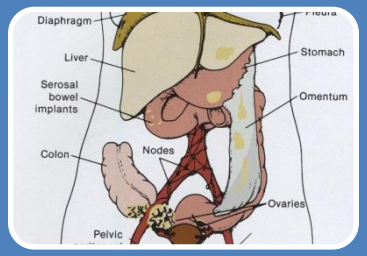
Munasarjasyövän kirurgisen hoidon rajat

SGY; Oulu; 16.11.2012

Ulla Puistola

Kuka leikkaa



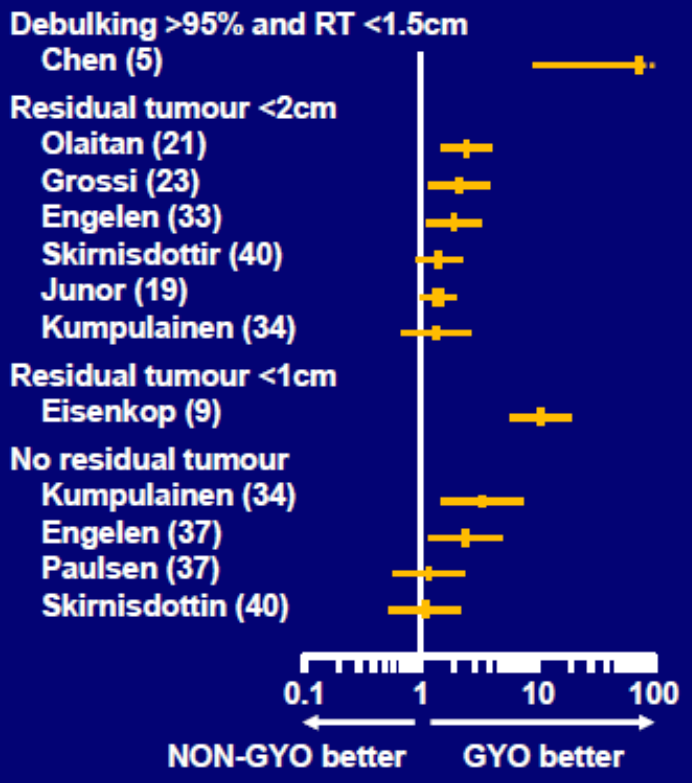
Mitkä ovat leikkauksen tavoitteet

- Suoliresektiot ja muut parenkyymileikkaukset
- Lymfadenektomiat
- Peritonektomiat

Mikä on leikkauksen oikea ajoitus

Who should do surgery for ovarian cancer? Results of a systematic review

- 14 studies involving 19,043 patients (54–12,316 patients/study)
- Treatment by gynaecologic oncologists (GYO) showed higher rates of:
  - comprehensive staging of FIGO I/II (4 of 4 studies)
  - 'optimal' debulking in FIGO III/IV (4 of 6 studies)
  - state-of-the-art chemotherapy (2 of 2 studies)
  - superior survival (5 of 9 studies)
- Significant advantage for at least 1 parameter in 13 of 14 studies



du Bois, et al. Gynecol Oncol 2009

Gynekologisten syöpien primäärihoito on keskitetty yliopistosairaaloiden gynekologisonkologisiin yksikköihin

STM: 28.8.2006/767

Mitkä ovat leikkauksen tavoitteet

Leikkauksen tavoitteet

R 0

- **No residual tumor**

R 1

- Residual <1cm

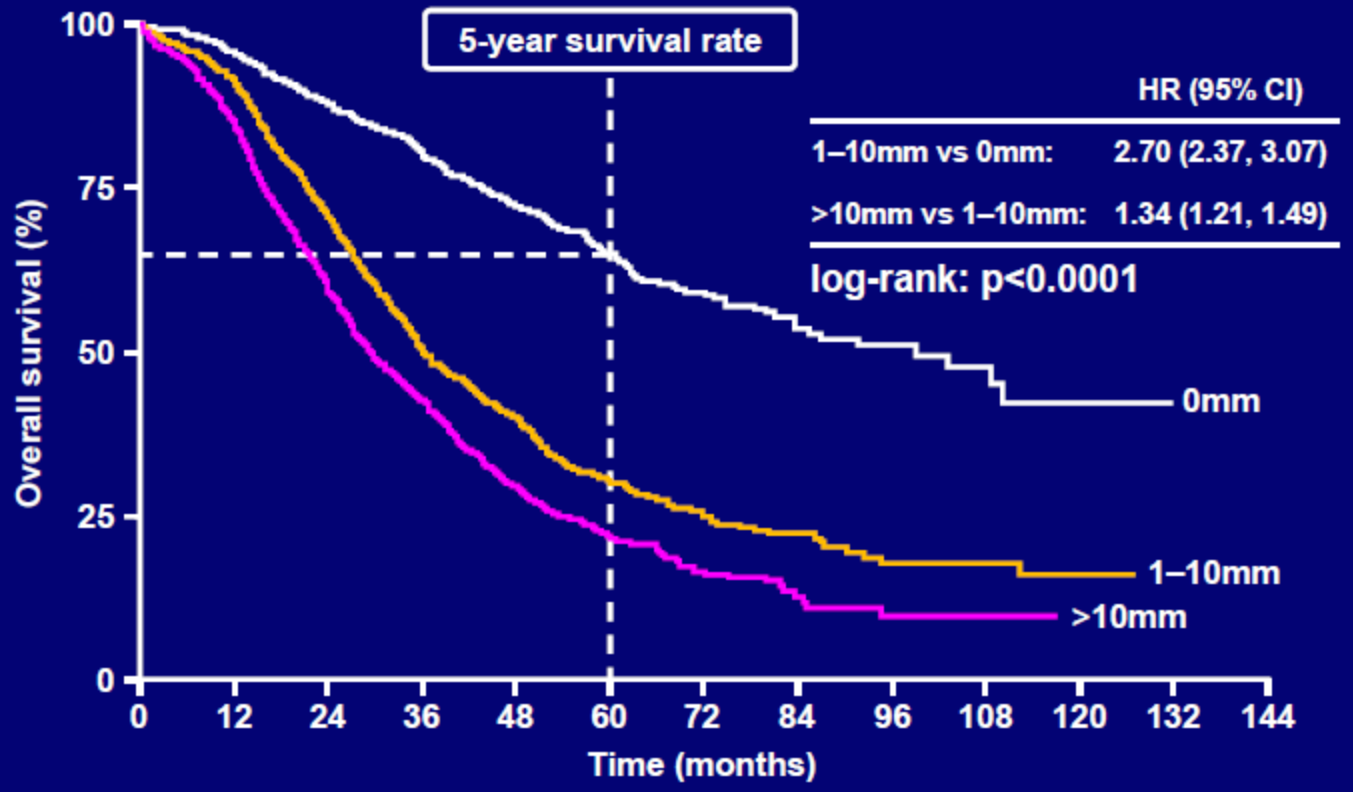
R 2

- Residual >1cm

- NGR (no gross residual)
- GR-1 (gross residual <1cm)
- GR-B (gross residual bulky >1cm)

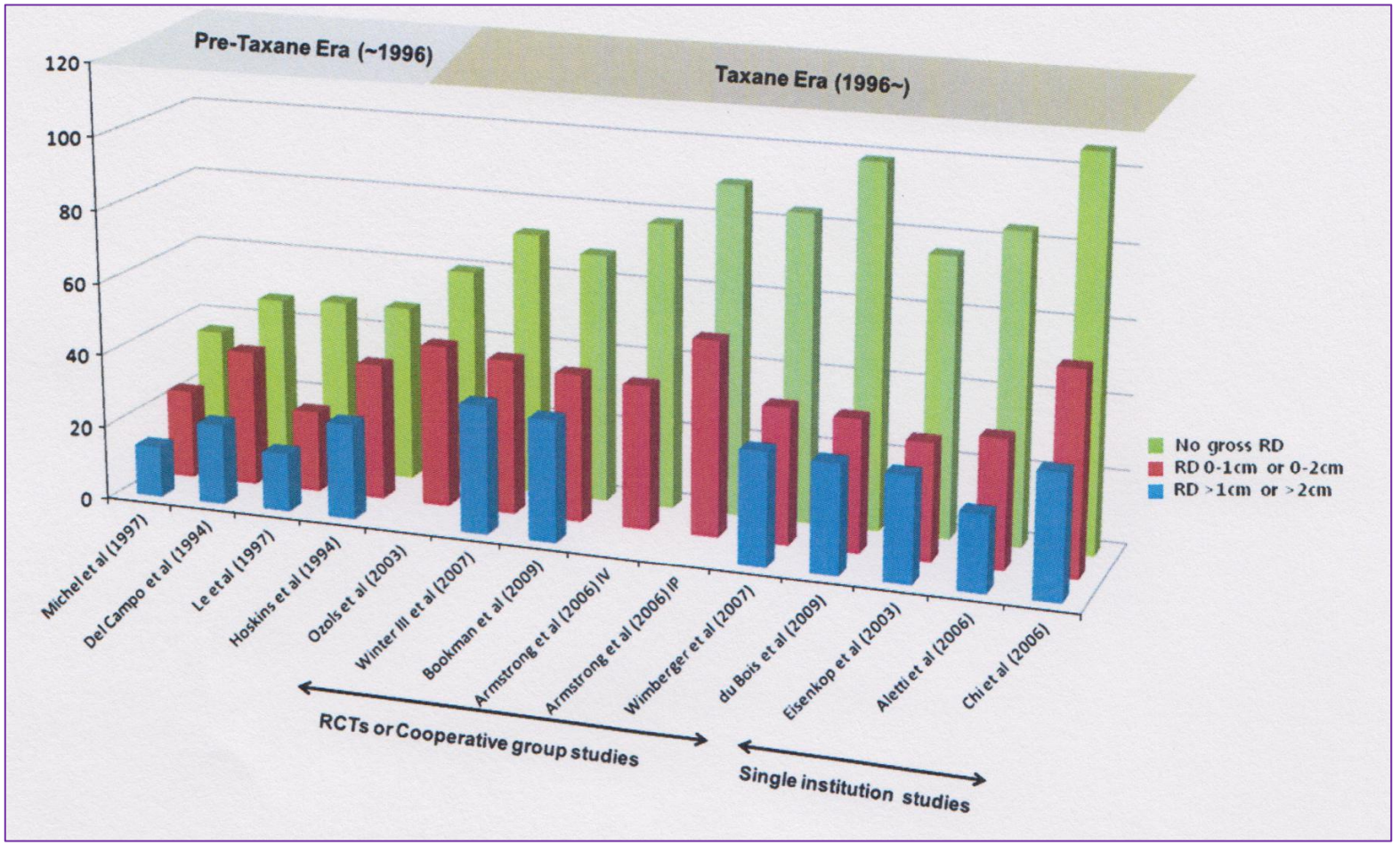
The impact of residual tumour on outcome in advanced ovarian cancer

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



du Bois, et al. Cancer 2009

Kemoterapia ei kompensoi huonoa leikkaustulosta



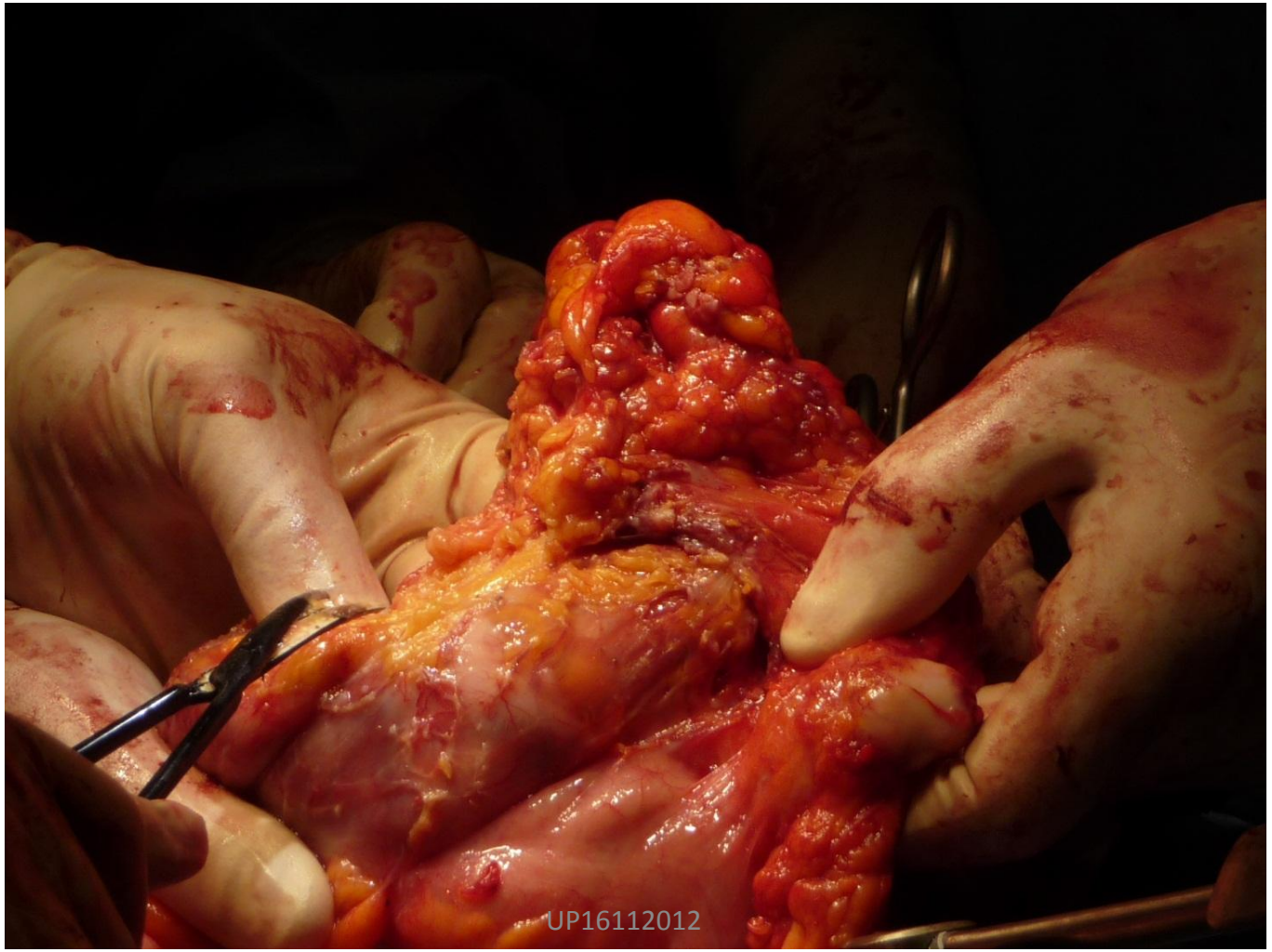
Chang SJ et al Gyn oncol 2012

	No. Patients	(%)
Hysterectomy	489	(92.8)
Salpingo-oophorectomy	504	(95.8)
Omentectomy	516	(97.9)
Small-bowel resection	52	(9.9)
Large-bowel resection	200	(38.0)
Multiple bowel resection	64	(12.2)
Appendectomy	339	(64.6)
Pelvic lymphadenectomy	412	(78.5)
Aortic lymphadenectomy	397	(75.8)
Right diaphragm stripping	193	(36.6)
Left diaphragm stripping	55	(10.4)
Splenectomy	50	(9.5)
Partial hepatic resection	17	(3.2)
Porta hepatis removal	10	(1.9)
Cholecystectomy	17	(3.2)
Surgical groups		

