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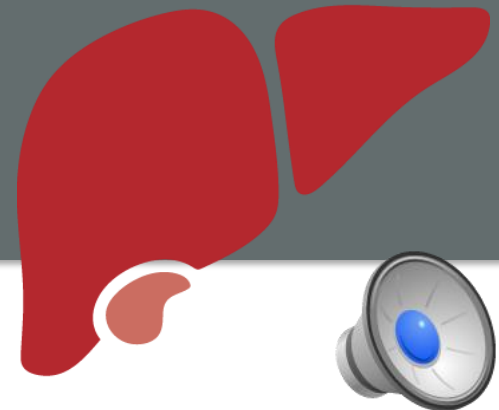
An Interventionalist's Perspective on Radioembolization: Technical Aspects, Efficacy, and Future Endeavors

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No conflicts of interest.



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Introduction

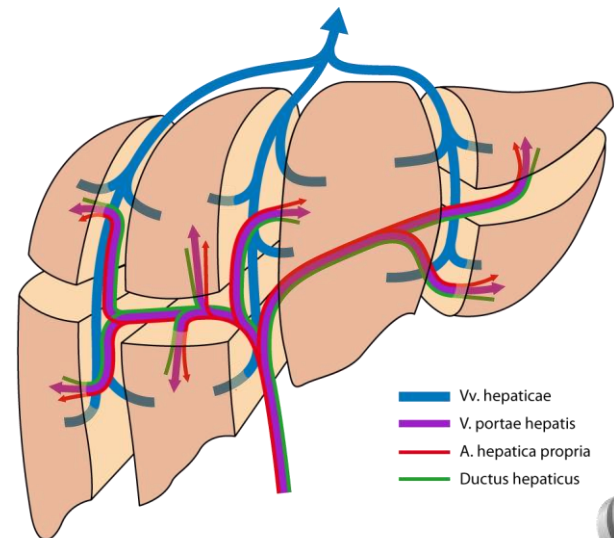
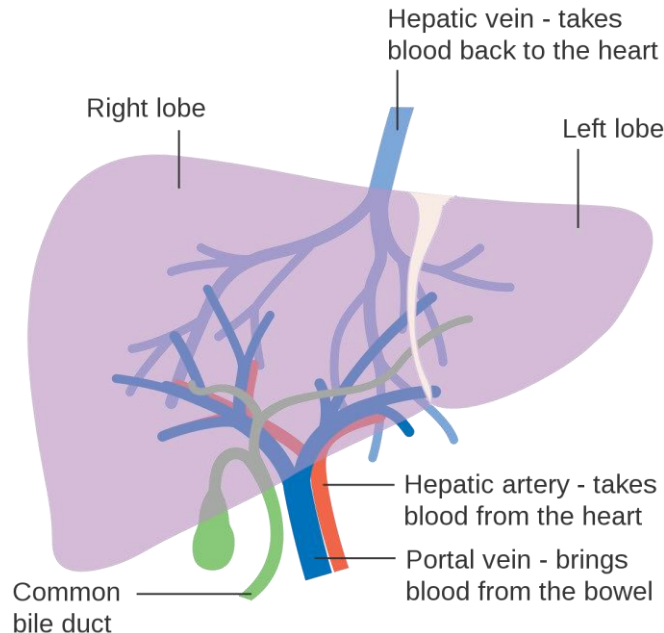
- Hepatic embolotherapy is an expanding field of interventional radiology, which utilizes therapeutic and embolic agents to perform bland embolization, transarterial chemoembolization (TACE) with ethiodized oil, intra-arterial chemotherapy with drug-eluting beads (DEB), and selective internal radiation therapy (SIRT) to treat primary malignancies of the liver.
- Tumors treated:
 - *Hepatocellular carcinoma*
 - *Cholangiocarcinoma*
 - *Sarcoma*
 - *Secondary liver malignancies: metastatic colorectal carcinoma, neuroendocrine tumors, breast carcinoma, and a myriad of other neoplasia with predilection to hepatic metastasis.*





