FACULTÉ DE MÉDECINE PARIS DESCARTES

HÔPITAUX UNIVERSITAIRES PARIS OUEST
Hôpital européen Georges-Pompidou

Faut il toujours faire plus de chimiothérapie néo-adjuvante ?

Fabrice Lécuru, Anne-Sophie Bats, Chérazade Bensaid, Nathalie Douay-Hauser, Julien Seror, Claude Nos.

Hôpital européen Georges Pompidou, Paris,
Université Paris Descartes,
INSERM U 747 S

www.cancerologiegynecologique.eu

Cytoréduction maximale

- La chirurgie supprime les lésions volumineuses, dont une partie est peu vascularisée.
- Le risque de chimiorésistance diminue, quand le nombre de cellules diminue.
- La chirurgie supprime les clones peu proliférant.
- La chirurgie supprime les lésions peu accessibles à la chimiothérapie (GG)
- L'immunocompétence est augmentée par l'exérèse des tumeurs volumineuses

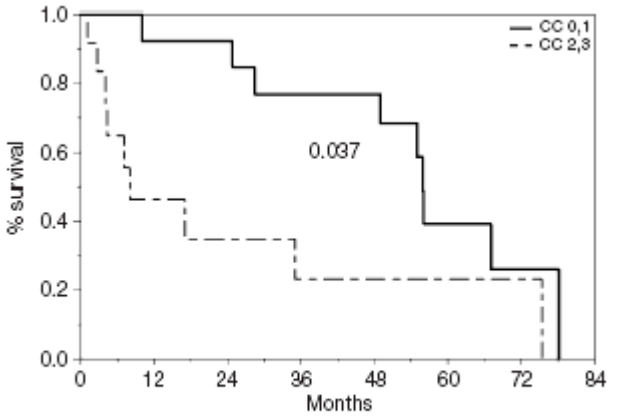


Fig. 3. Survival rates according to completeness of cytoreduction score ($P = 0.037$).

Griffiths CT. Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. Natl Cancer Inst Monogr 1975;42:101-4

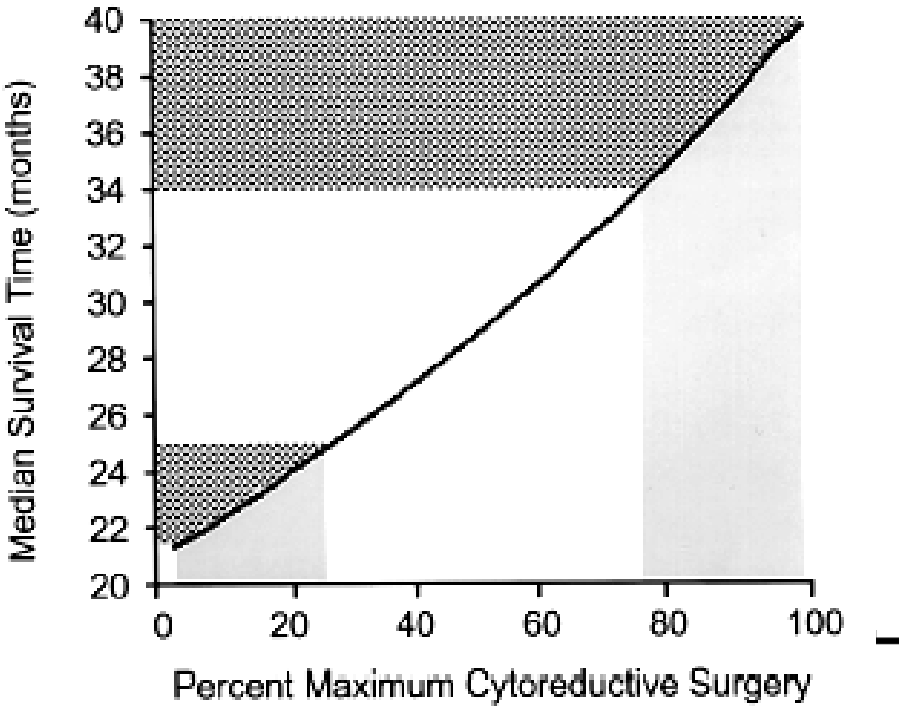


Fig 2. Simple linear regression analysis: de-logged median survival time plotted against percent maximal cytoreductive surgery. Gray area, maximal cytoreductive surgery ≤ 25% and > 75%; crosshatched area, corresponding range of median survival times.

Table 2. Multiple Linear Regression Analysis

Variable	Change in Median Survival Time		95% CI or CL	P
	%	Increase		
Percent maximal cytoreduction	5.5	10%	3.3-7.8	< .001
Year of publication	2.8	1 year	0.9-4.6	.004
Platinum dose-intensity	0.8	10%	–0.7, 2.3	.911
Cumulative platinum dose	1.4	1 U	–1.9, 4.7	.377
Percent stage IV disease	–2.2	10%	–8.5, 4.1	.495
Median age	–0.9	1 year	–3.1, 1.2	.371

Abbreviations: CI, confidence interval; CL, confidence limits.

