City of Hope®

Multidisciplinary Approaches to Cancer Symposium

Young Onset Colorectal Cancer Tumor Board

Panelist:

Surgery: Andreas M. Kaiser, MD & Mustafa Raoof, MD

Medical Oncology: Marwan Fakih, MD & Pashtoon Murtaza Kasi, MD, MS

Interventional Radiology: Jonathan Kessler, MD

Radiation Oncology: Yufei Liu, MD, PhD

Panel & Disclosures

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Professor of Surgery
Chief, Division of Colorectal Surgery
City of Hope National Medical Center (NCI-CCC)

- *No relevant financial relationships*

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- *Grant Research Support from Exact Sciences*

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Judy and Bernard Briskin Distinguished Director in Clinical Research Associate
Director for Clinical Sciences
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This presentation and/or comments will be free of any bias toward or promotion of the above referenced company 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.

Panel & Disclosures

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City of Hope

- *Consultant for Agenus, Astellas, AstraZeneca, Bayer, BostonGene, Daiichi Sankyo, Eli Lilly, Elicio Therapeutics, Foundation Medicine, Guardant Health, Illumunia, Merck, Natera, Neogenomics, Regeneron, SAGA Diagnostics, SeaGen, Taiho, Tempus, & Xilio; Founder of Precision BioSciences; Grant/Research for Agenus, Merck, & Novartis; and Scientific Board Advisor for Elicio Therapeutics*

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Assistant Professor, Department of Radiation Oncology
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- *No relevant financial relationships*

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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:

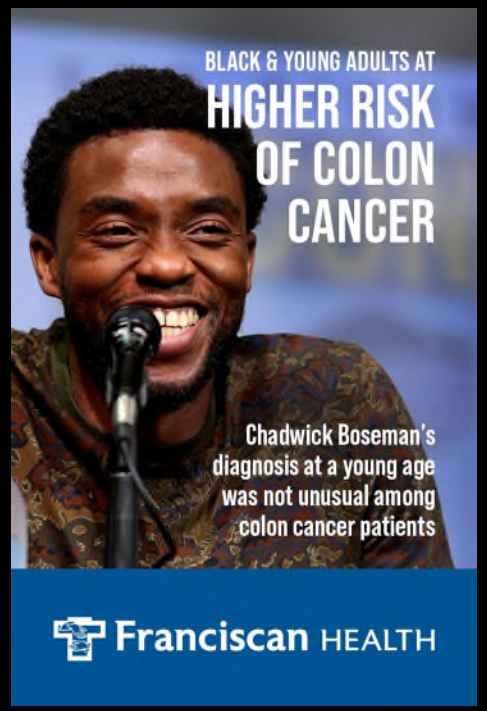
- *Utility of ctDNA testing/liquid biopsies across cultures, and in terms of young onset colorectal cancer, assessing/weighing its impact across patients from all backgrounds. Highlighting commonalities and differences among individuals in this patient population. And challenges and needs that would be appropriate to address.*
- *Highlighting disparities and access when it comes to young onset colorectal cancer. Moderate with eye on various populations*

SECTIONS HOME SEARCH

The New York Times

WELL | LIVE

More Young People Are Dying of Colon Cancer



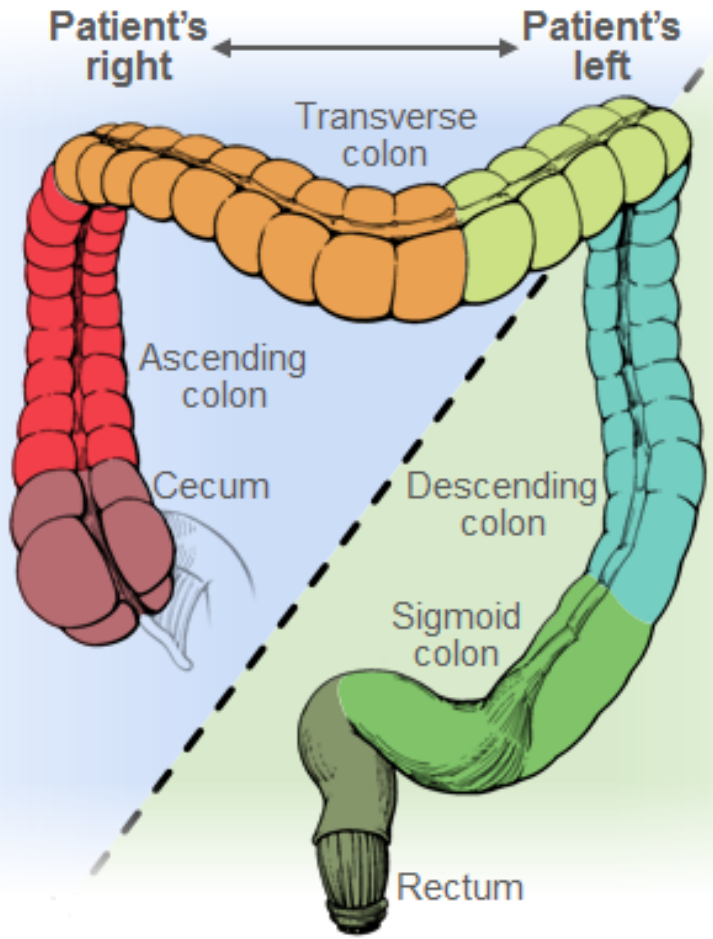
RIGHT vs. LEFT

MIDGUT DERIVATIVE

- ↑ females
- ↑ sessile serrated lesions
- ↑ mucinous tumors

Overall WORSE prognosis

- ↑ CIMP-high
- ↑ BRAF
- ↑ MSI-high
- ↑ CMS-1-MSI immune tumors
- ↑ CMS-3-metabolic tumors
  (↑ KRAS)



HINDGUT DERIVATIVE

- ↑ males

Overall BETTER prognosis

- ↑ CMS-4-MSI mesenchymal
- ↑ CMS-2-canonical distally
- ↑ TP53
- ↑ APC

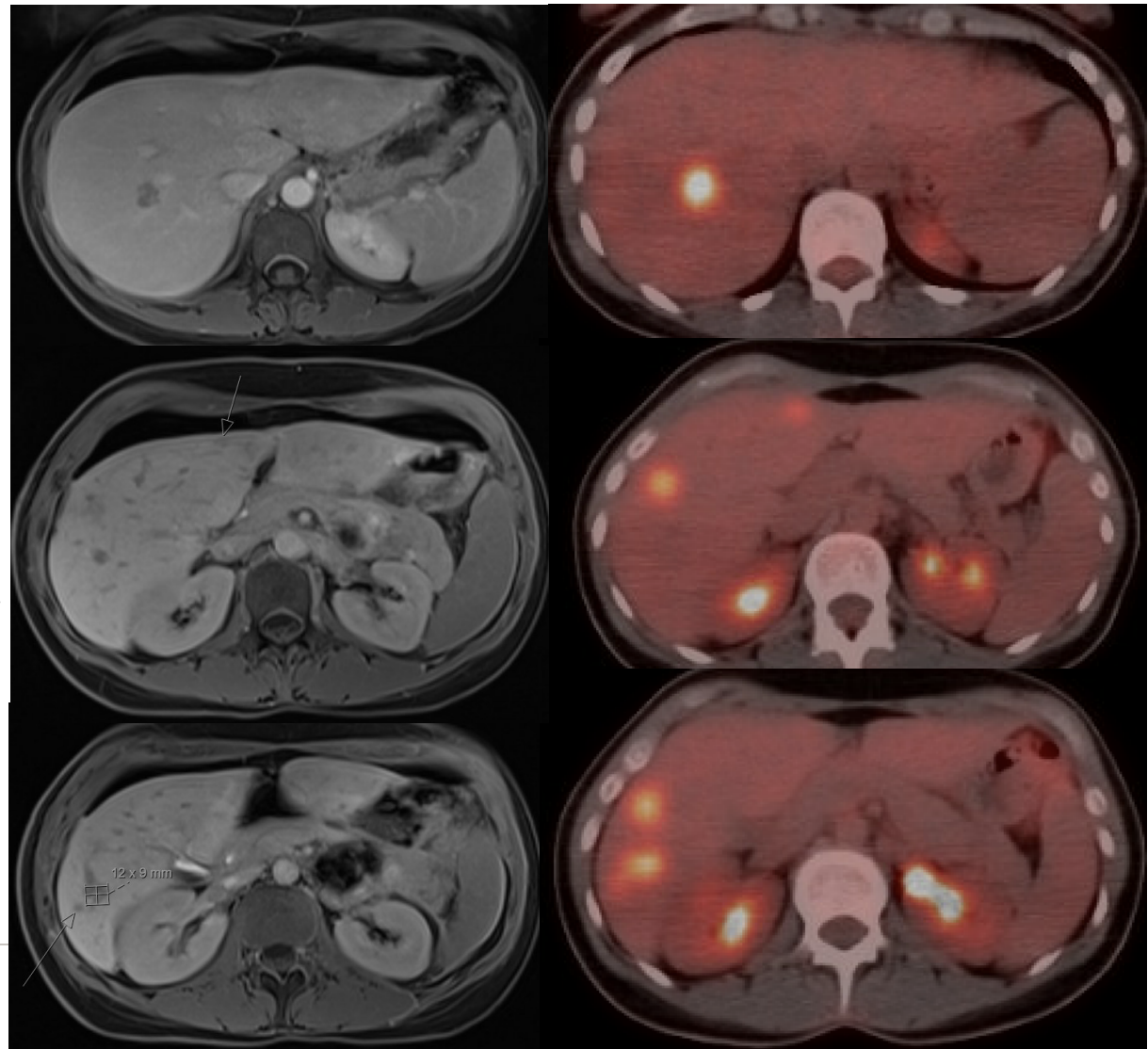
@pashtoonkasi

Kasi PM et al. Colorectal Cancer. Lancet Oct 2019.

