Frequency and Predictors of Renal Transplantation Among Patients Rendered Surgically Anephric for Sporadic Renal Cancer

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OBJECTIVE To assess the frequency of renal transplantation in patients rendered surgically anephric during treatment of renal cancers as well as the clinicopathologic factors associated with receipt of transplantation.

METHODS A retrospective review was conducted to identify patients rendered surgically anephric between 2001 and 2016 due to cancer in both renal units or cancer in an anatomically or functionally solitary kidney. Patient demographics, comorbidities, and cancer features were compared between patients who subsequently received a renal transplantation and those who did not. Time-to-event analysis was used to compare time to transplantation across varied identified parameters.

RESULTS Among 27 patients rendered anephric, 4 (15%) received a renal transplantation over a median follow-up of 21.6 months (interquartile range 7.2, 53.3). All transplanted patients were less than 70 years of age and had cT1a renal parenchymal mass at the time of nephrectomy. No patient undergoing completion nephrectomy for upper tract urothelial carcinoma received transplantation. Patients who were evaluated by the transplant service prior to nephrectomy were more likely to eventually undergo transplantation (60% vs 5%; $P < .01$). On time-to-event analyses, a cT1a renal parenchymal mass ($P < .01$) and a pre-nephrectomy transplant evaluation ($P < .01$) were associated with receipt of a transplant.

CONCLUSION Patients rendered anephric via nephrectomy for cancer are more likely to receive renal transplantation if they are less than 70 years old, have a cT1a renal parenchymal mass, and receive transplant consultation before nephrectomy. These data may inform future patient counseling. UROLOGY 126: 134–139, 2019. © 2019 Elsevier Inc.

Renal cancers represent the eighth most common cancer in the United States[1] and occasionally occur either bilaterally or in a solitary kidney. In these situations, surgical developments have focused on maximizing renal preservation, such as with partial nephrectomy for renal cell carcinoma and with endoscopic ablation of urothelial carcinoma, to avoid dialysis.[2-5] Indeed, dialysis significantly impacts patients' quality of life, involves a burden of time and cost, and has been associated with reduced life expectancy due to an increased risk of cardiovascular events as well as dialysis-related complications.[6-7] Nevertheless, when tumors are not amenable to a nephron-sparing approach, patients must make the difficult choice between suboptimal cancer treatment and dialysis.

In these scenarios, the possibility of eventual renal transplantation is often discussed with the patient as part of preoperative counseling. However, little data exist regarding the frequency of receiving a renal transplantation after completion nephrectomy for renal cancers. In fact, renal transplantation clinical practice guidelines recommend that patients with a history of malignancy demonstrate a minimum of 2 years without recurrence before being considered for transplant eligibility.[8] However, these recommendations may be subject to individual discretion while at the same time the rate of transplantation among such patients has not been well described, obscuring the ability to provide informed patient counseling.

Herein, therefore, we reviewed the outcomes of patients who underwent a completion nephrectomy (either

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bilateral nephrectomy, nephrectomy in an anatomically solitary kidney, or nephrectomy in a functionally solitary kidney) for renal cancers at our center and examined the frequency of and factors associated with subsequent transplantation.

MATERIALS AND METHODS

After institutional review board approval was obtained, we queried all adults who underwent nephrectomy/nephroureterectomy from 2001 to 2016 for renal parenchymal or collecting system malignancies at our center. We did not exclude patients on the basis of histology, and we specifically included renal cell carcinoma, upper tract urothelial carcinoma, sarcoma, and squamous cell carcinoma. We then identified patients with either malignancy bilaterally, in an anatomically solitary kidney, or in a functionally solitary kidney. A functionally solitary kidney was defined as a contralateral atrophic kidney with demonstrated negligible function (on either contrast imaging or dedicated nuclear renal scan). Patients not initiated on dialysis within 30 days of nephrectomy were excluded. Similarly, patients with a healthy-appearing contralateral kidney preoperatively who were rendered permanently dialysis-dependent due to perioperative acute kidney injury were also excluded ($n = 6$). Furthermore, we excluded patients determined to have a hereditary syndrome of renal cancer ($n = 2$).