Bristow R & al 2002

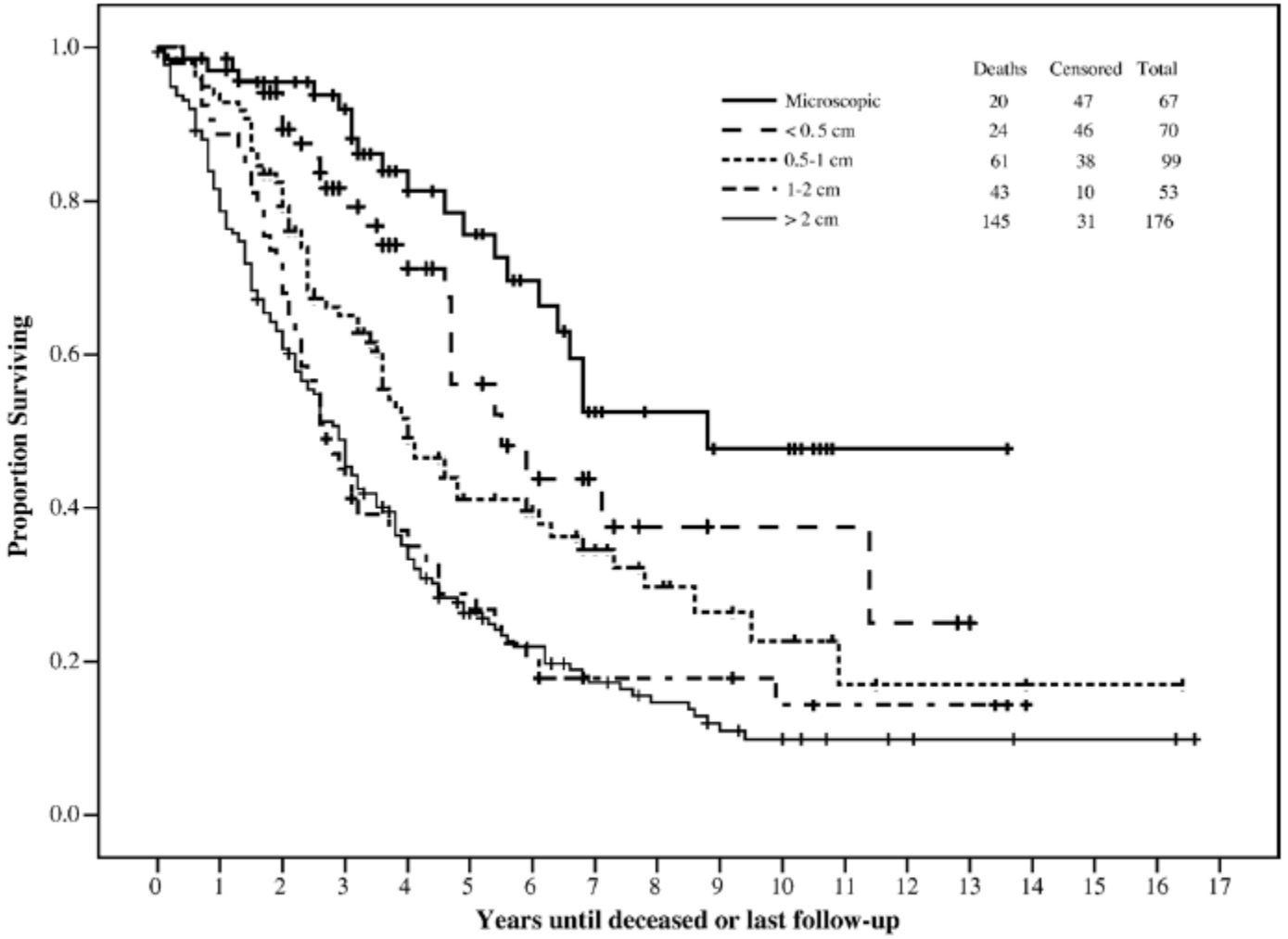


Fig. 1. Overall survival, stage IIIC ovarian cancer, 1989–2003.

Chi D & al. 2006

Résécable ou réséquée ?

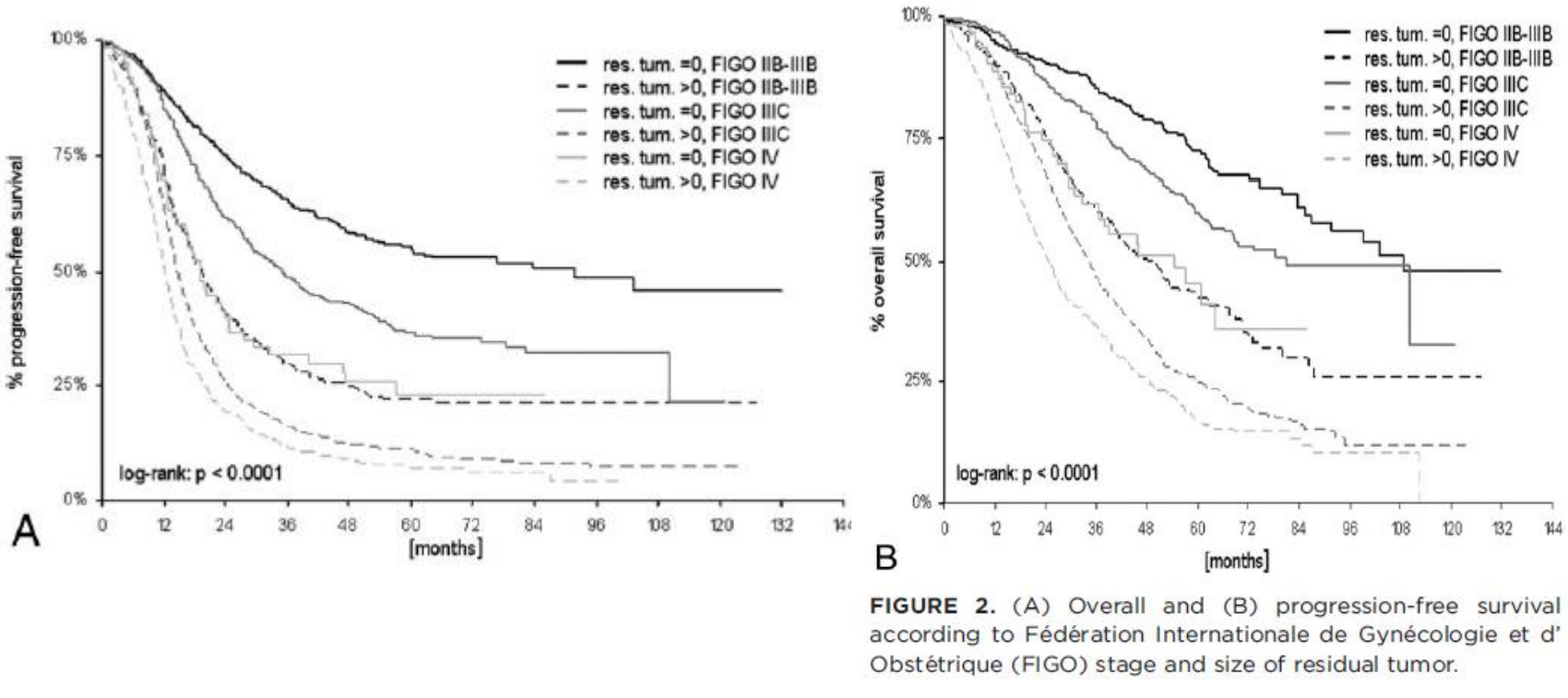


FIGURE 2. (A) Overall and (B) progression-free survival according to Fédération Internationale de Gynécologie et d' Obstétrique (FIGO) stage and size of residual tumor.

Du Bois A et al. 2009

Radicalité et survie

Table 3
Cytoreductive procedures performed.

Procedures performed	Group 1 ($n=168$)	Group 2 ($n=210$)
Standard		
Hysterectomy	129 (77%)	183 (87%)
USO/BSO	153 (91%)	184 (88%)
Omentectomy	135 (80%)	182 (87%)
Small bowel resection	6 (4%)	8 (4%)
Large bowel resection	10 (6%)	73 (35%)
Appendectomy	17 (10%)	37 (18%)
Pelvic lymph node dissection	11 (7%)	59 (28%)
Para-aortic lymph node dissection	11 (7%)	47 (22%)
Extensive upper abdominal		
Diaphragm peritonectomy/resection	0 (0%)	73 (35%)
Splenectomy	0 (0%)	26 (12%)
Distal pancreatectomy	0 (0%)	9 (4%)
Liver resection	0 (0%)	13 (6%)
Resection porta hepatis tumor	0 (0%)	11 (5%)
Cholecystectomy	0 (0%)	10 (5%)

USO, unilateral salpingo-oophorectomy; BSO, bilateral salpingo-oophorectomy.

