City of Hope

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TREATMENT MODALITIES

Rationale for Regional Therapies

Mustafa Raoof, MD, MS

Assistant Professor
Division of Surgical Oncology
Department of Surgery
Department of Cancer Genetics and Epigenetics, City of Hope

Disclosures

- I do not have any relevant disclosures.

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

The off-label or investigational use of Mitomycin C, Abraxane (Nab-Paclitaxel), Oxaliplatin, 5-FU, Cisplatin, and Doxorubicin will be discussed.

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.

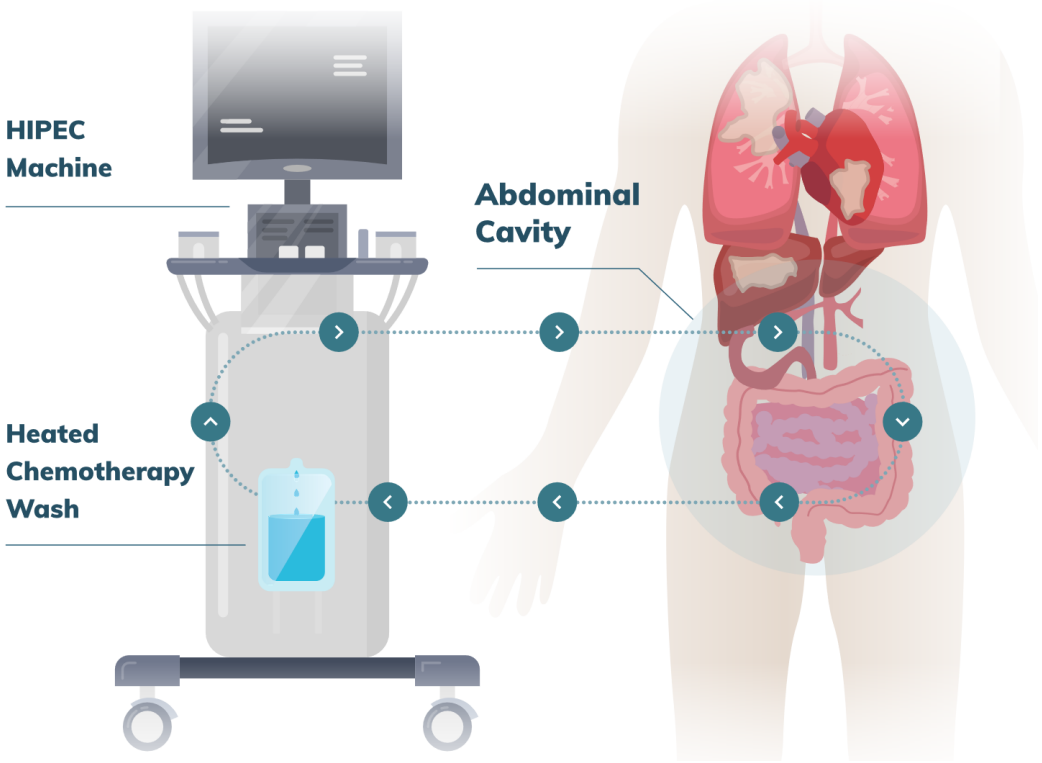
The following CLC & IB components will be addressed in this presentation:

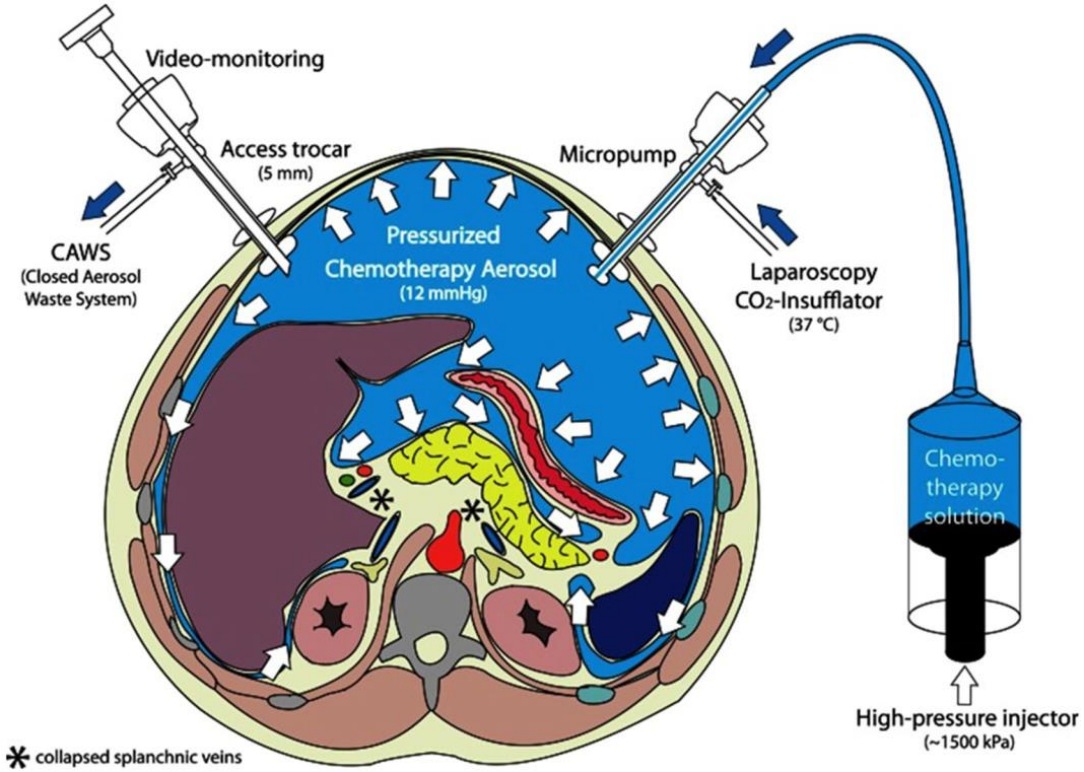
- Inclusion of patients in PIPAC trial should ensure racial and ethnic representation.
- Patients with peritoneal metastases are often considered end-stage with poor prognosis. There is an implicit bias that points to nihilism.

