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Development of urological cancers in renal transplant recipients: 30-year experience at the Frankfurt Transplant Center

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Fatal post-transplant malignancies with a high proportion of genitourinary neoplasms represent a serious long-term challenge. With continuous improvement of the allograft and patient survival, cancer development after renal transplantation may soon turn to the leading morbidity cause. In a retrospective single-center study of 1990 renal transplant recipients between November 1979 and November 2009, records of patients with urological neoplasms including epidemiological, clinical and survival parameters were accessed. Sixty-six de novo urological malignancies in 58 recipients were recorded in the study period, being most common after skin cancers (15.6% of enregistered tumors). From these, 29 were renal cell cancers, including five neoplasms of transplanted kidney, 24 transitional cell carcinomas, 11 prostate carcinomas, and two germ cell carcinomas with incidence rates of 1.5%, 1.2%, 0.9% and 0.2%, respectively. The patient follow up was virtually complete. Tumor-related death was found in 44% of cases. By multivariate analysis, no influence of either duration of dialysis, mode or duration of immunosuppression, gender or age at transplantation on overall patient survival could be demonstrated. This study, documenting a 30-year single center experience, emphasizes the increased risk for urological neoplasms occuring after renal transplantation. Screening strategies for urological cancers should be optimized. (*Cancer Sci* 2010; 101: 2430–2435)

Recipient acceptance of donor alloantigens in transplanted organs can be predominantly ensured through the immune response being down-regulated by immunosuppressive drugs. The development of potent immunosuppressive medication revolutionized the transplantation field and contributed to its nowadays consolidated role as a standardized therapeutic approach, especially in renal transplantation; however, there are various adverse effects arising with long-term administration of such drugs. Besides drug-specific pharmacological side-effects, other potentially dangerous issues, such as bacterial,[1] viral[2,3] and fungal infections,[4] the development of cardiovascular disease[5,6] and especially different neoplasms,[7–9] represent an increasing threat to the recipient.

Carcinogenic properties as well as cancer-progressing characteristics of some immunosuppressive agents have been described, such as calcineurin inhibitors like cyclosporine A (CsA) or tacrolimus (Tac) by interfering with TGF-β pathways,[10,11] also azathioprine (AZA) is associated with neoplastic transformation via DNA intercalation.[12] In addition, immunosuppression per se leads to an impairment of tumor cell monitoring that may be crucial in tumor pathogenesis. Other possible and additional factors include viral infections[13] and chronic uremia.[14,15] Newer immunosuppressive drugs such as mycophenolate mofetil (MMF) and most recently mammalian target of rapamycin (mTOR) inhibitors may possess antitumor properties,[16] but their precise mechanisms and potential need to be evaluated in future trials.

Actually, morbidity and mortality of renal transplant recipients (RTR) are still mainly of cardiovascular origin, but it has been suggested that within the next 20 years death due to tumor development will be the principal cause of death in this patient category.[17] The incidence of malignant tumors has been assessed to average out at 20% after 10 years[18] and almost at 30% after 20 years[19] after transplantation, and the overall malignancy risk is almost three times higher than in the general population.

Among urogenital tumors in RTR, a highly increased incidence rate of renal cell carcinoma (15-fold), bladder (three-fold), testicular (three-fold) and prostate cancer (two-fold) have been estimated compared with the general population.[9] Extending our knowledge on the occurrence of urogenital tumors in RTR may ultimately lead to better patient management.

Therefore, the purpose of our study was to provide clinical and statistical data of RTR associated with urological tumors over a period of 30 years of data registry at our transplant center.

Materials and Methods

Epidemiological and clinical data for this study were collected through retrospective analysis of archive documents at Frankfurt Transplant Center (Frankfurt, Germany) regarding pretransplant preliminaries, stationary procedures and follow-up examinations. Renal transplant recipients who developed de novo urological malignancies (prostate cancer [PCA], transitional cell carcinoma [TCC], renal cell cancer [RCC] and germ cell cancer [GCC]) in particular were evaluated; penile cancer did not occur in the study cohort. All patients were monitored in our transplant center by regular follow-up visits, including renal ultrasound examinations at least annually. Continuous personal medical attendance for years was essentially ensured by three of the authors, H.-G.K., J.G. and E.-H.S.

