# Cytoreductive Surgery or Chemotherapy for Advanced Ovarian Cancer Who goes first?

## ISGO; Friday June 13th;2014

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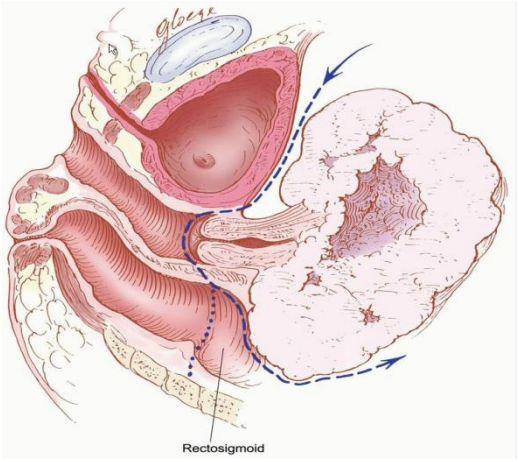
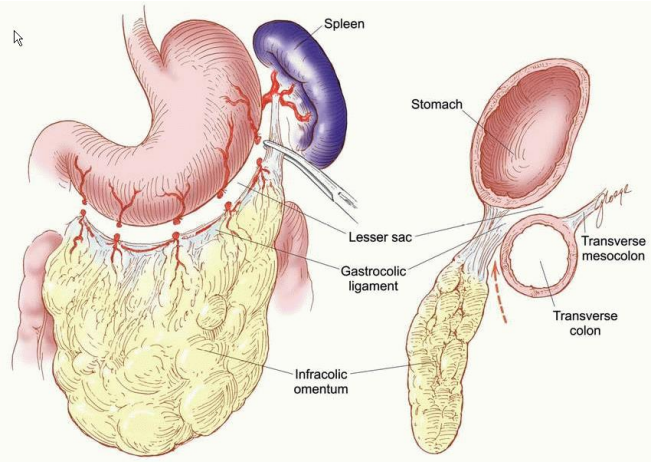
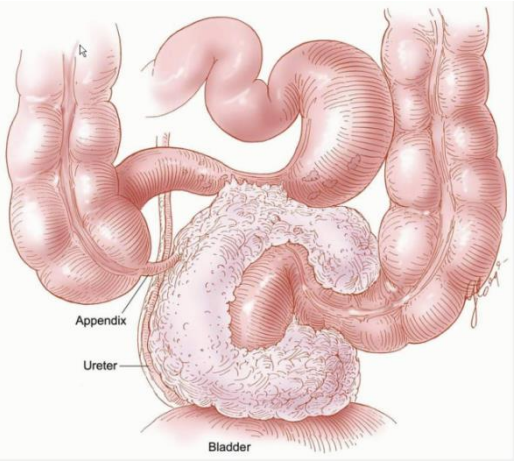
**The International Journal of Gynecological Cancer**

# Advanced Ovarian Cancer

- About 70-75% of women at presentation
- Accepted management: combination of surgery and platinum based chemotherapy
- This has been the approach for 4 decades, though the 5YS remains poor at about 30%



# What “advanced disease” are we discussing?

***It is not***

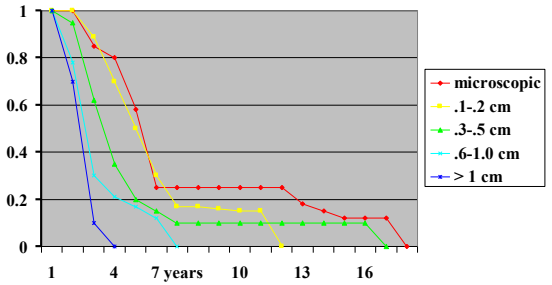
- Advanced due to **positive nodes**
- Advanced due to a **single mets** in the omentum
- Advanced due to **multiple liver metastases**,
- **Brain** or other distant disease

***–It is about the patient with advanced widespread/bulky intra-peritoneal disease***

# “Surgical resection of tumor bulk is the primary treatment of ovarian carcinoma”

- 102 patients with **stages II and III** ovarian cancer
- The most important factors were the **histological grade** of the tumor and the **size of the largest residual tumor mass after operation**
- **Survival time was uniformly poor if the diameter of the largest residual tumor mass exceeded 1.5 cm irrespective of total tumor volume** (mean=12.7 months, SE=1.6 mo)
- **Surgery improved survival relative to reduction in mass size below this limit**
- **Extensive resections of tumor bulk with failure to remove all masses greater than 1.5 cm in diameter did not influence survival.**
- **Surgery provides optimum benefit when all gross tumor can be excised safely**

**Griffiths,** Natl Cancer Inst Monogr. 1975 Oct;42:101-4.




Griffiths, Int J Gynecol Cancer 2002

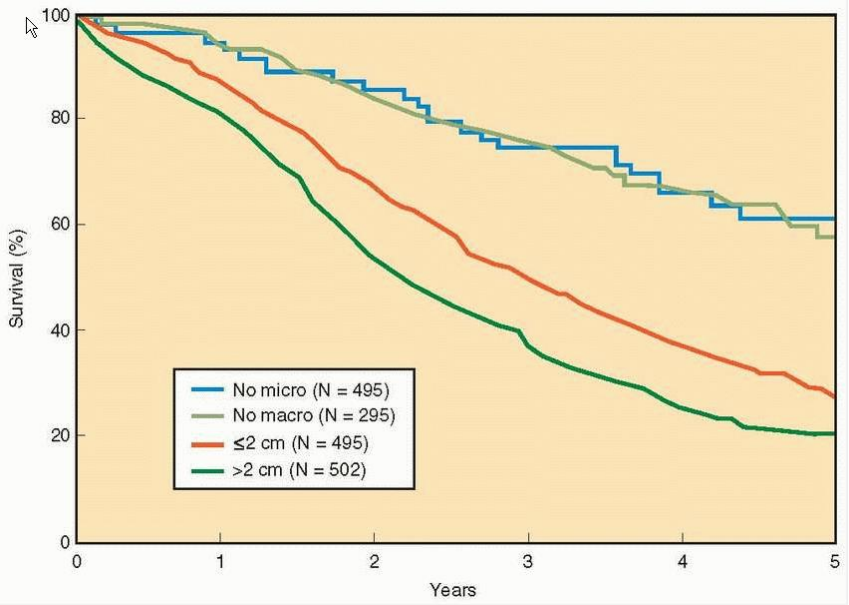
## Role of cytoreductive surgical treatment in the management of advanced ovarian cancer.

**Griffiths CT**, Parker LM, Fuller AF Jr.

Cancer Treat Rep. 1979 Feb;63(2):235-40

Twenty-eight abdominal operations were performed on **26 consecutive patients with stage III and IV** ovarian carcinoma over a 3-year period. The goal of each operation was to excise all tumors greater than 1 cm in diameter. This goal was achieved in 12 of 15 primary operations, **in seven of nine operations after induction chemotherapy**, and in three of four operations performed for tumor recurrence. There were two major complications but no postoperative deaths. ***Analysis of survival and disease status indicated that patients having operations followed by chemotherapy fared the best.*** Analysis of prognostic variables suggested that the administration of combination chemotherapy was the most important determinant of survival once the surgical goal had been accomplished. In this latter group, all nine patients who were evaluable by laparoscopy had responded to adriamycin-cyclophosphamide and eight of the nine had complete responses

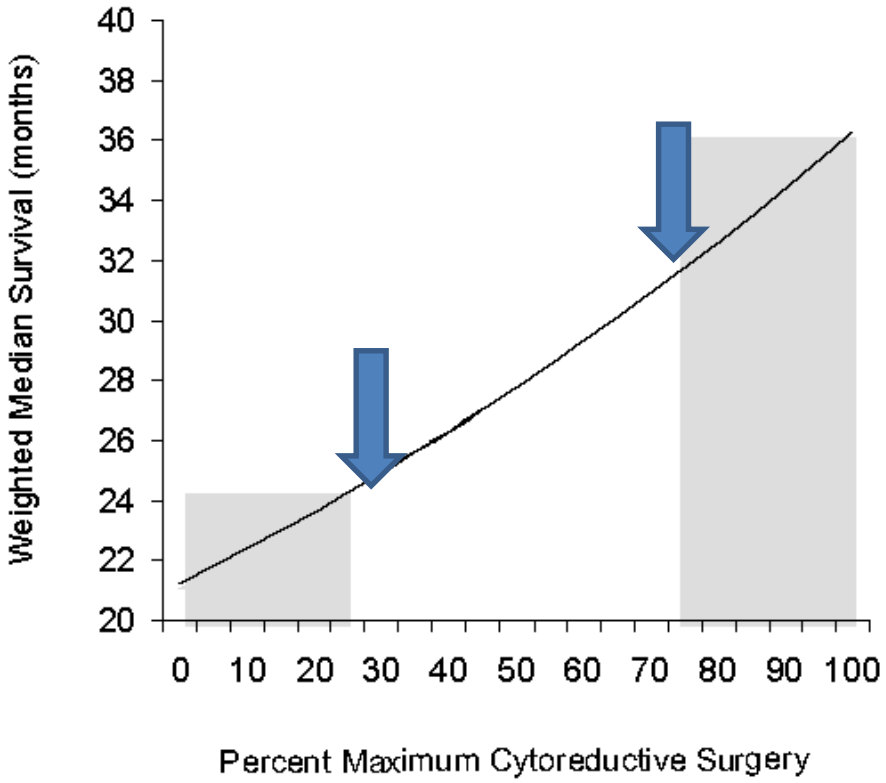
# Survival based on the maximum size of the residual tumor




- Optimal debulking = no residual tumor
- 60% of patients survived more than 5 years after optimal debulking

