Surgery for early (stage I-II) ovarian cancer

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Diagnosis

Surgery for early (stage I-II) invasive epithelial ovarian cancer. ESGO recommendations

- Clinical examination including abdominal, vaginal and rectal examinations, assessment of the groin, axilla, and supraclavicular areas, lung and breast should be performed
- Routine pelvic (transvaginal) ultrasound and if needed suprapubic must be used as a primary workup tool in any adnexal mass
- Specialized pelvic and abdominal complementary imaging (ultrasound and/or MRI and/or CT scan and/or PET-CT) should be performed in case of undetermined or suspicious masses at routine ultrasound examination

Preoperative workup

Surgery for early (stage I-II) invasive epithelial ovarian cancer. ESGO recommendations

- Recommendation : a thoraco-abdomino-pelvic imaging must be performed in patients with non emergency clinical presentation and suspected carcinoma of the ovary ; a blood sampling must be taken for blood markers assessment, at least Ca-125 levels

- Possible additional markers, including AFP, hCG, LDH, CEA, Ca 19-9, inhibin B or AMH, estradiol, testosterone, must be taken in specific circumstances : young patient, or imaging suggesting a mucinous, or non epithelial, or extra-adnexal tumor

Specialized multidisciplinary decision making

Surgery for early (stage I-II) invasive epithelial ovarian cancer. ESGO recommendations

Patients with non emergency clinical presentation and suspected malignancy of the adnexa should be referred to a specialist in gynecologic oncology (certified gynaecological oncologist or specialist surgeon as defined for advanced ovarian cancer surgery) and discussed preoperatively in a multidisciplinary meeting

All patients must be reviewed postoperatively at a gynaecological oncology multidisciplinary meeting

Early ovarian cancer

- 30% of the patients present in FIGO stage I or II.
- The most important prognostic factor is stage (5YOS:60-90%). Further prognostic factors: grading, histological subtype and ***quality of management*** (iatrogenic rupture, incomplete staging)

Surgical management (1)

Surgery for early (stage I-II) invasive epithelial ovarian cancer. ESGO recommendations

- Midline laparotomy is required to manage early ovarian cancers , with the exception of apparent stage I which can be managed laparoscopically by a gynaecological oncologist with specific expertise in laparoscopy, without rupture and without contamination of the abdominal cavity and wall

- Intraoperative rupture of a yet unruptured adnexal mass must be avoided

Staging-Operation im Stadium FIGO I-IIA*

(AGO)

Definition:

***early ovarian cancer:**

FIGO I A G> 1 or unknown

FIGO I B/C - IIA all G

Standard-Staging: **Laparotomy**

(9 Items) **TAH + BSO** (unless in fertility sparing surgery)

Omentectomy

Peritoneal-biopsies(all 4 quadrants)

cytology

pelvic and paraaortic LND

(appendectomy)

+ tumorfree!!

GOG Staging Procedure for Ovarian Cancer

1. Vertical incision
2. Send peritoneal fluid. If none, send peritoneal washings
3. Inspect and palpate all peritoneal surfaces
4. Omentectomy
5. TAH-BSO
6. Resect gross disease within the abdominal cavity
7. In absence of disease beyond the pelvis, peritoneal biopsies
8. Pelvic and para-aortic nodes for:

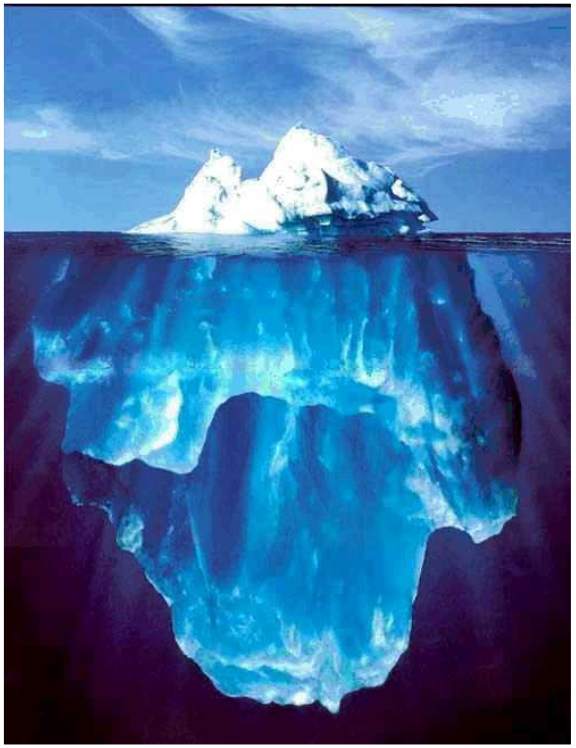
-Stage IIIB disease (microscopic disease in omentum 2 cm)

-Not required for stage 3C or 4 disease, unless only disease is a palpable node

Why staging in apparently early ovarian cancer ?

20-30% incidence of occult metastases :

- positive cytology 20 %
- omentum 6 %
- diaphragm 15 %
- peritoneal biopsies 13 %
- para-aortal LN 14 %
- pelvic LN 8 %



JB Trimbos Int J Gynecol Cancer 2000

Normal appearing peritoneum?

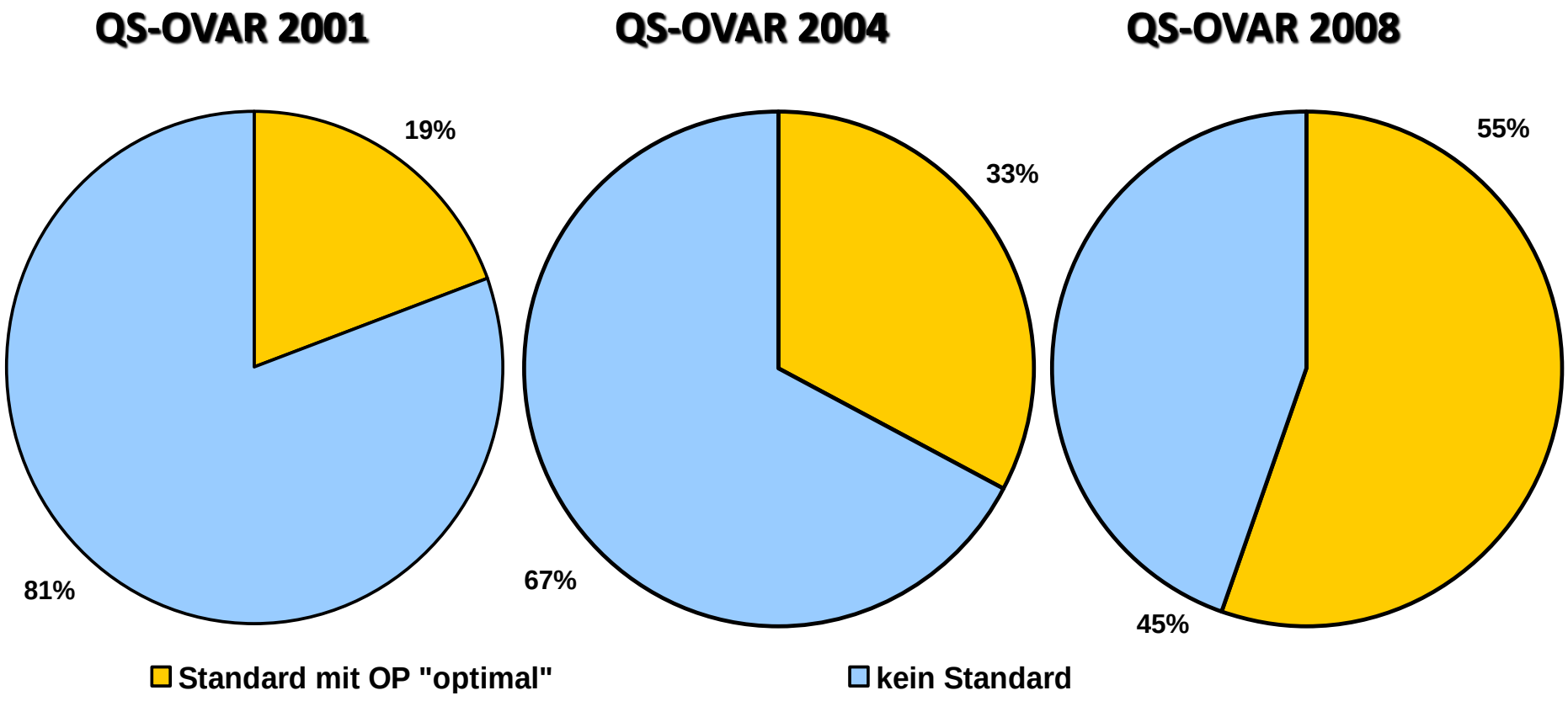
- 122 patients of mainly IA (33%) and IC (41%) stage → 19 patients had positive peritoneal biopsies (16%) at surgical staging.
- Even though only 6 (5%) of those were from normal-appearing tissue, comprehensive staging resulted in upstaging of 4% of all patients by the random peritoneal biopsies alone.
- 5 (4%) of the patients had even microscopic metastases to the omentum, 4 (3%) of whom were upstaged by this finding alone

Shroff R, et al.. Int J Gynecol Cancer. 2011;21(7):1208-12.

Treatment quality in early ovarian cancer

FIGO I-IIA

(„max. 1 nissing item fehlt“ and adequate chemotherapy)



p < 0,001

2001-2008: 53/ 488 (10.9pts died, of them 47/ 53 (88.7%) without any standart treatment

Surgical management (2)

Surgery for early (stage I-II) invasive epithelial ovarian cancer. ESGO recommendations

- Total hysterectomy and bilateral salpingo-oophorectomy is standard

– Fertility preserving surgery (unilateral salpingo-oophorectomy) should be offered to selected premenopausal patients with apparent stage IA*

- Discussion on fertility must be mentioned in the patient record
- Final decision based on final stage and grade : fertility preservation is accepted in case of stage IA or IC1, low-grade serous or endometrioid carcinoma, or expansile type mucinous tumors
- Other stage I substages or pathologic subtypes, subject to individualized decision
- Uterine preservation with bilateral salpingo-oophorectomy, can be considered in selected young patients with apparent stage IB low risk invasive carcinoma and normal endometrial biopsy finding. However, there is very few data to support this policy.

Role of frozen section

Surgery for early (stage I-II) invasive epithelial ovarian cancer. ESGO recommendations

- The availability of frozen section may allow the necessary surgical staging to be done 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 case of inconclusive frozen section, a two-step procedure should be prefered.

Surgical staging

Surgery for early (stage I-II) invasive epithelial ovarian cancer. ESGO recommendations

- Staging of patients with early ovarian cancer defines the indication for adjuvant treatment and also provides valuable prognostic information
- Up to 30% of patients are upstaged as a result of comprehensive staging
- Proper staging is an independent prognostic factor
- When early carcinoma is incidentally found at surgery for a suspected ‘benign’ condition, a second surgical procedure will be required. When the patient has not been comprehensively staged, a second surgical procedure must be considered routinely
- Laparoscopic surgery is an acceptable approach if performed by a gynecologic oncologist with adequate expertise to perform a comprehensive staging. Further studies are needed to definitively confirm the safety of the approach.

