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THERASPHERE™ Y-90 Glass Microspheres | Y-90 & Liver Transplant

Contemporary clinical trial data in select patients demonstrates achievement of surgical candidacy and preservation of transplant eligibility with longer duration of local tumor control in patients with unresectable Hepatocellular Carcinoma (HCC) treated with TheraSphere Y-90 Glass Microspheres.[1-4]

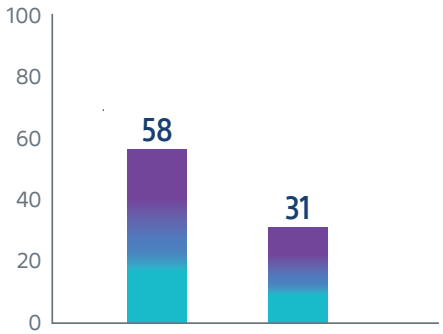
Key Advantages of downstaging HCC prior to or as a bridge to transplant[1]

- Successful downstage may impart insight into patient's tumor biology and improve patient selection for optimal post-transplant outcomes
- Patients are conferred UNOS priority status upgrade if they meet MILAN criteria of T2 or less

Aids in Achieving Transplant Candidacy

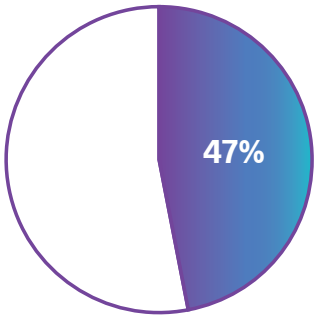
TheraSphere Y-90 Glass Microspheres was successfully utilized for T3 patients to downstage to T2, and T2+ patients downstaged to ≤ T2, 58% and 47% of the time respectively, allowing for achievement of transplant candidacy.

T3 DOWNSTAGED TO T2



Lewandowski, et. al., 2009[1]

T2+ DOWNSTAGED TO ≤T2

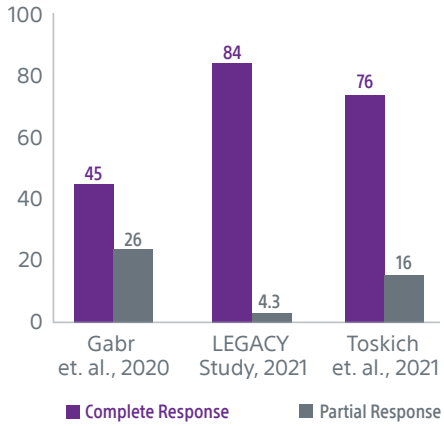


Gabr, et. al., 2020[2]

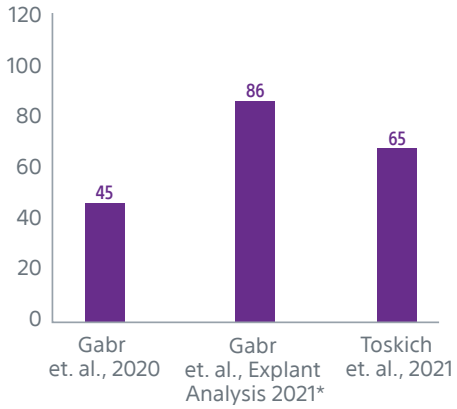
Produces Strong Local Tumor Control

TheraSphere provides strong local tumor response, and evidence demonstrating a high degree of complete pathologic necrosis.

Local Tumor Response Post Y-90 (%)
(Imaging Data)



Complete Pathologic Necrosis (%)
(Explant Data)

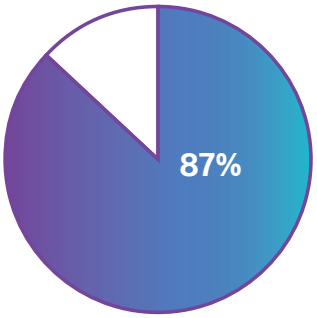


*A 45 patient multicenter analysis of individuals who underwent Y-90 from 2014 to 2017 and subsequently transplanted or resected, explant analysis showed twenty-four out of twenty-eight (86%) patients who had [a Y-90] dose > 190 Gy achieved CPN[5]

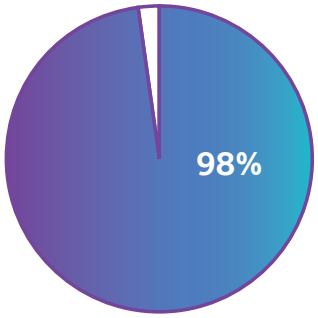
Locoregional Therapy (LRT) of Choice for Preserving Transplant Eligibility

Consistently high percentage of patients were bridged to liver transplant in contemporary clinical trials utilizing TheraSphere Glass Y-90 as the locoregional therapy of choice for bridging.

