

Prospective Phase II Study of Chemoembolization with Drug-eluting Beads for Hepatic Neuroendocrine Metastases: Interim Analysis

D Reyes¹, I Kamel¹, K Hong¹, C Georgiades¹, N Bhagat¹,
C Frangakis², JF Geschwind¹

¹ Department of Radiology, Johns Hopkins University school of Medicine

² Bloomberg School of Public Health, Johns Hopkins University, Baltimore, USA



JOHNS HOPKINS
M E D I C I N E

Partially supported by:
Biocompatibles, Inc

Introduction

- 46-93% of patients with NETs develop liver metastases (many with >50% liver involvement)
- Many NETs in the liver biologically active and secrete peptides causing significant adverse effects
- 5 year survival rate for localized NETs: 60-100%
 - Regional disease 5 year survival rate: 40-70%
 - Distant metastases 5 year survival rate: 17-40%
- Majority of NETs grow slowly
- Liver metastases present at time of diagnosis in majority of patients
- NETs variable grow rates
- Some NETs extremely aggressive

Treatment

- General management for NETs:
 - Control the endocrine syndrome
 - Determine the extent of the disease
 - Resect the tumor for cure (if possible) :10-20% patients
 - Long-term management of the tumor and its hormonal syndrome (if one is present) if resection is not possible
- TACE considered in patients with NET:
 - Significant hepatic metastases which are non-resectable or progressed in size despite previous therapy
 - Poorly or uncontrolled hormone related symptoms despite medical therapy

Due to limited clinical success and objective response with TACE in treatment of NET metastatic liver lesions and given activity of doxorubicin against NET, purpose of study:

Phase II trial of DEB-TACE in patients with NET

Patient selection

- Study approved by Institutional Review Board (IRB) and by the Food and Drug Administration (FDA) with a physician sponsored Investigational Device Exemption (IDE) to treat thirty patients with hepatic neuroendocrine metastases
- Eligibility criteria
 - ECOG performance status ≤ 2 , Child-Pugh A-B; absent or trace ascites, albumin > 2.0 g/dL, ALT and AST < 5 x upper normal limit, total bilirubin < 3.0 mg/dL, creatinine < 2.0 mg/dL, platelet count $\geq 50,000/\text{mm}^3$, INR ≤ 1.8 , and left ventricle ejection fraction of $\geq 50\%$
- Exclusion criteria
 - Any anti-cancer therapy for hepatic NE metastases except previous surgical therapy; predominant extrahepatic liver disease; diffuse hepatic NE metastases with $> 90\%$ tumor burden

Treatment protocol

- **Baseline: H&P, laboratory assessment, and MR imaging**
- **DEB-TACE technique**
 - 2 vials LC Beads (2 mL, BioCompatibles Ltd., UK) (100-300 μm) loaded with 100 mg of doxorubicin HCL (25mg/mL, Pharmacia-UpJohn) and mixed with an equal volume of non-ionic contrast media
 - Catheter (usually microcatheter) positioned close to the tumor bed before infusions of the DEBs
 - DEBs (up to 4 mL) administered by alternating injections- of the beads, and then contrast-always ensuring forward flow until complete delivery or reaching near stasis
 - Complete occlusion of feeding artery avoided to allow for re-treatment
- **Up to 6 DEB-TACE procedures (3 whole liver or 6 lobar treatments) allowed**
- **Follow-up visits at 1 month, than at 2- to 3-month intervals**

Primary Endpoints

- **Safety**

 - NCI CTCAE version 3.0

- **Efficacy**

 - MRI imaging performed 1 month after initial DEB-TACE treatment and 3 months after completion of the entire DEB-TACE cycle. For each patient, 1-3 treated lesions per lobe were evaluated

 - Response Evaluation Criteria in Solid Tumors (RECIST) modified to allow for measurement of targeted tumors used to measure change in targeted tumor size
 - European Association for the Study of the Liver (EASL) was used to measure change in contrast-enhancement
 - Apparent diffusion coefficient (ADC) value used to measure motion of water molecules (cell death)

Secondary endpoints

- Biochemical response
 - 5-HIAA 24-hr urine levels at baseline and with follow-up visits
- Symptomatic response
 - Scoring system for symptom severity in patients with NE/carcinoid syndrome
 - Measurement of octreotide dose at baseline and post treatment f/u visits
- Survival

Design and analysis

Statistical plan: Interim analysis (n=10) to assess therapeutic efficacy

- Defined as objective response (EASL or RECIST)
 - If objective response seen in 5 of initial 10 patients, continue to recruit another 20 patients
- FDA requirements for safety

Patient characteristics

Variable	Value
No. of pats enrolled	13
Mean age, years (range)	64 (47-80)
Sex (M/F)	9/4
ECOG (0/1)	7/6
Carcinoid syndrome	3
Tumor burden, range	12-75%
Chromogranin-A: number diagnostic, mean	10 (1037.46 ng/mL)
5-HIAA: number diagnostic, mean	6 (149 mg/24 hr)

Interim safety and efficacy analysis (n=10)

1. Imaging response at 1 month
 - RECIST: partial response 1 patient (11%), stable disease (8 patients (89%))
 - EASL: objective tumor response (78%), stable disease (2 patients, 12 %)
2. Interim analysis showed therapeutic efficacy
3. Safety: unusual number of bilomas
4. Continued protocol, modified patient selection

Imaging response at 1 and 3 months (n=32 lesions, 13 patients)

Features	Before DEB-TACE	1 month after DEB-TACE	3 months after DEB-TACE cycle
-Size of tumor \pm SD (cm)	4.5 \pm 2.5	4.1 \pm 2.7	3.1 \pm 2.6
-%change		p=0.0003 -12%	p<0.0001 -33%
-p-value			
-Enhancement of tumor (%) \pm SD (cm)	88 \pm 21.8	37 \pm 22	40 \pm 33
-%change		p<0.0001 -56%	p<0.0001 -54%
-p-value			
ADC	1.15 \pm 0.39	1.59 \pm 0.39	-
-p-value		p=0.003	

