City of Hope®

Multidisciplinary Approaches to Cancer Symposium

Regional Therapy Approaches for Metastatic Colorectal Cancer

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Disclosures

- Grant/Research Support from Exact Sciences and Reger, Inc.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

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

This presentation has been peer-reviewed and no conflicts were noted.

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.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

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

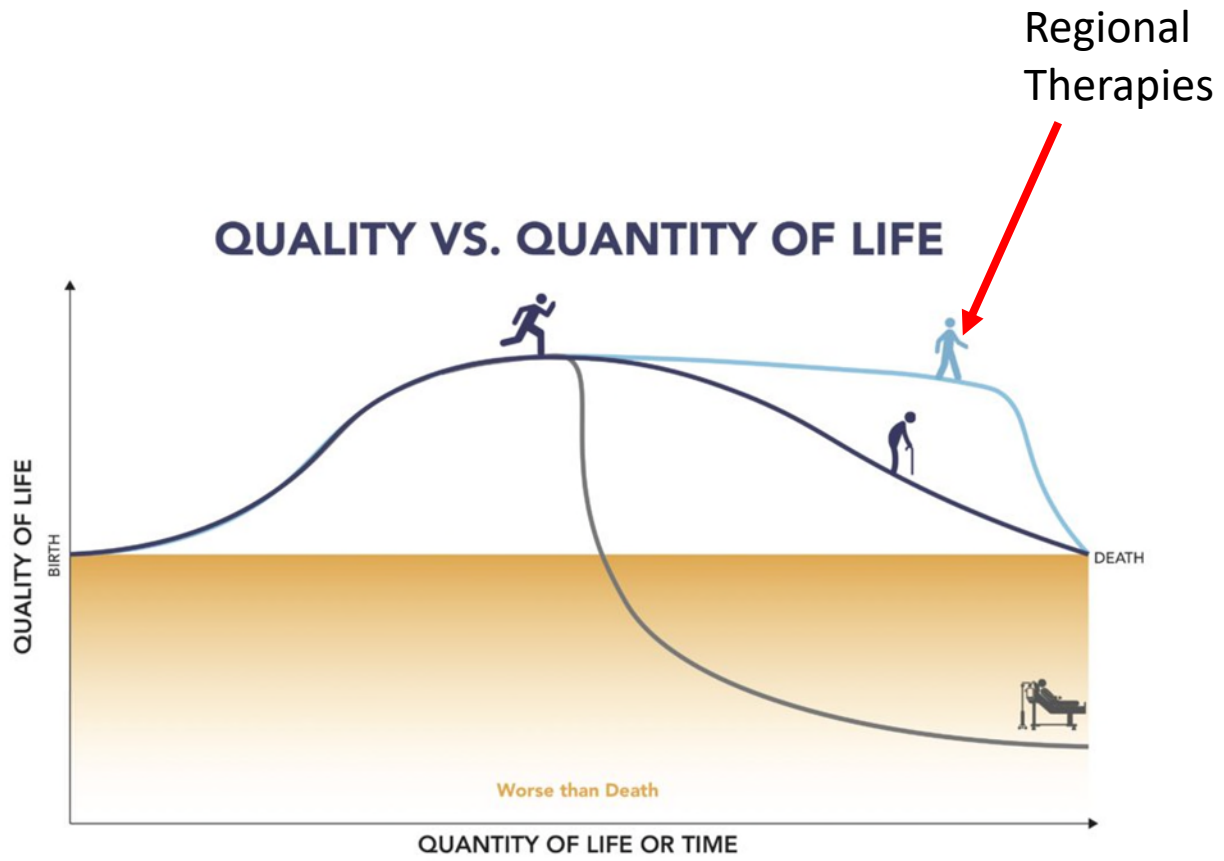
- *We will emphasize cultural diversity in clinical trial enrollment.*
- *There is nihilism in the treatment of peritoneal metastases. The presentation will impart knowledge necessary to advance the treatment of peritoneal metastases countering the nihilism.*

Regional Therapies

- Delivery of therapies directly to an anatomically defined region
- Purpose - Spare systemic toxicity
- Approaches:
    - Resection/ Transplantation
    - Ablative: Microwave/ Radiofrequency Ablation, SBRT
    - Cavitary: HIPEC, PIPAC, NIPEC
    - Vascular: HAIP, TARE

Regional Therapies - Principles

- Establish systemic control
- Select for better biology (time, mutation profiles, other biomarkers)
- Caution: Multi-organ metastases
- Morbidity of intervention and time to return to systemic therapy are key



Regional Therapies - Principles

- Underutilization of Regional Therapies – Requires Special Expertise
- Curative-intent:
  - Liver: Liver resection and HAIP; Liver ablation; SBRT; Transplantation
  - Peritoneum: Cytoreductive Surgery
  - Lung: Resection, SBRT
- Palliative:
  - Liver: Y90, HAIP, SBRT
  - Peritoneum: Palliative Debulking, PIPAC

Curative Intent – Liver

LIVER RESECTION

- A high proportion of liver metastases patients can be cured
- Many techniques to get patients to resection by augmenting liver remnant:
    - o PVE
    - o PVE + Hepatic Vein Embolizations
    - o ALPPS

Table 5. CLINICAL RISK SCORE FOR TUMOR RECURRENCE

	Survival (%)					
Score	1-yr	2-yr	3-yr	4-yr	5-yr	Median (mo)
0	93	79	72	60	60	74
1	91	76	66	54	44	51
2	89	73	60	51	40	47
3	86	67	42	25	20	33
4	70	45	38	29	25	20
5	71	45	27	14	14	22

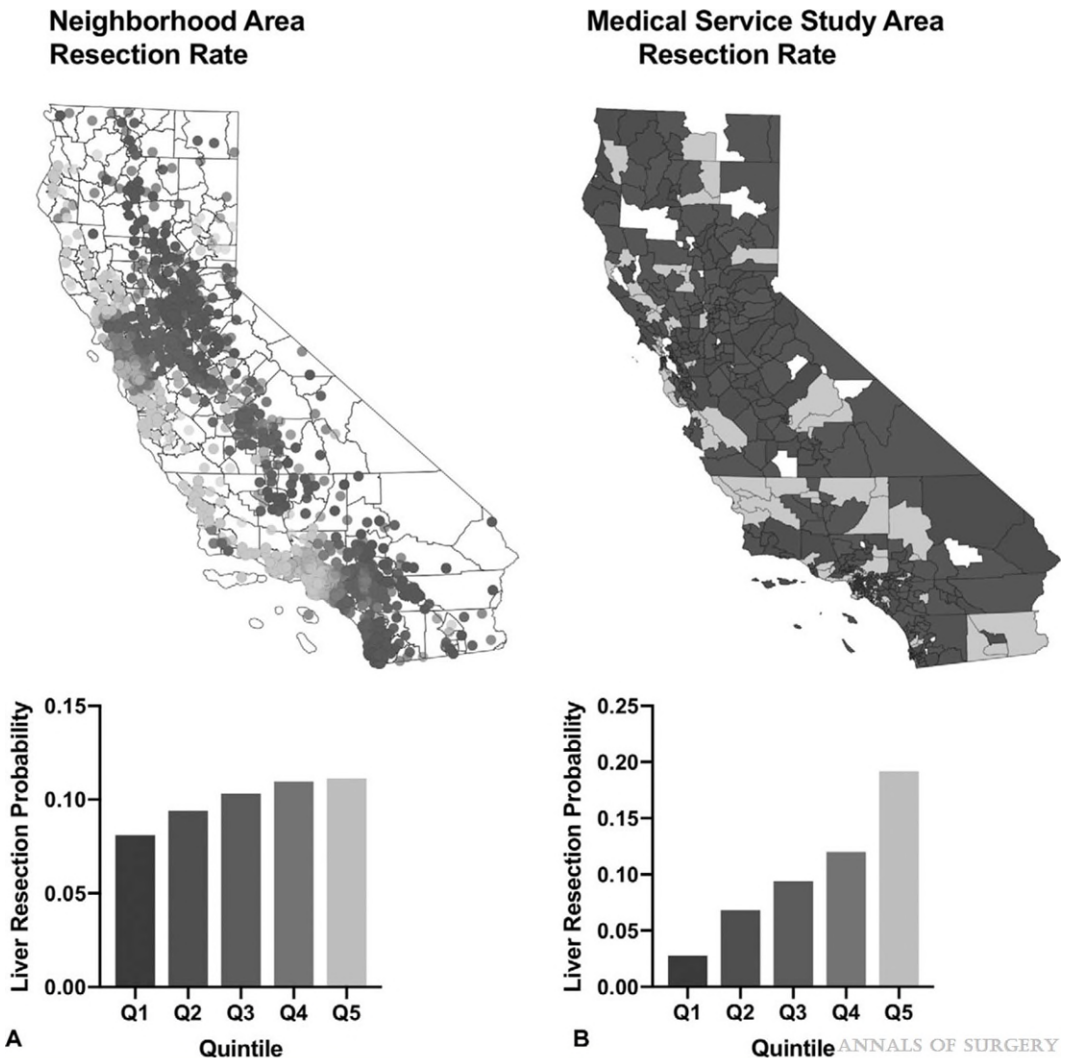
Each risk factor is one point: node-positive primary, disease-free interval <12 months, >1 tumor, Size >5 cm, CEA >200 ng/ml.

Fong Ann Surg 1999

Curative Intent – Liver

LIVER RESECTION

- Only 10% of patients actually get liver resection
- While there is no randomized trial, quasi-experimental studies have established extensive survival benefit
- Approximately 2 years on average

