De Novo Kidney Graft Tumors: Results From a Multicentric Retrospective National Study

X. Tillou a,b,* A. Doerfler a, S. Collon b, F. Kleinclauss c, J.-J. Patard d, L. Badet e, B. Barrou f, M. Audet g, H. Bensadoun h, E. Berthoux h, P. Bigot i, J.-M. Boutin i, Y. Bouzguenda j, D. Chambade k, R. Codas a, J. Dantai m, J. Deturmeny m, M. Devonec o, F. Dugardin p, J.-M. Ferrière q, A. Erauso r, B. Feuillu s, M. Gigante t, L. Guy u, G. Karam v, T. Lebret w, Y. Neuzillet x, C. Legendre y, T. Perez y, J.-P. Rerolle z, L. Salomon aa, F. Sallusto bb, C. Sénéchal cc, N. Terrier dd, R. Thuret ee, G. Verhoest ff, J. Petit gg and members of “Comité de Transplantation de l’Association Française d’Urologie (CTAFU)”

a CHU de Caen, Urology and Transplantation, Caen, France
b CHU de Besançon, Urology and Transplantation, Besançon, France
c CHU de Caen, Orthopedic Surgery, Caen, France
d Hôpital Kremlin Bicêtre, Urology and Transplantation, Paris, France
e Hôpital Edouard Herriot, Urology and Transplantation, Lyon, France
f Hôpital La Pitié Salpêtrière, Transplantation, Paris, France
g CHU de Strasbourg, Urology and Transplantation, Strasbourg, France
h CHU de Saint Etienne, Nephrology, Saint Etienne, France
i CHU d’Angers, Urology and Transplantation, Angers, France
j Hôpital Bretonneau, Urology and Transplantation, Tours, France
k Hôpital Jeanne de Flandre, Nephrology, Lille, France
l Hôpital Saint Louis, Urology and Transplantation, Paris, France
m CHU de Nantes, Nephrology, Nantes, France
n Hôpital de la Conception, Urology and Transplantation, Marseille, France
o CHU Lyon Sud, Urology and Transplantation, Lyon, France
p CHU de Rouen, Urology and Transplantation, Rouen, France
q CHU de Bordeaux, Urology and Transplantation, Bordeaux, France
r CHU de Brest, Urology and Transplantation, Brest, France
s CHU de Nancy, Urology and Transplantation, Nancy, France
t CHU de Nice, Urology and Transplantation, Nice, France
u CHU de Clermont-Ferrand, Urology and Transplantation, Clermont Ferrand, France
v CHU de Nantes, Urology and Transplantation, Nantes, France
w Hôpital Foch, Urology and Transplantation, Suresnes, France
x CHU de Reims, Urology and Transplantation, Reims, France
y CHU de Limoges, Nephrology, Limoges, France
za CHU Henri Mondor, Urology and Transplantation, Créteil, France
zb CHU de Toulouse, Urology and Transplantation, Toulouse, France
zc CHU de Point à Pitre, Urology and Transplantation, Point à Pitre, France
zd CHU de Grenoble, Urology and Transplantation, Grenoble, France
ze CHU de Montpellier, Urology and Transplantation, Montpellier, France
zf CHU de Rennes, Urology and Transplantation, Rennes, France
* Corresponding author: Xavier Tillou, xavtillou@hotmail.com

De novo tumors in renal allografts are rare and their prevalence is underestimated. We therefore analyzed renal cell carcinomas arising in renal allografts through a retrospective French renal transplant cohort. We performed a retrospective, multicentric survey by sending questionnaires to all French kidney transplantation centers. All graft tumors diagnosed after transplantation were considered as de novo tumors. Thirty-two centers participated in this study. Seventy-nine tumors were identified among 41,806 recipients (Incidence 0.19%). Patients were 54 men and 25 women with a mean age of 47 years old at the time of diagnosis. Mean tumor size was 27.8 mm. Seventy-four (93.6%), 53 (67%) and 44 tumors (55.6%) were organ confined (T1–2), low grade (G1–2) and papillary carcinomas, respectively. Four patients died of renal cell carcinomas (5%). The mean time lapse between transplantation and RCC diagnosis was 131.7 months. Thirty-five patients underwent conservative surgery by partial nephrectomy (n = 35, 44.3%) or radiofrequency (n = 5; 6.3%). The estimated 5 years cancer specific survival rate was 94%. Most of these tumors were small and incidental. Most tumors were papillary carcinoma, low stage and low grade carcinomas. Conservative treatment has been preferred each time it was feasible in order to avoid a return to dialysis.

