Gastrointestinal Stromal Tumor Metastatic to Liver

Role of Interventional Radiology

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GIST

- At presentation, approximately half of these tumors have already metastasized
- Liver is the most frequent site of metastases from GIST
- Liver metastases are a major determinant of survival
- Highly resistant to conventional systemic chemotherapy

GIST

- Imatinib (TKI)
  - Partial response or tumor stabilization in 70-85%
  - Median progression-free survival of 20-24 months
  - Median overall survival exceeding 36 months
  - Unfortunately, 15% of patients show no response
  - A proportion of patients (up to 25% in some studies) whose tumors do exhibit a response, develop resistance after an average of 2 years of treatment
  - Another TKI - Sunitinib - antitumor responses in imatinib-refractory GISTs

Verweij et al - Lancet, 2004; Van Glabbeke M et al - JCO, 2005

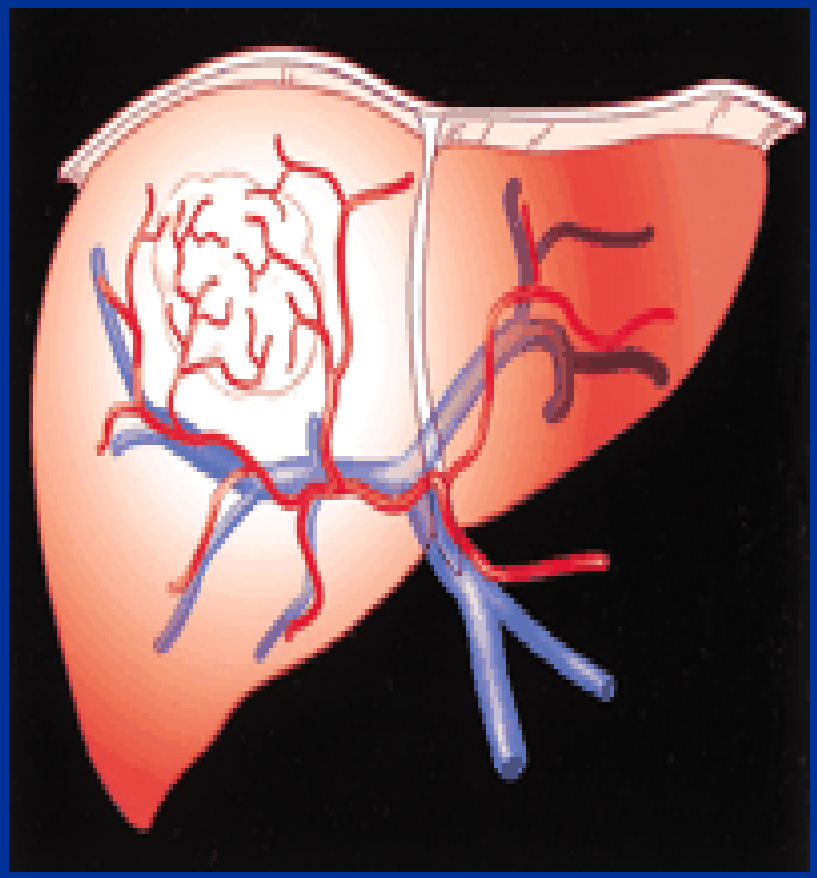
GIST

- Surgical resection - only potentially curable treatment for progressive liver metastases following imatinib treatment
  - Very few patients are surgical candidates
    - Solitary metastasis
    - Limited metastases

Local/Regional Treatment Options

- Ablation
  - Thermal - Radiofrequency, Laser, Microwave, Cryoablation
- Hepatic artery embolization
  - Bland embolization with particulate agents
- Hepatic artery chemoembolization
  - Particulate agents plus chemotherapeutic agents

Embolization And Chemoembolization - Liver Tumors



- tumor derives 95% of its blood supply from the hepatic artery
- normal liver parenchyma receives only 25% of its blood supply from the artery and the remaining 75% from the portal vein

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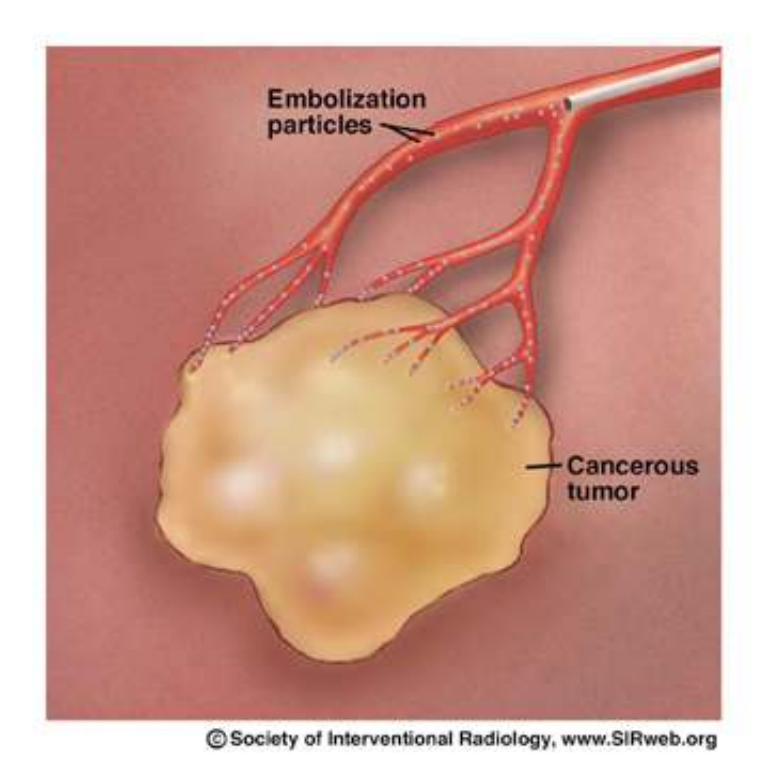


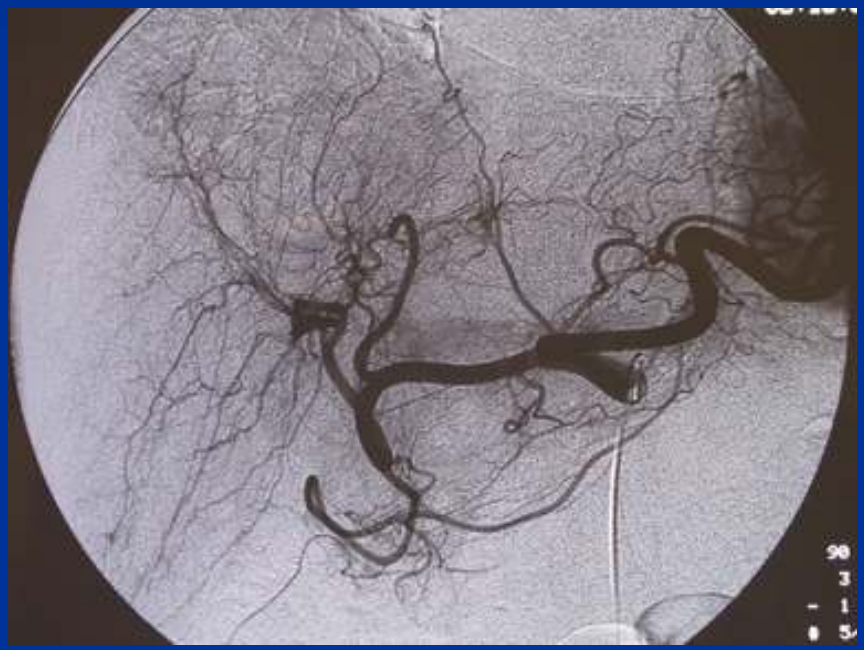
Hepatic Artery Embolization and Chemoembolization

- HAE
  - Hypoxia alone
  - Cuts off tumor blood supply depriving it of oxygen and nutrients
- HACE
  - Hypoxia + cytotoxicity
  - Tumor drug concentration 10-50 X > IV infusion
  - Traps drug in tumor; markedly prolongs dwell time
  - Decreases systemic toxicity

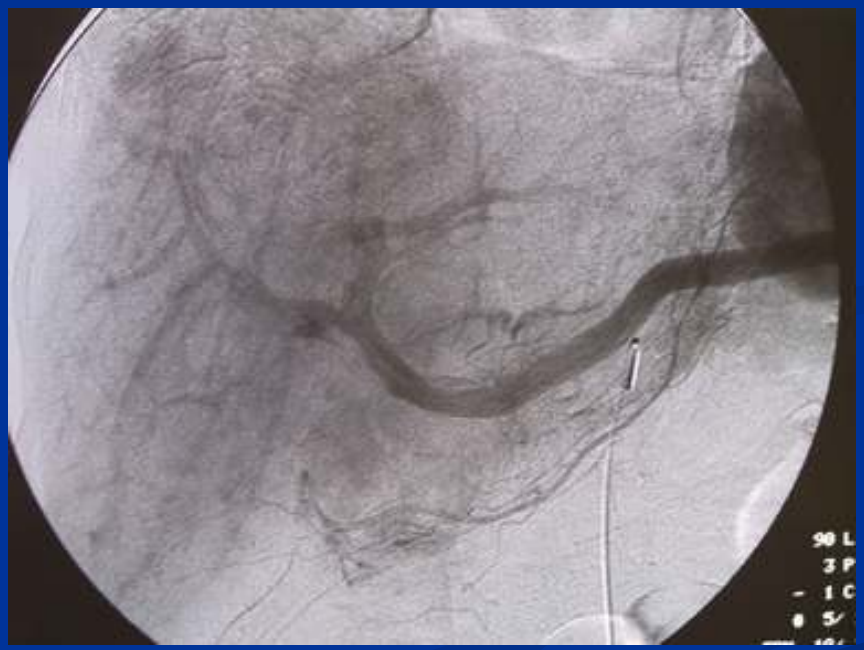
Procedure Technique

- Conscious sedation and Local anesthesia
- Diagnostic angiography
  - procedure used to visualize blood vessels
  - small tube inserted into femoral artery in the groin
  - catheter moved through vascular system to the vessel going to liver
  - fluoroscopy (real-time x-ray) used to advance the catheter.