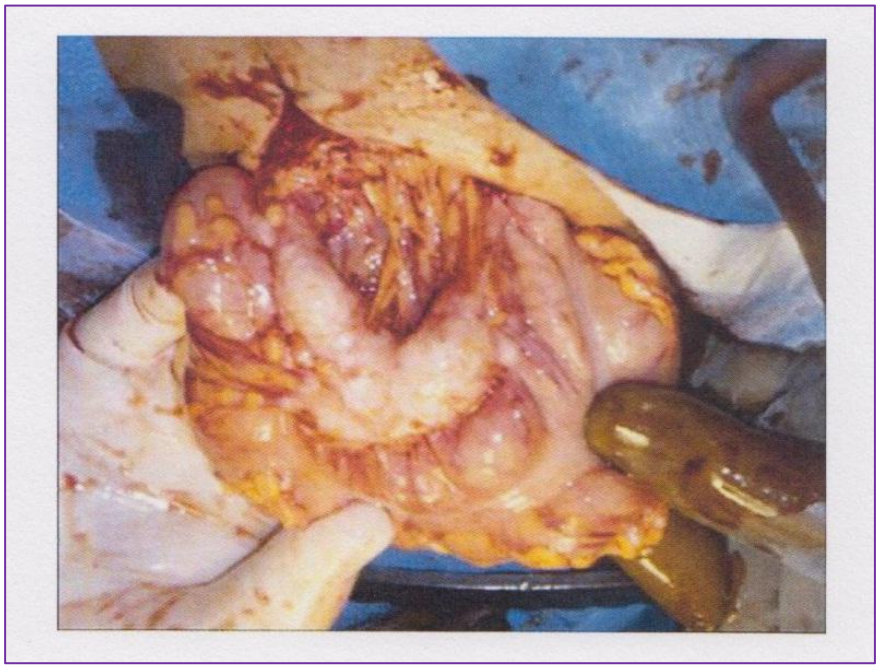
Luyckx M et al Int J Gyn Cancer 2012

Suoliresektiot

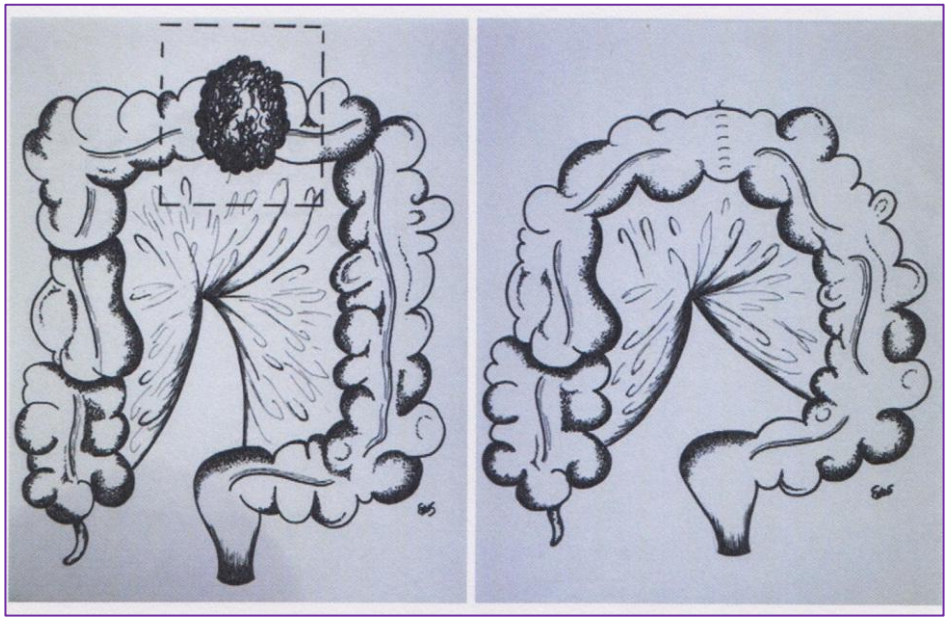
26% :lle primäärioperaatiossa (colon resektio)
35%:lle sekundaarisen sytoreduktion yhteydessä



Suoliresektiot munasarjasyövässä

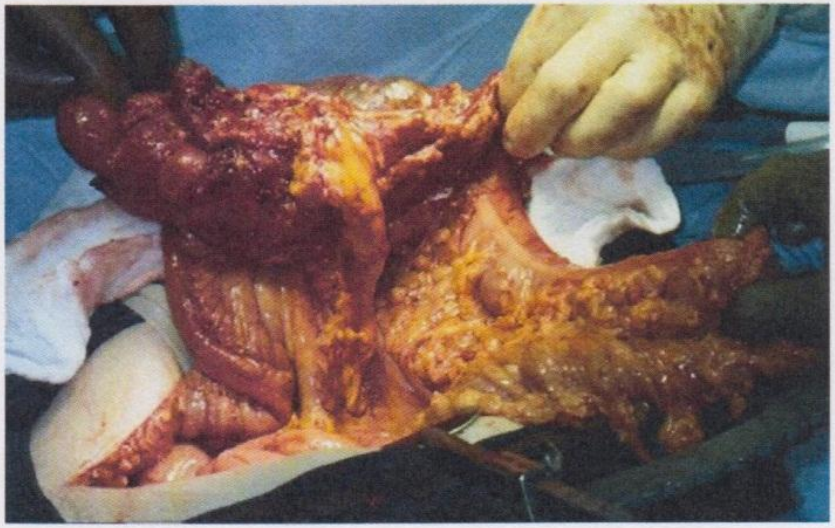


Omentti metastaasi
affisioiden colon transverumia

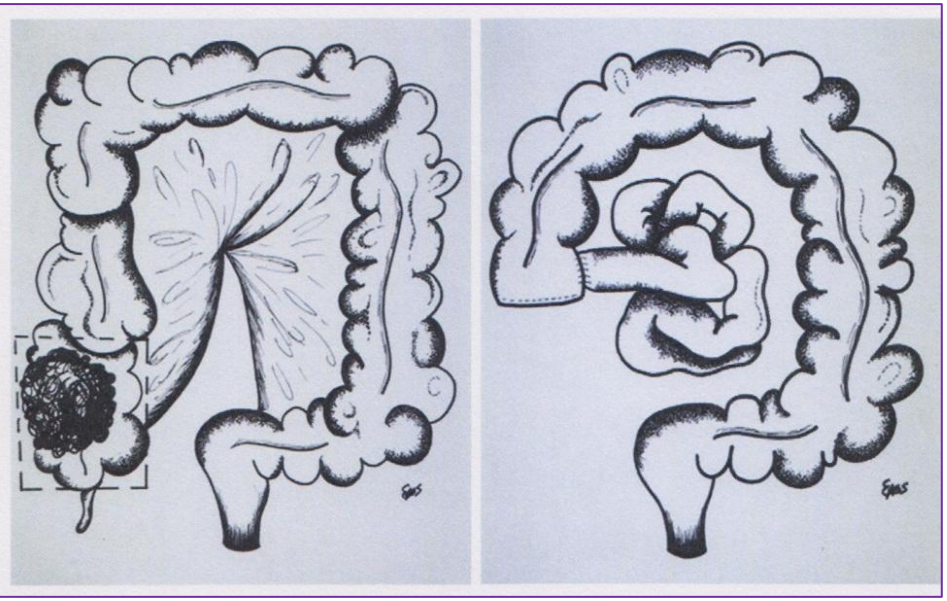


Colon transverumin resektio ja anastomoosi

Suoliresektiot munasarjasyövässä

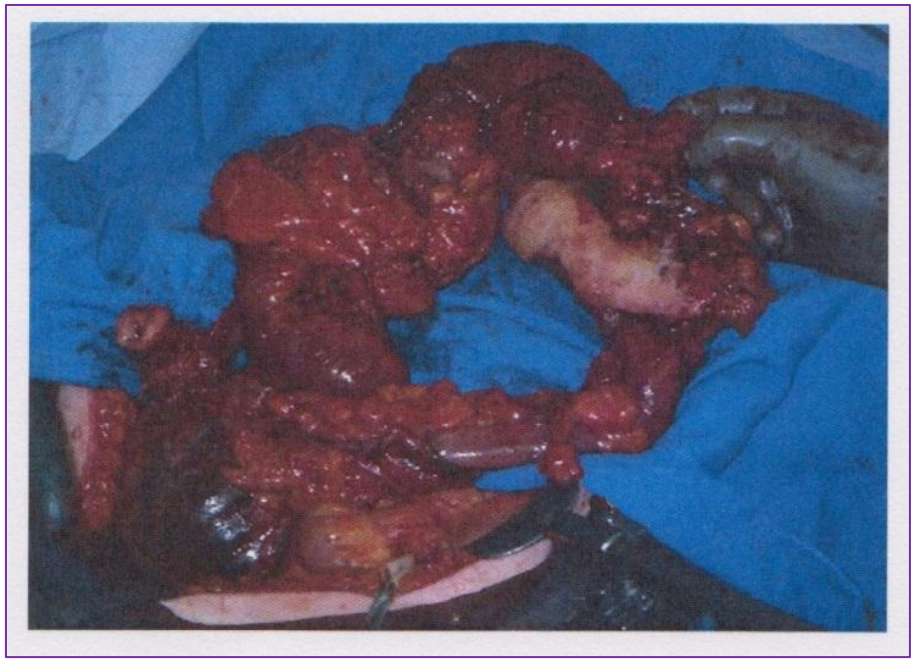


Ileokekaali metastaasi

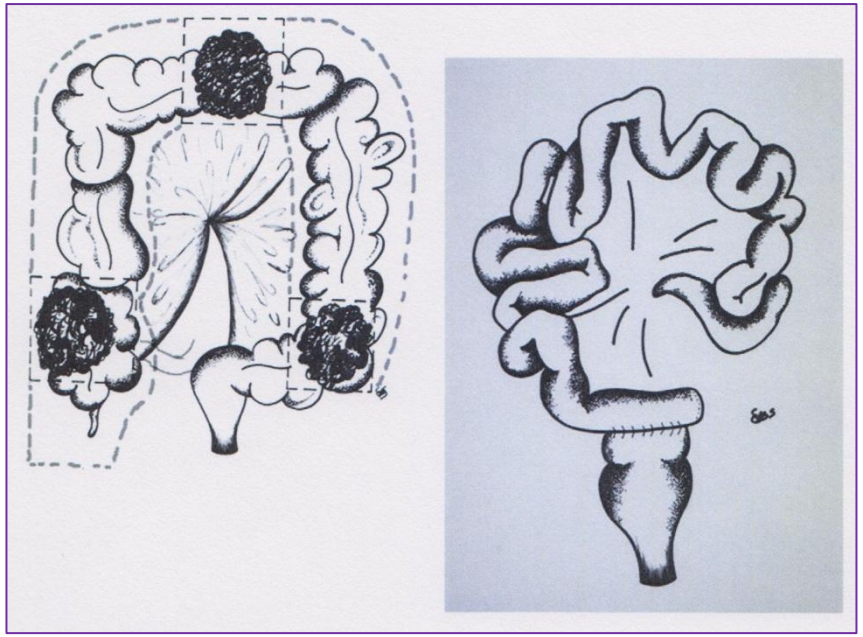


Ileokekaali resektio ja enterokolostomia

Suoliresektiot munasarjasyövässä



Multifokaali colonin meastasointi



Subtotaali kolectomia, ileorectostomia

Suoliresektiot munasarjasyövässä

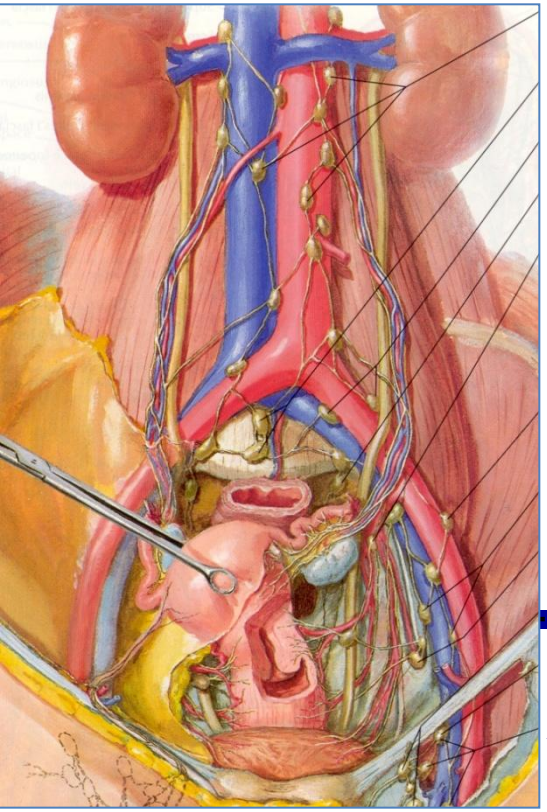
Komplikaatioriski:

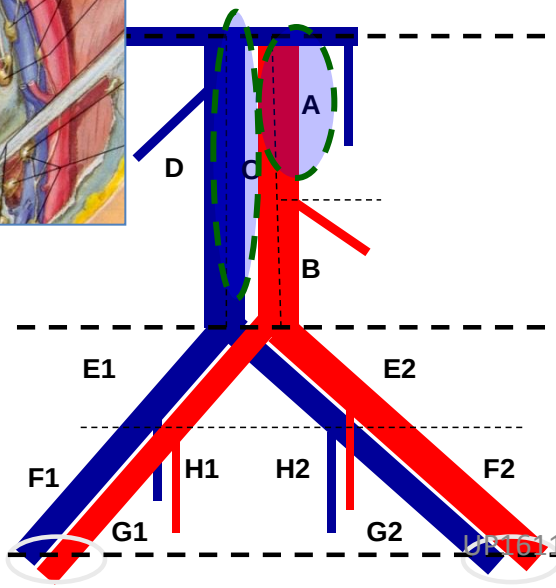
- fisteli 2.1%:lle
- mortaliteetti 0.8%,

Hoffman MS et al Gyn Oncol 2008

Lymfadenektoimat

Lokalisation von LK-Metastasen bei 195 Pat. mit systematischer LNE im Rahmen der Primär-OP eines invasiven Ovarialkarzinoms

