UNIVERSITEIT VAN PRETORIA
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Provisional Programme Controversies and Problems in Surgery Symposium - University of Pretoria
16TH SYMPOSIUM 05-06 OCTOBER 2012

Results of CRS and HIPEC in Peritoneal Mesothelioma, Ovarian and Gastric PSM

Marcello Deraco M.D.

Responsible

Peritoneal Surface Malignancies

FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI

Sotto l'alto patrocinio
Presidenza del Consiglio dei Ministri

INTRODUCTION

- aggressive malignancy arising from mesothelial cells within the serosal lining of the peritoneum;
- characterized macroscopically by thousands of tumor nodules that may coalesce to form plaques, masses or layers to cover the entire peritoneal surface;
- present epidemiological, biological and clinical behaviours different from its most know and frequent pleural counterpart as well as a better prognosis;
- low sensitivity and specificity of the diagnosis explain the misdiagnosed of Peritoneal Mesothelioma as a neoplasm originating from other abdominal organs.

EPIDEMIOLOGY AND ETIOLOGY

- age standardized incidence rates among men range from 0.5 to about 3 cases per million population (SEER and Eurocim data);
- 5-10% increase in annual mortality rate will be observed worldwide at least until 2020;
- the disease has likely already reached the incidence peak in the USA. On the contrary, in Europe and Australia the peaks is expected during this decade;
- 58% of peritoneal mesothelioma directly related to past asbestos exposure among men;
- only 20% of women with peritoneal mesothelioma had past asbestos exposure .

HISTOLOGY

Localized peritoneal mesothelioma

- Benign
  - adenomatoid
  - localized fibrous

Diffuse peritoneal mesothelioma

- Borderline
  - multicystic (MCPM)
  - well-differentiated papillary (WDPM)
- Malignant (DMPM)
  - epithelioid (75%)
  - poorly differentiated (6%)
  - biphasic (6%)
  - sarcomatoid (13%)

Guidelines for Pathologic Diagnosis of Malignant Mesothelioma

2012 Update of the Consensus Statement from the International Mesothelioma Interest Group

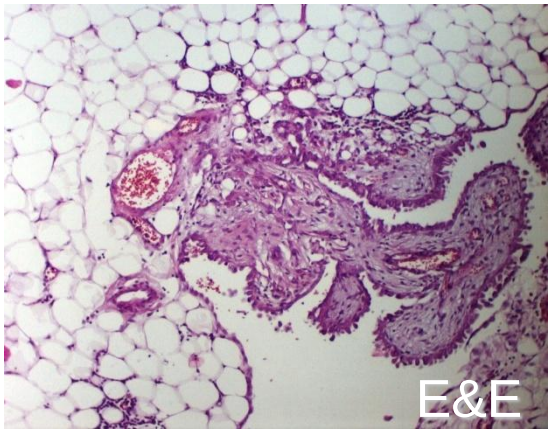
Aliya N. Husain, MD; Thomas Colby, MD; Nelson Ordonez, MD; Thomas Krausz, MD; Richard Attanoos, MB, BS; Mary Beth Beasley, MD; Alain C. Borczuk, MD; Kelly Butnor, MD; Philip T. Cagle, MD; Lucian R. Chirieac, MD; Andrew Churg, MD; Sanja Dacic, MD, PhD; Armando Fraire, MD; Francoise Galateau-Salle, MD; Allen Gibbs, MD; Allen Gown, MD; Samuel Hammar, MD; Leslie Litzky, MD; Alberto M. Marchevsky, MD; Andrew Nicholson, MB, BS; Victor Roggli, MD; William D. Travis, MD; Mark Wick, MD

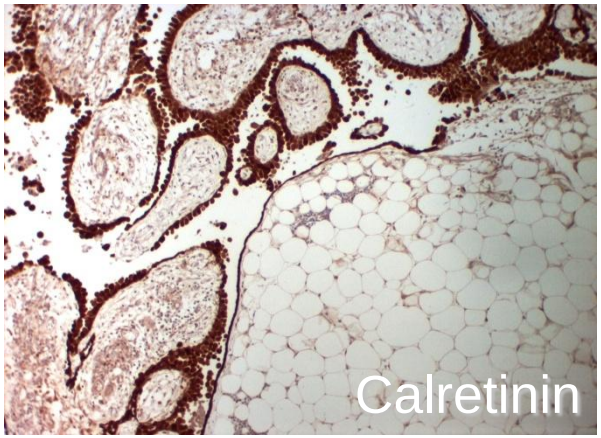
Table 4. Histologic Subtypes and Patterns[a] of Malignant Mesothelioma

Epithelioid mesothelioma
Tubulopapillary
Micropapillary
Trabecular
Acinar
Adenomatoid
Solid
Clear cell
Deciduoid
Adenoid cystic
Signet ring cell
Small cell
Rhabdoid
Pleomorphic
Sarcomatoid mesothelioma
Conventional, spindle cell
Desmoplastic
Heterologous differentiation (osteosarcomatous, chondrosarcomatous, etc)
Lymphohistiocytoid (may also be classified as epithelioid)
Biphasic/mixed

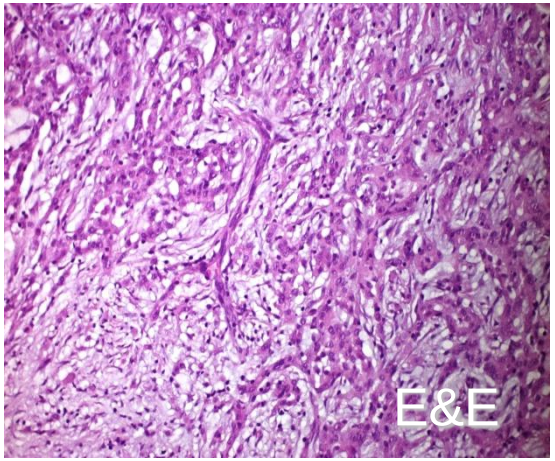
[a] Subtype must be given in the diagnosis, but histologic pattern, epithelioid or sarcomatous, may be described in a comment or microscopic description.

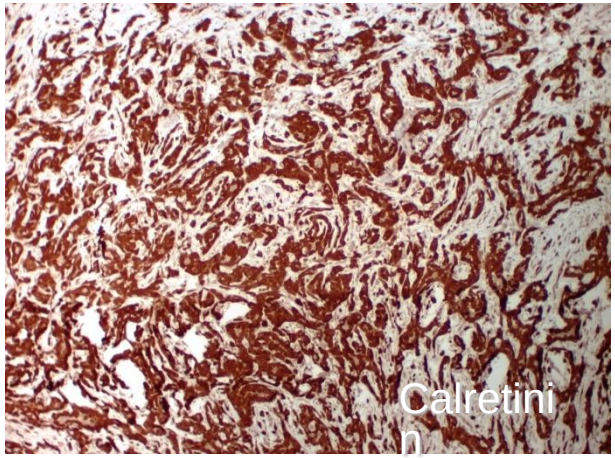
"A rare case of papillary well-differentiated peritoneal mesothelioma with transition into diffuse malignant mesothelioma."





WDPM Component: well defined papillary structures with myxoid cores, lined by bland, flattened, single layer of cuboidal or columnar mesothelial cells.





Tubulopapillary Mesothelioma Component: Glands lined by cuboidal cells, with outward branches and/or complex invaginations

Original Article

A Novel Tumor-Node-Metastasis (TNM) Staging System of Diffuse Malignant Peritoneal Mesothelioma Using Outcome Analysis of A Multi-institutional Database

Tristan D. Yan, BSc, (Med), MBBS, PhD[1]; Marcello Deraco, MD[2]; Dominique Elias, PhD[3]; Olivier Glehen, PhD[4]; Edward A. Levine, MD[5]; Brendan J. Moran, MD[6]; David L. Morris, PhD[7]; Terence C. Chua, MBBS[7]; Pompiliu Piso, PhD[8]; Paul H. Sugarbaker, MD[9]; and Peritoneal Surface Oncology Group*

Multiinstitutional Database: 405
Eligible: 294

- **Age ≤ 50 (p = 0.011)**
- **Female (p < 0.001)**
- **Epithelial subtype (p = 0.006)**

} **Intrinsic factors**

- **CC-0/1 (p < 0.001)** — **Postoperative variable**
- **PCI 1-10 (p < 0.001)** — **T**
- **Lymph node metastasis (p < 0.001)** — **N**
- **Extra-abdominal metastasis (p =0.004)** — **M**

Cancer 2010

Original Article

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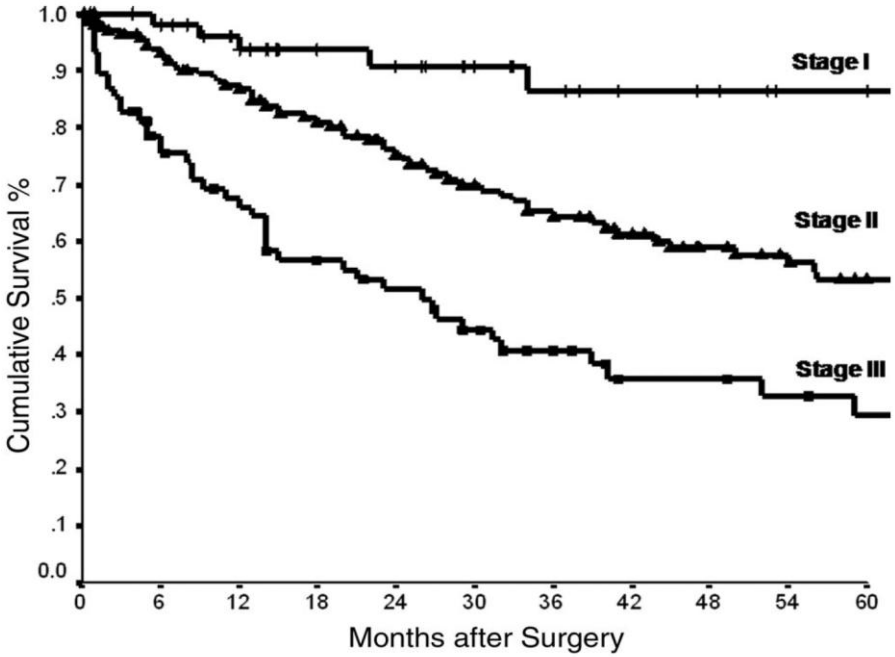
Tristan D. Yan, BSc, (Med), MBBS, PhD[1]; Marcello Deraco, MD[2]; Dominique Elias, PhD[3]; Olivier Glehen, PhD[4]; Edward A. Levine, MD[5]; Brendan J. Moran, MD[6]; David L. Morris, PhD[7]; Terence C. Chua, MBBS[7]; Pompiliu Piso, PhD[8]; Paul H. Sugarbaker, MD[9]; and Peritoneal Surface Oncology Group*



Stage	N	Median	1-year	3-year	5-year
I	52	Not reached	94	87	87
II	166	67	87	64	53
III	76	26	66	41	29

Stage	Tumour	Node	Metastasis
I	T1	N0	M0
II	T2-3	N0	M0
III	T4	N0-1	M0-1
	T1-4	N1	M0-1
	T1-4	N0-1	M1

Cancer 2010

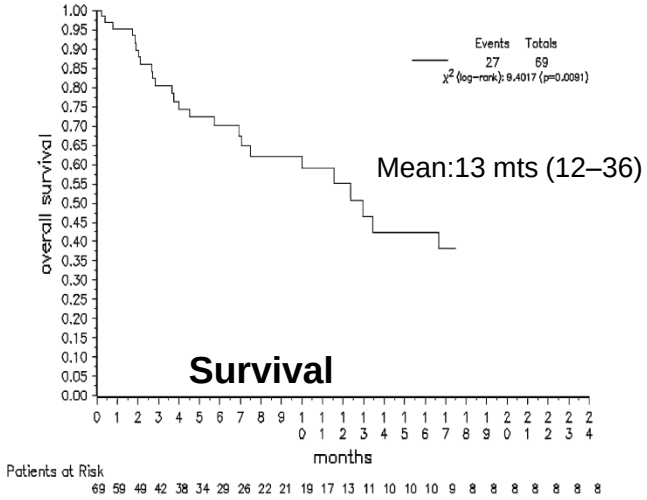
Malignant peritoneal mesothelioma: a multicenter study on 81 cases