Percentage of patients preserved within Milan Criteria for Transplant



Salem, et. al., 2016[3]
(PREMIERE Trial)



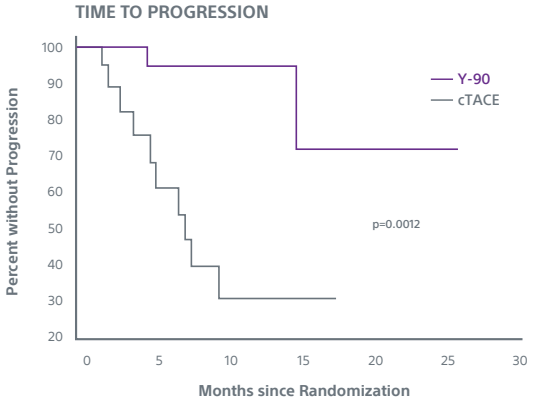
Gabr, et. al., 2020[2]

Extends Time to Tumor Progression

TheraSphere is proven to extend time to tumor progression, as evident in the Randomized Control Trials (RCT) of PREMIERE and TRACE trials showing significantly improved time to tumor progression when utilizing Glass Y-90 over conventional transarterial chemoembolization (cTACE) and drug eluting bead transarterial chemoembolization (DEB-TACE) respectively.

PREMIERE TRIAL[3]

Prospective, randomized, open label, single-center study of 45 patients from 2009-2015 cTACE vs. Glass Y-90 TARE for treatment of unresectable, unablatable HCC

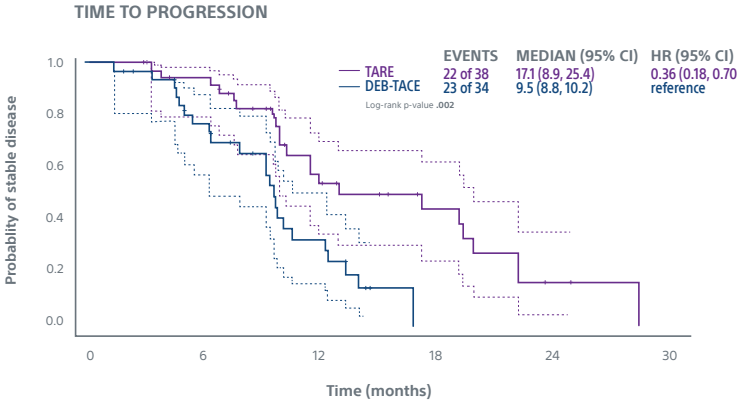


>26 mo Y-90 vs 6.8 mo cTACE, p=0.0012

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

TRACE TRIAL[4]

Prospective, randomized, open label, single-center superiority study of 72 patients from 2011-2018 DEB-TACE vs. Glass Y-90 TARE for treatment of unresectable HCC



17.1 mo TARE v 9.5 mo DEB-TACE, p=0.002

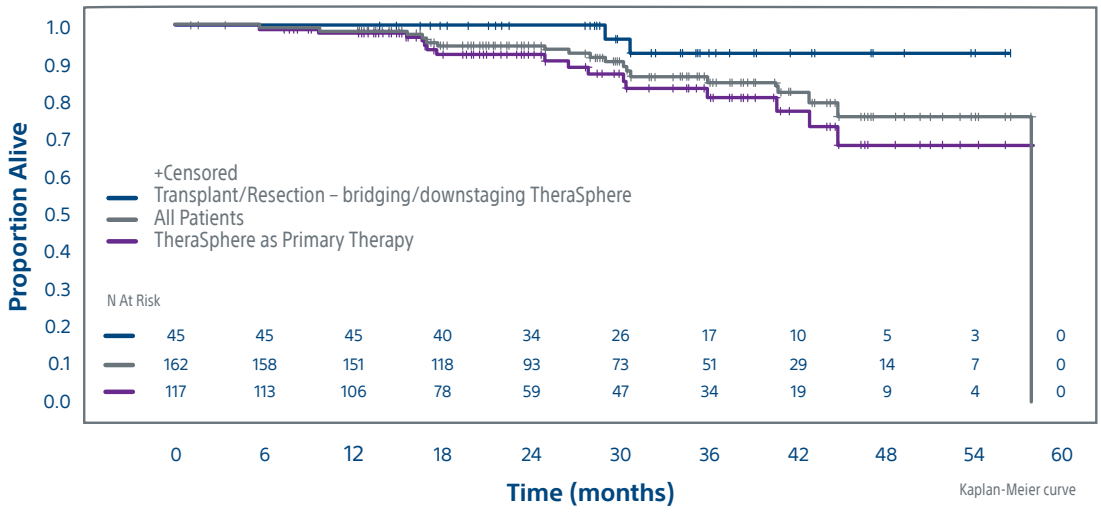
Glass Y-90 Treatment showed longer time to tumor progression than DEB-TACE

