My approach to Liver Metastases

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Disclosures

- **Research Support:**

- National Institute of Health (NIH)
  R21 CA131763-01A1; R21 CA128391-02; R01 CA240569-01

- Industry:
SIRTEX Medical Inc: Phase I Trial Y90 Post HAI: Clinical CRC 2013/ Active 2020: Y90 Pathologic Changes Correlation to Dosimetry

BTG: 2016 EPOCH Trial, BSX/BTG Active: 2021: Y90 Pathologic Changes Correlation to Dosimetry

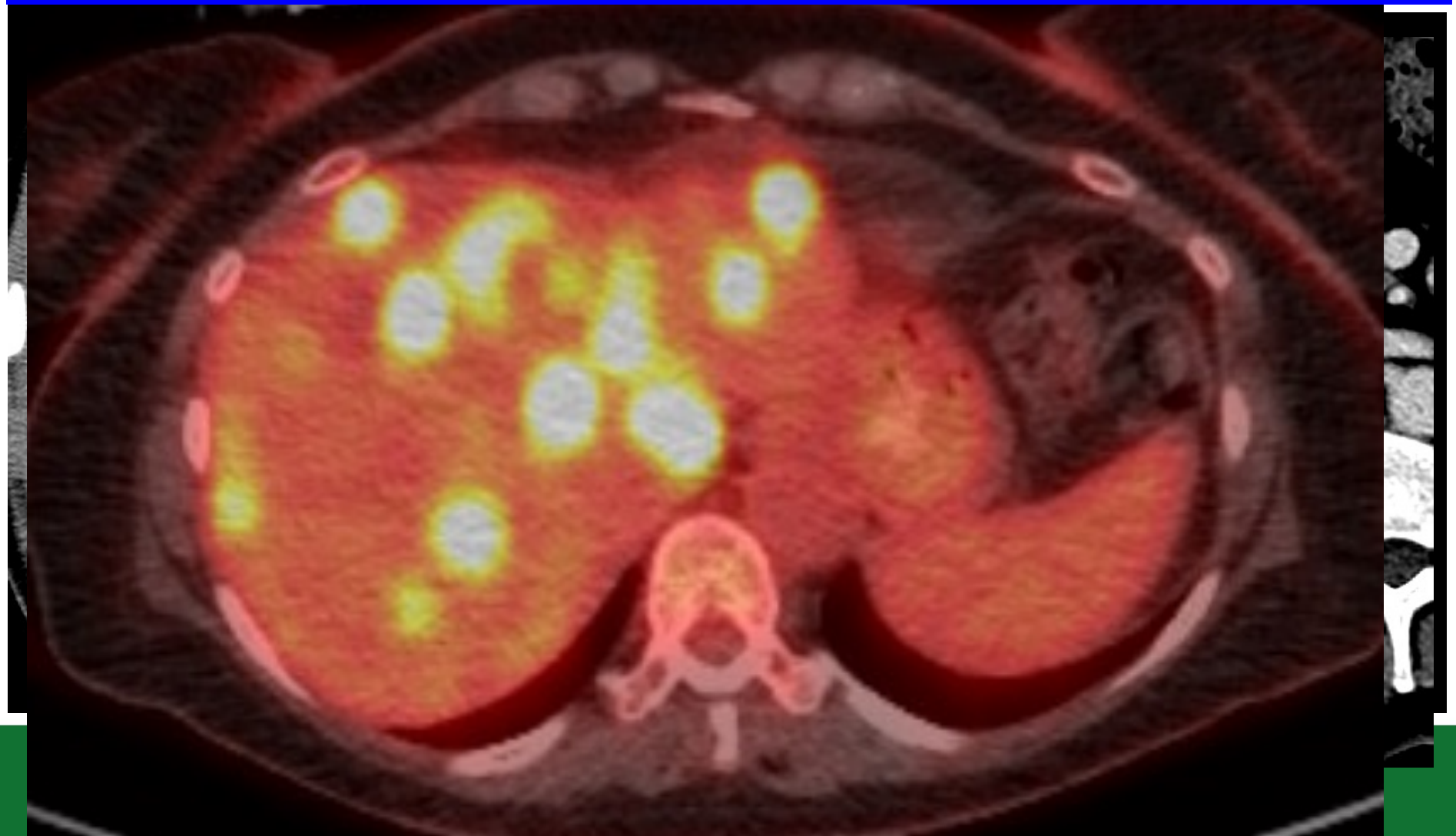
Ethicon: AC Software, Registry

- Consultant, Advisory Boards:

- J&J/ Ethicon
- Terumo
- BTG/Boston Scientific
- SIRTEX
- Varian

Not all Liver Mets are Equal

How about Multifocal Disease



Systemic Therapy +/- RFA

CLOCC trial

SURVIVAL	Median Months	3	5	8 years	P value
chemo	40.5	55.2	30.3%	8.9%	0.01
Chemo+RFA	45.6	56.9	43.1.%	35.9%	

Level 1 evidence

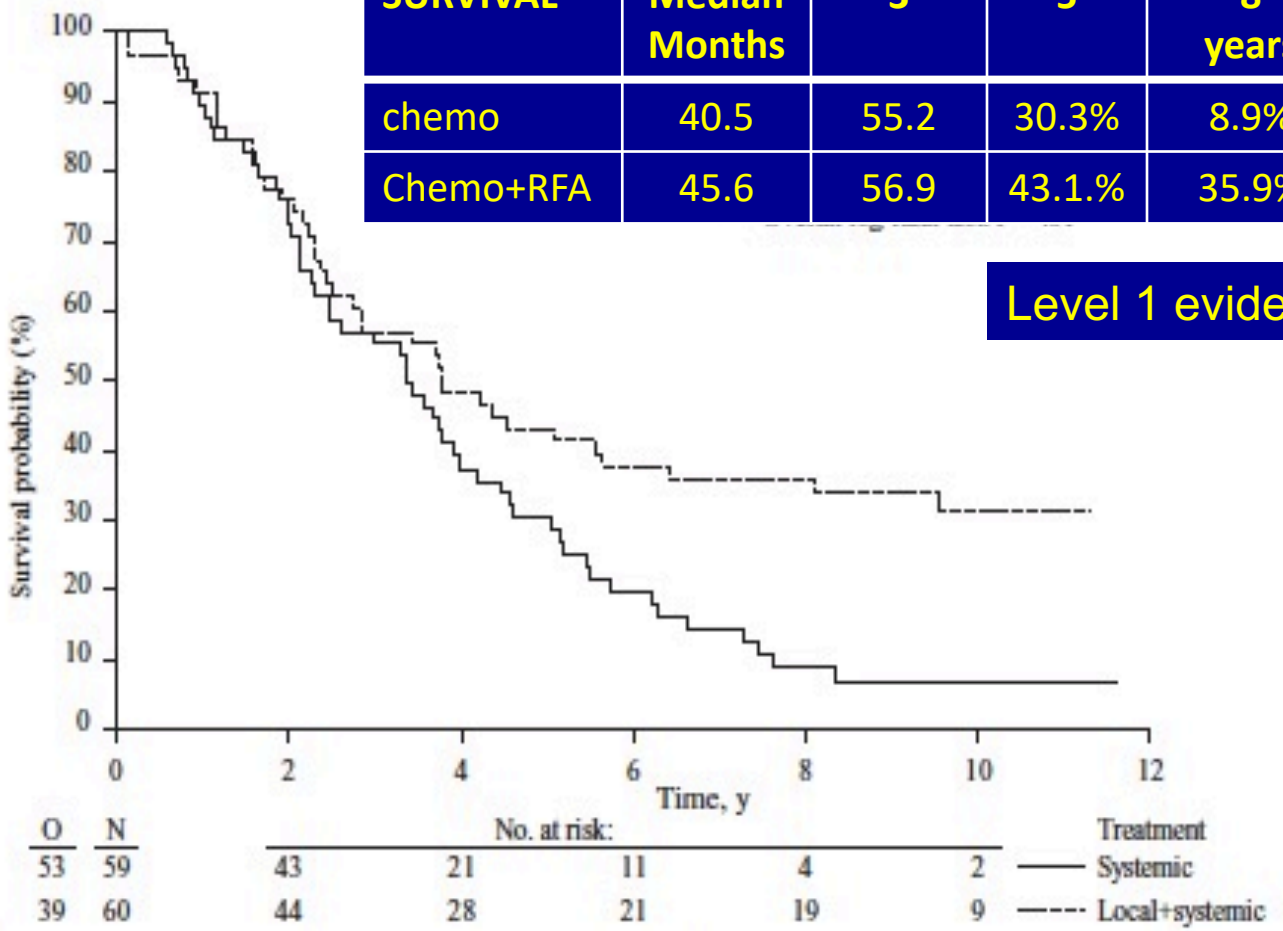


Figure 2. Kaplan-Meier curves for overall survival in patients with unresectable colorectal liver metastases treated by systemic treatment alone or combined modality treatment by systemic treatment plus aggressive local treatment by radiofrequency ablation ± resection (P = .01). P value was calculated using a two-sided log-rank test.

Ruers et al, Annals of Oncology 2012
Ruers et al ASCO 2015; JCO 33, abstract 3501
Ruers et al: JNCI Natl Cancer Inst (2017) 109 (9): djx015

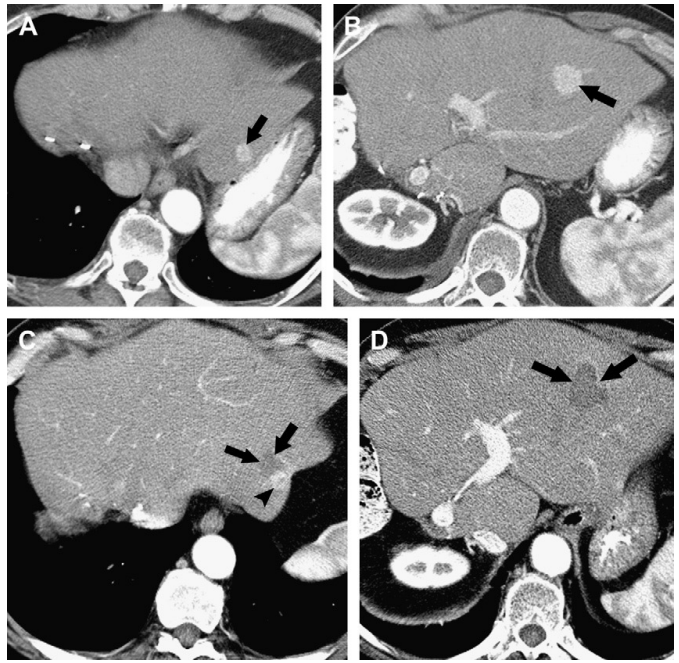
PRINCIPLES OF SURGERY
CRITERIA FOR RESECTABILITY OF METASTASES AND LOCOREGIONAL THERAPIES WITHIN SURGERY

- When hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches utilizing preoperative portal vein embolization[13] or staged liver resection[14]
- Ablative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to ablation or resection.
- Arterially directed catheter therapy, and in particular yttrium 90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.

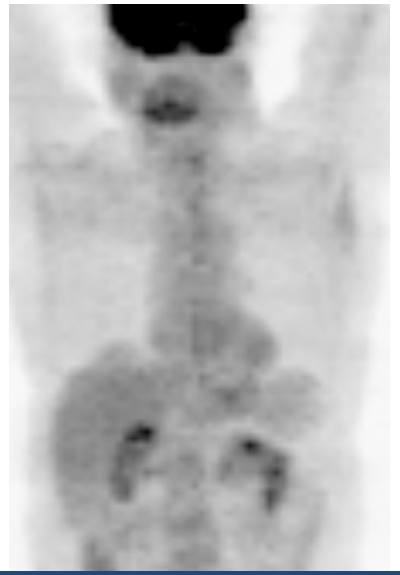
in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable.