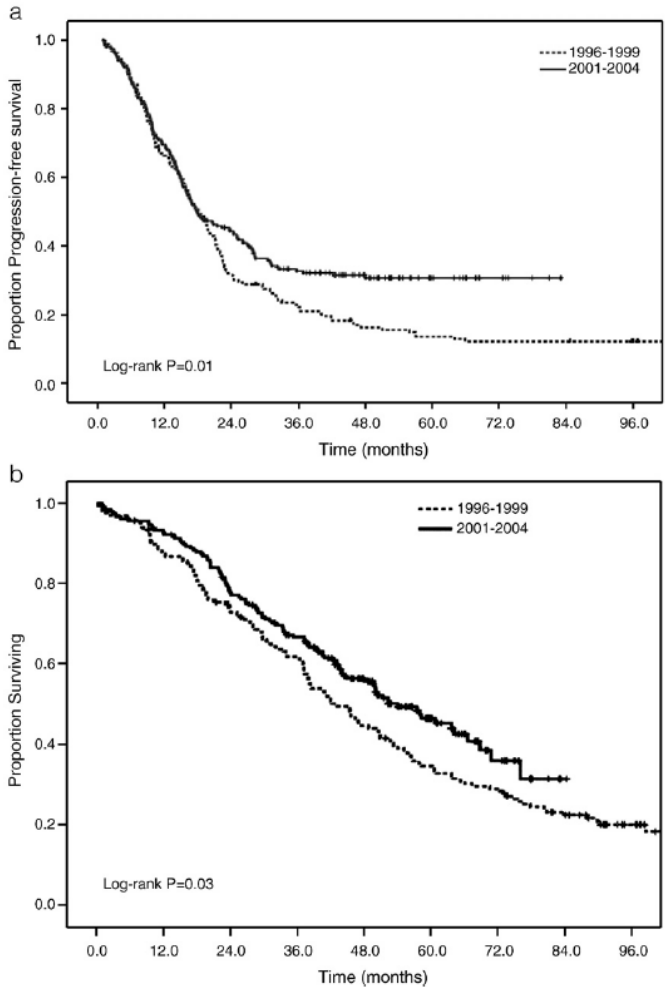


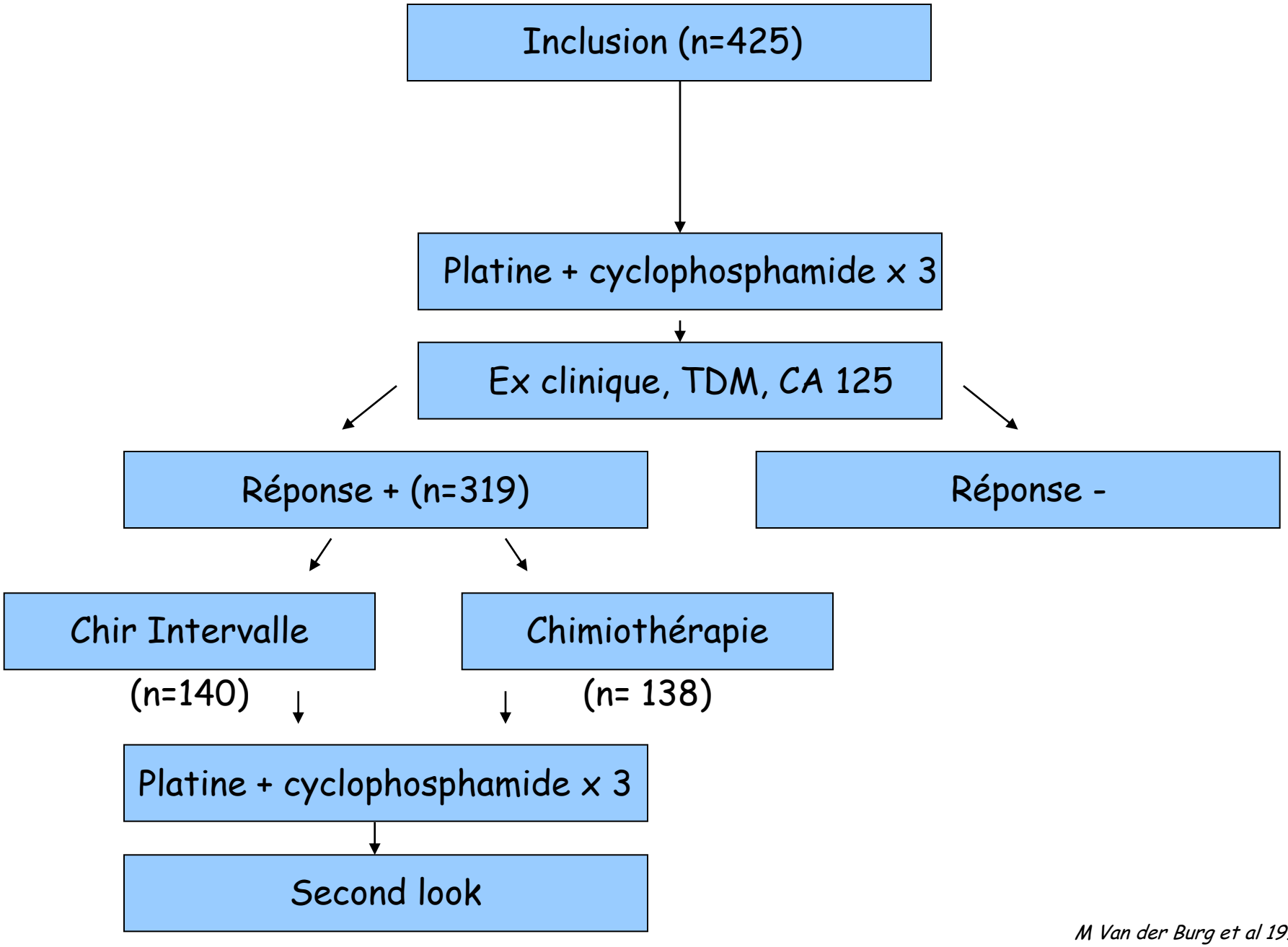
Fig. 1. (A) Progression-free survival, 1996–1999 vs 2001–2004. (B) Overall survival, 1996–1999 vs 2001–2004.

Chi D et al. 2009

Is neo-adjuvant therapy a new idea ?

