FRED & PAMELA BUFFETT CANCER CENTER

ROLE OF HIPEC IN COLORECTAL PERITONEAL METASTASIS (CRC-PM)

18th Annual Fall Midwest Thoracic and GI Conference

University of Nebraska Medical Center
BREAKTHROUGHS FOR LIFE

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University of Nebraska, Fred & Pamela Buffet Cancer Center

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GI CARCINOMATOSIS: HOW BAD IS IT?

EVOCAPE 1 (Evolution of Peritoneal Carcinomatosis)

- Mean 6 mo. Median 3mo.

Colorectal Cancer

- Mean 6.9 mo. Median 5.2mo.

Gastric cancer

- Mean 6.5 mo. Median 3.1mo.

Pancreatic cancer

- Mean 2.9 mo. Median 2.1mo.

Sadeghi et al Cancer 88(2): 358–63 2000

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CRC-PM SURVIVAL CHEMOTHERAPY ALONE

Author(s), year	Patients	Group	Treatment regimen	PM OS (mo.)	No PM OS (mo.)
Klaver et al, 2012 (CAIRO-1)	401	Sequential treatment	1st line - capecitabine 2nd line - irinotecan 3rd line - capectiabine + oxaliplatin	10.4	16.8
	402	Combination treatment	1st line - capectiabine + irinotecan 2nd line - capecitabine + oxaloplatin	7.8	17.9
Klaver et al, 2012 (CAIRO-2)	192	Without cetuximab	Capecitabine + oxaliplatin + bevacizumab	15.2	21.4
	197	With cetuximab	Capecitabine + oxaliplatin + bevacizumab + cetuximab	13.9	20.4
Franko et al, 2012 (N9741 and N9841)	2095	FU	Fluorouracil	12.7	17.6
		IFL or IRI	Irinotecan leucovorin, and fluorouracil or irinotecan		
		IROX	Irinotecan and oxaliplatin		
		FOLFOX	IV 5-FU, leucovorin, and oxaliplatin		

Hall B et al Surg Clin North Am. 2017 Jun;97(3):671-682

CRC-PM SITE HAS WORST PROGNOSIS 30-50% SHORTER THAN OTHER STAGE IV SITES

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COMMON PROBLEMS IN PSM

- HARD TO DETECT ACTIVE DISEASE
  - Radiographic & serological tests have limitations
    - Inaccurate at determining extent of disease burden
- PROGRESSION WITH SYMPTOMS IS COMMON
- SYMPTOMATIC DISEASE HARD TO CONTROL
  - Obstruction – bowel or genitourinary
  - Fistula
  - Acites
  - Pain
  - Malnutrition

SEPSIS

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WHAT ARE THE TOOLS IN PSM?

I. CHEMOTHERAPY

II. SURGICAL CYTOREDUCTION

1. Prevent or address symptoms – QoL.
2. Optimal CRS is the goal

III. INTRAPERITONEAL THERAPIES

1. Hyperthermic intraperitoneal chemotherapy -- HIPEC
2. Intrapertitoneal chemotherapy -- IP
3. Pressurized Intraperitoneal Chemotherapy – PIPAC

IV. **CRS/HIPEC – emerged as the surgical Tx for PSM**

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ROLE OF CRS & HIPEC

CRS:

→ ADDRESSES MACROSCOPTIC TUMOR

- Remove symptomatic disease
- Often requires multi-visceral organ resections

HIPEC:

→ADDRESS MICROMETS & small nodules

- Treats peritoneal space (micromets)
- Treats visceral & parietal peritoneal surfaces to depth 4 mm (nodules)