Definition of Regional Therapies

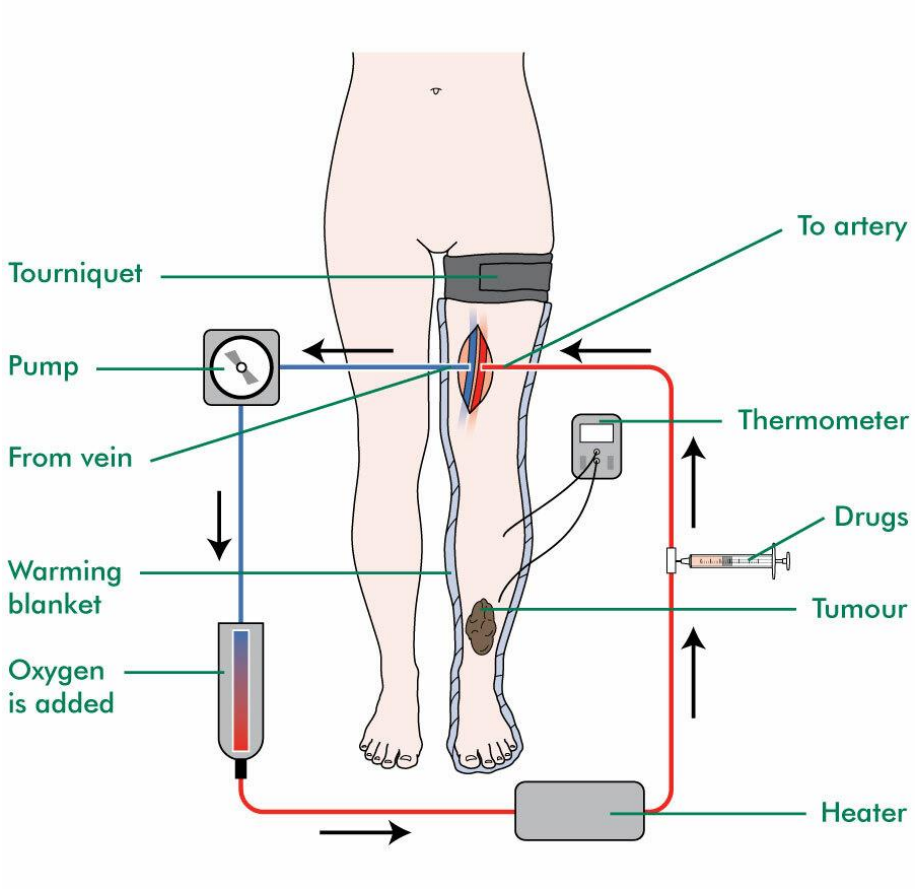
- Delivery of therapies directly to an anatomically defined region
- Purpose → Spare systemic toxicity
- Two broad categories:
    - Cavitary: Infusion/ Perfusion
    - Vascular: Infusion/ Perfusion

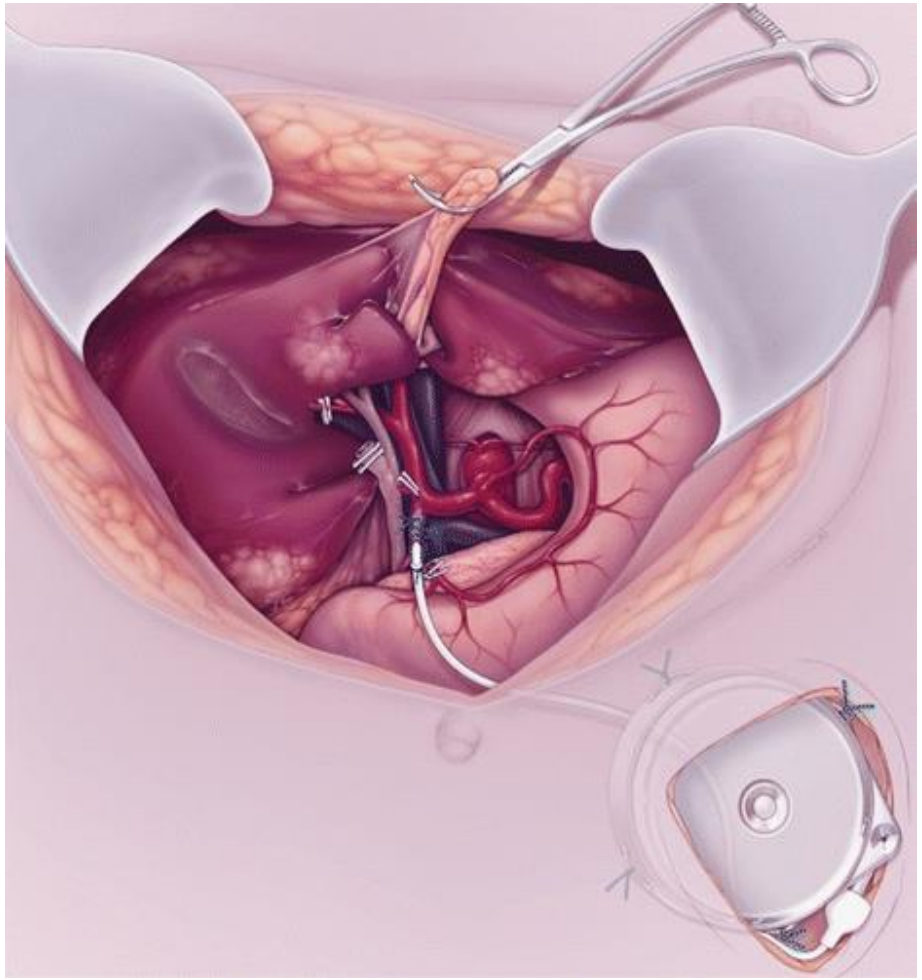
Cavitary


HIPEC
Machine
Abdominal
Cavity
Heated
Chemotherapy
Wash


Video-monitoring
Access trocar
(5 mm)
Micropump
CAWS
(Closed Aerosol
Waste System)
Pressurized
Chemotherapy Aerosol
(12 mmHg)
Laparoscopy
CO2-Insufflator
(37 °C)
Chemo-
therapy
solution
High-pressure injector
(~1500 kPa)
* collapsed splanchnic veins

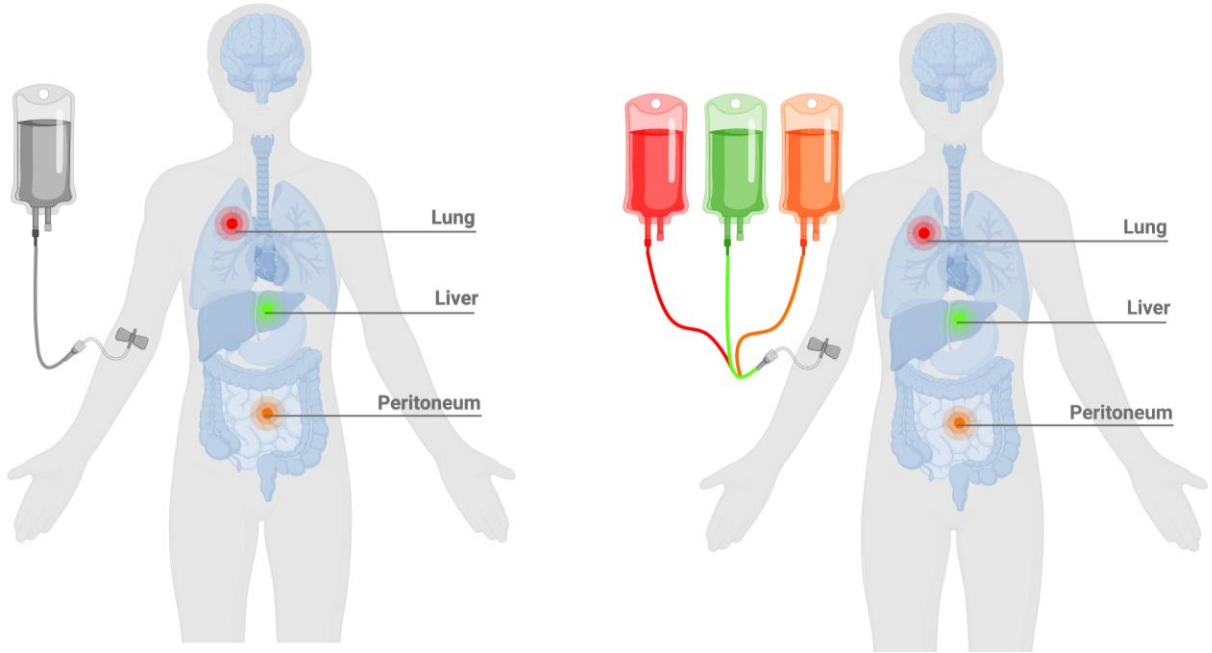
Vascular


Tourniquet
Pump
From vein
Warming blanket
Oxygen is added
To artery
Thermometer
Drugs
Tumour
Heater