"Certain very advanced cases with ascites, cachexia, large pelvic tumors and upper abdominal masses are readily recognisable as inoperable and these cases should have their treatment limited to external radiation"

Taylor Jr HC, New York State J Med 1934, vol 34



M Van der Burg et al 1995

- CR au 2ème look :
  70% vs 35%

<1 cm avant cytoredn : 41.6 M
<1cm après cytoredn : 26.6M
>1 cm après cytoredn : 19.4M
pas de debulking : 20M

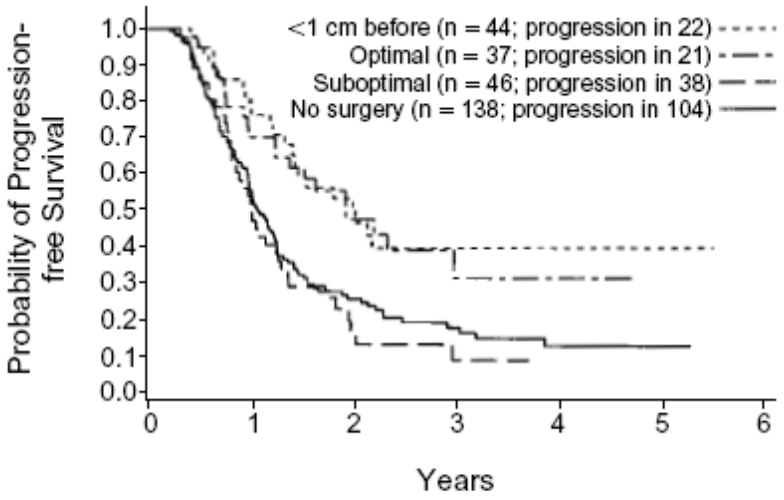


Figure 5. Progression-free Survival of Patients with Advanced Epithelial Ovarian Cancer Who Did Not Have Debulking Surgery and Patients Who Had Such Surgery, According to Whether the Lesions Were Less Than 1 cm in Diameter before Cytoreduction, Less Than 1 cm after Cytoreduction (Optimal), or More Than 1 cm after Cytoreduction (Suboptimal).

M Van der Burg et al 1995

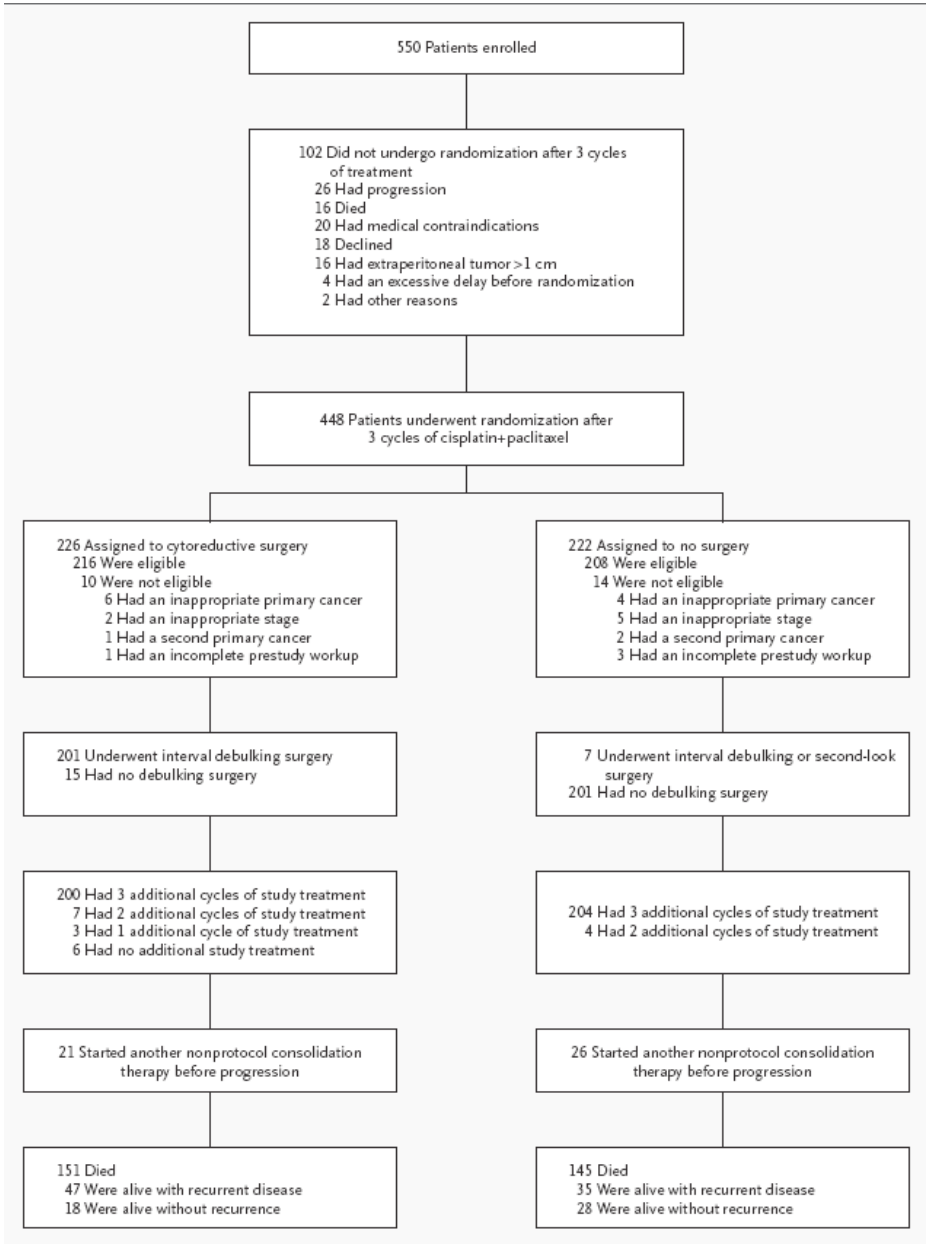
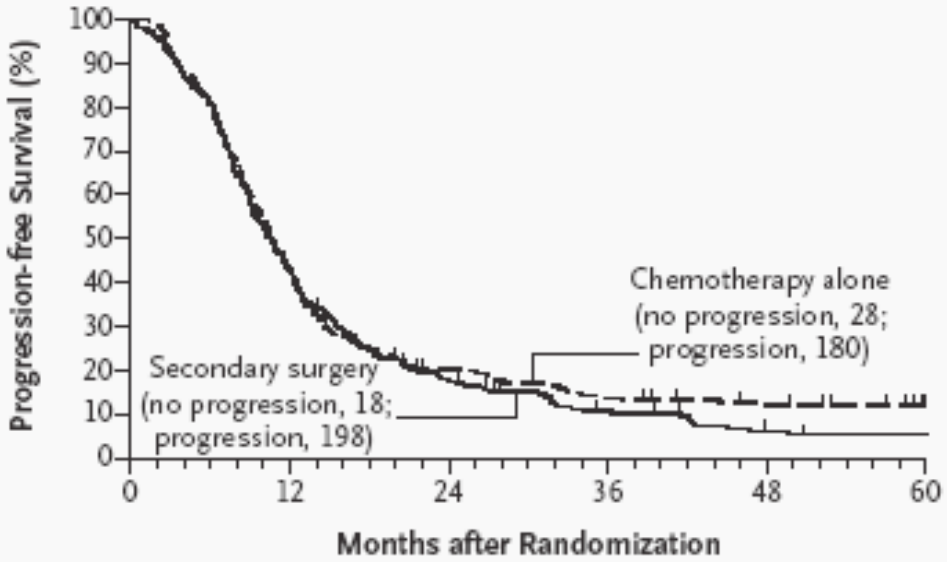


Figure 1. Enrollment and Outcomes.

