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Supported by an Independent Educational Grant from BAYER

LOCOREGIONAL TREATMENTS ON COLORECTAL CANCER LIVER METASTASES

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ABLATION TECHNIQUES

NIH NATIONAL CANCER INSTITUTE

Local ablation

Radiofrequency ablation has emerged as a safe technique (2% major morbidity and <1% mortality rate) that may provide for long-term tumor control.[18-24] Radiofrequency ablation and cryosurgical ablation [25-28] remain options for patients with tumors that cannot be resected and for patients who are not candidates for liver resection.

18. Rossi S, Buscarini E, Garbagnati F, et al.: Percutaneous treatment of small hepatic tumors by an expandable RF needle electrode. AJR Am J Roentgenol 170 (4): 1015-22, 1998. [PUBMED Abstract]

19. Solbiati L, Livraghi T, Goldberg SN, et al.: Percutaneous radio-frequency ablation of hepatic metastases from colorectal cancer: long-term results in 117 patients. Radiology 221 (1): 159-66, 2001. [PUBMED Abstract]

20. Lencioni R, Goletti O, Armillotta N, et al.: Radio-frequency thermal ablation of liver metastases with a cooled-tip electrode needle: results of a pilot clinical trial. Eur Radiol 8 (7): 1205-11, 1998. [PUBMED Abstract]

21. Curley SA, Izzo F, Delrio P, et al.: Radiofrequency ablation of unresectable primary and metastatic hepatic malignancies: results in 123 patients. Ann Surg 230 (1): 1-8, 1999. [PUBMED Abstract]

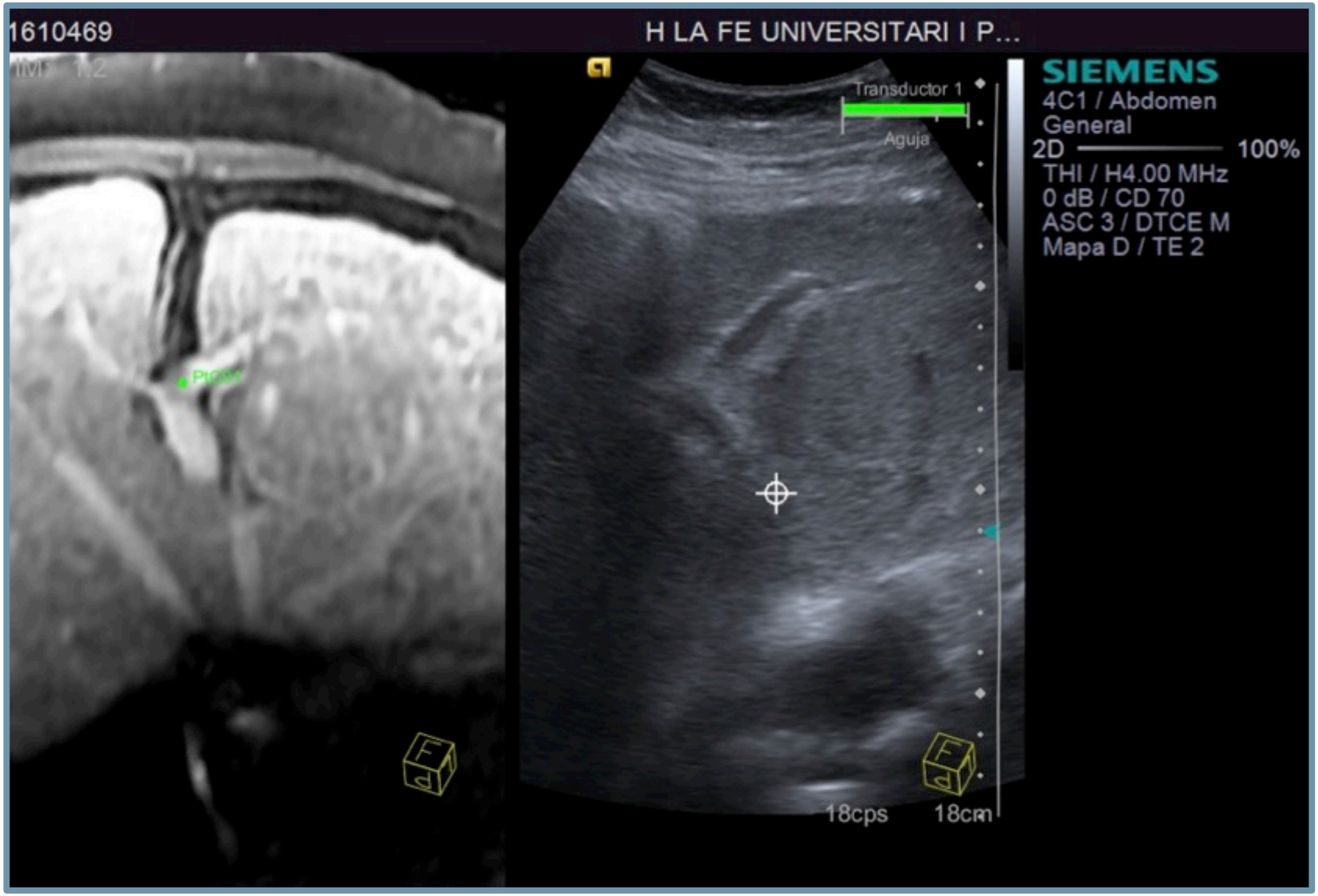
22. Oshowo A, Gillams A, Harrison E, et al.: Comparison of resection and radiofrequency ablation for treatment of solitary colorectal liver metastases. Br J Surg 90 (10): 1240-3, 2003. [PUBMED Abstract]

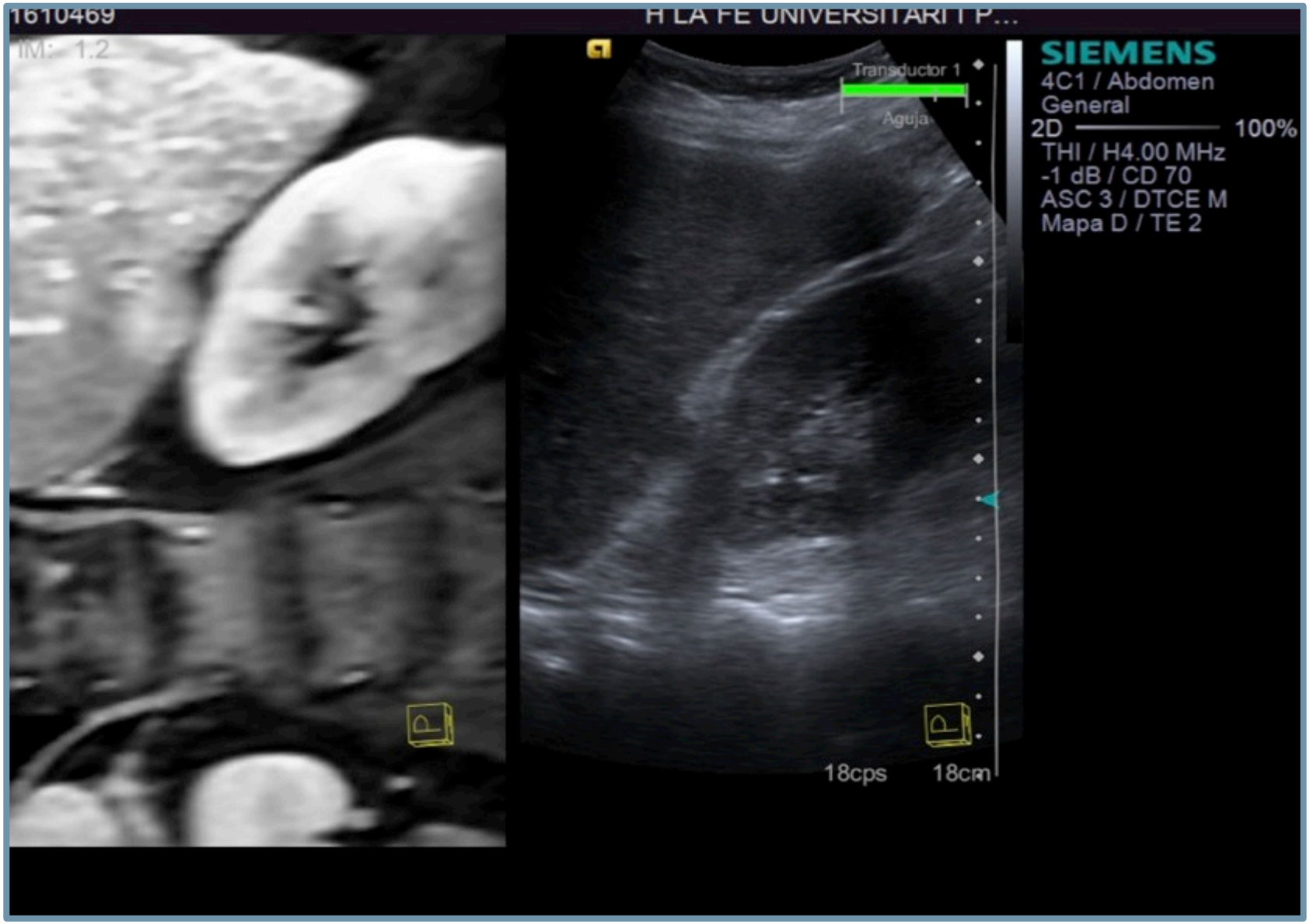
23. Livraghi T, Solbiati L, Meloni F, et al.: Percutaneous radiofrequency ablation of liver metastases in potential candidates for resection: the "test-of-time approach". Cancer 97 (12): 3027-35, 2003. [PUBMED Abstract]

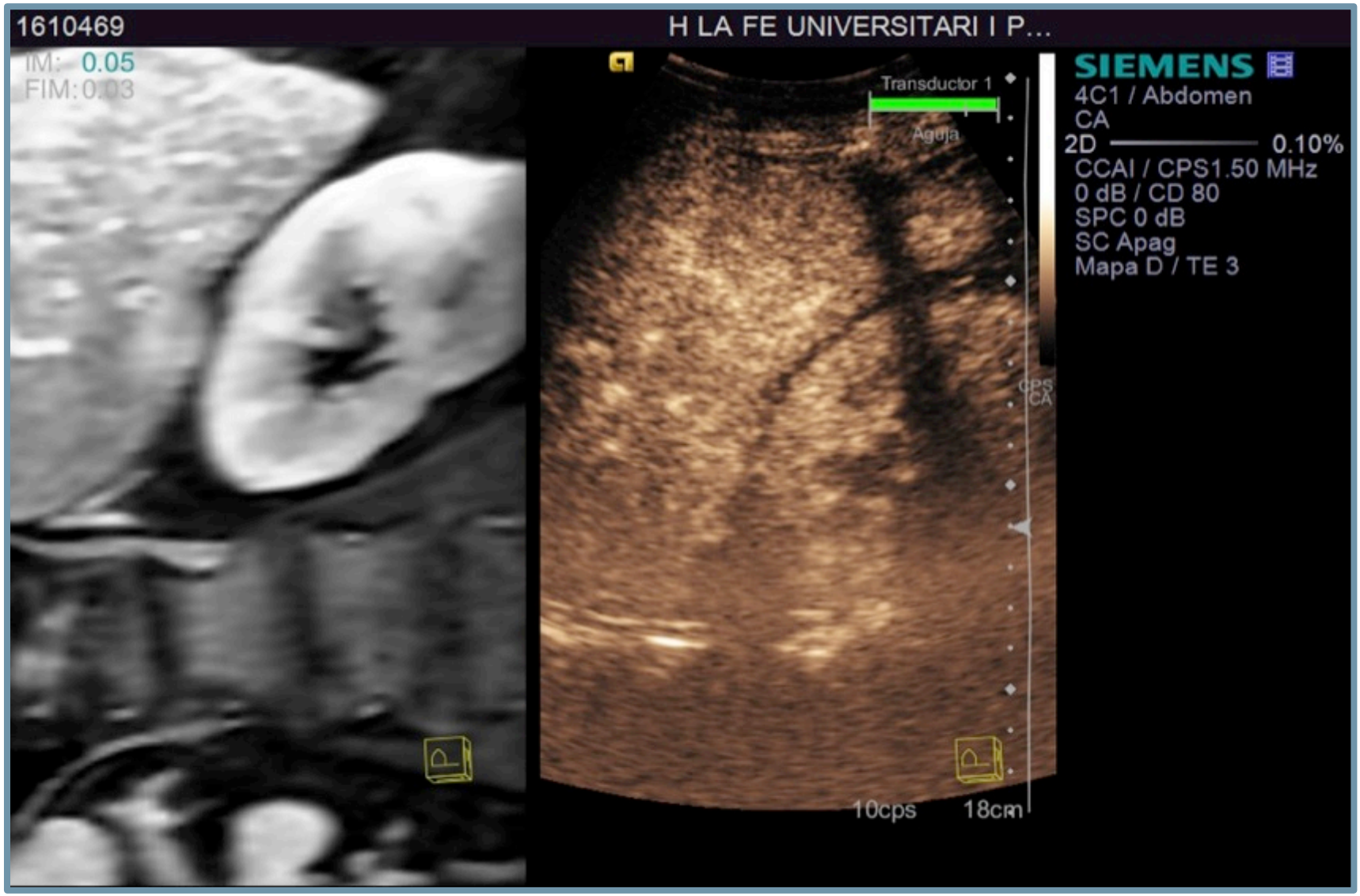
24. Pawlik TM, Izzo F, Cohen DS, et al.: Combined resection and radiofrequency ablation for advanced hepatic malignancies: results in 172 patients. Ann Surg Oncol 10 (9): 1059-69, 2003. [PUBMED Abstract]

