Where Science Becomes Hope

UPDATE ON LOCO-REGIONAL TREATMENTS OF METASTATIC GASTROINTESTINAL CANCERS

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FINANCIAL DISCLOSURE
NONE

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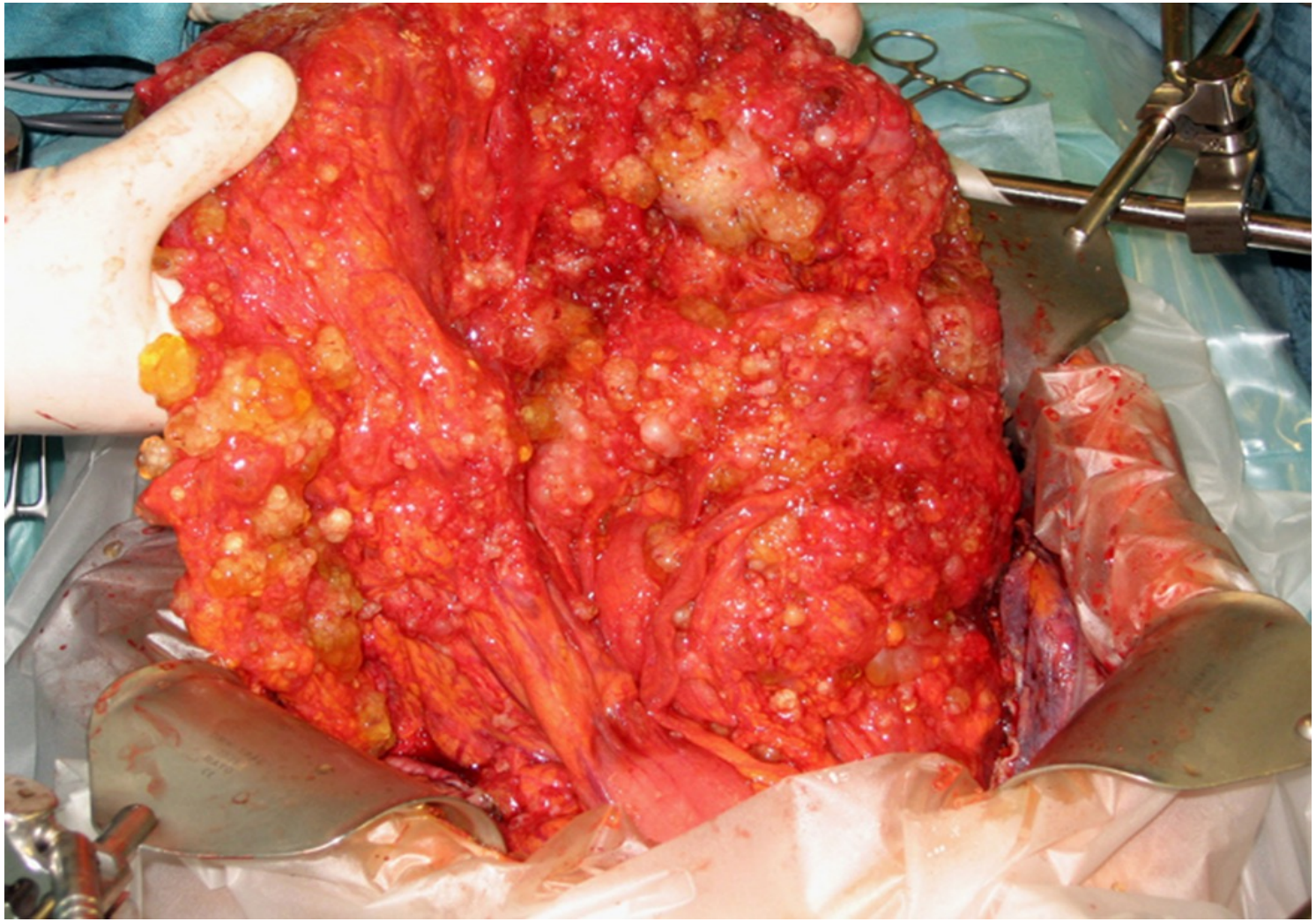
UPDATE AGENDA

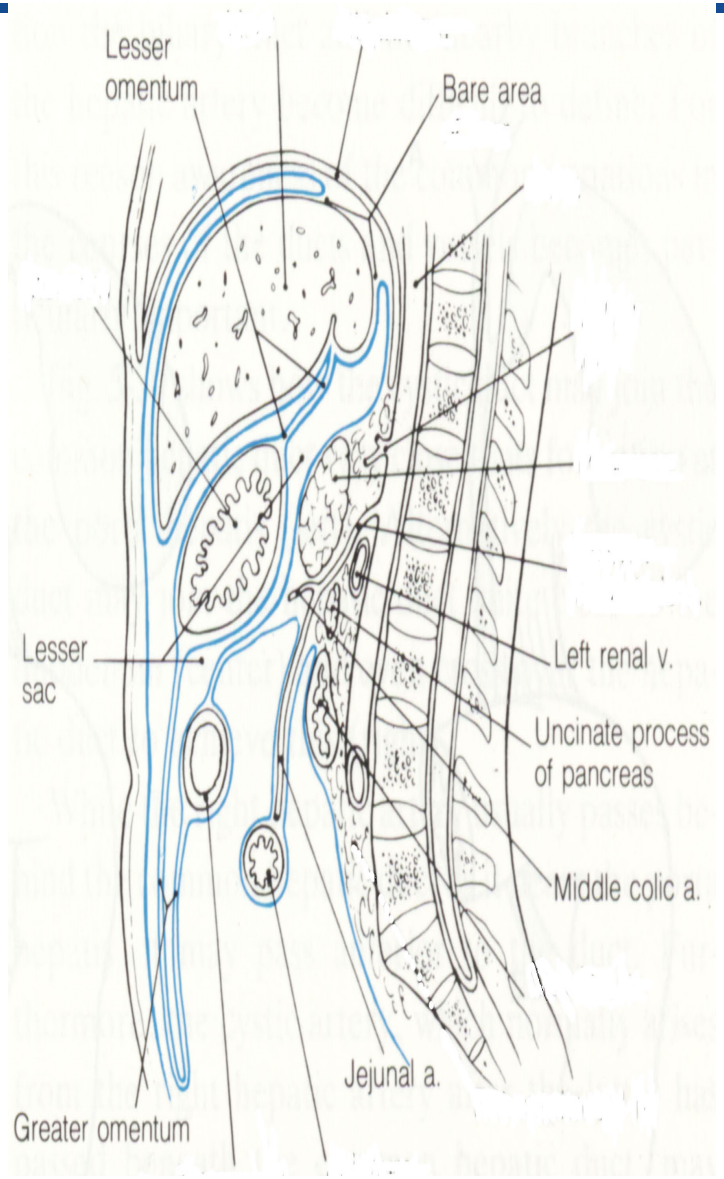
- Cytoreductive Surgery and HIPEC for Colorectal Cancer
- Normothermic Iterative Intraperitoneal Chemotherapy for Gastric Cancer
- Hepatic Artery Infusional Pump Chemotherapy for unresectable Colorectal Cancer Metastases

PERITONEAL CARCINOMATOSIS



RATIONALE FOR CYTOREDUCTION SURGERY

- **Consider the Peritoneum as Resectable, locoregional site of disease, not distant metastasis.**
- **Goal is to resect all macroscopic disease.**



Sugarbaker PH, et al. *Ann Surg.* 1995;221(2):124-132.

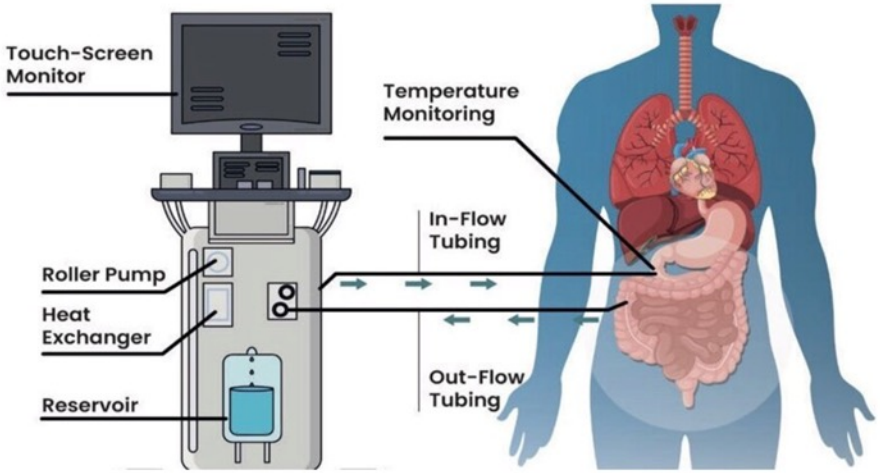
RATIONALE FOR HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

1-4mm of direct tumor absorption

Plasma-peritoneal barrier **high** intraperitoneal concentrations- **low** systemic concentrations

Tumor tissue more sensitive to heat than normal tissue

Hyperthermia synergistically enhances the chemosensitivity of tumor cells to Mitomycin C



CRS/HIPEC FOR CRC[1]

