The experience of the National Institute of Tumori in peritoneal mesothelioma

Marcello Deraco M.D.

Responsible

Peritoneal Surface Malignancies

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 .

Guidelines for Pathologic Diagnosis of Malignant Mesothelioma

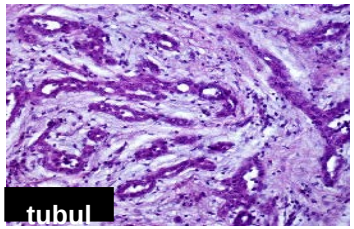
2012 Update of the Consensus Statement from the International Mesothelioma Interest Group

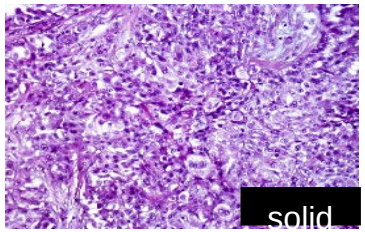
Aliya N. Husain, MD; Thomas Colby, MD; Nelson Ordonez, MD; Thomas Krausz, MD; Richard Attanoos, MB, BS; Mary Beth Beasley, MD; Alain C. Borczuk, MD; Kelly Butnor, MD; Philip T. Cagle, MD; Lucian R. Chirieac, MD; Andrew Churg, MD; Sanja Dacic, MD, PhD; Armando Fraire, MD; Francoise Galateau-Salle, MD;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

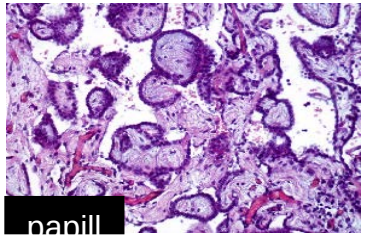
Table 4. Histologic Subtypes and Patterns[a] of Malignant Mesothelioma

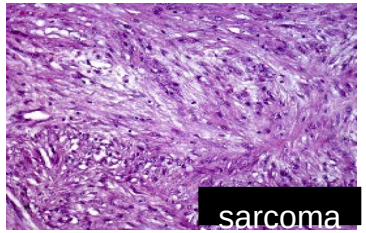
- Epithelioid mesothelioma
  - Tubulopapillary
  - Micropapillary
  - Trabecular
  - Acinar
  - Adenomatoid
  - Solid
  - Clear cell
  - Deciduoid
  - Adenoid cystic
  - Signet ring cell
  - Small cell
  - Rhabdoid
  - Pleomorphic
- Sarcomatoid mesothelioma
  - Conventional, spindle cell
  - Desmoplastic
  - 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.









Arch Pathol Lab Med

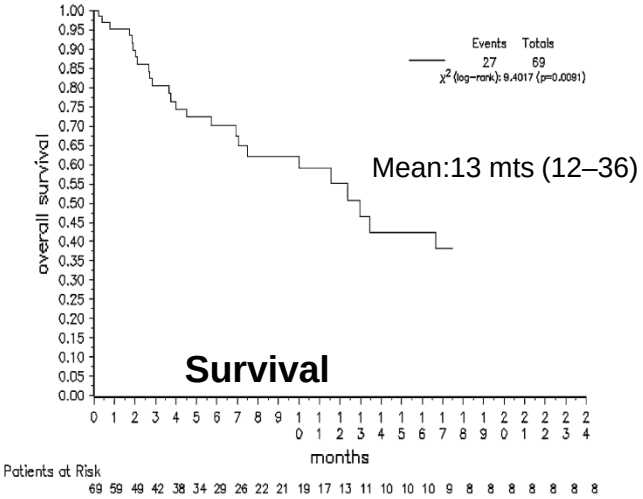
Malignant peritoneal mesothelioma: a multicenter study on 81 cases

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

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. 2011 May 1;117(9):1855-63

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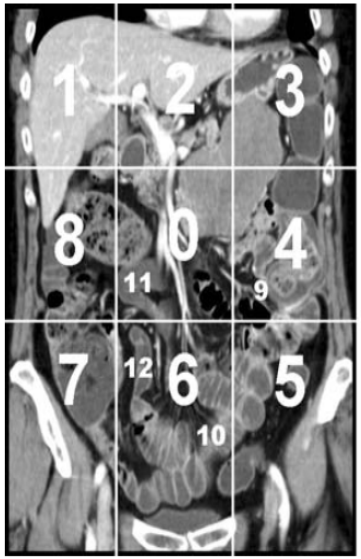


REGIONS

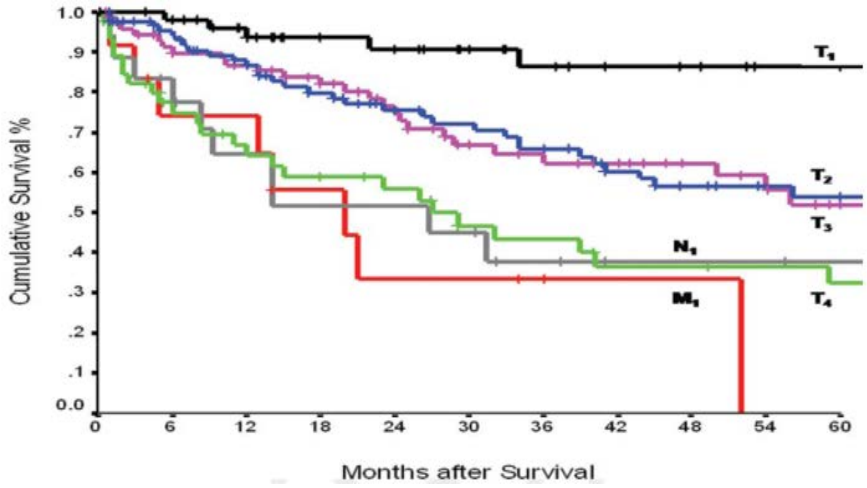
0 = Central
1 = Right upper
2 = Epigastrium
3 = Left upper
4 = Left flank
5 = Left lower
6 = Pelvis
7 = Right lower
8 = Right flank

9 = Upper jejunum
10 = Lower jejunum
11 = Upper ileum
12 = Lower ileum

Lesion size score	Cm
LSS-0	No detectable
LSS-1	<0.5
LSS-2	0-5-5
LSS-3	>5

Sugarbaker, Ann Surg 1995

PCI as a Prognostic Indicators of Survival



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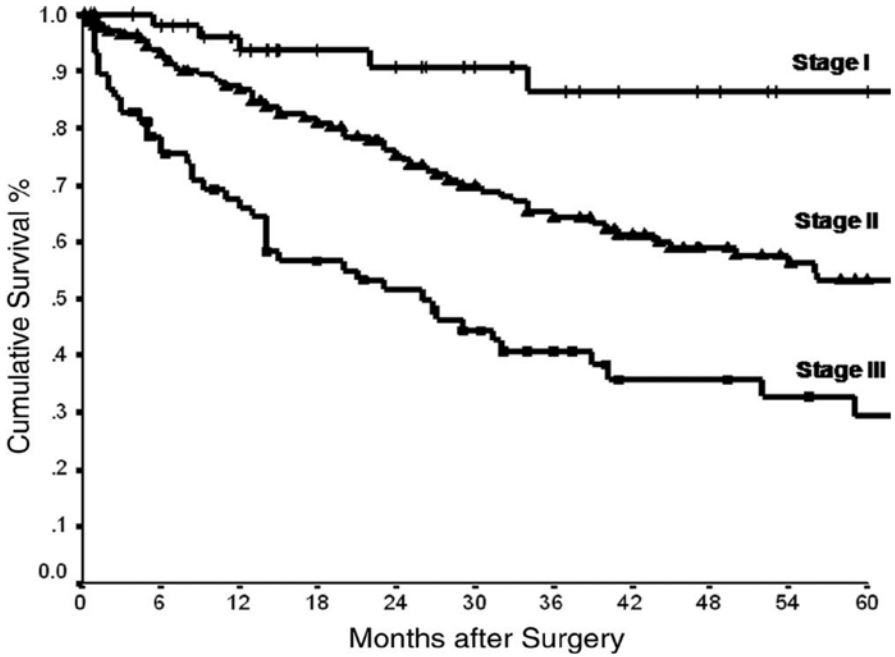


Stage	N	Median	1-year	3-year	5-year
I	52	Not reached	94	87	87
II	166	67	87	64	53
III	76	26	66	41	29

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. 2011 May 1;117(9):1855-63

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
Epithelial Malignant	CRS + HIPEC±EPIC + sCT
Biphasic/Sarcomatoid	CRS + HIPEC±EPIC + sCT

Peritonectomy Procedures

Paul H. Sugarbaker, M.D.

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

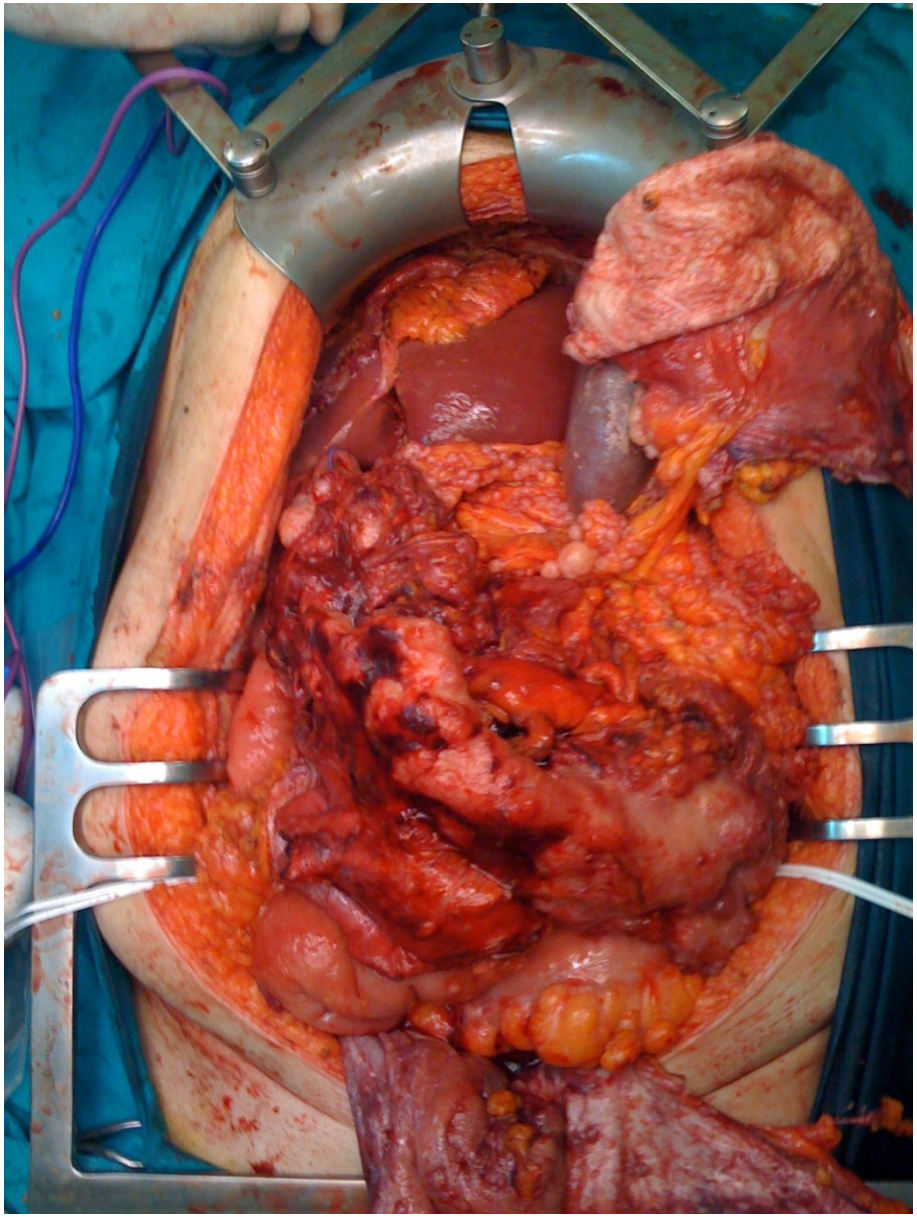
The Concept of Cytoreductive Surgery with Peritonectomy Procedures