**Heintz,** Int J Gynecol Oncol 2006

# Survival: Bristow meta-analysis




Optimal debulking

**75%** **25%**

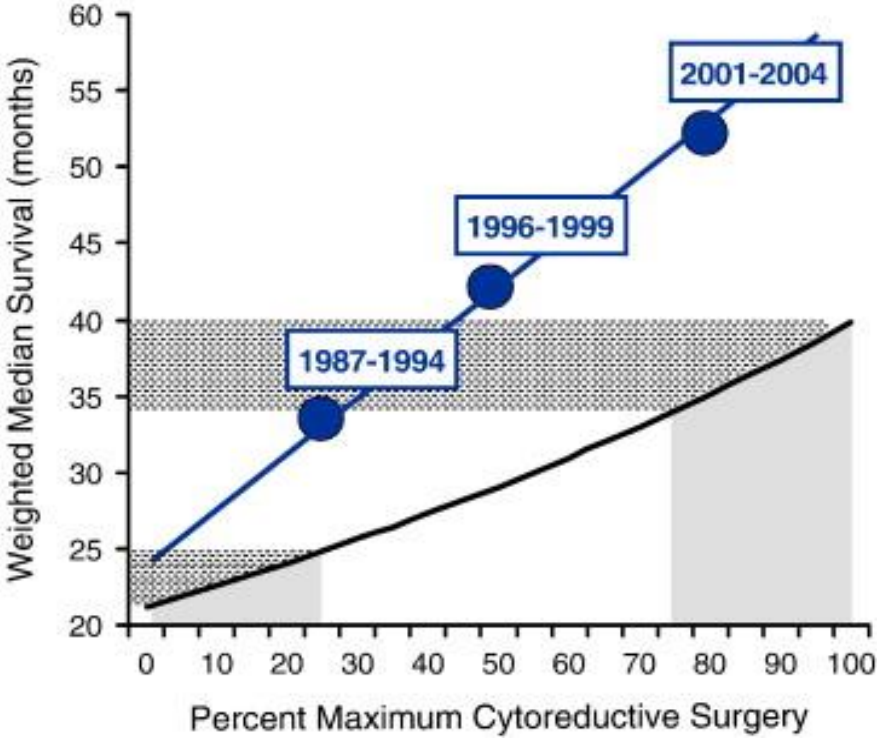
Median survival

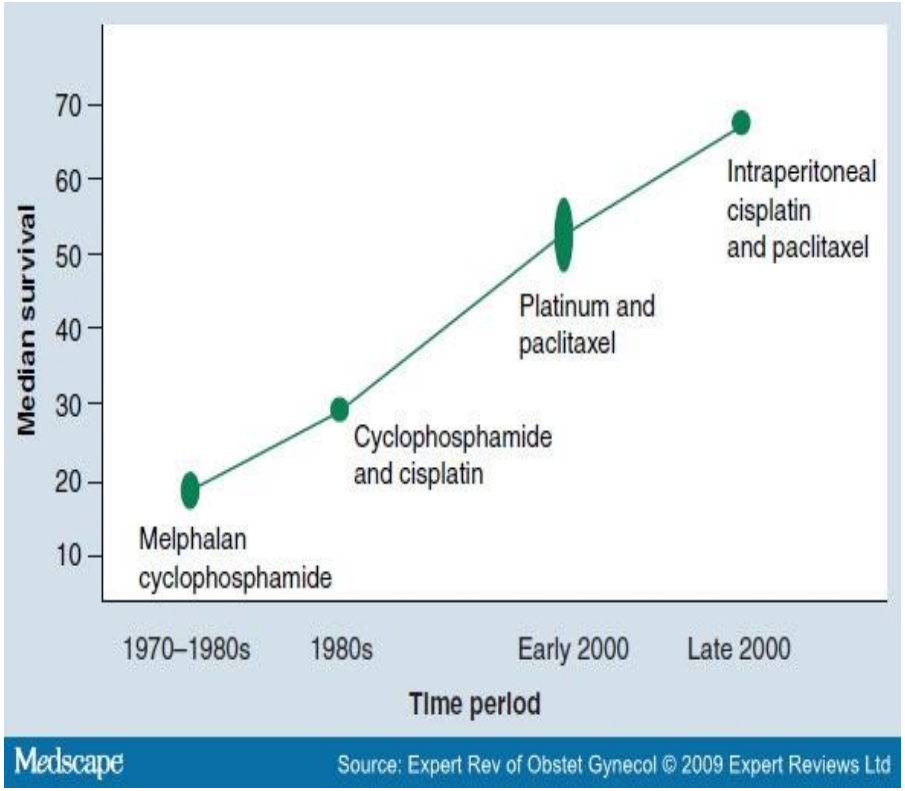
**34 months** **23 months**

**Each 10% increase in maximal cytoreduction was associated with a 1.9 month increase in median survival time**

**Bristow et al.** J Clin Oncol 2002

# AOC survival improvement: surgery or chemotherapy ?



# The mathematical model & biological rationale ..

- Likelihood of mutations resulting in drug resistance is depending upon the **amount of ca**ncer present when the chemotherapy is initiated
- Pts who are given chemotherapy with a **large tumor burden** may have a higher chance of developing drug resistance and consequently shorter PFS and OS

  **Goldie Coldman**, Cancer Treat Rep 1979; 63: 1727-33

**This phenomenon occurs before surgery!**

**Can the surgeon really select & excise the resistant cells?**

# Is this what they really meant ?

## Goldie-Coldman hypothesis

Definition: a mathematic model that predicts that tumor cells mutate to a resistant phenotype at a rate dependent on their **intrinsic genetic instability**. The probability that a cancer would contain drug-resistant clones depends on the mutation rate and the size of the tumor. According to this hypothesis, **even the smallest detectable cancers would contain at least one drug-resistant clone; therefore, the best chance of cure would be to use all effective chemotherapy drugs; in practice, this has meant using two different non–cross-resistant chemotherapy regimens in alternating cycles.**

# Debulking was totally accepted although..

- There is no surgical **standard or quality control,** especially in the private setting.
- There is no other solid malignancy in which this approach is accepted & practiced for **non-palliative** indications.
- The biological explanation **does not** exist.
- **Cannot be practiced** in many medical centers even with adequately trained surgeons.
- Too many patients do **not receive it**.

**"The final answer to the question of primary debulking surgery can be obtained from a prospective study in which patients will be randomized to primary chemotherapy followed by surgery vs. surgery followed by chemotherapy. Such a study is probably not feasible".**

**U. Beller and J. Speyer**
**NYU medical Center**

**Current Issues in the Evaluation and Treatment of Epithelial Carcinoma of the Ovary**

In: **Experimental and Clinical Progress in Cancer Chemotherapy**
**Franco M. Muggia (Editor), Martinus Nijhoff Publ, 1985**

To make a decision we need to look at

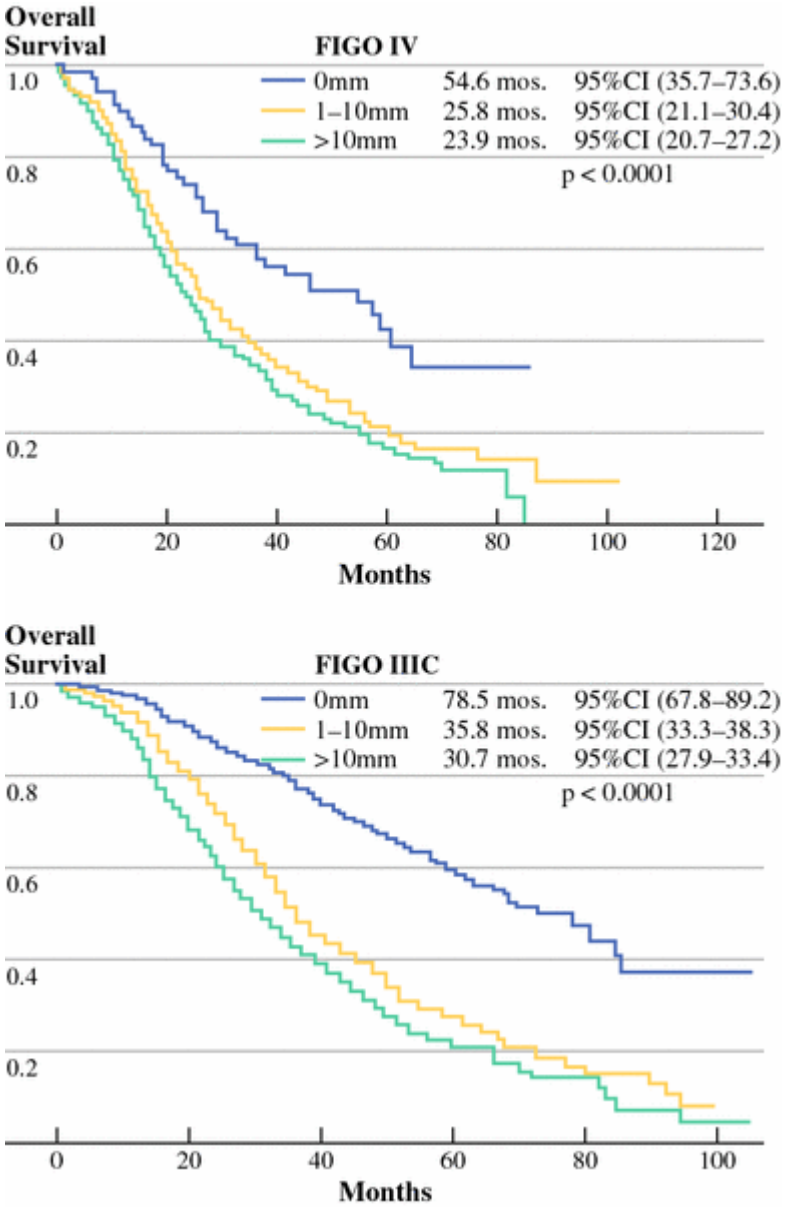
**Good Evidence !**

**Influence of residual tumor on outcome in ovarian cancer patients with FIGO stage IIIc, IV disease: an exploratory analysis of the AGO-OVAR (Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group).**

**Wimberger P**, Wehling M, Lehmann N, Kimmig R, Schmalfeldt B, Burges A, Harter P, Pfisterer J, du Bois A.
**Ann Surg Oncol. 2010 Jun;17(6):1642-8**

**3388** patients in trials/ **573** had stage IV.

**Level B evidence**



# Nonrandomized case control studies evaluating delayed debulking

| Name of Study | Colombo et al. [10] | Oksefjell et al. [11] | Hegazy et al. [12] | Le T et al. [13] | Rafii et al. [14] | Vergote [15] |
|---|---|---|---|---|---|---|
| N | 203 | 789(217 IDS 572 non IDS) | 59 all submitted to prior surgical exploration | 61 | 109 | 285 |
| FIGO stage | IIc-IV | All stages treated for 1st relapse | II-IV | IV without bowel obstruction | IV | III-IV |
| Important study data | Gr 1 conventional OS = 38 m Gr 2 with NACT OS = 26 m | Platinum single or combination/taxol single or combinationor other | *N = 27 (OS = 25 m) unresectable NACT with 18 for IDSN = 32 primary cytoreduction (OS = 28)* | NACT platinum-taxol OS = 41.7 m | NACT platinum- taxol + IDSOS = 45.5 m (under 20% of patients in study) | *Choice of treatment:* upfront surgery or NACT according to disease extent and patient PPS |
| Main conclusions | *Upfront surgery* for advanced operable disease<br>*NACT* for non operable or poor performance status with IDS ideally after 3 cycles | Benefit of IDS versus chemotherapy alone when tumour is localised.<br>Best OS (48 m) with radical primary cytoreduction, TFI >24 m & ≤ 39 years | *NACT* for unresectable tumours leads to a group of sensitive patients for successful IDS | Response rate to NACT comparable to that of upfront surgery stated in literature<br>Importance of maximal secondary cytoreduction in IDS | Benefit of IDS in patient responding to NACT<br>NACT can select patients for surgery | OS was higher for patients with high tumour load treated with NACT than with upfront surgery |

IDS: interval debulking surgery; m = months; NACT: neoadjuvant chemotherapy; OS: overall survival; PFS: progression free survival; PPS: patient performance status; TFI: treatment free interval.