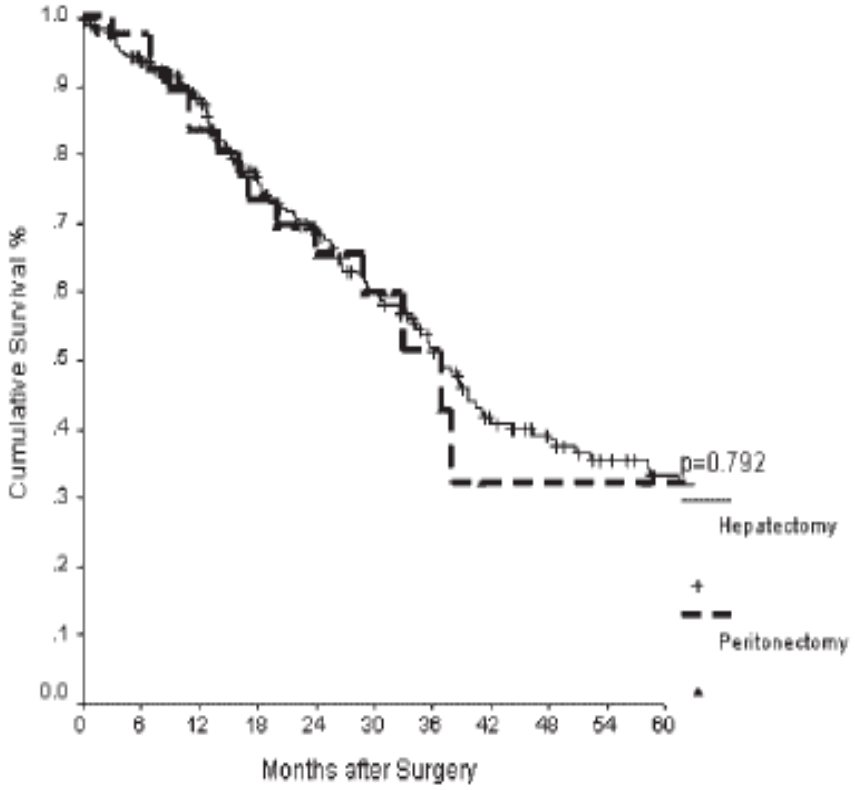


Fig. 1. Overall survival of patients with liver metastasis who underwent hepatectomy versus patients with peritoneal carcinomatosis who underwent peritonectomy.

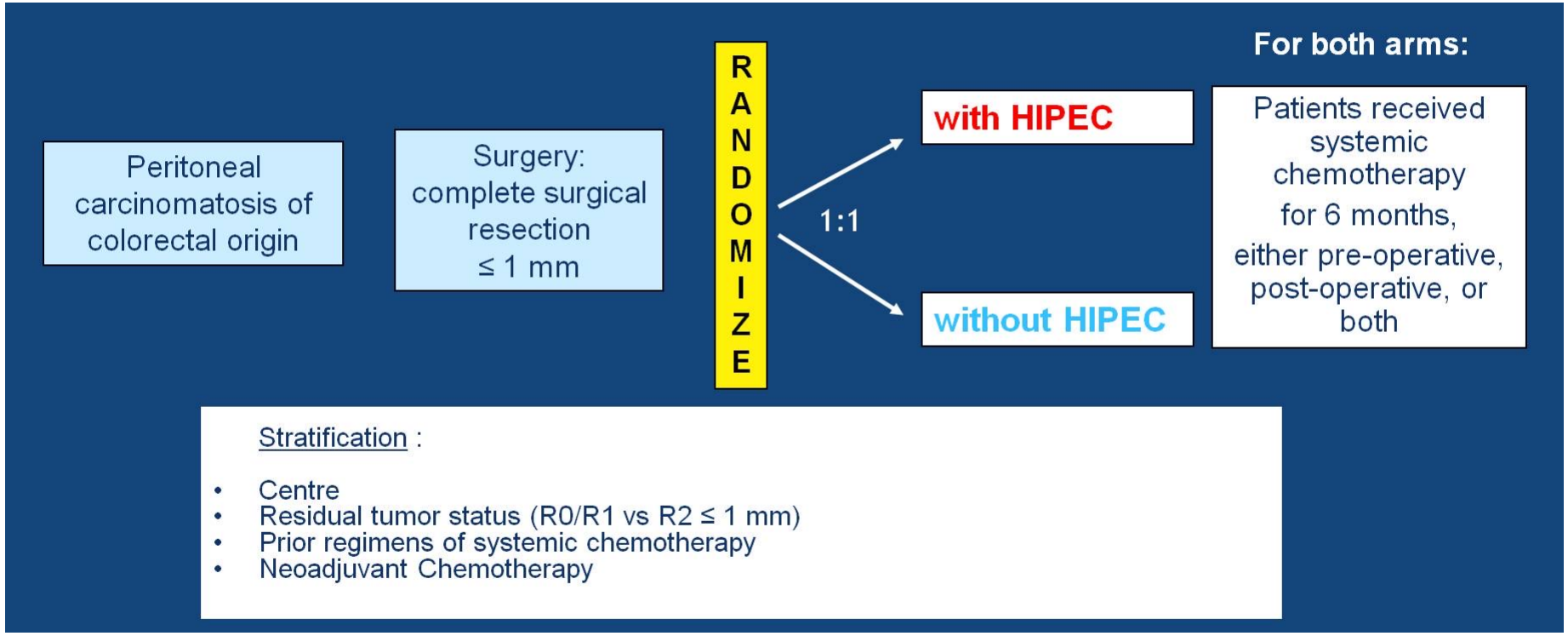
Table 1

Survival outcome of patients with CRC-PM undergoing CRS + HIPEC

Author	Year	N	Overall survival (mo)	Five-year survival (%)
Glehen (10)	2004	377	32	40
da Silva (11)	2006	70	33	32
Shen (12)	2008	121	34	26
Chua (13)	2009	54	33	NR
Franko (14)	2010	67	34	26
Elias (15)	2010	523	32	30
Elias (16)	2011	146	41	42
Ung (17)	2013	211	47	42
Chua (9)	2013	722	33	43
Esquivel (4)	2014	705	41	NR

1. Esquivel J. *J Gastrointest Oncol.* 2016;7:72-78.

PRODIGE 7 TRIAL DESIGN- PHASE 3 RCT

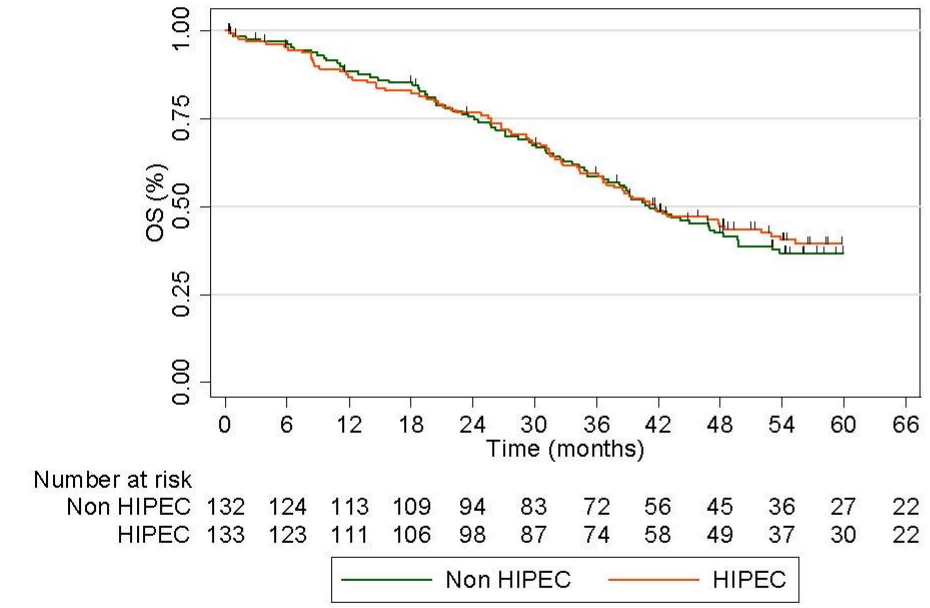


HIPEC- Oxaliplatin

1. Quenet F, et al. *J Clin Oncol.* 2018;36:LBA3503.

OVERALL SURVIVAL (ITT)

Median follow-up: 64 months (95% CI 58.9-69.8)

