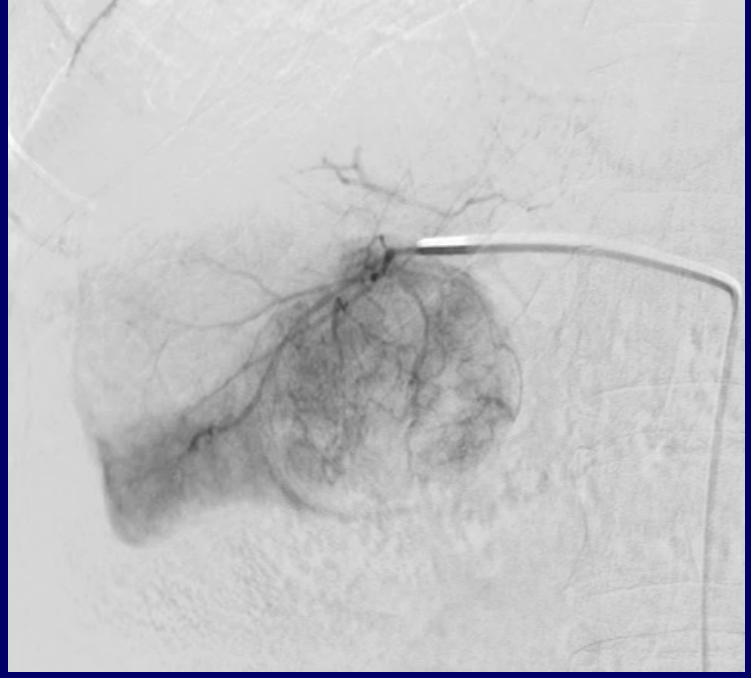


TACE and TARE : Why, When and How

Dr Shivanand Gamanagatti
Professor of Radiology
AIIMS, New Delhi

Concept of TACE

- Based on taking the advantage of dual blood supply (HA and Portal vein) to liver and tumoral supply by HA
- Delivery of high concentration of chemotherapeutic agent(s) to tumor : (Transarterial route)
- Reduction of damage to non-tumor tissue (selective)
- Prolong dwell time of chemotherapeutic agents within tumor (Embolisation)
- Minimize systemic escape of drugs (Embolisation or Use Beads)

Part 1: When

Patient selection : Indications and Contraindications

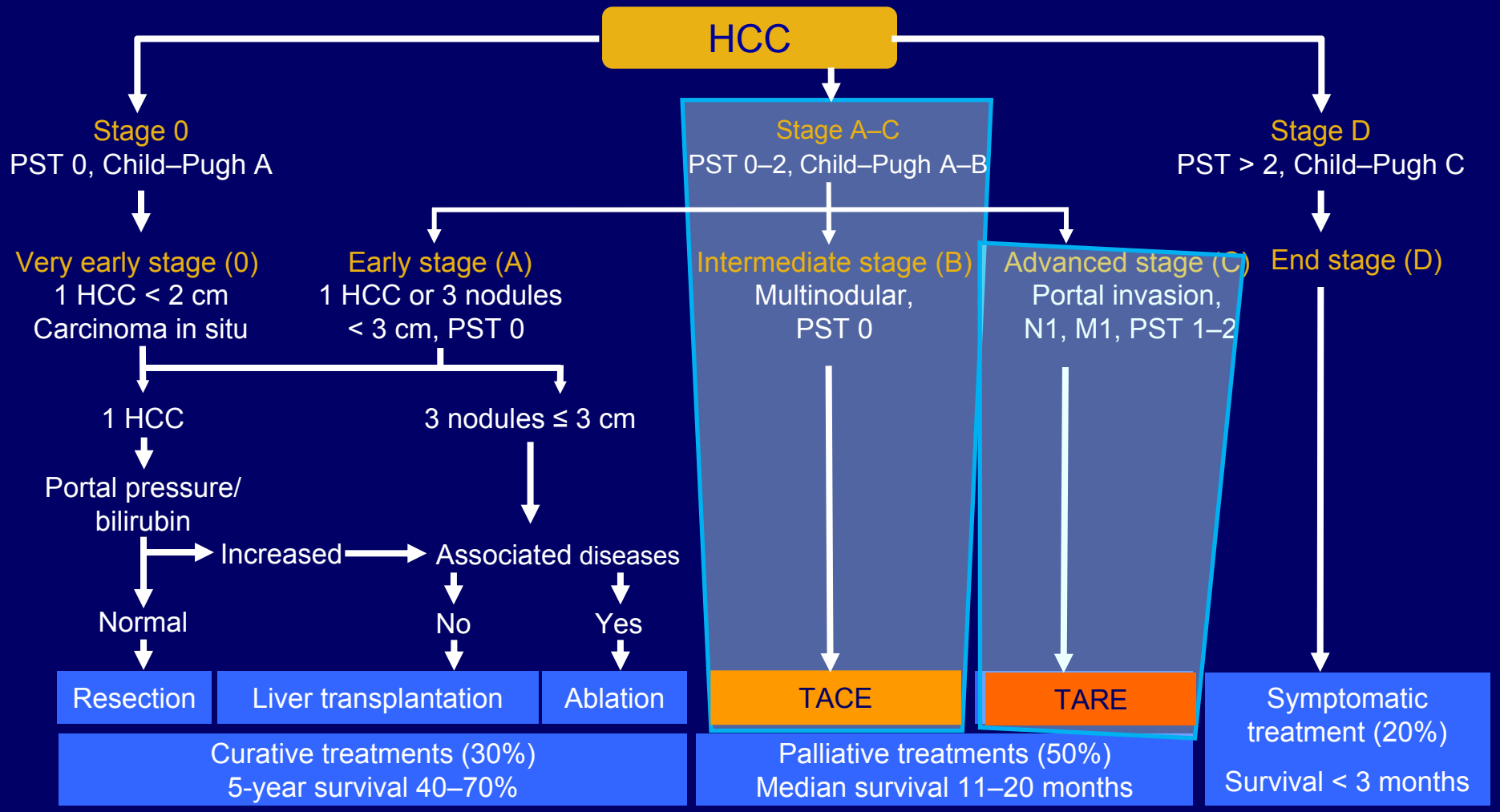
Part 2: How

Technique : ″Conventional″ TACE and New TACE

Part 3: Why

Results: Survival

Treatment of Hepatocellular Carcinoma (HCC): The BCLC Staging System



adapted from Llovet JM, DiBisceglie A, Lencioni R, et al.

When ?

Indications & Contraindications

Indications

- Nodular-encapsulated HCC >3cms
- Multinodular HCC

Neg. predictive factors

- High tumor burden
- Diffuse/infiltrative HCC
- Hypovascular HCC
- Extrahepatic spread

Contraindications

- Child C
- Occlusion main portal vein
- Relevant N or M stage
- Impaired liver / kidney function
  - bilirubin > 3 mg/dl
  - Creatinin > 150 mmol/l
- Karnofsky-Index < 50%
- Tumor burden > 70%
- Decompensated portal hypertension

How?

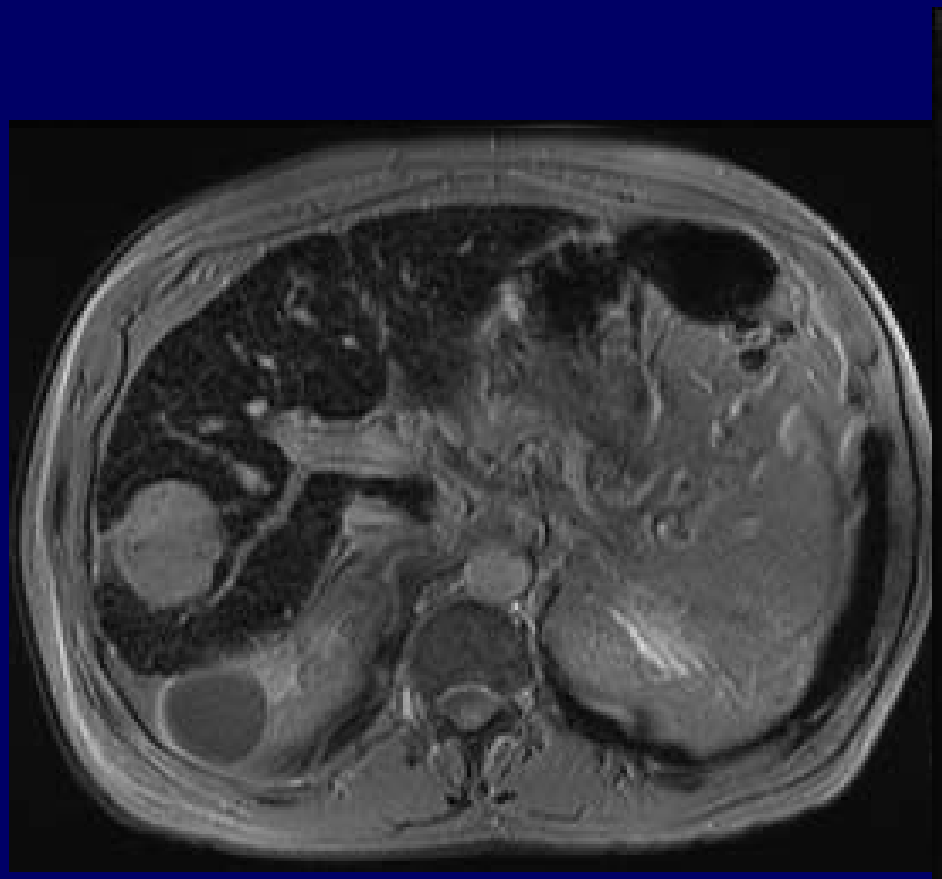
Technique

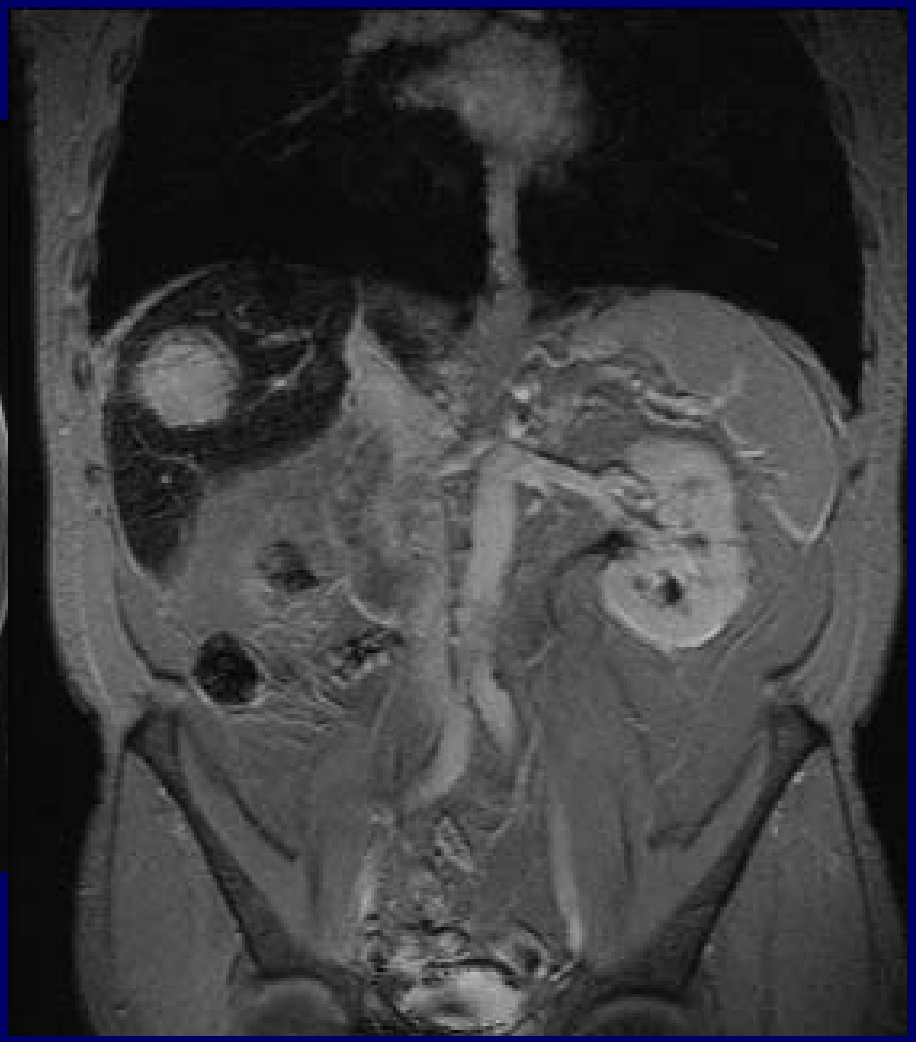
- Principle
  - Hyperconcentration of cytostatic drug
  - Synergistic effect: Reduced arterial inflow -diminish washout- prolong contact time