Surgical staging

Surgery for early (stage I-II) invasive epithelial ovarian cancer. ESGO recommendations

- Visual assessment of the entire peritoneal cavity
- Peritoneal washings or cytology, taken prior to manipulation of the tumour
- Blind peritoneal biopsies from the pelvis, paracolic spaces, and the subdiaphragmatic spaces bilaterally
- At least infracolic omentectomy
- 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)

- Restaging for the only purpose of performing appendectomy is not mandatory even in case of mucinous histology if the appendix has been examined and found normal

Quality indicators for **early** (stage I-II) ovarian cancer

A system of 7 quality indicators has been defined in relation to the recommendations elaborated by the International Development Group.
A new system of assessment of the quality of staging has been designed

Preoperative workup

Surgery for early epithelial ovarian cancer. Quality assurance criteria

- Recommendation : a thoraco-abdomino-pelvic imaging must be performed in patients with non emergency clinical presentation and suspected carcinoma of the ovary ; a blood sampling must be taken for blood markers assessment, at least Ca-125 levels

QI 1 : recommendation is met in over 95 % of patients

Specialized multidisciplinary decision making

Patients with non emergency clinical presentation and suspected carcinoma of the ovary should be referred to a specialist in gynecologic oncology (certified gynecologic oncologist or specialist surgeon as defined in QI 3 for advanced ovarian cancer surgery)

- All patients must be reviewed postoperatively at a gynaecologic oncology multidisciplinary meeting

QI 2 : requirement is met in 100 % of patients

Surgical management (1)

Surgery for early epithelial ovarian cancer. Quality assurance criteria

- Midline laparotomy is required to manage early ovarian cancers , with the exception of a few apparent stage I which can be managed laparoscopically without rupture and without contamination of the abdominal wall ***QI 3 : 100% of patients with early ovarian cancer meet the requirement***

- Intraoperative rupture of a yet unruptured adnexal mass should be avoided

QI 4 : 90% of early ovarian cancers are removed unruptured (pT IC1/pT IA+IB<0.1)

Surgical management (2)

Surgery for early epithelial ovarian cancer. Quality assurance criteria

- Total hysterectomy and bilateral salpingo-oophorectomy is standard
  - Discussion on fertility must be mentioned in the patient record wherever applicable

QI 5 : requirement is met in 100% of patients

Role of frozen section

Surgery for early epithelial ovarian cancer. Quality assurance criteria

- The availability of frozen section may allow the necessary surgical staging to be done 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 case of inconclusive frozen section, a two-step procedure must be considered.

QI 6 : frozen section is available in the institution

Quality assurance for surgical staging

ESGO modified Trimbos 2003* classification :

- optimal : all components of staging are present (inspection and palpation of all peritoneal surfaces; biopsies of any suspect lesions for metastases; peritoneal washing and routine peritoneal biopsies**; infracolic omentectomy; pelvic and paraaortic lymph node dissection)
- suboptimal : everything between inadequate and optimal
- inadequate : not performed, or information is not available

QI 7 : 100% of patients have optimal staging

* JNCI, 2003;95:113-25

** Suggested procedure for blind biopsies : right and left hemidiaphragm, right and left paracolic gutter, pelvic sidewalls, bladder peritoneum, and pouch of Douglas

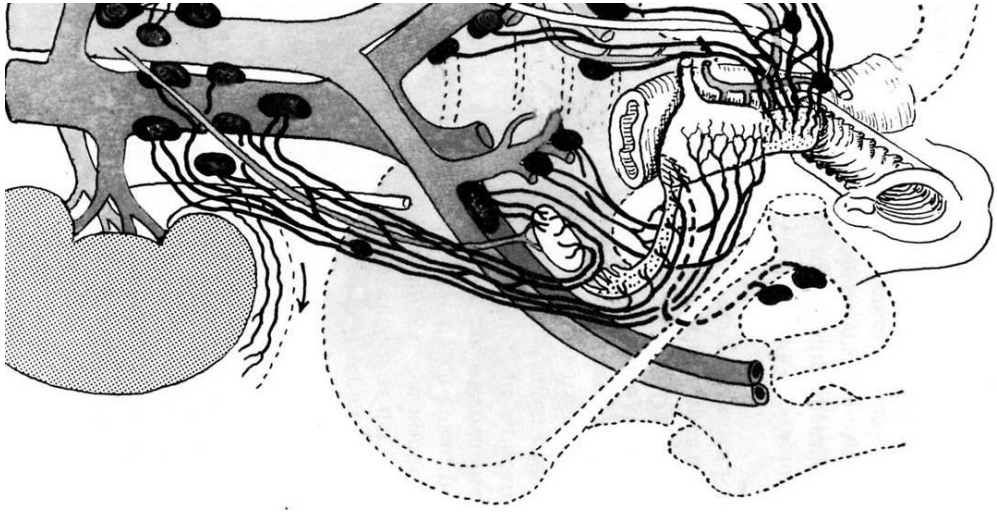
Lymph node metastases in ovarian cancer

- LN involvement

Stage I: 15-25%

Stage II: 20-40%

Stage III: 50-75%



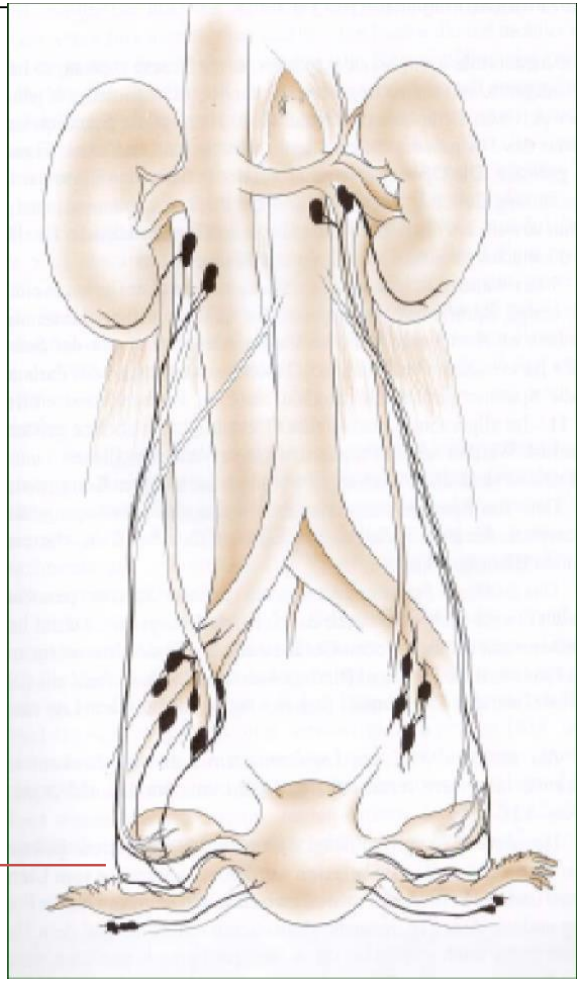
Paraaortal more often involved (75%) than pelvic (15%), solely contralateral 11%

Burghardt et al. Gynecol Oncol 1991; Morice et al. J Am Coll Surg 2003

Negishi et al. Gynecol Oncol 2004

ASCO 2002, Sakurai et al., VALIDITY OF COMPLETE PARAAORTIC AND PELVIC LYMPHADENECTOMY IN APPARENT STAGE I (PT1) OVARIAN CARCINOMA 1989-2000

- pT1a = N1: 10,6% (7/66)
- pT1b = N1: 55,6% (5/9)
- pT1c = N1: 18,1% (24/141)
- pelv. N1 + paraa. N1: 20 Pts.
- pelv. N0 + paraa. N1: 4 Pts.
- pelv. N1 + paraa. N0: 0 Pts.



Rate of patients with apparently early EOC that had positive pelvic and/or paraaortic lymph nodes after systematic lymph node dissection

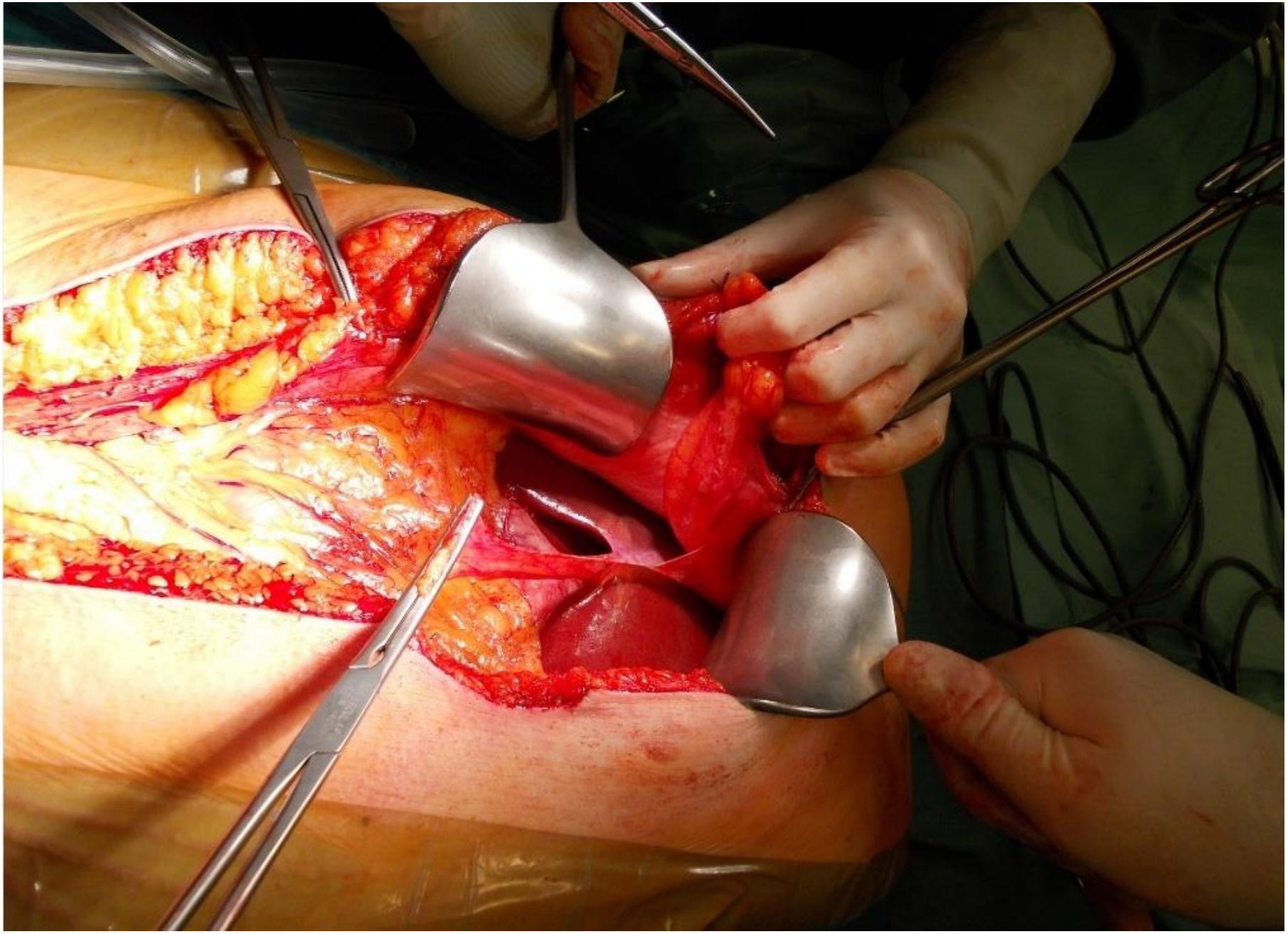
	n	*%*
Benedetti-Panici, *1993*	35	14
Petru, *1994*	40	23
Onda, *1996*	33	21
Baiocchi, *1998*	242	13
Suzuki, *2000*	47	11
Nomura, 2010	79	13
Harter, 2007	70	11

