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THERASPHERE™ Y-90 Glass Microspheres | **PUBLICATION SUMMARY**

Y-90 Radioembolization Significantly Prolongs Time to Progression Compared with Chemoembolization in Patients with Hepatocellular Carcinoma

Gastroenterology. 2016 Dec;151(6):1155-1163.e2. doi: 10.1053/j.gastro.2016.08.029. Epub 2016 Aug 27.
Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, Mulcahy MF, Baker T, Abecassis M, Miller F, Yaghmai V, Sato K, Desai K, Thornburg B, Benson AB, Rademaker A, Ganger D, Kulik L and Lewandowski RJ

OVERVIEW

Upon initial diagnosis, patients with HCC are frequently ineligible for curative options – transplant or surgical resection

- Locoregional therapies (ablation, cTACE, Y-90 radioembolization) can be applied to HCC patients deemed ineligible for curative options per the published guidelines[1,2]
- Ablation is commonly recommended for early-stage HCC, however, when contraindications to ablation exist, cTACE is typically determined to be the next best therapy and is considered standard-of-care for intermediate-stage HCC
- In this study, Y-90 radioembolization increased time to progression (TTP)[3], improved quality of life[4], served a neoadjuvant role prior to resection[5-7] and offered high tumor control in select patients with portal vein invasion[8]

OBJECTIVES

- Experts have strongly advocated for randomized trials that study cTACE versus Y-90 therapy
- The objective of this study was to compare cTACE versus Y-90 radioembolization in a prospective, randomized, phase II setting for the treatment of unresectable, unablatable HCC
- The primary endpoint of this study was TTP and the secondary endpoints included safety, response rate and overall survival
- The investigators hypothesized Y-90 would prolong TTP when compared to cTACE

METHODS

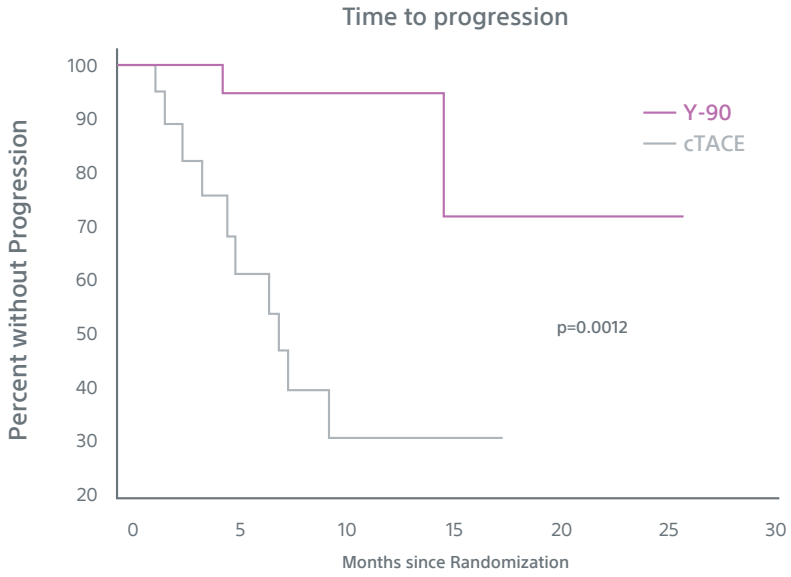
- Open label, single-center study that lasted from 2009-2015 [n= 45 randomized 1:1 to cTACE (n = 21) or Y-90 (n = 24)]
  - Inclusion criteria: image/biopsy confirmed HCC, unablatable/unresectable disease with no vascular invasion, Child Pugh A/B and bilirubin ≤ 2.0 mg/dl and AST/ALT ≤ 5x upper limit 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 Y-90 with post-treatment intent of liver transplantation

TREATMENT ARMS	
cTACE	**Y-90 Radioembolization**
• 75 mg/m2 dose of drug/lipiodol combination followed by embolic microspheres • Patients admitted for 24-48 hour observation	• Glass microspheres • Dose = 120 Gy • Outpatient treatment

RESULTS

- > 50% of all patients exhibited solitary lesions; selective treatment delivery was performed in 16 cTACE patients and 17 patients Y-90 patients
- Three cTACE patients experienced grade 3+ toxicities (hyperbilirubinemia, abdominal pain from progress and sepsis) and four Y-90 patients experienced delayed grade 3+ toxicities (ascites and bacterial peritonitis)

TTP	Imaging Response
Median TTP was significantly longer for the Y-90 group: 6.8 months for cTACE vs. not reached for Y-90 (>26 months), p=0.0012	Response rates were similar for both groups: – WHO Criteria: 63% (n=12) and 52% (n=12) for cTACE and Y-90, respectively – EASL Criteria: 74% (n=14) and 87% (n=20) for cTACE and Y-90, respectively
Overall Survival	**Bridge to Transplant**
OS was similar for both groups: – Median OS (censored to liver transplantation) was 17.7 months and 18.6 months for cTACE and Y-90, respectively	More patients in the Y-90 group (87%, n=13) were bridged to transplant as compared to the cTACE group (70%, n=7)



CONCLUSION

- This study showed Y-90 significantly increased time to progression compared with cTACE for early to intermediate stage HCC patients
- While longer TTP did not translate to increased overall survival, improved tumor control could potentially reduce dropout from transplant waitlists and increase bridging to transplantation
- Study Strengths: Randomized design, comprehensive imaging review, real-world clinically relevant patient flow of unablatable BCLC A/B patients
- Study Limitations: Required censoring of imaging/survival to transplant, difficulty in enrollment, patient compliance with follow-up and imaging

cTACE= conventional transarterial chemoembolization ; TTP= time to progression ; BCLC= Barcelona Clinic Liver Classification ; WHO= World Health Organization ; EASL= European Association for the Study of the Liver ; OS= overall survival

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Hepatobiliary Cancers. 2016 **2.** EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012; 56:908-43. **3.** Salem R, Lewandowski RJ, Kulik L, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology. 2011; 140:497-507.e2. **4.** Salem R, Miller FH, Yaghmai V, et al. Response assessment methodologies in hepatocellular carcinoma: complexities in the era of local and systemic treatments. J Hepatol. 2013; 58:1260-2. **5.** Gaba RC, Lewandowski RJ, Kulik LM, et al. Radiation lobectomy: preliminary findings of hepatic volumetric response to lobar yttrium-90 radioembolization. Ann Surg Oncol. 2009; 16:1587-96. **6.** Vouche M, Lewandowski RJ, Atassi R, et al. Radiation lobectomy: time-dependent analysis of future liver remnant volume in unresectable liver cancer as a bridge to resection. J Hepatol. 2013; 59:1029-36. **7.** Gabr A, Kallini JR, Gates VL, et al. Same-day 90Y radioembolization: implementing a new treatment paradigm. Eur J Nucl Med Mol Imaging. 2016. 8. Kulik LM, Carr BI, Mulcahy MF, et al. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. Hepatology. 2008; 47:71-81.

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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