Neoadjuvant chemotherapy in ovarian cancer

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Content

- Definition
- Rationale of neoadjuvant chemotherapy
- Possible benefits and down side
- Meta-analysis
- Prospective randomized trials
- Conclusion

Conventional art

Contemporary art

Advanced ovarian cancer

Conventional treatment

Contemporary treatment

Conventional treatment

- Aggressive surgery: optimum (≤ 1 cm., no gross residual), subobtimum
- Followed by platinum-base chemotherapy

Berek JS, et al. Ann Oncol 1999

“Contemporary considerations for neoadjuvant chemotherapy for advanced ovarian cancer”

Schwartz PE, et al. Current Oncology Reports 2009

Definition

- Neoadjuvant chemotherapy is the administration of cytotoxic chemotherapy before attempting aggressive cytoreductive surgery for treating women with advanced-staged epithelial ovarian cancer.

Schwartz PE. Oncol 2008

Neoadjuvant therapy vs interval debulking

Neoadjuvant therapy = chemical cytoreduction prior to any significant attempt at surgical debulking

In contrast, interval debulking implies that an attempt at optimal debulking has already been made prior to the patient receiving chemotherapy

Neoadjuvant Chemotherapy

Rationale:

- PDS yields complete tumor resection 40-60%
- Neoadjuvant chemotherapy might limit the morbidity of ineffective radical debulking
- Survival benefit?

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Rationale

- **‘A** meta-analysis of Bristow et al. which included 6,885 patients with stage**s** III and IV ovarian cancer, reported an optimal cytoreduction rate (< 2 cm. residual disease) of 42%. And only a small fraction of patients were cytoreduced to microscopic disease.

Bristow RE, et al. J clin Oncol 2002

Rationale (cont.)

- A recent Gynecologic Oncology Group (‘GOG) study reported that only 23% of 1,895 stage III patients and only 8% of 360 stage IV patients were cytoreduced to microscopic disease.

Winter WE, et al. J Clin Oncol 2007
Winter WE, et al. J Clin Oncol 2008

Data from Thailand

- **Ramathibodi Hospital**
- stages III and IV ovarian cancer, undergone PDS had an optimal cytoreduction rate (< 1 cm. residual disease) of 55%.
- Chiang Mai University Hospital
- Half of advanced EOC obtained optimal cytoreduction (< 2 cm. residual disease)

Neoadjuvant Chemotherapy

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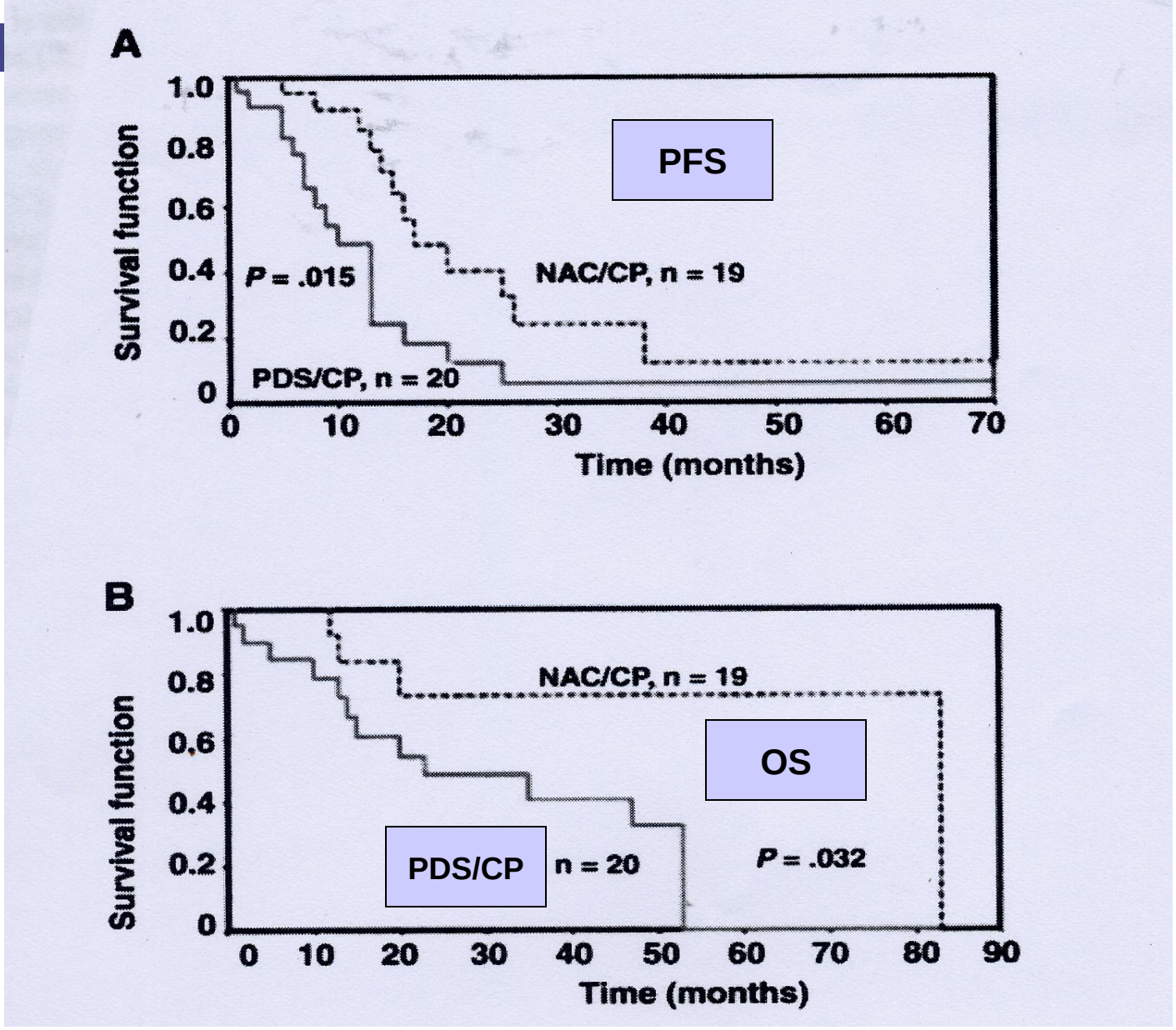
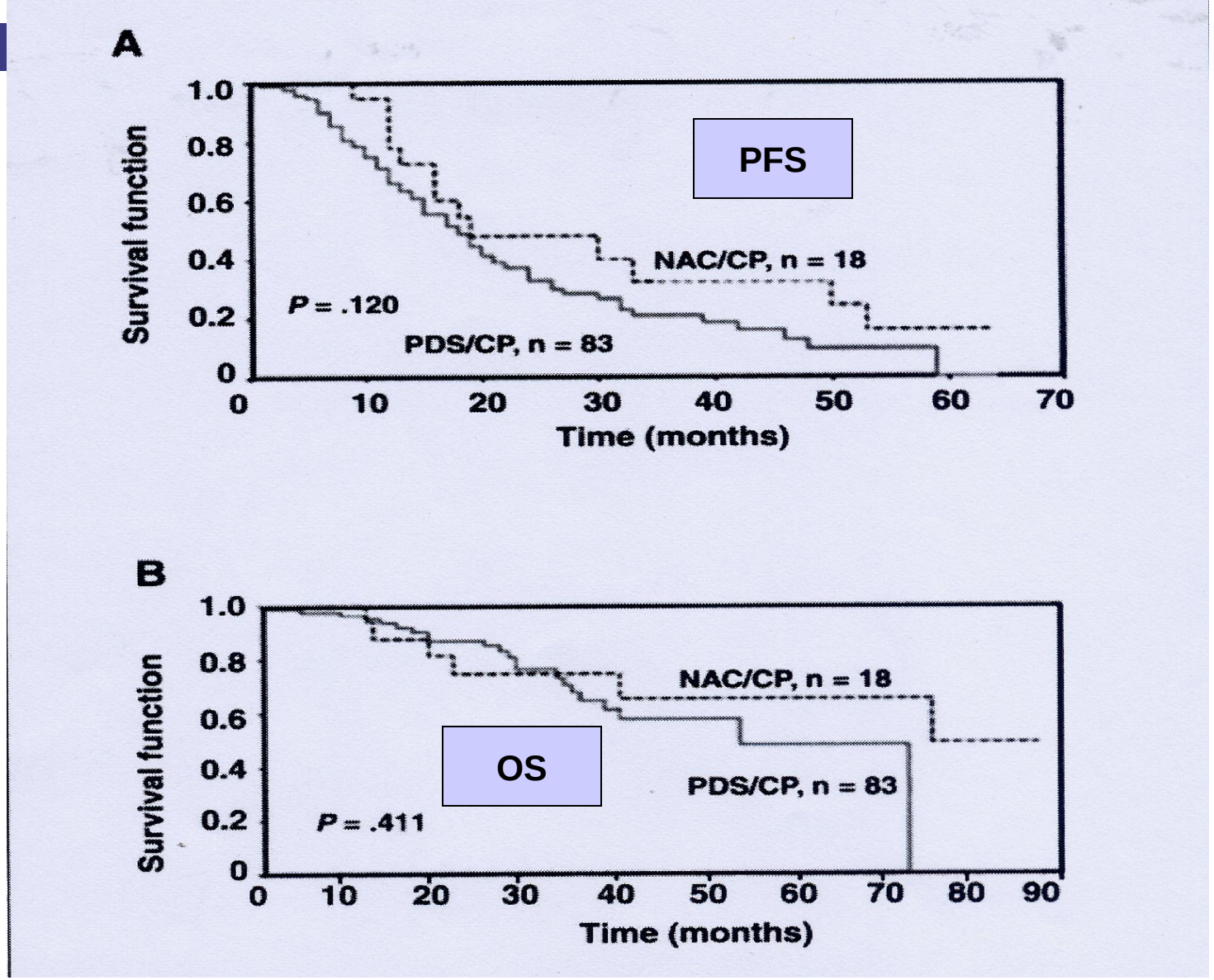


