HIPEC after cytoreduction of peritoneal carcinomatosis in primary and recurrent ovarian cancer. Favorable clinical scenarios

Marcello Deraco M.D.

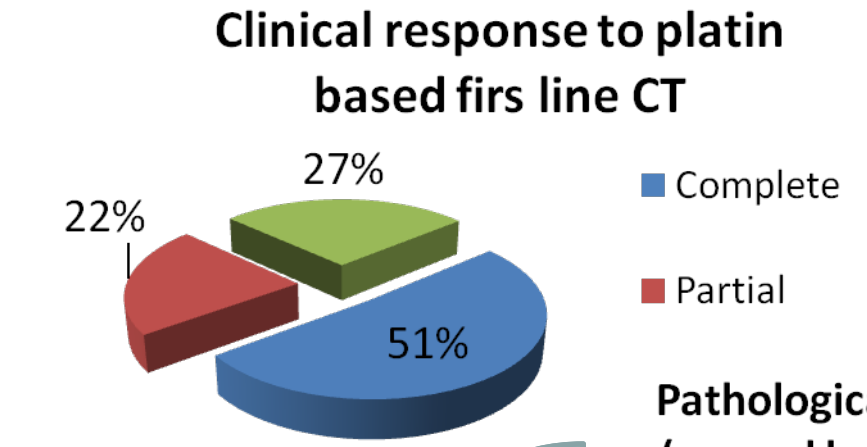
Responsible

Peritoneal Surface Malignancies

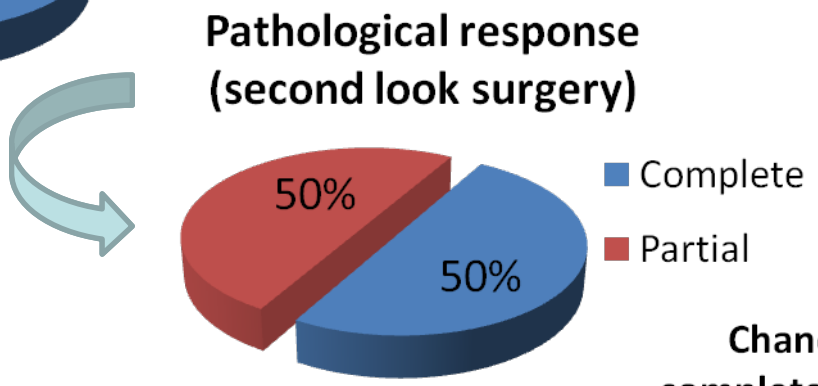
Epithelial ovarian cancer: Epidemiology

1. Epithelial ovarian cancer (EOC) affects more than 200,000 women per year worldwide
2. It causes around 125,000 deaths per year worldwide
3. Most often the disease has spread at presentation
   - 50.2% FIGO stage III
   - 13% in FIGO stage IV
4. 5-year overall survival (OS) remains at less than 50%

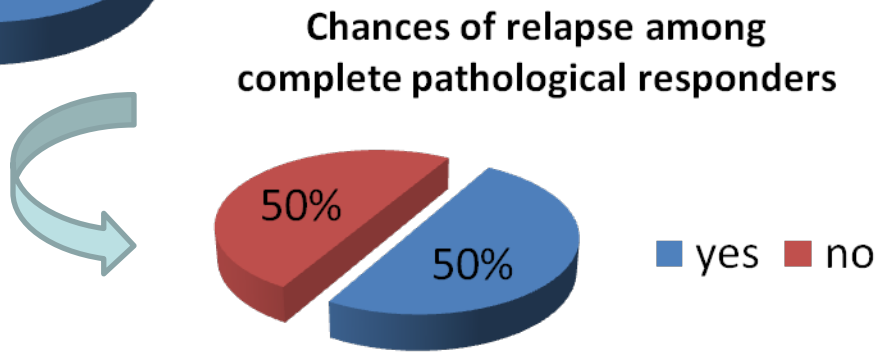
Epithelial ovarian cancer: Natural History



- High response to sCT
- 20-30% Platinum-resistant
- 60-70% Recur



Primary OC Treatment



OC Recurrence Treatment

Cannistra, NEJM, 1993
Macguire, NEJM, 1996Goff 2000; Smith 2005

Epithelial ovarian cancer: Key Points

1. Discussion about the sequence: NACT vs PDS (CRS)

2. The amount of residual disease at the end of cytoreductive surgery is a major prognostic factor in EOC

3. Initial response to platinum chemotherapy defines treatment and prognosis at the time of recurrence

4. Front-line chemotherapy should include a combination of a platinum analogue and a taxane

5. The case for addition of bevacizumab to front-line therapy has not been proven

6. Discussion about the possible role of HIPEC in the treatment of ovarian cancer must involve an understanding of current standard treatments

Epithelial ovarian cancer: Key Points

1. **Discussion about the sequence: NACT vs PDS (CRS)**

2. The amount of residual disease at the end of cytoreductive surgery is a major prognostic factor in EOC

Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer (Review)

Morrison J, Haldar K, Kehoe S, Lawrie TA

Analysis 1.1. Comparison 1 NACT vs PDS, Outcome 1 Overall survival.

Review: Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer

Comparison: 1 NACT vs PDS

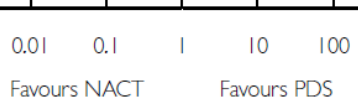
Outcome: 1 Overall survival

Study or subgroup	NACT N	PDS N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Hazard Ratio IV,Random,95% CI
EORTC 55971 (1)	334	336	-0.0202 (0.0937)		0.98 [0.82, 1.18]
Subtotal (95% CI)					**0.0 [0.0, 0.0]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable



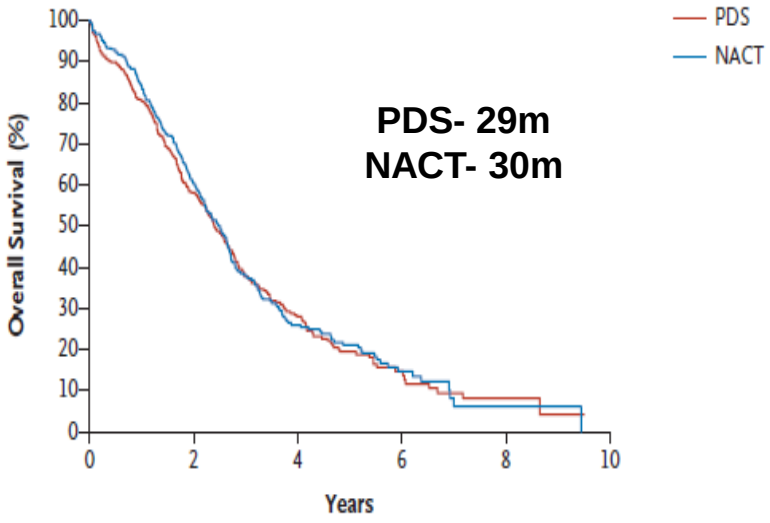
The NEW ENGLAND JOURNAL of MEDICINE

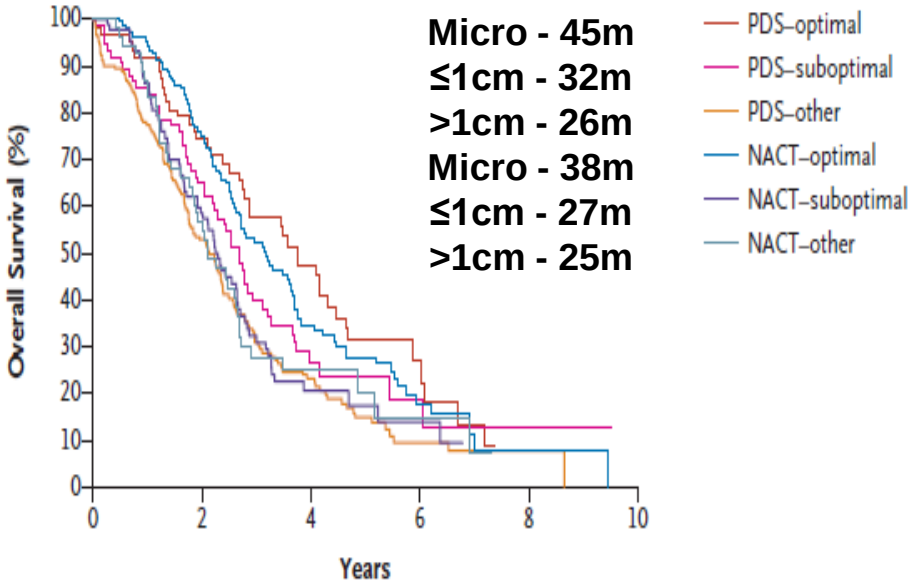
ORIGINAL ARTICLE

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

670 patients
59 institutions





NACT Hazard Ratio = 0.98 (90%CI = 0.84-1.13)

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Overall survival

Treatment arm and largest residual tumor	Patients (N)	Observed Events (O)	Hazard Ratio (90% CI)	P-Value (Wald Test)	Median (90% CI) (Months)	% at 5 Year(s) (90% CI)
PDS - No residual	62	42	1.00	0.0002 (df=5)	44.98 (34.3 45)	31.31 (20.77, 42.40)
PDS- 1 – 10 mm	74	52	1.37 (0.97, 1.93)	0.1309 (df=1)	32.26 (26.91, 37.39)	23.47 (14.63, 33.54)
PDS - > 10 mm	169	136	1.87 (1.39, 2.50)	0.0004 (df=1)	25.66 (21.62, 28.55)	14.82 (10.06, 20.45)
NACT- No residual	152	100	1.11 (0.82, 1.51)	0.5616 (df=1)	38.18 (32. 38,2)	27.50 (20.51, 34.92)
NACT- 1 – 10 mm	87	67	1.73 (1.25, 2.40)	0.0054 (df=1)	27.01 (24.28, 31.74)	17.52 (10.33, 26.27)
NACT- > 10 mm	53	41	1.71 (1.19, 2.46)	0.0144 (df=1)	25.49 (22.80, 32.16)	19.91 (10.24, 31.88)

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

ORIGINAL STUDY

Maximal Cytoreduction in Patients With FIGO Stage IIIC to Stage IV Ovarian, Fallopian, and Peritoneal Cancer in Day-to-Day Practice

A Retrospective French Multicentric Study

Mathieu Luyckx, MD,† Eric Leblanc, MD, PhD,‡ Thomas Filleron, PhD,* Philippe Morice, MD, PhD,§ Emile Darai, MD, PhD,|| Jean-Marc Classe, MD, PhD,¶ Gwenaël Ferron, MD,* Eberhard Stoeckle, MD, PhD,# Christophe Pomel, MD, PhD,** Bénédicte Vinet, MD,* Elisabeth Chereau, MD,|| Cécile Bergzoll, MD,** and Denis Querleu, MD, PhD*††*

- **Method**
  - Consecutive retrospective multi institutional cohort
    - 7 Expert Centers (with patients refered from other teams)
  - From January 2003 to December 2007
    - 527 patients, Stage IIIC and IV (only pleural) ovarian cancer
    - Surgery and first line platinum based IV chemotherapy
    - Primary surgery/ Neo adjuvant : 36%/64%

- **Results**
  - Complete surgery: 71% (bowel resection 38%, LN Dissection 75%)
    - In case of Neo Adj. Chemo: R0: 74%
    - In case of primary surgery: R0: 65%