- Materials
  - Selective / Superselective catheterisation
  - Drugs:
    - Doxorubicin
    - Cisplatin
    - Mitomycin C

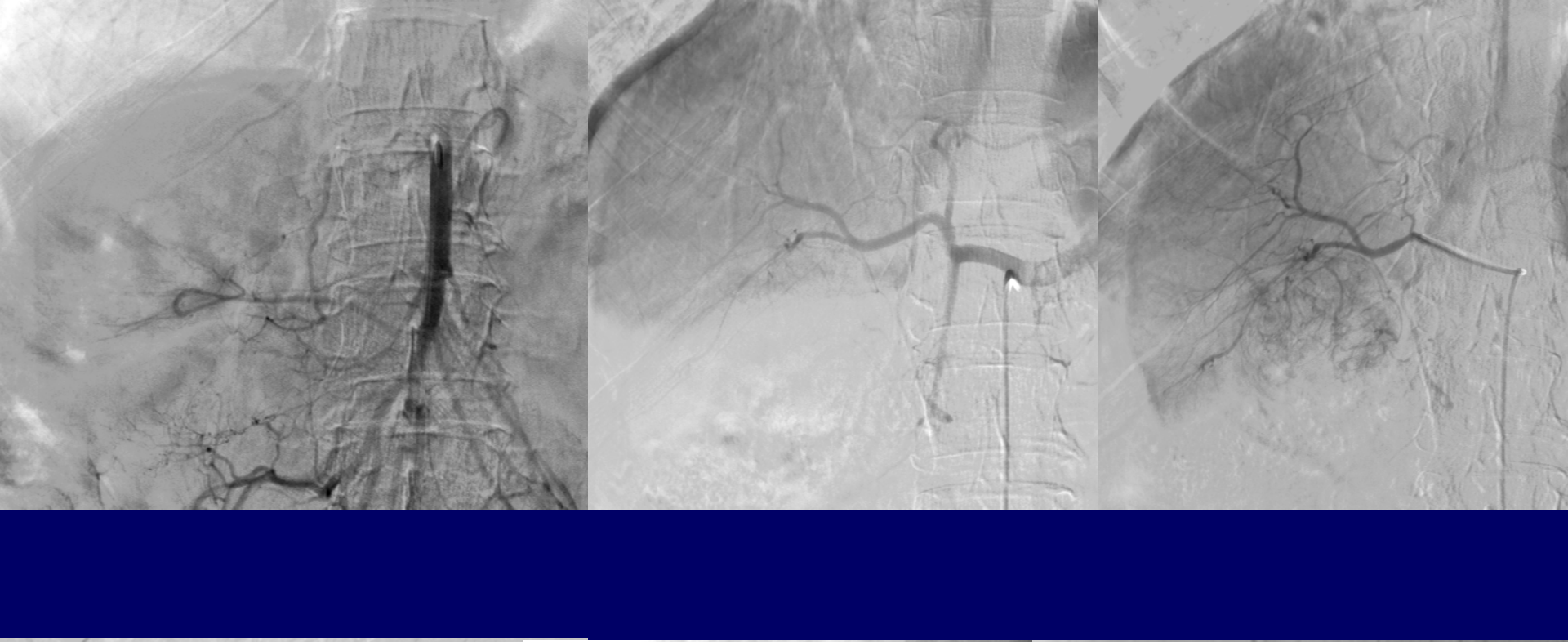
- Emulsification / embolisation material:
  - Lipiodol (arterio-portal connections – sinusoids – wash out) : Half-life 1 hr
  - Drug eluting beads (90% of drug is released over 7-10days)
  - Embolising agent: Gelfoam /PVA particles To reduce arterial inflow

