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THERASPHERE™ Y-90 Glass Microspheres | HEPATOLOGY

Liver Transplantation Following Y-90 for HCC

15-year, 207 patient experience evaluated TheraSphere™ as treatment for Bridging or Downstaging HCC to Liver Transplant therapy with a median overall survival* of 12.5 years

Liver Transplantation Following Yttrium-90 Radioembolization: 15-year Experience in 207-Patient Cohort - Ahmed Gabr, Laura Kulik, Samdeep Mouli, Ahsun Riaz, Rehan Ali, Kush Desai, RonaldA Mora, Daniel Ganger, Haripriya Maddur, Steven Flamm, Justin Boike, Christopher Moore, Bartley Thornburg, Ali Alasadi, Talia Baker, Daniel Borja-Cacho, Nitin Katariya, Daniela P Ladner, Juan Carlos Caicedo, Robert J Lewandowski, Riad Salem

METHODS

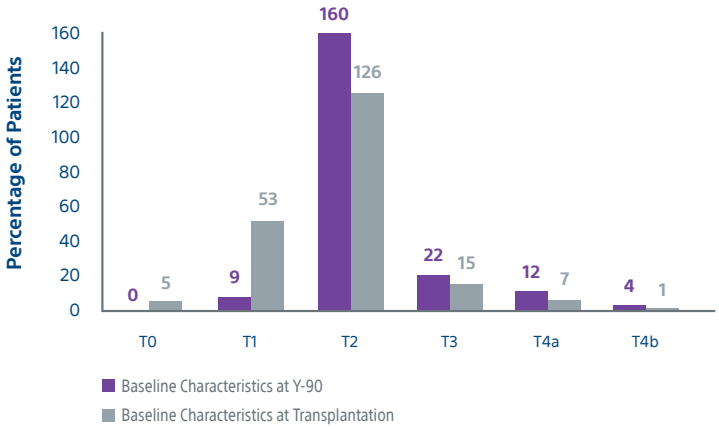
A multidisciplinary team comprised of hepatology, oncology, transplant surgery, and interventional radiology retrospectively reviewed data from 207 patients with unresectable HCC who underwent liver transplant after being treated with Y-90 as part of a bridging or downstaging care pathway.

RESULTS

Of the 207 patients included in these analyses, 38 (19%) patients were downstaged to within Milan transplant criteria and 169 (82%) bridged to transplant with TheraSphere either using lobar (18%, median dose of 124 Gy [IQR: 132-146]) or radiation segmentectomy (82%, median dose 260 Gy [IQR: 235-350]) administration.

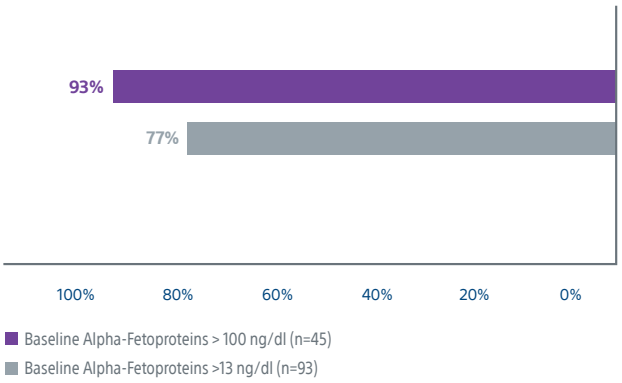
169 Patients were Bridged and 38 Patients were Downstaged to T2 for Liver Transplant
Median Time to LT was 7.5 Months