Rose P, 2004



No. at Risk

Secondary surgery	216	92	36	18	8	6
Chemotherapy alone	208	87	37	25	18	10

Figure 2. Progression-free Survival.

Rose P, 2004

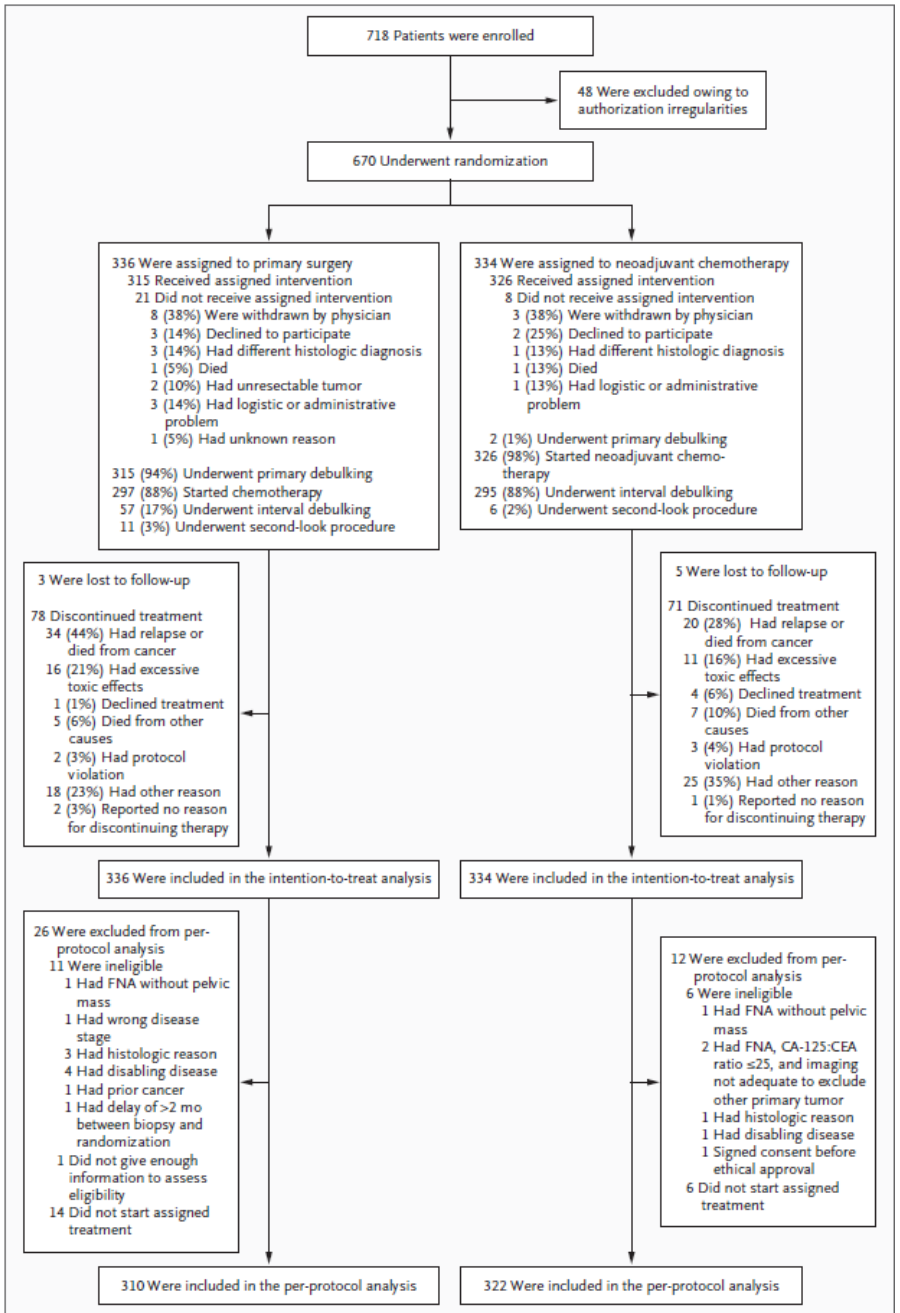


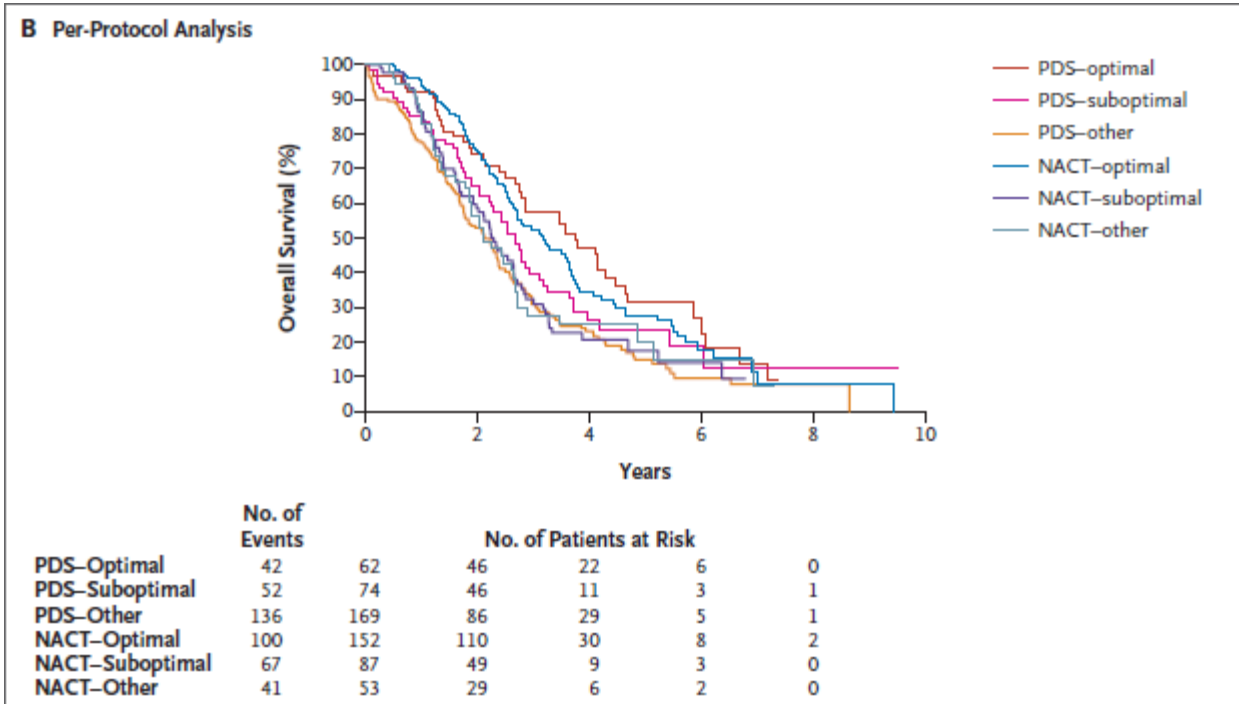
Figure 1. Numbers of Patients Who Were Enrolled, Randomly Assigned to a Treatment Group, and Included in the Analyses.
CA-125 denotes cancer antigen 125, CEA carcinoembryonic antigen, and FNA fine-needle aspiration. Percentages may not total 100% because of rounding.

