Focal Ablative Therapy for Renal Cell Carcinoma in Transplant Allograft Kidneys

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OBJECTIVE To evaluate outcomes after focal ablative therapy for renal cell carcinoma (RCC) in transplant allograft kidneys.

METHODS After institutional review board approval, patients with a history of RCC in a transplanted allograft kidney who underwent focal ablative therapy were identified. Complete chart reviews were performed and the relevant data were extracted for cumulative analysis.

RESULTS Six patients were treated with focal ablative therapy for RCC in a transplanted allograft kidney at our institutional between 2010 and 2017. Masses were diagnosed at a median of 8 years (range 1 month-8 years) after transplantation. Median mass size was 3 cm. Three patients were treated with microwave ablation, 1 with percutaneous irreversible electroporation, 1 with laparoscopic cryoablation, and 1 with open cryoablation. Median follow-up was 45 months (range 8-61 months). The median creatinine level was 1.65 before ablation and 1.58 1 year after ablation. No patients required dialysis after ablation. No patients developed local recurrence during the follow-up period. However, 1 patient developed lymph node metastases 4 years after ablation. Two patients died during follow-up of other causes. At the time of death both patients had functioning grafts.

CONCLUSION Focal ablative therapies are a feasible, renal-sparing intervention for the management of RCC in renal allografts at intermediate-term follow-up. UROLOGY 125: 118–122, 2019. © 2018 Elsevier Inc.

Renal transplantation is the gold-standard treatment for end-stage renal disease (ESRD). After transplant, long-term mortality rates are 48%-82% lower than those of patients remaining on the transplant wait list.[1] The number of transplants performed in the United States has steadily increased over the last several years from 17,513 in 2007[2] to 19,062 in 2016.[3] After transplant, patients are at an increased risk of developing several malignancies, including a 10- to 15-fold increased risk of developing renal cell cancer (RCC).[4,5] RCC in renal transplant patients can be donor or host derived, and the increased risk of de novo RCC is secondary to both ESRD and immunosuppression.[5]

When managing RCC in allograft kidneys, the physician must balance the need for renal preservation with achieving oncologic control. Focal ablative therapies, which have been shown to be a safe and effective treatment for small renal masses,[6] are minimally invasive, associated with a low morbidity, and can be performed percutaneously making them well suited for the treatment of RCC in renal allografts. However, little data exist on outcomes after tumor ablation in transplanted kidneys. The purpose of this study was to review a single institution's experience with focal ablative therapies for renal masses in allograft kidneys.

MATERIALS AND METHODS

After institutional review board approval, we retrospectively identified all patients with a tumor in a renal allograft that was treated with ablative therapy at our institution from 2010 to 2017. No exclusion criteria were utilized. When available, the following data were collected: age, date of kidney transplant, etiology of ESRD, living donor or cadaveric allograft, size of mass, method of diagnosis of the renal mass, immunosuppressive regimen, method of ablation, postoperative complications, tumor histology, Fuhrman grade, postintervention renal function, development of local recurrence or metastatic disease, postintervention imaging, and survival. Complications were graded according to the Clavian-Dindo classification.[7] Significant complications were defined as those that were grade III or higher. Descriptive statistics, including frequencies, medians, and ranges were calculated from the pooled data. Median values were reported due to the small data set and unclear distribution.

Conflict of Interest: *The authors declare that they have no conflict of interest.*

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Microwave ablation (MWA) and irreversible electroporation (IRE) of tumors were performed by a single interventional radiologist (AF). MWA was performed using the NeuWave Microwave Ablation System (NeuWave Medical Inc., Madison, WI). CT with or without ultrasound was used for guidance. A 6- to10-minute application was standard. Transcutaneous MWA was performed at 65 W and the transosseous MWA was performed at 90 W for 1 minute, 65 W for 2 minutes and 50 W for 3 minutes. IRE was performed with the NanoKnife System (Angiodynamics, Latham, New York, NY). Three probes were used during a 10-minute cycle. Cryoablation was performed by a single urologist (MP) with intraoperative ultrasound guidance. Three cryoprobes were used to perform a double freeze-thaw cycle with a 10-minute freeze in both cases.

