



THIRD ANNUAL
ISSPP
Congress 2022

*International Society
for the Study of Pleura
and Peritoneum*



FIRST GREAT DEBATE

Is There a Role of Regional Therapy in Colorectal Cancer? (PRO)

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Lyon, France

Disclosures

- Consultant for Gamida Cell.

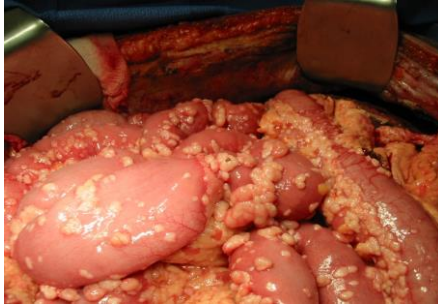
This presentation and/or comments will be free of any bias toward or promotion of the above referenced company or its product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Peritoneal metastases

Loco-regional disease



Macroscopic disease



Rational for loco-regional treatment

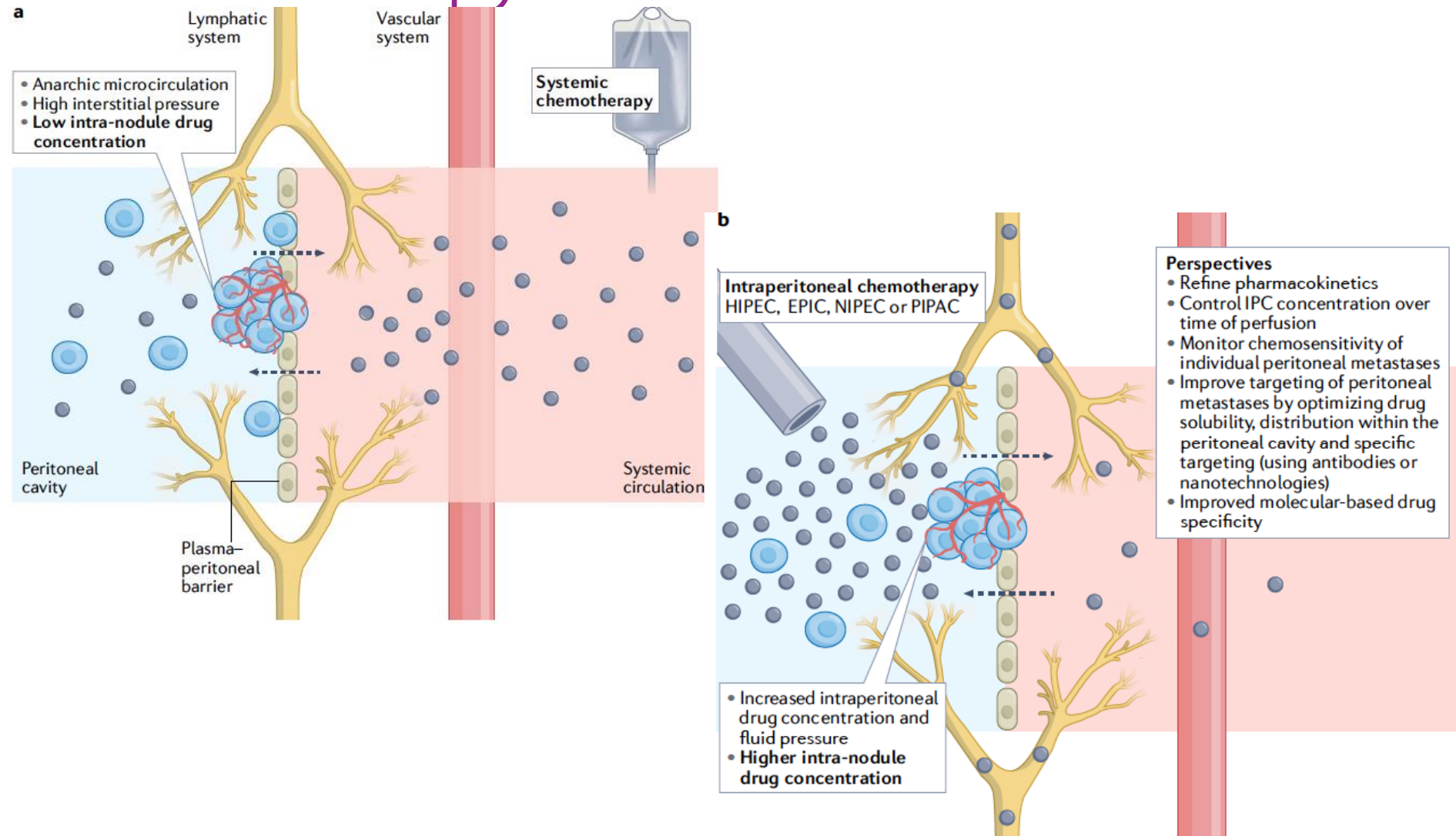
Cytoreductive Surgery
Peritonectomies

Microscopic disease



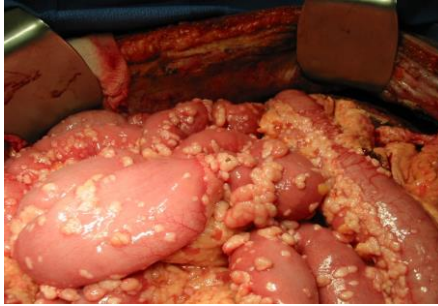
Intraperitoneal
chemotherapy
HIPEC

Key aspects on delivering IP chemotherapy



Peritoneal metastases

Loco-regional disease mainly associated with systemic metastasis



Macroscopic disease



Cytoreductive Surgery
Peritonectomies

Microscopic disease



Intraperitoneal
chemotherapy

Metastatic disease



IV Chemotherapy

Therapeutic strategies

Curative intent

Pseudomyxoma peritonei or resectable mesothelioma



PSM of ovarian, colorectal or gastric cancers (predominant sequences)



SPIC ± systemic chemotherapy for PSM of ovarian or colorectal cancer



Palliative intent or borderline

PSM of ovarian, colorectal or gastric cancers (palliative)



