SÉMINAIRE DE CHIRURGIE GYNÉCOLOGIQUE

niveau 2

Oncologie mammaire et pelvienne

DAKAR - du 6 au 10 JUIN 2011

Faculté de Médecine de Pharmacie et d'Odontologie
Université Cheikh Anta Diop
Hôpital de Pikine

Cancer de l'Ovaire

Pr Frédéric Goffin, MD, PhD.

Hôpital de la Citadelle
Département of Gynecologie & Obstetrique
Université of Liège

MINISTERE DE LA SANTE
ET DE LA PREVENTION

Epithelial Ovarian Cancer
Plan

- Dr R Perrin
  - *Epidémiologie*
  - *Histoire naturelle*
- Dr F Goffin
  - *Diagnostic*
  - *Traitement*

Ovarian Cancer
Surgical goals

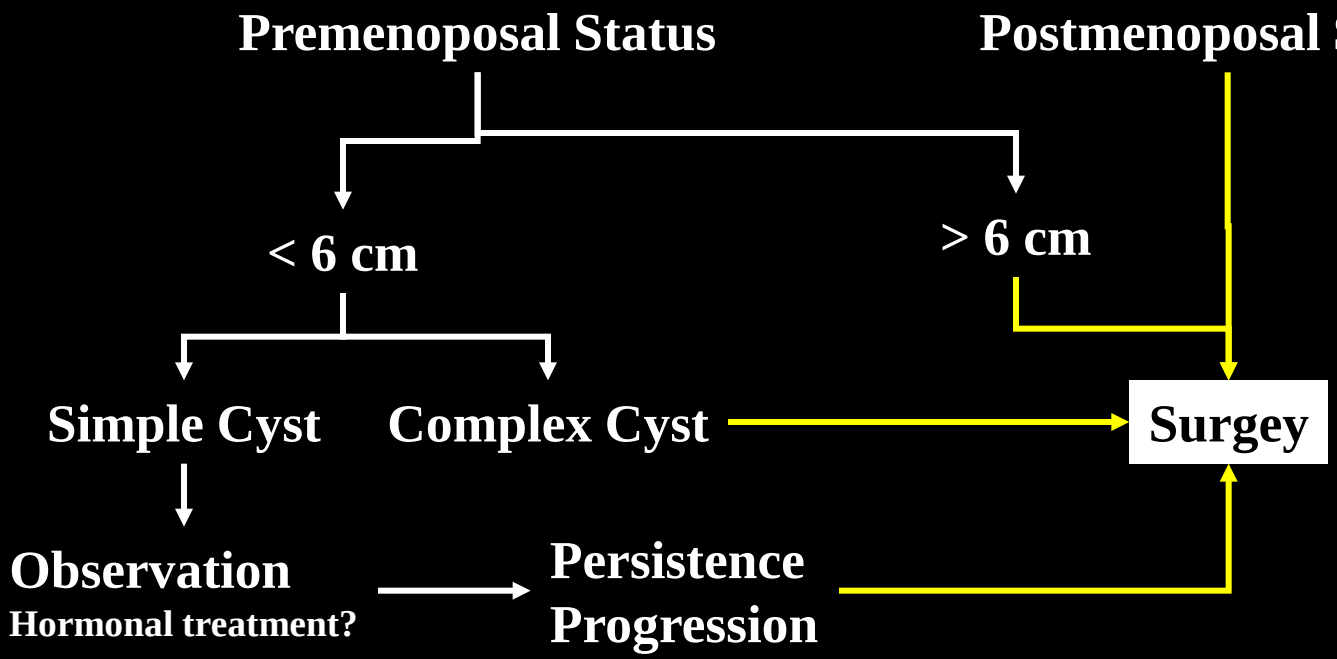
1. Diagnostic
2. Staging for apparent early stages
3. Cytoreduction for advanced stages
4. Palliative

Ovarian Cancer Diagnostic

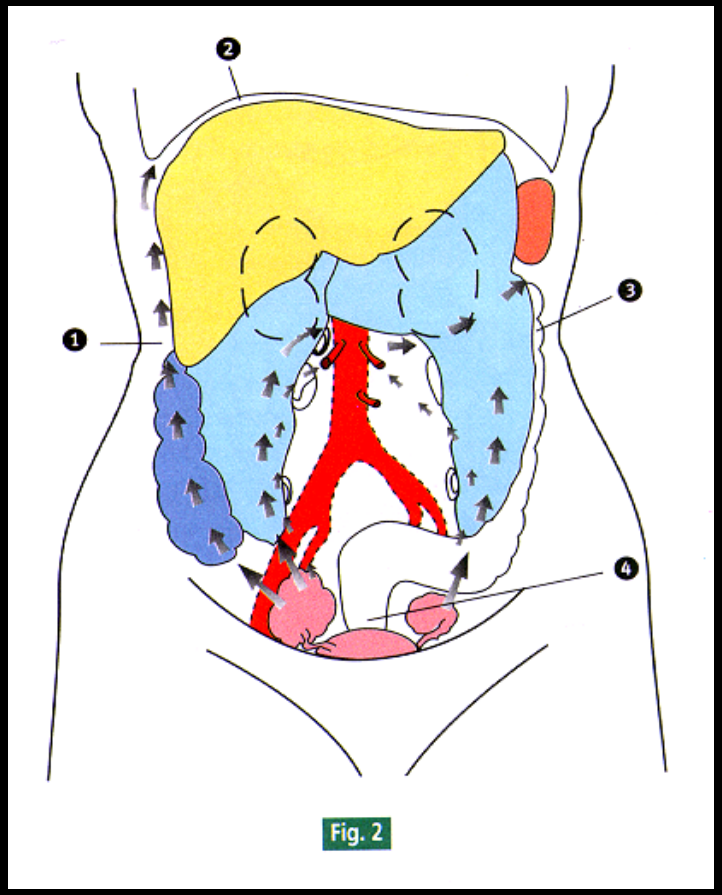
Diagnostic of ovarian ccarcinoma = management of complex pelvic mass

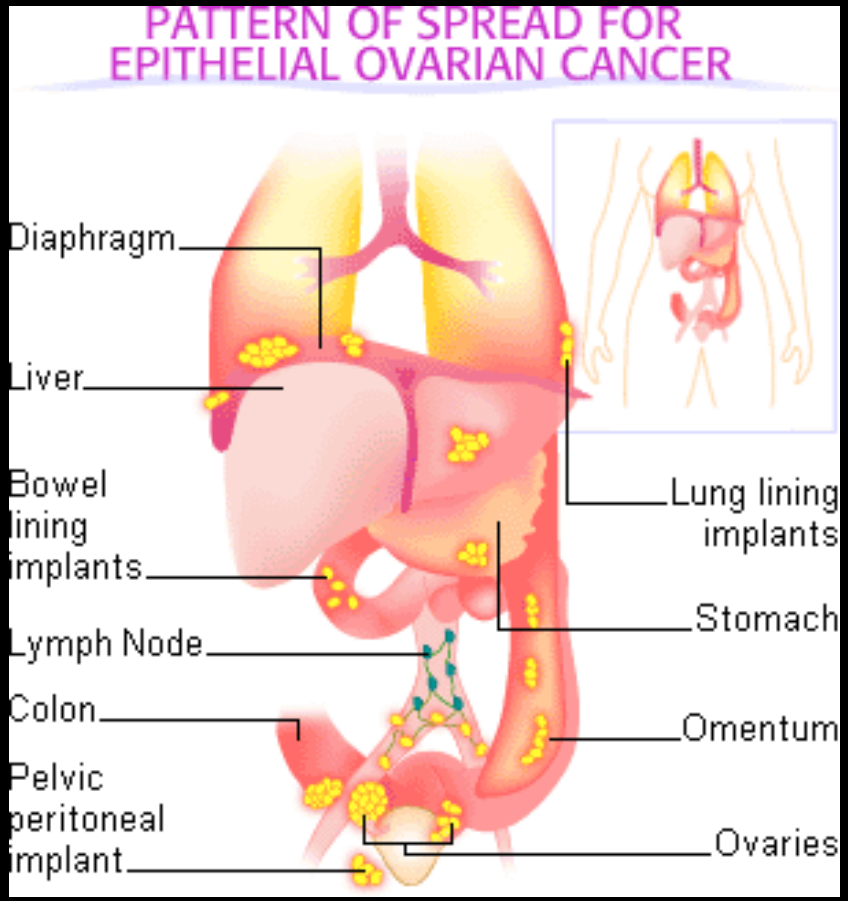
Complex Pelvic Mass

Exclude non ovarian mass (peri sigmoid abces, pelvic kidney)



Ovarian Cancer
Staging based on pattern of spread





http://www.cancerfacts.com

FIGO Staging for Ovarian Cancer 1998 - 2008

- Ovarian epithelial malignancies are staged according to the FIGO system (1988-2008 staging system),
- The FIGO staging is based on findings at surgical exploration,
- A preoperative evaluation should exclude the presence of extraperitoneal mets,
- The 2008 FIGO staging remains unchanged.

Early Epithelial Ovarian Cancer

EORTC & GOG Guidelines

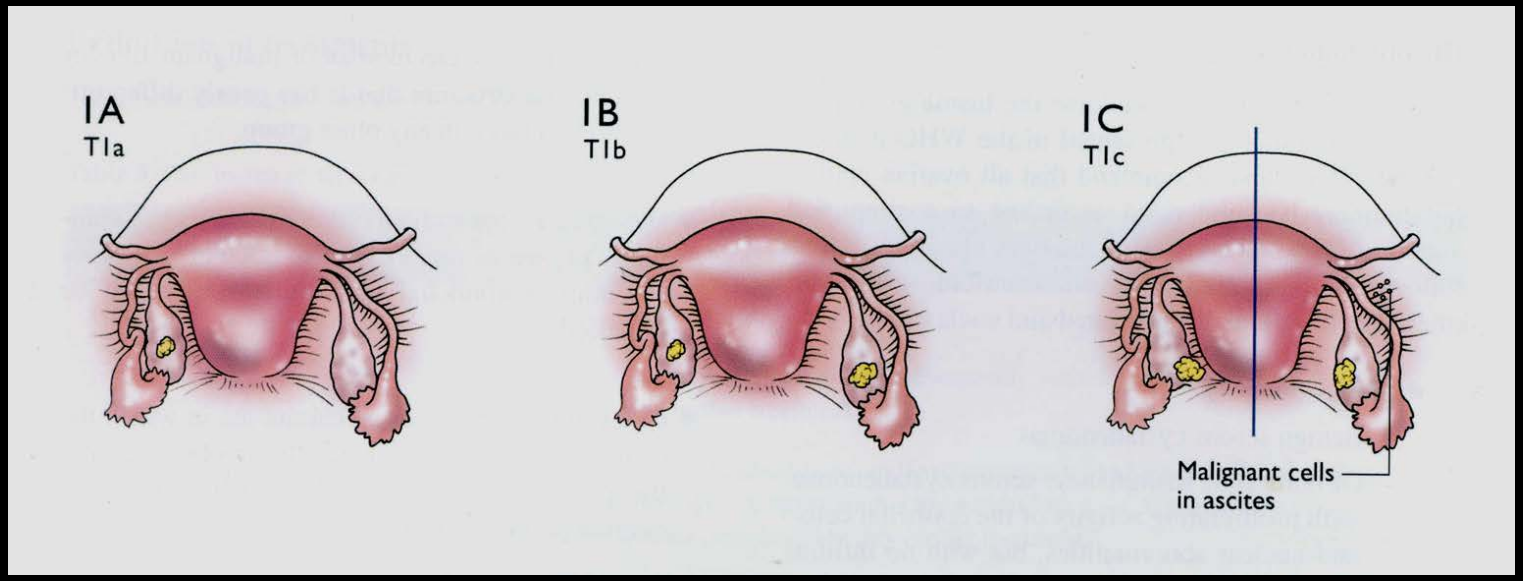
for staging high risk early ovarian carcinoma following HAT+BSO

- Washings & Infracolic omentectomy & Bx of all suspect lesions
- Pelvic & ParaAortic lymph node lymphadenectomy
- Blind Biopsies of the right hemidiaphragm,
- Right and left paracolic gutter,
- Pelvic side walls,
- Ovarian fossa,
- Bladder peritoneum, AND
- Pouch of Douglas

FIGO Staging for Ovarian Cancer 1998 - 2008

Stage I **Growth limited to ovaries**

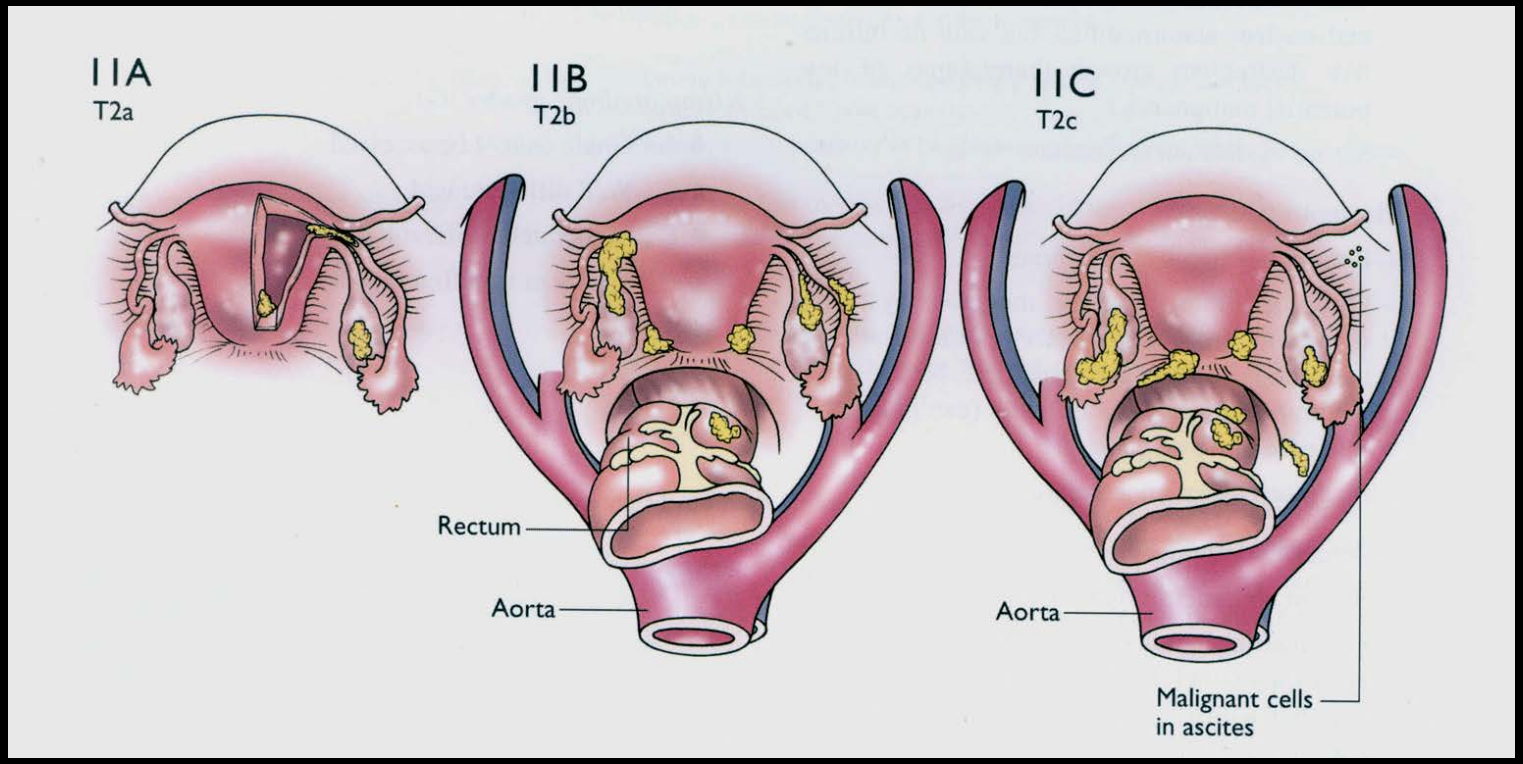
IA	Limited to one ovary; No ascites, No tumor on external surfaces, Capsule intact
IB	Limited to both ovaries; No ascites, No tumor on external surfaces, Capsule intact
IC	with tumor on surface, or capsule ruptured or malignant ascites present



FIGO Staging for Ovarian Cancer 1998 - 2008

Stage II **One or both ovaries with extension to pelvic structures**

IIA	Extension and/or metastases to uterus and/or tubes
IIB	Extension to other pelvic structures
IIC	with tumor on surface; or capsule ruptured; or malignant ascites present

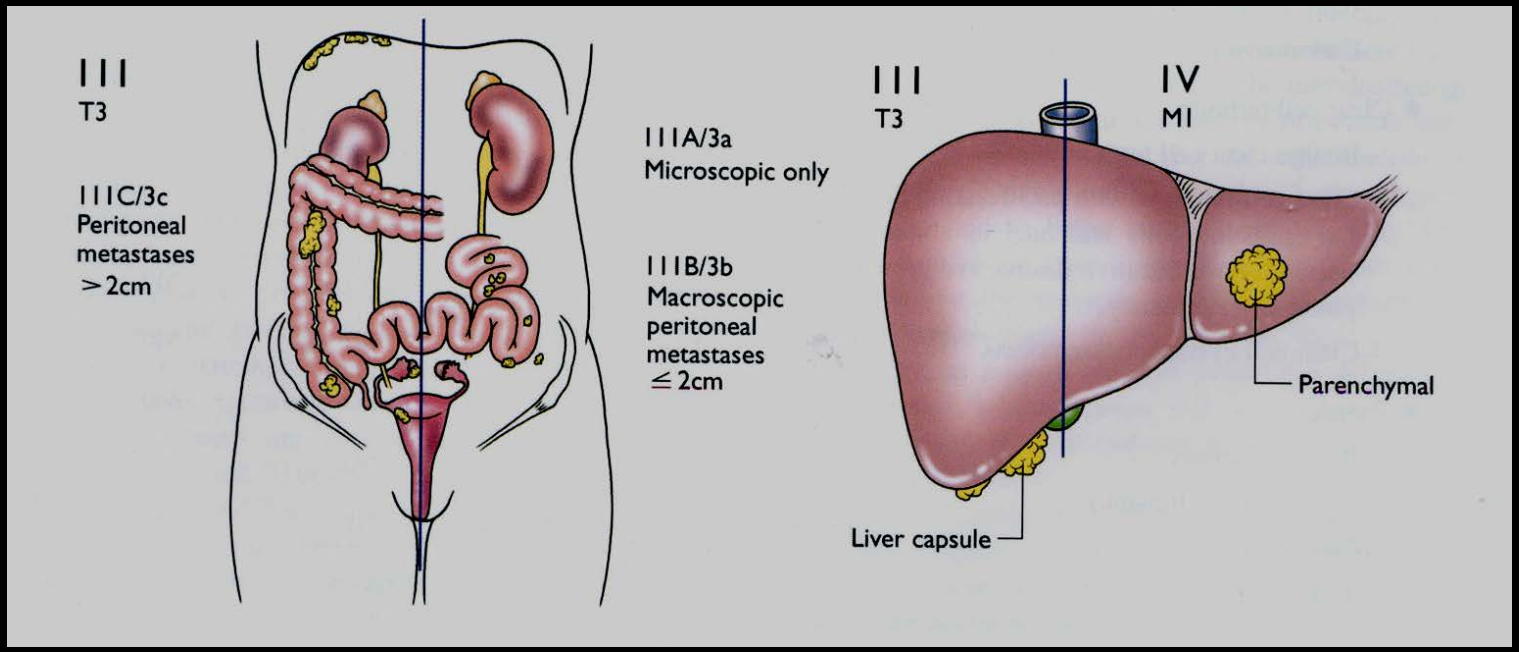


FIGO Staging for Ovarian Cancer 1998 - 2008

Stage III — **Implants outside the pelvis and/or positive nodes**

- IIIA — Tumor macroscopically confined to the pelvis with microscopic disease in the abdomen
- IIIB — Tumor macroscopically involving the abdomen but no single nodule measuring greater than 2 cm ; Nodes are negative
- IIIC — Abdominal implants greater than 2 cm or retroperitoneal or inguinal node involvement

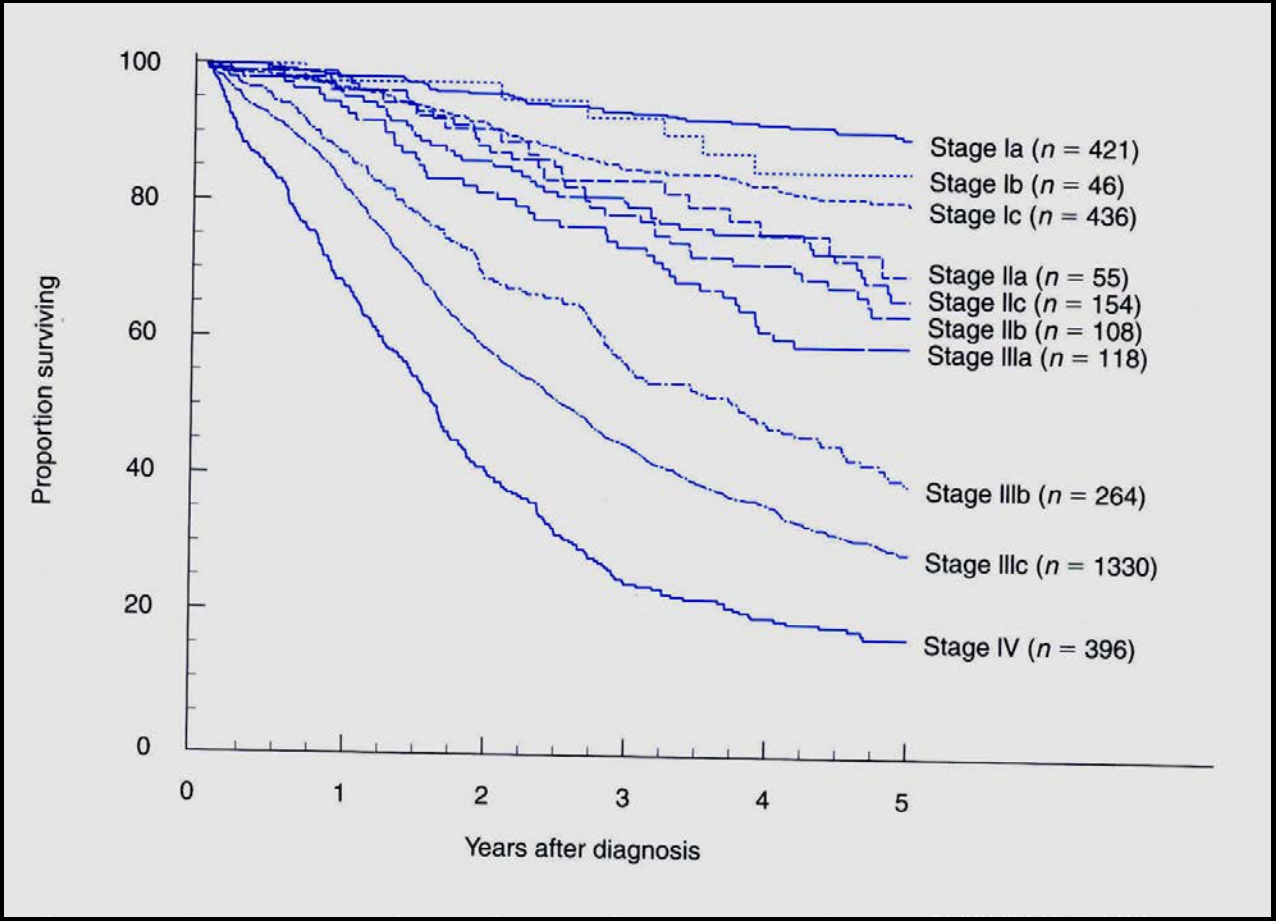
Stage IV — **Extra-abdominal disease or parenchymal liver disease**



Ovarian Cancer
Why surgical staging is important?

- **Surgical staging**
  - is the key to an accurate prognosis,
  - allow to determine proper adjuvant therapy (avoid undertreatment and overtreatment),
  - improve survival ,
  - clinical trial

Ovarian Cancer
Overall Survival

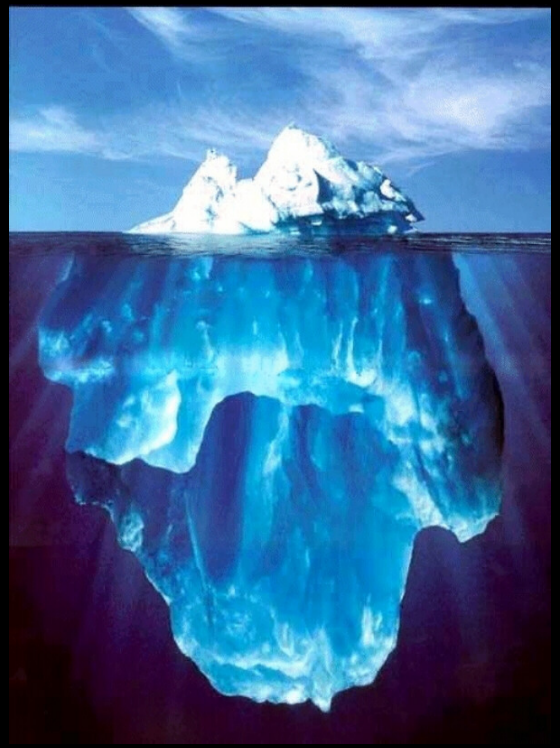


Ovarian Cancer
Surgical staging: adequate adjuvant therapy

After initial staging procedure	Recommendation
Stage IA, grade 1 or 2	Observation
Stage IB, grade 1 or 2	Observation
Stage IA or IB, grade 3, Stage IC, Stage II	Paclitaxel + carboplatin x 3
Stage III or IV	Paclitaxel + carboplatin x 6

Early Epithelial Ovarian Cancer

Presumed early ovarian cancer

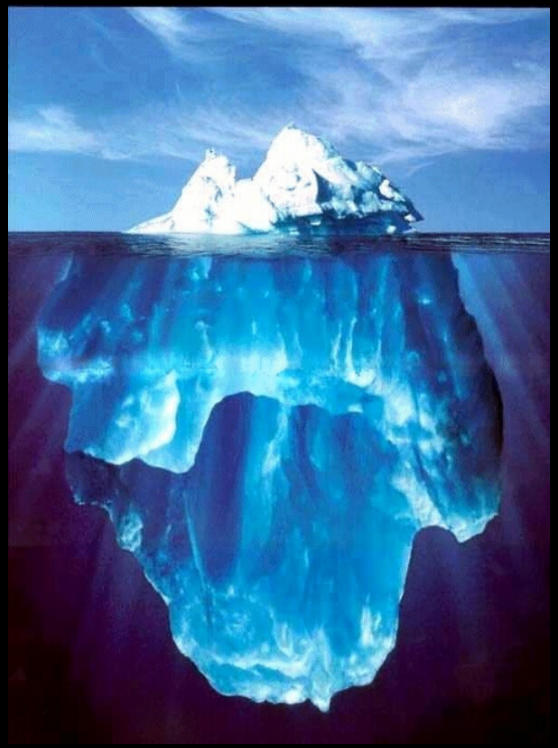


Early Epithelial Ovarian Cancer

Presumed early ovarian cancer : Upstaging

- 30% incidence of occult metastases in Presumed early ovarian cancer

Positive cytology	20 %
Omentum	10 %
Diaphragm	15 %
Peritoneal biopsies	13 %
Para-aortic LN	15 %
Pelvic LN	8 %



JB Trimbos, Int J Gyn Cancer 2000

Results of re-staging laparotomies : apparent early stage ovarian cancer

Authors (year)	No.	FIGO stage (initial)	% upstaged
Bagley 1973	5	I-II	60%
Young 1983	100	IA-IIB	31%
Helewa 1986	25	I	20-25%
Buchsbaum 1989	140	I-II	22,4%
Archer 1991	24	I-II	20,8%
Soper 1992	30	I-II	30%
Stier 1998	45	IA-IIB	16%
Leblanc 2000	28	I	21%

JAMA®

Staging laparotomy in early ovarian cancer

R. C. Young, D. G. Decker, J. T. Wharton, M. S. Piver, W. F. Sindelar, B. K. Edwards and J. P. Smith

Systematic restaging was performed prospectively in 100 patients referred to the Ovarian Cancer Study Group institutions with a diagnosis of "early" (stage Ia-IIb) ovarian cancer. -
- Before referral, only 25% of patients had an ***initial surgical incision*** that was adequate to allow complete examination of the pelvis and abdominal cavity.
-In patients referred to member institutions, 31 (31%) of 100 were found to have a ***more advanced stage*** and 23 (77%) of 31 of these actually had stage III disease.
- Sixty-one percent of the patients had their advanced stage detected by procedures other than a second laparotomy-nine (29%) of 31 by peritoneoscopy, six (19%) of 31 by peritoneal washings, and six (19%) of 31 by lymphangiography.
- Sites of unsuspected disease are most likely to be pelvic peritoneum, ascites fluid, other pelvic tissue, para-aortic nodes, and the diaphragms.
- Based on these data, we conclude that the initial staging approaches traditionally used in clinical evaluation of patients with early ovarian cancer are often incomplete and inadequate.

Young et al. JAMA 1983;250:3072-6.

30% Upstaging

=

Occult cancer metastases

Why do ovarian cancer patient does not receive surgical staging?

- Diagnosis of ovarian cancer is not anticipated
- Surgeons are inadequately trained to performed extensive staging and fear of surgical complication
- Results do not change management (i.e. wheter to recommend adjuvant therapy) but only prognosis

What to do with incomplete staging?

- “wait and see policy” and “treat-on-relapse” ?
- Restaging procedure ?
- Receive chemotherapy for the possibility of an occult advanced disease ?

Early Epithelial Ovarian Cancer

- After a comprehensive staging, only a minority of women will have local disease (FIGO Stage 1) (<20%),
- The primary treatment for stage 1 EOC is surgical,
  - total hysterectomy, bilateral SO & comprehensive staging,
  - In certain circumstances, a unilateral oophorectomy may be permitted
- Early stage EOC subdivided into low & high-risk disase,

Early Epithelial Ovarian Cancer

Early stage EOC subdivide into low & high-risk disase

Prognostic variables in early stage EOC	
Low Risk	High Risk
Low Grade	High Grade
Non Clear Cell histo type	Clear Cell histo type
Intact capsule	Tumor growth through capsule
No surface excrescences	surface excrescences
No ascitis	ascitis
Negative peritoneal cytology	Malignant cell in fluid
Unruptured or intraop rupture	Preop rupture
No dense adhesion	Dense adherence
Diploid tumor	Aneuploid tumor

Early Epithelial Ovarian Cancer:
Fertility Preservation ?

- If thorough staging,
- No evidence of spread beyond the ovary,
- the uterus and contralateral ovary can be retained
- FIGO stage 1A, 1B, grade 1 (2)
- Women with G 3 or higher stage : significant recurrence rates

Early Epithelial Ovarian Cancer :

Adjuvant chemotherapy

Low Risk (Stage IA/IB, G1-2)
GOG study : Melphalan vs observation 5-y OS : 94 vs 96% NO further adjuvant treatment
High Risk (Stage IA/IB, G1-2)
G3 Positive cytology Additional therapy is indicated
TWO LARGE RANDOMIZED Phase III Trials ICON 1, ACTION 1

Early Epithelial Ovarian Cancer :
Adjuvant chemotherapy

International Collaborative Ovarian Neoplasm Trial 1 and Adjuvant ChemoTherapy In Ovarian Neoplasm Trial: Two Parallel Randomized Phase III Trials of Adjuvant Chemotherapy in Patients With Early-Stage Ovarian Carcinoma

International Collaborative Ovarian Neoplasm 1 (ICON1) and European Organisation for Research and Treatment of Cancer Collaborators–Adjuvant ChemoTherapy In Ovarian Neoplasm (EORTC–ACTION)[1]

ICON1- ACTION-Rimbos-JNCI 2003

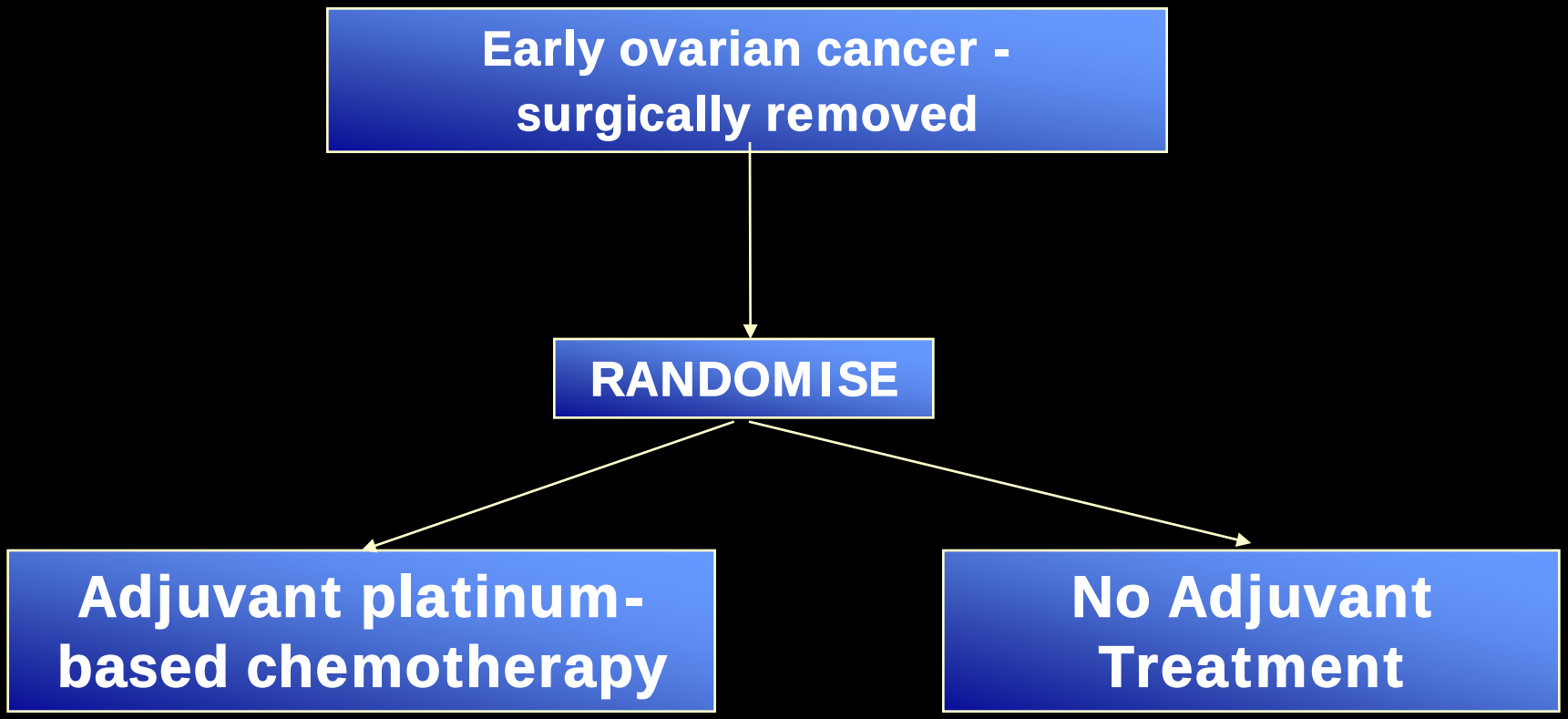
Early Epithelial Ovarian Cancer :
Adjuvant chemotherapy

Two Parallel Randomised Trials of Adjuvant Chemotherapy in Patients with Early Stage Epithelial Ovarian Cancer planned to be analysed together

ICON1 (International Collaborative Ovarian Neoplasm studies)
ACTION (EORTC: Adjuvant Clinical Trial In Ovarian Neoplasm)
JNCI 2003, 95:105-112, 113-125

Early Epithelial Ovarian Cancer :

Adjuvant chemotherapy



ICON1- ACTION-Rimbos-JNCI 2003

Early Epithelial Ovarian Cancer :
Adjuvant chemotherapy

Principal Differences in Eligibility Criteria

- **ICON1:**

  any patients in which the clinician was uncertain whether patient should receive chemotherapy

