

9th Gynaecological Cancer Symposium

Friday 26th February 2016

Ultra-Radical surgery: The way forward for the UK?

C. William Helm

Northern Gynaecological Oncology Center,
Gateshead, England

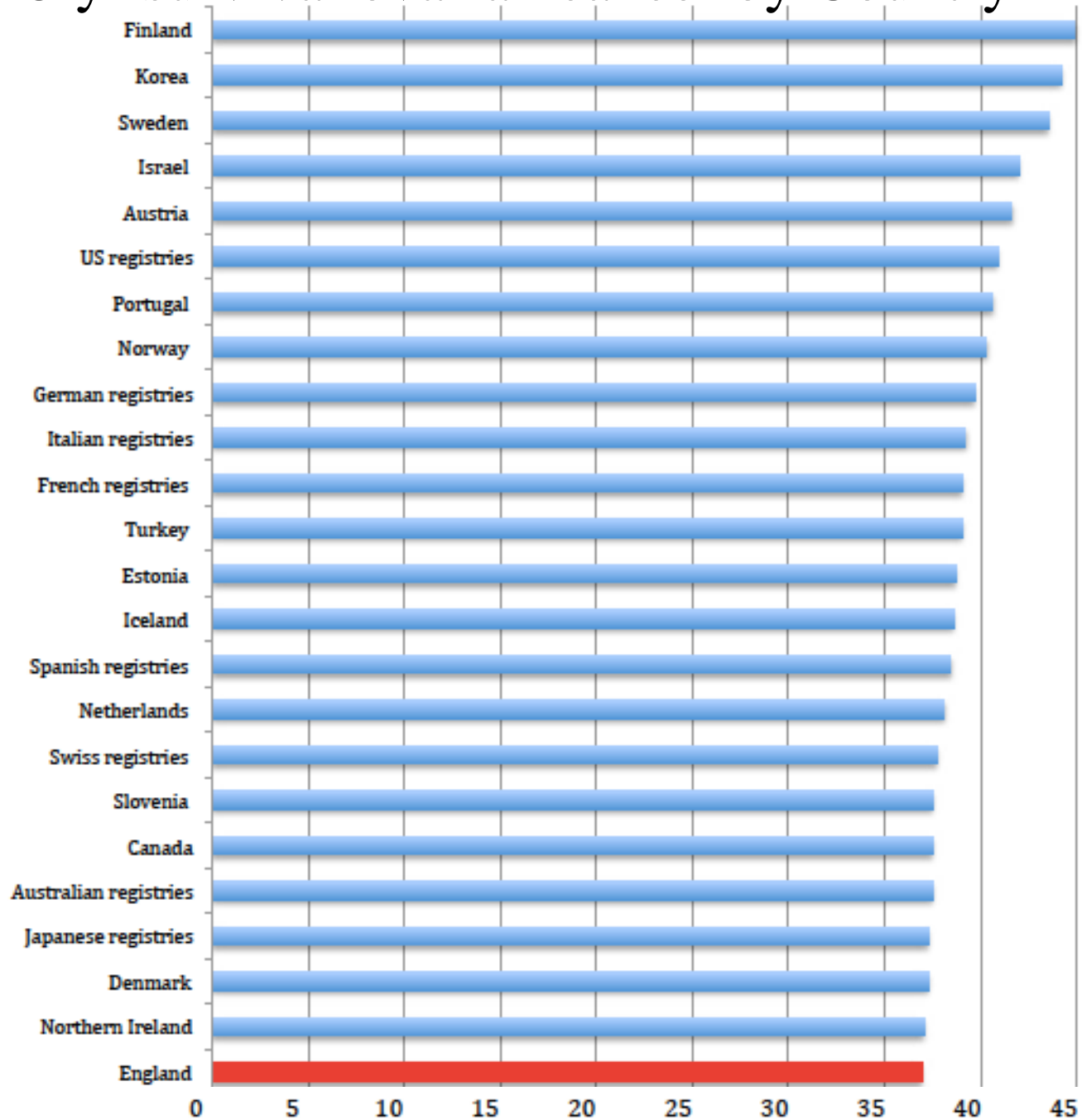
No Disclosures

Ultra-Radical surgery: The way forward for the UK?

Ovarian Cancer

- where we are
- how we got here
- how we can move forward

% 5 yr survival ovarian cancer by Country



Age-standardized % 5yr survival for ovarian cancer

Country	2005-2009
Sweden	43.5
Norway	40.3
Australia	37.5
Canada	37.5
Denmark	37.3
England	31.5

5-year Survival of Cancers in Women

Primary Site	% 5-year survival
Breast	89.2
Endometrium	81.6
Bladder	77.1
Colon/Rectum	65.0
Ovary	45.3
Lung/Bronchus	17.4

Ovarian Cancer Stage at Presentation

FIGO stage	%
I	28.3
II	8.4
IIIA	2.6
IIIB	5.6
IIIC	42.0
IV	13.0

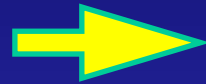
Ovarian Cancer

Remains confined to peritoneal cavity

Relatively non-invasive

ovarian cancer is sensitive to

surgery



resect bulky disease

AND

chemotherapy



mop up the small
volume residual

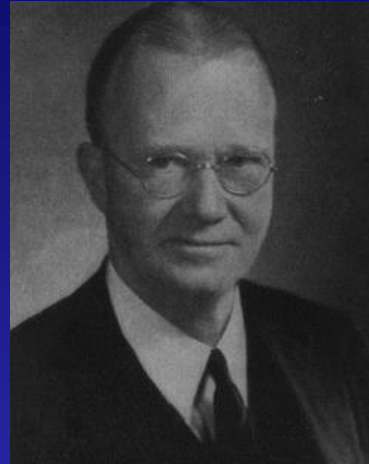
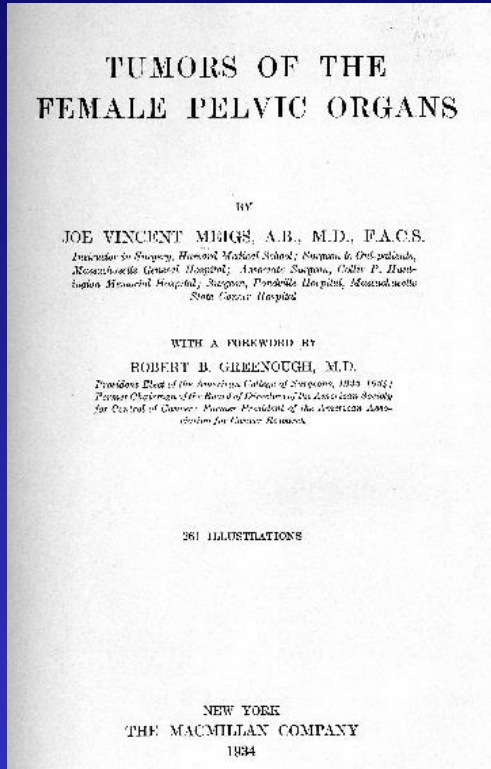
Chemotherapy for ovarian cancer

EFFECT OF 2-CHLORO-2'-HYDROXYDIETHYL SULFIDE
(HEMISULFUR MUSTARD) ON CARCINOMATOSIS
WITH ASCITES

ARNOLD M. SELIGMAN, M.D., ALEXANDER M. RUTENBURG, M.D.,

Seligman and Rutenberg *Cancer* 5:354-363, 1952

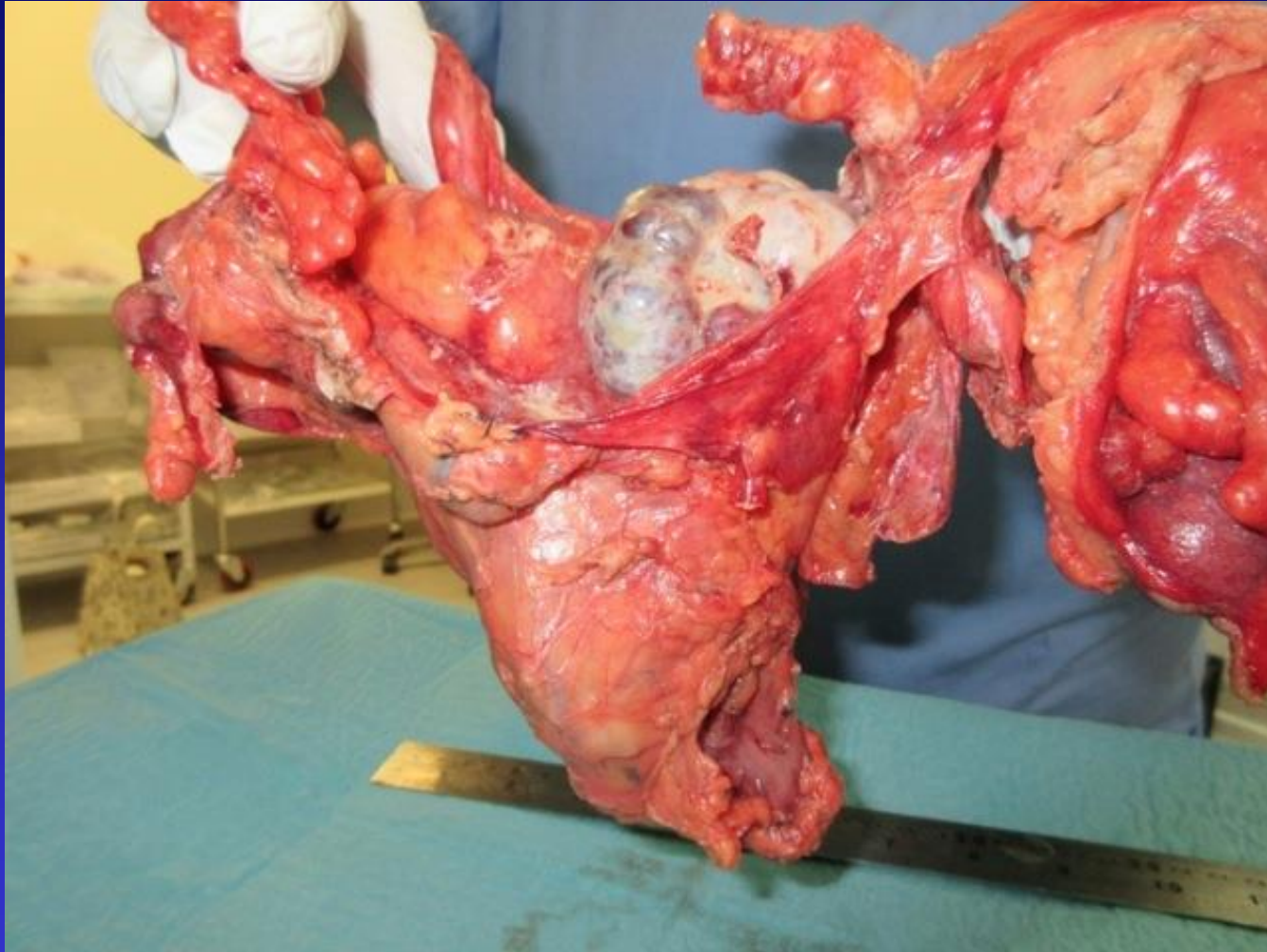
Surgery for ovarian cancer



‘as much tumor as possible should be removed to enhance the effectiveness of postoperative.....’