Predominantly peritoneal disease of ovarian, colorectal or gastric cancer origin



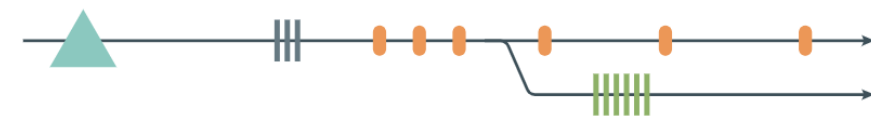
Non-resectable mesothelioma or isolated peritoneal disease of various origins



PSM of gastric or colorectal cancer (neoadjuvant bi-directional therapy)



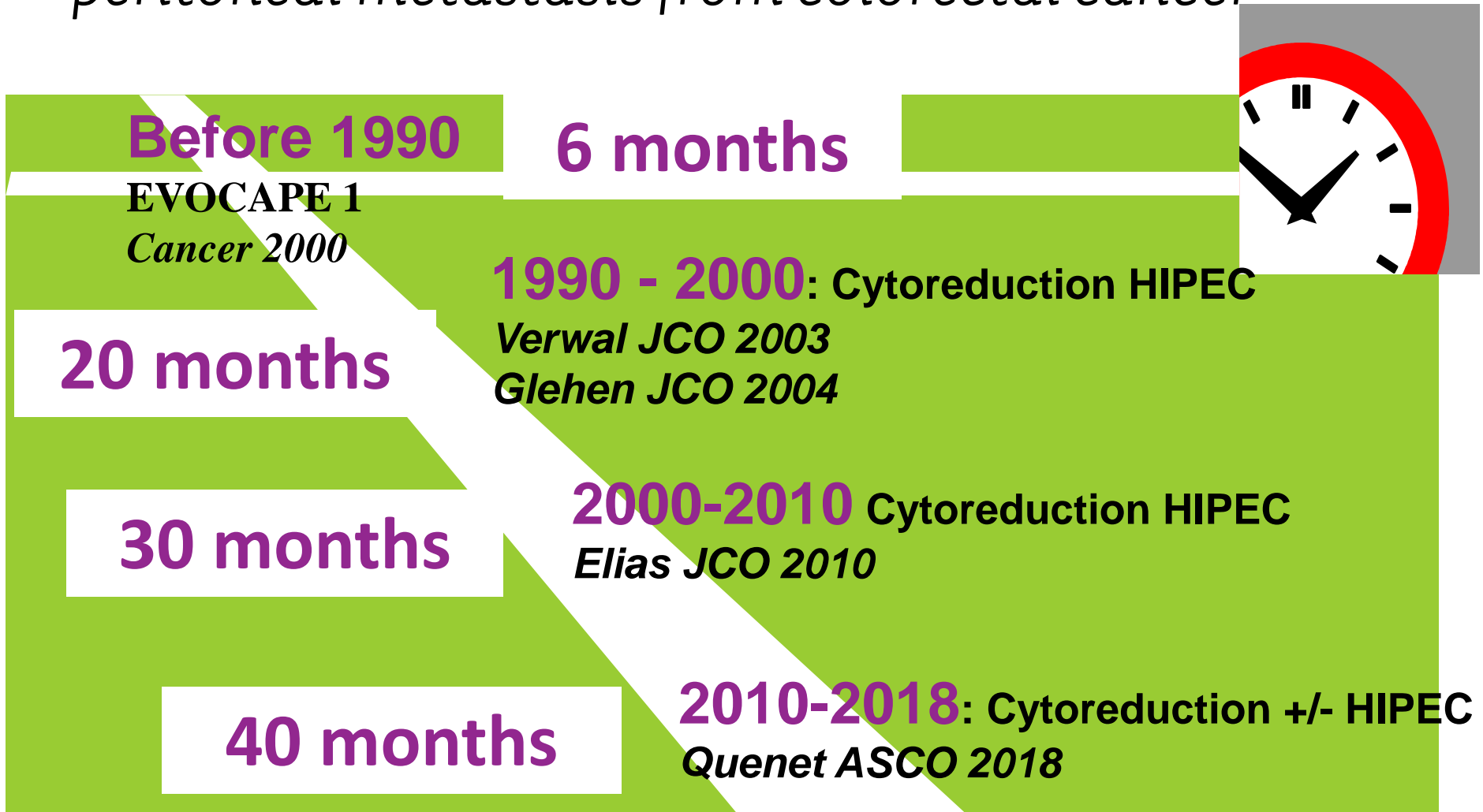
Non-resectable recurrence of mesothelioma



NIPS for advanced gastric and pancreatic peritoneal metastases



Evolution of median survival peritoneal metastasis from colorectal cancer



Reasons for success

- **Cytoreductive surgery (loco regional treatment)**
- **Patient's selection**
- **Progress of IV chemotherapy**
- **Establishment of specialized centers involved into peritoneal surface malignancies**