Basis of Therapy

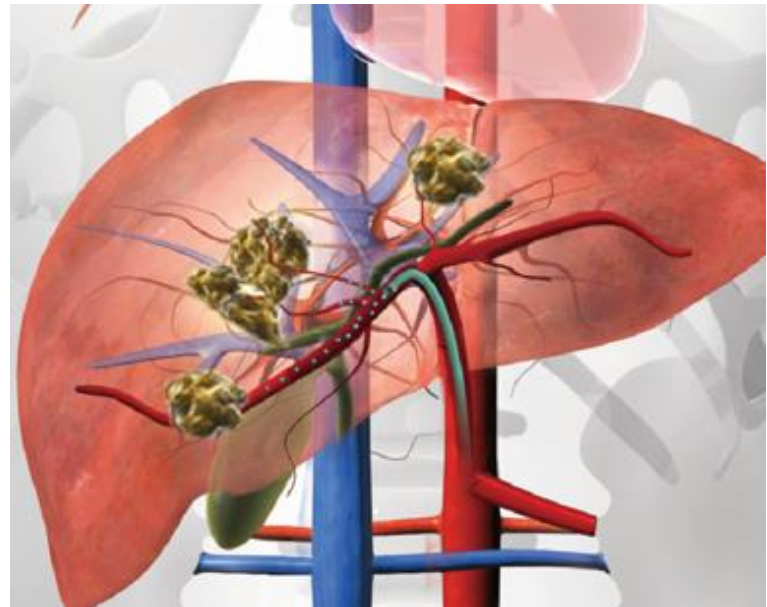
- Complex interaction between tumor cells and normal liver parenchyma is realized in the process of vascular recruitment = **tumor angiogenesis**
- Unique characteristic of hepatic tumors → almost exclusive recruitment of vascular supply from the **hepatic arterial system**





Targeting Arterial Vasculature

Any treatment or embolic agent that is delivered via the hepatic artery will result in a higher deposition of therapeutic into the tumor via its vasculature, thereby reducing exposure to and protecting the surrounding normal liver parenchyma.





History

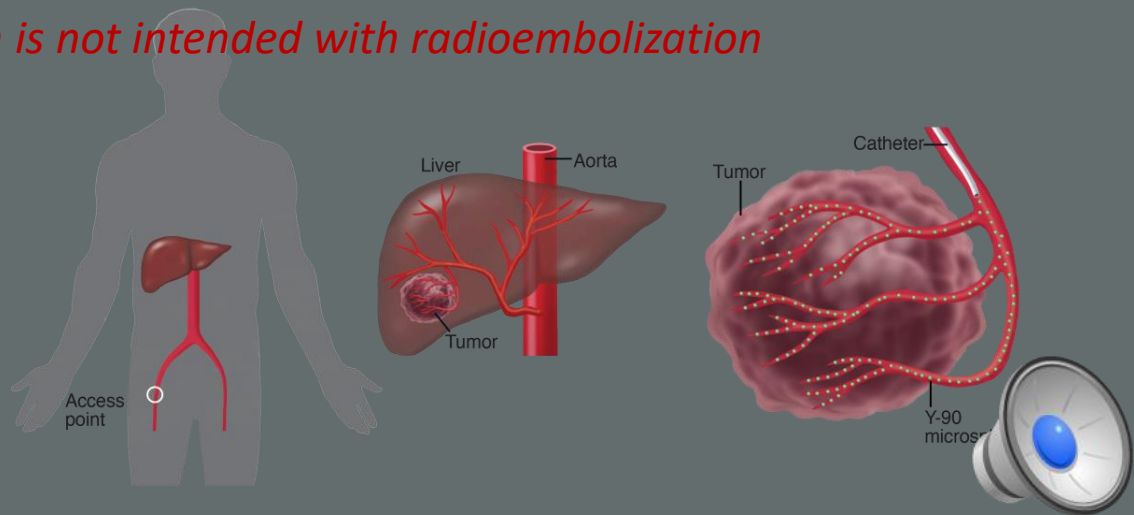
- Normal hepatic parenchyma is very sensitive to tumoricidal radiation doses.
- Radioembolization delivers high-dose internal radiation to the tumor via the hepatic artery.
 - Differs from external beam radiation therapy, where radiosensitivity of normal hepatocytes limits the amount of radiation that can be delivered before the development of radiation-induced liver disease (RILD)
- Intra-arterial injection of yttrium oxide ($^{90}\text{Y}_2\text{O}_3$) contained in a metal particle (50–100 μ micron) was first used by Nolan and Grady in 1969
 - Small number of patients but showed a favorable response, observed by the reduction in size of palpable masses