1934

Surgery for ovarian cancer

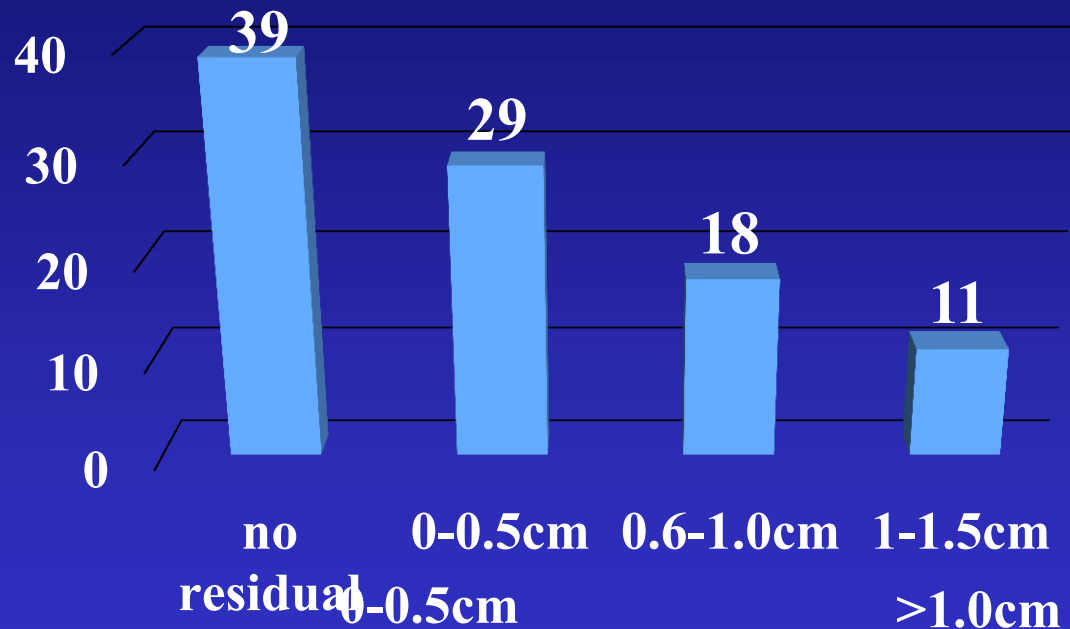


Hudson C. J Obstet Gynaecol Br CommonW 1968;75:1155-1160

Residual disease and survival

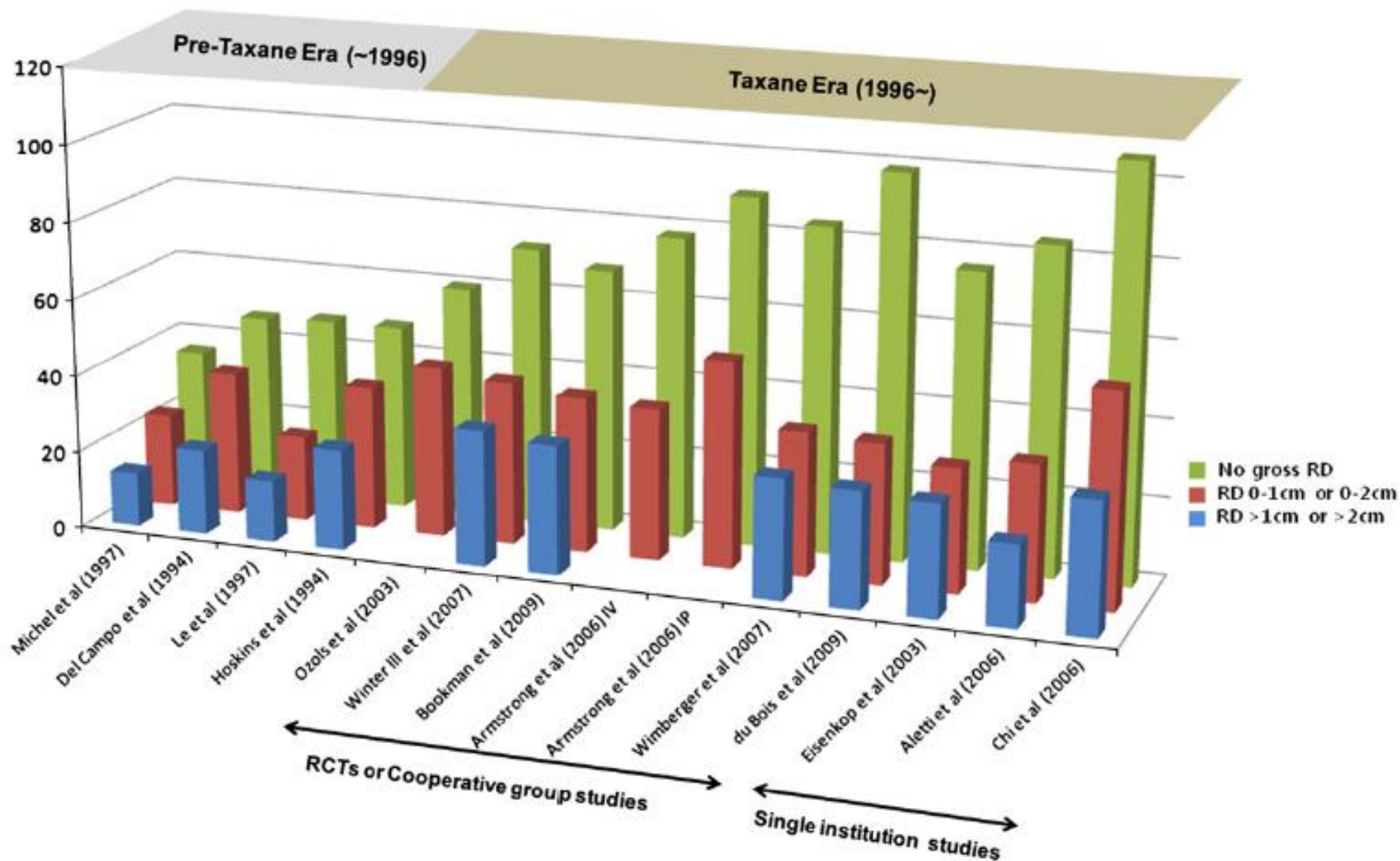
n=102 stage II and III

% 5yr
survival



Griffiths NCI Monograph 42:101-104, 1975

Survival related to residual disease



Prognostic Factors for Stage III Epithelial Ovarian Cancer: A Gynecologic Oncology Group Study

William E. Winter III, G. Larry Maxwell, Chunqiao Tian, Jay W. Carlson, Robert F. Ozols, Peter G. Rose, Maurie Markman, Deborah K. Armstrong, Franco Muggia, and William P. McGuire

n=1895

Residual	n	PFS (m)	OS (m)
microscopic	437	33.0	71.9
0.1-1.0cm	791	16.8	42.4
>1cm	667	14.1	35.0

Winter WE et al JCO 2007; 25:3621-3627

Prognostic Factors for Stage III Epithelial Ovarian Cancer: A Gynecologic Oncology Group Study

William E. Winter III, G. Larry Maxwell, Chunqiao Tian, Jay W. Carlson, Robert F. Ozols, Peter G. Rose, Maurie Markman, Deborah K. Armstrong, Franco Muggia, and William P. McGuire

Conclusions

- Longest survival associated with no residual disease

Winter WE et al JCO 2007; 25:3621-3627

Prognostic Factors for Stage III Epithelial Ovarian Cancer: A Gynecologic Oncology Group Study

William E. Winter III, G. Larry Maxwell, Chunqiao Tian, Jay W. Carlson, Robert F. Ozols, Peter G. Rose, Maurie Markman, Deborah K. Armstrong, Franco Muggia, and William P. McGuire

Conclusions

- There is a survival benefit associated with cytoreduction to ≤ 1 cm residual

Winter WE et al JCO 2007; 25:3621-3627

Prognostic Factors for Stage III Epithelial Ovarian Cancer: A Gynecologic Oncology Group Study