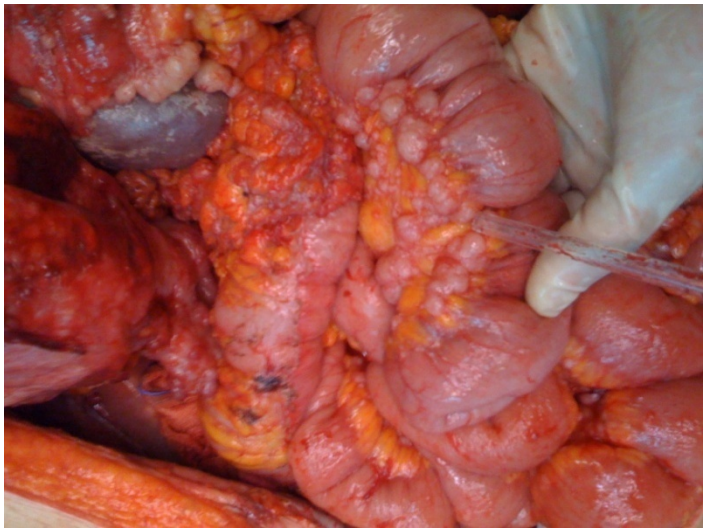
- Means a complete removal of all macroscopic tumor in the peritoneal cavity;

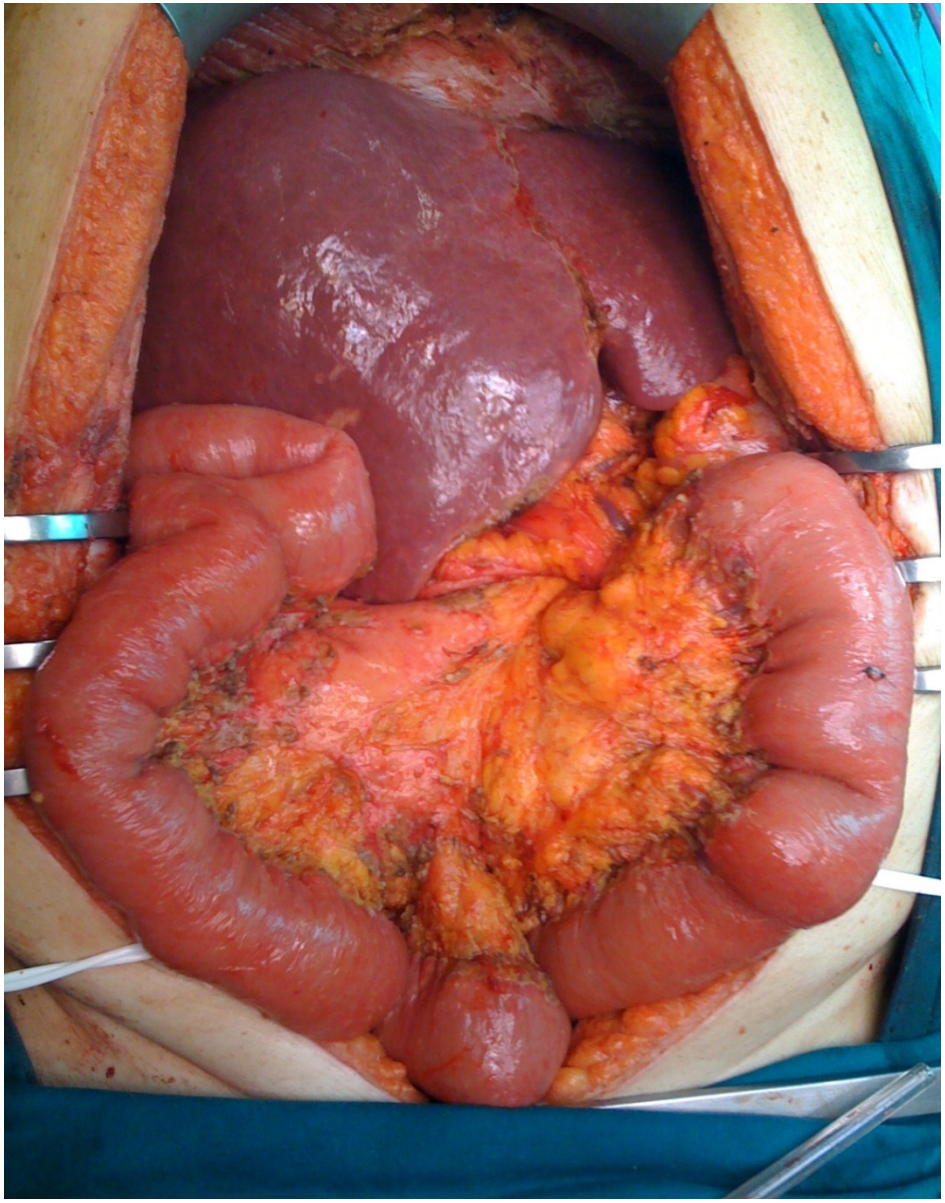
- It could require Peritonectomy Procedures eventually associated with intestinal and/or organ resection

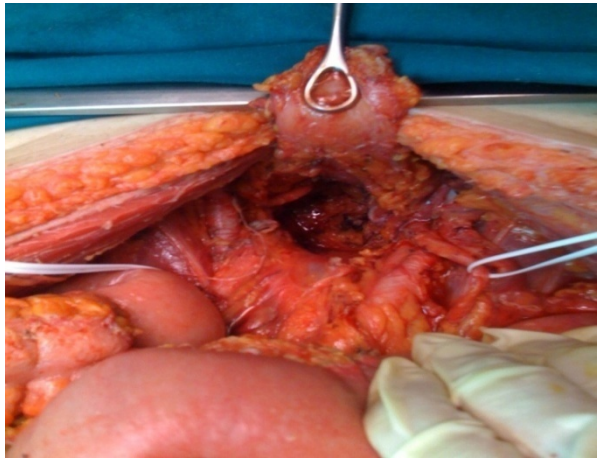
Abdominal regions	Peritonectomies	Visceral resections
Right upper	Right sub-phrenic peritonectomy, Glisson's capsule dissection	
Left upper	Left sub-phrenic peritonectomy	
Antero-lateral	Stripping of paracolic gutters, Greater omentectomy	Splenectomy, appendectomy, right colectomy
Sub-hepatic	Lesser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

Ann. Surg. • January 1995





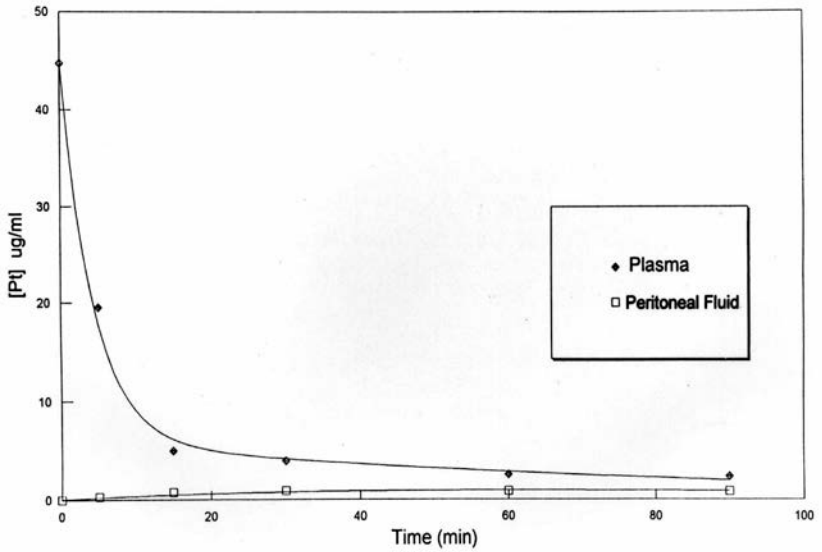


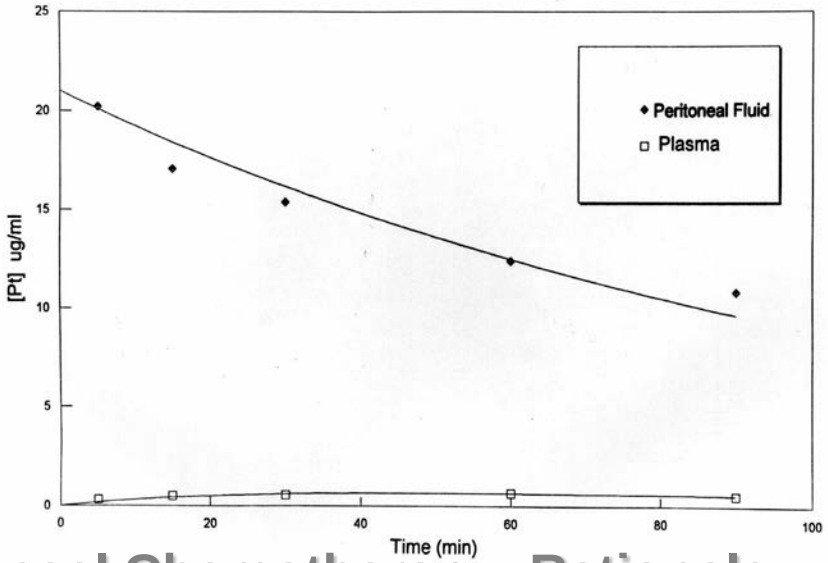


Intravenous Administration

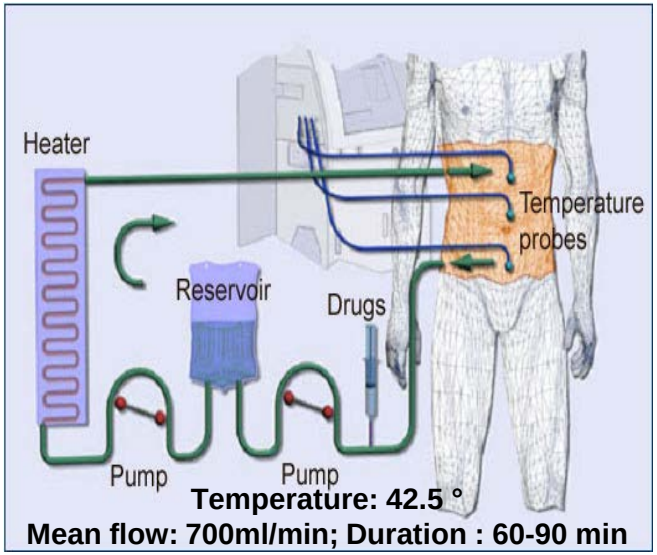
Intraperitoneal Administration

Pestieau SR, J Surg Oncol 2001





HIPEC (Hyperthermic Intra Peritoneal Chemotherapy: Rationale



Temperature: 42.5 °

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

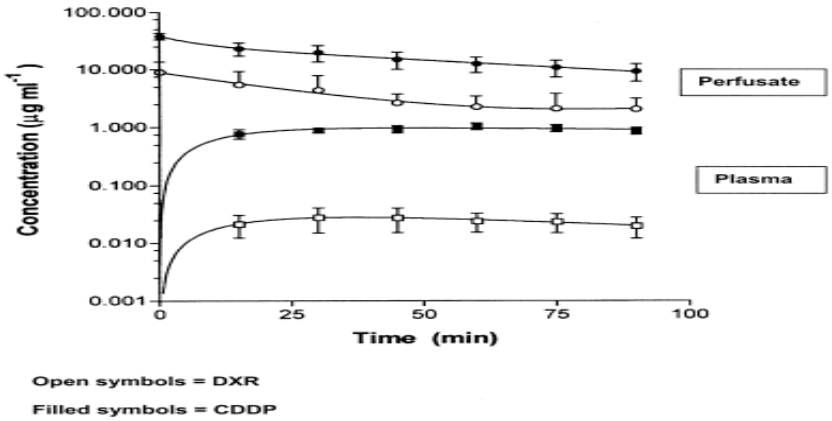
Hyperthermic Intraoperative Intraperitoneal Chemotherapy with Cisplatin and Doxorubicin in Patients Who Undergo Cytoreductive Surgery for Peritoneal Carcinomatosis and Sarcomatosis

