Prospective, Randomized Study of Coil Embolization versus Surefire Infusion System during Yttrium-90 Radioembolization with Resin Microspheres

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ABSTRACT

Purpose: To compare standard coil embolization versus the use of an antireflux microcatheter (ARM) in patients undergoing planning angiography before selective internal radiation therapy (SIRT).

Materials and Methods: A prospective, single-center trial was performed in which 30 patients were randomly assigned to undergo SIRT with coil embolization or the use of an ARM. The coil group underwent detachable coil embolization of nontarget vessels, and the ARM group underwent infusion of macroaggregated albumin with use of an ARM system, without coil embolization. Single-photon emission computed tomography (CT)/CT was then performed to assess for nontarget distribution. The primary endpoint was fluoroscopy time during planning angiography. Secondary endpoints included deployment time, total procedure time, radiation dose–area product, contrast agent used, and adverse events. Endpoints were evaluated during planning angiography and SIRT.

Results: Over a 9-month period, 30 consecutive patients were randomized at a 1:1 ratio between coil embolization and ARM groups. Technical success rates were 100% in both groups. Mean fluoroscopy time was significantly reduced in the ARM group versus the coil embolization group (1.8 min [range, 0.4–4.9 min] vs 6.0 min [range, 1.9–15.7 min]; P = .002). The planning procedure time (P < .001), deployment time (P < .001), dose–area product (P = .04), and amount of contrast agent used (P < .001) were also significantly less in the ARM group than in the coil embolization group. No nontarget distribution was detected in either group. There was no difference between groups in dose delivered on the day of SIRT (P = .71). There were no major or minor adverse events at 30 days.

Conclusions: The use of an ARM during planning angiography can significantly reduce fluoroscopy time, procedure time, and radiation dose.

ABBREVIATIONS

ARM = antireflux microcatheter, GDA = gastroduodenal artery, MAA = macroaggregated albumin, SIRT = selective internal radiation therapy, SPECT = single-photon emission computed tomography

In patients with advanced primary liver cancer or liver-predominant metastatic disease, selective internal radiation therapy (SIRT) has been shown to control tumor growth and prolong survival (1–4). Currently, a planning angiogram is routinely obtained before SIRT to prevent nontarget distribution to extrahepatic organs and ensure...
that there is not excessive lung shunting. Although there is currently no standard of care to prevent nontargeted delivery, patients can be pretreated by the permanent placement of embolic coils to prophylactically embolize nontargeted vessels such as the gastroduodenal artery (GDA) and the right gastric artery. However, coil embolization of these vessels increases fluoroscopy and procedural time and is not without risk, as coil migration and arterial dissection may occur. The Surefire Infusion Catheter System (Surefire Medical, Westminster, Colorado) is a new antireflux microcatheter (ARM) with an expandable tip fused to the distal end of an infusion microcatheter that has been recently introduced for the infusion of therapeutic agents. When the ARM is placed in the vessel, with the tip expanded, antegrade blood flow is allowed around the tip while retrograde flow is prevented (5,6). Therefore, our underlying hypotheses was that the use of an ARM may decrease fluoroscopy time, procedure time, procedural radiation dose, and contrast agent volume. To test these hypotheses, we performed a randomized prospective trial comparing coil embolization versus the use of the ARM, with fluoroscopy time as the primary endpoint.

**MATERIALS AND METHODS**

**Patients**

All data were handled in accordance with the Health Insurance Portability and Accountability Act. A local institutional review board approved the study. Study data were deidentified and stored on the primary investigator’s computer with password protection and digital encryption. Funding for this study was provided by Surefire Medical in the form of a restricted research grant. This study is a prospective, randomized, nonblinded trial performed at a single academic tertiary referral center. Planning angiography and SIRT were performed as ambulatory procedures by fellowship-trained interventional radiologists with Certificates of Added Qualification in interventional radiology. Patients who were to undergo planning angiography before SIRT with SIR-Spheres (Sirtex, North Sydney, Australia) were randomized at a 1:1 ratio into two groups. A random number table was created by the research coordinator for randomization. Sealed envelopes were pulled from a pool after consent for study participation was obtained.

