CRS + HIPEC

A qualcuno piace caldo

a cura di Pietro BAGNOLI
UO Chirurgia Generale Oncologica

Di cosa parliamo

- Procedura codificata da PH Sugarbaker 30 anni fa
- Sinergia fra asportazione completa della malattia, ipertermia e chemioterapia
- Alle alte temperature le cellule neoplastiche sono più permeabili ai farmaci chemioterapici

Il razionale della HIPEC -1

Il concetto fondamentale è rappresentato dalla tendenza di alcuni farmaci a concentrarsi a livello del peritoneo attraversandolo solo gradualmente. Tale probabilità dipende da molteplici fattori, tra cui la supposta presenza di una **barriera plasmatico-peritoneale**

Il razionale della HIPEC - 2

Tale ipotesi è basata su diversi studi che confermerebbero l'esistenza di un gradiente plasmatico-peritoneale. La barriera è rappresentata dal tessuto sottomesoteliale e dalla membrana basale dei capillari, che limitano il riassorbimento di farmaci idrofili o ad elevato peso molecolare come la mitomicina C, il cisplatino e la doxorubicina

l razionale della HIPEC – 3

È stato dimostrato che il cisplatino ha una maggiore capacità di penetrazione nel tessuto tumorale quando somministrato in condizioni ipertermiche. Inoltre, a 40-42 ° C le cellule neoplastiche diventano più chemiosensibili per l'aumentata concentrazione intracellulare dei farmaci, la maggiore attivazione, specialmente per gli agenti alchilanti,la diminuita capacità di riparo dei danni al DNA

Oggetto del trattamento

- Malattie primitive:
  - Mesotelioma
- Malattie primitive «forse sì e forse no»:
  - PMP
- Malattie secondarie:
  - CRC
  - EOC

Cosa sappiamo

- Per le malattie primitive è l’unico vero trattamento
- Nel carcinoma ovarico ed in una elevata percentuale di carcinoma del colon, la malattia rimane confinata all'addome per gran parte della sua storia naturale, conferendone una caratteristica evoluzione loco-regionale
- L'elevata concentrazione di farmaco ottenibile mediante un trattamento locoregionale, consente di superare la resistenza intrinseca od acquisita nei confronti del farmaco e simultaneamente ridurre gli effetti collaterali sistemici

Come funziona

- Il concetto fondamentale di un trattamento intraperitoneale è rappresentato dalla tendenza di alcuni farmaci a concentrarsi a livello del peritoneo attraversandolo solo gradualmente
- Tale probabilità dipende da molteplici fattori, tra cui la presunta presenza di una barriera Plasmatico-Peritoneale. Tale ipotesi è basata su diversi studi che confermano l'esistenza di un gradiente plasmatico-peritoneale. La barriera è – come detto – rappresentata dal tessuto sottomesoteliale e dalla membrana basale dei capillari, che limitano il riassorbimento di farmaci idrofili o ad elevato peso molecolare come la mitomicina C, il cisplatino e la doxorubicina

I vantaggi del caldo

- È stato dimostrato che il cisplatino ha una maggiore capacità di penetrazione nel tessuto tumorale quando somministrato in condizioni ipertermiche
- Inoltre, a 40-42 ° C le cellule neoplastiche diventano più chemiosensibili per l'aumentata concentrazione intracellulare dei farmaci, la maggiore attivazione, specialmente per gli agenti alchilanti,la diminuita capacità di riparo dei danni al DNA

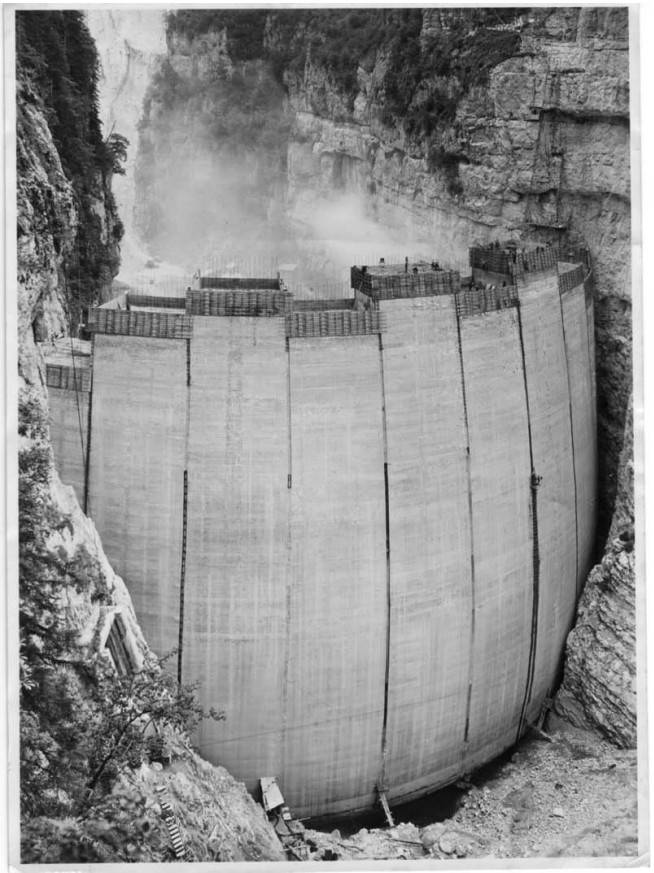
Carcinosi da colon: dalle esperienze allo studio randomizzato

- Sino a circa il 1998 erano stati pubblicati 11 studi di fase II che evidenziavano una 5-year OS fra il 20 e il 30%, analoga a quella dei pazienti resecati per LM. Questo trend avvalorava l'ipotesi di Sugarbaker, ma mancava ancora il trial randomizzato
- Dal 1998 al 2001 Verwaal al Netherlandse Cancer Institute elaborò il progetto di uno studio randomizzato di fase III in un singolo istituto

Lo spartiacque

Randomized Trial of Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy Versus Systemic Chemotherapy and Palliative Surgery in Patients With Peritoneal Carcinomatosis of Colorectal Cancer

By Vic J. Verwaal, Serge van Ruth, Belco de Bree, Goolie W. van Slooten, Horm van Tinteren, Henk Boot, and Frans A.N. Zoetmulder



La randomizzazione

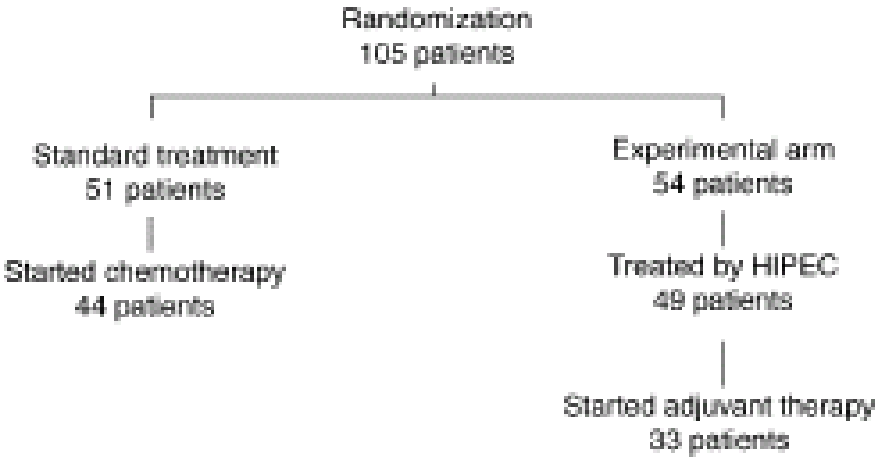


Fig 1. Trial profile of all 105 randomly assigned patients. HIPEC, hyperthermic intraperitoneal chemotherapy.

