



Πρωτογενής πλήρης χειρουργική εξαίρεση vs δευτερογενής κυτταρομείωση στον καρκίνο των ωοθηκών

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Επίκουρος Καθηγητής
Γ' Μαιευτική & Γυναικολογική Κλινική ΕΚΠΑ

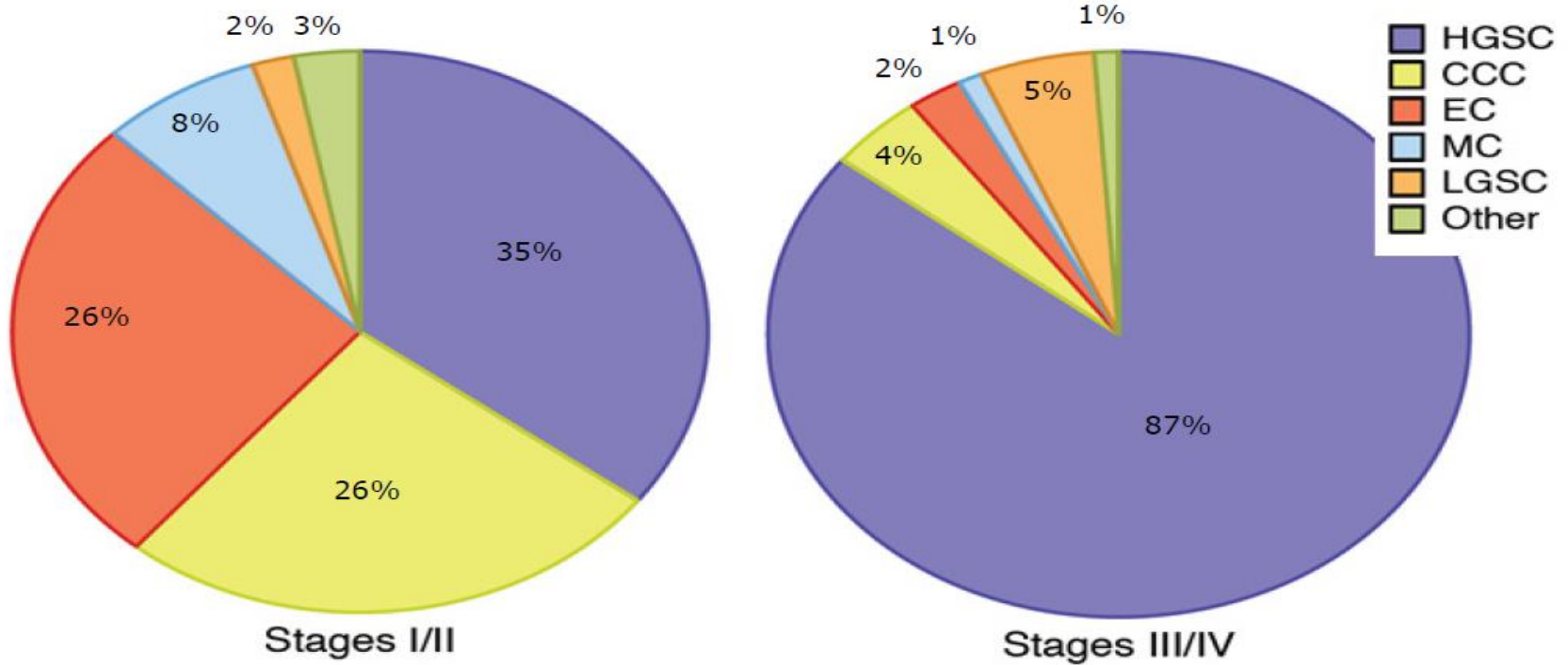


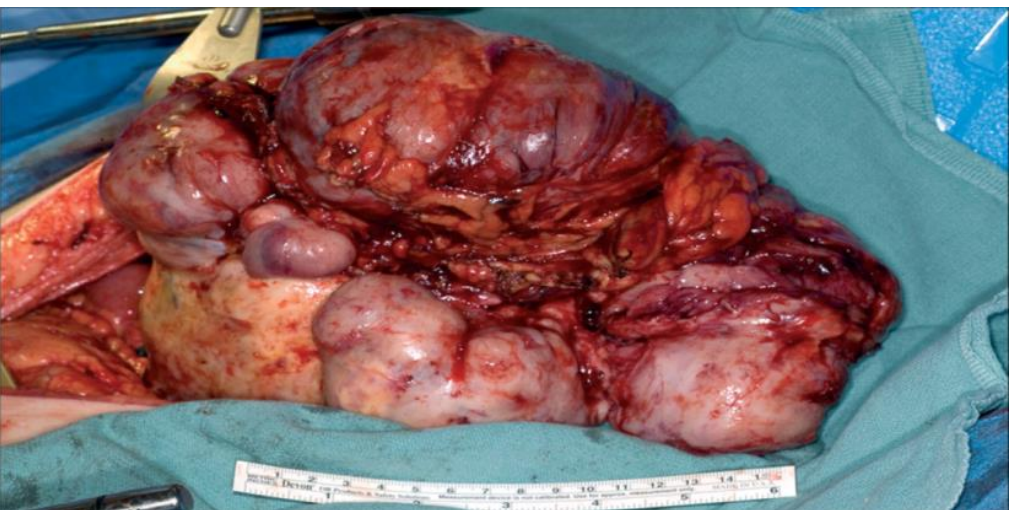
Εισαγωγή

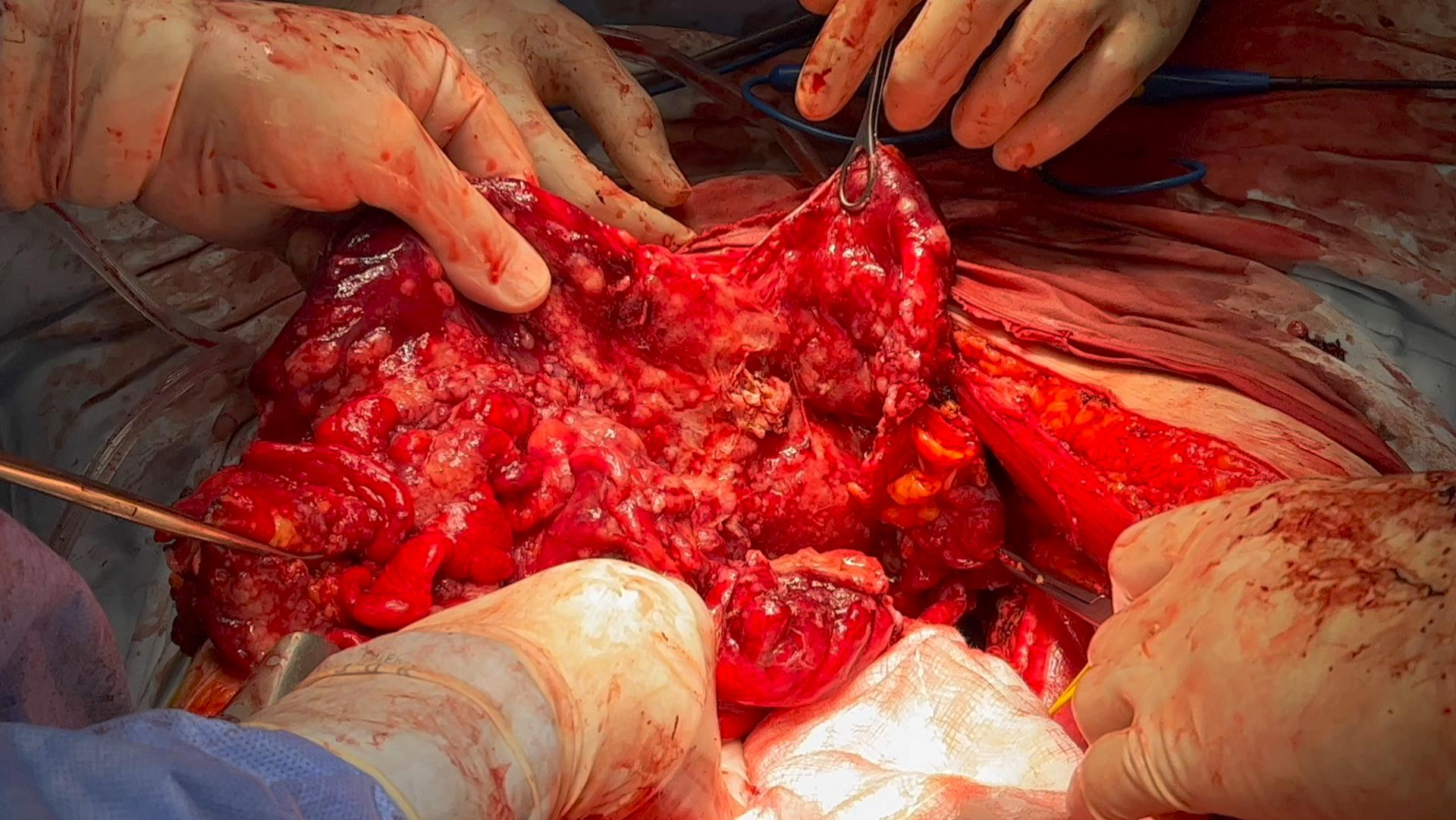
- Η πρώτη αιτία θανάτου ασθενών από γυναικολογικό καρκίνο
- 2/3 των ασθενών διαγιγνώσκονται σε St III/IV
- Βελτίωση χειρουργικών τεχνικών + νέα ΧΜΘ σχήματα → 50% των ασθενών θα καταλήξουν εντός 5 ετών από την 1^η διάγνωση

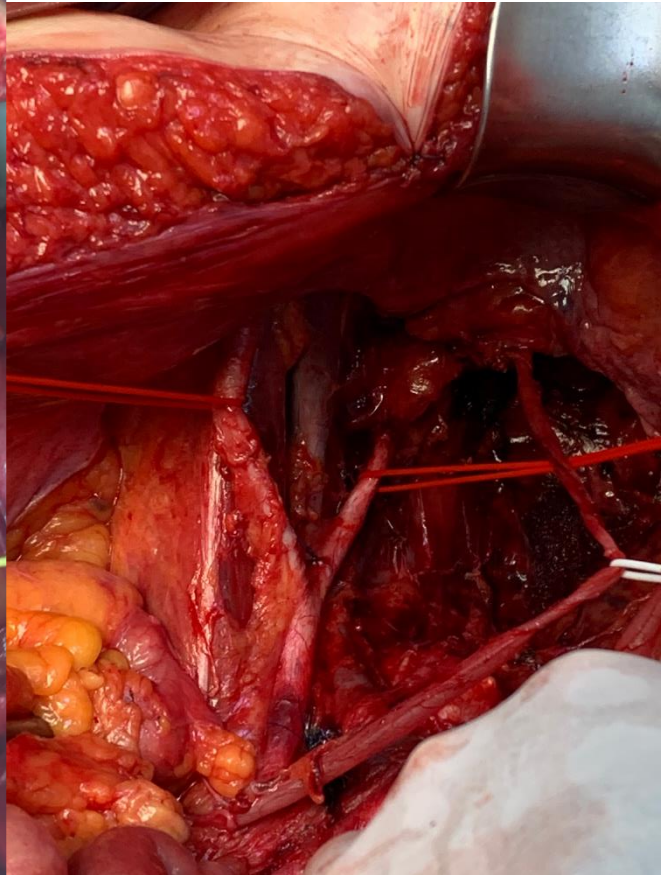
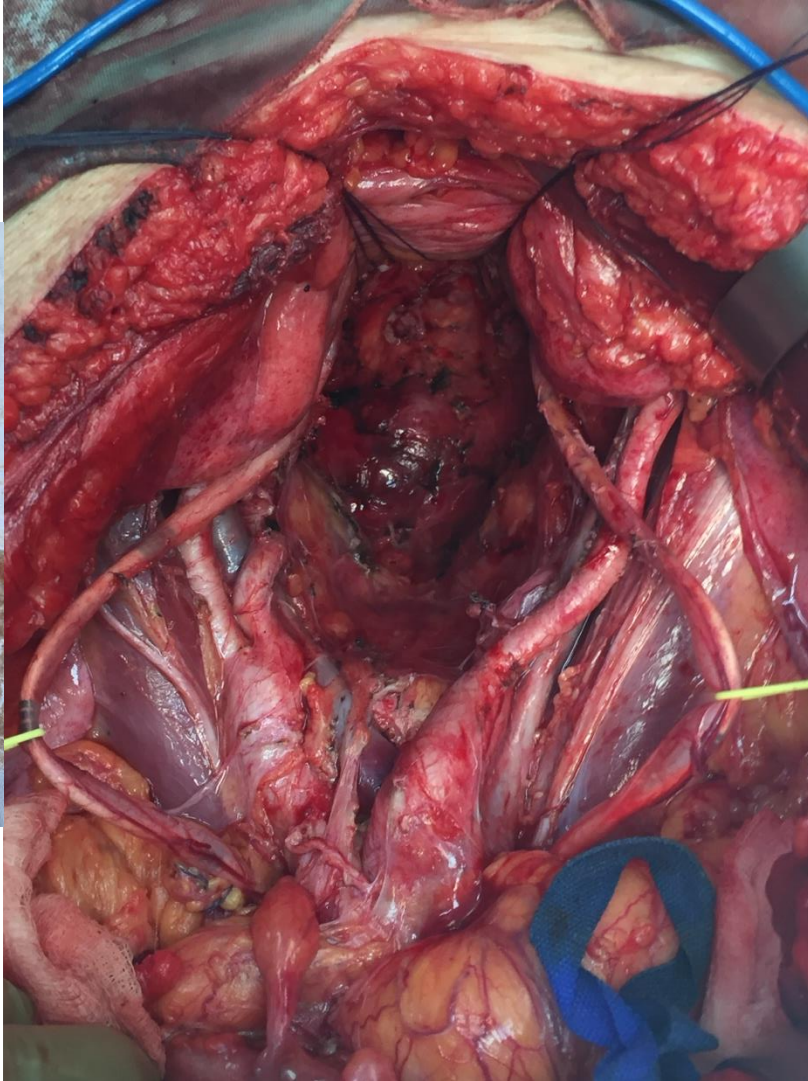
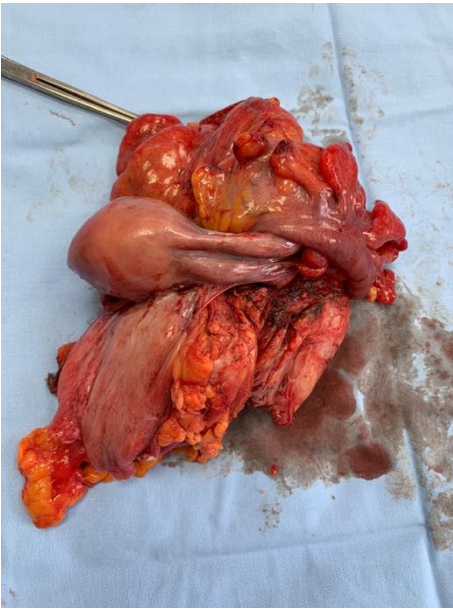