All patients underwent cross-sectional, surveillance imaging 3 months after treatment to confirm an adequate response. There was no uniform surveillance protocol; however, all patients underwent cross-sectional imaging every 6-12 months to monitor for tumor recurrence or metastases.

RESULTS

Six patients were treated with focal ablative therapy for a mass in an allograft kidney from 2010 to 2017 at our institution. Median age at diagnosis was 48 years (range 35-71 years). Tumors were diagnosed at a median of 8 years (range 1 month-8 years) after transplantation. One patient was diagnosed a month after transplantation with a 1.6 cm mass, suggesting a donor-derived RCC. The donor was a 45-year-old male who suffered brain death after a stroke. No mass was noted at the time of transplant. The same donor's second kidney was also transplanted into a patient at our institution. That recipient did not develop an RCC. Median mass size at diagnosis was 2.95 cm (range 1.6-3.4 cm). Five patients had biopsy proven RCC. One tumor was not biopsied because of its cystic appearance and risk of rupture. Although this patient did not have pathologically confirmed RCC, the MRI was suggestive of disease: it showed a multiseptated, complex mass that was 3.1 cm with an area of nodular enhancement that had become more significant when compared to the MRI 6 months prior and that showed diffusion restriction (consistent with a Bosniak 4). Additional patient and tumor characteristics can be found in Tables 1 and 2, respectively.

Three patients underwent percutaneous MWA. Each of the 3 remaining patients had either percutaneous IRE, laparoscopic cryoablation, or open cryoablation. Three patients experienced postoperative complications. One patient developed a symptomatic hematoma that required drainage (Clavien IIIa) after percutaneous MWA. Another patient also developed a hematoma, which was managed conservatively (Clavien I), after laparoscopic cryoablation. The third patient incurred nerve damage, which caused chronic leg pain that was treated with gabapentin after transosseous MWA (Clavien II; Table 3).

Median follow-up was 45 months (range 8-61 months). Median creatinine was 1.65 before ablation and 1.58 one year after ablation. No patients required dialysis after ablation. No patients developed a local recurrence during the follow-up period. However, 1 patient developed lymph node metastases 4 years after ablation. Two patients died during follow-up, one of a stroke 59 months after cryoablation and the other of complications from an influenza infection 38 months after IRE. At the time of death both patients had functioning grafts (Table 3).

The patient who developed metastatic lymphadenopathy 4 years after open cryoablation was found to have 2 perihilar soft tissue nodules (1.5 cm and 1.2 cm) on surveillance imaging. Initial management consisted of transitioning immunosuppression to a sirolimus based regimen. The patient then underwent exploratory laparotomy. However, during surgery no lymphadenopathy was appreciated, and the procedure was aborted. Repeat imaging 3 months after the initial diagnosis demonstrated interval growth of the lymph nodes, and therefore, a percutaneous biopsy was performed. The pathology was consistent with RCC. After multidisciplinary evaluation, the decision was made to withdraw immunosuppression, monitor the lymphadenopathy closely, and perform a radical transplant nephrectomy and lymph node dissection should the nodes continue to enlarge. Prior to any further surveillance imaging, the patient passed away from a cerebrovascular accident.

COMMENT

The incidence of RCC in transplant allografts is estimated to be about 0.5%.[8,9] Due to the low incidence, most studies on the management of renal tumors in transplant allografts come from case reports and short series,[10-15] with a few exceptions.[16-18] A 2016 meta-analysis of outcomes after ablative therapy for masses in renal allografts identified 48 tumors from 17 studies. All patients were treated with radiofrequency ablation (RFA) or cryoablation. There were no intraoperative or postoperative complications. Average follow-up was only 20 months and average tumor size was 2.1 cm. No information was provided on survival or graft function after ablation. However, there was 1 recurrence at 24 months.[19] The largest study comes from the radiology literature. Cornelis et al reported on 20 patients, with 24 tumors in renal allografts, treated with RFA or cryoablation. There were no intraoperative complications. Postoperative complications included 1 patient who developed infection at the ablation site that caused a cutaneous

