Aktualne standardy leczenia raka jajnika

/EBM up to date/

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Plan prezentacji

1. Epidemiologia raka jajnika w Polsce
2. Filozofia leczenia C56 (podział na etapy: frontline treatment, maintenance, supportive care)
3. Front-line treatment

Standardy leczenia chirurgicznego (stan na 2014r)

- PDS
- IDS

Evolution of surgical treatment paradigms for advanced-stage ovarian cancer: Redefining 'optimal' residual disease

- Dokumentowanie leczenia chirurgicznego: (opis zabiegu, wynik hist-pat)

Standardy chemioterapii I rzutu

- IV. (GOG-111, GOG-158)
- IP. (GOG-172)
- Dokumentowanie odpowiedzi na chemioterapię

http://www.educationalconcepts.net/pdf_resources/gyno24_ovarian.pdf

4. Czy trzeba spieszyć się z chemioterapią po operacji pierwotnej (PDS)?

The time interval from surgery to start of chemotherapy significantly impacts prognosis in patients with advanced serous ovarian carcinoma — Analysis of patient data in the prospective OVCAD study.

5. Miejsce Bevacizumabu w leczeniu raka jajnika

-front-line and maintenance (ICON7, GOG 218)
-recurrent EOC ['platinum-sensitive' (OCEANS Trial)]

Integrating bevacizumab into the management of epithelial ovarian cancer: the controversy of front-line versus recurrent disease.

6. Czy jest ważne kto leczy raka jajnika ?

High-volume ovarian cancer care: Survival impact and disparities in access for advanced-stage disease.

7. TAKE HOME: **Obowiązujące standardy nomenklaturowe: chirurgia, chemioterapia**

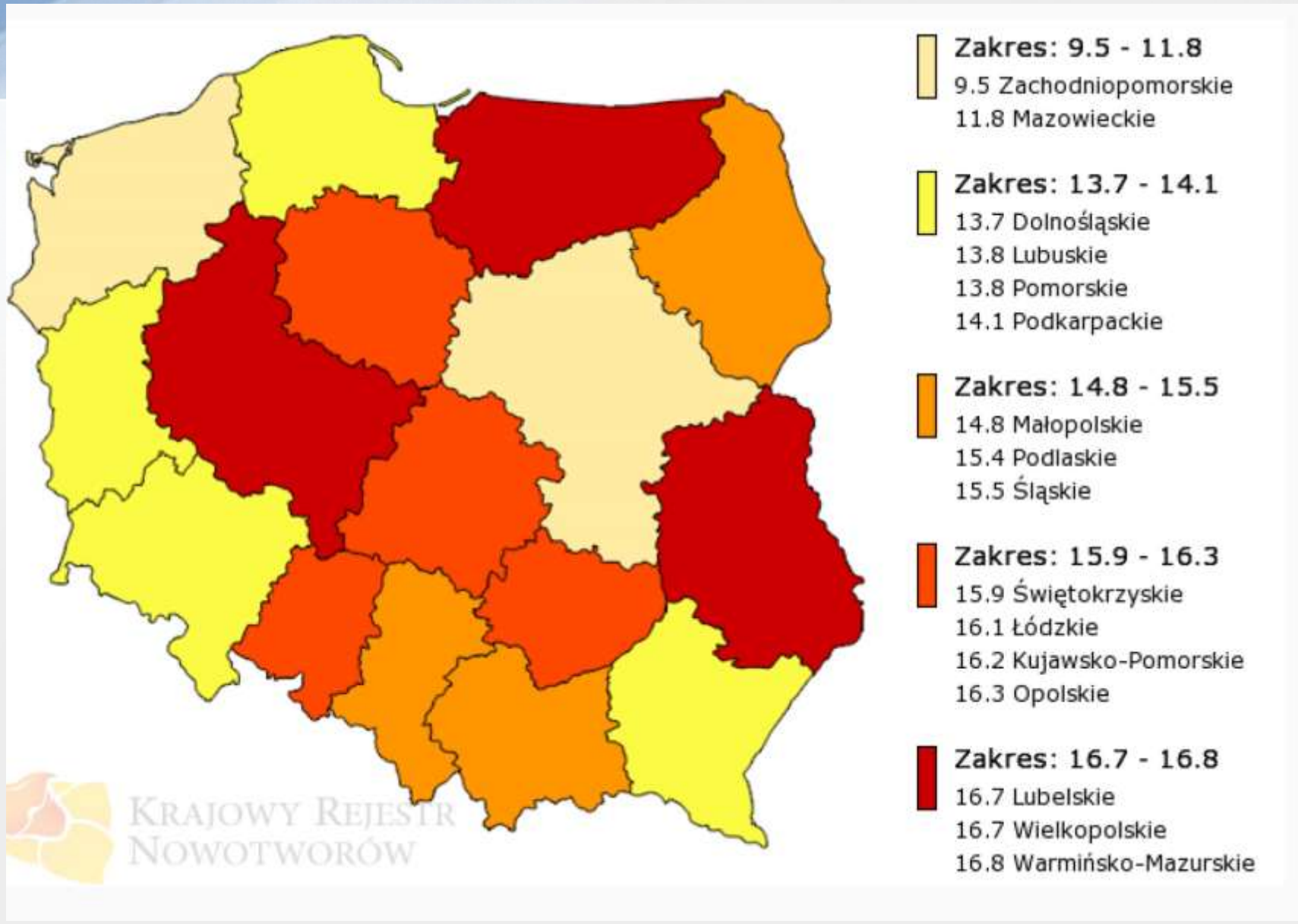
epidemiologia raka piersi/jajnika /miejsce uwarunkowań genetycznych/.

Jajnik /C56/

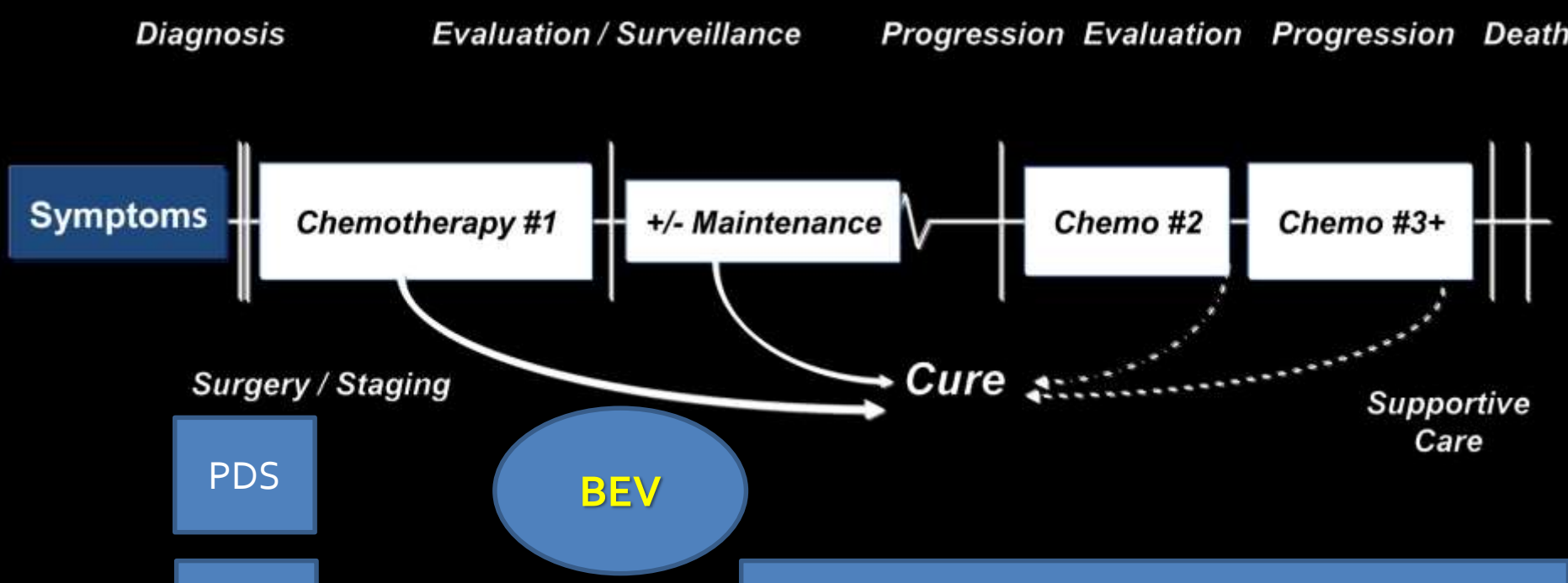
- 6 -ty nowotwór złośliwy u kobiet (5%)
- 11,05/100 000 – 3587 zachorowania w 2011 roku
- 6,99/100 000 – 2547 zgonów w 2011 roku
- Ryzyko ↑ z wiekiem, < 20 r.ż. sporadyczne przypadki

Jajnik /C56/

- Rokowanie złe – przeżycia 5-cio letnie:
  USA 53%, Europa 48.4%, Polska 42% (6% mniej)
- 25% chorych ma obciążenia rodzinne
- 5-10% przypadków raka jajnika ma podłoże dziedziczne (geny supresorowe BRCA1/2, mutatorowe i inne)
- Rokowanie raków dziedzicznych jest lepsze (IIIc 38,1 vs 24,5%)


Zakres: 9.5 - 11.8
9.5 Zachodniopomorskie
11.8 Mazowieckie
Zakres: 13.7 - 14.1
13.7 Dolnośląskie
13.8 Lubuskie
13.8 Pomorskie
14.1 Podkarpackie
Zakres: 14.8 - 15.5
14.8 Małopolskie
15.4 Podlaskie
15.5 Śląskie
Zakres: 15.9 - 16.3
15.9 Świętokrzyskie
16.1 Łódzkie
16.2 Kujawsko-Pomorskie
16.3 Opolskie
Zakres: 16.7 - 16.8
16.7 Lubelskie
16.7 Wielkopolskie
16.8 Warmińsko-Mazurskie
Krajowy Rejestr Nowotworów

ZASADY LECZENIA RAKA JAJNIKA



ETAPY CHOROBY vs. FILOZOFIA LECZENIA

LECZENIE CHIRURGICZNE

- PDS
- IDS
- SCS

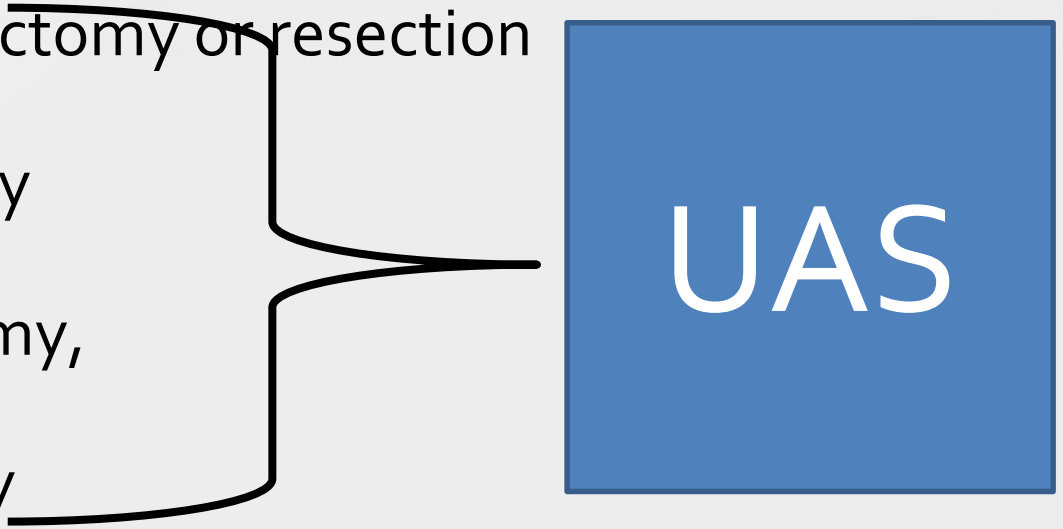
PDS/IDS – SIMPLE SURGERY:

- TAH+BSO;
- Infracolic omentectomy
- Limited excision of pelvic/para-aortic lymph nodes
- Peritoneal excision
- Segmental bowel resection

Ten zakres cytoredukcji jest do zrealizowania u większości pacjentów z rakiem jajnika praktycznie bez powikłań

RADICAL SURGERY:

- Radical oophorectomy
- Rectosigmoid colectomy
- Multiply bowel resections
- Extensive nodal debulking
- Diaphragm peritonectomy or resection
- Liver resection
- Porta hepatis surgery
- Splenectomy
- Distal pancreatectomy,
- Gastric resection
- Intrathoracic surgery



Literature on the impact of complete cytoreduction on survival of primary advanced epithelial ovarian cancer in the platinum/taxane era.

Study	Type of study	Age, yr	FIGO stage	No of Pts	Chemo agents[a]	Chemo route	Outcomes			Adjusted HR or RR (95% CI)	Adjustment
							RD, cm	N (%)	OS, mos		
Single institution study											
Eisenkop [10]	Retrospective	63	IIIC	408 (100%)	PC, TP	IV	0	351 (86%)	76.2	1 (Reference)	Completeness of cytoreduction and ranking system according to extent of disease
							0–1	41 (10%)	32.2	2.32 (1.20–5.37)	
							>1	16 (4%)	28.6	2.98 (1.74–5.23)	
Chi [11]	Retrospective	60	IIIC	465 (100%)	NA	IV	0	67 (15%)	106	1 (Reference)	Age, ascites, RD
							0–0.5	70 (15%)	66	2.07 (1.23–3.46)	
							0.6–1	99 (21%)	48		
							1–2	53 (11%)	33	3.70 (2.27–6.04)	
							>2	176 (38%)	34		
Aletti [12]	Retrospective	64	IIIC	194 (100%)	PC, TP	IV	0	46 (24%)	>84	1 (Reference)	Age, ASA, ascites, carcinomatosis, diaphragm involvement, bowel mesentery involvement, RD, and operative time
							0–1	85 (44%)	34	3.89 (2.27–7.11)	
							1–2	22 (11%)	25	6.25 (3.16–12.61)	
							>2	41 (21%)	16	13.00 (7.14–24.87)	
Salani [55]	Retrospective	63	III	97(78%)	PC, TP	IV	0	39 (31%)	46.5	1 (Reference)	Age, stage, ascites, number of bowel resections, and RD
			IV	28 (22%)			0–1	53 (42%)	28.3–37.8	2.2 (1.1–4.4)	
							>1	23 (18%)	12	5.9 (2.7–13.0)	
Peiretti [16]	Retrospective	58	IIIC	199 (76%)	NA	NA	0	115 (44%)	>61.3	1 (Reference)	NA
			IV	60 (24%)			0–0.5	50 (19%)	61.3	NA	
							0.6–1.0	33 (13%)	42.4	NA	
							1.0–2.0	18 (7%)	35.3	NA	
							>2	43 (17%)	42.6	NA	
Kommoss [18]	Retrospective	64	IIIB	23 (9%)	NA	IV	0	126 (47%)	49.6–68.8	1 (Reference)	Age, ECOG performance status, stage, histology, tumor grade, and RD
			IIIC	147 (55%)			0–1	87 (33%)	39.8–52.7	1.40 (0.70–2.82)	
			IV	97 (36%)			>1	54 (20%)	18.2	2.82 (1.49–5.33)	
Cooperative group trial											
Ozols [38]	Prospective	56	III	792 (100%)	TP, TC	IV	0	281 (35%)	>60	1 (Reference)	
							0–1	511 (65%)	44	NA	
Armstrong [43]	Prospective	56	III	415 (100%)	TP	IV, IP	0 (IP)	78 (38%)	NA	1 (Reference)	
							0–1 (IP)	127 (62%)	53	NA	
							0 (IV)	75 (36%)	78	1 (Reference)	
							0–1 (IV)	135 (64%)	39	NA	
Wimberger [56]	Retrospective	NA	IIB–IIIB	213 (28%)	PC, TP	IV	0	227 (30%)	>84	1 (Reference)	
			IIIC–IV	548 (72%)			0–1	247 (32%)	37	NA	
							>1	287 (38%)	31	NA	
Winter III [13]	Retrospective	57	III	1895 (100%)	TP, TC	IV	0	437 (23%)	71.9	1 (Reference)	Age, race, histology, tumor grade, GOG performance status, and RD
							0–1	791 (42%)	42.4	2.11 (1.78–2.49)	
							>1	667 (35%)	35	2.47 (2.09–2.92)	
Winter III [14]	Retrospective	59	IV	360 (100%)	TP, TC	IV	0	29 (8%)	64.1	1 (Reference)	Histology, disease site, and RD
							0–1	78 (21%)	28.7	1.93 (1.17–3.20)	
							1–5	164 (46%)	29.8	1.83 (1.14–2.94)	
							>5	89 (25%)	20.4	2.72 (1.65–4.47)	
du Bois [15]	Retrospective	59	IIB–IIIB	814 (26%)	TP, TC	IV	0	1046 (34%)	99.1	1 (Reference)	Age, performance status, stage, grade, histology, ascities, and RD
			IIIC	1779 (57%)	TC–TOP, TCE		0–1	975 (31%)	36.2	2.12 (1.85–2.43)	
			IV	530 (17%)			>1	1105 (35%)	29.6	1.20 (1.08–1.33)	
Bookman [40]	Prospective	59	III	3681 (85%)	TC–TOP, TCE		0	1044 (24%)	68	1 (Reference)	
			IV	631 (15%)	TC–others		0–1	1949 (45%)	40	NA	
							>1	1319 (31%)	33	NA	
Wimberger [17]	Retrospective	59	IV	573 (100%)	TP, TC	IV	0	70 (12%)	54.6	1 (Reference)	Age, ECOG performance status, stage, histology, disease site, carcinomatosis, and RD
							0–1	168 (29%)	25.8	1.87 (1.21–2.89)	
							>1	334 (58%)	23.9	2.13 (1.40–3.23)	

[a] PC, cisplatin/cyclophosphamide; TP, paclitaxel/cisplatin; TC, paclitaxel/carboplatin; TC–TOP, TC–Topotecan; TCE, TC-epirubicine; IV, intravenous; IP, intraperitoneal; HR, hazard ratio; RR, risk ratio; CI, confidence interval; RD, residual disease; NA, not available.

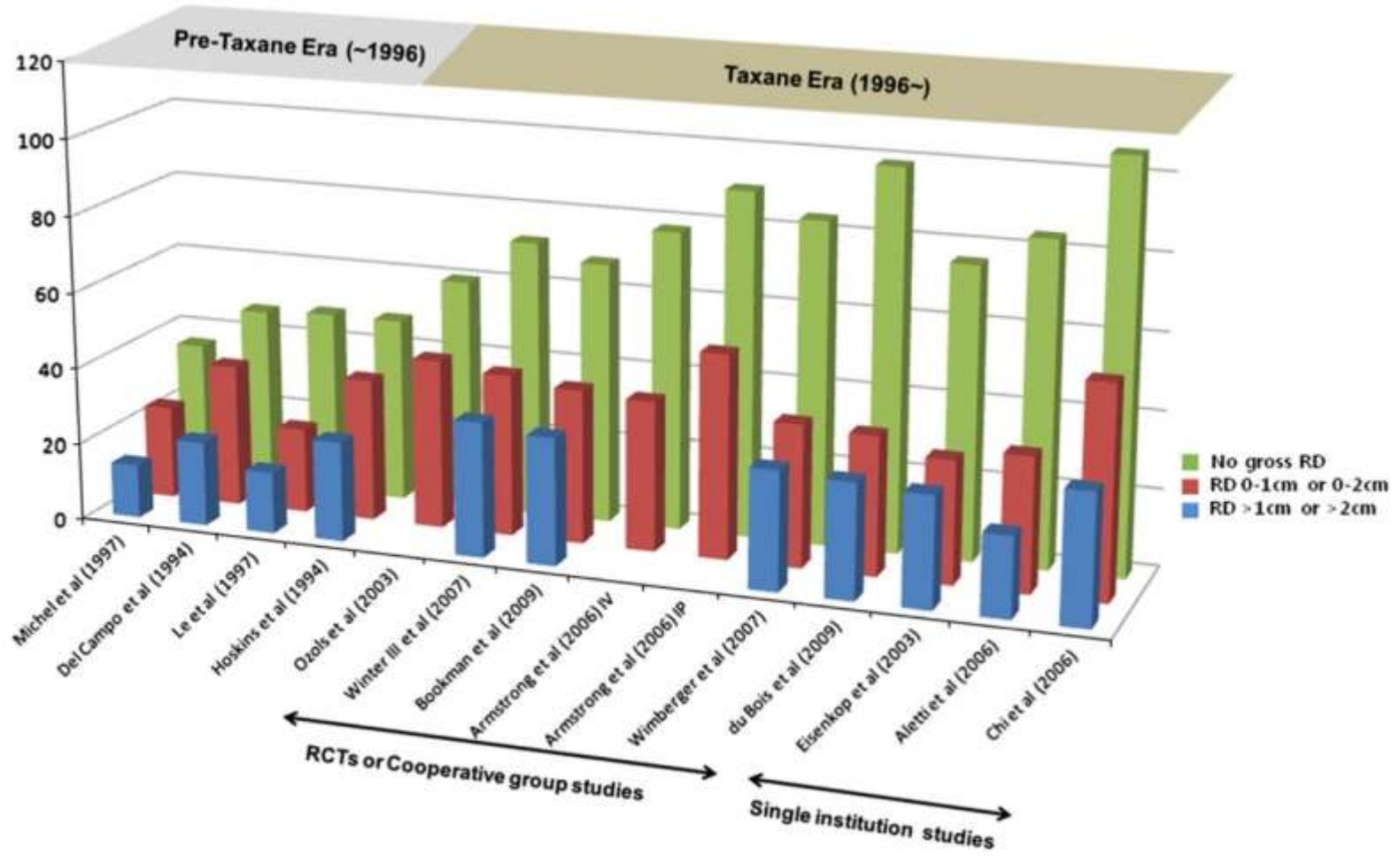


Fig. 1. Summary of literature demonstrating the survival differential according to the status of residual disease.