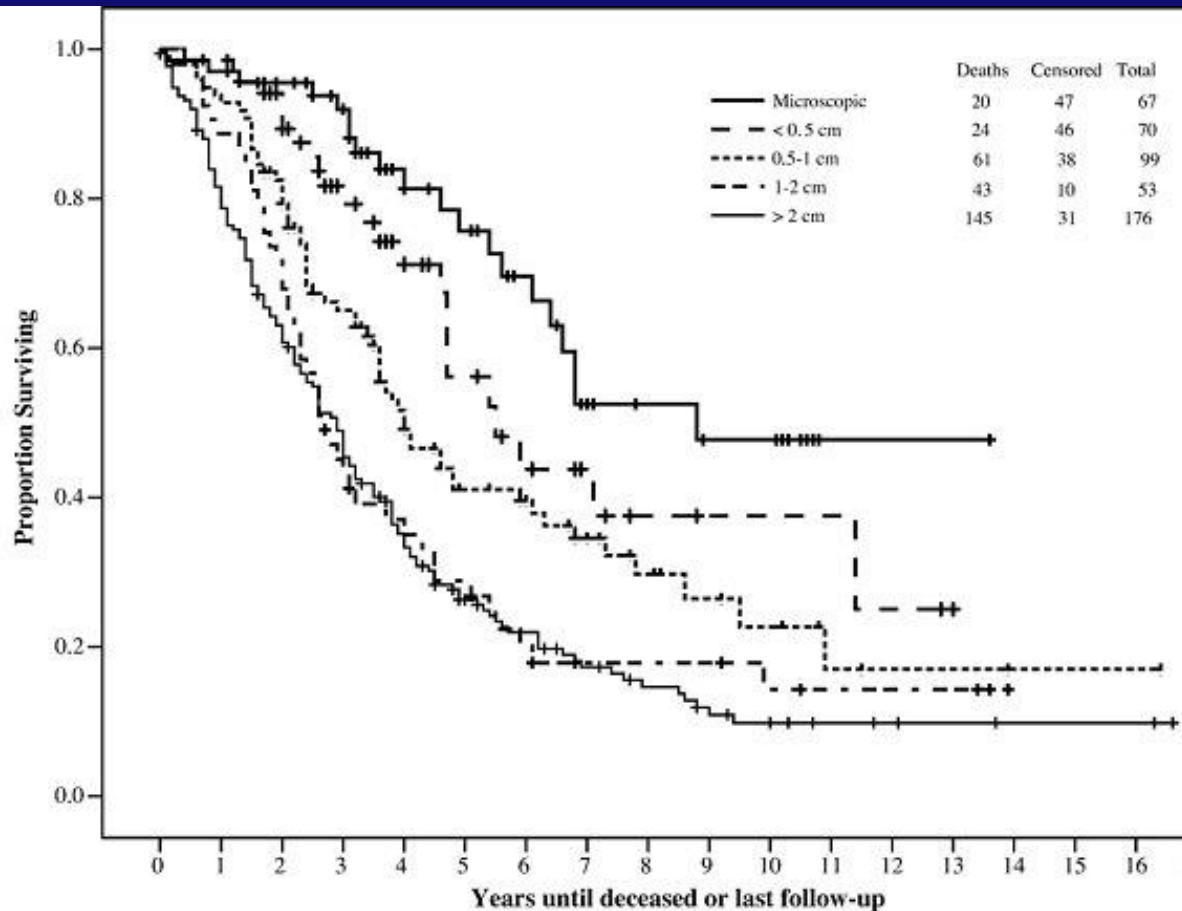
William E. Winter III, G. Larry Maxwell, Chunqiao Tian, Jay W. Carlson, Robert F. Ozols, Peter G. Rose, Maurie Markman, Deborah K. Armstrong, Franco Muggia, and William P. McGuire

Conclusions

- Cytoreduction to >1 cm residual has no benefit on overall survival

Winter WE et al JCO 2007; 25:3621-3627

survival in relation to extent of residual disease



residual size (cm)	median 5yr survival (m)
0	106
≤0.5cm	66
0.6-1cm	48
1-2cm	33
>2cm	34

Prognostic Factors for Stage III Epithelial Ovarian Cancer: A Gynecologic Oncology Group Study

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Prognostic Factors

- age
- histologic subtype
- performance status
- extent of residual disease

Winter WE et al JCO 2007; 25:3621-3627

Radical Surgery in Ovarian Cancer

NOTHING

is

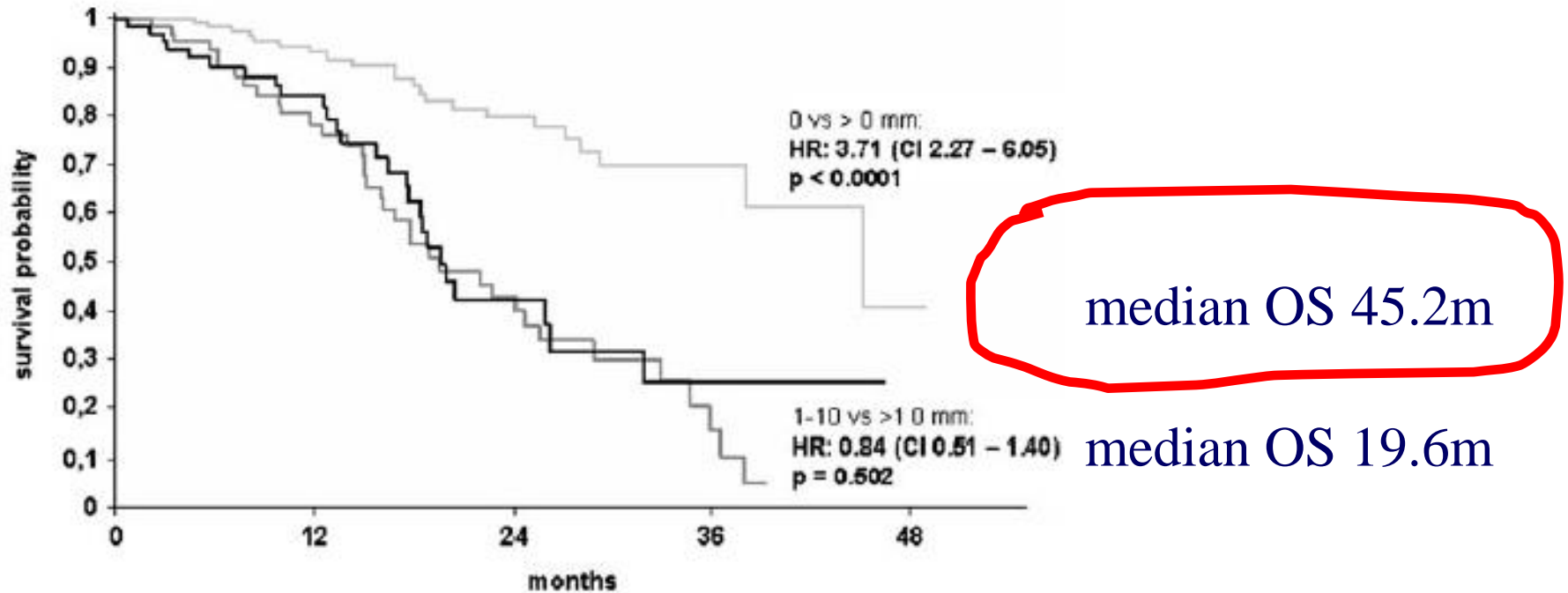
OPTIMAL

OPTIMAL

is

NOTHING

Surgery for Recurrent Disease – Residual Disease



Patients at risk

RD= 0 mm	133	78	40	8	1
RD=1-10 mm	69	38	15	3	0
RD >10 mm	65	37	11	3	0

What Are the Current Surgical Objectives, Strategies, and Technical Capabilities of Gynecologic Oncologists Treating Advanced Epithelial Ovarian Cancer?

Scott M. Eisenkop, M.D.,*¹ and Nick M. Spirto, M.D.†

*Womens' Cancer Center, Encino-Tarzana, 5525 Etiwanda Avenue, Suite 311, Tarzana, California 91356; and

†Womens' Cancer Center, Palo Alto, 900 Welch Road, Suite 300, Palo Alto, California 94304-1800

Received December 7, 2000; published online August 1, 2001

- **Reasons for suboptimal cytoreduction:**
 - Unresectable upper abdominal metastases 85%
- **Disease sites precluding optimal cytoreduction:**
 - Disease involving base of mesentery 83%
 - Portal triad disease 77%
 - Bulky diaphragmatic metastases 76%
 - Surface diaphragmatic metastases 51%

Eisenkop SM et al Gynecol Oncol 2001; 82, 489–497 (2001)

% of patients with upper abdominal metastases

n= 474

stage IIIC patients undergoing CRS between 1989-2005

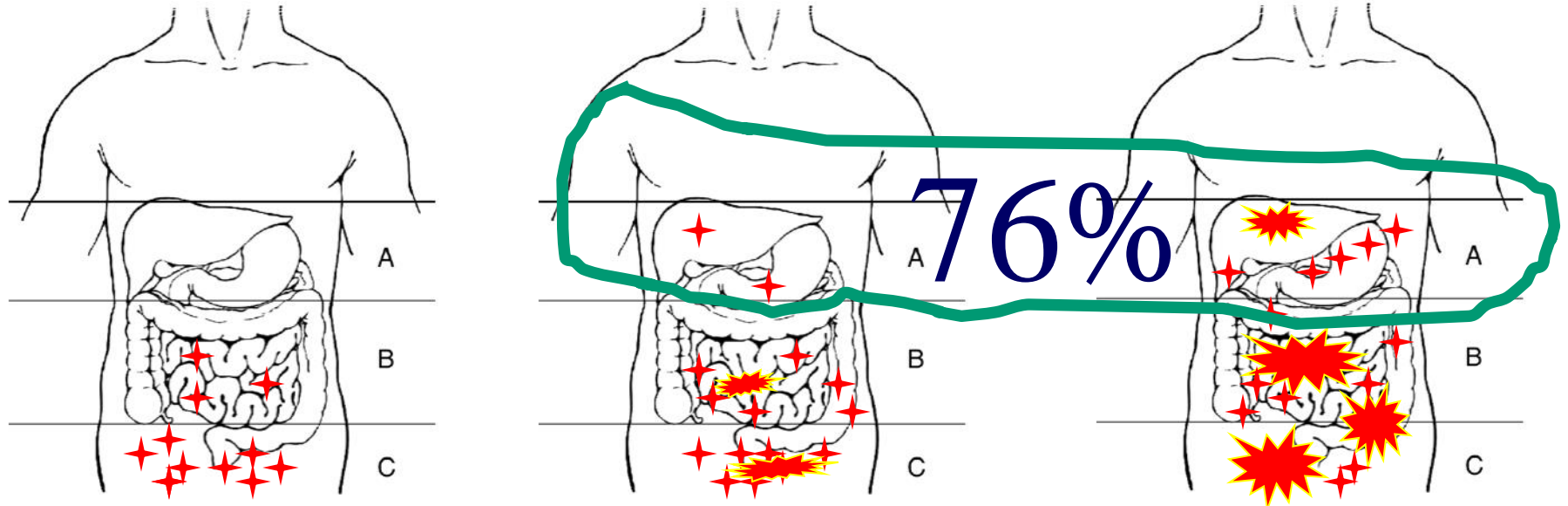


Fig. 1. Abdominopelvic regions. (A) Upper abdomen cephalad to the greater omentum. (B) Mid-abdomen. (C) Pelvis.