Between March 2013 and September 2013, 30 patients who met anatomic requirements for the study were randomized, 15 to undergo coil embolization and 15 to undergo treatment with the ARM. All received the randomized intervention. Demographic information is provided in Table 1. Patients in the coil embolization and ARM groups were not significantly different in regard to age, sex, type of hepatic malignancy, or lobe treated. No patient in either group had received treatment with bevacizumab or sorafenib before mapping angiography or SIRT. The most commonly treated cancer was hepatocellular carcinoma (n = 16), followed by colorectal cancer liver metastases (n = 6). During the study period, all patients to be treated with SIRT were screened for study eligibility. During the study period, approximately 100 patients were treated with SIRT.

The coil embolization group underwent standard coil embolization of nontarget vessels, macroaggregated albumin (MAA) infusion, and SIRT with the use of a standard microcatheter system. The ARM group underwent MAA infusion and SIRT with use of an ARM, without coil embolization. The ARM used in this study was the Surefire Infusion Catheter System (internal diameter, 0.027 inch; vessel size range, 2–6 mm; Surefire Medical). Informed consent for the procedure and study participation was obtained in all patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Coil Embolization (n = 15)</th>
<th>ARM (n = 15)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>64.7 ± 10.0</td>
<td>62.8 ± 10.7</td>
<td>.60</td>
</tr>
<tr>
<td>Male sex</td>
<td>9 (60)</td>
<td>11 (73)</td>
<td>.70</td>
</tr>
<tr>
<td>Tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td>7 (47)</td>
<td>9 (60)</td>
<td>.72</td>
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<tr>
<td>CRC</td>
<td>2 (13)</td>
<td>4 (27)</td>
<td>.65</td>
</tr>
<tr>
<td>NET</td>
<td>4 (27)</td>
<td>1 (7)</td>
<td>.33</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>1 (7)</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Gastric</td>
<td>1 (7)</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Appendiceal</td>
<td>0</td>
<td>1 (7)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hepatic lobe treated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>11 (73)</td>
<td>12 (80)</td>
<td>1.00</td>
</tr>
<tr>
<td>Left</td>
<td>3 (20)</td>
<td>3 (20)</td>
<td>1.00</td>
</tr>
<tr>
<td>Whole liver</td>
<td>1 (7)</td>
<td>0</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Values presented as means ± standard deviation where applicable. Values in parentheses are percentages. ARM = antireflux microcatheter, CRC = colorectal cancer, HCC = hepatocellular carcinoma, NET = neuroendocrine tumor.
Inclusion and Exclusion Criteria
Patients were considered candidates for the study if they had primary hepatocellular carcinoma or metastatic liver disease and were selected for SIRT at a multidisciplinary tumor board. Anatomic criteria included target tissue distal to the GDA and a GDA suitable for coil embolization based on review of computed tomography (CT) or magnetic resonance (MR) imaging (ie, diameter and specific location of the GDA). There was no age restriction. Patients were not considered for the study if the target tissue was not distal to the GDA, such as replaced right or left hepatic arteries, as determined by preprocedure CT or MR imaging.

Procedure
All procedures were performed under conscious sedation; intravenous fentanyl and midazolam were administered during continuous cardiovascular monitoring by independent interventional radiology nursing staff. All procedures were performed with right femoral artery access through a 5-F vascular sheath by one of two operators, each with experience performing more than 200 SIRT procedures. No changes to methods were made after trial commencement.