Table 2
Literature on the feasibility studies of radical cytoreductive surgical procedures for primary advanced epithelial ovarian cancer.

Study	No of Pts	Stage	Surgery	RD		Perioperative complications		
				0	≤1 or 2 cm	Overall	Related to procedure	Mortality
Radical oophorectomy, en bloc rectosigmoid colectomy, or modified posterior pelvic exenteration								
Hudson [57]	25	II–IV	Radical oophorectomy	NA	NA	2 (8.0)	2 (8.0)	1 (4)
Soper [58]	21	IIIC–IV	Rectosigmoid colectomy	2 (9.5)	9 (4.3)	NA	NA	NA
Scarabelli [59]	66	IIIC–IV	Rectosigmoid colectomy	24 (36.4)	28 (42.4)	13 (19.7)	1 (1.5)	0
Obermair [60]	65	IIIC–IV	Rectosigmoid colectomy	14 (21.5)	34 (52.3)	19 (29.2)	3 (4.6)	1 (1.5)
Clayton [61]	129	III–IV	Rectosigmoid colectomy	23 (17.8)	NA	38 (29.5)	3 (2.4)	4 (3.1)
Bristow [62]	31	IIIB–IV	Rectosigmoid colectomy	19 (61.3)	8 (25.8)	4 (12.9)	1 (3.2)	0
Mourton [63]	70	IIIC–IV	Rectosigmoid colectomy	19 (27.1)	36 (51.4)	22 (31.4)	4 (5.7)	1 (1.4)
Aletti [64]	57	IIIC–IV	Rectosigmoid colectomy	NA	NA	NA	1 (1.8)	0
Park [65]	46	III–IV	Rectosigmoid colectomy	20 (43.5)	25 (54.4)	15 (32.6)	2 (4.2)	0
Houvenaeghel [66]	168	II–IV	Posterior pelvic exenteration	85 (51.2)	NA	45 (26.8)	NA	NA
Tixier [67]	41	III–IV	Posterior pelvic exenteration	19 (46.3)	NA	14 (34.1)	4 (9.8)	3 (7.3)
Bowel resection								
Gillette-Cloven [68]	105	III–IV	Any	NA	33 (31.4)	18 (17.1)	10 (9.5)	6 (5.7)
Hoffman [69]	144	II–IV	Any	NA	NA	23 (16.0)	4 (2.8)	0
Estes [70]	48	IIIC–IV	Any	NA	25 (52.1)	5 (10.4)	4 (8.3)	2 (4.2)
Bidzinski [71]	39	III–IV	Any	NA	32 (82.1)	8 (20.5)	5 (12.8)	0
Salani [55]	125	IIIC–IV	Any	39 (31.2)	53 (42.4)	30 (29.4)	11 (8.8)	2 (5.9)
Bristow [72]	33	IIIC–IV	Transverse colectomy	11 (33.3)	19 (57.6)	NA	NA	1 (3.0)
Silver [73]	19	IIIC	Extended left colon resection	18 (94.7)	1 (5.3)	3 (15.8)	NA	1 (5.3)
Song [74]	22	IIIC–IV	Total colectomy	10 (45.5)	10 (45.5)	7 (31.8)	0	0
Diaphragm peritonectomy, resection, or coagulation								
Montz [75]	14	III	Peritonectomy/resection	10 (71.4)	3 (21.4)	NA	1 (7.1)	0
Silver [76]	7	III–IV	Resection	7 (100)	2 (28.6)	0	0	0
Cliby [77]	41	III–IV	Resection	33 (80.1)	4 (9.8)	8 (19.5)	6 (14.6)	0
Chêreau [78]	18	III–IV	Any	16 (88.9)	0	5 (27.8)	4(22.2)	0
Einenkel [79]	30	IIIC–IV	Any	17 (56.7)	3 (10.0)	14 (46.7)	11 (36.7)	1 (3.3)
Gouy [80]	63	IIIC–IV	Any	60 (95.2)	1 (1.6)	11 (17.5)	6 (9.5)	0
Splenectomy, distal pancreatectomy, or en bloc left upper quadrant (LUQ) resection								
Sonnendecker [81]	6	III–IV	Splenectomy	NA	NA	5 (83.3)	NA	1 (16.7)
Ayhan [82]	34	IIIC	Splenectomy	NA	34 (100)	10 (29.4)	NA	3 (8.8)
Yildirim [83]	6	IIIC	Splenectomy/distal pancreatectomy	NA	6 (100)	4 (66.7)	1 (16.7)	0
Eisenkop [84]	49	IIIC	Splenectomy	NA	49 (100)	20 (40.8)	3 (6.1)	1 (2.0)
Hoffman [85]	6	IIIC	En bloc LUQ resection	NA	6 (100)	3 (50)	2 (33.3)	0
Kehoe [86]	17	IIIC–IV	Splenectomy/distal pancreatectomy	NA	16 (94.1)	NA	4 (23.5)	0
Porta hepatis or celiac axis								
Song [87]	2	IIIC–IV	Tumor resection	1 (50)	1 (50)	0	0	0
Martinez [88]	20	III–IV	Celia LN dissection	NA	NA	10 (36%)	1 (0.5)	1 (0.5)

RD, residual disease; LN, lymph node; NA, not available.

PDS=IDS (brak różnic w R i OS)

Table 3
Literature on neoadjuvant chemotherapy and interval cytoreductive surgery for primary advanced epithelial ovarian cancer.

Study	Age, yr	Stage	Control	Neoadjuvant				Optimal RD		OS, mos
			N	N	Regimen	Cycles	Cytoreduction	RD, cm	Control vs. neoadjuvant	Control vs. neoadjuvant
Kuhn [97]	64	IIIC	31	32	TC	3	32 (100%)	≤2	20 (65%) vs. 26 (84%)	23 vs. 42
Morice [98]	56	IIIC	23	48	TP, TC	3	57 (98%)	0	15 (54%) vs. 29 (51%)	20 vs. 28
		IV	5	10				0–2	13 (46%) vs. 19 (33%)	46 vs. 28
Fanfani [99]	57	IIIC	111	73	TP, TC	3	62 (85%)	0	48 (43%) vs. 28 (37%)	NA
								0–2	63 (57%) vs. 24 (34%)	54 vs. 27
Hegazy [100]	56	IIIC	14	11	PC	3	18 (66%)	≤1	20 (63%) vs. 13 (72%)	28 vs. 25
		IV	18	16						
Hou [101]	63	IIIC	87	29	PC, TC	6	61 (97%)	≤1	77 (71%) vs. 58 (95%)	47 vs. 46
		IV	22	34						
Vergote [103]	62	IIIC	257	253	NA	3	295 (88%)	0	61 (19%) vs. 151 (51%)	38 vs. 45
		IV	77	81				0–1	70 (22%) vs. 87 (30%)	27 vs. 32

PC, cisplatin/cyclophosphamide; TP, paclitaxel/cisplatin; TC, paclitaxel/carboplatin; RD, residual disease; NA, not available.

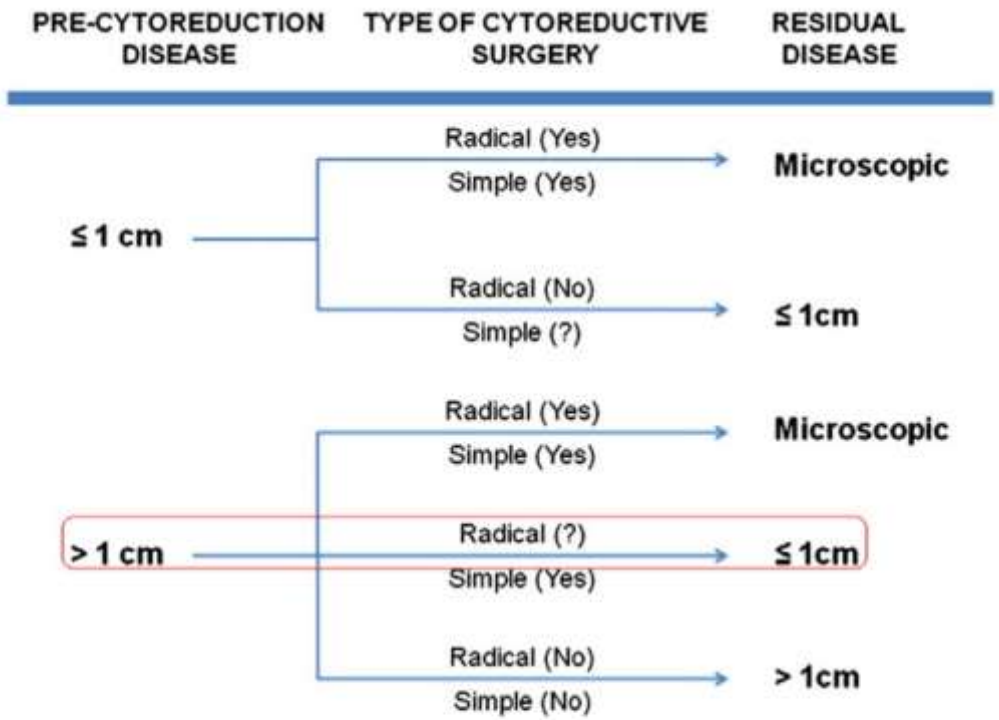


Fig. 2. Recommendations by Chang and Bristow for the extent of resection for primary cytoreductive surgery. Our study addresses the role of extensive surgery to go from bulky disease to disease ≤ 1 cm, highlighted in red.
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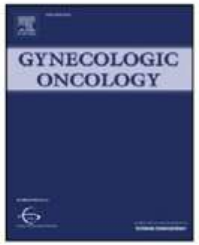


Optimal (≤1 cm) but visible residual disease: Is extensive debulking warranted?

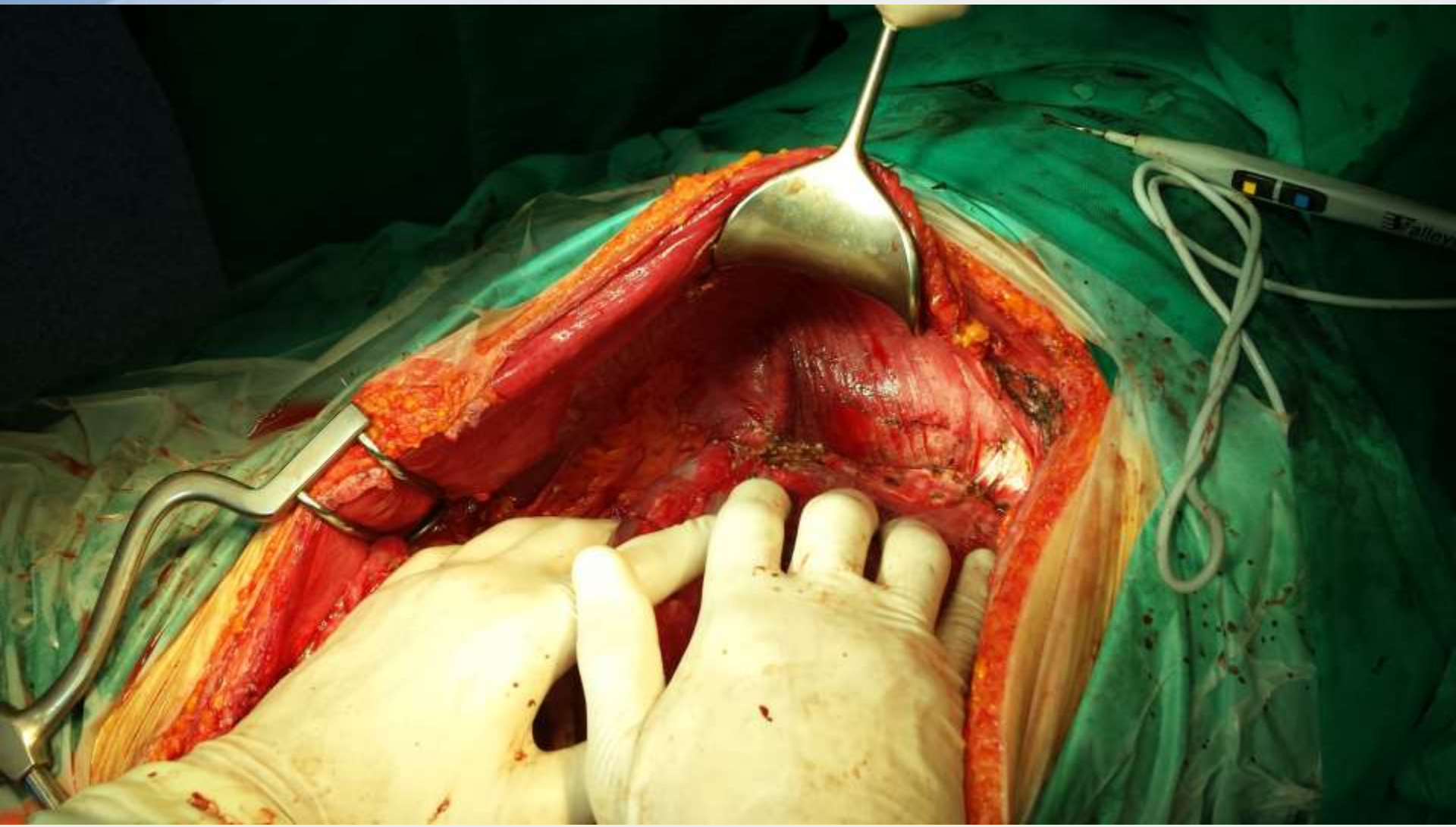
J.N. Barlin [a], K.C. Long [a], E.J. Tanner [a], G.J. Gardner [a,b], M.M. Leitao Jr. [a,b], D.A. Levine [a,b], Y. Sonoda [a,b], N.R. Abu-Rustum [a,b], R.R. Barakat [a,b], D.S. Chi [a,b,*]

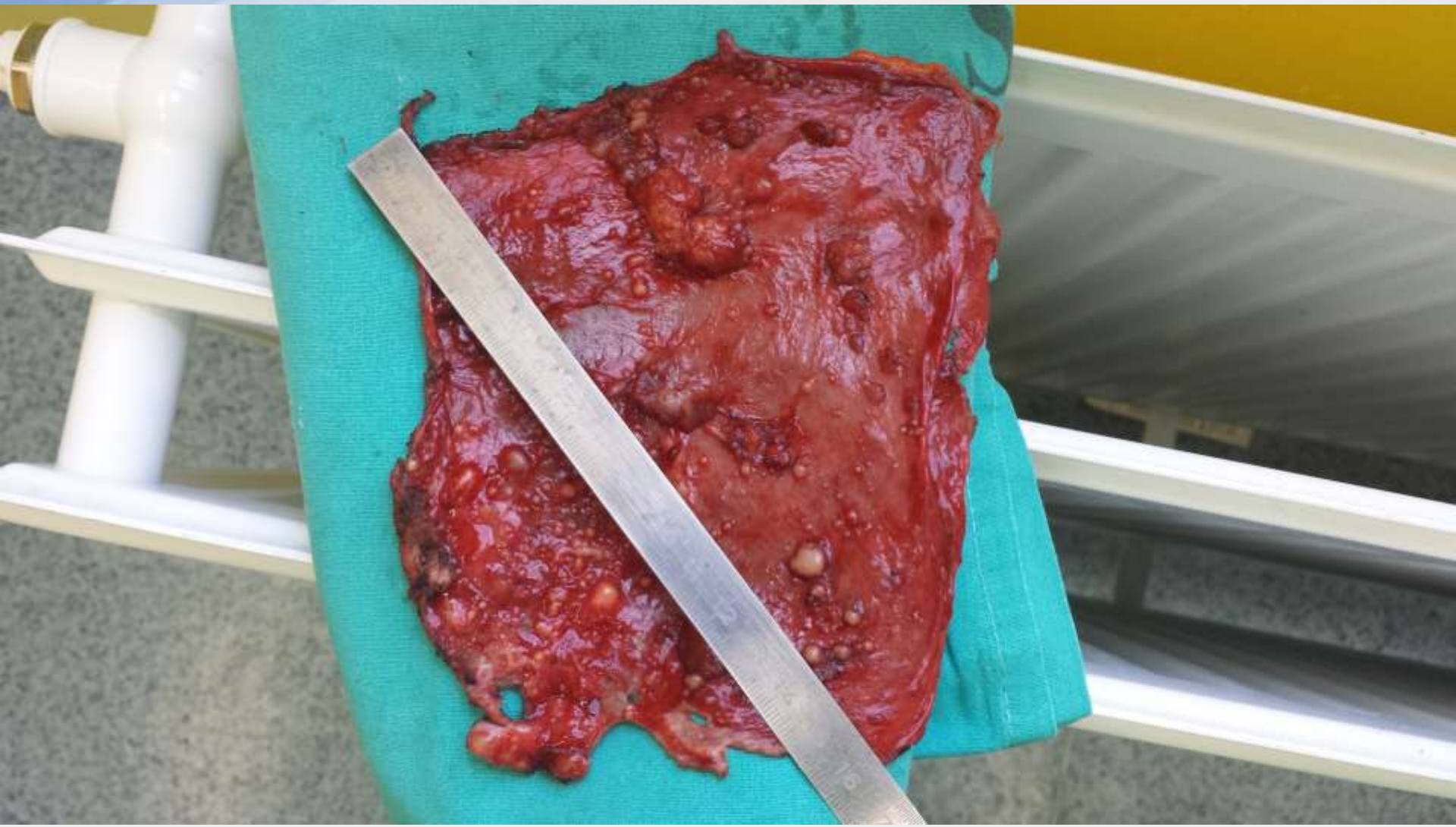
[a] *Department of Surgery, Gynecology Service, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA*
[b] *Department of Obstetrics and Gynecology, Weill Cornell Medical College, New York, NY 10065, USA*

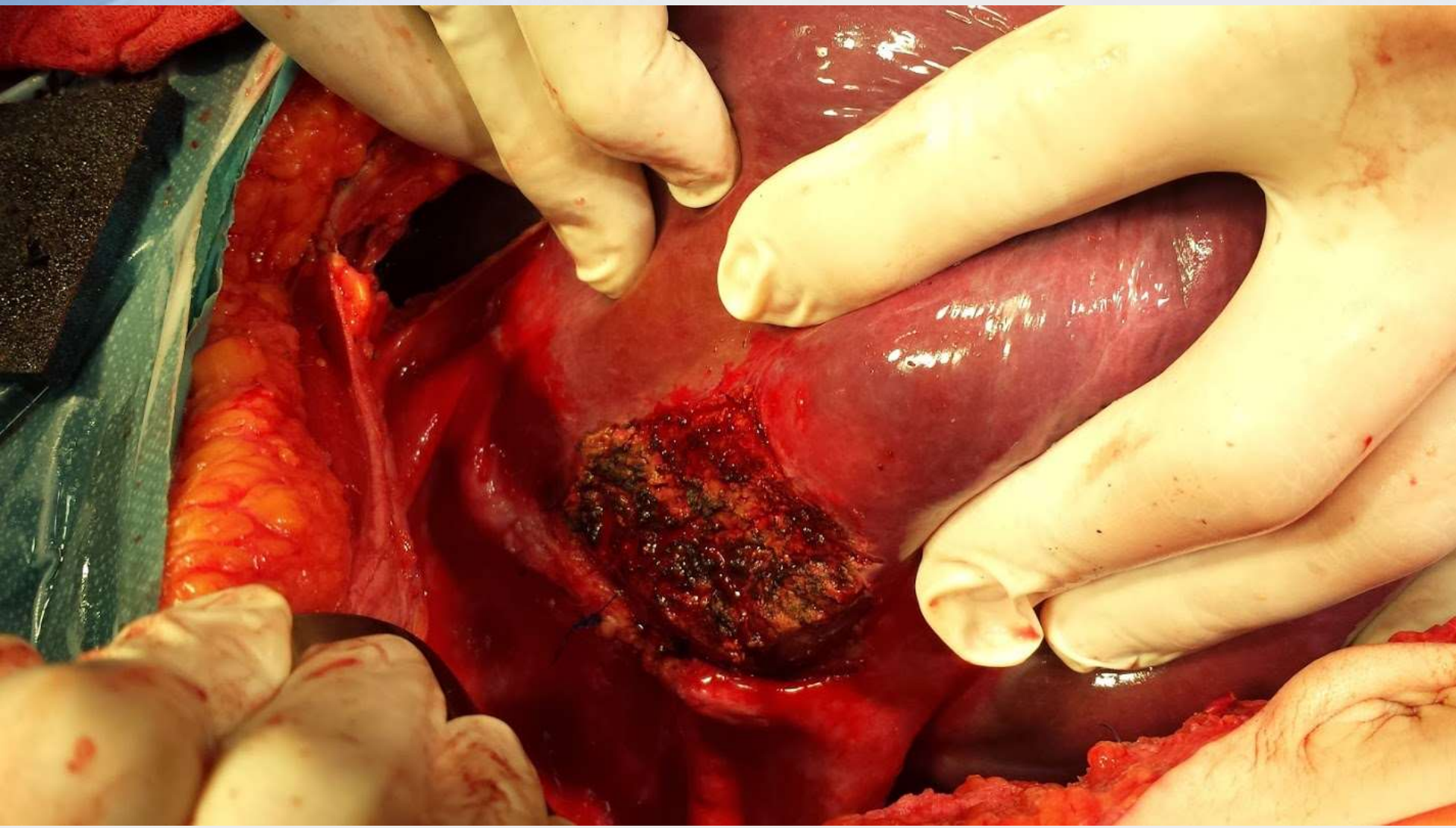
Tak ponieważ:

