Nephron Sparing Surgery for De Novo Kidney Graft Tumor: Results From a Multicenter National Study

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Nephron sparing surgery (NSS) results in the transplanted population remain unknown because they are only presented in small series or case reports. Our objective was to study renal sparing surgery for kidney graft renal cell carcinomas (RCC) in a multicenter cohort. Data were collected from 32 French transplantation centers. Cases of renal graft de novo tumors treated as RCC since the beginning of their transplantation activity were included. Seventy-nine allograft kidney de novo tumors were diagnosed. Forty-three patients (54.4%) underwent renal sparing surgery. Mean age of grafted kidneys at the time of diagnosis was 47.5 years old (26.1–72.6). The mean time between transplantation and tumor diagnosis was 142.6 months (12.2–300). Fifteen tumors were clear cell carcinomas (34.9%), and 25 (58.1%) were papillary carcinomas. Respectively, 10 (24.4%), 24 (58.3%) and 8 (19.5%) tumors were Fuhrman grade 1, 2 and 3. Nine patients had postoperative complications (20.9%) including four requiring surgery (Clavien IIIb). At the last follow-up, 41 patients had a functional kidney graft, without dialysis and no long-term complications. NSS is safe and appropriate for all small tumors of transplanted kidneys with good long-term functional and oncological outcomes, which prevent patients from returning to dialysis.

Abbreviations: CT, computer tomography; NSS, nephron sparing surgery; RCC, renal cell carcinomas; mTOR, mammalian target of rapamycin; US, ultrasonography

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Introduction

Renal transplantation is the first choice for the treatment of end-stage renal disease. The incidence of cancer has increased with immunosuppressive therapy in transplanted patients. The majority of renal cell carcinomas (RCC) occur in the native kidney, with only 10% of RCC occurring in the allograft (1). Overall incidence of RCC occurring in the transplanted population is 4.6%, which is higher than that in the general population. Partial nephrectomy for RCC was first described by Czerny in 1887 (2) and became a common technique for renal tumors. It was well described by Vermooten (3), especially for patients with a solitary kidney. For native kidneys, nephron sparing surgery (NSS) is recommended and currently accepted for tumors ≤7 cm in their greatest dimensions and limited to the kidney. For some certain tumors >7 cm limited to the kidney, partial nephrectomy is feasible if removable without important morbidity and with negative tumoral margins (4). There is no recommendation for transplanted patients. Before a recent report (5), the literature gave no results concerning NSS in the transplanted population because there were only small series or case reports. The purpose of this study was to describe the French
experience of renal sparing surgery in de novo kidney graft RCC in a large multicenter cohort. We analyzed the circumstances of diagnosis, the criteria leading to renal sparing surgery, and short- and long-term complications including specific and overall survival.

Materials and Methods
We conducted a national retrospective, multicenter study. Data were collected from 32 French transplantation centers. Each center was asked to report its cases of graft de novo tumors treated as RCC in their renal transplant population since the beginning of their transplantation activity. According to the HAS recommendations (Haute Autorité de Santé, November 2007), all transplanted patients are followed annually with abdominopelvic and renal graft computer tomography (CT) scan or ultrasonography (US). Renal graft tumors were classified using their radiological characteristics. The Fuhrman grading system and TNM staging 2009 were used. Since grafts are not surrounded by fatty tissue as are native kidneys, we adapted stages T3 and T4 of the TNM staging (Table 1) for gifted kidneys. Histologic subtypes were stratified according to the 1997 UICC classification. All charts were retrospectively reviewed. All donors underwent screening before procurement (CT scan or US) and no graft presented any suspect lesion. Only patients presenting de novo renal graft tumor treated by renal sparing surgery were included. Only renal transplant recipients with a functional renal graft were included. Clavien Dindo’s surgical complications grading system was used to analyze postoperative morbidity. Descriptive statistics were presented with Excel 2007 (Microsoft®, Redmond, WA) and statistical tests performed with statistical programs StatView® (SAS, Cary, NC) and Graphpad Prism® (GraphPad Software, La Jolla, CA). The Mann–Whitney t-test or one-way analysis of variance test was used to compare continuous variables, and the chi-squared test was used to determine differences in categorical variables.