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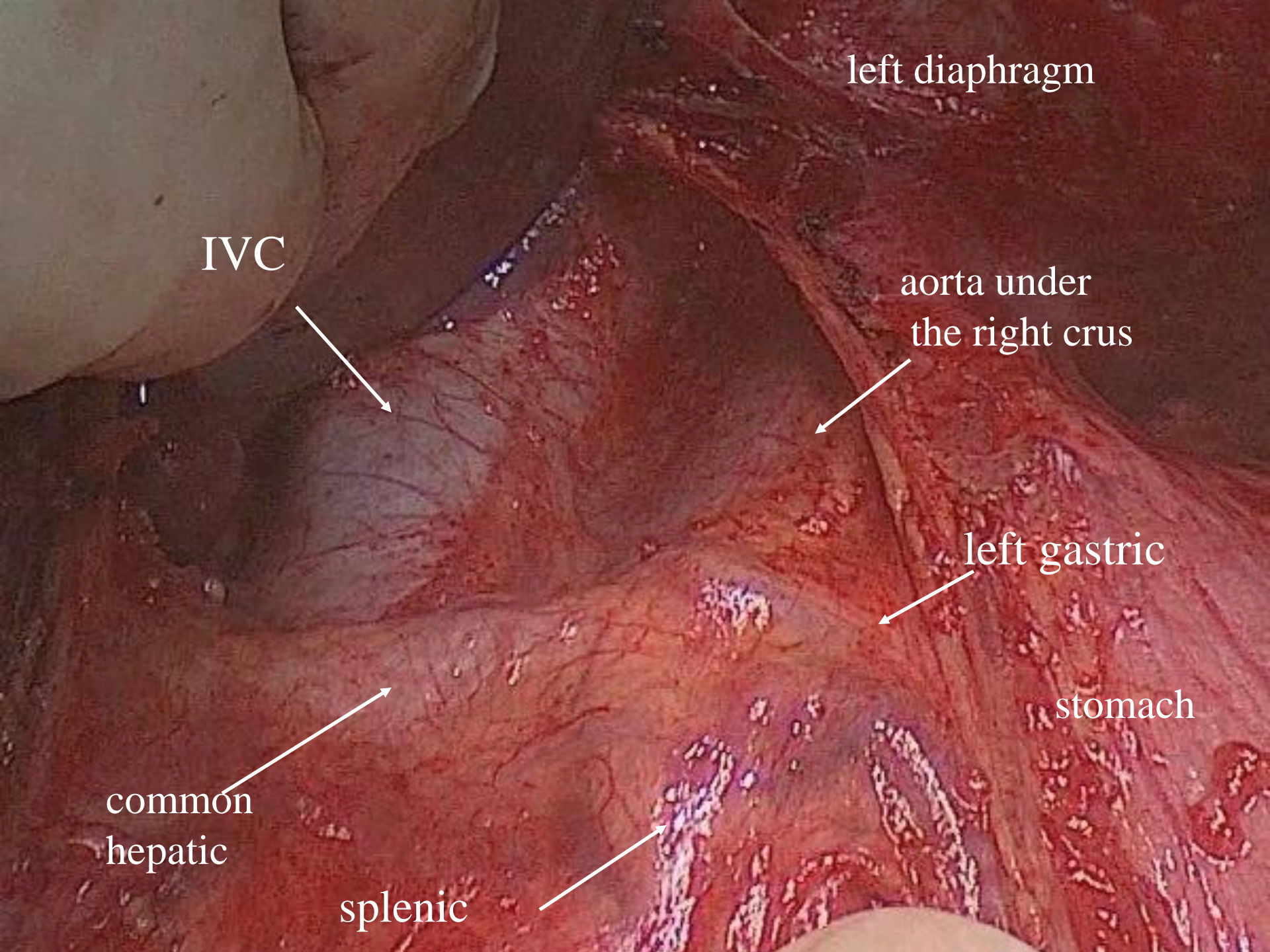
None
116 (24%)

Minimal (<1cm)
161 (34%)

Bulky
197 (42%)







left diaphragm

IVC

aorta under
the right crus

left gastric

stomach

common
hepatic

splenic

Gynaecologic Oncology Practice UK

surgical proc

	Procedure	PDS
	diaphragm stripping	2.7%
Infra-colic omentectomy	splenectomy	0.6%
Supra-colic omentectomy	supracolic omentectomy	53%
Pelvic lymphadenectomy/lymph node dissection		
Para-aortic lymphadenectomy/lymph node dissection		
Bowel resection		
Stoma raised		
Splenectomy		4
Diaphragmatic stripping	residual disease	% 7
Residual disease <2 cm		2
Residual disease <1 cm		5
No residual disease	no residual	35.6 6
	<1cm	47.3 7-351

Gynaecologic Oncology Practice UK

operating time

Average operating time (hours)

<2	8/41 (20%)
2-3	24/41 (58%)
3-4	8/41 (20%)
>4	1/41 (2%)

Primary Surgery followed by chemotherapy

or

Chemotherapy followed by surgery
followed by chemotherapy

for Ovarian Cancer?

Benefits of neoadjuvant chemotherapy

- fewer procedures
- shorter operating time
- increased rate of no residual
- reduced morbidity
- shorter hospital stay

BUT can you give NAC without impacting survival for the patient?

Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial

Sean Kehoe, Jane Hook, Matthew Nankivell, Gordon C Jayson, Henry Kitchener, Tito Lopes, David Luesley, Timothy Perren, Selina Bannoo, Monica Mascarenhas, Stephen Dobbs, Sharadah Essapen, Jeremy Twigg, Jonathan Herod, Glenn McCluggage, Mahesh Parmar, Ann-Marie Swart

Lancet 2015; 386: 249–57

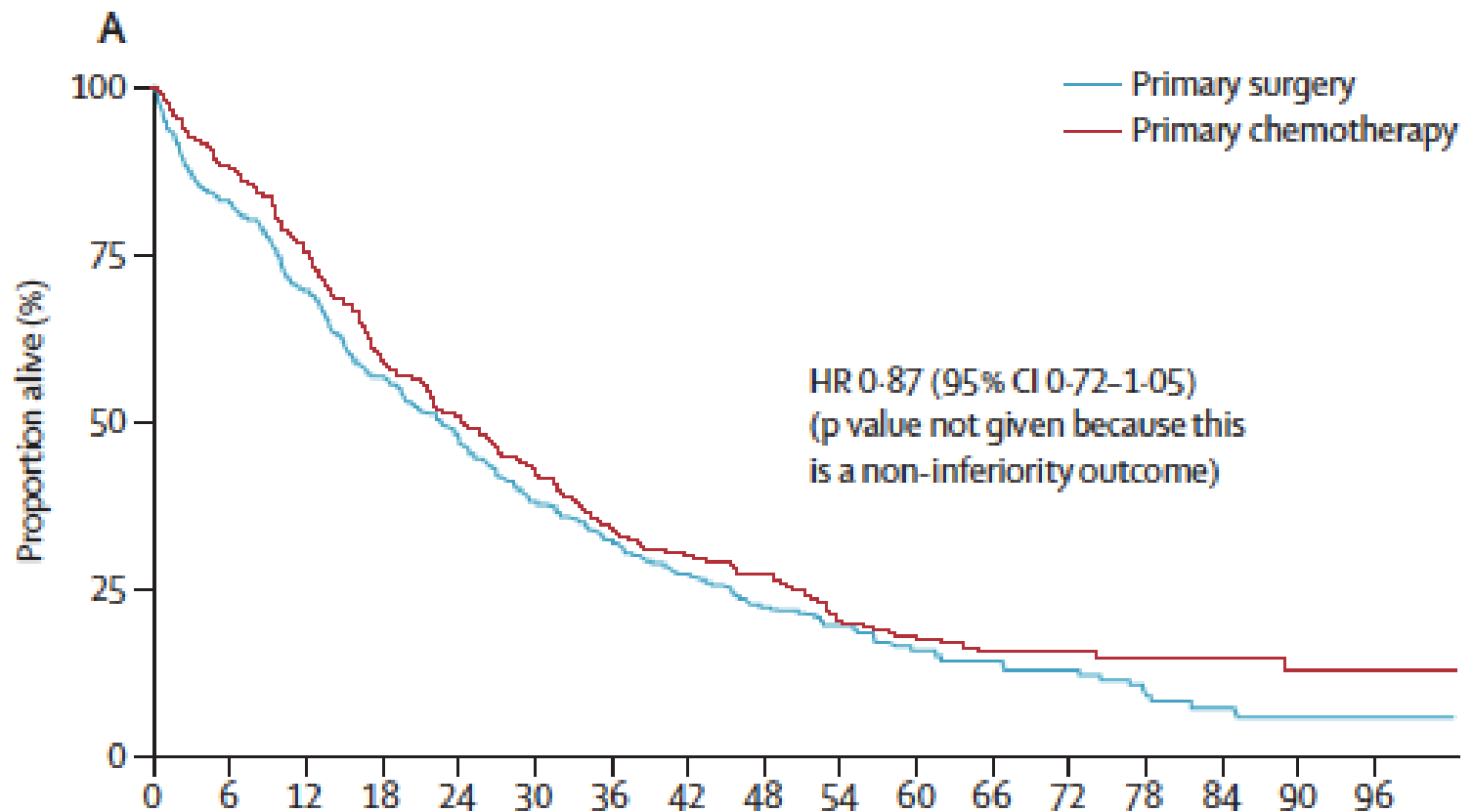
Eligibility:

imaging evidence of a pelvic mass with extra-pelvic disease compatible with FIGO 1988 stage III or IV ovarian, fallopian tube, or primary peritoneal cancer

fit for surgery and chemotherapy

Kehoe S. et al Lancet 2015;386:249-57

CHORUS: overall survival



Number at risk		0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96
Primary surgery		276	225	189	153	128	83	51	22	17	6	3						
Primary chemotherapy		274	239	205	161	137	88	59	31	21	14	3						

CHORUS: duration of surgery, residual disease

	Primary surgery (n=255)	Primary chemotherapy (n=219)
Median length of operation (min)	120 (12-450, 80-161)	120 (30-330, 90-155)
Missing data	27	32
Residual disease (all patients)		
0 cm	39 (17%)	79 (39%)
≤1 cm	57 (24%)	68 (34%)
>1 cm	137 (59%)	54 (27%)
Missing data	22	18

Post op grade 3/4 morbidity

	Primary surgery (n=255)	Primary chemotherapy (n=219)
Any grade 3 or 4 adverse event	60 (24%)	30 (14%)*
Haemorrhage	8 (3%)	14 (7%)
Venous thromboembolism	5 (2%)	0 (0%)
Dysrhythmia	3 (1%)	0 (0%)
Hypotension	6 (2%)	2 (1%)
Fever (no infection)	0 (0%)	0 (0%)
Diarrhoea	4 (2%)	2 (1%)
Intestinal or rectal fistula	2 (1%)	1 (<1%)
Nausea	12 (5%)	1 (<1%)
Vomiting	12 (5%)	1 (<1%)
Bowel obstruction	2 (1%)	1 (<1%)
Gastrointestinal pain	4 (2%)	2 (1%)
Vaginal or vesicovaginal fistula	1 (<1%)	1 (<1%)
Urethral obstruction	1 (<1%)	0 (0%)
Weight loss	0 (0%)	0 (0%)
Infection	16 (6%)	6 (3%)
Missing data	3	10