LOW vs HIGH STAGE





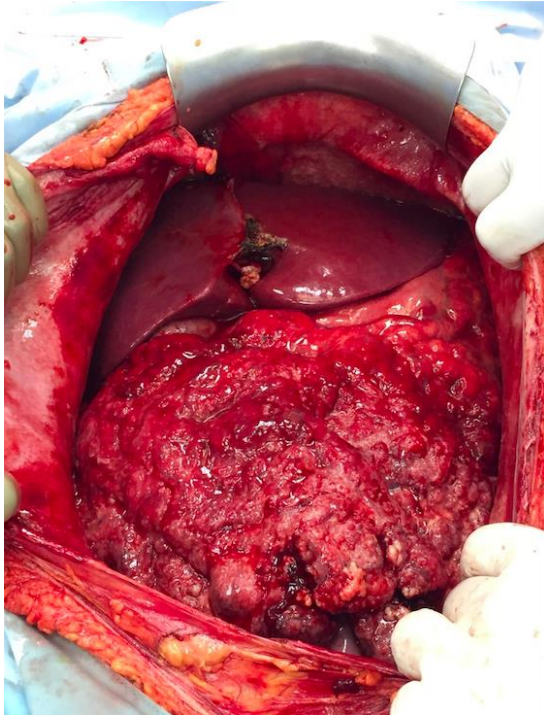






- Η υπολειπόμενη νόσος καθορίζει την επιβίωση
- Ο μοναδικός προγνωστικός παράγοντας (εκτός από τον τύπο της συστηματικής θεραπείας), που εξαρτάται από την χειρουργική ομάδα

High-grade serous OvCa



EOC

not just one disease but
several distinct entities !!!!!!!



WHO classification 1973

Table 21.2. Histologic classification of ovarian tumors: Common "epithelial" tumors*

<p>A. Serous tumors</p> <p>1. Benign</p> <p>(a) Cystadenoma and papillary cystadenoma</p> <p>(b) Surface papilloma</p> <p>(c) Adenofibroma and cystadenofibroma</p> <p>2. Of borderline malignancy (carcinomas of low malignant potential)</p> <p>(a) Cystadenoma and papillary cystadenoma</p> <p>(b) Surface papilloma</p> <p>(c) Adenofibroma and cystadenofibroma</p> <p>3. Malignant</p> <p>(a) Adenocarcinoma, papillary adenocarcinoma, and papillary cystadenocarcinoma</p> <p>(b) Surface papillary carcinoma</p> <p>(c) Malignant adenofibroma and cystadenofibroma</p> <p>B. Mucinous tumors</p> <p>1. Benign</p> <p>(a) Cystadenoma</p> <p>(b) Adenofibroma and cystadenofibroma</p> <p>2. Of borderline malignancy (carcinomas of low malignant potential)</p> <p>(a) Cystadenoma</p> <p>(b) Adenofibroma and cystadenofibroma</p> <p>3. Malignant</p> <p>(a) Adenocarcinoma and cystadenocarcinoma</p> <p>(b) Malignant adenofibroma and cystadenofibroma</p> <p>C. Endometrioid tumors</p> <p>1. Benign</p> <p>(a) Adenoma and cystadenoma</p> <p>(b) Adenofibroma and cystadenofibroma</p>	<p>2. Of borderline malignancy (carcinomas of low malignant potential)</p> <p>(a) Adenoma and cystadenoma</p> <p>(b) Adenofibroma and cystadenofibroma</p> <p>3. Malignant</p> <p>(a) Carcinoma</p> <p>(i) Adenocarcinoma</p> <p>(ii) Adenoacanthoma</p> <p>(iii) Malignant adenofibroma and cystadenofibroma</p> <p>(b) Endometrioid stromal sarcomas</p> <p>(c) Mesodermal (müllerian) mixed tumors, homologous and heterologous</p> <p>D. Clear cell (mesonephroid) tumors</p> <p>1. Benign: adenofibroma</p> <p>2. Of borderline malignancy (carcinomas of low malignant potential)</p> <p>3. Malignant: carcinoma and adenocarcinoma</p> <p>E. Brenner tumors</p> <p>1. Benign</p> <p>2. Of borderline malignancy (proliferating)</p> <p>3. Malignant</p> <p>F. Mixed epithelial tumors</p> <p>1. Benign</p> <p>2. Of borderline malignancy</p> <p>3. Malignant</p> <p>G. Undifferentiated carcinoma</p> <p>H. Unclassified epithelial tumors</p>
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Proposed new classification

Type 1

Endometrioid ca
Clear cell ca
Mucinous ca
Low grade serous ca (LGSC)

Type 2

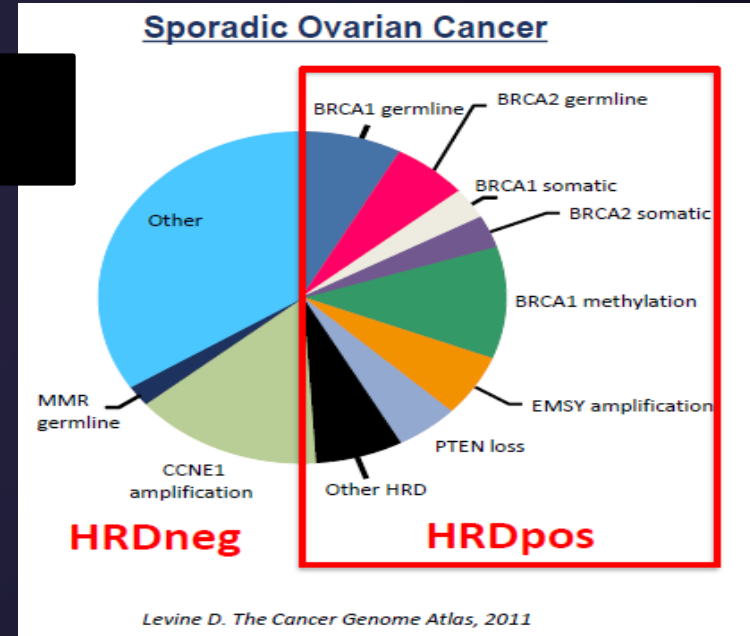
High grade serous ca (HGSC)

All these types have different molecular background, clinical presentation and prognosis

EOC – Serous type

- ~20% of patients harbor either germline or somatic BRCA1/2 mutations
- ~50% of OvCa patients bear defects in Homologous Repair mechanism

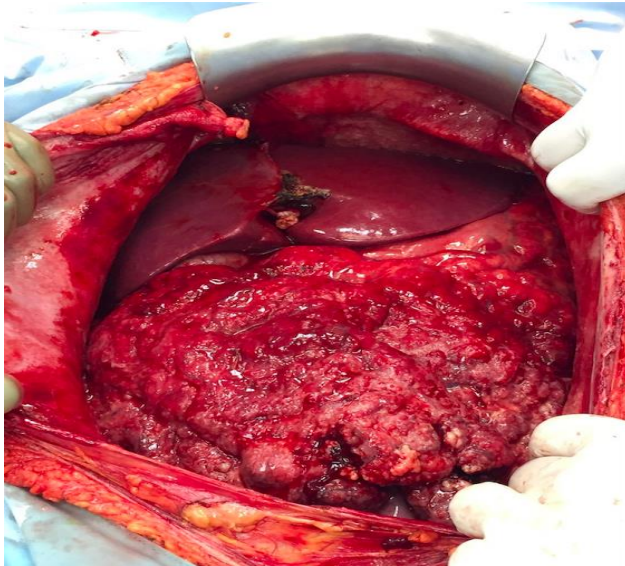
Evolution in the treatment of
Ovarian Ca with the use of
PARP's !!!!!!!!!!!!!!!





EOC – serous (management)

- Στόχος η πλήρης κυτταρομείωση
- Ειδικά σε περιπτώσεις LGSC λόγω χαμηλότερης ευαισθησίας στη ΧΜΘ από το HGSC





SPECIAL ARTICLE

ESGO—ESMO—ESP consensus conference recommendations on ovarian cancer: pathology and molecular biology and early, advanced and recurrent disease

J. A. Ledermann^{1*†}, X. Matias-Guiu^{2,3,4*†}, F. Amant^{5,6}, N. Concin^{7,8}, B. Davidson^{9,10}, C. Fotopoulou¹¹, A. González-Martin¹², C. Gourley¹³, A. Leary¹⁴, D. Lorusso^{15,16}, S. Banerjee¹⁷, L. Chiva¹⁸, D. Cibula¹⁹, N. Colombo^{20,21}, S. Croce²², A. G. Eriksson^{10,23}, C. Falandry^{24,25}, D. Fischerova¹⁹, P. Harter^{8,26}, F. Joly²⁷, C. Lazaro²⁸, C. Lok⁶, S. Mahner^{26,29}, F. Marmé^{26,30,31}, C. Marth⁷, W. G. McCluggage³², I. A. McNeish¹¹, P. Morice³³, S. Nicum¹, A. Oaknin³⁴, J. A. Pérez-Fidalgo³⁵, S. Pignata³⁶, P. T. Ramirez³⁷, I. Ray-Coquard³⁸, I. Romero³⁹, G. Scambia^{15,16}, J. Sehouli^{40,41}, R. Shapira-Frommer⁴², S. Sundar^{43,44}, D. S. P. Tan^{45,46,47,48}, C. Taskiran⁴⁹, W. J. van Driel⁶, I. Vergote⁵, F. Planchamp⁵⁰, C. Sessa⁵¹ & A. Fagotti^{15,16*}



Οδηγία 11

- Σε προχωρημένο καρκίνο ωοθηκών, θεραπεία πρώτης γραμμής είναι η πρωτογενής κυτταρομείωση (PCS)
- Για ασθενείς που δεν είναι υποψήφιος για PCS, προτείνεται NACT και ακολούθως ICS
- Παρόμοιο long-term survival rates και καλύτερο περιεγχειρητικό αποτέλεσμα

Lederman et al., *Ann Oncol.* 2024 Mar;35(3):248-266
Kehoe S, Hook J, Nankivell M, et al., *Lancet.* 2015;386(9990):249-257.
Onda T, Satoh T, Ogawa G, et al., *Eur J Cancer.* 2020;130:114-125.
Fagotti A, Ferrandina MG, Vizzielli G, et al., *Int J Gynecol Cancer.* 2020;30(11):1657-1664.
Vergote I, Tropé CG, Amant F, et al., *N Engl J Med.* 2010;363(10):943-953.



Εξαιρεσιμότητα

- CT και dwMRI
- Το PET-CT δε φαίνεται να υπερτερεί έναντι της CT στην εντόπιση περιτοναϊκής νόσου

Fuso L, Ferrero A, Vietti E, et al., *Int J Gynecol Cancer*. 2019;29(3):599-604.

Michielsen K, Dresen R, Vanslembrouck R, et al., *Eur J Cancer*. 2017;83:88-98.

Engbersen MP, van TSI, Lok C, et al., *Eur J Radiol*. 2019;114:146-151.

Michielsen K, Vergote I, Op de Beeck K, et al., *Eur Radiol*. 2014;24(4):889-901.

Khiewvan B, Torigian DA, Emamzadehfard S, et al., *Eur J Nucl Med Mol Imaging*. 2017;44(6):1079-1091.



Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up¹

J. A. Ledermann¹, F. A. Raja¹, C. Fotopoulou², A. Gonzalez-Martin³, N. Colombo⁴ & C. Sessa⁵, on behalf of the ESMO Guidelines Working Group*

¹UCL Cancer Institute, University College London, London; ²Imperial College, London, UK; ³MD-Anderson Cancer Centre, Madrid, Spain; ⁴European Institute of Oncology, University of Milan Bicocca, Milan, Italy; ⁵Oncology Institute of Southern Switzerland, Ospedale San Giovanni, Bellinzona, Switzerland

- ✓ In advanced epithelial ovarian cancer, the aim is complete cytoreduction of all macroscopic visible disease, since this has been shown to be associated with a significantly increased OS and PFS. In order to achieve this, a maximal surgical effort is required, including intestinal resection, peritoneal stripping, diaphragmatic resection, removal of bulky para-aortic lymph nodes and splenectomy.
- ✓ There is an increasing body of evidence that suggests specialist training and surgical expertise results in improvements in the rate of cytoreduction, with no increase in morbidity as a result of this process.
- ✓ Thus, women with advanced disease are advised to undergo surgery in specialised centres with adequate infrastructure and training

How to select patients for primary debulking surgery or neoadjuvant chemotherapy in advanced OC?

Summary of recommendations	LoE	GoR	Consensus
The selection of patients for primary debulking surgery or neo-adjuvant treatment must be performed in a specialist ovarian cancer centre (according to the ESGO Quality recommendations) in a multidisciplinary setting	IV	A	Yes: 100% (40 voters)
Complete tumour resection at upfront debulking is the most important prognostic factor for patients with advanced ovarian cancer and is the main goal of surgery	IV	A	Yes: 100% (40 voters)
When complete surgery with no macroscopic visible disease appears feasible (both spread of disease and general condition of the patient), primary upfront debulking should be offered	IV	B	Yes: 100% (40 voters)
<ul style="list-style-type: none"> Even debulking with residual disease <1cm in low grade serous ovarian carcinoma may improve survival when complete cytoreduction is not feasible 	IV	C	Yes: 95% (38 voters) Missing: 5% (2 voters)

Rationale for cytoreduction



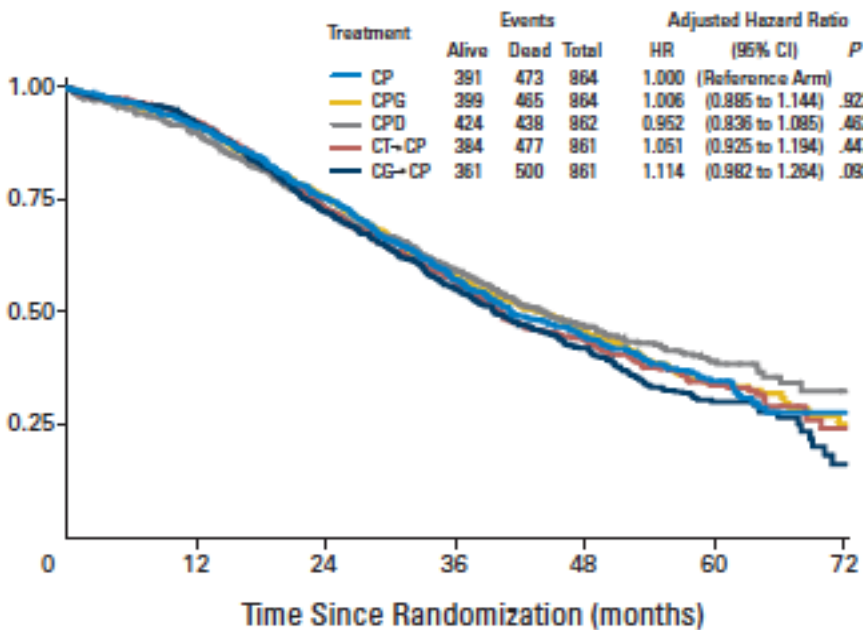
Evaluation of New Platinum-Based Treatment Regimens in Advanced-Stage Ovarian Cancer: A Phase III Trial of the Gynecologic Cancer InterGroup

Michael A. Bookman, Mark F. Brady, William P. McGuire, Peter G. Harper, David S. Alberts, Michael Friedlander, Nicoletta Colombo, Jeffrey M. Fowler, Peter A. Argenta, Koen De Geest, David G. Mutch, Robert A. Burger, Ann Marie Swart, Edward L. Trimble, Chrisann Accario-Winslow, and Lawrence M. Roth

From the Fox Chase Cancer Center, Philadelphia, PA; Gynecologic Oncology Group Statistical and Data Center, Buffalo, NY; Franklin Square Hospital; Baltimore, MD; Guy's Hospital, London, United Kingdom; Arizona Cancer Center, Tucson, AZ; Australian New

B

Progression-Free Survival (proportion)

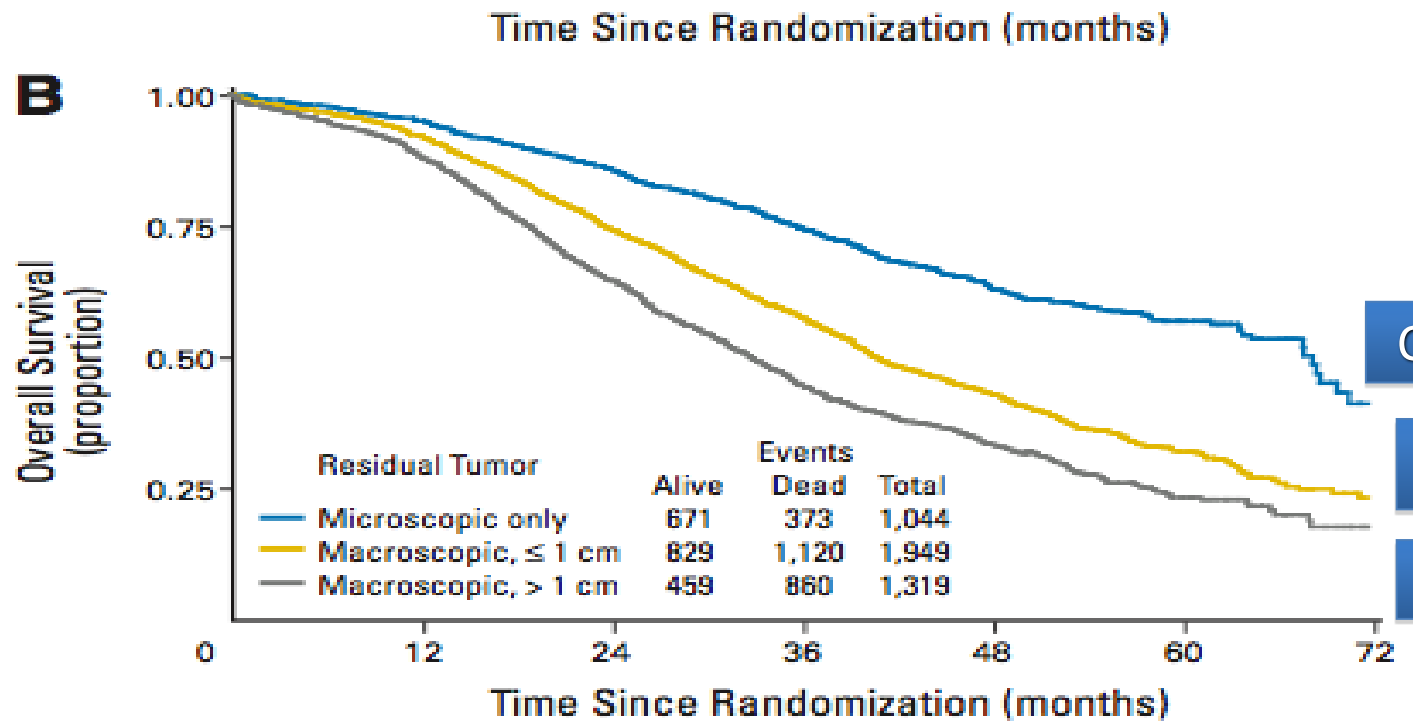


GOG 0182 – ICON 5
4312 pts with stages III-IV
ovarian Ca
Largest prospective trial in
ovarian Ca

OS: 44 months
PFS: 16 months



B



Complete 68months

< 1cm 40 months

> 1cm 33 months

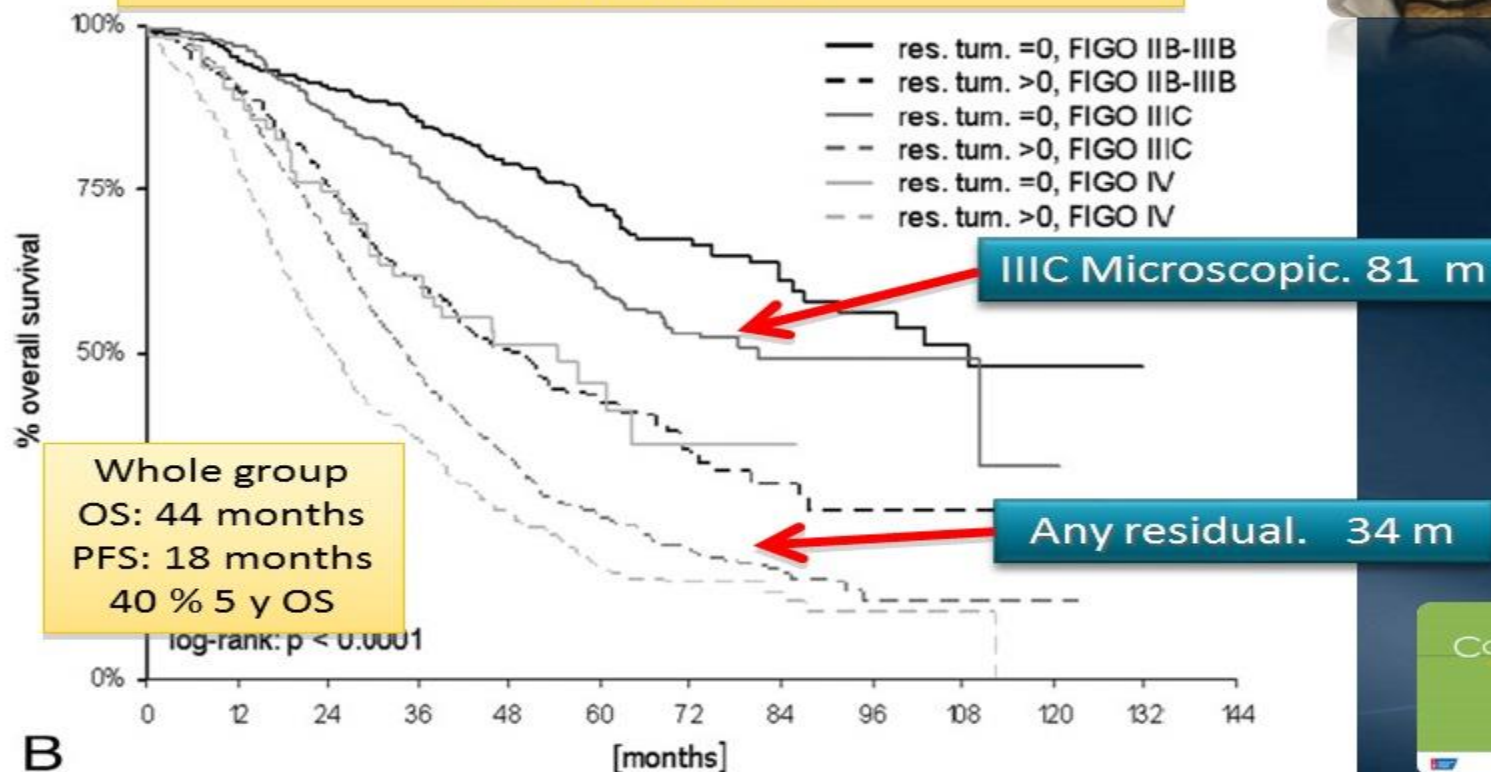
GOG 0182 – ICON 5
4312 pts with stages III-IV
ovarian Ca

The German experience.....



Du Bois, 2010: 1779 pt . Stage IIIC

AGO-OVAR # 1,3 and 5





ORIGINAL ARTICLE – GYNECOLOGIC ONCOLOGY

What Should We Expect After a Complete Cytoreduction at the Time of Interval or Primary Debulking Surgery in Advanced Ovarian Cancer?