V. de Pangher Manzini[1]*, L. Recchia[1], M. Cafferata[2], C. Porta[3], S. Siena[4], L. Giannetta[4], F. Morelli[5], F. Oniga[6], A. Bearz[7], V. Torri[8] & M. Cinquini[8]

[1]Division of Medical Oncology, Department of Internal Medicine and Oncology, Monfalcone Hospital, Monfalcone; [2]Division of Medical Oncology, Department of Internal Medicine and Oncology, Casale Monferrato Hospital, Casale Monferrato; [3]Department of Medical Oncology, Istituto di Ricovero e Cura a Carattere Scientifico, San Matteo University Hospital Foundation, Pavia; [4]The Falck Division of Medical Oncology, Niguarda Ca' Granda Hospital, Milan; [5]Department of Oncology, Istituto di Ricovero e Cura a Carattere Scientifico, Casa Sollievo della Sofferenza, San Giovanni Rotondo; [6]Division of Medical Oncology, Department of Oncology, Venice-Mestre Hospital; [7]Department of Medical Oncology, Centro di Riferimento Oncologico - Istituto di Ricovero e Cura a Carattere Scientifico, Aviano and [8]Department of Oncology, Mario Negri Institute, Milan, Italy

- 14 Italian institutions (1982-2007);
- 81 patients:57(70%) M, 24(30%) W;
- mean age: 64(19– 85): 63/M, 68/W;
- Asbestos Exposure: 59,6%/M, 33,3%/W;
- Monfalcone (shipyards), Casale Monferrato(Eternit factory);
- sCT(45),Surgery+sCT(21), Surgery(8), CRS+HIPEC(7)

Symtoms	Total		
	Patients	*n*	%
Ascites	62	81	77
Abdominal pain	56	81	69
Asthenia	35	81	43
Weight loss	26	81	32
Anorexia	24	81	30
Abdominal mass	24	81	30
Fever	18	81	22
Diarrhea	14	81	17
Vomiting	12	81	15



Imaging	Classic presentation		
	Patients	Total	%
CT ascites	47	59	80
CT abdominal mass	19	59	32
CT peritoneal thickening	37	59	63
CT mesenterial thickening	17	59	29
ECT ascites	32	59	54
ECT abdominal mass	11	59	19
ECT peritoneal thickening	5	59	8

Annals of Oncology Advance Access published July 27, 2009

Comprehensive management of diffuse malignant peritoneal mesothelioma

P.H. Sugarbaker*, T.D. Yan, O.A. Stuart, D. Yoo

Program in Peritoneal Surface Oncology, Washington Cancer Institute, Washington Hospital Center, 106 Irving Street, NW, Suite 3900, Washington, DC 20010, USA

Median survival of DMPM using traditional treatment modalities

Authors[Ref.]	Year	No. of patients	Median survival (months)
Chailleux et al.[5]	1988	11/167	10[a]
Antman et al.[6]	1988	37/180	15[a]
Sridhar et al.[7]	1992	13/50	9.5[a]
Markman et al.[8]	1992	19	9
Yates et al.[9]	1997	14/272	14[a]
Neumann et al.[10]	1999	74	12 (mean)
Eltabbakh et al.[11]	1999	15[b]	12.5

Median survival of DMPM using CRS + HIPEC

Authors[Ref.]	Year	No. of patients	Median survival (months)
Park et al.[12]	1999	18	26
Loggie et al.[13]	2001	12	34
Kerrigan et al.[14]	2002	25[a]	30
Feldman et al.[15]	2003	49	92
Sugarbaker et al.[16]	2003	67	68
Brigand et al.[17]	2005	15	46.7
Deraco et al.[18]	2005	49	N/A
Wagmiller et al.[19]	2005	27	68
Yan and Sugarbaker[20]	2005	65[b]	79

EJSO (2006)

Journal of Surgical Oncology 2008;98:268–272

5th International Workshop on Peritoneal Surface Malignancy
FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI MILANO
December 4 - 6, 2006 Milan (Italy)

Consensus Statement on Peritoneal Mesothelioma

MARCELLO DERACO, MD[1]* DAVID BARTLETT, MD,[2] SHIGEKI KUSAMURA, MD, PhD,[1] AND DARIO BARATTI, MD,[1]
[1]Department of Surgery, National Cancer Institute, Milan, Italy
[2]Department of Surgery, Division of Surgical Oncology, UPMC, University of Pittsburgh, Pittsburgh, Pennsylvania

Histology	Treatment
Multicystic	CRS + HIPEC
Papillary Well Differentiated	CRS + HIPEC
Epithelial Malignant	CRS + HIPEC±EPIC + sCT
Biphasic/Sarcomatoid	CRS + HIPEC±EPIC + sCT

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Malignant Peritoneal Mesothelioma: Multi-Institutional Experience

Tristan D. Yan, Marcello Deraco, Dario Baratti, Shigeki Kusamura, Dominique Elias, Olivier Glehen, François N. Gilly, Edward A. Levine, Perry Shen, Faheez Mohamed, Brendan J. Moran, David L. Morris, Terence C. Chua, Pompiliu Piso, and Paul H. Sugarbaker

- Patients: 405
- Institutions: 7
- Median follow-up:33 (1- 235)
- Mean age: 50 ys
- Epithelioid: 318 (79%)
- Biphasic or Sarcomatoid: 48 (12%)
- Positive Lymph node: (6%)
- Extra-abdominal metastases:(3%)
- CC: 0=102(25%); 1= 85(21%);
- 2: 86 (21%); 3= 39(10%)

Chemotherapy agent(s)	HIPEC		EPIC	
	n	%	n	%
Cisplatin + Doxorubicin or Cisplatin + Mitomycin C	325	87	16	17
Cisplatin alone	19	5	-	-
Mitomycin C	26	7	-	-
Paclitaxel	-	-	77	82
Others	2	1	1	1
Total	372	100	94	100

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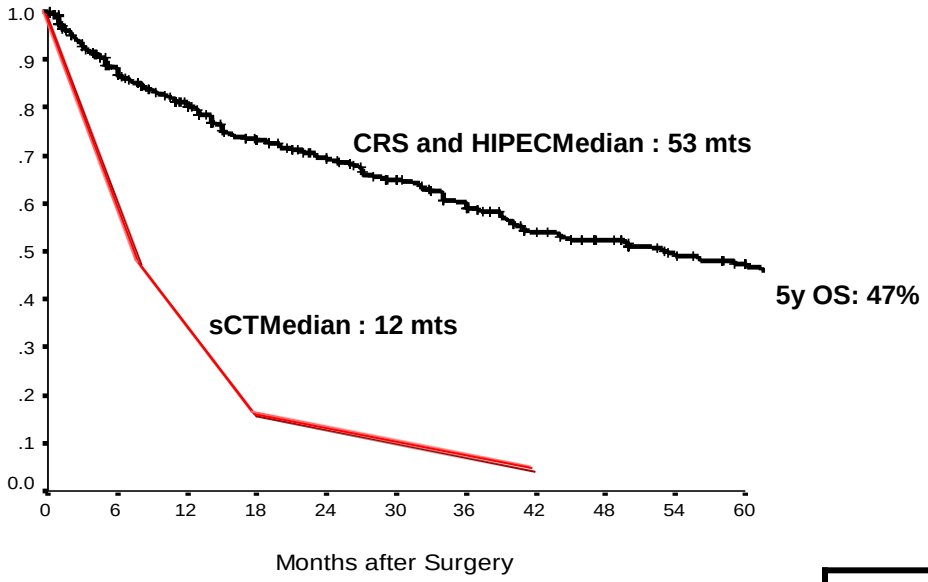

Multivariate analysis

Variable	hazard ratio	95% confidence interval	P Value
Epithelial Subtype	27.547	2.905 – 10.360	p < 0.001
Absence of Lymph Node Metastasis	13.929	1.749 – 6.017	p < 0.001
CCR-0/1	24.222	2.008 – 5.054	p < 0.001
HIPEC	9.489	0.219 – 0.713	p = 0.002

Annals of Oncology Advance Access published November 4, 2011

original article

Annals of Oncology
doi:10.1093/annonc/mdr477

Importance of gender in diffuse malignant peritoneal mesothelioma

C. Cao[1,2], T. D. Yan[1,2*], M. Deraco[3], D. Elias[4], O. Glehen[5], E. A. Levine[6], B. J. Moran[7], D. L. Morris[8], T. C. Chua[8], P. Piso[9] P. H. Sugarbaker[10]; Peritoneal Surface Malignancy Group[†]

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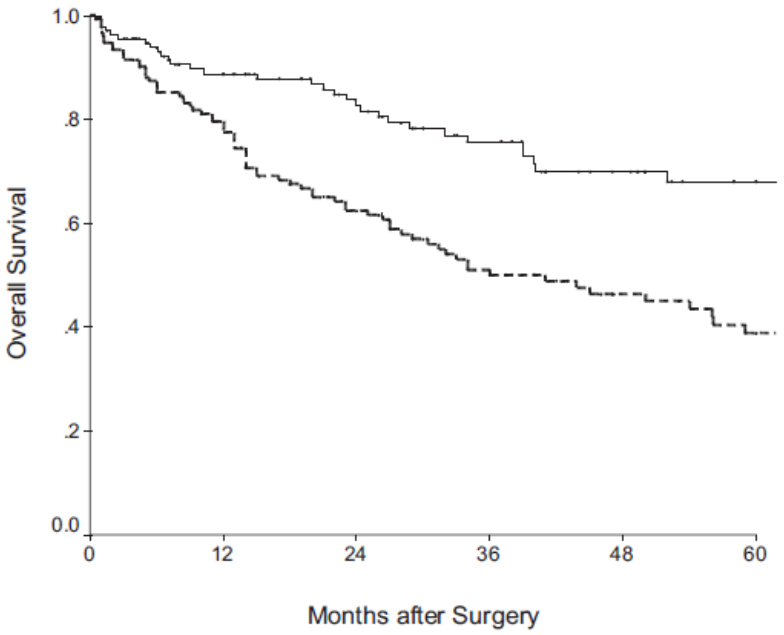
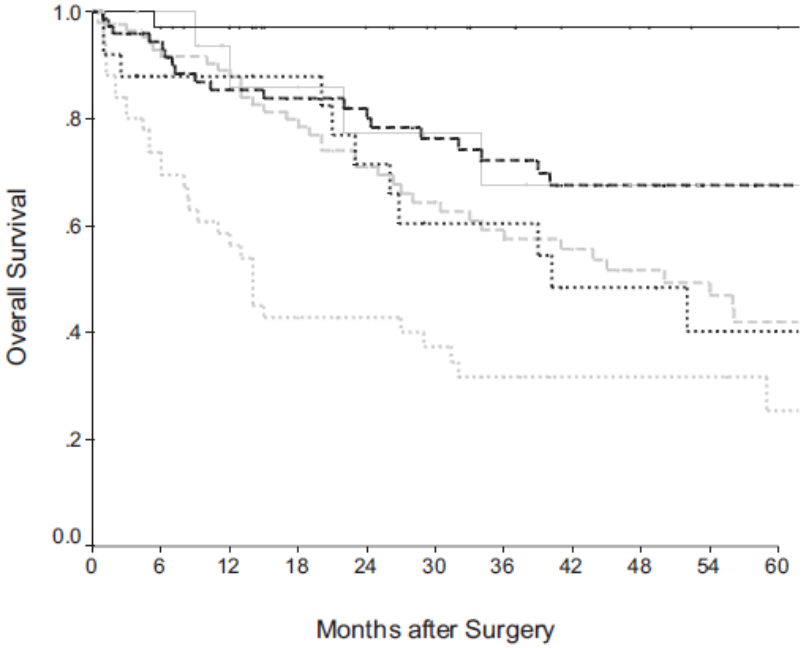
Received 7 July 2011; accepted 20 September 2011

Better Outcomes in Women





Multicystic and Well-differentiated Papillary Peritoneal Mesothelioma Treated by Surgical Cytoreduction and Hyperthermic Intra-peritoneal Chemotherapy (HIPEC)

D. Baratti, MD,[1] S. Kusamura, MD,[1] D. Nonaka, MD,[2] G. D. Oliva, MD,[1] B. Laterza, MD,[1] and M. Deraco, MD[1]

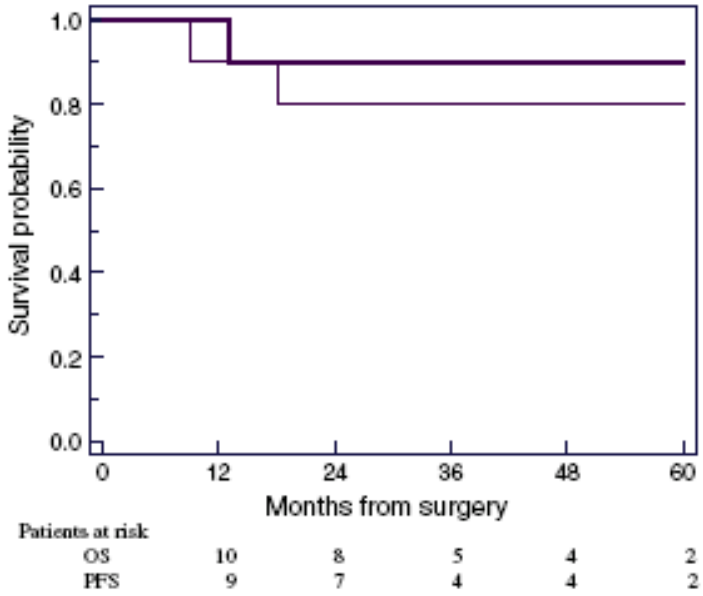


FIG. 1. Overall (heavier line) and progression-free survival (lighter line) in 12 patients treated with cytoreduction and HIPEC for multicystic and well-differentiated peritoneal mesothelioma.

