



11th
International
Symposium

Advanced Ovarian Cancer Optimal Therapy. Update

Cytoreductive Surgery for Advanced Ovarian Cancer How Far Should We Go To Achieve Optimal Status?

Jonathan S. Berek, MD, MMS

Laurie Kraus Lacob Professor
Stanford University School of Medicine
Director, Stanford Women's Cancer Center
Senior Scientific Advisor
Stanford Comprehensive Cancer Institute

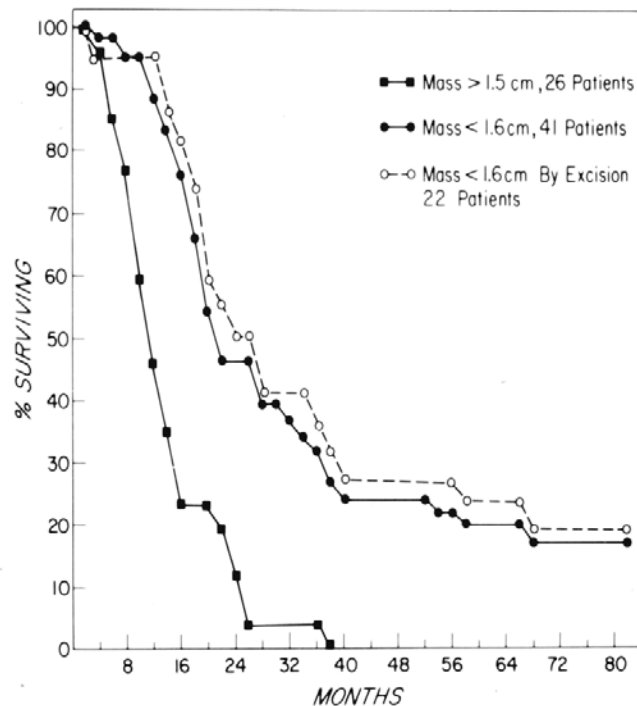




Stanford University

Credit: Linda A. Cicero /
Stanford News Service

Surgical Cytoreduction of Ovarian Cancer



- Optimal “debulking” (< 1.5 cm)
- median survival longer than suboptimal & similar to those whose disease small prior to resection*

*Griffiths CT. Seminars Oncol 1975
Berek JS, Leventhal J, Griffiths TC, Obstet Gynecol 1979

Cytoreductive Surgery for Advanced Ovarian Cancer

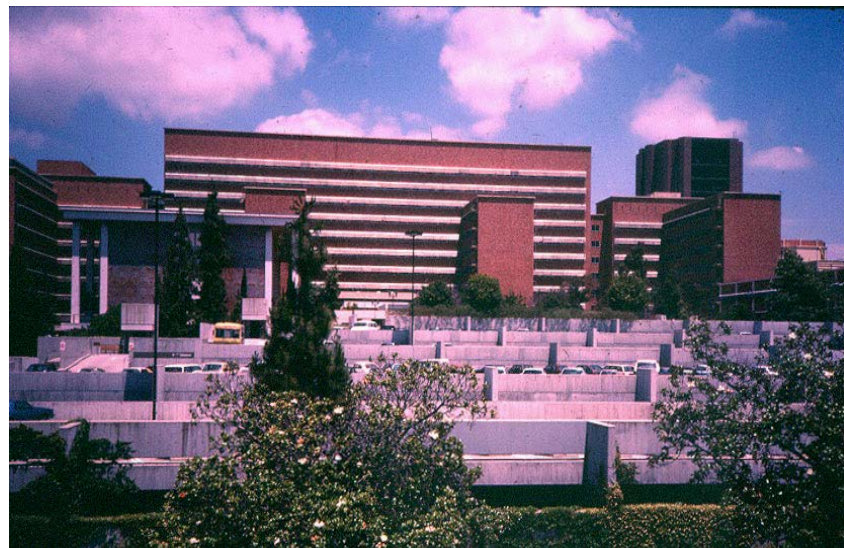
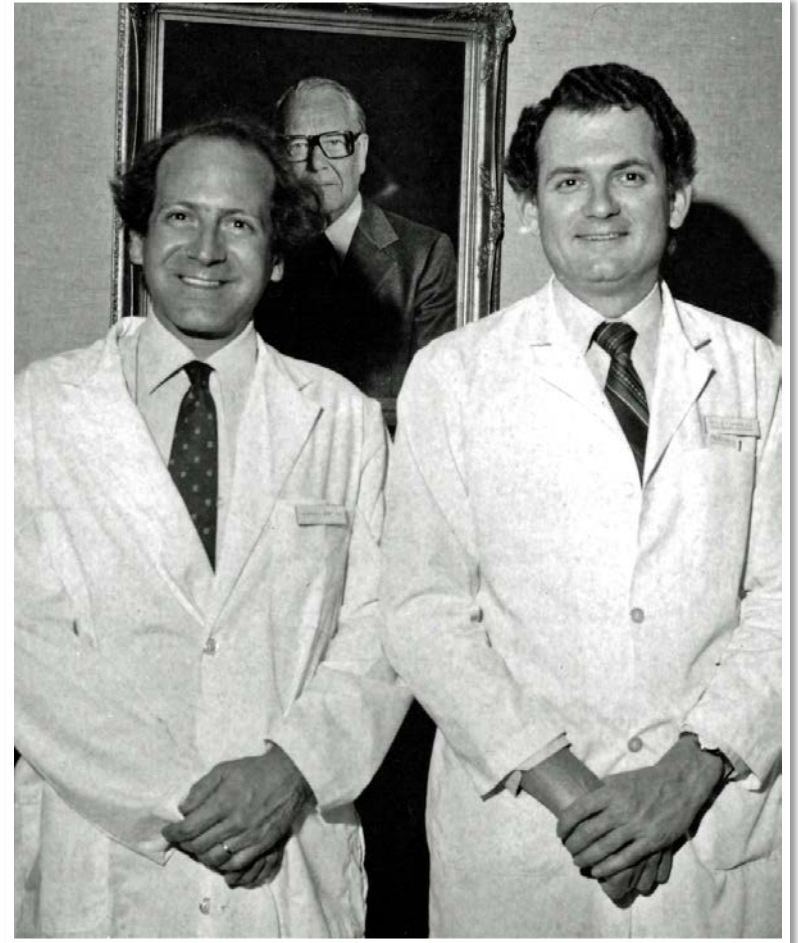
Acknowledgement

Neville F. Hacker, MD

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University of California Los Angeles



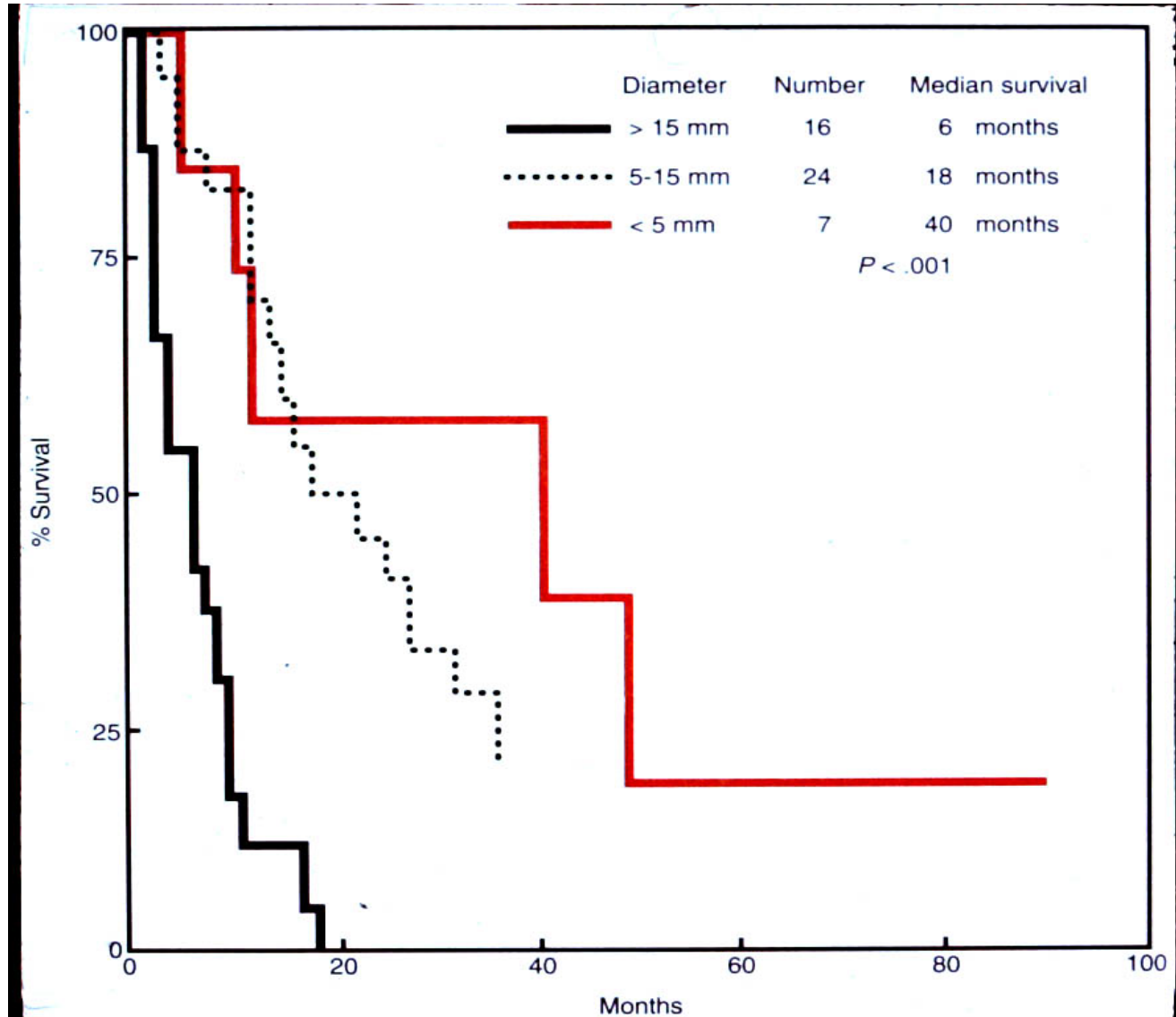
UCLA School of Medicine, 1982



Fellows in American College of Surgeons, 1984



1st Edition of Berek and Hacker, 1985



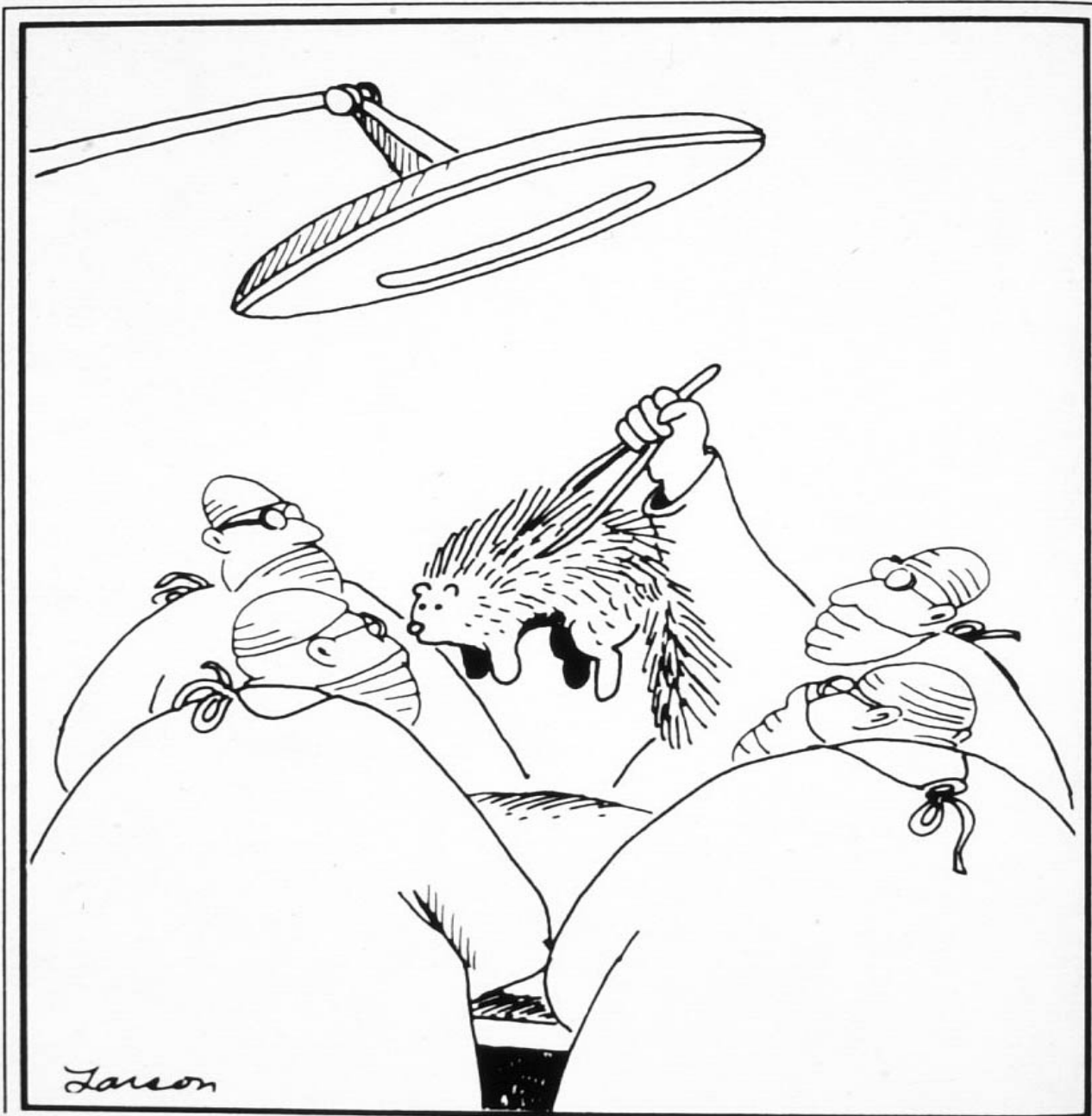
Hacker NF, Berek JS, et al. Primary cytoreduction. *Obstet Gynecol* 1983
 Berek JS, Hacker NF, et al. Secondary cytoreduction. *Obstet Gynecol* 1983

Cytoreductive Surgery in Ovarian Cancer

Is it the act of committing cytoreduction or the manner in which the disease grows, i.e., its tumor biology, that permits optimal debulking?

