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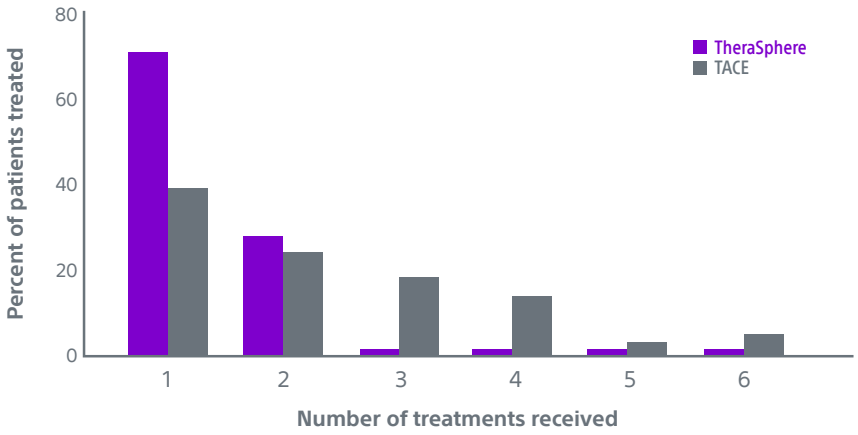
THERASPHERE™ Y-90 Glass Microspheres | Y-90 / DEB-TACE / cTACE

Comparison of contemporary transarterial radioembolization (TARE) treatment via TheraSphere Y-90 Glass Microspheres to drug-eluting bead transarterial chemoembolization (DEB-TACE) and conventional transarterial chemoembolization (cTACE) in patients with hepatocellular carcinoma (HCC) shows longer time to tumor progression as a cost-effective, efficient treatment option

GLASS Y-90 / DEB-TACE / CTACE

	Glass Y-90	DEB-TACE	cTACE
Mechanism of Action	Delivery of high dose β–radiation of radioactive glass microspheres	Delivery of chemo agent (e.g. doxorubicin) coupled with embolic effect of beads	Injection of oil-doxorubicin emulsion followed by embolization (via gelfoam slurry/beads)
Benefits	Targeted delivery of high dose β–radiation directly to the tumor, while minimizing damage to healthy tissue Well-tolerated with minimal side effects[1] Minimal concern of stasis or reflux[8-11]	Higher drug-dose to tumor, lower systemic concentration than cTACE[2,4,5] Comparable safety profile with lower side effects compared to cTACE[4,6,7] Alternative option in presence of high lung shunt	Visibility (Radiopacity of Lipiodol) Cost per infusion Historical familiarity
Challenges	Patient mapping required Patient performance status Medicaid Coverage	Patient admitted for 24-48 hr observation of post-embolic syndrome Permanent embolization of tumor-feeding vessels can create challenges for future treatment[17] Timelag with involvement of pharmacy for loading of beads with drug	Patient admitted for 24-48 hr observation of post-embolic syndrome Chemotherapy in Lipiodol washes out of tumor relatively quickly[3] leading to less effective tumoricidal effect and more systemic side effects[4,6,7]
Average # of Treatments	Typically 1x outpatient treatment (~1.2 per patient)[12]	Often more than 1 treatment required (~1.43 to 2.83 per patient)[12]	Often more than 1 treatment required (~2.5 to 3 per patient)[1,2]
Embolic Effect	Low	High	High
Approved for Unresectable HCC	☑		
Future Treatment Options	Any Therapy[3,4] (TACE, RFA, Y-90, etc)	Limited due to impact to vasculature tract	Limited due to impact to vasculature tract

Number of treatments received in patients treated with TACE vs. TheraSphere



A PROVEN CLINICAL AND ECONOMIC TREATMENT OPTION

- Fewer treatments and less hospitalizations than cTACE[13]
- A cost-effective bridging therapy as patients require lower number of LRT sessions prior to liver transplant[14]

