Hepatocellular Carcinoma:
A major global health problem

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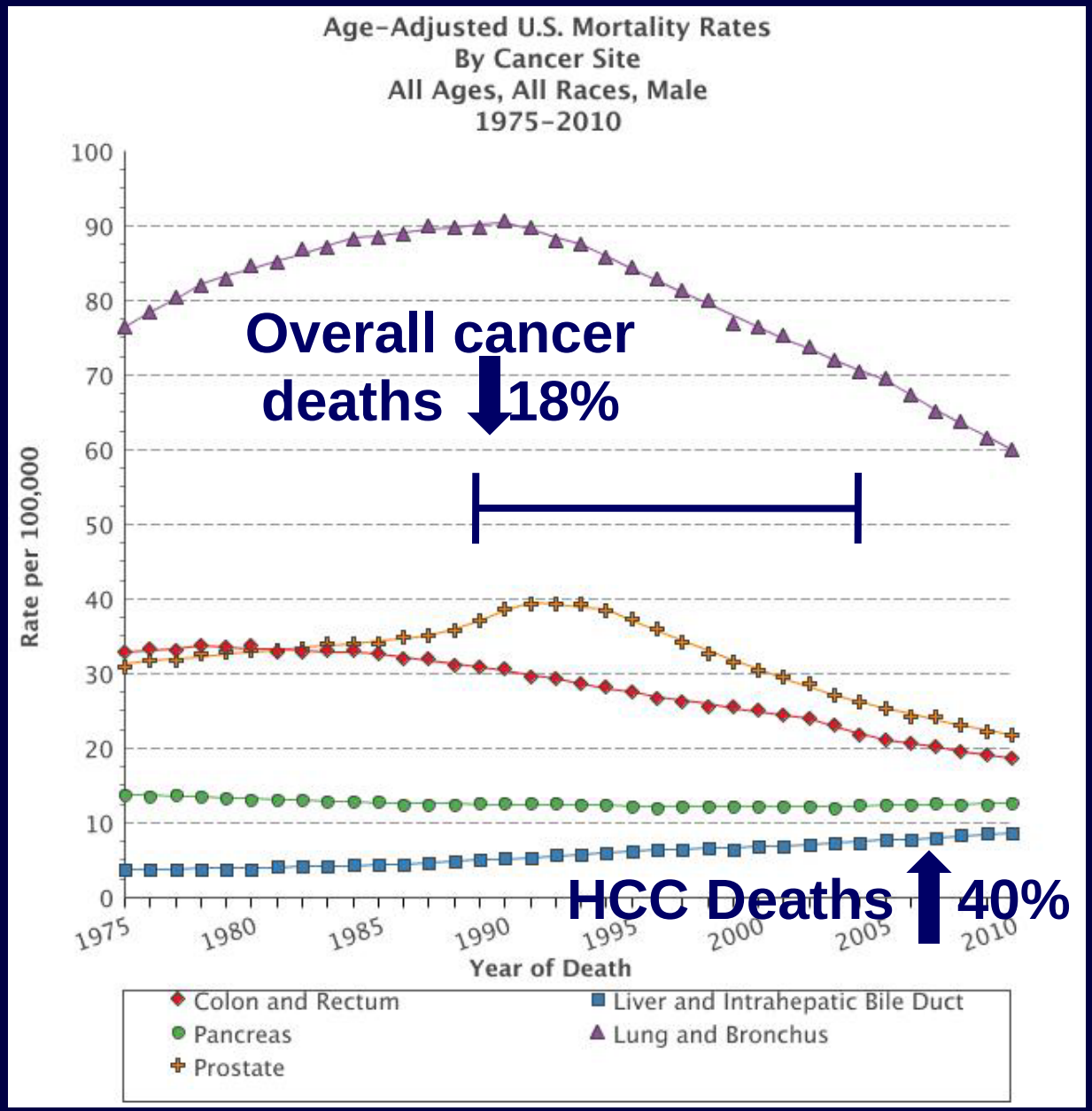
Hepatocellular Carcinoma

WORLDWIDE

The #2 Cancer Killer


Age-Adjusted U.S. Mortality Rates
By Cancer Site
All Ages, All Races, Male
1975-2010
Rate per 100,000
100
90
80
70
60
50
40
30
20
10
0
1975
1980
1985
1990
1995
2000
2005
2010
Year of Death
Overall cancer deaths ↓18%
HCC Deaths ↑ 40%
Colon and Rectum
Liver and Intrahepatic Bile Duct
Pancreas
Lung and Bronchus
Prostate

Hepatocellular Carcinoma

HEPATITIS C VIRUS

Hepatocellular Carcinoma

Geographic area	AAIR M/F	Risk factors HCV (%)	Risk factors HBV (%)	Alcohol (%)	Others (%)
Europe	6.7/2.3	60-70	10-15	20	10
Southern	10.5/3.3				
Northern	4.1/1.8				
North America	6.8/2.3	50-60	20	20	10 (NASH)
Asia and Africa		20	70	10	10 (Aflatoxin)
Asia	21.6/8.2				
China	23/9.6				
Japan	20.5/7.8	70	10-20	10	10
Africa	1.6/5.3				
WORLD	16/6	31	54	15	

*Updated from Llovet *et al.* [99], according to IARC data [4]. AAIR, age-adjusted incidence rate.

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Hepatocellular Carcinoma

Clinical Practice Guidelines

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma

European Association for the Study of the Liver*,
European Organisation for Research and Treatment of Cancer

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Surveillance

High risk groups must undergo surveillance imaging

1.	Cirrhotic patients, Child-Pugh stage A and B*
2.	Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation**
3.	Non-cirrhotic HBV carriers with active hepatitis or family history of HCC***
4.	Non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis F3****

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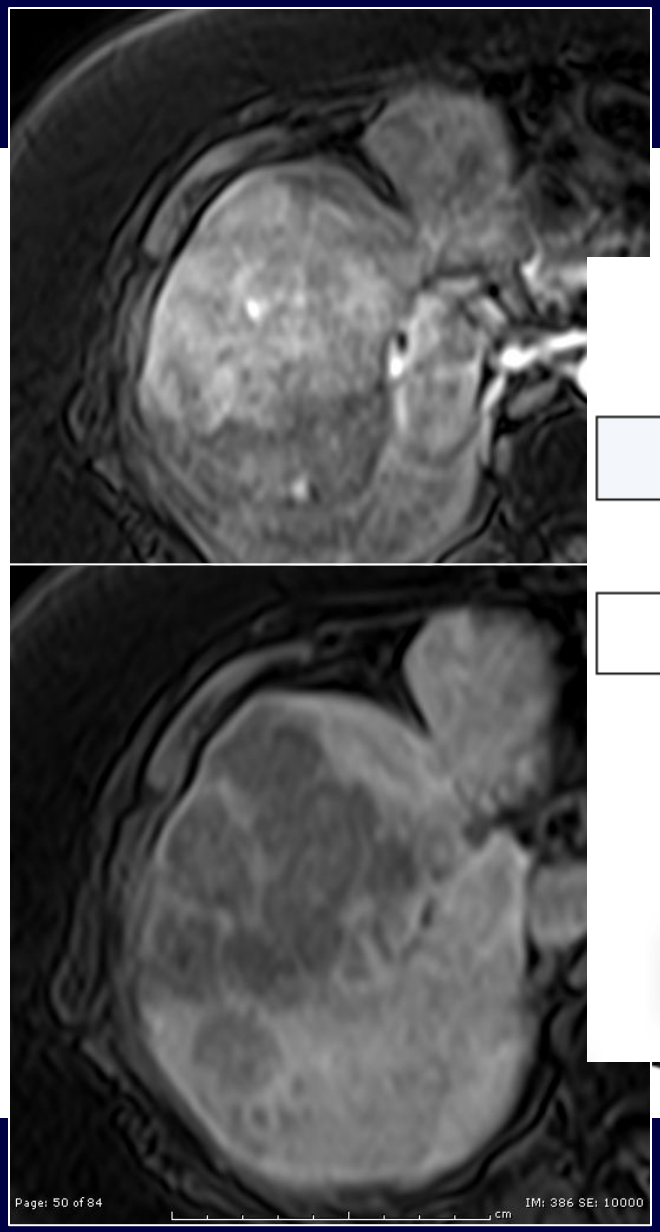
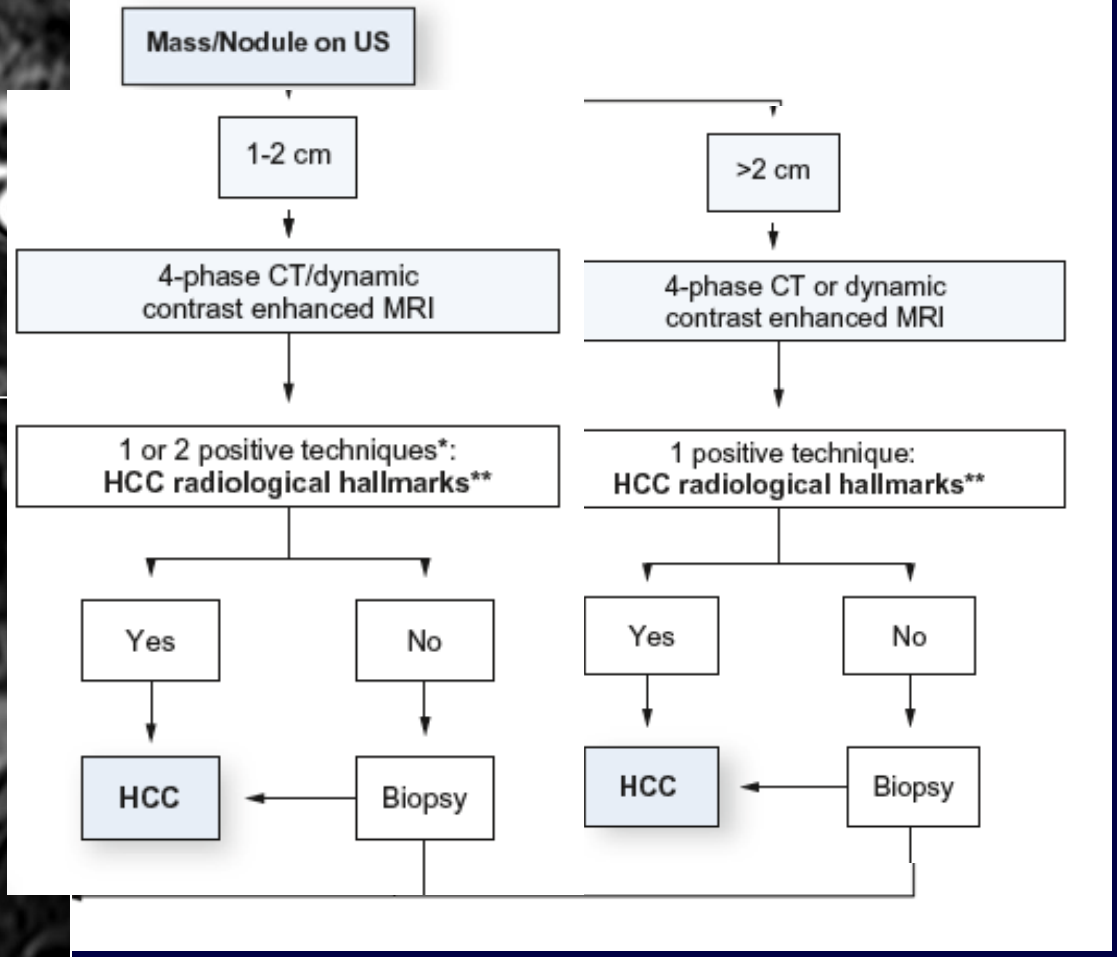
Surveillance

Ultrasound every 6 months

Multiphasic CT or MRI

Diagnosis





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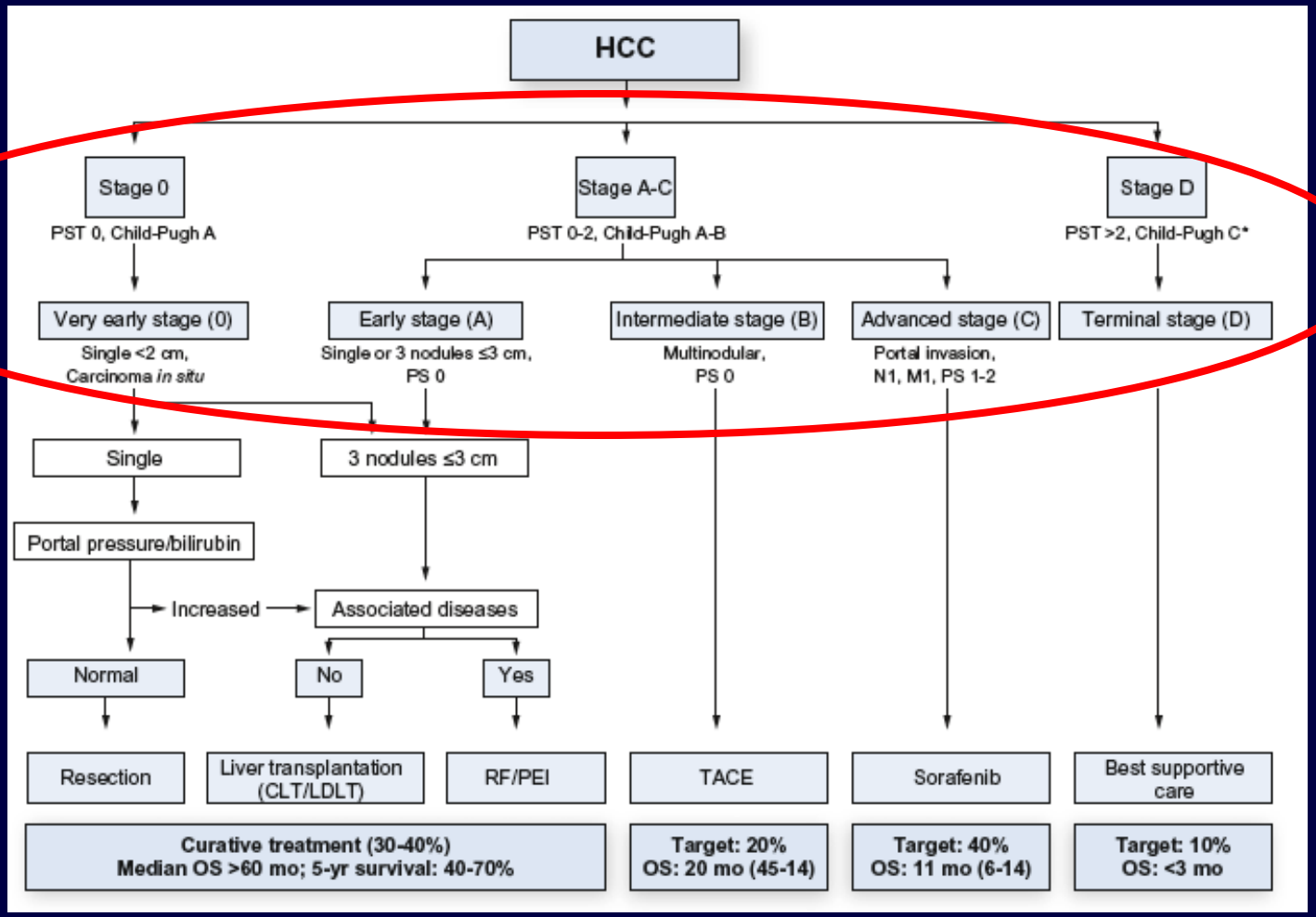
Barcelona-Clinic Liver Cancer (BCLC)



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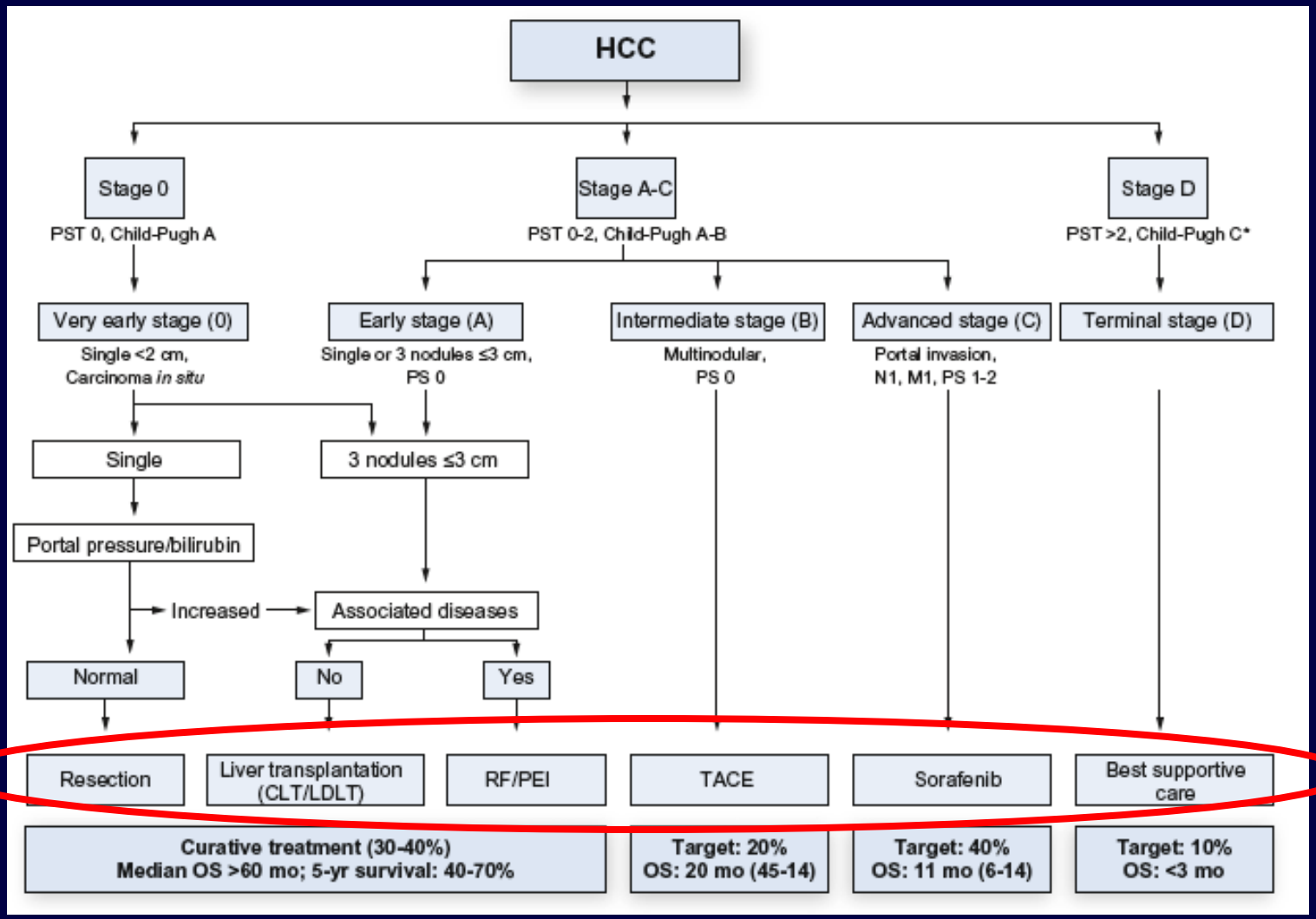
Barcelona-Clinic Liver Cancer (BCLC) Staging