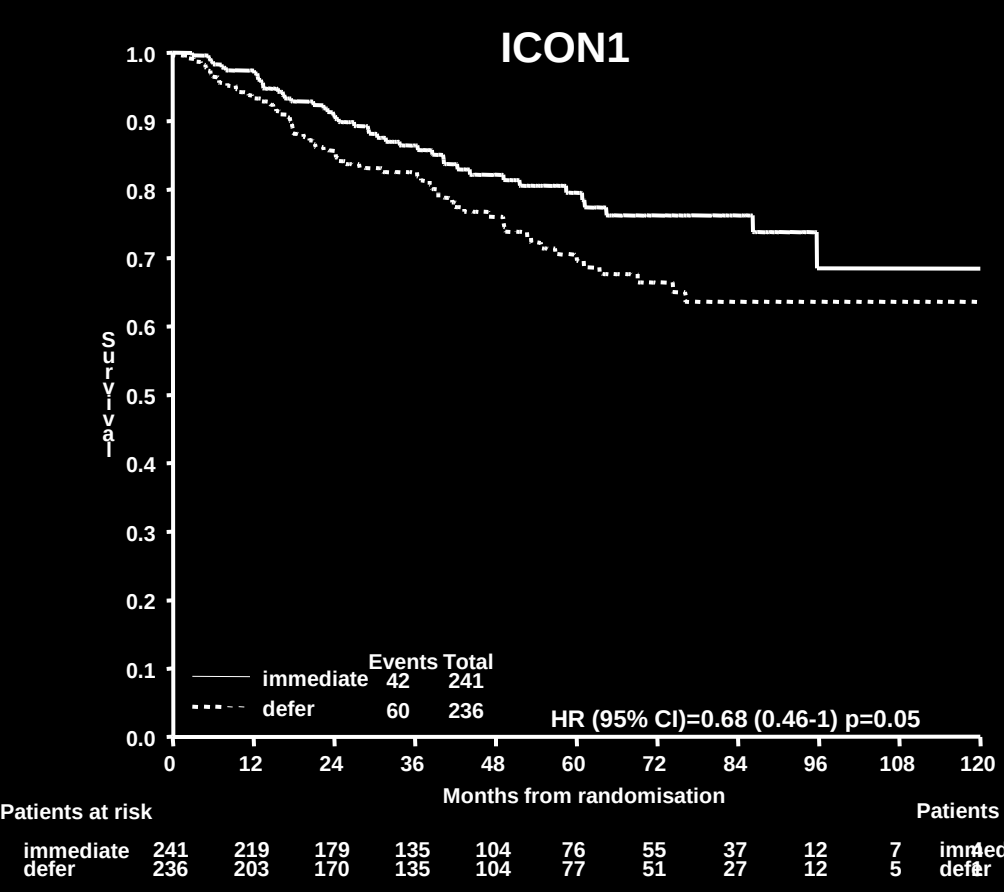
- **EORTC (ACTION):**

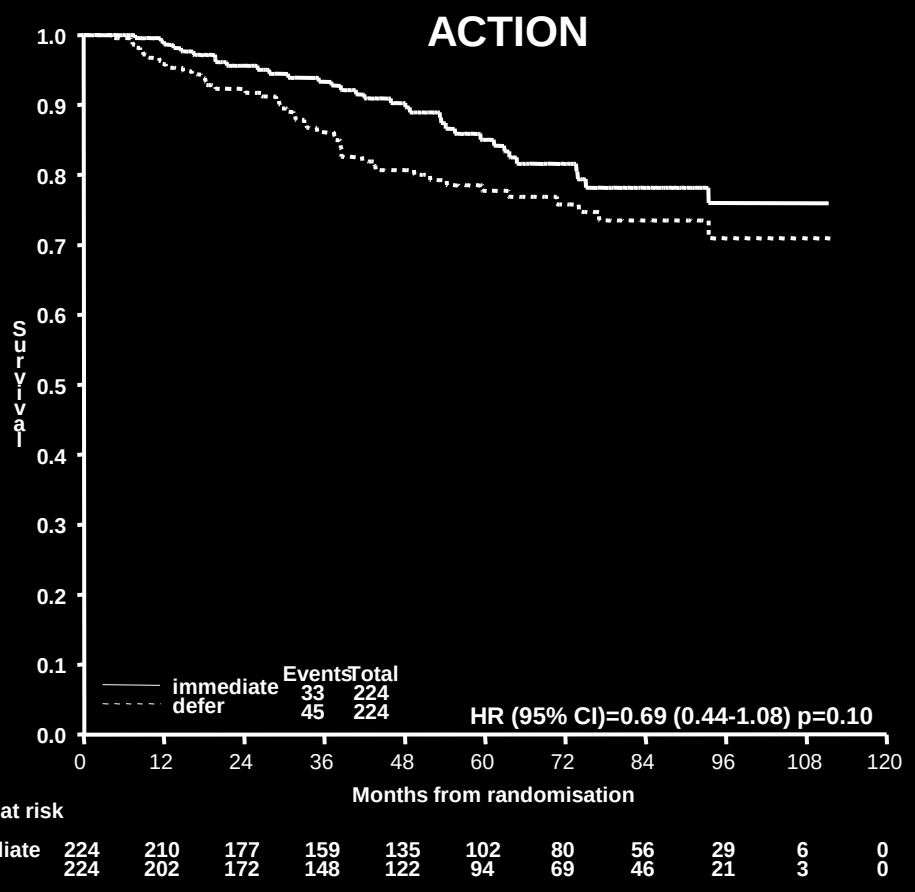
  Stages Ia, Ib Grades 2-3

  Stages Ic, IIa all grades

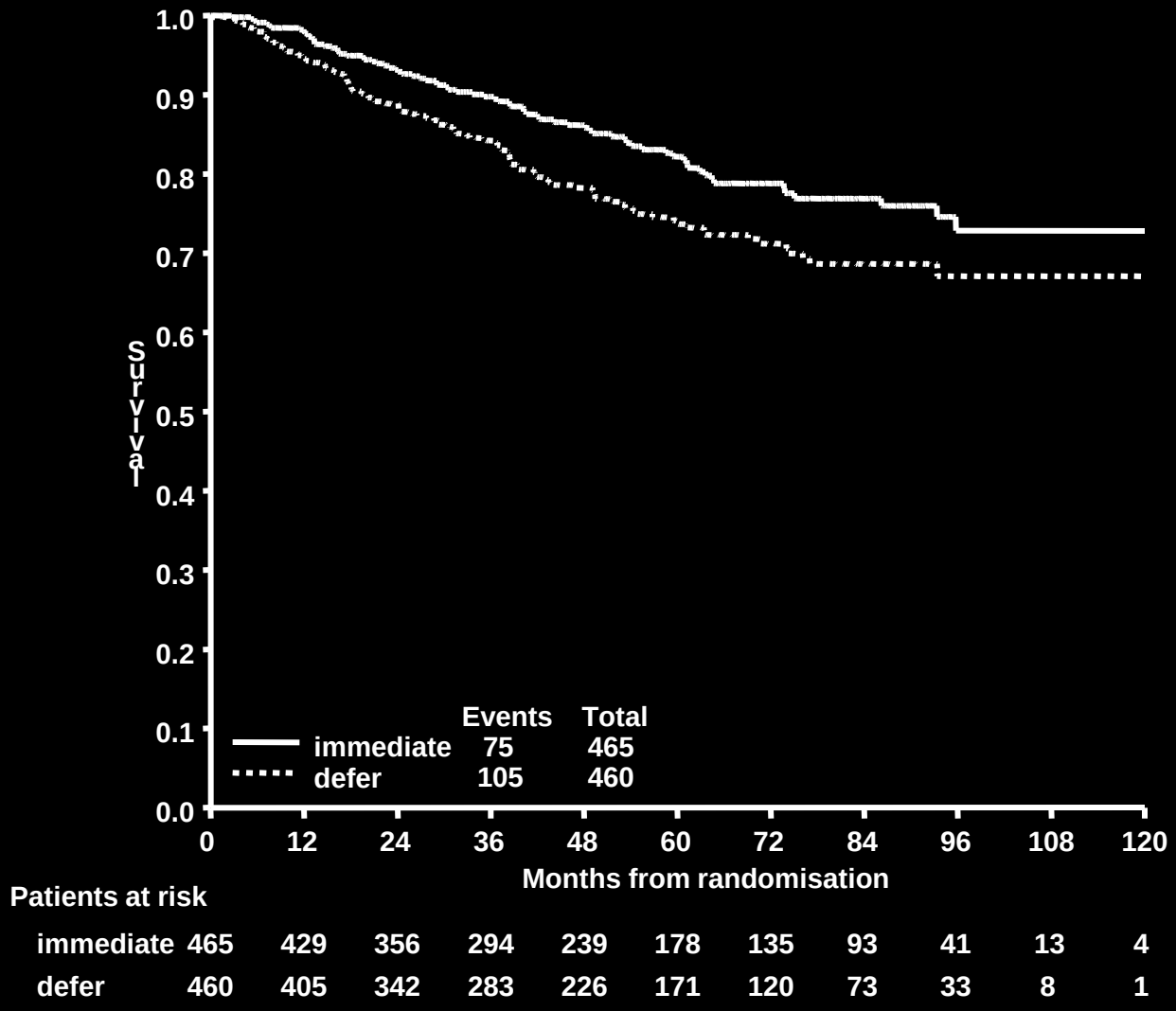
ICON1- ACTION-Rimbos-JNCI 2003

Overall Survival





Overall Survival
ICON and EORTC combined

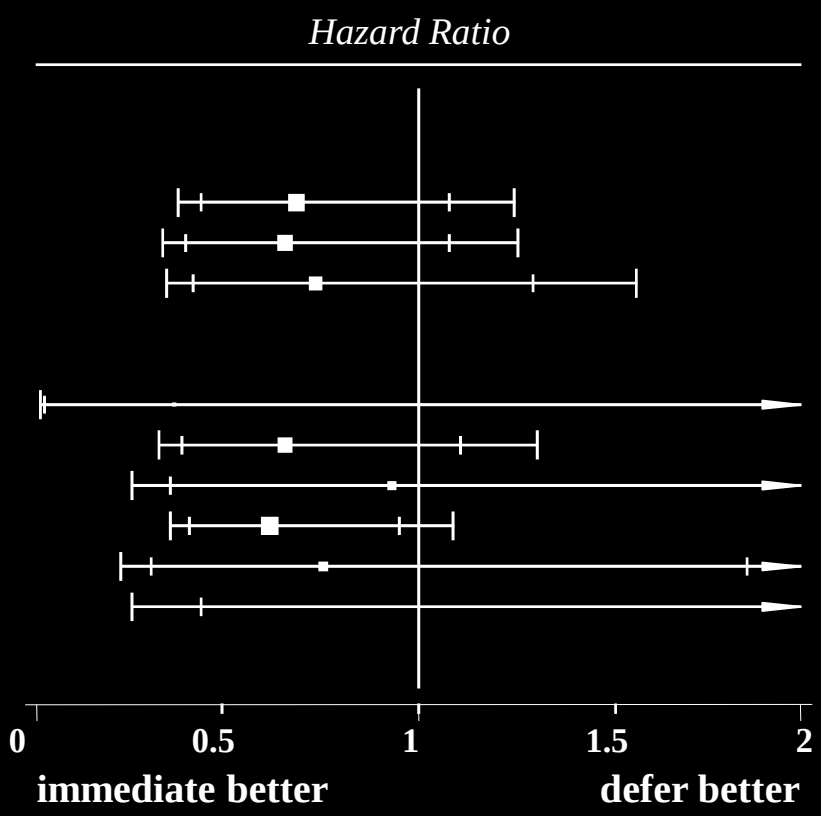


HR = 0.68, p=0.01
95%CI (0.51, 0.92)

Absolute difference at 5-year = 7%
(75%→82%)
95%CI (2%, 11%)

Survival by Age and stage

	(no. events/no. entered) immediate	defer	O-E	Variance
age				
<55	30/233	42/233	-6.92	17.93
55-65	22/126	39/147	-6.52	15.14
>65	23/105	24/80	-3.61	11.38
stage				
I	1/9	1/4	-0.42	0.41
Ia	22/168	33/172	-5.88	13.71
Ib	8/46	8/43	-0.31	3.97
Ic	32/208	49/204	-9.84	20.15
II	8/30	11/29	-1.34	4.60
III	3/3	3/6	1.13	1.23

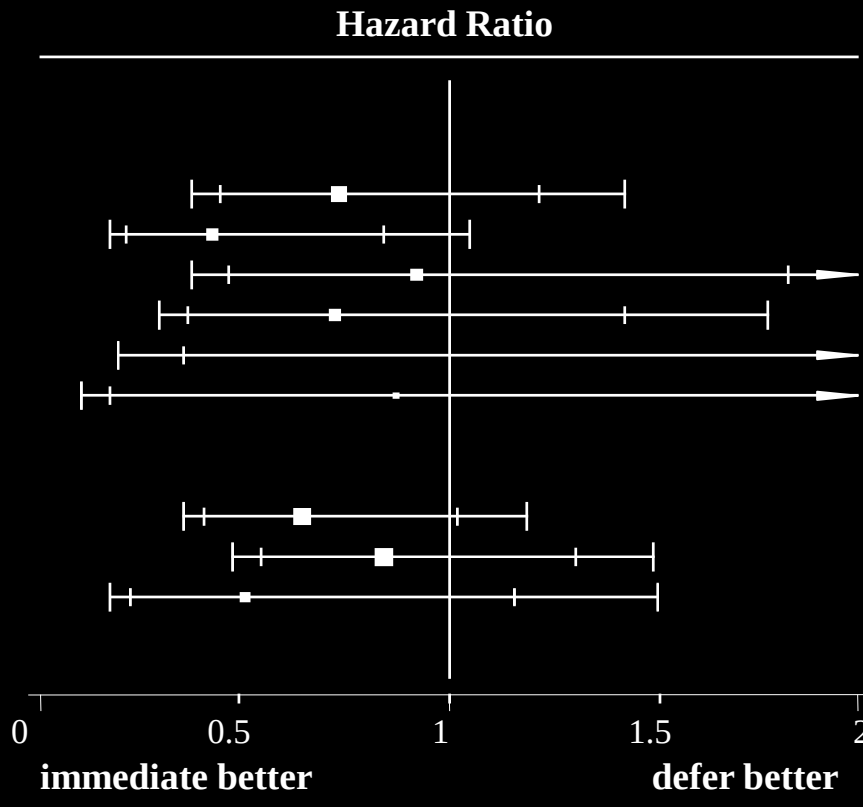


Age Trend $\chi^2_{(1)} = 0.023$, p=0.87

Stage Interaction $\chi^2_{(5)} = 2.919$, p=0.712 Trend $\chi^2_{(1)} = 0.367$, p=0.54

Survival by Histology and Differentiation

	(no. events/no. entered) immediate	defer	O-E	Variance
histology				
serous	27/161	32/139	-4.58	14.62
mucinous	10/90	22/90	-6.86	7.91
endometrioid	13/94	20/129	-0.71	7.99
clear cell	16/68	17/62	-2.67	8.02
undifferentiated	3/8	2/7	0.91	1.04
other	3/23	3/19	-0.20	1.46
differentiation				
poor	29/139	42/141	-7.81	17.59
intermediate	37/210	42/203	-3.40	19.72
well	7/97	15/100	-3.80	5.49



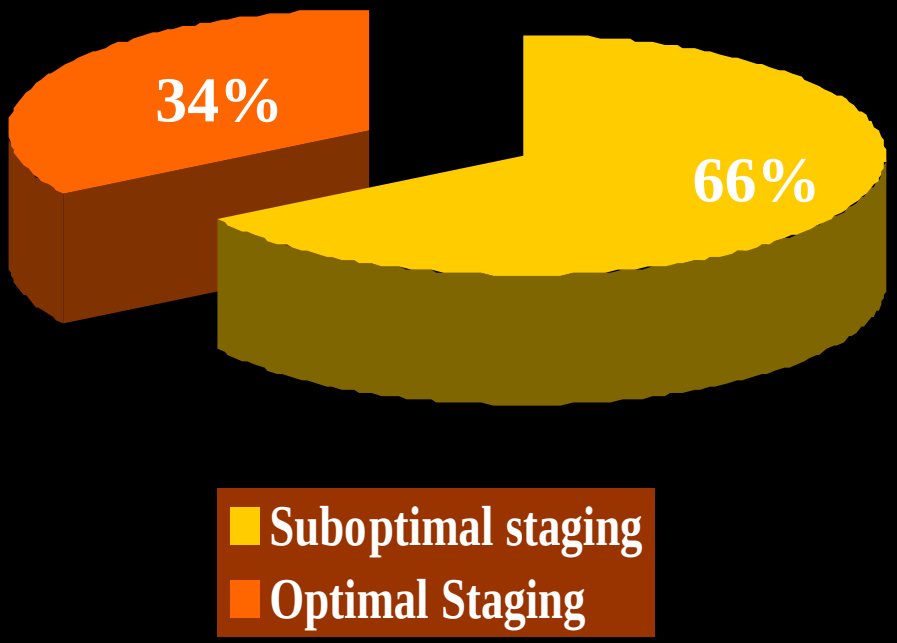
Histology Interaction $\chi^2_{(5)}$ =4.309, p=0.506

Differentiation Trend $\chi^2_{(1)}$ =0.003, p=0.956

Early Epithelial Ovarian Cancer :

Adjuvant chemotherapy

ACTION & ICON 1 : Staging Performance



ICON1- ACTION-Rimbos-JNCI 2003

Early Epithelial Ovarian Cancer :

Adjuvant chemotherapy

ICON 1 Trial	ACTION Trial
N= 477	N= 440
Stage I & IIA	Stage I1 & IIA, G2-3
Comprehensive staging NOT required	Surgical staging required Only 30 % was optimally staged...
Adjuvant Chemo :	Adjuvant Chemo :
5Y OS :	In the observation arm :
73 % (Chemo arm) vs 62 % (Obser arm)	Surgical staging : better survival
	In Chemo arm :
	- chemo : better survival
	... If optimally staged : no benefit of adj chemo...

EORTC Staging categories following HT+BSO* (1)

1. Optimal

- HT+BSO *(Ia: USO allowed) + Infracolic omentectomy + washings + biopsies of all suspect lesions , AND

- Pelvic and PAO lymph node sampling or lymphadenectomy, AND

- Blind biopsies of the right hemidiaphragm, right and left paracolic gutter, pelvic side walls, ovarian fossa, bladder peritoneum, AND cul-de-sac.

EORTC Staging categories following HT+BSO* (2)

- **2. Modified**

  - Everything between Optimal and Minimal.

- **3. Minimal**

  - HT + BSO *(Ia: USO allowed) + Peritoneal washings + infracolic omentectomy + biopsies of suspect lesion

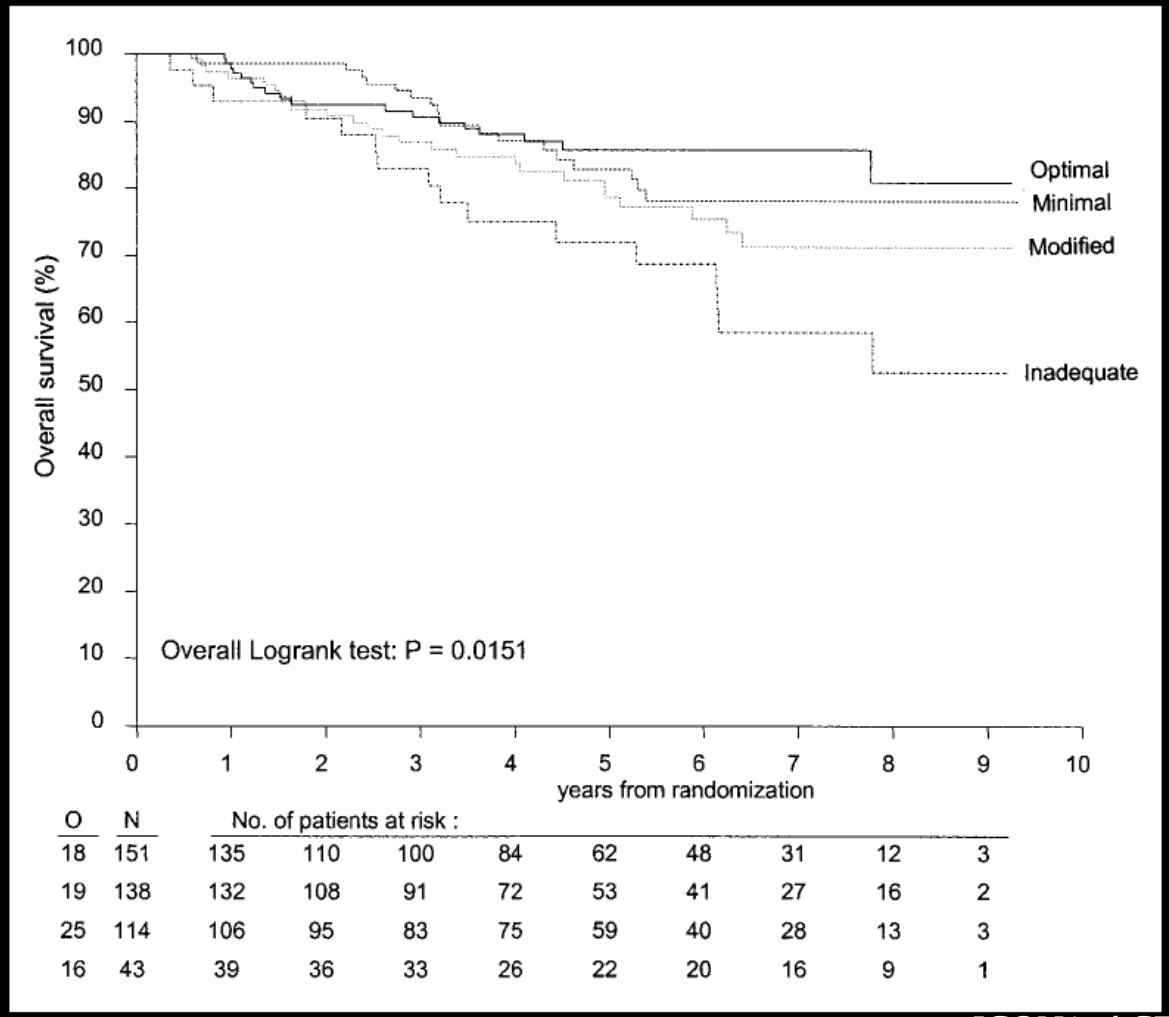
- **4. Inadequate**

  - Careful inspection and palpation of all peritoneal surfaces and retroperitoneal nodes + biopsies of suspect lesions

Early Epithelial Ovarian Cancer :

Adjuvant chemotherapy

EORTC-Action : OS by staging Performance



O	N	No. of patients at risk :								
18	151	135	110	100	84	62	48	31	12	3
19	138	132	108	91	72	53	41	27	16	2
25	114	106	95	83	75	59	40	28	13	3
16	43	39	36	33	26	22	20	16	9	1

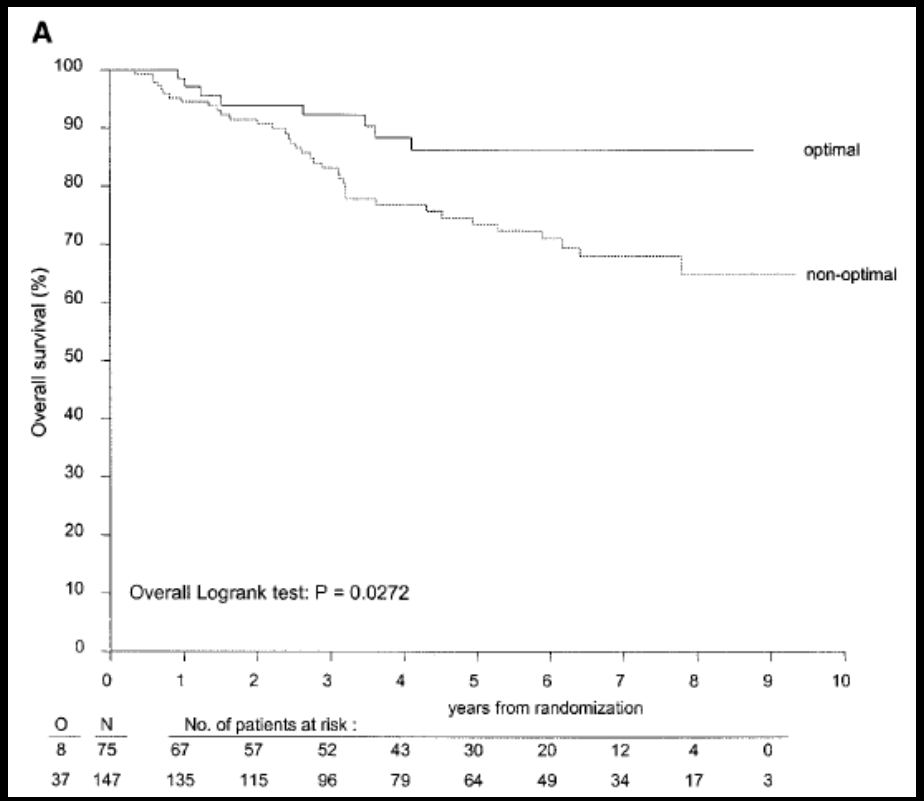
ICON1- ACTION-Rimbos-JNCI 2003

Early Epithelial Ovarian Cancer :

Adjuvant chemotherapy

EORTC-Action : OS by staging Performance

Observation Arm



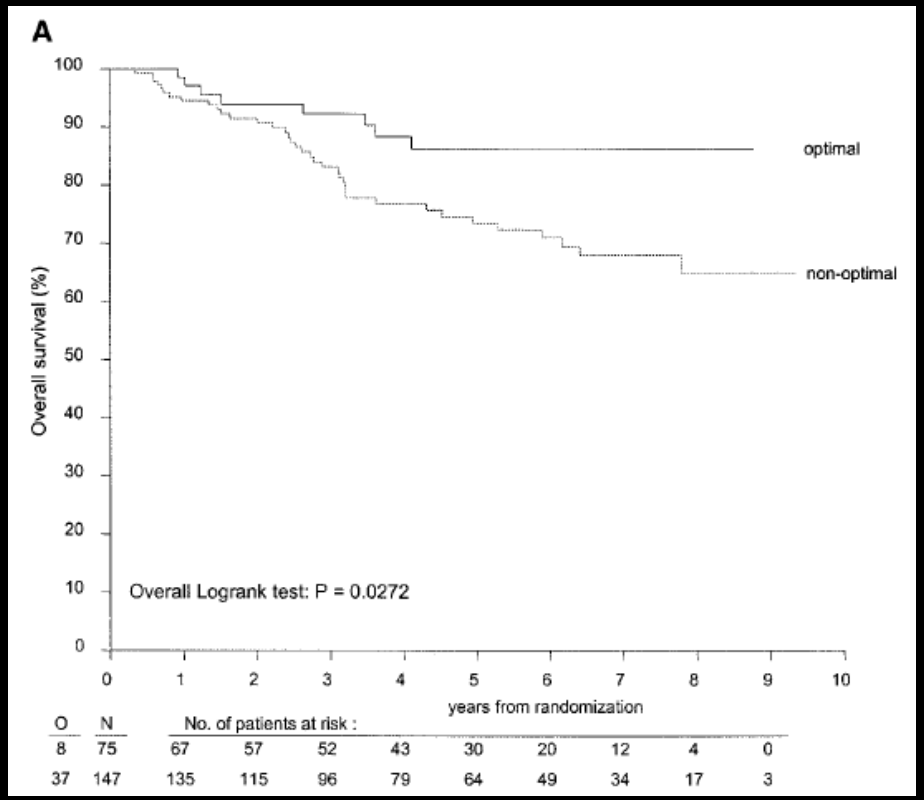
ICON1- ACTION-Rimbos-JNCI 2003

Early Epithelial Ovarian Cancer :

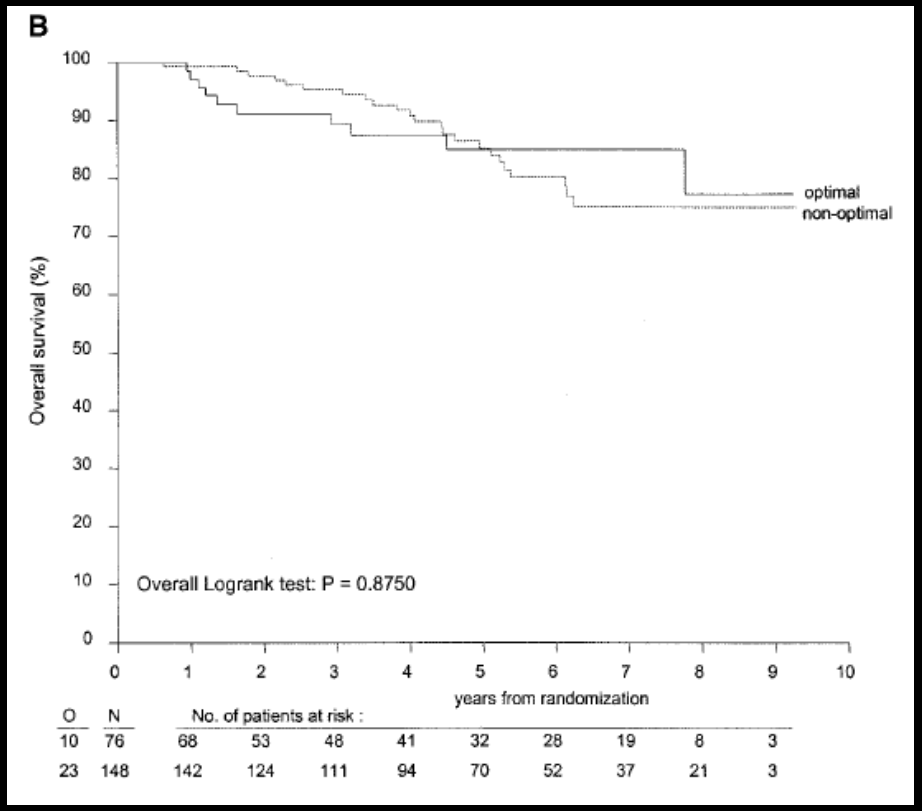
Adjuvant chemotherapy

EORTC-Action : OS by staging Performance

Observation Arm



Chemotherapy Arm



ICON1- ACTION-Rimbos-JNCI 2003

Conclusion

- Adjuvant chemotherapy improves
  - recurrence-free survival by 11% (65% to 76%) at 5 years
  - overall survival by 7% (75% to 82%) at 5 years
- No evidence that the effect of adjuvant chemotherapy is smaller or larger in any of the tested subgroups (age, differentiation, histological type, FIGO substage).
- In the subgroup of optimally staged patients the effect of adjuvant chemotherapy is not observed.

Early Epithelial Ovarian Cancer :
Surgical aspects

- Importance of staging
- Importance of rupture

Early Epithelial Ovarian Cancer :

Surgical aspects

Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma

Ignace Vergote, Jos De Brabanter, Anthony Fyles, Kamma Bertelsen, Nina Einhorn, Paul Sevelda, Martin E Gore, Janne Kærn, Herman Verrelst, Kjerstin Sjövall, Dirk Timmerman, Joos Vandewalle, Marleen Van Gramberen, Claes G Tropé

Invasive Ovarian Cancer Stage 1
Meta-analysis (n=1545)

- In the multivariate analysis, 5 variables were significant :

-1- Differentiation
-2- Rupture before surgery
-3- Rupture during surgery
-4- FIGO stage 1b
-5- Age

Early Epithelial Ovarian Cancer :

Surgical aspects

Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma

Ignace Vergote, Jos De Brabanter, Anthony Fyles, Kamma Bertelsen, Nina Einhorn, Paul Sevelda, Martin E Gore, Janne Kærn, Herman Verrelst, Kjerstin Sjövall, Dirk Timmerman, Joos Vandewalle, Marleen Van Gramberen, Claes G Tropé

Invasive Ovarian Cancer Stage 1
Meta-analysis (n=1545)

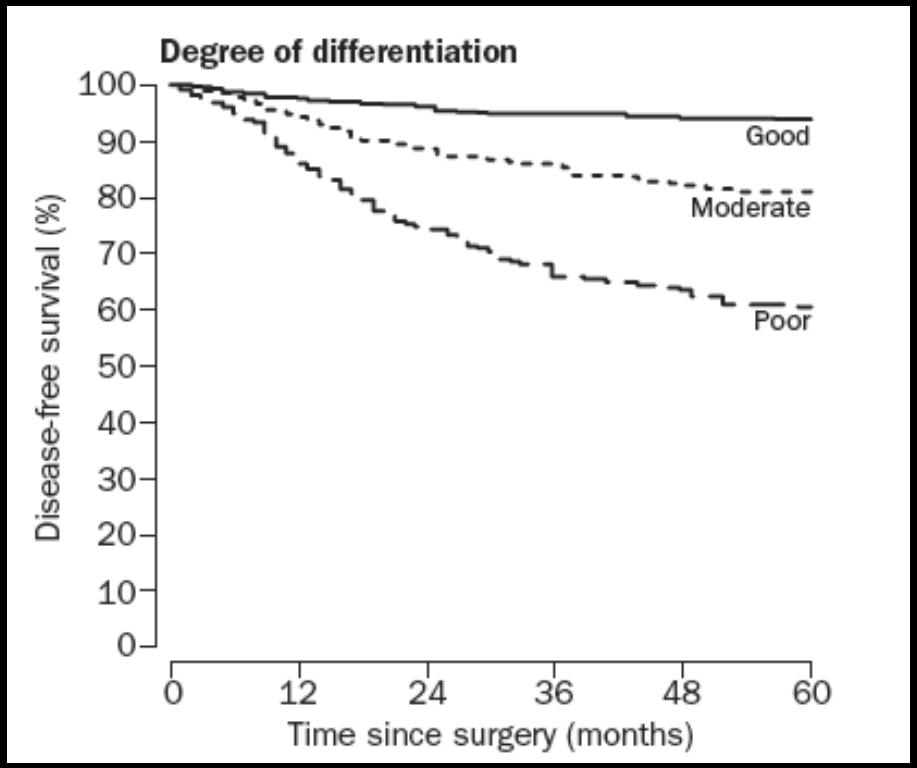
- In the multivariate analysis, 5 variables were significant :

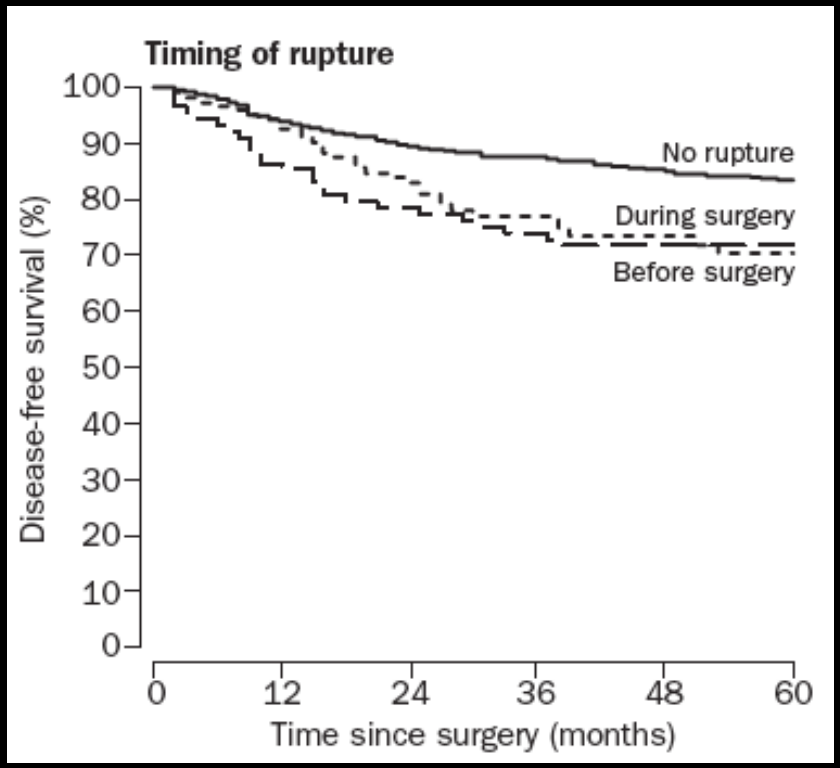
-1- Differentiation
-2- Rupture before surgery
-3- Rupture during surgery
-4- FIGO stage 1b
-5- Age

Early Epithelial Ovarian Cancer :

Surgical aspects

Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma





Vergote et al, Lancet 2001

Epithelial Ovarian Cancer Plan

- Introduction
- Role of Imaging
  - Diagnostic
  - Screening
- Surgical aspects
  - BORDERLINE TUMORS
  - Advanced stage disease
- Medical options
  - Chemotherapy
  - Targeted therapy

Table 1–1 HISTOLOGIC CLASSIFICATION OF OVARIAN TUMORS*

- Surface epithelial–stromal tumors
  - Serous tumors
    - Benign
    - Borderline (low malignant potential)
    - Malignant
  - Mucinous tumors (endocervical-like and intestinal types)
    - Benign
    - Borderline (low malignant potential)
    - Malignant
  - Endometrioid tumors
    - Benign
    - Borderline (low malignant potential)
    - Malignant
  - Epithelial-stromal and stromal tumors
    - Adenosarcoma
    - Mesodermal mixed tumor
    - Stromal sarcoma
  - Clear cell tumors
    - Benign
    - Borderline (low malignant potential)
    - Malignant
  - Transitional cell tumors
    - Brenner tumor
    - Brenner tumor of borderline malignancy
    - Transitional cell carcinoma (non-Brenner type)
  - Mixed epithelial tumors (specify types)
    - Benign
    - Borderline (low malignant potential)
    - Malignant
  - Undifferentiated carcinoma
- Sex cord–stromal tumors
  - Granulosa stromal cell tumors
  - Granulosa cell tumors
    - Adult
    - Juvenile
  - Thecoma-fibroma group
    - Thecoma
    - Fibroma
    - Fibrosarcoma
    - Unclassified
  - Sertoli stromal cell tumors (androblastomas)
    - Well-differentiated tumors
      - Sertoli cell tumor (tubular androblastoma)
      - Sertoli-Leydig cell tumor
      - Leydig cell tumor
    - Sertoli-Leydig cell tumor of intermediate differentiation
    - Sertoli-Leydig cell tumor, poorly differentiated (sarcomatoid)
    - Retiform tumor
  - Sex cord tumor with annular tubules
  - Gynandroblastoma
  - Unclassified
  - Steroid (lipid) cell tumors
    - Leydig cell tumor
    - Unclassified (not otherwise specified)
- Germ Cell Tumors
  - Dysgerminoma
  - Yolk sac tumor (endodermal sinus tumor)
    - Polyvesicular vitelline variant
    - Hepatoid variant
    - Glandular variant
  - Embryonal carcinoma
  - Polyembryoma
  - Choriocarcinoma
  - Teratomas
    - Immature
    - Mature: with secondary tumor (specify type)
    - Monodermal
      - Struma ovarii
      - Carcinoid tumor
      - Strumal carcinoid tumor
      - Mucinous carcinoid tumor
      - Others
    - Mixed germ cell tumor (specify type)
- Gonadoblastoma
- Tumors of uncertain origin and miscellaneous tumors
  - Small cell carcinomas
  - Others
- Gestational trophoblastic diseases
- Unclassified malignant tumors

*Abridged from the World Health Organization (WHO) classification.

Borderline Ovarian Tumor :

Generality

-Entité distincte définie par FIGO, OMS 1970

-15% de tous les cancers ovariens épithéliaux

-Pic incidence : 10-15 ans ans lésions invasives (mid’s 40)

-Présentation à un stade débutant (stade1) : 80%

-Pronostic : générallement excellent

-Stade I : Survie 5 ans proche de 100%

-Stades II-III : Survie 5 ans proche de 70-80%

Borderline Ovarian Tumor :
Management

- **Proper staging** (without lymphadenectomy) should be performed.

- For stage 1, **conservative surgery** consisting of USO,

or cystectomy, if bilateral tumors, can be considered in young patients wishing to preserve fertility

- In advanced disease or if no fertility wish, **HT+BSO and staging**

is recommanded without lymphadenectomy.