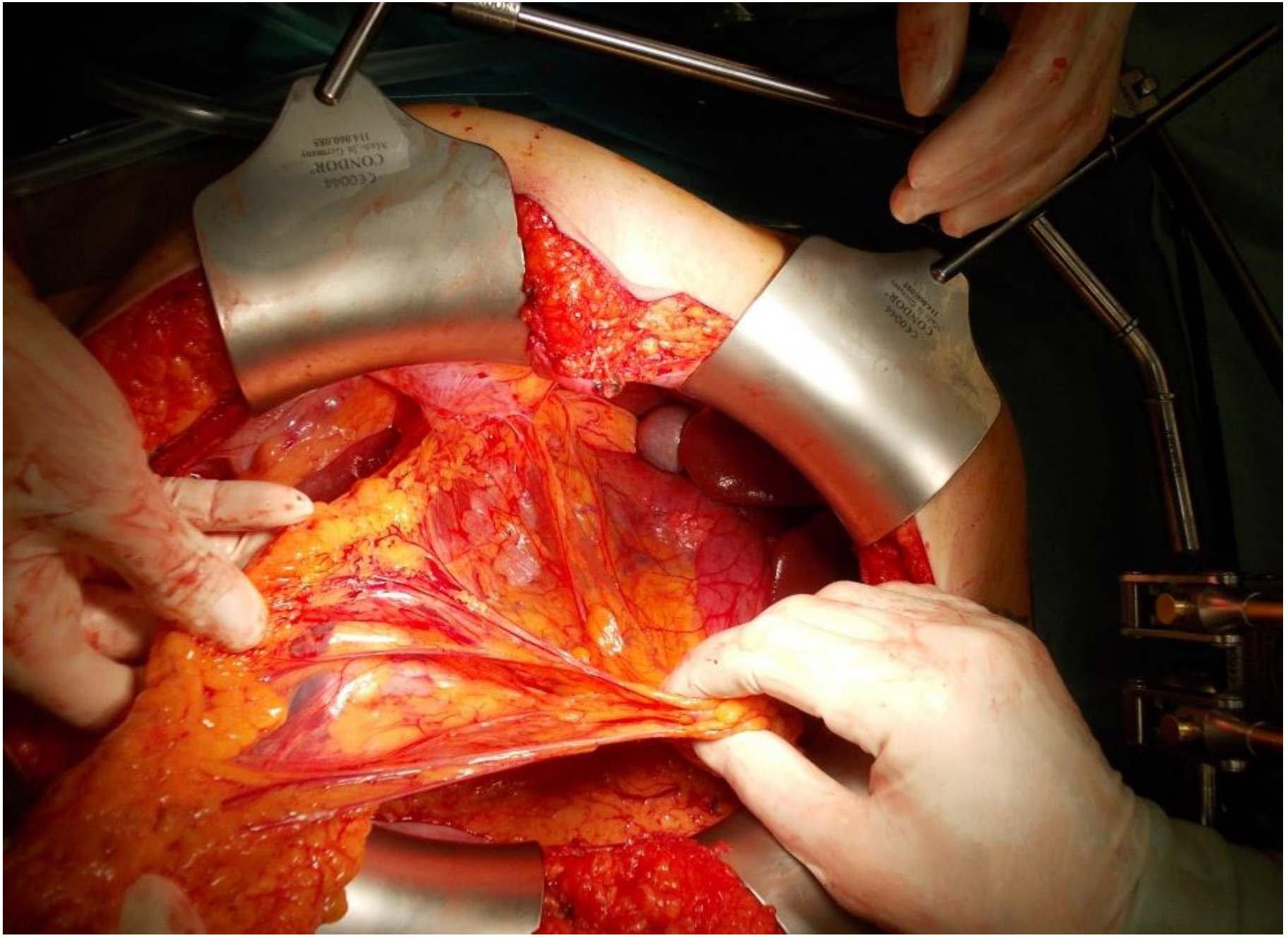
Conservative surgery for ovarian cancer in Europe: outcome by stage

Stage	No. of patients	Relapse (*N*)	Relapse ovary (*N*)	Deaths
IA	88	10	6[a]	4
IB	2			
IC	51	5	3[b]	3
II	2	2	1[b]	2
IIIA	3			
IIIC	6	1	1[b]	
Total	152	18 (11.8%)	11 (7%)	9 (5.9%)

[a]one of six patients had ovarian and distant metastases.
[b]All patients had ovarian + peritoneal and/or retroperitoneal metastases.

Colombo et.al. Int J Gyn Canc 2006

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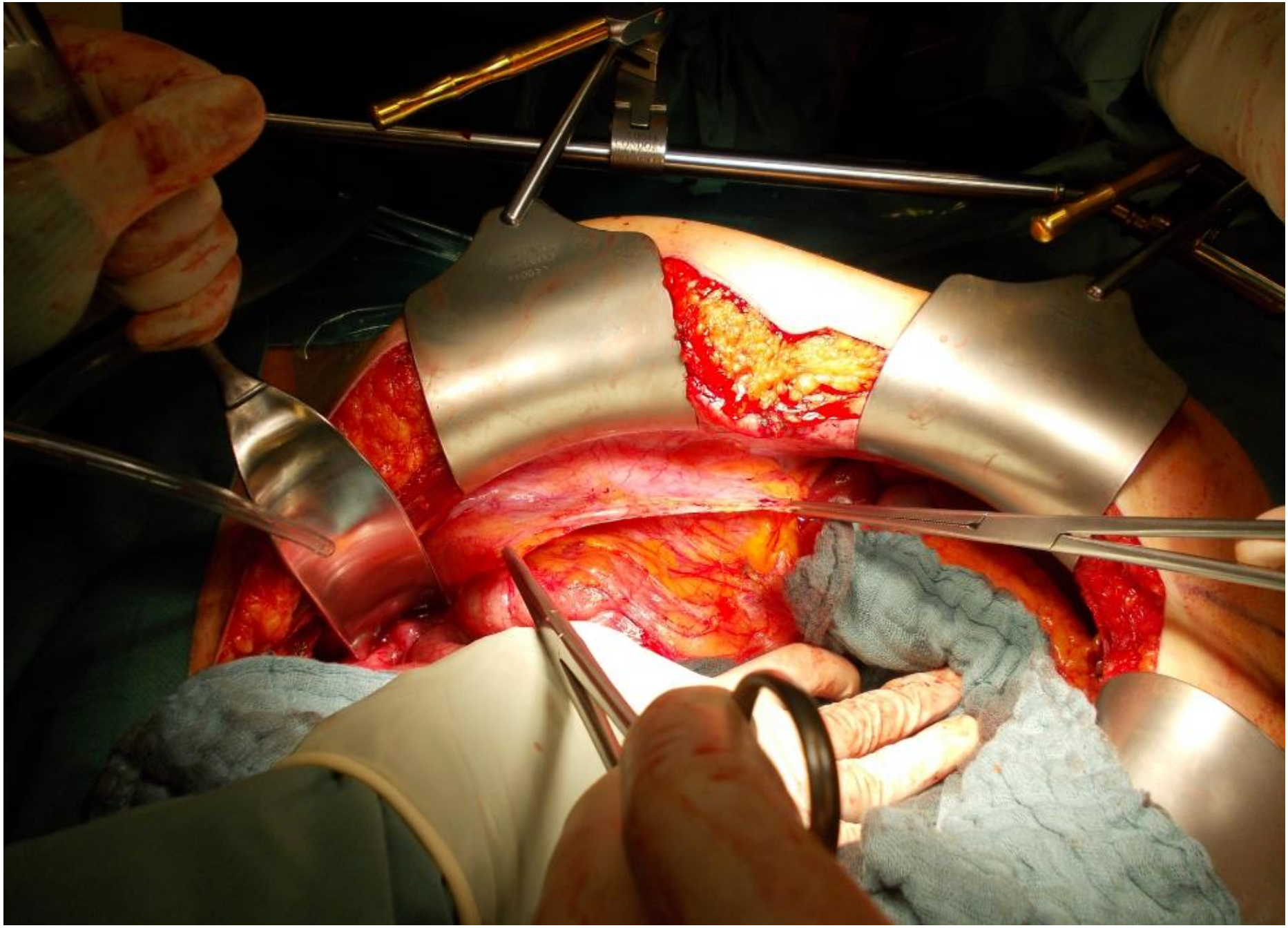