0 Very Early	A Early	B Intermed	C Advanced	D Terminal
Single <2cm	Single 3 ≤ 3cm	Multifocal	Invasion Mets Symptoms	Child C ECOG 3,4

Barcelona-Clinic Liver Cancer (BCLC)



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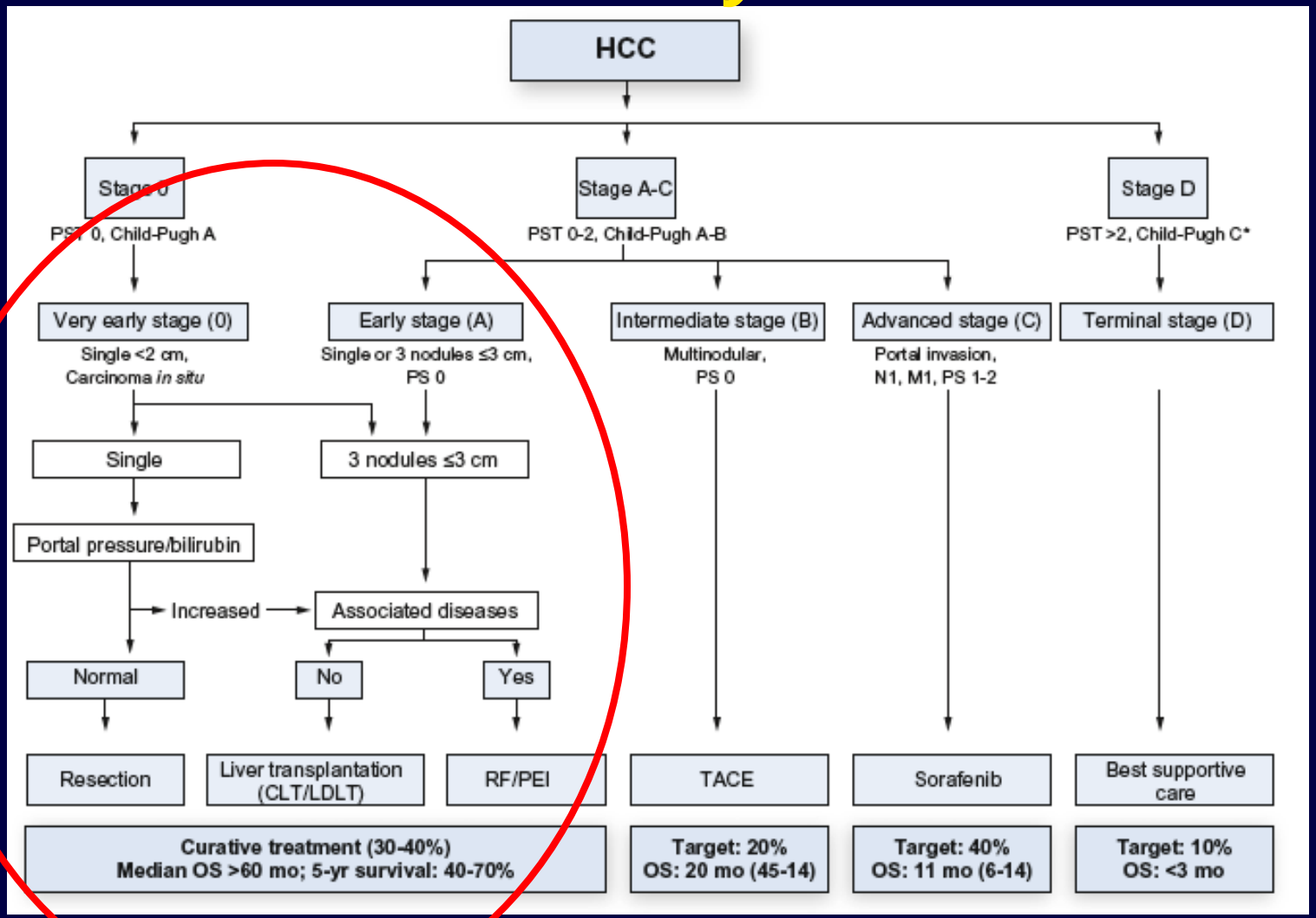
Early



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Early

RESECTION

Solitary Tumors
Very Well Preserved Liver Function

Early

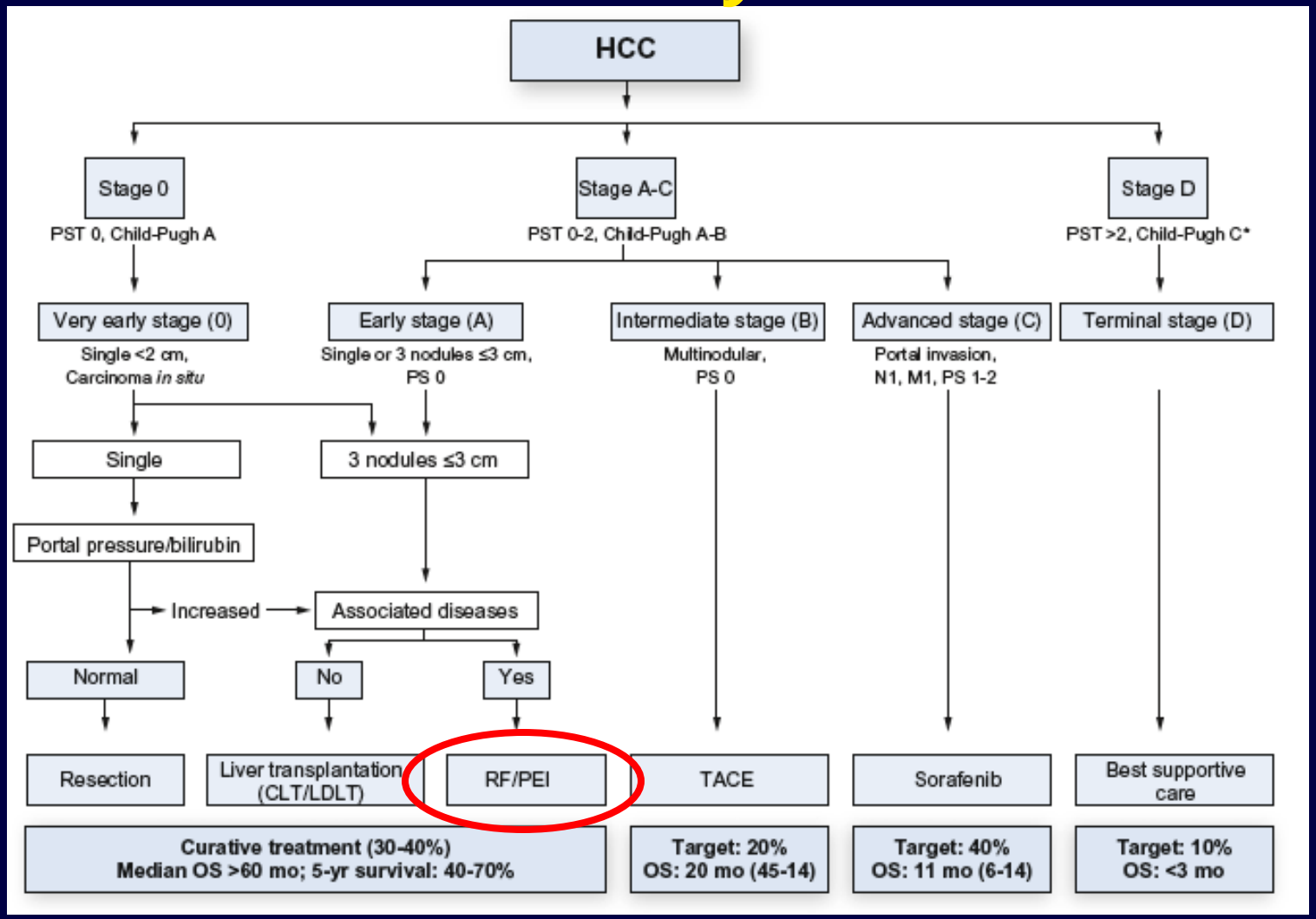
LIVER TRANSPLANTATION

Solitary Tumors ≤ 5 cm

≤3 Nodules ≤ 3 cm

Advanced Liver Dysfunction

Early



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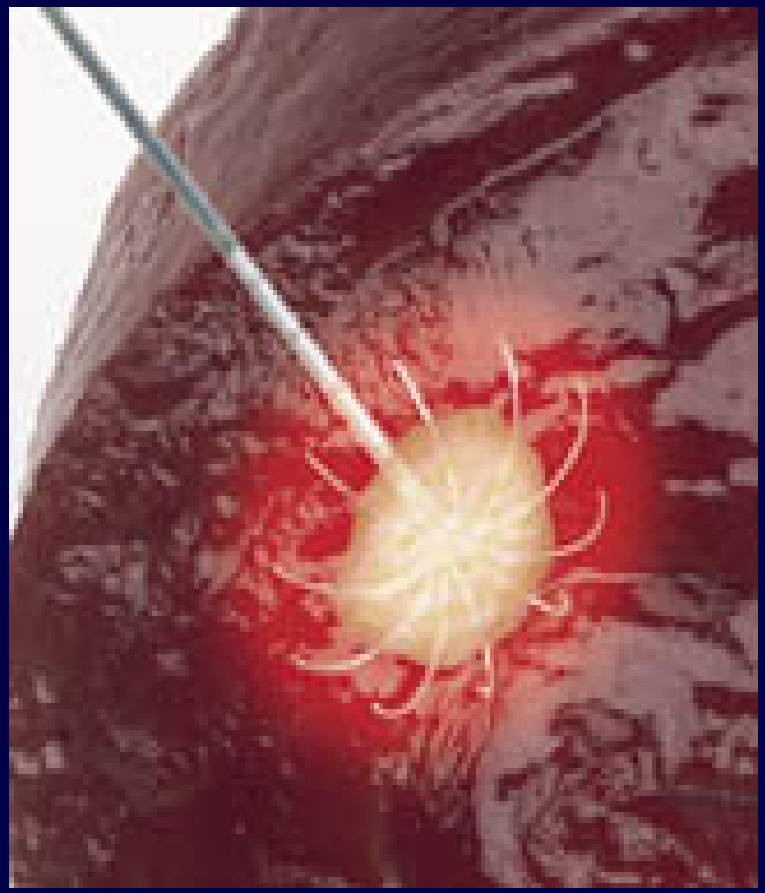
Early

