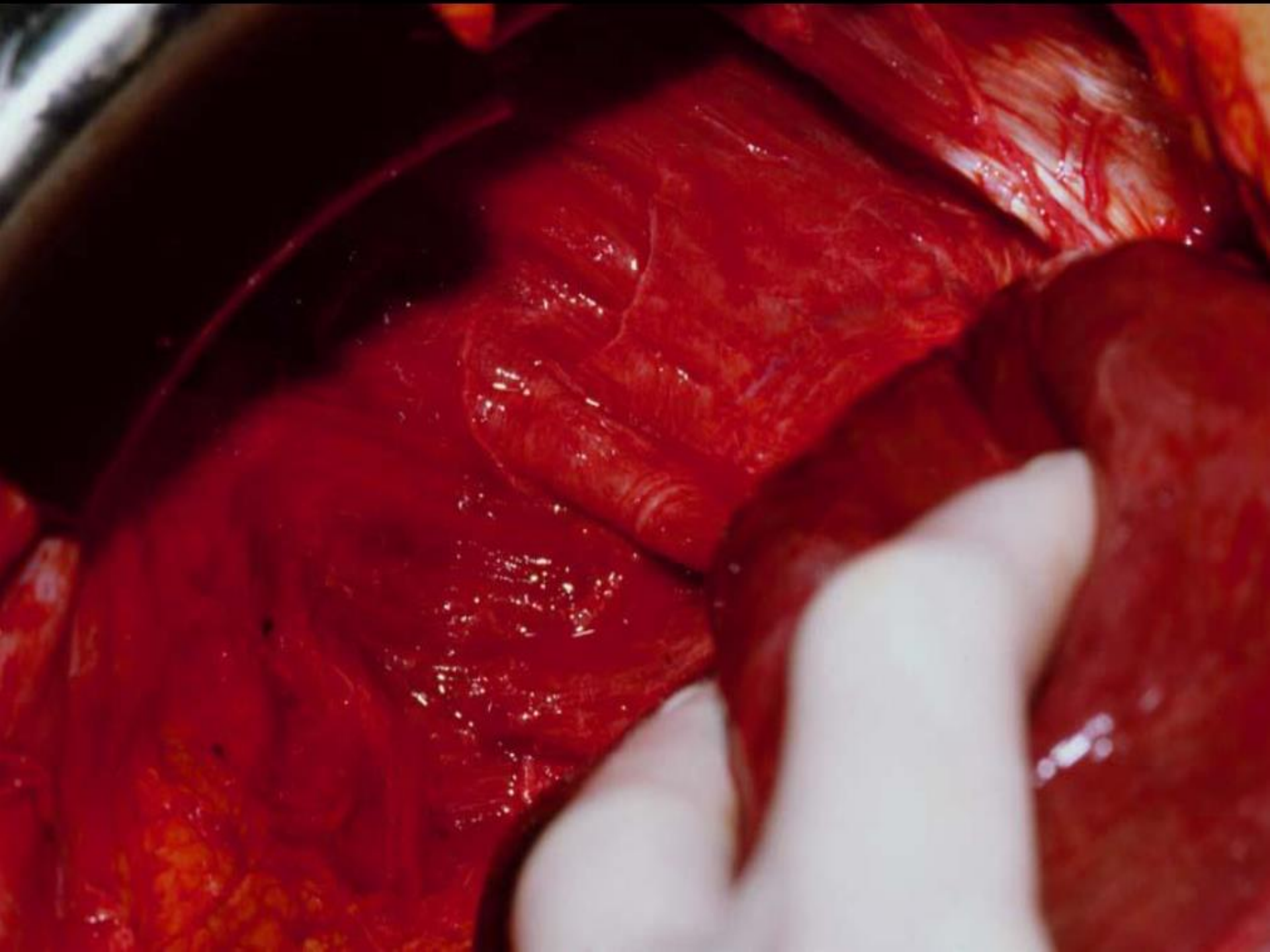
- **Theoretical Principles**
  - Reduces tumor volume
  - Removes poorly vascularized lesions
  - Decreases drug resistant clones
  - Alters cell kinetics (doubling time)
  - Enhances host immunocompetence
  - Augments chemoRx efficacy



Zaawansowany rak jajnika – obraz „ Frozen pelvis”