Imaging response at 1- and 3-months

1 month, 13 patients, 17 lobes

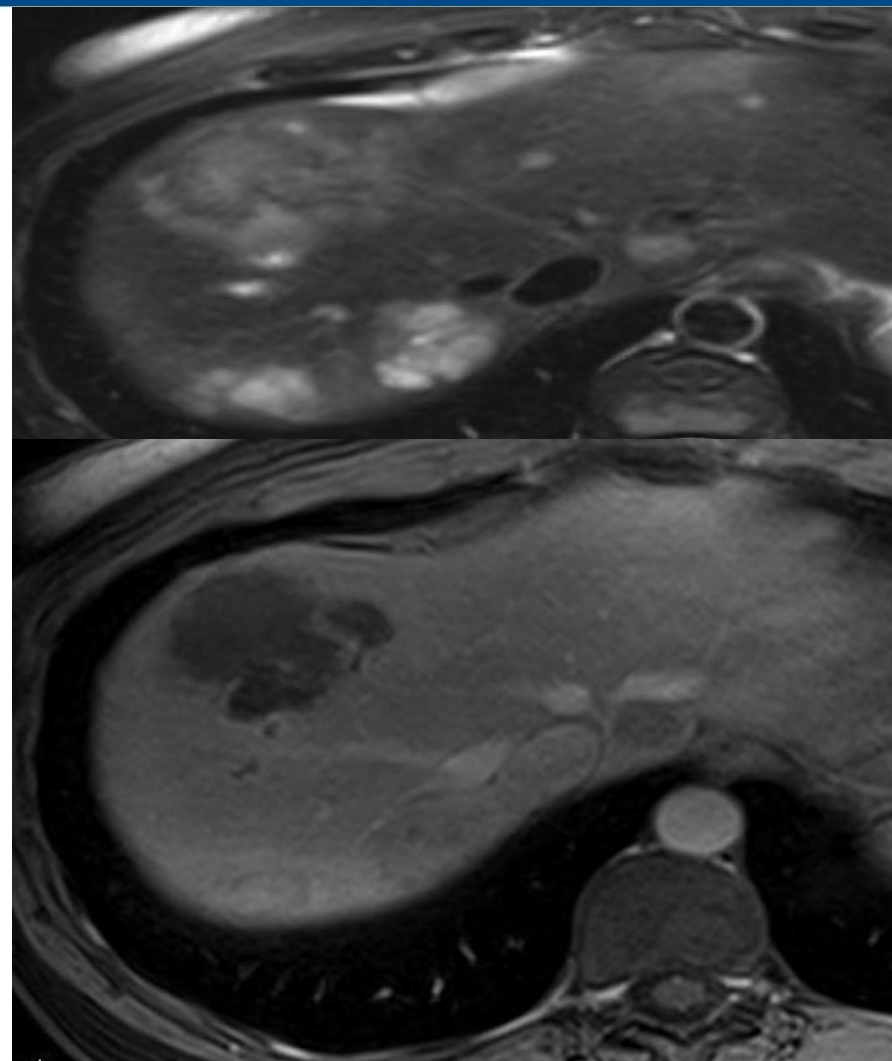
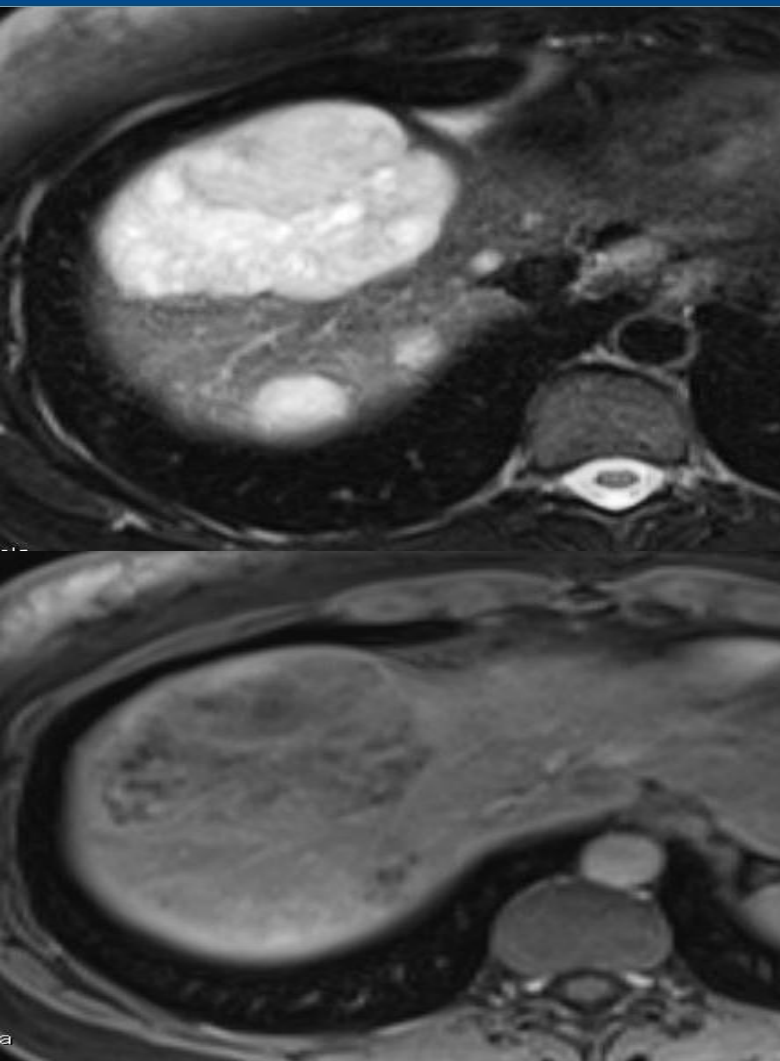
	RECIST	EASL
CR	-	-
PR	1/17(6%)	13/17 (76%)
SD	16/17 (94%)	4/17 (24%)
PD	-	-