Table 1. Patient and donor characteristics

Patient	Age at Diagnosis	CCI	Cause of ESRD	Date of Transplant	Donor Type	Age of Donor	Induction Thymoglobulin	Maintenance Immunosuppression
1	71	7	HTN	6/2002	Cadaveric	71	No	Tacrolimus, prednisone
2	39	5	DM	5/2005	Living	44	Yes	Tacrolimus, prednisone, MMF
3	35	3	GN	1/2006	Living	43	No	Tacrolimus, prednisone, MMF
4	63	7	DM	6/2012	Cadaveric	35	Yes	Tacrolimus, prednisone, MMF
5	57	5	HTN and DM	5/2015	Cadaveric	45	No	Tacrolimus, prednisone
6	39	4	HTN	9/2016	Cadaveric	19	Yes	Tacrolimus, prednisone, MMF

CCI, Charlson comorbidity index; ESRD, end-stage renal disease; GN, glomerulonephritis; HTN, hypertension; MMF, mycophenolate mofetil, DM, Diabetes Mellitus.

Table 2. Tumor characteristics

Patient	Time from Transplant to Diagnosis	Method of Diagnosis	Size	Histology	Fuhrman Grade
1	8 y	CT for pelvic fluid seen on ultrasound	3.4 cm	Clear cell	1-2
2	8 y	CT for pain	2.2 cm	Papillary	1-2
3	8 y	Screening ultrasound	3.1 cm	None available	None available
4	2 y	MRI for liver disease	2.8 cm	Clear cell	1-2
5	1 mo	CT for sepsis	1.6 cm	Clear cell	3
6	11 y	Screening ultrasound	3.1 cm	Papillary	2

fistula and a second patient who developed a transient genitofemoral nerve injury. No patients suffered from recurrence at a mean follow-up of 28 months, although there were 2 deaths from other causes. There was no significant change in allograft function at 3 months after tumor ablation.[16]

One advantage of this study is that it provides intermediate-term oncologic and functional outcomes, with a median follow-up of 45 months. Of note, the median tumor size in this study was 3 cm, which is larger than the average size in any of the previous series. Our complication rate was 50% which is higher than rates reported in the studies mentioned above. However, only one of these was a significant complication. All patients had stable creatinine levels 1 year after ablation and at their most recent follow-up. There was 1 patient who progressed to metastatic disease, without any evidence of local recurrence, who then died from a cerebrovascular accident, and a second patient who died from complications of an influenza infection. Although a 33% ($n = 2$) mortality is higher than mortality rates reported in previous studies, given our small sample size and the fact that most studies did not have follow-up data beyond 5 years, our outcomes are difficult to compare to these earlier reports.

To the best of our knowledge, this is the first report of MWA and IRE for the treatment of renal masses in allograft kidneys. Previous studies on the management of RCC in transplanted kidneys with focal therapies exclusively utilized RFA or cryoablation. RFA uses an electrical current to heat the tissue and cause coagulative necrosis. Cryoablation utilizes argon gas to cause intracellular and extracellular ice crystal formation, leading to direct injury to cellular structures and increased osmolality of the extracellular space, resulting in cell dehydration.[14] The current guidelines recommend the use of RFA or cryoablation for the management of RCC[6] because they have been studied relatively extensively with long-term follow-up and studies have found comparable oncologic outcomes after partial nephrectomy, RFA, and cryoablation.[20,21]

Newer ablative technologies include MWA and IRE. MWA, as the name implies, uses microwaves to heat the tissue. Although less well studied, the theoretical advantages of MWA include shorter ablation times and the ability to treat larger areas, a consequence of its superior tissue penetration and decreased susceptibility to the cooling effects of vasculature, referred to as "heat sinks."[14] Studies on the oncologic efficacy of MWA have yielded mixed results. While some studies have shown favorable outcomes[22] and a recurrence-free survival comparable to both cryoablation[23] and partial nephrectomy,[24] others have suggested inferior oncologic control with MWA.[25] The most recent development in ablative technology is IRE, which uses electoral pulses to cause nanopores in the cell membrane leading to cell death. A phase 2B clinical trial is currently in progress to evaluate the safety and efficacy of IRE, with results expected in 2018. An early report of IRE for treatment of renal masses showed that it was safe and caused CT proven ablation of 71% (5 of 7) RCCs.[26]

This study included 3 patients treated with MWA and 1 patient treated with IRE. The 2 patients who underwent MWA had a median follow-up of 38 months without any evidence of disease recurrence. The patient who had IRE did not have any evidence of disease recurrence on MRI obtained at 33 months postablation. These results demonstrate that MWA and IRE can be effective for the treatment of RCC in allograft kidneys and warrant further study.