- There is **no proven benefit of adjuvant chemotherapy** or radiotherapy

Even in advanced disease with invasive implants

Cadron et al, JCO 2007, 10;25(20):2928:37

Borderline Ovarian Tumor :
Histology

Tumeur ovarienne

- **-Séreuse ; mucineuse ; endométrioïde ; Cell Claires, Brenner**
- **-Pattern « micro-papillaire »**
- **-«micro-invasifs »**

Implants péritonéaux :

- **-Non-invasifs, +/- réaction desmoplasique**
- **-Invasifs**

Borderline Ovarian Tumor :
Management

Management of Borderline Ovarian Neoplasms

Isabelle Cadron, Karin Leunen, Toon Van Gorp, Frederic Amant, Patrick Neven, and Ignace Vergote

VOLUME 25 · NUMBER 20 · JULY 10 2007

JOURNAL OF CLINICAL ONCOLOGY

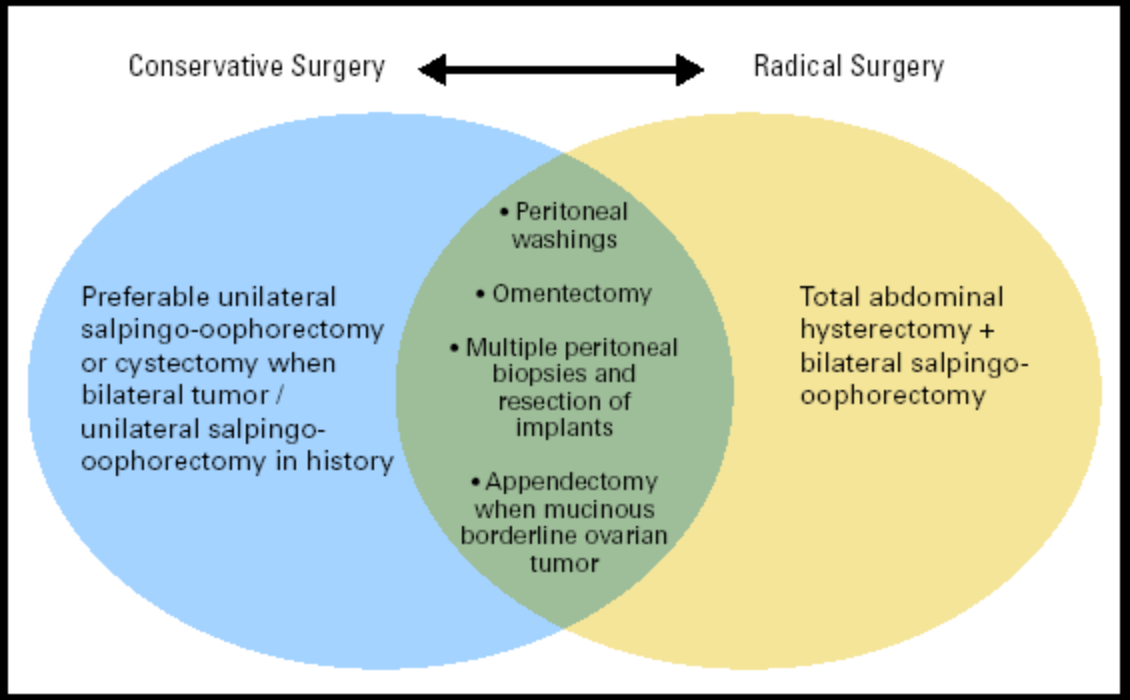
REVIEW ARTICLE

Cadron et al, JCO 2007, 10;25(20):2928:37

Borderline Ovarian Tumor :
Management

Management of Borderline Ovarian Neoplasms

Isabelle Cadron, Karin Leunen, Toon Van Gorp, Frederic Amant, Patrick Neven, and Ignace Vergote



Cadron et al, JCO 2007, 10;25(20):2928:37

MERCI

SÉMINAIRE DE CHIRURGIE GYNÉCOLOGIQUE

niveau 2

Oncologie mammaire et pelvienne

DAKAR - du 6 au 10 JUIN 2011

Faculté de Médecine de Pharmacie et d'Odontologie
Université Cheikh Anta Diop
Hôpital de Pikine

Cancer de l'Ovaire

Pr Frédéric Goffin, MD, PhD

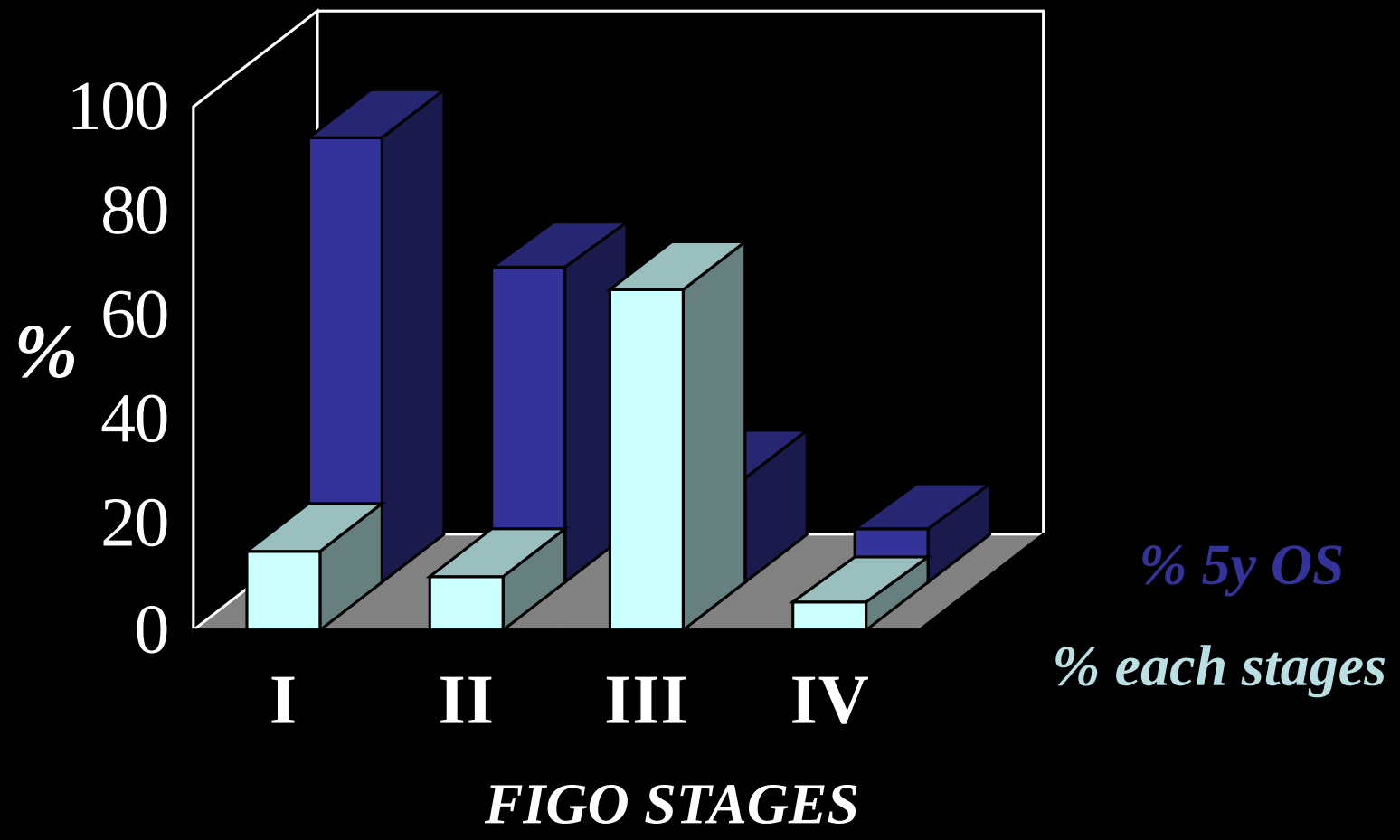
Hôpital de la Citadelle
Département of Gynecologie & Obstetrique
Université of Liège

MINISTERE DE LA SANTE
ET DE LA PREVENTION

Ovarian Cancer

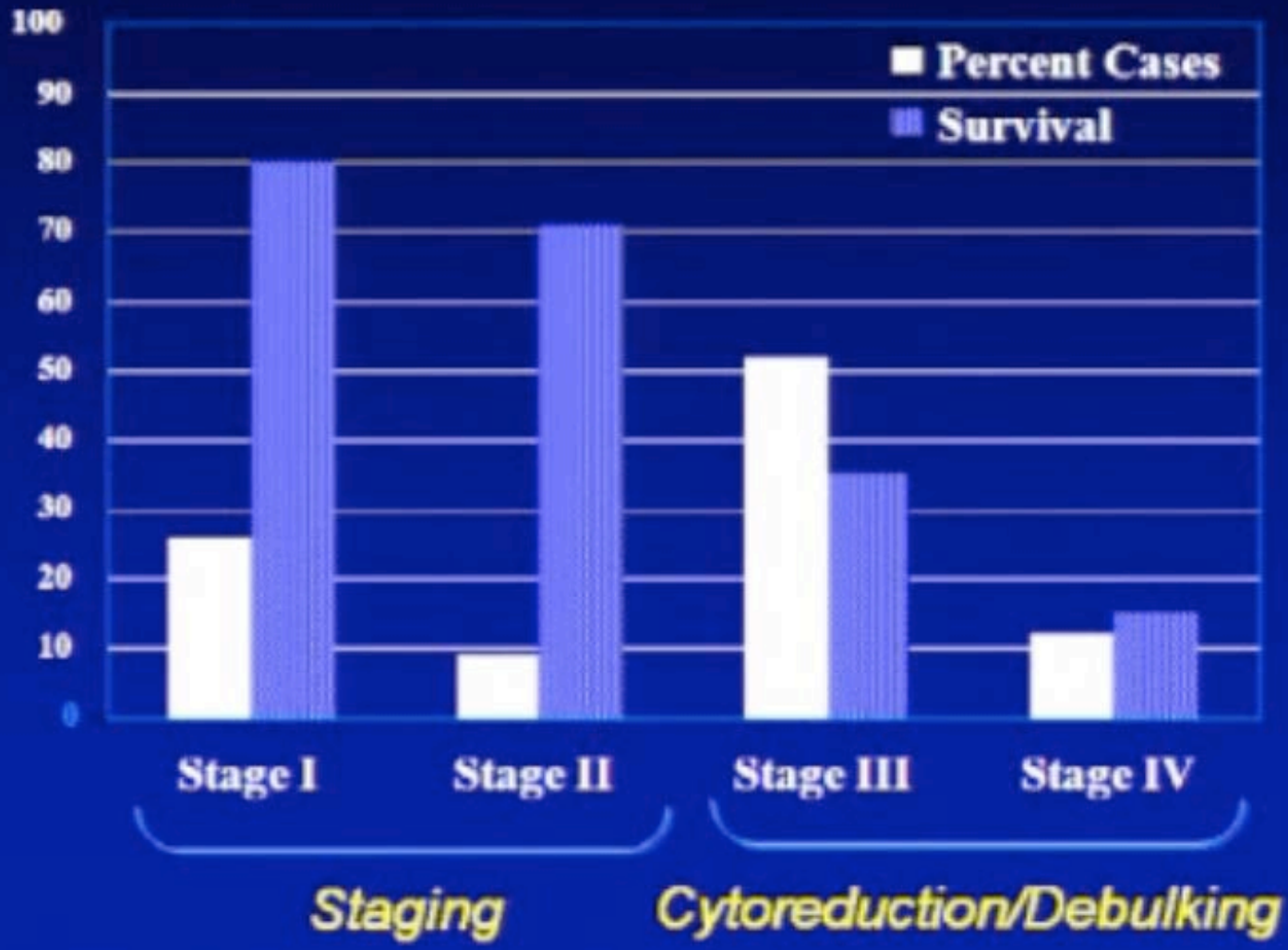
Plan

- Epidémiologie
- Histoire naturelle
- Diagnostique
- Traitment
  - Aspects chirurgicaux
    - Tumeurs débutantes
    - Tumeurs avancées
  - Aspects médicaux

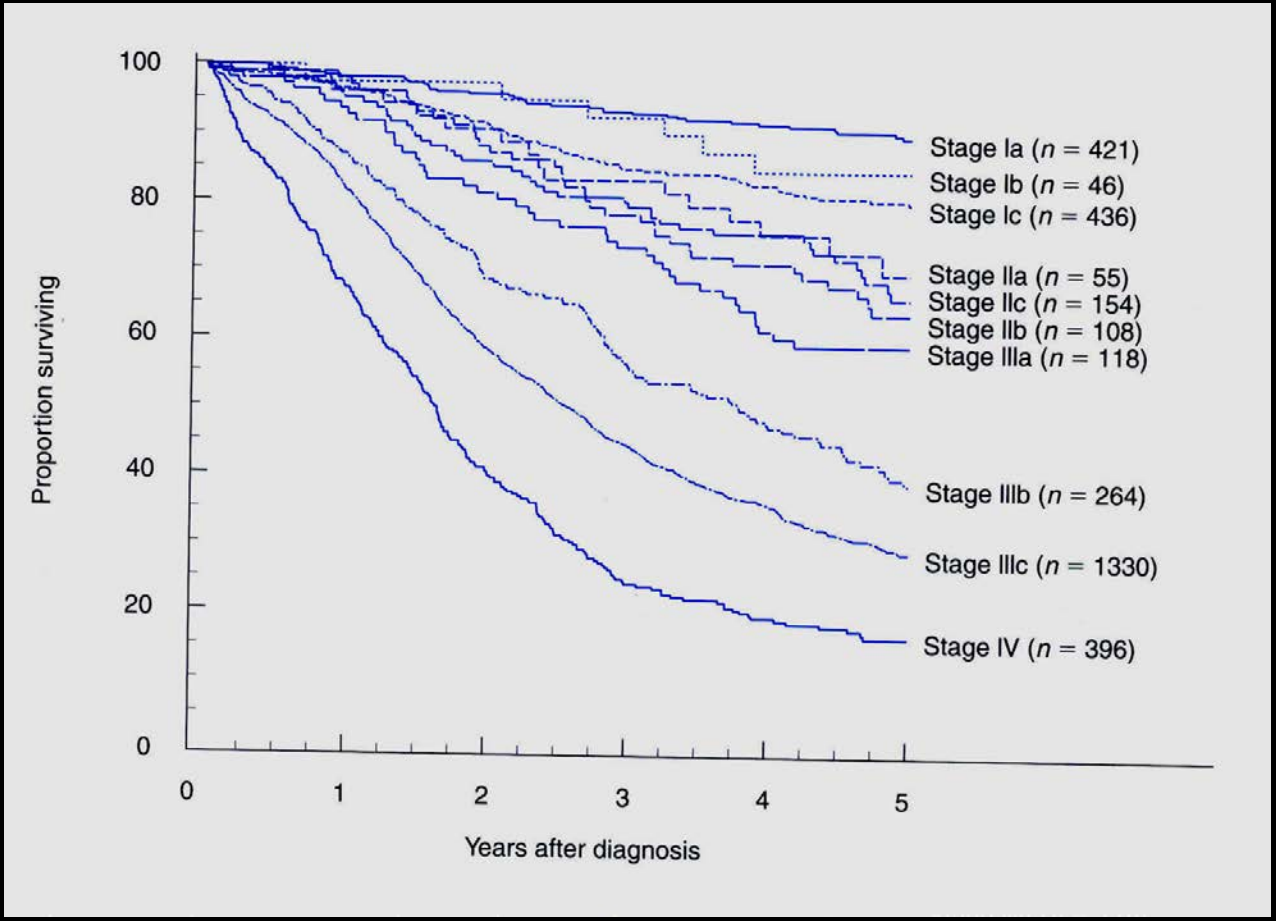


From I Jacobs, ESGO 2007.

Role of Surgery in Ovarian Cancer



Ovarian Cancer
Overall Survival

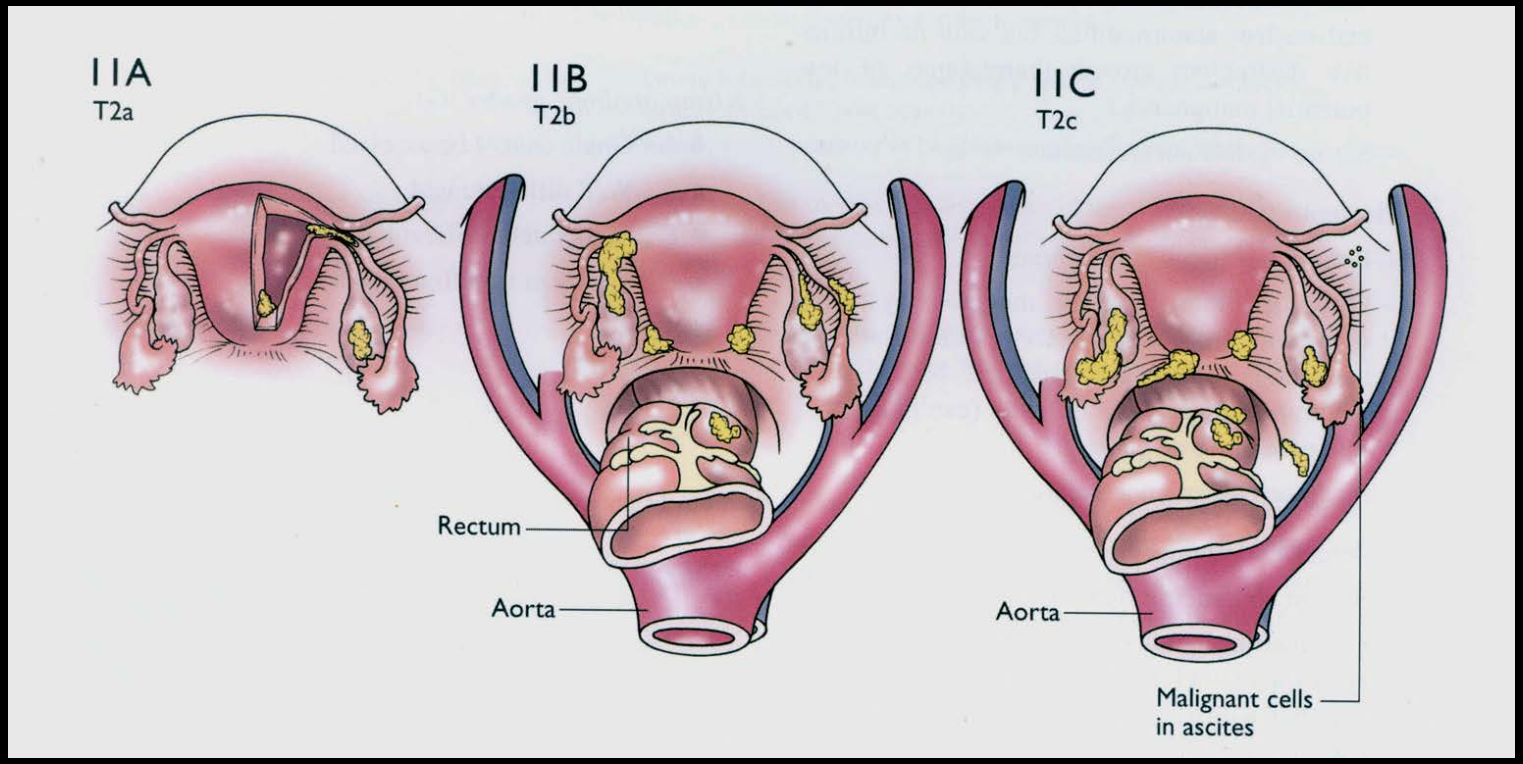


FIGO Staging of Ovarian Cancer

-1998, Rio de Janeiro-

Stage II **One or both ovaries with extension to pelvic structures**

IIA	Extension and/or metastases to uterus and/or tubes
IIB	Extension to other pelvic structures
IIC	with tumor on surface; or capsule ruptured; or malignant ascites present



FIGO Staging of Ovarian Cancer

-1998, Rio de Janeiro-

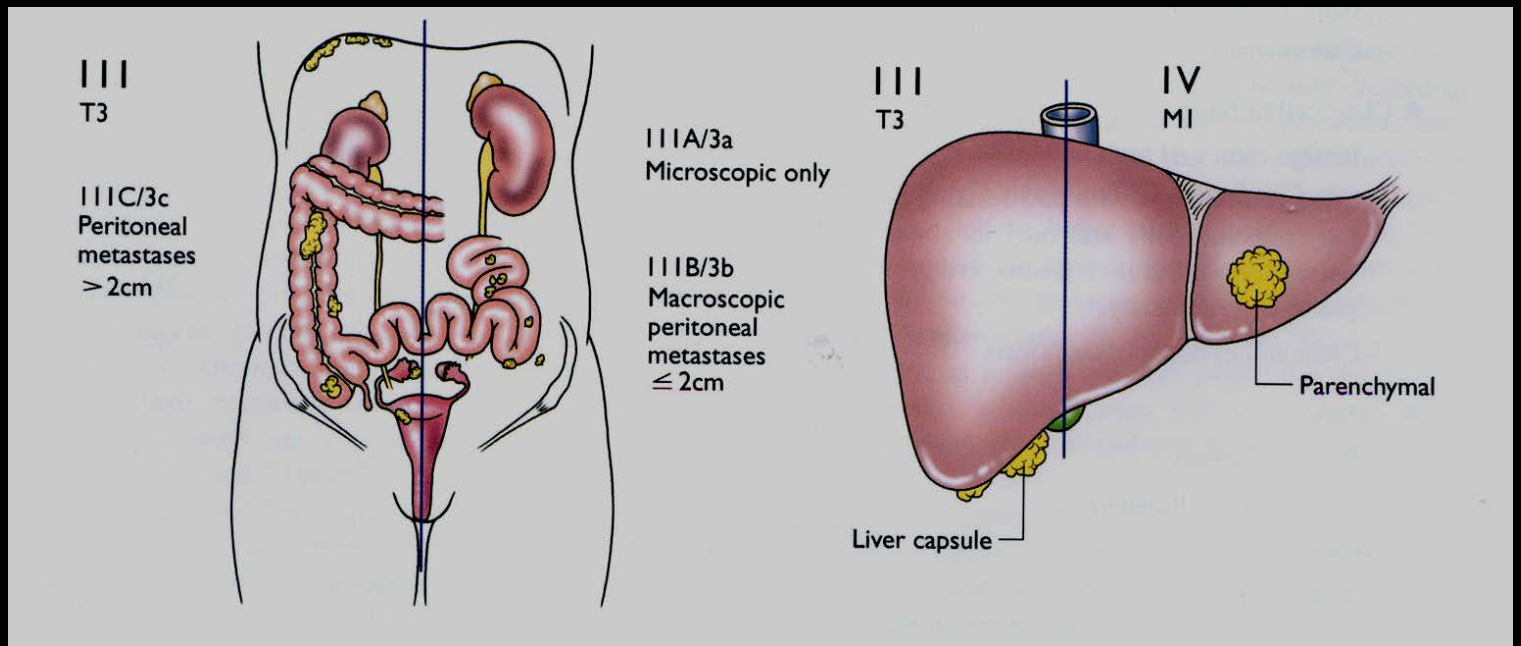
Stage III **Implants outside the pelvis and/or positive nodes**

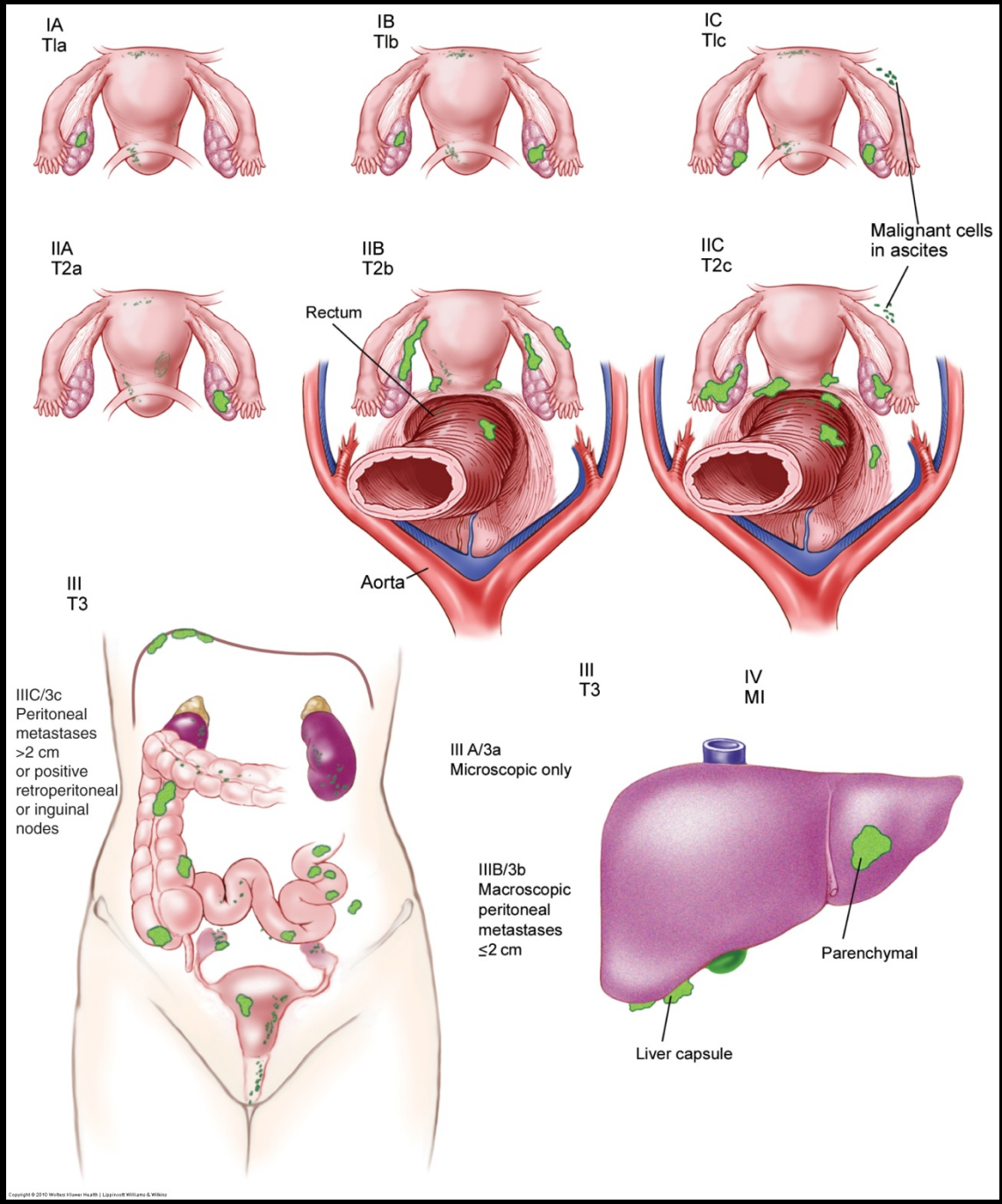
IIIA Tumor macroscopically confined to the pelvis with microscopic disease in the abdomen

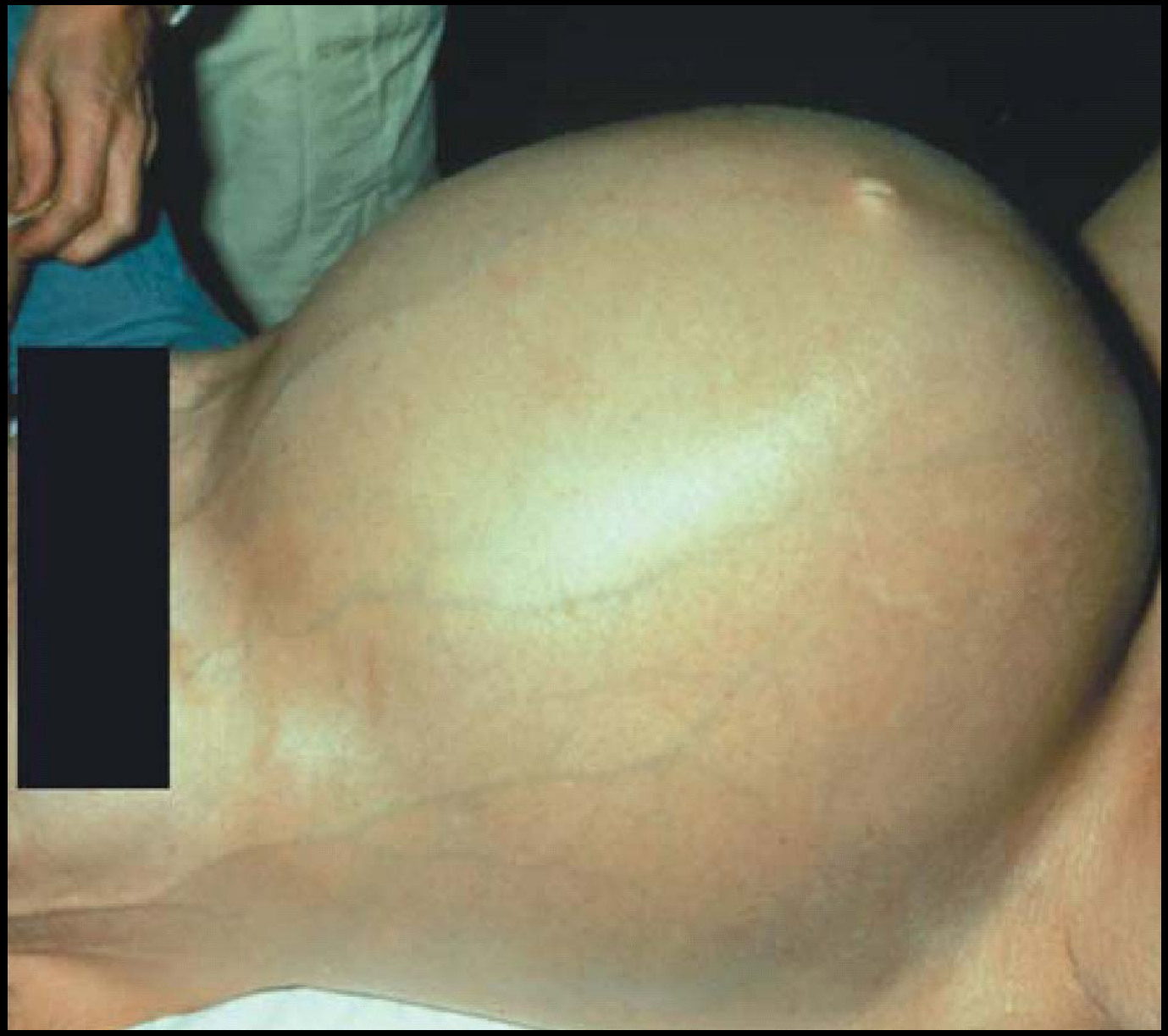
IIIB Tumor macroscopically involving the abdomen but no single nodule measuring greater than 2 cm ; Nodes are negative

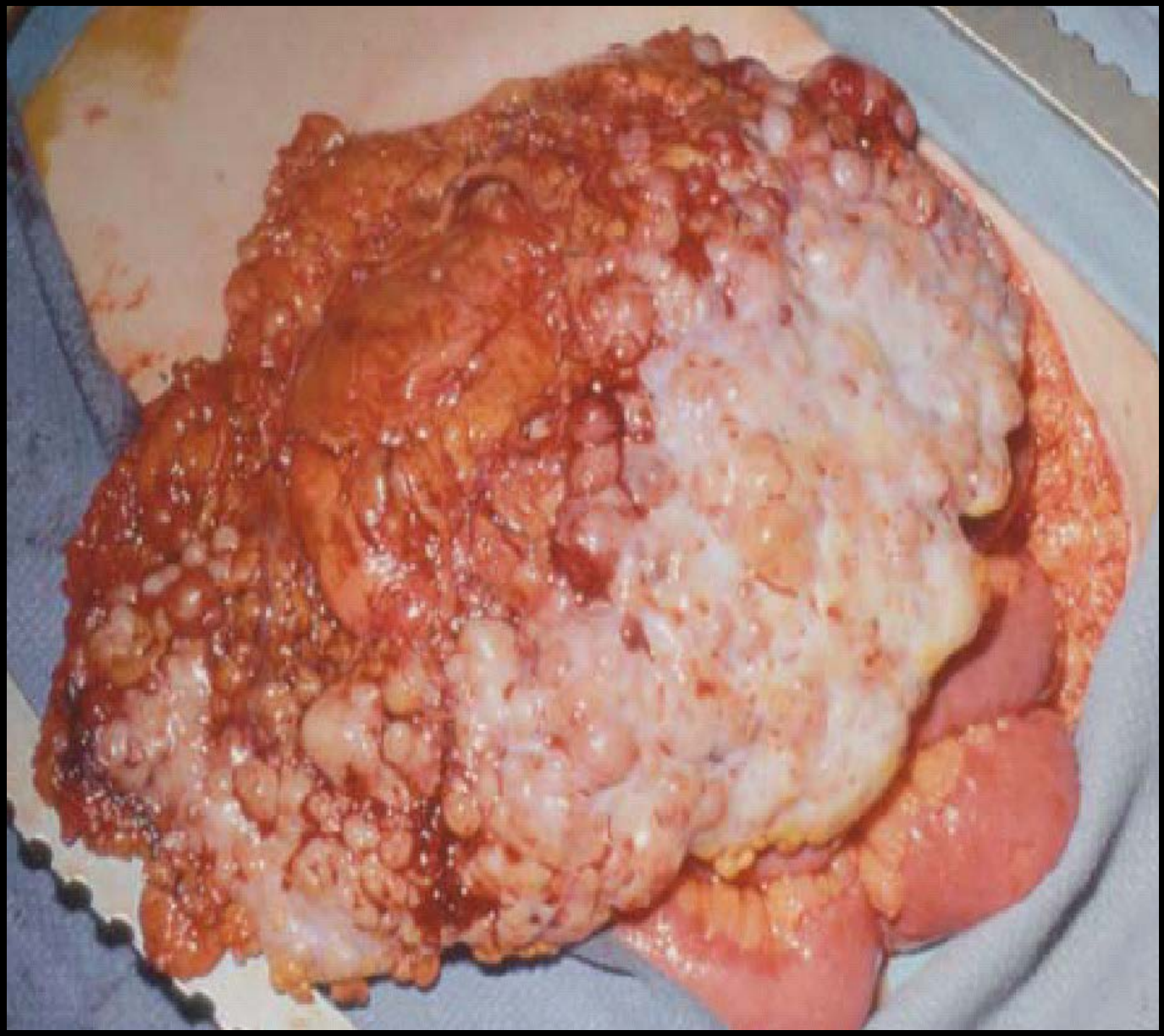
IIIC Abdominal implants greater than 2 cm or retroperitoneal or inguinal node involvement

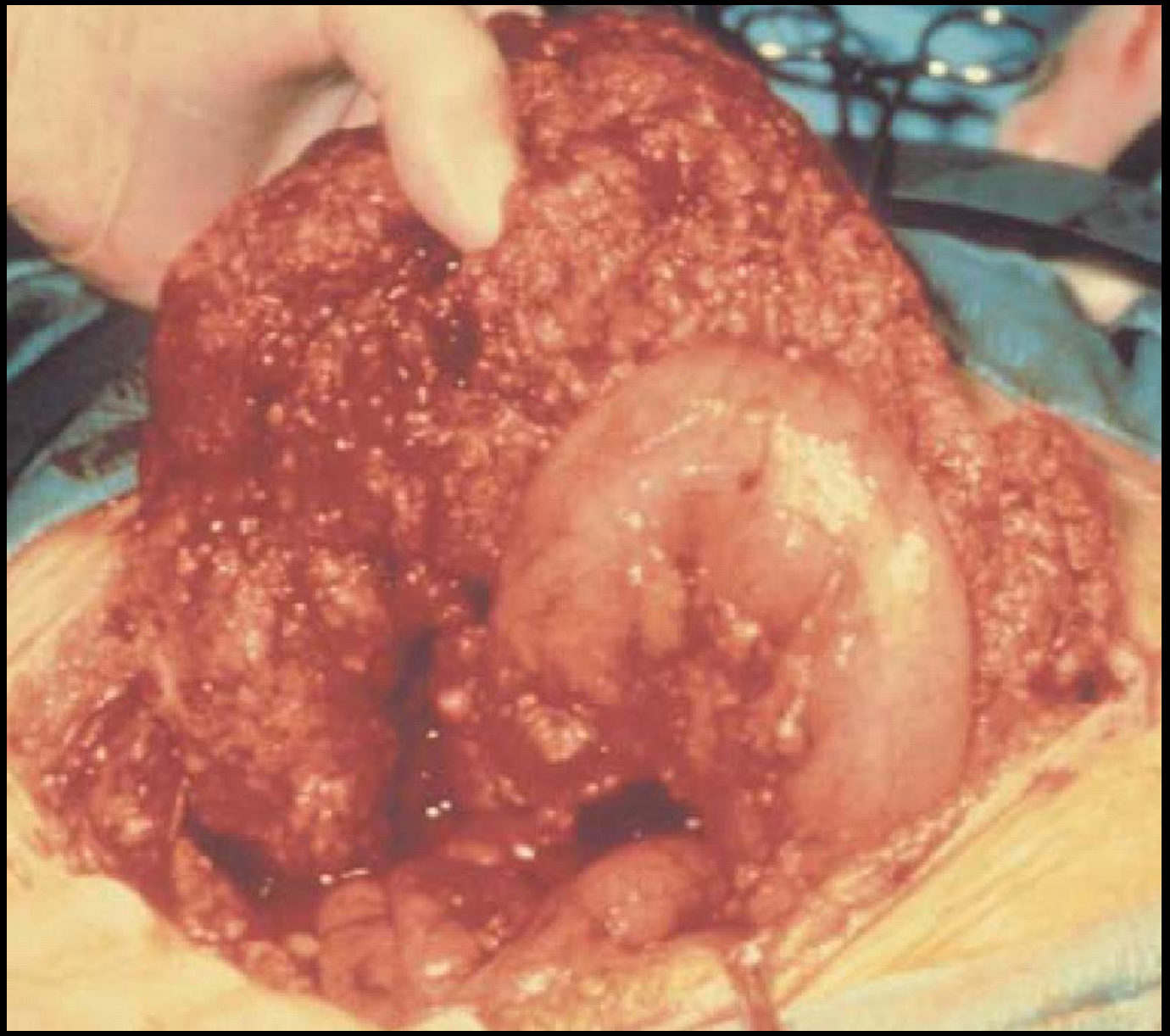
Stage IV **Extra-abdominal disease or parenchymal liver disease**




IA
T1a
IB
T1b
IC
T1c
Malignant cells
in ascites
IIA
T2a
IIB
T2b
Rectum
IIC
T2c
Aorta
III
T3
IIIC/3c
Peritoneal
metastases
>2 cm
or positive
retroperitoneal
or inguinal
nodes
III
T3
IV
M1
III A/3a
Microscopic only
IIIB/3b
Macroscopic
peritoneal
metastases
≤2 cm
Parenchymal
Liver capsule