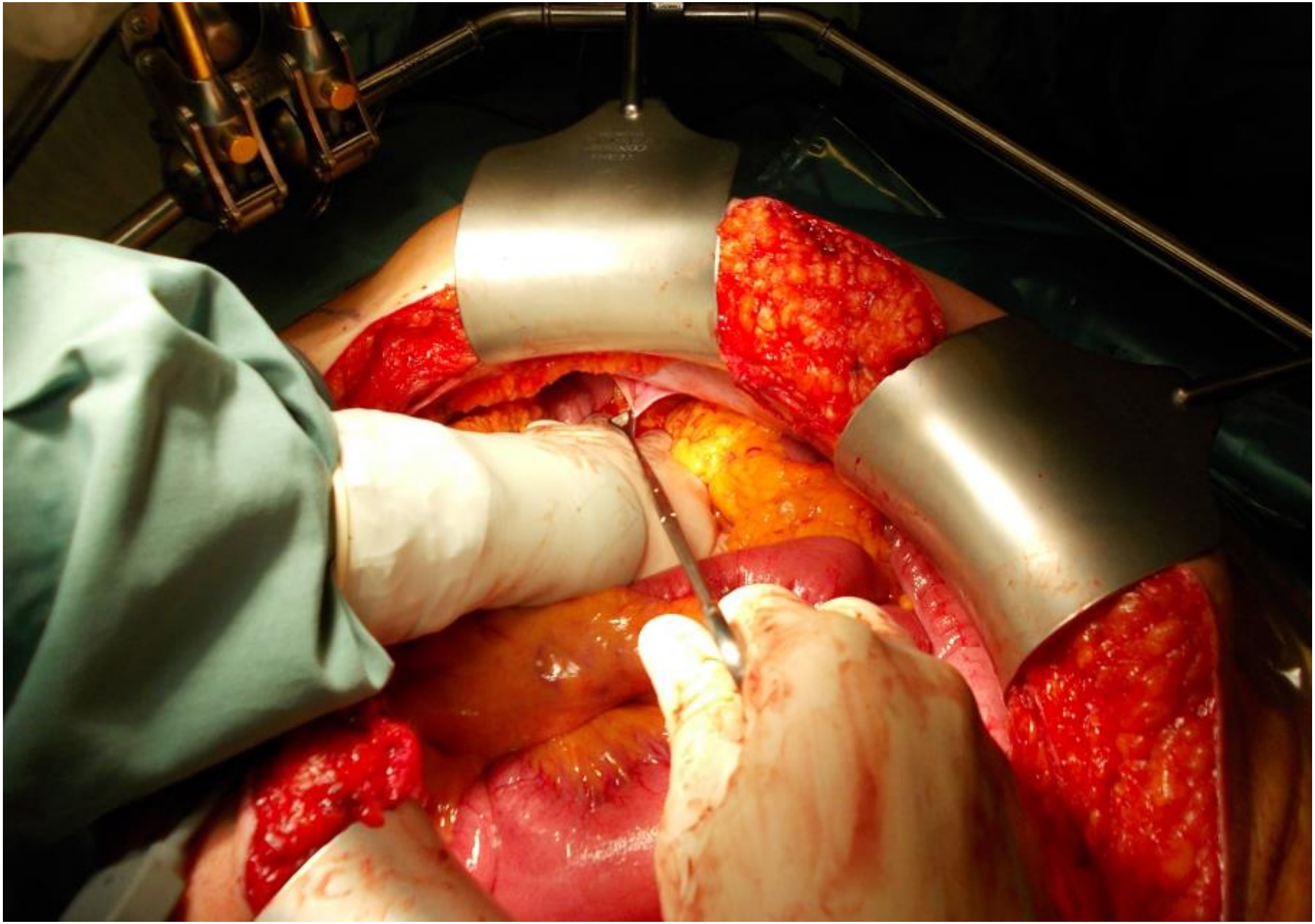

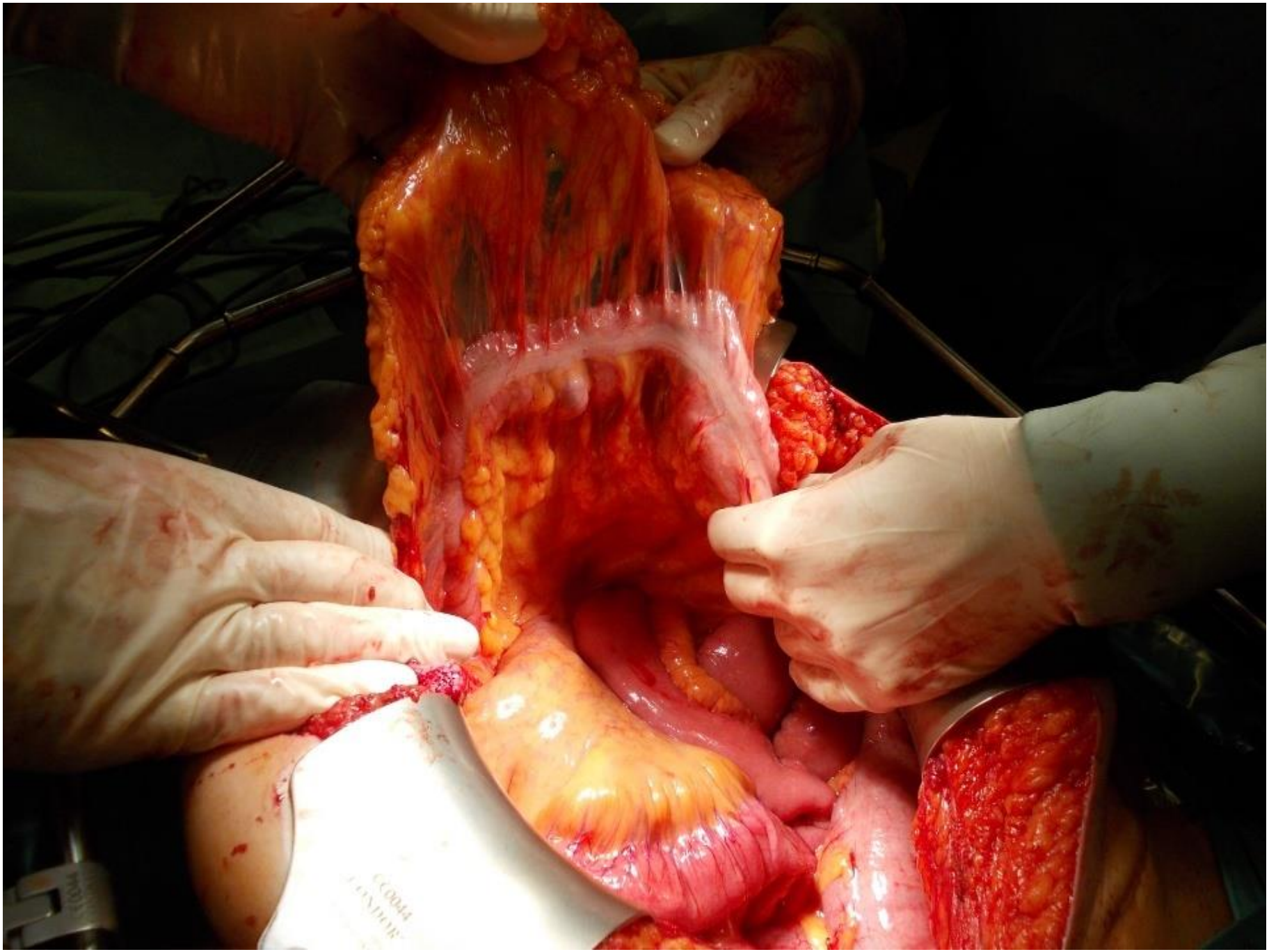

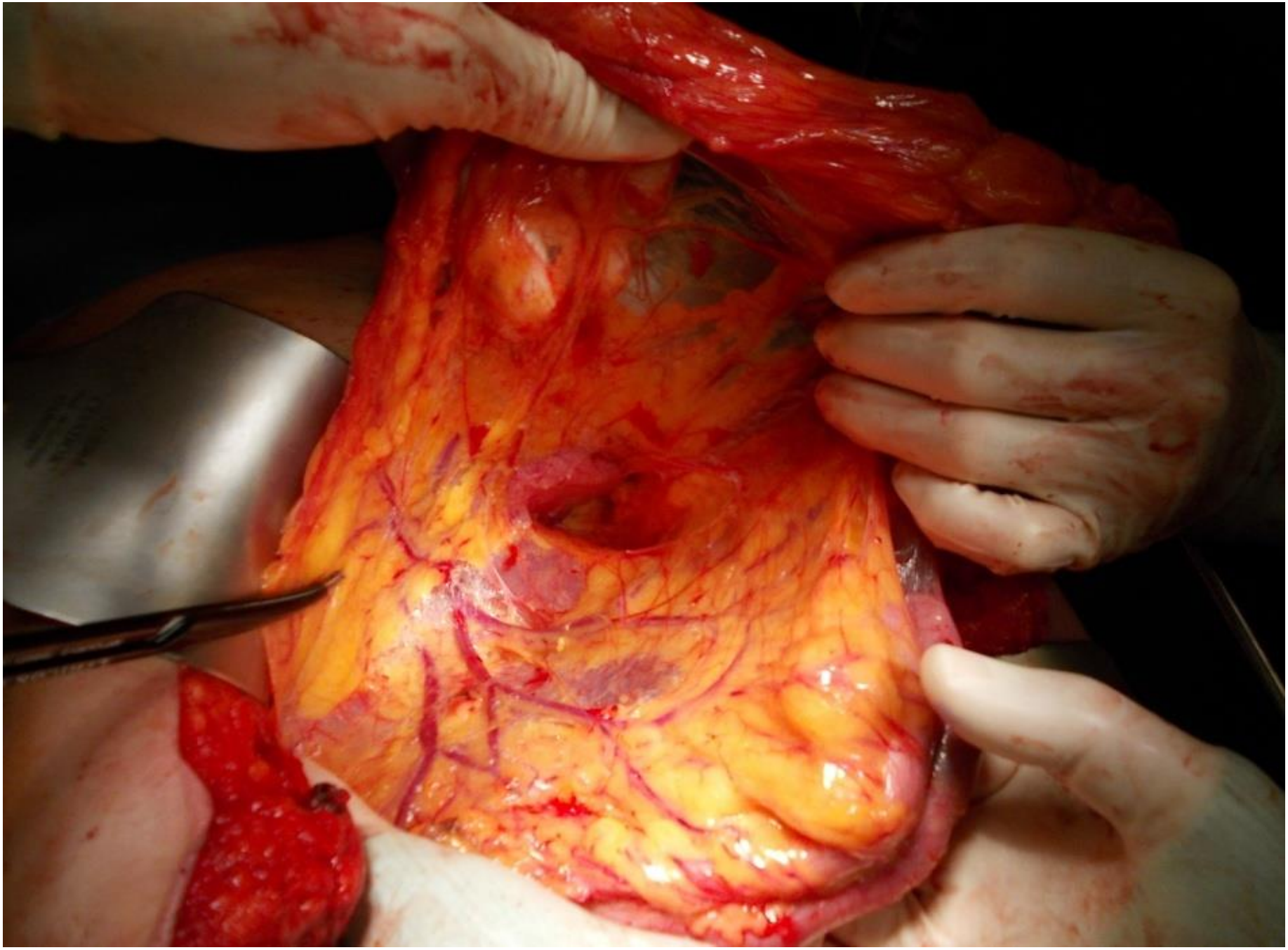

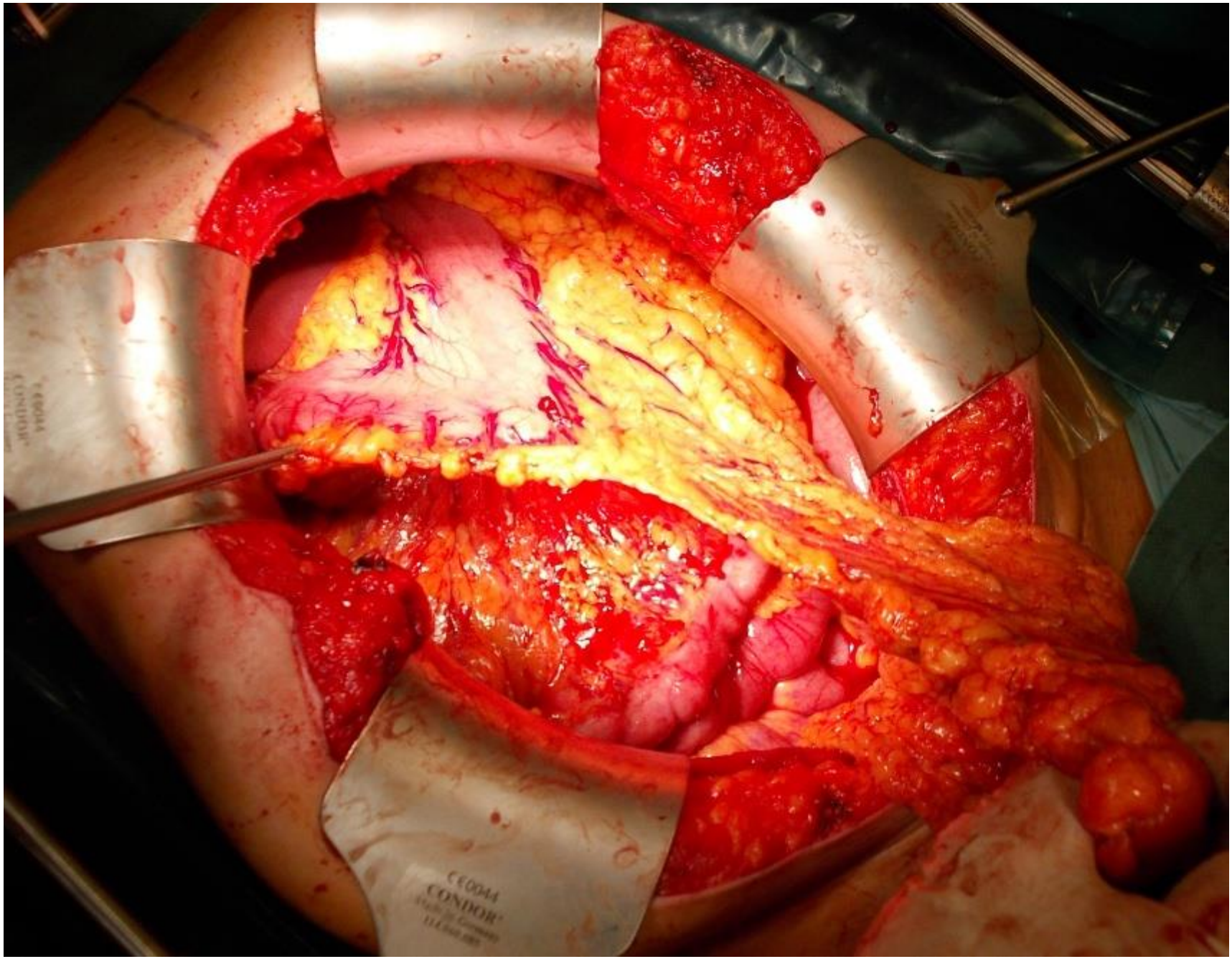