1 Case 1 – 36-year-old lady – post-partum

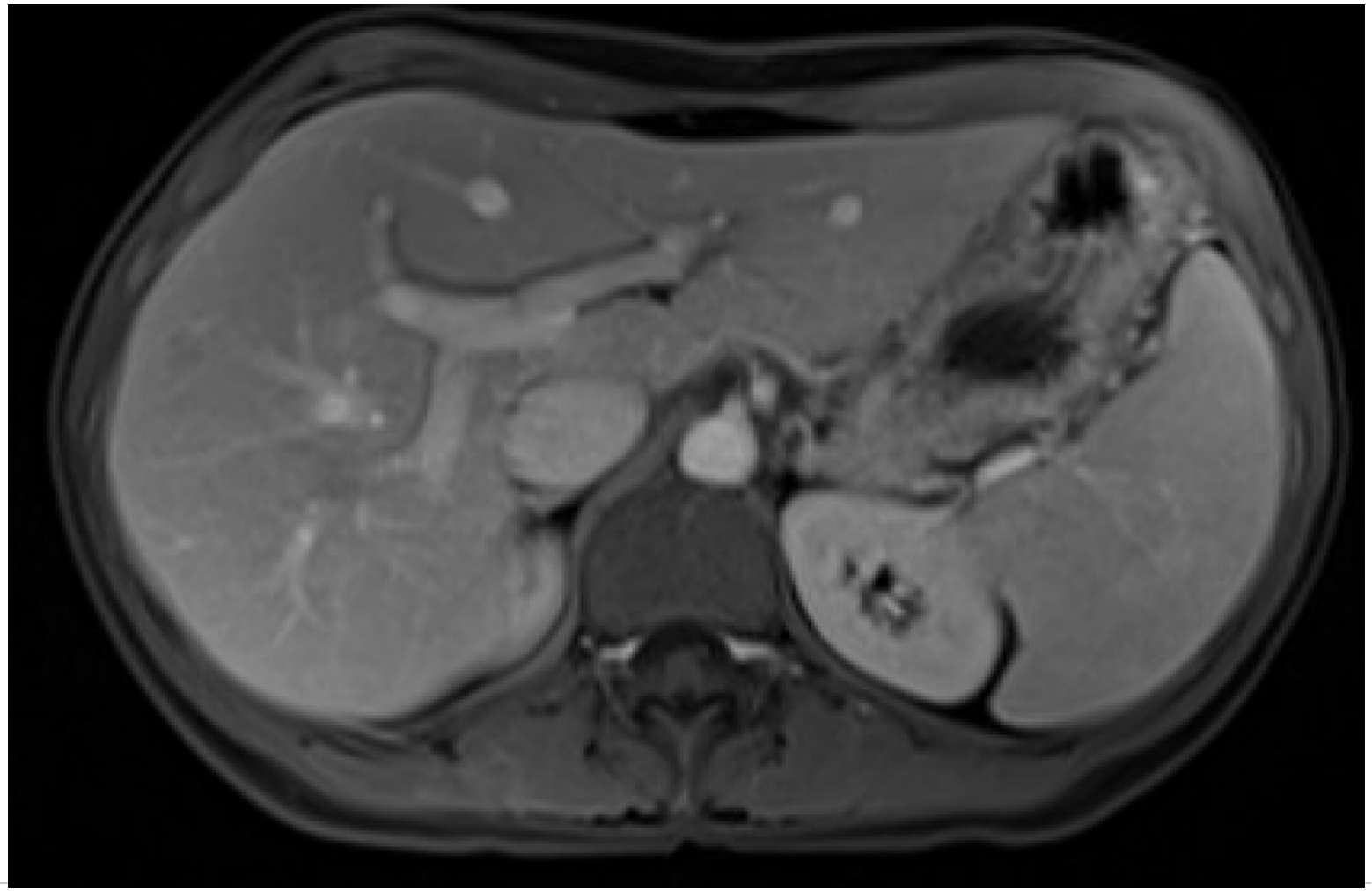
- Rectal bleeding attributed to hemorrhoids
- Prenatal testing 'inconclusive' – some concerns raised
- Obstruction/resection of sigmoid primary pT3N2 (7/18 lymph nodes +)
- Liver only metastases
- pMMR/MSS/low TMB
- RAS/RAF-wild-type

- *A 1.4 x 1.3 cm lesion in the inferior right liver*
- *A 1.4 x 0.7 cm lesion is detected in the posterior aspect of the inferior right liver (segment 6).*
- *There is an adjacent 0.5 cm lesion.*
- *A subtle 0.7 cm lesion is detected along the anterior aspect of the left liver (segment IVb).*
- *A 1.3 x 1.1 cm lesion is detected in the central right liver.*



1 Case 1 – 36-year-old lady – post-partum

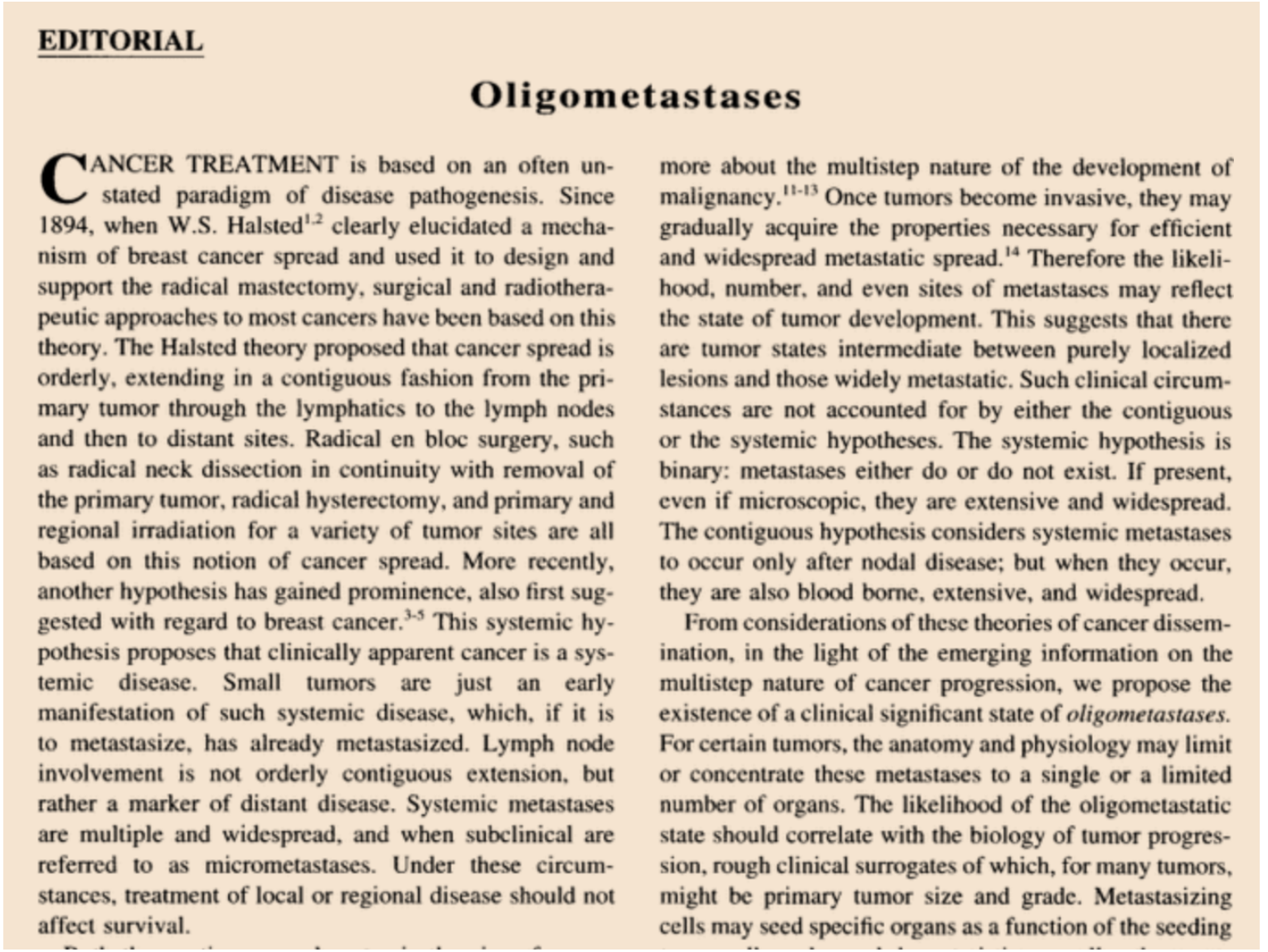
- Liver only metastases
- "Disappearing metastases"



Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

"Oligo"-metastases

Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol*. 1995;13(1):8-10.



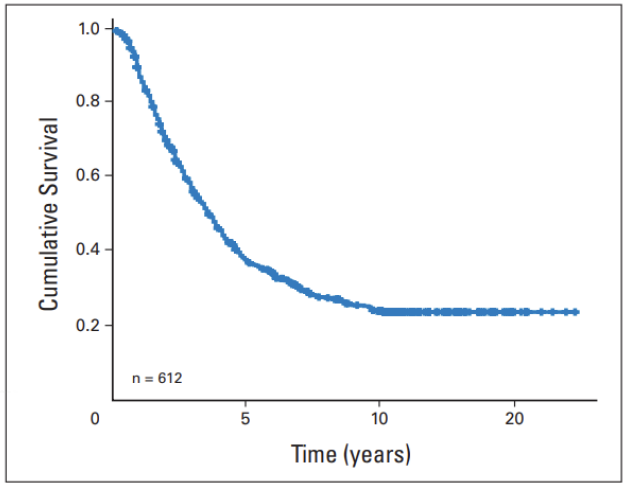
EDITORIAL

Oligometastases

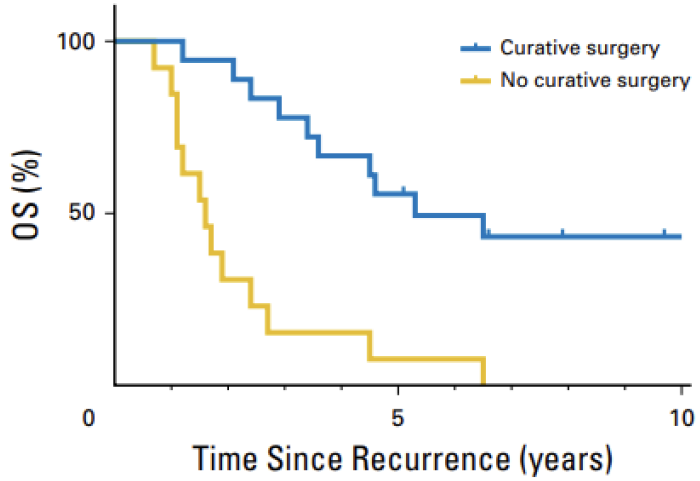
CANCER TREATMENT is based on an often unstated paradigm of disease pathogenesis. Since 1894, when W.S. Halsted[1,2] clearly elucidated a mechanism of breast cancer spread and used it to design and support the radical mastectomy, surgical and radiotherapeutic approaches to most cancers have been based on this theory. The Halsted theory proposed that cancer spread is orderly, extending in a contiguous fashion from the primary tumor through the lymphatics to the lymph nodes and then to distant sites. Radical en bloc surgery, such as radical neck dissection in continuity with removal of the primary tumor, radical hysterectomy, and primary and regional irradiation for a variety of tumor sites are all based on this notion of cancer spread. More recently, another hypothesis has gained prominence, also first suggested with regard to breast cancer.[3-5] This systemic hypothesis proposes that clinically apparent cancer is a systemic disease. Small tumors are just an early manifestation of such systemic disease, which, if it is to metastasize, has already metastasized. Lymph node involvement is not orderly contiguous extension, but rather a marker of distant disease. Systemic metastases are multiple and widespread, and when subclinical are referred to as micrometastases. Under these circumstances, treatment of local or regional disease should not affect survival.

more about the multistep nature of the development of malignancy.[11-13] Once tumors become invasive, they may gradually acquire the properties necessary for efficient and widespread metastatic spread.[14] Therefore the likelihood, number, and even sites of metastases may reflect the state of tumor development. This suggests that there are tumor states intermediate between purely localized lesions and those widely metastatic. Such clinical circumstances are not accounted for by either the contiguous or the systemic hypotheses. The systemic hypothesis is binary: metastases either do or do not exist. If present, even if microscopic, they are extensive and widespread. The contiguous hypothesis considers systemic metastases to occur only after nodal disease; but when they occur, they are also blood borne, extensive, and widespread.