Il risultato

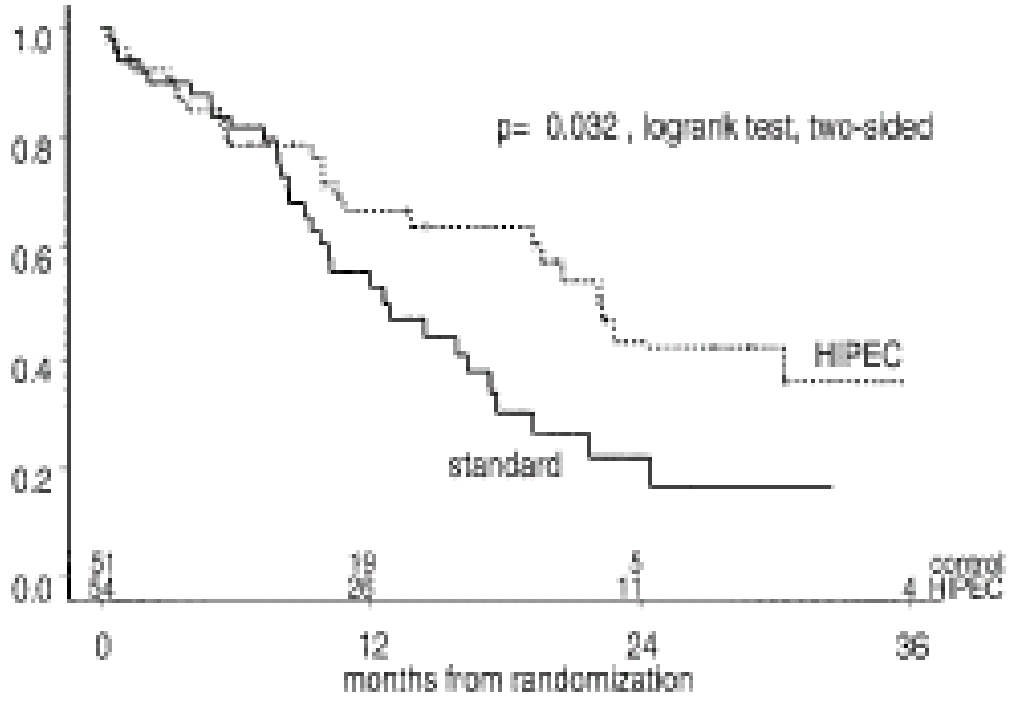
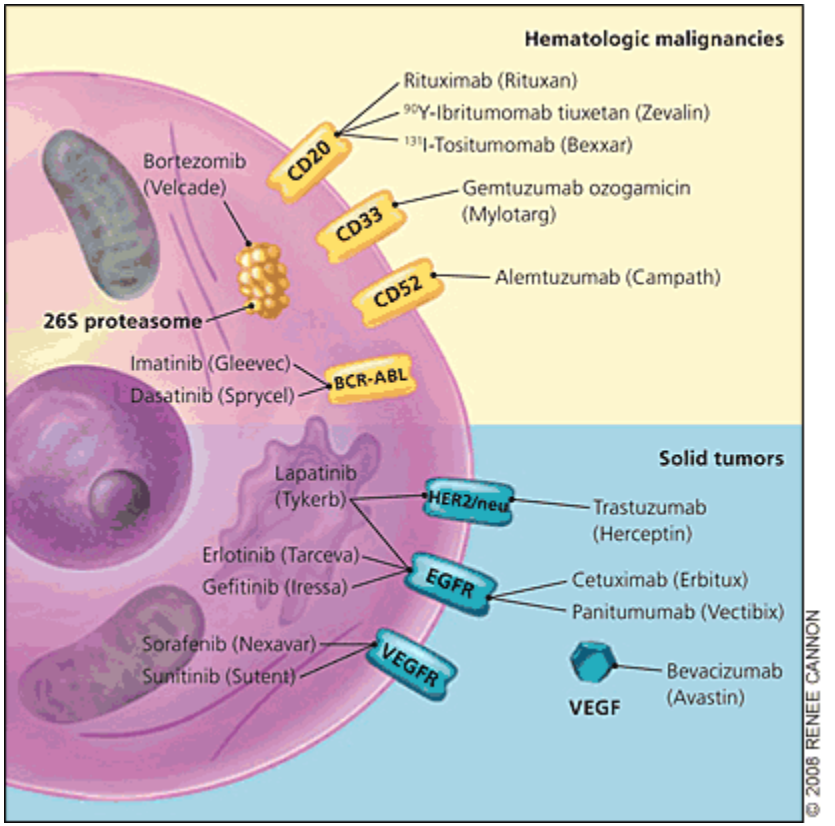


Fig 2. Kaplan-Meier survival curve, comparing standard treatment to hyperthermic intraperitoneal chemotherapy (HIPEC).

Le critiche allo studio

Al momento del lancio del trial, non erano ancora disponibili i nuovi protocolli terapeutici né le targeted-therapies



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DOI: 10.1245/s10434-008-9966-2

8-Year Follow-up of Randomized Trial: Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy Versus Systemic Chemotherapy in Patients with Peritoneal Carcinomatosis of Colorectal Cancer

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Introduction: The treatment of peritoneal carcinomatosis is based on cytoreduction followed by hyperthermic intraperitoneal chemotherapy and combined with adjuvant chemotherapy. In 2003, a randomized trial was finished comparing systemic chemotherapy alone with cytoreduction followed by hyperthermic intraperitoneal chemotherapy and systemic chemotherapy. This trial showed a positive result favoring the studied treatment. This trial has now been updated to a minimal follow-up of 6 years to show long-term results.

Patients and Methods: For all patients still alive, the follow-up was updated until 2007. In the original study, four patients were excluded—two because of no eligible histology/pathology and two because of major protocol violations. After randomization, four patients in the HIPEC arm and six in the control arm were not treated using the intended therapy, one patient because of withdrawal, one because of a life-threatening other malignant disease and the others because of progressive disease before initiation of the treatment. During the follow-up, one patient was crossed over from the control arm and underwent cytoreduction and HIPEC for recurrent disease, after the assigned treatment was completed. The data from these patients were censored at the moment of the cross-over. Progression-free and disease-specific survival were analyzed using the Kaplan Meier test and compared using the log rank method. The long-term results were studied in more detail to evaluate efficacy and toxicity.

Results: At the time of this update, the median follow-up was almost 8 years (range 72–115 months). In the standard arm, 4 patients were still alive, 2 with and 2 without disease; in the "HIPEC arm, 5 patients were still alive, 2 with and 3 without disease. The median progression-free survival was 7.7 months in the control arm and 11.6 months in the HIPEC arm ($P = 0.020$). The median disease-specific survival was 12.6 months in the control arm and 22.3 months in the HIPEC arm ($P = 0.028$). The 5-year survival was 45% for those patients in whom a R1 resection was achieved.

Conclusion: With 90% of all events having taken place up to this time, this randomized trial shows that cytoreduction followed by HIPEC does significantly add survival time to patients afflicted by peritoneal carcinomatosis of colorectal origin. For a selected group, there is a possibility of long-term survival.