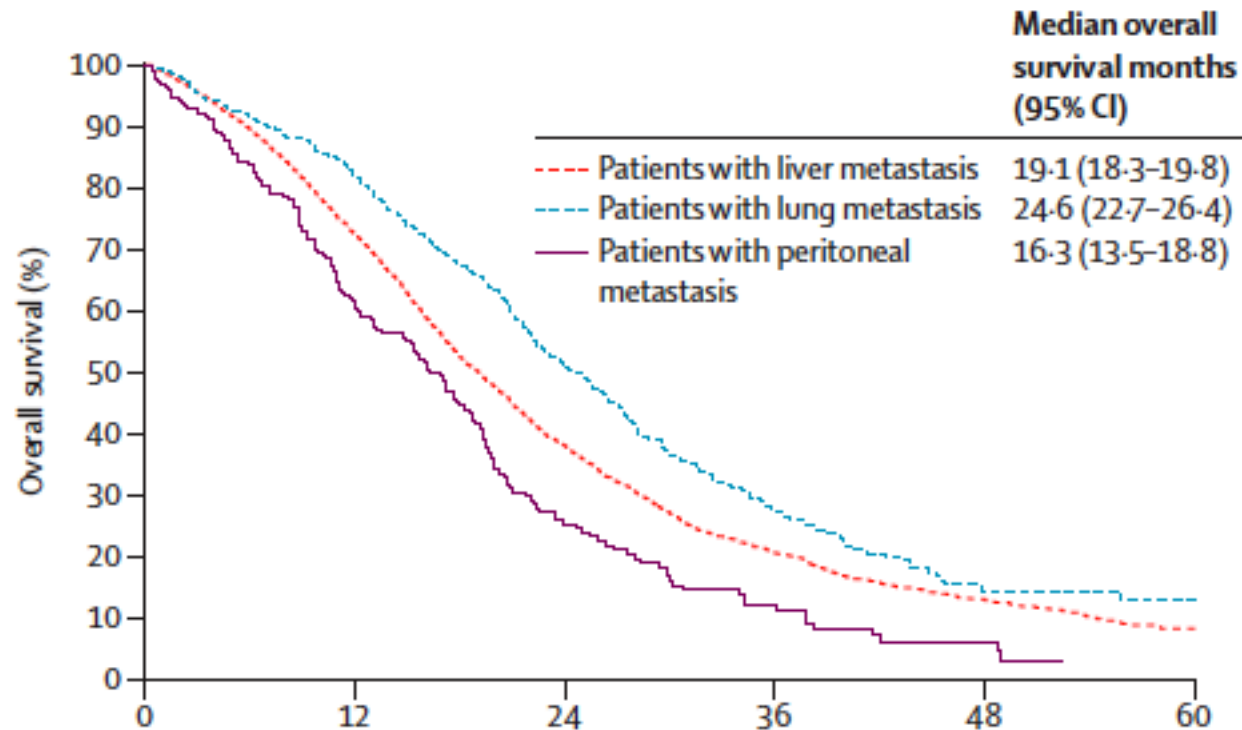
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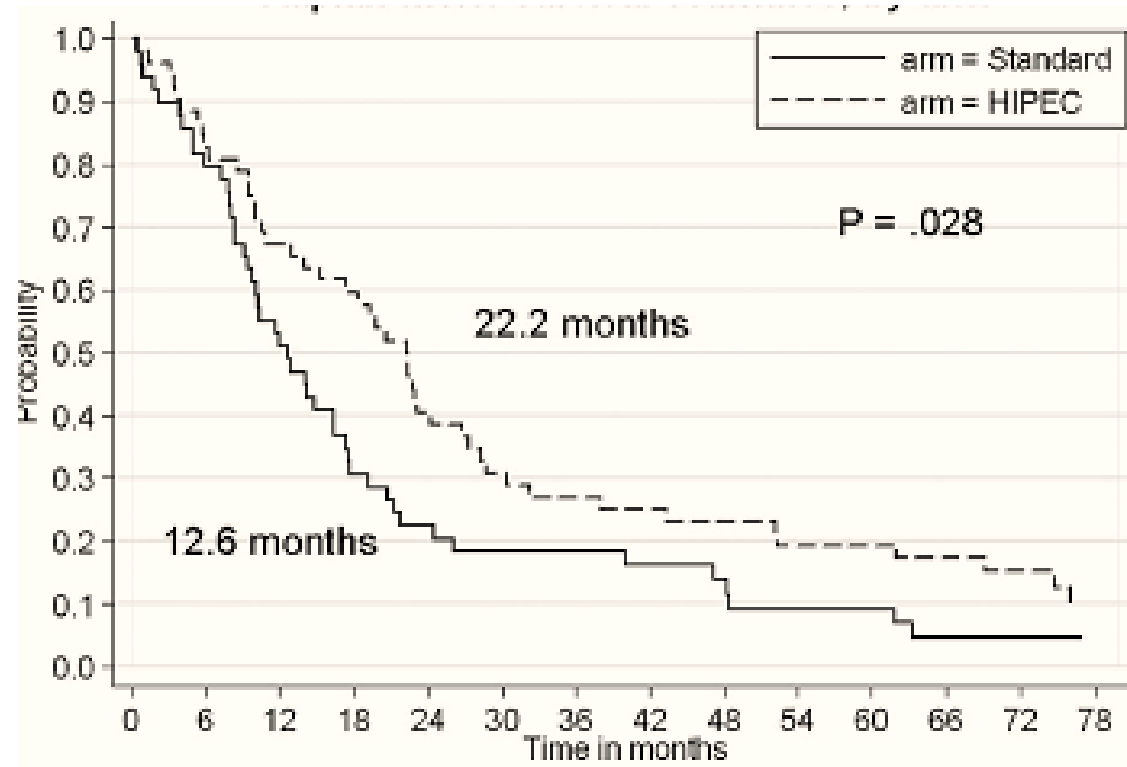
Intraperitoneal chemotherapy and
HIPEC ???

Median survival of peritoneal metastasis from colorectal cancer with systemic chemotherapy

16 months



A randomized study



Surgery + HIPEC > Systemic chemotherapy

Peritoneal Surface Disease Severity Score (PSDSS)

American Society of Peritoneal Surface Malignancies

1 013 patients

Median Survival (months)

PSDSS	Chemotherapy alone	Cytoreductive surgery and HIPEC
PSDSS 1	45	86
PSDSS 2	19	43
PSDSS 3	8	29
PSDSS 4	6	28

Median survival of peritoneal metastasis from colorectal cancer with CRS and HIPEC

More than 60 months

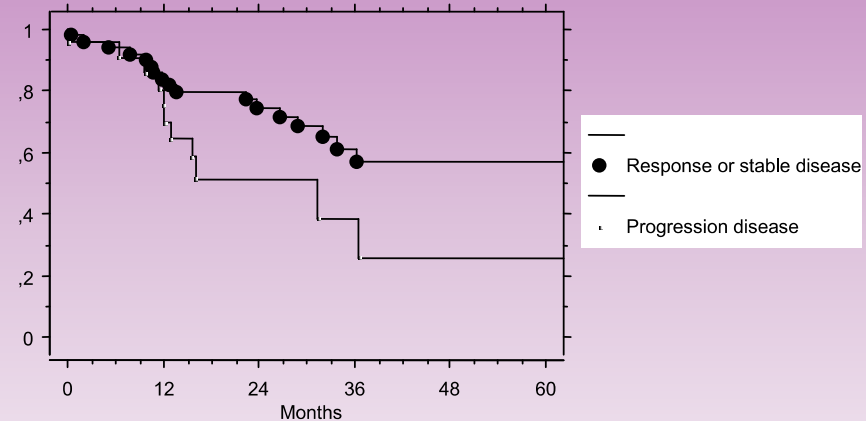
- We can cure PMI from colorectal cancer