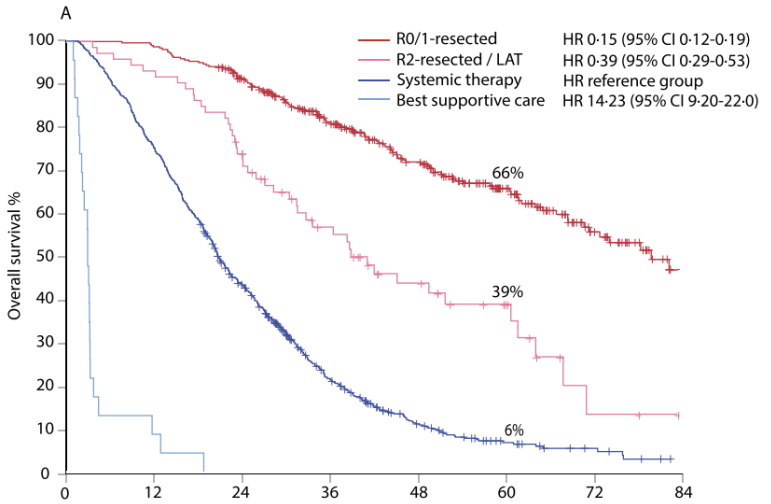
From considerations of these theories of cancer dissemination, in the light of the emerging information on the multistep nature of cancer progression, we propose the existence of a clinical significant state of *oligometastases*. For certain tumors, the anatomy and physiology may limit or concentrate these metastases to a single or a limited number of organs. The likelihood of the oligometastatic state should correlate with the biology of tumor progression, rough clinical surrogates of which, for many tumors, might be primary tumor size and grade. Metastasizing cells may seed specific organs as a function of the seeding



JCO 2007



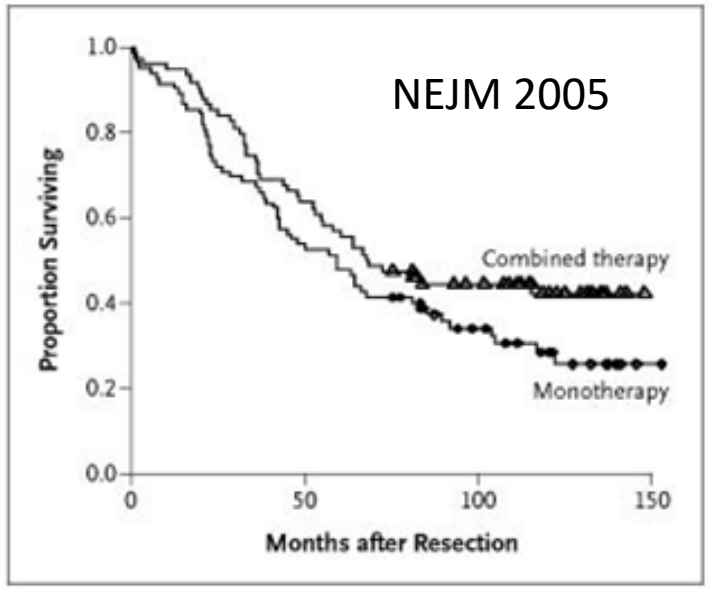
JCO 2017

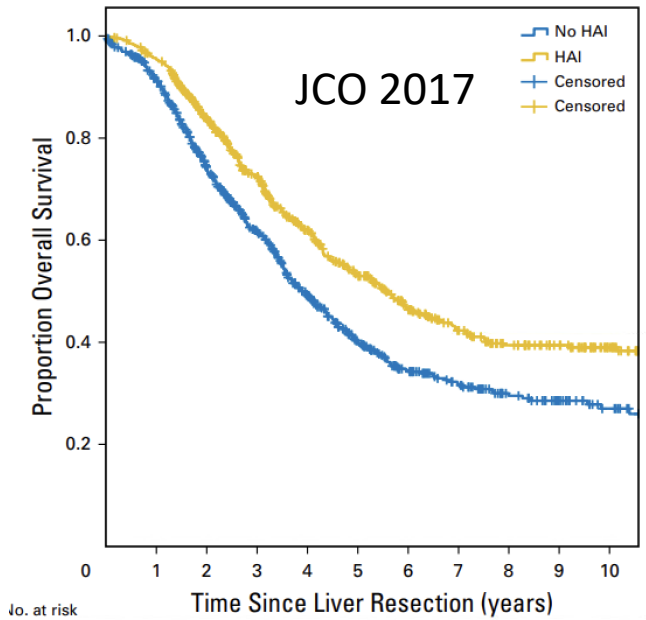


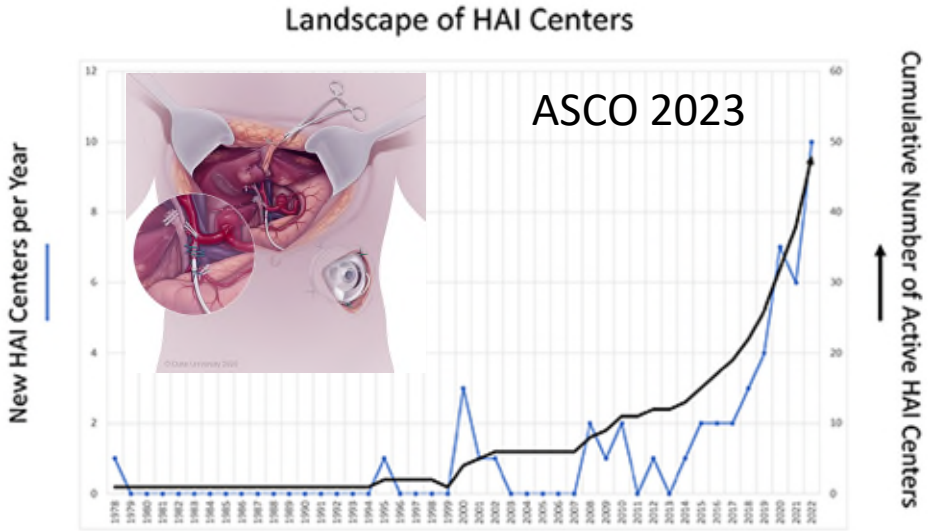
Lancet Reg Health Eur 2021

Surgery

Surgery + HAI (adjuvant)