- Re-resection can be considered in selected patients.[15]

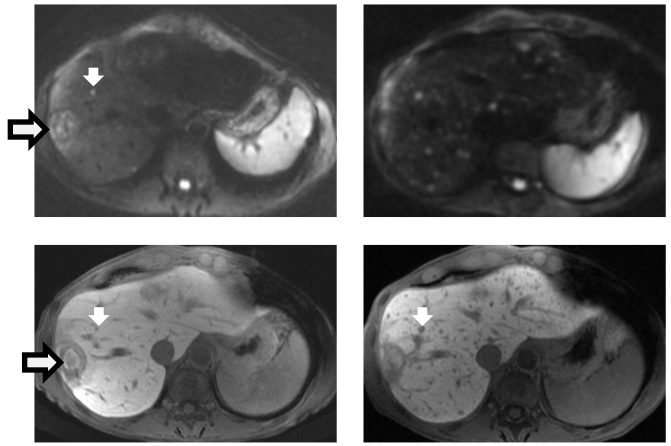
Current Status: Imaging Modalities



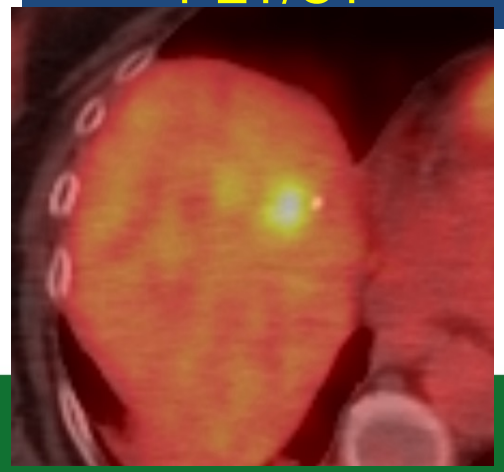
Computed Tomography

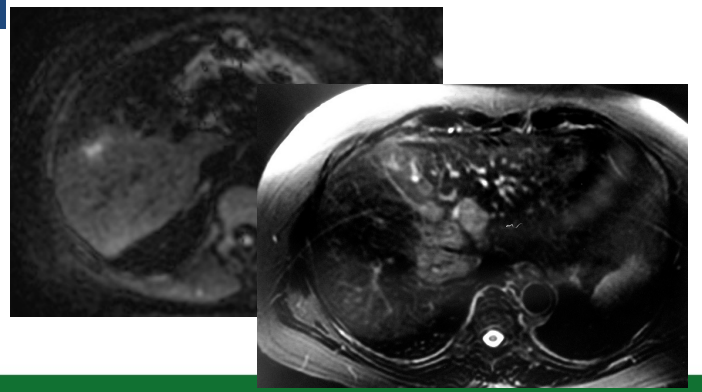


Positron Emission Tomography PET/CT



Magnetic Resonance Imaging





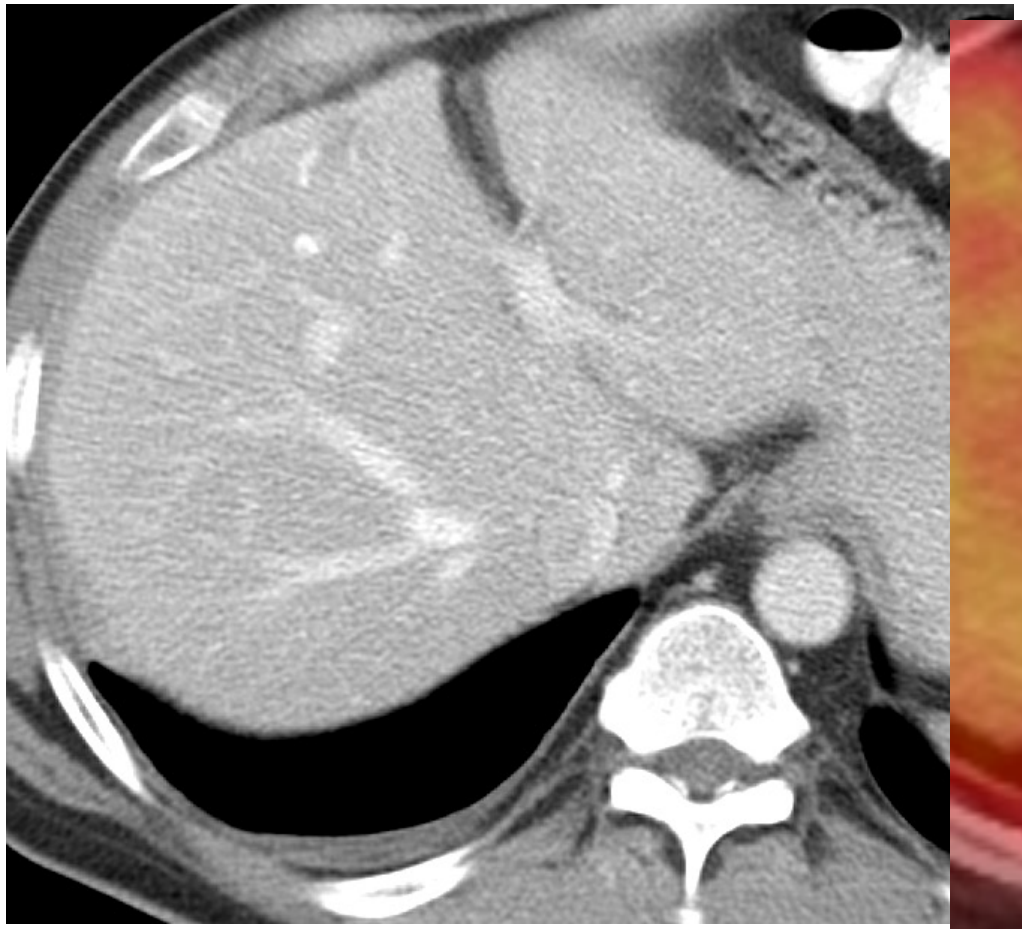
- Consider MRI of liver for liver metastases if potentially resectable.
- PET/CT is not routinely indicated.
  - PET/CT does not supplant a contrast-enhanced diagnostic CT or MR and should only be used to evaluate an equivocal finding on a
  - Consider PET/CT (skull base to mid-thigh)
    - If potentially surgically curable M1 disease in selected cases.
    - In selected patients considered for image-guided liver-directed therapies (ie, ablation, radioembolization).[4-8]
- If liver-directed therapy or surgery is contemplated, a hepatic MRI with intravenous routine extracellular or hepatobiliary GBCA is preferred over CT to assess exact number and distribution of metastatic foci for local treatment planning.

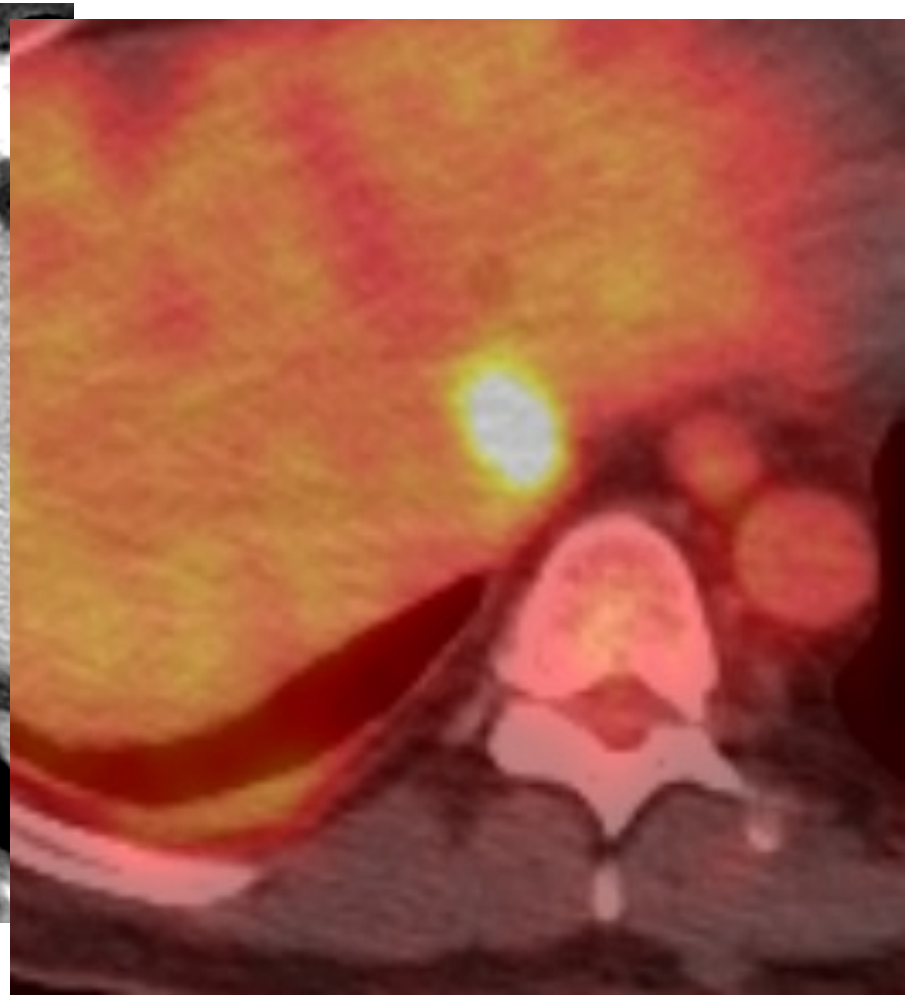
Monitoring

- Chest, abdomen, and pelvis CT with contrast
  - Prior to adjuvant treatment to assess response to primary therapy or resection
  - During re-evaluation of conversion to resectable disease
- PET/CT can be considered for assessment of response and liver recurrence after image-guided liver-directed therapies (ie, ablation, radioembolization)

[1] Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. Radiology 2010;257:674-684.
[2] van Kessel CS, Buckens CF, van den Bosch MA, et al. Preoperative imaging of colorectal liver metastases after neoadjuvant chemotherapy: a meta-analysis. Ann Surg Oncol 2012;19:2805-2813.
[3] ACR Manual on Contrast Media v10.3 https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf. Accessed May 25, 2017.
[4] Mauri G, Gennaro N, De Beni S, et al. Real-time US- ^{18} FDG-PET/CT image fusion for guidance of thermal ablation of ^{18} FDG-PET-positive liver metastases: the added value of contrast enhancement. Cardiovasc Intervent Radiol 2019;42:60-68.
[5] Sahin DA, Agcaoglu O, Chretien C, et al. The utility of PET/CT in the management of patients with colorectal liver metastases undergoing laparoscopic radiofrequency thermal ablation. Ann Surg Oncol 2012;19:850-855.
[6] Shady W, Kishore S, Gavane S, et al. Metabolic tumor volume and total lesion glycolysis on FDG-PET/CT can predict overall survival after (90)Y radioembolization of colorectal liver metastases: a comparison with SUVmax, SUVpeak, and RECIST 1.0. Eur J Radiol 2016;85:1224-1231.
[7] Shady W, Sotirchos VS, Do RK, et al. Surrogate imaging biomarkers of response of colorectal liver metastases after salvage radioembolization using 90Y-loaded resin microspheres. AJR Am J Roentgenol 2016;207:661-670.
[8] Cornelis FH, Petre EN, Vakiani E, et al. Immediate postablation ^{18} F-FDG injection and corresponding SUV are surrogate biomarkers of local tumor progression after thermal ablation of colorectal carcinoma liver metastases. J Nucl Med 2018;59:1360-1365.