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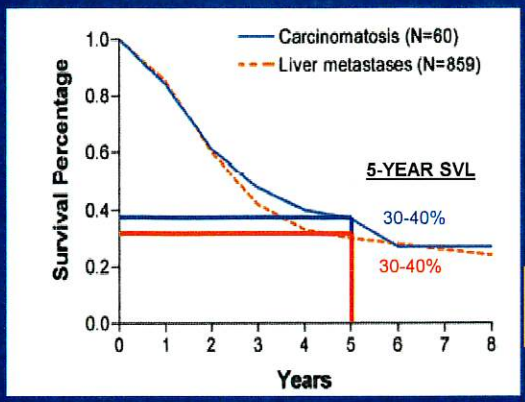
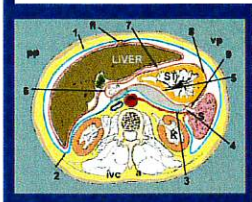
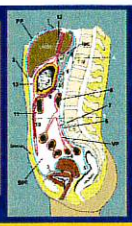
SURGICAL PERSPECTIVE: COLORECTAL METASTASIS



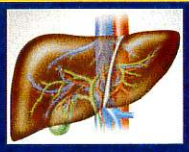
R1/R2a resection & HIPEC





R0 resected liver mets

Hughes et al Surgery 103 278-88, 1987



Sugarbaker Journal of Clinical Oncology 21: 762–764 2003

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CRC-PM HIPEC REGIMENS

Drugs	Dosage	Timing	Outflow Temperature	Duration
IP MMC IP Dox IV 5FU IV Leu	15mg/m² 15 mg/m² 400 mg/m² 20 mg/m²	All at time 0	41° C	
MMC	40 mg	30 mg at time 0	40° C	
MMC	40 mg	30 mg at time 0 10 mg at 45'	42° C	
MMC	10 mg/L perfusate up to 60 mg	2/3 at time 0 1/3 at 45'	41° C	
MMC Dox Oxali	20 mg/m² 15 mg/m² 300 mg/m²	All at time 0	41° C	
IP Oxali IV 5-FU	460 mg/m²	All at time 0 1 hour before	41° C	30 minutes
MMC	15 mg/m²	All at time 0	42° C	60 minutes
MMC	25 mg/m²	1/3 every 30'	42° C	90 minutes

AGENT	DURATION (min)	published data %
Mitomycin – MMC	90-120	60-65%
Oxaliplatin	30	25-30%
Other agent	60-90	5-10%

HIPEC drug (s) and doses	HIPEC duration (min)	Concomitant intravenous chemotherapy	EPIC	Indication
Mitomycin C, 15 mg/m² Doxorubicin, 15 mg/m²	90	5-FU, 400 mg/m² LV, 20 mg/m²	5-FU 4 d	Appendiceal, and colorectal carcinomatosis
Cisplatin, 50 mg/m² Doxorubicin, 15 mg/m²	90	5-FU, 400 mg/m² LV, 20 mg/m²	Taxol 4 d	Gastric cancer, peritoneal mesothelioma, ovarian cancer
Oxaliplatin, 130 mg/m²	60	5-FU, 400 mg/m² LV, 20 mg/m²	5-FU 4 d	Appendiceal, and colorectal carcinomatosis
		No	No	Carcinomatosis with incomplete cytoreduction
		5-FU, 400 mg/m² LV, 20 mg/m²	No	Colorectal carcinomatosis
		No	No	Appendiceal, and colorectal carcinomatosis
		No	No	Peritoneal mesothelioma, advanced ovarian cancer
		No	No	Appendiceal, and colorectal carcinomatosis, advanced ovarian cancer, peritoneal mesothelioma
Mitomycin C, 10 mg/mL of perfusate	90	No	No	Appendiceal, gastric and colorectal carcinomatosis
Mitomycin C, 0.5 mg/kg Cisplatin 0.7 mg/kg	90	No	No	Peritoneal mesothelioma
Cisplatin, 20 mg/m²/L	90	No	No	Recurrent and chemoresistant stage II ovarian cancer
Cisplatin, 250 mg/m²	90	No	5-FU + Taxol 1 d	Peritoneal mesothelioma