Primary outcome of interest was receipt of renal transplantation. We recorded whether the patient was approved for transplant (placed on the transplant list) and separately whether the patient then underwent transplantation, an important distinction due to the relatively low likelihood of receiving a transplant if the patient is low on the transplant list.[9-10]

Patient characteristics including age, gender, body mass index (BMI), Charlson comorbidity index (CCI) score,[11] serum creatinine (Cr), estimated GFR,[12] albumin, and preoperative cancer characteristics were obtained. Documentation prior to the index procedure was reviewed to determine if an evaluation for future kidney transplant was performed. Documented follow-up was also reviewed to identify, as applicable, date of recurrence, date of last follow-up, and/or date of death.

Baseline characteristics between the transplanted and nontransplanted cohorts were compared using standard descriptive statistics: Pearson's chi-squared test was used for categorical variables and the Wilcoxon/Kruskal-Wallis rank sum tests were used for continuous variables. Receipt of transplantation was analyzed in a time-dependent manner with the log-rank test to identify differences in transplantation rates between 2 groups. All statistical analyses were performed using JMP, version 10, SAS Institute Inc., Cary, NC, 2012, with a P value $< .05$ considered statistically significant.

RESULTS

We identified 27 patients who met inclusion criteria. Within this group, 17 patients underwent nephrectomy, while 10 underwent nephroureterectomy. No patients in this cohort were treated with partial nephrectomy; of the 7 patients with clinical T1 renal masses, 5 had pre-existing severe renal disease anticipating the need for renal replacement therapy, while 2 had tumors with a complexity that would not have been amenable to a nephron-sparing approach. A total of 19 patients were managed with open surgery, 8 with laparoscopic procedures. Five patients underwent bilateral synchronous renal extirpation, while 22 patients underwent unilateral nephrectomy/nephroureterectomy. Following the index procedure, 23 patients were anatomically anephric and 4 were functionally anephric. Median time to hemodialysis initiation after the index procedure was one day.

Of these 27 patients, 4 (15%) ultimately received a renal transplant over a median postnephrectomy follow-up of 21.6 months (interquartile range 7.2, 53.3). Baseline characteristics for patients who did vs did not subsequently undergo transplantation are provided in Table 1. Patients who received a transplant had a median age of 62 at the time of nephrectomy vs 70 in the nontransplanted group ($P = .06$). Other baseline characteristics were similar for the 2 groups with respect to gender ($P = .96$), CCI score ($P = .47$), BMI ($P = .85$), and a previously validated[13-14] 2-year dialysis mortality score ($P = .08$). Similarly, procedure type and technique was not significantly different between the 2 groups.

Meanwhile, tumor characteristics were significantly different between the transplanted and not transplanted groups. That is, all patients who received a transplant had cT1a renal parenchymal neoplasms, and in fact only 1 patient receiving a nephrectomy for such a cT1a mass did not eventually receive a renal transplant. On the other hand, all nontransplanted patients had cT1b or higher RCC or other histologies. Indeed, no patients with upper tract urothelial carcinoma, squamous cell carcinoma, or sarcoma subsequently received a renal transplant.

Interestingly, 3 of 5 patients (60%) who received a transplant evaluation preoperatively eventually received a renal transplantation, compared to only 1 of 22 (5%) patients who did not undergo a preoperative transplant evaluation ($P < .01$). One patient (with high-grade invasive upper tract urothelial carcinoma) was initially approved for a transplant 2 years postoperatively but developed worsening comorbidities that precluded transplantation soon after eligibility. Meanwhile, 74% (17/23) of nontransplanted patients had not received a prenephrectomy transplant evaluation.

Incidence curves demonstrate that patients undergoing a preoperative transplant evaluation were more likely to receive renal transplantation compared to those who did not receive a preoperative evaluation (Fig. 1; $P < .01$). The 3 patients who were approved for transplant preoperatively were all transplanted within 5 months after the index procedure; all 3 were living donor transplants. The remaining patient received his transplant at 7 years and this was a deceased donor transplant.

