REVIEW ARTICLE

Conservative treatment of renal cell carcinoma in kidney transplantation☆

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Abstract
Purpose: To evaluate the new treatment strategies in renal cell carcinoma (RCC) that affects the graft in renal recipients.
Methods: A literature review is made, analyzing all the published cases of conservative surgery in renal graft RCC.
Synthesis of evidence: A total of 51 partial nephrectomies in renal graft patients have been described, with a graft survival rate of 88% and a recurrence rate of 6%. Most of the patients (75%) were asymptomatic at the time of diagnosis, and the mean lesion size was 2.8 cm. Enucleation was the most frequent technique employed. 77% of all immunosuppressor regimens included cyclosporine A. Six patients with graft RCC were subjected to radiofrequency ablation and two patients underwent percutaneous cryoablation, with a single case of relapse and a graft survival rate of 100%.
Conclusions: Nephron-sparing surgery is a good management option in renal graft RCC, affording good oncological control and graft survival. Modification of immunosuppression with the withdrawal of cyclosporine A and the introduction of mTOR inhibitors is an adequate measure in such patients.

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KEYWORDS
Kidney transplantation; Partial nephrectomy; Renal cell carcinoma; Cryosurgery; Radiofrequency ablation

PALABRAS CLAVE
Trasplante renal; Nefrectomía parcial;

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Partial nephrectomy

After performing the first operation in 1992 by Feldman and Jacobs, 1 51 cases of nephron sparing surgery have been described on the renal graft (Table 1). 1-12 In most cases, removal of the mass was carried out (66%).

The pathological result was RCC in 86.3% of the cases, oncocytoma in 4%, angiomyolipoma in 6%, and in 3.7% it was not specified. Of the malignant lesions, the most frequent subtype was clear cell carcinoma (41%), followed by the papillary (29%) and collecting duct (7%) origin. In the remaining 23%, the origin was not specified. The diagnosis was made an average of 10 years after the implantation. In most cases (75%), the tumors were detected incidentally during the routine ultrasound scan of the graft. The remaining patients had different symptoms (elevated baseline creatinine, microscopic hematuria, pain), which gave rise to imaging tests that led to the diagnosis. In 2 patients (4%), the lesion was detected during the transplantation. In one of them, 23 removal of a middle-sized cyst was carried out in bench surgery during the making of a living donor transplant, detecting RCC in its wall and performing polar nephrectomy 2 weeks after the first surgery. In the other one, 24 a 1-cm solid mass was detected during bench surgery, we proceeded to its excision, and after patient consent, the graft was implanted.

The average lesion size was 2.8 cm, with a variability between 0.7 and 9 cm. In 3 patients, 2 synchronous tumors were detected in the graft, 1,4,28 that were removed during the same surgical procedure. In 16.3% of the cases, 9,12,14,15,21,23 ultrasond was intraoperatively to confirm the location of the lesion and delimit its margins; in the rest (83.7%), we did without it, since in most cases they were exophytic and macroscopically well-delimited lesions. In 3 patients we used the harmonic scalpel during surgery, being highlighted by the authors for its contribution in reducing the bleeding of the bed and the best definition of the surgical plane. 21,26