**Colombo**, Europ J of Surg Oncol,2009
**Oksefjell**, Annals Oncol, 2009
**Hegazy**, World J Surg Oncol, 2009

**Le**, J Obst Gyn Canada, 2009
**Rafii**, Int J Gyn Cancer, 2007
**Vergote**, Gyn Oncol 1998

# Two meta-analyses: conflicting results

**Platinum-based neoadjuvant chemotherapy and interval surgical cytoreduction for advanced ovarian cancer: a meta-analysis**

- Each 10% increase in maximal cytoreduction was associated with a 1.9 month increase in median survival time
- Median OS was positively correlated with **platinum-taxane chemotherapy** and **increasing year of publication**
- Each incremental **increase in NACT cycles was associated with a decrease in median survival** time of 4.1 months

**Bristow, Chi.** Gynecol Oncol **2006**:103:1070-6

**Does neoadjuvant chemotherapy increase optimal cytoreduction rate in advanced ovarian cancer? Meta-analysis of 21 studies**

- The patients who received NACT had a lower risk of suboptimal cytoreduction than the patients with favorable conditions
- Heterogeneity in **year of publication**, **taxane use**, and **optimal cytoreduction** rate influenced median OS significantly
- The between-studies variation of the **number of NACT cycles did not influence survival**

**Kang, Nam.** Ann Surg Oncol **2009**;16:2315-20

# Two meta-analyses: conflicting results

- **Neoadjuvant chemotherapy is associated with inferior overall survival compared to initial surgery**
- Increasing percent maximal cytoreduction is positively associated with median cohort survival
- The negative survival effect of increasing number of chemotherapy cycles prior to interval surgery suggests that **definitive operative intervention should be undertaken as early in the treatment program as possible**

**Bristow, Chi.** Gynecol Oncol 2006:103:1070-6

- **Survival was similar in NACT/IDS and PDS/Chemo group**
- Pts treated with NACT presented more often with Stage IV disease and received less paclitaxel
- **NACT helped the gynecologic oncologist achieve an increased rate of optimal cytoreduction**

**Kang, Nam.** Ann Surg Oncol 2009;16:2315-20

**But where is the LEVEL A / I Evidence ?**

**The RCT's addressing Primary Intervention vs NACT in Advanced Ovarian cancer.**

# 2010: “Neo-adjuvant era”

The NEW ENGLAND JOURNAL of MEDICINE

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., Frédéric Amant, M.D., Ph.D., Gunnar B. Kristensen, M.D., Ph.D., Tom Ehlen, M.D., Nick Johnson, M.D., René H.M. Verheijen, M.D., Ph.D., Maria E.L. van der Burg, M.D., Ph.D., Angel J. Lacave, M.D., Pierluigi Benedetti Panici, M.D., Ph.D., Gemma G. Kenter, M.D., Ph.D., Antonio Casado, M.D., Cesar Mendiola, M.D., Ph.D., Corneel Coens, M.Sc., Leen Verleye, M.D., Gavin C.E. Stuart, M.D., Sergio Pecorelli, M.D., Ph.D., and Nick S. Reed, M.D., for the European Organization for Research and Treatment of Cancer–Gynaecological Cancer Group and the NCIC Clinical Trials Group* — a Gynecologic Cancer Intergroup Collaboration

N ENGL J MED 363;10 NEJM.ORG SEPTEMBER 2, 2010

# EORTC 55971

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

Ignace Vergote, M.D., Ph.D.,et al.

***N Engl J Med 2010;363:943-53.***

**718 Patients Randomized**

# The EORTC 55971-NCIC study

**Randomized trial in women with AOC comparing**:

primary debulking surgery followed by platinum-based chemotherapy

platinum-based neoadjuvant chemotherapy followed by interval debulking surgery and additional platinum-based chemotherapy

# Randomization

**primary debulking**

**neoadjuvant chemotherapy**

non optimal cytoreduction

interval debulking surgery was permitted if stable disease or a response was documented, and these patients were included in the primary-surgery group for analyses.

# Randomization

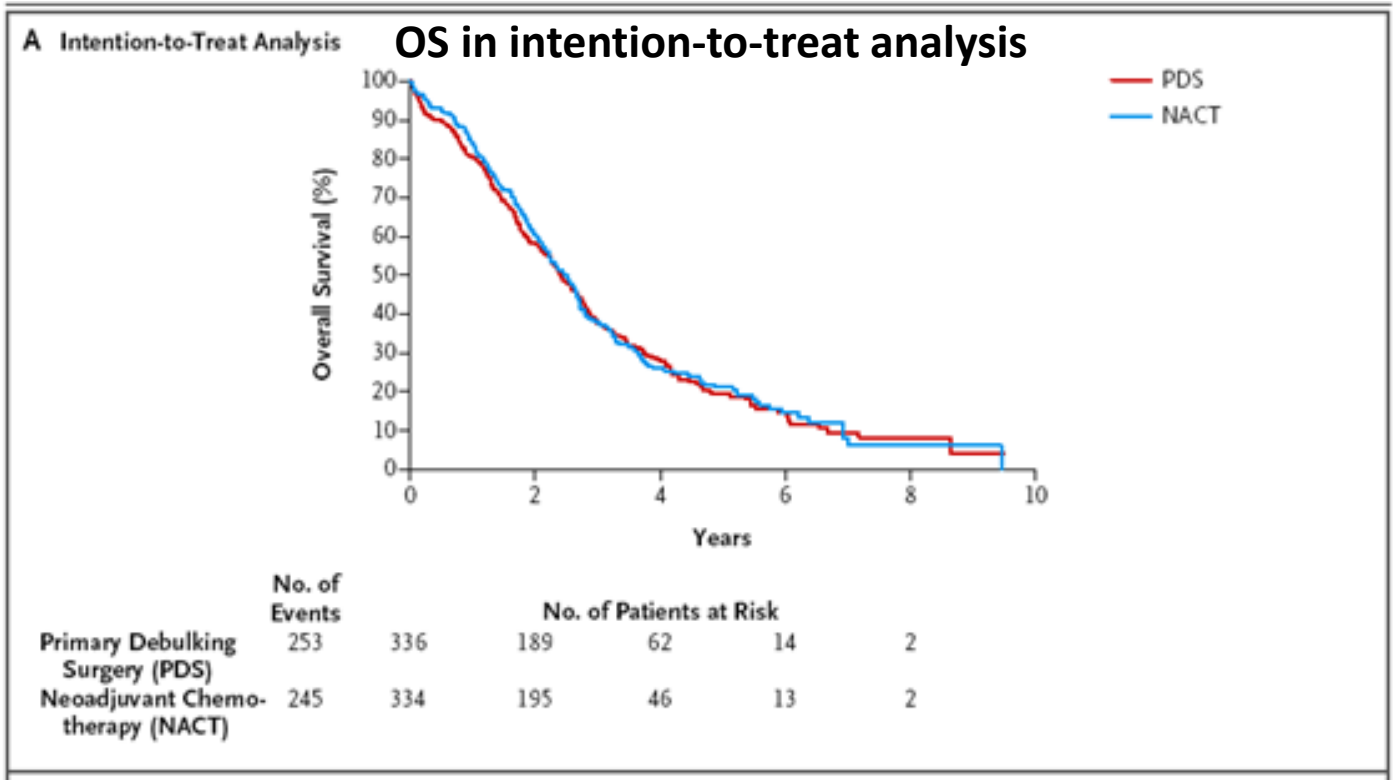
**primary debulking**

**neoadjuvant chemotherapy**

Interval debulking surgery was to be performed as soon as possible after hematological recovery, but within 6 weeks after the completion of the third chemotherapy cycle.
The first cycle of chemotherapy after surgery was to be administered as soon as possible, but no more than six weeks later.

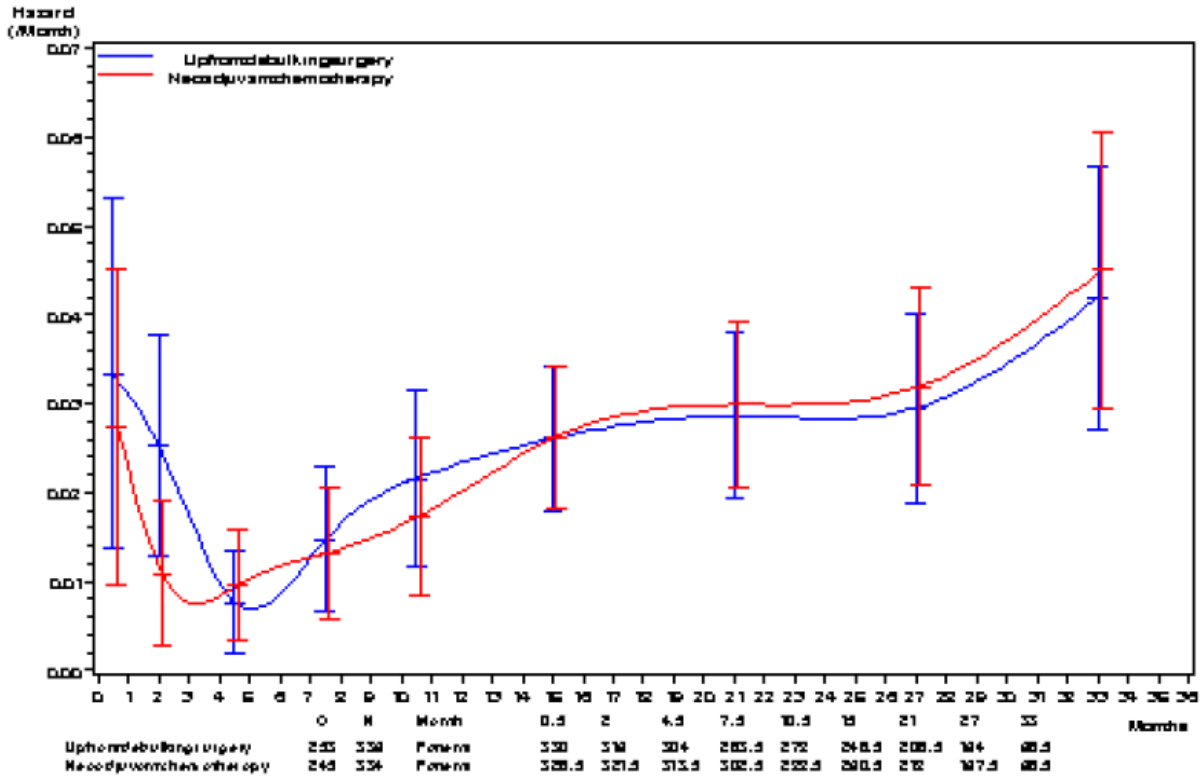
# Median survival (months)

**PDS: 29** **NACT: 30**




**Vergote et al**, N Engl J Med 2010; 363: 943-53

# Overall survival rates at different time points




**Blue line:**
**primary debulking**

**Red line:**
**neoadjuvant chemotherapy**

It can be seen that at 2 months the hazard in the PDS arm looks larger compared to the NACT arm, probably due to the fore mentioned post operative deaths. However the trend is reversed around month 5 and any difference disappears at later times.