Of the 23 patients who did not undergo transplantation, 14 (61%) were due to advanced age, competing comorbidity, or death prior to eligibility, whereas transplantation was precluded by recurrent malignancy in 3 (13%). The absence of transplant in the remaining patients was secondary to patient choice in 2 (9%) or unspecified in 4 (17%).

Importantly, none of the patients who received a renal transplant developed cancer recurrence, in contrast compared to 6 (26%) of the nontransplanted group (Fig. 2; $P = .19$). Moreover, patients who received a transplant had a significantly better 5-year overall survival (100% vs 14%; $P = .01$; Fig. 3). The cause of death in patients who did not undergo a transplant was metastatic cancer in 6 (26%), perioperative events (stroke or cardiac arrest) in 2 (9%), and advancing comorbidity in 7 (30%). The cause of death was unspecified in 3 (13%) of these patients.

Table 1. Baseline, procedure, and oncological characteristics of transplanted vs nontransplanted patients

	Transplanted	Not Transplanted	*P* Value
Total	4	23	
Gender			
Male	75% (3)	74% (17)	.96
Female	25% (1)	26% (6)	
Age at completion nephrectomy (yr) median (IQR)	62 (59, 67)	70 (63, 78)	.06
CCI median (IQR)	2 (2, 2)	2 (2, 3)	.47
BMI median (IQR)	31 (24, 36)	29 (26, 33)	.85
Cr prior to completion nephrectomy (mg/dL) median (IQR)	3.7 (3.0, 4.4)	1.8 (1.4, 2.1)	.01
eGFR prior to completion nephrectomy (mL/min/1.73^2) median (IQR)	17.3 (16.1, 19.1)	37.7 (25.2, 50.6)	.01
Dialysis 2-year mortality score[13-14] median (IQR)	75% (75%, 86%)	67% (57%, 75%)	.08
Procedure			
Nephrectomy	100% (4)	57% (13)	.10
Nephroureterectomy	0% (0)	43% (10)	
Surgical approach			
Open	50% (2)	74% (17)	.33
Laparoscopic	50% (2)	26% (6)	
Laterality			
Bilateral	50% (2)	13% (3)	.14
Right	0% (0)	35% (8)	
Left	50% (2)	52% (12)	
Reason for dialysis			
Anatomically anephric	75% (3)	87% (20)	.53
Functionally anephric	25% (1)	13% (3)	
Tumor histology			
RCC	100% (4)	52% (12)	.20
UTUC	0% (0)	39% (9)	
UTSCC	0% (0)	4% (1)	
Sarcoma	0% (0)	4% (1)	
Pathological T stage			
RCC T1a	100% (4)	4% (1)	<.01
T1b	0% (0)	9% (2)	
T2	0% (0)	0% (0)	
T3 or T4	0% (0)	39% (9)	
UTUC Ta or Tis	0% (0)	17% (4)	
T1 or T2	0% (0)	9% (2)	
T3 or T4	0% (0)	13% (3)	
UTSCC	0% (0)	4% (1)	
Sarcoma	0% (0)	4% (1)	
Pathological N stage			
N0 or Nx	100% (4)	96% (22)	.67
N1 or N2	0% (0)	4% (1)	

COMMENT

We found here that only 15% of patients undergoing completion nephrectomy for cancer subsequently received a renal transplantation. Notably, patients with a cT1a renal parenchymal mass and patients who underwent a prenephrectomy transplant evaluation were significantly more likely to be transplanted. These findings may assist with patient counseling regarding management options, including partial nephrectomy, cryoablation, or active surveillance instead of radical nephrectomy, and the possibility of eventual transplantation.

To date, there have been limited reported data regarding the rate of postnephrectomy transplant in patients with renal cancer. In the largest historic series of patients undergoing completion nephrectomy, 12 of 23 patients were transplanted after nephrectomy, but this study included pediatric patients and Wilms tumor patients which inflated their transplantation rates compared to ours.[15] Meanwhile, in a multi-institutional review of von Hippel-Lindau syndrome patients with bilateral RCC undergoing transplantation after nephrectomy, Goldfarb et al found that such patients had a similar survival as other transplant populations,[16] and other case reports have noted similar results.[17-19]