Advanced Ovarian Cancer

Cytoreduction

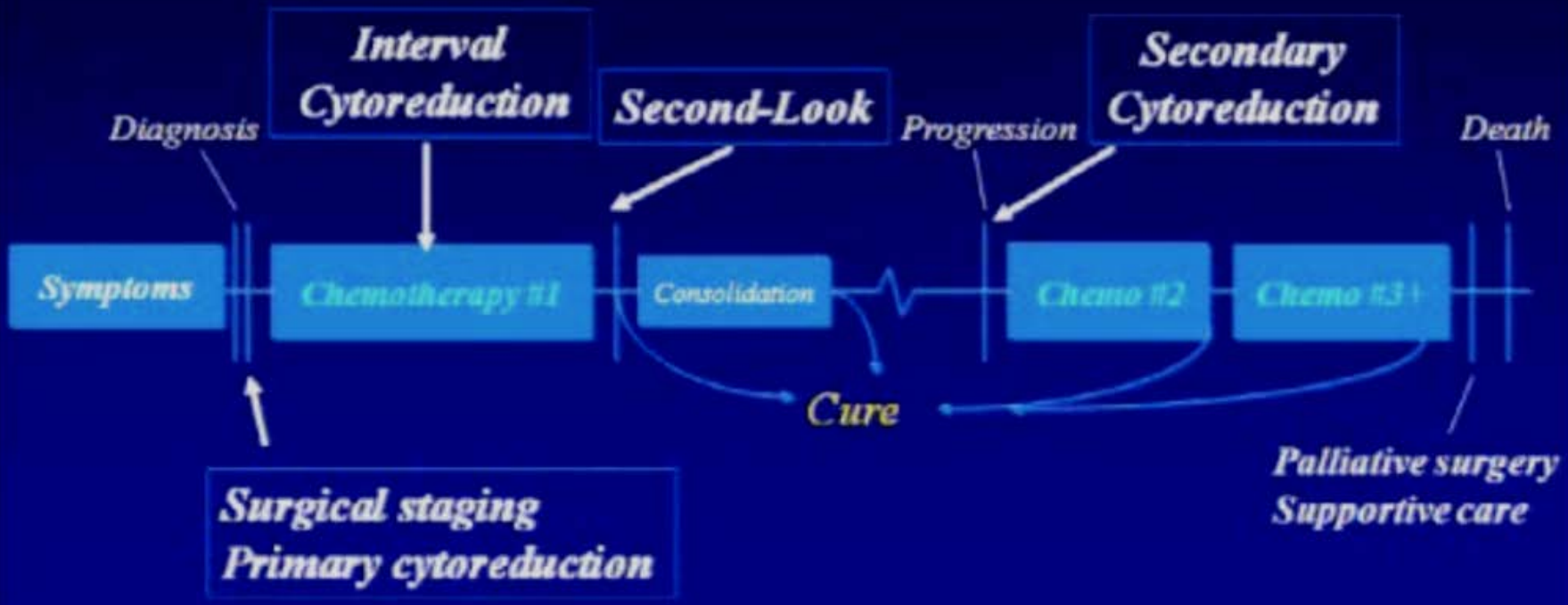
- Theoretical benefit
- Reduce volume of hypoxic tumor,
- Remove chemoresistant clones,
- Improve growth fraction of residual cells, potentiating effects of chemotherapy
- Improve host immunocompetence with decreasing tumor burden
- Immediate physiologic improvement
- Increase response to chemostatics
- Prolonged remission
- Practical
- Timing
- Surgical effort

Advanced Ovarian Cancer

Cytoreduction rules

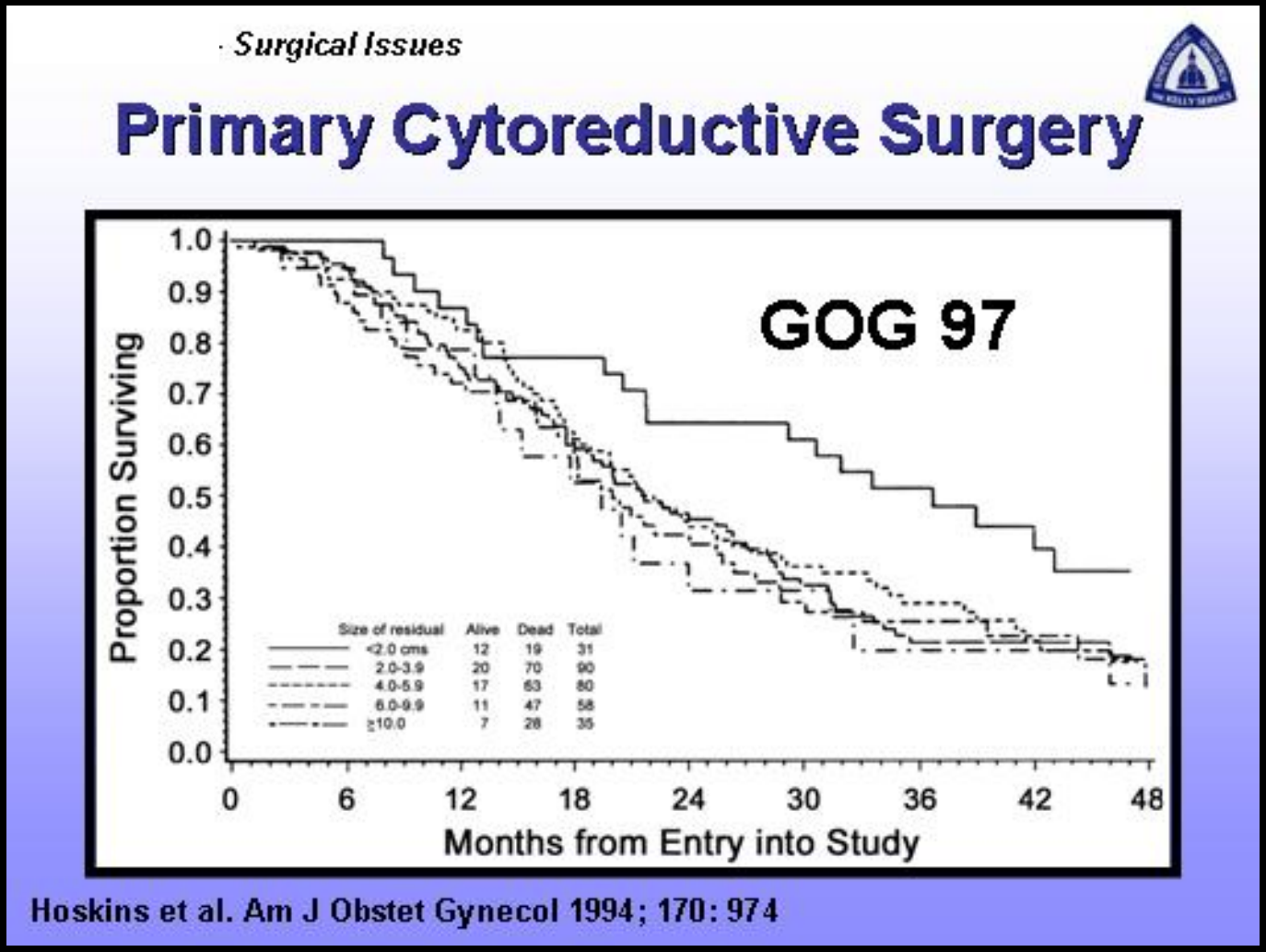
- Through midline incision
- Methodic inspection and palpation
- Determine the « resectability », establish a surgical strategy
  - Optimal cytoreducetion without any macro disease
  - « Optimal » cytoreduction, residual disease < 1cm
  - Suboptimal cytoreduction, residual disease > 1 cm

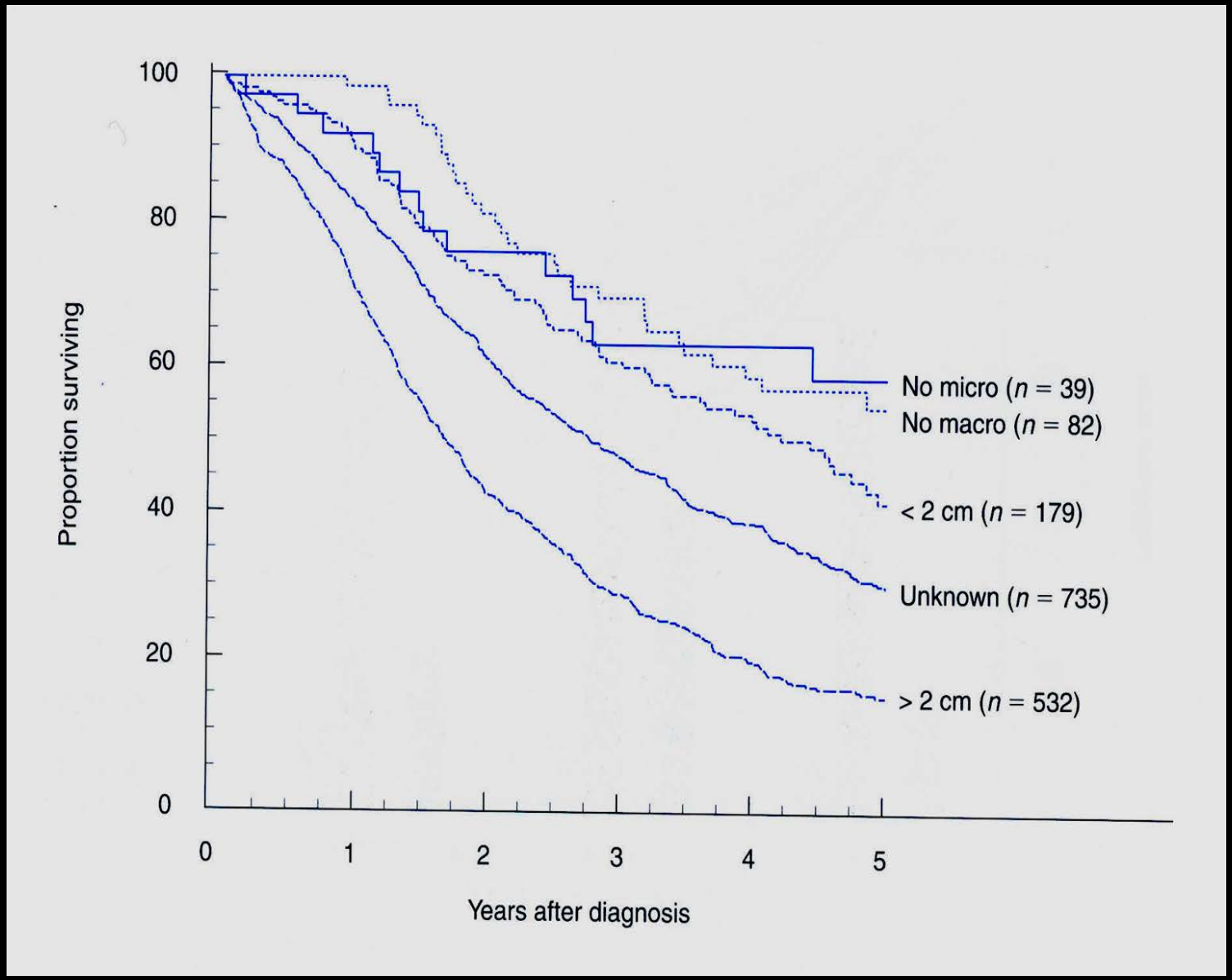
Surgical Terminology



Advanced Ovarian Cancer

Cytoreduction Rationale




100
80
60
40
20
0
Proportion surviving
0
1
2
3
4
5
Years after diagnosis
No micro (n = 39)
No macro (n = 82)
< 2 cm (n = 179)
Unknown (n = 735)
> 2 cm (n = 532)

Advanced Ovarian Cancer

Cytoreduction

Meta-Analysis, Bristow et al, JCO 2002

Study Characteristics

- 6885 patients, stage 3-4
- 81 patients cohort
  - Randomized prospective trials (55 cohorts)
  - Prospective trials (24 cohorts)
  - Retroscective trials (2 cohorts)
- Mean median survival - 29 months-

Bristow et al, JCO 2002

Advanced Ovarian Cancer

Cytoreduction

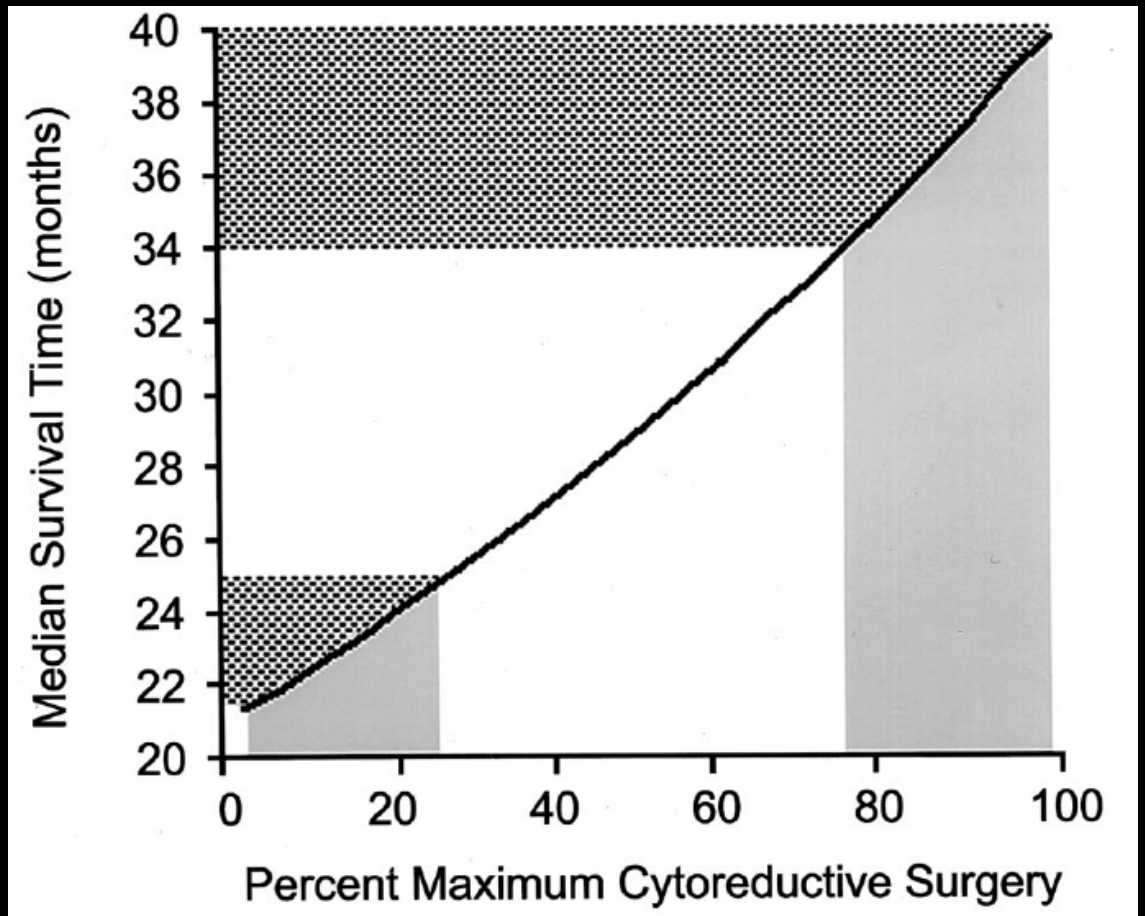


Fig 2. Simple linear regression analysis: de-logged median survival time plotted against percent maximal cytoreductive surgery. Gray area, maximal cytoreductive surgery ≤ 25% and > 75%; crosshatched area, corresponding range of median survival times.

Bristow et al, JCO 2002

Advanced Ovarian Cancer

Cytoreduction

Optimal Cytoreduction Rates for advanced ovarian carcinoma With STANDARD surgical techniques

Authors	Year	No.	Optimally cytoreduced
Smith	1979	792	24 %
Wharton	1984	395	39 %
Neijt	1993	265	46 %
Makar	1995	455	27 %
Chi	2001	282	25 %
Total		2159	30 %

Chi et al, GynOnc

Advanced Ovarian Cancer

Cytoreduction

Improved Optimal Cytoreducyion Rates
For Stages IIIC and IV Epithelial Ovarian:
A change in surgical approach

- Group 1 : primary surgery 11/98 - 5/00
  - Extensive procedures not routinely used
- Group 2 : primary surgery 1/01 - 5/02
  - Extensive procedures used as needed

- Extensive Upper Abdominal Procedures :
  - Liver Resection, diaphragm peritonectomy/resection, Resection of tumor from porta hepatis, cholecystectomy, splenectomy, distal pancreatectomy

Chi et al, GynOnc 2004

Advanced Ovarian Cancer

Cytoreduction

Improved Optimal Cytoreducyion Rates : A change in surgical approach

Variable	Group 1	Group 2	P value
Extensive Procedures	2 (3%)	19 (27%)	< 0,001
Optimal cytoreduction (< 1 cm)	35 (50%)	53 (76%)	< 0,01
Average Operative time	174 min	264 min	< 0,001
Complication Rates	3 (4,3%)	4 (5,7%)	ns
Lenght of Stay	8 days	9 days	ns

Chi et al, GynOnc 2004

Advanced Ovarian Cancer

Cytoreduction

Does Improved Optimal Cytoreduction Rates leads to improved OS

Variable	Group 1 (n=168) 1996-1999	Group 2 (n=209) 2001-2004	P value
Median age	60 y	62 y	NS
Stage IIIC	147 (88%)	173 (83%)	NS
Primary Ovary	149 (89%)	180 (86%)	NS
Extensive Procedures	2 (1%)	77 (37%)	< 0,001
Optimal Cytoreduction	78 (50%)	166 (80%)	< 0,01
Median OS	43 mo	58 mo	0,042

No difference in chemotherapy between Group1 and group 2

Chi et al, GynOnc 2007

Advanced Ovarian Cancer

Cytoreduction

Extensive Upper Abdominal Surgery to achieve Optimal Cytoreduction Improves Survival in advanced Ovarian Cancer

- Analyses of 262 patients with stages IIIC-IV ovarian carcinoma who underwent primary surgery between 1998-2003

- Divided into 3 groups
  - Optimal residual (< 1cm) with extensive upper abdominal surgery
  - Optimal residual (< 1cm) without need for extensive upper abd surg
  - Suboptimal residual (>1cm)

Eisenhauer et al, GynOnc 2006

Advanced Ovarian Cancer

Cytoreduction

Extensive Upper Abdominal Surgery to achieve Optimal Cytoreduction Improves Survival in advanced Ovarian Cancer

Variable	Group 1 (n=57)	Group 2 (n=122)	Group 3 (n=83)
Extensive Procedures	57 (100%)	0 (0%)	0 (0%)
Optimal cytoreduct (< 1 cm)	57 (100%)	122 (100%)	0 (0%)
Clinical CR	47 (82%)	95 (78%)	47 (57%)
PFS	24 mo	23 mo	11 mo
Median OS	> 68 mo	> 86 mo	38 mo

Eisenhauer et al, GynOnc 2006

Advanced Ovarian Cancer

Cytoreduction

Surgical treatment of diaphragm disease correlates with improved survival in optimally debulked advanced stage ovarian cancer

Giovanni D. Aletti, Sean C. Dowdy, Karl C. Podratz, William A. Cliby *

Abstract

Background. Diaphragm involvement by ovarian cancer is often considered to be a major obstacle to successful cytoreductive surgery. Lack of evidence of survival benefit, concerns over safety and lack of experience are common justifications for this belief. In this study, we sought to ev

19
cu
Au

Surgical procedures to treat diaphragm disease increase the rate of complete And optimal debulking and correlate with improved survival even compared To patients optimally debulked without diaphragm surgery perfored

entire cohort, residual disease (RD) was the only independent prognostic factor in multivariate analysis ($P < 0.0001$) when considering other factors including demographic, intraoperative findings and procedures performed. For the subgroup of patients with tumor involving the diaphragm ($N = 181$), patients who underwent diaphragm surgery (stripping of the diaphragmatic peritoneum, full or partial thickness diaphragm resection, excision of nodules or CUSA) had improved 5-year OS relative to those that did not (53% vs. 15%; $P < 0.0001$). Furthermore, in multivariate analysis of patients with diaphragm disease, both RD and performance of diaphragm surgery were independent predictors of outcome ($P < 0.001$). Considering the subgroup of patients with RD < 1 cm, we noted a strong survival advantage for those patients who underwent diaphragm surgical procedures (5-year survival: 55% vs. 28%; $P = 0.0005$). Over time, we noted a statistically significant increase in the rate of diaphragm procedures for patients with diaphragm involvement from 1994–98 relative to 2002–3 (22.5% vs. 40%: $P = 0.022$).

Conclusions. Surgical procedures to treat diaphragm disease increase the rate of complete and optimal debulking and correlate with improved survival even compared to patients optimally debulked without diaphragm surgery performed.

Surgical treatment of diaphragm disease correlates with improved survival in optimally debulked advanced stage ovarian cancer

Giovanni D. Aletti, Sean C. Dowdy, Karl C. Podratz, William A. Cliby *

Gynecologic Oncology 100 (2006) 283 – 287

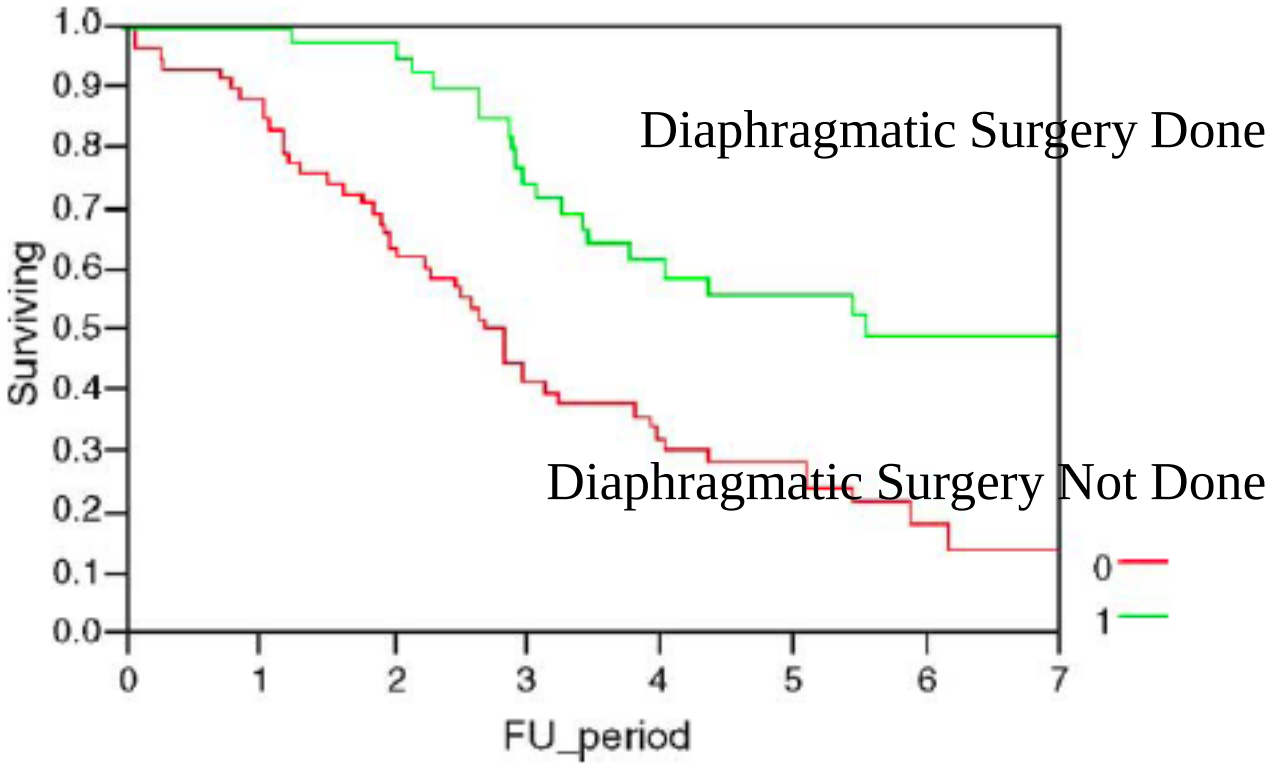
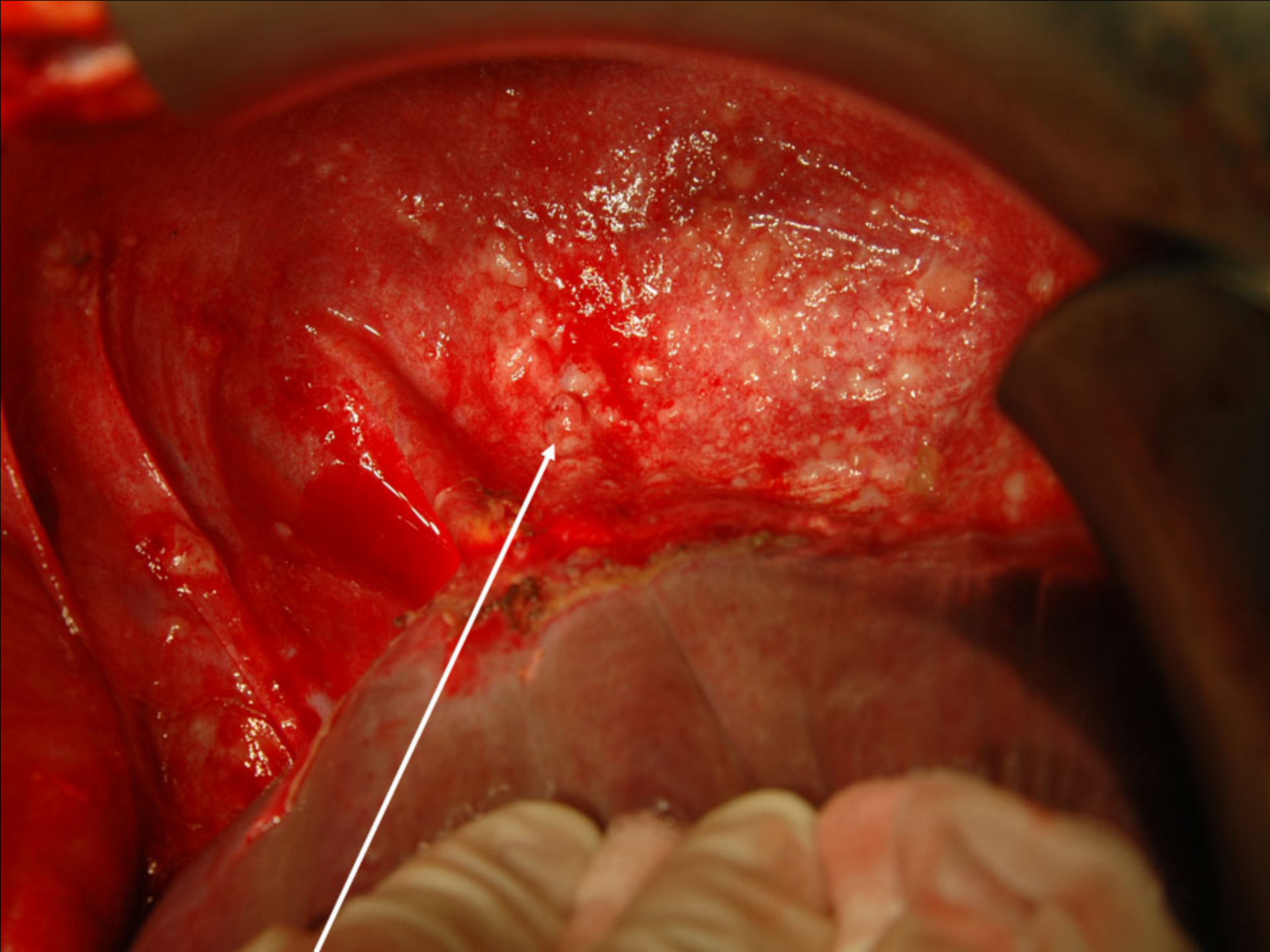
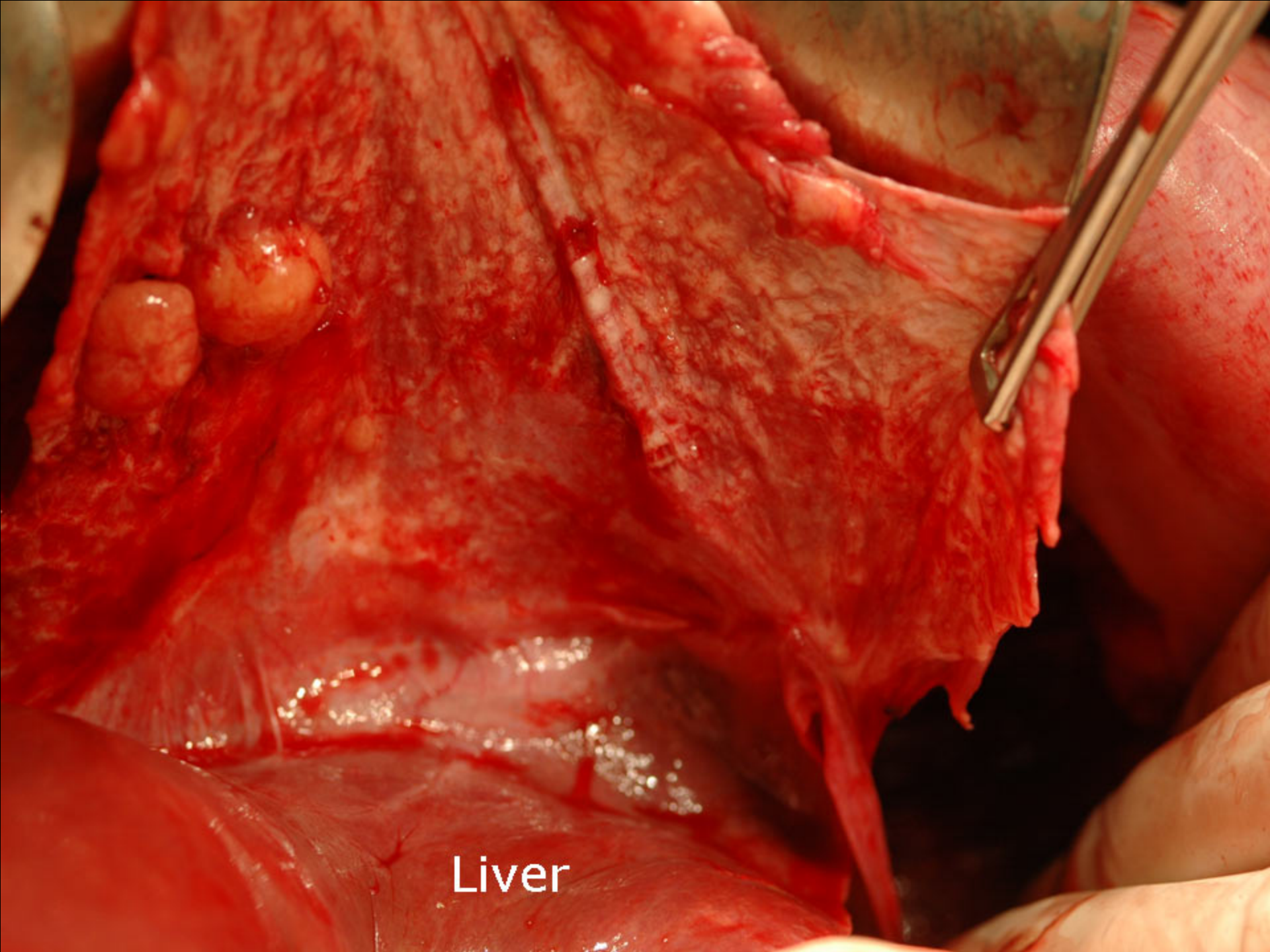


Fig. 2. Kaplan–Meier curves in IIIC–IV ovarian cancer patients with RD less than 1 cm and diaphragm involvement (*n* patients: 131), stratified by performance of diaphragmatic surgery: 0: not done; 1: done ($P = 0.0005$, log rank).



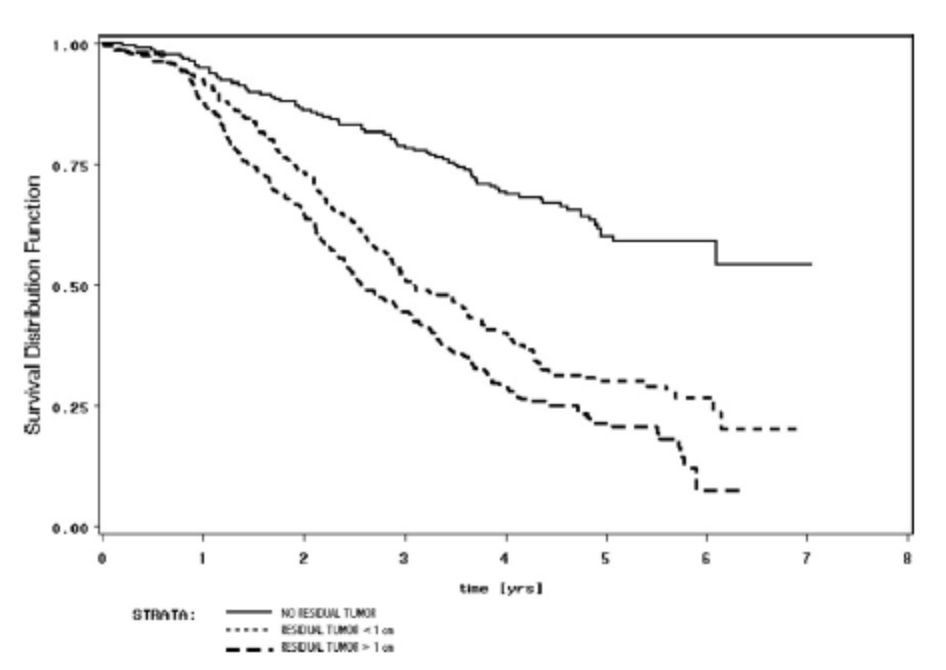

Liver

Advanced Ovarian Cancer

Cytoreduction

Prognostic factors for complete debulking in advanced ovarian cancer and its impact on survival. An exploratory analysis of a prospectively randomized phase III study of the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group (AGO-OVAR)☆

Pauline Wimberger [a,*], Nils Lehmann [b], Rainer Kimmig [a], Alexander Burges [c], Werner Meier [d], Andreas Du Bois [e]
for the AGO-OVAR



No Residual disease OS : 4,7 y

Residual < 1 cm OS : 3,5 y

Residual > 1 cm OS : 3 y

Advanced Ovarian Cancer

Cytoreduction

Standard of care

Primary debulking is the standard of care

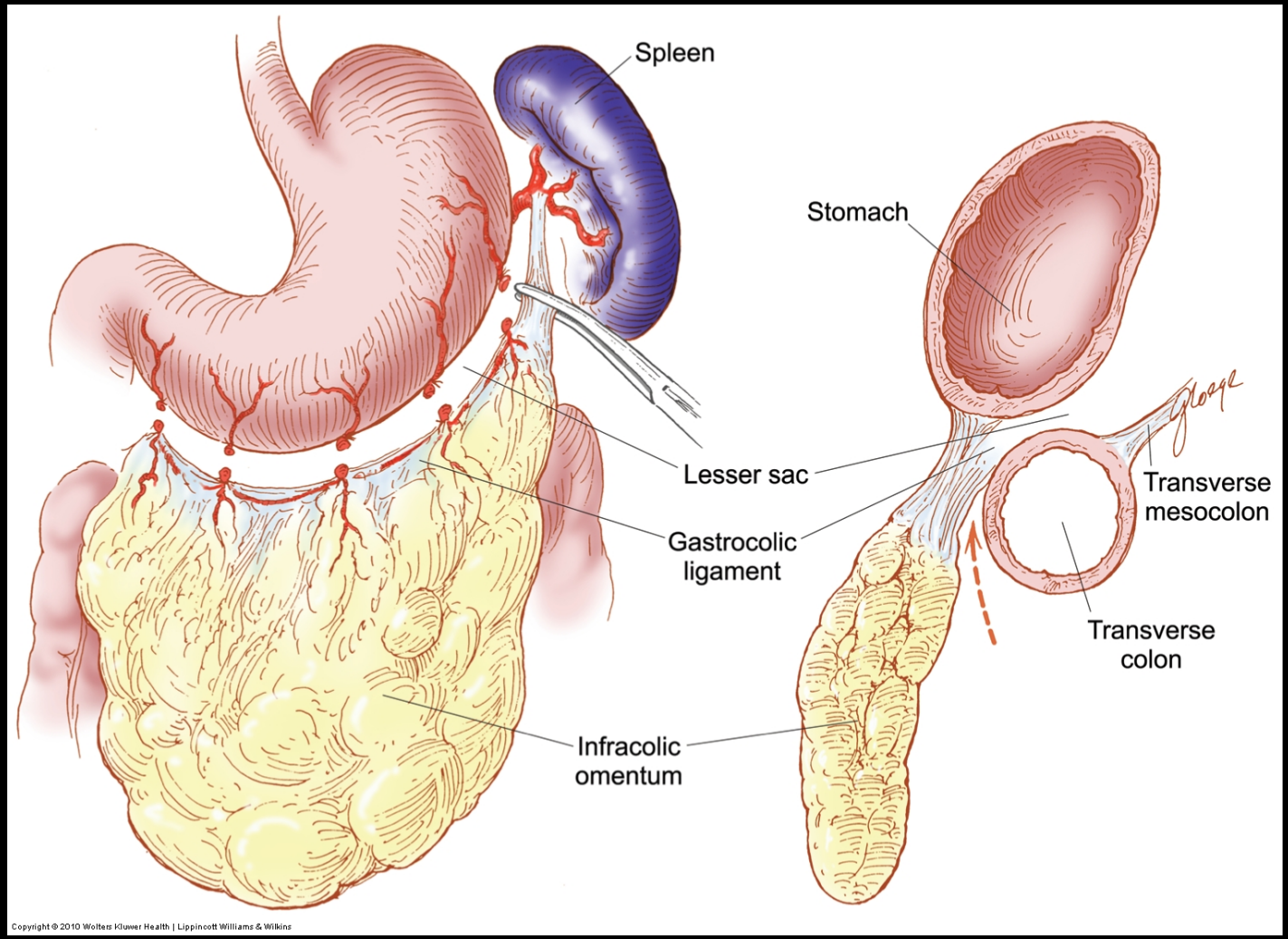
Optimal surgery = **no residual tumor**

All patients should have at least one surgical
Attempt by a **gynecological oncologist, surgeon**
trained in radical surgery in the **pelvis and the upper abdomen**.

Neoadjuvant chemotherapy should not be the easy solution
for poor surgical skills.