Planning Angiogram with Coil Embolization
Diagnostic angiography of the superior mesenteric artery and celiac artery was performed by using a 5-F SOS 1 diagnostic catheter (AngioDynamics, Latham, New York). Subsequently, a Renegade STC microcatheter (Boston Scientific, Natick, Massachusetts) was used to perform diagnostic angiography of the common hepatic, right hepatic, and left hepatic arteries. Detailed bilateral angiograms were obtained in each case regardless of the tumor location to identify potential collateral vessels and/or tumor vessel supply from the contralateral lobe (ie, segment IV). Coil embolization of nontarget vessels was then performed in a standard fashion with Interlock 0.018-inch detachable coils (Boston Scientific). The microcatheter was then advanced into the hepatic vessel supplying the tumor(s), and a standard dose of 5 mCi of technetium-99m (\(^{99m}\text{Tc}\)) MAA was infused. Images from a planning angiogram performed with coil embolization are provided in Figure 1.

Planning Angiogram with ARM
A 5-F Axis guiding catheter with an 0.054-inch inner lumen (Surefire Medical) was used to perform diagnostic angiography of the superior mesenteric artery and celiac artery. Subsequently, the ARM was used to perform diagnostic angiography in the common hepatic artery and the right or left hepatic arteries. In this group, coil embolization of nontarget vessels was not performed. The ARM was then advanced into the hepatic vessel supplying the tumor(s). Before deployment of the tip, 200 \(\mu\)g nitroglycerin and 2.5 mg verapamil were administered intraarterially through the ARM to prevent spasm. Although this is not recommended by the manufacturer, this is standard procedure at the authors’ institution with the use of this device. After deployment of the ARM tip, a standard dose of 5 mCi \(^{99m}\text{Tc}\) MAA was infused into the target artery. Images from a planning angiogram obtained with the ARM are provided in Figure 2.

All patients were then transferred to the nuclear medicine unit for single-photon emission CT (SPECT)/

Figure 1. Planning angiography performed with coil embolization. (a) Celiac artery angiogram in a 65-year-old man with HCC demonstrates a patent GDA (arrow) originating from the common hepatic artery. (b) Right hepatic artery angiography performed at the location of MAA administration demonstrates tumor blush supplied by the right hepatic artery and the coil-embolized GDA (arrow).
Patients were not candidates for SIRT if there was nontarget distribution to the bowel or hepatopulmonary shunt ratio greater than 20%. All patients were discharged home the same day of the procedure.

**SIRT with Coil Embolization**

In the coil embolization group, hepatic angiography was performed before SIRT. The standard microcatheter was advanced to the position of MAA administration, and the SIRT dose was then administered as prescribed to the target tissue.

**SIRT with ARM**

In the ARM group, hepatic angiography was performed before SIRT. The ARM was advanced to the position of MAA administration and deployed. The same medication regimen was used as described earlier to prevent spasm. The SIRT dose was then administered through the ARM as prescribed to the target tissue.

The patient was then transferred to the nuclear medicine unit for Bremsstrahlung imaging to ensure extrahepatic activity was not present (7). All patients were discharged home the same day with oral analgesic and antiemetic agents to be taken as needed. Patients were also prescribed a 7-day course of levofloxacin 500 mg/d.

**Study Endpoints**

The primary endpoint was the fluoroscopy time during planning angiography as measured from the insertion of the microcatheter or ARM (after completion of diagnostic angiography) until confirmation of position for safe infusion. Secondary endpoints during planning angiography were (i) deployment time (defined as total time from insertion of the microcatheter or ARM to confirmation of position for safe infusion), (ii) total procedure radiation dose (ie, dose–area product and air kerma), (iii) total contrast agent dose, (iv) contrast agent dose administered from the time of insertion of the microcatheter or ARM to confirmation of position for safe infusion, (v) procedure time (defined as time from access sheath placement to delivery catheter removal), and (vi) complications related to embolization. Potential complications included vasospasm, coil migration, arterial dissection, arterial thrombosis, and technical
failures. Technical failure is defined as the inability to catheterize and administer MAA or SIRT at the desired vessel. Secondary endpoints during the SIRT procedure included (i) intended infusion dose, (ii) delivered infusion dose, (iii) procedure time, (iv) contrast agent dose, (v) infusion fluoroscopy time, (vi) total infusion time, and (vii) recanalization rate of coil-embolized arteries.