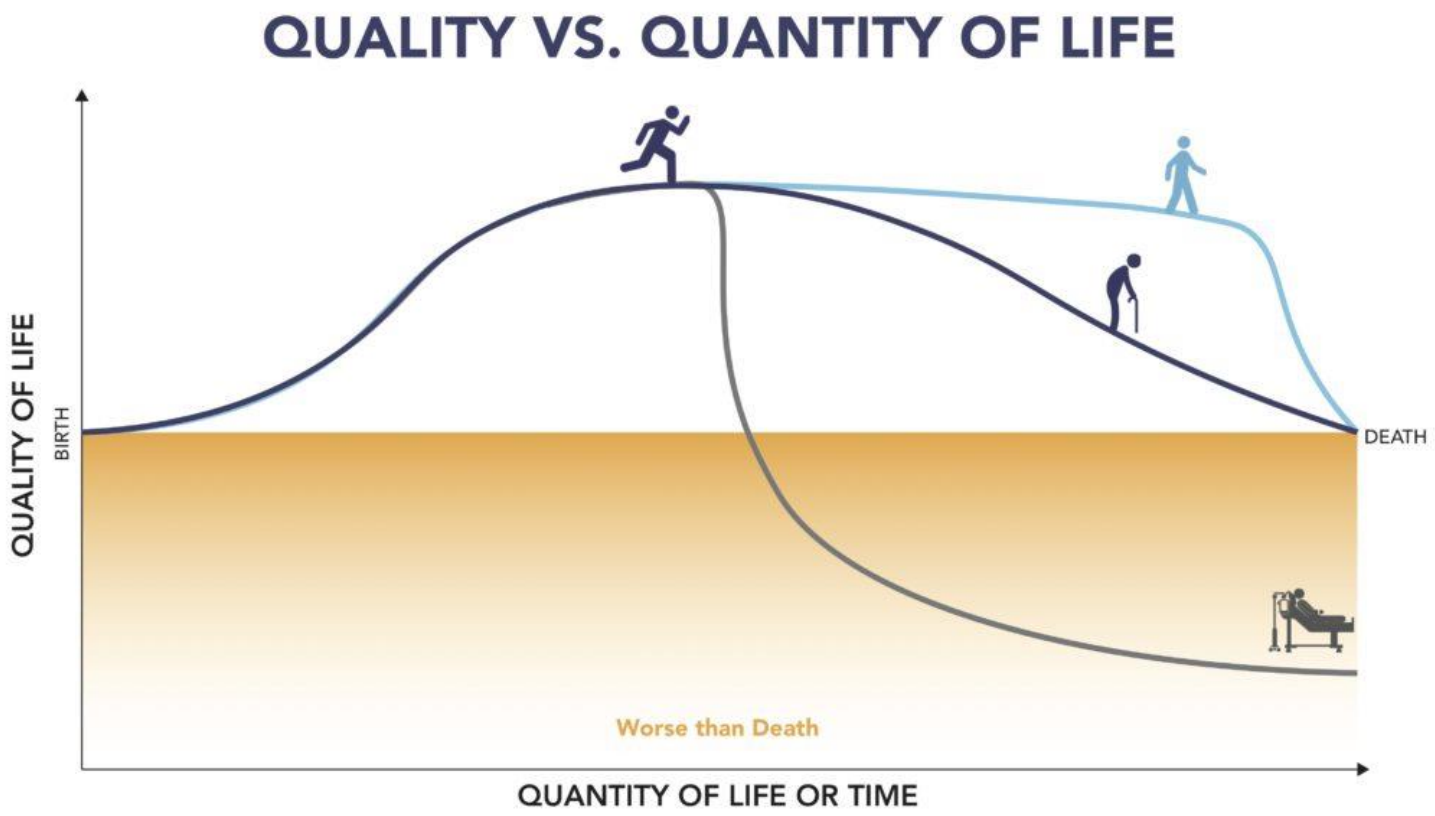


Regionally-directed

- Targeting a cancer vulnerability that manifests because of the anatomic location of the tumor (administered systemically or locally)



Goals of Treatment

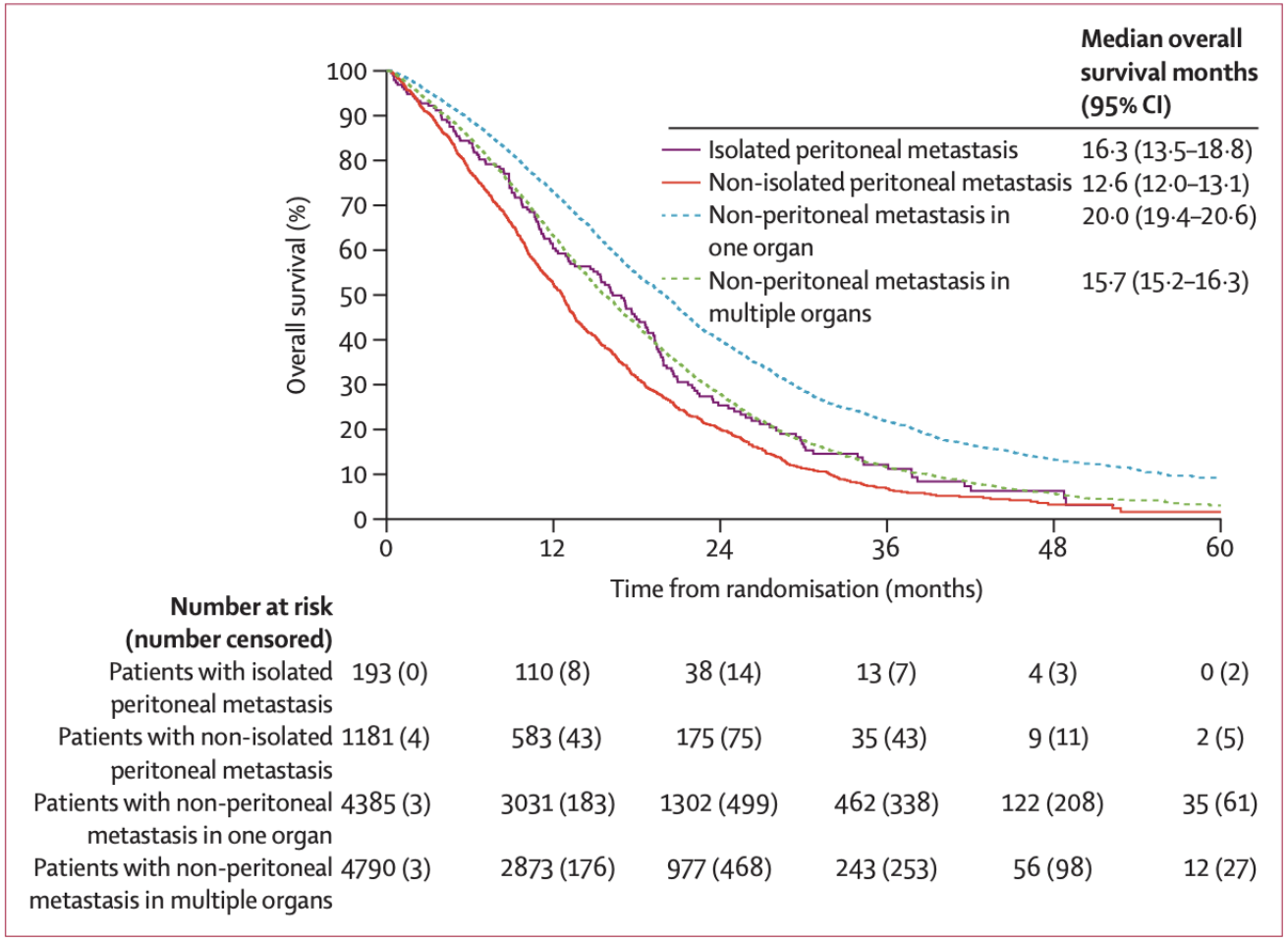


Rationale for Regional Therapies for Peritoneal Metastases

- Modern systemic therapy is less effective
- Peritoneal disease limits quality of life
- Pharmacokinetic advantage
- Biologically distinct

