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THERASPHERE™ Y-90 Glass Microspheres | OCHSNER TUMOR DOSE ANALYSIS

New TheraSphere™ analysis: Durable, reproducible outcomes demonstrated with high dose and high radiation per microsphere (RPM).[1]

Single-center data builds on previously published radiation segmentectomy studies (LEGACY[2] and RASER[3]) to demonstrate consistent outcomes with late first week/early second week dosing.

Sandow T, Gimenez J, Nunez K, Tramel R, Gilbert P, Oliver B, Cline M, Fowers K, Cohen A, Thevenot P, Using Voxel-based Dosimetry to evaluate sphere concentration and tumor dose in Hepatocellular Carcinoma treated with Y-90 Radiation Segmentectomy with glass microspheres, Journal of Vascular and Interventional Radiology (2024), doi: https://doi.org/10.1016/j.jvir.2024.05.020.

OVERVIEW

Retrospective, single-center analysis of solitary HCC patients (n=56) treated with Therasphere Y-90 Glass Microspheres.

OBJECTIVE

Explore the relationship between microsphere deposition and distribution and various outcomes following radiation segmentectomy; validate current literature regarding efficacy, pathologic outcomes and adverse events.

ANALYSIS DESIGN/METHODS

Post-treatment voxel-based dosimetry was evaluated using Simplicit90Y™ software and utilized to calculate sphere concentration to tumor. Time to progression (TTP), treatment response, pathologic response, and adverse events were studied.

RESULTS: STRONG RADIOLOGIC AND PATHOLOGIC OUTCOMES ACHIEVED IN RADIATION SEGMENTECTOMY WITH ABLATIVE DOSING AND HIGH RADIATION PER MICROSPHERE

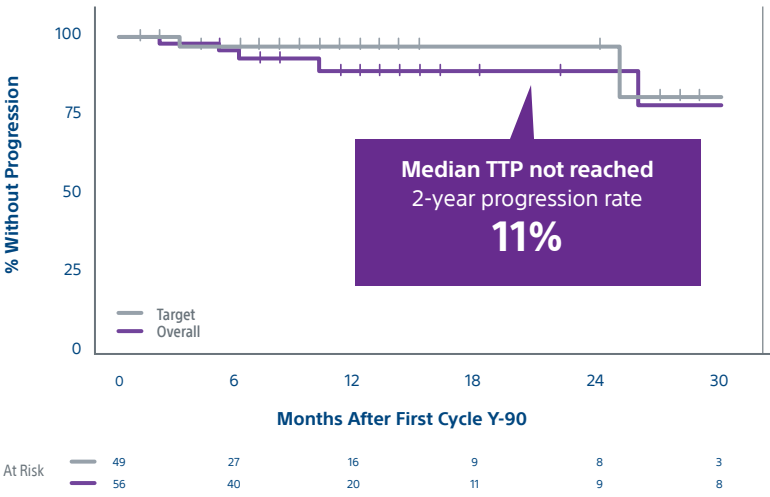
474 Gy
(177–1,290)
Median targeted dose to perfused volume

732 Gy
(252–1,776)
Median Tumor Absorbed Dose

1,446 Bq
Week 1 Thursday
(217-2,621)
Median RPM and Treatment Day

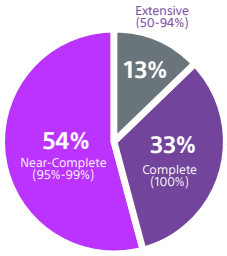
Duration of Response and Response Rates in line with LEGACY[2] and RASER[3] TheraSphere Radiation Segmentectomy Data

97% DURABLE RESPONSE AT 2 YEARS



STRONG ORR RESULTS n=51
(Targeted mRECIST)

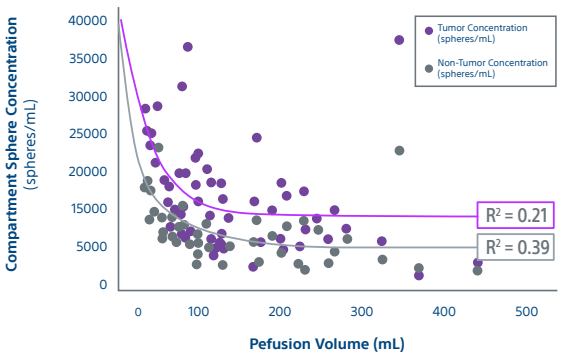
HIGH DEGREE OF NECROSIS ACHIEVED



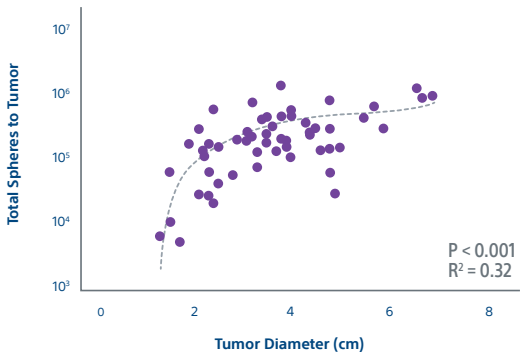
99%
Median Target Tumor Necrosis in the 15 patients that received liver transplant

