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WHY PIPAC?

HIPEC for Peritoneal Carcinomatosis

I. Benjamin Paz, MD, MS

Clinical Professor of Surgery

Vice-Chair, Department of Surgery

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Disclosures

- I do not have any relevant financial relationships.

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

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

The following CLC & IB components will be addressed in this presentation:

- Access to care.
- Bias determined by insurance access.

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Peritoneal Malignancies

- Primary Peritoneal Malignancy
  - Mesothelioma
  - Desmoplastic Round Cell Tumor
- Secondary Peritoneal Malignancy
  - Peritoneal carcinomatosis
    - Gastrointestinal Primary (gastric, pancreas, colorectal, appendix)
    - Gynecological Primary (ovary, fallopian tube, uterine, Mullerian organs, etc.)
    - Extra abdominal organs (breast, lung, melanoma)
  - Pseudomyxoma Peritonei arising primarily from the appendix (PMP does not arise from mucinous epithelial ovarian carcinoma)

Pseudomyxoma Peritonei

- The term “pseudomyxoma peritonei” was introduced by Richard Werth (1850-1915) in 1884, when he described the case of a woman with gelatinous masses in the peritoneal cavity from alleged ruptured pseudomucinous cystadenoma of the ovary, and in which he found to be pseudomucin instead of mucin.
- Olshausen (1835-1915), a German gynecologist, discussed the hypothesis that epithelial cells from the lining of the ruptured cyst were transplanted to the peritoneum, where they took root and continued to secrete gelatinous material
- Frankel recovered the term and described the case of a man with ruptured cyst of mucinous content from the cecal appendix

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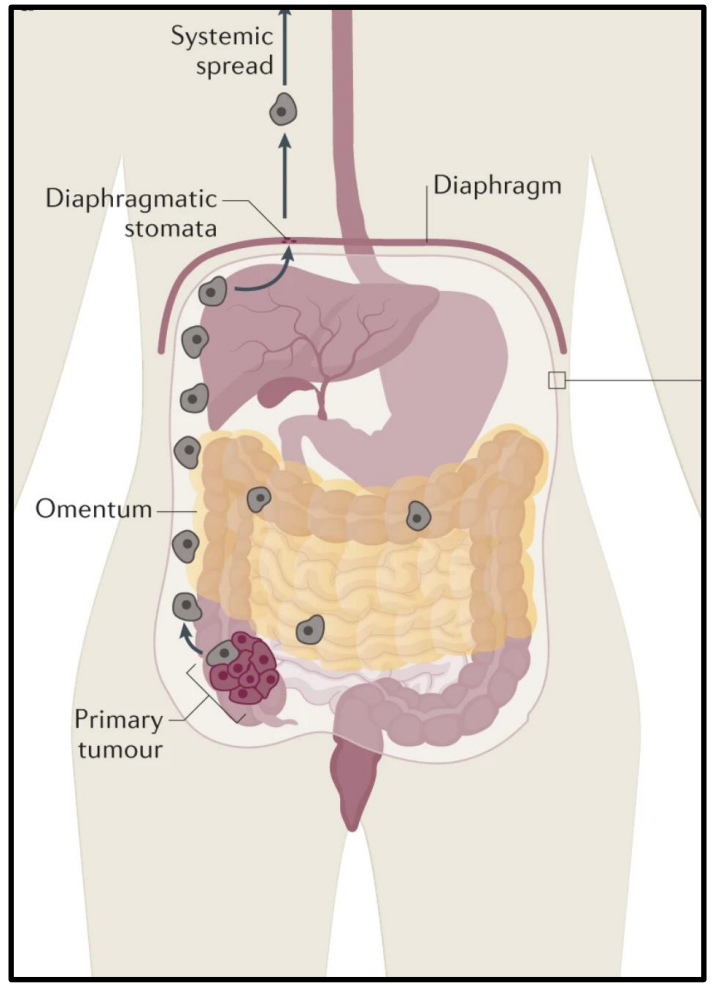
Intraperitoneal Tumor Spread

- Steps in the peritoneal metastatic cascade
  - Liberation of cells from primary tumor
    - T4 or perforated tumors (colon)
    - Iatrogenic spill
    - Elevated Interstitial Fluid Pressure (IFP)
  - Transport throughout the peritoneal cavity
  - Adhesion and invasion
  - Systemic spread



Cortés- Guiral D, et al. Primary and metastatic peritoneal surface malignancies. Nature Reviews Primer:7: (91) 1-23 (221)

Free cancer cells in the peritoneum

- Free cancer cells were detected prior to tumor resection in colorectal cancer 125/822 (15.2%) of patients and following resection in 64/533 (12%) of patients.
- Pre-resection: the absence of tumor cells was associated with a lower overall recurrence (25.2%) compared to the presence of tumor cells [46.4%, odds ratio (OR) = 0.41, confidence interval (CI) 0.19–0.88]; as well as a significantly lower local recurrence (12.2% versus 21.1%, OR = 0.42, CI 0.21–0.82).
- Postresection: the absence of tumor cells also resulted in significantly lower overall recurrence (17.3%) when compared to the presence of tumor cells (52.6%, OR = 0.07, CI 0.03–0.18).

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S Rekhraj, et al. Can intra-operative intraperitoneal free cancer cell detection techniques identify patients at higher recurrence risk following curative colorectal cancer resection: a meta-analysis. Ann Surg Oncol, 15 (2008), pp. 60-68

