Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Colorectal Cancer: Indications, Outcomes, and Controversies

Ian Solsky, MD, MPH
Assistant Professor
University of Tennessee Health Science Center

Disclosures

- No disclosures

Outline and Objectives

BACKGROUND	Discuss the motivation for and outcomes of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC)
PATIENT SELECTION	Identify eligible candidates for CRS-HIPEC
CONTROVERSIES	Review areas of controversy in the surgical management of patients with colorectal cancer (CRC) peritoneal metastases (PMs)

BACKGROUND

Motivation for CRS-HIPEC

Historical Background

The Dutch Trial

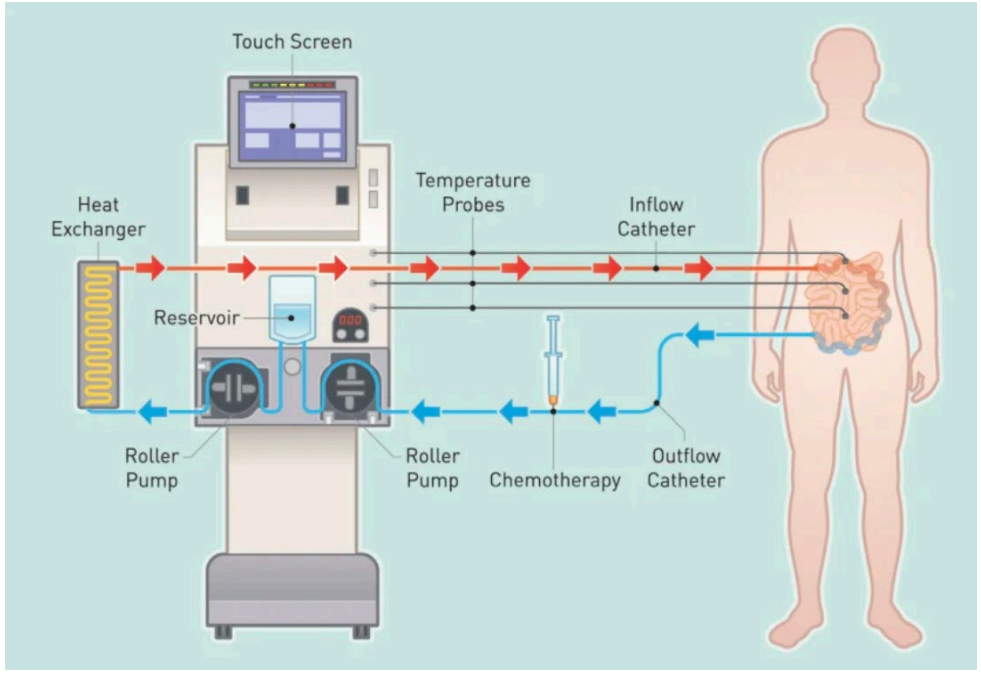
30 Years of Data

Background

- Colorectal cancer (CRC) peritoneal metastases (PMs) occur in 8-25%
- Median survival with best supportive care: 5.2 months
- Median survival with chemo alone: up to 24 months with modern agents
- Locoregional therapies like cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) may improve outcomes

Jacobson R et al. Ann Surg Oncol. 2018;25(8):2145-2151.
Sadeghi et al. Cancer. 2000 Jan 15;88(2):358-63.
Elias et al. J Clin Oncol. 2009 Feb 10;27(5):681-5.

CRS-HIPEC History



Benefits of HIPEC

- Direct peritoneal delivery (high chemo concentrations)
- Minimization of systemic side effects
- Hyperthermia: direct cytotoxic effects and synergism with chemo (increased drug penetration)

1930s
J.V. Meigs describes tumor debulking in ovarian cancer with adjuvant chemo or radiation therapy

1960s
E.W. Munnell and C. Griffiths report improved survival in Stage IV ovarian cancer patients with aggressive cytoreductive surgery to residual tumor burden <2 cm

1969
R.T. Long *et al.* report success with aggressive regional therapy approach on patients with pseudomyxoma peritonei

1977
J.S. Spratt designs a delivery system for hyperthermic intracavitary perfusate

1977
J.R. Palta develops therapeutic infusion filtration system

1977
J.M. Larkin reports on systemic thermotherapy reducing overall tumor burden

1979
J.S. Spratt treats first patient with hyperthermic thiotepa for pseudomyxoma peritonei

1980s
P.H. Sugarbaker investigated efficacy of technique for variety of GI malignancies

1980s
Targeted chemotherapeutic agents for specific malignancies

1987
Phase I trial establishes pharmacokinetic advantage of IP chemo over IV chemo with cisplatin and etoposide

1990s
Peritoneal Cancer Index is developed for quantifying peritoneal tumor burden

1995
P.H. Sugarbaker: formally describes technique of peritonectomy

Early 2000s
O. Glehen and F.N. Gilly describe the completeness of cytoreduction (CC) score for measuring extent of CRS achieved

Neuwirth. J Gastrointest Oncol. 2016 Feb; 7(1): 18-28.
HIPEC diagram from: https://physicianresources.foxchase.org/news/peritoneal-surface-malignancies