THERASPHERE™ Y-90 Glass Microspheres | OCHSNER TUMOR DOSE ANALYSIS

AS PERFUSED VOLUMES DECREASED, BOTH TUMOR AND NORMAL TISSUE SPHERE CONCENTRATION INCREASED



HIGH RATES OF DURABLE IMAGING AND PATHOLOGIC RESPONSE WITH VARYING SPHERE CONCENTRATION



83%
of patients had a tumor sphere concentration < 20,000 spheres/mL

Despite tumor heterogeneity, high RPM (Week 2 Tuesday or earlier) can achieve:

- Reproducible high rates of complete radiologic response
- Durable tumor control
- Pathologic necrosis

ADVERSE EVENTS

Ablative radiation segmentectomy with high radiation per microsphere is well-tolerated with limited AEs in patients with preserved liver function.

0
Grade ≥ 3 AEs at 60 day follow up

2
Grade ≥ 3 AEs* at 180 day follow up

*Platelet count decrease

PATIENT CHARACTERISTICS

All patients in this analysis recieved radiation segmentectomies.

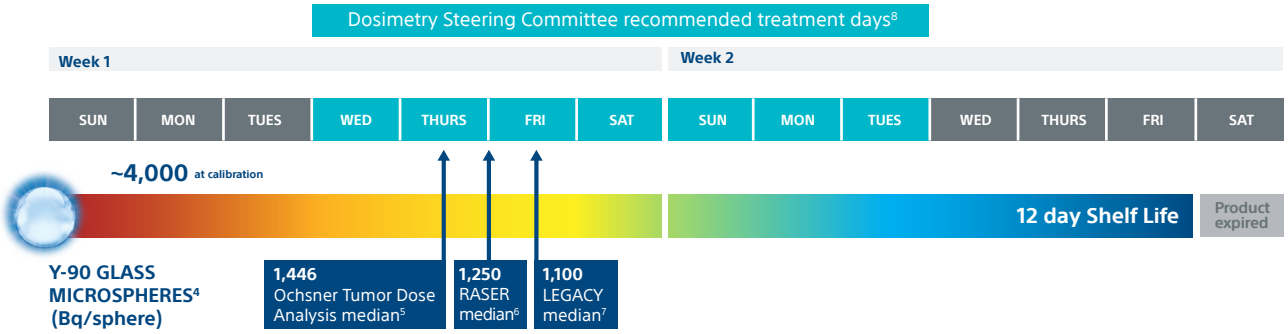
PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS			
GENERAL DEMOGRAPHICS	**n=56**	**CIRRHOSIS BACKGROUND**	
Age at HCC Diagnosis (years), median (range)	66 (42-73)	Etiology, total (%)	
Sex, total male (%)	44 (79)	HCV	32 (57)
Race, total (%)		NASH	10 (18)
Caucasian/White	39 (70)	HCV + ALD	7 (13)
African American/Black	13 (23)	ALD	4 (7)
Other	4 (7)	Other	3 (5)
HCC BASELINE		CHILD PUGH, total (%)	
Surgical Track, total (%)		A5	22 (39)
Transplant Track	21 (38)	A6	14 (25)
HCC BURDEN, total (%)		B7	11 (20)
Solitary	56 (100)	B8-B9	9 (16)
Index HCC Diameter (cm), median (range)	3.4 (1.2-6.8)	**ALBI GRADE**	
TRANSPLANT CRITERIA AT DIAGNOSIS, total (%)		Grade 1	16 (29)
Milan	50 (89)	Grade 2	36 (64)
UNOS-DS	6 (11)	Grade 3	4 (7)
AFP (ng/mL), median (IQR)	5.9 (3.5-40)	MELD COMPONENT and MELD, median (IQR)	
		MELD–Na	9 (7-12)
		MELD 3.0	10 (7-13)

Abbreviations: ^{90}Yittrium (^{90}Y), hepatocellular carcinoma (HCC), interquartile range (IQR), hepatitis C virus (HCV), alcholic liver

CONCLUSION

Ablative dosing for radiation segmentectomy with high RPM yields durable radiologic and pathologic outcomes with limited adverse events. The study further supports contemporary radiation segmentectomy techniques by targeting doses greater than 400 Gy to the perfused volume and treating within recommended treatment days (Week 1 Wednesday – Week 2 Tuesday). This approach optimizes radiation per microsphere and allows more critical hits in the "coldest" areas of the tumor, maximizing tumor dose coverage.