Our dataset is unique from the above studies as it represents what is to our knowledge the largest report of nonsyndromic patients to date. Furthermore, we identified patient characteristics associated with an increased likelihood of receiving transplantation. Specifically, we found that transplanted patients tended to be younger than

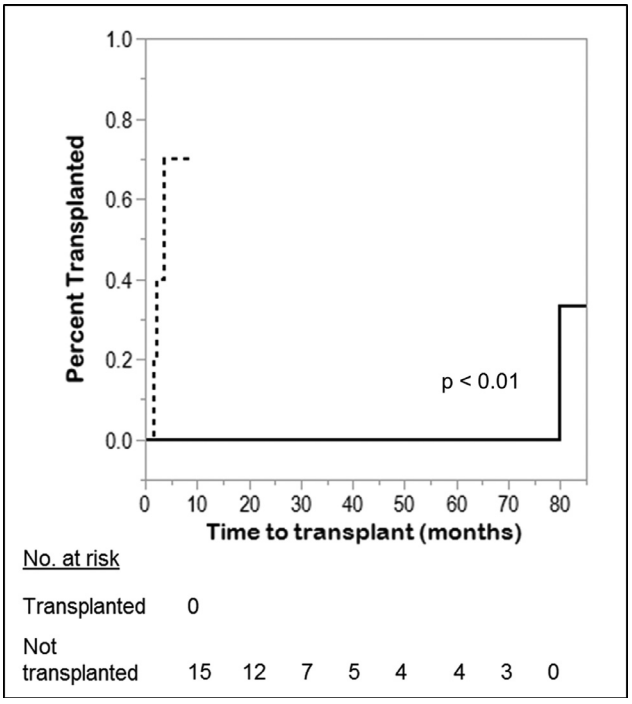

Figure 1. Time-to-event analysis showing transplantation rates between patients receiving prenephrectomy transplant evaluation (dashed line) vs those not receiving evaluation (solid line).

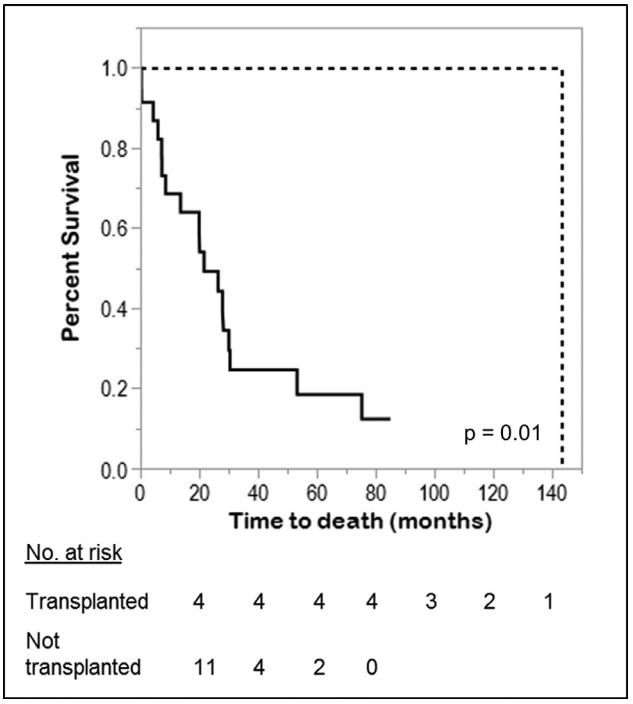

Figure 3. Overall survival for transplanted (dashed line) vs not transplanted (solid line) patients.

those not transplanted. The oldest patient receiving a transplant was 68 years old at the time of nephrectomy. While the association of younger age with transplant did not achieve statistical significance ($P = .06$) in our study, this is likely due to our small sample size as age is a factor in transplant eligibility. This can facilitate patient counseling, in that younger patients may expect to have a higher chance of receiving a transplant, and those 70 or older may expect a higher likelihood of remaining on dialysis. This may inform their decision to go forward with the completion nephrectomy in the first place, since only 14% of our dialysis cohort was alive at 5 years.

