



Futuro del tratamiento HIPEC tras
citorreducción radical en cancer de
ovario

Marcello Deraco M.D.

**Responsible Peritoneal Surface
Malignancies**



**FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI**



NO DISCLOSURE

Worldwide Incidence/Prevalence of Primary Neoplasms Generating Peritoneal Dissemination

BOTH GENDERS	Worldwide 2012 incidence (new cases)	Worldwide 2015 incidence expected (new cases)	Worldwide 2017 incidence expected (new cases)
Primary PSM			
1. Serous papillary peritoneal carcinoma ¹	20.000	20.000+	30.000
2. Pseudomixoma peritonei ²	4.000	4.000+	5.000
3. Peritoneal mesotheliom ^{3a}	2.500	2.500+	3.000
4. Desmoplastic small round cell tumor - DSRCT ⁴	100	100+	100
BOTH GENDERS	Worldwide 2012 incidence (new cases)	Worldwide 2015 prevalence expected	Worldwide 2017 prevalence expected
Secondary PSM⁵			
1. Foregut			
- Gastric cancer	951.000	1.070.769	1.538.127
- Pancreatobiliar cancer	338.000	165.199	211.544
2. Colorectal cancer (includes appendix)	1.360.000	2.409.465	3.543.582
3. Ovarian cancer	239.000	407.584	586.624

¹ Halperin 2001; ² National Organization for rare disorders; ³ Robinson 2005, Moore 2008; Yang 2008 ⁴ Jordan 2015, Gerald 1998;

⁵ GLOBOCAN 2012, WHO.

PSM: Worldwide expected cases

BOTH GENDERS	% peritoneal dissemination	Expected 2015 cases of peritoneal carcinomatosis	Expected 2017 cases of peritoneal carcinomatosis
1. Serous papillary peritoneal carcinoma ¹	100	20.000	30.000
2. Pseudomixoma peritonei ²	100	4.000	5.000
3. Peritoneal mesothelioma ^{3a}	100	2.000	3.000
4. Desmoplastic small round cell tumor - DSRCT ⁴	100	100	100
Secondary peritoneal surface malignancies ⁵			
1. Foregut			
- Gastric cancer ⁶	40	428.307	615.250
- Pancreatobiliar cancer	25	41.299	52.886
2. Colorectal cancer (includes appendix) ⁷	15	361.419	531.537
3. Ovarian cancer	60	244.550	351.974

¹ Halperin 2001; ² National Organization for rare disorders; ³ Robinson 2005, Moore 2008; Yang 2008 ⁴ Jordan 2015, Gerald 1998 ⁵ GLOBOCAN 2012, WHO; ⁶ Ikeguchi 1994, Thomassen 2014, Florian 2014, ⁷ Chu 1989, Jayne 2002, Sadeghi 2000

National Cancer Institute of Milan: PSM treated with CRS +HIPEC: 1995-2015

Contacts: 2000 y

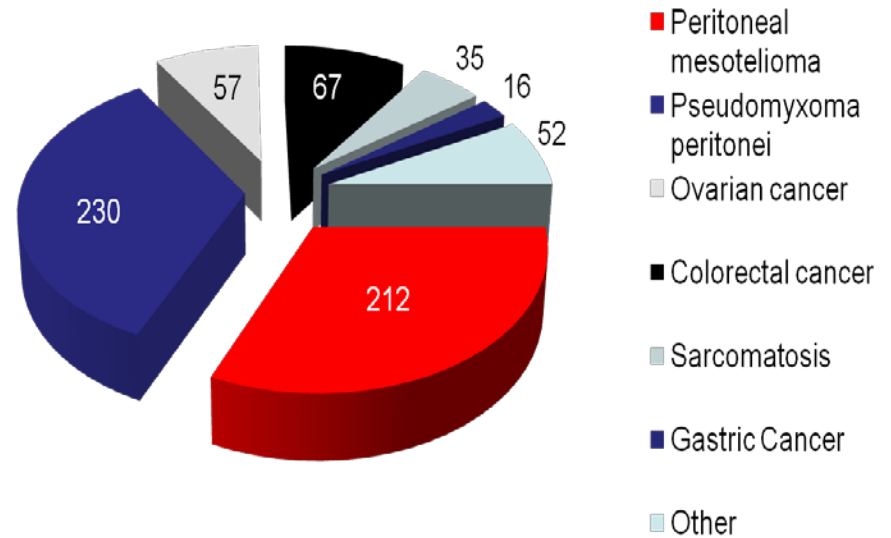
Clinical Evaluations: 800 y

Selection for CRS HIPEC: 120 y

Mean duration of operation 681.7 min. (110-1360)

Mean PCI 19 (1-39)

Grade 3-5 morbidity 33.5%



Peritoneal Surface Malignancies Program



**FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI**



Sotto l'alto patrocinio



Presidenza del Consiglio dei Ministri

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,
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PATIENTS: 26; STAGE III-IV EOC

Cytoreductive surgical and HIPEC procedure.

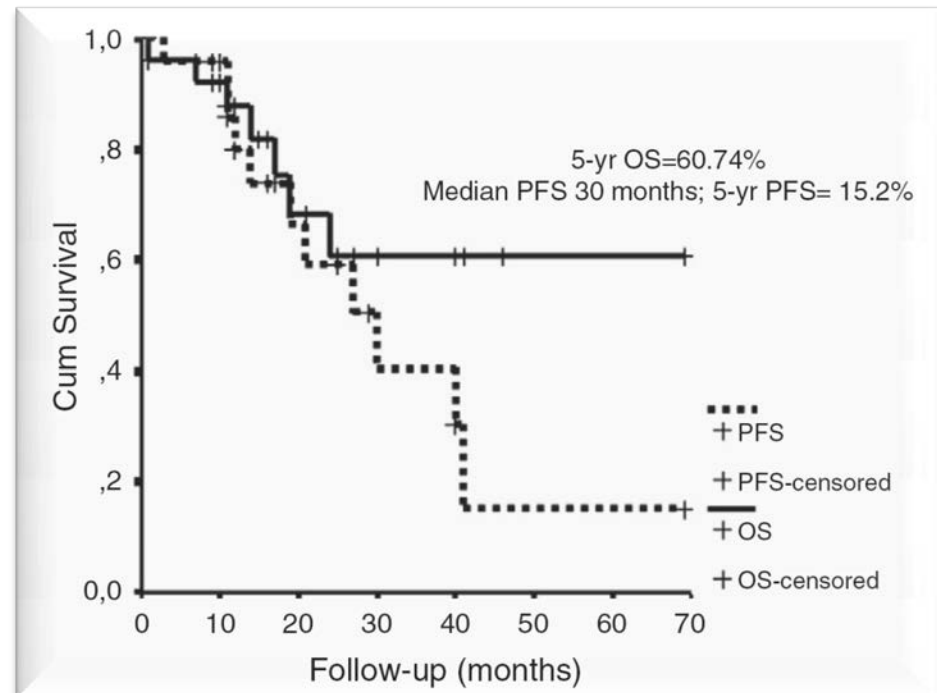
Peritonectomies	N
Greater omentectomy	24
Right upper quadrant peritonectomy	16
Left upper quadrant peritonectomy	16
Pelvic peritonectomy	26
Lesser omentectomy	18
Visceral resections	
Splenectomy	10
Liver capsulectomy	3
Cholecystectomy	14
Partial gastrectomy	1
Sigmoidectomy	15
Right colectomy	9
Total 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.