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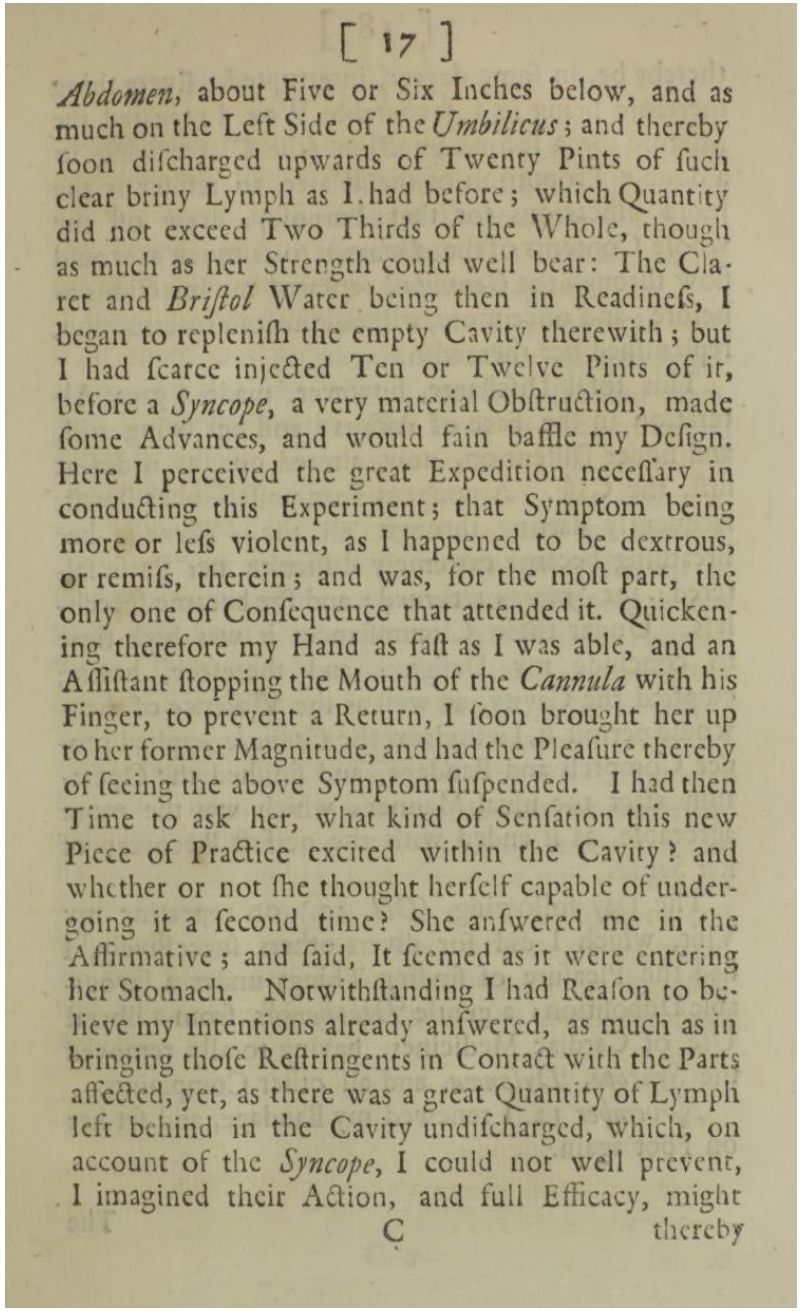
Origins Intraperitoneal Chemotherapy

- Decreased peritoneal surfaces vascularity decreases the therapeutic index of systemic chemotherapy
- Intraperitoneal delivery of chemotherapy achieves effective therapeutic concentrations of the drugs without systemic toxicity
- Dedrick (1970) proposed the intraperitoneal drug delivery (IPDD), taking advantage of the faster systemic drug clearance (PK) compared to the peritoneum, he also noted the limited tissue penetration
- Euler (1974) combined IPDD with hyperthermia as a hyperthermic IP chemoperfusion (HIPEC) in rats with malignant ascites
- Spratt (1980) performed hyperthermic chemoperfusion with thiotepa in a patient with pseudomyxoma peritonei (PMP) followed by IP methotrexate
- Koga (1984) studied combined hyperthermia and intraperitoneal mitomycin C in the treatment of implanted peritoneal hepatoma carcinomatosis in rat
- Sugarbaker (1987) initiated cytoreductive surgery for carcinomatosis from gastrointestinal malignancies followed by Early Postoperative Intraperitoneal Chemotherapy (EPIC)

Intraperitoneal Therapy

- An improvement on the practice of tapping; whereby that operation, instead of a relief for symptoms, becomes an absolute cure for an ascites, exemplified in the case of Jane Roman; and recommended to the consideration of the Royal Society, by Christopher Warrick, of Truro, Surgeon
- Philosophical Transactions of the Royal Society of London; June 15, 1744, 43I:473 (12-19)



[17]

Abdomen, about Five or Six Inches below, and as much on the Left Side of the *Umbilicus*; and thereby ſoon diſcharged upwards of Twenty Pints of ſuch clear briny Lymph as I had before; which Quantity did not exceed Two Thirds of the Whole, though as much as her Strength could well bear: The Claret and *Briſtol* Water being then in Readineſs, I began to repleniſh the empty Cavity therewith; but I had ſcarce injected Ten or Twelve Pints of it, before a *Syncope*, a very material Obſtruction, made ſome Advances, and would fain baffle my Deſign. Here I perceived the great Expedition neceſſary in conducting this Experiment; that Symptom being more or leſs violent, as I happened to be dextrous, or remiſs, therein; and was, for the moſt part, the only one of Conſequence that attended it. Quickening therefore my Hand as faſt as I was able, and an Aſſiſtant ſtopping the Mouth of the *Cannula* with his Finger, to prevent a Return, I ſoon brought her up to her former Magnitude, and had the Pleaſure thereby of ſeeing the above Symptom ſuſpended. I had then Time to ask her, what kind of Senſation this new Piece of Practice excited within the Cavity? and whether or not ſhe thought herſelf capable of undergoing it a ſecond time? She anſwered me in the Affirmative; and ſaid, It ſeemed as it were entering her Stomach. Notwithſtanding I had Reaſon to believe my Intentions already anſwered, as much as in bringing thoſe Reſtringents in Contact with the Parts affected, yet, as there was a great Quantity of Lymph left behind in the Cavity undiſcharged, which, on account of the *Syncope*, I could not well prevent, I imagined their Action, and full Efficacy, might

C thereby

Rationale for Intraperitoneal Chemotherapy

- Intraperitoneal drug delivery reaches a high IP drug concentration.
- Anticancer efficacy depends on the tissue drug concentration.
- Efficacy of IPDD is determined by the drug transport into the tissue:
  - Two major mechanisms determine the transport of drug into tumor tissue:
    - convection or bulk fluid flow, which is driven by a pressure gradient (large particles)
      - The hydrostatic pressure exerted by the intraperitoneal fluid column can be estimated as 10–20 cm H_2O (7.4–14.8 mm Hg). The tissue pressure that resides in the peritoneal cancer tissue is much higher compared to normal tissue.
    - diffusion, resulting from a concentration gradient (small particles)
      - Diffusion is driven by a concentration gradient. In addition, the rate of drug diffusion depends on temperature, physicochemical drug properties, and on the stromal architecture