ESGO
European Society of Gynaecological Oncology

POCKET GUIDELINES
OVARIAN CANCER SURGERY

based on

ESGO Guidelines for
Ovarian Cancer Surgery

DIAGNOSIS AND PREOPERATIVE WORKUP

✓	Clinical examination, including abdominal, vaginal, and rectal examinations; assessment of the breast, groins, axilla, and supraclavicular areas; and auscultation of the lungs should be performed.
B	Routine pelvic (transvaginal and transabdominal) ultrasound should be used as a primary workup tool in any adnexal mass.
B	Specialised pelvic, abdominal, and thoracic complementary imaging should be performed in case of suspected carcinoma of the ovary, or indeterminate or suspicious masses at routine ultrasound examination.
✓	A tumour marker assessment should be performed for at least CA 125 levels. HE4 has also been proposed. Additional markers, including AFP, hCG, LDH, CEA, CA 19-9, inhibin B or AMH, estradiol, testosterone, would be useful in specific circumstances such as young age, or imaging suggesting a mucinous, or non-epithelial, or tumour of extra-adnexal origin.

SPECIALISED MULTIDISCIPLINARY DECISION-MAKING

C	Women with non-emergency clinical presentation and suspected adnexal/peritoneal malignancy should be referred to a specialist in gynaecologic oncology[2].
✓	Surgery in low-volume and low-quality centres is discouraged. The existence of an intermediate care facility and access to an intensive care unit management are required. Participation in clinical trials is a quality indicator.
C	Treatment should be preoperatively planned at a multidisciplinary team meeting, after a workup aimed at ruling out (1) unresectable metastases and (2) secondary ovarian and peritoneal metastasis from other primary malignancies when family history, symptoms, radiological features, or Ca125/CEA ratio is suggestive. Informed consent of the patient must be obtained.
✓	All patients should be reviewed postoperatively at a gynaecological oncology multidisciplinary meeting.

[2] Certified gynaecological oncologist or, in countries where certification is not organized, by a trained surgeon dedicated to the management of gynaecologic cancer (accounting for over 50% of his or her practice) or having completed an ESGO-accredited fellowship.

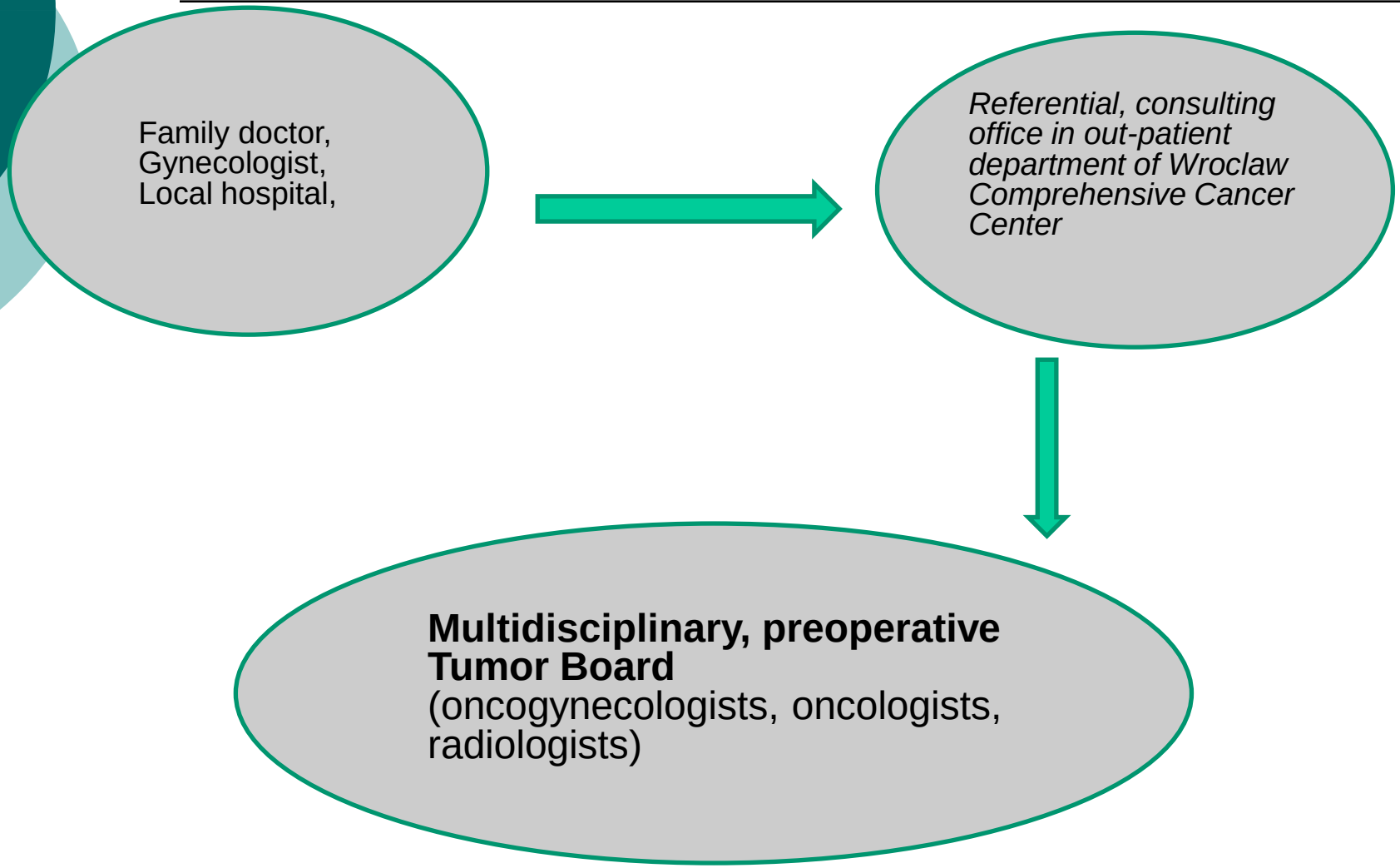
SURGICAL MANAGEMENT FOR STAGE I-II OVARIAN CANCER