PET/CT: Important in evaluation of disease





CLM Referred for Ablation

47 yo male metastatic colorectal cancer

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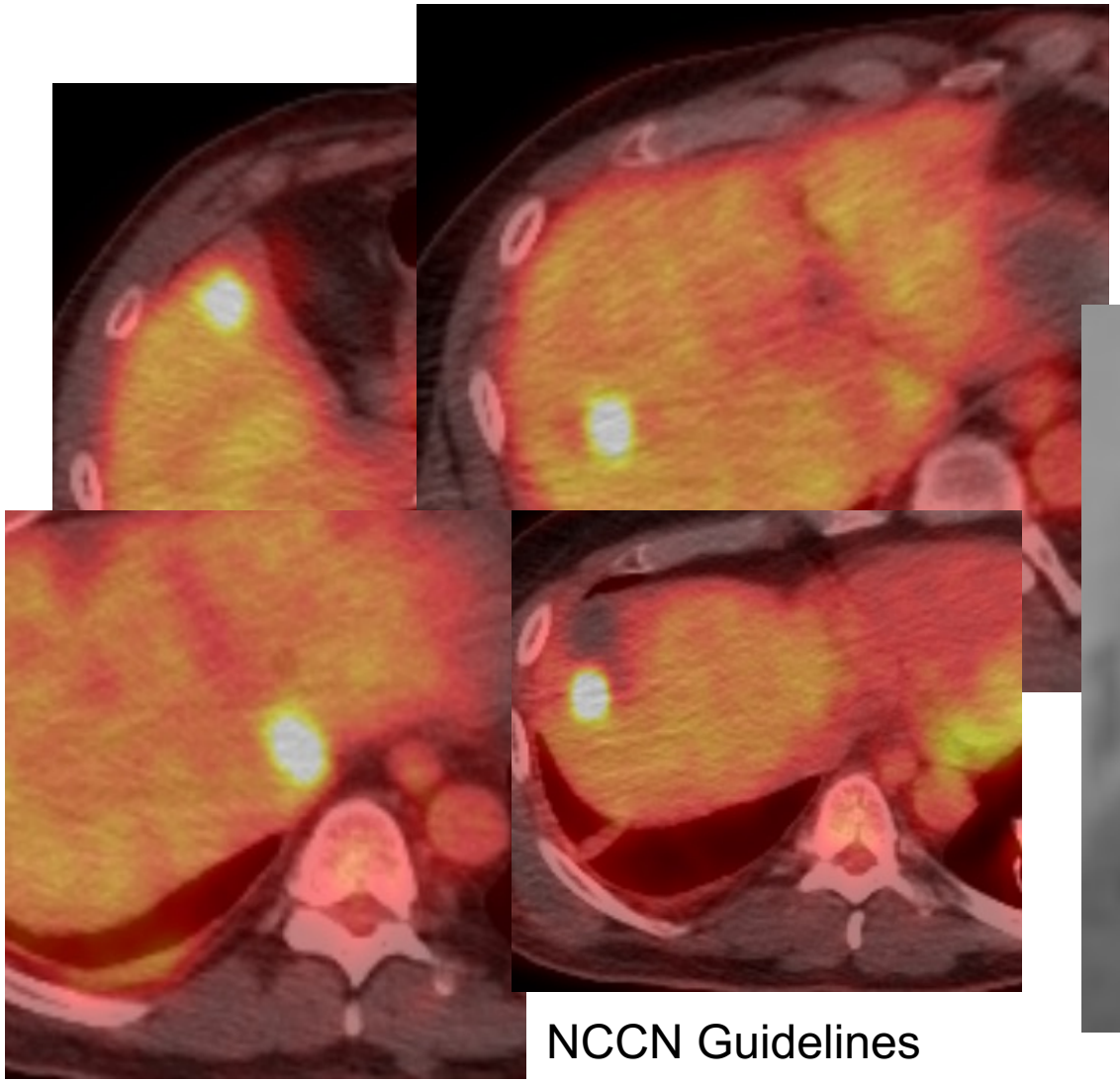
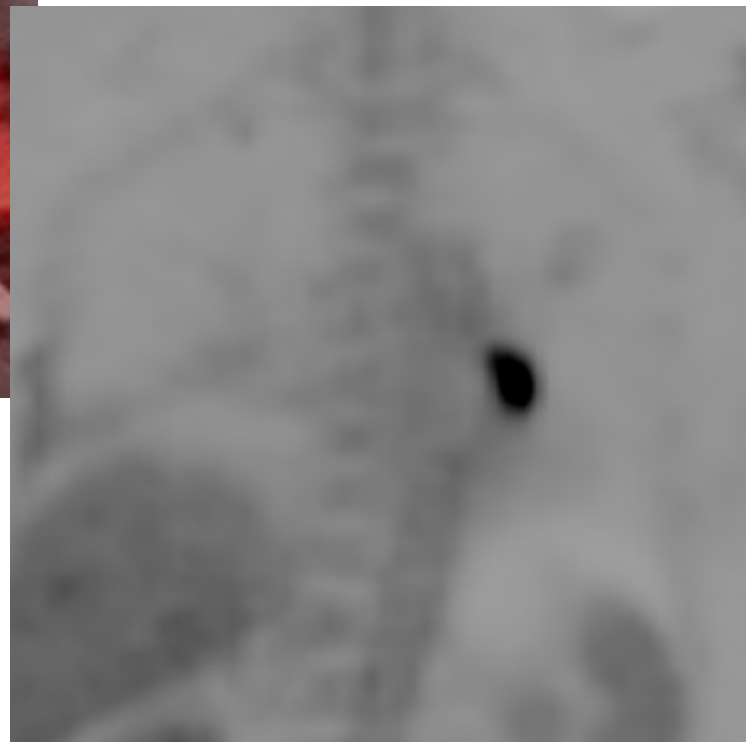
PET CT recommended prior to CLM Referred for any debulking



Evaluate Extend
of disease



NCCN Guidelines

sofoclec@mskcc.org

Ablation for CLM: Indications

Non-surgical candidate/Recurrence post Resection

Limited Number of tumors (<4)

Relatively Small Tumor (<5cm)

Ideal Candidate:

Solitary lesion < 3cm

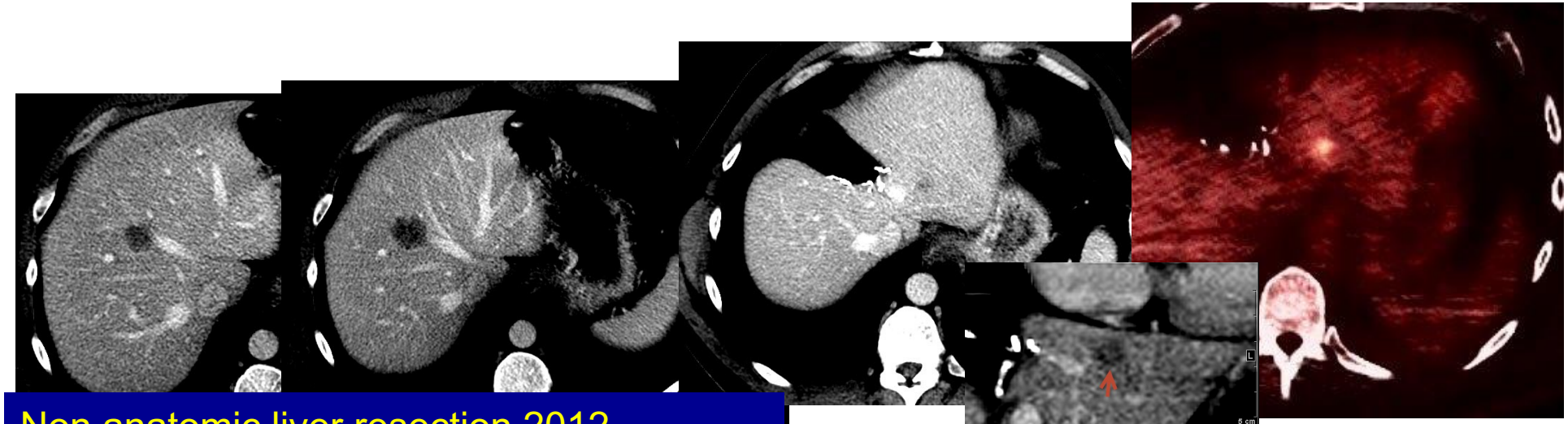
Surgical Candidate

Test of Time

Intraoperative RFA

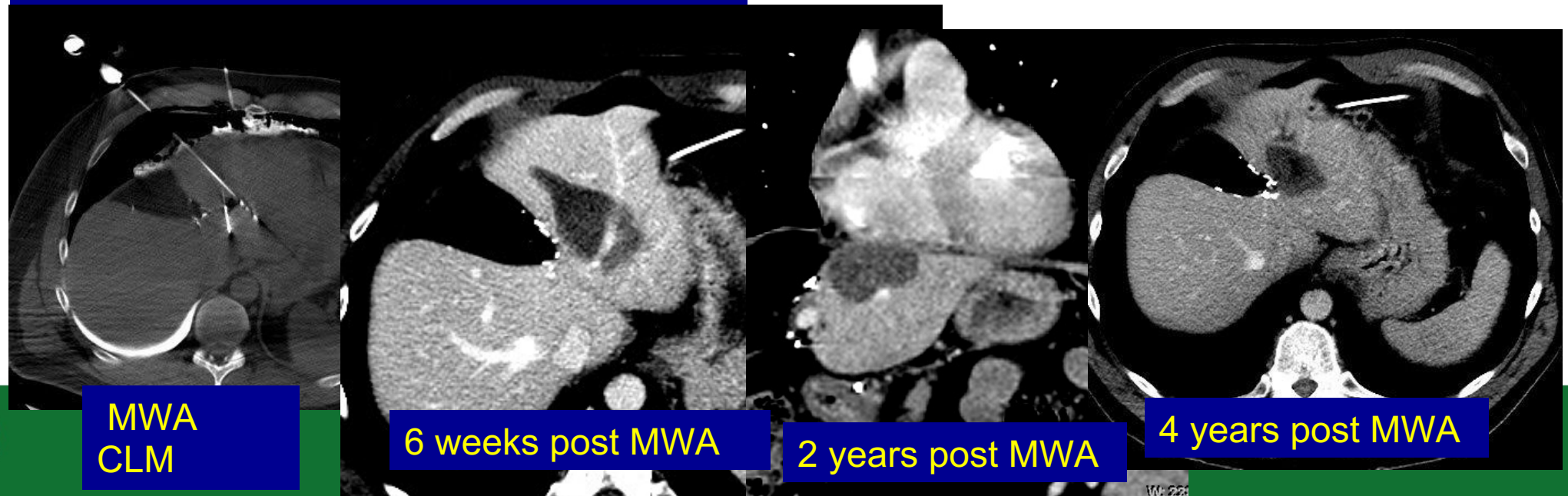
Gillams A, Solbiati L et al: Eur Radiol. 2015 May 22. Thermal ablation of CLM: A position paper by an international panel of ablation experts the interventional oncology sans frontieres meeting 2013

43 yo with CLM 18 months post resection of primary



Non anatomic liver resection 2012
Hepatic Arterial Chemotherapy 2102-2014
Systemic chemotherapy