Mortality

Death within 28 days after surgery	14 (6%)	1 (<1%)
Disease progression	5 (2%)	--
Pulmonary emboli	2 (<1%)	1 (<1%)
Sepsis	3 (1%)	--
Problems related to fluid balance or renal failure	2 (<1%)	--
Coagulopathy or disseminated intravascular coagulation	1 (<1%)	--
Respiratory failure	1 (<1%)	--

ORIGINAL ARTICLE

Neoadjuvant Chemotherapy or Primary
Surgery in Stage IIIC or IV Ovarian Cancer

Ignace Vergote, M.D., Ph.D., Claes G. Tropé, M.D., Ph.D.,

NEJM 2010; 363:943-953

Randomized Trial

n = 632

ORIGINAL ARTICLE

Neoadjuvant Chemotherapy or Primary
Surgery in Stage IIIC or IV Ovarian Cancer

Ignace Vergote, M.D., Ph.D., Claes G. Tropé, M.D., Ph.D.,

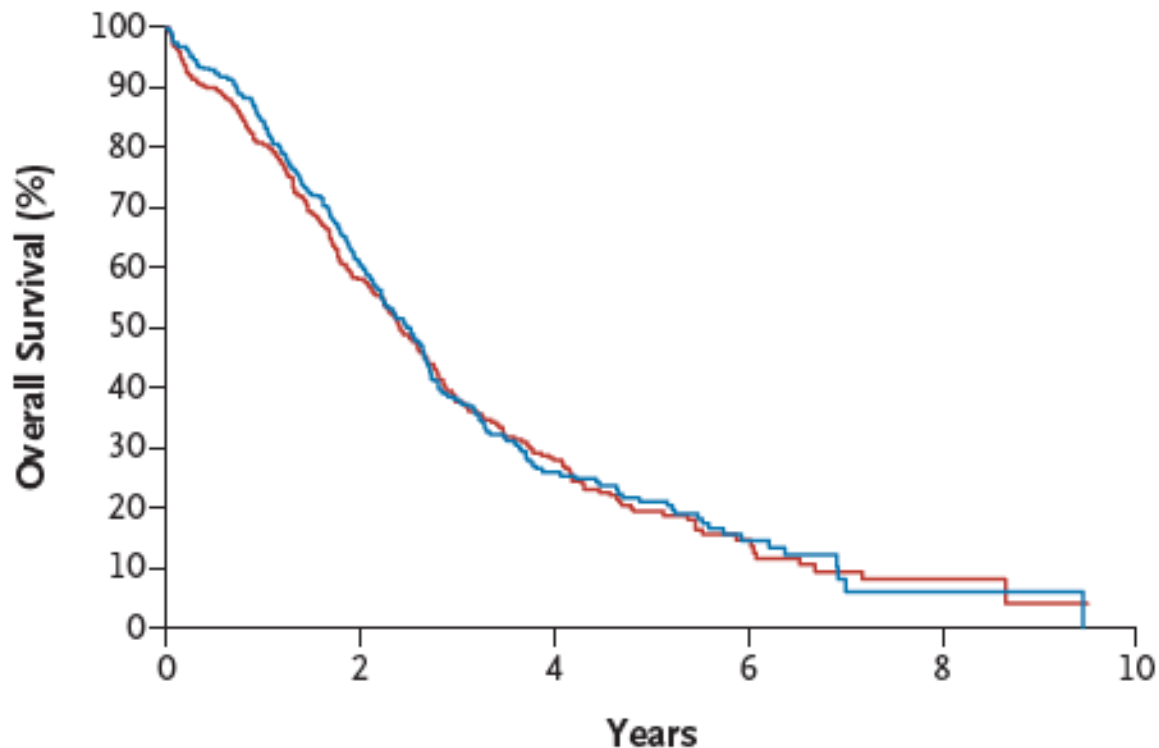
Eligibility:

biopsy-proven Stage IIIC or IV invasive
epithelial ovarian carcinoma, primary peritoneal or FT

Vergote I. et al NEJM 2010; 363:943-953

Overall survival NAC versus Frontline Surgery

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

Interpretation

CHORUS is the second trial to investigate timing of surgery in the first-line treatment of advanced ovarian cancer. We recruited a population with a poor outlook; patients were older and had a worse performance status than patients in other trials where patients were recruited after surgery. Our findings were consistent with the results of the EORTC 55971 trial (figure 3).²¹ These two trials confirm that primary chemotherapy before delayed surgery is an alternative clinical management strategy to primary surgery, which could reduce morbidity in many women with advanced ovarian cancer.

Median Survival after maximal surgery

author	year	n	months
Eisenkop	2003	408	58.2
Panici	2005	189	62.1
Chi	2009	210	54
Vergote	2010	334	29
Kehoe	2015	225	22.6

Eisenkop et al 2003; 90 (2003) 390–396

Panici et al 2005 JNCI 2005;97:560-566

Chi et al Gynecol Oncol 2009;114:26-31

Ignace Vergote versus Dennis Chi

author	year	n	median PFS (m)	median OS (m)
Vergote	2010	334	12	29
Chi	2012	285	17	50

Vergote I. et al NEJM 2010; 363:943-953

Chi DS. et al Gynecol Oncol 2012;124:10–14

Survival after maximal surgery

author	year	n	median (m)
Eisenkop	2003	408	58.2
Panici	2005	189	62.1
Chi	2009	210	54
Vergote	2010	334	29
Chi	2012	285	50
Kehoe	2015	225	22.6

Eisenkop et al 2003; 90 (2003) 390–396

Panici et al 2005 JNCI 2005;97:560-566

Chi et al Gynecol Oncol 2009;114:26-31

Is perioperative visual estimation of intra-abdominal tumor spread reliable in ovarian cancer surgery after neoadjuvant chemotherapy?

Systematic visual evaluation of tumour spread at the start of

- primary surgery/diagnostic laparoscopy (n=39)
- interval surgery (n=16).

Compared with histopathological analysis

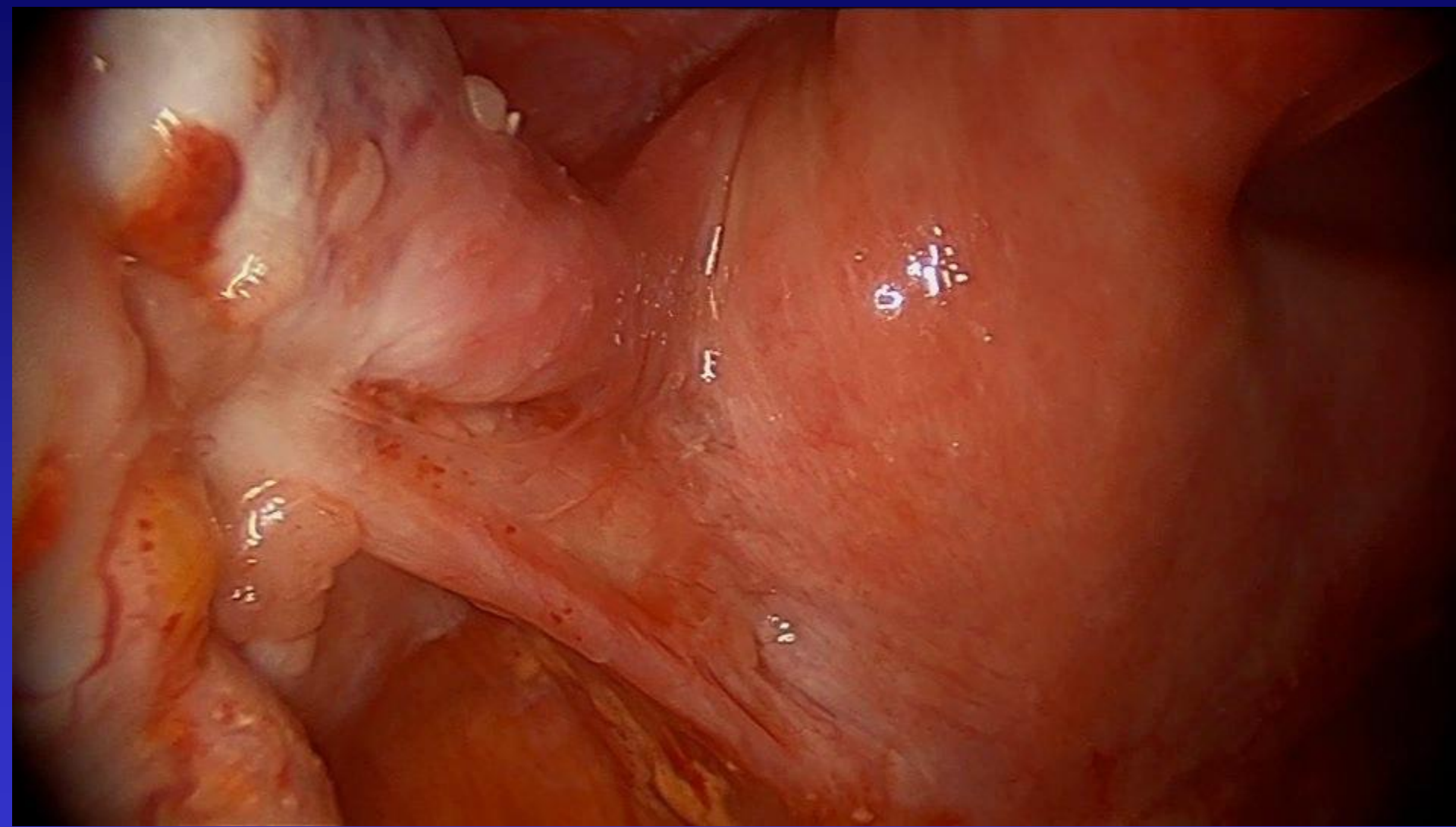
220 biopsies from primary and 92 biopsies from interval surgery

