Treatment of Early – Stage Liver Cancer

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Disclosures

- Participant in multiple clinical trials that are ALL US-based

Objectives

- Define early vs late hepatocellular carcinoma (HCC)
- Epidemiology of HCC
- State incidence of HCC
- Outline the etiologies of HCC: cirrhotic vs non-cirrhotic
- Determine the risk Factors for HCC
- Review Child-Pugh System and BCLC classification
- Therapeutic Options for HCC
- Summary and Conclusions

Early versus Late HCC:

- Hepatocellular carcinoma (HCC) is an aggressive tumor that occurs in the setting of chronic liver disease or cirrhosis
- Presentation can be variable
- Typical diagnosis is late in its course
- Early diagnosis facilitated by surveillance programs
- Median survival is 6 to 20 months.

Incidence of HCC:

- HCC in adult men is 5th most frequently diagnose cancer and 9th in females.
- It is the 4th leading cause of cancer-related deaths in the world
- In the US, annual incidence is 6 per 100,000.
- Persons born between 1945 and 1965 have highest incidence in the US.
- Asian/Pacific Indians have highest incidence of all ethnic groups
- Highest incidence regions: sub-Sahara Africa, People's Republic of China, Hong Kong, and Taiwan.

Incidence of hepatocellular carcinoma in various countries and ethnic groups (per 100,000 per year)

Country	Males	Females
Mozambique	112.9	30.8
Zimbabwe	64.6	25.4
Gambia	33.1	12.6
Senegal	25.6	9.0
South Africa (Cape)		
Black	26.3	8.4
Colored	1.5	0.7
Caucasian	1.2	0.6
Algeria	1.6	1.4
Nigeria	15.4	3.2
Argentina	9.9	5.8
Brazil	3.5	3.7
Peru	4.0	2.9
Jamaica	6.1	2.1
United States		
Chinese	19.1	3.6
Black	3.9	1.8
Japanese	3.0	0.4
Caucasian	2.9	1.1
Canada		
Eskimos	6.9	3.7
Alberta	1.3	0.5
Switzerland	10.2	1.5
Italy	8.6	3.3
Spain	7.2	5.5
France	3.7	1.0
Germany	4.5	1.7
Denmark	3.6	2.3
Yugoslavia	2.9	1.2
Czechoslovakia	5.1	2.8
United Kingdom	1.6	0.8
Ireland	0.1	0.3
China	34.4	11.6
Singapore		
Chinese	31.6	7.2
Malay	15.6	5.3
Indian	14.1	2.8
Korea	13.8	3.2
Japan		
Miyagi	11.2	4.0
Nagasaki	25.8	7.9
India	4.9	2.5
Philippines	19.9	6.2
Hong Kong	32.3	7.4
Pakistan	0.7	0.8
New Zealand		
Maori	11.2	4.2
Non-Maori	2.4	1.1
Pacific Polynesian		
Islands	26.6	2.3
Australia	2.0	0.7
Hawaii	7.8	2.4

Reference: Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011; 61:69.

Etiologies and Associations

- Nonmodifiable risk factors: HBV carrier state, chronic HCV, hereditary hemochromatosis, cirrhosis of any cause.
- Modifiable risk factors:
  - Environmental factors
  - Tobacco and alcohol abuse
  - Diabetes mellitus
  - NASH (nonalchohoic fatty liver disease)
  - Obesity
  - Iron overload

Protective Factors: HCC

- Vaccination to prevent viral hepatitis
- Treatment of viral hepatitis(HCV, HBV)
- Statin use
- Aspirin
- Diet: fish, white meat, omega-3 fatty acids, vegetables
- Coffee consumption: approximately 2 cups per day

Diagnosis of HCC:

- Imaging and serologic markers remain the mainstay of diagnostic modalities
- Lesions <1 cm: monitor every 3-6 months for 2 years
- Lesions >1 cm: diagnostic MRI. Typical characteristics may avert the need for biopsy.
- In patients WITHOUT liver disease: CEA, AFP, biopsy

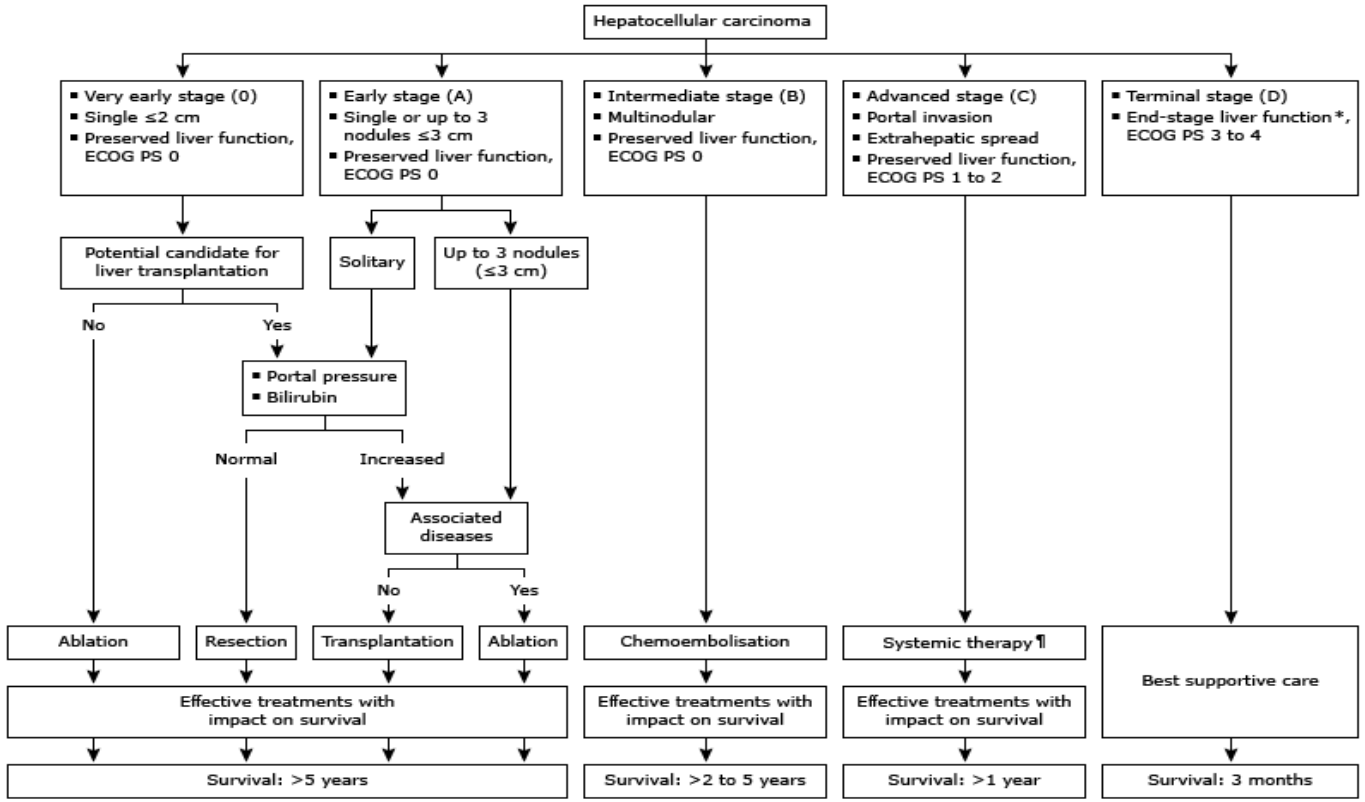
Treatment Algorithms for HCC

- Staging systems
- Child-Pugh Classification of cirrhosis
- Barcelona Clinic Liver Cancer (BCLC)
- Milano/Mazzaferro Criteria

Child-Pugh Classification: Cirrhosis

- **Main Factors** considered:
- -- ascites, bilirubin, albumin, prothrombin time
- --INR
- --Encephalopathy

Barcelona Clinic Liver Cancer (BCLC) staging classification and treatment algorithm



The BCLC system establishes a prognosis in accordance with the five stages that are linked to first-line treatment recommendation. The expected outcome is expressed as median survival of each tumor stage according to the available scientific evidence. Note that liver function should be evaluated beyond the conventional Child-Pugh classification or the Model for End-Stage Liver Disease (MELD) score. None of them serves to properly gauge the liver function status, and this evaluation should take into account biochemistry parameters as well as the compensated or decompensated status of the patient. Preserved liver function includes a group of patients with different degrees of liver function reserve that has to be carefully evaluated. For most treatment options, compensated liver disease (Child-Pugh stage A without ascites) is required to obtain optimal outcomes. The sole option that could be applied irrespective of liver function is liver transplantation.

ECOG: Eastern Cooperative Oncology Group; PS: performance status.
* Patients with end-stage cirrhosis due to heavily impaired liver function (Child-Pugh stage C or earlier stages with predictors of poor prognosis or high a MELD score) should be considered for liver transplantation. In these patients, hepatocellular carcinoma might become a contraindication if it exceeds enlistment criteria.
¶ Currently, sorafenib followed by regorafenib has been shown to be effective. Lenvatinib has been shown to be noninferior to sorafenib, but no second-line option after lenvatinib has been explored.

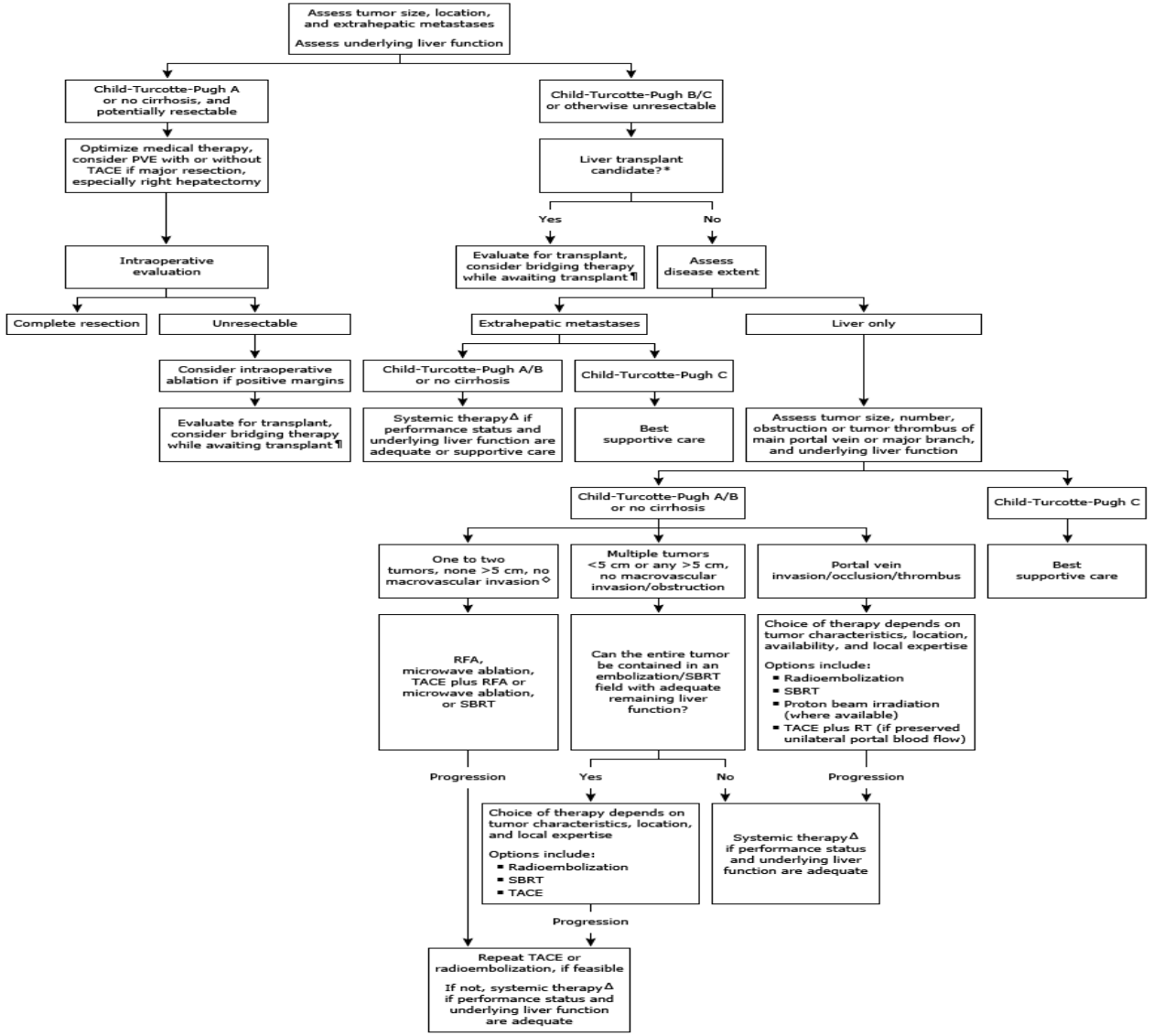
BCLC Dissent:

- BCLC combines ALL single nodules into. STAGE A
- Does not address value of resection for some subgroups (early versus intermediate stage).
- All single lesions are resectable. T2 lesions may be resectable if liver function permits.
- BCLC STAGE C is heterogenous.

Treatment Modalities: Surgical and Nonsurgical

- Partial resection and Liver transplantation
- Radiofrequency ablation , microwave ablation and cryoablation
- Transarterial radioembolization (TARE)
- Transarterial chemoembolization (TACE)
- Percutaneous ethanol or acetic acid ablation
- Irreversible electroporation
- Radiation therapy and stereotactic radiation therapy
- Systemic Chemotherapy
- Immunotherapy

Overview of treatment algorithm for hepatocellular carcinoma



PVE: portal vein embolization; TACE: transarterial chemoembolization; RFA: radiofrequency ablation; SBRT: stereotactic body radiation therapy; RT: radiation therapy.

* In the United States, patients with underlying chronic liver disease (cirrhosis, hepatitis C virus infection) are potentially eligible for orthotopic liver transplant if they fulfill the Milan criteria (solitary hepatocellular carcinoma ≤5 cm in diameter or up to three separate lesions, none of which is larger than 3 cm; no evidence of gross vascular invasion; and no regional nodal or distant metastases). If not a liver transplantation candidate because disease is outside transplant (Milan) criteria, downstaging therapy (eg, RFA, TACE) could be considered, followed by reassessment for liver transplantation.

¶ Bridging therapy refers to local treatment (typically RFA or TACE) while awaiting orthotopic liver transplantation in order to reduce the risk of progressing beyond Milan criteria.

