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ORIGINAL ARTICLE

Significance of atypical urinary cytology in the evaluation of patients with end-stage renal disease for kidney transplantation – a retrospective study

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SUMMARY

To determine what percentage of renal transplant candidates have atypical urinary cytology, what proportion have urothelial carcinoma and whether cystoscopy is necessary with atypical cytology. All end-stage renal disease (ESRD) patients (703) presenting for renal transplantation at our institution were retrospectively reviewed. Individuals producing sufficient urine were screened with urine cytology and those with atypical cytology or risk factors for bladder cancer underwent cystoscopy. Four hundred and thirty patients had available urinary cytology and, of these, 151 (35%) had atypical cytology. Of patients with atypical cytology, three were identified to have urothelial carcinoma. However, three additional patients with urothelial carcinoma did not present with atypical cytology. In total, 6 of 703 (0.85%) patients had bladder cancer. All were treated with transurethral resection and eventually underwent renal transplant. One patient has had disease progression post-transplant to distant metastases. This is the largest study to date evaluating the incidence of urothelial carcinoma in ESRD patients presenting for transplant workup. We found the incidence of bladder cancer to be higher than in the general Canadian population, however, most lesions were low grade. We found atypical cytology in transplant candidates to be a poor predictor for these low-grade lesions and do not recommend routine cystoscopy for atypical cytology.

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Introduction

Renal transplantation is the optimal method of treating patients with end-stage renal disease (ESRD). A successful kidney transplant improves the quality of life and reduces the mortality risk for most patients when compared with maintenance dialysis [1–3]. Careful preoperative work-up of all transplant candidates is mandatory to promote organ and patient survival in the post-transplant period. Several guidelines have been published to help direct preoperative work up [4–8].

Active malignancy is typically a contraindication to renal transplantation because immunosuppression may aggravate underlying malignancy. Malignancy accounts for 9–12% of deaths following transplantation and elimination of cancer in transplant candidates is expected to decrease post-transplant mortality [8]. In general, kidney transplant candidates are screened for cancer

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according to recommendations that apply to the general population including biennial screening mammography for women, PAP smear in women over 21 years old, as well as colorectal cancer and PSA screening in individuals over 50 years old [4,5,8]. Moreover, renal transplant candidates with a previous history of malignancy should be tumour free before proceeding with transplantation. Most renal transplant candidates with a history of malignancy should wait a period of time between successful treatment and transplantation. The length of time will depend on the type of malignancy [4–6,8].

Urine cytology is currently used in screening and surveillance of urothelial cancer. Atypical urinary cytology includes urothelial cells with high nuclear to cytoplasmic ratio >0.5 as well as one of hyperchromasia, irregular clumpy chromatin, or irregular nuclear contours [9]. Cytology suspicious/positive for high-grade urothelial carcinoma (HGUC) includes cells with nuclear to cytoplasmic ratio >0.7 and hyperchromasia and one of irregular clumpy chromatin, and irregular nuclear membranes [9].

The European Association of Urology guidelines on renal transplantation currently recommend urinary cytology to screen for urothelial carcinoma in patients with microscopic haematuria, analgesic nephropathy or a prior history of urothelial carcinoma [4]. However, whether atypical cytology is a good predictor for urothelial carcinoma in the pre-transplant population has not been studied.

In this study, we present our experience with urothelial carcinoma in ESRD patients preparing for potential renal transplantation. The primary objectives of this study were to determine the incidence of urothelial carcinoma in ESRD patients being worked up for renal transplantation and establish the incidence of urothelial malignancy in ESRD patients with atypical urinary cytology. In addition, we wanted to establish whether the use of urinary cytology is applicable to this population and determine whether patients with ESRD are being over-investigated with screening cystoscopy prior to transplant.