Hynninen, J et al. Gynecol Oncol 2013;128:229-232

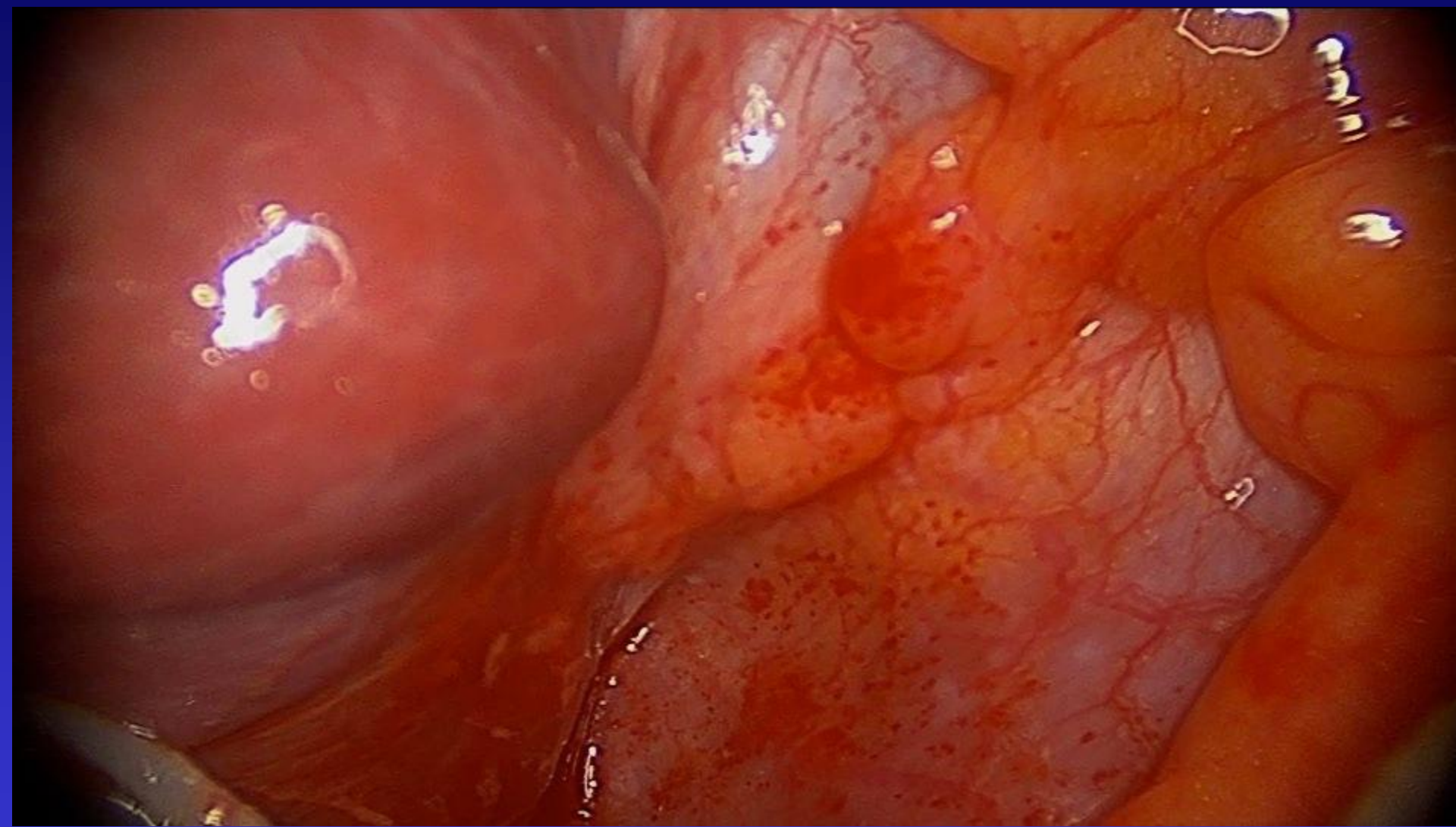
Accuracy of surgeon being able to tell cancer from benign disease

	primary surgery	NAC	P value
sensitivity	98	86	<0.001
specificity	76	76	ns
accuracy	95	84	<0.001

Hynninen, J et al. Gynecol Oncol 2013;128:229-232







Platinum resistance after neoadjuvant chemotherapy compared to primary surgery in patients with advanced epithelial ovarian carcinoma[☆]

n =425 patients, retrospective

95

NAC-IDS

330

Primary surgery.

Following retreatment with platinum on recurrence

32 (88.8%) in the NACT-IDS group were PR

62 (55.3%) in the PDS

p=0.001

Disadvantages of neoadjuvant chemotherapy

- surgery more difficult
- assessment of cancer less accurate
- rate of no residual?
- platinum resistance increased?
- survival worse

Primary Surgery versus NAC



The incidence of major complications after the performance of extensive upper abdominal surgical procedures during primary cytoreduction of advanced ovarian, tubal, and peritoneal carcinomas[☆]

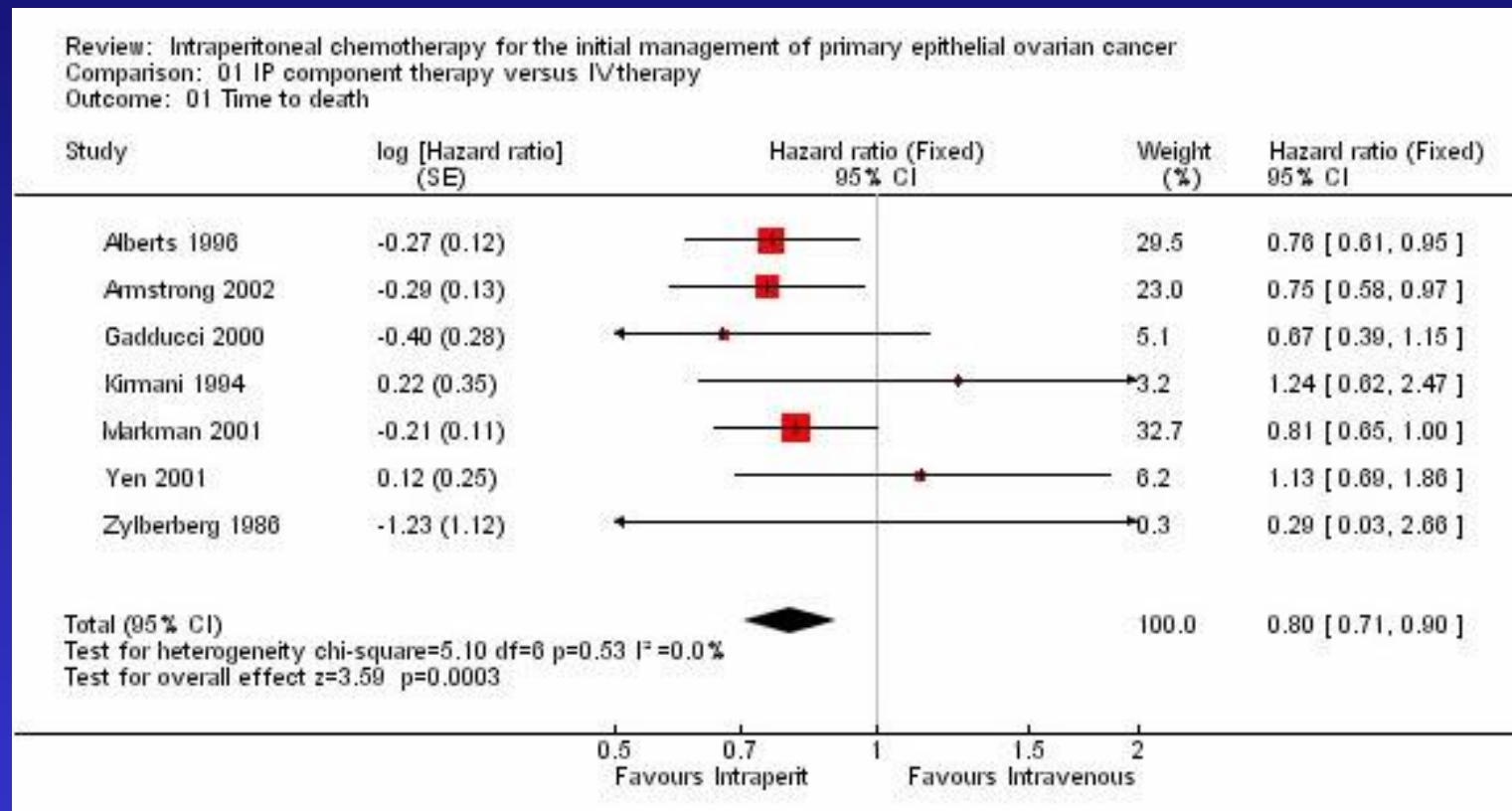
n=141

- **Grade 3–5 complications** 31 (22%)
- **Mortality** 2 (1.4%)
- 21/31 (68%) managed with percutaneous drainage of infected or non-infected collections