Δ Options for initial systemic therapy include participation in a clinical trial (preferred), sorafenib, lenvatinib, or cytotoxic chemotherapy (refer to UpToDate text).

◇ The best results with RFA are in patients with a smaller tumor size, and many institutions restrict RFA to lesions <4 cm.

Key to Therapy: Multidisciplinary Care

- SURGERY
- INTERVENTIONAL RADIOLOGY
- MEDICAL ONCOLOGY
- RADIATION RADIOLOGY

Early HCC:
Treatment options: resectable disease

- Preferred therapy for localized disease surgical resection.
- Partial hepatectomy can be curative.
- Ideal patient: Child-Pugh A cirrhosis
  - Adequate liver function
  - Lesion confined to the liver
  - < than 5 cm in size

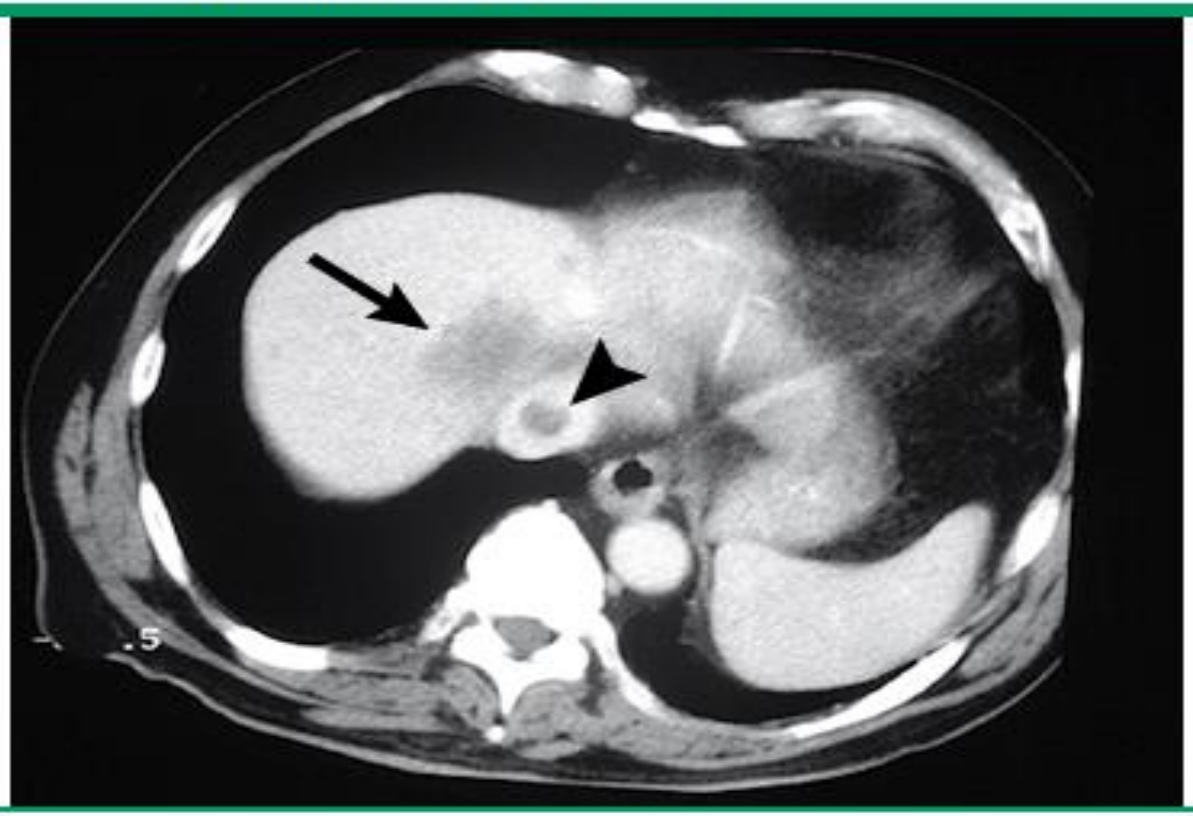
Surgical Options

- Two considerations:
- Resection
- Orthotopic liver transplantation

Who get a resection?

- Why resection?
- Advantages vs disadvantages
- Likely candidates

Hepatoma invading major vessels



A contrast-enhanced computed tomography (CT) scan demonstrates an ill-defined mass in the dome of the liver representing the region of the hepatoma (long arrow). A filling defect in the contrast filled inferior vena cava (IVC; arrowhead) reflects tumor thrombus extending from the primary tumor into the IVC.

Courtesy of Jonathan Kruskal, MD.

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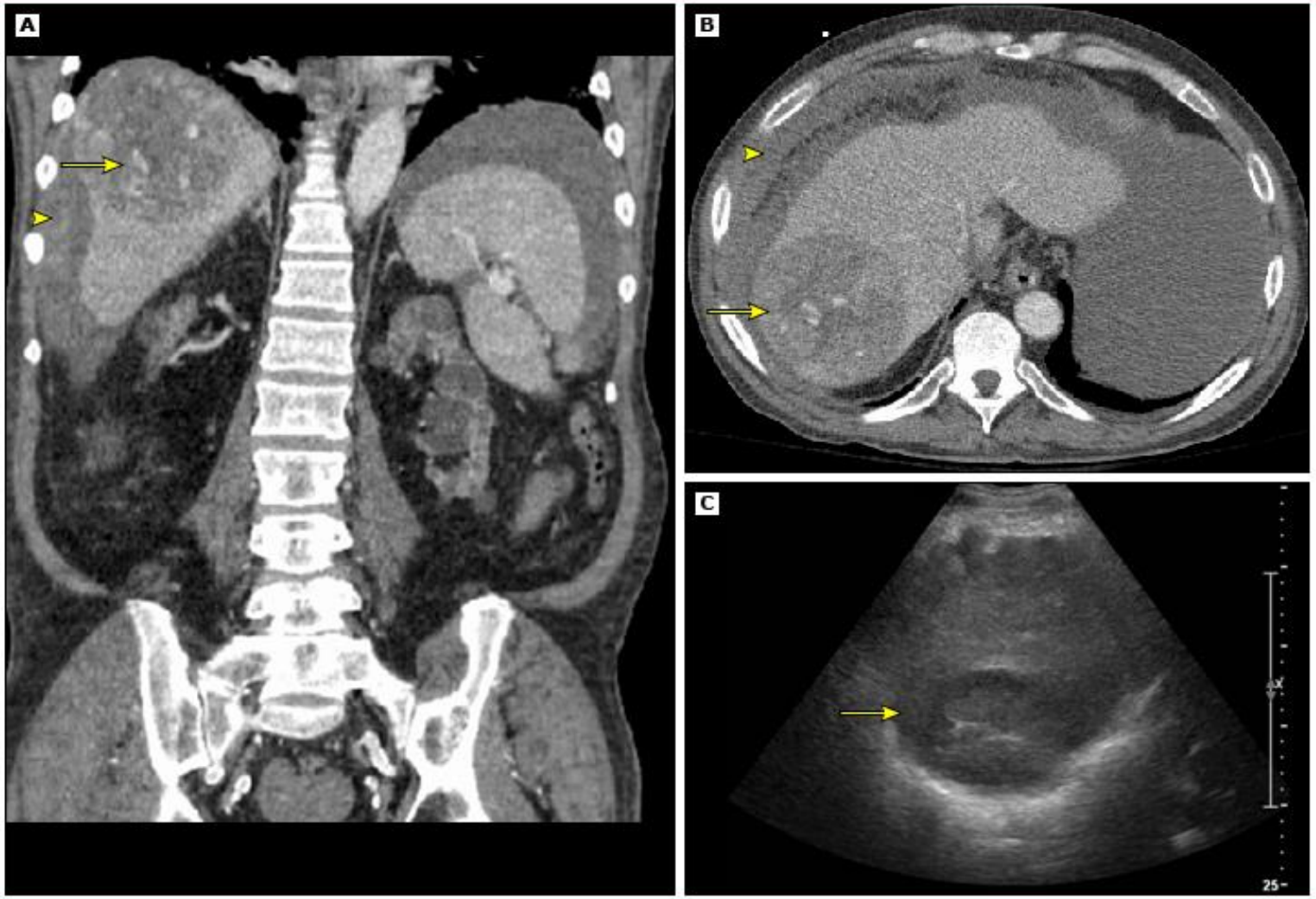
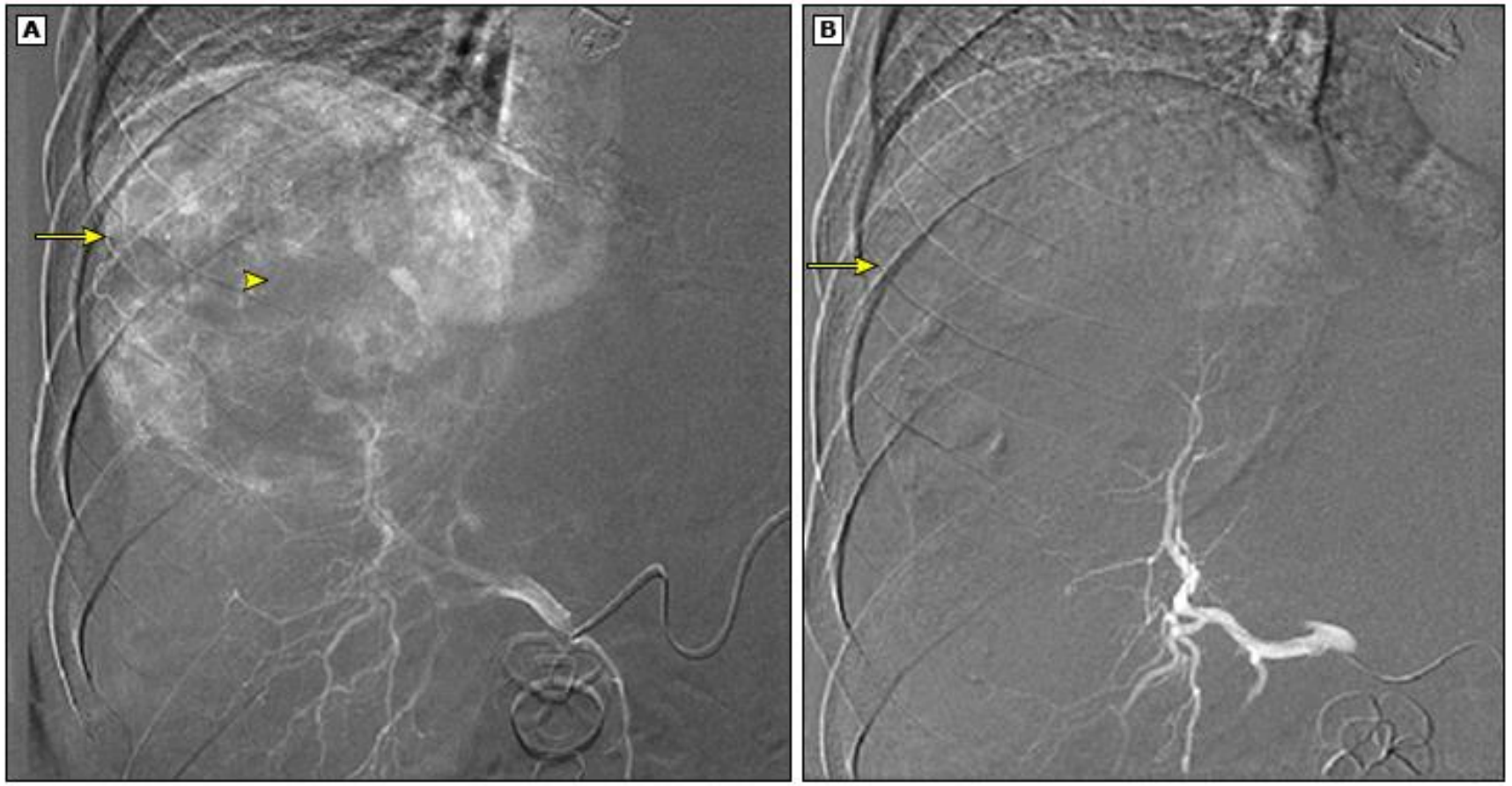
HCC on CT and US



A coronal reconstruction of a CT shows a large hemorrhagic HCC in the dome of the right lobe of the liver (arrow) with perihepatic high-density clot (arrowhead). Image B shows an axial CT through the HCC (arrow) with abnormal vascular channels associated with perihepatic hemorrhage (arrowhead). Image C is an ultrasound showing a heterogeneous mass in the dome of the right lobe of the liver (arrow).

HCC: hepatocellular carcinoma; CT: computed tomography; US: ultrasound.

Hemorrhagic HCC treated with embolization



An angiogram of a hemorrhagic HCC (A) shows a hypervascular mass in the dome of the liver (arrow) with a central region of hypovascularity (arrowhead) likely representing intratumoral clot or necrosis. Image B is an angiogram of the right hepatic artery following microsphere embolization and shows an avascular mass (arrow).

HCC: hepatocellular carcinoma.