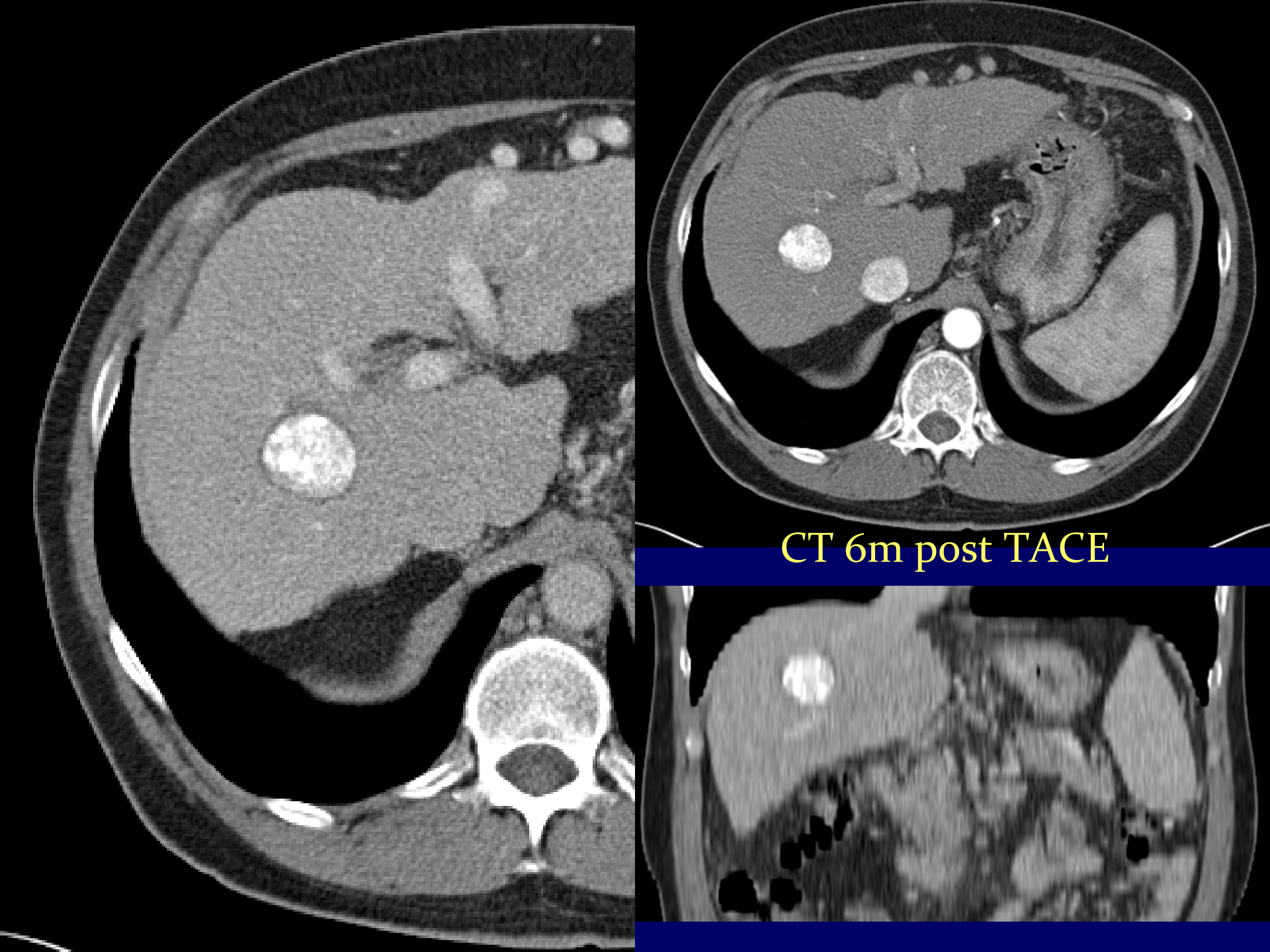
TACE - HCC

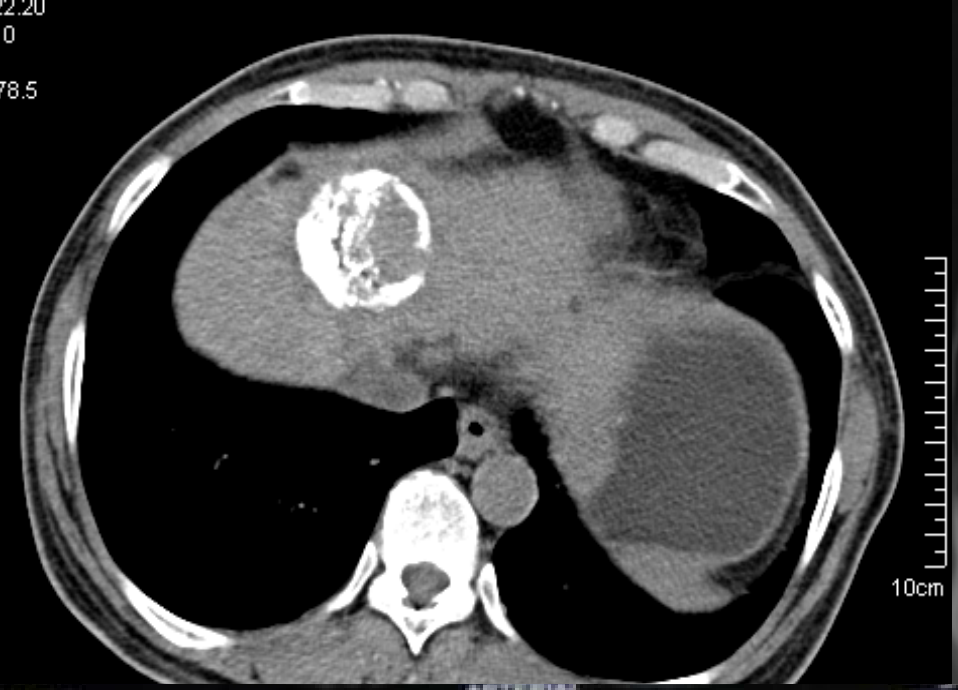


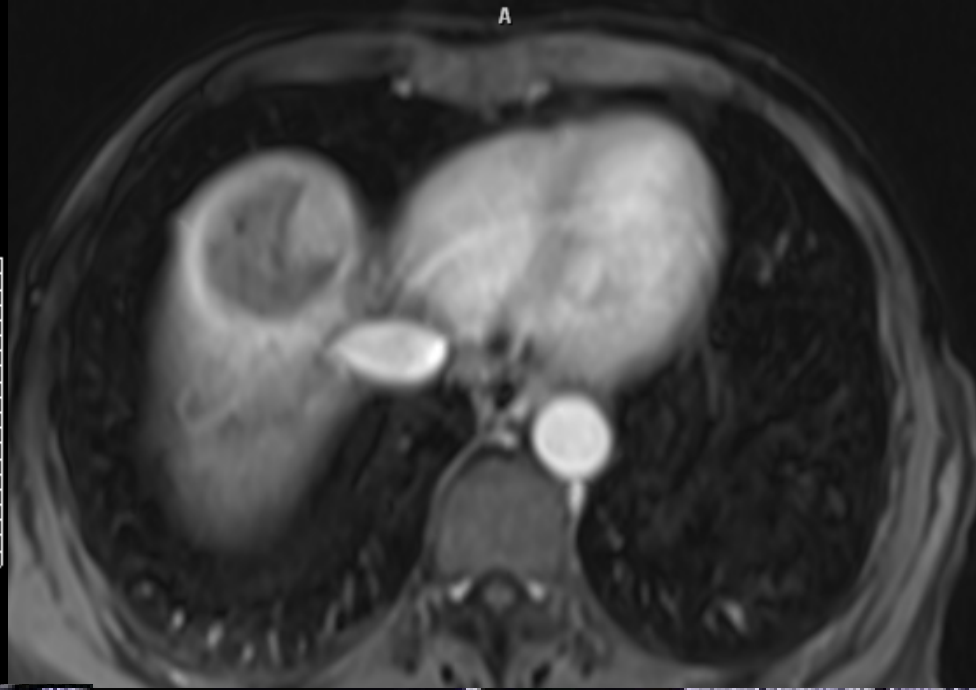


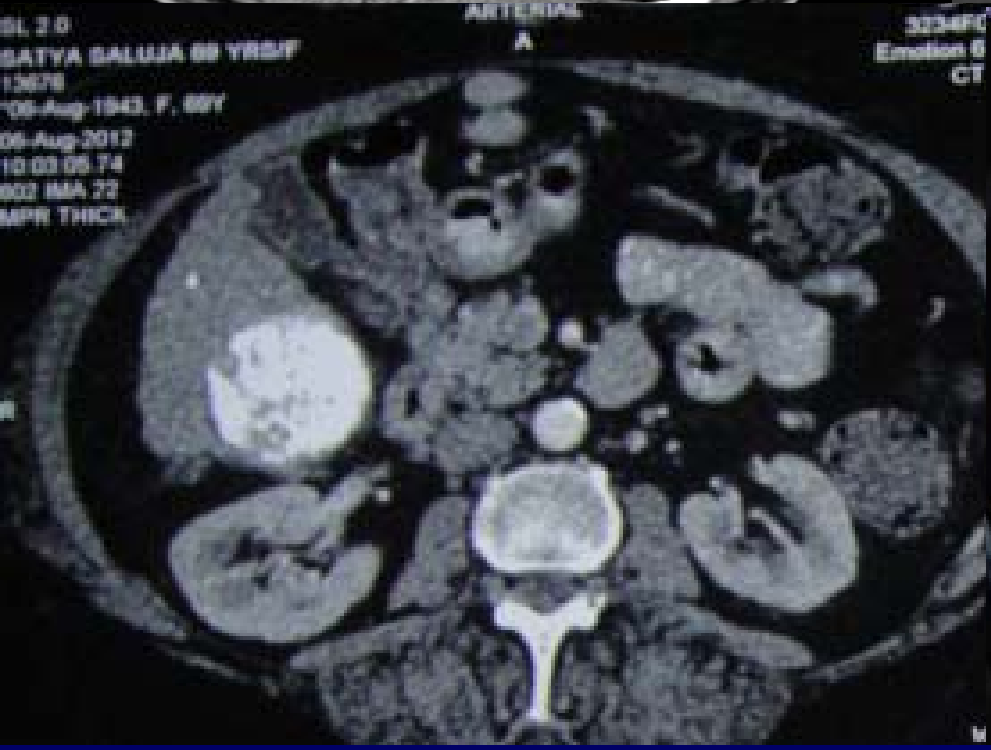
MRI prior to TACE

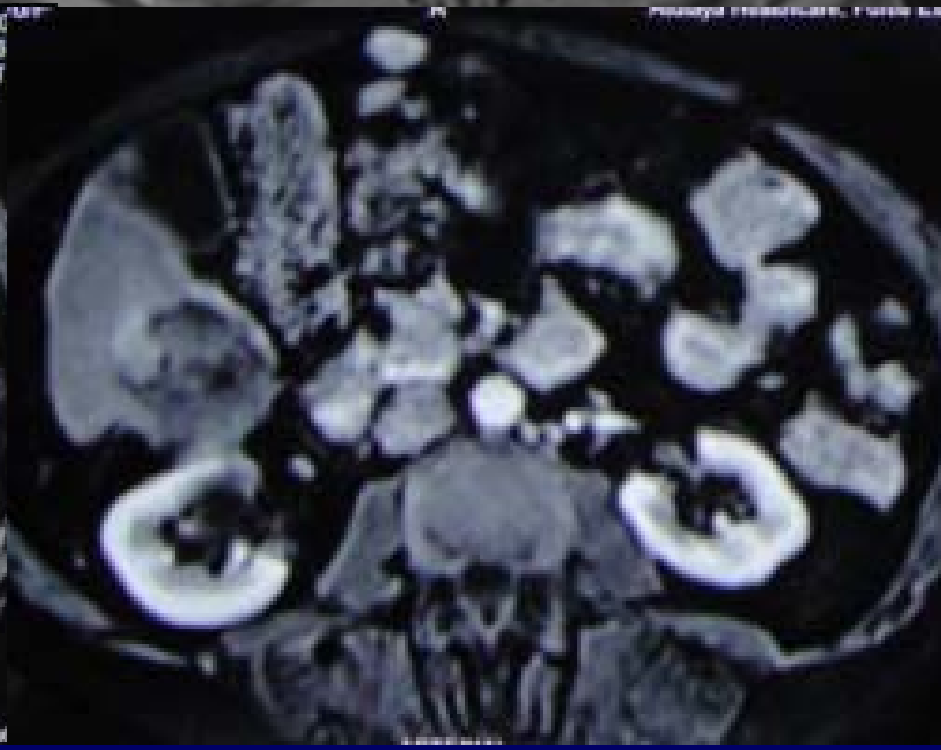


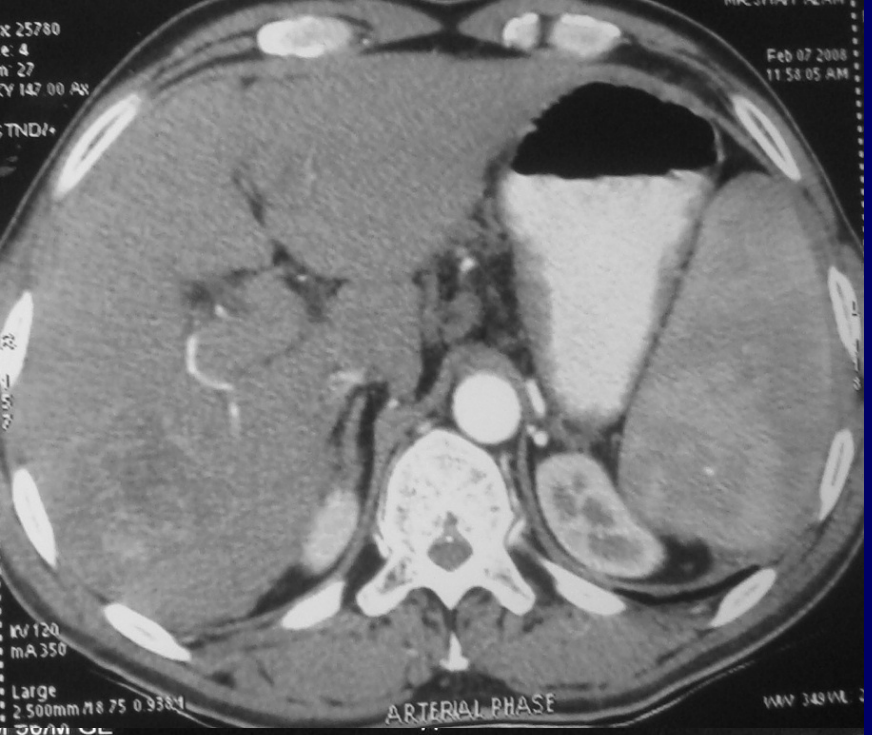

CT 6m post TACE


10cm





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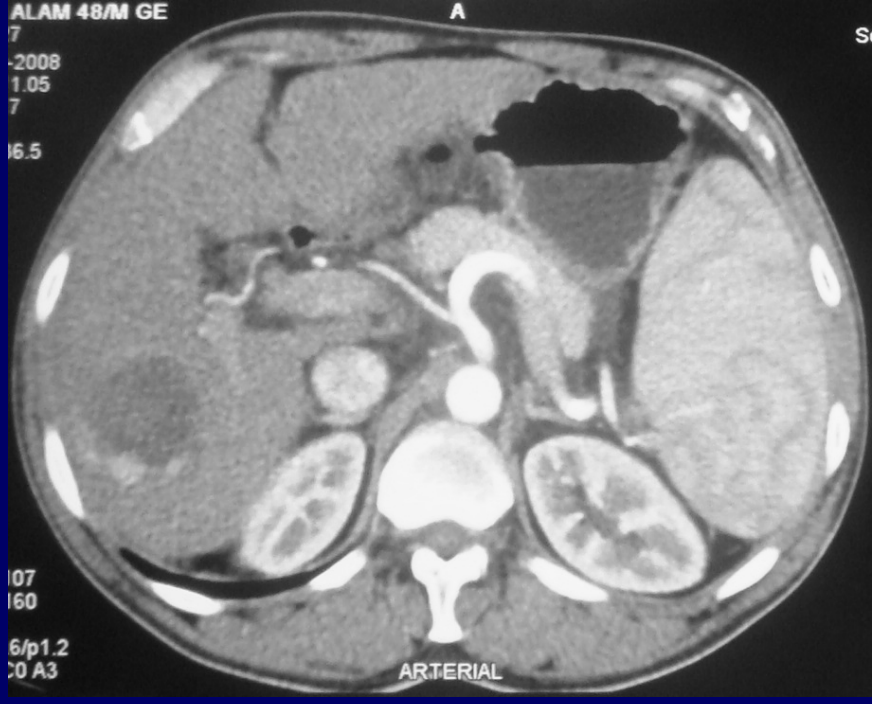
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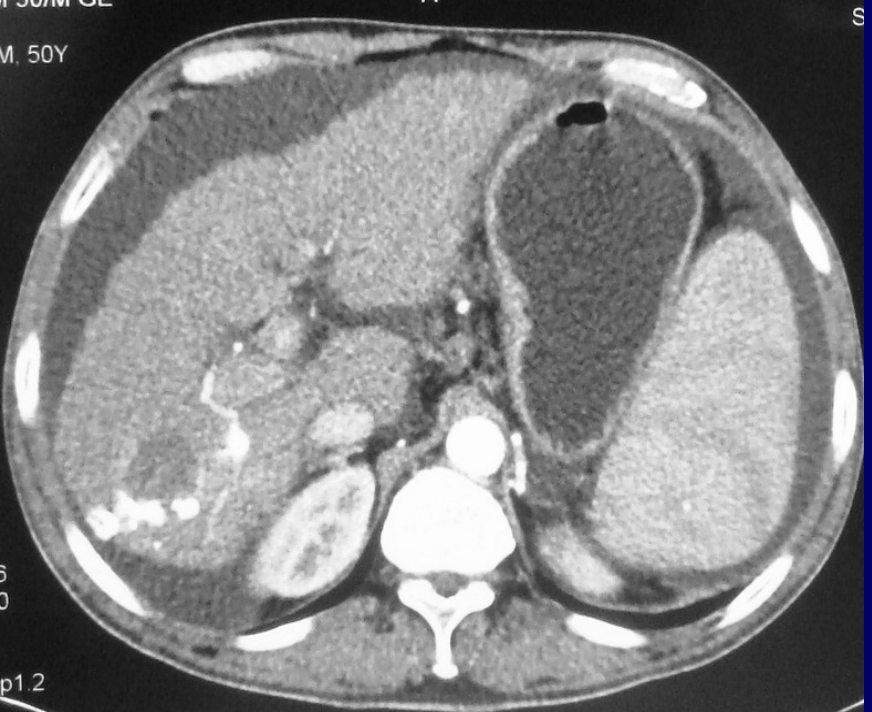
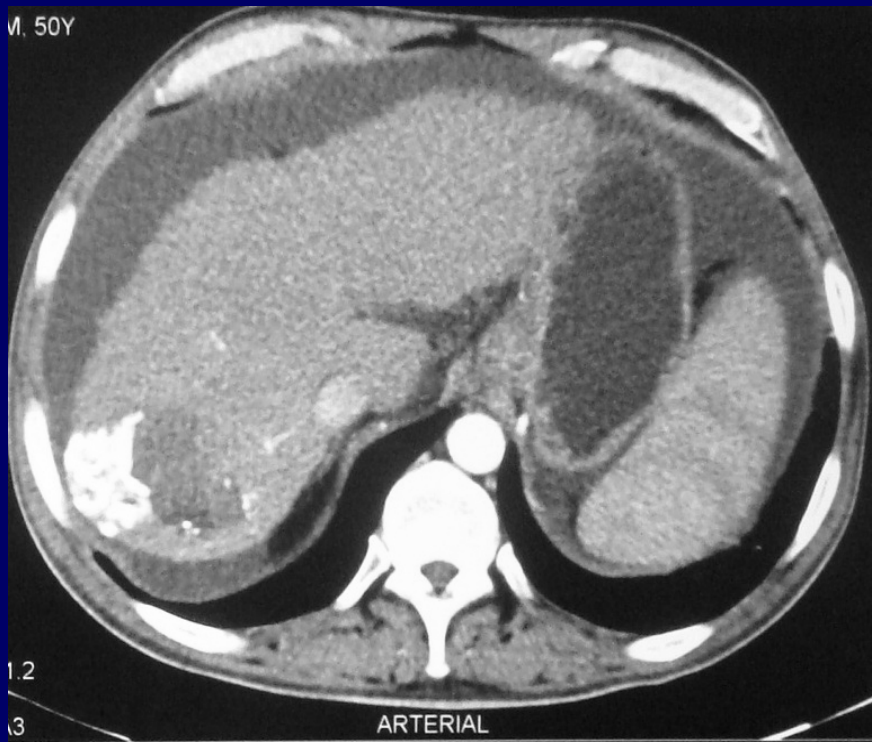