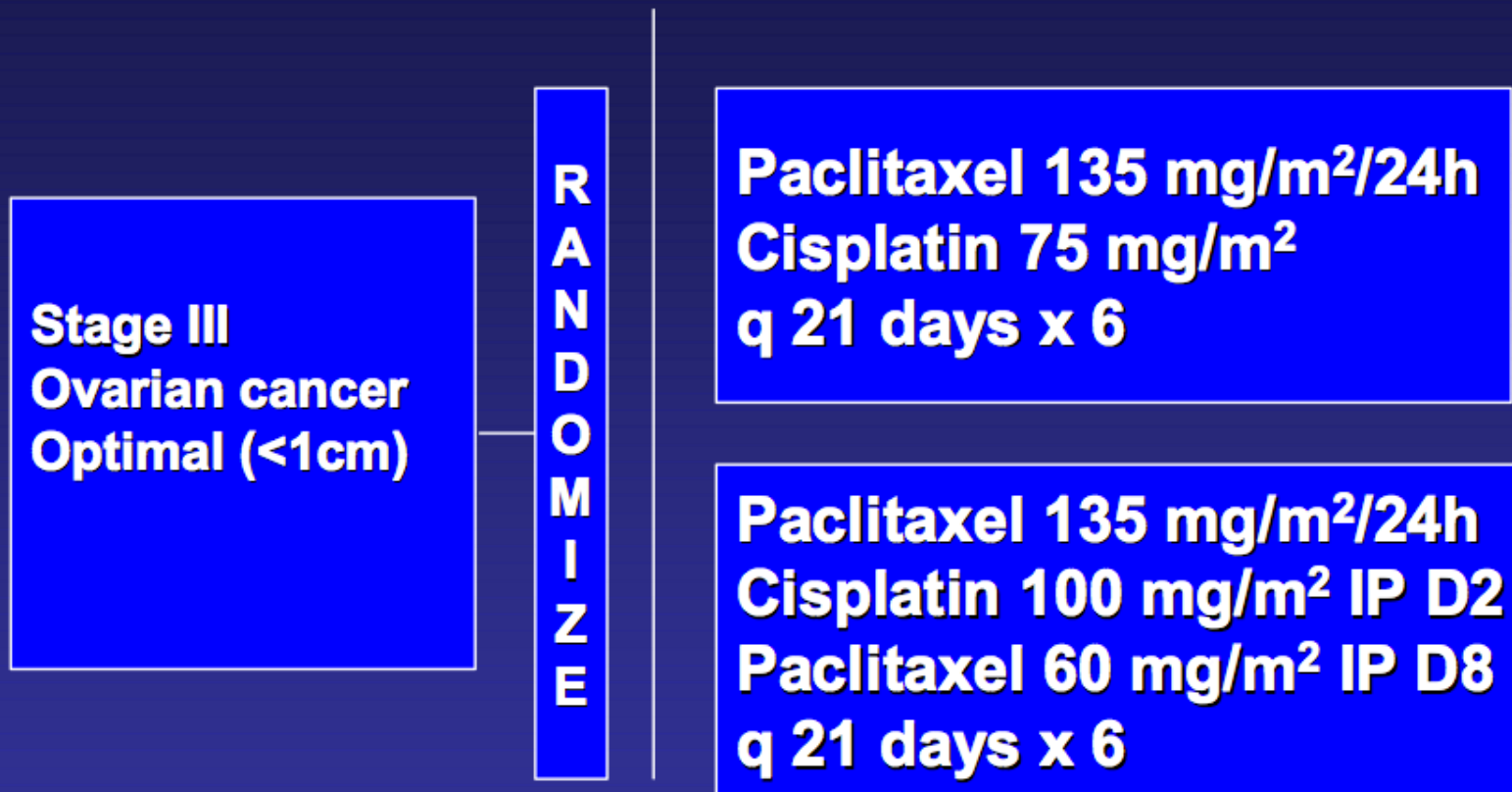
overall median survival 57 months

Cochrane meta-analysis

IP versus IV chemotherapy for ovarian cancer

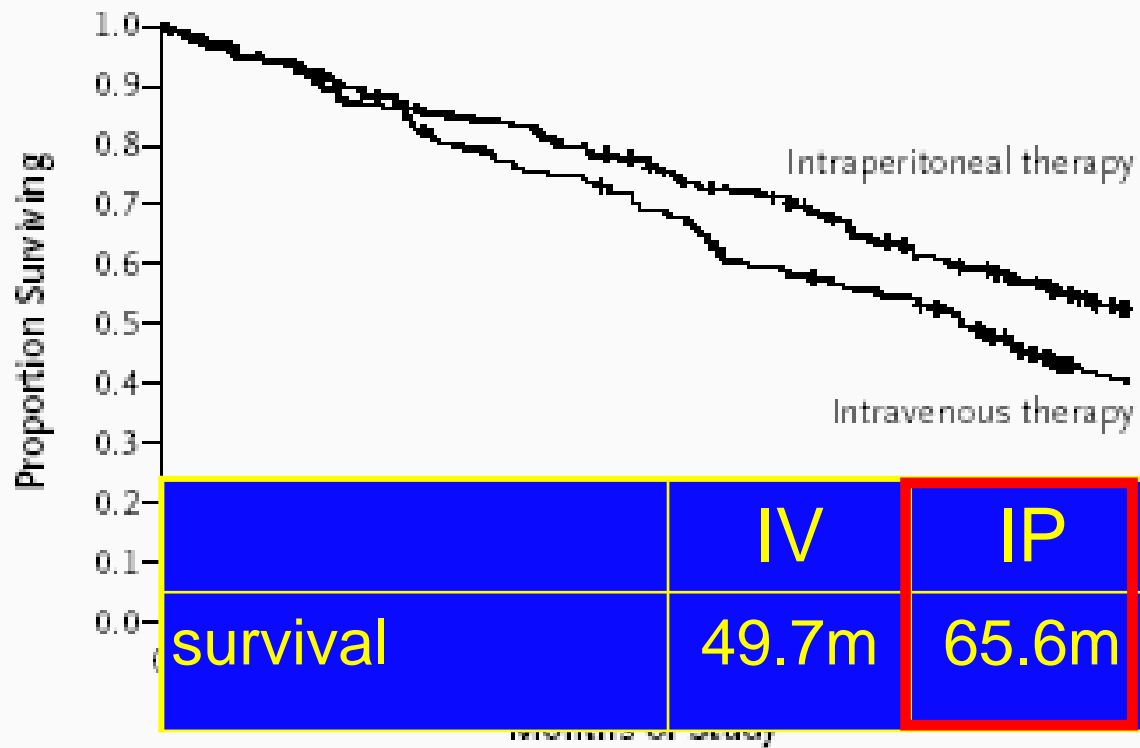


GOG protocol 172



Armstrong et al NEJM 354:34-43 2006

Overall survival by treatment arm GOG 172



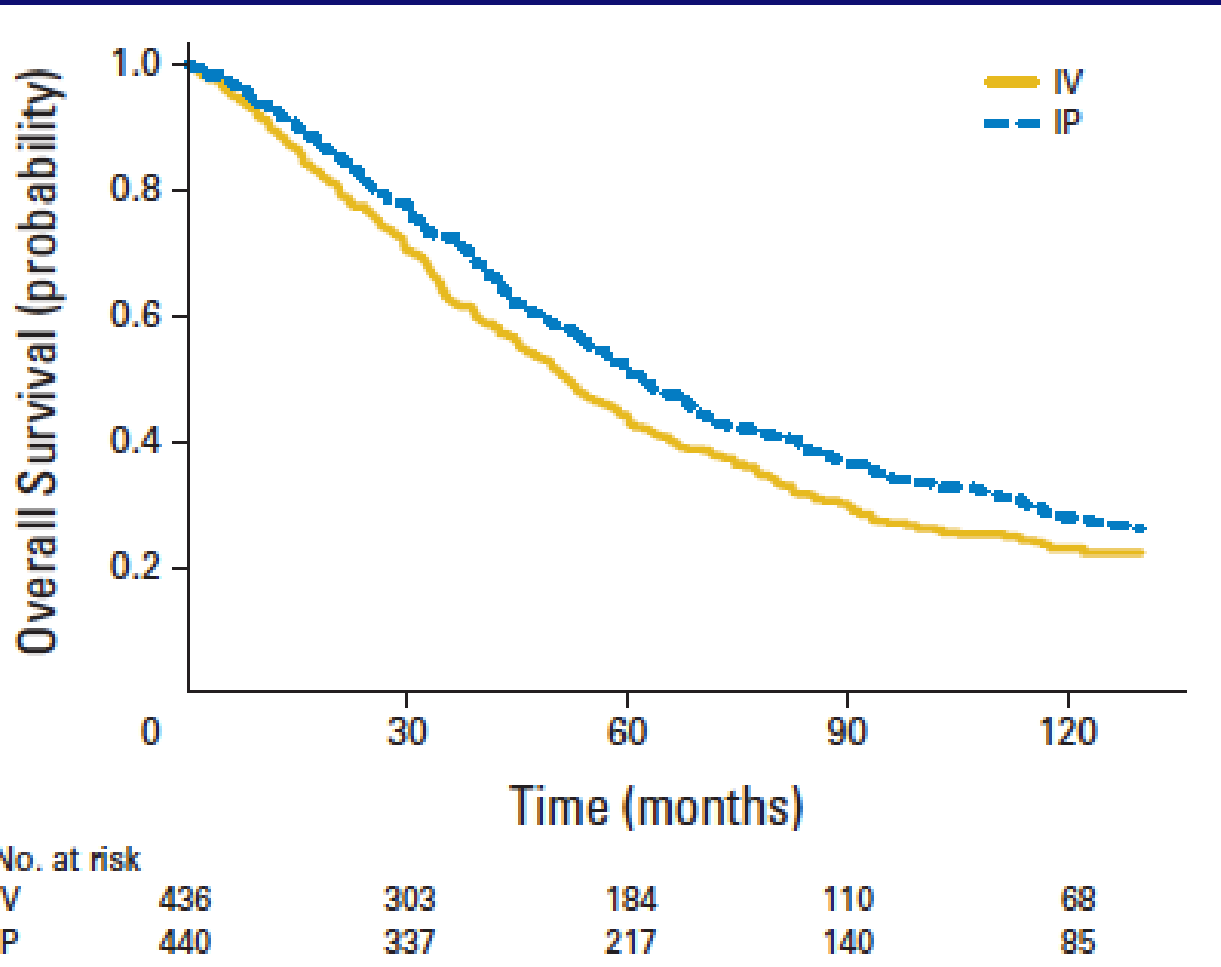
No. at Risk						
Intravenous therapy	210	183	157	123	106	63
Intraperitoneal therapy	205	183	165	142	114	77

Armstrong et al NEJM 2006, 354:34-43

GOG 172: patients with no residual disease at frontline CRS who received IP with IV therapy