Goere et al Ann Surg 2012

- Median survival > 60 months

- Strict selection of patients
- Systemic chemotherapy

Passot et al. Ann Surg 2012



International Position Statement (Amsterdam 2014)

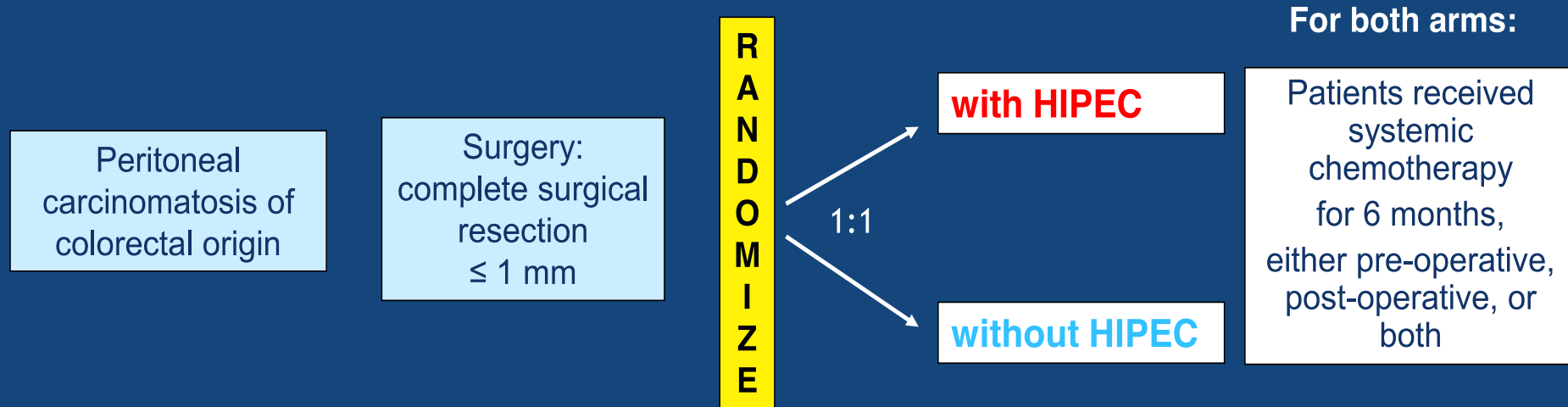


National Guidelines

All studies compared
Systemic chemotherapy alone
Vs
The combination CRS and HIPEC

- Moderate to small volume of disease
- Complete cytoreductive surgery necessary
- Experienced centers

Unicancer Prodiges 7 trial design



Stratification :

- Centre
- Residual tumor status (R0/R1 vs R2 ≤ 1 mm)
- Prior regimens of systemic chemotherapy
- Neoadjuvant Chemotherapy



HIPEC Arm (open or closed technique)

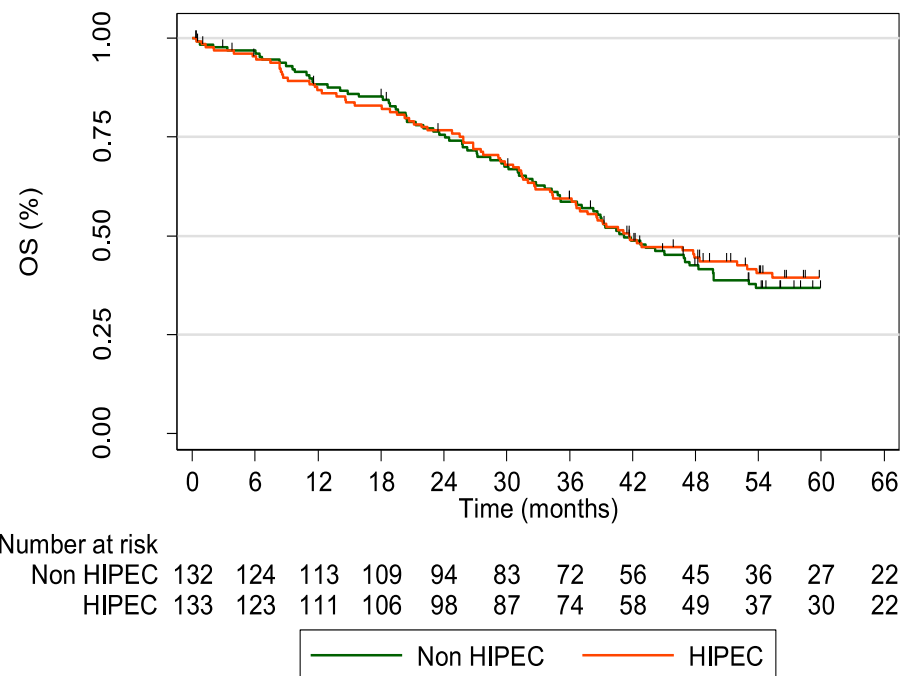
After Cytoreductive surgery

IP → Oxaliplatin 460mg/m² in 30 minutes (360mg/m² in closed procedures)

IV → Folinic Acid 20mg/m²
5 FU 400mg/m² } During HIPEC



Overall survival (ITT)



Median Follow Up: 64 months [95% CI:58.9-69.8]

	HIPEC	Non-HIPEC	P-value
Median Survival (months) [95% CI]	41.7 [36.2-52.8]	41.2 [35.1-49.7]	0.995
1-year Survival	86.9%	88.3%	
5-year Survival	39.4%	36.7%	

HR=1.00: 95%CI [0.73 - 1.37] p=0.995



1st conclusion of PRODIGE 7

Cytoreductive surgery into experienced centers is the key of curative treatment of PM from colorectal metastasis

2nd Conclusion of PRODIGE 7

HIPEC did not improve prognosis of patients curatively treated for colorectal peritoneal metastasis?