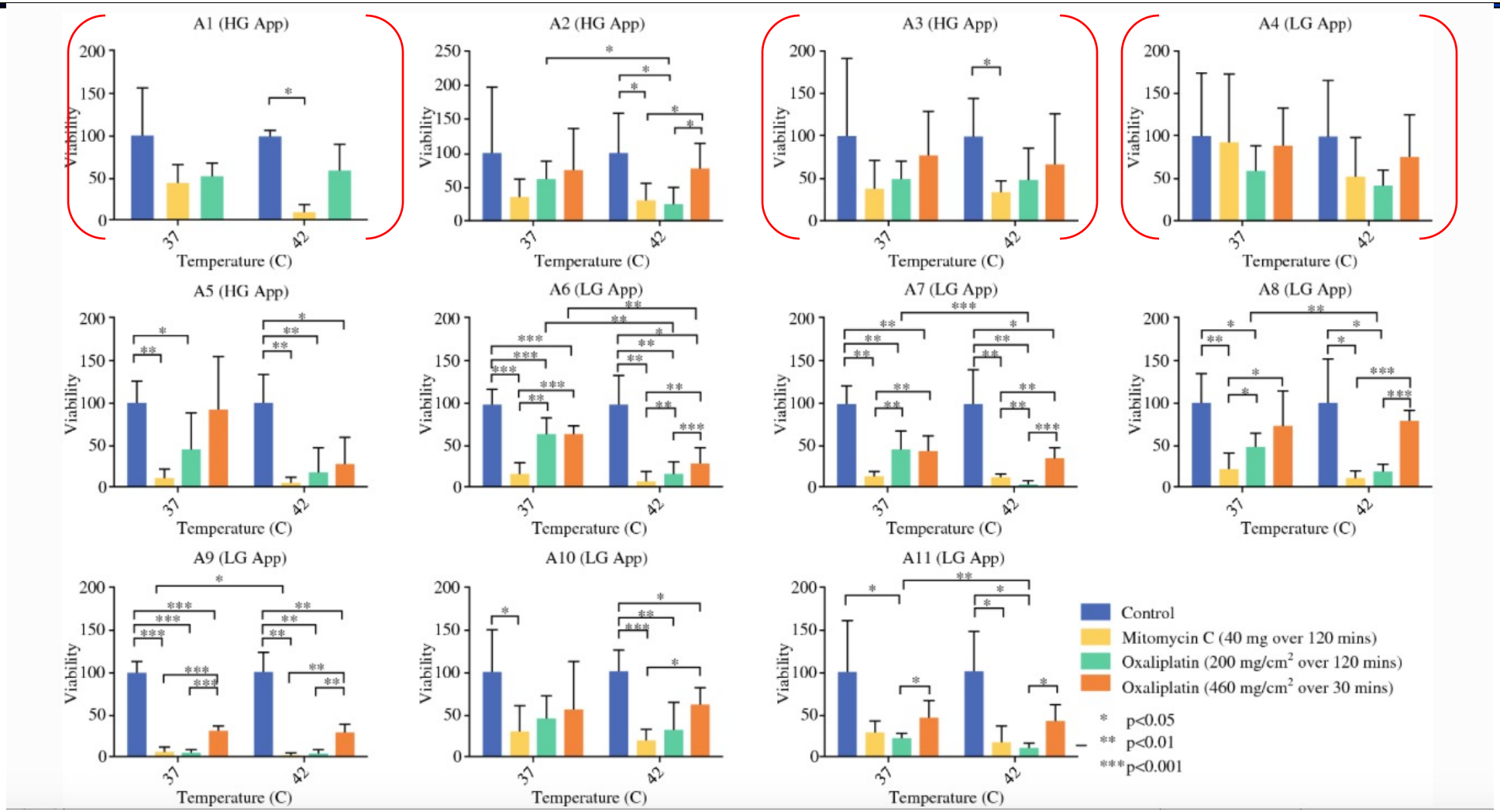


	HIPEC	Non-HIPEC	P value
Median Survival, months [95% CI]	41.7 [36.2-52.8]	41.2 [35.1-49.7]	0.995
1-year Survival	86.9%	88.3%	
5-year Survival	39.4%	36.7%	

HR = 1.00, 95% CI [0.73-1.37], *P* = 0.995

1. Quenet F, et al. *J Clin Oncol.* 2018;36:LBA3503.

INDIVIDUAL RESPONSES TO HIPEC



Ann Surg Oncol. 2020 July 6. doi:10.1245/s10434

WFORCE (Wake Forest Organoid Research Center)

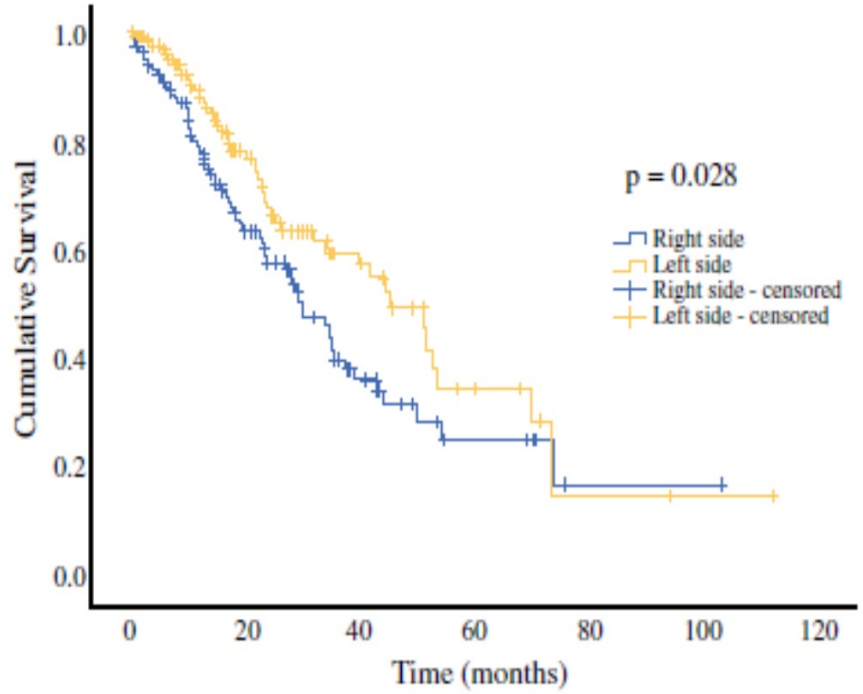
WAKE FOREST UNIVERSITY
SCHOOL of MEDICINE

PRODIGE 7 CONCLUSIONS

The addition of oxaliplatin-HIPEC compared to cytoreductive surgery alone does not influence OS and RFS

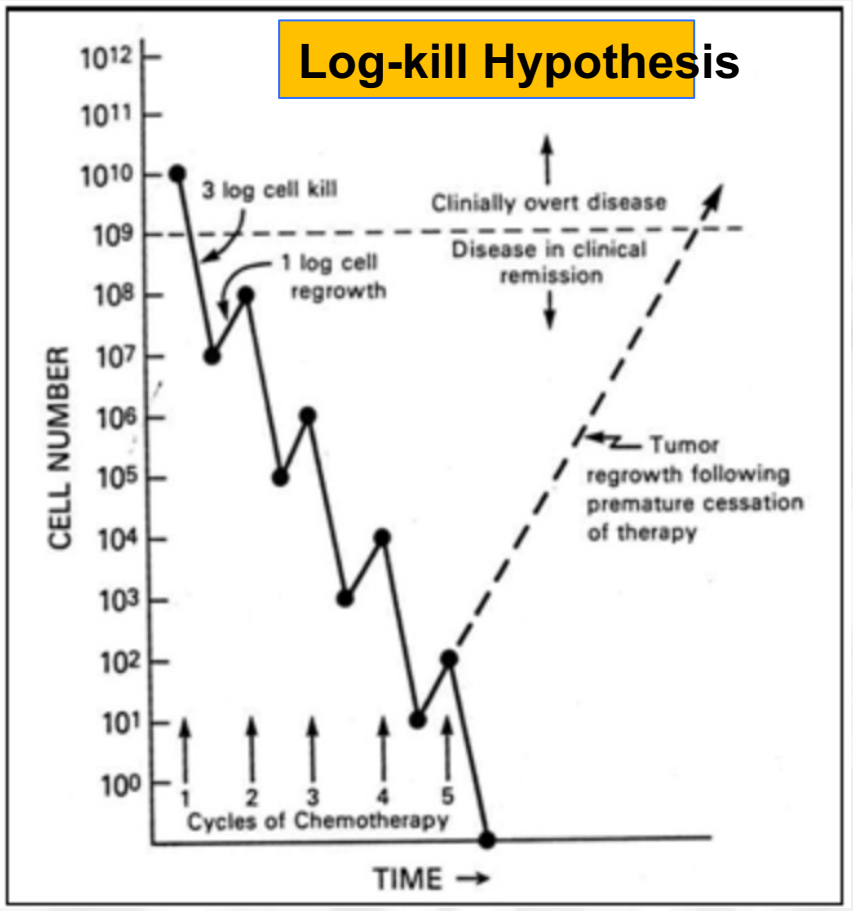
The curative management of PC from colorectal cancer by cytoreductive surgery alone shows unexpected excellent survival results

<u>Limitations</u>: heterogeneous group, prognostic factors- Ras, BRAF, sidedness, chemo resistance using same drug, HIPEC factors- 30 vs 90 min perfusion, poor chemotherapy choice, short hyperthermia



1. Quenet F, et al. *J Clin Oncol.* 2018;36:LBA3503.

ITERATIVE INTRAPERITONEAL TREATMENT



Heat augments cytotoxicity

Heat is not required to achieve desirable cytotoxic effects

- Right Drug
- Right Dose
- Right Frequency
- Synergistic effects with systemic therapy

Skipper et al., Cancer Chemother Rep 1964; 54: 431–450

PHOENIX GC TRIAL

VOLUME 36 · NUMBER 19 · JULY 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Trial Comparing Intraperitoneal and Intravenous Paclitaxel Plus S-1 Versus Cisplatin Plus S-1 in Patients With Gastric Cancer With Peritoneal Metastasis: PHOENIX-GC Trial

Hironori Ishigami, Yoshiyuki Fujiwara, Ryoji Fukushima, Atsushi Nashimoto, Hiroshi Yabusaki, Motohiro Imano, Haruhiko Imamoto, Yasuhiro Kodera, Yoshikazu Uenosono, Kenji Amagai, Shigenori Kadowaki, Hiroto Miwa, Hironori Yamaguchi, Takuhiro Yamaguchi, Tempei Miyaji, and Joji Kitayama