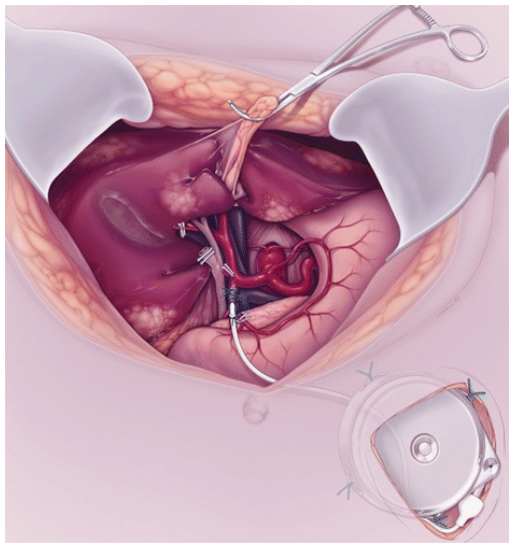


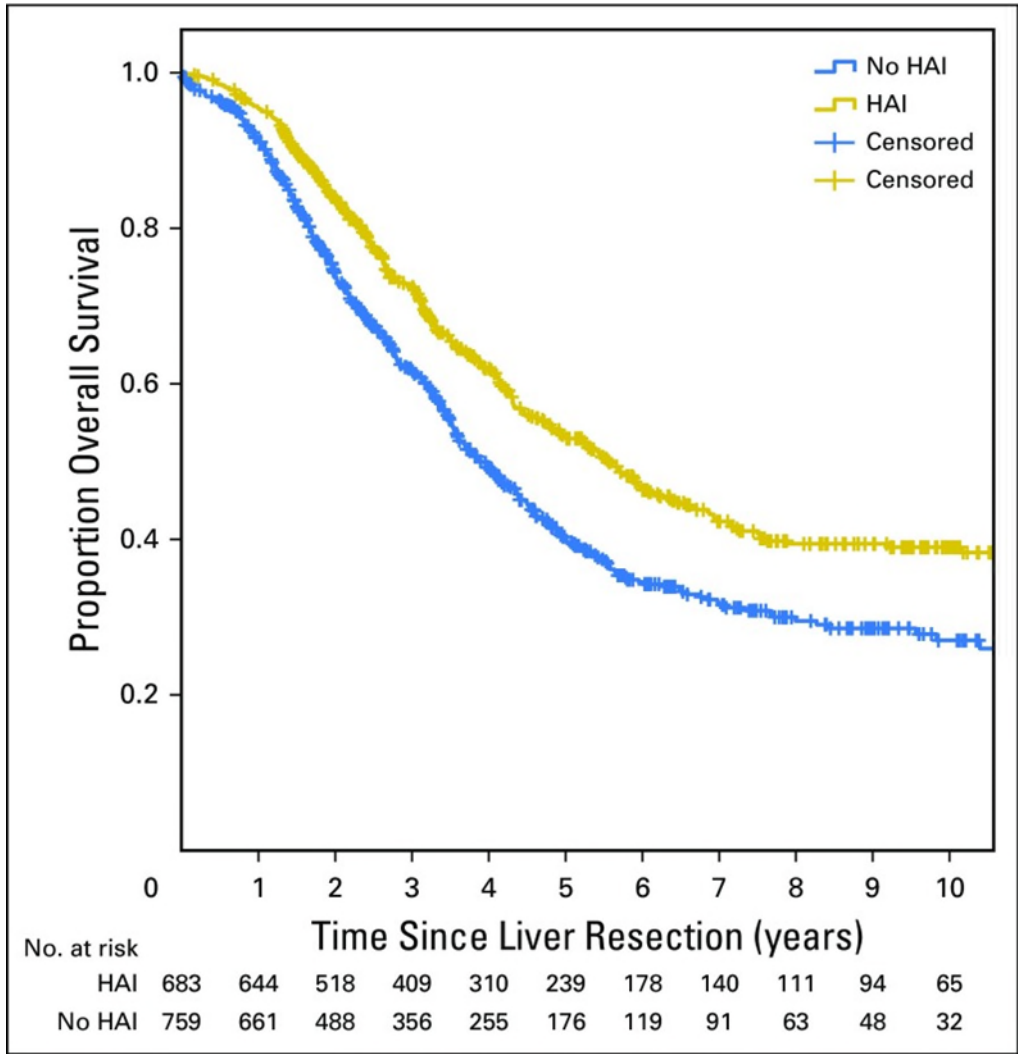
Raoof Ann Surg 2019

Curative Intent – Liver

LIVER RESECTION AND HAIP

- Adjuvant Hepatic Artery Infusion Pump may prevent liver relapse and prolong survival after liver resection
- Indication:
    - 3+ Liver Mets
    - Liver-limited

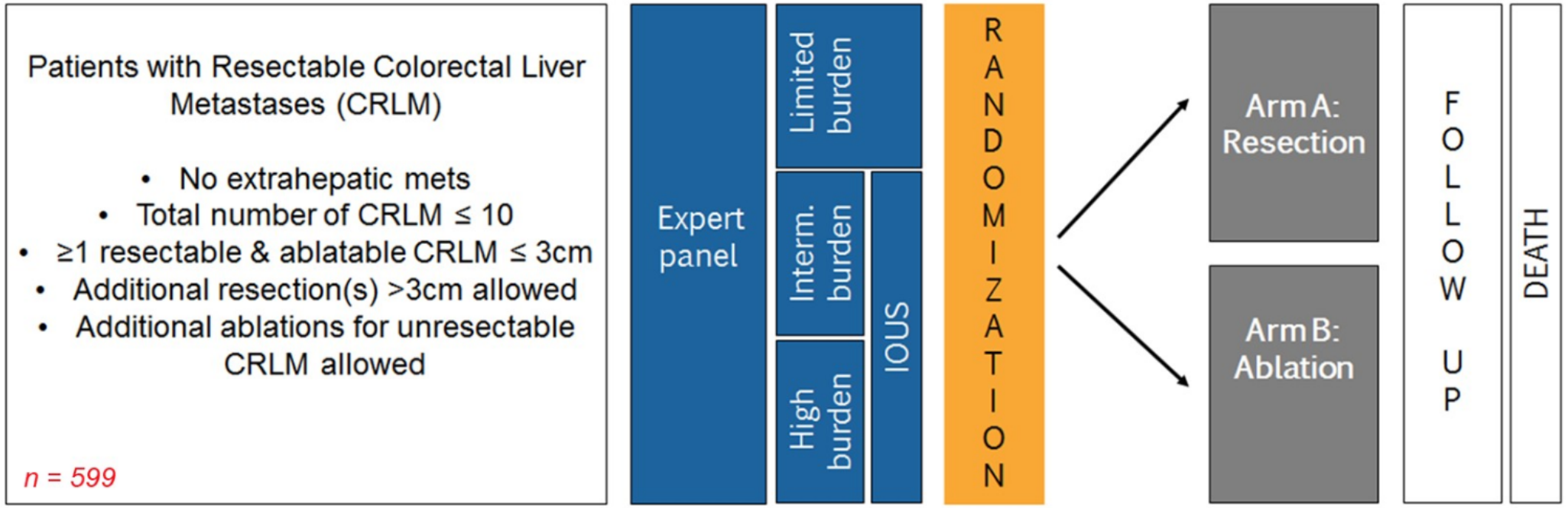




Koerkamp JCO 2017

Curative Intent – Liver

LIVER ABLATION



Phase III international multicenter randomized controlled trial to prove / disprove hypothesis of non-inferiority of thermal ablation compared to surgical resection for small-size colorectal liver metastases (CRLM)

- Approach (percutaneous, laparoscopic or open) according to local expertise
- If limited disease burden (max 3 CRLM ≤ 3cm) consider percutaneous / laparoscopic approach
- If intermediate or high disease burden randomize after eligibility check (after IOUS) during OR (single-blind)

Curative Intent – Liver

LIVER ABLATION

Procedure-related characteristics		N = 148	N = 148	
Subgroup	A low disease burden	89 (60.1%)	94 (64.2%)	0.469
	B intermediate disease burden	50 (33.8%)	41 (27.7%)	
	C high disease burden	9 (6.1%)	12 (8.1%)	
Preprocedural systemic therapy	No	112 (75.7%)	118 (79.7%)	0.485
	Yes	36 (24.3%)	30 (20.3%)	
	Capecitabine	2 (1.4%)	2 (1.4%)	
	CAPOX	2 (1.4%)	3 (2.0%)	
	CAPOX-B	23 (15.6%)	21 (14.2%)	
	FOLFOX-B	2 (1.4%)	2 (1.4%)	
	FOLFIRI-B	2 (1.4%)	1 (0.7%)	
	FOLFIXIRI-B	4 (2.7%)	1 (0.7%)	
	Missing	1 (0.7%)	0 (0%)	
Procedures	Resection alone	90 (60.8%)	0 (0%)	
	Ablation alone	1 (0.72.0%) *	118 (79.7%)	
	Resection + ablation	52 (35.1%)	27 (18.2%)	
	No local treatment	5 (3.4%)	3 (2.1%)	
Cycles of systemic therapy	Median (range)	5.5 (2 – 10)	6 (3 – 12)	0.420
Approach ◦	Percutaneous	2 (1.4%)	84 (56.8%)	
	Laparoscopic	68 (46.6%)	10 (6.8%)	
	Open	76 (52.1%)	54 (36.5%)	
Anesthesia ◦	General	146 (100%)	111 (75.0%)	
	Propofol	0 (0.0%)	37 (25.0%)	
Number of CRLM	Median number CRLM (range)	2 (1 – 10)	2 (1 – 12)	0.964
Tumor-related characteristics		**N = 446**	**N = 447**	
CRLM ◦	Target	304 (68.2%)	349 (78.1%)	
	Non-target (unresectable / unablatable)	142 (31.8%)	98 (21.9%)	
Size CRLM randomization (mm)	Mean size target CRLM (range)	14 (2 – 34)	13 (3 – 34)	0.457
Size CRLM treatment (mm)	Mean size target CRLM (range)	14 (2 – 40)	14 (2 – 50)	0.459

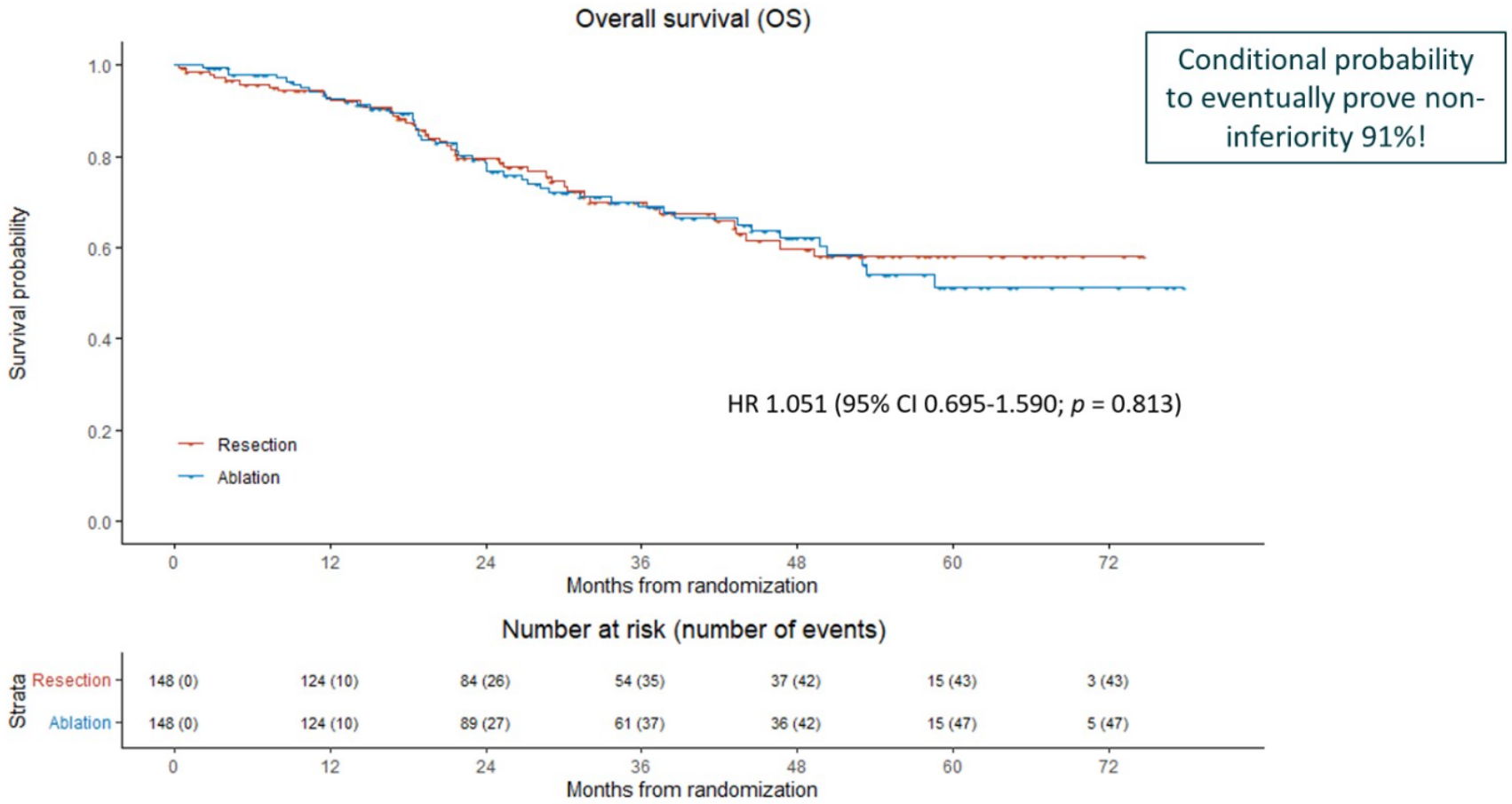
- 62% low disease burden
- **22% chemo first**
- median number CRLM = 2
- mean-size CRLM 14mm

- ***64% of resections in low disease burden group performed using (robot) laparoscopy***