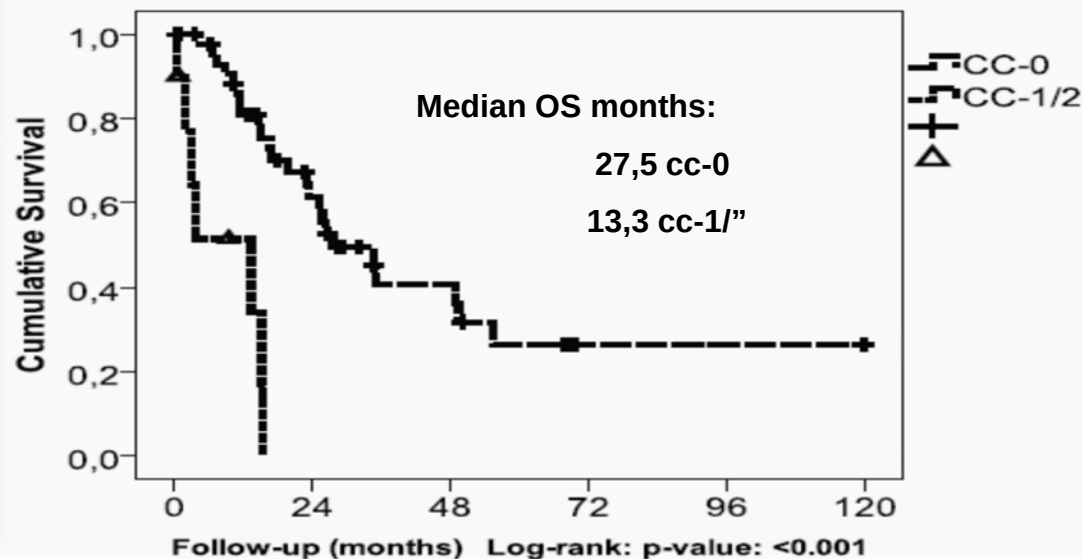


Secondary cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for recurrent epithelial ovarian cancer: a multi-institutional study

M Deraco,^a S Virzi,^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 2: Overall survival according to completeness of cytoreduction



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

Sub-hepatic

Lesser omentectomy, stripping of the omental bursa

Pelvis

Pelvic peritonectomy

Splenectomy, appendectomy, right colectomy

Gastric antrectomy, cholecystectomy

Sigmoidectomy, hysterectomy, bilateral adnexectomy

Total gastrectomy



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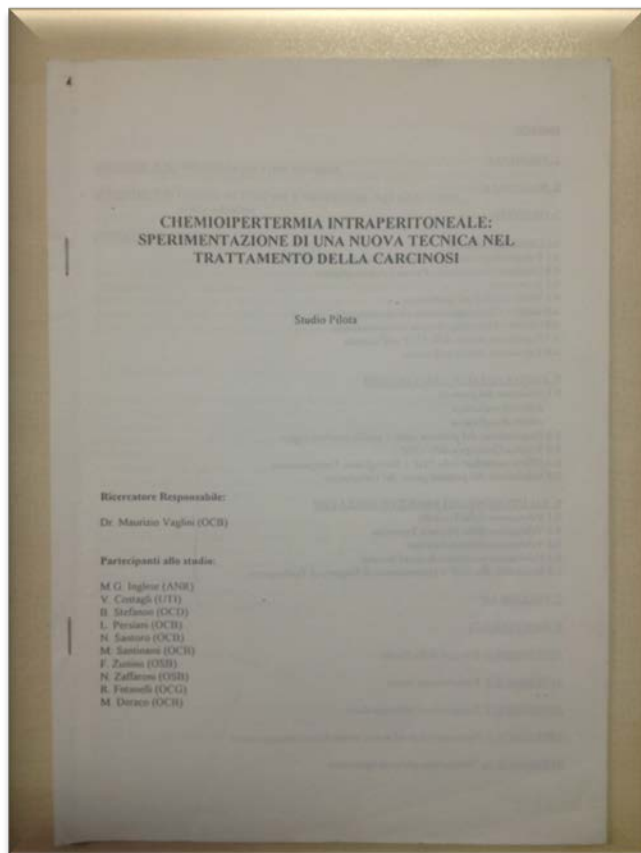