PHOENIX GC TRIAL- STRATIFICATION ISSUES

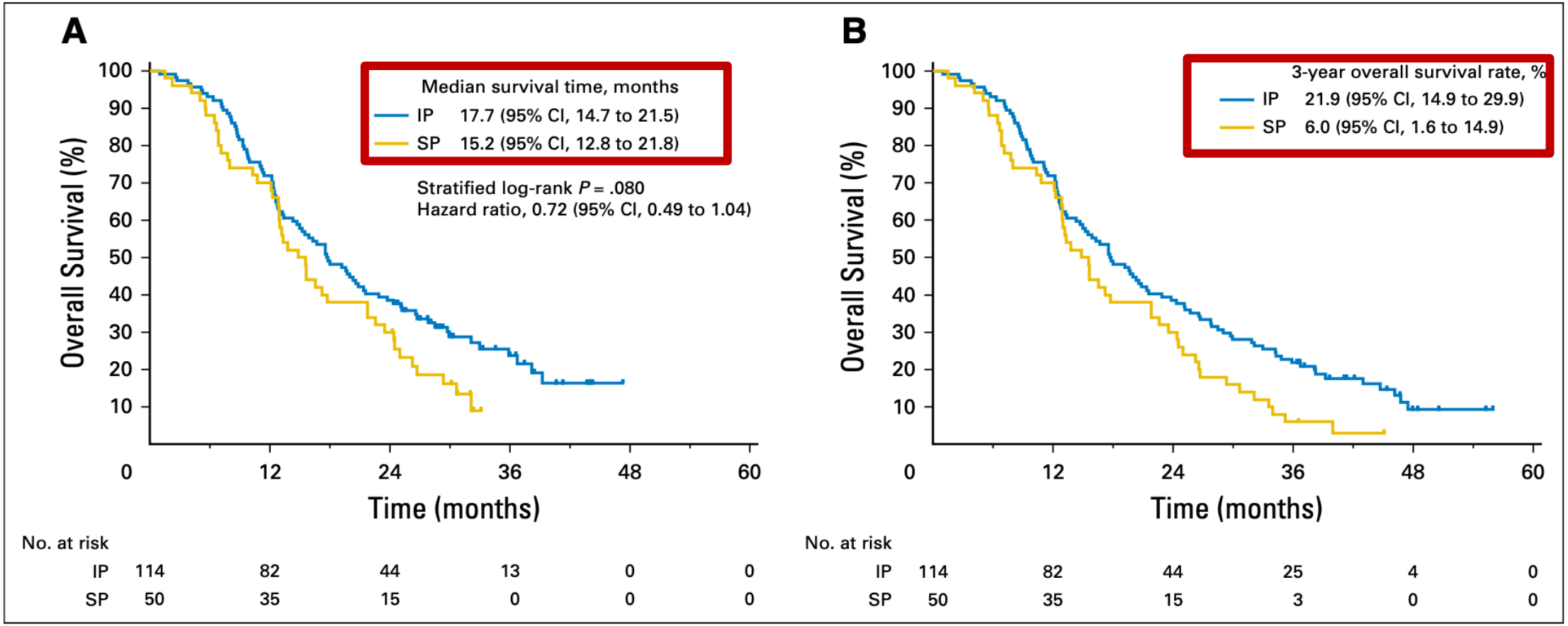


Fig 2. Kaplan-Meier curves of overall survival. (A) Primary analysis of the full analysis set. (B) Additional 1-year follow-up analysis of the full analysis set. IP, intraperitoneal and intravenous paclitaxel plus S-1; SP, S-1 plus cisplatin.

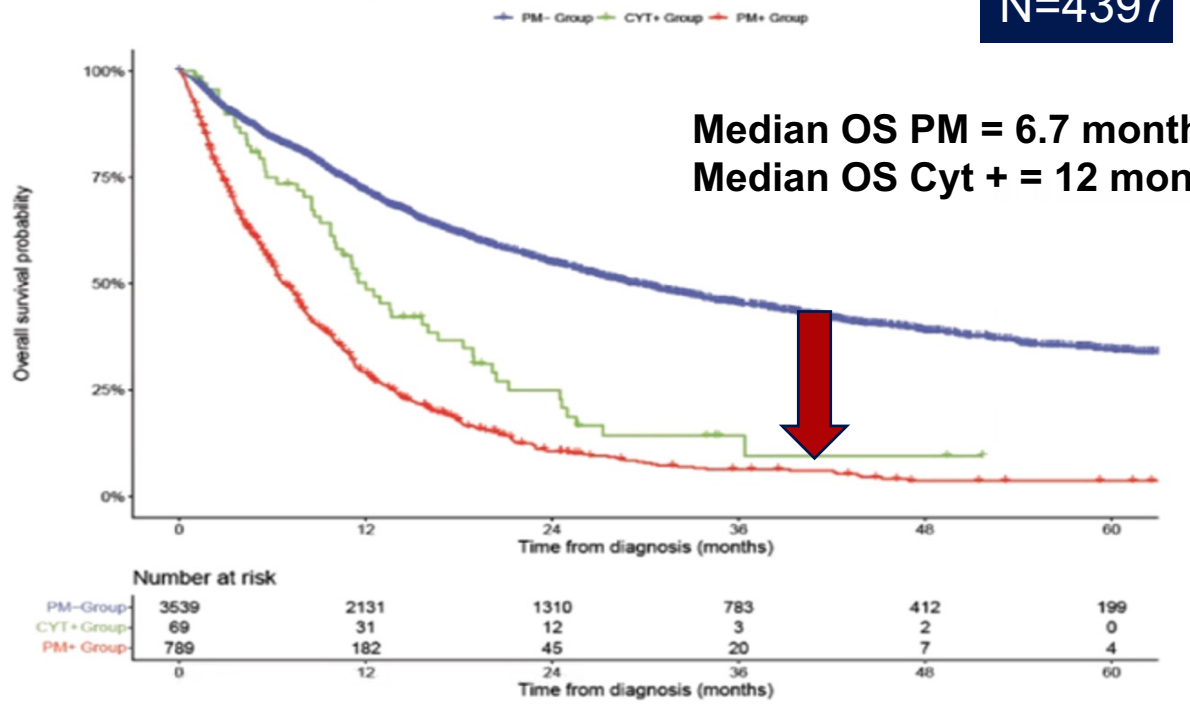
Ishigami…..Kitayama et al, J Clin Oncol 2018;36:1922-1929

Tumor-positive Peritoneal Cytology in patients with Gastric Cancer is associated with poor outcome: a Nationwide study.

Gastric cancer patients (2016-2021)
Registered in Netherlands Cancer Registry
Paired to Nationwide Pathology Database

- Patients without metastases (PM-)
- Patients with solitary tumor-positive cytology (CYT+)
- Patients with macro-scopic peritoneal metastases (PM+)