Pre-Embolization Angiography

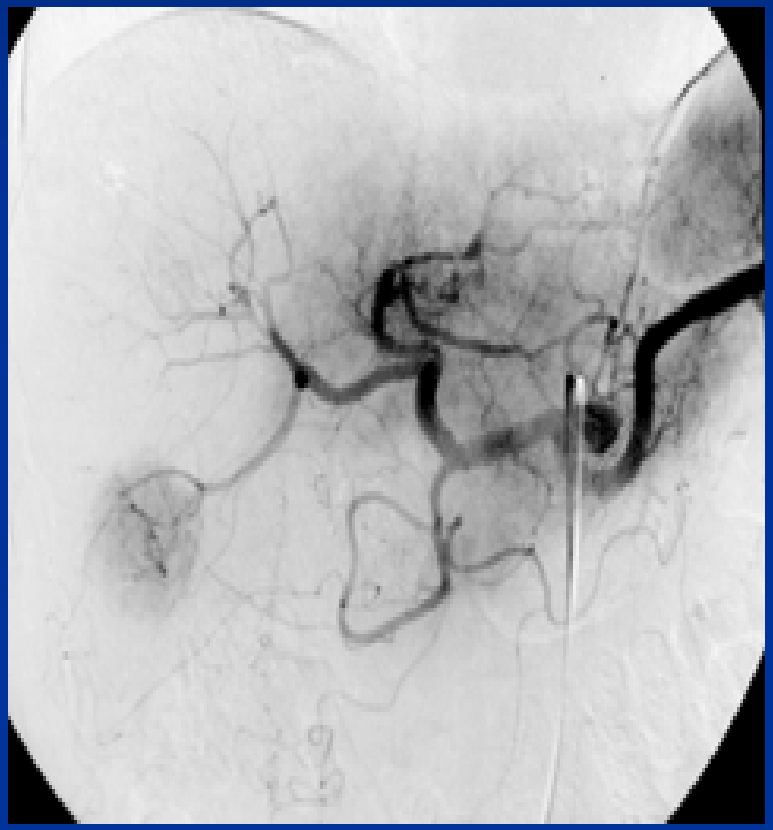


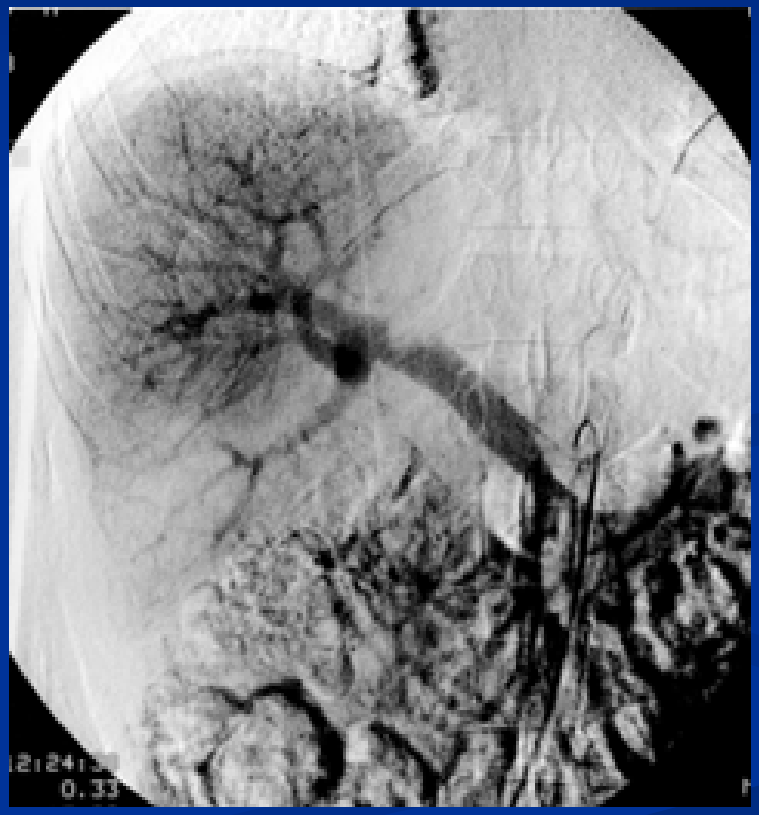
Arterial phase



Portal venous phase

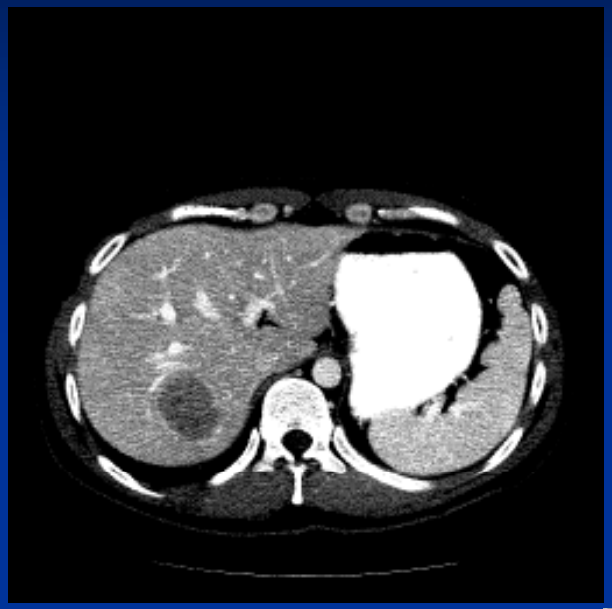
Portal Vein Thrombus

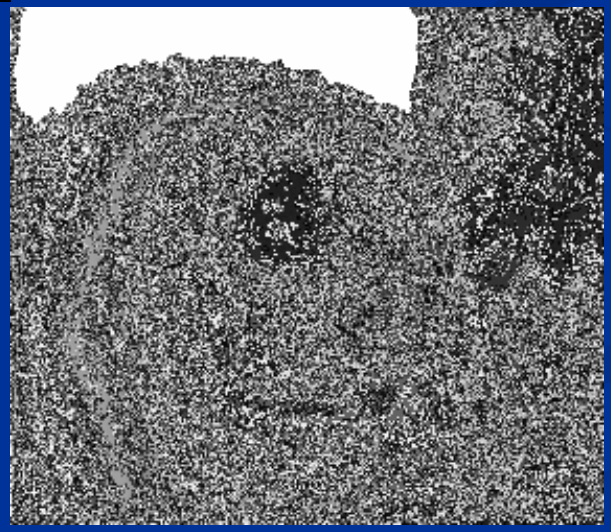




Left portal vein thrombus

Selective catheterization





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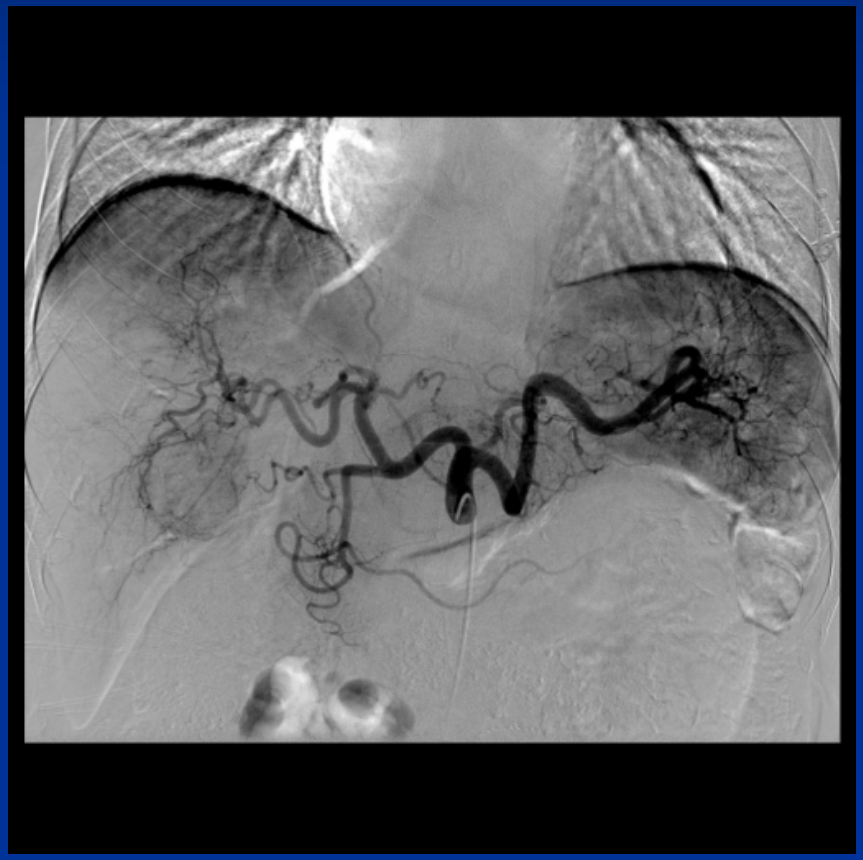