Survival after treatment for stage IV ovarian cancer

Hou JY, et al. Gynecol Oncol 2007

Vergote I, et al. Gynecol Oncol 1998 Rafii A, te al. Int J Gynecol Caner 2007



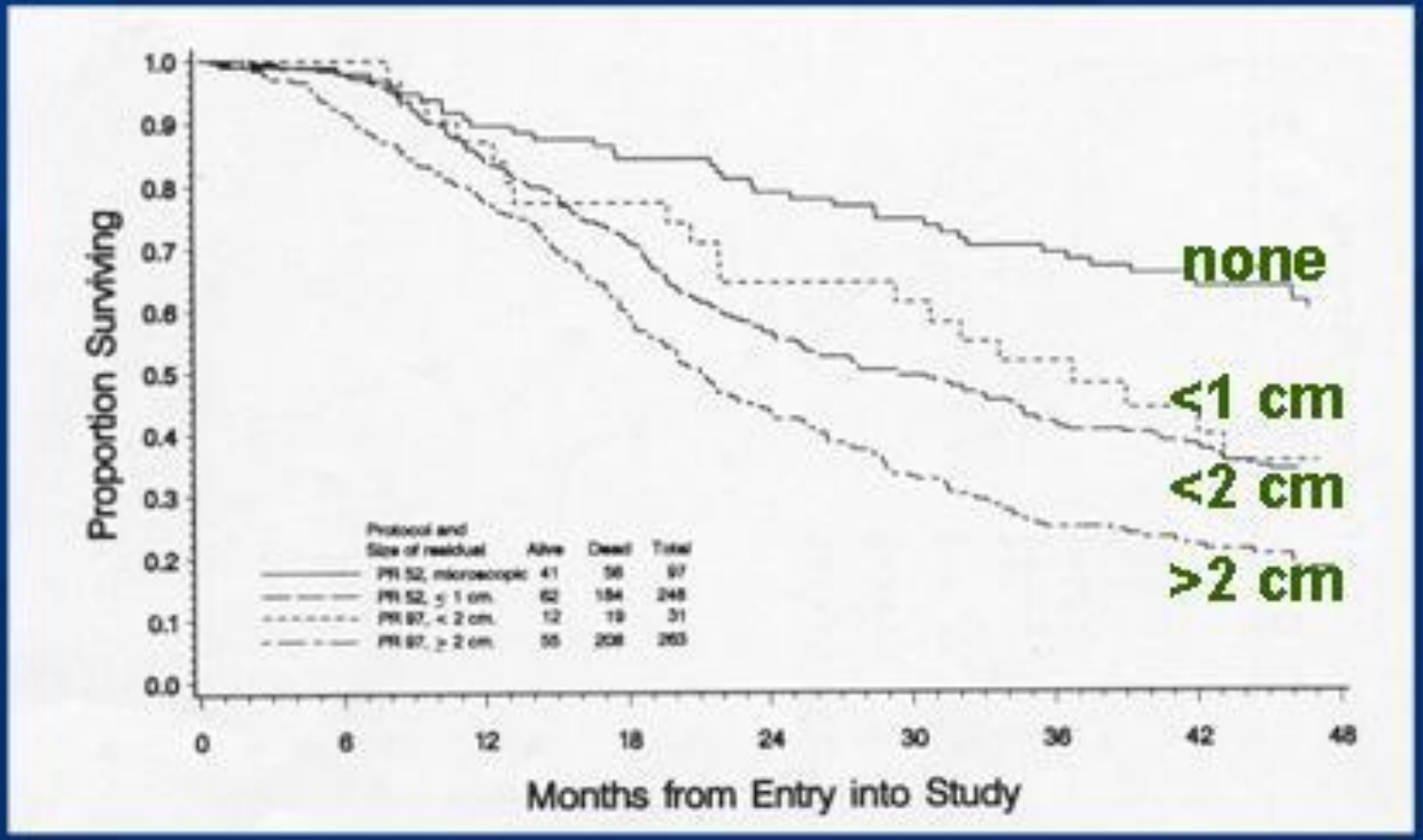
Survival after treatment for stage IIIC ovarian cancer