A. Overall survival of all patients according to the extent of peritoneal disease (n=4397)

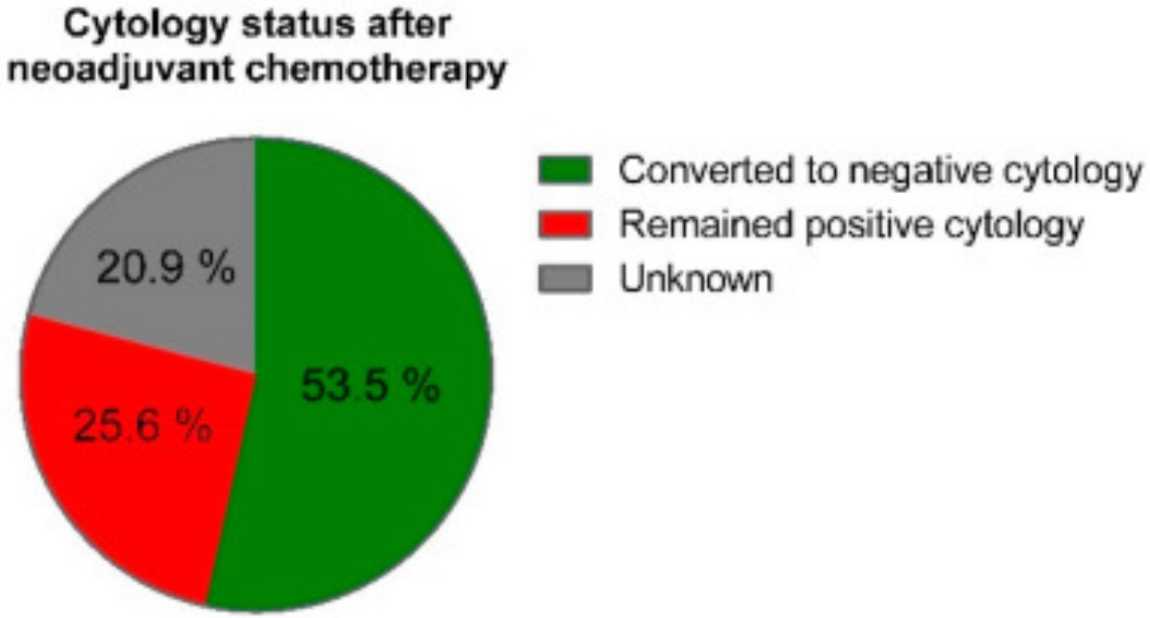


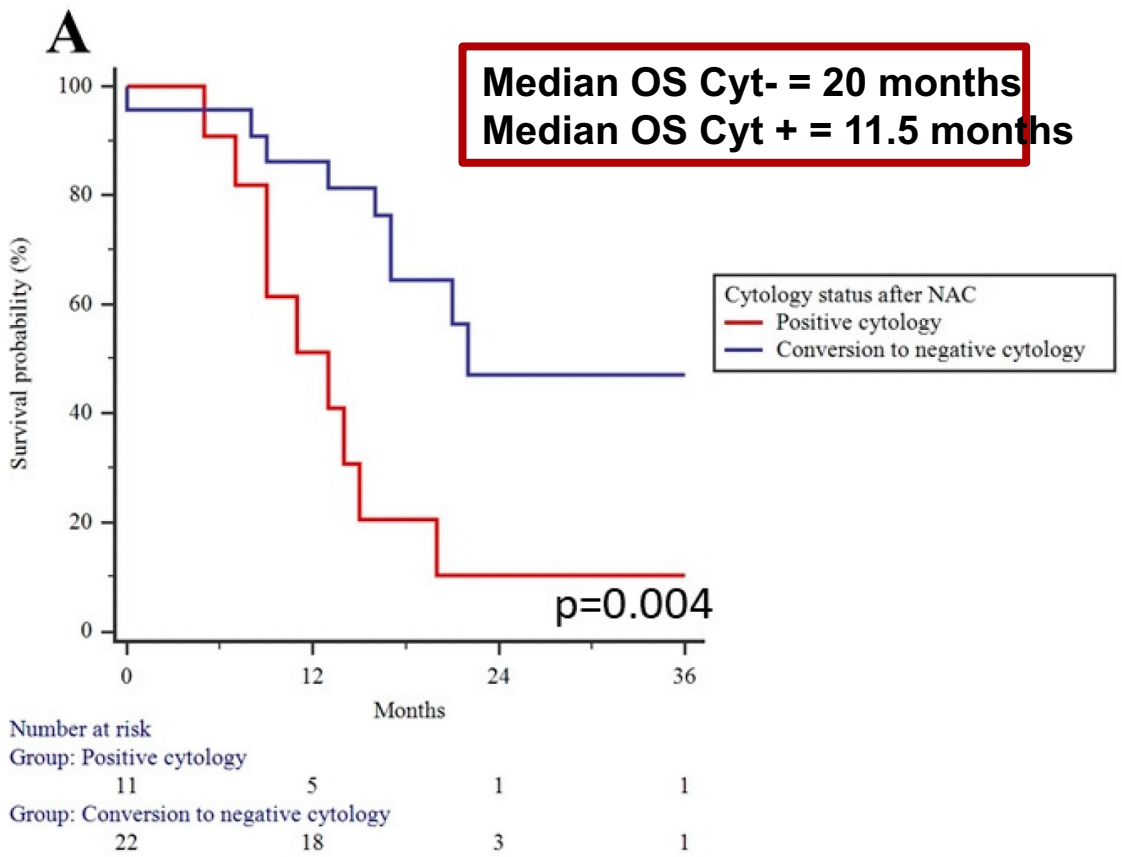
N=4397

Median OS PM = 6.7 months
Median OS Cyt + = 12 months

Der Sluis et al,. Eur J Cancer 2024 Mar:199:113541

OUTCOMES OF CYTOLOGY POSITIVE DISEASE AFTER SYSTEMIC TREATMENT AND GASTRECTOMY – EASTERN EUROPEAN STUDY





Basuys et al cancers (Basel) 2023 Dec 11;15(24):5794

UCI University of California, Irvine

STOPGAP I - Phase II Single-arm Study University of California, Irvine

Senthil and Dayyani *BMC Cancer* (2023) 23:209
https://doi.org/10.1186/s12885-023-10680-1

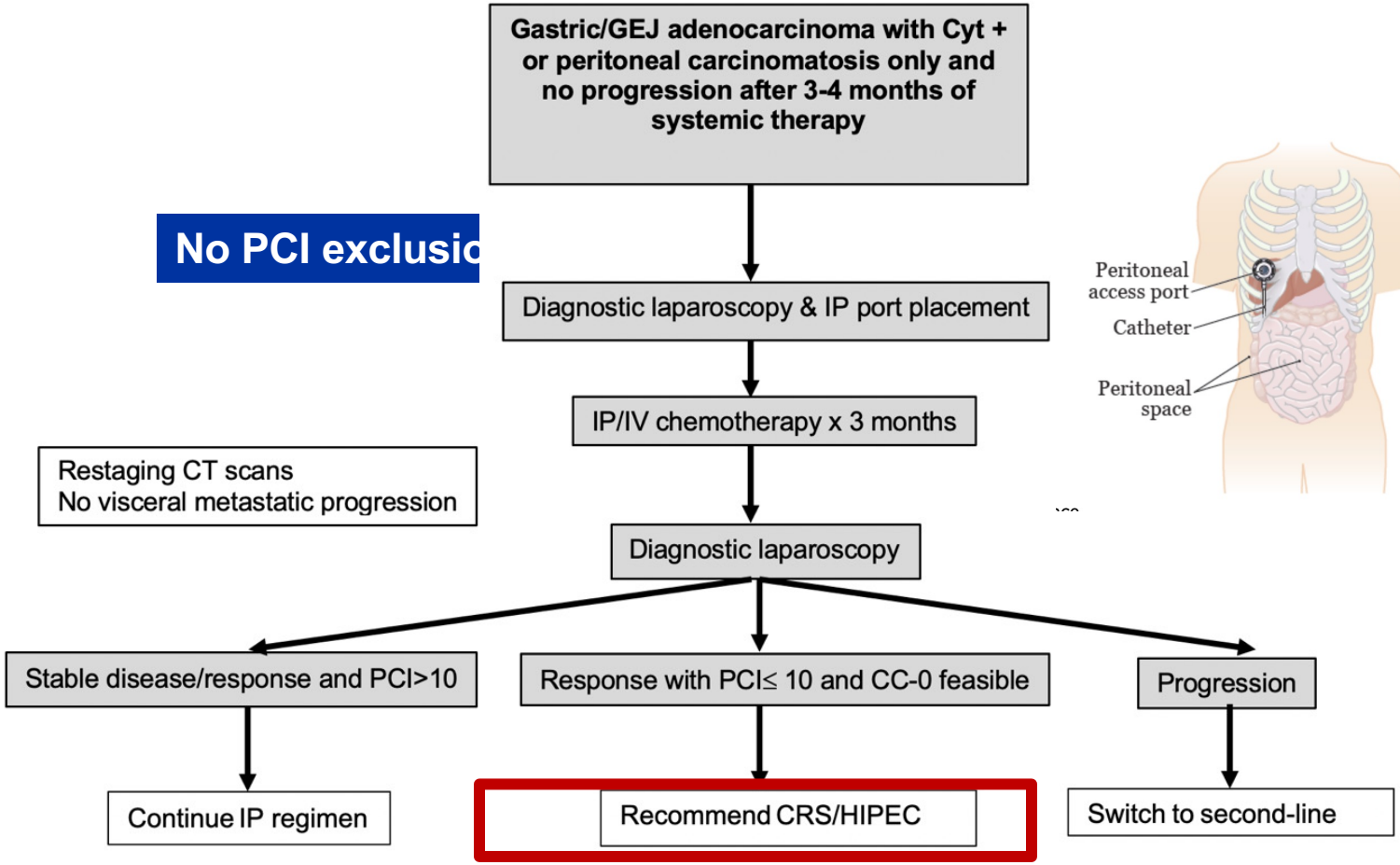
BMC Cancer

RESEARCH Open Access

Phase II clinical trial of sequential treatment with systemic chemotherapy and intraperitoneal paclitaxel for gastric and gastroesophageal junction peritoneal carcinomatosis - STOPGAP trial

Maheswari Senthil[1*] and Farshid Dayyani[2]

STOPGAP I- ITERATIVE PTX NIPEC



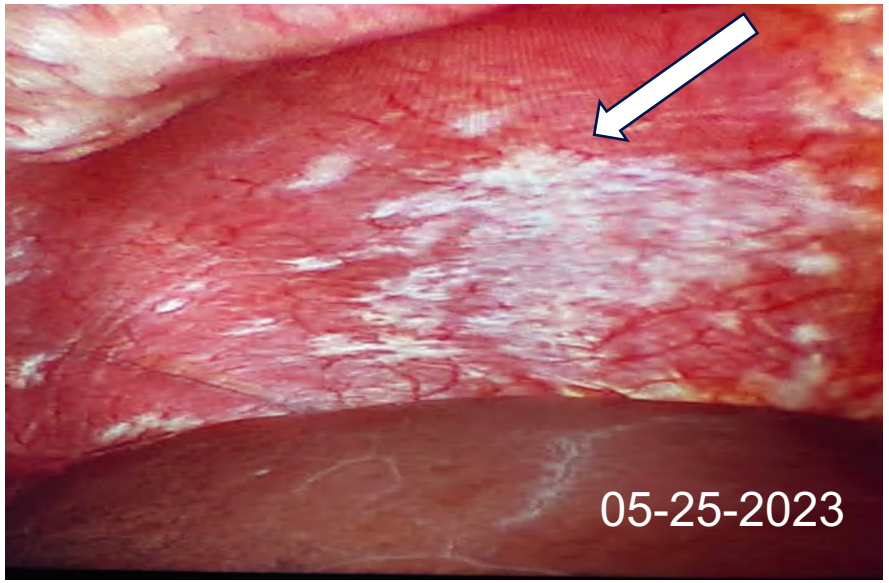
Leucovorin	20mg/m2	IV
5-FU	400mg/m2	IV
Paclitaxel	50mg/m2	IV
Paclitaxel	40mg/m2	**IP**

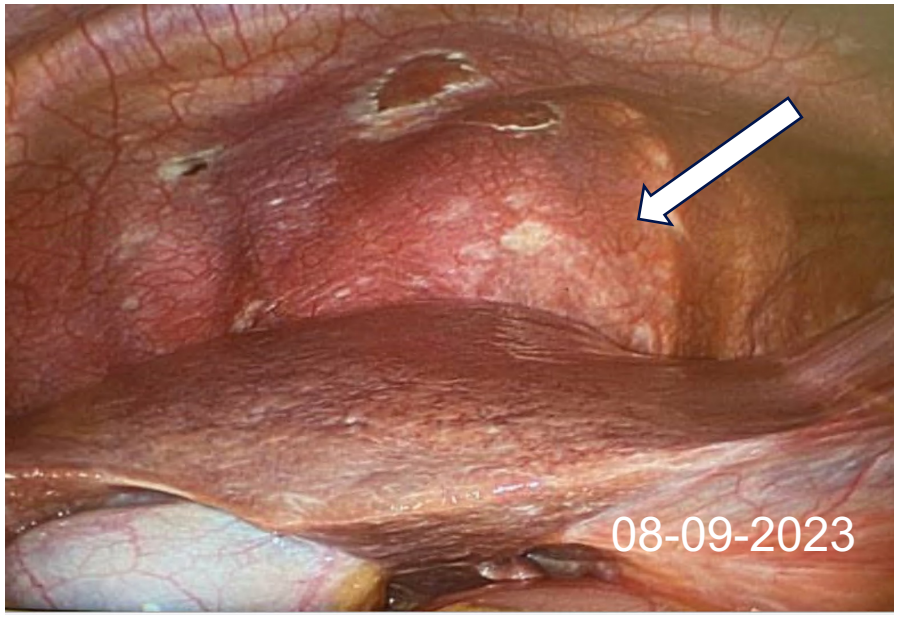
Targeted agent allowed (Nivo, Trastuzumab etc.)
Days 1&8, Q 3 weeks cycle for 4 cycles