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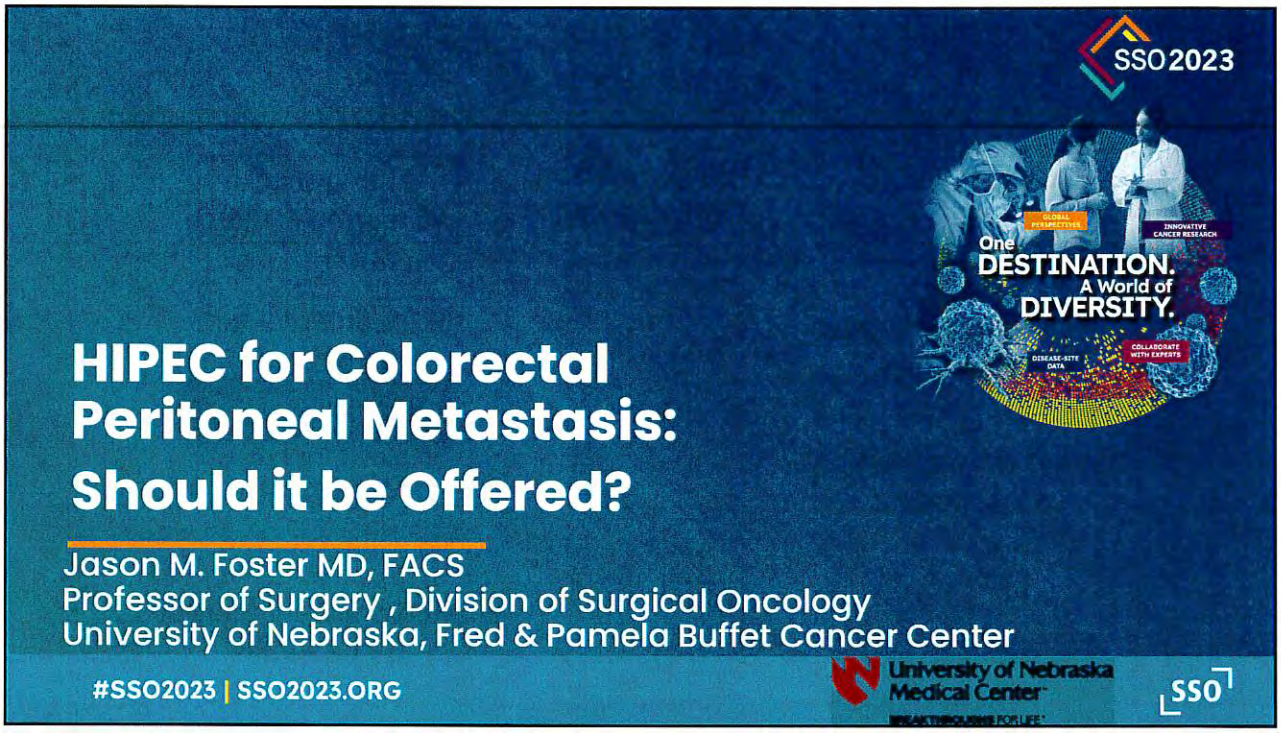

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CONTEMPORARY OUTCOME CRS ALONE COMPARED TO CRS-HIPEC RESTROSPECTIVE DATA

	CRS ALONE						CRS-HIPEC				
Author Year	Total # Pts	Sys. Chemo Tx	PCI	CC 0/1 %	OS mo.	OS mo.	Author Year	Total # Pts	Sys. Chemo Tx	PCI	CC 0/1 %
Elias 2004	19	5-FU	15-25	100	25	32	Glehen 2004	377	>60%	NR	100%
Scaringi 2009	27	NR	NR	82%	15	33	da Silva 2006	70	NR	14	100%
Mulsow 2011	31	5-FU, oxl/iri	NR	100	22	30	Elias 2010	523	50%	NR	84%
Kobayashi 2010	20	5-FU	NR	100	24	37	Ung 2013	109	NR	NR	100%
Kobayashi 2014	484	5-FU, oxal/iri	NR	100	25	41	Esquivel 2014	705	NR	NR	82%

Baratti D et al Ann Surg Oncol. 2020 Jan;27(1):98-106.

