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THERASPHERE™ Y-90 Glass Microspheres | PUBLICATION SUMMARY

Radiation Segmentectomy: Potential Curative Therapy for Early Hepatocellular Carcinoma

Radiology, 2018 Jun; 287(3); https://pubs.rsna.org/doi/10.1148/radiol.2018171768 Lewandowski RJ, Gabr A, Abouchaleh N, Ali R, Al Asadi A, Mora RA, Kulik L, Ganger D, Desai K, Thornburg B, Mouli S, Hickey R, Caicedo JC, Abecassis M, Riaz A and Salem R

OVERVIEW

Curative treatment options for early-stage HCC (BCLC 0 or A) include transplantation, surgical resection and RF ablation with good survival outcomes ranging between 60-80%*[1], however many patients are not candidates for these therapies

- Radiation segmentectomy is the application of selective ablative radiation doses of Yttrium-90 (Y-90) to tumors, usually delivered to no more than two hepatic segments[2]
- The threshold dose of 190 Gy has been confirmed[3] to maximize cytotoxicity and selective delivery minimizes risk of damage to surrounding parenchyma[4]

OBJECTIVES

- To report one center's long term outcomes of patients with HCC ≤ 5 cm, not amenable to transplantation, resection or RF ablation, who underwent radiation segmentectomy
- The authors hypothesized radiation segmentectomy could be considered potentially curative based on the same rationale as transplantation, resection and RF ablation

METHODS

- Retrospective, single center study looked at 70 patients with solitary HCC ≤ 5 cm, preserved liver function (Child Pugh A) and no vascular invasion or extrahepatic metastases who underwent radiation segmentectomy with Y-90 glass microspheres (target dose >190 Gy)
- Patients who had surgical resection or transplant after a radioembolization procedure were excluded
- A sub-analysis of patients with HCC ≤ 3 cm was also performed (cohort comparable to RF ablation)
- All patients underwent long-term imaging (contrast material-enhanced magnetic resonance [MR] imaging or computed tomography [CT]) and clinical follow-up (toxicity assessment at 1 and 3 months and response assessment in clinic 1 month post and subsequently at 3-month intervals)

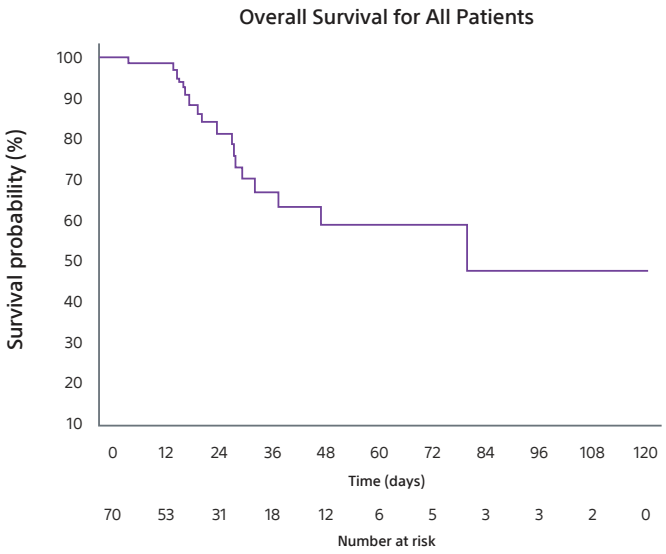
KEY RESULTS

RADIOGRAPHIC RESPONSE	TIME TO PROGRESSION (TTP)	LOCAL TUMOR CONTROL	OVERALL SURVIVAL (OS)
63 out of 70 patients (90%) responded according to EASL criteria, of whom 41 (59%) showed complete response (CR).	Median TTP was 2.4 years, or 29 months.	72% of patients had no target lesion progression at 5 years. Local recurrence in complete responders occurred in 4 patients (9.8%).	Median OS (n=70) was 6.7 years, or 80 months. 1-, 3-, and 5-year survival probabilities were 98%, 66% and 57%, respectively. A sub-analysis of patients with tumor size ≤ 3 cm (n = 45) resulted in 1-, 3-, and 5-year survival probabilities of 100%, 82% and 75%, respectively.