Vergote I & al 2010

Table 1. (Continued.)

Characteristic	Primary Debulking Surgery (N=336)	Neoadjuvant Chemotherapy (N=334)
Primary tumor — no. (%)		
Epithelial ovarian	293 (87.2)	283 (84.7)
Peritoneal	22 (6.5)	26 (7.8)
Fallopian tube	0	4 (1.2)
Adenocarcinoma	17 (5.1)	20 (6.0)
Missing data	4 (1.2)	1 (0.3)
Serum CA-125 at entry (U/ml)		
Median	1130	1180
Range	16.0–27,185	15.0–41,456
Serum CA-125 >30 U/ml — no. (%)	330 (98.2)	330 (98.8)
Largest metastatic tumor at randomization — no. (%)		
0 cm	2 (0.6)	1 (0.3)
>0–2 cm	2 (0.6)	9 (2.7)
>2–5 cm	90 (26.8)	85 (25.4)
>5–10 cm	90 (26.8)	88 (26.3)
>10–20 cm	105 (31.3)	113 (33.8)
>20 cm	26 (7.7)	24 (7.2)
Missing data	21 (6.3)	14 (4.2)
Size of metastases at the time of surgery — no. (%)†		
No metastasis	1/310 (0.3)	14/322 (4.3)
>0–1 cm	2/310 (0.6)	36/322 (11.2)
>1–2 cm	14/310 (4.5)	40/322 (12.4)
>2–5 cm	50/310 (16.1)	74/322 (23.0)
>5–10 cm	40/310 (12.9)	42/322 (13.0)
>10 cm	191/310 (61.6)	78/322 (24.2)
Missing data	12/310 (3.9)	38/322 (11.8)

Vergote I & al 2010



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

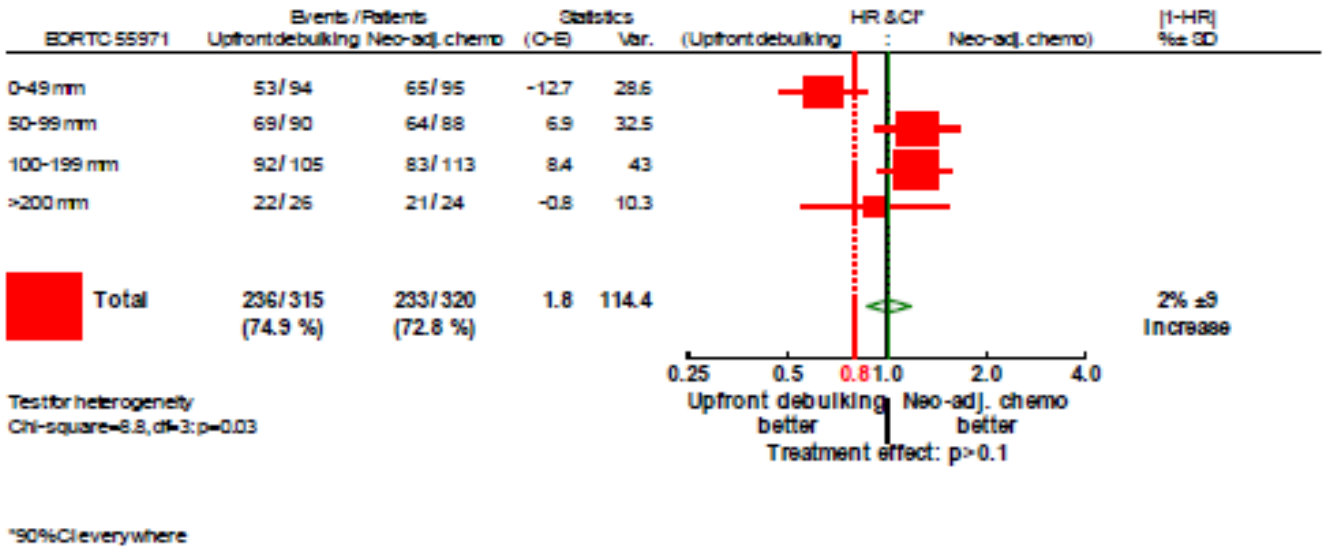
Figure 2. Overall Survival in the Intention-to-Treat Population and Overall Survival According to Treatment Received and Status with Respect to Residual Tumor.

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

Vergote I & al 2010

- Durée opératoire : 180 min.
- PFS médiane : 12 mois
- SG médiane : 29 vs 30 mois
- Chir optimale = le facteur PNC le + impt
- Pays = facteur PNC
- Pourquoi la variation du % de CC0 ne se traduit elle pas par une variation de la survie ? ???

OS: Largest metastatic tumor size



Vergote I & al 2010

FACULTÉ DE MÉDECINE PARIS DESCARTES

HÔPITAUX UNIVERSITAIRES PARIS OUEST
Hôpital européen Georges-Pompidou

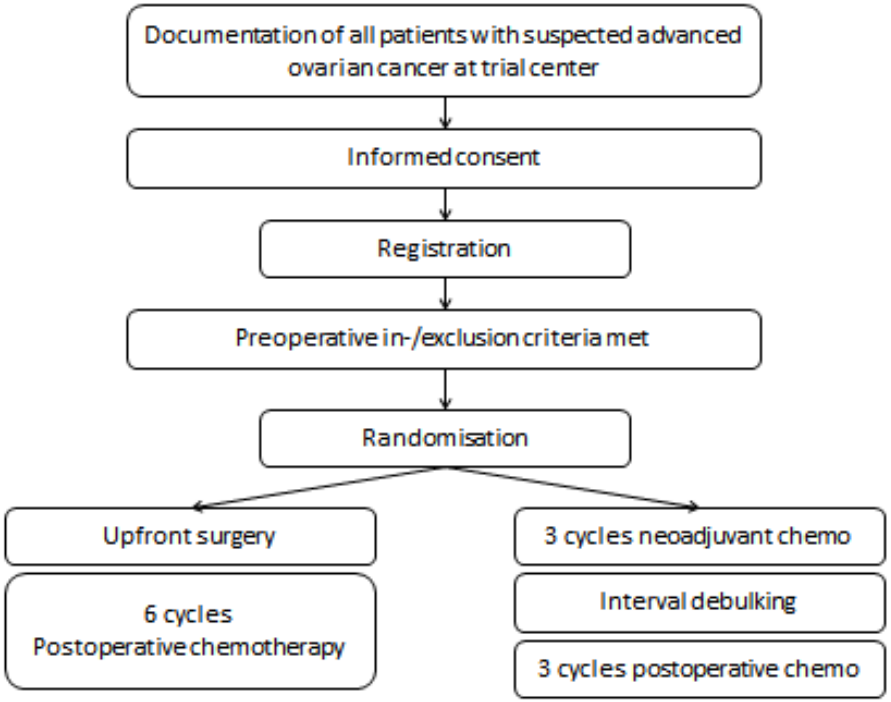
2.6 Overall survival rates according to largest residual tumor and treatment arm.