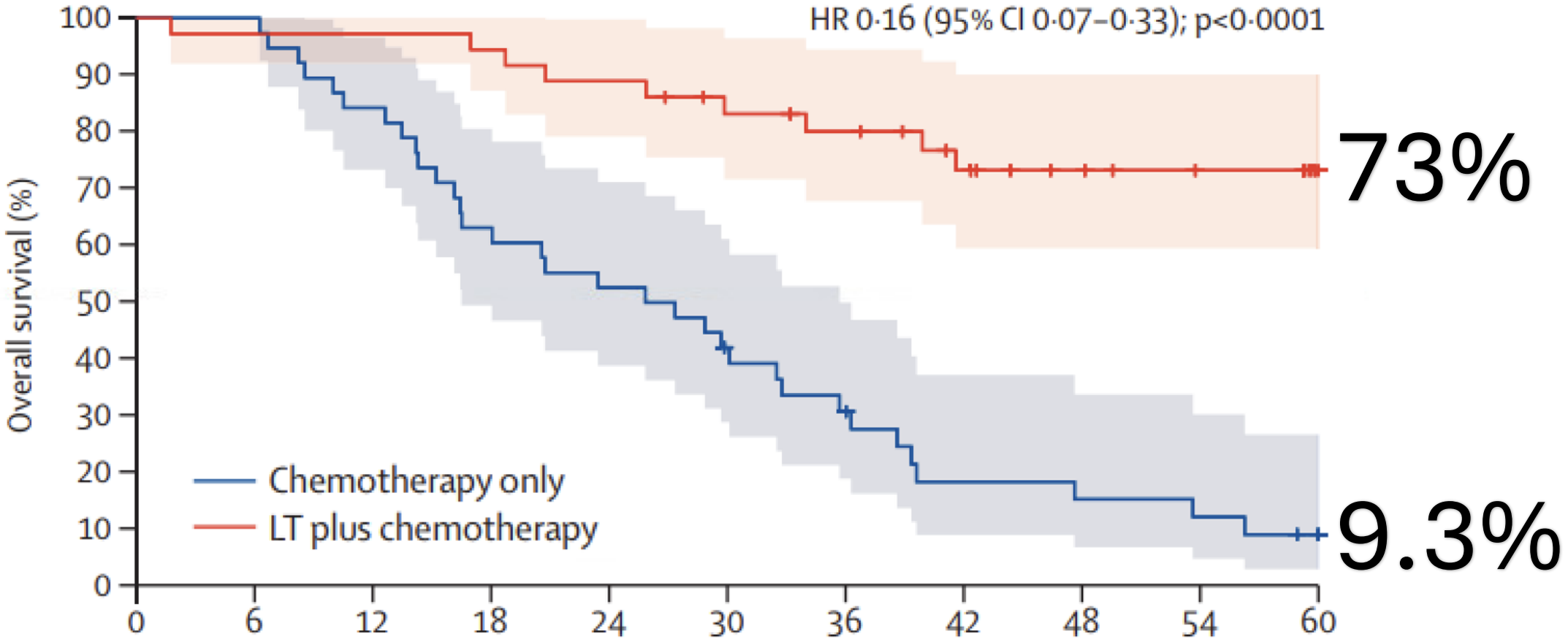






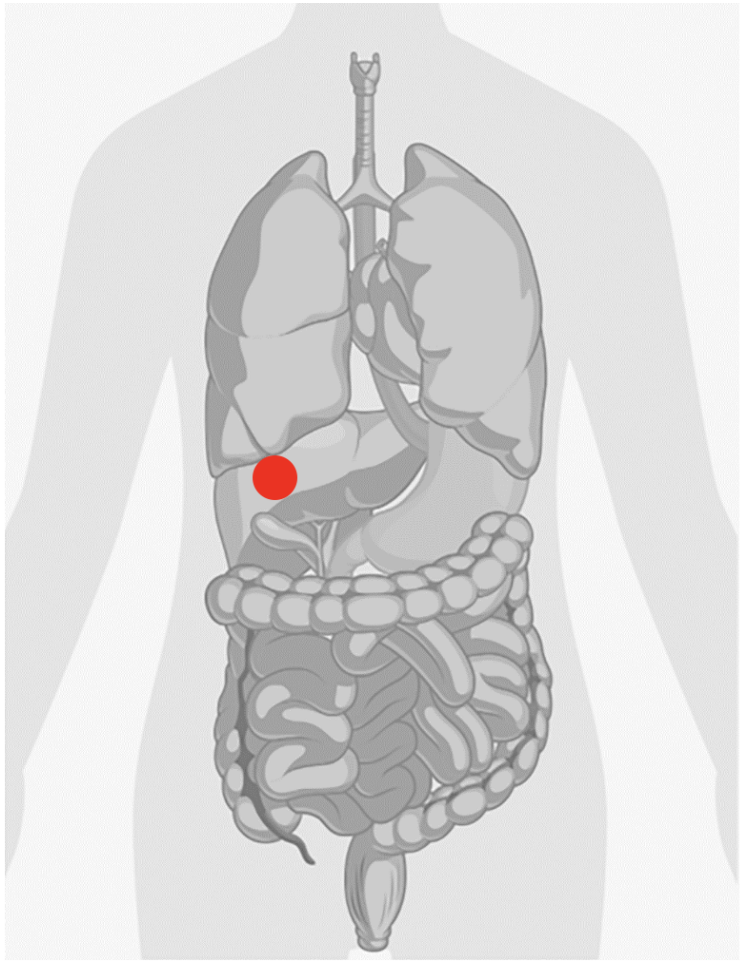
EA2222 - A Randomized Phase III Study of Systemic Therapy With or Without Hepatic Arterial Infusion for Unresectable Colorectal Liver Metastases: The PUMP Trial. PI: Dr. Michael Lidsky

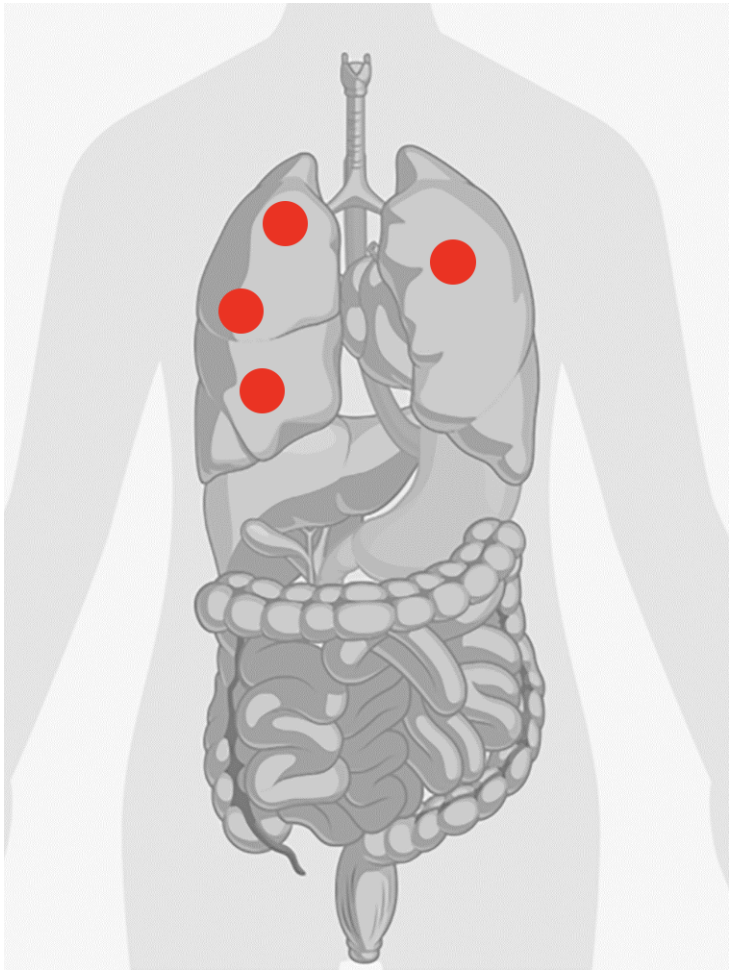
TransMet Trial: Liver transplantation

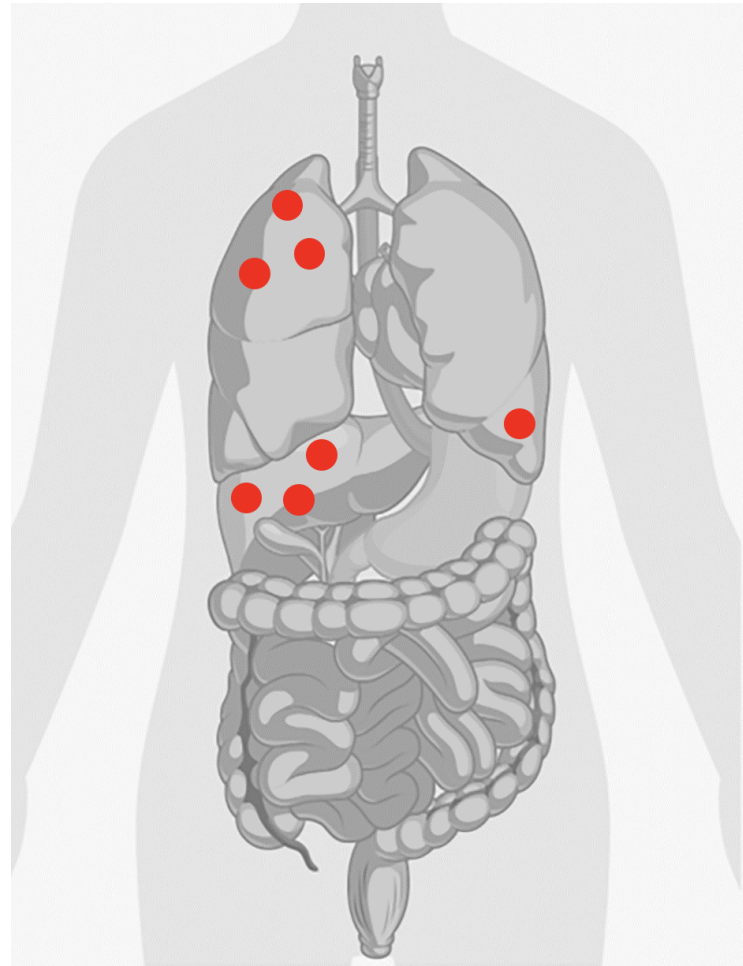


Liver transplantation plus chemotherapy versus chemotherapy alone in patients with permanently unresectable colorectal liver metastases (TransMet): results from a multicentre, open-label, prospective, randomised controlled trial. Lancet. 2024 Sep 21;404(10458):1107-1118.