Dutch Study (1998-2001, n=105)

- CRS-HIPEC vs. chemo alone
- All patients received 5FU chemo
- HIPEC: Mitomycin C (MMC) for 90 minutes
- OS: 22.3 vs 12.6 months (p=0.032)
- OS low vs. high disease burden: 29 vs 5.4 months (p<0.0001)
- 5-year OS for ideal CRS: 45%
- 8% mortality

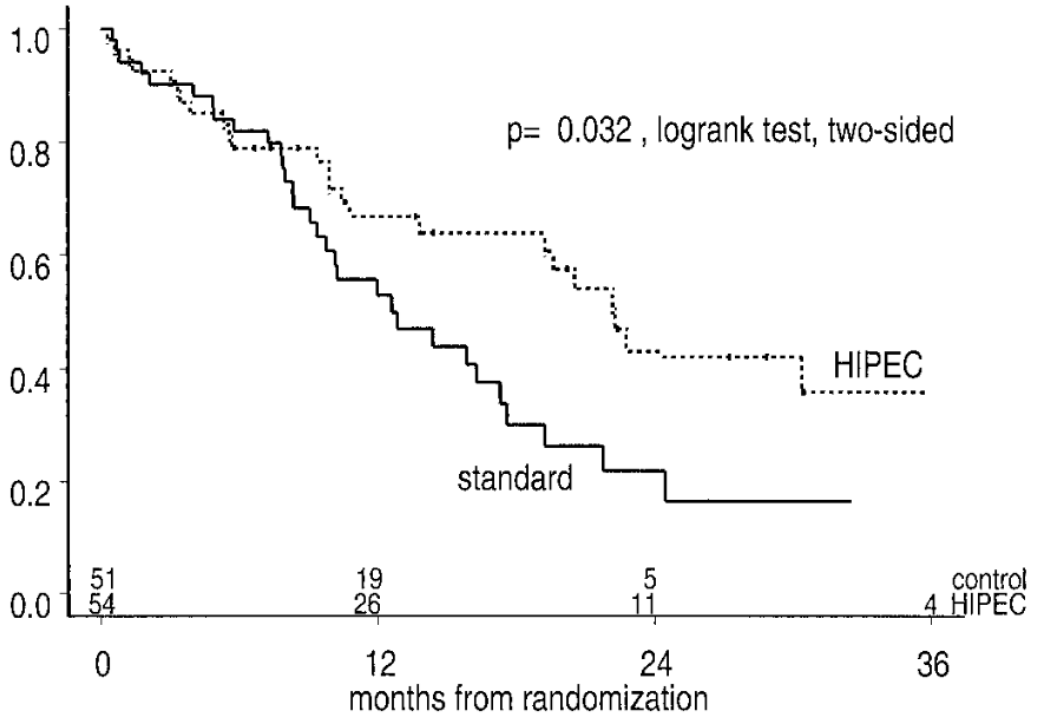


Fig 2. Kaplan-Meier survival curve, comparing standard treatment to hyperthermic intraperitoneal chemotherapy (HIPEC).

Verwaal et al. J Clin Oncol. 2003. Oct 15;21(20):3737-43.

Outcomes improving over time…

Table 5. Median Survival, Sample Size, and Proportions in 10-Year Intervals

Resection type	1991-2000 Median OS, mos, n (%)	2001-2010 Median OS, mos, n (%)	2010-2020 Median OS, mos, n (%)	p Value
Overall	13.5 (66, 100)	19.3 (139, 100)	29.1 (140, 100)	0.0082*
Complete resection	32.3 (23, 35)	31.1 (76, 55)	34.1 (107, 76)	0.52
Incomplete resection	5.2 (43, 65)	14.4 (63, 45)	14.6 (33, 24)	0.041*

…but still significant major morbidity (15.1-47.2%) and mortality (0-4.5%)

Lundy et al. J Am Coll Surg. 2022 Apr 1; 234(4):546-556.
Flood et al. Surgeon. 2021 Oct;19(5):310-320.