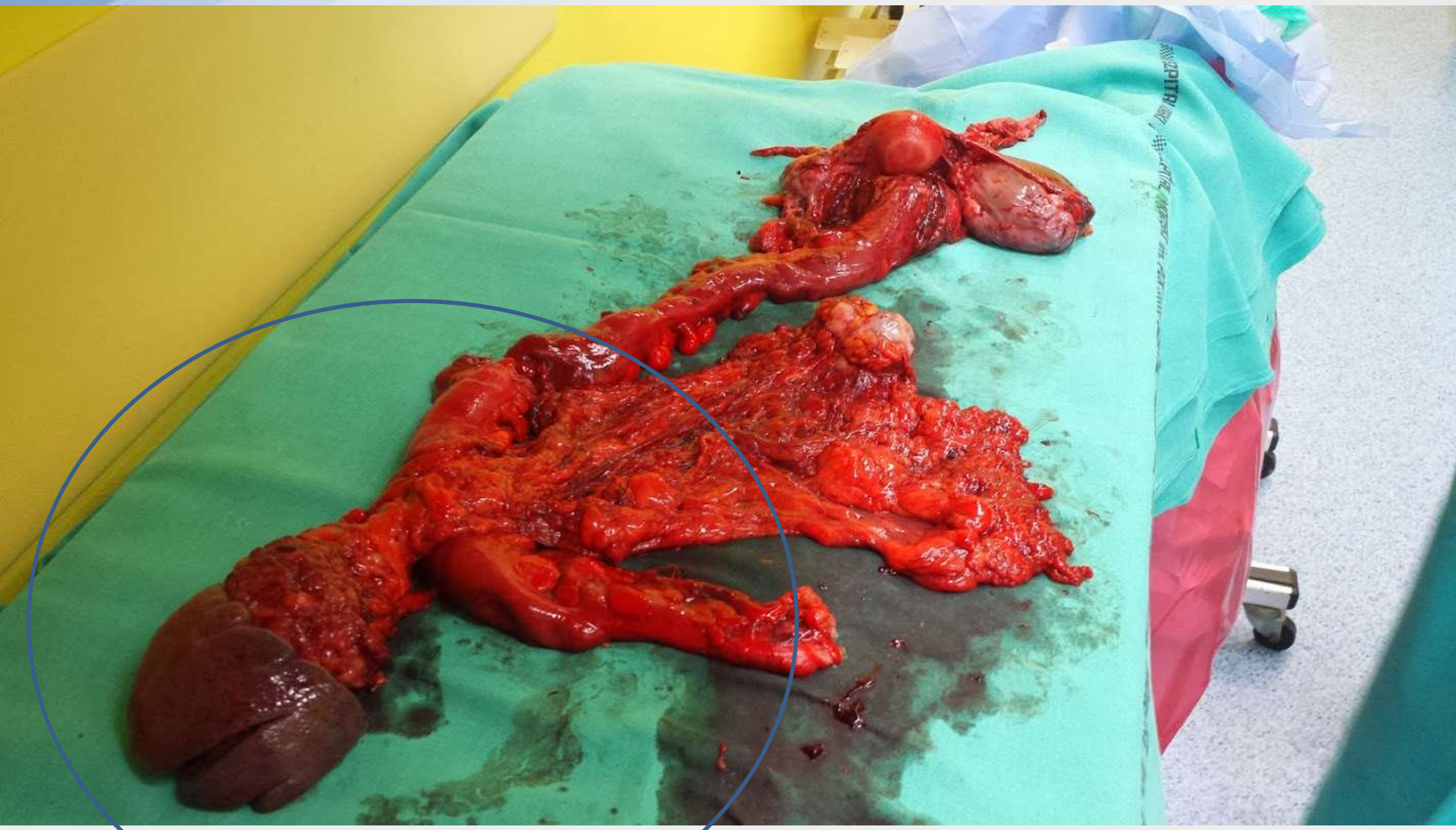
- Konieczność wykonania UAS nie obniża przeżycia u pacjentek z widzialną chorobą resztkową do 1 cm
- Dodatkowo pozostawienie choroby resztkowej do 1 cm na jelicie cienkim (surowicówka/krezka) nie pogarsza rokowania chorych
- Nie należy dyskwalifikować pacjentek u których osiągnięto optymalną cytoredukcję (R<1cm) z UAS tylko dlatego że pozostanie u nich widzialna choroba resztkowa nawet jeśli zlokalizowana jest na krezce jelita cienkiego.