What is Radioembolization?

- Performed with small microspheres loaded with yttrium-90, a beta-emitting isotope with short half-life (64.2 hours)
- Decays into the stable element zirconium 90
- Microspheres emit high-energy, low-penetration radiation (2.5 mm) to the tumor
- *Hepatic artery occlusion is not intended with radioembolization*





Available Devices

- **TheraSphere** (MDS Nordion, Ottawa, Canada)
 - Nonbiodegradable glass microspheres with diameters ranging between 20 and 30 μ microns
 - High specific activity (2,500 Bq) per sphere
 - 1.2 million microspheres are present in a vial
 - Approved by the US Food and Drug Administration (FDA) for treatment of hepatocellular carcinoma (HCC) patients
- **SIR-Sphere** (Sirtex, Lane Cove, Australia)
 - Biodegradable resin microspheres with diameters ranging between 20 and 60 μ microns
 - Lower specific activity (50 Bq) per sphere
 - Approved by the FDA for use in patients with metastatic colorectal cancer to the liver





Pretreatment Evaluation

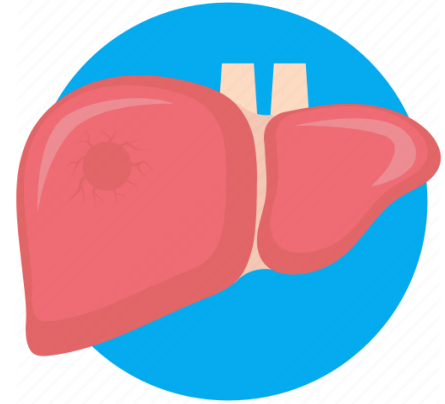
- Baseline laboratory work-up is essential to determine the pretreatment functional status of the liver
 - **Childs Pugh Score**: Evaluate the synthetic function of the liver (i.e., total bilirubin level, serum albumin, and international normalized ratio, or INR) and clinical assessment (i.e., degree of ascites and degree of hepatic encephalopathy).
 - **ALBI Score**: Evaluate the synthetic function of the liver (i.e. albumin and total bilirubin)
- Patients should have a bilirubin ***less than or equal to 2 mg/dL***