In the follow-up of the patients, we used various imaging techniques. In 23.5% we carried it out by means of
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of cases</th>
<th>Histology</th>
<th>Tumor size (cm)</th>
<th>Time after treatment (months)</th>
<th>Graft function</th>
<th>Immunosuppression</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribal et al.(^1)(^--)(^14)</td>
<td>1992–2006</td>
<td>18</td>
<td>Multiple(^a)</td>
<td>Mean 3.5 (0.7–9)</td>
<td>Mean 134 (1–258)</td>
<td>All (2 cases not evaluated)</td>
<td>8 not modified, 6 reduced, 4 not specified</td>
<td>No (2 cases not evaluated)</td>
</tr>
<tr>
<td>Kunisch-Hoppe et al.(^1)(^6)</td>
<td>1998</td>
<td>1</td>
<td>Clear cell</td>
<td>3.3</td>
<td>72</td>
<td>Dialysis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Thomáliá(^17)</td>
<td>2004</td>
<td>1</td>
<td>Papillary carcinoma</td>
<td>4.2</td>
<td>120</td>
<td>Yes</td>
<td>Reduced</td>
<td>No</td>
</tr>
<tr>
<td>Amirzargar et al.(^1)(^8)</td>
<td>2004</td>
<td>1</td>
<td>Clear cell</td>
<td>4.5</td>
<td>50</td>
<td>Yes</td>
<td>Reduced</td>
<td>No</td>
</tr>
<tr>
<td>Moudouni et al.(^1)(^9)</td>
<td>2005</td>
<td>3</td>
<td>(1) Collecting duct; (2) Papillary carcinoma; (3) clear cell</td>
<td>(1) 4; (2) 3; (3) 3</td>
<td>(1) 156; (2) 60; (3) 300</td>
<td>Yes</td>
<td>Not modified</td>
<td>No</td>
</tr>
<tr>
<td>Barama et al.(^2)(^0)</td>
<td>2005</td>
<td>5</td>
<td>4 clear cell and a papillary carcinoma</td>
<td>Mean 2.2 (0.9–4)</td>
<td>Mean 139.2 (48–204)</td>
<td>Yes in 2 cases One death and 2 dialyses(^b)</td>
<td>Reduced in 4 cases. Suspended in one</td>
<td>A multifocal case: radical nephrectomy. Rest no deaths</td>
</tr>
<tr>
<td>Cox et al.(^2)(^1)</td>
<td>2005</td>
<td>2</td>
<td>(1) RCC; (2) Collecting duct</td>
<td>(1) 4; (2) 2.2</td>
<td>(1) 180; (2) 192</td>
<td>Yes</td>
<td>Modified</td>
<td>No</td>
</tr>
<tr>
<td>Genevois et al.(^2)(^2)</td>
<td>2005</td>
<td>1</td>
<td>Clear cell</td>
<td>3.5</td>
<td>48</td>
<td>Yes</td>
<td>Not specified</td>
<td>No</td>
</tr>
<tr>
<td>Goeman et al.(^2)(^2)</td>
<td>2006</td>
<td>1</td>
<td>Chromophobe cell</td>
<td>2</td>
<td>132</td>
<td>Yes</td>
<td>Not specified</td>
<td>Yes (RFA)</td>
</tr>
<tr>
<td>Neipp et al.(^2)(^3)</td>
<td>2006</td>
<td>1</td>
<td>Clear cell</td>
<td>7</td>
<td>51</td>
<td>Yes</td>
<td>Modified</td>
<td>No</td>
</tr>
<tr>
<td>Hernández-Sánchez et al.(^2)(^4)</td>
<td>2007</td>
<td>1</td>
<td>Papillary carcinoma</td>
<td>1.5</td>
<td>51</td>
<td>Yes</td>
<td>Not modified</td>
<td>No</td>
</tr>
<tr>
<td>Lledo-García et al.(^2)(^5)</td>
<td>2007</td>
<td>1</td>
<td>Chromophobe cell</td>
<td>2.1</td>
<td>24</td>
<td>Yes</td>
<td>Not modified</td>
<td>No</td>
</tr>
<tr>
<td>Mundel et al.(^2)(^6)</td>
<td>2007</td>
<td>1</td>
<td>Papillary carcinoma</td>
<td>2</td>
<td>143</td>
<td>Yes</td>
<td>Not modified</td>
<td>No</td>
</tr>
<tr>
<td>Chambade et al.(^2)(^8)</td>
<td>2008</td>
<td>5</td>
<td>4 papillary carcinomas + 1 clear cell</td>
<td>Mean 2 (15–30)</td>
<td>Mean 165.6 (108–240)</td>
<td>Yes</td>
<td>Not modified</td>
<td>No</td>
</tr>
<tr>
<td>Hoda et al.(^2)(^7)</td>
<td>2009</td>
<td>1</td>
<td>Clear cell</td>
<td>3.8</td>
<td>180</td>
<td>Yes</td>
<td>Not modified</td>
<td>Yes (nephrectomy)</td>
</tr>
<tr>
<td>González-López et al.(^1)(^5)</td>
<td>2009</td>
<td>1</td>
<td>Clear cell</td>
<td>3</td>
<td>108</td>
<td>Yes</td>
<td>Modified</td>
<td>No</td>
</tr>
<tr>
<td>Monllau et al.(^2)(^1)</td>
<td>2009</td>
<td>1</td>
<td>Papillary carcinoma</td>
<td>3</td>
<td>96</td>
<td>Yes</td>
<td>Not specified</td>
<td>No</td>
</tr>
<tr>
<td>Tsaur et al.(^2)(^9)</td>
<td>2010</td>
<td>2</td>
<td>(1) Papillary carcinoma; (2) clear cell</td>
<td>2</td>
<td>177 and 151</td>
<td>Yes</td>
<td>Not specified</td>
<td>No</td>
</tr>
<tr>
<td>Ponce Díaz-Reixa et al.(^2)(^0)</td>
<td>2010</td>
<td>4</td>
<td>4 RCC</td>
<td>Mean 2.4 (1.5–3.5)</td>
<td>Mean 101 (42–192)</td>
<td>Yes in 2 cases; 2 deaths</td>
<td>Not specified</td>
<td>No</td>
</tr>
</tbody>
</table>

