Transarterial embolization of renal cell carcinoma as an adjunctive therapy prior to cryoablation: a propensity score matching analysis

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PURPOSE
We aimed to assess the safety and effectiveness of transarterial embolization (TAE) prior to percutaneous cryoablation (PCA) in the management of renal cell carcinoma (RCC) compared with PCA alone using a propensity score matching analysis to minimize confounding factors.

METHODS
A retrospective review of all PCAs performed for renal masses identified 9 patients who underwent TAE prior to PCA. These patients were matched in a 2:1 ratio with patients who underwent PCA only using age, gender, and tumor size to create the propensity score model for matching. Other demographic, clinical, and outcomes data were collected.

RESULTS
The TAE+PCA group included 5 males and 4 females with a mean age of 67.9 years and mean tumor diameter of 51.7 mm. The PCA only group included 11 males and 7 females with a mean age of 66.8 years and mean tumor diameter of 46.2 mm. No significant differences in these propensity score matched characteristics were identified. Further, the groups had no significant differences in tumor geometry ($P = 0.831$), R.E.N.A.L. nephrometry scores ($P = 0.144$), or comorbidity indices ($P = 0.392$). TAE was technically successful and without complication in all cases. PCA was technically successful in 8 of 9 patients in the TAE+PCA group and in 14 of 18 patients in the PCA only group ($P = 0.483$). No significant differences in the rate of complications ($P = 0.483$), change in eGFR ($P = 0.691$), or change in hematocrit ($P = 0.152$) were identified between the two groups.

CONCLUSION
TAE of RCC prior to PCA is safe and technically feasible; however, no objective benefits over PCA alone were identified by propensity score matching analysis. Due to small sample size and limitations of the study, no definite conclusions should be drawn. Larger, prospective studies of this therapeutic approach are warranted.

There will be an estimated 64,000 new cases of renal cell carcinoma (RCC) diagnosed in 2017, accounting for approximately 4% of all new cancer diagnoses in the United States (1). Classically, some patients will present with flank pain, gross hematuria, or a palpable flank mass, while others may present late with symptoms secondary to local tumor progression or distant metastases (2). Yet, an increasing number of patients are being diagnosed with asymptomatic, incidentally found RCC due to both increased utilization of cross-sectional imaging and improved imaging techniques (3–7). These incidentally discovered RCCs are typically smaller, of lower grade, and are associated with longer patient survival than symptomatic masses (8). Traditionally, standard therapeutic options for patients with RCC included either radical or partial nephrectomy (2). However, given the increasing number of smaller RCCs, minimally invasive and nephron-sparing approaches such as laparoscopic ablation and percutaneous ablation have been successfully employed as alternatives to surgery (8–14). Percutaneous ablation is an attractive treatment option for patients who are not optimal surgical candidates or who may wish to avoid traditional surgery that has similar outcomes to partial nephrectomy in T1a RCC (15).

Although RCC includes a variety of histologic subtypes, the most common subtype, clear cell RCC, is characterized as a hypervascular tumor on contrast-enhanced imaging (16).
The vascularity of RCC tumors may provide practitioners with an opportunity to deliver adjunctive therapies either prior to or in combination with percutaneous ablation via a transarterial route. For example, transarterial embolization (TAE) prior to percutaneous ablation has already been shown to improve oncologic outcomes in hepatocellular carcinoma (HCC), which is another highly vascular tumor (17). Apart from potential oncologic benefits, it has been theorized that TAE of RCC prior to percutaneous ablation may also reduce the risk of bleeding (18). Furthermore, if TAE is undertaken with ethiodized oil as the contrast agent, tumor localization and lesion coverage during computed tomography (CT)-guided percutaneous ablation may also be enhanced (19). Indeed, prior investigations have found that the combination of TAE followed by percutaneous ablation is safe and technically feasible (18–25). Nevertheless, prior reports are limited by their descriptive design (case reports and case series). Therefore, the purpose of this study is to compare the technical and clinical outcomes of patients whose renal masses were treated with combined TAE and percutaneous cryoablation (PCA) to those treated with PCA alone using a propensity score matching analysis.