- ***83% of ablations in low disease burden group performed percutaneously***

Curative Intent – Liver

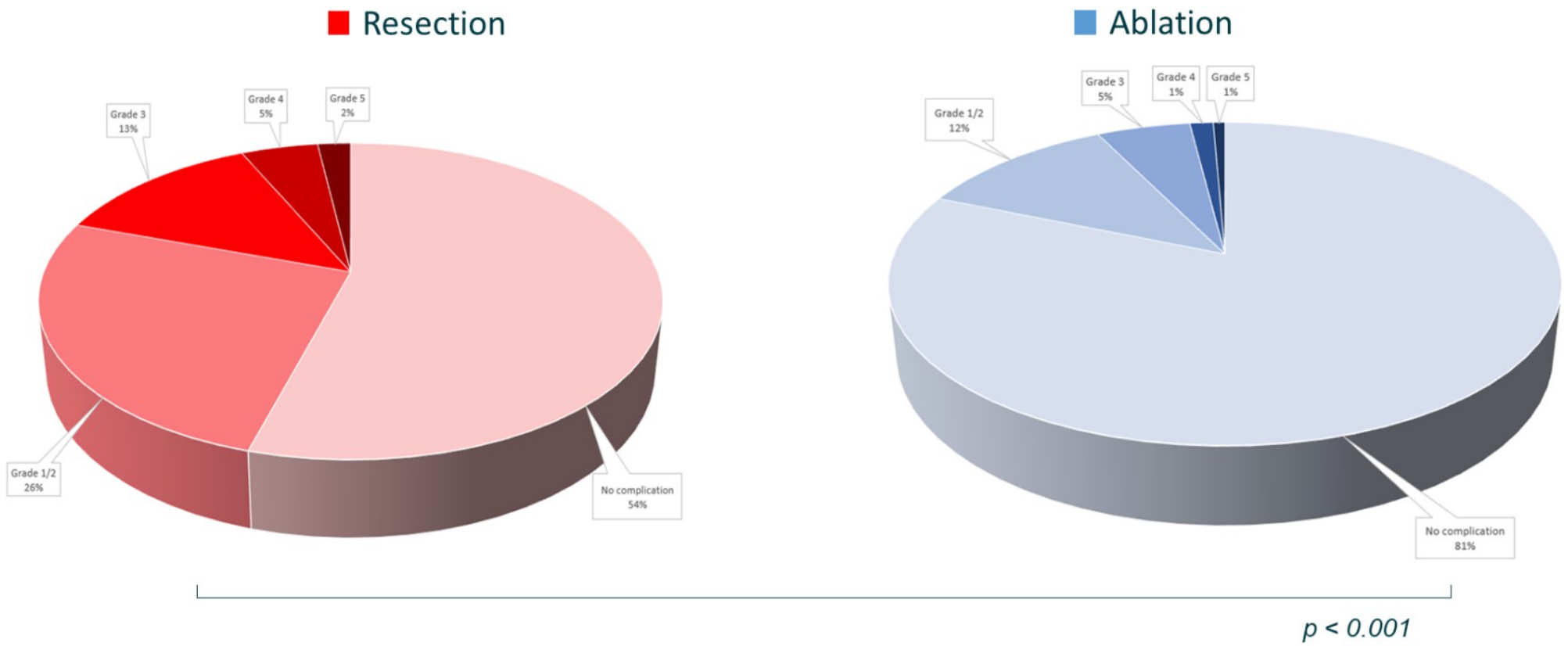
LIVER ABLATION



Conditional probability to eventually prove non-inferiority 91%!

Curative Intent – Liver

LIVER ABLATION



Curative Intent – Liver

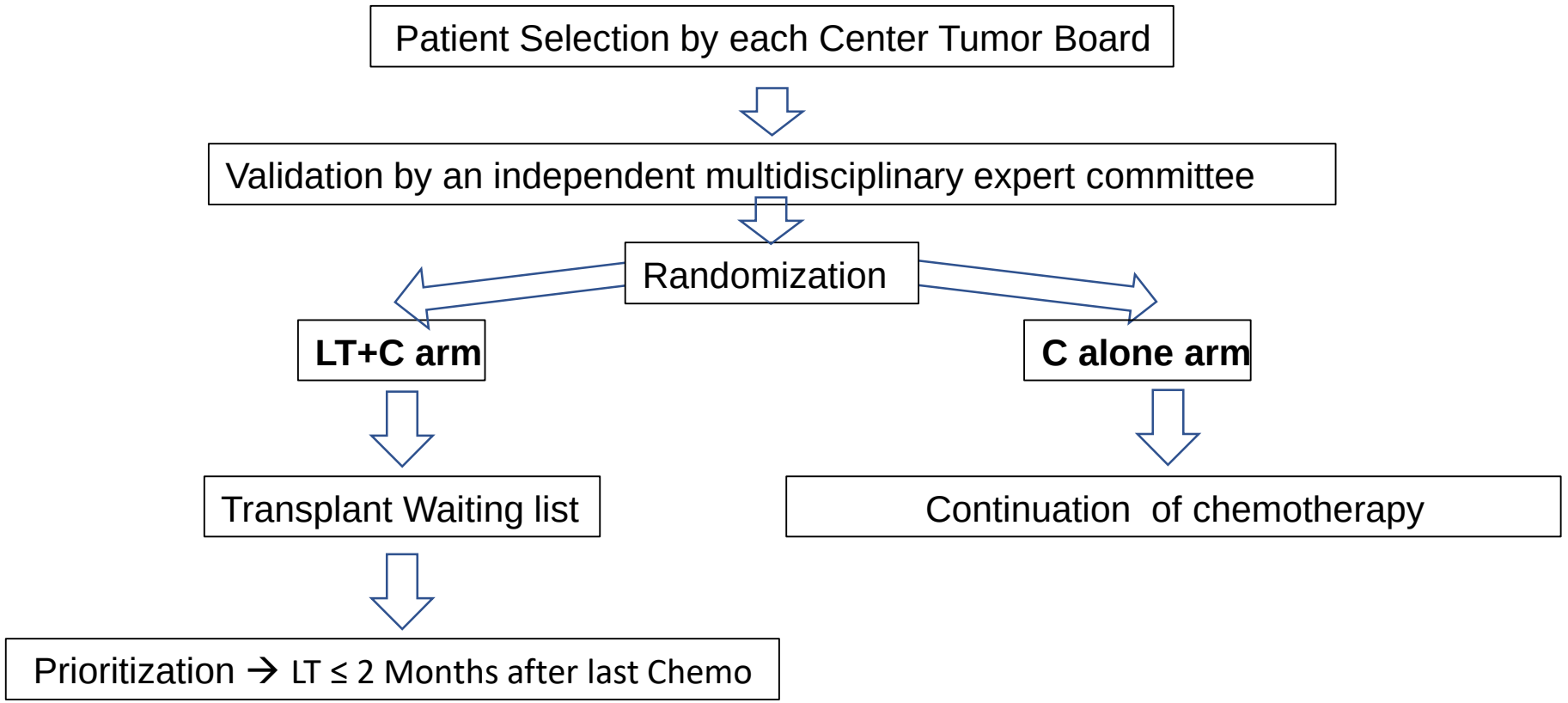
LIVER ABLATION

- Collision stopped at halftime based on predefined stopping rules
- Reduced morbidity and mortality
- Comparable local control to surgery
- Did not compromise survival

Curative Intent – Liver

LIVER TRANSPLANTATION

TransMet Trial : Study Design



Adam et al, eClinical Medicine 2024

Curative Intent – Liver

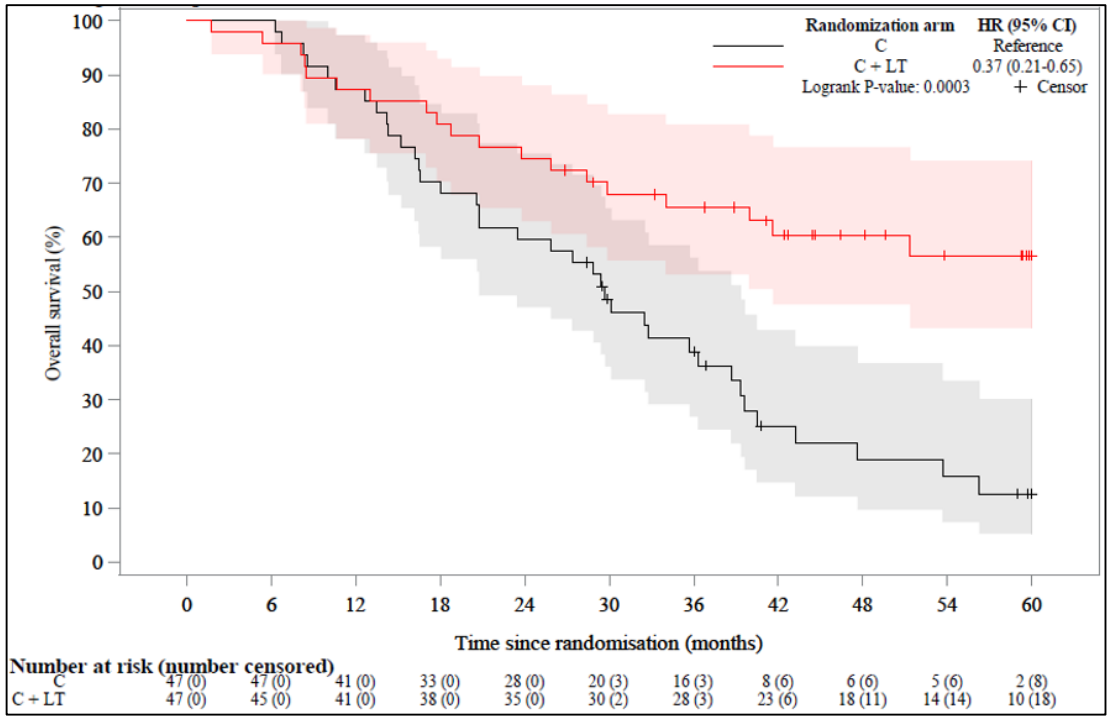
LIVER TRANSPLANTATION (TransMet)

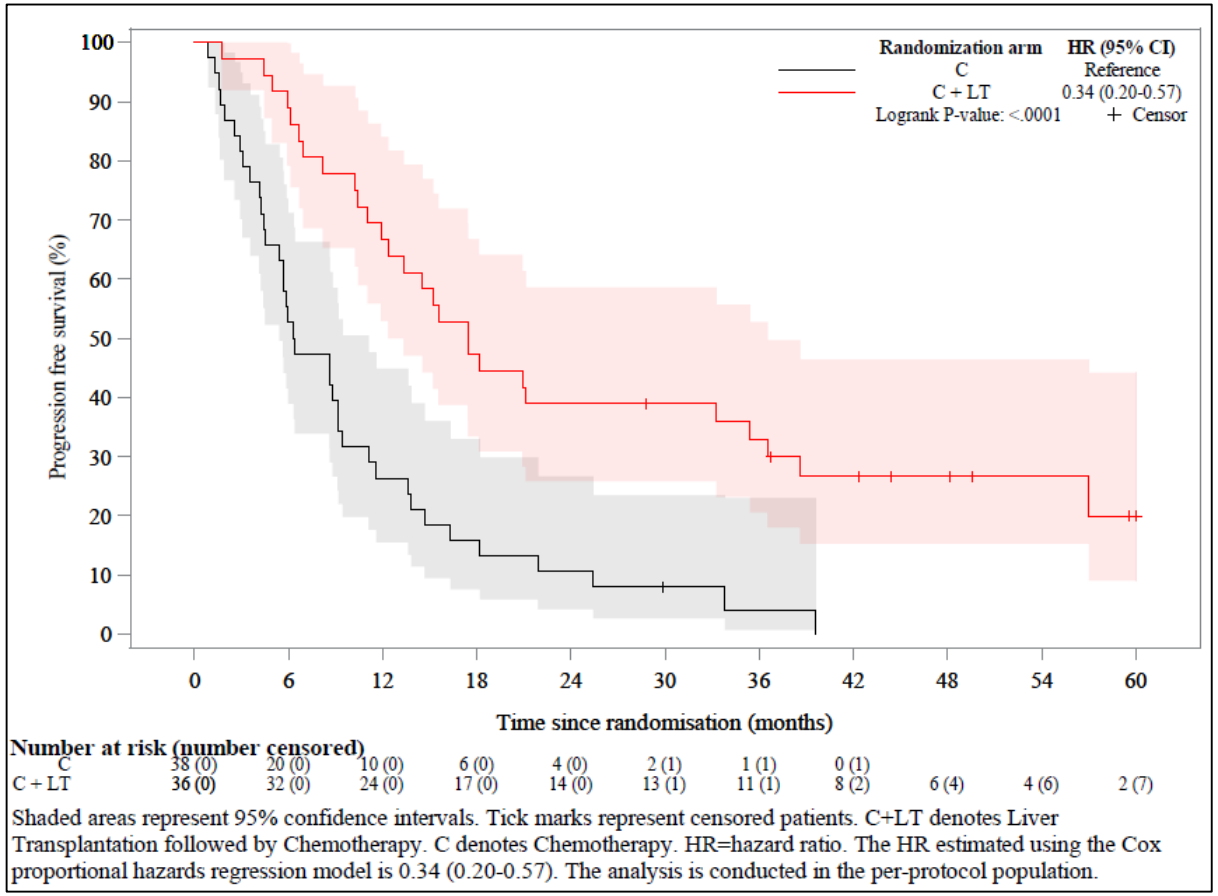
- **Eligibility**
  - ≤ 65 years
  - Good performance status (ECOG 0 or 1)
  - Confirmed **unresectability** of CLM by expert surgeons
  - Gold standard Resection of the primary
  - No extrahepatic disease
  - **Partial Response or Stability with Chemo : ≥ 3 months, ≤ 3 lines**
  - No BRAF mutation; CEA < 80 ng/ml or 50% decrease from baseline