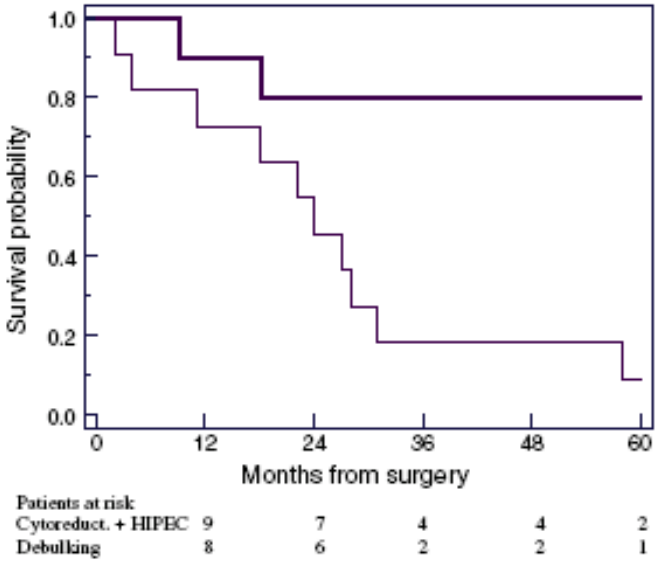


FIG. 2. Progression-free survival after cytoreduction with HIPEC for multicystic and well-differentiated peritoneal mesothelioma (heavier line) and after 11 debulking procedures performed in seven patients during their previous clinical history (lighter line) ($P = .0156$).

Peritoneal Surface Malignancies Program:The Team

- ***Experimental Oncology Unit***
- ***(N Zaffaroni)***
- Raffaella Villa
- Marzia Pennati
- Cinzia De Marco
- Mara Binda

- ***Dept Anestesiology (Prof. Langer)***
- Luca Fumagalli

- ***Medical Oncology Rare Tumor Unit (P Casali)***
- Rossella Bertulli

- ***PSM UNIT (M.Deraco)***
- Dario Baratti
- Shigeki Kusamura

- ***Dept. Pathology (G. Pelosi)***
- Silvana Pilotti
- Antonello Cabras
- Federica Perrone
- Genny Jocollé

- ***Nutrition Unit (C Gavazzi)***
- *A Sironi*

- ***ICU (M Favaro)***
- Valerio Costagli
- Fortunato D'Elia
- Renato Manzi
- Gabriella Perego
- Maurilia Rizzi
- Marco Faustini

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Sotto l'alto patrocinio
Presidenza del Consiglio dei Ministri

Peritoneal Mesothelioma

Multimodality Treatment with CRS and HIPEC

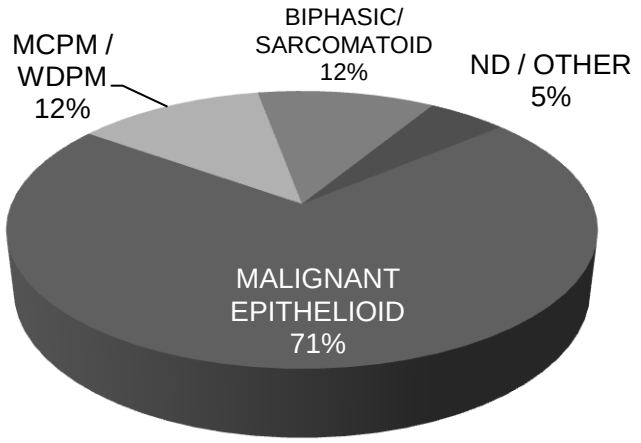
Patients: 155

Median estimated follow-up: 54.8 months

Median actuarial survival: 71.9 months

5-year actuarial survival: 55.6% (47%)

50% of patients: Cured



Mean duration of operations: 577 Min.

Mean Peritoneal cancer index: 19 (0-39)

G3-5 Morbidity rate: 33.5%

Peritoneal Surface Malignancies Program

FUTURE DIRECTIONS

MicroRNAs;

Telomere maintenance mechanisms:

Cancer stem cells:

RTKs;

Cytotoxic activity of new biological drugs

Mesothelin and Osteopontin

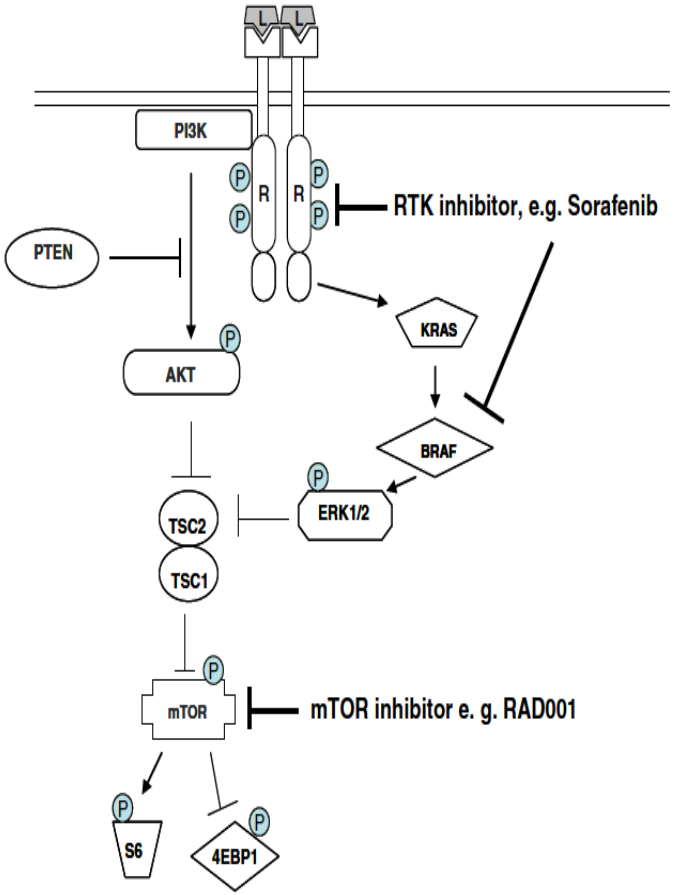
Etiology

Personalised Therapy and Translational Research

Receptor tyrosine kinase and downstream signalling analysis in diffuse malignant peritoneal mesothelioma

Federica Perrone [a], Genny Jocollè [a], Marzia Pennati [b], Marcello Deraco [c], Dario Baratti [c], Silvia Brich [a], Marta Orsenigo [a], Eva Tarantino [a], Cinzia De Marco [b], Claudia Bertan [a], Antonello Cabras [a], Rossella Bertulli [d], Marco Alessandro Pierotti [e], Nadia Zaffaroni [b], Silvana Pilotti [a,]*

- **study period: 2007-2008;**
- **frozen surgical samples specimens from 20 patients treated by CRS and HIPEC**



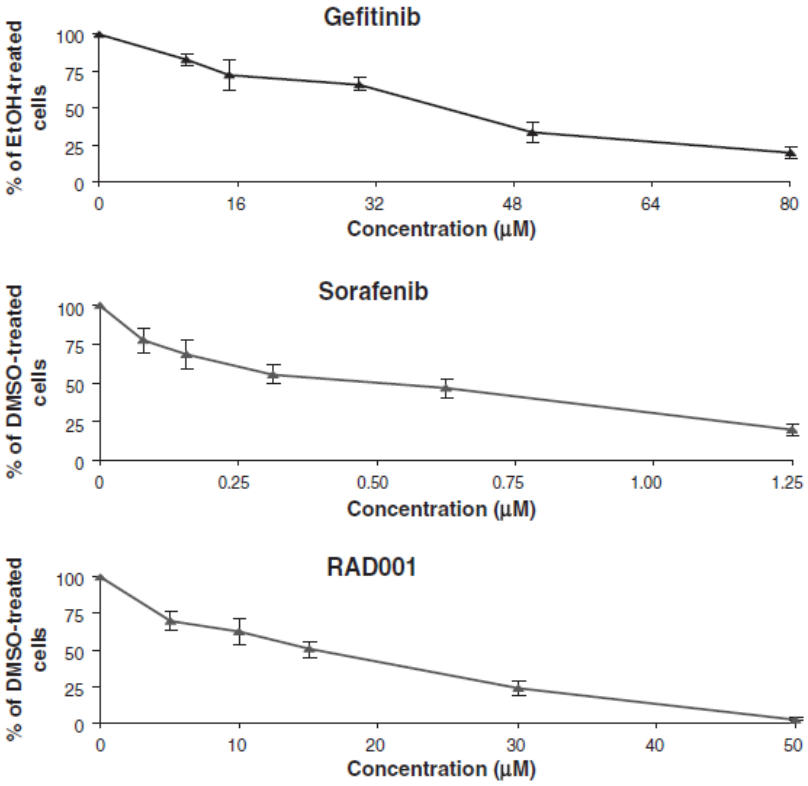
- 100% expression/ 90-75%phosphorylation of EGFR and PDGFRB;
- 85% expression/45%phosphorylation of PDGFRA;
- absence of RTK mutation and amplification;
- activation/expression of ERK1/2, AKT and mTOR, together with S6 and 4EBP1, in almost all the DMPMs;
- No KRAS/BRAF mutations,
- PI3KCA mutations/amplifications or PTEN; inactivation were observed.

Eur J Cancer (2010).