Modern systemic therapy is less effective

Colorectal Cancer



Number at risk (number censored)						
Patients with isolated peritoneal metastasis	193 (0)	110 (8)	38 (14)	13 (7)	4 (3)	0 (2)
Patients with non-isolated peritoneal metastasis	1181 (4)	583 (43)	175 (75)	35 (43)	9 (11)	2 (5)
Patients with non-peritoneal metastasis in one organ	4385 (3)	3031 (183)	1302 (499)	462 (338)	122 (208)	35 (61)
Patients with non-peritoneal metastasis in multiple organs	4790 (3)	2873 (176)	977 (468)	243 (253)	56 (98)	12 (27)

Franko et. al. Lancet Oncology 2016

Undertreatment does not explain poor-prognosis

CAIRO

	Arm A: Sequential chemotherapy arm			Arm B: Combination chemotherapy arm		
	No PC	PC	*p*- value (PC vs no PC)	No PC	PC	*p*- value (PC vs no pc)
Number of treatment cycles given in 1st line of treatment	median (range)	median (range)		median (range)	median (range)	
	6.0 (0–53)	6.0 (1–14)	0.158	7.0 (0–42)	6.5 (1–18)	0.918

CAIRO 2

Number of treatment cycles given and primary reasons for treatment discontinuation for patients in the CAIRO2 trial, by treatment arm and presence of PC.

	Arm A: CB			Arm B: CBC		
	No PC	PC	*p* value (PC vs no PC)	No PC	PC	*p* value (PC vs no PC)
Number of treatment cycles given	median (range)	median (range)		median (range)	median (range)	
	9.0 (9–48)	8.5 (3–24)	0.388	9.0 (1–52)	9.0 (0–34)	0.732

Klaver et. al. EJSO 2012

Poor response rates explain poor survival

	Complete response *n* (%)	Partial response *n* (%)
Liver (*n* = 361)	13 (3.8)	124 (36.2)
Lung (*n* = 134)	3 (2.4)	23 (18.4)
Locoregional (*n* = 133)	1 (0.9)	16 (14.4)
Nodal (*n* = 118)	4 (3.7)	16 (15.0)
Peritoneal (*n* = 91)	–	7 (10.4)

*Non-evaluable patients not included in the denominator for response by site

5-FU- based systemic therapy, RECIST Response

5-FU- based systemic therapy, RECIST Response
Assersohn et. al. BJC 1999

Poor response rates explain poor survival

- PM: CAIRO6 →Peri-op chemo* arm → Objective Response 28%
- LM: EORTC → Peri-op chemo* arm → Objective Response 43%

DRUG DELIVERY vs. THERAPEUTIC RESISTANCE

*Modern systemic therapy
Rovers et. al. JAMA Surg 2021
Nordlinger et. al. Lancet 2008

Under-representation in RCTs limits generalizability of systemic therapy efficacy to peritoneal metastases

Autopsy studies: 20-51%

	Number of patients in treatment groups	Number of patients with peritoneal disease (%)
Ducreux, *Lancet Oncology* 2011[3]	410	63 (15·4%)
Hong, *Lancet Oncology* 2012[4]	340	73 (21·5%)
Jonker, *NEJM* 2007[5]	572	45 (7·9%)
Seymour, *Lancet* 2007[6]	2135	288 (13·5%)
Seymour, *Lancet Oncology* 2013[7]	460	99 (21·5%)
Tournigand, *Lancet Oncology* 2015[8]	700	83 (11·9%)
Yoshino, *Lancet Oncology* 2012[9]	169	28 (16·6%)

Table: **Clinical trials that included patients with peritoneal metastases from published clinical trials for metastatic colorectal cancer (72 clinical trials, 45 783 patients)**

Two main reasons for exclusion:

- Performance status
- RECIST non-measurable disease

Tseng, J,.. Turaga et. al. Lancet Oncology 2017

Peritoneal disease limits quality of life

Colorectal Cancer

	Patients with isolated peritoneal metastasis (n=194)	Patients with non-isolated peritoneal metastasis (n=1181)	Patients with non-peritoneal metastasis in one organ (n=4385)	Patients with two or more sites of non-peritoneal metastasis (n=4793)	Total (N=10 553)	p value
ECOG performance status						<0·0001†
0	93 (48%)	489 (41%)	2396 (55%)	2357 (49%)	5335 (51%)	
1	79 (41%)	577 (49%)	1762 (40%)	2130 (45%)	4548 (43%)	
2	22 (11%)	114 (10%)	222 (5%)	299 (6%)	657 (6%)	
Missing data	0	1	5	7	13	