ARTERIAL

Disadvantages of c TACE

- 1-3 chemotherapeutic drugs in an aqueous

All these disadvanatges are now overcome by DE bead TACE

- Lipiodol acts as carrier but max amount of drug is released within 1 hr
- Toxicity rate is high

Part 1:

Patient selection & technique

Part 2:

"Conventional" TACE

Part 3:

"New " TACE (DEB)

Why Do We need Drug-eluting Technology?

Clear Rationale:

1. Maximize drug delivery
2. Consistent and standrad protocol (scientifically reproducible)
3. Long lasting effect/slow release (sustained)
4. Tumor effect Vs systemic side effects

Drug Eluting Beads

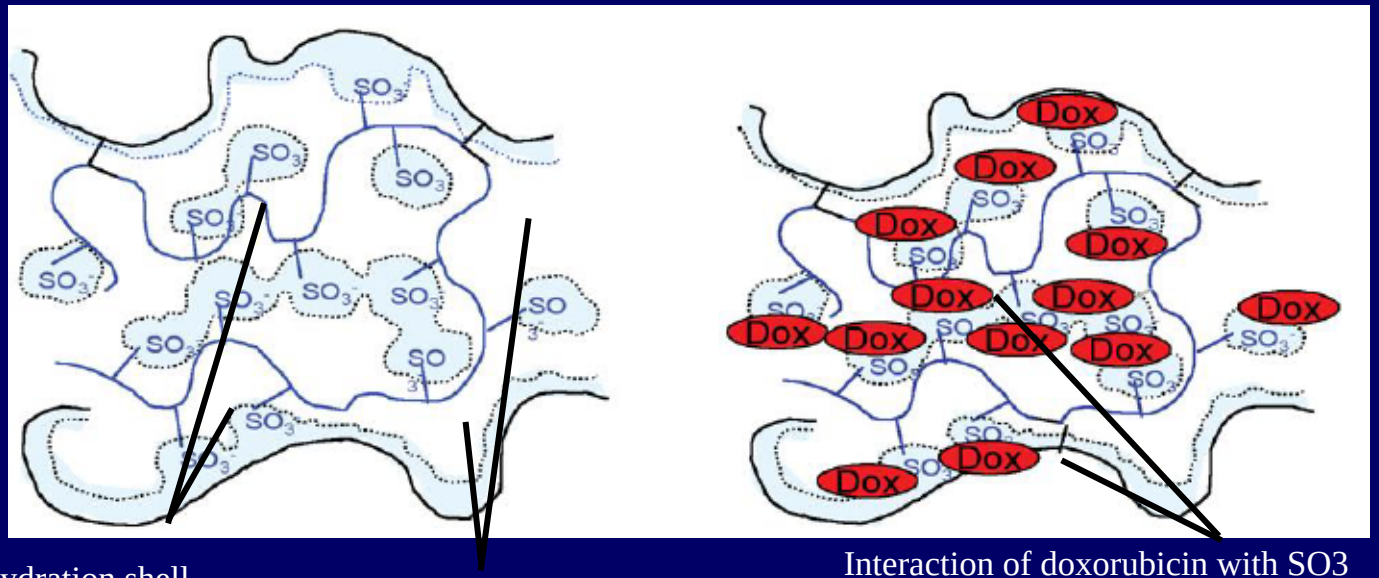
- Novel N-filtechnology sulphonate modified hydrogel polymer

- Embolization system
  - capable of loading drug
  - controlled release of drug

MECHANISM OF LOADING THE DEB WITH DOXORUBICIN

The DEB has a negative charge where as doxorubicin has a positive charge

The doxorubicin is loaded and eluted by an `reversible ionic exchange mechanism

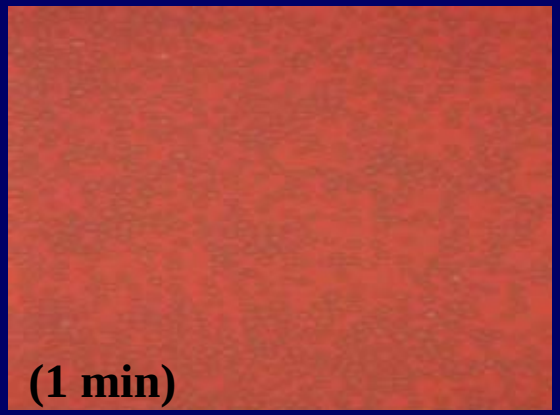


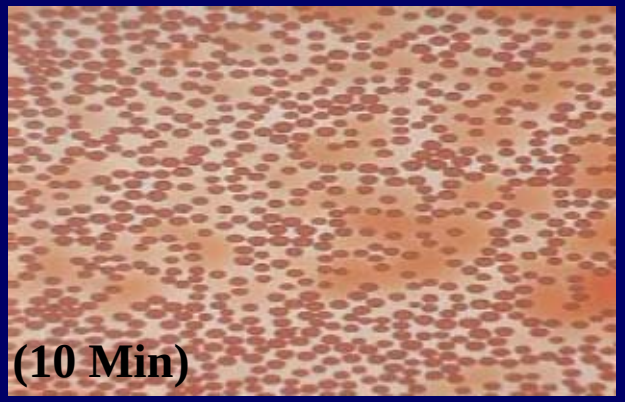
Hydration shell associated with PVA and ionic groups

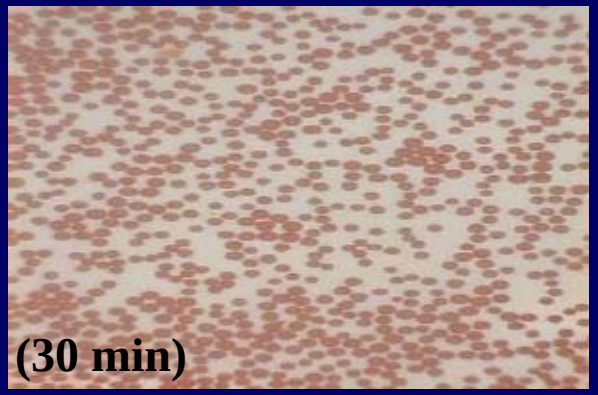
Bulk (non-bound) water

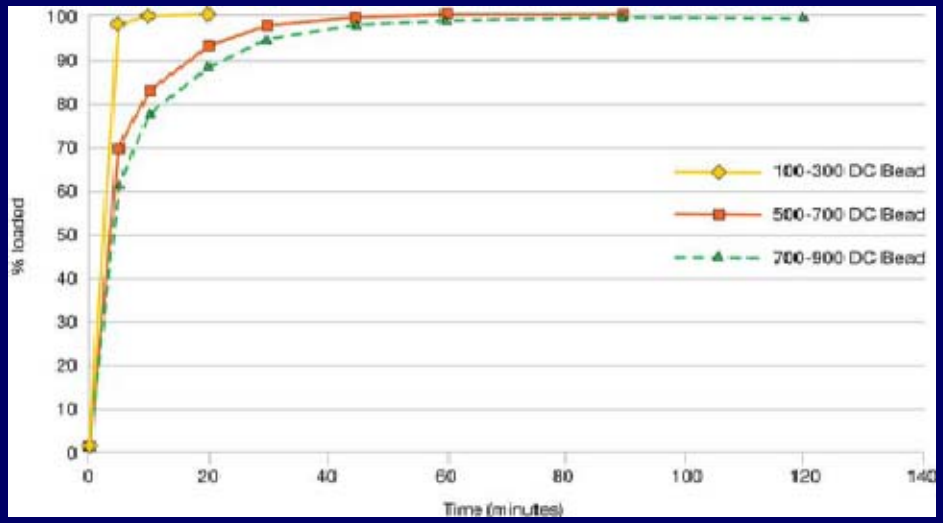
Interaction of doxorubicin with SO3 groups displaces water from the hydration shells