Specific parameters of study interest such as age at kidney transplantation and cancer diagnosis, gender, cause of end-stage renal disease (ESRD) leading to dialysis, date of dialysis initiation and transplantation, immunosuppressive therapy, date of urological cancer diagnosis, cancer therapy regimen, serum creatinine values at cancer diagnosis, throughout therapy and at the last follow up were selected. Study endpoints were death or end of the study period (November 2009) with virtually completed

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follow up for the whole study cohort. Descriptive statistics were presented with commercially available Microsoft Office Excel 2007 and statistical tests performed with statistical program PASW version 18 (SPSS Inc., Chicago, IL, USA). The most descriptive findings were presented as mean, median and standard deviation. Relative risk (RR) for cancer development compared with the general population was calculated using age-, gender- and period-matched comparison data of the general population provided by the Saarland Tumor registry (http://www.krebsregister.saarland.de/datenbank/datenbank.html). Multivariate analysis with the Cox-regression model to examine the influence of different parameters on overall and (tumor-)specific patient and graft survival, and Kaplan–Meier estimation concerning overall, (tumor-)specific patient survival as well as graft survival was performed. Tumor staging and grading were presented according to currently valid (tumor-)specific TNM- and histopathological grading classifications. Moreover, the Gleason score (Gl) for prostate carcinoma and the clinical staging system for testicular cancer were provided.

Results

General aspects. Out of 1990 patients being successfully transplanted at our institution between 1979 and 2009 (Table 1), 374 individuals developed 423 malignancies (cumulative incidence 21.3%; Table 2). Fifty-eight patients (44 men, 14 women) developed 66 de novo urological malignancies (cumulative incidence 3.3%), including 29 RCC, 11 PCA, 24 TCC and two GCC (see data summary of clinical epidemiology in Table 3). The mean patient follow-up time period was 61.6 ± 62.1 months (median 42.0, range 0–290 months).

Table 1. Numerical statistics of renal (mono or combined) transplantations at the Frankfurt Transplant Center between November 1979 and November 2009

Transplanted organ	Male	Female	Total (%)
Kidney from deceased donor	1061	638	1699 (85.38)
Kidney from living donor	153	79	232 (11.66)
Liver/kidney	7	5	12 (0.60)
Heart/kidney	4	1	5 (0.25)
Pancreas/kidney	25	17	42 (2.11)
Total patient numbers†	1250	740	1990 (100)

†Each number represents one case = patient.

Table 2. Cumulative numbers of all malignancies in renal transplant patients during the study period

Localization or type of malignant tumor	Male	Female	Total tumor cases (%)
Urological	49	17	66 (15.6)
Skin	126	62	188 (44.4)
Gastrointestinal	31	19	50 (11.8)
Lung	14	10	24 (5.7)
Hematological	20	17	37 (8.7)
Gynecological	0	33	33 (7.8)
Kaposi's sarcoma	3	1	4 (0.9)
Atrial sarcoma	0	1	1 (0.2)
Oropharynx	2	0	2 (0.5)
Thyroid gland	4	1	5 (1.2)
Salivary gland	2	0	2 (0.5)
Jaw	1	0	1 (0.2)
Tongue	2	3	5 (1.2)
Pleuramesothelioma	1	0	1 (0.2)
Brain	2	2	4 (0.9)
Total tumor cases†	257	166	423 (100)

†Each number represents one tumor case.

Ten patients with RCC and 15 with TCC presented clinical symptoms leading to diagnosis. One patient with PCA was clinically symptomatic at presentation without prostate-specific antigen (PSA)-elevation (cut-off 4 ng/mL), while 10 others experienced PSA-elevation with clinical symptoms only in two cases. Both patients with GCC had overt clinical disease manifestations.

Chronic glomerulonephritis represented the most frequent cause of ESRD (Table 4). Two patients received grafts from living donors (3.4%), but most were from deceased donors. Three second but no third transplantations were carried out in the study cohort. After tumour diagnosis, an immunosuppressive regimen was not commonly modified in our center. The mean serum creatinine level at diagnosis was 1.8 mg/dL (median 1.6). The immunosuppressive strategy included, in general, the use of steroids in combination with a calcineurin inhibitor and/or an antimetabolite (AZA or MMF).

