PROTOCOL NUMBER:	**16-1313**
PROTOCOL TITLE:	**SPEED 1 Trial: Bridge to Orthotopic Liver Transplantation (OLT) - (Surefire Precision vs Endhole Embolization with DEBTACE)**
Principal Investigator:	**Thor Johnson, MD, PhD**
Study Device:	**Surefire Precision Infusion System**
Version:	**06/20/2018**

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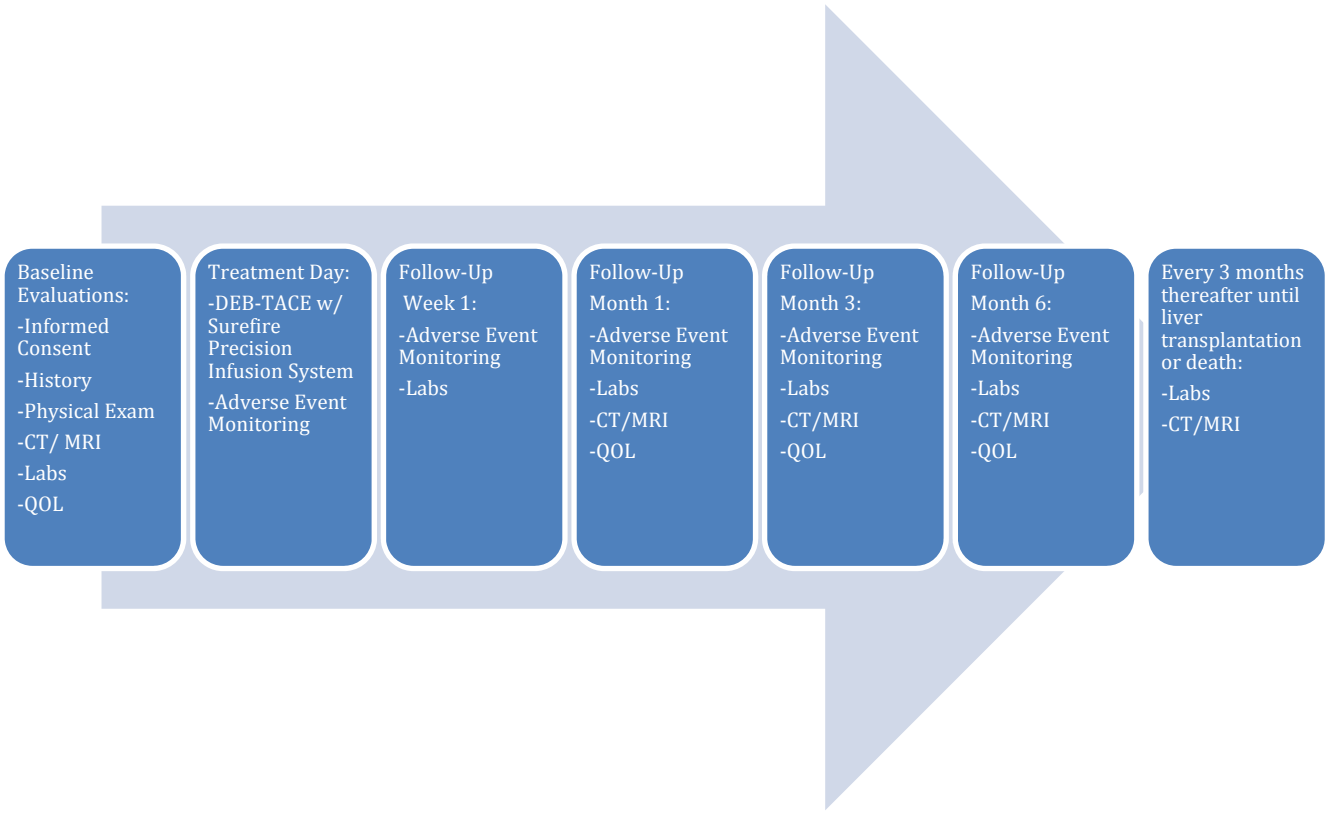
1. STUDY OVERVIEW

1.1 Study Flowchart



1.2 Study Summary

Title	Bridge to Orthotopic Liver Transplantation (OLT) - (Surefire Precision vs Endhole Embolization with DEBTACE)
Short Title	SPEED 1
Protocol Number	16-1313
Phase	Phase IV – Post Market
Methodology	Single Arm Prospective
Study Duration	2 years
Study Center(s)	University of Colorado Hospital
Objectives	Prospectively evaluate the outcomes of patients with hepatocellular carcinoma (HCC) who undergo DEB-TACE with the Surefire Precision Infusion System for intentional effect of down-staging patients to OLT.
Primary Endpoints	• Tumor Response (mRECIST criteria) at 1 month • Local recurrence rate (LRR) at 6 months
Number of Subjects	50
Diagnosis and Main Inclusion Criteria	Patients with HCC and who are being evaluated for liver transplantation but outside Milan criteria and have been prescribed DEB-TACE for tumor down-staging.
Study Product(s), Dose, Route, Regimen	DEB-TACE delivered with the Surefire Precision Infusion System

2. BACKGROUND AND RATIONALE

2.1 Disease Background

2.1.1 TACE: TransArterial ChemoEmbolization

Conventional transarterial chemoembolization with lipiodol/doxorubicin (cTACE) is known to prolong survival compared to supportive therapy in certain patients with unresectable HCC,(1) including patients with unilateral portal vein invasion (PVI).(2-4) TACE with doxorubicin-eluting beads (DEB-TACE) is a relatively new modality associated with favorable systemic doxorubicin exposure/toxicity and liver-specific toxicity compared to cTACE and studies have documented its safety and efficacy.(5, 6) DEB-TACE is currently utilized for a) patients who have unresectable HCC b) patients who meet the Milan Criteria and currently on liver transplantation lists and c) down-staging patients into Milan Criteria for possible liver transplantation (OLT)

2.1.2 Downstaging for OLT

As selection criteria for transplantation and liver allocation policies evolve, bridging and downstaging therapies play an integral role in the waitlist management of patients with Hepatocellular Carcinoma (HCC). Patients with HCC are only conferred on the UNOS priority status upgrade if they meet the Milan (T2) criteria. Therefore, if a patient can be downstaged from T3 (no conferred listing advantage) to T2, the immediate advantage is a significant gain in status and therefore much quicker access to a potentially life-saving organ (7, 8).