Materials and methods

This study was a retrospective chart review approved by our local research ethics board. Inclusion criteria included all ESRD patients over 18 years of age, presenting to clinic at the London Health Sciences Centre, Ontario, Canada for evaluation of renal transplantation. No patient who met the inclusion criteria were excluded from the study. In total, 703 patient charts were reviewed by two individuals (Fig. 1).

The following data points were collected: gender, age at transplant, dialysis use, history of smoking (including current versus former smoking), and presence of haematuria. All study data was recorded on a secure data collection form. All patients with sufficient urine production underwent urinary cytology testing via a midstream voided sample. All ESRD patients referred for transplant workup with persistent microscopic haematuria and risk factors for bladder cancer including (smoking, exposure to textile, rubber, leather, dye, paint and print industries, cyclophosphamide, pelvic radiation, chronic bladder irritation [10]) or those with atypical or suspicious/positive urinary cytology underwent pretransplant cystoscopy for screening to rule out urothelial carcinoma in the bladder (Fig. 1). All patients also underwent routine kidney and bladder ultrasonography to rule out upper tract abnormalities such as hydronephrosis or urothelial masses as a screening test for malignancy.

Patients identified to have urothelial carcinoma underwent surveillance cystoscopy every 3 months for the first 2 years following bladder tumour resection surgery, with subsequent cystoscopy every 6 months for the next 2 years, then yearly afterwards. Any recurrence of malignancy reset this schedule. The histopathology of the resected tumour determined whether or not the ESRD patient should be put on hold from transplant as per clinical guidelines [4–8].

Basic descriptive statistics were performed to illustrate the demographics of the studied population including mean age of patient, percentage of ESRD patients who have a history of dialysis or smoking. We will also identify the percentage of ESRD patients with haematuria or urinary atypia who are found to have bladder malignancy by cystoscopy. Student's *t*-test was used to determine significance where $P < 0.05$ was considered statistically significant.

Results

Of the 703 patients, 430 had undergone voided urinary cytology testing. The remaining patients did not undergo urinary cytology testing as they did not have any of the risk factors previously listed or were anuric. No patients had a prior history of urothelial carcinoma.

In terms of comparing baseline characteristics between patients with and without urothelial carcinoma, patients found to have urothelial malignancy were significantly older than those without (64.7 ± 12.3 years vs. 50 ± 14.3 years, $P < 0.05$). However, there was no difference in terms of smoking status or presence of microscopic haematuria (Table 1). None of the patients

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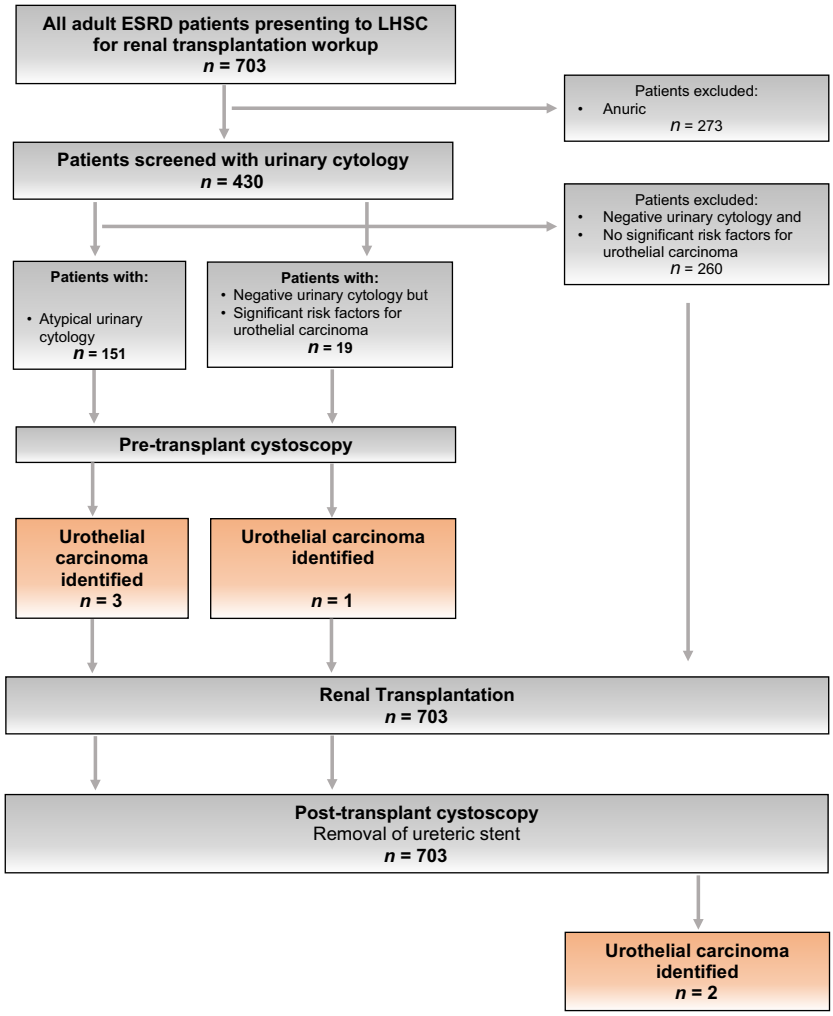