Luyckx M et al, Internat J Gynecol Cancer 2012

Maximal Cytoreduction in Patients With FIGO Stage IIIC to Stage IV Ovarian, Fallopian, and Peritoneal Cancer in Day-to-Day Practice

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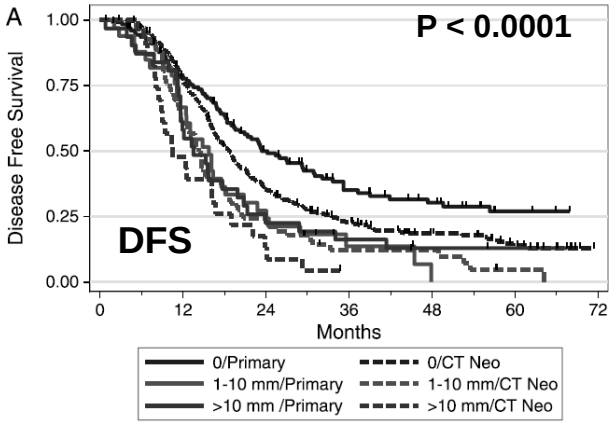
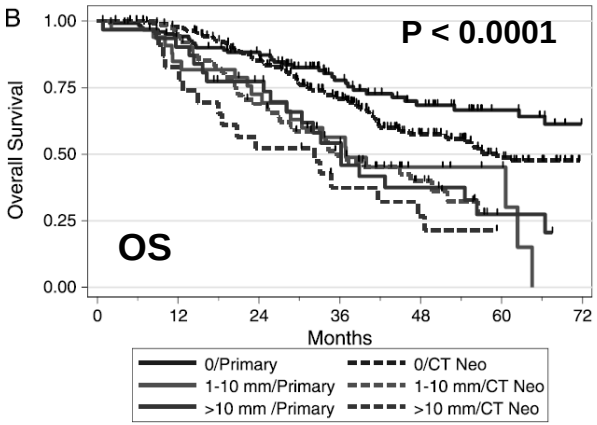
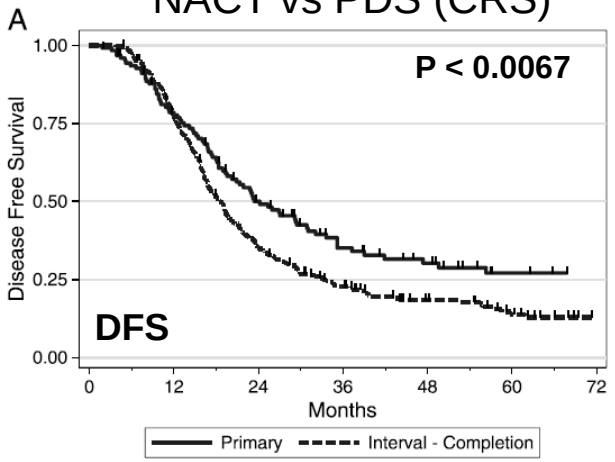
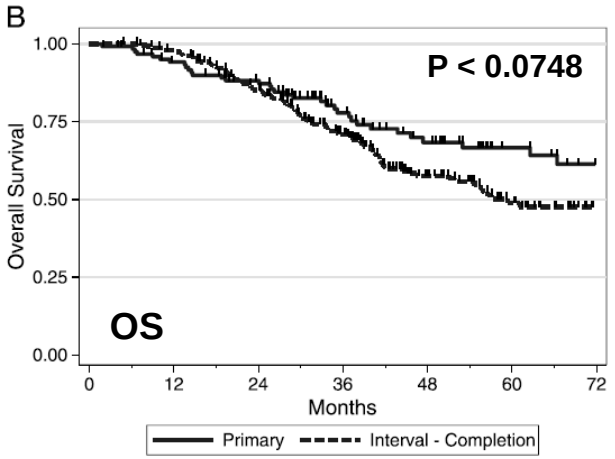
Residual Disease





NACT vs PDS (CRS)





The most significant predictive factor for OS/DFS: amount of residual

Luyckx M et al, Internat J Gynecol Cancer 2012

National Comprehensive Cancer Network®

JNCCN

JNCCN.org Journal of the National Comprehensive Cancer Network

Ovarian Cancer, Version 3.2012

The NCCN Ovarian Cancer Panel recommendations

Upfront CRS (to achieve a gross total resection) followed by adjuvant chemotherapy is considered the preferred treatment (ie, gold standard) in the U.S, for resectable advanced ovarian cancer (including epithelial ovarian, fallopian tube, or primary peritoneal)

NACT can be considered (category 1) for patients with bulky stage IIIC or IV who are not candidates for up-front aggressive cytoreduction .

J Natl Compr Canc Netw 2012;10:1339-1349

National Comprehensive Cancer Network®

JNCCN

JNCCN.org Journal of the National Comprehensive Cancer Network

Ovarian Cancer, Version 3.2012

The NCCN Ovarian Cancer Panel recommendations:

Patients not candidates for up-front aggressive cytoreduction:

- Medical comorbidities
- Advanced age
- Extra-abdominal disease
- No access to experienced gynecologic oncologist
- CRS is not possible
- Extensive debilitating surgery required to achieve optimal cytoreduction
- Refusing surgery

J Natl Compr Canc Netw 2012;10:1339-1349

Epithelial ovarian cancer: Key Points

1. Discussion about the sequence: NACT vs PDS (CRS)

2. **The amount of residual disease at the end of cytoreductive surgery is a major prognostic factor in EOC**

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Conclusion:

Complete resection of all macroscopic disease, whether performed as primary treatment or after Neoadj. Chemo, **remains the objective** whenever cytoreductive surgery is performed.

Survival Effect of Maximal Cytoreductive Surgery for Advanced Ovarian Carcinoma During the Platinum Era: A Meta-Analysis

By Robert E. Bristow, Rafael S. Tomacruz, Deborah K. Armstrong, Edward L. Trimble, and F.J. Montz

- 81 cohorts of patients with stage III/IV EOC (6,885 pts)
- Statistically significant correlation between percent maximal CRS and log median survival time
- Correlation remained significant after controlling for all other variables (P <.001)
- Each 10% increase in maximal CRS -> 5.5% increase in median survival time.

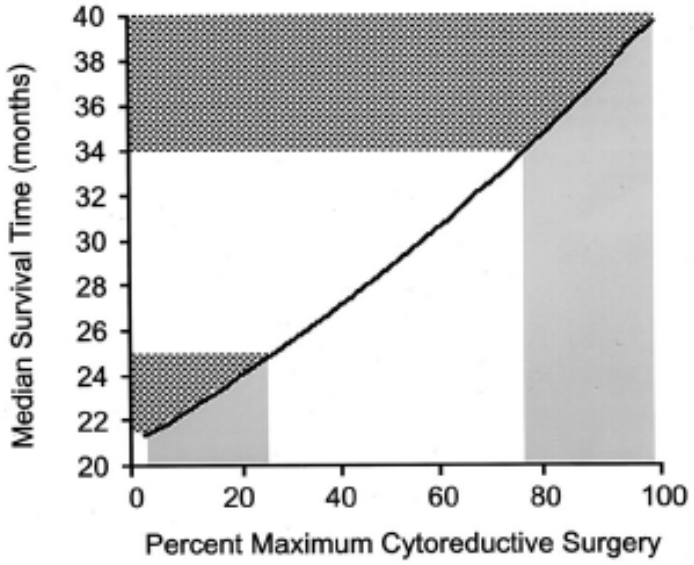


Fig 2. Simple linear regression analysis: de-logged median survival time plotted against percent maximal cytoreductive surgery. Gray area, maximal cytoreductive surgery ≤ 25% and > 75%; crosshatched area, corresponding range of median survival times.

J Clin Oncol. 2002 Mar 1;20(5):1248-59.

Impact of the residual: from « cm » to « mm »

- **Residual >1cm** compared with Residual **millimetric**
  - Meta analysis of 4 studies
    - n= 2 893 patients, primary surgery
    - R millimetric 3 time less risk of death / R >1cm (HR: 3.16)
- **Residual <1cm** compared with Residual **millimetric**
  - Meta analysis of 6 studies
    - n= 3 347 patients, primary surgery
    - R millimetric 2 time less risk of death / R >1cm (HR: 2.2)
  - **Conclusion**: the best residual is no residual

Elattar A, et al, The Cochrane Collaboration, 2011

THE COCHRANE COLLABORATION®

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

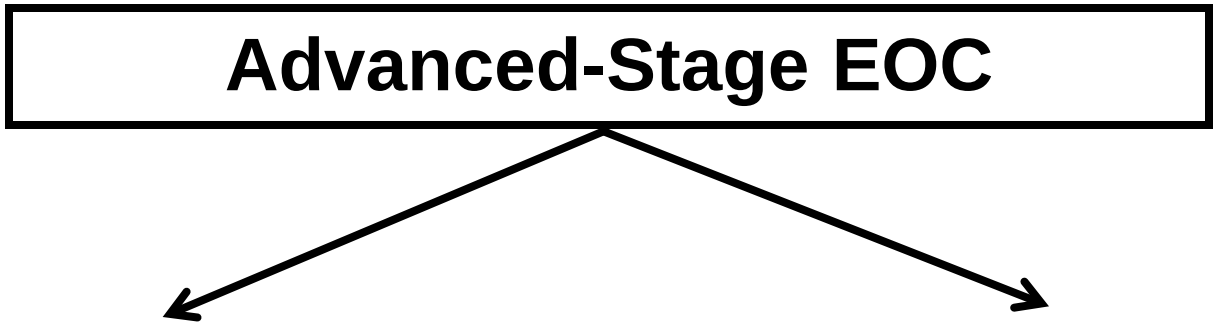
Report From the Fourth Ovarian Cancer Consensus Conference

Gavin C.E. Stuart, MD, FRCSC, Henry Kitchener, MD,† Monica Bacon, RN,‡*
Andreas duBois, MD, PhD,§ Michael Friedlander, MD, PhD,|| Jonathan Ledermann, MD, FRCP,†
*Christian Marth, MD, PhD,¶ Tate Thigpen, MD, PhD,# Edward Trimble, MD,***
and on behalf of the participants of the 4th Ovarian Cancer Consensus Conference (OCCC)

- 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 cyto-reduction (at least microscopic vs macroscopic).