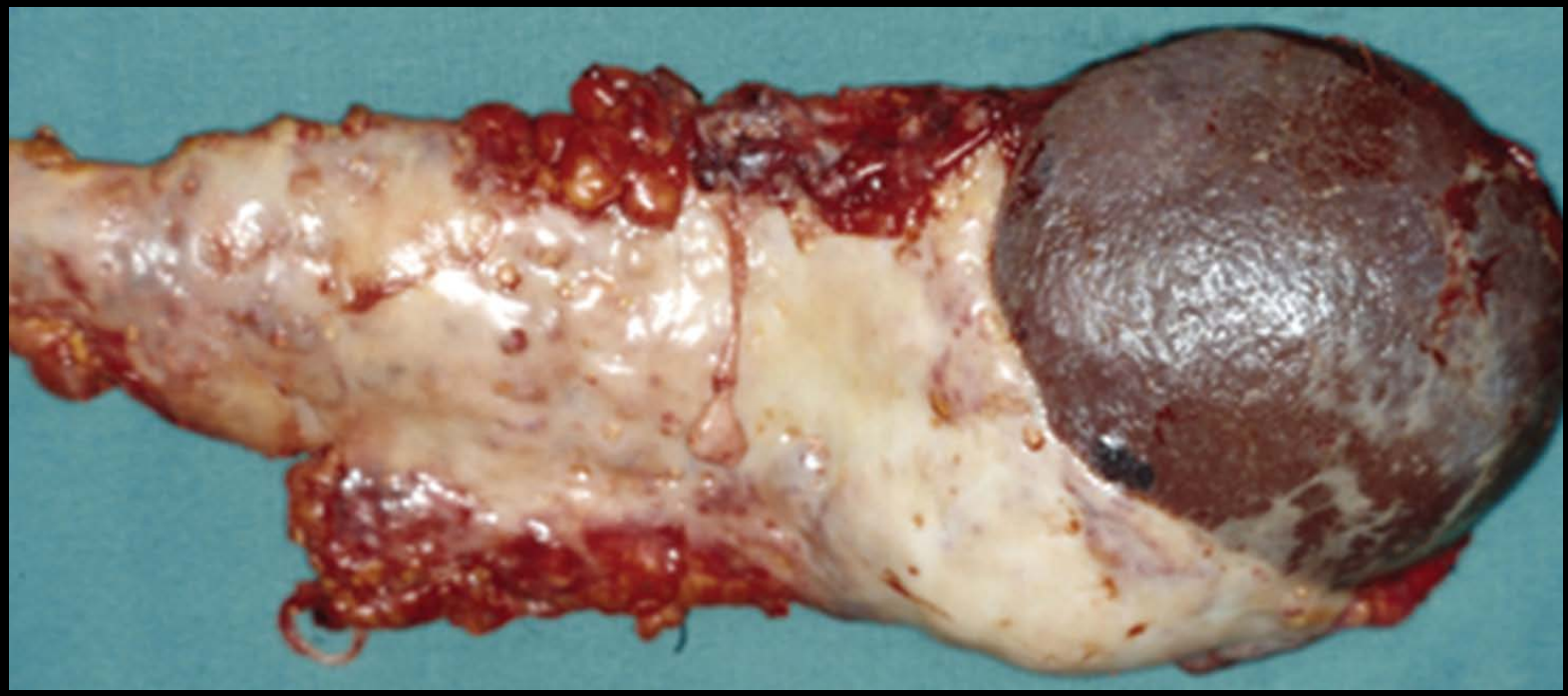
Advanced Ovarian Cancer

Cytoreduction



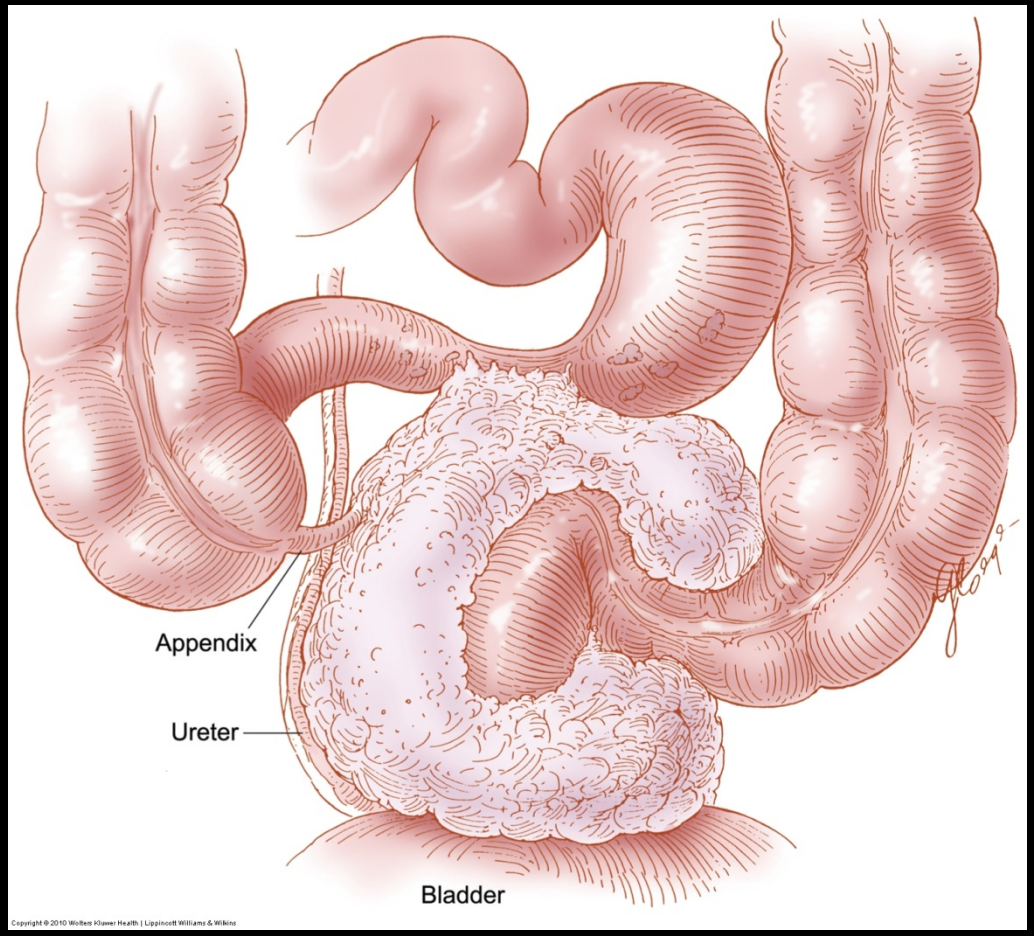
Advanced Ovarian Cancer

Cytoreduction



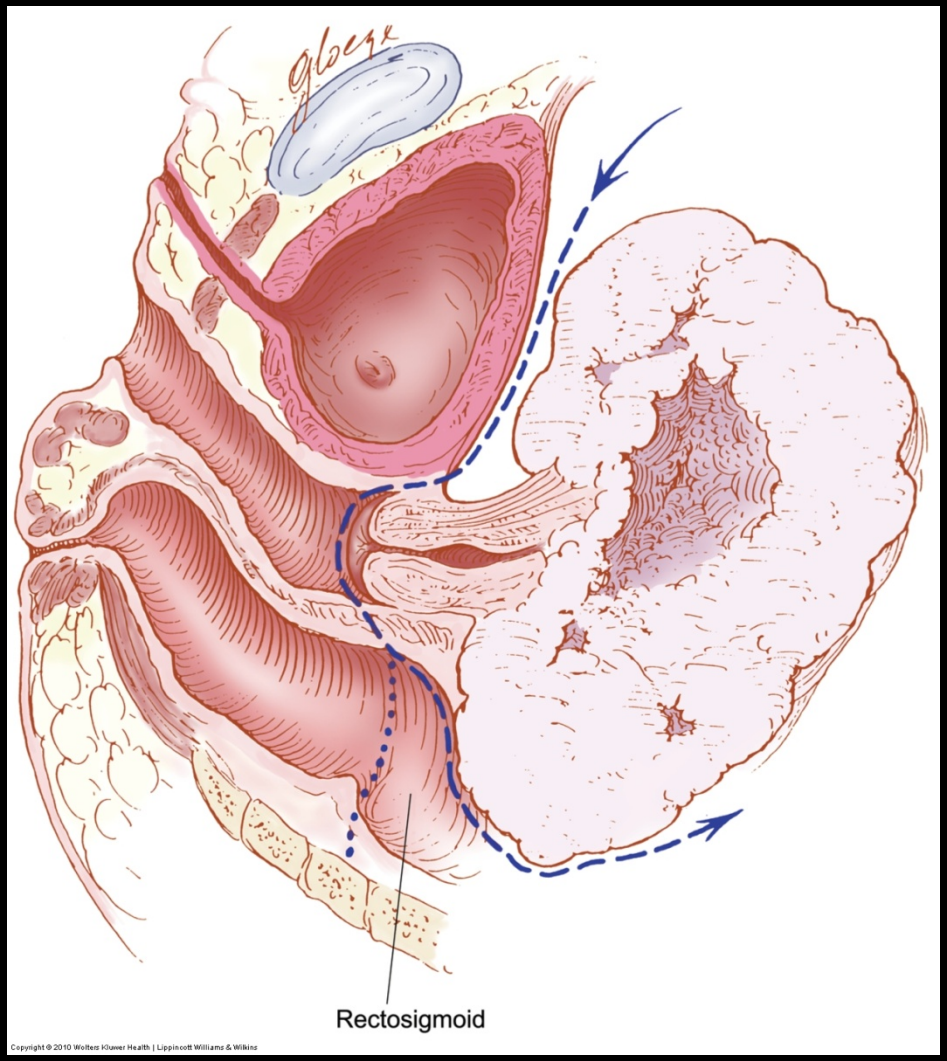
Advanced Ovarian Cancer

Cytoreduction



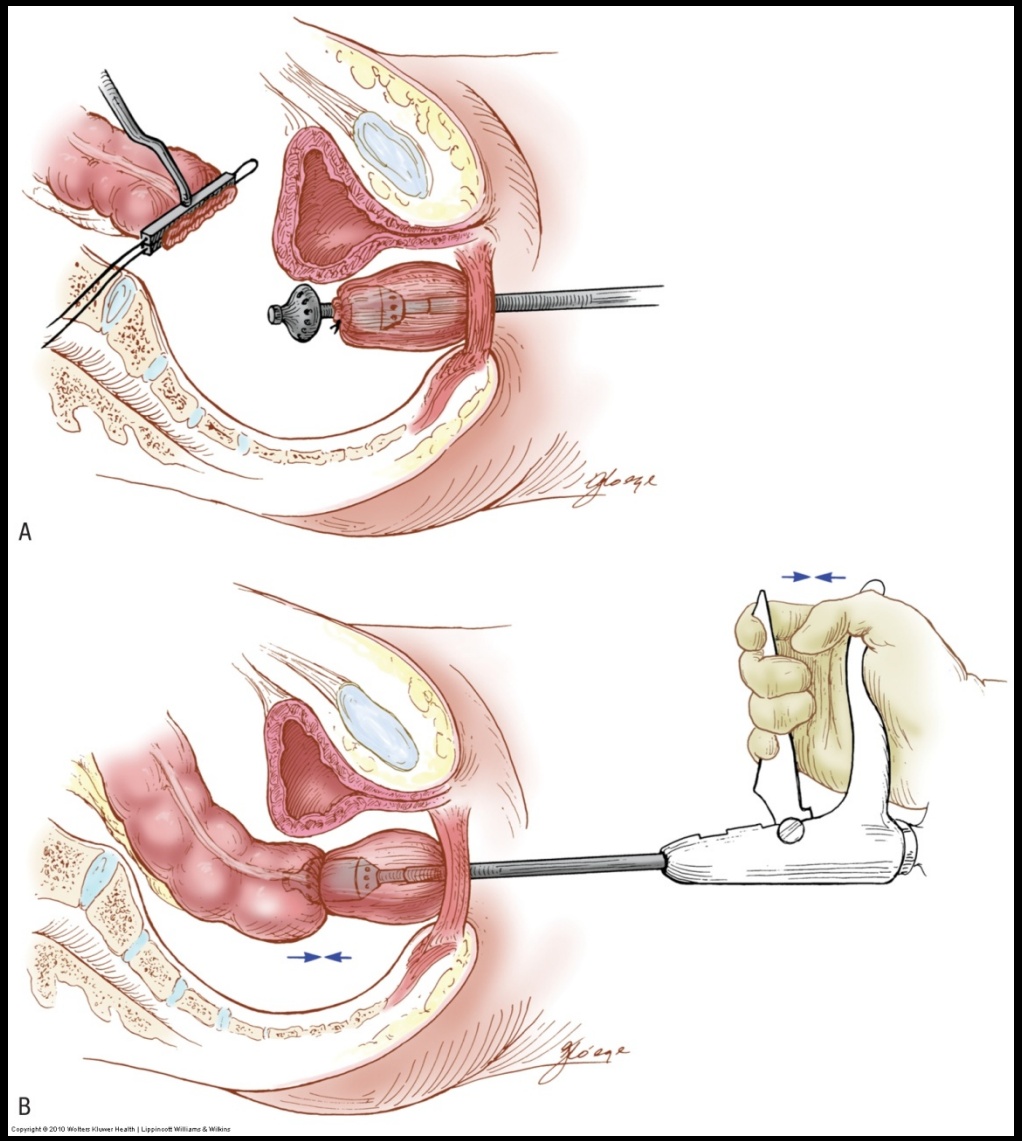
Advanced Ovarian Cancer

Cytoreduction : « En bloc posterior exenteration »



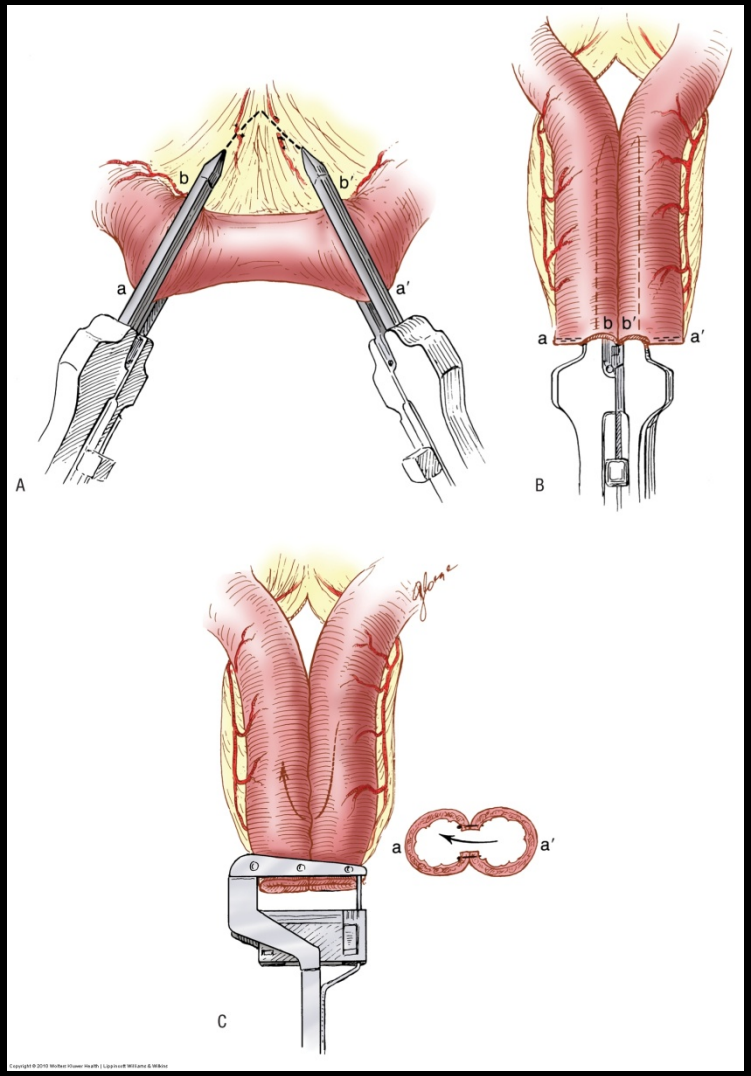
Advanced Ovarian Cancer

Cytoreduction



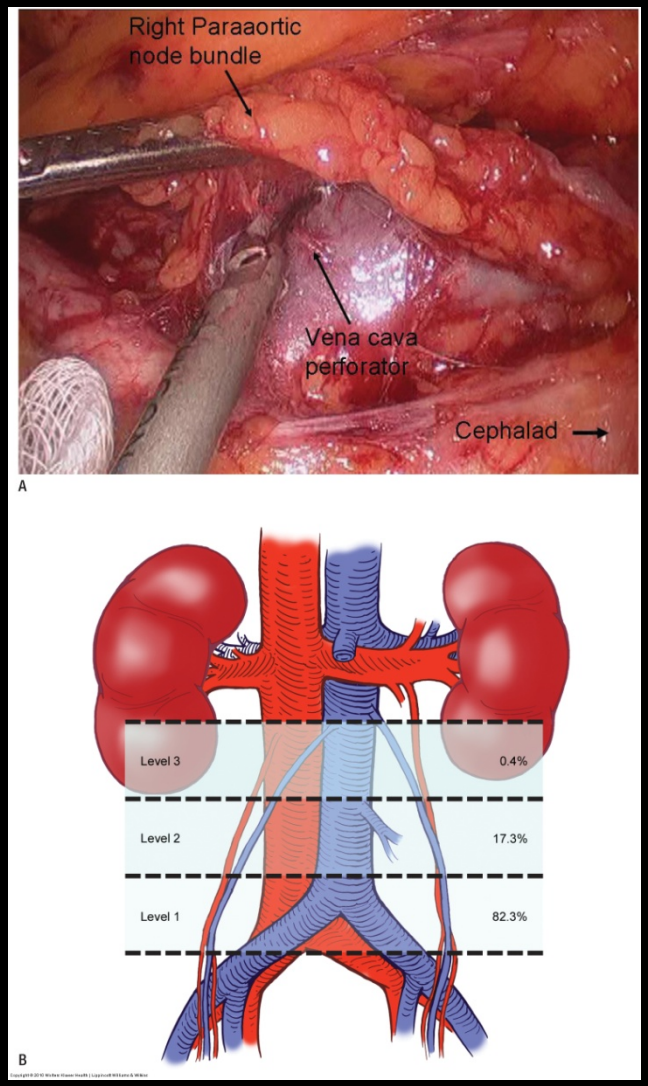
Advanced Ovarian Cancer

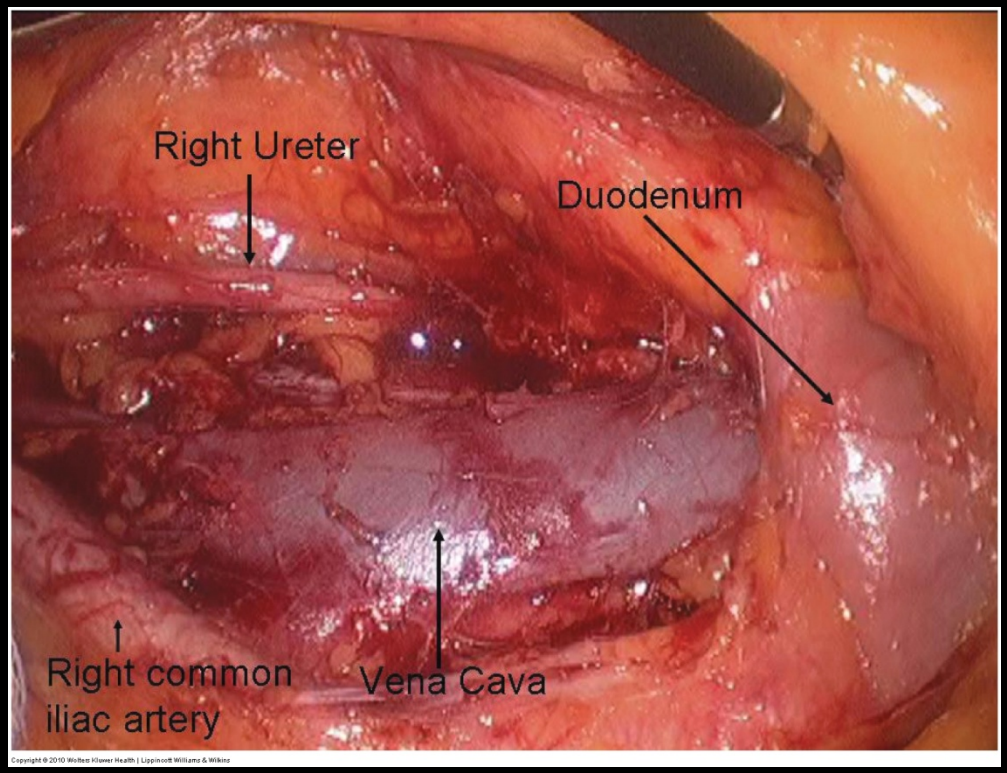
Cytoreduction : small bowel resection



Advanced Ovarian Cancer

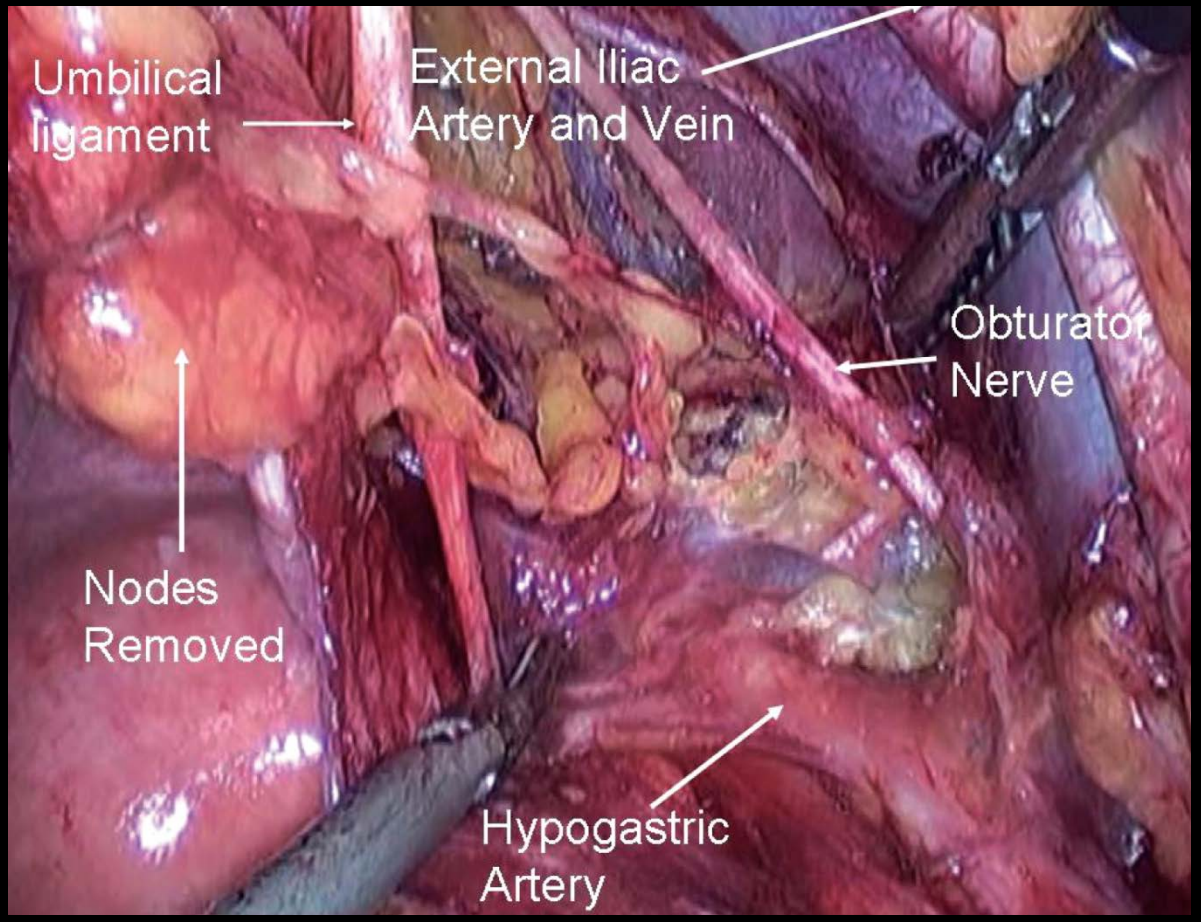
Cytoreduction





Advanced Ovarian Cancer

Cytoreduction



Ovarian Cancer

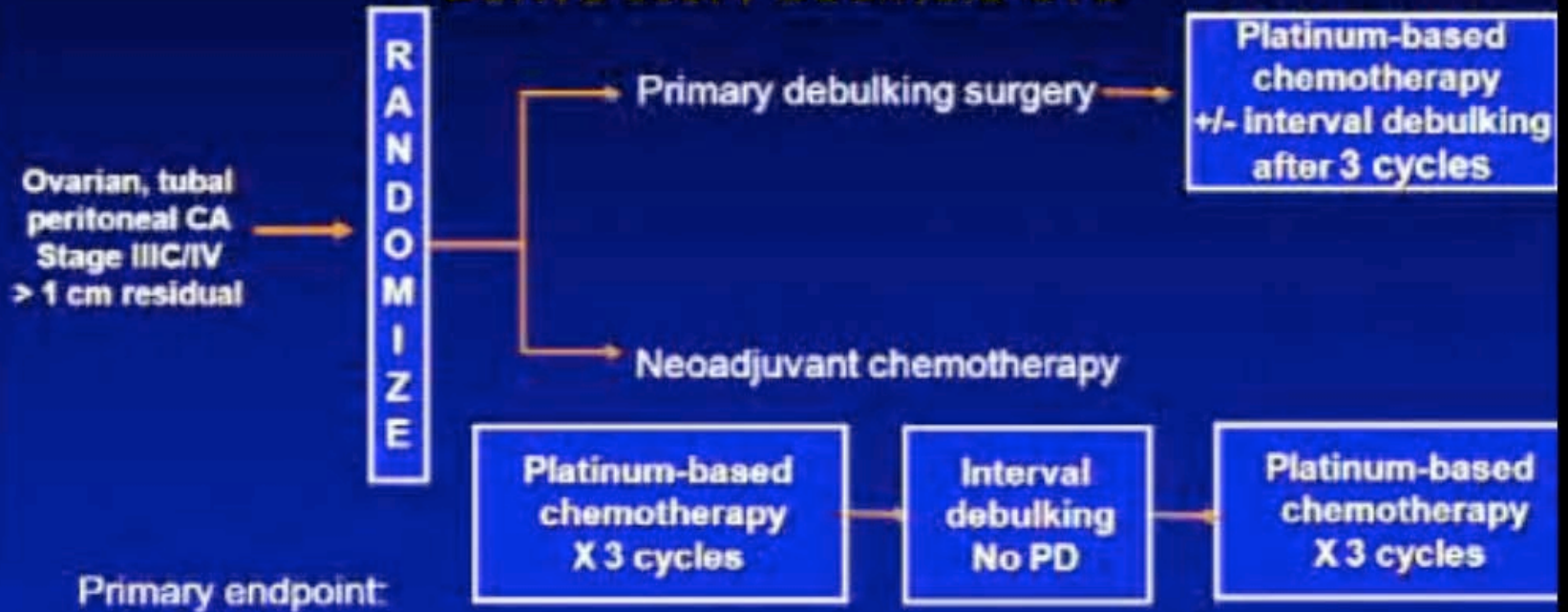
- Role of surgery
- Timing of surgery
  - Upfront cytoreduction
  - Interval debulking after neoadjuvant Chemo

Advanced Ovarian Cancer

Interval debulking

Neoadjuvant Chemotherapy with Interval Debulking vs Primary Debulking and Adjuvant Chemotherapy

EORTC 55971-GCG/NCIC-CTG



Primary endpoint:
Overall survival

Secondary endpoints:
PFS, QOL, complications

Vergote I, IGCS meeting 2008

Advanced Ovarian Cancer

Interval debulking

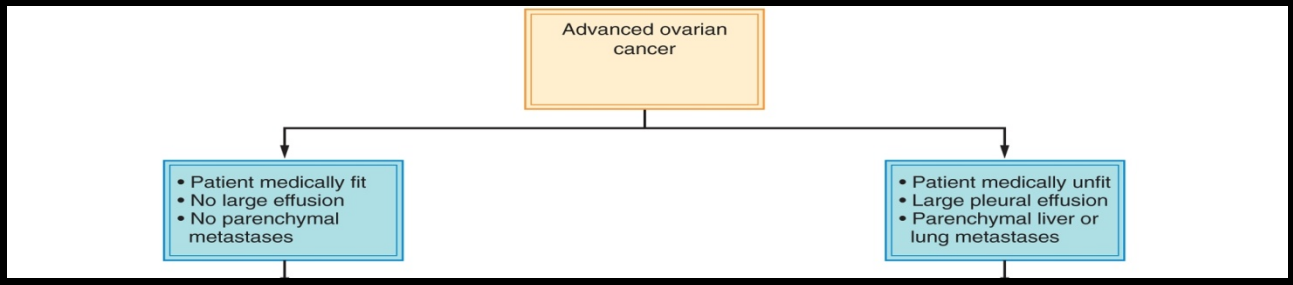
Neoadjuvant Chemotherapy with Interval Debulking vs Primary Debulking and Adjuvant Chemotherapy

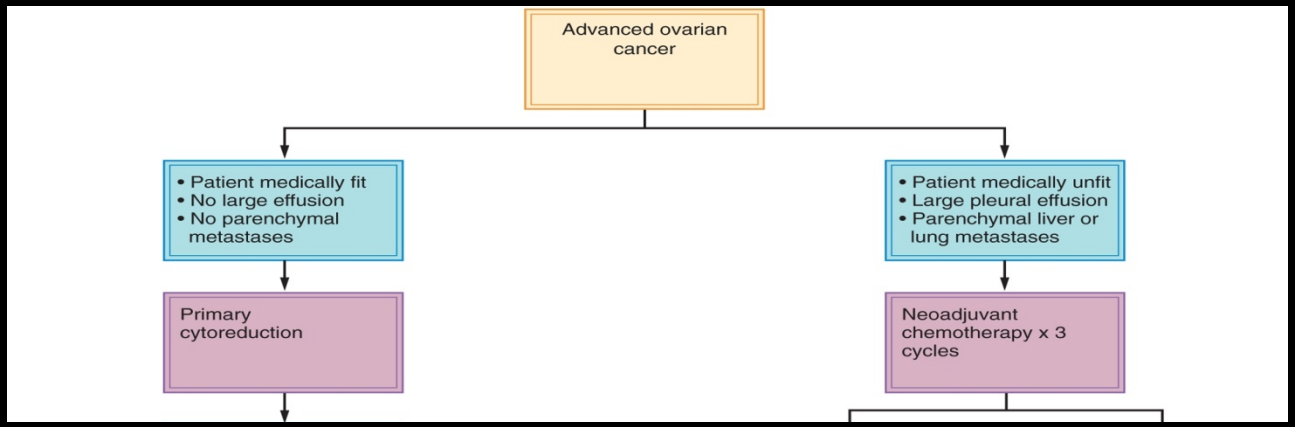
- A Large Phase III Multi-centre Randomised Trial To Determine the Impact of Timing of Surgery and Chemotherapy in Newly Diagnosed Patients with Advanced Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer (CHORUS) (MRC and RCOG, UK)

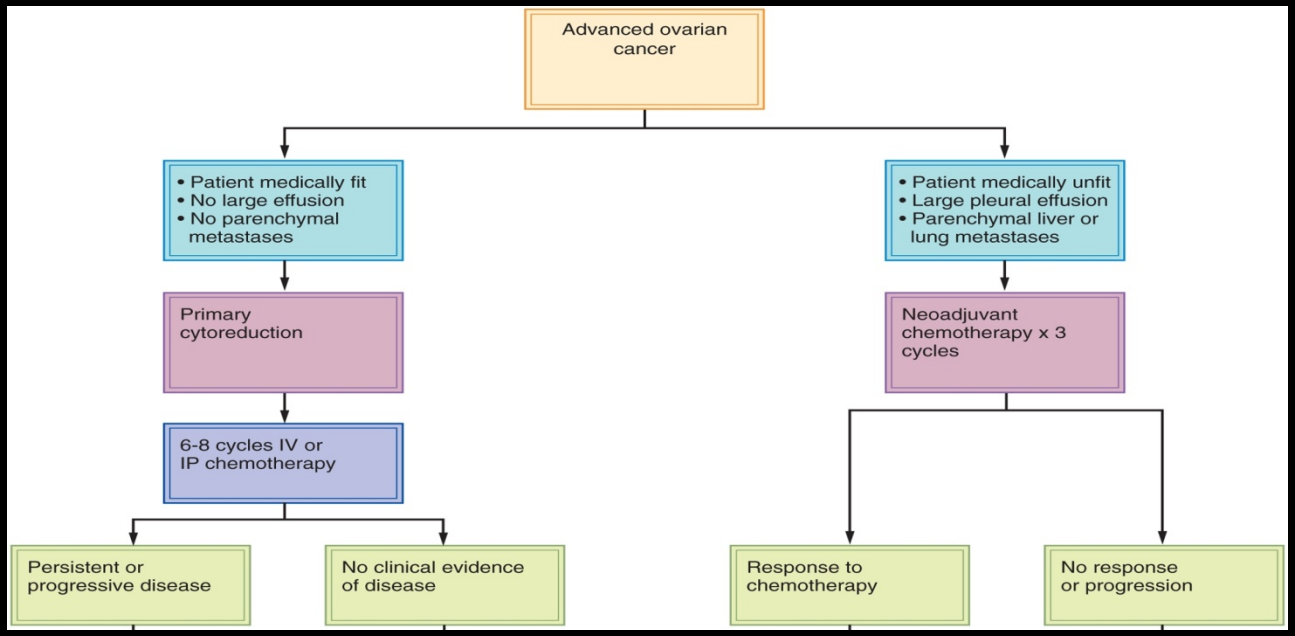
  -estimated accrual 550 patients

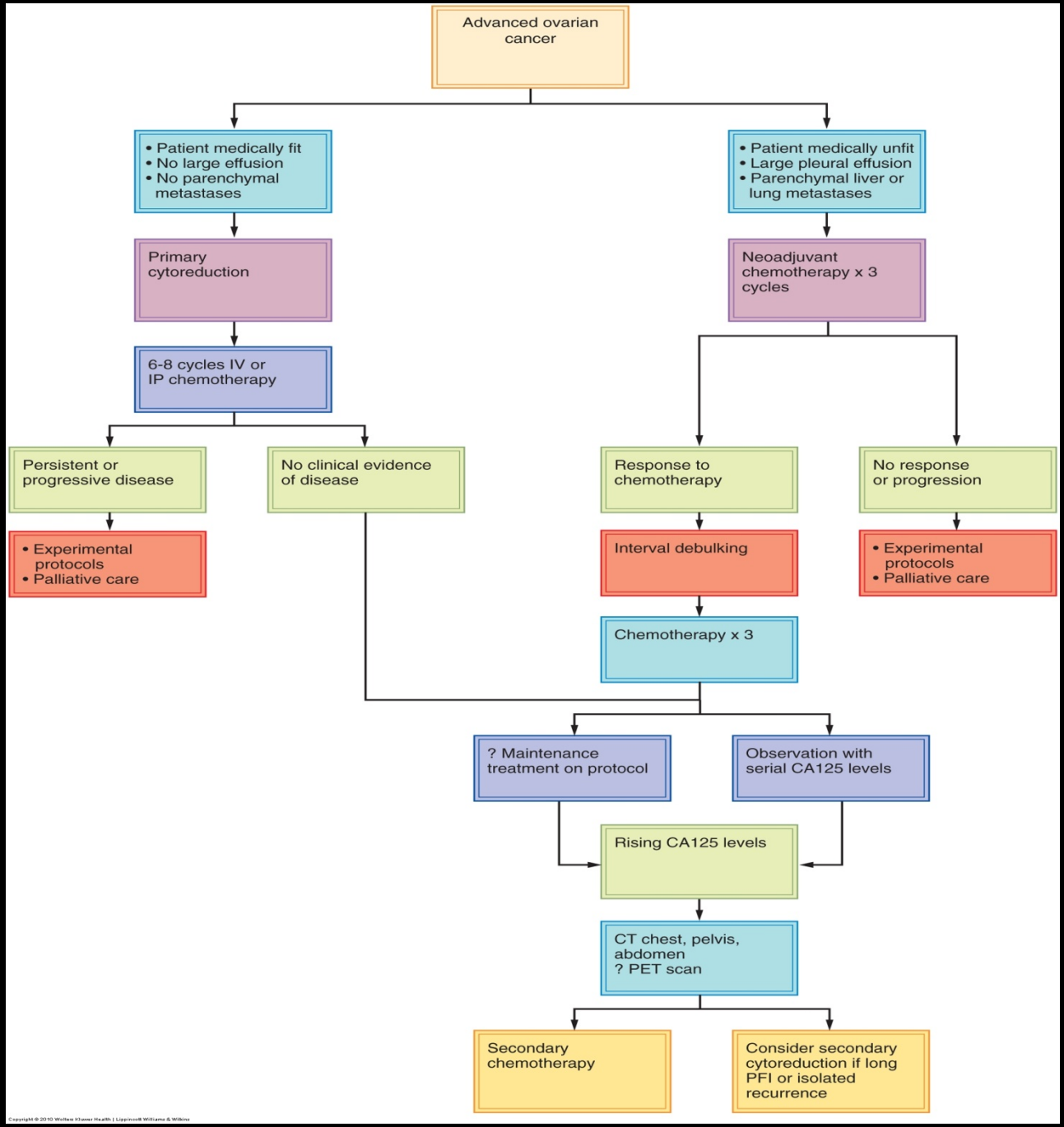
- Phase III Trial of Upfront Debulking Surgery vs Neoadjuvant Chemotheapy for Stage III/IV Ovarian, Tubal and Peritoneal Cancers- a Randomized Controlled Non-Inferiority Trial (Japanese Clinical Oncology Group, JCOG)

  -estimated accrual 300 patients


Advanced ovarian cancer
• Patient medically fit
• No large effusion
• No parenchymal metastases
• Patient medically unfit
• Large pleural effusion
• Parenchymal liver or lung metastases


Advanced ovarian cancer
• Patient medically fit
• No large effusion
• No parenchymal metastases
Primary cytoreduction
• Patient medically unfit
• Large pleural effusion
• Parenchymal liver or lung metastases
Neoadjuvant chemotherapy x 3 cycles


Advanced ovarian cancer
• Patient medically fit
• No large effusion
• No parenchymal metastases
• Patient medically unfit
• Large pleural effusion
• Parenchymal liver or lung metastases
Primary cytoreduction
Neoadjuvant chemotherapy x 3 cycles
6-8 cycles IV or IP chemotherapy
Persistent or progressive disease
No clinical evidence of disease
Response to chemotherapy
No response or progression



Factors That Impact Survival

- Age
- Performance status
- FIGO stage IIIC-IV vs IIB-IIIB
- Ascites
- Grade 2/3 vs 1
- Residual tumor

du Bois A et al., *Cancer* 115:1234, 2009

Advanced Stage Ovarian Cancer Patients

- Patients who are acceptable surgical candidates should undergo primary cytoreductive surgery with maximal surgical effort
- Surgery should be performed at centers with expertise
- Neoadjuvant chemotherapy can be given first to advanced age patients and patients with poor performance status to decrease morbidity
- Patients who have not had a maximal attempt at cytoreduction with initial surgery may benefit from interval debulking if they have a response to chemotherapy

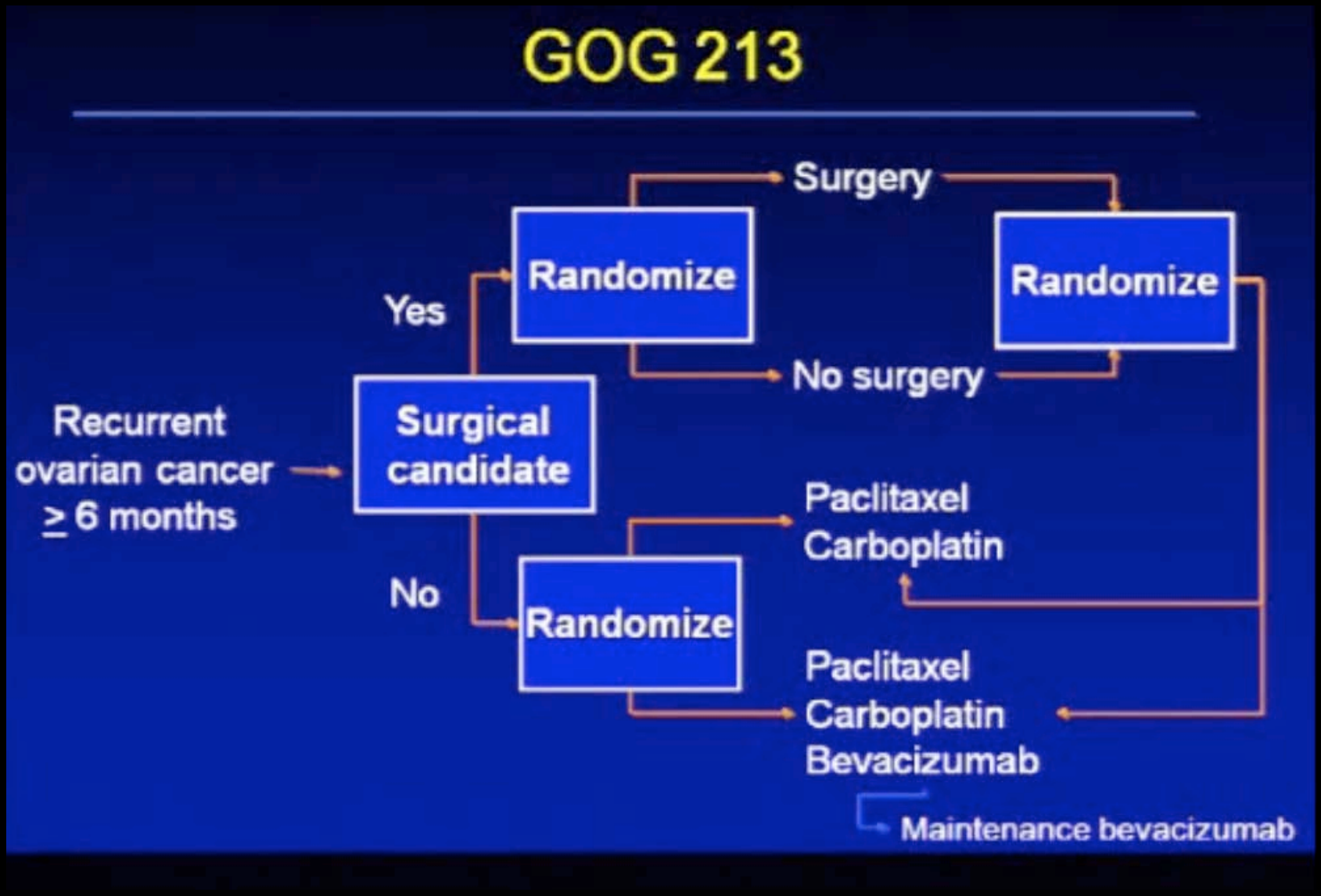
Secondary Cytoreduction

- Any benefit?
- Patients Selection?