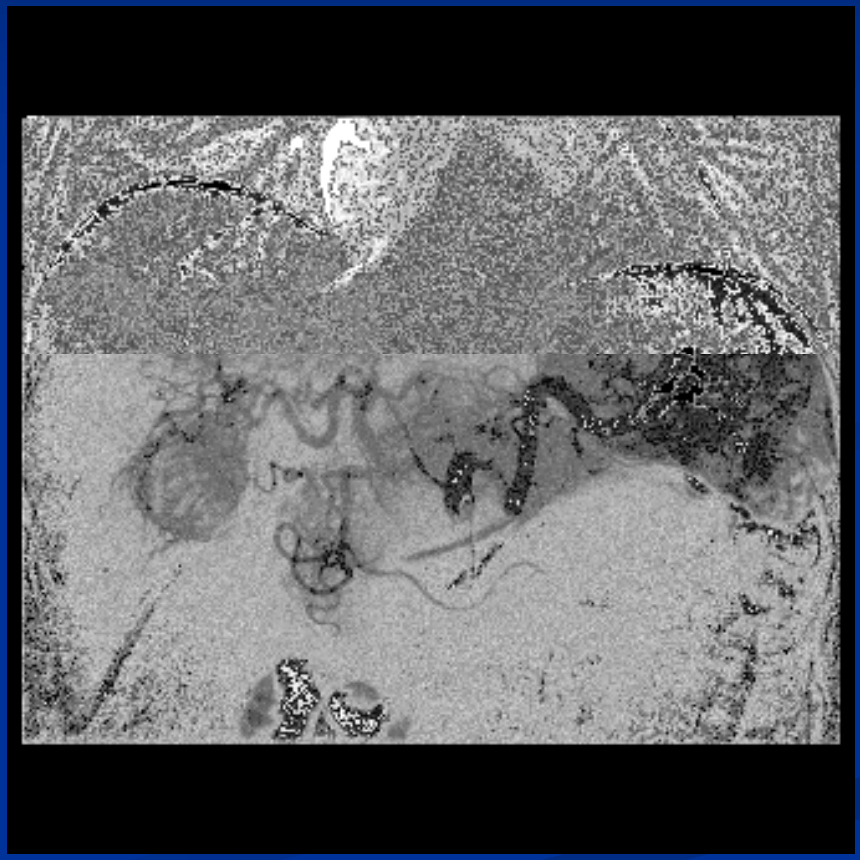

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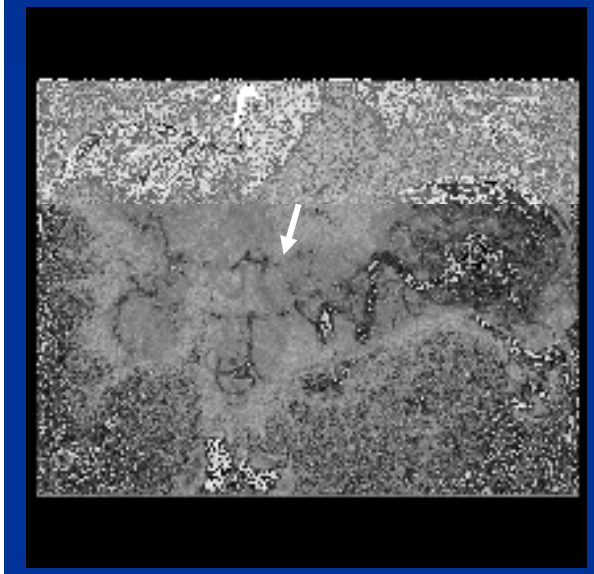

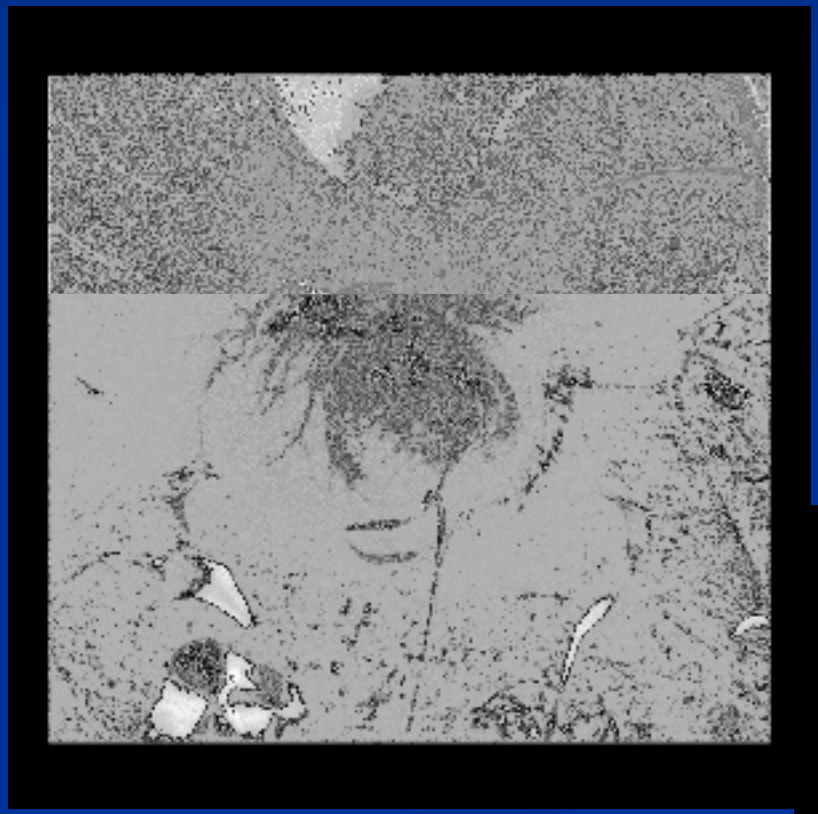

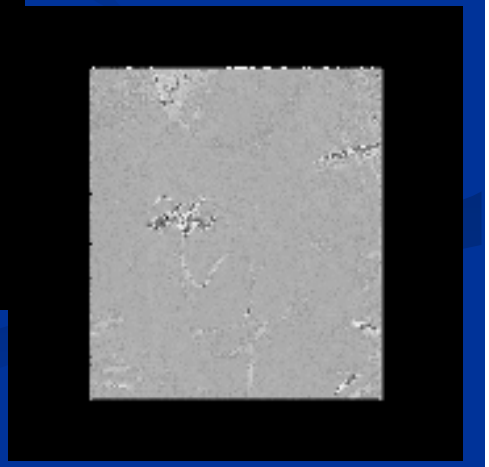

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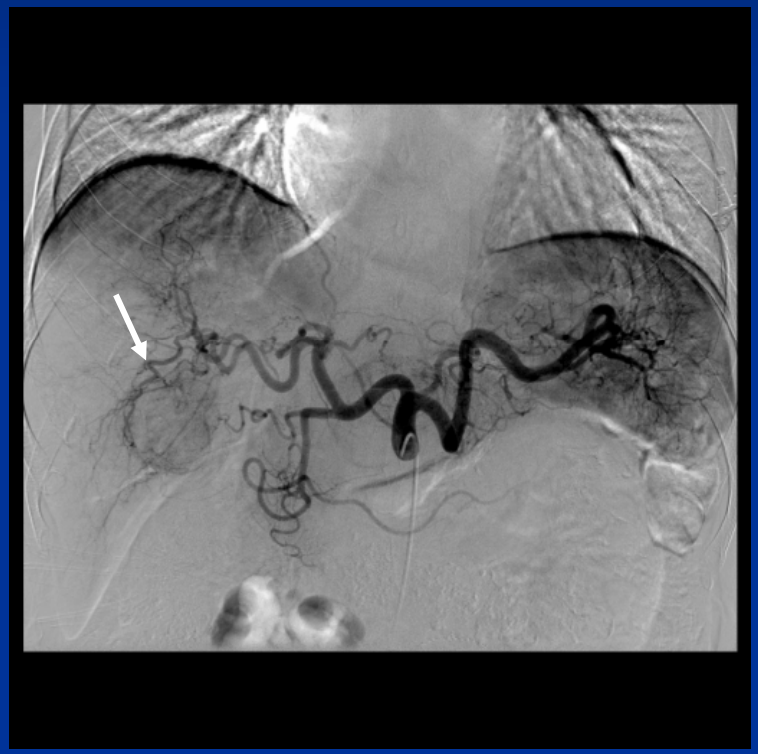