Luis Chiva, MD, PhD¹, Fernando Lapuente, MD¹, Teresa Castellanos, MD¹, Sonsoles Alonso, MD, PhD¹, and Antonio Gonzalez-Martin, MD²

Review 2008-2014
11871 patients III-IV ovarian cancer
with Primary Debulking

Primary Debulking: 11871 patients

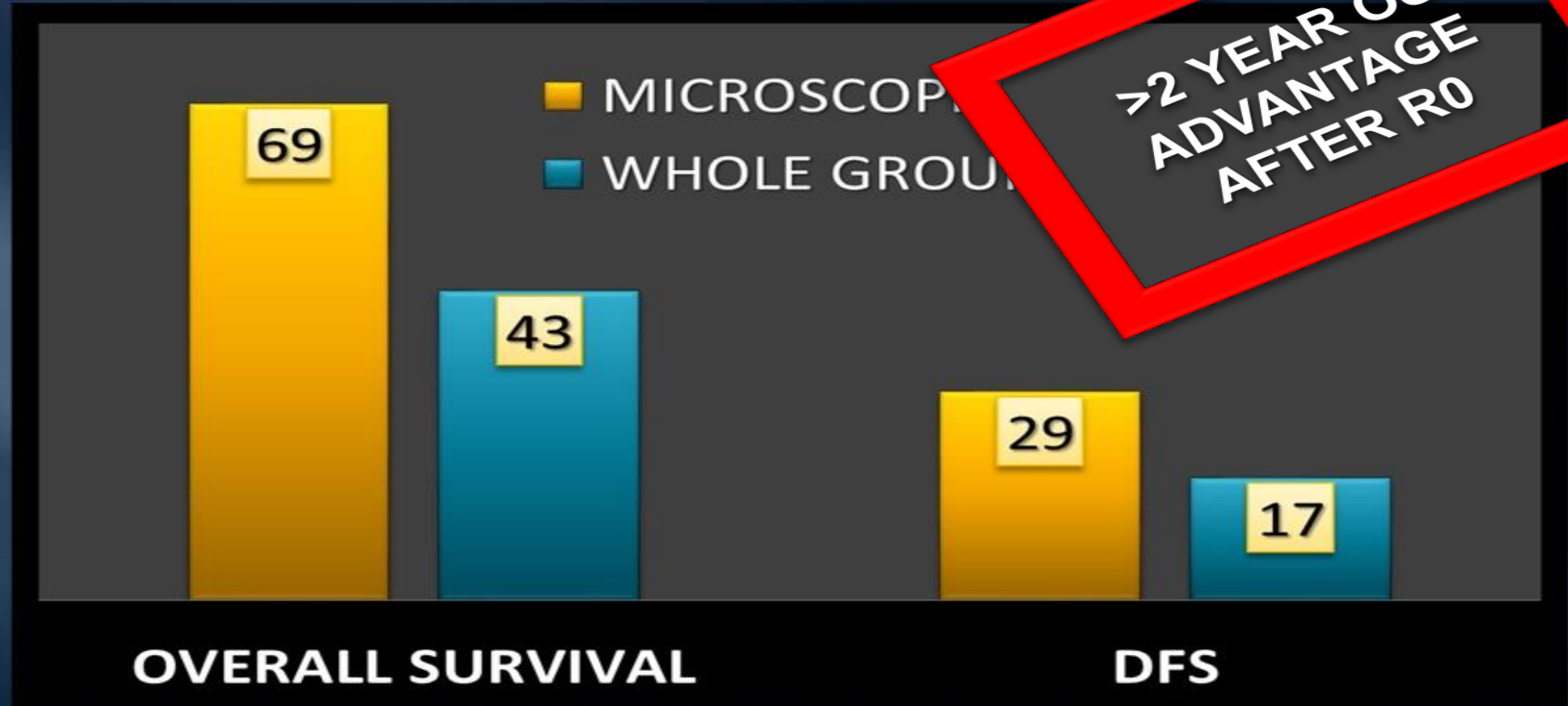
Avg.
59 yo

77 %
Serous

20 %
Stg IV

27 % R0
3205 pt

11871 pt .
SURVIVAL (months)



>2 YEAR OS
ADVANTAGE
AFTER R0

What Should We Expect After a Complete Cytoreduction at the Time of Interval or Primary Debulking Surgery in Advanced Ovarian Cancer?

Luis Chiva, MD, PhD¹, Fernando Lapuente, MD¹, Teresa Castellanos, MD¹, Sonsoles Alonso, MD, PhD¹, and Antonio Gonzalez-Martin, MD²

Review 2008-2014

Stage IV:
1796 pt

IDS: 308 pt

PDS: 1488 pt

35 % R0

35 months

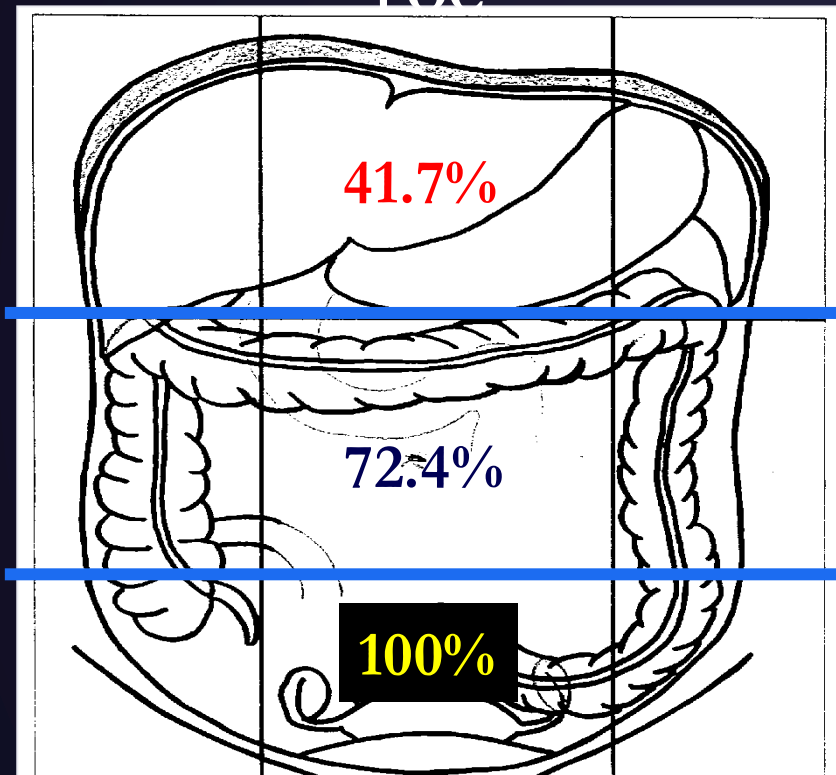
15 % R0

63 months

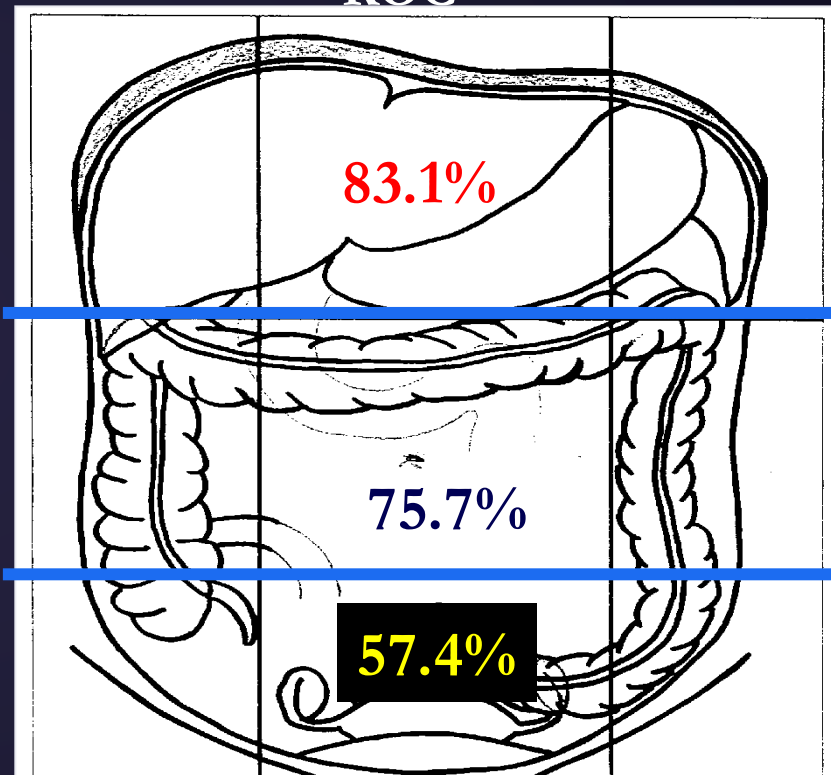
Tumor dissemination patterns in ovarian cancer surgery

POC

ROC



p
<0.001



0.6
<0.001

70 Months and..... beyond

MICROSCOPIC
RESIDUAL

30 MONTHS
OF ADVANTAGE

<1 cm

40-44 Months

7-10 MONTHS
OF ADVANTAGE

>1 cm

30-35 Months



EVOLUTION OF QUALITY OF SURGERY OVER TIME DIRECTLY ASSOCIATED WITH IMPROVED SURVIVAL

Continuous effort nationally and internationally to increase surgical expertise

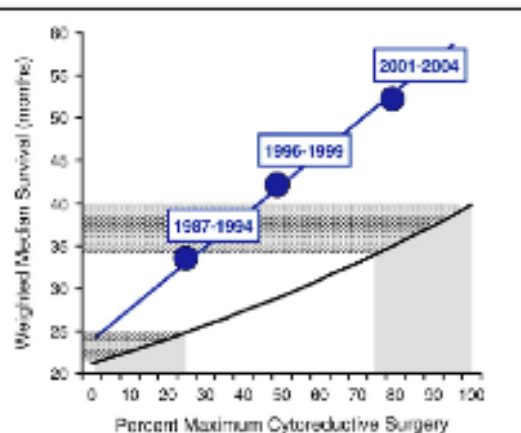
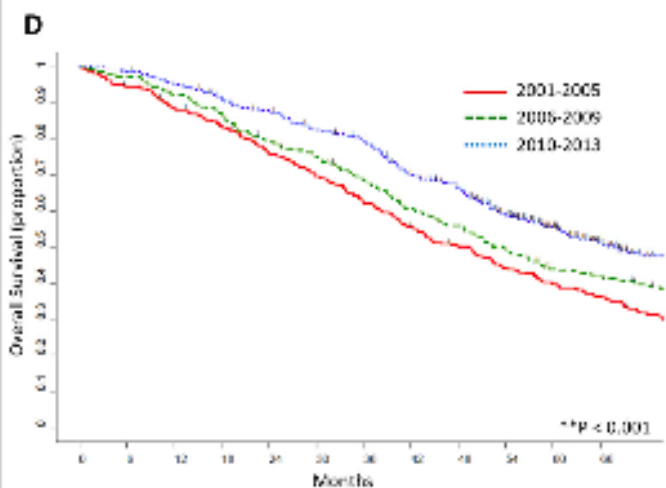


Fig. 1. Median overall survival as a function of percent maximum or optimal cytoreductive surgery. MSKCC survival 1987-2004 superimposed on model by Bristow et al. (Modified with permission Brizone BE, Tomacruz IS, Armstrong DK, et al: Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 20: 1248-1256, 2002).

[Bristow et al JCO 2002](#)



[Tseng et.al. 2018 Gynecol Oncol](#)



Figure 2. Improvement in optimal and complete resection rates after quality-improvement initiative. Patients with stage IIIc ovarian cancer and carcinomatosis ($p = 0.006$; Pearson's chi-square).

[Aletti et.al. 2009 Am Coll Surg](#)



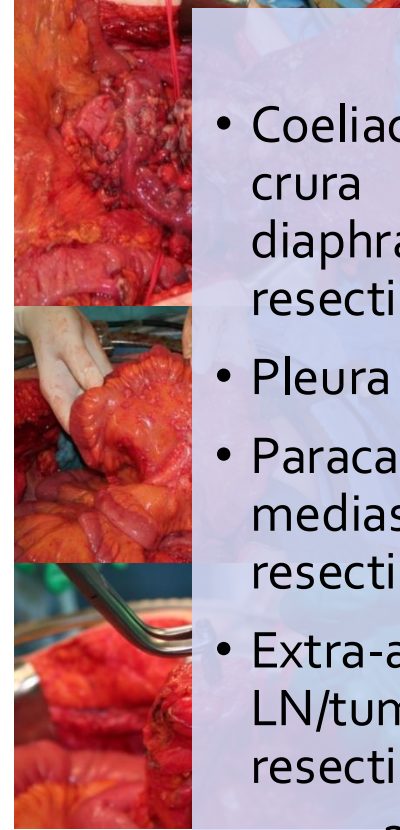
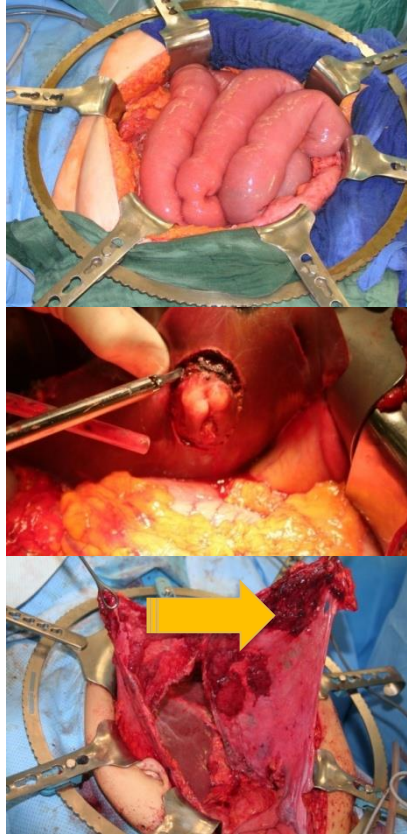
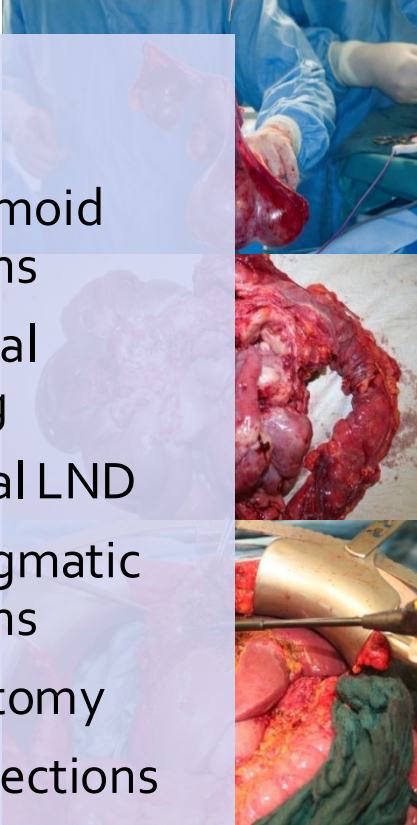
Αλλαγές στη χειρουργική πρακτική

	Group 1 (n=70) „Standard“ before 2000	Group 2 (n=70) incorporation of extensive upper abdominal debulking after 2001	
Complete or optimal (<1cm) tumor resection	50%	76%	p<0.01
Operative time	174 min	264 min	p<0.001
Blood loss	460 ml	880 ml	p<0.001

*Other complication rates and length of hospitalization **not significantly different** between the two groups.*

Παραθυρο εξαιρεσιμότητας

- En bloc rectosigmoid resections
- Peritoneal stripping
- Infrarenal LND
- Diaphragmatic resections
- Splenectomy
- Liver resections



- Coeliac trunk and crura diaphragmatica resections
- Pleura resections
- Paracardiac/mediastinal LN resections
- Extra-abdominal LN/tumor resections
- ??

