Renal Cell Carcinoma in Renal Transplantation: The Case for Surveillance

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ABSTRACT

Introduction. Between January 2013 and September 2015, 135 consecutive renal transplant patients were screened prospectively with ultrasound for renal cell carcinoma (RCC).

Results. Eighteen ultrasound abnormalities were identified with 4 solid lesions detected. Fifty-six other patients were screened retrospectively by referring nephrology groups, with 6 additional malignancies found.

Conclusion. As a result of our data, we recommend and have instituted annual ultrasound screening of native kidneys in all renal transplant patients.

PATIENTS with end-stage renal disease evaluated for kidney transplant candidacy are carefully screened for malignancy due to higher risk of cancers while taking immunosuppressive drugs. A required screening test used in our practice is a pretransplant complete abdominal ultrasound. One indication for this test is to diagnose acquired cystic disease (ACD) and detect solid lesions suggestive of renal cell carcinoma RCC. Kidney transplant recipients have a relative risk of 5 to 10 for RCC compared with the age-matched general population. Most of these tumors arise in kidneys with ACD, which develops during the course of progressive chronic renal failure [1–3]. We re-evaluated our screening practice due to a notable case—a pretransplant patient with a negative ultrasound who presented with widespread, metastatic RCC less than 1 year post-transplant. There are currently no standard guidelines for RCC screening in the transplant population. A literature review revealed various recommendations from many individual center studies. The aim of this study is to evaluate the use of ultrasound for screening and early detection of RCC in renal transplant patients.

PATIENTS AND METHODS

Beginning on January 1, 2013, 135 prospective retroperitoneal ultrasounds were performed on all new kidney transplant recipients at 6 months and 1 year postoperatively during routine appointments. The ultrasounds were interpreted by a group of 3 radiologists unfamiliar with the clinical course of the patient to maintain objectivity. Patients with ACD, defined as 4 or more cysts in native kidneys, continued with ultrasound screening every 6 months. During this period, we also retrospectively reviewed data on 56 ultrasounds done at outside nephrology offices before 2013.

RESULTS

Patient characteristics are shown in Table 1 for the prospectively screened group (n = 135). Table 2 shows that 18 ultrasounds (13.3%) were identified as abnormal: 14 of the 135 (10.4%) were defined as ACD and 4 (2.9%) solid lesions were detected. Three of the solid lesions were subsequently histologically confirmed as RCC, and one was a benign inflammatory mass in a patient with prior pretransplant RCC.

Fifty-six other ultrasounds were reviewed retrospectively; results were reported to us by outside nephrology groups that screened their patients. Of the 56 ultrasounds of native kidneys, 6 (10.7%) showed lesions later found to be RCC. We do not know the total number of patients screened by these nephrologists or the number of patients with negative studies.

Table 3 shows pathology reports and descriptions for all 9 patients diagnosed with RCC (3 in the prospectively screened group and 6 in the retrospectively screened group). Figure 1 shows pathology results of a 76-year-old patient from 2013. None of the tumors found in our study had

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Table 1. Patient Characteristics (n = 135)

	Males (n = 67)	Females (n = 48)
Age (y), mean (range)	68 (21–76)	48 (26–77)
Ethnicity		
African American	0	2
Hispanic	7	6
Asian	6	3
Caucasian	54	37
Etiology of ESRD		
Diabetes	13 (19%)	11 (23%)
ADPKD	4 (6%)	7 (15%)
GN/hypertension	43 (64%)	18 (38%)
Other	12 (18%)	12 (25%)

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ESRD, end-stage renal disease; GN, glomerulonephritis.

molecular characterization, although 2 of them had papillary features.

DISCUSSION

Malignancy post-renal transplant is a common cause of death. We argue that early detection and treatment of RCC through routine screenings of kidney transplant recipients is best practice. Ultrasound is a simple, convenient test to diagnose and prevent development of advanced-stage cancer, which has an unfavorable prognosis [4]. In a large, retrospective study of the Medicare population on hemodialysis, the relative risk of malignancy was most elevated for cancers in the kidney, ureter, and bladder. This relative risk of RCC was increased fourfold and was found to correlate with length of time on dialysis. Furthermore, 10% of patients in the study were evaluated for kidney transplant. Of these patients, the incidence of RCC was again increased, likely due to more intensive pretransplant screening [1].

Patients with chronic kidney disease, even those with a moderate decline in glomerular filtration rate, have an increased risk of RCC. The risk of RCC increases as glomerular filtration rate decreases. Schwarz et al showed that post-transplant patients virtually always had ACD prior to the diagnosis of RCC. In their study of 561 patients screened, 23% had ACD with 8 (1.5%) having newly diagnosed RCC. The authors suggest that screening protocols be established pre- and post-renal transplantation [2].

In a large study of patients in Asia who were transplanted in other countries, 23 of 307 (7.5%) patients were retrospectively diagnosed with urothelial carcinomas as the most common malignancy after kidney transplantation. The authors suggested regular screening by cytology or ultrasound [5]. The standard incidence ratio for kidney cancer in a recent study was 4.65 in the United States, 7.3 in Australia, and 7.9 in the United Kingdom. These data would make a surveillance strategy logical and relatively easy to implement without excessive cost [6].

Table 2. Ultrasound Results on Prospective Patients (n = 135)

	Male	Female
New acquired cystic disease	7	7
Solid lesions	2*	2

*Nephrectomy in one case revealed 2 cm inflammatory nonmalignant mass.

There is also increased risk of bladder cancer and transitional cell cancer in the transplant population. Large epidemiologic studies have shown that this risk includes many kidney transplant recipients, perhaps due to immunosuppression [7]. Our data, along with an accompanying editorial, suggest that a targeted screening program may prevent late-stage renal cancers from going undetected in renal transplant recipients [8].

Most renal transplant candidates are screened pretransplant by ultrasound or computed tomography for suspicious lesions in native kidneys. In the 15-year history of our kidney transplant program (1223 transplants), we have screened all pretransplant candidates. We found 17 (1.4%) suspicious lesions on pretransplant screening tests, which were subsequently diagnosed as malignant RCCs on surgical pathology.

Although we excluded patients with bilateral nephrectomies, we decided to include patients with autosomal dominant polycystic kidney disease (ADPKD). It has been thought that renal cancer in patients with ADPKD is less common than in the non-PKD end-stage renal disease population [9]. Although this is likely true, it does not obviate the fact that post-transplant renal cancers can occur in any native kidneys. Diagnostic determination of small renal tumors in the PKD setting is difficult, and it is possible that incidence of RCC is underdiagnosed in the ADPKD population even when surveillance has taken place.

It should be noted that we had 4 instances of widely disseminated metastatic RCC. Two of these were multifocal in patients with APPKD. Although the literature suggests that malignancy in these patients is uncommon, the multifocal nature of the tumors and the widespread metastases in these patients is striking. Thus, until the literature is definitive about the nature of malignant change in such kidneys, we feel it is justified to screen these patients as well [9].

There were limitations in the study. The timeline we chose for screening was at 6 months and annually because this is when post-transplant patients are routinely seen in the clinic. However, the ideal initiation and frequency of screening is unknown. Also, we chose ultrasound as screening modality due to low risk, low cost, and convenience. It may be that screening with computed tomography is more effective. Future studies would be necessary to determine best timing and modality of RCC screening.

All tumors that were analyzed in our prospective study were confined to the kidneys, and patients were likely to be completely cured by unilateral nephrectomy. We cannot comment on patients who died from malignant disease outside our center because pathology could not be obtained for analysis. Future studies should look for biologically distinct alterations in molecular pathways to better assess prognosis and direct therapy [10].