Figure 1 Study flow chart.

identified to have urothelial carcinoma in this study had previous cyclophosphamide exposure or history of pelvic radiation. There was also no difference in dialysis vintage between these two groups (Table 1). None of the patients identified to have urothelial carcinoma had gross haematuria.

Of the 430 patients who had undergone urinary cytology testing, 151 (35%) had atypical cytology. No patients had urinary cytology suspicious or positive for urothelial carcinoma. All patients with atypical cytology underwent pretransplant cystoscopy. Of the 151 patients with atypical cytology, there were three patients (patients 1, 2 and 3; 2.0%) discovered to have urothelial cancer with cystoscopy. One of these three patients was an ex-smoker and had microscopic haematuria whereas the other 2 had neither a smoking history nor microscopic haematuria.

Of 279 patients with negative urinary cytology, patients with persistent microscopic haematuria or significant risk factors for urothelial carcinoma also underwent pretransplant cystoscopy. One such patient (patient 4) was identified to have urothelial carcinoma (Table 2). Patient 5 also had negative urinary cytology but did not undergo pretransplant cystoscopy because of the absence of above indications. Patient 5 did not have urothelial carcinoma identified until post-transplant at time of ureteral stent removal (Table 3).

Patient 6 was not able to undergo urinary cytology testing because of anuria and was ultimately also found to have urothelial carcinoma at time of post-transplant cystoscopy for ureteral stent removal (Tables 2 and 3). This patient had a previous smoking history.

In summary, four patients had urothelial carcinoma identified through pre-transplant cystoscopy, and all were subsequently diagnosed to have low-grade non-muscle invasive bladder cancer (pTaN0M0) and were treated with transurethral resection of bladder tumour (patients marked with *, Table 3). One patient had multiple tumours at time of discovery and received intravesical mitomycin C after resection.

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Table 1. Patients with urothelial carcinoma were significantly older compared to patients with no malignancy.

	Patients w/o urothelial carcinoma	Patients with urothelial carcinoma
Males	447	4
Females	253	2
Mean age	50 ± 14.3 years	64.7 ± 12.3 years*
Smoking		
Yes	335	4
No	303	2
Microscopic haematuria		
Yes	275	2
No	174	4
History of cyclophosphamide exposure		
Yes	29	0
No	674	6
History of pelvic radiation		
Yes	2	0
No	701	6
Mean dialysis vintage		
Months	28.9 ± 21.8	32 ± 24.1

*Significance with $P < 0.05$.

Table 2. Atypical cytology did not identify three patients with urothelial carcinoma.