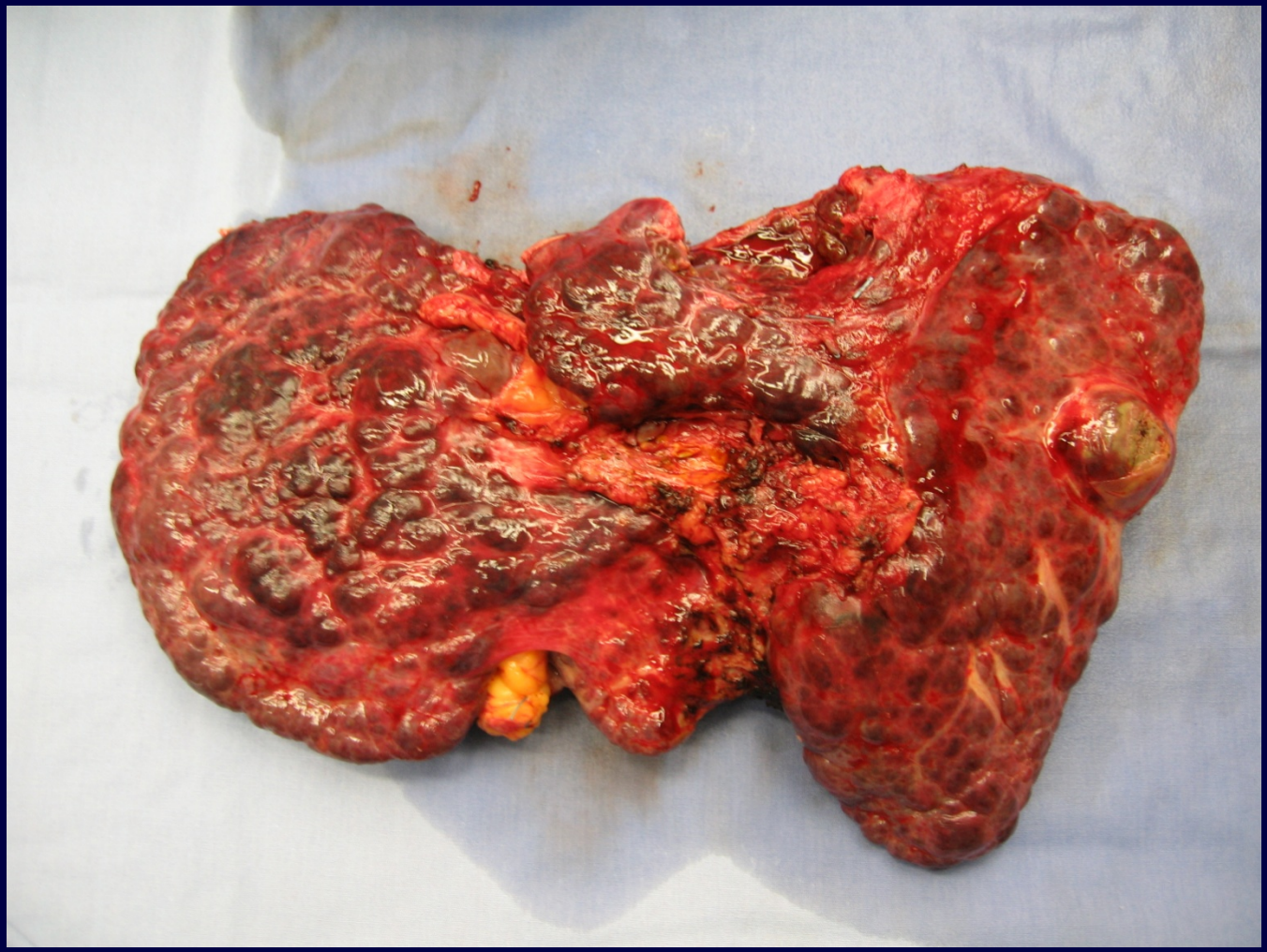
RADIOFREQUENCY ABLATION

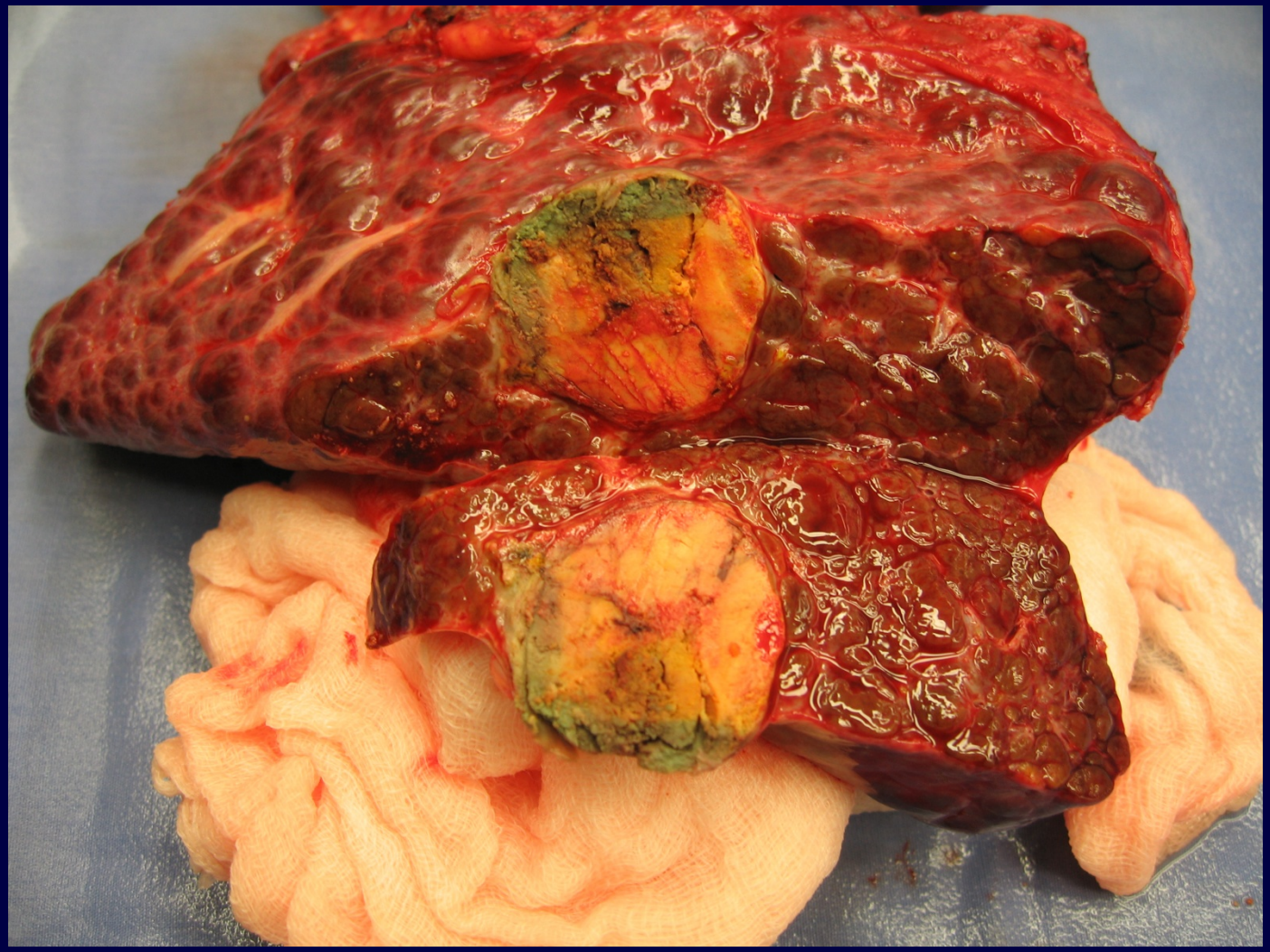
Early Stages
Not Suitable for Surgery

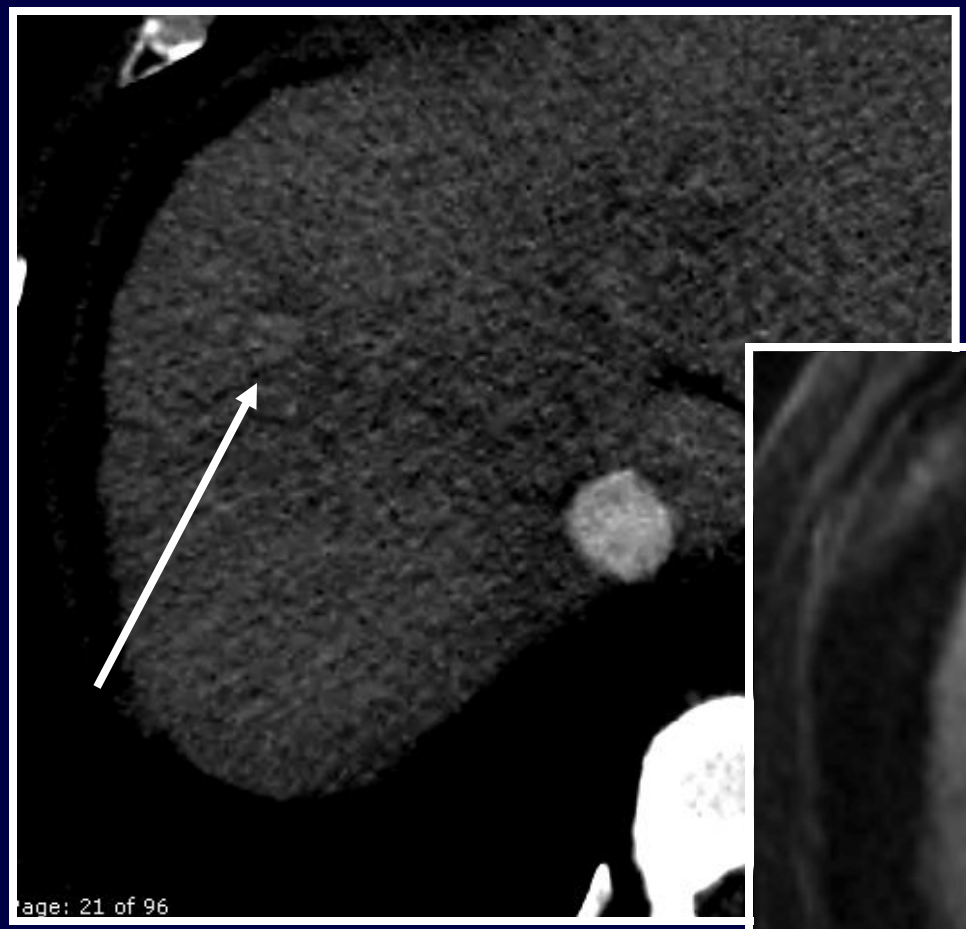
Radiofrequency Ablation

Heat destroys cells





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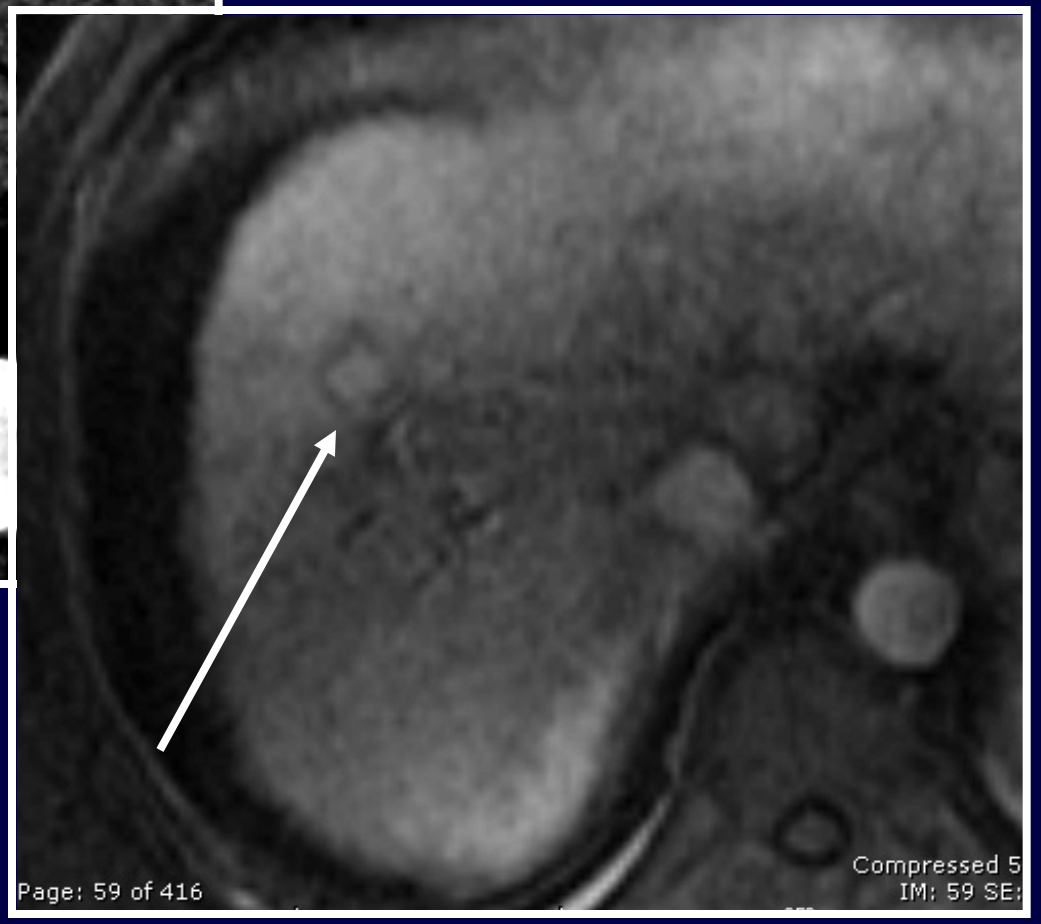
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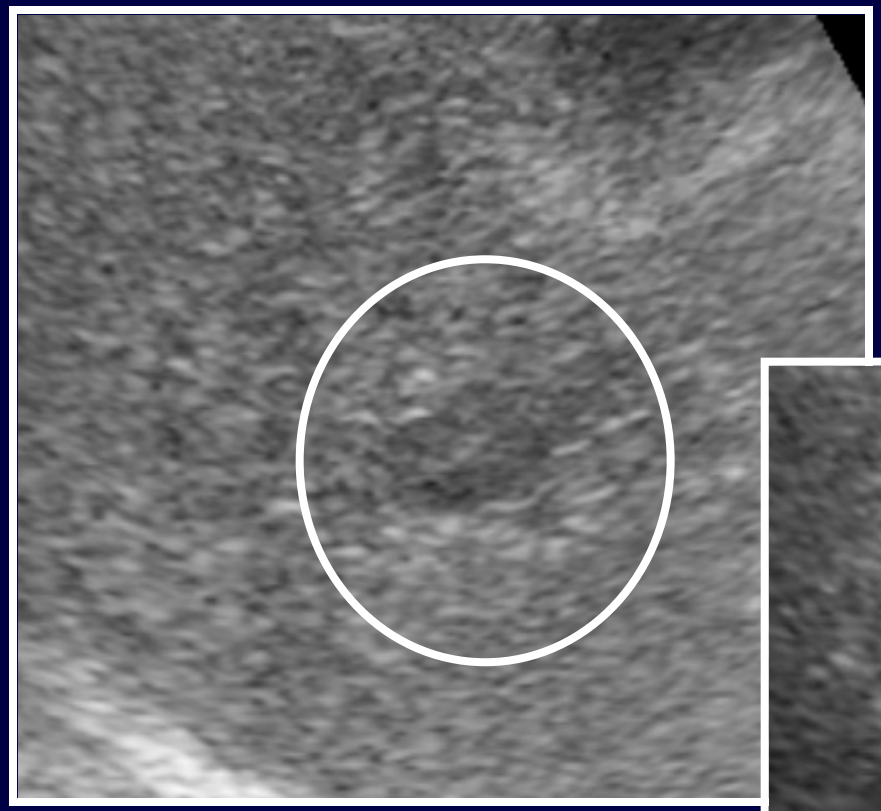