Results
Between January 1988 and April 2012, 41 806 patients were transplanted in 32 centers in France. Seventy-nine de novo tumors of allograft kidneys were diagnosed. Among this cohort, 43 patients (54.4%) underwent renal sparing surgery. The mean patient age at the time of diagnosis was 50 years old (27.4–81.6), and 38 years old (14.8–62.5) was the mean age at the time of transplantation. The mean time between the first day of dialysis and the date of transplantation was 46.9 months (0.7–219.8). The sex ratio was 2.3 (30 male, 13 female patients). Mean donor age was 36.8 years old (17–64). Mean age of the grafted kidney at the time of diagnosis was 47.5 years old (26.1–72.6). The mean time between transplantation and tumor diagnosis was 142.6 months (12.2–300). Etiologies of recipients’ end-stage renal disease were glomerulonephritis (n = 22), vascular nephritis (n = 7), uropathy (n = 6), hypertension (n = 3), diabetic nephropathy (n = 2), acute infection (n = 1) and genetic (n = 2). All tumors were asymptomatic except one discovered on an US performed for a decreased renal function. Asymptomatic tumors were diagnosed during the systematic follow-up: 31 with US, 10 with CT scan and 1 with MRI screenings. As recommended by the HAS, in France all transplanted patients were followed annually with an abdominopelvic and graft US or CT scan. The mean time between diagnosis and surgery was 246.8 days (10–2449). All patients underwent NSS, which was justified by each team when the tumor size was less than 4 cm and had a cortical localization. All tumors were analyzed and classified by histological type, Fuhrman grade and pTNM stage.

Histology
Nineteen tumors had biopsies prior to surgery (44.2%). Biopsy results and postsurgical histology were discordant in two cases (benign on biopsies and RCC on definitive histology). Fifteen tumors were clear cell carcinomas (34.9%), and 25 (58.1%) were papillary carcinomas. One (2.3%) had both characteristics (mixed tumor: clear cell and papillary carcinoma) and two were oncocytomas (4.65%). The mean tumor size was 26 mm (12–45) (Table 2). Ten RCC (24.4%) were Fuhrman grade 1, 24 were Fuhrman grade 2 (58.3%) and 8 were RCC tumors characterized as Fuhrman grade 3 (19.5%). According to our modified pTNM classification, 39 tumors were pT1a (95.1%), 1 was pT1b (2.4%) and 1 was pT3a (2.4%). All surgical margins were negative.

Renal graft function
Preoperative mean creatinine was 152.7 μmol/L (80–250) and 167.4 μmol/L (73–289) 1 month after surgery. The increase in the creatinine level was not significant. No recipients returned to dialysis after surgery.

Surgical complications
Nine patients had postoperative complications (20.9%). Among them, three had a urinary fistula; two needed revision surgery (one Clavien II and two Clavien IIIb). None of them had dialysis after surgery. Two had ureteral strictures, one secondary to entrapment in the aponeurosis running suture (Clavien IIIb), the other secondary to a
postseptic ischemia (Clavien IIIb). Other complications were one lymphocele (Clavien I), one hematoma (Clavien I), one deep venous thrombosis (Clavien II) and one urinary tract infection (Clavien II).

**Immunosuppression**

All immunosuppressive regimen modifications were done after surgery and definitive histologic results. The immunosuppressive regimens used are described in Table 3. Among the 43 cases of NSS, six patients were taken off calcineurin inhibitor (three cyclosporine and three tacrolimus). Six patients received additional mTOR (mammalian target of rapamycin) after the surgery and the RCC diagnosis. Among these patients, three had papillary RCC and three clear cell RCC. Switch time-lapse was unknown but no related surgical complication was reported (such as delayed wound healing). Data were missing for seven cases.

**Long-term outcomes and statistical analysis**

The mean time of follow-up was 35.2 months (6–108.7). At the last follow-up, 41 patients had a functional kidney graft without dialysis and no long-term complications. One patient had a nonfunctional grafted kidney, requiring dialysis after chronic allograft rejection. Patient-specific survival was 100%. One patient died 29.5 months after the transplantation from mesenteric ischemia with a functional grafted kidney. All patients were cured from their cancer without any local or distant recurrence.

No statistical differences were found between the renal clear cell carcinoma group and the papillary carcinoma group for all the variables described in Table 2.

**Discussion**

The incidence of RCC among kidney transplanted patients is between 0.19% (6) and 0.5% (7). This incidence will probably increase progressively because renal transplant recipients and donors are older. It is accepted that NSS in the general population can achieve long-term survival for the treatment of incidental and low-stage RCC without compromising the efficacy of cancer treatment (8,9) and with a 15-year survival rate of 96.4%. The review of literature remains poor about the treatment of kidney graft tumors using NSS. Indeed there are fewer than 30 case reports in the literature (5,10–15) with acceptable outcomes.