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ORIGINAL REPORT

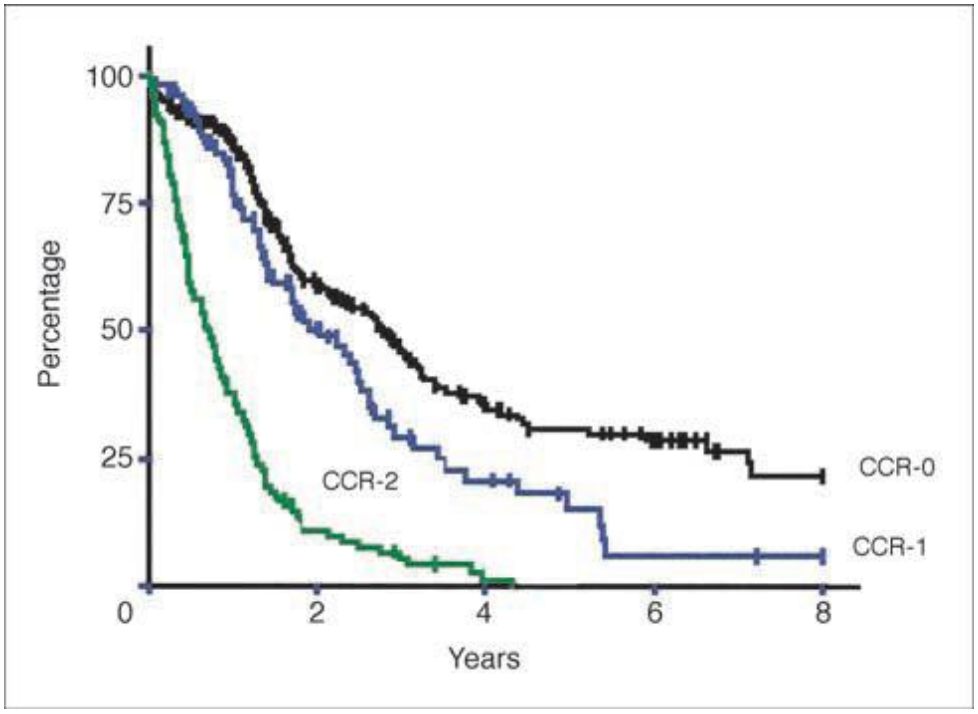
Cytoreductive Surgery Combined With Perioperative Intraperitoneal Chemotherapy for the Management of Peritoneal Carcinomatosis From Colorectal Cancer: A Multi-Institutional Study

O. Glehen, F. Kwiatkowski, P.H. Sugarbaker, D. Elias, E.A. Levine, M. De Simone, R. Barone, Y. Yonemura, F. Cavaliere, F. Quenet, M. Gutman, A.A.K. Tentes, G. Lorimier, J.L. Bernard, J.M. Bereder, J. Porcheron, A. Gomez-Portilla, P. Shen, M. Deraco, and P. Rat

I numeri di Glehen

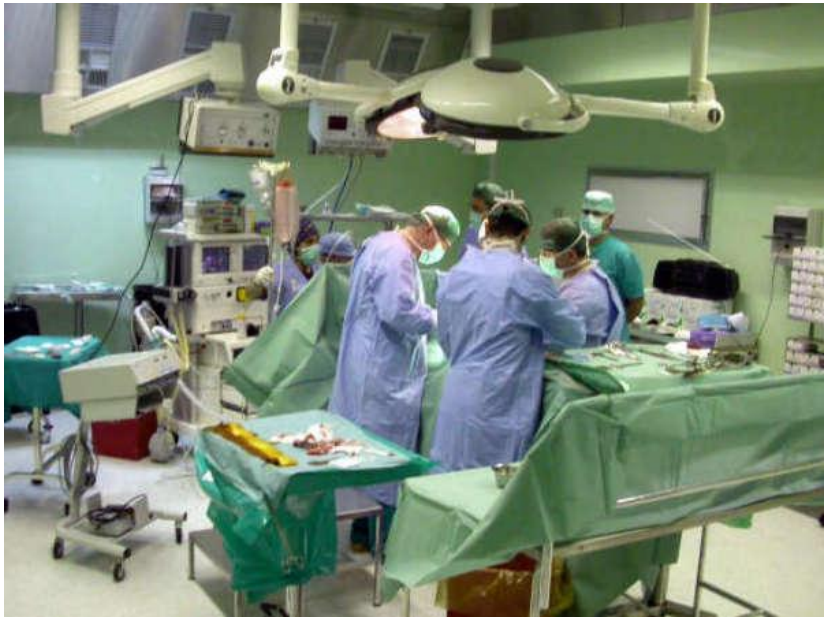
I risultati pubblicati da Glehen riguardanti uno studio retrospettivo condotto su 506 pazienti sottoposti a peritonectomia e HIPEC hanno evidenziato una sopravvivenza mediana globale è stata di **19,2** mesi; i pazienti che hanno ottenuto una citoriduzione completa, hanno avuto una prognosi migliore con una sopravvivenza mediana di **32,4** mesi. La completezza della citoriduzione si è rivelata essere una variabile statisticamente significativa ($p < .001$)

Sopravvivenza attuariale di 506 pazienti che hanno subito CRS + HIPEC in rapporto alla completezza della CRS

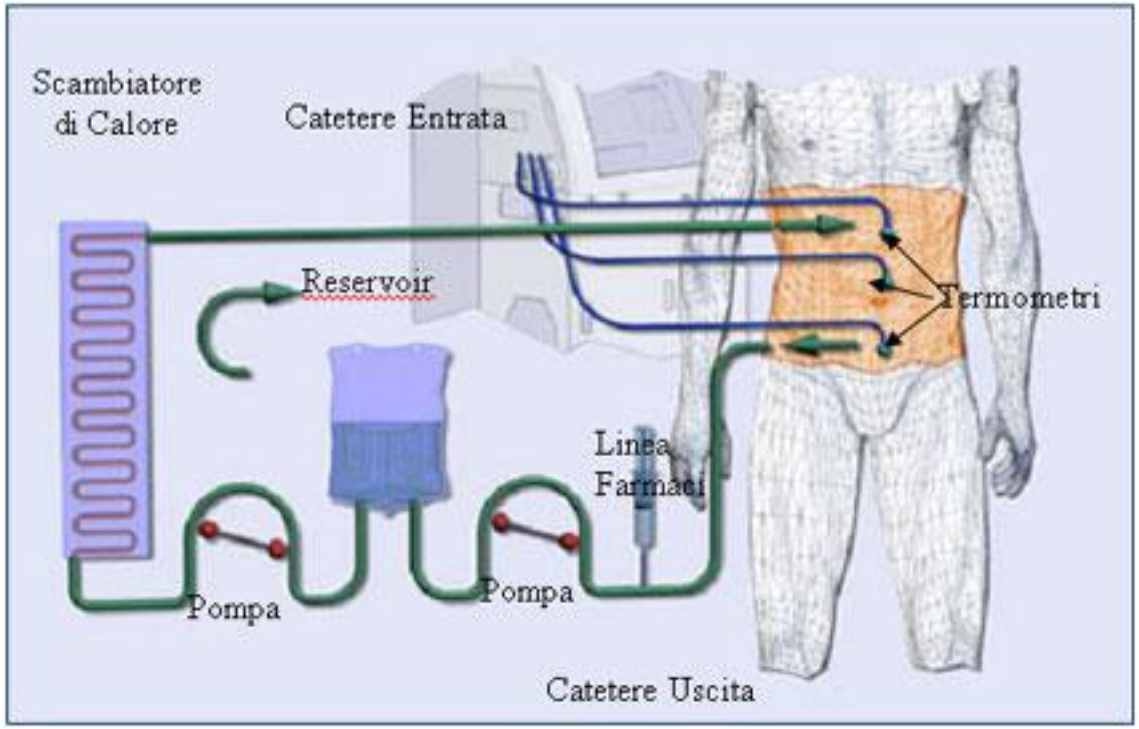


CRS

1. Peritonectomia pelvica, resezione del sigma-retto isterectomia ed annessectomia bilaterale;
2. Peritonectomia diaframmatica e parietale sinistra in blocco con omentectomia e splenectomia;
3. Peritonectomia diaframmatica destra, glissoniana, tasca di Morrison, bursa omentis, colecistecti
4. Resezione del piccolo omento e ilo epatico
5. Altre resezione intestinali
6. Citoriduzione mesentere
7. Anastomosi intestinali ev. ileostomia