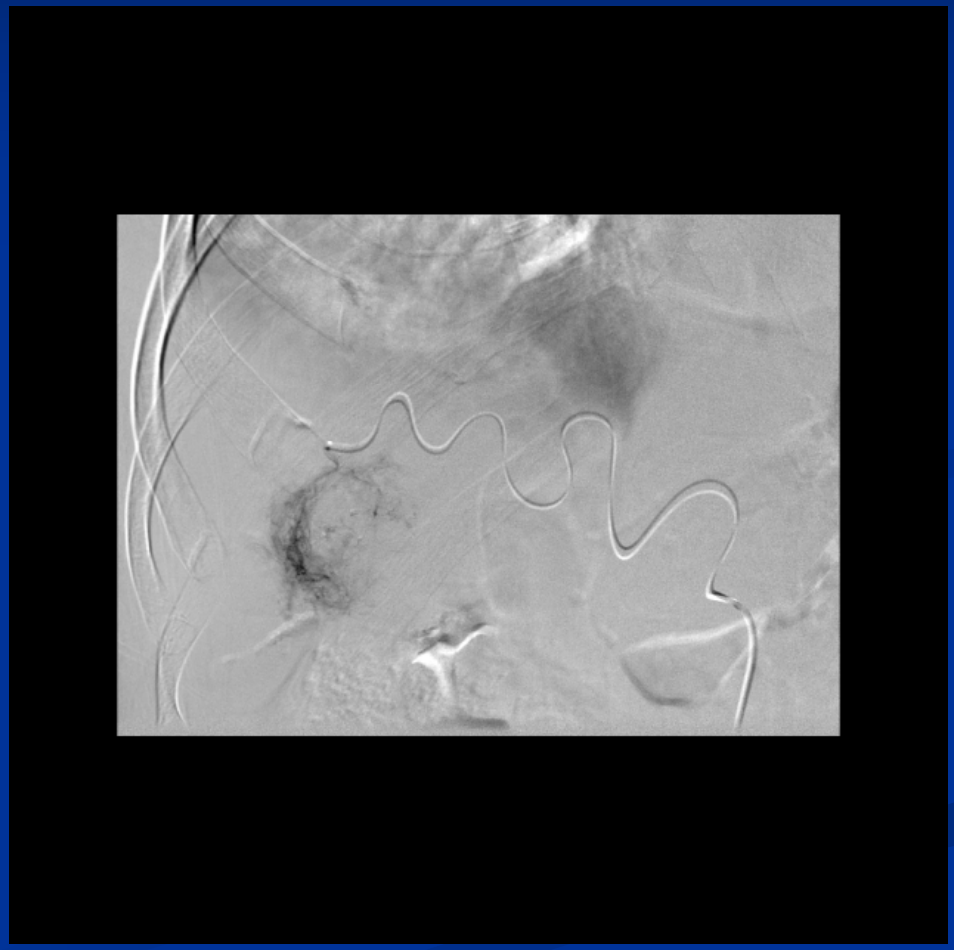

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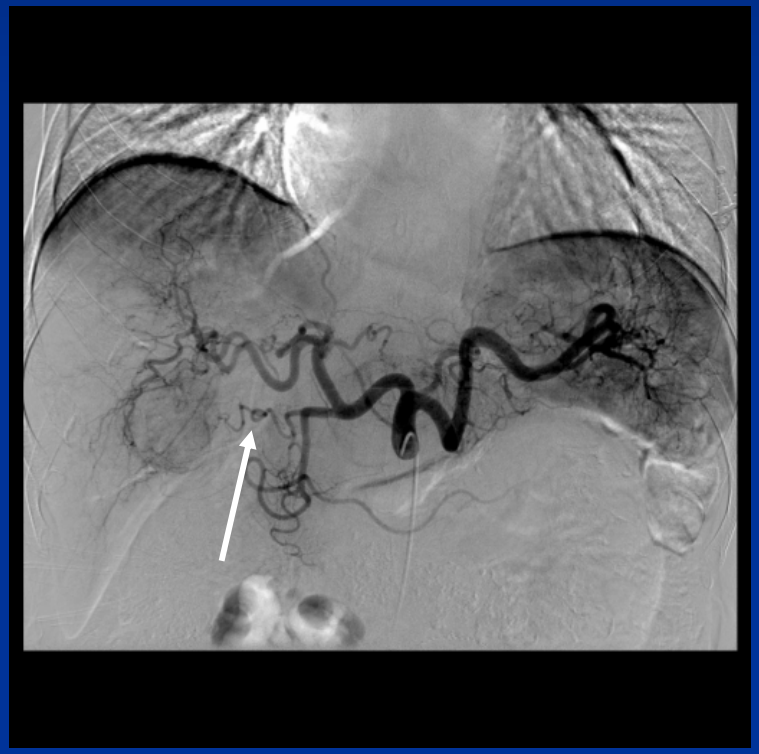

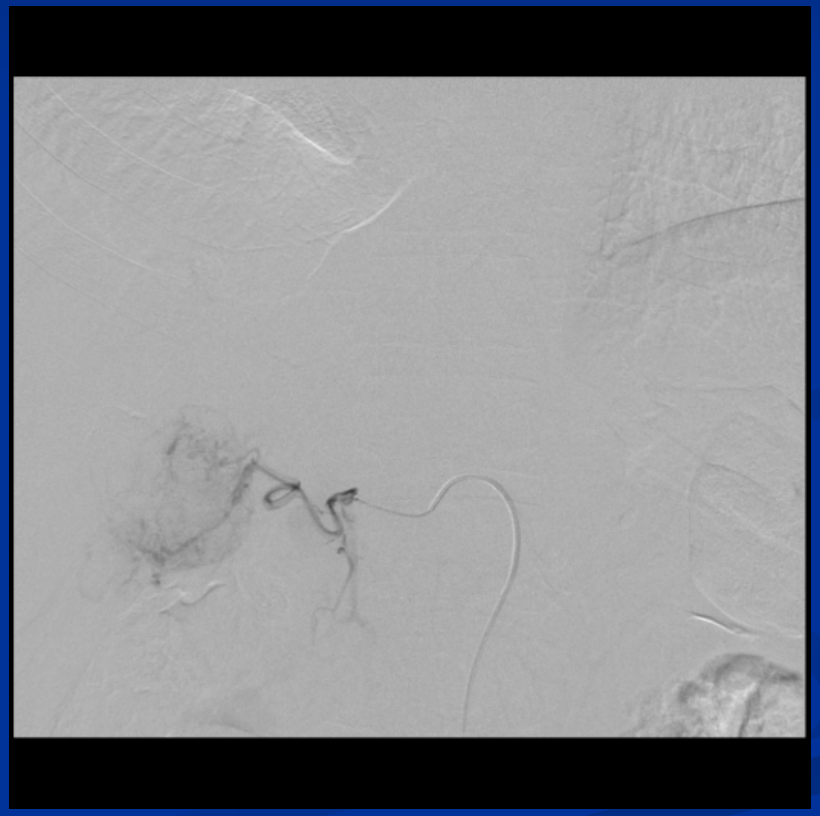

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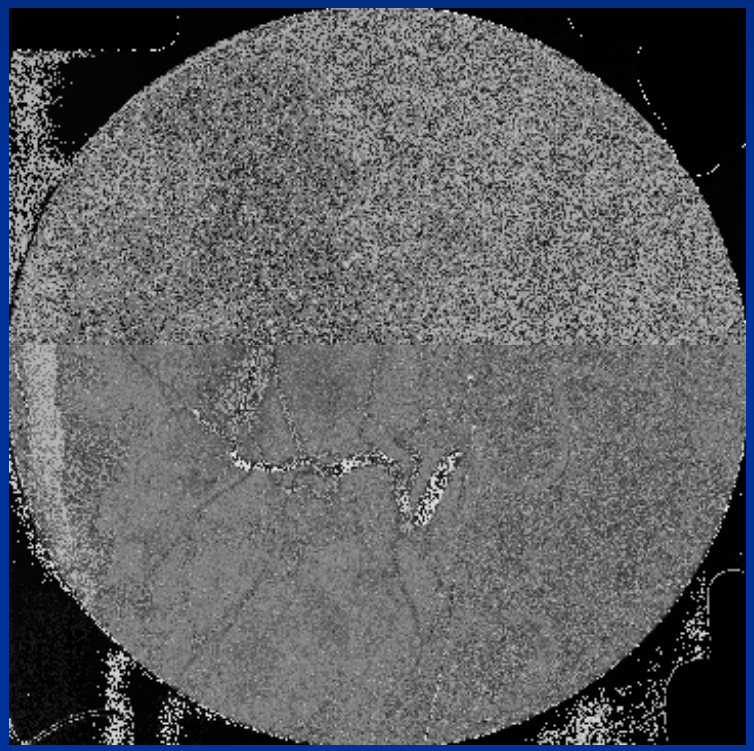
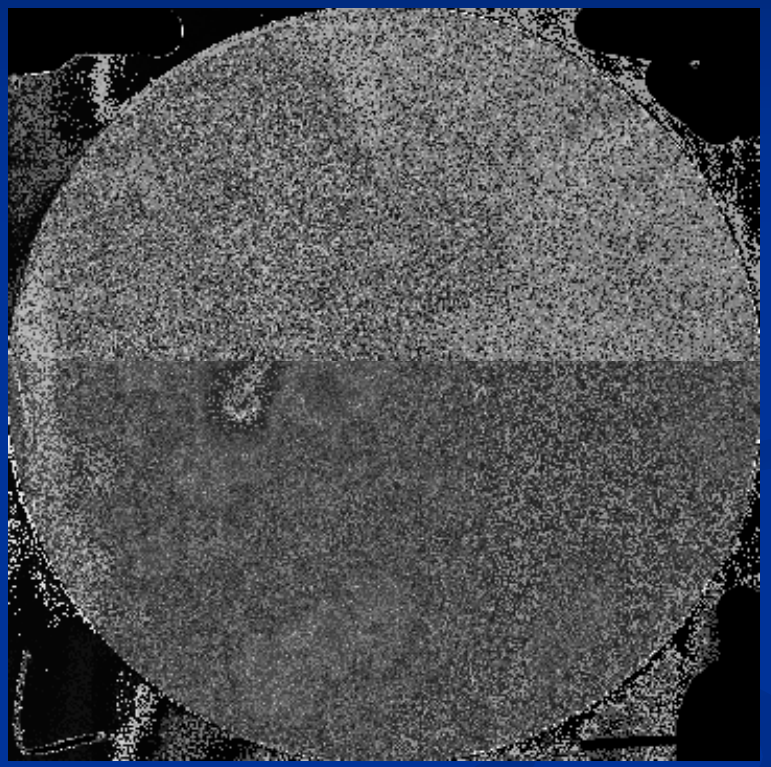