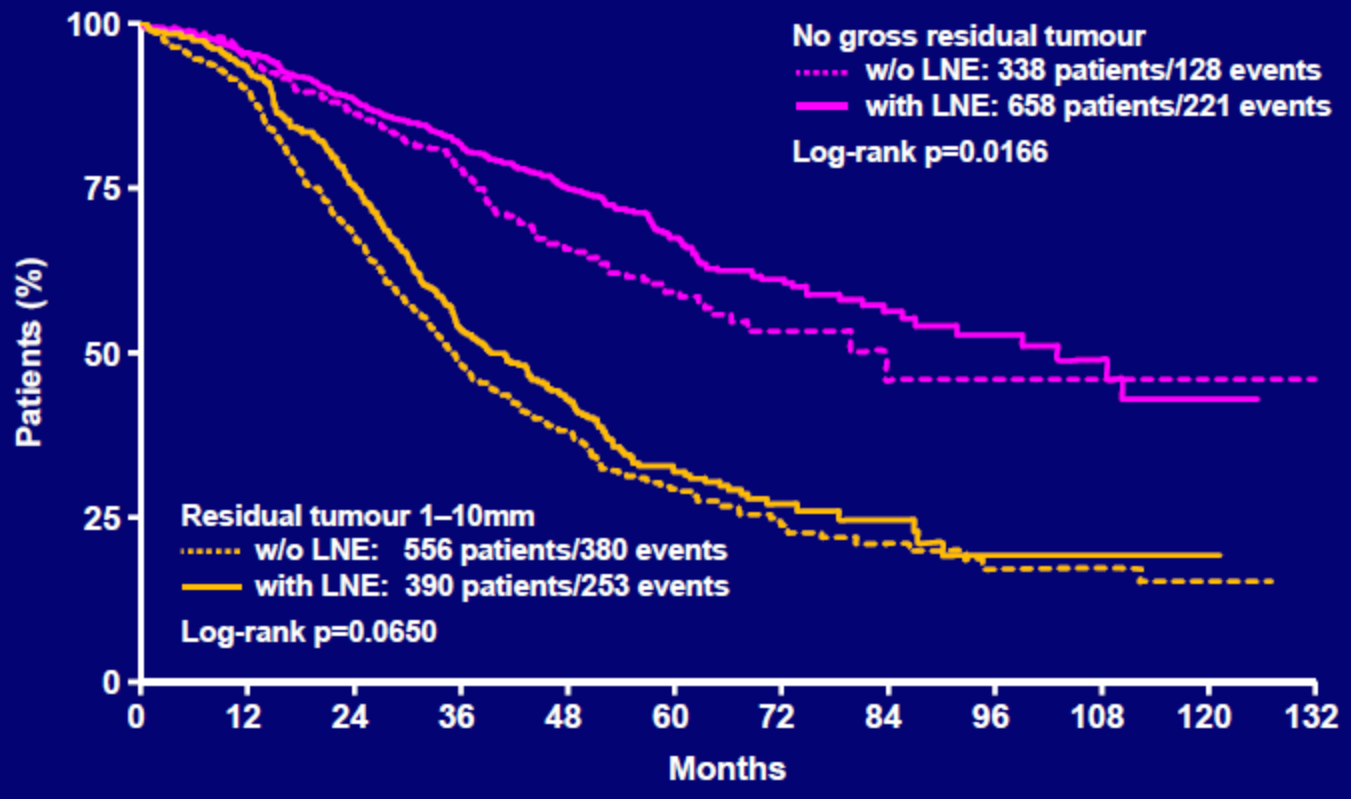




localization of positive lymphnodes	% of all pts.	% of pts. with pN1
A: upper para-aortic	32	**61**
B: lower para-aortic	23	43
C: inter-aorto-caval	36	**68**
D: para-caval	22	40
Σ para-aortic	***48***	***89***
E1: right iliaca communis	16	29
E2: left iliaca communis	17	32
F1: right iliaca externa	18	35
F2: left iliaca externa	26	49
G1: left fossa obturatoria	14	27
G2:right fossa obturatoria	18	35
H1: left iliaca interna	13	24
H2: right iliaca interna	7	13
Σ pelvic	***41***	***77***

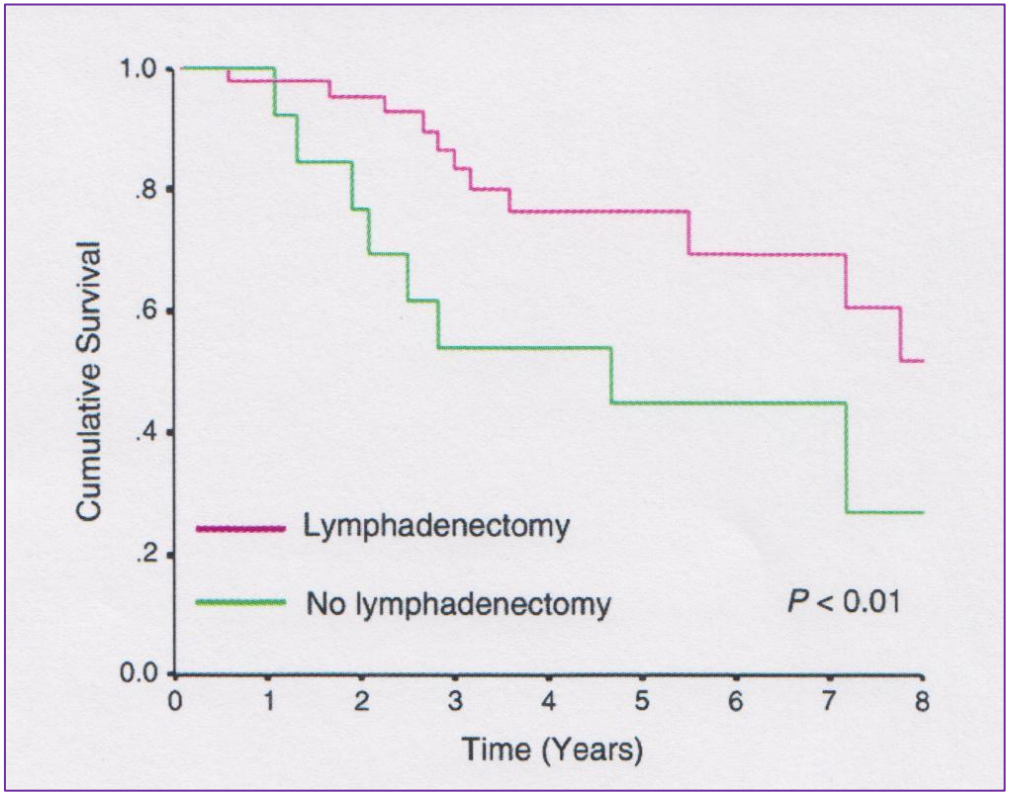
Harter et.al. Int J Gyn Can 2007

Overall survival in patients with or without LNE and no gross residual tumour or post-operative residual tumour 1–10mm



du Bois, et al. JCO 2010

Lymfadenektomian merkitys munasarjasyövän primäärileikkauksessa



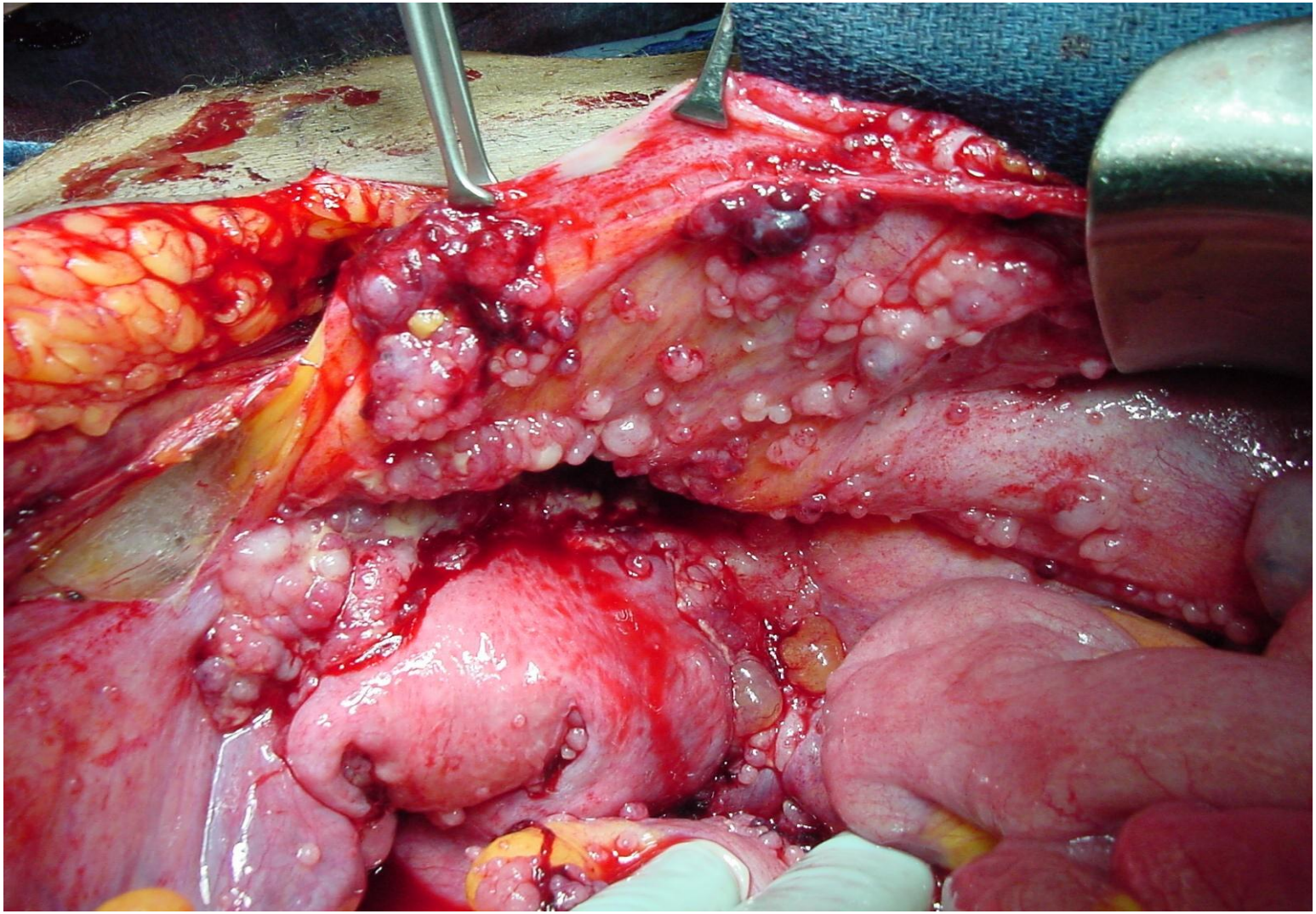
R0 potilailla:

- OS: **86 kk** vs **46 kk**

R1 ja R2 potilailla ei eroa tehtiinpä LAE tai ei

Chang SJ et al Gyn Oncol 2012

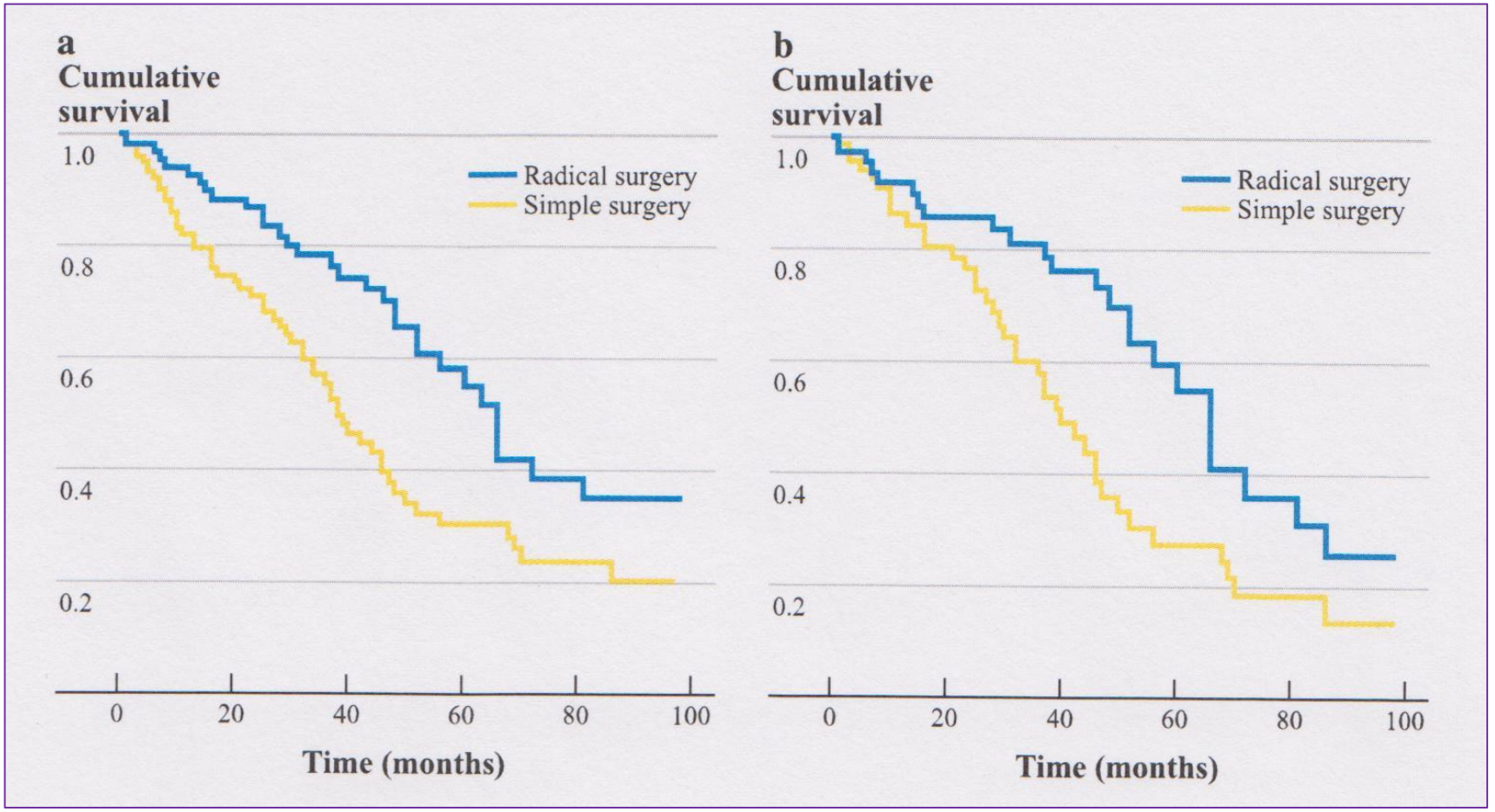
Peritoneaali karsinoosi



UP16112012

Simple: TAH,BSO, Omnetti res, LAE

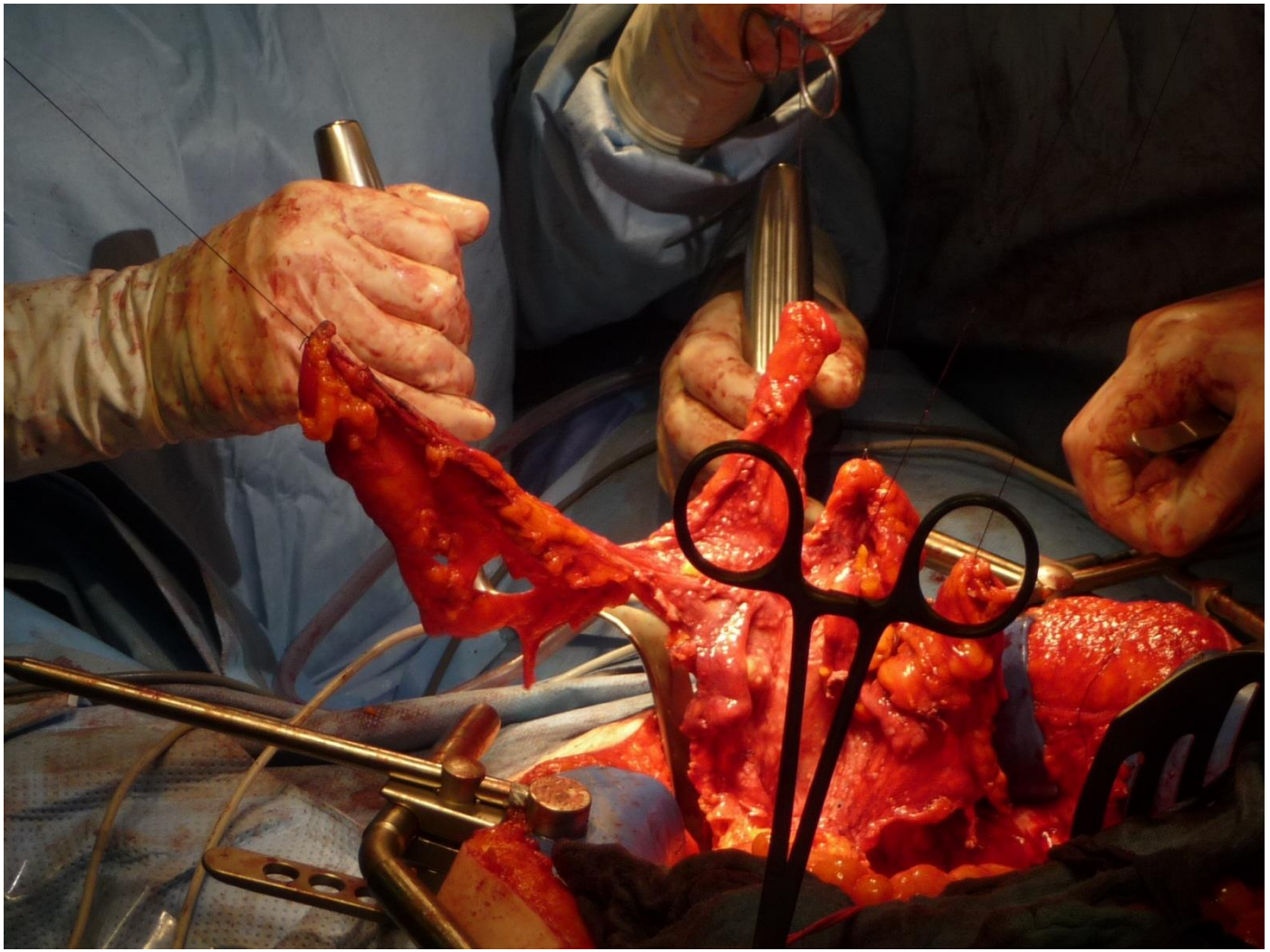
Radical: +rectosigmoid colectomy, omentectomy, multiple bowel resections, diaphragm peritonectomy, liver resection, splenectomy, distal pancreatectomy, gastric resection



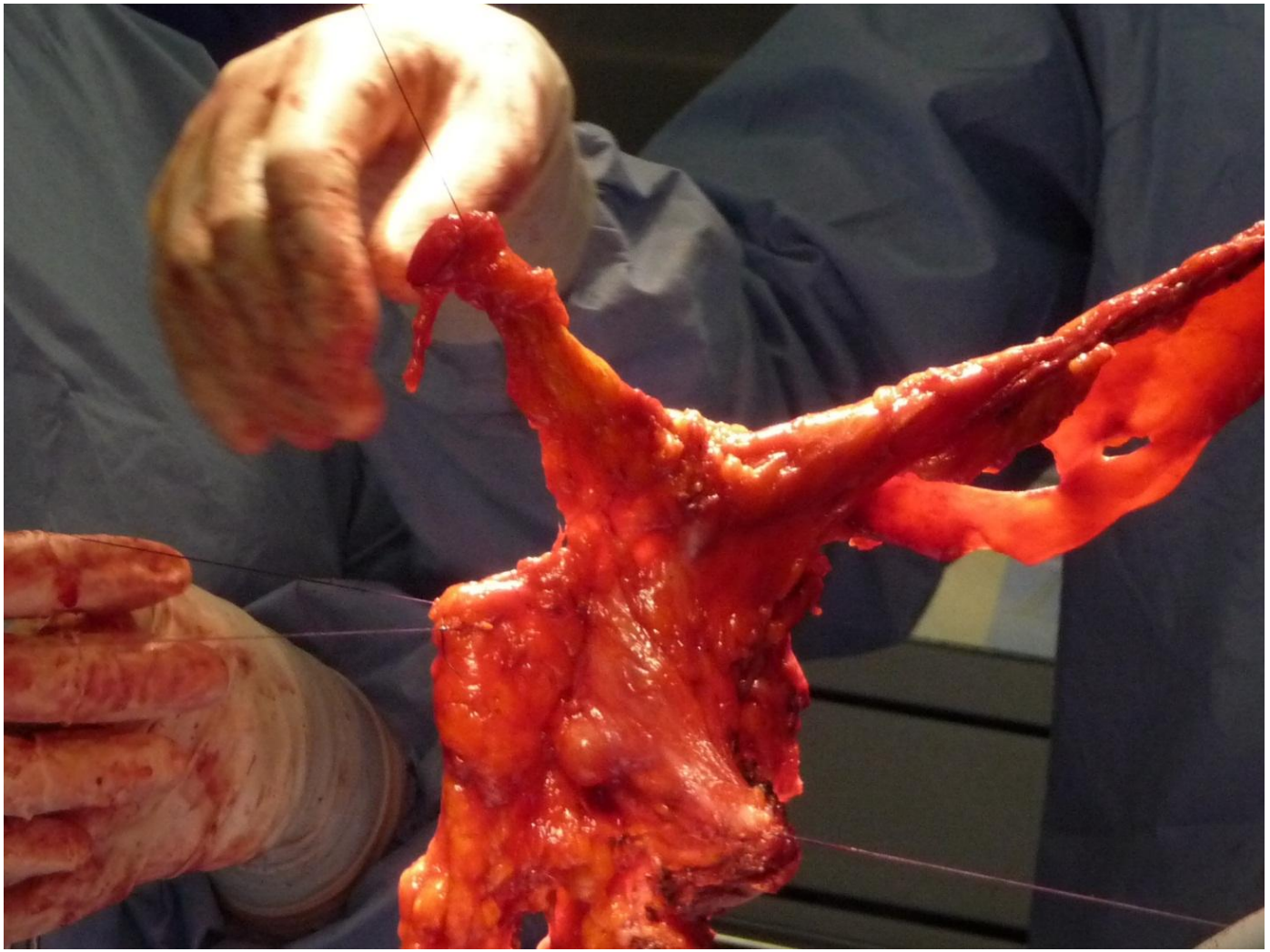
UP16112012B;, peritoneal carsinomatosis

Chang SJ et al Ann Surg oncol 2012

Peritoneal stripping



UP16112012



UP16112012

Radikaalileikkausiin liittyvä morbiditeetti

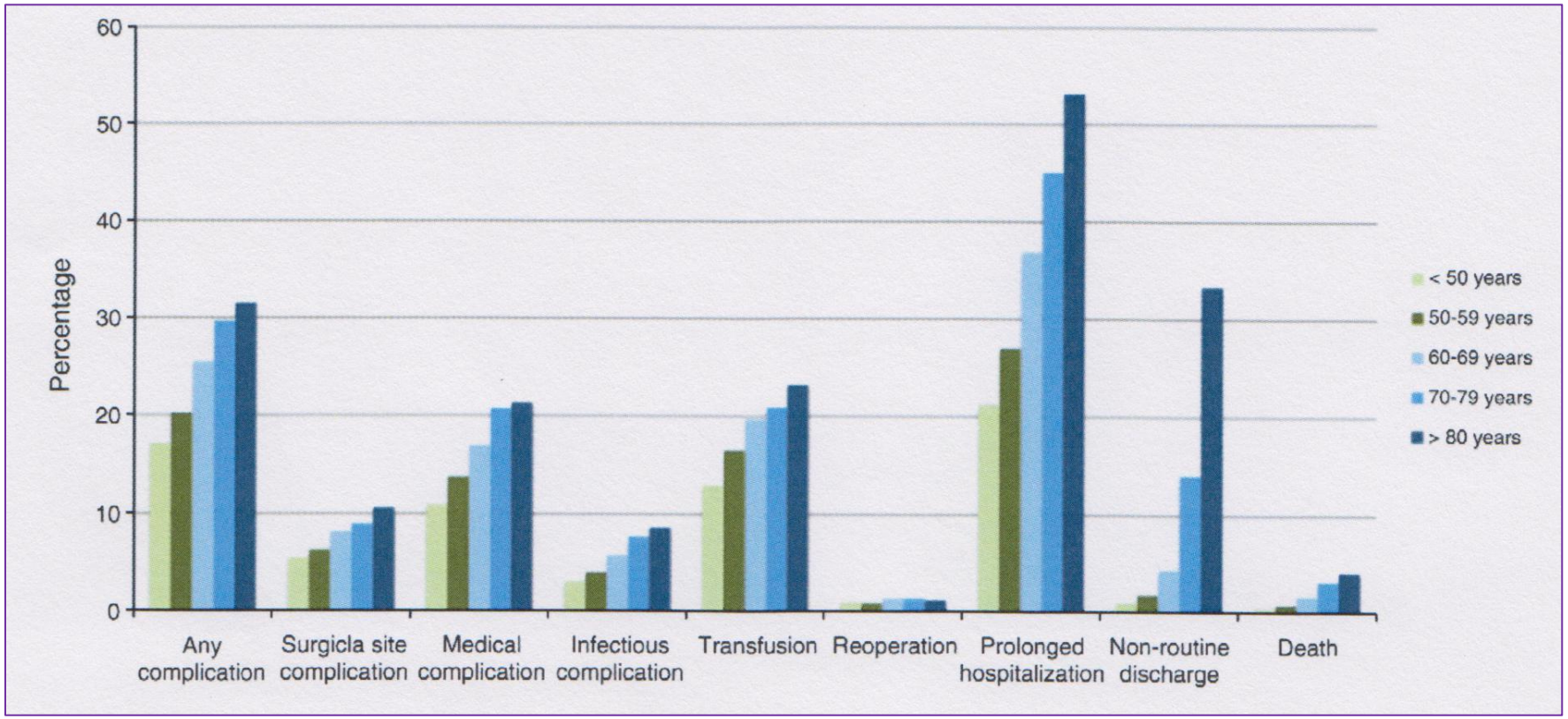
Simple operation (TAH, BSO, LAE, Omentti resektio)

- **11.8% morbidity**

Radical operation (+ parenkyymielinresektiot, peritoneal stripping)

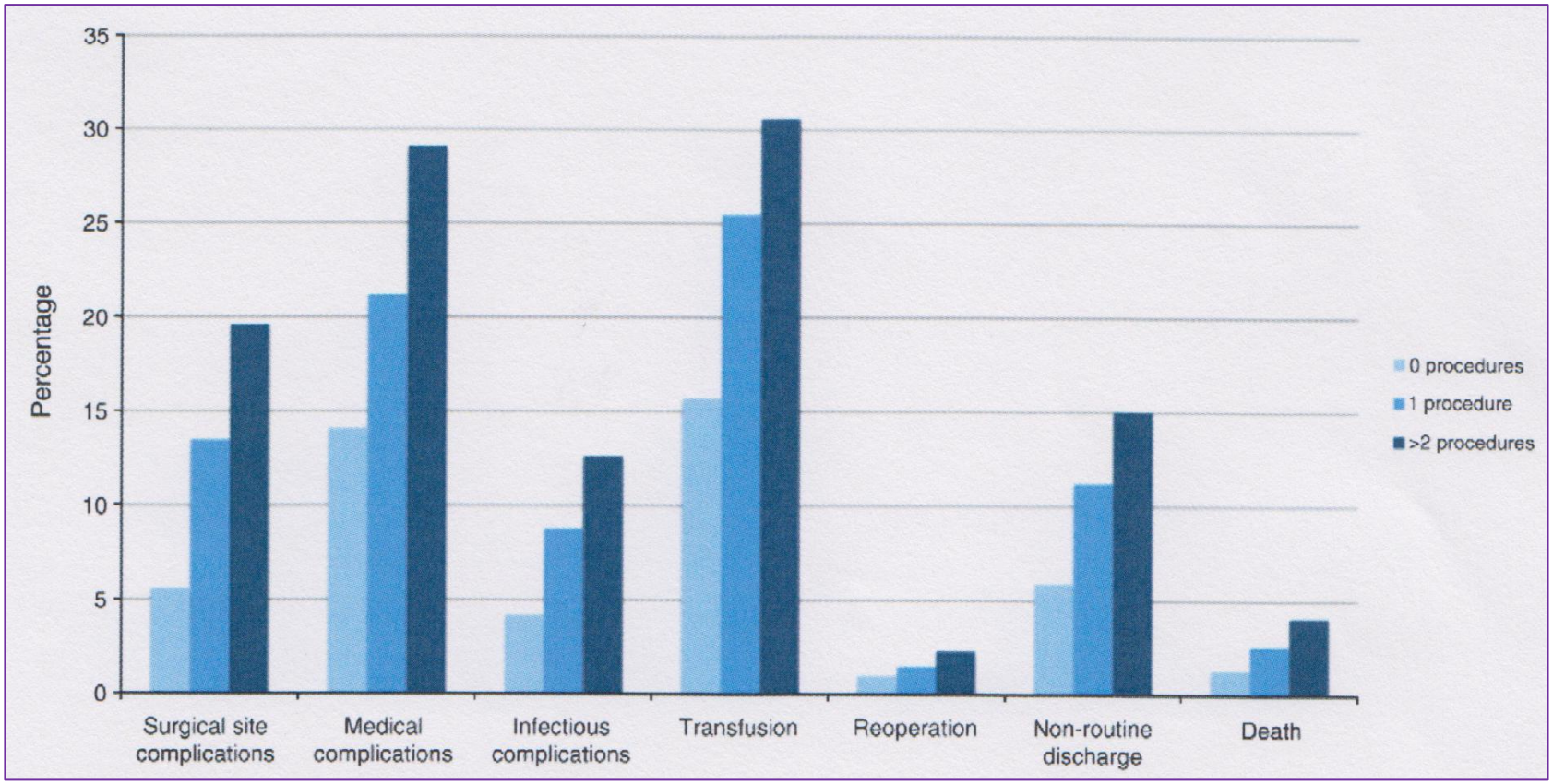
- **38.1% morbidity**

Morbiditeetti kasvaa suhteessa ikään (N=28 000)



Wright JD et al Gyn Oncol 2011

Morbiditeetti kasvaa suhteessa toimenpiteiden määrään



Wright JD et al Gyn Oncol 2011

Radikaalileikkauksiin liittyvät komplikaatiot

Muuttuja		Komplikaatio %
<50 v		17 %
70-79		30
>80		32
Lisätoimenpiteet	0	20
	1	34
	>2	44