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Liver Transplantation in HCC

- Qualification Criteria
- Limitations
- Resources

Resectable lesions: Transplantation (OLT)

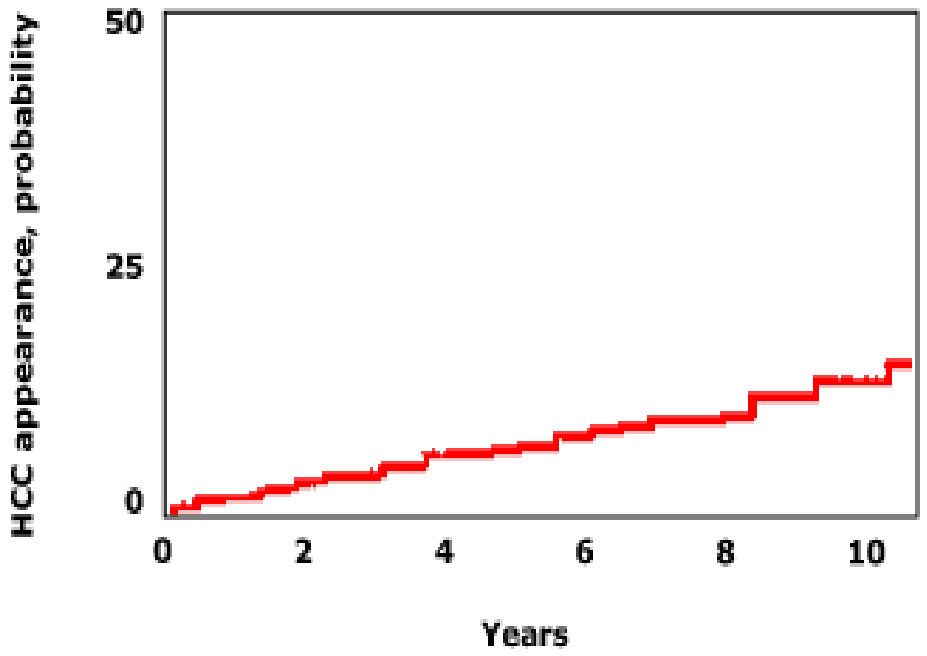
- Beside resection, only other potentially curative option
- **Criteria:** solitary lesion < 5 cm or 3 separate lesions each less than 3 cm
- No vascular invasion
- No regional or distant metastases (Milan criteria)
- **MELD score** (Model for End-Stage Liver Disease).
- KEY: prioritization given to patients with HCC.
- Major disadvantage is **WAIT TIME** for ***DONOR***.
- Bridging therapy: locoregional therapies

Summary of recommendations for transplantation for hepatocellular carcinoma from an International Consensus Conference

	Level of evidence	Strength of recommendation
Assessment of candidates with HCC for liver transplantation		
1. When considering treatment options for patients with HCC, the BCLC staging system is the preferred staging system to assess the prognosis of patients with HCC.	2b (P)	Strong
2. The TNM system (7th edition), including pathological examination of the explanted liver, should be used for determining prognosis after transplantation with the addition of assessment of microvascular invasion.	2b (P)	Strong
3. Either dynamic CT or dynamic MRI with the presence of arterial enhancement followed by washout on portal venous or delayed imaging is the best non-invasive test to make a diagnosis in cirrhotic patients suspected of having HCC and for preoperative staging.	1b (D)	Strong
4. Extrahepatic staging should include CT of the chest and CT or MRI of the abdomen and pelvis.	3b (D)	Strong
5. Tumor biopsy is not required in cirrhotic patients considered for liver transplantation who have high-quality dynamic CT or MRI findings typical for HCC and a lesion larger than 1 cm according to current AASLD guidelines.	1b (D)	Weak
6. For patients with lesions smaller or equal to 10 mm, non-invasive imaging does not allow an accurate diagnosis and should not be used to make a decision for or against transplantation.	1b (D)	Strong
Criteria for listing candidates with HCC in cirrhotic livers for DDLT		
7. Liver transplantation should be reserved for HCC patients who have a predicted five-year survival comparable to non-HCC patients.	NA	Weak
8. Preoperative assessment of the size of the largest tumor or total diameter of tumors should be the main consideration in selecting patients with HCC for liver transplantation.	2a (P)	Strong
9. The Milan criteria are currently the benchmark for the selection of HCC patients for liver transplantation and the basis for comparison with other suggested criteria.	2a (P)	Strong
10. A modest expansion of the number of potential candidates may be considered on the basis of several studies showing comparable survival for patients outside the Milan criteria.	3b (P)	Weak
11. Patients with worse prognosis may be considered for liver transplantation outside the Milan criteria if the dynamics of the waiting list allow it without undue prejudice to other recipients with a better prognosis.	NA	Weak
12. α-fetoprotein concentrations add prognostic information in HCC patients and may be used for making decisions regarding transplantation in combination with imaging criteria.	2b (P)	Weak
13. Biomarkers other than α-fetoprotein cannot yet be used for clinical decision making regarding liver transplantation for HCC.	2b (P)	Strong
14. Indication for liver transplantation in HCC should not rely on microvascular invasion because it cannot be reliably detected prior to transplantation.	2b (P)	Strong
Criteria for HCC candidates with non-cirrhotic livers		
15. The Milan criteria and its modifications are not applicable to patients with HCC developing in a non-cirrhotic liver. Such patients with non-resectable HCC and absence of macrovascular invasion and extrahepatic spread may be considered as appropriate candidates for liver transplantation.	4 (P)	Weak
16. Patients with HCC in non-cirrhotic liver who were treated by resection, and have intrahepatic recurrence of HCC and no evidence of lymph node or macrovascular invasion, may be considered for salvage transplantation.	4 (P)	Weak
Role of downstaging		
17. Transplantation may be considered after successful downstaging.	5 (P)	Weak
18. Liver transplantation after successful downstaging should achieve a five-year survival comparable to that of HCC patients who meet the criteria for liver transplantation without requiring downstaging.	5 (P)	Strong
19. Criteria for successful downstaging should include tumor size and number of viable tumors.	4 (P)	Strong
20. α-fetoprotein concentrations before and after downstaging may add additional information.	4 (P)	Weak
21. Based on existing evidence, no recommendation can be made for preferring a specific locoregional therapy for downstaging over others.	NA	None
Managing patients on the waiting list		
22. Periodic waiting-list monitoring should be performed by imaging (dynamic CT, dynamic MRI, or contrast-enhanced ultrasonography) and α-fetoprotein measurements.	5 (P)	Strong
23. Based on current absence of evidence, no recommendation can be made on bridging therapy in patients with UNOS T1 (≤2 cm) HCC.	NA	None
24. In patients with UNOS T2 (one nodule 2 to 5 cm or three or more nodules each ≤3 cm) HCC (Milan criteria) and a likely waiting time longer than six months, locoregional therapy may be appropriate.	4 (P)	Weak
25. No recommendation can be made for preferring any type of locoregional therapy to others.	NA	None
26. Patients found to have progressed beyond criteria acceptable for listing for liver transplantation should be placed on hold and considered for downstaging.	5 (P)	Strong
27. Patients with progressive disease in whom locoregional intervention is not considered appropriate, or is ineffective, should be removed from the waiting list.	5 (P)	Strong
Role of LDLT		
28. LDLT is acceptable for HCC patients who have an expected five-year survival similar to comparably staged patients receiving a deceased donor liver. In LDLT, careful attention should be given to psychosocial considerations regarding both donor and recipient.	NA	Weak
29. LDLT must be restricted to centers of excellence in liver surgery and liver transplantation to minimize donor risk and maximize recipient outcome.	NA	Strong
30. In patients following LDLT for HCC within the accepted regional criteria for DDLT, retransplantation for graft failure is justified.	5 (P)	Weak
31. In patients following LDLT for HCC outside the accepted regional criteria for DDLT, retransplantation for graft failure using a deceased donor organ is not recommended.	5 (P)	Strong
Posttransplant management		
32. Posttransplant monitoring may include 6 to 12 monthly contrast-enhanced CT or MRI imaging and α-fetoprotein measurements.	5 (P)	Weak
33. There is currently insufficient evidence from clinical trials to base a recommendation for choosing the type or dose of immunosuppression therapy to influence the incidence of HCC recurrence or its prognosis.	NA	None
34. Based on current evidence, no recommendation can be made on the use of mTOR inhibitors solely to reduce the risk of HCC recurrence outside clinical trials.	NA	None
35. The current evidence does not justify the routine use of adjuvant antitumor therapy after liver transplantation for HCC outside of a controlled clinical trial.	NA	Weak
36. HCC recurrence after liver transplantation may be treated by surgery for resectable lesions or by locoregional therapy or systemic therapy (including sorafenib) for unresectable lesions.	4 (p)	Weak
37. Liver retransplantation is not appropriate treatment for recurrent HCC.	NA	Strong

Level of evidence for each recommendation refers to the Oxford classification.
HCC: hepatocellular carcinoma; BCLC: Barcelona Clinic Liver Cancer; TNM: tumor, node, metastasis; P: prognosis; D: diagnosis; AASLD: American Association for the Study of Liver Diseases; NA: not applicable; OLT: orthotopic liver transplantation; UNOS: United Network for Organ Sharing; LDLT: living donor liver transplantation; DDLT: deceased donor liver transplantation; mTOR: mammalian target of rapamycin.

Hepatocellular carcinoma in HBV-related cirrhosis



Cumulative probability of developing hepatocellular carcinoma in patients with compensated cirrhosis related to hepatitis B virus (HBV) infection.

Data from: Fattovich G, Giustina G, Schalm SW, et al. Hepatology 1995; 21:77.

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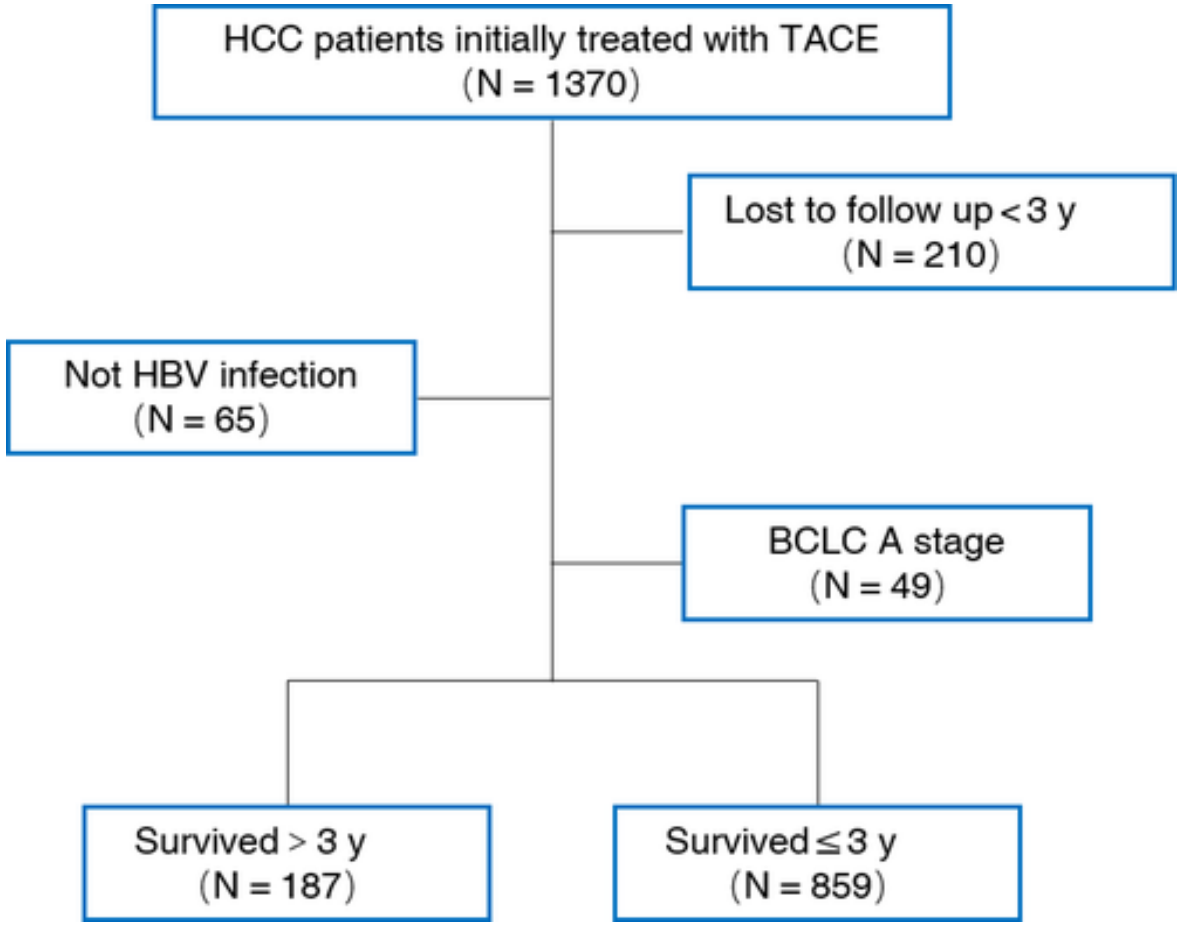
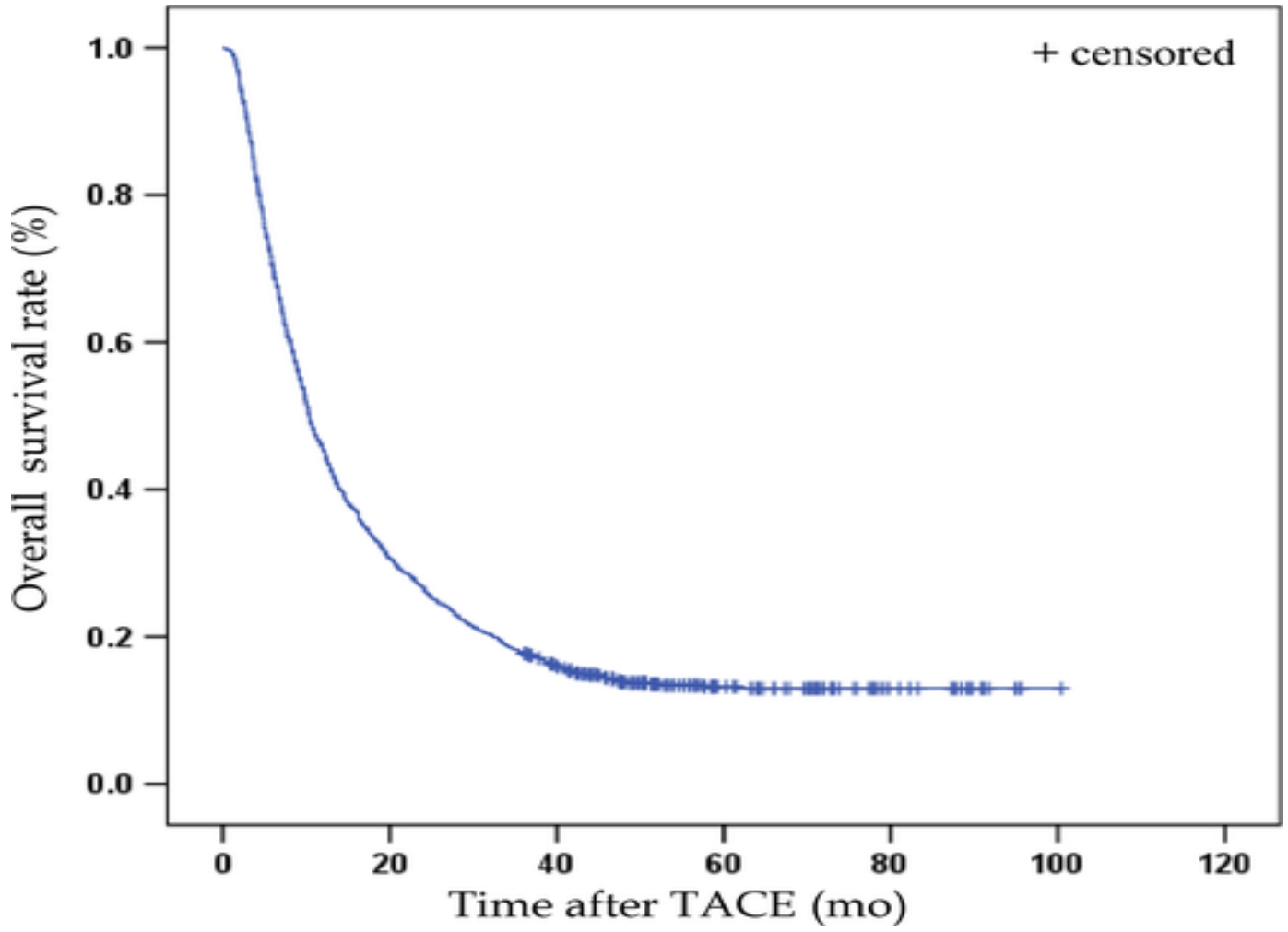
Localized Therapy: HCC