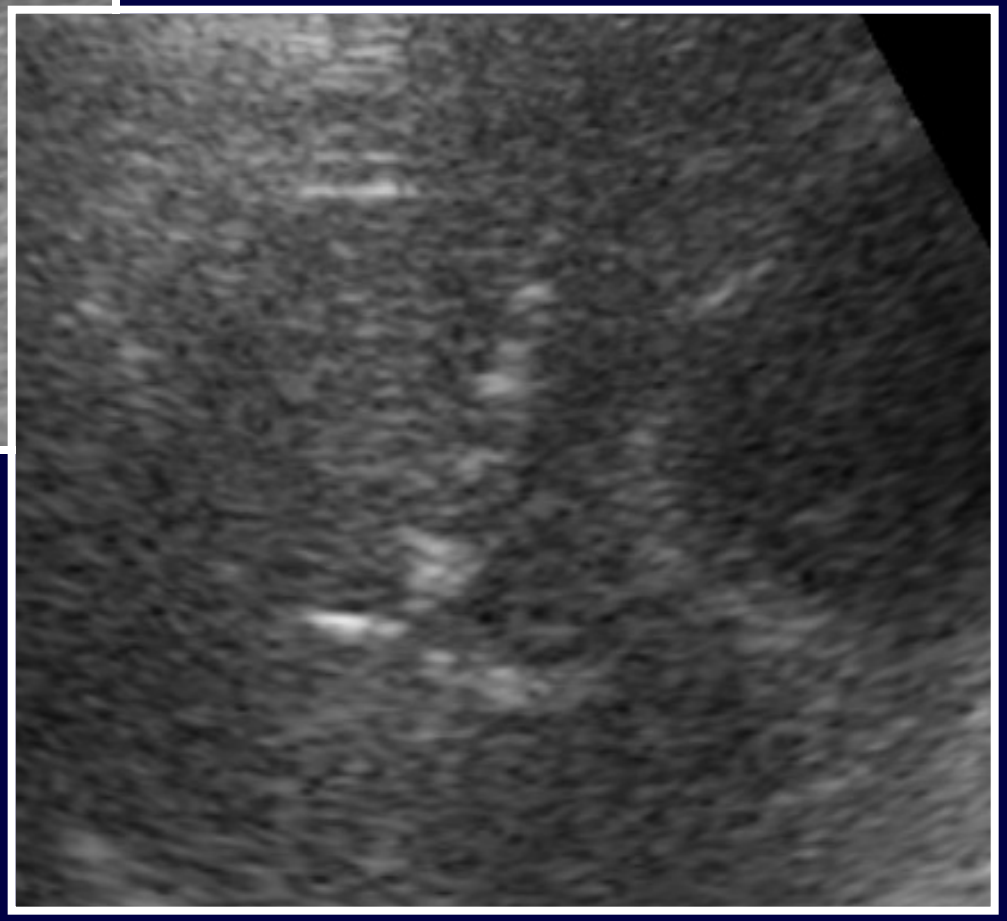

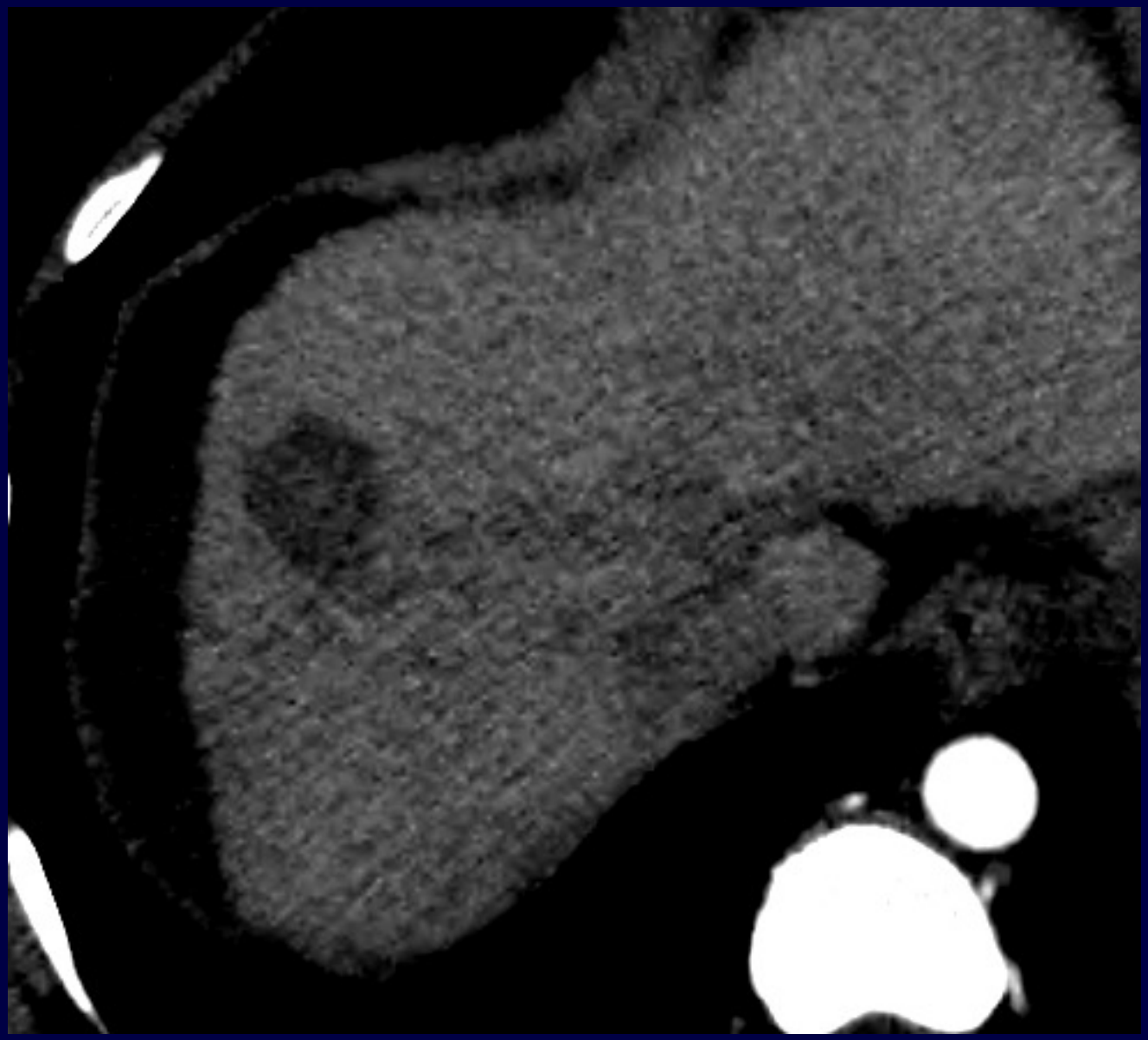

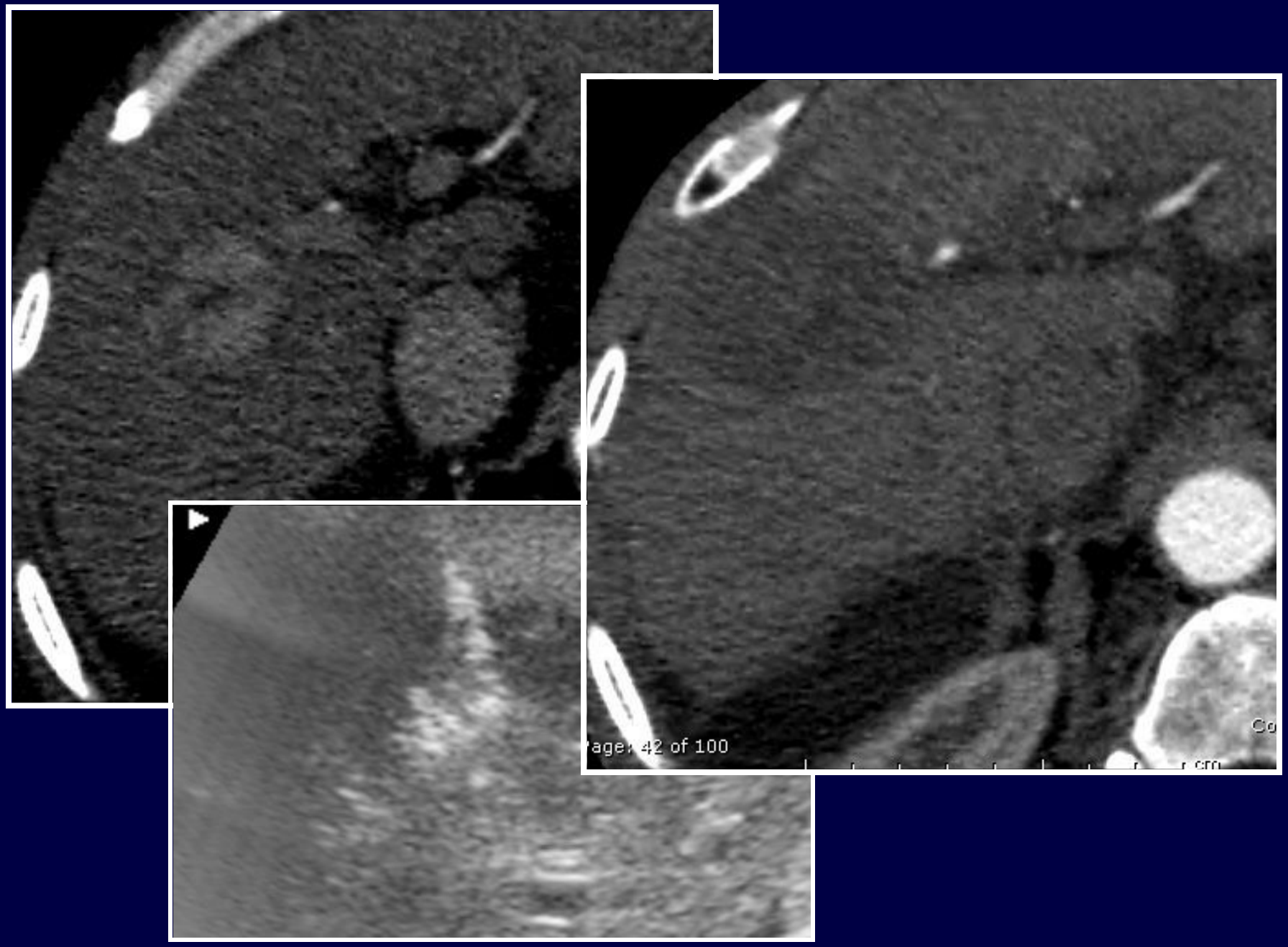
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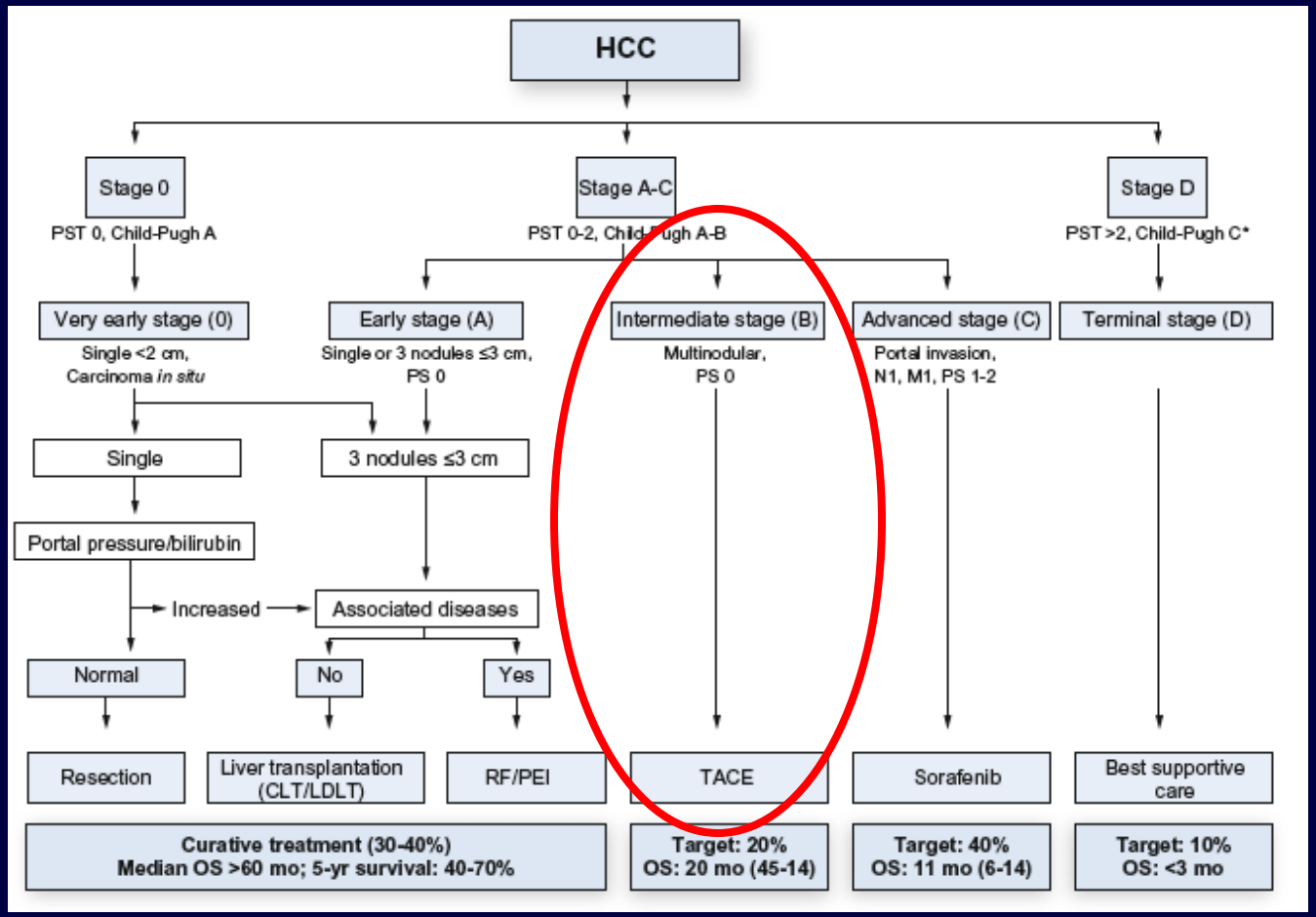
Intermediate



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Intermediate

TRANSARTERIAL CHEMOEMBOLIZATION

Multinodular

Unresectable

TACE

Chemotherapeutic agents

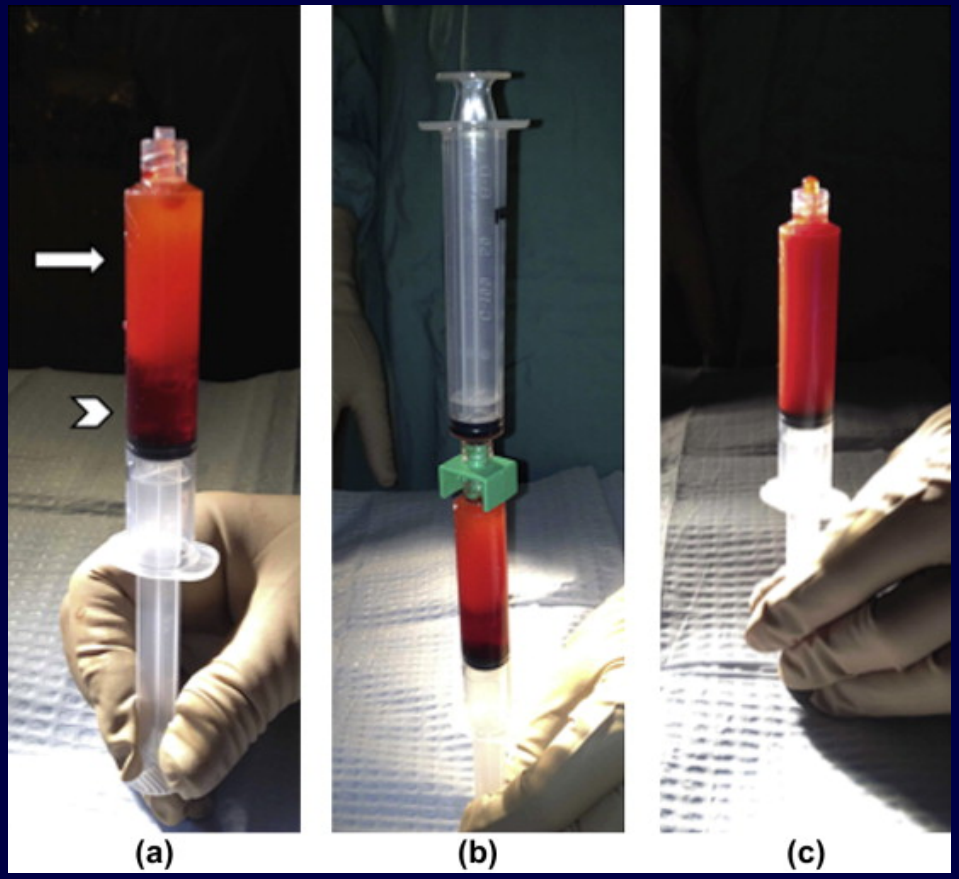
Embolization with particles

TACE

CISPLATIN
DOXORUBICIN
MITOMYCIN C

VEHICLE

TACE



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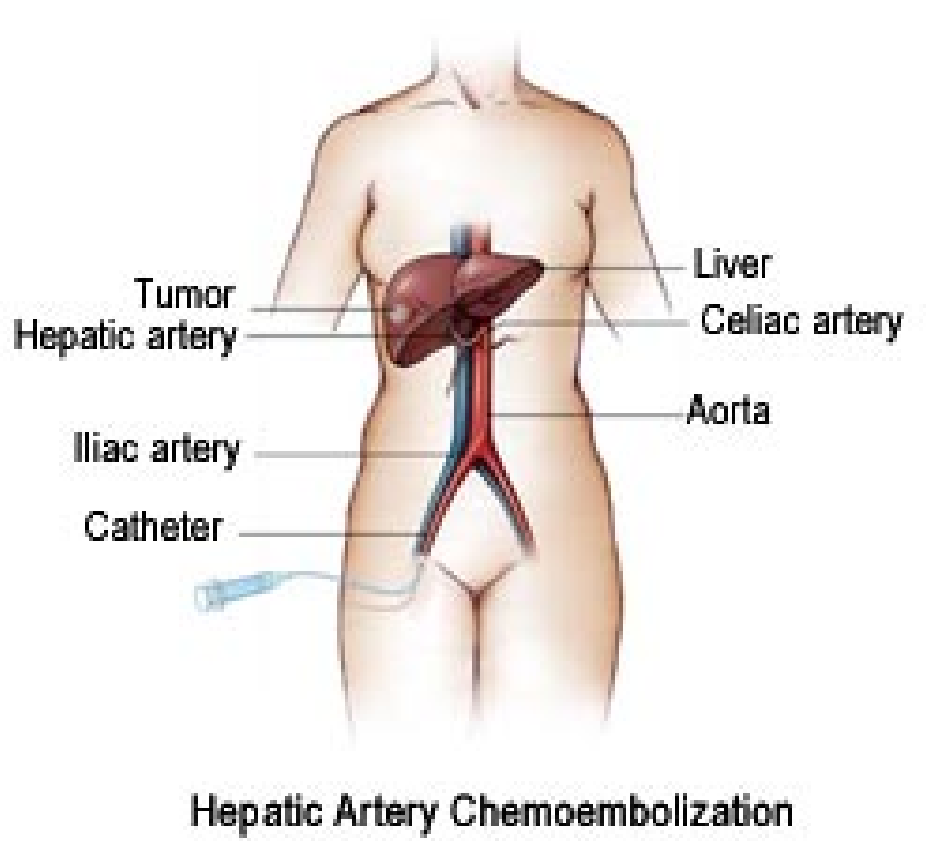
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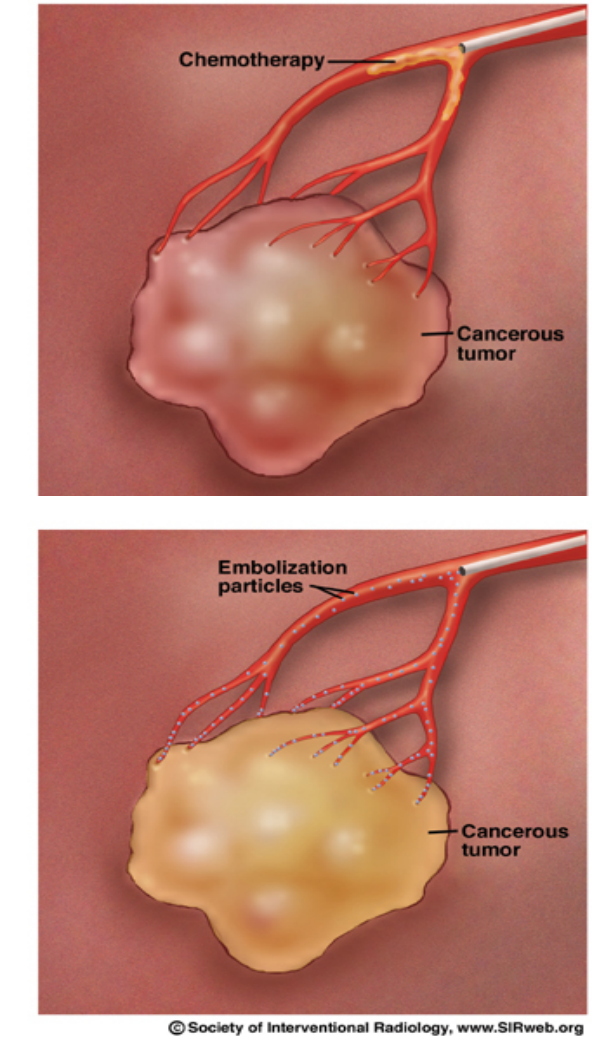
Hepatic artery
Liver
Celiac artery
Aorta
Iliac artery
Catheter
Hepatic Artery Chemoembolization


Chemotherapy
Cancerous tumor
Embolization particles
Cancerous tumor
©Society of Interventional Radiology, www.SIRweb.org

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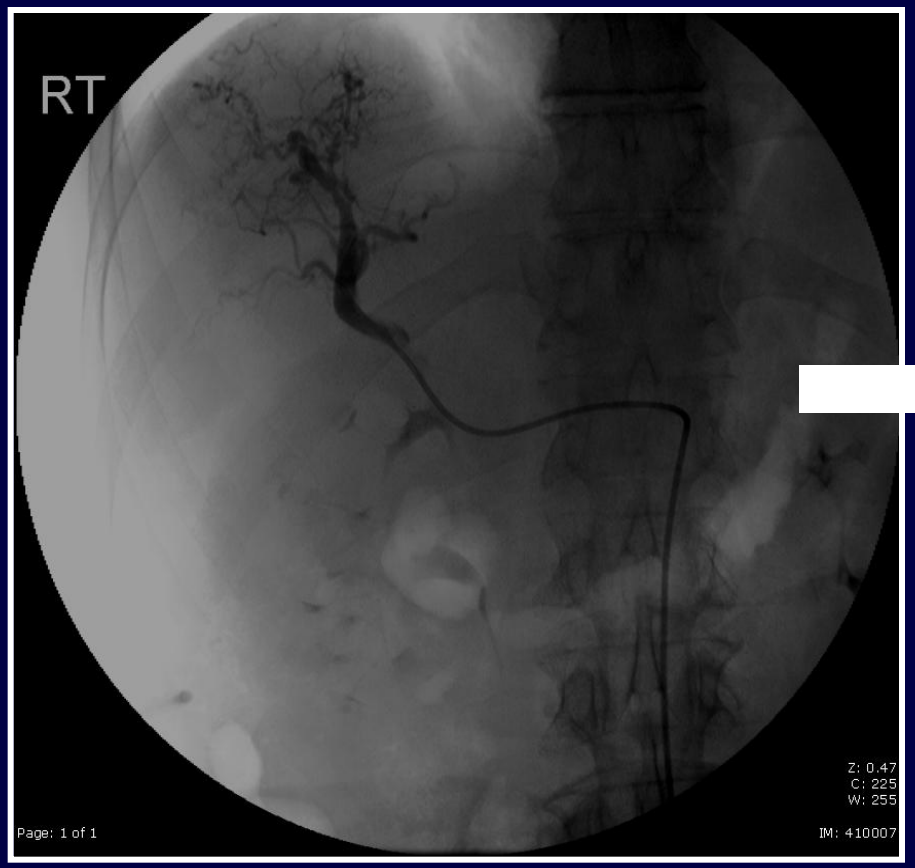

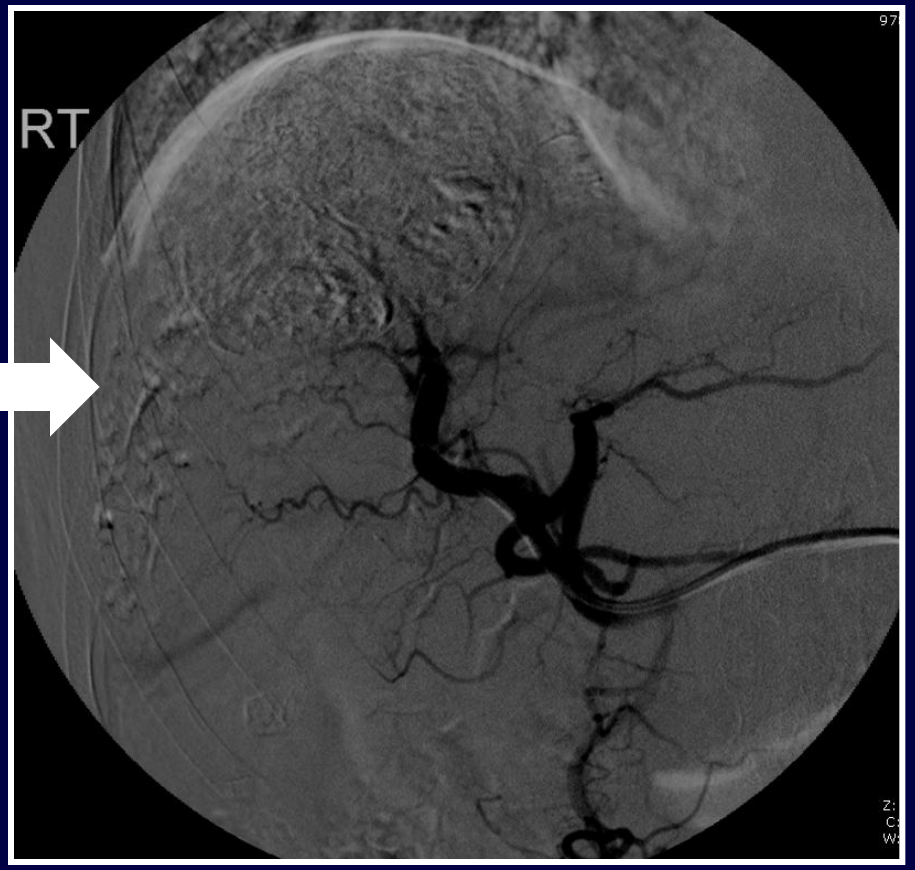

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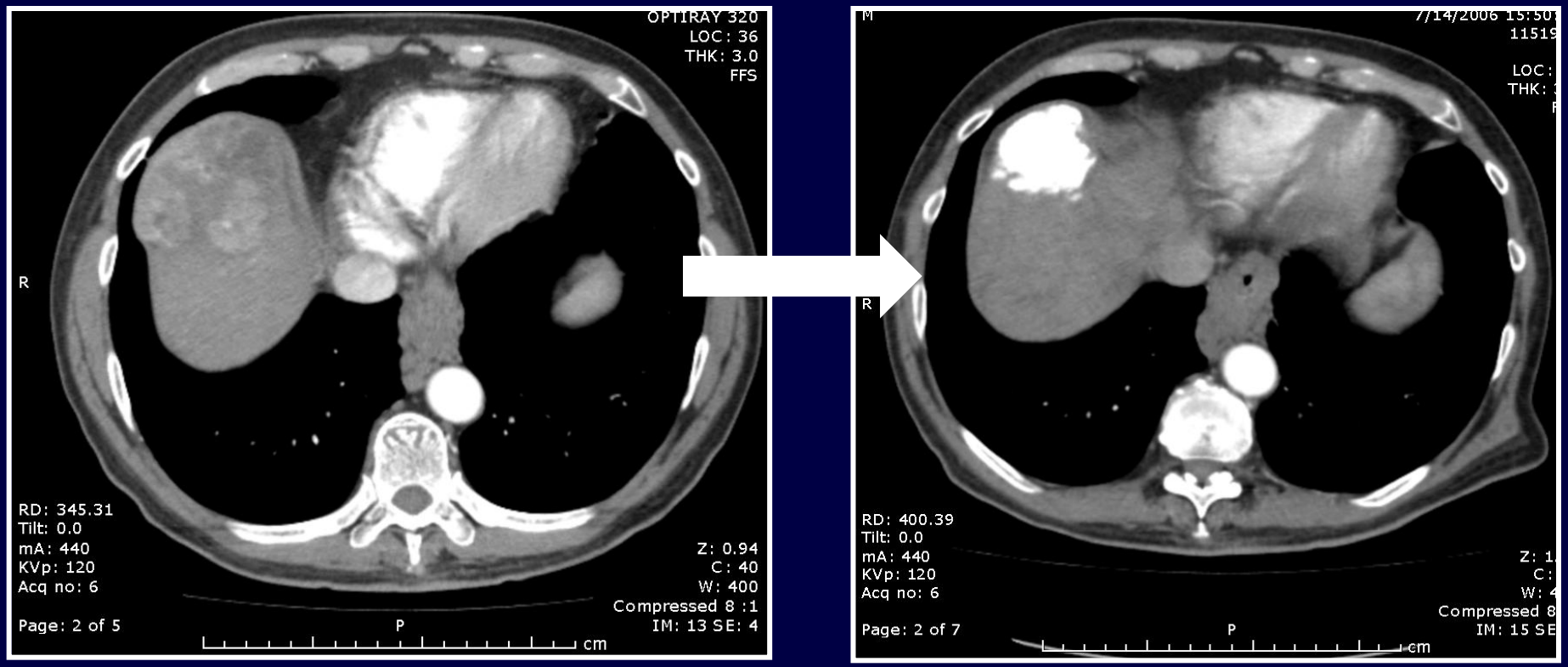
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Page: 2 of 7
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cm