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

MTD

CDDP: 42 mg/l

DX: 15 mg/l

30

20

10

0

PERITONEUMMUSCLE FAT NEOPLASM

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

J Clin Oncol 27. © 2009 by American Society of Clinical Oncology

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

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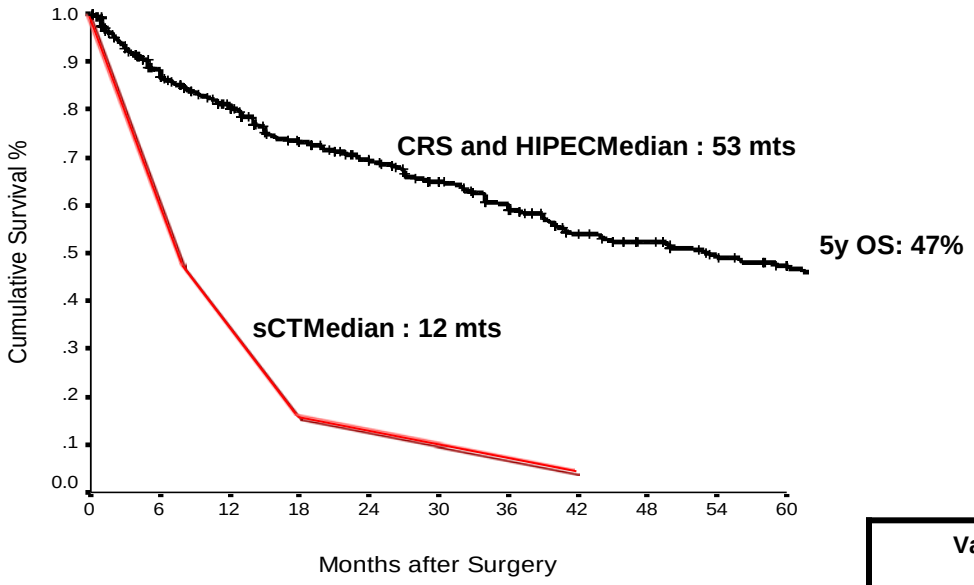

Multivariate analysis

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

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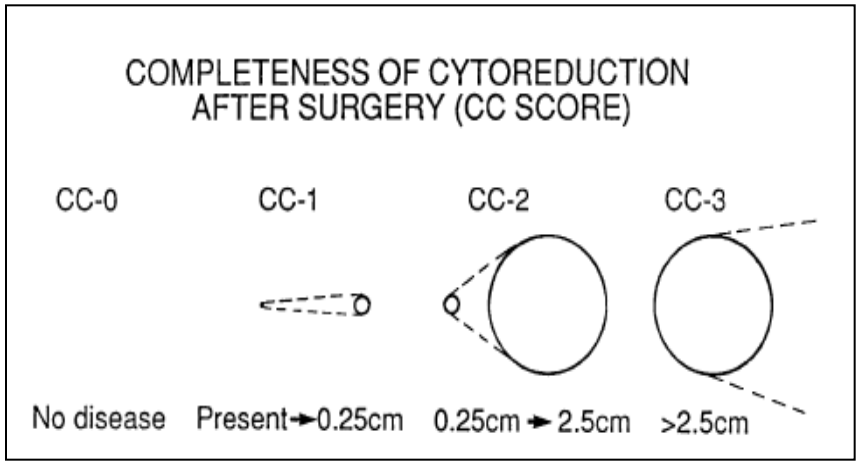
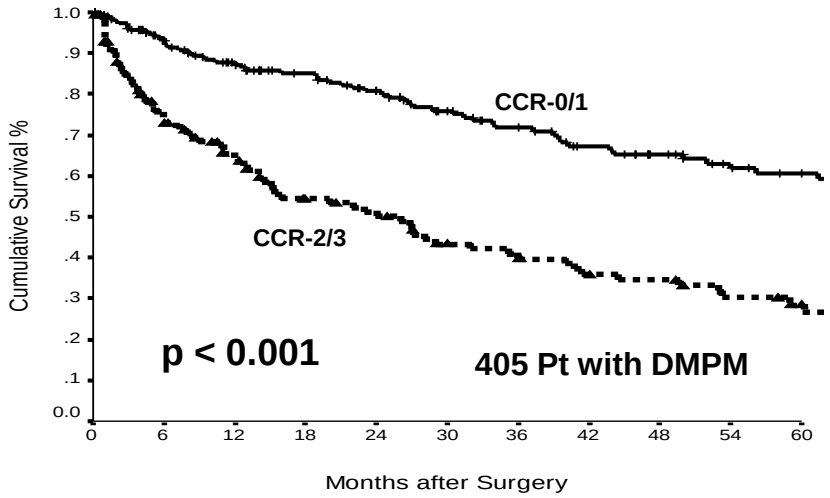
CC-Score as a Prognostic Indicators of Survival





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original article

Annals of Oncology
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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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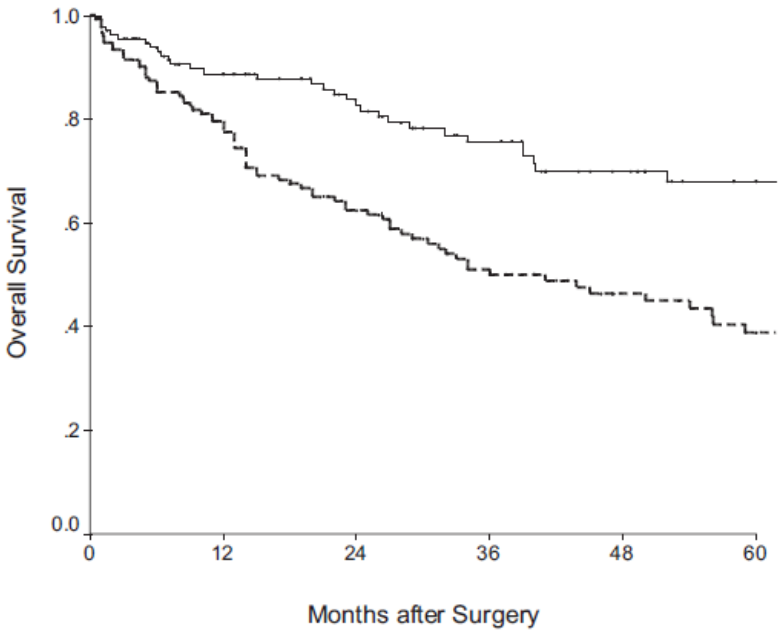
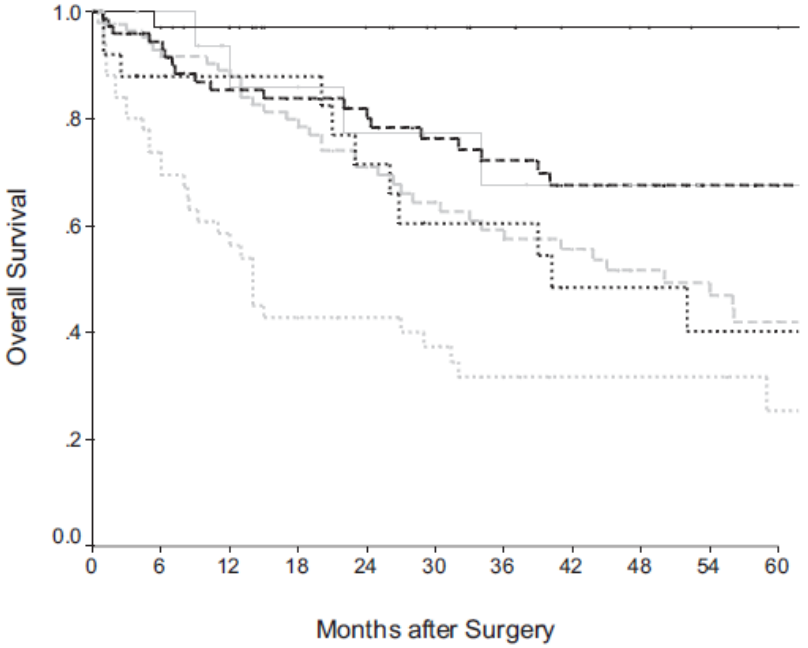
Better Outcomes in Women





The Team

- ***Dept Anestesiology ICU (M. Langer)***

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

- ***Medical Oncology (F. De Braud)***
- Filippo Pietrantonio

- **Colorectal Cancer Unit (E. Leo)**

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

- ***Dept. Pathology (G. Pelosi)***
- Silvana Pilotti
- Massimo Milione
- Antonello Cabras
- Federica Perrone

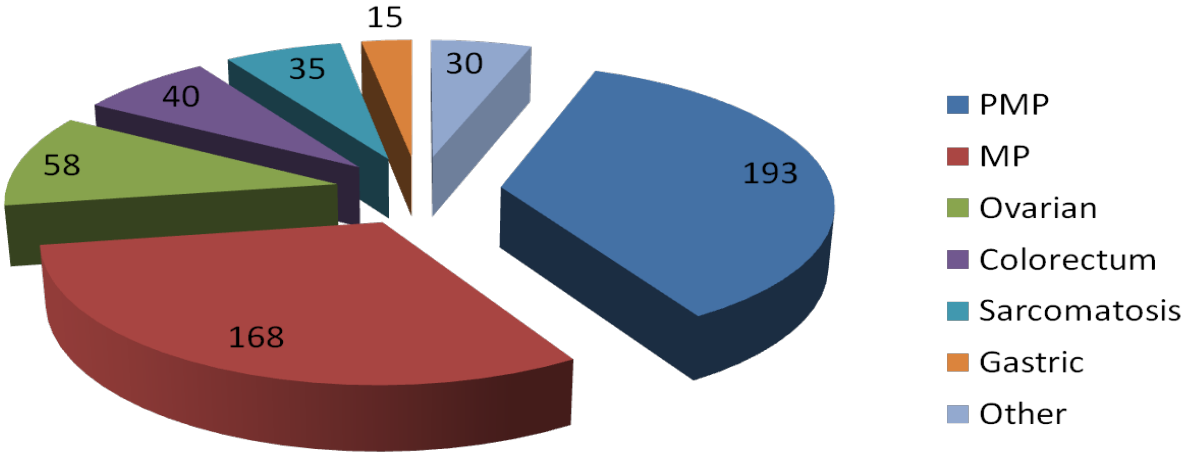
- ***Nutrition Unit (C Gavazzi)***

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

www.marcelloderaco.com

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

Peritoneal Mesothelioma

Multimodality Treatment with CRS and HIPEC

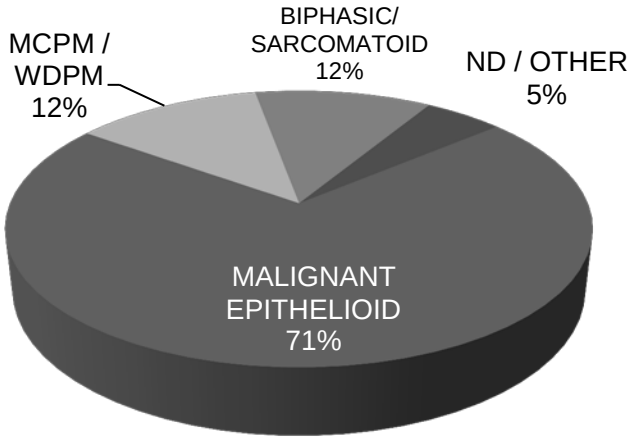
Patients: 168

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.

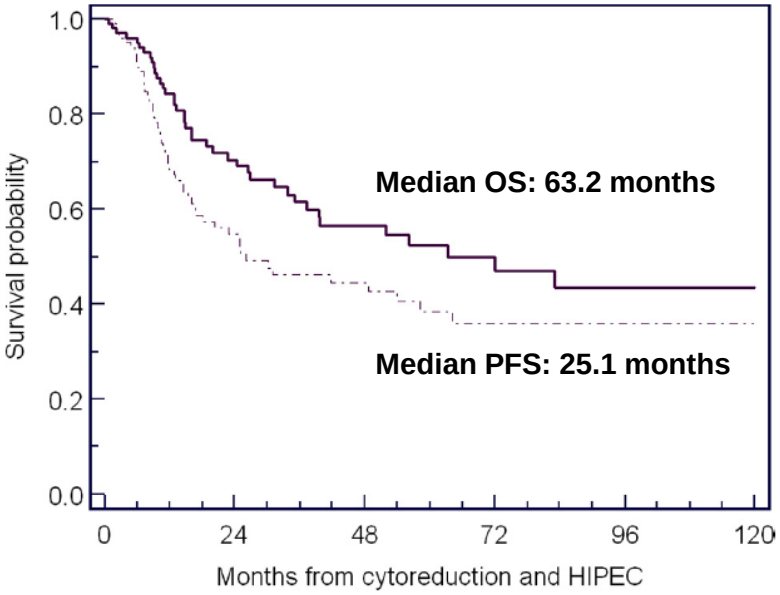
Mean Peritoneal cancer index: 19 (0-39)