Sotto l'alto patrocinio



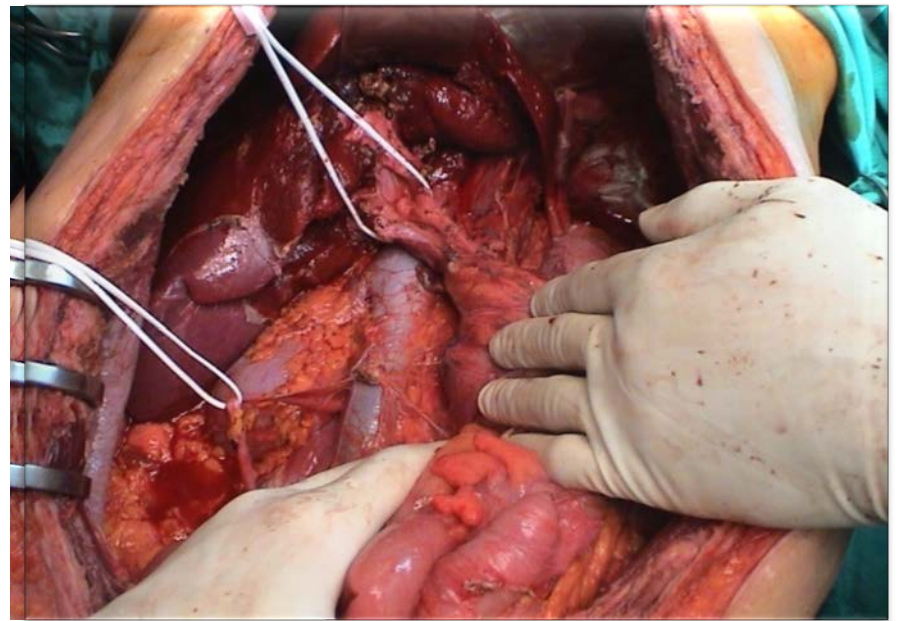
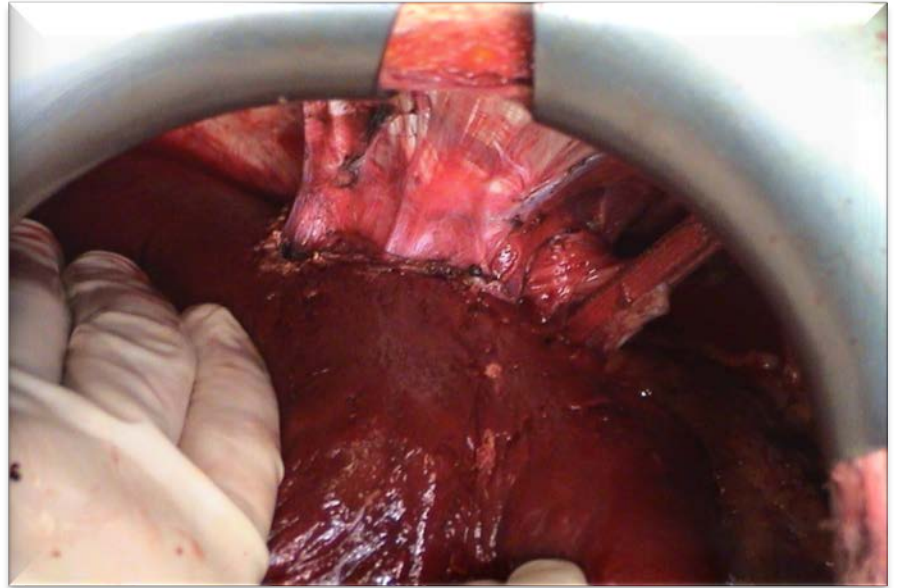
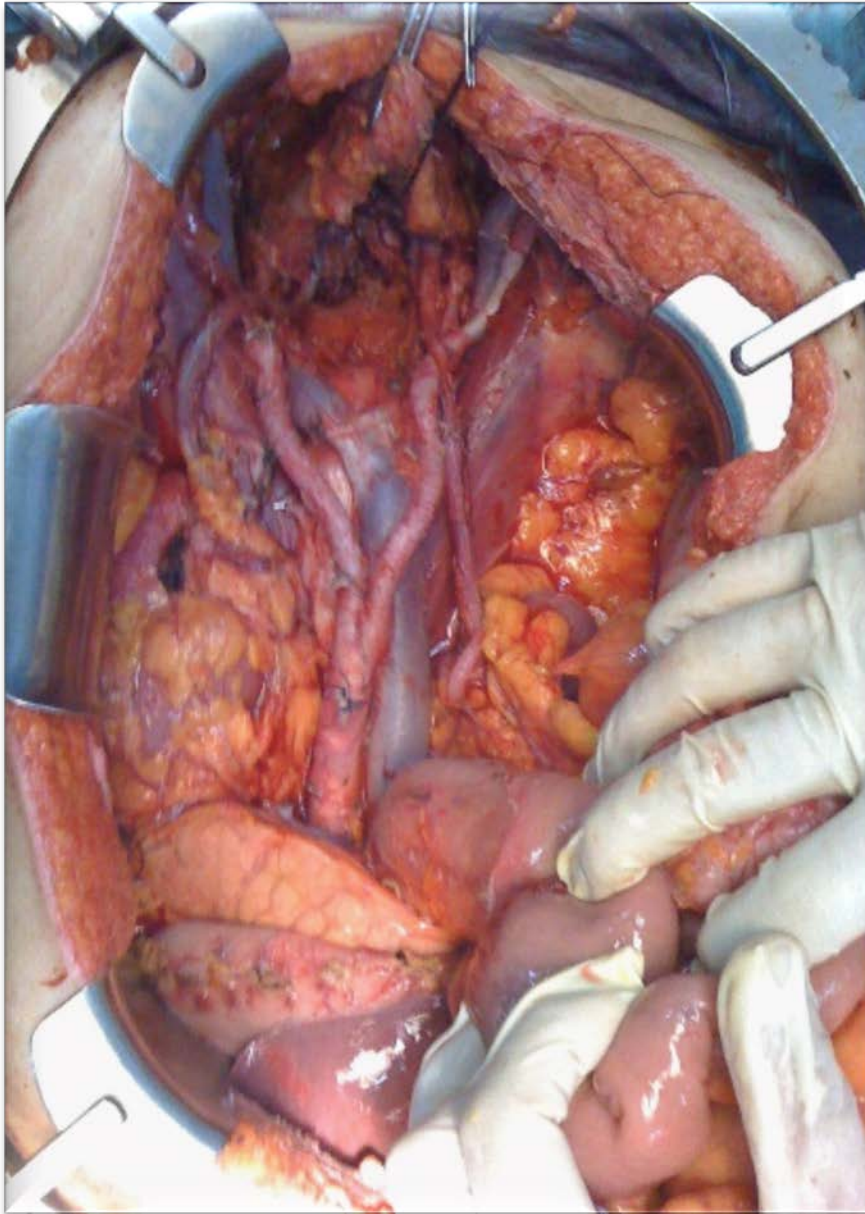
Presidenza del Consiglio dei Ministri

February 1995-February 2013



THANK YOU FOR YOUR ATTENTION

CC-0 Score after CRS-PP



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

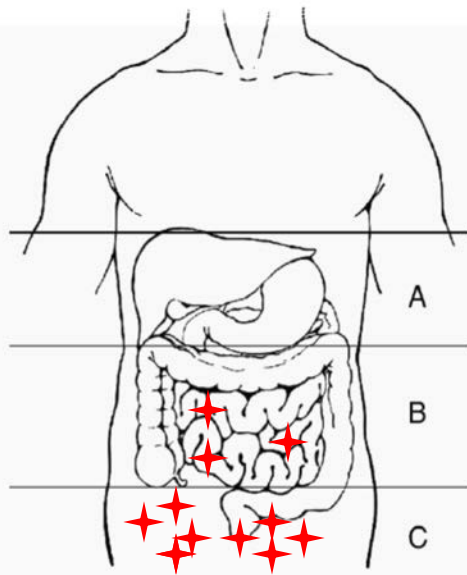


Fig. 1. Abdominopelvic regions. (A) Upper abdomen cephalad to the greater omentum. (B) Mid-abdomen. (C) Pelvis.

**No UAD
116 (24%)**

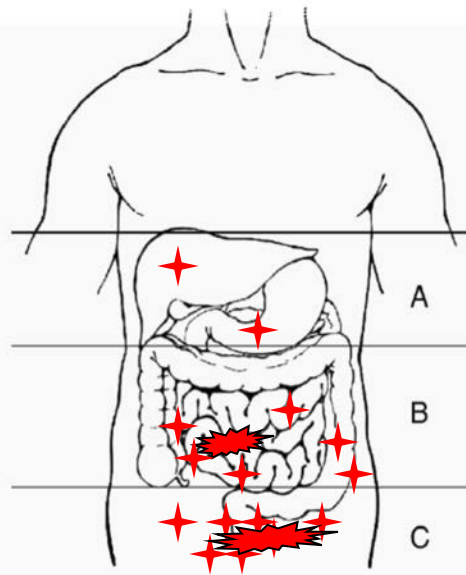


Fig. 1. Abdominopelvic regions. (A) Upper abdomen cephalad to the greater omentum. (B) Mid-abdomen. (C) Pelvis.

