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THERASPHERE™ Y-90 Glass Microspheres | PUBLICATION SUMMARY

Institutional Decision to Adopt Y-90 as A Primary Treatment for HCC Informed by a 1000-Patient 15-Year Experience

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Salem R, Gabr A, Riaz A, Mora R, Ali R, Abecassis M, Hickey R, Kulik L, Ganger D, Flamm S, Atassi R, Atassi B, Sato K, Benson AB, Mulcahy MF, Abouchaleh N, Asadi AA, Desai K, Thornburg B, Vouche M, Habib A, Caicedo J, Miller FH, Yaghmai V, Kallini JR, Mouli S and Lewandowski RJ

OVERVIEW

- Locoregional (LRT) therapies such as ablation, TACE and TARE with Yttrium-90 (Y-90) are treatment options for HCC patients who are not eligible for curative resection or outside transplant criteria[1,2]
- TARE has become an increasingly accepted alternative to TACE. With the addition of TARE to the BCLC algorithm[3], the authors evaluated the outcomes of TARE across all BCLC disease stages:
  - BCLC A: successful downstaging of tumors to liver transplant, hypertrophy of the future liver remnant for potential resection, treats recurrences following resection, significantly prolongs time to progression compared with TACE and represents an alternative to ablation for unablatable lesions[4-7]
  - BCLC B*: comparable survival yet superior quality of life compared to TACE[8,9]
  - BCLC C: applicable in patients with portal vein thrombosis*, minimizing the risk of ischemic hepatitis[10]

OBJECTIVES

- To report data from an institution's 15-year, 1,000-patient experience that led to an institutional decision to adopt Y-90 TARE as the primary transarterial locoregional treatment for HCC

METHODS

- From 2003 to 2017, 1,000 HCC patients were treated with Y-90 glass microspheres as part of a prospective cohort study (the largest single-center cohort conducted) with 1,577 total treatments (median: 1, range: 1-8)
- Standard pre-treatment angiography and Tc-99m MAA were performed
- Target dose was 120 Gy for lobar infusions, however practice evolved with the application of radiation segmentectomy and lobectomy and target doses were modified to >190 Gy (potentially curative ablative dose) and 150 Gy, respectively
- Median dose per treatment was 119 Gy
- Follow-up included 4 to 6 week post-treatment scans and then subsequently at 2 to 3 month intervals
- Overall survival (OS) outcomes were reported using censoring and intention-to-treat (ITT) methodologies

BASELINE CHARACTERISTICS	
ECOG	0 (56%); 1 (40%); 2 (4%)
Child-Pugh	A (51%); B (45%); C (4%)
BCLC	A (26%); B (15%); C (54%); D (4%)

*The safety and effectiveness of Therasphere in patients with HCC tumors involving the portal vein have not been established.

RESULTS

- Survival for BCLC stages A–C patients treated with Y-90 (47, 25 and 15 months, respectively) compared favorably with survival expectations of BCLC A (36–50 months), BCLC B (18–26 months) and BCLC C (11 months) cited by EASL-EORTC guidelines
- Properly selected BCLC D patients may benefit from selective Y-90 glass therapy followed by liver transplantation**
- Overall, 49 (5%) patients developed new grade 3/4 albumin toxicities and 110 (11%) showed grade 3/4 bilirubin toxicities for all Child-Pugh classes
- No patient developed radiation pneumonitis or gastritis

BCLC Stage	Child-Pugh (CP) score	Median OS [Censored] (months)	P-value	Median OS [ITT] (months)	P-value
A	CP A	47.3	<0.0001	102	0.005
	CP B	27		38	
B	CP A	25	0.037	30	0.2
	CP B	15		16	
C	CP A	15	<0.0001	16.6	<0.0001
	CP B	8		8.4	
D	C (non-transplanted)	4.6	—	—	—
	C (transplanted)	—		92% (n=14) alive at 5 years	

**Off label use

- Multivariate models confirmed baseline bilirubin, albumin, ascites, vascular invasion, metastases, distribution, performance status, alpha-fetoprotein (AFP) <100 and index tumor < 5 cm to be significant predictors of survival
- Survival was not affected by hepatitis C virus status
- Overall cohort mortality within 30 days of treatment was 1.6% (n=16)

CONCLUSION

- Northwestern University adopted Y-90 glass microsphere therapy as their first line transarterial locoregional therapy for liver-only HCC compared to TACE because it allows for fewer treatments, longer time to progression and has demonstrated versatile application.
- Their decision was informed by prospectively collected and incrementally reported outcomes over 15 years
- Moving Y-90 earlier in the disease care continuum may improve overall HCC outcomes
- Study Strengths: Largest single-center prospective cohort of HCC patients treated with Y-90 glass microspheres, sample size and follow-up permitted meaningful analyses that compensate for heterogeneity of lesion size and liver function
- Study Limitations: Single-center study, overestimation of survival in advanced HCC attributed by ECOG 1

TACE= transarterial chemoembolization ; TARE= transarterial radioembolization ; HCC= hepatocellular carcinoma ; BCLC= Barcelona Clinic Liver Classification ;
ECOG= Eastern Cooperative Oncology Group ; EASL= European Association for the Study of the Liver ; EORTC= European Organization for Research and Treatment of Cancer

1. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-943. **2.** NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines); Hepatobiliary Cancers. In; 2016. **3.** Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2021;S0168-8278(21)02223-6. doi:10.1016/j.jhep.2021.11.018. **4.** Vouche M, Habib A, Ward TJ et al. Unresectable solitary hepatocellular carcinoma not amenable to radiofrequency ablation: Multicenter radiology-pathology correlation and survival of radiation segmentectomy. Hepatology 2014;60:192-201. **5.** Lewandowski RJ, Kulik LM, Riaz A et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. Am J Transplant 2009; 9:1920-1928. **6.** Ali R, Riaz A, Gabr A et al. Clinical outcomes of Y90 radioembolization for recurrent hepatocellular carcinoma following curative resection. Eur J Nucl Med Mol Imaging 2017. **7.** Salem R, Gordon AC, Moulli S et al. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 2016;151:1155-1163.e1152. **8.** Salem R, Gilbertsen M, Butt Z et al. Increased quality of life among hepatocellular carcinoma patients treated with radioembolization, compared with chemoembolization. Clin Gastroentrol Hepatol 2013;11:1358-1365.e1351. **9.** Gabr A, Kallini JR, Gates VL et al. Same-day 90Y radioembolization: implementing a new treatment paradigm. Eur J Nucl Med Mol Imaging 2016;43:2353-2359. **10.** Sato K, Lewandwoski RJ, Bui JT et al. Treatment of unresectable primary and metastatic liver cancer with yttrium-90 microspheres (TheraSphere): assessment of hepatic arterial embolization. Cardiovasc Intervent Radiol 2006;29:522-529

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 the liver does not exceed 150 Gy.

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