Primary Surgical Treatment Paradigms

The Contemporary Divergence



Deceleration Paradigm

- Initial chemotherapy
- Contracted surgical repertoire
- Lower risk
- Lower reward (survival)

Acceleration Paradigm

- Evolving surgical goals
- Expanded surgical repertoire
- Higher risk
- Higher reward (survival)

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RESULTS

Primary surgery group

- optimal residual disease in 41.6% (Estimated 50%)
- complete cytoreduction in 18.4%
- hysterectomy in 58.1% (previous in 9.7%)
- BSO/USO in 79.6%
- no gross RD in pelvis in 35.8%
- bowel resection in 15.5%
- median operative time 165 min (312 min for NGR)

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm☆

Dennis S. Chi [a,*], Eric L. Eisenhauer [a], Oliver Zivanovic [a], Yukio Sonoda [a], Nadeem R. Abu-Rustum [a], Douglas A. Levine [a], Matthew W. Guile [b], Robert E. Bristow [b], Carol Aghajanian [c], Richard R. Barakat [a]

Method (Memorial New-York): stage III

Group 1: 1996 – 1999 (n= 168 patients)

- **Residual: R0: 11%, R optimal<1cm: 45%**
- **Upper abdominal surgery: 0%**
- **Duration >4h: 15%**

Group 2: 2001-2004,(n= 210 patients)

- **Residual: R0: 27%, R optimal<1cm: 57%,**
- **Upper abdominal surgery: 38%**
- **Duration >4h: 52%**

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

Gynecologic Oncology 114 (2009) 26–31

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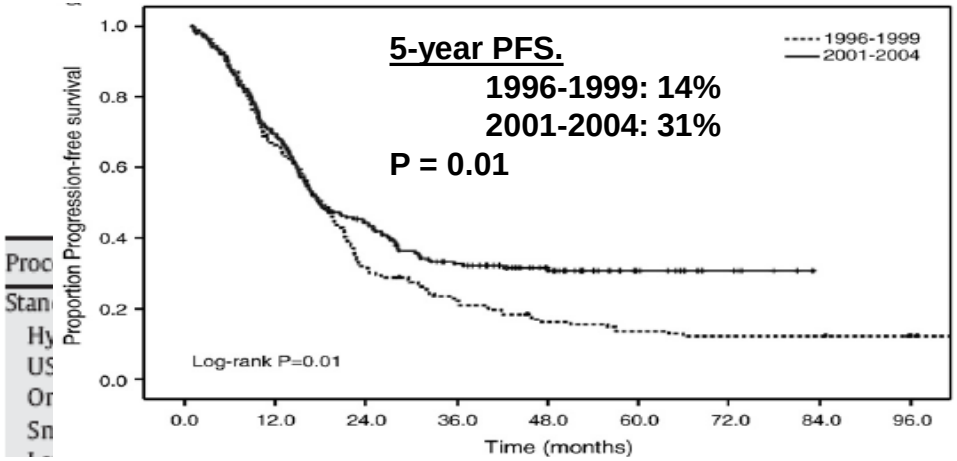
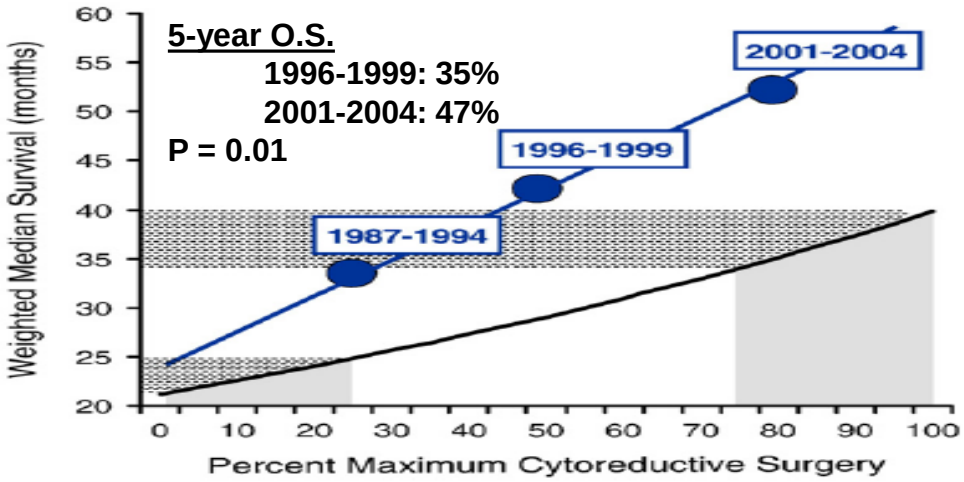




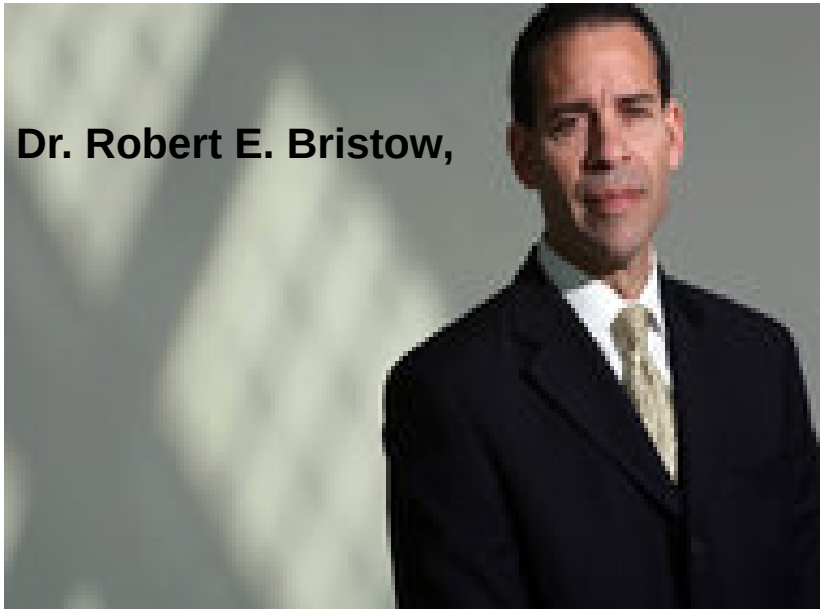
Gynecologic Oncology 114 (2009) 26–31

The New York Times

March 15 2013

Are Ovarian Cancer Patients Receiving Inadequate Treatment?

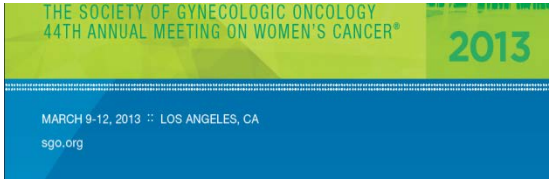
Most women with ovarian cancer receive inadequate care and miss out on treatments that could add a year or more to their lives, a new study has found…..



"If we could just make sure that women get to the people who are trained to take care of them, the impact would be much greater than that of any new chemotherapy drug or biological agent,"

NCCN treatment guidelines for ovarian cancer: A population-based validation study of structural and process quality measures

R. Bristow, J. Chang, A. Ziogas, H. Anton-Culver
University of California Irvine - Medical Center, Orange, CA



California Cancer Registry 1/1/99 and 12/31/06:

13,321 patients with epithelial ovarian cancer underwent Surgery

Aderence to NCCN guideline defined by:

•stage-appropriate surgical procedures

•recommended chemotherapy.

Only **37.2% received NCCN** guideline-adherent care:

•High-volume hospitals 50.8%

•Low-volume hospitals 34.1%,

P<0.001

•High-volume surgeons 47.6%

•Low-volume surgeons 34.5%,

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THE SOCIETY OF GYNECOLOGIC ONCOLOGY
44TH ANNUAL MEETING ON WOMEN'S CANCER®
2013
MARCH 9-12, 2013 :: LOS ANGELES, CA
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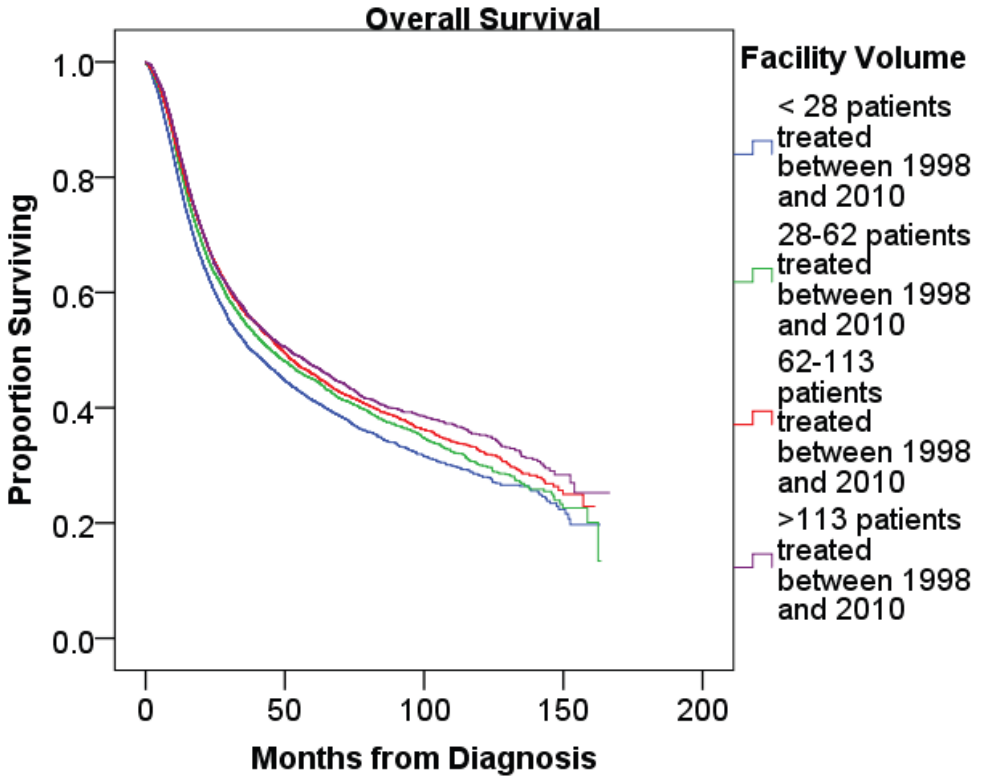
Non adherence to NCCN guideline care was independently associated with inferior overall survival

Low-volume hospitals and surgeons independently associated with deviation from NCCN guidelines and worse overall survival



The impact of bulky upper abdominal disease cephalad to the greater omentum on surgical outcome for stage IIIC epithelial ovarian, fallopian tube, and primary peritoneal cancer

Oliver Zivanovic [a], Eric L. Eisenhauer [a], Qin Zhou [b], Alexia Iasonos [b], Paul Sabbatini [c], Yukio Sonoda [a], Nadeem R. Abu-Rustum [a], Richard R. Barakat [a], Dennis S. Chi [a,*]

474 stage IIIC patients between 1989-2005 stratified by UAD

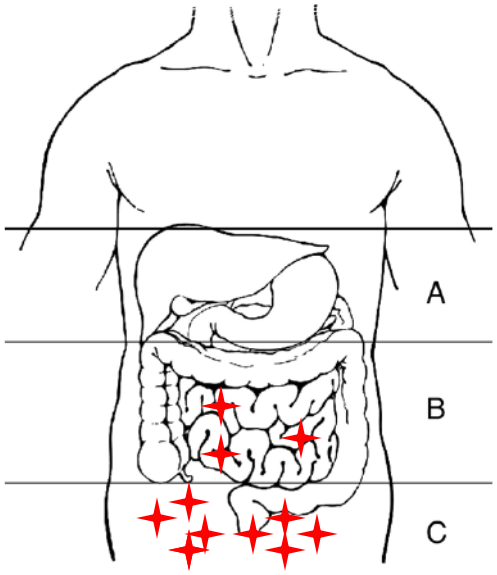


Fig. 1. Abdominopelvic regions. (A) Upper abdomen cephalad to the great omentum. (B) Mid-abdomen. (C) Pelvis.