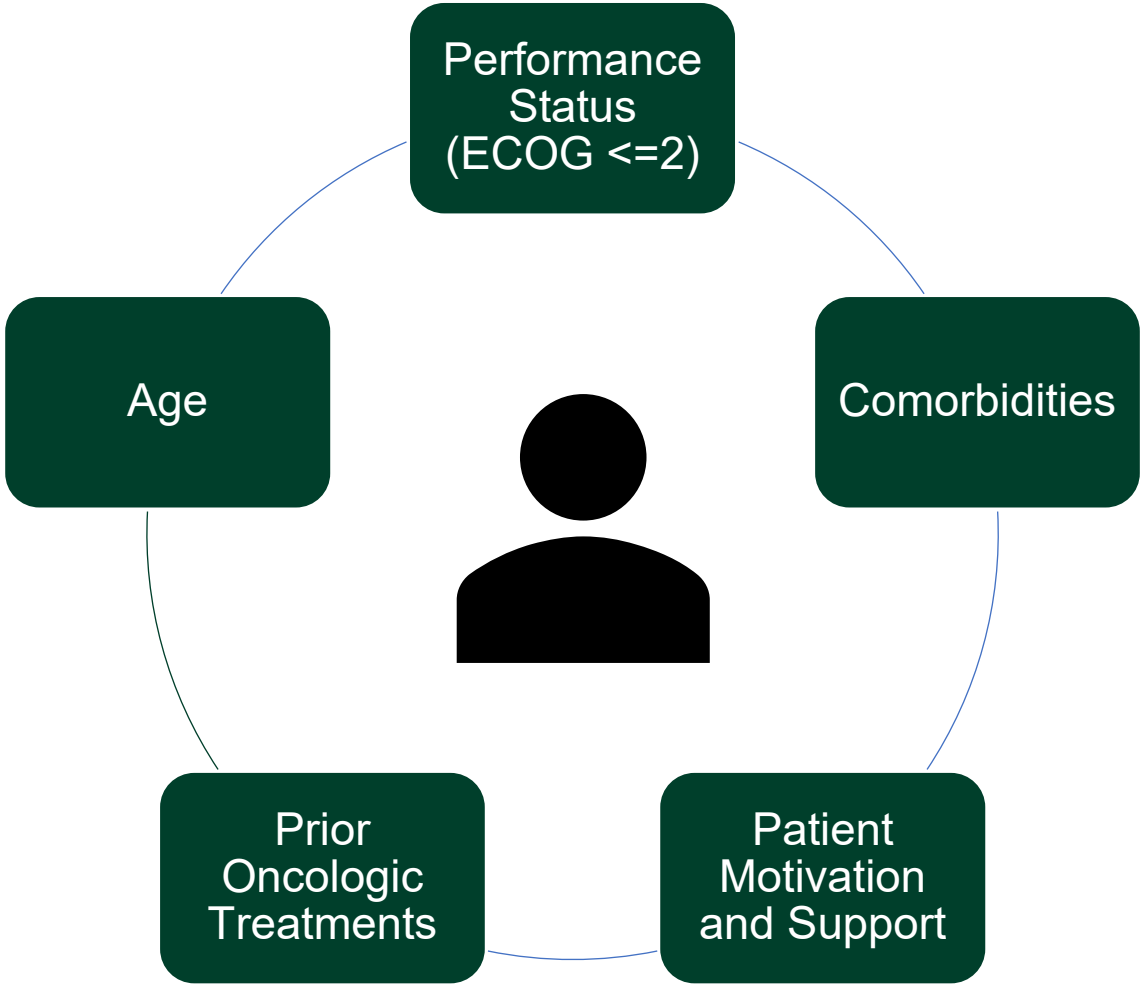
PATIENT SELECTION

Patient Variables

Resectability / Burden of Disease

Molecular Markers

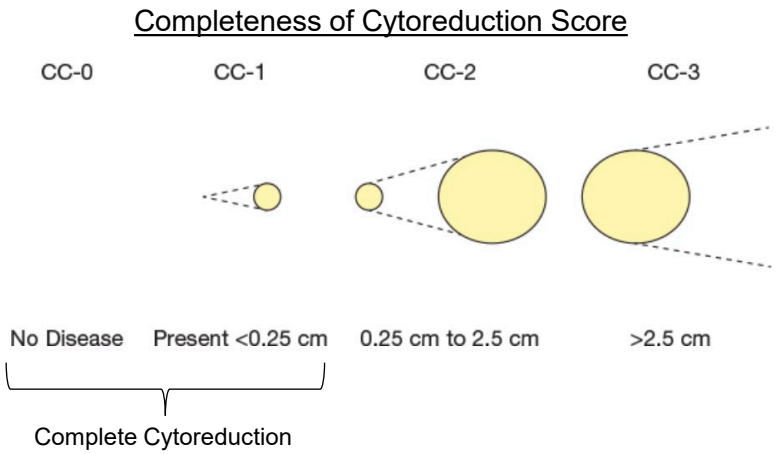
Patient Variables



Resectability / Disease Burden

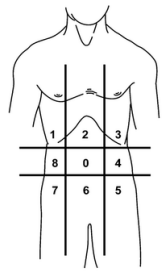
Resectability

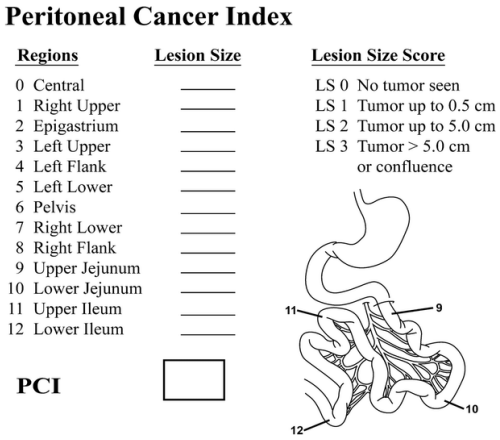
- CRS-HIPEC only if complete cytoreduction obtainable
- Complete resection: tumor nodules < 2.5mm



Peritoneal Carcinomatosis Index (PCI)