2 years post wedge resection new CLM



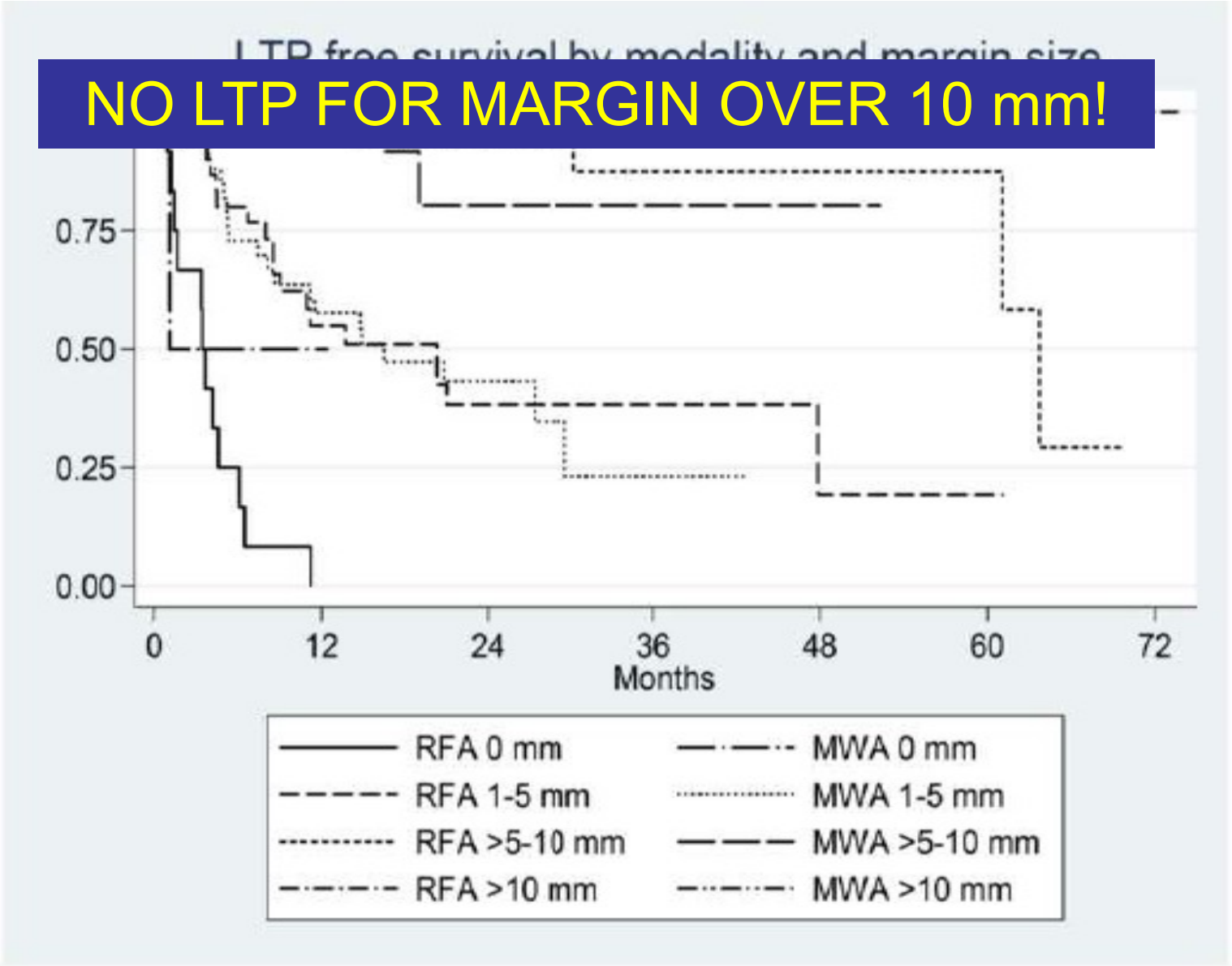
MWA
CLM

6 weeks post MWA

2 years post MWA

4 years post MWA

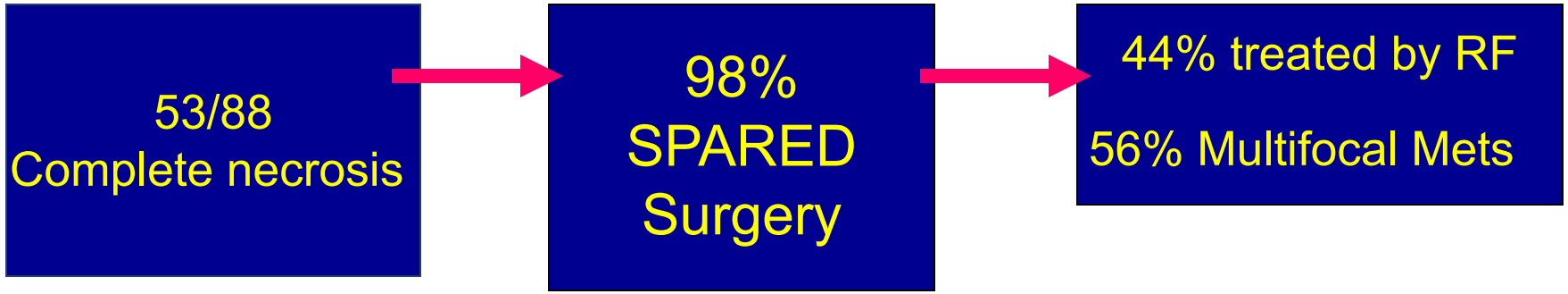
NO LTP FOR MARGIN OVER 10 mm!



Shady W, Solomon SB, Kemeny NE, Sofocleous CT: Comparison of RFA and MWA in the treatment of CLM; JVIR 2018

Kurilova I et al: Clinical Colorectal Cancer 2021

Test of Time Approach: Ablation ahead of Surgery

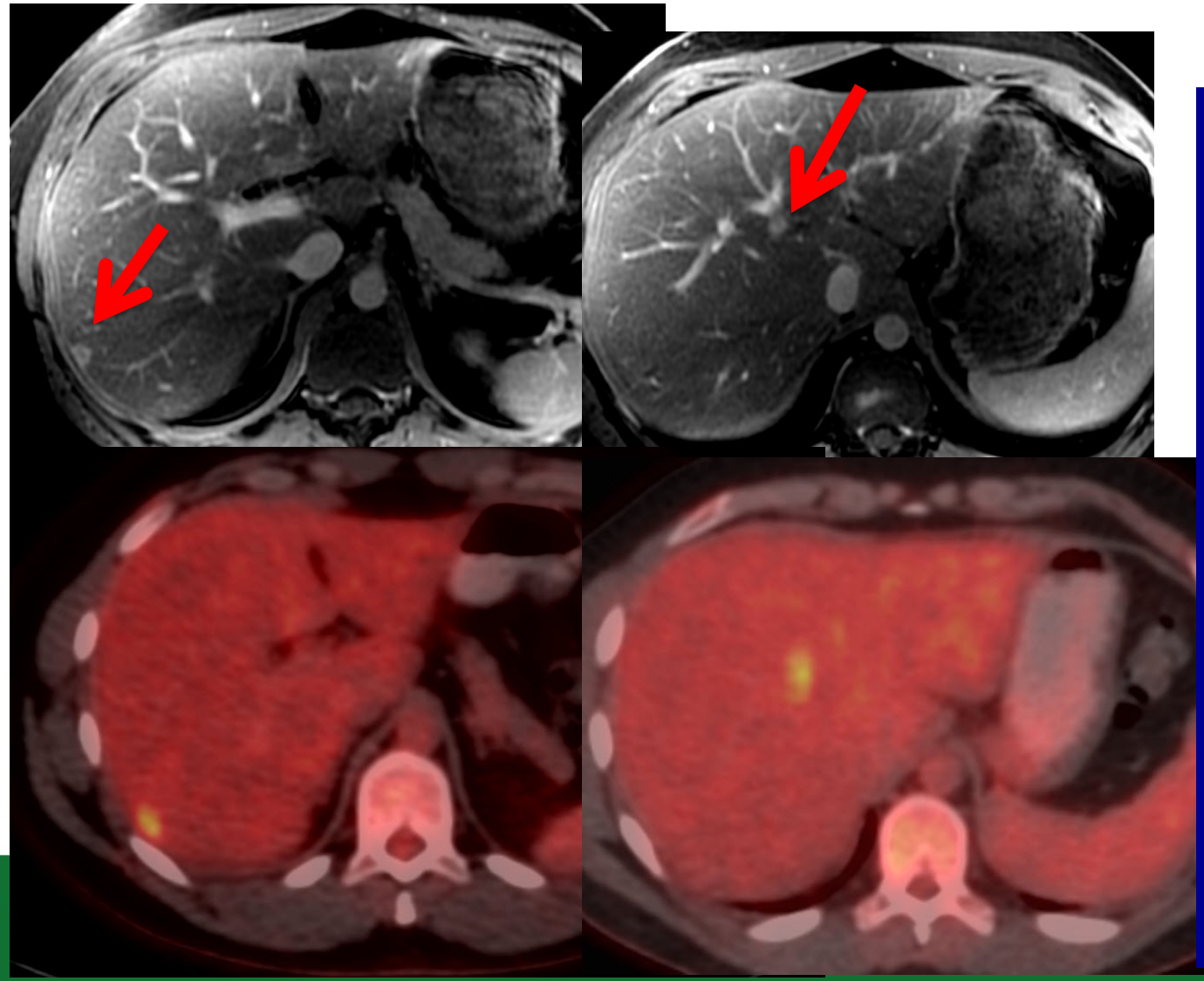


52/88, 59% patients SPARED Unnecessary Surgery

Livraghi et al; Cancer 2003; 97:3027-3035.

34 yo with CLM 15 months post resection of primary

Resection vs Ablation

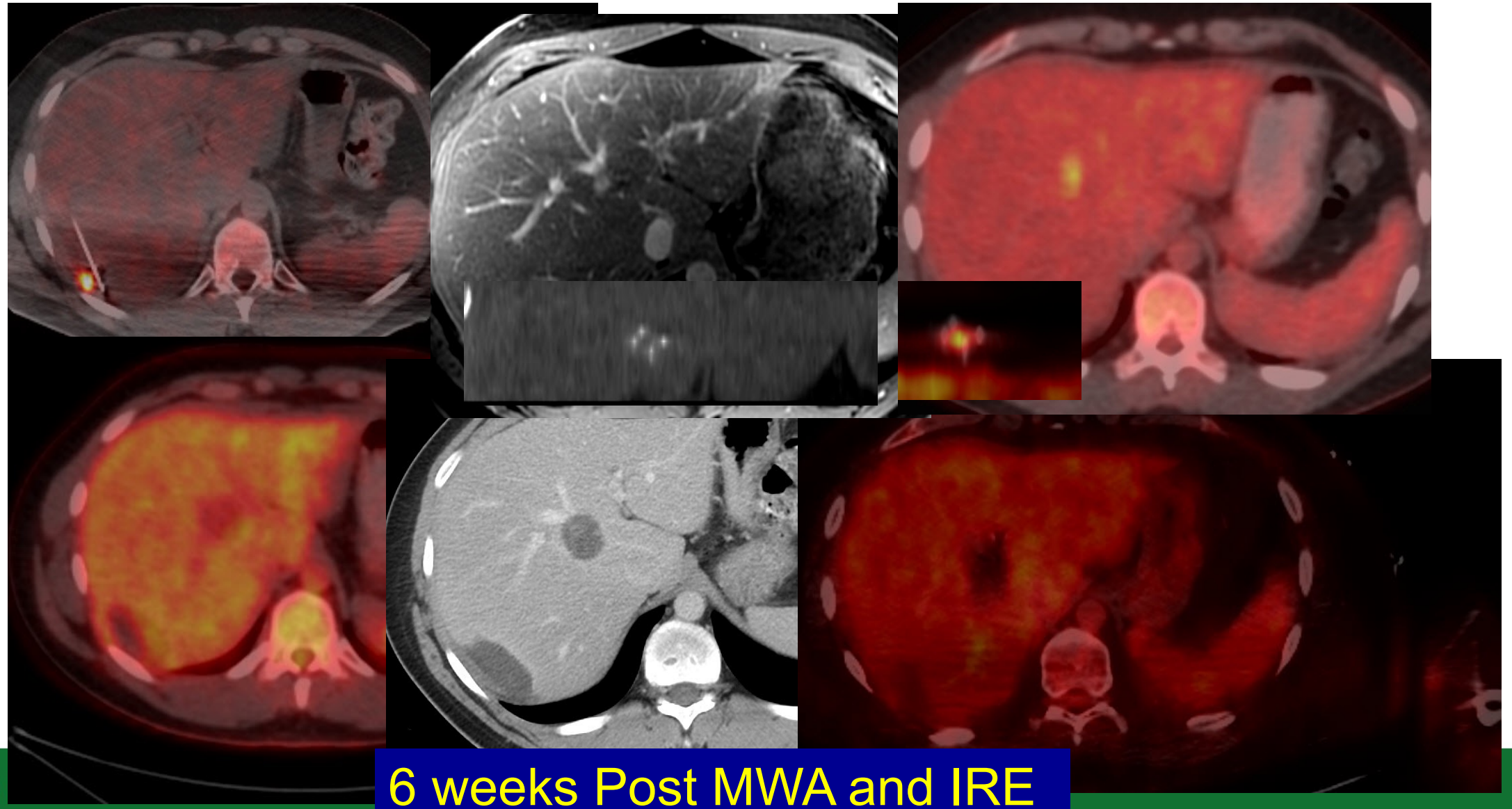


Peripheral can be treated with A0

Central:
IRE anyway!!!