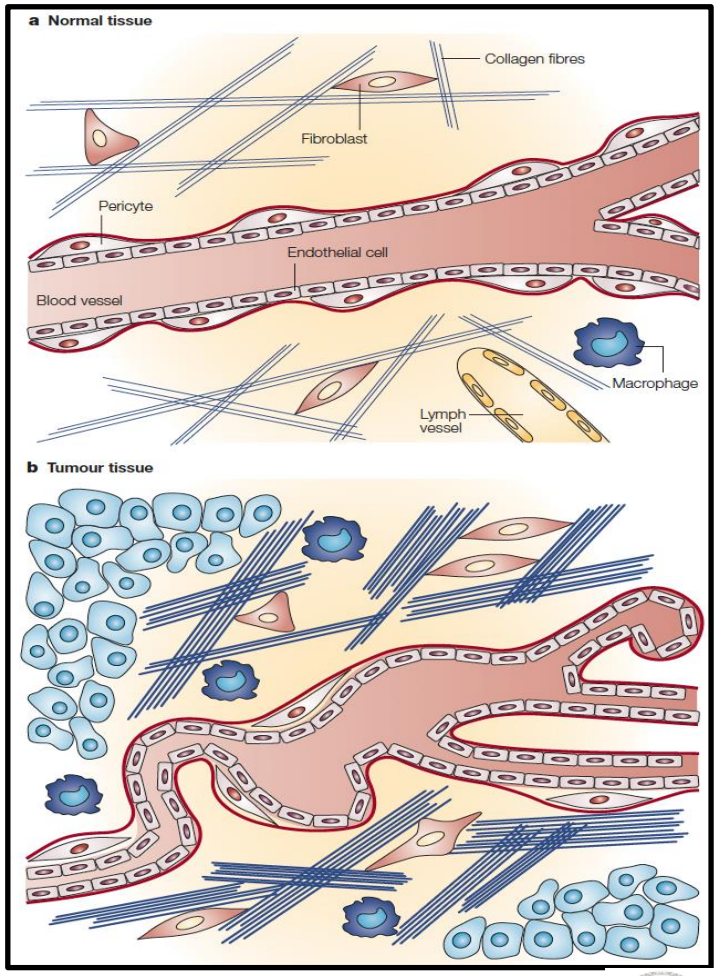
Rationale for Intraperitoneal Chemotherapy (IP)

- Pharmacokinetic advantage
  - Intraperitoneal chemotherapy clearance is much slower than systemic clearance, a high IP dose results in only moderate systemic levels
  - The advantage of IP drug delivery is usually expressed as the ratio of the area under the concentration-time curve (AUC) in the peritoneal over the plasma compartment (AUC peritoneum/AUC plasma), and ranges from approximately 2–1000 depending on the drug and model used
- Tissue Penetration
  - Limited tissue penetration (1-2 mm at most) is due to physical barriers and effects that prevent the chemotherapy from reaching the tumor cells
    - high interstitial fluid pressure (IFP)
    - dense extracellular matrix (ECM))
    - chemical (binding, sequestration, metabolism and degradation) effects
  - Increase in drug diffusion or decrease in vascular clearance is required to increase tissue penetration

Charlotte C, et al. Tumour tissue transport after intraperitoneal anticancer drug delivery . Int J Hyperthermia, 2017, 33: 534–5

Stroma-Tumor Barriers to Drug Transport

- High tumor interstitial fluid pressure (IFP)
  - Elevated IFP results from rapid cell proliferation, contraction of the stroma by activated fibroblasts, hyperpermeable capillaries and deficient lymphatic drainage.
- Drug delivery within tumor tissue primarily depends on diffusion.
  - Diffusive transport depends on properties of the:
    - Chemotherapy (size, charge and configuration)
    - Extracellular Matrix (cellular composition, density, viscoelasticity, geometrical arrangement and electrostatic properties



Carl-Henrik Heldin , et al., High Interstitial Fluid Pressure- an obstacle in cancer therapy. (2004) Nature Reviews 4:808-12

Rationale for Hyperthermia

- Einstein–Stokes equation asserts that diffusion is proportional to temperature and inversely proportional to the viscosity of the medium
- Hydraulic conductivity (determines drug convective transport into the cell) is increased due to enhanced matrix permeability and a reduced fluid viscosity at higher temperatures
- Increase temperature may cause vasodilatation and an increase in drug clearance decreasing hyperthermia effectivity and increasing toxicity

Charlotte C, et al. Tumour tissue transport after intraperitoneal anticancer drug delivery . Int J Hyperthermia, 2017, 33: 534–5

Hyperthermia Preclinical Studies

- Facy et al. no difference in cisplatin concentrations of ovarian peritoneal tumors in a rat model after normothermic or hyperthermic (42℃ during 60 min) chemoperfusion
- Zeamari et al. perfusion with cisplatin (40℃ during 90 min) did not improve drug uptake in small IP tumors in a rat model
- Klaver et al. no survival benefit by the addition of hyperthermia in a syngeneic rat colorectal carcinomatosis model

Facy et al. (2011) J Exp Clin Cancer Res 30:4.
Zeamari et al. (2003). Anticancer Res 23:1643–8.
Klaver, et al. (2011). Ann Surg 254:125–30

Current Indications for HIPEC

Primary Tumor	Level & Grade of evidence	Comments	Reference
Colorectal	1- Low	One negative RCT (PRODIGE 7). Case Controlled study showed benefit of HIPEC vs. CRS alone	Quénet F, et al. Lancet Oncol. Online: Jan 18, 2021
Stomach	3- Low	Observational study with propensity score-matching (HR >0.5 for CRS+HIPEC vs. CRS alone	Bonnot PE, et al. :J Clin Oncol. 2019;37:2028–40
Pseudomyxoma Peritonei	3- Low	Observational study with propensity score-matching (HR >0.5 for CRS+HIPEC vs. CRS alone	Kusamura S, et al. JAMA Surg. 2021;156(3):e206363.
Ovary	1- Moderate	Randomized trial	van Driel WJ, et al. N Engl J Med. 2018;378:230–40.
Mesothelioma	4- Low	CRS+HIPEC shows benefits over historical controls	Yan TD, et al. J Clin Oncol. 2009;27:6237–42.