3 months, 10 patients, 12 lobes

	RECIST	EASL
CR	-	1/12 (8%)
PR	4/12 (33%)	6/12 (50%)
SD	7/12 (58%)	5/12 (42%)
PD	1/12 (8%)	-

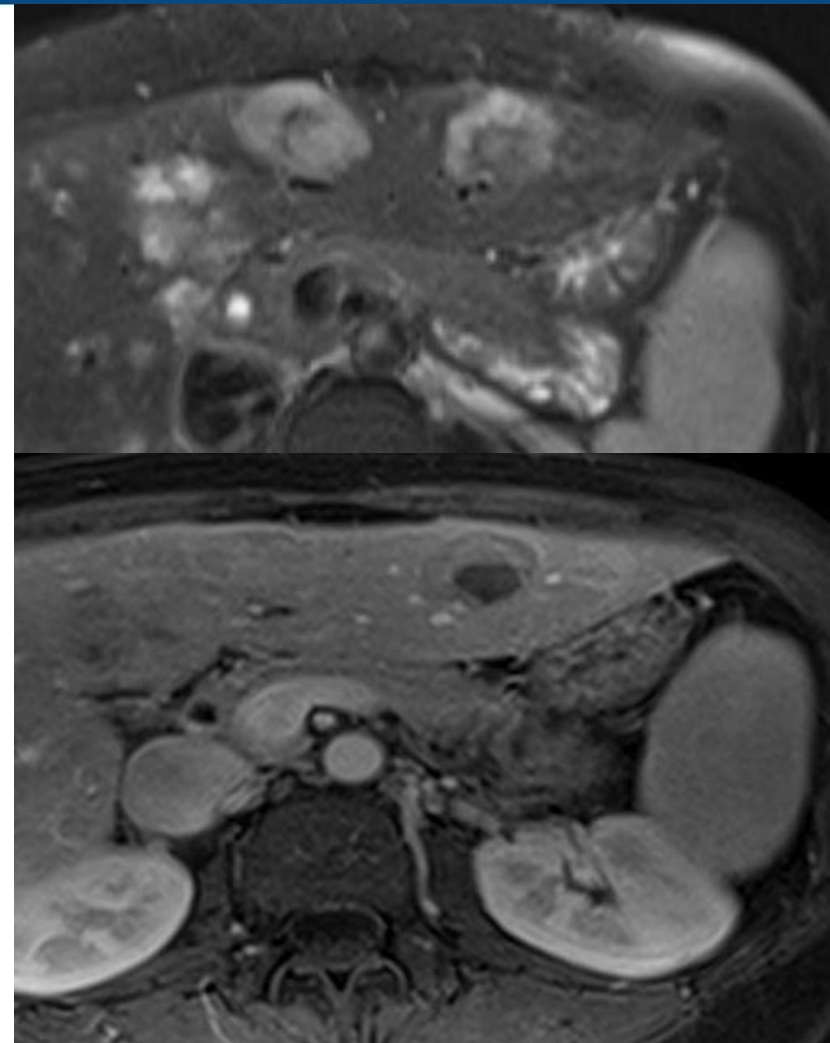
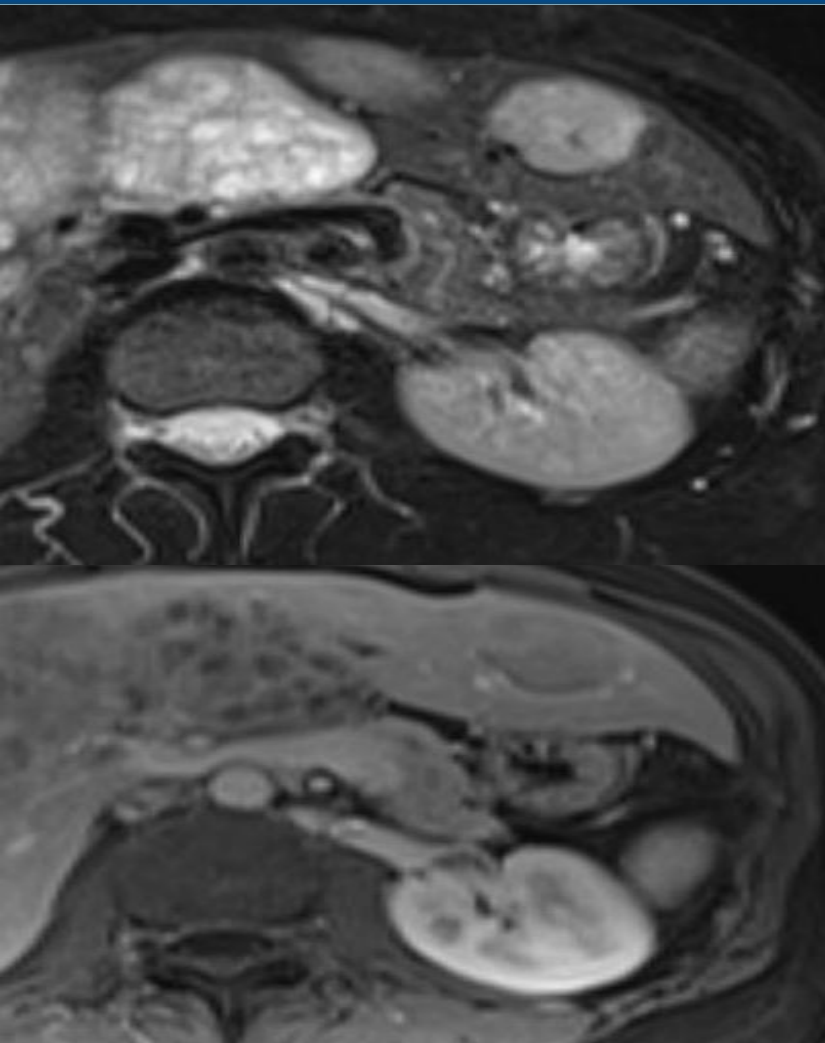
T2, and T1 contrast enhanced images

47 y/o female, right lobe lesions, s/p 2 treatments of DEB-TACE
1 month post treatment, stable >3 months