Hall B et al Surg Clin North Am. 2017 Jun;97(3):671-682

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FIRST PHASE III CRC-CRS/HIPEC DUTCH TRIAL

6 months 5FU/LV +Palliative surgery

Randomization 105 patients

CRS/HIPEC +6 months 5FU/LV

Standard treatment 51 patients

Started chemotherapy 44 patients

Experimental arm 54 patients

Mitomycin 90- minutes 42C

Treated by HIPEC 49 patients

Started adjuvant therapy 33 patients

Verwaal Journal of Clinical Oncology 2003 21(20): 3737-3743

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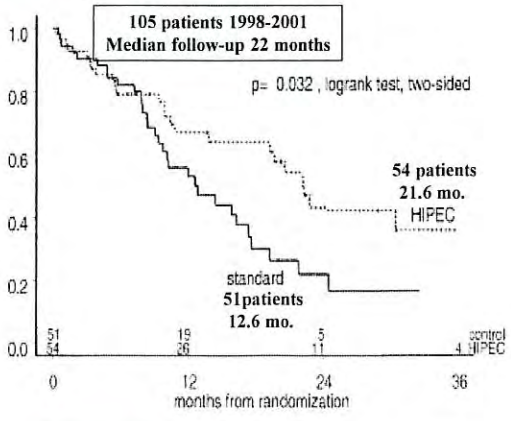
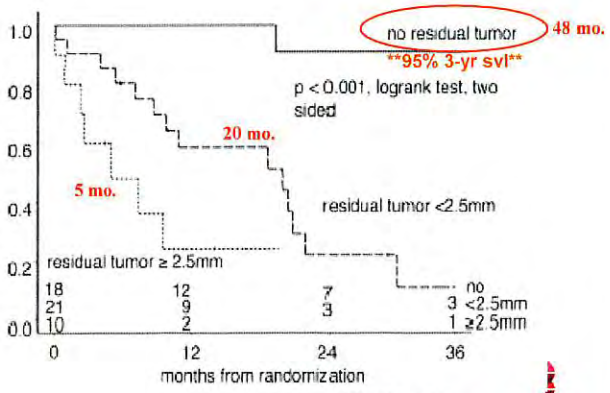
FIRST PHASE III CRC-CRS/HIPEC DUTCH TRIAL





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Verwaal Journal of Clinical Oncology 2003 21(20): 3737-3743

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PROGIDE 7

Unicancer Prodige 7 trial design

Peritoneal carcinomatosis of colorectal origin

Surgery: complete surgical resection ≤ 1 mm

RANDOMIZE

1:1

with HIPEC

Oxaliplatin 460 mg/m2 + IV 5-FU 30 minutes 43 C

without HIPEC

For both arms:

Patients received systemic chemotherapy for 6 months, either pre-operative, post-operative, or both

Stratification :

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

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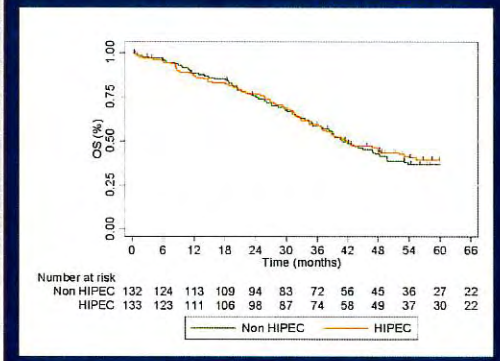
PROGIDE 7

Overall survival (ITT)



Mortality & Complications

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

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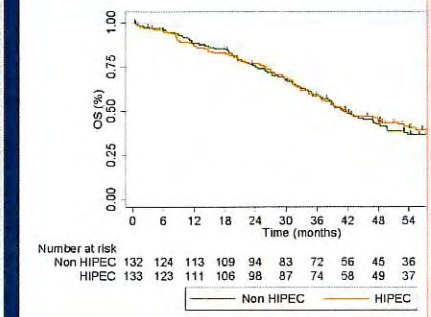
PROGIDE 7