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

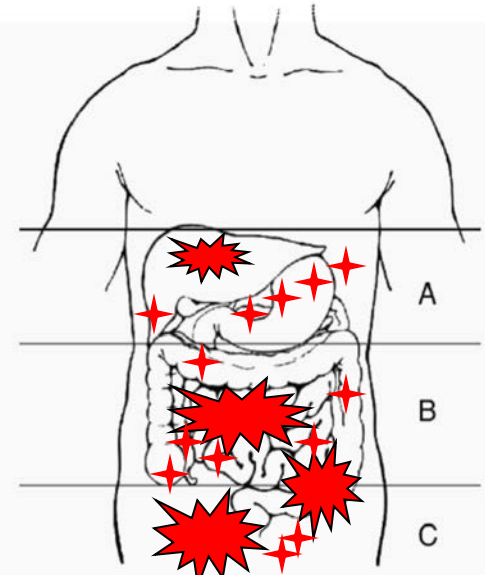
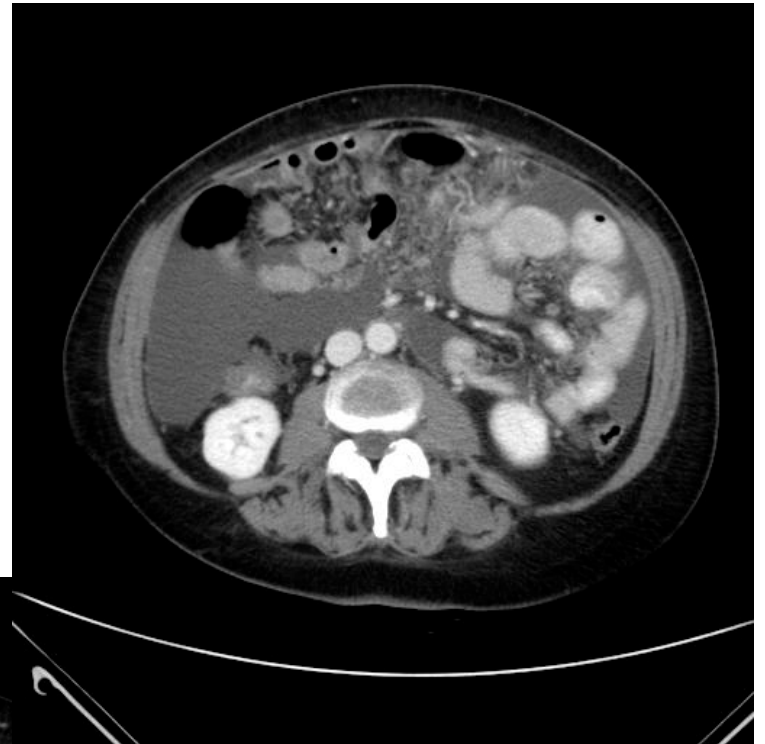


Fig. 1. Abdominopelvic regions. (A) Upper abdomen cephalad to the greater omentum. (B) Mid-abdomen. (C) Pelvis.

**Bulky UAD
197 (42%)**

AEOC: CTscan



Ultra-radical (extensive) surgery versus standard surgery for the primary cytoreduction of advanced epithelial ovarian cancer (Review)

Ang C, Chan KKL, Bryant A, Naik R, Dickinson HO

Standard Surgery if only:

- Hysterectomy,
- Bilateral salpingo-oophorectomy,
- Removal of enlarged lymph nodes
- Complete omentectomy
- Stripping of pelvic peritoneum
- Limited resection of peritoneal-based nodules

Ultra-Radical Surgery if any:

- Diaphragmatic surgery
- Bowel resection
- Splenectomy
- Extensive abdominal peritoneal stripping
- Urinary tract surgery
- Resection of pancreatic tail

- Low quality evidence ;
- Only one reference (Aletti 2006) reported a study that met the inclusion criteria ;
- The evidence suggested that ultra-radical surgery may result in better survival;**
- RCT required



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

Potential future improvements in CRS

- **More Consistent rate of eligible patients to primary CRS;**
- **Treatment with CRS-PP instead of classic CRS;**
- **If neoadjuvant sCT is mandatory, mapping of the extension of the disease (VLS) before sCT to optimize the Interval Debulking CRS.**

Build a Rationale for HIPEC

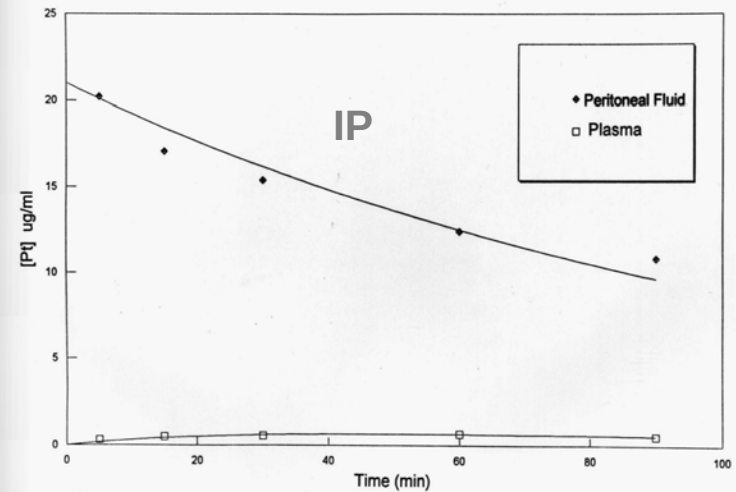
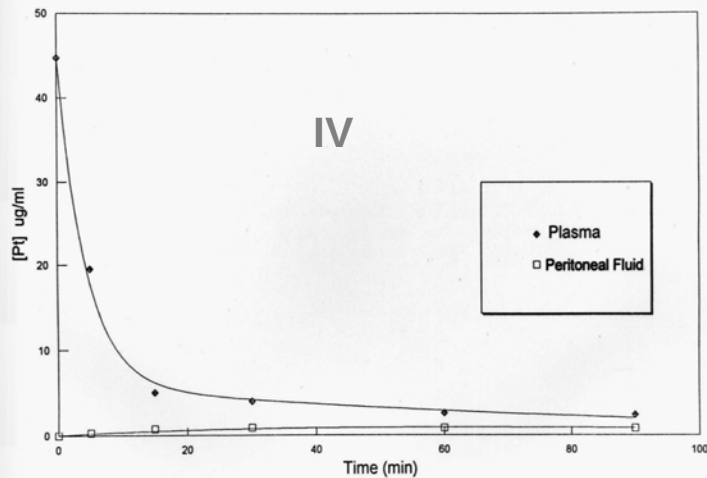
- Standard frontline treatment for primary EOC involves optimal CRS with perioperative chemotherapy administered intravenously and/or intraperitoneally with a combination of platinum- and taxane-based chemotherapy;
- The intraperitoneal administration of chemotherapy theoretically
 - improves treatment efficacy by targeting therapy to the site of disease, whilst minimising systemic toxicities;
- However, the full benefits of adjuvant intraperitoneal therapy are often not achieved as less than half of patients complete the intraperitoneal chemotherapy regime due to complications;
- HIPEC is an alternative method for delivering intraperitoneal heated chemotherapy directly into the abdominal cavity allows for a much higher concentration for peritoneal tumours, and is thought to improve its cytotoxic effect