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META-ANALYSIS OF 7 RCT

Overall Survival 20 mo vs 16 mo
Cisplatin or doxorubicin

Hepatology 2003; 37: 429-442

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Clinical Practice Summary

Diagnosis

- Diagnosis of HCC is based on non-invasive criteria or pathology
  (evidence 2D; recommendation 1A)
- Pathological diagnosis of HCC is based on the recommendations of the International Consensus Panel. Immunostaining for GPC3, HSP70, and glutamine synthetase and/or gene expression profiles (GPC3, *LYVE1* and survivin) are recommended to differentiate high grade dysplastic nodules from early HCC
  (evidence 2D; recommendation 2B)
  Additional staining can be considered to detect progenitor cell features (K19 and EpCAM) or assess neovascularisation (CD34)
- Non-invasive criteria can only be applied to cirrhotic patients and are based on imaging techniques obtained by 4-phase multidetector CT scan or dynamic contrast-enhanced MRI. Diagnosis should be based on the identification of the typical hallmark of HCC (hypervascular in the arterial phase with washout in the portal venous or delayed phases). While one imaging technique is required for nodules beyond 1 cm in diameter (evidence 2D; recommendation 2B), a more conservative approach with 2 techniques is recommended in suboptimal settings. The role of contrast-enhanced ultrasound (CEUS) and angiography is controversial. PET-scan is not accurate for early diagnosis

Staging systems

- Staging systems in HCC should define outcome prediction and treatment assignment. They should facilitate exchange of information, prognosis prediction and trial design. Due to the nature of HCC, the main prognostic variables are tumor stage, liver function and performance status
- The BCLC staging system is recommended for prognostic prediction and treatment allocation
  (evidence 2A; recommendation 1B)
  This staging system can be applied to most HCC patients, as long as specific considerations for special subpopulations (liver transplantation) are incorporated
- Other staging systems applied alone or in combination with BCLC are not recommended in clinical practice
- Molecular classification of HCC based on gene signatures or molecular abnormalities is not ready for clinical application
  (evidence 2A; recommendation 1B)

Treatment

- Treatment allocation is based on the BCLC allocation system

Resection

- Resection is the first-line treatment option for patients with solitary tumors and very well-preserved liver function, defined as normal bilirubin with either hepatic venous pressure gradient ≤10 mmHg or platelet count ≥100,000
  (evidence 2A; recommendation 1B)
  Anatomical resections are recommended
  (evidence 3A; recommendation 2C)
- Additional indications for patients with multifocal tumors meeting Milan criteria (≤3 nodules ≤3 cm) or with mild portal hypertension not suitable for liver transplantation require prospective comparisons with loco-regional treatments
  (evidence 3A; recommendation 2C)
- Peri-operative mortality of liver resection in cirrhotic patients is expected to be 2-3%
- Neo-adjuvant or adjuvant therapies have not proven to improve outcome of patients treated with resection (or local ablation)
  (evidence 1D; recommendation 2C)
- Tumor recurrence represents the major complication of resection and the pattern of recurrence influences subsequent therapy allocation and outcome. In case of recurrence, the patient will be re-assessed by BCLC staging, and re-treated accordingly

Liver Transplantation

- Liver transplantation is considered to be the first-line treatment option for patients with single tumors less than 5 cm or ≤3 nodules ≤3 cm (Milan criteria) not suitable for resection
  (evidence 2A; recommendation 1A)
- Peri-operative mortality and one-year mortality are expected to be approximately 3% and ≤10%, respectively
- Extension of tumor limit criteria for liver transplantation for HCC has not been established. Modest expansion of Milan criteria applying the "up-to-seven" in patients without microvascular invasion achieves competitive outcomes, and thus this indication requires prospective validation
  (evidence 2B; recommendation 2B)
- Neo-adjuvant treatment can be considered for loco-regional therapies if the waiting list exceeds 6 months due to good cost-effectiveness data and tumor response rates, even though impact on long-term outcome is uncertain
  (evidence 2D; recommendation 2B)
- Down-staging policies for HCCs exceeding conventional criteria cannot be recommended and should be explored in the context of prospective studies aimed at survival and disease progression end-points
  (evidence 2D; recommendation 2C)
  Assessment of downstaging should follow modified RECIST criteria
- Living donor liver transplantation is an alternative option in patients with a waiting list exceeding 6-7 months, and offers a suitable setting to explore extended indications within research programs
  (evidence 2A; recommendation 2B)

Local ablation

- Local ablation with radiofrequency or percutaneous ethanol injection is considered the standard of care for patients with BCLC 0-A tumors not suitable for surgery
  (evidence 2A; recommendation 1B)
  Other ablative therapies, such as microwave or cryoablation, are still under investigation
- Radiofrequency ablation is recommended in most instances as the main ablative therapy in tumors less than 5 cm due to a significantly better control of the disease
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  Ethanol injection is recommended in cases where radiofrequency ablation is not technically feasible (around 10-15%)
- In tumors <2 cm, BCLC 0, both techniques achieve complete responses in more than 90% of cases with good long-term outcome. Whether they can be considered as competitive alternatives to resection is uncertain
  (evidence 1A; recommendation 1C)

Chemoembolization and transcatheter therapies

- Chemoembolization is recommended for patients with BCLC stage B, multinodular asymptomatic tumors without vascular invasion or extra-hepatic spread
  (evidence 1IIA; recommendation 1A)
  The use of drug-eluting beads has shown similar response rates than gelfoam-lipiodol particles associated with less systemic adverse events
  (evidence 1D; recommendation 2B)
  Chemoembolization is discouraged in patients with decompensated liver disease, advanced liver dysfunction, macroscopic invasion or extrahepatic spread
  (evidence 1IIA; recommendation 1B)
  Bland embolization is not recommended
- Internal radiation with ^{131}I or ^{90}Y glass beads has shown promising anti-tumoral results with a safe profile, but cannot be recommended as standard therapy. Further research trials are needed to establish a competitive efficacy role in this population
  (evidence 2A; recommendation 2B)
- Selective intra-arterial chemotherapy or lipiodolization are not recommended for the management of HCC
  (evidence 2A; recommendation 2B)
- External three-dimensional conformal radiotherapy is under investigation, and there is no evidence to support this therapeutic approach in the management of HCC
  (evidence 3A; recommendation 2C)

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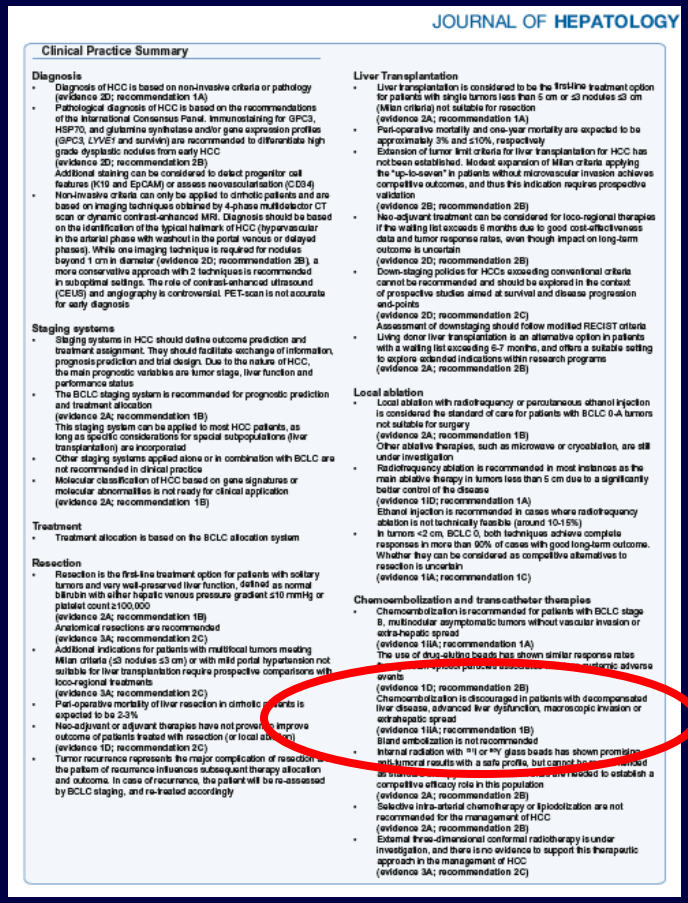

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  The use of drug-eluting beads has shown similar response rates [illegible] systemic adverse events (evidence 1D; recommendation 2B)
  Chemoembolization is discouraged in patients with decompensated liver disease, advanced liver dysfunction, macroscopic invasion or extrahepatic spread (evidence 1IIA; recommendation 1B)
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- Selective intra-arterial chemotherapy or lipiodolization are not recommended for the management of HCC (evidence 2A; recommendation 2B)
- External three-dimensional conformal radiotherapy is under investigation, and there is no evidence to support this therapeutic approach in the management of HCC (evidence 3A; recommendation 2C)

CONTRAINDICATIONS

Child-Pugh B8, B9, or C

Macrovascular invasion

Extrahepatic spread

Cancer symptoms

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TACE

COMPLICATIONS

Acute hepatic failure (7.5%)

Ascites (8.3%)

Post-embolization syndrome-extended stay (4.6%)

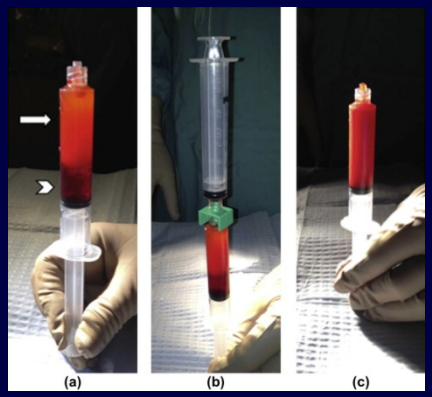
Liver abscess (1.3%)

Upper GI bleeding (3%)

Acute Renal Failure (1.8%)

Encephalopathy (1.8%)

Marelli, *Cardiovascular & Interventional Radiology* 2007; 30:6-25.



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POST-EMBOLIZATION SYNDROME:

up to 90%

Nausea, vomiting, pain, fever

Admission for supportive care

Ischemia and inflammatory response

Leung, JVIR 2001; 12: 321-326

TACE 2.0

Sustained intra-tumoral concentration

Minimal systemic exposure

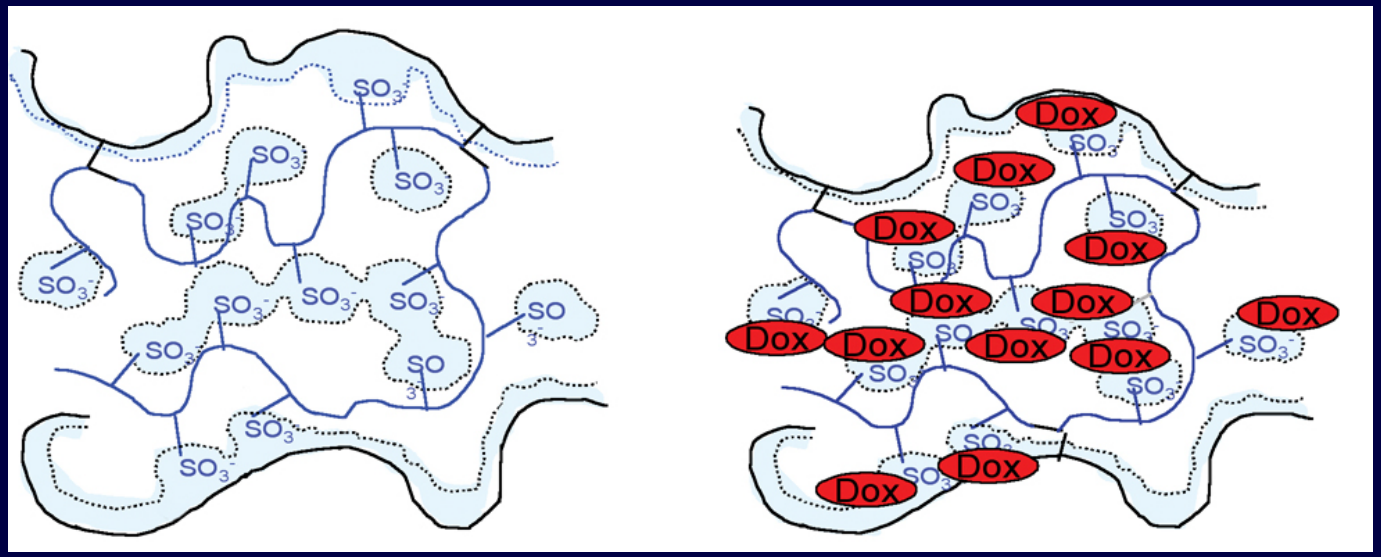
Drug-Eluting Beads

Highly sulfonated, hydrogel modified PVA embolic microsphere

FDA approved embolic for treatment of hypervascularized tumors or AVM’s

Drug loading is off-label use

Drug-Eluting Beads

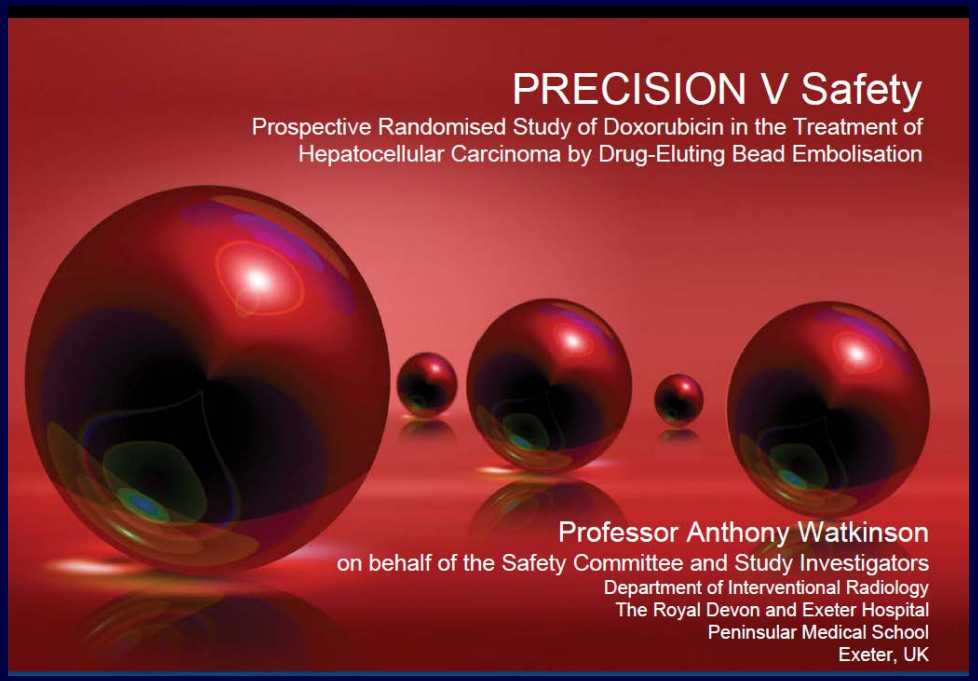


Chemoembolization of hepatocellular carcinoma with drug eluting beads: Efficacy and doxorubicin pharmacokinetics☆

María Varela[1], María Isabel Real[2], Marta Burrel[2], Alejandro Forner[1], Margarita Sala[1], Mercé Brunet[3], Carmen Ayuso[2], Lluis Castells[4], Xavier Montañá[2], Josep M. Llovet[1,5], Jordi Bruix[1,*]

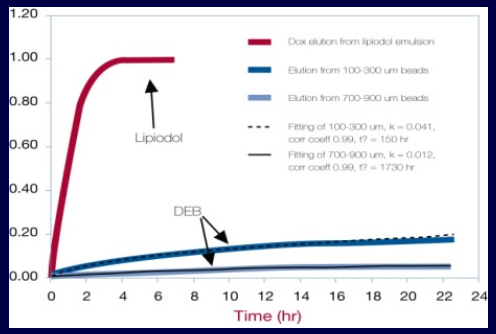
[1]*Liver Unit, IMDM, Barcelona Clínic Liver Cancer (BCLC) Group, Hospital Clínic, CIBER HEPAD, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi I Sunyer, IDIBAPS, Barcelona, Spain*

