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Debate: HIPEC plays a role in the treatment of advanced ovarian cancer: PRO



What we know today in AEOC

- ✓ **Prognostic role of Residual Tumor**
- ✓ **Prognostic role of Time To Chemotherapy**
- ✓ Efficacy of IP route
- ✓ Increased activity of existing drugs

Prognostic role of RT in AEOC: recommendations for primary surgery



2015

Progress and Controversies in
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National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 3.2014
Epithelial Ovarian Cancer/ Fallopian Tube Cancer/
Primary Peritoneal Cancer

PRINCIPLES OF SURGERY

***Every effort should be made to achieve
maximal cytoreduction***



NICE accredited

www.nice.org.uk/accreditation

***Standard therapy to treat AEOC consists of
PDS to achieve macroscopic complete
resection***

***When performing surgery for AEOC the
objective should be complete resection of all
macroscopic disease***

Prognostic role of RT in AEOC: what we have to do to achieve complete resection

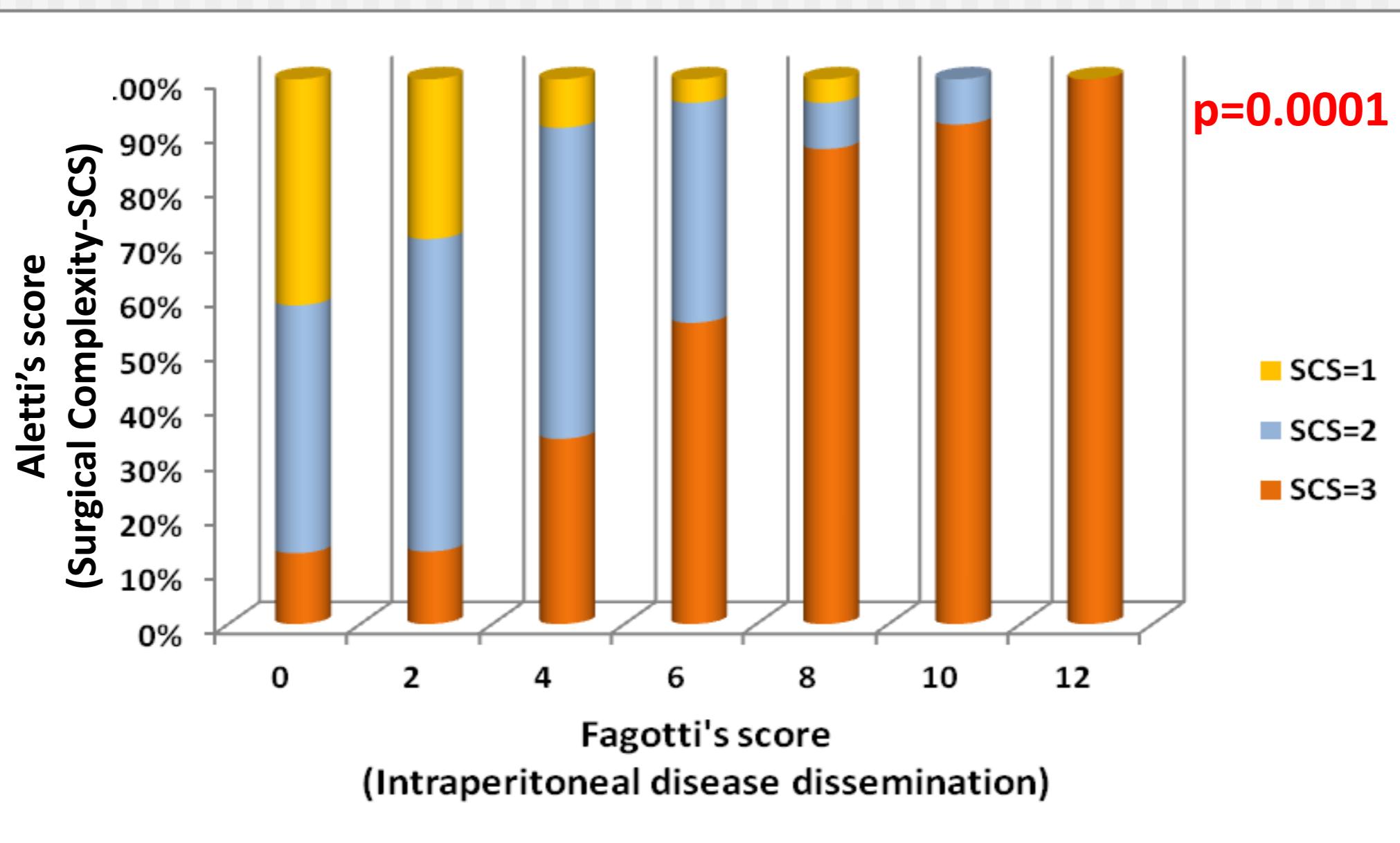
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2015

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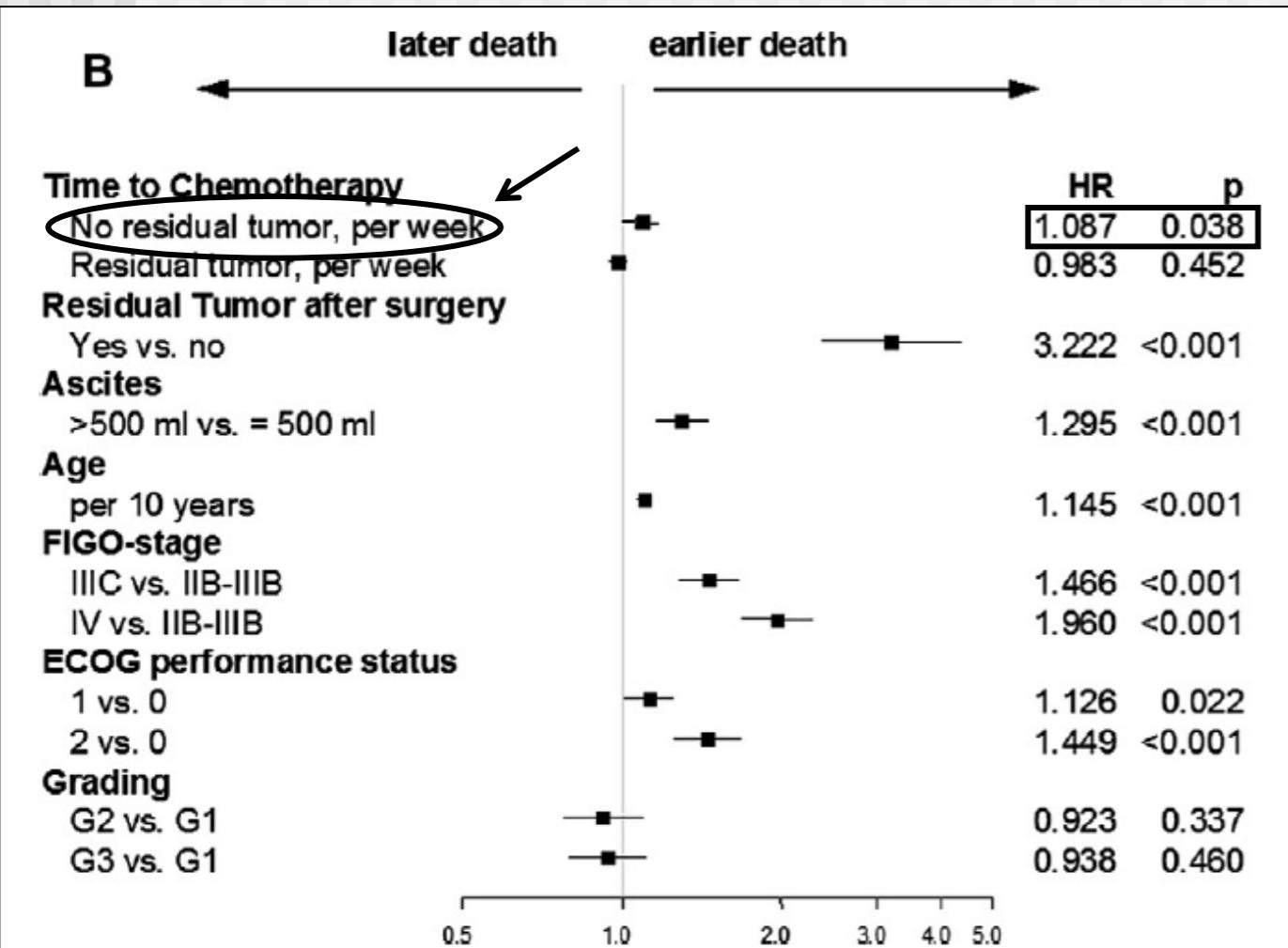


Correlation between extent of disease and complexity of surgery at PDS in 348 completely resected AEOC pts