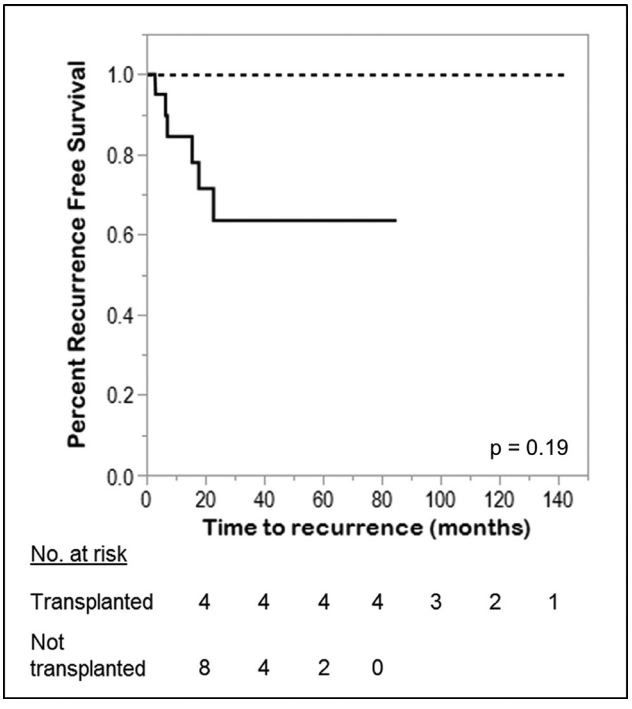

Figure 2. Cancer recurrence-free survival for transplanted (dashed line) and not transplanted (solid line) patients.

Interestingly, the severity of comorbidities as indicated by the CCI did not correlate with the likelihood of transplantation. This finding likely reflects patient selection, as those patients with severe comorbidity profiles may have been deemed not eligible for completion nephrectomy. While there are data supporting that surgically induced chronic kidney disease results in a lower rate of progression to end-stage renal disease than medical chronic kidney disease,[20] our investigation only concerns patients rendered surgically dialysis-dependent. In this setting, Nguyen et al found that only 0.5% of all dialysis patients in the United States had surgically induced end-stage renal disease, but these patients had a significantly shorter median overall survival relative to the medical end-stage renal disease patients (1.9- vs 3.4-year median overall survival).[21] Their 5-year survival rates of surgical dialysis patients (20%) agree with our estimates (14%). These figures may help inform the decision for patients contemplating surgical end-stage renal disease for renal malignancies.

We further found that the only patients who ultimately received a renal transplant after completion nephrectomy

were those patients with a cT1a renal parenchymal neoplasm. This occurred despite the fact that, in our cohort of cT1b and cT2 renal parenchymal masses, no patient experienced recurrence during follow-up. Furthermore, 61% of our nontransplanted cohort did not have cancer recurrence at 5 years. Nevertheless, these patients did have a higher mortality (only 14% overall survival at 5 years in the nontransplanted cohort). As such, studying conditional survival curves at various time points of follow-up may increase the likelihood of transplantation for patients who have met the prerequisite disease-free survival intervals but have tumors larger than cT1a.

We also demonstrated that patients who received a prenephrectomy transplant evaluation were more likely to eventually receive transplantation. Indeed, 60% of patients receiving an anticipatory transplant evaluation were transplanted, vs only 5% of patients not evaluated prenephrectomy. While this relationship may not be causal, it is likely that the evaluation gave patients a better understanding of their individual odds of receiving a transplant. At the same time, we recognize that patients who were poor candidates may thus have elected not to go forward with a nephrectomy and were thereby not captured in our cohort. Regardless of the mechanism behind this association, it is intuitive that patients may benefit from prenephrectomy transplant evaluation, and we now routinely recommend it for patients contemplating completion nephrectomy for renal cancers at our center.

We recognize that our study is limited by its retrospective design, which introduces considerable selection bias. Further, we focused our analyses on clinical factors commonly available to the urologist treating the patient's cancer, as we were unable to evaluate several of the key factors known to impact transplant eligibility and waiting time such as blood group, preformed anti-HLA antibodies, and availability of a living donor. As these variables are typically obtained at the time of transplant consultation, they highlight again the value of a prenephrectomy transplant evaluation to help patients understand the risks and benefits of a renal transplant as well as their potential candidacy and anticipated waiting times. Moreover, given limited overall patient numbers, we could not perform multivariable analyses of factors associated with transplantation. Nevertheless, given the existing paucity of data on these patients, we believe that these data provide usable evidence to guide patient counseling.