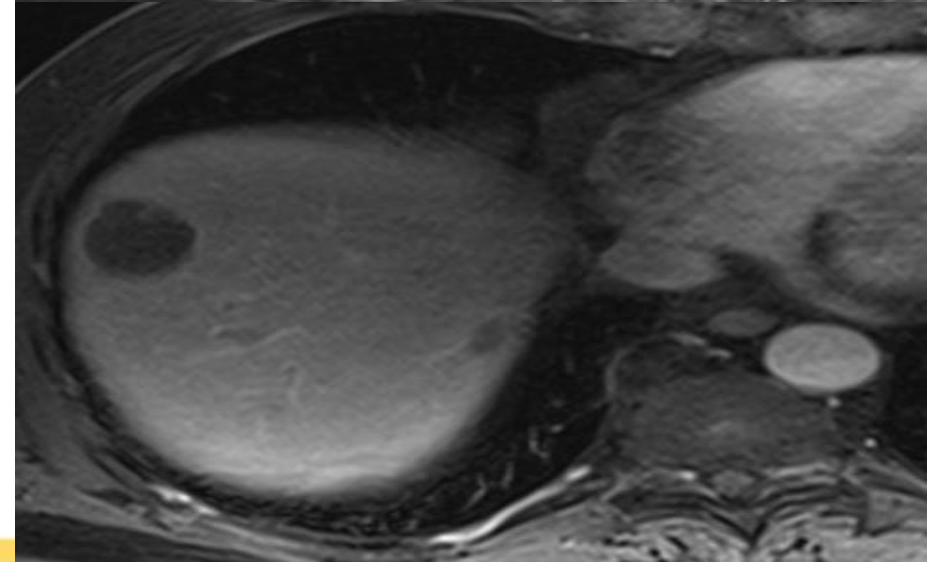
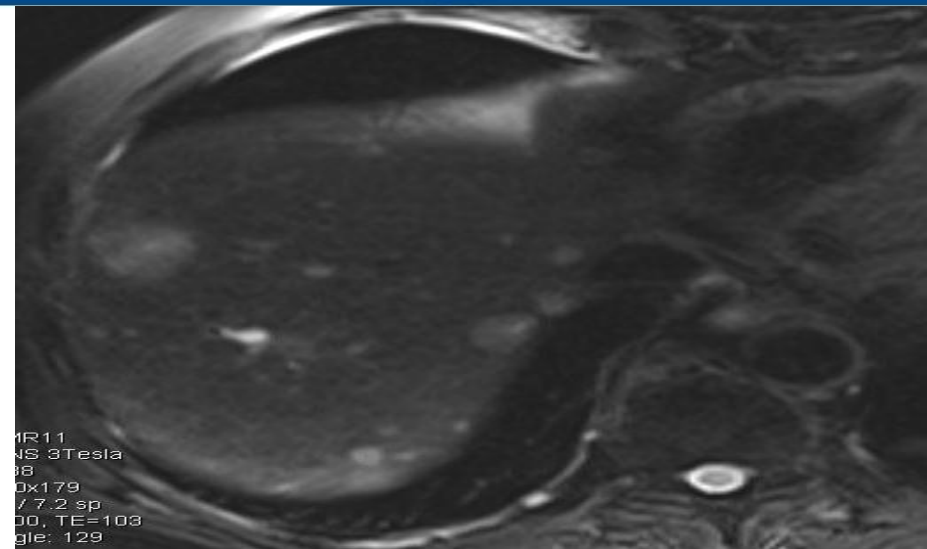
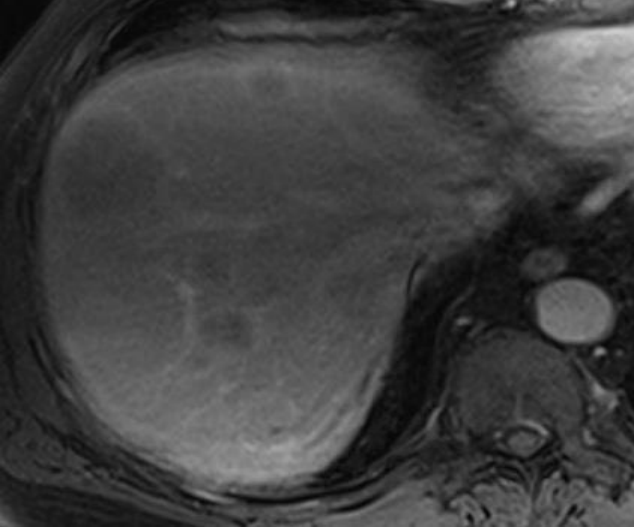
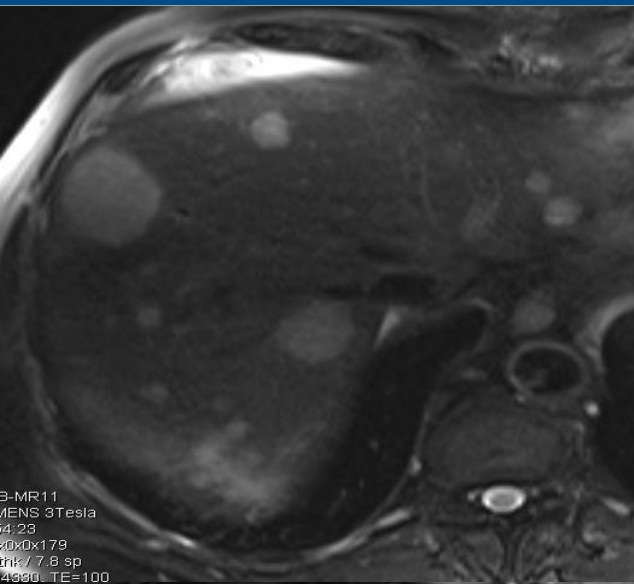
T2, and T1 contrast enhanced images

47 y/o female, left lobe lesions, s/p 1 treatment of DEB-TACE
3 months post treatment, stable >4 months

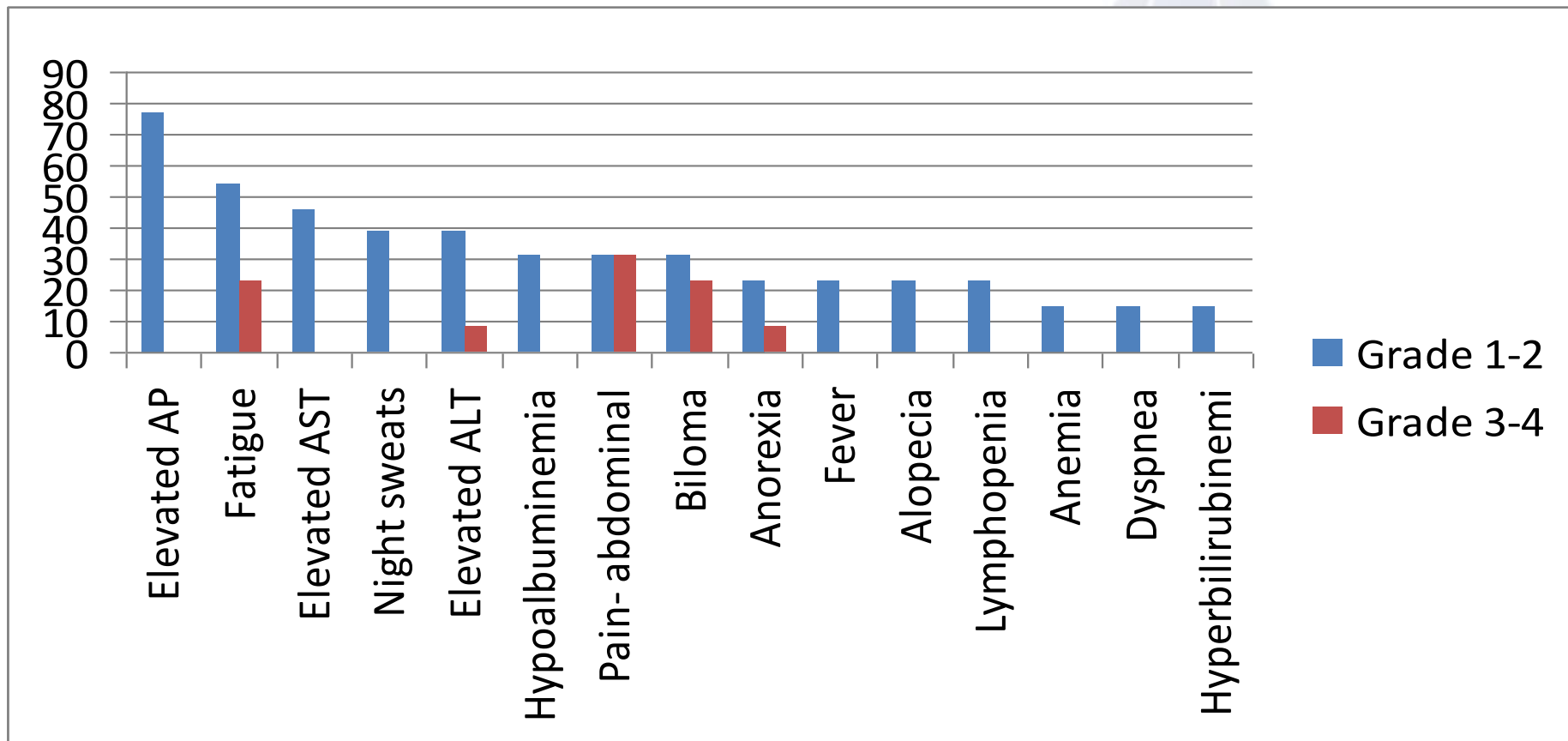


T2, and T1 contrast enhanced images

68 y/o male, right lobe lesions, s/p 2 treatments of DEB-TACE
1 months post treatment



