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Segmental Yttrium-90 Radioembolization as an Initial Treatment for Solitary Unresectable HCC

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Abstract

Objectives To evaluate the objective response rate (ORR), time to progression (TTP), and overall survival (OS) in patients with unresectable solitary HCC less than 5 cm who were treated with ^{90}Y glass microspheres infused at a segmental level.

Materials and Methods Single-institution retrospective study of 35 patients with unresectable HCC deemed not suitable for percutaneous ablation who underwent segmental transarterial radioembolization (TARE) treatment. Eligibility criteria included patients with solitary, unilobar, <5 cm unresectable HCC lesions who underwent TARE as a primary treatment strategy between November 2012 and April 2020. Imaging follow-up was performed on each patient at 3-, 6-, and 12 months post-treatment. Local and the overall tumor response was evaluated using mRECIST criteria, and primary endpoints were ORR, TTP, and OS. Adverse events (AEs) were graded for severity using the Common Terminology Criteria for Adverse Events (CTCAE) v.5.0.

Statistical Analysis Patient demographics, baseline characteristics, and treatment characteristics were analyzed using descriptive statistics. Predictors of survival were analyzed with Cox proportional hazards regression. Kaplan–Meier analysis was used to evaluate OS.

Results Median tumor size was 3 cm (range: 1.0-4.8 cm) in the 35 patients studied, with 25.7% (9/35) being the Eastern Cooperative Oncology Group (ECOG) 0 and 62.9% (22/35) ECOG 1. Most patients (88.5%, 31/35) were of the Barcelona Clinic Liver Cancer (BCLC) stage C, with one patient each classified as BCLC-A and BCLC-0, respectively. For 34.2% (12/35), TARE functioned as a bridge to transplantation. Transplanted patients exhibited a median pathologic necrosis of 98% (IQR 7.5). Combined ORR for local and overall mRECIST at 12 months post-TARE was 94.3% and 85.7%, respectively. All patients had a mean local TTP of 11.9 months (CI: 2.7–21.0) and global TTP of 13.2 months (CI: 6.4–20.0). Among the 14.3% (5/35) of patients who experienced AEs

Keywords
- TARE
- hepatocellular carcinoma
- segmental
- radioembolization

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following treatment, 80% (4/5) were Grade 1, one patient experienced a Grade 4, and all events resolved within 1 month of treatment. Total OS at 1 year was 97%, whereas patients who underwent OLT had an OS of 100%.

Conclusion Segmental TARE was a safe and effective treatment for solitary unresectable HCC less than 5 cm. When used as a bridge to transplant, explants showed near complete pathologic necrosis of treated lesions.

Introduction

Liver cancer is the third leading cause of cancer-related mortality worldwide, with an abysmal 5-year survival rate of 20%, necessitating continued advancement of therapeutic strategies.[1] Over the past decade, primary liver cancer incidence rates have continued to increase globally and in the United States, with hepatocellular carcinoma (HCC) accounting for 75 to 85% of cases.[2,3] The Barcelona Clinic Liver Cancer (BCLC) classification system incorporates HCC tumor staging, liver function, performance status, and projected prognosis to create treatment guidelines for improved survival outcomes.[4–6] Surgical resection, transplantation, and thermal ablation serve as curative approaches for patients with early-stage (BCLC-0, BCLC-A) disease. At the same time, liver-directed therapies, including transarterial chemoembolization (TACE) and transarterial radioembolization (TARE), have been traditionally reserved for advanced disease serving as bridges to curative management.

Radiation segmentectomy using yttrium (^{90}Y) is an innovative approach to radioembolization, utilizing selective ^{90}Y delivery to maximize local administration of cytotoxic radiation and minimize side effects and damage to the surrounding parenchyma.[7–9] Promising response rates and durable outcomes from the recent LEGACY trial led to the inclusion of segmental radioembolization as a treatment option for patients with BCLC 0 and A HCC in the most recent BCLC guidelines.[9,10] These data support the continued evaluation of segmental TARE for the treatment of early-stage HCC. Herein, the present study aims to evaluate the objective response rate (ORR), time to progression (TTP), and overall survival (OS) in patients with unresectable solitary HCC less than 5 cm who were treated with segmental delivery of ^{90}Y glass microspheres.