# Overall survival (months) and residual tumor

| | No residual tumor | < 10 mm | > 10 mm |
|---|---|---|---|
| PDS | 45 | 32 | 26 |
| NACT | 38 | 27 | 25 |

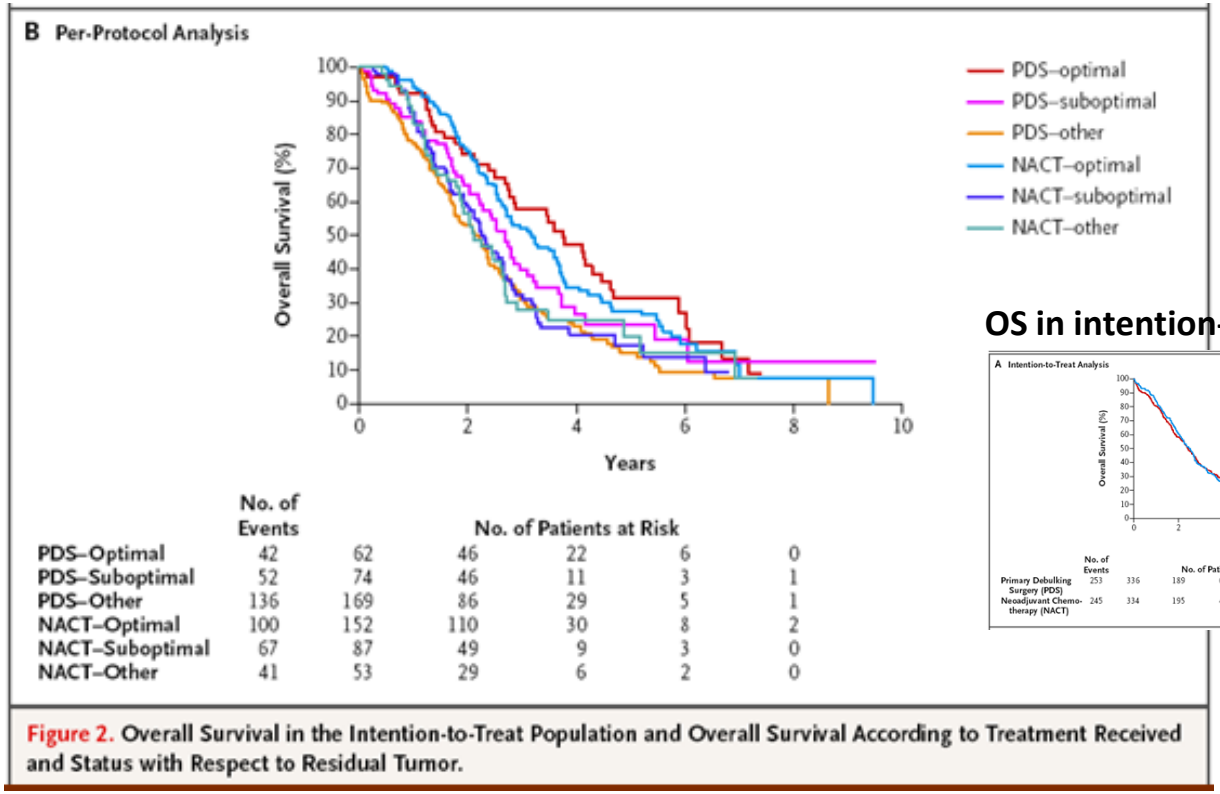
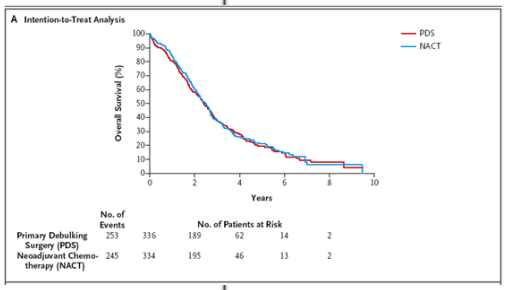



Figure 2. Overall Survival in the Intention-to-Treat Population and Overall Survival According to Treatment Received and Status with Respect to Residual Tumor.

**OS in intention-to-treat analysis**



# Post-op morbidity and mortality

| | Primary debulking | Neoadjuvant chemotherapy |
|---|---|---|
| Peri- and postoperative adverse events – no.(%)[#,&] | | |
| Postoperative death (< 28 days) | 8 (2.5) | 2 (0.7) |
| Hemorrhage grade[¤] | | |
| 3 | 17 (5.5) | 11 (3.8) |
| 4 | 6 (1.9) | 1 (0.3) |
| Venous grade[¤] | | |
| 3 | 5 (1.5) | - |
| 4 | 3 (1.0) | - |
| Infection grade[¤] | | |
| 3 | 20 (6.5) | 3 (1.0) |
| 4 | 5 (1.6) | 2 (0.7) |
| Gastrointestinal fistula | 3 (1.0) | 1 (0.3) |
| Urinary fistula | 1 (0.3) | 1 (0.3) |
| **Total** | **20.8 %** | **7.1 %** |

# EORTC-NCIC study: primary outcome

Survival after NACT followed by IDS

**is similar**

to survival after PDS followed by chemotherapy.

**OS**: 30 vs. 29 months

**PFS**: 12 months

**NACT = Neo-Adjuvant Chemotherapy**

**IDS = Interval Debulking Surgery**

**PDS = Primary Debulking Surgery**

**OS = Overall Survival**

**PFS = Progression Free Survival**

# EORTC-NCIC study: conclusion

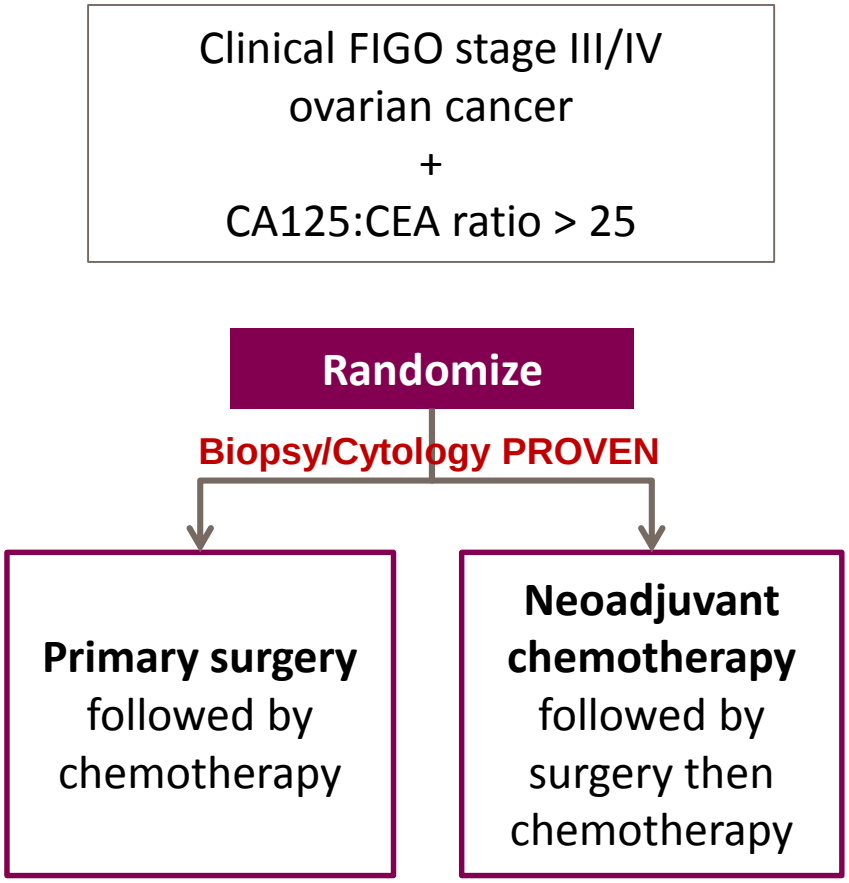
**NACT followed by IDS was not inferior to PDS followed by chemotherapy as a treatment option for patients with bulky stage IIIC or IV AOC**

# Chemotherapy or upfront surgery for newly diagnosed advanced ovarian cancer

## Results from the MRC CHORUS trial

S Kehoe, JM Hook, M Nankivell, GC Jayson, HC Kitchener, T Lopes, D Luesley, TJ Perren, S Bannoo, M Mascarenhas, S Dobbs, S Essapen, J Twigg, J Herod, WG McCluggage, M Parmar, AM Swart on behalf of the CHORUS trial collaborators and NCRI Gynaecological Cancer Studies Group