Is the outcome a result of the surgery, or just the natural history of the cancer?





“Well, I guess that explains the abdominal pains.”

Cytoreductive Surgery for Advanced Ovarian Cancer

- Gold standard for most patients with stage III metastatic epithelial ovarian, fallopian tube & peritoneal (Ov-FT-P) cancers
- Requires appropriate surgical expertise
- Best performed in regional cancer centers



Cytoreductive Surgery for Advanced Ovarian Cancer

What are the factors that influence the maximal
cytoreductive effort?

- Performance status of patient
- Biology of the disease
- Extent of metastatic disease
- Distribution of disease
- Aggressiveness of surgeon



Cytoreductive Surgery for Advanced Ovarian Cancer

What is the most optimal status?

- < 0.5 cm
- 0

Hoskins, et al. Gynecol Oncol 1992

Farias-Eisner, Berek, Hacker, et al. Gynecol Oncol 1994

Du Bois A, et al. Cancer 2009



Cytoreductive Surgery for Advanced Ovarian Cancer

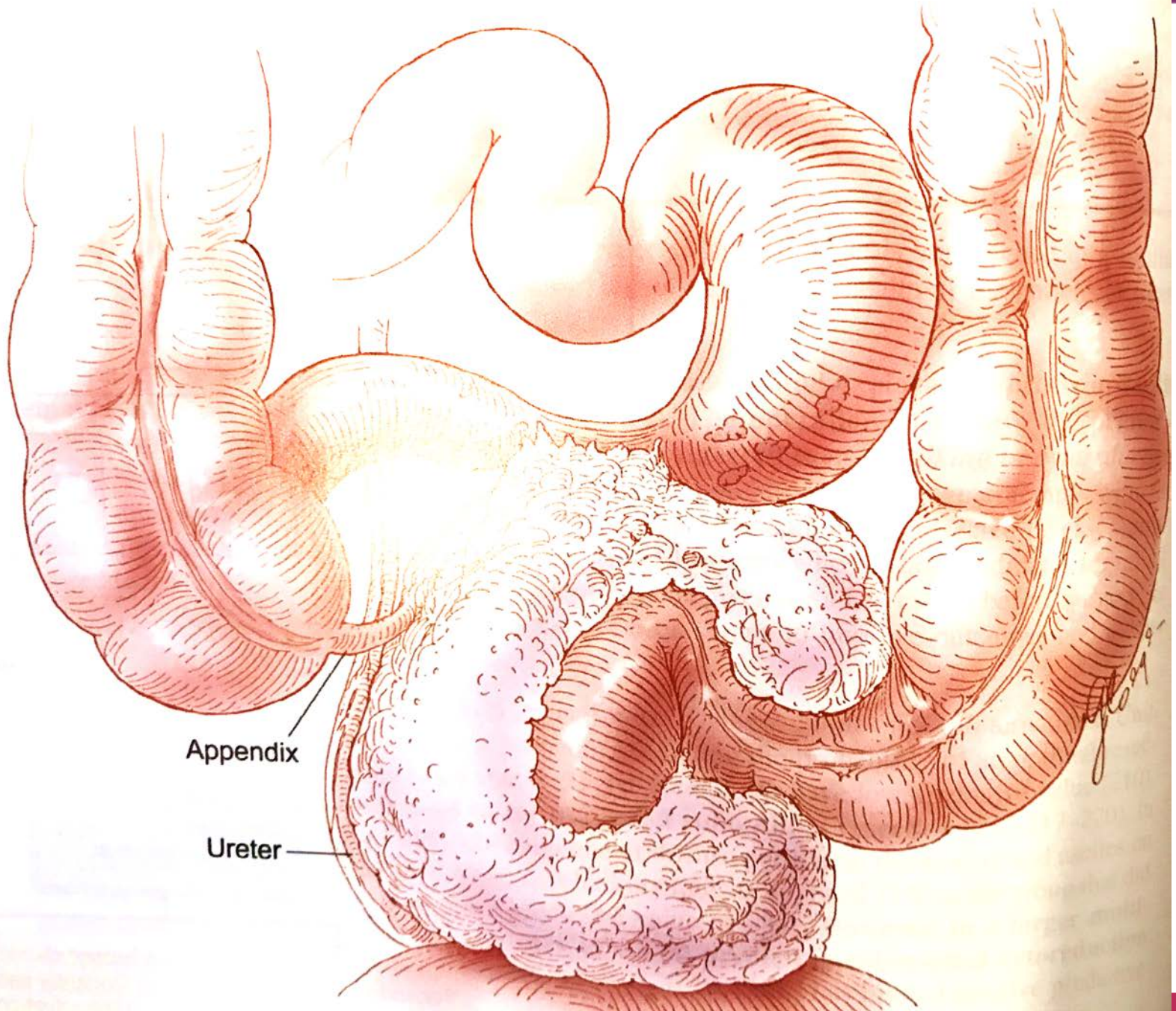
- Stage IV disease
 - less clear how effective



How aggressive should we be?

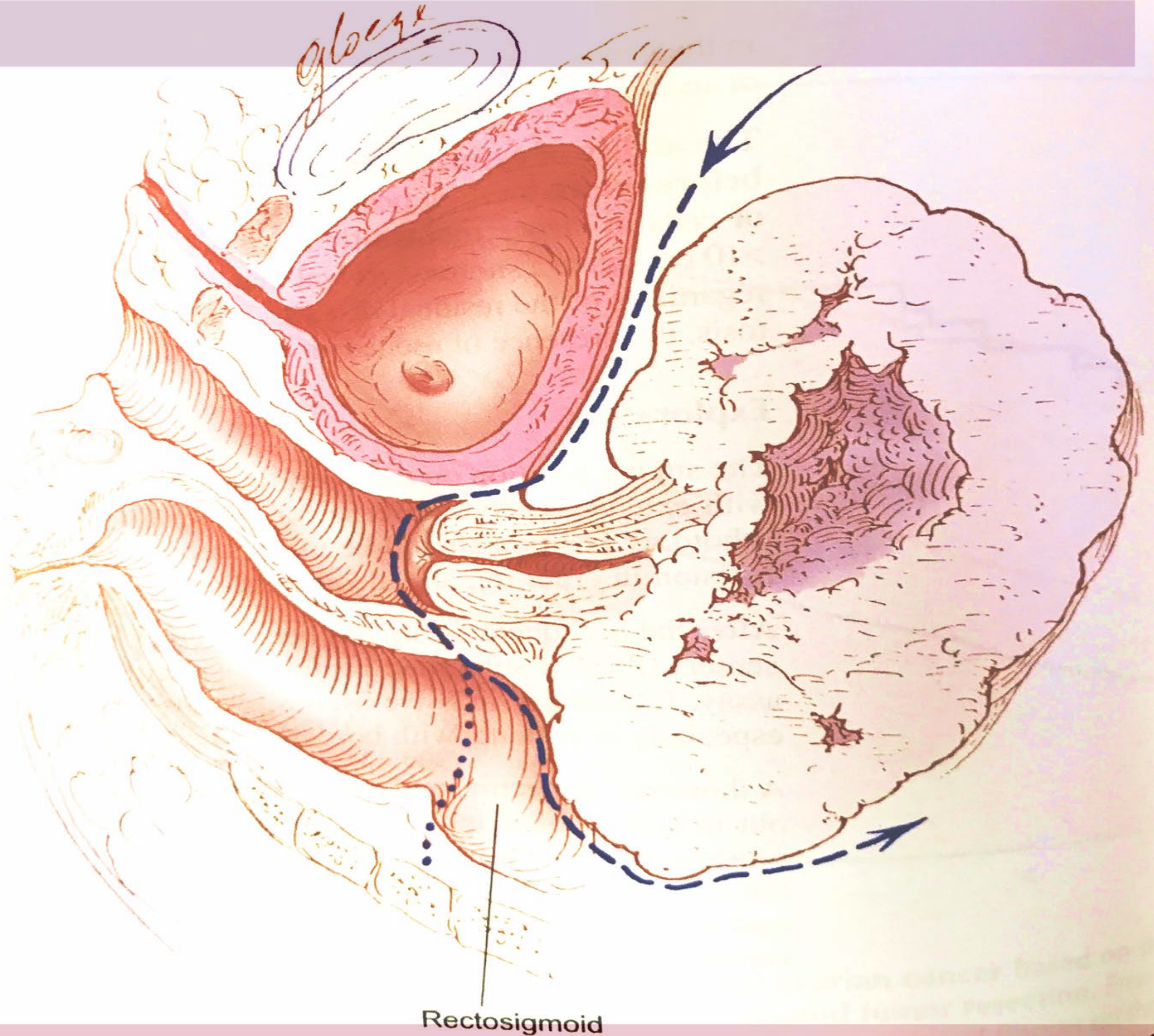
- Pelvic viscera- colectomy
- Lymphadenectomy
- Small intestinal resection
- Splenectomy
- Diaphragm resection
- Hepatic resection
- Pulmonary-pleura resection