upper abdomen surgery

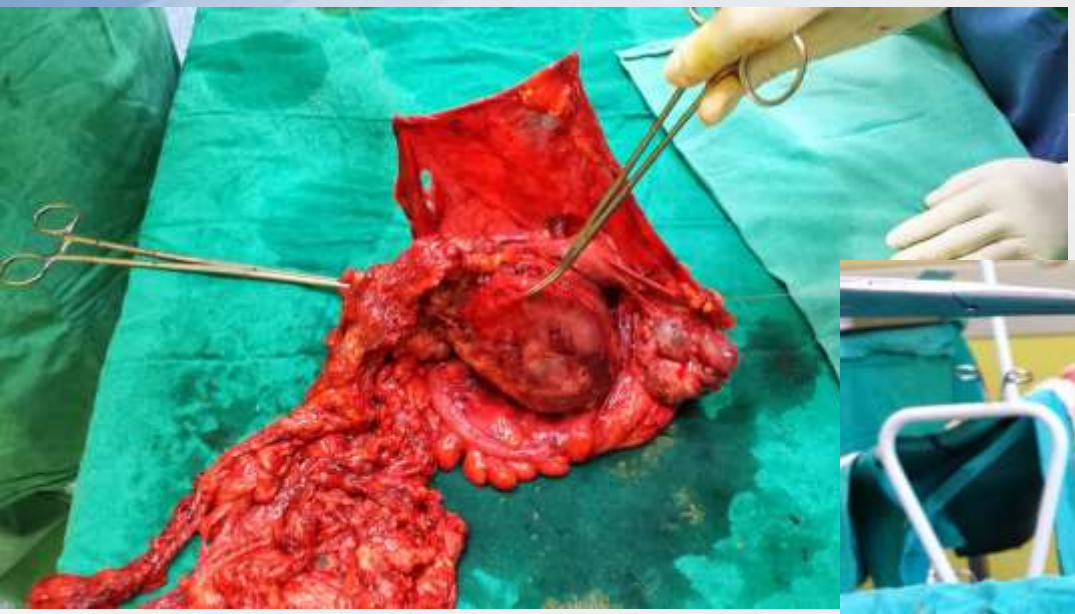


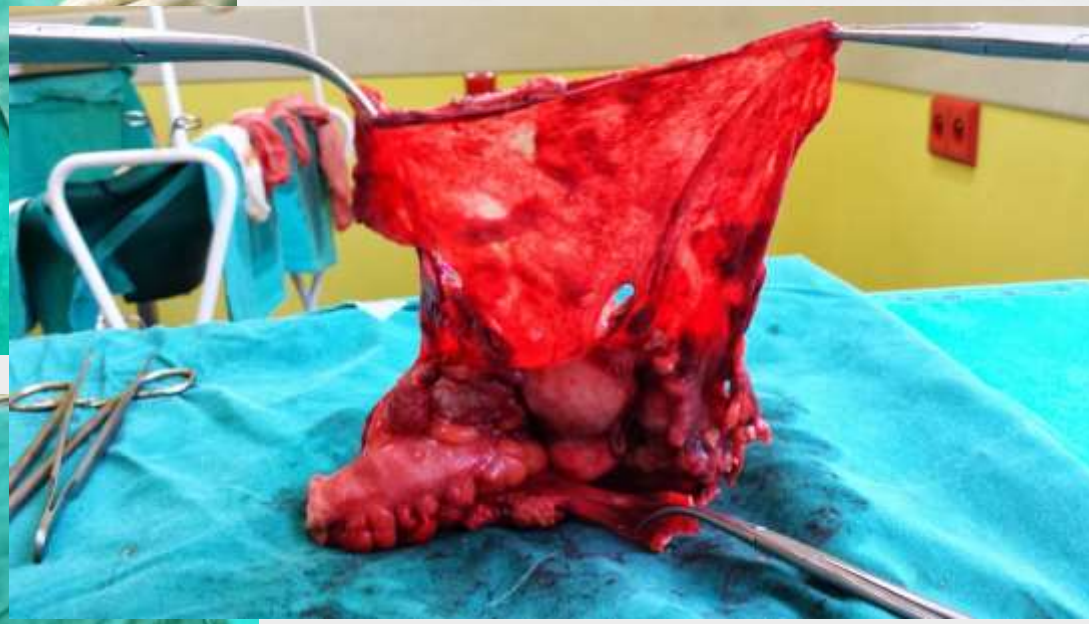


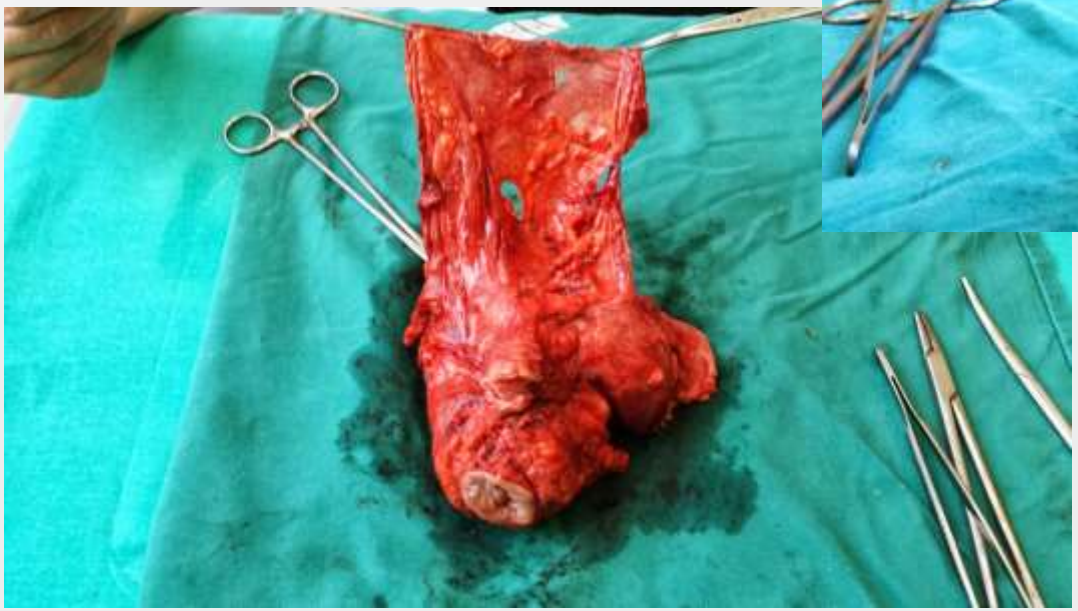


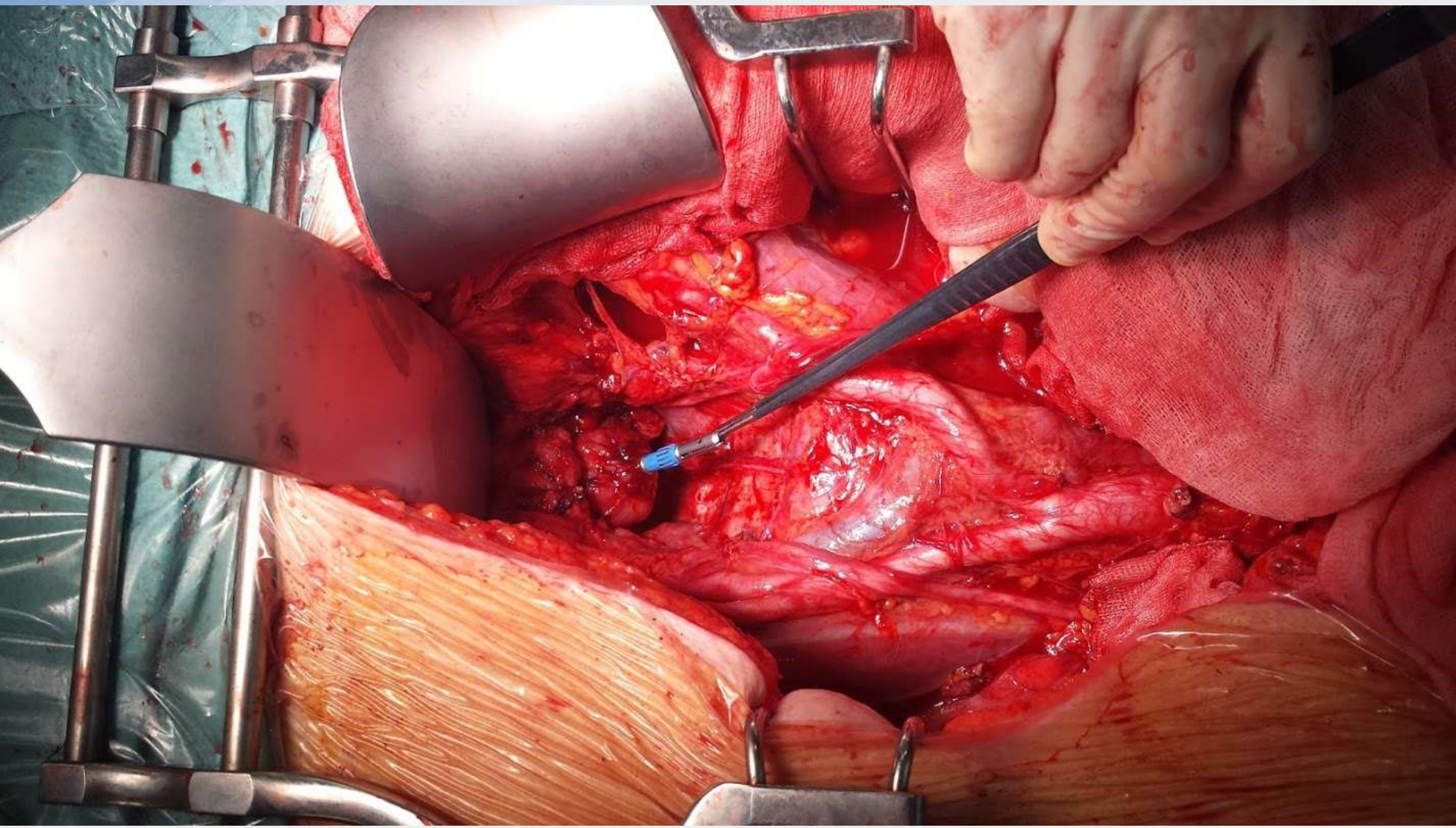


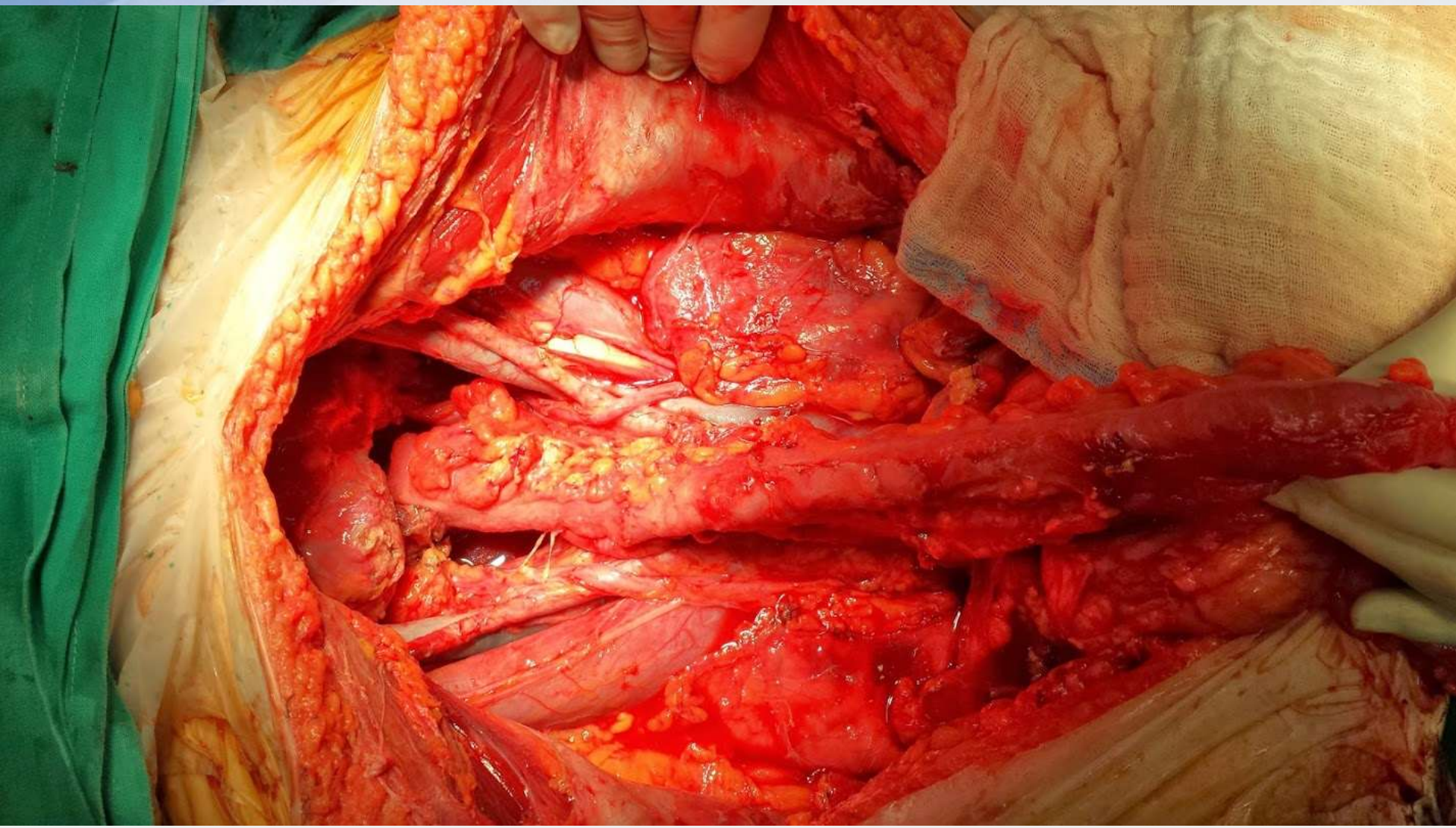
Radykalna miednica mniejsza



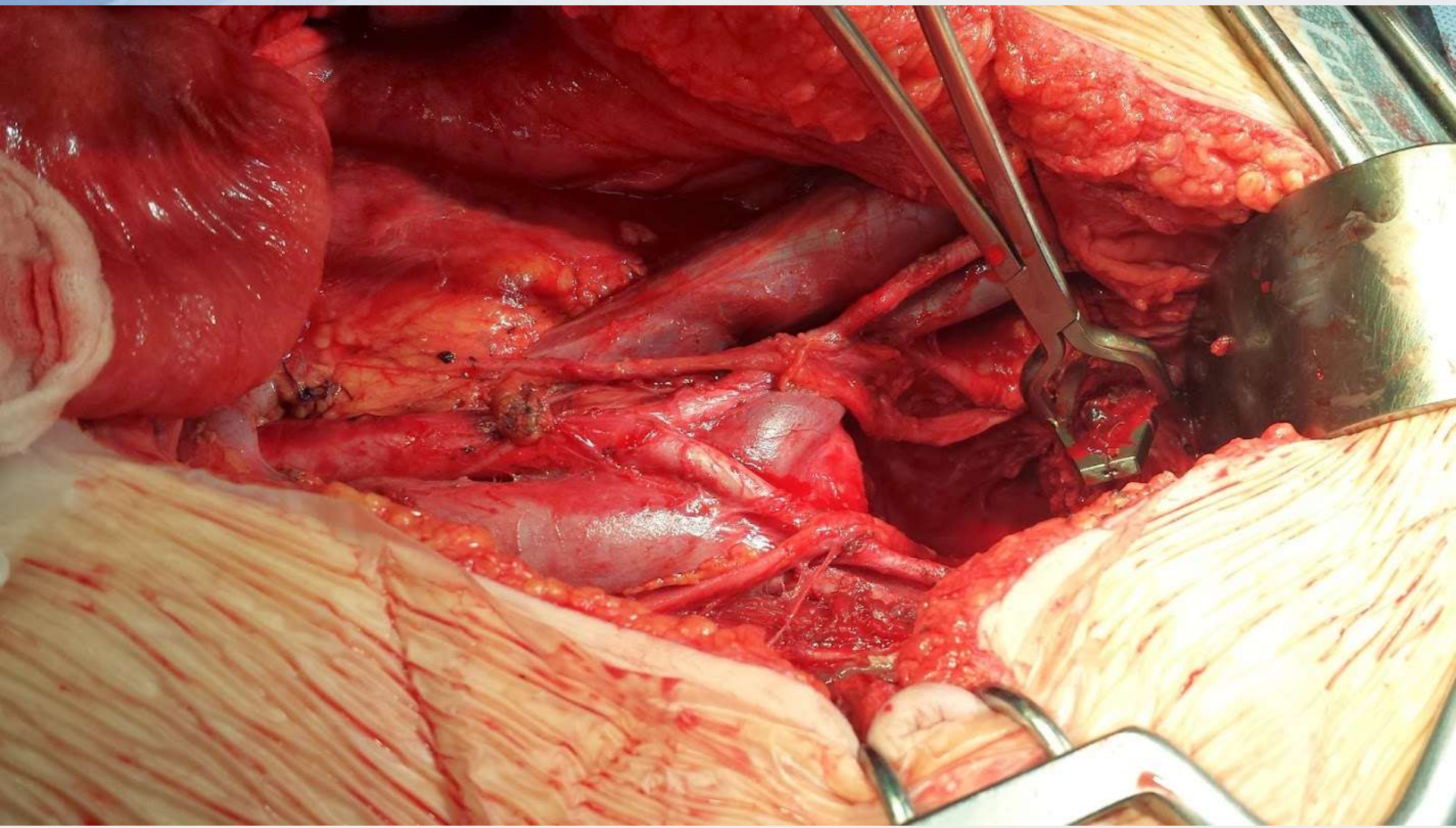




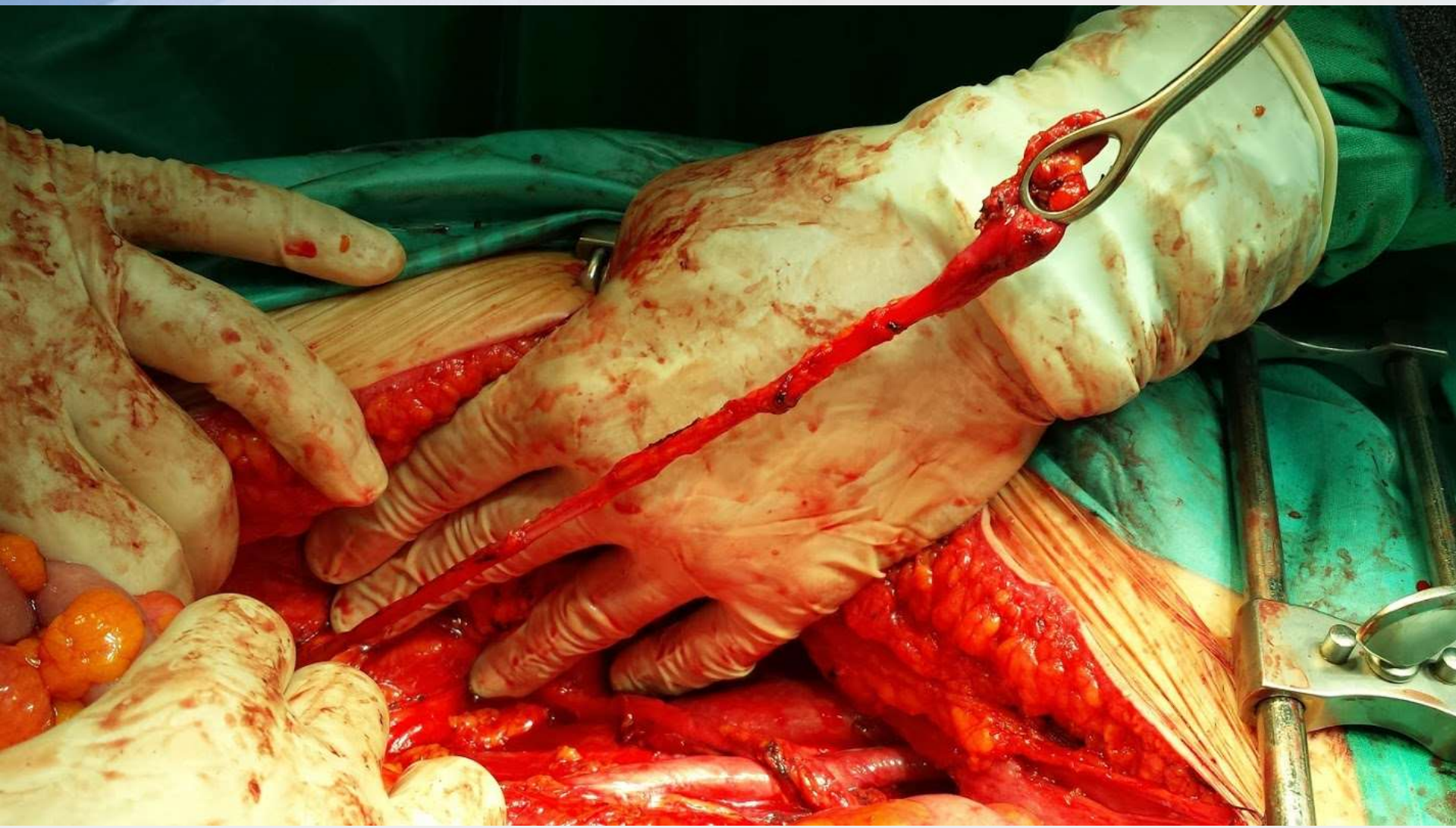




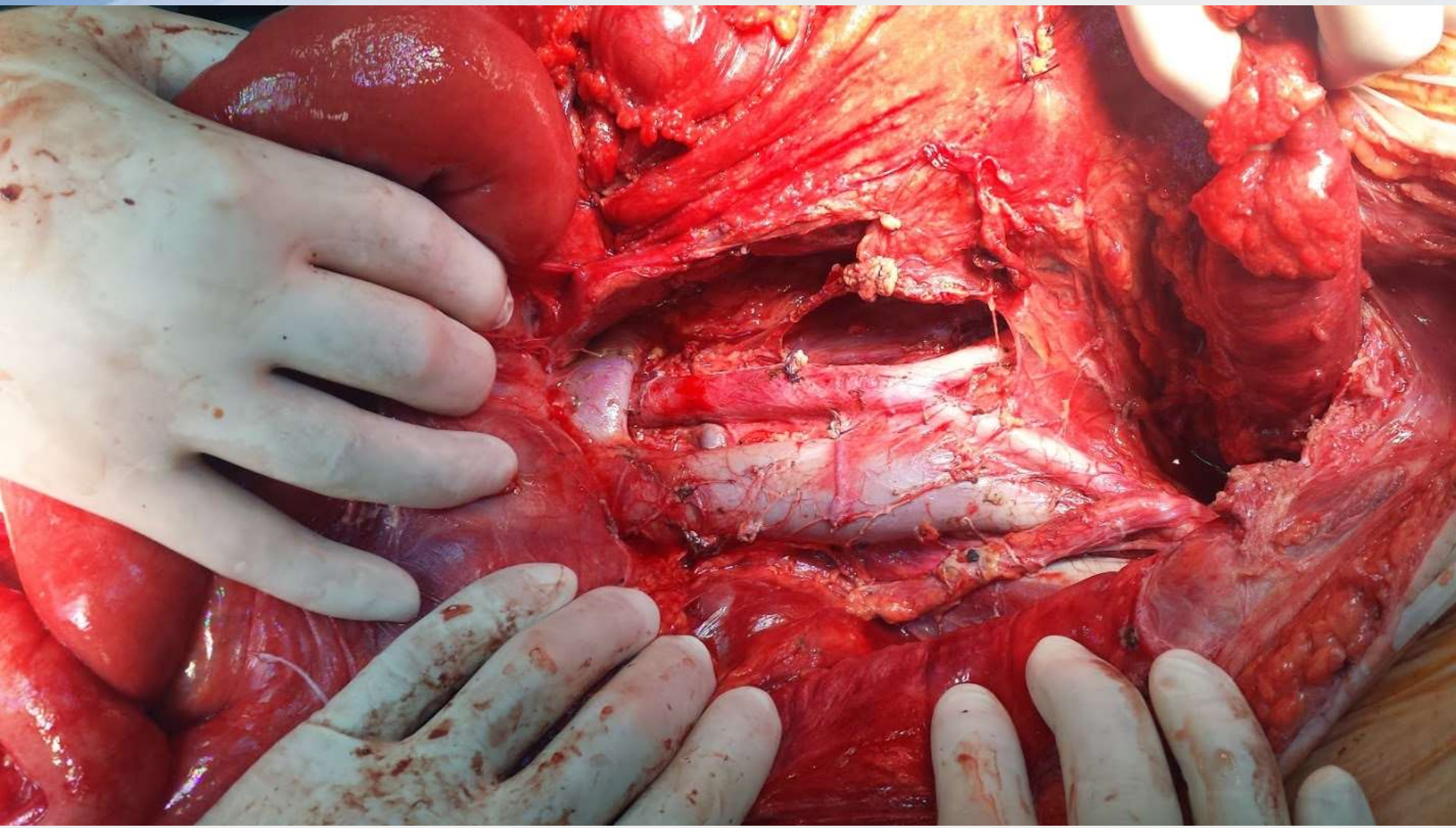
PLND



naczynia jajnikowe



PALND



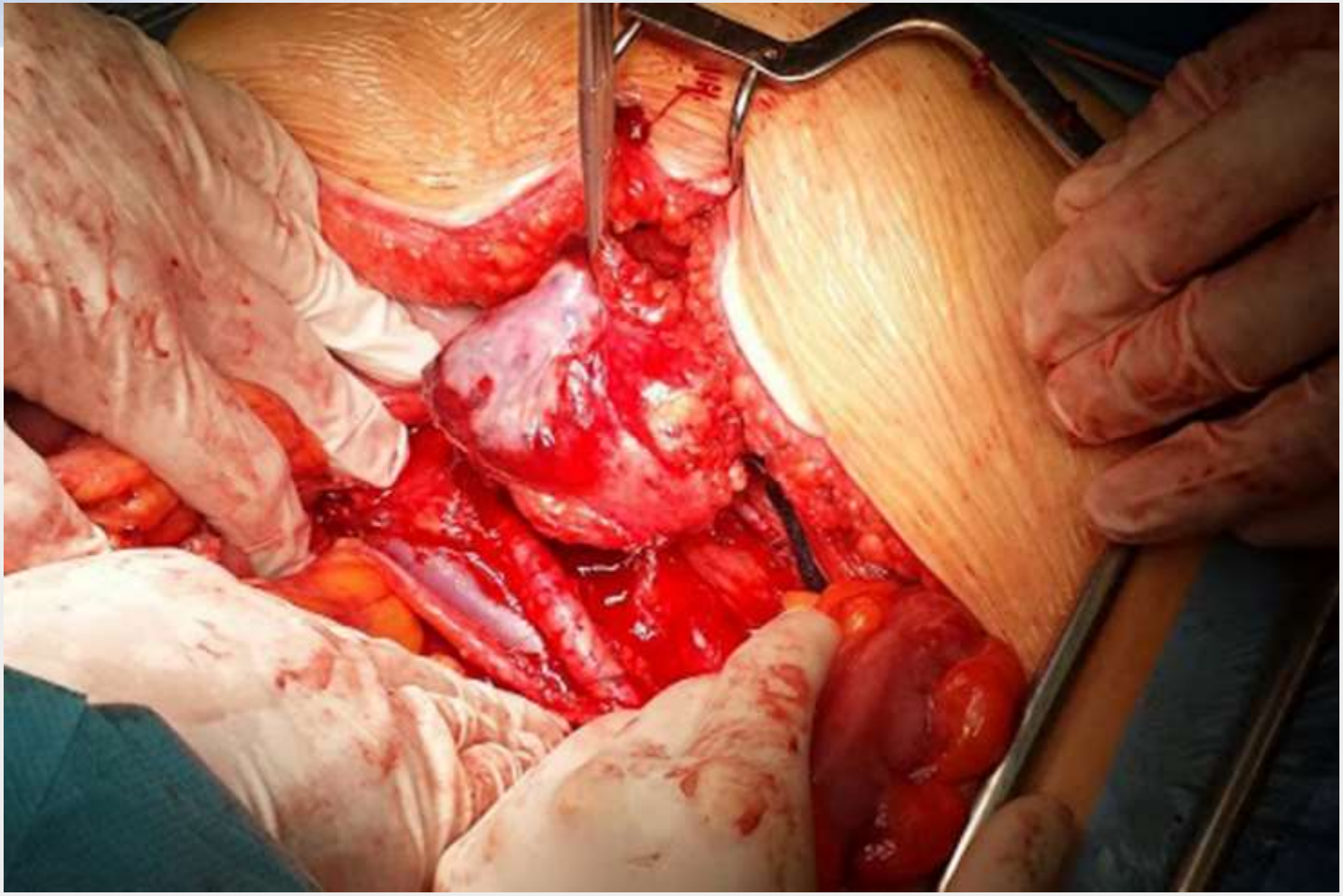
Secondary Cytoreductive Surgery

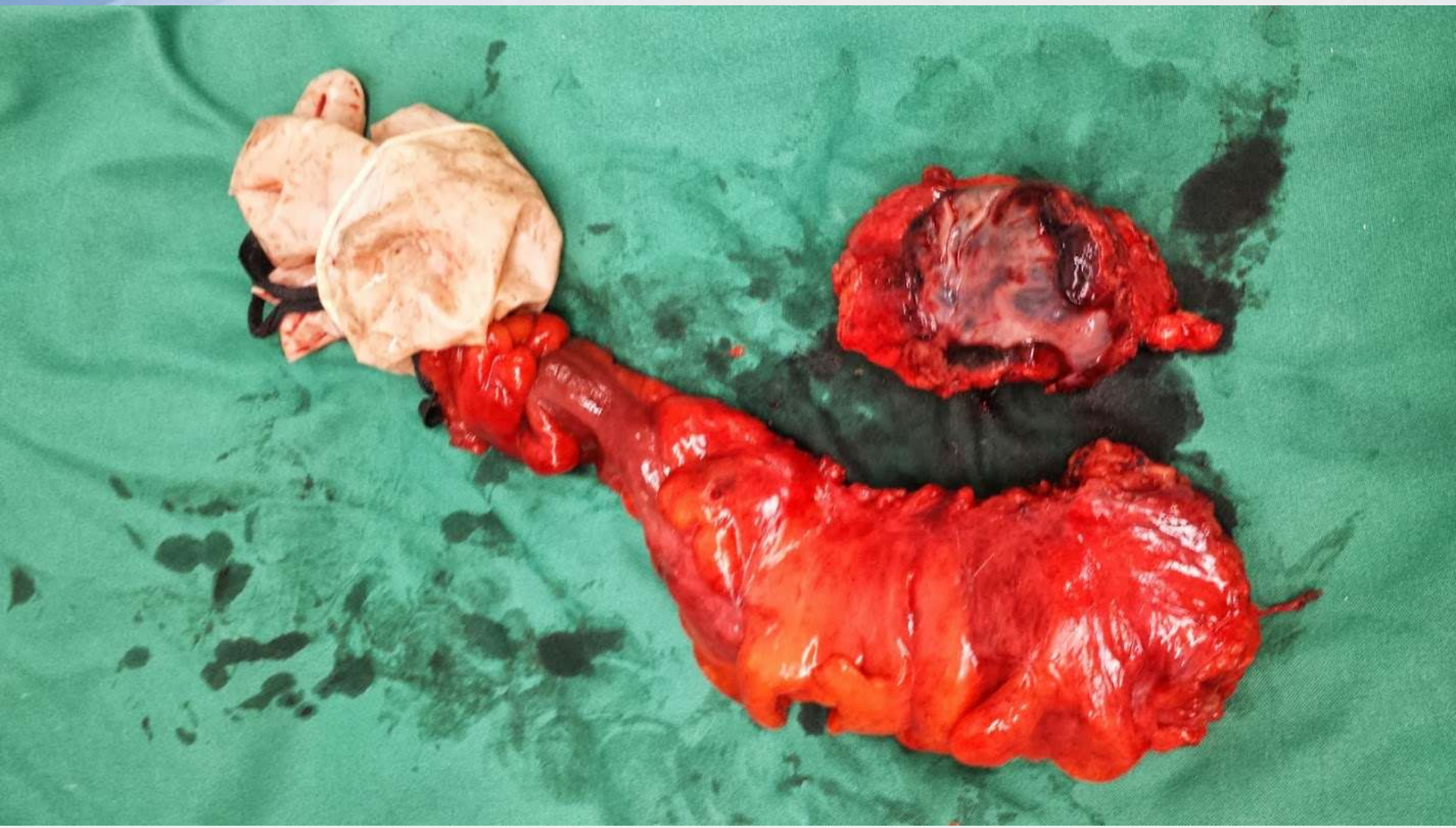
Goal of surgery: No gross residual disease

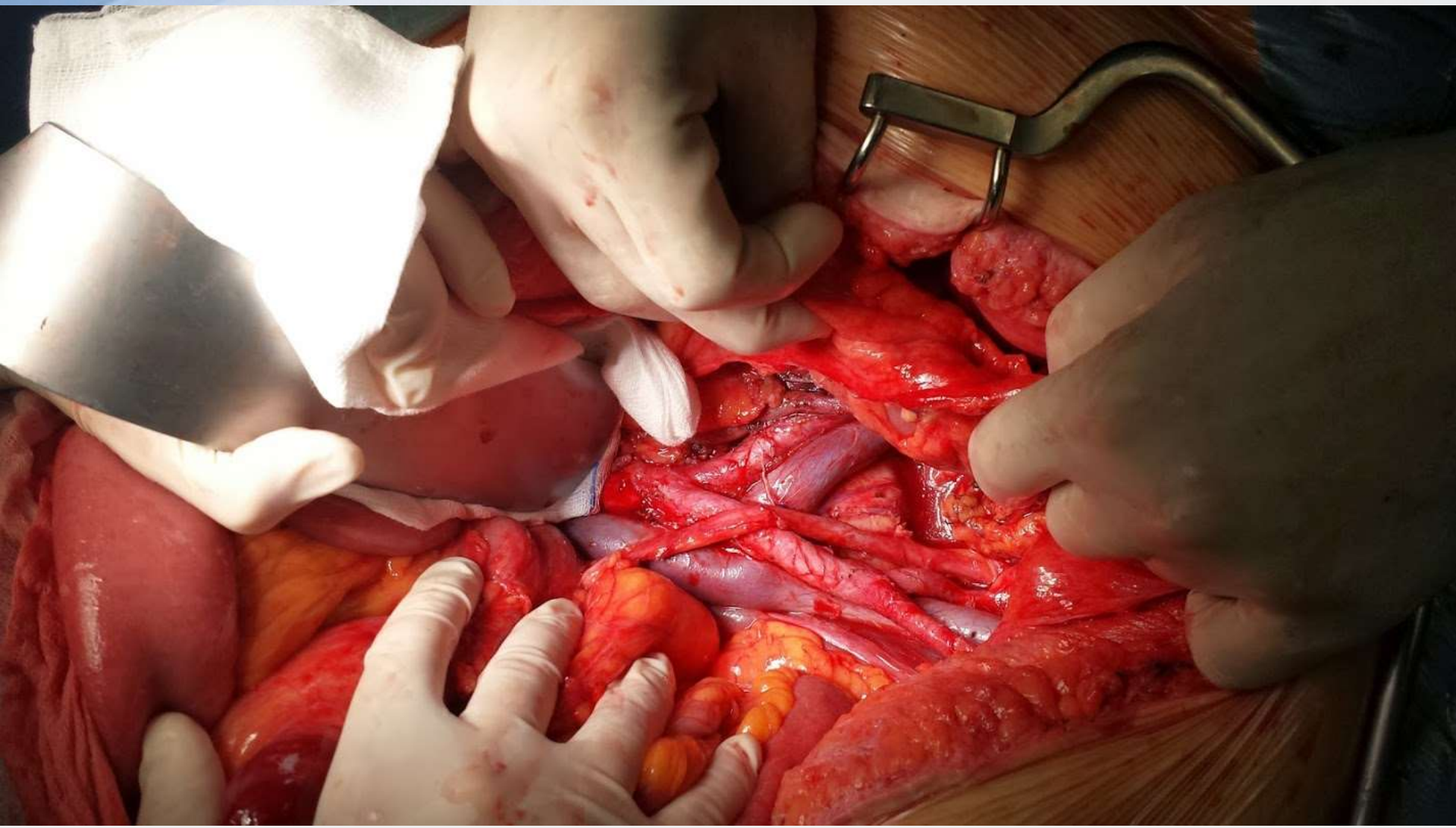
DFI	Single Site	Multiple Sites: No Carcinomatosis	Carcinomatosis
6-12 mos	**Suggest SC**	**Offer SC**	**No SC**
12-30 mos	**Suggest SC**	**Suggest SC**	**Offer SC**
> 30 mos	**Suggest SC**	**Suggest SC**	**Suggest SC**

DFI = disease-free interval; mos = months; SC = secondary cytoreduction.

Chi DS, et al. *Cancer.* 2006;106(9):1933-1939.







Dokumentowanie leczenia chirurgicznego

- Wynik hist-pat. dostarcza informacji do stagingu
- Opis choroby resztowej dostarcza informacji do:

  -Terapii adjuvantowej/ podtrzymującej

  -Odróżnienie prawdziwej wznowy od choroby przetrwałej.

R<1 cm -optimal microscopic; **R<1cm** optimal macroscopic; **R>1** cm suboptimal

Take home

NOWE FIGO 2014

FIGO Ovarian Cancer Staging
Effective Jan. 1, 2014

(Changes are in italics.)

STAGE I: Tumor confined to ovaries				
OLD			NEW	
IA	Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washings/ascites.		IA	Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washings.
IB	Tumor involves both ovaries otherwise like IA.		IB	Tumor involves both ovaries otherwise like IA.
IC	Tumor involves 1 or both ovaries with any of the following: capsule rupture, tumor on surface, positive washings/ascites.		*IC Tumor limited to 1 or both ovaries*	
			IC1	*Surgical spill*
			IC2	*Capsule rupture before surgery or tumor on ovarian surface.*
			IC3	*Malignant cells in the ascites or peritoneal washings.*

STAGE II: Tumor involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer				
OLD			NEW	
IIA	Extension and/or implant on uterus and/or Fallopian tubes		IIA	Extension and/or implant on uterus and/or Fallopian tubes
IIB	Extension to other pelvic intraperitoneal tissues		IIB	Extension to other pelvic intraperitoneal tissues
IIC	IIA or IIB with positive washings/ascites.			