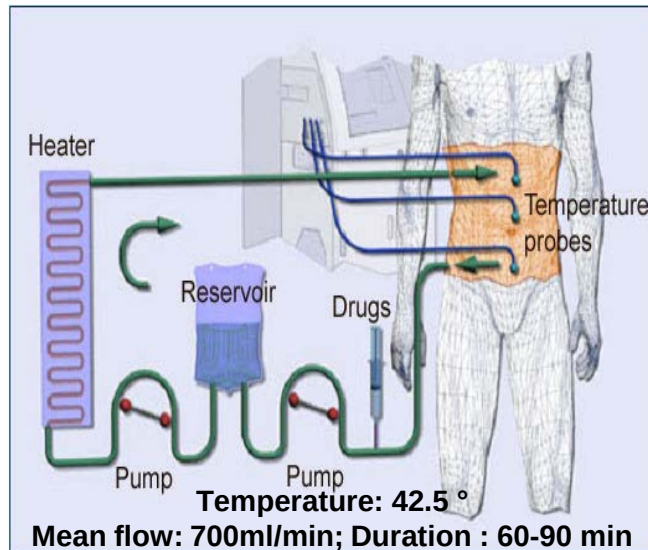
John Spratt
Professor of Surgery
University of Louisville

HYPERTHERMIC INTRA PERITONEAL CHEMOTHERAPY (HIPEC)

Is a treatment that allow to expose the abdominal cavity to high drug concentration in hyperthermic condition trough a perfusional procedure.



HIPEC (Hyperthermic Intra Peritoneal Chemotherapy: Rationale





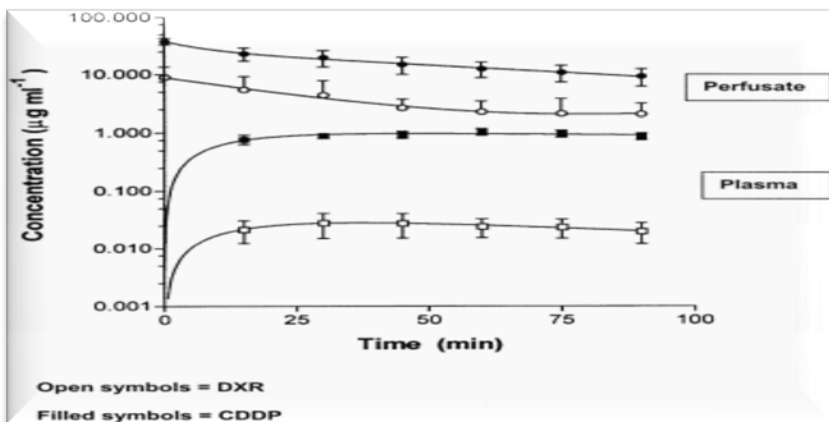
Hyperthermic Intraoperative Intraperitoneal Chemotherapy with Cisplatin and Doxorubicin in Patients Who Undergo Cytoreductive Surgery for Peritoneal Carcinomatosis and Sarcomatosis

Phase I Study

Carlo R. Rossi, M.D.¹
 Mirto Fioletto, M.D.¹
 Simone Mocella, 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 Sciarra, 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 pharmacokinetic



30

20

10

0

PERITONEUM MUSCLE

FAT

NEOPLASM

MTD:

CDDP: 42,5 mg/L

DX: 15,2 mg/L



Dr. Robert E. Bristow,

University of California, Irvine Medical Center,
Orange, CA, USA

...incorporation of hyperthermic intraperitoneal chemotherapy at the time of surgical resection has gained attention as an alternate therapeutic option, in an attempt to obviate toxicities encountered with repetitive cycles of intraperitoneal chemotherapy.

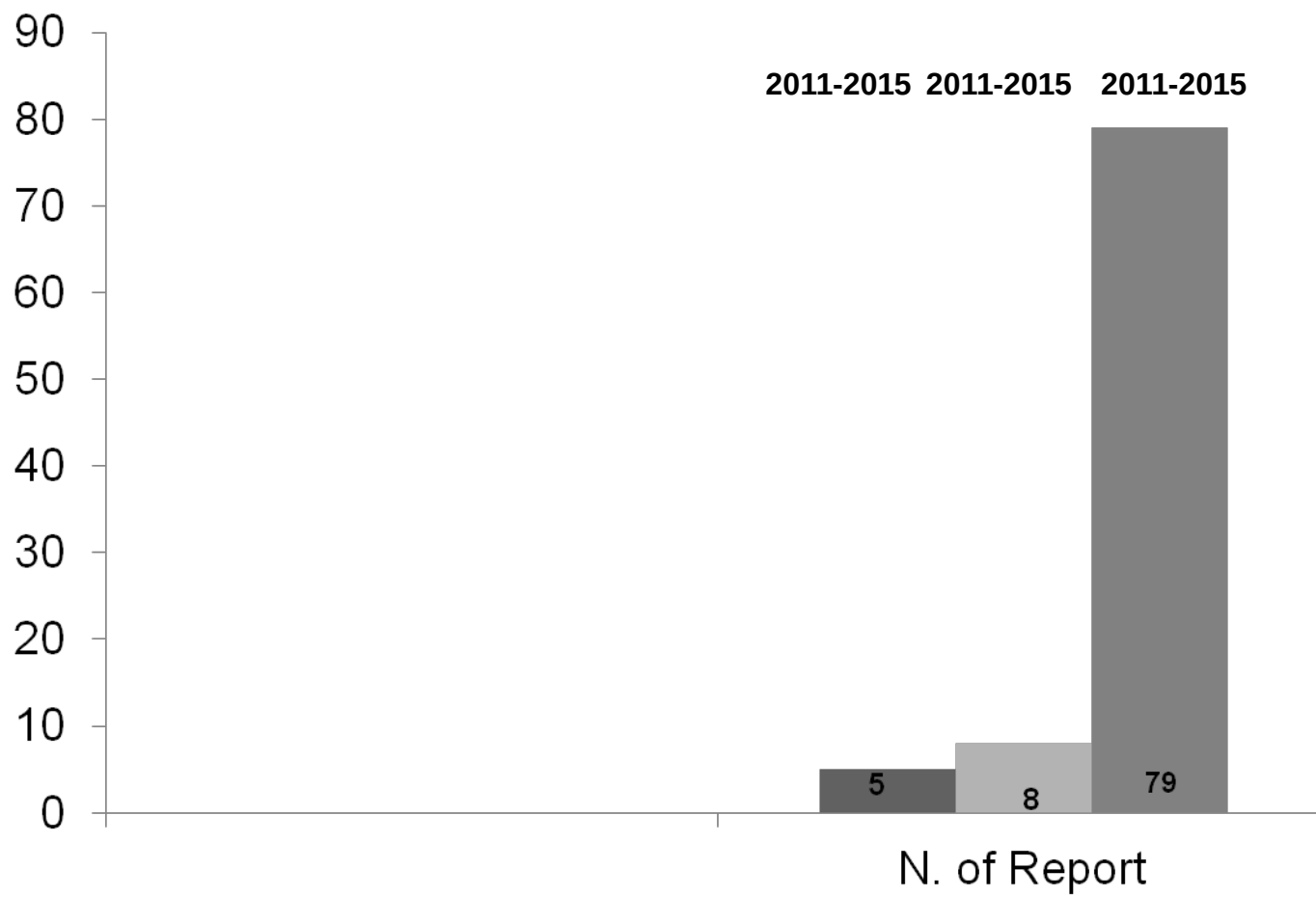
Additional investigation regarding the oncologic outcomes and morbidity of hyperthermic intraperitoneal chemotherapy **is warranted**.