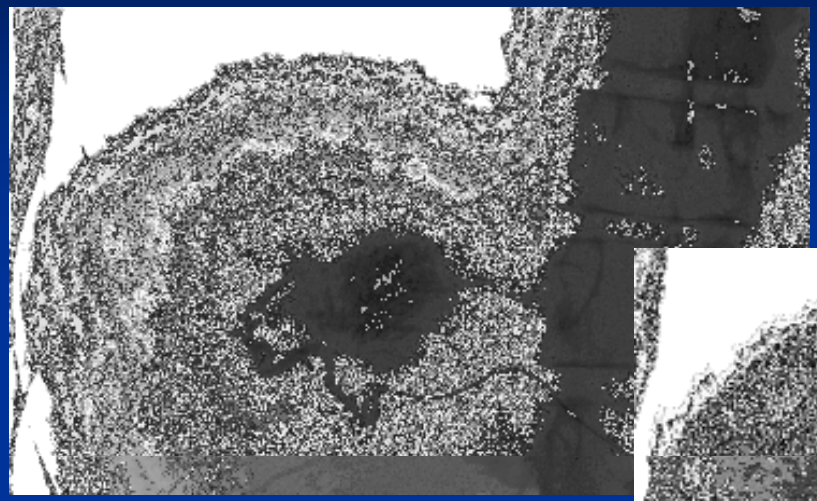


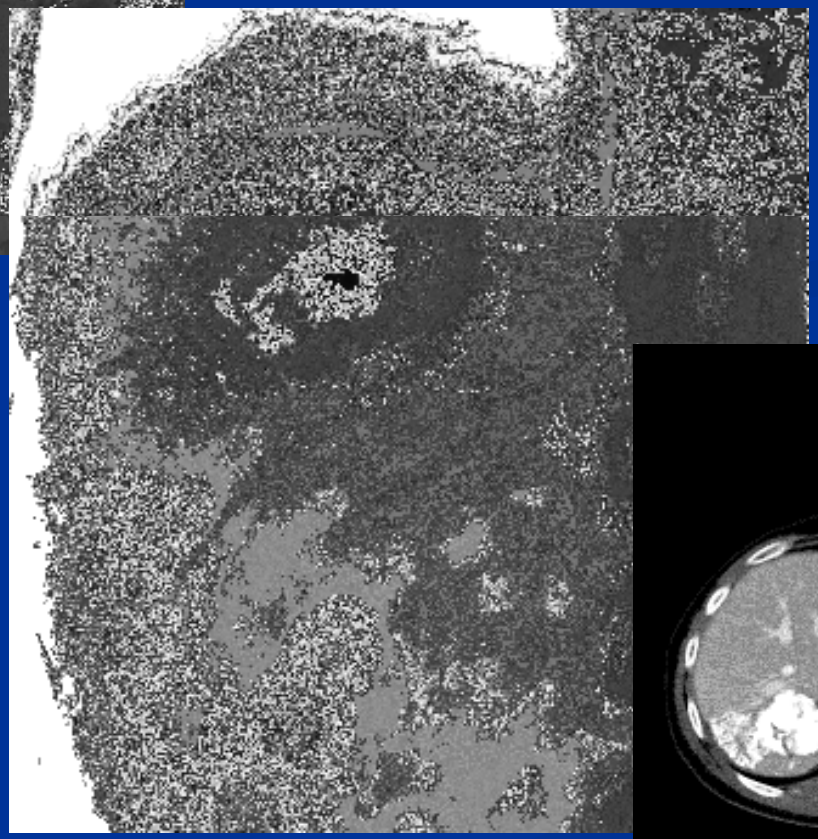
EMBOLIZATION AND CHEMOEMBOLIZATION

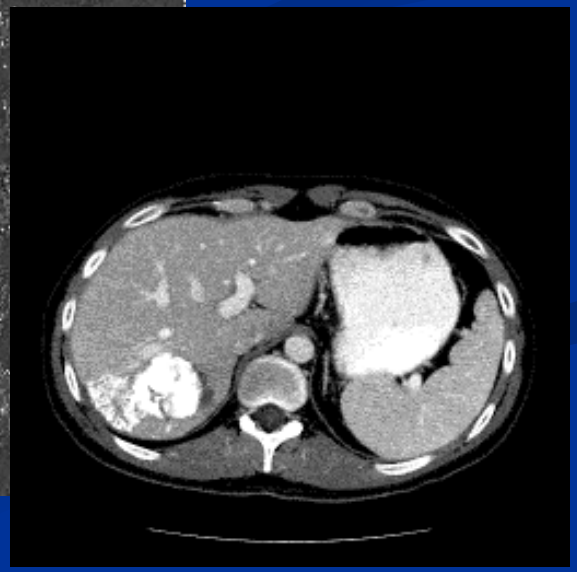
- Technique
  - Chemotherapeutic agent
    - Cisplatin
    - Vinblastine
    - Other
  - Embolic material
    - Iodized oil
    - PVA, Embospheres
    - Gelfoam
  - Drug eluting beads

Iodized Oil Via Hepatic Artery

Iodized oil deposition in tumors

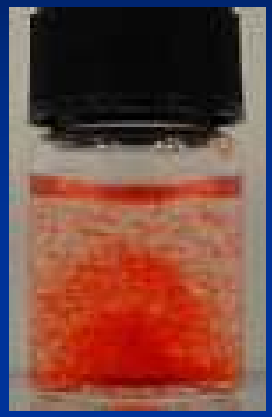






Drug Eluting Beads

- Embolic microsphere



- Sequester drug and release it in a controlled and sustained fashion
- Presumed advantages
  - single agent provides both local ischemia and increase concentration of chemotherapeutic agent within the tumor

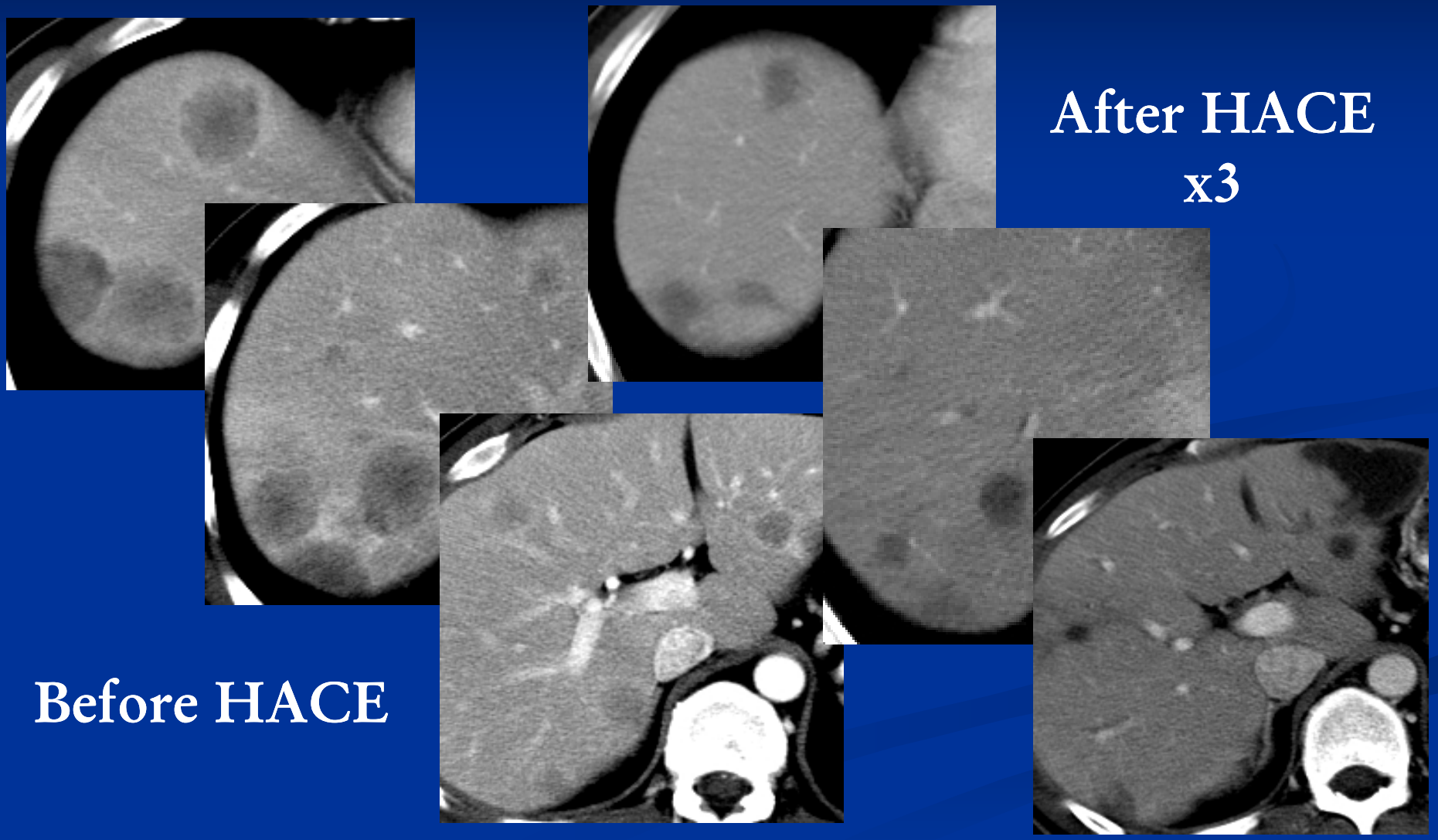
  - prolonged exposure to chemotherapeutic agent