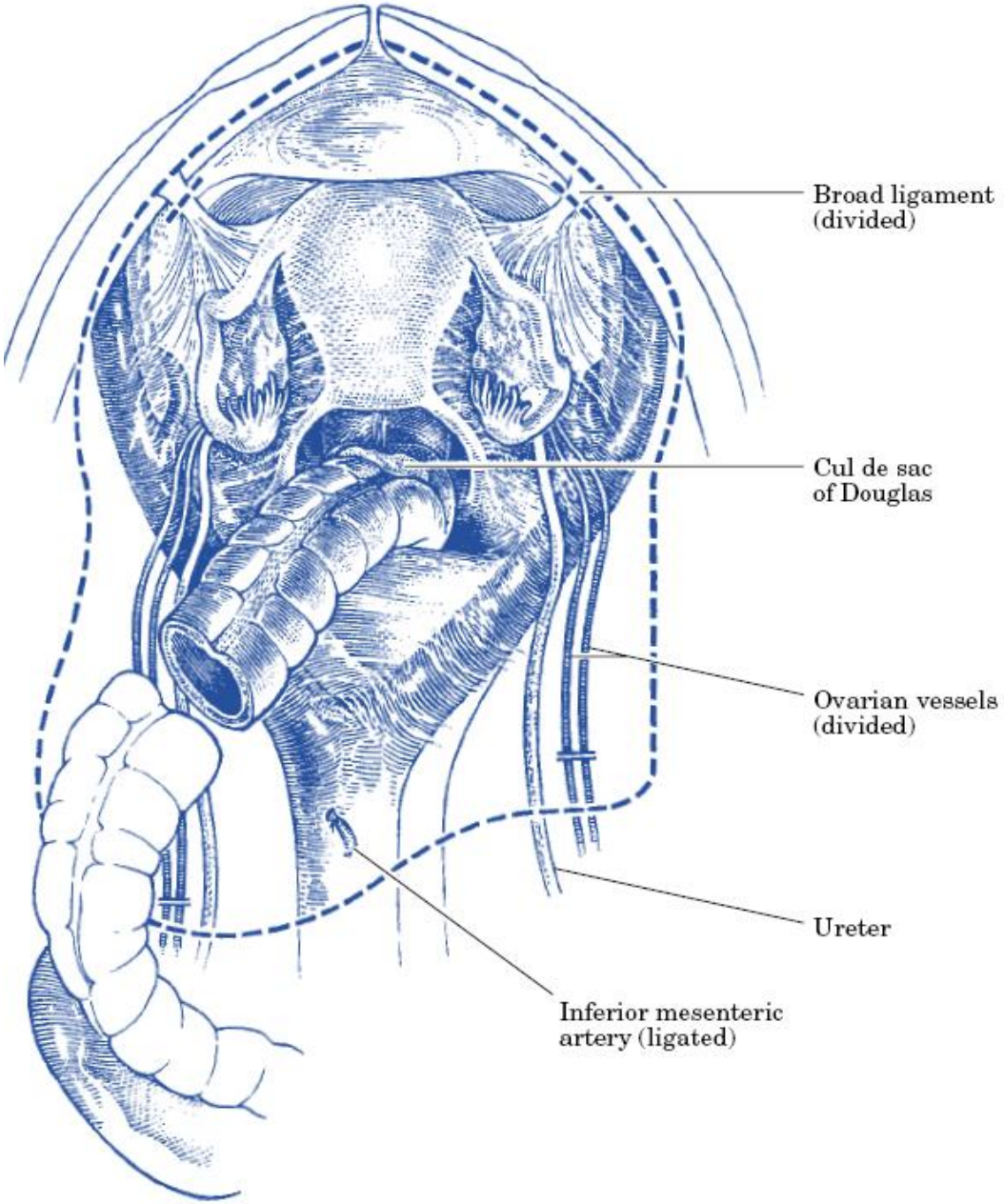
Il circuito della HIPEC

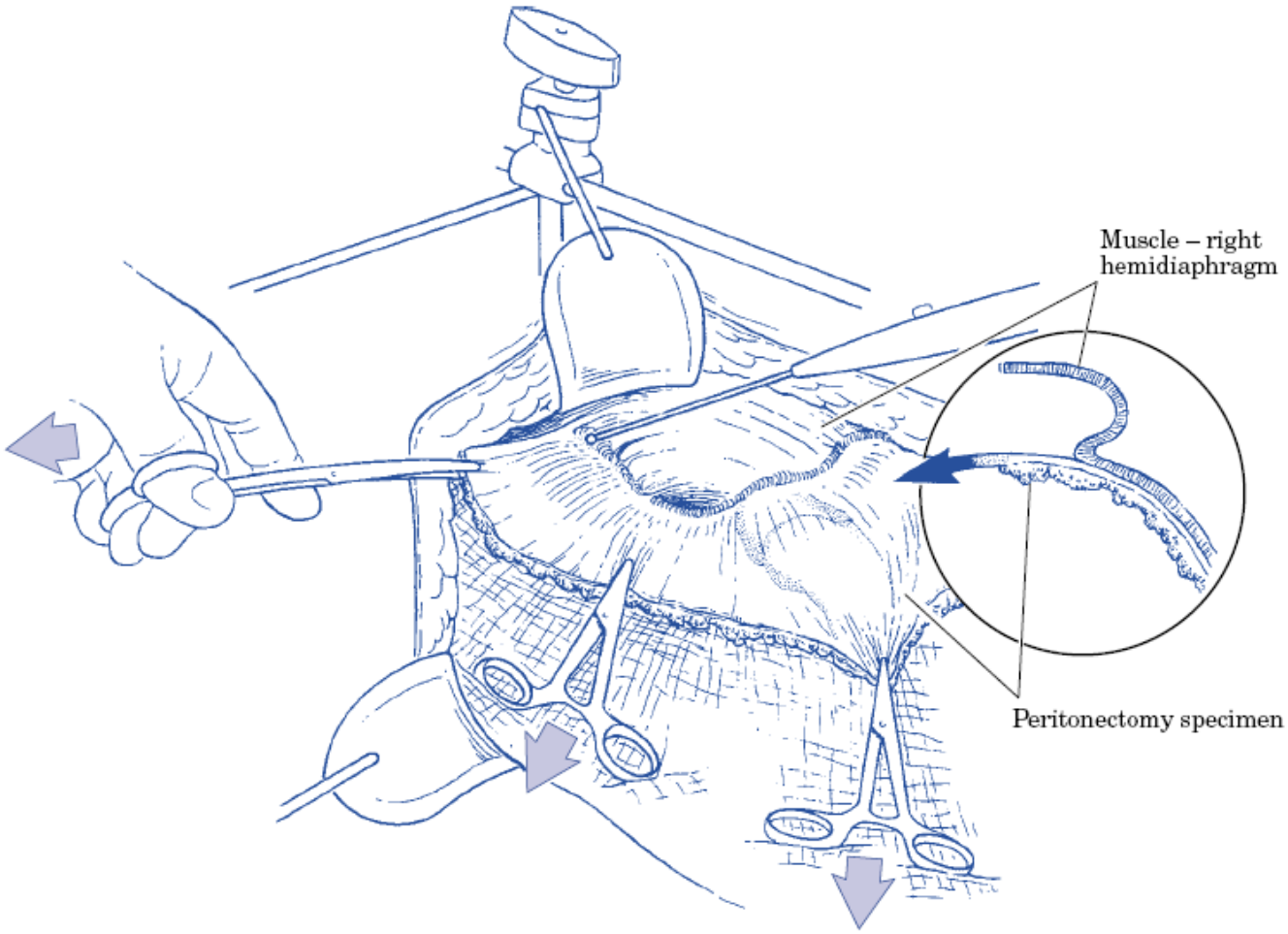


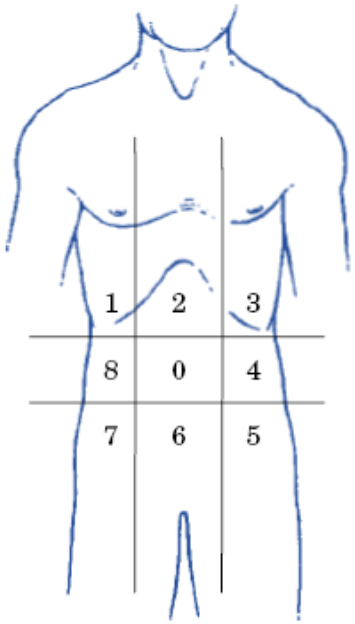
Cosa ci mettiamo dentro?