Methods
Patients, data collection, and propensity score matching model
This study was approved by our Institutional Review Board and was compliant with the Health Insurance Portability and Accountability Act. Given its retrospective nature, informed consent from patients was not required. A review of our radiology information system identified nine patients who underwent combined TAE plus PCA for a renal mass between January 1, 2008 and December 31, 2016 as well as 167 additional patients treated with thermal ablation. The vascularity of RCC tumors may provide practitioners with an opportunity to deliver adjunctive therapies either prior to or in combination with percutaneous ablation via a transarterial route. For example, transarterial embolization (TAE) prior to percutaneous ablation has already been shown to improve oncologic outcomes in hepatocellular carcinoma (HCC), which is another highly vascular tumor (17). Apart from potential oncologic benefits, it has been theorized that TAE of RCC prior to percutaneous ablation may also reduce the risk of bleeding (18). Furthermore, if TAE is undertaken with ethiodized oil as the contrast agent, tumor localization and lesion coverage during computed tomography (CT)-guided percutaneous ablation may also be enhanced (19). Indeed, prior investigations have found that the combination of TAE followed by percutaneous ablation is safe and technically feasible (18–25). Nevertheless, prior reports are limited by their descriptive design (case reports and case series). Therefore, the purpose of this study is to compare the technical and clinical outcomes of patients whose renal masses were treated with combined TAE and percutaneous cryoablation (PCA) to those treated with PCA alone using a propensity score matching analysis.

Main points
- Transarterial embolization (TAE) prior to percutaneous cryoablation for renal cell carcinoma (RCC) is technically feasible.
- TAE prior to percutaneous cryoablation for RCC did not result in any adverse outcomes or increased complications.
- TAE prior to percutaneous cryoablation for RCC did not provide improved technical success or clinical outcomes.

Figure 1. a–d. A 55-year-old male with a 2.8 cm mass in the upper pole of the left kidney. Digital subtraction angiography (DSA) image (a) with the diagnostic catheter in the left renal artery (white arrow) identifies subtle vascular irregularity in the upper pole (black arrows). DSA image (b) with the microcatheter in the renal arterial branch feeding the tumor (black arrow). Postembolization DSA image (c) demonstrates no residual vascularity in the tumor (white arrows). Embolization was performed with ethanol mixed with contrast followed by particles mixed with contrast. Unsubtracted postembolization DSA image (d) demonstrates the embolized mass in the upper pole (black arrow).
Transarterial embolization of the renal mass

A board-certified interventional radiology physician performed all TAE. Blood thinning-medications were appropriately held (28). The vascular access site (the right common femoral artery in all cases) was prepared and draped in standard sterile fashion. Vascular access was obtained under sonographic guidance using a micropuncture set (Angiodynamics), as is standard at our institution. A 6 F vascular sheath (Terumo) was then placed over a 0.035-inch wire that comes with the set to secure arterial access. After accessing the appropriate renal artery with a 5 F diagnostic catheter (Cobra 2 or Sos Omni® 2, Angiodynamics) angiography was performed to identify the tumor and its supplying vessels (Fig. 1). The artery or arteries supplying the tumor were selected using a microcatheter and microwire combination (2.8F Progreat®, Terumo). Once appropriate positioning had been confirmed, embolization was performed under fluoroscopy to prevent reflux into nontarget vessels. Technical success for TAE was defined as the embolization of all feeding arteries to stasis without further tumor blush on postembolization angiography. Complications were classified according to criteria from the SIR (29). Measures of oncologic outcomes such as need for repeat ablation, recurrence, and patient survival were also recorded.

Statistical analysis

Patient and procedural parameters were compared across the two propensity score matched patient cohorts (TAE+PCA vs. PCA only). Categorical statistics were compared using chi-square probability testing with Fischer exact modification when warranted by frequency observed. For continuous variables, a normal distribution is expected in the patient population from which these cases were derived and are thus reported as mean±standard deviation (SD). Continuous variables were compared using Student’s t-test. A predetermined P value of 0.05 was considered the threshold for statistical significance.