The most commonly used downstaging therapies include transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) (5–9). TACE in particular has been examined closely as a downstaging treatment in recent years (10). While some investigators have cited downstaging rates of approximately 50%, the criteria for designating a patient as downstaged have often not been explicit in these reports or have deviated from strict UNOS T2 criteria based on size (11). Nevertheless, the literature has shown that progression-free survival following TACE may be indicative of less biologically aggressive tumors and hence could be used to select patients outside criteria for orthotopic liver transplantation (OLT). Thus, the aims of bridging treatments include decreasing the waiting list dropout rate before transplantation, reducing HCC recurrence, and improving post-transplant overall survival. To date, no data from prospective randomized studies are available; however, for HCC patients listed for OLT within the Milan criteria, prolonging the waiting time over 6-12 months is one of the biggest risk factors for tumor spread (7, 9, 10)

2.1.3 Downstaging Rates:

Toso, et al recently reviewed the practice of downstaging before transplantation by both TACE and Radioembolization from eight reports published between 2003 and 2009 in which rates ranged from 24% to 90%. The wide range of downstaging rates across studies can be explained by non-uniform inclusion criteria, variability in locoregional treatment techniques, distinct systems for assessment of imaging response, and different criteria used to define downstaged disease. (11)

2.1.4 High Recurrence Rates after standard TACE

The likelihood to achieve any response following TACE significantly depends on treatment, tumor number [66] and tumor size with radiologic Complete Response (CR) rates of up to 77% in tumors <2 cm in size but only 25% in tumors with diameters of >5 cm after the first TACE [68]. Similar size dependent differences in radiologic response also apply to repeated TACE sessions. While retreatment with multiple treatments shows a CR rate of 55% and 40% respectively in lesions <5 cm, CR rates are 25% and 0% in a tumor >5 cm. (12)

Furthermore, once complete radiologic response is achieved, overall 72% will suffer tumor recurrence after a median of 8.5 months of which 31% will present as local, 40% as distant intrahepatic and 27% a mixed (local and distant intrahepatic) relapse of disease and again, tumors >5 cm showed a significantly shorter time to recurrence (6 months, $p < 0.05$) (12)

Thus, typical patients requiring downstage have tumors > 5cm but have the poorest response rates requiring multiple procedures and hampered by a high recurrence rates.

2.1.5 Current Delivery Techniques with Standard Endhole catheters.

Currently the best results for TACE occur when the dose is delivered in a highly targeted manner into the tumor. Dense accumulation of embolic spheres or lipiodol into the tumor as documented by CT has been shown to have improved outcomes (13, 14). However, with standard endhole catheters achieving maximum delivery of embolic agents is limited by the development of stasis, non-target delivery and subsequently non target injury. Thus, often Interventional Radiologist use a crude angiographic endpoint of stasis or substasis as the current endpoint.

As DEB-TACE is performed through an endhole catheter with either stasis or substasis as an endpoint, this current methodology is extremely subjective, lacks a quantifiable endpoint and results in various degrees of embolization on patients. Thus, a significant variability on the delivery techniques and endpoints.

2.2 Study Device

2.2.1 Device Description

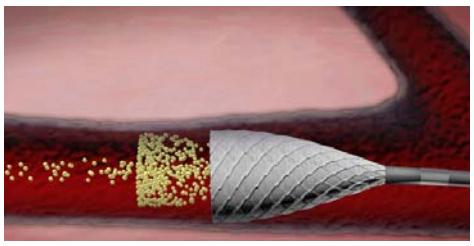
The Surefire® Precision Infusion System (Surefire Medical, Inc., Westminster, CO) is a 0.021" lumen coaxial microcatheter with the Surefire Expandable Tip at the distal end. It has an outer sheath to facilitate expanding and collapsing the Surefire Expandable Tip. The Surefire Precision serves as the conduit for physician-specified agents such as contrast agents, flush solutions, and embolic beads. It is compatible with standard 0.018" guide wires, infusion syringes, rotating hemostatic valves (RHVs/Tuohy Borsts), and embolic hydrogel particles 500µm or less in size and glass microspheres 110µm or less in size. The soft, pliable, funnel-shaped Surefire Expandable Tip is sized for use in vessels of 1.5mm to 3.5 mm.

The Surefire tip can be expanded or collapsed re-positioning during an interventional procedure by simply retracting or advancing the inner microcatheter while holding the outer sheath stationary. The Surefire expandable tip collapses during forward flow, and then dynamically seals off the vessel with reversal of flow, analogous to a valve. The Surefire expandable tip is designed to improve infusion efficiency of compatible embolic agents while maintaining antegrade flow in the vessels.

The expandable tip of the Surefire Infusions System has been clinically demonstrated to cause a slight decrease in intra-arterial pressure in the antegrade or downstream vascular compartment (15, 16). Although this device was designed primarily to prevent retrograde reflux of embolic agents, it also enables improved penetration of embolic spheres into the target tissue. Furthermore, by eliminating reflux, this catheter enables the ability to control the dosimetry, so now the dose can be tailored to the tumor size and not depend upon the flow dynamics of the tumor.

The primary difference between the Surefire® Infusion System and other standard catheters used for chemoembolization, specifically, Boston Scientific Renegade® HI-FLO™ Fathom System and the Terumo Progreat™ Microcatheter, is that the Surefire Expandable Tip is fused to the distal end of the Infusion Microcatheter (See fig 1). The tip is flexible such that when placed in the vessel, the antegrade blood flow around the device is not significantly affected. The Surefire Expandable Tip obstructs the ability of the infusate to reflux backwards through the artery and allows the device to more efficiently deliver the intended media to the target location. In addition, the tip is intended to minimize reflux. High pressures generated while infusing material has the potential to force the infusate against blood flow and into unintended locations in the patient. The Surefire Expandable Tip is designed to obstruct the infused material from travelling against the blood flow which will improve the physician's ability to deliver the intended dosage to the correct location.

Figure 1: Surefire Infusion System has an expandable tip that stops reflux during infusion of therapeutics



2.2.2 Indications for Use

The Surefire Precision Infusion System is intended for use in angiographic procedures. It delivers radiopaque media and therapeutic agents to selected sites in the peripheral vascular system.

2.2.3 Regulatory Status

The Surefire® Precision Infusion System has been cleared by the U.S. FDA under 510(k) K143588 (January 12, 2015).

The FDA 510(k) clearance letter is provided in Appendix 6.1.

The manufacturer's Instructions for Use are located in Appendix 6.2.

To date, over 5000 embolization cases have been performed with the Surefire Infusion Systems.

2.2.4 Relevant Pre-Clinical Experience

2.2.4.1 SIS Stops Reflux of Embolic Spheres: Anti-reflux microcatheter eliminates reflux and allows deeper penetration of vascular bed (18).

The goal of this study was to demonstrate in a porcine model, that reflux during embolotherapy can be quantified (infusion efficiency) and non-target embolization can be reduced utilizing an anti-reflux microcatheter (Fig 2). In six swine, embolization of renal arteries was performed utilizing radiopaque tantalum beads (mean size 44 µm) at a concentration of 1gm/20cc. Second order left renal arteries underwent embolization with a standard 4Fr diagnostic catheter as a control (N=3) and a 3Fr anti-reflux microcatheter as the experimental arm (N=3). After embolization, kidneys were explanted and underwent micro CT imaging. 3D volumetric/multiplanar MIP imaging of the kidneys were created to assess the vascular distribution of tantalum beads and a thresholded binary image was used to determine infusion efficiency as a ratio of positive counts in a region of interest. Successful embolization with tantalum beads occurred in all animals and was readily visible. MicroCT provided high resolution visualization of the renal parenchyma with 0.7 µm isotropic resolution. In control renal arteries, a standard 4Fr catheter had an infusion efficiency of 70.8 ± 4.4% versus 99.1 ± 1.2% with an anti-reflux microcatheter ($P<0.005$, Fig 3). In addition, the anti-reflux microcatheter can generate deeper penetration of embolic beads into the target organ parenchyma (Fig 3).