DEB Loading with Doxorubicin







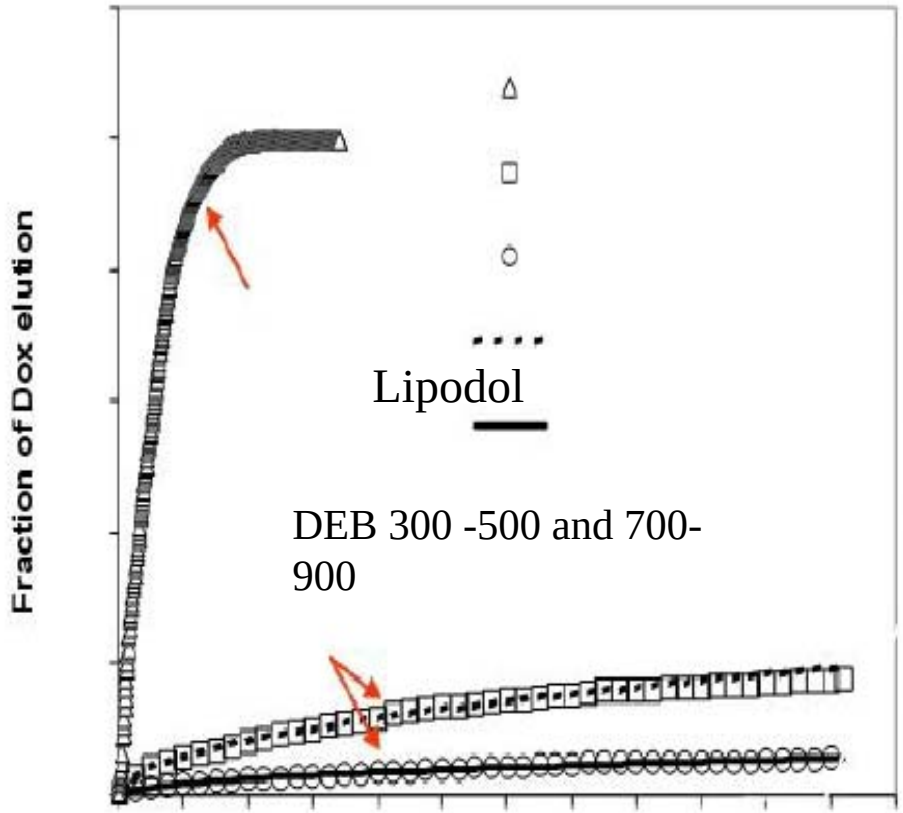


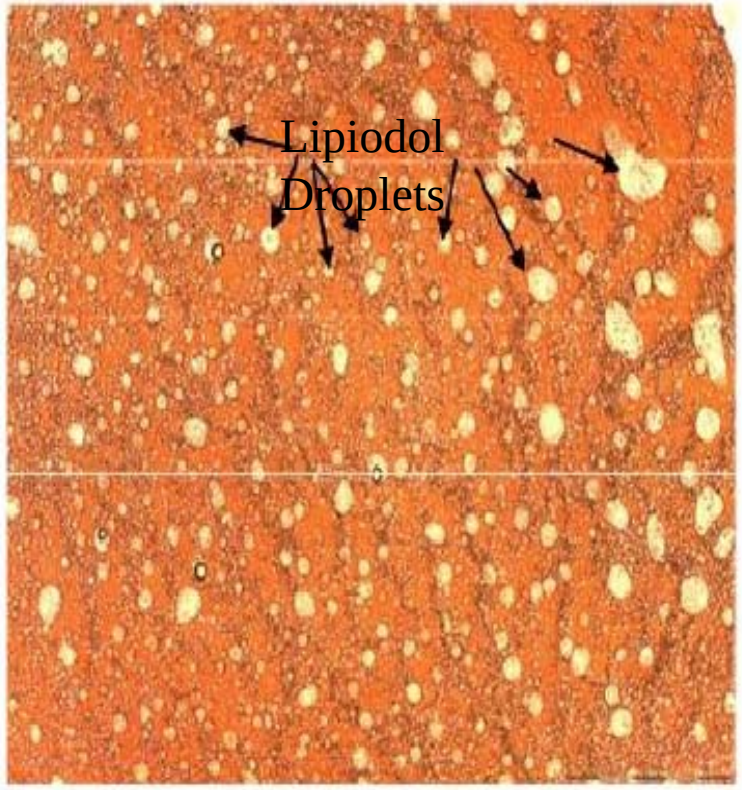
Efficient uptake (>98% of drug removed from solution)

Reproducible, dependent on size
Maximum recommended loading 37.5mg/ml

Each 2ml vial may be loaded with up to 75 mg

Controlled Elution from DEB: In Vitro

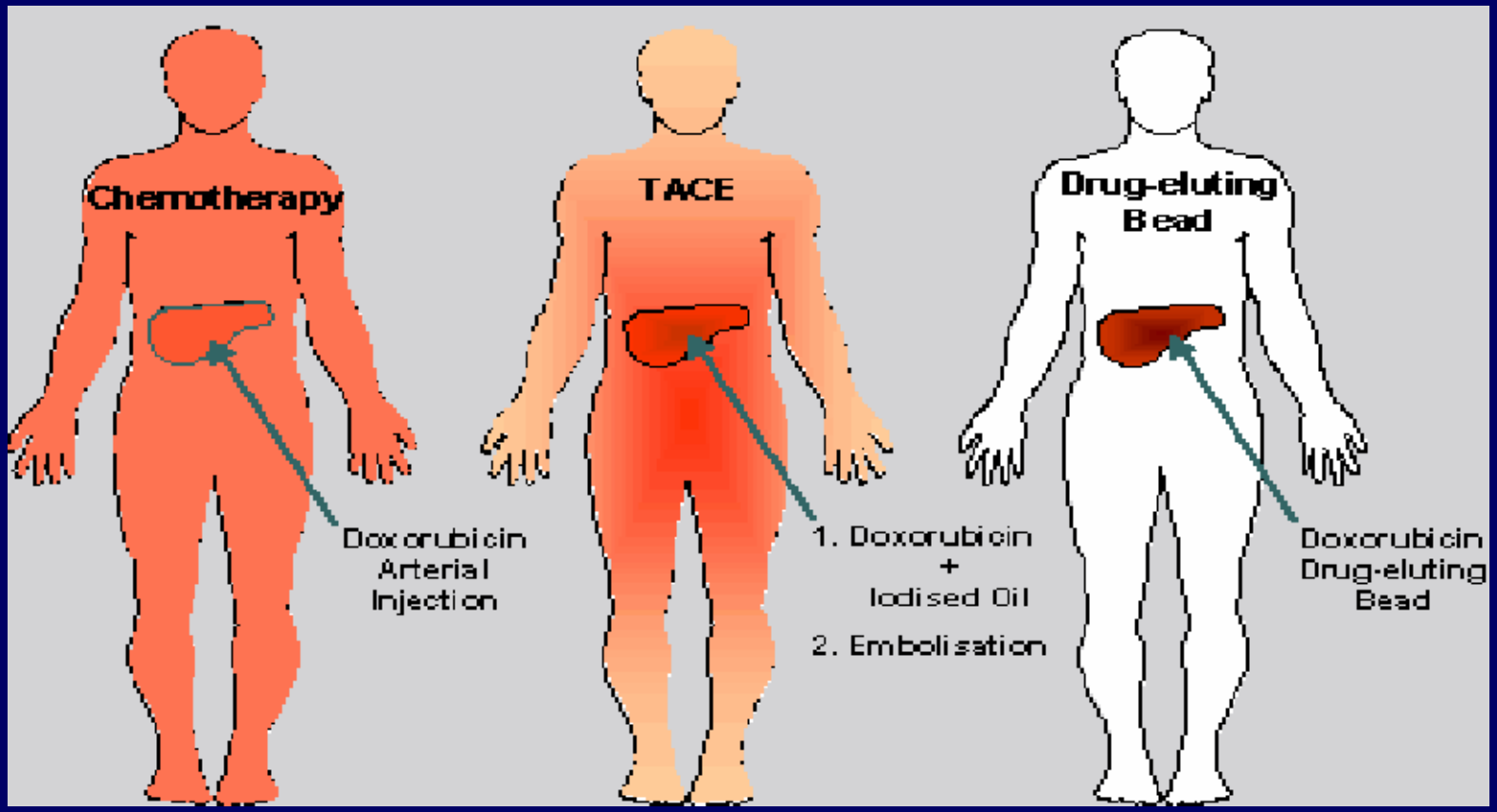




Slow sustained elution dependent upon bead size and controlled by ion exchange

Result is less Systemic Exposure

Relative Drug Distributions



So What this Means to the Patient is .....

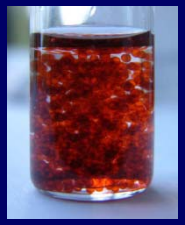
- Patients have better response rates
- With less Post Embolization Syndrome
- Reproducible results

Key Technique Points for DEB TACE

- Utilize adequate sedation and pain management,
- Identify and protect the cystic artery
- For discrete lesions, be as superselective as possible. Use a microcatheter whenever possible
- Additional embolic is not recommended. Do not use lipiodol with DEB
- Aim for a `near stasis'embolization endpoint

Drug Eluting Beads (DEB)

1. Add sterile water to a vial containing doxorubicin hydrochloride powder
2. Remove the saline solution from the beads
3. Add the doxorubicin solution
4. Wait for a time until the red coloration in the solution had diminished and the beads had taken on a red color
5. This time is dependent on drug loading solution concentration and bead size
6. Loaded beads are aspirated into a syringe and nonionic contrast medium is added in a 50:50 ratio
7. The maximum recommended dose is 150mg dose doxorubicin



DC Bead in HCC: Development of Procedural Standards and Technical Recommendations

Loading Dose of Doxorubicin

- Each vial of DC Bead (2 ml of beads) should be loaded with 50-75 mg doxorubicin (loading dose, 25-37.5 mg doxorubicin / ml of beads).

DC Bead in HCC: Development of Procedural Standards and Technical Recommendations

Planned Dose: Single / Small HCC

- Each treatment:
  - 1 vial
  - up to 75 mg doxo

Planned Dose: Large / Multiple HCC

- Each treatment:
  - 2 vials
  - up to 150 mg doxo

Recommended Dosage and choice of bead size

Tumor size	DEB
<3 cm	1 vials of 100-300 µ
3-8 cm	2 vial of 100-300 µ
>8 cm	2 vials of 300-500 µ Next session after 2-4 wks

Bilobar disease : each lobe should be treated separately with a gap of 2-4 weeks

DC Bead in HCC: Development of Procedural Standards and Technical Recommendations

Catheter Positioning

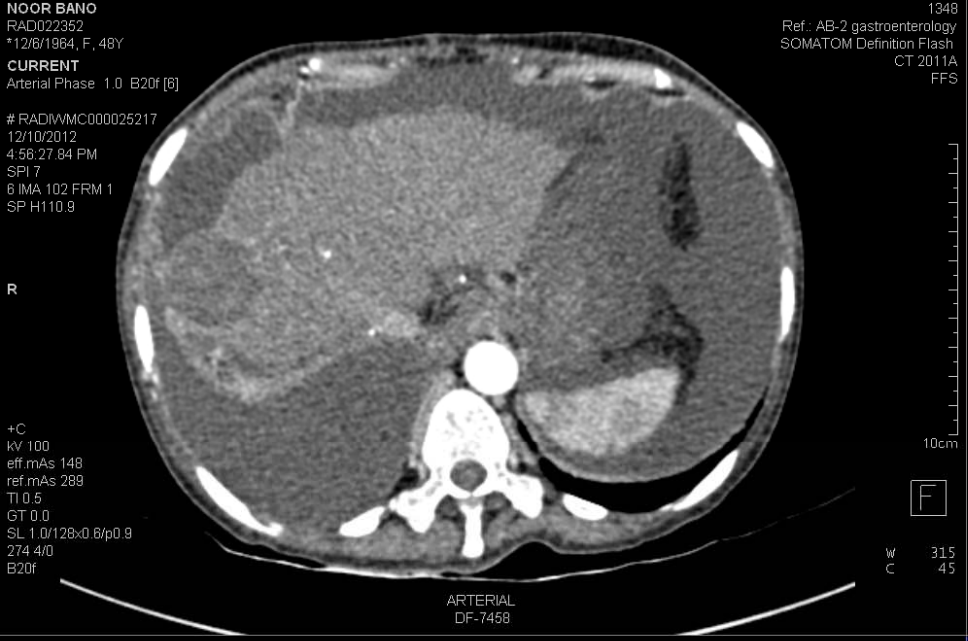
- A superselective (i.e., segmental or subsegmental) approach should be used whenever possible by using a microcatheter.

- Use of C-arm rotational angiography with a flat-panel detector system (cone-beam CT) is recommended, if available, to improve the accuracy in identifying tumor-feeding arteries and to confirm adequate targeting and saturation of the tumor(s).