Results

Patient characteristics are summarized in Table 1. Patients were well-matched across the two propensity score matched patient cohorts (TAE+PCA vs. PCA only). Categorical statistics were compared using chi-square probability testing with Fisher’s exact test. A predetermined P value of 0.05 was considered the threshold for statistical significance. Further details are recorded in Table 2. Biopsy, when performed, was done at the time of ablation. Pathology was available for 8 of 9 patients (89%) in the TAE+PCA group and demonstrated clear evidence of destruction of the ablated area. Complications were classified according to criteria from the SIR (29). Measures of oncologic outcomes such as need for repeat ablation, recurrence, and patient survival were also recorded.
cell RCC (n=5), oncocytoma vs. oncocytic chromophobe hybrid RCC (n=1), necrotic tissue (n=1), and normal renal parenchyma not felt to represent the lesion in question (n=1). Pathology was available for 10 of 18 patients (56%) in the PCA only group and demonstrated clear cell RCC (n=6), papillary RCC (n=3), and normal renal parenchyma not felt to represent the lesion in question (n=1). No instances of the embolic material interfering with the pathologic analysis were recorded.

All TAE was done as an outpatient procedure except for one patient who was already hospitalized due to ongoing symptomatic hematuria. Conscious sedation was provided using a combination of fentanyl and midazolam in eight patients, while general anesthesia was used in one patient at that patient’s request. The choice of embolic material was operator-dependent but included particles mixed with contrast (n=4), particles mixed with ethiodized oil (n=2), particles mixed with contrast followed by microcoils (n=1), ethanol mixed with contrast followed by particles mixed with contrast (n=1), and microcoils alone (n=1). The ratios of mixed embolic agents (i.e., particles mixed with ethiodized oil) were not available in the medical record. However, particle size ranged from 250–900 µm. TAE was technically successful in all patients.

No major or minor complications were encountered.

PCA was performed at a mean of 10.8±6.4 days (range, 1–20 days) in the nine patients in the TAE+PCA group. After ablation, six patients were admitted for overnight monitoring, two patients were discharged the same day, and one patient had the procedure as an in-patient for symptomatic hematuria from the renal mass. In the PCA alone group, nine patients were admitted for overnight observation and nine patients were discharged home the same day. Per review of the notes, the decision to observe patients overnight was made due to either the size of the lesion ablated, patient preference, or treating physician preference. Conscious sedation using a combination of fentanyl and midazolam was used in eight patients (89%) in the TAE+PCA group with one patient requesting general anesthesia. Conscious sedation was used in 17 of 18 patients in the PCA group (94%), with one patient receiving general anesthesia due to treating physician preference. A mean of 3.0±1.3 probes were used to ablate the lesions in the TAE+PCA group compared

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TAE+PCA</th>
<th>PCA only</th>
<th>P</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>67.9±12.5</td>
<td>66.8±11.4</td>
<td>0.831</td>
</tr>
<tr>
<td>Sex (M/F), n (%)</td>
<td>5 (56)/4 (44)</td>
<td>11 (61)/7 (39)</td>
<td>0.783</td>
</tr>
<tr>
<td>Tumor diameter (mm)</td>
<td>51.7±17.9</td>
<td>46.2±7.0</td>
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</tr>
<tr>
<td>Tumor geometry, n (%)</td>
<td></td>
<td></td>
<td>0.831</td>
</tr>
<tr>
<td>Exophytic</td>
<td>4 (44)</td>
<td>6 (33)</td>
<td></td>
</tr>
<tr>
<td>Endophytic</td>
<td>2 (22)</td>
<td>4 (22)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>3 (33)</td>
<td>8 (44)</td>
<td></td>
</tr>
<tr>
<td>R.E.N.A.L. nephrometry score, n (%)</td>
<td></td>
<td></td>
<td>0.144</td>
</tr>
<tr>
<td>≤ 6</td>
<td>2 (22)</td>
<td>7 (39)</td>
<td></td>
</tr>
<tr>
<td>7–9</td>
<td>6 (67)</td>
<td>5 (28)</td>
<td></td>
</tr>
<tr>
<td>≥ 9</td>
<td>1 (11)</td>
<td>6 (33)</td>
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</tr>
<tr>
<td>CCI score, n (%)</td>
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<td>0.392</td>
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<tr>
<td>1–3</td>
<td>3 (33)</td>
<td>4 (22)</td>
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<tr>
<td>4–6</td>
<td>4 (44)</td>
<td>12 (67)</td>
<td></td>
</tr>
<tr>
<td>≥7</td>
<td>2 (22)</td>
<td>2 (11)</td>
<td></td>
</tr>
</tbody>
</table>

TAE, transarterial embolization; PCA, percutaneous cryoablation; M, male; F, female; R.E.N.A.L., Radius Exophytic/endophytic properties Nearness to collecting system Anterior/posterior Location relative to polar lines; CCI, Charlson comorbidity index.