- I farmaci utilizzati nel perfusato per HIPEC per carcinosi peritoneale da colon sono: oxaliplatino (460 mg/m2) oppure MMC (3.3 mg/m2/l) + CDDP (25 mg/m2/l).
- Il regime proposto è:

- Oxaliplatino 460 mg/m2 in 2 l/m2 di soluzione per perfusione alla temperatura di 43°C per 30 minuti dal momento in cui si è raggiunta la temperatura endoaddominale di 42°C con un flusso di 2 L/min
- Durante la citoriduzione, **prima dell'inizio dell'HIPEC**, il paziente riceve la somministrazione endovenosa di 5FU ev 400 mg/m2 + leucovorin 20 mg/m2 allo scopo di potenziare l'azione dell'oxaliplatino. Il 5FU non può essere somministrato assieme all'oxaliplatino per via intraperitoneale a causa di incompatibilità di pH


Broad ligament
(divided)
Cul de sac
of Douglas
Ovarian vessels
(divided)
Ureter
Inferior mesenteric
artery (ligated)


Muscle – right hemidiaphragm
Peritonectomy specimen



Regions		Lesion size
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	____

PCI ☐

Lesion size score

LS 0 No tumour seen

LS 1 Tumour up to 0.5 cm

LS 2 Tumour up to 5.0 cm

LS 3 Tumour >5.0 cm or confluence

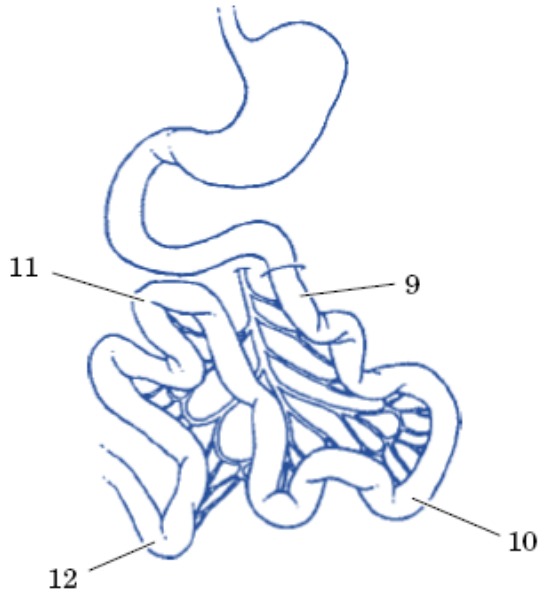


Figure 5 Peritoneal cancer index. The volume of tumour as assessed by the lesion size score is determined for the 13 abdomino–pelvic regions. The sum of these scores (0–39) is the peritoneal cancer index.

Sino a che punto ci si può spingere?

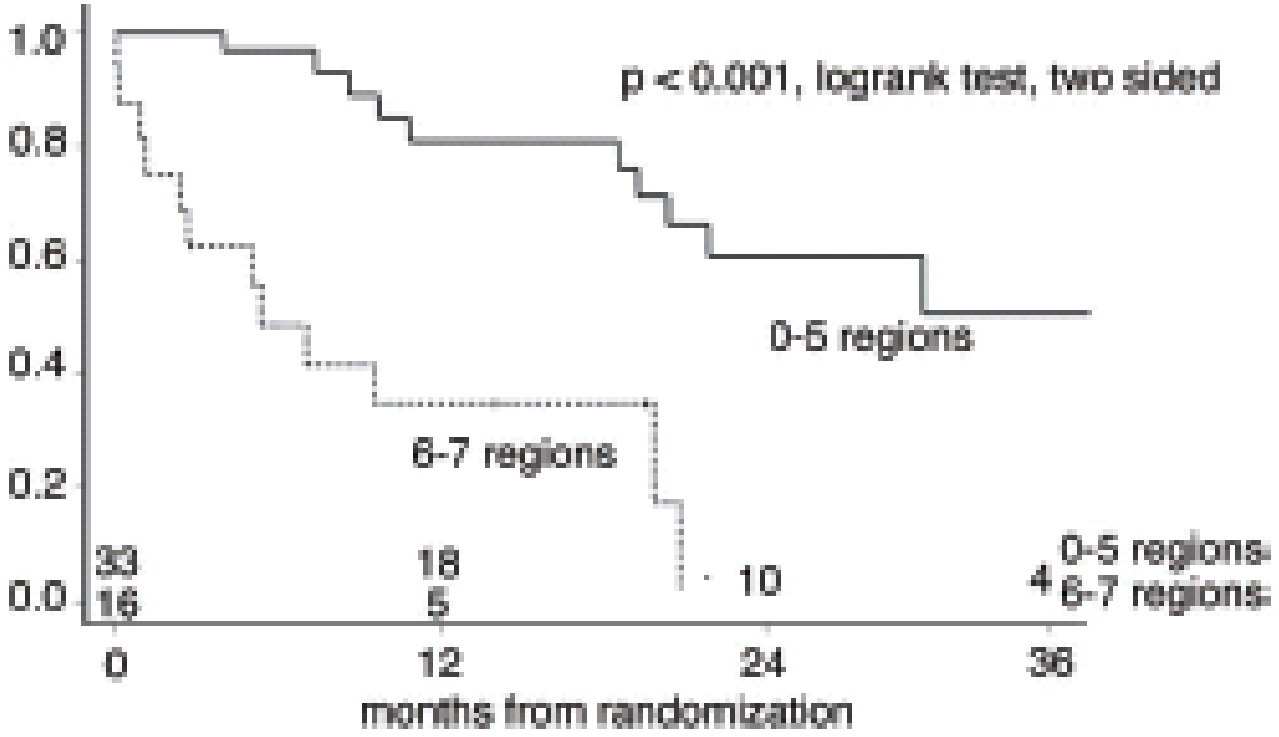


Fig 5. Kaplan-Meier survival curve of 49 patients with peritoneal carcinomatosis treated by cytoreduction followed by HIPEC, comparing the number of regions with residual tumor.

Fattori prognostici negativi

- **<u>citoriduzione non completa!!!</u>**
- **<u>estensione della carcinosi!!!</u>**
- coinvolgimento linfonodale
- dedifferenziazione
- metastasi a distanza

La malattia residua

- Viene utilizzata la classificazione di Sugarbaker:
- CC-0: assenza di malattia residua
- CC-1: malattia residua di diametro fra 0 e 2.5 mm
- CC-2: malattia residua fra 2.5 mm e 2.5 cm
- CC-3: malattia residua >2.5 cm
-
- La completezza della citoriduzione è **essenziale per la riuscita del trattamento**; la scarsa prospettiva di ottenere una buona citoriduzione dovrebbe portare a scartare il candidato al trattamento

Cosa fare per metastasi epatiche singole scoperte incidentalmente?

- Il numero delle metastasi non deve essere superiore a 3
- Non ci deve essere invasione dell'ilo, della VCI o delle VSE
- Adeguato "equilibrio" fra malattia peritoneale ed epatica

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Treatment of synchronous peritoneal carcinomatosis and liver metastases from colorectal cancer

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Importanza della qualità della CRS

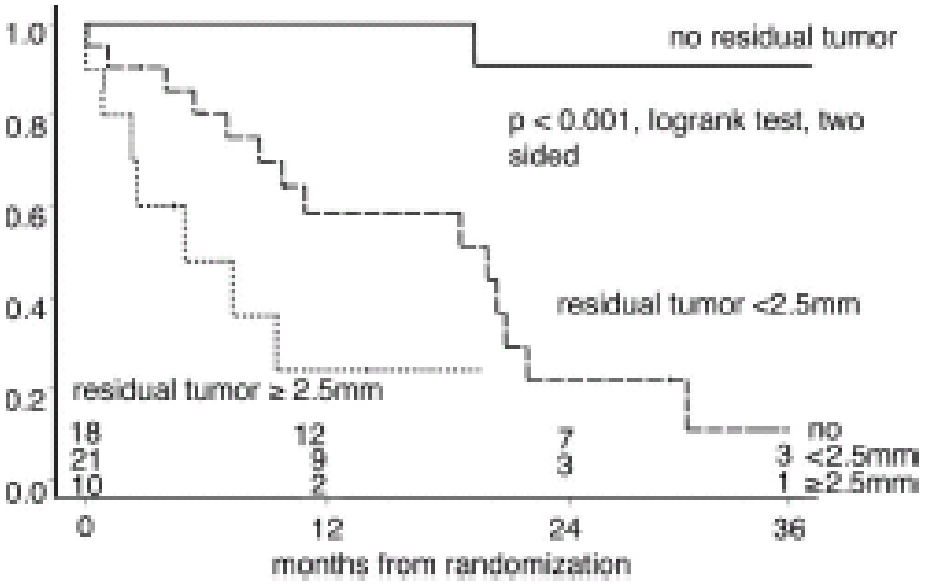

Fig 4. Kaplan-Meier survival curve of 49 patients with peritoneal Carcinomatosis (PC) treated by cytoreduction followed by hyperthermic intraperitoneal chemotherapy, comparing the number of regions affected with PC.

