



Role of Angio-Embolization for Renal Cell Carcinoma

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Abstract

Purpose of Review To provide the technical aspects of, clinical indications for, status of the current literature on, and emerging concepts in trans-arterial embolization (TAE) for renal cell carcinoma.

Recent Findings TAE has been evaluated in several retrospective series as a neoadjuvant therapy prior to surgical resection of RCC to reduce tumor vascularity and minimize intra-operative blood loss. TAE has also been examined retrospectively as a neoadjuvant therapy prior to the percutaneous ablation of RCC to reduce blood loss and procedural complications. TAE can potentially palliate symptoms of RCC such as pain and hematuria. Trans-arterial chemoembolization and trans-arterial radioembolization are emerging concepts for RCC.

Summary Although there have been no prospective, randomized trials demonstrating improved clinical or oncologic outcomes from TAE for patients with RCC, several retrospective studies have shown encouraging results.

Keywords Renal cell carcinoma · Embolization · Ablation · Nephrectomy · Palliation

Introduction

Renal cell carcinoma (RCC) comprises approximately 4% of all new cancer diagnoses in the USA annually [1]. Surgical approaches, such as partial nephrectomy (PN) and radical nephrectomy (RN), remain the gold standard therapeutic option for treating RCC. Yet, minimally invasive, percutaneous, and image-guided therapies including radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation (CA), and irreversible electroporation (IRE) are both safe and effective therapies for patients who are not surgical candidates or do not want to undergo traditional surgery [2–5]. In fact, percutaneous ablation has similar oncologic outcomes when compared to PN in pa-

tients with T1a disease [6••]. This fact becomes especially important when considering that the incidental detection of smaller, low-grade, and asymptomatic RCCs is on the rise [7, 8], which may lead to an increasing role for minimally invasive approaches. As the treatment paradigm evolves, a renewed interest has been given to the potential role of catheter-directed, trans-arterial embolization (TAE) of RCC due, in part, to its hyper-vascular nature on contrast-enhanced imaging [9]. For example, catheter-directed, image-guided renal arterial embolization is already a safe and accepted therapy for patients with renal trauma and renal angiomyolipomas [10]. However, the role of TAE in RCC is less well-defined. In one of its earliest descriptions, TAE of RCC was advocated as a means to (1) reduce tumor vascularity and intra-operative blood loss, (2) debulk the tumor in non-surgical candidates, and (3) palliate symptoms such as flank pain and hematuria [11]. Since that time, there have been significant technologic advances in imaging capabilities, mirco-catheters, micro-wires, embolic agents, and arterially delivered therapies. Subsequently, investigators have attempted to expand the clinical indications for TAE of RCC, as either an adjuvant or stand-alone therapy, but its utility remains under-studied. The purpose of this article will be to provide the technical aspects of, clinical indications for, status of the current literature on, and emerging concepts in TAE for RCC.

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Technical Aspects of Renal Arterial Embolization

Patient Selection Once the decision has been made to proceed with TAE, the patient should have a consultation with the treating interventional radiologist (IR) where the risks, benefits, and alternatives to therapy can be outlined in detail and all questions can be answered. Prior imaging should be reviewed for the number and location of the renal masses, supernumerary renal arteries, renal atherosclerotic disease, abdominal aortic aneurysms, or peripheral vascular disease that could complicate the procedure. The pre-procedure evaluation should also include a review of relevant laboratory values with special attention to platelets (should be $> 50 \times 10^3/\mu\text{L}$), international normalized ratio (INR; should be < 1.5), and glomerular filtration rate (GFR). For patients with compromised renal function, generous intravenous (IV) hydration both prior to and after the procedure should be considered. Carbon dioxide is an alternative contrast agent for patients with severely compromised renal function. The IR should discuss the patient's medication history, especially as it applies to blood-thinning medications and allergies. Patients with a documented allergy to iodinated contrast material can typically be pre-medicated with a combination of diphenhydramine and oral steroids prior to the procedure. Again, carbon dioxide is an alternative contrast agent for patients with severe contrast allergies. Blood-thinning medications should be held according to published guidelines [12]. The vast majority of TAE cases can be performed using moderate conscious sedation.