# CHORUS Trial Design




**Imaging +/- clinical evidence of pelvic mass with extra-pelvic metastases**

**→Compatible with FIGO stage III/IV**

**Serum CA 125:CEA ratio > 25**

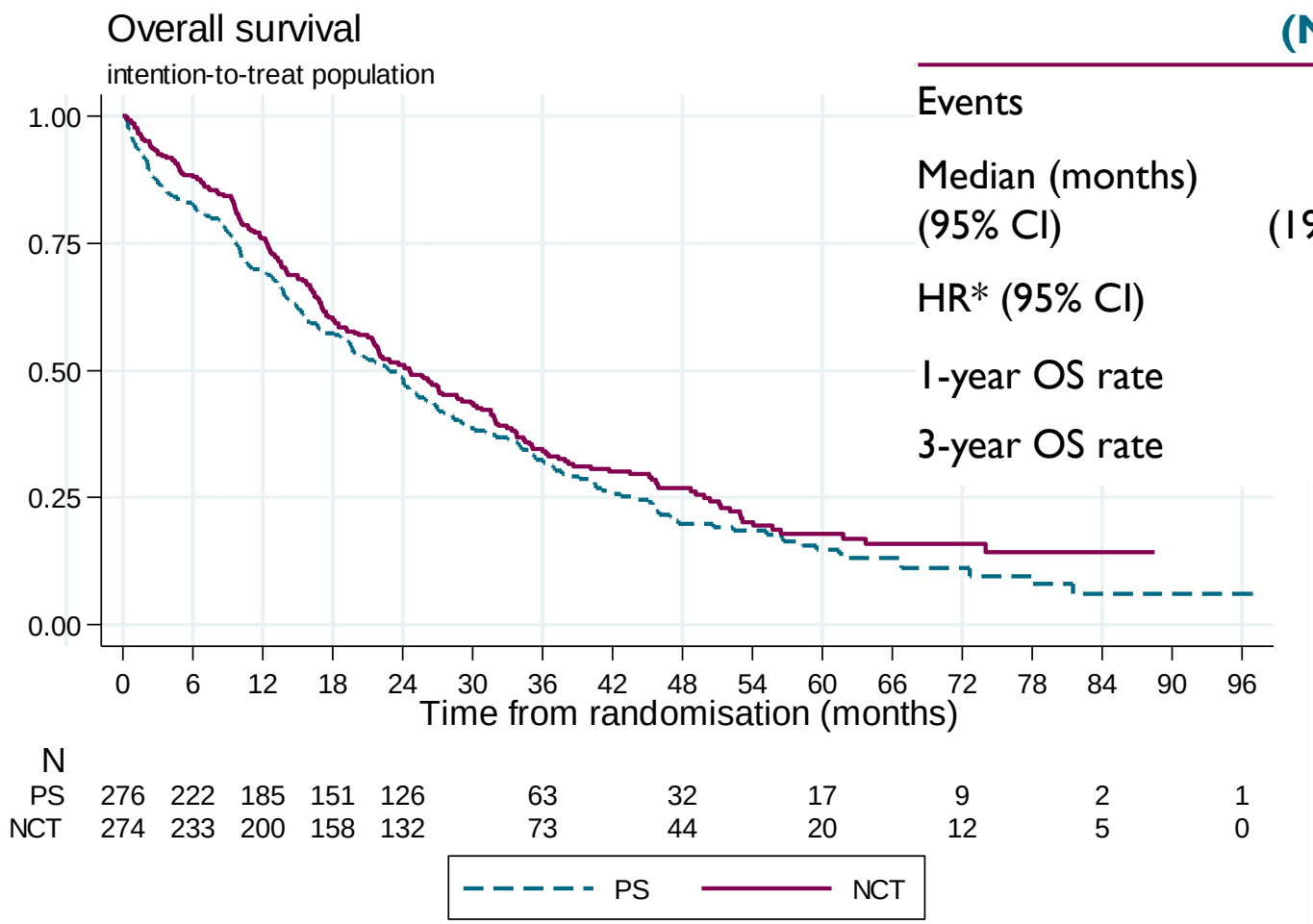
**Investigation to exclude GI cancer mandated if ≤25 & serum CEA > ULN**

**Planned to receive carboplatin-based chemotherapy**

**Fit to undergo protocol treatment**

**Written informed consent**

# Overall survival




| | PS (N=276) | NCT (N=274) |
|---|---|---|
| Events | 211 | 199 |
| Median (months) (95% CI) | 22.8 (19.1, 26.0) | 24.5 (21.3, 29.1) |
| HR* (95% CI) | 0.87 (0.71, 1.05) | |
| 1-year OS rate | 70% | 76% |
| 3-year OS rate | 32% | 34% |

* HR adjusted for baseline stratification factors.

# Both Trials Showed..

***Reduction in Morbidity for the Neo-adjuvant Arms***

**CHORUS**

| | | |
|---|---|---|
| Any grade 3/4 complication | **PS = 24%** | **NCT = 14%** |
| Discharge within 14 days post-op | **PS = 74%** | **NCT = 92%** |

| **EORTC** | **PS** | **NCT** |
|---|---|---|
| Postoperative sepsis | **8%** | **2%** |
| Fistula (bowel/GU) | **1.2% / 0.3%** | **0.3% / 0.6%** |
| Red blood cell transfusion | **51%** | **53%** |
| Haemorrhage Grade ¾ | **7%** | **1%** |
| Venous Gr ¾ | **2.4%** | **0.3%** |

# So we have..

- **Two Prospective Randomised Trials – LEVEL A/I**
- **Both Showing that Neoadjuvant chemotherapy is NOT inferior to Primary Debulking Surgery with respect to Survival**
- **Both Showing that *Treatment related Morbidity is decreased in the Neo-adjuvant setting!***

# We must operate upfront

Tumour debulking at primary surgery affords the best outcome –

**[*based on what prospective RCT?]***

These trials do not address quality of primary debulking surgery –

**[*they never claimed to do this*]**

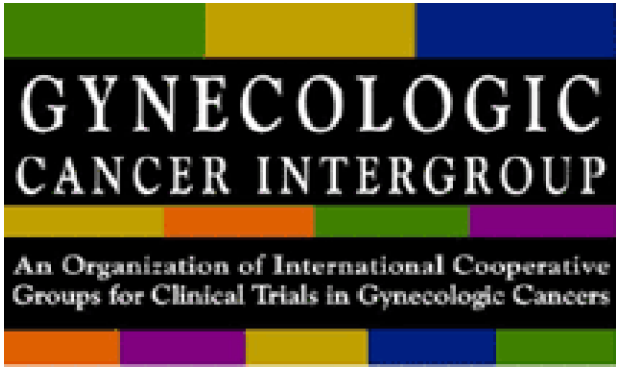
We need a trial with **'best'** surgery

**[should *we do it again?*]**


# PRIMIUM NON NOCERE

***First Do No Harm***

# The 4th Ovarian Cancer Consensus Conference




**The 4th Ovarian Cancer Consensus Conference, Vancouver 2010**

**2010 Gynecologic Cancer InterGroup (GCIG) Consensus Statement on Clinical Trials in Ovarian Cancer**

**Int J Gynecol Cancer 2011;21: 750-755**

# Level of consensus:
# 21 of the 23 member groups

**Surgery remains an integral component of the successful treatment of women with advanced ovarian cancer.**
**New evidence has affected the timing of this surgery and the extent of initial efforts to achieve optimal cytoreduction.**
**This evidence needs to be accommodated in the design of new trials in this population.**

**The 4th Ovarian Cancer Consensus Conference, Vancouver 2010**

2010 Gynecologic Cancer InterGroup (GCIG) Consensus Statement on Clinical Trials in Ovarian Cancer

**Int J Gynecol Cancer 2011;21: 750-755**

# Minority statement
# (2 from 23 members groups)

**Neoadjuvant chemotherapy cannot be regarded as adequate routine therapy strategy of advanced ovarian cancer** and should be limited to selected patients with very advanced FIGO stage IIIC or IV disease and contraindications against upfront debulking surgery or tumor dissemination, implying no chance for complete resection.

**Minority Vote to statement A 5 of the 4th Ovarian Cancer Consensus Conference, Vancouver 2010**

Gynecologic Cancer InterGroup (GCIG) Consensus Statement on Clinical Trials in Ovarian Cancer

**Int J Gynecol Cancer 2011;21: 750-755**

# Two reasons led to a minority vote

**Statement was based on unpublished but only presented evidence**

**"We interpret available data of the EORTC trial and others with more caution and come to different conclusions"**

**Minority Vote to statement A 5 of the 4th Ovarian Cancer Consensus Conference, Vancouver 2010** Gynecologic Cancer InterGroup (GCIG) Consensus Statement on Clinical Trials in Ovarian Cancer

Int J Gynecol Cancer 2011;21: 750-755

# Inclusion criteria unique to this study

## Pre- selection of patients with more advanced disease before randomization

- Median tumor size 8 cm in both arms
- 62% of patients extrapelvic disease > 10 cm
- Very low median survival - 29 months
- Other studies of advanced ovarian cancer-
  median survival of 43- 49 months (AGO-OVAR 3,5,7,9)

**Cannot be compared to other studies with similar FIGO stages**

**du Bois** et al, Int J Gyn Cancer, Feb 2012

# Heterogeneity of chemo regimens

## Variety of chemotherapy regimens allowed

- The recommended chemotherapy regimen was paclitaxel + carboplatin
- However, other regimens including cisplatin every 3 weeks, or carboplatin were allowed.
- Distribution of regimens not properly randomized:
  - ❖ **72.3%** of primary surgery arm received platinum + Taxane regimen
  - ❖ **84.7%** of NACT arm received this regimen

**Obvious advantage in chemo administered to NACT arm**

**du Bois** et al, Int J Gyn Cancer, Feb 2012

# Complete resection and survival

- Complete resection rate of 19.4% in PDS arm is low in comparison to other studies
- Median length of surgery 180 min indicates **"reduced surgical effort"**
- Improved resection rate in NACT arm vs. PDS arm (32%) **did not result in improved survival**

**NACT nullifies the effect of optimal debulking:**

**du Bois** et al, Int J Gyn Cancer, Feb 2012

# Variable & suboptimal surgical success

**Surgical outcome heterogeneous**

Complete resection rates (primary debulking)

- Holland **3.9%**, Italy **6.3%**
- Belgium **62.9%**

**du Bois** et al, Int J Gyn Cancer, Feb 2012

# Variable & suboptimal surgical success

| | Primary debulking | NACT | Δ |
|---|---|---|---|
| Complete resection (%) | 19.4 | 51.2 | **31.8** |
| Residua < 10 mm (%) | 41.6 | 80.7 | **39.1** |

**Low rate of optimal debulking**

**du Bois** et al, Int J Gyn Cancer, Feb 2012

# Variable & suboptimal surgical success

**Arm advantage was heterogeneous between different countries**

- Canada, Spain, Italy: advantage to **PDS**
- Holland and others: advantage to **NACT**
- Overall no advantage to either arm

**The sum effect of no advantage is an average of opposite trends**

**du Bois** et al, Int J Gyn Cancer, Feb 2012

# Residual disease and survival

| | No residual tumor | < 10 mm | > 10 mm |
|---|---|---|---|
| PDS | 45 | 32 | **26** |
| NACT | 38<br>**Δ 7 months** | 27<br>**Δ 5 months** | **25** |

**Only patients with residual disease > 1 cm after surgery showed no advantage to surgery arm**
**(but majority of patients was in this group)**

**du Bois** et al, Int J Gyn Cancer, Feb 2012

# Peri- operative m & m

**Significant differences in m&m reported**

- PDS arm: 8 peri-operative deaths
- NACT arm: 2 peri-operative deaths
- No surgery in 12% of NACT population (too sick / disease progression)