Old stage IIC has been eliminated

STAGE III: Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes

OLD		NEW		
IIIA	Microscopic metastasis beyond the pelvis.	*IIIA (Positive retroperitoneal lymph nodes and /or microscopic metastasis beyond the pelvis)*		
		IIIA1	*Positive retroperitoneal lymph nodes only*	
			IIIA1(i)	*Metastasis ≤ 10 mm*
			IIIA1(ii)	*Metastasis > 10 mm*
		IIIA2	*Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes*	
IIIB	Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm in greatest dimension.	IIIB	*Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.*	
IIIC	Macroscopic, extrapelvic, peritoneal metastasis > 2 cm in greatest dimension and/or regional lymph node metastasis.	IIIC	*Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.*	

STAGE IV: Distant metastasis excluding peritoneal metastasis				
OLD			NEW	
IV	Distant metastasis excluding peritoneal metastasis. Includes hepatic parenchymal metastasis.		*IVA*	*Pleural effusion with positive cytology*
			IVB	Hepatic and/or *splenic parenchymal* metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Other major recommendations are as follows:

- Histologic type including grading should be designated at staging
- Primary site (ovary, Fallopian tube or peritoneum) should be designated where possible
- Tumors that may otherwise qualify for stage I but involved with dense adhesions justify upgrading to stage II if tumor cells are histologically proven to be present in the adhesions

CHEMIOTERAPIA I rzutu

- IV

  GOG-111

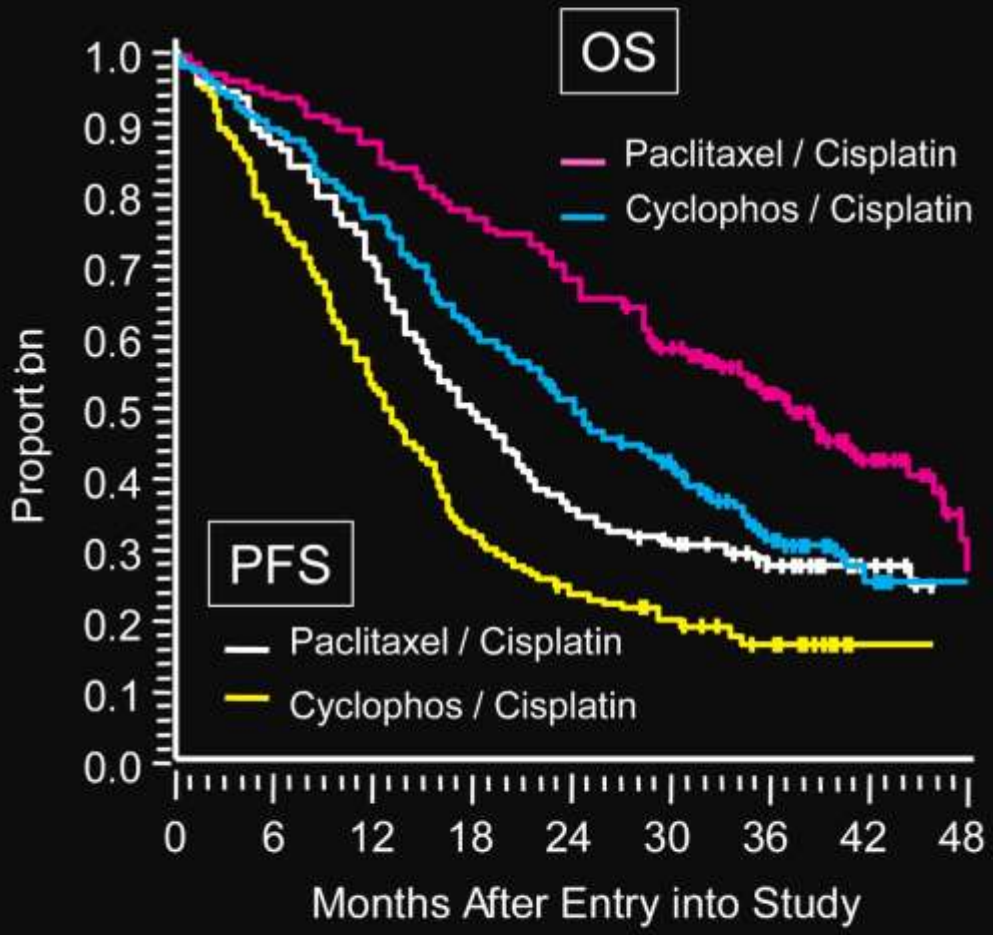
  GOG-158

- IP

  GOG-172

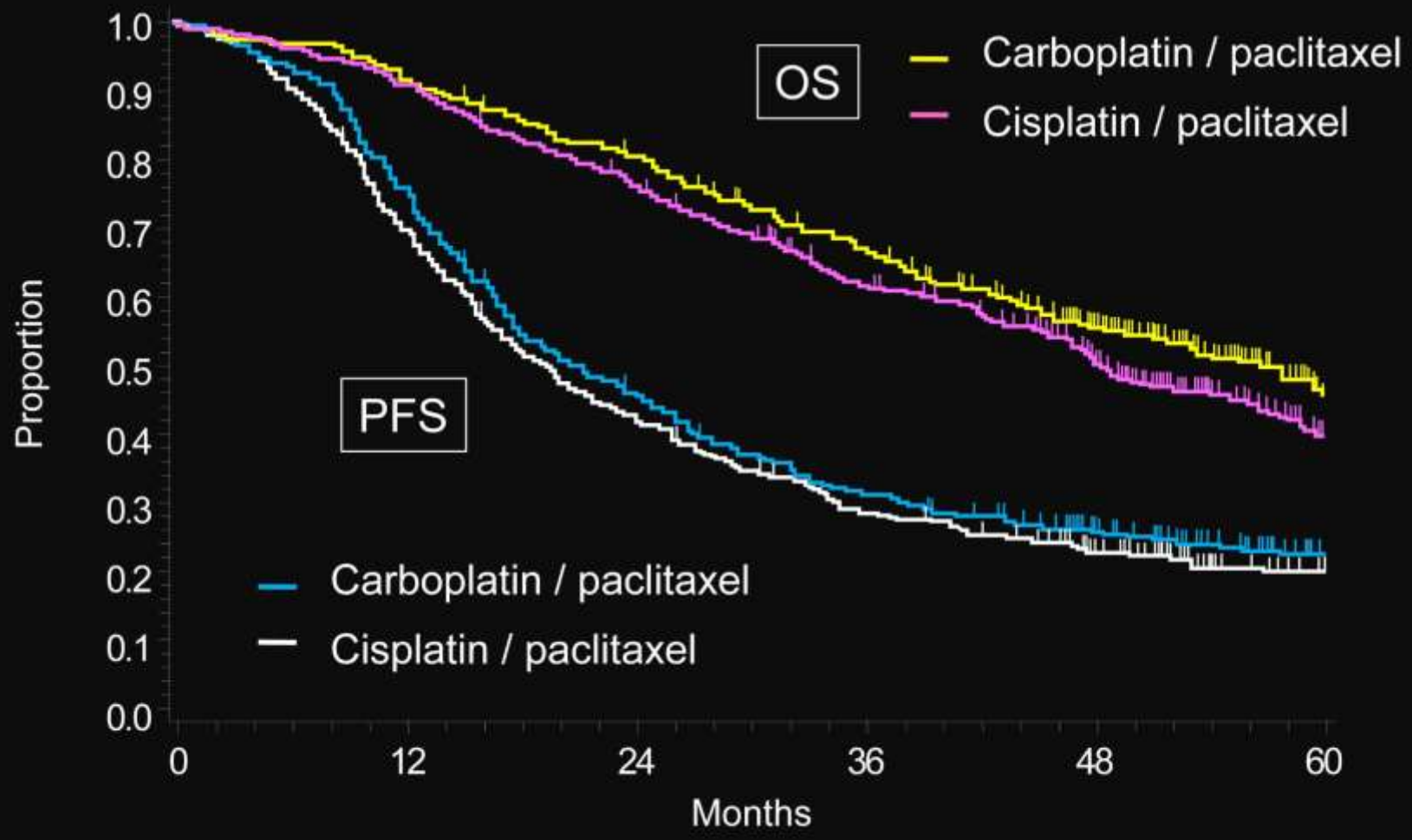
GOG-111

- Cisplatin / cyclophosphamide vs cisplatin / paclitaxel
- Firstline paclitaxel ↑ PFS and OS in advanced disease



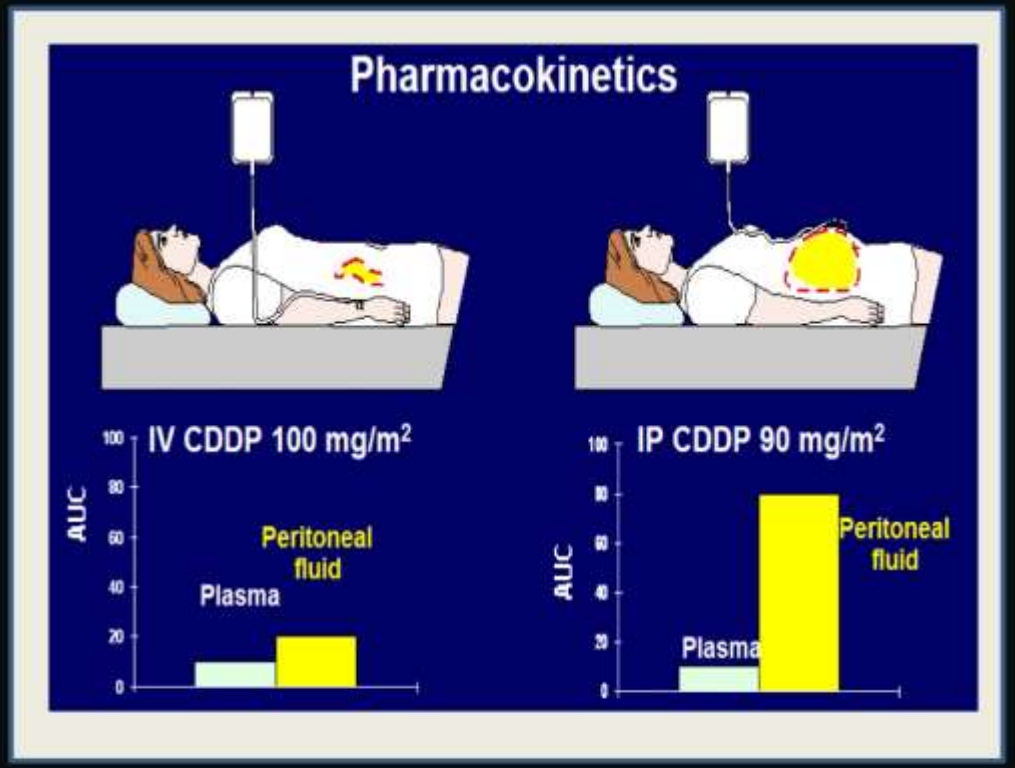
McGuire WP, et al. *N Engl J Med.* 1996;334(1):1-6.

GOG-158



Ozol RF, et al. *J Clin Oncol.* 2003;21(17):3194-3200.

- **GOG-172**
  - Paclitaxel + IV cisplatin vs paclitaxel + IP cisplatin
  - IP cisplatin ↑ OS in optimally debulked stage III disease



CDDP = cisplatin.

Armstrong DK, et al. *N Engl J Med.* 2006;354(1):34-43; Figure from GOG Intraperitoneal Chemotherapy Workshop, 2006. Available at: http://www.gog.org/ipchemoed/ipchemoed.html. Accessed March 11, 2011.

GOG-172: SCHEMAT

Regimen 1
Intravenous

D1 IV — D2 IV

D1: IV Paclitaxel 135 mg/m²/24h
D2: IV Cisplatin 75 mg/m²

Regimen 2
Intraperitoneal

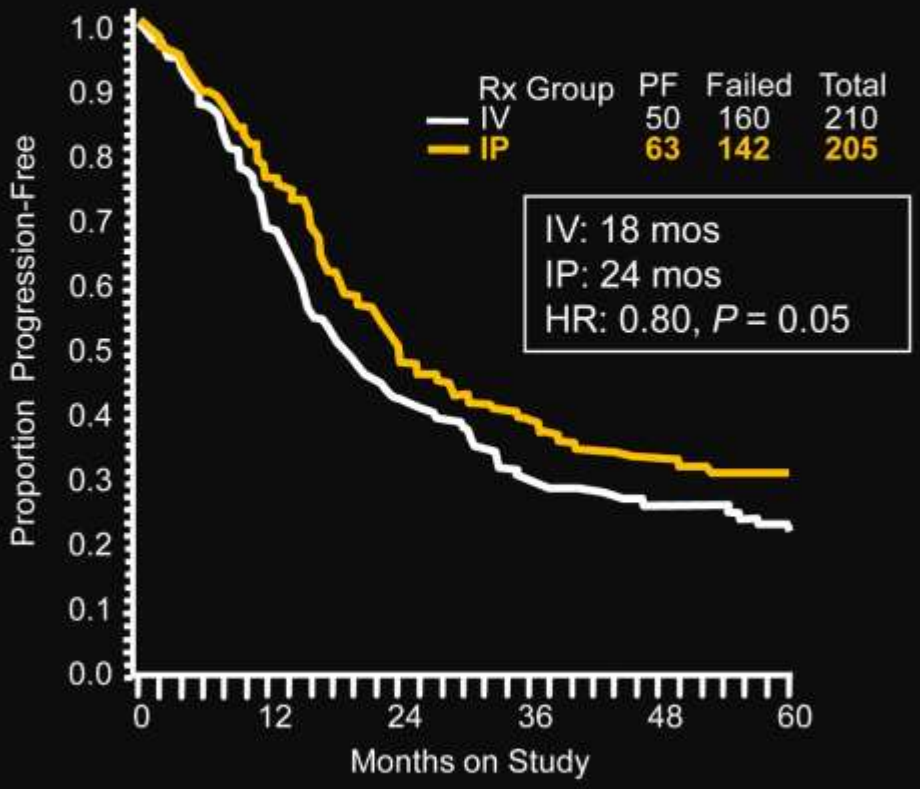
D1 IV — D2 IP — D8 IP

D1: IV Paclitaxel 135 mg/m²/24h
D2: IP Cisplatin 100 mg/m²
D8: IP Paclitaxel 60 mg/m²

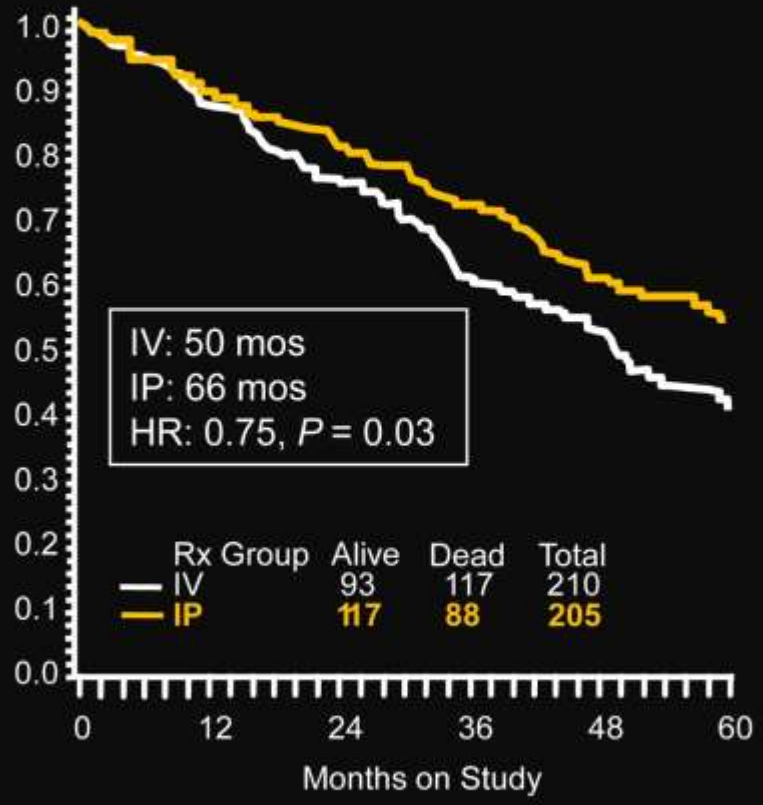
Armstrong DK, et al. *N Engl J Med*. 2006;354(11):34-43.

GOG-172: PRZEWAGA IP.

Progression-Free Survival

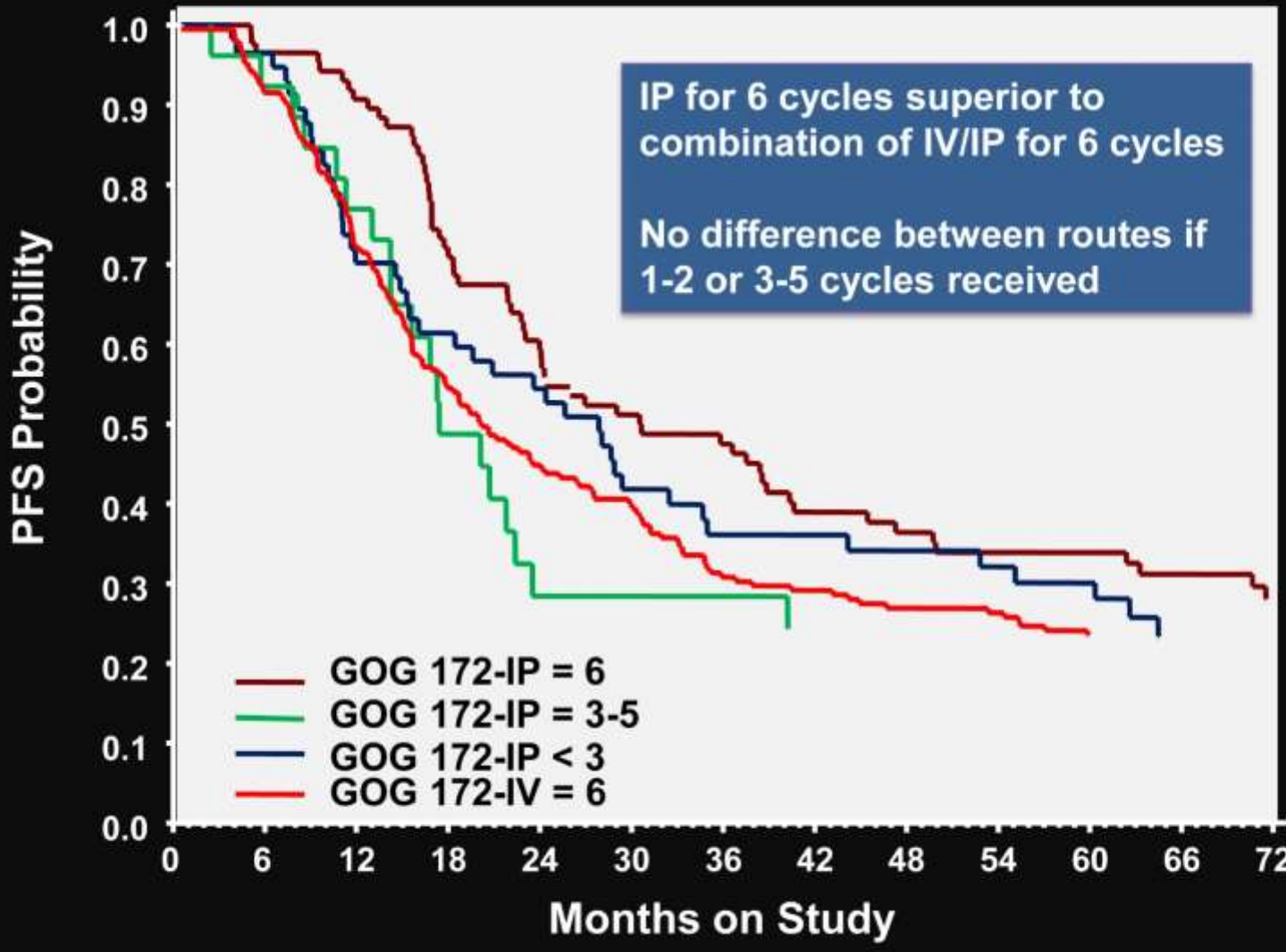


Overall Survival



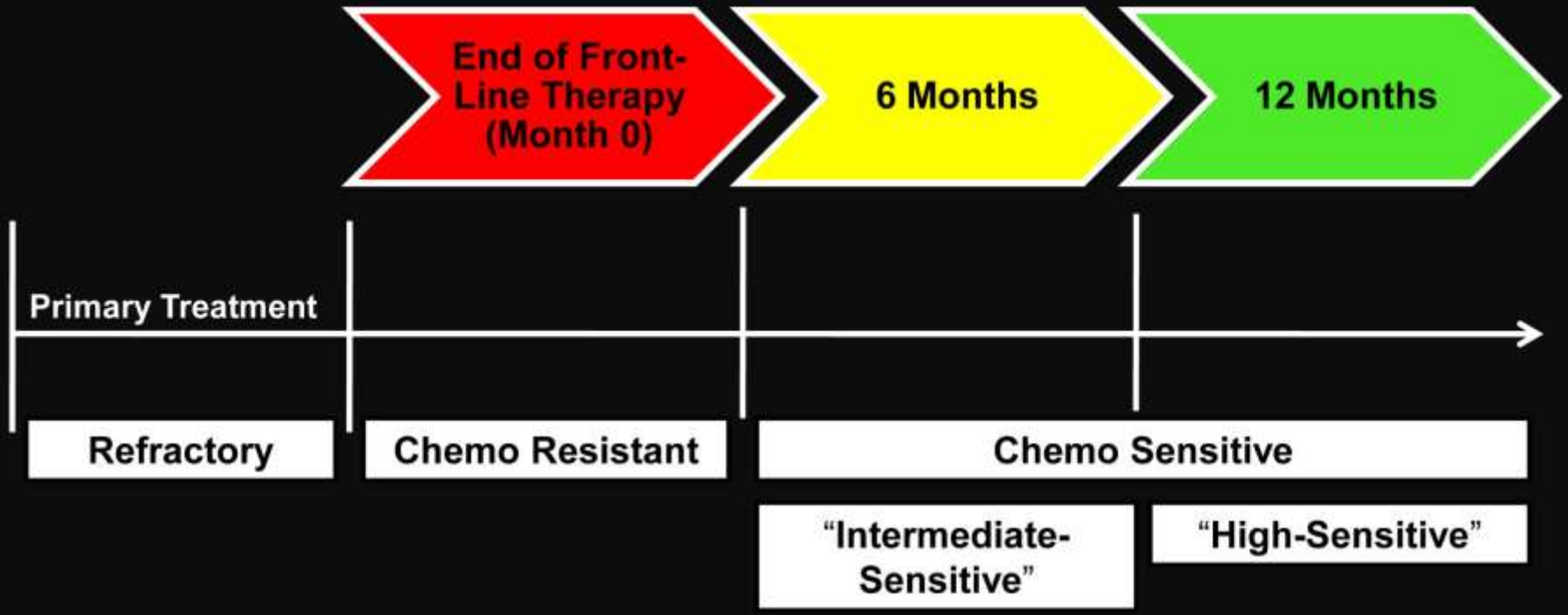
Armstrong DK, et al. *N Engl J Med*. 2006;354(11):34-43.