Primary end point
- 1-year PFS

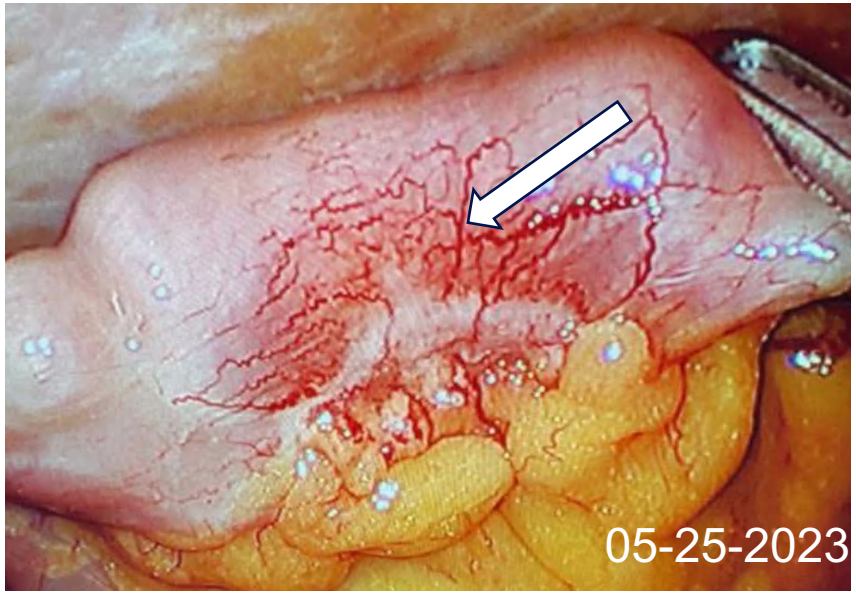
Secondary Endpoint
- Overall Survival
- PRO -QOL – EuroQol-5D-5L

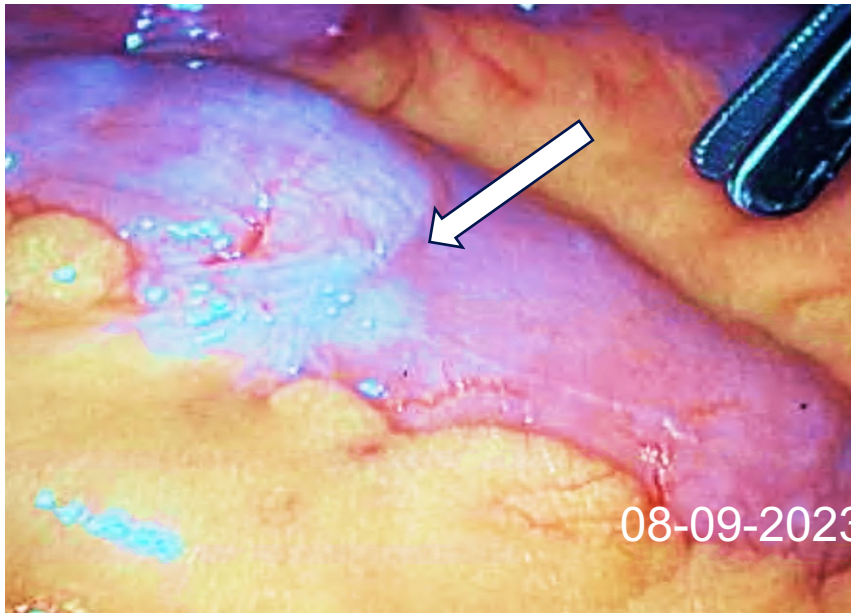
STOPGAP TREATMENT RESPONSE – 4 CYCLES OF IP PTX





Peritoneal cancer index decreased from 13 to 8





STOPGAP I DATA (05-16-24)

22 patients enrolled in 28 months

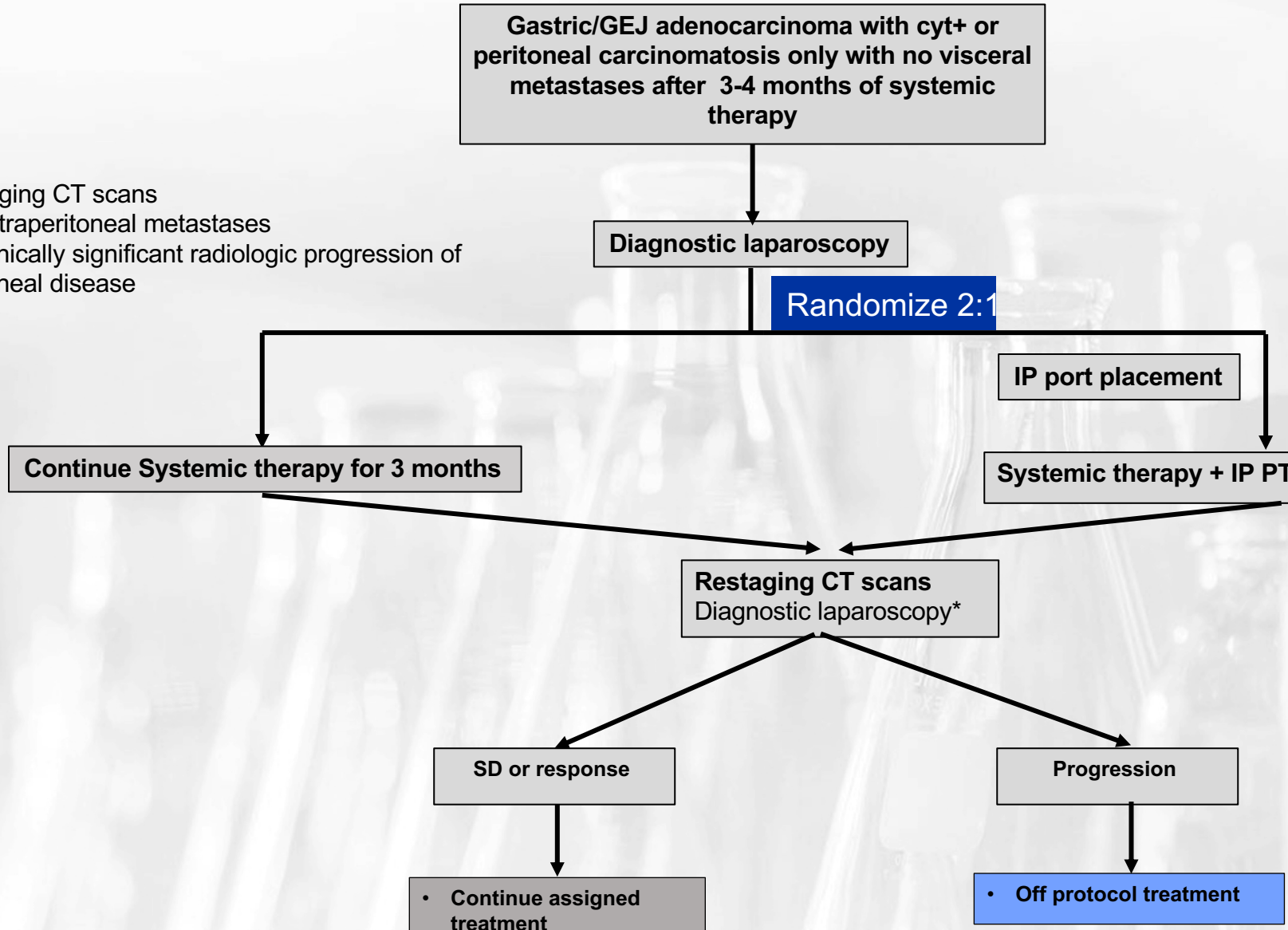
Safety and feasibility of bidirectional chemotherapy has been established

Median PFS – 14 months

7/20 patients have undergone cytoreductive surgery with no major postoperative complications

- 3 distal and 4 total gastrectomy procedures

EA2234 –STOPGAP Phase II/III Study Schema



Restaging CT scans
No extraperitoneal metastases
No clinically significant radiologic progression of peritoneal disease

MSI-H excluded
Stratification:
PCI = 0, 1-6, 7-14, 15 or greater
Chemo + targeted agent / IO vs. Chemo alone

