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LETTER TO THE EDITORS

Nephron-sparing surgery for malignancies in kidney allografts

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Dear Editors,

Nephron-sparing surgery (NSS) is a well-recognized and established surgical procedure that was, historically, first proposed for patients with tumors of native kidneys in which renal parenchyma must be preserved [1].

NSS has undergone vast development in the last decades, and current American Urologist Association guidelines identify this surgical technique as the standard of care for localized RCC tumors ≤7 cm (stages T1a and T1b) [2].

Various reports have shown successful cases of NSS in RCC tumors of kidney allografts, although the indications and limits of this procedure are not well defined.

We report our single-center experience in partial nephrectomies for malignancies of kidney allografts in an attempt to discuss the main clinical and technical aspects.

We retrospectively reviewed the following clinical parameters: age, date of transplantation, time interval between transplant and tumor diagnosis, adaption of immunosuppressive therapy, creatinine levels before and 1 month after surgery, localization of the tumor, number and size of the lesions, histological type, TNM staging, Fuhrman grading system, operative time, need for hilar clamping, surgical access, postoperative complications, tumor recurrence, follow-up, cause of death, 1-year graft survival and patient survival.

Wilcoxon matched pairs test was used to evaluate the kidney graft function, comparing the serum creatinine levels before and 1 month after surgery.

After transplantation, all patients underwent clinical follow-up, including laboratory tests at least twice a year and ultrasound (US) once a year. In cases of suspicious lesions in the allograft found at US, an abdominal contrast CT scan was performed.

For all suspicious RCC confirmed at CT scan, and with a size ≤7 cm and limited to the allograft (Stage T1), we adopted a conservative approach to NSS.

Depending on the location of the tumor, we adopted a different surgical approach. In the case of peripheral lesions localized on the convex edge of the allograft, we opted for an extraperitoneal access, while an intraperitoneal approach, through a midline incision with renal hilum isolation, was preferred in the case of tumors on the medial side of the kidney, close to the hilum, or attached medially to the peritoneum.

Of the 1735 kidney transplants performed in our center from 1983 to 2014, eight patients (0,45%) developed a malignancy in the kidney allograft. Of these, 5 (62,5%) were stage 1 (tumor size of < 7 cm) and underwent NSS. The mean follow-up was 31.4 months (range 13–77 months).

Table 1 shows the main surgical data of the patients and the characteristics of the tumors.

All five surgical procedures were uneventful, and no postoperative complications were registered after surgery. Surgical margins were found to be negative in all cases. Mean creatinine levels before surgery and 1 month after surgery were 1.28 mg/dl and 1.32 mg/dl, respectively (P = NS).

Graft and patient survivals were 100% after 1 year of follow-up. No cases of tumor recurrence were diagnosed during the follow-up in any of the five patients. Patient 1 was noncompliant and suspended the immunosuppressive therapy, with consequent progressive chronic renal failure, and died 31 months after surgery. Patient 2 had an intestinal occlusion caused by a strangulated incisional hernia and died 13 months after NSS. The other three patients were alive, with a normal renal function, at the end of follow-up.

Traditionally, radical transplantectomy associated with the withdrawal of immunosuppression has been the treatment of choice for these tumors. Nevertheless, since the early 1990s, several studies have reported successful, isolated, cases of partial nephrectomy of the kidney allograft, with consequent graft salvage and avoidance of return to dialysis. To date, the literature on this topic is limited to around 30 case reports and only one, recent, multicenter study by a French group [3–7].

Consonant with our five successful cases, all the published studies have reported favorable results with partial nephrectomies, supporting the feasibility and the effectiveness of this surgical technique for kidney allograft tumors.

Table 1. Clinical data of the patients and characteristic of the tumors.

	Case 1	Case 2	Case 3	Case 4	Case 5
Year of NSS procedure	2004	2005	2008	2013	2014
Year of transplantation	1994	1996	1995	1986	1995
Age at transplantation (years)	50	61	11	37	47
Age at diagnosis of RCC (years)	60	70	24	64	65
Time lapse after transplant (years)	10	9	13	27	19
Creatinine before surgery (mg/dl)	1.1	1.6	1.0	1.5	1.2
Creatinine 1 month after surgery (mg/dl)	1.1	1.7	1.2	1.4	1.2
Immunosuppressive regimen	CSA + steroids	CSA+ steroids	CSA +steroids	CSA +steroids	CSA +steroids
Immunosuppressive modifications	No modifications	No modifications	CSA replaced by sirolimus	CSA replaced by sirolimus	CSA replaced by everolimus
Number of tumors	1	2	1	1	1
Tumor site on allograft	Upper pole/medial side	Upper pole/external side	Upper pole/medial side	Upper pole/external side	Upper pole/external side
Tumor size (mm)	20	40 and 30	45	18	10
Tumor histological type	Papillary carcinoma	Solitary fibrous tumor	Clear cell carcinoma	Papillary carcinoma	Clear cell carcinoma
p-TNM	pT1a	n.d.	pT1b	pT1a	pT1a
Fuhrman grade	G2	n.d.	G2	G1	G2
Surgical access	intraperitoneal	extraperitoneal	intraperitoneal	extraperitoneal	extraperitoneal
Hilar clamp	no	yes	yes	no	no
Surgical time (min.)	120	144	260	100	90

Tillou *et al.* recently reported the results of a multicenter study of 43 cases in which NSS was always performed and never was converted or required a total nephrectomy. Moreover, there were no cases of significant postoperative renal function impairment, and none of the recipients returned to dialysis within the first year after surgery. Patient-specific survival was 100%, with no case of tumor recurrence [7].