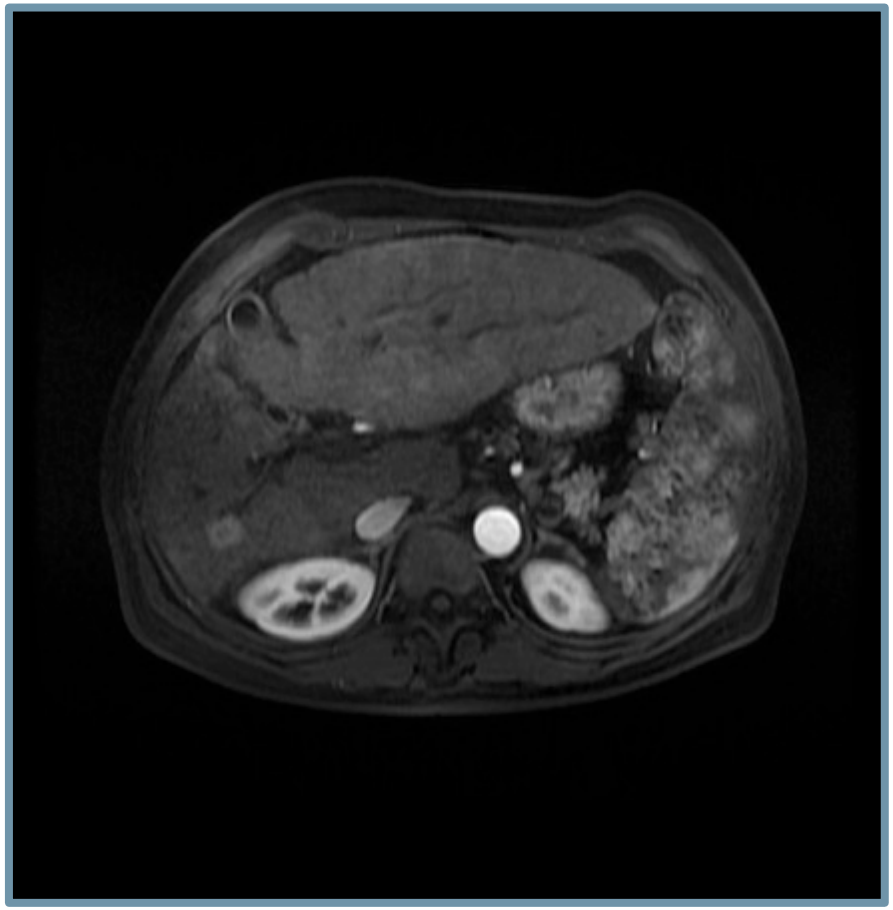
MULTIMODALITY IMAGE FUSION

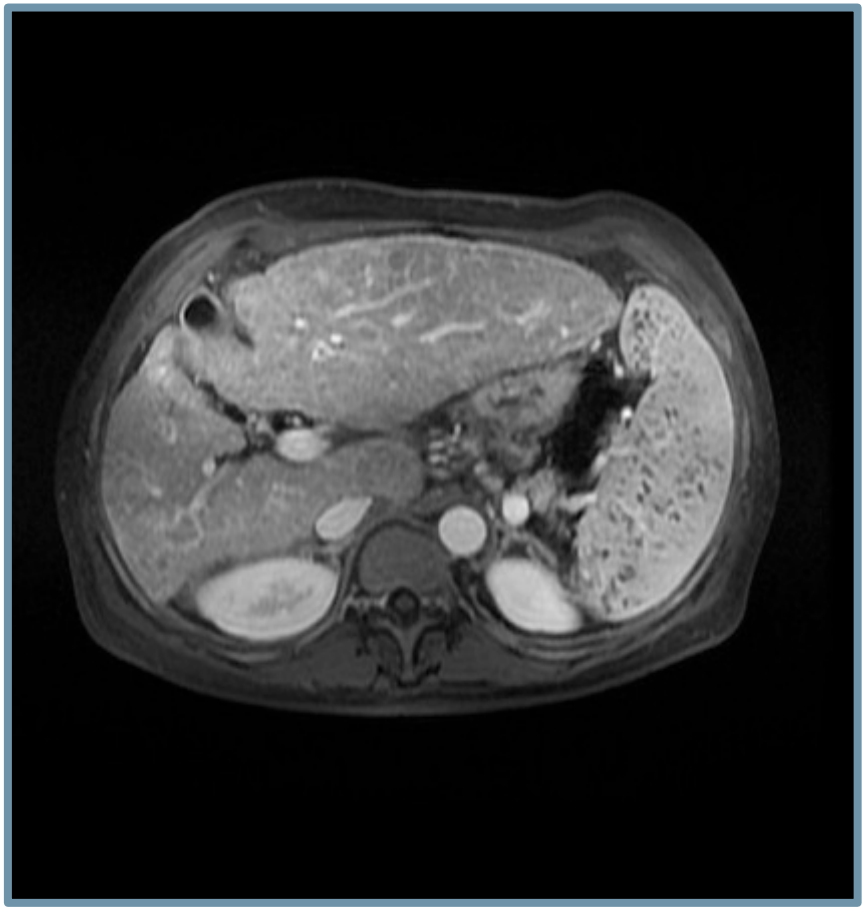
IMPROVES NODULES IDENTIFICATION

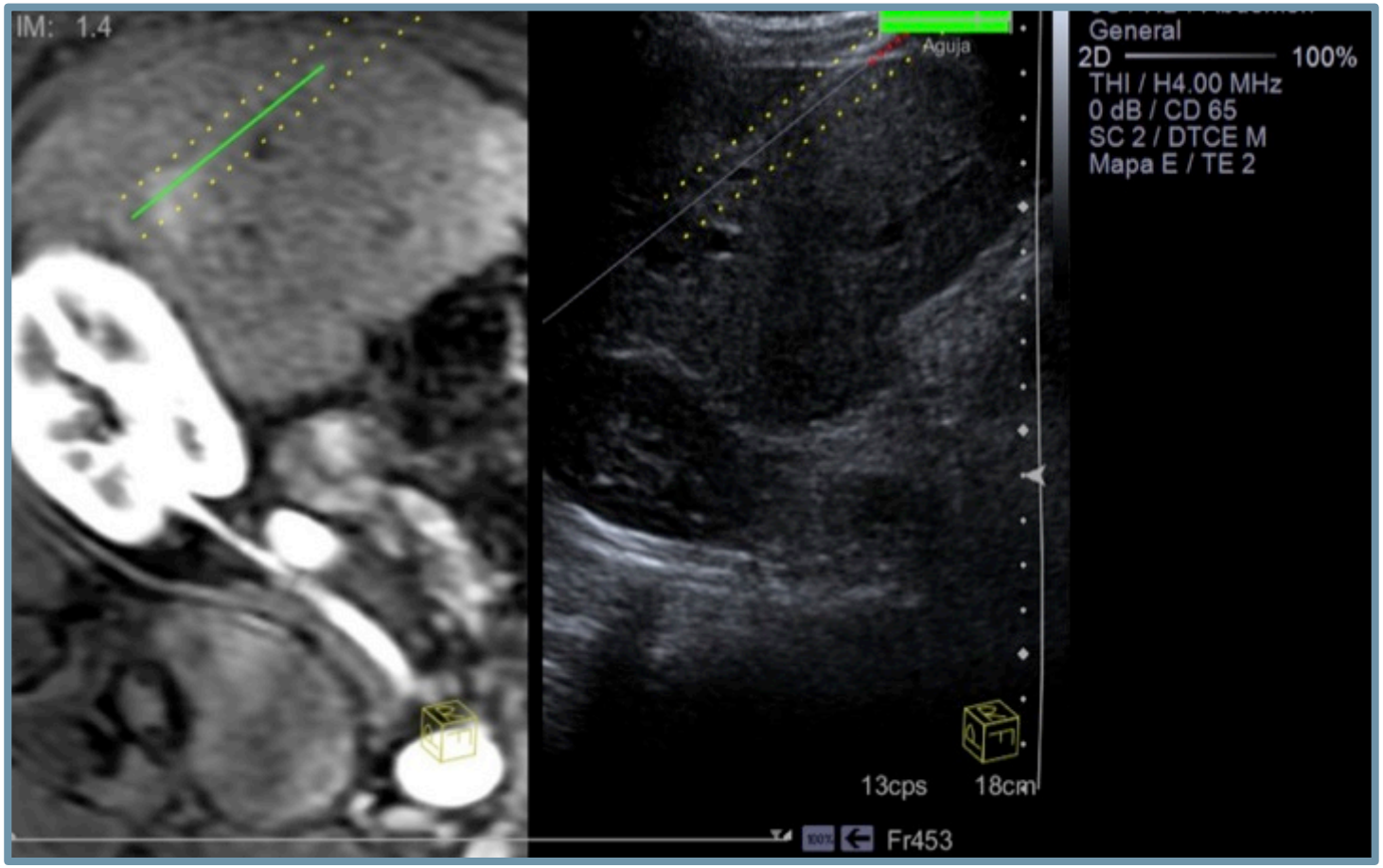


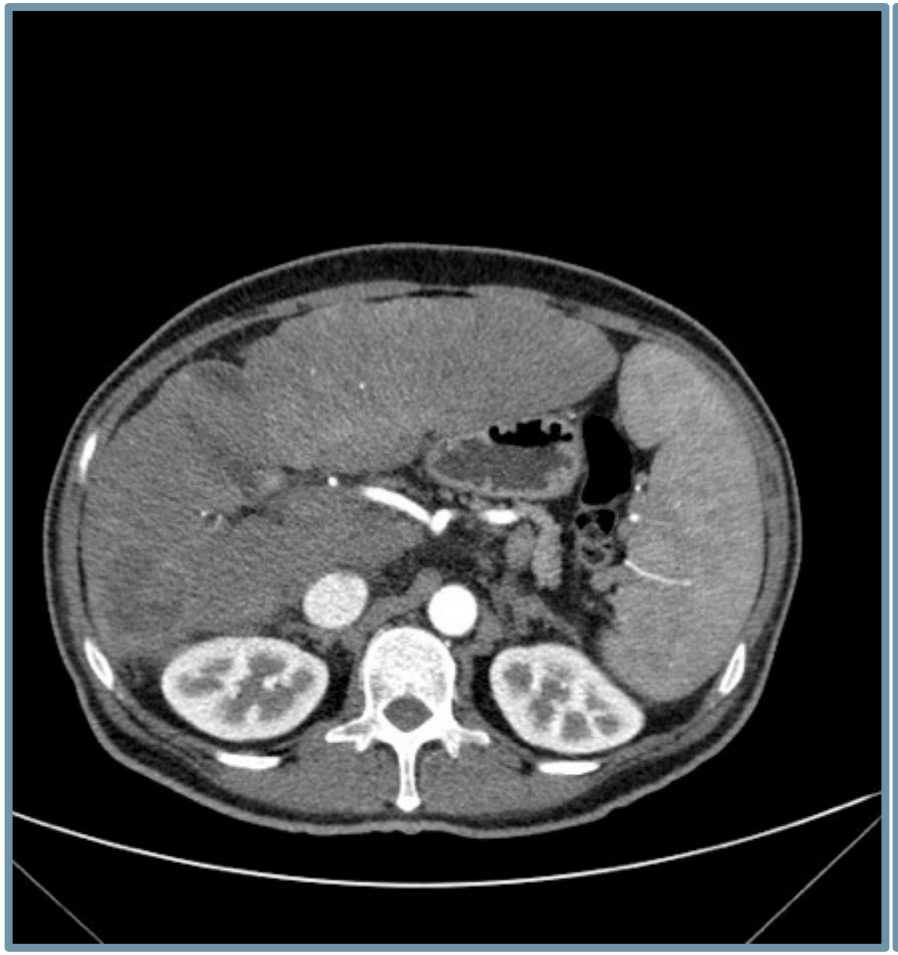


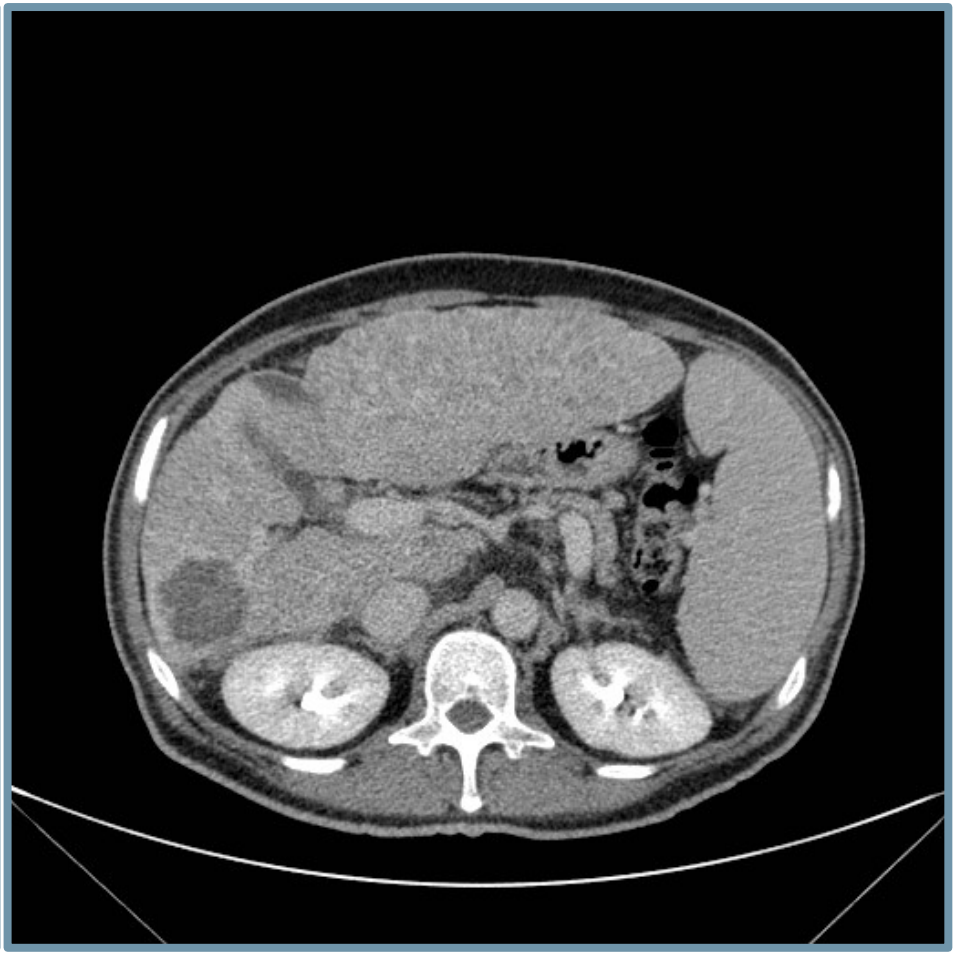












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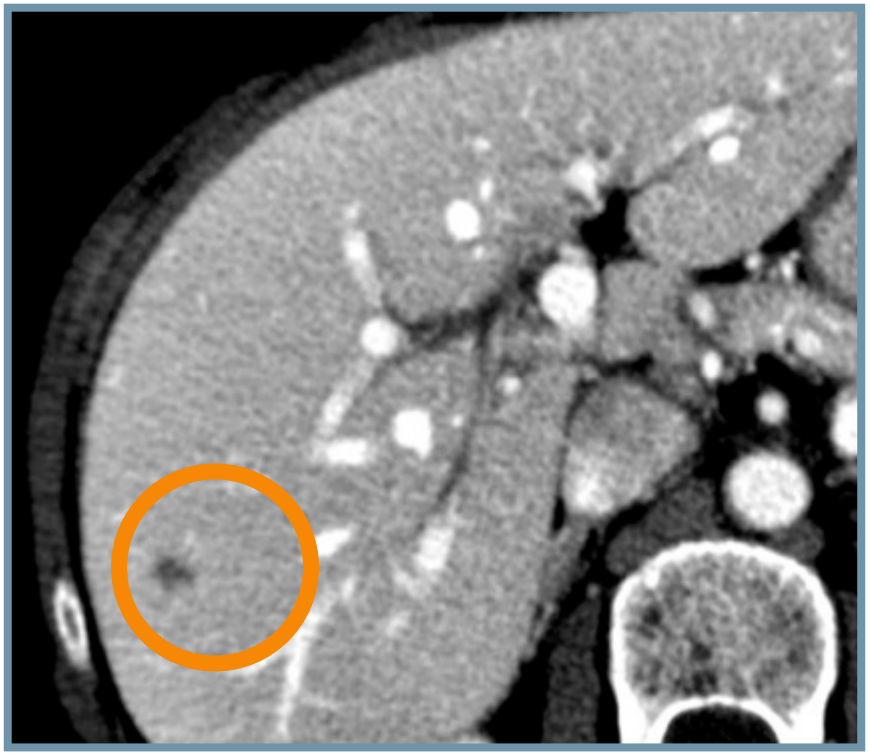
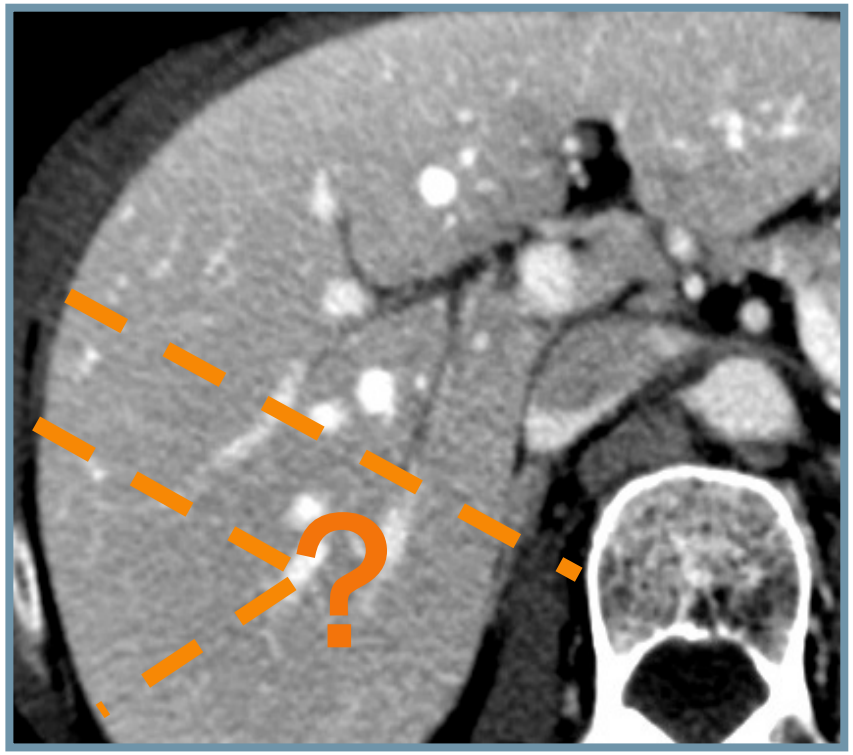
ALLOWS THE TREATMENT OF MISSING METASTASIS



Before systemic CT



After 6 cycles of CT

Wait for it to come back?

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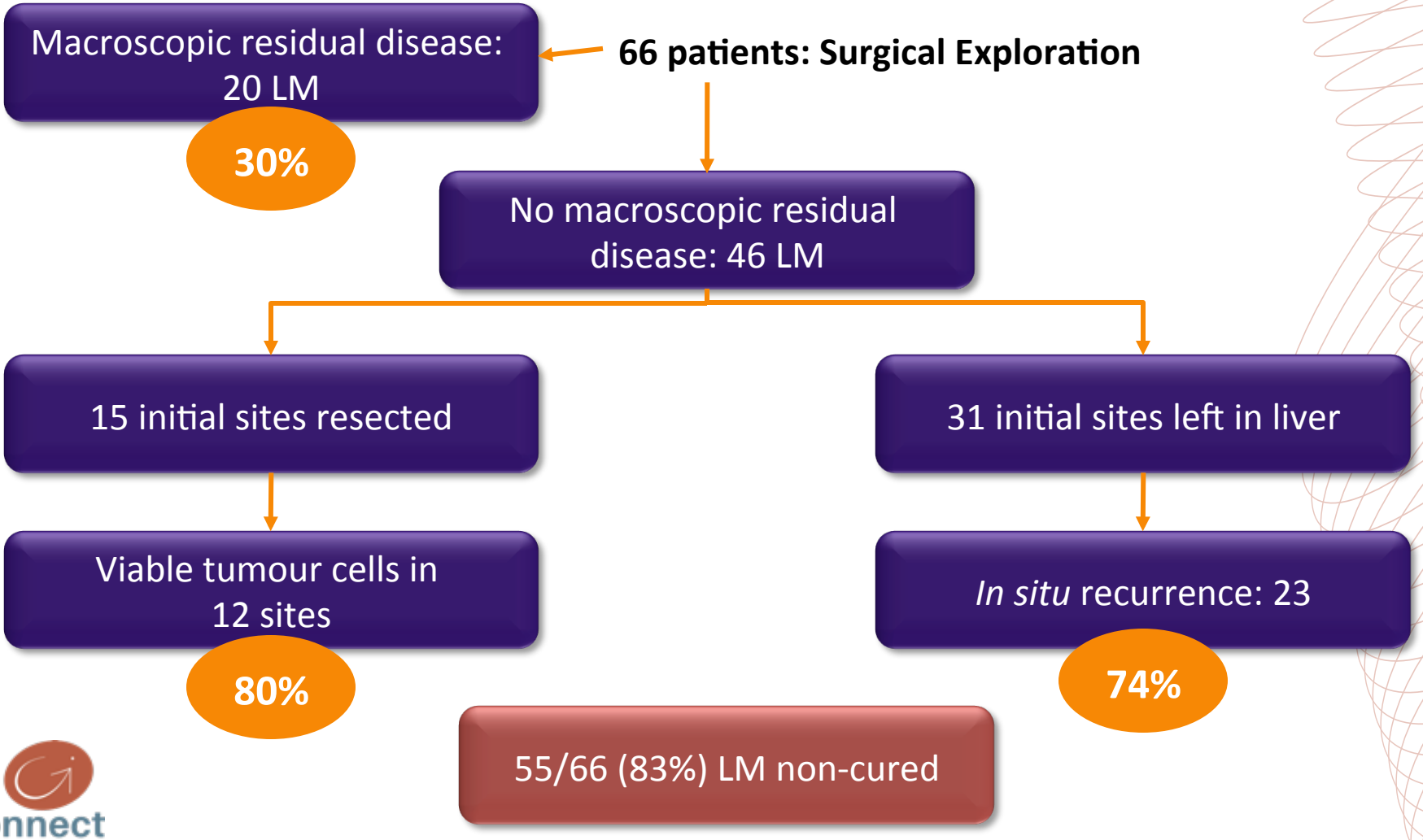
COMPLETE RESPONSE OF COLORECTAL LIVER METASTASES AFTER CHEMOTHERAPY: DOES IT MEAN CURE?



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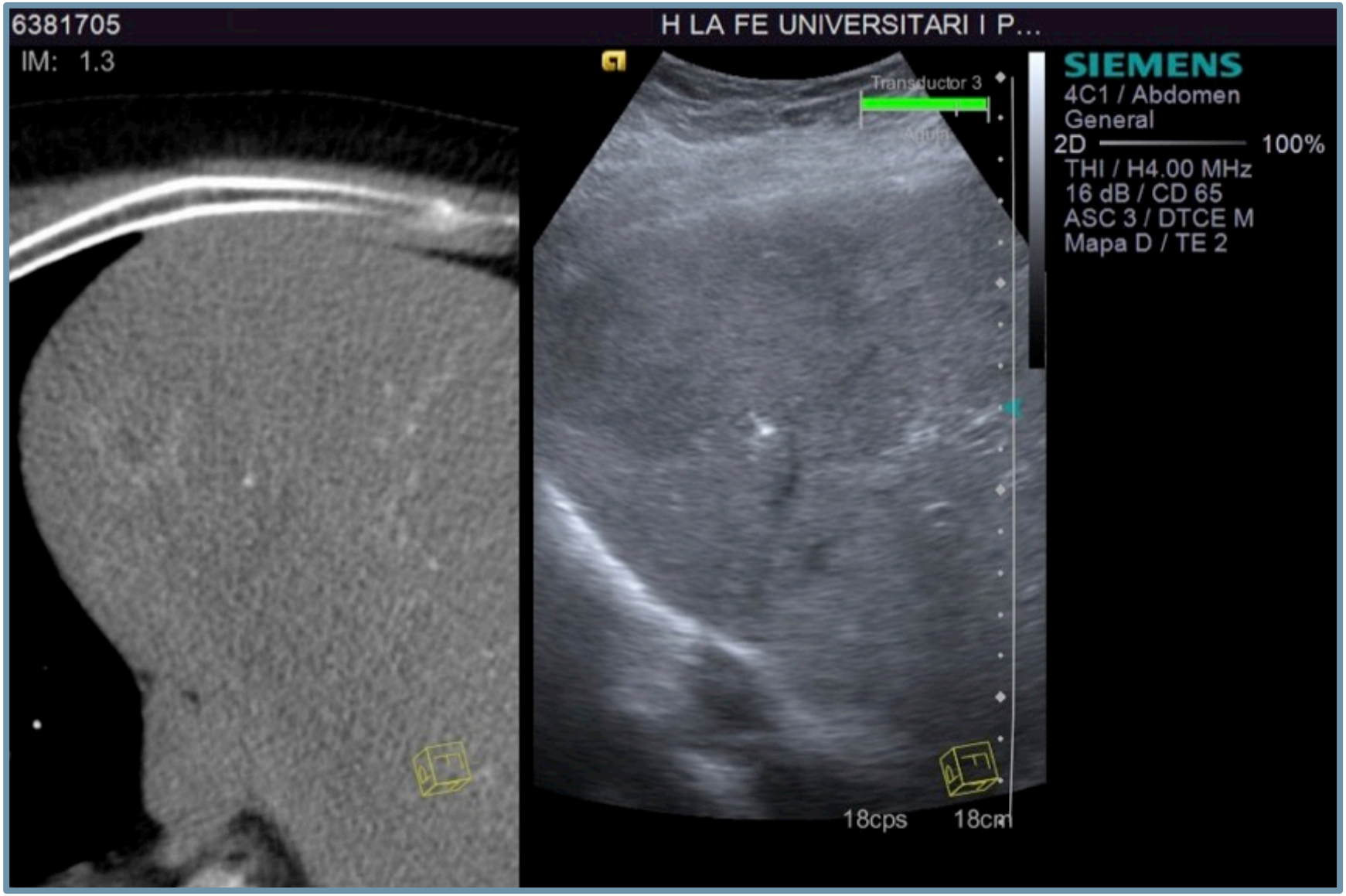
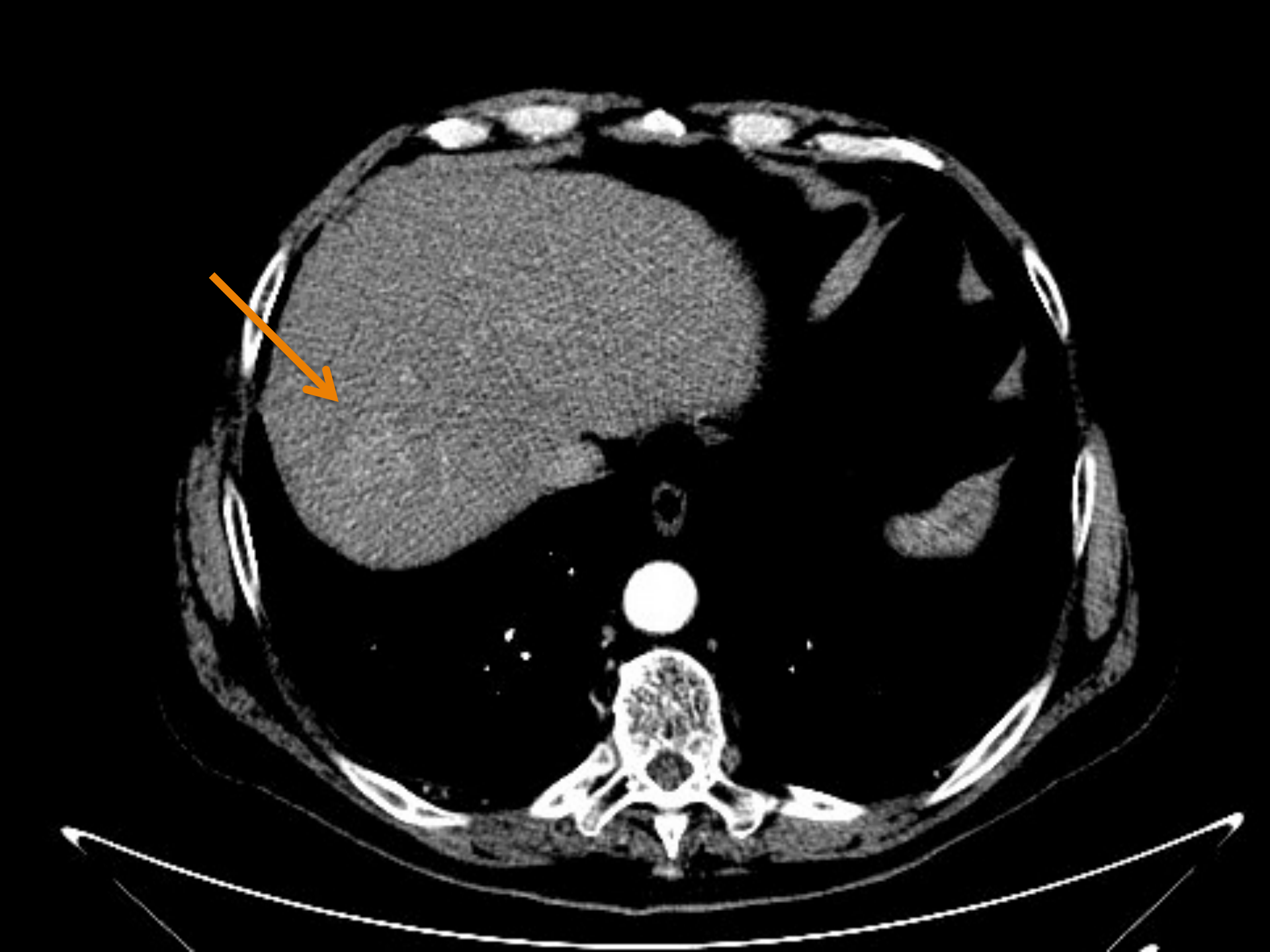
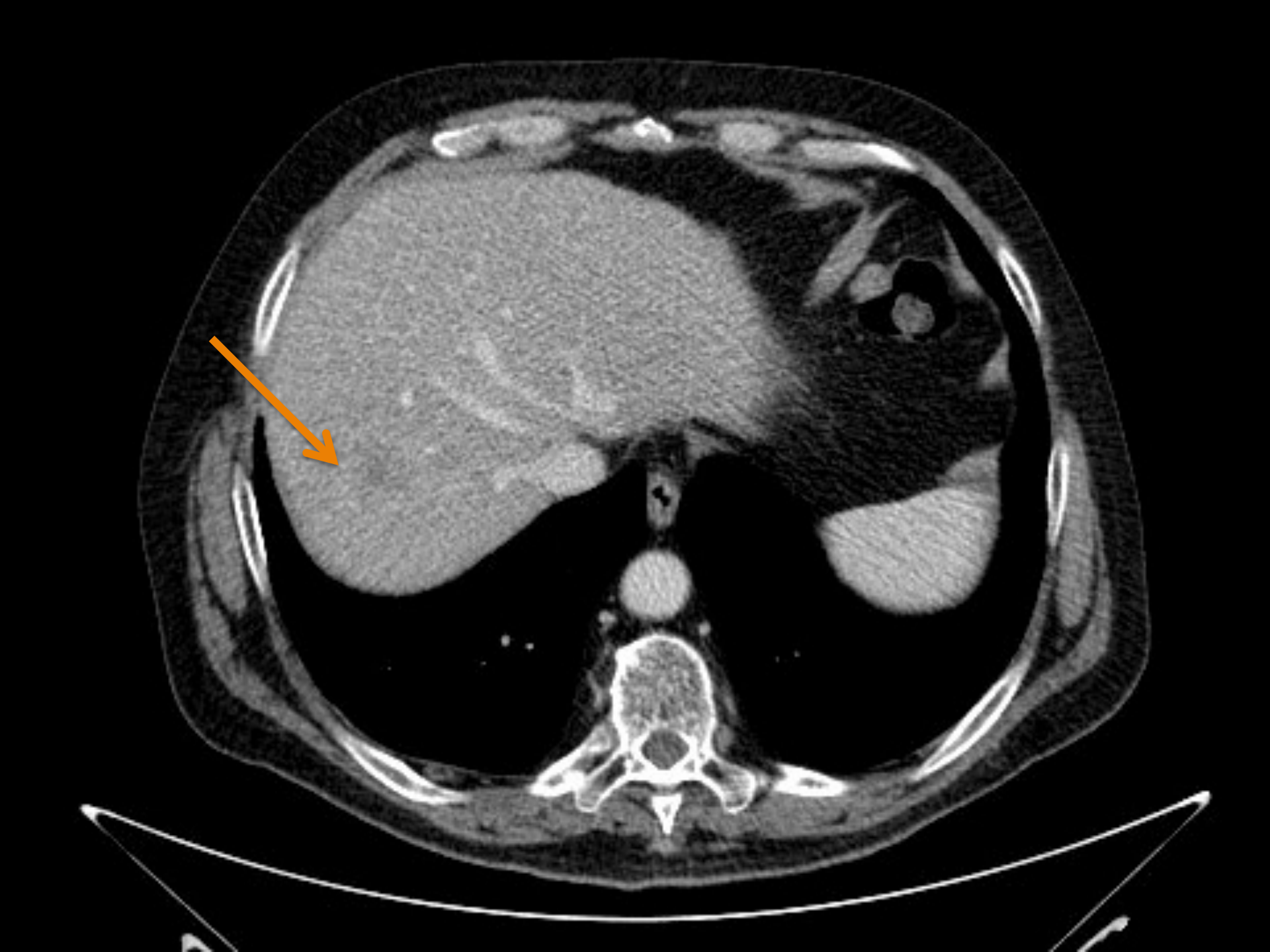
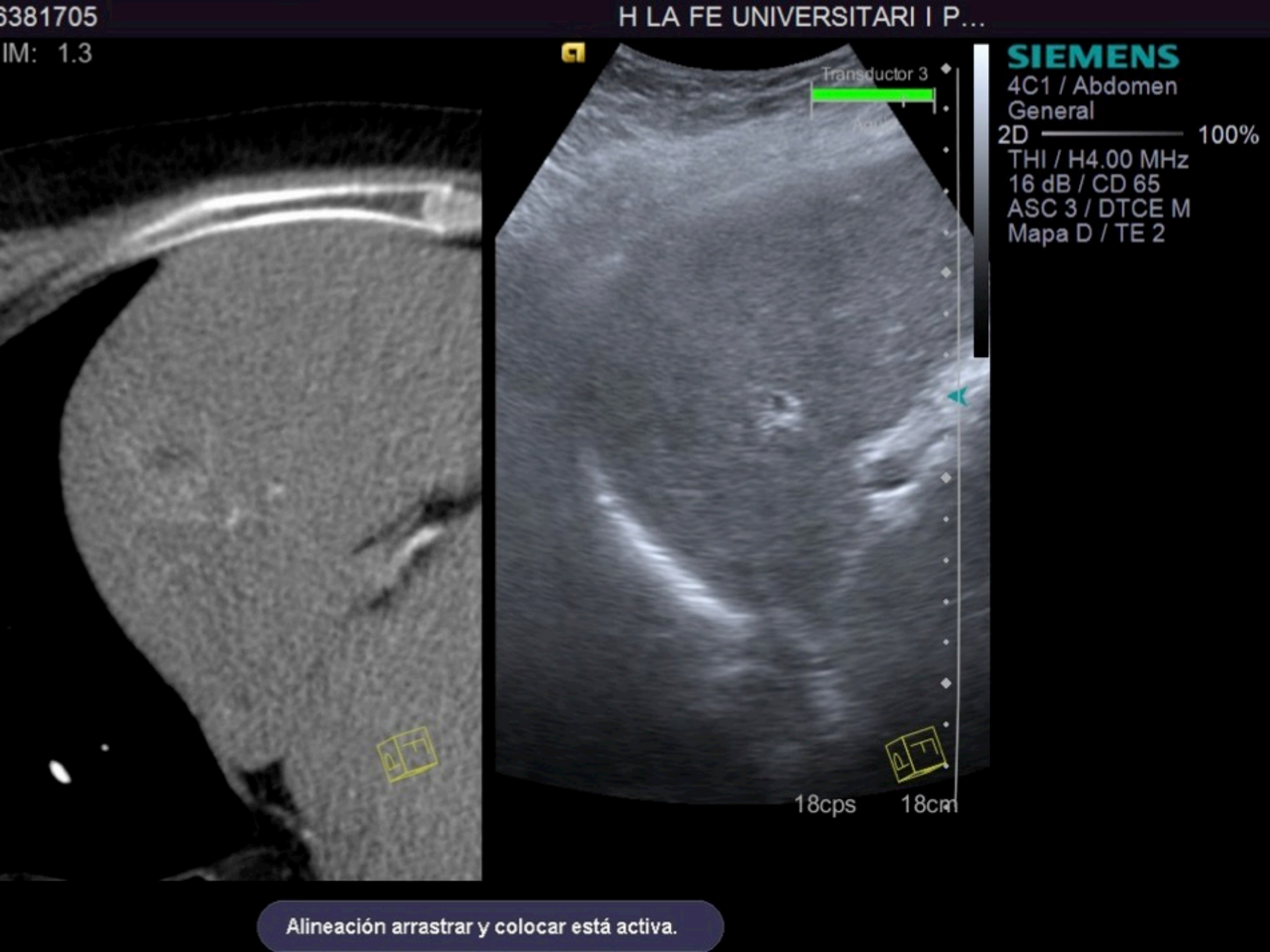
Benoist et al. J Clin Oncol 2006;24:3939-45