DC Bead in HCC: Development of Procedural Standards and Technical Recommendations

Embolization Endpoint

- Injection should be continued until “near stasis” is observed in the artery directly feeding the tumor (i.e., the contrast the contrast column should clear within 2-5 heart beats). At that point, injection should be stopped – regardless of the amount of beads that have been actually administered – to avoid reflux of embolic material.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B20f
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F
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C 45
ARTERIAL
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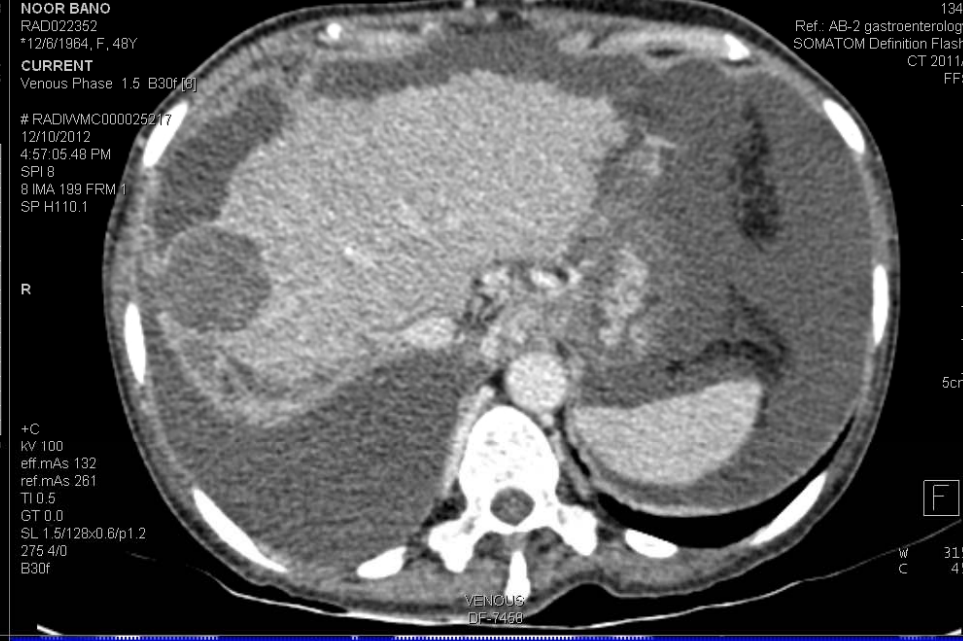
A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5cm
F
W 315
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VENOUS
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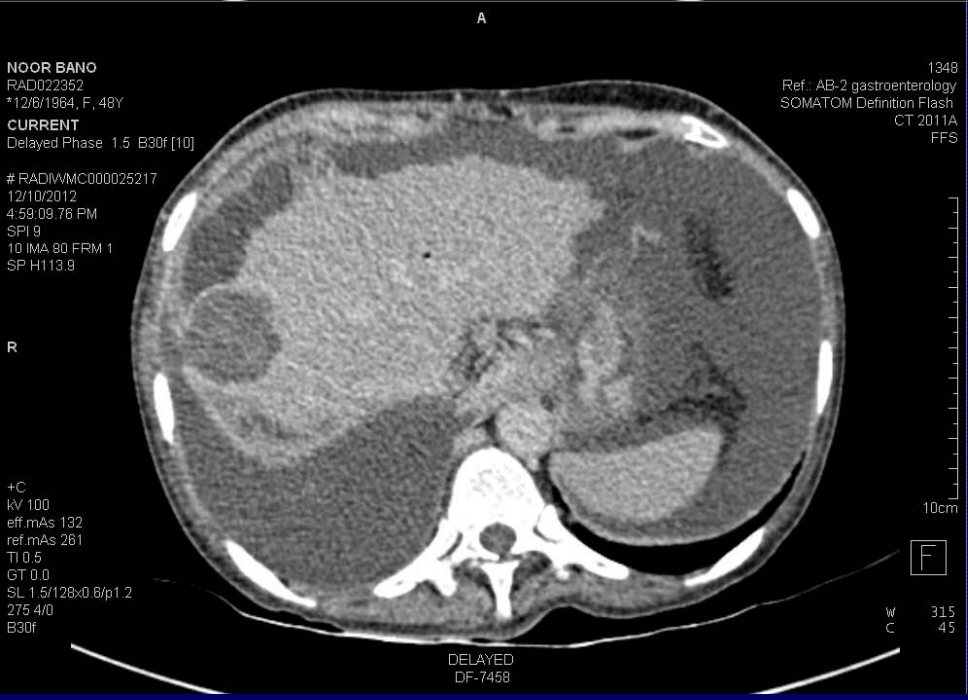
H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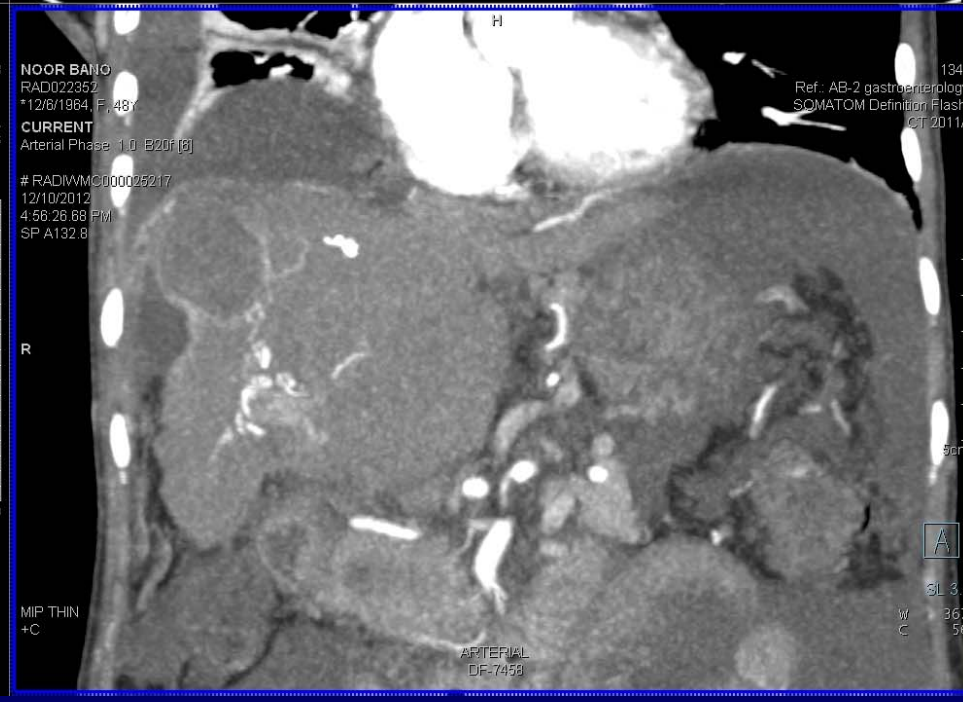
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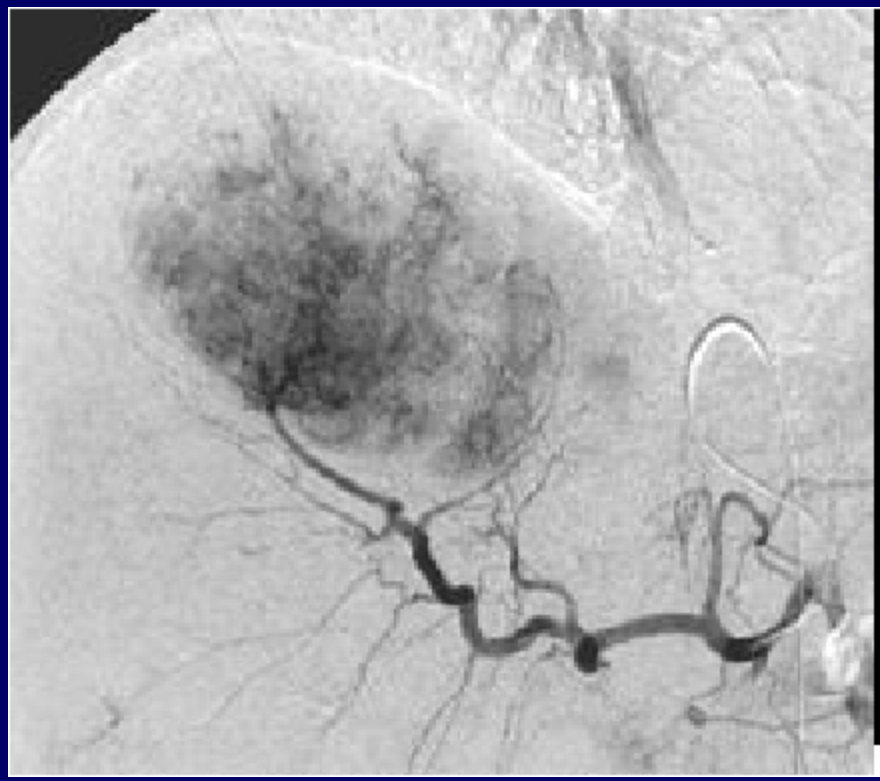
Conclusions- NEW -TACE

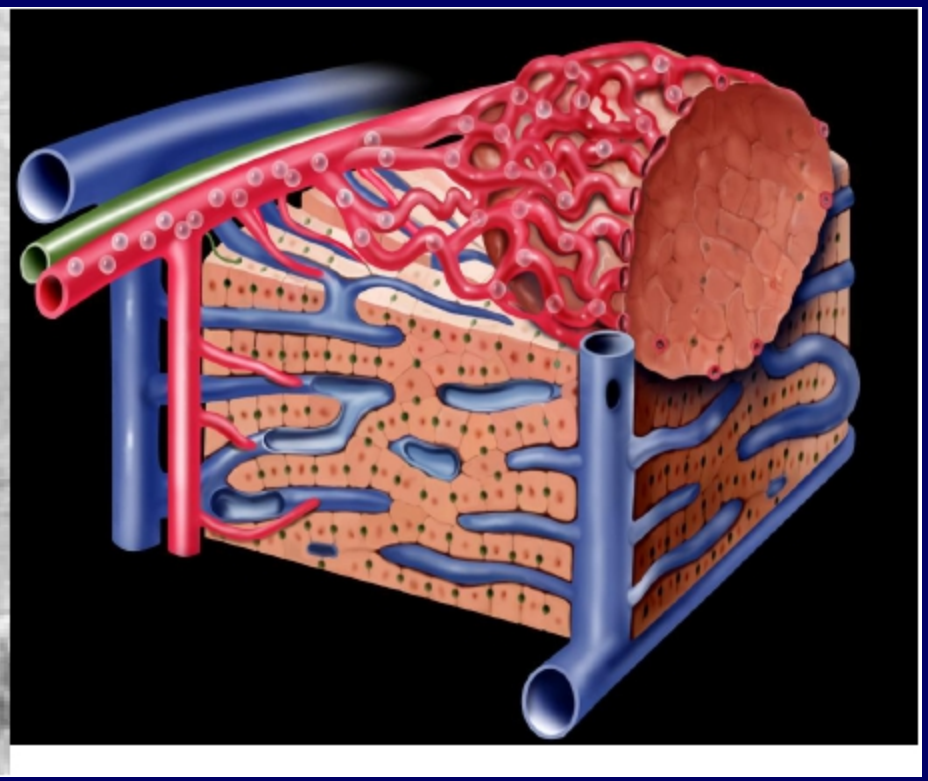
- DEB-TACE: Proven Rationale
- Extension of cTACE
- Excellent PK profile
- Minimal toxicities

- Efficacy: Tumor response 75-85%
- Survival: ~26 months BCLC B-C
- Randomized trial vs. cTACE?