Urological malignancy was the most frequent cause of death (12 of 27 patients, 44.4%) within the study cohort (Table 5). (Tumor-)specific survival data are presented in Table 3. The 1-, 5- and 10-year overall patient survival rates were 86.8%, 63.9% and 39.7%, respectively; and the overall graft survival rates were 100%, 85.1% and 63.2%, respectively. The mean transplant survival rate constituted 141.4 ± 88.0 months (median 128). By multivariate analysis, there was no significant influence of the duration of dialysis, duration and mode of immunosuppression, gender and age at the time of cancer diagnosis or transplantation on the overall patient or graft survival of RTR with urological cancers. However, there was slightly improved graft-specific survival in patients with immunosuppressive regimens including AZA compared with those with MMF ($P = 0.02$). Of the study cohort, 23 (39.7%) patients died with functioning grafts and eight (13.8%) went back on dialysis. During the study follow up, 17 additional non-urological malignancies were found in 14 patients with urological cancers (incidence 29.8%). These comprised skin (six cases), lung (one case), hematological (three cases), gastrointestinal (two cases), breast (one case) and oropharyngeal cancers (two cases), as well as Kaposi's sarcoma (two cases).

Renal cell cancer. Twenty-five RTR developed 24 RCC of native kidneys with two cases of synchronous bilateral and two others of bifocal unilateral tumors, as well as five cancers of the renal graft (43.9% of all urological neoplasms detected, incidence 1.5%, RR 4.9, in addition see Table 3). Six patients received anti-thymocyte globulin (ATG) and one patient received basiliximab as induction or anti-rejection treatment. Thirteen recipients had CsA/AZA/Steroids (Ster) as the initial immunosuppressive combination with AZA omitted in the further course in 11 patients and CsA omitted in two patients, and Tac substituted for CsA in one and MMF substitued for AZA in two cases, respectively. Three patients received AZA/Ster initially with a switch to Tac/Ster in one case; four other patients had CsA/MMF/Ster with CsA omitted in one patient in the course. Three further RTR were treated with CsA/Ster with a switch to Tac/Ster and AZA/Ster in one case, respectively. The last patient received Tac/MMF/Ster initially with a further switch to CsA/Ster. A switch to rapamycin (RAP)/Ster was carried out in two cases with systemically advanced metastatic disease at the primary diagnosis (one patient with nephrectomy and the other one without operative therapy), as well as in another case of cancer progression 33 months after nephrectomy with systemic filialisation. Mean serum creatinine at tumor diagnosis was 1.9 ± 0.9 mg/dL. Twenty-four patients underwent an operation as the initial treatment. Histologically, surgical specimens revealed 18 clear-cell and 10 papillary carcinomas and were

Table 3. Epidemiological, clinical characteristics and (tumor)-specific survival of renal transplant patients with de novo urological tumors

	Prostate carcinoma	Transitional cell carcinoma	Renal cell carcinoma	Germ cell carcinoma	All urological malignancies
Male/female (patient numbers)	11/0	12/8	19/6	2/0	44/14
Age at renal transplantation (years)	53.5 (58.0) ± 10.2†	54.0 (53.5) ± 7.7	46.6 (49.0) ± 12.8	28.0 (28.0) ± 14.1	49.8 (52.0) ± 11.9
Kidney from deceased donor/living donor (patient numbers)	11/0	20/0	23/2	2/0	56/2
Age at tumor diagnosis (years)	61.3 (61.0) ± 5.0	59.9 (60.5) ± 6.5	55.7 (56.0) ± 11.9	38.5 (38.5) ± 17.7	57.6 (59.5) ± 10.1
Hemodialysis/peritoneal dialysis (patient numbers)	11/0	18/2	25/0	2/0	56/2
Duration of dialysis until renal transplantation (months)	54.9 (60.0) ± 29.5	56.7 (49.5) ± 32.3	46.8 (43.0) ± 30.4	92.0 (92.0) ± 52.3	53.3 (49.5) ± 31.8
Time period of tumor development after renal transplantation (months)	72.6 (58.0) ± 84.1	83.5 (62.0) ± 67.8	107.6 (102.0) ± 61.1	60.5 (60.5) ± 37.5	95.4 (86.5) ± 67.3
Tumor-specific survival at 1-/5-year after cancer diagnosis (%)	100.0/85.7	84.7/67.2	90.4/83.5	50.0/50.0	88.6/76.5

†Variables are presented as mean (median) ± standard deviation.