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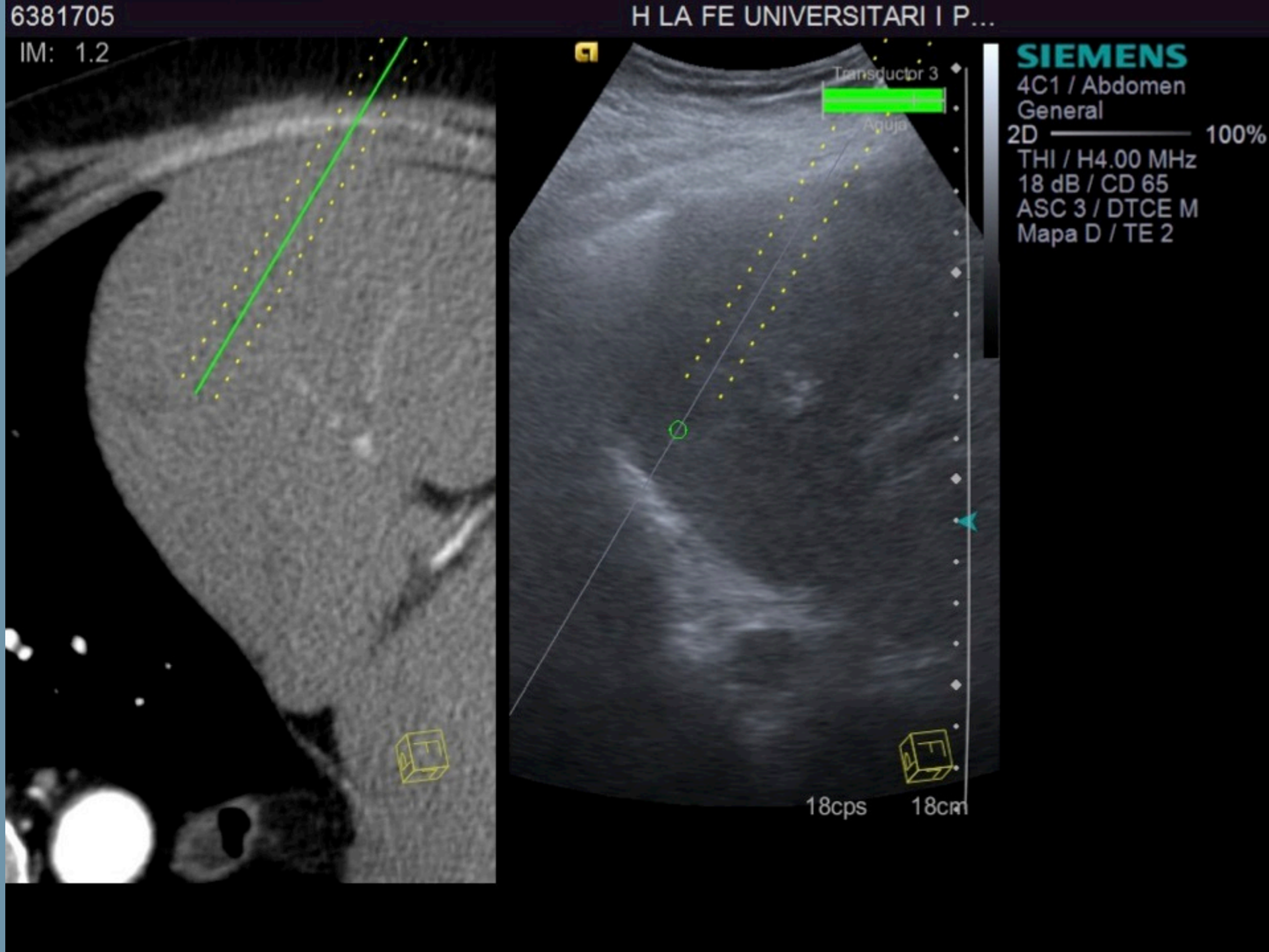
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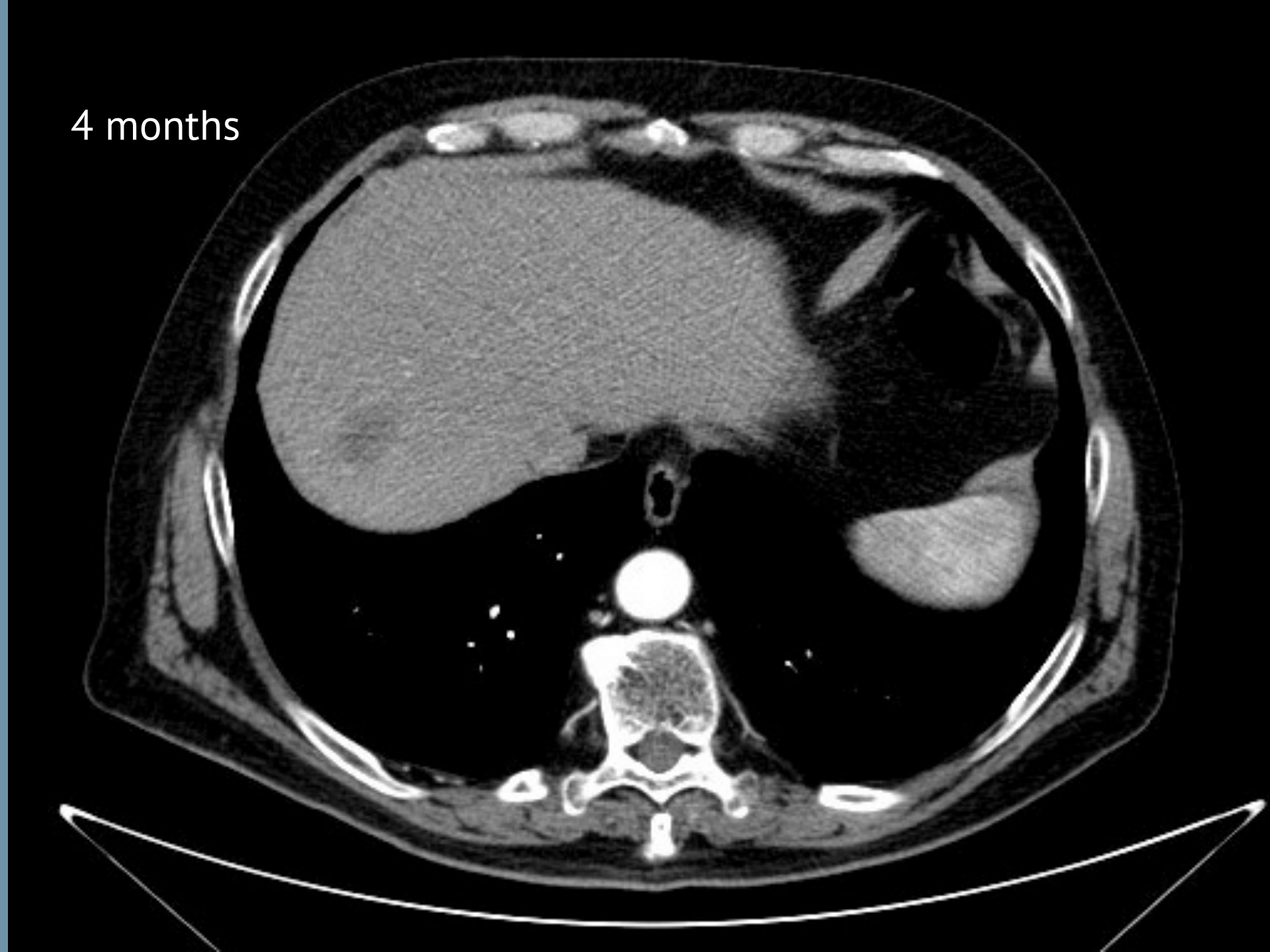
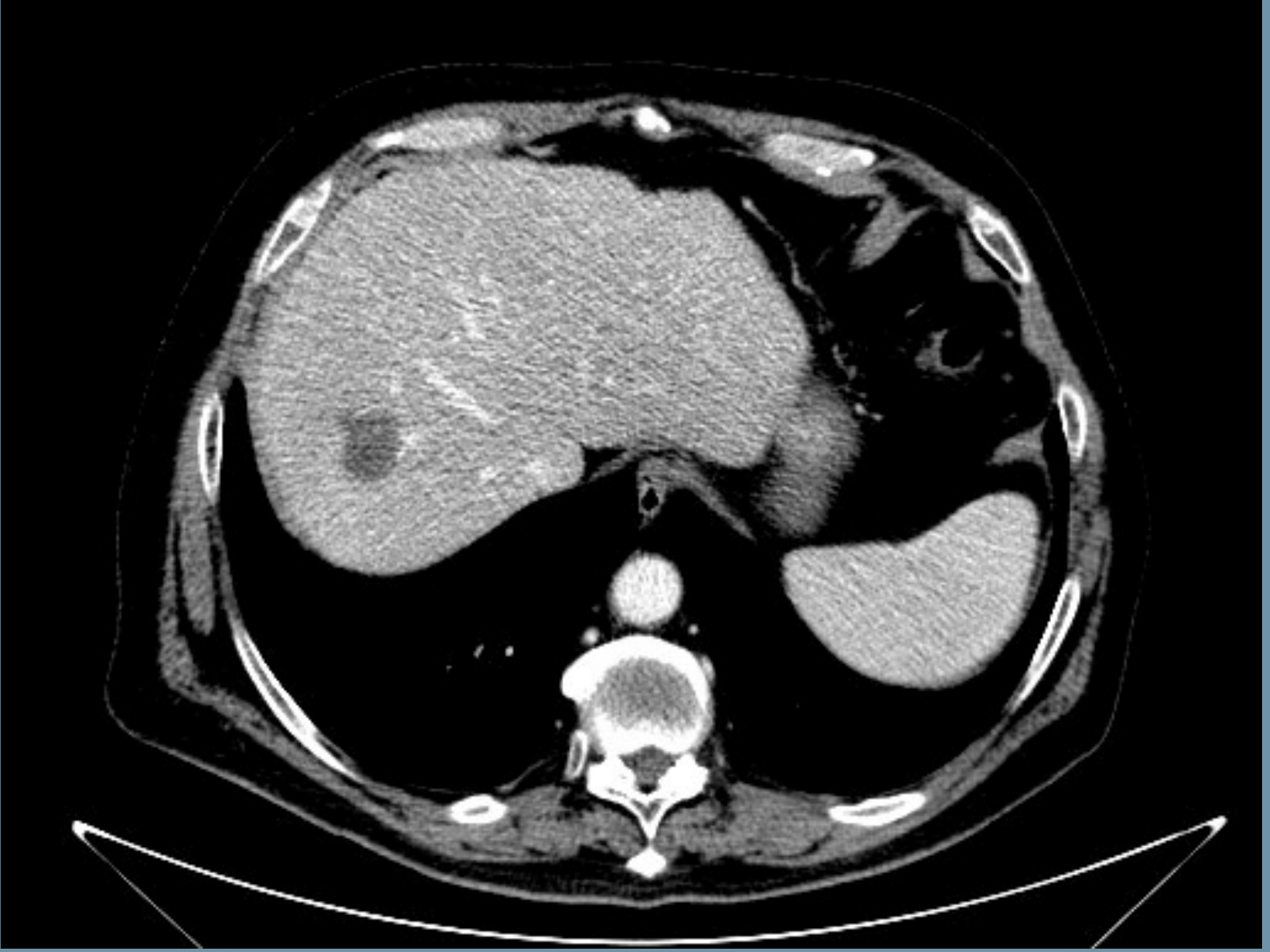
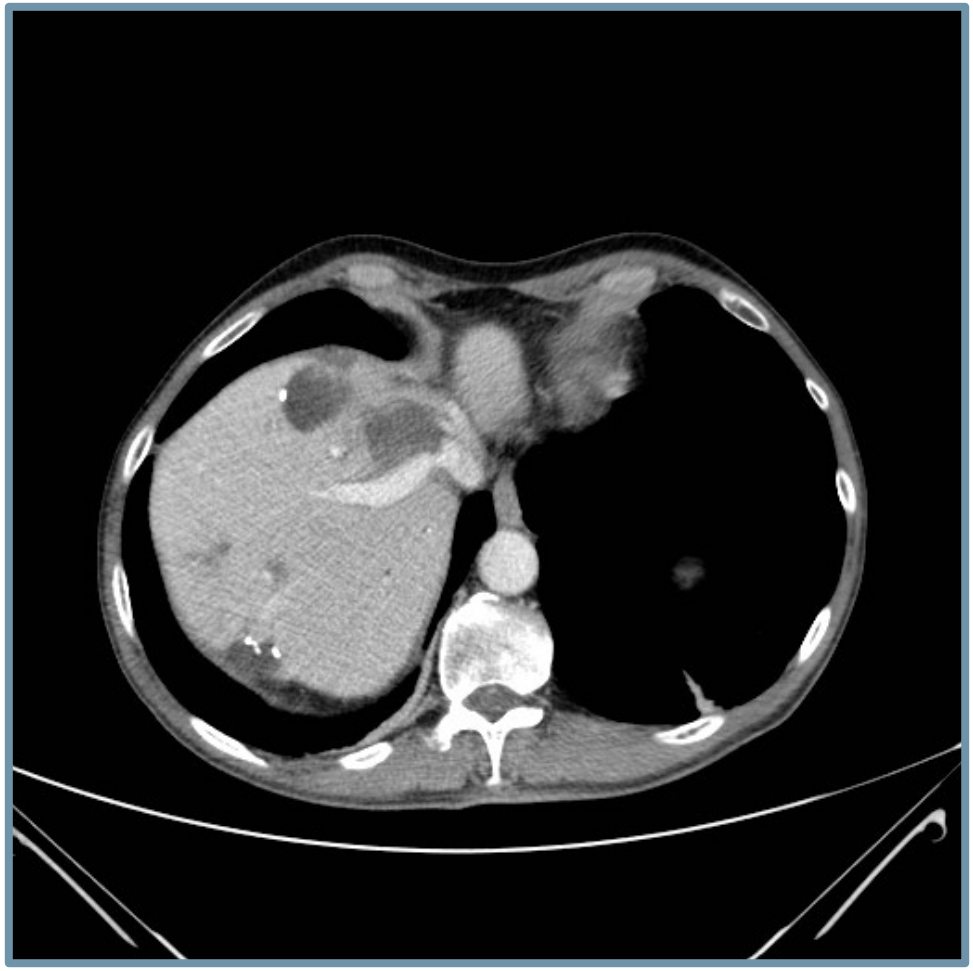
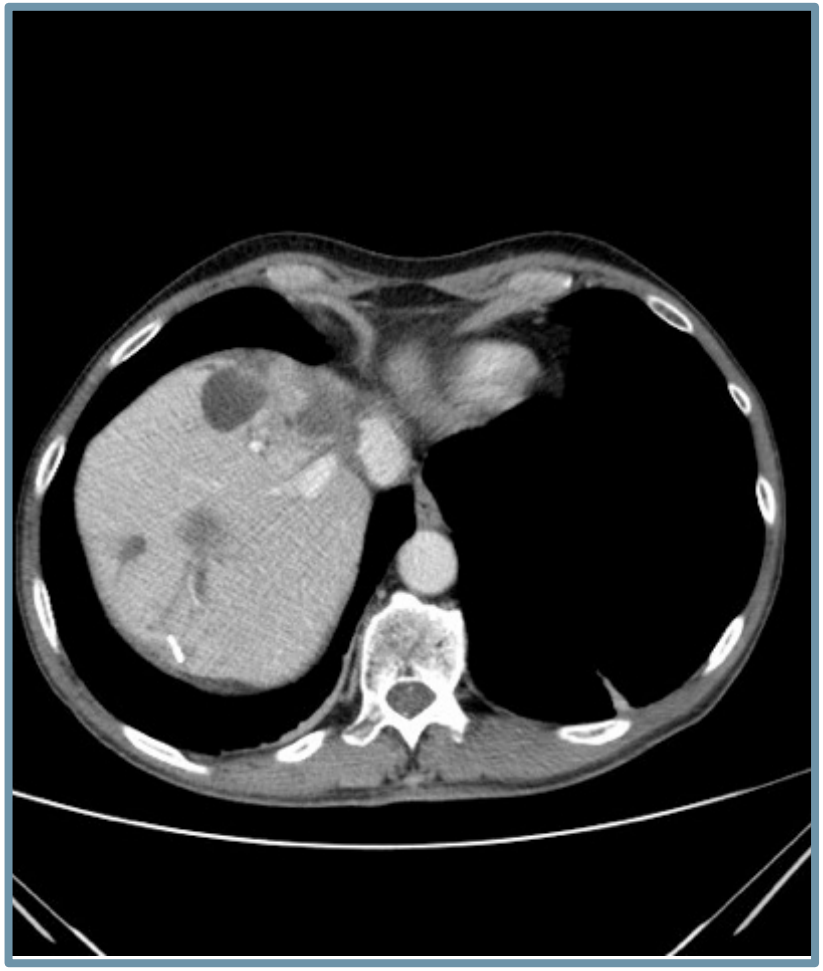
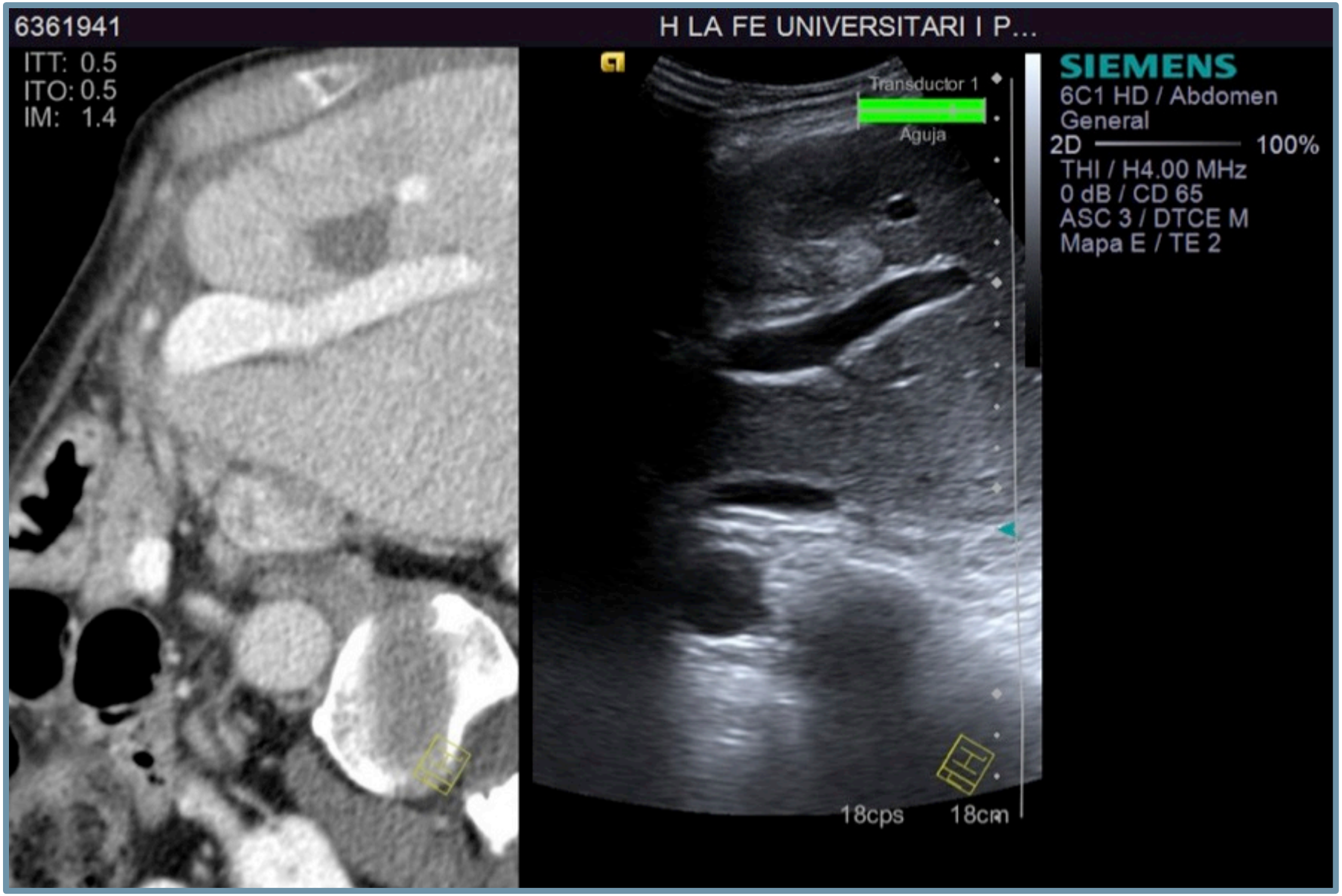

4 months









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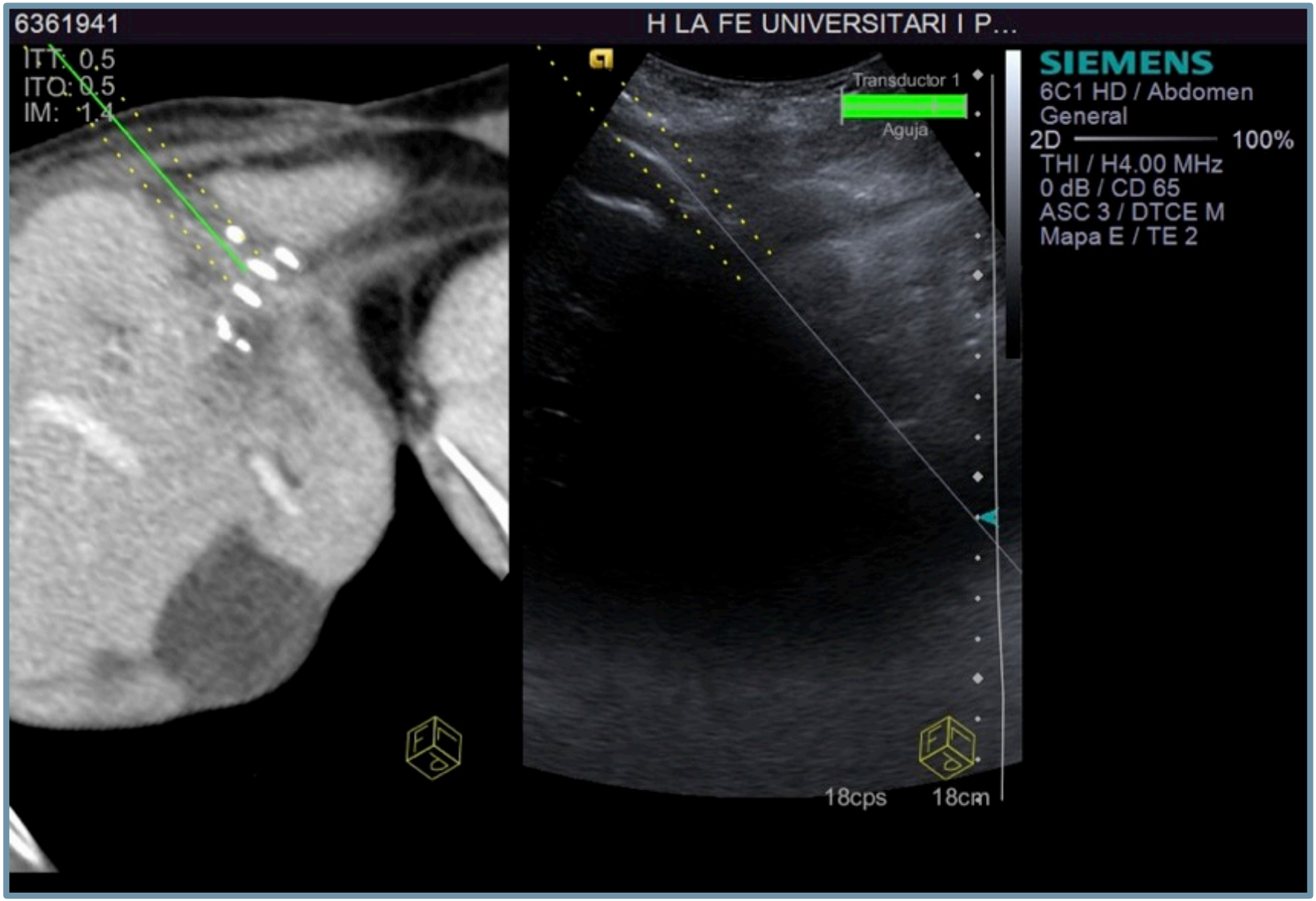