GOG-172: PFS Estimate by Total Cycles Administered



Tewari D, et al. *J Clin Oncol*. 2008;26(18S). Abstract 5549.

Chemotherapy Sensitivity



Dokumentowanie odpowiedzi na chemioterapię I-rzutu

Current Standard of Care for Ovarian Cancer

take home

- Primary surgical staging/debulking
- IV Paclitaxel + IV Carboplatin chemotherapy
- IV/IP Paclitaxel + IP Cisplatin chemotherapy in optimally debulked (≤ 1 cm residual disease) patients with FIGO stage III cancer

Czy trzeba spieszyć się z chemioterapią po operacji pierwotnej?

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

The time interval from surgery to start of chemotherapy significantly impacts prognosis in patients with advanced serous ovarian carcinoma — Analysis of patient data in the prospective OVCAD study

G. Hofstetter [a,1], N. Concin [a,*,1], I. Braicu [b], R. Chekerov [b], J. Sehouli [b], I. Cadron [c], T. Van Gorp [d], F. Trillsch [e], S. Mahner [e], H. Ulmer [f], C. Grimm [g], D. Cacsire Castillo-Tong [g,h], R. Zeillinger [g,h], A.G. Zeimet [a], I. Vergote [c]

Nie wpływa na OS

- [1] Rosa DD, Clamp A, Mullamitha S, Ton NC, Lau S, Byrd L, et al. The interval from surgery to chemotherapy in the treatment of advanced epithelial ovarian carcinoma. Eur J Surg Oncol 2006;32:588–91.
- [2] Gadducci A, Sartori E, Landoni F, Zola P, Maggino T, Maggioni A, et al. Relationship between time interval from primary surgery to the start of taxane- plus platinum-based chemotherapy and clinical outcome of patients with advanced epithelial ovarian cancer: results of a multicentre retrospective Italian study. J Clin Oncol 2005;23:751–8.
- [3] Aletti GD, Long HJ, Podratz KC, ClibyWA. Is time to chemotherapy a determinant of prognosis in advanced stage ovarian cancer? Gynecol Oncol 2007;104:212–6.
- [4] Paulsen T, Kaern J, Kjaerheim K, Haldorsen T, Tropé C. Influence of interval between primary surgery and chemotherapy on short-term survival of patients with advanced ovarian, tubal or peritoneal cancer. Gynecol Oncol 2006;102:447–52.
- [5] Flynn PM, Paul J, Cruickshank DJ, Scottish Gynaecological Cancer Trials Group. Does the interval from primary surgery to chemotherapy influence progression-free survival in ovarian cancer? Gynecol Oncol 2002;86:354–7.
- [6] Warwick J, Kehoe S, Earl H, Luesley D, Redman C, Chan KK. Long-term follow-up of patients with advanced ovarian cancer treated in randomised clinical trials. Br J Cancer 1995;72:1513–7.

⇩OS

- [1] Wright J, Doan T, McBride R, Jacobson J, Hershman D. Variability in chemotherapy delivery for elderly women with advanced stage ovarian cancer and its impact on survival. Br J Cancer 2008;98:1197–203.
- [2] Wright JD, Herzog TJ, Neugut AI, Burke WM, Lu YS, Lewin SN, et al. Effect of radical cytoreductive surgery on omission and delay of chemotherapy for advance-stage ovarian cancer. Obstet Gynecol 2012;120:871–81.
- [3] Mahner S, Eulenburg C, Staehle A, Wegscheider K, Reuss A, Pujade-Lauraine E, et al. Prognostic impact of the time interval between primary surgery and chemotherapy in patients with advanced ovarian cancer: analysis of prospective randomized phase III trials. Eur J Cancer 2013;49:142–9.

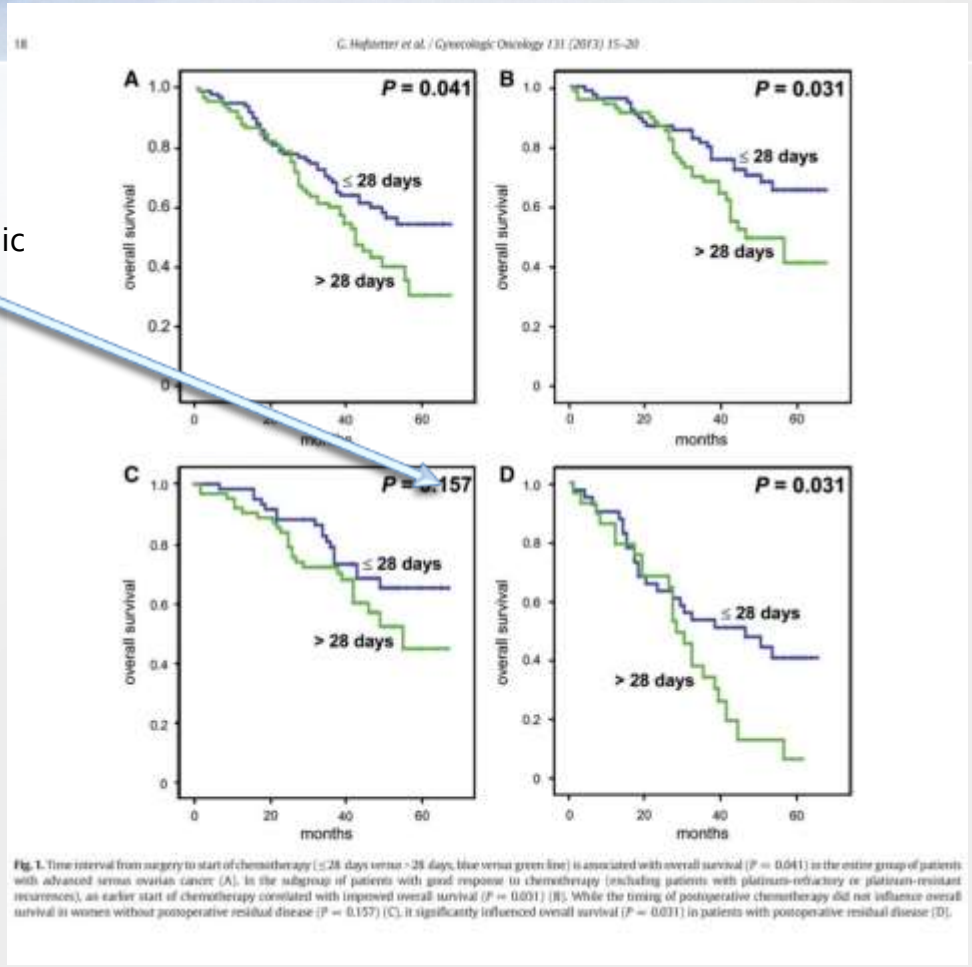
Znaczenie prognostyczne czasu pomiedzy PDS i Chth.

CEL pracy

- Czy długość przerwy pomiędzy leczeniem chirurgicznym a chemioterapią wpływa na wyniki leczenia pacjentek z surowiczym rakiem jajnika

- Grupa SOC włączonych do wieloośrodkowego, prospektywnego badania OVCAD (ovarian Cancer Diagnosis of a Silent Killer).

Brak różnic



OS

A. Cała grupa 191
B. Grupa 145 wrażliwych na platyne (wykluczono 46 casów refractory oraz resistant)
C. 121 chorych R0 (microscopic)
D. 70 chorych >=R1 (macroscopic)

PFS

Timing PDS-Chth: <28 dni versus >28 dni nie miał wpływu na PFS w całej cohorcie oraz w żadnej z analizowanych podgrup (B, C, D).

Rezultaty

- Nie ma liniowej zależności pomiędzy czasem podania adjuwantowej Chth a OS (HR 1.01, 95%CI 1.00-1.02, p=0.077)

- W oknie czasowym pomiędzy **3 a 6 tygodni** po PDS różnice w czasie podania adjuwantowej Chth mają znaczenie prognostyczne.

Wniosek

- Wydłużona przerwa pomiędzy PDS a adjuwantową CHTH skraca OS w grupie zaawansowanych przypadków surowiczego raka jajnika (SOC, FIGO III/IV) a w szczególności zoperowanych optymalnie (R<1cm) ale z widzialną chorobę resztkową.

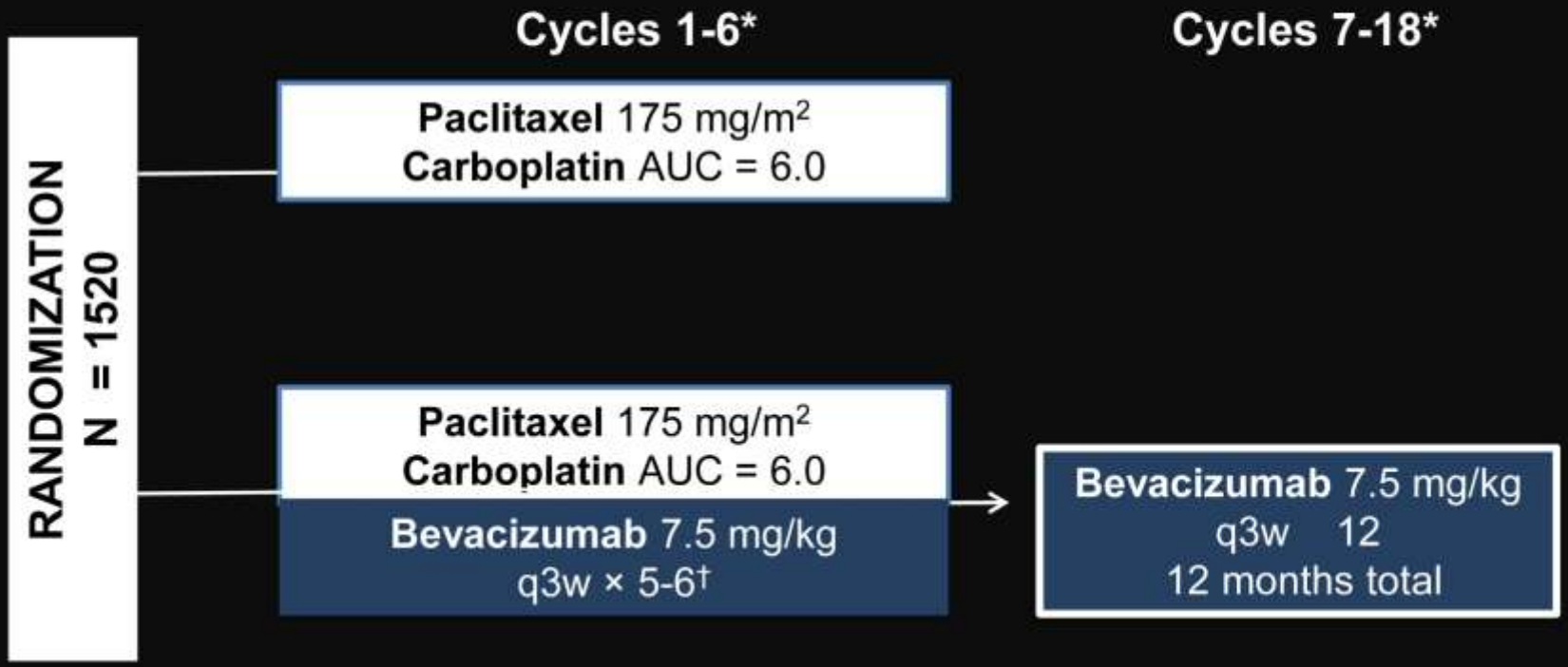
- Im szybciej tym lepiej tylko w okienku 3-6 tygodni

Miejsce Bevacuzimabu w leczeniu raka jajnika

- Front-line adjuvant and maintenance
  GOG218
  ICON7

- Recurrent EOC
  OCEANS – platin-sensitive
  AURELIA – platin-resistant

ICON-7 First-Line Bevacizumab



Inclusion Criteria

- EOC, fallopian, or PPC
- Optimal or suboptimal cytoreduction
- Stage I-IV

Primary Endpoint: PFS

Randomization closed Feb 2009

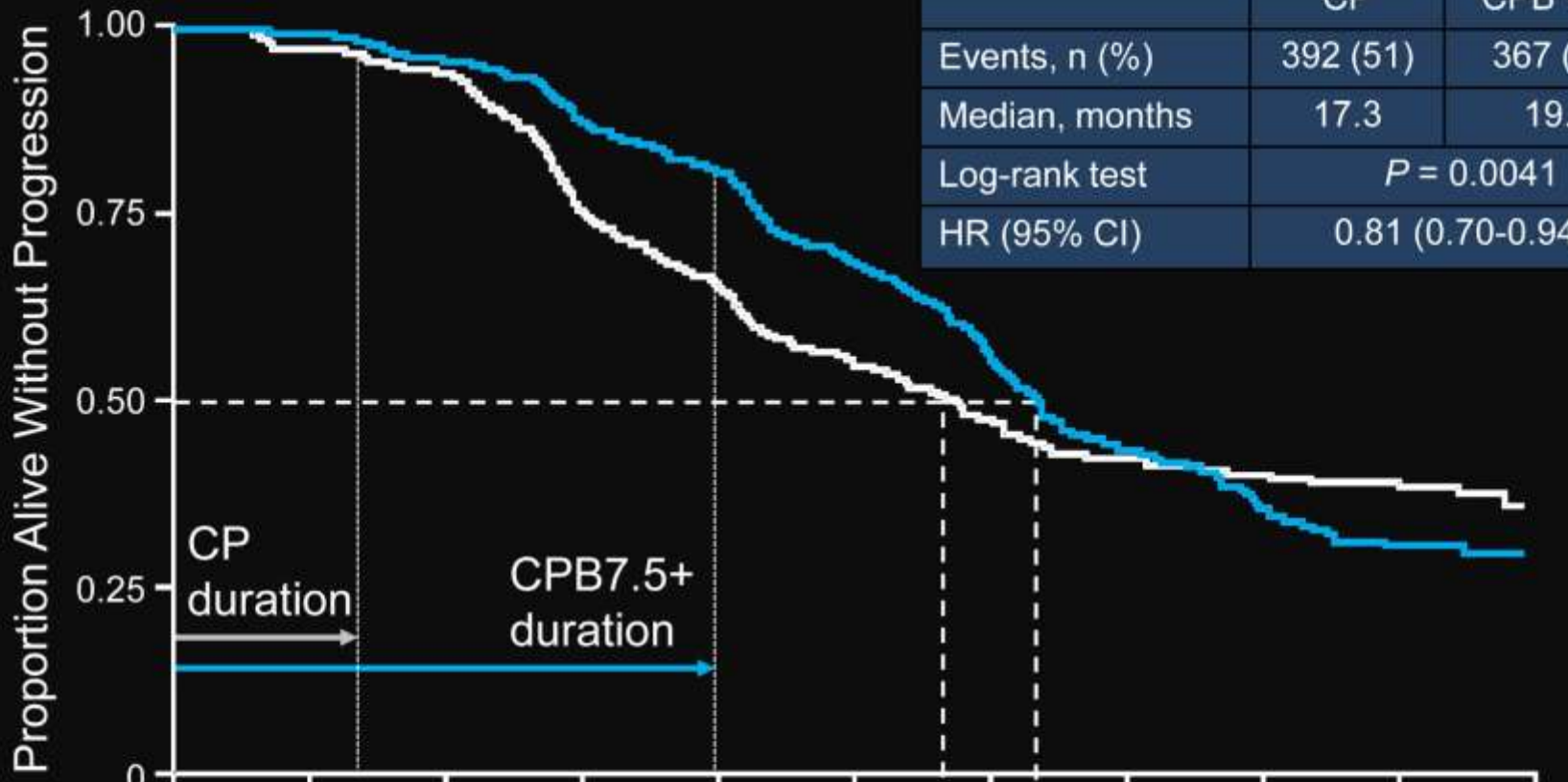
*3-week cycles; †Begin cycle 2, bevacizumab can be omitted from the first cycle if cytotoxic chemotherapy must be started within 4 weeks of surgery.

Primary Investigator: T Perren. Available at: http://www.icon7trial.org/. Accessed February 22, 2011.

ICON-7: PFS Benefit

From Date of Last CT or Last Clinical Follow-up, Whichever Was Later

	CP	CPB 7.5+
Events, n (%)	392 (51)	367 (48)
Median, months	17.3	19.0
Log-rank test	*P* = 0.0041	
HR (95% CI)	0.81 (0.70-0.94)	

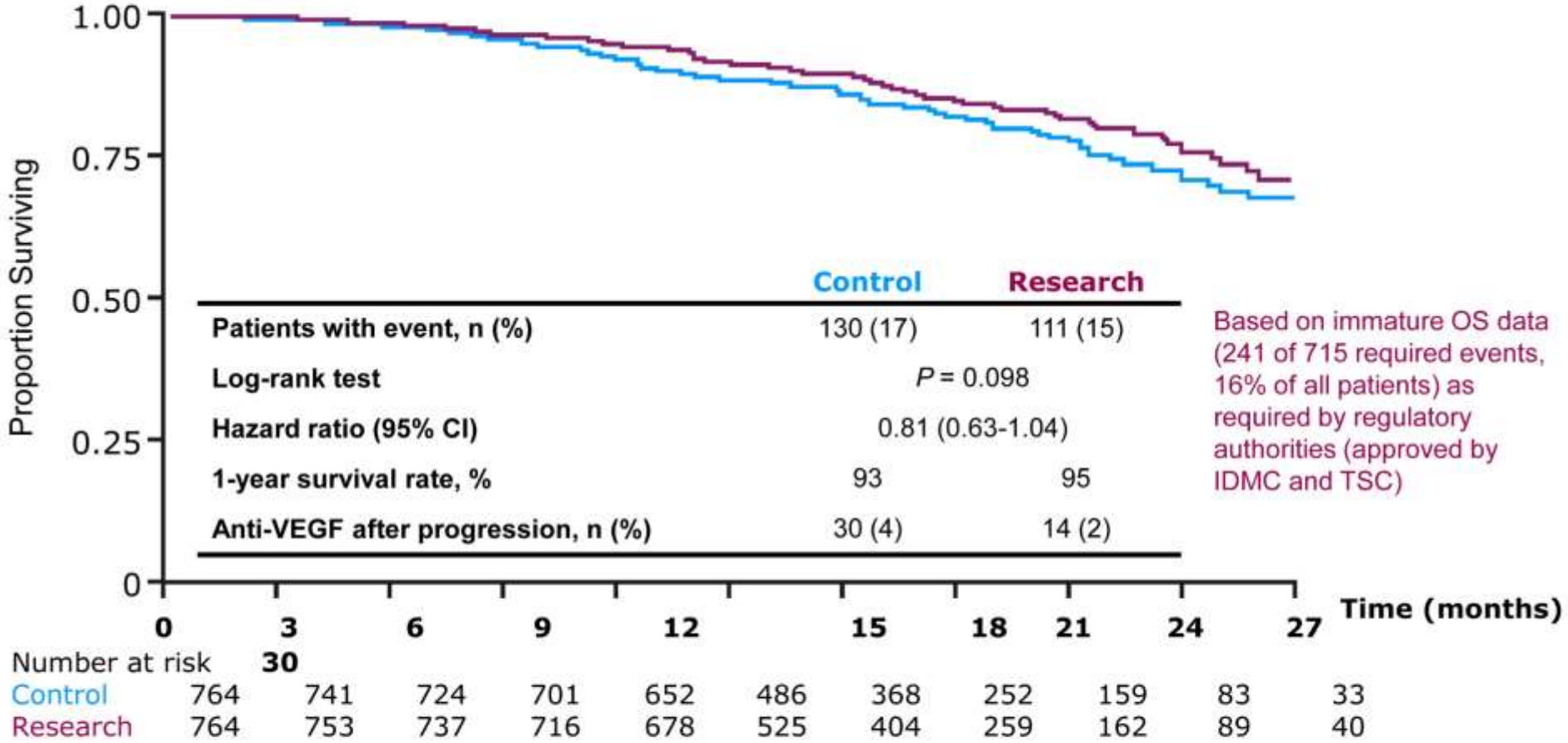


Number at risk

CP	764	723	693	556	464	307	216	143	91	50	25
CPB 7.5+	764	748	715	647	585	399	263	144	73	36	19

Perren T, et al. ESMO 2010. Abstract LBA4. Available at: http://www.icon7trial.org/. Accessed February 22, 2011.