Curative Intent – Liver

15 pts (**42%**) NED after 50 Mo FU

LIVER TRANSPLANTATION (TransMet)



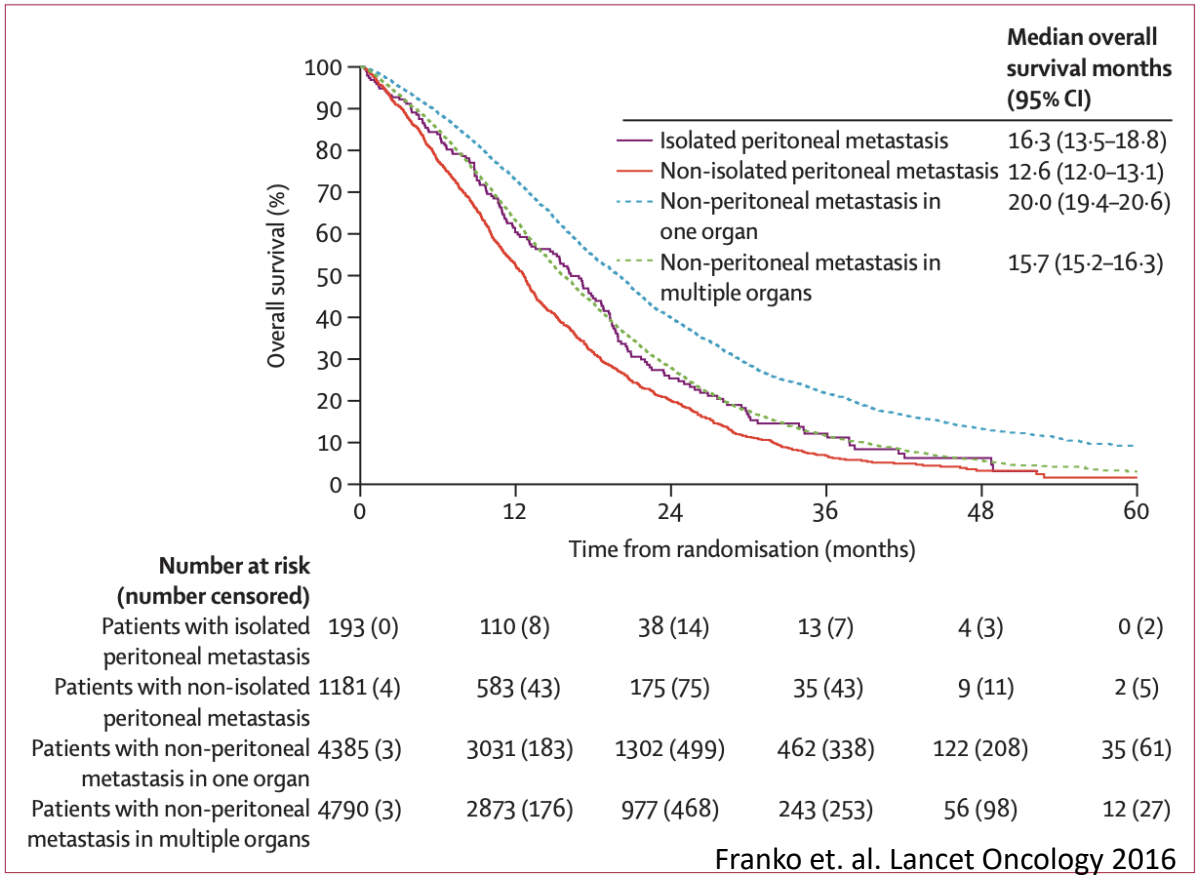


These results support LT as a new standard option that could change our practice in treating patients with liver-only, definitively unresectable CLM.

Curative Intent – Peritoneum

Autopsy studies: 20-51%

PERITONEAL CYTOREDUCTION



Franko et. al. Lancet Oncology 2016

	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)**

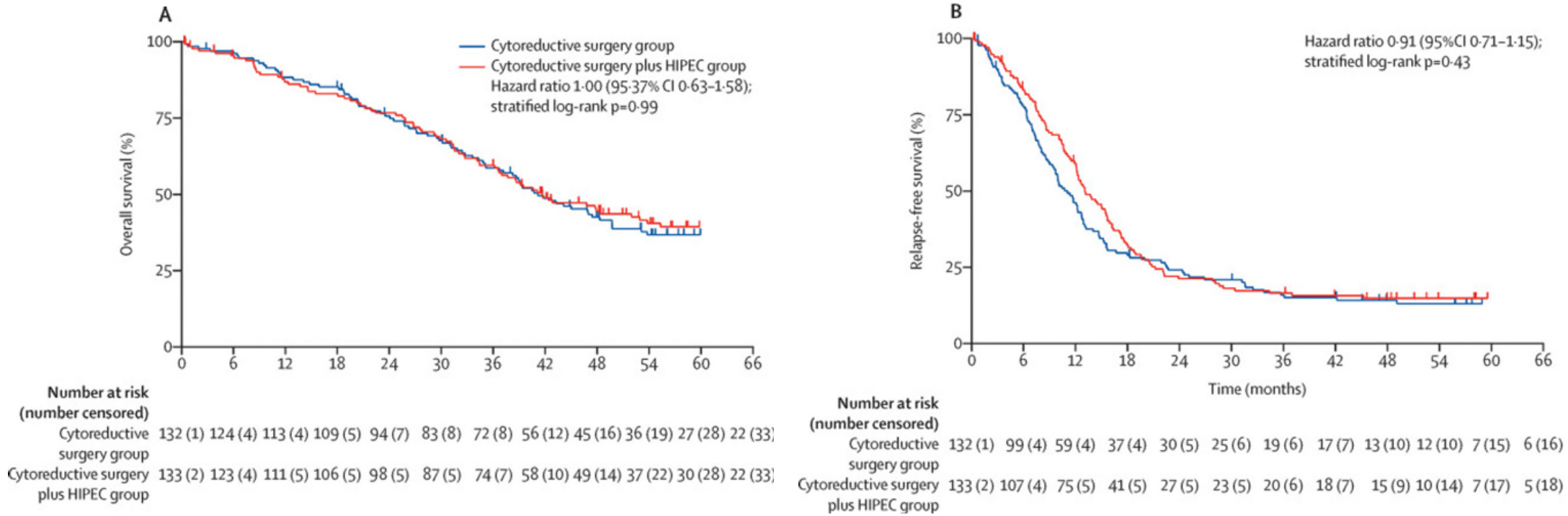
Two main reasons for exclusion:

- Performance status
- RECIST non-measurable disease

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

Curative Intent – Peritoneum

PERITONEAL CYTOREDUCTION

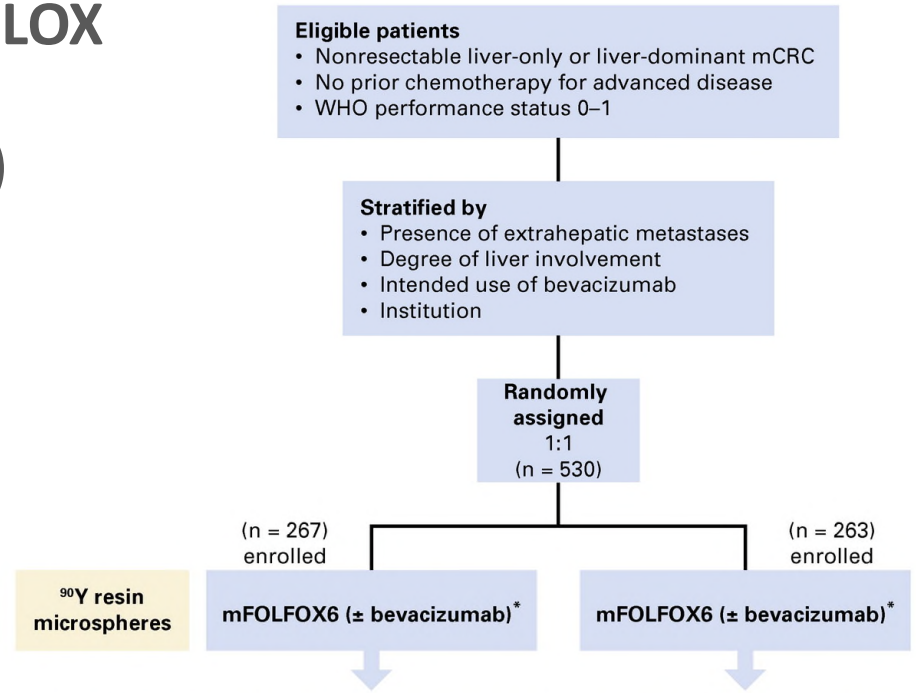


Quenet Lancet Oncology 2021

Palliative Intent – Liver

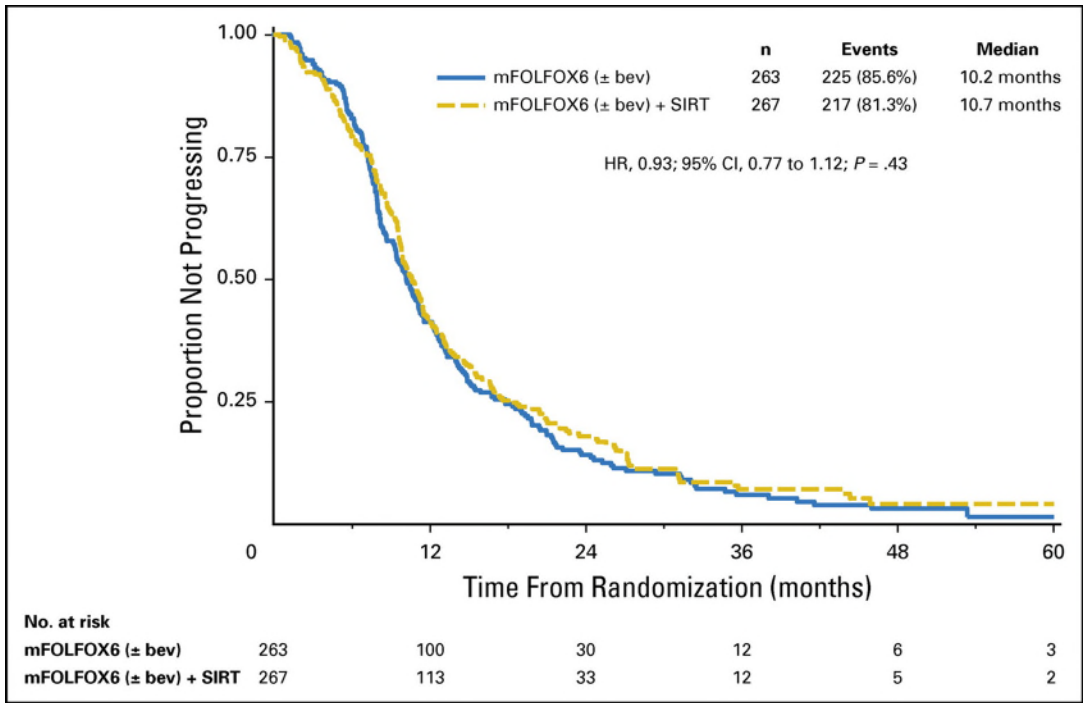
Y90 – SIRFLOX

(First Line)