**Deaths prior to surgery in NACT arm not counted: misleading advantage**

**du Bois** et al, Int J Gyn Cancer, Feb 2012

# Criticism of EORTC-NCIC study (2)

**Chi** et al: Single center non-randomized study from MSKCC, NY, 01/2012

Gyn Oncol, Jan 2012, 10-14

# An analysis of patients with bulky advanced stage ovarian, tubal, and peritoneal carcinoma treated with primary debulking surgery (PDS) during an identical time period as the randomized EORTC-NCIC trial of PDS vs neoadjuvant chemotherapy (NACT)

**342 pts**

316 (90%) - PDS, 31 (10%) - NACT

Optimal debulking (< 1 cm residua) – 71%

**Chi et al**, Gynecol Oncol, 124 (2012) 10-14

# An analysis of patients with bulky advanced stage ovarian, tubal, and peritoneal carcinoma treated with primary debulking surgery (PDS) during an identical time period as the randomized EORTC-NCIC trial of PDS vs neoadjuvant chemotherapy (NACT)

| | EORTC-NCIC | MSKCC |
|---|---|---|
| PFS (months) | 12 | 17 |
| OS (months) | 29/30 | 50 |

**Vergote et al**, N Engl J Med 2010; 363: 943-53

**Chi et al**, Gynecol Oncol, 124 (2012) 10-14

# MSKCC study: 31 (10%) pts in NACT “arm”

| | EORTC-NCIC | MSKCC NACT “arm” |
|---|---|---|
| PFS (months) | 12 | 13 |
| OS (months) | 29/30 | 37 |

- **Extra-abdominal disease**
- **Extensive unresectable intra-abdominal disease**
- **Advanced age**

# MSKCC study conclusions

- PDS should continue to be the preferred **initial** management
- Although NACT hase been associated with decreased surgical morbidity, OS is 30-36 months, comparable with **sub-optimally** debulked during PDS
- New GOG trial – **DENIED !!**
- NACT should be reserved for pts who do **not have access to well-trained surgeon**, **cannot tolerate** the procedure or for whom **optimal cytoreduction is not feasible**

# MSKCC paper criticised

- Comparing the results of a **retrospective non-randomized one tertiary referral center study** excluding 17% of pts from PDS “arm” and the results of **multicenter Phase III RCT**
- Survival in EORTC-NCIC study was lower, but
  - Stages IIIa and IIIb were excluded
  - Stage IIIc due to para-aortic mts < 2 cm were not eligible (the better prognosis expected in this group)
- Percentage of pts with **no residual tumor** is only slightly higher in MSKCC study(24% vs. 19% in EORTC)

# What role does surgery play today?


- **Surgical staging should be mandatory** and should be performed by a gynecologic oncologist.
- **The ultimate goal is cytoreduction to microscopic disease**. There is evidence that reduction of macroscopic disease to 1 cm or less is associated with some benefit. **The term "optimal" cytoreduction should be reserved for those with no macroscopic residual disease**.
- **Documentation must be provided as to the level of cytoreduction** (at least microscopic vs. macroscopic).
- **Delayed primary surgery after neoadjuvant chemotherapy is an option for selected patients with stage IIIC or IV ovarian cancer as included in EORTC 55971**

**The 4th Ovarian Cancer Consensus Conference, Vancouver 2010**

2010 Gynecologic Cancer InterGroup (GCIG) Consensus Statement on Clinical Trials in Ovarian Cancer
Int J Gynecol Cancer 2011;21: 750-755

# Decision making: PDS vs. NACT

- Tumor stage & bulk ( surgical exploration? )
- Possibility of optimal cytoreduction
- Institutional commitment
- Age
- Coexisting illnesses
- Performance status
- Technical possibility of “super-radical” surgery
- Supporting subspecialties

# In the Neo-adjuvant era

**The most important question now is not when a debulking surgery should be performed, but how to select pts for PDS or NACT/IDS with the aim of leaving no residual tumor at the time of surgery**

**Vergote**. Gynecol Oncol 2012;124:1-2

# Leuven 2011 criteria for NACT/IDS in AOC (FIGO stage IIIc and IV )

- Poor general conditions
- Tumors around superior mesenteric artery or porta hepatis
- Exrta-abdominal mts
  (excluding resectable inguinal nodes and pleural fluid containing malignant cells without presence of pleural tumors)
- Extensive serosal invasion of the intestines
- PTS that cannot be “easily” debulked to no residual tumor (expected operative time > 4 h)

**50% of PTS will be selected to NACT/IDS**

**Adapted from: Vergote et al**. Eur J Cancer 2011;47(Suppl.3):S88-92

Gynecologic Oncology 128 (2013) 6–11

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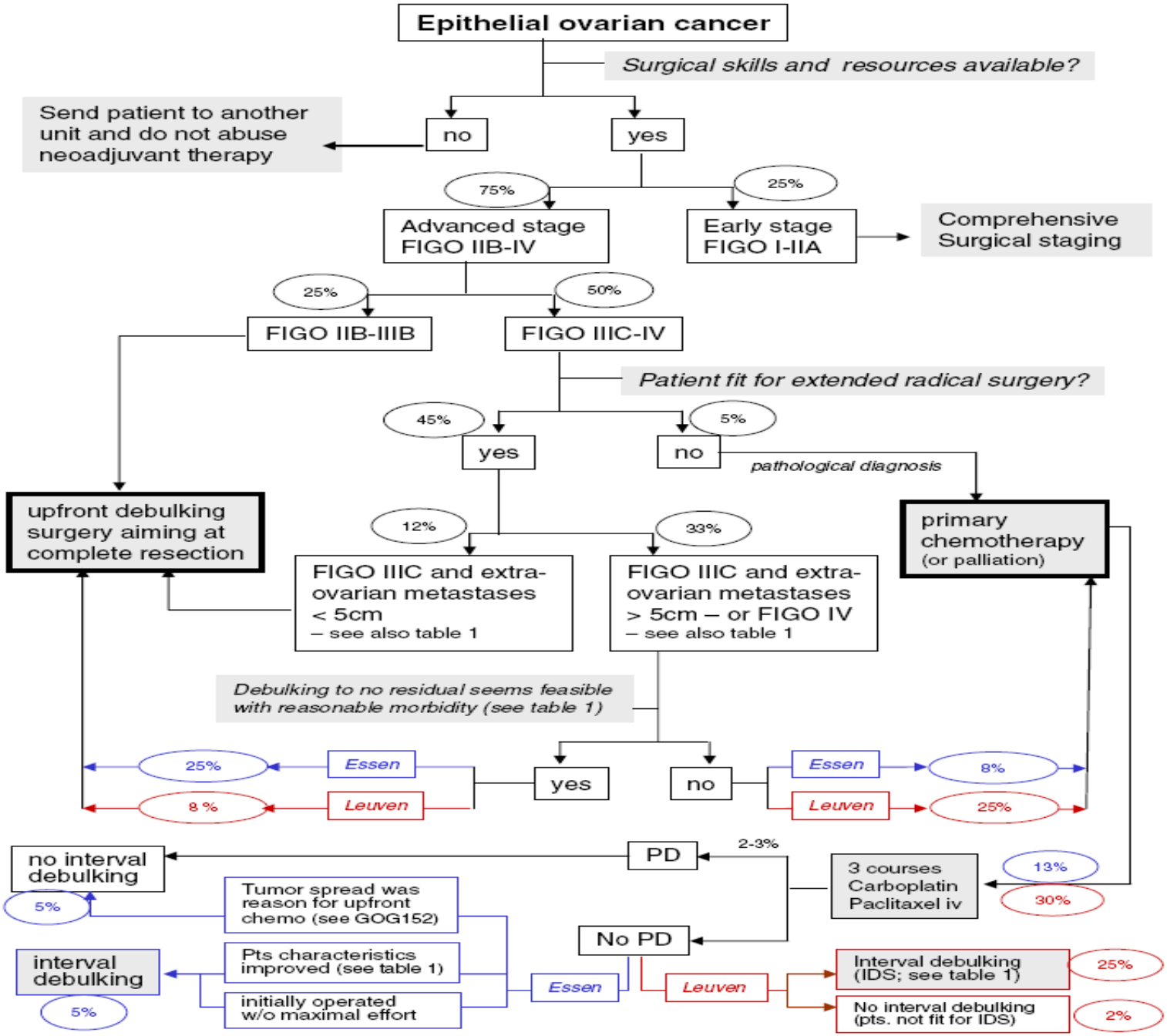
Clinical Commentary

# Neoadjuvant chemotherapy in advanced ovarian cancer: On what do we agree and disagree?

Clinical Commentary :
Gynecol Oncol 128(2013)
I. Vergote & A. DuBois et al

# Neoadjuvant chemotherapy in advanced ovarian cancer:

# On what do we agree and disagree?


Epithelial ovarian cancer
Surgical skills and resources available?
Send patient to another unit and do not abuse neoadjuvant therapy
no
yes
75%
25%
Advanced stage FIGO IIB-IV
Early stage FIGO I-IIA
Comprehensive Surgical staging
25%
50%
FIGO IIB-IIIB
FIGO IIIC-IV
Patient fit for extended radical surgery?
45%
5%
yes
no
pathological diagnosis
upfront debulking surgery aiming at complete resection
primary chemotherapy (or palliation)
12%
33%
FIGO IIIC and extra-ovarian metastases < 5cm – see also table 1
FIGO IIIC and extra-ovarian metastases > 5cm – or FIGO IV – see also table 1
Debulking to no residual seems feasible with reasonable morbidity (see table 1)
25%
Essen
8 %
Leuven
yes
no
Essen
8%
Leuven
25%
no interval debulking
5%
PD
2-3%
3 courses Carboplatin Paclitaxel iv
13%
30%
Tumor spread was reason for upfront chemo (see GOG152)
No PD
interval debulking
5%
Pts characteristics improved (see table 1)
initially operated w/o maximal effort
Essen
Leuven
Interval debulking (IDS; see table 1)
25%
No interval debulking (pts. not fit for IDS)
2%

Criteria for primary chemotherapy and for interval debulking surgery in FIGO stages IIIC and IV ovarian carcinoma.