Table 4. Causes of end-stage renal disease in studied renal transplant patients with de novo urological cancers

	PCA	TCC	RCC	GCC	Total
Chronic glomerulonephritis	6	8	15	1	30
Autosomal-dominant polycystic kidney disease	1	2	2	0	5
Diabetic nephropathy	1	0	0	0	1
Nephrosclerosis	1	1	0	0	2
Renal artery stenosis	1	0	0	0	1
Urate nephropathy	1	0	1	0	2
Vesicoureteral reflux	0	0	1	1	2
Chronic pyelonephritis	0	3	3	0	6
Balkan endemic nephropathy	0	2	0	0	2
Analgesic nephropathy	0	3	0	0	3
Congenital megaureter	0	0	1	0	1
Congenital renal dysplasia	0	0	1	0	1
Wegener's granulomatosis	0	0	1	0	1
Unknown	0	1	0	0	1
Total patient numbers†	11	20	25	2	58

†Each number represents one patient. GCC, germ cell carcinoma; PCA, prostate carcinoma; RCC, renal cell carcinoma; TCC, transitional cell carcinoma.

staged to pT1 in 18 cases, pT2 in five cases and pT3 in four cases (the classification of the pT-stage was not possible in one shrunken kidney); in all cases, R0-resection was accomplished. The grading was G1 (six cases), G2 (20 cases) and G3 (two cases). In one case with systemic progression after surgical approach, cytokine therapy with interferon alpha was conducted, followed by therapy with RAP/capecitabine at progress of metastatic disease. The regimen was then changed to MMF/capecitabine and lastly switched to everolimus/capecitabine. The patient's tumor-specific survival was 64 months after diagnosis of metastatic disease. Cytokine therapy led to transient deterioration of kidney function (serum creatinine elevation from 1.4 to 2.5 mg/dL and significant proteinuria) with improvement after the therapy ended. Another patient with metastatic disease at diagnosis received chemotherapy with 5-fluorouracil after nephrectomy leading to a serum creatinine elevation from 2.2 to 3.4 mg/dL during treatment and rapid amelioration after the therapy ended. No other cases of impairment of kidney function due to tumor therapy were explored in this subgroup. The mean creatinine at the last follow up was 2.7 ± 2.2 mg/dL. Six patients returned to dialysis during follow up after a period of 145.7 ± 69.6 months. At the end of the study, 14 patients were in complete remission, one patient had progressive disease, four patients with RCC had died and five patients with other causes (pancreas cancer, rectum cancer, breast cancer, cardiac failure, septic cholangitis) had died. One patient was lost to late follow up due to relocation to another region.

Transitional cell cancer of the bladder and upper urinary tract. Eighteen de novo malignant cancers of the bladder and six tumors of the upper urinary tract occurred in 20 individuals out of 1990 RTR (36.4%, incidence 1.2%, RR 1.9 [for bladder cancer]; Table 3). One patient had a unilateral cancer of the pelvis 4 years before the RT and remained in complete remission until the RT; he experienced TCC of the contralateral pelvis and bladder further on in the course. Three RTR had analgesic nephropathy and two others suffered from balkan endemic nephropathy, being known as risk constellation for the development of TCC. Anti-thymocyte globulin (ATG) (four cases), interleukin 2 receptor antagonist (one case) and OKT3 (one case) were used as induction or anti-rejection agents. In 14 cases, the initial immunosuppressive treatment consisted of CsA/AZA/-Ster with AZA omitted in the further course of treatment and a switch to Tac/Ster in another patient already before cancer diagnosis. In two cases, the initial combination of CsA/Ster was changed to AZA/Ster in the further course of treatment, and in one patient, this protocol remained unchanged after the RT; three other patients received AZA/Ster continuously from the beginning. There was no modification in the immunosuppressive regimen along with the cancer diagnosis. Mean serum creatinine at cancer diagnosis was 1.7 ± 1.1 mg/dL. As the definitive treatment depending on the tumor stage, transurethral resection of the bladder (TUR) was sufficient in seven RTR with non-muscle-invasive (pT < 2) bladder cancer; radical cystectomy was performed 11 times in cases with muscle-invasive cancer (pT ≥ 2) or high-risk constellations for local or systemic progression (e.g.