### Table 2. Indications for referral for percutaneous ablation

<table>
<thead>
<tr>
<th>TAE+PCA group</th>
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<tbody>
<tr>
<td>Presence of a second malignancy</td>
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</tr>
<tr>
<td>Cardiac comorbidities*</td>
<td>3</td>
</tr>
<tr>
<td>History of prior surgery that would increase operative risk</td>
<td>2</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>2</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>2</td>
</tr>
<tr>
<td>Obesity</td>
<td>1</td>
</tr>
<tr>
<td>Advanced age</td>
<td>1</td>
</tr>
<tr>
<td>PCA only group</td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>9</td>
</tr>
<tr>
<td>Cardiac comorbidities*</td>
<td>6</td>
</tr>
<tr>
<td>Obesity</td>
<td>4</td>
</tr>
<tr>
<td>Patient preference</td>
<td>3</td>
</tr>
<tr>
<td>Presence of a second malignancy</td>
<td>3</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>3</td>
</tr>
<tr>
<td>History of prior surgery that would increase operative risk</td>
<td>2</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>2</td>
</tr>
<tr>
<td>Advanced age</td>
<td>1</td>
</tr>
</tbody>
</table>

Note that some patients had multiple reasons listed in the chart.

*Includes: coronary artery disease, congestive heart failure, history of mitral valve repair, and atrial fibrillation.
with 3.2±1.1 probes in the PCA alone group (P = 0.733). Ablations were technically successful in 8 of 9 (89%) and 14 of 18 (78%) patients in the TAE+PCA and PCA alone groups, respectively (P = 0.483). In the TAE+PCA group, the unsuccessful ablation was due to a rim of tissue left purposefully outside the ablation zone given its proximity to the renal pelvis. Similarly, three of the technically unsuccessful ablations in the PCA alone group were due to a portion of the tumor approximating critical structures. The fourth technically unsuccessful ablation was due to bleeding encountered during the ablation. No major complications occurred in either group. Three Minor A complications (all perinephric hematomas) were observed in the TAE+PCA group. Six Minor A complications (five perinephric hematomas, one asymptomatic pneumothorax after an intentional transpleural approach) and two Minor B complications (postprocedural hypertension requiring medication and perinephric bleeding requiring thrombin injection via a percutaneous needle) occurred in the PCA alone group. The patient requiring thrombin injection was the same patient who had an unsuccessful ablation due to bleeding. This tumor was 5.3 cm in size and centrally-located with a R.E.N.A.L. nephrometry score of 11. No difference in the complication rate between the two groups was found (P = 0.483).

Since one potential benefit of TAE prior to PCA is decreased bleeding, we compared preprocedural hematocrit (HCT) to postprocedural HCT as a surrogate for bleeding. There was a 2.1%±15.4% decrease in HCT after the combined therapeutic approach of TAE+PCA. In the PCA alone group, there was a 9.3%±8.3% decrease in HCT. However, the difference in percent change in HCT between the two did not reach statistical significance (P = 0.152). Given that one potential drawback of a combined TAE+PCA approach is the extra iodinated contrast material delivered to the kidney, we compared the patients’ pre- and postprocedural estimated glomerular filtration rates (eGFR). In the TAE+PCA group, there was a 2.8%±20.9% decrease in eGFR after the combined therapy. There was a 1%±23.2% increase in eGFR after therapy in the PCA alone group. No significant difference was found in the change in eGFR between the two groups (P = 0.691).