Even if these encouraging results seem to suggest NSS as the treatment of choice for *de novo* small tumors in kidney allografts, some aspects, such as diagnosis, surveillance, and treatment of these tumors, remain unclear and are the subject of debate.

In our patients, the preoperative diagnostic assessment of the tumors was limited to US and CT scan imaging, while other studies [5–7] recommend a systematic application of percutaneous biopsy prior to surgery. Halverson *et al.* [8]. found high sensitivity and specificity of biopsy in determining small renal masses, while Tillou *et al.* [7]. underlined that preoperative biopsies for tumors of grafted kidneys carry a low rate of complications and may prevent surgery for benign lesions.

Biopsies in native kidneys have evidenced a minimum risk of such complications as renal bleeding, subcapsular hematoma or, more rarely, tumor seeding, and it is conceivable that there are similar risks for biopsies of kidney allografts [9]. For these reasons, and because the role of preoperative biopsy in allograft tumors has yet to be validated and standardized, we think its use should not be adopted paradigmatically, but limited to cases of unclear preoperative radiological features.

Concerning the surgical technique, all the cases reported were undertaken with an extraperitoneal approach, usually through the previous Gibson incision, and the tumor was freed and enucleated by transecting the parenchyma with no renal pedicle control.

Otherwise, we adopted a different surgical approach depending on the location of the tumor. In two cases, the lesion lied on the medial side of the graft, very close to the hilar vessels, and we opted for an intraperitoneal approach, judging crucial the vascular control of the renal hilum. Our two cases of laparotomic NSS had a longer surgical time than those performed with extraperitoneal approach, but in these cases, we consider this surgical approach likely more appropriate and safer because the tumor is approached from a virgin territory, permitting an easier vascular control with possible hilar clamping, and minimizing the risks of bowel injuries.

There are still no specific recommendations regarding possible modifications of the immunosuppressive regimen after discovery of the renal graft tumor, and the various changes in regimens reported are quite heterogeneous. Before the arrival of mTOR (mammalian target of

rapamycin) inhibitors in the early 2000s, the main variations reported concerned withdrawal of azathioprine, minimization of CNI (calcineurin inhibitors) administration, or switching from cyclosporine to tacrolimus [3].

In the last 10 years, since there is some evidence to suggest that mTOR inhibitors have antitumor activity, there has been a trend toward an expanding use of these drugs after tumor diagnosis in transplanted patients. Everolimus is also specifically considered one of the target drugs for RCC and is currently approved for the treatment of advanced renal cancers [10]. Moreover, these drugs have a low nephrotoxicity and their use may help to prevent the long-term CNI-induced renal failure. Given our poor experience with these drugs just appeared on the market, we did not adopt any modification of the immunosuppressive therapy in the first two cases, while as our third patient, we decided to systematically replace cyclosporine with sirolimus or everolimus after diagnosis of the renal graft tumor. Otherwise, the French group [7] reported that only six of their 43 patients (14%) were switched to mTORs. Because of the lack of data, further detailed studies are necessary to establish the appropriate immunosuppressive regimen for these rare renal graft tumors.

In conclusion, our case series confirms that malignancies affecting kidney allografts are a rare but threatening event. NSS is a safe and effective procedure that, by preserving the graft function and avoiding the return of patient to dialysis, should be considered the best therapeutic option for small malignant kidney allograft neoplasms. In cases of medial side lesions close to the renal hilum, a laparotomic approach may be considered a safer and helpful choice. The role of preoperative biopsy and modification of immunosuppression remain unclear in the management of these tumors.

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References

1. Tsui KH, Ophoven A, Shvarts O, *et al.* Nephron-sparing surgery for renal cell carcinoma. *Rev Urol* 1999; **1**: 216.
2. Bellmunt J, Puente J, De Muro G, *et al.* SEOM clinical guidelines for treatment of renal cell carcinoma. *Clin Transl Oncol* 2014; **16**: 1043.
3. Barama A, St- Louis G, Nicolet V, *et al.* Renal cell carcinoma in kidney allografts: a case series from a single center. *Am J Transplant* 2005; **5**: 3015.
4. Chambade D, Meria P, Tariel E, *et al.* Nephron sparing surgery is a feasible and efficient treatment of T1a renal cell carcinoma in kidney transplant: a prospective series from a single center. *J Urol* 2008; **180**: 2106.
5. Tuzuner A, Cakir F, Akyol C, *et al.* Nephron-sparing surgery for renal cell carcinoma of the allograft after renal transplantation: report of two cases. *Transplant Proc* 2013; **45**: 958.
6. Swords DC, Al-Geizawi SM, Farney AC, *et al.* Treatment options for renal cell carcinoma in renal allografts: a case series from a single institution. *Clin Transplant* 2013; **27**: E199.
7. Tillou X, Guleryuz K, Doerfler A, *et al.* Nephron sparing surgery for de novo kidney graft tumor: results from a multicenter national study. *Am J Transplant* 2014; **20**: 1.
8. Halverson SJ, Kinju LP, Bhalla R, *et al.* Accuracy of determining small renal mass management with risk stratified biopsies: confirmation by final pathologist. *J Urol* 2013; **189**: 441.
9. Gautam G, Zorn K. The current role of renal biopsy in the management of localized renal tumors. *J Urol* 2009; **25**: 494.
10. Escudier B, Albigies l, Sonpavde G. Optimal management of metastatic renal cell carcinoma: current status. *Drugs* 2013; **73**: 427.