Problematiche prevedibili

Ferme restando le difficoltà correlate al lancio di ogni nuova attività clinica, questa – nello specifico – presenta una serie di problematiche peculiari, in primis i costi. Vanno considerati:

- prolungata occupazione della sala operatoria
- noleggio dell'apparecchio per la perfusione e del perfusionista
- prolungata ospedalizzazione
- eventuale TIG (in INT è di principio sempre per i primi 3 giorni, ma per casi da peritonectomia totale)
- DRG per il momento non ancora favorevole, ma la CRS + HIPEC è entrata nella Rete Oncologica Lombarda come trattamento per le carcinosi peritoneali

Complicanze attese

- Fistola anastomotica
- tossicità ematologica
- ileo paretico prolungato
- infezione di ferita
- versamento pleurico
- sepsi sistemica
- ascesso intraperitoneale
- emorragia
- TVP
- insufficienza renale
- respiratory distress

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Table 5. Details of Major Postoperative Complications (grade 3/4 according to the National Cancer Institute's Common Toxicity Criteria)

Type of Complication	No.	%
Digestive fistula	42	8.3
Hematologic toxicity	12	2.4
Systemic sepsis	10	2
Postoperative bleeding	9	1.8
Intra-abdominal abscess	9	1.8
Respiratory distress	8	1.6
Pneumonia	8	1.6
Urinary fistula	5	1
Line sepsis	5	1
Bowel obstruction	5	1
Pulmonary embolism	2	0.4
Peritonitis	2	0.4
Other	6	1.2
Combined morbidity	116	22.9
Mortality	20	4

The combination of two aggressive locoregional therapeutic approaches can lead to increased morbidity and mortality rates. This study reported morbidity and mortality rates of 22.9% and 3.7%, respectively, with 8.3% of digestive fistula. These results are comparable to those previously reported by the two most important trials dedicated to the analysis of the complications that occur after cytoreductive surgery and perioperative intraperitoneal chemotherapy and that concluded that morbidity was correlated with the magnitude of surgery.[37,38] No evaluation of the magnitude of surgery was recorded in the present study, but we observed that extended carcinomatosis that required extensive cytoreductive surgery had a significant negative influence on the rate of complications. Elias et al,[16] who treated patients with the combined procedures only when complete cytoreductive surgery was possible, previously reported that morbidity rates were correlated with carcinomatosis extent. Surgeons must use their judgment to achieve a balance between the postoperative risk of extensive surgery and potential benefit in survival and quality of life. Extended carcinomatosis was also an independent negative prognostic indicator. Its association with other negative prognostic indicators, such as lymph node involvement, poor differentiation, and liver metastasis, may lead to contraindicate patients for aggressive surgery combined with perioperative intraperitoneal chemotherapy with a curative intent. The high but acceptable rate of complications emphasizes the necessity for careful patient selection.

Vantaggi - 1

- I lavori in Letteratura sono globalmente concordi nell'indicare questo tipo di trattamento come **l'unico veramente efficace** per una condizione che, sinora, è sempre stata considerata pre-terminale. A confermare tale tendenza, va sottolineata l'attenzione sempre maggiore della ricerca di farmaci più efficaci per la HIPEC

Vantaggi - 2

- L’effettuazione di un trattamento sempre più al centro dell’attenzione
- Potenziale indotto correlato, includendo le carcinosi da ovaio e, in prospettiva futura, anche i tumori primitivi di difficile smaltimento nei Centri di riferimento come l’INT
- Alleanza con l’Istituto Nazionale Tumori di Milano
- Le procedure per le carcinosi da colon e ovaio sono *relativamente* più semplici di quelle per tumori primitivi. Secondo la Letteratura questa procedura è quindi propedeutica per le altre, decisamente più complesse
- la padronanza della metodica potrebbe portare all’attivazione di una vera e propria “Peritoneal Unit”

Possibili ulteriori campi di applicazione HIPEC

- Arti (sarcomi e melanomi)
- Stomaco: tutto da vedere, in linea di massima macroscopico affioramento sulla sierosa e/o ascite. Attenzione: NON carcinosi evidente e/o Krukenberg

Domande sull'ovaio

1. In che punto della storia naturale della malattia possiamo "piazzare" il trattamento?
2. Perché fare un trattamento così impegnativo in una malattia altamente chemio-responsiva?

Risposte

Although great strides have been made in the treatment of EOC, the enigma remains that a disease that is initially highly sensitive to chemotherapy compared with many other types of cancer is associated with an overall 5-year survival rate of just over 50%. There is an urgent need for an improvement in outcome for these women. This review discusses the role that hyperthermic intraperitoneal chemotherapy (HIPEC) could play in improving outcomes for women with EOC.

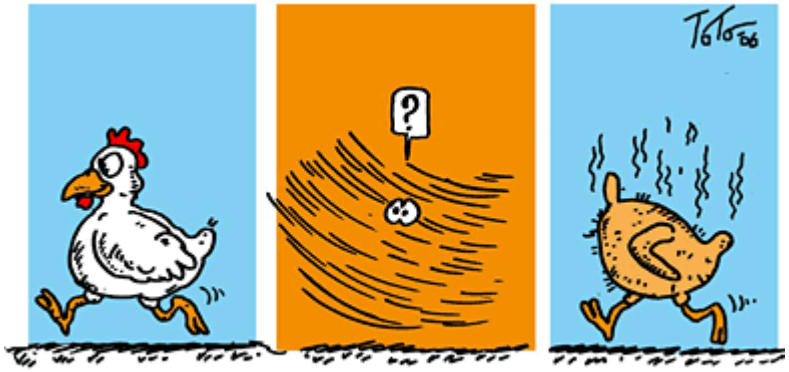
The standard of care for patients with EOC is initial cytoreductive surgery (CRS) followed by platinum–taxane chemotherapy. The finding that a better outcome was associated with small-volume disease was reported by Munnell [2] and confirmed by Griffiths [3] and multiple subsequent reports [4–6]. Although no randomized studies have been performed, a meta-analysis of 6,885 patients undergoing CRS during the platinum era reported that, for each 10% increase in the percentage of patients undergoing maximal CRS at any single institution, there was a 5.5% increase in the median duration of survival [7].

The significance of cytoreduction prior to chemotherapy is probably that it removes large-volume disease, which is known to contain poorly oxygenated, nonproliferating cells that are either resistant or potentially resistant to chemotherapy, and optimally leaves behind only small-volume residual tumors in which a greater percentage of cells are in the proliferative phase, making them more susceptible to chemotherapy. Also, the chemotherapy agents can achieve more complete tissue penetration.

ble 1) [9]. In January 2006, the results of a Gynecologic Oncology Group (GOG) study randomizing patients with optimal front-line surgery to receive combination normothermic cisplatin and paclitaxel via either the i.v. route only or combined i.v. and i.p. routes were reported [10]. Patients receiving at least part of their chemotherapy through the i.p. route had a median survival duration 16 months greater than patients in the control arm (65.6 months versus 49.7 months). That study followed two other large, randomized

Il caldo in più

Despite the 16-months longer median overall survival time in the GOG-172 trial, the median progression-free survival was only 5 months longer, 23.8 months versus 18.3 months, and the recurrence rate was still 65% in the investigational arm. Clearly, superior treatment methods are still needed for these women. One possibility is the incorporation of hyperthermia together with chemotherapy.