PATIENTS PREFERENCES FOR ATTRIBUTES OF PDS VS NAC FOR TREATMENT OF NEWLY DIAGNOSED OVARIAN CANCER

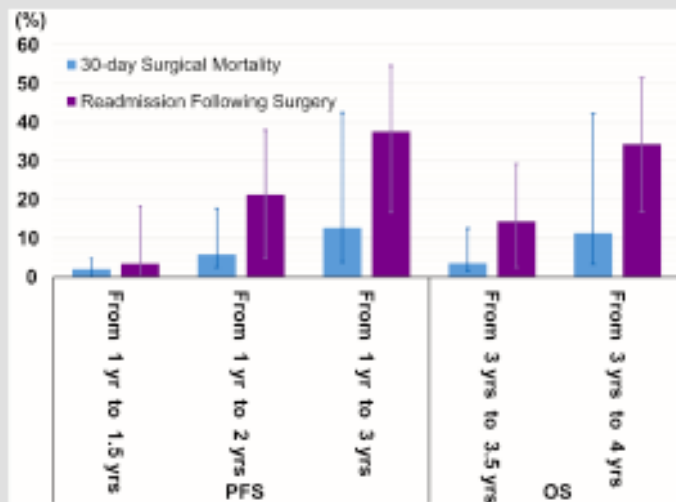


Figure 3. Risk equivalents, indicating additional levels of surgical risk participants accepted in exchange for improvements in survival outcomes. The vertical bars represent 95% confidence intervals. OS, overall survival; PFS, progression-free survival.

Patients would accept:

- ✓ **a 15% increase in risk of major complications**
- and
- ✓ **a 4% increase in surgical mortality**, in exchange for substantial gains in survival.




This provides clinicians a framework to discuss preferences with patients and to incorporate preferences into clinical trial design.



Original research



European Society of Gynaecological Oncology guidelines for the peri-operative management of advanced ovarian cancer patients undergoing debulking surgery

Christina Fotopoulou ¹, François Planchamp,² Tugce Aytulu,³ Luis Chiva ⁴, Alessandro Cina,⁵ Önder Ergönül,³ Anna Fagotti,^{5,6} Dimitrios Haidopoulos,⁷ Annette Hasenburg,⁸ Cathy Hughes,⁹ Pawel Knapp,¹⁰ Philippe Morice,¹¹ Stephanie Schneider,¹² Jalid Sehouli,¹³ Emmanouil Stamatakis,¹⁴ Stephanie Suria,¹⁵ Cagatay Taskiran ¹⁶, Ralf Ulrich Trappe,¹⁷ Jeremy Campbell¹⁸



Απόλυτες αντενδείξεις για PCS

1. Compromised performance status
2. Age > 75 + extensive disease + malnutrition
3. Pleural infusions, especially bilateral
4. Parenchymal liver mets especially if in both lobes
5. Extensive porta hepatis disease – obstruction of common duct or portal vein
6. Extensive disease of the mesentery (retractile mesenteritis)
7. Extensive disease of the abdominal wall
8. Multiple bowel obstructions requiring > 2 anastomoses



Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Defining the limits of radical cytoreductive surgery for ovarian cancer

Jason D. Wright ^{a,e,*}, Sharyn N. Lewin ^{a,e}, Israel Deutsch ^{b,e}, William M. Burke ^a, Xuming Sun ^a, Alfred I. Neugut ^{c,d,e}, Thomas J. Herzog ^{a,e}, Dawn L. Hershman ^{c,d,e}^a Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, USA^b Department of Radiation Oncology, Columbia University College of Physicians and Surgeons, USA^c Department of Medicine, Columbia University College of Physicians and Surgeons, USA^d Department of Radiation Oncology, Columbia University College of Physicians and Surgeons, USA^e F

J.D. Wright et al. / Gynecologic Oncology 123 (2011) 467–473

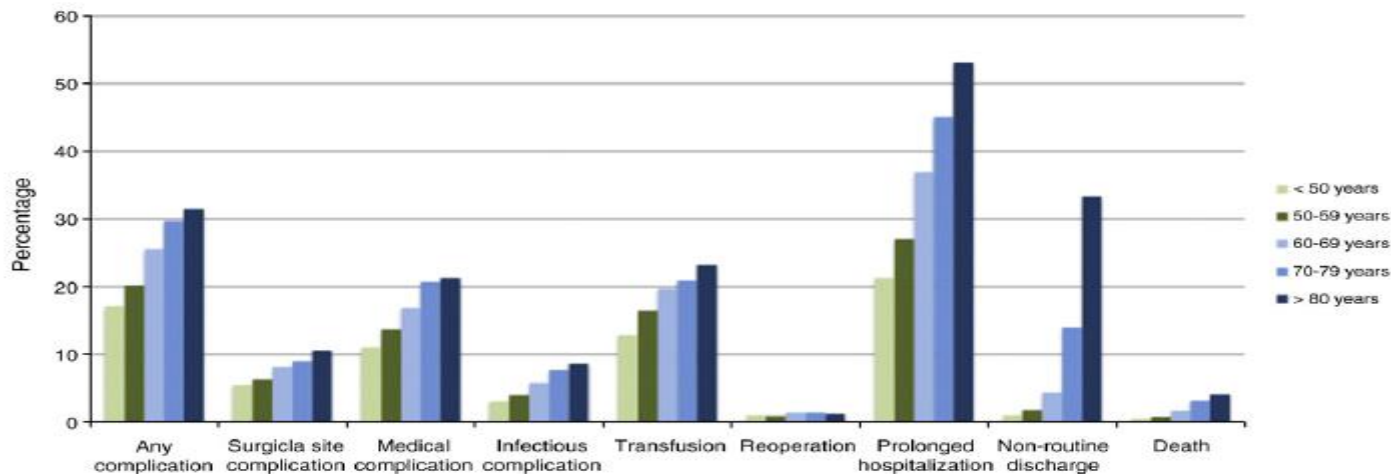
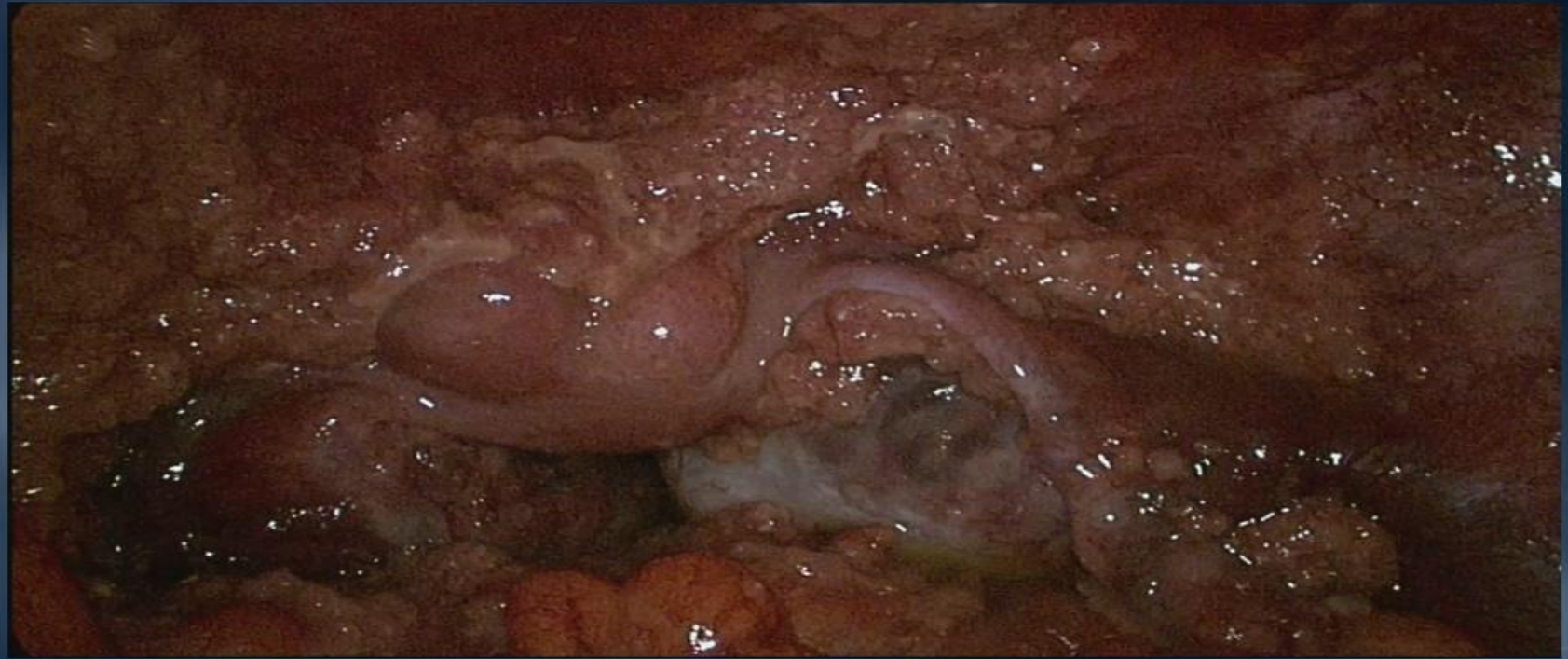


Fig. 1. Morbidity and mortality associated with cytoreductive surgery in women with ovarian cancer stratified by age at diagnosis (n = 28,651).

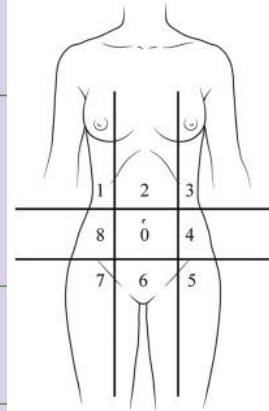


Διαγνωστική λαπαροσκόπηση





Laparoscopic Feature	Score 0	Score 2
Peritoneal carcinomatosis	Carcinomatosis involving a limited area (along the paracolic gutter or the pelvic peritoneum) and surgically removable by peritonectomy	Unresectable massive peritoneal involvement as well as with a miliary pattern of distribution
Diaphragmatic disease	No infiltrating carcinomatosis and no nodules confluent in most of the diaphragmatic surface	Widespread infiltrating carcinomatosis or nodules confluent in most of the diaphragmatic surface
Mesenteric disease	No large infiltrating nodules and no involvement of the root of the mesentery as would be indicated by limited movement of the various intestinal segments	Large infiltrating nodules or involvement of the root of the mesentery indicated by limited movement of the various intestinal segments
Omental disease	No tumor diffusion observed along the omentum up to the large stomach curvature	Tumor diffusion observed along the omentum up to the large stomach curvature
Bowel infiltration	No bowel resection was assumed and no miliary carcinomatosis on the serosa observed	Bowel resection assumed or miliary carcinomatosis on the serosa observed
Stomach infiltration	No obvious neoplastic involvement of the gastric wall	Obvious neoplastic involvement of the gastric wall
Liver metastases	No surface lesion	Any surface lesion

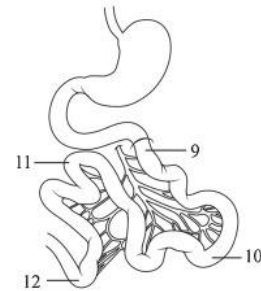


Peritoneal cancer index

Regions	Lesion size
0 Central	_____
1 Right upper	_____
2 Epigastrium	_____
3 Left upper	_____
4 Left flank	_____
5 Left lower	_____
6 Pelvis	_____
7 Right lower	_____
8 Right flank	_____
9 Upper jejunum	_____
10 Lower jejunum	_____
11 Upper ileum	_____
12 lower ileum	_____
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Lesion size score

- LS 0 No tumor seen
- LS 1 Tumor up to 0.5 cm
- LS 2 Tumor up to 5.0 cm
- LS 3 Tumor > 5.0 cm or confluence





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

CONCLUSIONS

Neoadjuvant chemotherapy followed by interval debulking surgery was not inferior to primary debulking surgery followed by chemotherapy as a treatment option for patients with bulky stage IIIC or IV ovarian carcinoma in this study. Complete resection of all macroscopic disease, whether performed as primary treatment or after neoadjuvant chemotherapy, remains the objective whenever cytoreductive surgery is performed. (Funded by the National Cancer Institute; ClinicalTrials.gov number, NCT00003636.)