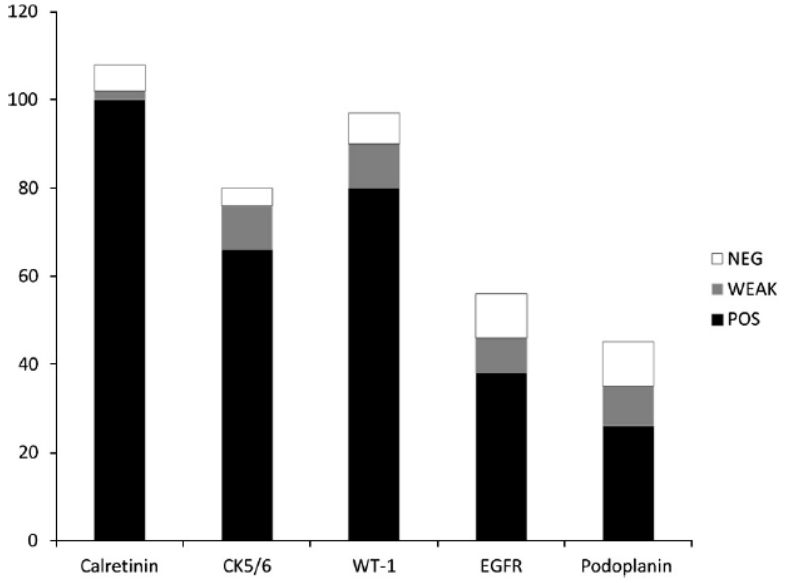
G3-5 Morbidity rate: 33.5%

Peritoneal Surface Malignancies Program

Diffuse malignant peritoneal mesothelioma: Long-term survival with complete cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (HIPEC)

Dario Baratti [a], Shigeki Kusamura [a], Antonello Domenico Cabras [b], Rossella Bertulli [c], Ionut Hutanu [d], Marcello Deraco [a,*]

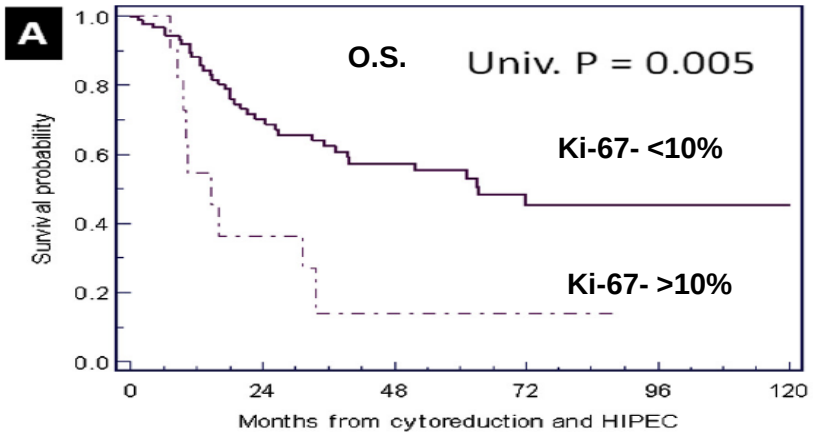


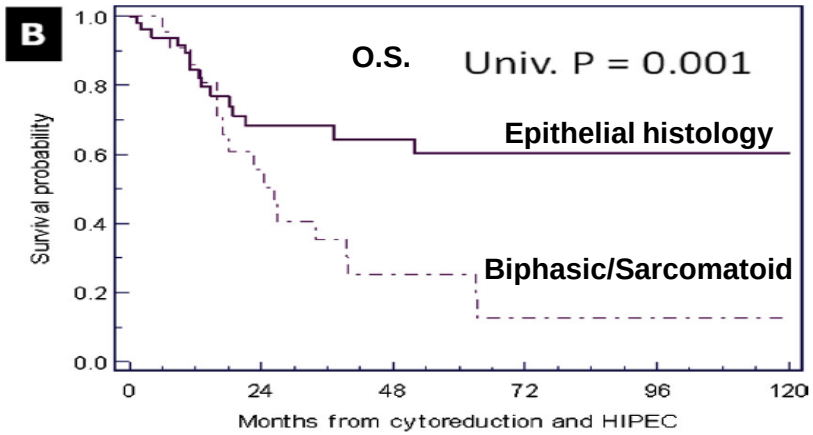


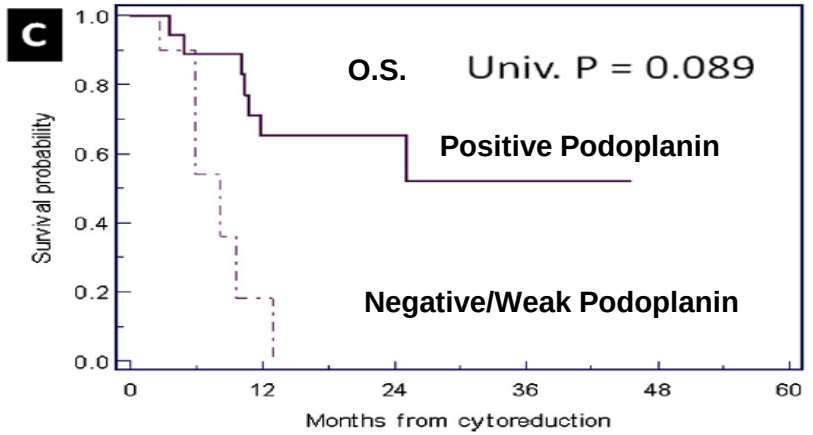
European Journal of Cancer (2013)

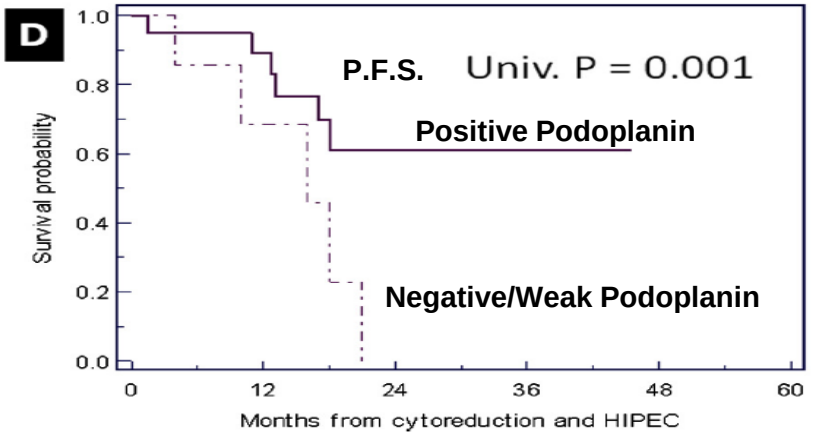
Diffuse malignant peritoneal mesothelioma: Long-term survival with complete cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (HIPEC)

Dario Baratti [a], Shigeki Kusamura [a], Antonello Domenico Cabras [b], Rossella Bertulli [c], Ionut Hutanu [d], Marcello Deraco [a,*]









European Journal of Cancer (2013)

Ann Surg Oncol
DOI 10.1245/s10434-012-2237-2

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – REGIONAL CANCER THERAPIES

Cytoreductive Surgery with Selective Versus Complete Parietal Peritonectomy Followed by Hyperthermic Intraperitoneal Chemotherapy in Patients with Diffuse Malignant Peritoneal Mesothelioma: A Controlled Study

Dario Baratti, MD[1], Shigeki Kusamura, PhD[1], Antonello Domenico Cabras, MD[2], and Marcello Deraco, MD[1]

[1]Department of Surgery, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [2]Department of Pathology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

CPP better result vs SPP

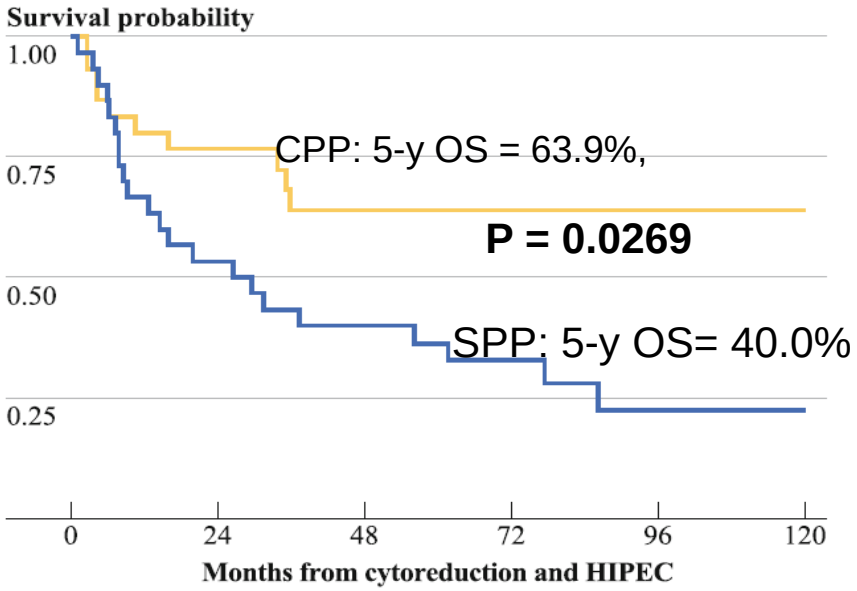


FIG. 1 Overall survival in patients undergoing surgical cytoreduction with selective (*blue line*) or complete (*yellow line*) parietal peritonectomy, combined with hyperthermic intraperitoneal chemotherapy (HIPEC). The difference was statistically significant ($P = 0.027$, log rank test)

- Selective (SPP): 30 vs Complete(CPP): 30
- Median follow-up 86.2 months(SPP), 50.3 (CPP);
- Median OS 29.6 (SPP)not reached (CPP)
- 5-year OS 40.0%(SPP); 63.9%,(CPP) p=0.0269
- Morbidity not different No operative mortality;
- 50% discordant surgical and pathology in CPP

Ann Surg Oncol
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Dario Baratti, MD[1], Shigeki Kusamura, PhD[1], Antonello Domenico Cabras, MD[2], and Marcello Deraco, MD[1]

[1]Department of Surgery, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [2]Department of Pathology, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

TABLE 4 Surgical and pathologic findings in 24 patients undergoing cytoreduction with routine complete parietal peritonectomy and hyperthermic intraperitoneal chemotherapy

Parietal peritoneum region	Macroscopic tumor at surgical exploration ($n = 109$)				Negative at surgical exploration ($n = 35$)			
	Pathologic diagnosis				Pathologic diagnosis			
	Macroscopic tumor	Microscopic tumor	No tumor	Total	Macroscopic tumor	Microscopic tumor	No tumor	Total
Right diaphragmatic	18	1	1	20	–	2	2	4
Left diaphragmatic	10	2	2	14	4	5	1	10
Parietal anterior	19	–	–	19	1	1	3	5
Pelvic	17	1	2	20	1	2	1	4
Greater omentum	19	–	2	21	1	–	2	3
Lesser omentum	13	2	–	15	–	2	7	9
Total	95	6	7	–	7	12	16	–

In 12 of 24 patients undergoing CPP, pathologic examination detected disease involvement on parietal surfaces with no evident tumor at surgical exploration.

Ann Surg Oncol (2009) 16:463–472
DOI 10.1245/s10434-008-0219-1

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Diffuse Malignant Peritoneal Mesothelioma: Failure Analysis Following Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

D. Baratti, MD[1], S. Kusamura, MD, PhD[1], A. D. Cabras, MD[2], P. Dileo, MD[3], B. Laterza, MD[1], and M. Deraco, MD[1,4]

[1]Department of Surgery, National Cancer Institute, Milan, Italy; [2]Department of Pathology, National Cancer Institute, Milan, Italy; [3]Department of Oncology, National Cancer Institute, Milan, Italy; [4]Fondazione IRCCS, Istituto Nazionale Tumori Milano, Milan, Italy

70 patients with DMPM undergoing CRS + HIPEC

median followup: of 43 months,

disease progression: 38 patients (cc 0/1=28)

CC-0 vs CC-1 correlated to failure

- peritoneal progression (n = 31), small bowel: (n = 27)
- liver metastases (n = 1),
- abdominal lymph-node involvement (n = 2),
- pleural seeding (n = 4).