“Oligo”-metastatic

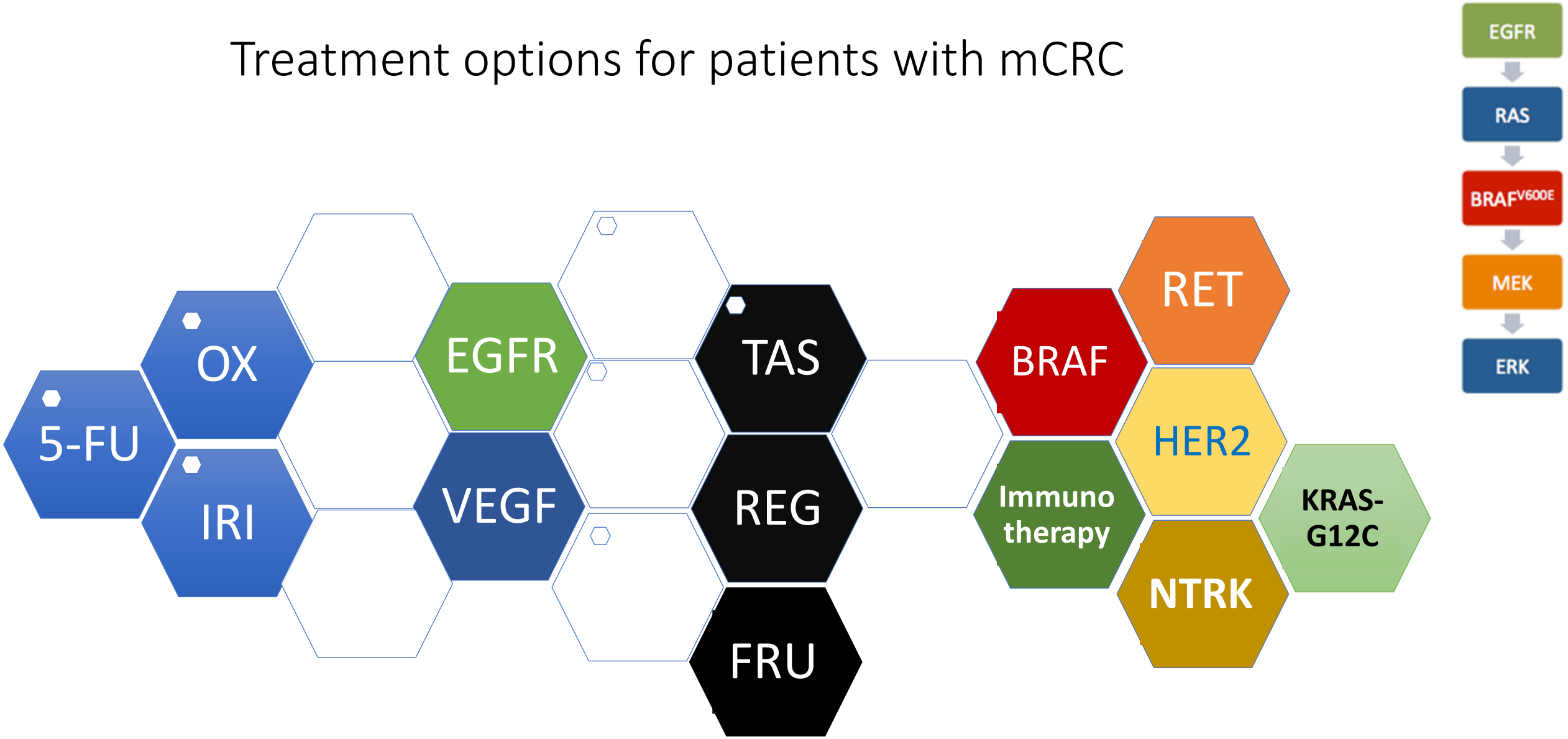






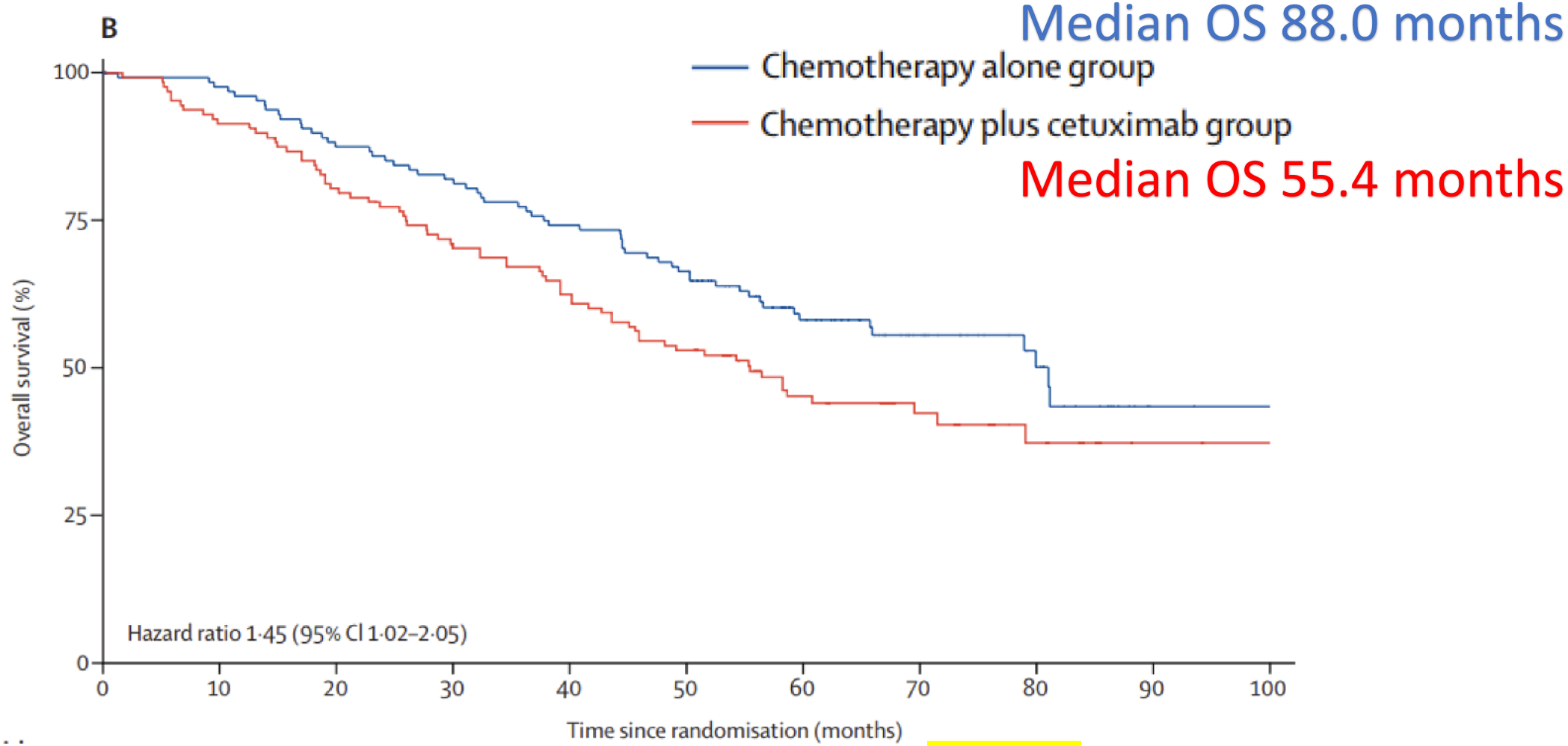
A Pragmatic Randomized Phase III Trial Evaluating Total Ablative Therapy for Patients with Limited Metastatic Colorectal Cancer: Evaluating Radiation, Ablation, and Surgery (ERASur Trial) A022101/NRG-GI009. PI: Dr. Eric Miller.

Treatment options for patients with mCRC



Kasi PM et al. Colorectal Cancer. Lancet Oct 2019.

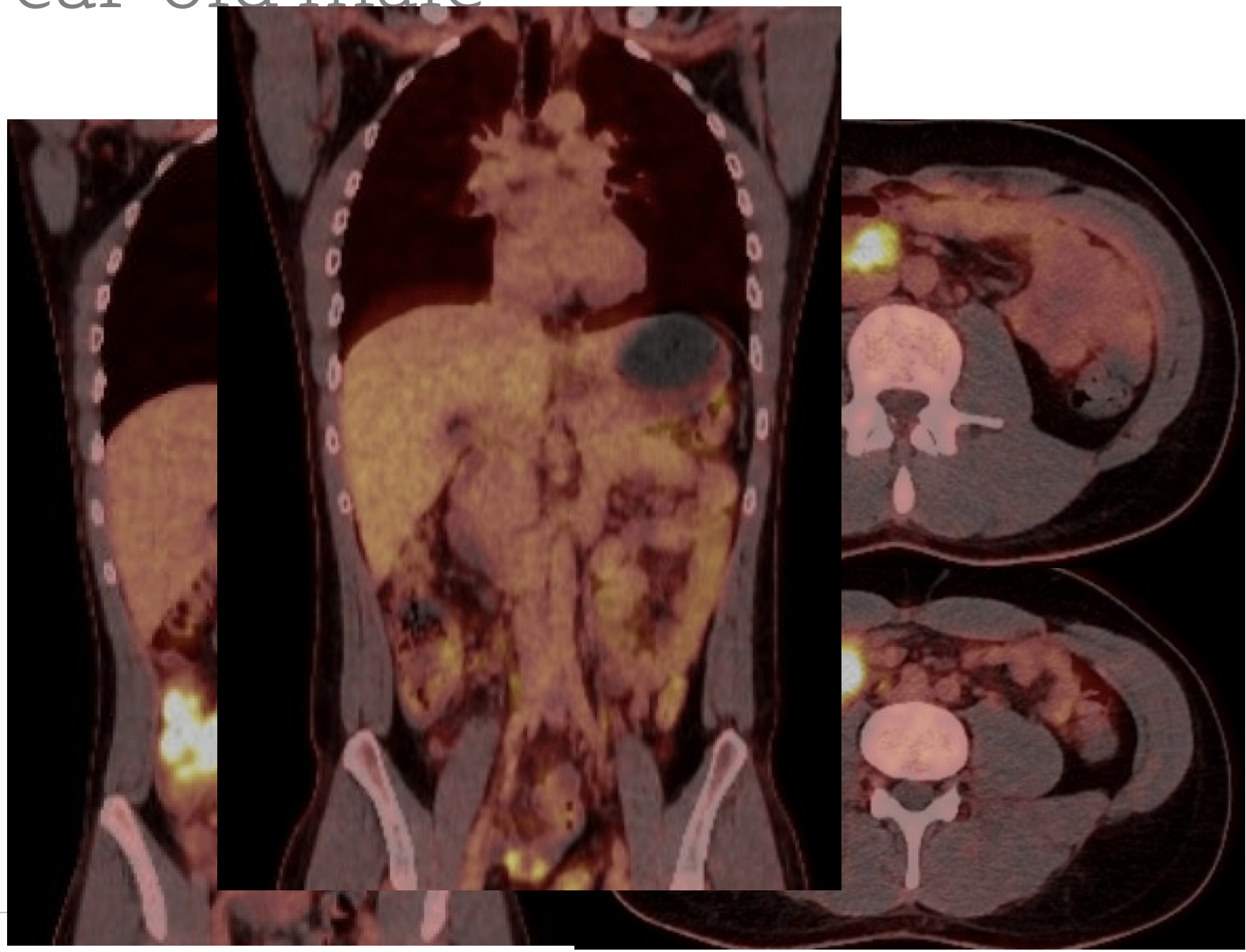
Systemic chemotherapy with or without cetuximab in patients with **resectable** colorectal liver metastasis - New EPOC Trial



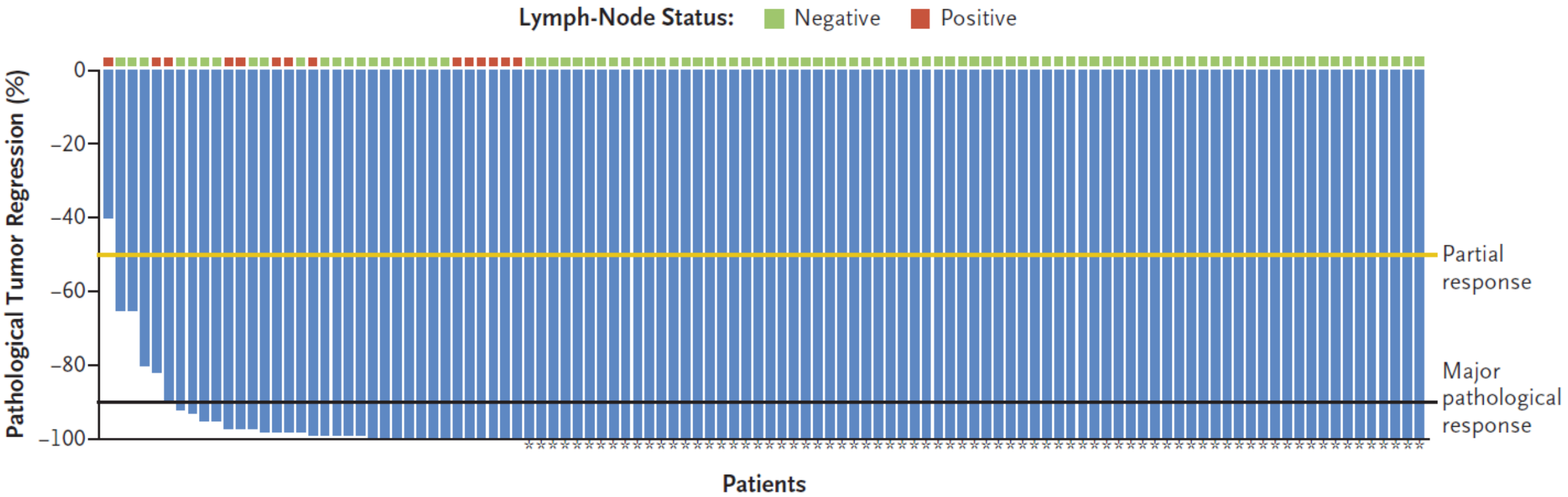
Bridgewater JA. Systemic chemotherapy with or without cetuximab in patients with **resectable** colorectal liver metastasis (New EPOC): long-term results of a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2020;21(3):398-411.