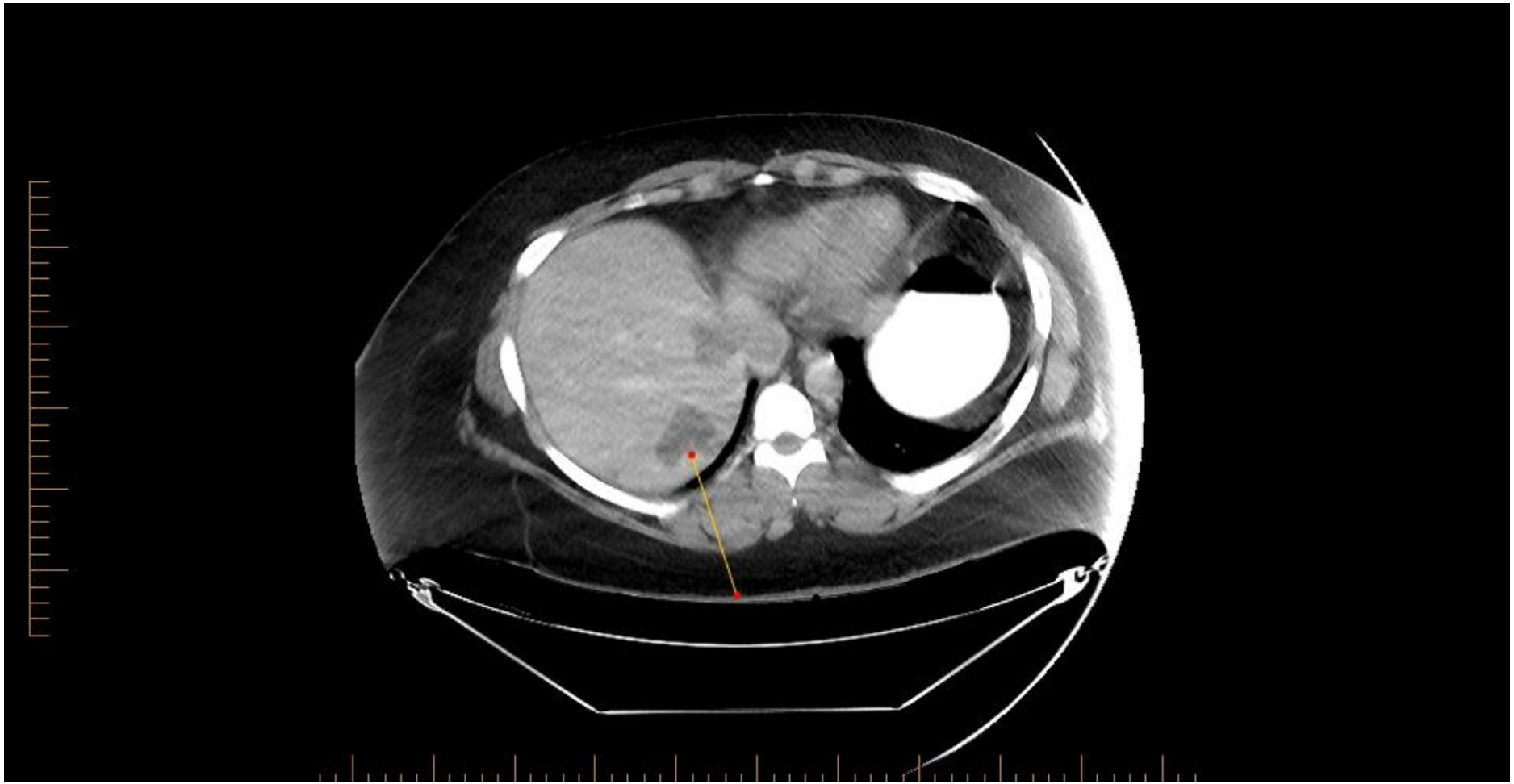
- Radiofrequency Ablation (RFA)
- Radioembolization
- TACE
- TARE
- Cryoablation
- Embolization
- Percutaneous ethanol or acetic acid
- Combination Therapy