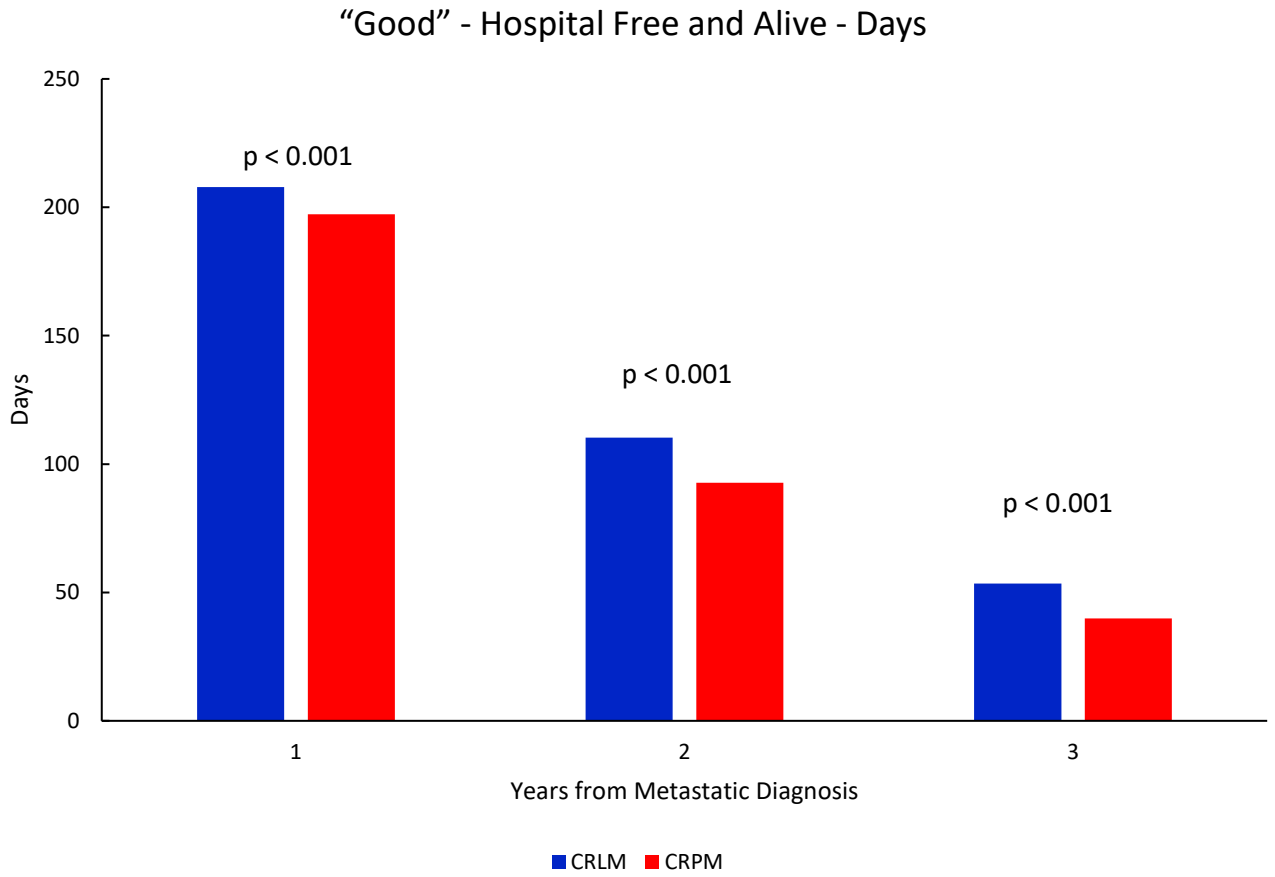
Franko et. al. Lancet Oncology 2016

Population-based data – California Cancer Registry

Variable	CRLM, n (%)	CRPM, n (%)	*P*
Patients	11,510	4724	
Number Hospitalization/Year of Life	3.2	4.2	0.002
Number of Hospitalized Days/Year of Life	44.4	66.2	0.002
Median OS (mo)	9.9	7.5	<0.001
Median Disease Specific OS (mo)	10.3	8.3	<0.001
Need for Supplemental Nutrition			
Parenteral Nutrition	1,206 (10.5)	957 (20.3)	<0.001
Gastrostomy Tube	253 (2.2)	314 (6.7)	<0.001

O'leary and Raoof. Unpublished

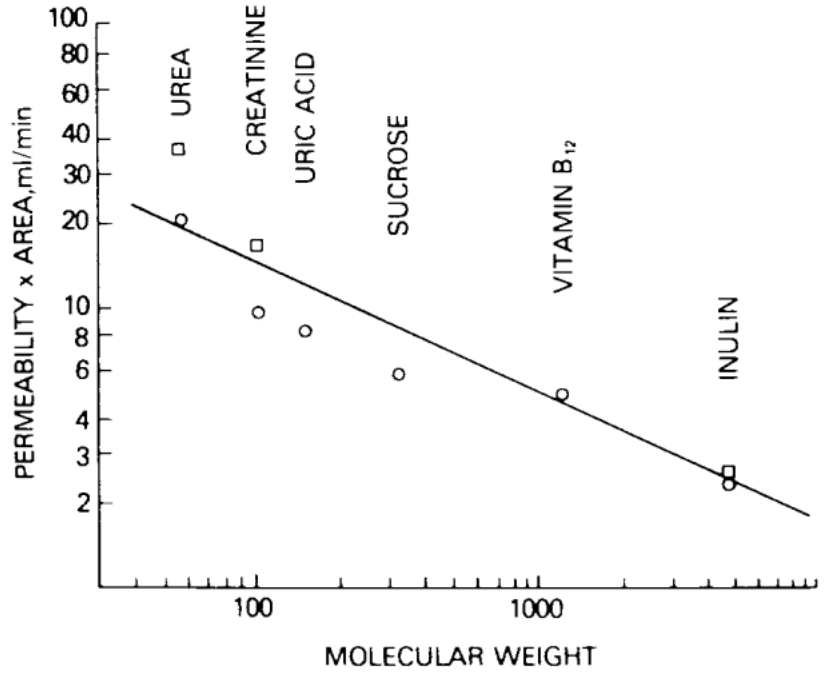
Population-based data – California Cancer Registry



O'leary and Raoof. Unpublished

Pharmacokinetic advantage

1. Peritoneal clearance << Plasma clearance
2. Hydrophilic drugs with a high molecular weight and ionized compounds have favorable pharmacokinetics
3. Locoregional therapeutic effect with limited systemic toxic effects



Dedrick et. al. Cancer Treatment Reports 1978

Pharmacokinetic advantage

Peritoneal clearance << Plasma clearance

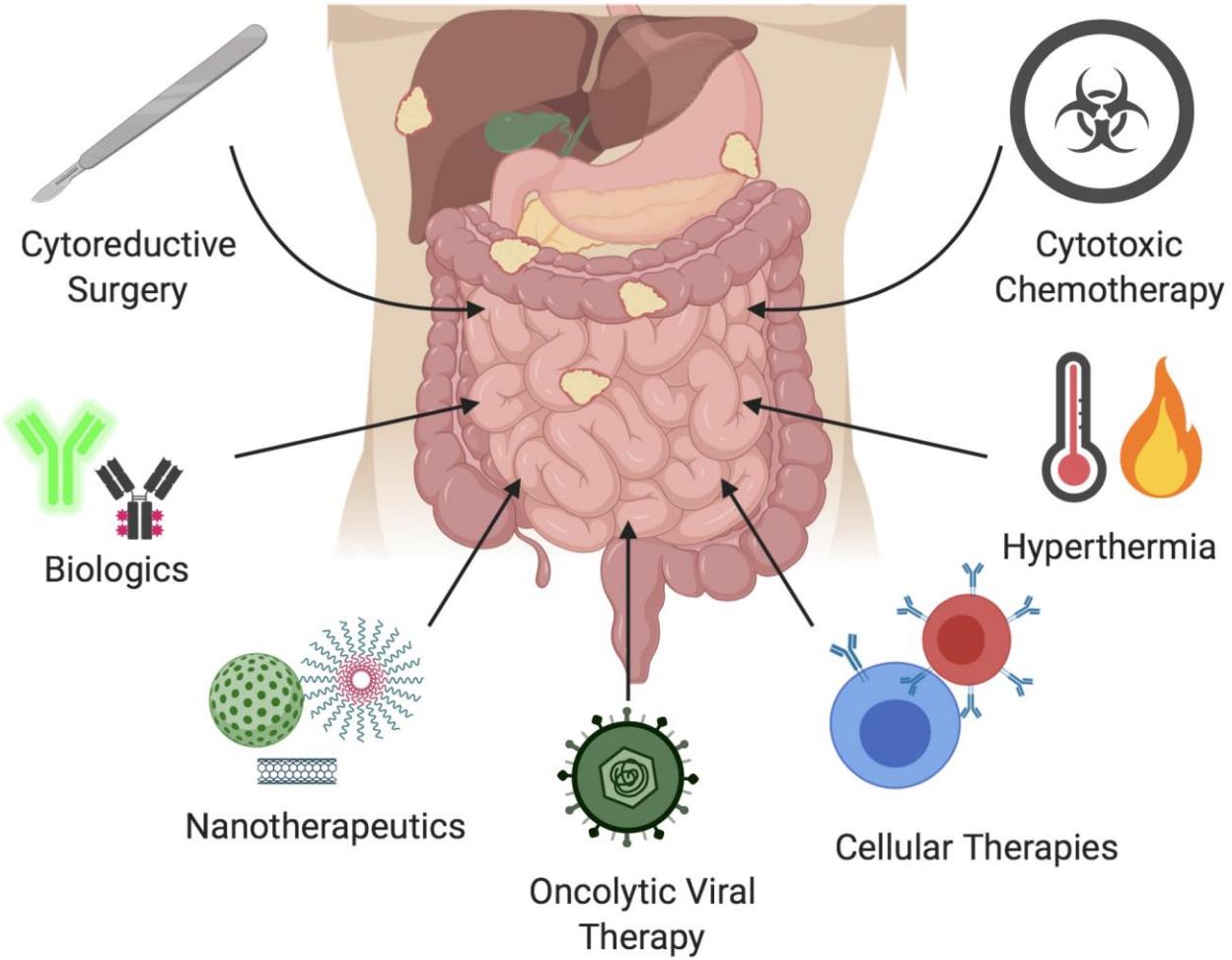
Table. Cytotoxic Drugs Commonly Used for Intraperitoneal Administration