Hou JY, et al. Gynecol Oncol 2007

The amount of residual disease after cytoreductive surgery is among the most important prognostic factors when predicting survival in women with advanced ovarian cancer

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Residual Disease vs. Survival (GOG 52/97)



Epithelial ovarian cancer treated by platinum or platinum analogue with cyclophosphamide: experience in Ramathibodi Hospital.

Patients who underwent optimal debulking surgery had significantly longer progression-free interval ($P = 0.001$) than those who had sub-optimal surgery.

Linasmita V, Wilailak S, Srisupundit S, Tangtrakul S, Bullangpoti S, Israngura N.

J Med Assoc Thai. 1998 Jan;81(1):10-6. Department of Obstetrics and Gynecology, Faculty of Medicine, Ramathibodi Hospital

Neoadjuvant chemotherapy

Possible benefits

- Tolerate the chemotherapy better than those receiving the same chemotherapy after aggressive cytoreductive surgery

  Schwartz PE, et al. Gynecol Oncol 1994

- A higher rate of optimum surgical cytoreduction

  Hue JY, et al. Gynecol Oncol 2007
  Schwartz PE, et al. Gynecol Oncol 1999

Possible benefits (cont.)

- Less surgical morbidity
- Reduced blood loss
- Shorter operating time
- Less time in the intensive care unit
- Shorter postoperative hospital stay
- Less aggressive surgery to achieve optimum surgical cytoreduction
- Patients are often much better prepared emotionally

Schwartz PE, et al. Oncol 2008
Bristow RE, et al. Gynecol Oncol 2006
Bristow RE, et al. Gynecol Oncol 2007
Hue JY. Gynecol Oncol 2007
Schwartz PE, Gynecol Oncol 1994
Surwit E, et al. Int J Gynecol Cancer 1996
Schwartz PE, Gynecol Oncol 1999

Down side

- The possibility of misdiagnosing a nonmullerian cancer, resulting in treating a patient with inappropriate chemotherapy
- Missing an opportunity to optimally cytoreduce a patient with upfront surgery, thereby compromising her survival

Schwartz PE. Current Oncology Reports 2009

Conventional treatment of advanced ovarian cancer

Primary cytoreductive surgery
(Maximal primary surgical attempt)

Optimal

Suboptimal

No gross residual

< 1 cm.

≥ 1 cm.

Chemotherapy

Chemotherapy:

Secondary cytoreductive surgery
(interval debulking)

Neoadjuvant chemotherapy (NACT) in advanced ovarian cancer

In 1979, at Yale University

Patients who were too medically infirmed to tolerate aggressive cytoreductive surgery → NACT

↓

Patients who, by CT criteria, were unlikely to be optimally surgically cytoreduced → NACT

Chambers JT, et al. Gynecol Oncol 1990
Schwartz PE, et al. Gynecol Oncol 1999

Meta-analysis

- Bristow and Chi. Gnecol Oncol 2007
- Kang and Nam Ann Surg Oncol 2009

Table 2. Meta-analyses of stage III and IV ovarian cancer patients treated with neoadjuvant chemotherapy

Study	Years	Studies, *n*	Taxane use when 3 cycles of NACT administered	Taxane use when > 3 cycles of NACT administered	Improved survival				
					Taxane use	Optimum cyto-reduction	Stage IV	Preoperative chemo-therapy cycles	NACT vs upfront surgical cytoreduction
Bristow et al. [20]	1989–2005	22	9 of 11 studies (range, 20%–100%; median, 94.9% of patients received taxane)	5 of 10 studies (range, 8.5%–77.7%; median, 57.4% of subjects received taxane)	Yes	Yes	Significantly decreased survival	> 3 cycles significantly decreased survival	Upfront cytoreduction significantly better
Kang and Nam [26••]	1989–2008	21	9 of 11 studies (range, 0%–100%; median, 69% of subjects received taxane)	10 of 10 studies (range, 41%–95%; median, 70.5% of subjects received taxane)	Yes	Yes	No significant effect on survival	Between studies variation had no effect on survival	No statistical difference in survival