Materials and Methods

This study was approved by the Institutional Review Board. Data of patients who underwent ^{90}Y radioembolization for the treatment of unresectable HCC at a single institution between November 2012 and April 2020 were retrospectively reviewed. HCC diagnosis was based on contrast imaging following the American Association for the Study of Liver Disease (AASLD) guidelines.[11] The following inclusion criteria were adopted patients who underwent TARE segmentectomy with treatment-naïve, solitary, unilobar, unresectable HCC less than 5 cm in maximal diameter. The decision to perform TARE was based on a multidisciplinary tumor board discussion comprised hepatobiliary surgery, transplant surgery, hepatology, gastroenterology, oncology, diagnostic radiology, interventional radiology, and radiation oncology. Patients were excluded who had metastatic disease, hepatic encephalopathy, undergone prior orthotopic liver transplant (OLT) or resection or had received prior systemic or regional treatment. Patients with a potential absorbed dose in the lungs >30 Gy (>16.5 mCi of injected ^{90}Y) per procedure based on the initial mapping phase were also excluded.

^{90}Yttrium (^{90}Y) Microspheres Protocol

All patients who received TARE treatment underwent two separate outpatient procedures for mapping and administration. Pre-treatment mapping of eligible patients included a hepatic angiogram and ^{99}Tc MAA (^{99}technetium macroaggregated albumin) scan to evaluate hepatic vasculature and pulmonary or gastrointestinal shunting. Dosing of ^{90}Y microspheres (TheraSphere; Boston Scientific, Natick MA) was calculated referencing liver mass and volume determined by baseline CT/MR scan or intra-procedural CT using methods previously described in the literature.[12] Dosing range for this study was 21.4 to 131.70 mCi. On the day of administration, TARE microspheres were delivered through a hepatic arterial catheter under fluoroscopic guidance according to the administration procedures outlined in the package.[12] Hepatic arterial catheterization was selective to the segmental level to the maximize tumor dose delivery and minimize collateral liver injury with target dosimetry > 250 Gy.[7] Patient follow-up and survival surveillance were led by the principal oncologist/hepatologist and recorded from electronic medical records for this study.

Data Collection

Patient demographics, comorbidities, laboratory values, MELD and ECOG scores, baseline disease, and tumor characteristics were abstracted from the electronic medical records (EPIC Systems; Verona, WI). Lung shunt fractions, radiation dosimetry, subsequent treatment cycles, and the presence of cirrhotic morphology on imaging (CT or MRI) were also recorded for each patient. Pathological necrosis was documented for patients who received an OLT. Treatment-related adverse events were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Survival time from first treatment and follow-up treatments, including OLT, TACE, and radiofrequency ablation (RFA), were also documented.

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Response Assessment

Follow-up imaging was performed on each patient at 3-, 6-, and 12 months post-treatment. Tumor response was evaluated using the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria and graded as complete (CR), partial (PR), stable disease (SD), or progressive (PD) based on contrast-enhanced imaging.[13] The response/progression within the radioembolization-treated zone was determined by local mRECIST. mRECIST included a combined assessment of treatment response in the targeted region, and a new hepatic lesion development was observed in progressive disease.

Outcomes Assessment

The primary outcomes were objective response rate (ORR), time to progression (TTP), and overall survival (OS). ORR was defined as the combined proportion of patients who exhibited CR and PR following Y90 treatment. Patients were followed until death or the last imaging encounter. TTP was defined as the time from treatment response to local or global progressive disease. The incidence of adverse events and serious adverse events were reported as counts and percentages and coded according to the Medical Dictionary for Regulatory Activities.[14]

Statistical Analysis

Patient demographics, baseline characteristics, and treatment characteristics were analyzed using descriptive statistics, including interquartile ranges (IQR). TTP was summarized as percentages and confidence intervals (CI). Survival was calculated from the time of initial therapy to either the date of death or last known follow-up. Patients were censored at the time of transplantation. Predictors of survival were analyzed with Cox proportional hazards regression. Covariates with a *P*-value < 0.1 in univariate analysis were subjected to multivariate analysis in a stepwise approach. A *P*-value < 0.05 was considered statistically significant. Analyses were performed using Stata Version 13 (StataCorp LP, College Station, Texas). Kaplan–Meier analysis was performed using Prism9 (GraphPad Software, San Diego, California). Plots were constructed using a standard statistical software package (R; R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Demographics and Clinical Characteristics