Drug	Heat synergy	Penetration depth, mm	Cell cycle-specific	Molecular weight	AUC IP:IV ratio
Carboplatin	Yes	0.5	No	371	2-10
Cisplatin	Yes	1.0-3.0	No	300	8-21
Mitomycin C	Yes	2.0	No	334	10-23.5
Oxaliplatin	Yes	1.0-2.0	No	397	3.5-16
Paclitaxel	Minimal	0.5	Yes	854	1000
Fluorouracil	Minimal	0.2	Yes	130	250

Abbreviations: AUC, area under the curve; IP:IV, ratio of intraperitoneal concentration to plasma concentration.

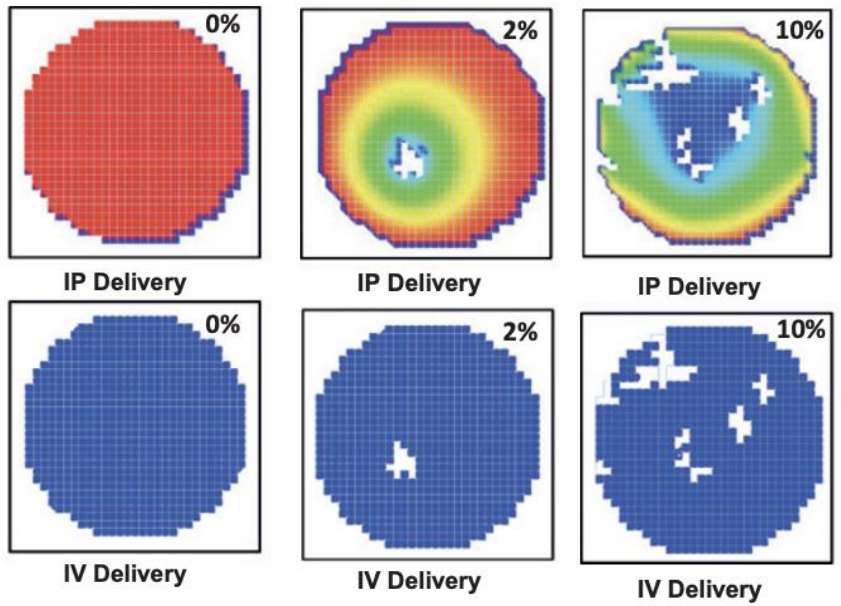
Penetration depth into the tumor is 1-2 mm and remains a significant challenge

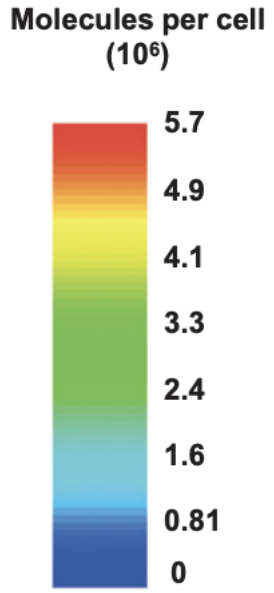
Pharmacokinetic advantage?



Pharmacokinetic advantage?

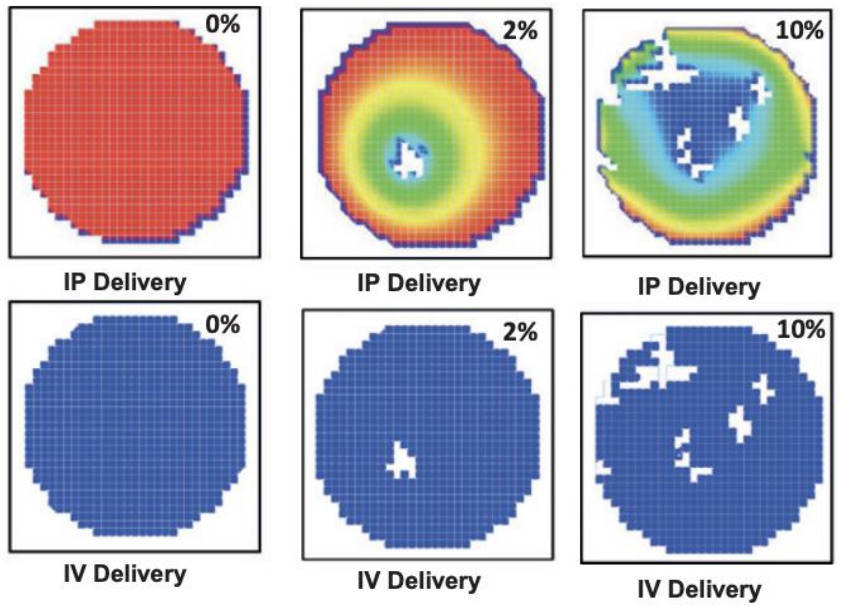
Cisplatin Accumulation

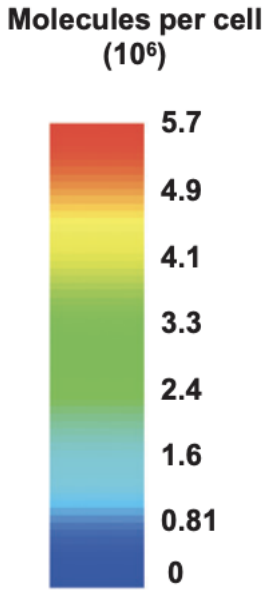




Pharmacokinetic advantage?