# Of patients	Patients with urothelial carcinoma	% With urothelial carcinoma
Patients with atypical cytology (151)	3	2.0
Patients with normal cytology (279)	2	0.72
Anuric patients (273)	1	0.36

The remaining two patients were not identified to have urothelial malignancies pretransplant and were diagnosed at the time of the cystoscopy for removal of their ureteric stent. At time of identification, one patient had low grade (pTaN0M0) and one patient had high-grade nonmuscle invasive bladder cancer (NMIBC) and both were treated with TURBT (patients not marked with *, Table 3). The patient with high-grade NMIBC received intravesical mitomycin C after resection.

All four patients who had urothelial carcinoma discovered preoperatively eventually underwent renal transplantation. Of these four patients, patients 1, 2, 3 with solitary pTa low-grade lesions were listed immediately for renal transplantation (Table 4). They ultimately underwent renal transplantation within 1–5 months. Patient 4 had multiple low-grade lesions and underwent a 1 year surveillance period with cystoscopy every 3 months before being listed. This patient underwent renal transplantation at 33 months from initial TURBT (Table 3).

Patient 3 has had disease recurrence and progression. This patient has had multiple local recurrences requiring repeat TURBT and mitomycin instillation and progression of disease within the bladder as well as positive cytology from the left collecting system necessitating partial cystectomy with left-sided native nephroureterectomy. This patient has since had disease recurrence in the remaining bladder and ultimately distant metastatic spread (Table 4).

Patients 5 and 6 had urothelial carcinoma discovered post-operatively (Table 4). Patient 6 who had high-grade muscle invasive bladder cancer has also had multiple local recurrences of low-grade disease requiring recurrent TURBT and courses of mitomycin C (Table 4). None of the patients aside from patient 3 have been identified to have upper tract urothelial carcinoma.

All transplant candidates also underwent routine preoperative abdominal-pelvic ultrasound for assessment of anatomy. No patients were identified to have renal carcinoma or upper tract urothelial carcinoma requiring pretransplant resection. None of the patients positive for bladder cancer had tumour readily visible on ultrasound.

Discussion

Patients with ESRD are known to have higher rates of cancer compared to the general population [11,12]. Given the high mortality with ESRD, however, routine cancer screening in these patients is controversial and often not indicated for most patients as they will likely die before cancer develops and is detected. Cancer screening for transplant candidates, however, is generally required as these patients are typically expected to have better survival. As such, candidates at our institution are screened for cancer according to recommendations that apply to the general population including mammography, PAP smear and colorectal cancer. In our study population, no patients were screened to have clinically significant breast, cervical, colorectal or skin cancer that excluded them from transplant candidacy. Many serum tumour markers are unreliable in ESRD patients because of dialysis and haemoconcentration,

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Table 3. Only 3/6 patients with urothelial carcinoma presented with atypical cytology.

Pt #	Cytology	Smoking history	Tumour staging	Therapy received	Surveillance time before listing for transplant	Total time elapsed between TURBT and transplantation
1*	Atypical cytology	Nonsmoker	Low-gradeTaN0M0	TURBT	0 months	5 months
2*	Atypical cytology	Former smoker	Low-gradeTaN0M0	TURBT	0 months	3 months
3*	Atypical cytology	Nonsmoker	Low-gradeTaN0M0	TURBT	0 months	1 month
4*	Negative cytology	Former smoker	Low-gradeTaN0M0	TURBT + mitomycin C	12 months	33 months
5	Negative cytology	Former smoker	Low-gradeTaN0M0	TURBT	–	–
6	No cytology done pretransplant	Former smoker	High-gradeTaN0M0	TURBT + mitomycin	–	–

All patients had urothelial carcinomas that were nonmuscle invasive and treated with TURBT. One patient had high-grade NMIBC. Two patients had mitomycin either due to multiple tumours or high grade.

*Signifies patients who underwent pretransplant cystoscopy.

Table 4. Patients 3 and 6 have developed recurrence post transplant – patient 3 has also had progression post-transplant.