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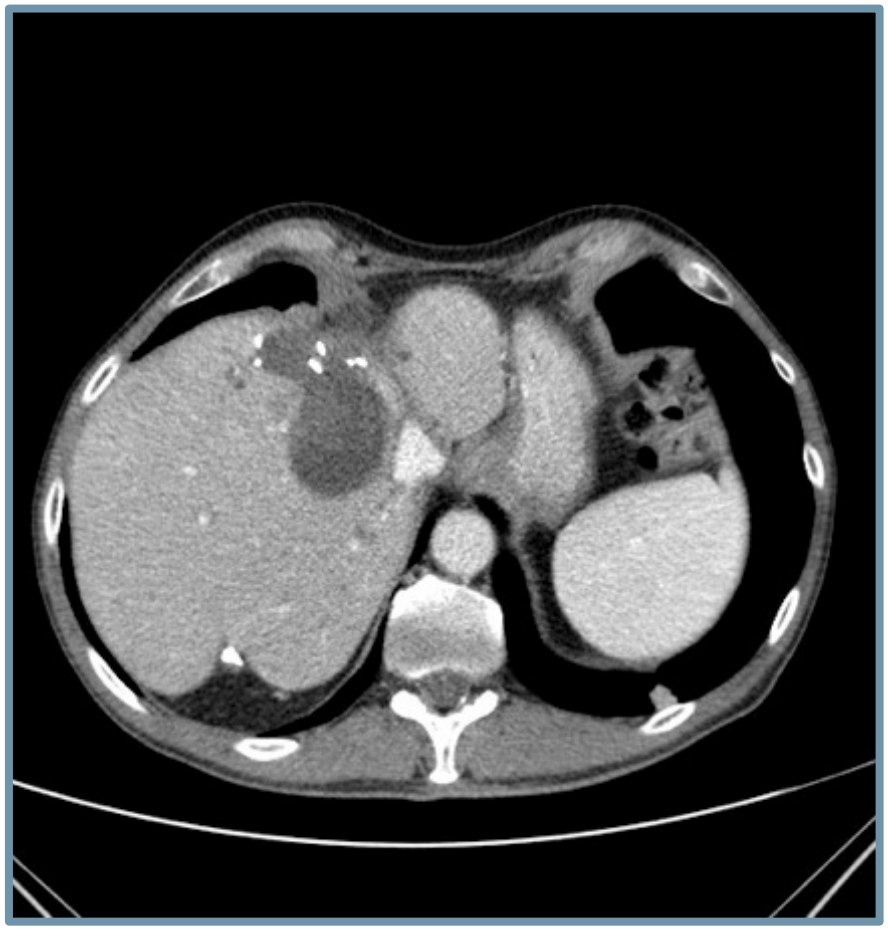

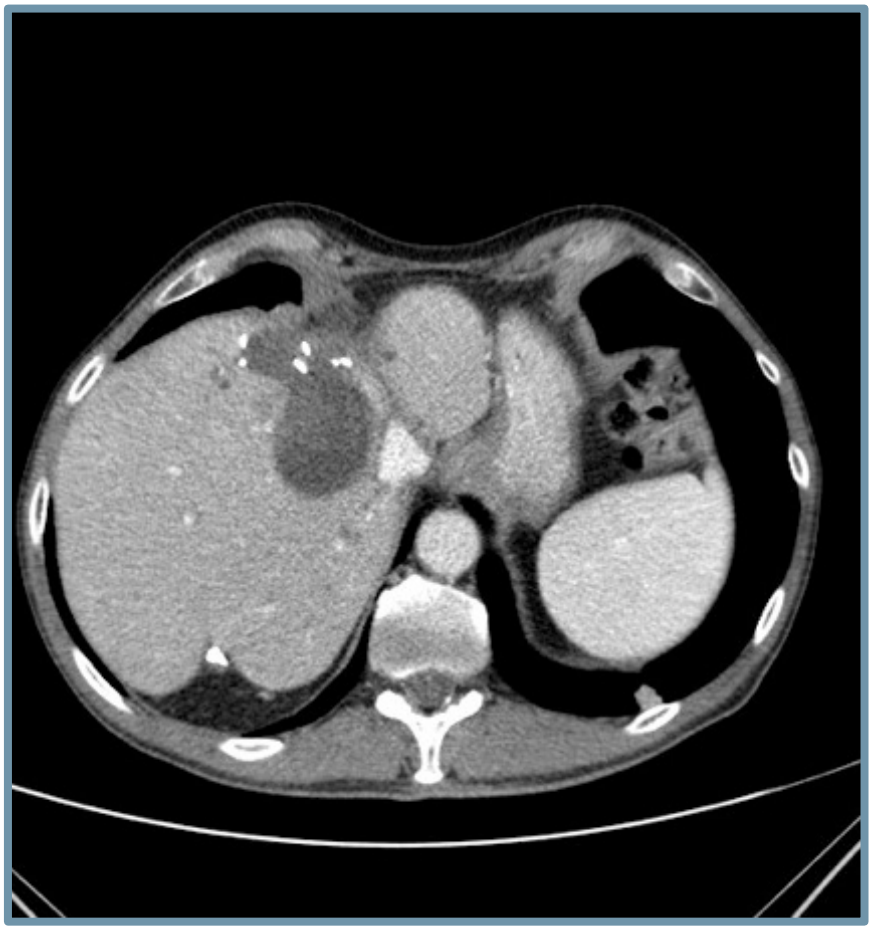

3 months control

DRUG ELUTING BEADS INFUSION

Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481)

Kemeny NE et al. J Clin Oncol. 2006 Mar 20;24(9):1395-403.

CALGB 9481

- 135 prospective patients
- M1 liver, non resectable
- First line
- HAI: Floxuridine (0.18 mg · kg · 30 mL) + Leucovorin (4 mg · m2 · 30 mL)
- Systemic: Fluorouracil (425 mg/m2) + Leucovorin (20 mg/m2)

Kemeny NE et al. J Clin Oncol. 2006 Mar 20;24(9):1395-403.

	HAI	Systemic	p
OS	24 months	20 months	.0034
Response	47 %	24 %	.012
Time hepatic progression	9.8 months	7.3 months	.034
Time extrahepatic progression	7.7 months	14.8 months	.029
Neutropenia: grade > 3	2 %	45 %	< .01
Estomatitis	0 %	24 %	< .01
Rise Brb	18.6 %	0 %	< .01

Kemeny NE et al. J Clin Oncol. 2006 Mar 20;24(9):1395-403.

Conclusion

HAI therapy increased overall survival, response rate, THP, and was associated with better physical functioning compared with systemic therapy. Additional studies need to address the overall benefit and cost of new chemotherapy agents versus HAI alone or the combination of HAI with new agents.

J Clin Oncol 24:1395-1403. © 2006 by American Society of Clinical Oncology

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Kemeny NE et al. J Clin Oncol. 2006 Mar 20;24(9):1395-403.

Hepatic arterial infusion combined with oral UFT/ UZEL systemic chemotherapy for unresectable liver metastasis of colorectal cancer

Tsutsumi S et al. Hepatogastroenterology.2008 Jul-Aug;55(85): 1419-22.

TSUTSUMI S ET AL.

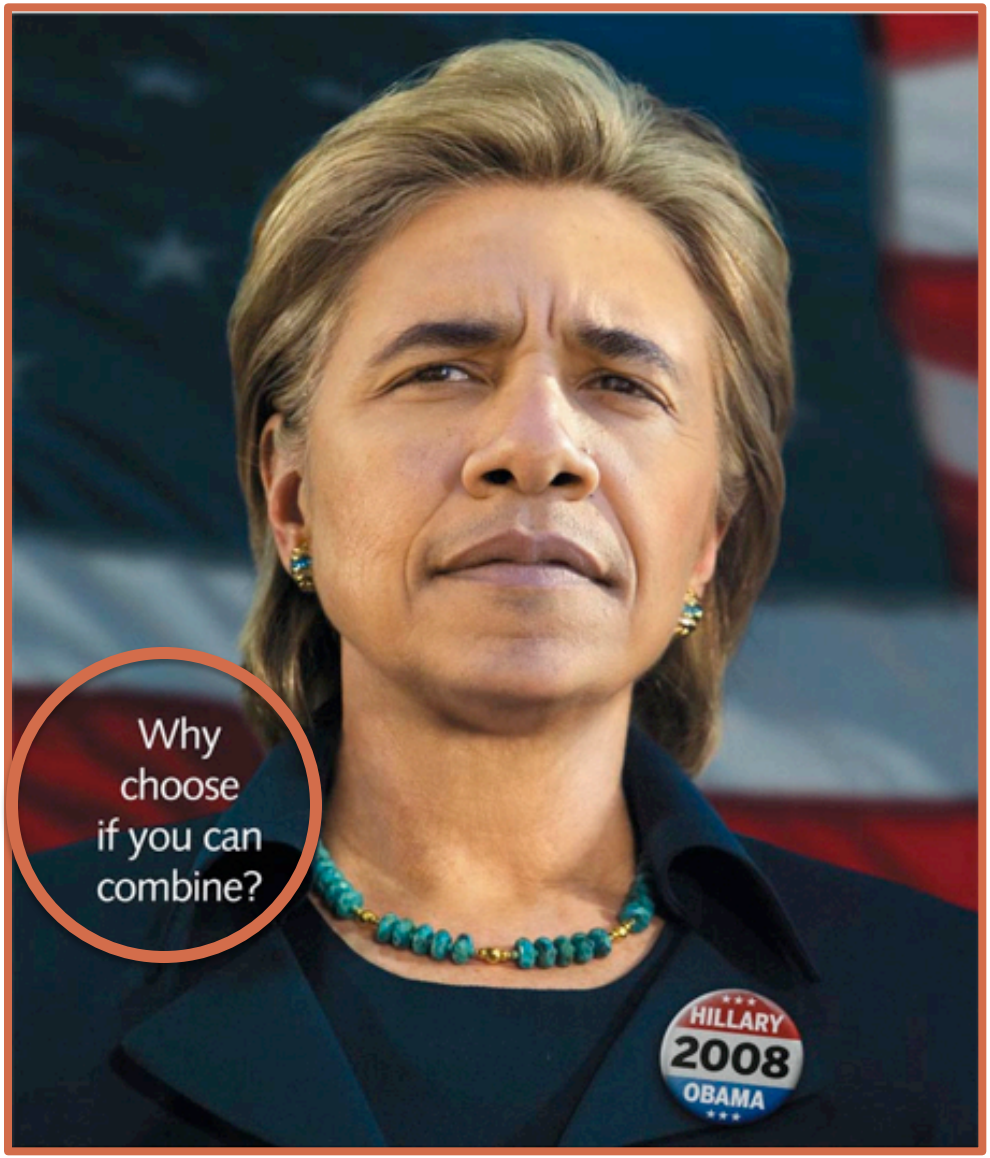
- 16 patients
- M1 hepatic non resectable
- First line
- HAI 5-FU (1000 mg/m2) and Leucovorin (50 mg/m2)
- Together with systemic Uracil/Tegafur (UFT) (300 mg/m2) and Leucovorin (75 mg)

Tsutsumi S et al. Hepatogastroenterology.2008 Jul-Aug;55(85): 1419-22.

TSUTSUMI S ET AL.

- Response rate: 87.5% (14 RPR and 2 DE)
- Free progression survival: 9.2 months
- Mean Survival: 22 months.
- No side effects grade > 2

Tsutsumi S et al. Hepatogastroenterology.2008 Jul-Aug;55(85): 1419-22.



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Conversion to resectability using hepatic artery infusion plus systemic chemotherapy for the treatment of unresectable liver metastases from colorectal carcinoma

Kemeny NE et al. J Clin Oncol. 2009 Jul 20;27(21): 3465-71. Epub 2009 May 26.

KEMENY NE ET AL.

- 49 prospective patients
- 24 of them 1st line
- M1 liver non resectable
- HAI floxuridine (0.12 mg/kg · 30/flujo) and dexametasone (1 mg/kg ·30/flujo)
- Plus oxaliplatine (85-100mg/m2) and irinotecan (100-200mg/m2)

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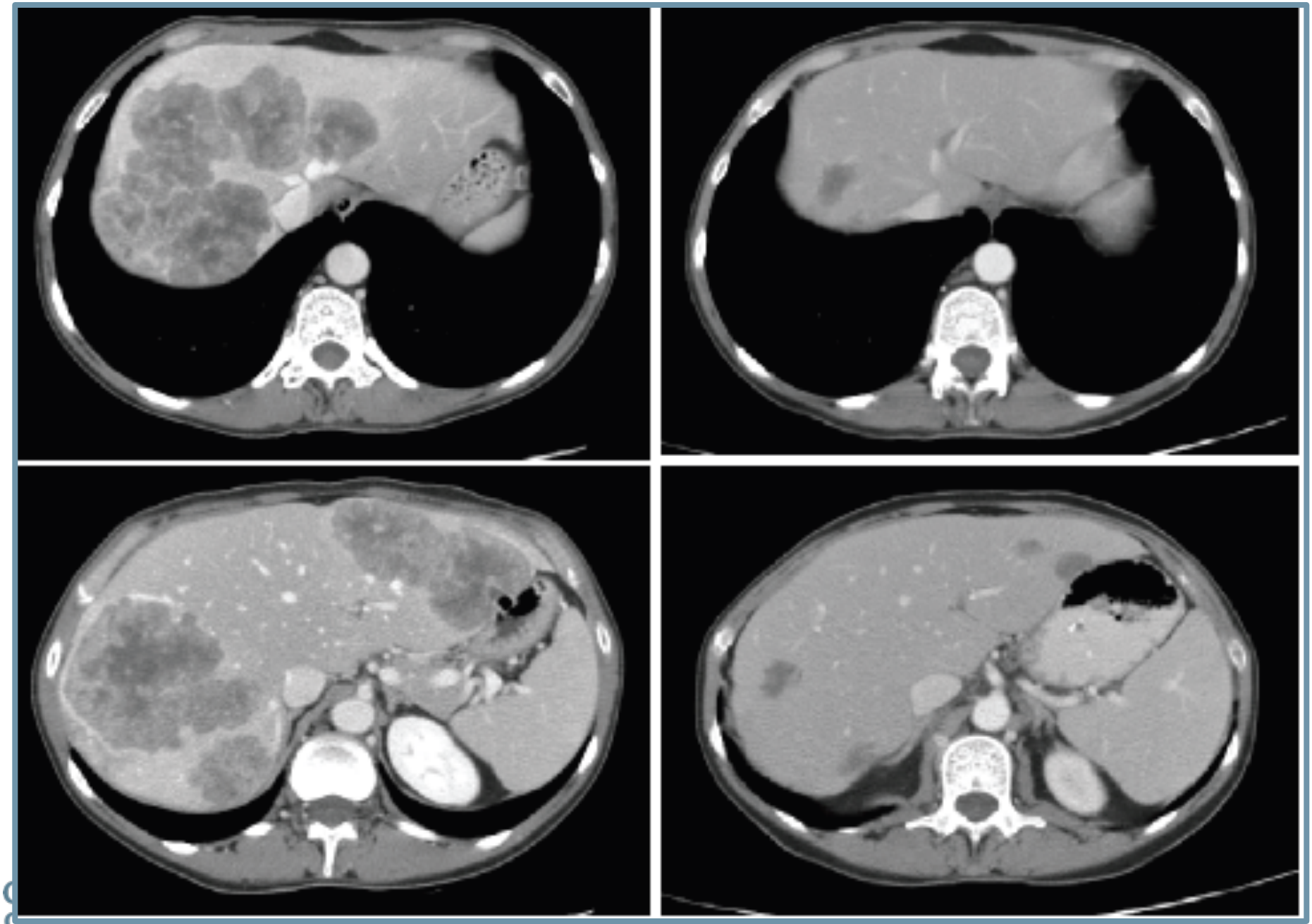
Kemeny NE et al. J Clin Oncol. 2009 Jul 20;27(21): 3465-71. Epub 2009 May 26.

KEMENY NE ET AL.

- 45 patients (92%): PR (84%) or CR (8%)
- 47% resectable
- Survival mean: 39,8 m
  - Among those 1st line:
    - Response rate 100%
    - Resectability 57%
    - Mean of survival 50,8 m

Kemeny NE et al. J Clin Oncol. 2009 Jul 20;27(21): 3465-71. Epub 2009 May 26.



J Clin Oncol. 2009 Jul 20;27(21): 3465-71. Epub 2009 May 26.

Comparison of Adjuvant Systemic Chemotherapy With or Without Hepatic Arterial Infusional Chemotherapy After Hepatic Resection for Metastatic Colorectal Cancer

House MG et al. Ann Surg. 2011 Oct 4.

Results: The median follow-up for all patients was 43 months. There were no differences in clinical risk score, disease-free interval, size of largest CRLM, number of CRLM, or prehepatectomy CEA level between the 2 groups. Adjuvant HAI-FUDR was associated with an improved overall and liver recurrence-free survival (liver RFS) and disease-specific survival (DSS). For the adjuvant HAI-FUDR group, the 5-year liver RFS, overall RFS, and DSS were 75%, 48%, and 79%, respectively, compared to 55%, 25%, and 55% for the systemic alone group ($P < 0.01$). On multivariate analysis, adjuvant treatment including HAI-FUDR was independently associated with improved liver RFS (HR = 0.34), overall RFS (HR = 0.65), and DSS (HR = 0.39), $P < 0.01$.

Conclusions: Adjuvant HAI-FUDR combined with modern systemic chemotherapy is independently associated with improved survival compared to adjuvant systemic chemotherapy alone. A randomized clinical trial between these 2 regimens is justified.

(*Ann Surg* 2011;00:1–6)

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House MG et al. Ann Surg. 2011 Oct 4.

SYSTEMIC CHEMOTHERAPY LIMITATIONS

- Do not reach the target site in optimal quantities
- Not effective enough in tumour microenvironment
- Non functioning lymphatic system allows drug escaping

Jain RK. J et al. Control. Release, 2001, 74, 7-25
Reddy LH et al. J. Pharm. Pharmacology, 2005, 57, 1231-1242

SYSTEMIC CHEMOTHERAPY LIMITATIONS

Several reasons contribute to this failures:

- Unfavourable pharmacokinetics of drugs (rapid clearance and biodegradation determining a short plasma life)
- Large biodistribution and non-intended extravasation of chemotherapy agents induce severe toxicity in non-targeted lesion
- Poor tumour selectivity
- Susceptibility to induce drug resistance in tumour cells
- Unfavourable physiological properties (ex: hydrophobicity) promotes unsuccessful drug accumulation at desired region

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Duran JDG et al. J Pharm Sci. 2008, 13, 2340-2369

SYSTEMIC CHEMOTHERAPY

Possible solutions:

- Biodegradable polymeric particles
- **Hydrogels**
- Vesicular systems: liposomes and niosomes
- Magnetic drug delivery systems
- Lipoproteins
- Clay minerals and anionic clays
- Metals
- Ion exchange resins

IA DEB ADVANTAGES

1. Lesion/organ targeting (tumour selectivity)
2. Anoxia to the tumor
3. Prolonged chemotherapy release

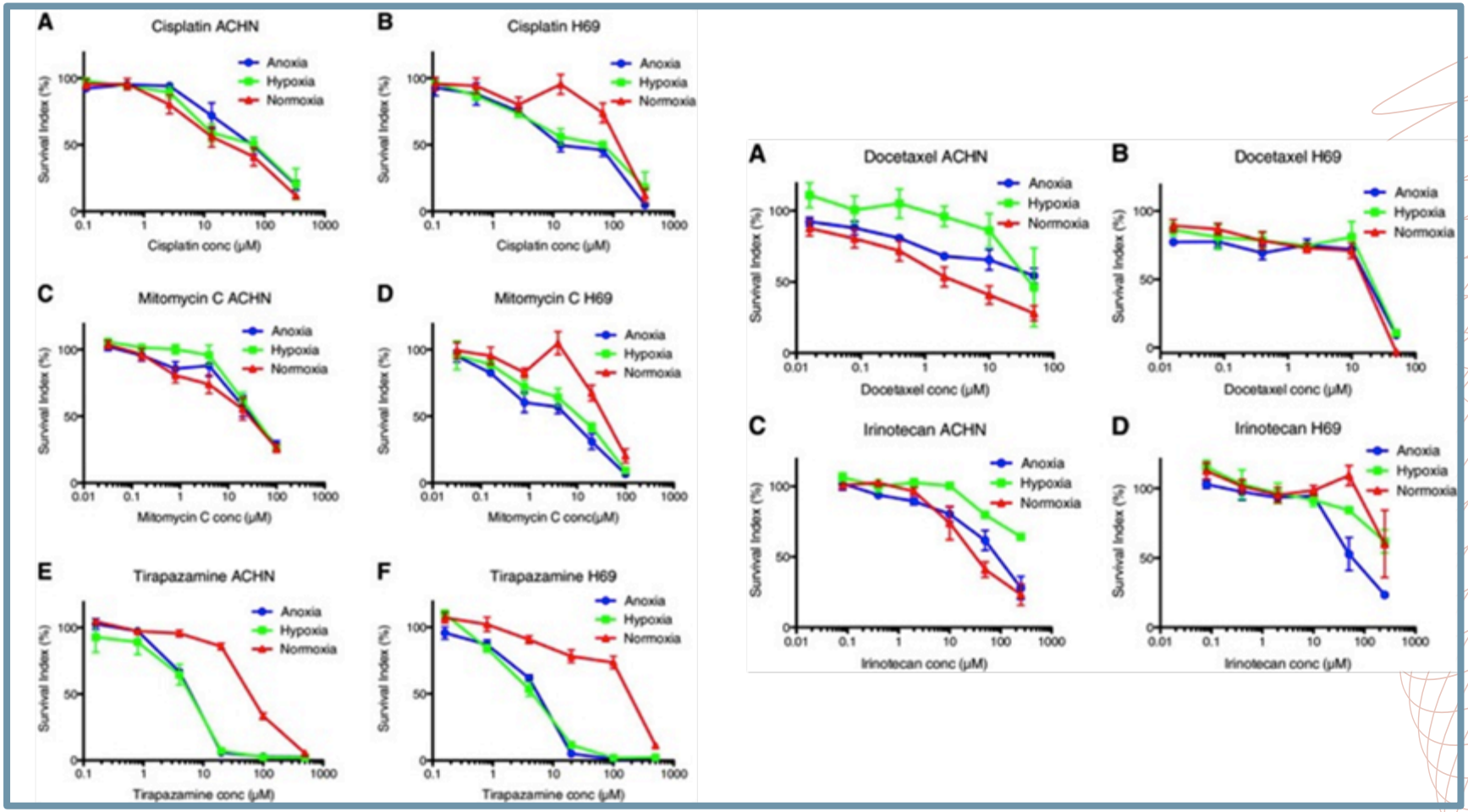
   (high exposure and high drug dose to metastases)
4. Low systemic exposure

NON DESIRED EFFECTS OF TACE

- Increased circulating cells and metastases
- Increased HIF 1 α
- Increased release of factors promoting angiogenesis
- Increased interstitial pressure
- Low pH environment
- Hypoxia

WHAT DO YOU PREFER? NORMOXIA, HYPOXIA OR ANOXIA?