Bhatt A, et al. HIPEC Methodology and Regimens: The Need for an Expert Consensus. Ann Surg Oncol (2021) 28:9098–9113

HIPEC Procedure

- HIPEC procedure involves the circulation of a heated chemotherapy solution in the peritoneal cavity for 30 to 120 min using a roller pump and heat exchanger
  - HIPEC is performed after cytoreductive surgery (CRS)
  - Chemotherapy dosing is based on threshold dose (minimum dose required to produce a therapeutic effect) and peak dose (maximum dose above which no additional benefit is observed or there is toxicity)
  - Multiple factors may influence the efficacy of HIPEC including chemosensitivity and drug pharmacokinetics (molecular weight, carrier solution and concentration, intrabdominal pressure, etc.) as well as tumor and anatomical considerations
    - Dose calculations can be done based on BSA or drug concentration
    - Perfusion time depends on peritoneal half-life of the chemotherapy (30-120 min)
    - Perfusate temperature (41-43 C^{o}), type (hypo, iso or hypertonic), and volume
    - Single agent vs combination
    - Open vs closed perfusion, intraperitoneal pressure (perfusate volume, exchange rate)

Bhatt A, et al. HIPEC Methodology and Regimens: The Need for an Expert Consensus. Ann Surg Oncol (2021) 28:9098–9113

Studies Comparing Different HIPEC Regimens

Author	Year	N	Disease	Regimens Compared	Outcome
Quénet et al.	2011	146	Colorectal	460 mg/m2 oxaliplatin and 360 mg/m2 irinotecan vs oxaliplatin alone	ND OS, morbidity
Hompes et al.	2014	95	Colorectal	460 mg/m2 oxaliplatin vs 35mg/m2 mitomycin C	ND RFS, OS.
Votanopoulos et al.	2013	187	Colorectal & Appendiceal	200 mg/m2 oxaliplatin vs mitomycin C	Mit. C 3y-OS improv. trend
Glockzin	2014	32	Colorectal	300 mg/m2 oxaliplatin vs 300 mg/m2 irinotecan	Oxali. 3y-OS improv. trend
Prada-Villaverde et al.	2014	584	Colorectal	460 mg/m2 oxaliplatin vs 40 mg/m2 mitomycin C	Better OS with Mit. C
Leung et al.	2017	201	Colorectal	350 mg/m2 oxaliplatin vs 12.5 mg/m2 mitomycin C	Better OS with Oxali.
Van Eden et al.	2018	177	Colorectal	460 mg/m2 oxaliplatin vs 35 mg/m2 mitomycin C	ND OS, morbidity
Sipok et al.	2018	48	Colorectal	40 mg/m2 mitomycin vs 60 mg/m2 melphalan	Better OS with Mit. C
Bakkers et al	2020	297	Colorectal	Mitomycin C vs oxaliplatin	ND OS
Levine (randomized)	2018	121	Appendiceal	Mitomycin 40 mg/m2 vs oxaliplatin 200 mg/m2	ND OS

The Role of HIPEC in Pseudomyxoma Peritonei After Cytoreductive Surgery

- Peritoneal Surface Oncology Group International (PSOGI) registry data
  - Data were collected from 3495 patients with PMP from appendiceal CA who underwent CRS with or without HIPEC from 1993, to 2017.
  - 1924 patients had complete preoperative and postoperative data, 1548 had CRS+ HIPEC and 376 had CRS alone.
  - Propensity scores were used to account for the bias consistent with a nonrandom assignment of treatment in the study groups leaving 305 patients in the CRS alone and 300 patients in the CRS+HIPEC for the analysis that were appropriately matched
  - HIPEC was administered after CRS using an, open coliseum or closed technique:
  - The perfusate was heated to achieve a temperature ranging from 40 to 43.
  - HIPEC drug regimens included:
    - mitomycin, 35 mg/m2, or a fixed dose of 40 mg;
    - oxaliplatin, 360 to 460 mg/m2 plus combined fluorouracil and leucovorin, 400 mg/m2;
    - oxaliplatin,200mg/m2;
    - cisplatin, 25mg/m2 per liter of perfusate associated with mitomycin, 3.3 mg/m2 per liter of perfusate

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Kusamura S, et al. The Role of Hyperthermic Intraperitoneal Chemotherapy in Pseudomyxoma Peritonei After Cytoreductive Surgery. JAMA Surg. 2021;156(3):e206363.