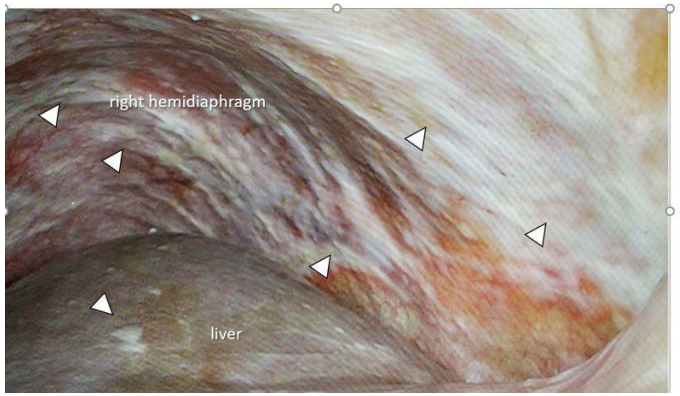
- Preop PCI (radiographically, laparoscopically) often underestimates disease
- No precise PCI cutoff: 12-20





Tumor Location

- Location/extent of disease may preclude resection: small bowel, porta hepatis, liver, lung



Carignani et al. Clin Transl Oncol. 2003;5:192-198.
Sugarbaker et al. Recent Results in Cancer Research. Vol. 169. Springer; 2007:1-9.
ACS. Operative Standards for Cancer Surgery. Volume 3

Molecular Markers

- BRAF, RAS, MSI/MMR testing recommended for metastatic CRC
- Impact of these markers still to be determined for PMs

Table 1 Predictive and prognostic biomarkers in patients with CRC-PM

Author *N*	Tumour type	Mutation, MSI status %	PFS, months MUT vs WT MSI vs MSS	OS, months MUT vs WT MSI vs MSS	Other results, months
Massalou et al. [29] *N* = 91	Mucinous, 38% SRC, 6%	*KRAS*, 44% *NRAS*, NR *BRAF*, 11% MSI, 27%	17.5 vs 11.6; $p=0.15$ NR 11.6 vs 13.6; $p=0.54$ 24.9 vs 12.4; $p=0.01$	51.3 vs 35.7; $p=0.22$ NR 32.2 vs 42.2; $p=0.78$ 85.0 vs 35.7; $p=0.13$	All patients OS: 39.7 Sidedness: NR
Schneider et al. [21] *N* = 494	Mucinous, 13% SRC, 7%	*KRAS*, 38% *NRAS*, 5% *BRAF*, 6% MSI, NR	NR NR NR NR	CSS 38; $p=0.048$ CSS 49; $p=0.700$ CSS 18; $p\leq0.001$	CSS in *RAS/BRAF* WT: 52 Sidedness: NR
Arjona-Sanchez et al. [20] *N* = 77	Poorly differentiated or SRC, 36%	*RAS*, 49% *BRAF*, NR MSI, NR	NR NR NR	27.0 vs 76.0; $p=0.045$ NR NR	All patients DFS: 16.3 All patients OS: 31.1 Sidedness: NR
Graf et al. [30] *N* = 111	CRC, 88% Appendiceal, 12% Mucinous, 40% SRC, 22%	*KRAS*, 46% *NRAS*, NR *BRAF*, 11% MSI, NR	NR NR NR NR	24 vs 24; $p=0.126$ NR 12 vs ≈30; $p=0.028$ NR	Sidedness: NR
Baratti et al. [100] *N* = 152	Mucinous, 27% SRC, 3%	*KRAS*, 47%) *NRAS*, 5% *BRAF*, 7% MSI, 8%	NR NR NR NR	49.3 vs 49.7; $p=0.710$ NR 21.9 vs 49.3; $p=0.001$ 44.1 vs 49.2; $p=0.390$	Right- vs left-sided tumour OS: 34.4 vs 61.2; $p=0.03$
Tonello et al. [31] *N* = 437	Mucinous, 31% SRC, 2.5%	*KRAS*, 46% *NRAS*, 3% *BRAF*, 6.6% MSI, 13%	11.5; $p<0.001$ 10.4; $p=0.01$ 10.5; $p<0.001$ 19.2 vs 14.1; $p=0.007$	33.2; $p=0.005$ 32.3; $p=0.540$ 21.5; $p=0.017$ 95.0 vs 41.0; $p=0.040$	All patients: DFS: 13.6; OS: 42.3 Right-sided tumour patients: DFS: 12.8; OS: 32.4

Grávalos et al. Clin Transl Oncol. 2023 May 4. Online ahead of print.
Hamed et al. Ann Surg Oncol. 2023 Jul; 30(7):4459-4470.