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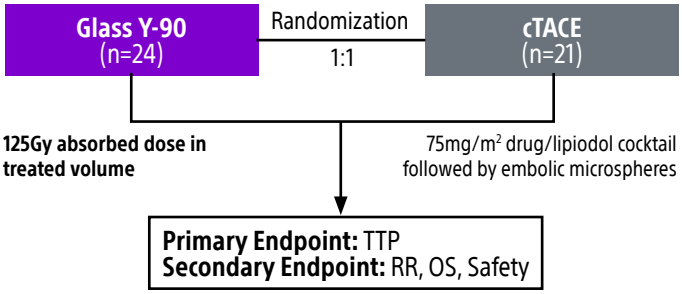
Contemporary randomized-control trials of PREMIERE and TRACE show improved time to tumor progression when utilizing Glass Y-90 over cTACE and DEB-TACE respectively.

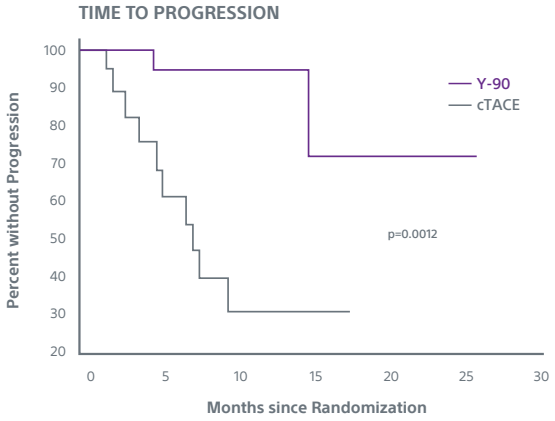
PREMIERE TRIAL[15]

Prospective, randomized, open label, single-center study from 2009-2015
cTACE vs. Glass Y-90 TARE for treatment of unresectable, unablatable HCC



Inclusion:

- Image/biopsy confirmed HCC, unablatable/unresectable HCC with no vascular invasion, Child-Pugh A/B, Bilirubin ≤2.0 mg/dl, AST/ALT ≤5x upper limit of normal
- BCLC A patients not eligible for ablation or resection due to lesion size/location, liver function, multifocal disease, or presence of portal hypertension
- BCLC B patients were considered eligible for cTACE or Glass Y-90 with the curative intent of liver transplantation

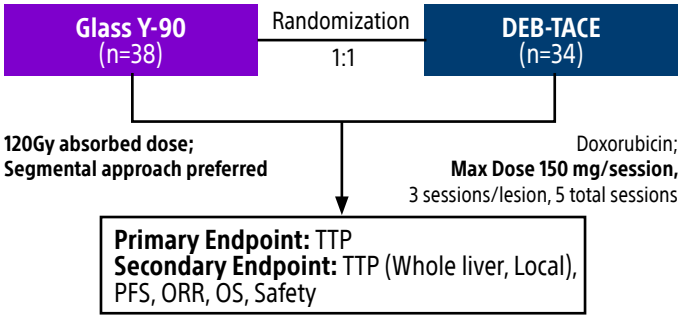


>26 mo vs. 6.8 mo; p=0.0012

Glass Y-90 Treatment showed longer time to tumor progression than cTACE

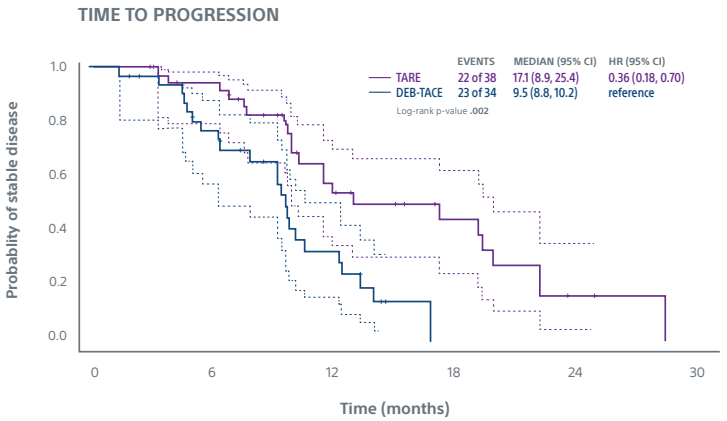
TRACE TRIAL[16*]

Prospective, randomized, open label, single-center superiority study from 2011-2018
DEB-TACE vs. Glass Y-90 TARE for treatment of unresectable HCC



Inclusion:

- Image/biopsy confirmed, unablatable, unresectable HCC not eligible for transplant
- BCLC B, extended to BCLC A not amendable to surgery or ablation, Child-Pugh A, ECOG 1



17.1 mo vs. 9.5 mo; HR: 0.36, p=0.002

Glass Y-90 Treatment showed longer time to tumor progression than DEB-TACE

*The loading of doxuribicin to LCBeads is outside of the indication for use in the USA.