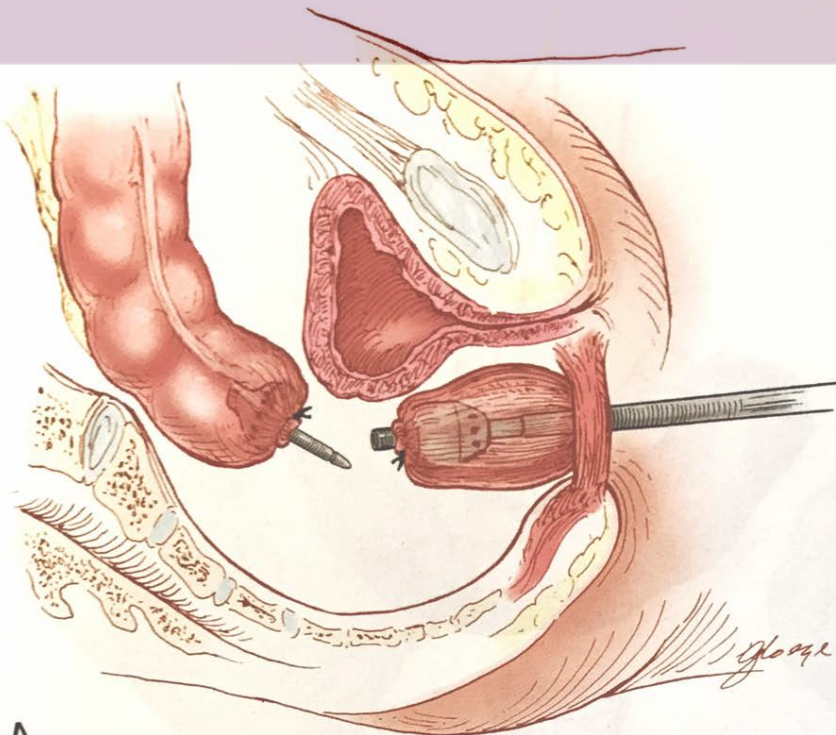




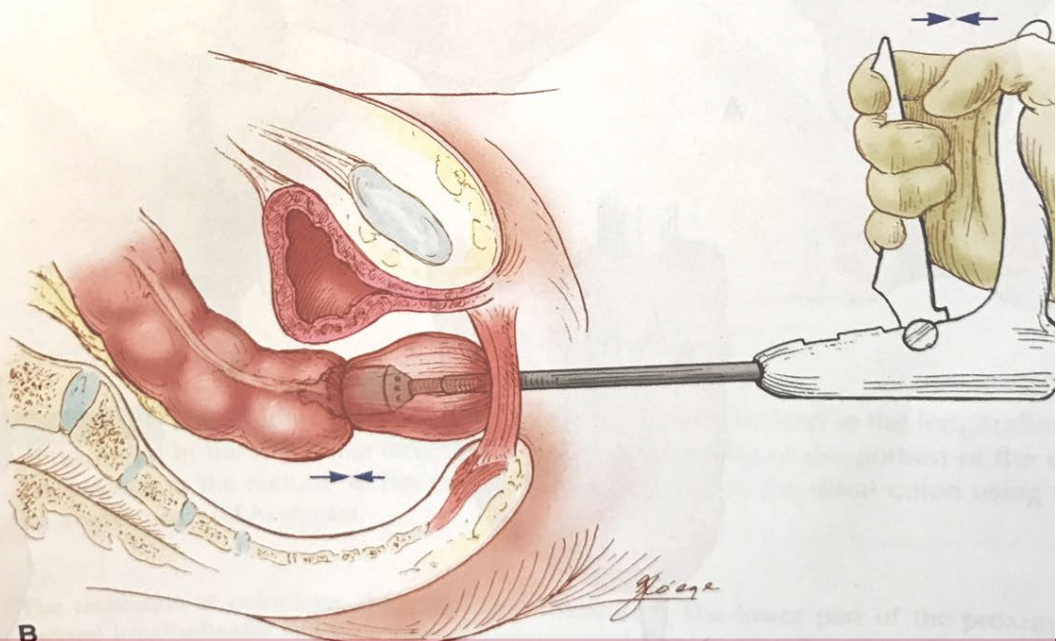
Appendix

Ureter



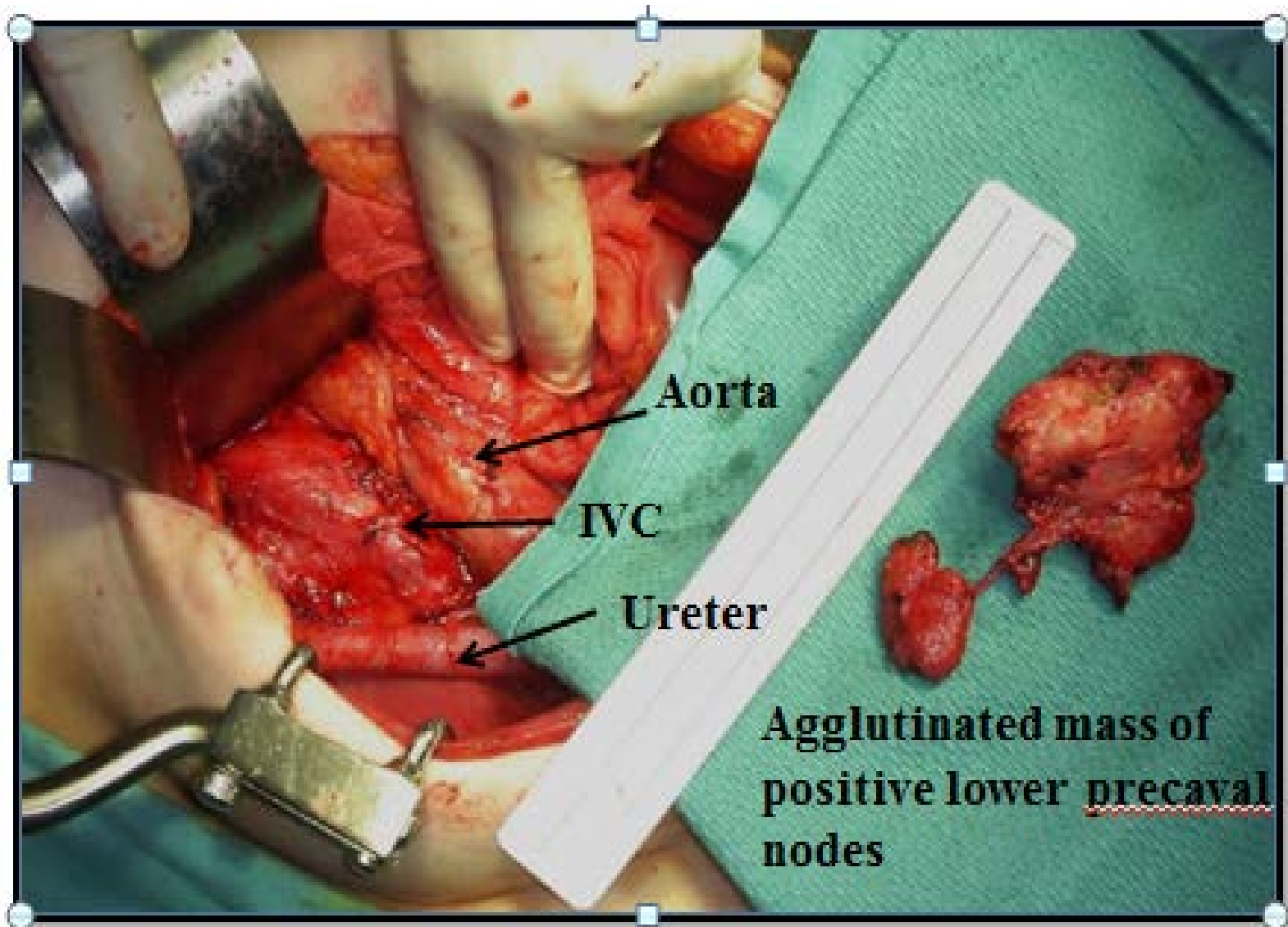


A



B

Resection of a bulky, positive lower precaval lymph nodes, which were causing partial obstruction of the right ureter



Resection of Lymph Nodes During Cytoreductive Surgery

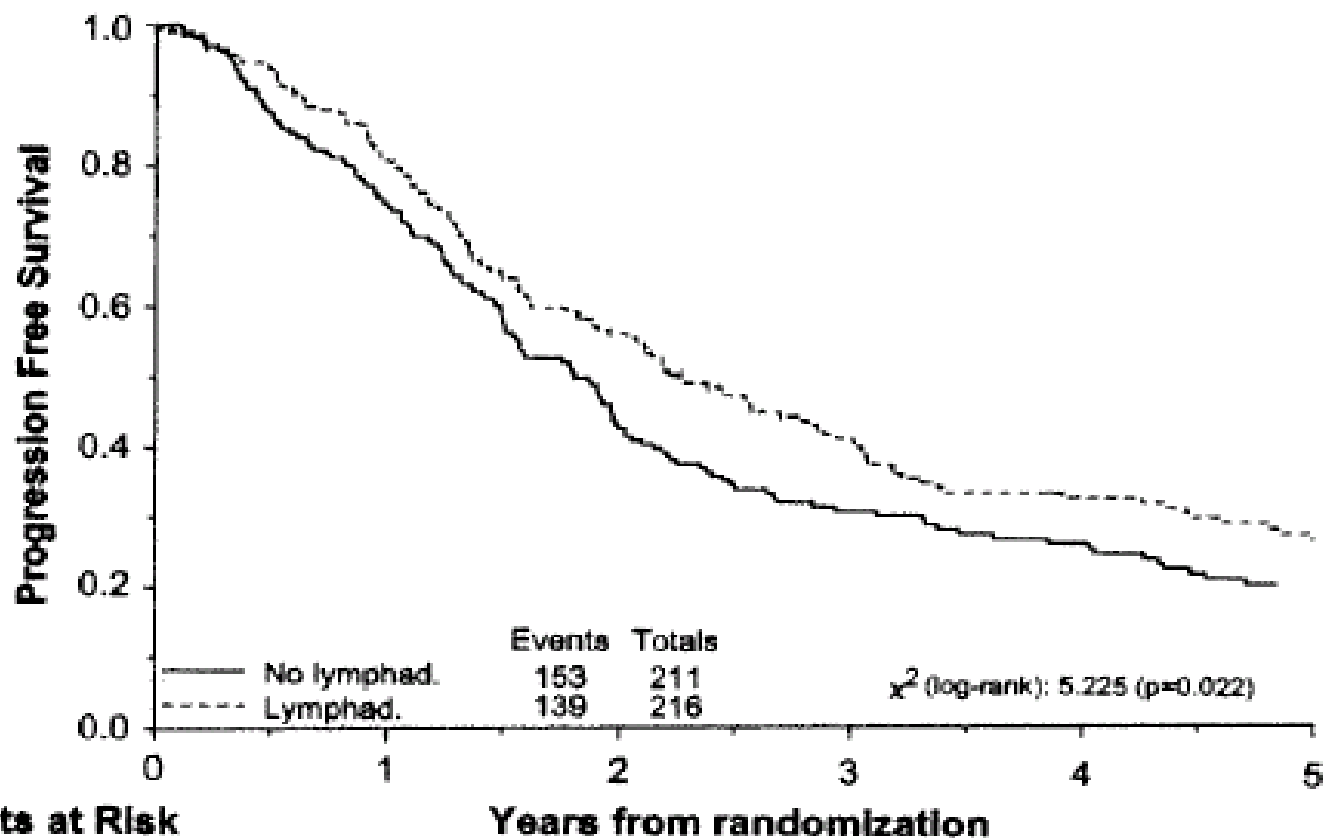
- Prospective, randomized study of patients whose tumors were optimally cytoreduced in the peritoneal cavity underwent systematic pelvic and paraaortic lymphadenectomy vs. resection of bulky nodes only.
- Well matched arms

Systematic lymphadenectomy = 216 (189 eval) pts
Nodal debulking = 211 (195 eval) pts

- PFS = 27.4 vs. 22.4 (5 mo +)
- 5-year OS 48.5% vs. 47 % (95% CI =8.4-10.6%)