Journal of Hepatology 46 (2007) 474–481



Cardiovasc Intervent Radiol 2010; 33: 41-52

Drug-Eluting Beads

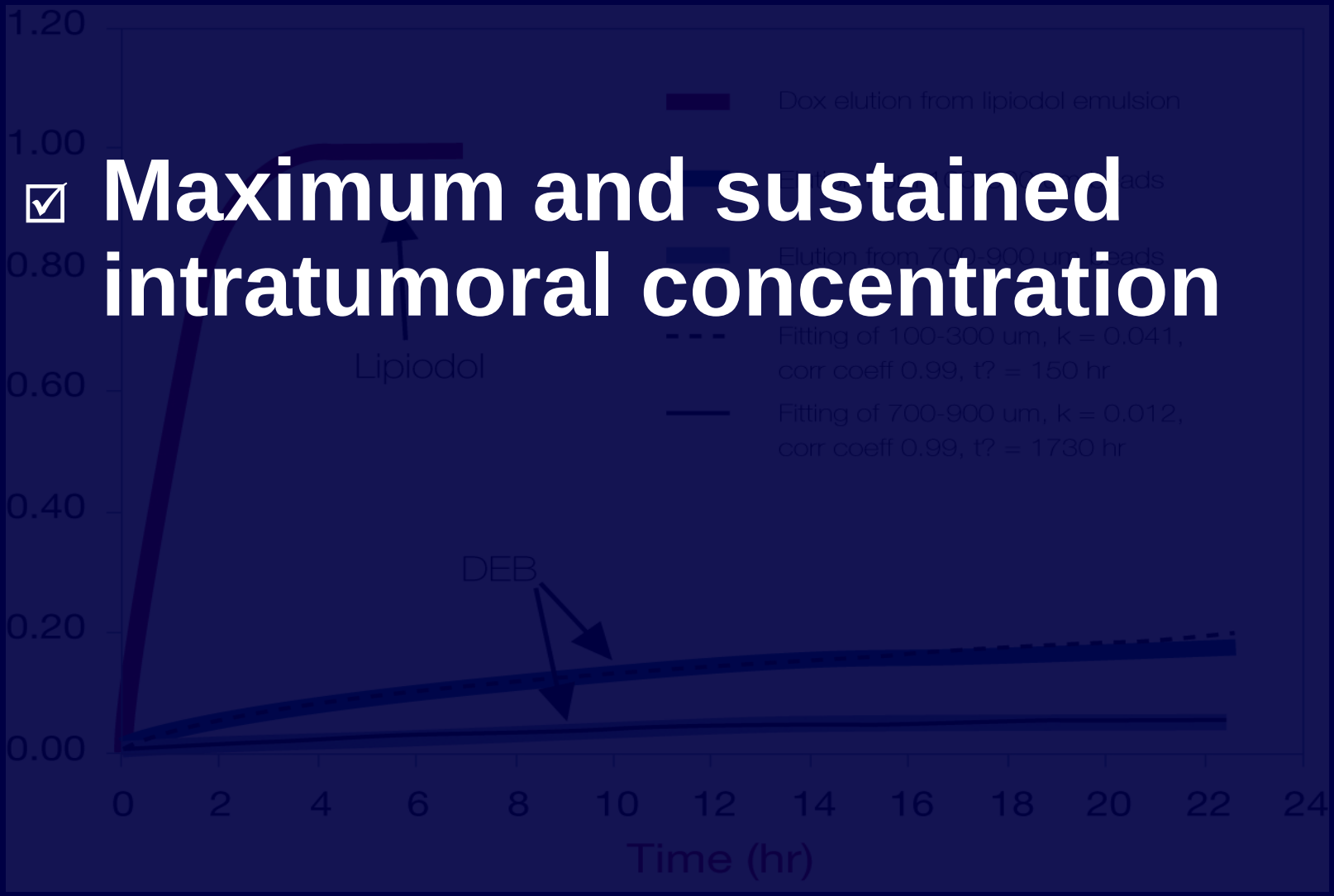


Slower release

Varela et al., *J of Hepatology* 2007; 46: 474-481.

Drug-Eluting Beads

- ☑ **Maximum and sustained intratumoral concentration**



Varela et al., *J of Hepatology* 2007; 46: 474-481.

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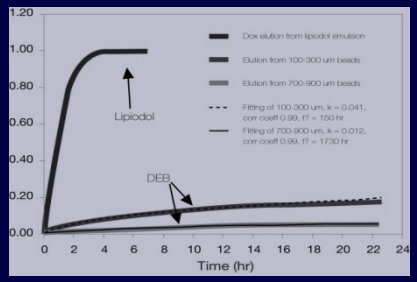
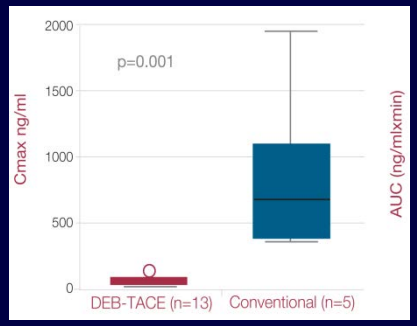


Slower release

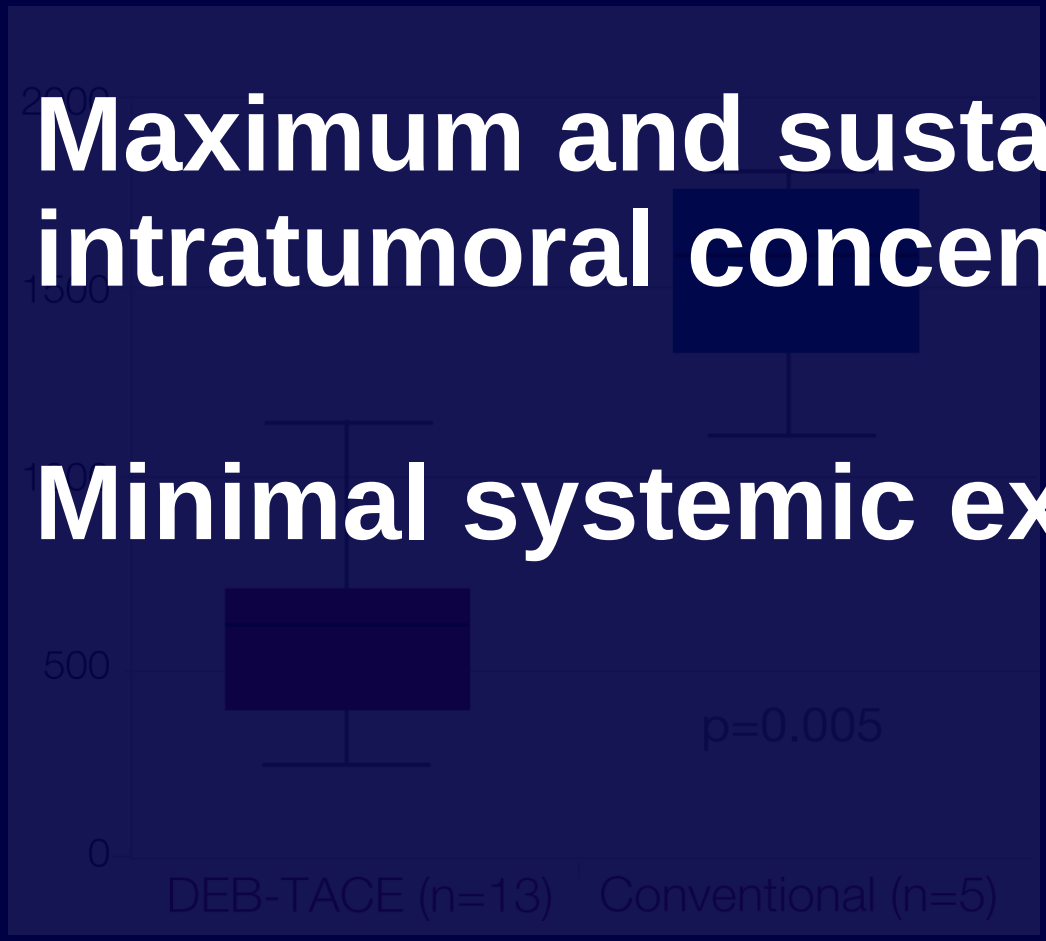


Lower systemic exposure

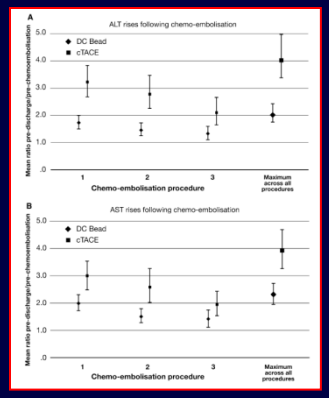
Varela et al., *J of Hepatology* 2007; 46: 474-481.

Drug-Eluting Beads

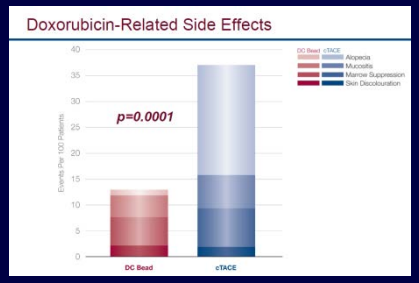
- ☑ **Maximum and sustained intratumoral concentration**
- ☑ **Minimal systemic exposure**



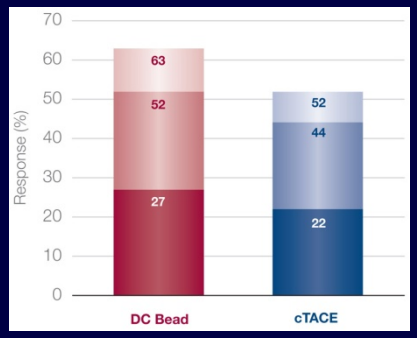
Drug-Eluting Beads



Reduced liver toxicity



Fewer adverse events



Trend toward better tumor response

Cardiovasc Intervent Radiol 2010; 33: 41-52

Drug-Eluting Beads

EASL 2012

Chemoembolization with Drug-Eluting Beads (TACE-DEB)
Strategies to improve anti-tumoral activity and clinical benefits with chemoembolization have been launched. The ideal TACE scheme should allow maximum and sustained intratumoral concentration of the chemotherapeutic agent with minimal systemic exposure, along with calibrated tumor vessel obstruction. Embolic microspheres have the ability to sequester chemotherapeutic agents and release them in a controlled mode over a 1-week period. This strategy has been shown to increase the local concentration of the drug with negligible systemic toxicity [166]. A randomized phase II study comparing TACE and TACE-DEB reported a significant reduction in liver toxicity and drug related adverse events for the latter arm, associated with a non-significant trend of better antitumoral effect [295].

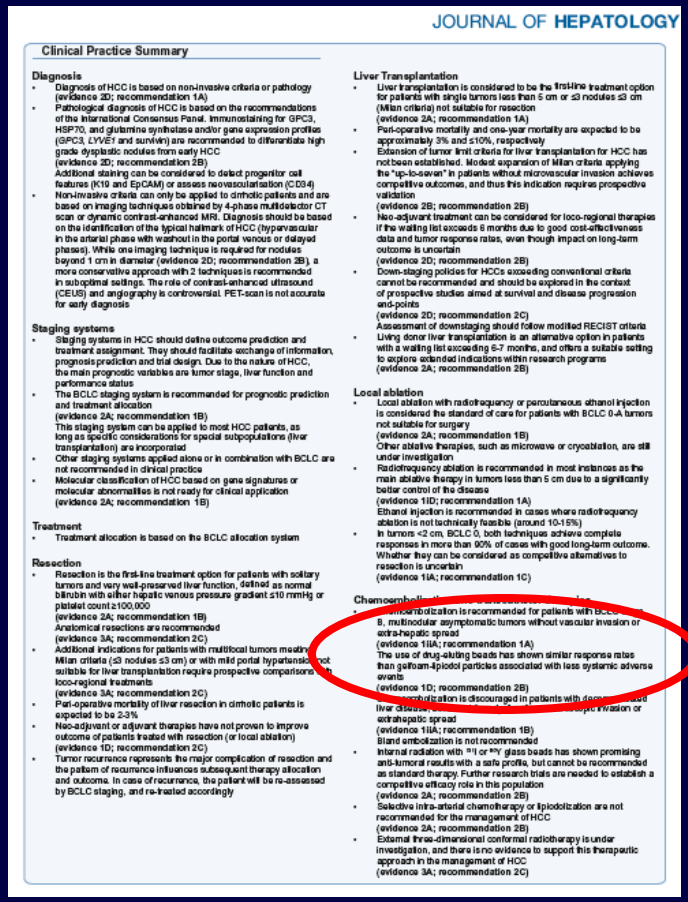
COMPARED TO TACE:

Increased local concentration

Negligible systemic toxicity

Journal of Hepatology **2012** vol. 56 | 908–943

Drug-Eluting Beads



JOURNAL OF HEPATOLOGY

Clinical Practice Summary

Diagnosis

- Diagnosis of HCC is based on non-invasive criteria or pathology (evidence 2D; recommendation 1A)
- Pathological diagnosis of HCC is based on the recommendations of the International Consensus Panel. Immunostaining for GPC3, HSP70, and glutamine synthetase and/or gene expression profiles (GPC3, *LYVE1* and survivin) are recommended to differentiate high grade dysplastic nodules from early HCC (evidence 2D; recommendation 2B)
  Additional staining can be considered to detect progenitor cell features (K19 and EpCAM) or assess neovascularisation (CD34)
- Non-invasive criteria can only be applied to cirrhotic patients and are based on imaging techniques obtained by 4-phase multidetector CT scan or dynamic contrast-enhanced MRI. Diagnosis should be based on the identification of the typical hallmark of HCC (hypervascular in the arterial phase with washout in the portal venous or delayed phases). While one imaging technique is required for nodules beyond 1 cm in diameter (evidence 2D; recommendation 2B), a more conservative approach with 2 techniques is recommended in suboptimal settings. The role of contrast-enhanced ultrasound (CEUS) and angiography is controversial. PET-scan is not accurate for early diagnosis

Staging systems

- Staging systems in HCC should define outcome prediction and treatment assignment. They should facilitate exchange of information, prognosis prediction and trial design. Due to the nature of HCC, the main prognostic variables are tumor stage, liver function and performance status
- The BCLC staging system is recommended for prognostic prediction and treatment allocation (evidence 2A; recommendation 1B)
  This staging system can be applied to most HCC patients, as long as specific considerations for special subpopulations (liver transplantation) are incorporated
- Other staging systems applied alone or in combination with BCLC are not recommended in clinical practice
- Molecular classification of HCC based on gene signatures or molecular abnormalities is not ready for clinical application (evidence 2A; recommendation 1B)

Treatment

- Treatment allocation is based on the BCLC allocation system

Resection

- Resection is the first-line treatment option for patients with solitary tumors and very well-preserved liver function, defined as normal bilirubin with either hepatic venous pressure gradient ≤10 mmHg or platelet count ≥100,000 (evidence 2A; recommendation 1B)
  Anatomical resections are recommended (evidence 3A; recommendation 2C)
- Additional indications for patients with multifocal tumors meeting Milan criteria (≤3 nodules ≤3 cm) or with mild portal hypertension not suitable for liver transplantation require prospective comparisons with loco-regional treatments (evidence 3A; recommendation 2C)
- Peri-operative mortality of liver resection in cirrhotic patients is expected to be 2-3%
- Neo-adjuvant or adjuvant therapies have not proven to improve outcome of patients treated with resection (or local ablation) (evidence 1D; recommendation 2C)
- Tumor recurrence represents the major complication of resection and the pattern of recurrence influences subsequent therapy allocation and outcome. In case of recurrence, the patient will be re-assessed by BCLC staging, and re-treated accordingly

Liver Transplantation

- Liver transplantation is considered to be the first-line treatment option for patients with single tumors less than 5 cm or ≤3 nodules ≤3 cm (Milan criteria) not suitable for resection (evidence 2A; recommendation 1A)
- Peri-operative mortality and one-year mortality are expected to be approximately 3% and ≤10%, respectively
- Extension of tumor limit criteria for liver transplantation for HCC has not been established. Modest expansion of Milan criteria applying the "up-to-seven" in patients without microvascular invasion achieves competitive outcomes, and thus this indication requires prospective validation (evidence 2B; recommendation 2B)
- Neo-adjuvant treatment can be considered for loco-regional therapies if the waiting list exceeds 6 months due to good cost-effectiveness data and tumor response rates, even though impact on long-term outcome is uncertain (evidence 2D; recommendation 2B)
- Down-staging policies for HCCs exceeding conventional criteria cannot be recommended and should be explored in the context of prospective studies aimed at survival and disease progression end-points (evidence 2D; recommendation 2C)
  Assessment of downstaging should follow modified RECIST criteria
- Living donor liver transplantation is an alternative option in patients with a waiting list exceeding 6-7 months, and offers a suitable setting to explore extended indications within research programs (evidence 2A; recommendation 2B)

Local ablation

- Local ablation with radiofrequency or percutaneous ethanol injection is considered the standard of care for patients with BCLC 0-A tumors not suitable for surgery (evidence 2A; recommendation 1B)
  Other ablative therapies, such as microwave or cryoablation, are still under investigation
- Radiofrequency ablation is recommended in most instances as the main ablative therapy in tumors less than 5 cm due to a significantly better control of the disease (evidence 1D; recommendation 1A)
  Ethanol injection is recommended in cases where radiofrequency ablation is not technically feasible (around 10-15%)
- In tumors <2 cm, BCLC 0, both techniques achieve complete responses in more than 90% of cases with good long-term outcome. Whether they can be considered as competitive alternatives to resection is uncertain (evidence 1A; recommendation 1C)

Chemoembol[illegible]

- [illegible]embolization is recommended for patients with BCLC [illegible] B, multinodular asymptomatic tumors without vascular invasion or extra-hepatic spread (evidence 1IIA; recommendation 1A)
  The use of drug-eluting beads has shown similar response rates than gelfoam-lipiodol particles associated with less systemic adverse events (evidence 1D; recommendation 2B)
- [illegible]embolization is discouraged in patients with decompensated liver disease, [illegible] vascular invasion or extrahepatic spread (evidence 1IIA; recommendation 1B)
  Bland embolization is not recommended
- Internal radiation with ^{131}I or ^{90}Y glass beads has shown promising anti-tumoral results with a safe profile, but cannot be recommended as standard therapy. Further research trials are needed to establish a competitive efficacy role in this population (evidence 2A; recommendation 2B)
- Selective intra-arterial chemotherapy or lipiodolization are not recommended for the management of HCC (evidence 2A; recommendation 2B)
- External three-dimensional conformal radiotherapy is under investigation, and there is no evidence to support this therapeutic approach in the management of HCC (evidence 3A; recommendation 2C)