Overall survival (ITT)



Mortality & Complications

	Cytoreductive surgery plus HIPEC group (n=133)	Cytoreductive surgery group (n=132)	p value
Mortality			
Overall	4 (3%)	3 (2%)	..
Day 1–30	2 (2%)	2 (2%)	..
Day 31–60	2 (2%)	1 (1%)	..
Grade ≥3 adverse events (Day 1–30)			
Any complication	56 (42%)	42 (32%)	0·083
Intra-abdominal complications	36 (27%)	24 (18%)	0·084
Extra-abdominal complications	36 (27%)	29 (22%)	0·33
Haematological complications			
Neutropenia	22 (17%)	10 (8%)	0·025
Thrombopenia	12 (9%)	2 (2%)	0·011
Grade ≥3 adverse events (Day 31–60)*			
Any complication	34 (26%)	20 (15%)	0·035
Intra-abdominal complications	8 (6%)	4 (3%)	0·38
Extra-abdominal complications	28 (21%)	18 (14%)	0·11

Data are n (%). HIPEC=hyperthermic intraperitoneal chemotherapy. *Because of the two deaths in each group, percentages were calculated based on the available data for the remaining 131 patients in the cytoreductive surgery plus HIPEC group and 130 patients in the cytoreductive surgery group.

Table 3: Mortality and morbidity in intention-to-treat population

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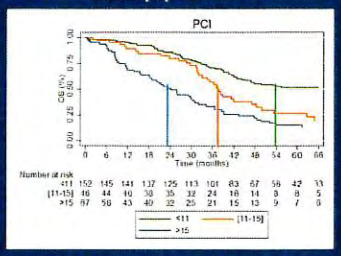
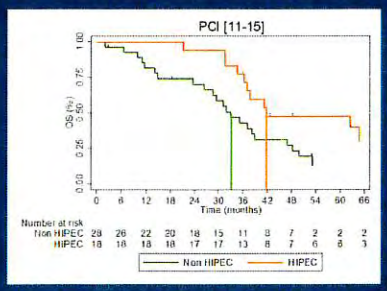
PROGIDE 7

Overall survival and PCI

Entire population





<11 HR= 1
[11-15] HR= 1 88 95%CI [1 25-2 88] p=0 003
16-24 HR= 3 57 95%CI [2 43-5 23] p<0 001

OS PCI [11-15]	HIPEC	Non-HIPEC	HR	P-value
Median Survival (months) [95% CI]	41.6 [36.1-nor reach]	32.7 [23.5-38.9]	0.437 [23.5-38.9]	0.0209

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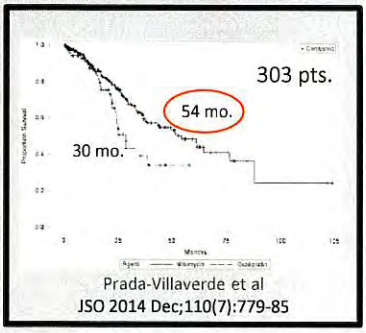
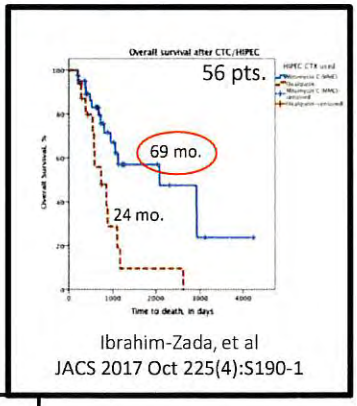
LIMITATION #2: OXALIPLATIN INFERIOR HIPEC AGENT TO MITOMYCIN