\(^a\) 5 RCCs, 5 clear cells, 2 papillary, 2 oncocytomas, one angiomyolipoma, one collecting duct, and 2 not specified.

\(^b\) One radical nephrectomy due to multifocal tumor and a non-functioning graft 2 years after the surgery.
computed tomography (CT), in 21.5% by combining ultrasound and nuclear magnetic resonance (NMR), and in 19.5% exclusively with ultrasound. In 18 cases (35.5%), the technique was not specified. Most of the centers performed a check-up a month after the treatment, and then every 3–6 months during the first years until becoming yearly after more than 3–5 years after surgery.

88% of the grafts maintained their function. Only 4 patients required dialysis again, 2 after performing transplantection (one for multicenter tumor\textsuperscript{20} and the other one for local recurrence\textsuperscript{16}), and 2 for chronic graft dysfunction.\textsuperscript{20,27} In 2 cases, the outcome was not assessed (4%). Three patients died during the follow-up, with the functioning graft. In 94% of the patients, there was neither local disease recurrence nor metastatic spread.

Recurrence occurred in 3 cases. One patient\textsuperscript{16} had metastatic disease at diagnosis, performing partial nephrectomy and suspension of immunosuppression. After local recurrence at 3 months, we performed transplantection and systemic immunotherapy, with regression of metastatic lesions and follow-up of 6 months free of disease. In another case,\textsuperscript{22} the patient had a local recurrence at 2 years after graft surgery, successfully conducting RFA. In the latter case, the patient had chronic graft dysfunction 4 years after surgery, returning to dialysis again, and relapsed a year later, so nephrectomy was performed.\textsuperscript{17}

Among the associated complications, only 2 fistulas were described, one urinary\textsuperscript{12} and the other one lymphatic\textsuperscript{21} – which evolved successfully with conservative treatment – a deep vein thrombosis\textsuperscript{2} and 2 chronic graft dysfunctions.\textsuperscript{20,27}

Regarding immunosuppression, in 43% of the patients the same pattern was maintained after surgery. In a third of the patients it was modified, either by reducing the dose (25%) or by substitution of the drugs (8%). One patient\textsuperscript{16} discontinued the medication after transplantection, and in 11, the postoperative immunosuppressive pattern (22%) was not described. Of the 43 patients in whom the treatment prior to tumor detection was specified, and cyclosporine A (CsA) was within the immunosuppressive pattern in 77% of them.