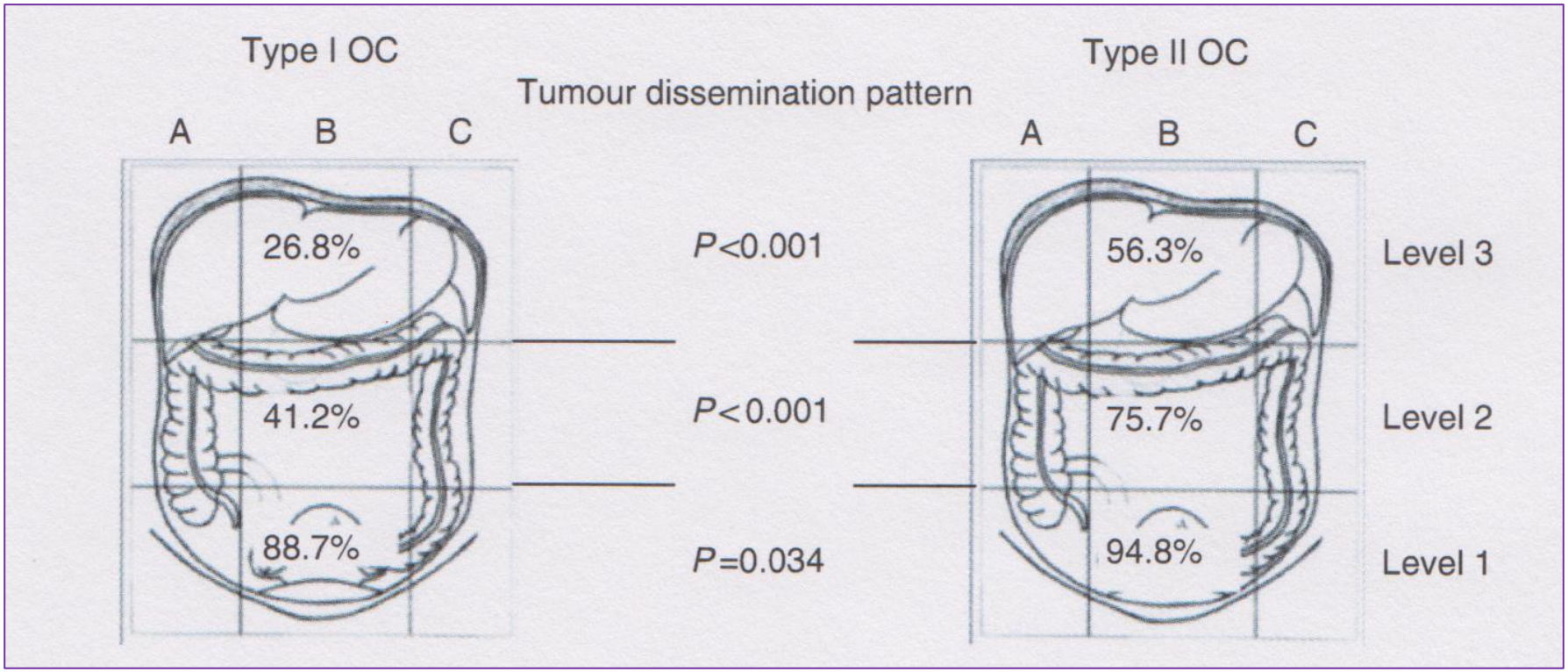
Wright JD et al Gyn Oncol 2011

Korkein morbiditeetti liittyy palleakirurgiaan

N=148	102 potilaalle komplikaatio
Morbiditeetti	**69%**
Infection	55%
lymphocyst	18%
Digestive fistula	7%
Pulmonary complications	**43%**
Pleural effusion	37%
Pulmonary embolism	5%
Pulmonary infection	2%
Mortality	**3%**

Chereau E et al EJSO 2011

Mikä on leikkauksen oikea ajoitus



Suboptimaalinen leikkaus	15%	vs	34%
23 kk kuluttua relapsi	17%	vs	35%
PFS: p=0.003			
OS: p= 0.021			

Braicu E et al BJC 2011

Määrääkö tuumorin biologia operabiliteetin

Tuumorin biologia ja operabiliteetti

Protein/gene	Increased	p
C-erb2	Optimal	0.02
P53	suboptimal	0.01
Maspin	suboptimal	0.04
COX-2	suboptimal	0.03
Cyclin E	suboptimal	0.001
ERCC1	suboptimal	0.001
GLUT-1	suboptimal	0.01
AEG-1	suboptimal	0.001
IGF-1R geeni	suboptilmal	0.03
TGFb1 geeni	suboptimal	0.03

Primäärileikkaus vs Neoadjuvanttihoito edenneissä syövissä

FIGO stage IIIc-IV (n = 718)

Randomisaatio

Primäärileikkaus

6 x Platinum pohjaista kemohoitoa

Neoadjuvantti kemoterapia

3 x Platinum pohjaista hoitoa

↓

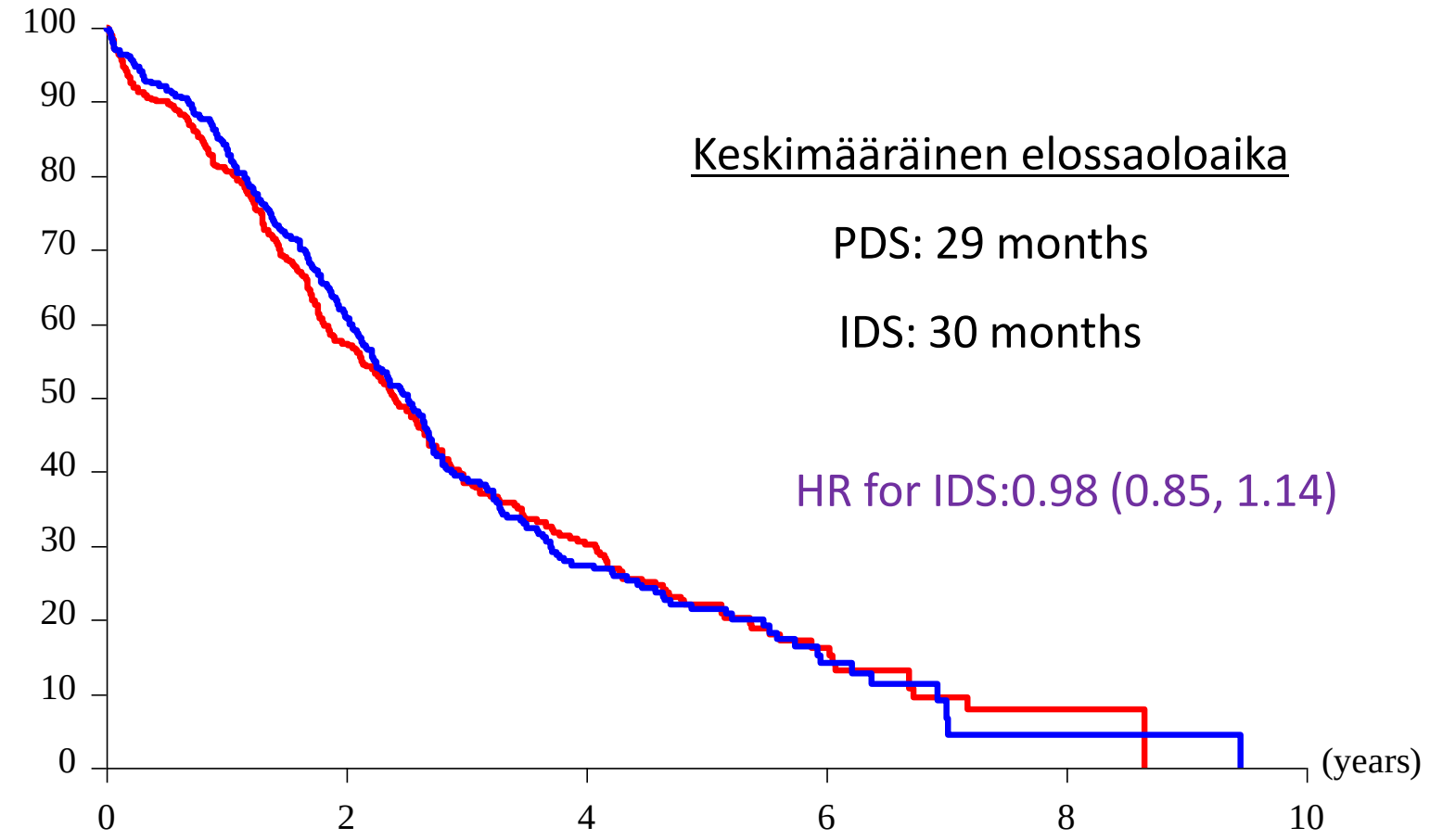
Leikkaus

↓

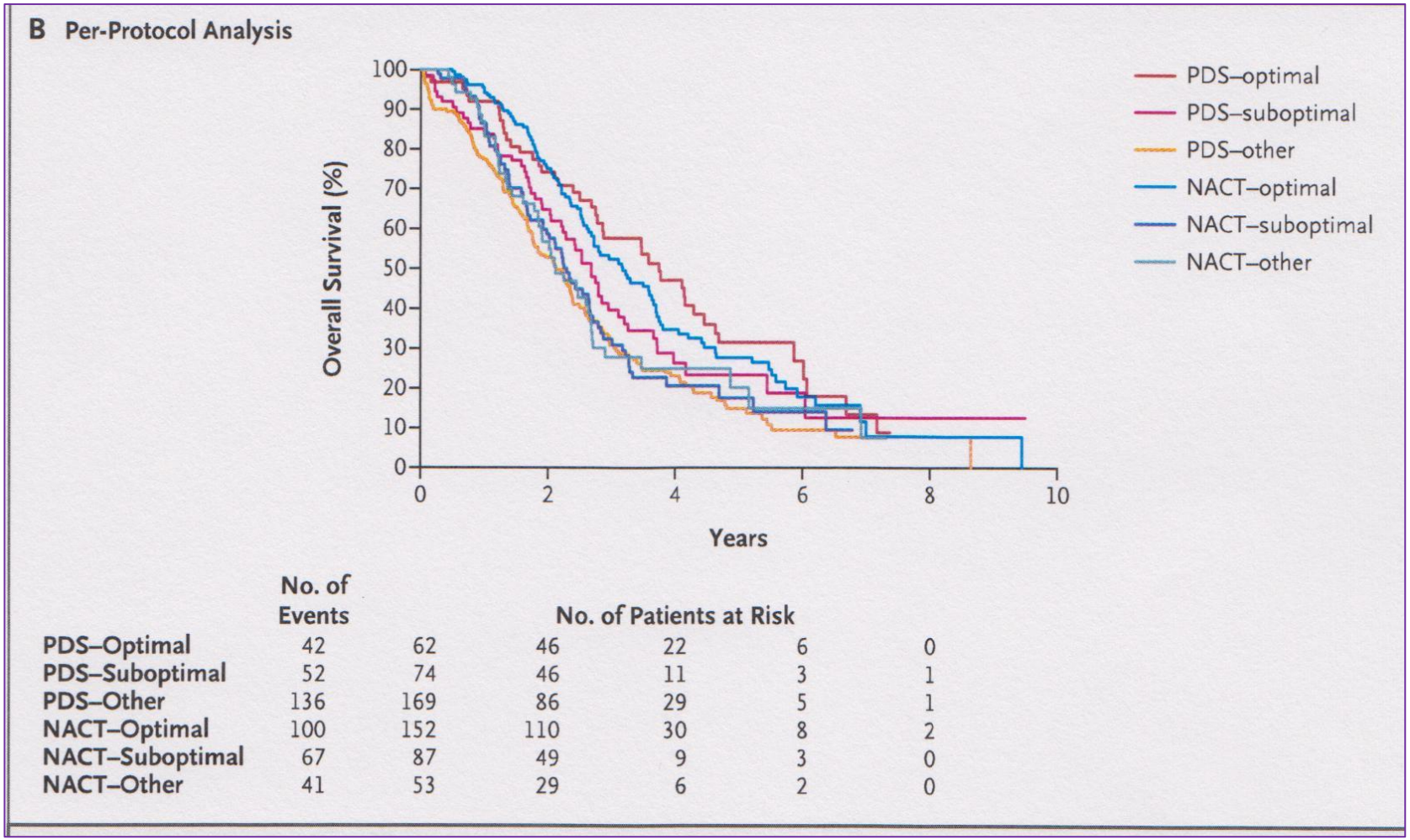
≥ 3 x Platinum pohjaista hoitoa

NEJM:363:943-953: 2010

Primäärileikkaus vs Neoadjuvanttihoito edenneissä syövissä



Primäärileikkaus vs Neoadjuvanttihoito edenneissä syövissä



	No. of Events	No. of Patients at Risk				
PDS–Optimal	42	62	46	22	6	0
PDS–Suboptimal	52	74	46	11	3	1
PDS–Other	136	169	86	29	5	1
NACT–Optimal	100	152	110	30	8	2
NACT–Suboptimal	67	87	49	9	3	0
NACT–Other	41	53	29	6	2	0

Kuka leikkaa	• **Gynekologi onkologi**
Mitkä ovat leikkauksen tavoitteet	• **R 0- ei näkyvää jäännöstuumoria**
Mikä on leikkauksen oikea ajoitus	• **Primäärileikkaus jos mahdollisuus R 0 tulokseen** • **NACT jos edennyt tauti ja /tai radikaalileikkauksen riskit suuret**

527

- St IIIC 83%
- St IV 16%

Primäärileikkaus 36%

- R 0 – 65%

Neoajuvantti 64%

- R 0 – 71%

	No. Patients	(%)
Hysterectomy	489	(92.8)
Salpingo-oophorectomy	504	(95.8)
Omentectomy	516	(97.9)
Small-bowel resection	52	(9.9)
Large-bowel resection	200	(38.0)
Multiple bowel resection	64	(12.2)
Appendectomy	339	(64.6)
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Splenectomy	50	(9.5)
Partial hepatic resection	17	(3.2)
Porta hepatis removal	10	(1.9)
Cholecystectomy	17	(3.2)
Surgical groups		

Luyckx M et al Int J Gyn Cancer 2012

TABLE 3. Multivariate analysis using Cox proportional hazard modeling

	Disease-Free Survival			Overall Survival		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Stage						
IIIC	1			1		
IV	1.28	(0.92–1.79)	0.142	1.39	(0.93–2.08)	0.111
Grade (1, low; 2–3, high)						
1	1			1		
2	1.39	(0.87–2.22)	0.171	1.28	(0.68–2.41)	0.439
3	1.24	(0.79–1.94)	0.351	1.04	(0.56–1.92)	0.904
Surgical groups						
1	1			NA		
2A	1.54	(1.07–2.23)	0.020	NA		
2B	1.66	(1.16–2.39)	0.005	NA		
Upper abdominal disease						
0	1			1		
>10 mm	1.03	(0.74–01.44)	0.859	1.11	(0.77–1.62)	0.566
Residual disease after surgery						
0	1			1		
1–10 mm	1.68	(1.20–2.35)	0.002	1.85	(1.20–2.86)	0.005
>10 mm	2.69	(1.68–4.31)	<0.001	2.06	(1.26–3.37)	0.004
Timing of surgery						
Primary	1					
Interval	1.51	(1.13–2.03)	0.006	NA		
After 6 cycles	1.49	(1.08–2.32)	0.019	NA		

NA, not applicable (not significant at univariate analysis).