Among the 35 included patients, the median age was 67 (range: 57–82) years, with 60.6% (21/35) being male. Cirrhosis was present in all patients (35/35, 100%). Predominant HCC etiology was hepatitis C (18/35, 51.4%). The median tumor size was 3 cm (range: 1.0–4.8 cm). A total of 29/35 patients were Child–Pugh class A (82.9%). The median Model for End Stage Liver Disease (MELD) score was 9, with 85.7% (30/35) of patients between 6 and 14. 9/35 patients (25.7%) were Eastern Cooperative Oncology Group (ECOG) 0, and 22/35 were 62.9% ECOG 1; 68.5% (31/35) patients were Barcelona Clinic Liver Cancer (BCLC) stage C. Additional baseline characteristics of included patients are described in ►**Table 1** and ►**Fig. 1**.

Treatment Characteristics

The median segmental infusion administered dose was 49.5 mCi (IQR: 32.1, 80.9). Also, 77.1% (27/35) of patients underwent one TARE treatment. Treatment served as bridging therapy to surgery for 37.1% (13/35) of patients, and 12 out of 13 underwent transplantation (92.5%) at the time of this manuscript preparation. Non-local hepatic tumor recurrence developed in 8/35 (22.9%) of patients by 12 months. Among those with recurrence who did not undergo OLT, three patients received percutaneous microwave ablation (MWA), one patient received TACE, one patient received nivolumab as salvage therapy. One patient received MWA post-TARE and prior to OLT (►**Table 2**).

Treatment Response

Local mRECIST responses at 3 months post-treatment included 88.6% CR, 5.7% PR, 5.7% SD, and 2.9% PD, with a combined ORR of 94.3% (►**Fig. 2**, ►**Table 3**). mRECIST ORR at 3 months post-TARE was 85.7%, with patients having 82.9% CR, 2.9% PR, 2.9% SD, and 8.6% PD. Treatment responses evaluated at 3-, 6-, and 12 month intervals are summarized in ►**Fig. 3**. For the 12 patients who underwent transplantation, the median pathologic necrosis of the targeted region was 98% (IQR: 7.5).

Time to Progression following ^{90}Y Treatment

TTP following ^{90}Y treatment is listed in ►**Table 4**. The mean local TTP among all patients was 11.9 months (CI: 2.7–21.0), and mRECIST TTP was 13.2 months (CI: 6.4–20.0). Among transplant-eligible patients, 1 (7.7%) had local, and 3 (23.1%) had nonlocal hepatic recurrence prior to OLT. Of the transplant-ineligible patients, 3 (13.6%) developed local progression, 1 (4.5%) patient had local and non-local progression, and 8 (36.4%) had non-local progression by 12 months.

Survival Analysis

In the univariate analysis summarized in ►**Table 5**, none of the following variables are statistically significant predictors of OS: age ≥ 70, Caucasian, ECOG, lesion size, AFP level, MELD score, and Child-Pugh Classification ($P > 0.10$). The overall survival at 12 months was 97%, while patients who underwent OLT exhibited an OS of 100%. Kaplan–Meier survival curve for both transplant-eligible and transplant-ineligible patients is shown in ►**Fig. 4**.

Adverse Events

Grade 1 adverse events (AE) were present in 4/35 participants, including mild fatigue ($N = 1$), constipation ($N = 2$), and mild right upper quadrant pain ($N = 1$). One patient experienced grade 4 AEs (hypoxia and encephalopathy) after radioembolization. All AEs resolved within 1 month of initial TARE treatment. No deaths occurred secondary to TARE-related complications.