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

Neoadjuvant use for Liver Transplant showed strong Overall Survival (OS) Outcomes

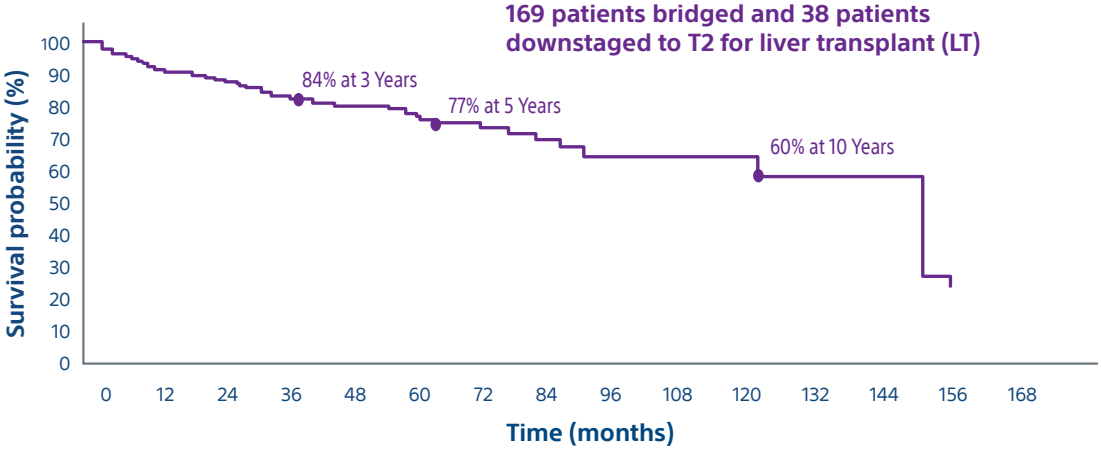
In the following trials, unresectable HCC patients receiving liver transplant following TheraSphere Glass Y-90 showed strong overall survival outcomes with an OS of 93% at 3 years and a median overall survival of 12.5 years after liver transplant.

LEGACY Study, 2021
Overall Survival
(Treated Population)



Gabr, et. al., 2020
Survival Probability Post Transplant
(N = 207 patients)

169 patients bridged and 38 patients downstaged to T2 for liver transplant (LT)



CONCLUSION:

Contemporary clinical trials examining use of TheraSphere shows consistent strong local tumor control to achieve transplant candidacy and time to tumor progression to preserve transplant eligibility in specific patient populations. Patients who achieved extensive or complete necrosis had better recurrence-free survival, supporting the practice of neoadjuvant treatment before liver transplant.[2]

Y-90 is an effective local therapy for bridging patients within Milan Criteria, selecting patients for liver transplant who present outside of Milan Criteria, and delivers sustainable long-term outcomes post transplantation with minimal risks of tumor recurrence.[6]