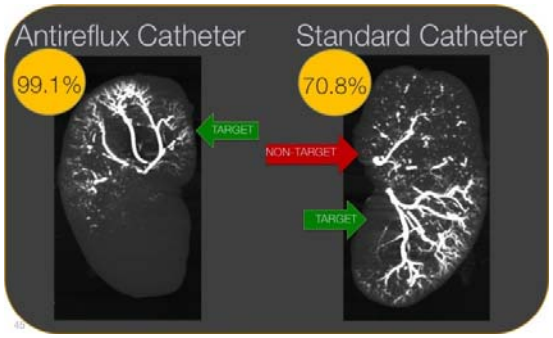


Fig 2: Comparison of the Surefire Catheter to a commercially available infusion catheter. CBCT was performed on explanted kidneys after embolization. Left: The Surefire catheter achieved 99.6% infusion efficiency. Right: The commercially available catheter achieved 68.2% infusion efficiency, with over 30% of the dose being delivered to non-target tissue.

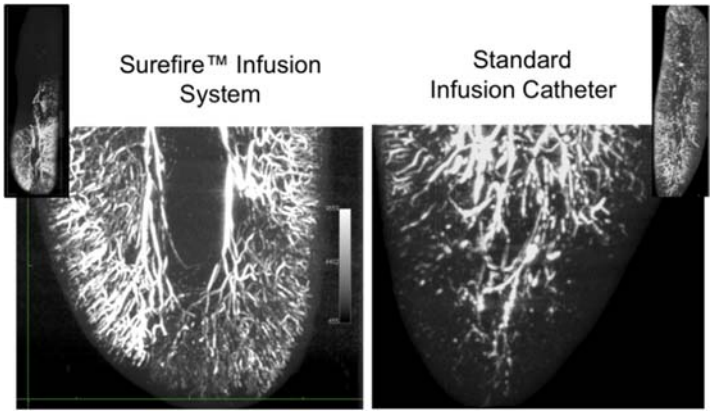


Figure 3 MicroCT comparison of the Surefire Infusion System vs. a standard 4 Fr microcatheter, in renal parenchyma, demonstrating effusion efficiency and penetration of embolic beads.

2.2.4.2 Quantification of Embolization with Surefire Infusion System

Purpose: The goal of this study was to demonstrate in a porcine model, that transcatheter embolization performed with a Surefire Infusion System (SIS) enables direct numerical quantification of embolization utilizing hemodynamic manometric pressure measurements.

Methods: Seven hepatic artery embolizations were performed with 100 micron calibrated spheres in two swine utilizing SIS. After catheterization of the hepatic arteries, baseline manometric pressure measurements (systolic, diastolic, and mean) in the hepatic artery were obtained with SIS deployed, and after delivery of 1cc of calibrated spheres. Baseline pressures through the femoral artery sheath were also recorded at each time point. Angiographic evaluation was performed after each aliquot and categorized as normal, substasis and stasis.

Baseline vascular gradients (systolic, diastolic and MAP) were calculated by subtracting the pressure in the femoral artery minus the hepatic artery pressure. After the delivery of 1ccs of calibrated spheres, repeat vascular gradients were recorded. Different degree of embolization was performed in each artery ranging from 3cc to 7cc of calibrated spheres in the hepatic arteries. Linear regression analysis was performed with the vascular gradients (systolic, diastolic, MAP)) versus volume of embolics delivered. Correlation of pressure recordings was also performed versus angiographic flow.

Results: The mean baseline systemic, diastolic and mean femoral sheath pressures were respectively: 78.1 mm Hg (+/-2.7)/45.1 (+/-1.8)/57 (+/-2.3). After deployment of SIS, the mean baseline systemic, diastolic and mean hepatic artery pressures significantly decreased to: 33.7 mm Hg (+/-14.3)/26.4 (+/-7.4)/29.1 (+/-9.2). Thus the mean change gradient in the vessel after deployment of the tip in the hepatic artery was: systolic =44.4 mmHg (+/-14) diastolic=18.7 (+/-8.2) and mean=27.7 (+/-9.2). During embolization, the hemodynamic pressure gradients from the hepatic artery to systemic pressure decreased based upon the degree of embolization. During embolization, linear regression analysis identified the slopes of diastolic gradient ($R2$ = .91) and MAP ($R2$ = .83) and systolic gradients ($R2$ = .67) as significant (Figure 4) All three dependent variables fit to a line with significance, but individually, diastolic gradients had the highest F statistic (p=0.0002), so correlated best with embolics delivered. In comparing pressure gradients versus angiographic flow, normal flow, substasis, and static flow are all significantly different from one another for systolic and diastolic and MAP gradients. The difference between substatic flow and static flow is

most significant with diastolic pressures. In normal flow, SIS created a mean baseline diastolic gradient of 17.4 mm Hg (+/-8.8). At substasis, mean diastolic gradient decreased to 7mm Hg (+/-7.6); at stasis, baseline gradient was -1.9 mmHg (+/- 2.3) (Figure 5).

Conclusions: Embolization can be quantified using SIS and there is a linear correlation between hemodynamic manometric pressure changes and the volume of embolic agent. Diastolic pressures changes is the most sensitive parameter to differentiate between normal flow, substasis and full stasis. A zero vascular gradient correlates with full stasis.

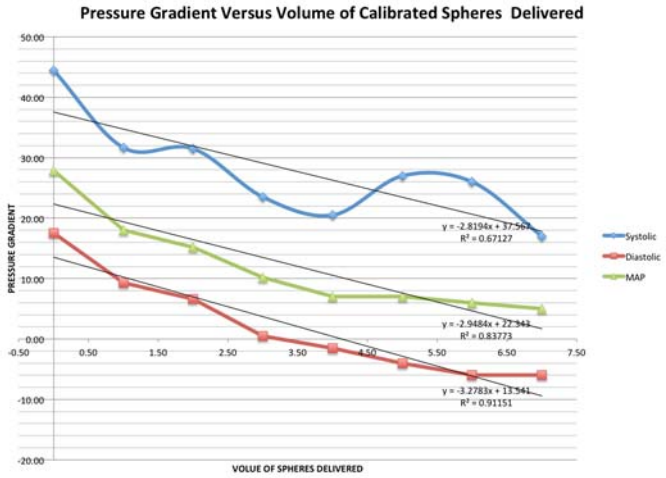


Figure 4: The change in pressure gradient has linear correlation as the volume of calibrated spheres delivered is increased

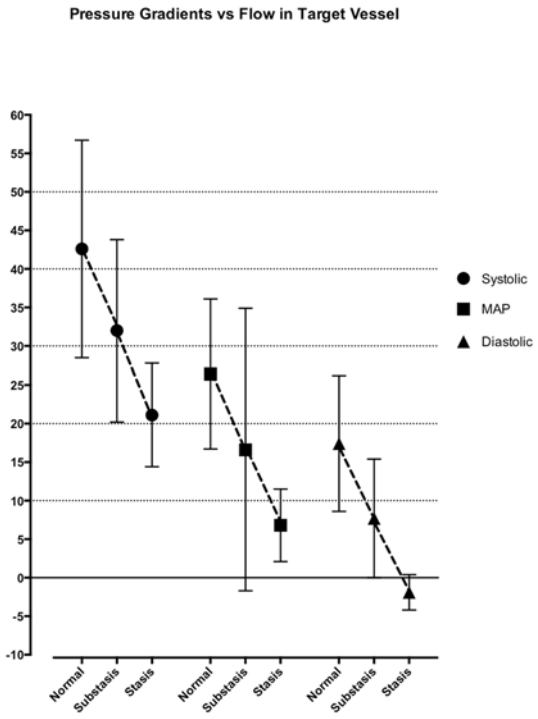


Figure 5: The change in systolic, MAP and diastolic gradients during normal flow, substasis and static flow.