Anatomic Considerations The renal arteries most commonly arise from the anterolateral aspect of the abdominal aorta around the L1 or L2 vertebral body level. Most patients have a single left and single right renal artery; however, approximately 25% of patients have an accessory renal artery either above or below the main renal artery that supplies the upper or lower pole of the kidney, respectively [13]. At the level of the renal hilum, the main renal artery separates into anterior and posterior branches. Each of these branches then further subdivides into upper, middle, and lower pole segmental arteries. These segmental arteries further subdivide as they enter the renal parenchyma into interlobar branches that ultimately become the afferent arterioles that enter the glomeruli.

Procedural Details of Renal Arterial Embolization The technique for TAE of renal masses has been previously described [14]. After access is obtained and a vascular sheath is placed, a flush catheter (i.e., Omni™ Flush, AngioDynamics, Latham, NY, USA) is then inserted over the wire and an aortogram is obtained to visualize the location of the renal arteries and assess for any vascular anomalies. The flush catheter is then exchanged over a wire for a diagnostic catheter (i.e., 5F SOS 2 Omni™ (AngioDynamics, Latham, NY, USA) or the 5F

Simmons 1 (Terumo, Somerset, NJ, USA)) which is used to select the appropriate renal artery. Once the appropriate renal artery is selected with the diagnostic catheter, angiography is again performed in order to identify the RCC, assess its vascularity, and plot the appropriate course for sub-selection of the renal arterial system. For total renal arterial embolization, we prefer to advance a micro-catheter distally into the main renal artery prior to embolization to prevent reflux of embolic agents into the aorta. For selective renal arterial embolization, the artery or arteries supplying the tumor are then accessed using a micro-catheter and micro-wire. There are any number of appropriate micro-wire and micro-catheter combinations that would suffice for this purpose. Once the renal artery or arteries supplying the tumor are selected, angiography is again performed to confirm catheter location prior to embolization. No particular embolic agent has been shown to be superior to any other embolic agent for renal arterial embolization; thus, the choice of embolic material is operator-dependent [15–17, 18, 19–22]. The authors prefer to use embolic agents such as particles or ethanol. All embolization is performed under careful fluoroscopic guidance to prevent reflux into non-target vessels. To achieve visibility, embolic agents like particles or ethanol need to be mixed during the procedure with either contrast or ethiodized oil, respectively. Regardless of the agent, embolization is performed until stasis is achieved in the target vessels. When performed, TAE should take place within 24–48 h of either RN, PN, or percutaneous ablation to prevent revascularization of the renal arteries and reduce the chance of vascular collateralization from other arteries that could complicate subsequent interventions.

Clinical Indications and Current Data

Renal Arterial Embolization Prior to Nephrectomy Though safe in many cases of small, early-stage RCC, both RN and PN can pose a risk for certain patients, particularly those with significant medical co-morbidities or prior medical or surgical histories that would complicate the surgical approach. One of the most common complications of RN and PN is bleeding, which is due to both the highly vascular nature of the kidney itself and the increased tumor vascularity associated with the majority of RCCs [9, 23]. The risk of life-threatening hemorrhage, occurring either intra-operatively or post-operatively and necessitating additional interventions, is increased in the setting of larger tumors and complex surgeries [24, 25]. For these reasons, pre-operative renal arterial embolization has appeal as a means of reducing intra-operative blood loss. To date, no randomized, controlled studies have been performed to assess the utility of TAE prior to the surgical resection of RCC. Many of the early retrospective series evaluating the use of renal arterial embolization prior to surgical resection reported decreases in intra-operative blood loss, procedure time, and