Pretreatment Evaluation

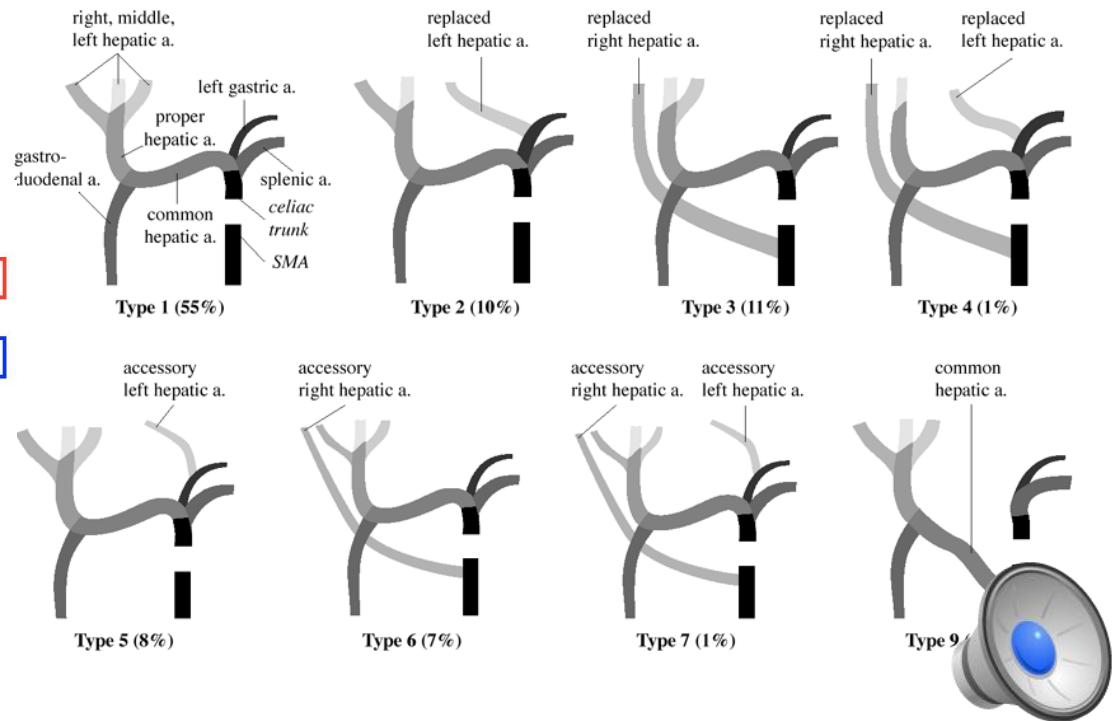
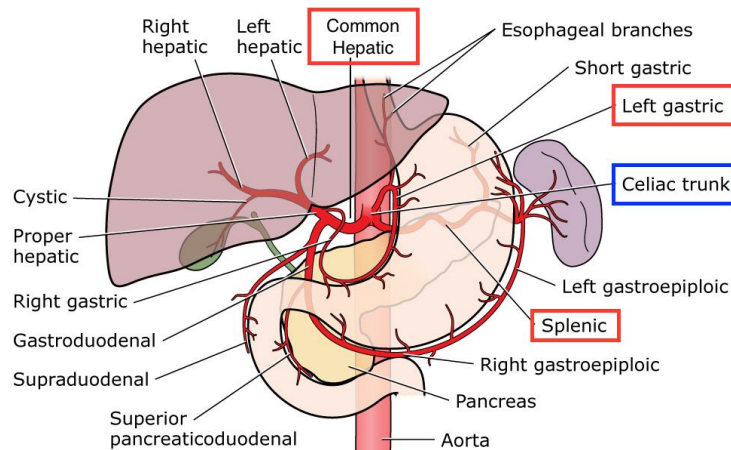
- Establish baseline tumor marker levels
 - *Serum α -fetoprotein (AFP)*
- Clinical evaluation is required
 - Eastern Cooperative Oncology Group (ECOG) performance status assesses how the disease affects the daily living abilities of the patient
 - ECOG status *2 and above* are **not** considered ideal candidates for this treatment
- Pretreatment cross-sectional imaging (with and without contrast) is essential for treatment planning and for comparison to post-treatment scans
 - Ideal candidates have HCC confined to the liver with tumor comprising less than 70% of the liver volume