Percutaneous with
Test Of Time

MWA and IRE



6 weeks Post MWA and IRE

Tumor Progression and Survival

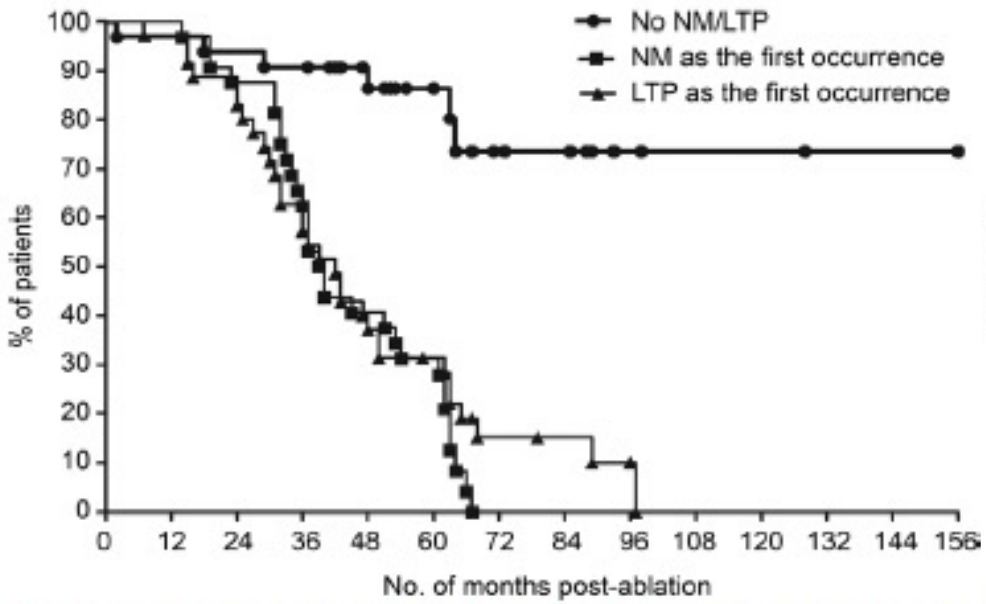


Figure 5: Kaplan-Meier curves show long-term survival in patients without NM or LTP, NM as first occurrence, and LTP as first occurrence. Best overall survival was observed in patients without either LTP or NM. No difference in overall survival was observed between patients with LTP versus those with NM remote from the treated site.

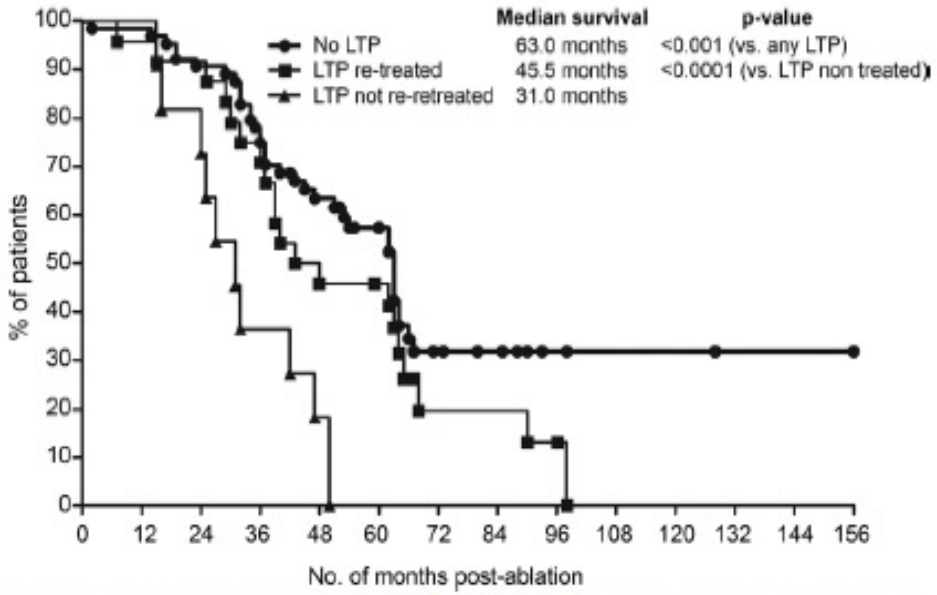
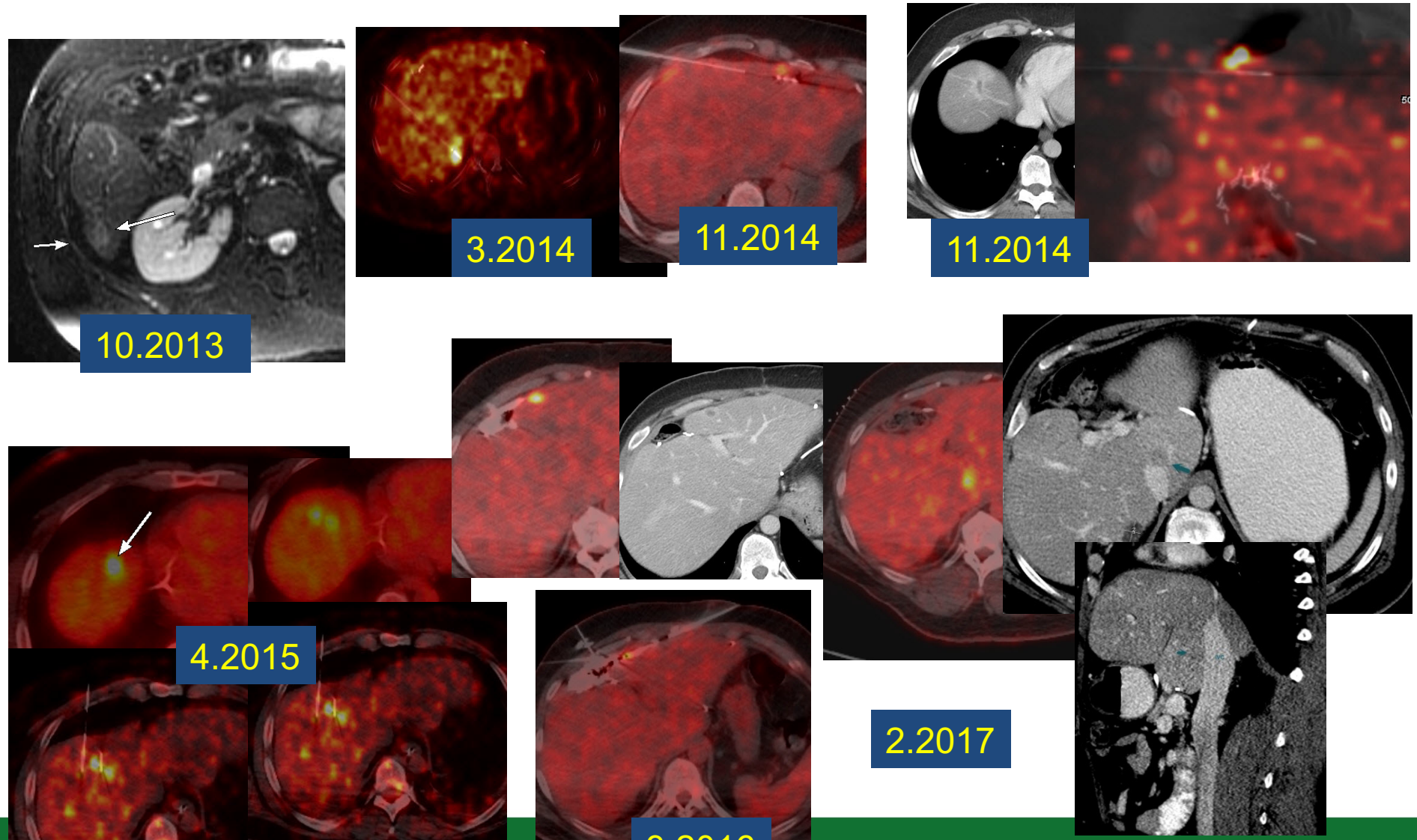


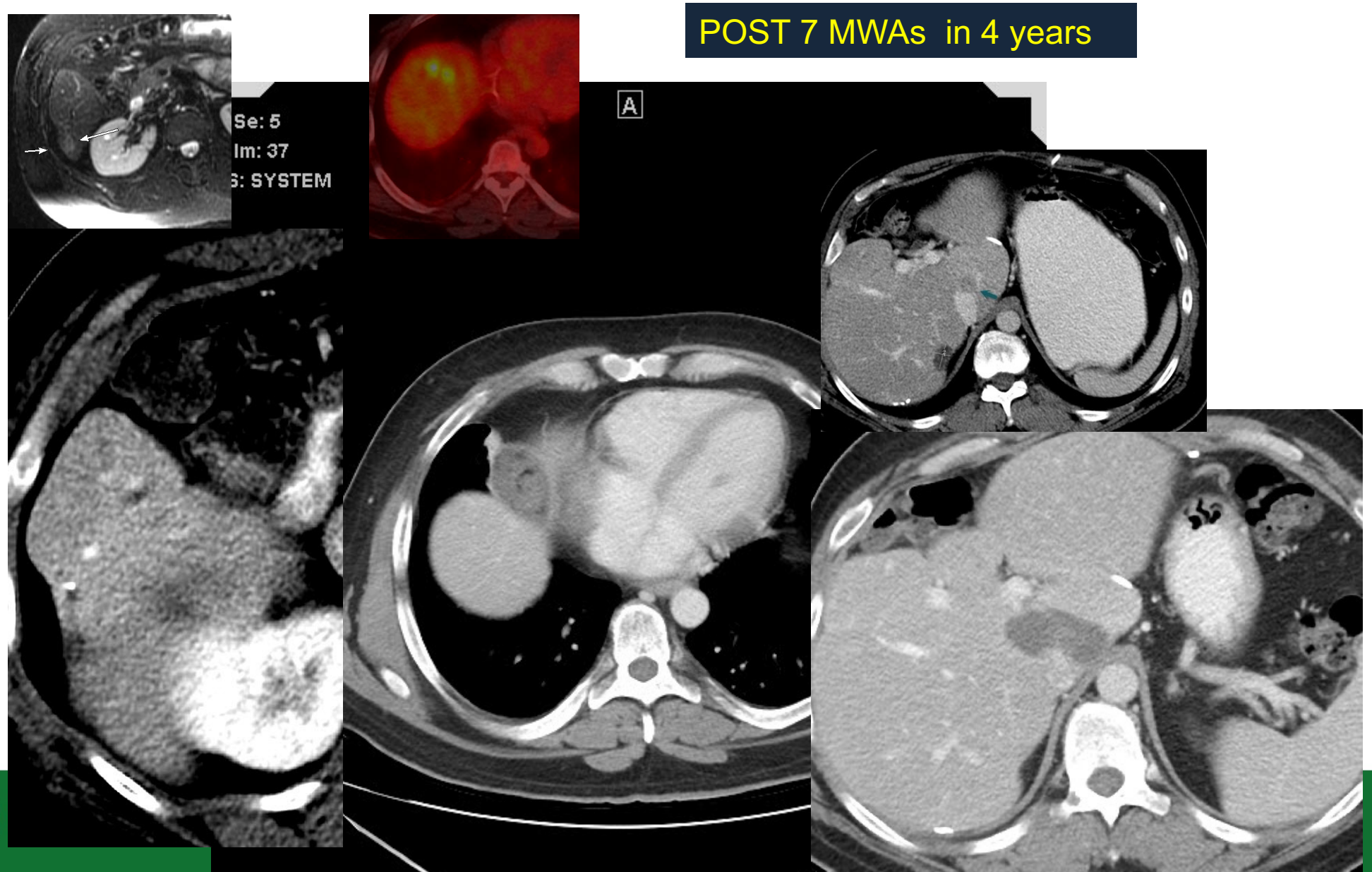
Figure 3: Kaplan-Meier curves of overall survival stratified by LTP and re-treatment. Highest survival rate was observed for patients without LTP (median survival: 63.0 months), followed by patients with LTP who underwent re-treatment (median survival: 45.5 months); lowest survival rate observed was for patients with LTP and no re-treatment (median survival 31.0 months; log-rank test for all comparisons in survival was significant at $P < .001$).