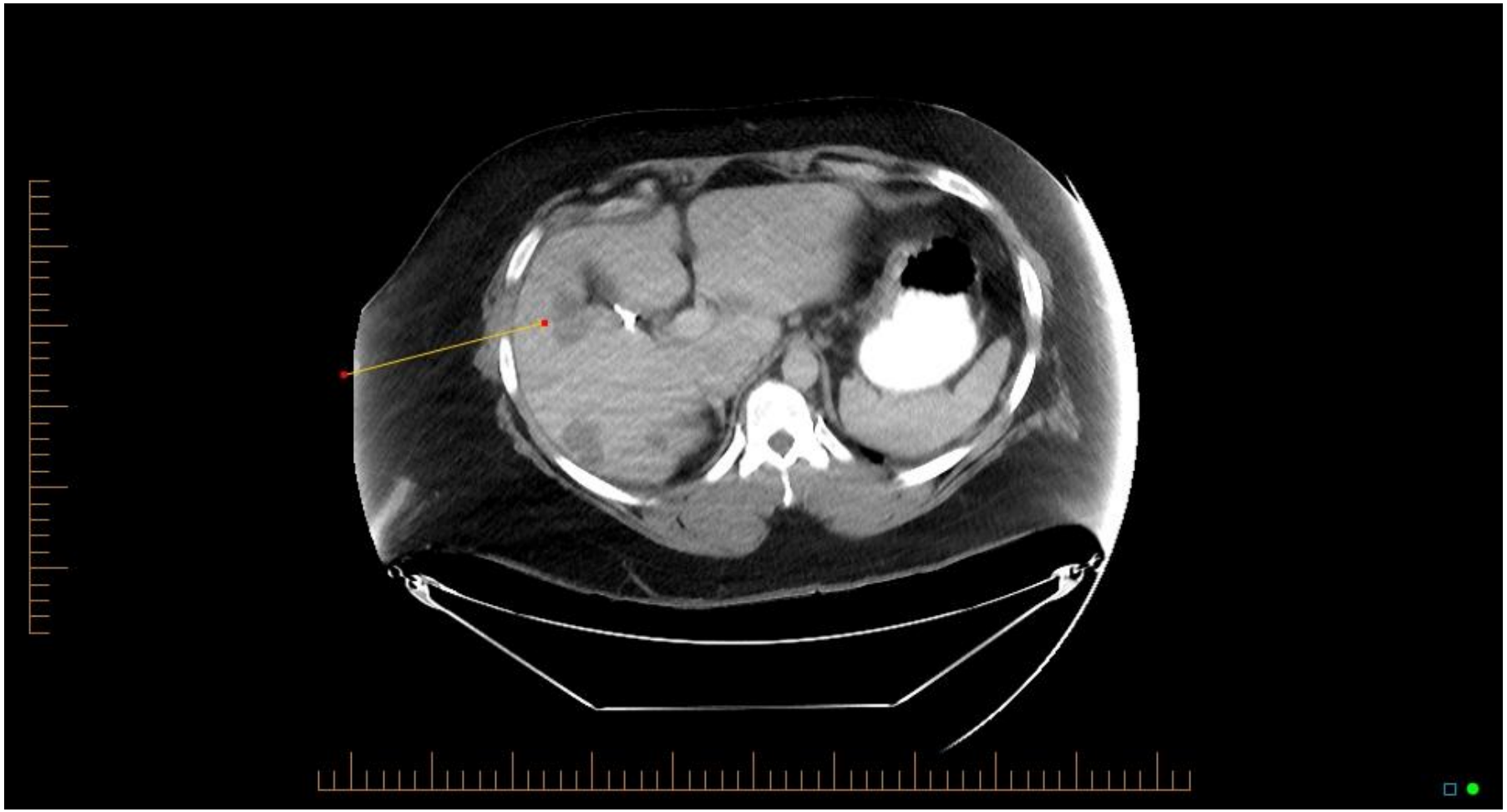
TACE treatment for HCC: Survival



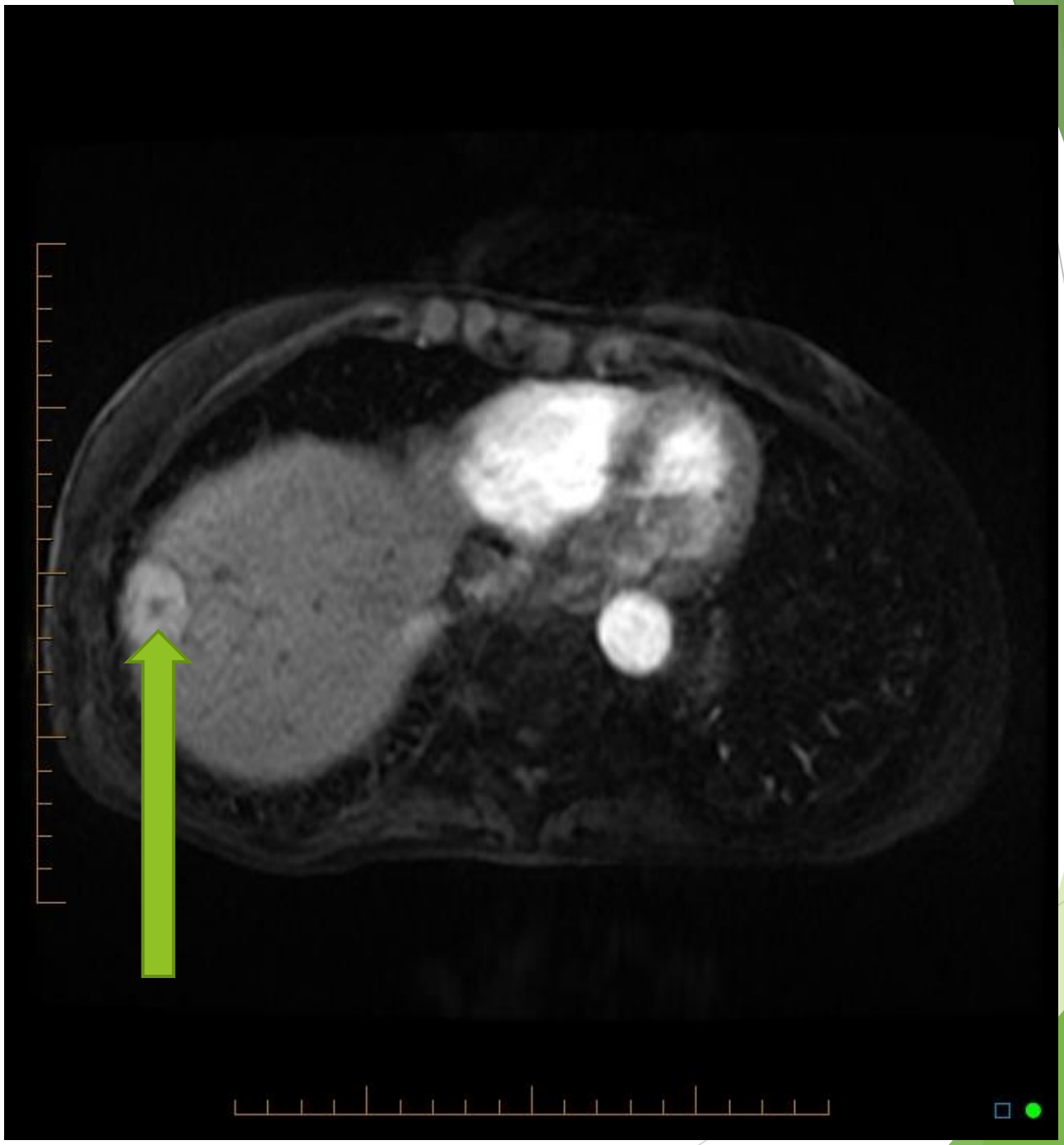
TACE: Overall Survival



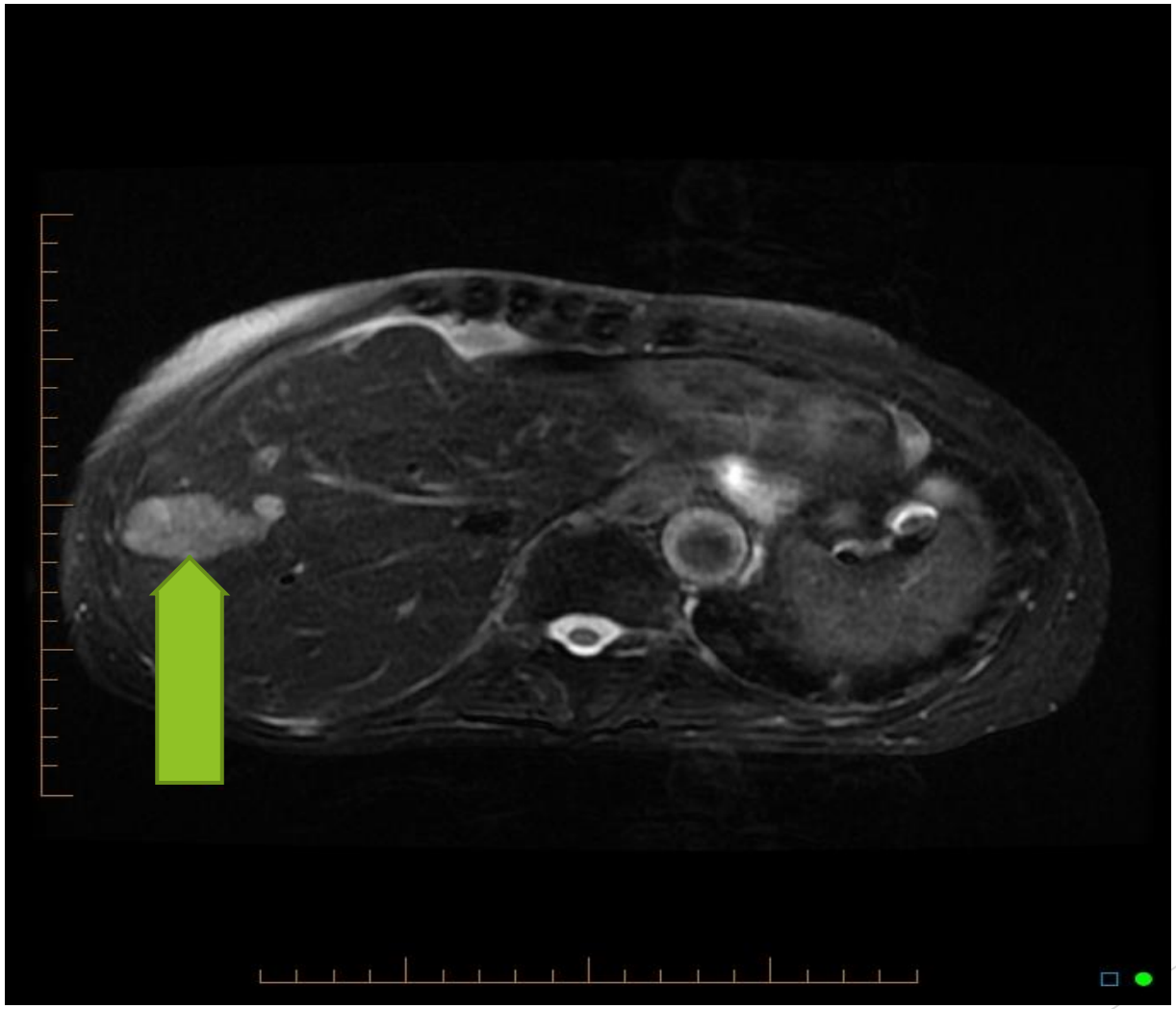




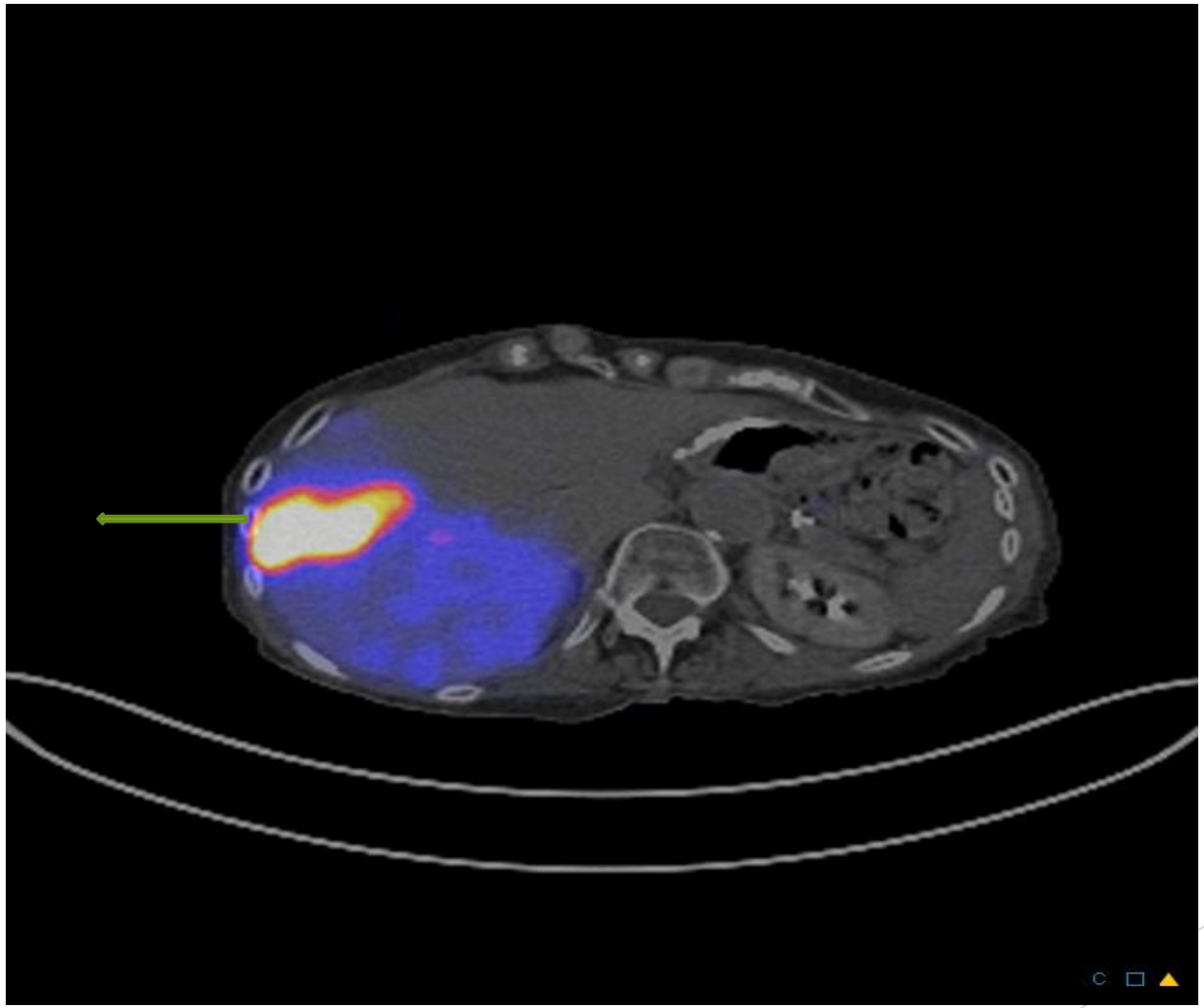
HCC on CT: Pre treatment

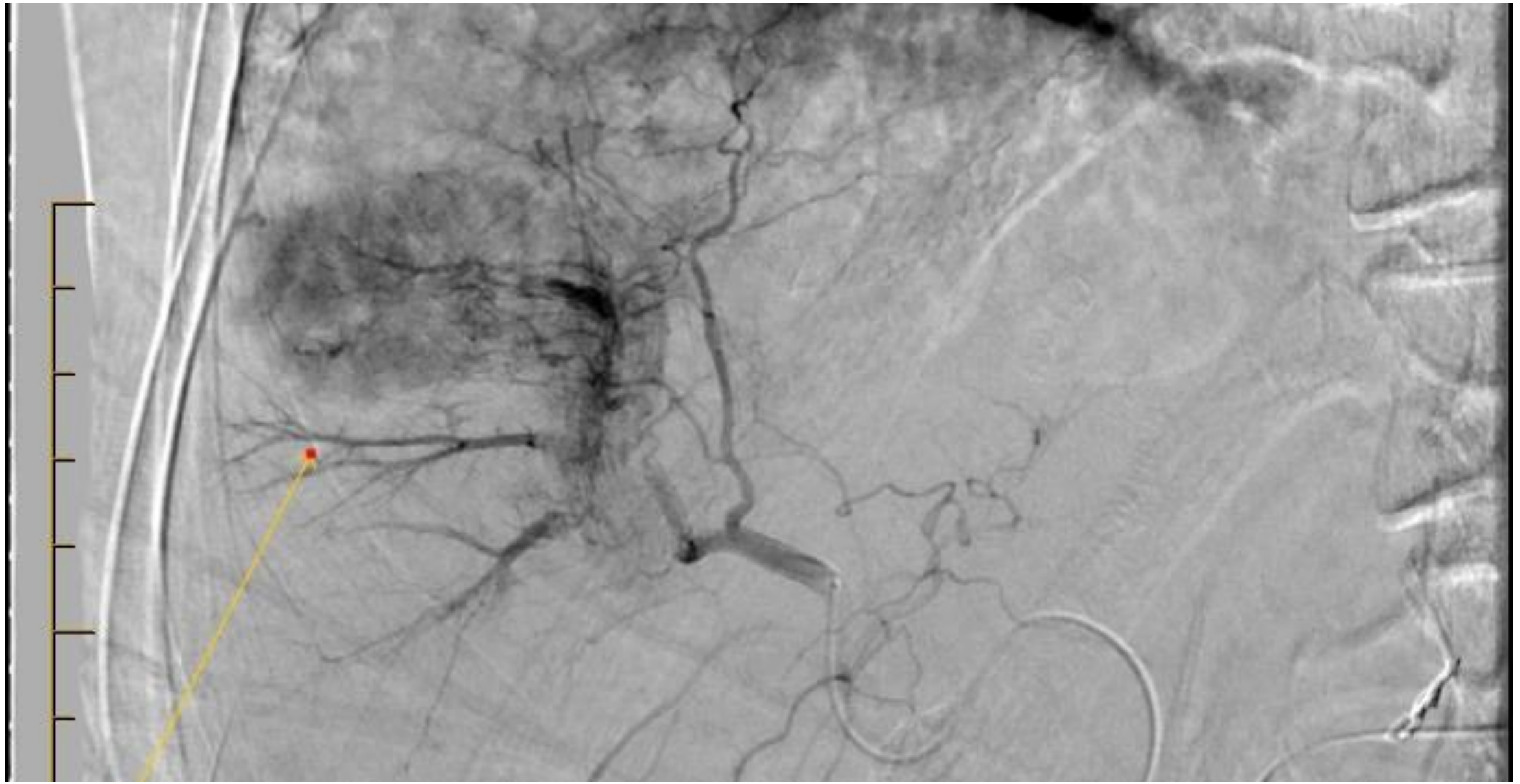


HCC on MRI: Pre-treatment

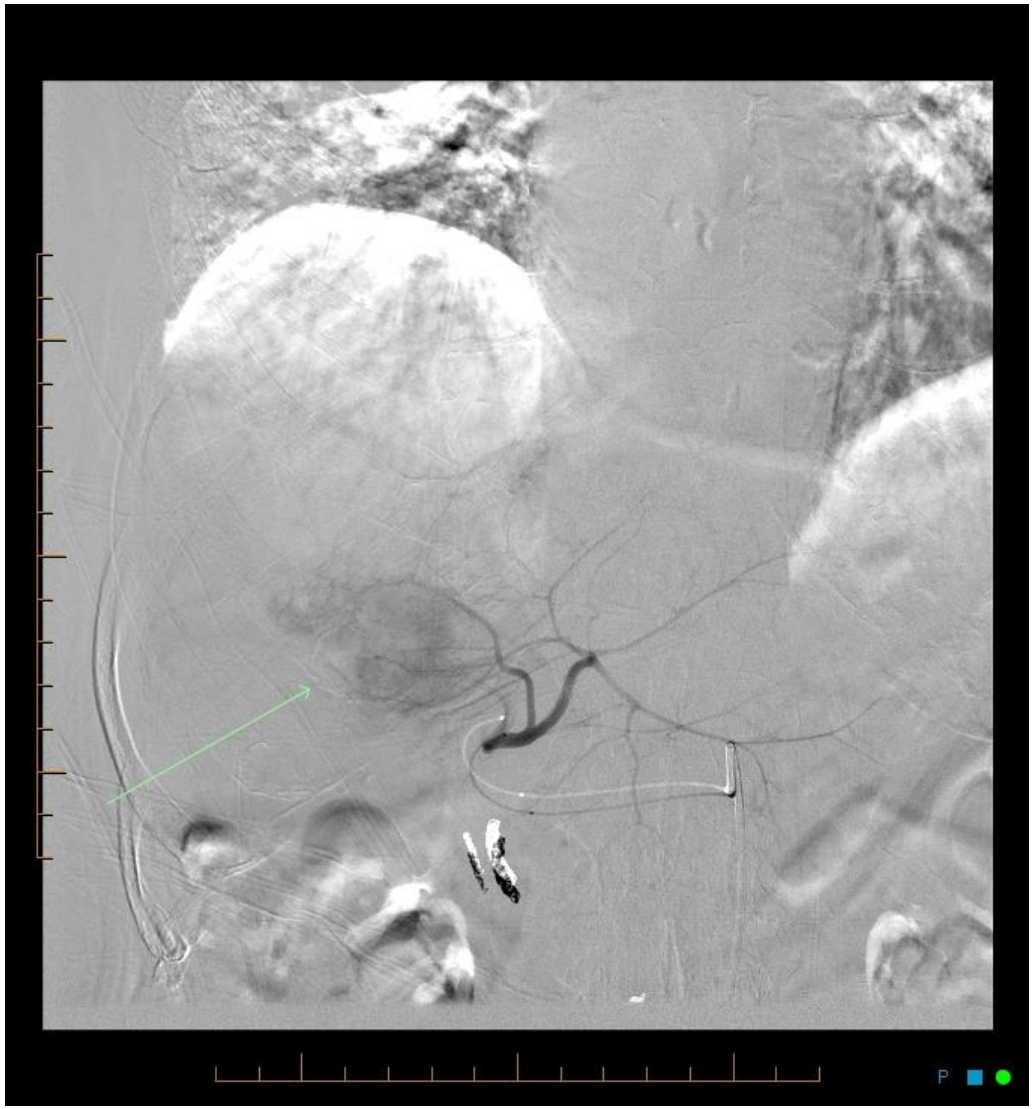