Receptor tyrosine kinase and downstream signalling analysis in diffuse malignant peritoneal mesothelioma

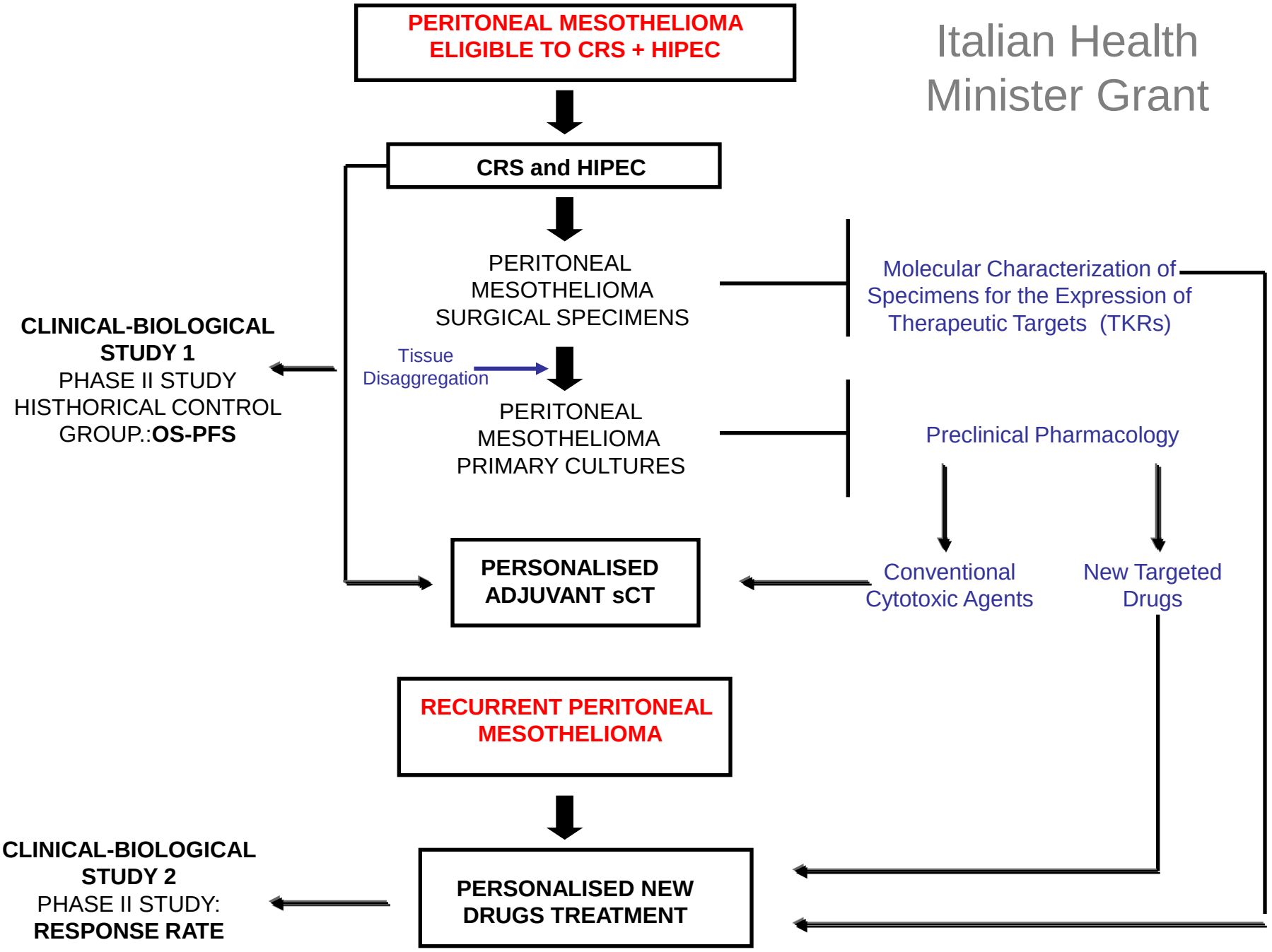
Federica Perrone [a], Genny Jocollè [a], Marzia Pennati [b], Marcello Deraco [c], Dario Baratti [c], Silvia Brich [a], Marta Orsenigo [a], Eva Tarantino [a], Cinzia De Marco [b], Claudia Bertan [a], Antonello Cabras [a], Rossella Bertulli [d], Marco Alessandro Pierotti [e], Nadia Zaffaroni [b], Silvana Pilotti [a,]*

Cytotoxic activity of gefitinib, sorafenib and RAD001 in a peritoneal mesothelioma cell line



- STO cell line (KRAS mutation G12D)
- resistant to gefitinib
- and sensitive to sequential treatment with RAD001 and sorafenib;

Eur J Cancer (2010).


PERITONEAL MESOTHELIOMA
ELIGIBLE TO CRS + HIPEC
Italian Health
Minister Grant
CRS and HIPEC
PERITONEAL
MESOTHELIOMA
SURGICAL SPECIMENS
Molecular Characterization of
Specimens for the Expression of
Therapeutic Targets (TKRs)
CLINICAL-BIOLOGICAL
STUDY 1
PHASE II STUDY
HISTHORICAL CONTROL
GROUP.:OS-PFS
Tissue
Disaggregation
PERITONEAL
MESOTHELIOMA
PRIMARY CULTURES
Preclinical Pharmacology
PERSONALISED
ADJUVANT sCT
Conventional
Cytotoxic Agents
New Targeted
Drugs
RECURRENT PERITONEAL
MESOTHELIOMA
CLINICAL-BIOLOGICAL
STUDY 2
PHASE II STUDY:
RESPONSE RATE
PERSONALISED NEW
DRUGS TREATMENT

PERITONEAL MESOTHELIOMA: CONCLUSION

DMPM appears as a disease characterized by various types of presentation, and by a poor prognosis;

comparing with pleural mesothelioma:

- similar pathologic behavior
- higher rate of women
- lower mean age
- lower association of asbestos exposure
- higher rate of resecability
- better prognosis

CRS + HIPEC IS THE STANDARD OF CARE

CPP better result vs SPP

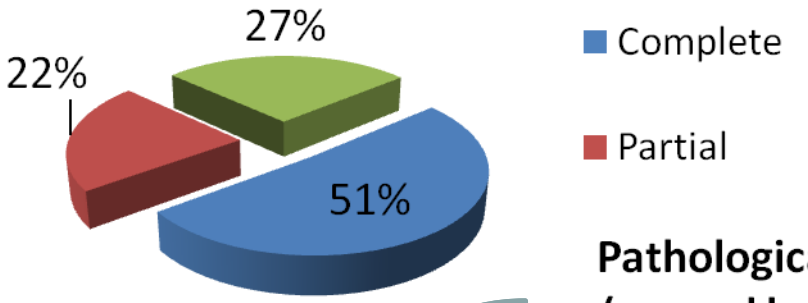
CC-0 vs CC-1 correlated to failure in critical anatomical areas, suggesting the need for maximal cytoreductive surgical efforts

sCT reccomended but differences beetwen pre or post operative

Research Programs are neded

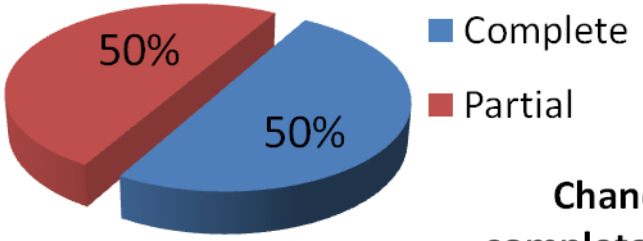
Epithelial ovarian cancer: Natural History

Clinical response to platin based firs line CT

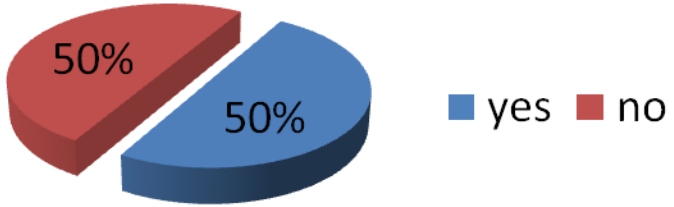


- High response to sCT
- 20-30% Platinum-resistant
- 60-70% Recur

Pathological response (second look surgery)



Chances of relapse among complete pathological responders



Primary OC Treatment

OC Recurrence Treatment

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

Primary EOC Treatment

Equinn W. Munnell

The changing prognosis and treatment in cancer of the ovary

A report of 235 patients with primary ovarian carcinoma 1952-1961

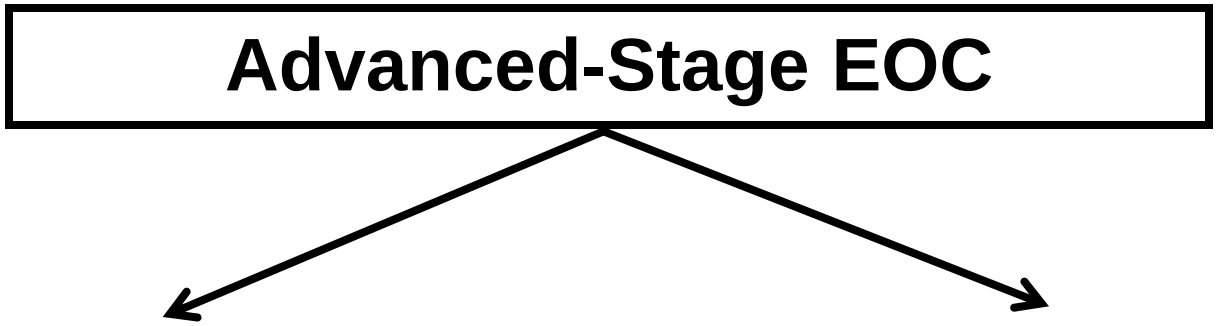
more extensive surgery and that the basic concept of surgery in cancer of the ovary should be the maximum surgery possible, when necessary resorting to omentectomy, appendectomy, and resection of localized peritoneal or intestinal metastases in addition to total hysterectomy and bilateral salpingo-oophorectomy.

recent 5 year survival rate of 40 per cent represents a significant improvement over the 28 per cent survival rate for the two previous studies. The reports analyzes the results and concludes the improvement was not due to earlier diagnosis or to a more favorable distribution of cases or to chemotherapy. It concludes that the improvement was due to the more frequent use of postoperative irradiation as well as to more aggressive and more extensive surgery and that the basic concept of surgery in cancer of the ovary should be the maximum surgery possible, when necessary resorting to omentectomy, appendectomy, and resection of localized peritoneal or intestinal metastases in addition to total hysterectomy and bilateral salpingo-oophorectomy.

Munnell. Am J Obstet Gynecol 1968; 100: 790.

Primary Surgical Treatment Paradigms

The Contemporary Divergence



Acceleration Paradigm

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

Deceleration Paradigm

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

Primary Cytoreductive Surgery

Simple Procedures

Pelvis	Abdomen
TAH+BSO	Infracolic omentectomy
Pelvic lymph node excision	Para-aortic node excision
Peritoneal nodules	Peritoneal nodules
Peritonectomy	Segmental bowel resection

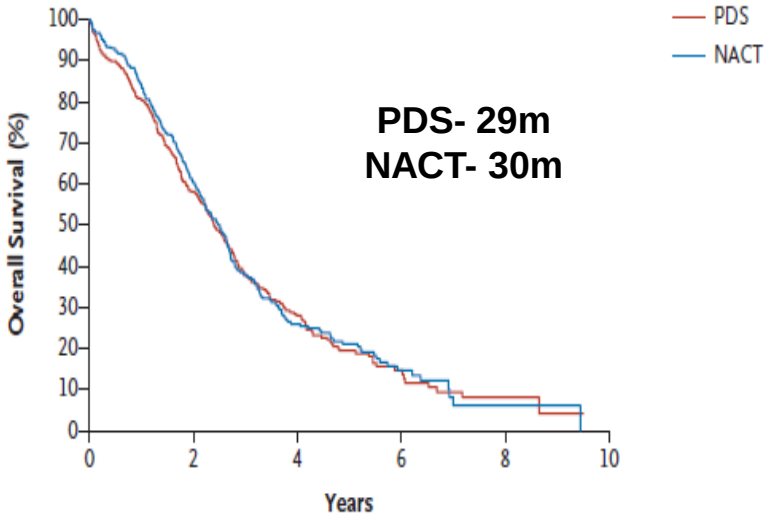
The NEW ENGLAND JOURNAL of MEDICINE

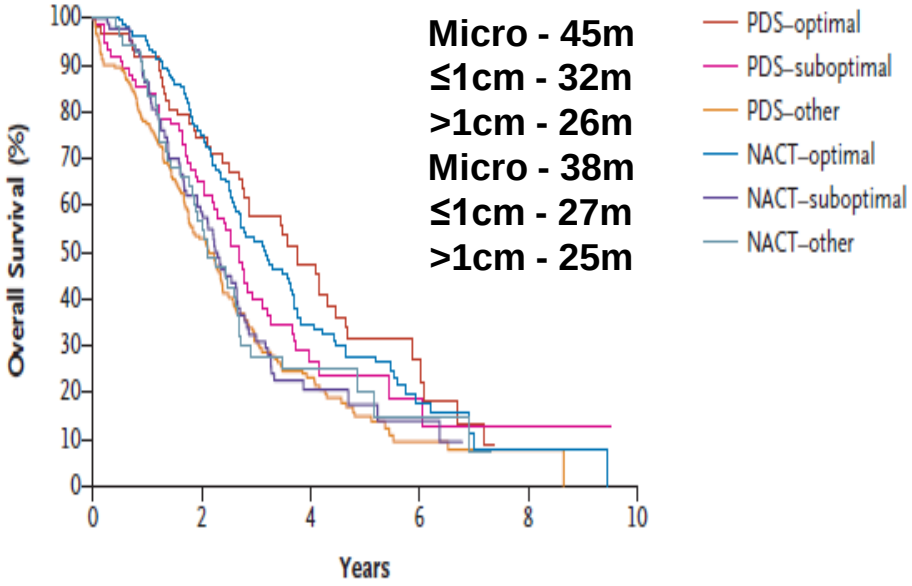
ORIGINAL ARTICLE

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 (median 5 patients)