Safety: adverse events (all causes, percentages) at 1 month* (n=13)



Some bilomas developed after 1 month f/u

Safety

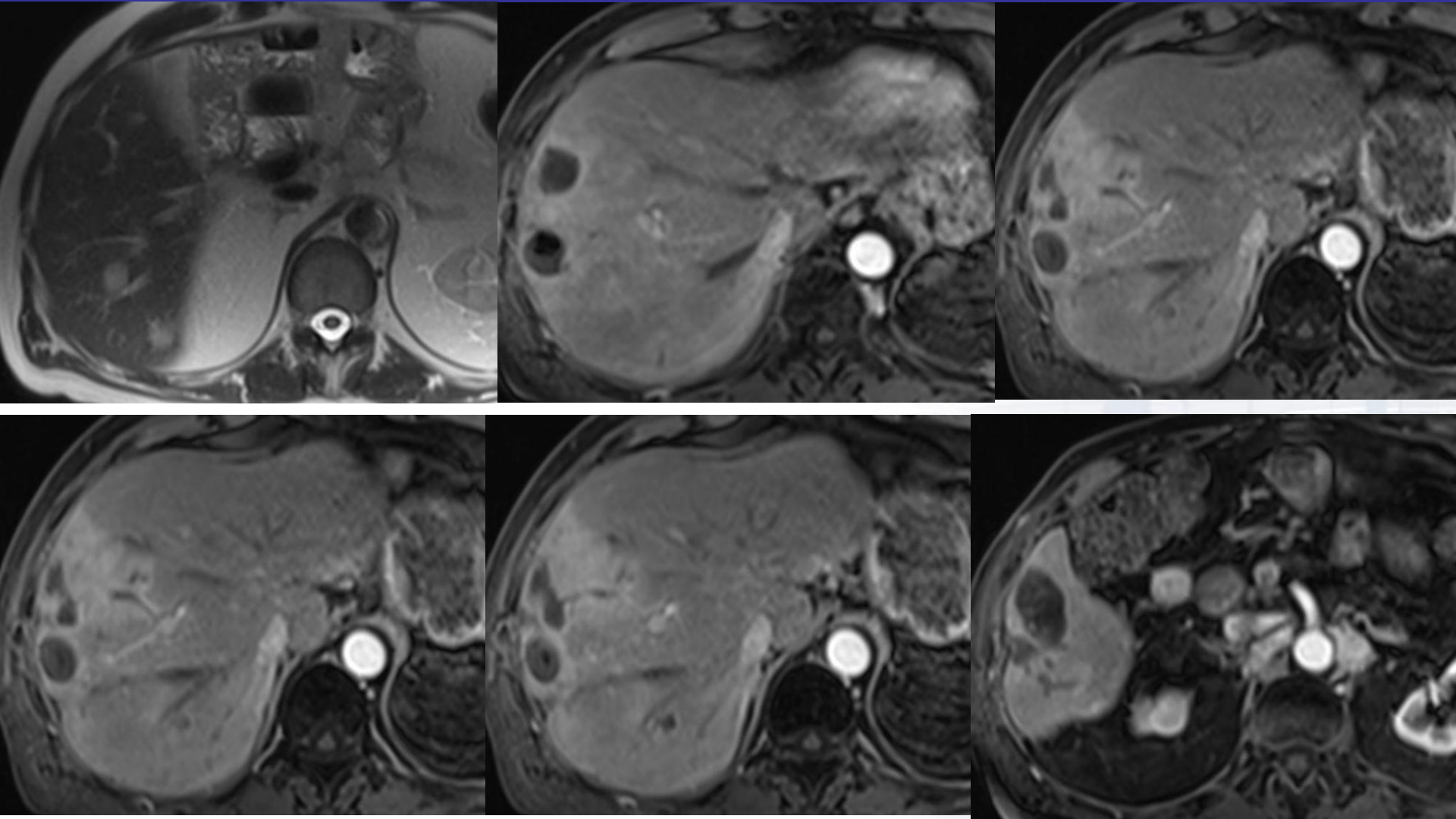
- Unexpectedly high number of bilomas:
n=7/13 (54%)
3 patients with grade 3 requiring drainage
- No deaths within 30 days of the procedure