CONTROVERSIES

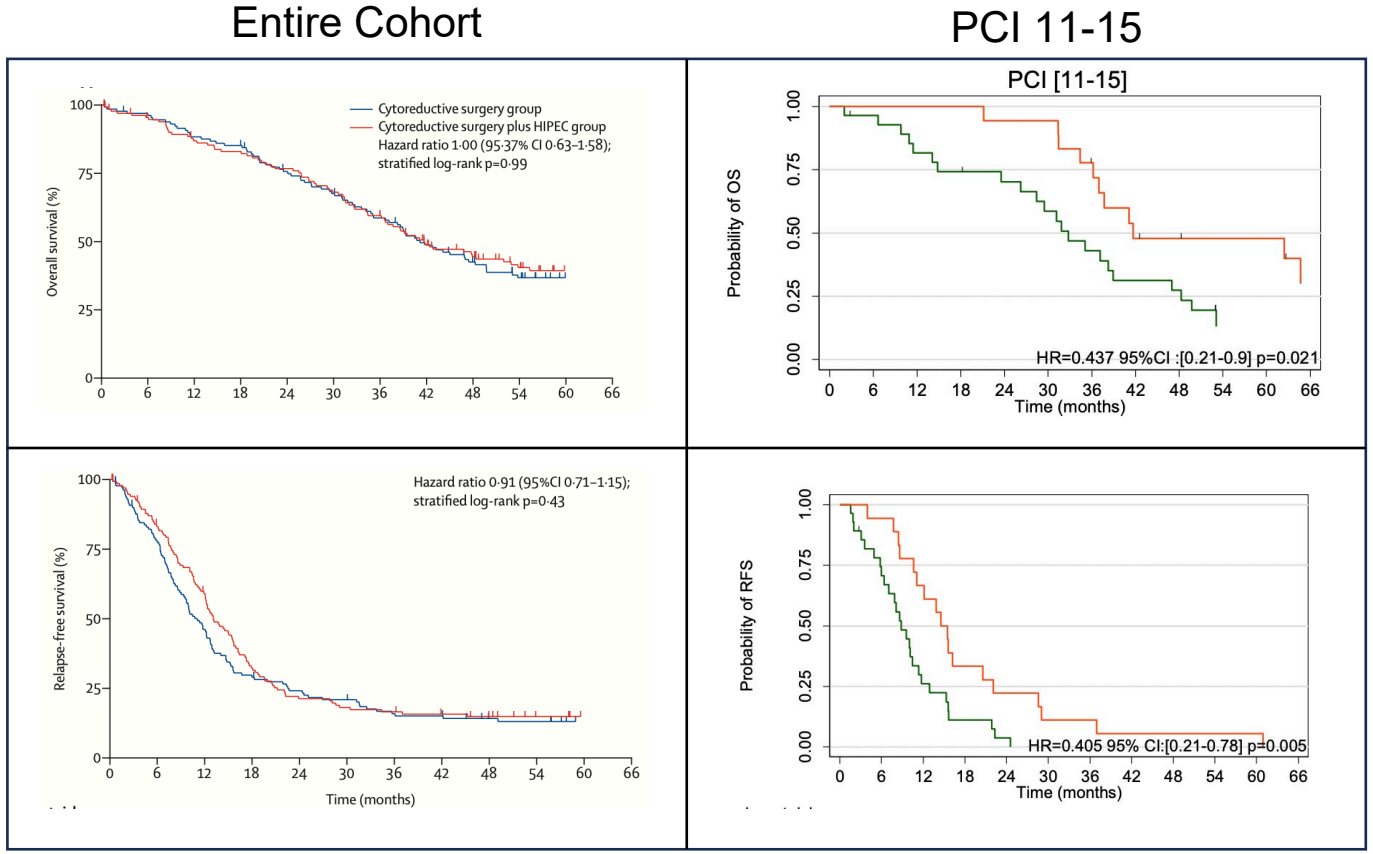
CRS alone vs. CRS-HIPEC

Prophylactic HIPEC

Perioperative Chemotherapy and Other Ongoing Investigations

PRODIGE7 (2008-2014, n=265)

- CRS-HIPEC vs. CRS alone
- HIPEC: oxaliplatin 360mg/m2 open (460 closed), 43°C, 30 minutes with 400 mg/m2 5-FU
- Systemic chemo for all
- Median PCI: 10 vs. 9 (p=0.50)
- CC-0: 89% vs. 92% (p=0.54)
- **OS: 41.7 vs. 41.2 months (p=0.99)**
- RFS: 13.1 vs. 11.1 months (p=0.43)
- PCI 11-15 with improved OS and RFS



Cytoreductive surgery should be the cornerstone of treatment for CRC PMs!

Should HIPEC be offered?

YES

- PRODIGE7 limitations
  - Mitomycin C is superior to Oxaliplatin
  - 30 minute HIPEC is too short
  - OS benefit was seen in PCI11-15

NO

- PRODIGE7 results
- HIPEC adds risk w/o clear benefit
- ICARuS Trial supports PRODIGE7
  - HIPEC (40mg MMC, 100 min, 41-43C) vs. EPIC (1g/m2, FUDR, POD1-3)
  - PFS: 7.7 vs. 8.8 months (p=0.14)

NCCN Colorectal Guidelines

"The panel currently believes that complete cytoreductive surgery and/or intraperitoneal chemotherapy **can be considered** in experienced centers for selected patients with limited peritoneal metastases for whom R0 resection can be achieved. However, the significant morbidity and mortality associated with HIPEC, as well as the conflicting data on clinical efficacy, make this approach **very controversial**."