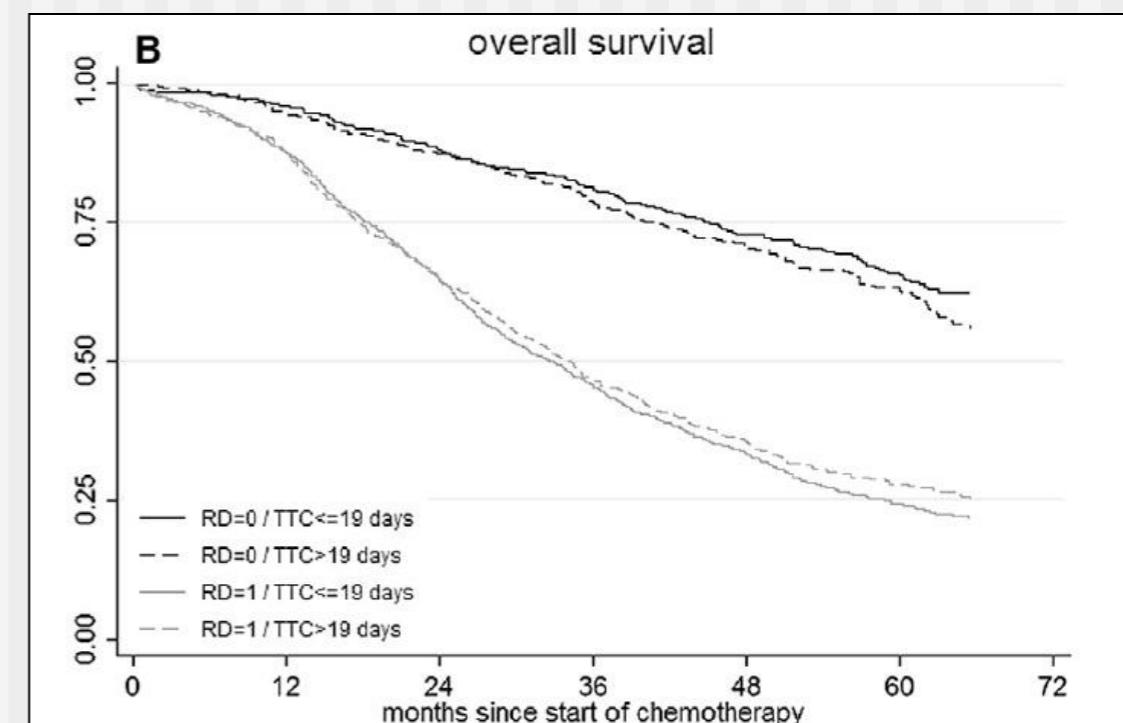


Prognostic impact of the time interval between surgery and chemotherapy in advanced ovarian cancer: Analysis of prospective randomised phase III trials

S. Mahner^{a,*1,2}, C. Eulenburg^{b,1,2}, A. Staehle^{c,1}, K. Wegscheider^{b,1}, A. Reuss^{d,1}, E. Pujade-Lauraine^{e,3}, P. Harter^{f,1}, I. Ray-Coquard^{g,3}, J. Pfisterer^{h,1}, A. du Bois^{f,1}



A delay of chemotherapy by 7 days resulted in 8.7% increase of mortality in patients with complete surgical debulking.



Correlation between extent of surgery and Time To CHT : a challenging issue.

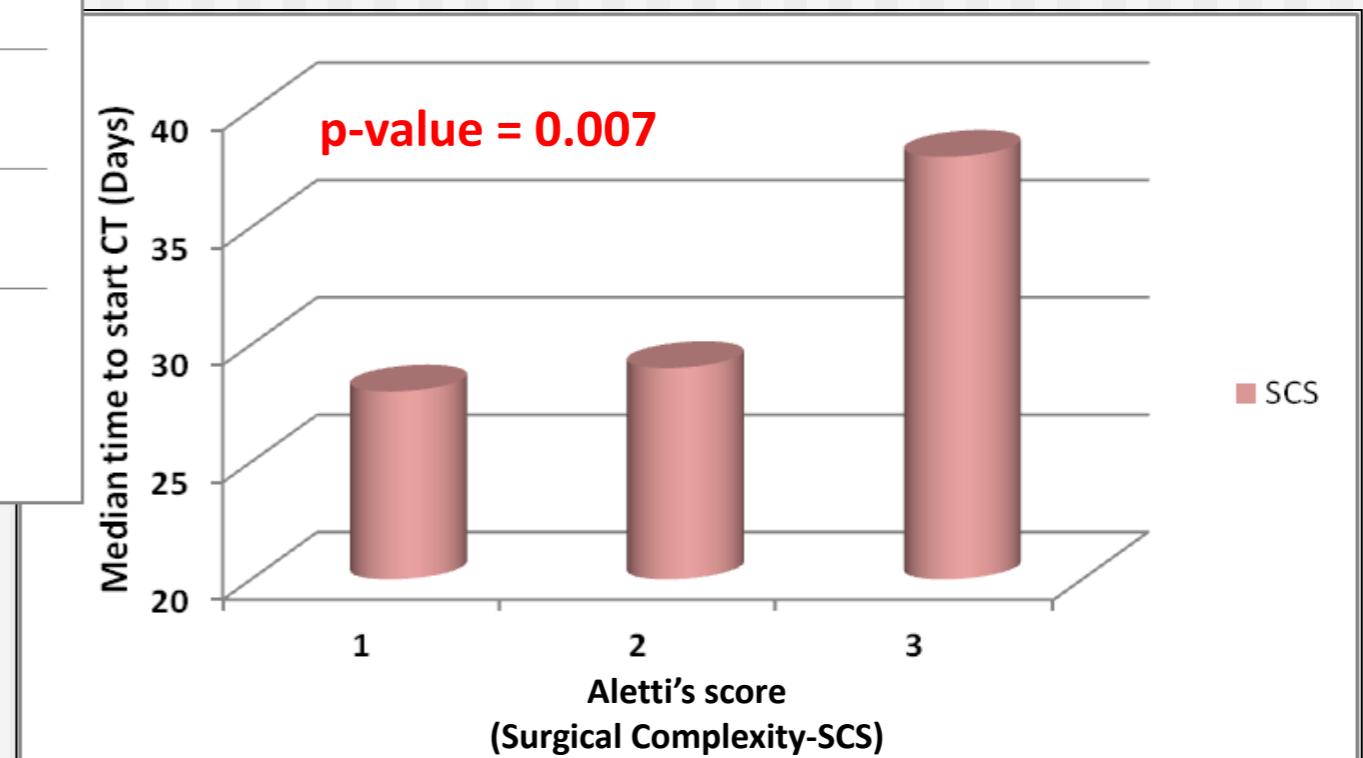
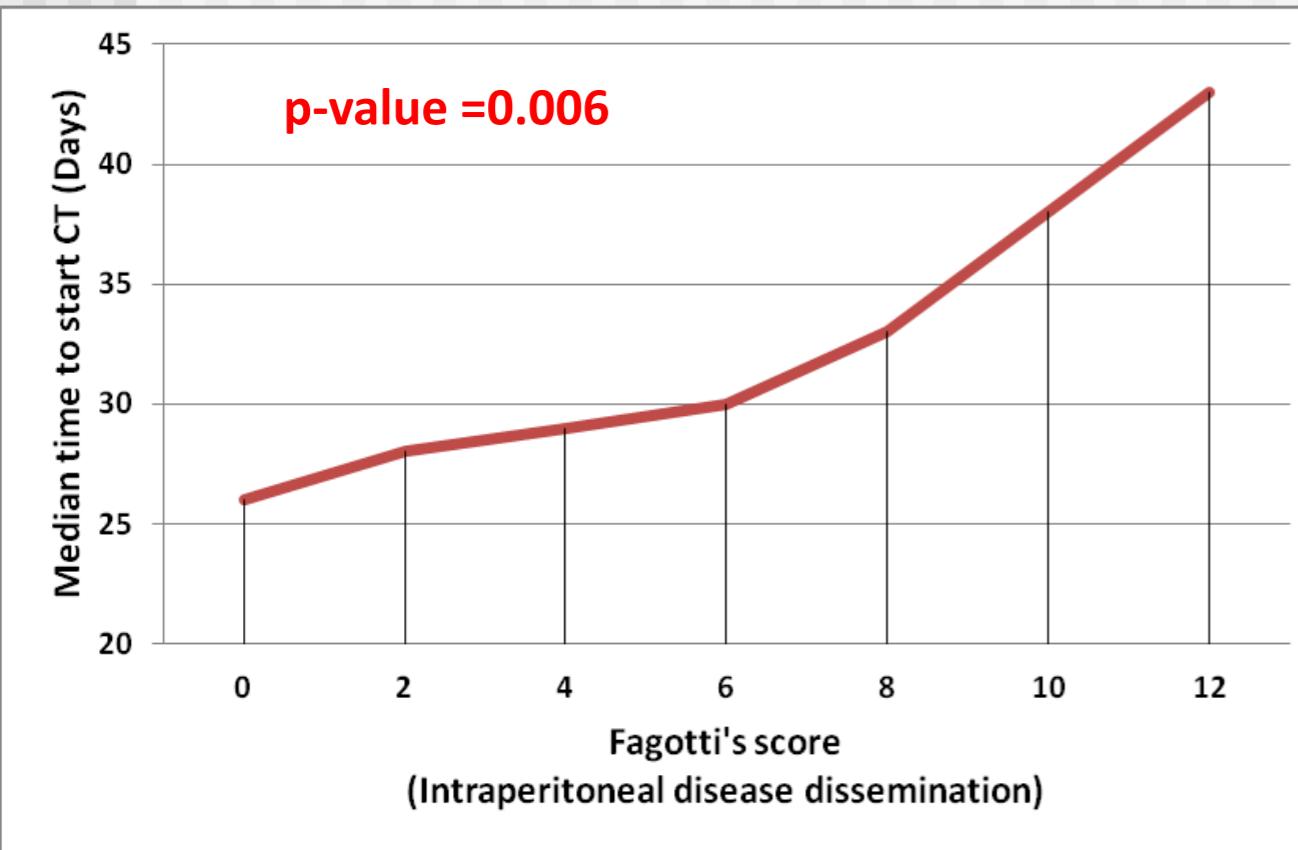
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In presence of high tumor dissemination, and increased SCS, more than one month is required prior to start chemotherapy.