Benedetti Panici P, Mangioni A, Hacker NF, et al
J Natl Cancer Inst 2005;97:560

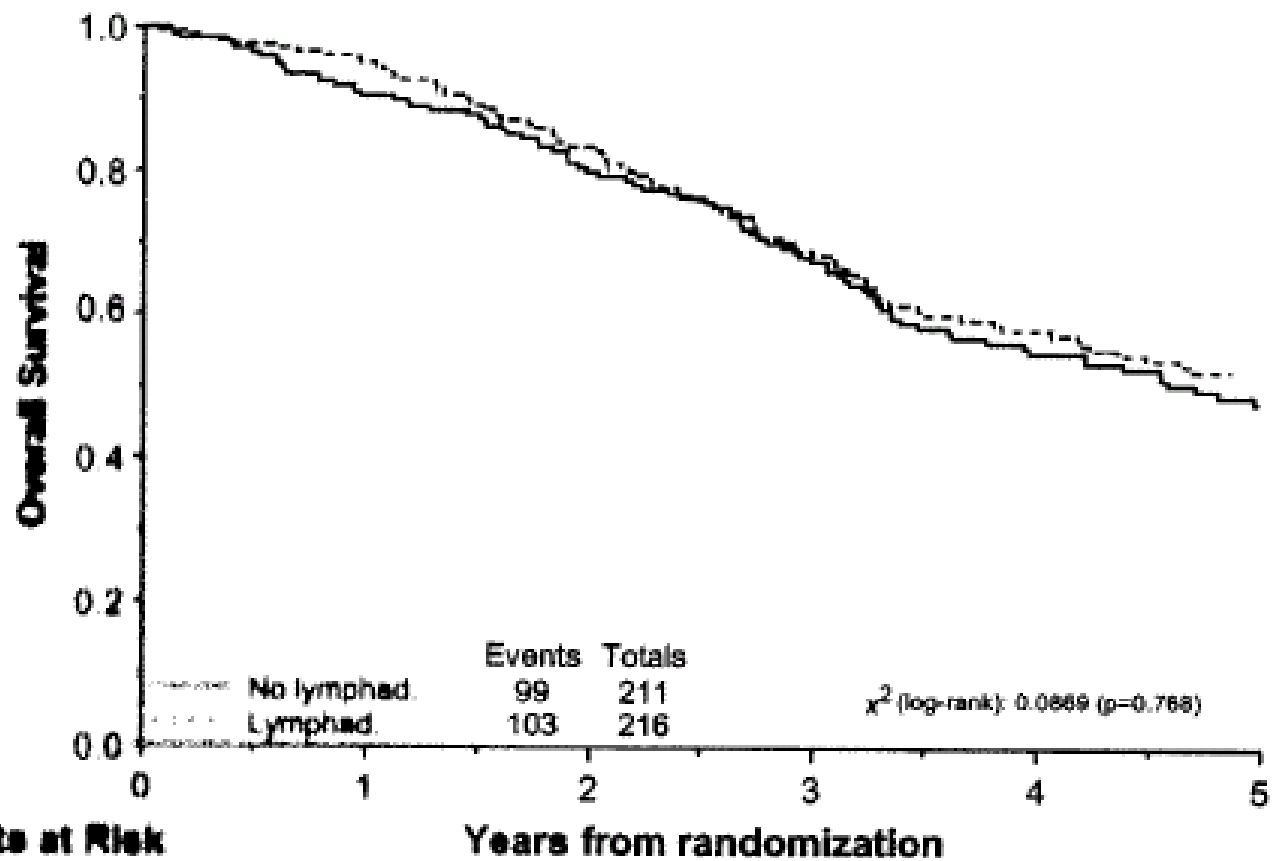




Patients at Risk

	0	1	2	3	4	5
No lymphad.	211	148	78	51	41	27
Lymphad.	216	166	107	67	51	34





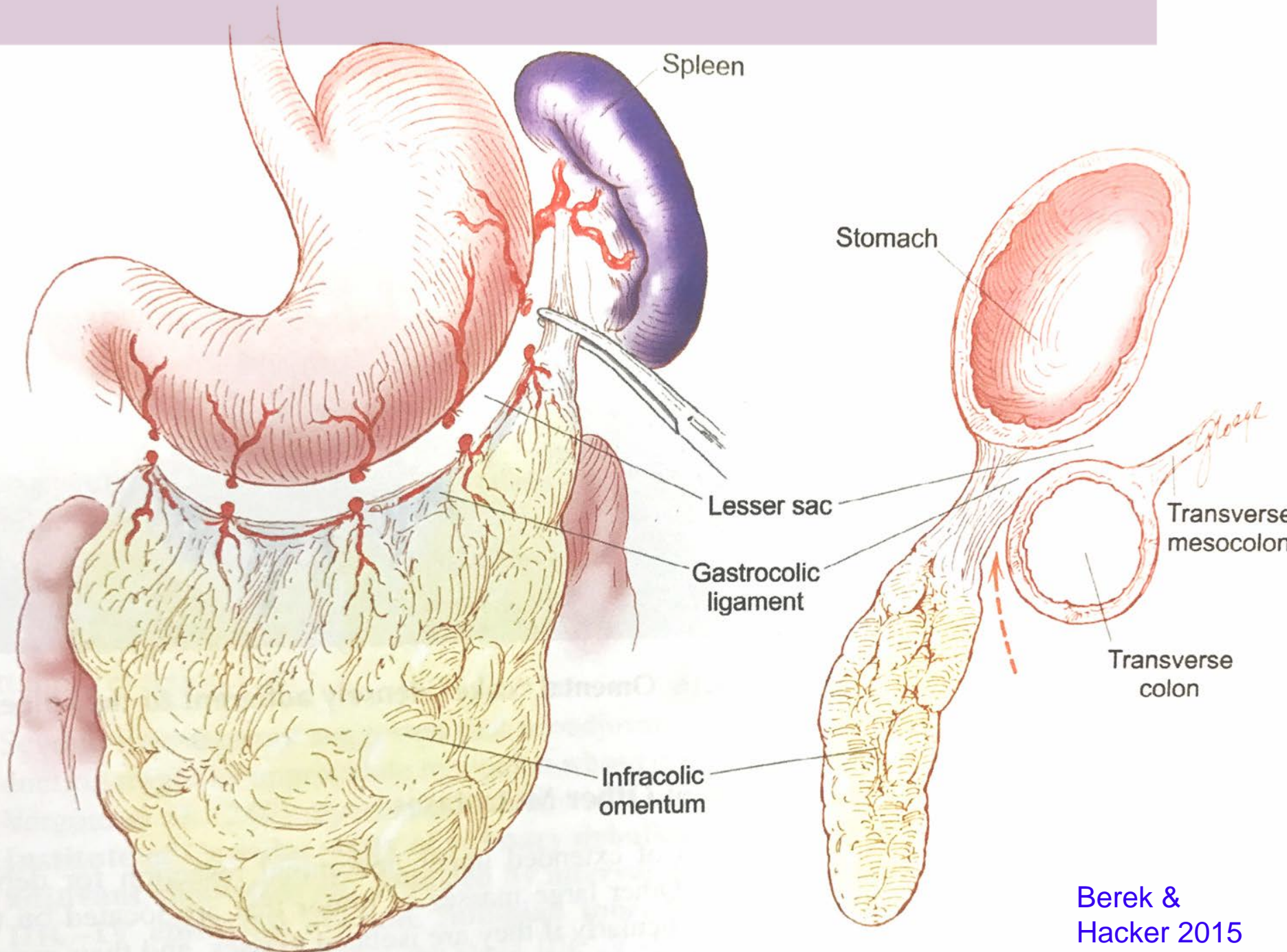
Patients at Risk

	0	1	2	3	4	5
No lymphad.	211	177	136	104	78	56
Lymphad.	216	198	153	110	84	64

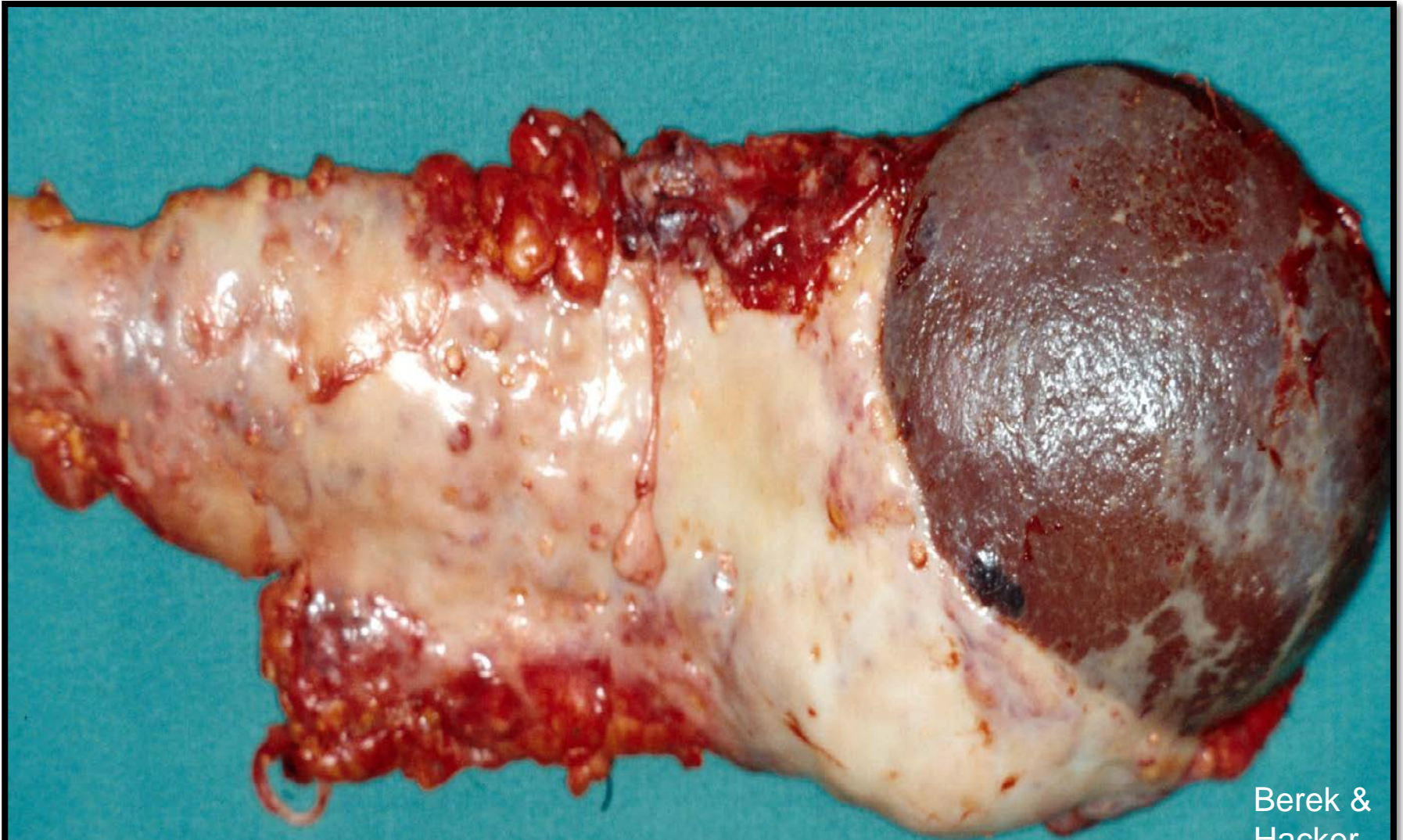


Carcinomatosis



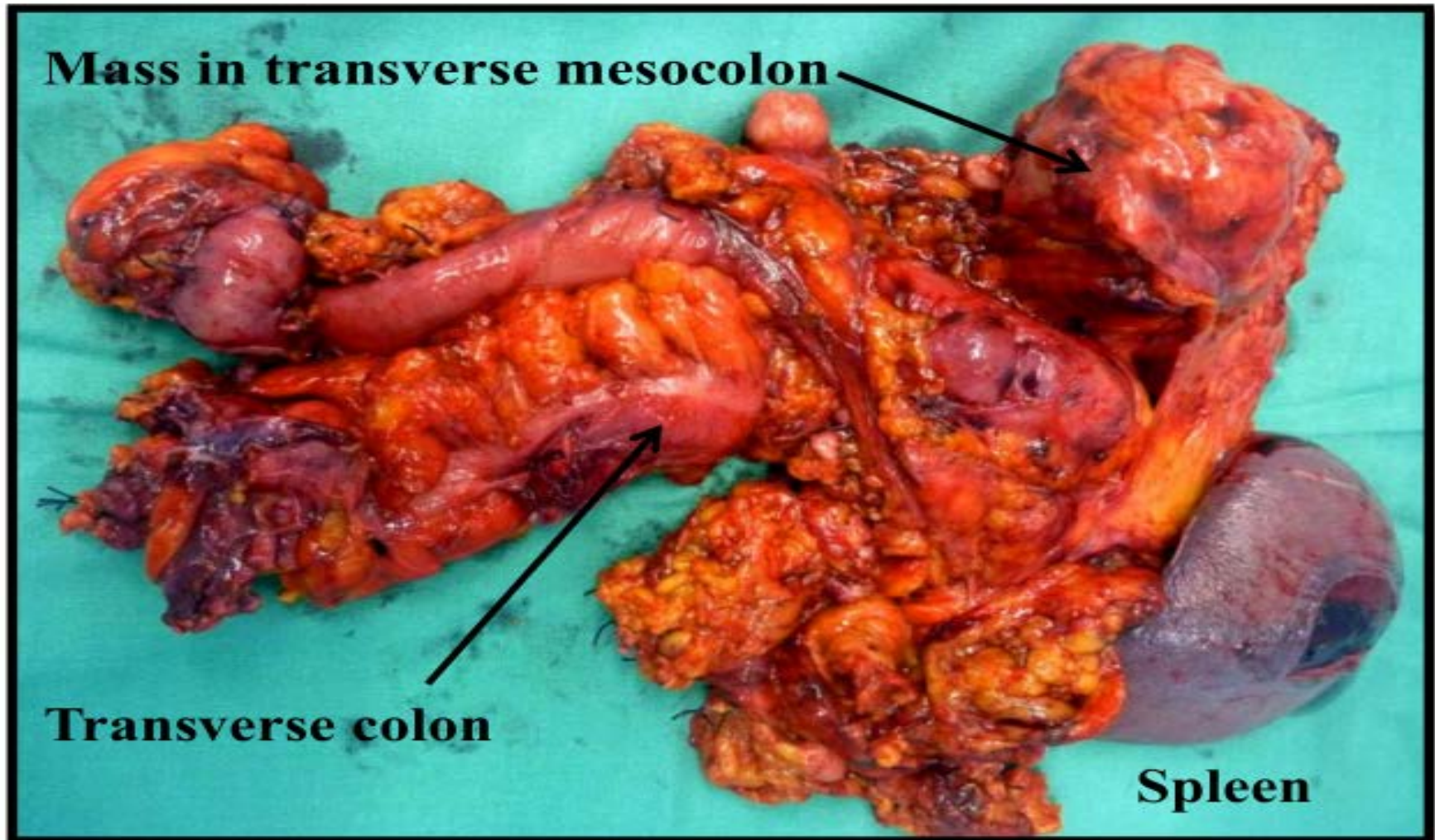


Large omental cake densely adherent to and infiltrating into the spleen

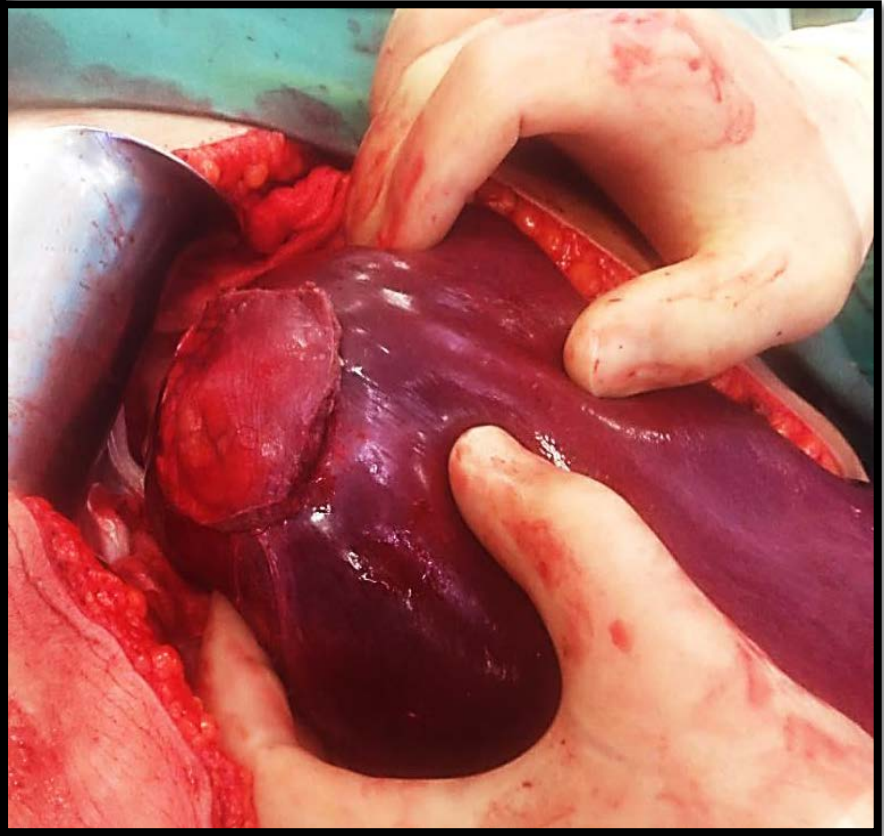
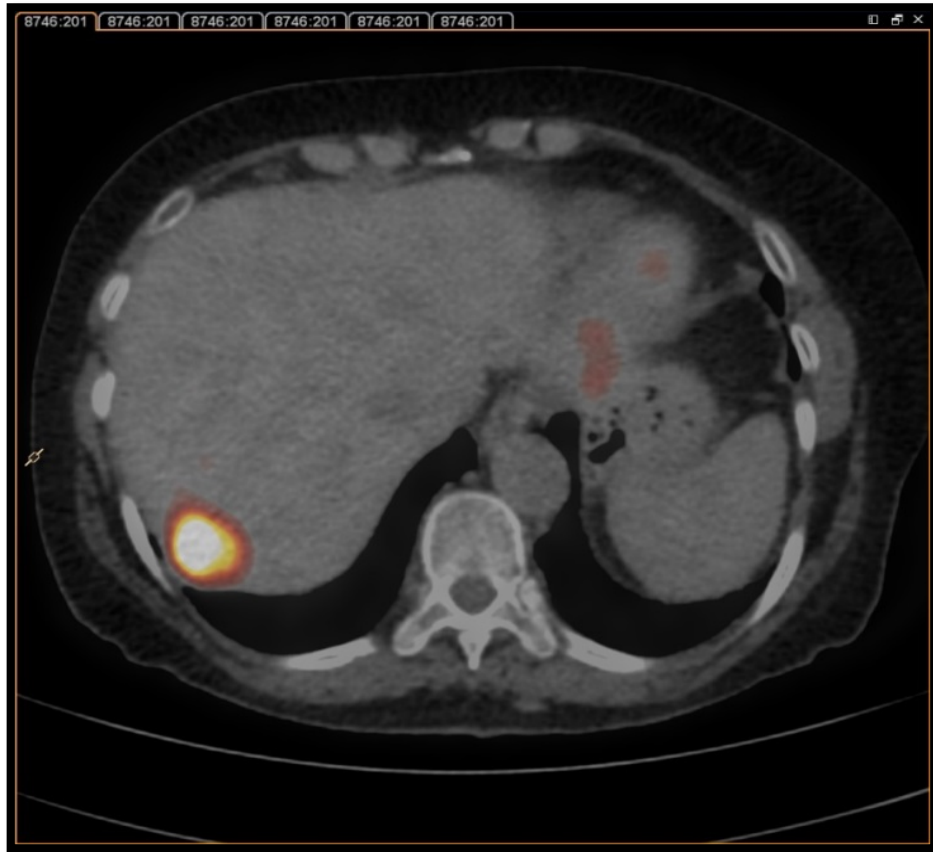


Radical Upper Abdominal Surgery

Resection of transverse colon, omentum, spleen & distal pancreas to remove metastatic disease involving the omentum, spleen, & transverse mesocolon



PET/CT scan - ovarian cancer metastasis involving the liver & right diaphragm (L)
Involved segment of right diaphragm resected, still attached to disease in liver (R)



Resection of underlying disease in the liver.
Hemostasis secured by sutures and application of hemostatic material



HERMAN By Jim Unger



3-26

© Jim Unger/dist. by United Media, 2002

“Let’s hope we never have to use it!”

Cytoreductive Surgery for Advanced Ovarian Cancer

- Primary Debulking Surgery (PDS)

vs.

Neoadjuvant Chemotherapy (NACT) >
Interval debulking surgery (IDS)



Meta-analysis of the randomized EORTC and CHORUS Neoadjuvant versus Primary Debulking trials in advanced Ovarian Cancer



National
Cancer Institute
of Canada

Institut national
du cancer
du Canada

Ignace Vergote,