ICON-7: Preliminary Analysis of Overall Survival

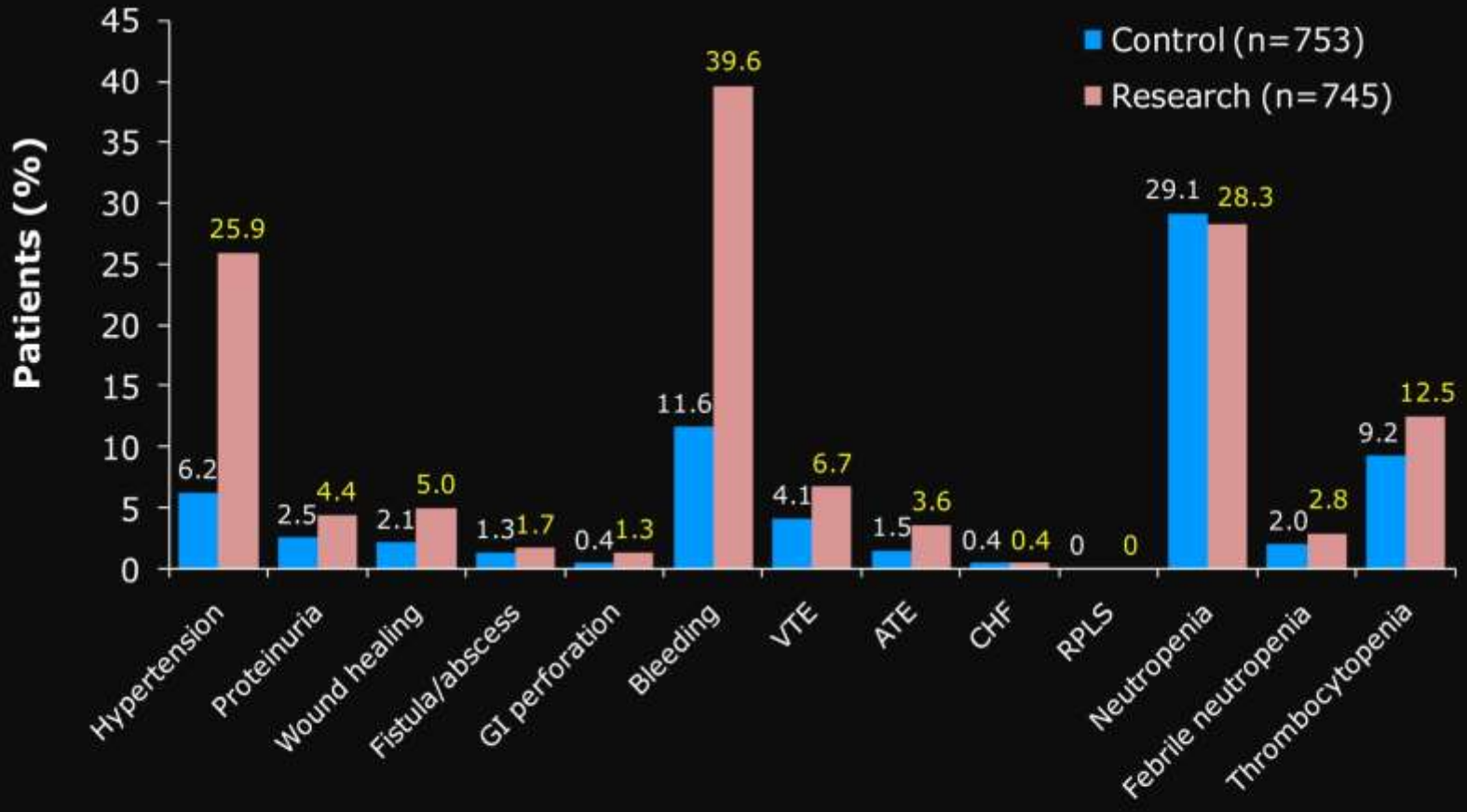


	Control	Research
Patients with event, n (%)	130 (17)	111 (15)
Log-rank test	*P* = 0.098	
Hazard ratio (95% CI)	0.81 (0.63-1.04)	
1-year survival rate, %	93	95
Anti-VEGF after progression, n (%)	30 (4)	14 (2)

Based on immature OS data (241 of 715 required events, 16% of all patients) as required by regulatory authorities (approved by IDMC and TSC)

Perren T, et al. *35th ESMO Congress Milan, Italy.* October 2010. Abstract LBA4.

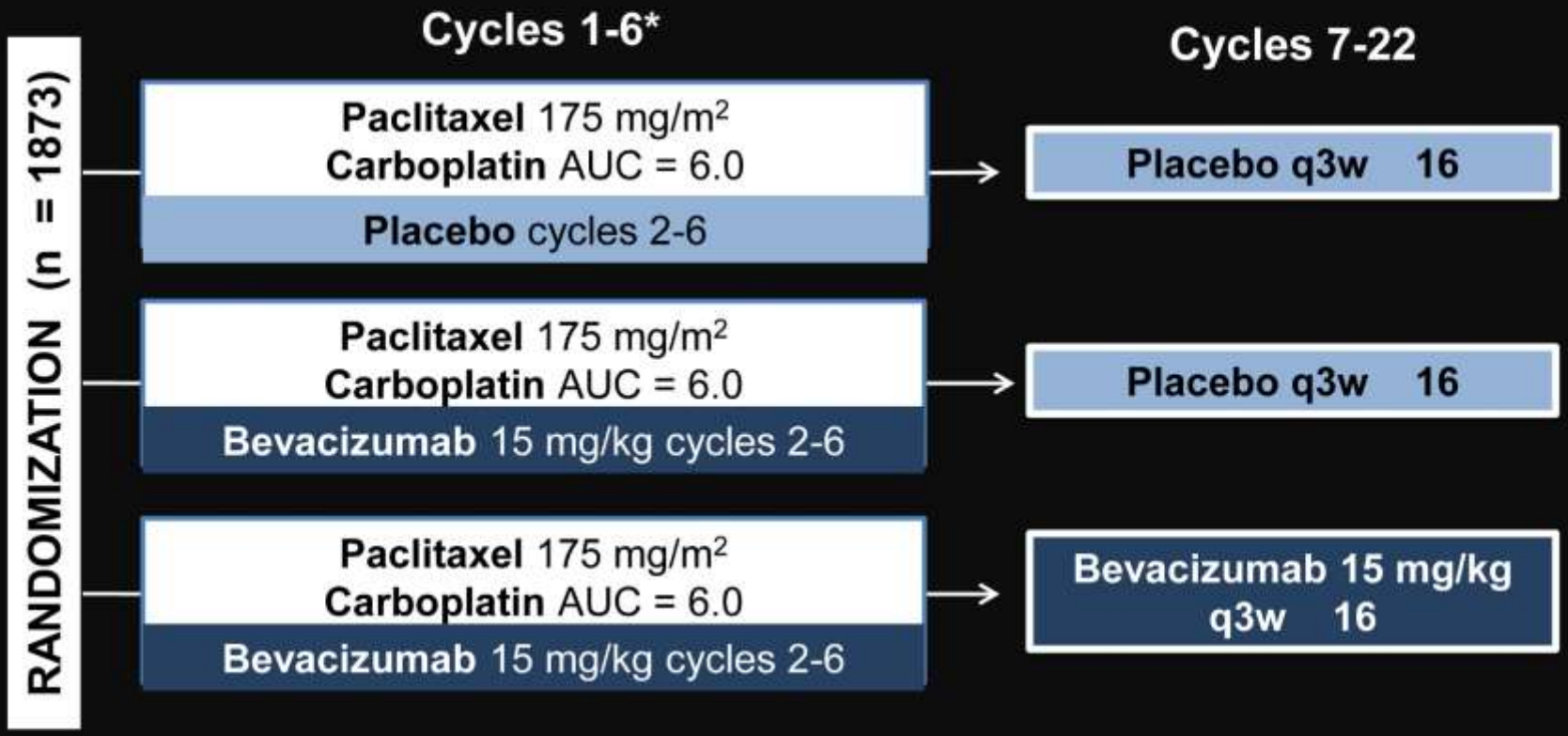
ICON-7: Selected Adverse Events (all grades)



ATE = arterial thromboembolism; CHF = congestive heart failure;
RPLS = reversible posterior leukoencephalopathy syndrome; VTE = venous thromboembolism

Perren T, et al. ESMO 2010. Abstract LBA4. Available at: http://www.icon7trial.org/. Accessed February 22, 2011.

GOG-218
Primary Adjuvant and Maintenance Therapy



Inclusion Criteria

- EOC, FT, or primary peritoneal CA
- Stage III with any gross (macroscopic or palpable) residual disease OR stage IV disease

15 months total treatment

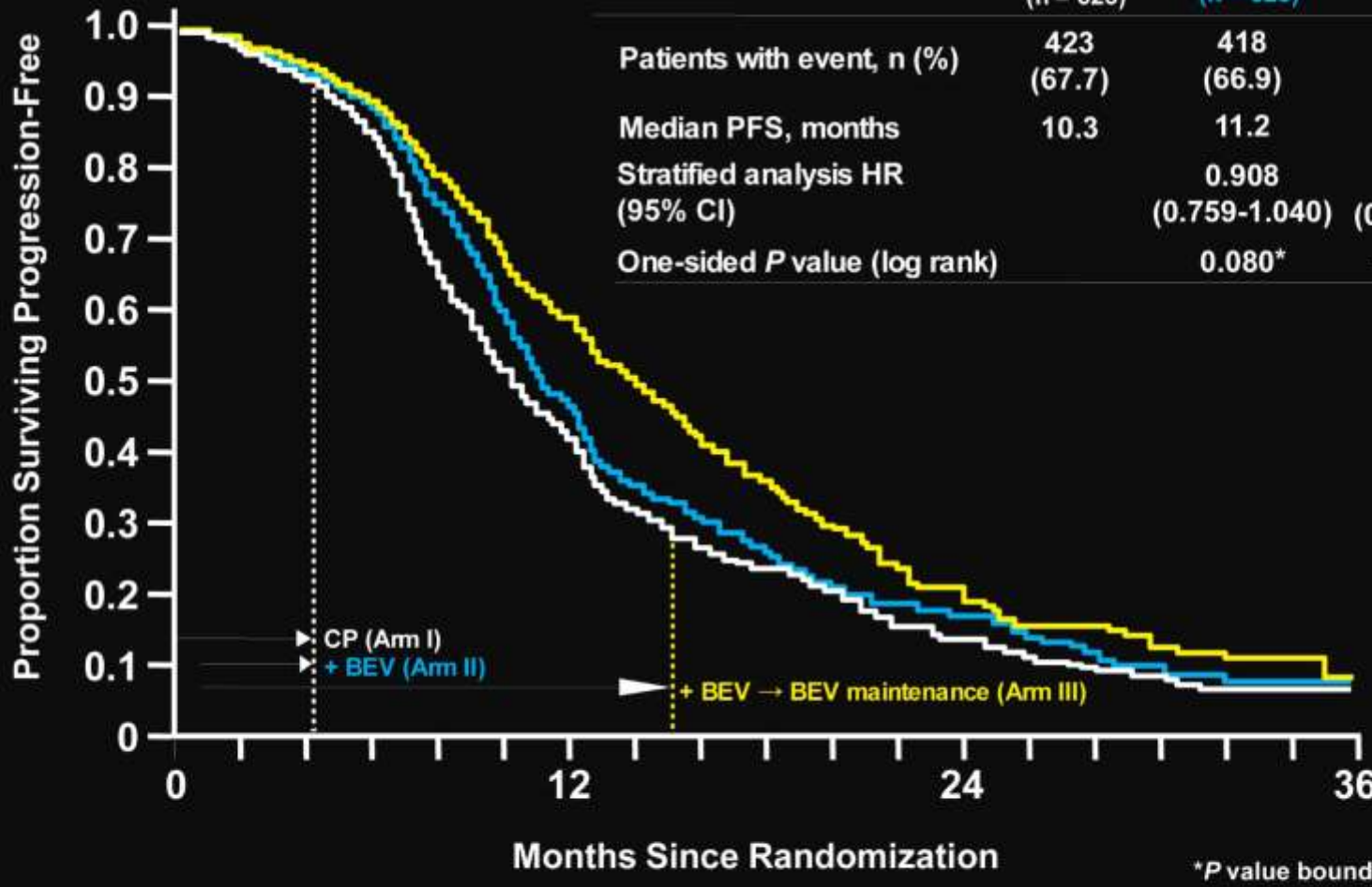
Primary Endpoint: PFS

*3-week cycles.

Burger R, et al. *J Clin Oncol.* 2010;28(18S). LBA1.

GOG-218: Progression-Free Survival

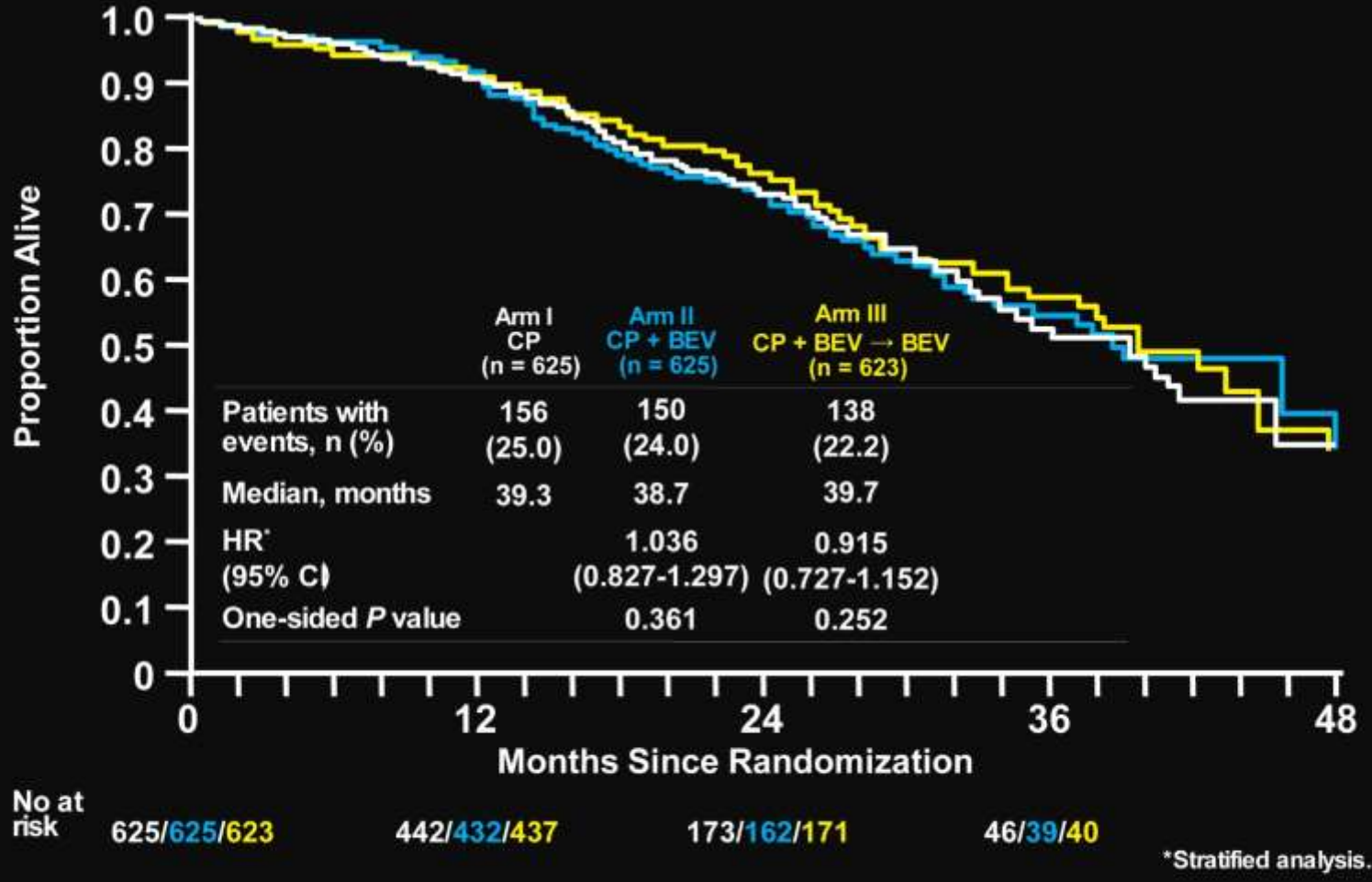
	Arm I CP (n = 625)	Arm II CP + BEV (n = 625)	Arm III CP + BEV → BEV (n = 623)
Patients with event, n (%)	423 (67.7)	418 (66.9)	360 (57.8)
Median PFS, months	10.3	11.2	14.1
Stratified analysis HR (95% CI)		0.908 (0.759-1.040)	0.717 (0.625-0.824)
One-sided *P* value (log rank)		0.080*	< 0.0001*



*P value boundary = 0.0116.

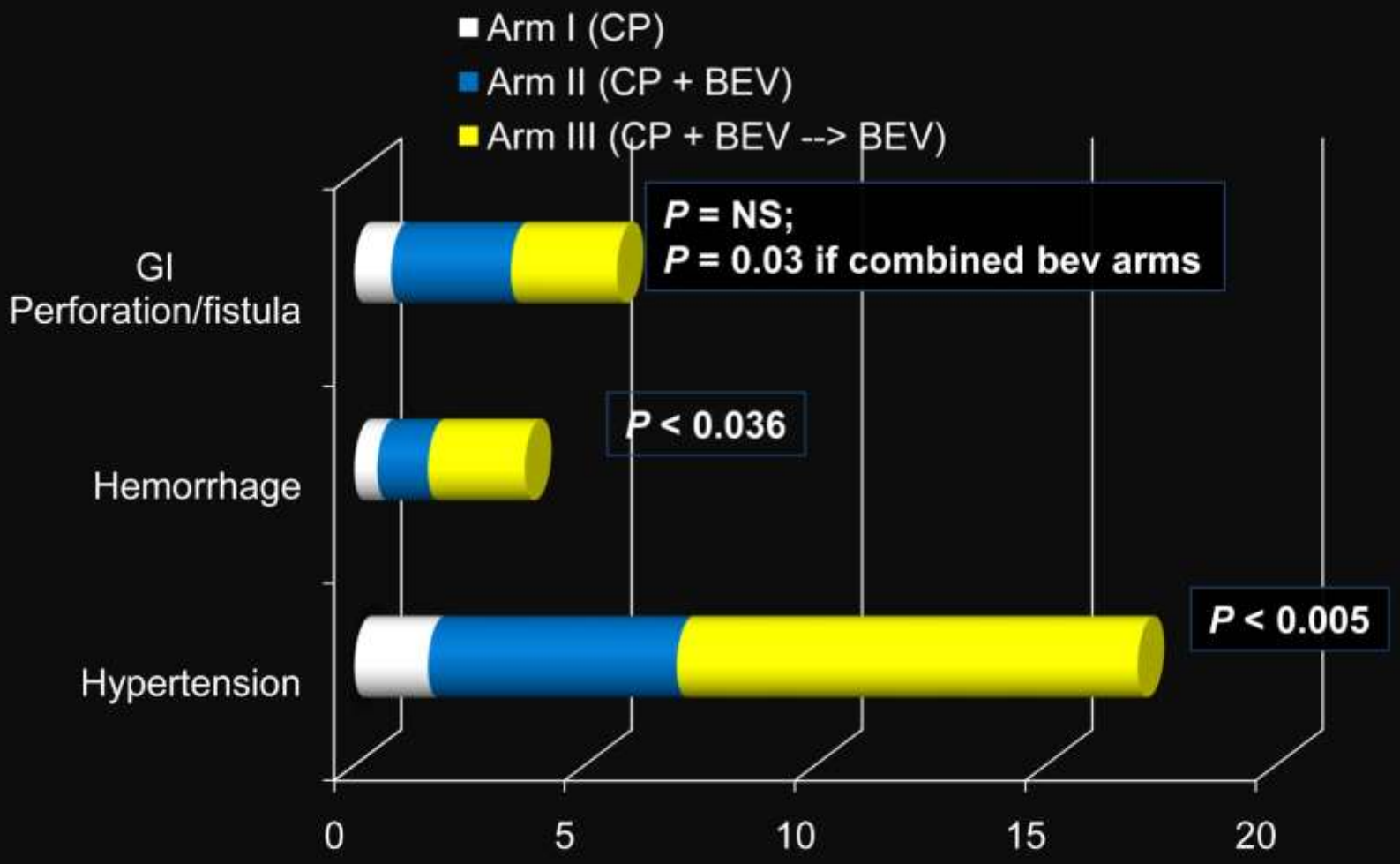
Burger R, et al. *J Clin Oncol.* 2010;28(18S). LBA1.

GOG-218: Overall Survival



Burger R, et al. *J Clin Oncol.* 2010;28(18S). LBA1.

GOG 218: Toxicity Comparisons



Burger R, et al. *J Clin Oncol.* 2010;28(18S). LBA1.