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EASL 2012

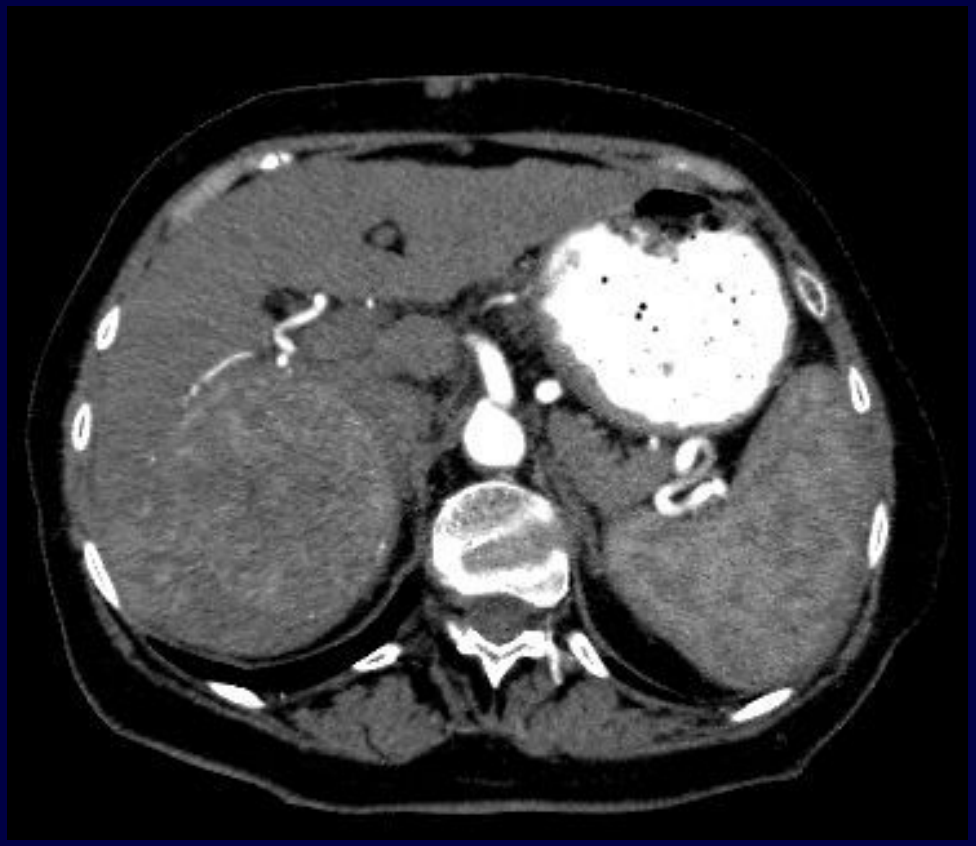
COMPARED TO TACE:

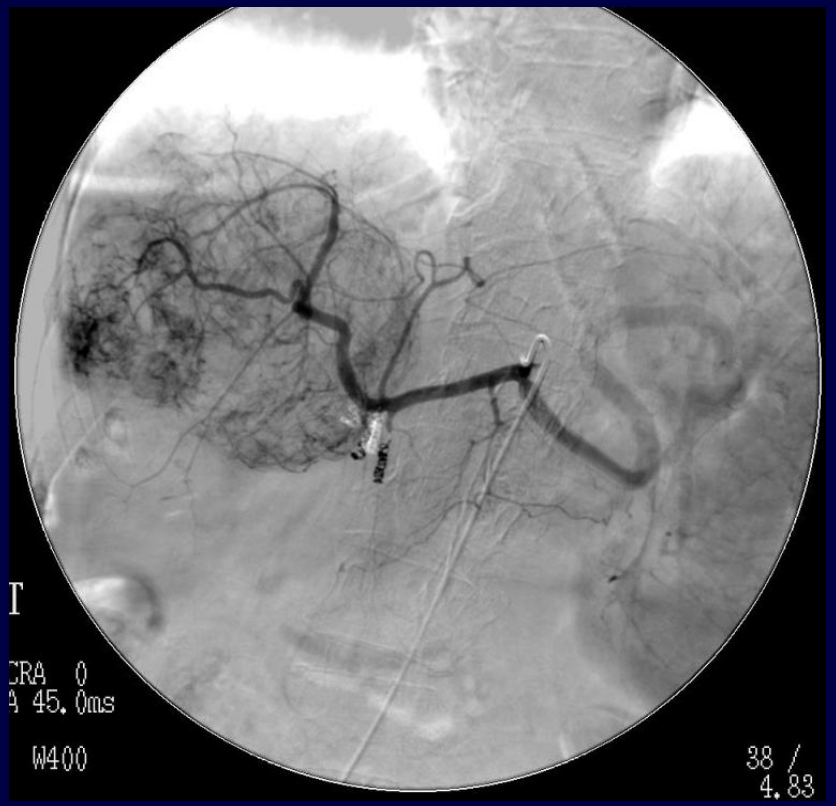
Reduced liver toxicity

Reduced adverse events

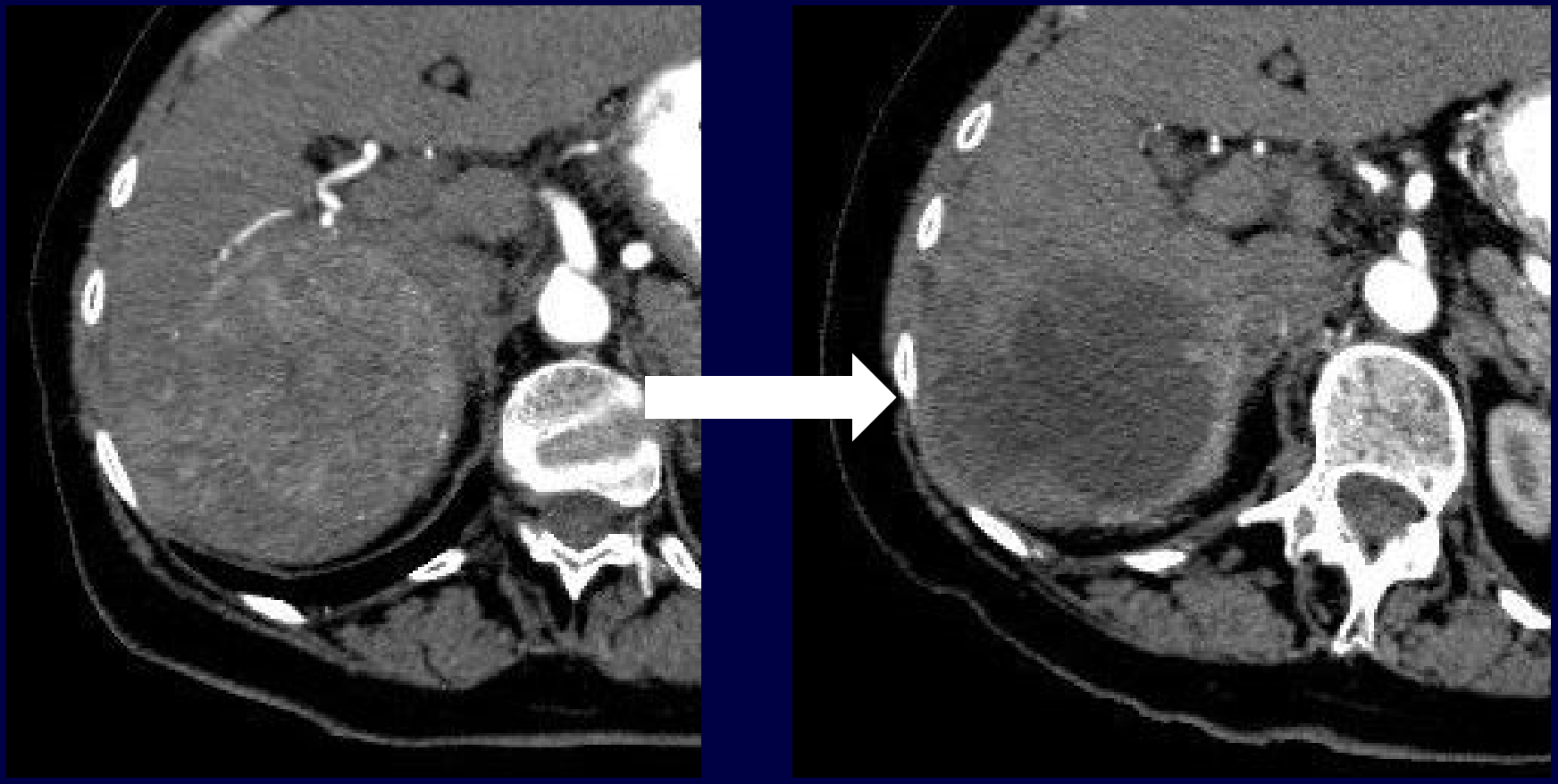
Trend toward better antitumoral effect

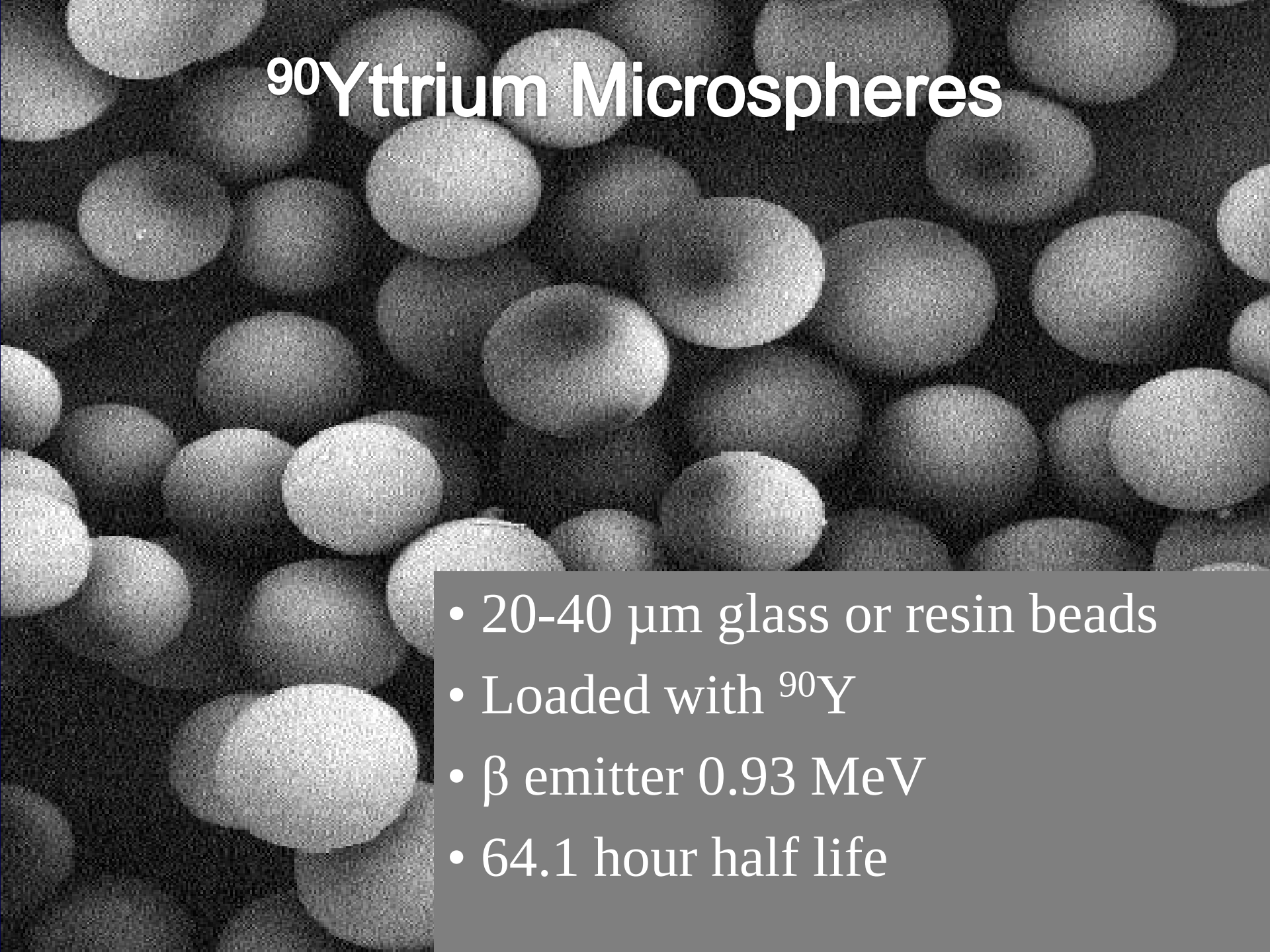
Drug-Eluting Beads





Drug-Eluting Beads

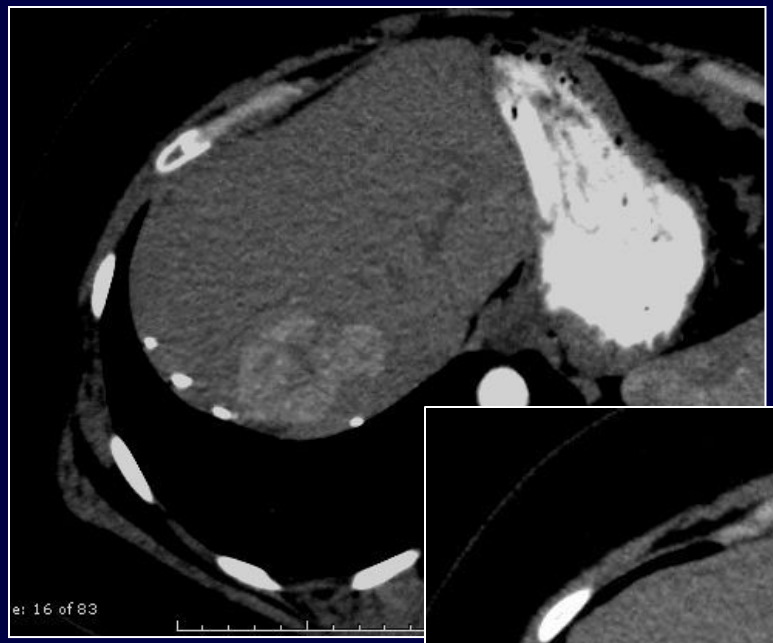


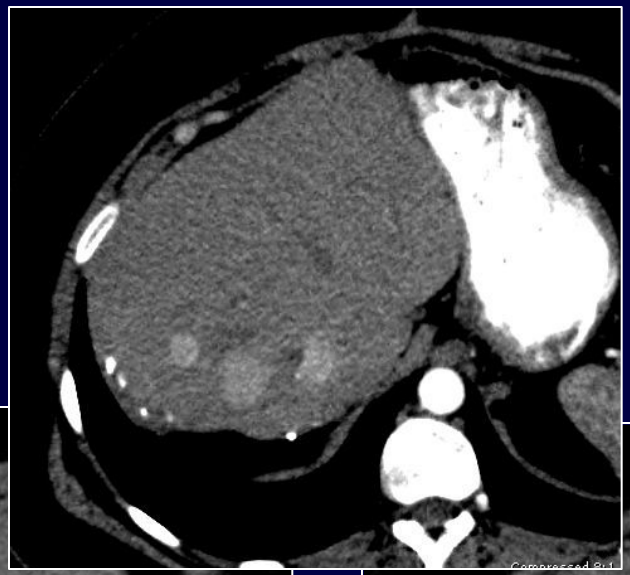


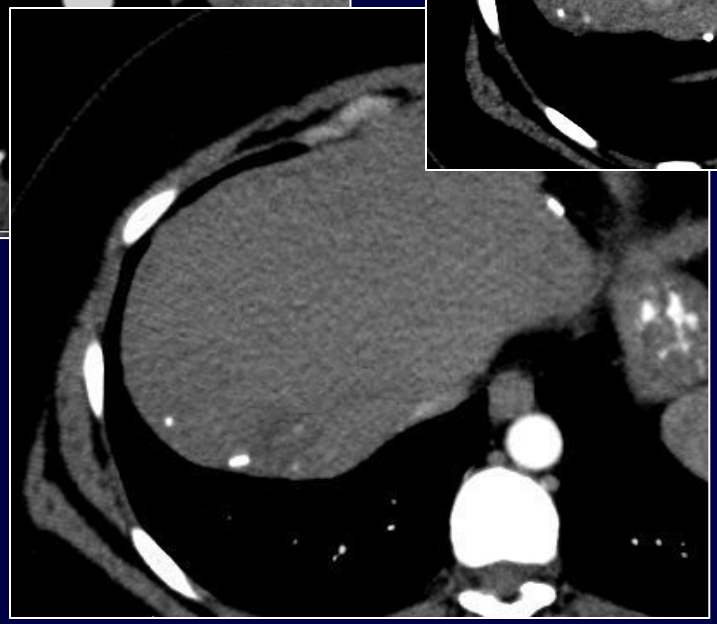
^{90}Yttrium Microspheres

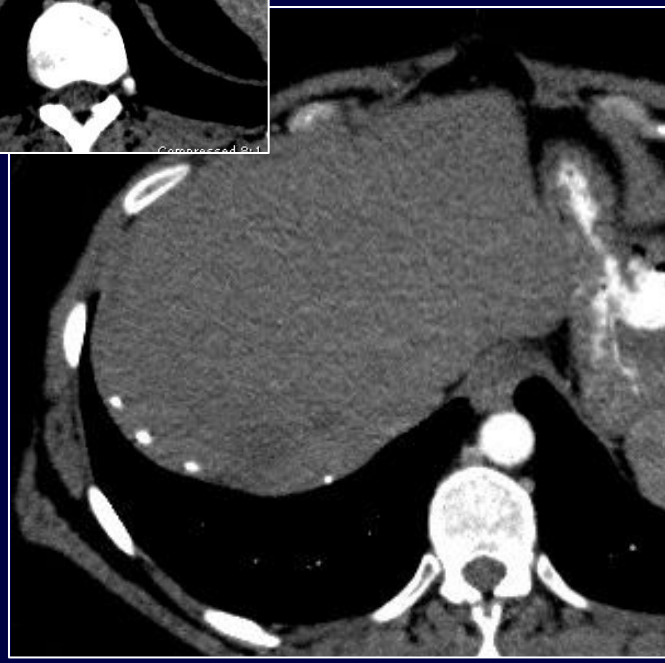
- 20-40 μm glass or resin beads
- Loaded with ^{90}Y
- β emitter 0.93 MeV
- 64.1 hour half life