adjacent organ involvement allowing for a more complete resection [22]. Nevertheless, heterogeneity in embolic materials and advances in technology render these studies less applicable to modern practice. In fact, more recent retrospective analyses have had conflicting results that have limited the widespread adoption of this technique. For example, one retrospective study of 66 patients that received TAE prior to surgical resection found that patients had less operative blood loss and experienced shorter procedural times [26]. Similarly, an additional small series of eight patients reported that TAE prior to nephrectomy for RCC resulted in decreased operative blood loss and the resection of larger, more advanced-stage tumors [27]. Finally, one report matched 118 RCC patients who underwent TAE prior to RN to a group of 116 patients that did not receive pre-operative TAE according to sex, age, stage, tumor size, and tumor grade [28•]. The analysis demonstrated a 5- and 10- year survival benefit from TAE prior to surgical resection. Conversely, a later study evaluated 227 RCC patients who received TAE prior to surgery to a propensity score-matched group of patients that was treated with surgery alone in order to evaluate for both cancer-specific and overall survival [29•]. These investigators were unable to show any significant differences between the groups in surgical complications, cancer-specific survival, or overall survival. In fact, patients in this cohort that were treated by surgery alone actually experienced less operative blood loss. Lastly, a retrospective analysis of RCC patients with caval involvement compared 135 patients that received neoadjuvant TAE to 90 patients that were treated with surgery alone [30]. These authors found that the embolization patients had more operative blood loss, longer operative times, more post-operative complications, and increased peri-operative mortality. Clearly, well-designed, prospective studies are needed to improve understanding of this clinical question.

Renal Arterial Embolization Prior to Percutaneous Ablation

Image-guided, percutaneous ablation is an excellent, minimally invasive therapeutic alternative in RCC 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 disease [6]. Percutaneous ablation can be guided by either ultrasound (US) or CT imaging. There are several ablative technologies currently available, including RFA, MWA, CA, and IRE. Each of these has its own advantages and physicians would do well to be familiar with more than one type of probe. Nonetheless, the selection of a particular ablative technology is primarily operator-dependent since there is no good evidence to support the use of one modality over the other in RCC [2]. As with RN and PN, one of the most common complications of ablation is bleeding, which can occur in 3.5–14% of patients [31, 32]. Thus, it has been postulated that TAE of RCC prior to percutaneous ablation may reduce the risk of serious bleeding [21]. But again, no

prospective, randomized data has been published to date to confirm this hypothesis although several retrospective series exist. In one of the earliest cases series, the authors treated 12 RCCs in 11 patients with sizes ranging from 3.5 to 9 cm [15]. Embolization was performed with ethanol mixed with either ethiodized oil or particles (200 μ m) followed by percutaneous RFA. All tumors showed a significant reduction in size and remained controlled during the 13-month follow-up period and no major bleeding complications were seen. The largest published cohort to date examined the results of TAE prior to RFA in 36 RCCs (mean diameter 3.1 cm; range 1.2–6.5 cm) in 31 patients [18•]. The authors of this study embolized the RCCs with ethanol mixed with either ethiodized oil or particles 6 days prior to percutaneous RFA. In this group, there were no recurrent tumors for patients with RCCs < 4 cm in size even though the recurrence rate was 2.8% overall. No major bleeding complications were reported. A smaller series assessed the feasibility and safety of TAE immediately prior to percutaneous RFA in ten patients with 12 RCCs (mean diameter 3.1 cm; range 1.8–6.6 cm) [16]. The authors reported technical success in all patients for both procedures without any significant bleeding complications or evidence of recurrence. One major limitation in the interpretation of these results is that none of these series had a control group for a comparative analysis. Thus, two recent retrospective reviews did attempt to compare outcomes between patients who underwent TAE prior to percutaneous CA for RCC to those treated with percutaneous CA alone but had conflicting results. In the first, the outcomes of 17 RCCs (mean diameter 3.6 cm) treated with CA alone were compared to those of 4 lesions (mean diameter 4 cm) treated with a combined TAE and CA approach [33••]. The authors of this small series demonstrated a significant decrease in complications between size-matched lesions. A larger, subsequent retrospective study did a propensity score matching analysis based on patient's age, sex, and tumor diameter to compare nine patients treated with TAE and CA (mean diameter 5.2 cm) to 18 matched patients that underwent CA alone (mean diameter 4.6 cm) [34••]. The two groups were not significantly different according to tumor geometry, R.E.N.A.L nephrometry score, or Charlson co-morbidity index despite not being matched for these characteristics. In this study, no differences in technical success, complications, blood loss, or recurrences were identified between the two groups. The authors of this study concluded that larger, prospective data is needed to understand the role of TAE prior to percutaneous ablation in patients with RCC.