Luyckx M et al Int J Gyn Cancer 2012

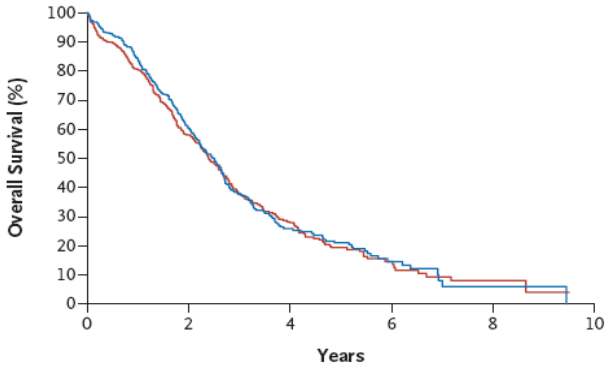
säästävä leikkaus munasarjasyövässä

Aineisto 10 eri julkaisusta 2000 luvulta

N	Stage I a / b /c	Grade 1 / 2 / 3	Relapse	Death	Rec	
783	**475 /7 /294**	**532/145/107**	**12%**	**6%**	**St I, gr1-2**	

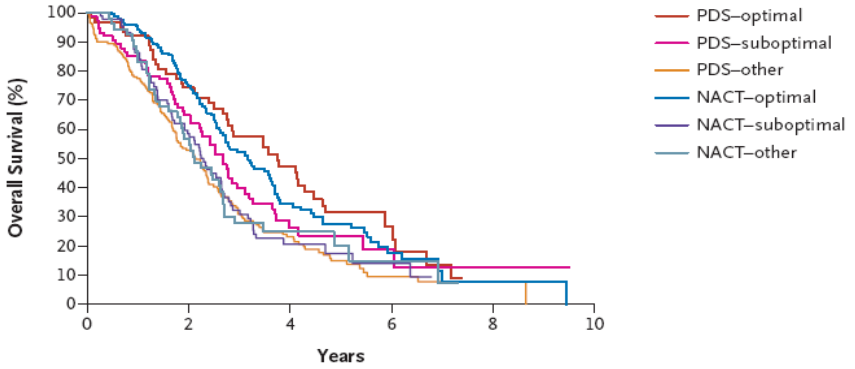
Frusio R et al Ann Oncol 2012

A Intention-to-Treat Analysis



	No. of Events	No. of Patients at Risk				
Primary Debulking Surgery (PDS)	253	336	189	62	14	2
Neoadjuvant Chemotherapy (NACT)	245	334	195	46	13	2

B Per-Protocol Analysis



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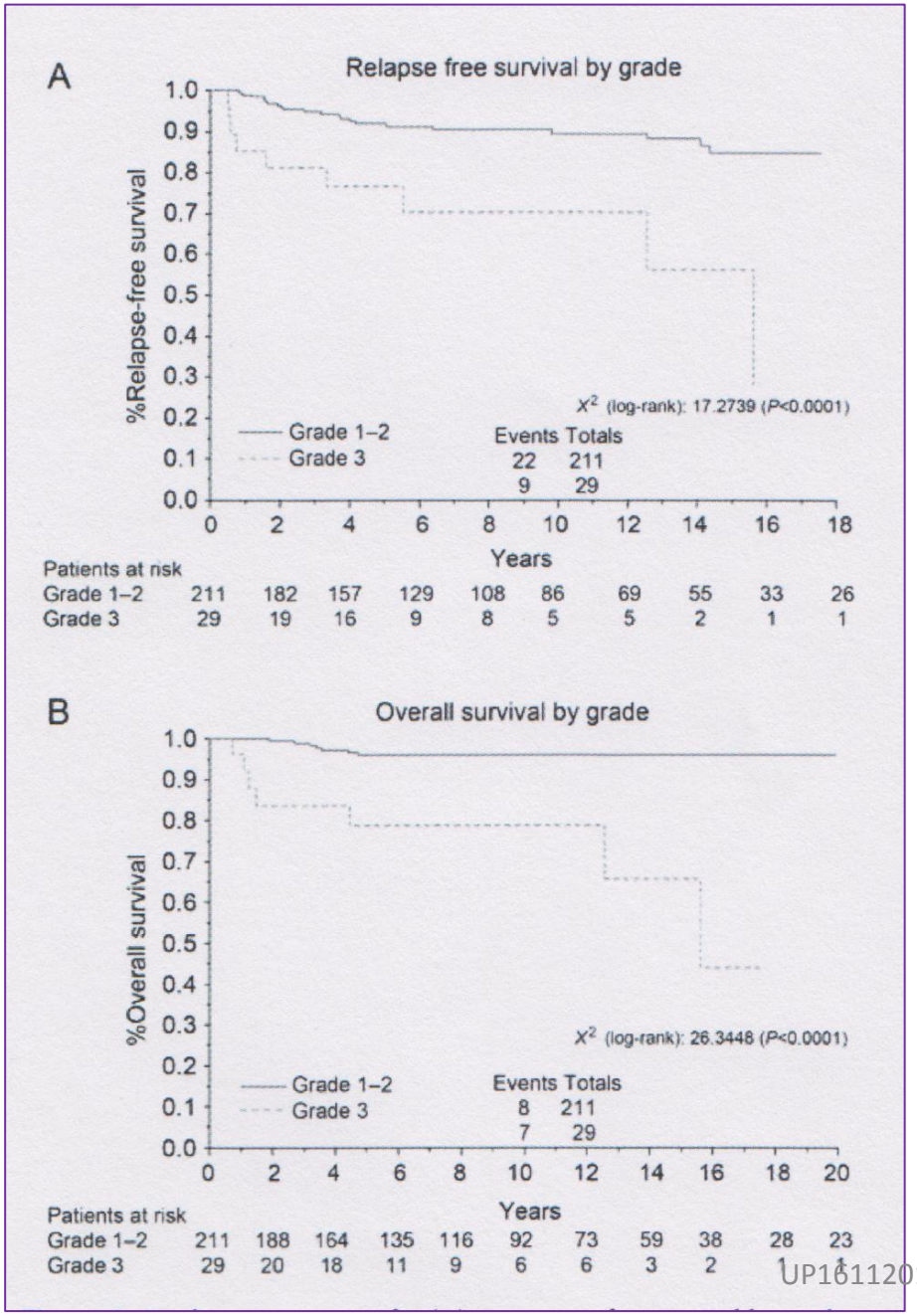
NACT–Optimal	100	152	110	30	8	2
NACT–Suboptimal	67	87	49	9	3	0
NACT–Other	41	53	29	6	2	0

Figure 2. Overall Survival in the Intention-to-Treat Population and Overall Survival According to Treatment Received and Status with Respect to Residual Tumor.

The median overall survival was 29 months among the women assigned to primary debulking surgery and 30 months among those assigned to neoadjuvant chemotherapy (Panel A). The median overall survival for women with no residual tumor (optimal result), those with residual tumors that measured 1 to 10 mm in diameter (suboptimal result), and those with residual tumors larger than 10 mm (other result) was 45, 32, and 26 months, respectively, in the group that underwent primary debulking surgery and 38, 27, and 25 months, respectively, in the group that underwent neoadjuvant chemotherapy (Panel B).

Vergote et.al. NEJM 2010



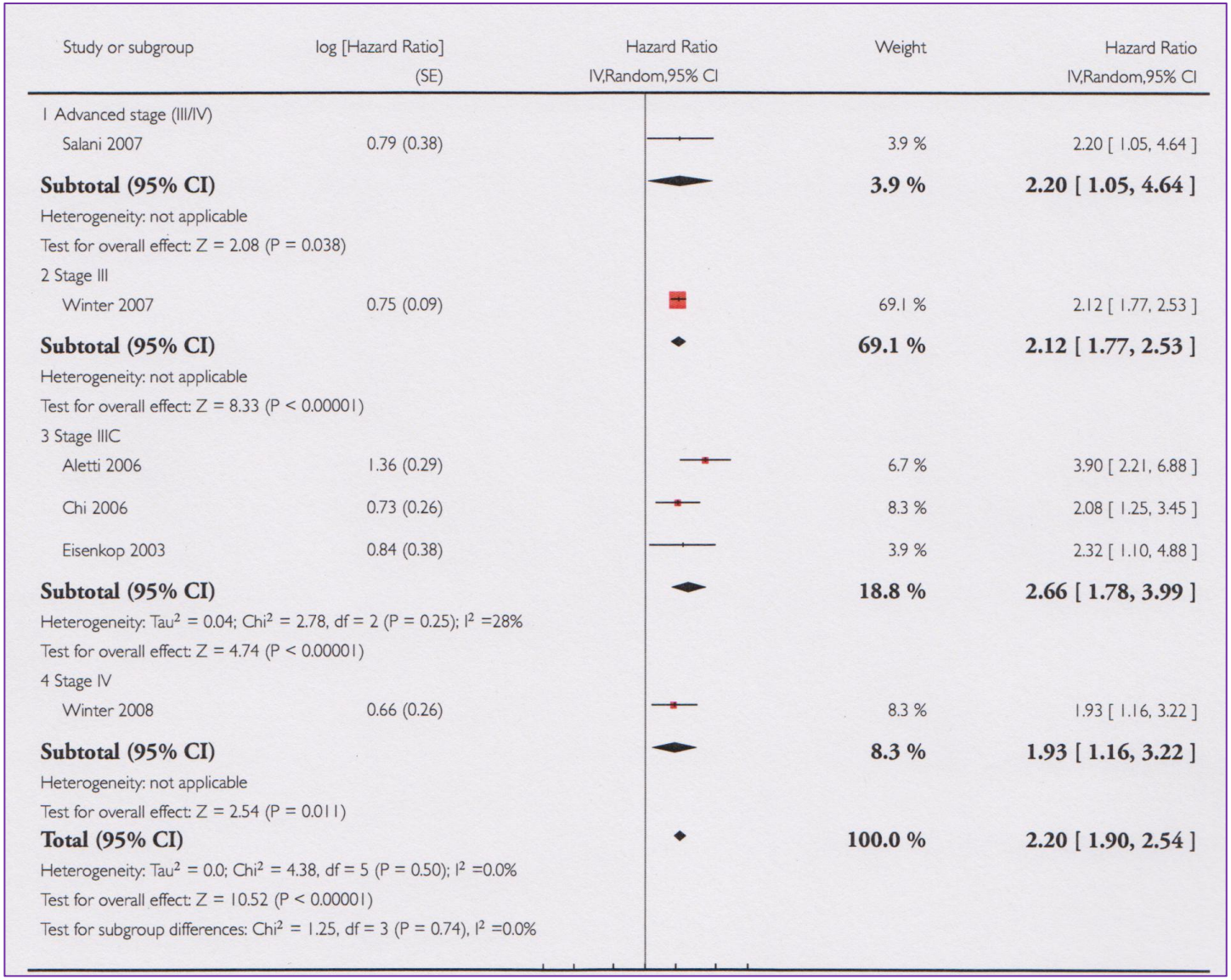
Grade 3 tuumorit korkeimmassa riskissä
Uusiutua ja johtaa kuolemaan