No UAD
116 (24%)

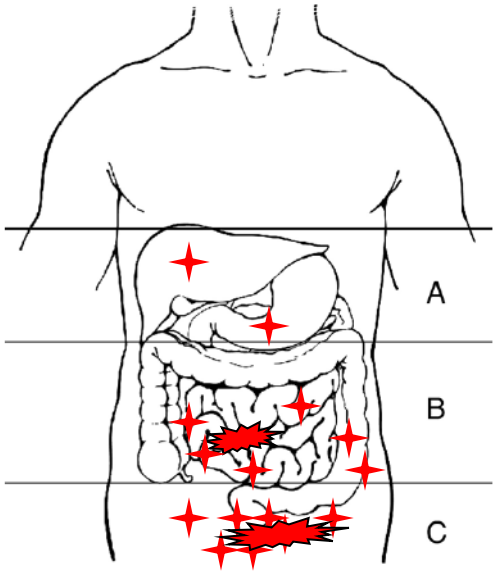


Fig. 1. Abdominopelvic regions. (A) Upper abdomen cephalad to the greater omentum. (B) Mid-abdomen. (C) Pelvis.

Minimal UAD (<1cm)
161 (34%)

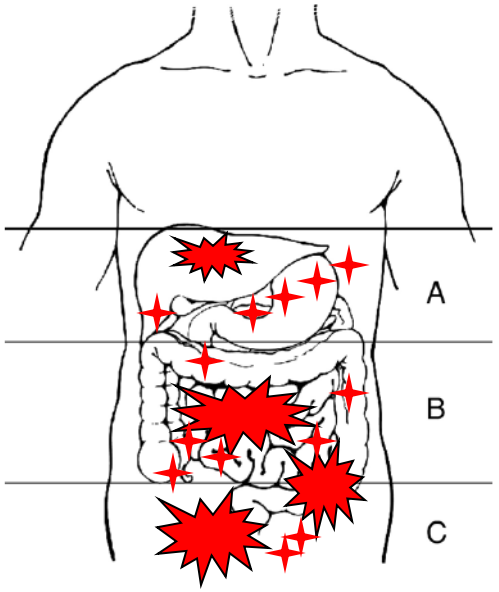


Fig. 1. Abdominopelvic regions. (A) Upper abdomen cephalad to the greater omentum. (B) Mid-abdomen. (C) Pelvis.

Bulky UAD
197 (42%)

Gynecologic Oncology 108 (2008) 287–292

Peritonectomy Procedures

Paul H. Sugarbaker, M.D.

From The Cancer Institute, Washington Hospital Center, Washington, District of Columbia

The Concept of Cytoreductive Surgery with Peritonectomy Procedures

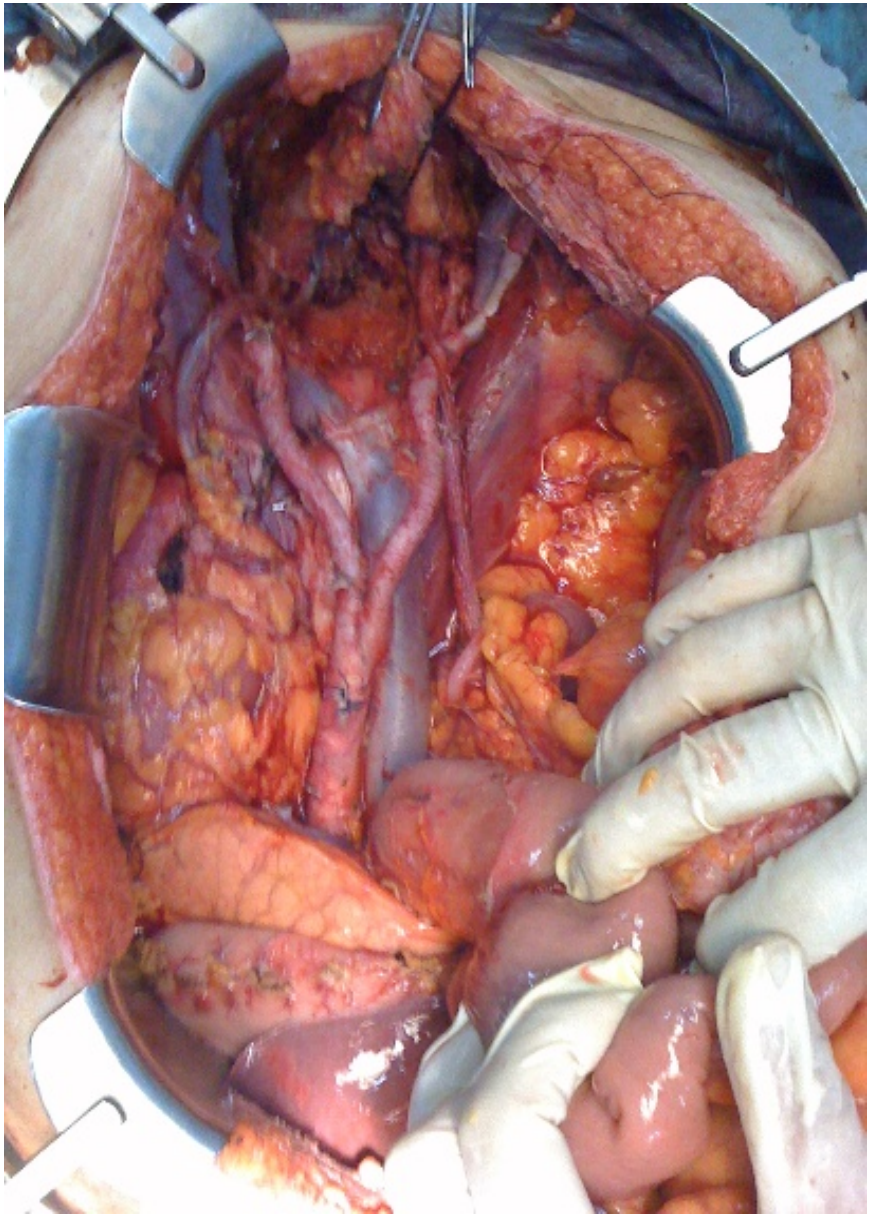
- Means a complete removal of all macroscopic tumor in the peritoneal cavity;

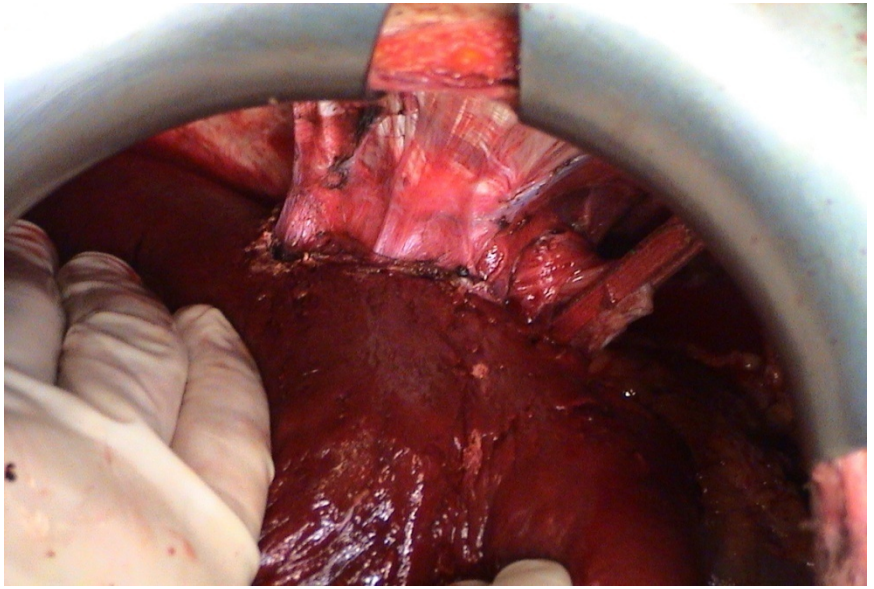
- It could require Peritonectomy Procedures eventually associated with intestinal and/or organ resection

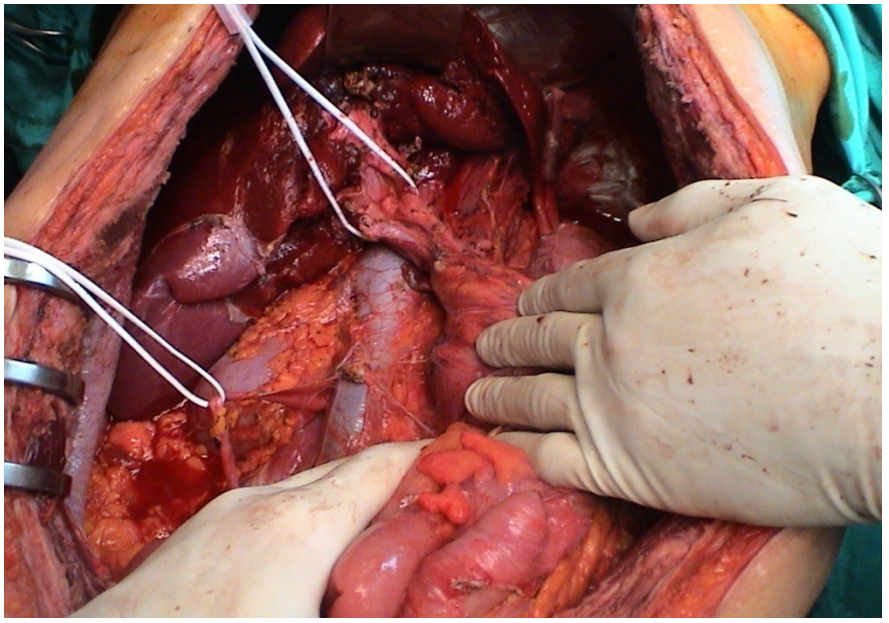
Abdominal regions	Peritonectomies	Visceral resections
Right upper	Right sub-phrenic peritonectomy, Glisson's capsule dissection	
Left upper	Left sub-phrenic peritonectomy	
Antero-lateral	Stripping of paracolic gutters, Greater omentectomy	Splenectomy, appendectomy, right colectomy
Sub-hepatic	Lesser omentectomy, stripping of the omental bursa	Gastric antrectomy, cholecystectomy
Pelvis	Pelvic peritonectomy	Sigmoidectomy, hysterectomy, bilateral adnexectomy
		Total gastrectomy