Renal Arterial Embolization in Palliative Care The classic RCC triad of hematuria, flank pain, and a palpable flank mass is uncommon, occurring in approximately 5% of patients [35]. Even though the majority of patients present with symptoms from RCC, these can be clinically quiescent for a long period

of time [35]. Given this, up to 30% of RCC patients will have distant metastatic disease at the time of diagnosis precluding curative surgical or image-guided interventions [35]. For these patients, systemic chemotherapy is the mainstay of treatment although cure is rarely achieved. In this setting, renal arterial embolization has been used in several small case series as a palliative measure to control the symptoms of RCC such as pain, hematuria, and paraneoplastic syndromes (Fig. 1). For example, one of the largest published series on this topic evaluated TAE in 73 RCC patients who were experiencing hematuria and/or pain [36•]. TAE was successful in eliminating hematuria in all of the patients and in improving pain in 72% of subjects. A smaller study of 25 RCC patients who either had inoperable disease or were too ill to undergo an operation found that 17/25 patients (68%) experienced symptomatic control while five patients experienced a decrease in tumor volume after embolization [37]. Similarly, another group was able to effectively control hematuria and pain from inoperable RCC by TAE [38]. Only one study has attempted to compare outcomes between patients undergoing TAE and those receiving best supportive care for inoperable RCC [39•]. In this paper, 24 patients with unresectable RCC underwent

TAE and were compared to 30 similar patients that did not receive TAE. While no significant difference was found between the two groups with regard to performance status, tumor diameter, vascular invasion, lymph node involvement, adjuvant therapies, or number of metastases, 75% of TAE patients experienced symptomatic control. Further, those that had undergone TAE had a longer median survival (229 days vs 116 days). While there is no strong evidence to support the palliative role of TAE in advanced RCC, its use may provide some benefit to certain patients that are experiencing pain and/or hematuria.

Emerging Concepts

Apart from prophylactic embolization to reduce bleeding complications from surgery or percutaneous ablation, the hyper-vascularity of RCC could also provide an important route for the delivery of stand-alone therapies. For example, a recent prospective, controlled trial evaluated TAE versus trans-arterial chemoembolization (TACE) in 12 RCC patients prior to surgery [40••]. In TACE, a chemotherapeutic