Primary end point: PFS in the ITT population by independent centralized imaging review

Secondary end points:
- PFS in the liver
- Tumor response rate in the liver
- Tumor response rate at any site (RECIST 1.0)
- Liver resection rate
- Hepatic and extrahepatic recurrence rate
- Toxicity and safety (NCI CTCAE v3.0)
- Health-related quality of life
- Overall survival (in a preplanned combined analysis)

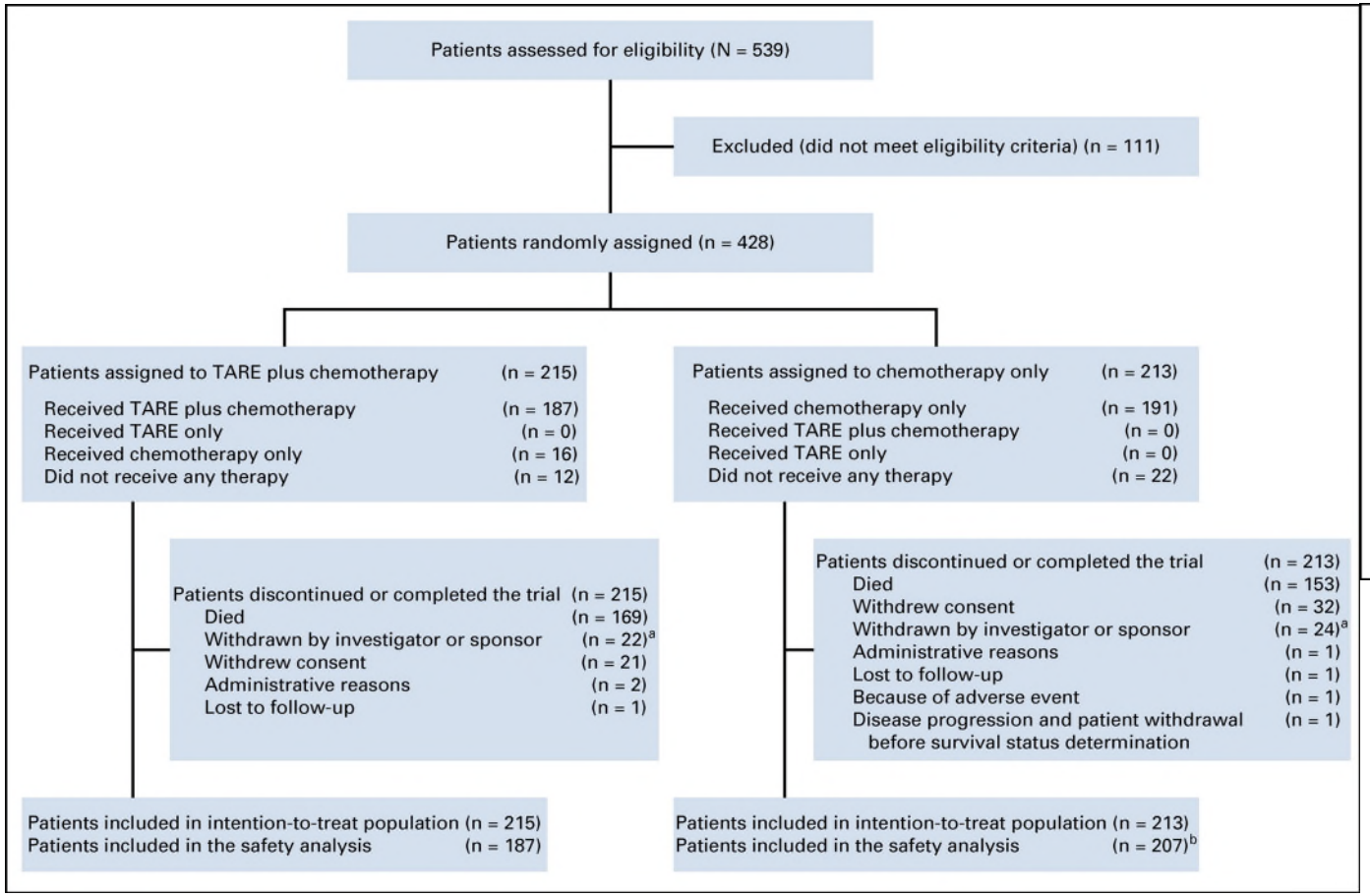


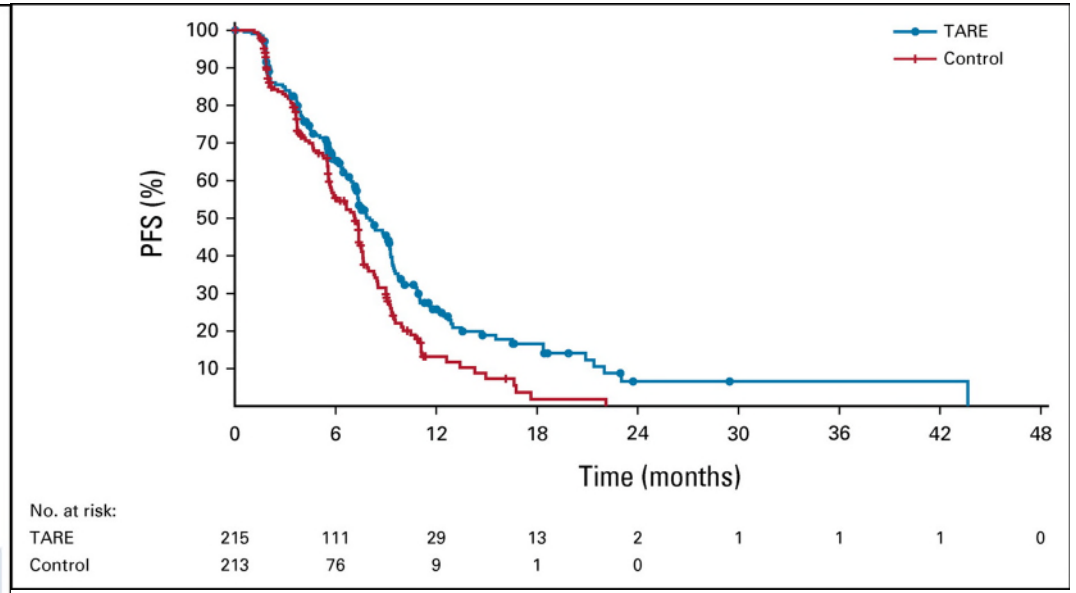
Median PFS at any site was similar for control and SIRT (10.2 versus 10.7 months, respectively; hazard ratio [HR], 0.93; 95% CI, 0.77 to 1.12; *P* = .43)

Hazel JCO 2016

Palliative Intent – Liver

Y90 – EPOCH (Second Line)





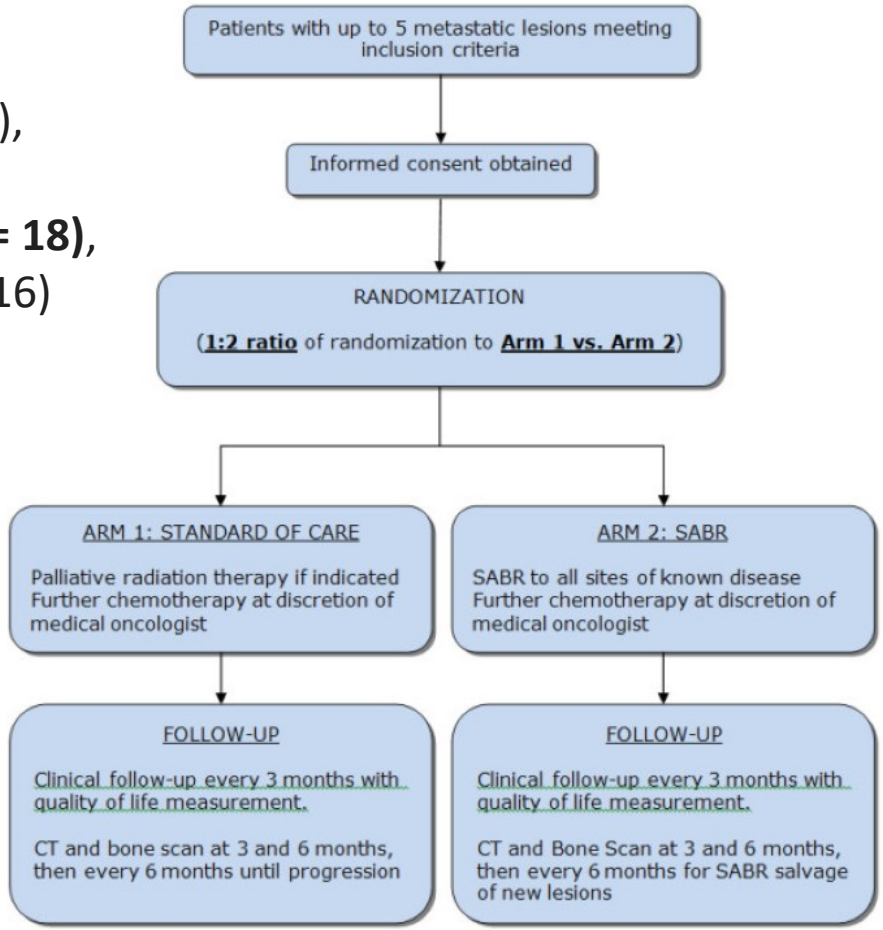
The HR for PFS was 0.69 (95% CI, 0.54 to 0.88; 1-sided *P* = .0013), with a median PFS of 8.0 and 7.2 months, respectively