Concept of Radioembolization

Produce selective tumoral necrosis by direct radiation





Concept of Radioembolisation

- Radioactive sources into a tumor
- Effective radiation range is short (mm)
- Administrate a high radiation dose to liver tumor irrespective of their number, size and location
- Delivers a low radiation to normal tissues
- Do not modify arterial blood flow, hence associated with better hepatic tolerance

Transarterial Radioembolization (TARE)

- Performed with iodine-131 (131I) or rhenium-118 labeled lipiodol or yttrium-90 (90Y) microspheres
- Exert local radiation effect
- Relatively limited concurrent injury to surrounding normal tissue
- Major Role of TARE: HCC with Main Portal vein thrombosis (Malignant)
- Limitation: Expensive

Properties of Radioactive agents

Isotope	Emission	Half-life	Mean soft tissue penetration (mm)
Iodine-131	β, γ	8 days	0.4
Rhenium-188	β, γ	16.9 h	4.0
Yttrium-90	β	2.7 days	3.0

Contraindications

- Lung shunting > 20% or estimated radiation doses to the lungs > 30 Gy
- Inability to prevent embolization of microespheres into the gastrointestinal tract
- History of prior liver external irradiation
- Relative: Inadequate liver reserve

Technique of TARE

- Delivery Vehicles
  - Lipiodol for Rhenium and Iodine
  - Microspheres (glass and resin) for Yttrium

- Injection Technique:
  - Simple one step procedure with I-131 and Re-188.
  - 3–5 ml of the radiolabeled product is injected non-selectively into the proper hepatic artery if there are multiple tumor foci, or selectively in the case of a single tumor

Yttrium Microsphere injection

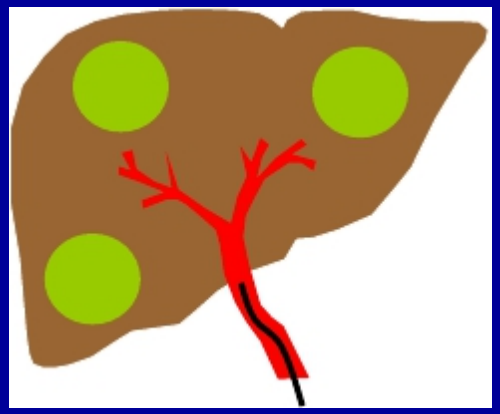
Complex, Two step procedure

1st STEP : Arterial mapping, embolisation of arteries that supply extrahepatic tissues GDA, Right gastric artery)

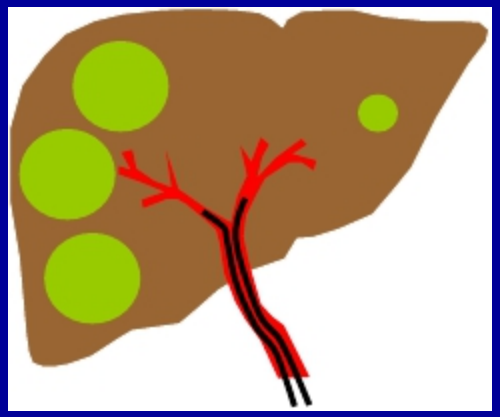
- Labeled macroagglutinated albumin simulating the microspheres is then injected to rule out diffusion into adjacent gastrointestinal organs and to quantify hepatopulmonary shunting
- The activity to be delivered to the target hepatic tissue (the whole liver, lobe or segment where the tumor is located) is then determined.

2ND STEP : Scheduled dose is then administered a few days later

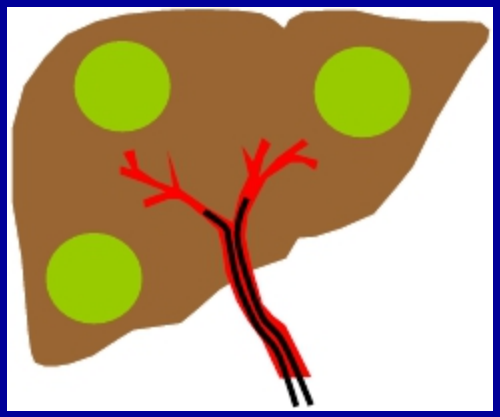
Therapeutic Decision: Treatment Strategies



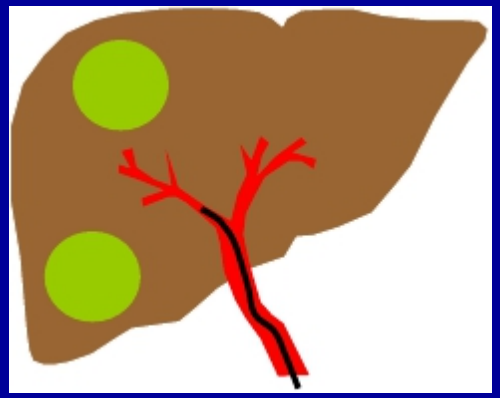
whole-liver



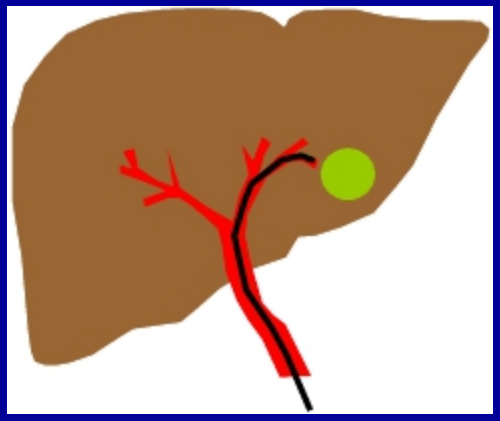
bilobar



sequential



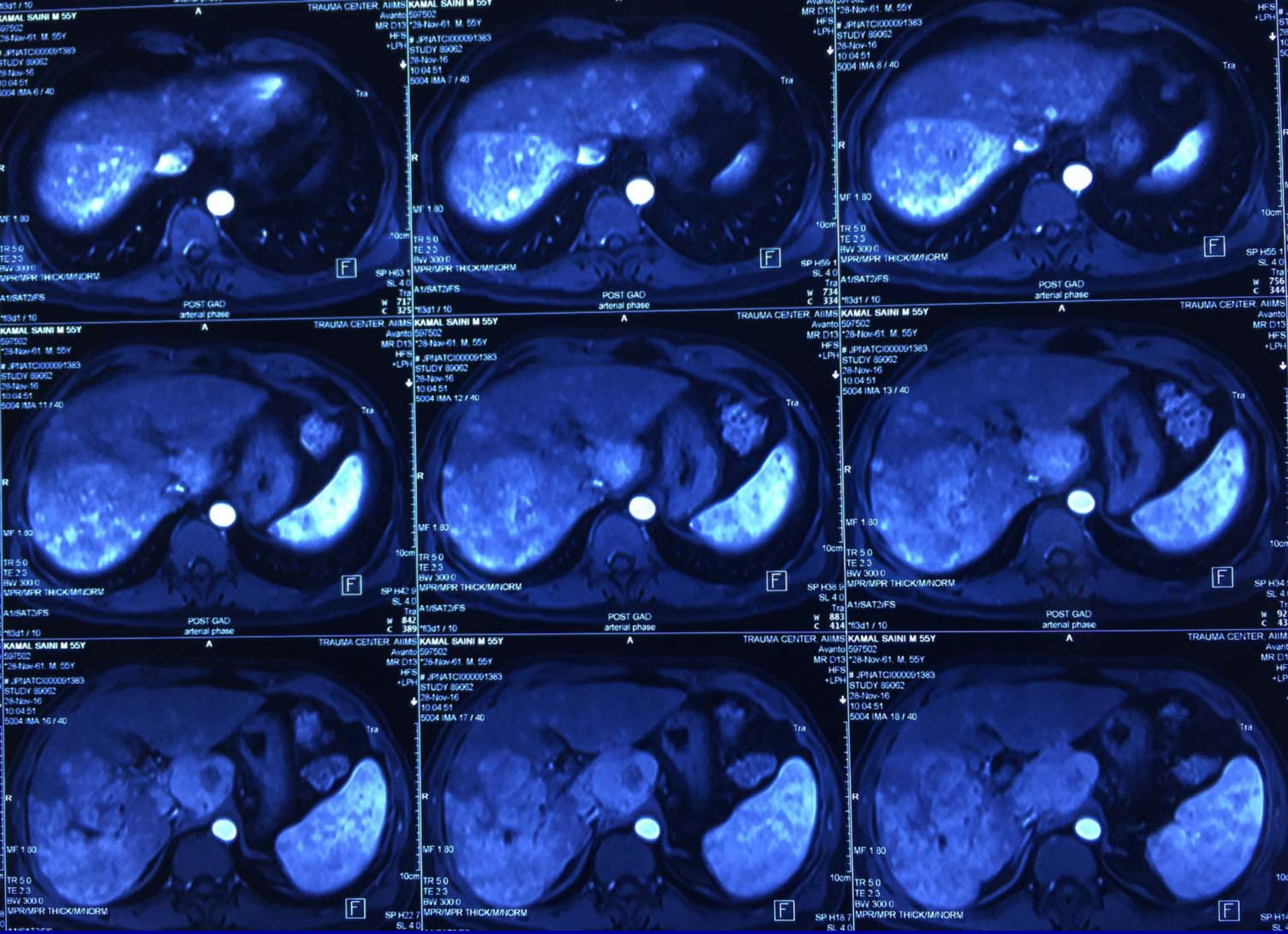
segmental



subsegmental

Radioembolization in HCC: Which patients?