2 Case 2 – 32-year-old male

- Strong family history; mother with endometrial cancer
- Maternal Uncles with early-onset colorectal cancer
- Right-side colon cancer
- Loss of nuclear expression for MLH1 and PMS2
- POSITIVE - Pathogenic variant identified in the *MLH1* gene called p.S685F (c.2054C>T), previously identified in relatives



NICHE-2



Chalabi M. Neoadjuvant Immunotherapy in Locally Advanced Mismatch Repair-Deficient Colon Cancer. N Engl J Med. 2024 Jun 6;390(21):1949-1958. PMID: 38838311.

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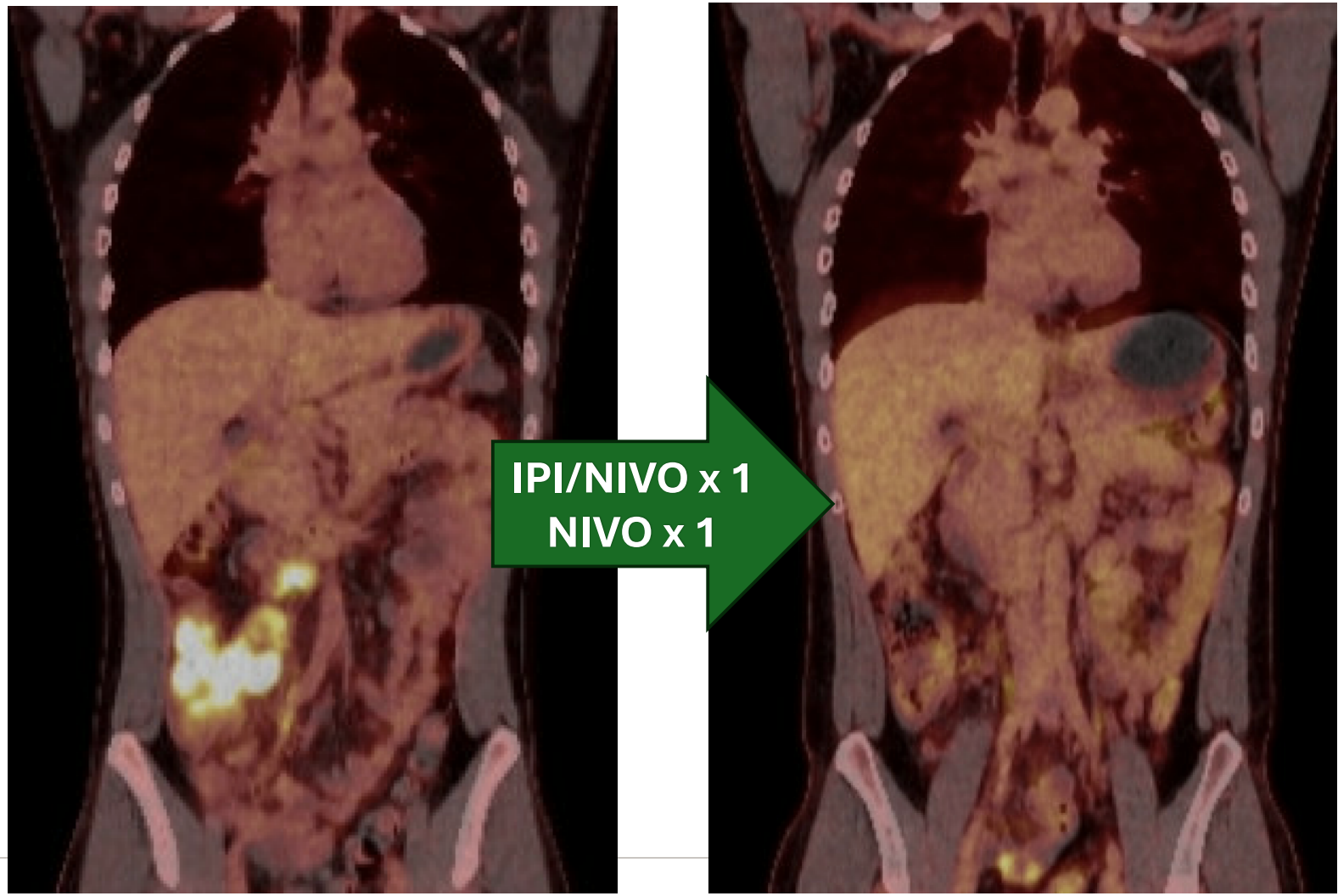
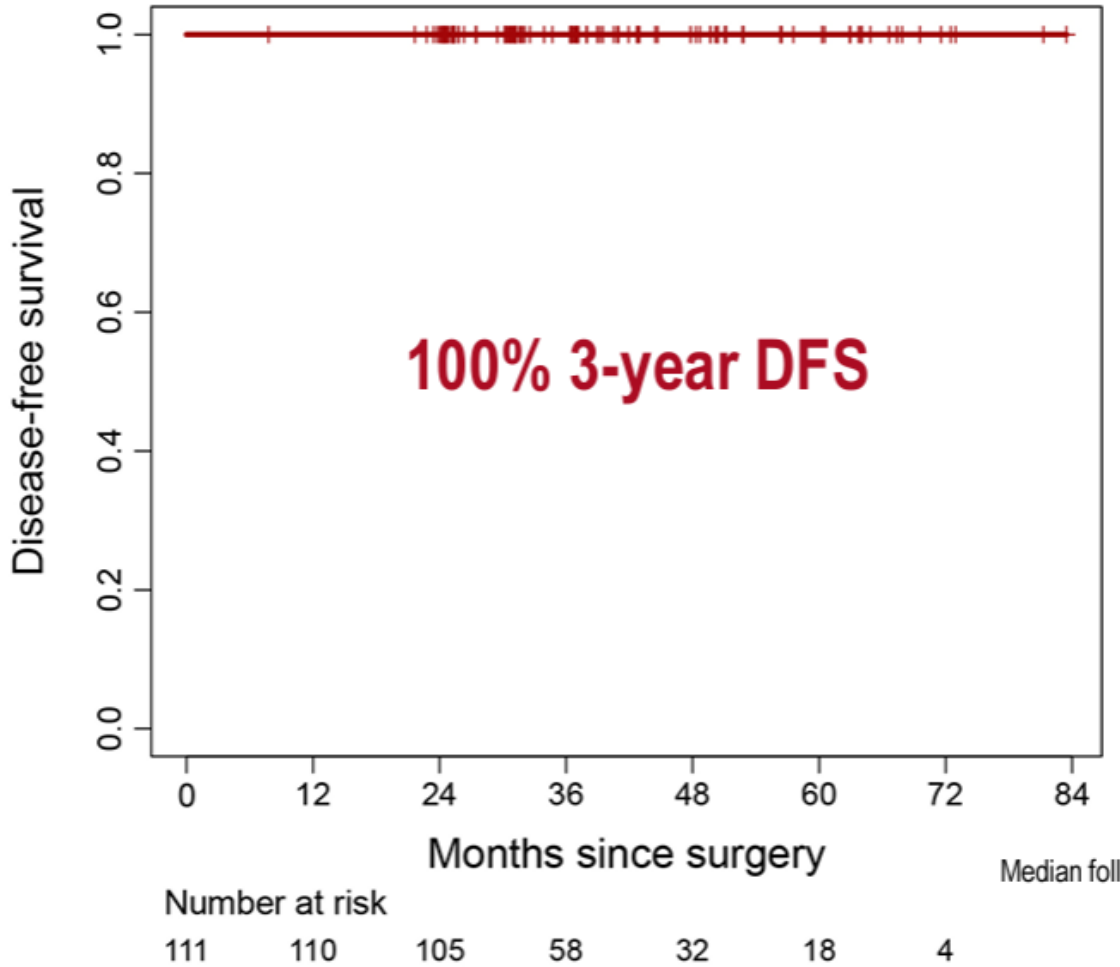