Conclusions of PRODIGE 7

HIPEC did not improve prognosis of patients
with colorectal ~~peritoneal~~ metastasis?

HIPEC with oxaliplatin for 30 min at 460-
360 mg/m² at 43° C did not improve
prognosis of patients with colorectal
peritoneal metastasis?

HIPEC with high dose of oxaliplatin for 30 min was not the best choice?

« The QUICK CHIP »

- No experimental rational for hyperthermic augmentation with oxaliplatin
- Effect of oxaliplatin without 48H of FU: 20% response rate
 - *Becouarn et al J Clin Oncol 1998*
- Higher rate of complications (**Hemorrhagical complications +++**)
- **Oxaliplatin resistance for patients already treated by FOLFOX**
- Insufficient duration
 - Effect of drug exposition and hyperthermia
- Inadequate carrier solution
 - Glucose perfusate is procarcinogen and limits the defense of peritoneum

The end of HIPEC?

NO

**Clinical
studies in favor of HIPEC**

**Validate the potential benefit of adding
HIPEC to cytoreductive surgery**

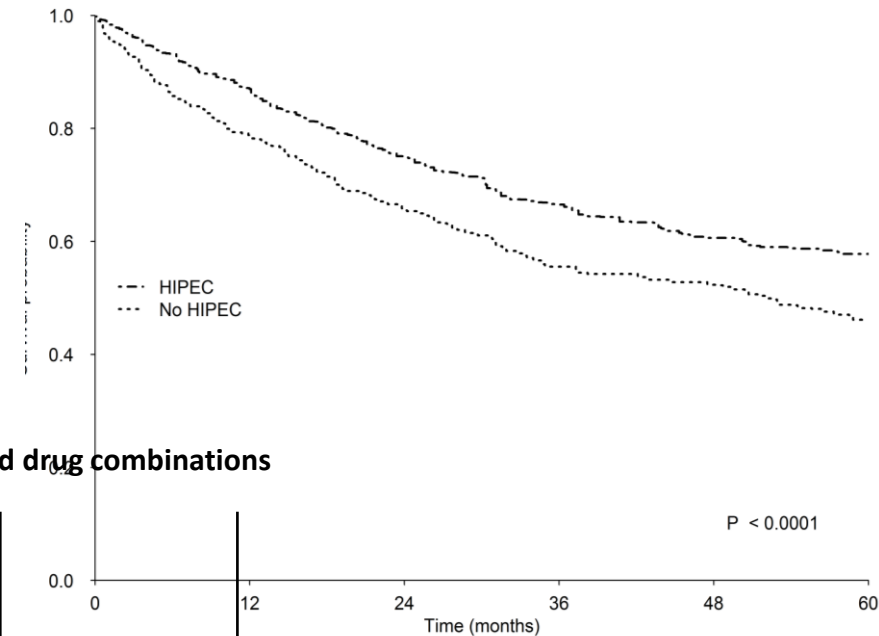


Cytoreductive surgery and HIPEC

Pseudomyxoma peritonei

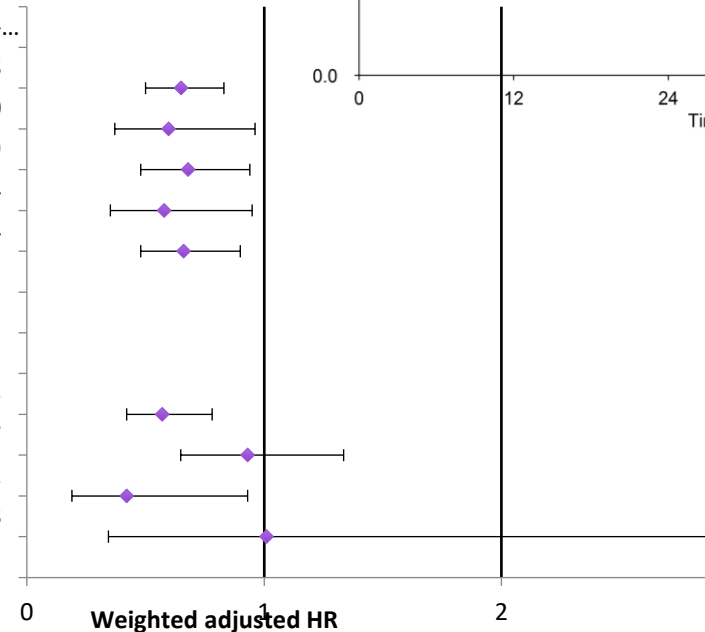
3 495 patients

International Registry
Propensity analysis



Effect size of HIPEC according to prognostic scenarios and drug combinations

Prognostic scenarios	Weighted adjusted HR (95%CI)	p-value
Overall	0.65 (0.50 to 0.83)	0.0008
Low grade PMP	0.60 (0.37 to 0.96)	0.0430
High grade PMP	0.68 (0.48 to 0.94)	0.0209
CC-0/1	0.58 (0.35 to 0.95)	0.0304
CC-2/3	0.66 (0.48 to 0.90)	0.0094
HIPEC drug schedules		
CDDP+MMC	0.57 (0.42 to 0.78)	0.0005
MMC	0.93 (0.65 to 1.34)	0.7067
Ox+5FU	0.42 (0.19 to 0.93)	0.0331
Ox based	1.01 (0.34 to 2.94)	0.9918