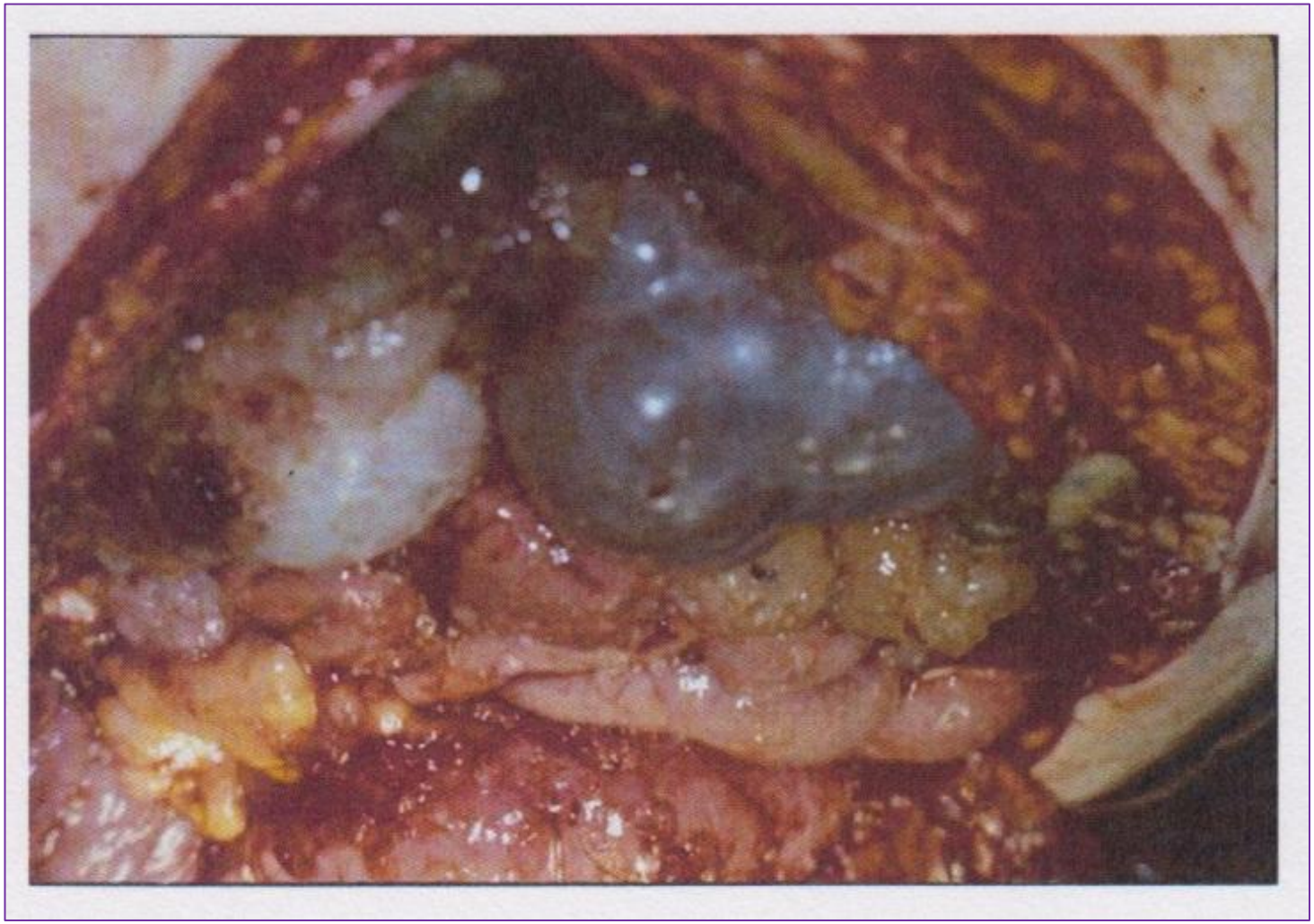
Frusio R et al Ann Oncol 2012

PFS, Figo St III

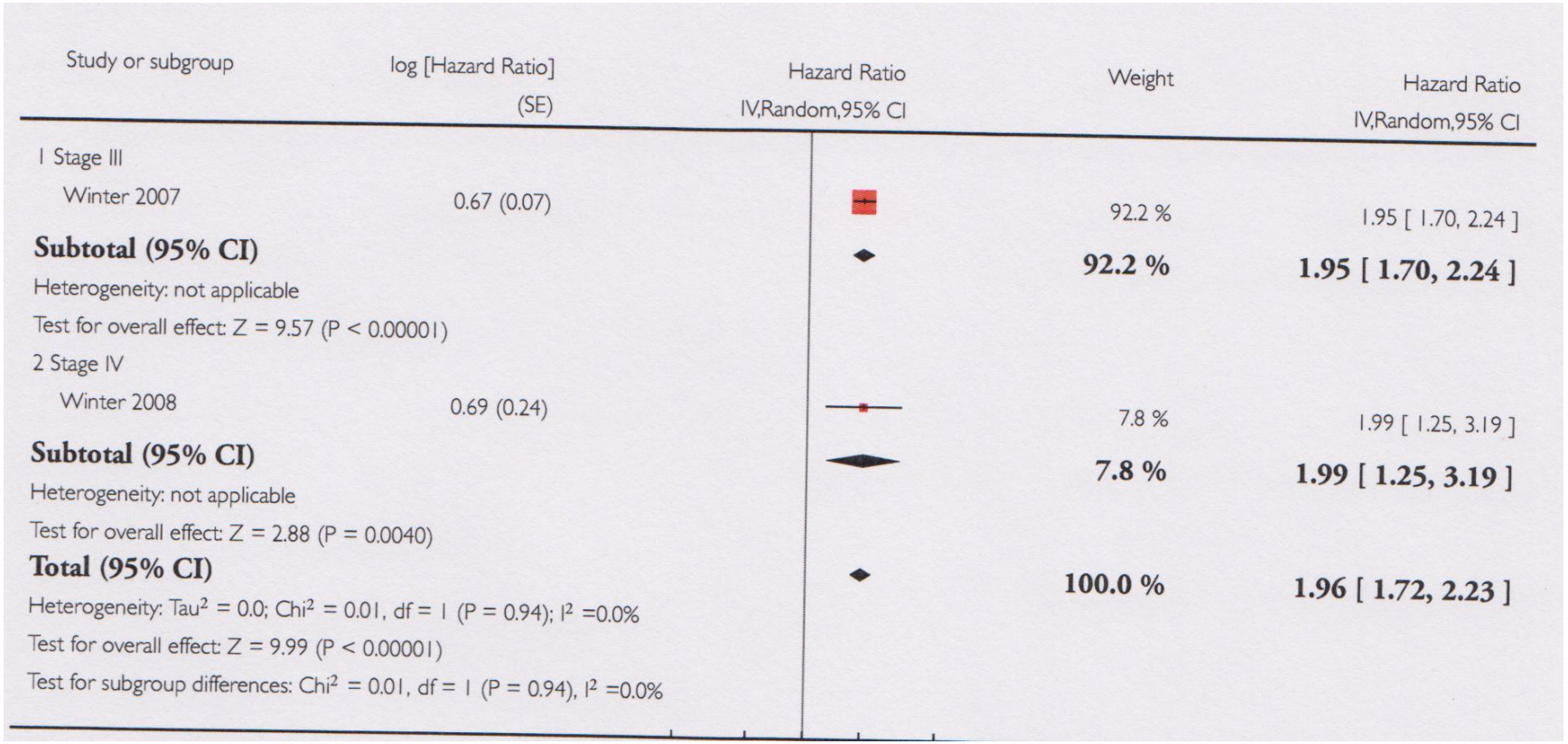
Jäännöstuumori	HR	
1-2cm vs <1cm	1.70	(95% CI 1.1-2.6)
>2cm vs <1cm	2.00	(95% CI 1.3-2.9)
	2.83% mortality for surgery	

Elattar A et al


Study or subgroup
log [Hazard Ratio] (SE)
Hazard Ratio IV,Random,95% CI
Weight
Hazard Ratio IV,Random,95% CI
1 Advanced stage (III/IV)
Salani 2007 0.79 (0.38) 3.9 % 2.20 [1.05, 4.64]
Subtotal (95% CI) 3.9 % 2.20 [1.05, 4.64]
Heterogeneity: not applicable
Test for overall effect: Z = 2.08 (P = 0.038)
2 Stage III
Winter 2007 0.75 (0.09) 69.1 % 2.12 [1.77, 2.53]
Subtotal (95% CI) 69.1 % 2.12 [1.77, 2.53]
Heterogeneity: not applicable
Test for overall effect: Z = 8.33 (P < 0.00001)
3 Stage IIIC
Aletti 2006 1.36 (0.29) 6.7 % 3.90 [2.21, 6.88]
Chi 2006 0.73 (0.26) 8.3 % 2.08 [1.25, 3.45]
Eisenkop 2003 0.84 (0.38) 3.9 % 2.32 [1.10, 4.88]
Subtotal (95% CI) 18.8 % 2.66 [1.78, 3.99]
Heterogeneity: Tau² = 0.04; Chi² = 2.78, df = 2 (P = 0.25); I² =28%
Test for overall effect: Z = 4.74 (P < 0.00001)
4 Stage IV
Winter 2008 0.66 (0.26) 8.3 % 1.93 [1.16, 3.22]
Subtotal (95% CI) 8.3 % 1.93 [1.16, 3.22]
Heterogeneity: not applicable
Test for overall effect: Z = 2.54 (P = 0.011)
Total (95% CI) 100.0 % 2.20 [1.90, 2.54]
Heterogeneity: Tau² = 0.0; Chi² = 4.38, df = 5 (P = 0.50); I² =0.0%
Test for overall effect: Z = 10.52 (P < 0.00001)
Test for subgroup differences: Chi² = 1.25, df = 3 (P = 0.74), I² =0.0%



Diffuse peritoneaali karsinoosi affisioiden laajasti suolen paritaalipintoja


Study or subgroup
log [Hazard Ratio] (SE)
Hazard Ratio IV,Random,95% CI
Weight
Hazard Ratio IV,Random,95% CI
1 Stage III
Winter 2007
0.67 (0.07)
92.2 %
1.95 [1.70, 2.24]
Subtotal (95% CI)
92.2 %
1.95 [1.70, 2.24]
Heterogeneity: not applicable
Test for overall effect: Z = 9.57 (P < 0.00001)
2 Stage IV
Winter 2008
0.69 (0.24)
7.8 %
1.99 [1.25, 3.19]
Subtotal (95% CI)
7.8 %
1.99 [1.25, 3.19]
Heterogeneity: not applicable
Test for overall effect: Z = 2.88 (P = 0.0040)
Total (95% CI)
100.0 %
1.96 [1.72, 2.23]
Heterogeneity: Tau² = 0.0; Chi² = 0.01, df = 1 (P = 0.94); I² =0.0%
Test for overall effect: Z = 9.99 (P < 0.00001)
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² =0.0%

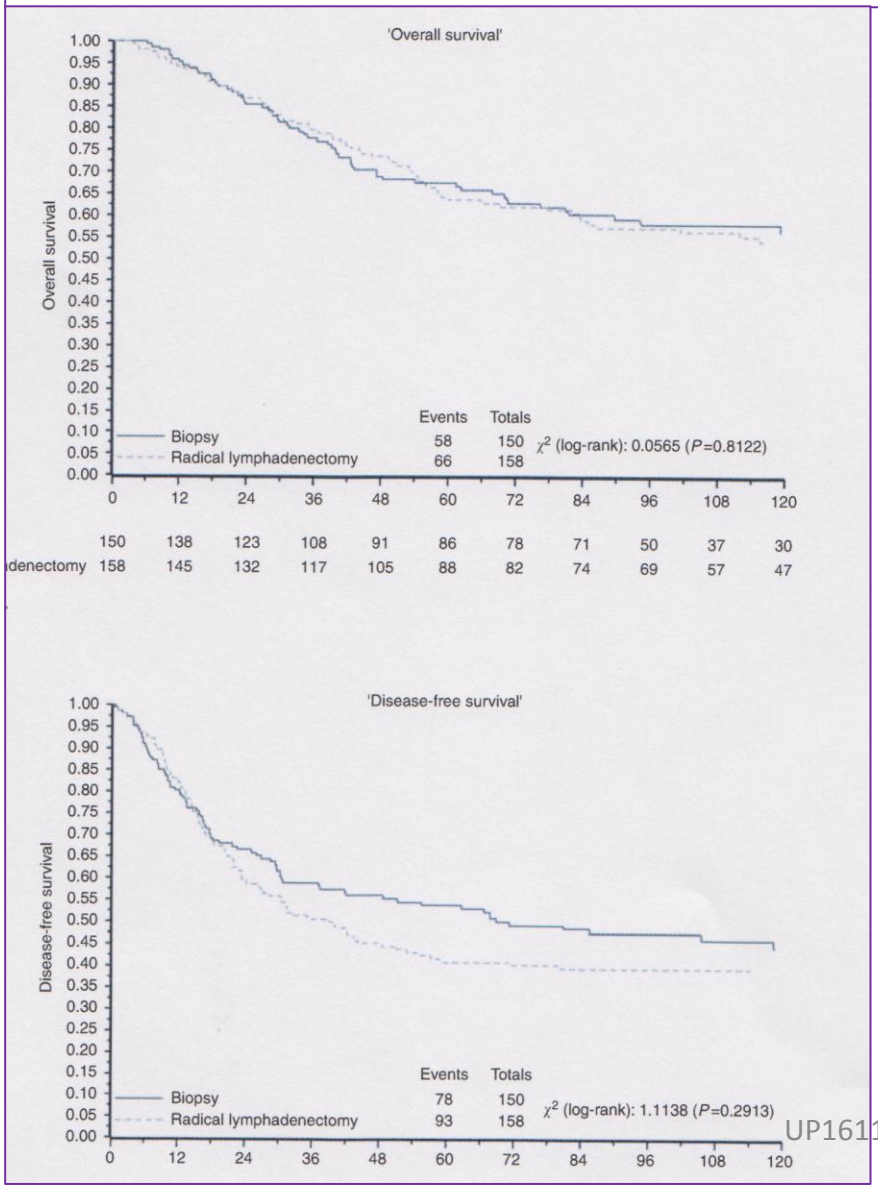
Morbiditeetti primääri vs intervalli radikaali leikkauksessa

	PCS Group n = 50	ICS Group n = 13	*P*
Perioperative complications, n (%)	10 (20)	1 (8)	0.43
Bladder injury	2 (4)	1 (8)	0.51
Intestinal injury	1 (2)	0	1
Ureteral injury	2 (4)	0	1
Pleural effusion	4 (8)	0	1
Other	1 (2%)	0	1
Operative time, man (range), min	464 (240–650)	430 (240–660)	0.46
Estimated blood loss, mean (range), mL	1223 (100–5000)	937 (300–2500)	0.41
Units of blood transfused, mean (range)	2.1 (0–8)	2.1 (0–6)	0.97

Ero tehohoitopäivien määrässä NACT hyväksi

Revaux A et al Int J Gyn Cancer 2012

Lymfadenektomian merkitys second-look kirurgiassa



- PFS 41% vs 54%
- OS 63% vs 67%

DellAnna T etal BJC 2012

- 1998-2007
- N=28 651
- Morbiditeetti iän ja toimenpiteiden suhteen

Optimal primary surgical treatment for advanced epithelial ovarian cancer
Cochrane katsaus 2011; 1274 julkaisua (11 mukaan)

Jäännöstuumori:

Kokonaiselinaika ennuste (OS)

<1cm vs miksoskooppinen tauti(MD) (N=3447)

- -2x kuoleman riski

1-2cm vs MD

- -6x kuolemanriski

>1cm vs MD (N=2893)

- -3x kuolemanriski

>2cm vs MD

- -12x kuolemanriski

- Progressiovapaa aika (PFS)

<1cm vs MD

- -2x riski progressioon

>1cm vs MD

- - yli 2x riski

>5cm vs MD

- -yli 2x riski

Elattar A et al

St III; PFS ja OS suhteessa jäännöstuumoriin

PFS

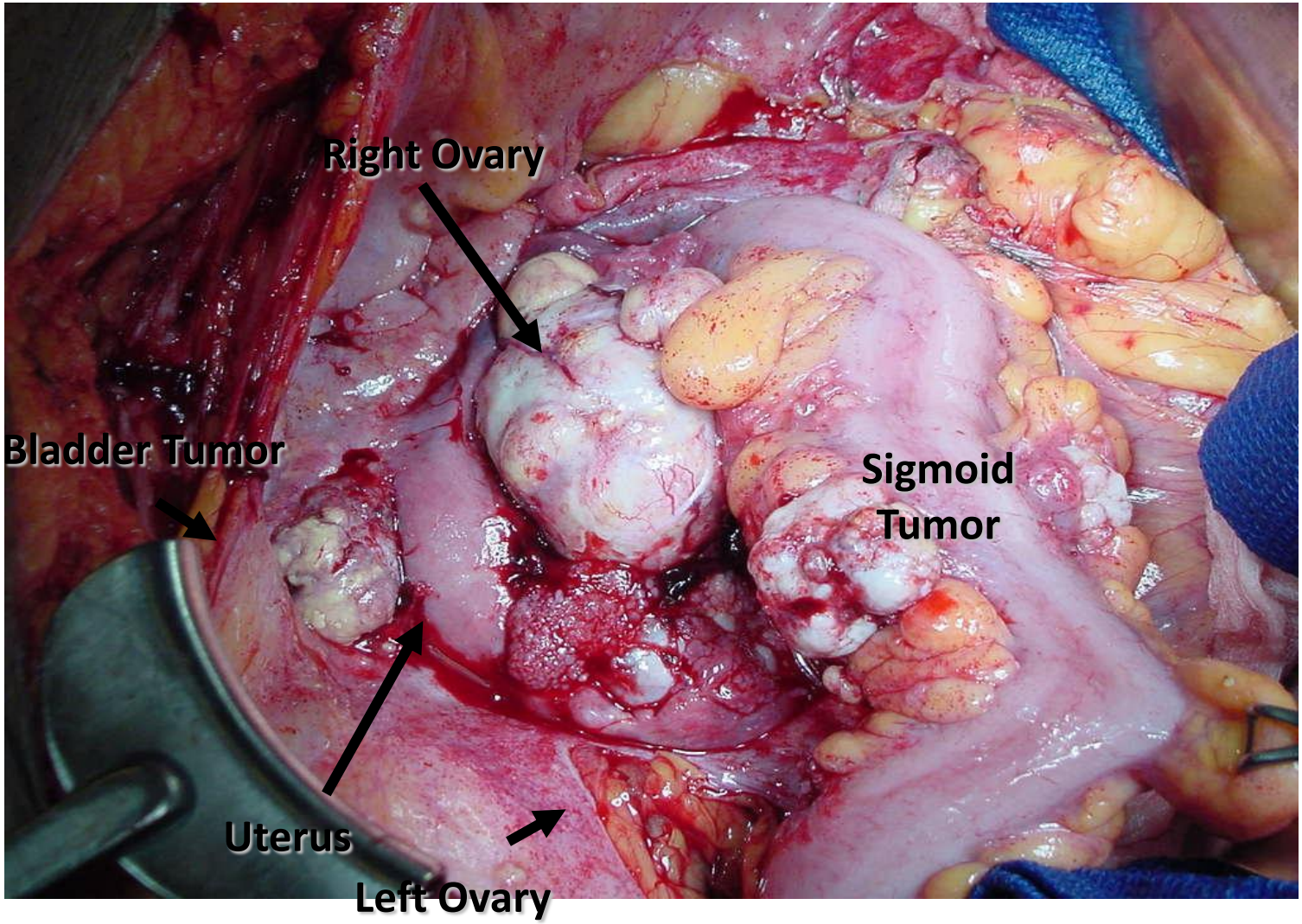
Residua		kk
<1cm		33 kk
1-2cm		17 kk
>2cm		14 kk