T2 and T1-weighted contrast enhanced images

66 y/o male, right lobe lesions, s/p 2 treatments of DEB-TACE

1 month post treatment

Multiple bilomas / abscesses

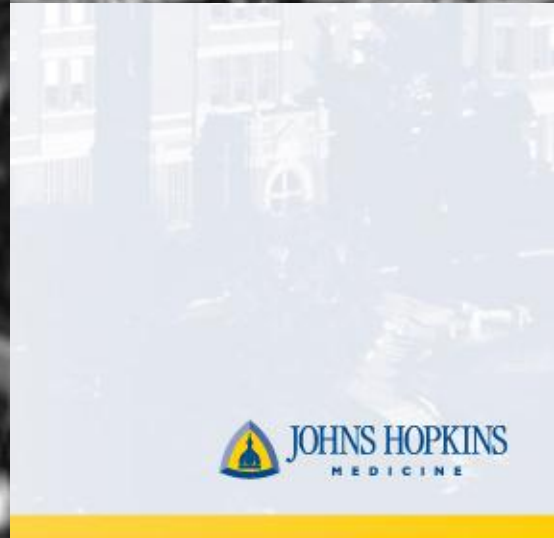
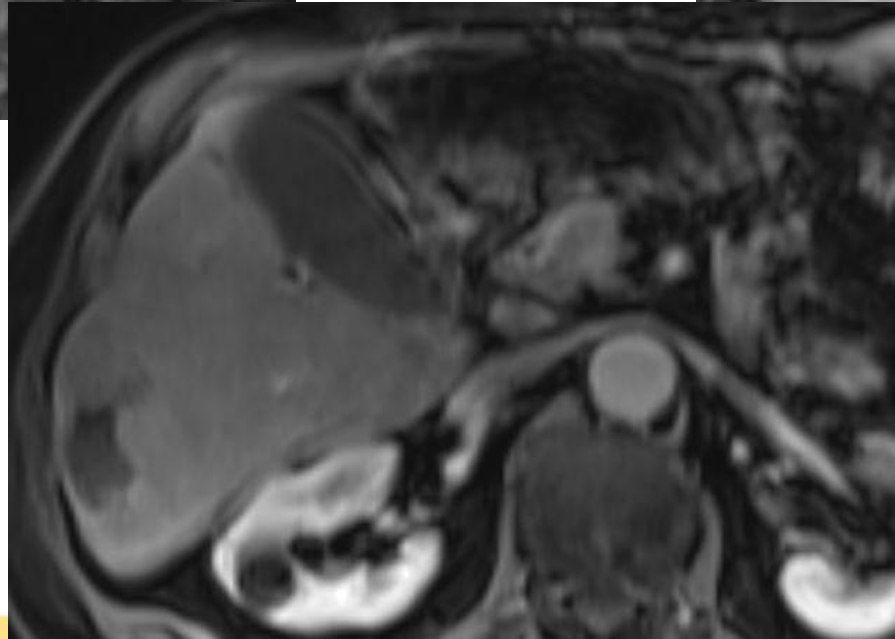
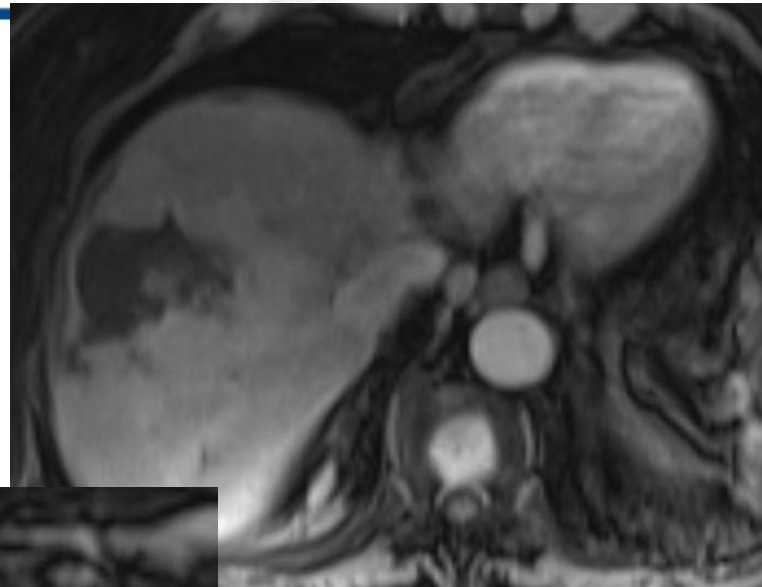
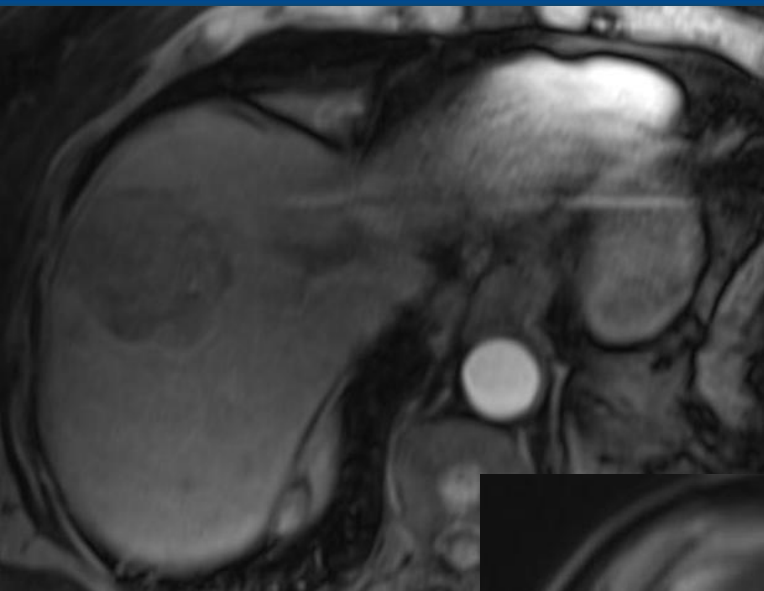


T1-weighted Contrast Enhanced Images

80 y/o male single right lobe lesion, 1 treatment with DEB-TACE

1 month post treatment

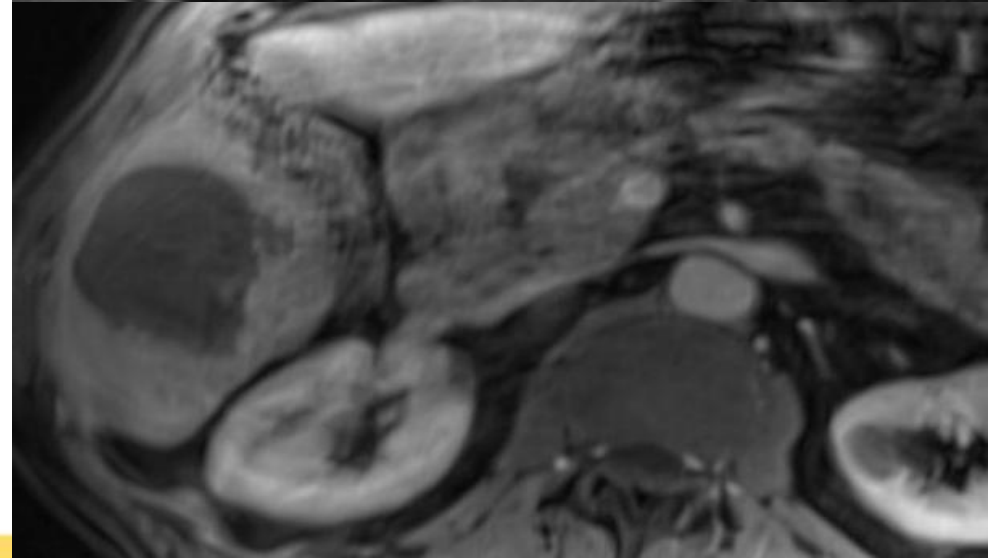
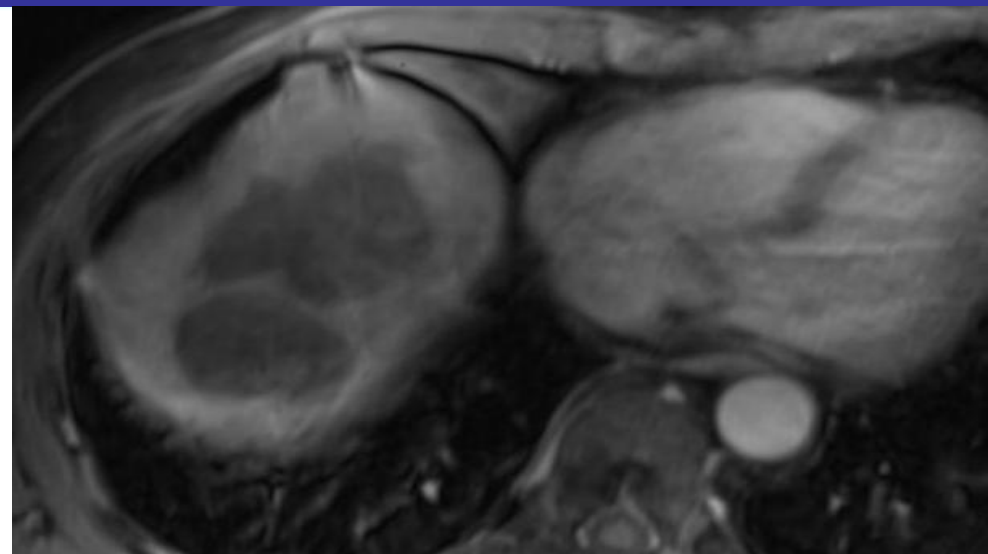
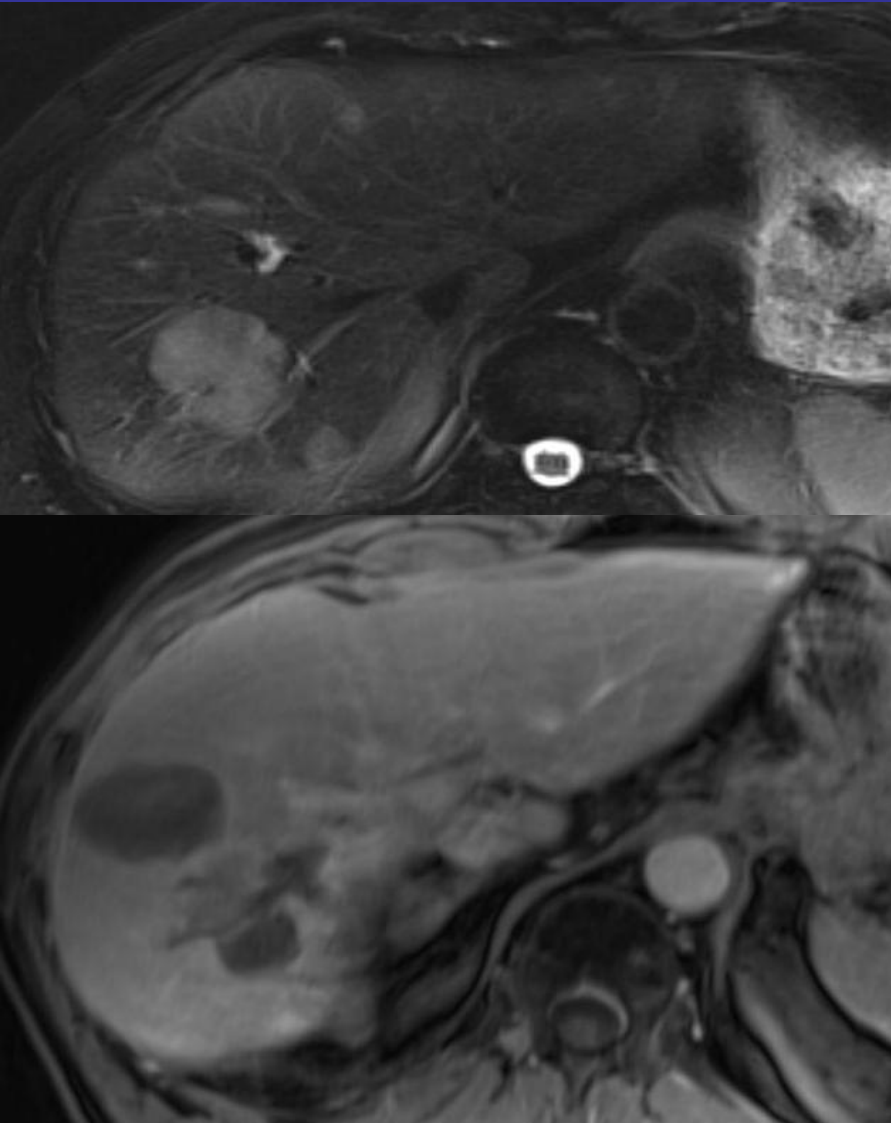
Biloma