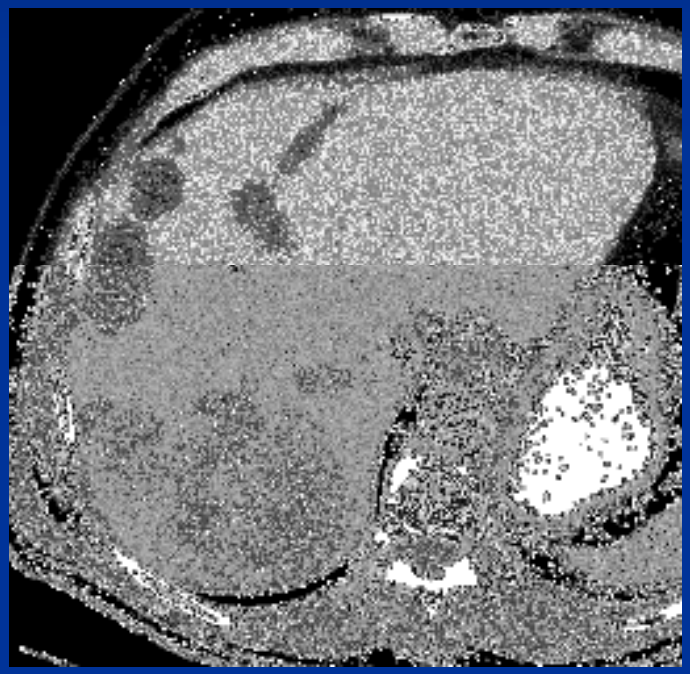
Drug Eluting Beads

- Sequesters drugs and releases it in a controlled and sustained fashion
  - Doxorubicin
  - Irinotecan
  - Oxaliplatin
- HCC - Improved response rates with HACE using drug-eluting beads as compared to standard HACE
- Colorectal cancer, cholangiocarcinoma
- **No experience with GIST**

Complications

- post-embolization syndrome 80-90% (fever, pain, nausea & vomiting)
- liver failure – 1%
- liver infarction 1-3%; abscess 1-3%
- pleural effusion; ascites
- renal failure
- cholecystitis, infarction
- gastric or duodenal ulceration (non-target embolization)


After HACE
x3
Before HACE



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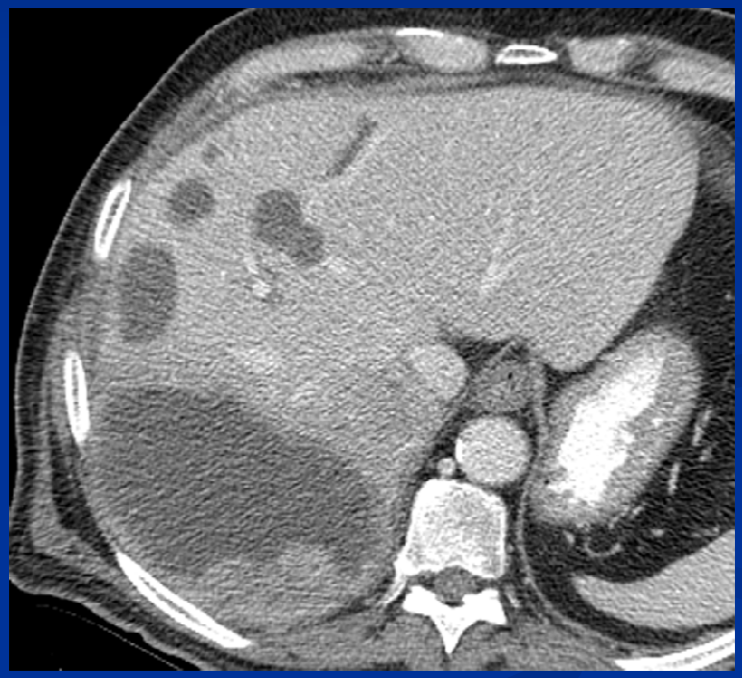

- After HACE

HAE and HACE - Results

Before the advent of imatinib

Study	Number of patients	Treatment	Response	Survival
Maluccio et al, 2006	24 Sarcomas (16 GIST)	HAE - PVA or Embosphere	NA	1 yr - 62%; 2 yr - 41%; 3 yr - 29%; median survival - 24 months
Mavligit et al. 1995 (MDACC)	14 GIST	HACE - Cisplatin, Vinblastine, PVA	Response - 70%	Median survival - 12 months
Rajan et al. 2001	16 Sarcomas (11 GIST)	HACE- Cisplatin, dox, mitomycin-C, iodized oil, PVA	Response -13%; Stable Disease – 69%	1 yr - 67%; 2 yr - 50%; 3 yr - 40%; median survival - 13 months
Kobayashi et al, 2006 (MDACC)	85 GIST	HACE - Cisplatin and PVA	Response -14%; Stable Disease - 74%	1 yr - 62%; 2 yr - 32%; 3 yr - 20%; median survival - 17 months

Mavligit GM et al - Cancer 1995; Maluccio et al - Cancer, 2006; Rajan et al – JVIR 2001; Kobayashi et al – Cancer, 2006

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HAE and HACE - Results

- Prognostic factors
  - Extent of liver disease
  - Presence of extrahepatic disease
  - Use of imatinib

Kobayashi et al, 2006 (Cancer)

HAE and HACE - Results

Variable		Overall Survival (months)	Hazards Ratio	P value
No. of liver lesions	1	22.8	0.279	0.0172
	2-5	23.5	0.616	0.0997
	>5	8.9	1.0	
Extent of liver disease	≤50%	17.6	1.0	
	50-75%	16.7	1.963	0.0733
	>75%	3.8	7.097	0.0029
Extrahepatic metastatic disease	No	22.8	1.0	
	Yes	12.1	5.169	<0.0001
Imatinib	No	15.7	1.0	0.0003
	Yes	42.8	0.126	
Radiologic response	PR + SD	19.6	1.0	
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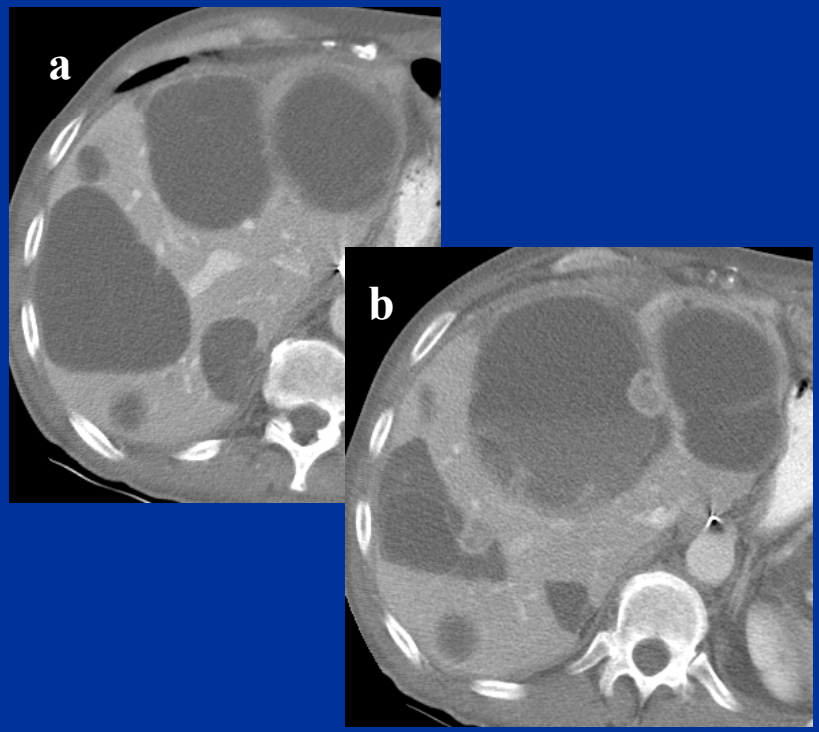
HAE and HACE - Results

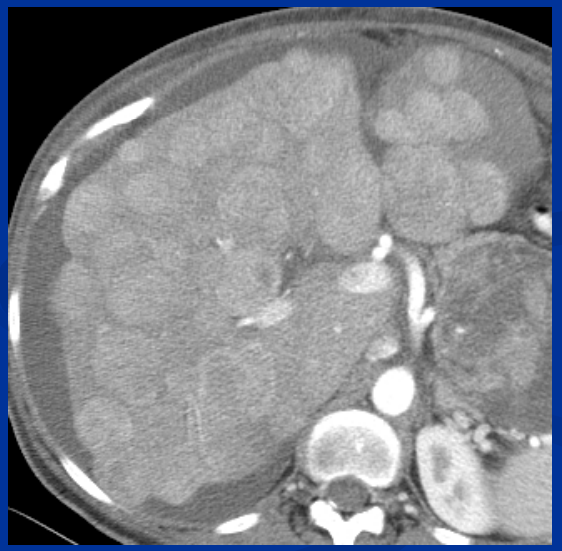
After the advent of imatinib

- Kobayashi et al, 2009 (MDACC); Kit (+) GISTs refractory to imatinib
- 13 patients who had been treated with imatinib for 7 to 61 months, and developed progressive liver metastases
- HAE – 6; HACE - 7
- PR - 7; SD – 6
- Overall survival rates - 78.6 %, 45.8%, and 45.8% at 6 months, 1 and 3 years

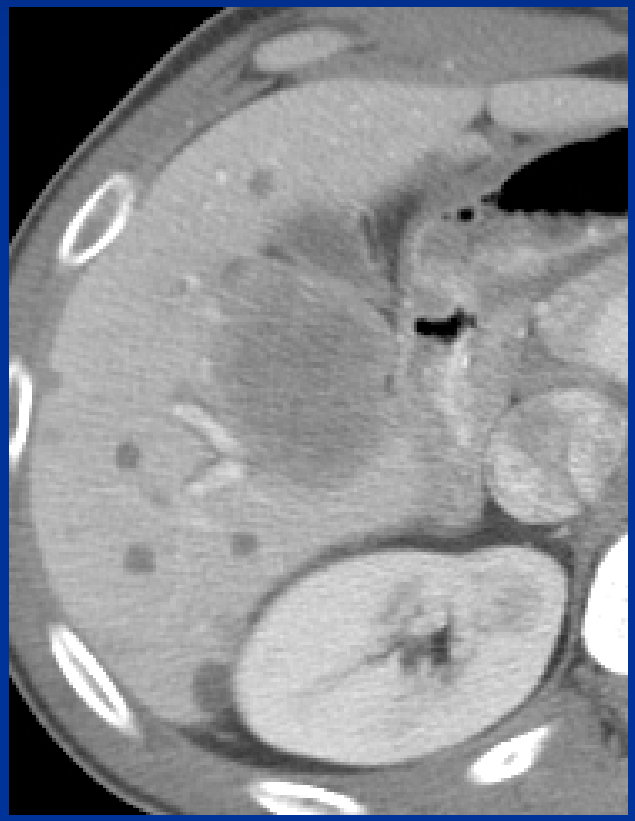
- **Pattern of disease progression** **after imatinib treatment**