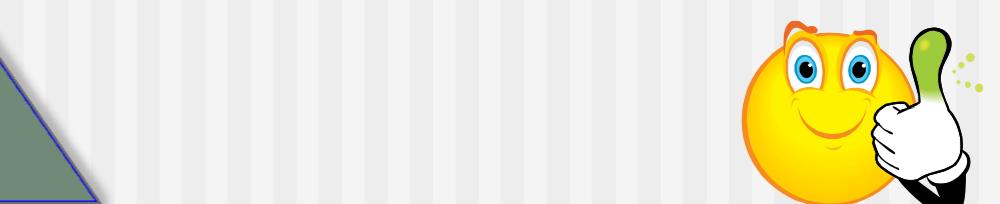
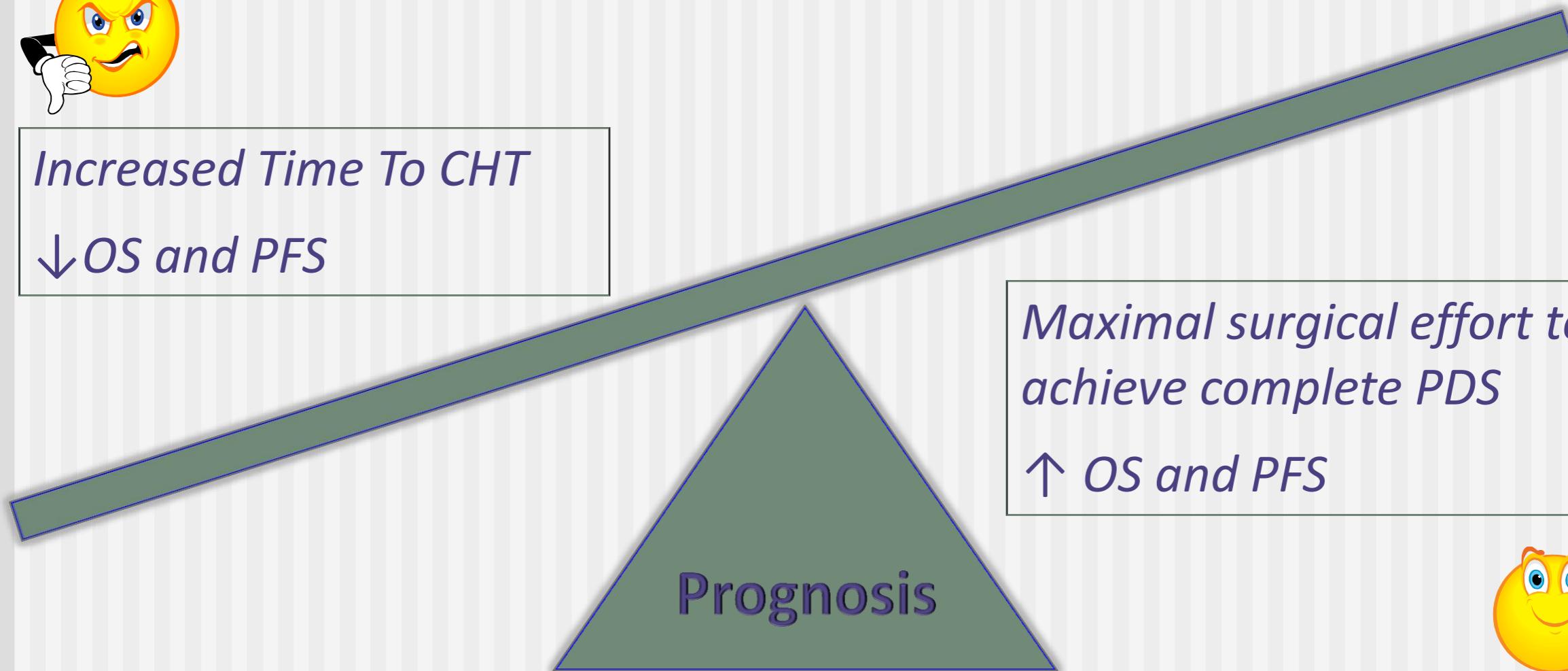
Correlation between extent of surgery and Time To CHT : How to find a balance?



Chemotherapy at the time of PDS : the way out strategy



*Increased Time To CHT
↓OS and PFS*



Debate: HIPEC plays a role in the treatment of advanced ovarian cancer: PRO



What we know today in AEOC

- ✓ Prognostic role of Residual Tumor
- ✓ Prognostic role of Time To Chemotherapy
- ✓ **Efficacy of IP route**
- ✓ Increased activity of existing drugs

IP chemotherapy in AEOC: Rationale

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➤ IV drug administration is associated with a limited submesothelial penetration (40-50µm) due to the presence of the peritoneal plasma barrier and the high interstitial pressure of tumor tissues.

➤ IP drug delivery increases peritoneal penetration up to 3-5 mm according with the molecular weight of the compound.

Alberts DS, NEJM, 1996

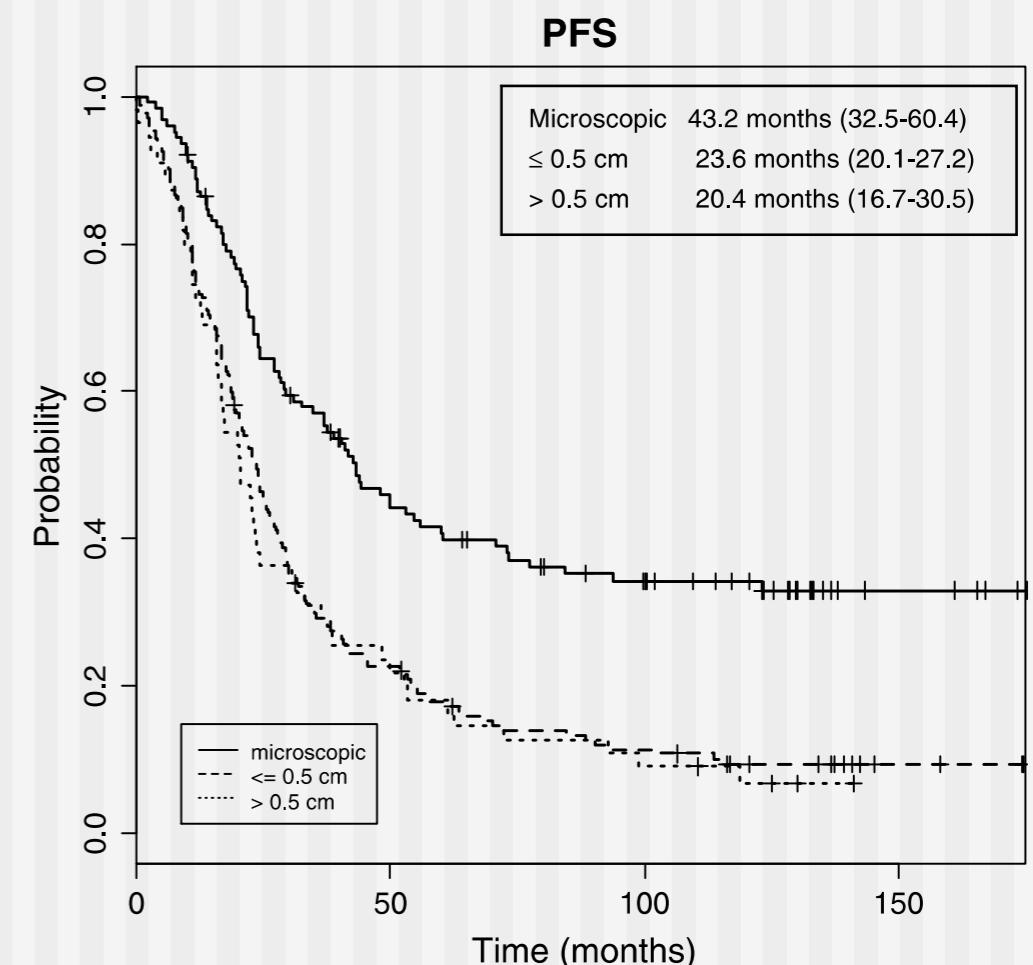
Markman M, JCO, 2001

Armstrong DK, NEJM, 2006

Prognostic factors for stage III epithelial ovarian cancer treated with intraperitoneal chemotherapy: A Gynecologic Oncology Group study*

Lisa M. Landrum ^{a,*}, James Java ^b, Cara A. Mathews ^a, Grainger S. Lanneau Jr. ^c, Larry J. Copeland ^d, Deborah K. Armstrong ^e, Joan L. Walker ^a

L.M. Landrum et al. / Gynecologic



Efficacy/Toxicity of ip-CHT : How to find a balance?

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One shot IP administration at the time of
PDS ensures the benefit of IP route
without related toxicities.



IP chemotherapy is associated
with an increased toxicity profile
compared to iv route

Gore, JCO, 2006

IP chemotherapy is effective
in treating AEOC, as reported
in several RCTs

Prognosis



Debate: HIPEC plays a role in the treatment of advanced ovarian cancer: PRO



What we know today in AEOC

- ✓ Prognostic role of Residual Tumor
- ✓ Prognostic role of Time To Chemotherapy
- ✓ Efficacy of IP route
- ✓ Increased activity of existing drugs

Increase the efficacy of platinum compounds: the role of hyperthermia

➤ **Hyperthermia** has proved to enhance cytotoxicity of anticancer drugs including alkylating agents, platinum compounds, and doxorubicin.