Pt #	Recurrence post-transplant	Further bladder cancer treatments post-transplant
1*	No	None
2*	No	None
3*	Yes – multiple local recurrences requiring TURBT and mitomycin. Eventual progression to MIBC and left native kidney showing cytology positive for malignant cells	Left-sided laparoscopic nephroureterectomy with partial cystectomy in March 2017 Final pathology pT3N0 HGUC with squamous differentiation Eventual widespread high-grade recurrence in remaining bladder and subsequent distant metastatic progression
4*	No	None
5	No	None
6	Yes	Low-grade NMIBC recurrences requiring recurrent TURBT and multiple courses of mitomycin

Both patients have required further surgical therapy.

*Signifies patients who underwent pretransplant cystoscopy.

however, total PSA appears to be valid in this population [13,14] and we continue to screen for prostate cancer in our transplant candidates.

While screening for bladder cancer is not routinely done in the general population, several studies have reported bladder cancer to be more common in ESRD patients and for this reason, we have been using urine cytology as such a test in renal transplant candidates. De Sala O'shea *et al.* [15] reported that bladder cancer was present in 4 of 14 (28.5%) patients on haemodialysis, whereas Pecqueux *et al.* [16] reported that kidney and bladder cancers make up 36% (12 of 33) of all malignancies found in ESRD patients. In a large cohort study of 831 804 patients, Maisonneuve *et al.* reported that the incidence of bladder cancer was higher in patients on maintenance HD than in the general population. Overall the standardized incidence ratio of bladder and ureteric carcinoma is thought to be in the range of 1.5–16.4 in the ESRD population [12]. In our study population, we studied ESRD patients, in particular those presenting for renal transplant work up and identified 6 of 703 (0.85%) with bladder cancer. This suggests that the incidence of bladder cancer in renal transplant candidates remains significantly higher than that of the general Canadian population where the lifetime incidence is 0.018% and 0.006%, in males and females respectively [17]. These values are likely representative of a North American population as previous studies have identified that the incidence of urothelial carcinoma in ESRD to be higher in Chinese patients with cumulative incidence of urothelial carcinoma between 0.77% and 1.7% in haemodialysis patients [18–

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20] and 3.1–4.1% in renal transplantation recipients [21,22].

Despite several studies showing increased incidence of bladder cancer in ESRD patients, the actual pathogenesis remains unclear. Possible aetiologies that have been suggested include presence of chronic infection, especially in the urinary tract, a weakened immune system, previous treatment with immunosuppressive or cytotoxic drugs with the development or treatment of kidney disease (oral cyclophosphamide use, analgesic use leading to chronic tubulointerstitial disease) [12], nutritional deficiencies and altered DNA repair [11].

Urine examination is considered to be one of the oldest clinical laboratory tests known to humans. The examination of urine sediment smears was first popularized by George Papanicolaou and Marshall in the 1940s for bladder cancer detection and follow-up. Indications for urine cytology fall mainly into three categories; the most common one is patients with haematuria. The second indication is follow-up of patient with bladder cancer and third is as screening of high-risk groups for bladder cancer such as those exposed to aniline dye or to aromatic amines and those with history of urinary bilharziasis [23]. The accuracy of urine cytology diagnosis depends on several factors that are related to tumour grade, type of the specimen and sampling. In the non-ESRD population, it has been widely accepted for the diagnosis of high-grade urothelial carcinoma with a sensitivity as high as 50–85% [24]. However, low-grade tumours are not detected reliably by cytology, with sensitivity and specificity values as low as 8.5% and 50% respectively [25].

There are several situations that can affect the cellularity and the cytology of the cells, including instrumentation, inflammation, infection, surgical manipulation, treatment with chemo and radiotherapy and calculi, making it difficult even for the experts to reliably discriminate malignant cells. These cases often fall into the atypical categories [26].