Discussion

The LEGACY study demonstrated that TARE administered with an ablative intent is a promising treatment for solitary,

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Table 1 Baseline characteristics

		Treated population ($N = 35$) N (%)
Age (y)		
	Younger than 60	2 (6)
	61–70	25 (71)
	71–80	6 (17)
	Older than 80	2 (6)
	Median age	67
Sex		
	Female	14 (40)
	Male	21 (60)
Ethnicity and race		
	Hispanic or Latino	4 (11.4)
	Native American, Native Alaskan	1 (2.9)
	Black or African American	7 (20)
	Asian or Mideast Indian	2 (5.7)
	White or Caucasian	23 (65.7)
	Not available	2 (5.7)
Etiology		
	HCV	12 (34.2)
	HCV/alcohol	5 (14.3)
	HCV/hemochromatosis	1 (2.9)
	Alcohol	4 (11.4)
	HBV	1 (2.9)
	NAFLD	1 (2.9)
	NASH	7 (20)
	Idiopathic/unknown	4 (11.4)
Tumor size		
	Median (cm)	3
	Range (cm)	1.4-4.8
Child–Pugh		
	A	29 (82.9)
	B	6 (17.1)
BCLC	0	1 (2.9)
	A	1 (2.9)
	C	31 (88.5)
	Not available	2 (5.7)
MELD		
	6–14	30 (85.7)
	15–24	5 (14.3)
	Median score	9
ECOG		
	0	9 (25.7)
	1	22 (62.9)
	2	2 (5.7)
	Not available	2 (5.7)

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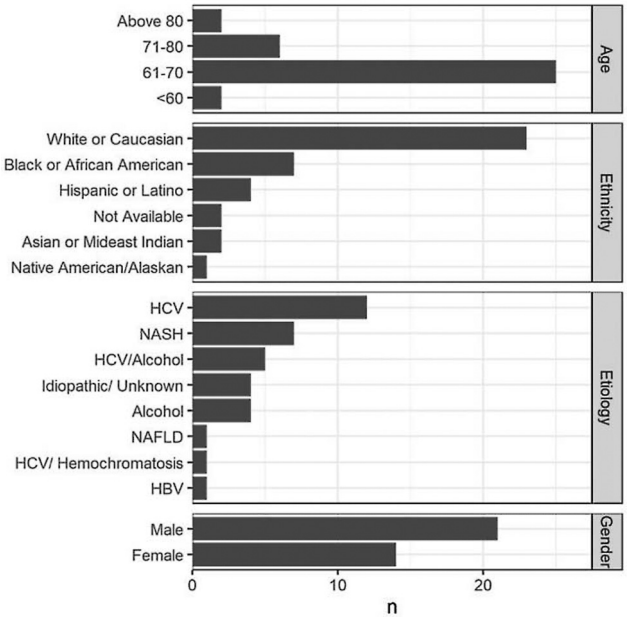

Fig. 1 Patient demographics. Baseline patient demographics including age, gender, ethnicity, and HCC etiology were abstracted and compiled from electronic health records and listed above.

unresectable HCC, and prompted updated BCLC guidelines to include TARE as a treatment for patients with early-stage HCC.[9] Nearly 60% of patients received radiation segmentectomy in the LEGACY study, suggesting the potential therapeutic role of this technique among transplant candidates due to increased localized cytotoxicity and reduced collateral damage. Herein, this single-center study shows that segmental ^{90}Y radioembolization is safe and effective in achieving durable radiological response, tumor pathological necrosis, prolonged patient survival, and bridge to transplant for patients with treatment-naïve, unresectable, solitary HCC lesions less than 5 cm.

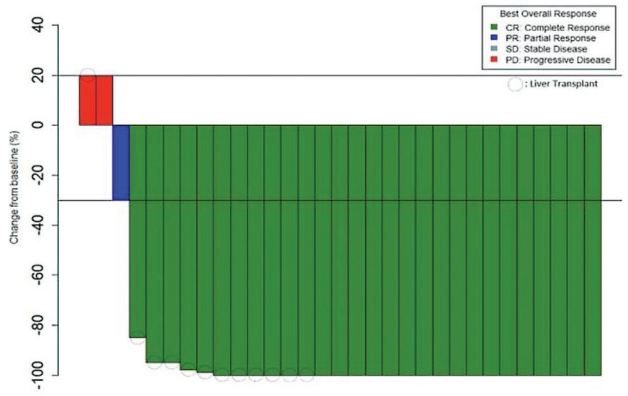

Fig. 2 Waterfall plot of best overall tumor response by localized mRECIST. Response rates were reported as CR, PR, SD, or PD, and the best response rate for each patient is graphically represented as a percent change from baseline.