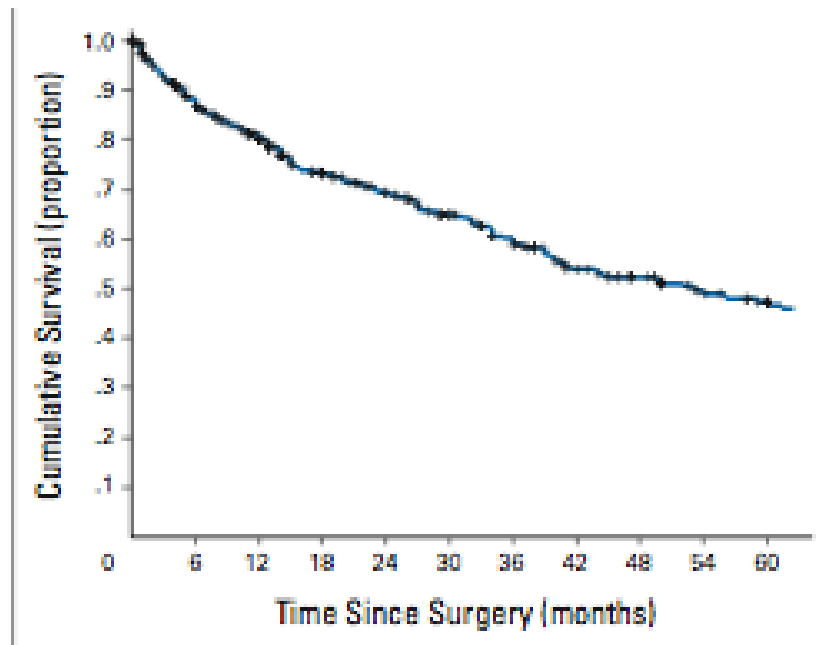
HIPEC significantly
improves prognosis
In all sub-groups

CRS HIPEC is better CRS alone better

Jama Surg 2021

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



401 Patients

Cytoreductive surgery and perioperative intraperitoneal chemotherapy

Median survival of 53 months

Independant prognostic factor : HIPEC
80% of HIPEC with cisplatin and doxorubicin for 90 mn

ORIGINAL ARTICLE

Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

W.J. van Driel, S.N. Koole, K. Sikorska, J.H. Schagen van Leeuwen,

HIPEC with cisplatin
100mg/m²

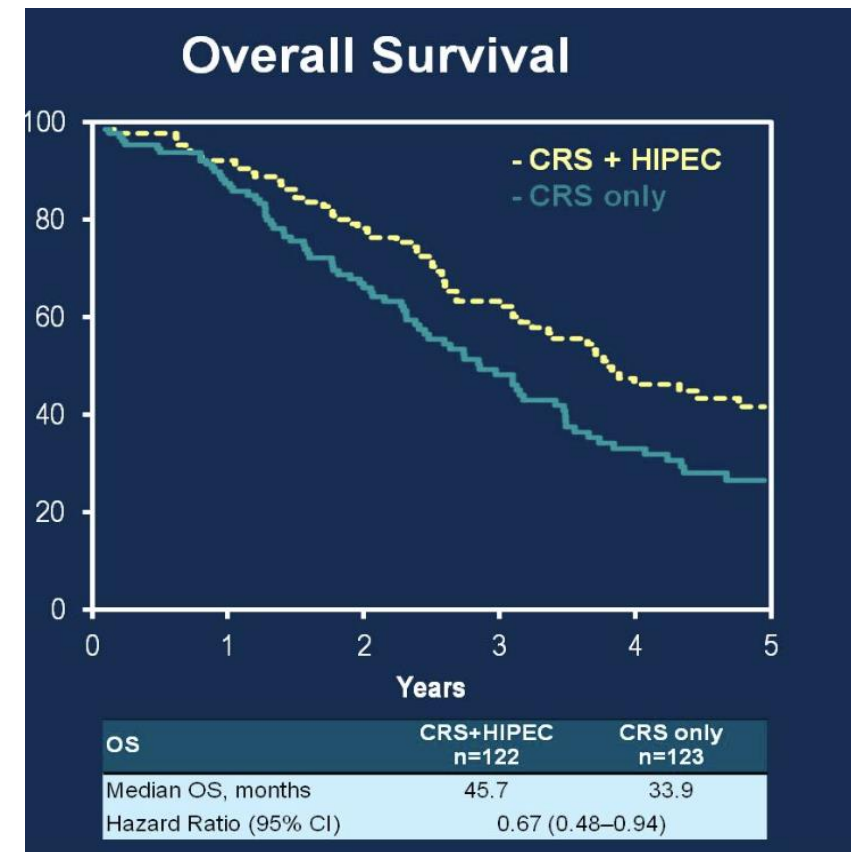
90 mn

Temperatures of 40 ° C

3 fractions

No added complication with
HIPEC

No delay for postoperative
chemotherapy



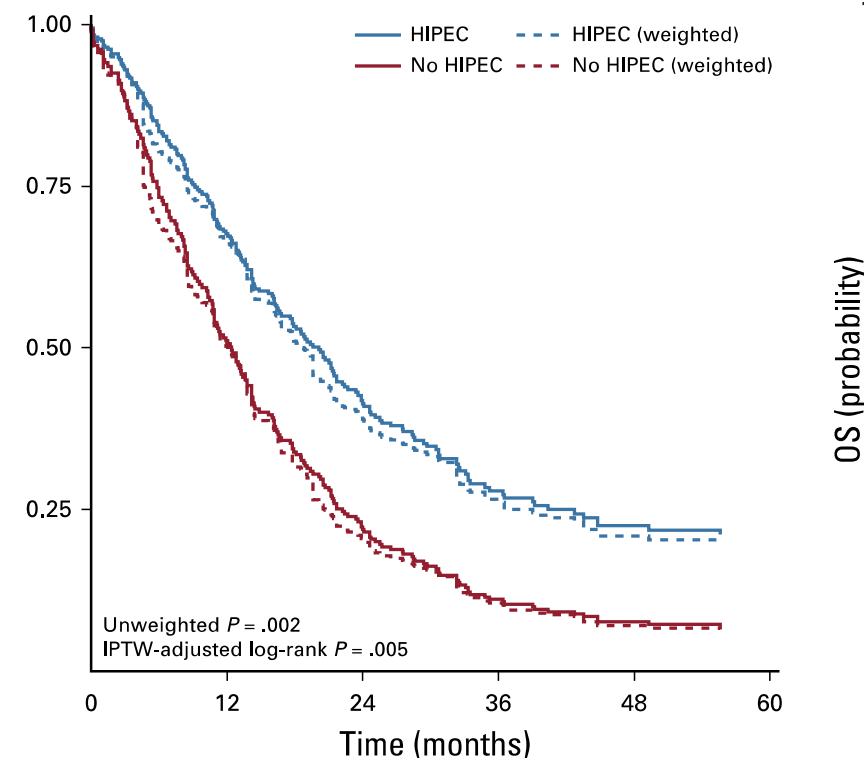
Cytoreductive Surgery With or Without Hyperthermic Intraperitoneal Chemotherapy for Gastric Cancer With Peritoneal Metastases (CYTO-CHIP study): A Propensity Score Analysis