Table 5. Causes of death of the studied renal transplant patients with urological cancer during follow up

	Urological malignancy	Other malignancy	Cardiovascular Disease	Uremia	Gastrointestinal disease	Sepsis
Male/female (%)† of all deaths	9/3 (44%)	3/1 (15%)	4/1 (19%)	0/1 (4%)	2/1 (11%)	2/0 (7%)

†Percentages refer to 27 deceased patients.

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pT1G3 in TUR), failure of adjuvant instillation therapy after TUR with tumor progression or multifocal recurrence. Nephroureterectomy was performed 16 times (causal and prophylactic in cases of high-risk cancer), and all operations were R0 resections. All tumors were histologically urothelial carcinomas with the grading distribution of bladder cancers as G1 (five cases), G2 (five cases) and G3 (eight cases), and upper urinary tract tumors as G2 (three cases) and G3 (two cases); additionally, in one case, a locally advanced ureter tumor (T4) was diagnosed by autopsy without performing a tumor grading. In five patients with non-muscle-invasive cancer, intravesical instillation of mitomycin (four cases) and epirubicin (one case) was performed as treatment for recurrent cancer. One patient with systemically advanced disease received three courses of palliative systemic combination chemotherapy with methotrexate and vindesine. There were no cases of impaired renal function due to cancer therapy in this group. The mean serum creatinine level at the last follow up was 2.5 ± 2.2 mg/dL. Four patients in this group went back on dialysis after the mean time of 109 ± 33.4 months after transplantation. At the end of the study, six patients were in complete remission, one patient developed progressive disease, six recipients died due to TCC and seven other patients died due from other causes (apoplex, cardiac infarction, cardiac failure in two cases, uremia, pancreatitis, pharynx cancer).

Prostate cancer. Eleven de novo PCA were detected (16.7%, incidence in male RTR 0.9%, Table 3); histologically, all were adenocarcinomas, nine were diagnosed by prostate biopsy because of PSA elevation and two were detected incidentally by transurethral resection of prostate hyperplasia. One patient had a history of RCC with unilateral nephrectomy 20 years before the RT with complete remission of this entity over the entire follow-up period before and after transplantation. The immunosuppressive regimen in this group consisted of CsA/MMF/Ster (three patients) with a switch to Tac/Ster in two patients before cancer diagnosis; furthermore, CsA+AZA/Ster (four patients) with withdrawal of AZA in the further course of three patients. Two patients received CsA/Ster, with CsA changing to AZA in one case and MMF added in the other; two other patients continuously received AZA/Ster. Anti-thymocyte globulin (ATG) was used as induction therapy in one case. The mean serum creatinine at tumor diagnosis was 1.7 ± 0.5 mg/dL. Changes in the immunosuppressive regimen due to cancer were performed in two cases, with reduction of the AZA dosage in the first (localized stage) and a complete switch of immunosuppression to RAP/Ster in the second (systemically advanced stage) without subsequent impairment of kidney function. The median serum PSA value at diagnosis was 8.6 ng/mL (range 2.8–299.0). The primary treatment approach depending on the tumor stage and the patients' comorbidities consisted of radical prostatectomy (five of 11 cases, 45.4%), each classified as follows: pT2aG2N0R0 Gl 2 + 3 = 5; pT2bG1N0R0 Gl 1 + 2 = 3; pT2cG2N0R0 Gl 3 + 3 = 6; pT3aG2-3N0R0 Gl 3 + 5 = 8; pT3aG2N0R1 Gl 2 + 3 = 5, with the latter patient receiving percutaneous radiation therapy at the biochemical progress in the later course and androgen deprivation at systemically detected progression. Radiation therapy was applied as the primary approach (4 of 11, 36.4%), classified as pT1aG2 Gl 3 + 3 = 6 (two cases), pT1cG1 Gl 1 + 2 = 3 (one case) and pT1cG3 Gl 3 + 4 = 7 (one case). One patient primarily received a high-intensity-focused ultrasound and was categorized as pT1cG2 Gl 3 + 3 = 6. One patient with osseous metastases at presentation, classified as pT1cG2-3M1 Gl 3 + 5 = 8, was treated with androgen deprivation and after the occurrence of androgen resistance, chemotherapy with 10 courses of docetaxel was carried out without a negative influence on kidney function. There was only one registered episode of perioperative renal function deterioration (serum creatinine level elevation from 1.3 to 21 mg/dL) achieving preoperative values shortly afterwards. Mean serum creatinine level at the last follow up was 2.3 ± 1.6 mg/dL. During the entire follow up, only one patient went back on dialysis in this group 91 months after the RT. At the end of the study, six patients were in complete remission, one patient experienced progressive disease, one patient died of PCA and three other patients died of PCA-independent causes (i.e. cardiac failure, acute gastrointestinal bleeding and lung cancer).