Radiofrequency ablation

First used in 1997 by Zlotta,\textsuperscript{33} RFA has been applied in the treatment of multiple tumors, including native kidney tumor. Its use in transplantation is very new, having been described only in 6 cases, in 5 cases primarily,\textsuperscript{34–38} and in one as a rescue from a local recurrence after partial nephrectomy\textsuperscript{12} (Table 2). All the patients had significant comorbidity that justified the indication of the technique, mainly respiratory and cardiovascular.

In 5 cases, the histology was confirmed by means of fine-needle aspiration (FNA), all of them being RCC (3 papillary,\textsuperscript{34,36,38} one clear-cell\textsuperscript{35} and another one chromophobe-cell\textsuperscript{12}). In the sixth case, it was not confirmed due to technical approach problems, making a presumptive diagnosis.\textsuperscript{32} The mean size was 2 cm (range: 3.2–1 cm) and the mean time from the transplantation to the diagnosis was 12 years, being in the case of recurrence 2 years after surgery. In 4 patients, there were symptoms which induced to perform diagnostic tests.

The RFA was performed using a different technique, according to the authors, guided with ultrasound\textsuperscript{12,34} or with CT.\textsuperscript{35–37} The temperatures reached ranged between 80°C and 104°C and the treatment length between 10 and 38 min. Roy et al.\textsuperscript{38} did not specify the technique used. After a follow-up time ranging between 3 and 14 months, all the grafts showed good function, having detected a single case of recurrence.\textsuperscript{39} While all the authors considered as a criterion of success the absence of enhancement on CT or control MRI, Aron et al.\textsuperscript{36} indicated the need for biopsies of the bed to detect residual tumor, as it happened in this case. They detected a papillary RCC microfocus on the bed and they proceeded to make a new RFA session with negative biopsy 6 months later and excellent tolerance by the patient and the graft.

None of the patients had complications in the immediate postoperative period or during the follow-up. We must note that in one case there was synchronous diagnosis of RCC in native kidney,\textsuperscript{38} without being able to rule out that one of the 2 lesions was metastatic from the other, since both histologies were equal and no DNA analysis was performed which checked the origin of the tumors.

The case of a polar nephrectomy performed using an online RF device that allows for parenchymal resection using radiofrequency-induced coagulation, similar to the resection used in the liver, has recently been published. This emerging technique needs more follow-up to ensure the true disease control.\textsuperscript{39}

Percutaneous cryoablation

Shingleton et al.,\textsuperscript{40} in 2002, performed the first percutaneous cryoablation of a 1.7-cm tumor in a graft, after extensive experience in native kidneys. The diagnosis was performed 8 years after the implantation, after deterioration of the graft function. In the confirmation RMI, an injury was detected in the native kidney and another one in the graft. After confirming by means of FNA that both lesions were RCC (in the native kidney of papillary origin and in the graft of clear cell), the patient underwent radical nephrectomy of the native kidney and percutaneous cryoablation of the graft, guided by RMI, in which −140°C were reached. After a month of follow-up, the graft showed good function and in the control MRI the lesion had decreased in size, without enhancement after contrast administration, which according to the authors corroborated the success of the treatment.

Hruby et al.,\textsuperscript{41} in 2006, described the incidental finding of a 3.2-cm mass in the graft 8 years after the transplantation, performing ultrasound-guided cryotherapy. Nine months after the technique, we assessed the residual lesion with RMI, having decreased in size and presenting no contrast uptake. The histological diagnosis was oncocytoma and the graft showed good residual function.

Nine months after the technique, the residual lesion with RMI was assessed, having decreased in size and presenting no contrast uptake. The histological diagnosis was oncocytoma and the graft showed good residual function.

Discussion

RCC is the most common malignant tumor of the renal parenchyma. Its incidence in transplant patients and in
patients with chronic renal failure (CRF) is slightly higher than that in the general population (4.8 vs 2.3%).