Sample Size Calculation
Based on publications by Bester et al (1) and Gates et al (3), the historical fluoroscopy time for planning angiography is 3.3 minutes ± 1.5. Assuming a 1.4-minute (40%) reduction in fluoroscopy time with the use of an ARM, it was determined that a total of 30 patients randomized at a 1:1 ratio would be needed to allow the detection of a statistically significant difference with a power of 80%. Power calculations were performed and validated by an independent statistician.

Statistical Analysis
Continuous data are presented as means with standard deviations. Categoric data are presented as counts and percentages. Statistical analysis was performed at a descriptive level with SPSS suite (version 21.0; IBM, Armonk, New York). The unpaired t test was used for continuous data, and the Fisher exact test was used for categoric data. An α-value less than 0.05 was considered statistically significant. All statistical data analysis was performed and validated by an independent statistician.

RESULTS
The technical success rate of mapping angiography was 100% in both groups. Two patients, one in each treatment group, did not undergo SIRT because of a hepatopulmonary shunt ratio greater than 20%. One patient with HCC in the coil embolization group died before SIRT as a result of rapid disease progression, unrelated to planning angiography. SIRT was performed between 9 and 57 days after mapping angiography (median, 21 d) for the entire cohort.

Coil embolization of nontarget vessels during planning angiography was successful in all patients in the coil embolization group, with a mean number of 3.4 coils ± 1.5 (standard deviation) deployed during coil embolization. The 6-mm × 20-mm Interlock coil was the most common coil used during coil embolization. Overall, 51 coils were placed (6 × 20 mm, n = 34; 5 × 15 mm, n = 6; 5 × 15 mm, n = 3; 4 × 15 mm, n = 3; 8 × 20 mm, n = 1; 3 × 8 mm, n = 1; 3 × 6 mm, n = 1). The GDA was coil-embolized in all 15 patients in the coil embolization, with nine patients having only the GDA embolized. Five patients had two nontarget vessels embolized, and one had three nontarget vessels embolized. The numbers and vessels embolized in the coil embolization group are provided in Table 2.

There was a significant reduction in the primary endpoint, planning angiogram fluoroscopy time, with ARM compared with coil embolization (mean, 1.8 min [range, 0.4–4.9 min] vs 6.0 min [range, 1.9–15.7 min]; \( P = .002 \)). A reduction in radiation dose was also observed, as measured by dose-area product (mean, 189 Gy·cm² ± 98 [range, 41–355 Gy·cm²] vs 346 Gy·cm² ± 241 [range, 84–877 Gy·cm²]; \( P = .04 \)) and air kerma (mean, 671 J/kg ± 353 [range, 108–1149 J/kg] vs 1,469 J/kg ± 1,042 [range, 626–3,638 J/kg]; \( P = .01 \)).

The amount of contrast agent administered during planning angiography was also significantly lower when an ARM was used. For the total procedure, a mean of 93 mL of contrast agent (range, 62–142 mL) was administered in the coil embolization group, compared with 56 mL (range, 31–89 mL) in the ARM group (\( P < .001 \)). The contrast agent administered during the deployment phase of planning angiography was also significantly reduced when an ARM was used (23 mL [range, 15–36 mL] vs 9.6 mL [range, 6–22 mL]; \( P < .001 \)). The full results of primary and secondary endpoints from planning angiography are provided in Table 3. All patients went on to undergo SPECT/CT immediately after mapping angiography and MAA infusion, and no distribution of radiotracer to the stomach or bowel was seen in any patient.

During SIRT, the intended and administered treatment dose was not significantly different when coil embolization or an ARM was used. The intended dose with coil embolization was 1.18 GBq (range, 0.62–1.73 GBq), compared with 1.22 GBq (range, 0.43–1.79 GBq) with an ARM (\( P = .79 \)). The administered doses for coil embolization and ARM groups were 1.15 GBq (range, 1.62–1.49 GBq) and 1.20 (range, 0.43–1.77 GBq), respectively (\( P = .71 \)). This resulted in mean administered-to-intended dose ratios of 0.97 with coil embolization and 0.98 with ARM. Mean contrast agent dose administered (coil embolization, 62 mL ± 18; range, 12–36 mL; ARM, 49 mL ± 8; range, 6–22 mL; \( P = .03 \)) was the only parameter decreased with the use of an ARM during SIRT.