Nash et al. J Clin Oncol. 2023. 41:4_suppl, 160-160.
NCCN Colon Cancer Guidelines. Version 3.2023—September 21, 2023.

Impact of PRODIGE7

“Although their personal opinions of CRS-HIPEC were barely influenced by PRODIGE 7, they reported a substantial impact on daily practice.”

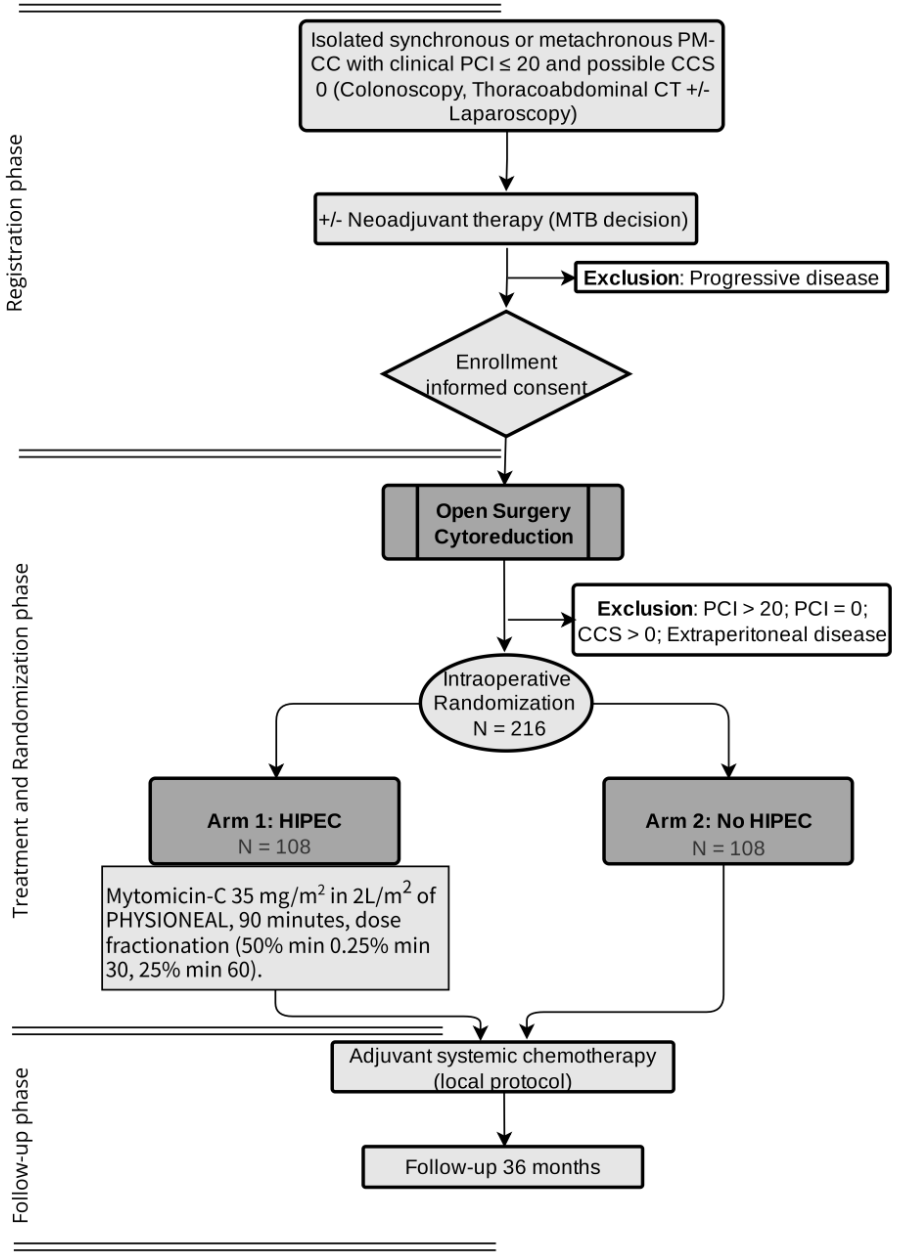
- Switch to Mitomycin-C
- Prolongation of HIPEC perfusion time
- Reduction in referrals from non-HIPEC centers
- Reduction in national consensus
- Removal of HIPEC from national guidelines
- Reduced reimbursement rate

- Survey of 18 international CRS-HIPEC experts

van de Blasakker. Eur J Surg Oncol. 2021 Nov;47(11):2888-2892.

More data needed!

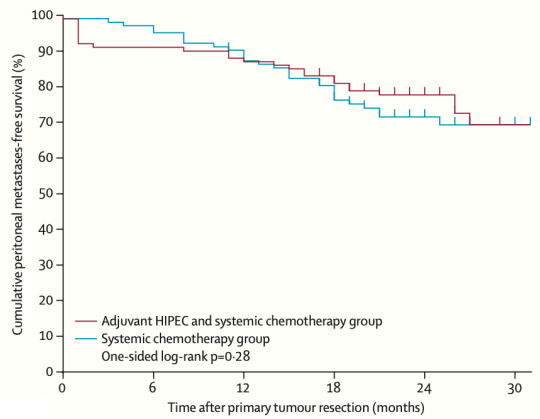
- GECOP-MMC RCT
  - Mitomycin C 35mg/M2, 90 min perfusion
  - PCI 1-20 enrolled and CC0 only
  - 31 Spanish HIPEC centers
  - Primary endpoint: 3-year peritoneal RFS
  - Secondary endpoint: OS, DFS, AEs, QoL



HIPEC for prophylaxis in resected CRC at high-risk of PMs?