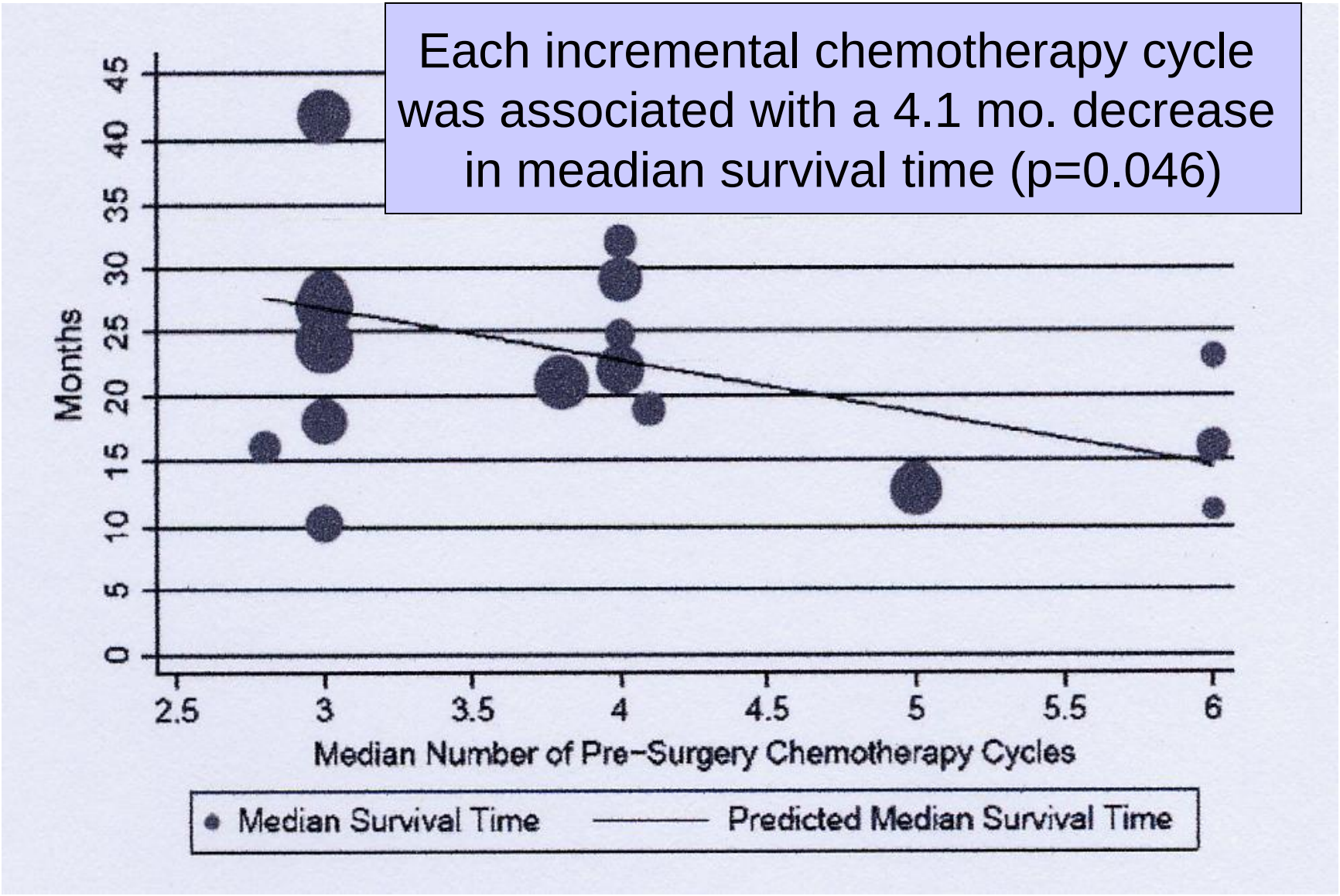
NACT—neoadjuvant chemotherapy.