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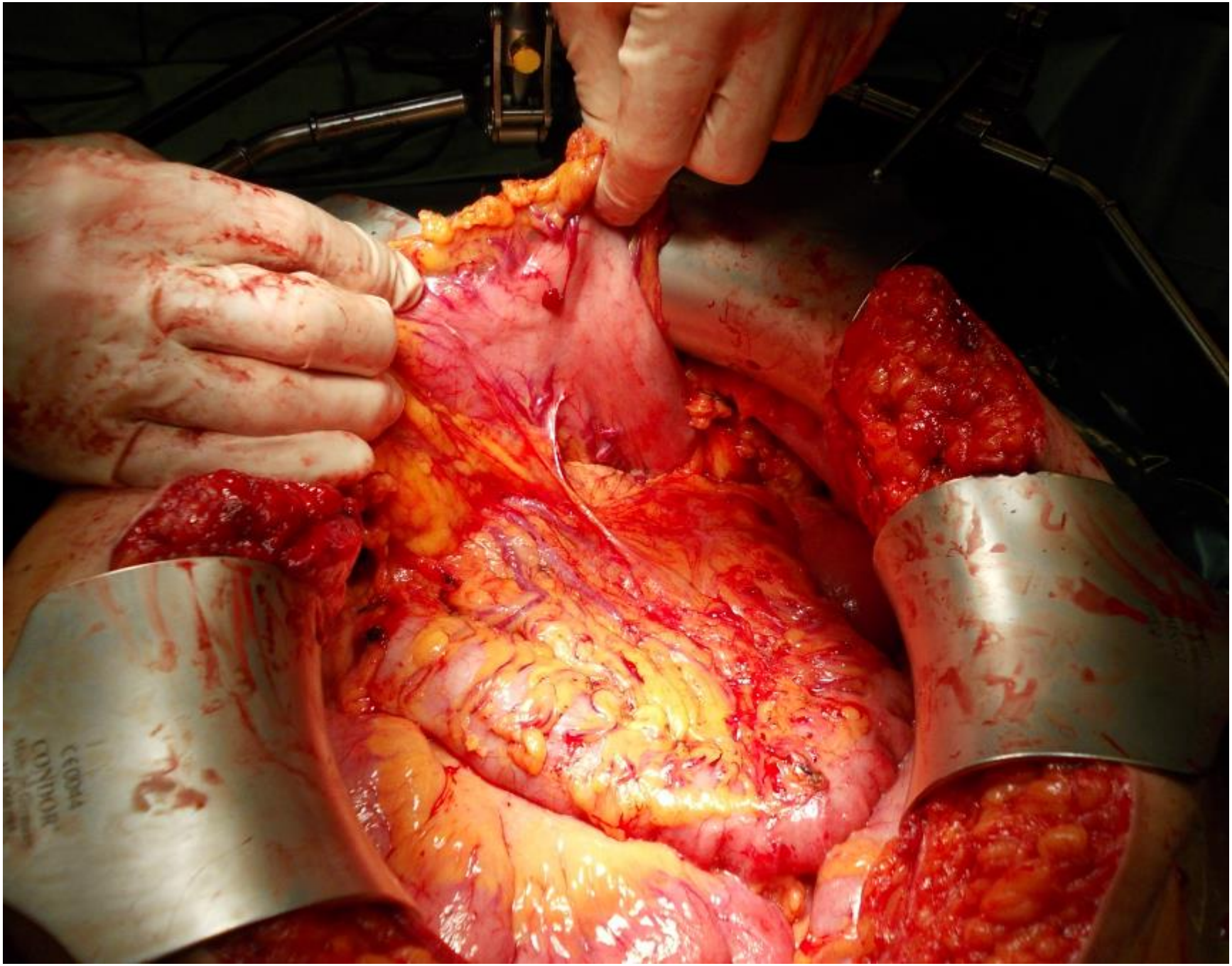
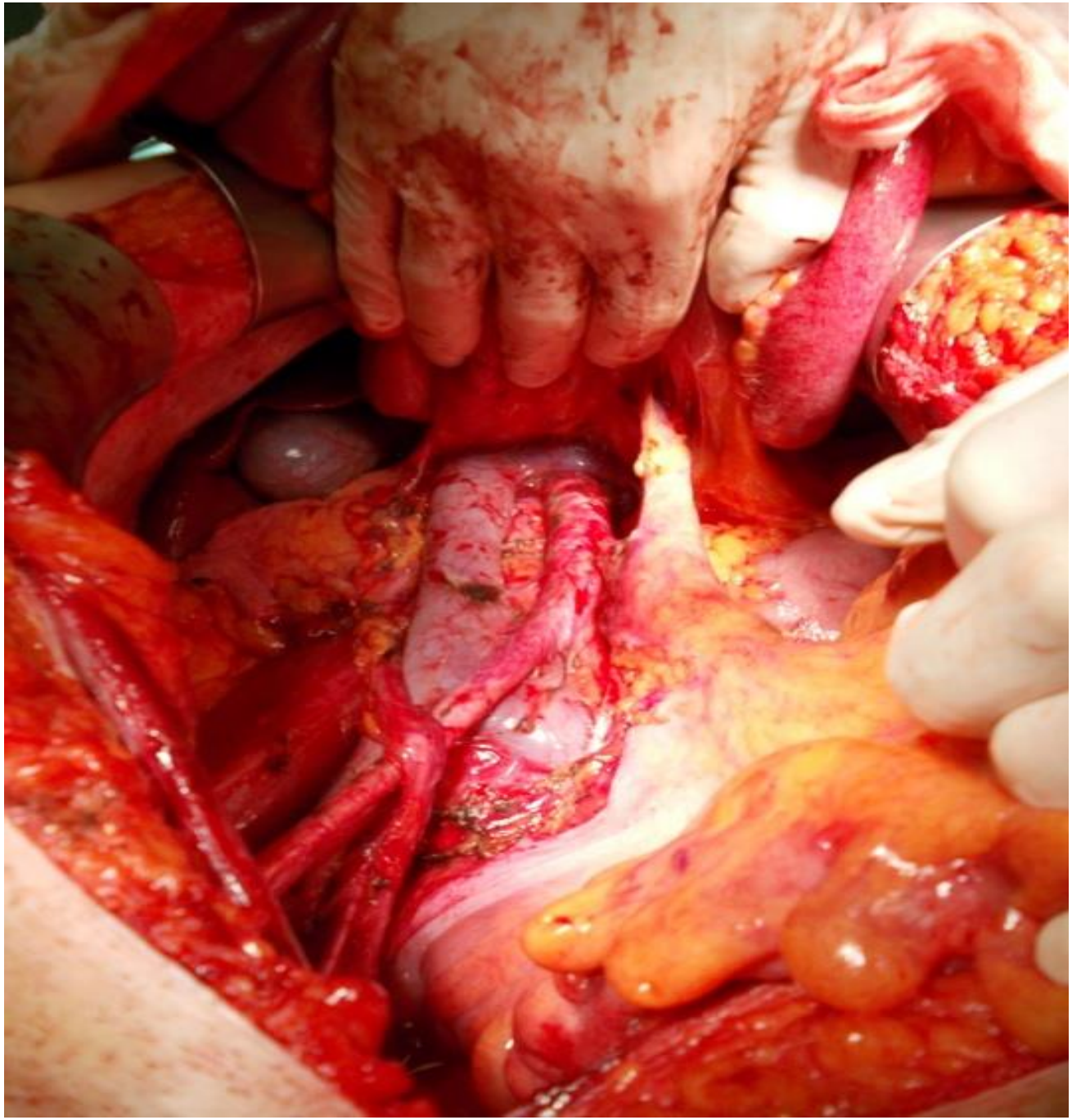