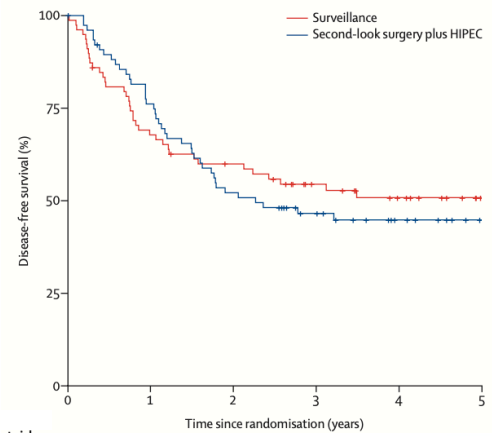
COLOPEC (2015-2017, n=204)

- Resected perforated or T4N0-2M0
- Adjuvant HIPEC vs. surveillance
- All received adjuvant chemo
- Adjuvant HIPEC (simultaneously or within 5-8 weeks after index surgery): oxaliplatin 460mg/m2 open, 42°C, 30 minutes; 400 mg/m2 5-FU
- **18-month peritoneal metastasis-free survival: 80.9% vs 76.2% (p=0.28)**
- **18-month OS: 93% vs 94.1% (p=0.82)**



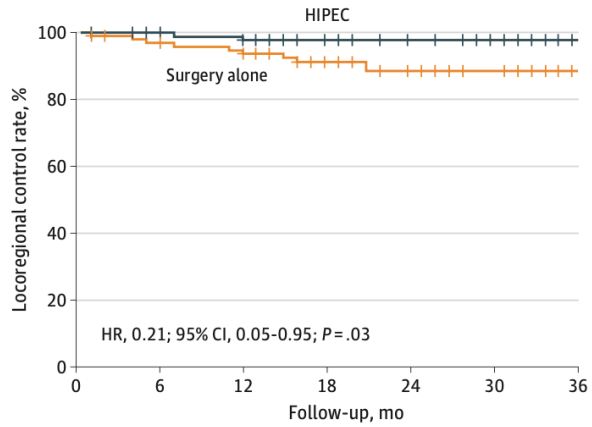
PROPHYLOCHIP (2010-2015, n=150)

- Resected perforated or PMs
- 2nd look HIPEC vs. surveillance after 6 months of postop chemo
- 2nd look HIPEC: oxaliplatin, oxaliplatin + irinotecan, or mitomycin (neuropathy)
- **3-year DFS: 44% vs 53% (p=0.82)**
- **3-year OS: 79% vs. 80% (p=NS)**



HIPECT4 (2015-2021, n=184)

- Radiographic T4N0-2M0
- CRS-HIPEC vs. CRS alone
- Adjuvant chemo for all
- HIPEC at index operation: MMC 30mg/m2 60 min
- **3-year locoregional control (LC): 97.6% vs. 87.6% (p=0.03)**
- 3-year DFS: 78% vs 81.2% (p=0.22)
- 3-year OS: 92.9% vs 91.7% (p=0.68)
- **pT4 LC: 98.3% vs 82.1% (p=0.003)**



Arjona-Sánchez et al. JAMA Surg. 2023;158(7):683-691.
Klaver et al. Lancet Gastroenterol Hepatol. 2019; 4: 761–70.
Goéré et al. Lancet Oncol 2020; 21: 1147–54.

Impact of HIPECT4

- HIPEC's role: peritoneal control
- Future trials should emphasize peritoneal PFS
- Benefits of improving peritoneal PFS:
  - Less symptoms and improved QoL
  - More time off chemotherapy
  - Fewer hospitalizations and interventions
  - Decreased disease burden may allow for salvage with iterative CRS