Key words: renal transplantation, graft tumor
Introduction

Incidence of renal cell carcinoma (RCC) in dialyzed and renal transplant recipients (RTR) has often been studied. Most publications focus on cancers developing on native kidneys. Incidence of such cancers varies from 1% to 5% (1–3) and the rate of papillary carcinoma was found to be higher than in nondialyzed and nontransplanted populations, (25–35% vs. 10–15%, respectively). There is no such data available on tumors developing on kidney transplants. These tumors can arise in three circumstances: renal carcinoma transmitted by the donor, de novo malignancies arising in the recipient after transplantation with a functional, or a nonfunctional graft. De novo cancers arising in kidney grafts are rarely described in the literature and their prevalence is probably underestimated. In The Cincinnati Transplant Tumor Registry, Penn found that kidney cancers represented 4.6% of all cancers occurring in transplant recipients. Among these cancers, only 10% occurred in kidney grafts (2). Then Incidence has only been calculated on small series (4,5).

The purpose of our study was the calculation of the incidence of de novo kidney graft RCC in a large retrospective cohort in France, and the analysis of the circumstances of diagnosis, treatment and outcome.

Patients and Method

We conducted a national retrospective, multicenter study. Thirty-two transplant centers, belonging to the Renal Transplantation Committee of the French Urological Association (CTAFU) were asked to participate in this study. Each center was asked to report its cases of kidney graft tumors and the number of kidney transplantations performed since the beginning of their transplantation activity. The survey concerned demographic characteristics of RTR, diagnosis, staging, treatment and outcomes of RCC as well as the type and duration of immunosuppression. As recommended by the HAS (Haute Autorité de Santé, November 2007), in France all transplanted patients were to be followed annually with an abdominopelvic and graft ultrasonography (US) or CT scan. RCC were classified according to the 2002 TNM staging and to the Fuhrman grading systems. Since grafts are freed of all surrounding fatty tissue before transplantation the usual T3 and T4 stages relative to Gerota’s fascia cannot apply. We adapted the TNM staging system with the stages described in Table 1. Histologic subtypes were stratified according to the 1997 UICC classification (6). We included all RTR presenting with a de novo graft tumor diagnosed after the transplantation. In all cases, donors underwent pretransplantation screening (by CT or US) which was normal. RCC arising in functional or nonfunctional grafts were included. Graft lymphoma, benign oncocytomas and neuroendocrine tumors, which are not specifically kidney cancers, were excluded from the study.

Seventy-nine patients transplanted, between January 1988 and December 2009, were included in the study. All patients underwent preoperative staging with an abdominal CT scan and a chest X-Ray. Statistical analyses were done with GraphPad Prism v5.0© (GraphPad, San Diego, CA, USA). Prognostic survival factors were analyzed using a univariate analysis with a log rank-Mantel Cox test and graphs were represented according to the Kaplan Meier method. For specific survival and prognostic factors, events used to create Kaplan-Meyer plots were patient’s death due to graft RCC (excluding death from others causes). Patients continued to be followed during dialysis until death or until another renal transplantation. Date of follow-up was last in-office examination or the date of the death.

Results

Between January 1988 and December 2009, 41 806 patients were transplanted in the 32 centers participating to this study. Among this cohort, 79 RTR were diagnosed with a kidney graft RCC and were included in the study. The calculated incidence was 0.19%. The mean patient age at the time of diagnosis was 47 years (14.2–81.6) and 35.5 years (5.7–66.4) at the time of transplantation. Results are given in Table 2. The mean time between transplantation and diagnosis was 131.7 months (0.9–244). Fifteen grafts were nonfunctional and patients had returned to dialysis before the tumor was diagnosed. The sex ratio was 2.16 with 54 men and 25 women. The mean donor age was 36 years old (13–64). Mean age of kidney grafts at the time of diagnosis was 45.8 years (14.9–67.6). Etiology of end stage renal disease for RTR was: glomerulonephritis (38), interstitial nephritis (6), uropathy (19), arterial hypertension (3), diabetic nephropathy (3), acute infection (3), genetic disease (1) and unknown (6).