Table 3 Local mRECIST and mRECIST responses to TARE

	Local mRECIST %	mRECIST %
ORR	94.3	85.7
CR	88.6	82.9
PR	5.7	2.9
SD	5.7	2.9
PD	2.9	8.6

The ORR for local mRECIST and overall mRECIST at 12 months post-^{90}Y radioembolization was 94.3% and 85.7% in the present study, respectively. These results indicate that segmental TARE provided clinically significant local control and were comparable to ORR rates reported in the LEGACY trial and 6-month response rates reported by

Table 2 Treatment characteristics and course

		Treated Population ($N = 35$) N (%)
Lung shunt fraction		
	Mean (SD)	13.16 (0.6)
	Median (IQR)	2.49 (3.0)
Treatment approach	Segmental	35 (100)
Number of ^{90}Y Treatments		
	1	27 (77.1)
	>2	8 (22.9)
Post-procedure treatment		
	TACE	1 (2.9)
	MWA	3 (8.6)
	Chemotherapy (nivolumab)	1 (2.9)
	Resection	1 (2.9)
	OLT	12 (34.3)

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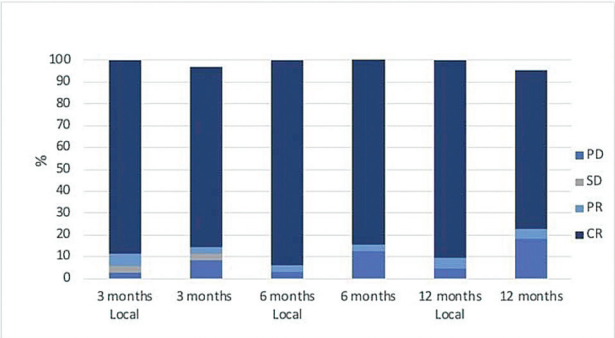

Fig. 3 Local mRECIST and mRECIST responses to TARE. Response rates for all 35 patients at 3-,6-, and 12-months post-TARE treatment.

Table 4 Time to progression following TARE

	Local mRECIST mean (95% CI)	mRECIST mean (95% CI)
TTP overall in months	11.9 (2.7–21.0)	13.2 (6.4–20.0)
TTP transplant-ineligible patients in months	14.6 (8.7–20.5)	16 (7.4–24.5)
TTP transplant-eligible patients in months	3.7 (0)	5 (−0.8–10.9)

Table 5 Univariate analysis of predictors of overall survival

Variables	HR	*p*-Value
Age (≥70 y)	2.12 (0.85–5.29)	0.11
Sex	0.99 (0.41–2.43)	0.99
Caucasian vs. non-Caucasian	1.40 (0.53–3.64)	0.50
ECOG	0.56 (0.23–1.37)	0.21
Lesion size	1.12 (0.80–1.78)	0.39
AFP (normal range vs. elevated)	0.64 (0.23–1.81)	0.40
MELD	1.02 (0.88–1.19)	0.75
Child–Pugh classification	0.88 (0.29–2.69)	0.83

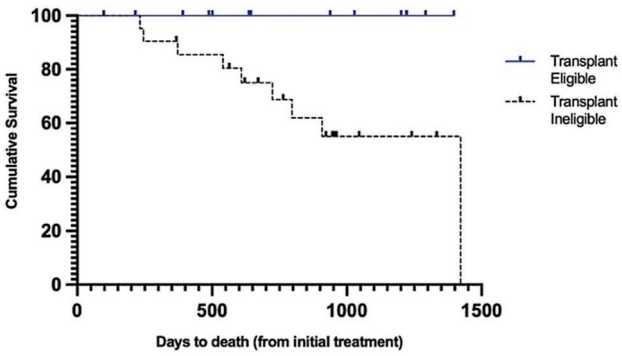

Fig. 4 Kaplan–Meier survival cure for overall survival by transplantation eligibility. X-axis represents days to death or last imaging since ^{90}Y treatment. Y-axis represents cumulative surviving proportion or patients. Tick marks represent last imaging since ^{90}Y for individual surviving patients.