Overall survival

Treatment arm and largest residual tumor	Patients (N)	Observed Events (O)	Hazard Ratio (90% CI)	P-Value (Wald Test)	Median (90% CI) (Months)	% at 5 Year(s) (90% CI)	
PDS - No residual	62	42	1.00	0.0002 (df=5)	44.98 (34.30, 53.59)	31.31	(20.77, 42.40)
PDS- 1 – 10 mm	74	52	1.37 (0.97, 1.93)	0.1309 (df=1)	32.26 (26.91, 37.39)	23.47	(14.63, 33.54)
PDS -> 10 mm	169	136	1.87 (1.39, 2.50)	0.0004 (df=1)	25.66 (21.62, 28.55)	14.82	(10.06, 20.45)
NACT- No residual	152	100	1.11 (0.82, 1.51)	0.5616 (df=1)	38.18 (32.69, 43.96)	27.50	(20.51, 34.92)
NACT- 1 – 10 mm	87	67	1.73 (1.25, 2.40)	0.0054 (df=1)	27.01 (24.28, 31.74)	17.52	(10.33, 26.27)
NACT-> 10 mm	53	41	1.71 (1.19, 2.46)	0.0144 (df=1)	25.49 (22.80, 32.16)	19.91	(10.24, 31.88)

PDS: Primary debulking surgery; NACT: Neoadjuvant chemotherapy: CI: Confidence intervals.

Vergote I & al 2010



TRUST AGO Pr A du Bois

FACULTÉ DE MÉDECINE PARIS DESCARTES

HÔPITAUX UNIVERSITAIRES PARIS OUEST

ôpital européen Georges-Pompidou

Table 6. Risk Factors for Postoperative Pulmonary Complications

Patient-related factors
Age > 60 y[55-60]
Chronic obstructive pulmonary disease (COPD)[55,56,58-60]
American Society of Anesthesiologists (ASA) class II or greater[56,58,59]
Functional dependence*[55,58-60]
Congestive heart failure[56,58,59]
Obstructive sleep apnea[58,59,61]
Pulmonary hypertension[62-64]
Current cigarette use[58-60]
Impaired sensorium†[56,58-60]
Preoperative sepsis[56]
Weight loss > 10% in 6 months[58-60]
Serum albumin < 3.5 mg/dL[55,56,58,59]
Blood urea nitrogen (BUN) ≥ 7.5 mmol/L (≥21 mg/dL)[58-60]
Serum creatinine >133 μmol/L (>1.5 mg/dL)[59,66]
Surgery-related factors
Prolonged operation > 3 h[57-59]
Surgical site‡[55,56,58-60]
Emergency operation[55,56,58-60]
General anesthesia[58-60]
Perioperative transfusion[56,58-60]
Residual neuromuscular blockade after an operation[58,65]
Not risk factors
Obesity[58,59]
Well-controlled asthma[58,59]
Diabetes[58,59]

*Total dependence was the inability to perform any activities of daily living. Partial dependence was the need for equipment or devices and assistance from another person for some activities of daily living.

†Acutely confused or delirious patient who is able to respond to verbal or mild tactile stimulation, or mental status changes or delirium in the context of current illness.

‡Highest risk procedures: upper abdominal, thoracic, neurosurgical, head and neck, vascular (eg, aortic aneurysm repair).

Chow W & al J Am Coll Surg 2012

Coupole droite

- Cœlioscopie
  - Exploration systématique
  - Points bloquants
  - Histologie
  - Information pré-opératoire

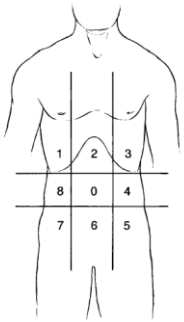
FACULTÉ DE MÉDECINE PARIS DESCARTES

HÔPITAUX UNIVERSITAIRES PARIS OUEST

Hôpital européen Georges-Pompidou

EVALUATION DE L'ETENDUE DE LA CARCINOSE

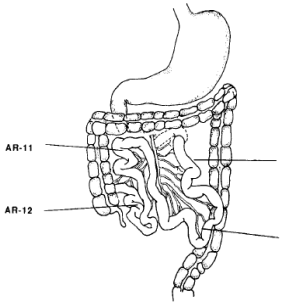
Peritoneal Cancer Index (PCI) de Sugarbaker



0 Central
1 Right upper
2 Epigastrium
3 Left upper
4 Left flank
5 Left lower
6 Pelvis
7 Right lower
8 Right flank

Cotation par région :

- **0** : pas de lésion
- **1** : L ≤ 0,5 cm
- **2** : 0,5 < L ≤ 5 cm
- **3** : L > 5 cm



Régions du grêle :

- **R9** : jéjunum haut
- **R10** : jéjunum bas
- **R11** : iléon haut
- **R12** : iléon bas

	Avant debulking	Après debulking
Région 0		
Région 1		
Région 2		
Région 3		
Région 4		
Région 5		
Région 6		
Région 7		
Région 8		
Région 9		
Région 10		
Région 11		
Région 12		
Totaux		

	Régions	Structures anatomiques
0	Centrale	Incision médiane – grand épiploon – colon transverse
1	Supérieure droite	Surface supérieure du lobe droit du foie – Péritoine pariétal sous-diaphragmatique droit – Espace rétro-hépatique droit
2	Epigastre	Ligament rond – lobe gauche du foie – petit épiploon – ligament falciforme
3	Supérieure gauche	Péritoine pariétal sous-diaphragmatique gauche– rate – queue du pancréas – surfaces antérieure et postérieure de l'estomac
4	Flanc gauche	Colon gauche– gouttière pariéto-colique gauche
5	Fosse iliaque gauche	Péritoine pariétal latéro-sigmoïdien – sigmoïde
6	Pelvis	Organes génitaux internes féminins (ovaires, trompes et utérus) – vessie, cul de sac de Douglas – charnière recto-sigmoïdienne
7	Fosse iliaque droite	Péritoine pariétal latéro-cæcal– cæcum – appendice
8	Flanc droit	Colon droit– gouttière pariéto-colique droite