HYPOXIA AND ANOXIA

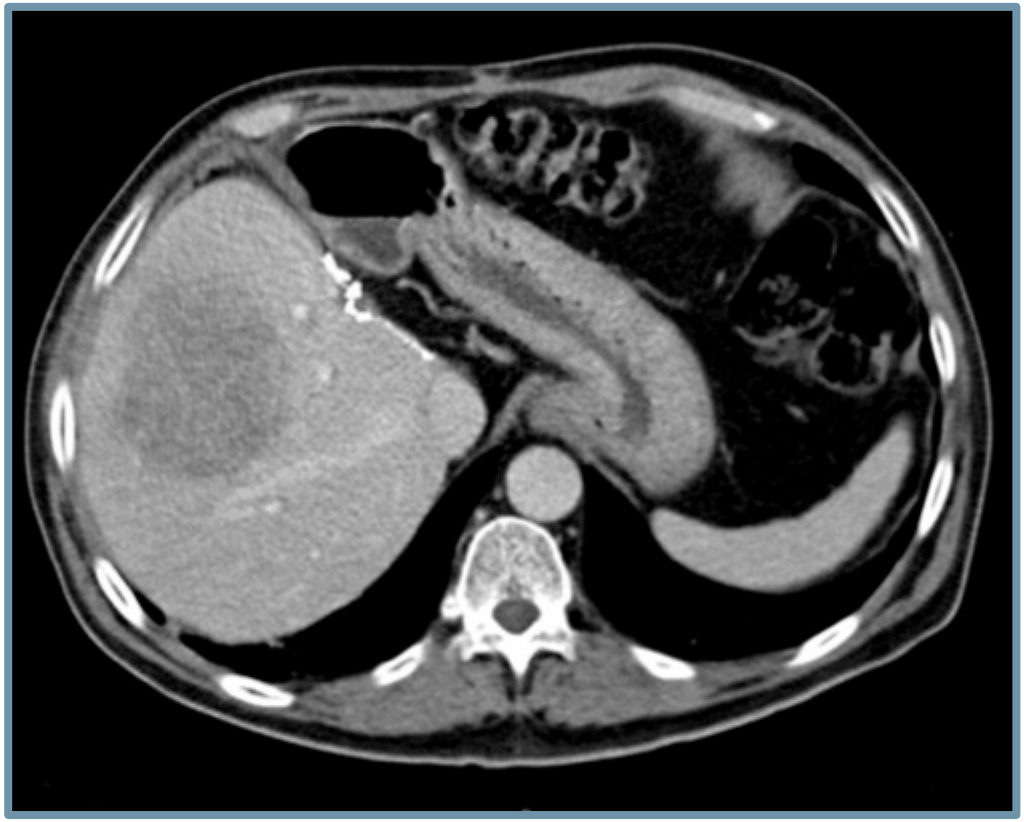


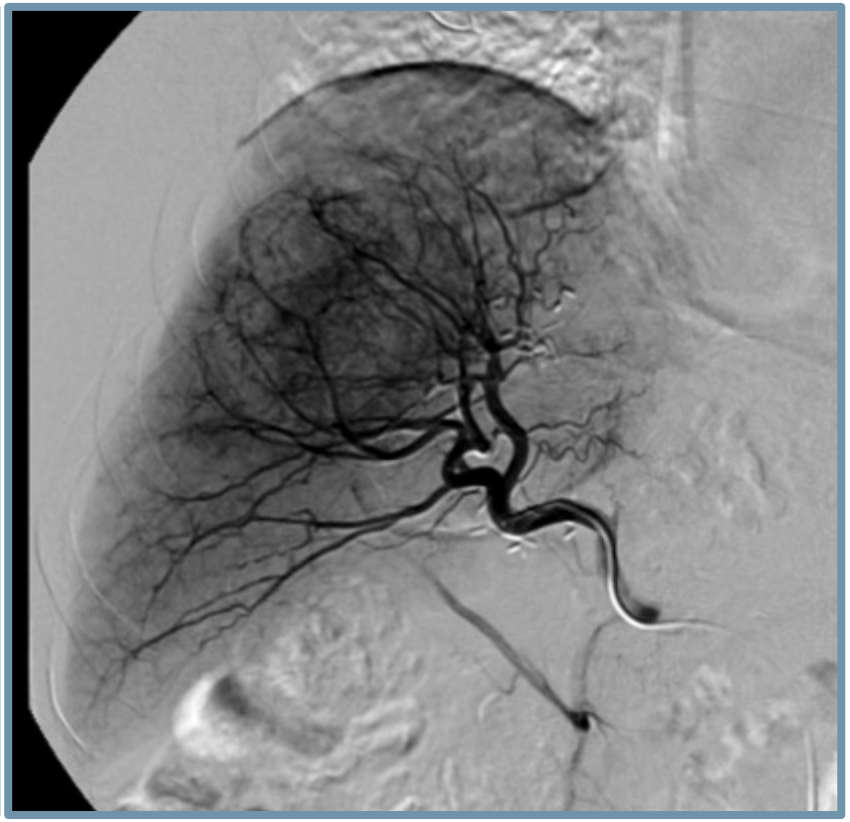
Strese S et al. BMC Cancer. 2013 Jul 5;13:331.

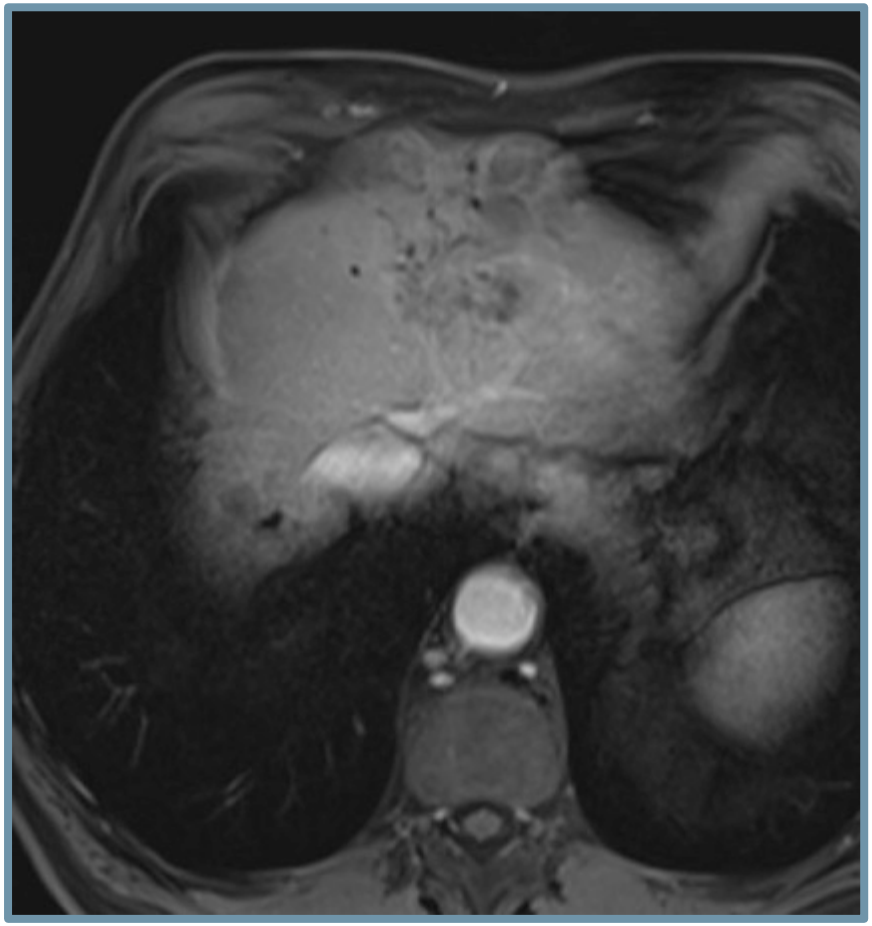
HYPOXIA AND ANOXIA

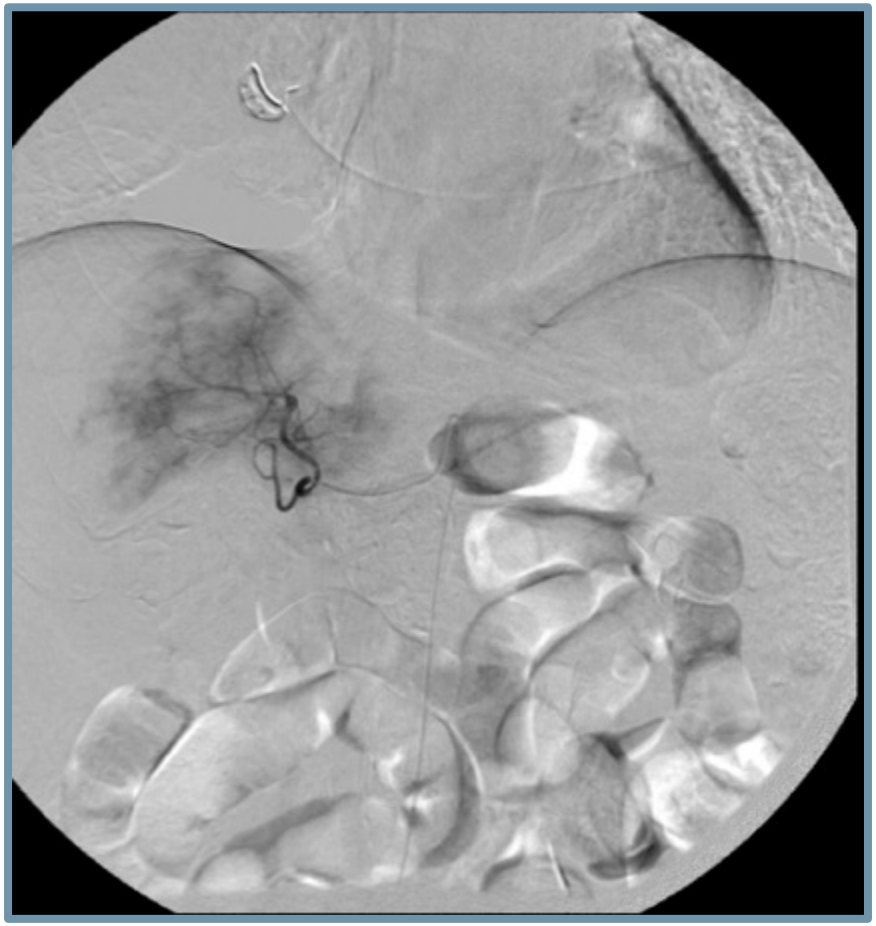
- Murono K et al. ***SN-38 overcomes chemoresistance of colorectal cancer cells induced by hypoxia, through HIF1alpha***. Anticancer Res. 2012 Mar;32(3):865-72

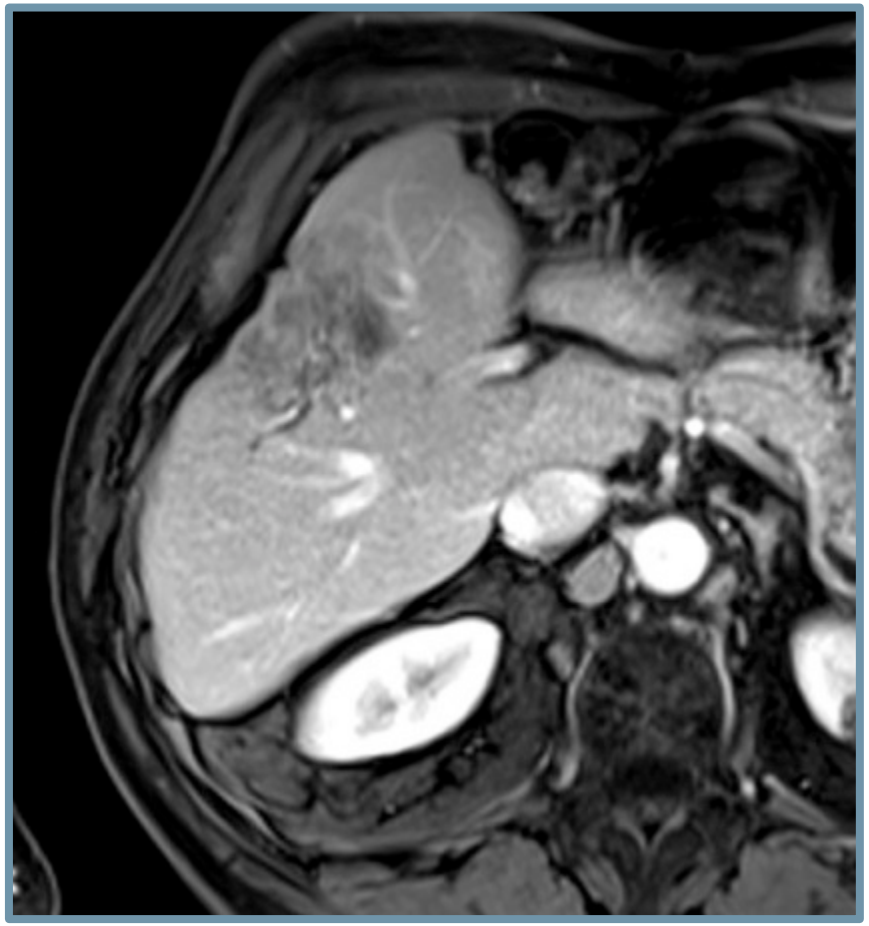
- Jones RP et al. ***Hepatic activation of irinotecan predicts tumour response in patients with colorectal liver metastases treated with DEBIRI: exploratory findings from a phase II study***. Cancer Chemother Pharmacol. 2013 Aug;72(2): 359-68