Corneel Coens, Matthew Nankivell, Gunnar B. Kristensen, Max Parmar, Tom Ehlen,
Gordon C. Jayson, Nick Johnson, Ann Marie Swart, René Verheijen, W. Glenn
McCluggage, Tim Perren, Pier-Luigi Benedetti, Gemma Kenter, Antonio Casado, Cesar
Mendiola, Gavin Stuart, Nick S. Reed,

Sean Kehoe

Meta-analysis of the randomized EORTC and CHORUS Neoadjuvant versus Primary Debulking trials in advanced ovarian cancer

- Background and aims.
 - Pre-planned meta-analysis of 2 randomized trials (EORTC 55971-*NEJM* 2010;363:943 - and MRC CHORUS- *Lancet* 2015;6763: 62223) comparing neoadjuvant chemotherapy (NACT) with primary debulking surgery (PDS) in advanced ovarian-fallopian tube cancer
- Methods.
 - The patient data of both trials were updated and merged in one data base (data base lock EORTC June 6, 2015 and CHORUS May 20, 2015)
- Median follow-up: 7.6 years:
 - EORTC: 9.2 y
 - Chorus: 5.9 y

Randomized EORTC-GCG/NCIC-CTG Trial

NACT + IDS vs PDS

Ovarian, fallopian tube, or peritoneal cancer
FIGO stage IIIc-IV (n = 718)

Randomization

48 patients excluded from
1 center → N = 670

**Primary
debulking surgery**

3 x platinum-based CT

Interval debulking
(not obligatory)

≥3 x platinum-based CT

**Neoadjuvant
chemotherapy**

3 x platinum-based CT

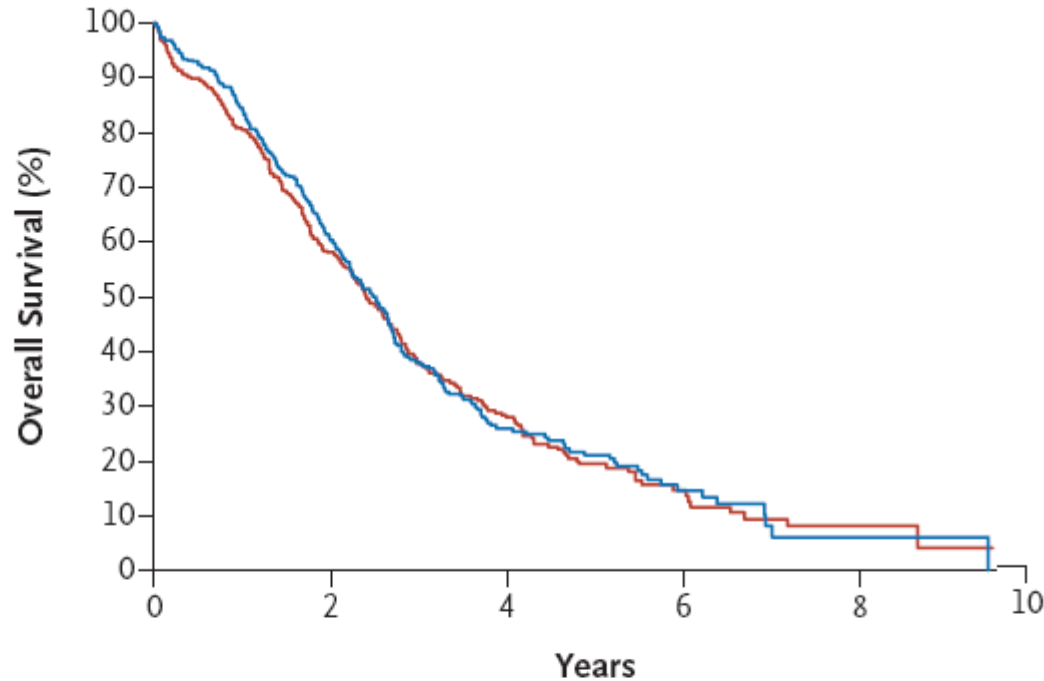
Interval debulking if no PD

≥3 x platinum-based CT

Primary endpoint: Overall survival

Secondary endpoints: Progression-free survival, quality of life, complications

EORTC: NACT + IDS vs PDS: ITT Overall Survival

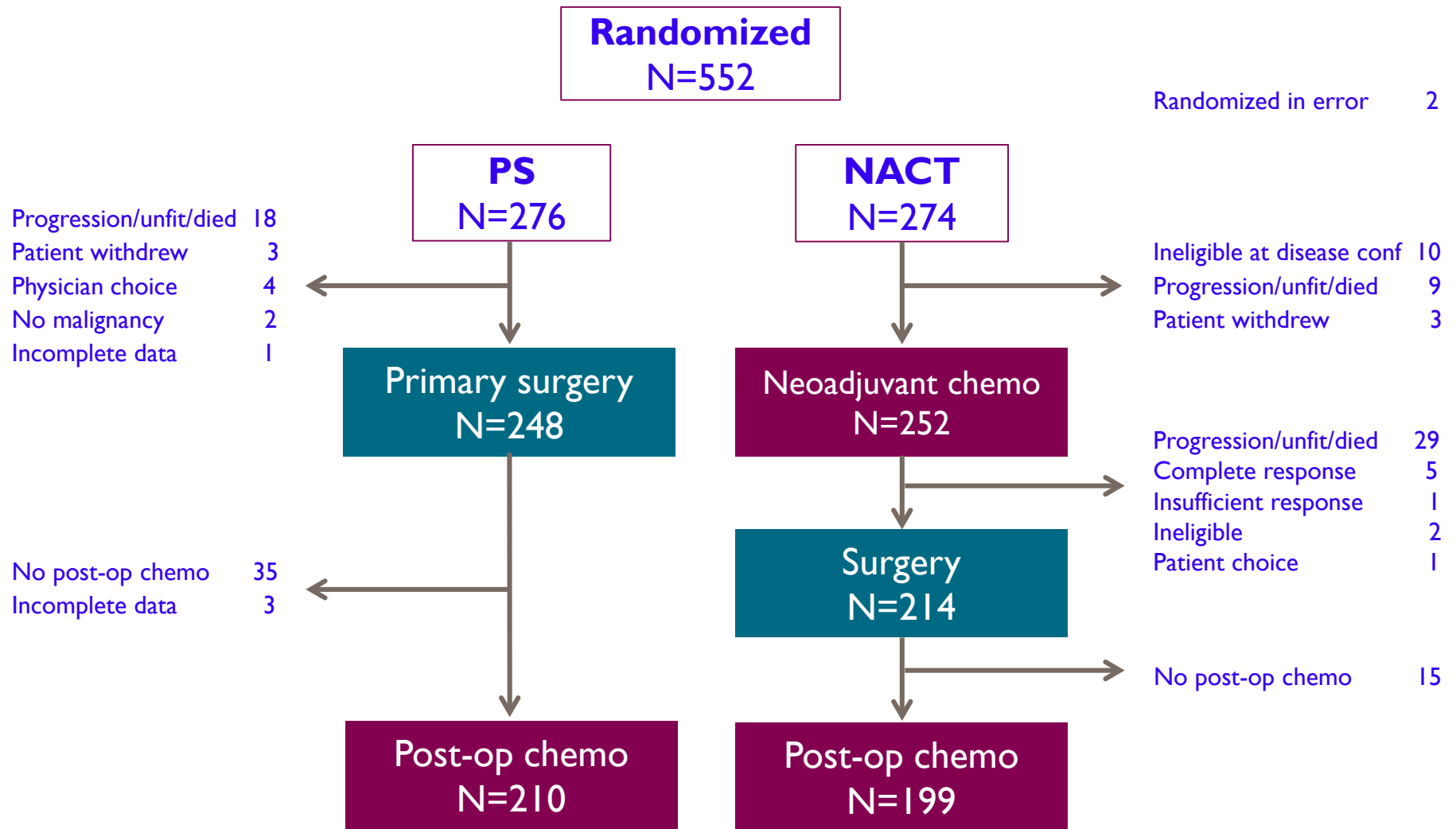


Median survival
PDS: 29 months
IDS: 30 months
HR for IDS 0.98
(0.84, 1.13)