Planning Angiography

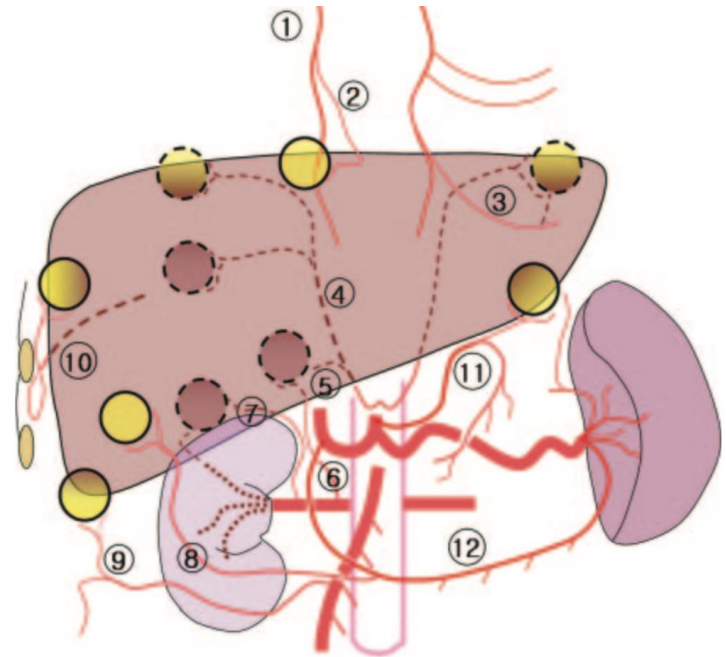
Pretreatment aortic, superior mesenteric, and celiac trunk angiography to accurately assess the hepatic vasculature, surrounding structures, portal vein patency, and the presence of arterioportal shunting



Planning Angiography

Tumor may parasitize blood flow from surrounding vessels

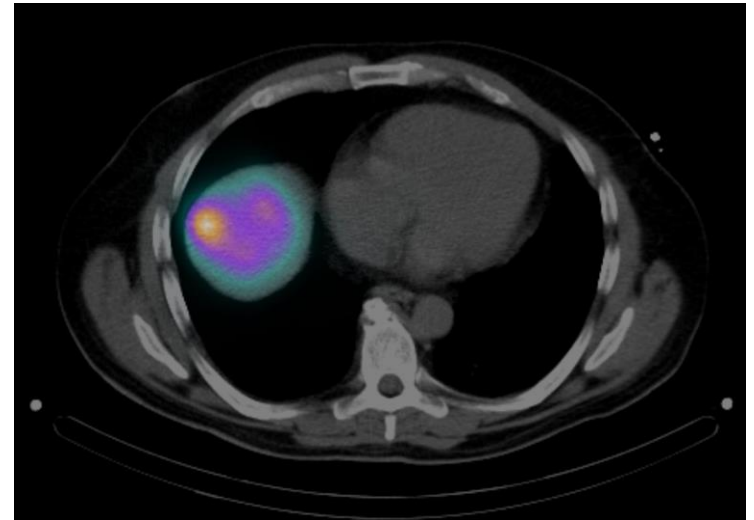
- *Internal mammary artery*
- *Pericardiophrenic artery*
- *Musculophrenic artery*
- *Inferior phrenic artery*
- *Superior adrenal artery*
- *Inferior adrenal artery*
- *Superior renal capsular artery*
- *Omental branch* ?
- *Colic branch Intercostal artery*
- *Left gastric artery*
- *Gastroepiploic artery*





^{99m}Tc Macroaggregated Albumin Nuclear Scan

- About 4–5mCi of ^{99m}Tc-MAA is injected into the cannulated hepatic artery to assess splanchnic and pulmonary shunting.
- Performed to discern whether arteriovenous shunts associated with the tumor are diverting blood flow to the lungs or bowel.



- $LSF = (total\ lung\ counts) / (total\ lung\ counts + total\ abdomen\ counts)$
 - A lung dose greater than 30 Gy per treatment or cumulative lung dose of 50 Gy places the patient at increased risk