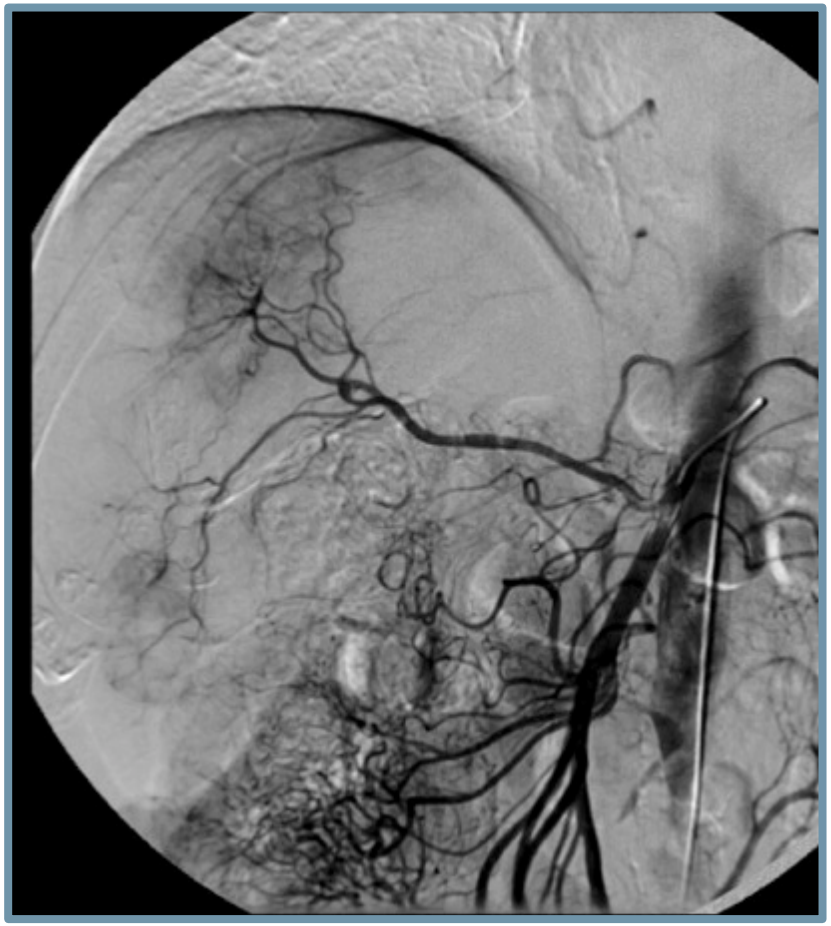


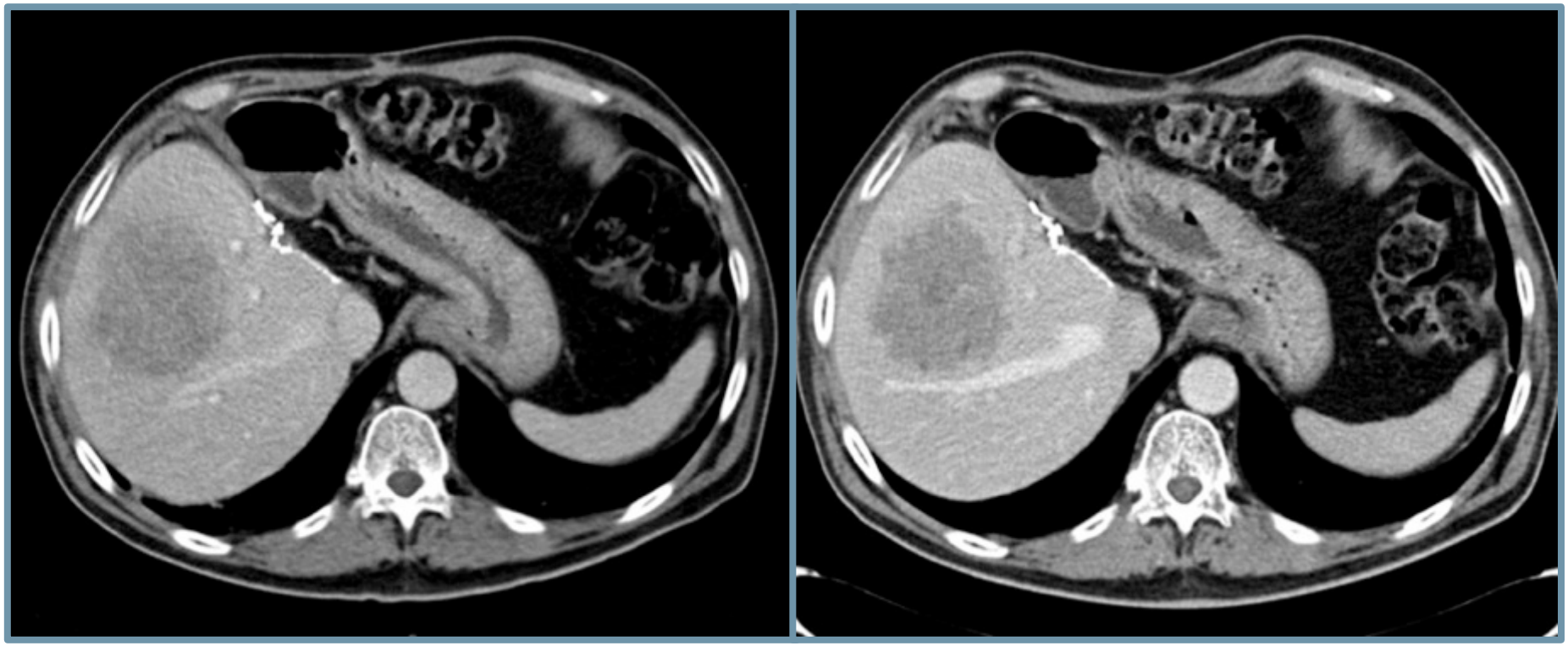


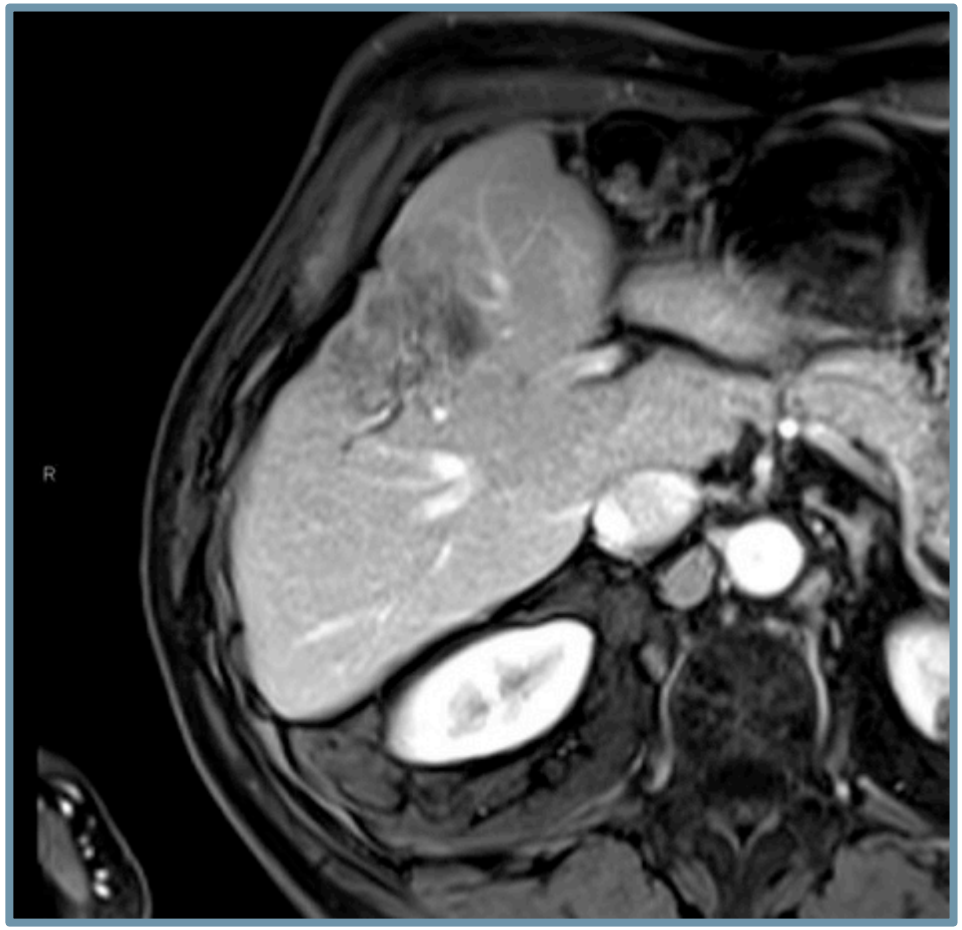


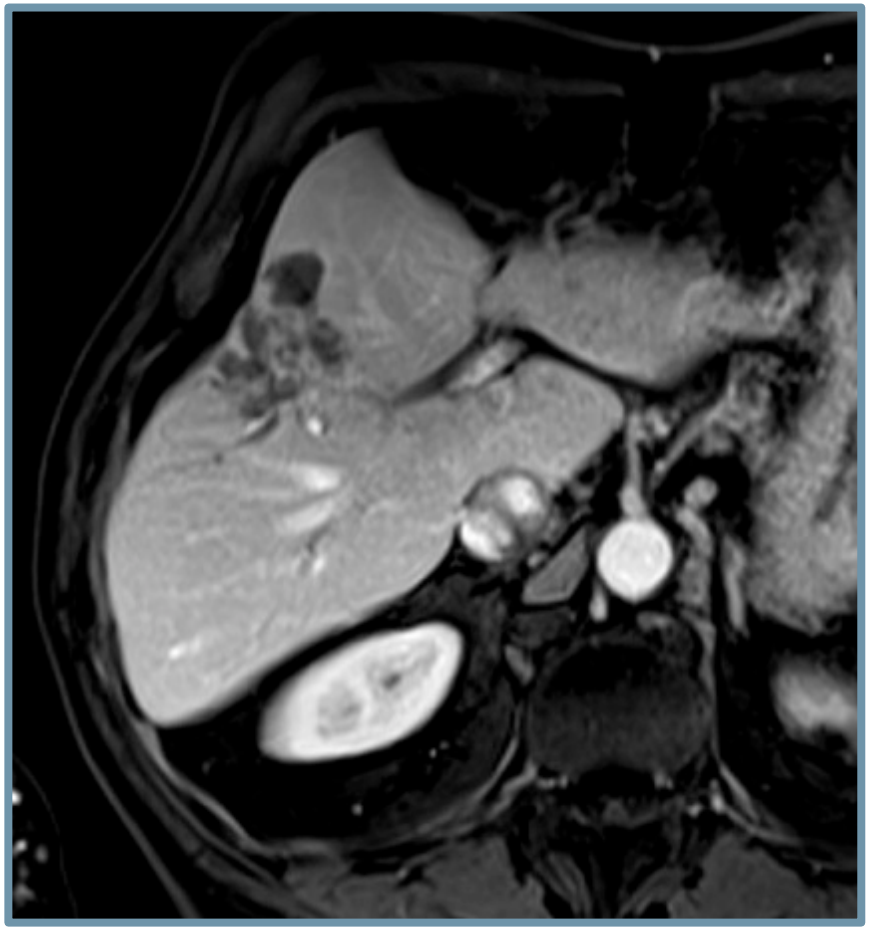




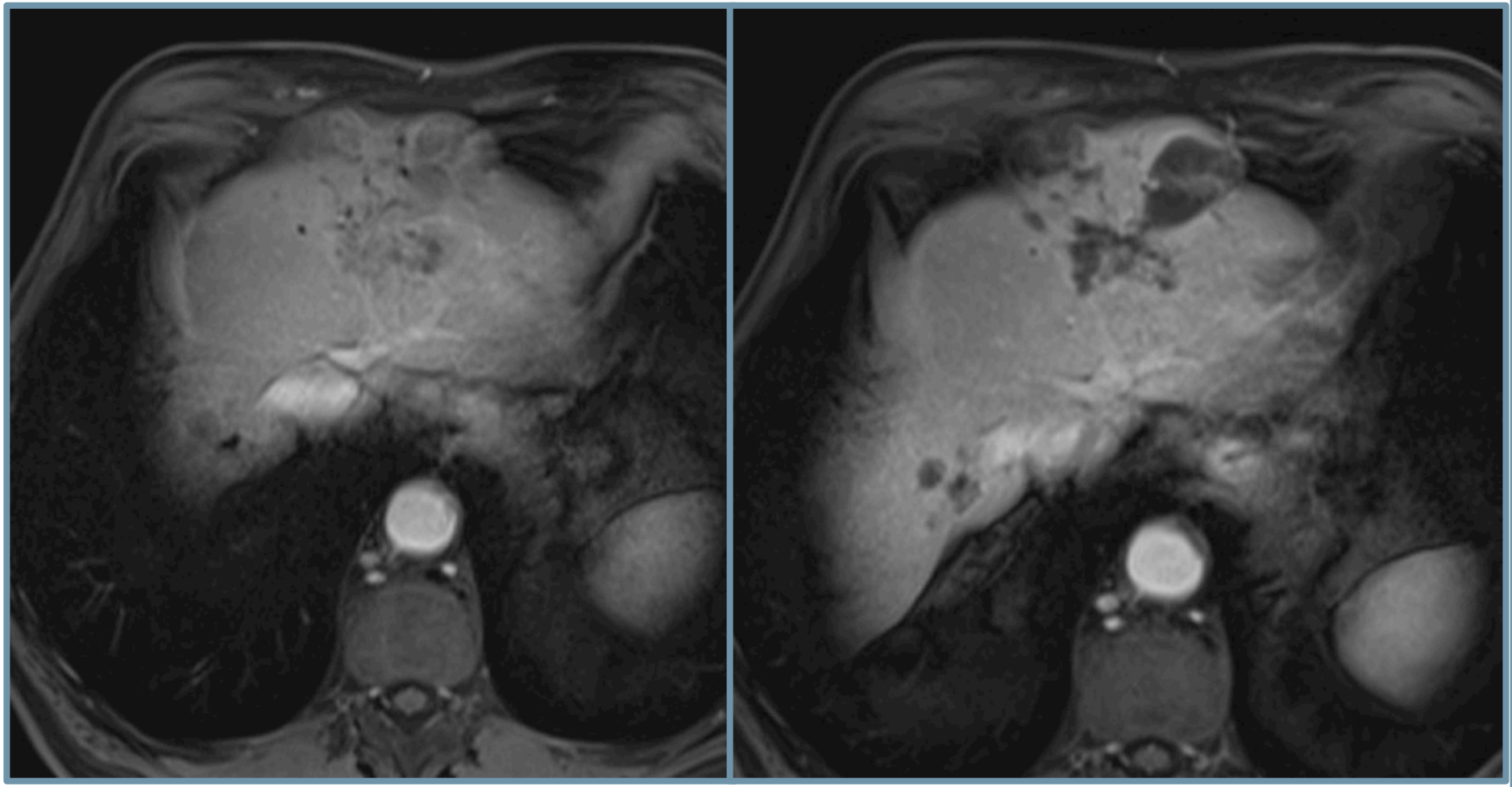








100 mg irinotecan en LHD



100 mg irinotecan en LHI

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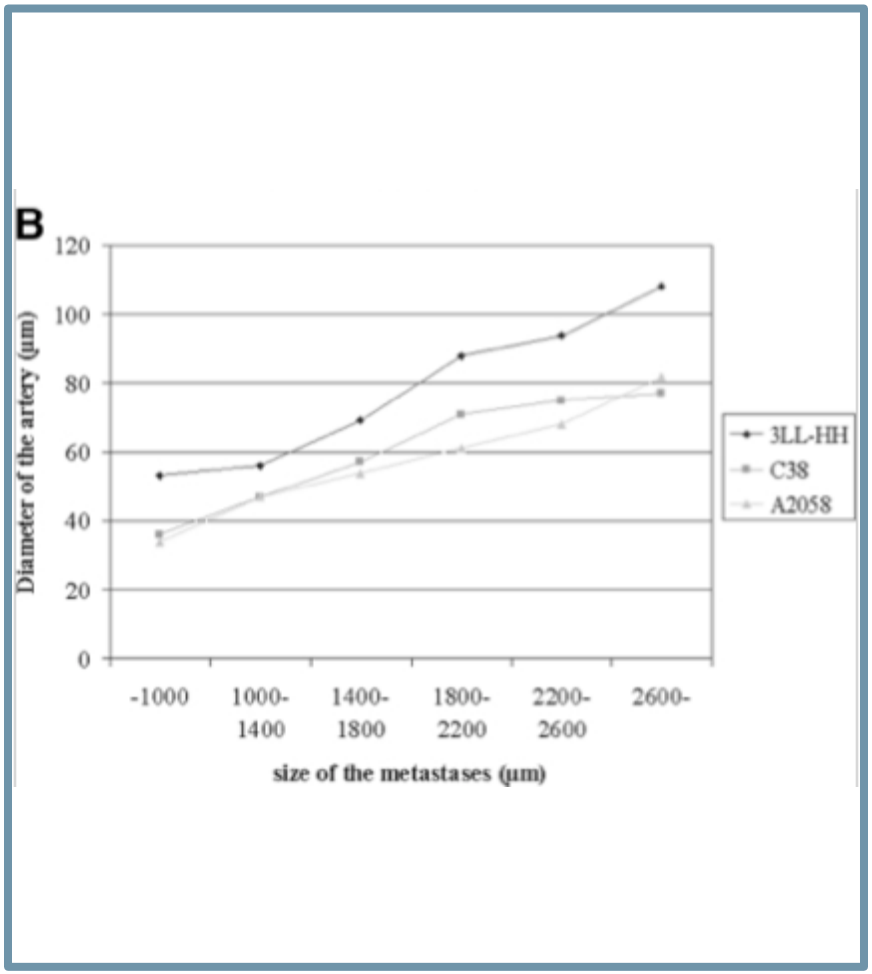
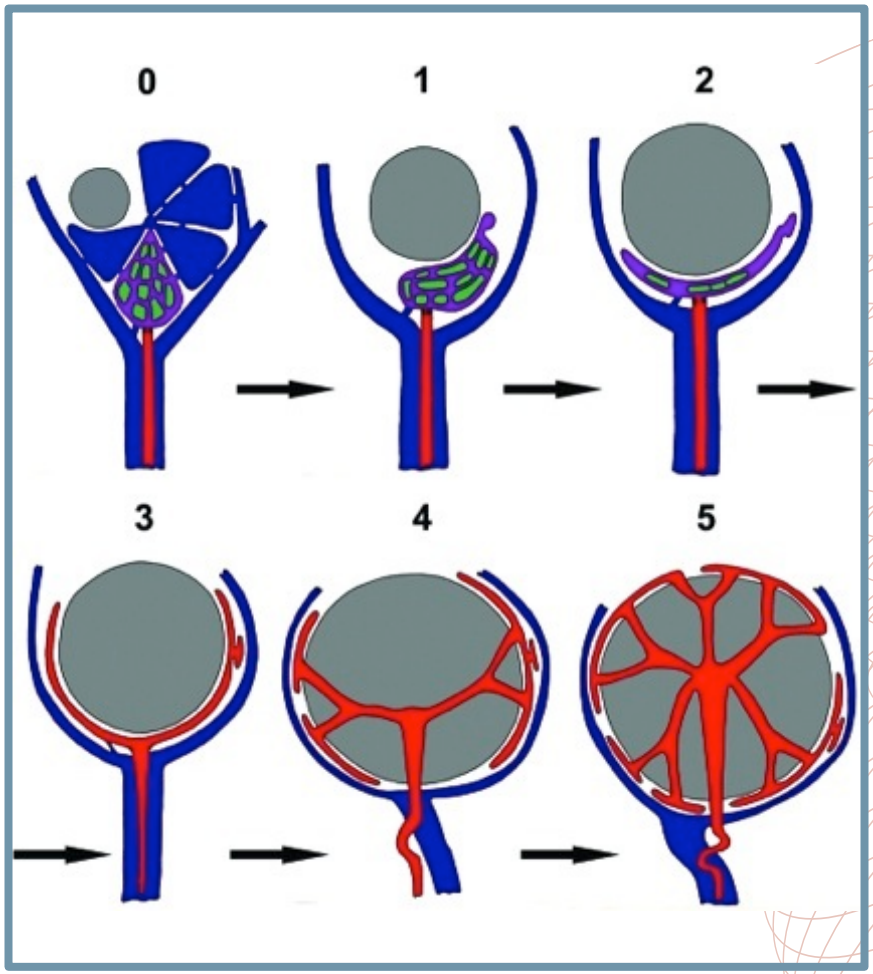
SEGMENTAL OR LOBAR DEB TACE FOR METASTASES?

SEGMENTAL OR LOBAR





Dezso K et al. Am J Pathol. 2009 August; 175(2): 835–843.

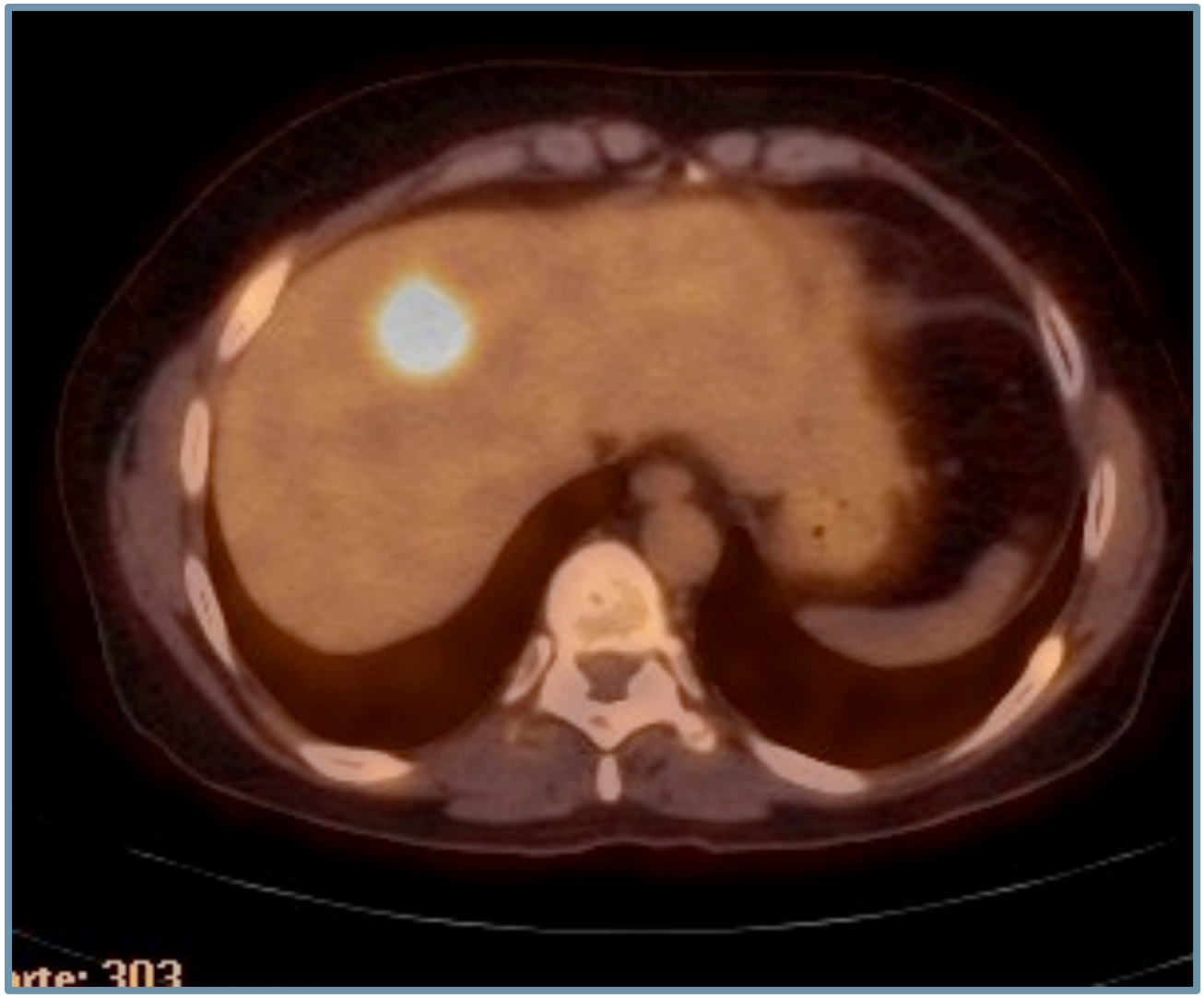
SEGMENTAL OR LOBAR

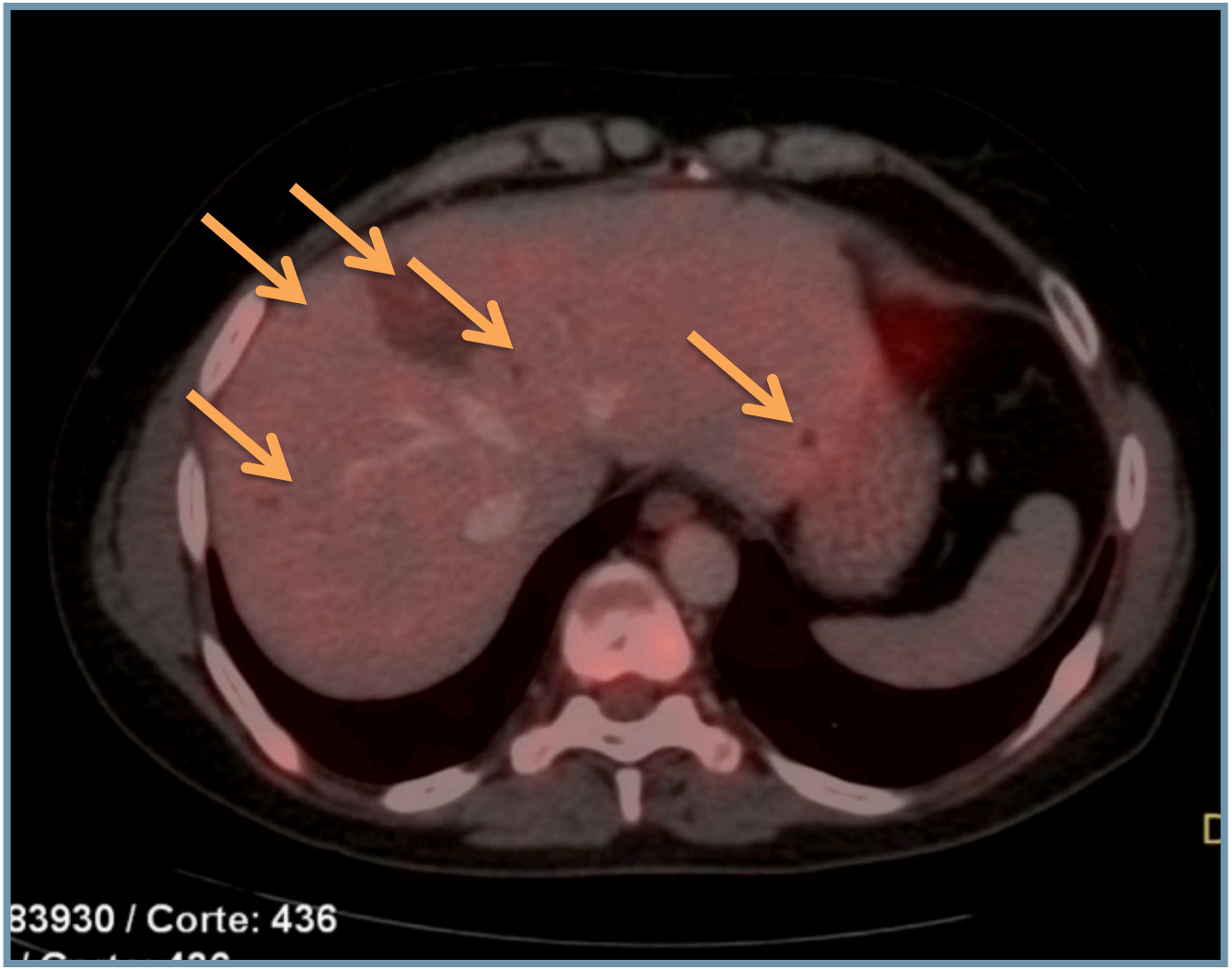
Vessel co-option

- Unresponsive to VEGF family blocking
- Perfect target for DEB-TACE while controlling angiogenesis?

SEGMENTAL OR LOBAR

- Jones RP et al. *Segmental and lobar administration of drug-eluting beads delivering irinotecan leads to tumour destruction: a case-control series*. HPB (Oxford). 2013 Jan; 15(1):71-7.





Bruixola G, García-Marcos R, Gómez FM, Montalvá E,
SEOM 2013:

- December 2011 - April 2013: 22 DEBIRI en 9 patients
- Mean time from diagnosis to 1st DEBIRI: 17 months
- Response: RECIST 1.1
- Toxicity: CTCAE v3.0 and VAS

Patient characteristics	Frequency
Age (median)	62 years (range 42-67)
Sex male/female	7 (78%)/2 (22%)
ECOG PS 0/ 1	8 (89%)/1 (11%)
KRAS mutated/native	5 (56%)/ 4 (44%)
Primary tumor Colon/Recto	8 (89%)/1 (11%)
Metastasis chronology synchronic/methacrhonous	8 (89%)/1 (11%)
Previous metastasectomy	6 (67%)
CEA pre-DEBIRI (mean)	65 ng/mL
CEA post-DEBIRI (mean)	22 ng/mL

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Patients characterstics	Frecuency
Lines of CT before (mean)	2 (range 1-4)
DEBIRI 2nd line CT DEBIRI en 3rd line CT DEBIRI en 4th line CT	2 (22%) 6 (67%) 1 (11%)
Administration Bevacizumab	8 (89%)
Nº cycles Bevacizumab (mean)	8 (range 4-24)
Anti-EGFR - Cetuximab - Panitumumab Mean cycles anti-EGFR	4 (44,4%) 2 (22,2%) 2 (22,2%) 8 (range 1-16)

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RESULTS

- Median DEBIRIs: 3 (range: 1-6)
- Irinotecan dose: *255,5 mg (range:100-600 mg)*
- Follow-up: 17´5 months
- *PFS: 5 months (IC 95%= 3-6)*
- *12 months OS: 89%*

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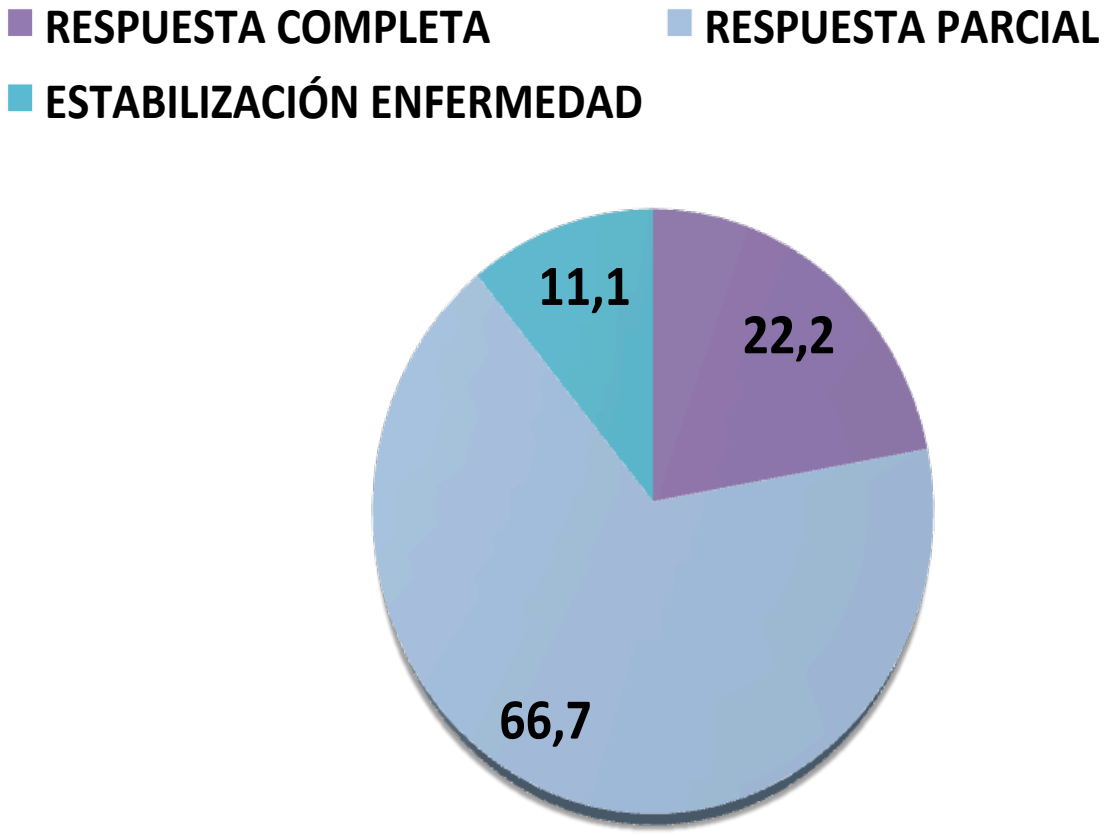
TASA DE RESPUESTA



Acute Toxicity (24h): n=22		
Effect	**G3**	**G1-2**
Hyperbilirrubinemia	2 (9%)	0
Emesis	1 (4,5%)	2 (9%)
Haemorrhage	0	1 (4,5%)
Pain	1 (4,5%)	8 (36,3%)

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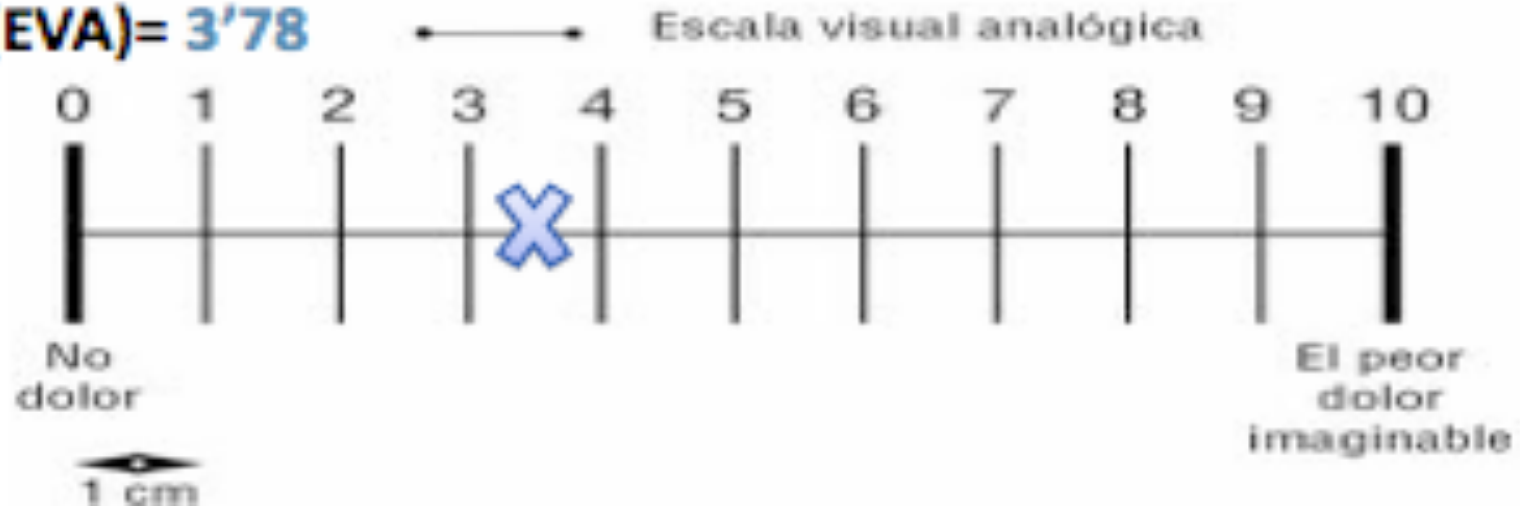
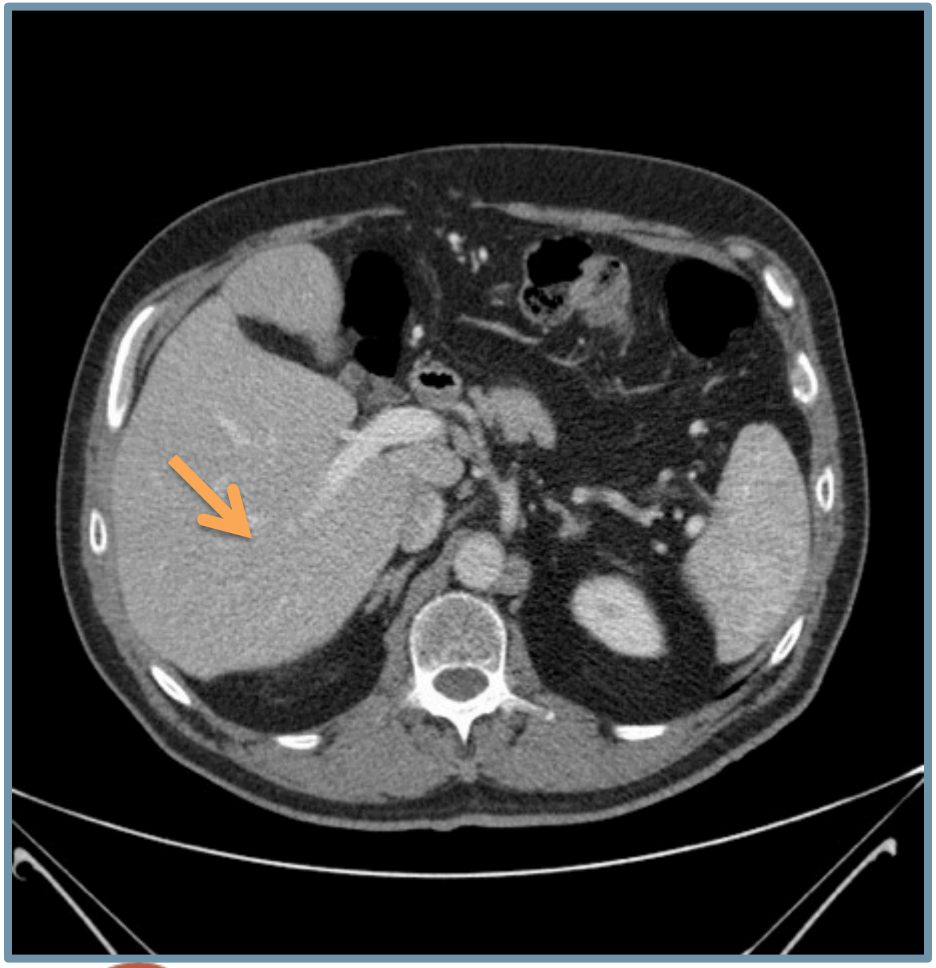
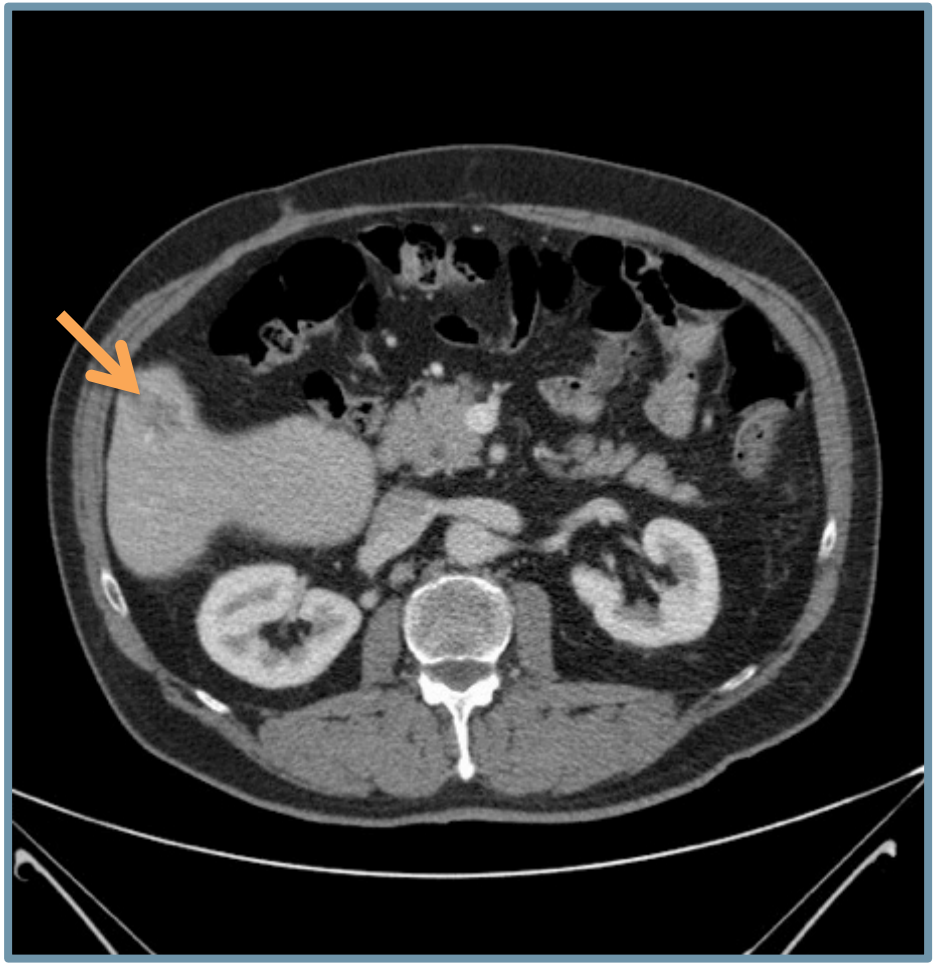
Dolor- Puntuación media en la Escala Visual Analógica (EVA)= 3’78