Secondary Cytoreduction: Who Benefits?

Variable	*Median survival (mos)*	*p-value*
Disease free interval		0.004
6-12 months	30	
13-30 months	39	
> 30 months	51	
Number of recurrence sites		0.01
Single site	60	
Multiple sites	42	
Carcinomatosis	28	
Residual disease after surgery		0.001
≤ 0.05 cm	56	
> 0.05 cm	27	

Chi *Cancer* 106:1933 2006



ASCO 2008, (Virtual Meeting, www.Asco.org)

MERCI

SÉMINAIRE DE CHIRURGIE GYNÉCOLOGIQUE

niveau 2

Oncologie mammaire et pelvienne

DAKAR - du 6 au 10 JUIN 2011

Faculté de Médecine de Pharmacie et d'Odontologie
Université Cheikh Anta Diop
Hôpital de Pikine

Cancer de l'Ovaire

Pr Frédéric Goffin, MD, PhD

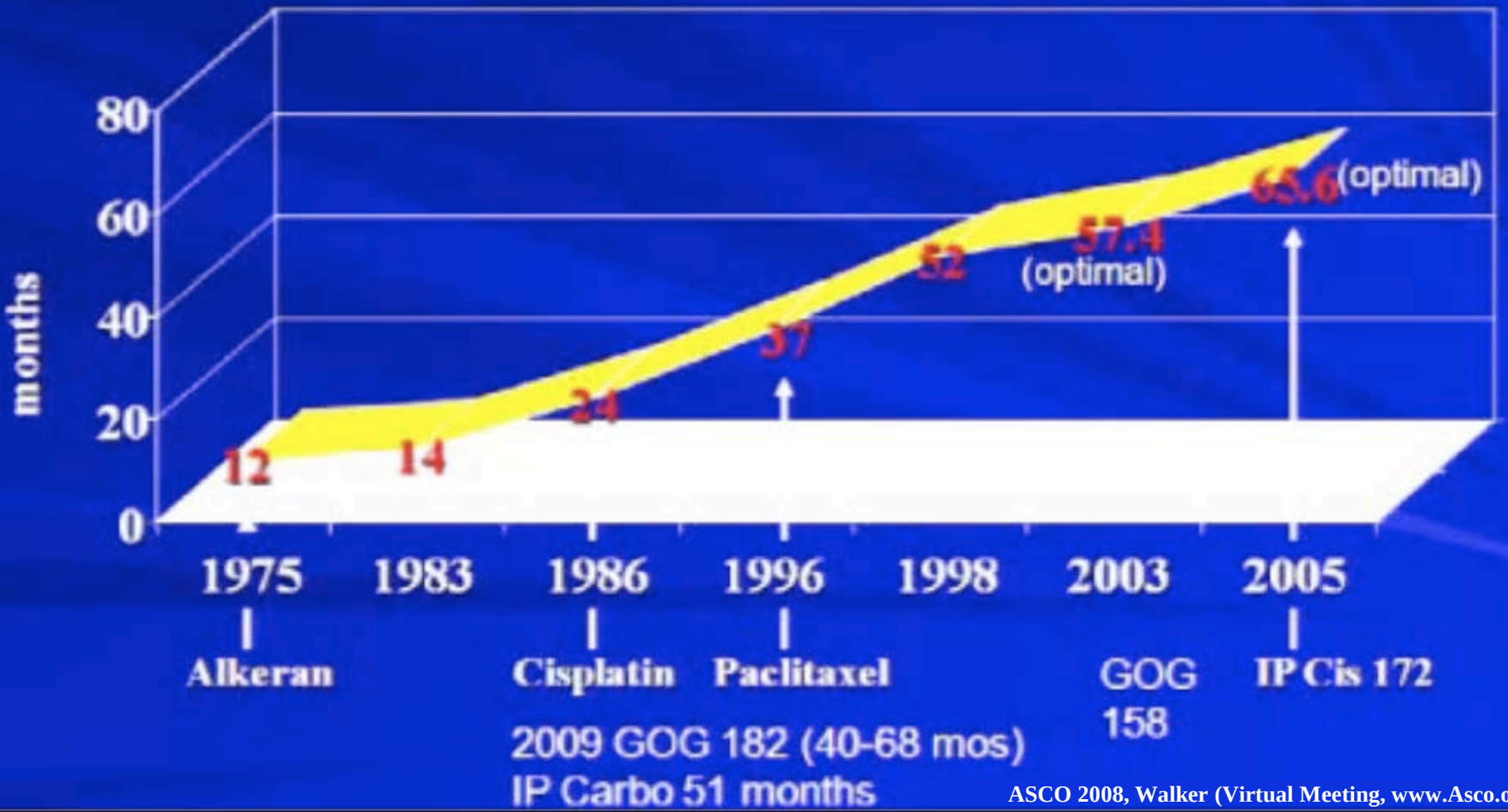
Hôpital de la Citadelle
Département of Gynecologie & Obstetrique
Université of Liège

MINISTERE DE LA SANTE
ET DE LA PREVENTION

CANCER DE L'OVAIRE
Chimiothérapie de première ligne

Advanced Ovarian Cancer

Median Survival: 1975 - 2009



ASCO 2008, Walker (Virtual Meeting, www.Asco.org)

Ovarian Cancer
Chemotherapy for Early Stages

COMBINED ANALYSIS (ACTION/ICON-1 TRIALS)

International Collaborative Ovarian Neoplasm Trial 1 and Adjuvant ChemoTherapy In Ovarian Neoplasm Trial: Two Parallel Randomized Phase III Trials of Adjuvant Chemotherapy in Patients With Early-Stage Ovarian Carcinoma

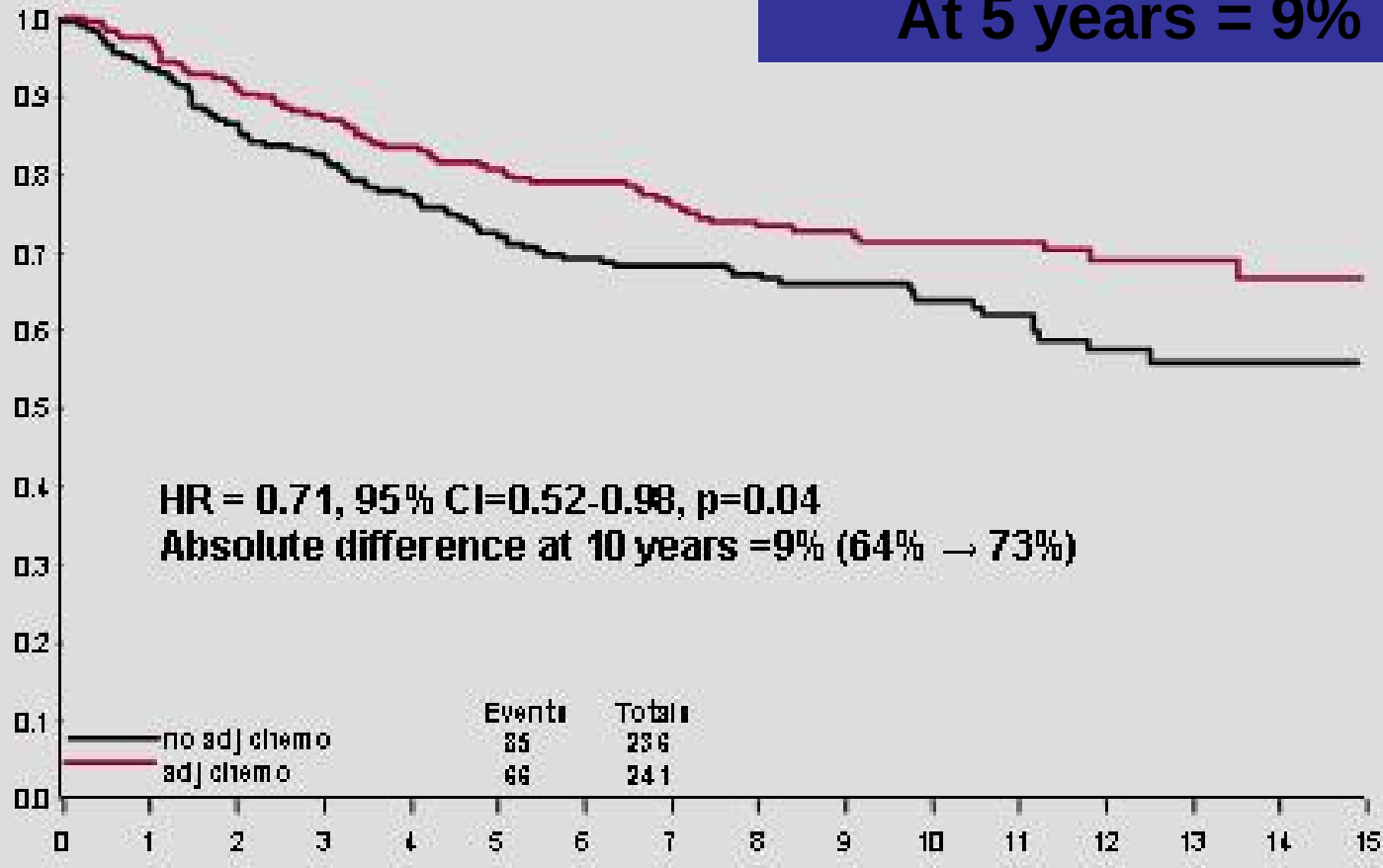
International Collaborative Ovarian Neoplasm 1 (ICON1) and European Organisation for Research and Treatment of Cancer Collaborators–Adjuvant ChemoTherapy In Ovarian Neoplasm (EORTC–ACTION)[1]

Journal of the National Cancer Institute, Vol. 95, No. 2, January 15, 2003

Overall Survival- all women

MRC Clinical Trials Unit

At 5 years = 9%



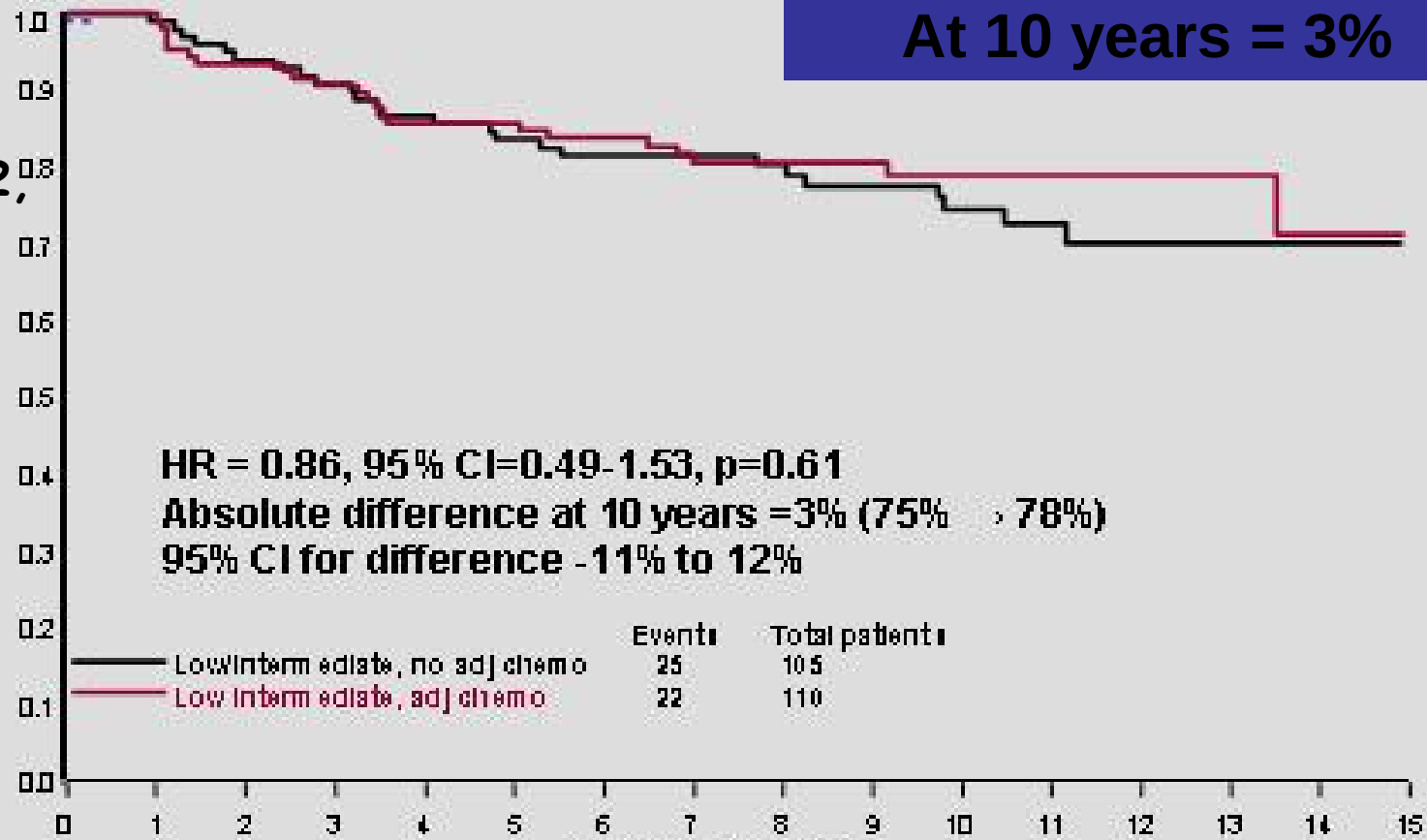
PATIENTS at Risk

no adj chemo	236	213	195	184	170	158	146	134	118	101	80	63	41	27	15	6
adj chemo	241	231	215	202	190	179	172	151	128	111	91	69	52	39	17	8

Overall survival: low/intermediate stage I risk group

At 10 years = 3%

IA/B G1/2, IC G1



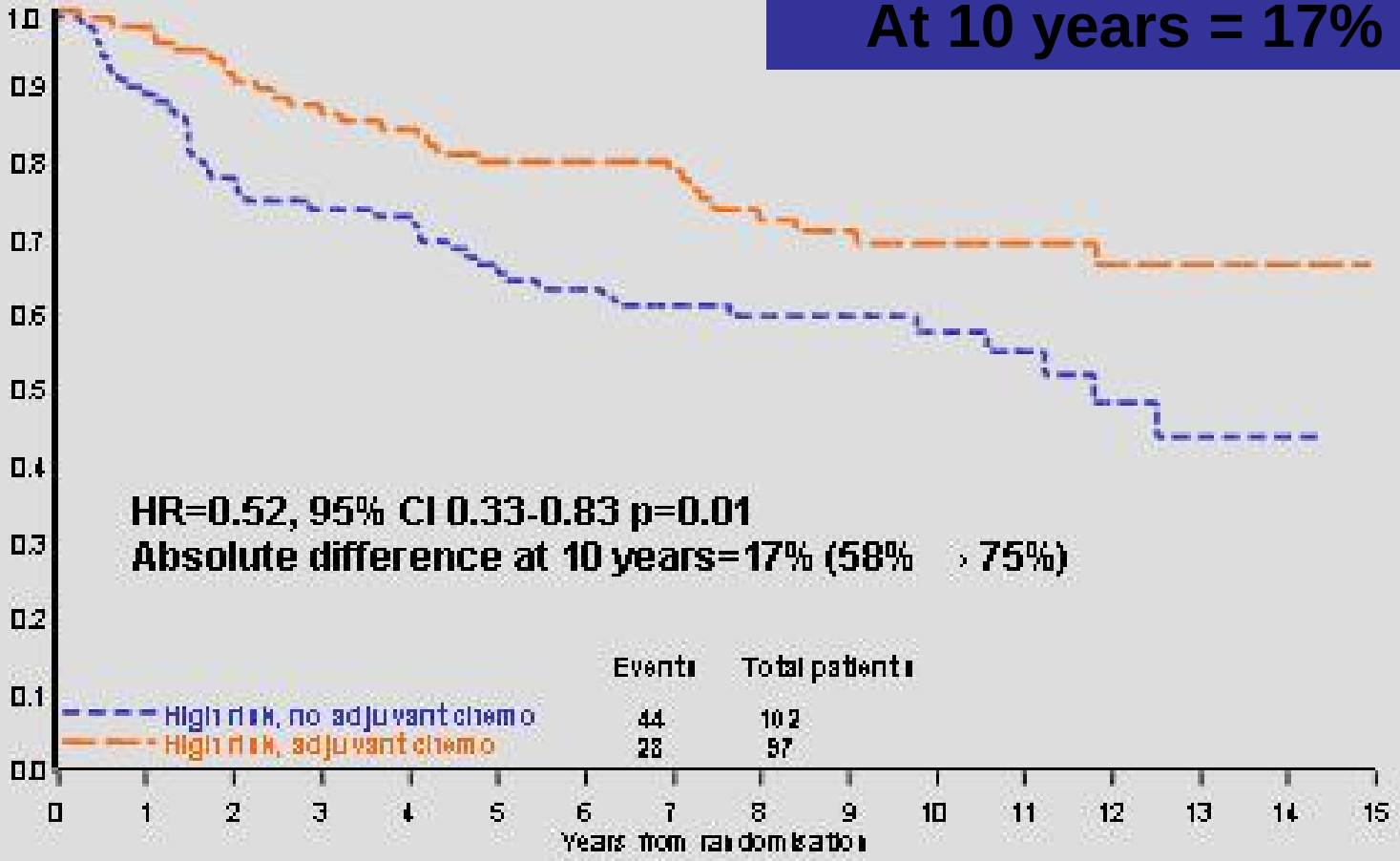
PATIENTS at Risk

IA/IB G1/2, IC G1, no adj	99	88	80	71	55	33	14	5
IA/IB G1/2, IC G1, adj	107	96	86	70	55	31	14	1

Overall survival: high risk stage I risk group

At 10 years = 17%

IA/B G3, IC G2/3, clear cell



PATIENTS at Risk

IA/B G3, IC G2/3, clear cell, no adj	89	73	63	50	34	19	7	0
IA/B G3, IC G2/3, clear cell, adj	96	82	75	67	46	31	19	4

EARLY-STAGE DISEASE

FIGO Ia-Ib, grade I
No clear cell
Complete staging

→ **No treatment**

FIGO Ia-Ib, grade II-III
FIGO Ic, all grades
All stage clear-cell

→ **chemotherapy**

- **chemotherapy = carboplatin +/- paclitaxel x 6 cycles**

UNANSWERED QUESTIONS

- **Addition of paclitaxel ?:** **regimens, including taxanes, have not been studied in this patient population; therefore, extrapolation may not be appropriate**

- **Optimal length of chemotherapy ?:** **6 cycles? Less or more?**

Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: A Gynecologic Oncology Group study

Jeffrey Bell [a,*,1], Mark F. Brady [b], Robert C. Young [c], Janice Lage [d], Joan L. Walker [e], Katherine Y. Look [f], G. Scott Rose [g], Nick M. Spirtos [h]

GO 102(2006); 432-439

- **457 patients**
- **Pas de difference entre 3 versus 6 cycles**
- **plus de toxicités**

Ovarian Cancer
Chemotherapy for Advanced stages

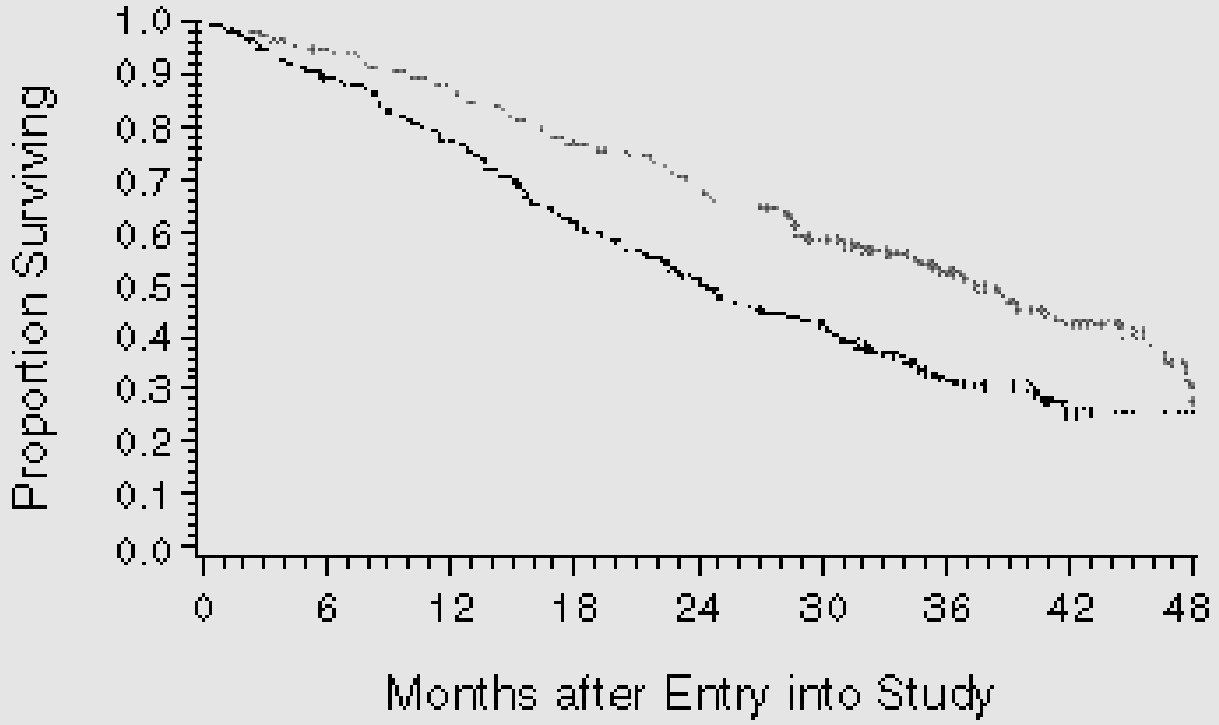
Basis for Current Standard: Systemic Therapy

- Studies showing paclitaxel/cisplatin superior to cyclophosphamide/cisplatin
  - GOG Protocol 111[1]
  - EORTC-NCIC OV 10[2]
- Studies showing paclitaxel/carboplatin at least equivalent to paclitaxel/cisplatin in efficacy
  - AGO Trial[3]
  - GOG Protocol 158[4]

1. McGuire WP, et al. N Eng J Med .1996;334:1-6.
2. Piccart MJ, et al. J Natl Cancer Inst. 2000;92:699-708.
3. DuBois A, et al. J Natl Cancer Inst. 2003;95:1320-1329.
4. Ozols RF, et al. J Clin Oncol. 2003;21:3194-3200.

First-Line Chemotherapy

-GOG 111, Phase III , McGuire, NEJM, 1996-



Treatment	No. Alive	No. Dead	Total	Median Survival (mo.)
—— Cisplatin + cyclophosphamide	65	137	202	24
- - - - Cisplatin + paclitaxel	86	98	184	38

Standard of Care: 2011

- Maximum attempt at surgical cytoreduction
- Chemotherapy following surgery
- Regimen of choice
  - Paclitaxel 175 mg/m^2/3 hrs IV +
  - Carboplatin AUC 6-7.5 IV
  - Repeat every 3 wks for 6 cycles

Recurrent/Persistent Ovarian Cancer: Scope of the Problem

Long-term control of disease not achieved in most patients

Disease Stage	Relapse Risk, %
Limited (low risk)	10
Limited (high risk)	20
Advanced (small volume)	60-70
Advanced (large volume)	80-85

Overall, 62% of patients will have either recurrent or persistent disease

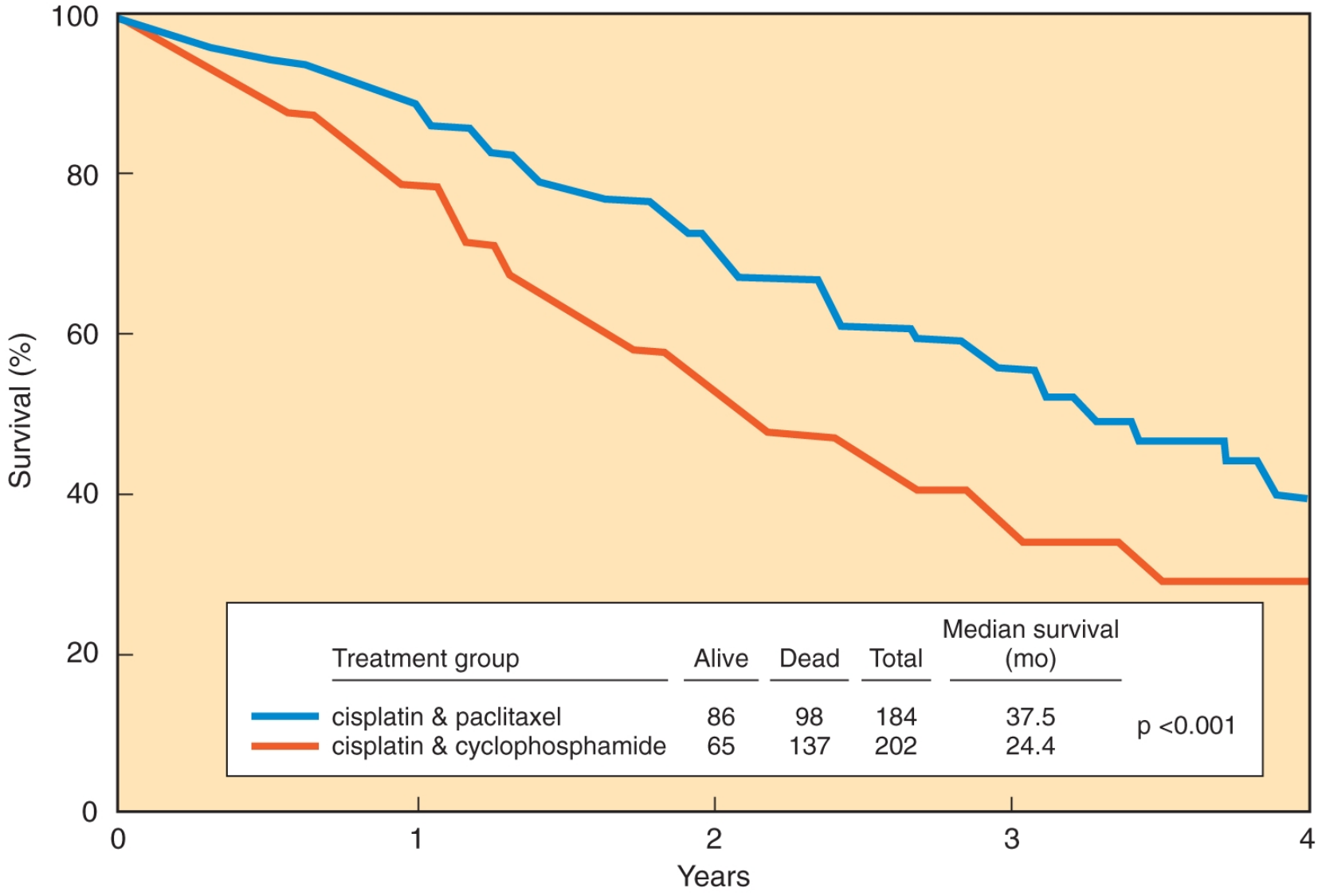
Candidates for further therapy

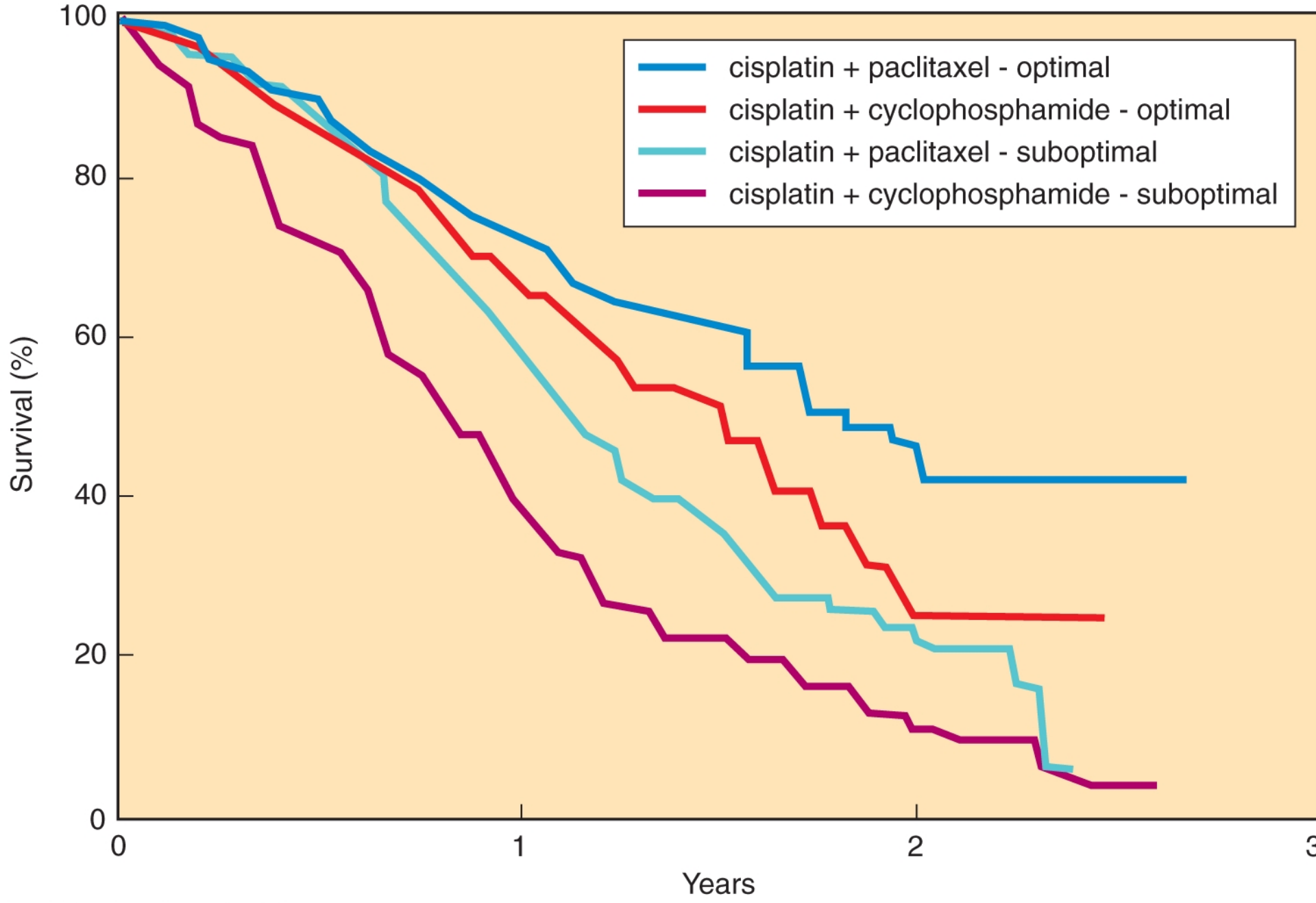
Thigpen JT, personal communication.

Ovarian Cancer: Initial Chemotherapy

- Standard *frontline* chemotherapy is
  - paclitaxel 175 mg/m^2 plus
  - carboplatin AUC 5-7,
  - every 21 days for 6 cycles
- Result of several studies over last decade
  - GOG 111[1] and OV 10[2]:
    - paclitaxel/cisplatin vs cyclophosphamide/cisplatin
  - GOG 158[3] and AGO OVAR-3[4]:
    - carboplatin instead of cisplatin

1. McGuire WP, et al. N Engl J Med. 1996;334:1-6. 2. Piccart MJ, et al. J Natl Cancer Inst. 2000;92:699-708.
3. Ozols RF, et al. J Clin Oncol. 2003;21:3194-3200. 4. du Bois AD, et al.
J Natl Cancer Inst. 2003;95:1320-1329.





GYNECOLOGIC CANCER INTERGROUP

An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

AGO ANZGOG EORTC GEICO GINECO GOG JGOG MRC/NCRI NCI NCIC CTG NSGO RTOG SGCTG

Third International Ovarian Cancer Conference Baden-Baden September 3-5, 2004.

4-A4: Which regimen / kind of regimens can be regarded as standard comparator for future first-line trials?

- *Within a given trial the chemotherapy regimen should be standardized and consistent with respect to drugs, dose, and schedule.*
- *The recommended standard comparator for trials on medical treatment in advanced ovarian cancer (FIGO IIB-IV) is carboplatin-paclitaxel*
- *The recommended regimen is carboplatin with a dose of AUC 5 - 7.5 and paclitaxel 175 mg/m^2/ 3h given every three weeks for 6 courses*
- *The recommended standard in early stage ovarian cancer (FIGO I-IIA) patients in whom adjuvant chemotherapy is indicated should contain at least carboplatin AUC 5 -7.5*

Level of acceptance: 13/13

- Standard Front line Therapy

- Alternative Taxane Therapy?
- Will Adding a third Drug Help?
- What About IP Therapy?
- Will Adding a Targeted Therapy Help?