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



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

Interpretation In women with stage III or IV ovarian cancer, survival with primary chemotherapy is non-inferior to primary surgery. In this study population, giving primary chemotherapy before surgery is an acceptable standard of care for women with advanced ovarian cancer.



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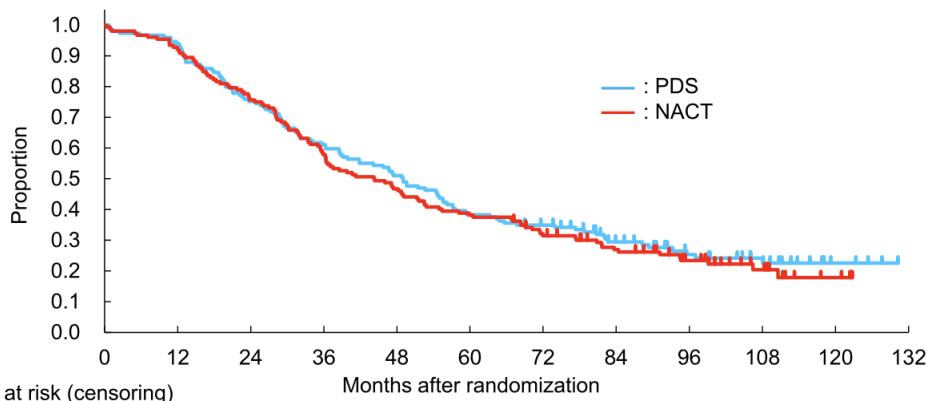


Clinical Trial

Comparison of survival between primary debulking surgery and neoadjuvant chemotherapy for stage III/IV ovarian, tubal and peritoneal cancers in phase III randomised trial



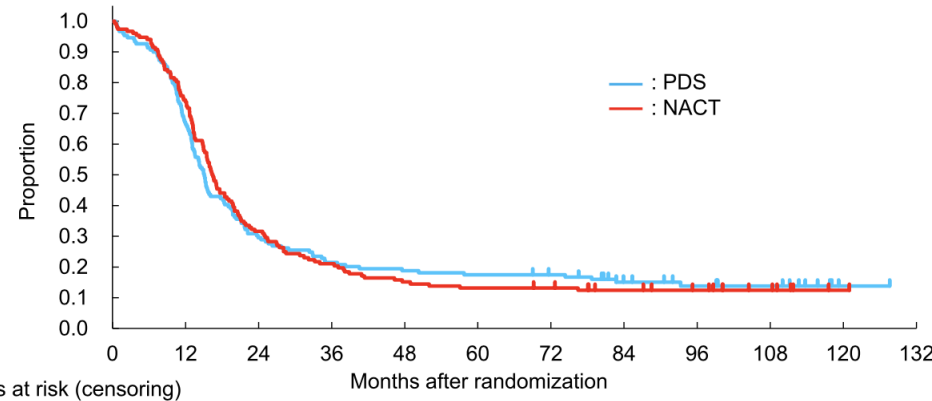
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ts at risk (censoring)

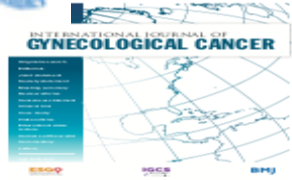
PDS	149 (0)	140 (0)	112 (0)	91 (0)	76 (0)	57 (0)	50 (2)	34 (9)	22 (8)	15 (6)	4 (10)	0 (4)
NACT	152 (0)	140 (0)	115 (0)	88 (0)	71 (0)	58 (0)	46 (2)	35 (5)	22 (9)	11 (9)	3 (7)	0 (3)

B



Pts at risk (censoring)

PDS	149 (0)	99 (0)	44 (0)	32 (0)	28 (0)	26 (0)	24 (2)	15 (6)	11 (3)	9 (2)	1 (8)	0 (1)
NACT	152 (0)	112 (0)	48 (0)	32 (0)	23 (0)	20 (0)	19 (1)	14 (4)	11 (3)	6 (5)	1 (5)	0 (1)

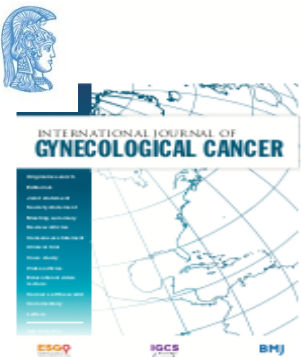


Randomized trial of primary debulking surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer (SCORPION-NCT01461850)

Anna Fagotti ^{1,2}, Maria Gabriella Ferrandina,^{1,2} Giuseppe Vizzielli,¹ Tina Pasciuto,³ Francesco Fanfani,^{1,2} Valerio Gallota,¹ Pasquale Alessandro Margariti,¹ Vito Chiantera,^{4,5} Barbara Costantini,¹ S. Gueli Alletti,¹ Francesco Cosentino,⁶ Giovanni Scambia^{1,2}

- Prospective randomized trial
- 171 pts randomized to PDS vs NACT
- Rate of complete resection: 47,5% vs 77%
- Major complications: 25,9% vs 7,6%
- Median FU 59 months
- Median OS 41m vs 43m
- Median PFS 15m vs 14m

Conclusion: PDS and NACT have the same efficacy when used at their maximal possibilities but the toxicity profile is different



Neoadjuvant chemotherapy for advanced ovarian cancer: the tail of the scorpion for radical debulking surgery?

Christina Fotopoulou 

- Bias of a monocentric study
- 8,3% of the pts of the debulking arm died of surgical complications
- Long operating rooms times (7,5h)
- 52,4% stoma formation despite the younger age of the pts
- Why despite the better complete clearance rates, OS was not better in the NACT arm ????

40% of the UK pts and 32% of the Northern America pts NEVER get the chance to be debulked



Τρωτά σημεία

- **Very poor performance and surgical QL of the PDS arm:**
- ✓ 8.3% mortality due to surgical complications, long theatre times (7.5 hours) and 52.4% of stoma formation despite the comparably young average age of the included patients (56 years) (SCORPION)
- ✓ 12% "R0"- resection, 1/3 of the PDS patients underwent IDS "to complete the debulking", 27% rate of abdominal organ resection apart from standard TAH/BSO/omentectomy (JCOG0602)
- ✓ 6% mortality, 2hrs operation time, 11% bowel resection with all receiving a stoma (10%), 17% "R0"- resection, 23 mo median OS (CHORUS)
- ✓ Very strong variation of surgical QL between centres (3.9% - 62.9% "R0"- resection), 15% bowel resection, 6% splenectomy, 2,5 hrs theatre time (ranging from 10min), 29 mo OS (EORTC)
- **The significantly higher complete tumor resection rates at IDS, failed to translate into an – expected- equivalent improvement of survival: a paradigm shift of the value of residual disease after NAC? (TuR0 ≠ TuR0 post-CTX)**



TRUST: Trial of Radical Uprfront Surgical Therapy in Advanced Ovarian Cancer (ENGOT ov33 / AGO-OVAR OP.7)

Sven Mahner¹, Florian Heitz², Sahar Salehi³, Alexander Reuss⁴, Frederic Guyon⁵, Andreas du Bois², Philipp Harter², Christina Fotopoulou⁶, Denis Querleu⁷, Berit Jul Mosgard⁸, Bernhard Krämer⁹, Francesco Raspagliesi¹⁰, Björn Lampe¹¹, Alexander Burges¹, Barbara Schmalfeldt¹², Pauline Wimberger¹³, Holger Bronger¹⁴, Dennis Chi¹⁵, Jalid Sehouli¹⁶, Giovanni Aletti¹⁷
and the TRUST investigators

¹AGO Study Group & Department of Obstetrics and Gynecology, LMU University Hospital, Munich, Germany; ²AGO Study Group & Department for Gynecology and Gynecologic Oncology; Kliniken Essen Mitte, Essen, Germany; ³NSGO & Department of Women's and Children's Health, Karolinska Institutet and Department of Pelvic Cancer, Theme Cancer, Karolinska University Hospital, Stockholm, Sweden; ⁴AGO Study Group & KKS Marburg, Marburg, Germany; ⁵GINECO & Institut Bergonié Bordeaux, Bordeaux, France; ⁶AGO Study Group & Division of Cancer, Department of Surgery and Cancer, Imperial College London, London, UK; ⁷GINECO & UOC ginecologia oncologica, dipartimento di scienze della donna, del bambino e di sanità pubblica, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy; ⁸NSGO & Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark; ⁹AGO Study Group & University Hospital Tuebingen, Tuebingen, Germany; ¹⁰MaNGO & Istituto Tumori di Milano, Milano, Italy; ¹¹AGO Study Group & Kaiserswerther Diakonie, Duesseldorf, current address: Staedtsche Kliniken, Moenchengladbach, Germany; ¹²AGO Study Group & University Medical Center Hamburg Eppendorf, Hamburg, Germany; ¹³AGO Study Group & Dresden University Hospital, Dresden, Germany; ¹⁴AGO Study Group & TUM School of Medicine and Health, Technical University of Munich (TUM), Munich, Germany; ¹⁵AGO Study Group & MSKCC, New York, USA; ¹⁶AGO Study Group & Charite University Hospital, Berlin, Germany; ¹⁷MaNGO & Istituto Europeo di Oncologia, IRCCS, Milano, Italy



TRUST Key Takeaway Points

Patients with advanced ovarian cancer in TRUST had excellent PFS and OS after maximal effort cytoreductive surgery. Complete resection rates were high and morbidity and mortality were low.

A statistically significant OS improvement for primary compared to interval cytoreductive surgery was not observed.

TRUST is the first randomized phase III trial to show improved median PFS for primary compared to interval cytoreductive surgery without compromising short- or long-term quality of life.



TRUST Background



- The aim of surgery in advanced ovarian cancer is to prolong patients' remission and improve overall survival while sustaining quality of life.
- Complete gross tumor resection is associated with favorable outcome.^{1,2}
- Primary cytoreductive surgery (PCS) followed by chemotherapy was considered standard over decades.
- An alternative strategy with neoadjuvant chemotherapy (NACT) followed by interval cytoreductive surgery (ICS) in selected patients (pts) was subsequently reported by randomized phase III trials.³⁻⁶
- However, these studies had limitations regarding patient- as well as center-selection and surgical quality metrics.
- **As a result, the optimal timing of surgery in pts with advanced ovarian cancer considered resectable remains controversial.**

¹du Bois et al. Cancer 2009; ²Bristow et al. J Clin Oncol 2023; ³Vergote et al. N Engl J Med 2011; ⁴Kehoe et al. Lancet 2016;

⁵Fagotti et al. Int J Gynecol Cancer 2020; ⁶Onda et al. Eur J Cancer 2020



TRUST Rationale



TRUST was designed to evaluate the optimal timing of maximal effort cytoreductive surgery in patients with advanced ovarian cancer

- considered resectable
- fit enough to tolerate radical surgery
- treated in gynecologic cancer centers with defined surgical quality assurance criteria.



TRUST Quality Assurance



- Centers were required to obtain accreditation for the trial including onsite quality assurance review.¹
- Quality criteria were based on ESGO certification² and extended for TRUST including
 - evaluation of cytoreductive surgery in the operating room
 - assessment of surgical proficiency and infrastructure
 - complete resection rates ($\geq 50\%$ in upfront surgery for FIGO IIIB-IVB pts)
 - surgical volume (≥ 36 cytoreductive surgeries/year).