Ann. Surg. • January 1995

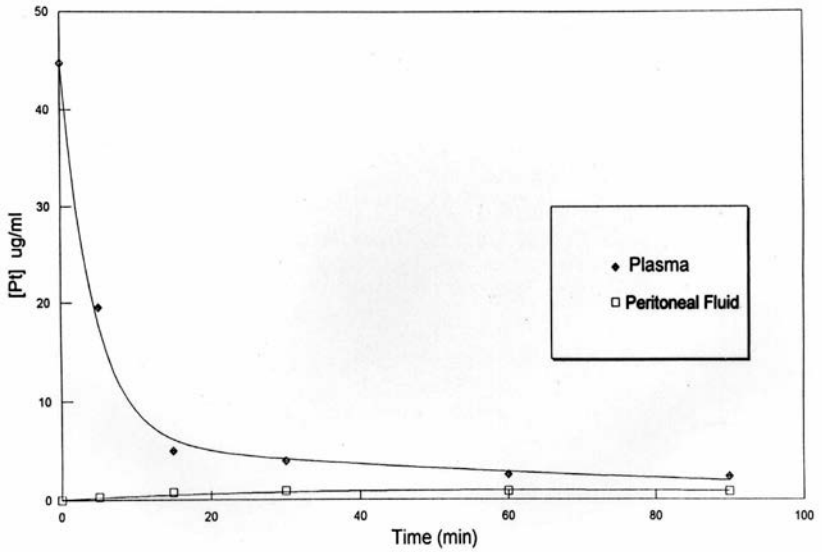
CRS-PP





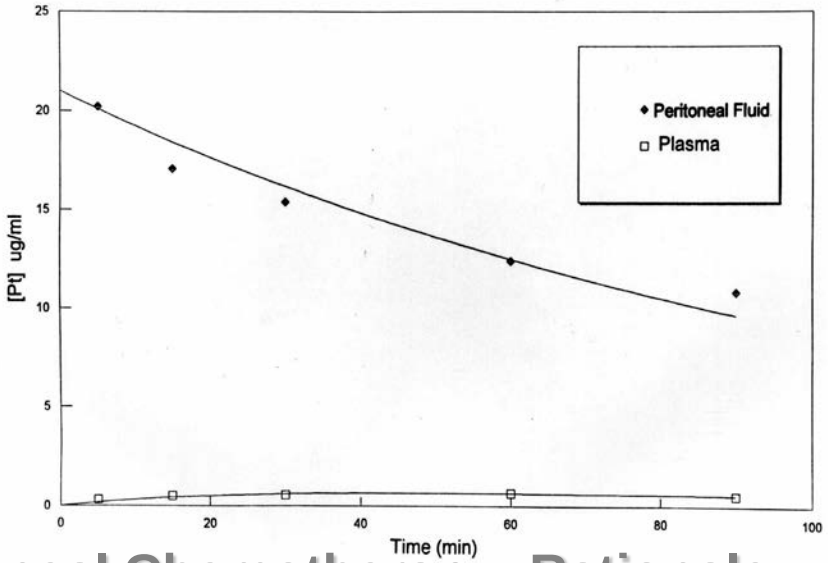


Intravenous Administration

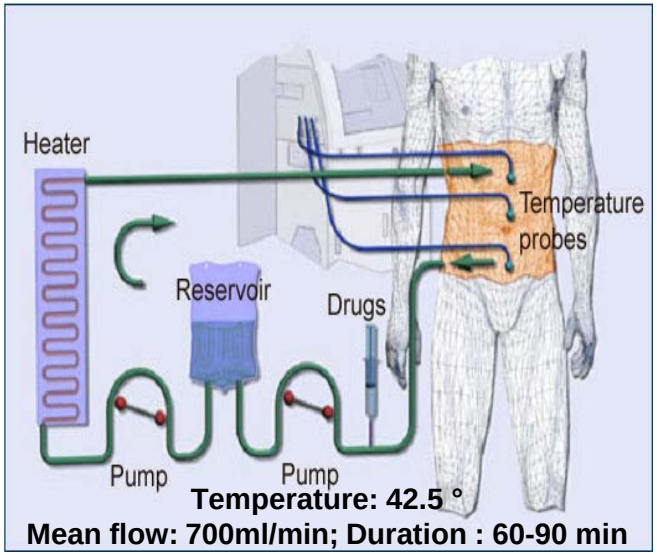


Intraperitoneal Administration

Pestieau SR, J Surg Oncol 2001



HIPEC (Hyperthermic Intra Peritoneal Chemotherapy: Rationale

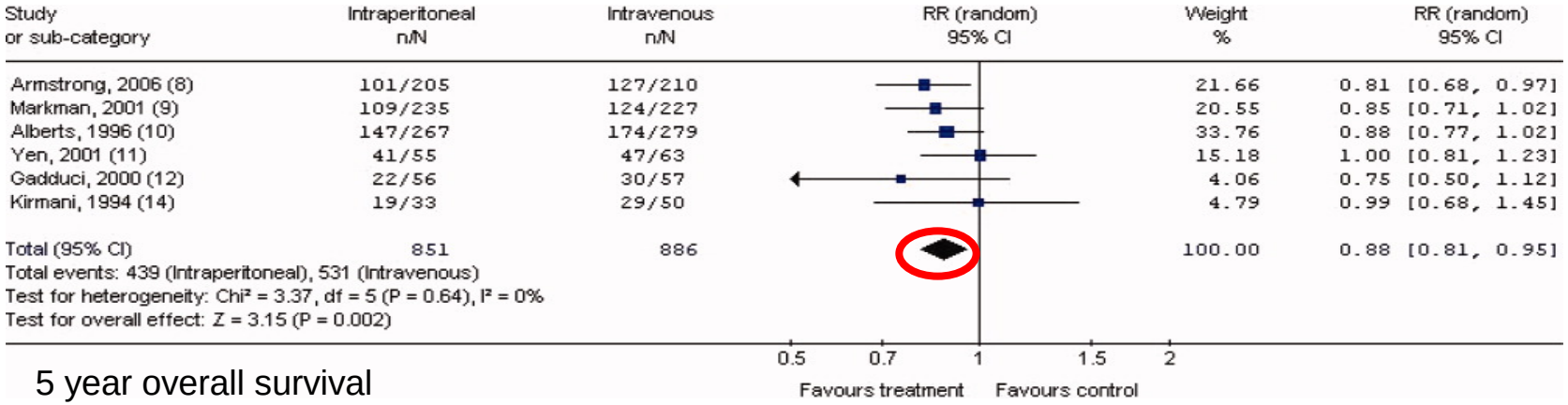


Temperature: 42.5 °

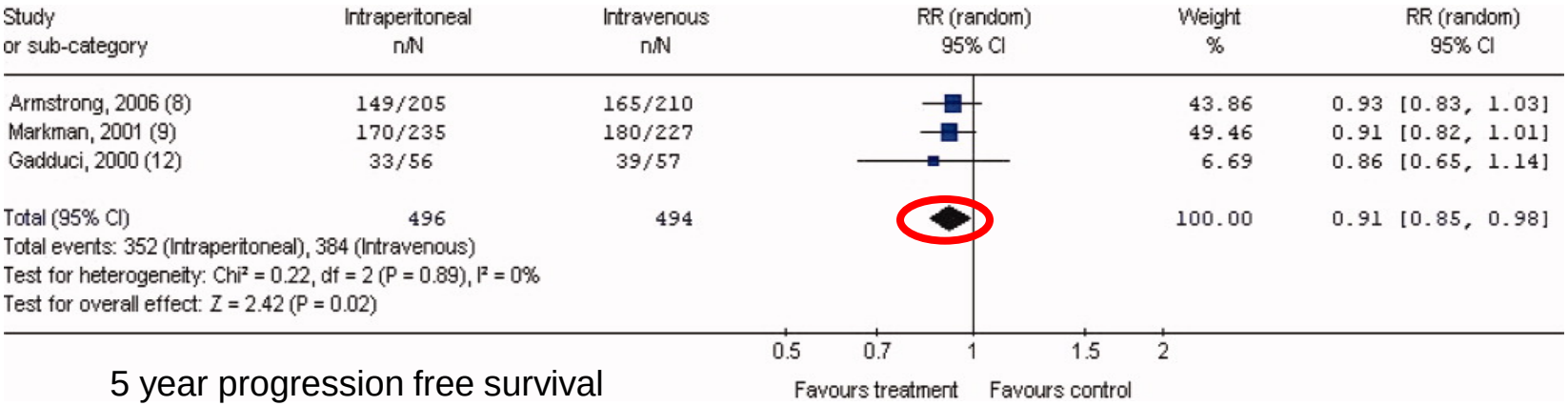
Mean flow: 700ml/min; Duration : 60-90 min

Intraperitoneal Chemotherapy in the First-line Treatment of Women With Stage III Epithelial Ovarian Cancer

A Systematic Review With Metaanalyses



5 year overall survival



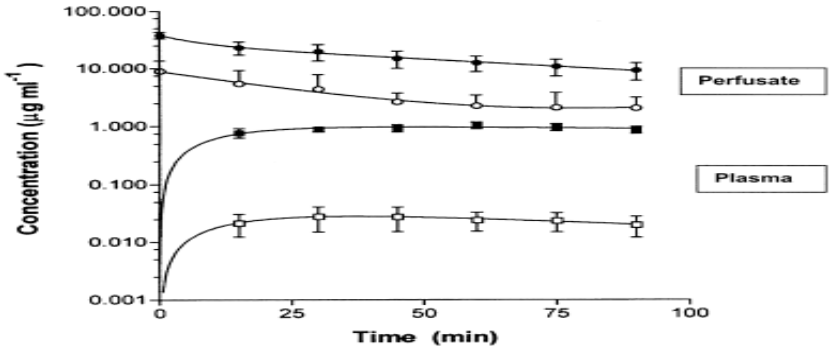
5 year progression free survival

Hyperthermic Intraoperative Intraperitoneal Chemotherapy with Cisplatin and Doxorubicin in Patients Who Undergo Cytoreductive Surgery for Peritoneal Carcinomatosis and Sarcomatosis

Phase I Study

Carlo R. Rossi, M.D.[1]
Mirto Foletto, M.D.[1]
Simone Mocellin, M.D.[1]
Pierluigi Pilati, M.D.[1]
Michele De Simone, M.D.[2]
Marcello Deraco, M.D.[3]
Francesco Cavaliere, M. D.[4]
Pietro Palatini, Ph.D.[5]
Fabiola Guasti, M.Sc.[6]
Romano Scalerta, M.Sc.[1]
Mario Lise, M.D.[1]

BACKGROUND. Hyperthermic Intraperitoneal Intraoperative chemotherapy (HIIC) combined with cytoreductive surgery (CS) has been proposed as a new multimodal treatment mainly for carcinomatosis of gastrointestinal origin. To evaluate whether this regimen could be used for other tumor types, the authors conducted a Phase I study on HIIC with doxorubicin and cisplatin in patients with peritoneal carcinomatosis or sarcomatosis.
PATIENTS AND METHODS. Thirty-one patients with peritoneal carcinomatosis or sarcomatosis (PCS) were enrolled for the study. After completion of CS, HIIC was administered with drug doses that were increased for each consecutive cohort following a three-patient cohort scheme. Thereafter, the accrual was stopped when Grade 4 locoregional or systemic toxicity was observed. The maximum tolerated dose (MTD) was considered the dose in the previous triplet. Drug pharmacokinet-



Open symbols = DXR

Filled symbols = CDDP

30

20

10

0

PERITONEUM MUSCLE FAT NEOPLASM

MTD:

CDDP: 42,5 mg/L

DX: 15,2 mg/L

CURRENT STATUS OF HIPEC IN FRONT-LINE EOC

Key Points:

1. The use of HIPEC in EOC makes theoretic sense in view of the high rates of recurrence following standard treatment

2. Experience reported in the literature is increasing

3. There are no RCTs to date

4. HIPEC should ideally be performed on a research protocol

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REVIEW

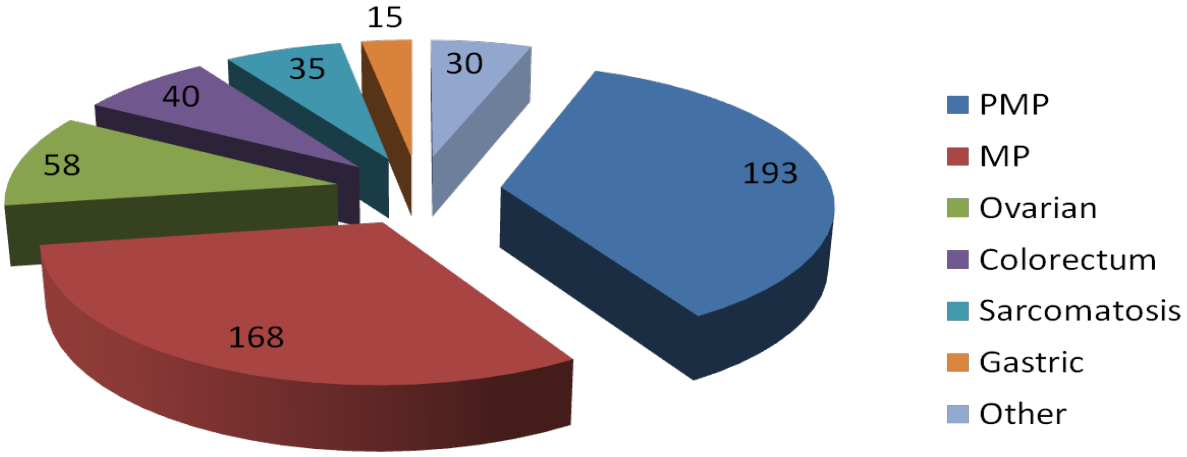
Intraperitoneal chemotherapy in ovarian cancer: a review of tolerance and efficacy