Issels RD, EJC 2008

➤ **Hyperthermia** increases tumor blood supply and oxygenation of exposed tissues, thus resulting in increased tissue penetration and sensitivity to chemotherapy and radiation therapy.

Sun XR, Radiother Oncol 2008

➤ **Hyperthermia** increases the cytotoxicity of Cisplatin in a linear manner

Critical Reviews in Oncology/Hematology 43 (2002) 33–56

The cellular and molecular basis of hyperthermia

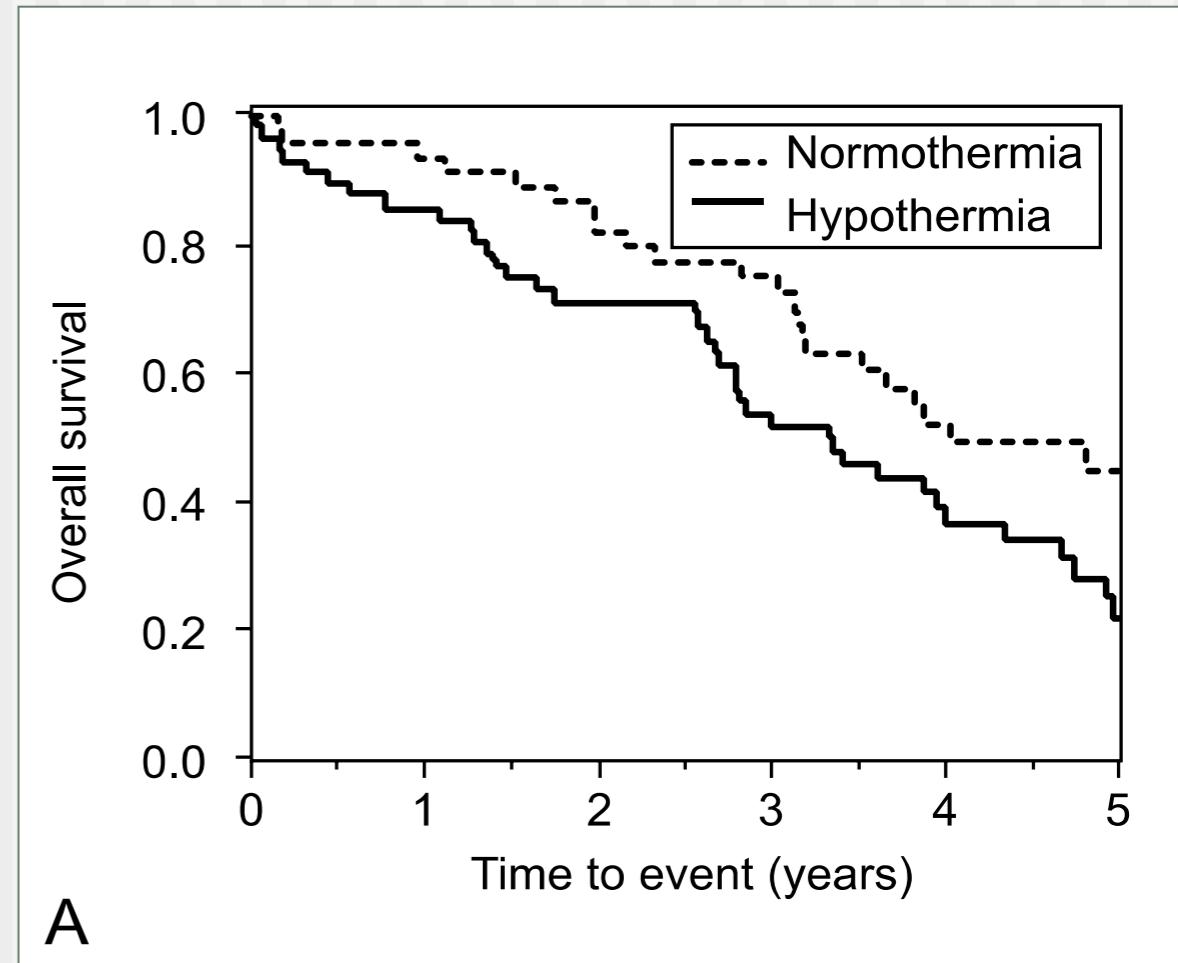
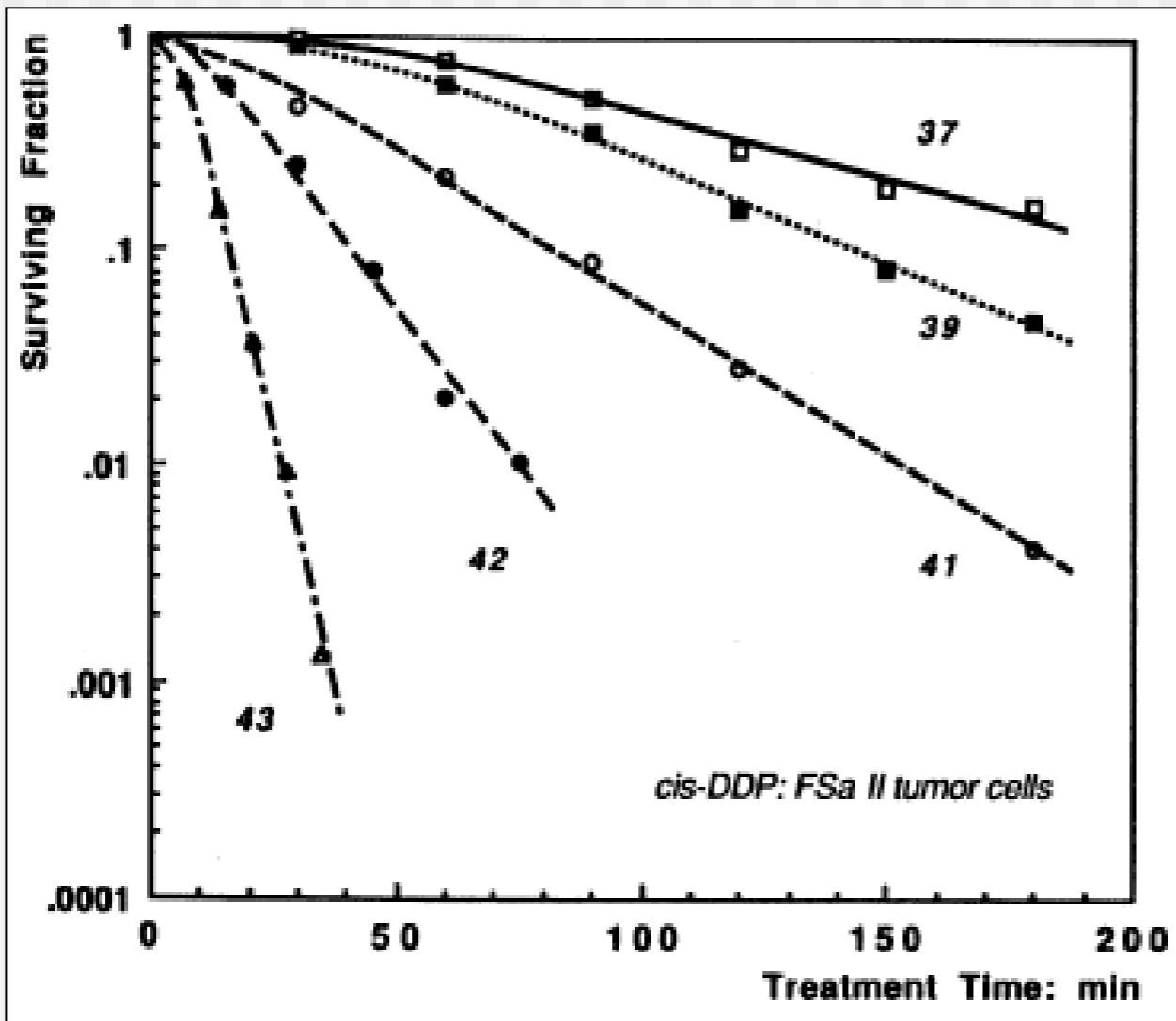
Bert Hildebrandt ^{a,*}, Peter Wust ^b, Olaf Ahlers ^c, Annette Dieing ^a, Geetha Sreenivasa ^b,
Thoralf Kerner ^c, Roland Felix ^b, Hanno Riess ^a



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Intraoperative Hypothermia During Cytoreductive Surgery for Ovarian Cancer and Perioperative Morbidity

Mehdi Moslemi-Kebria, MD, Sherif A. El-Nashar, MBBCh, MS, Giovanni D. Aletti, MD,
and William A. Cliby, MD

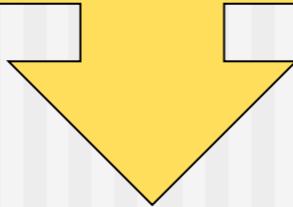


Debate: HIPEC plays a role in the treatment of advanced ovarian cancer

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**HIPEC is an attracting multimodal strategy
able to offer several potential
concomitant benefits**



Complete Debulking
Minimize TTC
Safe use of IP route
Exploit the benefit of hyperthermia

Debate: HIPEC plays a role in the treatment of advanced ovarian cancer

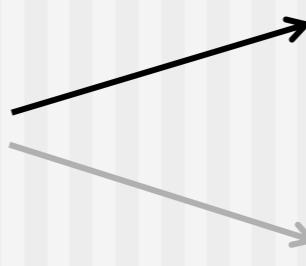


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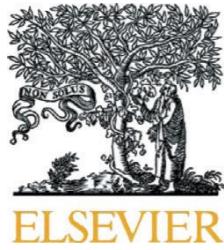
The future challenges in the use of HIPEC

Low level of evidence



Focus on Safety

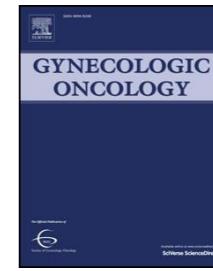
Focus on Efficacy



Contents lists available at ScienceDirect

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



Review

A critical appraisal of hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of advanced and recurrent ovarian cancer

Luis M. Chiva ^{*}, Antonio Gonzalez-Martin

MD Anderson Cancer Center Madrid, Spain

Table 1
Main surgical variables at the time of HIPEC.