Tumor Characteristics at Y-90 and Transplant



Changes from Baseline AFP post Y-90

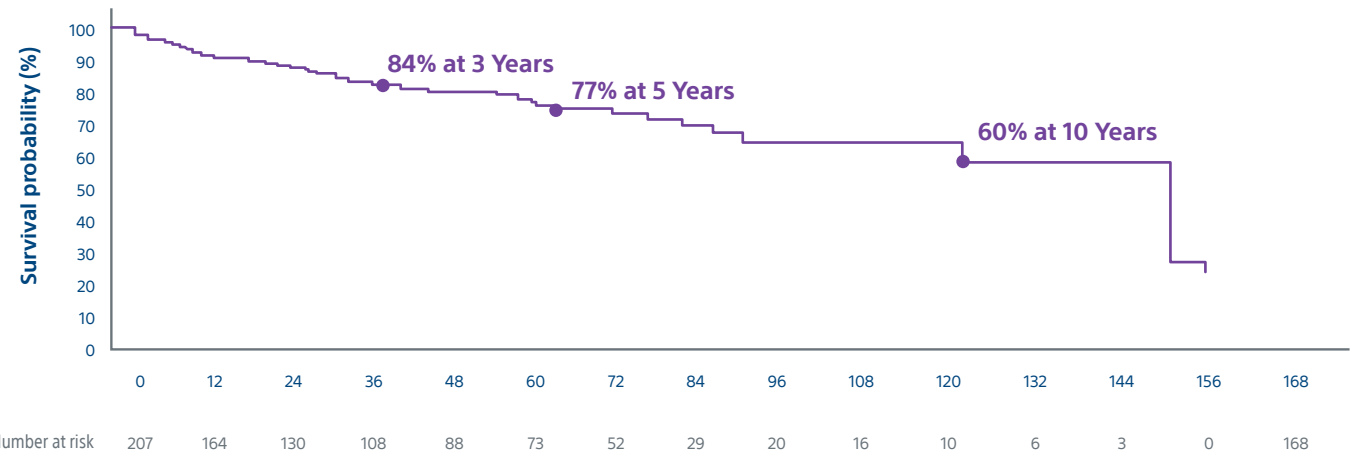
(median % decrease)



Median Overall Survival after Liver Transplant was 12.5 years

Survival Probability Post Transplant

(N = 207 patients)



* Post transplant

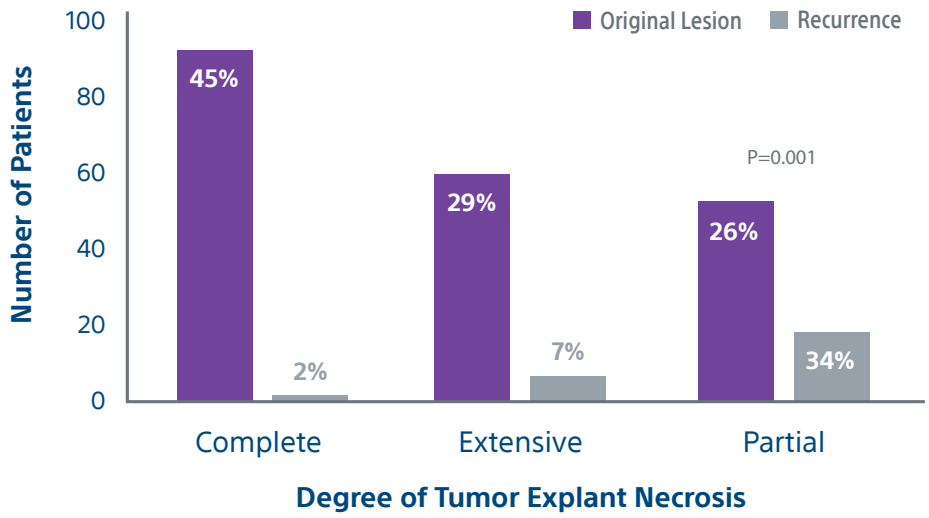
HEPATOLOGY: Liver Transplantation Following Y-90

RESULTS & CONCLUSIONS

Three, five and ten-year Overall Survival (OS) rates were 84%, 77%, and 60% respectively. 94 (45%), 60 (29%) and 53 (26%) of patients showed complete (no viable tumor), extensive (50-99% necrosis) and partial tumor necrosis (<50% necrosis) on histopathology of which 2%, 7% and 34% had recurrence in each group, respectively. There was a trend towards better OS for patients achieving complete/extensive tumor necrosis (p=0.056). Median recurrence free survival (RFS) post transplant was 120 Months (95%CI: 69-150). There was no differences in OS or RFS for bridged versus downstaged patients.

74% of Patients Showed Complete or Extensive Tumor Necrosis on Histopathology with an average 10 Year Recurrence-Free Survival following Liver Transplant

Histopathology and Recurrence Rate Post TheraSphere



SURVIVAL AND RECURRENCE OUTCOMES (N = 207)

	Median	3-year	5-year	10-year
Overall Survival from Y-90	157 mo. (13.1 years) [CI: 120-157]	87%	80%	62%
Overall Survival from LT	150 mo. (12.5 years) [CI: 120-150]	84%	77%	60%
Recurrence-Free Survival from LT	120 mo. (10.0 years) [CI: 69-150]	77%	65%	43%
Disease-Specific Mortality Rate	Not Reached	6%	11%	16%
Time-to-Recurrence (Reccurrence-Free Probability)	Not Reached	88%	79%	76%
Overall Survival <65 years	Not Reached at 150 mo.	88%	85%	71%
Overall Survival ≥65 years P=0.003	12.5 years	73%	58%	43%