Late toxicity (30 days): n=22		
Effect	**G3**	**G1-2**
Hypertransaminasemia	0	1 (4,5%)
Liver failure	1 (4’5%)	0

NEOADJUVANT DEBIRI FOR RFA?





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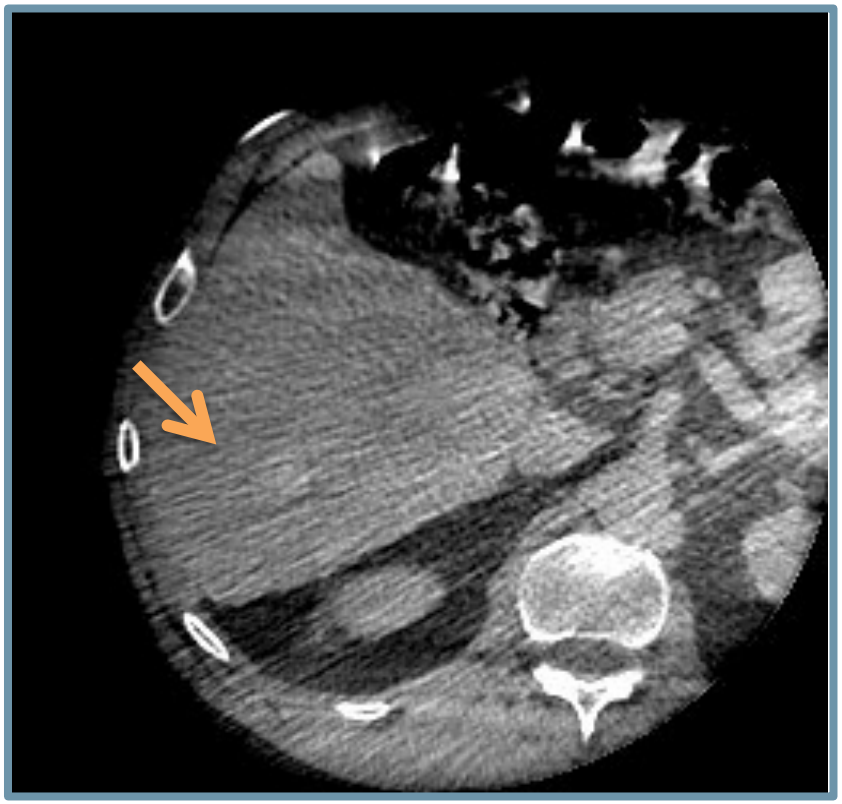
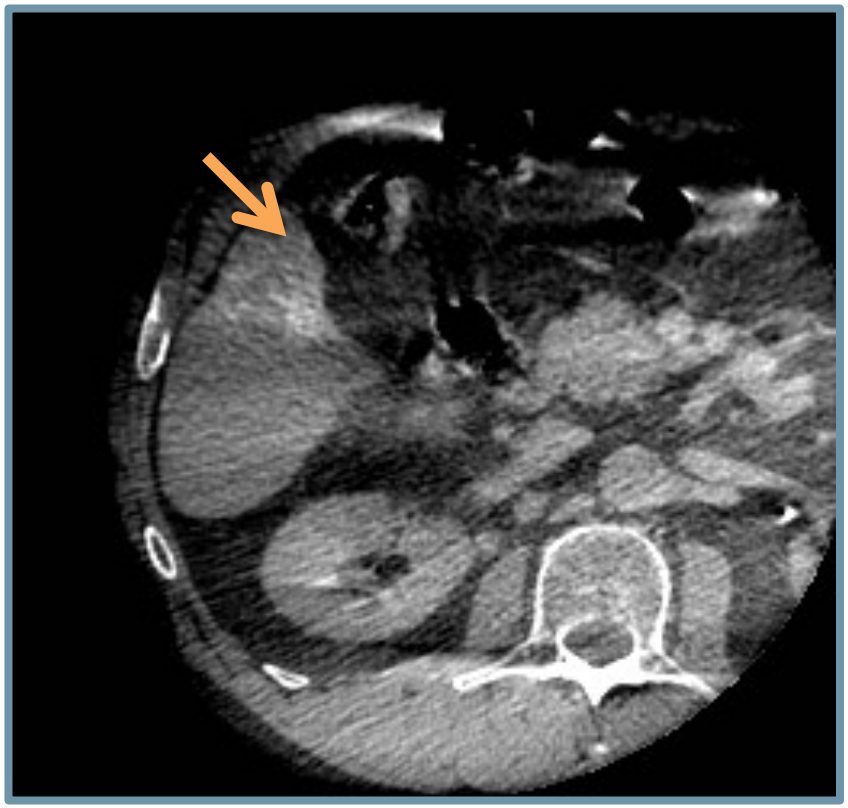
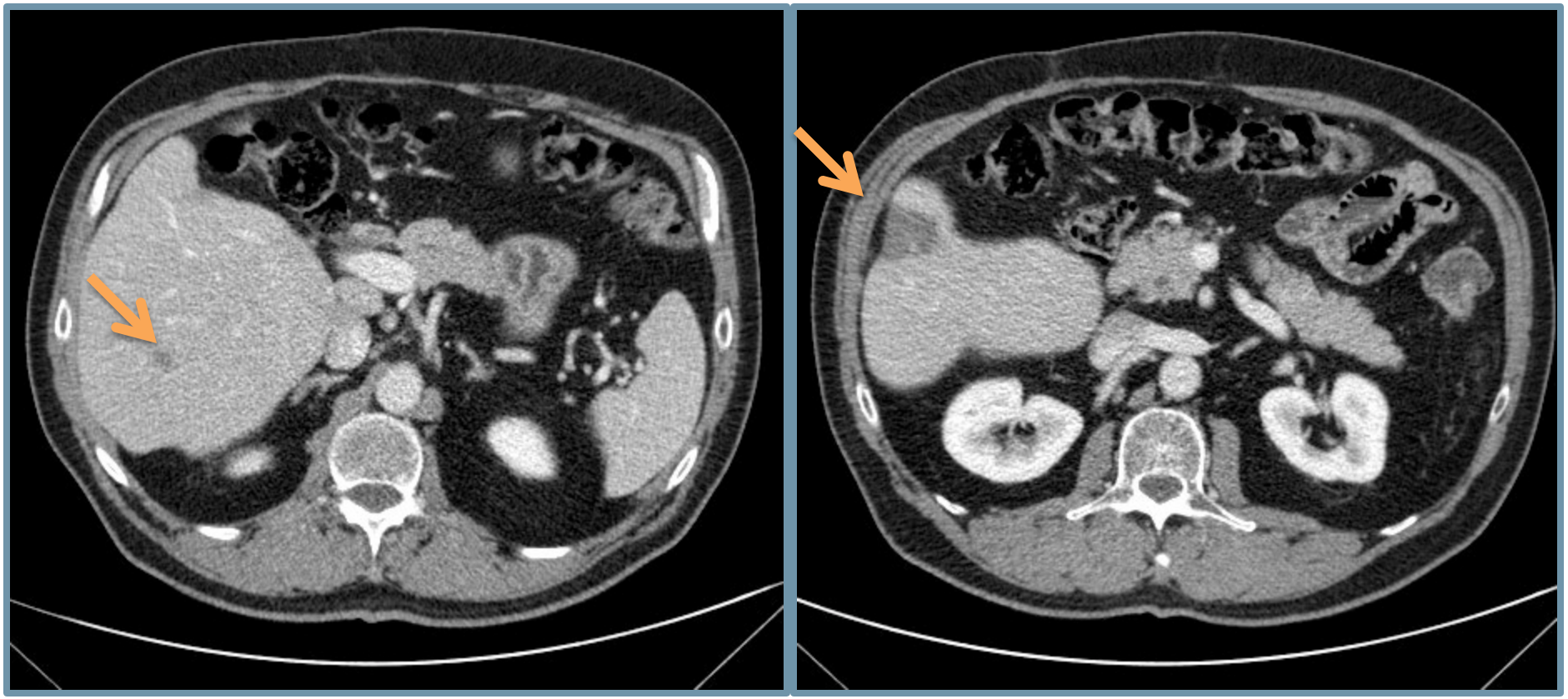
NEOADJUVANT DEBIRI FOR RFA?

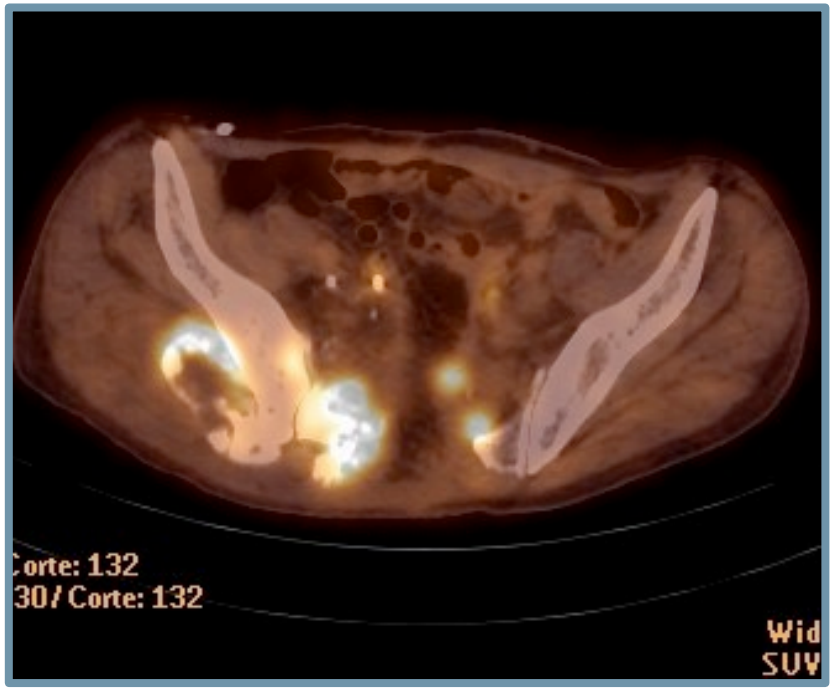


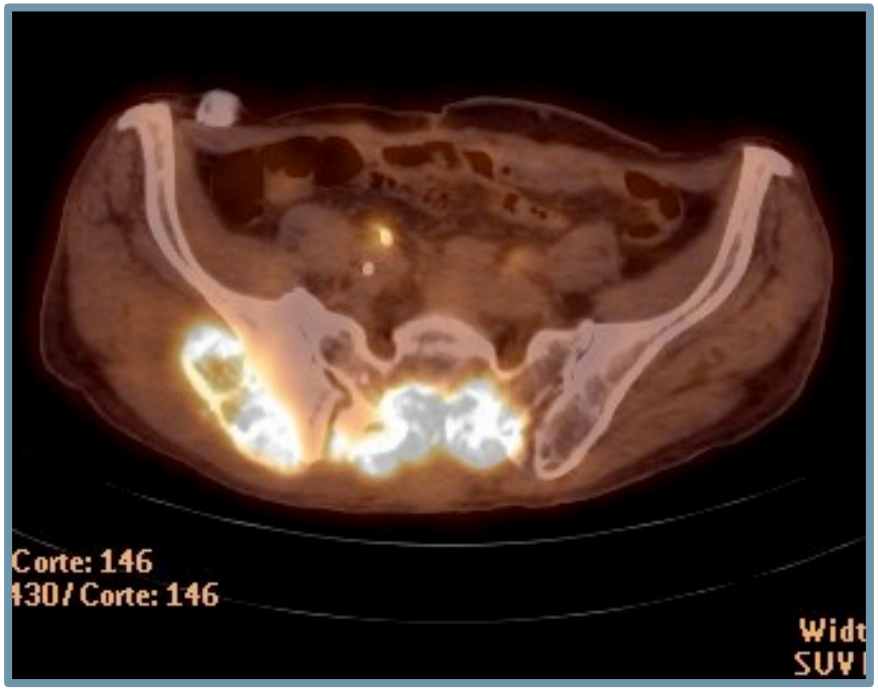


NEOADJUVANT DEBIRI FOR RFA?



DEBIRI IN OTHER LOCATIONS





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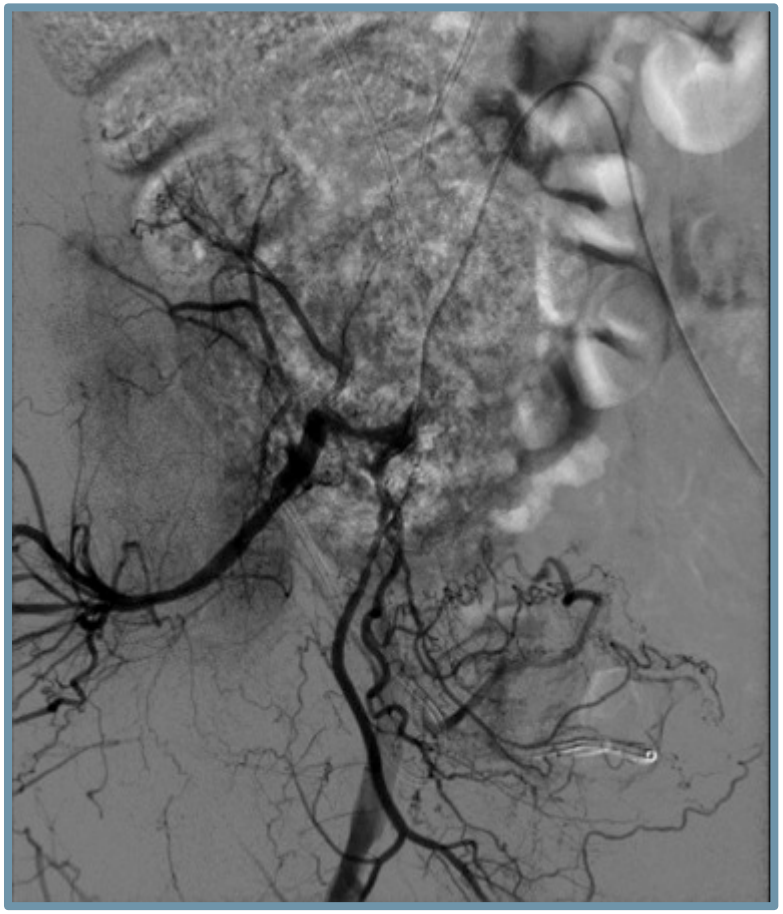
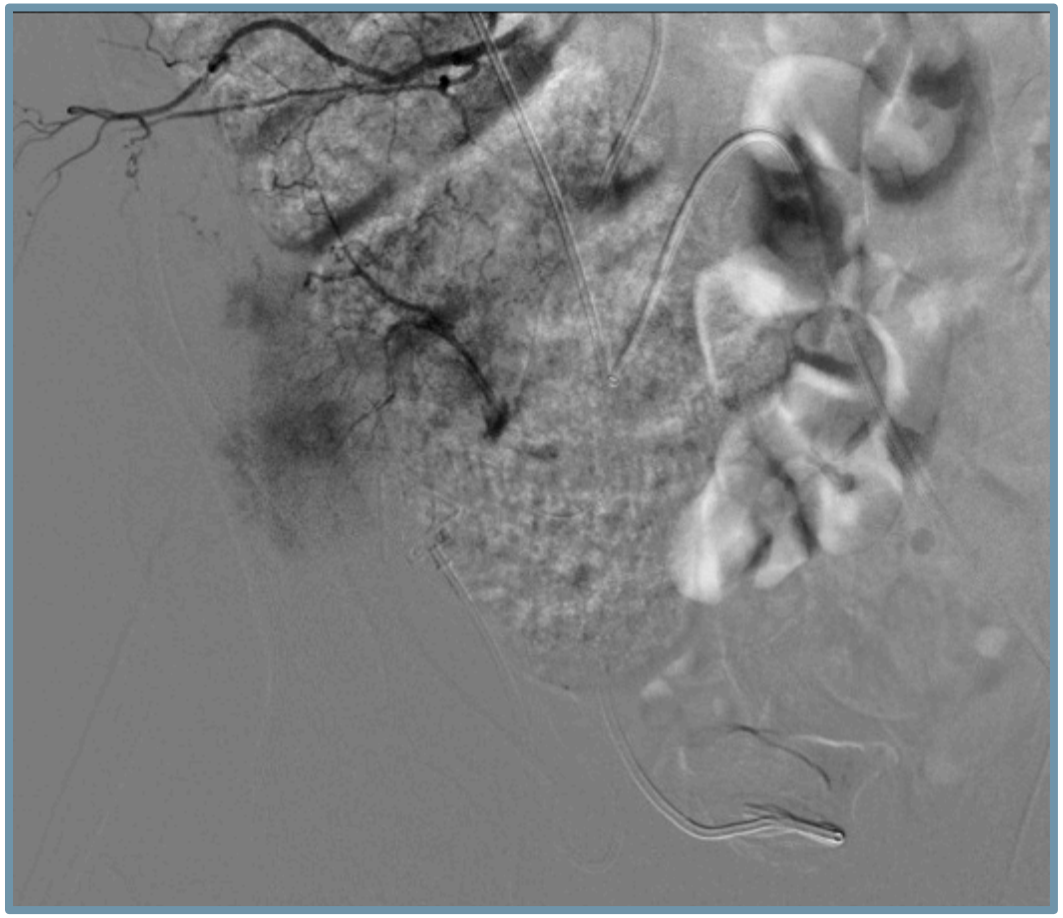
DEBIRI IN OTHER LOCATIONS