Solbiati L, et al Radiology;263(5):958-68

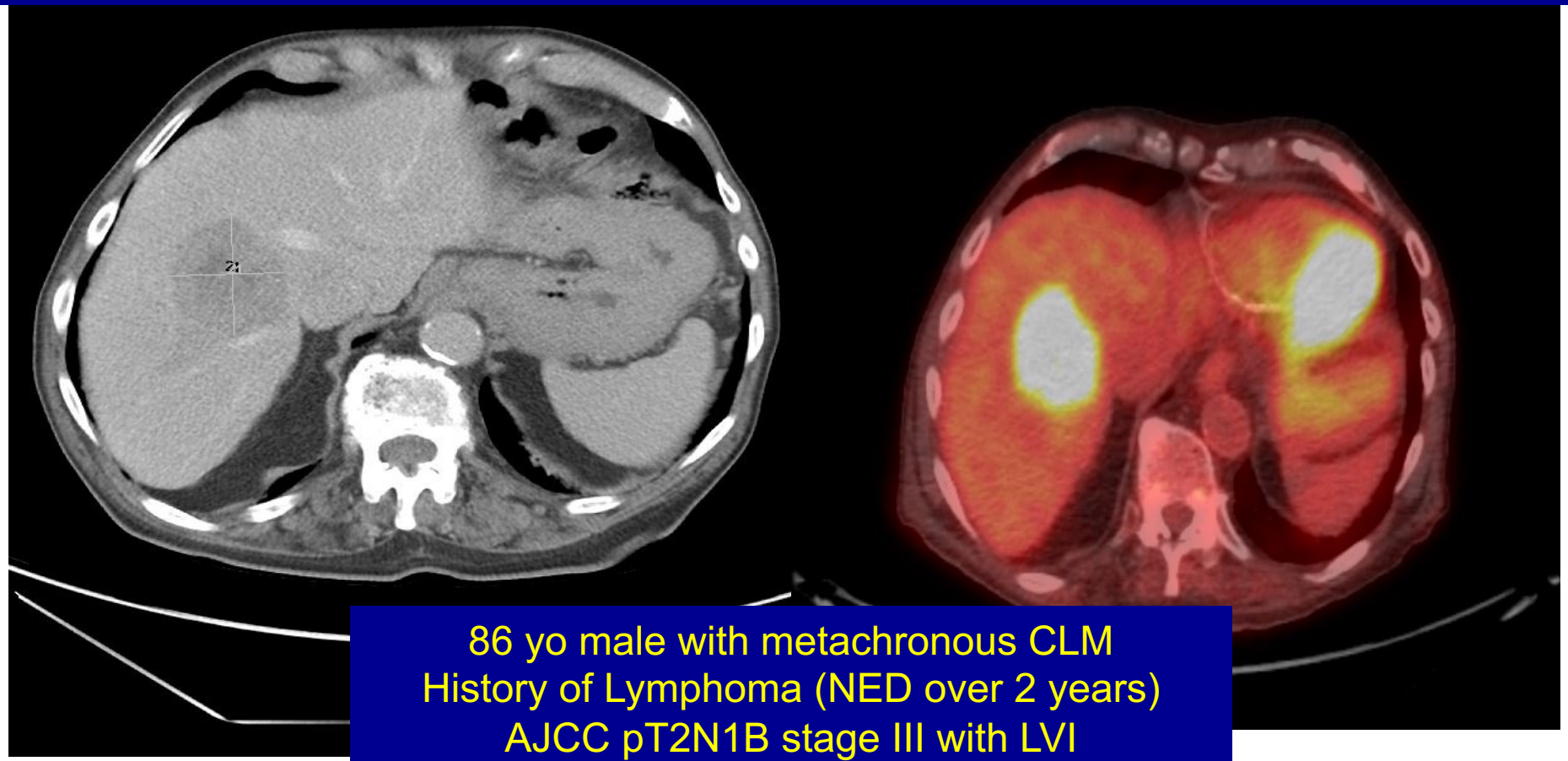
Example of of Surveillance and retreatment
39 yo male post resesction and HAIP



Example of of Surveillance and retreatment
39 yo male post resection and HAIP 4 years Follow-up



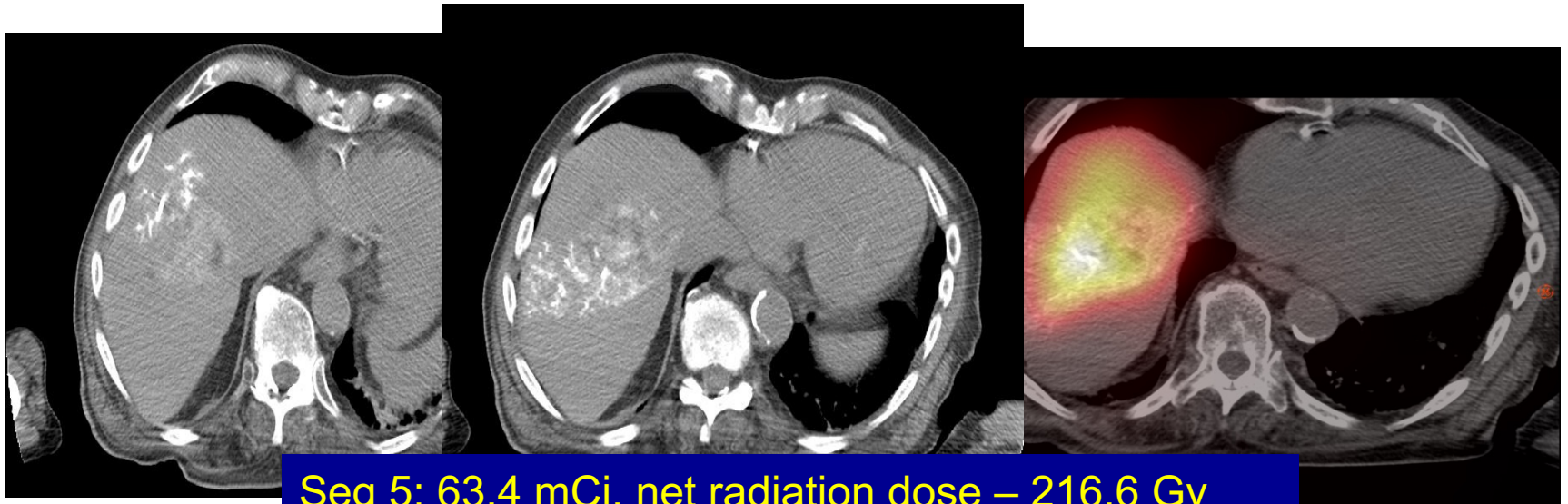
Technical Resectable but comorbitidies preclude Resection
Technically Impossible to achieve A0



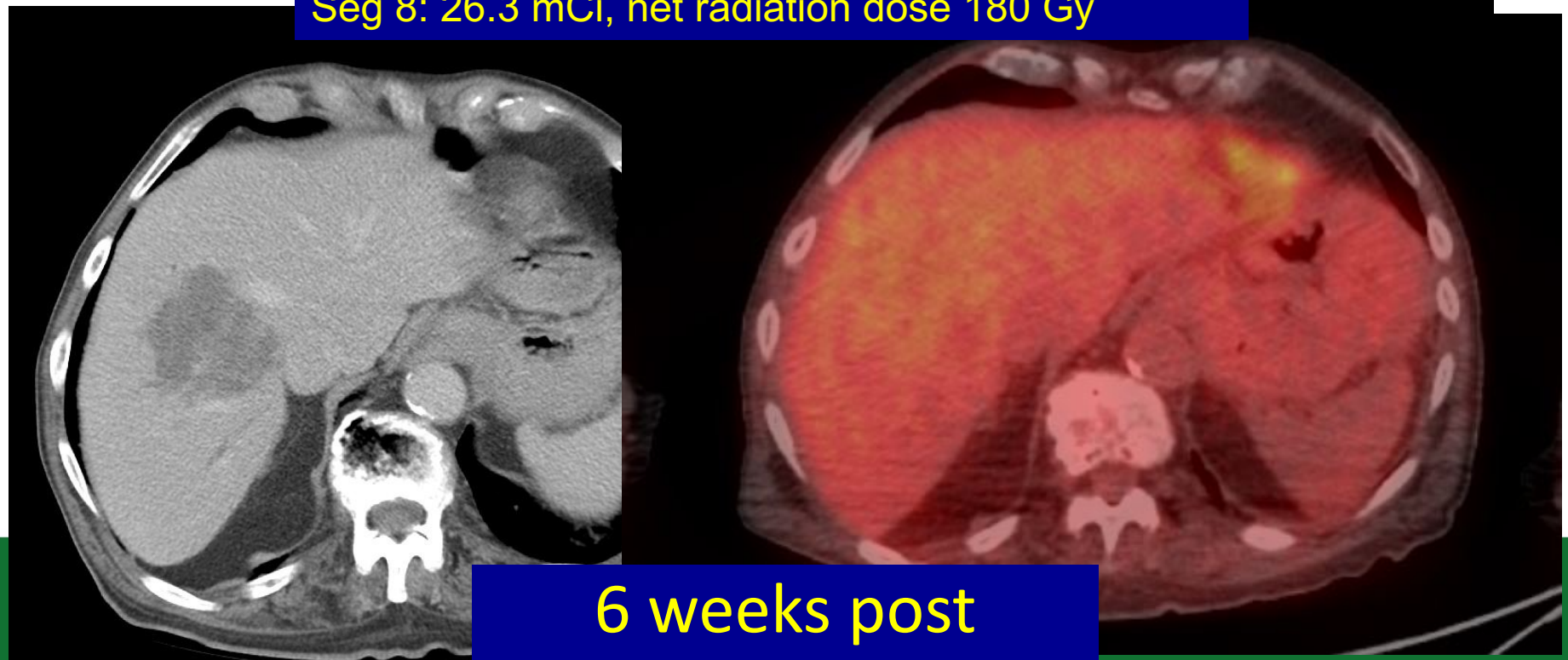
86 yo male with metachronous CLM
History of Lymphoma (NED over 2 years)
AJCC pT2N1B stage III with LVI
6 months 5 FU/not tolerating Ox and Irinotecan
TIA /Afib

Kurilova I, et al: Radiation segmentectomy of hepatic metastases with Y-90 glass microspheres. Abdom Radiol (NY). 2021 Feb 19. doi: 10.1007/s00261-021-02956-6. PMID: 33606062.