Efforts have been made to sub-classify atypical urine cytology results. Brimo *et al*. [27] subcategorized atypical cytology cases into favour reactive process versus unclear but did not find significant increased risk of urothelial neoplasia compared with benign category. Similarly, Chau *et al*. [28] subclassifed atypical cytology results into atypical favour benign versus favour not otherwise specified/LG/HG/neoplasm, however, there was no statistically significant difference in sensitivity and specificity to detecting high- and low-grade cancers. Ubago *et al*. attempted to characterize atypical cytology and identified that atypia was most common in urinary diversion specimens (16%) and least common in upper tract cytology (3.8%). Atypical upper tract specimens had highest percentage of progression to high-grade carcinoma [29]. The role of urinary cytology has not been well studied in the ESRD population and has only been investigated in the context of small studies or case reports. In a report, nine dialysis patients with analgesic nephropathy were screened with urinary cytology, leading to the diagnosis of urothelial malignancy in three individuals [30]. In a case report, bladder washing cytology was reported to be effective in identification of bladder cancer in an anuric haemodialysis patient [31]. Our study is the first and largest to investigate cytology in the specific context of screening in renal transplant candidates.

Our study shows for the first time that the rate of atypical cytology in this population (36%) is much higher compared to the general population which has been previously reported as low as 1.9% [32]. We discovered that not only did very few patients with atypical cytology actually have urothelial carcinoma, not all patients with urothelial carcinoma had atypical cytology at pretransplant workup suggesting that it is an unreliable screening test in the population being worked up for transplantation. Overall, we found the sensitivity of atypical cytology to identify urothelial carcinoma to be 0.6 (3/5), specificity 0.65 (277/425), with a positive and negative predictive value of 0.02 (3/151) and 0.65 (277/425) respectively. We speculate that this high rate of atypical cytology in the ESRD population may be a result of low urine output and subsequent injury to urothelial cells within stagnant urine or urothelial cell damage directly secondary to ESRD. None of the studied patients had suspicious or positive cytology. This is not entirely surprising given that urinary cytology is mainly sensitive for high-grade disease but has poor sensitivity for low-grade tumours and the majority of cases identified in our patient population were of low grade.

End-stage renal disease can complicate bladder cancer diagnosis in patients as gross haematuria, which is the general presentation of bladder cancer is hard to determine because of anuria or oliguria in ESRD patients. Thus the detection of bladder cancer may be delayed and the tumour stage at diagnosis will be advanced [33]. Urothelial carcinomas in patients on haemodialysis have generally been found to be high-grade malignancies and are diagnosed at an advanced stage [33,34]. Whether length of time on dialysis increases risk of bladder cancer remains unclear. While Maisonneuve *et al*. [11] did not find such an association, Sato *et al*.