Minerva Ginecol. 2014

Cytoreductive surgery plus HIPEC is feasible in patients with ovarian cancer with 65.6 % grade 3/4 morbidity and no deaths. Balancing these complications with potential survival benefits is important in centers considering implementing HIPEC protocols

Ann Surg Oncol. 2015

N. of Report on CRS-HIPEC for Ovarian Cancer on Pubmed



Survival Benefit of Adding Hyperthermic IntraPERitoneal Chemotherapy (HIPEC) at the Different Time-points of Treatment of Ovarian Cancer: Review of Evidence

Stefaan Mulier^{1*}, Jean-Pierre Claes², Vincent Dierieck¹, Jean-Olivier Amiel³, Jean-Philippe Pahaut³, Luc Marcelis⁴, Fabienne Bastin⁴, Denis Vanderbeeken⁴, Claude Finet⁵, Sophie Cran⁶ and Thierry Velu⁷

Evidence of potential benefit of CRS and HIPEC at the different time point of EOC Treatment

Time-point	Non Comparative Trials*	Comparative Trials	Randomized Phase 3 Trials
upfront CRS	(-)		
interval CRS	(+)		1 ongoing (the Netherlands) 1 ongoing (Italy)
consolidation CRS	(0)	(+)	
secondary CRS stage I-II		0	
secondary CRS stage III	0	+	1 ongoing (the Netherlands)
salvage CRS	+	+	2 ongoing (France, Italy)
palliative (HIPEC only)	quality of life ↑		

Survival Benefit of Adding Hyperthermic IntraPERitoneal Chemotherapy (HIPEC) at the Different Time-points of Treatment of Ovarian Cancer: Review of Evidence

Stefaan Mulier^{1*}, Jean-Pierre Claes², Vincent Dierieck¹, Jean-Olivier Amiel³, Jean-Philippe Pahaut³, Luc Marcelis⁴, Fabienne Bastin⁴, Denis Vanderbeeken⁴, Claude Finet⁵, Sophie Cran⁶ and Thierry Velu⁷

Upfront CRS and HIPEC

Reference	treatment	n	FIGO III-IV	FIGO III	FIGO IV	CC0	mortality	follow-up	5 y PFS	PFS	5 y OS (all)	5 y OS (CC0)	OS (all)	OS (CC0)
3	CRS and HIPEC	2	100%	100%	0%		0%			5 m			14.5 m	
4	CRS and HIPEC	51	100%			40%		98 m			28%		28.5 m	47 m
5	CRS and HIPEC	8	100%	75%	25%								29 m *	
6	CRS and HIPEC	31	100%	100%	0%								34.1 m	
7	CRS and HIPEC	19	100%	100%	0%	47%	0%			25 m	37%	60%	38 m*	
8	CRS and HIPEC	26							19.7%	24.8 m	33.3%		41.7 m	
8	CRS and HIPEC	26	100%	96%	4%	58%	3.8%	25 m	15.2%	30 m	60.7%		NR	
10	CRS and HIPEC	14	100%	100%	0%	79%	0%				55%			NR
11	CRS only	336	100%	76%	24%	20%	2.6%	56 m		12 m	19.5%	31.3 %	29 m	45.0 m
12	CRS only	68	100%					42 m		15 m			39 m	
13	CRS only	279	100%	100%	0%	26%							41 m	
14	CRS only	55	100%	100%	0%		0%	74 m					48 m	
15	CRS only	210	100%	100%	0%	68%		48 m		18.3 m			49.7 m	
16	CRS only	285	100%	87%	13%	24%	0.7%			17 m			50 m	78 m
17	CRS only	332	100%	78%	22%	60%	2.7%	23 m*		33.2 m			51.3 m	65.4 m
18	CRS only	227	100%	100%	0%	36%	0.9%			22.2 m			52.2 m	
19	CRS only	210	100%	83%	17%	27%	1.0%	54 m	31.0%		47.0%		54.0 m	
20	CRS only	408	100%	100%	0%	86%		33 m			49.0%		58.2 m	76.2 m

SUMMARY

HIPEC GROUP:

Median OS: 14.5-41.7 month (70)

5 year OS: 28-60.7%whole group

5year OS cc-0: 47 months and 60.0%.

Median 5 year DFS: 5-30 months

5 year DFS: 15.2-19.7%

NO HIPEC GROUP:

Median OS: 29-58,2 month

5 year OS: 19,5-49% whole group

5year OS cc-0: 45-78 months and 31,3.0%.

Median 5 year DFS: 12-33,2 months

5 year DFS: 31.0%%

Hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery (CRS) in ovarian cancer: A systematic review and meta-analysis

Y.R. Huo ^{a,b}, A. Richards ^b, W. Liauw ^c, D.L. Morris ^{a,b,*}

^aDepartment of Surgery, St George Hospital, University of New South Wales, Kogarah, Sydney, NSW 2217, Australia

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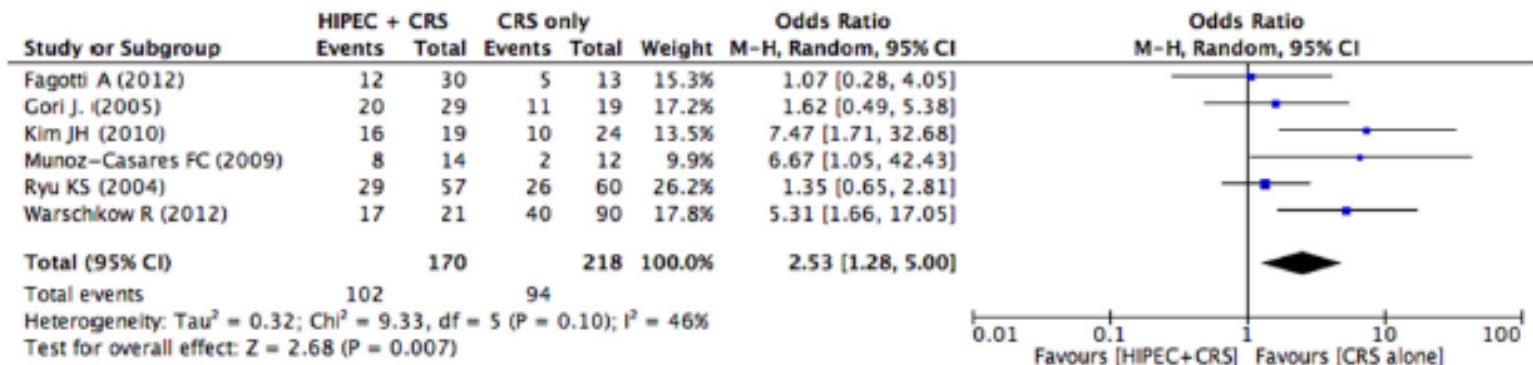
^cCancer Care Centre, St George Hospital, Kogarah, Sydney, NSW 2217, Australia