Nine tumors (11.4%) were diagnosed following imaging for graft pain (n = 5, 6.3%), gross hematuria (n = 2, 2.5%), asthenia and loss of weight (n = 1, 1.2%) and/or hyperthermia (n = 3, 3.8%). Two (2.5%) tumors were diagnosed by US, which was performed for increased serum creatinine, and
systematic imaging, by US or CT scan. One tumor was diagnosed by Magnetic Resonance Imaging performed because of arterial hypertension. Before treatment, 30 patients had graft tumor biopsies and nine series of biopsies were fresh-mounted for microscopic examinations. Table 3 compare symptomatic tumors and tumors diagnosed by screening or incidental imaging or nephrectomy.

### Treatment

Total nephrectomy was performed in 38 cases, among which 23 grafts were functional. Criteria for a total nephrectomy were: a low functioning graft, the papillary subtype, a central localization and size superior to 4 cm. Nephron sparing surgery was performed on 35 recipients with functional graft. Criteria for partial surgery were a cortical localization and a tumor size below 4 cm. Partial nephrectomy did not compromise renal function in our series and no patient returned to dialysis after surgery. Five tumors were removed by percutaneous radiofrequency. This option was chosen in three cases because patients refused surgery, in one case because the patients was morbidly obese and in one cases because the patient had multiple cancers.

### Immunosuppression

The immunosuppressive regimens used are described in Table 4. Among the 35 cases of nephron sparing surgery, six patients were taken off ciclosporine and four patients received additional mTOR (target of rapamycin). Data were missing for seven cases.

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**Table 2**: *De novo* graft tumors characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of kidney graft tumors</td>
<td>79</td>
</tr>
<tr>
<td>Recipient’s gender</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>54</td>
</tr>
<tr>
<td>Women</td>
<td>25</td>
</tr>
<tr>
<td>Mean age at transplantation (year)</td>
<td>35.5 (5.7–66.4)</td>
</tr>
<tr>
<td>Mean age at diagnostic (year)</td>
<td>47 (14.2–81.6)</td>
</tr>
<tr>
<td>Mean age of the allograft at diagnosis (year)</td>
<td>45.8 (14.9–67.6)</td>
</tr>
<tr>
<td>Diagnosis time-lapse (month)</td>
<td>131.7 (0.9–244)</td>
</tr>
<tr>
<td>Mean size of tumor (mm)</td>
<td>27.8 (6–100)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>32</td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>44</td>
</tr>
<tr>
<td>Mixed</td>
<td>3</td>
</tr>
<tr>
<td>Fuhrman grade</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Nephron sparing surgery</td>
<td>35</td>
</tr>
<tr>
<td>Transplantectomy</td>
<td>38</td>
</tr>
<tr>
<td>Radiofrequency</td>
<td>5</td>
</tr>
<tr>
<td>Medical supervision</td>
<td>1</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
</tr>
<tr>
<td>Mean time (month)</td>
<td>38.1 (0.7–148.5)</td>
</tr>
<tr>
<td>Specific DeathsVar</td>
<td>4</td>
</tr>
<tr>
<td>Variation of sera creatinine (µmol/L)</td>
<td>14 (–58 +100)</td>
</tr>
</tbody>
</table>

2 (2.5%) on graft biopsies performed to assess acute or chronic rejection. Six (7.6%) tumors were diagnosed after nephrectomy for chronic rejection of nonfunctional grafts. Sixty tumors (76%) were diagnosed thanks to an annual systematic imaging, by US or CT scan. One tumor was diagnosed by Magnetic Resonance Imaging performed because of arterial hypertension. Before treatment, 30 patients had graft tumor biopsies and nine series of biopsies were fresh-mounted for microscopic examinations. Table 3 compare symptomatic tumors and tumors diagnosed by screening or incidental imaging or nephrectomy.