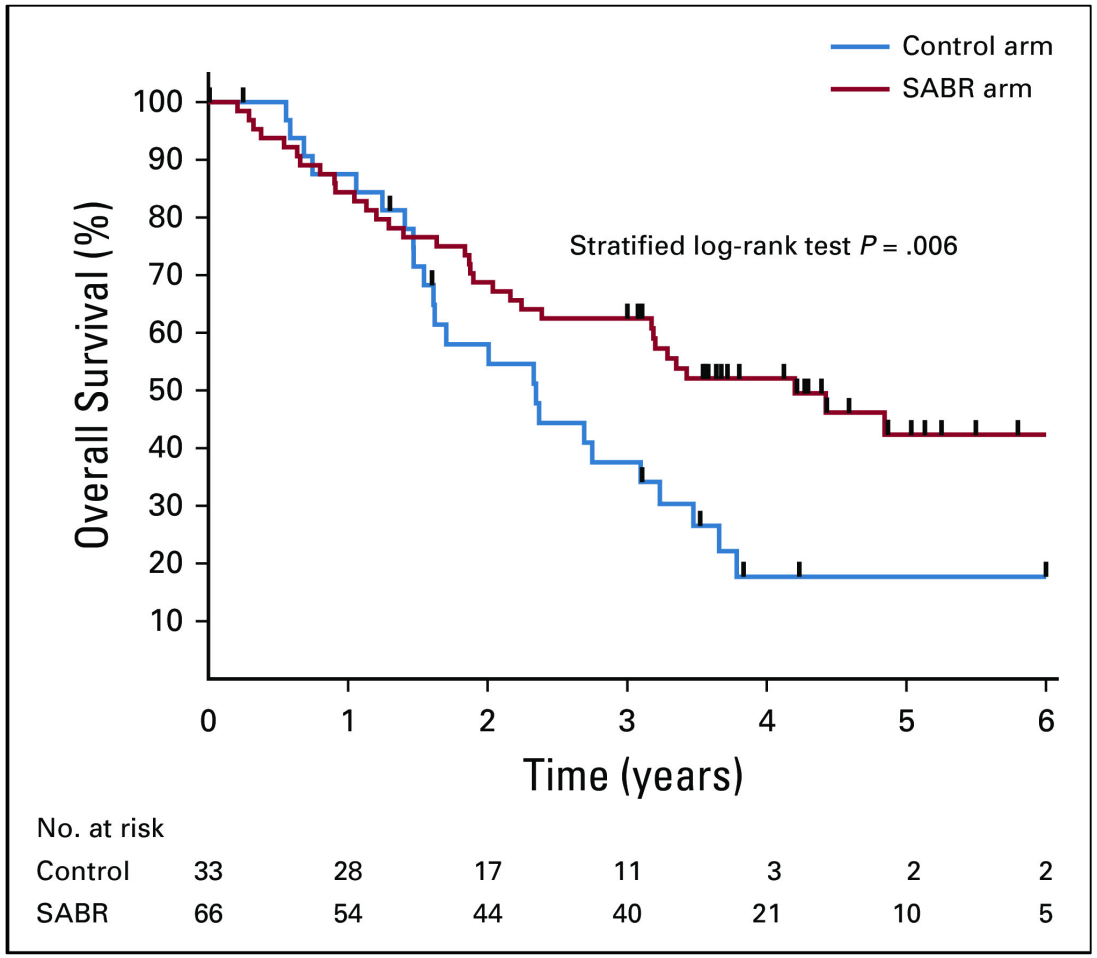
Mulcahy JCO 2021

Palliative Intent – Liver

SBRT –SABR-COMET

breast (n = 18),
lung (n = 18),
colorectal (n = 18),
prostate (n = 16)



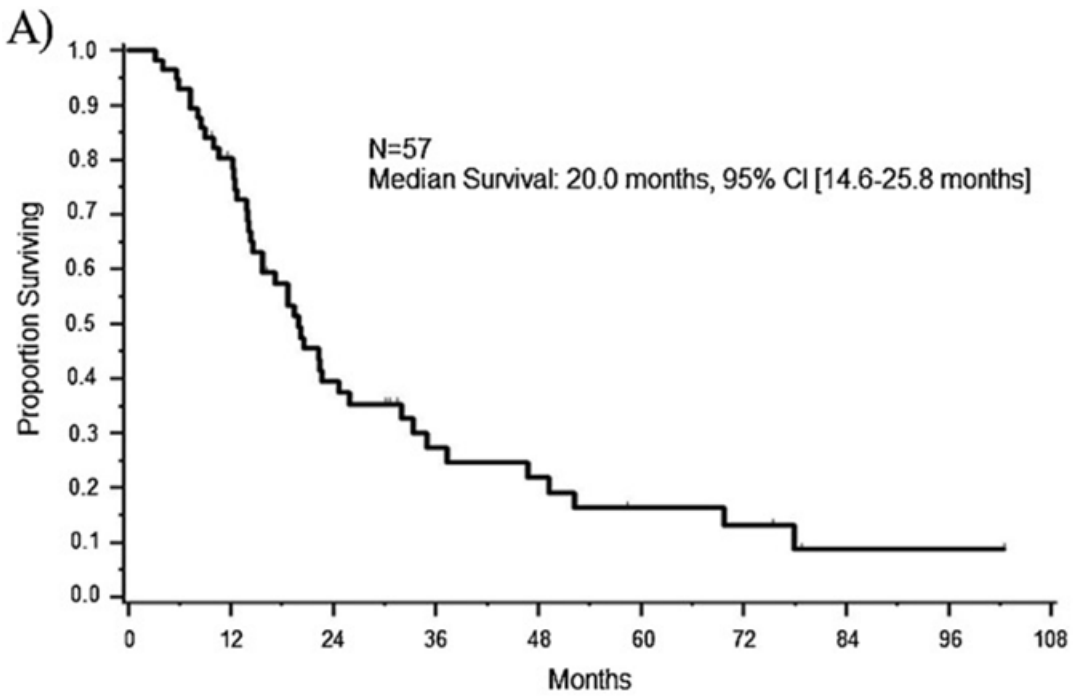


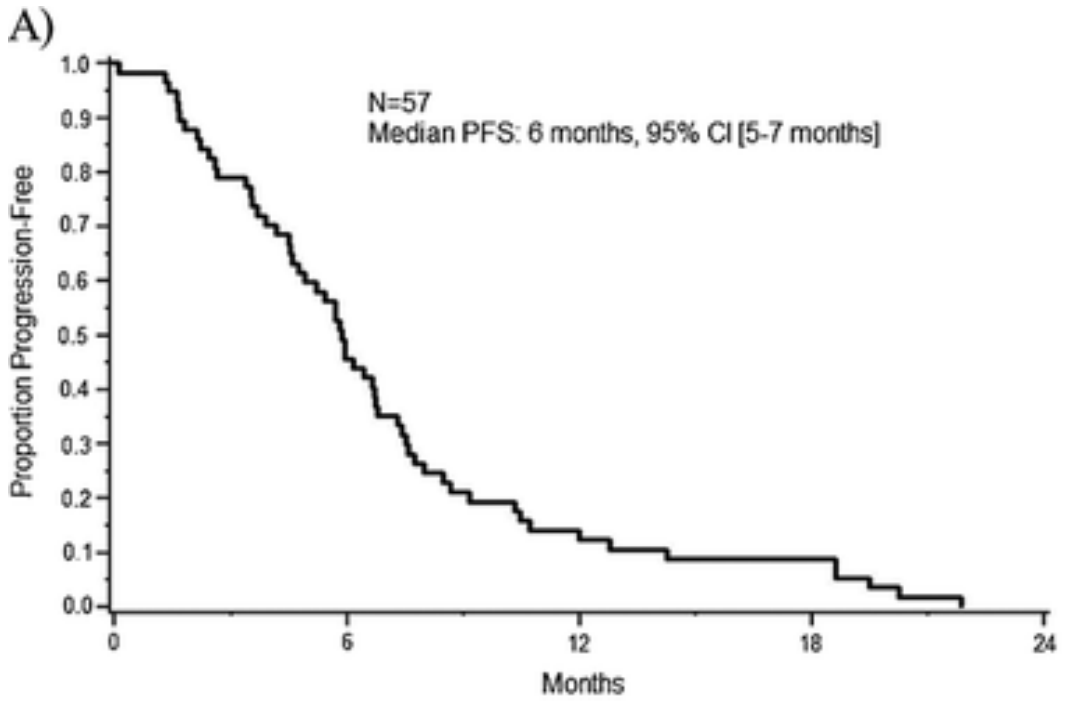
The 5-year OS rate was 17.7% in arm 1 (95% CI, 6% to 34%) versus 42.3% in arm 2 (95% CI, 28% to 56%; stratified log-rank *P* = .006)

Palliative Intent – Liver

HAIP –Chemotherapy Refractory - MSKCC

-Liver-limited or with minimal extrahepatic disease **(30% Response rate)**

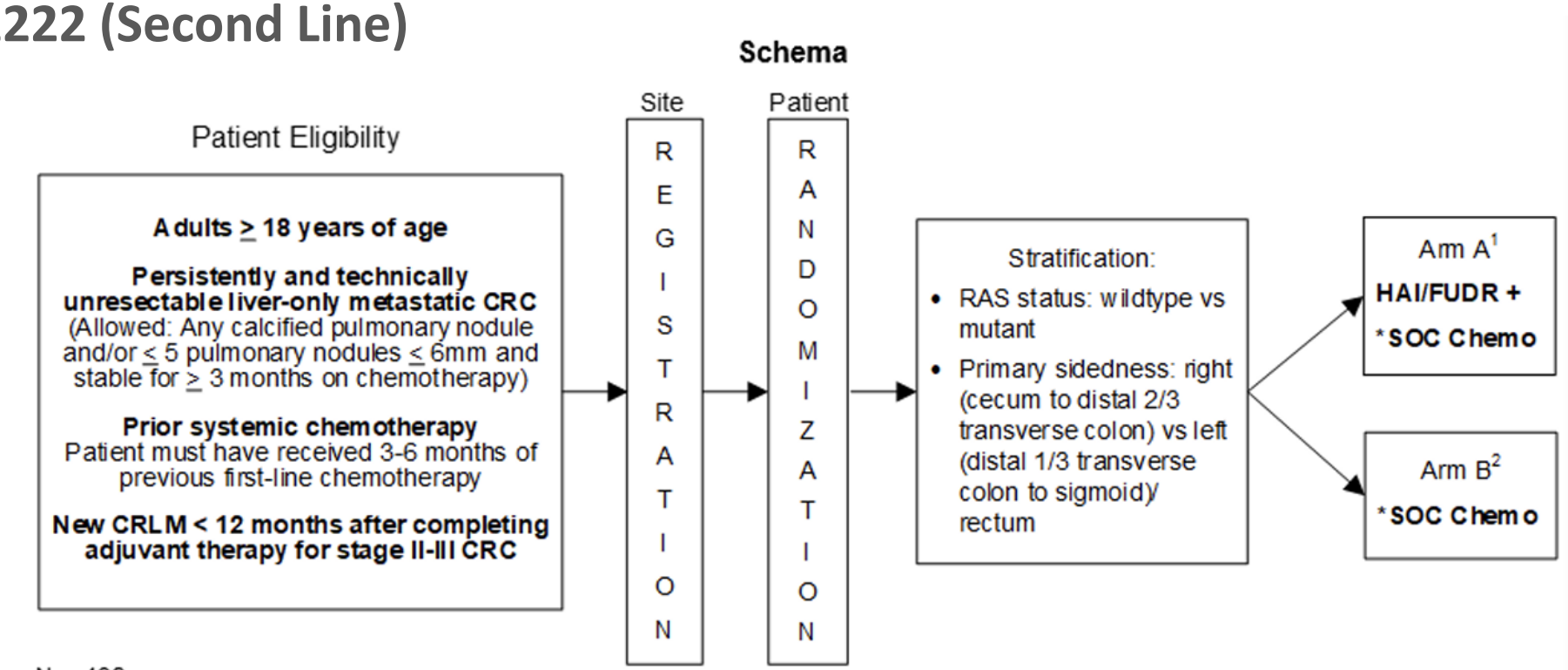




Cercek JSO 2016

Palliative Intent – Liver

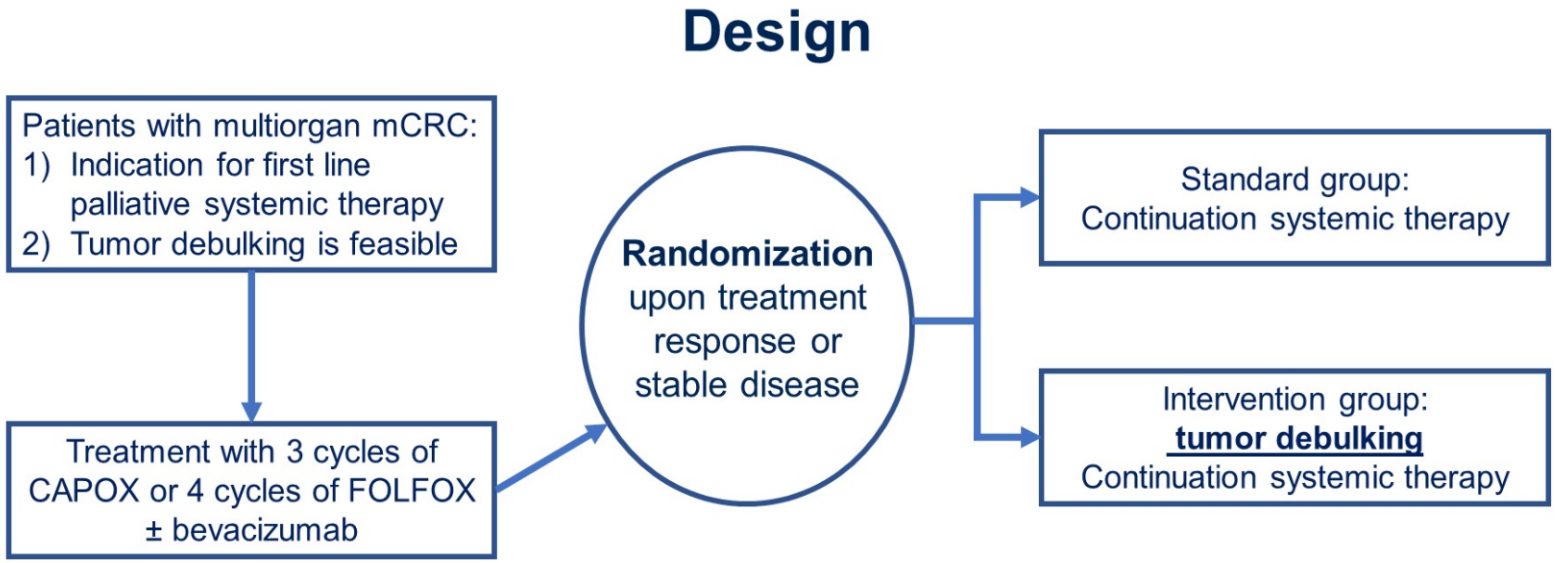
HAIP – EA2222 (Second Line)



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.