PREVISTA ONDATA DI CALDO

Gli studi sull'ovaio

Table 3. Published English-language studies of hyperthermic intraperitoneal chemotherapy for epithelial ovarian cancer

Study	Type	Situation	*n*	Agent	Dose	Time (min)	Temperature (°C)
Loggie et al. (1994) [100]	Pilot	Advanced	1	Mitomycin	30 mg	120	39–40.5
Steller et al. (1999) [52]	Pilot	Front-line	6	Carboplatin	800–1,200 mg/m²	90	41–43
van der Vange et al. (2000) [89]	Pilot	Recurrent/persistent	5	Cisplatin	50/75 mg/m²	90	40
Cavaliere et al. (2000) [101]	Retrospective	Recurrent/persistent	20	Cisplatin	25 mg/m²/l	90	41.5–42.5
Deraco et al. (2001) [90]	Phase II	Recurrent/persistent	27	Cisplatin	25 mg/m²/l	60	42.5
Panteix et al. (2002) [102]	Pharmacokinetic	Recurrent	16	Cisplatin	60/80/100 mg	90	41–43
de Bree et al. (2003) [65]	Prospective	Recurrent/persistent	19	Docetaxel	75 mg/m²	120	41–43
Chatzigeorgiou et al. (2003) [91]	Prospective	Recurrent/persistent	20	Cisplatin	50–70 mg/m²	120	39–40
Zanon et al. (2004) [92]	Phase II	Recurrent/persistent	30	Cisplatin	100/150 mg/m²	60	41.5–42.5
Look et al. (2004) [54]	Retrospective	Front line, recurrent/ persistent	12[a]	Cisplatin, mitomycin	[b]	60	41.5–42.5
Piso et al. (2004) [55]	Retrospective	Primary/recurrent	19	Cisplatin or mitoxantrone	75 mg/m², 15 mg/ m²	90	41.5
Ryu et al. (2004) [66]	Retrospective	Interval debulking/ second look	57	Carboplatin interferon-α	350 mg/m², 5 × 10^6 IU/m²	90	43–44
Gori et al. (2005) [81]	Retrospective	Second look	32	Cisplatin	100 mg/m²	60	41–43
Reichman et al. (2005) [67]	Retrospective	Recurrent/interval debulking	13	Cisplatin	50 mg/m²	90	40
Yoshida et al. (2005) [56]	Retrospective	Front line/interval debulking/second look	10	Cisplatin, mitomycin, etoposide	100 mg, 20 mg, 100 mg	50	41–44.5
Raspagliesi et al. (2006) [93][c]	Retrospective	Recurrent/persistent	40	Cisplatin/MMC or cisplatin/ doxorubicin	25/3.3 mg/m²/l or 43/15.25 mg/l	[c]	42.5
Rufián et al. (2006) [57]	Retrospective	Front line/recurrent	33	Paclitaxel	60 mg/m²	60	41–43
Helm et al. (2007) [94]	Retrospective	Recurrent/persistent	18	Cisplatin or mitomycin	100 mg/m² or 40 mg	90	42–43
Cotte et al. (2007) [58]	Prospective	Front line, recurrent/ persistent	81	Cisplatin	20 mg/m²/l, max 80 mg	90	44–46 inflow
Bae et al. (2007) [80]	Retrospective	Second look, persistent	67	Paclitaxel or carboplatin	175 mg/m² or 350 mg/m²	90	43–44
Di Giorgio et al. (2008) [59]	Prospective	Front line, interval debulking, second look, recurrent	45	Cisplatin	75 mg/m²	60	41–43

Excludes case report [53].
Adapted from Helm CW, Bristow RE, Kusamura S et al. Hyperthermic intraperitoneal chemotherapy with and without cytoreductive surgery for epithelial ovarian cancer. J Surg Oncol 2008;98:283–290.
[a] Some patients received early postoperative i.p. chemotherapy.
[b] Not stated.
[c] Some previously reported in Deraco M, Rossi CR, Pennacchioli E et al. Cytoreductive surgery followed by intraperitoneal hyperthermic perfusion in the treatment of recurrent epithelial ovarian cancer: A phase II clinical study. Tumori 2001;87: 120–126.
Abbreviation: MMC, mitomycin.

International Experience With Cytoreduction Plus HIPEC in Advanced Ovarian Cancer

Authors	Year	No. of cases	Disease setting	Follow-up, mo	% PCI	% CC score	% Major complications	% Mortality	% 5-Year Survival	Mean overall and DF survival, mo
Look[17]	2004	28	Primary/Secondary	0.5–79.1	9.8 (0–26)	CC 0–1, 57	11	0	NR	45.8
				26.9*	—	CC 2–3, 43				17.3†
Zanon[18]	2004	30	Primary/Secondary	2–68.2	<12, 44.3	CC 0–1, 77	16.7	3.30	NR	28.1
				18.9*	≥12, 56.7	—				17.1†
Piso[19]	2004	19	Primary/Secondary	24*	<15, 47.3	CC 0/1, 47.4	28	5	15	33
				—	≥15, 52.7	CC 2/3, 52.6				
Reichman[20]	2005	13	Primary/Secondary	6–36	6 (2–16)	CC 0, 38.5	NR	0	11‡	NR
				13.7*	—	CC 2/3, 61.5				
Rufian[21]	2006	33	Primary/Secondary	7–91	NR	R0, 52	36	0	37§	NR
				—	—	R1≤1 cm, 33			51‖	
				—	—	R2>1 cm, 15			—	
Raspaglieli[22]	2006	40	Secondary	0.3–117.6	NR	CC 0/1, 83	5	0	15	41.4
				26.1*	—	—				23.9†
Cotte[23]	2007	81	Secondary	9–237	11.5 (1–30)	CC 0, 55.6	13.6	2.50	NR	28.4
				47.1*	—	CC 1, 24.7				19.2†
				—	—	CC 3, 19.7				—
Helm[24]	2007	18	Secondary	30	NR	CC 0, 61.1	≥22.2	5.5	NR	31
				—	—	CC 1, 22.2				10†
				—	—	CC 2/3, 16.7				—
Current series	2007	47	Primary/Secondary	0.5–83	14.9 (6–28)	CC 0, 59.6	21.3	4.20	16.70	30.4
				—	<15, 46.8	CC 1, 27.7				27.4†
				—	<15, 53.2	CC 2/3, 12.7				—

PCI indicates peritoneal cancer index; NR, not reported; CC score, completeness of cytoreduction; DF, disease-free.

* Median.

† Disease-free.

‡ At 3 years.

§ Primary.

‖ Recurrent.

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Review

Advanced cytoreduction as surgical standard of care and hyperthermic intraperitoneal chemotherapy as promising treatment in epithelial ovarian cancer

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A recent retrospective review of 360 patients stage IV EOC who underwent primary surgery followed by 6 cycles of IV platinum/paclitaxel has provided important element to clear the issue. Median OS for microscopic, 0.1−5.0 cm, and >5.0 cm RD was 64, 30, and 19 months, respectively. The authors concluded that ultraradical surgeries might be targeted for selected patients in whom microscopic RD is achievable.[6]

According to the consensus statement (Milan 2006), the procedure could be employed in all time points (primary treatment, interval debulking, secondary cytoreduction, salvage treatment) with the exception of platinum resistant relapsing disease.[32] The studies published since then do not allow further conclusion other than that established by the 2006 consensus statement.