TABLE 2 Univariate and multivariate analysis of factors affecting progressive disease involvement in 28 patients undergoing initial complete/nearly complete cytoreduction by anatomical region

	Completeness of cytoreduction CC-1 versus CC-0			Lesion size LS-3 versus LS-2 versus LS-1 versus LS-0	
	Univariate	Multivariate		Univariate	Multivariate
	P value	OR (95% CI)	*P* value	*P* value	*P* value
0. Central	NA	1.77 (0.65–11.75)	0.643	NS	NS
1. Right upper	0.443	1.87 (0.59– 5.89)	0.280	NS	NS
2. Epigastric	0.001	7.23 (1.05–49.69)	0.044	NS	NS
3. Left upper	0.527	1.57 (0.61–4.15)	0.355	NS	NS
4. Left flank	1.00	1.68 (0.55–5.06)	0.356	NS	NS
5. Left lower	1.00	1.54 (0.56–4.24)	0.396	NS	NS
6. Pelvis	NA	1.19 (0.47–2.99)	0.708	NS	NS
7. Right lower	0.339	1.03 (0.51–2.07)	0.933	NS	NS
8. Right flank	1.00	0.85 (0.27–2.72)	0.796	NS	NS
9. Upper jejunum	0.001	5.11 (1.12–23.28)	0.035	0.043	NS
10. Lower jejunum	0.001	15.40 (2.5–94.88)	0.003	0.037	NS
11. Upper ileum	0.008	7.48 (1.22–45.60)	0.029	0.051	NS
12. Lower ileum	0.210	3.82 (0.871–16.81)	0.075	0.099	NS

Completeness of cytoreduction: CC-1 = residual disease ≤2.5 mm; CC-0 = no visible residual tumor; lesion size: LS-3 >50 mm; LS-2 >5 mm and ≤50 mm; LS-1 ≤5 mm; LS-0 = no tumor; *NA* not applicable; *NS* not significant; *OR* odds ratio; *CI* confidence interval

ORIGINAL ARTICLE – REGIONAL CANCER THERAPIES

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

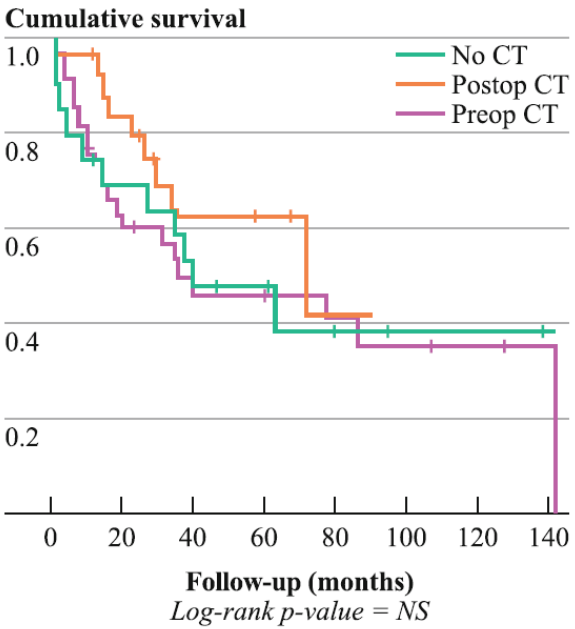
The Role of Perioperative Systemic Chemotherapy in Diffuse Malignant Peritoneal Mesothelioma Patients Treated with Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

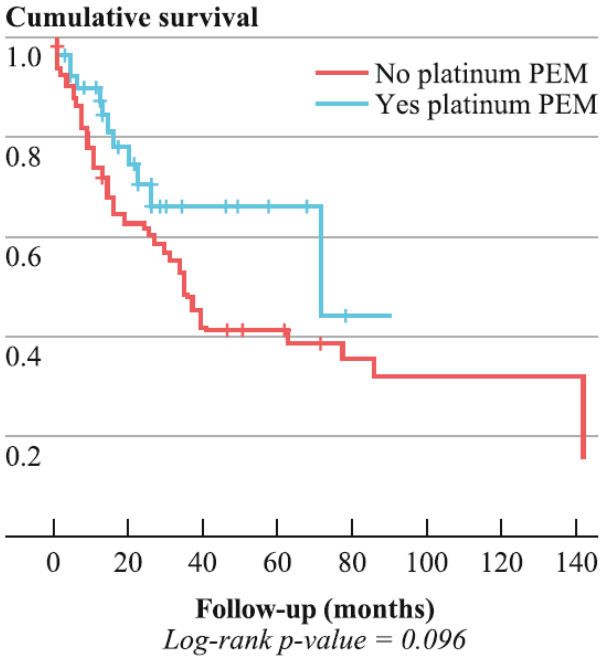
Marcello Deraco, MD[1], Dario Baratti, MD[1], Ionut Hutanu, MD[2], Rossella Bertuli, MD[3], and Shigeki Kusamura, MD, PhD[1]

[1]Peritoneal Surface Malignancy Program, Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy; [2]University of Medicine and Pharmacy "Gr T Popa", Iasi, Romania; [3]Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy

No differences pre or post operative sCT

- retrospective analysis from a prospectively collected database;
- 116 DMPM patients treated with CRS and HIPEC (August 1995 to October 2011)
- preCT=53%; postCT=25%; noCT=22%





Published online: 02 March 2013

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]

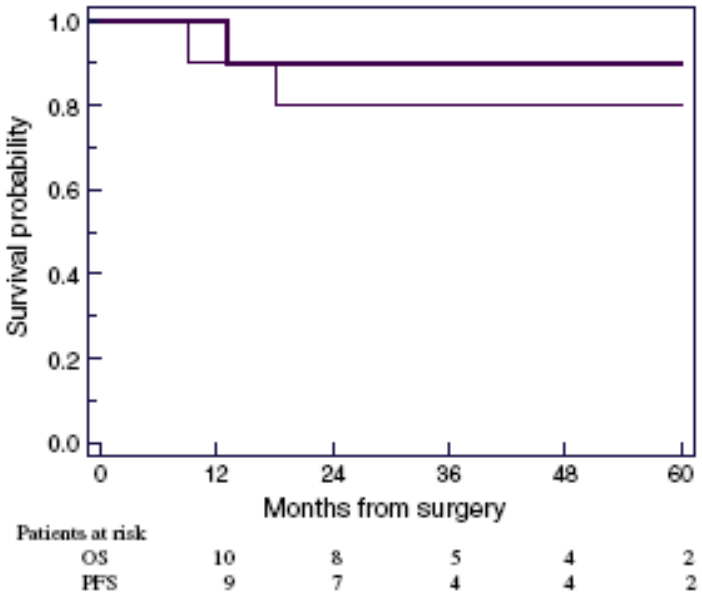


FIG. 1. Overall (heavier line) and progression-free survival (lighter line) in 12 patients treated with cytoreduction and HIPEC for multicystic and well-differentiated peritoneal mesothelioma.

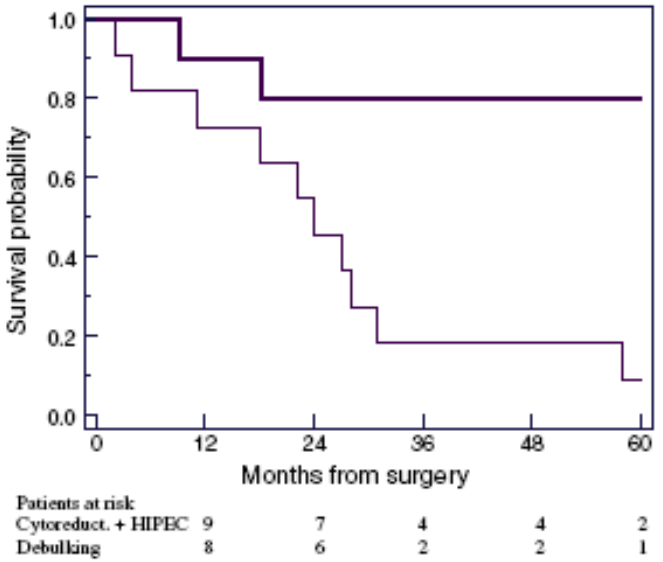
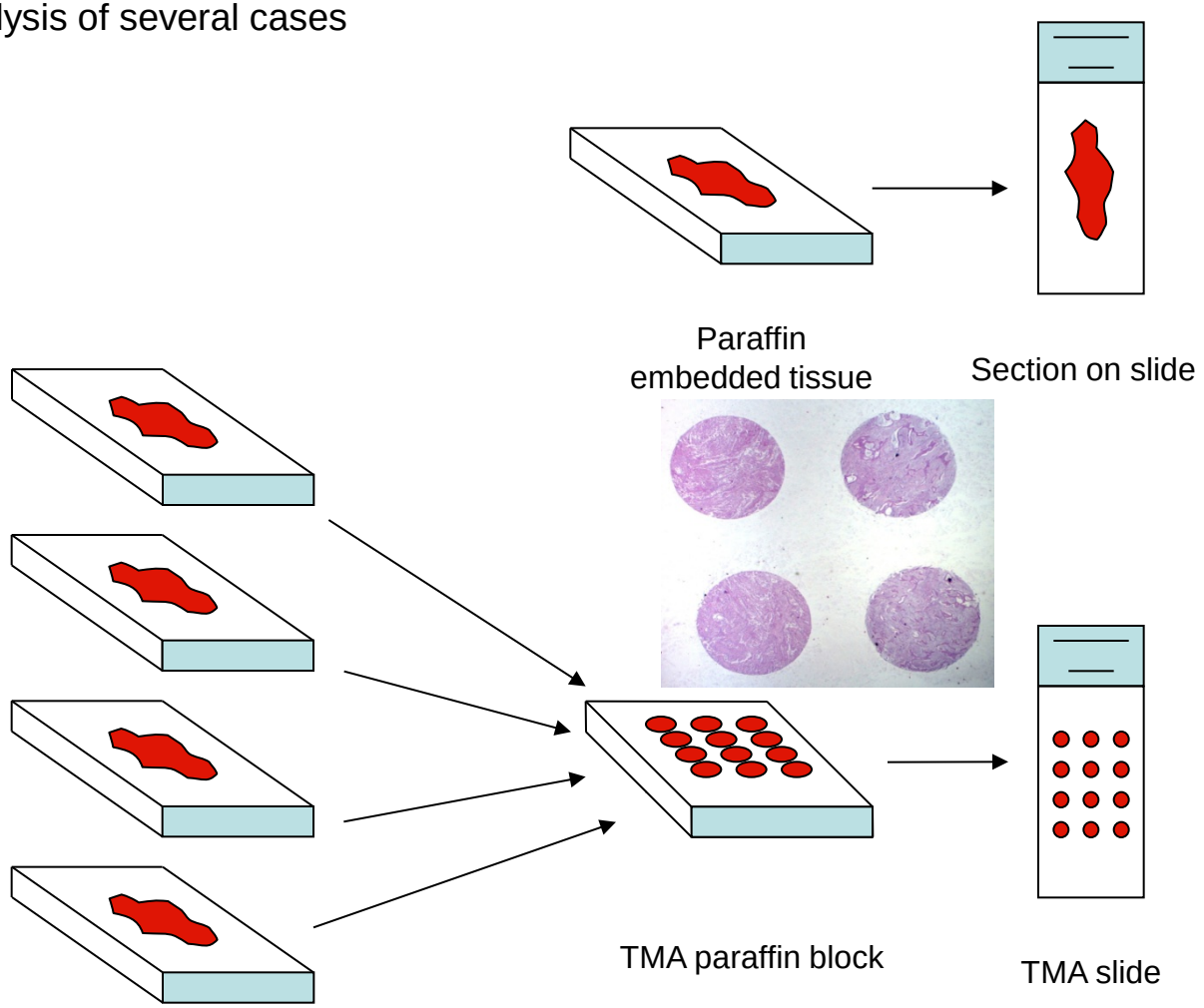


FIG. 2. Progression-free survival after cytoreduction with HIPEC for multicystic and well-differentiated peritoneal mesothelioma (heavier line) and after 11 debulking procedures performed in seven patients during their previous clinical history (lighter line) ($P = .0156$).