CONCLUSIONS:

- Contemporary prospective randomized control trials of patients with HCC shows consistently longer time to tumor progression using TheraSphere Y-90 Glass Microspheres than conventional or drug-eluting bead TACE treatments.
- Unlike TACE, TheraSphere Y-90 Glass Microspheres with the microembolic effect better maintains patient eligibility for future treatment for HCC.
- Typically with 1 outpatient treatment, requiring fewer treatments than DEB-TACE or cTACE, TheraSphere Y-90 Glass Microspheres is a cost-effective treatment option for patients with HCC.

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TheraSphere™ Yttrium-90 Glass Microspheres

INDICATION FOR USE: TheraSphere is indicated for use as selective internal radiation therapy (SIRT) for local tumor control of solitary tumors (1-8 cm in diameter), in patients with unresectable hepatocellular carcinoma (HCC), Child- Pugh Score A cirrhosis, well-compensated liver function, no macrovascular invasion, and good performance status. **CONTRAINDICATIONS:** TheraSphere is contraindicated in patients: whose Tc-99m macroaggregated albumin (MAA) hepatic arterial perfusion scintigraphy shows any deposition to the gastrointestinal tract that may not be corrected by angiographic techniques • who show shunting of blood to the lungs that could result in delivery of greater than 16.5 mCi (0.61 GBq) of Y-90 to the lungs. Radiation pneumonitis has been seen rarely in patients receiving doses to the lungs greater than 30 Gy in a single treatment. • in whom hepatic artery catheterization is contraindicated, such as patients with vascular abnormalities or bleeding diathesis • who have pulmonary insufficiency (conventionally defined by an arterial oxygen pressure (Pa,O2) of < 60 mmHg, or oxygen saturation (Sa,O2) of < 90%) or severe liver dysfunction, including hepatic encephalopathy, clinically evident ascites or treatment with diuretics for ascites • with portal vein thrombosis (PVT) Type 4 involvement and lack of Tc-99m MAA deposition on the PVT seen on the Tc-99m MAA imaging with >70% tumor replacement in the liver • with comorbidities or poor overall health (e.g., ECOG performance status rating > 2) which may make the patient a poor candidate for locoregional radiation treatment. • who are pregnant. **WARNINGS:** The following pre-treatment, high-risk factors (disease characteristics) have been associated with serious adverse events deemed possibly related to use of the device: infiltrative tumor type • tumor nodules too numerous to count • AST or ALT > 5 times ULN • bilirubin > 2 mg/dL • tumor volume > 50% combined with albumin < 3 g/dL. Keep the TheraSphere dose vial upright and stored in its lead pot before and during patient treatment, except as required for radiation measurement. Do not open the dose vial acrylic shield prior to patient treatment. Post-treatment, waste materials require caution to prevent contamination and beta shielding due to residual glass microspheres. PRECAUTIONS: GENERAL PRECAUTIONS: As in any intra-arterial procedure, aseptic technique should be practiced, and care should be taken to ensure minimum patient anesthesia exposure extraneous to therapeutic objective. • Consideration of patient comorbidities should be used when determining the type and volume of fluid to infuse via catheter to avoid electrolyte imbalance, fluid shift, and hyperglycemia. • It is important to avoid any aggressive arterial procedure that may lead to arterial spasm that impairs TheraSphere distribution into the perfused liver target volume which may lead to underdosing or non- target deposition of TheraSphere. PRECAUTION IN PATIENTS WITH IMPAIRED LIVER FUNCTION: No efficacy or safety data from the LEGACY study are available to support the use of the device in patients with Child-Pugh score B or C cirrhosis. PRECAUTION IN VULNERABLE PATIENTS: No effectiveness or safety data are available to support the use of the device in children or breast- feeding women. ENDOCRINE DISRUPTION, CARCINOGENICITY, MUTAGENICITY, TOXICITY TO REPRODUCTION: Ideally the use of this radioactive device in women of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses. RADIATION SAFETY: Radioactive