Advanced ovarian cancer

Authors	n	Morbidity and mortality			Survival			
		Peri-op mortality (%)	Minor morbidity (%)	Major morbidity (%)	Median DF survival (months)	Median overall survival (months)	3-year survival (%)	5-year survival (%)
Tentes et al[21]	23 of 43	5	49	19	nr	37[a]	nr	54
Cascales Campos et al[24]	35 of 46	0	22	15	nr	nr	nr	nr
Parson et al[25]	51	0	nr	nr	nr	29	48	28
Deraco et al[27]	26	4	16	20	30	nr	nr	61
Roviello et al[28]	45	nr	nr	nr	nr	nr	nr	57
Pomel et al[29]	31	nr	nr	29	nr	nr	27[b]	nr
Lim et al[31]	30	0	90	40	nr	nr	nr	nr
Bereder et al[32]	62 of 246	0	nr	12	13	49	60	35
Pavlov et al[33]	31	nr	nr	nr	nr	34	nr	nr
Guardiola et al[34]	47	0	nr	13	14	nr	63[b]	nr
Di Giorgio et al[35]	22	nr	nr	nr	26	27	nr	nr
Bae et al[36]	67	0	27	0	56	nr	nr	66
Gori et al[39]	29	nr	nr	nr	54[a]	64	nr	nr
Look et al[40]	28	0	nr	11	17	46	nr	nr
Ryu et al[41]	57	4	19	4	26	61	nr	54

National Cancer Institute of Milan: PSM treated with CRS +HIPEC

Histological Distribution: 540 cases



Mean duration of operations: 577 Min.

Mean Peritoneal cancer index: 19 (0-39)

G3-5 Morbidity rate: 33.5%

Peritoneal Surface Malignancies Program

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy as upfront therapy for advanced epithelial ovarian cancer: Multi-institutional phase-II trial

Marcello Deraco [a,*], Shigeki Kusamura [a], Salvatore Virzì [b], Francesco Puccio [c], Antonio Macrì [d], Ciro Famulari [d], Massimiliano Solazzo [c], Serena Bonomi [b], Domenico Rosario Iusco [b], Dario Baratti [a]

[a] Peritoneal Surface Malignancy Program, Department of Surgery, National Cancer Institute, via Venezian 1, 20133 Milan, Italy
[b] General Surgery Unit, Bentivoglio Hospital, AUSL Bologna, Via Marconi 35, 40010 Bentivoglio (BO), Italy
[c] General Surgery Unit, Manerbio Hospital, Azienda Ospedaliera di Desenzano, Via Marconi, 7, 25025 Manerbio (BS), Italy
[d] General Surgery Unit, G. Martino Hospital, University of Messina, Via Consolare Valeria, 98125 Messina, Italy

STUDY STRUCTURE

- Phase II Study
- 4 Italian centers: Milan NCI, Messina University, Bentivoglio and Manerbio Hospital
- 26 Patients with advanced epithelial ovarian cancer
- Study period: November 2004 to July 2010

Gynecologic Oncology 122 (2011) 215–220

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy as upfront therapy for advanced epithelial ovarian cancer: Multi-institutional phase-II trial

Marcello Deraco [a,*], Shigeki Kusamura [a], Salvatore Virzì [b], Francesco Puccio [c], Antonio Macrì [d], Ciro Famulari [d], Massimiliano Solazzo [c], Serena Bonomi [b], Domenico Rosario Iusco [b], Dario Baratti [a]

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[d] General Surgery Unit, G. Martino Hospital, University of Messina, Via Consolare Valeria, 98125 Messina, Italy

SURGICAL PROCEDURES

- Mean number of peritoneal resections /patient
  3.8
- Mean number of visceral resections /patient
  4.0
  - Total n° Bowel resection
    30
  - Total n° Ostomy
    11
  - Total n° BSO + TAH
    19 (7)

Gynecologic Oncology 122 (2011) 215–220

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy as upfront therapy for advanced epithelial ovarian cancer: Multi-institutional phase-II trial

Marcello Deraco [a,*], Shigeki Kusamura [a], Salvatore Virzì [b], Francesco Puccio [c], Antonio Macrì [d], Ciro Famulari [d], Massimiliano Solazzo [c], Serena Bonomi [b], Domenico Rosario Iusco [b], Dario Baratti [a]

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[d] General Surgery Unit, G. Martino Hospital, University of Messina, Via Consolare Valeria, 98125 Messina, Italy

ADVERSE EVENTS: NCI CTCAEv3

- G3-5 morbidity rate: 15.2%
- 4 patients experienced 9 G3-5 complications
    - Pleural effusion
    - Pneumothorax
    - Abdominal abscess requiring reoperation
    - Central line infection
    - Anastomosis bleeding
    - Bladder fistula
    - G3 haematological toxicity
    - Pneumonia
    - Sepsis
- Post operative death: 1 case (39th day)

Gynecologic Oncology 122 (2011) 215–220

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy as upfront therapy for advanced epithelial ovarian cancer: Multi-institutional phase-II trial

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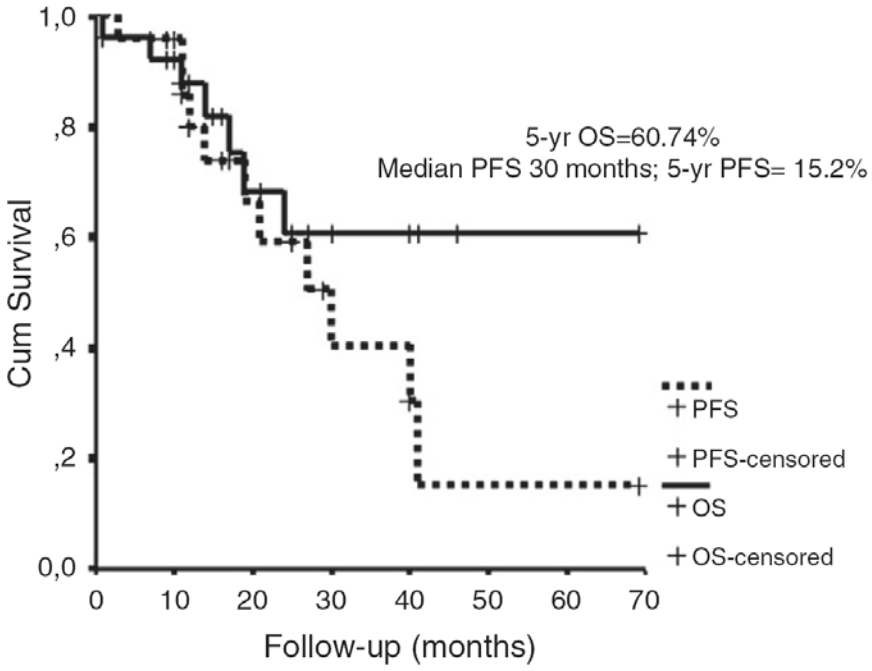
[d] General Surgery Unit, G. Martino Hospital, University of Messina, Via Consolare Valeria, 98125 Messina, Italy

PATIENTS: 26; STAGE III–IV EOC

Cytoreductive surgical and HIPEC procedure.

Peritonectomies	N
Greater omentectomy	24
Right upper quadrant peritonectomy	16
Left upper quadrant peritonectomy	16
Pelvic peritonectomy	26
Lesser omentectomy	18
Visceral resections	
Splenectomy	10
Liver capsulectomy	3
Cholecystectomy	14
Partial gastrectomy	1
Sigmoidectomy	15
Right colectomy	9
Total colectomy	3
Small bowel resection	3
Total hysterectomy[a]	18
Bilateral salpingo-oophorectomy[b]	19
Appendectomy	3
Para aortic and pelvic lymphadenectomy	4
Proximal vagina resection	1
Other	2
Ileostomy[c]	11
HIPEC	
Cisplatin total dose, median (range)	150 mg (80–250)
Doxorubicin total dose, median (range)	70 mg (40–80)

HIPEC: hyperthermic intraperitoneal chemotherapy; SD: standard deviation.
[a] Eight patients underwent TAH previously (two of them for non-neoplastic cause).
[b] Seven patients underwent BSO previously.
[c] No colostomy was done.



Gynecologic Oncology 122 (2011) 215–220

CURRENT THERAPY AND ROLE OF HIPEC FOR RECURRENT EOC

Key Points:

1. Recurrence following front-line treatment of ovarian cancer is common

2. 70% with recurrence will have peritoneal carcinomatosis (PC)

3. Systemic chemotherapy is not curative

4. Surgery followed by systemic chemotherapy may be beneficial in selected cases with localized disease, which is platinum sensitive with a long interval to recurrence

5. HIPEC may have a significant role to play in conjunction with CRS in many patients with recurrent disease.

THE COCHRANE COLLABORATION®

Cytoreductive surgery plus chemotherapy versus chemotherapy alone for recurrent epithelial ovarian cancer (Review)

Galaal K, Naik R, Bristow RE, Patel A, Bryant A, Dickinson HO

- **Medline: 1004**
- **Embase :1089**
- **Central: 123**
- **Specialised Register: 77**

Results of the search

- ***We did not identify any studies*** **that compared the effectiveness and safety of secondary surgical cytoreduction and chemotherapy for women with recurrent epithelial ovarian cancer.**
- **Therefore *the questions* of whether secondary cytoreductive surgery and chemotherapy is associated with a survival benefit when compared to chemotherapy alone in terms of overall and progression-free survival *cannot be answered by this review.***

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REVIEW

Intraperitoneal chemotherapy in ovarian cancer: a review of tolerance and efficacy

Recurrent ovarian cancer

Authors	n	Morbidity and mortality			Survival			
		Peri-op mortality (%)	Minor morbidity (%)	Major morbidity (%)	Median DF survival (months)	Median overall survival (months)	3-year survival (%)	5-year survival (%)
Tentes et al[21]	20 of 43	5	49	19	nr	37[a]	nr	54
Königsrainer et al[22]	31	0	nr	nr	nr	nr	nr	nr
Fagotti et al[23]	41	0	nr	49	24	38	92[b]	nr
Spiliotis et al[26]	24	nr	nr	nr	nr	19	50	nr
Bereder et al[32]	184 of 246	0	nr	12	13	49	60	35
Celeen et al[30]	42	0	43	7	13	37	nr	41
Pavlov et al[33]	25	nr	nr	nr	nr	40	nr	nr
Di Giorgio et al[35]	25	nr	nr	nr	16	23	nr	nr
Cottee et al[37]	81	3	7	7	19	28	nr	nr
Raspagliesi et al[38]	40	0	20	nr	24[a]	41[a]	nr	15
Zanon et al[42]	30	3	30	14	17	28	35	12
Chatzigeorgiou et al[43]	20	10	90	0	21	nr	nr	nr
Cavaliere et al[44]	20	nr	nr	nr	nr	25	50[c]	nr