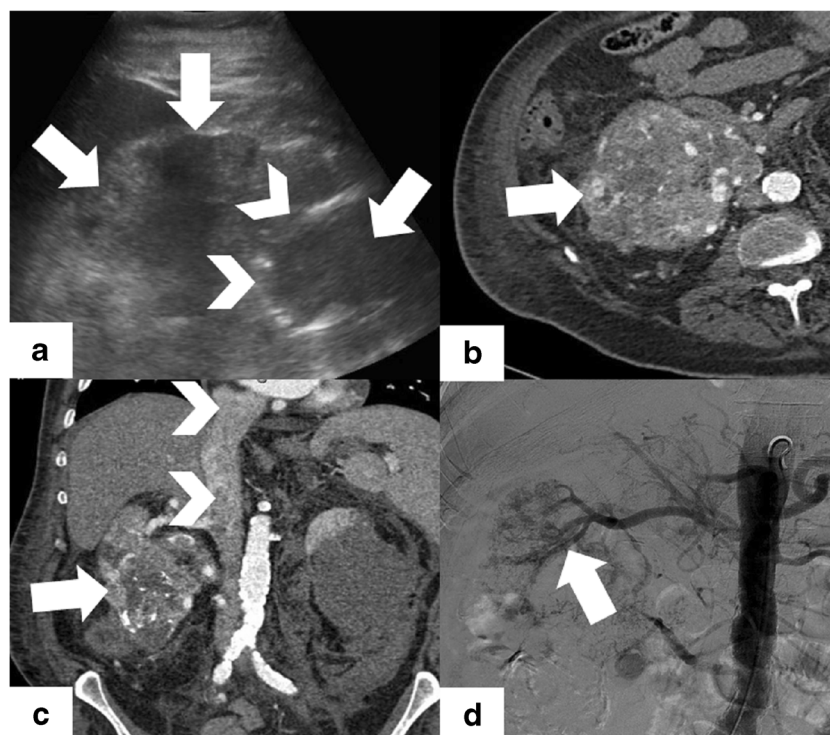


Fig. 1 A 63-year-old male who presented with hematuria, pain, and a palpable right flank mass. **a**, gray-scale ultrasound of the right flank shows a large, primarily hypo-echoic mass (white arrows) with internal calcifications (white arrowheads). **b** Axial slice from a contrast-enhanced CT scan shows a heterogeneously enhancing mass occupying nearly the entire right kidney (white arrow). **c** Coronal reformat image from a contrast-enhanced CT scan shows the heterogeneously enhancing mass (white) with tumor extension into

the inferior vena cava and right atrium (white arrow heads). **d** Digital subtraction aortogram demonstrates irregular vascularity and neovascularity associated with the right renal mass (white arrow). A percutaneous biopsy confirmed the diagnosis of grade 3 clear cell renal carcinoma. Due to tumor extension into the right atrium and ventricle, the patient was not an operative candidate. He was treated with palliative trans-arterial embolization

agent (in this case doxorubicin) is attached to the embolic agent (clinically available beads). In theory, the added effect of a chemotherapeutic agent should enhance cytotoxicity. Six patients were randomized to each group. The mean tumor diameter was 3.2 cm. The response to TAE and TACE was assessed by imaging prior to surgery and histologically after surgery. TACE resulted in a significantly higher degree of necrosis as evaluated by post-procedural imaging although no differences in necrosis were seen histologically. Importantly, no major complications were encountered. The authors note that curative surgical and ablative technologies should still be considered first-line therapies but that TACE could be considered as an alternative palliative option for select patients. Similarly, a recent phase I clinical study investigated the use of trans-arterial radioembolization (TARE) in RCC [41••]. In TARE, clinically available beads are labeled with yttrium 90 (Y90), a β emitter, which are then selectively delivered into the artery or arteries supplying the tumor under imaging guidance. TARE relies on the internal delivery of radiotherapy to cause cell death. In this trial, 21 patients with RCC were able to be treated with TARE and no dose-limiting toxicities were identified. Undoubtedly, further investigation is required but it is clear that TAE has the potential to deliver novel chemotherapeutic, immunologic, or radiolabeled agents directly into the vessels supplying RCCs.

Conclusion

TAE plays an important, albeit primarily adjunctive, role in the management of patients with RCC. TAE has been used in RCC as a means to improve operative outcomes, reduce ablative complications, and palliate symptoms. Although there have been no prospective, randomized trials demonstrating improved clinical or oncologic outcomes, several retrospective studies have shown encouraging results. Additionally, the role of TACE and TARE in RCC may provide an important area of future research.

Compliance with Ethical Standards

Conflict of Interest Andrew J. Gunn is a paid speaker for BTG.

Anand R. Patel declares no potential conflicts of interest.

Soroush Rais-Bahrami is a section editor for *Current Urology Reports*.

Human and Animal Rights All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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