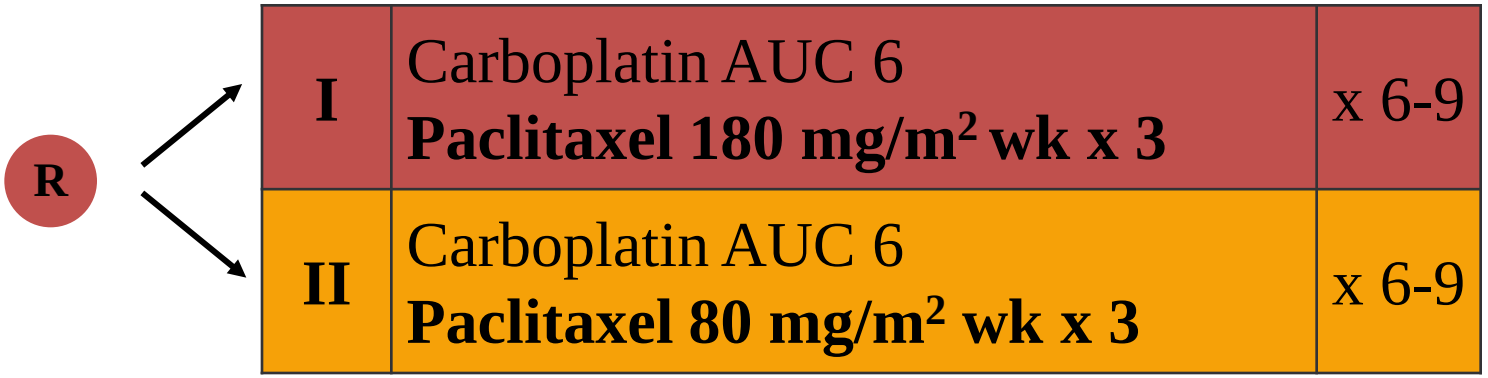
Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial

*Noriyuki Katsumata, Makoto Yasuda, Fumiaki Takahashi, Seiji Isonishi, Toshiko Jobo, Daisuke Aoki, Hiroshi Tsuda, Toru Sugiyama, Shoji Kodama, Eizo Kimura, Kazunori Ochiai, Kiichiro Noda, for the Japanese Gynecologic Oncology Group**

Lancet 2009; vol 374; october 17; 1331-1338

- FIGO II, III et IV

JGOG: Dose-Dense Wkly Paclitaxel in Stage II-IV



Dose-dense paclitaxel associated with greater hematologic toxicity, and fewer patients completed all protocol therapy

Accrual: 637 patients (631 intent to treat)

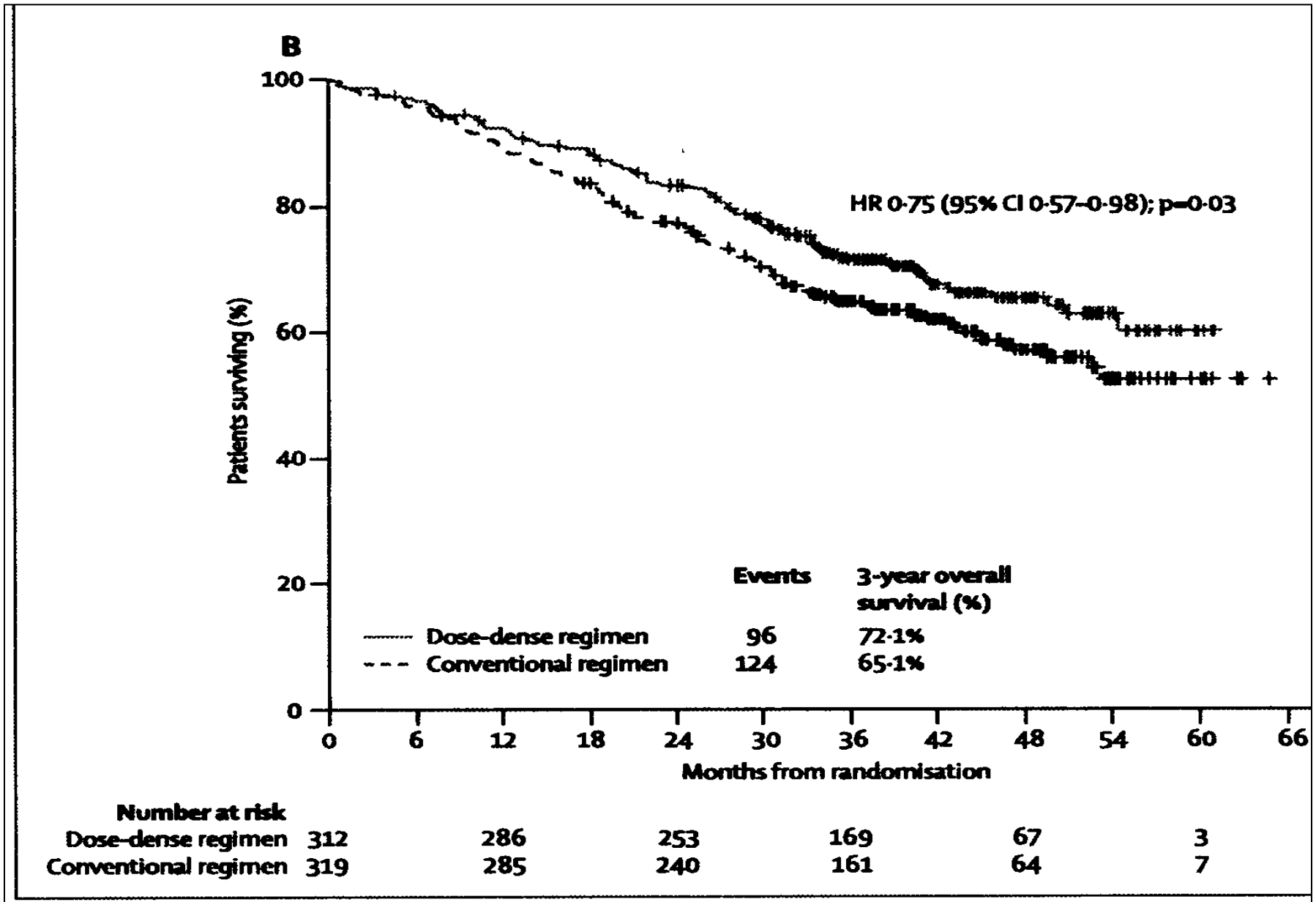
Katsumata N, et al. Lancet. 2009;374:1331-1338.

JGOG: Dose-Dense Wkly Paclitaxel

Treatment Arm	n	Median PFS (mos)	*P* Value
Carboplatin AUC 6 **Paclitaxel 180 mg/m^2 3 x wkly**	319	17.2	.015 (HR: 0.714 (95% CI: 0.581-0.879)
Carboplatin AUC 6 **Paclitaxel 80 mg/m^2/wk x 3**	312	28.0	

- OS at 3 yrs: wkly (72.1%) > 3 wkly (65.1%); HR: 0.75 (95% CI: 0.57-0.98; *P* = .03)

Katsumata N, et al. Lancet. 2009;374:1331-1338.


B
100
80
60
40
20
0
Patients surviving (%)
HR 0·75 (95% CI 0·57–0·98); p=0·03
Events
3-year overall survival (%)
Dose-dense regimen
96
72·1%
Conventional regimen
124
65·1%
0
6
12
18
24
30
36
42
48
54
60
66
Months from randomisation
Number at risk
Dose-dense regimen 312 286 253 169 67 3
Conventional regimen 319 285 240 161 64 7

	Dose-dense regimen group (n=312)	Conventional regimen group (n=314)	p value
Neutropenia	286 (92%)	276 (88%)	0·15
Thrombocytopenia	136 (44%)	120 (38%)	0·19
Anaemia	214 (69%)	137 (44%)	<0·0001
Febrile neutropenia	29 (9%)	29 (9%)	1·00
Nausea	32 (10%)	36 (11%)	0·70
Vomiting	9 (3%)	11 (4%)	0·82
Diarrhoea	10 (3%)	8 (3%)	0·64
Fatigue	15 (5%)	8 (3%)	0·14
Arthralgia	3 (1%)	5 (2%)	0·72
Myalgia	2 (1%)	4 (1%)	0·69
Neuropathy (motor)	15 (5%)	12 (4%)	0·56
Neuropathy (sensory)	21 (7%)	20 (6%)	0·87

Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0.[18]

Table 3: Frequency of grade 3 or 4 adverse events

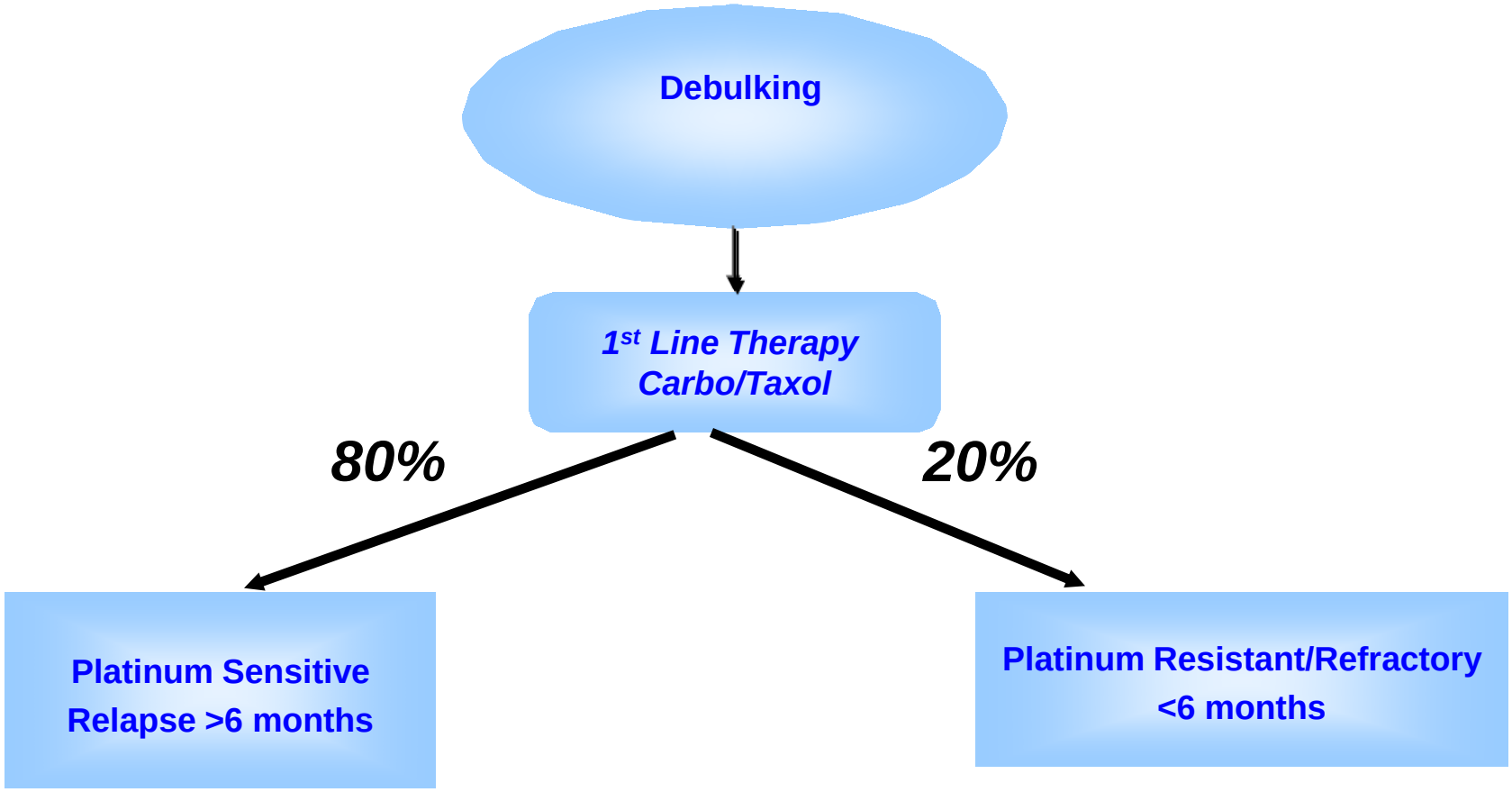
- **ADMINISTRATION:**

- **hopital de jour; mise en place Port-a-cath**
- **carboplatine AUC 5 en 1h au J1; paclitaxel (taxol®) 80mg/m² en 1h; ceci au J1-8-15, toutes les 3 semaines**

- **!!!! PRÉMÉDICATION: corticostéroïdes (dexamethasone 10mg) + anti-histaminique (fenistil), la veille au soir et le matin de la chimio**

Will Adding a Third Drug Help?

Standard of Care: 2011



CONSOLIDATION

- **1) whole abdomen radiotherapy**
- **2) intraperitoneal chromic phosphate**
- **3) radio-immunotherapy**
- **4) high-dose chemotherapy with hematopoietic support**

➔ no benefits

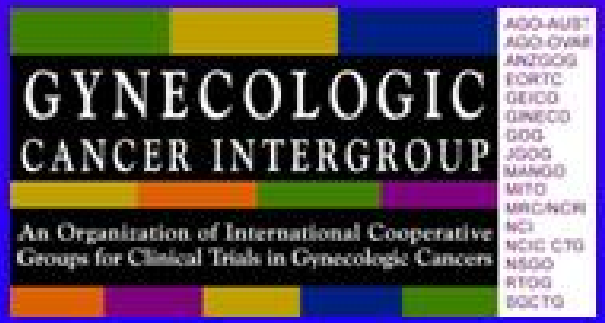
Other Recent 3-Drug Frontline Trials

Group(s)	Standard Arm	Experimental Arm (s)	N	Benefit
AGO/GINECO[1]	Paclitaxel/carboplatin (TC)	TC epirubicin	1282	NS
NSGO/EORTC NCIC CTG[2]	Paclitaxel/carboplatin (TC)	TC epirubicin	888	NS
Bolis[3]	Paclitaxel/carboplatin (TC)	TC topotecan	326	NS
AGO/GINECO[4]	Paclitaxel/carboplatin (TC)	TC → topotecan consolidation	1308	NS
AGO/GINECO NSGO[5]	Paclitaxel/carboplatin (TC)	TC gemcitabine	1742	NS
NCIC CTG EORTC/GEICO[6]	Paclitaxel/carboplatin (TC)	Cis topotecan → TC	819	NS

1. Du Bois A, et al. J Clin Oncol. 2006;24:1127-1135. 2. Kristensen G, et al. ASCO 2002. Abstract 805.
3. Scarfone G, et al. ASCO 2006. Abstract 5003. 4. Pfisterer J, et al. J Natl Cancer Inst. 2006;98:1036-1045.
5. Herrstedt J, et al. ASCO 2009. Abstract LBA5510. 6. Hoskins PJ, et al. ASCO 2008. Abstract LBA5505.

GOG0182-ICON5:

Phase III Randomized Trial of Paclitaxel and Carboplatin *vs* Combinations with Gemcitabine, PEG-Lipososomal Doxorubicin, or Topotecan in Patients with Advanced-Stage Epithelial Ovarian or Primary Peritoneal Carcinoma



Michael A Bookman, MD
on behalf of GCIG, including GOG, MRC, SWOG, ANZGOG, M Negri, and NCI-CTSU

Fox Chase Cancer Center
Philadelphia, PA

Proc ASCO 25: Abstract 5002

-4312 patients

GOG0182-ICON5: Schema

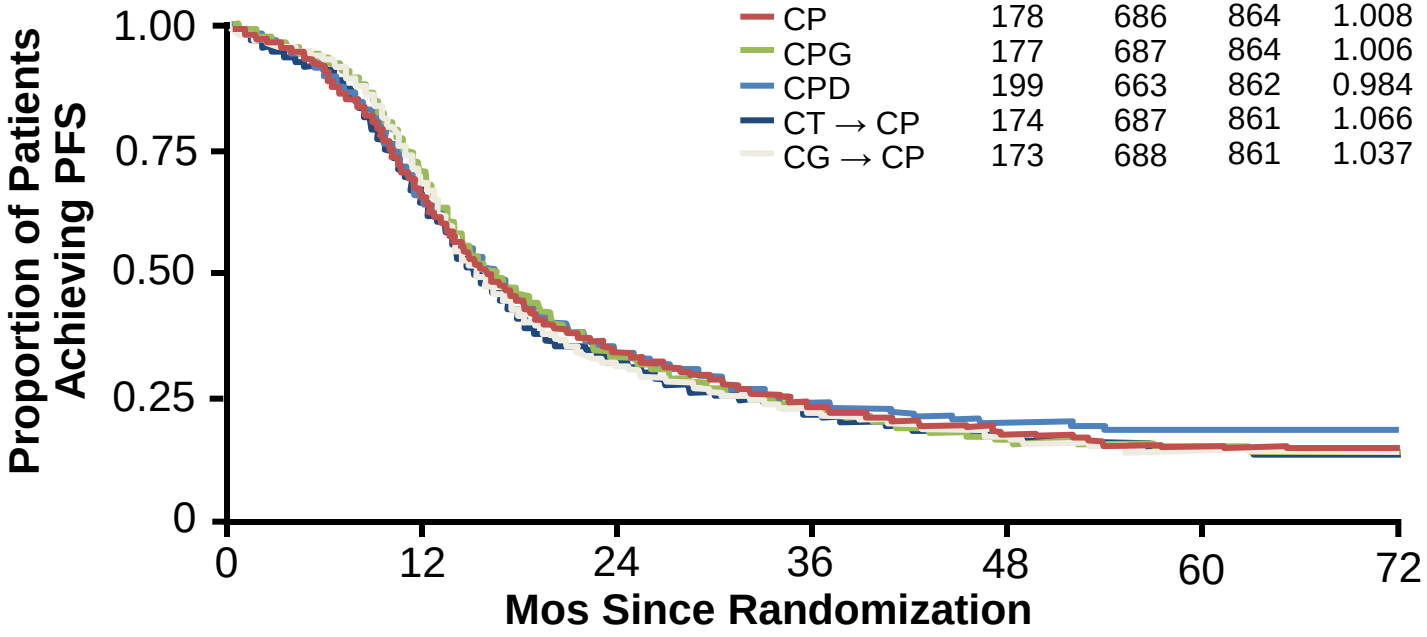
RANDOMIZE

I	Carboplatin AUC 6 (d1) Paclitaxel 175 mg/m^2 (d1)	x8
II	Carboplatin AUC 5 (d1) Paclitaxel 175 mg/m^2 (d1) Gemcitabine 800 mg/m^2 (d1,8)	x8
III	Carboplatin AUC 5 (d1) Paclitaxel 175 mg/m^2 (d1) Doxil 30 mg/m^2 (d1, every other cycle)	x8
IV	Carboplatin AUC 5 (d3) Topotecan 1.25 mg/m^2 (d1-3)	x4
V	Carboplatin AUC 6 (d8) Gemcitabine 1 g/m^2 (d1,8)	x4

→ Carboplatin AUC 6 (d1)
Paclitaxel 175 mg/m^2 (d1) x4

Proc ASCO 25: Abstract 5002

GOG0182-ICON5: PFS



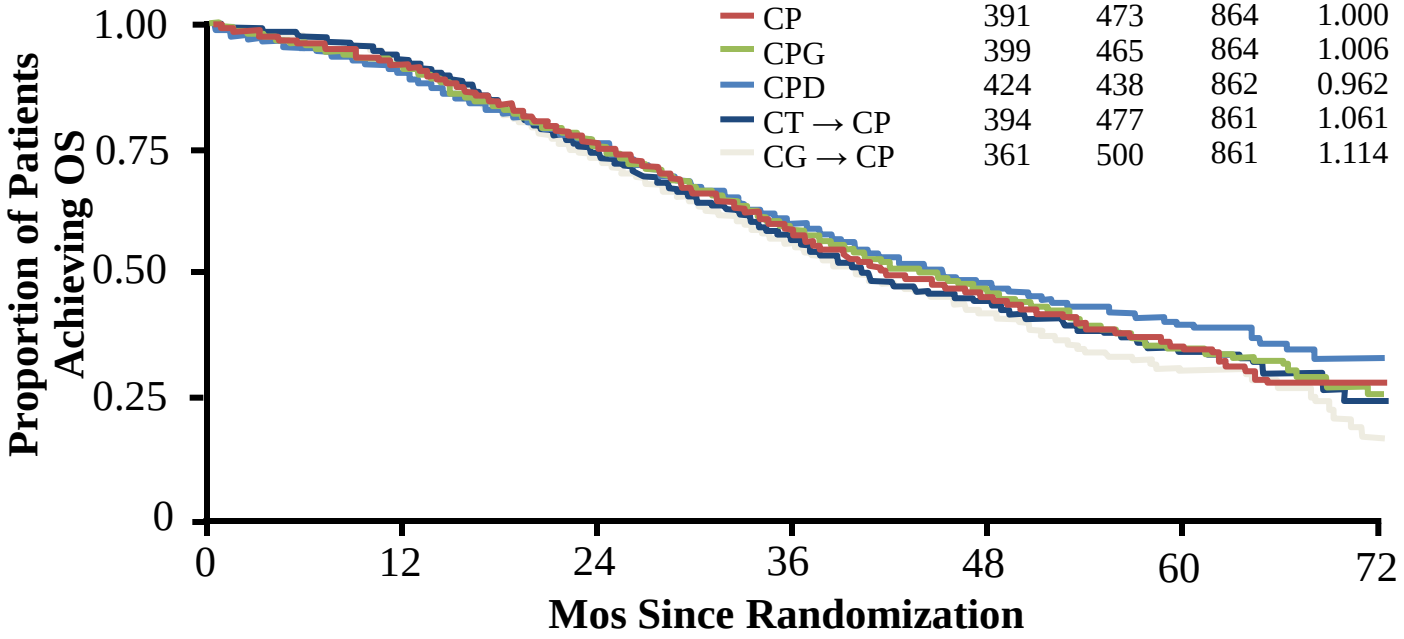
Treatment	Events: Cancer	Events: Prog	Events: Total	Adjusted HR: HR	Adjusted HR: (95% CI)	*P*
CP	178	686	864	1.008	Reference Arm	
CPG	177	687	864	1.006	(0.924-1.143)	.610
CPD	199	663	862	0.984	(0.884-1.095)	.796
CT → CP	174	687	861	1.066	(0.958-1.186)	.239
CG → CP	173	688	861	1.037	(0.932-1.253)	.503

Patients at risk, n

CP	864	565	284	174	80	27
CPG	864	579	275	153	68	27
CPD	862	574	277	162	63	32
CT → CP	861	547	259	154	67	27
CG → CP	861	563	255	153	78	23

 Bookman MA, et al. J Clin Oncol. 2009;27:1419-1425.

GOG0182-ICON5: Overall Survival



Treatment	Events: Alive	Events: Dead	Total	Adjusted HR: HR	Adjusted HR: (95% CI)	*P*
CP	391	473	864	1.000	Reference arm	
CPG	399	465	864	1.006	(0.895-1.144)	.923
CPD	424	438	862	0.962	(0.836-1.085)	.462
CT → CP	394	477	861	1.061	(0.925-1.194)	.447
CG → CP	361	500	861	1.114	(0.982-1.264)	.093

Patients at Risk, n

CP	864	780	625	426	203	72
CPG	864	780	622	424	214	70
CPD	862	762	592	425	209	80
CT → CP	861	778	593	423	200	73
CG → CP	861	773	589	395	203	66

 Bookman MA, et al. J Clin Oncol. 2009;27:1419-1425.

- **<u>ADMINISTRATION</u>:**

- **hopital de jour; mise en place Port-a-cath**
- **carboplatine AUC 5 en 1h; paclitaxel (taxol®) 175mg/m² en 3h; ceci au J1,toutes les 3 semaines**

- **<u>!!!! PRÉMÉDICATION:</u> corticostéroïdes (dexamethasone 2Omg) + anti-histaminique (fenistil), la veille au soir et le matin de la chimio**

EFFETS SECONDAIRES:

- alopécie
- nausées, vomissements
- myélosuppression
- neurotoxicité
- arthralgies, myalgies
- réaction d’hypersensibilité
- asthénie, …

What About IP Therapy?

Role of IP Chemotherapy: Optimally Debulked Ovarian Cancer

GOG 104[1]	Improved outcome in CTX cisplatin-treated patients when cisplatin given IP (relative risk: 0.76)
GOG 114[2]	Improved outcome in patients when cisplatin administered IP (relative risk: 0.78)
GOG 172[3]	Improved outcome in patients when paclitaxel and cisplatin administered IP (relative risk: 0.73)

1. Alberts DS, et al. N Engl J Med. 1996;335:1950-1955.
2. Markman M, et al. J Clin Oncol. 2001;19:1001-1007.
3. Armstrong DK, et al. N Engl J Med. 2006;354:34-43.

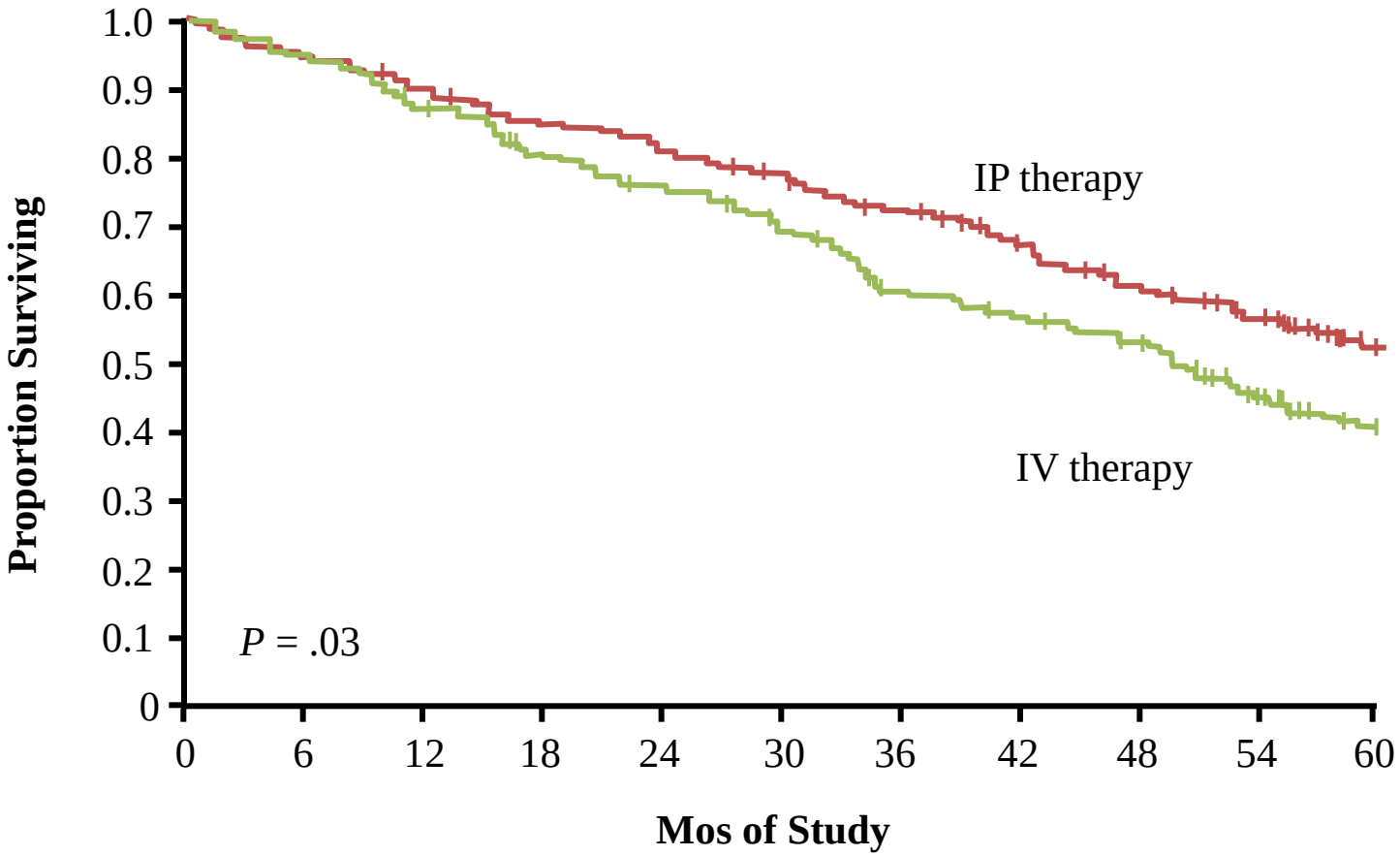
GOG 172: Survival

Outcome	IV	IP	RR	*P* Value
Median PFS, mos	18.3	23.8	0.80	.05
• Visible	15.4	18.3	0.81	
• Micro	35.2	37.6	0.80	
Median OS, mos	49.7	65.6	0.75	.03
• Visible	39.1	52.6	0.77	
• Micro	78.2	NA	0.69	

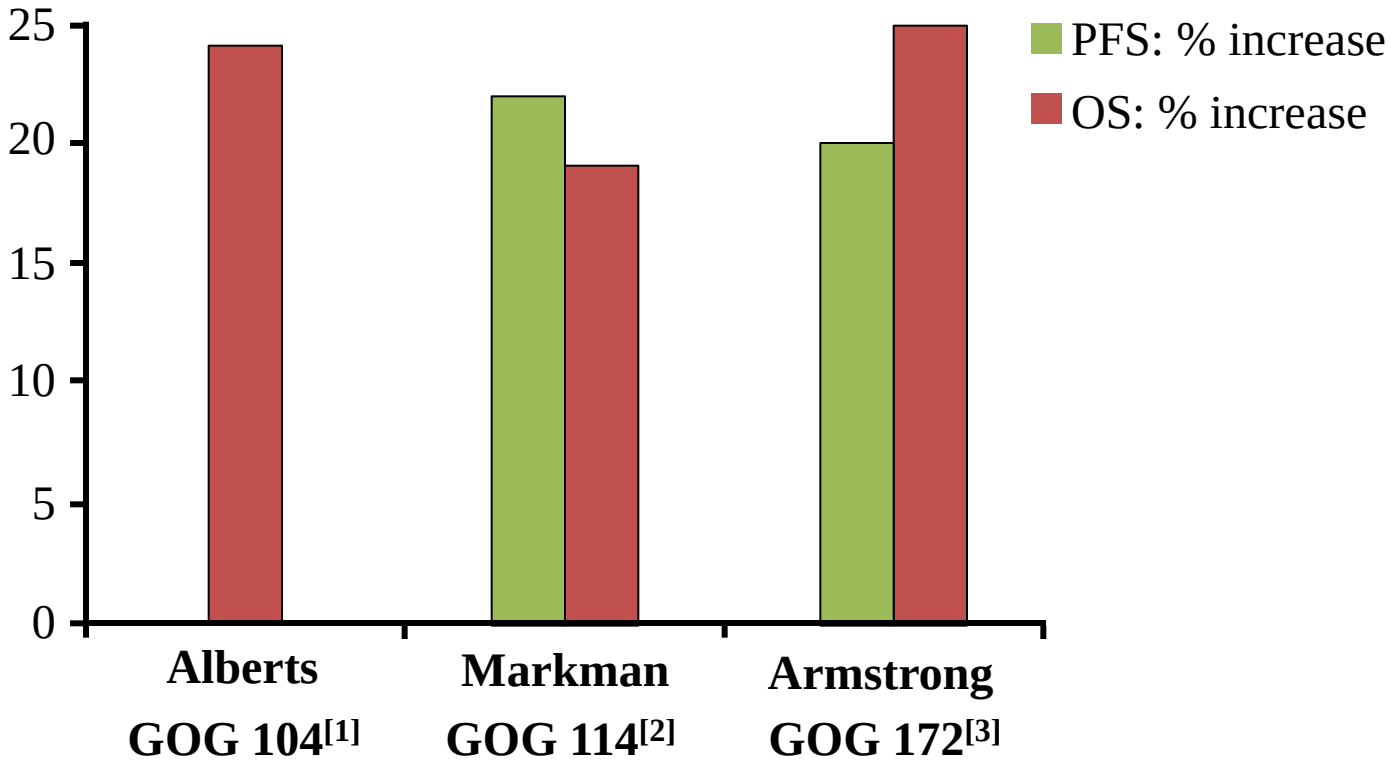
GOG 172: Survival

Outcome	IV	IP	RR	*P* Value
Median PFS, mos	18.3	23.8	0.80	.05
• Visible	15.4	18.3	0.81	
• Micro	35.2	37.6	0.80	
Median OS, mos	49.7	65.6	0.75	.03
• Visible	39.1	52.6	0.77	
• Micro	78.2	NA	0.69	

GOG 172: OS



IP Compared With IV Chemotherapy Phase III Trials



1. Alberts DS, et al. N Engl J Med. 1996;335:1950-1955. 2. Markman M, et al. J Clin Oncol. 2001;19:1001-1007. 3. Armstrong DK, et al. N Engl J Med. 2006;354:34-43.

Will Adding a Targeted Therapy Help?

Angiogenesis and invasion

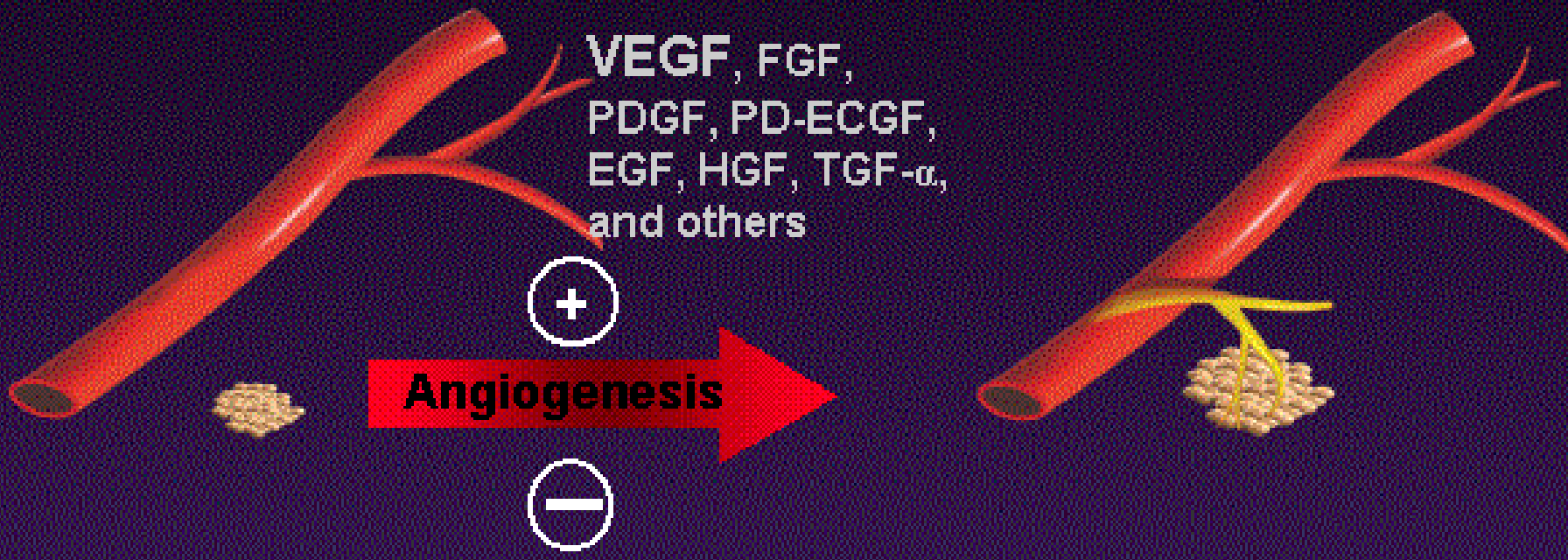
The major cause of death from cancer
is due to metastasis
resistant to conventional therapy

L. Vakaet, 2002

Angiogenic Switch

Stimulators

VEGF, FGF, PDGF, PD-ECGF, EGF, HGF, TGF-α, and others

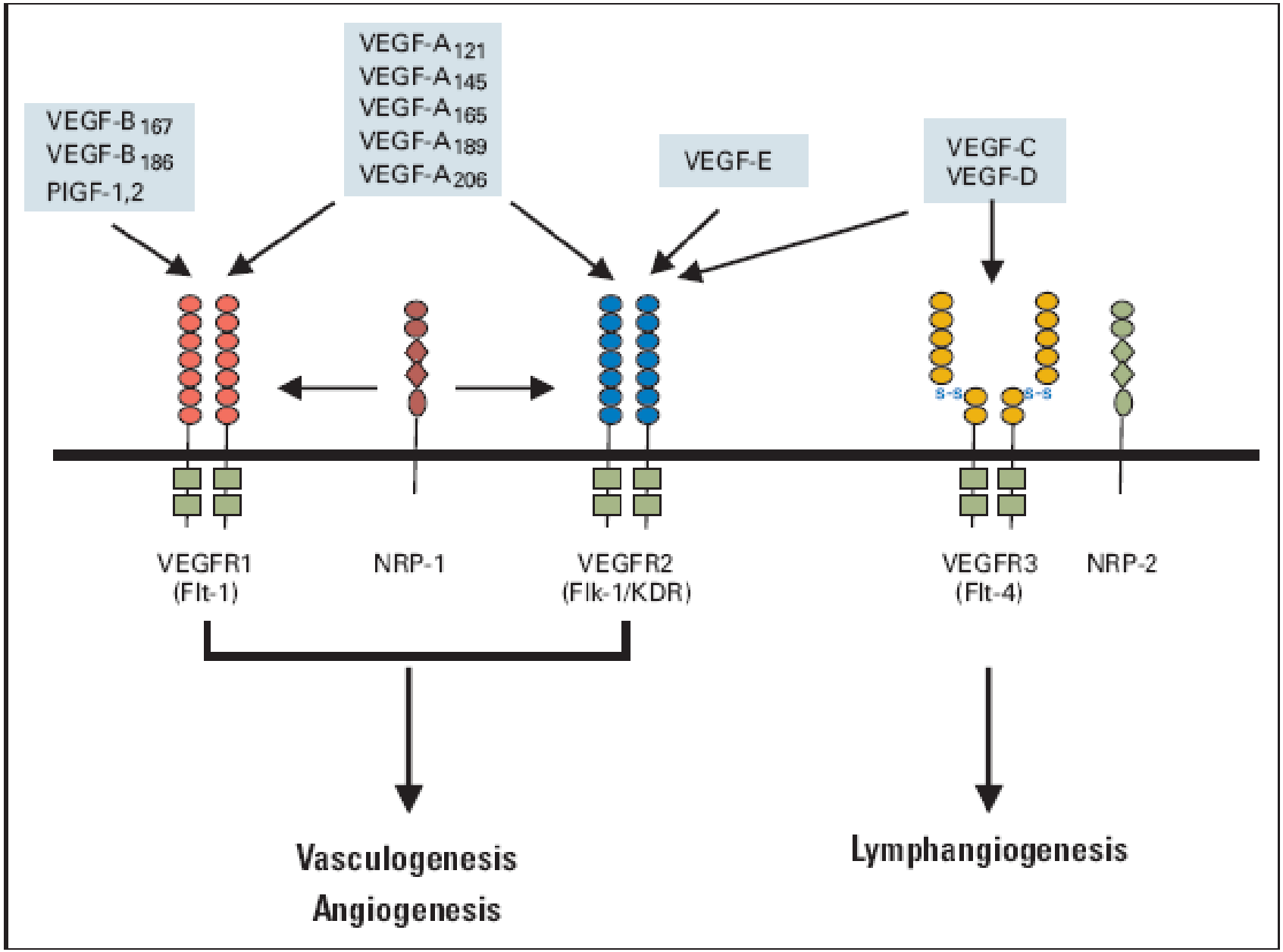


Inhibitors

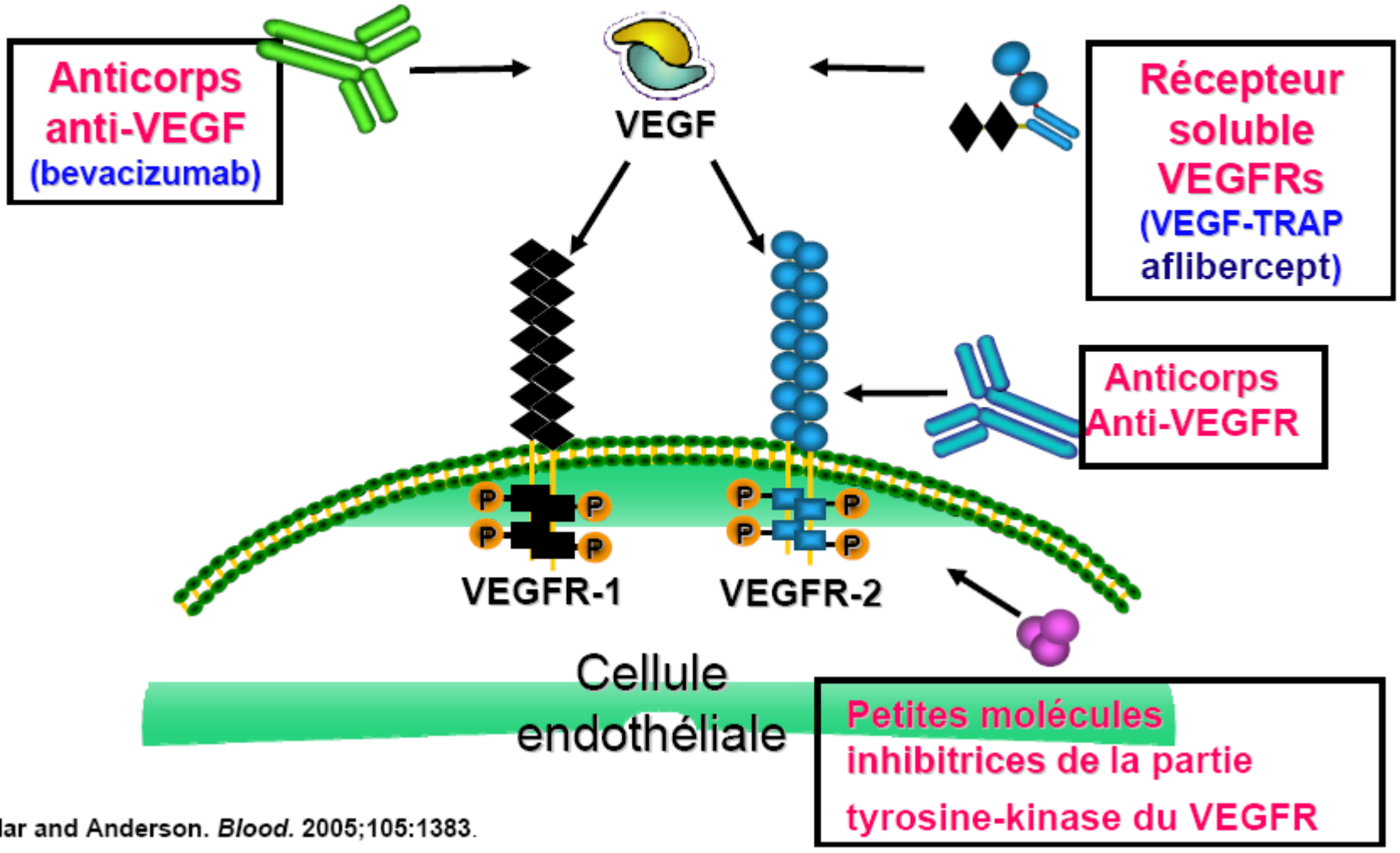
Thrombospondin, endostatin, angiostatin, interferons,

Angiogenesis as a target in cancer treatment

- Selectivity (neovasculature)
- Potential for activity in all tumors
- Few physical barriers to drug delivery
- Potentially complementary to other regimens
- Potential for long-term tumor control


VEGF-A121
VEGF-A145
VEGF-A165
VEGF-A189
VEGF-A206
VEGF-B167
VEGF-B186
PIGF-1,2
VEGF-E
VEGF-C
VEGF-D
S-S
S-S
VEGFR1
(Flt-1)
NRP-1
VEGFR2
(Flk-1/KDR)
VEGFR3
(Flt-4)
NRP-2
Vasculogenesis
Angiogenesis
Lymphangiogenesis

⇢ Agents ciblant la voie VEGF



Podar and Anderson. *Blood.* 2005;105:1383.