Results – 3-year disease-free survival 100%

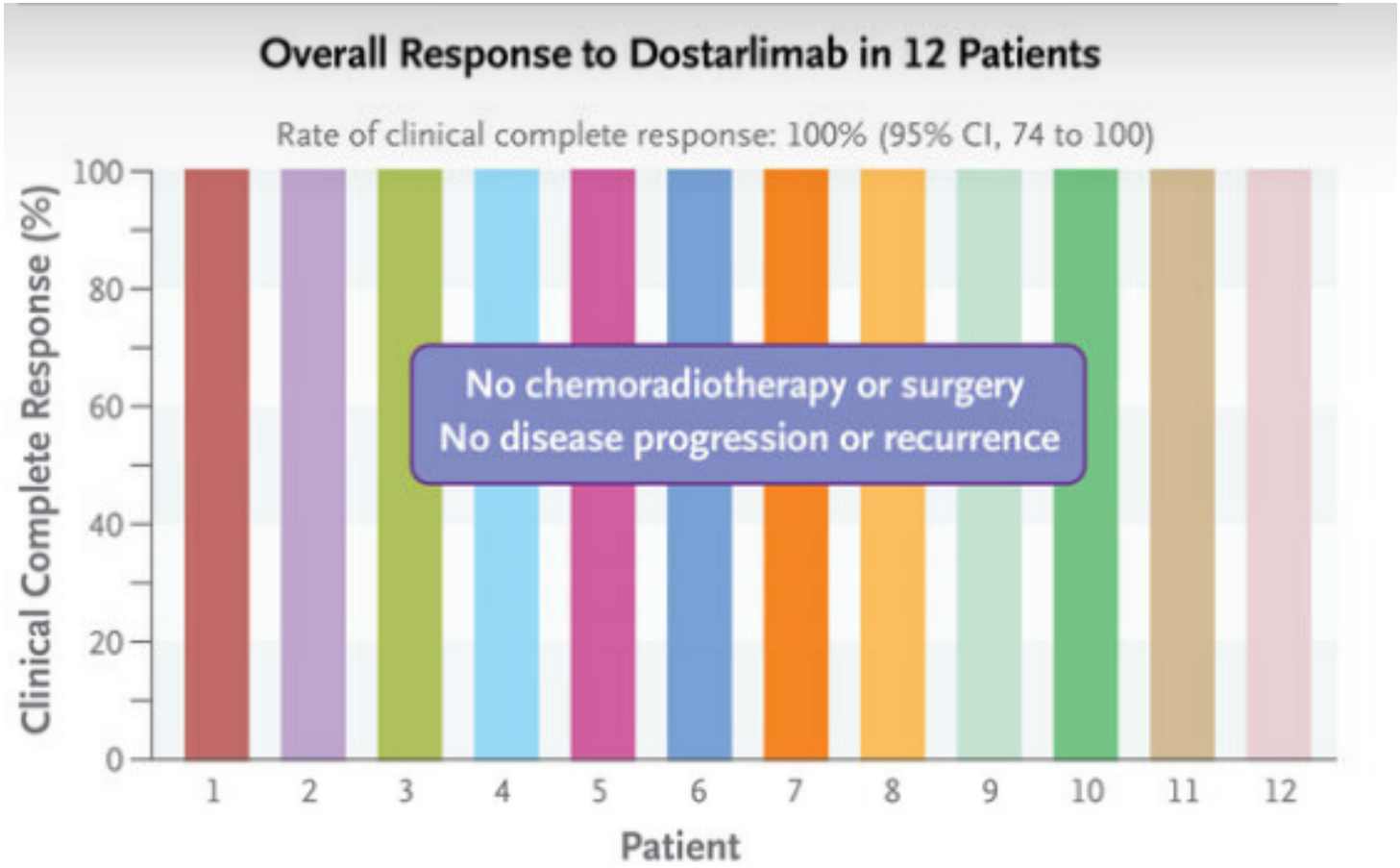


Median follow-up after surgery: 36.6 months (7.8 - 83.4)

BARCELONA 2024 ESMO congress

Data cut-off: 11 September 2024

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

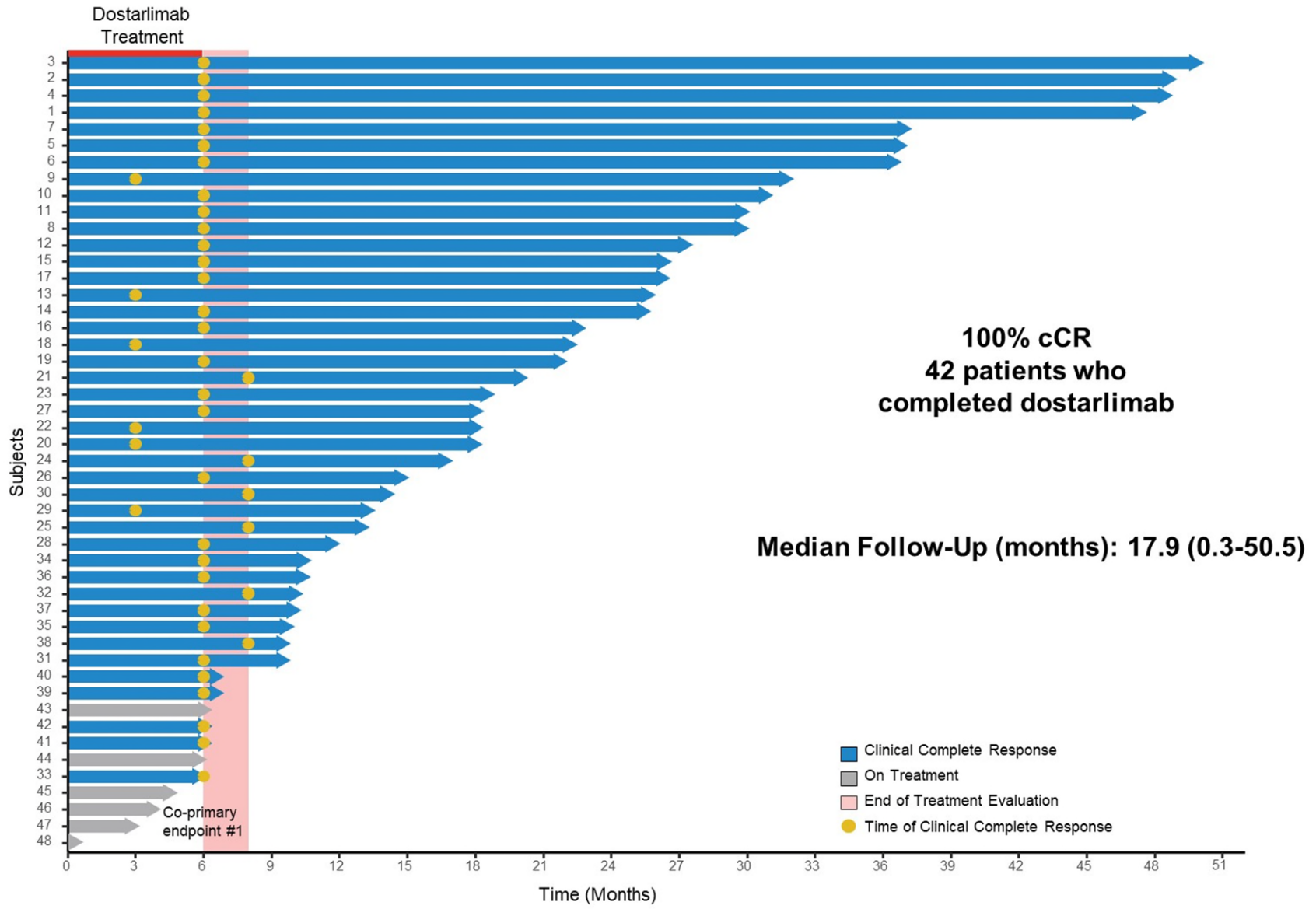


Cercek A. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. N Engl J Med. 2022 Jun 23;386(25):2363-2376. PMID: 35660797.

Individual responses to PD-1 blockade with dostarlimab

Patients who completed 6-months of dostarlimab

ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response 100%
1	38	T4	N+	23.8	CR	CR	CR	cCR
2	30	T3	N+	20.5	CR	CR	CR	cCR
3	61	T1/2	N+	20.6	CR	CR	CR	cCR
4	28	T4	N+	20.5	CR	CR	CR	cCR
5	53	T1/2	N+	9.1	CR	CR	CR	cCR
6	77	T1/2	N+	11.0	CR	CR	CR	cCR
7	77	T1/2	N+	8.7	CR	CR	CR	cCR
8	55	T3	N+	5.0	CR	CR	CR	cCR
9	68	T3	N+	4.9	CR	CR	CR	cCR
10	78	T3	N-	1.7	CR	CR	CR	cCR
11	55	T3	N+	4.7	CR	CR	CR	cCR
12	27	T3	N+	4.4	CR	CR	CR	cCR
13	26	T3	N+	0.8	CR	CR	CR	cCR
14	43	T3	N+	0.7	CR	CR	CR	cCR


Dostarlimab
Treatment
Subjects
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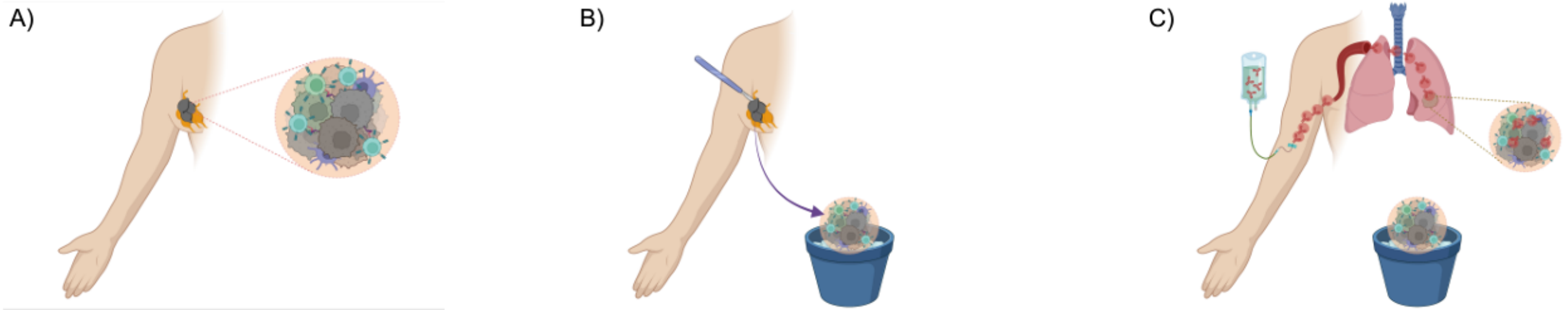
Time (Months)
100% cCR
42 patients who
completed dostarlimab
Median Follow-Up (months): 17.9 (0.3-50.5)
Clinical Complete Response
On Treatment
End of Treatment Evaluation
Time of Clinical Complete Response

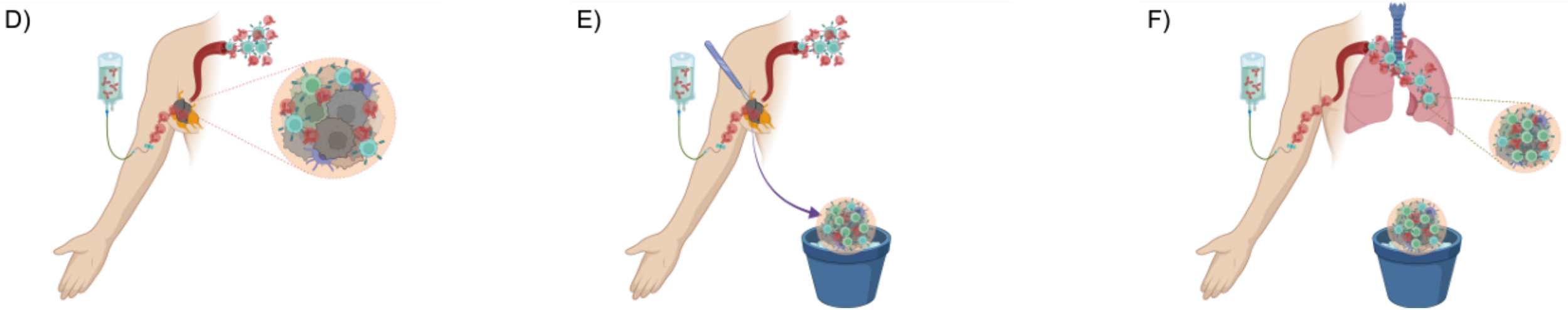
Mechanisms: Adjuvant Therapy



A, B and C) Adjuvant therapy. Before surgery, **the majority of antitumor T cells inhibited by PD-1 are located at the sites of locally advanced disease** (A), which are **resected** with surgery (B).