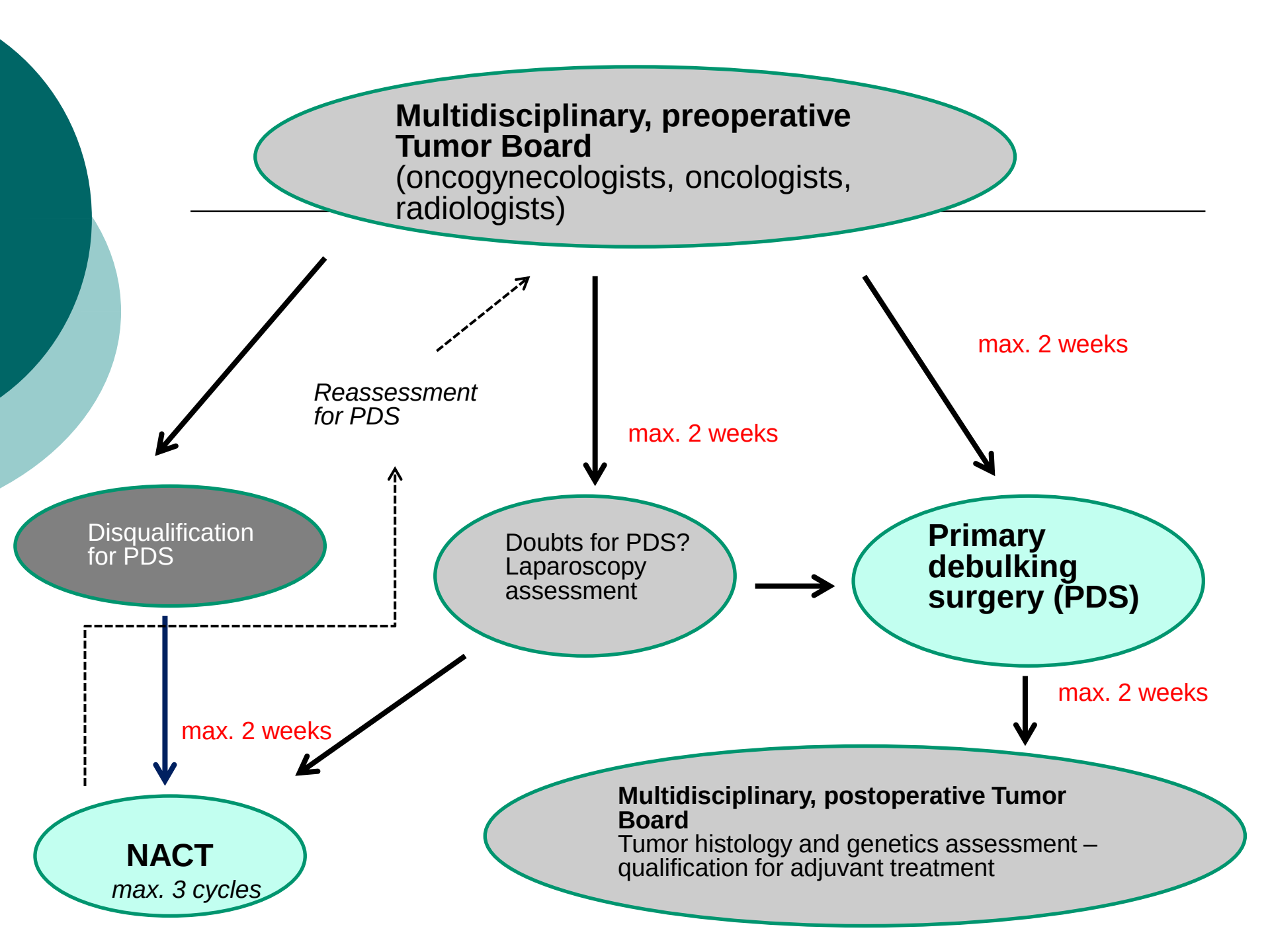
B	Midline laparotomy is recommended to surgically manage early ovarian cancers. Apparent stage I could potentially be managed laparoscopically by a gynaecological oncologist with the appropriate expertise able to perform an adequate surgical staging laparoscopically. Rupture of an intact primary tumour with spillage of tumour cells at the time of dissection and extraction of the specimen should be avoided.
B	Intraoperative rupture of a yet-unruptured adnexal mass should be avoided.
B	The availability of frozen section may allow the necessary surgical assessment to be completed at the time of initial surgery. It is understood that frozen section may not be conclusive and that definitive pathology is the gold standard of diagnosis.
✓	In the absence of frozen section or in the case of an inconclusive frozen section, a two-step procedure should be preferred.
✓	Total hysterectomy and bilateral salpingo-oophorectomy are standard.
C	Fertility-preserving surgery (unilateral salpingo-oophorectomy) should be offered to selected premenopausal patients desiring fertility[3].
B	Laparoscopic restaging is an acceptable approach if performed by a gynaecologic oncologist with adequate expertise to perform a comprehensive assessment.
✓	Visual assessment of the entire peritoneal cavity is recommended.
C	Peritoneal washings or cytology, taken prior to manipulation of the tumour, are recommended.
C	When no suspicious implants are found in the pelvis, paracolic areas, and subdiaphragmatic areas, blind peritoneal biopsies are recommended.
C	At least infracolic-omentectomy is recommended.
B	Bilateral pelvic and para-aortic lymph node dissection up to the level of the left renal vein (with the exception of stage I expansile type mucinous adenocarcinomas) are recommended.