Lewandowski et al in their evaluation of radiation segmentectomy for early-stage HCC.[9,15] Long-term responses were observed with a mean local mRECIST TTP of 11.9 months (CI: 2.7–21.0) and non-local mRECIST TTP of 13.2 months (CI: 6.4–20.0). The greatest duration of local control was observed in patients ineligible for transplant who showed a mean TTP of 14.6 months (CI: 8.7–20.5). These results are comparable to the median 13.3 months TTP reported by Salem et al in their posthoc analysis of patients who received radioembolization for HCC.[16] While surmounting evidence for the use of ^{90}Y in early-stage (BCLC-0/A) HCC has led to updated BCLC guidelines,[10] similar results observed in this study, in which a majority of patients had a slightly worse performance status indicate clinical utility in more advanced disease as well.

Segmental ^{90}Y radioembolization served as a neoadjuvant therapy bridging 37.1% (13/35) patients to surgery, of which 92.5% (12/13) received OLT. With an average transplant wait time of 286 days at the institution in the present study, TARE was useful to ensure eligible patients stayed within Milan transplantation criteria until surgery. Pathologic review of explants exhibited a median necrosis of 98% (IQR 7.5) in regions treated with ^{90}Y. Near complete pathologic necrosis noted following treatment indicates the effectiveness of radioembolization on reducing local tumor burden and supports similar explant results reported by Gabr et al and Tohme et al.[17–19] Survival analysis at 1 year following radioembolization revealed a total OS of 100% for transplant-eligible patients. At 1 year, the remaining 20 patients ineligible for surgery also exhibited a desirable OS of 95% (19/20). Comparable survival outcomes indicate therapeutic benefit of segmental ^{90}Y treatment for patients with unresectable, solitary HCC lesions, regardless of eligibility for curative therapy.

The toxicity profile was acceptable in the present study and paralleled previous reports.[9,16,17,19] Among the 14.3% (5/35) patients who experienced an AE following radioembolization, one patient experienced a Grade 4 event involving hypoxia and encephalopathy, while all remaining events classified as Grade 1 included mild fatigue, constipation, and mild right upper quadrant pain. All reported AE resolved within 1 month of the procedure. A well-documented benefit of TARE as a localized therapy for HCC is its improved safety profile compared to chemoembolization, reducing the likelihood of postembolization syndrome and rehospitalization and enabling safe outpatient administration.[20–22] The limited number of adverse events and the survival benefits observed in this study support existing literature showing selective segmental radioembolization approaches enable higher radiation doses with improved safety profiles.[7]

This study is limited by its single-center retrospective design, lack of randomization, and control arm, and small sample size. Longer follow-up for patients who were treated more recently will be of benefit moving forward to enable more robust survival analysis. Larger, multi-center, prospective studies will enable further identification of clinical correlates predictive of segmental radioembolization response and overall survival to enhance treatment stratification.

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In summary, favorable response rates, TTP, OS, and degree of pathologic necrosis observed on the explant indicate that segmental ^{90}Y radioembolization effectively treats HCC less than 5 cm and provides durable local tumor control. Segmental TARE is safe and effective as a bridge to curative treatment and a stand-alone therapy for unresectable solitary HCC in patients with ECOG performance status of 0 or 1.

Authors' Contributions

Study concept and design, O.A., data acquisition, N.J.R., statistical Analysis, N.J.R., Q.Y., manuscript preparation, N. J.R., S.K.R., and O.A., manuscript editing, revision, and review, O.A., N.J.R., Q.Y., T.V.H., S.Z., and R.N.

Earlier Presentation

This preliminary results of this study were presented at the PAIRS conference as a poster on May 11, 2022.

Study Approval

This study was approved by the Institutional Review Board at University of Chicago and conducted in accordance with the Declaration of Helsinki.

Conflict of Interest

Osman Ahmed, MD is a consultant for Cook, Canon, Penumbra, Bard, Medtronic, and Philips. He is on the advisory board for Boston Scientific, Johnson and Johnson and Argon, and receives research funding from Canon. Dr. Osman Ahmed reported Grants or contracts from Canon; Consulting fees Cook, Canon, Penumbra, Bard, Medtronic, Philips; Participation on a Data Safety Monitoring Board or Advisory Board of Boston Scientific, Argon, Johnson and Johnson. All other authors listed do not have financial or advisory disclosures.

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