	Primary n = 248	Recurrent n = 499
% CC-0	66% (40–90)	71% (50–95)
% CC-1	22% (7–42)	22% (7–42)
Peritoneal cancer index	14.5	9.8
Operative time (min)	458 min	421 min
* Severe morbidity (3–4)	19%	25%
** Mortality (%)	0–7%	0–7%
Average stay (days)	15	15
Follow-up (months)	32	30

* vs. 10–12 %

** vs. 3.4%

Kommooss Rochon J, Harter P, Heitz F, Grabowski JP, Ewald-Riegler N, Haberstroh M, et al. Prognostic impact of additional extended surgical procedures in advanced-stage primary ovarian cancer. Ann Surg Oncol Jan 2010;17(1):279–86.

HIPEC in recurrent ovarian cancer patients: Morbidity-related treatment and long-term analysis of clinical outcome

Gynecologic Oncology 122 (2011) 221-225

Anna Fagotti ^{a,*}, Barbara Costantini ^a, Giuseppe Vizzielli ^a, Federica Perelli ^a, Alfredo Ercoli ^b, Valerio Gallotta ^a, Giovanni Scambia ^a, Francesco Fanfani ^a

Parameter	N° (%)	Post-operative parameters
Number of patients transfused		
Blood	19 (43.9)	
Plasma	6 (9.8)	
30-day mortality	0	
Post-operative major morbidity	15 (34.8)	
Haemorrhage	7 (16.3)	
Pleural effusion requiring drainage	2 (4.6)	
Fistula	1 (2.3)	
Pneumonia	0	
Heart arrhythmia	0	
Small bowel obstruction	0	
Heart failure	0	
Tissue necrosis	0	
Central vein thrombosis	1 (2.3)	
Femoral neuropathy	0	
Pulmonary embolus	0	
Septicemia	1 (2.3)	
Line sepsis	0	
Abdominal abscess	3 (7)	
Wound seroma	0	
Urinary infection	0	
Re-operation rate	6 (14.0)	
Open	3 (7.0)	
Endoscopic	3 (7.0)	

Complications

2005/2006 (5/11), 45.5%

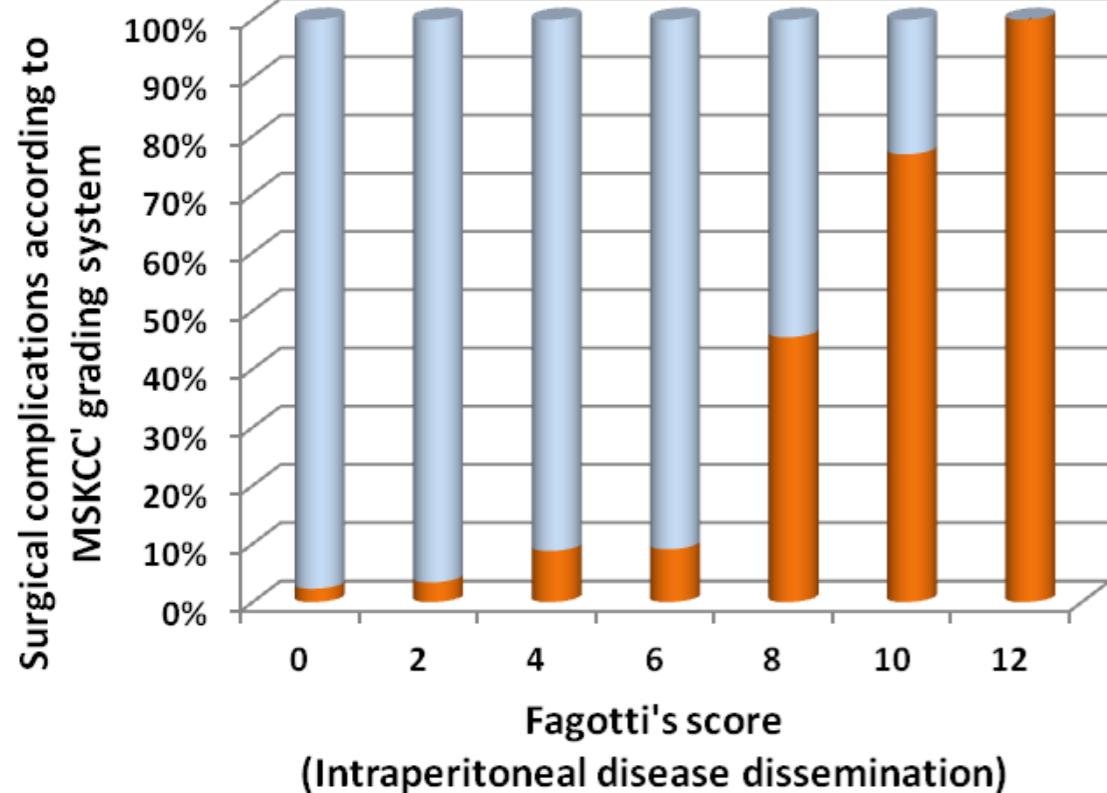
2007/2008 (2/14) 14.0%

p=0.024

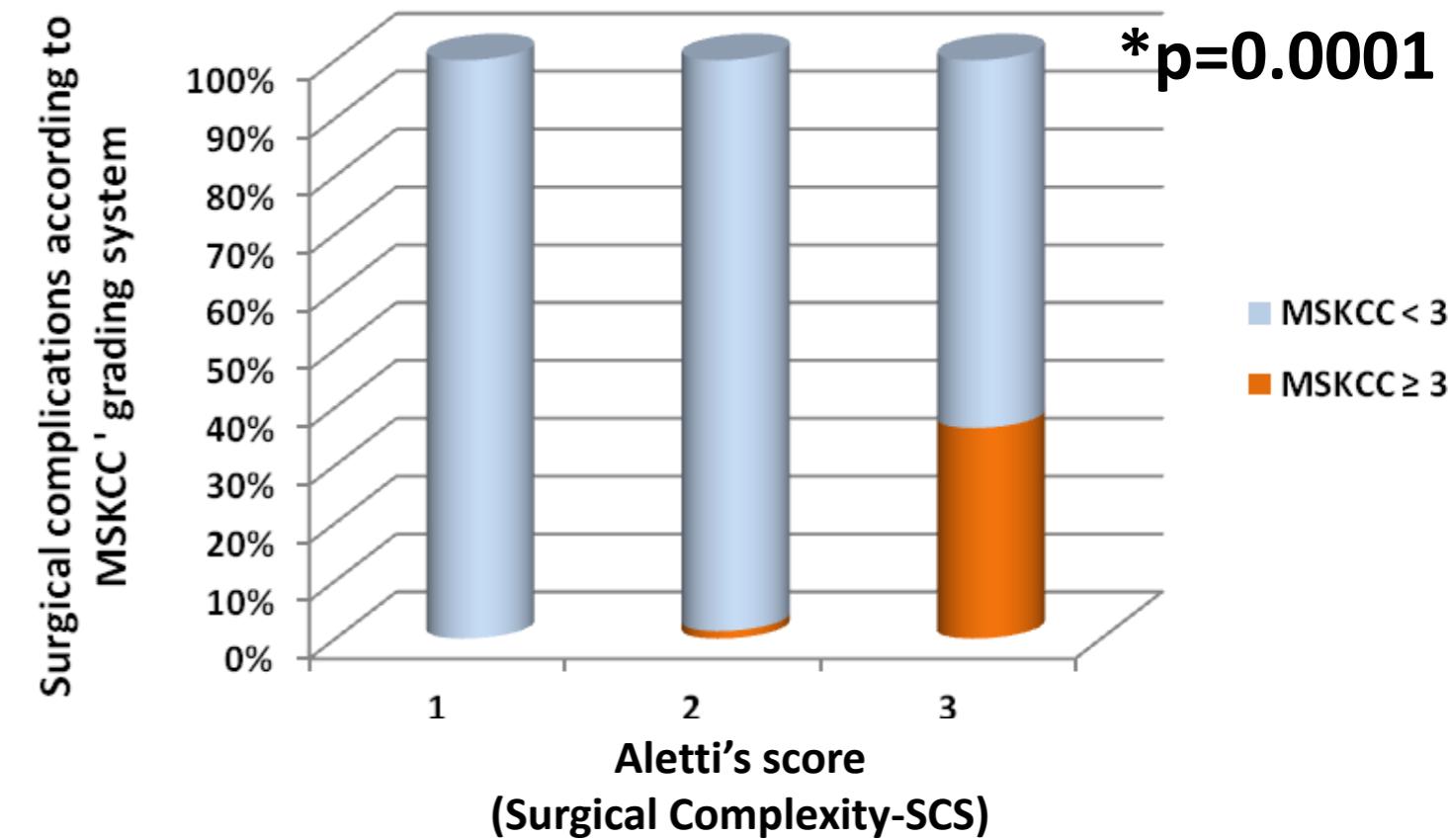
Rate of MSKCC post-op complication in a series of 348 AEOC submitted to PDS.