2.2.4.3 Use of Surefire Infusion System for intra-arterial liver cancer treatments results in favorable particle-fluid dynamics (19)

Background: Liver tumors are increasingly treated with radioembolization. Here, we present first evidence of catheter design effect on particle-fluid dynamics and downstream branch targeting during microsphere administrations.

Materials and Methods: A total of 7 experiments were performed in a bench-top model of the hepatic arterial vasculature with recreated hemodynamics. Fluorescent microspheres and clinically used holmium microspheres were administered with a standard microcatheter (SMC) and an anti-reflux catheter (ARC) positioned at the same level along the longitudinal vessel axis. Catheter-related particle flow dynamics were analyzed by reviewing video recordings of UV-light illuminated fluorescent microsphere administrations. Downstream branch distribution was analyzed by quantification of collected microspheres in separate filters for two first-order branches. Mean deviation from a perfectly homogenous distribution (DHD) was used to compare the distribution homogeneity between catheter types.

Results: The SMC administrations demonstrated a random off-centered catheter position (in 71 % of experiments), and a laminar particle flow pattern with an inhomogeneous downstream branch distribution, dependent on catheter position and injection force. The ARC administrations demonstrated a fixed centro-luminal catheter position, and a turbulent particle flow pattern with a more consistent and homogenous downstream branch distribution. Quantitative analyses confirmed a significantly more homogeneous distribution with the ARC; the mean DHD was 40.85 % (IQR 22.76 %) for the SMC and 15.54 % (IQR 6.46 %) for the ARC (p = 0.047).

Conclusion: Catheter type has a significant impact on microsphere administrations in an in-vitro hepatic arterial model. A within-patient randomized controlled trial has been initiated to investigate clinical catheter-related effects during radioembolization treatment

2.2.5 Relevant Clinical Experience

2.2.5.1 Intrahepatic Hemodynamic Changes with SIS (15):

Purpose: To evaluate blood pressure changes caused by deployment of the Surefire® anti-reflux expandable tip. The relevance is that there will be implied blood flow changes in the distal hepatosplanchnic arterial blood flow during delivery of embolic cytotoxic agents into the hepatic arteries via the Surefire Infusion System.

Methods: After positioning the Surefire® anti-reflux system in the target hepatic artery, blood pressure was obtained initially with the tip collapsed, then again after the tip was expanded prior to chemoembolization or Yttrium 90 (90Y) radioembolization.

Results: 11 patients with liver malignancy underwent 15 procedures in 15 hepatic arteries (2 common hepatic, 10 lobar, 3 segmental). Systolic, diastolic, mean blood pressure and pulse amplitude were all reduced by a mean of 25 mmHg (p=0.004), 47 mmHg (p=0.00002), 21 mmHg (p=0.00003), and 8mmHg (p=0.134), respectively. Blood pressure reduction was less in the common hepatic arteries (12 mmHg) than lobar (21 mmHg) or segmental hepatic arteries (21 mmHg) (p=0.009).

Conclusion: When the Surefire® expandable tip is deployed to prevent retrograde reflux of agents, it also results in significant reduction in blood pressure in the antegrade distribution, likely resulting in hepatopedal blood flow in difficult to embolize hepatosplanchnic vessels such as the supraduodenal arteries.

2.2.5.2 Hi-Risk Registry: Radioembolization without Prophylactic Coil Embolization of Patent Proximal Extrahepatic Vasculature: Use of an Anti-Reflux Infusion System

Purpose: Reflux of yttrium-90 microspheres into extrahepatic arteries during transarterial radioembolization (TARE) procedures can result in severe gastrointestinal complications. We hypothesized that use of an anti-reflux infusion system can enhance safety by preventing non-target microsphere deposition in patients at high anatomic risk due to patent proximal extrahepatic vasculature.

Materials and Methods: In this retrospective multicenter review, 36 patients with hepatic malignancy and high-risk vascular anatomy were treated with TARE using resin microspheres delivered through an anti-reflux infusion system (Surefire Infusion System, Surefire Medical). Anatomy considered to be high risk for non-target deposition included: variant vascular anatomy, proximal extrahepatic vasculature not amenable to coil embolization, recanalized vessels after coil embolization, or combinations of the above. All patients were followed clinically for gastrointestinal toxicity.

Results: Technical success of deployment of the microcatheter was achieved in 100% of patients with an 11% rate of reversible vasospasm. The median dose delivered was of 1.4 Gbq (+/- .6 Gbq) with a median of 94% of the planned dose delivered. Stasis or sub-stasis was reached in 28% of procedures, but no reflux was observed in any procedure. The most common patent arteries protected during infusions were the supraduodenal artery (39.4%), gastroduodenal artery (19.4%), and right gastric artery (8.3%). There were no gastrointestinal complications recorded during follow-up.

Conclusions: Use of the anti-reflux microcatheter is feasible and safe in patients at high risk of nontarget deposition into patent proximal extrahepatic vasculature. This infusion system appears to deliver the entire desired radioembolic dose without reflux despite reaching stasis of flow.

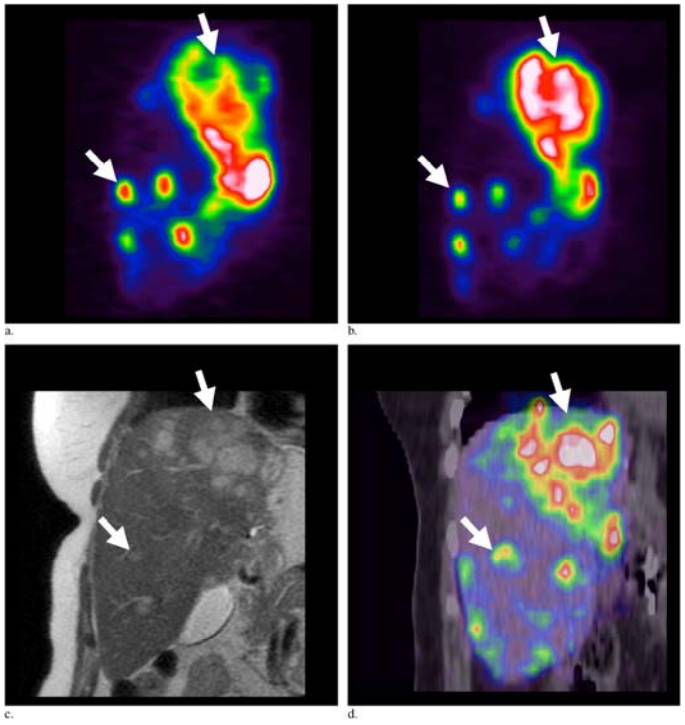
2.2.5.3 The Impact of an Anti-reflux Catheter on Target Volume Particulate Distribution in Liver-Directed Embolotherapy: A Pilot Study (16)

Purpose: To determine if there are differences in hepatic distribution of embolic particles following infusion with a standard end-hole catheter versus an anti-reflux microcatheter.