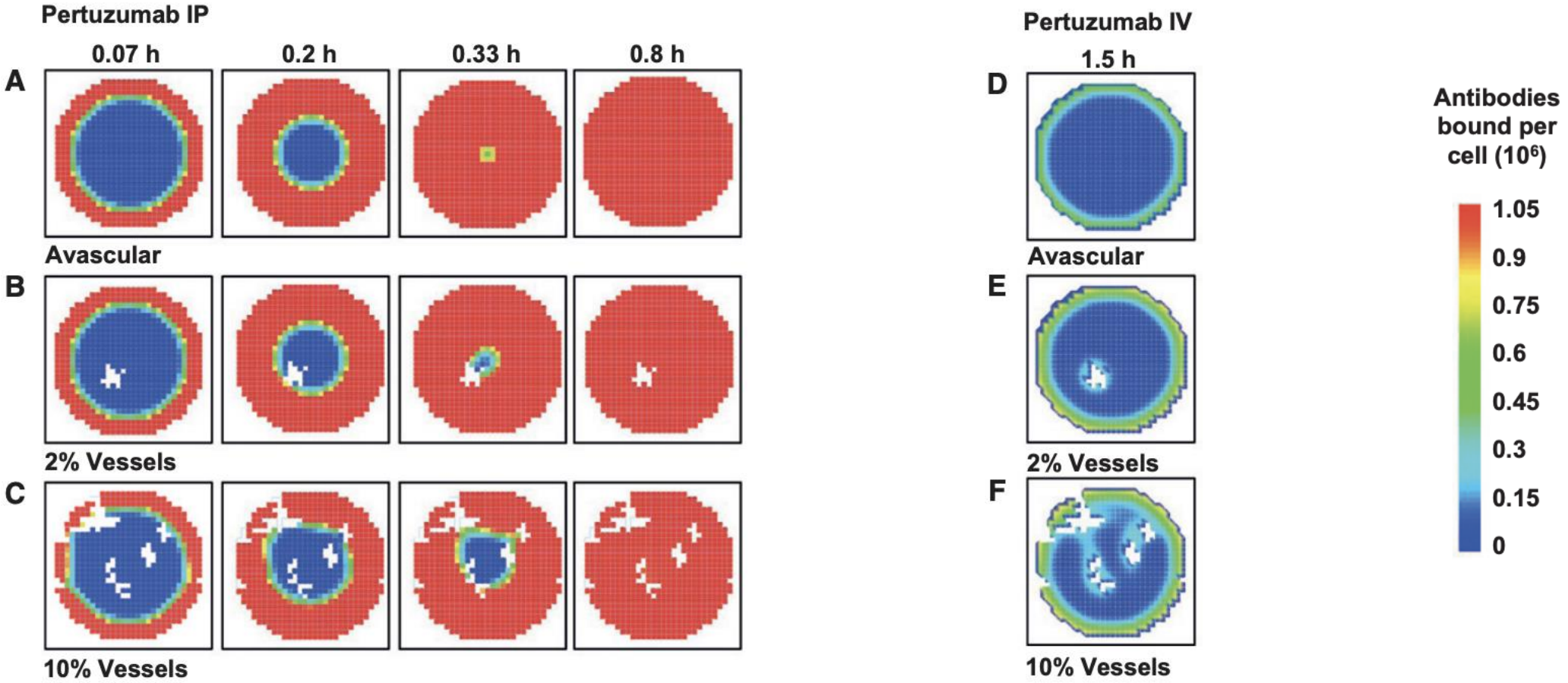
Cisplatin Accumulation





Winner et. al. Cancer Research 2016

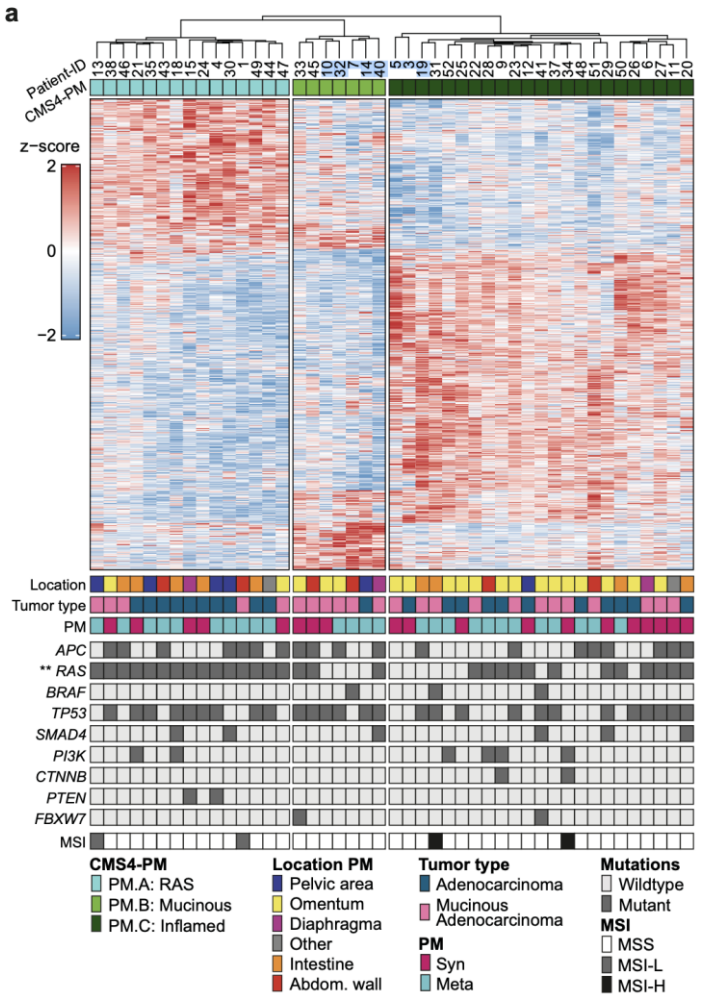
Pharmacokinetic advantage?