Primary endpoint:
- PFS – Phase II
- OS- Phase III

Secondary Endpoints:
- Adverse events
- QOL

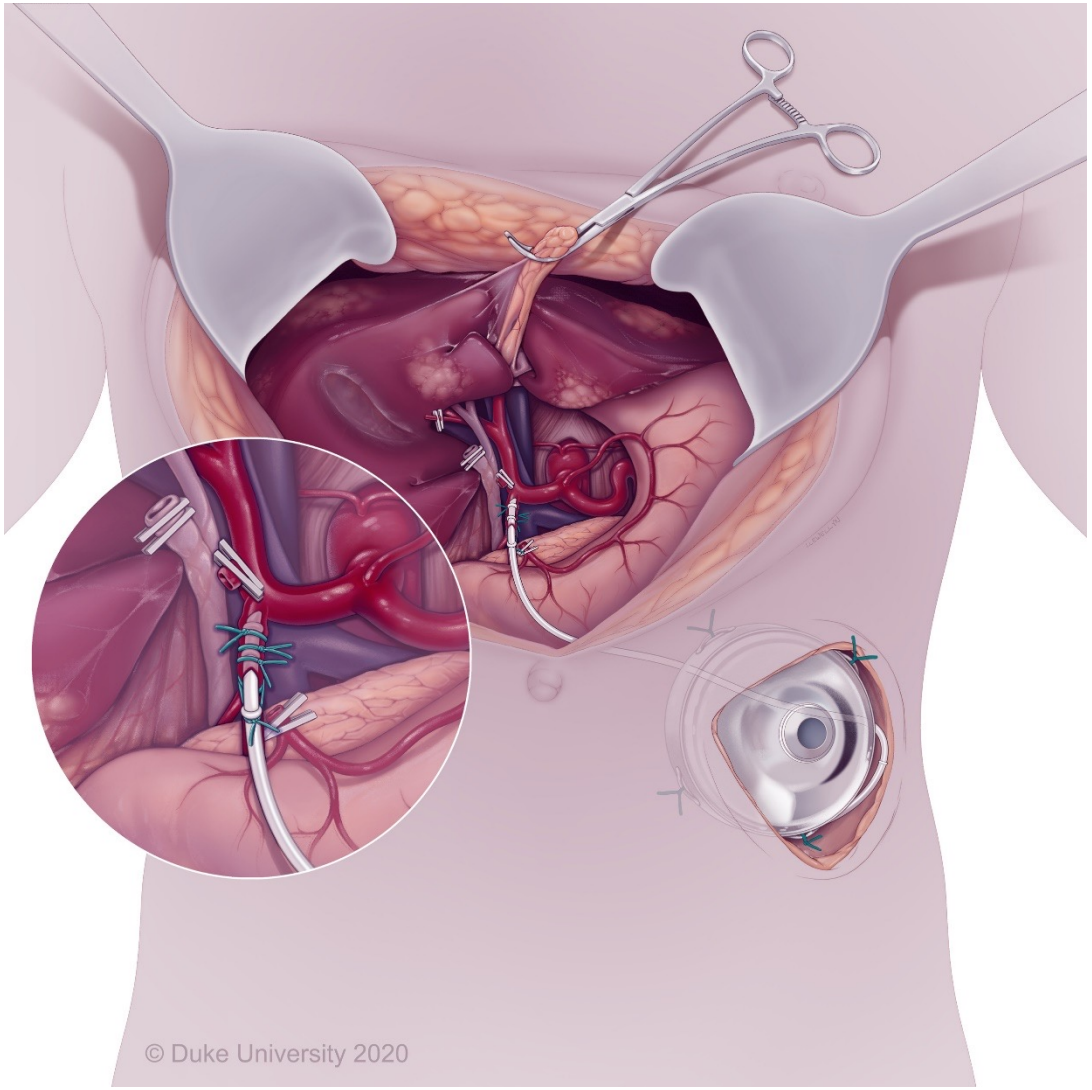
* If clinically indicated to assess surgical candidacy

Hepatic Artery Infusion (HAI): Concept

Physiologic and pharmacologic isolation of the liver

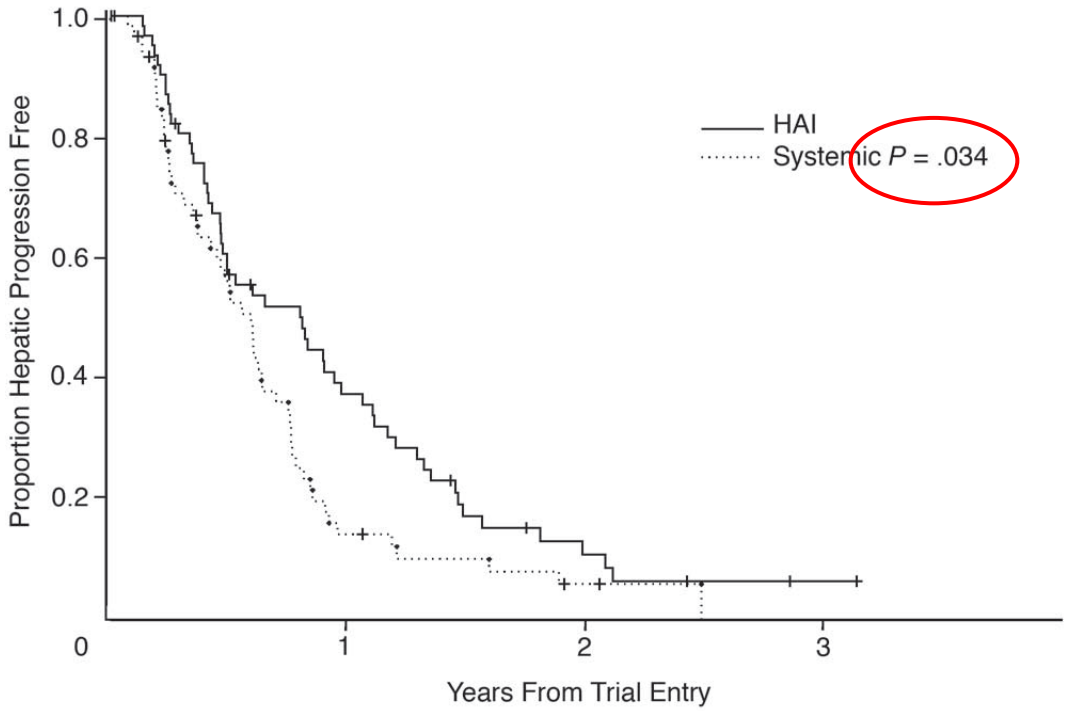
- Liver tumors are perfused by the hepatic artery
- Normal parenchyma is perfused by both the portal vein and hepatic artery
- FUDR: short half-life and 99% hepatic clearance →100-400x hepatic exposure

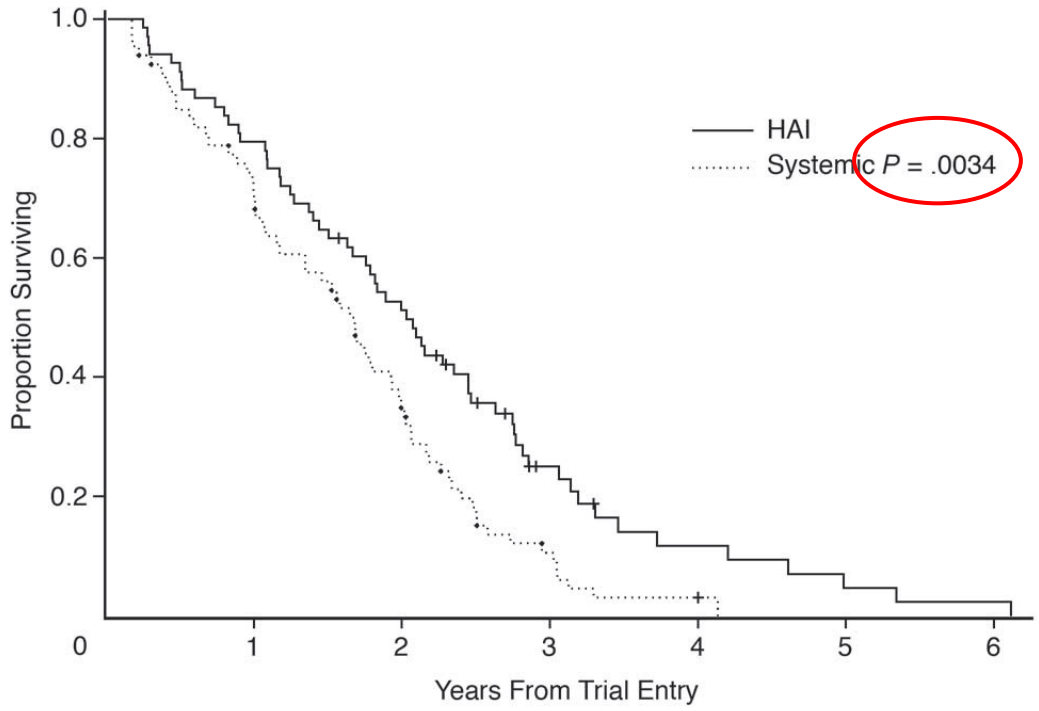
HAI = HAI + Systemic



Ensminger WD. Cancer Res. 1978. 28(11 pt 1):3784-92.
Ensminger WD. Semin Oncol. 1983. 10(2):176-82.

2006 RCT: FUDR vs 5FU





Median Hepatic-PFS: 9.8 vs 7.3 months

2-yr OS: 51% vs 35%

Median OS: 24.4 vs 20 months

- **Response rate: 47% vs 24%**

Kemeny N, et al. J Clin Oncol. 2006. 24(9)1395-403.