Dose Calculation

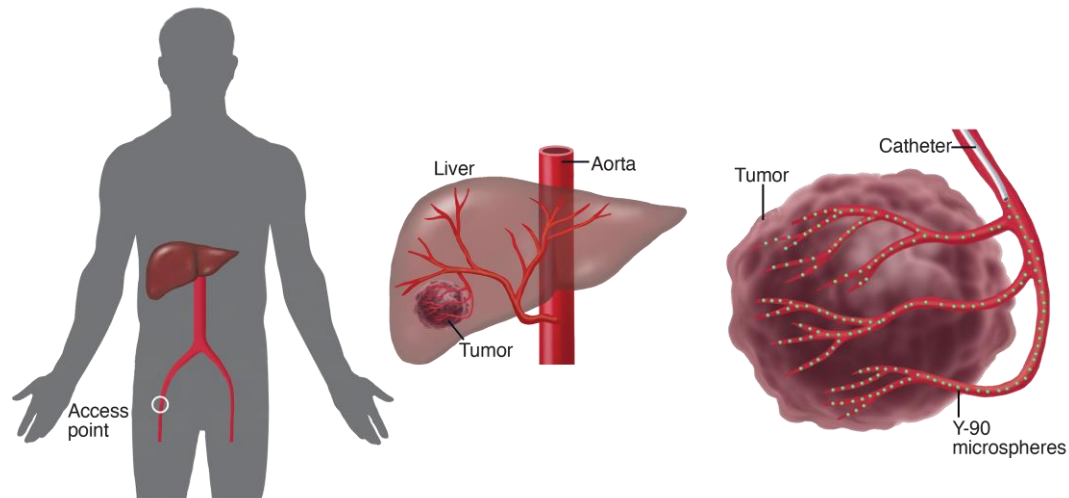
- Dose activity is determined based on taking into consideration the body surface area (BSA method) or treated volume of tissue (partition method), after which the dose is ordered when the patient returns approximately 1-2 weeks later





Yttrium 90 Administration

- Procedure is performed on an outpatient basis
- Initial access into femoral or radial artery
- Selective catheterization of the vessel chosen by pretreatment angiography is performed
- Administration of radiotracer utilizing standard protocol





Hospital Course

- Acute and subacute toxicities associated with radioembolization are less severe and better tolerated than those toxicities associated with conventional hepatic embolization procedures
- Better toxicity profile, combined with the lower incidence of postembolization syndrome associated with radioembolization, allows for same day discharge
- At discharge:
 - *Zofran/Phenergan, Oxycodone/NSAIDs, Colace 100 mg BID*





Complications

- **Liver abscess**
 - *Risk*: 50% if sphincter of Oddi compromised
 - *Risk factors*: Compromised sphincter of Oddi
 - *Risk mitigation*: Broad spectrum antibiotics + Bowel prep
 - *Postcomplication care*: Drainage, Antibiotics
 - Inpatient: Piperacillin/Tazobactam; Ceftriaxone + Metronidazole
 - Outpatient: Ciprofloxacin + Metronidazole
 - Signs and symptoms of intrahepatic abscess appear 2 to 4 weeks post TARE
- **Liver failure**
 - *Risk*: 1 - 2 %
 - *Risk factors*: Child Pugh C, Elevated bilirubin (> 3 mg/dL), Low albumin (< 2 mg/dL) independent risk factors
 - *Risk mitigation*: Superselective embolization
 - *Postcomplication care*: Supportive care





Complications

- **Radiation Pneumonitis**
 - *Risk*: < 1 %
 - *Risk factors*: Tumor AV shunting (shunting should not exceed 10%)
 - *Risk mitigation*: Bland embolization of shunt
 - *Postcomplication care*: Supportive care
- **Nontarget Embolization**
 - *Risk*: 10-15%
 - *Risk factors*: Aberrant anatomy
 - *Risk mitigation*: Superselective embolization
 - *Postcomplication care*:
 - Gastric: Supportive care, proton pump inhibitors, hydration/NPO; gastrectomy
 - Gallbladder: Hydration, NPO status, and pain control; cholecystectomy





Post-Treatment Assessment

- Tumor response of patients treated with Y90 is evaluated with cross-sectional abdominal imaging, commonly computed tomography (CT) or magnetic resonance imaging (MRI)
- Follow-up imaging with either CT or MRI is typically obtained 1 month after the procedure
- During follow-up outpatient visits, patients are assessed for adverse events
- Alpha-fetoprotein (AFP) response seen after transarterial locoregional therapy could be used as an ancillary method of assessing tumor response





EXAMPLE CASE #1

- 60 year old male with history of HCV complicated by HCC
- Expansile mass at the hepatic dome with extension into the right anterior branch of the portal vein.
 - *Childs Pugh Score A (TB 0.9; Albumin 4.7)*
 - *ECOG 2*
 - *AFP 396*
- Post treatment AFP decreased to 6.6