Meta-analysis

- Bristow and Chi. Gnecol Oncol 2007
- Kang and Nam Ann Surg Oncol 2009

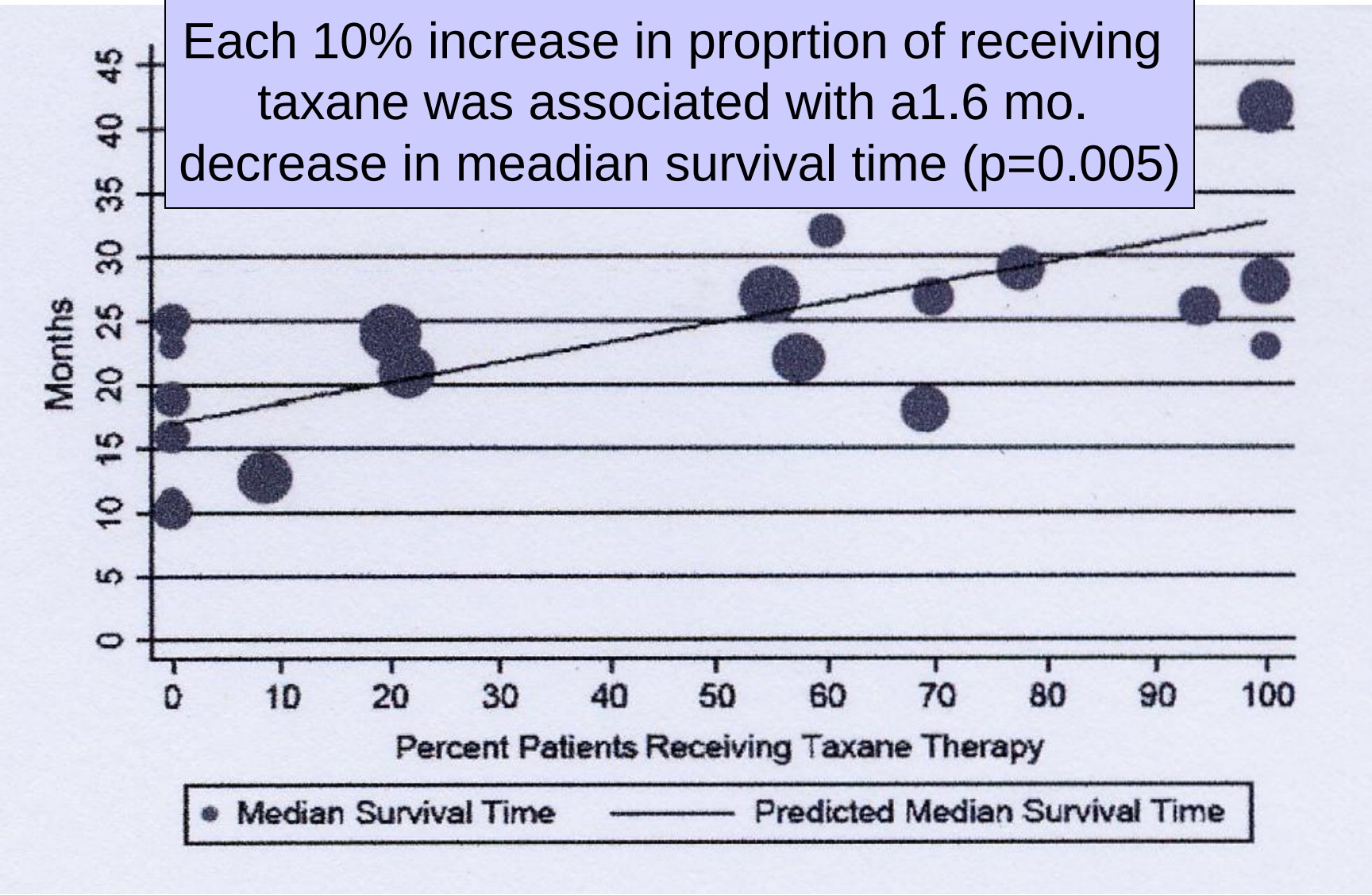
Meta-analysis

- Bristow and Chi. Gnecol Oncol 2007
- The authors concluded that neoadjuvant chemotherapy survival outcomes are overall inferior compared to conventional primary surgery



Simple linear regression analysis: median survival plotted against the median number of cycles of NACT

Each 10% increase in proprtion of receiving taxane was associated with a1.6 mo. decrease in meadian survival time (p=0.005)



Simple linear regression analysis: median survival plotted against the % of patients receiving taxane

Meta-analysis

- Kang and Nam Ann Surg Oncol 2009
- The neoadjuvant affords greater optimal cytoreduction rates.
- Interestingly, they found a trend for increased median overall survival in the neoadjuvant group. However, this was not significant under the between-studies variation analysis.

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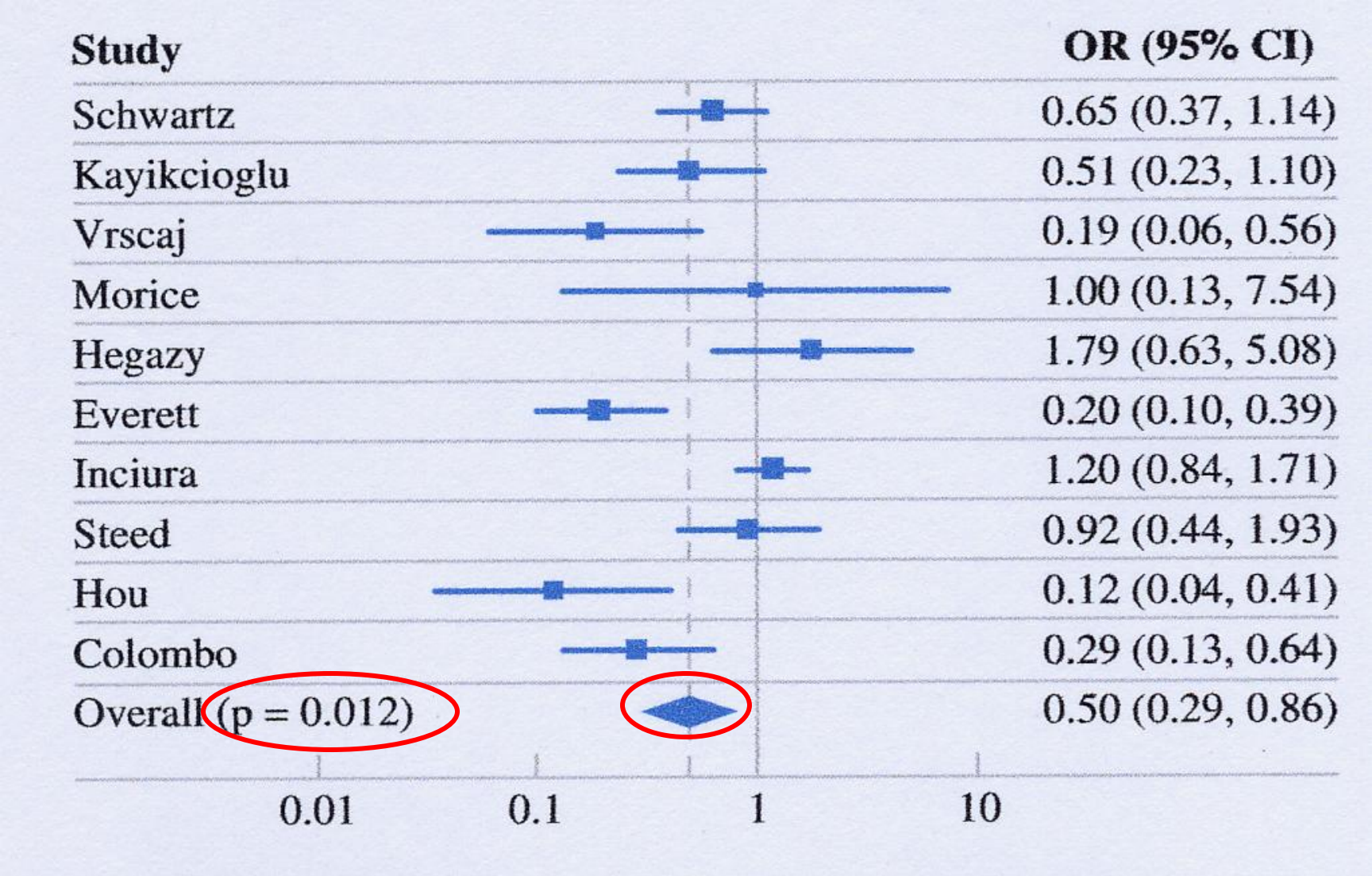


Forest plot illustrating the individual and pooled odds ratio of suboptimal debulking in NACT

Prospective randomized trials

- EORTC-GCG/NCIC-CTG
- JGOG
- CHORUS

Prospective randomized trials

- EORTC
- JGOG
- CHORUS

IGCS BANGKOK
OCTOBER 25TH 2008

RANDOMISED EORTC-GCG/NCIC-CTG TRIAL ON NACT + IDS VERSUS PDS

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

Randomisation

Primary Debulking Surgery	Neoadjuvant chemotherapy
3 x Platinum based CT	3 x Platinum based CT
↓	↓
Interval debulking	Interval debulking
(not obligatory)	If no PD
↓	↓
≥3 x Platinum based CT	≥3 x Platinum based CT