HCC: PET pre treatment

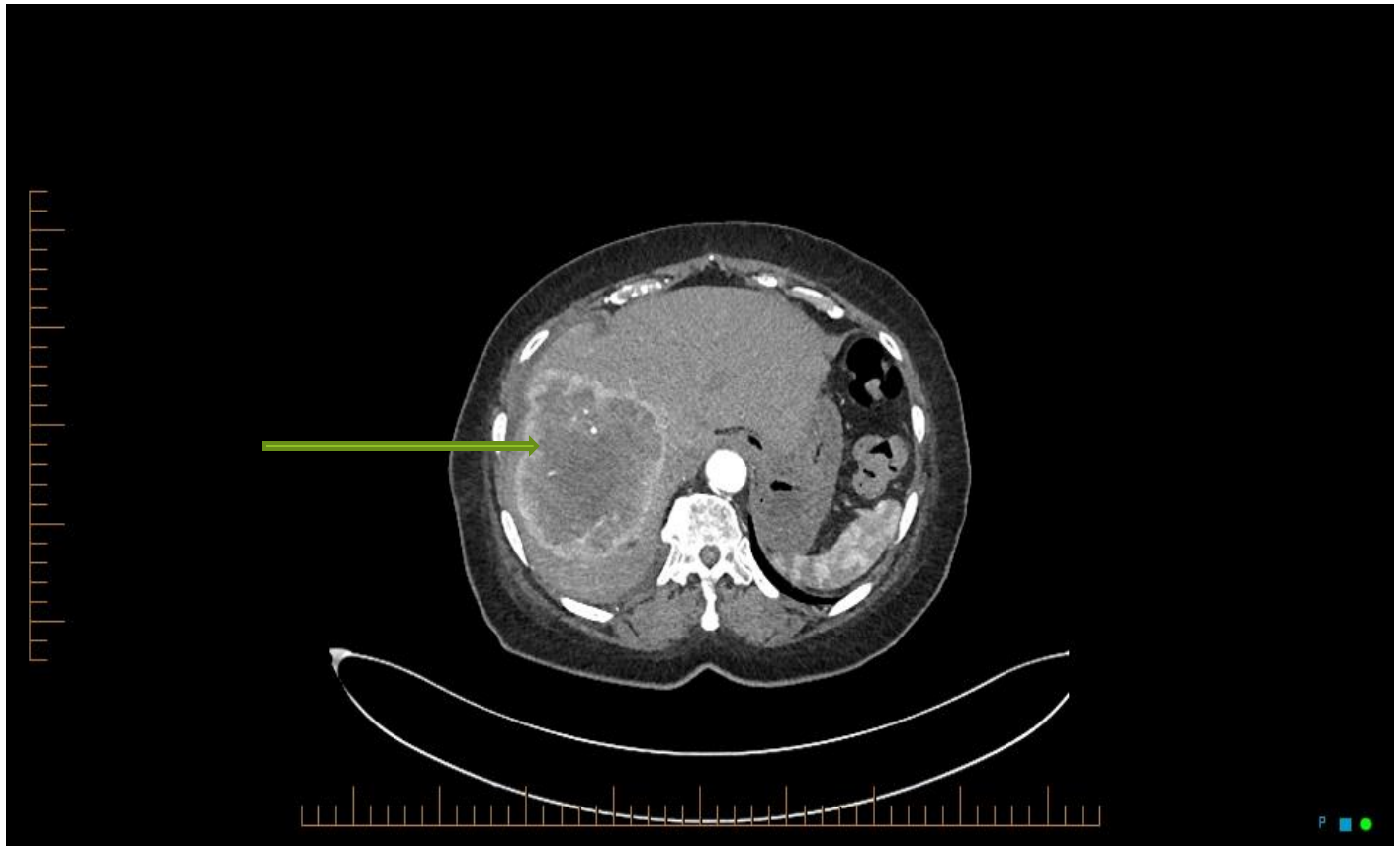




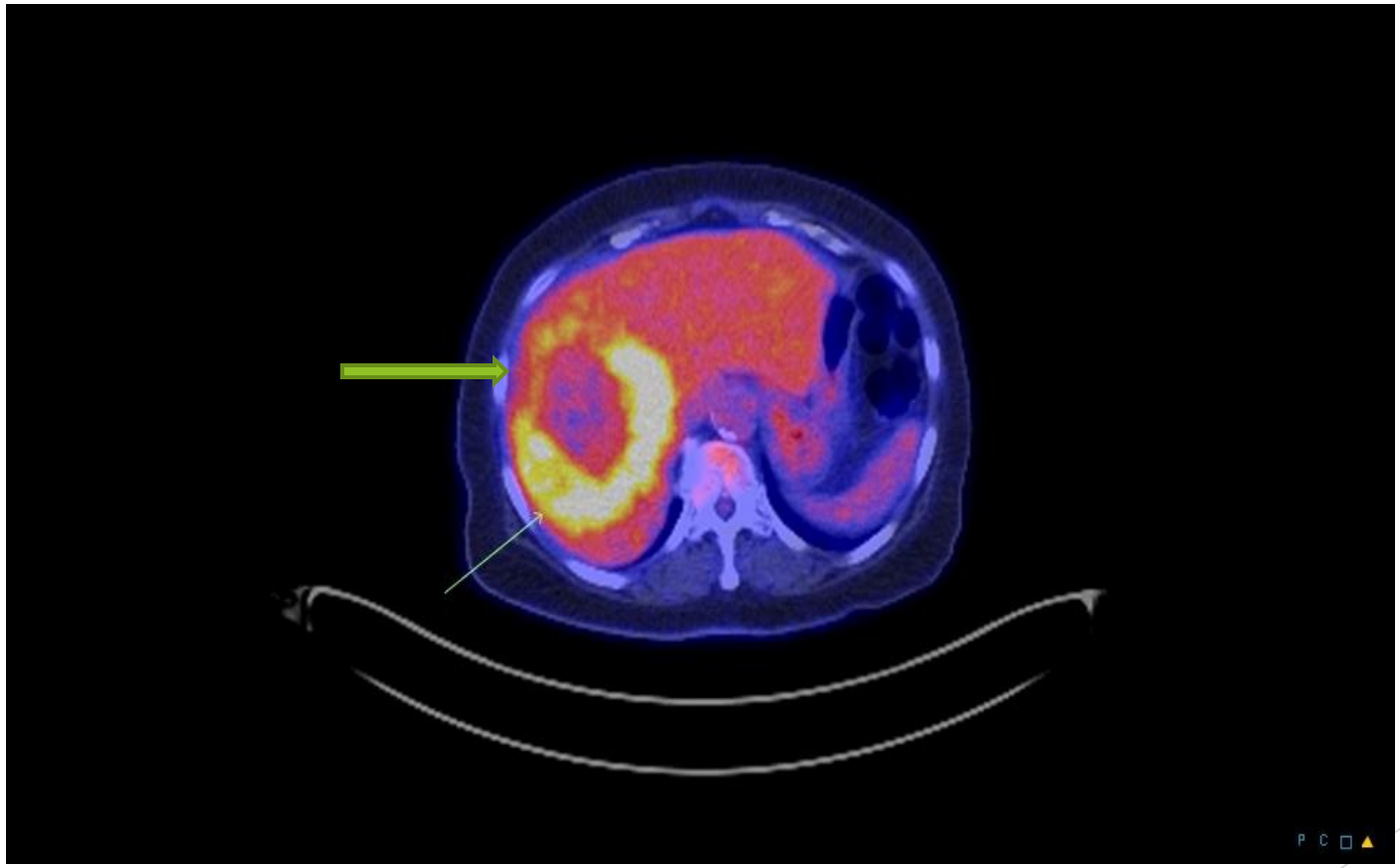
Y-90 Therapy:



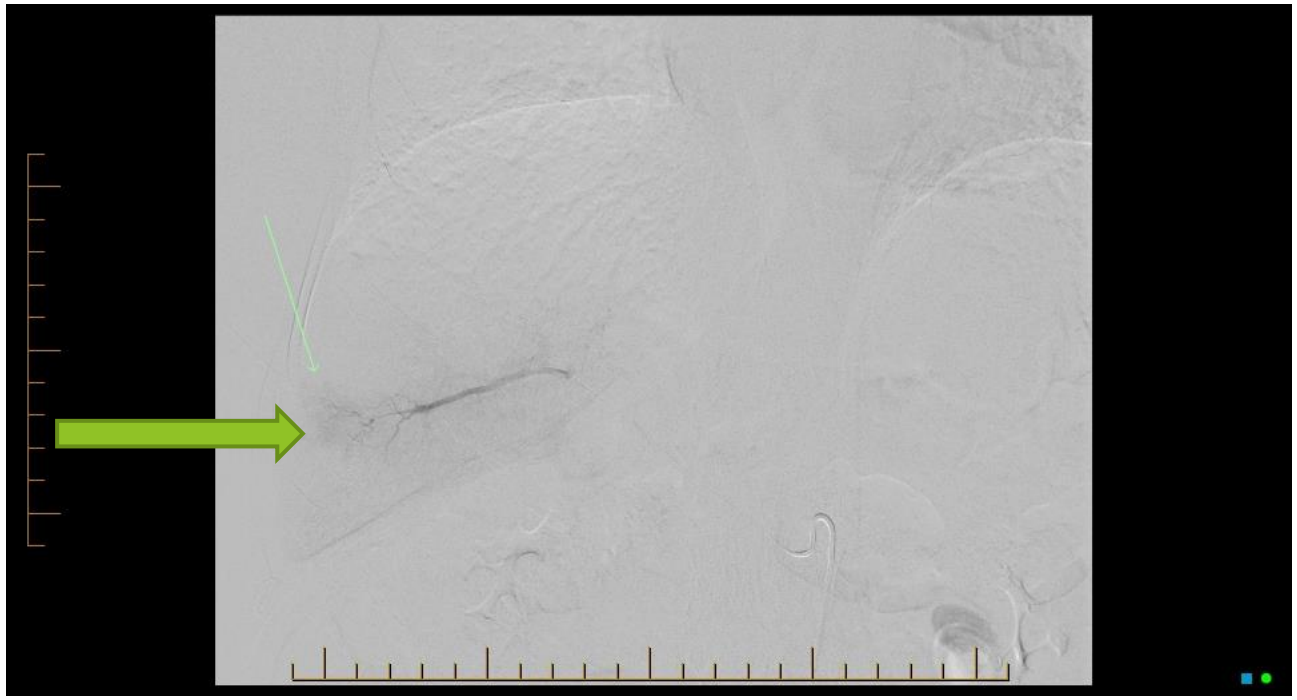
Y-90 :*Pre treatment*



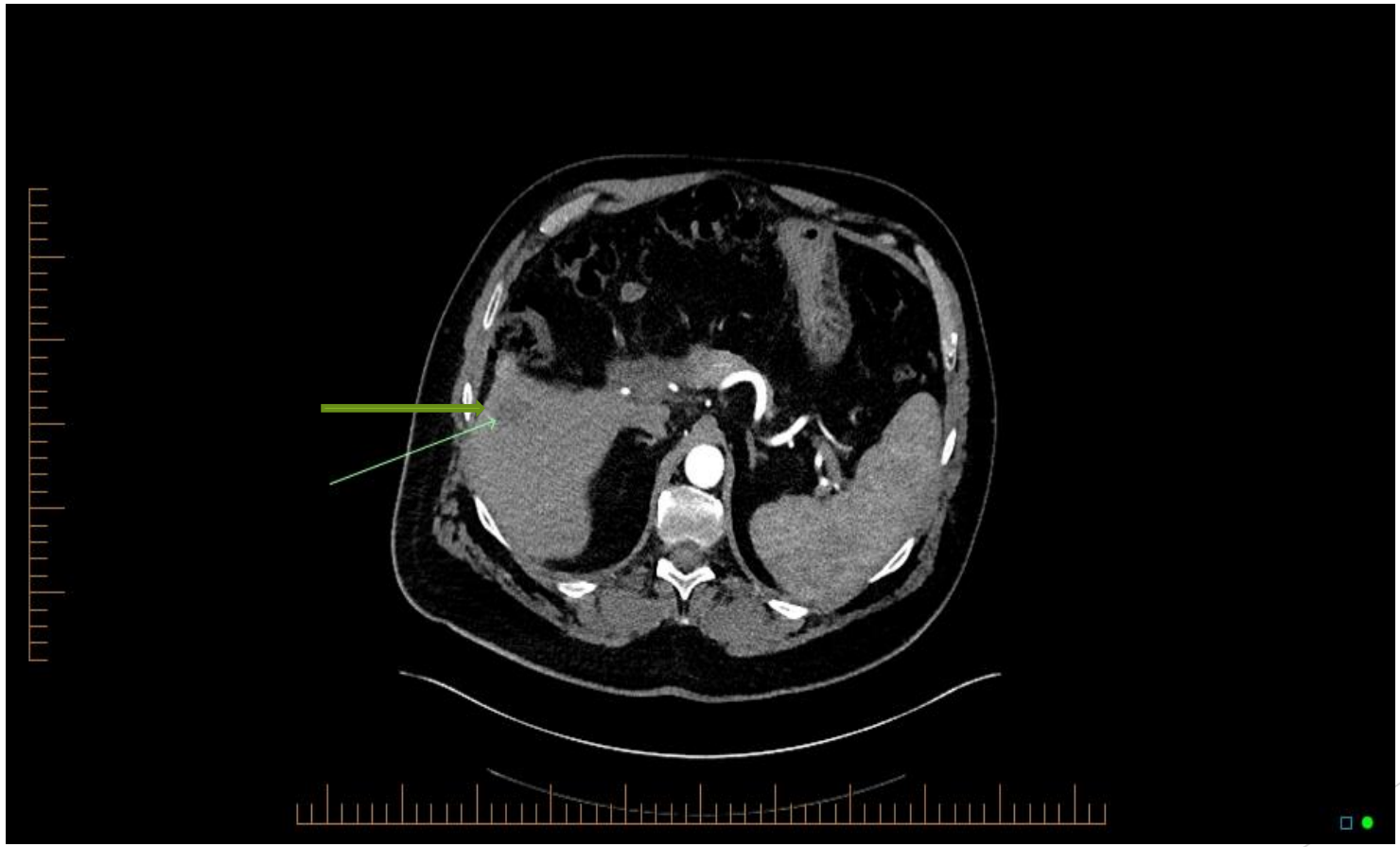
Y-90 pre treatment: ***PET scan***



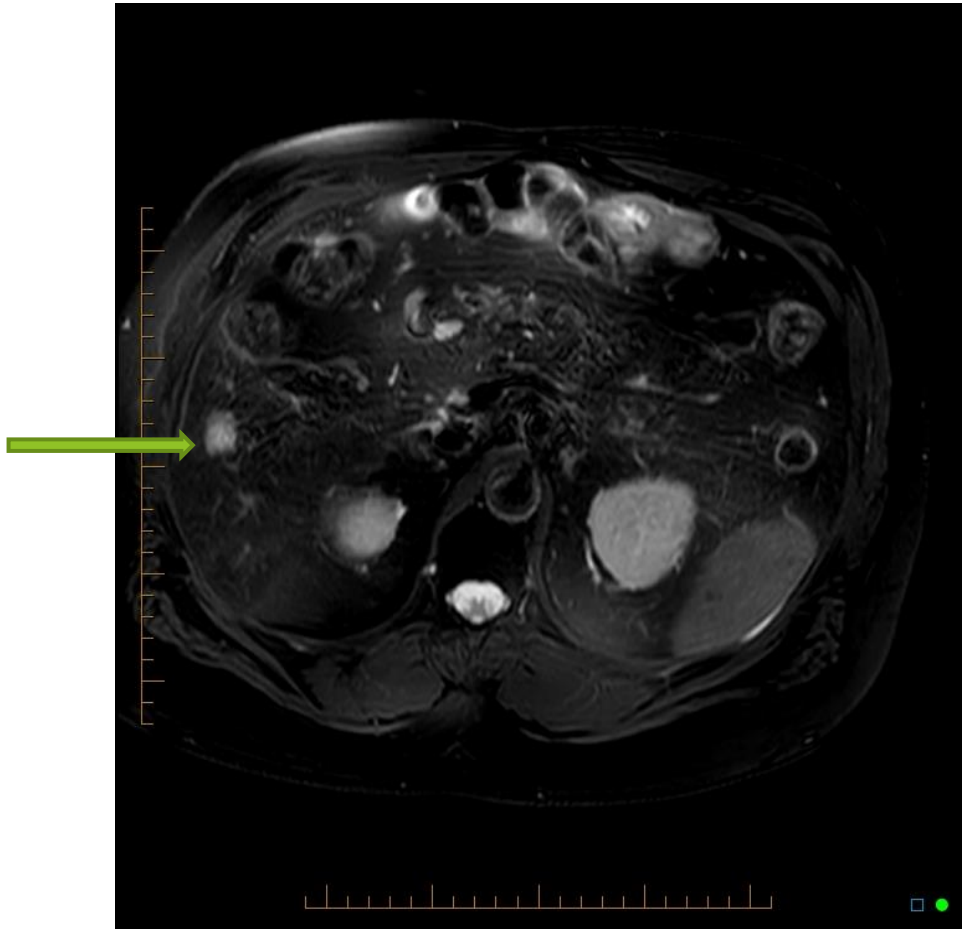
Combination Therapy: Y-90 and Microwave Techniques