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**Table 2: Recipients and tumors characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Clear cell carcinoma</th>
<th>Papillary carcinoma</th>
<th>Other</th>
</tr>
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<tbody>
<tr>
<td>Number of kidney graft tumors</td>
<td>43</td>
<td>15</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>Recipient’s gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30</td>
<td>12</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>2</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Mean age at diagnostic (year)</td>
<td>50 (27.4–81.6)</td>
<td>53.32 (33.8–81.6)</td>
<td>46.42 (27.4–64.8)</td>
<td>63.78 (57.2–69.9)</td>
</tr>
<tr>
<td>Mean age at transplantation (year)</td>
<td>38 (14.8–62.5)</td>
<td>40.7 (20.5–62.5)</td>
<td>34.8 (14.8–60.4)</td>
<td>54.5 (50.4–57.6)</td>
</tr>
<tr>
<td>Mean age of the allograft at diagnosis (year)</td>
<td>47.54 (26.1–72.6)</td>
<td>52.33 (36.1–62.8)</td>
<td>42.65 (26.1–60.2)</td>
<td>57.67 (42.6–72.6)</td>
</tr>
<tr>
<td>Diagnosis time-lapse (month)</td>
<td>142.6 (12.2–300)</td>
<td>152.58 (36.1–300)</td>
<td>140.34 (12.1–232.4)</td>
<td>112.05 (19.9–212.5)</td>
</tr>
<tr>
<td>Mean size of tumor (mm)</td>
<td>26 (12–45)</td>
<td>24.8 (12–38)</td>
<td>26.2 (12–45)</td>
<td>30 (20–40)</td>
</tr>
<tr>
<td>Mean time between diagnosis and surgery (day)</td>
<td>246.8 (10–2449)</td>
<td>158.5 (14–950)</td>
<td>327.3 (10–2449)</td>
<td>41 (29–59)</td>
</tr>
<tr>
<td>pTNM</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>pT1a</td>
<td>39</td>
<td>15</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>pT1b</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>pT3a</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Follow-up mean time (month)</td>
<td>29.6 (0.65–100.62)</td>
<td>35.16 (1–83.8)</td>
<td>24.12 (0.65–76.7)</td>
<td>46.96 (18.2–100.6)</td>
</tr>
</tbody>
</table>

**Table 3: Immunosuppressive regimens**

<table>
<thead>
<tr>
<th>Immunosuppressive regimens</th>
<th>Number</th>
<th>Modifications after graft tumor diagnosis</th>
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</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>AZA + corticosteroid</td>
<td>2</td>
<td>AZA replaced by rapamycin (1 patient)</td>
</tr>
<tr>
<td>Cyclosporine + corticosteroid</td>
<td>6</td>
<td>None</td>
</tr>
<tr>
<td>Cyclosporine + AZA + corticosteroid</td>
<td>17</td>
<td>Cyclosporine replaced by everolimus (1 patient)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyclosporine and AZA replaced by tacrolimus (1 patient)</td>
</tr>
<tr>
<td>Cyclosporine + MMF + corticosteroid</td>
<td>10</td>
<td>Cyclosporine replaced by everolimus (1 patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyclosporine withdrawal (1 patient)</td>
</tr>
<tr>
<td>Tacrolimus + AZA + corticosteroid</td>
<td>3</td>
<td>AZA withdrawal</td>
</tr>
<tr>
<td>Tacrolimus + MMF + corticosteroid</td>
<td>4</td>
<td>Tacrolimus replaced by rapamycin (1patient)</td>
</tr>
<tr>
<td>Tacrolimus + corticosteroid</td>
<td>2</td>
<td>Tacrolimus replaced by rapamycin (1 patient)</td>
</tr>
</tbody>
</table>

AZA, azathioprine; MMF, mycophenolate mofetil.
outcomes for surgery. No multicenter study has been established yet. The kidney-transplanted population is a sensitive population because of immunosuppressive therapies and the presence of a single functional kidney. No consensus is established about diagnosis and treatment of these tumors. Most de novo renal graft tumors were asymptomatic and discovered on systematic annual screenings as previously described (6,15). Two percutaneous renal mass biopsies (10.2%) were discordant with the final pathological analysis of the tumor (benign on biopsies and RCC on definitive histology). Annual follow-up of transplanted patients with abdominopelvic and renal graft CT scan or US allows early asymptomatic small tumor diagnosis. Halverson showed a sensitivity of 96% and a specificity of 100% for biopsies of small renal masses, which is better than in our series (16). However, systematic biopsies for tumors of grafted kidneys should be performed. Indeed, biopsies may reveal benign lesions in 15.9% (17) to 21% of patients (18) with tumors smaller than 4 cm. The complications of percutaneous renal mass biopsies are minor and biopsy may prevent surgery for benign lesions (19). In these cases, watchful waiting is indicated. In case of radiological modifications of the tumor, a new biopsy or treatment should be discussed in order to diagnose “false negative” patients. In our cohort, two patients had oncocytomas on the final pathologic microscopic analysis of the tumor. Those patients did not have primary biopsies and were treated according to CT-scan data. We believe that surgery could be elected by a systematic application of percutaneous biopsies of tumors.