Analysis further supports results from previously published landmark trials by following Dosimetry Steering Committee Guidelines



	LEGACY (n=162)	RASER (n=29)	OCHSNER (n=56)
PATIENT/TUMOR CHARACTERISTICS			
BCLC	A (60.5%), C (39.5%)	A (100%)	0/A (100%)
CHILD PUGH	A5 (66.7%), A6 (33.3%)	A5 (48%), A6 (41%), B7 (10%)	A5 (39%), A6 (25%), B7 (20%), B8-B9 (16%)
MEDIAN PERFUSED VOLUME	155.0 mL (19 - 1,363)	153.6 mL (Mean)	141.0 mL (43 - 325)
MEDIAN TUMOR SIZE	2.7 cm (1.0 - 8.1)	2.1 cm (Mean)	3.4 cm (1.2 - 6.8)
MEDIAN DOSE TO PERFUSED VOLUME	410.1 Gy (70 – 2980)	584 Gy (181 – 3340)	474 Gy (177 – 1290)
OUTCOMES			
MEDIAN TIME TO PROGRESSION	NR (2 years)	NR (2 years)	NR (2 years)
OBJECTIVE RESPONSE RATE	88.3% (84% CR) Localized mRECIST	100% (90% CR) mRECIST	96% (82% CR) Localized mRECIST
DURATION OF REPSONSE	76.1% (≥ 6 months)	635 Days (Median)	97% (2 years)

1. Radiation per microsphere (RPM) is a number that refers to the specific activity (SA) of a microsphere (Bq/Sphere). **2.** Salem R, Johnson GE, Kim E, Riaz A, Bishay V, Boucher E, Fowers K, Lewandowski R, Padia SA. Yttrium-90 Radioembolization for the Treatment of Solitary, Unresectable Hepatocellular Carcinoma: The LEGACY Study. Hepatology. 2021 Mar 19. doi: 10.1002/hep.31819. **3.** Kim E, Sher A, Abboud G, et al. Radiation segmentectomy for curative intent of unresectable very early to early stage hepatocellular carcinoma (RASER): a single-centre, single-arm study [published online ahead of print, 2022 May 23]. Lancet Gastroenterol Hepatol. 2022;S2468-1253(22)00091-7. doi:10.1016/S2468-1253(22)00091-7 **4.** Radiation per microsphere (RPM) is a number that refers to the specific activity (SA) of a microsphere (Bq/Sphere). The RPM for TheraSphere is calculated based on targeted values and process means. Actual RPM can vary between microspheres. All numbers as of Noon Eastern Time. Ref Technical Report 97124387. **5.** Sandow T, Gimenez J, Nunez K, Tramel R, Gilbert P, Oliver B, Cline M, Fowers K, Cohen A, Thevenot P, Using Voxel-based Dosimetry to evaluate sphere concentration and tumor dose in Hepatocellular Carcinoma treated with Y-90 Radiation Segmentectomy with glass microspheres, Journal of Vascular and Interventional Radiology (2024), doi: https://doi.org/10.1016/j.jvir.2024.05.020. **6.** TheraSphere™ Y-90 Glass Microspheres RASER Study. Data on file. **7.** TheraSphere™ Y-90 Glass Microspheres LEGACY Study. Data on file. **8.** Salem, R., Padia, S.A., Lam, M. et al. Clinical, dosimetric, and reporting considerations for Y-90 glass microspheres in hepatocellular carcinoma: updated 2022 recommendations from an international multidisciplinary working group. Eur J Nucl Med Mol Imaging 50, 328 -343 (2023). https://doi.org/10.1007/s00259-022-05956-w

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. **Note:** Dose to the liver does not exceed 150 Gy.

Results from case studies are not necessarily predictive of results in other cases. Results in other cases may vary. **CAUTION:** The law restricts these devices to sale by or on the order of a physician. Indications, contraindications, warnings, and instructions for use can be found in the product labelling supplied with each device or at www.IFU-BSCI.com. Products shown for INFORMATION purposes only and may not be approved or for sale in certain countries. This material not intended for use in France.

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