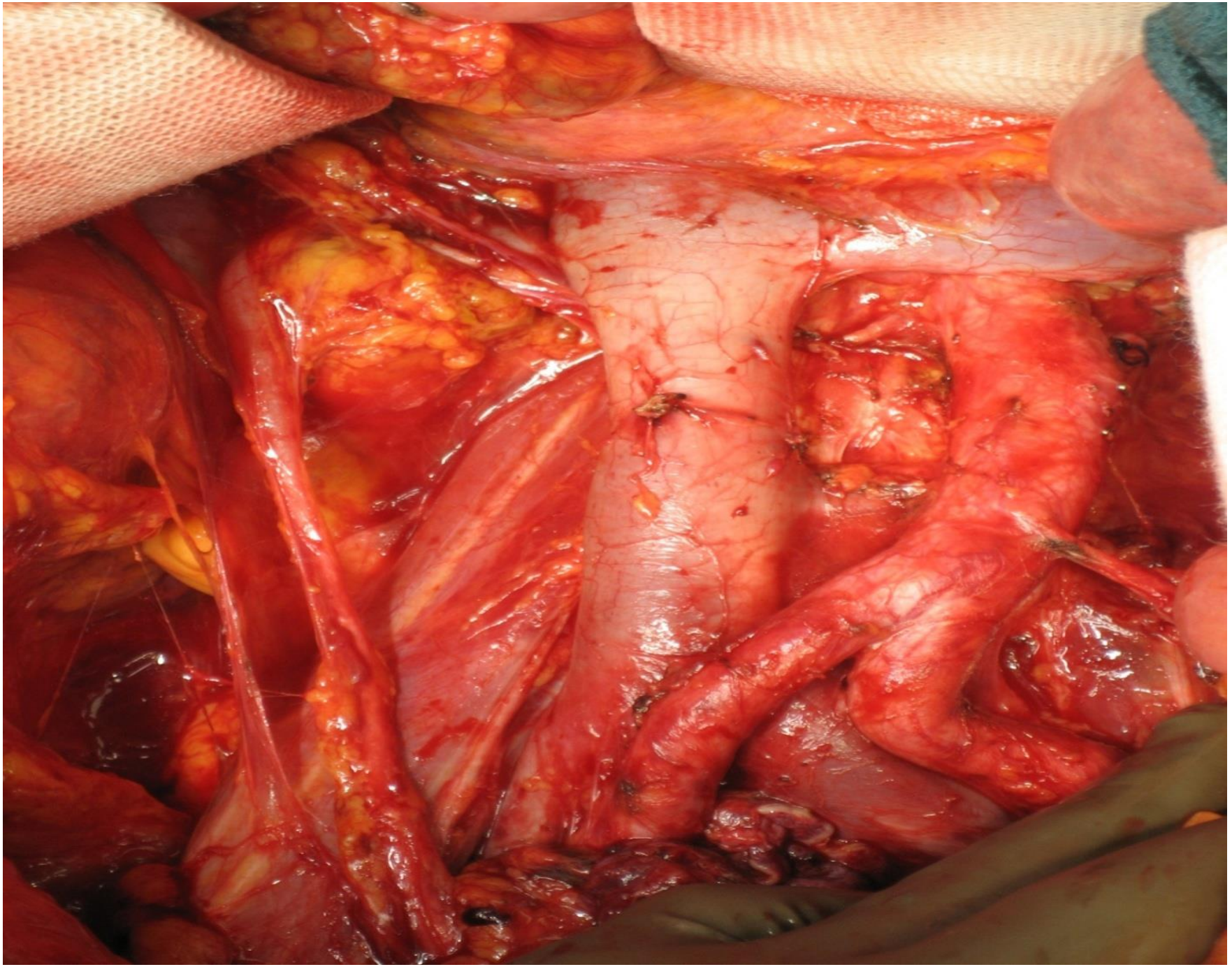
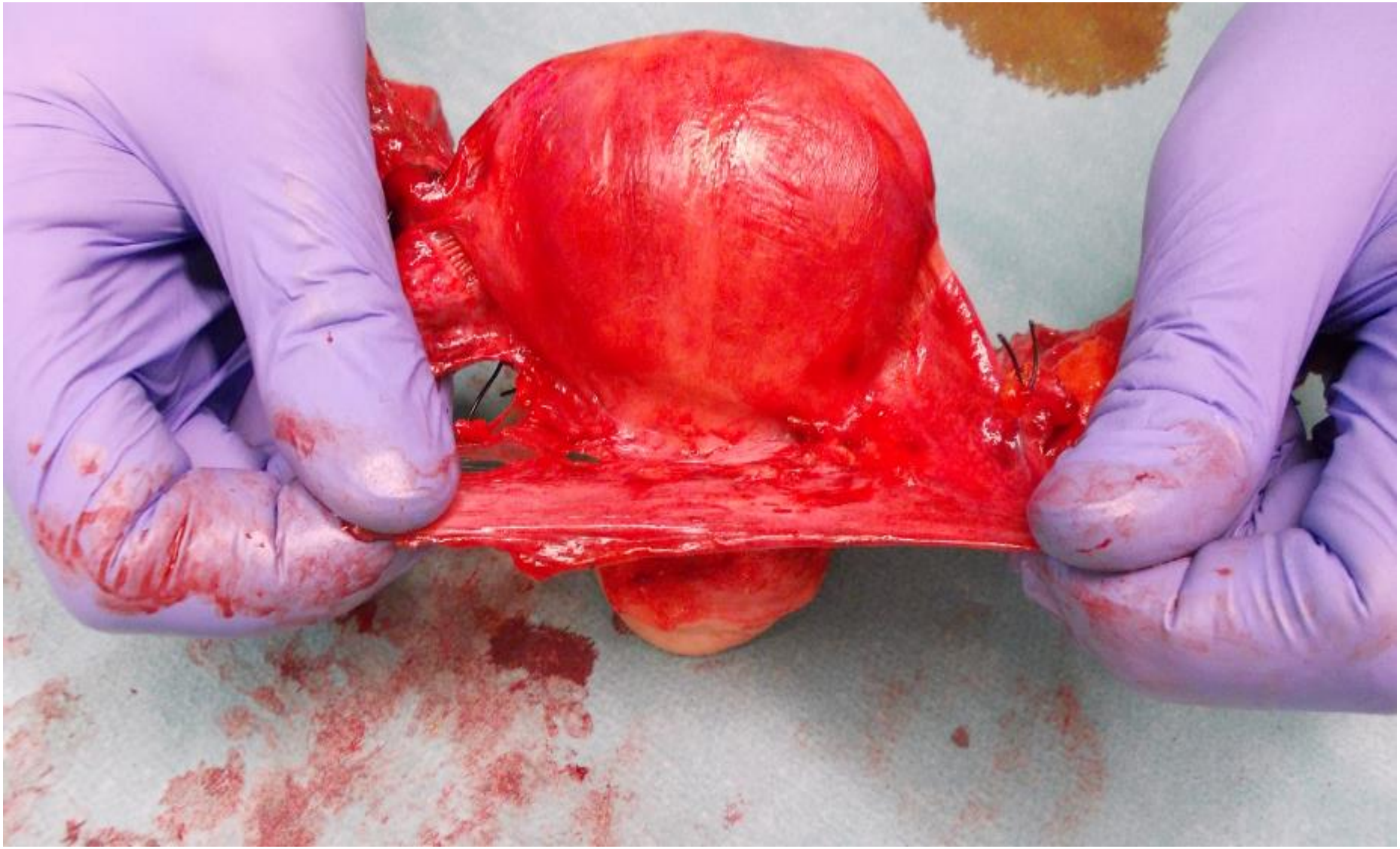
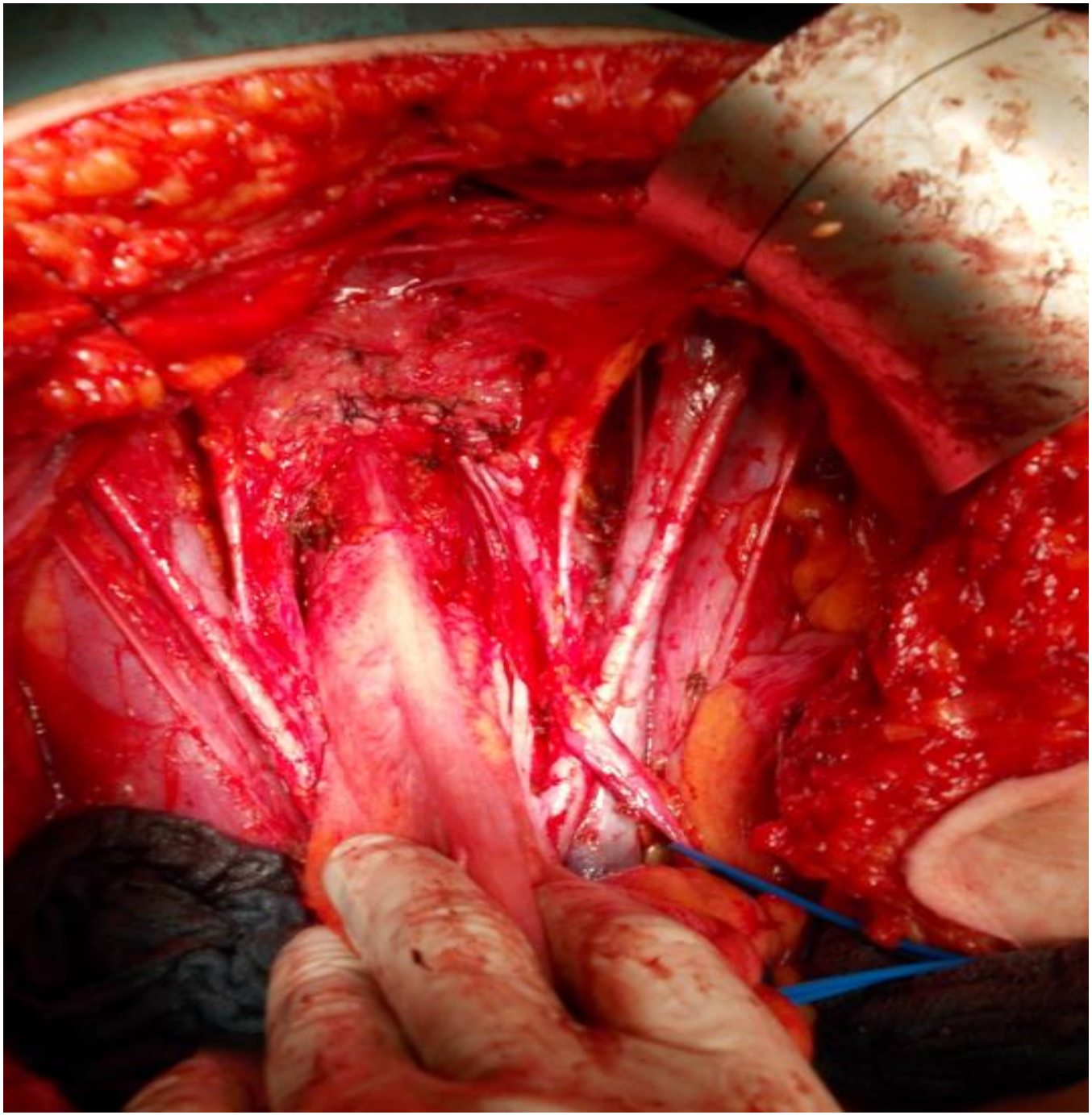
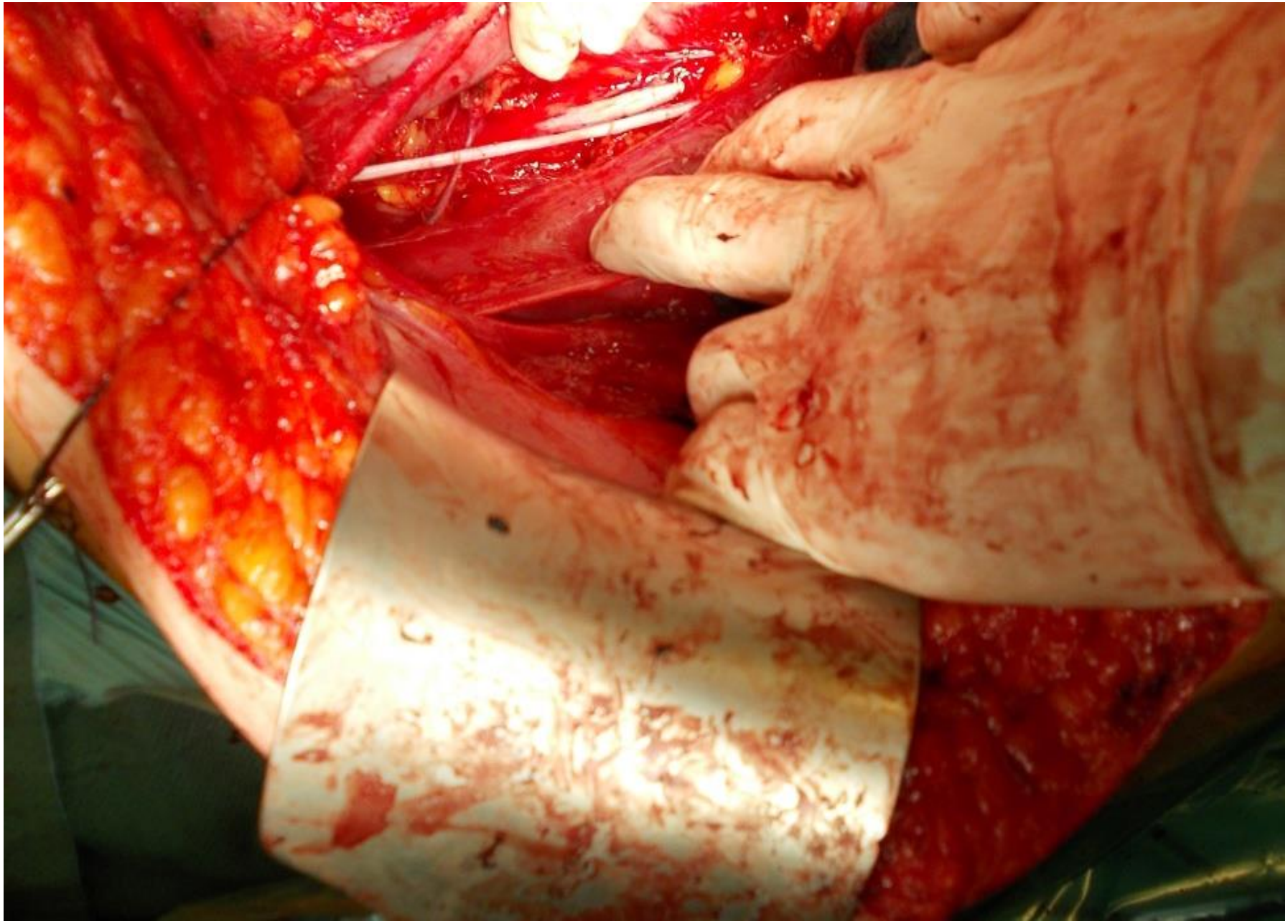