No other parameter showed a significant difference during SIRT. Full results are provided in Table 4. At SIRT, no instances of coil-embolized vessel recanalization were observed. No new nontarget or intrahepatic collateral vessels were observed at the time of SIRT in patients who had undergone coil embolization.

Table 2. Vessels Embolized with Coils

<table>
<thead>
<tr>
<th>Vessel Embolized</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroduodenal</td>
<td>15</td>
</tr>
<tr>
<td>Right gastric</td>
<td>5</td>
</tr>
<tr>
<td>Cystic</td>
<td>1</td>
</tr>
<tr>
<td>Accessory phrenic</td>
<td>1</td>
</tr>
</tbody>
</table>
No major or minor complications were observed in either group. Of particular interest, there were no instances of arterial vasospasm, arterial dissection, arterial thrombosis, or coil migration in either group.

**DISCUSSION**

The primary finding in the present study demonstrates that the use of an ARM can significantly reduce fluoroscopy time, procedure time, contrast agent dose, and radiation dose without coil embolization of non-target vessels. The use of an ARM was safe, with no arterial-related complications observed in the study population. Finally, as shown by SPECT/CT, the use of an ARM successfully prevented reflux in patients who did not undergo coil embolization of nontarget vessels.

Investigators have described the use of various permanent occlusive devices such as coils, plugs, and liquid embolic agents to occlude the extrahepatic network before SIRT; often, this requires extensive detailed catheterization of very small vessels resulting in extra fluoroscopy time and radiation dose (8–11). In patients with aberrant anatomy, such as a gastrohepatic trunk, placement of embolic coils in all extrahepatic vasculature may not be feasible. In these cases, the only solution has been to advance the microcatheter distal to these vessels, risking incomplete treatment of proximal branches supplying the tumor(s) (12,13).

Currently, the most widespread technique used to occlude the extrahepatic vasculature is coil embolization. However, coil embolization can be technically challenging. Rarely, coil dislodgment into the intrahepatic vasculature can occur (14–16). In addition, embolic coils may not provide a consistent, durable occlusion, as nearly 35% of patients may require additional adjunctive embolization or revision immediately before SIRT (8,9). Uncertain durability introduces an additional time constraint...
on SIRT therapy because a delay in scheduling may favor the development of new collateral vessels (8,9,17). More recently, the use of liquid glue has been described as another alternative to eliminate collateral vessels, but this is technically more demanding than coil deployment and potentially also has a high risk of treatment-limiting reflux into the hepatic circulation (11).

With coil embolization, various reports have described their impact on fluoroscopic time and radiation. Dudeck et al (15) compared standard pushable coils versus detachable coils in a randomized prospective trial. In this study (15), use of detachable coils resulted in reduction of fluoroscopic time from 5 hours 23 minutes to 1 minute 50 seconds and also a reduction in radiation dose; however, this study evaluated coil embolization of the GDA only. In a similar manner, in the GDA alone, the AMPLATZER plug (St. Jude Medical, St. Paul, Minnesota) was shown to be associated with a significant decrease in fluoroscopy time and radiation compared with platinum coils (14).

In the present report, we describe the use of an ARM system as the sole mechanism to eliminate reflux during SIRT. Compared with a standard end-hole catheter, the expandable tip of the Surefire Infusion System partially collapses during forward blood flow of cardiac systole, allowing antegrade delivery of the agent, and fully expands if the infusion pressure (ie, pressure at the tip of the microcatheter) is greater than the blood pressure in the vessel to prevent reversal of blood flow and retrograde reflux of agents. Therefore, compared with a balloon occlusion catheter or a standard end-hole catheter, the system described here functions more as a vascular valve in that it can simultaneously maintain antegrade flow and eliminate reflux. In animal and clinical studies to date (6), the hemodynamic effects of this infusion system have been established.