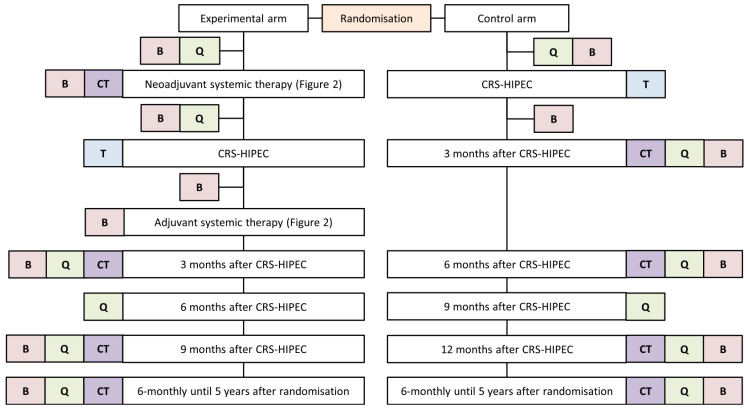
Ongoing Trials

Trial	Arms Primary endpoint	HIPEC	Adjuvant CT	pDFS 3-yrs %	DFS 3-yrs %	Survival, %
CHECK, NCT03914820 Phase III, *N* = 330 Italy, Recruiting	A: Standard surgery B: Prophylactic S + HIPEC C02 LRFS 3 years	MMC, 90 min	FOLFOX or XELOX	Pending	Pending	Pending
NCT04370925 Phase III, *N* = 688 China, Recruiting	A: RC B: RC + HIPEC pDFS 3 years	MMC, 90 min	FOLFOX or XELOX	Pending	Pending	Pending
APEC, NCT02965248 Phase III, *N* = 147 China, Recruiting	A: RC B: RC + HIPEC C: RC + HIPEC pDFS at 3 years	B: Raltitrexed, 60 min C: Oxaliplatin, 30 min	FOLFOX, XELOX or 5FU/LV	Pending	Pending	Pending
WUHIPEC02 NCT04845490 Phase II, *N* = 201 China, Not yet recruiting	A: S B: S + HIPEC C: S + HIPEC pDFS at 3 years	B: MMC, 60 min C: Lobaplatin, 60 min	FOLFOX or XELOX	Pending	Pending	Pending
NCT02830139 Phase II, *N* = 100 China, Not yet recruiting	A: S B: S + HIPEC Survival 5 years	CDDP + 5FU, 60 min	XELOX	Pending	Pending	Pending
COLOPEC-II, NCT03413254 Phase III, *N* = 389 The Netherlands, Recruiting	A: 2nd look DLS B: 2nd + 3rd look DLS % PM	NR	Permitted	Pending	Pending	Pending
NCT01628211 Phase II, *N* = 140 Italy, Recruiting	A: Standard follow-up B: 2nd look DLS Survival 2 years	NR	Permitted	Pending	Pending	Pending

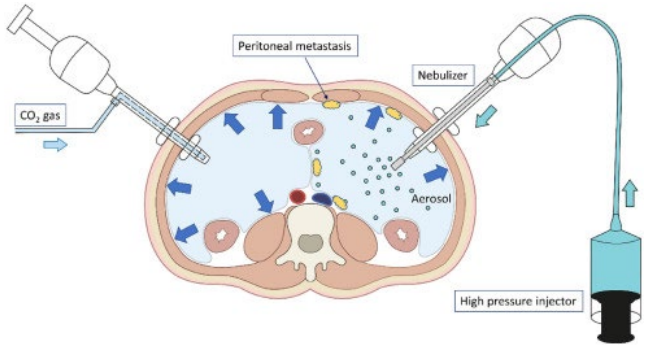
Future Areas of Investigation

Perioperative Chemotherapy

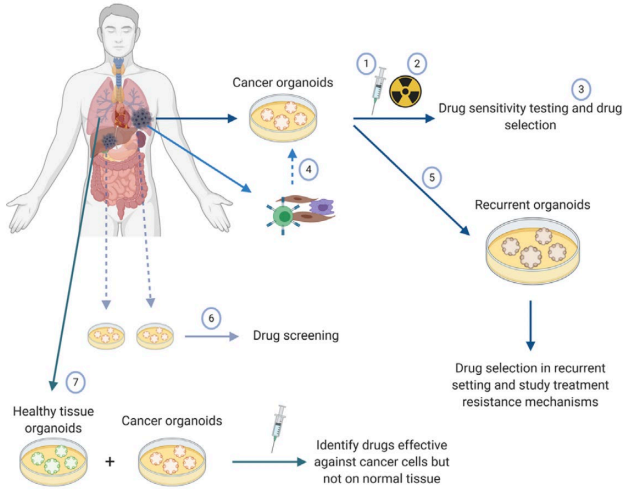
CAIRO6: Phase III Trial Ongoing



Pressurized Intraperitoneal Aerosolized Chemotherapy (PIPAC)



Patient-derived tumor organoids



Rovers et al. BMC Cancer. 2019. Apr 24;19(1):390.
Alyami et al. Lancet Oncol. 2019. Jul;20(7):e368-e377.
Erali et al. J Gastrointest Cancer. 2022 Nov 29. Online ahead of print.

Conclusion

Objective 1
Discuss the motivation for and outcomes of CRS-HIPEC
	• Greatest OS benefit for CRC PMs seen w/ locoregional therapy
	  • CRS +/- HIPEC + systemic chemo: 40+ months
	  • Systemic chemo alone: 24 months
	  • Supportive care: 5 months

Objective 2
Identify eligible candidates
	• Patient selection is key to good outcomes
	  • ECOG <=2, minimal comorbidities, motivated/supported
	  • CRS-HIPEC only if complete cytoreduction possible (PCI <20)
	  • Favorable tumor biology

Objective 3 *Review areas of controversy*	• CRS is the mainstay of treatment for resectable CRC PMs • HIPEC for PMs and ppx? Not w/ oxaliplatin but possibly with MMC • CRS-HIPEC is a promising locoregional tx in mCRC armamentarium