¹Reuss et al. Int J Gynecol Cancer 2019, ²Fotopoulou et al. Int J Gynecol Cancer 2020
ESGO: European Society of Gynecologic Oncology



TRUST Study Design



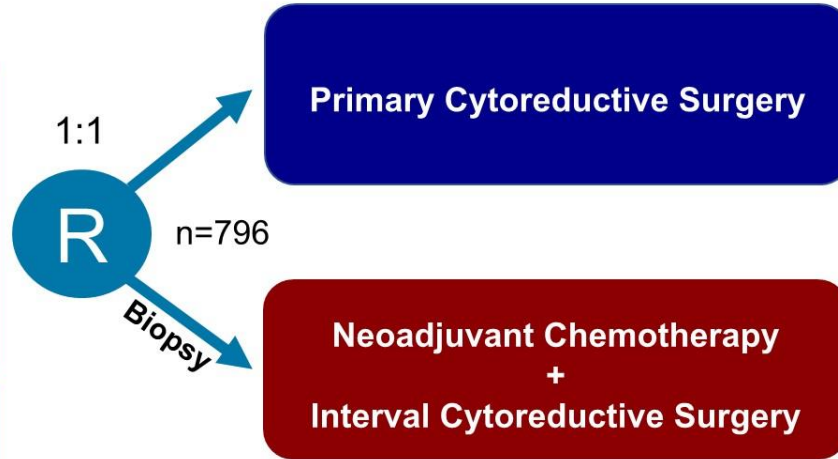
Main Inclusion Criteria

- Epithelial ovarian, fallopian tube or peritoneal cancer
 - FIGO stage IIIB/C, IVA/B
 - Considered resectable
- Fit enough to tolerate radical surgery

Stratification factors

- Center
- Age-ECOG-combination
ECOG0 and age ≤65y vs.
ECOG>0 or age >65y

Qualification process for participating centers to ensure surgical quality



Primary endpoint

- Overall survival

Key secondary endpoints

- Progression-free survival
- Complete resection rate
- Surgical procedures
- Surgical morbidity
- Quality of life

Predefined exploratory and translational endpoints

Recommended systemic treatment:

- Carboplatin AUC5, Paclitaxel 175mg/m² q3w
- Bevacizumab 15mg/kg q3w as indicated
- PARPi as indicated
- Study participation or any other treatment as long as applicable for both study arms

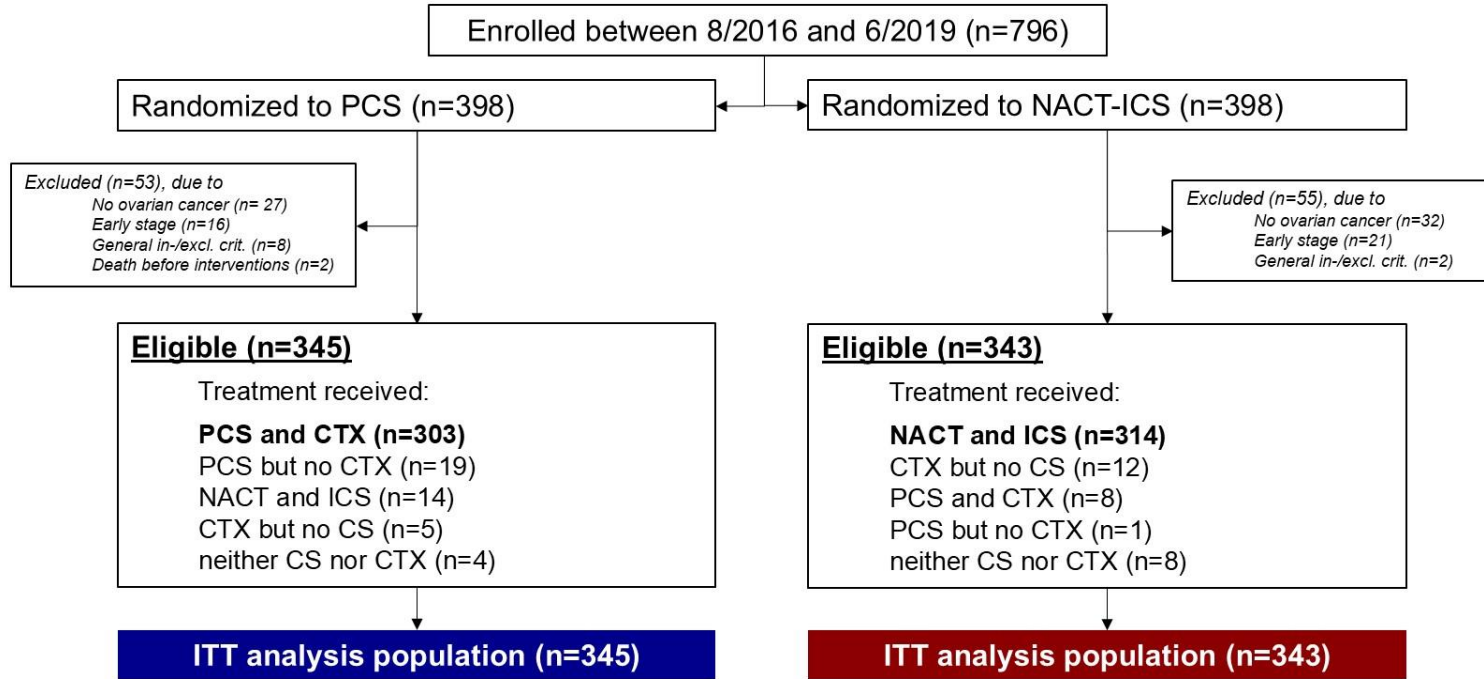


TRUST Endpoints and Statistical Design

- Primary endpoint was overall survival, calculated from the date of randomization.
- Secondary endpoints include progression-free survival, rate of complete tumor resection, surgical procedures, surgical morbidity and health related quality of life.
- A 1:1 randomization stratified by center and age-ECOG combination (ECOG 0 and age ≤ 65 years vs ECOG > 0 or age > 65 years) was performed.
- The primary endpoint overall survival was compared between the two treatment arms using a two-sided stratified log-rank test with significance level 0.05.
- **Observation of 380 deaths in eligible patients was calculated to provide a power of 80% assuming a hazard ratio of 0.75 in a test for superiority of PCS.**
- The planned sample size was 386 per arm to account for a drop-out rate of $\sim 20\%$.



TRUST Patient Disposition



CS: Cytoreductive surgery; CTX: Chemotherapy; ITT: Intention-to-treat



TRUST Baseline Characteristics



	PCS (n=345)	NACT-ICS (n=343)	Total (n=688)
Median age, years (range)	63 (34-83)	64 (32-83)	63.5 (32-83)
Median BMI, kg/m² (range)	24.6 (15.6-50.1)	24.9 (15.9-47.2)	24.8 (15.6-50.1)
ECOG, n (%)			
0	267 (77%)	263 (77%)	530 (77%)
1	78 (23%)	80 (23%)	158 (23%)
Confirmed FIGO stage (highest), n (%)			
IIIB	30 (8.7%)	18 (5.3%)	48 (7.0%)
IIIC	203 (59%)	217 (63%)	420 (61%)
IVA	31 (9.0%)	35 (10%)	66 (9.6%)
IVB	79 (23%)	68 (20%)	147 (21%)
Not reported	2 (0.6%)	5 (1.5%)	7 (1.0%)
Histological subtype, n (%)			
High grade serous	320 (93%)	312 (91%)	632 (92%)
Low grade serous	18 (5.2%)	23 (6.7%)	41 (6.0%)
Other*	4 (1.2%)	4 (1.2%)	8 (1.2%)
Not reported	3 (0.9%)	4 (1.2%)	7 (1.0%)

*Other: PCS: 3 endometrioid, 1 seromucinous; NACT-ICS: 2 clearcell, 1 seromucinous, 1 mucinous,



TRUST Results: Surgical Effort and Procedures



Procedure, n* (%)	PCS (n=331)	NACT-ICS (n=328)
Median duration of surgery, minutes (IQR)	331 (253-432)	284 (213-360)
Median blood loss, mL (IQR)	500 (300-800)	400 (200-600)
Mean number of RBC units transfused (SD)	0.9 (1.5)	0.6 (1.1)
Upper abdominal procedures	263 (79%)	221 (67%)
Splenectomy	91 (27%)	42 (13%)
Intestinal resections	224 (68%)	123 (38%)
Colorectal resection	187 (56%)	95 (29%)
Large bowel resection	135 (41%)	74 (23%)
Small bowel resection	70 (21%)	33 (10%)
Stoma formation	66 (20%)	27 (8.2%)
Lymph node dissection	197 (60%)	156 (48%)
Pelvic nodes	166 (50%)	135 (41%)
Paraaortic nodes	172 (52%)	134 (41%)
Chest procedures	63 (19%)	35 (11%)
Pericardiophrenic nodes	33 (10%)	15 (4.6%)
Open assessment of the pleura	47 (14%)	23 (7.0%)
Pleurectomy	15 (4.5%)	5 (1.5%)

* patients with documented debulking surgery; analyzed as treated;



TRUST Results: Surgical Outcome



	PCS (n=345)	NACT-ICS (n=343)	Total (n=688)
Residual disease, n (%)			
complete gross resection	235 (68%)	271 (79%)	506 (74%)
macroscopic residual disease	99 (29%)	49 (14%)	148 (22%)
<i>0.1-0.5 cm</i>	39 (11%)	29 (8.5%)	68 (9.9%)
<i>0.6-1 cm</i>	25 (7.3%)	7 (2.0%)	32 (4.7%)
<i>> 1 cm</i>	35 (10%)	13 (3.8%)	48 (7.0%)
not operated / not reported	11 (3.2%)	23 (6.7%)	34 (4.9%)

**Documented complete resections
in operated patients, n (%)**

235/334 (70%)

271/320 (85%)

506/654 (77%)



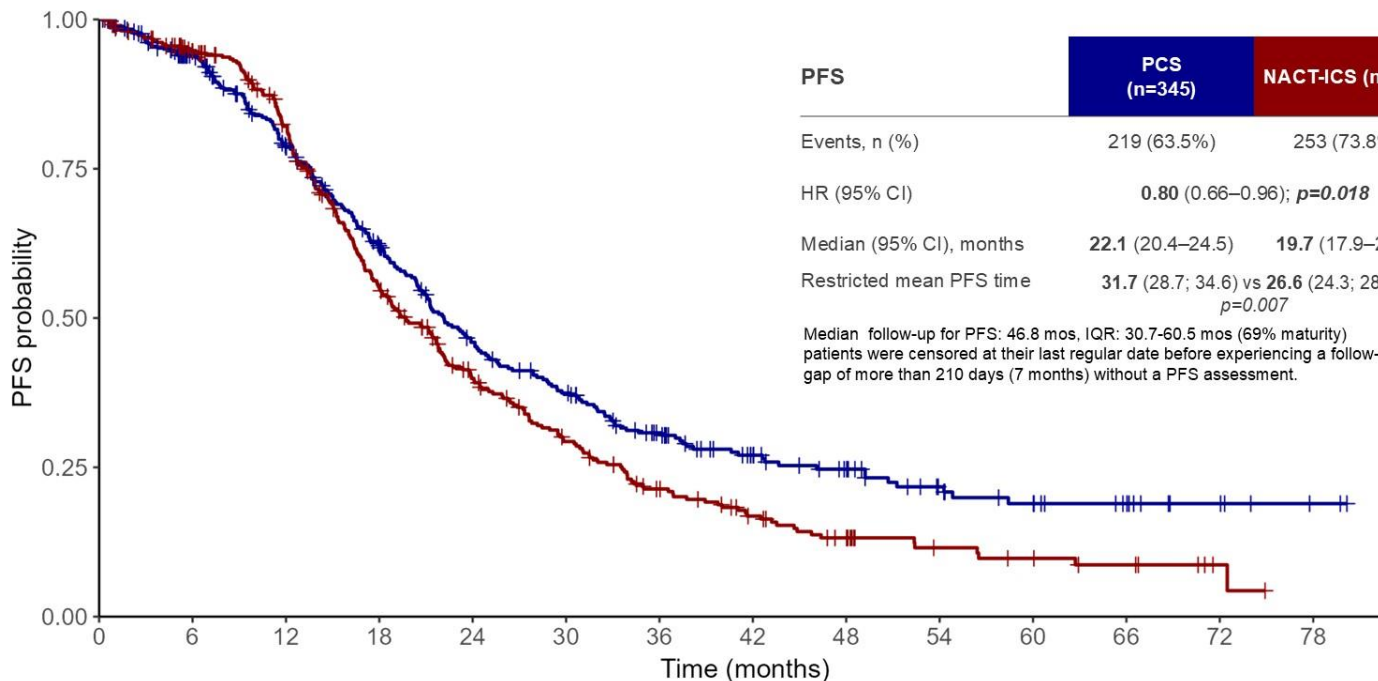
TRUST Results: Details on Systemic Therapy



Treatment n* (%)	PCS (n=345)	NACT-ICS (n=343)
First line chemotherapy	322 (93%)	334 (97%)
Platinum	322 (93%)	334 (97%)
Taxane	311 (90%)	330 (96%)
Bevacizumab treatment at any time	225 (65%)	201 (59%)
PARPi treatment at any time	86 (25%)	104 (30%)



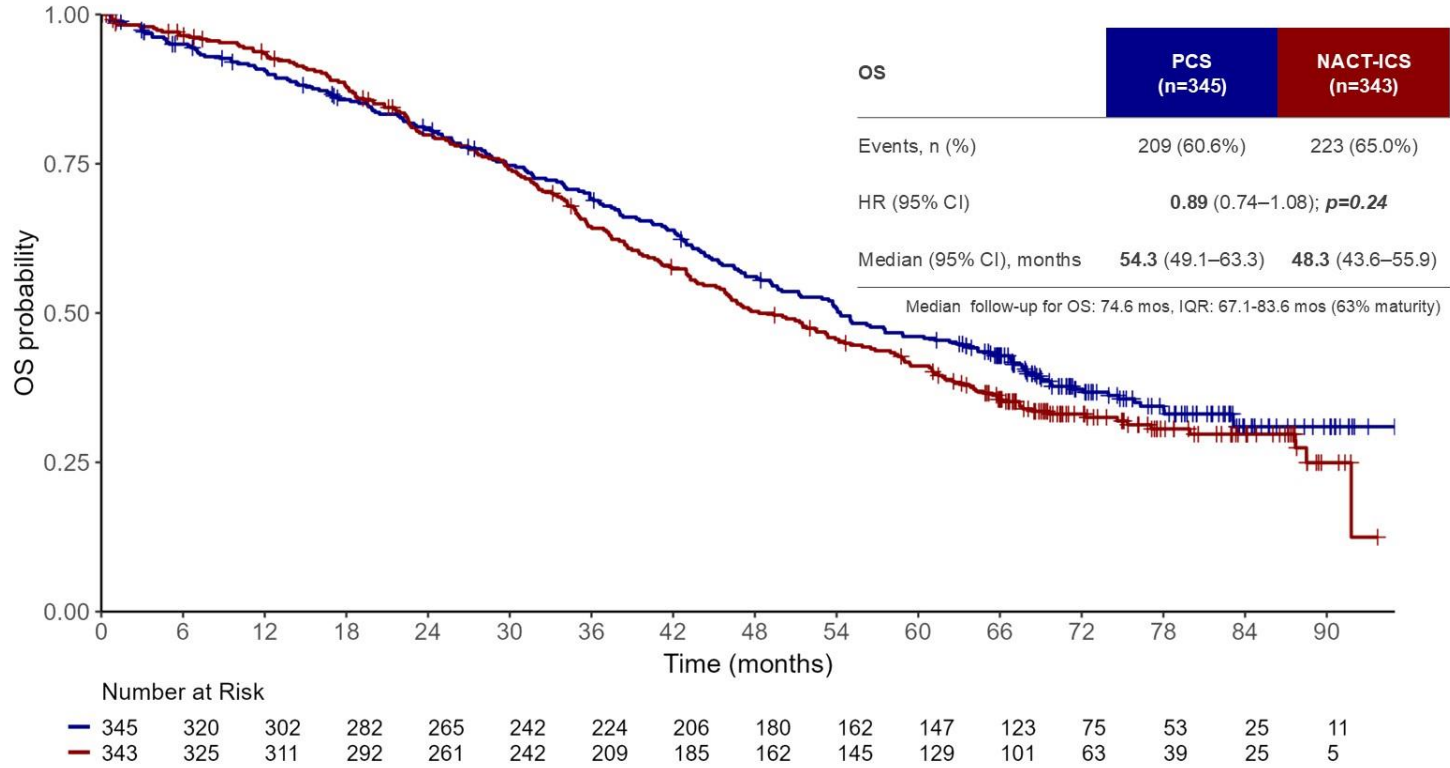
TRUST Results: Progression-free Survival (ITT)