**Table 3**: Comparison of symptomatic tumors and tumors diagnosed by screening or incidental imaging or nephrectomy

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Symptomatic</th>
<th>Incidental</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of kidney graft tumors</td>
<td>9</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Recipient’s gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>4</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>5</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Mean age at transplantation (years)</td>
<td>34.4 (14.2–58)</td>
<td>36.4 (5.7–63.4)</td>
<td>0.71</td>
</tr>
<tr>
<td>Mean age at diagnostic (years)</td>
<td>43.4 (31–63)</td>
<td>47.6 (14.2–69)</td>
<td>0.36</td>
</tr>
<tr>
<td>Mean age of the allograft at diagnosis (years)</td>
<td>41.3 (25.1–63.4)</td>
<td>46.9 (14.9–72.6)</td>
<td>0.35</td>
</tr>
<tr>
<td>Diagnosis time-lapse (months)</td>
<td>109.4 (60–172.9)</td>
<td>138.9 (0.9–300)</td>
<td>0.17</td>
</tr>
<tr>
<td>Mean size of tumor (mm)</td>
<td>41.6 (10–100)</td>
<td>26.1 (6–80)</td>
<td>0.53</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>3</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>5</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>1</td>
<td>2</td>
<td></td>
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<tr>
<td>Fuhrman grade</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1</td>
<td>1</td>
<td>14</td>
<td></td>
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<tr>
<td>2</td>
<td>7</td>
<td>31</td>
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</tr>
<tr>
<td>3</td>
<td>1</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephron sparing surgery</td>
<td>0</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Transplantectomy</td>
<td>8</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Radiofrequency</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Medical supervision</td>
<td>0</td>
<td>1</td>
<td></td>
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<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean time (months)</td>
<td>25.7 (0.7–92.7)</td>
<td>40.7 (1–148.5)</td>
<td></td>
</tr>
<tr>
<td>Specific deaths</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Histology

Forty-four tumors were papillary carcinomas (55.7%) and 32 were clear cell carcinomas (38.3%; Table 2). Three were mixed carcinomas (papillary and clear cell carcinoma). Twelve tumors were multifocal (seven papillary carcinomas, three mixed RCC and two clear cell carcinomas) and seven were cystic tumors. Sixteen tumors were Fuhrman grade 1, thirty-eight were Fuhrman grade 2 and fifteen were Fuhrman grade 3. Mean size was 27.8 mm (6–100). According to our modified TNM classification of kidney tumors, 74 tumors (93.6%) were classified T1 or T2N0M0, five (6.3%) were invasive (three with lymph nodes invasion, one with vascular extension and one with a metastatic disease).

Oncological outcomes and follow-up

Mean time of follow up was 38.1 months (0.7–148.5). The 5 years specific survival rate was 94%. Four patients died from their graft tumor and all had symptomatic tumors at the time of diagnosis. There TNM status were: one pT2N2M0, one pT3aN0M0, one pT3N2M0 and one pT4N0M0 (psosas muscle invasion). Two patients with locally invasive tumors were still alive but had a short-term follow-up (<6 months). After graft loss, if transplantectomy was chosen as treatment, mean follow up time was 45.4 months (0.7–164.2). However, for 12 patients follow up didn’t exceed 18 months. Five patients were transplanted a second time with mean delay after transplantectomy of 58.6 months (21.9–71.9).

Functional outcomes

No graft was lost when a conservative treatment was performed. The main complications after nephron sparing surgery were urinary leaks in three patients (8.5%) and hematomas in another three patients (8.5%). Renal function after conservative treatment did not change. The mean variation of sera creatinine after conservative surgery was 16 μmol/L (56–100).

Specific survival prognostic factors

Univariate analysis of specific survival was statistically significant for the presence of symptoms at the time of diagnosis (p = 0.01) and for a tumor size above 40 mm (p < 0.0001). Histological type and tumor grade were not significant prognostic factors (Figure 1).

Discussion

Characteristics of de novo kidney allograft RCCs is currently unknown. The first case of a de novo tumor arising in a transplanted kidney was reported in 1988 by Scott (7), then 42 cases were described in 35 international publications excluding French reports (4,8–41). These publications were mostly case reports or small series that did not exceed five cases. Only Penn (2) from the Cincinnati Transplant Tumor Registry, reported 24 cases among 8091 de novo cancers in RTR. Incidence, treatment and histological types of these tumors were not detailed. Barama (4) reported respectively three cases of de novo cancer in kidney allografts. Incidence was 0.5% in his series, which is higher than our 0.19% incidence. Our series was compromised by the very low incidence of kidney graft tumor. Thus data presented in this study must be interpreted with cautious. However, being the largest study so far, we can nonetheless derive from it valuable information about an unknown pathology.