Primary Endpoint : Overall survival
Secondary endpoints : Progression Free Survival, Quality of Life, Complications

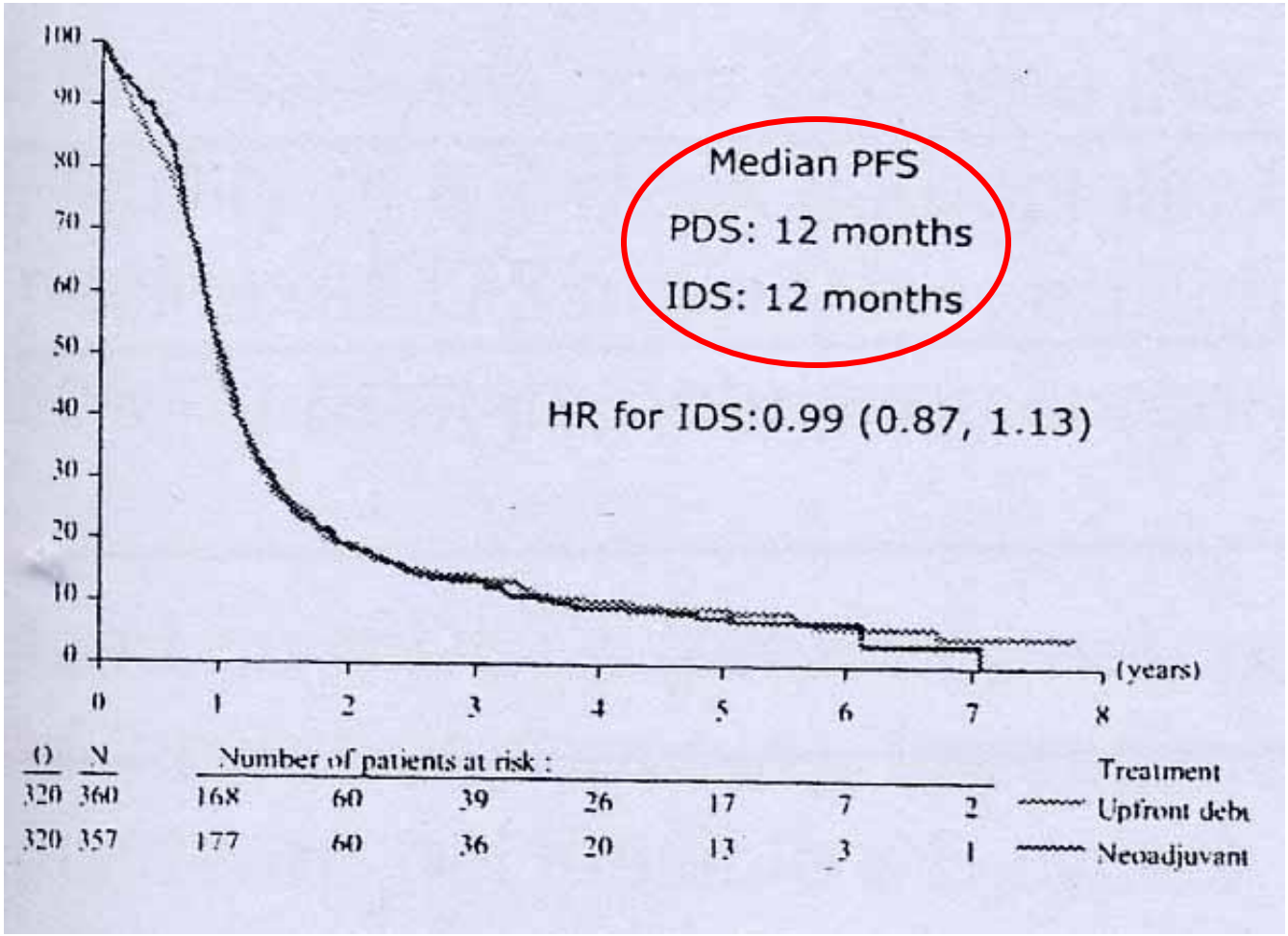
Randomised EORTC-GCG/NCIC-CG trial on NACT + IDS versus PDS

Study conduct

- BetweenSeptember 1998 and December 2006, 718 patients were randomized in 60 institutions
- 498 events were needed to perform the final analysis, and were reached in August 2008
- Median follow-up was 4.8 years.