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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

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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)

Primary Cytoreductive Surgery

Radical Procedures

Pelvis

Radical oophorectomy

Rectosigmoid colectomy

Pelvic node debulking

Resection of bladder/ureter

Resection of iliac vessels

Abdomen

Total omentectomy

Partial gastrectomy

Splenectomy

Distal pancreatectomy

Diaphragm peritonectomy

Diaphragm resection

Liver resection

Para-aortic node debulking

Nephrectomy

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

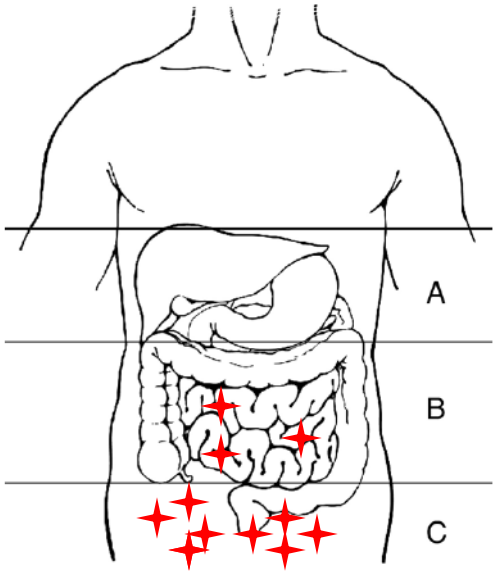


Fig. 1. Abdominopelvic regions. (A) Upper abdomen cephalad to the great omentum. (B) Mid-abdomen. (C) Pelvis.

No UAD
116 (24%)

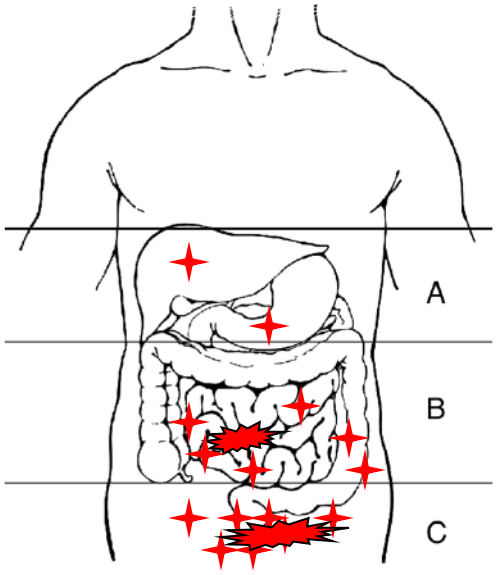


Fig. 1. Abdominopelvic regions. (A) Upper abdomen cephalad to the greater omentum. (B) Mid-abdomen. (C) Pelvis.

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

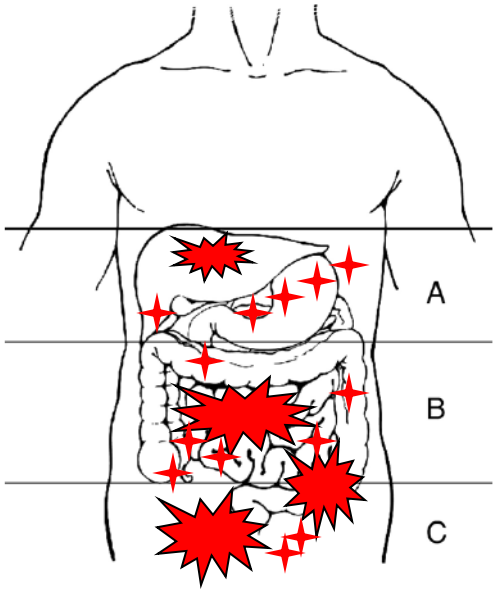


Fig. 1. Abdominopelvic regions. (A) Upper abdomen cephalad to the greater omentum. (B) Mid-abdomen. (C) Pelvis.

Bulky UAD
197 (42%)

Gynecologic Oncology 108 (2008) 287–292

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.

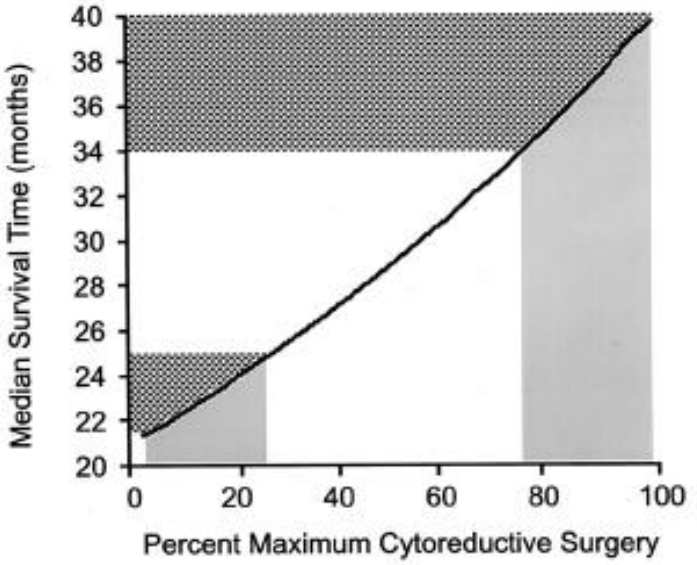


Fig 2. Simple linear regression analysis: de-logged median survival time plotted against percent maximal cytoreductive surgery. Gray area, maximal cytoreductive surgery ≤ 25% and > 75%; crosshatched area, corresponding range of median survival times.

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

Review

"Optimal" cytoreduction for advanced epithelial ovarian cancer: A commentary

Scott M. Eisenkop [a,*], Nick M. Spirtos [b], Wei-Chien Michael Lin [a]

[a] *Women's Cancer Center, Southern California, 4835 Van Nuys Blvd., Suite 109, Sherman Oaks, CA 91403, USA*
[b] *Women's Cancer Center, University of Nevada School of Medicine, 3131 La Canada Ave., Suite 110, Las Vegas, NV 89101, USA*

Received 8 May 2006
Available online 31 July 2006

Conclusions:

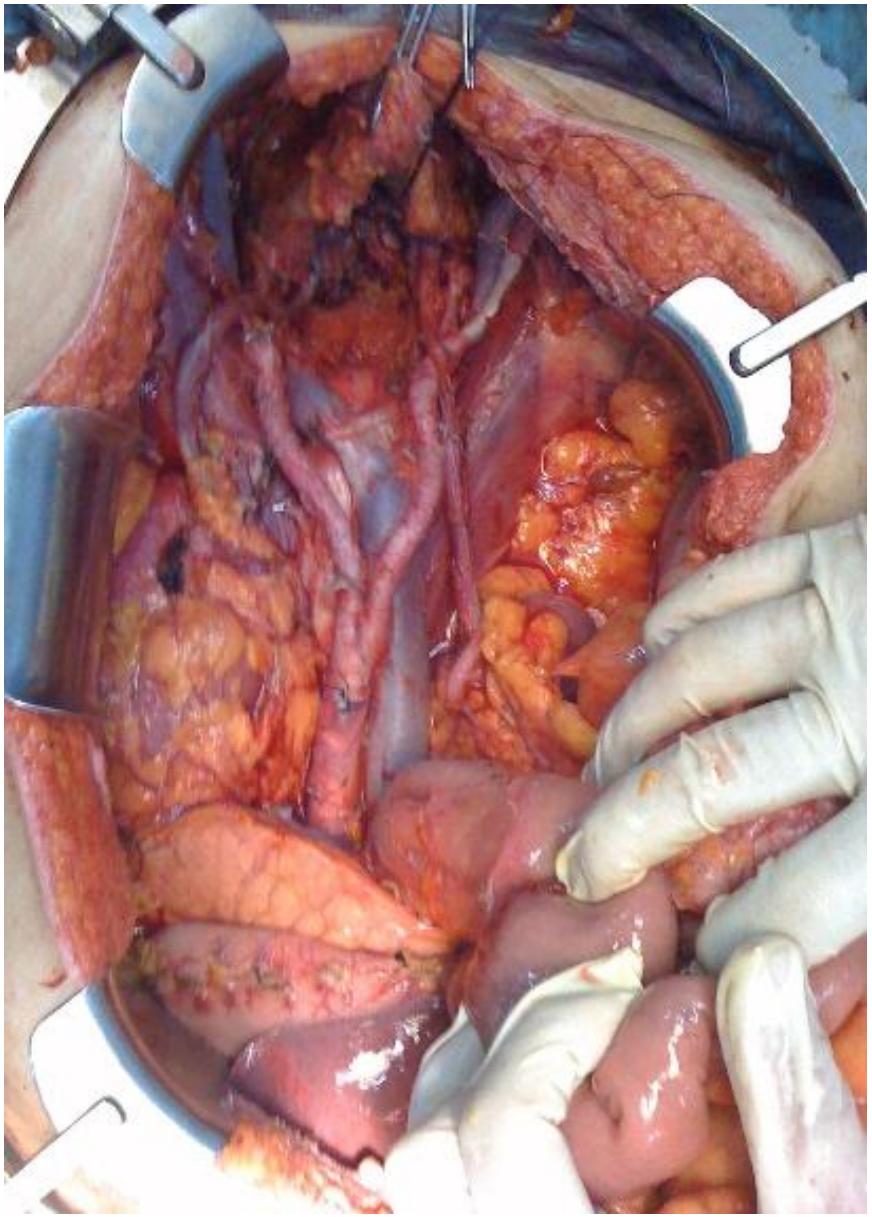
•Complete primary cytoreduction improves the prognosis for survival significantly more than a small dimension of residual disease

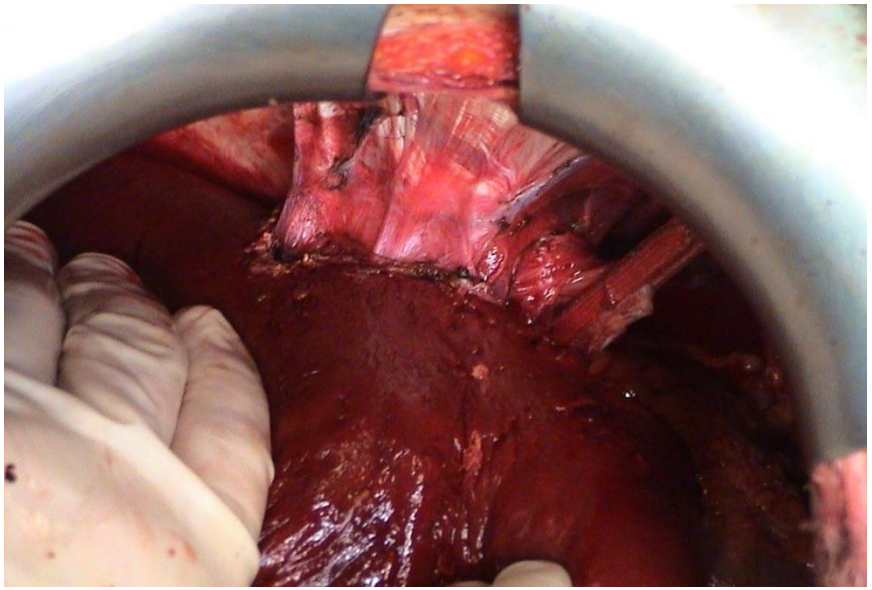
•Available data justify elimination of macroscopic disease to be the most appropriate objective of primary cytoreductive surgery

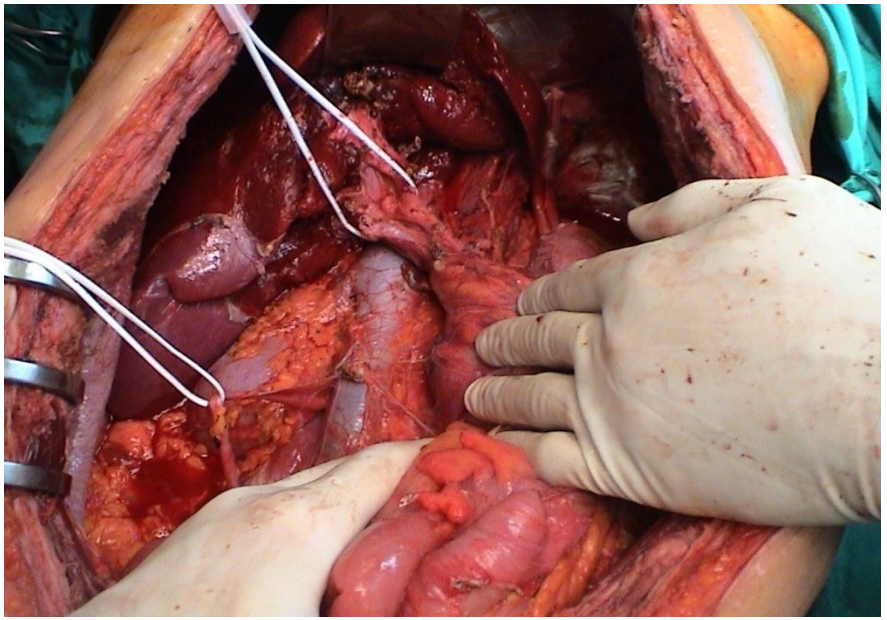
•The term "optimal" should be applied to patients undergoing complete cytoreduction.