The reported time between the date of transplantation and the development of kidney carcinoma in transplanted kidneys is extremely variable, ranging from 9 to 228 months (4,12). This finding is consistent with our series. A short period of time, between the transplantation and the diagnosis of kidney graft tumor, may suggest that it is transmitted from the donor. The time limit between transmitted tumors or de novo tumor remains unclear. Penn (2) considered tumors diagnosed less than 2 years after transplantation as transmitted kidney tumors, but few sustain this arbitrary cut off line. Wunderlich et al. (42), in their retrospective study of 10 997 donor kidneys, identified 30 kidneys (0.273% of kidneys and 0.546% of donors) with renal carcinomas at the time of the graft preparation before transplantation. Sixty seven percent of these tumors were smaller than 20 mm and were removed before transplantation. After transplantation, 16 of the 30 grafts developed a RCC between 3 and 12 years after transplantation. The authors conclude that a significant number of these cancers...
were present in the parenchyma at the time of transplantation. Park (32) reports a case of a kidney graft tumor occurring 258 months after transplantation and considers it as transmitted from the donor. He further supports this argument by performing DNA banding thereby confirming that the tumor originated from donor cells. DNA analysis could be useful to distinguish the origin of the tumor between the renal allograft and the native kidneys as described by Lotan (29). Gunji (20) suggested that de novo kidney graft cancer may develop rapidly after transplantation, as their case was diagnosed after only 9 months. The natural history of independent tumors is difficult to define, particularly in an immunodepressed patient. It is impossible to categorically state whether a tumor arising from an allograft kidney represents de novo transformation or transplanted cancer.

The diagnosis of a native kidney malignancy in RTR was typically incidental, usually during regular follow-up imaging. The diagnosis was made using routine US or diagnostic tomography. As reported by Roupret (5), similar to the case of native kidney tumors, when kidney graft tumors were symptomatic, they had a worse prognosis (43).

Transplantectomy was justified by a tumor with a size above 40 mm or deeply located in the graft. Nephron sparing surgery is now recommended for native kidney tumors 40 mm in size. All series in the literature showed excellent carcinologic and functional results (44). Moreover, thickness of margins is not important and only positivity of margins constitutes a negative prognostic factor (45). For an optimal result, clear frozen section margins should be confirmed intraoperatively. In our series, nephron-sparing surgery (NSS) was the main alternative to transplantectomy in small tumors with a relatively low risk of recurrence in the remaining parenchyma. The recurrence after NSS in nontransplanted patients is estimated to be 0.6% (46). Multiple case reports have mentioned its feasibility in transplanted kidneys. In selected patients, NSS seems to be a safe procedure that allows an acceptable quality of life, avoiding immediate dialysis. After partial resection, kidney function is dependent on the quality of the remaining parenchyma. In our series, graft function did not change after partial surgery. Penn (2) reported eight cases of donor transmitted graft tumors, in which no recurrence was observed after conservative treatment. Opponents of partial surgery are mainly concerned by risks of recurrence (local and systemic), and by plurifocal localizations, especially in papillary carcinomas. Johnson (47) demonstrated the feasibility of repeated nephron sparing surgery on the same kidney for small tumors and argues that transplantectomy remains possible in case of recurrence. Others treatments were described in the literature such as radiofrequency and cryosurgery. In our series, patients treated with radiofrequency were not eligible for surgery for several reasons: surgery refusal, old age or other treated cancers. In the
literature, radiofrequency is used as treatment in similar cases (8, 12). However, Hui (48), in a meta-analysis comparing percutaneous radiofrequency and nephron sparing surgery, found no difference in carcinologic results. The potential advantages of radiofrequency over surgery include minimal invasiveness, avoiding damage to adjacent tissues, preserving the surrounding renal parenchyma and reducing complications rate, resulting in a shorter hospital stay. Radiofrequency was chosen in cases of a superficial localization, an excellent visualization of the lesion by US, and possible surgical difficulties. Cryosurgery is another treatment option described in the literature. Despite good results reported by authors, this therapeutic option is still under evaluation (36).