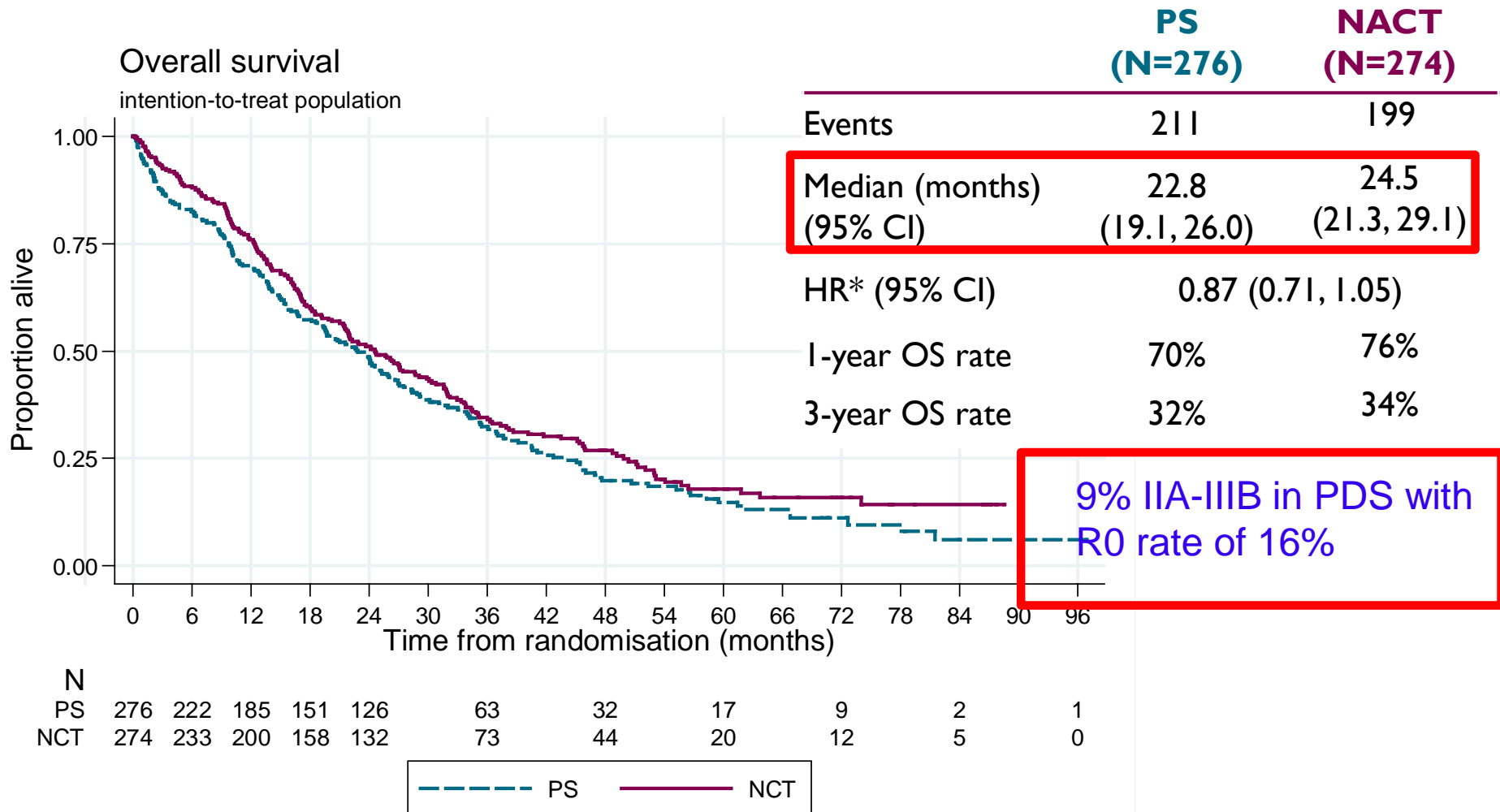
	No. of Events		No. of Patients at Risk			
Primary Debulking Surgery (PDS)	253	336	189	62	14	2
Neoadjuvant Chemotherapy (NACT)	245	334	195	46	13	2

— PDS
 — NACT

CHORUS trial (Kehoe S et al)



Overall survival CHORUS TRIAL



Kehoe S, Lancet 2015, 386:249

* HR adjusted for baseline stratification factors.

Meta-analysis

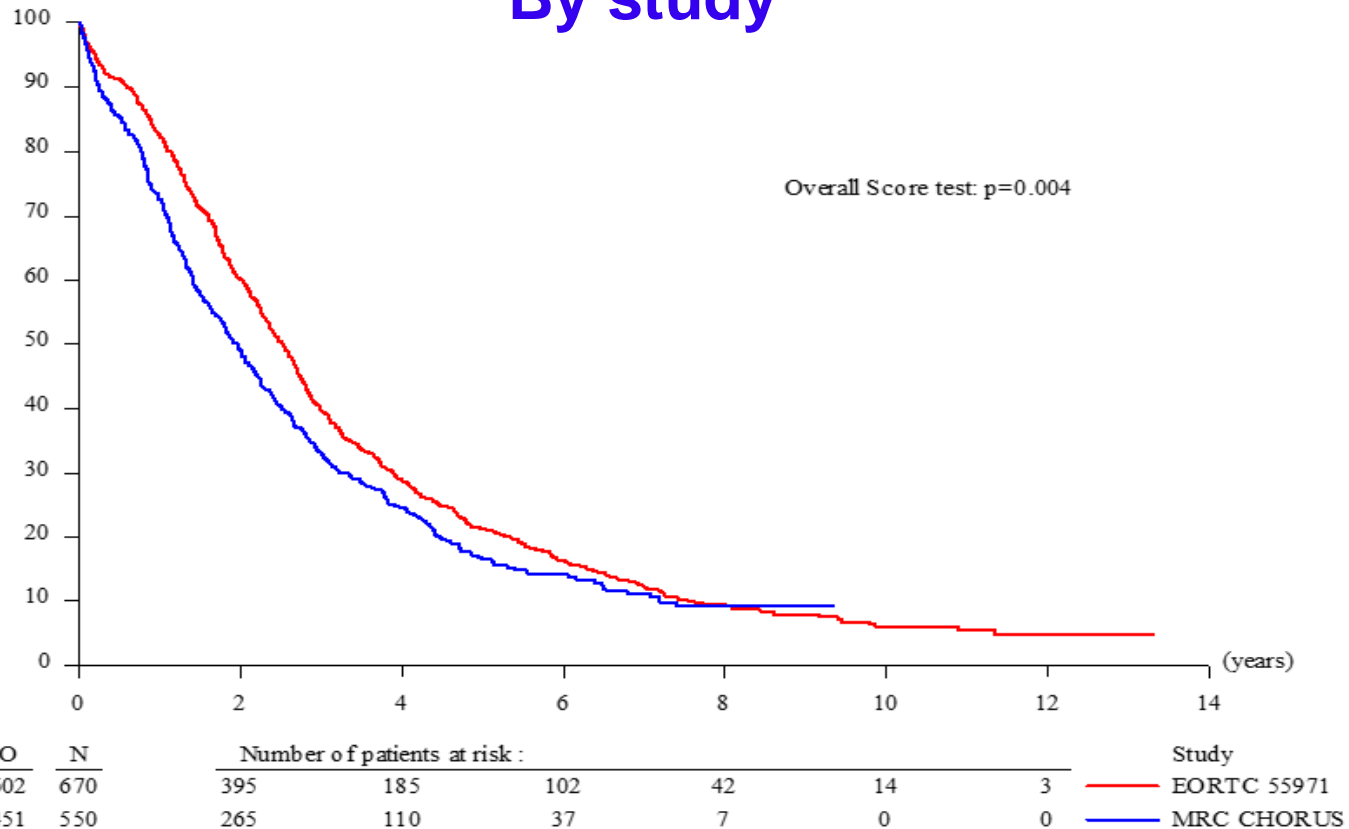
EORTC & Chorus trials (n = 1220)

	EORTC (n= 670)	Chorus (n=550)	TOTAL
Median Age (y)	62	65	63
Largest metastatic tumor size (mm)	80	80	80
CA125 at entry (KU/L)	1161	1016	1089
WHO performance			
0	44.8%	31.1%	38.6%
1	42.4%	49.3%	45.5%
2	12.5%	18.5%	15.2%
3	0%	0.9%	0.4%
Missing	0.3%	0.2%	0.2%
FIGO stage			
II	0%	3.5%	1.6%
IIIA	0%	2.5%	1.1%
IIIB	0.1%	3.8%	1.8%
IIIC	76.1%	58.4%	68.1%
IV	23.6%	13.1%	18.9%
Missing	0.1%	18.7%	8.5%

Meta-analysis EORTC and Chorus trials (n = 1220)

Overall survival

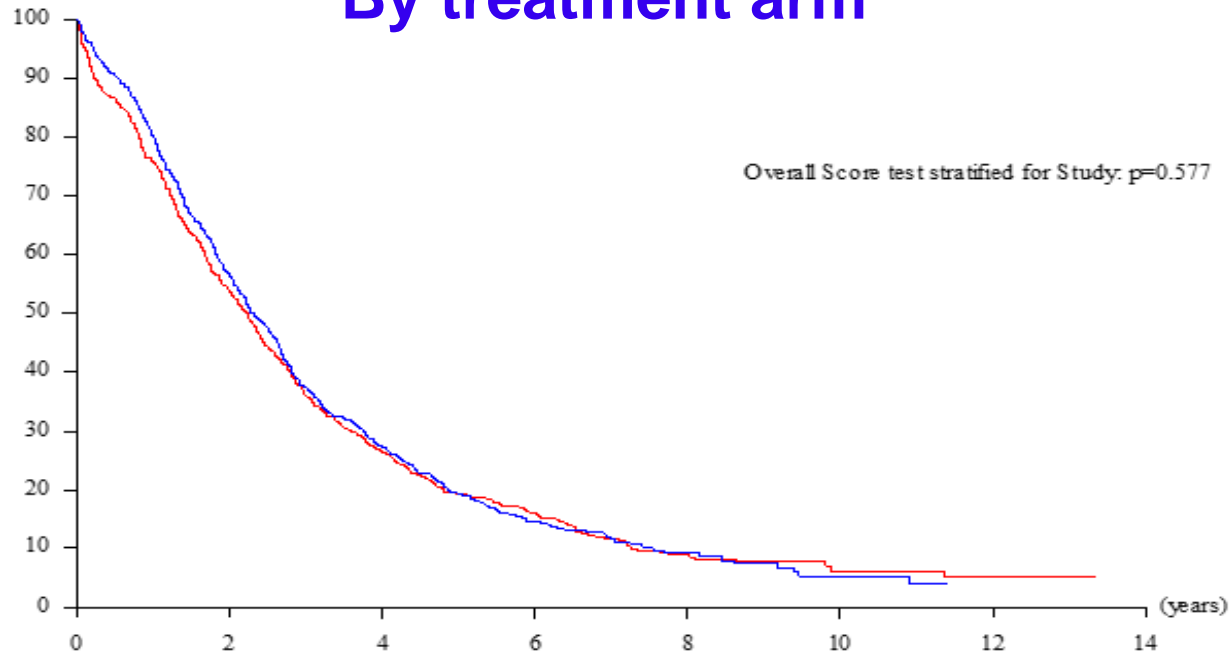
By study



Overall survival			Non-parametric		Cox model	
Study	Patients (N)	Observed Events (O)	Median (95% CI) (Years)	% at 5 Year(s) (95% CI)	Hazard Ratio (95% CI)	P-Value (Score test)
EORTC 55971	670	602	2.52 (2.32, 2.69)	21.3 (18.3, 24.5)	1.00	0.004
MRC CHORUS	550	451	1.95 (1.71, 2.18)	16.5 (13.2, 20.1)	1.20 (1.06, 1.36)	
					Log-rank test:	p-value=0.004

Meta-analysis EORTC and Chorus trials (n = 1220)

Overall survival By treatment arm



O	N	Number of patients at risk :						Treatment
528	612	322	149	74	27	7	3	— Upfront debulking s
525	608	338	146	65	22	7	0	— Neoadjuvant chemo

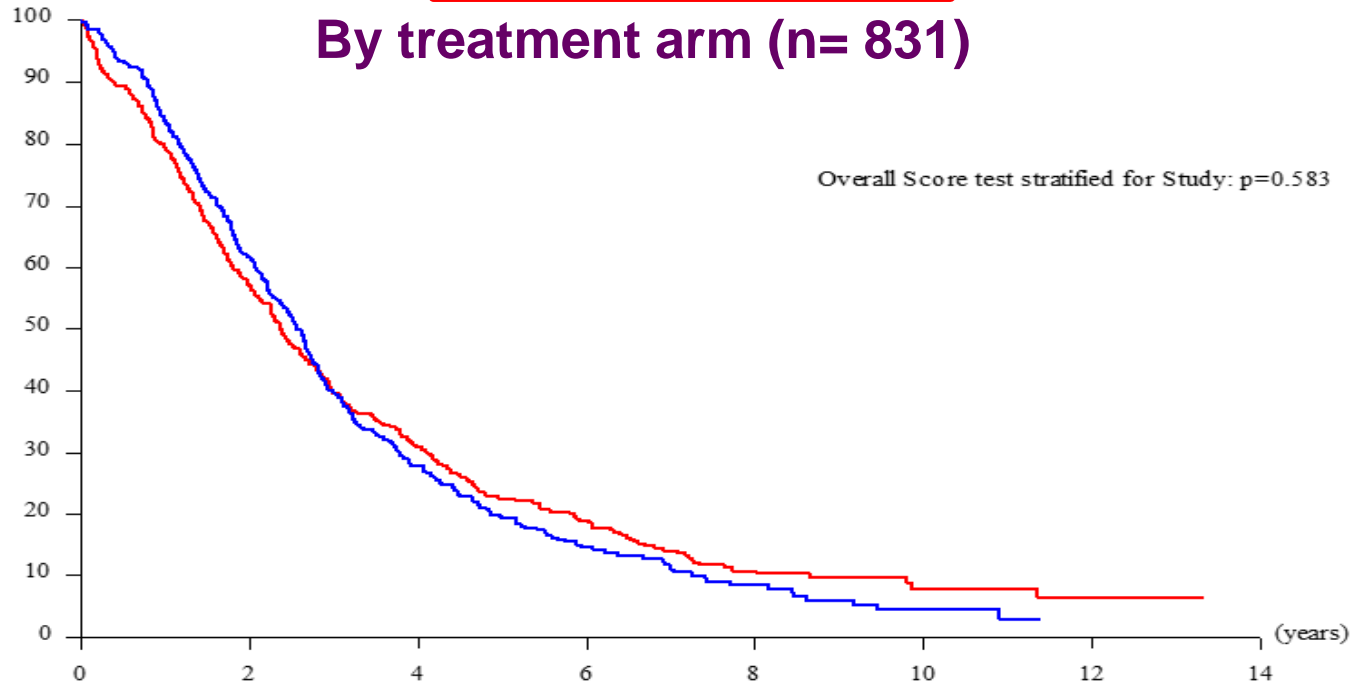
Overall survival (Stratified for Study)			Non-parametric		Cox model	
Treatment	Patients (N)	Observed Events (O)	Median (95% CI) (Years)	% at 5 Year(s) (95% CI)	Hazard Ratio (95% CI)	P-Value (Score test)
Upfront debulking surgery	612	528	2.24 (1.97, 2.40)	19.3 (16.2, 22.7)	1.00	0.577
Neoadjuvant chemotherapy	608	525	2.30 (2.12, 2.56)	19.3 (16.1, 22.6)	0.97 (0.86, 1.09)	
Log-rank test:						p-value=0.577