| Criteria | Essen criteria | Leuven criteria |
|---|---|---|
| Diagnosis: | Biopsy with histologically proven epithelial ovarian (or tubal or peritoneal) cancer FIGO stage IIIC-IV | |
| | - | Or fine needle aspiration proving the presence of carcinoma cells in patients with a suspicious pelvic mass if CA125 (KU/L)/CEA (ng/mL) ratio is > 25. If the serum CA125/CEA ratio is ≤ 25, imaging or endoscopy is obligatory to exclude a primary gastric, colon or breast carcinoma |
| Abdominal metastases: | Involvement of the superior mesenteric artery | |
| | Diffuse deep infiltration of the radix mesenterii of the small bowel | |
| | Diffuse and confluent carcinomatosis of the stomach and/or small bowel involving such large parts that resection would lead to a short bowel syndrome or a total gastrectomy | |
| | Multiple parenchymatous liver metastases in both lobes | Intrahepatic metastases |
| | Tumor involving large parts of the pancreas (not only tail) and/or the duodenum | Infiltration of the duodenum and/or pancreas and/or the large vessels of the ligamentum hepatoduodenale, truncus coeliacus or behind the porta hepatis |
| | Tumor infiltrating the vessels of the lig. Hepatoduodenale or truncus coeliacus | |
| Extra-abdominal metastases: | Not completely resectable metastases, as eg.<br>- Multiple parenchymal lung metastases (preferably histologically proven)<br>- Non resectable lymphnode metastases<br>- Brain metastases | All excluding:<br>- Resectable inguinal lymph nodes<br>- Solitary resectable retrocrual or paracardial nodes<br>- Pleural fluid containing cytologically malignant cells without proof of the presence of pleural tumors |
| Patients characteristics/others | Impaired performance status and co-morbidity not allowing a "maximal surgical effort" to achieve a complete resection | |
| | Patients' non-acceptance of potential supportive measures as blood transfusions or temporary stoma | |
| Criteria for interval debulking: | - Upfront surgical effort in an institution without expert surgical skills/infrastructure<br>- Barrier for initial surgery has disappeared (eg. improved medical condition)<br>- Not, if reason for primary chemotherapy was tumor growth pattern diagnosed during open surgery by an experienced gynecologic oncologist under optimal circumstances (as in GOG study 152) | - No progressive disease, and<br>- In case of extraabdominal disease at diagnosis the extra abdominal disease should be in complete response or resectable, and<br>- Performance status and co-morbidity allowing a maximal surgical effort to no residual diseases. |

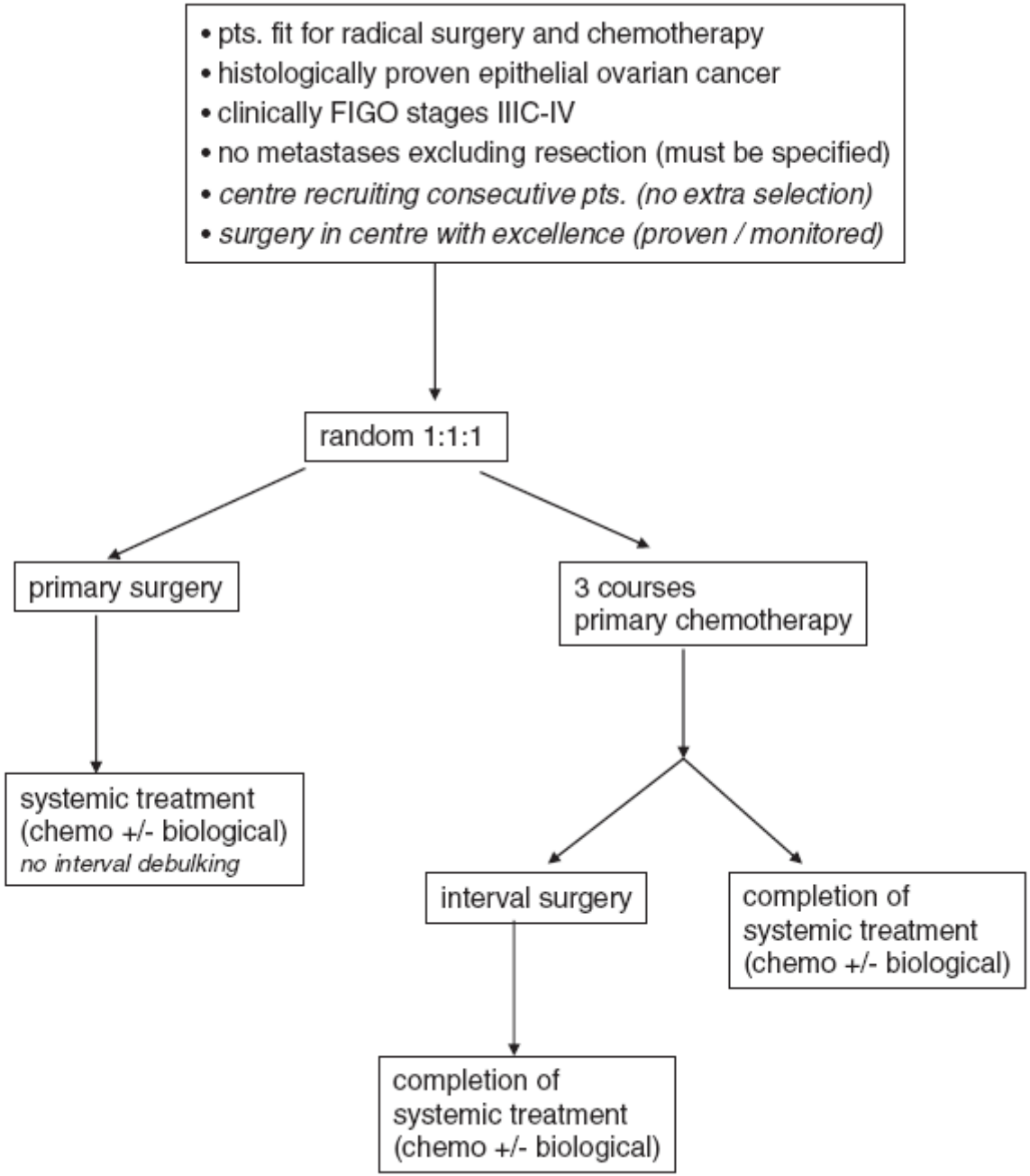


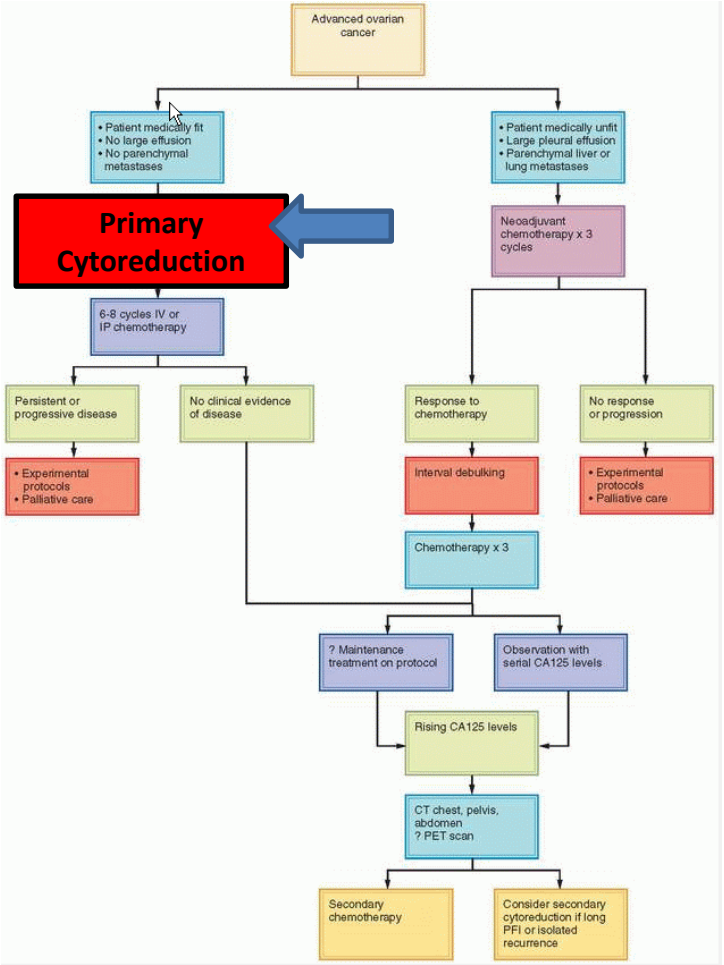

Fig. 2. Design of a theoretical future trial evaluating the role of surgery in advanced ovarian cancer.

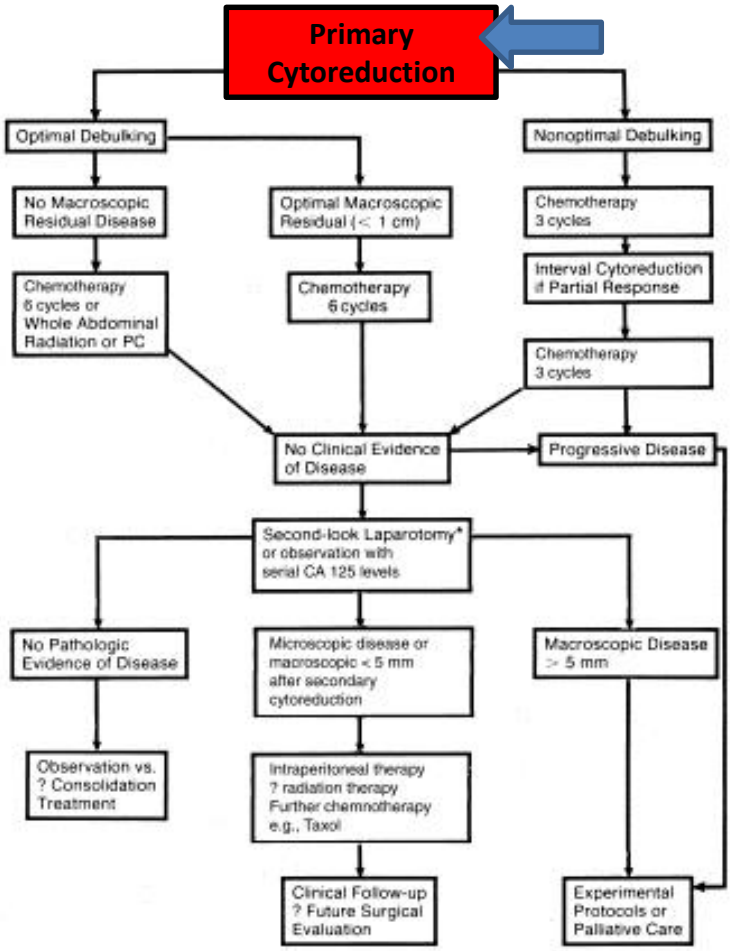
# Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer.