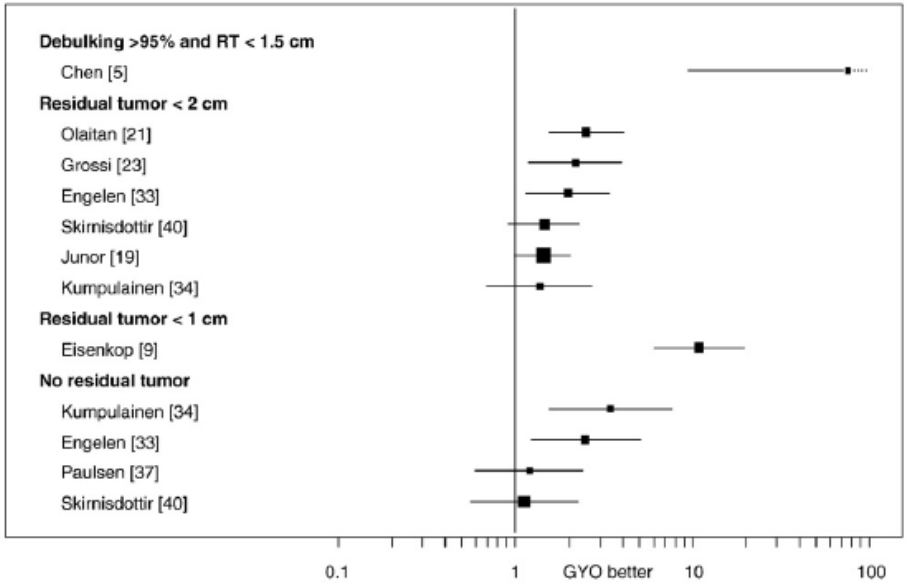


Fig. 2. Odds ratio of achieving debulking to minimal residual disease in patients with advanced disease, GYO compared with OB/GYN or other specialty. GYO = gynecologic oncologist, OB/GYN = obstetrician/general gynecologist, RT = residual tumor.

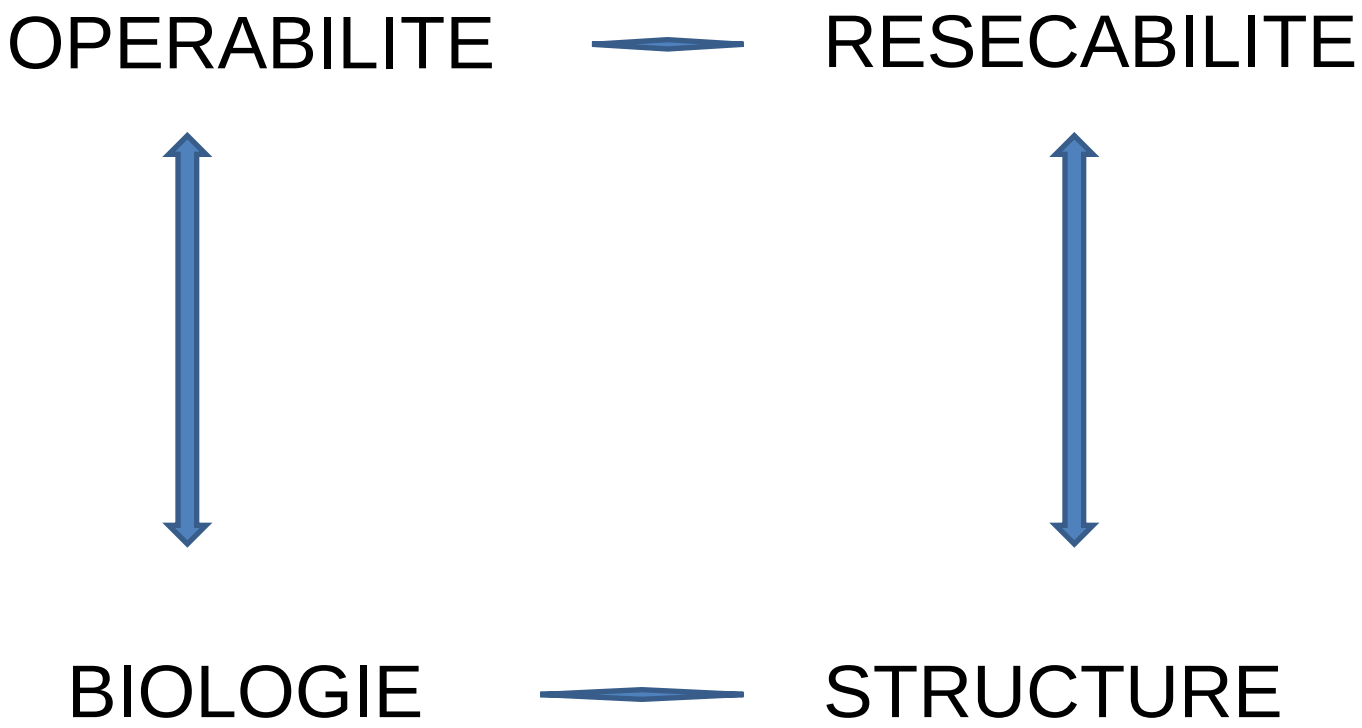
Certification du chirurgien,
Volume du chirurgien, volume de l'hôpital, spécialisation de l'hôpital
Recherche clinique

Structure : Critères de qualité (INCa)

- Au moins 2 chirurgiens entraînés à la chirurgie pelvienne et abdominale pour obtenir une résection complète. Au moins 10 interventions par chirurgien et par an.
- Collaboration formalisée avec un oncologue médical.
- Participation à des essais cliniques dans le cancer de l'ovaire.
- Bilan pré-opératoire conforme
- RCP pré-opératoire
- Laparotomie médiane
- Curages pelviens et aortico-caves en cas de CC0
- Description analytique des lésions initiales et résiduelles
- Examen extemporané possible
- CR pathologique conforme aux recommandations
- Taux de résection complète >70% (stades IIIc – Iva)
- Database (complications)

Querleu D & al 2013

Tumeurs de type I	Tumeurs de type II
• **Évolution lente**	• **Tumeurs agressives**
• Diagnostiquées à un **stade précoce** confiné à l'ovaire	• Diagnostiquées à un **stade avancé**
• **Types histologiques :** carcinomes de type séreux de bas grade, endométroïdes de bas grade, à cellules claires, mucineux et transitionnels	• **Types histologiques :** carcinomes de type séreux de haut grade, carcinomes indifférenciés et carcinosarcomes
• Mutations impliquées : KRAS, BRAF, ERBB2, CTNNB1, PTEN et PIK3A	• Mutations impliquées : gène p53 et gènes BRCA
• **Stabilité génétique**	• **Instabilité génétique**


OPERABILITE
RESECABILITE
BIOLOGIE
STRUCTURE

- La résection macroscopique complète est l'objectif unique

- Stades IIIc et métastases <5cm : chirurgie
- Stades IIIc et métastases >5cm : chimio ?
- Stades IV : chimiothérapie néoadjuvante

- La cœlioscopie est l'outil de sélection
- Ne pas faire de chimiothérapie par manque de ressource chirurgicale …

FACULTÉ
DE MÉDECINE
PARIS DESCARTES

HÔPITAUX
UNIVERSITAIRES
PARIS OUEST

Hôpital européen Georges-Pompidou

FACULTÉ
DE MÉDECINE
PARIS DESCARTES

HÔPITAUX
UNIVERSITAIRES
PARIS OUEST

Hôpital européen Georges-Pompidou

FACULTÉ
DE MÉDECINE
PARIS DESCARTES

HÔPITAUX
UNIVERSITAIRES
PARIS OUEST

Hôpital européen Georges-Pompidou