Number at Risk		0	6	12	18	24	30	36	42	48	54	60	66	72	78
—	345	296	234	176	126	100	72	50	38	25	19	12	6	2	
—	343	306	252	165	109	76	50	34	23	13	10	7	2	0	



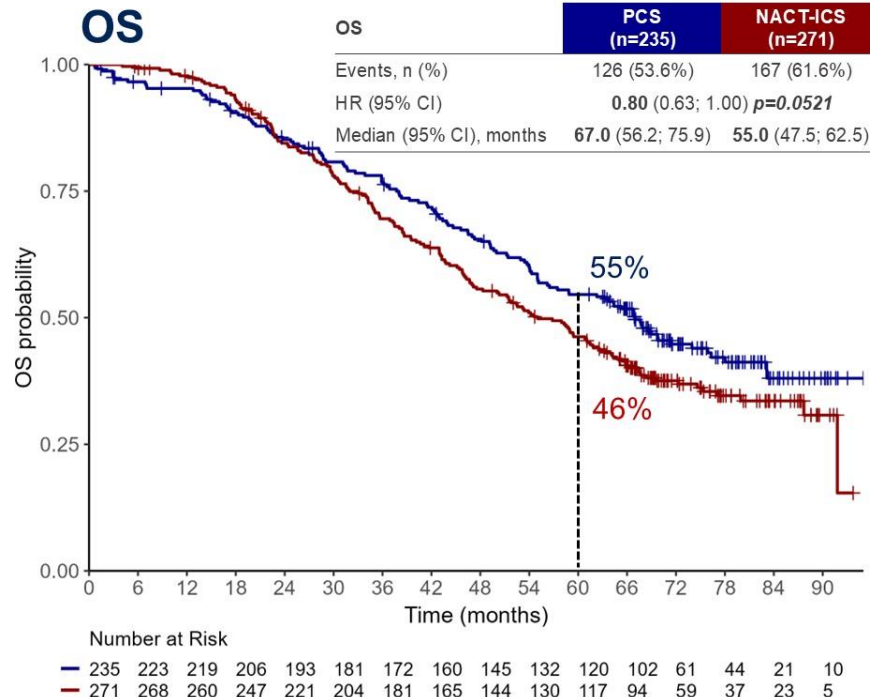
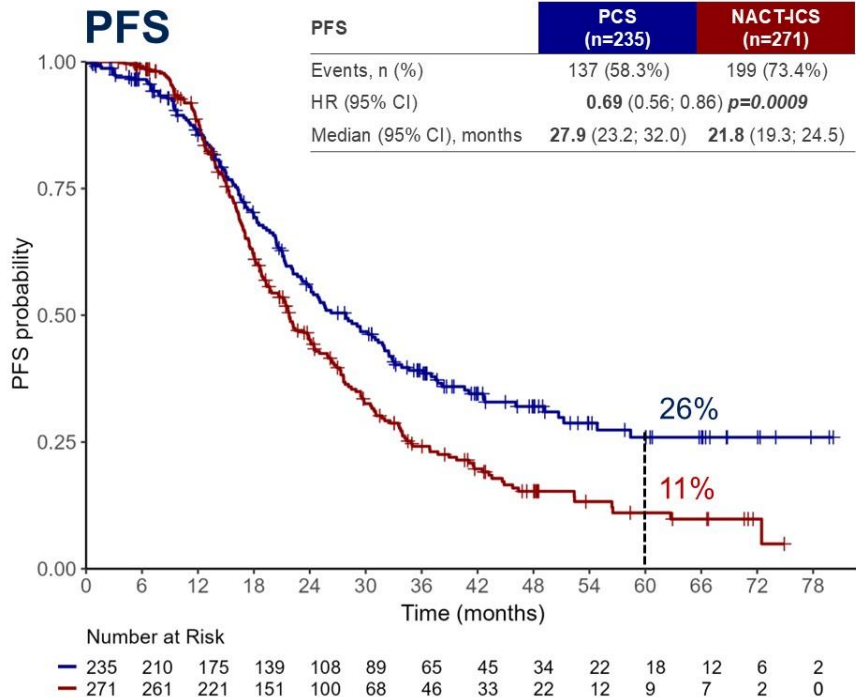
TRUST Results: Overall Survival (ITT)





TRUST Results: Prespecified Exploratory Subgroup Analysis

Complete Gross Resection in All FIGO Stages





TRUST Results: Surgical Morbidity

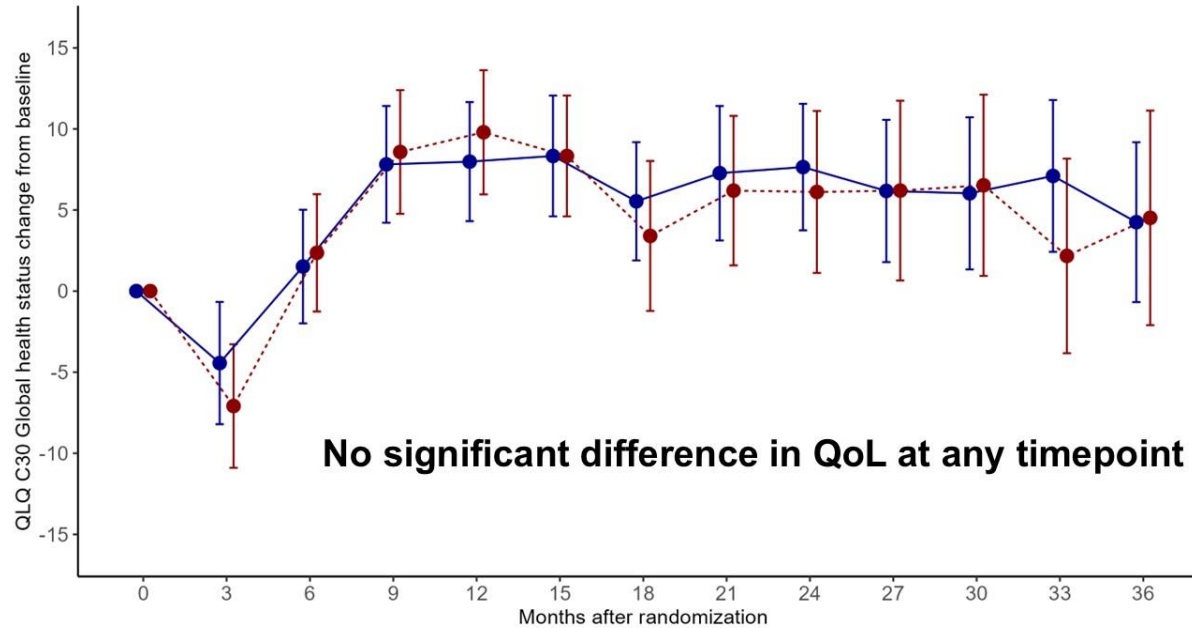


Complication, n* (%)	PCS (n=331)	NACT-ICS (n=328)
Any complication	60 (18%)	39 (12%)
>10 packed red blood cells within 24h	0	0
30-day post-op mortality	3 (0.9%)	2 (0.6%)
Re-laparotomy	21 (6.3%)	12 (3.7%)
Wound breakdown	11 (3.3%)	11 (3.4%)
Deep venous thrombosis	3 (0.9%)	1 (0.3%)
Pulmonary embolism	5 (1.5%)	3 (0.9%)
Sepsis	6 (1.8%)	4 (1.2%)
Anastomotic leak / fistula	11 (3.3%)	7 (2.1%)
Intraabdominal abscess	2 (0.6%)	1 (0.3%)
Nerve damage	1 (0.3%)	3 (0.9%)
Liver/renal failure	6 (1.8%)	2 (0.6%)
Serious cardiovascular event	8 (2.4%)	1 (0.3%)
Readmittance b/o any other complication	11 (3.3%)	5 (1.5%)

*: patients with documented cytoreductive surgery; analyzed as treated; complications that occurred within 28 days of debulking surgery



TRUST Results: Overall Quality of Life



PCS
NACT-ICS

291	184	220	193	191	182	161	165	146	143	123	115	100
293	241	226	203	205	182	169	156	139	121	106	96	83



TRUST Conclusions



- The primary endpoint of the study, a statistically significant OS improvement after primary versus interval cytoreductive surgery, was not met.
- TRUST is the first randomized phase III trial to show a benefit in median PFS for primary over interval cytoreductive surgery without compromising short- or long-term quality of life.
- Observed benefits were linked to high complete resection rates, reinforcing the value of radical upfront surgery in pts with resectable advanced ovarian cancer.
- The high rate of complete cytoreduction with low morbidity and mortality along with excellent PFS and OS emphasize the importance of surgical quality assurance programs.



Association between time to diagnosis, time to treatment and ovarian cancer survival in the United States

Objective

Evaluate the association between time to diagnosis and treatment of advanced ovarian cancer with overall and ovarian cancer specific mortality

Setting/Locations

The University of Texas
MD Anderson Cancer Center
Houston, Texas, USA

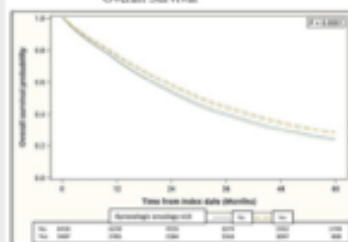
Methods/Intervention

A Surveillance, Epidemiology, and End Results-Medicare search from 1992 to 2015 for women aged ≥ 66 years with epithelial ovarian cancer and abdominal/pelvic pain, bloating, difficulty eating or urinary symptoms within 1 year of presentation to diagnosis and treatment were evaluated as outcomes and covariables

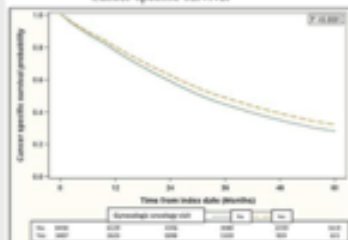
Results

- N= 13872 women
- Better survival was associated with longer time from presentation to diagnosis (overall survival hazard ratio (HR) 0.95, 95% confidence interval (CI) 0.94 to 0.95; cancer specific survival HR 0.95, 95% CI 0.94 to 0.96) and diagnosis to treatment (overall survival HR 0.94, 95% CI 0.92 to 0.96; cancer specific survival HR 0.93, 95% CI 0.91 to 0.96).
- There was no longer time from presentation to diagnosis in Hispanic women (relative risk (RR) 1.21, 95% CI 1.12 to 1.32) and from diagnosis to treatment in non-Hispanic black women (RR 1.36, 95% CI 1.21 to 1.54)
- Lower likelihood of survival at 5 years after adjustment for time to diagnosis and treatment among non-Hispanic black women (HR 1.15, 95% CI 1.05 to 1.26) compared with non-Hispanic white women.
- Gynecologic oncology visit was associated with improved overall ($p<0.001$) and cancer specific ($p<0.001$) survival despite a longer time from presentation to treatment ($p<0.001$)

Overall Survival



Cancer-specific survival



Conclusion

Longer time to diagnosis and treatment were associated with improved survival, suggesting that tumor specific features are more important prognostic factors than the time interval of workup and treatment. Significant sociodemographic disparities indicate social determinants of health influencing workup and care. Gynecologic oncologist visits were associated with improved survival, highlighting the importance of appropriate referral for suspected ovarian cancer.





Συμπεράσματα

- Νόσος με μεγάλη ετερογένεια
- Απαραίτητη η σωστή επιλογή ασθενών
- Εξαιρεσιμότητα νόσου
- Εκπαιδευμένη χειρουργική ομάδα
- Ογκολογικό κέντρο
- Αποφάσεις στα πλαίσια MDT