Pierre-Emmanuel Bonnot, MD^{1,2}; Guillaume Piessen, MD, PhD³; Vahan Kepenekian, MD^{1,2}; Evelyne Decullier, PhD⁴; Marc Pocard, MD, PhD⁵; Bernard Meunier, PhD⁶; Jean-Marc Bereder, MD⁷; Karine Abboud, MD⁸; Frédéric Marchal, MD, PhD⁹; François Quenet, MD¹⁰; Diane Goere, MD, PhD¹¹; Simon Msika, MD, PhD¹²; Catherine Arvieux, MD, PhD¹³; Nicolas Pirro, MD, PhD¹⁴; Romuald Wernert, MD¹⁵; Patrick Rat, MD, PhD¹⁶; Johan Gagnière, MD, PhD¹⁷; Jeremie H. Lefevre, MD, PhD¹⁸; Thomas Courvoisier, MD¹⁹; Reza Kianmanesh, MD, PhD²⁰; Delphine Vaudoyer, MD^{1,2}; Michel Rivoire, MD, PhD²¹; Pierre Meeus, MD²¹; Guillaume Passot, MD, PhD^{1,2}; and Olivier Glehen, MD, PhD^{1,2}; on behalf of the FREGAT and BIG-RENAPE Networks



Most of HIPEC performed with Cisplatin and Mitomycin C

90 mn



The end of oxaliplatin use for HIPEC?

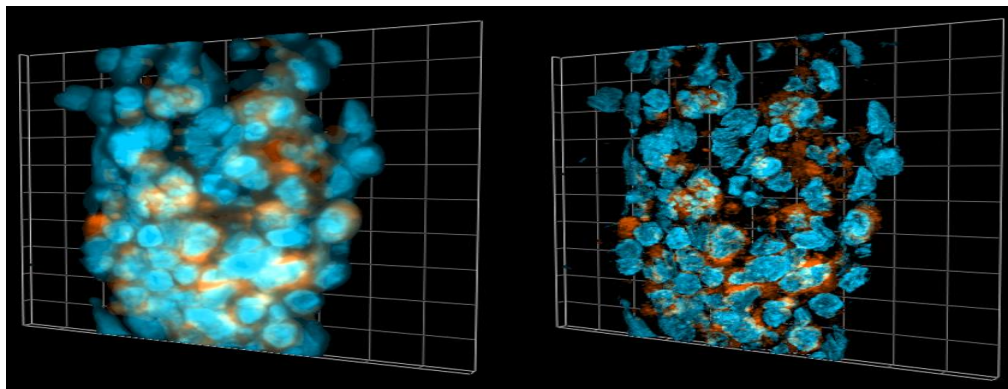
NO !!!! But with a different HIPEC

- Oxaliplatin at lower dose
 - 200 to 250 mg/m²
 - No increase of complications



Gastrichip protocol
American Phase I-II study and comparative study with mitomycin

- Oxaliplatin for a longer time



No apoptosis after
30 min

Apoptosis after 2
hours



Van der Speeten (unpublished data)

What kind of HIPEC in colorectal cancer?

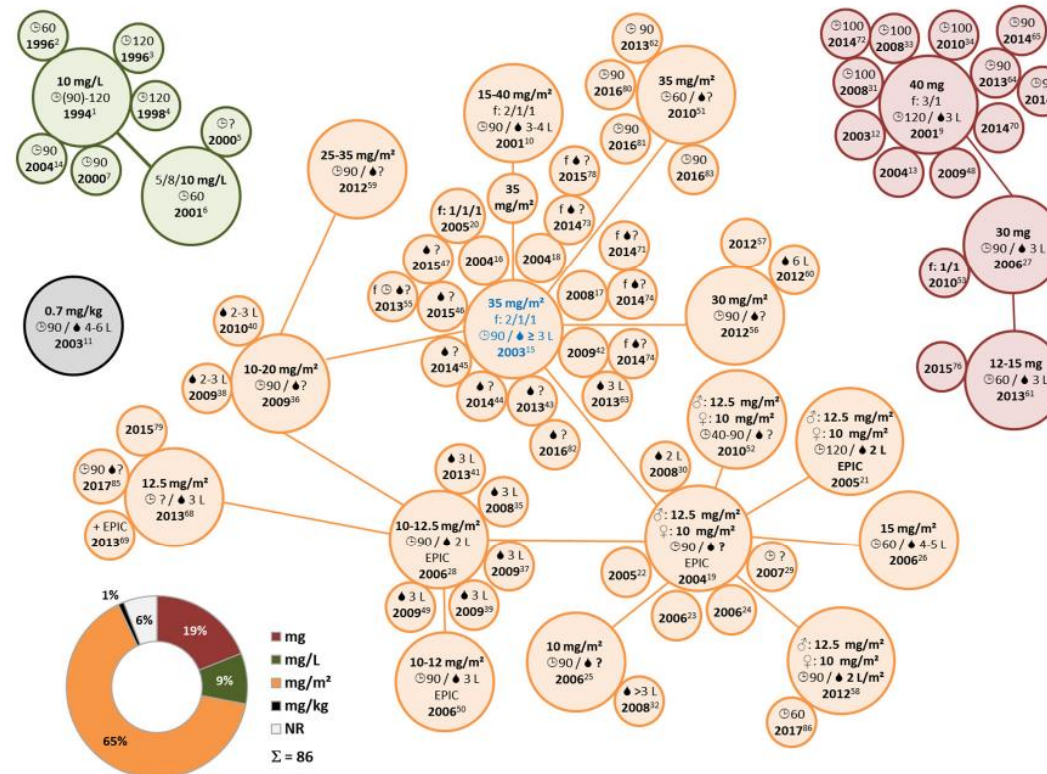
Mitomycin C ??