Gynecologic Oncology 103 (2006) 329–335

CRS-PP







Evolution of Surgical Treatment Paradigms for Advanced-Stage EOC

What is 'optimal' residual disease, really?

Optimal: complete cytoreduction to a visibly disease-free state (microscopic residual)

Sub-optimal: residual disease measuring ≤1cm in maximal diameter

Non-optimal: residual disease measuring >1cm in maximal diameter

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]

Variable	Group 1 ($n=168$)	Group 2 ($n=210$)	P value
Extensive upper abdominal procedure	0 (0%)	79 (38%)	<0.001
Upper Abdominal Procedure(s)			
Residual disease	19 (11		
None grossly visible			
0.1–1 cm	59 (35		
>1 cm	90 (54		
Estimated blood loss (L)			
<1	142 (85		
1–2	16 (10		
2–3	3 (2%		
>3	1 (1%		
N/A	6 (4%		
Intraoperative units blood transfused Units Blood Tr			
None	134 (80		
1–2	20 (12		
3–4	6 (3%		
≥5	0 (0%		
N/A	8 (5%		
Operative time (minutes)			
≤120	38 (23		
120–240	86 (51		
241–360	20 (12		
>360	5 (3%		
N/A	19 (11		
Major complications			
Infectious	7 (4%		
Gastrointestinal	3 (2%		
Hematologic	0 (0%)	5 (2%)	
Cardiopulmonary	1 (0.6%)	4 (2%)	
Thromboembolic	3 (2%)	3 (1%)	
Systemic taxane–platinum chemotherapy Taxane–Platinum Chemotherapy			
Initiated therapy			NS
Completed ≥5 cycles	141 (84%)	184 (88%)	NS
Intraperitoneal chemotherapy after second-look surgery	70 (42%)	77 (37%)	NS

Gynecologic Oncology 114 (2009) 26–31

Recurrent EOC Treatment

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.***

Secondary Cytoreductive Surgery

Most of the evidence for surgical treatment in rEOC are based on platinum sensitive disease;

Secondary CRS is usually not offered for:

- *progression disease during the first line platinumchemotherapy (platinum refractory)*
- *recurrent disease within less than six months of primary treatment (platinum resistant).*

These patients usually have poor prognosis and do not benefit from further surgical attempts at cytoreduction

(Eisenkop 2000; Scarabelli 2001; Tebes 2007).

Review

Cytoreductive surgery for recurrent ovarian cancer: A meta-analysis

Robert E. Bristow [a,*], Isha Puri [a], Dennis S. Chi [b]

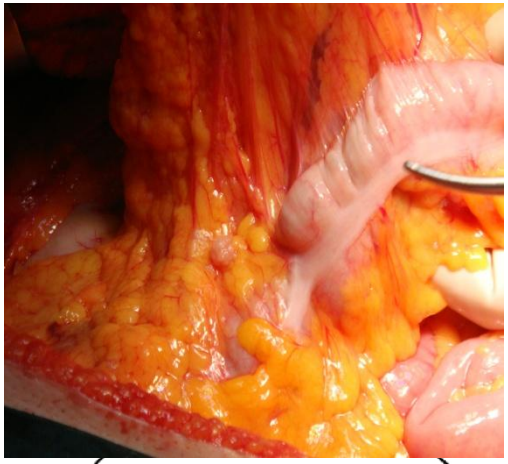
[a] The Kelly Gynecologic Oncology Service, Departments of Gynecology and Obstetrics and Oncology, The Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins Medical Institutions, 600 North Wolfe Street, Phipps #281, Baltimore, Maryland 21287, USA
[b] Gynecology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

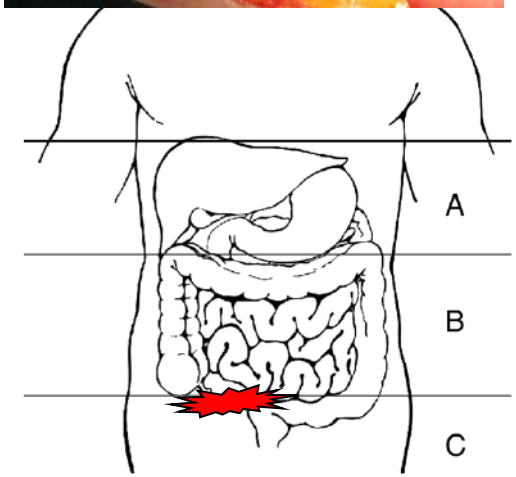
Parameters	Mean Weighted Proportion	Range
Optimal Surgical Resection	70.3%	22.2% to 100%.
Complete Cytoreduction	52.2%	9.4% to 100%
Median Estimated Blood Los	587 cm3	300 -1000 cm3
Median Operative Time	233 min.	130-588 min.
Bowel Resection	45%	0-80%
Peri-Operative Morbidity	19,2%	0-88%
Peri-Operative Mortality	1,3%	0-5,5%
Median Survival Time	30,3 months	10-62 months

- IP or postoperative sCT: 1221 pts;
- HIPEC: 62 pts

R.E. Bristow et al. / Gynecologic Oncology 112 (2009) 265–274

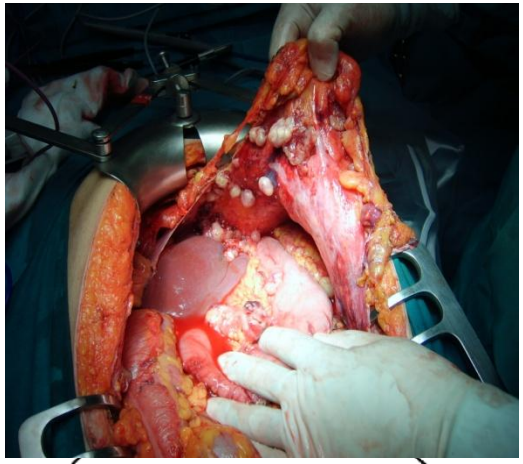
Recurrent EOC: Scenarios

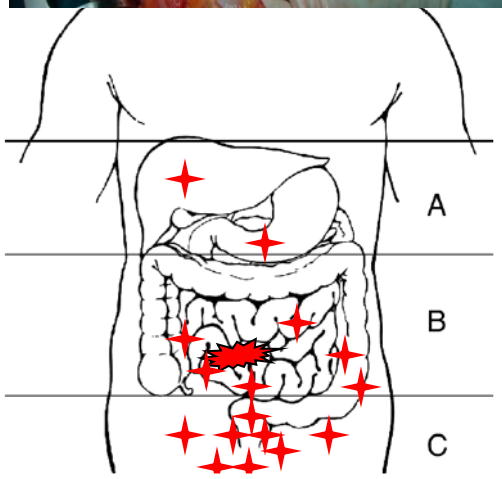




Single Site

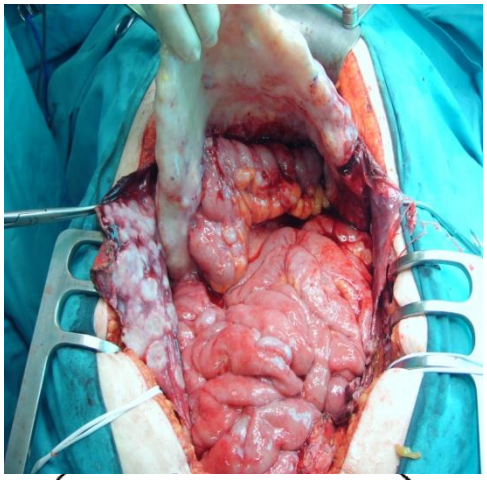
Ascite: NO

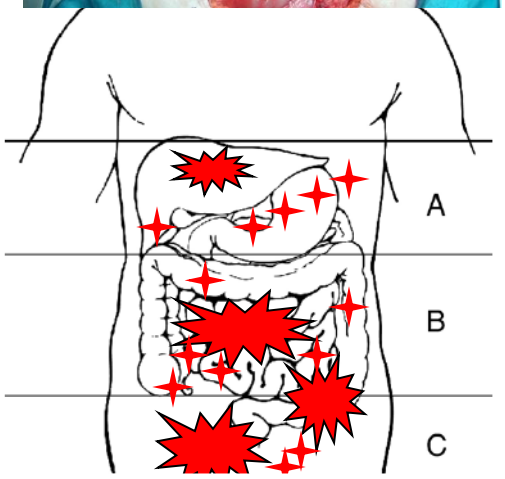




Multiple Site

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)	

The Role of HIPEC after CRS

Primay EOC

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

PATIENTS' CHARACTERISTIC

Histological subtype **Serous AdenoCA**		26
Grade	1/2	4
	3	22
Stage	III	25
	IV	1 (proximal vagina)
CA125	>35	24

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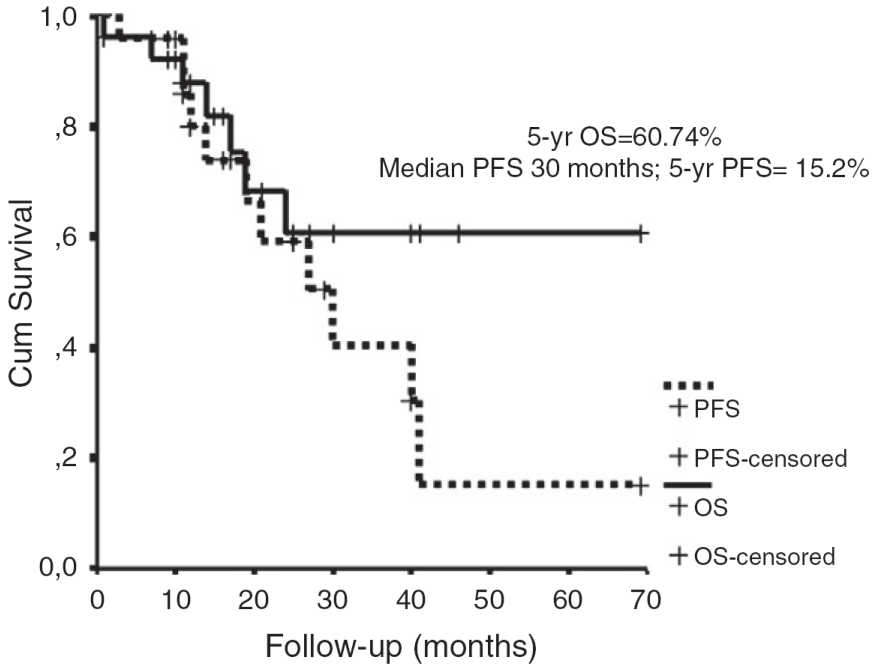
[d] General Surgery Unit, G. Martino Hospital, University of Messina, Via Consolare Valeria, 98125 Messina, Italy