Accepted 24 August 2015

Available online ■ ■ ■

HIPEC + CRS + chemotherapy had significantly better 1-year survival compared with CRS + chemotherapy alone (OR: 3.76, 95% CI 1.81e7.82). The benefit of HIPEC p CRS continued for 2-, 3-, 4-, 5- and 8-year survival

5YR Overall Survival



Hyperthermic intraperitoneal chemotherapy (HIPEC) and cytoreductive surgery (CRS) in ovarian cancer: A systematic review and meta-analysis

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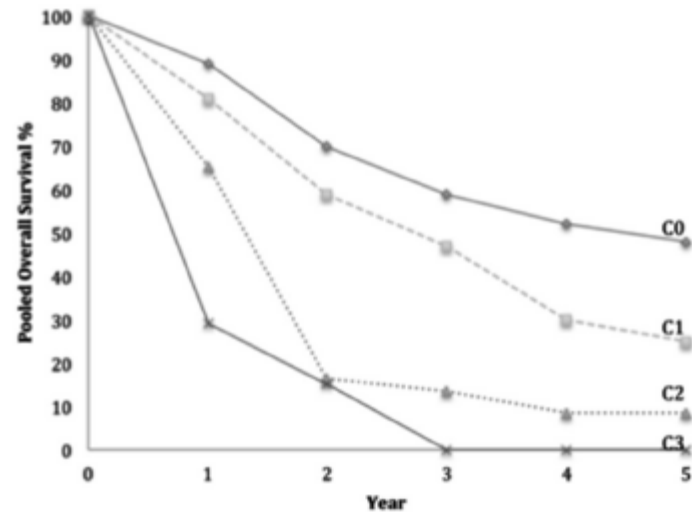
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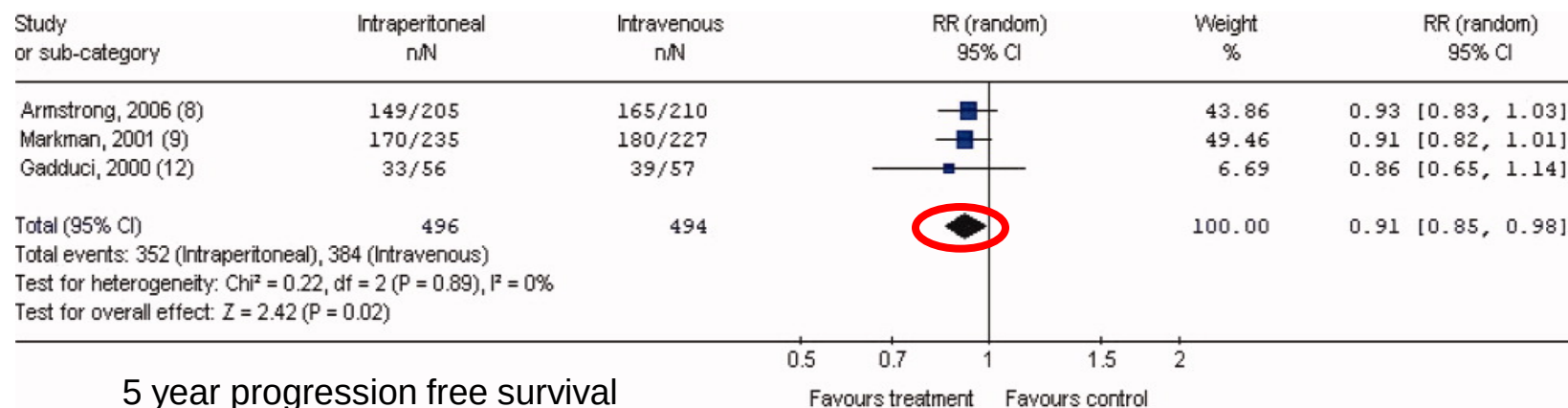
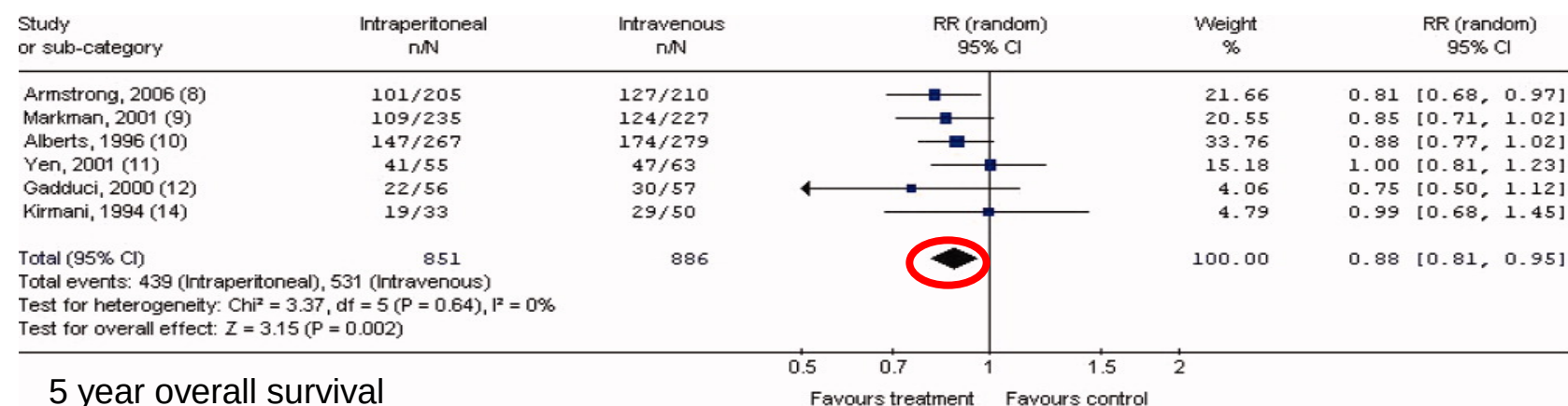


Cytoreduction completeness	N Studies	N	Median OS (months)	OS (%)				
				1yr	2yr	3yr	4yr	5yr
C0	9	268	45	90.1	74.3	64.4	51.7	48.4
C1	4	48	24	81	59	47	30	25
C2	3	43	12.5	65	16.5	13.5	8.5	8.5
C3	1	7	7	29	15	0	0	0
C0/1	16	473	35.6	88	69	56	46	41
C2/3	9	111	14.8	55	28	22	14	9