Palliative Intent – Debulking

ORCHESTRA TRIAL



Primary endpoint:	overall survival (OS)
Primary aim:	>6 months OS benefit
Patients needed for randomization:	382

Palliative Intent – Debulking

ORCHESTRA TRIAL

Main eligibility criteria

1) Metastases **in at least <u>two different</u> organs AND**:

    1) >1 extrahepatic metastases
    OR
    2) 1 extrahepatic metastasis if:
        - >5 hepatic metastases not located in one lobe *OR*
        - para-aortal lymph or celiac nodes *OR*
        - adrenal gland metastases *OR*
        - peritoneal/pleural carcinomatosis

2) Prior to start of systemic therapy **maximal tumor debulking is feasible**, defined as at least 80% of metastatic lesions

Palliative Intent – Debulking

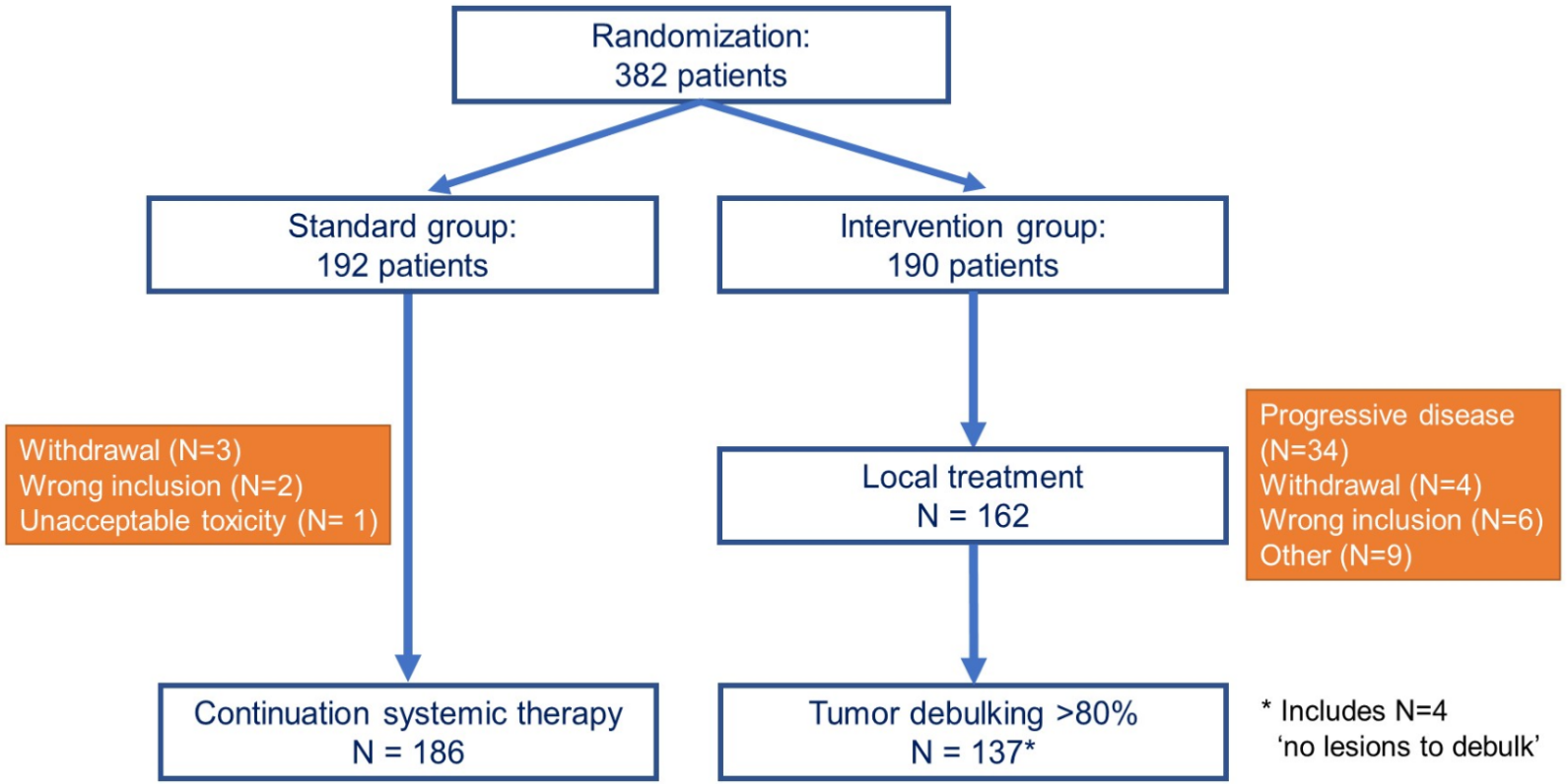
ORCHESTRA TRIAL

Metastatic pattern of randomized patients

		Standard N = 192	Intervention N = 190
>2 organs involved		72 (38)	74 (40)
Liver and lung only		81 (42)	86 (45)
Peritoneal disease present		63 (33)	60 (32)
Number of metastases	<5	76 (40)	67 (35)
(peritoneal excluded)	5-10	84 (44)	94 (50)
	>10	32 (17)	29 (15)

Palliative Intent – Debulking

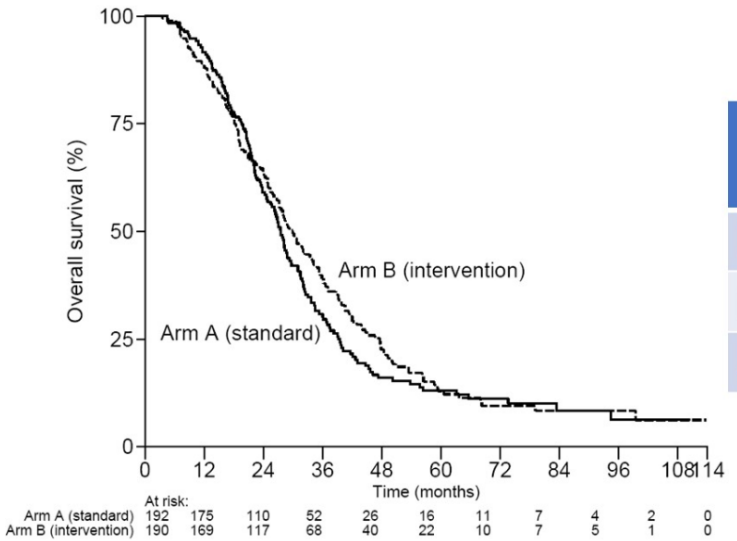
ORCHESTRA TRIAL



Palliative Intent – Debulking

ORCHESTRA TRIAL

Overall Survival (OS)



	Standard	Intervention
Nº of events	153	155
Median OS (months)	27.5	30.0
Adjusted HR 0.88 [95% CI 0.70-1.10] p=0.23		

Median FU 32.3 months

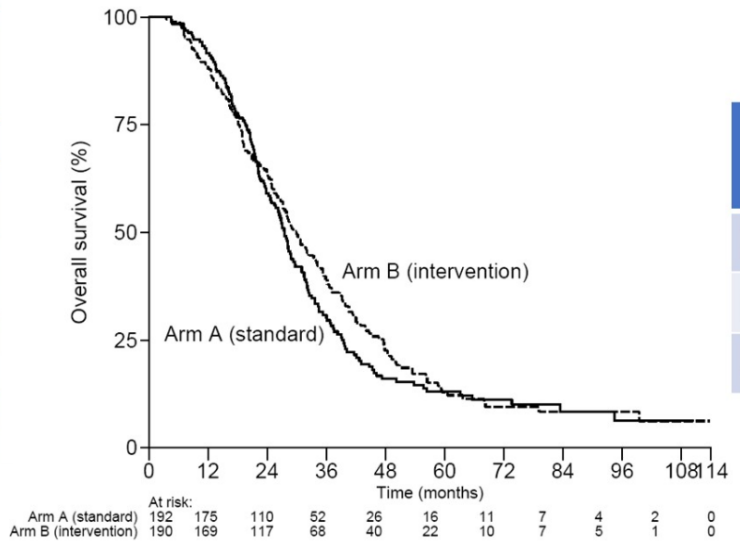
Palliative Intent – Debulking

ORCHESTRA TRIAL

Local treatment characteristics

Intervention group	N = 190 (%)
Tumor debulking >80%	137 (72)
Maximal (80-100%)	*64 (34)*
Radical (100%)	*73 (38)*
Local treatment	**N = 162 (%)**
One modality	74 (46)
Surgery only	*46 (28)*
Two modalities	70 (43)
Surgery and Radiotherapy	*36 (22)*
Three modalities *Surgery, RFA/MWA and Radiotherapy*	18 (11)
Complications Clavien Dindo >3a	41 (25)
Unplanned readmissions	18 (11)
90-day mortality	6 (4)

Overall Survival (OS)



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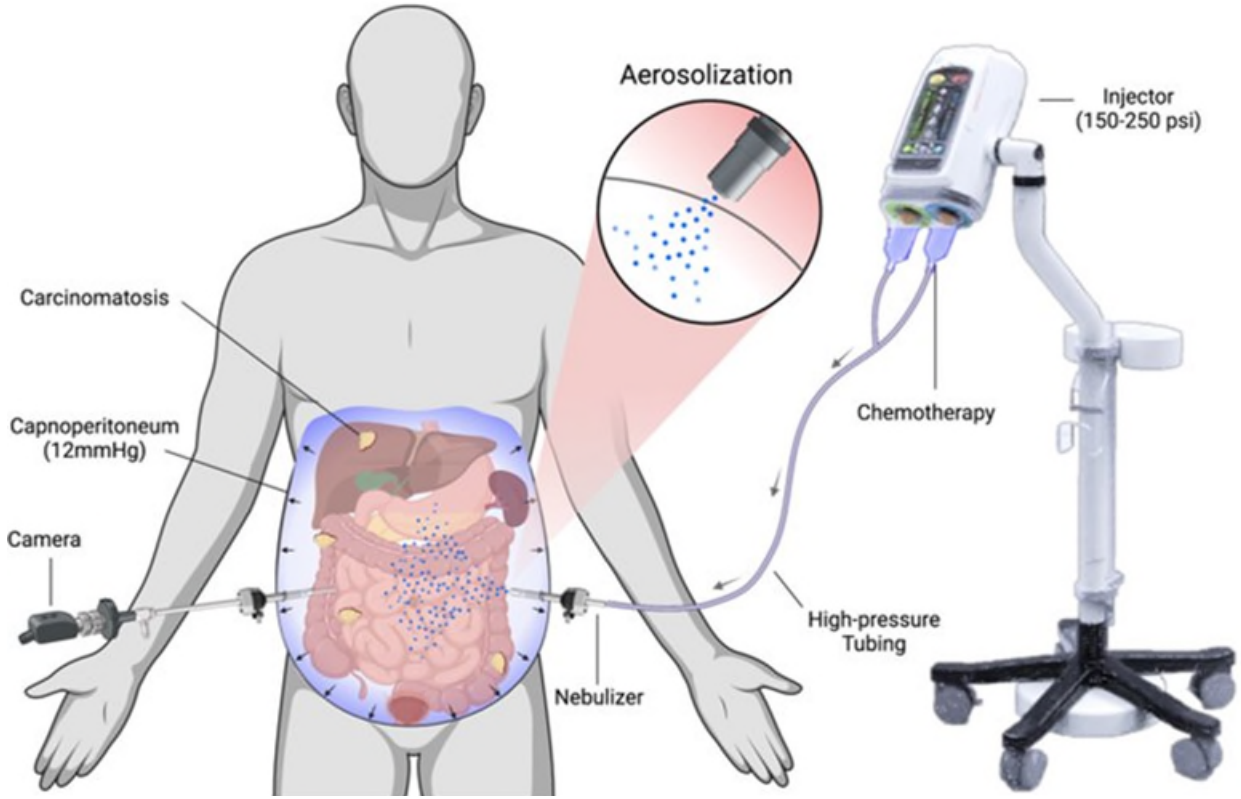
Median FU 32.3 months