Based on the present study, the use of an ARM provided several unique advantages versus standard embolic coils. First, use of an ARM resulted in significant reduction in fluoroscopy time, procedural time, radiation dose, and contrast agent volume. Planning fluoroscopy time was reduced from 6.0 minutes to 1.8 minutes ($P = .002$) in the ARM group. The mean total procedure time was also decreased, from 30 minutes to 16 minutes. Therefore, use of an ARM resulted in comparable time reductions as described by Dudeck et al (15) and Pech et al (16). Second, unlike glue and coil embolization, use of the ARM system did not require extensive catheterization of microvessels, thereby providing a reduction in procedural time that impacts workflow and room use. Therefore, we were able to achieve these reductions in procedural and fluoroscopic time without placing permanent occlusive agents. In addition, the use of an ARM did not decrease the ability to deliver the intended treatment dose.

However, the use of an ARM has inherent limitations. First, there is a cost difference between an ARM and coils. Although the direct purchase cost is higher for an ARM, no coils are used for collateral vessel embolization. However, a cost analysis of coil embolization versus ARM is beyond the scope of the present study. From a cost standpoint, the decision for coil embolization or ARM is likely best left to the performing institution, with its variable device costs and inventory requirements. Second, use of the ARM necessitates a learning curve to use the system and therefore requires experience before using the device in complex vascular anatomies. An example of a markedly tortuous hepatic artery is provided in Figure 3. Finally, a minimum vascular diameter of 2 mm is necessary for the use of an ARM during embolization procedures.

There are limitations to the present study. Only two operators performed the procedures, somewhat limiting the generalizability of our findings. As mentioned, the use of any new device, an ARM included, comes with a learning curve. The operators in the present study have significant experience performing SIRT, and, as a result, may have gained comfort with the ARM quicker than a less experienced operator would have. This was not assessed during the present trial, so a definitive statement to this point cannot be made. The most significant limitation of the present study is the inability to blind the operator to treatment group, which can introduce bias. The coil length used has the possibility to affect procedure time. In the present study, the most common coil size was a 6-mm × 20-mm coil, with most patients requiring multiple coils. It is reasonable to assume that, if longer coils were used, fewer coils would be needed, reducing fluoroscopy time. However, the use of longer coils was balanced against the need for precise placement of the coils and not the need to ensure that coils would not extend proximally into the proper hepatic artery. Perhaps the most significant limitation of the present study is the clinical relevance of a 4.2-minute reduction
in fluoroscopy time in patients with nonresectable liver cancer. It is extremely unlikely that the control group in the present trial will ever experience ill effects of their increased radiation exposure during their SIRT procedure given their limited life expectancy. However, the authors believe the goal of reducing fluoroscopy time while preserving the ability to achieve technical success is universal. In addition, these results may inspire research into the use of an ARM in patient populations in which limiting fluoroscopy time is more of a concern, e.g., patients presenting for uterine artery embolization.

Finally, the practice of coil embolization of the GDA before radioembolization has been called into question over the past several years. A study by Hamoui et al (18) revealed that GDA embolization before radioembolization with glass microspheres is unnecessary. It is the authors’ belief that the use of this practice before radioembolization with glass microspheres may be decreasing at larger-volume centers. However, resin microspheres are considerably more embolic, and the authors believe the practice of coil embolization is still needed with this procedure, particularly in lower-volume institutions with less experience with these devices. At our center, during the past 5 years, the incidence of gastrointestinal ulcers is considerably low, at less than 1%, which may be lower than what is seen at lower-volume centers. It is the opinion of the authors that, even though the use of the ARM should reduce this rate and reduce radiation exposure by standardizing the delivery method, it would be hard to estimate the rate of ulcer reduction because there is significant variability among institutions. In addition, the present study was not powered to detect such a difference.

In the present randomized prospective study, we have shown that the use of an ARM can significantly reduce fluoroscopy time and radiation dose during planning angiography before SIRT and can safely avoid non-target deposition.

REFERENCES