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

The Role of HIPEC after CRS

Recurrent EOC

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

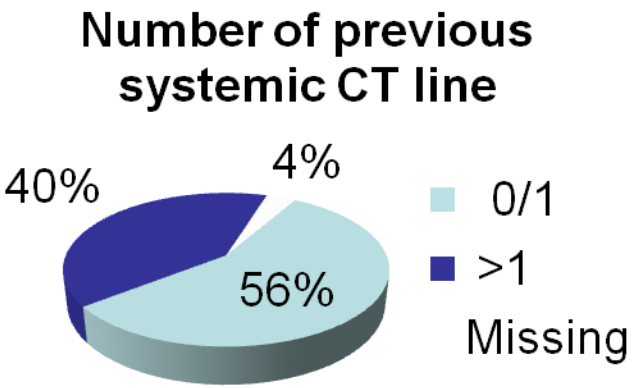
Four Italian centres:

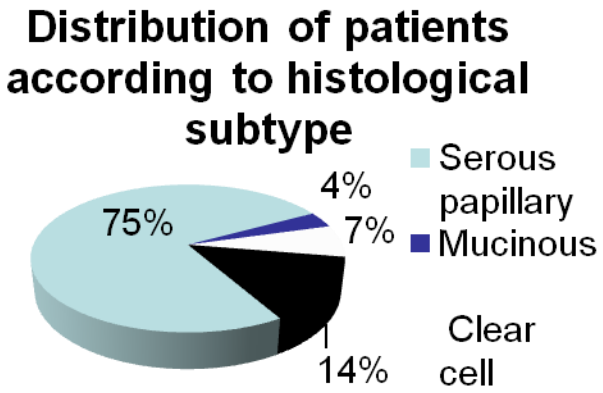
- National Cancer Institute (NCI) of Milan
- General Surgery Unit of Messina's University
- Bentivoglio's hospital
- Manerbio's hospital

BJOG An International Journal of Obstetrics and Gynaecology

PATIENT'S CHARACTERISTICS

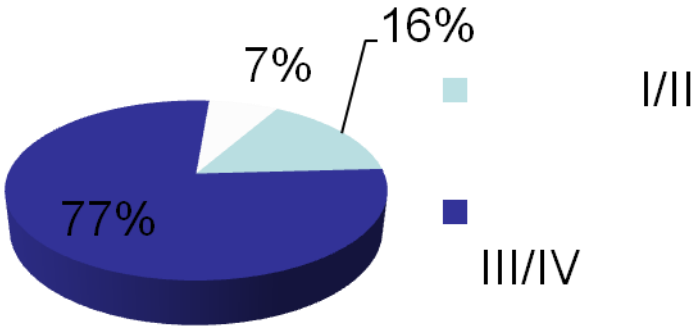
- April 1995 to May 2010
- Fifty-six patients
- Mean age: 55.2 years (30-75)
- Mean preoperative serum albumin: 4.0 g/dl (2.2-5.4)
- Performance Status: 33 = PS-0, 19 = PS-1, 5= PS-2.
- Previous surgical score (PSS):23= PPS-0, 13=PPS-1, 19=PPS-2, 2=PPS-3.
- Ca 125 (U/ml) >35: 46%



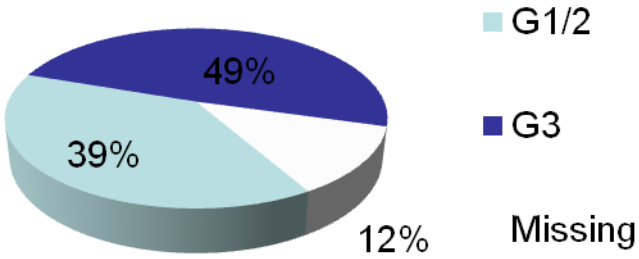


PATIENT'S CHARACTERISTICS

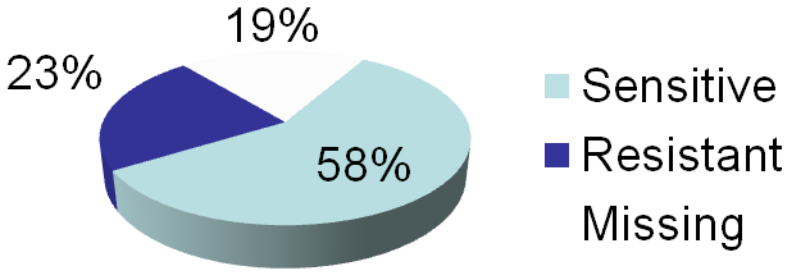
Distribution of patients' according to FIGO stage



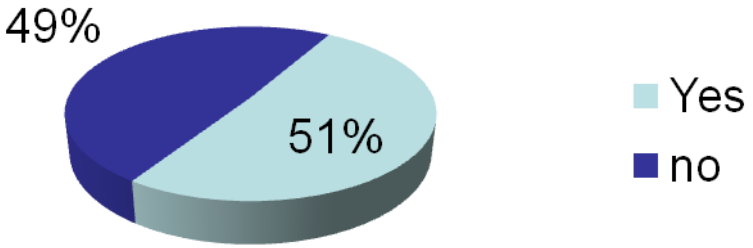
Distribution of patients according to tumor grading



Distribution of patients' according to platin-resistance



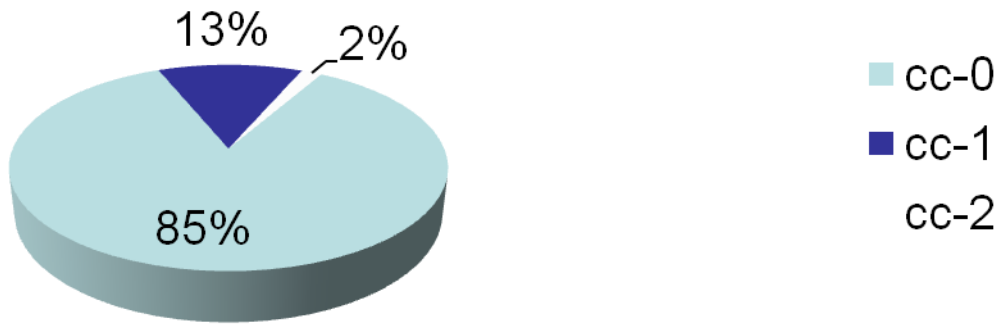
Distribution of patients' according to presence of ascites



RESULTS

- Median PCI: 15.2 (range: 4–30)
- Median operative time: 563 minutes (240-840)
- Median length of stay: 27.6 days (7–108)

Distribution of patients' according to completeness of cytoreduction



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

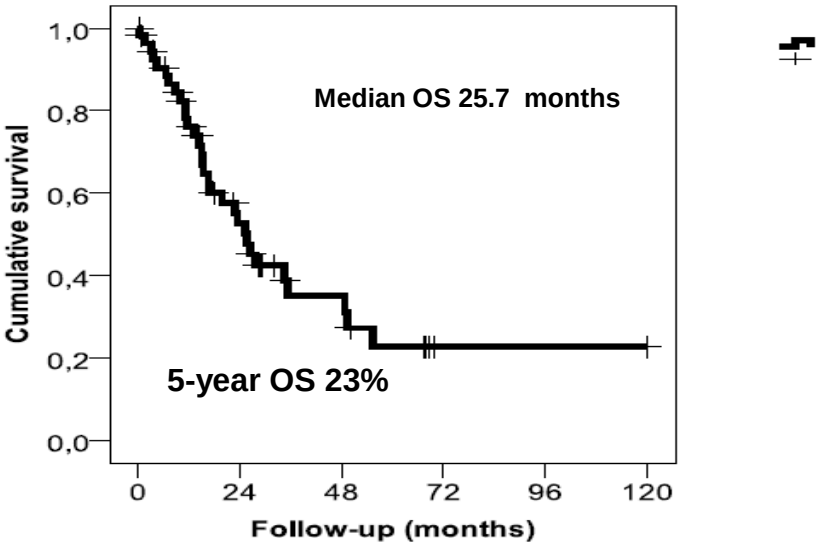
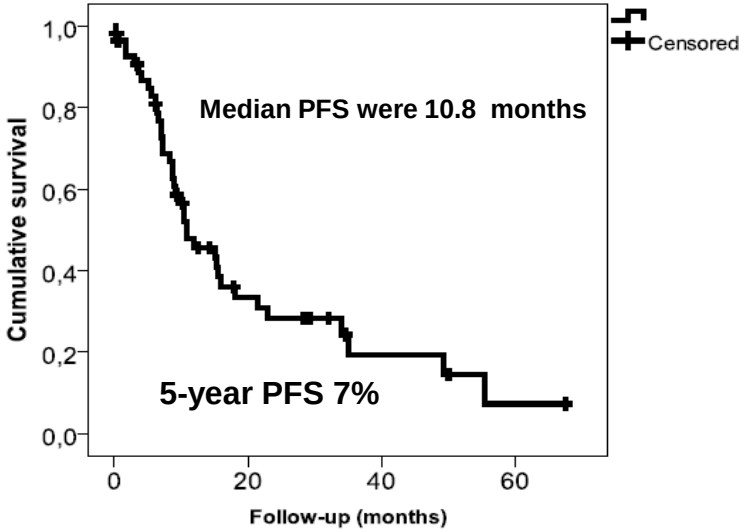


Figure 1B: PFS in recurrent EOC treated by CR+HIPEC



BJOG An International Journal of Obstetrics and Gynaecology

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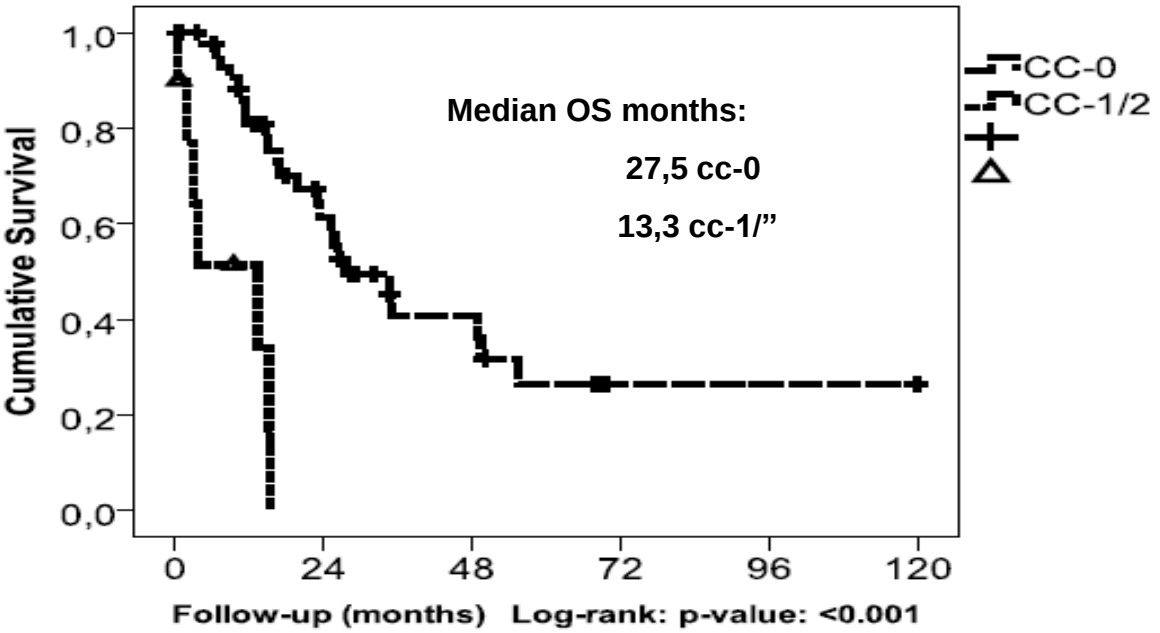
Figure 2: Overall survival according to completeness of cytoreduction



ANALYSIS

Variables correlated with OS by univariate analysis:

•ECOG performance status;

• Preoperative serum albumin level;

• Histological grading;

•Previous surgical score;

•Completeness of cytoreduction.