Materials and Methods: This prospective study included nine patients (age, 48-86 y) enrolled for treatment of hepatocellular carcinoma (n = 6), liver-dominant metastatic disease (n = 2), or intrahepatic cholangiocarcinoma (n = 1) with resin yttrium-90 ((90)Y) microspheres. Before (90)Y treatment, each patient received two same-day sequential lobar infusions of technetium 99m ((99m)Tc) macroaggregated albumin (MAA) via a conventional end-hole catheter and an anti-reflux microcatheter positioned at the same location. Differences in technetium 99m-MAA distribution within tumor and nontarget sites were evaluated by single-photon emission computed tomography (SPECT) on a qualitative and semiquantitative basis. The anti-reflux microcatheter was used for the ensuing (90) Y treatment, with posttreatment (90)Y positron emission tomography/computed tomography to assess distribution of (90)Y microspheres.

Results: Decreases in hepatic nontarget embolization were found in all patients when the anti-reflux catheter was used. These decreases ranged from a factor of 0.11 to a factor of 0.76 (mean, 0.42; $\sigma = 0.19$), representing a 24%-89% reduction. Increased tumor deposition was also noted in all patients, ranging from a factor of 1.33 to a factor of 1.90 (mean, 1.68; $\sigma = 0.20$), representing a relative increase of 33%-90%. Both findings were statistically significant ($P < .05$).

Conclusions: Although this pilot study identified differences in the downstream distribution of embolic particles when the anti-reflux catheter was used, further investigation is needed to determine if these findings are reproducible in a larger patient cohort and, if so, whether they are associated with any clinical impact.



In all images, arrows indicate corresponding areas of disease on each image and imaging modality. ***(a)*** *Distribution of ^{99m}Tc MAA on coronal SPECT following infusion with an end-hole catheter in a 48-year-old woman with HCC (patient 6;* ***Table 1****).* ***(b)*** *Coronal SPECT demonstrates the distribution of MAA following infusion with an anti-reflux catheter.* ***(c)*** *Pretreatment coronal hepatic protocol MR imaging demonstrates multicentric hepatic masses.* ***(d)*** *Posttreatment coronal ^{90}Y PET/CT following infusion of radioembolic materials with an antireflux catheter. Quantitative analysis showed a change in MAA deposition by a factor of 1.67 (67% increase) with the antireflux catheter in the large superior mass (top arrow).*

2.3 Clinical Rationale

In summary, current techniques for down-staging patients for OLT into Milan Criteria is hindered by several vital issues:

a. Poor conversion rates

b. High recurrence rates

c. Variable delivery techniques

d. Variable dosimetry.

The aims of bridging treatments include decreasing the waiting list dropout rate before transplantation, reducing HCC recurrence, with the goal of standardizing dosimetry and delivery methods. To date, no data from prospective randomized studies are available to support these aims.

Despite the effectiveness of DEB-TACE for the treatment of primary malignancy, this procedure is limited by the lack of a consistent endpoint for therapy. The dosage and delivery mechanism is

not standardized and often patients often have to undergo multiple procedures with varying dosages to effectively control the tumor.

Thus, this research protocol will provide critical information on how to perform DEB-TACE in patients undergoing down-staging protocol for OLT. By proving our hypothesis, we envision that this procedure may improve outcome of therapies and minimize repeat treatments by providing a consistent standard of therapy.

2.4 Study Objectives

2.4.1 Purpose

The purpose of this study will be to prospectively evaluate the outcomes of patients with hepatocellular carcinoma (HCC) who undergo DEB-TACE with the Surefire Precision Infusion System for intentional effect of down-staging patients to OLT.

Patients with HCC and who are being evaluated for liver transplantation but outside Milan criteria and meet the eligibility criteria will be enrolled in the prospective single arm study.

Results of the prospective cohort will be compared to matched historical control patients who were previously treated with DEB-TACE, delivered with standard endhole catheters. This includes all patients treated at the University of Colorado since 2009 treated with 100-300 micron beads for whom follow-up is available.[1] The data are as follows.

Total Targeted Lesions	152
Total Number of Patients	137
Patients with Solitary Lesion	123
Patients with 2 Targeted Lesions	13
Patients with 3 Targeted Lesions	1
Number of Patients Transplanted before 6 months	22

1-Month Response

	Dr. Johnson's Range Criteria				Vesselle, G., et al. (2015) Range Criteria		
	0-3 cm	3-7 cm	>7 cm	Total	<5 cm	>=5 cm	Total
Count	84	60	8	152	129	23	152
Range	1.3-3.0 cm	3.2-7.0 cm	7.6-17.0 cm	1.3-17.0 cm	1.3-4.8 cm	5.0-17.0 cm	1.3-17.0 cm
Number Complete Response	33	15	0	48	47	1	48
Percentage Complete Response	39.29%	25.00%	0.00%	31.58%	36.43%	4.35%	31.58%
Number Partial Response	32	39	6	77	58	19	77
Percentage Partial Response	38.10%	65.00%	75.00%	50.66%	44.96%	82.61%	50.66%
Number Stable Disease	14	4	1	19	17	2	19
Percentage Stable Disease	16.67%	6.67%	12.50%	12.50%	13.18%	8.70%	12.50%
Number Progressive Disease	5	1	1	7	6	1	7
Percentage Progressive Disease	5.95%	1.67%	12.50%	4.61%	4.65%	4.35%	4.61%
Number Lost To Follow-up*	0	1	0	1	1	0	1
Percentage Lost To Follow-up*	0.00%	1.67%	0.00%	0.66%	0.78%	0.00%	0.66%
Total	84	60	8	152	129	23	152

[1] We have robust follow-up on these patients, which is the main reason that we are intending to use this historical comparator.

6-Month Recurrence (Complete & Partial Response)							
	Dr. Johnson's Range Criteria				Vesselle, G., et al. (2015) Range Criteria		
	0-3 cm	3-7 cm	>7 cm	Total	<5 cm	>=5 cm	Total
Patients with Complete Response at 1-month	33	15	0	48	47	1	48
Number Lost To Follow-up at 6-months	2	3	0	5	5	0	5
Percentage Lost To Follow-up at 6-months	6.06%	20.00%		10.42%	10.64%	0.00%	10.42%
Number No Recurrence at 6-months	19	4	0	23	23	0	23
Percentage No Recurrence at 6-months	57.58%	26.67%		47.92%	48.94%	0.00%	47.92%
Number Recurrent Disease at 6-months	12	8	0	20	19	1	20
Percentage Recurrent Disease at 6-months	36.36%	53.33%		41.67%	40.43%	100.00%	41.67%
Subtotal	33	15	0	48	47	1	48
Patients with Partial Response at 1-month	32	39	6	77	58	19	77
Number Transplanted	5	3	0	8	7	1	8
Percentage Transplanted	15.63%	7.69%	0.00%	10.39%	12.07%	5.26%	10.39%
Number Continue TACE to Complete Response	4	0	0	4	4	0	4
Percentage Continue TACE to Complete Response	12.50%	0.00%	0.00%	5.19%	6.90%	0.00%	5.19%
Number Continue TACE to Partial Response	6	12	4	22	15	7	22
Percentage Continue TACE to Partial Response	18.75%	30.77%	66.67%	28.57%	25.86%	36.84%	28.57%
Number Continue TACE to Stable Disease	1	5	0	6	2	4	6
Percentage Continue TACE to Stable Disease	3.13%	12.82%	0.00%	7.79%	3.45%	21.05%	7.79%
Number Continue to Progressive Disease	12	10	0	22	21	1	22
Percentage Continue to Progressive Disease	37.50%	25.64%	0.00%	28.57%	36.21%	5.26%	28.57%
Number Continue TACE unknown status	3	3	0	6	5	1	6
Percentage Continue TACE unknown status	9.38%	7.69%	0.00%	7.79%	8.62%	5.26%	7.79%
Number Change Tx	1	4	2	7	2	5	7
Percentage Change Tx	3.13%	10.26%	33.33%	9.09%	3.45%	26.32%	9.09%
Number Deceased by 6-months	0	2	0	2	2	0	2
Percentage Deceased by 6-months	0.00%	5.13%	0.00%	2.60%	3.45%	0.00%	2.60%
Subtotal	32	39	6	77	58	19	77

2.4.2 Hypothesis

Delivery of DEB-TACE with the Surefire Precision Infusion System in patients with HCC who are being considered for liver transplant and are being treated for the purpose of tumor down-staging results in improved tumor response (mRECIST criteria) at 1 month as shown by contrast enhanced CT/MRI as compared to matched historical control patients who received DEB-TACE delivered with a standard endhole catheter.