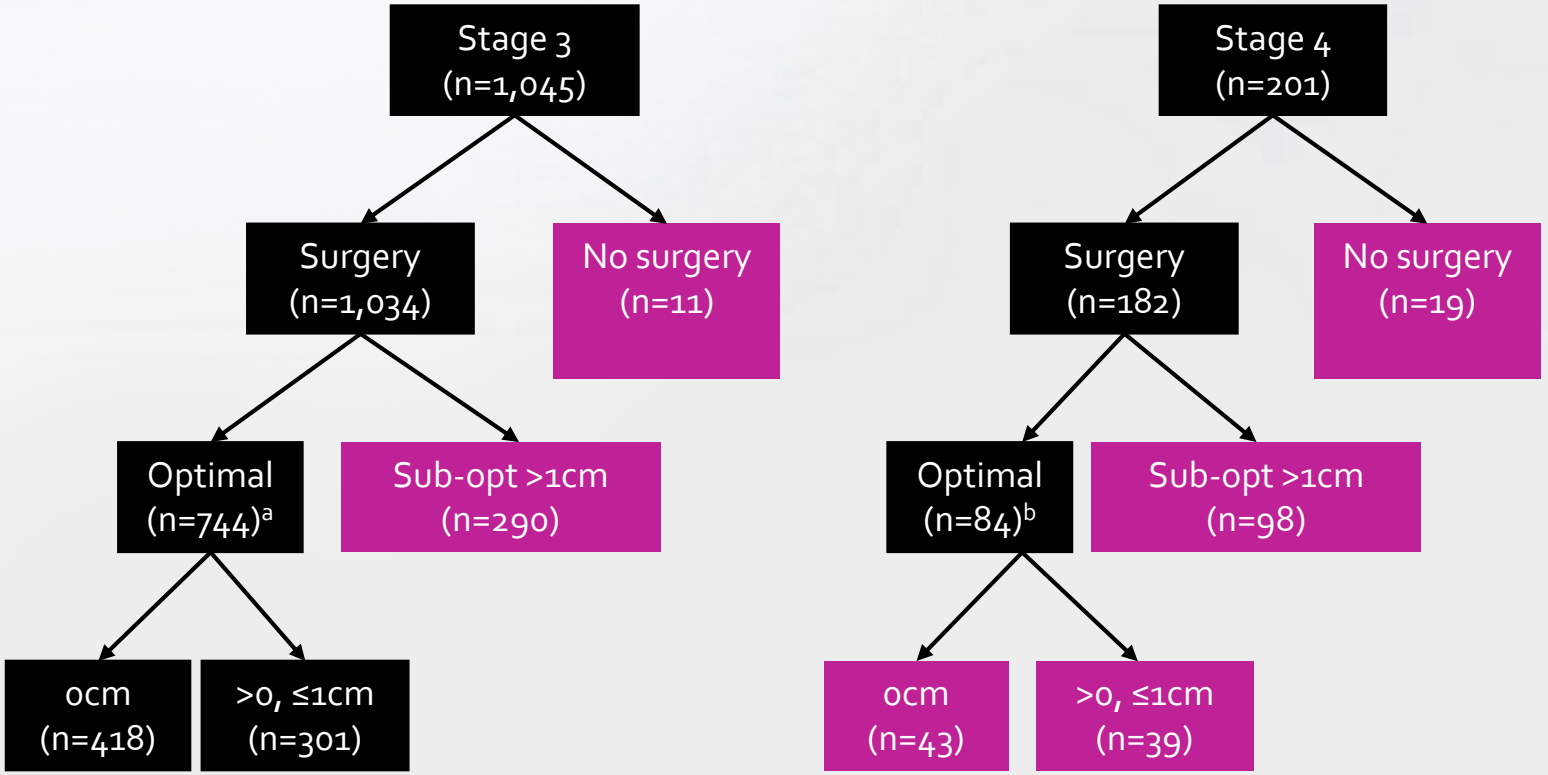
KLUCZOWE RÓŻNICE POMIĘDZY

GOG-218 i ICON-7

Trial	GOG-218	ICON-7
Setting / Design	• Double-blinded, placebo-controlled • Three-arm study • Bev for **15 months** • Bev dose: **15 mg q3w**	• Open-label • Two-arm study • Bev for **12 months** • Bev dose: **7.5 mg q3w**
Patient Population	• Stage III (suboptimal) • Stage III (optimal, visual / palpable) • Stage IV	• Stage I or IIA (grade 3 / clear cell histology) • Stages IIB-IV (all)
Additional Endpoint	• OS analysis (formal testing at time of PFS) • IRC	• Defined final OS analysis (end 2012) • No IRC

Dla kogo zarejestrowano AVASITN?

ICON7: definition of high-risk subgroup



Modified ICON7 high-risk group (n=502)

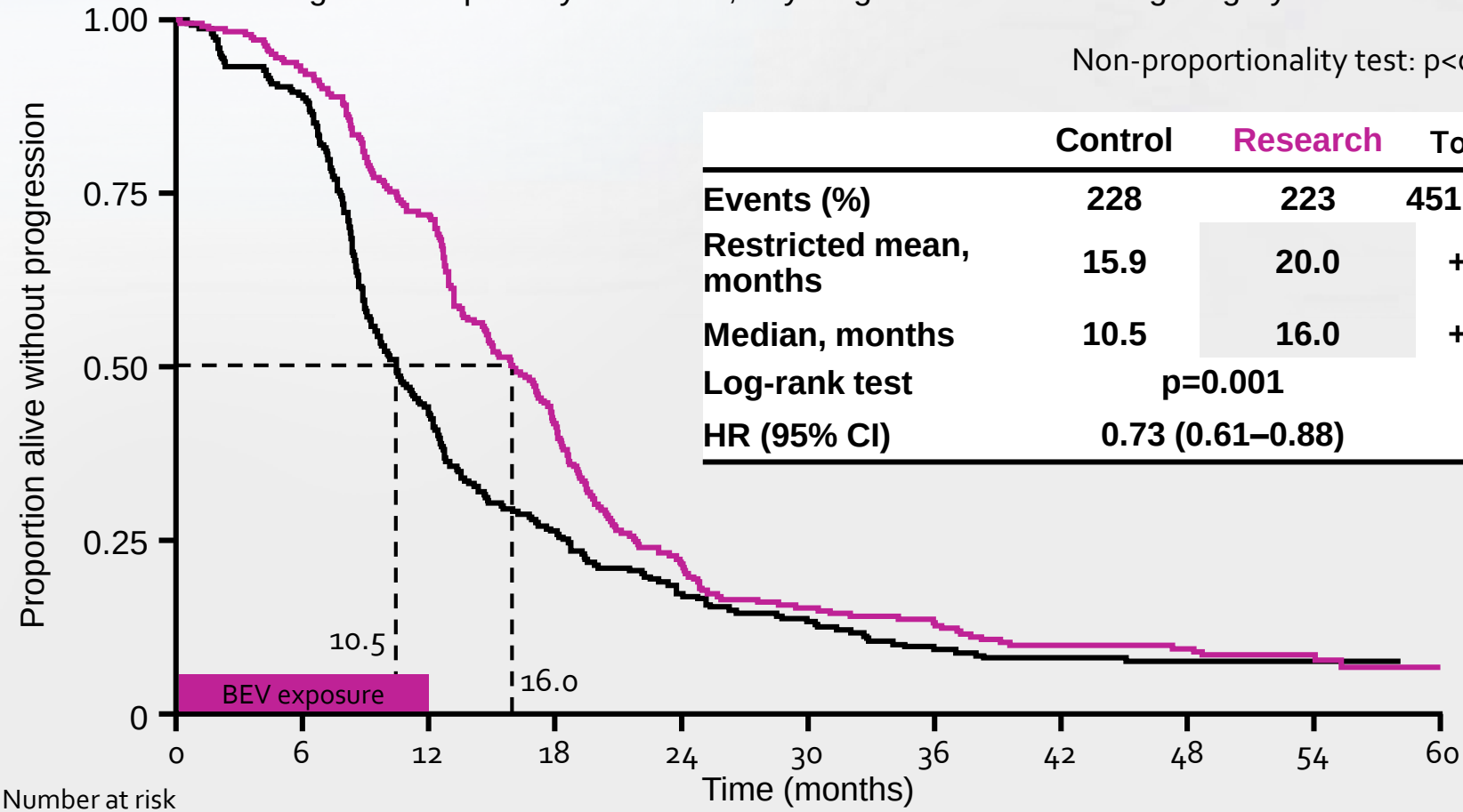
Original ICON7 high-risk group (n=472)

[a]Optimal unknown residual size (n=25)
[b]Optimal unknown residual size (n=2)

Oza, et al. ECC 2013 (LBA6)

ICON7: PFS (2013 update) high-risk (n=502)

Stage III suboptimally debulked , any stage IV or no debulking surgery



Non-proportionality test: p<0.0001

	Control	Research	Total
Events (%)	228	223	451 (90)
Restricted mean, months	15.9	20.0	+4.1
Median, months	10.5	16.0	+5.5
Log-rank test	p=0.001		
HR (95% CI)	0.73 (0.61–0.88)		

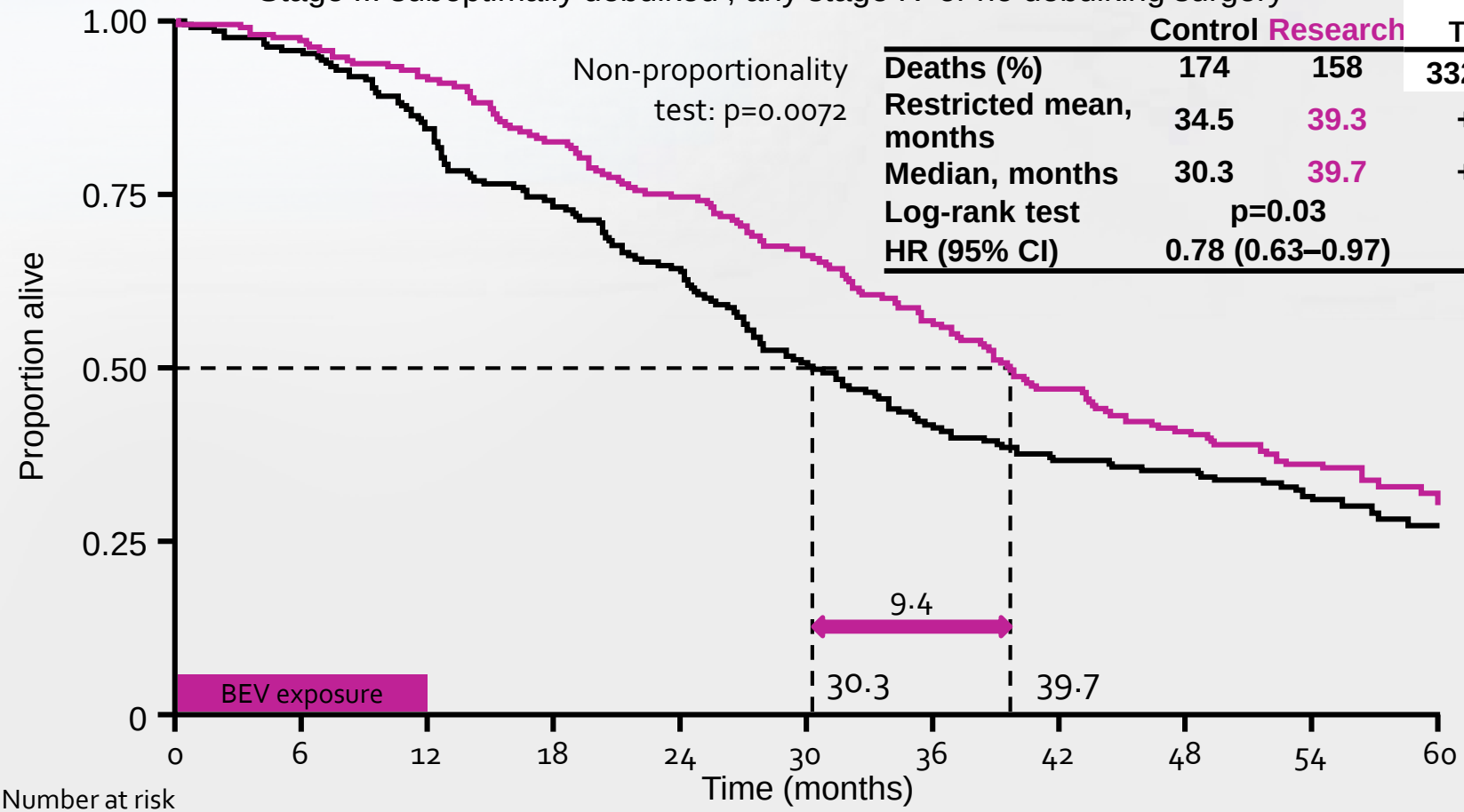
Number at risk

Control	254	109	43	24	18	6
Research	248	175	53	32	23	5

Oza, et al. ECC 2013 (LBA6)

ICON7: final OS high-risk (n=502)

Stage III suboptimally debulked , any stage IV or no debulking surgery



	Control	Research	Total
Deaths (%)	174	158	332 (66)
Restricted mean, months	34.5	39.3	+4.8
Median, months	30.3	39.7	+9.4
Log-rank test	p=0.03		
HR (95% CI)	0.78 (0.63–0.97)		

Number at risk

Control	254	208	156	101	82	21
Research	248	224	180	135	95	27

Oza, et al. ECC 2013 (LBA6)

AVASTIN w raku nawrotowym

OCEANS recurrent – platin sensitive

AURELIA recurrent – platin resitant

PODSUMOWANIE SKUTECZNOSCI BEV

Table 1. Summary of the four positive phase III studies adding bevacizumab to chemotherapy in epithelial ovarian carcinoma

Study	Arms	Sample size	Median PFS (months)	Hazard ratio	*P*-value	Survival advantage
GOG 218 [7]	Arm 1: carboplatin + paclitaxel + placebo	625	10.3 (12.0 π)			
	Arm 2: carboplatin + paclitaxel + bevacizumab + placebo	623	11.2	0.91	0.16	No
	Arm 3: carboplatin + paclitaxel + bevacizumab with maintenance (total 15 months)	625	14.1 (18.0 π)	0.72 0.65 π	<0.0001 <0.0001 π	Stage IV
ICON7 [8]	Arm 1: carboplatin + paclitaxel	764	17.3 α			
	Arm 2: carboplatin + paclitaxel + bevacizumab with maintenance (total 12 months)	764	19.0 α	0.81	0.004	'Patients at high risk for progression'
AURELIA [9]	Arm 1: chemotherapy*	182	3.4 α			
	Arm 2: chemotherapy* + bevacizumab	179	6.7 α	0.48	0.001	No
OCEANS [10]	Arm 1: carboplatin + gemcitabine + placebo	242	8.4 α			
	Arm 2: carboplatin + gemcitabine + bevacizumab until progression	242	12. 4 α	0.48	<0.0001	No

PFS, progression-free survival; π, increased CA125 levels censored; α, Response Evaluation Criteria In Solid Tumors (RECIST); *, weekly paclitaxel, topotecan, or pegylated liposomal doxorubicin

PODSUMOWANIE TOXYCZNOŚCI BEV

Table 2. Toxicity of interest during bevacizumab treatment in first-line (GOG 218 and ICON7 trials) and in relapse (OCEANS and AURELIA trials)

Adverse event (%)	GOG 218 [7]	ICON7 [8]	AURELIA [9]	OCEANS [10]
GI events	2.6[a]	3[b]	4.4[c]	2.4[d]
Hypertension	22.9 (grade ≥2)	18 (grade ≥3)	20 (grade ≥2)	17.4 (grade ≥3)
Proteinuria (grade ≥3)	1.6	<1	1.7	8.5
Thromboembolic event[e]	7.4	8	5.0	6.8
Bleeding (grade ≥3)	2.4	1	1.1	6.5
PRES	0.2	0	0.6	1

[a]Perforation, fistula, necrosis, and leak grade ≥2.
[b]Perforation, fistula, abcess, and wound-healing complications grade ≥3.
[c]Perforation and fistula/abcess grade ≥2.
[d]Perforation, fistula, and abcess all grades, wound-healing complications grade ≥3.
[e]Arterial any grade, venous grade ≥3.
PRES, posterior reversible encephalopathy syndrome.

Czy jest ważne kto leczy raka jajnika ?

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High-volume ovarian cancer care: Survival impact and disparities in access for advanced-stage disease ☆

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CEL pracy

- Ocena wpływu referencyjności szpitala oraz doświadczenia lekarza chirurga/onkologa (ovarian cancer volume of hospital/physician) na przeżycie pacjentów z zaawansowanym rakiem jajnika

- Poszukiwanie czynników socjalno demograficznych ograniczających dostęp do wyspecjalizowanych ośrodków i doświadczonych lekarzy.

MATERIAŁ I METODA

- Kolejno leczone pacjentki C56 (California Cancer Registry) n=21044
- 10 lat (1/1/1996 do 31/12/2006) koniec obserwacji 2008
- 400 szpitali leczących
- Podzielono szpitale na: HVH >20 chorych/ rok; LVH <20 chorych/rok
- Lekarzy (chirurg ginekolog, onkolog kliniczny) podzielono na: HVP>10 chorych/rok; LVP<10 chorych /rok
- Wpływ kategorii leczenia (HVH/HVP, HVH/LVP, LVH/HVP, LVH/LVP) na Cancer-Specific OS

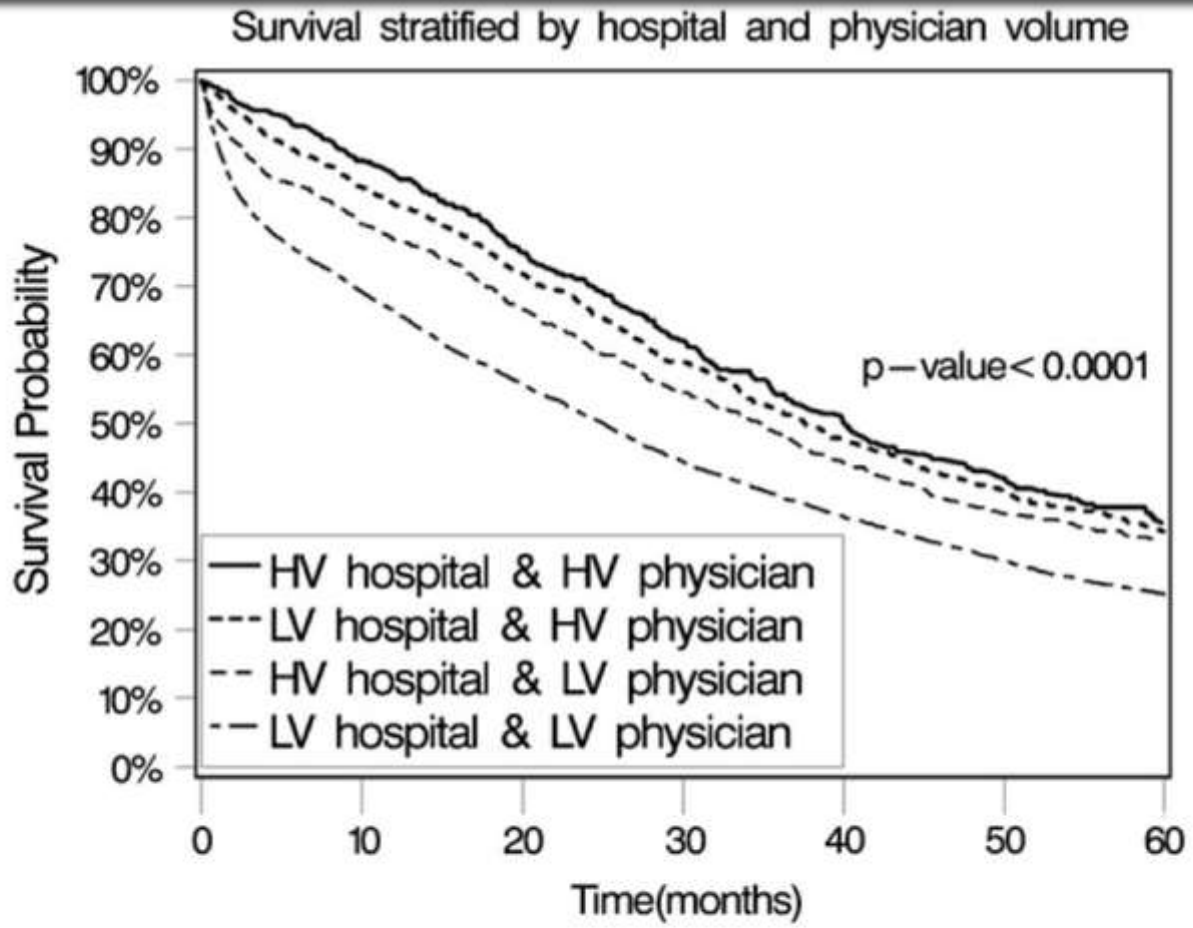

Fig. 1. Ovarian cancer-specific survival stratified by hospital and physician volume: HV-hospital/HV-physician n = 515, HV-hospital/LV-physician n = 1038, LV-hospital/HV-physician n = 1276, LV-hospital/LV-physician n = 6303 ($p < 0.0001$).

- HVH/HVP = 40.2 months (95%CI=35.6-45.5 months)
- HVH/LVP = 34.9 months (95%CI=31.6-37.4 months)
- LVH/HVP = 37.6 months (95%CI=34.8-41.0 months)
- LVH/LVP = 25.1 months (95%CI=23.9-26.0 months)

Median ovarian cancer-specific survival – 28.2 months

Dziękuję za uwagę

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