Secondary cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for recurrent epithelial ovarian cancer: a multi-institutional study

M Deraco,[a] S Virzì,[b] DR Iusco,[b] F Puccio,[c] A Macrì,[d] C Famulari,[d] M Solazzo,[c] S Bonomi,[b] A Grassi,[b] D Baratti,[a] S Kusamura,[a]

STUDY DESIGN

Retrospective study

Data extracted from a multi-institutional prospective database

Four Italian centres:

- National Cancer Institute (NCI) of Milan
- General Surgery Unit of Messina's University
- Bentivoglio's hospital
- Manerbio's hospital

BJOG An International Journal of Obstetrics and Gynaecology

Secondary cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for recurrent epithelial ovarian cancer: a multi-institutional study

M Deraco,[a] S Virzì,[b] DR Iusco,[b] F Puccio,[c] A Macrì,[d] C Famulari,[d] M Solazzo,[c] S Bonomi,[b] A Grassi,[b] D Baratti,[a] S Kusamura,[a]

OUTCOMES

Figure 1A: OS in recurrent EOC treated by CRS and HIPEC

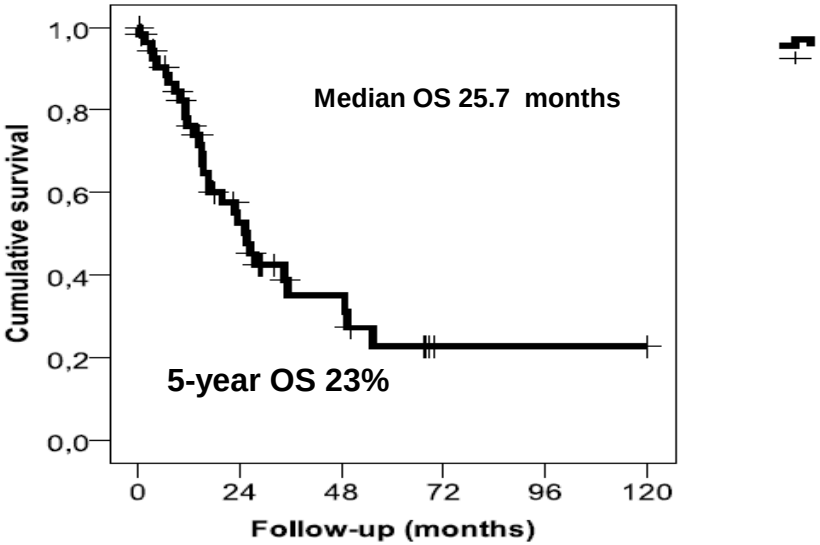
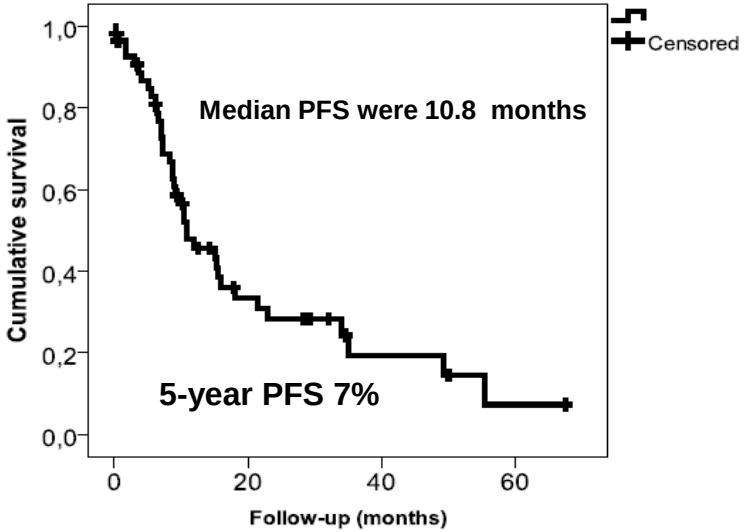


Figure 1B: PFS in recurrent EOC treated by CR+HIPEC



BJOG An International Journal of Obstetrics and Gynaecology

Secondary cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for recurrent epithelial ovarian cancer: a multi-institutional study

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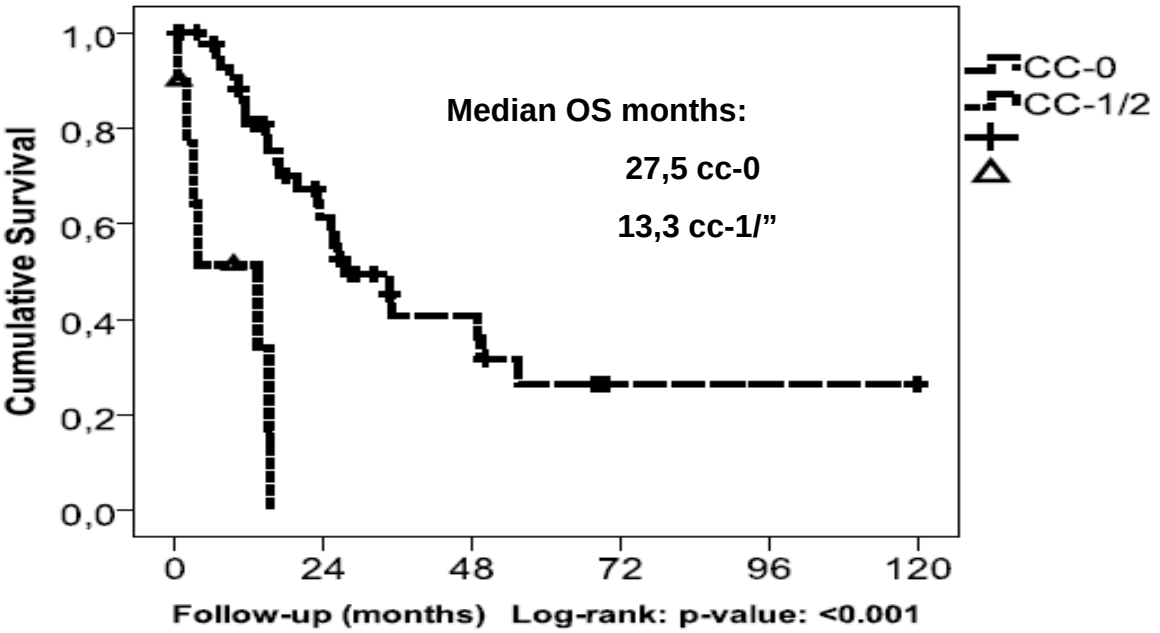
Figure 2: Overall survival according to completeness of cytoreduction



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]

[a] Division of Gynecologic Oncology, Catholic University of the Sacred Heart, Rome, Italy
[b] Department of Gynecology and Obstetrics, AO Mauriziano Umberto I, University of Turin, Turin, Italy

Case–control study

Recurrent EOC

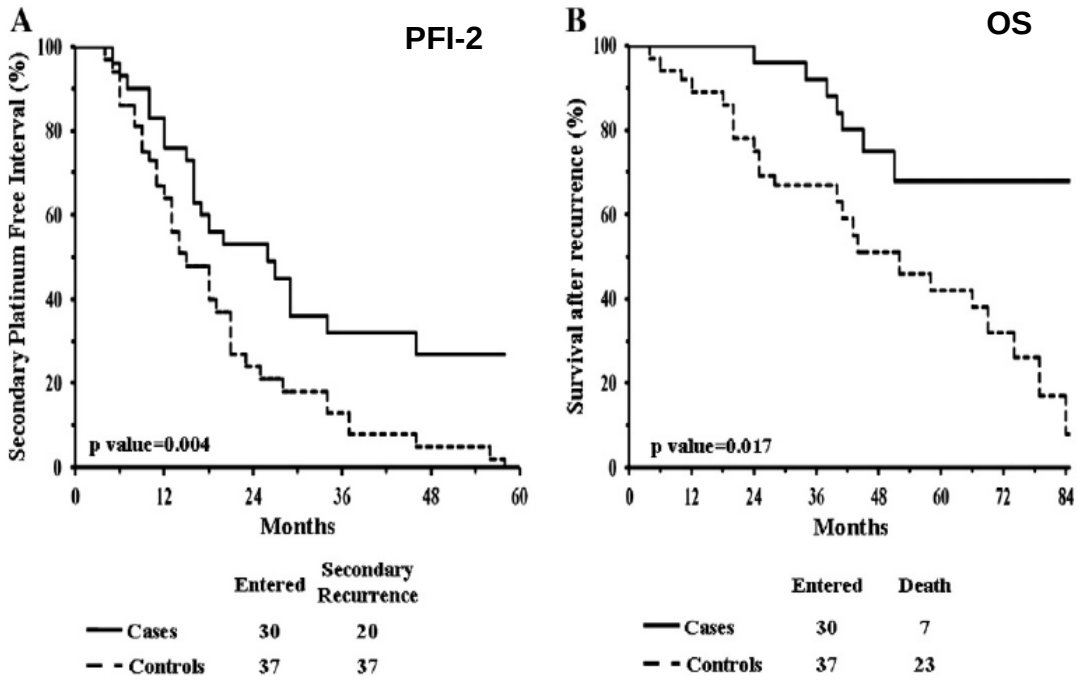
Platin Sensitive ≥6 months

Matching:

30 Cases CRS+HIPE

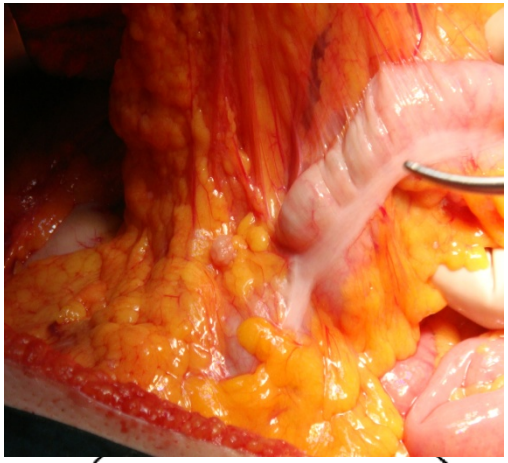
37 Controls

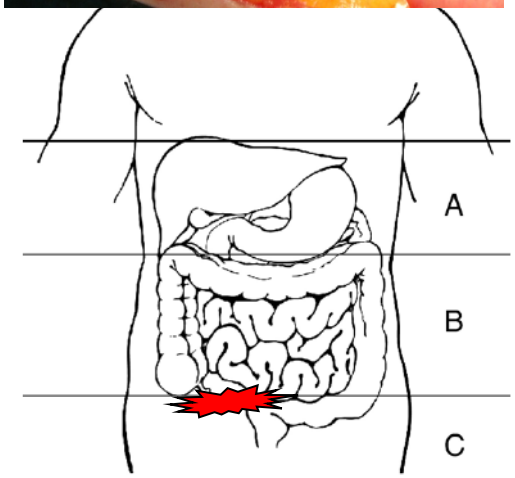
Follow-up ≥ 24 months



A. Fagotti et al. / Gynecologic Oncology 127 (2012) 502–505

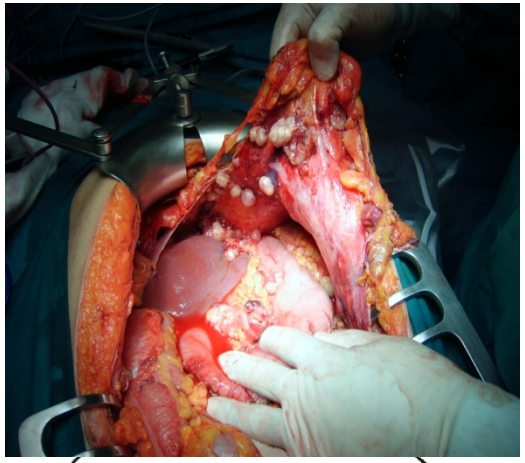
Recurrent EOC: Scenarios

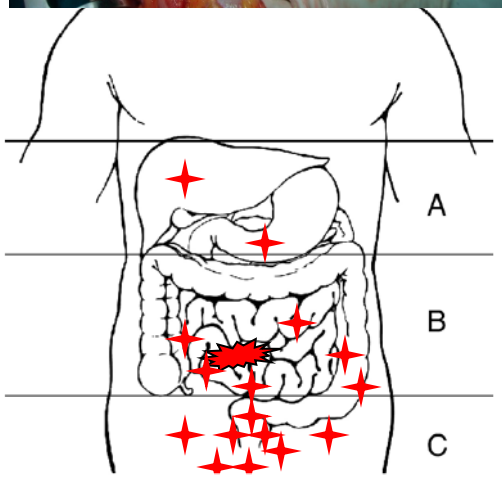




Single Site

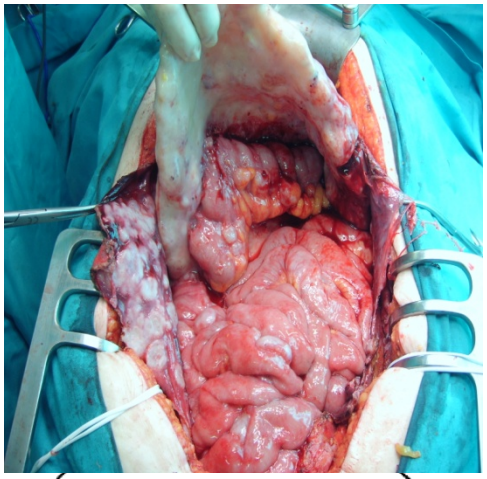
Ascite: NO

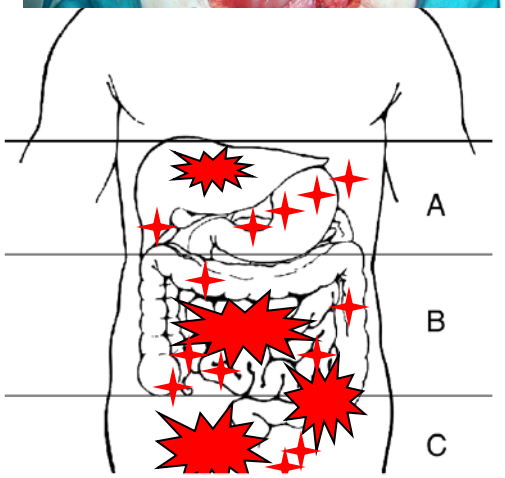




Multiple Site

Ascite: Rare





Confluent or Diffuse PC

Ascite: Frequent

Dennis S. Chi, M.D.[1]
Kristina McCaughty, M.D.[1]
John P. Diaz, M.D.[2]
Jae Huh, M.D.[1]
Sarah Schwabenbauer, M.D.[1]
Amanda J. Hummer, M.S.[3]
Ennapadam S. Venkatraman, Ph.D.[3]
Carol Aghajanian, M.D.[4]
Yukio Sonoda, M.D.[1]
Nadeem R. Abu-Rustum, M.D.[1]
Richard R. Barakat, M.D.[1]

[1] Gynecology Service, Department of Surgery; Memorial Sloan-Kettering Cancer Center, New York, New York.

[2] Department of Obstetrics and Gynecology; University of Miami, Jackson Memorial Hospital, Miami, Florida.

Guidelines and Selection Criteria for Secondary Cytoreductive Surgery in Patients with Recurrent Platinum-Sensitive Epithelial Ovarian Carcinoma

153 Pts

Recommendation for Secondary Cytoreduction Based on Disease-free Interval, the Number of Recurrence Sites, and Evidence of Carcinomatosis

DFI	Single Site	Multiple Sites: No Carcinomatosis	Carcinomatosis
6–12 Mo	Offer SC	Consider SC	No SC
12–30 Mo	Offer SC	Offer SC	Consider SC
>30 Mo	Offer SC	Offer SC	Offer SC

DFI: disease-free interval; Mo: months; SC: secondary cytoreduction.

Univariate Analysis

Variable	Total No.	% Alive	Median Survival (95% CI), Mo	HR (95% CI)	*P*
Ascites					
No	91	37	48.9 (41.8–56.2)	1.00	<.001
Yes	29	14	28.0 (23.7–33.7)	2.25 (1.42–3.57)	
No. of sites					
One	41	44	60.3 (46.5–102.2)	1.00	<.001
Multiple, no carcinomatosis	68	32	41.7 (33.7–51.4)	1.85 (1.10–3.11)	
Carcinomatosis	44	18	27.5 (20.8–36.0)	3.81 (2.17–6.69)	
Residual after second debulking					
≤0.5 cm	79	44	56.2 (48.2–66.6)	1.00	<.001
>0.5 cm	73	16	26.7 (21.9–31.0)	3.12 (2.08–4.67)	

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Morbidity and mortality outcomes of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with primary and recurrent advanced ovarian cancer

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Adverse postoperative events after citorreductive and HIPEC in ovarian peritoneal carcinomatosis.

Postoperative morbidity	NCI-CTCAE 3.0			
	I–II	III	IV	Total
Hematological				
Neutropenia	1	–	–	1
Thrombopenia	–	–	–	
Gastrointestinal				
Diarrhea	1	–	–	10
Paralytic ileus	7	–	–	
Anastomotic leakage	–	–	1	
Rectal pouch leakage	1	–	–	
Hemorrhage				
Self-limited postoperative bleeding	2	–	–	6
Wound hematoma	1	–	–	
Hemoperitoneum	–	–	2	
Upper gastrointestinal bleeding	–	1	–	
Infectious				
Wound infection	–	3 (1[a])	–	5
Intra-abdominal abscess	–	1[a]	1[a]	
Respiratory				
Respiratory distress	1	–	–	6
Pleural effusion	–	3	–	
Hydroneumothorax	–	1	–	
Diaphragmatic relax	1[a]	–	–	
Urinary				
Fistula	–	1	–	1
Total	15	10	4	29

[a] Patients who required hospital readmission within 30 days postoperatively after hospital discharge.

Multivariate analysis for postoperative morbidity in patients with peritoneal dissemination from ovarian cancer treated with cytoreductive surgery and HIPEC.

Variable	Morbidity I–IV		p	Morbidity III–IV		p
	Odds ratio (OR)	IC 95%		Odds ratio (OR)	IC 95%	
PCI > 12						
No	1		0.044	1		0.032
Yes	2.94	1.89–9.59		6.69	1.97–45.67	
Digestive anastomosis						
No	1		0.117	1		0.046
Yes	3.20	0.75–13.71		4.99	1.35–27.62	
Colon resection						
No	1		0.465	1		0.059
Yes	1.75	0.39–7.77		3.46	0.95–23.79	
Diaphragmatic peritonectomy						
No	1		0.130	1		0.538
Yes	2.60	0.75–8.99		1.68	0.32–8.73	
Intraoperative blood transfusion						
No	1		0.075			
Yes	3.69	0.88–15.43				
CC-0 Cytoreduction						
No	1		0.342			
Yes	1.96	0.49–7.81				
Surgery time <360 min						
No	1		0.606			
Yes	1.39	0.39–4.92				

EOC: CONCLUSION

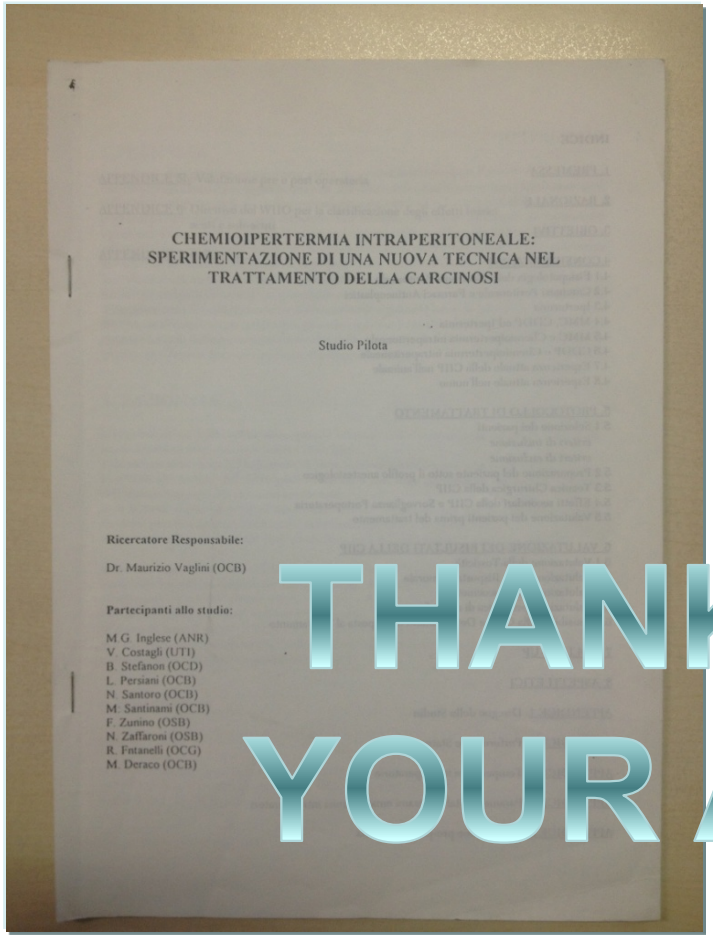
•Confirmation of the role of CRS (CC-0) on outcomes effort to spread this concept

•Promising results for CRS and HIPEC on Primary and Recurrent EOC

•Randomised Study are necessary to asses the real benefit of HIPEC

TITLE	CODE
Hyperthermic Intra-peritoneal Chemotherapy (HIPEC) in Ovarian Cancer Recurrence	NCT01539785
Phase 3 Trial Evaluating Hyperthermic Intraperitoneal Chemotherapy in Upfront Treatment of Stage IIIC Epithelial Ovarian Cancer	NCT01628380
Feasibility Study of HIPEC for Patients With Stage III or Only Pleural Stage IV Ovarian Carcinoma in First Line Therapy	NCT01709487
Secondary Debulking Surgery +/- Hyperthermic Intraperitoneal Chemotherapy in Stage III Ovarian Cancer	NCT00426257
Outcomes After Secondary Cytoreductive Surgery With or Without Carboplatin Hyperthermic Intraperitoneal Chemotherapy (HIPEC) Followed by Systemic Combination Chemotherapy for Recurrent Platinum-Sensitive Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	NCT01767675
Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) in Relapse Ovarian Cancer Treatment	NCT01376752
A Phase II Combined Modality Protocol of Debulking Surgery With HIPEC Followed by Intraperitoneal Chemotherapy for the Treatment of Recurrent Ovarian, Primary Peritoneal & Fallopian Tube Cancers	NCT01659554

February 1995-February 2013



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