CONCLUSION

We found that 15% of patients undergoing completion nephrectomy for nonsyndromic renal cancer eventually received a renal transplantation. Patients were more likely to receive renal transplantation if they were less than 70 years of age at the time of nephrectomy, had a cT1a renal parenchymal mass, and received transplant consultation before nephrectomy. Furthermore, patients who did not receive a transplant had significantly worse survival. These data may be used to inform future patient counseling, particularly highlighting the value of a prenephrectomy transplant evaluation and suggesting consideration of active surveillance or renal sparing options in patients unlikely to receive a postnephrectomy transplant.

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EDITORIAL COMMENT

The authors report 27 patients rendered surgically ($N = 23$) or functionally ($N = 4$) anephric after kidney cancer operations. Sixteen patients had renal cell carcinoma (RCC, histologic subtype not specified) and 9 transitional cell carcinoma. No partial nephrectomies were done in the 7 T1 patients (5 due to severe preexisting chronic kidney disease (CKD) and 2 due to anatomic complexity). Only 4 patients underwent renal transplantation, all T1a RCC (<4 cm) and age less than 70 years, after a median wait time of 21.6 months (7.2-53.3 months), and none developed cancer recurrence. The nontransplant patients did not fare as well with 2 dying from perioperative events, 6 from metastatic disease, and 7 from comorbidities.

Not that long ago the correct board answer for the optimal treatment of bilateral renal tumors was bilateral nephrectomy and eventual transplantation. Over the last 20 years, the fields of renal transplantation, renal tumor biology, and kidney sparing surgery have developed in parallel. Kidney tumors, diverse diseases with distinct molecular defects, have variable prognoses ranging from benign, to indolent, to highly malignant and metastatic.[1] Medical comorbidities (hypertension, diabetes, and cigarette smoking related vascular disease) coupled with the aging process, cause CKD. CKD is highly prevalent in the United States (12%-14%),[2] but more so in kidney tumor patients (26%),[3] and is an independent risk factor for the development of kidney cancer.[4] The adoption of elective partial nephrectomies and its oncological equivalency to radical nephrectomy for T1 tumors in healthy patients with long life expectancy coupled with active surveillance strategies for elderly and co morbidly ill patients with limited life expectancy, has undoubtedly reduced the number of patients with treatment related end-stage renal disease (ESRD), almost all of whom would never receive a transplant.[5]

NIDDK data from 2013 indicate that there are 661,000 patients in the United States with ESRD, 468,000 on dialysis, 193,000 with a functional kidney transplant, and 17,600 transplants performed yearly. Five-year survival for patients on dialysis is only 34% and 47,000 patients die yearly.[6] The shortage of donor kidneys leads to long waiting lists. Optimum outcomes are achieved for ESRD patients receiving a kidney in less than 1 year but most transplant teams force kidney cancer patients to wait 2-5 years during which time comorbid cardiovascular disease progression can lead to ineligibility and death. Today, nephrologists, oncologists, and transplant teams are reformulating transplant guidelines[6] based on integrated cancer risk tools[7] recommending low-risk patients (ie, small low-grade tumors, those with limited metastatic potential such as chromophobe or clear cell papillary) be treated the same as noncancer bearing ESRD patients whereas those with poor-risk tumors (distal nephron, sarcomatoid features, IVC extension) would be excluded due to the high risk of metastatic disease in the near term. Other intermediate patients require conference with oncological and transplant teams to decide the appropriate waiting time.

Urologic surgeons contemplating kidney tumor operations that can lead to ESRD must balance both the oncologic and renal medical risks of surgical intervention with the anticipated prognosis based on ESRD. Transplantation, though effective, is not a likely solution for the vast majority of such patients. Liberal use of kidney sparing operations and active surveillance strategies will reduce the number of patients that face the difficult straits the authors described in this paper.

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