T2- and T1-weighted Contrast Enhanced Images

72 y/o male, single right lobe lesion (satellites), 1 treatments of DEB-TACE; 1 month post treatment

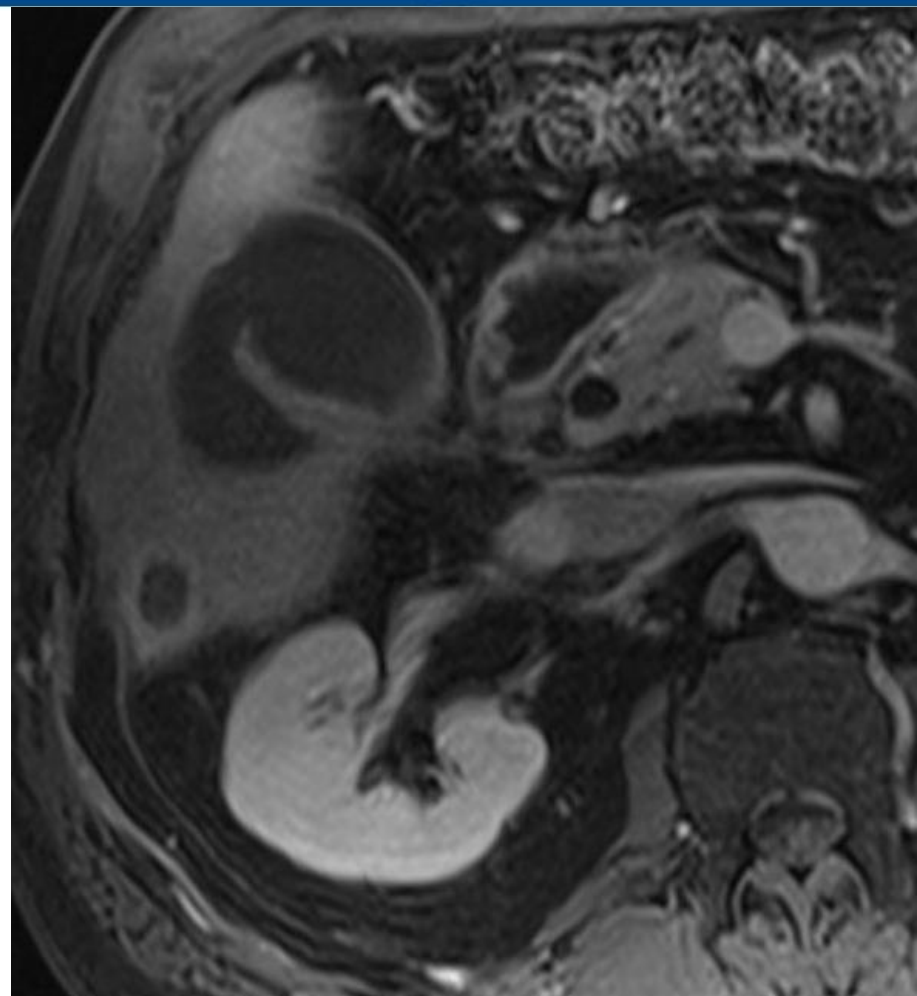
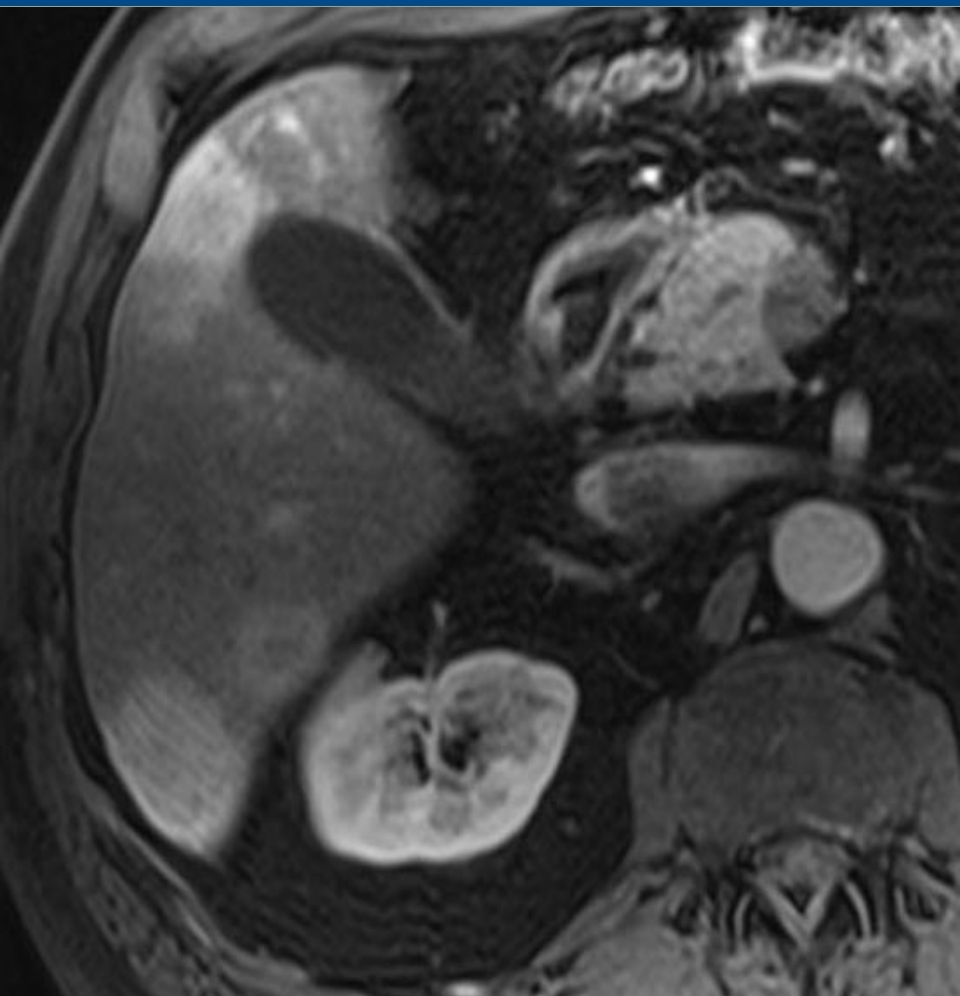
Multiple bilomas