Limitations of this study include its retrospective design, small sample size, and variability in follow-up. These

Table 3. Procedure, complications, and outcomes

Patient	Intervention	30-Day Complication	Local Recurrence	Metastases	Alive	Follow-Up
1	Open cryoablation	Hematoma	No	Lymph node	No, died of CVA	59 mo
2	Percutaneous MWA	None	No	None	Yes	61 mo
3	Laparoscopic cryoablation	Hematoma requiring drainage	No	None	Yes	52 mo
4	Percutaneous MWA	None	No	None	No, died of flu	38 mo
5	Percutaneous IRE	None	No	None	Yes	34 mo
6	Transosseous MWA	Leg pain	No	None	Yes	8 mo

CVA, cerebrovascular accident; MWA,microwave ablation.

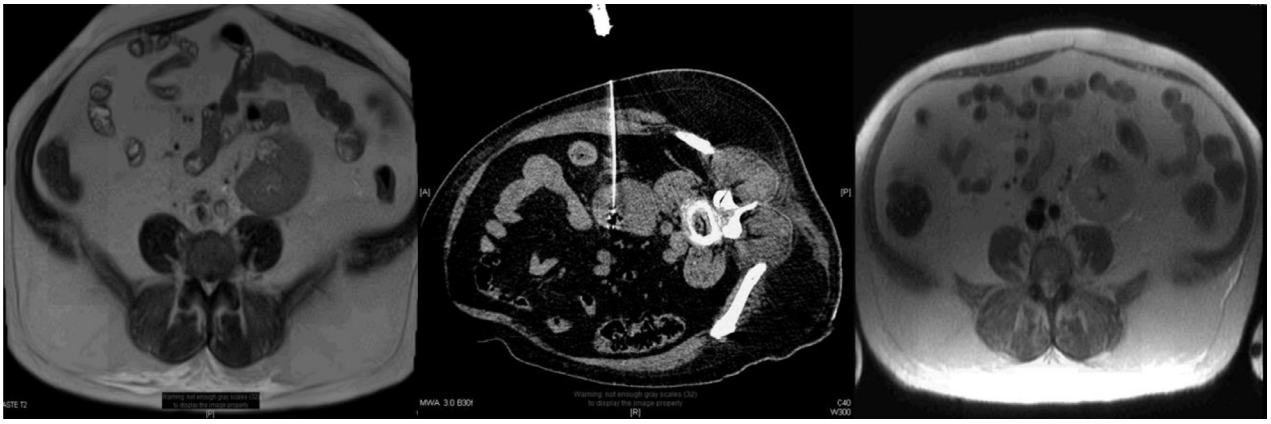

Figure 1. A renal mass in a transplant kidney, MWA and Post-MWA. MWA, microwave ablation. (Color version available online.)

limitations are in part due to the low incidence of RCC in transplant kidneys. Because this is a retrospective study, there is a risk of selection bias and there is heterogeneity in patient management. We believe that the risk of selection bias is minimized since all patients at our institution, except for 1, who developed RCC in a renal allograft, were treated with ablative therapy. Further research with prospective studies and larger patient cohorts would continue to expand our understanding of this rare clinical presentation and help determine the intervention that maximizes renal preservation along with recurrence-free survival.

There is a growing body of literature supporting the use of focal ablative therapies for small renal masses. These techniques are particularly useful for masses in transplanted kidneys due to the imperativeness of renal preservation, non-naïve surgical planes, and multiple medical comorbidities in this patient population. While focal ablative therapies may not be appropriate for all patients, they do represent a reasonable alternative to surgical extirpation for RCC in renal allografts (Fig. 1).

CONCLUSION

Focal ablative therapies are a feasible, renal-sparing intervention for management of RCC in renal allografts at intermediate-term follow-up.

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