Prada-Villaverde et al
JSO 2014 Dec;110(7):779-85



Ibrahim-Zada, et al
JACS 2017 Oct 225(4):S190-1

Patients with similar PCI & CC0
MMC OS: 54-64 months

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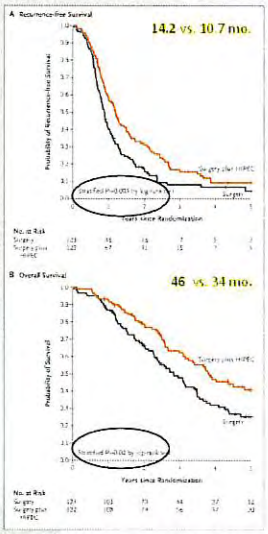
POSITIVE OUTCOMES WITH LONGER HIPEC DURATION

OVHIPEC-1 (N = 245)



van Driel WJ et al. N Engl J Med 2018;378:230-240

60-minute HIPEC 42.5 C

12-15 months OS improvement with HIPEC

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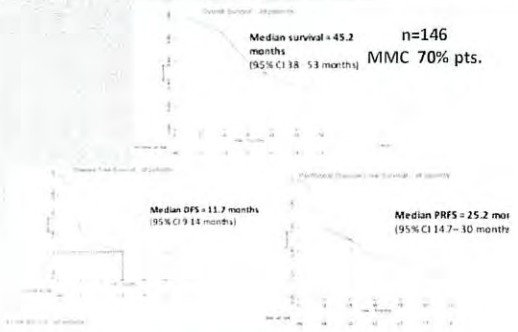
PERTONEAL PFS (PerPFS): IS THE PRIMARY ENDPOINT FOR HIPEC EFFICACY

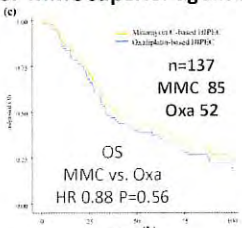
Systemic progression occurs earlier than Peritoneal

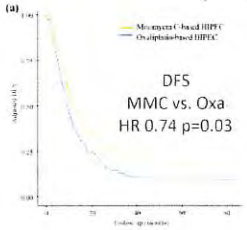


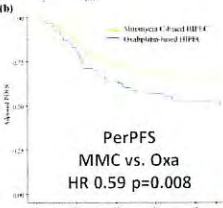
Study	Prodige-c	Prodige-E
DFS (mo)	12	11	13
PerPFS (mo)	25	15	17

Hassan Eur J Surg Oncol. 2023 Jan;49(1):202-208.

PerPFS: MMC superior agent to Oxal







J Delhorme Ann Surg Oncol. 2022 Nov;29(12):7568-7576

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REMEMBER: PURPOSE OF HIPEC IS PERITONEAL CONTROL

- Decrease the rate of peritoneal recurrence
- Extend time to peritoneal recurrence (PePFS)
- Decrease the burden of peritoneal recurrence
  - Symptomatic events
- Patient(s) benefit:
  - Less events
  - Less symptomatic peritoneal disease
  - Higher rate of iCRS
    - Due to less tumor at recurrence amenable to CC0/1

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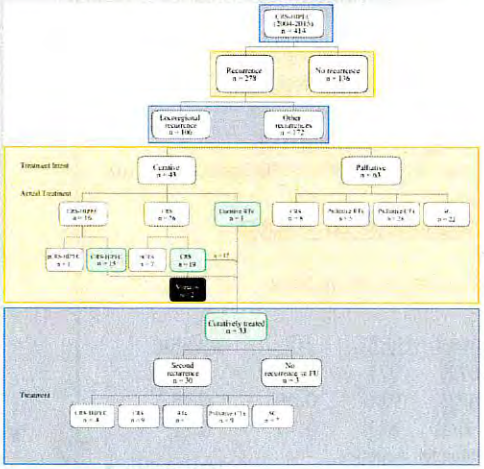
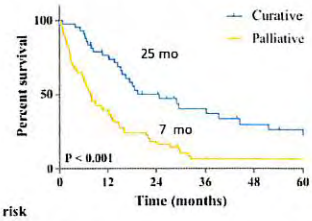
iCRS a factor to consider in OS for CRC-PM