Immunohistochemical evaluation on Tissue Microarray (TMA)

- Several selected tissue samples in a single slide.
- Simultaneous and homogeneous analysis of several cases

Calretinin
Claudin
WT-1
Podoplanin
Ck5/6
Topoisomerase II
MCM7
ER
PGR
Melan A



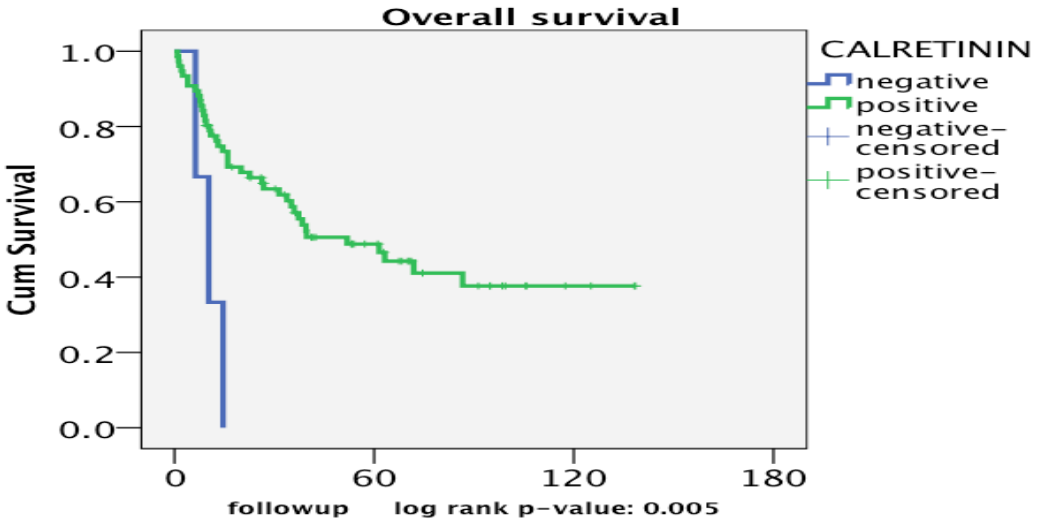
AIMS

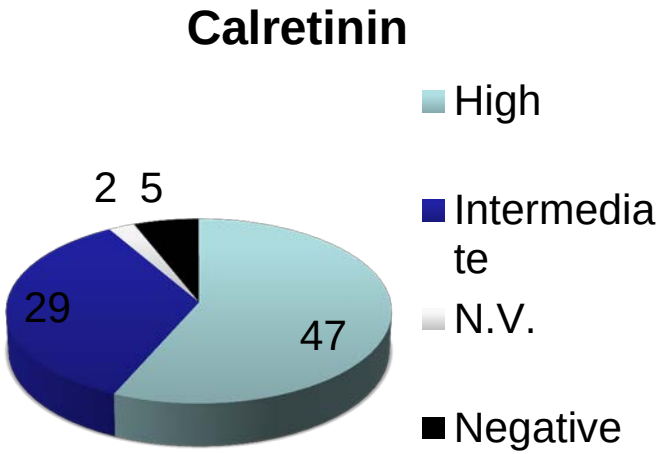
- To perform a descriptional evaluation of Calretinin, claudin, WT-1, podoplanin, Ck5/6, topoisomerase IIa, MCM7, ER, PGR, Melan A using immunohistochemistry

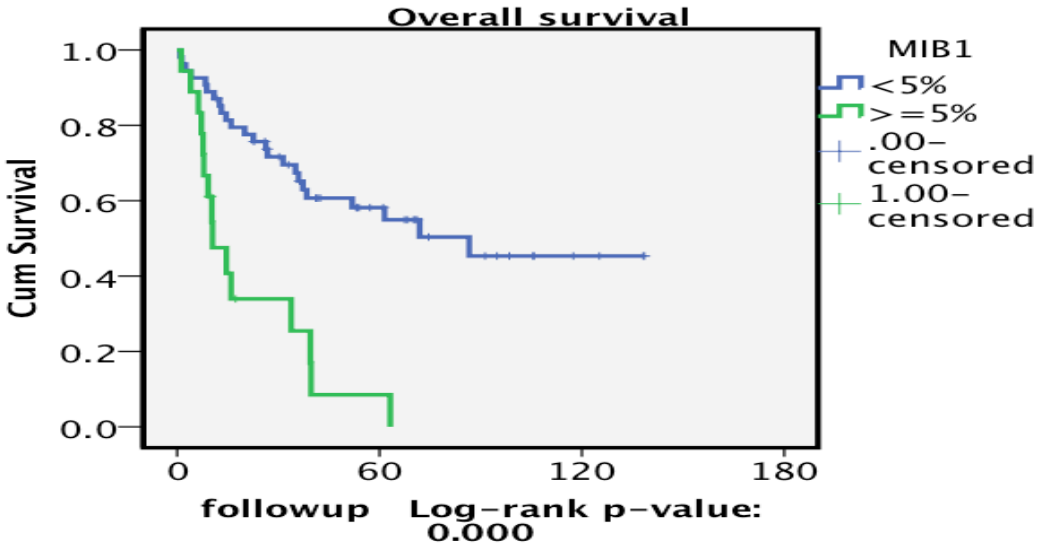
- To evaluate the prognostic role of these markers.

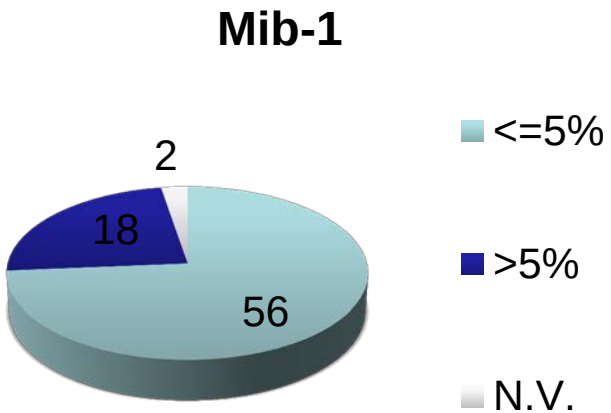
Overall survival

Multivariate Cox regression				
	OR	95% C.I.		P-value
Preop serum albumin <3.5gr/dl	3.8	1.8	8.1	0.00
Completeness of cytoreduction	5.0	2.2	10.9	0.00
Postoperative morbidity G3-5	2.1	1.1	4.0	0.03
MIB-1 > 5%	4.3	1.9	9.7	0.00


Overall survival
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
60
120
180
followup
log rank p-value: 0.005
CALRETININ
negative
positive
negative-censored
positive-censored

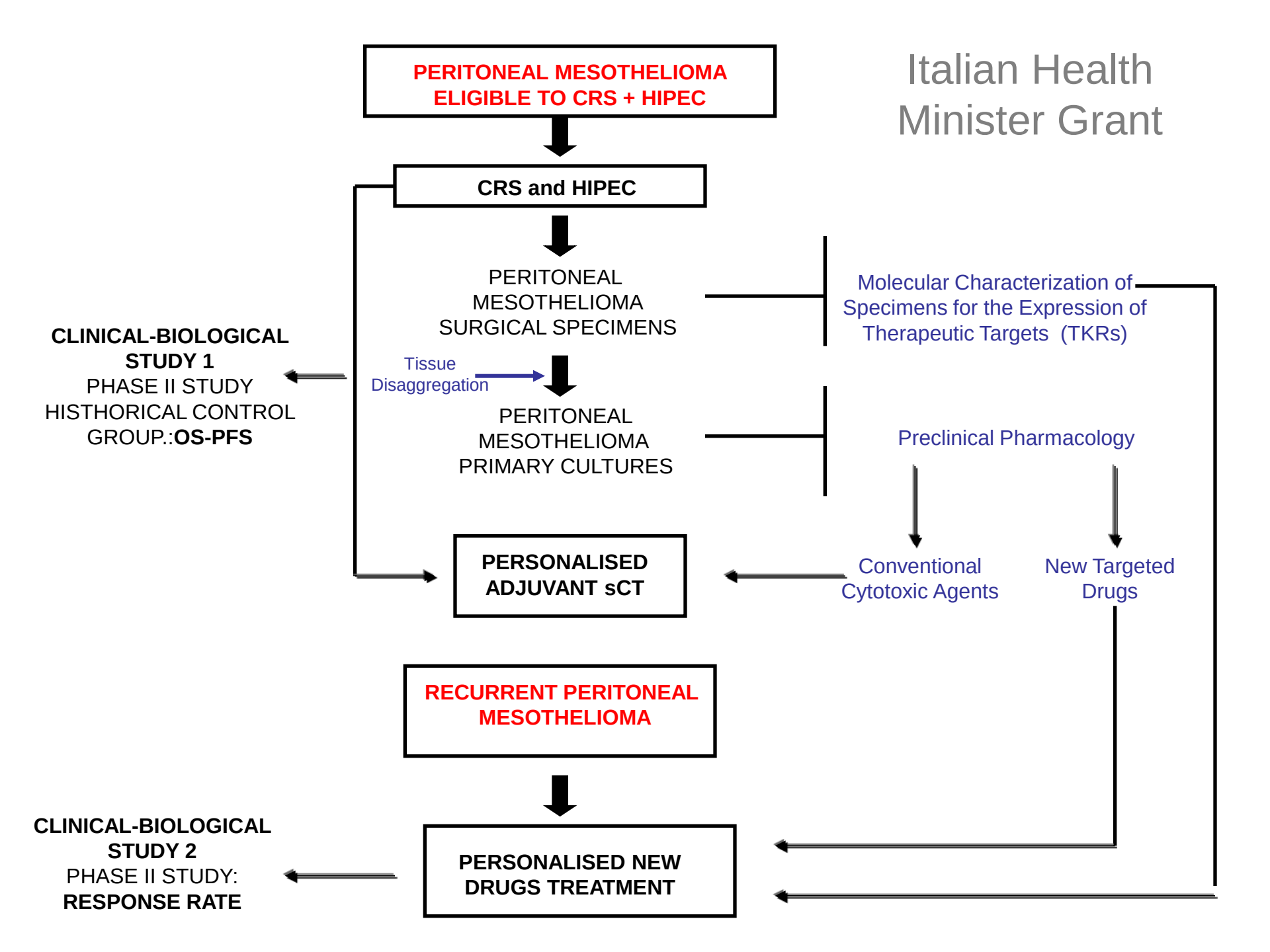

Calretinin
2
5
29
47
High
Intermediate
N.V.
Negative


Overall survival
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
60
120
180
followup
Log-rank p-value: 0.000
MIB1
<5%
>=5%
.00-censored
1.00-censored


Mib-1
2
18
56
<=5%
>5%
N.V.

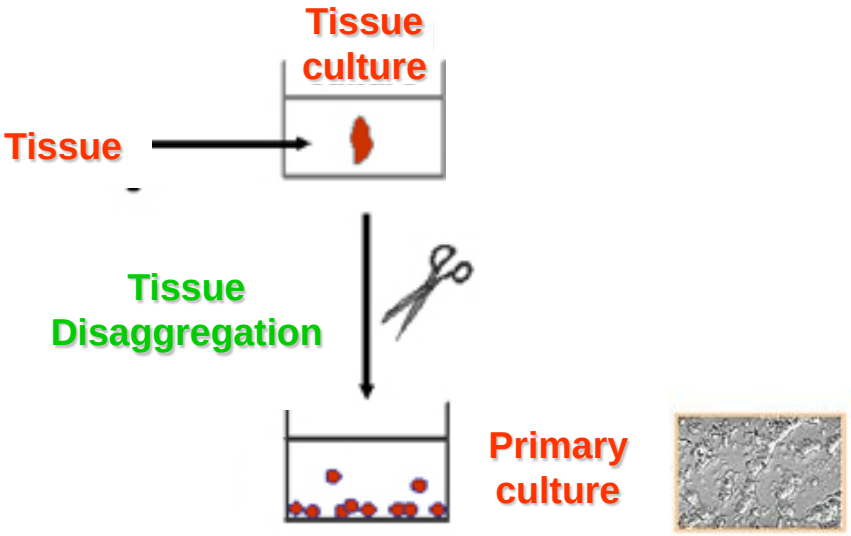
Progression free survival

Multivariate Cox regression				
	OR	95% C.I.		P-value
ECOG	0.3	0.1	0.8	0.010
Preop serum albumin <3.5 gr / dl	3.7	1.8	7.6	0.000
Charlson comorbidity index > 3	2.4	1.3	4.5	0.005
Previous systemic chemotherapy	2.5	1.3	4.6	0.004
Postoperative morbidity G3-5	2.0	1.1	3.4	0.021
MIB-1 > 5%	2.7	1.3	5.6	0.007


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 PRIMARY CULTURES

Evaluation of Cell Sensitivity Profile to Conventional and Investigational New Drugs



- Cells were surgically or enzymatically removed from an organism and placed in suitable culture environment
- Primary culture contains a very heterogeneous population of cells