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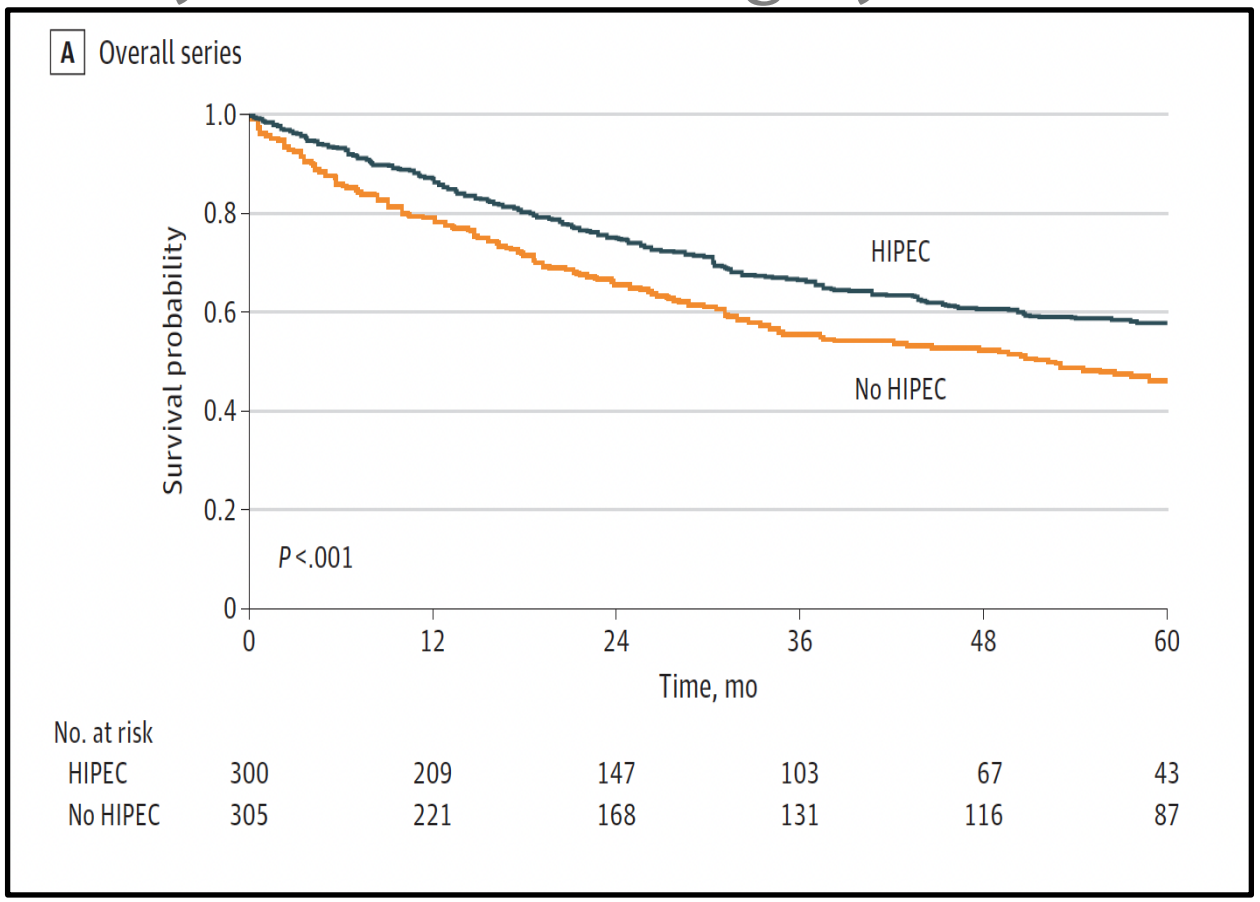
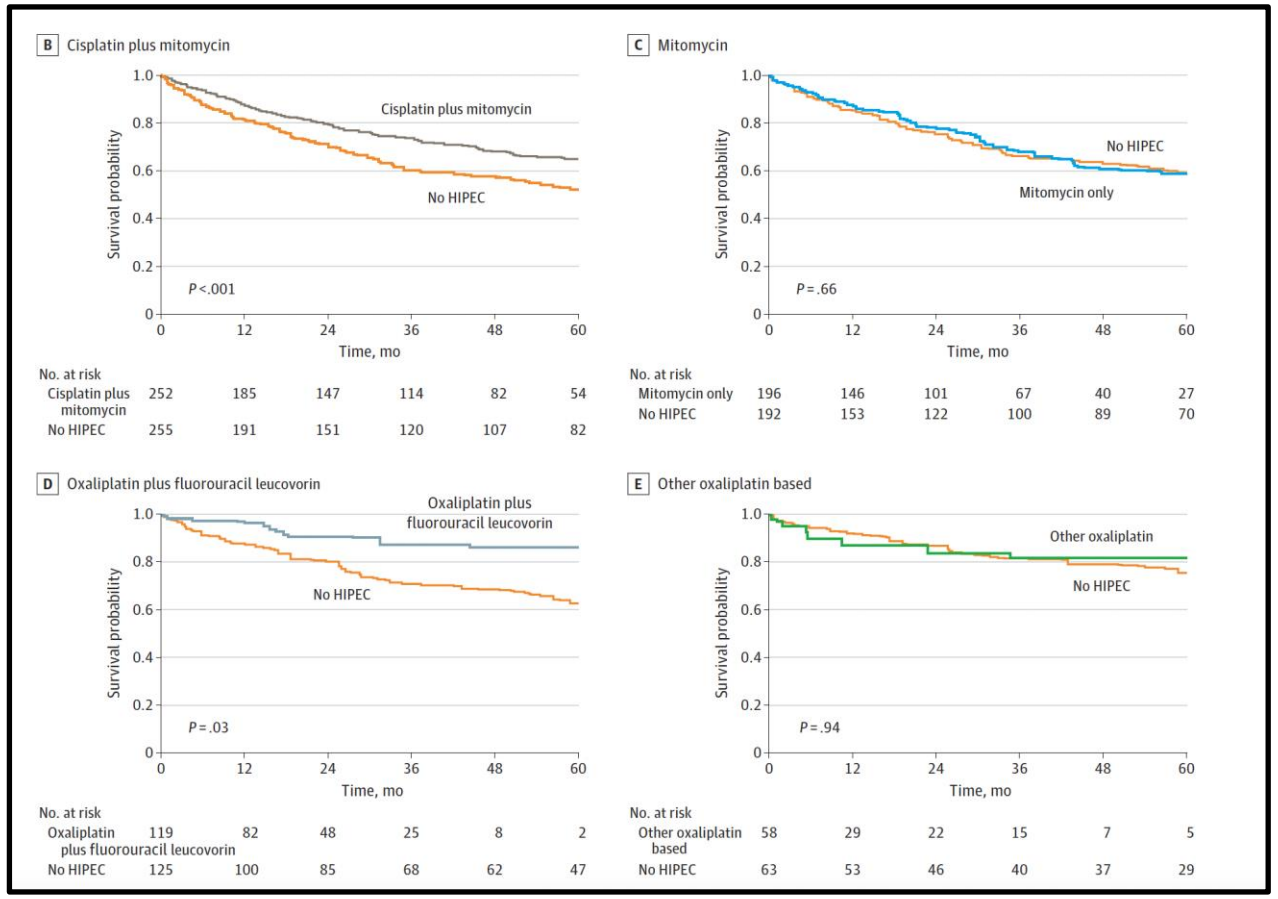
The Role of HIPEC in Pseudomyxoma Peritonei After Cytoreductive Surgery

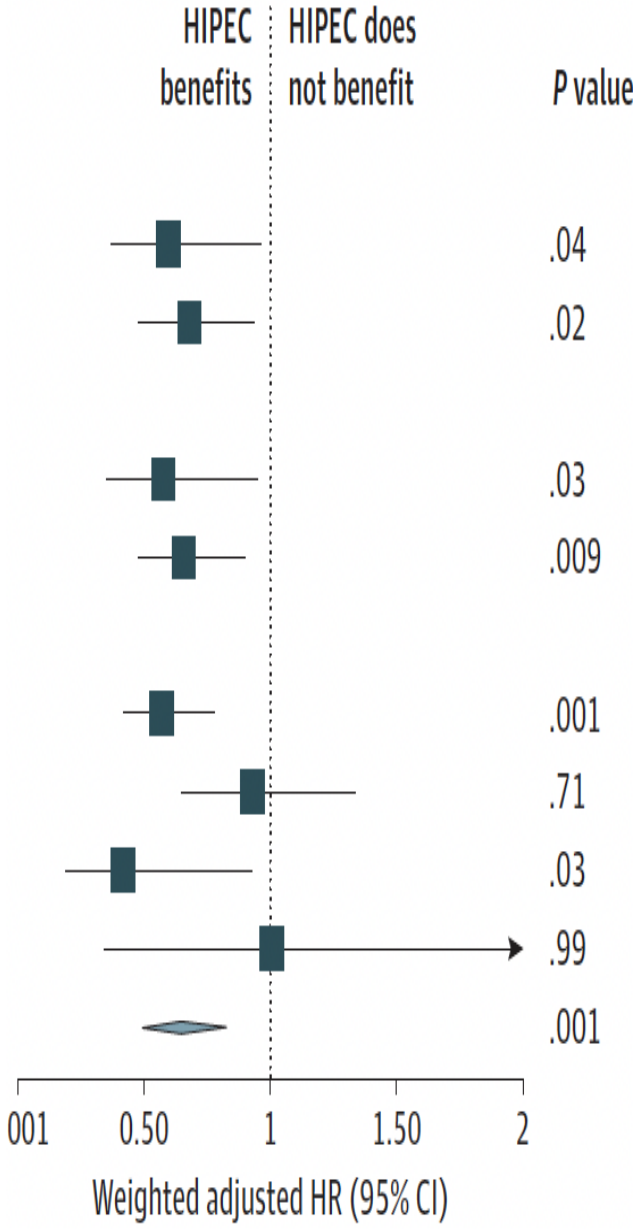




Kusamura S, et al. The Role of Hyperthermic Intraperitoneal Chemotherapy in Pseudomyxoma Peritonei After Cytoreductive Surgery. JAMA Surg. 2021;156(3):e206363.