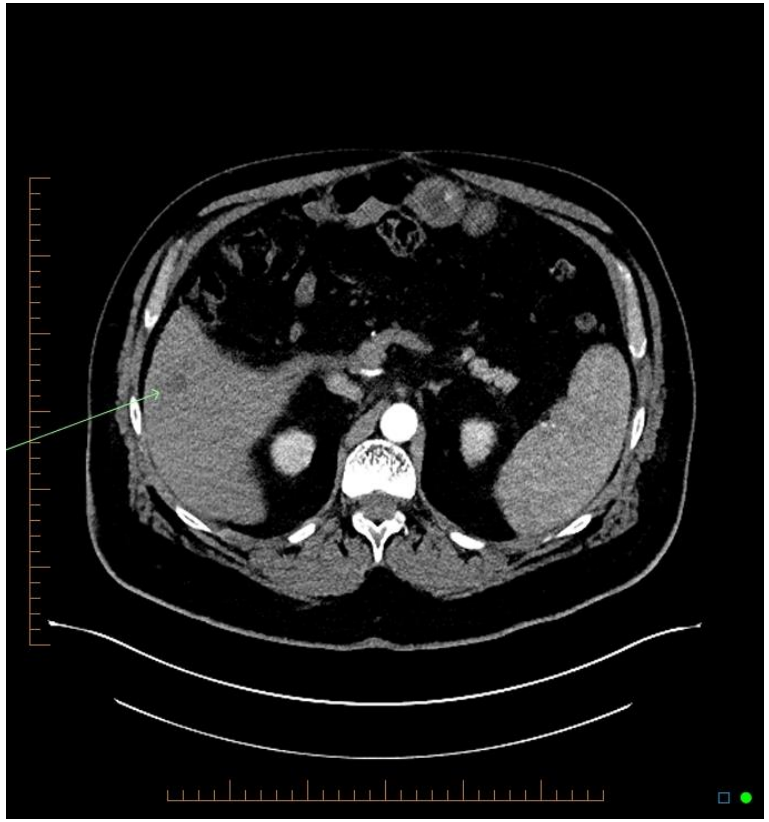
Combo Therapy: Y-90 and Microwave CT ***Pre Treatment***



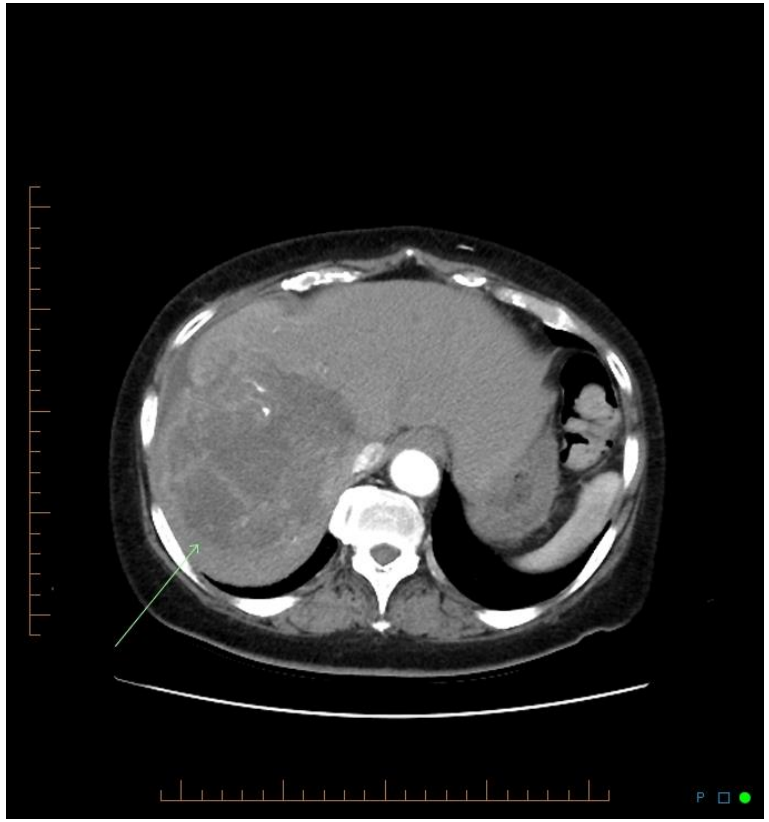
Combo Therapy: Y-90 and Microwave MRI ***Pre Treatment***



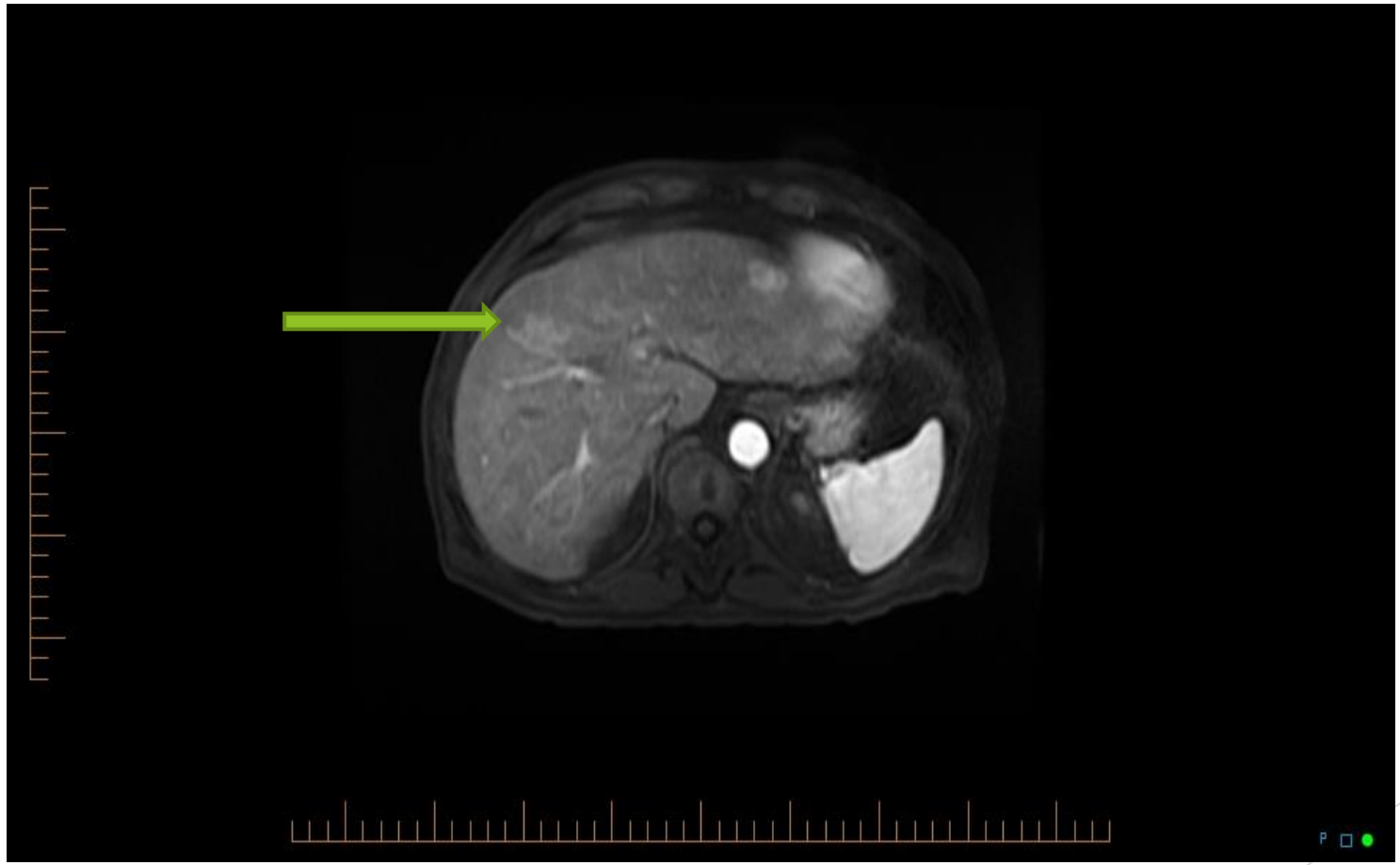
Combo Therapy: Y-90 and Microwave CT *Post treatment*