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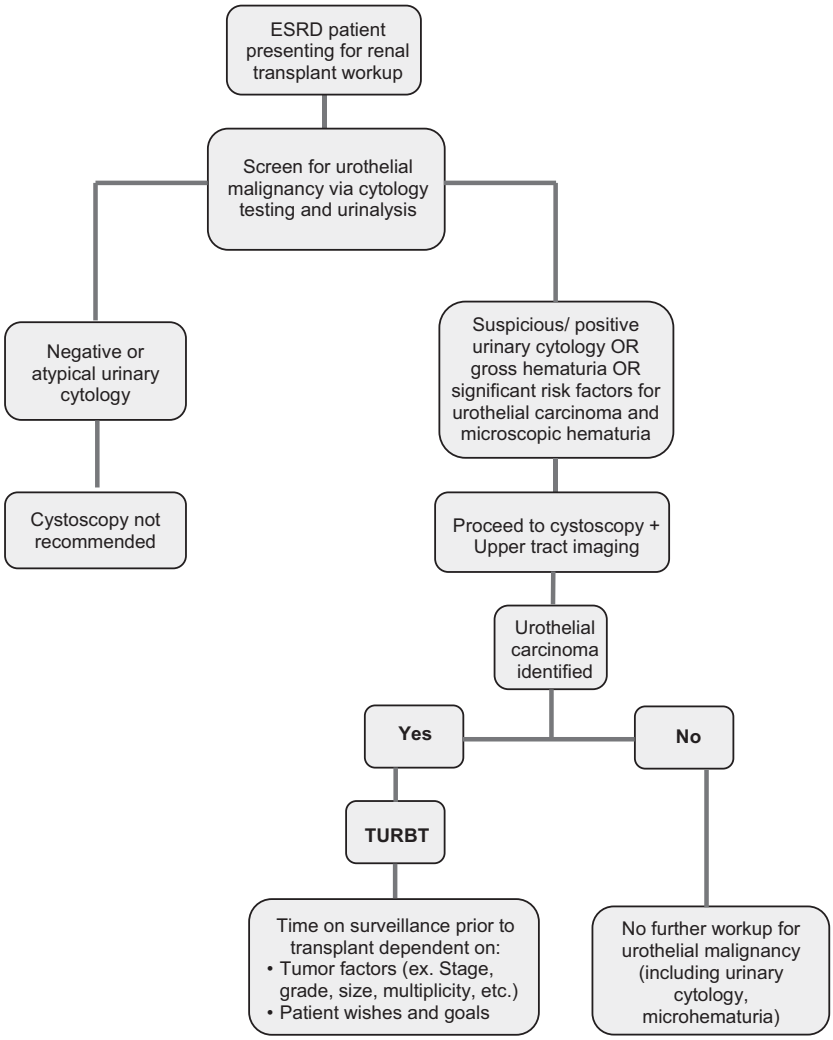

Figure 2 Proposed urothelial cancer screening decision tree for end-stage renal disease patients presenting for renal transplant work up.

[33] found that patients with muscle invasive or high-grade T1 stage cancer at initial visit had a tendency to have a longer duration of dialysis than those with bladder cancer that was more superficial. While in some previous studies, asymptomatic gross haematuria or bloody urethral discharge allowed the detection of bladder cancer in dialysis patients [33–35], none of the patients in our study reported any gross haematuria possibly because most cases identified were low grade. On the other hand, microscopic haematuria is also common in patients with ESRD because of their underlying renal disease and over 60% of patients in our study had microscopic haematuria at time of transplantation workup, highlighting the lack of specificity of this to ESRD patients with bladder cancer.

As part of the renal transplant work up at our institution, all candidates also undergo ultrasound assessment of their kidneys and bladder. Renal cell carcinoma is generally more common in the ESRD population (standardized incidence ratio 3.6–24.1) [12]. Guidelines recommend that patients with localized RCC should wait 2 years from successful treatment to transplantation (5 years for large or invasive tumours) but patients with incidental small renal masses may not require any waiting period. We did not identify any patients with renal masses requiring surgical resection pretransplant. The increased risk of renal cancer is partly because of acquired cystic disease (ARCD) from dialysis. Patients less than 3 years of dialysis have only 10–20% incidence of ARCD [36] and given that our mean dialysis vintage before transplantation (Fig. 1) was within this timeframe may be reason for lack of renal cancer identified. Ultrasound also did not identify presence of upper tract urothelial carcinoma in any renal transplant candidates. Moreover, of the patients identified to have bladder cancer, no such lesions were identified on ultrasound supporting the high false negative rate of this imaging modality, especially for tumours superficial tumours of smaller size. Thus while not of high value for excluding malignancy, ultrasound evaluation is still useful for

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assessment of the pelvic vessels, urinary obstruction and need for native kidney nephrectomy.