New solid area within cystic change
Increase in size or number of solid tumors
Combination of both

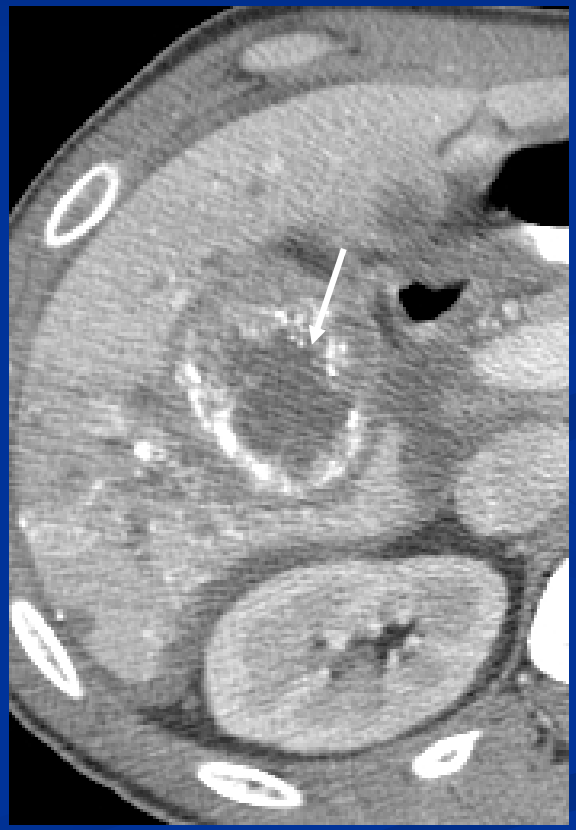




HACE in Patients With Disease Progression after Imatinib



- **Before HACE**



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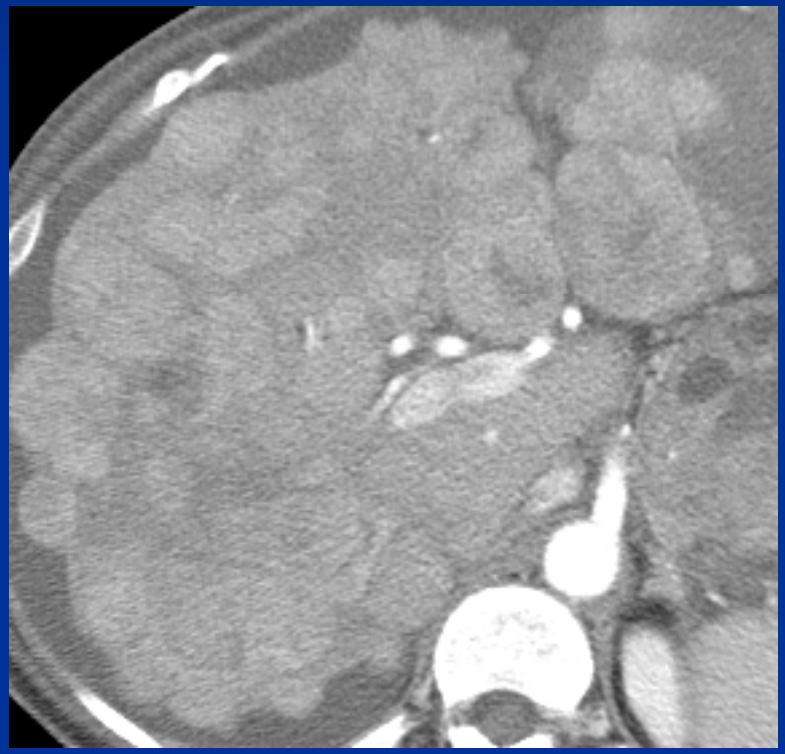

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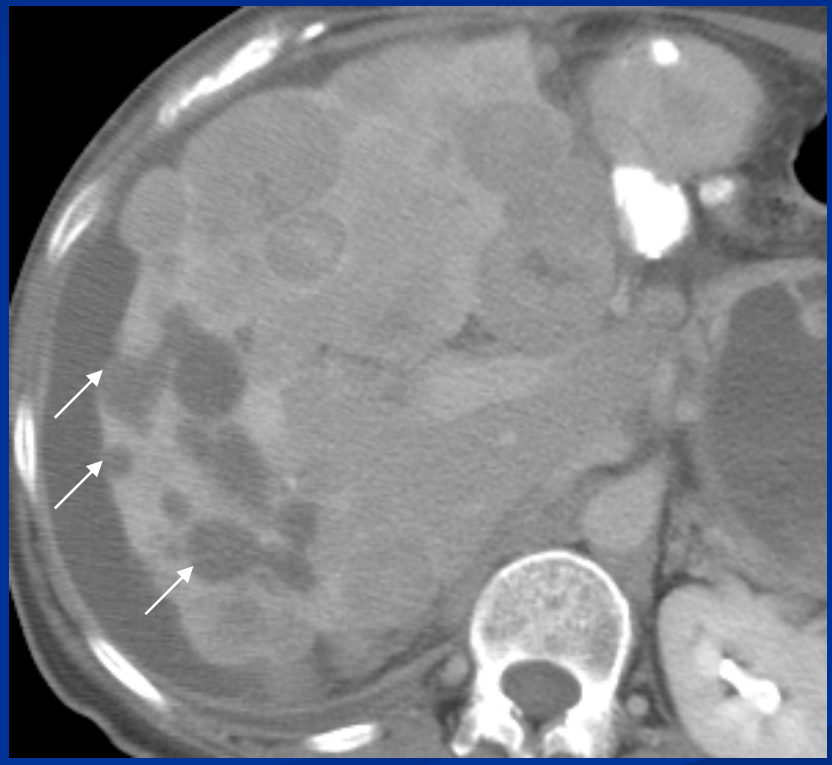


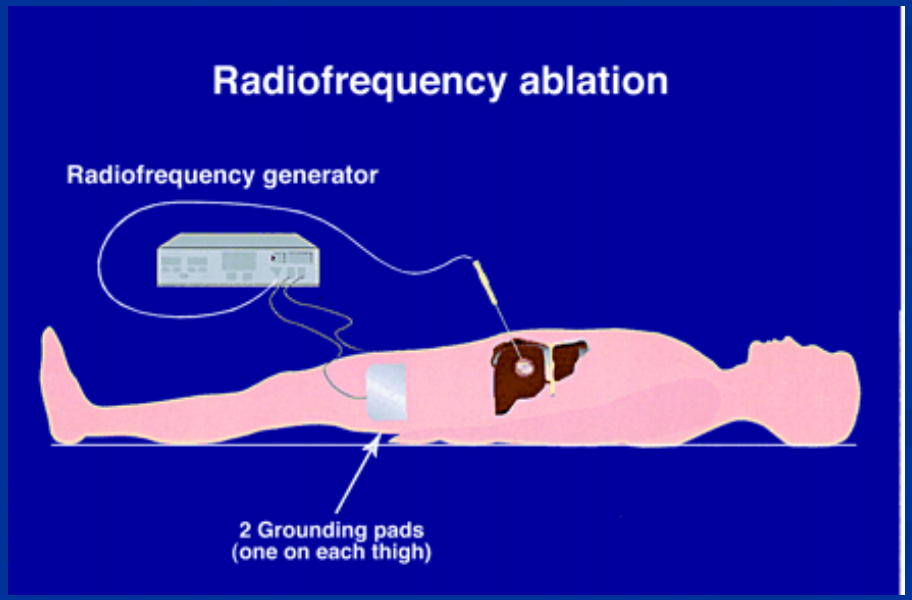
- **Before HACE X2**

Ablation

- Radiofrequency ablation (RFA)
  - Patients exhibiting partial response to imatinib with focal residual disease
    - Liver
    - Peritoneal
  - Not surgical candidates

RF ABLATION

- Mechanism
  - alternating electric current operated in the range of radiofrequency - focal thermal injury (95^0 -100^0) in living tissue - coagulative necrosis



RF ABLATION

- Tissue reaction to thermal injury
  - < 40°C– homeostasis
  - 42°C to 45°C – susceptible to chemotherapy or radiation; takes several hours to produce irreversible cell damage
  - 50°C to 55°C – irreversible damage in 4-6 minutes
  - 60°C to 100°C – near immediate coagulation
  - > 100°C – vaporization/carbonization and charring
  - *50°C to 100°C – ideal ablation temperature*