^{90}Yttrium Microspheres









^{90}Yttrium Microspheres

COMPLICATIONS

GI ulcer

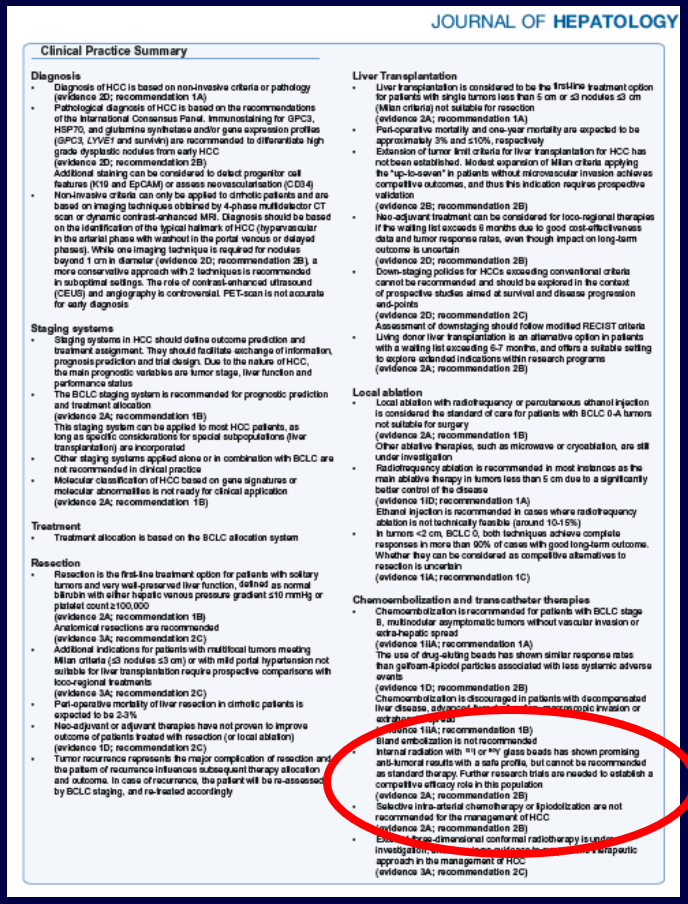
Acute Pancreatitis

Radiation Pneumonitis

Acute Gastritis

Radiation Hepatitis

Internal Radiation



JOURNAL OF **HEPATOLOGY**

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- Neo-adjuvant treatment can be considered for loco-regional therapies if the waiting list exceeds 6 months due to good cost-effectiveness data and tumor response rates, even though impact on long-term outcome is uncertain (evidence 2D; recommendation 2B)
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- In tumors <2 cm, BCLC 0, both techniques achieve complete responses in more than 90% of cases with good long-term outcome. Whether they can be considered as competitive alternatives to resection is uncertain (evidence 1A; recommendation 1C)

Chemoembolization and transcatheter therapies

- Chemoembolization is recommended for patients with BCLC stage B, multinodular asymptomatic tumors without vascular invasion or extra-hepatic spread (evidence 1IIA; recommendation 1A)
  The use of drug-eluting beads has shown similar response rates than gelfoam-lipiodol particles associated with less systemic adverse events (evidence 1D; recommendation 2B)
  Chemoembolization is discouraged in patients with decompensated liver disease, advanced [illegible] macroscopic invasion or extra-hepatic spread (evidence 1IIA; recommendation 1B)
  Bland embolization is not recommended
- Internal radiation with ^{131}I or ^{90}Y glass beads has shown promising anti-tumoral results with a safe profile, but cannot be recommended as standard therapy. Further research trials are needed to establish a competitive efficacy role in this population (evidence 2A; recommendation 2B)
- Selective intra-arterial chemotherapy or lipiodolization are not recommended for the management of HCC (evidence 2A; recommendation 2B)
- Experimental three-dimensional conformal radiotherapy is under investigation, [illegible] base guidance to [illegible] therapeutic approach in the management of HCC (evidence 3A; recommendation 2C)

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EASL 2012

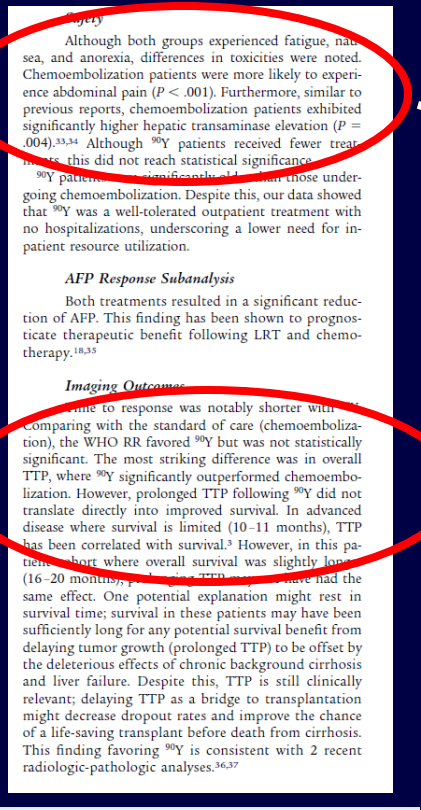
Promising anti-tumoral results

Safe profile

Further research trials are needed

^{90}Yttrium Microspheres

Cohort comparison with TACE in 245 patients



Although both groups experienced fatigue, nau-
sea, and anorexia, differences in toxicities were noted. Chemoembolization patients were more likely to experience abdominal pain ($P < .001$). Furthermore, similar to previous reports, chemoembolization patients exhibited significantly higher hepatic transaminase elevation ($P = .004$).[33,34] Although ^{90}Y patients received fewer treat-
ments, this did not reach statistical significance.
^{90}Y patients were significantly older than those undergoing chemoembolization. Despite this, our data showed that ^{90}Y was a well-tolerated outpatient treatment with no hospitalizations, underscoring a lower need for inpatient resource utilization.

AFP Response Subanalysis

Both treatments resulted in a significant reduction of AFP. This finding has been shown to prognosticate therapeutic benefit following LRT and chemotherapy.[18,35]

Imaging Outcomes

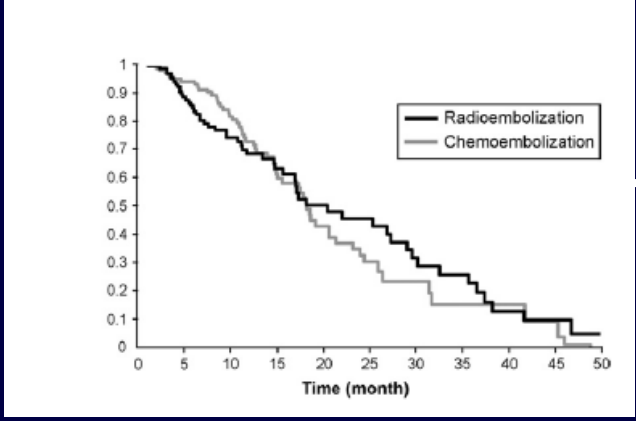
Time to response was notably shorter with ^{90}Y. Comparing with the standard of care (chemoembolization), the WHO RR favored ^{90}Y but was not statistically significant. The most striking difference was in overall TTP, where ^{90}Y significantly outperformed chemoembolization. However, prolonged TTP following ^{90}Y did not translate directly into improved survival. In advanced disease where survival is limited (10–11 months), TTP has been correlated with survival.[3] However, in this patient cohort where overall survival was slightly longer (16–20 months), prolonging TTP may not have had the same effect. One potential explanation might rest in survival time; survival in these patients may have been sufficiently long for any potential survival benefit from delaying tumor growth (prolonged TTP) to be offset by the deleterious effects of chronic background cirrhosis and liver failure. Despite this, TTP is still clinically relevant; delaying TTP as a bridge to transplantation might decrease dropout rates and improve the chance of a life-saving transplant before death from cirrhosis. This finding favoring ^{90}Y is consistent with 2 recent radiologic-pathologic analyses.[36,37]

GASTROENTEROLOGY 2011;140:497–507

TACE: more pain, higher transaminase elevation

TTP: ^{90}Y significantly outperformed TACE (8 vs 13 mos)

^{90}Yttrium Microspheres



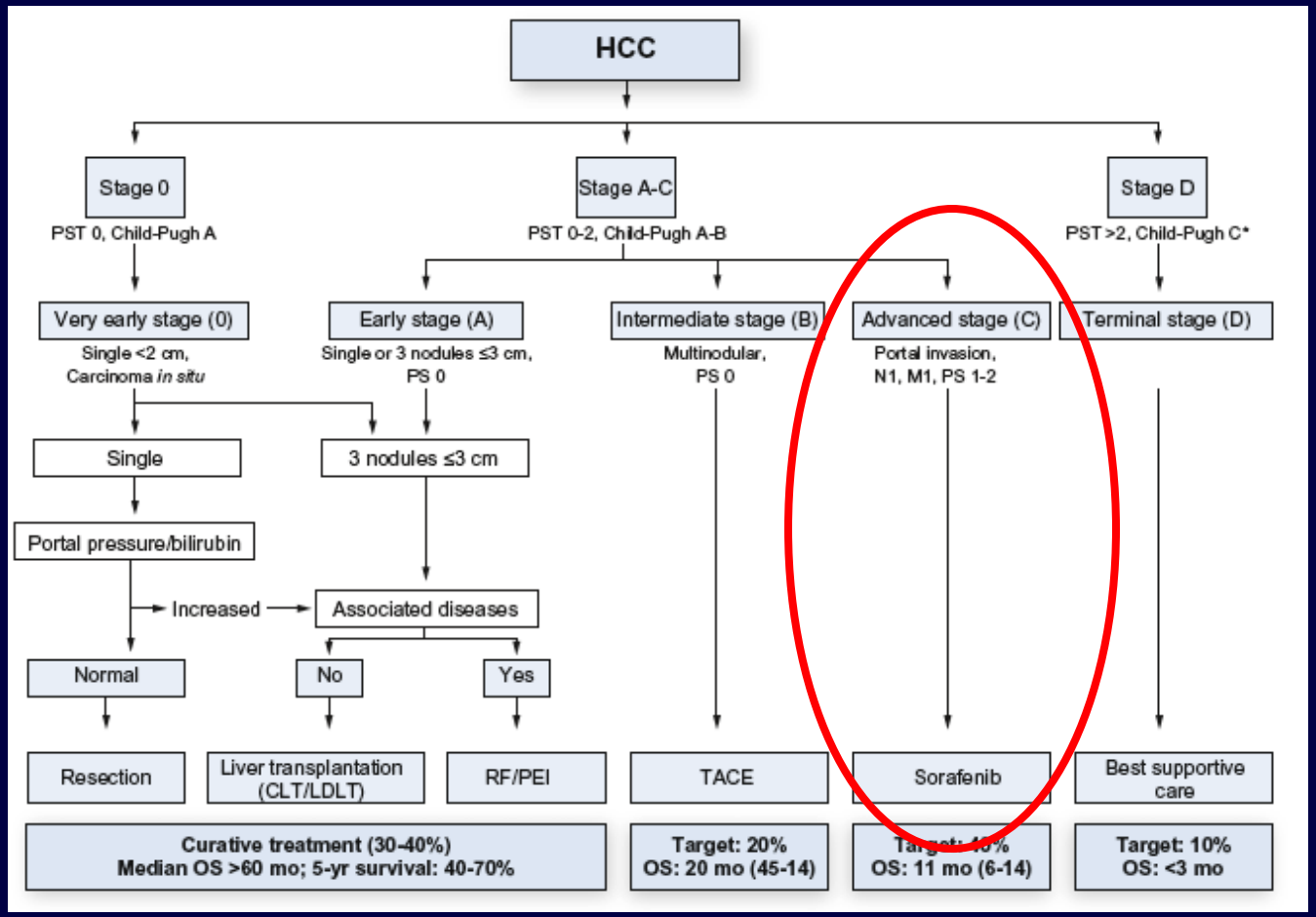
Survival: No difference

Intermediate

Segmental: Drug-Eluting Beads

Lobar: ^{90}Yttrium Microspheres

Advanced



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Advanced

In 2006: No systemic therapy

2007: SHARP Trial

Placebo	Sorafenib
7.9 mo	10.7 mo

$p = 0.00058$

Advanced

SORAFENIB

A Multi Tyrosine Kinase Inhibitor

BCLC C: 9.5 mo (vs 6 mo)

Advanced

EASL 2012

- Sorafenib is the standard systemic therapy for HCC. It is indicated for patients with well-preserved liver function (Child-Pugh A class) and with advanced tumors (BCLC C) or those tumors progressing upon loco-regional therapies
(evidence 1iA; recommendation 1A)

SORAFENIB:

Advanced HCC

Or

Failed Arterial Tx

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Advanced

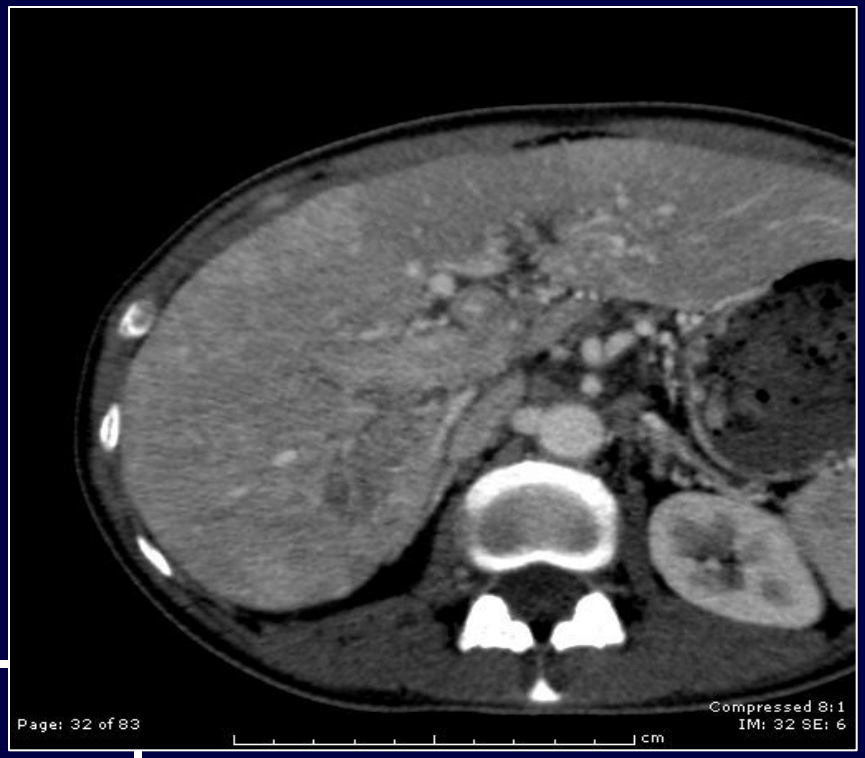
EASL 2012

Chemoembolization is recommended for patients with BCLC stage B, multinodular asymptomatic tumors without vascular invasion or extra hepatic spread **(evidence 1iiA; recommendation 1A)**

The use of drug-eluting beads has shown similar response rates than gelfoam-lipiodol particles associated with less systemic adverse events **(evidence 1D; recommendation 2B)**

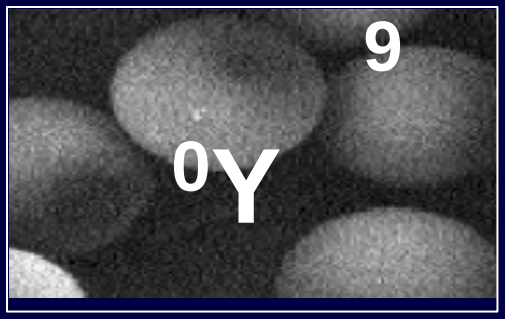
Chemoembolization is discouraged in patients with decompensated liver disease, advanced liver dysfunction, macroscopic invasion or extrahepatic spread **(evidence 1iiA; recommendation 1B)**

Bland embolization is not recommended



TACE discouraged in patients with macroscopic invasion

Advanced



BCLC								
A		Overall BCLC A	48 (46)	36 (78)	21 (46)	25.1 (8–27)	26.9 (17–30.2)	14 (29)
		Child–Pugh A	27 (25)	22 (88)	13 (52)	27.1 (7.5–n.c.)	20.5 (15–27.4)	9 (33)
		Child–Pugh B	21 (21)	14 (67)	8 (38)	13 (6.4–25.2)	29.1 (17–n.c.)	5 (24)
B		Overall BCLC B	83 (82)	57 (70)	42 (51)	13.3 (4.4–18.1)	17.2 (13.5–29.6)	13 (16)
		Child–Pugh A	48 (48)	34 (71)	24 (50)	13.3 (8–25.9)	17.3 (13.7–32.5)	7 (15)
		Child–Pugh B	35 (34)	23 (68)	18 (53)	17.4 (5.8–n.c.)	12.5 (6.4–25.4)	6 (17)
		Overall BCLC C	107 (99)	44 (44)	40 (40)	6.0 (4.6–8.8)	7.3 (6.5–10.1)	2 (5)
	Child–Pugh A	Overall	41 (40)	22 (55)	22 (55)	6.2 (3.7–11.7)	13.8 (8.8–17.7)	2 (5)
		PVT Absent	6 (6)	5 (83)	5 (83)	23.8 (10.8–n.c.)	47.4 (n.c.)	0
		PVT present	35 (34)	17 (50)	17 (50)	5.6 (2.3–7.6)	10.4 (7.2–16.6)	2 (6)
	Child–Pugh B	Overall	66 (59)	22 (37)	18 (31)	6.0 (4.5–8.8)	6.4 (4.9–7.7)	3 (5)
		PVT absent	9 (9)	6 (67)	4 (44)	13.7 (n.c.–23.6)	11.8 (n.c.–34)	1 (11)
		PVT present	57 (50)	16 (32)	14 (28)	5.9 (4.2–7.9)	5.6 (4.5–9.7)	2 (4)
	Non-(Child–Pugh B + PVT)		50 (47)	22 (47)	18 (38)	8.9 (4.2–13.6)	13.8 (10.2–20.4)	3 (6)
D (Child–Pugh C)			7 (5)	1 (20)	0	2.1 (n.c.–2.3)	2.5 (1–3.7)	0

291 patients

Child-Pugh A, BCLC C:
Safe
Survival 10.4 months

Gastroenterology 2010; 138: 52-64

Conclusions

HCC Increasing Worldwide

Surveillance

Referral to Transplant Center

Early: Surgery, Ablation

Intermediate: TACE or ^{90}Y

Advanced: Sorafenib

Thank You

Downstaging

A Comparative Analysis of Transarterial Downstaging for Hepatocellular Carcinoma: Chemoembolization Versus Radioembolization

Cohort comparison of 86 T3 patients

	TACE	**^{90}Y**
UNOS T3 ⟶ T2	31%	58%

p=0.023

American Journal of Transplantation 2009; 9: 1920–1928

Portal Vein Thrombosis

Safety and Efficacy of ^{90}Y Radiotherapy for Hepatocellular Carcinoma With and Without Portal Vein Thrombosis

macroscopic embolization. When compared with other embolic treatments, the safety of radioembolization in patients with portal vein thrombosis and hepatofugal flow represents a unique opportunity for investigation.

Given the incidence of PVT in this patient population, we conclude that the use of minimally embolic ^{90}Y glass microspheres to treat patients with HCC complicated by branch/lobar PVT is safe with favorable tumor response rates. Further investigation is needed in addressing recurrence rate and long-term survival benefit.

Branch/Lobar PVT: ^{90}Y safe, favorable tumor response rates

Hepatology 2008; 47: 71-81