*In presence of high tumor dissemination, and increased SCS,
more than one month is required prior to start chemotherapy.*



* $p=0.0001$



* $p=0.0001$

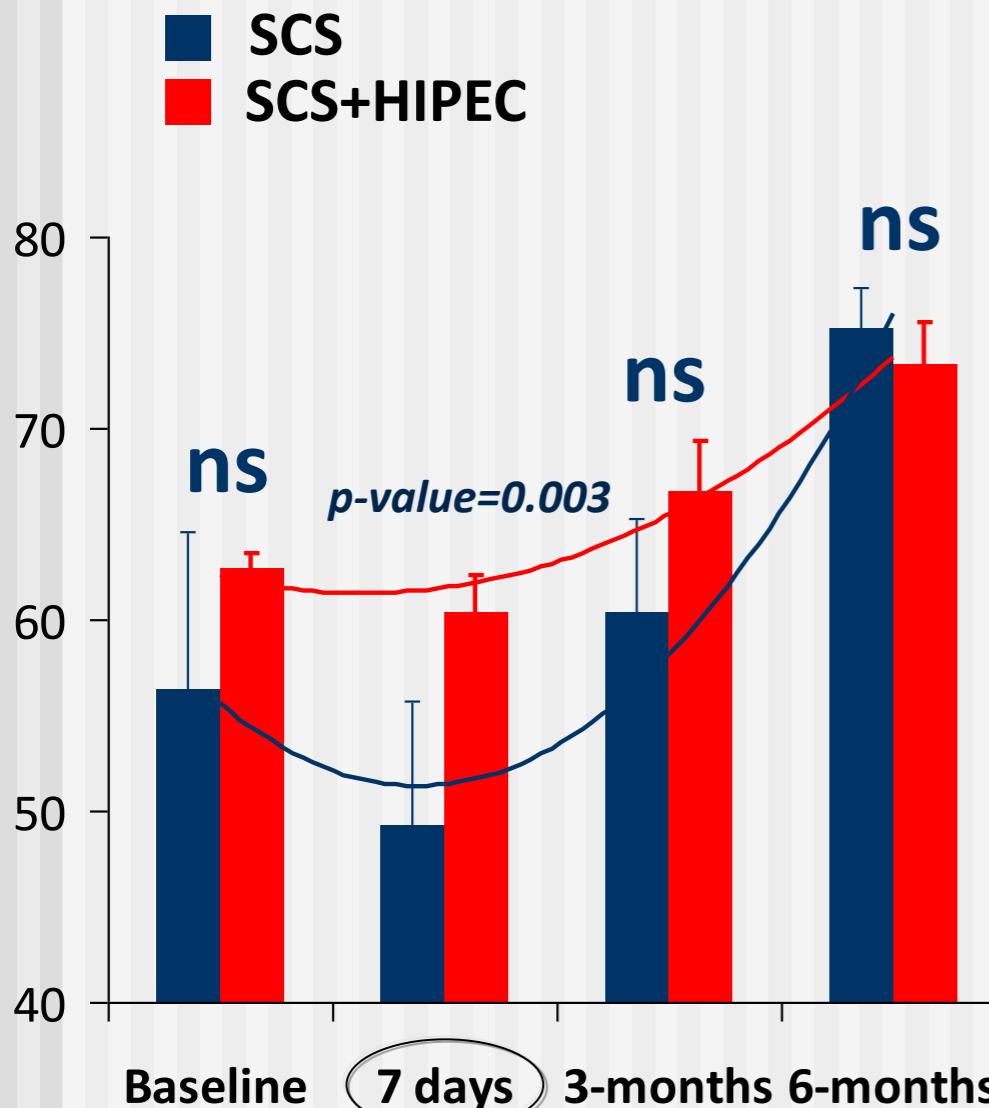
HORSE/MITO-18 (NCT01537895) Hyperthermic Intra-peritoneal Chemotherapy (HIPEC) in Ovarian Cancer Recurrence: preliminary analysis on morbidity.

Variables	Arm A (HIPEC)	Arm B (No HIPEC)	p value
Total Patients' Number	24	24	-
Median Age (years) (range)	56 (35 - 72)	54 (45 - 67)	0.409
BMI (range)	25 (21 - 33)	26 (21 - 39)	0.335
ECOG Performance Status			
≤ 2	24 (100)	24 (100)	n.a.
> 2	0 (0)	0 (0)	
Peritoneal cancer index (PCI)*			
PCI ≤ 10	19 (79.2)	17 (70.8)	0.505
PCI > 10	5 (20.8)	7 (29.2)	
Completeness of cytoreduction (CC)			
CC-0	20 (83.3)	23 (95.8)	0.149
CC-1	4 (16.7)	1 (4.2)	
Surgical Complexity Score			
1	18 (75.0)	16 (66.7)	0.147
2	4 (16.7)	7 (29.2)	
3	2 (8.3)	1 (4.2)	
Post-operative complications			
1	3 (12.5)	1 (4.2)	0.150
2	3 (12.5)	3 (12.5)	
3	4 (16.7)	1 (4.2)	
4	0 (0)	0 (0)	
5	0 (0)	0 (0)	

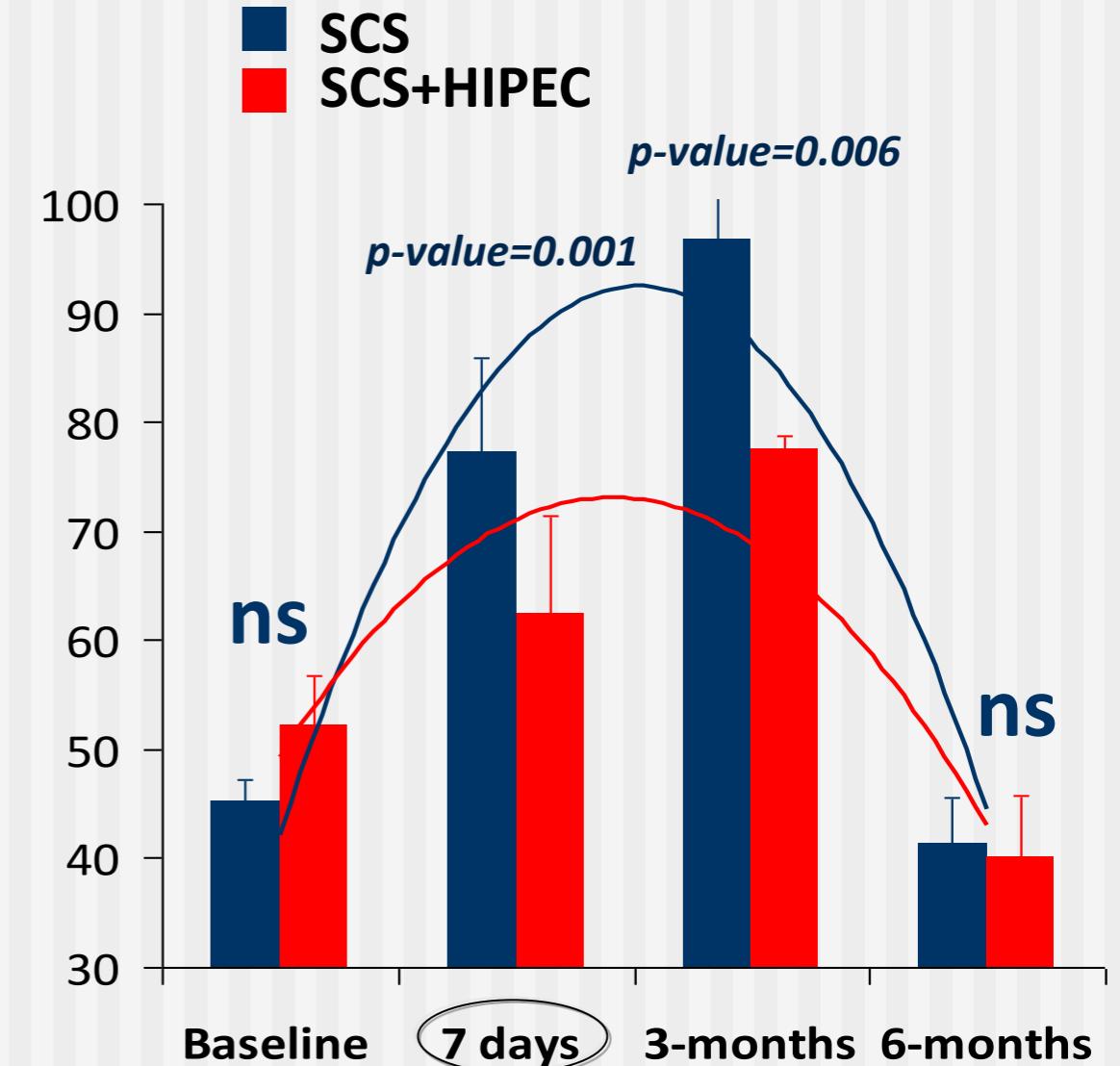
Comparison of QoL measures after SCS + HIPEC: PRELIMINARY ANALYSIS FROM HORSE TRIAL

EORTC QLQ-C30 and EORTC OV28

Functioning: GHS



Symptoms: Attitude to disease



Debate: HIPEC plays a role in the treatment of advanced ovarian cancer

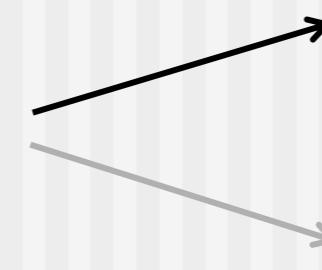


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The future challenges in the use of HIPEC