KEY TRIAL DESIGN AND BASELINE CHARACTERISTICS

	Local Tumor Control				Time to Tumor Progression	
	Lewandowski, et. al., 2009	**Gabr, et. al., 2020**	**LEGACY Study, 2021**	**Toskich, et. al., 2021**	**PREMIERE Trial, 2016**	**TRACE Trial, 2022**
Trial Design	Single-center, US	Single-center, US	Multicenter, US	Single-center, US	Prospective, randomized open label Single-Center, US	Open label, Single-Center, randomized Controlled Trial, EU
	Retrospective	Retrospective	Retrospective	Retrospective	Prospective	Prospective
	N=86	N=207	N=162	N=37	N=45	N=66
Objective	To compare the downstaging ability of transarterial chemoembolization (TACE) versus transarterial radioembolization.	To report long-term outcomes of liver transplantation for HCC patients bridged/ downstaged by Y-90.	To evaluate objective response rate (ORR) and duration of response (DoR) in patients with solitary unresectable HCC treated with Yttrium-90 glass microspheres.	To evaluate the pathologic outcomes HCC treated with Yttrium-90 radiation segmentectomy using glass microspheres prior to liver transplantation and explore parameters associated with pathologic necrosis.	To compare the effects of cTACE and Y-90 radioembolization in patients with HCC.	To compare the efficacy and safety of TARE with TACE for unresectable HCC.
Primary Endpoints	Imaging Analysis Secondary: Response rates (RR) Time to Progression (TTP) Event-Free Survival (EFS) Recurrence Free Survival (RFS) Overall Survival (OS)	Disease Specific Mortality Rate (DSMR) Time to Recurrence (TTR) Overall Survival (OS) Recurrence Free Survival (RFS)	Objective Response Rate (ORR) Duration of Response (DoR)	Pathologic necrosis Objective response rate (ORR)	Time to progression (TTP) Secondary: Response rates RR, OS, Safety	Time to progression (TTP) (Secondary: TTP (whole liver, local), PFS, ORR, OS, Safety)
Baseline Patient Characteristics	BCLC B (79%) C (21%)	BCLC A (51%) B (10%) C (31%) D (8%)	BCLC A (60.5%) C (39.5%)	BCLC A (70%) C (21%) D (9%)	BCLC A (75%) B (25%)	BCLC A (12%) B (88%)
	(TNM unavailable) **Median Tumor size:** TACE = 5.7 cm TARE/Y-90 = 5.6 cm	**UNOS TNM:** T1 (4%) T2 (77%) T3 (11%) T4(a) (6%) T4(b) (2%) (status at the time of Y-90)	**(TNM unavailable)** **Median Tumor size:** 2.7 cm (range: 1.0 – 8.1 cm)	**UNOS TNM:** T2 (91%) T3 (9%)	**(TNM unavailable)** **Median Tumor size:** TACE = 2.6 cm TARE/Y-90 = 3.0 cm	**TNM unavailable)** **Median Tumor size:** TARE/Y-90 = 4.2 cm DEB-TACE = 4.7 cm

†The safety and efficacy of TheraSphere in treatment of patients with PVT has not been established.

1. Lewandowski RJ, Kulik LM, Riaz A, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. Am J Transplant 2009;9:1920-8.
2. Gabr A, Kulik L, Mouli S, Riaz A, Ali R, Desai K, Mora RA, Ganger D, Maddur H, Flamm S, Boike J. Liver transplantation following Yttrium-90 radioembolization: 15-year experience in 207-patient cohort. Hepatology. 2021 Mar;73(3):998-1010.
3. Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, Mulcahy MF, Baker T, Abecassis M, Miller FH, Yaghmai V, Sato K, Desai K, Thornburg B, Benson AB, Rademaker A, Ganger D, Kulik L, Lewandowski RJ. Y-90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma. Gastroenterology. 2016 Dec;151(6):1155-1163.e2.
4. Dhondt E, Lambert B, Hermie L, Huyck L, Vanlangenhove P, Geerts A, Verhelst X, Aerts M, Vanlander A, Berrevoet F, Troisi RI. 90Y Radioembolization versus Drug-eluting Bead Chemoembolization for Unresectable Hepatocellular Carcinoma: Results from the TRACE Phase II Randomized Controlled Trial. Radiology. 2022 Jun;303(3):699-710.
5. Gabr A, Riaz A, Johnson GE, Kim E, Padia S, Lewandowski RJ, Salem R. Correlation of Y-90-absorbed radiation dose to pathological necrosis in hepatocellular carcinoma: confirmatory multicenter analysis in 45 explants. European Journal of Nuclear Medicine and Molecular Imaging. 2021 Feb;48(2):580-3.
6. Qadan M, Fong ZV, Delman AM, Gabr A, Salem R, Shah SA. Review of Use of Y-90 as a Bridge to Liver Resection and Transplantation in Hepatocellular Carcinoma. J Gastrointest Surg. 2021 Oct;25(10):2690-2699.

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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