Most of these tumors in transplant patients are found in native kidneys, less than 10% of them affecting the graft. The occurrence of multifocal tumors (43–50%) is more frequent, the papillary origin being the most commonly found in the pathological analysis of patients with CRF or transplant (57%), whereas in the general population, clear cell tumors are more frequent (80%). In patients with end-stage kidney disease and/or kidney transplantation, no differences have been shown in the prognosis depending on the cell line. Acquired cystic kidney disease and certain immunosuppressants, such as CsA, have been typically associated to colon RCC in transplant patients, although the data in the literature are contradictory.

The mean interval of occurrence after transplantation is estimated at 3.5 years, although cases have been reported in graft up to 26 years after the transplantation. The most common typical symptoms are usually diffuse abdominal pain or febrile syndrome, accompanied or not by the presence of leucocyturia, proteinuria or hematuria. Currently, the largest number is diagnosed during the follow-up.

Renal receptors typically have a higher risk of metastasis at the time of diagnosis, occurring in up to 53% of patients, while in the general population the incidence is much lower.

The de novo treatment of RCC on the renal graft classically consisted in graft nephrectomy. This technique ensures the complete removal of the lesion, although it involves a decrease in the quality of life of patients because of the immediate need for dialysis and the required waiting for the retransplantation. Currently, this time has decreased to less than 2 years in the located cases. With the development of new conservative surgical techniques of the renal parenchyma and improved imaging techniques, minimally invasive surgery has become an option with good long-term outcomes (survival approaching 100% at 10 years) in patients with single functioning kidney s. The results in the graft with these techniques are good so far, despite the small number of cases.

A small-size lesion (usually smaller than 4 cm, but not always), single and peripherally located can be treated by means of nephron sparing surgery. This allows for preservation of the graft, thereby avoiding the radical treatment of 'false positives'. Nephron-sparing surgery in the kidney graft has a high technical difficulty, so previous experience is required in the native kidney. According to some authors, it has a higher range of complications than percutaneous techniques, such as increased bleeding and increased incidence of fistulas and graft dysfunction, although most of the authors and our own data do not indicate it. 88% of the grafts remained functioning during the follow-up, including the 3 patients who died. The occurrence of relapse was only described in 3 patients.

Recently, RFA and percutaneous cryoablation have been used in cases where the patient or graft condition did not allow for surgery. Their advantages are minimal invasiveness, preservation of the surrounding renal parenchyma, fewer complications, and a shorter hospital stay. Of the 8 cases treated with these techniques published so far, all preserved their function and there were no complications in any of them. There was only one recurrence, which was successfully treated with a new cycle of RFA after 6 months of follow-up. The follow-ups in these techniques are shorter than in the cases of partial nephrectomy, so their results must be assessed more cautiously, although recent data support their safety and long-term effectiveness.

In recent years it has been postulated that the modification of the immunosuppressive regimen, with the reduction or suspension of calcineurin inhibitors and the introduction of mTOR inhibitors are associated to a decrease in the potential for recurrence and progression of the tumor disease after surgical treatment. Although many authors advocate for this practice, there is no consensus at present to establish an immunosuppressive regimen after treatment of the tumor.

Conclusions

RCC is one of the most common tumors in transplant patients, with an incidence greater than the normal population. Radical nephrectomy is preferred in the organ-confined native kidney RCC, while nephron sparing surgery and minimally invasive percutaneous techniques are proving to be a therapeutic alternative in RCC cases in the graft. Avoiding
the immediate need for dialysis and improving the quality of life of patients after treatment of the tumor is a target that can be accomplished by these techniques, and with good oncological results so far. Modification of the immunosuppression, with the suspension of the CsA, or mini-
mization of the calcineurin inhibitor and introduction of mTOR inhibitors, are advisable for these patients.

Conflict of interest

The authors declare that they have no conflict of interest.

References

35. Baughman SM, Sexton WJ, Glanton CW, Dalrymple NC, Bishoff JT. Computerized tomography guided radio frequency