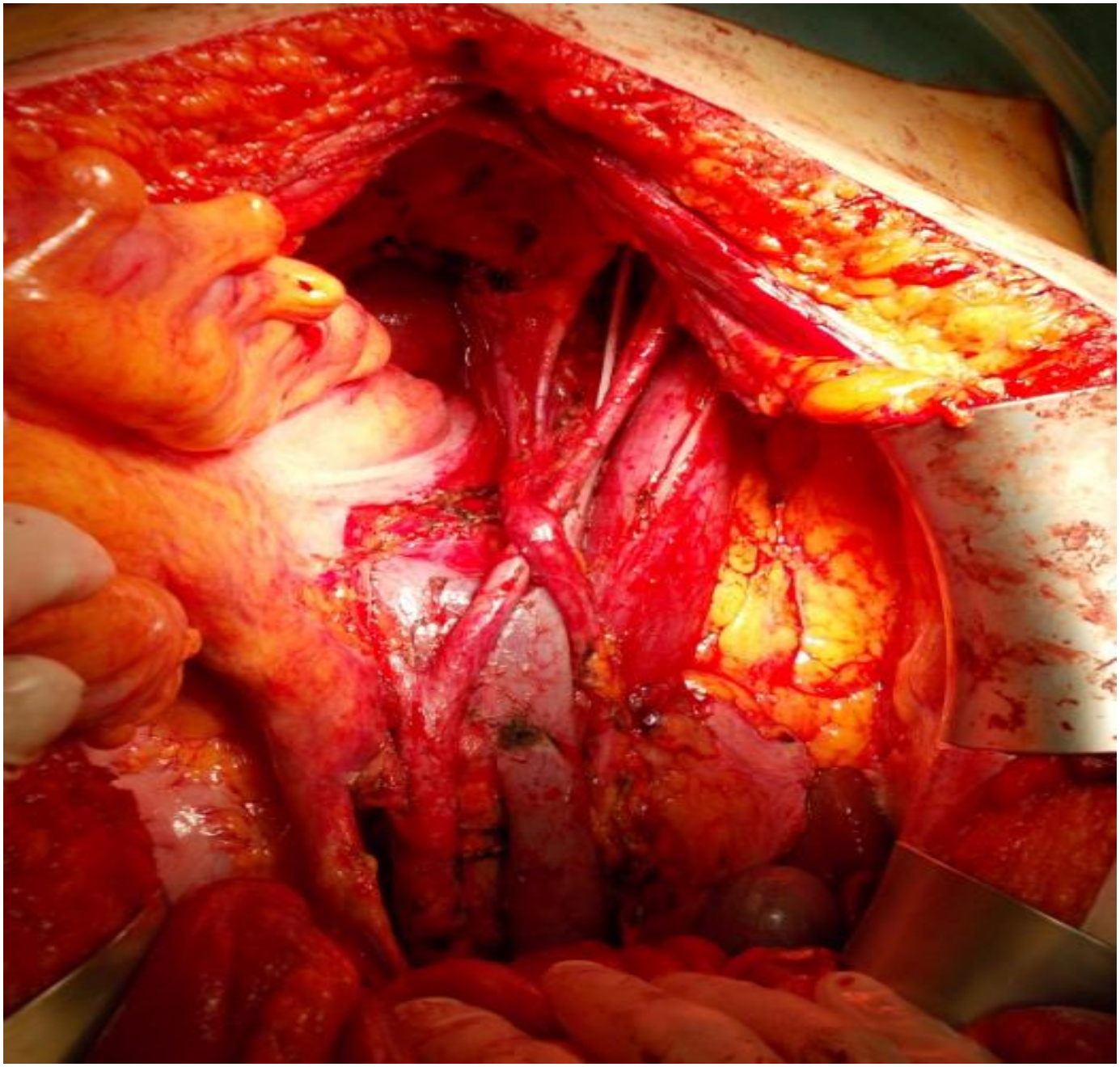












Oncologic outcome after fertility sparing treatment in early ovarian cancer (FIGO I-II)

- Relapse rates: 4-17%
- Relapsed free intervall: 7-63 Monate
- 5-YOS: 80-94%
- High conception rates; no higher risk of abortions, prematurity, congenital malformation

Fotopoulou et.al. Review
Obstet Gynecol Int. 2012

....but what about?

- Iatrogenic Ic disease
- Nonserous or non-endometrioid histologic subtypes
- G3
- IIIc due to „only“ LN involvement

Table 1: Relevant case series reports in the literature concerning fertility-sparing surgery in epithelial ovarian cancer: oncologic outcome.

Author [reference]	Pts *N*	Median Age (y)	FIGO stage *N* (%)	Grade *N* (%)	Histology *N* (%)	Relapse rate *N* (%)	Mean PFS (mo) or 5 y DFS	Characteristics of pts who relapsed	5 y OS	Death	LND
Kwon et al. 2009 [18]	21	26.7	17 (81%) IA 4 (19%) IC	16 (76%) G1 3 (14%) G2 2 (9.5%) G3	16 (76%) muc 2 (9.5%) endom 2 (9.5%) clear cell 1 (4.7%) serous	1 (4.7%)	34	IC, muc	NR	NR	Yes
Kajiyama et al. 2008 [19]	10	35.9	4 (40%) IA 6 (60%) IC	NR	10 (100%) clear cell	1 (10%)	33	IC, G2, clear cell	NR	1 (10%)	Optional
Schlaerth et al. 2009 [3]	20	27	11 (55%) IA 9 (45%) IC	14 (70%) G1 5 (25%) G2 1 (5%) G3	11 (55%) muc 1 (5%) serous 6 (30%) endom 1 (5%) clear cell	3 (15%)	4.3 (9–22)	2 IC, 1 IA	84%	3 (15%)	Yes
Borgfeldt et al. 2007 [20]	11	NO	IA IC	G1 G3	NR	1 (9%)	NR	IC, G3	NR	NR	Yes
Schilder et al. 2002 [11]	52	26	42 (81%) IA 10 (19%) IC	38 (73%) G1 9 (17%) G2 5 (9.6%) G3	25 (48%) muc 10 (19%) serous 5 (9.6%) clear cell 2 (4%) mixed	5 (9.6%)	14 (8–78)	4 IA, G1 1 IC, G2 2 muc 2 serous 1 endom	98%	2 (4%)	Yes
Kajiyama et al. 2011 [21]	74	<40	36 (48%) Ia 1 (1.3%) Ib 37 (50%) Ic	57 (77%) G1/G2 4 (5.4%) G3	4 (5.4%) serous 43 (58%) muc 13 (18%) clear cell 4 (5.4%) endom	NR	87.9% 5 y DFS	NR	90.8%	2 (2.7%)	Yes
Zanetta et al. 1997 [12]	56	29	32 (57%) : IA 2 (3.5%) : IB 22 (39%) : IC	35 (62%) G1 14 (25%) G2 7 (12%) G3	18 (32%) serous 23 (41%) muc 13 (23%) endom	5 (9%)	NR	2 IA,G2, endom 1 IA, G3, muc 1 IA, G1, serous 1 IC, G2, serous	NR	4 (7%)	Yes
Satoh et al. 2010 [16]	211	29	126 (60%) IA 85 (40%) IC	G1: 160 (76%) G2: 15 (7%) G3 6 (2.8%) clear cell: 30 (14.2%)	126 (60%) muc 27 (13%) serous 27 (13%) endom 30 (14.2%) Clear cell	18 (8.5%)	33.3–100% 5 y DFS	Mostly Ic,G3 Ia, G3 Ic, clear cell	66.7–100%	5 (2.4%)	Yes
Kajiyama et al. 2011 [13]	41	<40 y	27 (66%) : IA 14 (34%) : IC	NR	100% muc	3 (7.3%)	90.5%		97.3%	1 (2.5%)	Yes
Kajiyama et al. 2011 [22]	80	35	40 (50%) IA 40 (50%) IC	—	45 (56%) muc 3 (3.75%)serous 15 (19%) endom 16 (20%) clear cell	10 (12.5%)	85.5%–92.9% 5 y DFS	2: IA 8: IC	89.3%–90.5%	0	Yes
Kajiyama et al. 2010 [23]	60	30	IA 30 (50%) IB 1 (1.7%) IC 29 (48%)	41 (68%) G1 7 (12%) G2 2 (3.3%) G3	Serous 5 (8.3%) Muc. 34 (56.7%) Endom 11 (18 %) Clear cell 10 (17%)	8 (13%)	89.8%	2 IA, 1 IB 5 IC	89.8%	0	
Total	580	26–35.9	333 (57%) IA 4 (0.7%) IB 234 (40%) IC	334 (57%) G1 39 (6.7%) G2 20 (3.4%) G3	300 (52%) muc 51 (9%) serous 128 (22%) clear cell 65 (11%) endom	50 (8.6%)	33.3–100% 5 y DFS		66.7–100%	18 (3.1%)	Yes