Low level of evidence



Focus on Safety

Focus on Efficacy

Debate: HIPEC plays a role in the treatment of advanced ovarian cancer

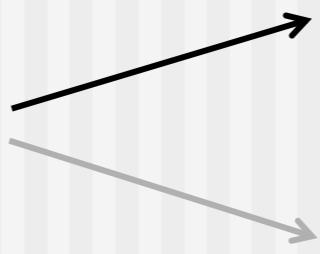


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The future challenges in the use of HIPEC

Low level of evidence



No evidence of
HIPEC-related
additional toxicities

Focus on Efficacy

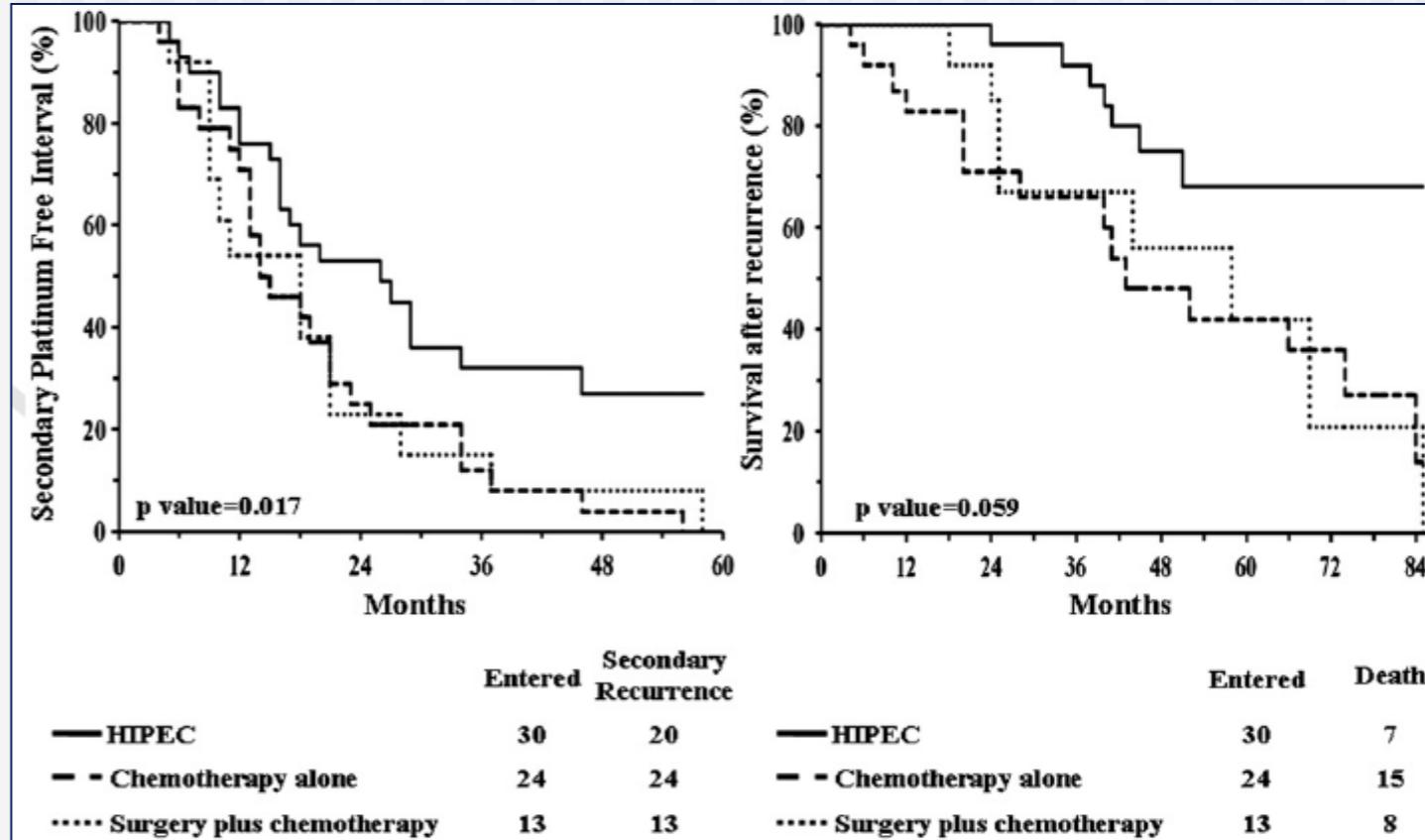
Case-control studies on HIPEC in recurrent ovarian cancer

Author (year)	CDDP sens.	Nr. cases	Nr. controls	% CC-0 + CC-1	Ip Drug	Morb.	OS
Munoz (2009)	?	14	12	100	TAX	29 % vs. 25%	57% vs. 17% (5yr)
Spiliotis (2011)	?	24	24 (CRS)	83	CDDP + DOXO	40 % (na)	50% vs. 18% (3yr)
Fagotti (2012)	YES	30	37 (CRS/CHT)	100	OXA	35 % (na)	68% vs. 43% (5yr)
Le Brun (2013)	YES	23 (NACT)	19 (NACT)	100	CDDP/ OXA/ MMC	na	76% vs. 19% (4yr)

Cytoreductive surgery plus HIPEC in platinum-sensitive recurrent ovarian cancer patients: A case-control study on survival in patients with two year follow-up

Anna Fagotti ^{a,*}, Barbara Costantini ^a, Marco Petrillo ^a, Giuseppe Vizzielli ^a, Francesco Fanfani ^a, Pasquale Alessandro Margariti ^a, Luigi Carlo Turco ^a, Elisa Piovano ^{a,b}, Giovanni Scambia ^a

Parameters	Cases	Controls	P value
	Nr (%)	Nr (%)	
All patients	30	37	
Median age (range) (years)	51 (41-63)	55 (32-69)	0.128 ^a
ECOG PS (range) [10]	0 (0-1)	0 (0-1)	0.345
FIGO stage at diagnosis			
I-II	4 (13.3)	5 (13.5)	0.213 ^b
III-IV	26 (86.7)	32 (86.5)	
Residual tumor 1st surgery			
RT = 0	18 (60)	21 (56.8)	0.450 ^b
0 < RT ≤ 1	9 (36.7)	14 (37.8)	
RT > 1	1 (3.3)	2 (5.4)	
Pathway of tumorogenesis (sec. Kurman) [15]			
Type I	12 (40.0)	18 (48.6)	0.622 ^b
Type II	18 (60.0)	19 (51.4)	
Median PFI-1 (range) (months)	20 (7-67)	22 (8-126)	0.571
Median CA-125 serum levels (range) at recurrence (U/ml)	73 (8-434)	139 (11-400)	0.539
Type of i.p. recurrence [9]			
Single	6 (20)	19 (51.4)	0.011 ^b
Multiple	24 (80)	18 (48.6)	





Cytoreductive surgery plus HIPEC in platinum-sensitive recurrent ovarian cancer patients: A case-control study on survival in patients with two year follow-up

Anna Fagotti ^{a,*}, Barbara Costantini ^a, Marco Petrillo ^a, Giuseppe Vizzielli ^a, Francesco Fanfani ^a, Pasquale Alessandro Margariti ^a, Luigi Carlo Turco ^a, Elisa Piovano ^{a,b}, Giovanni Scambia ^a

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Multiple	24 (80)	18 (48.6)	

Significantly longer PFI-2 than PFI-1

Parameters	Cases		P
	Nr. (%)	Nr. (%)	
Secondary recurrence	20 (66.6)	37 (100)	0.001 ^a
Median PFI-2 (range) (months)	26 (5-73)	15 (4-58)	0.004
PFI-2>PFI-1			
No	14 (46.6)	25 (67.6)	0.070 ^a
Yes	16 (53.4)	12 (32.4)	
Deaths	7 (23.3)	23 (62.2)	0.003 ^a
2-year OS	96.7	75.7	
5-year OS	68.4	42.7	

Updated results on 40 pts with a median FU = 51.5 months (12-102):
Median PFI-2= 37 mths vs PFI-1= 22 mths (p=0.001)

Cytoreductive Surgery and HIPEC in Recurrent Epithelial Ovarian Cancer: A Prospective Randomized Phase III Study