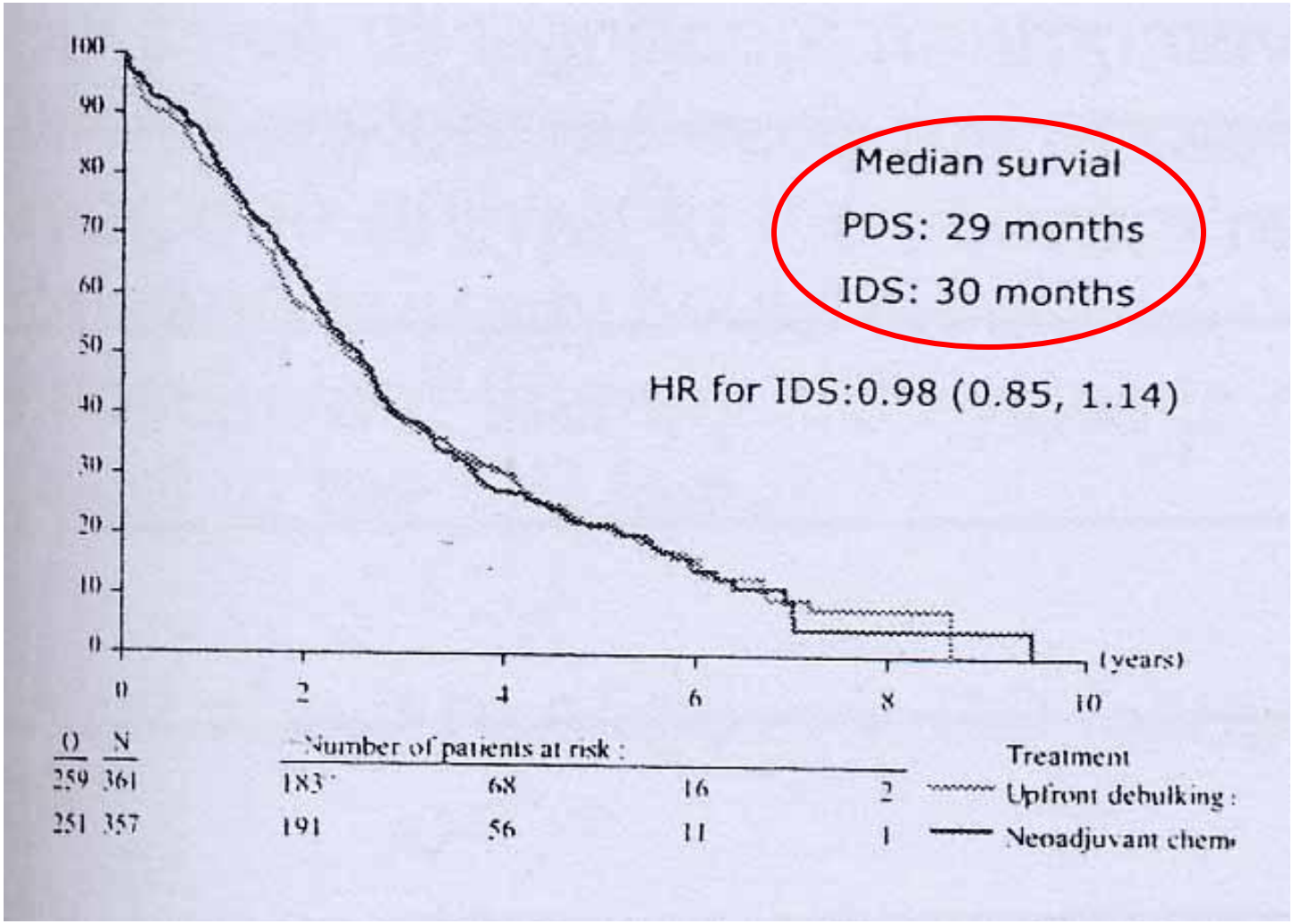
NACT + IDS versus PDS : ITT

Progression-free survival



NACT + IDS versus PDS : ITT

Overall survival



Conclusions

Due to the lower morbidity of IDS compared with PDS and the similar survival, 'NACT can be considered a preferred treatment in these patients with stage IIIC/IV ovarian cancer

Prospective randomized trials

- EORTC
- JGOG
- CHORUS

There are ‘ongoing confirmatory trials (Ondo Japanese JCO 2008 : (paclitaxel / carbo x 4 IDS paclitaxel / carbo x 4 vs PDS f/b paclitaxel / carbo x 8) aimed for accruing 350 patients.

Questions ‘remain as to how to incorporate neadjuvant therapy into other strategies such as IP, dose dense, biologics and new drugs

Prospective randomized trials

- EORTC
- JGOG
- CHORUS

- A very similar trial, “Chemotherapy or Upfront Surgery) is now accruing patients in the UK aimed for 550 patients

Which patients might best benefit from receiving neoadjuvant chemotherapy?

Criteria to identify who would be ± successfully cytoreduced upfront

- Patient's condition and performance status
- Extent of disease
- The aggressiveness of the surgeon

Aletti GO, et al. Obstet Gynecol 2006

Criteria to identify who would be ± successfully cytoreduced upfront

- Patient's condition and Performance status
- Extent o
- The agg

ASA performance status > 2

(American Society of Anesthesiology)

Aletti GO, et al. Obstet Gynecol 2006

Nutritional status

- Poor nutrition has been associated with postoperative morbidity and mortality
- Neoadjuvant chemotherapy for patients with advanced ovarian cancer is recommended in patients who present with prealbumin levels lower than 10 mg/dL that do not rise above 10 mg/dL while receiving 10 days of total parenteral nutrition

- Geisler JP, et al. Gynecol Oncol 2007

Patient selection for NACT

Poor general condition

Advanced disease

??? Can we charaterize subpopulation who, if receive primary cytoreductive surgery

will achieve optimal residual disease

will not achieve optimal residual disease

Eisenhauer EL, et al. Gynecol Oncol 2008
Winter WEIII, et al. J Clin Oncol 2008
Aletti GD, et al. Gynecol Oncol 2007
Salani R, et al. Gynecol Oncol 2008

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How could we predict surgical outcome by assessing tumor extent?

- CT imaging
- CA 125
- Laparocsopy assessment
- Pattern of gene expression
- ISF-deoxy-glucose (FDG) PET

CT imaging (‘Nelson criteria for inablity to yield optimal surgery)

- Presence of an omental cake extending to the spleen
- A diaphragm coated by tumor that extends to the liver serosa
- Greater than 2 cm. lesions in the suprarenal para-aortic lymph nodes
- Porta hepatis, parenchymal liver disease
- Pulmonary metasteses
- Enlarged pericardial lymph nodes:

Nelson BE, et al. J Clin Oncol 1993

- Only patients with disease outside of the peritoneal cavity or those with multiple large liver metasteses are unlikely to be optimally cytoreduced.

Chi DS, et al. Gynecol Oncol 2004

Chi DS, et al. Gynecol Oncol 2008

CA 125

- Currently, CA 125 levels do not seem to be a significant predictor of tumor resectability

Chi DS, et al. Gynecol Oncol 2000

Obeidat B, et al. Gynecol Obstet Invest 2004

Germer O, et al. Eur J Surg Oncol 2005

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Gynecologic Oncology 96 (2005) 729–735

Gynecologic Oncology

www.elsevier.com/locate/ygyno

Role of laparoscopy to assess the chance of optimal cytoreductive surgery in advanced ovarian cancer: a pilot study

Anna Fagotti[a], Francesco Fanfani[a], Manuela Ludovisi[b], Roberto Lo Voi[b], Giuseppe Bifulco[a], Antonia Carla Testa[b], Giovanni Scambia[a,*]

[a]*Division of Gynecologic Oncology, Catholic University of the Sacred Heart, Largo Agostino Gemelli 8, 00168 Campobasso, Rome, Italy*
[b]*Division of Gynecologic Oncology, Catholic University of the Sacred Heart, Rome, Italy*

Study Design

95 pts accrued

64 pts enrolled

31 pts excluded (34%)
(51.6% ASA III-IV)
(35.5% large-size mass)
(4.7% adhesions)