Meta-analysis EORTC and Chorus trials (n = 1220)

Overall survival

FIGO IIIc

By treatment arm (n= 831)



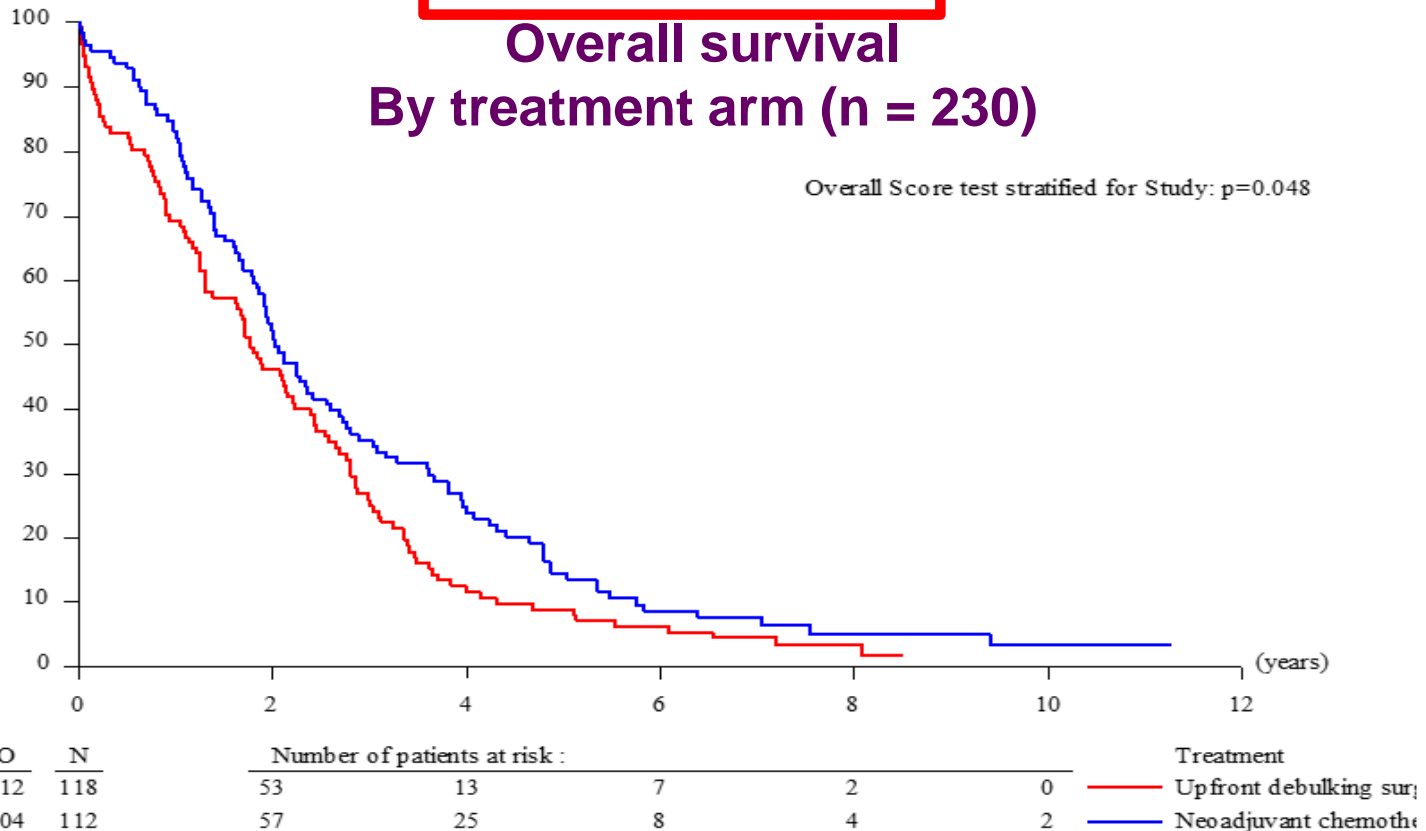
O	N	Number of patients at risk :						Treatment
366	433	243	125	63	24	7	3	— Upfront debulking s
347	398	241	98	44	15	5	0	— Neoadjuvant chemo

Overall survival (Stratified for Study)			Non-parametric		Cox model	
Treatment	Patients (N)	Observed Events (O)	Median (95% CI) (Years)	% at 5 Year(s) (95% CI)	Hazard Ratio (95% CI)	P-Value (Score test)
Upfront debulking surgery	433	366	2.37 (2.11, 2.66)	22.5 (18.6, 26.7)	1.00	0.583
Neoadjuvant chemotherapy	398	347	2.56 (2.30, 2.72)	19.4 (15.5, 23.6)	1.04 (0.90, 1.21)	
					Log-rank test:	p-value=0.583

Meta-analysis EORTC and Chorus trials (n = 1220)

FIGO IV

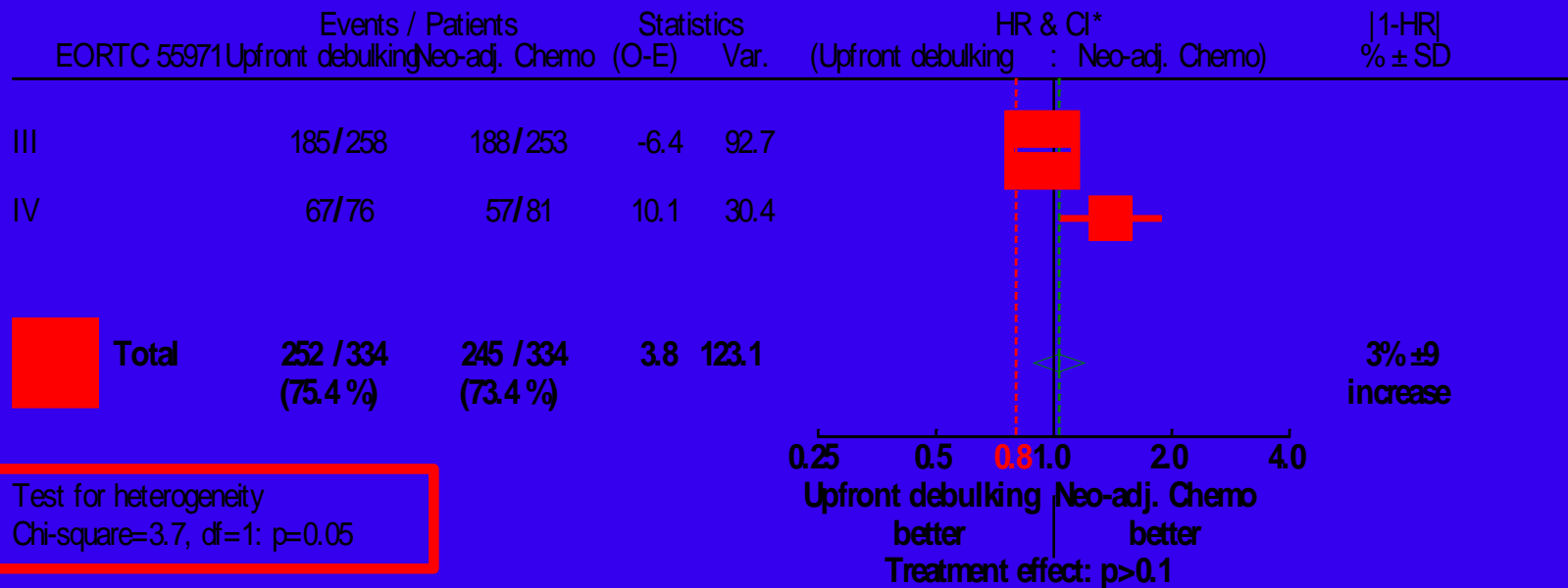
Overall survival By treatment arm (n = 230)



Overall survival (Stratified for Study)			Non-parametric		Cox model	
Treatment	Patients (N)	Observed Events (O)	Median (95% CI) (Years)	% at 5 Year(s) (95% CI)	Hazard Ratio (95% CI)	P-Value (Score test)
Upfront debulking surgery	118	112	1.77 (1.30, 2.21)	9.0 (4.6, 15.1)	1.00	0.048
Neoadjuvant chemotherapy	112	104	2.02 (1.80, 2.55)	14.4 (8.6, 21.8)	0.76 (0.58, 1.00)	
Log-rank test:						p-value=0.048