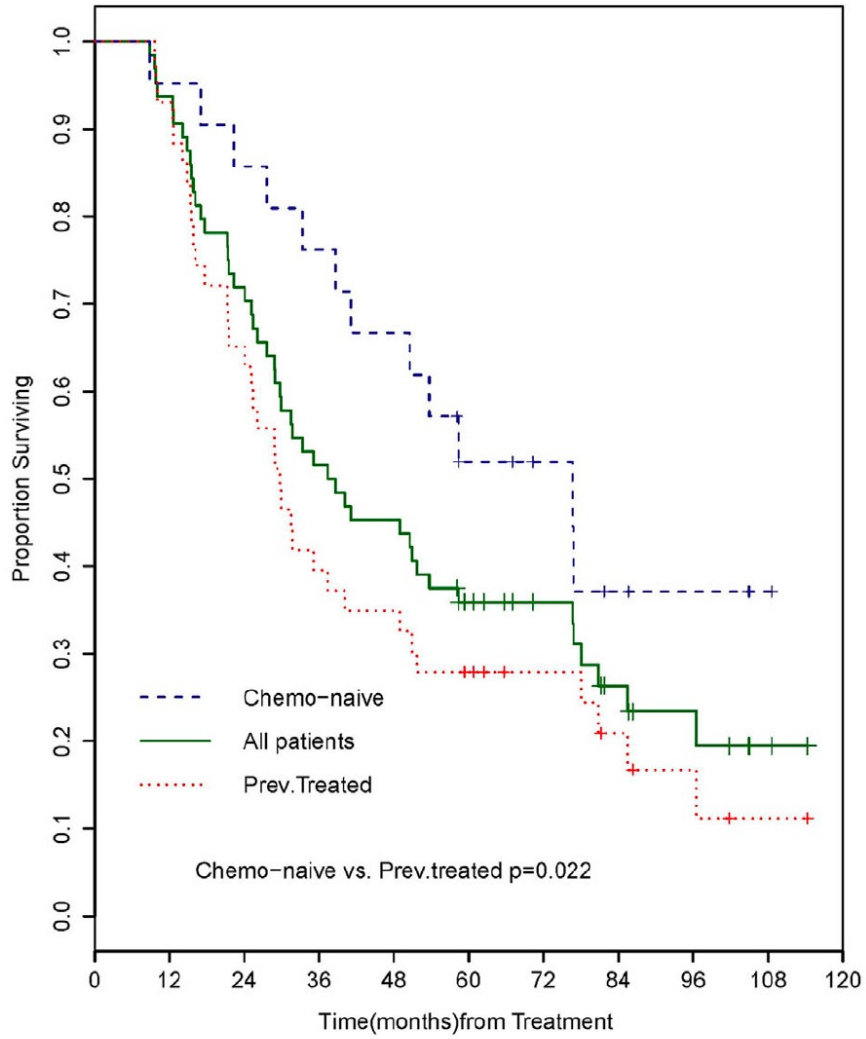
Modern HAI: Response and Conversion

64 patients at MSKCC with unresectable CRLM (Phase 2, single arm)

-2nd or 3rd line chemotherapy in **67%**

-Median number of tumors = 13

- Response rates:
  - 86% in chemo-naïve patients
  - 67% in previously treated patients
- Survival = 46 months
  - Chemo-naïve = 77 mo
  - Previously treated = 30 mo
- KRAS WT vs mutant = similar 5 yr OS (41% vs 35%)

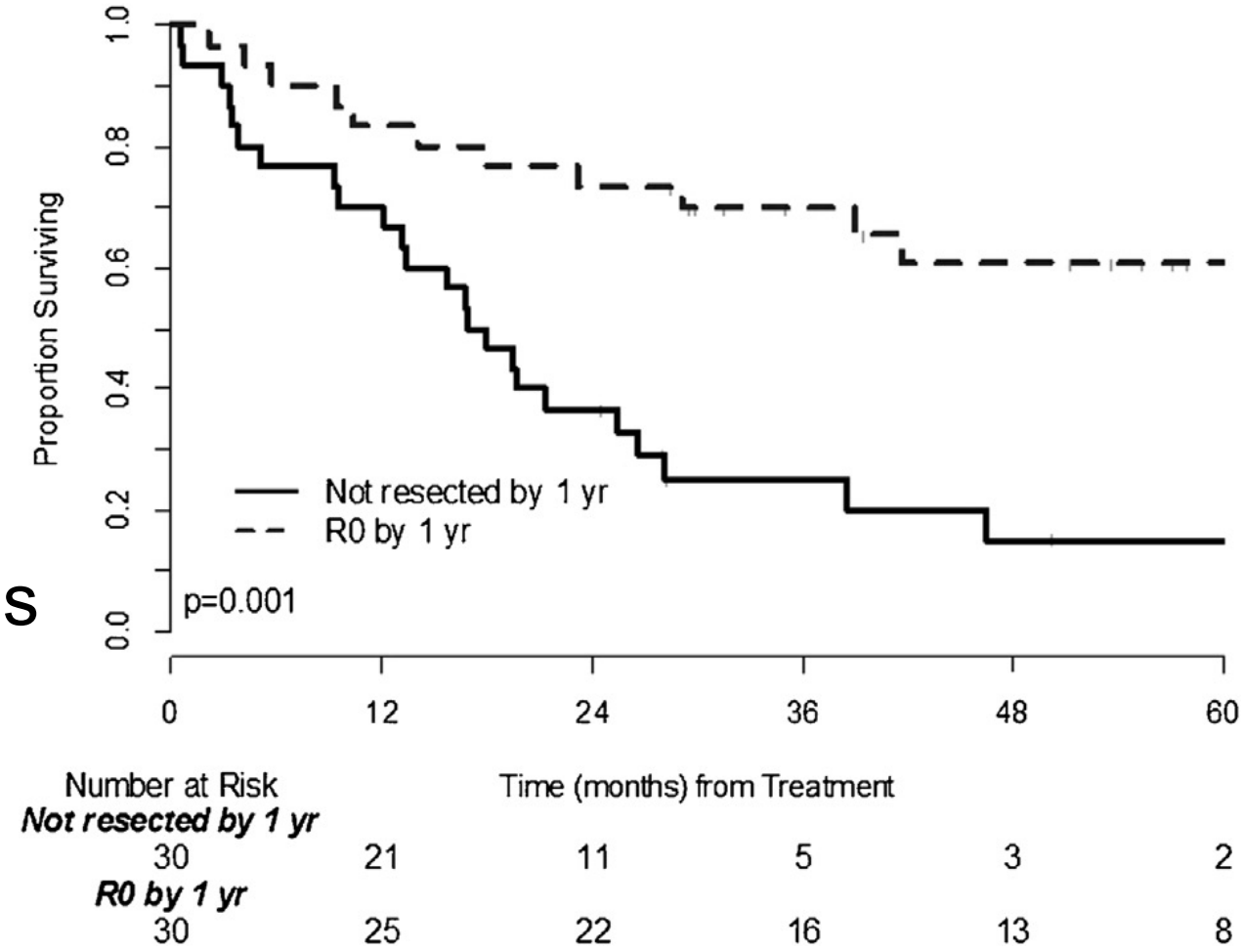


D'Angelica M, et al. Ann Surg. 2015. 261(2):353-60.

Pak LM and D'Angelica MI, et al. J Surg Oncol. 2018. 117(4):634-643.

Modern HAI: Response and Conversion

- Conversion to resection: 52%
- 5 yr Survival:
  - Resected = 63%
  - Not resected = 13%
- 14% NED a median of 94 months after diagnosis



D'Angelica M, et al. Ann Surg. 2015. 261(2):353-60.
Pak LM and D'Angelica MI, et al. J Surg Oncol. 2018. 117(4):634-643.

WHY IS A TRIAL JUSTIFIED?

- Most recent RCT is 15 years old and used now outdated HAI and systemic regimens
- HAI still not widely accepted despite outcomes
- Many patients do not have access to HAI
- No data comparing HAI to modern systemic chemotherapy regimens

- Window of Opportunity
  - There are now enough centers nation-(world)-wide to conduct a prospective, multicenter ‘real world’ randomized trial

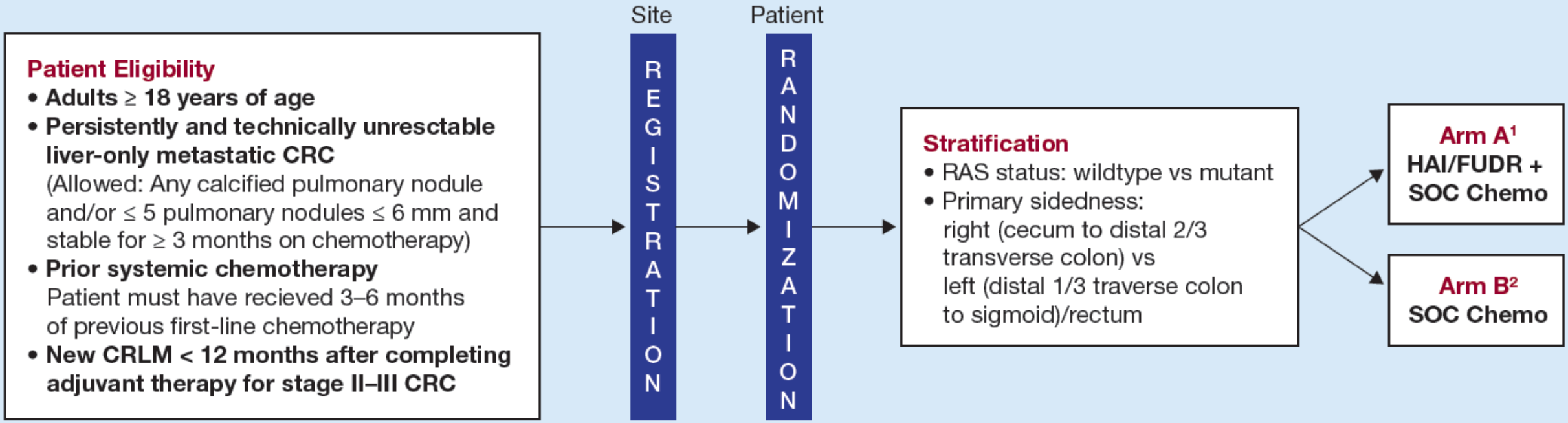
- Goal: Determine whether HAI plays a meaningful role in a standardized approach to patients with unresectable colorectal liver metastases

ECOG-ACRIN cancer research group

EA2222 - A Randomized Phase III Study of Systemic Therapy With or Without Hepatic Arterial Infusion for Unresectable Colorectal Liver Metastases: The PUMP Trial

NCT05863195

Study Chair: Michael Lidsky, MD



N = 408
2:1 Randomization
[1]Arm A consists of HAI/FUDR (Hepatic arterial infusion/floxuridine) plus standard of care chemotherapy options that are outlined in Section 5.1.1.3.
[2]Arm B consists of standard of care chemotherapy options that are outlined in Section 5.1.2.1.

Activated October 19, 2023!

CONCLUSIONS

- There are opportunities to add locoregional therapies to the treatment of patients with stage 4 gastrointestinal cancers
- Understanding the genetic/molecular characteristics of individual tumors should help identify who can benefit from these locoregional therapies
- Incorporating these concepts in timely clinical trials is the only way to define their benefit