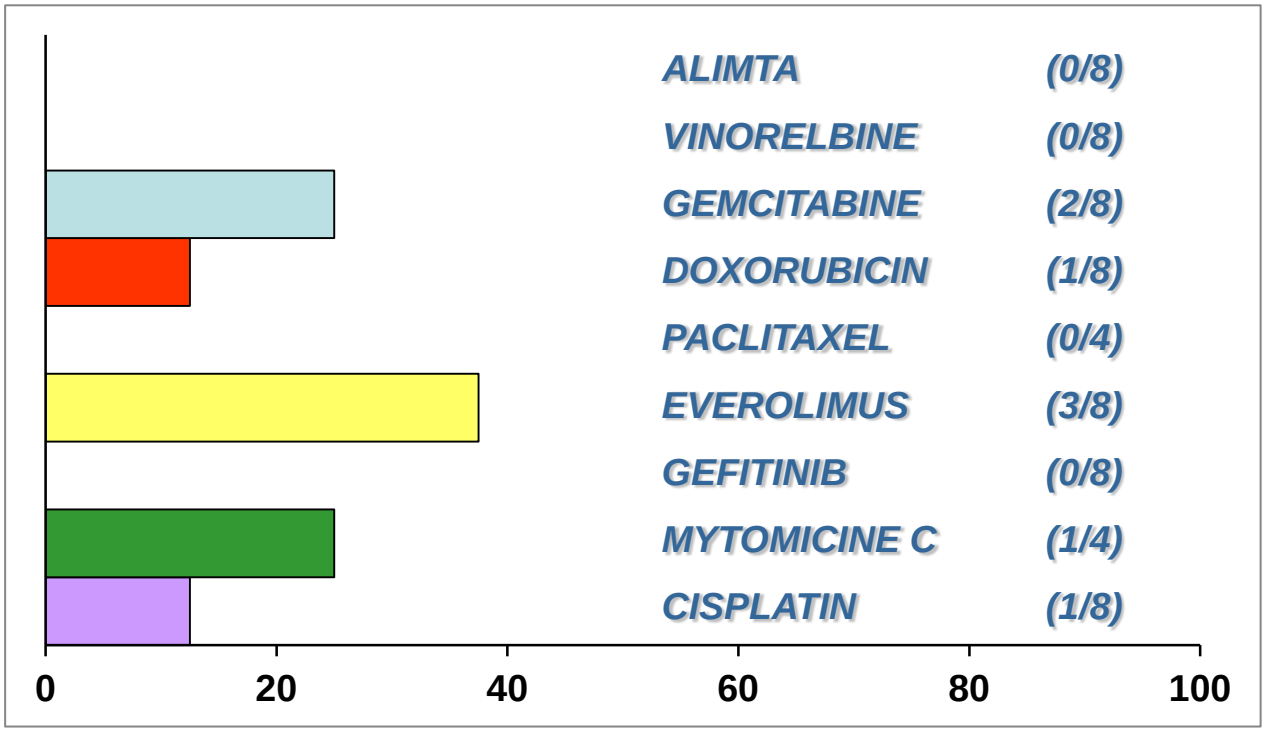
Advantages

- May represent the best experimental *in vitro* models
- May retain characteristics of the organ

Disadvantages

- Difficult to obtain
- Susceptible to contamination
- Limited lifespan

Chemosensitivity Profile of Diffuse Malignant Peritoneal Mesothelioma



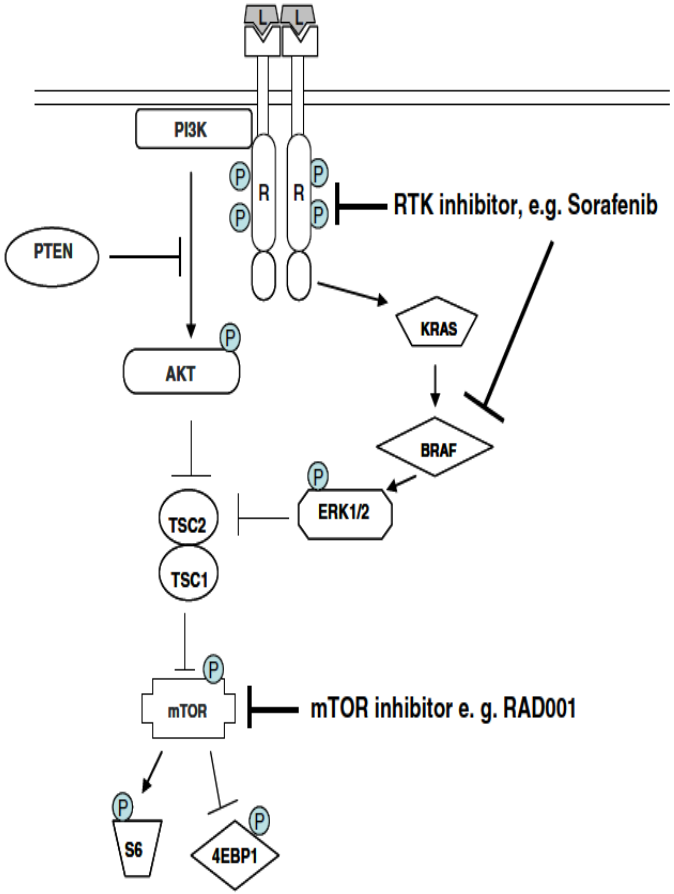
% SENSITIVE CULTURES

(Results obtained from 8 primary cultures)

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**



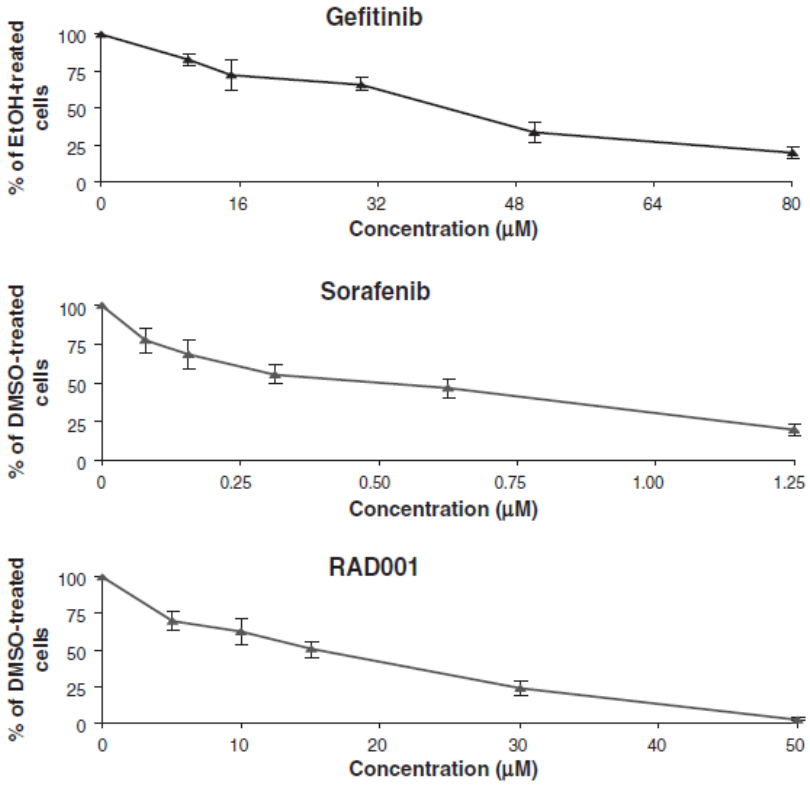
- 100% expression/ 90-75%phosphorylation of EGFR and PDGFRB;
- 85% expression/45%phosphorylation of PDGFRA;
- absence of RTK mutation and amplification;
- activation/expression of ERK1/2, AKT and mTOR, together with S6 and 4EBP1, in almost all the DMPMs;
- No KRAS/BRAF mutations,
- PI3KCA mutations/amplifications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

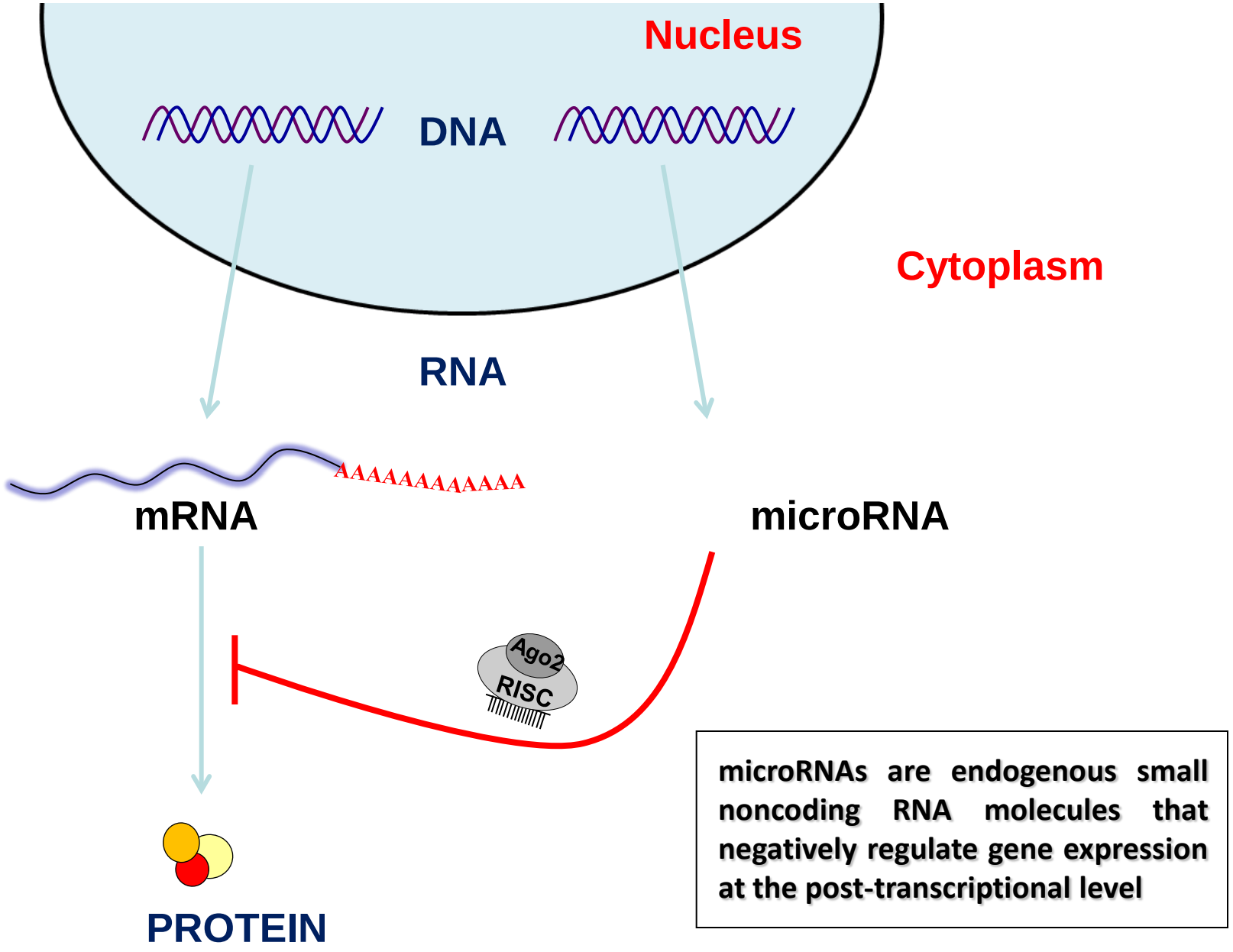
Cytotoxic activity of gefitinib, sorafenib and RAD001 in a peritoneal mesothelioma cell line



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

Eur J Cancer (2010)

MICRORNAS & GENE SILENCING

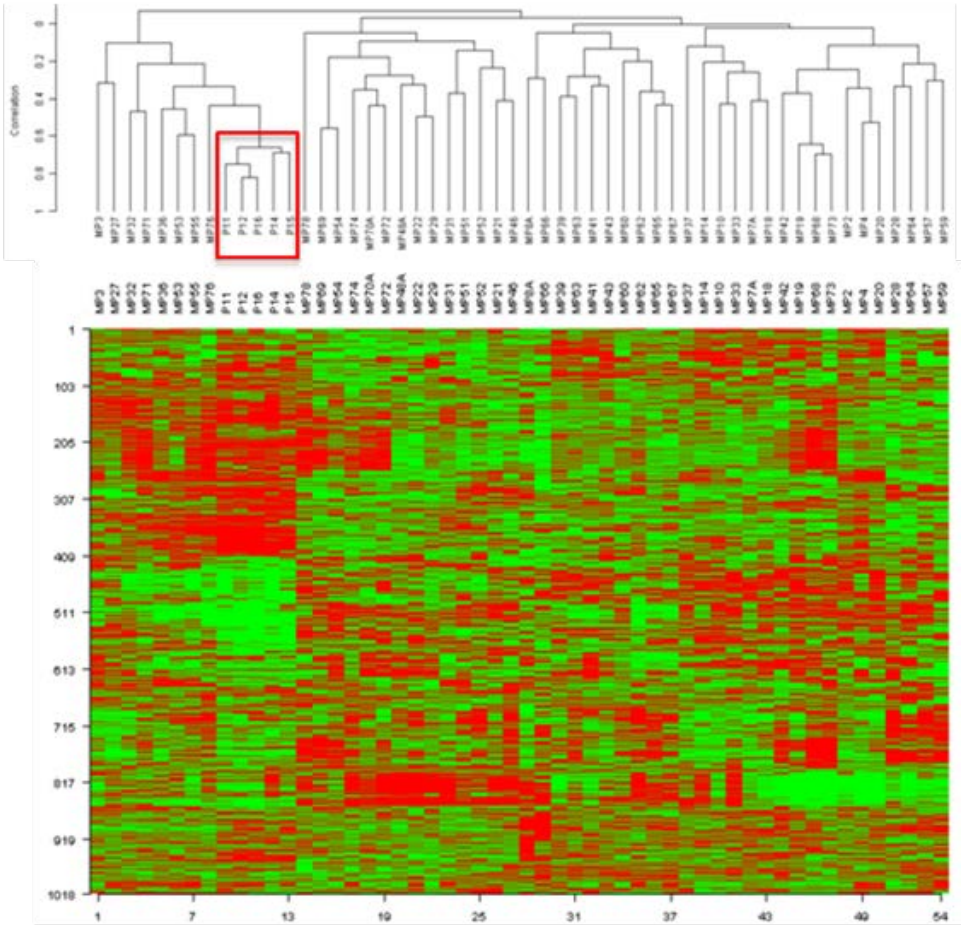


microRNAs are endogenous small noncoding RNA molecules that negatively regulate gene expression at the post-transcriptional level