Level of Evidence

- *A 2010 study by Hilgard et al reported the outcome of 108 patients with advanced HCC treated with glass radioembolization. Time to progression (TTP) was 10 months with a median overall survival of 16.4 months, which compares favorably with sorafenib (TTP 5.5 months, survival 10.7 months, SHARP data). No lung or visceral toxicity was observed.*
- *Salem et al. reported an overall survival (OS) of 17.2 months in Child–Pugh A disease*

Table 1 Clinical outcomes of transarterial radioembolization for hepatocellular carcinoma

	Salem et al. [19]	Hilgard et al. [30]	Sangro et al. [31]	Mazzaferro et al. [32]
Patients	291 TARE pts	108 TARE pts	325 TARE pts	52 TARE pts with BCLC B and C
Response rate	WHO: 42% EASL: 57%	EASL: 40%	Not assessed	WHO: 40% EASL: 40%
Time-to-progression (months)	7.9	10	Not assessed	11
Survival (months)	CP ^a A: 17.2 CP B: 7.7	16.4	BCLC ^b A: 24.4 BCLC B: 16.9 BCLC C: 10.0	15

BCLC Barcelona Clinical Liver Cancer, CP Child–Pugh, *pts* patients

^a WHO: World Health Organization criteria that assesses tumor response on cross-sectional imaging based on size of the largest diameter of the tumor

^b EASL: European Association for the Study of the Liver criteria that assess tumor response on cross-sectional imaging based on the degree of necrosis





TACE vs. TARE

- Many studies in interventional oncology have compared TARE to its transarterial counterpart TACE. No prospective randomized control trials (RCTs) have shown a statistically significant difference in OS.
 - *A large comparative effectiveness study published in 2011 matched 122 TACE vs. 123 radioembolization patients. Radioembolization resulted in a significantly longer TTP (13.3 months) versus TACE (8.4 months, $p = 1/4 0.046$). However, overall survival of the two techniques was not statistically different (TACE: 17.4 months and radioembolization: 20.5 months).*
- TARE was better tolerated than TACE, required less hospitalization, and necessitated fewer treatment sessions
- TARE also more effective at down staging patients





Chemotherapy vs. TARE

- Oral sorafenib chemotherapy is considered the standard of care for advanced stage HCC on the basis of the 2008 Sorafenib Hepatocellular carcinoma Assessment Randomized Protocol (SHARP) trial
- **TARE results in similar survival outcomes to sorafenib**
- Some studies have suggested that TARE is more advantageous than sorafenib in PVT.
 - *Edeline et al. calculated a median OS of 26.2 versus 8.7 months in patients treated with TARE versus sorafenib, respectively.*





Can radioembolization be curative?

Radiation Segmentectomy

- Historically, resection and ablation are curative treatment options for HCC < 3 cm
- Highly selective radioembolization (so-called *radiation segmentectomy*), is a **novel** treatment alternative to ablation
- Dosing achieved by infusing a calculated lobar dose (120–150 Gy) into a segmental tumor-feeding vessel. As such, segmental doses are higher than lobar doses by the ratio of lobar:segmental liver volumes.
- Radiation segmentectomy not only treats lesions in high-risk locations for ablation, it also avoids the need for transhepatic tumor puncture and the small potential risk of tumor tract seeding.
- Studies confirm **90 to 100% necrosis** observed in all lesions at explant
- Ablation vs. TARE OS comparable for tumors < 5 cm and Child-Pugh A/B





EXAMPLE CASE #2

- 65 year old male with history of NASH cirrhosis presenting with abdominal pain
- MRI abdomen with/without contrast confirming right hepatic mass in segment VIII, suspicious for hepatocellular carcinoma and confirmed by biopsy
 - *Childs Pugh Score A (TB 0.8; Albumin 4.3)*
 - *ECOG 3*
 - *AFP 2.1*





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Thanks!

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