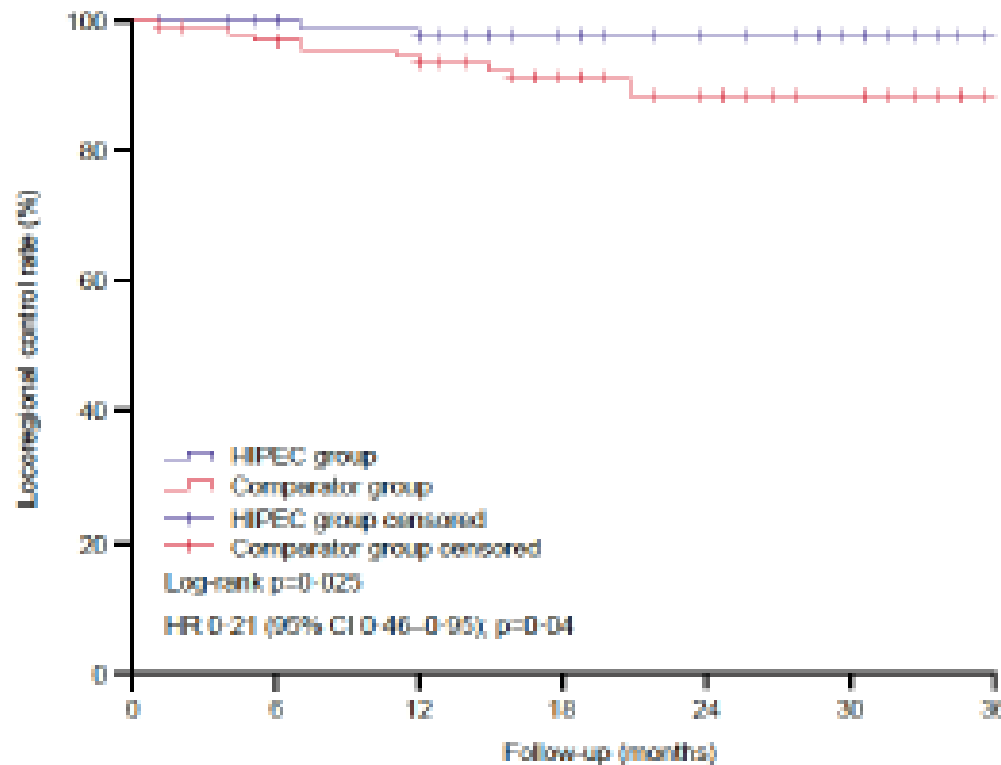
Journal of
Clinical Medicine

Review

Systematic Review of Variations in Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Peritoneal Metastasis from Colorectal Cancer



Randomized Phase III study HIPEC with Mitomycin significantly reduce locoregional recurrence of T4 colorectal tumors



HIPEC

No HIPEC

$P = 0.025$

Patients at risk (censored)	0 m	12 m	24 m	36 m
Comparator	95	88 (4)	68 (15)	47 (19)
HIPEC	89	82 (5)	65 (17)	49 (16)

The current situation in colorectal cancer ?

**Your quick CHIP is
not fresh !!!**



**Your Mito is not
better**



CRS is sufficient

Delphi HIPEC regimens



Methods

- Review of literature
- Questions divided in 3 parts
 1. Expert's recommendations for the use of HIPEC (PICO method with grade and strength)
 2. Expert's opinion (open questions)
 3. Future research recommendations

Table 3 GRADE assessment of evidence¹⁵

Assigned GRADE quality	Description
High	Further research is very unlikely to change confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Table 4 GRADE assessment of strength of recommendations¹⁵

Assigned GRADE strength of recommendation	Description
Strong	Desirable effects of intervention clearly outweigh undesirable effects, or clearly do not
Weak	Trade-offs are less certain, either because of low-quality evidence or because evidence suggests desirable and undesirable effects are closely balanced

145 International EXPERTS
31 Countries and 104 centers

Summary of PICO method

1) **MMC based regimens (+/-CDDP)** seem to be the most advisable ones for HIPEC in PM-CRC due to the followings:

- Positive pooling HR when compared to no-HIPEC, without increasing severe morbidity
- Less toxic according to meta analysis (Zhang), even when compared to low-dose oxaliplatin (200mg 120 min).

2) **MMC 10-15 mg/m² was proven to be worse** than Oxaliplatin Elias' regimen, in terms of OS

3) Therefore, by exclusion, **CDDP + MMC and MMC 35 mg/m² and MMC 40 mg remain as the combinations with “less disadvantages”** and more potential benefits.

2nd Round of vote

More than 90% recommend HIPEC using

Mitomycin C regimens

Mitomycin C with high dose in 3 fractions

for 90 min

New randomised studies required

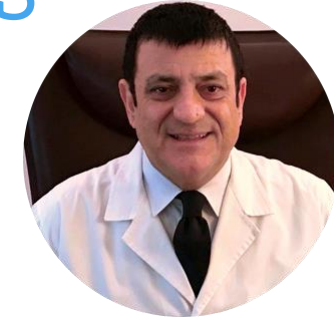
Principals Take home messages

The role of **loco-regional treatment** is fundamental for a **loco-regional disease**

- **Cytoreductive surgery** into specialized centers is the principal key of curative treatment
- HIPEC with **Mitomycin C** is currently the best choice in colorectal cancer (high dose – 90 min – fractionned doses)
- New trials and new strategies are needed (organoids, vaccin, nanoparticules, long-term IP)

Personnalized and integrated loco-regional treatment is needed for metastatic patient

WEBINAR for specific diffusion of Delphi results



Friday 20th January 2023