Effect Size of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) on Overall Survival According to Subsets and HIPEC Regimens

Subset	HR (95% CI)
Histological type	
Low grade	0.60 (0.37-0.96)
High Grade	0.68 (0.48-0.94)
Cytoreduction	
CC0/1	0.58 (0.35-0.95)
CC2/3	0.66 (0.48-0.90)
HIPEC Chemotherapy	
Cisplatin + mitomycin	0.57 (0.42-0.78)
Mitomycin C	0.93 (0.65-1.34)
Oxaliplatin + 5FU	0.42 (0.19-0.93)
Oxaliplatin	1.01 (0.34-2.94)
Overall	0.65 (0.50-0.83)



Results of the Weighted Multivariable Cox Proportional Hazards Model Including HIPEC and the Main Prognostic Factors for Overall Survival

Factor	HR (95% CI)	p value
HIPEC yes vs no	0.65 (0.50-0.83)	0.001
Prior systemic chemotherapy, yes vs no	1.58 (1.23-2.03)	<0.001
Lymph node involvement, yes vs no	1.69 (0.95-3.01)	0.08
Peritoneal cancer index, 29 vs 10	4.12 (2.75-6.18)	<0.001
Higher histologic grade, yes vs no	2.36 (1.83-3.04)	<0.001
Age, 65 vs 45 y	1.24 (1.04-1.48)	0.007

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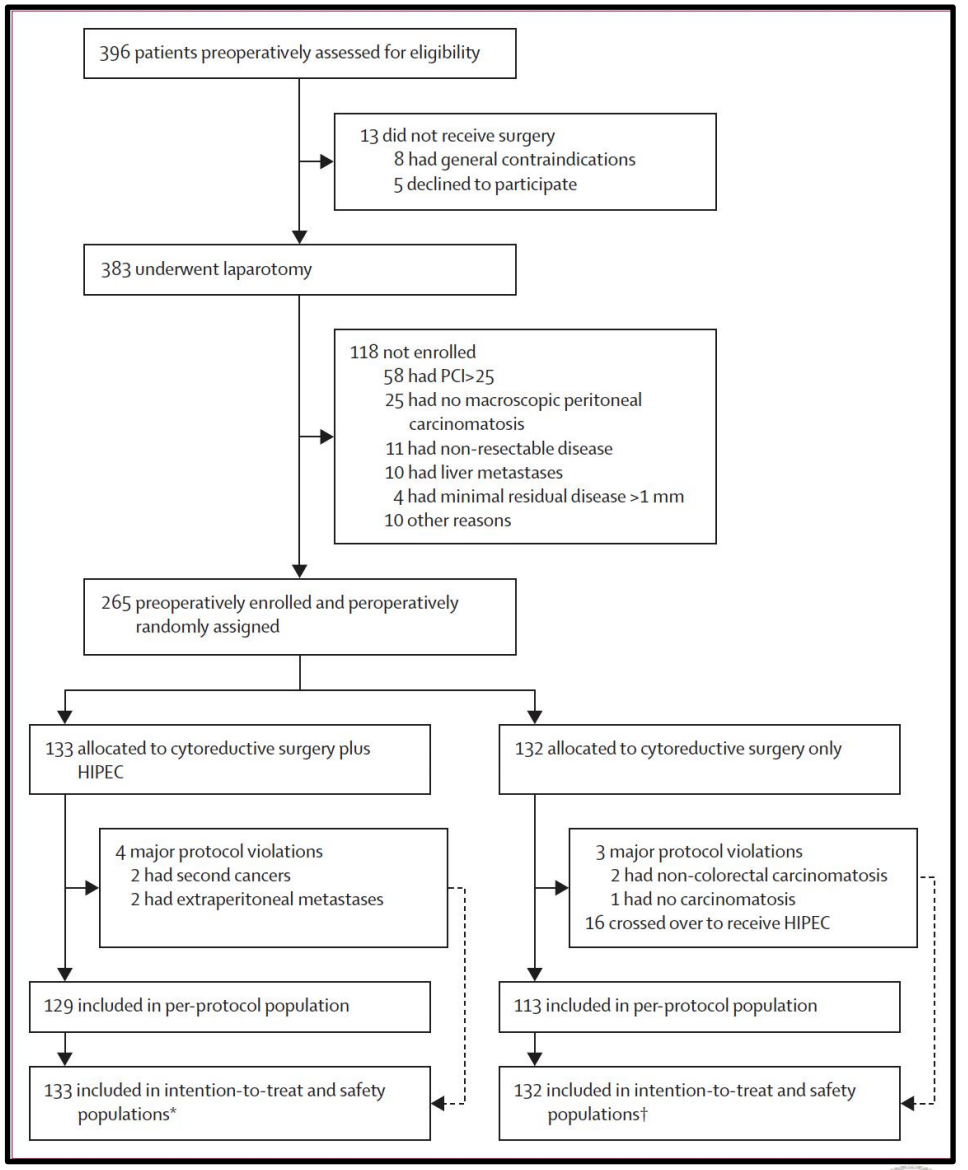
PRODIGE 7

- PRODIGE 7 a randomized, open-label, phase 3 trial done at 17 cancer centers in France
- Eligibility:
  - patients aged 18–70 years;
  - histologically confirmed colorectal cancer with peritoneal metastases, a
  - peritoneal Cancer Index (PCI) of 25 or less and WHO performance status of 0 or 1,
  - adequate hematological , renal and liver function
  - eligible to receive systemic chemotherapy for 6 months
  - Any previous treatments were allowed, and no washout period was mandatory
- Exclusion criteria were extraperitoneal metastases, non-colorectal carcinomatosis, previous HIPEC treatment, and grade 3 or worst neuropathy

Quenét F, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial. The Lancet Oncology, Volume 22, Issue 2, February 2021, Pages 256-266

Randomization

- Complete cytoreduction to <1mm tumor size
- HIPEC was administered with either the closed or open abdomen approach.
- Systemic chemotherapy (400 mg/m² fluorouracil and 20 mg/m² folinic acid) was delivered intravenously 20 min before HIPEC
- HIPEC with oxaliplatin (460 mg/m² if the open technique was used and 360 mg/m² if the closed technique was used) in 2 L/m² of dextrose at 43°C over 30 min.