2014

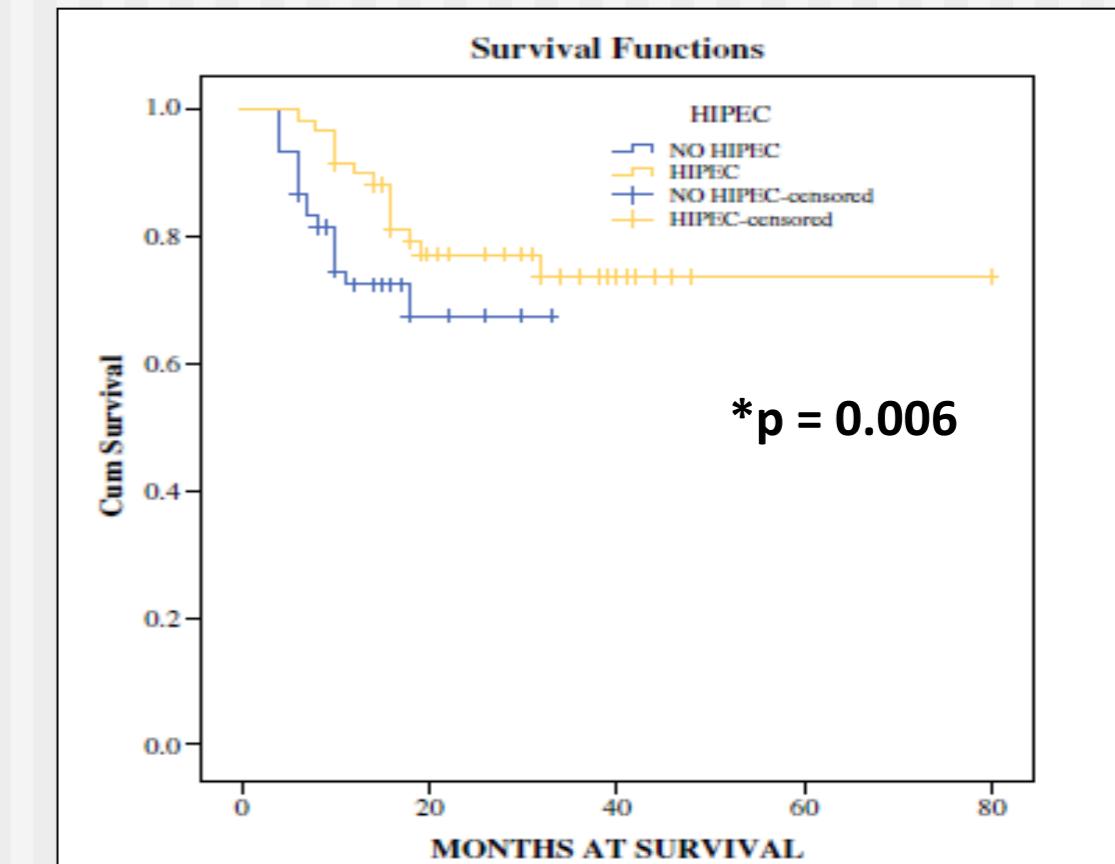
J. Spiliotis, MD, PhD¹, E. Halkia, MD, PhD^{1,2}, E. Lianos, MD³, N. Kalantzi, MD⁴, A. Grivas, MD³, E. Efstathiou, MD¹, and S. Giassas, MD²

¹First Department of Surgical Oncology, Metaxa Cancer Hospital, Piraeus, Greece; ²Peritoneal Surface Malignancy Unit, IASO General Hospital, Athens, Greece; ³Department of Medical Oncology, Metaxa Cancer Hospital, Piraeus, Greece;

⁴Department of Anesthesiology, Metaxa Cancer Hospital, Piraeus, Greece

60 pts 60 pts

Characteristic	HIPEC		Non-HIPEC	
	n	%	n	%
Stage				
III _c	41	68.3	35	58.3
IV	19	31.7	25	41.7
Platinum responsiveness				
Sensitive	38	63.3	36	60
Resistant	22	36.7	24	40
Ascites				
Yes	18	30	16	26.7
No	42	70	44	73.3
Optimal cytoreduction at primary surgery	51	85	46	76.6
PCI				
PCI < 5	7	11.7	8	13.3
5 ≤ PCI < 10	24	40	22	36.7
PCI ≥ 10	29	48.3	30	50
CC				
CC-0	39	65	33	55
CC-1	12	20	20	33.3
CC-2	9	15	7	11.7



Ongoing RCT comparing HIPEC Vs no-HIPEC in AEOC

Protocol (NCT)	Clinical Setting	Phase (pts to be enrolled)	IP Regimen	Study End date
Korea Cancer Institute (1539785)	Optimally debulked (RT≤1cm) newly diagnosed EOC	II/III (170)	CDDP 75 mg/msq	2013→2017
Mercy-USA (2124421)	Optimally debulked (RT≤1cm) newly diagnosed EOC	II (40)	CBDA 6AUC	2020
CHORINE-Italy (1628380)	Stage IIIC unresectable EOC after NACT	III (94)	CDDP 100mg/msq+ PTX 175mg/msq	2014→2016
OVHIPEC- Netherlands (426257)	Stage IIIC-IV unresectable or suboptimally debulked (RT>1cm) EOC after NACT	III (280)	CDDP 100mg/msq	2013→2015
HORSE-Italy (1539785)	Upfront Platinum Sensitive Recurrent EOC	III (158)	CDDP 75 mg/msq	2015→2018
MSKCC-USA (1767675)	Upfront Platinum Sensitive Recurrent EOC	II (98)	CBDA 1000mg/msq	2018
CHIPOR-France (1376752)	Platinum Sensitive Recurrent EOC after NACT	III (444)	CDDP 100mg/msq	2018

Debate: HIPEC plays a role in the treatment of advanced ovarian cancer

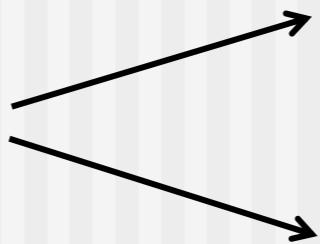


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The future challenges in the use of HIPEC

Low level of evidence



No evidence of
HIPEC-related
additional toxicities

Preliminary
encouraging data

Can we safely combine HIPEC with new drugs ?

Integration of HIPEC with novel target-based systemic treatments

Protocol (NCT)	Clinical Setting	Phase (pts to be enrolled)	IP Regimen	Study End date
CHIPASTIN- France (2217956)	Stage IIIC unresectable EOC after NACT with BEVACIZUMAB	I (30)	CDDP dose escalation	2015
GO HYPEC- Italy	Stage IIIC (PIV<8) completely resected Followed by JM8/Taxol/BEVACIZ UMAB	II (40)	CDDP	2016

Debate: HIPEC plays a role in the treatment of advanced ovarian cancer



The future challenges in the use of HIPEC

Low level of evidence

- Focus on Safety
- Focus on Efficacy

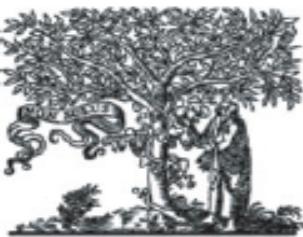
Can we safely combine HIPEC with new drugs ?

No evidence of
HIPEC-related
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Preliminary
encouraging data

PHASE I/II STUDIES
ONGOING

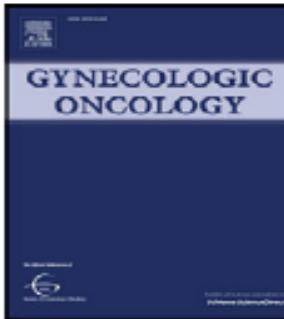
HIPEC and MIS



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

Minimally invasive secondary cytoreduction plus HIPEC for recurrent ovarian cancer: A case series

A. Fagotti ^{a,*}, M. Petrillo ^b, B. Costantini ^b, F. Fanfani ^c, V. Gallotta ^b, V. Chiantera ^d, L.C. Turco ^b, C. Bottoni ^b, G. Scambia ^b

Gynecologic Oncology 132 (2014) 3



Patient	Age (years)	BMI (median)	Site of disease/nodule size	Surgical procedures	Approach	Median OT (min)/EBL (cm ³) ^a	Length of hospital stay (days)	PFI-2 (months)
1	65	26	Gastrocolic ligament/5 cm	Radical omentectomy	Laparoscopy	100/100	4	37
2	61	22	Left paracolic gutter/3 cm	Adhesiolysis/selective peritonectomy	Laparoscopy	120/50	3	13
3	68	27	Spleen/4 cm	Splenectomy	Laparoscopy	140/50	7	11
4	50	21	Douglas peritoneum/3 cm	Adhesiolysis/pelvic peritonectomy	Laparoscopy	125/100	4	11
5	55	22	Gastrosplenic ligament/3.5 cm	Adhesiolysis/radical omentectomy	Robot	115/50	4	10
6	53	25	Gastrocolic ligament/3 cm	Radical omentectomy	Robot	95/50	3	10
7	59	22	Right paracolic gutter/2 cm	Adhesiolysis/selective peritonectomy	Laparoscopy	130/50	4	9
8	63	24	Gastrosplenic ligament/4 cm	Radical omentectomy	Robot	125/100	3	9
9	48	21	Douglas peritoneum/2.5 cm	Adhesiolysis/selective peritonectomy	Laparoscopy	115/50	5	8
10	45	23	Spleen/3 cm	Splenectomy	Laparoscopy	140/50	6	6

Minimally invasive secondary cytoreduction plus HIPEC is safe without increased toxicities and acceptable operative time in localized relapse.

Pharmacokinetics of Cisplatin during SCS + HIPEC: an Experimental Study comparing LPT vs. MIS

Published evidences demonstrated improved PK profile in pig models treated with MIS versus LPT approach; no data on OC patients.

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T0

T20

T40

T60

T120

- ✓ Blood
- ✓ Urine
- ✓ Fluid Drain
- ✓ Tissue Biopsy



Pre

HIPEC

Post

Conclusions

1. A solid rational supports the use of HIPEC in AEOC with several potential benefits (CRS, TTC, IP, hyperthermia...).
2. Data from Case-Control studies and preliminary analysis from RCTs show a significant survival benefit without additional morbidity.
3. HIPEC remains **an experimental strategy**, and its use is recommended within well-designed, prospective and controlled clinical trials. *Harter P, Mahner S, et al. Statement by the Kommission OVÄR of the AGO Study Group on the Use of HIPEC to Treat Primary and Recurrent Ovarian Cancer. Geburtshilfe Frauenheilkd Mar 2013;73(3):221–3.*



Waiting...

for the perfect trial



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