Palliative-intent Debulking (>80%) approaches for disease involving 2 or more organs do not prolong survival

Palliative Intent – Peritoneum

PIPAC

- Minimally Invasive (Laparoscopic technique)
- Ambulatory Surgery
- Repeatable (64%)
- High-dose therapy delivered directly to the most threatening tumors
- High relative tumor penetration due to pressure
- Preserved or improved quality of life
- Encouraging clinical responses: Colorectal 71-86%
- Significant adverse events: 12-15%

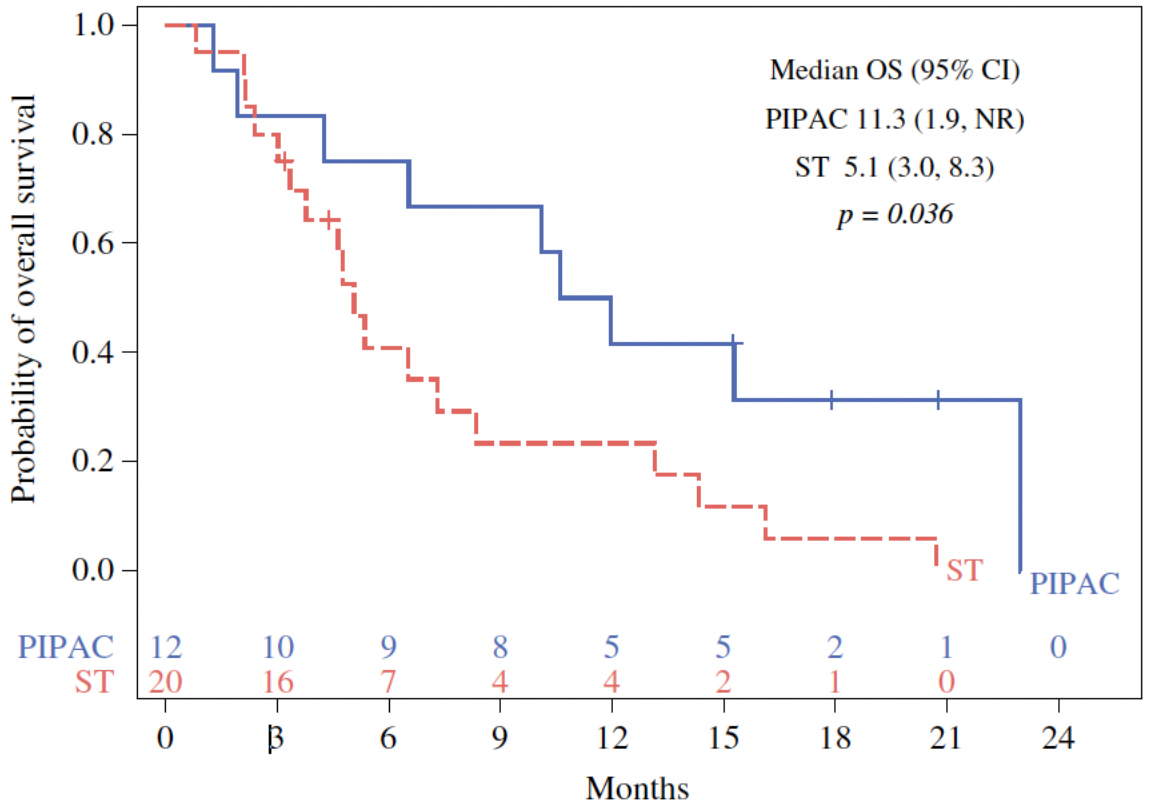


Raoof, ASO 2023; Alyami, Lancet Oncology 2019

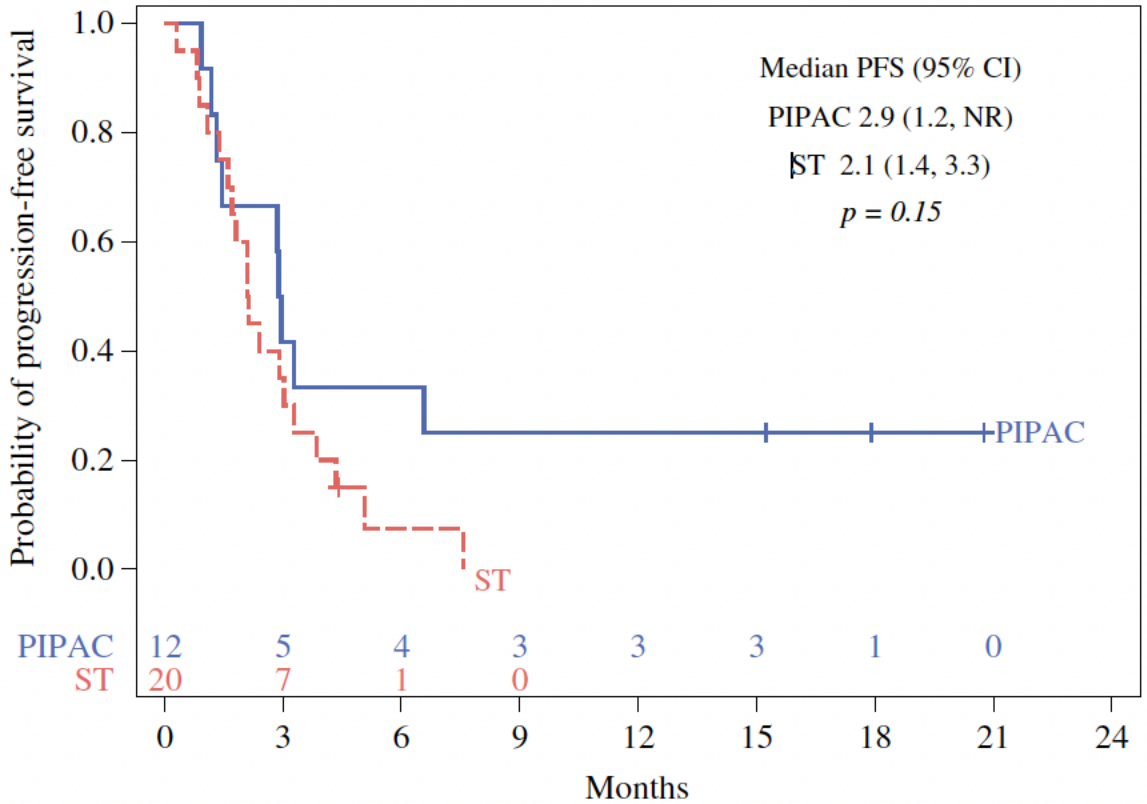
Palliative Intent – Peritoneum

PIPAC

OS



PFS

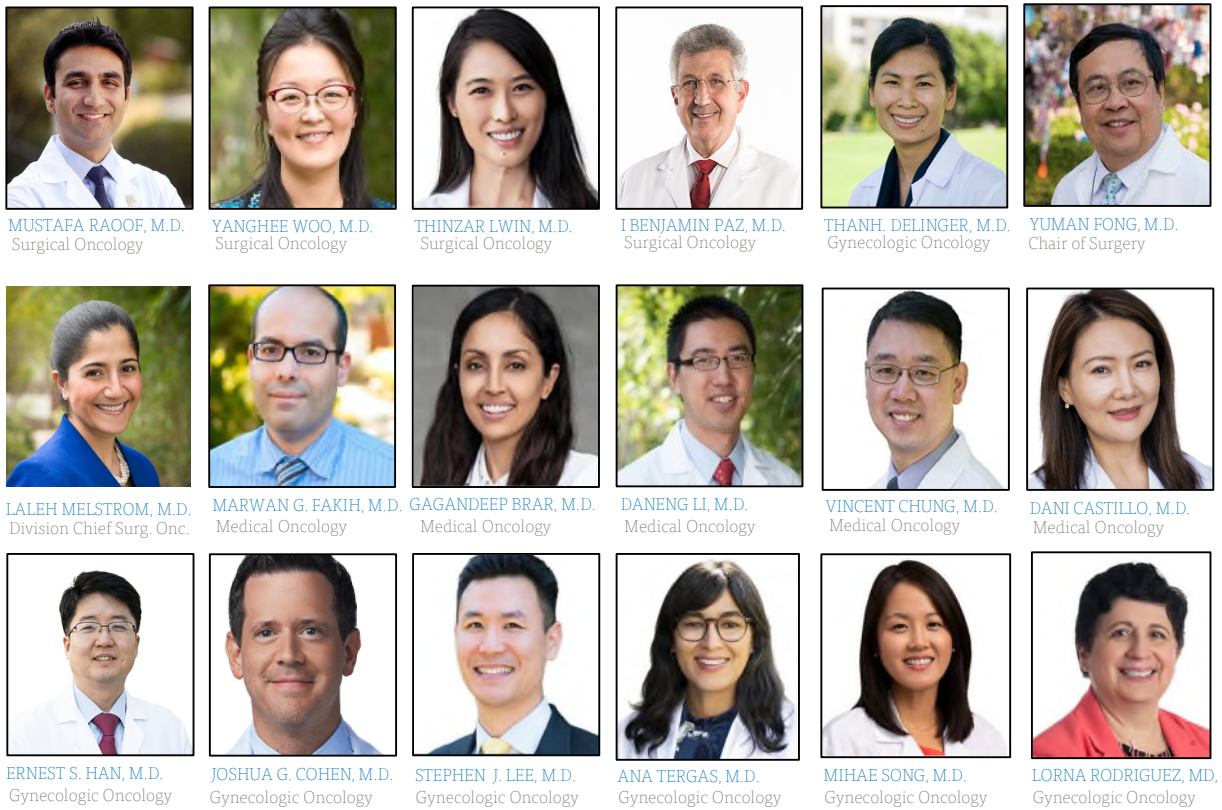


Raoof, ASO 2024

Take-home

- Liver
  - Liver resection should be considered in all patients with liver metastases
  - HAIP may improve survival in patients undergoing liver resection
  - Ablation is equivalent to resection, with potentially less morbidity
  - SBRT provides excellent local control, ideally suited for oligo-progressive disease
  - For liver-limited disease transplantation is a potentially curative option
  - Palliative: HAIP, Y90, SBRT are options for control of liver mets and may improve systemic therapy outcomes
- Peritoneum
  - Cytoreductive Surgery should be considered in all patients with peritoneum-limited disease
  - HIPEC should be performed only on clinical trials
  - Palliative: PIPAC is an emerging treatment for unresectable peritoneal metastases
- Debulking (not to be confused with complete cytoreduction) approaches do not prolong survival (ORCHESTRA)

COH PSM TEAM – "The Village"



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