Germ cell cancer (GCC). Two patients developed GCC (3.0%, incidence in male recipients 0.2%, one late-onset seminoma [pT1R0 (clinical stage [CS] I with negative serum tumor markers), diagnosed at the age of 51], and one malignant trophoblastic teratoma (pT2R0 [CS III with elevation of lactate dehydrogenase]), diagnosed at the age of 26; Table 3). In both cases, induction therapy with ATG was performed, maintaining a combination of AZA/Ster at cancer diagnosis. The clinical appearance was a painless growth of unilateral testis in the first case and vomiting, nausea and dyspnoe in the second case (with a prior history of unilateral maldescensus testis). The seminoma was treated with two courses of carboplatin chemotherapy after orchidectomy without any deterioration of the kidney graft function and showed a progression-free survival of almost 10 years. The patient with a teratoma had a systemically advanced disease at diagnosis with pulmonary and cerebral metastases and died shortly after orchidectomy.

Discussion

The present retrospective analysis comprises all de novo urological malignancies in RTR diagnosed over a period of 30 years and therefore provides, to our knowledge, the largest data set from a single transplant center assessing this issue. Notably, not only deceased donors, but also living donors and combined transplantations were recorded. The data therefore cover a very long period in the field of renal transplantation, which allowed us to collect and study a greater number of transplanted patients with urological neoplasms for appropriate follow-up periods, and thereby temporally comprising the transition from older to more recently established immunosuppression regimes.

By now, there is no doubt that RTR bear a strikingly increased mortality risk when compared with the general population.[8,20] Malignancies at large thereby represent an increasing cause of mortality, which even begins to overtake cardiovascular disease in some series (for a review see Marcen and references therein).[21] Our registry data underscore this notion, demonstrating a cumulative cancer incidence of over 21%, which is high, also in light of other available data, but naturally depends on the duration of follow up after transplantation.[20,22–24]

Of special interest, urological tumors in the body accounted for a remarkable proportion of all tumors occurring in RTR at our center, with 15.4% of the tumor entities registered, and ranging statistically in second place behind the known high-incidence rates for skin cancers. Comparable statistical data have also been reported from other data records, identifying urological tumors as the second or third most common malignancies.[22,23,25,26] Thus, in line with other reports, RTR hold a strikingly increased risk of developing urological neoplasms compared with the general population.[24]

The cumulative incidence rates for all urological tumors observed in our transplant collective are in the range of data obtained by others. A more recent investigation reported a 3.1% overall incidence of urological neoplasms, similar to the rates we observed in our study with 3.3%.[27] Of note, analysis of the causes of death within RTR with urogenital tumors in our collective clearly reveals that urological tumors themselves account for the prevailing numbers of deaths, by far more than other non-urological tumors or cardiovascular deaths.

In our investigation, renal cell cancer was the predominant urological tumor entity found, followed by transitional cell

carcinoma and prostate carcinoma; a similar ranking was also observed in the UK transplant population.[24] In contrast, prostate carcinoma was the most common de novo urological malignancy in RTR in a recent publication.[27] Others also document prostate carcinoma and renal cell carcinoma as the most common genitourinary cancers after solid organ transplantation.[25] However, renal cell cancer is mostly found to represent the prevailing urological neoplasm in RTR.[16]

One reason for the discrepancies with regard to the incidence of prostate carcinoma may lie in the fact that over- or underestimation of prostate carcinoma incidence according to applied PSA levels and consecutive indication for biopsy affect the diagnosis in different countries; however, this issue still remains unclear, as well as the true incidence of this malignancy in RT patients. Of note, information from Australia and New Zealand dialysis and transplant registry (ANZDATA) records[20] did not reveal an increased risk for prostate carcinoma.