T2, and T1 contrast enhanced images

68 y/o male, 1 treatment of DEB-TACE, 1 month post therapy

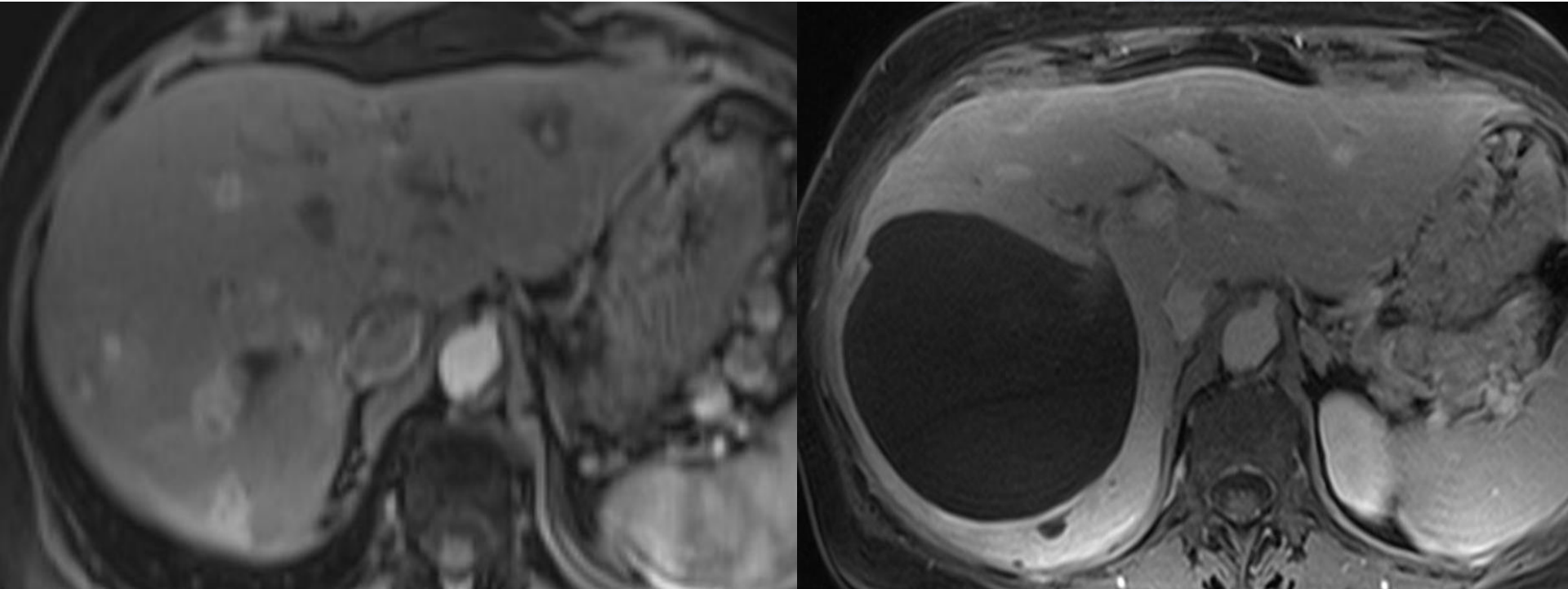
Biloma/abscess eroded into gallbladder



T2, and T1 contrast enhanced images

69 y/o female, 2 treatments of DEB-TACE; 4 months post therapy

Biloma/abscess



Recommendations

- WHY so many bilomas?
 - TECHNICAL: Unlikely
 - VULNERABILITY of peri-biliary plexus in non-cirrhotic patients (this high incidence of bilomas not seen in HCC)
 - DEB-TACE perhaps too effective in tumor destruction and also damaging arterial supply to biliary tree resulting in bilomas
- For NET: DEB-TACE best for patients with large focal, diffuse or dominant masses in a segment even if spread out.
- Not recommending DEB-TACE for multifocal nodular widespread tumors, or miliary disease.

Conclusions

- Interim analysis therapeutic efficacy of DEB-TACE in NET
 - Excellent tumor kill
 - Safety: Beware of high incidence of bilomas and abscesses
 - Do not treat patients with relatively low tumor burden and multifocal widespread or miliary disease
- DEB-TACE best suited for NET patients with highly vascular tumors (focal or segmental) or diffuse disease

T2 images-baseline presentation

Treated patients who did not develop biloma (n=6)