64 Complete clinico-radiological examination

↓

64 Laparoscopy

↓

64 Standard longitudinal laparotomy

A Laparoscopy-Based Score To Predict Surgical Outcome in Patients With Advanced Ovarian Carcinoma: A Pilot Study

Anna Fagotti,[1] Gabriella Ferrandina,[2] Francesco Fanfani,[1] Alfredo Ercoli,[2] Domenica Lorusso,[3] Marco Rossi,[3] and Giovanni Scambia, MD[1]

Predictive index parameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Point value
Ovarian masses (mono-bilateral)	60	29	29	60	39	0
Omental cake	57	81	63	77	73	2
Peritoneal carcinosis	69	79	67	81	75	2
Diaphragmatic carcinosis	69	84	65	80	80	2
Mesenteral retraction	50	95	85	77	78	2
Bowel infiltration	70	89	78	84	82	2
Stomach infiltration	11	100	100	82	82	2
Liver metastases	35	94	75	76	76	2

Ann Surg Oncol, in press

- A final score $\geq$ 8 is deemed unresectable
- 100% PPV, 70% NPV

Fagotti A, et al. 2008

Laparoscopic prediction of optimum debulking

	N	Residual D. (cm)	PPV	NPV
Vergote 1998	87	1	96%	NA
Angioli 2006	77	0.5	79%	NA
Deffieux 2006	15	1	91%	NA
Fagotti 2008	95	1	100%	70%

Pattern of gene expression using microarray

- Patterns of expression of 32 genes can distinguish between optimal and suboptimal debulking with 72.7% predictive accuracy.

Burchuck et al. Am J Obstet Gynecol 2004

ISF-deoxy-glucose (FDG) PET

- Seems to be sensitive and specific (almost 100%) in detecting metastatic disease spread preoperatively and whether they will eventually have utility in predicting disease resectability remain to be seen

‘Yoshida Y, et al. J Ovarian Res 2009

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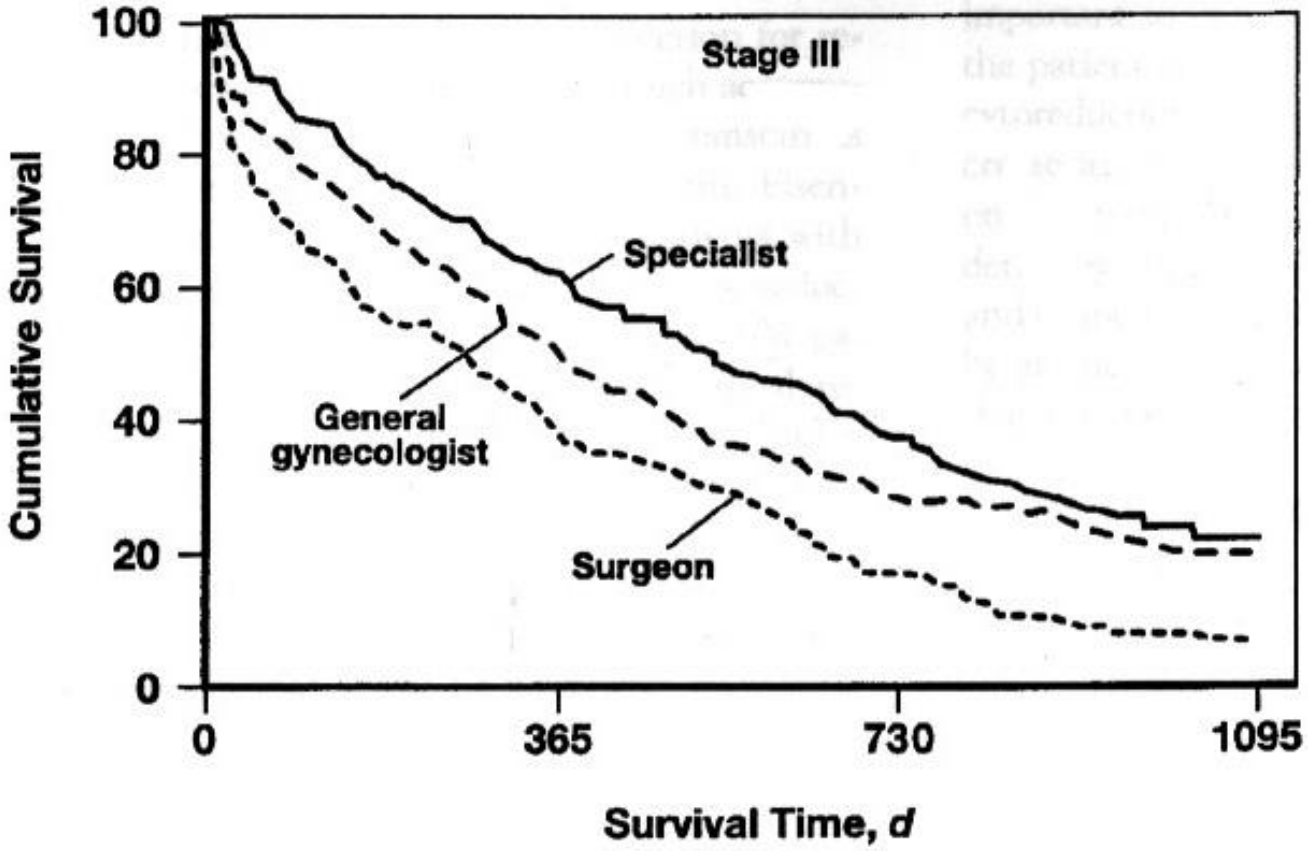
Aletti GO, et al. Obstet Gynecol 2006

OVERALL SURVIVAL OF STAGE III OC ACCORDING TO SURGEON SPECIALTY



(Junour et al., 1999, BJOG)

The number? of chemotherapy cycles administered before and after surgery is performed

- Chemoresistant?

- “Today, it is believed that the major value of neoadjuvant chemotherapy is in preparing patients for aggressive cytoreductive surgery, so that these patients can be optimally cytoreduced”

- Pecorelli S, et al. Best Practi Res Clin Obstet Gynaecol 2007

Conclusion

- NACT is best suited for patients with medical co - morbidities not able to undergo aggressive cytoreductive surgeries and for patients deemed to have unresectable disease
- The ability to predict unresectable disease in selecting patients who would be appropriate candidates for NACT is crucial
- The proper number of cycles given prior to surgery is to be defined.