It is currently unclear what the recurrence rate is for patients with pre-existing bladder carcinoma following transplantation. Studies to date demonstrate an overall recurrence rate of 18–26% following transplantation [37,38]. Patients with superficial lesions (pTa, unifocal, low grade) have a high risk of local recurrence (up to 60%) but low risk of progression to invasive or metastatic disease [39]. Of our 6 patients with urothelial malignancy who underwent renal transplantation, all had pTa disease and two developed recurrence (33.3%). One case of low-grade urothelial carcinoma identified preoperatively recurred and progressed postoperatively into muscle invasive disease.

Most renal transplant candidates with a history of malignancy should wait a period of time between successful treatment and transplantation [4–7]. Length of time will depend on the type of malignancy and its associated rate of recurrence. The KDIGO guidelines do not recommend any additional waiting time for treated superficial bladder cancer[5] but given that there is a chance of cancer recurrence/progression post-transplant (due to immunosuppression), we feel it is reasonable that waiting time be individualized based on standard pathologic prognostic factors (i.e. stage, grade, size, multiplicity, CIS, LVI, variant histology). Post resection, superficial tumours should receive continued surveillance as per cancer specific guidelines. In our study, the wait time between initial TURBT and transplant ranged from 1 to 33 months. The patient with the shortest time between TURBT and transplant did ultimately have progression to muscle invasive bladder cancer necessitating partial cystectomy and left nephroureterectomy postoperatively. This patient was not able to undergo BCG therapy because of their immunocompromised state. BCG exerts its antitumour activity through induction of pro-inflammatory cytokines, while immunosuppressive agents prevent organ rejection by suppressing pro-inflammatory and promoting anti-inflammatory responses. Thus, in the setting of transplant populations, the use of intravesical BCG for bladder cancer has the possibility of either promoting allograft rejection or being rendered ineffective by the action of the immunosuppressive agents that blocks the proinflammatory response [40].

Given that all transplants were done at a single institution, all urine cytology specimens were analysed through a single pathology laboratory. The cytopathologists at our institution did not have prior knowledge that patients were in renal failure. Since ESRD is a potential known cause of abnormal urine cytology, lack of this knowledge may have resulted in an increased rate of atypical cytology. Moreover, the cytologic characteristics leading to calling atypical urines in these patients was not noted. One common ancillary tests used to clarify inconclusive cytological findings is the UroVysion FISH test. This is an FDA approved test based on *in situ* hybridization of cytogenetic changes specific to urothelial carcinoma [41]. None of the patients in our study underwent UroVysion testing as this is not available at our institution, however, this may be a possible second layer of screening for patients with atypical cytology especially, for those patients in whom cystoscopy is best avoided.

Our study is the largest to date evaluating the incidence of urothelial carcinoma in ESRD patients presenting for renal transplant workup. Our data suggests that the incidence of bladder cancer in renal transplant candidates is higher than general population, and hence we continue to support the use of urinary cytology during the transplant screening process, especially for patients who are at high risk for bladder cancer. However, patients with atypical cytology alone (without any risk factors) should not undergo cystoscopy as our data suggests that although 35% of our study population had atypical cytology, almost none had bladder cancer. Most cases were superficial low-grade disease, however, and atypical cytology appears to be poor at identifying these lesions in renal transplant candidates. While some of these superficial low-grade tumours may be not identified preoperatively with this strategy, these lesions are not absolute contraindications to renal transplantation and may not require any waiting time [6]. A limitation of our study was that we did not have any patients with suspicious or positive cytology because of lack of high-grade lesions and this is why we cannot just broadly dismiss use of urine cytology. These patients with suspicious or positive cytology should undergo cystoscopy, along with other high-risk patients including those with gross haematuria, significant smoking history, cyclophosphamide or pelvic radiation. The use of microscopic haematuria in the ESRD population however, is debatable as it is not sensitive or specific in this population. Our proposed decision tree for urothelial cancer screening is outlined in Fig. 2.

Authorship

JL, OA, PPL and AS: designed research/study. JL, OA and AS: participated in writing of the paper. JL, AD, OA and HB: participated in data collection and analysis.

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Conflicts of interest

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