Post Glass Y90

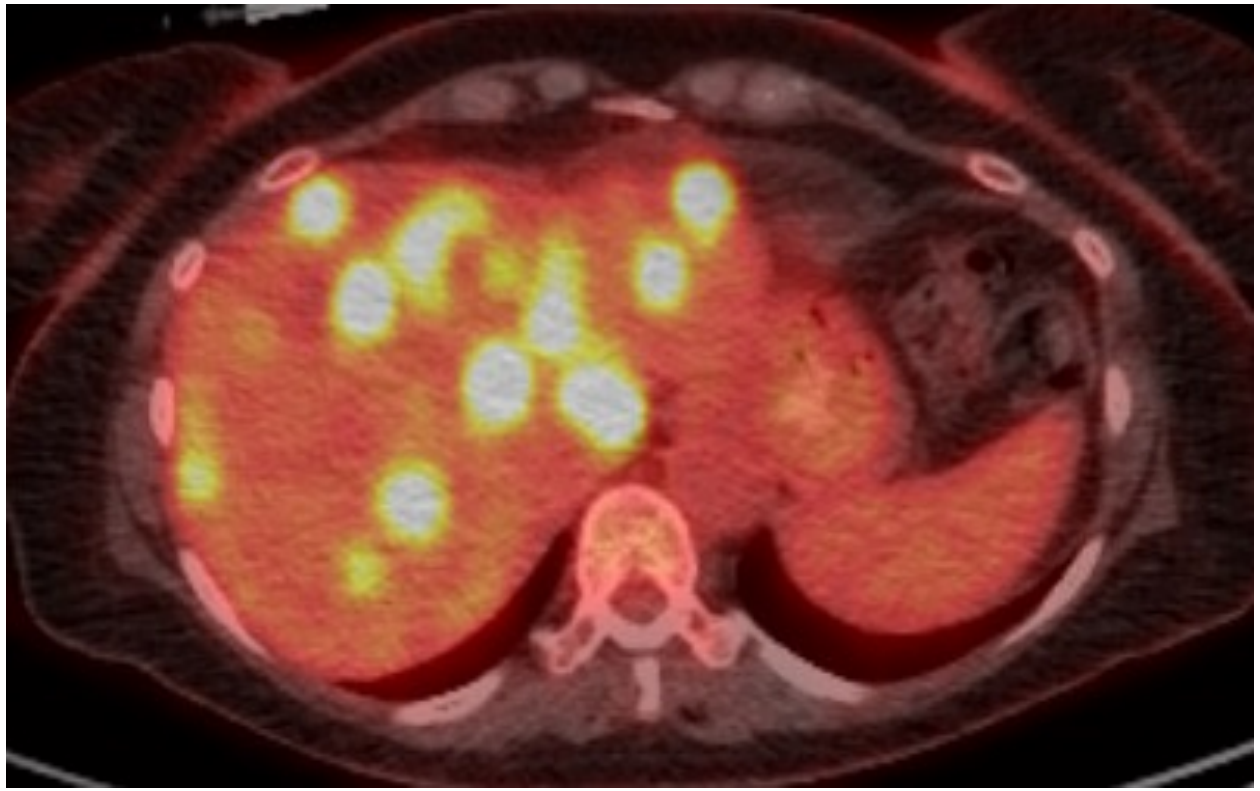


Seg 5: 63.4 mCi, net radiation dose – 216.6 Gy
Seg 8: 26.3 mCi, net radiation dose 180 Gy



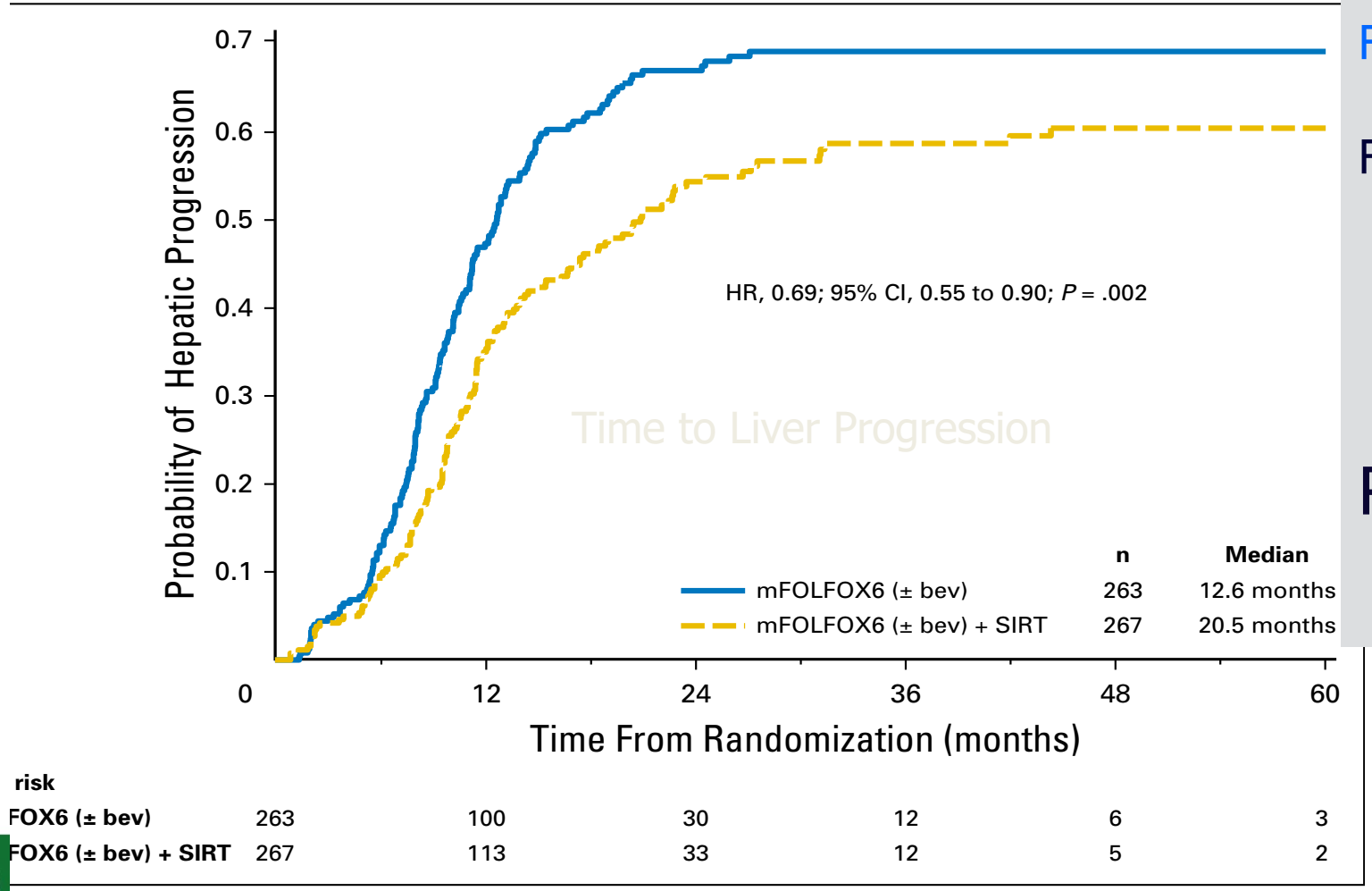
6 weeks post

60 yo Female with chemorefractory Mutifocal CRC Liver POD/Minimal EHD Post-multiple prior therapies



SIRFLOX: Randomized Phase III Trial Comparing First-Line mFOLFOX6 (Plus or Minus Bevacizumab) Versus mFOLFOX6 (Plus or Minus Bevacizumab) Plus Selective Internal Radiation Therapy in Patients With Metastatic Colorectal Cancer

Guy A. van Hazel, Volker Heinemann, Navesh K. Sharma, Michael P.N. Findlay, Jens Ricke, Marc Peeters, David Perez, Bridget A. Robinson, Andrew H. Strickland, Tom Ferguson, Javier Rodríguez, Hendrik Kröning, Ido Wolf, Vinod Ganju, Euan Walpole, Eveline Boucher, Thomas Tichler, Einat Shacham-Shmueli, Alex Powell, Paul Eliadis, Richard Isaacs, David Price, Fred Moeslein, Julien Taieb, Geoff Bower, Val Gebski, Mark Van Buskirk, David N. Cade, Kenneth Thurston, and Peter Gibbs



Folfox+SIRT

Folfox

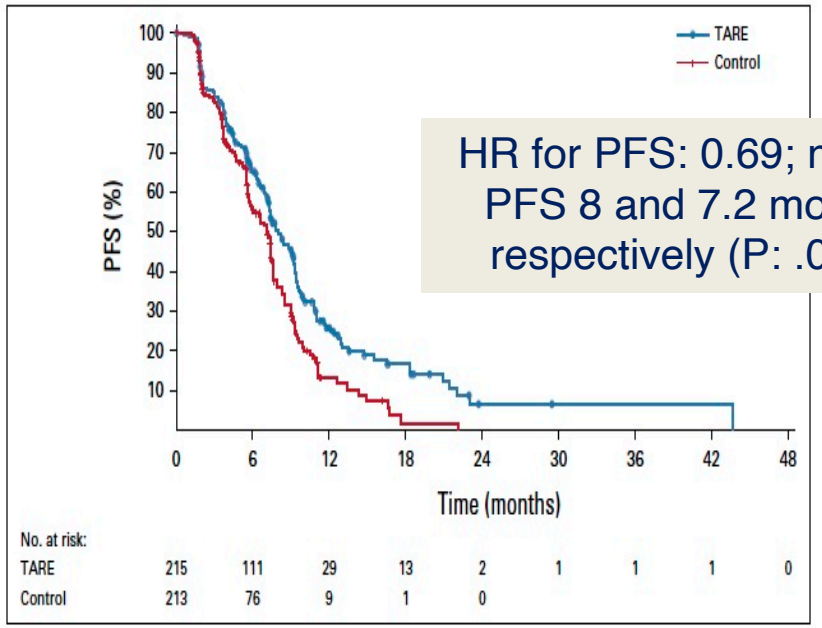
P: 0.002

SIRFLOX: 1st-line FOLFOX +/- Y90:

Radioembolization With Chemotherapy for Colorectal Liver Metastases: A Randomized, Open-Label, International, Multicenter, Phase III Trial