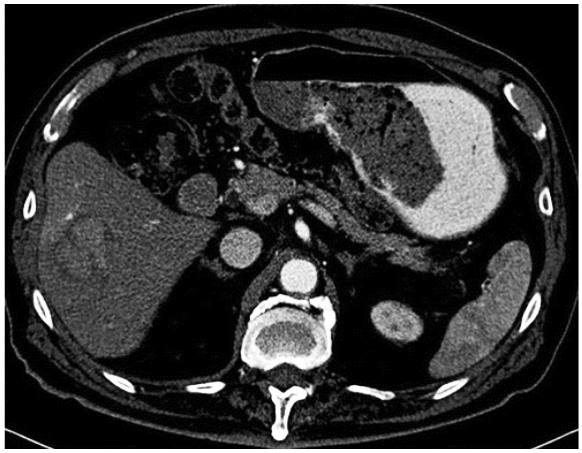
* RF ablation shows similar reported survival outcomes to resection and transplantation for HCC ≤ to 3 cm

BCLC = Barcelona Clinic Liver Cancer; HCC= hepatocellular carcinoma; RF= radiofrequency; EASL= European Association for the Study of the Liver

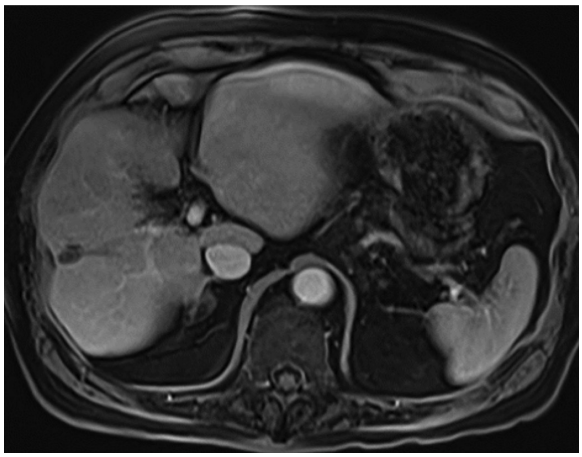
RESULTS



OVERALL SURVIVAL RATE	Tumor Sizes		
	≤ 3cm (n=45)	> 3cm (n=25)	All ≤ 5cm (n=70)
1-year	100%	96%	98%
3-year	82%	46%	66%
5-year	75%	37%	57%



Contrast material–enhanced CT scan before Y-90 of an 87-year-old man with 4 cm hepatocellular carcinoma in right lobe.



Contrast-enhanced MR image at subsequent 9-year follow-up (now aged 96 years) shows complete necrosis.

CONCLUSION

- Liver transplantation, surgical resection and RF ablation are considered curative treatment options based on phase II randomized studies with limited data demonstrating improved survival
- Radiation segmentectomy data from the present publication showed similar outcomes as therapies considered curative in patients with unablatable BCLC stage 0 or A lesions ≤ 5cm with preserved liver function (Child Pugh A):
  - Provided local tumor control
  - Prolonged time to progression
  - Overall survival outcomes comparable to RF ablation, resection, and transplantation for patients with BCLC stage 0 or A HCC
- Additionally, radiation segmentectomy is an outpatient, minimally invasive intra-arterial therapy with a low toxicity profile that may be a convenient treatment option for patients
- Study Strengths: homogeneity of patient cohort, >10 years of follow-up, strict patient selection
- Study Limitations: retrospective and nonrandomized analysis, selection bias, comparisons to published literature versus an internal control group

1. Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. Gastroenterology 2016;150(4):835-853 **2.** Riaz A, Gates VL, Atassi B et al. Radiation segmentectomy: a novel approach to increase safety and efficacy of radioembolization. Int J Radiat Oncol Biol Phys 2011;79(1):163-171 **3.** 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(1):192-201 **4.** 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(5):1029-1036

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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PI-789805-AB