2.4.3 Primary Endpoints

1. Tumor response (modified RECIST criteria) at 1 month as shown by contrast enhanced CT/MRI. (Note: Tumor response will be determined on a per-treated lesion basis.)
2. Local recurrence rate (LRR) at 6 months as shown by contrast enhanced CT/MRI
3. Absolute Tumor enhancing maximum diameter at 1M and 6M.

2.4.4 Secondary Endpoints

1. Tumor response (mRECIST criteria) at 3 and 6 months as shown by contrast enhanced CT/MRI
2. Successful downstage to Milan criteria or UCSF criteria
3. Time to progression
4. Treatment-related toxicity
5. Change in Liver Functions Tests
6. Change in Quality of life
7. Changes in AFP levels

3. STUDY DESIGN

3.1 Study Design

This is a single institution prospective clinical trial with historical matched controls.[2]

This protocol standardizes DEB-TACE delivery with the Surefire Precision Infusion System.

This protocol does not change patient therapy as the Surefire Precision Infusion System is a standard of care device. All patient safety monitoring, treatment procedures and follow-up procedures will be performed in accordance with standard clinical practice.

3.2 Study Sites

The study will be performed by the Division of Interventional Radiology at the University of Colorado Hospital.

3.3 Sample Size

Fifty (50) subjects will be enrolled in the prospective arm.

Data from one hundred (100) historical randomly sampled control subjects (1:2 ratio) will be selected.

The statistical basis for the sample size is provided in Section 4.3.

3.4 Study Duration

The study was closed by the sponsor on June 18, 2018. All screening, data entry and follow-up visits were ceased on this day. Adverse event follow-ups are still occurring, and are outlined in more detail in Section 4.6.

3.5 Subject Selection (Eligibility)

Patients will no longer be screened for this study as of 06/18/2018.

3.5.1 Recruitment Population

Patients with HCC that are being evaluatedfor liver transplantation and scheduled to received DEB-TACE treatment for tumor down-staging.

No advertising will be done for the purpose of recruitment since patients are routinely referred to the transplant center for evaluation. All consecutive patients who meet the eligibility criteria will be approached to assess for interest in participating in the study. Patients who are not interested in participating will receive treatment with either standard TACE or the SUREFIRE system, depending on the treating physician's prerogative, since both are FDA approved.

3.5.2 Inclusion Criteria

1. Patients aged 18 years or older with the diagnosis of HCC currently being evaluated for liver transplantation and considered for downstaging.
2. Patients undergoing Surefire DEB-TACE procedure as clinically determined to be part of their standard of care treatment plan.

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[2] In order to test the hypothesis (section 2.4), this prospective study has been designed for eligible participants to receive DEB-TACE with the Surefire Precision Infustion System. Historical matched patients, who previously underwent the DEB-TACE using a standard endhole catheter, will serve as the control group for this study (section 3.1). Given the lack of available comparator data, it is most appropriate to gather the data single arm and with the data develop an appropriate statistical framework for comparison.

3. Meets Milan criteria: a single tumor that is < 5cm or a maximum of 3 tumors with each tumor <3cm AND/OR meets UCSF criteria: a single tumor that is < 6.5 cm in diameter or 2 lesions < 4.5cm with total tumor diameter <8 cm AND/OR is outside of both Milan and UCSF criteria and is being evaluated for downstaging.
4. No portal invasion or extrahepatic spread.
5. No previous chemotherapy, radiotherapy or transarterial embolization (with or without chemotherapy).
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
7. Preserved liver function (Child-Pugh Class A or B).

3.5.3 Exclusion Criteria:

1. Advanced bilirubin levels > 3 mg/dl
2. INR > 2 in the absence of anticoagulation therapy
3. AST or ALT>5 upper limit of normal or >250 U/l
4. Advanced tumoral disease, defined as vascular invasion, extrahepatic spread, or diffuse HCC (50% liver involvement)
5. Contraindications for doxorubicin administration.
6. Child's Class C

3.6 Informed Consent

No more patients will be consented for this study as of 06/18/2018.

Eligible study subjects will be provided with a study overview and written informed consent form to review.

Only patients that sign the informed consent form will be enrolled in the study. The form is dually signed by the person who conducted the informed consent discussion.

3.7 Baseline / Pre-Treatment Procedures

No more patients will undergo baseline / pre-treatment procuedures as of 06/18/2018.

The following evaluations/activities will be performed at baseline:

- Informed Consent
- Medical history
- Physical Exam
- Data Collection of Standard of Care CT/ MRI within 1 month of the visit date.
- Data Collection of Standard of Care Lab Values including CBC, CMP, AFP and INR.
- Quality of Life Questionnaire

3.8 Treatment Procedures

No more patients will undergo treatment procedures as of 06/18/2018.

All patients enrolled in this protocol will receive DEB-TACE, which is the standard of care prescribed by their physician.

Lactate whole blood venous will be collected prior to procedure.

Standard 5 Fr and 3 Fr catheters will be used to perform diagnostic angiography to map the hepatic vasculature to the tumor. Using standard technique, the target vessel feeding the tumor will be catheterized and DEB-TACE administered using the Surefire Precision catheter.

The Doxorubicin dosing used in the DEB-TACE will be based upon tumor volume as follows:

Doxorubicin Dosimetry by Tumor Volume		
Tumor Diameter (cm)	**Tumor Volume (cc)**	**Doxorubicin (mg)**
3	14.14	75
4	33.51	75
5	65.45	100
6	113.10	150
7	179.59	150
8	268.08	150

DEB-TACE will be administered until the first of the following endpoints is reached:

- Achievement of target dose with stasis
- Leeching of contrast through the expandable tip
- Development of distal intrahepatic collaterals

Note: In hypervascular tumors, the additional use of bland spheres may be needed to achieve the DEB-TACE delivery endpoint.

3.9 Post-Treatment Procedures

No more patients will undergo post-treatment procedures as of 06/18/2018.

The following procedures will be performed following the DEB-TACE procedure:

- Cone Beam CT of the liver will be performed to determine distribution and density of the beads in the tumor.
- Lactate whole blood venous will be collected 2 hours post-procedure.
- Adverse events monitoring

Patients will be discharged the same day if clinically indicated. Patients may be admitted to the hospital after the embolization procedure if clinically indicated.

3.10 Follow-Up Procedures

As of 06/18/2018, patients already enrolled will only be followed for ongoing, related adverse events. This is outlined further in Section 4.6.