OS

Residua	5-v	MS
<1cm	50%	56 kk
1-2cm	28%	31 kk
>2cm	21%	28 kk

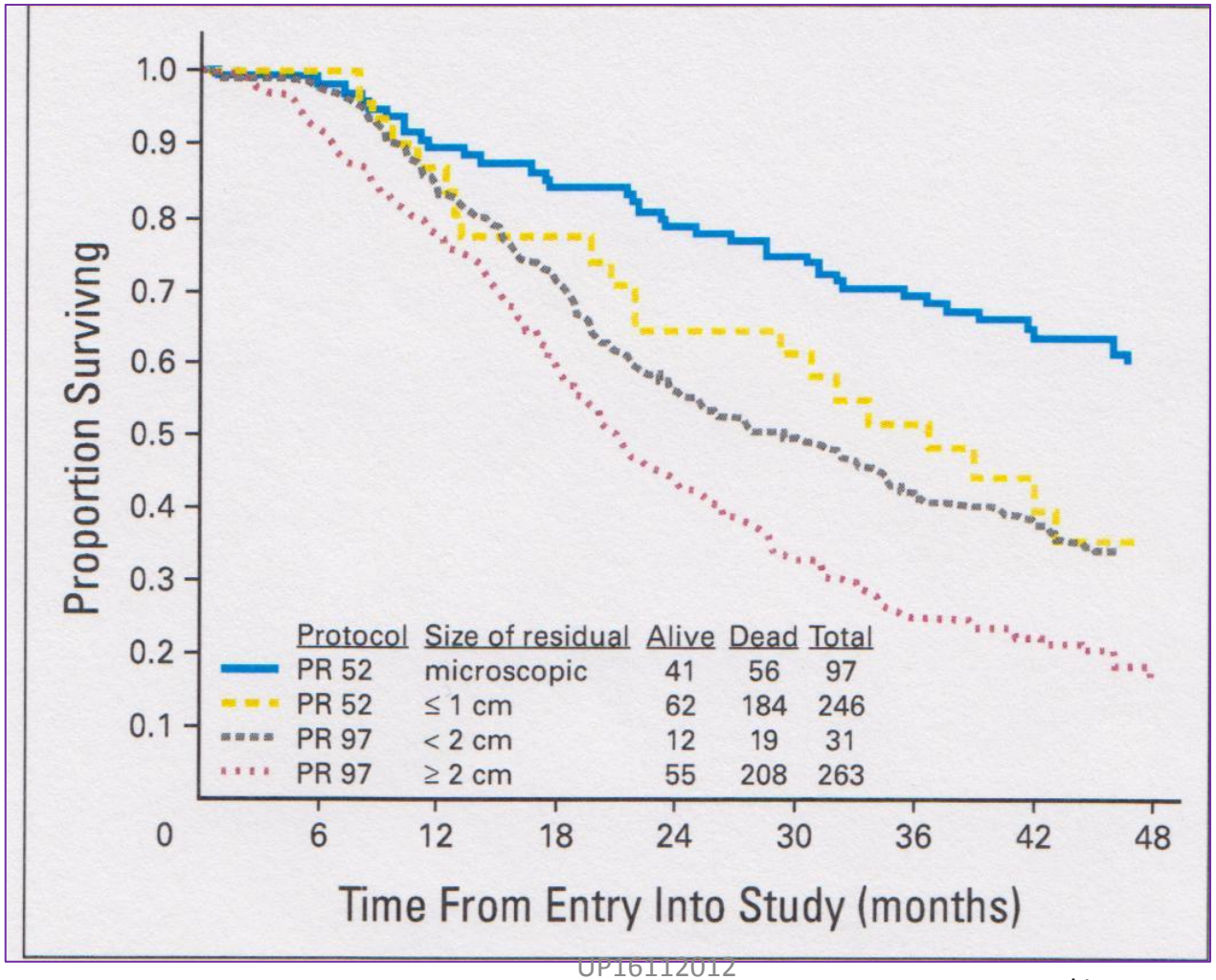
Elattar A et al

Ovarian cancer: Surgery



UP16112012

Jäännöstuumorin merkitys ennusteeseen



Hoskins WJ et al Am J Obst Gyn 1994

Milloin pyritään radikaalileikkaukseen

Jos voidaan vähentää tuumorimäärää

- R1 ⟹ R0, niin radikaalileikkaus
- R2 ⟹ R1 , radikaali leikkauksen hyötyä ei osoitettu

Chang SJ et al Gyn oncol 2012

Optimal primary surgical treatment for advanced epithelial ovarian cancer

Cochrane katsaus 2011; 1274 julkaisua (11 mukaan)

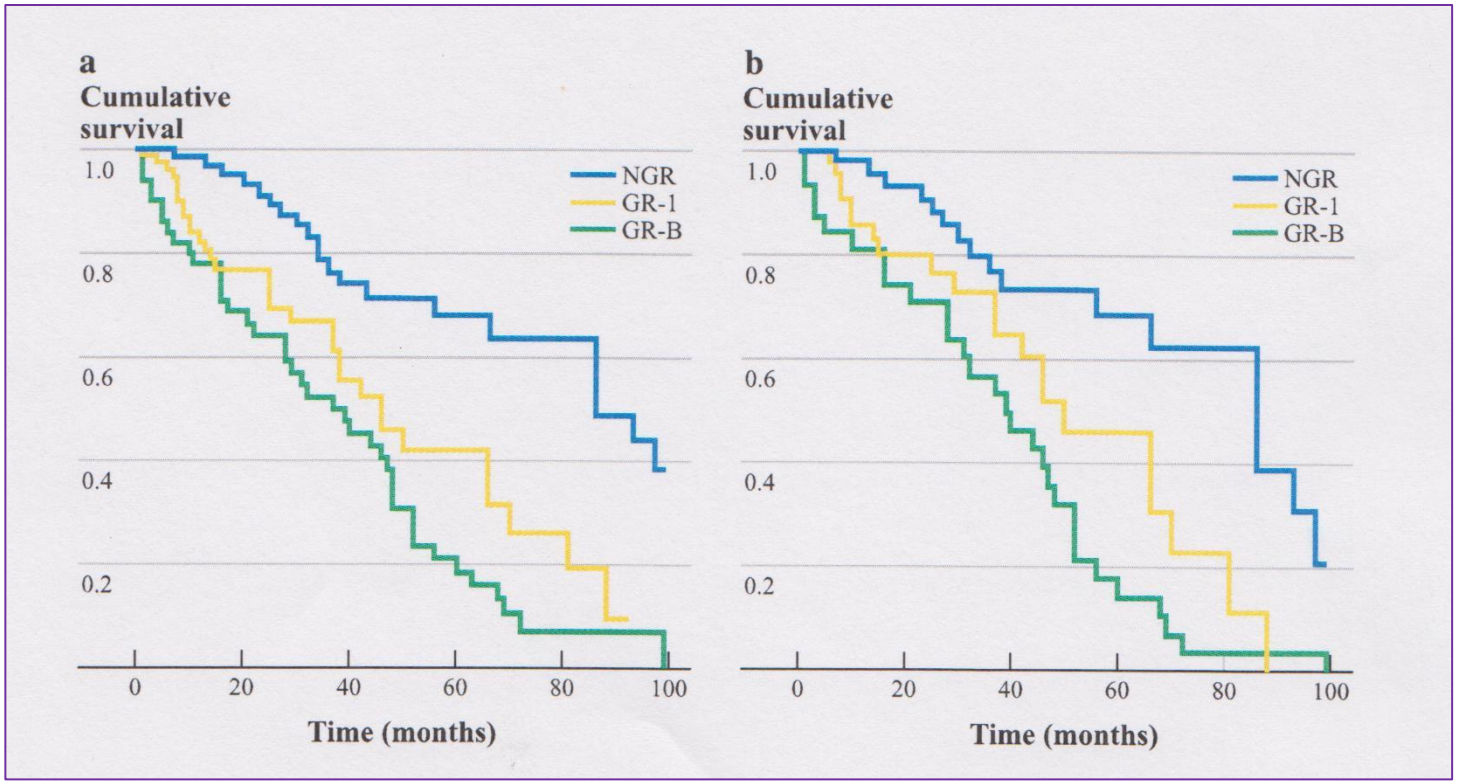
Jäännöstuumori	HR	OS
<1cm vs 0	3.89	(95% CI 2.27-7.11)
1-2cm vs 0	6.25	(95% CI 3.16-12.61)
>2cm vs 0	13.00	(95% CI 7.14-24.87)

Elattar A et al

Lymphadenectomy in ovarian cancer: scenarios

Stage	Intraabdominal residual tumour (intra-OP)	Clinically (intra-OP) / radiologically (pre-OP) negative LN	Clinically (intra-OP) / radiologically (pre-OP) positive LN (≥1cm)
FIGO III/IV	0	*Yes or no?*	**Yes** → *LNE for debulking to no gross residual tumour*
	1–10 mm	**Yes or no?** 7 months PFS gain, but no OS gain in Int LNE study (Benedetti)	**Yes** → *LNE for debulking to residual tumour ≤1cm*
	>1 cm	**No**	**No**

Radikaali leikkauksen merkitys munasarjasyövässä



A; N=203

B; N=139 StIIIC, peritoneal carsinomatosis

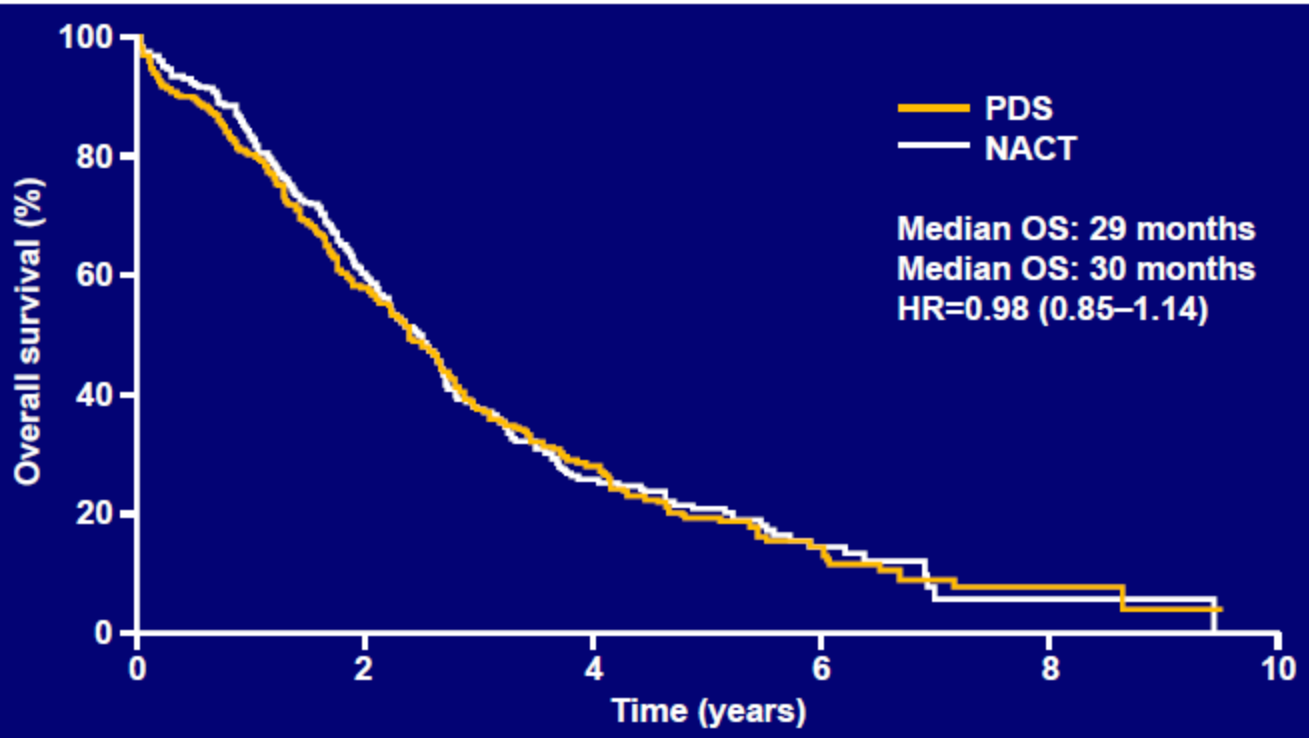
Chang SJ et al Ann Surg oncol 2012

Neoadjuvanttihoito

	stage	P	N	cycles	R 0	OS
Morice	IIIC IV	23 5	48 10	3	54% vs 51% 46% vs 33%	20 vs 28 26 vs 28
Hergazy	IIIC IV	14 18	11 16	3	63% vs 72%	28 vs 25
Hou	IIIC IV	87 22	29 34	6	71% vs 95%	47 vs 46
Vergote	IIIC IV	257 77	253 81	3	19% vs 51% 22% vs 30%	38 vs 45 27 vs 32

Chang SJ et al Gyn oncol 2012

EORTC/NCIC study: neoadjuvant chemotherapy + interval surgery vs primary surgery



Wrongly interpreted as NACT is equivalent to primary surgery in FIGO IIIC/IV

Vergote, et al. NEJM 2010

UP16112012

St III; PFS ja OS suhteessa jäännöstuumoriin

PFS

Residua		kk
<1cm		33 kk
1-2cm		17 kk
>2cm		14 kk

OS

Residua	5-v	MS
<1cm	50%	56 kk
1-2cm	28%	31 kk
>2cm	21%	28 kk

Cochrane katsaus 2011; 1274 julkaisua (11 mukaan)

Miten arvioida potilaan operabiliteettia ja leikkausriskejä

Albumin <2.7	**1**
Bowel mesentry involvement >2cm 2 separate locations	**1**
Ca125 >500	**1**
Diffuse peritoneal studding	**2**
Para-aortic lymfadenopathy >2cm	**1**
Splenic disease	**1**

Pisteytys:
Leikkaus onnistuu : 1 (0-4)
Leikkaus suboptimaalinen tai komplikaatioita : 3 (0-6)

Stashwick C et al Int J Gyn Cancer 2011