IDENTIFICATION OF DEREGULATED MICRORNAS IN DMPM

Deregulated microRNA expression in DMPM

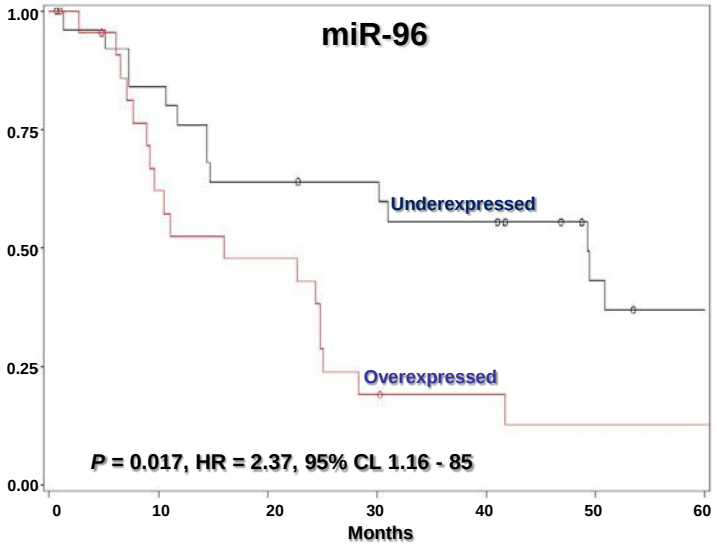
Dendrogram for clustering experiments using centered correlation and average linkage

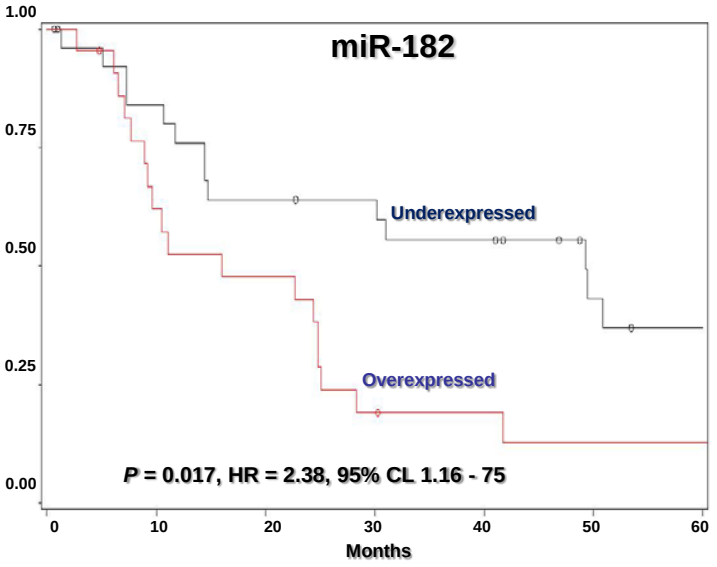


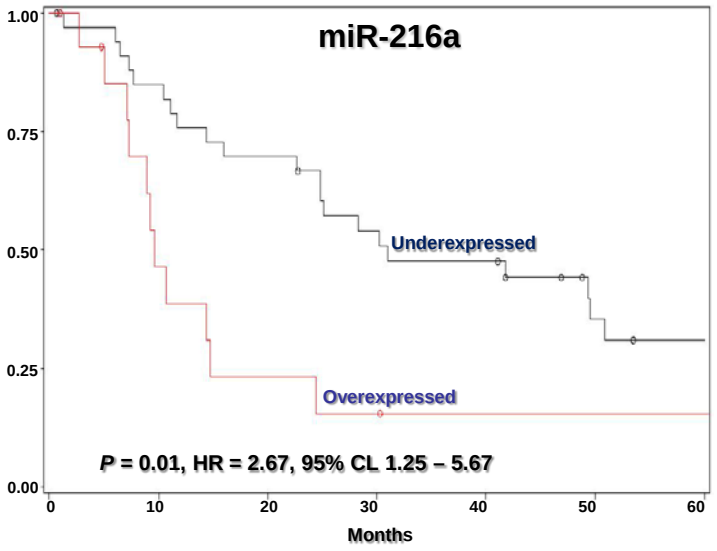
67 microRNAs proved to be differentially expressed (*P*-value <1x10^{-6}) between DMPM and normal peritoneum

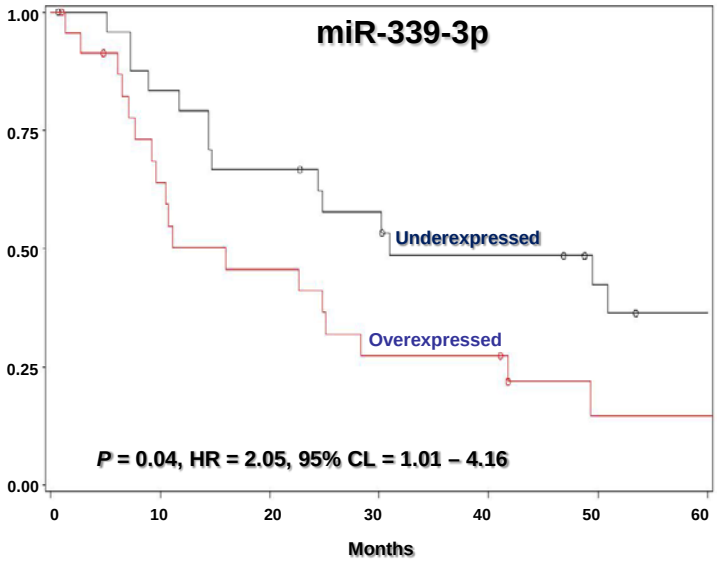
IDENTIFICATION OF MICRORNAS SIGNIFICANTLY ASSOCIATED TO PATIENT PROGNOSIS

microRNA expression & patient prognosis (5-year progression-free survival)









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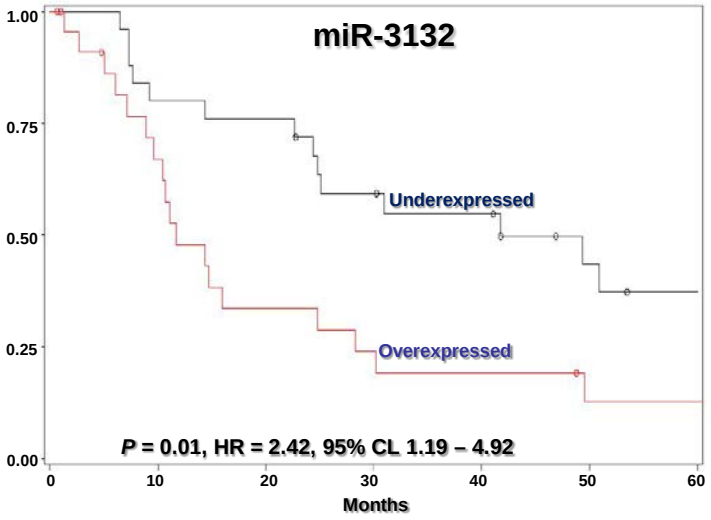

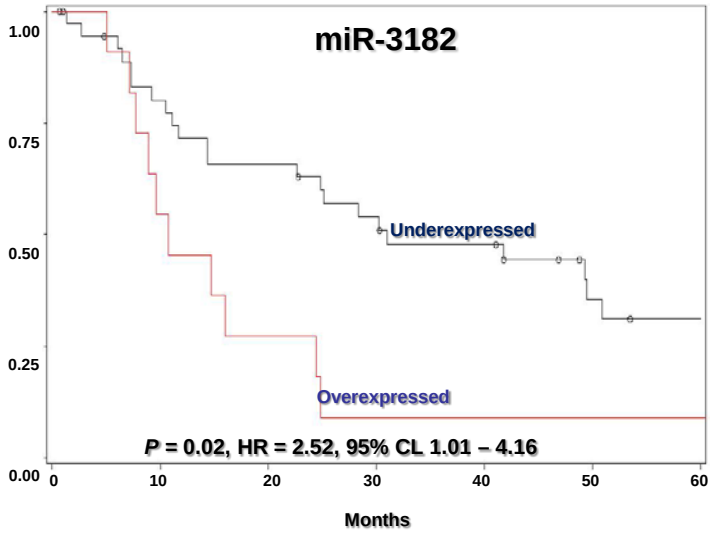

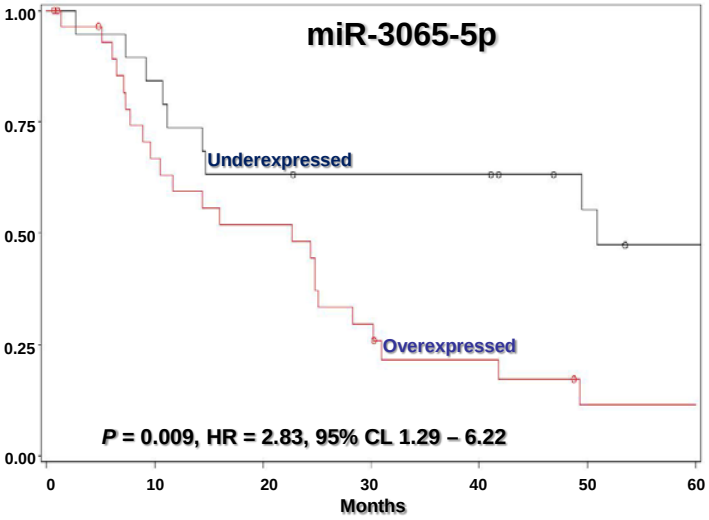

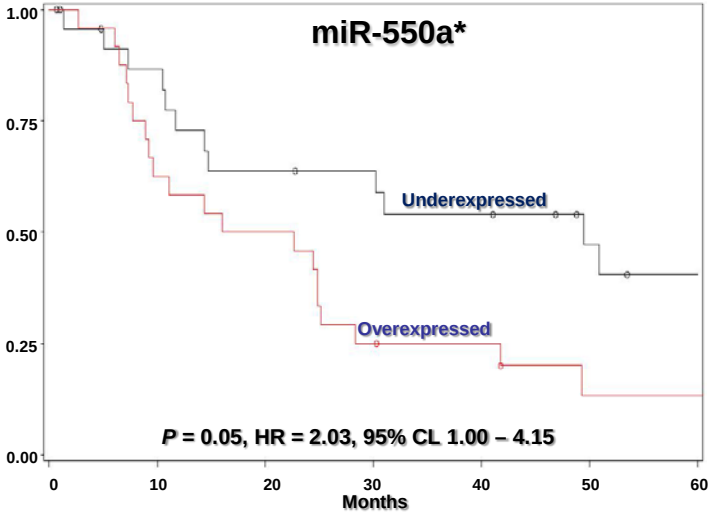

PERITONEAL MESOTHELIOMA: CONCLUSIONS

MPM 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 despite limited efficacy with no differences beetwen pre or post operative

Research Programs are neded

PERITONEAL MESOTHELIOMA: CONCLUSIONS 2

Research Programs are neded

1. Apparently low efficacy of chemotherapeutic drugs
2. Potential effects of Targeted Biological Therapy
3. miRNA as Prognostic Factors and Therapeutic Targets
4. TMA as potential model for large series evaluation