Points of attention in clinical practice

- Overseing „occult“ advanced stage patients through inadequate staging
- Discuss and offer fertility sparing options in young patients with ov ca
- Special attention to rare histologies with limited experience
- PREOPERATIVE Decision making process after discussion with the patient about 1-stage / 2-stage procedure

Backup Folien

Molekularbiologische und klinikopathologische Charakteristika verschiedener histologischer Typen des Ovarialkarzinoms (WHO-Klassifikation 2014)

	High grade serös	Low grade serös	Muzinös / seromucinös	Endometrioid	Klarzellig
Häufigkeit (%)	40–70	5–10	~ 5	~ 10	~ 10
Risikokonstellation	BRCA1/2			HNPCC	
Vorläuferläsion	STIC (p53-Mutation)	SBOT	MBOT	Endometriose	Endometriose
Ausbreitungsmuster	Diffus abdominal	Abdomen	Ovar	Kleines Becken	Kleines Becken
Molekularpathologie	BRCA, p53-Mutation	B-raf-, K-ras-Mutation	B-raf-, K-ras- Mutation (mucinös) ARID-1A-Expression/-Mutation (seromucinös)	ARID-1A-Expression/-Mutation	ARID-1A-Expression/-Mutation
Chemotherapie-Response	**Hoch**	**Eher niedrig**	mucinös: niedrig seromucinös:etwas höher	**Hoch**	Niedrig
Prognose	Schlecht	Intermediär	Gut	Gut	Intermediär
Neue Therapieansätze	**PARP-Inhibitoren** WEE-1-Inhibitor (p53-Mutation - CDK 1) ?	MEK-Inhibitoren? Endokrine Therapie?	?	PARP-Inhibitoren ?	?

Undifferenzierte Karzinome und Karzinosarkome mit schlechter Prognose.

Krukenberg Krebszentrum Halle

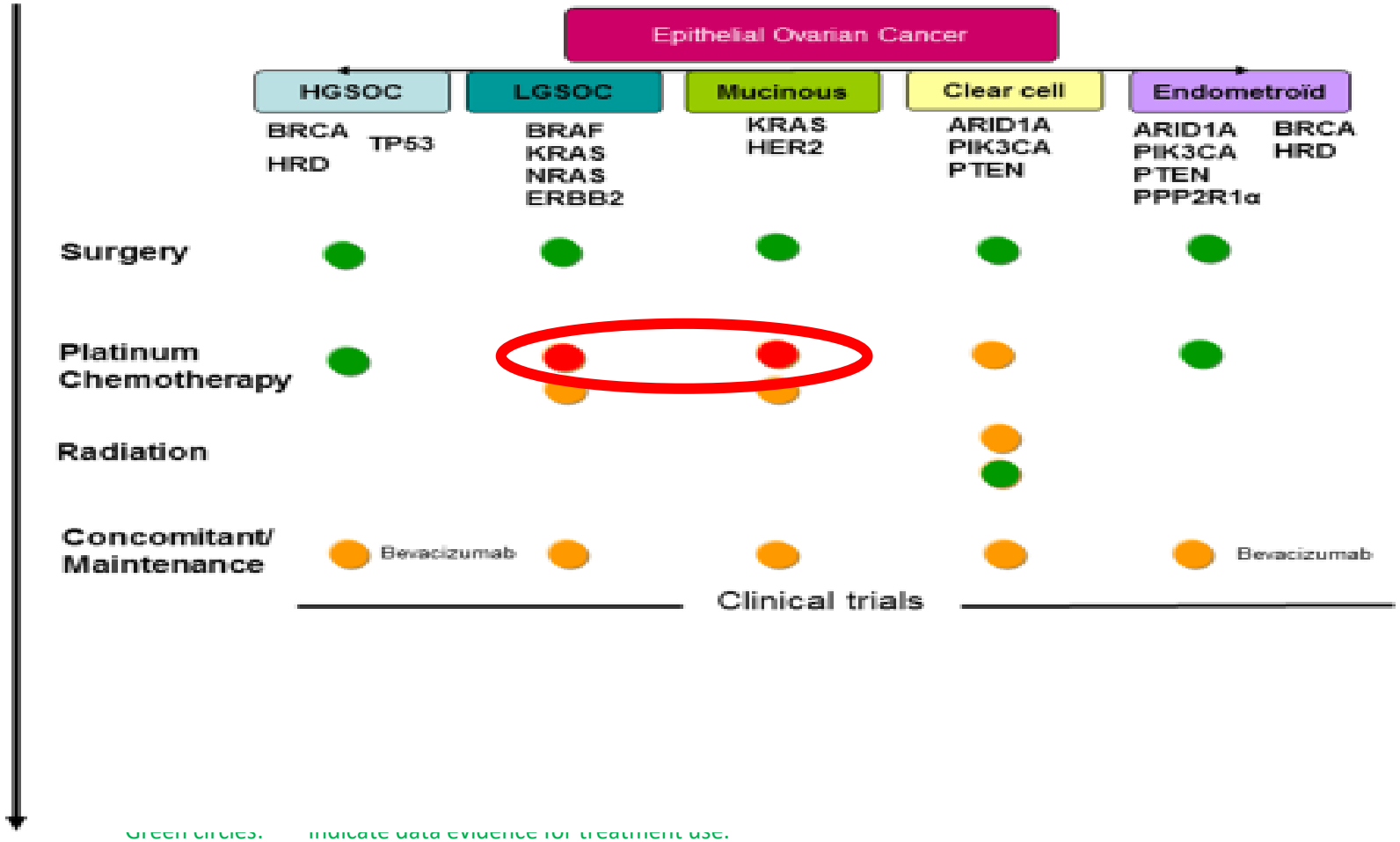
GYNÄKOLOGISCHES KREBSZENTRUM Universitätsklinikum Halle

Universitätsklinikum Brustzentrum Halle

UKH Universitätsklinikum Halle (Saale)

Ovarian cancer – the end of empiricism?

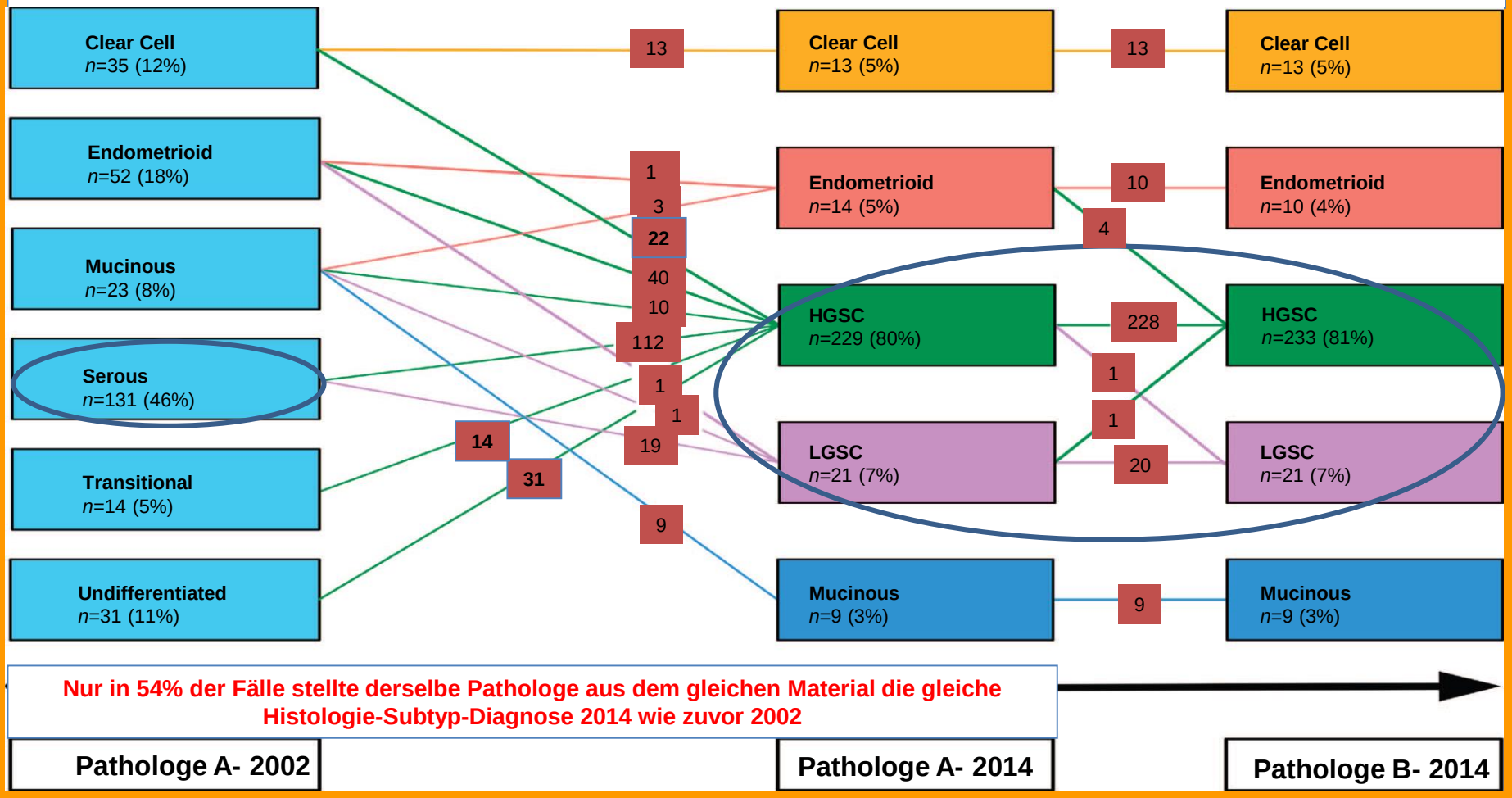
Cancer Volume 121, Issue 18, pages 3203-3211, 10 JUN 2015 DOI: 10.1002/cncr.29481



Green circles: Indicate data evidence for treatment use.
Orange circles: Lack of validation to support treatment use.
Red circles: No evidence for treatment use.

Ovarian carcinoma diagnosis: the clinical impact of 15 years of change - S.Kommoss et al; B J Cancer 2016

Low value of achival ovarian carcinoma histotypes - n = 286 samples – AGO OVAR 3 trial



Nur in 54% der Fälle stellte derselbe Pathologe aus dem gleichen Material die gleiche Histologie-Subtyp-Diagnose 2014 wie zuvor 2002

Pathologe A- 2002 | **Pathologe A- 2014** | **Pathologe B- 2014**

Krukenberg Krebszentrum Halle

GYNÄKOLOGISCHES KREBSZENTRUM Universitätsklinikum Halle

Universitätsklinikum Brustzentrum Halle

UKH Universitätsklinikum Halle (Saale)