STUDY SUMMARY
25% isolated recurrent PM
-40% candidates iCRS
-77% underwent 3rd CRS

IMPACT OF iCRS in RCT
- crossover CRS to CRS/HIPEC at recurrence
(15% of patient crossed over in Prodige)
Impact the OS results

MEDIAN SURVIVAL AFTER RECURRENCE



Numbers at risk						
Curative patients	43	31	18	12	8	6
Palliative patients	63	24	9	3	1	1

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van Eden et al Ann Surg Oncol. 2018 Jul;25(7):1992-2001.

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MITOMYCIN HIPEC: COMPLETED & ONGOING PHASE III CLINICAL TRIAL

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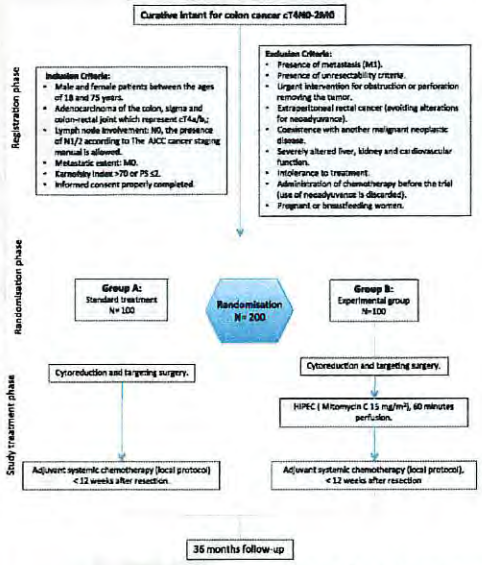
HIPECT4 TRIAL



BRIEF OVERVIEW

-Radiographic T4 (MRI/CT)
-Omentectomy appy, & oophorectomy performed both arms
-HIPEC at index surgery (Open or laparoscopic)
--MMC 30 mg/m2 60 minutes
Primary endpoint: **local-regional control (LC)**
Control 64% vs. 84% HIPEC arm at 3-years
-15 Spanish HIPEC centres

ESMO 2022 REPORTED RESULTS

- No add morbidity
- No difference in OS or DFS at 36 months

3-years	Control	HIPEC	HR	p-value
LC All (95/89)	87%	97%	0.20	**0.02**
LC T4 (61/62)	82%	98%	0.09	**0.04**
DFS All (95/89)	78%	**81%**	0.77	0.22
#1 Site of mets	peritoneal	**hepatic**		

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Alvaro Arjona-Sanchez et al BMC Cancer. 2018 Feb 13;18(1):183. doi: 10.1186/s12885-018-4096-0. PMID: 29439668

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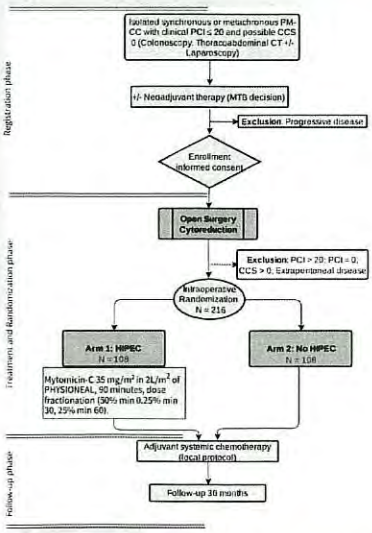
GECOP-MMC RCT



BRIEF OVERVIEW

-Optional preop laparoscopy but encouraged.
-At least 3-4 cycles NAC
MMC 35 mg/M2 (50% at t0 & t60) 90-minute perfusion
PCI: 1-20 enrolled & CC0 only

-31 Spanish HIPEC centres

DESIGN & ENDPOINTS

Primary Endpoint: 3-year peritoneal RFS
Control 50% vs. 70% HIPEC arm
Secondary Enpoints: OS, DFS (global) AEs, QoL

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Pereira et al . BMC Cancer. 2022 May 12;22(1):536. doi: 10.1186/s12885-022-09572-7. PMID: 35549912.