A follow-up phone call visit is being added to assess adverse events. Upon approval of this protocol, currently enrolled patients will be mailed a letter explaining the change in study status (Appendix 6.5) and be contacted via telephone (Appendix 6.6). The study closeout letter will be sent certified with return receipt requested. A copy of the letter sent and mailing receipt will be filed in the patient binder. The phone call will ensure all possible existing adverse events have been captured and provide an opportunity to assess ongoing, related adverse events before study completion. Only patients still being monitored for adverse events during the first six months post initial treatment procedure will receive this phone call. Patients outside of this first 6 month window will not be called as adverse event data collection for new adverse events has already ceased. The phone call will be documented in the communication log in the patient binder.

3.11 Re-Treatment

No patient data collection or follow-up relative to re-treatment will occur after 06/18/2018.

Patients may be retreated with DEB-TACE if clinically indicated prior to the three month endpoint.

Retreatment DEB-TACE procedures will be performed in accordance with the study treatment procedures described above. If patients have residual disease at one month they will be included as 1 month data but will not be evaluated for six month recurrence. They will be assessed only for 1 month response and then will be treated according to standard of care. The 1 month response evaluation will be 1 month counted from the retreatment procedure, not the initial procedure. This excludes only the downstaging population which will be evaluated on successful vs. unsuccessful downstaging to within Milan as a binary finding.

3.12 Removal of Subject from Study

All patients will be treated and followed in accordance with this protocol unless one of the following occurs:

- Technical failure of the DEB-TACE procedure due to:
    - Excessive vasospasm
    - Arterial dissection
    - Arterial thrombosis
- Inter-current illness that prevents further inclusion in this protocol
- Unacceptable adverse event(s)
- Subject decides to withdraw from the study

General or specific changes in the patient's condition render the subject unacceptable for further treatment and/or follow-up in the judgment of the investigator.

4. SCIENTIFIC SOUNDNESS

4.1 Economic Impact on Subjects

The study will not have an economic impact on the subjects.

4.2 Vulnerable Populations

The following vulnerable populations will be excluded from participation in this study.

- Cognitively Impaired Adults / Adults who may be unable to consent
- Individuals who are not yet adults (e.g. infants, children, teenagers)
- Wards of the State (e.g. foster children)
- Pregnant women
- Prisoners

4.3 Justification of Sample Size

The sample size for this study is based on the primary outcome of local recurrence rate (LRR). We conducted a power analysis to assess detectable difference in proportion recurring and the associated power for a Fisher' exact test. The test can be conceptualized by the following two by two table (2x2 plus margins are presented). We will test the null hypothesis of no difference in the proportion of patients with local recurrence by catheter type.

Tumor recurred	Endhole catheter	Precision catheter	Total
Yes	30 expected	?	30 + ?
No	70 expected	?	70 + ?
Total	100	50	150

Based on the existing literature, we expect our historical controls (endhole catheter) to have a local recurrence rate of 30%.[3] The following table presents some possible scenarios for power and sample size. All of these estimates assume a 30% LRR in the control group and a type I error rate of 0.05. We have included sample sizes for the pilot phase of the study in the table below.. The pilot study will also include an interim analysis after treating at least 20 patients with the precision catheter. At this point we will compare the proportions of LRR in the control and comparison groups; although we do not expect statistical differences in LRR between the two groups due to low power, the funder has asked that we provide these data. This interim analysis will be soley used to provide a brief progress report to the funder; these interim data will not be published, nor will they be applied to any stopping rules for the study.

The data generated in this pilot study will be used to estimate power and sample size for a multicenterclinical trial.

Expected LRR: Endhole catheter	Expected LRR: Precision catheter	Detectable difference (absolute difference)	Type I error rate (alpha)	Power (1-beta)	N control group (Endhole catheter)	N comparator group (Precision catheter)
Pilot Phase						
30%	25%	5%	0.05	0.07	100	50

[3] Thirty percent was selected as an anticipated amount to see an improvement in care. This seemed reasonable, given the current efficacy of therapy.

30%	20%	10%	0.05	0.21	100	50
30%	15%	15%	0.05	0.47	100	50
30%	10%	20%	0.05	0.78	100	50
Interim pilot phase analysis						
30%	25%	5%	0.05	0.05	100	20
30%	20%	10%	0.05	0.10	100	20
30%	15%	15%	0.05	0.21	100	20
30%	10%	20%	0.05	0.41	100	20

4.4 Statistical Analysis Plan

All statistical tests use a type I error rate of 0.05. We will calculate descriptive statistics for all variables of interest including means, medians and standard deviations for continuous measures, and frequencies and percents for categorical variables. These calculations will be performed overall and stratified by treatment assignment. We will compare baseline characteristics between the treatment and retrospective groups. We will test for differences using independent samples t-tests (alternatively, Wilcoxon-Mann-Whitney tests if data are skewed) for continuous variables, and Chi-square tests (alternatively Fisher's exact tests if some cells are sparse) for categorical variables.

For the outcome of local recurrence rate (LRR) we will test the null hypothesis of no difference in the proportion of patients with local recurrence by catheter type using a Fisher's exact test.

For the outcome of tumor response measured as the change in enhancing tumor size (pretreatment – post treatment) we will evaluate changes at 1 month and 6 month separately. We will calculate the difference in tumor enhancement size at 1 month and 6 months using enhancement size at initial treatment as the reference group (i.e. we will have two continuous outcomes which can be positive or negative values). The analyses are exactly parallel for 1 month and 6 month outcomes. We will describe the approach for 6 months. We will fit a general linear model with Kenward-Roger denominator degrees of freedom. The outcome will be the first-differenced 6 month tumor enhancement size. We will use a random intercept to account for correlation between lesions within a given patient. The independent variables will include catheter type, age and sex. We will test the null hypothesis of no association between catheter type and change in tumor enhancement size. In the case that this model fails to converge, or in the case that most patients have only one tumor, we will use an alternative approach. In this alternative approach we will sample one lesion per patient and use ordinary least squares regression and include age and sex as covariates with catheter type as the primary predictor of interest. We will test the null hypothesis of no association between change in tumor enhancement size and catheter type. Should this model also fail to converge, we will simplify further and use a paired t-test comparing initial and 6 month tumor enhancement sizes in a sampled data set (i.e. one tumor per patient), or we will use a Wilcoxon-Mann-Whitney test if the sizes are skewed. We will test the null hypothesis of no association between catheter and tumor enhancement size change.

For the outcome of time to progression, we will quantify the number of weeks from treatment until tumor progression. Failures (or events) will be defined as progression of the tumor per CT examination or AFP level and extrahepatic disease by CT examination, or death due to complications related to the tumor. Censored observations will be defined as patients who we did not observe tumor progression, patients who were lost to follow up, or patients who had a

liver transplant before evidence of progression was found. For censored observations the time at risk will be calculated as the time from treatment initiation to the last known clinical encounter (for no progression or lost to follow up), or to liver transplant (for patients who had a liver transplant before evidence of progression was found); this will be measured in weeks. To test for differences in time to tumor progression between the treatment and the retrospective group, we will use Cox proportional hazards regression. Treatment group will be our primary predictor of interest, and we will include age, sex and a variable approximating stage/severity at time of treatment using homogenous groups. We will test the null hypothesis of no association between time to progression and treatment group.