Un’idea per uno studio randomizzato multicentrico?…

Results of Systematic Second-Look Surgery in Patients at High Risk of Developing Colorectal Peritoneal Carcinomatosis

Dominique Elias, MD, PhD, Diane Goéré, MD,* Daniela Di Pietrantonio, MD,* Valérie Boige, MD,† David Malka, MD, PhD,† Max Kohneh-Shahri, MD,* Clarisse Dromain, MD,‡ and Michel Ducreux, MD, PhD†*

Criteri di inclusione

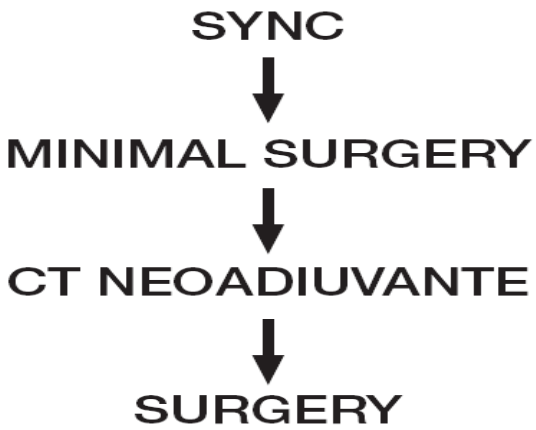
- Pazienti che hanno subito un intervento curativo per CRC e che hanno:
- associata una minima PC asportata radicalmente con il primitivo
- metastasi ovariche, anch'esse resecate en bloc
- tumore perforato nella cavità peritoneale
- Nell'esperienza monoistituzionale di Elias, 29 pazienti dal 1999 al 2006

Il “design” del trial

- Il look 6 mesi dopo il termine della CT, quindi a 12 dall’intervento primario
- Se PC macroscopica, CRS + HIPEC
- Se NON PC macroscopica, HIPEC solo nei pazienti che avevano PC nell’intervento primitivo

CP Sync Met:

- PCI < 20
- NO ASCITE
- NO HIGH GRADE
- < 70 ys
- GOOD PERFORMANCE STATUS

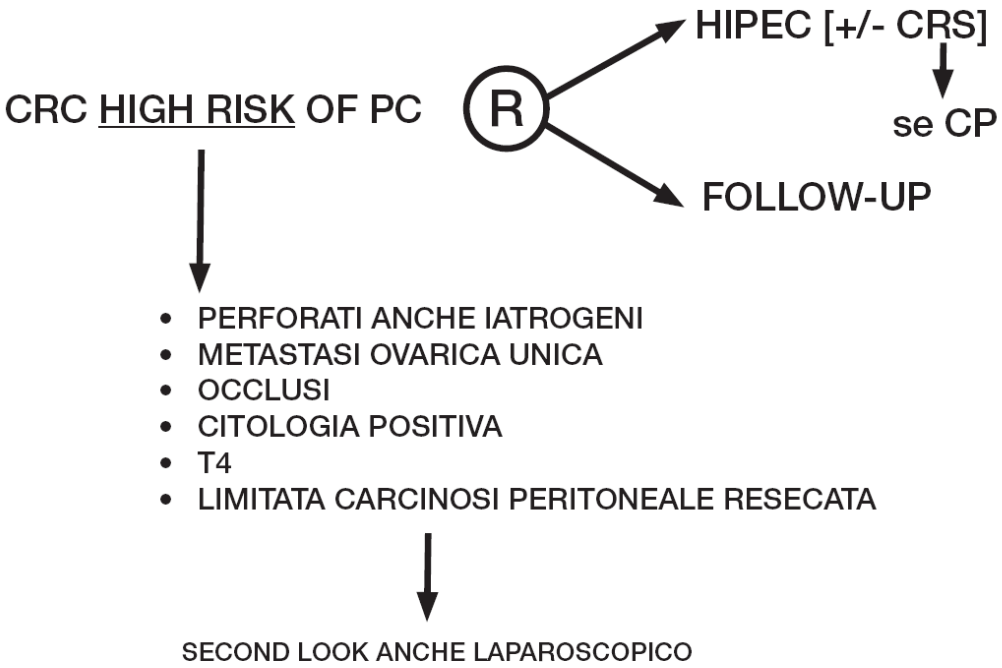


Primary End Point:

- OS con gruppo storico

Secondary End Point:

- DFS
- MORBILITY
- MORTALITY



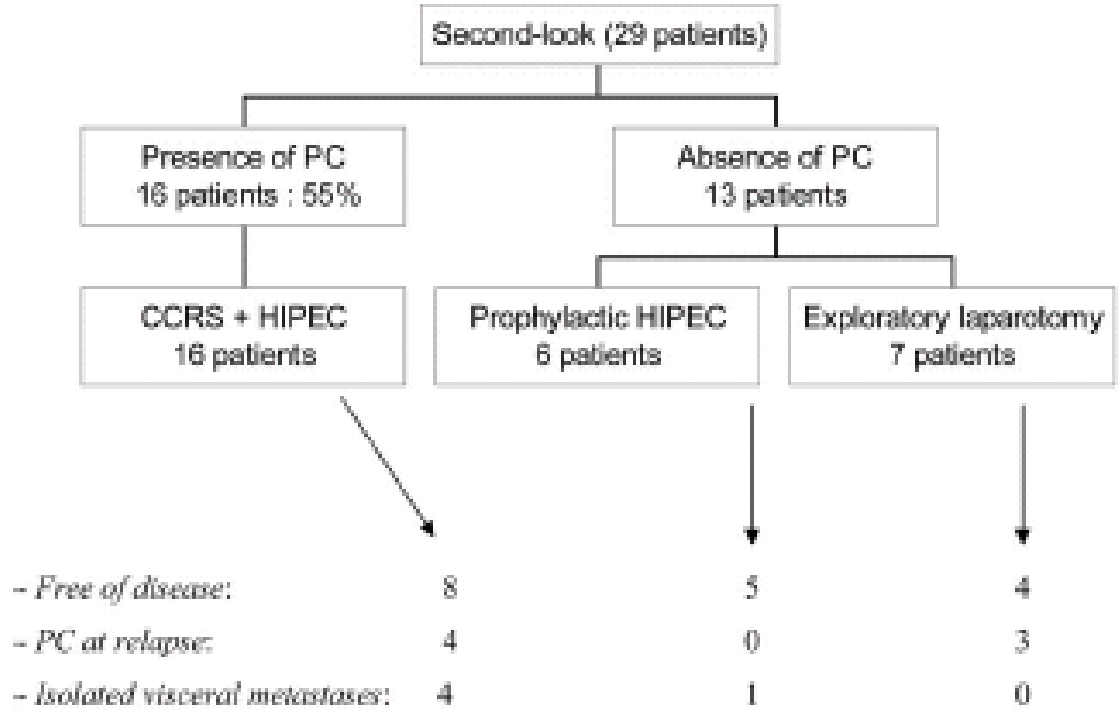
Primary End Point:

- DFS

TABLE 1. Patients and Primary Tumor Characteristics

	Synchronous PC (n = 16)	Ovarian Metastases (n = 4)	Perforated Tumor (n = 9)
Mean age ± SD (yr)	50 ± 10.5	49 ± 3	45 ± 13
Primary tumor site (n)			
Colon	14	3	9
Rectum	2	1	0
Primary tumor stage (n)			
T2	1	0	0
T3	8	3	7
T4	7	1	2
N0	3	0	3
N1–2	13	4	6
Adjuvant chemotherapy (n)			
Fufol	2	1	4
Folfox	9	2	5
Folfiri	5	1	0
Second-look surgery (n)			
PC present	10	3	3
CCRS + HIPEC	10	3	3
HIPEC	6	0	0
Exploration	0	1	6

PC indicates peritoneal carcinomatosis, macroscopically detectable; Folfox, bimonthly oxaliplatin with 5-fluorouracil and leucovorin; Folfiri, bimonthly irinotecan with 5-fluorouracil and leucovorin; Fufol, bimonthly 5-fluorouracil and leucovorin.



PC: Peritoneal Carcinomatosis,

CCRS: Complete cytoreductive surgery; HIPEC: Hyperthermic peritoneal chemotherapy

FIGURE 1. Results of second-look surgery to detect early peritoneal carcinomatosis in high-risk patients.

Quindi…si-può-fare?!?

Only with your help!

GRAZIE PER L'ATTENZIONE!