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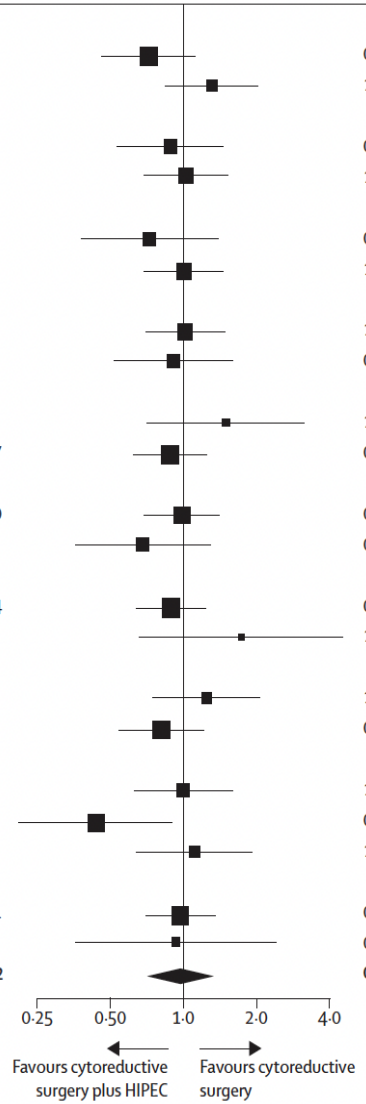
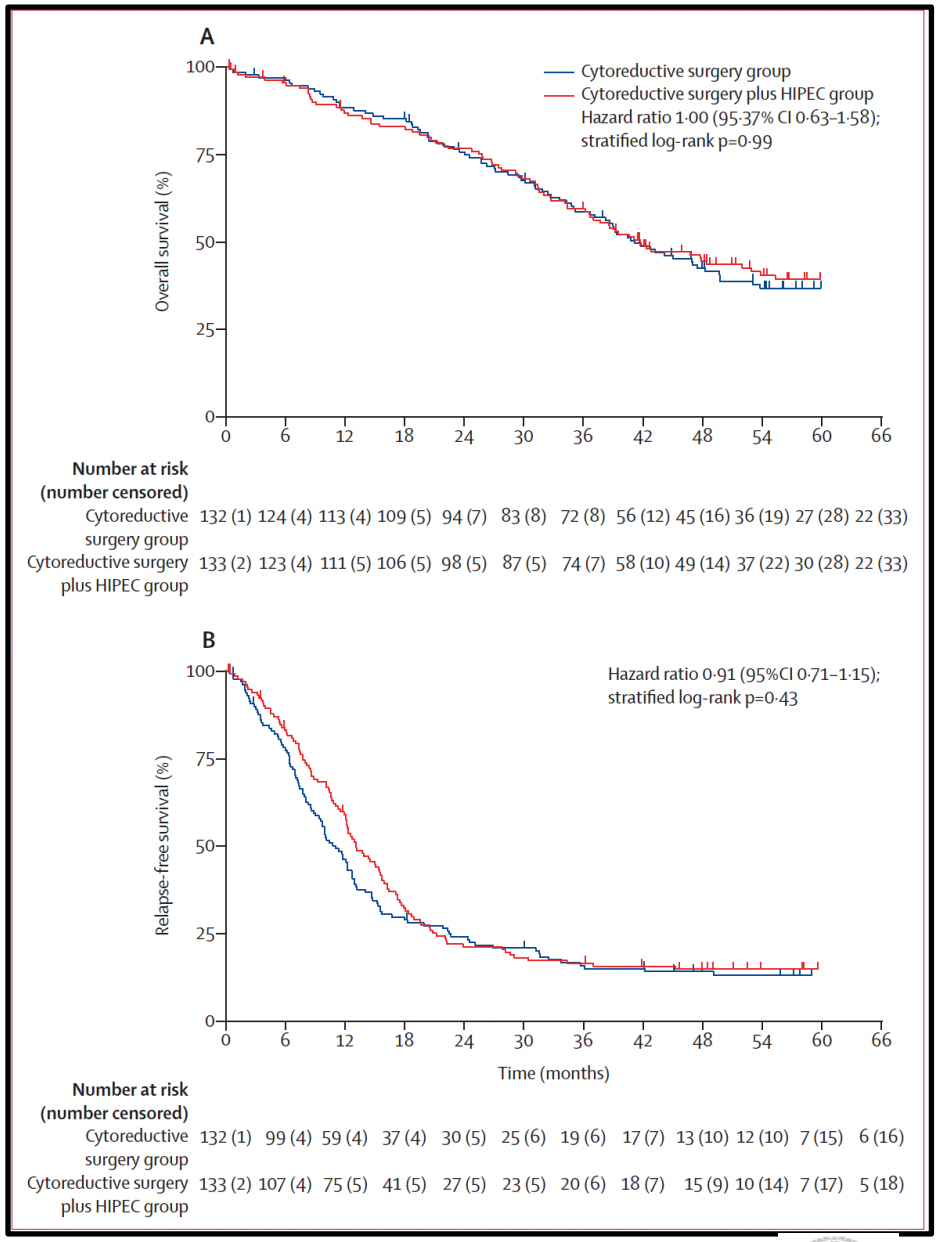
	Cytoreductive surgery plus HIPEC group	Cytoreductive surgery group	Unstratified hazard ratio (95% CI)	p value
Sex				0·06
Male	35/65	44/67	0·72 (0·46–1·12)	
Female	44/68	36/65	1·31 (0·84–2·03)	
Primary tumour side				0·65
Right colon	28/51	33/51	0·89 (0·53–1·46)	
Other	51/82	47/81	1·03 (0·69–1·53)	
Positive lymph nodes (primary tumour)				0·39
No	18/40	18/30	0·72 (0·38–1·39)	
Yes	54/84	58/95	1·01 (0·69–1·46)	
Previous chemotherapy				0·75
First line	57/99	52/89	1·02 (0·70–1·48)	
Second or third line	22/34	28/43	0·91 (0·52–1·59)	
Preoperative nutrition				0·21
No	14/21	14/24	1·50 (0·71–3·14)	
Yes	63/109	65/107	0·88 (0·62–1·25)	
Preoperative systemic chemotherapy				0·32
No	58/103	63/110	0·99 (0·69–1·41)	
Yes	21/ 30	17/ 22	0·68 (0·36–1·29)	
Postoperative systemic chemotherapy				0·20
No	69/117	73/114	0·89 (0·64–1·24)	
Yes	10/ 16	7/ 18	1·73 (0·66–4·55)	
Preoperative and postoperative systemic chemotherapy				0·19
No	37/ 53	26/ 45	1·25 (0·75–2·06)	
Yes	42/ 80	54/ 87	0·81 (0·54–1·21)	
PCI				0·14
<11	34/75	36/77	1·00 (0·63–1·60)	
11–15	11/18	23/28	0·44 (0·21–0·90)	
>15	34/40	21/27	1·11 (0·64–1·92)	
Resection				0·94
Complete macroscopic cytoreduction	70/119	72/121	0·97 (0·70–1·35)	
Complete macroscopic residual disease <1 mm	9/14	8/11	0·93 (0·36–2·41)	
Overall	**79/133**	**80/132**	**0·97 (0·71–1·33)**	