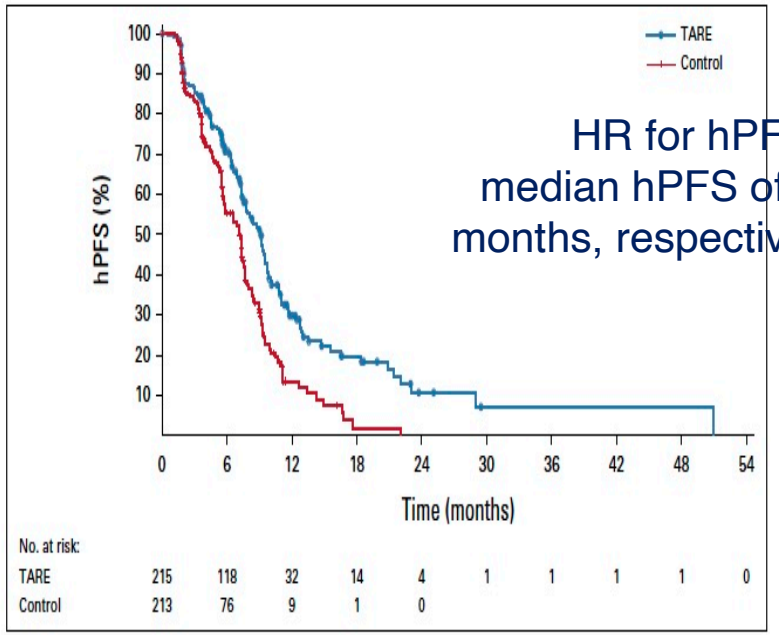
Mary F. Mulcahy, MD[1]; Armeen Mahvash, MD[2]; Marc Pracht, MD[3]; Amir H. Montazeri, MD[4]; Steve Bandula, MD, PhD[5]; Robert C. G. Martin II, MD[6]; Ken Herrmann, MD[7]; Ewan Brown, MD[8]; Darryl Zuckerman, MD[9]; Gregory Wilson, MD[10]; Tae-You Kim, M Andrew Weaver, MD[12]; Paul Ross, MD[13]; William P. Harris, MD[14]; Janet Graham, MD[15]; Jamie Mills, MD[16]; Alfonso Yubero Esteban, M Matthew S. Johnson, MD[18]; Constantinos T. Sofocleous, MD[19]; Siddharth A. Padia, MD[20]; Robert J. Lewandowski, MD[21]; Etienne Garin, MD[22]; Philip Sinclair, PhD[23]; and Riad Salem, MD, MBA[21]; for the EPOCH Investigators

TARE plus chemotherapy: 215/ chemotherapy alone: 213



HR for PFS: 0.69; median PFS 8 and 7.2 months, respectively (P: .0013)

FIG 2. Kaplan-Meier analysis of overall PFS for TARE plus chemotherapy versus chemotherapy in the intention-to-treat population. PFS, progression-free survival; TARE, transarterial yttrium-90 radioembolization.

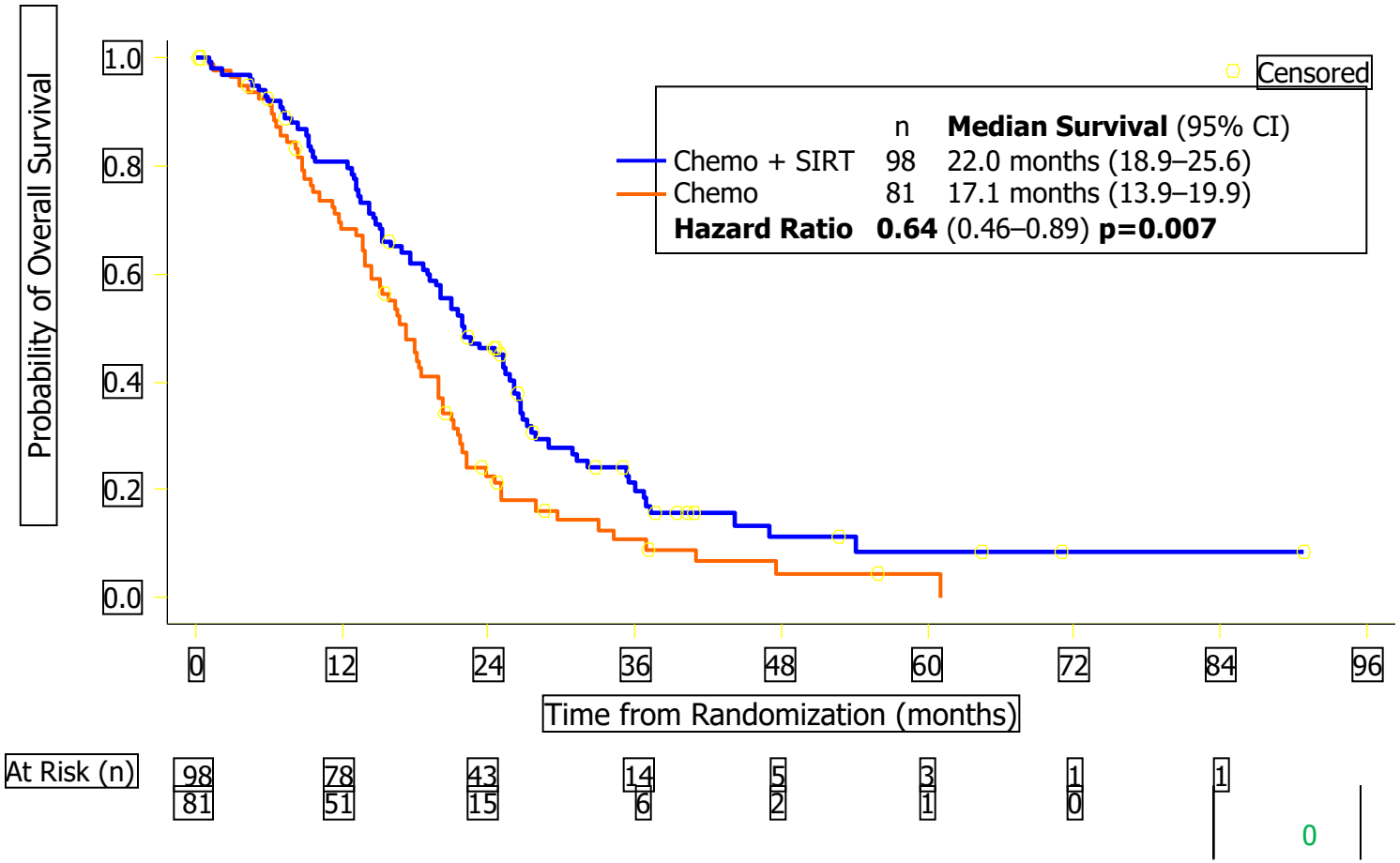


HR for hPFS: 0.59
median hPFS of 9.1 and 7.2 months, respectively (P: .0001)

FIG 3. Kaplan-Meier analysis of hPFS for TARE plus chemotherapy versus chemotherapy in the intention-to-treat population. hPFS, hepatic progression-free survival; TARE, transarterial yttrium-90 radioembolization.

Objective response rates 34.0% vs 21.1% (P: .0019) for TARE vs ChemoTx group, respectively.
31% protection against POD and 41% protection against Liver POD in the TARE group

Post Y90: Overall Survival for mCRC Patients with Right-Sided Primary Tumors

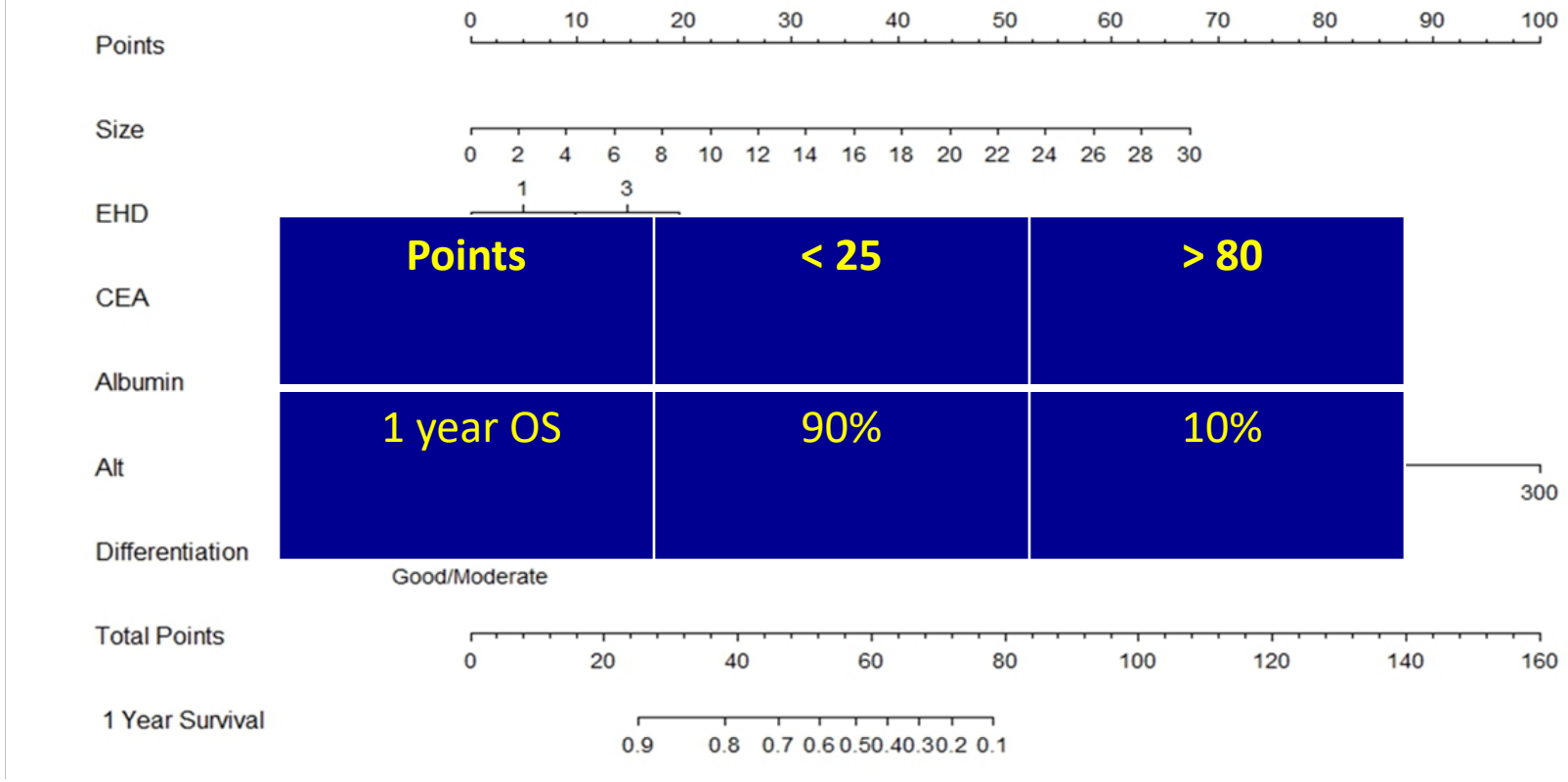


5 months prolongation of Median Survival and 36% protective effect against death

Impact of primary tumour location on survival in patients with metastatic CRC receiving SIRT and chemotherapy as first-line therapy. *Van Hazel G et al: SIRFLOX and FOXFIRE Global trial Investigators; Annals of Oncology*, (28) 3; 2017, mdx302.005. https://doi.org/10.1093/annonc/mdx302.005

Factors Affecting Oncologic Outcomes of 90Y Radioembolization of Heavily Pre-Treated Patients With Colon Cancer Liver Metastases

103 patients; 77% EHD, Median OS: 11.4 months



NOMOGRAM: 1-year OS of patients with total points of **<25 vs. >80 was 90% and 10%,** respectively

Bootstrap resampling showed **good discrimination** (optimism corrected c-index=0.745) and **calibration** (mean absolute prediction error=0.299) of the nomogram

Summary

- Use Imaging to define extent of disease and choose appropriate therapy
- Ablation +/- resection with chemotherapy prolongs patient survival
- Repeated ablations for LTP or new metastases prolongs survival without toxicity
- Tumor Biology can be assessed with Test of Time offering the least invasive treatment initially and close follow-up
- For small tumors that can be ablated with A0; ablation can be offered ahead of Surgery
- Consider IRE /Radiation Segmentectomy/ SBRT for Tumors that cannot undergo R0/AO

Thank You!

Thank You!