The mean clinical follow-up was 30.8 months (range, 7–59 months) and 22.1 months (range, 3–98 months) in the TAE+PCA and PCA alone groups, respectively. Four patients that received combined therapy required a second ablation session for residual disease on initial surveillance imaging performed at 3 months. All of these patients had renal masses greater than 5 cm in size (range, 5.1–8.4 cm). None underwent a second TAE session prior to their second PCA. Five patients in the PCA alone group required additional cryoablation sessions for residual disease (mean tumor diameter, 4.9 cm; range, 4.0–6.2 cm) on initial surveillance imaging. In the follow-up period, one patient in the TAE+PCA group with a 2.8 cm mass was found to have recurrent tumor at approximately 13 months postablation and was re-treated with PCA alone. One patient in the PCA alone group with a 4.4 cm mass was also found to have recurrent tumor at approximately 35 months postablation and was re-treated with PCA alone. Otherwise, the remainder of patients in both groups had no recurrent or residual disease during the follow-up period. Mean survival calculations and a Kaplan-Meier analysis were not performed because 6 of 9 patients are still living in the TAE+PCA group while the same is true for 10 of 18 patients in the PCA alone group.

**Discussion**

RCC is a hypervascular tumor that may benefit from TAE prior to percutaneous ablation, similar to HCC and other hypervascular tumors, in order to improve oncologic outcomes, decrease bleeding, and enhance tumor localization during ablation (31). Hall et al. (18) were the first to describe TAE prior to percutaneous ablation for RCC in the radiology literature. Their case report described the treatment of a 67-year-old female with an incidentally found 3.0 cm RCC. The mass was noted to bleed significantly during biopsy so the decision was made to embolize the lesion with 300 μm polyvinyl alcohol (PVA) particles prior to radiofrequency ablation (RFA). The authors were technically successful and the patient had no evidence of residual or recurrent disease at the 3-month follow-up examination. Yamakado et al. (21) published one of the earliest case series examining the safety and efficacy of TAE prior to RFA for RCCs larger than 3.5 cm. The authors treated 12 RCCs in 11 patients with sizes ranging from 3.5 to 9 cm. Embolization was performed with either ethanol mixed with ethiodized oil or PVA particles (200 μm) followed by percutaneous RFA. All tumors showed a significant reduction in size and remained controlled during the 13 month follow-up period. One patient developed a delayed abscess that was treated with percutaneous drainage. Arima et al. (22) published the largest case series of TAE followed by RFA to date in 2007. In this report, 28 RCCs were embolized with either ethanol mixed with ethiodized oil or PVA particles (size not specified) six days prior to percutaneous RFA. The mean diameter of tumors was 3.1±1.2 cm (range, 1.2–6.5 cm). The authors reported that all tumors were adequately treated after two RFA sessions and the recurrence rate was only 2.8% during a mean follow-up period of approximately two years, but all recurrences occurred in tumors larger than 4 cm. No major complications were encountered although five minor complications occurred (pyonephrosis, n=1; perinephric hematoma, n=2; retroperitoneal bleeding, n=1; postprocedural nausea, n=1). Michimoto et al. (19) described TAE prior to PCA in 17 patients with small (12–36 mm), endophytic RCCs. In this report, the authors performed TAE between one and five days prior to CT-guided PCA with a mixture of ethanol and ethiodized oil in order to improve tumor localization. TAE was technically successful in 16 of 17 patients (unable to identify the tumor on angiography in one patient). PCA was technically successful in all patients with local control of RCC in 93% of patients at a mean follow-up of 15.4 months. The authors noted a statistically significant drop in patients’ eGFR after the combined therapeutic approach.