In our experience, papillary carcinomas were more frequent (58.1%) than RCC (34.9%). Papillary carcinoma was commonly accepted as an indication of transplantectomy because of its multifocal characteristics. Nevertheless according to Mejean et al (20), papillary carcinoma histology is not an argument against conservative surgery. On the contrary, they are less aggressive with a better prognosis than clear cell carcinomas (21). This is in agreement with our results; long-term oncologic and functional outcomes were similar in papillary carcinomas and clear cell carcinomas. Even if local recurrence occurs, Johnson et al (22) demonstrated the feasibility of repeated NSS on the same kidney for small tumors and argued that transplantectomy remains possible in case of recurrence. Some tumors such as renal lymphoma could mimic renal RCC. Posttransplant lymphoma disorder could thus be another diagnosis for a renal graft mass, especially when associated with regional adenopathy. Its reported incidence in the literature is very low (0.5% of all renal tumors) (23) and biopsies are recommended when imaging features are atypical (24). All margins were negative after surgery. Thickness of margins is not important and only positivity of margins constitutes a negative prognostic factor. This allowed preserving a functional nephron capital as much as possible without a guaranteed return to dialysis as in transplantectomy. NSS is an excellent treatment of RCC less than 4 cm in grafted kidneys. We believe that the indications of NSS should be broadened to tumors more than 4 cm in width. As shown by Becker et al (25), specific survival was 100% after 15 years of follow-up in the general population. Feasibility of large NSS in a renal transplant was demonstrated recently by Kaouk et al (26).

Alternatives for NSS are focal treatments such as cryoablation (CA) or radiofrequency (RF) ablation. A few cases are described in the transplanted population (27,28). However, Hui et al (29), in a meta-analysis comparing percutaneous RF and NSS, found no difference in carcinologic results. This was confirmed in single kidney populations with RF (30) and CA (31). Some authors showed a 100% cancer-free survival for a median follow-up of 46 months for CA (32) with excellent renal function outcomes (33–35). A few series comparing RF ablation to CA did not show significant differences in oncological and functional outcomes (36,37). However, a meta-analysis showed that local recurrence is overall more frequent after RF (11.7%) than CA (4.6%) (38). According to the American Urological Association, operative complications were similar between open NSS (6.3%), CA (4.9%) and RF (6%), with a significantly higher complication rate for laparoscopic NSS (9%) (39). Furthermore, ablative therapies can be used as a treatment of post-NSS recurrence (40). These results are attractive for solitary kidney populations such as transplanted patients because of their low morbidity and have to be confirmed by long-term functional and oncological outcomes.

De novo kidney graft tumors were less aggressive than in the general population. According to our results, mean time between diagnosis and treatment was 8.2 months (0.3–81.6). This long time lapse can be explained by the lack of guidelines for the treatment of these tumors, their small size and slow growth rate leading to a period of watchful waiting before treatment. Some teams decided upon a watchful waiting management with regular CT scan or US screenings for small renal masses. This alternative is currently discussed in the literature for native renal carcinomas (41). However, could such management be proposed in immunosuppressed patients? The patient treated 81.6 months after the diagnosis did not have local or distant recurrence. The final staging was pT1. We believe this can be explained by the more frequent occurrence of papillary and low-grade carcinoma in the transplanted population compared with the general population (6). Evolution of such tumors can be very slow and some teams may choose watchful waiting with repeat CT scan or US.

There are no recommendations about the posttreatment follow-up. We believe that patients should undergo baseline chest and abdominal scan (CT or MRI) within 3 to 6 months following surgery with continued imaging (US, CT or MRI) every 6 months for at least 3 years, and annually thereafter until year 5 as recommended by the American Urological Association for moderate- and high-risk patients (42).
Immunosuppressive regimens before graft tumor diagnosis and their adjustments after diagnosis were very heterogeneous. The relationship between immunosuppression and de novo graft tumors was impossible to highlight. After partial nephrectomy or minimally invasive treatment, immunosuppressive treatment was maintained in 83% of patients. There are no current recommendations concerning modifications of immunosuppressive regimens after cancer in transplanted organs. Anti-tumoral properties of mTOR inhibitors seem to be the most interesting targeted therapy in these indications. None of the six patients switched to mTORs had postoperative complications and the disease-free survival was 100%.

The limitations of our study are the retrospective and historical characteristics of this study and, despite being the largest cohort described, the small number of patients. The rare character of kidney graft tumors makes the feasibility of a large prospective study difficult. Missing data were the type of clamping (if done during the surgery), warm ischemia time during NSS and exact surgical technique. We do not believe that these data affect the oncological outcomes regarding our results.

This is the largest series of NSS in renal allografts reported so far. NSS is a safe and appropriate indication for all small tumors of transplanted kidneys with very good long-term functional and oncological outcomes preventing patients from returning to dialysis. Percutaneous renal mass biopsies may prevent unnecessary surgery of benign masses. Noninvasive therapies must be considered as alternatives for certain tumors and should gain interest in the future.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

References