EORTC: NACT + IDS vs PDS: ITT

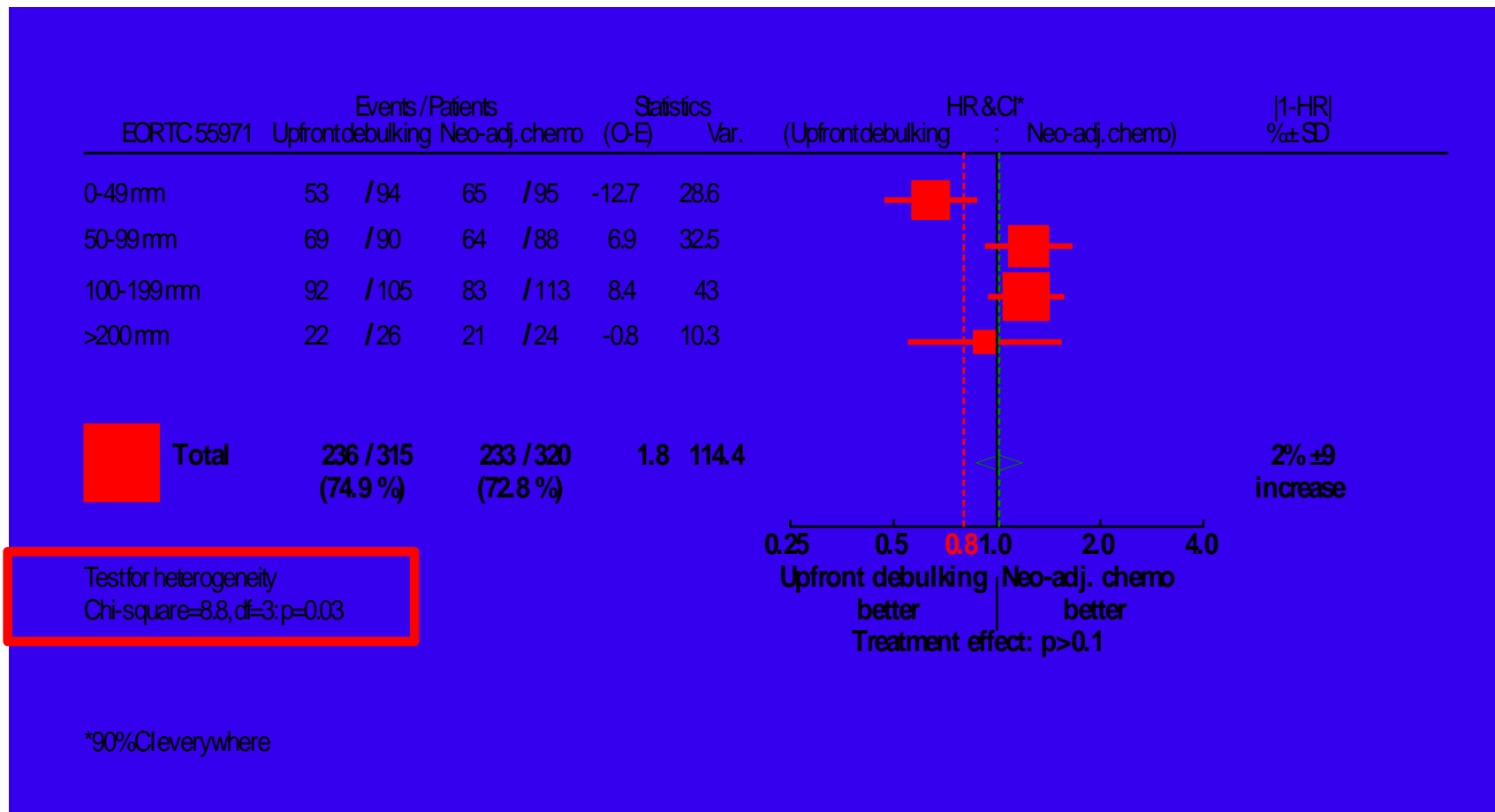
Survival Time: FIGO Stage



*90% CI everywhere

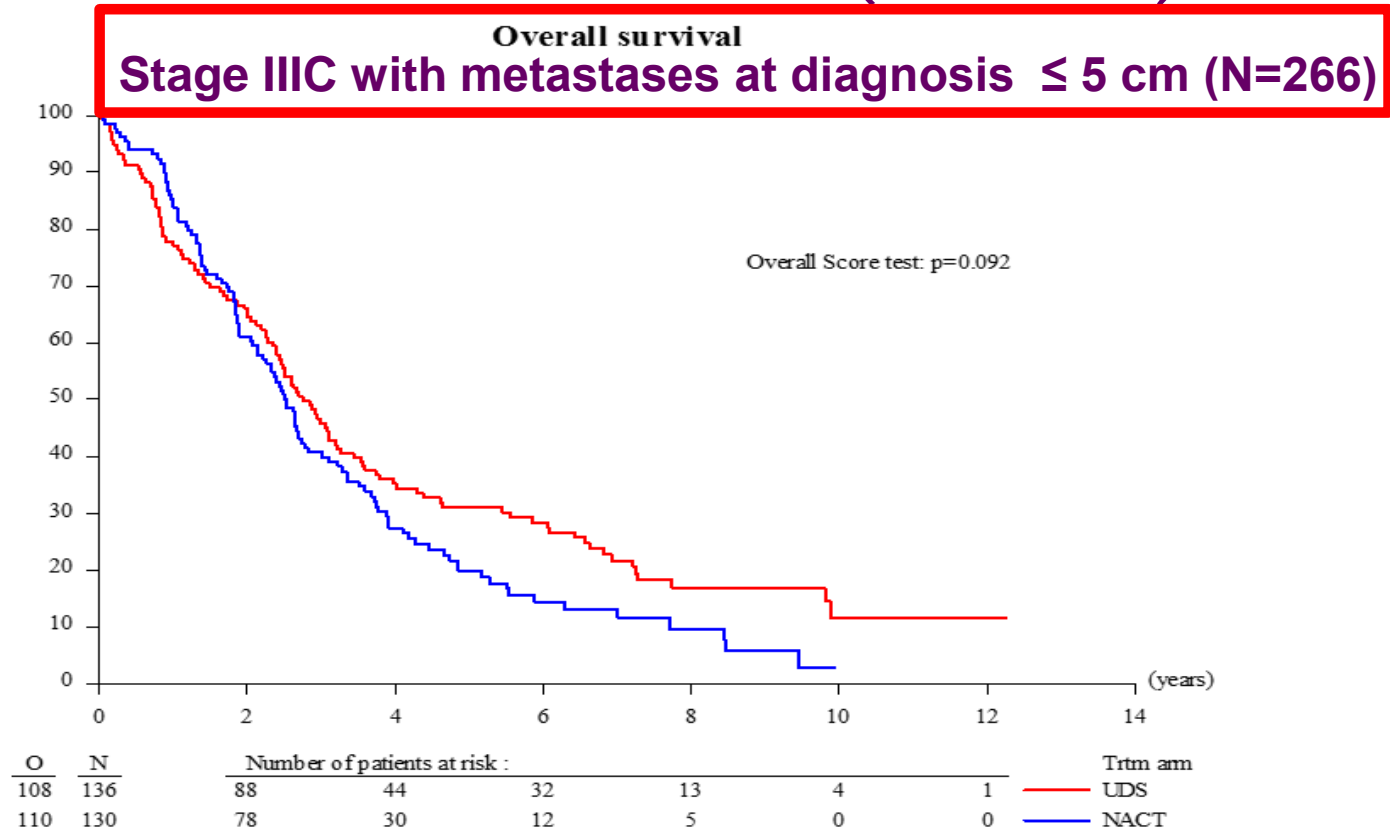
EORTC: NACT + IDS vs PDS: PP1

Overall Survival: Largest Metastatic Tumor Size



- **<5 cm: HR, 0.64; 95% CI: 0.45-0.93**

Meta-analysis EORTC and Chorus trials (n = 1220)



Overall survival			Non-parametric		Cox model	
Trtm arm	Patients (N)	Observed Events (O)	Median (95% CI) (Years)	% at 5 Year(s) (95% CI)	Hazard Ratio (95% CI)	P-Value (Score test)
UDS	136	108	2.75 (2.37, 3.20)	31.1 (23.4, 39.1)	1.00	0.092
NACT	130	110	2.51 (2.14, 2.77)	19.9 (13.2, 27.6)	1.26 (0.96, 1.65)	
Log-rank test:						p-value=0.092

Conclusions

EORTC-CHORUS meta-analysis

1. 1220 patients with this group of Stage IIIC-IV ovarian cancer with long-term follow-up (7 years)
 - NACT results in similar survival compared with PDS
2. Only patients with biopsy proven stage IIIC or IV are candidates for neoadjuvant chemotherapy
3. Interval debulking should be planned after 3 courses of chemotherapy

Conclusions

EORTC-CHORUS meta-analysis

4. Patients with stage IIIc and metastases ≤ 5 cm are generally better treated with primary debulking, depending on good general medical condition and no extensive spread on the bowel, or tumor on inoperable sites, e.g. around superior mesenteric artery
5. Patients with Stage IV disease are generally better treated with neoadjuvant chemotherapy, except for those with pleural effusions only and easily resectable Stage IV, e.g., inguinal nodes, spleen

How to Select Patients?



Laparoscopy to predict the result of primary cytoreductive surgery in patients with advanced ovarian cancer: randomized controlled trial

Arm	n	"futile"	PDS+ IDS	p
Laprosoc	102	10 (10%)	3 (3%)	< 0.001
PDS	99	39 (39%)	28 (28%)	< 0.001
Total	201			

NACT- IDS vs. PDS

Criticisms of Studies

- Low percentage of patients had optimal (no residual) resection of disease
16-40% (4-10%)
- Poorer performance status than in most upfront randomized prospective studies (high of 19-20% PS 2-3)



Discussion: PDS vs. NACT-IDS

Performance Status

<u>Study</u>	<u>0</u>	<u>2-3</u>
EORTC	44-45%	12-13%
CHORUS	30-32%	19-20%
Mito7	74-75%	3%

Presented by: Jonathan S. Berek



Discussion: PDS vs. NACT-IDS

Age years median (Range)

PDS

NCT

CHORUS

276 pts

274 pts

66 yrs (26-87)

65 yrs (34-88)

EORTC

336 pts

334 pts

62 yrs (25-86)

63 yrs (33-81)

JGOG 3016 **57** yrs (25-87), MITO7 **59** yrs (23-87)



Deaths within 28 days Postop

Surgery

PDS

NACT

CHORUS

14 (5.6%)

1 (0.5%)

EORTC

(2.5%)

(0.7%)

PDS

- Disease progression = 4
- Pulmonary embolism = 2; infection = 3; problems with fluid balance or renal failure = 2; hemorrhage = 1; intra-operative problems = 1
- *Still under review* = 1

NACT Pulmonary embolism = 1



Primary Debulking vs. Neoadjuvant chemoRx + Interval Debulking

- **Controversial Points**
 - Extent of debulking surgery/surgical expertise
 - High mortality in PDS
- **Median survivals much shorter than in most upfront RCT in stage III ovarian cancer**



Primary Debulking vs. Neoadjuvant chemoRx + Interval Debulking

Compared to most up-front RCT in Ov-FT-P patients-

- **Poorer than expected patient characteristics**
 - Highly selected- older, sicker, larger mets!
- **Higher tumor burden of recruited patients**
 - 62% pts in EORTC mets > 10 cm
 - 20% pts in CHORUS PS > 2

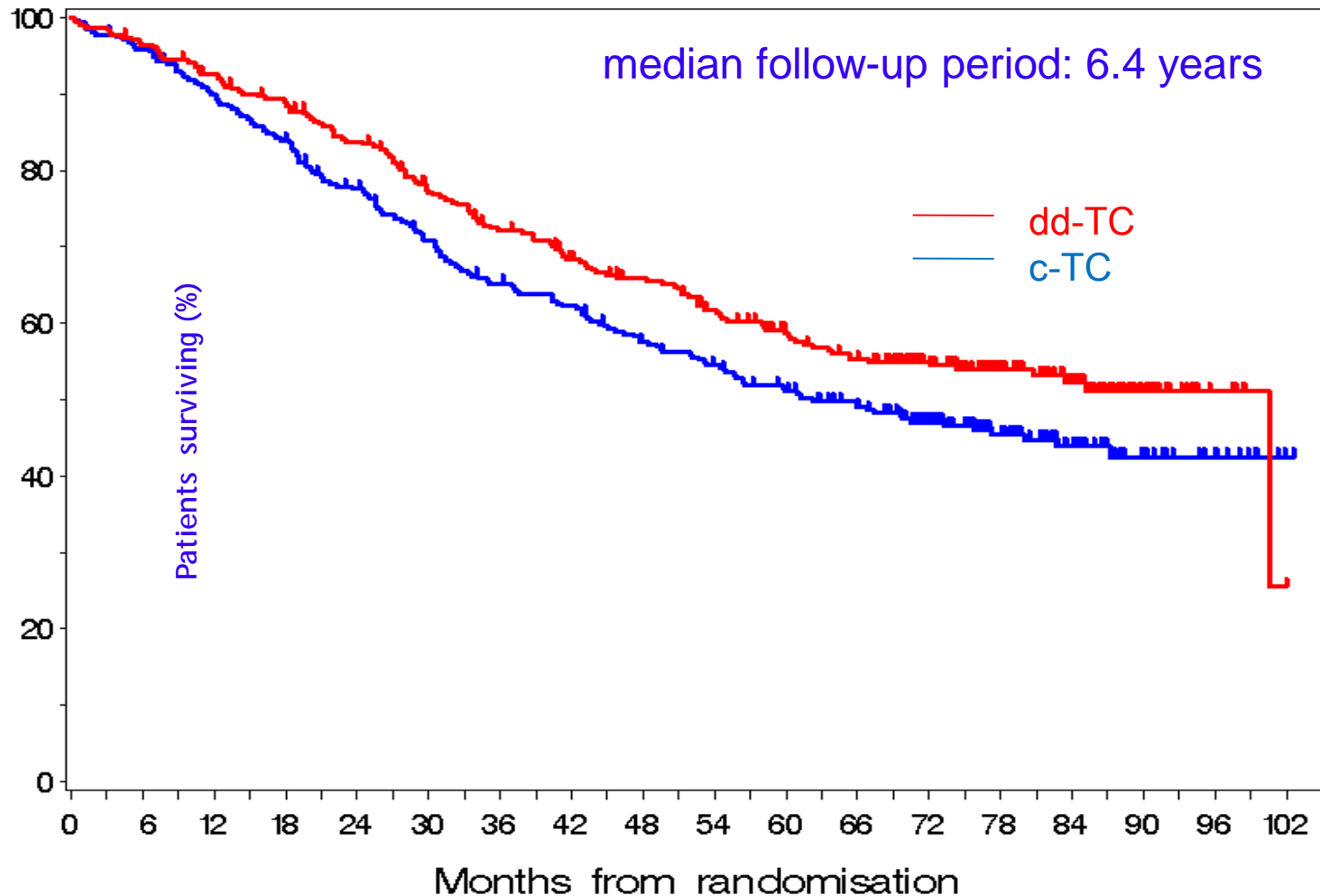
Discussion: PDS vs. NACT-IDS

Comparison of JGOG Dose-dense vs. CHORUS/EORTC NACT

- Overall median survivals much shorter in these two studies than in JGOG
 - **PFS 10-11 months vs. 28+ months**
 - **OS 22-24 months vs. 62+ months**
- Differences in performance status & age
- Good prognosis vs. poor prognosis patients-study populations in are very different!



JGOG3016: Updated Overall Survival



Treatment	n	Deaths, n (%)	Median OS	5-yr survival	P value	HR	95%CI
dd-TC	312	139 (45)	not reached	58.7%	0.039	0.79	0.63-0.99
c-TC	319	168 (53)	62.2 mos.	51.1%			

Primary Debulking vs. Neoadjuvant chemoRx + Interval Debulking

- Therefore

“the generalization of results from such highly selected adverse subgroups risks extrapolation to patients who are fit and present with potentially resectable disease.”

Discussion: PDS vs. NACT-IDS

How do we best select patients who should undergo PDS?

- Patient selection is key
- Need to minimize operative mortality—gynecologic oncologic surgeons in major centers
- Can we select patients by ‘Gestalt’
e.g., a ‘clinical scoring algorithm’?
- Can we develop a molecular assay that can help us predict?



TRUST

Trial on Radical Upfront Surgical Therapy

Upfront radical debulking surgery
versus interval radical debulking
surgery in advanced ovarian cancer

Design-proposal neoadjuvant chemotherapy International phase III

Pts. With ovarian-, fallopian-tube or peritoneal-cancer FIGO stage IIIB, IIIC and resectable stage IV (VATS or open assessment if pleural effusion recommended/mandatory)



- Primary Endpoint OS ITT population; co primary Endpoint „per Protocol“=50% resec.
- Secondary Endpoints PFS, resection rates, MⁿM after 6 months, QoL, „fragility Index“
- Strata: FIGO stage (III / IV), group/country, ECOG 0 vs 1/2
- **Defined qualification process for participating centers to ensure highest surgical quality (>50% complete resection rate, >25 procedures/year)**

S surgery **C** Carboplatin AUC5 **P** Paclitaxel 175 mg/sq  Bev. 15mg 15 mon
suggested therapy, also weekly paclitaxel possible if preferred or omission of Bev

Discussion: PDS vs. NACT-IDS

Take-Home Message!

- Because this is by definition a poorer prognosis group, the findings of the 2 RCTs cannot be generalized to all patients with stage III ovarian cancer!
- **Standard of care should still be primary debulking surgery followed by chemotherapy for most patients.**