Variables correlated with OS at the multivariate analysis

•ECOG performance status (HR: 5.89, 95%CI: 2.08-16.71, p-value: 0.001);

•Preoperative serum albumin (HR: 3.89, 95%CI: 1.42-10.69, p-value: 0.008);

•Completeness of cytoreduction (HR: 4.40, 95%CI: 1.55-12.51, p-value: 0.005).

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

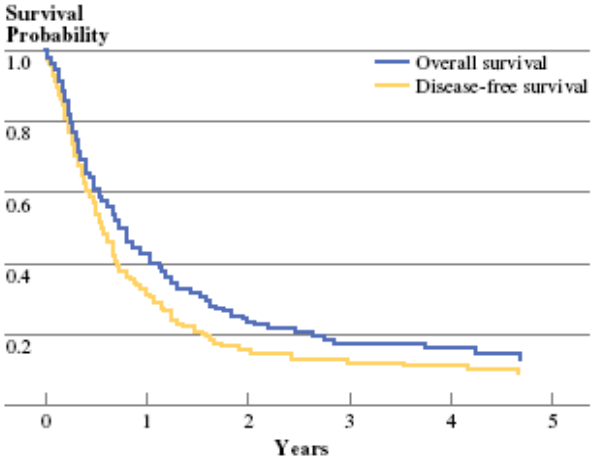
Gastric Cancer

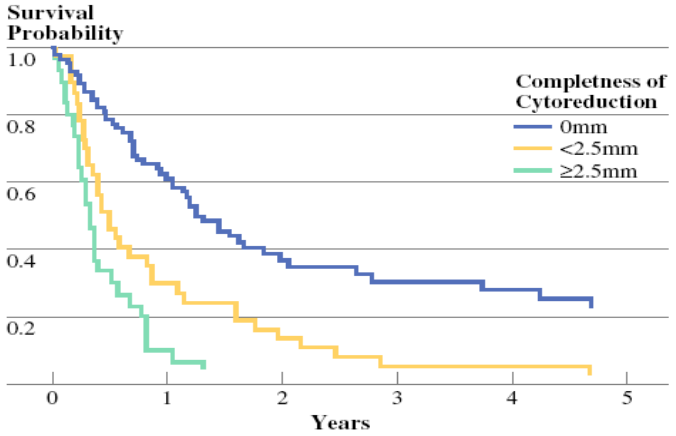
- **5th most common form of cancer (171,000 cases) in Europe (2004)**

- **3th most common cause of death due to cancer (137,000 deaths)**

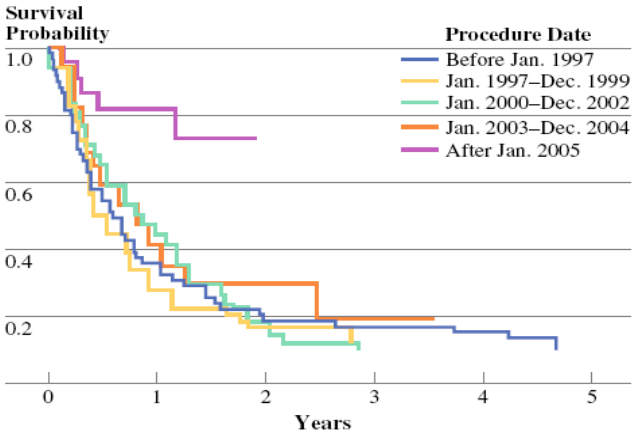
Peritoneal Carcinomatosis from Gastric Cancer: A Multi-Institutional Study of 159 Patients Treated by Cytoreductive Surgery Combined with Perioperative Intraperitoneal Chemotherapy

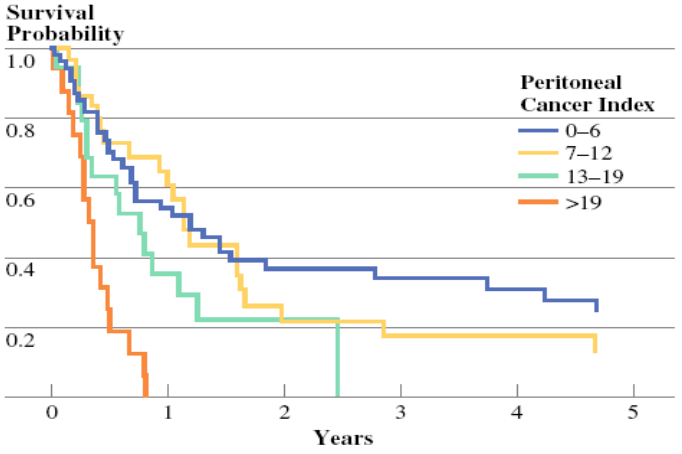
Olivier Glehen, MD, PhD[1], François Noel Gilly, MD, PhD[1], Catherine Arvieux, MD, PhD[2], Eddy Cotte, MD[1], Florent Boutitie[3], Baudouin Mansvelt, MD, PhD[4], Jean Marc Bereder, MD[5], Gérard Lorimier, MD[6], François Quenet, MD[7], Dominique Elias, MD, PhD[8] and Association Française de Chirurgie





159 Pt WITH PC from GC





Ann Surg Oncol 2010

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy Improves Survival of Patients with Peritoneal Carcinomatosis from Gastric Cancer: Final Results of a Phase III Randomized Clinical Trial

Xiao-Jun Yang, MD[1], Chao-Qun Huang, MD[1], Tao Suo, MD[2], Lie-Jun Mei, MD[1], Guo-Liang Yang, MD[1], Fu-Lin Cheng, MD[1], Yun-Feng Zhou, MD, PhD[1], Bin Xiong, MD, PhD[1], Yutaka Yonemura, MD, PhD[3], and Yan Li, MD, PhD[1]

Patients: 68

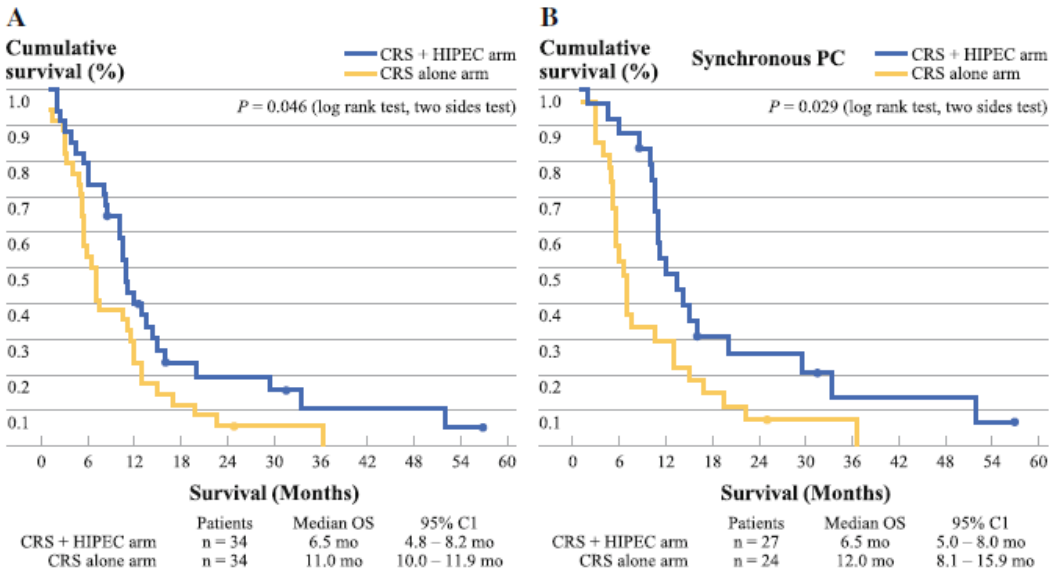
•Sync: 51

•Rec: 17

Median OS

•CRS+HIPEC: 11.0 mts

•CRS: 6,5 mts



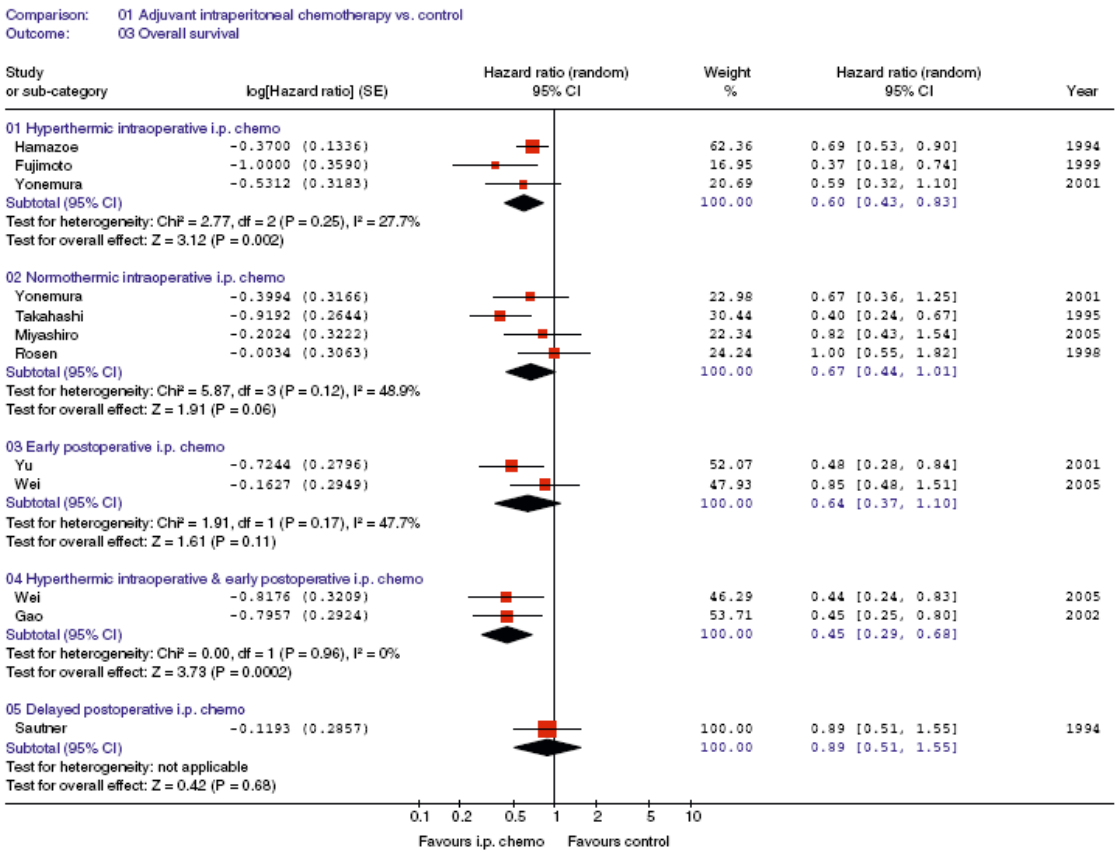
Covariate	χ^2	*P* value	Hazard ratio	95% CI
Sex (M vs. F)	0.099	0.753	1.101	0.605–2.002
Age (<60 years vs. ≥60 years)	0.638	0.425	1.275	0.702–2.317
PCI (low PCI vs. high PCI)	0.292	0.589	1.222	0.590–2.529
Treatment (CRS + HIPEC vs. CRS alone)	9.871	0.002	2.617	1.436–4.769
PC state (synchronous vs. metachronous)	5.438	0.02	2.228	1.136–4.367
CC (0–1 vs. 2–3)	8.585	0.003	2.794	1.405–5.556
Chemotherapy (≥6 vs. <6 cycles)	15.649	0	3.344	1.838–6.061
SAE (no vs. yes)	13.765	0	4.295	1.989–9.274

PCI Peritoneal carcinomatosis index, *CRS* cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *PC* peritoneal carcinomatosis, *CC* completeness of cytoreduction, *SAE* serious adverse events

Ann Surg Oncol (2011) 18:1575–1581

A Systematic Review and Meta-analysis of the Randomized Controlled Trials on Adjuvant Intraperitoneal Chemotherapy for Resectable Gastric Cancer

Tristan D. Yan, BSc (Med) MBBS,[1,2] Deborah Black, BSc DipEd MStat PhD,[3] Paul H. Sugarbaker, MD,[2] Jacqui Zhu, BSc (Med),[4] Yutaka Yonemura, MD, PhD,[5] George Petrou, BSc (Med) MBBS,[1] and David L. Morris, MD, PhD[1]



Annals of Surgical Oncology 14(10):2702–2713

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