	survival (m)
progression-free	60
overall	127

Long-term overall survival of patients treated with IV versus IP chemotherapy



n = 876
median FU 10.7y

median OS

IP 61.8m

IV 51.4m

p=0.04

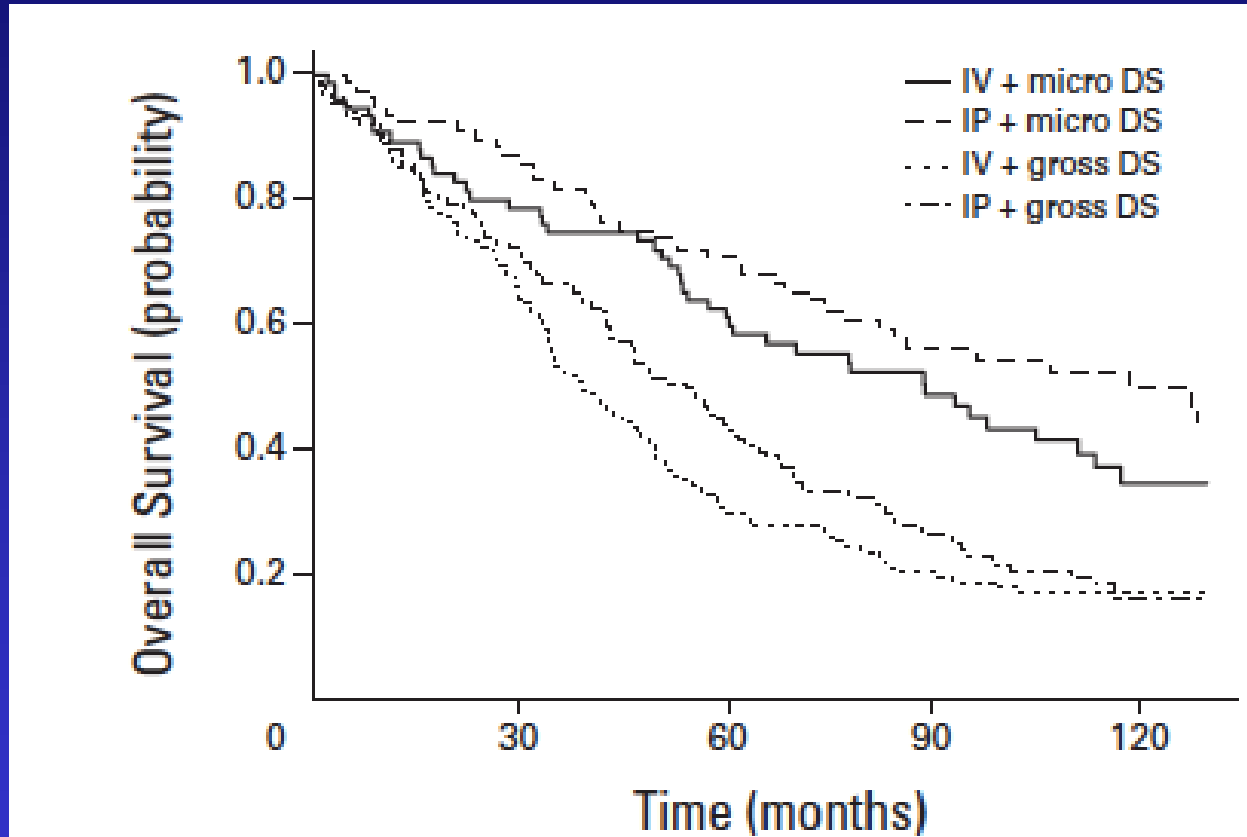
Long-Term Survival Advantage and Prognostic Factors
Associated With Intraperitoneal Chemotherapy Treatment
in Advanced Ovarian Cancer: A Gynecologic Oncology
Group Study

*Devansu Tewari, James J. Java, Ritu Salani, Deborah K. Armstrong, Maurie Markman, Thomas Herzog,
Bradley J. Monk, and John K. Chan*

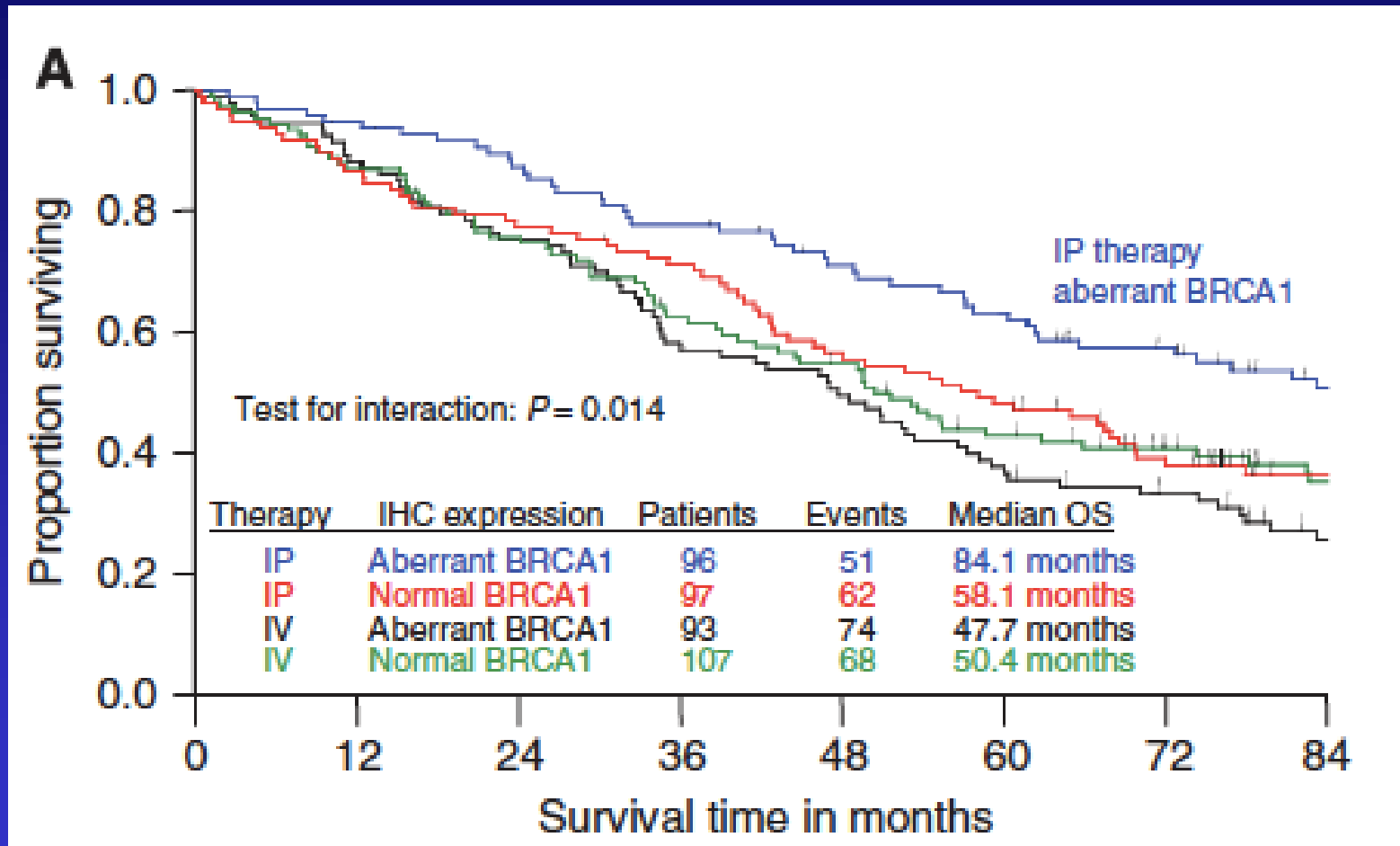
IP chemotherapy associated with

- 23% decreased risk of death
- 12% decreased risk of death per IP cycle

Long-term overall survival of patients treated with IV versus IP chemotherapy



GOG 172: Survival by BRCA status



Future of Ultra Radical Surgery in UK

Annual Report of the
Chief Medical Officer, 2014

Prof Dame Sally Davies

Women's Health

- Radical surgery for women with ovarian
- Obesity

Gynaecologic Oncology Practice UK

Caseload (number per year)

Average	46.5
Median	45
Min	6
Max	100

Patients receiving NAC (%)

Average	37.4
Median	30
Min	0
Max	95

need 100 surgeons doing 60 cases per year

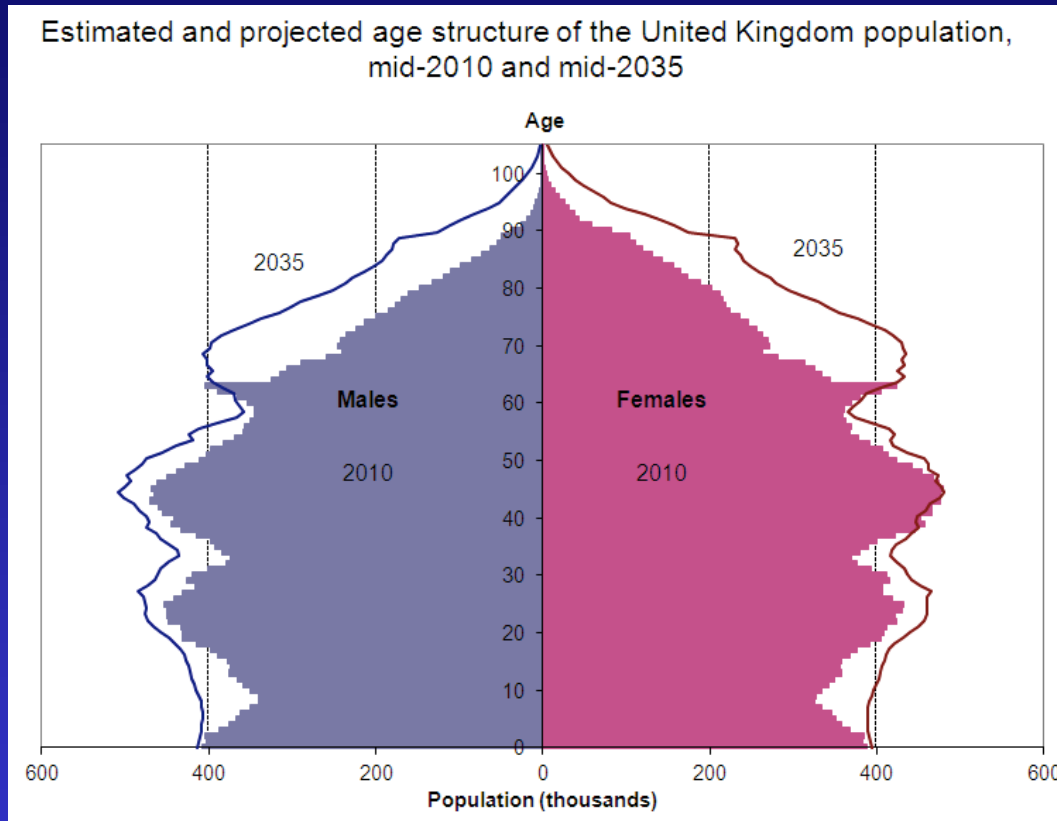
factors involved in poor outcomes

- extent of surgery
- delay in referral
- delay in diagnosis
- waiting time for surgery
- time to chemotherapy
- no regional chemotherapy

The Future

- Catching up
- Swimming against the tide of
 - Increasing population
 - Aging population
 - Lifestyle factors
 - Funding
 - Politics

Age structure of UK population 2010 and 2035



1974 to 2014

>65y ↑ 47%

>75y ↑ 89%

Future of Ovarian Cancer Treatment in UK

How to get there?

Education

Training

Audit

Research

Regional Centres

Public awareness

Community care

Depoliticisation

Investment

A glowing crystal ball is held by two hands, one on the left and one on the right. The crystal ball is the central focus, emitting a bright, warm light. The hands are positioned as if they are about to touch or are just releasing the ball. The background is dark, making the glowing ball stand out. The text 'Ultra-Radical Surgery in the UK' is overlaid on the crystal ball in a serif font.

Ultra-Radical
Surgery
in the UK