When giving adjuvant anti-PD-1, the therapy **relies on the existence of antitumor T cells inhibited by PD-1 at micrometastases sites** (C).

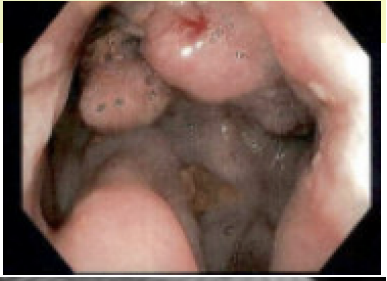
Mechanisms: Neoadjuvant Therapy



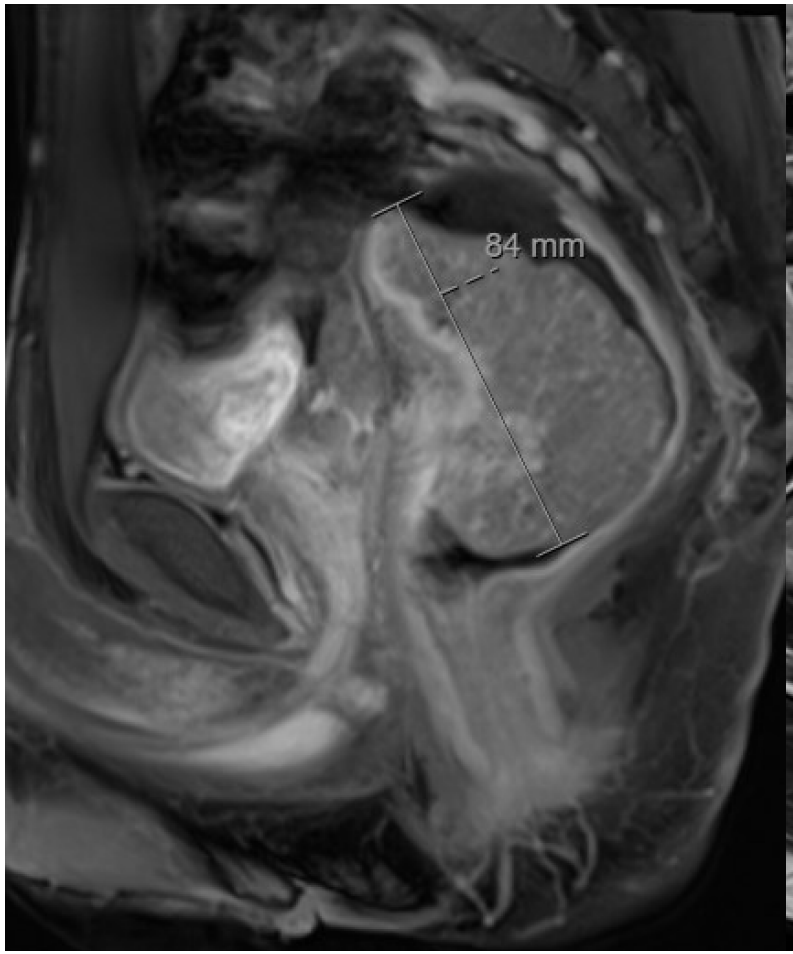
D, E and F) Neoadjuvant therapy. Administering neoadjuvant anti-PD-1 therapy is **intended to activate the large numbers of antitumor T cells at the tumor site** (D) **before the definitive surgery** (E).

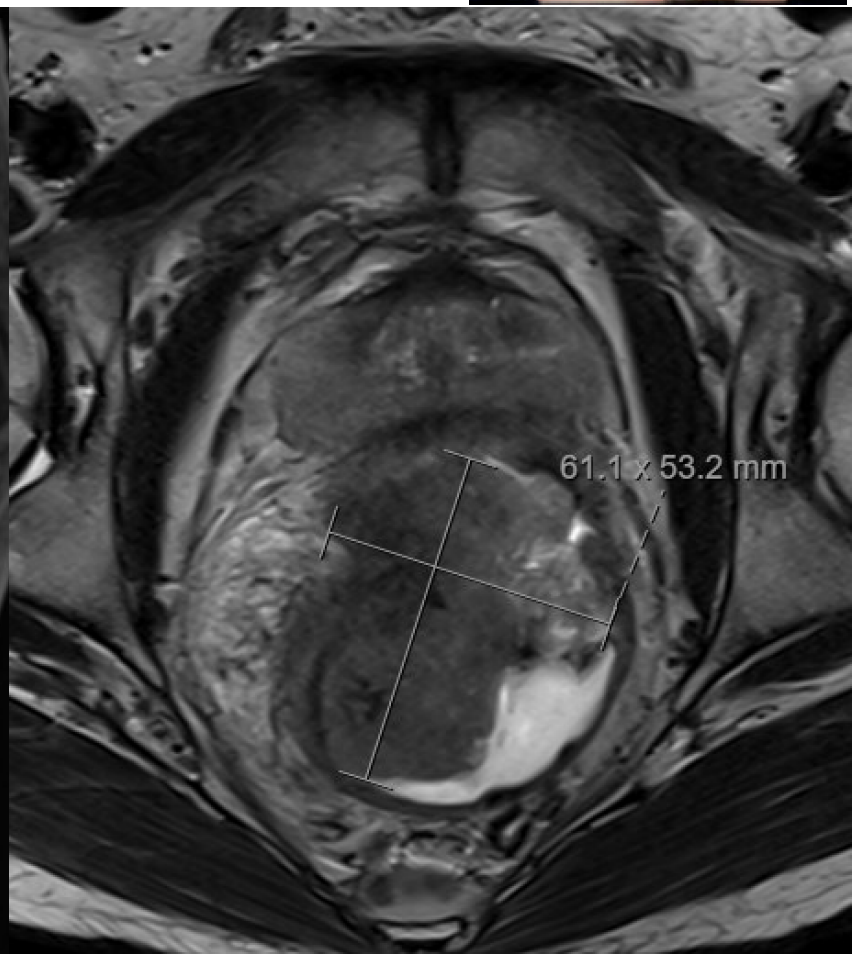
The locally-activated antitumor T cells then go onto induce a **systemic immune response** able to recognize distant micrometastatic sites (F)

3 Case 3 – Rectal cancer



- MSS
- 6 cm from anal verge
- Deemed a candidate for total neoadjuvant therapy (TNT)
- pMMR/MSS
- Germline testing negative

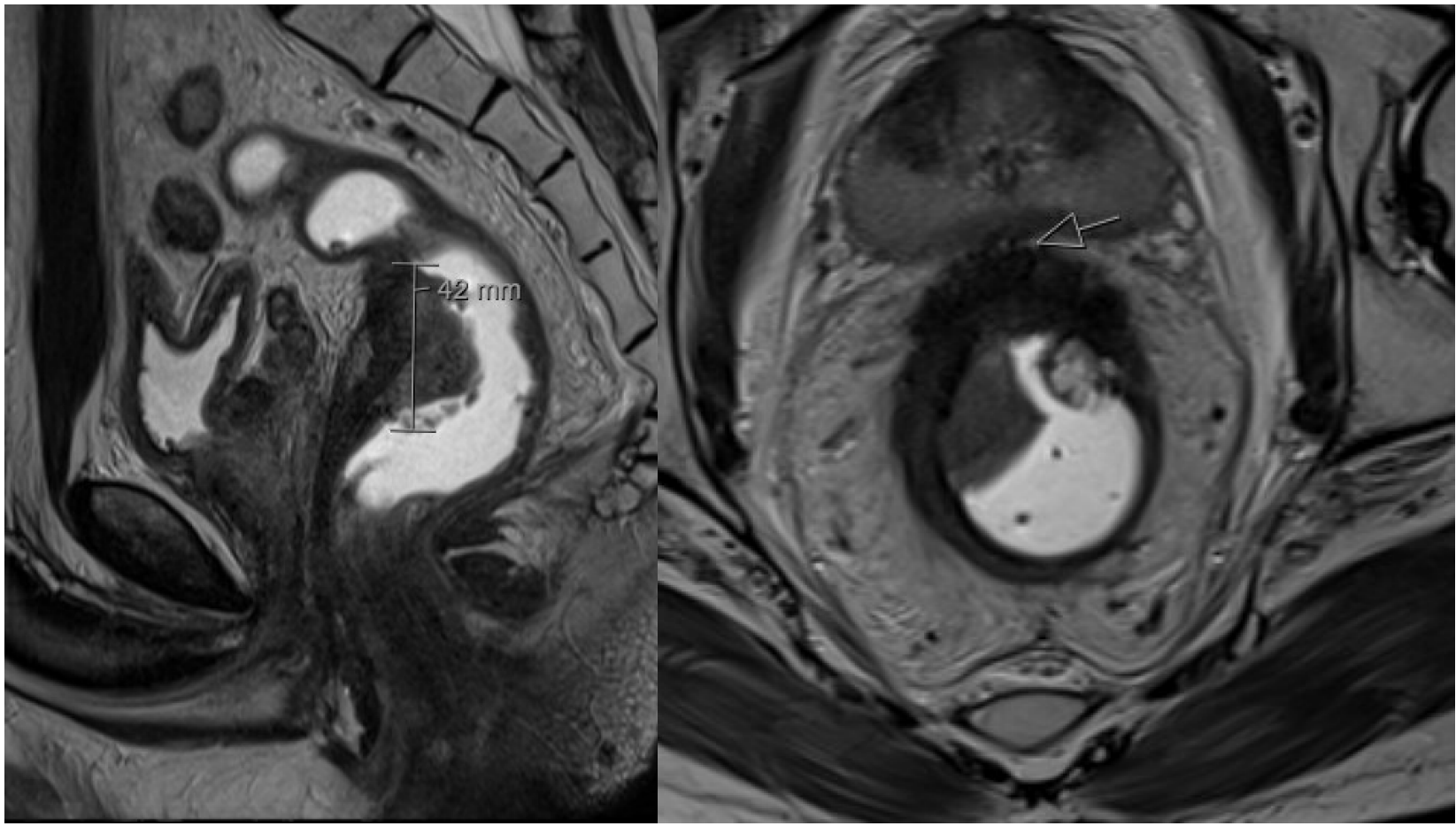




3

Case 3 – Rectal cancer

- MSS
- 6 cm from anal verge
- pMMR/MSS
- Partial response



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