Phase III Trial of Bevacizumab in the Primary Treatment of Advanced Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer: A Gynecologic Oncology Group (GOG) Study

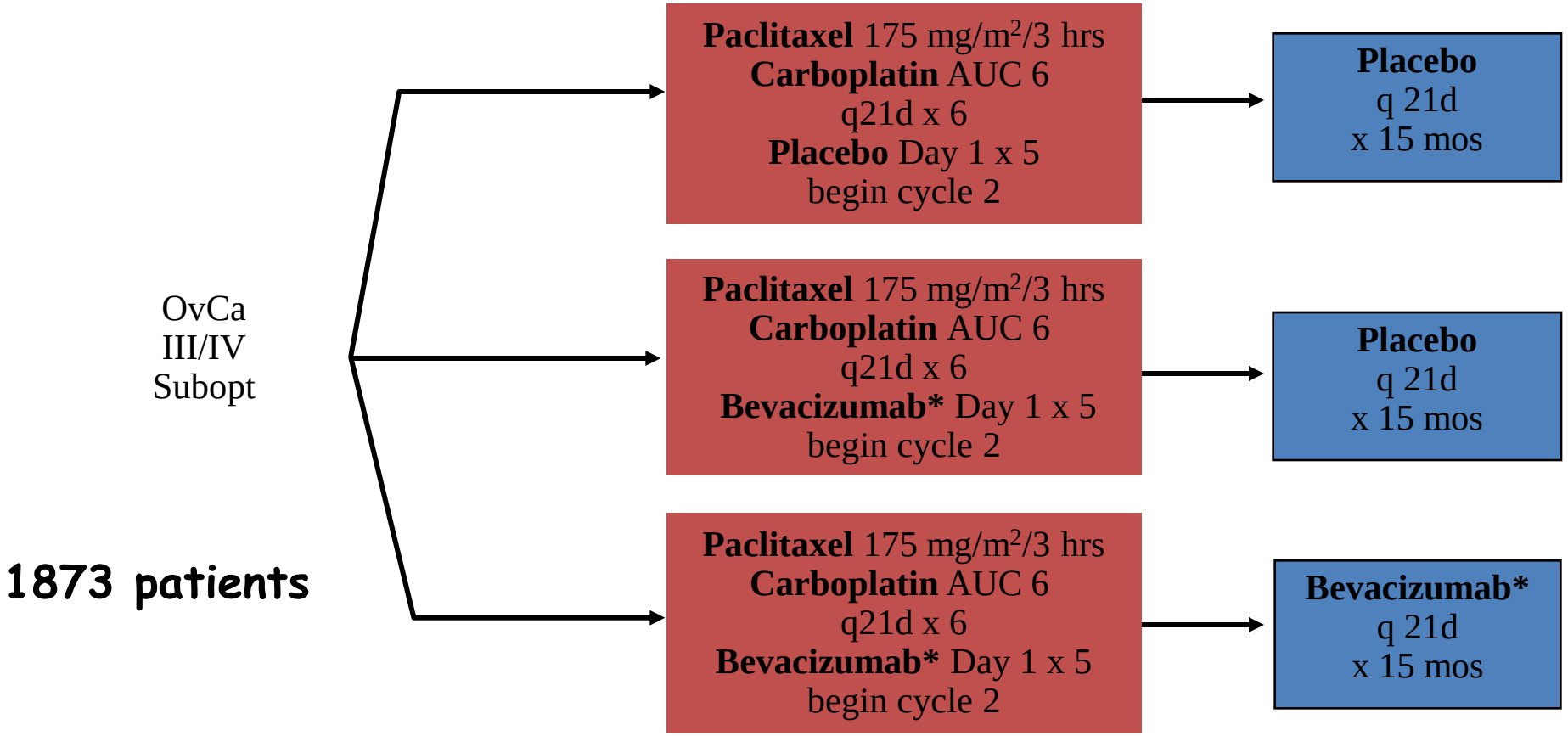
R.A. Burger,[1] M.F. Brady,[2] M.A. Bookman,[3]
J.L. Walker,[4] H.D. Homesley,[5] J. Fowler,[6]
B.J. Monk,[7] B.E. Greer,[8] M. Boente,[9] S.X. Liang[10]

[1]Fox Chase Cancer Center, Philadelphia, PA; [2]Gynecologic Oncology Group Statistical and Data Center, Roswell Park Cancer Institute, Buffalo, NY; [3]University of Arizona Cancer Center, Tucson, AZ; [4]University of Oklahoma Health Sciences Center, Oklahoma City, OK; [5]Brody School of Medicine, Greenville, NC; [6]James Cancer Hospital at the Ohio State University, Hilliard, OH; [7]University of California, Irvine Medical Center, Orange, CA; [8]Seattle Cancer Care Alliance, Seattle, WA; [9]Minnesota Oncology and Hematology, Minneapolis, MN; [10]State University of New York at Stony Brook, Stony Brook, NY, USA

ASCO Annual '10 Meeting

GOG Gynecologic Oncology Group

GOG 218



PI: Burger RA

ClinicalTrials.gov. NCT00262847.

*Bevacizumab 15 mg/kg IV

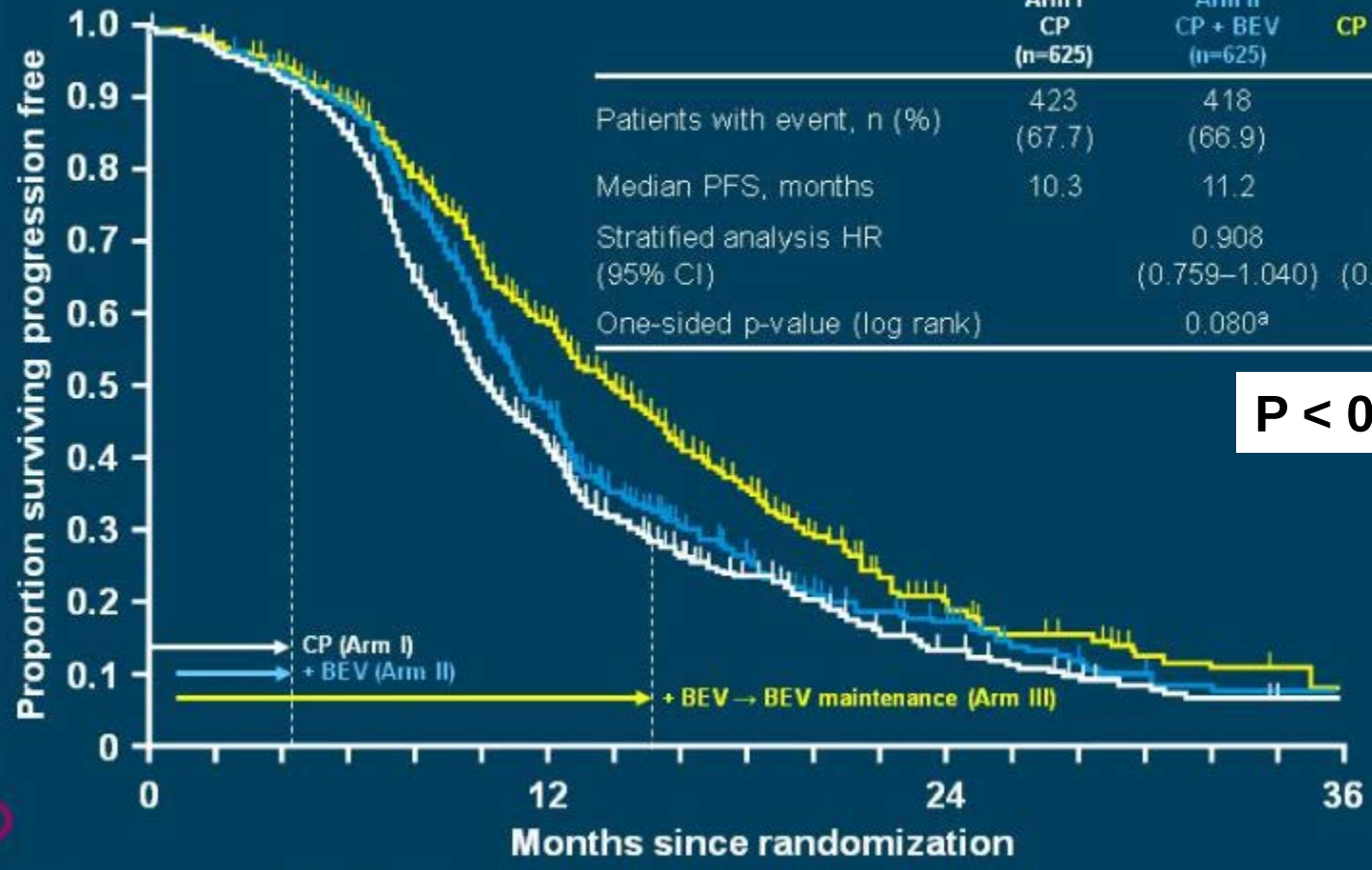
GOG-0218: Select Adverse Events

Onset between cycle 2 and 30 days after date of last treatment

Adverse event (grade when limited), n (%)	Arm I CP (n=601)	Arm II CP + BEV (n=607)	Arm III CP + BEV → BEV (n=608)
GI events[a] (grade ≥2)	7 (1.2)	17 (2.8)	16 (2.6)
Hypertension (grade ≥2)	43 (7.2)[b]	100 (16.5)[b]	139 (22.9)[b]
Proteinuria (grade ≥3)	4 (0.7)	4 (0.7)	10 (1.6)
Pain (grade ≥2)	250 (41.7)	252 (41.5)	286 (47.1)
Neutropenia (grade ≥4)	347 (57.7)	384 (63.3)	385 (63.3)
Febrile neutropenia	21 (3.5)	30 (4.9)	26 (4.3)
Venous thromboembolic event	35 (5.8)	32 (5.3)	41 (6.7)
Arterial thromboembolic event	5 (0.8)	4 (0.7)	4 (0.7)
CNS bleeding	0	0	2 (0.3)
Non-CNS bleeding (grade ≥3)	5 (0.8)	8 (1.3)	13 (2.1)
RPLS	0	1 (0.2)	1 (0.2)

RPLS = reversible posterior leukoencephalopathy syndrome
[a]Perforation/fistula/necrosis/leak
[b]$p<0.05$

GOG-0218: Investigator-Assessed PFS



	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[a]	<0.0001[a]

P < 0.0001

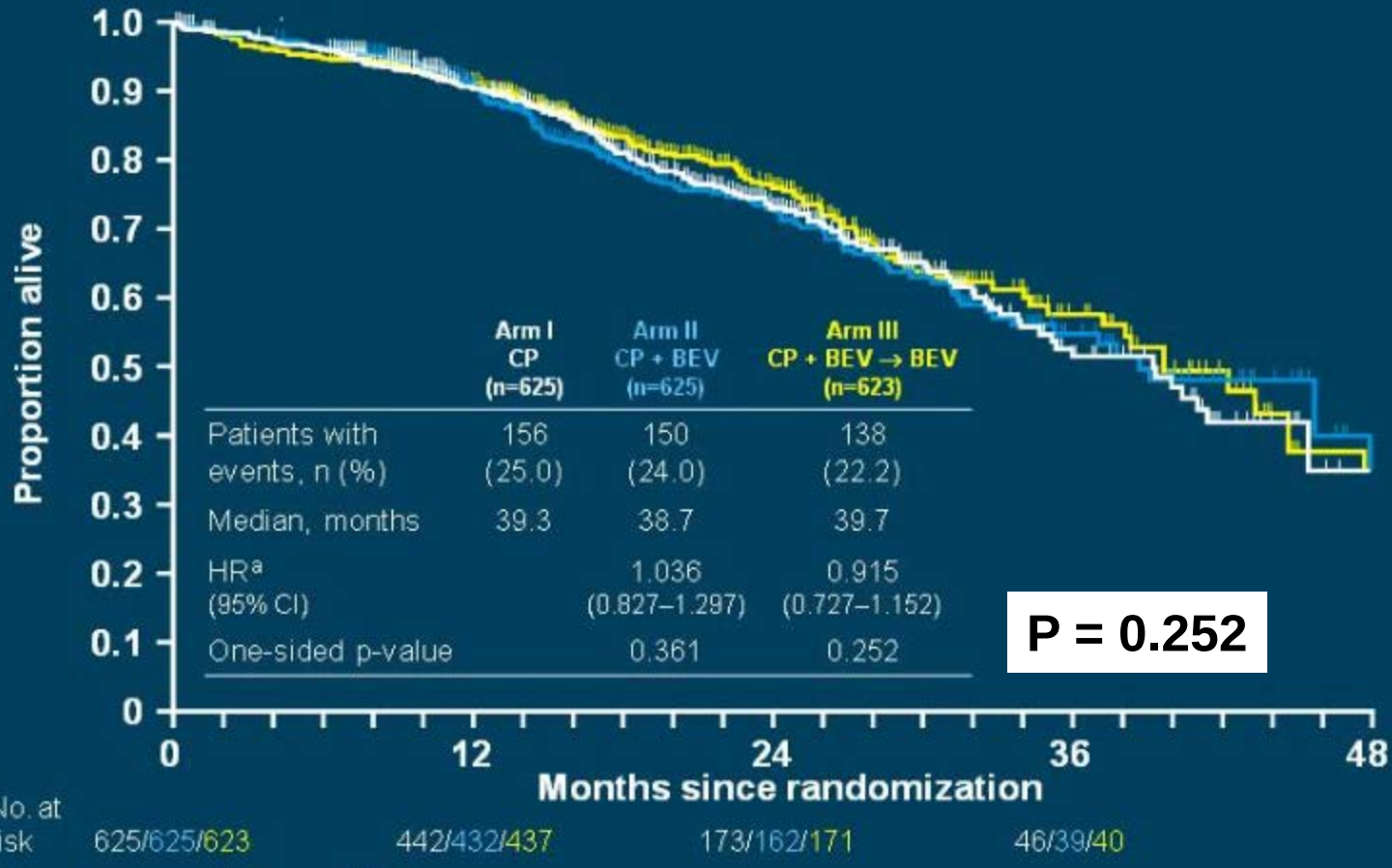
ASCO | Annual '10

ARM1/ARM3 = 10.3 / 14.1mois

[a]p-value boundary = 0.0116

GOG-0218: Overall Survival Analysis

At time of final PFS analysis



	Arm I CP (n=625)	Arm II CP + BEV (n=625)	Arm III CP + BEV → BEV (n=623)
Patients with events, n (%)	156 (25.0)	150 (24.0)	138 (22.2)
Median, months	39.3	38.7	39.7
HR[a] (95% CI)		1.036 (0.827–1.297)	0.915 (0.727–1.152)
One-sided p-value		0.361	0.252

P = 0.252

ASCO | Annual '10

ARM1/ARM3 = 39.3 / 39.7 mois

[a]Stratified analysis

ICON7: A phase III Gynaecologic Cancer InterGroup (GCIG) trial of adding bevacizumab to standard chemotherapy in women with newly diagnosed epithelial ovarian, primary peritoneal or fallopian tube cancer

Tim Perren, Ann Marie Swart, Jacobus Pfisterer, Jonathan Ledermann, Alain Lortholary, Gunnar Kristensen, Mark Carey, Philip Beale, Andreas Cervantes, Amit Oza

on behalf of GCIG ICON7 collaborators
(MRC/NCRI, AGO-OVAR, GINECO, NSGO, ANZGOG, GEICO, NCIC-CTG)

GYNECOLOGIC CANCER INTERGROUP
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

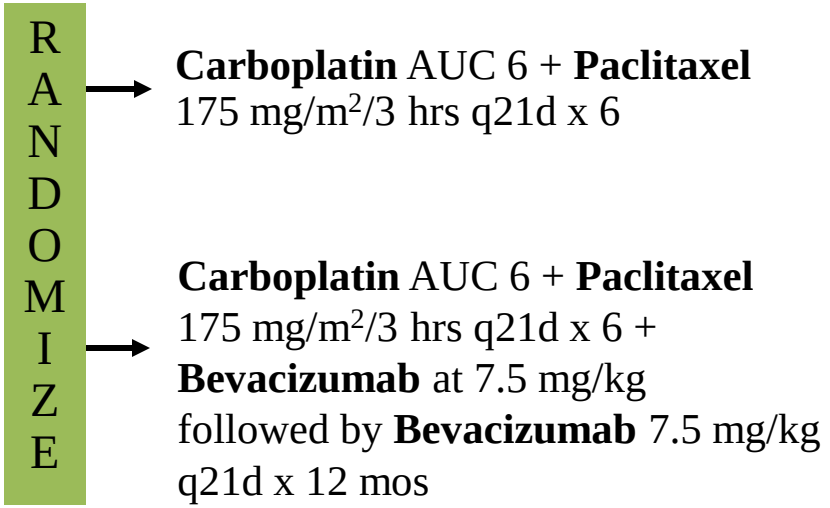
ESMO congress
Milan 2010

ICON7
Bevacizumab in Ovarian Cancer

ICON 7 (Frontline European Trial)

Stages I-IV ovarian and peritoneal cancer

- Stratified according to stage, optimal status region or country



Accrual goal: 1444 patients

Primary endpoint: PFS

Other endpoints: OS (10 mos), RR, Toxicity

Translational Research

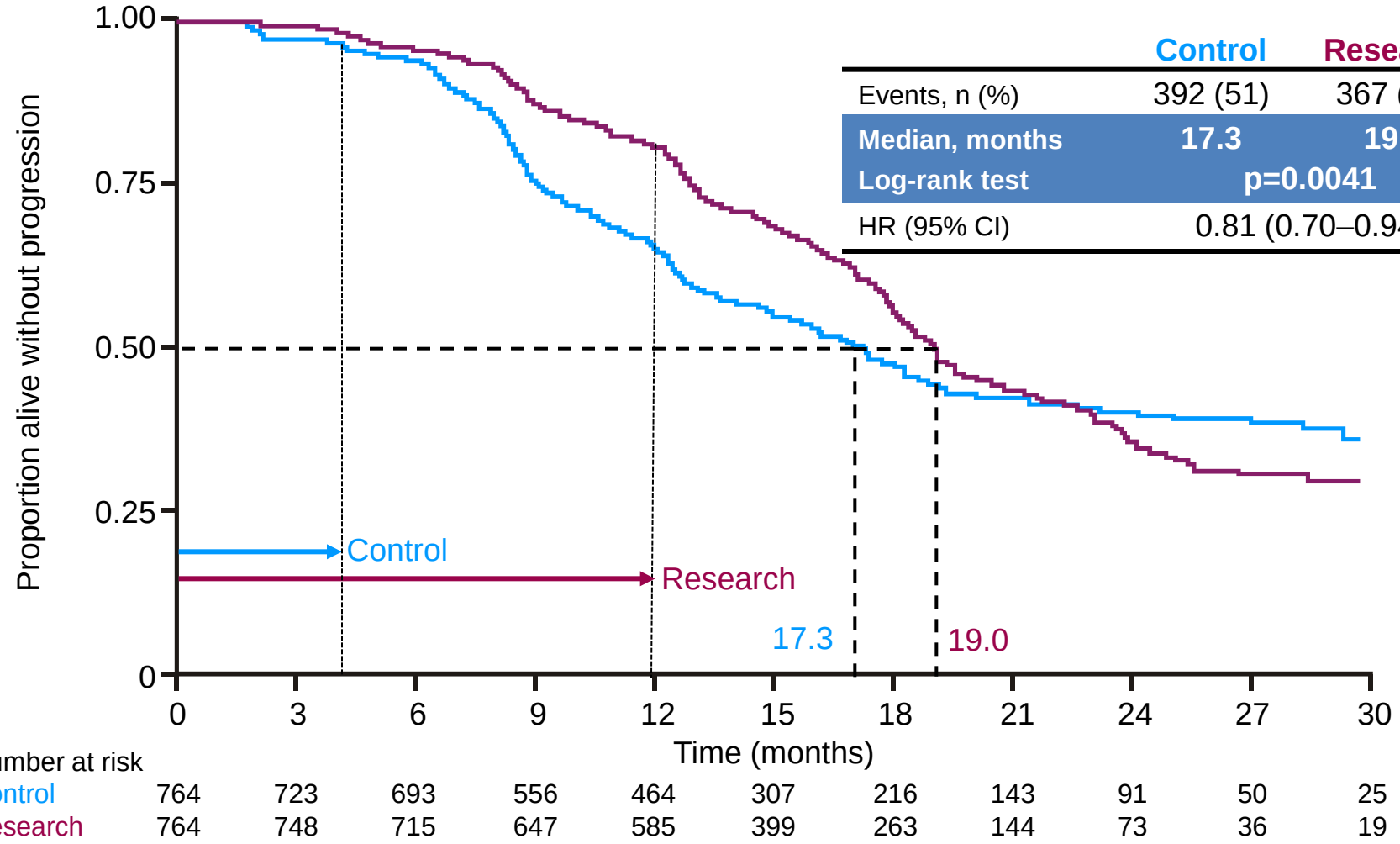
- Tissue and serum markers of angiogenesis
- Genomics
- DCE-MRI
- Quality of life
- Health economics

ClinicalTrials.gov. NCT00483782.

ICON7
Bevacizumab in Ovarian Cancer

Progression-free survival

Academic analysis



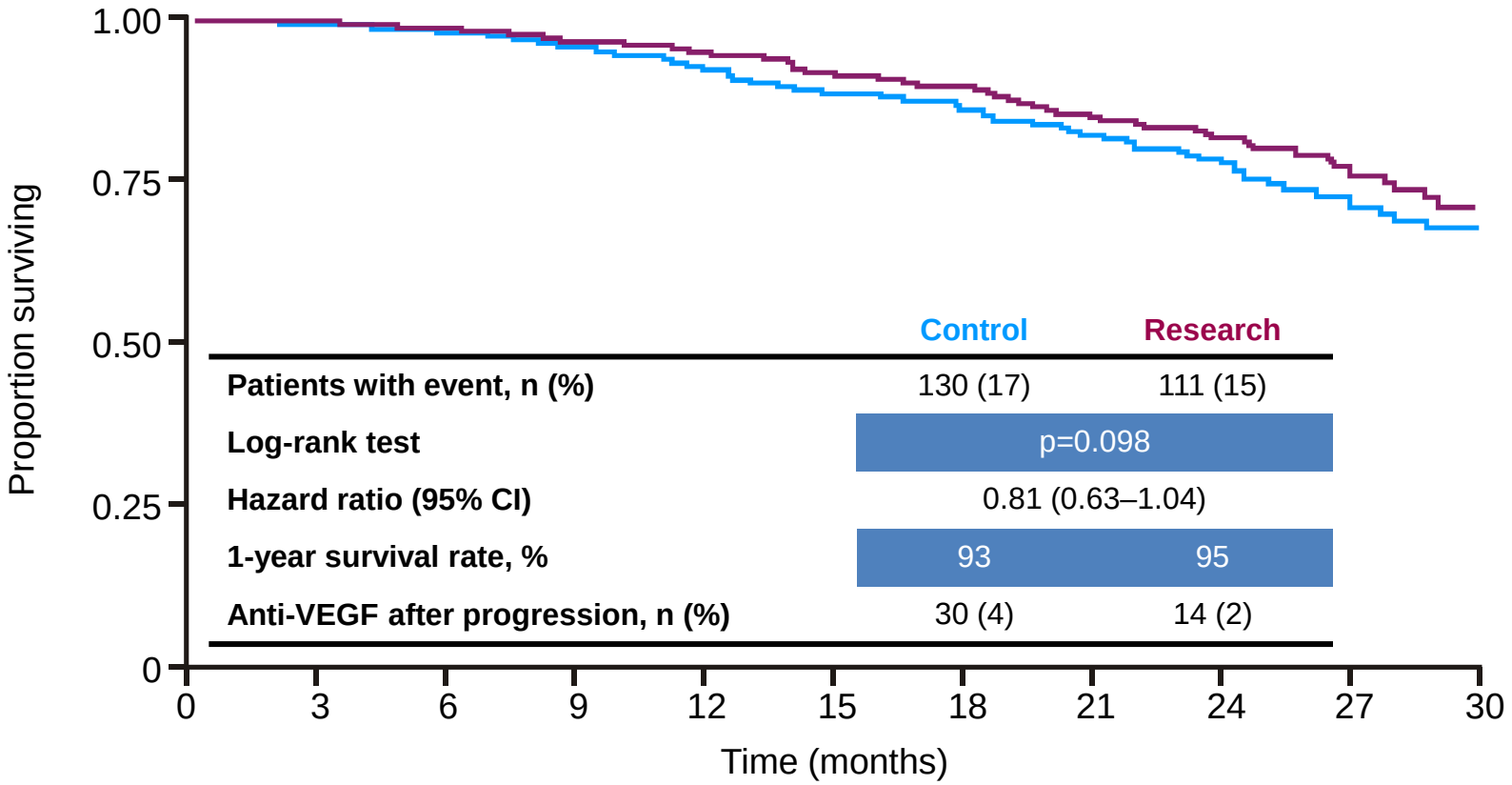
	Control	Research
Events, n (%)	392 (51)	367 (48)
Median, months	17.3	19.0
Log-rank test	p=0.0041	
HR (95% CI)	0.81 (0.70–0.94)	

Number at risk

Control	764	723	693	556	464	307	216	143	91	50	25
Research	764	748	715	647	585	399	263	144	73	36	19

ICON7
Bevacizumab in Ovarian Cancer

Preliminary analysis of overall survival



Number at risk

Control	764	741	724	701	652	486	368	252	159	83	33
Research	764	753	737	716	678	525	404	259	162	89	40

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

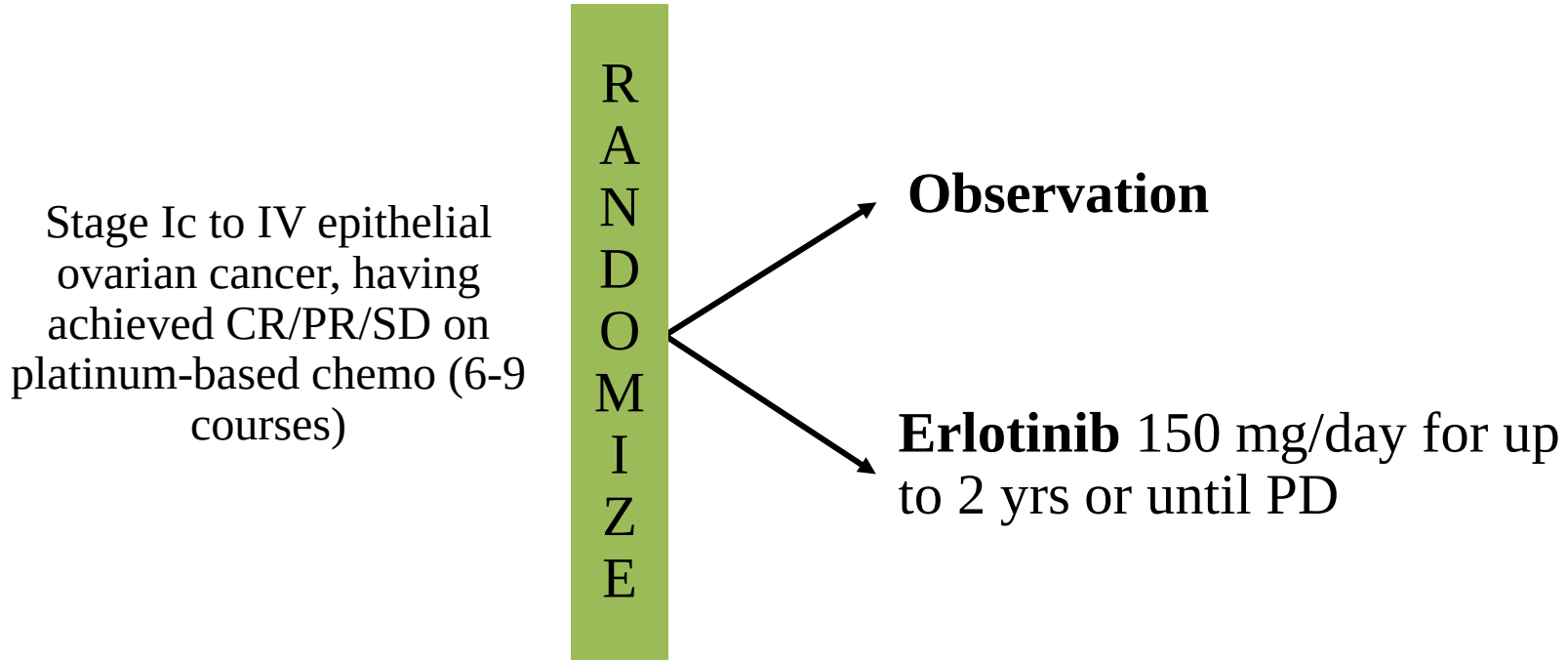
- **1) impact de 1.7-3.8 mois en PFS; pas d'impact en OS**
- **2) autres études avec « maintenance » négatives en OS…**
- **3) pas de notion que augmentation de PFS améliore la qualité de vie**
- **4) pas d'idées que augmentation de PFS « prédit » augmentation d'OS…**
- **5) effets secondaires « acceptables »**
- **6) qui en bénéficie**

- **5.76 $ /mg de Bevacizumab (15mg/kg)**
- **Poids moyen = 60kg**
- **Nombre moyen de cycles = 14**
- **15 X 60 X 5.76 X 14 = 72576$ = +/- 58000 euros**
  - **pour 3.8 mois de PFS gagnée !!!**

TOXICITES

- 1) protéinurie
- 2) hypertension
- 3) thromboembolisme artérielle
- 4) épistaxis
- 5) perforations GI/fistules

First-line Maintenance (EORTC)



N = 830
Endpoints: PFS and OS
Recruitment completed, study ongoing

ClinicalTrials.gov. NCT00263822.

CONCLUSIONS

Early stage Disease

FIGO Ia-Ib, grade I
No clear cell → **No treatment**

FIGO Ia-Ib, grade II-III
FIGO Ic, all grades
All stage clear-cell → **Chemotherapy**
Carbo AUC 5, Paclitaxel 175 mg/m2
Q3S, X3 to 6

Advanced-stage Disease

Up-Front
Maximal Cytoreduction → **Chemotherapy**
Carbo AUC 5, Paclitaxel 175 mg/m2
Q3S, x 6

NACT
Q3S, x 3 → **Interval**
Maximal Cytoreduction → **Adjuv Chemo**
Q3S, x 3

PROTOCOLS (targeted therapies, HIPEC, Immunotherapies, etc

Prognostic Factors in Ovarian Cancer

Age and Ovarian Cancer Outcome

Age, Yrs	Median PFS, Mos	*P* Value	Median OS, Mos	*P* Value
< 40	21.8	.03	60.1	< .001
40-50	17.8		47.9	
50-59	17.5		47.7	
60-69	16.8		44.5	
≥ 70	15.8		36.6	

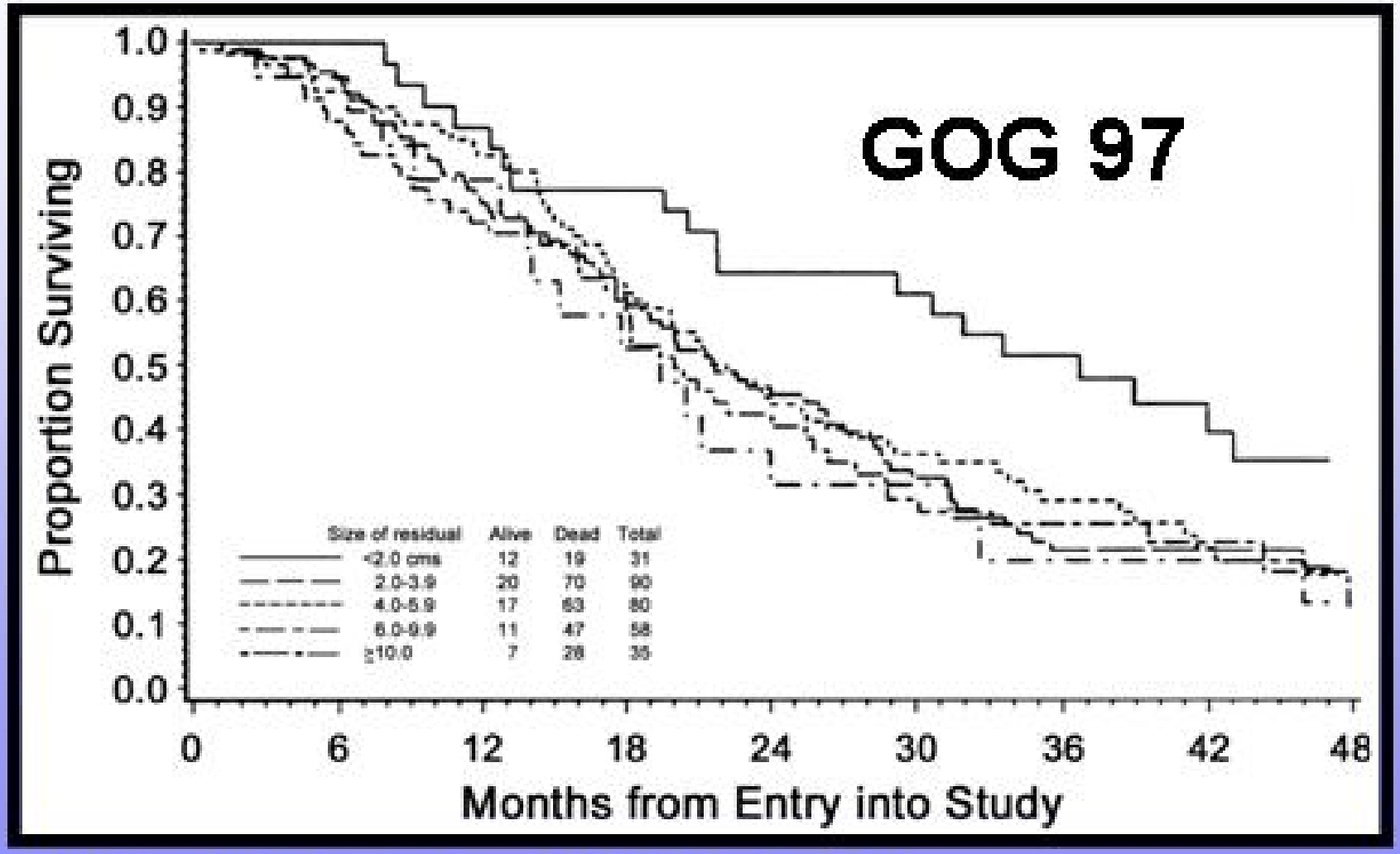
Winter WE III, et al. J Clin Oncol. 2007;25:3621-3627.

Other Prognostic Factors: Debulking Status

Disease Residual	Median PFS, Mos	*P* Value	Median OS, Mos	*P* Value
Microscopic	33.0	< .001	71.9	< .001
0.1-1 cm	16.8		42.4	
> 1 cm	14.1		35.0	

Winter WE III, et al. J Clin Oncol. 2007;25:3621-3627.

Primary Cytoreductive Surgery



Hoskins et al. Am J Obstet Gynecol 1994; 170: 974

Other Prognostic Factors: Histology

Histology	Median PFS, Mos	*P* Value	Median OS, Mos	*P* Value
Serous	16.9	.006	45.1	< .001
Endometrioid	24.8		56.0	
Clear cell	11.4		24.0	
Mucinous	10.5		14.8	

Winter WE III, et al. J Clin Oncol. 2007;25:3621-3627.

Elderly Patients: Prognostic Analysis

- Analysis of 2 consecutive trials from the Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens

Patient Characteristic	HR	95% CI	*P* Value
Age (continuous)	1.07	1.01-1.13	.013
Stage (IV vs III)	3.05	1.58-5.89	.001
Performance score (2-3 vs 0-1)	1.84	0.97-3.51	.064
Symptoms of depression	5.20	2.46-10.99	< .001
Paclitaxel-based chemotherapy (CP vs CC combination)	2.14	1.10-4.15	.025

This table reports the prognostic factors of *poorer survival* identified in the proportional hazards model (Cox Regression Model)

Trédan O, et al. Ann Oncol. 2007;18:256-262.