Jo Morrison[1,*], Krishnayan Haldar[2], Sean Kehoe[3], Theresa A Lawrie[4]
Editorial Group: Cochrane Gynaecological Cancer Group
**Published Online: 15 AUG 2012**

***We consider the use of NACT in women with stage IIIc/IV ovarian cancer to be a reasonable alternative to PDS, particularly in bulky disease. With regard to selecting who will benefit from NACT, treatment should be tailored to the patient and should take into account resectability, age, histology, stage and performance status. These results cannot be generalised to women with stage IIIa and IIIb ovarian cancer; in these women, PDS is the standard. We await the results of three ongoing trials, which may change these conclusions.***

# AOC: evolution of treatment scheme



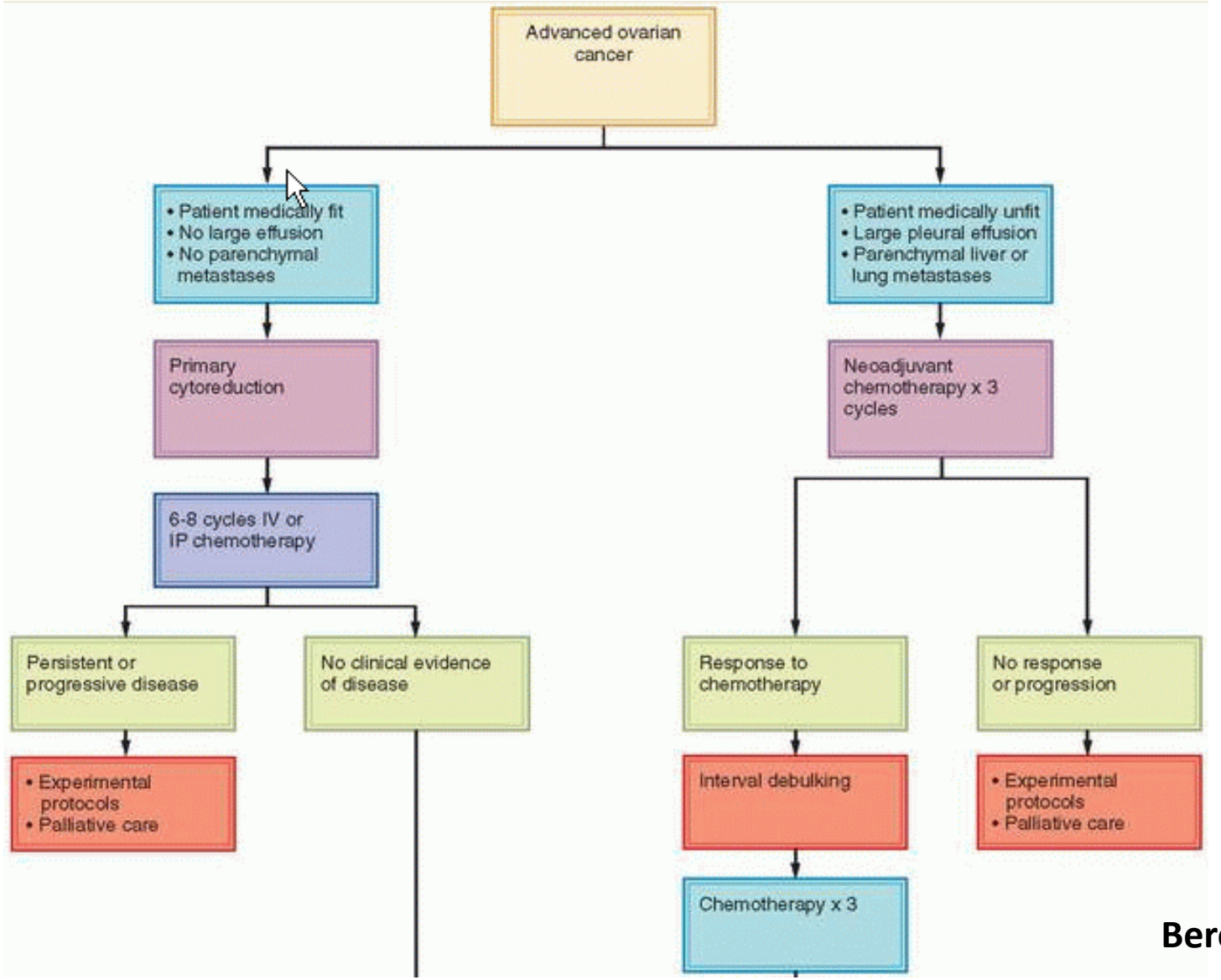




**Berek JS.** Practical gynecologic oncology

5th ed. **2009**

3rd ed. **2000**

# AOC: treatment scheme

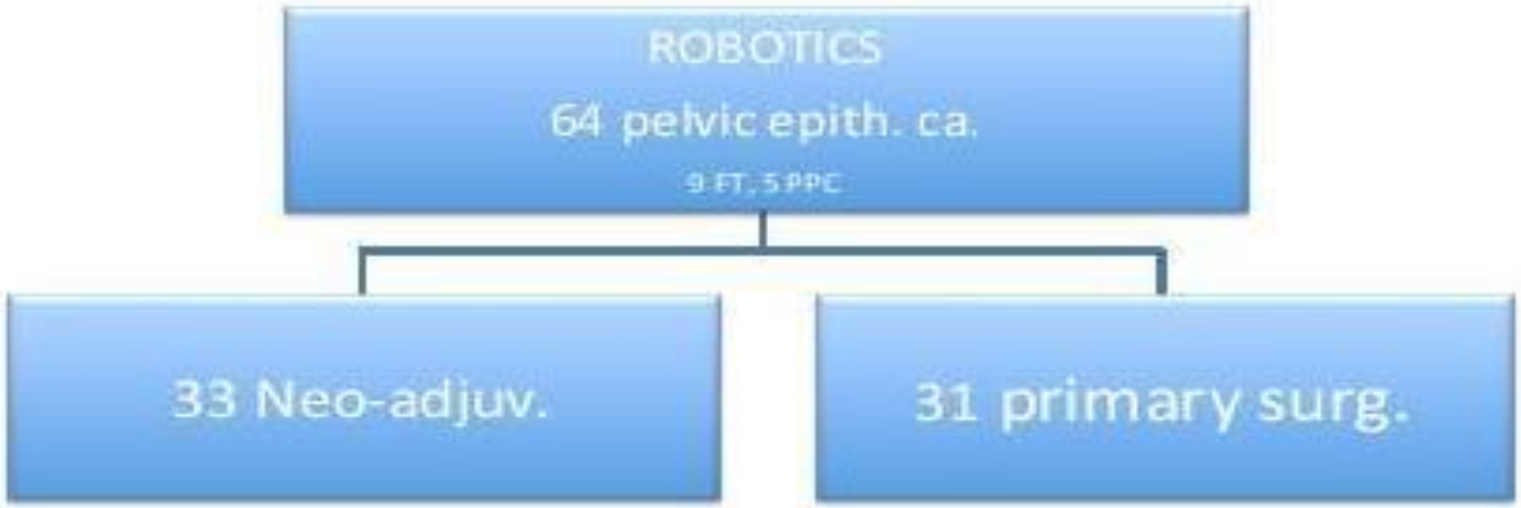



**Berek**, 2009

**Only one person can convince US surgeons to move to NACT..**

# Da Vinci

# Pelvic epith. Cancer



| | NACT (33) | PDS (31) |
|---|---|---|
| St Ic | 2 | 12 |
| St IIc | 1 | 6 |
| **St IIIc** | **22** | **11** |
| **St IV** | **8** | **2** |
| | | |
| Serous | 29 | 22 |
| Endometrioid | 3 | 6 |
| Clear cell | 1 | 2 |
| Adenosquamous | | 1 |

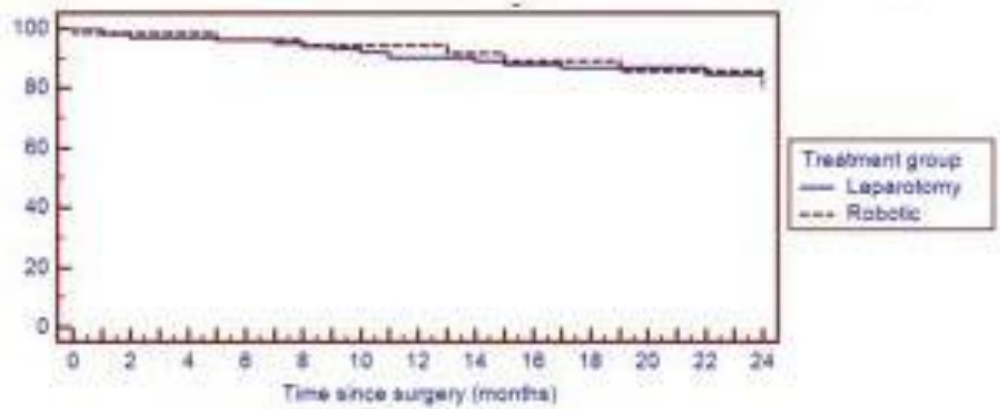
# Patient characteristics

| | NACT (33) | PDS (31) |
|---|---|---|
| Age | 60.1 (24-87) | 60.5 (29-88) |
| BMI | 26.1 (17.4-35) | 28.3 (18.5-56.2) |
| ASA > 2 | 18 | 17 |
| Surgical Time | 299 (228-445) | 303 (229-473) |
| LOS | 2.6 (1-17) | 2.6 (1-10) |
| < 24h | 56% | 43% |
| < 48h | 78% | 73% |
| Complete cytoreduction | 21 | 24 |
| < 1 cm | 12 | 4 |
| Suboptimal | 0 | 3 |

# Peri-operative complications

| | NACT (33) | PDS (31) |
|---|---|---|
| EBL (median) | 60 (20-1000) | 150 (20-500) |
| Enterotomy | 0 | 3 (trt robot) |
| Cystotomy | 1 (trt robot) | 1 (trt robot) |
| VV fistula | 1 | 0 |
| Vessel injury | 2 (trt robot) | 2 (trt robot) |
| Conversions | 2 (massive dz, low ant.) | 3 (2 rectal invasion,1 massive dz) |
| Lymphocyst | 1 | 1 |
| Re-operation | 2 | 1 |
| Death | 0 | 1 (84yo, sepsis) |

# O.S.: Robotics (2008-2012)
# L-tomy (2003-2007)





# Preliminary cautious interpretation

- Feasible in selected cases both early/late dz
  - Acceptable complete cytoreduction st IIIc
    - NACT 70%  PDS 64%
  - Conversion
    - NACT: 6%  PDS: 10%
  - Short term oncologic outcome: similar
  - Remain very shy and humble

# My Personal conclusions..

- **Neo-adjuvant chemotherapy is here to stay**
  (awaiting more randomized trials, as usual…)
- Optimal cytoreduction is still the **desired goal**
- Optimal PDS or Optimal IDS **do not differ**
- **Avoid** suboptimal cytoreduction !!
- If optimal PDS seems **unachievable:**
  (patient - tumor - surgeon) – **do not hesitate: The NACT/IDS option is well established.**

**Thank you**

**for your attention**