SURGICAL MANAGEMENT FOR STAGE III-IV OVARIAN CANCER

✓	Midline laparotomy is required to manage stage III-IV ovarian cancers.
A	Complete resection of all visible disease is the goal of surgical management. Voluntary use of incomplete surgery (upfront or interval) is discouraged.
✓	Criteria against abdominal debulking are: • Diffuse deep infiltration of the root of small bowel mesentery; • Diffuse carcinomatosis of the small bowel involving such large parts that resection would lead to short bowel syndrome (remaining bowel < 1.5 m), • Diffuse involvement/deep infiltration of Stomach/duodenum (limited excision is possible), and Head or middle part of pancreas (tail of the pancreas can be resected); • Involvement of truncus coeliacus, hepatic arteries, left gastric artery (coeliac nodes can be resected).
✓	Metastatic (stage IVB) disease may be resectable. Central or multisegmental parenchymal liver metastases, multiple parenchymal lung metastases (preferably histologically proven), nonresectable lymph node metastases, and multiple brain metastases are not resectable.
A	Primary surgery is recommended in patients who can be debulked upfront to no residual tumour with a reasonable complication rate.
✓	Risk-benefit ratio is in favour of primary surgery when: • There is no unresectable tumour extent • Complete debulking to no residual tumour seems feasible with reasonable morbidity, taking into account the patient's status. Decisions are individualised and based on multiple parameters[4]. • Patient accepts potential supportive measures as blood transfusions or stoma.
A	Interval debulking surgery should be proposed to patients fit for surgery with response or stable disease compatible with complete resection.
✓	If a patient did not have the opportunity of surgery after 3 cycles, then a delayed debulking after more than 3 cycles of neoadjuvant chemotherapy may be considered on an individual basis.

The dedicated route for a patient with suspition for ovarian cancer




Multidisciplinary, preoperative Tumor Board
(oncogynecologists, oncologists, radiologists)
max. 2 weeks
Reassessment for PDS
max. 2 weeks
Disqualification for PDS
Doubts for PDS? Laparoscopy assessment
Primary debulking surgery (PDS)
max. 2 weeks
max. 2 weeks
NACT
max. 3 cycles
Multidisciplinary, postoperative Tumor Board
Tumor histology and genetics assessment – qualification for adjuvant treatment


Oddział Ginekologii Onkologicznej
DCO

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Ass. Prof. Dimitrios Haidopoulos
Chair, ESGO Fellowships and accreditations committee

Prague,
May 12, 2017

The European Voice of Gynaecological Oncology