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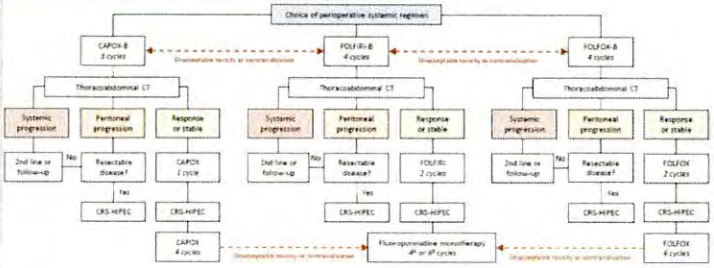
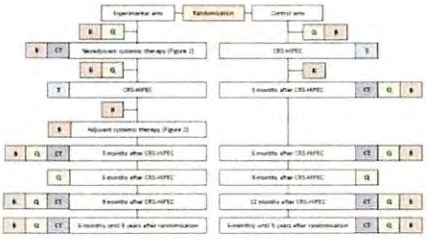
CAIRO 6 Phase II/III
CRS/HIPEC VS CRS/HIPEC+SCT

PHASE II Schema



PHASE III Schema



Rovers KP et al Dutch Peritoneal Oncology & Colorectal Cancer Group. Phase 2 Randomized Clinical Trial. JAMA Surg. 2021 Aug 1;156(8):710-720. doi: 10.1001/jamasurg.2021.1642. PMID: 34009291
Rovers KP et al Dutch Peritoneal Oncology & Colorectal Cancer Group. BMC Cancer. 2019 Apr 25;19(1):390. doi: 10.1186/s12885-019-5545-0. PMID: 31023318; PMCID: PMC6485075.

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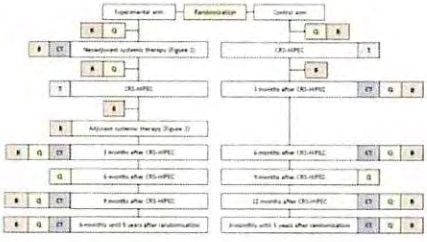
CAIRO 6 Phase II/III
CRS/HIPEC VS CRS/HIPEC+SCT



PHASE II

i. NAC is safe
   - 25% unable to complete therapy

ii. Major progression was **NOT** observed

iii. Radiographic & Pathologic response occurred
   - 38% had major 38% (TRG1-2)
   - 24% CR

PHASE III
Awaited the efficacy of CRS/HIPEC alone (control)
MMC 35 mg/M2 90 minutes

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SUMMARY

I. 30-minute oxaliplatin HIPEC did not demonstrate efficacy in Phase III trial.

II. 90-minute mitomycin HIPEC has documented efficacy
   i. Pre-clinical data
   ii. Retrospective clinical data:
      ✓ OS of 54-62 months higher than oxaliplatin
      ✓ Superior peritoneal control compared to oxaliplatin

III. HIPECT4 provides 1st prospective RCT evidence of MMC efficacy in CRC cancer in the setting contemporary chemo Tx

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CONCLUSION

SSO 2023

I. **HIPEC with Mitomycin 90-120 minutes should be offered**
   i. Efficacy in CRC is support by preclinical, retrospective and now prospective data.

II. **More level 1 data is needed before discontinuing MMC HIPEC**
   i. GECOP trial will answer efficacy regarding peritoneal control
   ii. CAIRO 6 will provide data regarding CRS-HIPEC alone

III. **Target of regional therapies is peritoneal control**
   i. Reduce peritoneal recurrence (PR)
   ii. Extend time to peritoneal recurrence (PerPFS)
   iii. Reduce burden PR decrease symptoms & ability for salvage iCRS
   iv. Improve survival

IV. **Any new regional therapy would be compared to CRS/HIPEC not CRS alone**