Ample evidence exists about an increased risk of native kidney malignancies in RTR compared with the general population.[28] However, even before the RT, the prevalence of native kidney malignancies is increased in ESRD patients.[14] Some investigators are suggesting an additional increased risk for developing a RCC that bear RTR in the post-transplant period, a notion that had been attributed to the effect of immunosuppressive therapy.[8,29] Within our collective, five RCC originated from the allograft kidney, a proportion which is not far away from other observations.[22,27] Moreover, our data demonstrate a 4.9-fold risk of renal cancer development compared with the general population and thus substantiates the work of others.[29]

We also revealed a high portion of transitional cell carcinoma from which bladder cancer constituted most of it. Our data give evidence for an increased relative cancer risk, demonstrating an incidence of 1.2% that is slightly higher than previous reports.[24,25,27] However, our data comprised all transitional cell cancers, and thus also upper urinary tract carcinoma (incidence 0.3%). Some reports point to an aggressive nature of bladder cancers in RT patients,[30] a factor that should impact on surveillance in the post-transplant period. In our collective, most of the patients with a diagnosis of TCC presented with clinical symptoms, a circumstance that is also arguing for more accurate screening measures. Differences in the mode of screening and treatment of urogenital tumors (especially RCC and TCC) in RT patients between institutions or countries may still be a major issue[31,32] that needs to be addressed by broad adoption of conjointly designed guidelines. A recent report favors more aggressive and early management when suspected lesions are detected in native kidneys, yielding a favorable prognosis for patients with malignant lesions.[33] Also, some authors argue for more frequent control examinations to detect renal malignancies in the kidneys after RT.[34]

Further information obtained from our tumor collective is that when analysing the impact of different factors, such as the duration and mode of immunosuppression with regard to overall patient survival, no statistical significant influence for any of them could be shown. Thus, the overall influence of immunosuppression regimes might be too weak to exert resounding effects on survival in this group. Only graft-specific survival seemed to be slightly affected by the mode of immunosuppression, yet demonstrated a weak statistical advantage for AZA-*versus* MMF-containing treatment. However, this result could be biased because, for example, patients being transplanted in the azathioprine era on average received a kidney transplant earlier and were younger compared with the situation nowadays.

Interestingly, operative procedures and the application of diverse chemotherapeutical regimes for uro-oncological therapy were only exceptionally associated with a decline of graft function, which was in any case only modest and of transient nature. Thus, an obviously negative effect of the applied therapeutic measures on allograft function cannot be noticed in the studied collective.

It is obvious that immunosuppression in renal transplantation has been widely modified since the mid-90s and the beginning of the last decade to more powerful regimes and this strategy has been adopted by our center with Tac and especially MMF replacing their predecessors CsA and AZA, in many cases not only at the initiation of immunosuppression but also in the sequel after renal transplantation. However, our data recording many patients from the AZA/CsA era cannot adequately address the question, whether introduction of the newer and stronger immunosuppressive protocols affect the development of individual urological tumor entities in RT patients.

Only three patients in our urological tumor collective were treated with an mTOR-inhibitor, although only in the sequel of tumor disease. Immunosuppressive regimens with mTOR-inhibitors have been introduced in a slightly growing number in renal transplantation only recently. Besides its well-established immunosuppressive properties, evidence also suggest that, for example, sirolimus may confer a decreased risk of certain malignancies,[16,35] a concept that needs a careful look at in the future.

In conclusion, this single-center study experiencing 1990 RTR over a period of 30 years documents the importance of urological neoplasms occuring in the sequel of renal transplantation in the adult. Because of the possible increase in their incidence numbers, optimized guideline-directed recommendations for appropriate urological cancer screening and therapy in these patients are warranted.

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Disclosure statement

The authors have nothing to disclose.

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