CRS without HIPEC for Peritoneal Carcinomatosis from Colorectal Cancer

Author	N	CCR 0/1 %	PCI Median	EPD %	OS median	Chemo	Selection Criteria
Kobayashi	484	100	NS	20.7	25	5-FU	CCR-0/1; only synchronous PM
Desolneu	50	100	8	52	32.4	Oxl/iri-based ± beva/cetux	CCR-0; C 12 cycles of s-CT
Baratti	48	93.7	5	25	39.3	Oxl/iri-based ± beva/cetux	Low PCI; potential CCR-0/1; no PRO during preop. s-CT
PRODIGE 7	132	100	9	0	41.2	Oxl/iri-based ± beva/cetux	PCI < 25; CCR-0/1

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Baratti D ,et al. Colorectal Peritoneal Metastases Treated by Perioperative Systemic Chemotherapy and Cytoreductive Surgery With or Without Mitomycin C-Based HIPEC: A Comparative Study Using the Peritoneal Surface Disease Severity Score (PSDSS). Ann Surg Oncol (2020) 27:98–106

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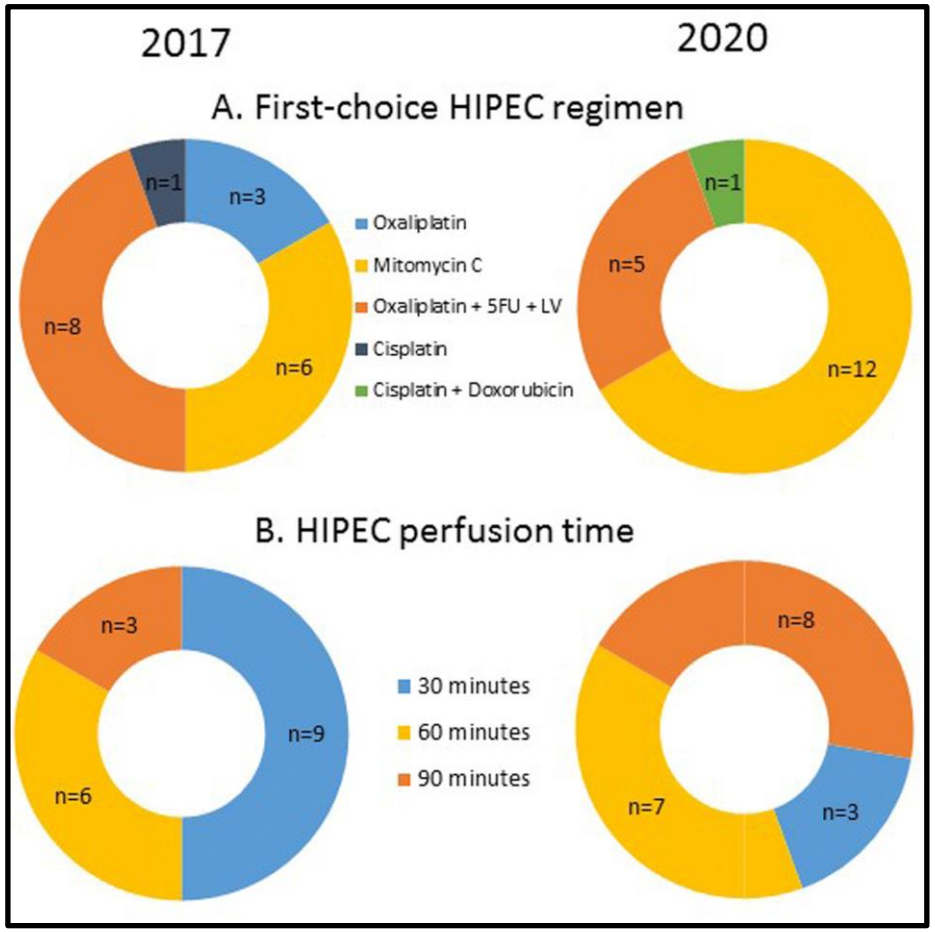
Criticism to PRODIGE 7

- Oxaliplatin resistance might be acquired after initial exposure to systemic chemotherapy
- Cytotoxicity of chemotherapeutic agents is dependent on exposure time (30-min HIPEC-perfusion-time may have been sub-optimal to achieve adequate oncological activity.
- Insufficient dose of 5-FU along with the HIPEC oxaliplatin
- Crossover of 16% of patients
  - There is an early recurrence-free survival benefit up to 18 months. The hazard ratio was 0.90 (non-significant due to sample size).
  - The 1-year recurrence-free survival rates were 46.1% vs. 59% (Fisher exact P=0.049, posthoc analysis)



van de Vlasakkera V, et al. The impact of PRODIGE 7 on the current worldwide practice of CRS-HIPEC for colorectal peritoneal metastases: A web-based survey and 2021 statement by Peritoneal Surface Oncology Group International. European Journal of Surgical Oncology 47 (2021) 2888e2892

Cashin P, Sugarbaker P. Hyperthermic intraperitoneal chemotherapy (HIPEC) for colorectal and appendiceal peritoneal metastases: lessons learned from PRODIGE 7. J Gastrointest Oncol 2021;12(Suppl 1):S120-S128

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Conclusion

- Complete cytoreductive surgery (CRS) for peritoneal carcinomatosis from colorectal and appendiceal CA prolongs survival and might lead to cures in 15-20% of patients
- The delivery of intraperitoneal chemotherapy increases the drug tissue concentration in the abdominal cavity without increasing systemic toxicity
- Further studies are needed to standardize the selection and dosing of the chemotherapy agents (↑threshold & ↓peak dose), the method of delivery (concentration, perfusate, temperature, open vs close) and the duration of the treatment (60-120 min).