The use of a propensity score matching model for patient age, sex, and tumor diameter in order to create a comparison group for standard PCA alone therapy is an advancement upon the existing literature (18–25). Our groups were also similar in several other important clinical parameters such as Charlson comorbidity index, R.E.N.A.L. nephrometry score, and tumor geometry. Our data suggest that TAE+PCA is safe as no added patient complications or ill effects on patient eGFR were seen. Ideally, however, an objective benefit should be identified with a combined approach that justifies the costs and risks associated with the extra procedure. The clinical outcomes of both groups of patients compare well with existing literature, especially given the large size of the treated lesions (18–25). Yet,
we were unable to demonstrate an objective advantage of this combined approach in improving the technical success of PCA or in reducing its complications. For example, one of the most common complications of PCA is bleeding, which can occur in 3.5%–14% of patients (32, 33). Theoretically, performing a TAE prior to PCA should lessen the risk of serious bleeding events. There was a smaller absolute drop in HCT after TAE+PCA compared to PCA alone, though not statistically significant. This result was likely skewed by a single patient who had a 27% increase in HCT after TAE+PCA. Upon review, this patient was the same patient described previously who underwent both TAE and PCA as an in-patient for preexisting, symptomatic hematuria. Already anemic prior to undergoing any therapy for RCC (HCT, 26%), the patient was transfused prior to her next lab draw despite not having any complication or blood loss during her procedures resulting in a postprocedural HCT of 33%.

Identifying the RCC prior to percutaneous ablation may not pose a problem for larger, exophytic tumors but can be difficult when there are multiple masses in the same kidney, endophytic tumors, or smaller lesions. Operators may depend on anatomic landmarks or give intravenous contrast to localize the RCC during CT-guided percutaneous ablation procedures. Nonetheless, one subjective benefit of TAE prior to percutaneous ablation may be enhanced tumor localization when ethiodized oil is the contrast agent employed (19). Ethiodized oil is also an embolic agent; however, it is most commonly used to make other embolic agents visible during fluoroscopy. After the TAE, it is retained within the RCC, allowing for better appreciation of the mass during PCA (Fig. 3). Improved tumor localization can help to assure the treating physician that the entire tumor is being included within the ablation zone. This could potentially reduce the number of re-treatments due to residual tumor. Additionally, complete tumor coverage during the initial ablation session has important oncologic benefits as well given that incomplete ablation may have stimulatory effects on tumor progression secondary to alterations in the tumor microenvironment (34). However, these subjective observations would need to be verified with further investigations and larger patient series powered to evaluate these endpoints.

There are several limitations to this study. First, its retrospective design did not allow us to control for important variables such as the embolic agent or mixture of embolic agents, timing of laboratory assessments, time between TAE and PCA, and follow-up imaging intervals. Second, even though our report is similar in size to previously published case series, it is hindered by small sample size despite the 2:1 matching algorithm employed. Third, despite using propensity score matching, the tumors in the TAE+PCA group tended to be larger than the PCA alone tumors which was seen based on the weighted average given to the tumor diameter characteristic in the propensity score assignments being most significant over age and sex. This fact is important to note given that larger tumors are more difficult to ablate and are associated with higher recurrence rates (4). The matching overcame this limitation as much as possible given the TAE+PCA patient data available. Importantly, this difference did not reach statistical significance. This is representative of a clear operator bias where the larger and more difficult to ablate lesions were selected for the combined therapeutic approach. This limitation could be rectified if evaluated in a prospective manner. Fourth, we do not have pathologic results on all the lesions treated. Even though all lesions were suspicious of RCC by their appearance, pathologic confirmation on all masses would add strength to our findings. Additionally, we did not have imaging results on all the lesions treated. Even though all lesions were suspicious of RCC by their appearance, pathologic confirmation on all masses would add strength to our findings. Finally, given that the majority of patients were still living, we were unable to make a comparison about overall or disease-specific mortality between the two groups. Given these limitations, the small sample size, and nonstatistically significant results, no defi-
nite conclusions should be drawn. Yet, the current report adds to the body of literature on this subject by attempting to control for confounding variables.

In conclusion, future directions in research should include data collection in a prospective, randomized fashion or a meta-analysis of existing retrospective studies. Other directions could include a focus on newer embolic agents (i.e., liquid embolics, radiopaque particles) and different ablative technologies (i.e., microwave ablation, irreversible electroporation). Prior reports have demonstrated that dynamic, contrast-enhanced CT and CT perfusion may be able to help predict the vascularity of RCC (35, 36). Thus, there remains an open question of whether it is possible to objectively identify patients who may benefit more than others from TAE prior to PCA. Further, there may be value in objectively assessing the success of TAE by measuring embolic uptake within the lesion by intraprocedural cone-beam CT or preablation CT if ethiodized oil or radiopaque particles are used.

Conflict of interest disclosure
The authors declared no conflicts of interest.

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