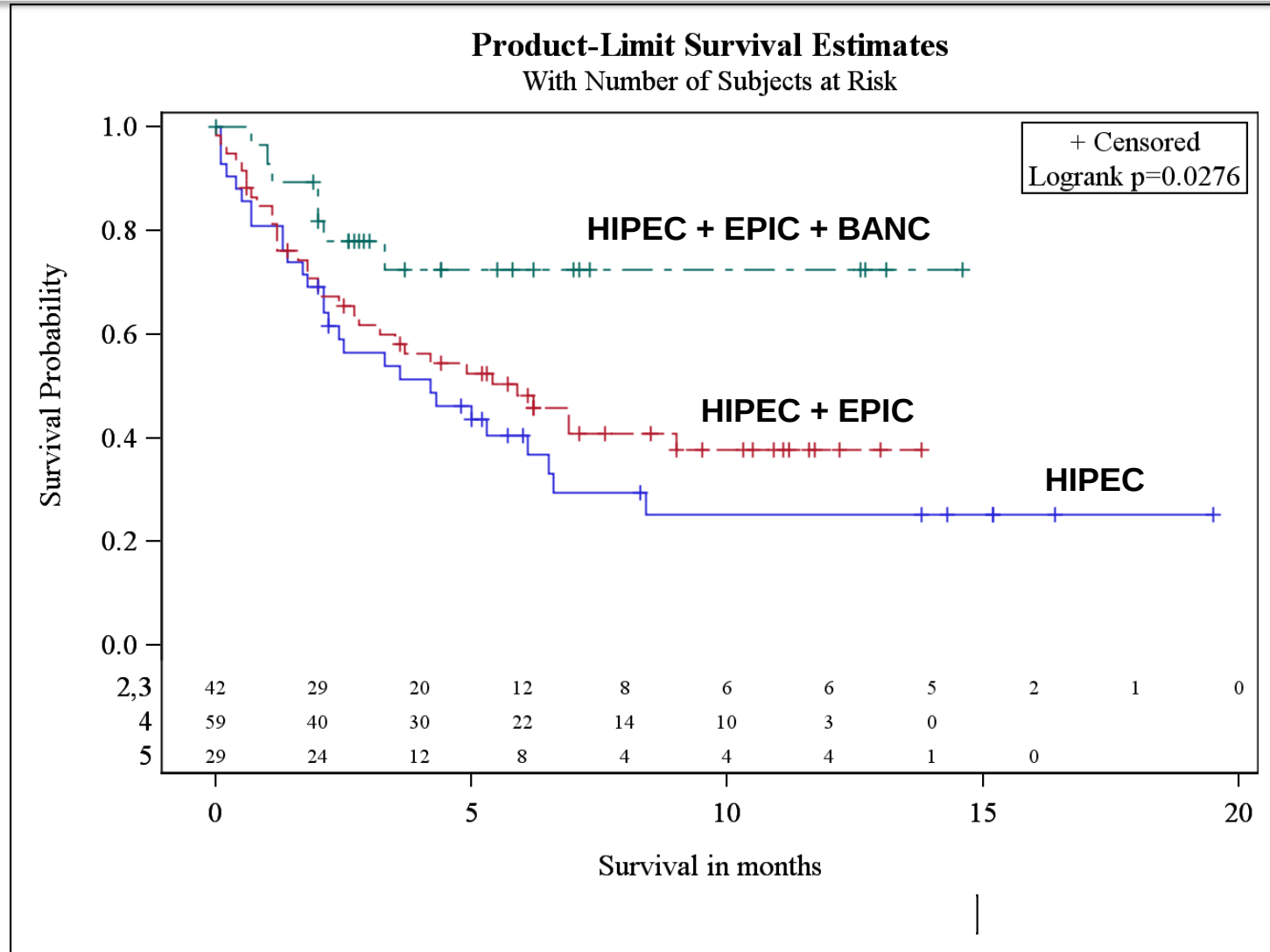
Figure 2. Pooled overall survival of all studies according to completeness of cytoreduction.

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

A Systematic Review With Metaanalyses



BANC long-term can help maintain the surgical complete response in peritoneal mesothelioma



Survival of peritoneal mesothelioma by three different treatment plans

EOC: Ongoing Trial on CRS-HIPEC

- **Outcomes in CRS/HIPEC as initial treatment of ovarian, fallopian tube and primary peritoneal cancer.** Available: <https://clinicaltrials.gov/ct2/show/NCT02124421?term¼hyperthermicpintraperitoneal&rank¼8>.
- **Intraoperative hyperthermic intraperitoneal chemotherapy with ovarian cancer.** Available: <https://clinicaltrials.gov/ct2/show/NCT01091636?term¼hyperthermicpintraperitoneal&rank¼10>. 75.
- **Secondary debulking surgery þ/- hyperthermic intraperitoneal chemotherapy in stage III ovarian cancer.** Available: <https://clinicaltrials.gov/ct2/show/NCT00426257?erm¼hyperthermicpintraperitoneal&rank¼13>.
- **Phase 3 trial evaluating hyperthermic intraperitoneal chemotherapy in upfront treatment of stage IIIC epithelial ovarian cancer (CHORINE).** Available: <https://clinicaltrials.gov/ct2/show/CT01628380?term¼hyperthermicpintraperitoneal&rank¼17>. 77.
- **Hyperthermic intra-peritoneal chemotherapy (HIPEC) in ovarian cancer recurrence (HORSE).** Available: <https://clinicaltrials.gov/ct2/show/NCT01539785?term¼hyperthermicpintraperitoneal&rank¼7>. 78

EOC: Ongoing Trial on CRS-HIPEC

- **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.** Available: <https://clinicaltrials.gov/ct2/show/NCT01767675?term¼hyperthermicþintraperitoneal&rank¼2;>.
- **Hyperthermic intra-peritoneal chemotherapy (HIPEC) in relapse ovarian cancer treatment (CHIPOR).** Available: [https:// clinicaltrials.gov/ct2/show/NCT01376752?term¼hyperthermicþintraperitoneal&rank¼23;](https://clinicaltrials.gov/ct2/show/NCT01376752?term¼hyperthermicþintraperitoneal&rank¼23;).
- **Cytoreduction with or without intraoperative intraperitoneal hyperthermic chemotherapy (HIPEC) in patients with peritoneal carcinomatosis from ovarian cancer, fallopian tube or primary peritoneal carcinoma (CARCINOHIPEC)** Available: <https://clinicaltrials.gov/ct2/show/NCT02328716?term¼hyperthermicþintraperitoneal&rank¼59;>
- **Surgery and chemotherapy with or without chemotherapy after surgery in treating patients with ovarian, fallopian tube, uterine, or peritoneal cancer [Online].** Available: [http://www.cancer.gov/ clinicaltrials/search/view?cdrid¼754204&version¼HealthProfessional&protocolsearchid¼13874015..](http://www.cancer.gov/clinicaltrials/search/view?cdrid¼754204&version¼HealthProfessional&protocolsearchid¼13874015..)

FUTURE OF CRS-PP AND HIPEC ON EOC:: CONCLUSION

- Promising results for HIPEC after CRS-PP on Primary (No RCTs available- No level 1 EBM) Experience reported in the literature is increasing
- Optimize the CRS by Introducing ntroducing more and more extensively, the concept of radicality by the use of PP
- Privilege Primary CRS-PP instead of NACT that should be considered for patients with bulky stage IIIC or IV who are not candidates for up-front CRS
- This requires surgeons or gynecologists specialize in cutting methods.
- When neoadjuvant sCT is necessary, mapping of the extension of the disease (VLS) before sCT to optimize the Interval Debulking CRS;
- Ongoing studies guide us on the best treatment in the future as the addition of HIPEC to the standard treatment.
- HIPEC must not esclude IPCT and viceversa

PROGRAMMA TUMORI PERITONEALI

Tumori Peritoneali: 20 Anni di Esperienza all'Istituto Nazionale dei Tumori di Milano



**FONDAZIONE IRCCS
ISTITUTO NAZIONALE
DEI TUMORI**