For the outcome of survival time, we will quantify the number of weeks from treatment until death. Failures (or events) will be defined as death related to the tumor. Censored observations will be defined as patients who we did not die during the follow up period, or patients who were lost to follow up. For censored observations the time at risk will be calculated as the time from treatment initiation to the last known clinical encounter; this will be measured in weeks. To test for differences in survival time between the treatment and the control group, we will use Cox proportional hazards regression. Treatment group will be our primary predictor of interest, and we will include age, sex and a variable approximating stage/severity at time of treatment using homogenous groups. We will test the null hypothesis of no association between survival time and treatment group.

4.5 Endpoint Measurement

4.5.1 Tumor Response (mRECIST criteria)

Evaluation of Target Lesions

Complete Response (CR): Disappearance of any intratumoral arterial enhancement in all target lesions

Partial Response (PR): At least 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions.

Stable Disease (SD): Any cases that do not qualify for either PR or PD.

Progressive Disease (PD): An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal

progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

4.5.2 Overall Response (mRECIST criteria)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	IR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	Yes or No	SD
PD	Any	Yes or No	PD
Any	PD	Yes	PD
Any	Any		PD

4.5.3 Milan Criteria

1 tumor ≤ 5 cm

OR

≤ 3 tumors, each ≤ 3 cm

4.5.4 UCSF Criteria

1 tumor ≤ 6.5 cm

OR

≤ 3 tumors with largest diameter ≤ 4.5 cm and total of all tumor diameters ≤ 8 cm

4.5.5 Local Recurrence

Local recurrence will be evaluated in subjects at the six month post procedure follow-up visit. Subjects will continue to be evaluated every three months thereafter by CT/MRI until liver transplantation or death.

4.5.6 Time to Progression

Time to progression will be tracked as a secondary measure based on the standard of care CT/MRI that all subjects will receive every three months as a requirement to remain on the liver transplant waitlist.

4.6 Adverse Event Reporting

A final phone call, as described in Section 3.10, will be the final adverse event data collection step. No adverse event data collection will occur after that phone call for any patient. The phone call will ensure all possible related adverse events have been identified prior to study closure.

At this point, all ongoing adverse events that have been assessed by the PI to be related to the study intervention will be monitored until resolution or until 3 months has passed since the treatment procedure and use of the study device, the Surefire catheter. These include all adverse events labeled as uncertain, possible, or probable in relation to the study device on the adverse event log. Should an adverse event still be ongoing at 3 months post treatment

procedure, the PI will re-assess the adverse event. While it is expected that most ongoing adverse events at 3 months time would no longer be related, the PI will make the final decision on a per patient basis. Should the PI assess the ongoing adverse event to still be related to the study device, the adverse event will be followed until resolution or until deemed unrelated to the study intervention.

Adverse event data entry in the REDCap database will be incomplete but all adverse events will have full documentation and PI assessment in the patient binders. A drafted revision to the REDCap database was underway when the study was closed by the sponsor and this revision had put a halt to data entry of adverse events in the database. No further data entry will occur for the study as of 06/18/2018 per the sponsor. Final adverse event documentation will be kept in patient binders (to include source documentation and PI review and assessment documentation) and a cumulative adverse event log (to include adverse event name, indication for an SAE, grade, and relationship to intervention) for all patients will be filed in the Regulatory binder. An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms.

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) and version number specified in the protocol. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below:

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events (SAEs) are those events which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

A subject who dies or may be hospitalized due to the progression of his/her primary cancer will not be reported as a SAE. A planned hospitalization for a pre-existing condition, or a procedure required by this protocol, without serious deterioration in health, is not considered a SAE. However, any SAEs that are a result of DEB-TACE will be reported as a SAE.

Adverse events are reported to the responsible IRB in accordance with institution requirements and procedures.

4.7 Protocol Deviations

A study deviation is defined as an event where the Investigator or site personnel did not conduct the trial according to the protocol, applicable laws or regulations, or the Investigator Agreement. Regulations require that Investigators maintain accurate, complete and current records, including documentation of any deviations from the investigational plan including the date of and reason for the deviation.

Investigators are required to obtain prior approval from the IRB before initiating changes in or deviations from the protocol except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval will be documented in writing and maintained in the study files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control (e.g. subject did not return for scheduled visits, lost laboratory samples) however, the event is still considered a deviation. Deviations will be reported to the IRB following the IRB guidelines.

4.8 Data Safety Monitoring Committee

The sponsor investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all clinical studies at the CU Cancer Center, which is the coordinating institution of this trial. A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all unanticipated adverse device effects, serious adverse events (SAEs), unanticipated problems (UAPs) and reportable adverse events (AEs)
- Has the authority to close and/or suspend trials for safety or trial conduct issues
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs, UAPs and reportable AEs are reported to the DSMC, IRB and the sponsor investigator per protocol. All SAEs, UAPs and reportable AEs including unanticipated adverse device effects are to be reported to the DSMC within 5 business days of the sponsor investigator receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the site PI and appropriate staff at regularly scheduled meetings. Data regarding number of subjects, adverse device effects, treatment modifications and treatment responses will be discussed and documented in the meeting's minutes.

The sponsor investigator will provide a DSM report to the CU Cancer Center DSMC on a six month basis. The DSM report will include a protocol summary; current enrollment numbers; summary of adverse device effects to include specific unanticipated adverse device effects, SAEs, UAPs and AEs; any treatment modifications; all protocol deviations; and protocol amendments. The DSM report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this six month report by the DSMC will then be provided to the sponsor investigator in a DSMC review letter. The sponsor investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review.

5. STUDY MANAGEMENT

5.1 Institutional Review Board (IRB) Approval

This protocol and associated informed consent form and data collection forms will be reviewed and approved by the responsible institutional review board prior to initiating patient enrollment.

5.2 Informed Consent

All participating patients will sign the approved informed consent form prior to initiating treatment under this protocol.

5.3 Data Collection / Case Report Form

All study data will be collected on a standardized paper or electronic case report form (CRF).

5.4 Data Monitoring

A final monitoring visit will be conducted after all related adverse events have resolved. Monitoring will be limited to ensuring proper study closeout documentation is included and all adverse events have been followed until resolution per this protocol. As necessary, requests for clarification or correction will be sent to the investigator. Risk-based monitoring will be conducted throughout the course of this study.

Independent auditors from the sponsor investigator's authorized representative will be allowed by the site investigator to audit previously monitored data. In addition, audits may be conducted at any time by appropriate regulatory authorities and/or IRB.

5.5 Data Management and Confidentiality

The sponsor investigator will ensure that the confidentiality of subjects' identification is maintained and medical records are protected. A unique subject identification (ID) will be assigned by the data collection system for each subject enrolled in the clinical study. Subject records may be reviewed by independent monitors and auditors to verify the quality of the reported data; however, confidentiality will be maintained.

5.6 Records Retention

Study documentation includes all Case Report Forms, source documents, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and/or institutional policy require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. Study documents should be kept on file until three years after the completion and issuance of the final study report and/or publication of this clinical study.

5.7 Investigator Obligations

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-

investigators and other study staff members, adhere to the study protocol and all regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator is responsible for assuring that all the required data will be collected and entered onto the Case Report Forms.

Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data.

At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

5.8 Protocol Adherence and Amendments

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB.

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Appendices

6.1 FDA 510(k) Clearance Letter – Surefire Precision Infusion System

6.2 Instructions for Use – Surefire Precision Infusion System

6.3 Informed Consent Form

6.4 Case Report Form

6.5 Closeout letter to enrolled patients

6.6 Phone call script for enrolled patients