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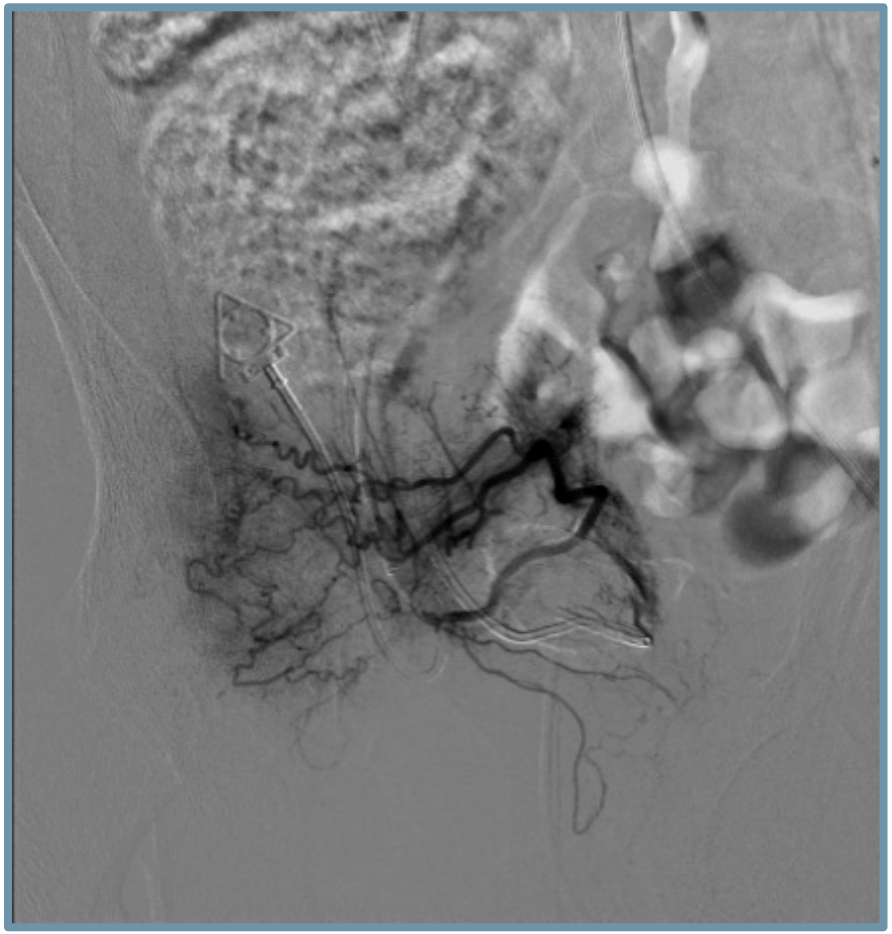
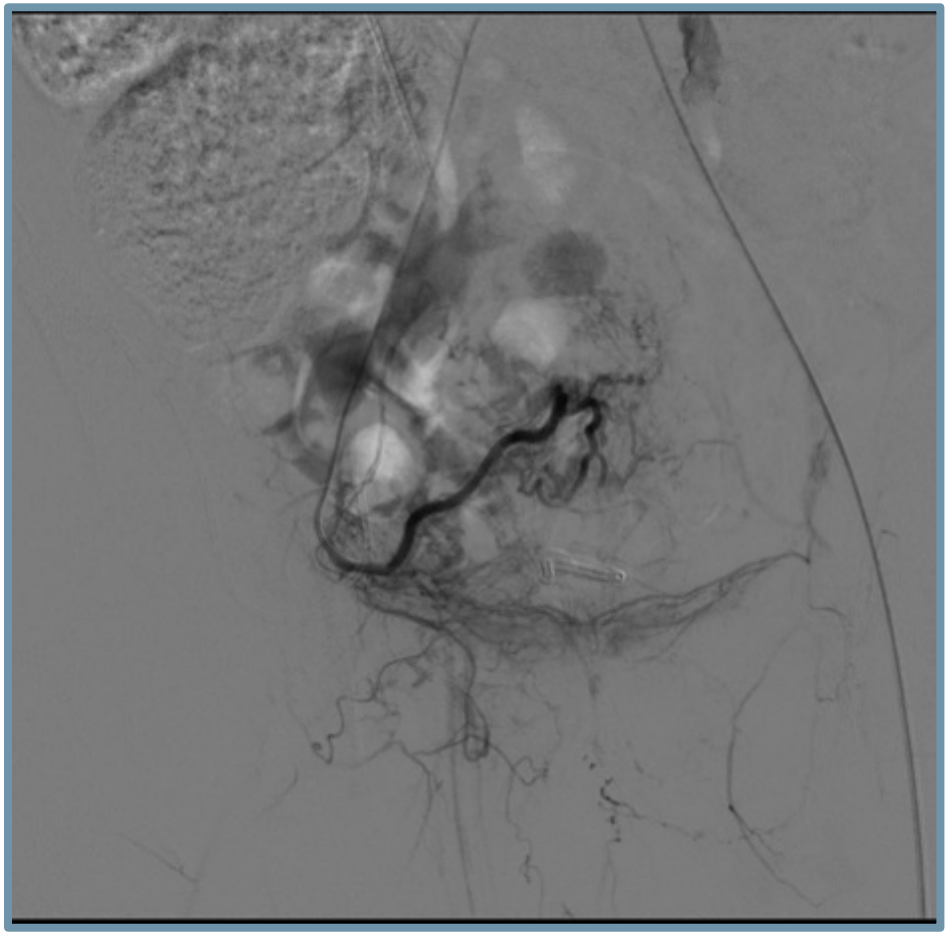
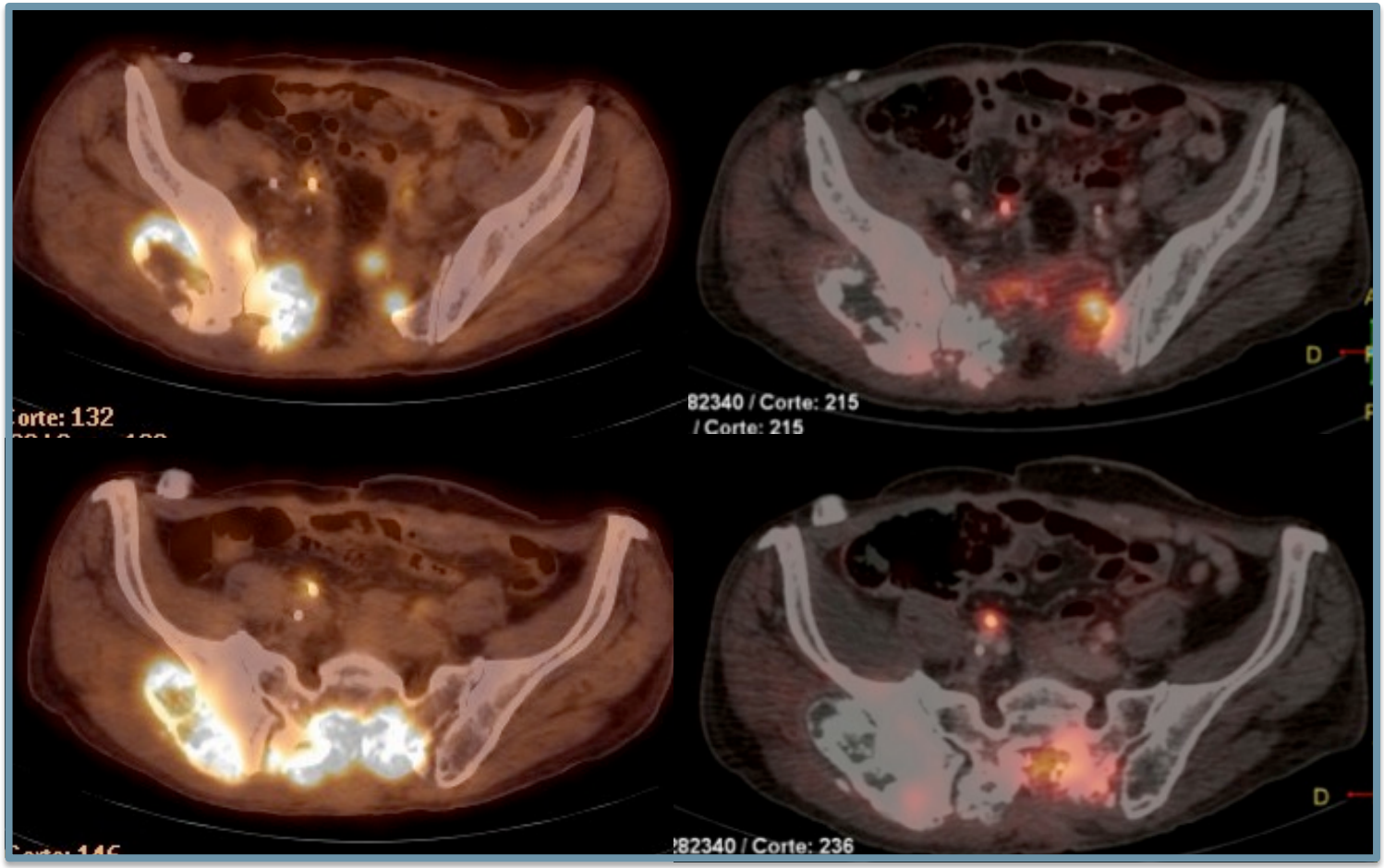
DEBIRI IN OTHER LOCATIONS





DEBIRI IN OTHER LOCATIONS



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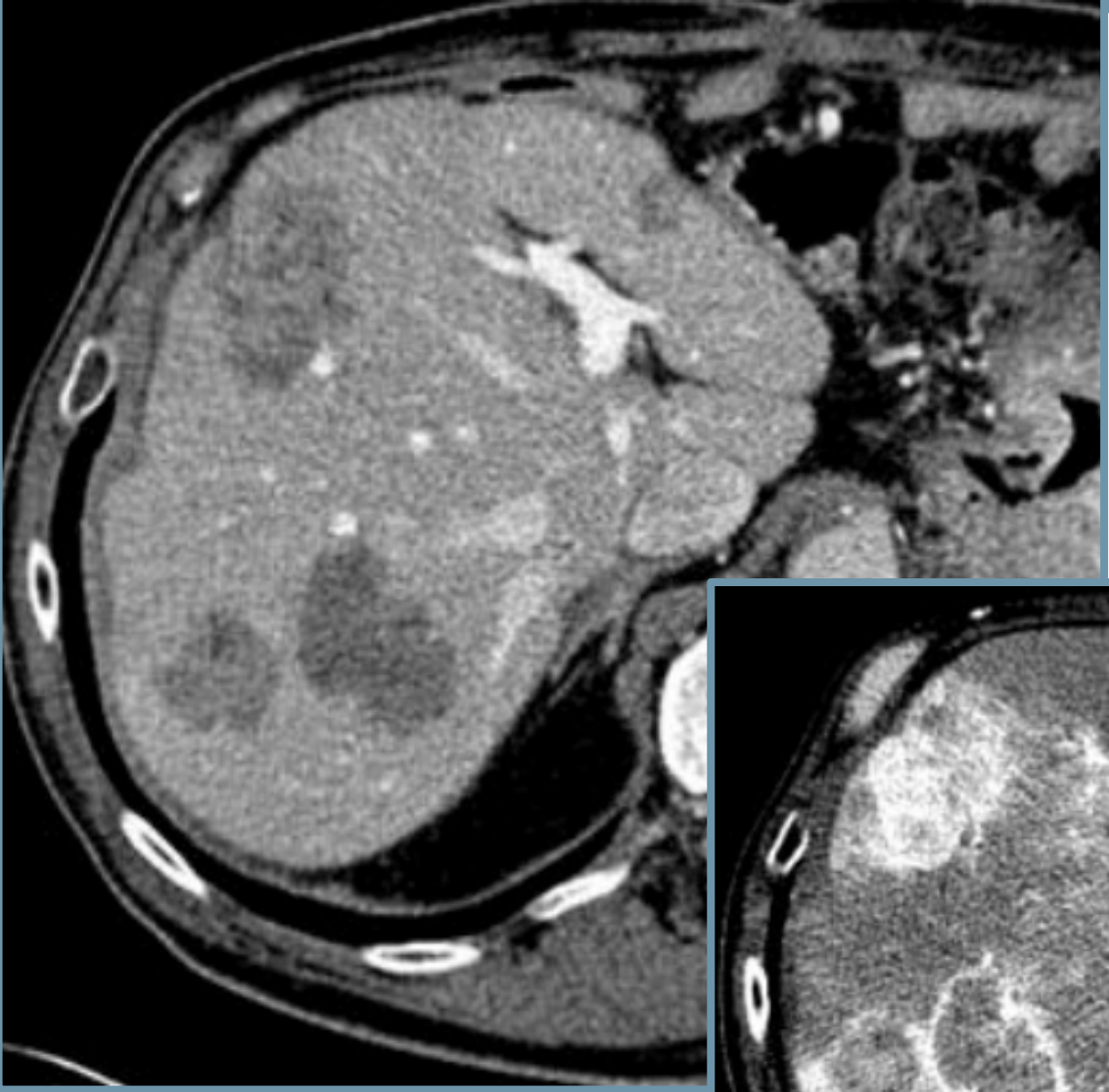
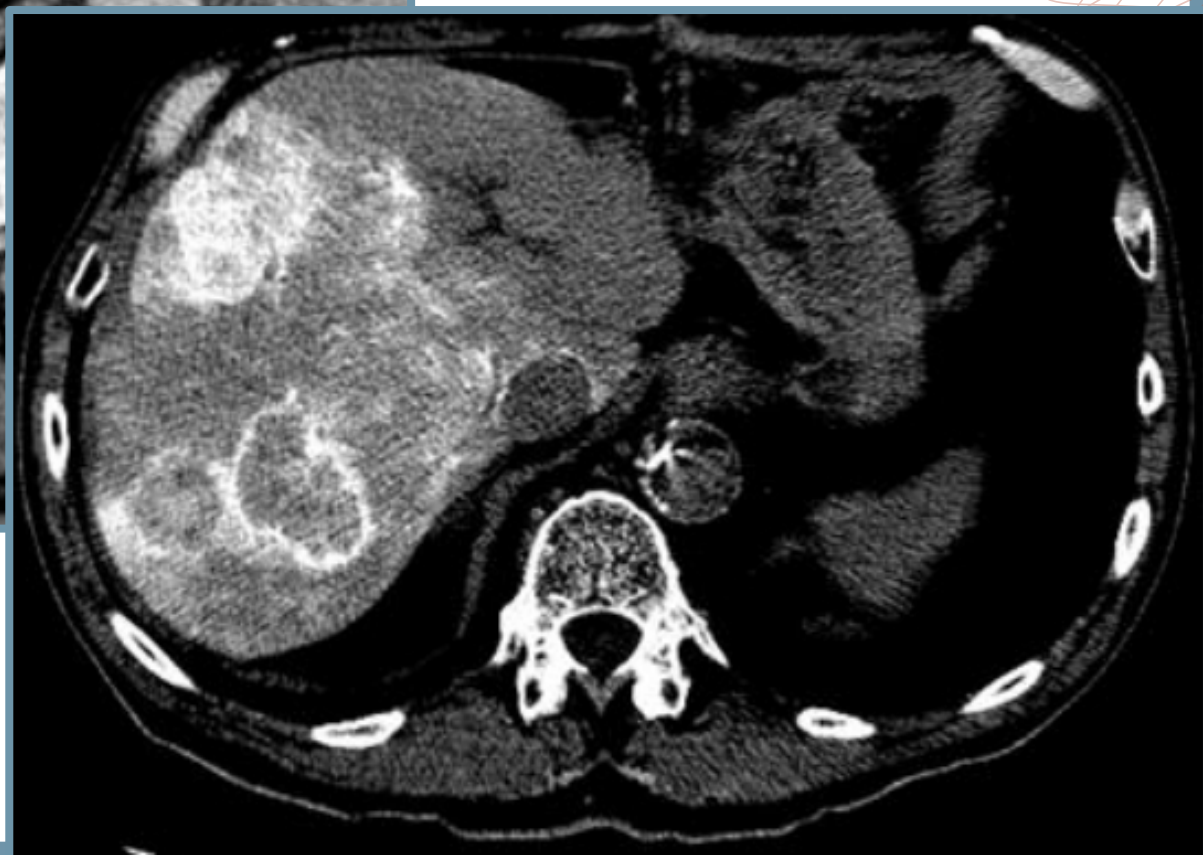
INTRA-ARTERIAL RADIATION THERAPY (^{90}Y)





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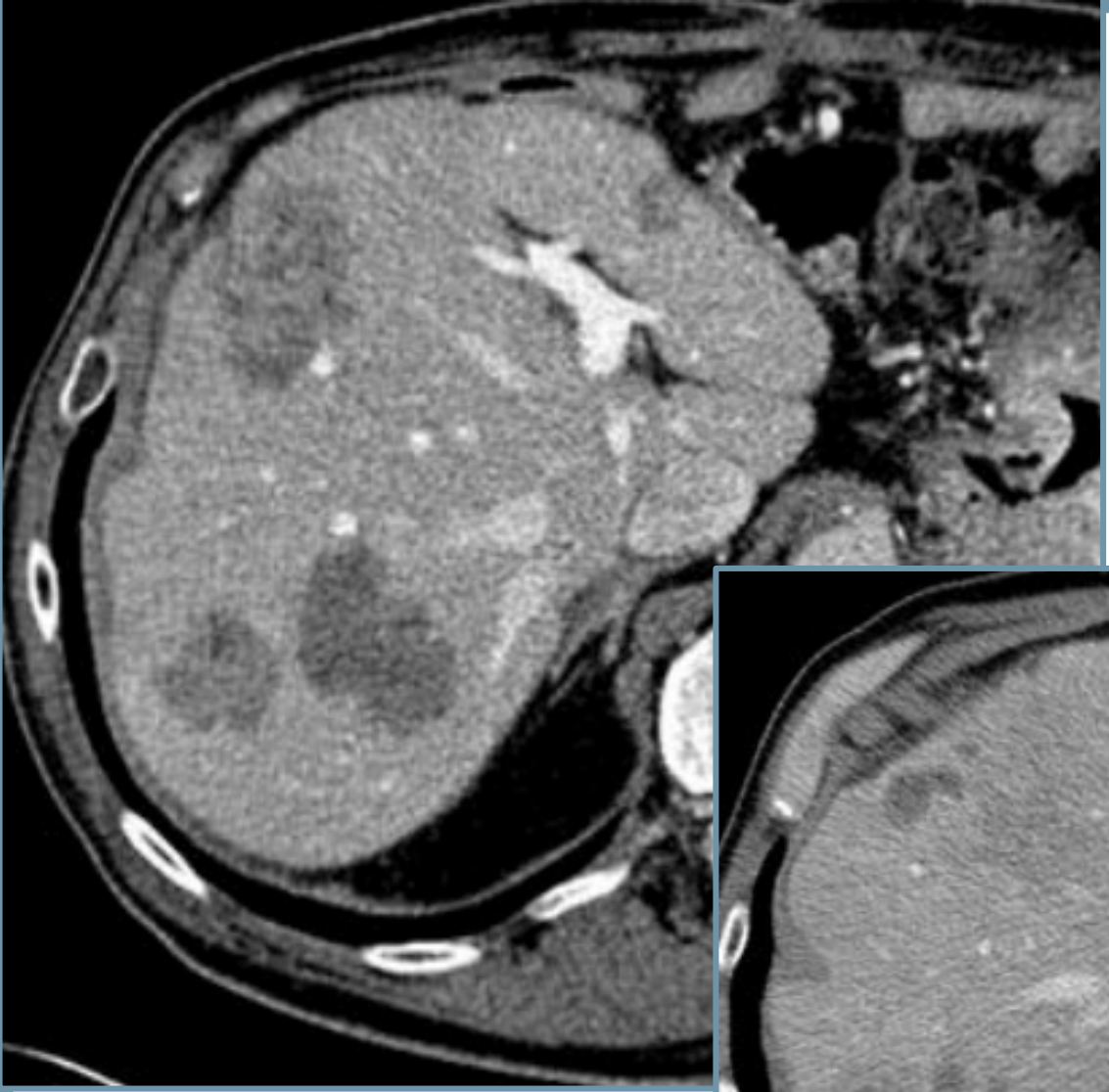
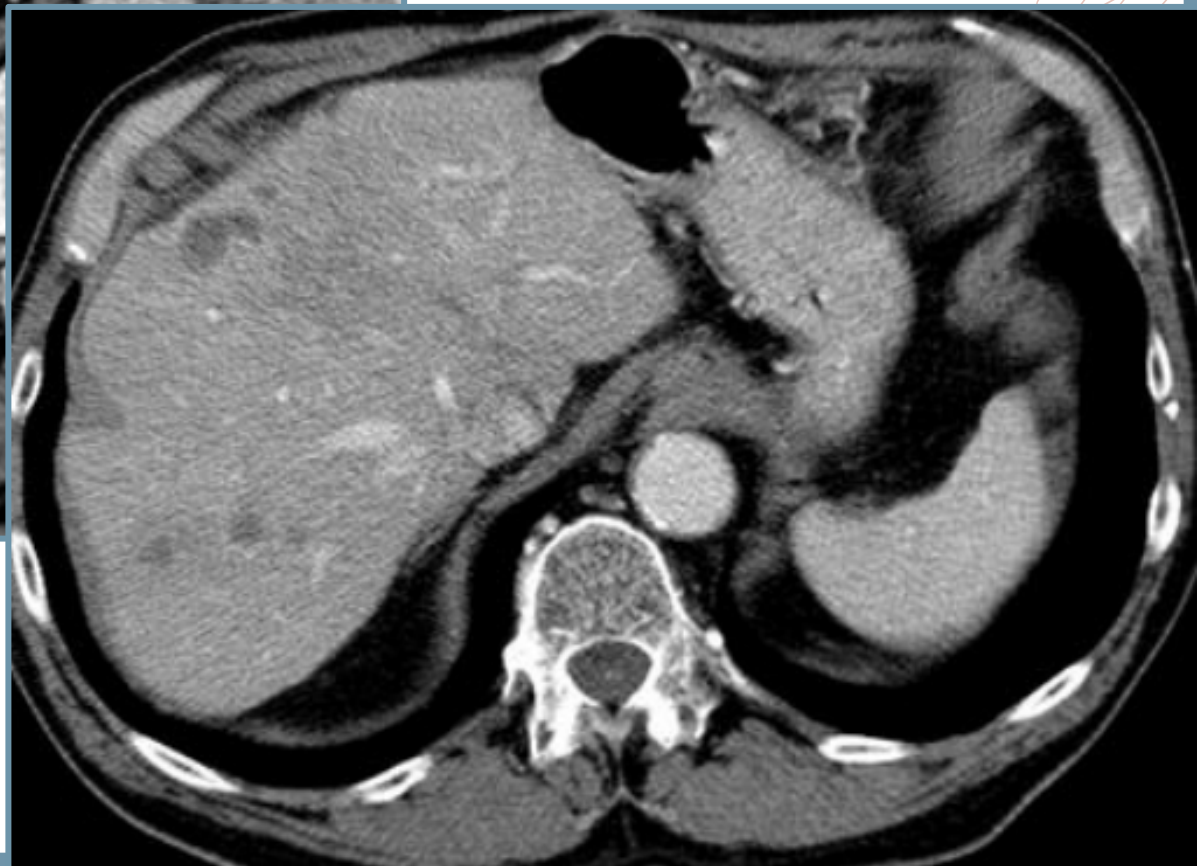
Salem R. CIRSE 2014





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Salem R. CIRSE 2014

TS-102 EPOCH STUDY DESIGN

Study Design

- A phase III, open label, prospective, multi-center, randomized clinical trial

- 24 months accrual and 12 months additional follow- up (with up to a maximum of 33 months accrual based on sample size re-estimation)
- 340 patients with up to a maximum of 500 patients based on sample size re-estimation
- 100 sites in US, Canada, EU and Asia

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TS-102 EPOCH STUDY DESIGN

Randomization 1: 1 between treatment and control group

Stratified according to:

- unilobar or bilobar disease
- first-line chemotherapy
- KRAS status

TS-102 EPOCH
STUDY OBJECTIVES/PRIMARY ENDPOINT

Study Objective:

To evaluate the efficacy and safety of TheraSphere® in patients with metastatic colorectal cancer of the liver scheduled to receive second line chemotherapy

Primary Endpoint:

Progression-Free Survival (PFS) according to RECIST Criteria v1.1 from time of randomization

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TS-102 EPOCH
SECONDARY ENDPOINTS

Overall Survival (OS) Time

Calculated from randomization to death

Hepatic Progression-Free Survival (HPFS):

The time from randomization to the date of disease progression in the liver according to RECIST 1.1

Time to symptomatic progression (TTSP)

- From the time of randomization to assessment of ECOG performance status >2
- Deterioration in performance status is to be confirmed at one subsequent evaluation 8 weeks later

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TS-102 EPOCH
SECONDARY ENDPOINTS

Disease Control Rate

Per RECIST criteria v1.1 for all targeted [liver] tumors

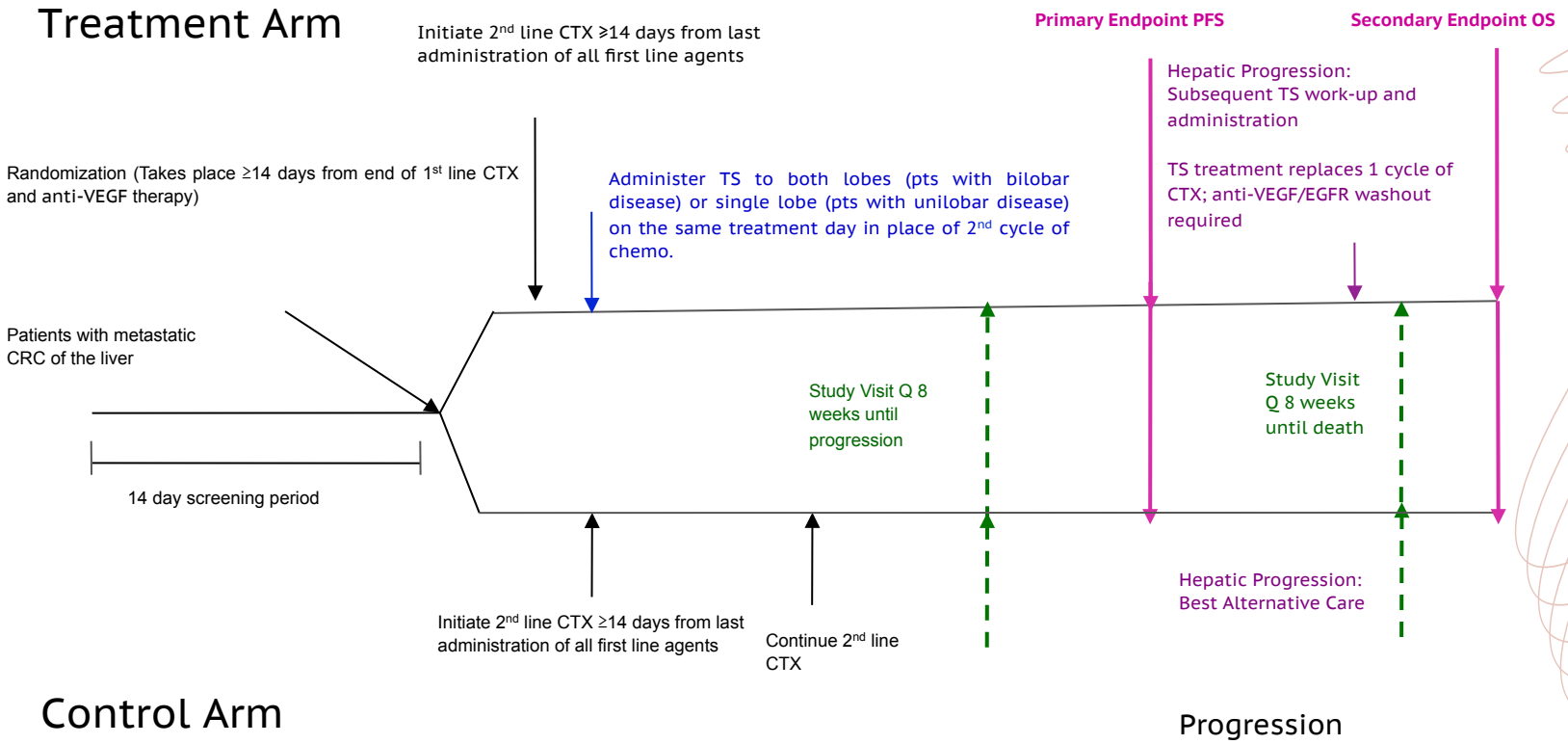
Quality of Life

Functional Assessment of Cancer Therapy colorectal cancer (FACT-c)

Adverse events and reportable serious adverse events

Defined by the study protocol (NCI Common Toxicity Criteria for Adverse Events; CTCAE v. 4.0)

TS-102 EPOCH



***Note –one cycle of chemotherapy is given prior to treatment with TheraSphere**

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Version date 06-Jun-2013 (protocol V 5.1 30-May-2014)

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Supported by an Independent Educational Grant from BAYER