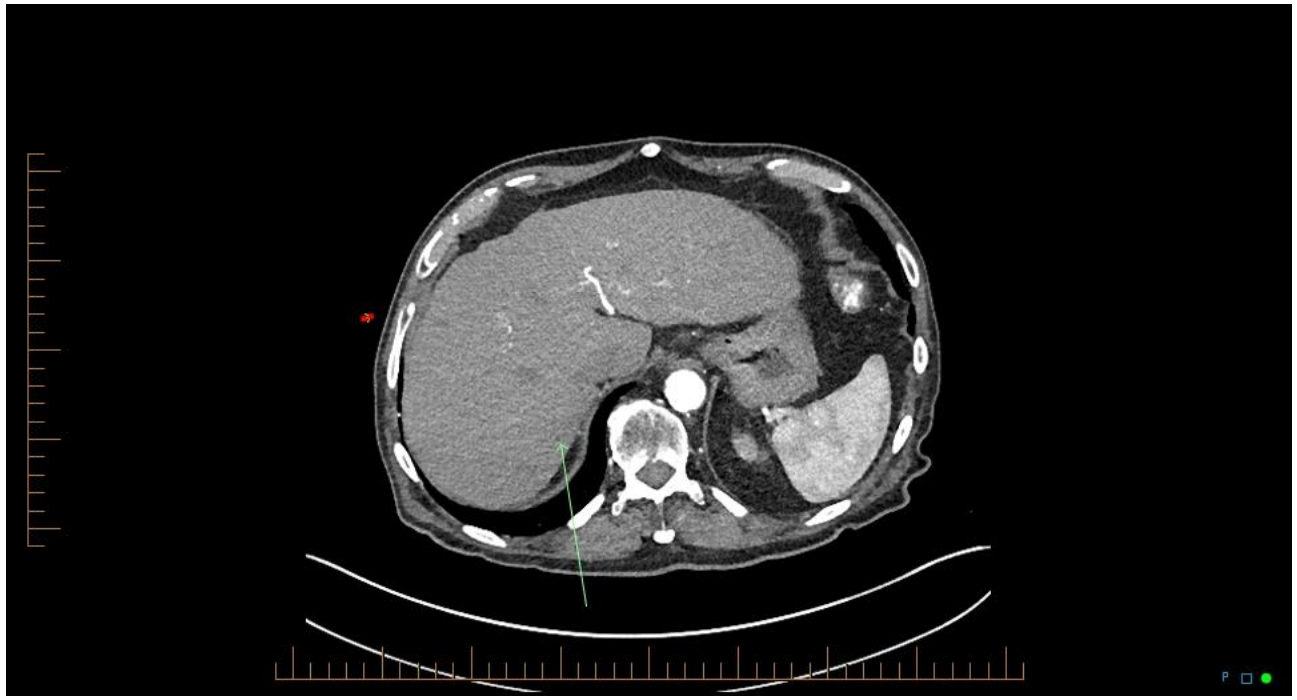
Y-90 Post Treatment: CT



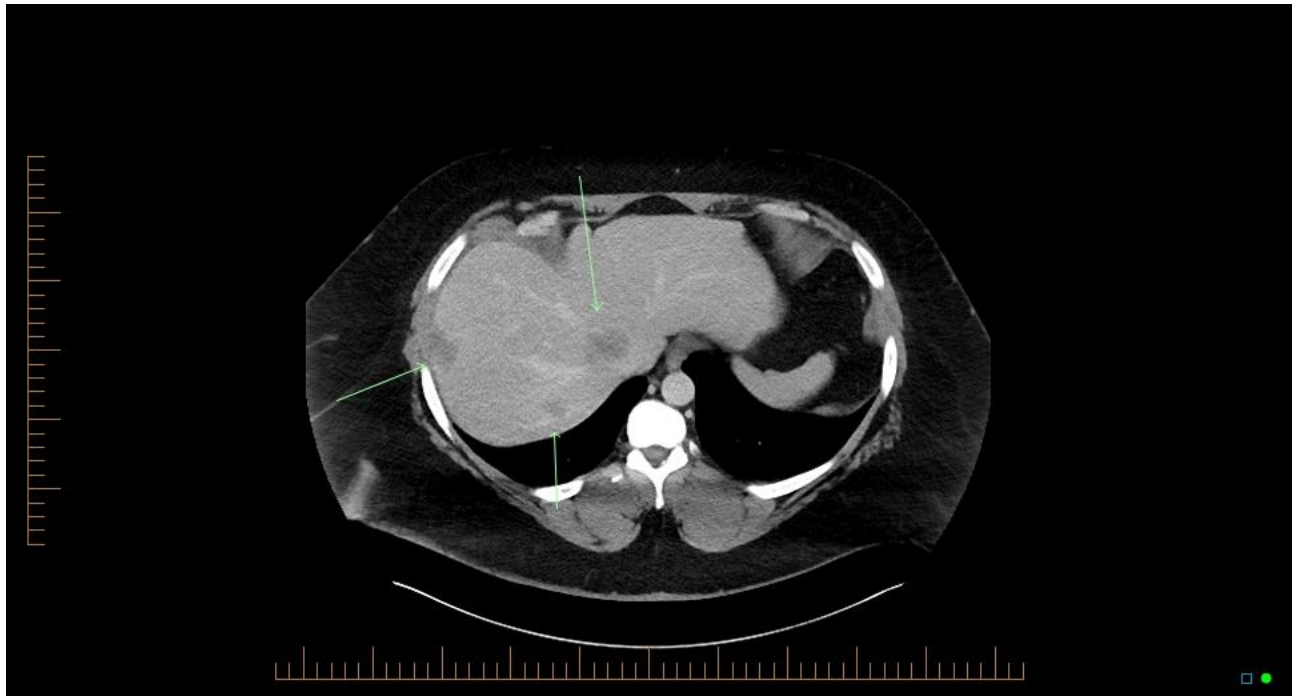
Pre Treatment MRI: HCC



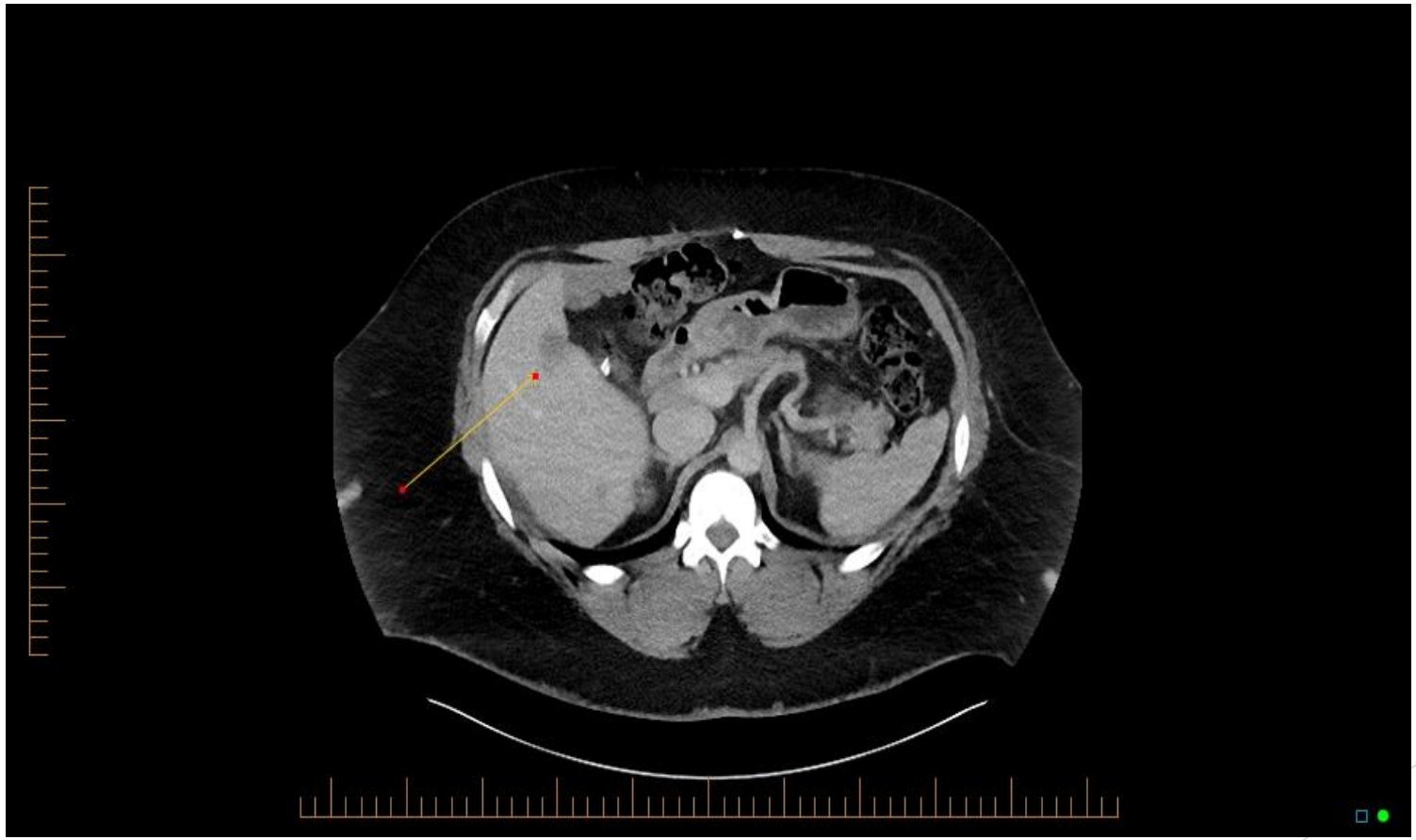
Post Treatment: HCC



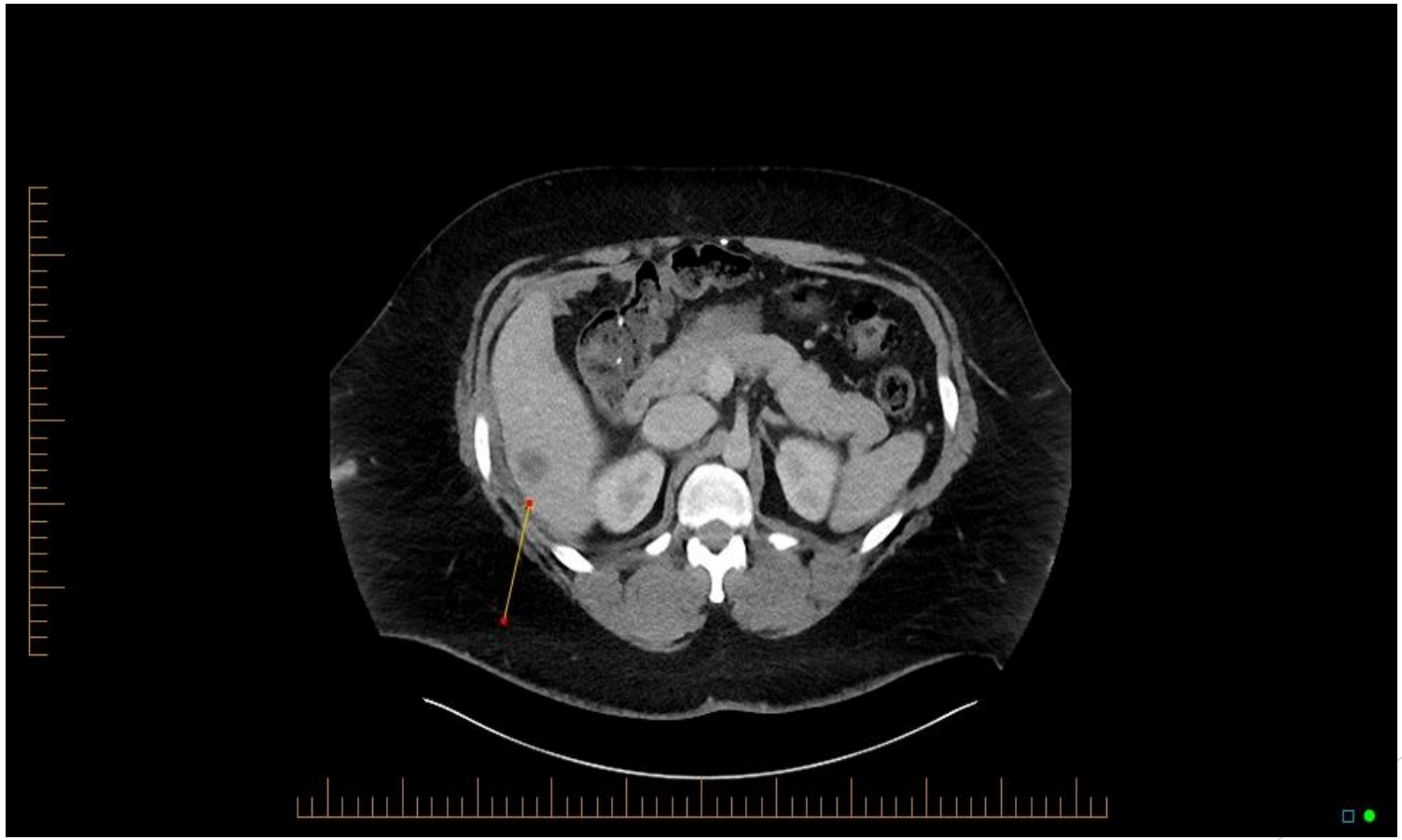
Pt #1: Pre treatment: A



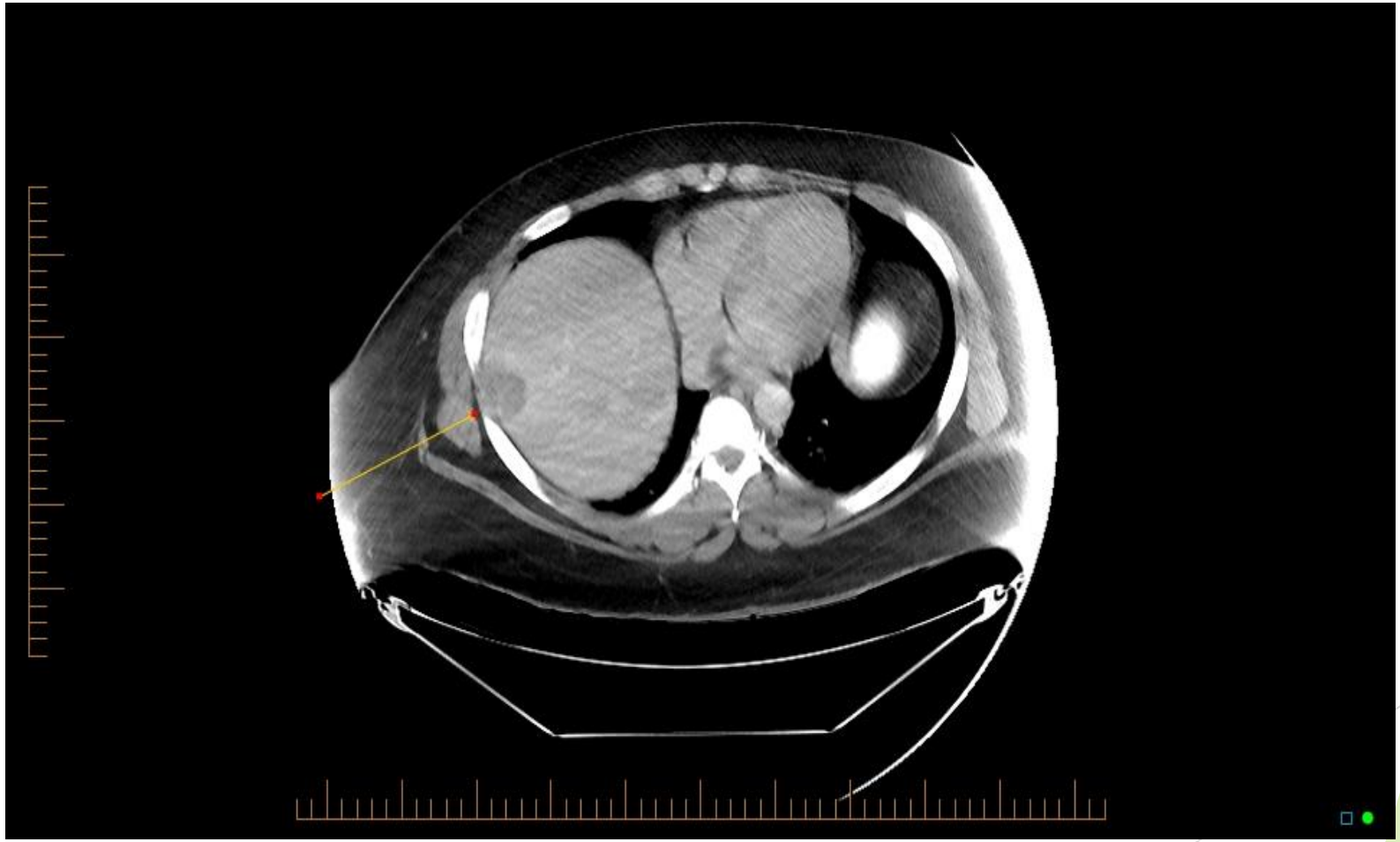
Pt #1: Pre treatment: B



Pt #1: Pre Treatment C



Pt #1: Post treatment; A, B, C



Systemic and Combination Therapy

Types of systemic therapy

Why the need for systemic therapy?

-- microinvasion

--rapid decline

--aggressive disease progression

Stereotactic Body Radiation Therapy

- Advantages of SBRT:
- -- liver is very radiosensitive
- --liver can tolerate 20Gy
- --OPTIMAL: 3D conformal radiation therapy
- --targeted RT

  -- all beams of radiation converge on a single spot

Advanced Therapies:

Immunotherapy

Proton beam irradiation

- Likely candidates: large tumor or portal vein thrombus

Summary and Recommendations:

- HCC is an aggressive tumor that typically occurs in settings of chronic liver disease and cirrhosis
- Algorithms for therapy give various treatment options but may not be applicable in all settings
- Preferred therapy for localized HCC is surgical resection
- Limitations for resection are tumor extent or underlying liver dysfunction
- Liver transplantation is the ONLY other potentially curative option

Summary and Recommendations

- For patients with disease isolated to the liver, there are multiple local nonsurgical methods of liver-directed tumor ablation which all downstaging of lesions.
- TACE, RFA, TARE, ETOH and AA infusion
- Microwave, cryotherapy
- Embolization
- External beam radiation therapy
- Systemic therapy is appropriate for patients with unresectable, non transplantable disease

THANK YOU!!