- RE as an ablative treatment
- RE as a downstaging treatment
- RE in non-surgical candidates
- RE in advanced HCC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TR 5.0
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BW 300.0
MPR/MPR THICK/M/NORM
A1/SAT2/FS
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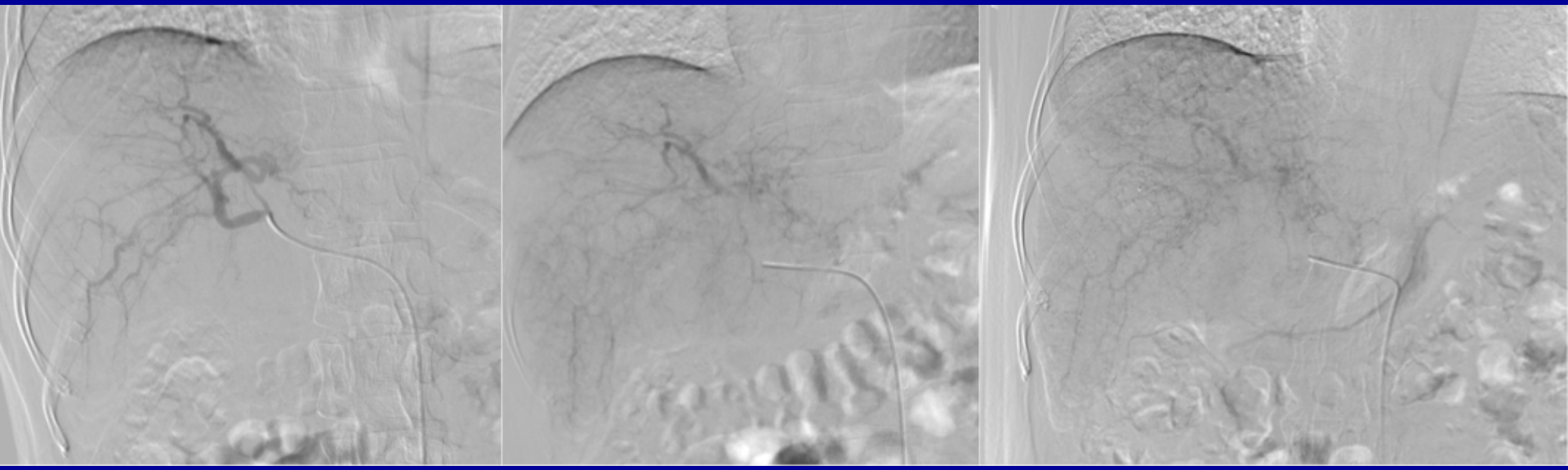
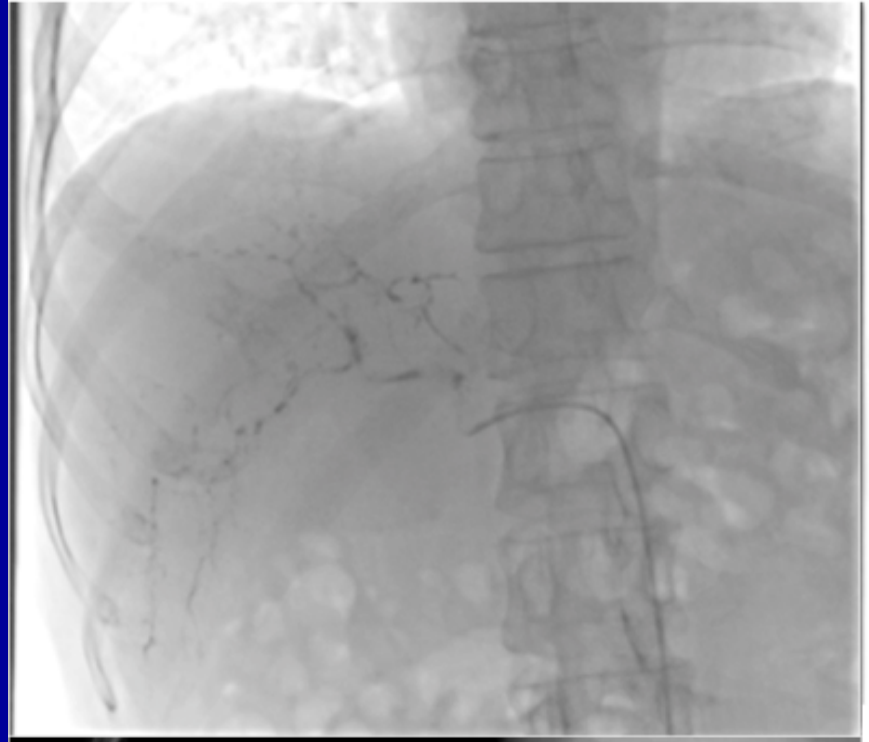
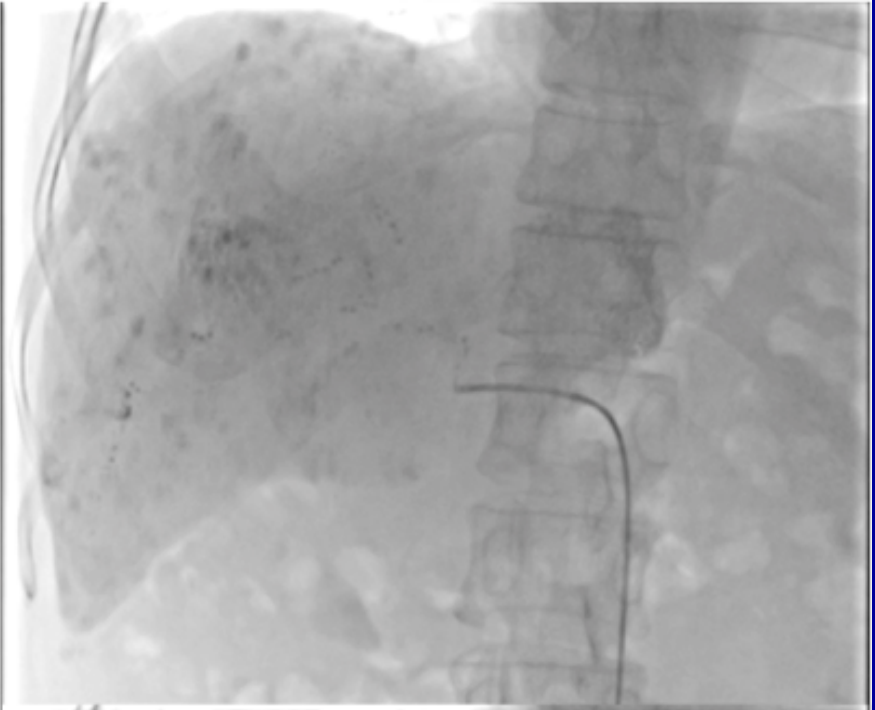
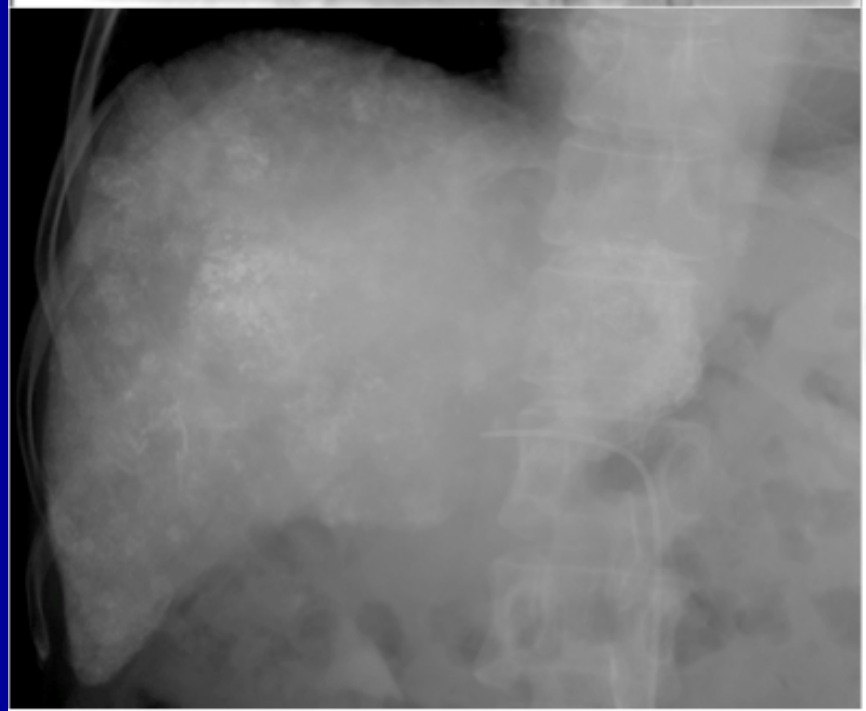
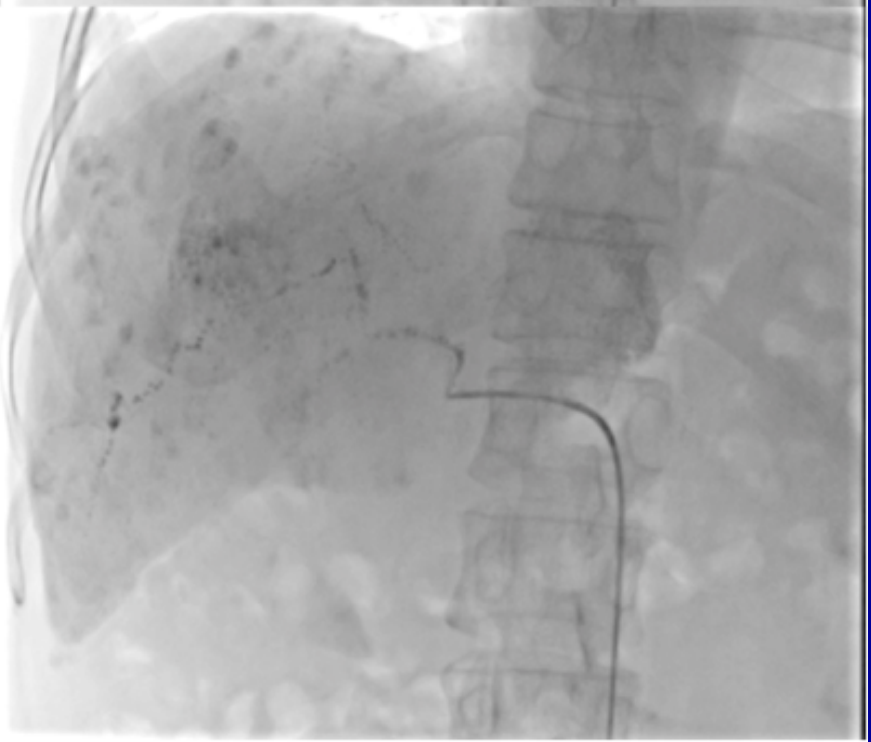
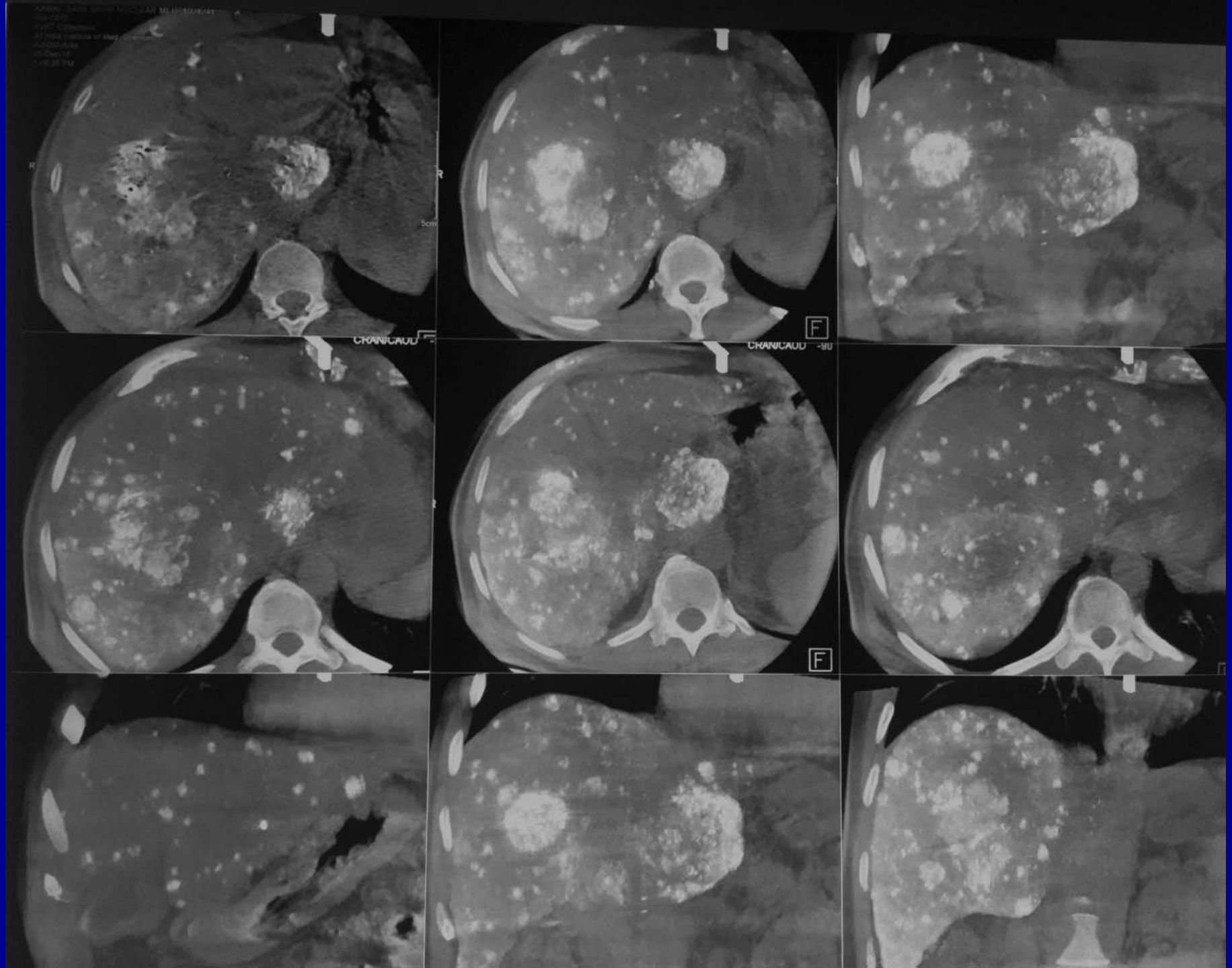
POST GAD
arterial phase
SL 4.0





THANK YOU