Abbreviations:

HCC: hepatocellular carcinoma
LT: Liver transplantation
Y90: Yttrium-90 radioembolization
MELD: Model of endstage liver disease
BCLC: Barcelona Clinic Liver Cancer
cTACE: conventional chemoembolization
LRT: locoregional therapy
OS: Overall survival
RFS: Recurrence-free survival
TTP: time-to-progression
TTR: Time-to-recurrence
DSM: Disease-specific-mortality
MRI: gadolinium-enhanced magnetic resonance imaging
CT: triphasic contrast-enhanced computerized tomography
CP: Child-Pugh
IQR: Interquartile range
KM: Kaplan-Meier analysis
CI: 95% Confidence Interval
ECOG: Eastern Cooperative Oncology Group
UNOS: United Network for Organ Sharing
AFP: Alpha fetoprotein
ETOH: Alcoholic cirrhosis
NASH: Non-alcoholic steatohepatitis
PBC: Primary biliary cirrhosis
PSC: Primary sclerosing cholangitis
HCV: Hepatitis C virus infection
HBV: Hepatitis B virus Infection
TNM: Tumor, Node, Metastasis

HEPATOLOGY: Liver Transplantation Following Y-90

Baseline Characteristics at Y-90

		Median [IQR] N (%)
Age (years)	60 [56-65]	
ECOG	0	145 (70%)
	1	61 (29.5%)
	2	1 (0.5%)
Child-Pugh	A	99 (48%)
	B	91 (44%)
	C	17 (8%)
BCLC	A	106 (51%)
	B	20 (10%)
	C	64 (31%)
	D	17 (8%)
UNOS TNM	T1	9 (4%)
	T2	160 (77%)
	T3	22 (11%)
	T4a	12 (6%)
	T4b	4 (2%)
AFP (ng/dL)	<13 (normal)	114 (55%)
	13-100	48 (23%)
	>100	45 (22%)
	Range	0.8-15735
Prior Liver therapy	Surgical Resection	8 (3.5%)
	Prior HCC LRT	35 (17%)
	Treatment Naive	164 (79.5%)
Listing	Prior to Y-90	117 (57%)
	After Y-90	90 (43%)
Y-90 Administration	Lobar	37 (18%)
	Segmental	170 (82%)
Y-90 Dose (Gy)	Lobar	124 [132-146]
	Segmental	260 [235-350]

Baseline Characteristics at Liver Transplant

		Median [IQR] N (%)
Age (years)	62 [57-66]	
MELD-Na Score	13 [10-17]	
Wait-list time (months)	7 [4-10]	
Time from Y-90 (months)	7.5 [4.4-10.3]	
Etiology of HC	Autoimmune hepatitis	3 (1.5%)
	Alpha 1 antitrypsin	1 (0.5%)
	Biliary Atresia	1 (0.5%)
	Cryptogenic	13 (6%)
	ETOH	30 (14%)
	HCV + ETOH	11 (5%)
	HV	102 (49%)
	HBV	22 (10%)
	NASH	13 (6%)
	PBC	7 (3%)
	Wilson's	1 (0.5%)
	PSC	1 (0.5%)
	Hemochromatosis	2 (1%)
AFP (ng/dL)	<13 (normal)	132 (64%)
	13-100	62 (30%)
	>100	13 (6%)
	Range	0.8-13774
Liver Parenchyma	Cirrhosis	202 (97.5%)
	Bridging Fibrosis	5 (2.5%)
Tumor Grade	Grade 1	37 (18%)
	Grade 2	69 (33%)
	Grade 3	6 (3%)
	Fibromellar	1 (0.5%)
	Mixed HCC - cholangiocarcinoma	4 (2%)
	Unable to identify due to extensive necrosis	90 (43.5%)
Tumor Necrosis	Complete (100%)	94 (45%)
	Extensive (51-99%)	60 (29%)
	Partial (<50%)	53 (26%)

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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_2O2) of < 60 mmHg, or oxygen saturation (Sa_2O2) 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 the liver does not exceed 150 Gy.

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Peripheral Interventions
300 Boston Scientific Way
Marlborough, MA 01752-1234
www.bostonscientific.com

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