products should be used only by healthcare professionals who are qualified by specific training in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides. • As in the use of any radioactive material, ensure minimum radiation exposure to the patient extraneous to the therapeutic objective, and to minimize radiation exposure to workers and others in contact with the patient. RELEASE AND POST-TREATMENT PRECAUTIONS: Post treatment patient care: use universal precautions for body fluid contact. Trace Y-90 may be detectible in blood and urine; handle with gloves and dispose as normal body fluids. The radiation field is expected to be less than 1 mrem/h (10 µSv/h) at 3 ft (1 m) from the patient's abdomen. Supplemental shielding and segregation of the patient are not required to maintain exposure to others below regulated limits. • Release instructions: The patient should follow good hygiene (e.g., proper hand washing). Caregivers, family, and others do not require restrictions on patient contact; however, they can minimize their radiation exposure by avoiding prolonged time (>12 hours per day) within 1 ft (0.3 m) of the patient's abdomen for the first week post therapy. Patients should be advised that radiation emitted from the patient may be detectible at security screening (e.g., international travel). • Special precautions post-administration: If the patient requires hospitalization, surgery, medical assessment or treatment regarding any part of their thorax or abdomen within first 2 weeks of treatment, the patient should advise the hospital and treating physician of the Y-90 TheraSphere implant. The physician should consult their radiation safety staff for handling and disposal of liver tissue. • Special liver tissue handling: Special liver tissue handling may be required for post-treatment surgery, explant, or transplant since the glass microspheres remain permanently implanted in the liver tissue. Disclosure of the treatment will be required if cremation is considered. **POTENTIAL ADVERSE EVENTS:** The use of this product leads to irradiation of both tumorous and normal liver tissue. As a result, patients with compromised liver function may be at greater risk of liver function impairment and hence could experience complications. Clinical side effects usually occur within the first 4 to 6 weeks after treatment. Based on clinical trial data, literature reviews and post market surveillance, adverse events potentially associated with treatment using Y-90 microspheres, including TheraSphere, may include the following: Allergic reaction • Altered liver function, acute or chronic • Anorexia • Anxiety • Ascites • Bile Duct injury • Bleeding/hemorrhage • Chills / rigors • Cholecystitis (inflammatory or infectious) • Colitis • Death • Dehydration • Diarrhea • Dizziness • Dyspnea • Edema (any location) • Electrolyte abnormalities • Elevated BUN/creatinine • Fall • Fatigue • Fever • Gastrointestinal bleeding / hemorrhage • Gastrointestinal ulcer or ulceration • Hepatic encephalopathy • Hepatorenal failure • Hiccups • Hypertension • Hypotension • Infection (any location) • Liver failure, acute or chronic • Lymphopenia • Malaise • Mood alteration • Muscle weakness • Nausea • Neutropenia • Pain (any location) • Pancreatitis • Platelet count abnormalities • Pleural effusion • Portal hypertension • Pre-existing chronic liver disease decompensation • Pulmonary edema • Pulmonary fibrosis • Radiation hepatitis • Radiation induced disease, acute • Radio Embolization Induced Liver Disease (REILD) • Sepsis • Supraventricular arrhythmia • Thrombosis (arterial or venous) • Tumor inflammation (including tumor edema) • Tumor-lysis syndrome • Vomiting • Weight loss. Complications related to the administration procedure itself may include: Allergic reaction: Arterial injury including vessel dissection • Aspiration pneumonia • Bruising/bleeding/hematoma at site • Constipation/abdominal distension • Fatigue • Flushing • Infection • Nausea • Nerve damage. **CAUTION:** Federal (USA) law restricts this device to sale by or on order of a physician. **PI-992004-AA Note:** Dose to liver does not exceed 150 Gy.

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