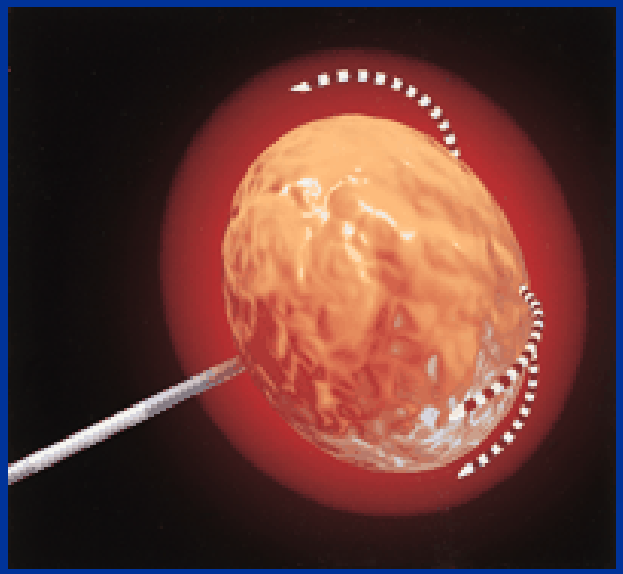
RF ABLATION

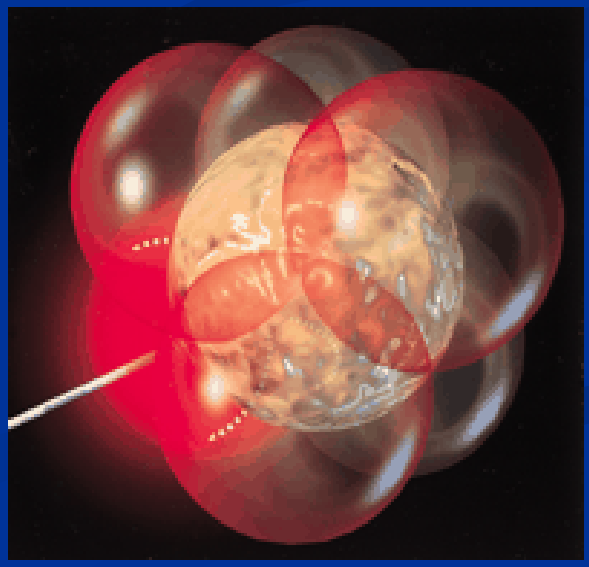
- Probe configurations



RF ABLATION

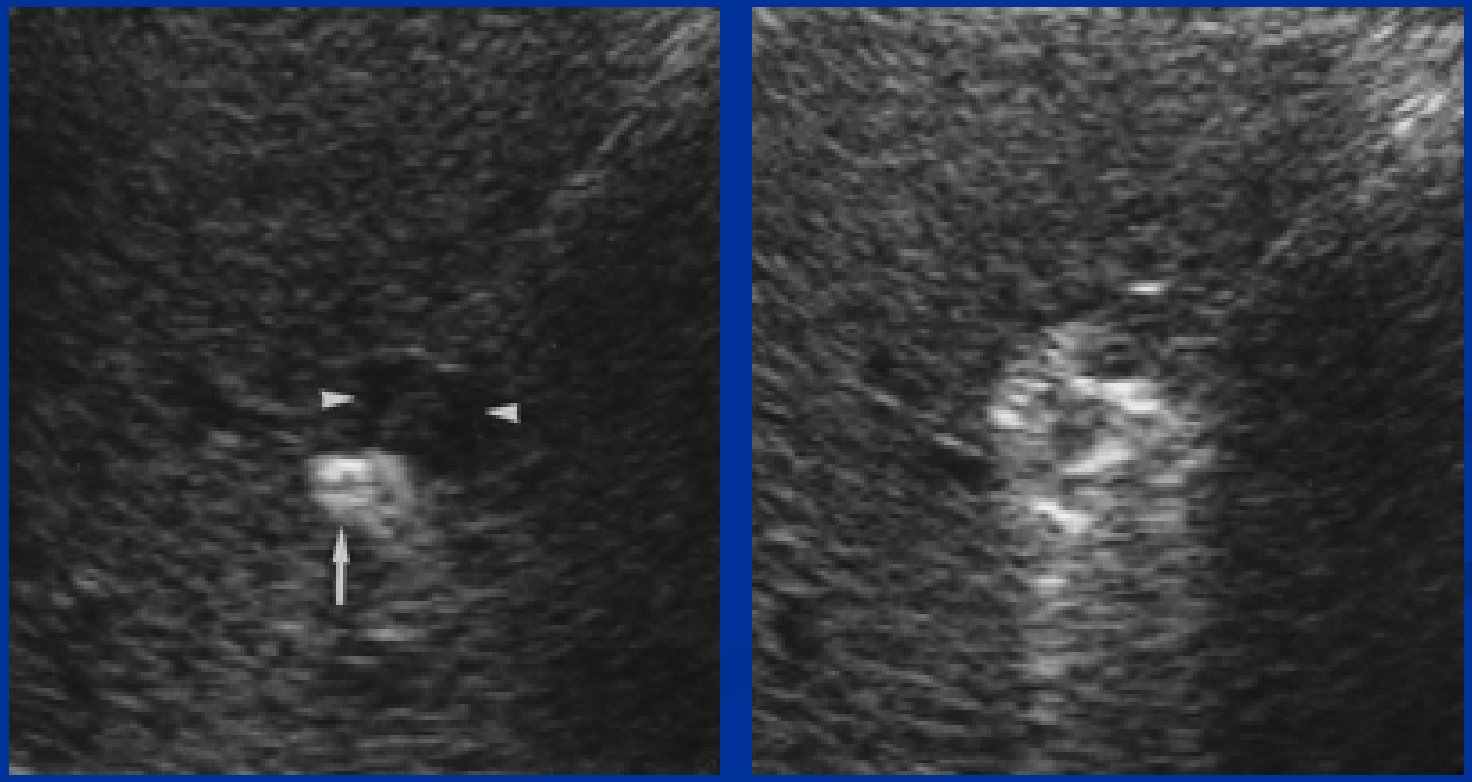
- Technique
  - 2–5-cm spherical thermal injury
  - larger lesions may require overlapping ablation





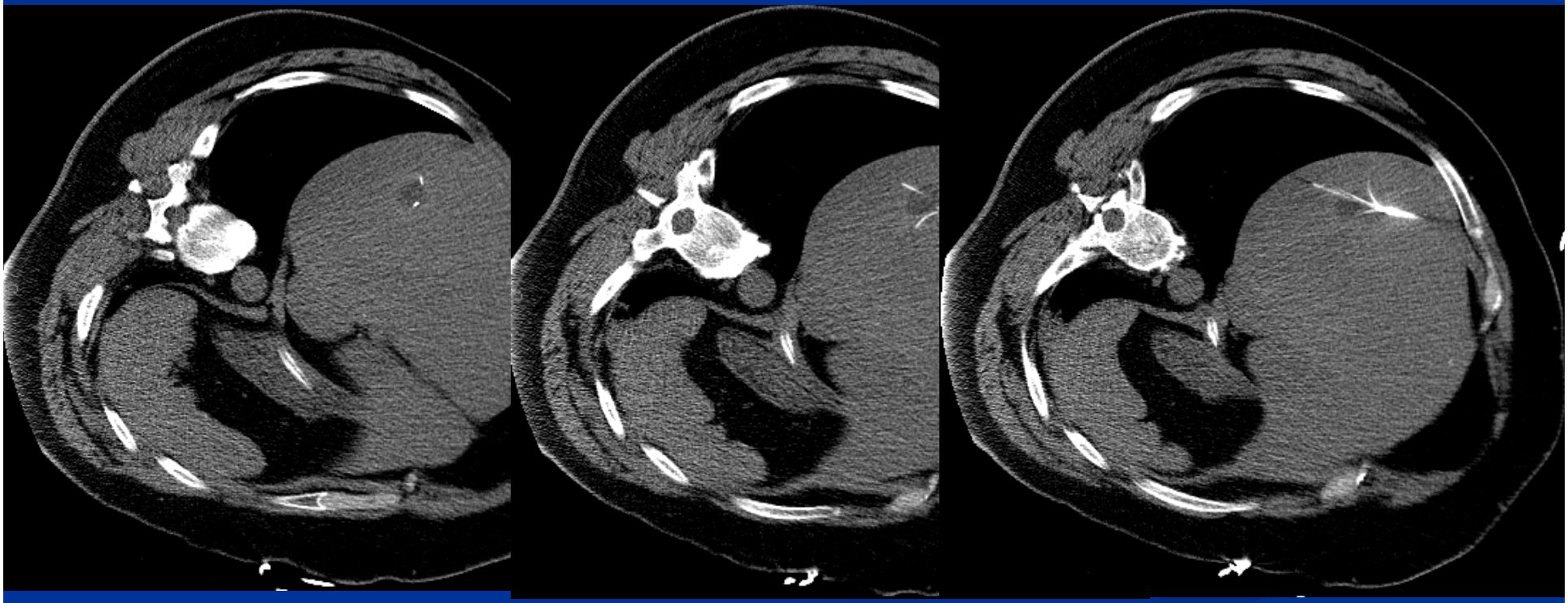
RF ABLATION

- Technique
  - percutaneous/laparoscopy/laparotomy
  - US / CT / MRI for guidance



RFA of Liver Tumors

CT Guidance



RFA - GIST

Study	Number of patients	Treatment	Response
Dileo et al, 2004	9 GIST; Liver and Peritoneal	RFA	Stable Disease – 4 patients at 5.8 months
Hasagewa et al, 2007	3 GIST; Liver	RFA	Progression free at 8, 15, and 16 months
Jones et al, 2010	13 GIST; Liver	RFA	Response -12/13 Stable Disease - 1/13

Dileo et al, J Clin Oncol 2004; Hasagewa et al, Int J Clin Oncol 2007; Jones et al, EJSO 2010

Conclusions

- Imatinib mesylate is now established as the first-line therapy for metastatic GIST
- The emergence of this targeted agent has dramatically affected the management and outcome of patients with advanced GIST, decreasing the role of local/regional therapy

Conclusions

- Local/Regional Treatments (HAE/HACE/Ablation) can be offered to patients with GISTs and liver-dominant metastasis
  - who have primary or acquired resistance to imatinib
  - particularly suitable for patients who exhibit an initial response to imatinib in all lesions but later develop progression of focal disease in the liver, e.g., one solitary lesion that continues to grow