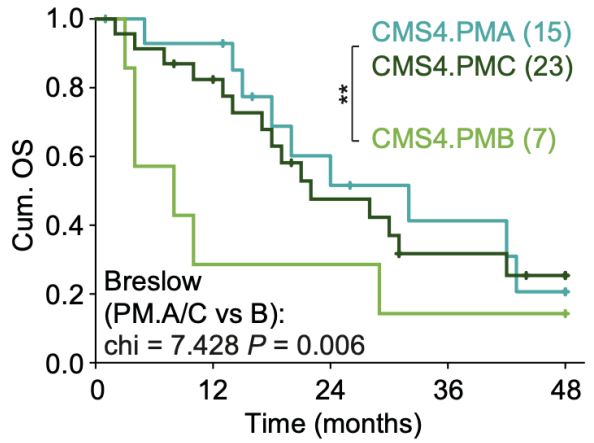


Winner et. al. Cancer Research 2016

Peritoneal Metastases are Biologically Distinct

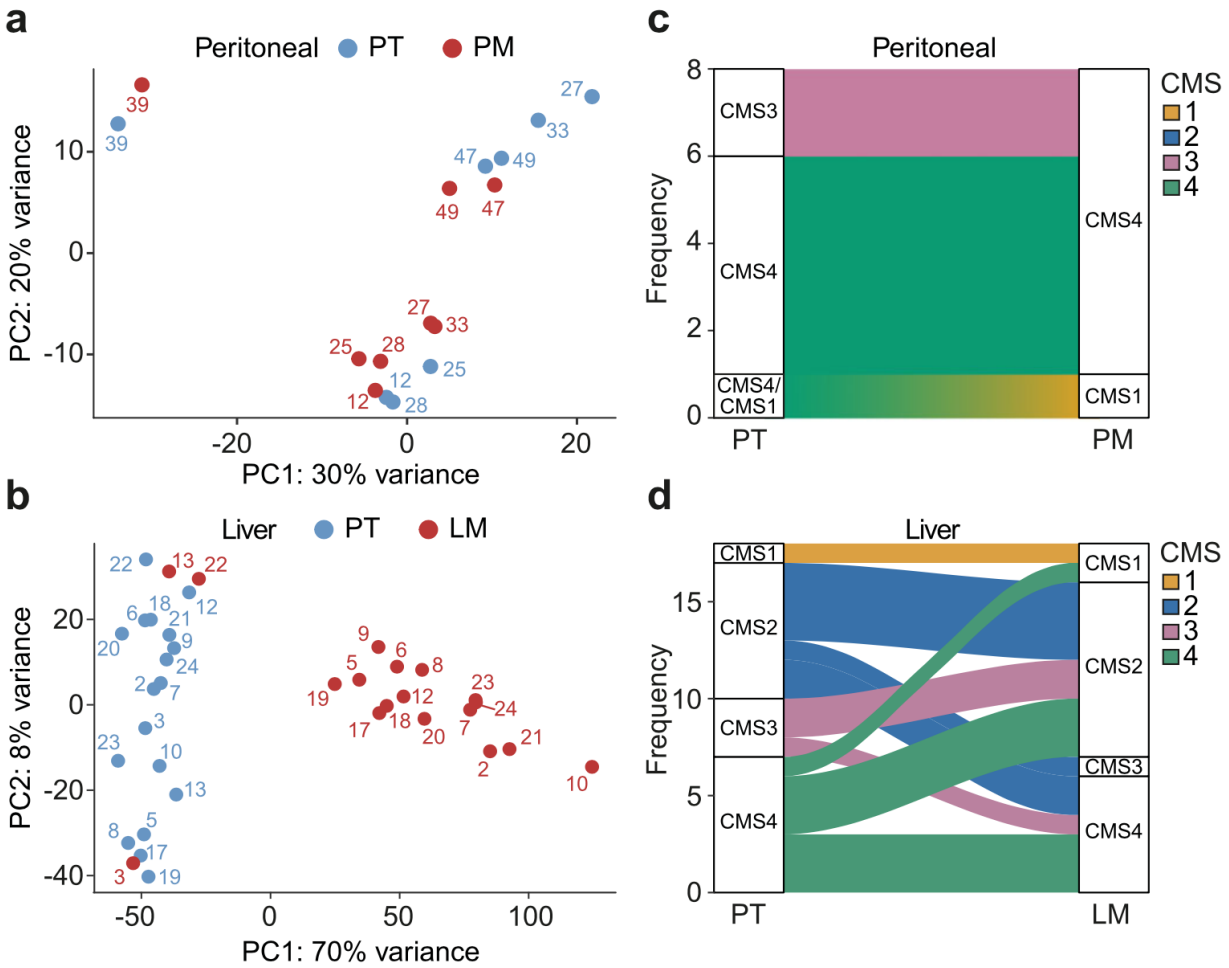
- 85% CMS4
- CMS4 subtypes:
  - RAS mutations (CMS4-PM.A)
  - Mucinous phenotype (CMS4-PM.B)
  - Inflamed (CMS4-PM.C)





Lenos et. al. Nat. Comm 2022

Peritoneal Metastases are Biologically Distinct

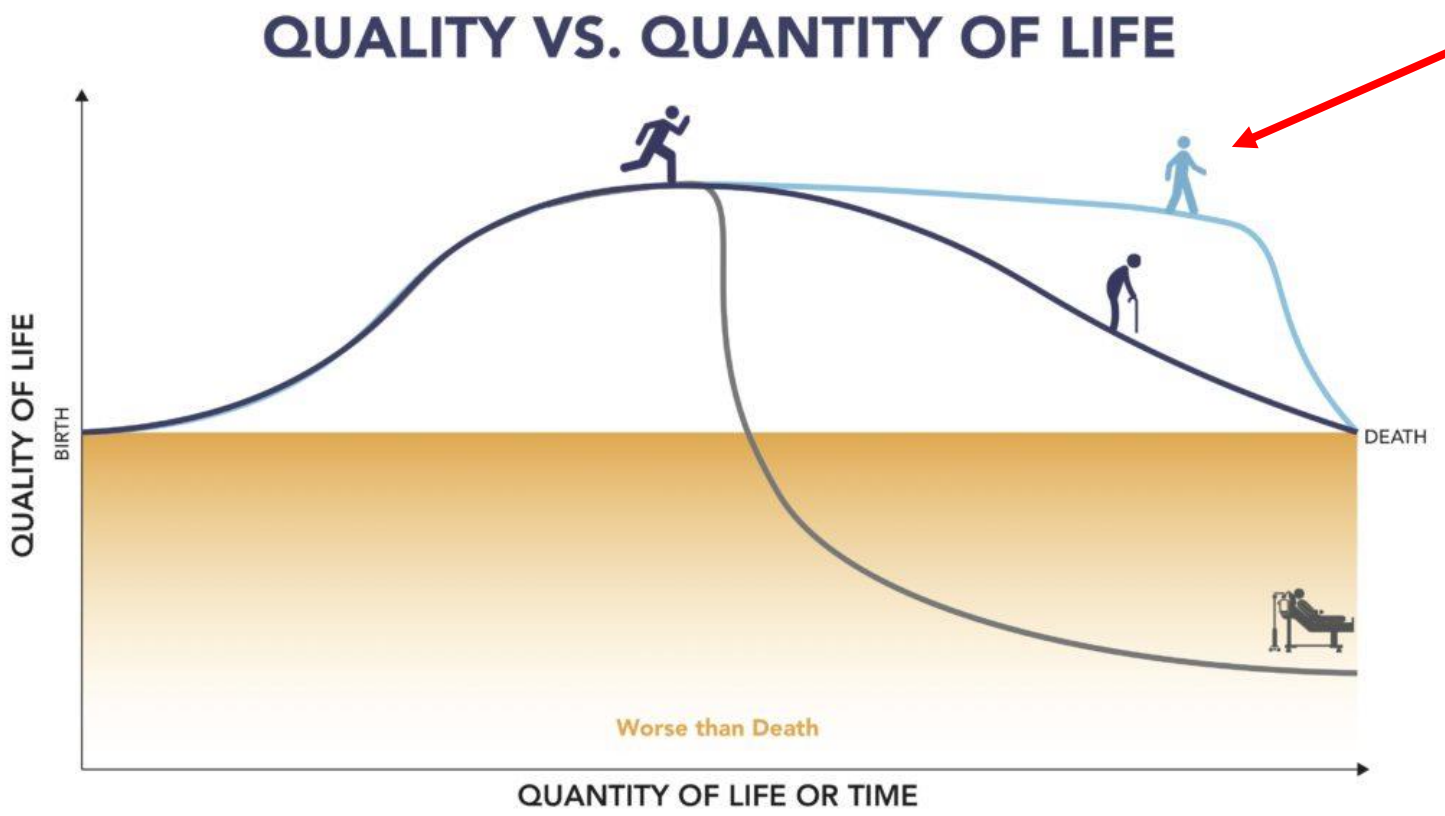


Lenos et. al. Nat. Comm 2022

Rationale for Regional Therapies for Peritoneal Metastases

- Regional drug delivery may overcome barriers to systemic drug delivery
- Regional drug delivery treats tumors most likely to impact quality of life
- Regional therapies minimize systemic toxicity
- Regional approaches could cater to distinct biology of peritoneal metastases

Thank you



Regional Therapies