Immunosuppressive regimens before the discovery of the graft tumor and their adjustments after its diagnosis were very heterogeneous. The relationship between immunosuppression and de novo graft tumor was impossible to demonstrate. After partial nephrectomy or minimally invasive treatment, immunosuppressive treatment was maintained in 83% of our patients. There are no 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. Experience of immunotherapy or chemotherapy is seldom reported in the literature. Kunisch-Hope (24) and Kooistra (49) described treatment by interferon for a de novo metastatic kidney graft tumor after transplantectomy. The cancer completely disappeared, but the impact of immunosuppression interruption alone is not easy to evaluate. Among 20 adult RTR with metastatic RCC reported by Penn, there was a 50% fatal outcome despite discontinuation of immunosuppression, graft nephrectomy, cytotoxic therapy, immunotherapy and radiotherapy. Reduction of the tumor burden by nephrectomy and withdrawal of immunosuppressive therapy resulted in complete remission except in four patients. Presumably, in these patients the depressed immune system was not able to recover and to reject the donor-associated cancer. When there is evidence of rapid spontaneous regression of distant metastases, it is possible to avoid chemotherapy.

The most important information revealed by this study is the high rate of papillary and low-grade carcinomas. Hetet (50), in a review of the literature, finds that the proportion of these histological types of kidney graft cancers was similar to those in native kidneys cancers: 20–30%. However, in our series, papillary carcinomas represented more than 50% of the tumors. Papillary tumors have a better prognosis than clear cell carcinomas or other tumor types (51). In a review of the literature, Mejean (52) showed that the Fuhrman tumor grade is an independent survival prognostic factor. Our study did not confirm it in graft kidneys. The literature review carried out for this study found an overall 65% of low-grade tumors (Grade 1 and 2 of Fuhrman) in kidney graft tumors, which is similar to the findings in our series. We therefore conclude that de novo graft tumors seemed to be predominantly low grade and not aggressive. The recommended delay for transplantation after treatment of a neoplastic disease is 2 years (53). In our study, the average delay before transplantation of another kidney was 55 months. Development of tumors from the donor after transplantectomy had a good prognosis if the tumor was localized inside the graft. In cases of invasive tumors, discontinuation of immunosuppression allows, in theory, the immune system to eliminate neoplastic cells through the allo-reactivity, as described by Barrou (54). In our study when the tumor continued to grow despite discontinuation of immunosuppression, the survival delay was less than 6 months. The patient cared for by Barrou was retransplanted after 26 months. Tyden (39) reported a new transplant after only 7 months. This time lapse before retransplantation must be adapted to the tumor stage and patient follow-up, even if the graft tumor was locally invasive or metastatic. A period of 24 months free of recurrences or secondary suspicious lesions and after discontinuation of immunosuppression seems reasonable, as suggested by Ghasemian (17) and Barrou (54).

In France, HAS recommended an annual abdominopelvic and graft US screening at least. This recommendation was discussed regarding to American Society of Transplantation (AST) and European Dialysis and Transplantation Association (EDTA) publications. Despite many studies, AST and EDTA concluded, there are no prospective data to indicate how useful and cost-effective these screening strategies might be for RTR.

In France, HAS recommends at least an annual abdominopelvic and graft US screening. This recommendation was made following AST (55) and EDTA (56) publications. Despite many studies, AST and EDTA concluded that no prospective data indicates how useful and cost-effective these screening strategies might be for RTR. Given the absence of data, French Health institution such as HAS recommend such annual screening.

**Conclusion**

Ours is the largest series of RCCs arising in renal allografts reported so far. Even though occurring in the context of immune suppression, most of these tumors seemed to be small, incidental, low stage and low-grade carcinomas. Papillary histology is more frequent than in the general RCC population suggesting that distinct molecular pathways are involved in that setting. Oncological outcome was good except in case of symptomatic tumors. Conservative treatment, following recommendations of kidney cancer treatment, has been preferred each time it was feasible in order to avoid return to dialysis.

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Disclosure

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