ORIGINAL ARTICLE

De novo noncutaneous malignancies after kidney transplantation are associated with an increased risk of graft failure: results from a time-dependent analysis on 672 patients

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SUMMARY

The aim of this study was to evaluate the association between cancer occurrence and risk of graft failure in kidney transplant recipients. From November 1998 to November 2013, 672 adult patients received their first kidney transplant from a deceased donor and had a minimum follow-up of 6 months. During a median follow-up of 4.7 years (3523 patient-years), 47 patients developed a nonmelanoma skin cancer (NMSC) and 40 a noncutaneous malignancy (NCM). A total of 59 graft failures were observed. The failure rate was 6 per 100 patient-year (pt-yr) after NCM versus 1.5 per 100 pt-yr in patients without NCM. In a time-dependent multivariable model, the occurrence of NCM appeared to be associated with failure (HR = 3.27; 95% CI = 1.44–7.44). The effect of NCM on the cause-specific graft failure was different ($P = 0.002$) when considering events due to chronic rejection (HR = 0.55) versus other causes (HR = 15.59). The reduction of the immunosuppression after NCM was not associated with a greater risk of graft failure. In conclusion, our data suggest that post-transplant NCM may be a strong risk factor for graft failure, particularly for causes other than chronic rejection.

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Key words
chronic rejection, graft failure, kidney transplantation, malignancy, nonmelanoma skin cancer, post-transplant lymphoprolipherative disorder

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Introduction

Malignancies are an ominous complication following kidney transplantation (KTx): Their incidence is higher than in the general population [1–4], and in kidney transplant recipients (KTR), their behavior is usually more aggressive [1,5,6]. Nonmelanoma skin cancer (NMSC) is the most common post-transplant malignancy [7–10]; however, the highest morbidity and mortality are related to noncutaneous malignancies (NCM), including solid and hematologic tumors [1,3,5,8]. Therefore, in the past decades, screening and active surveillance programmes have been implemented to perform early diagnoses [11,12]: These strategies have not changed substantially cancer incidence [13,14], but have dramatically improved the survival of KTRs after a diagnosis of NCM. Indeed, in Italy, patient survival is as high as 71.3% at 10 years after the diagnosis of a

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NCM [13]. Consequently, novel questions arise about the long-term outcomes of KTR with a post-transplant malignancy, such as the risk of a second tumor [13,15] and the risk of long-term graft failure in patients who survived a NCM.

However, it is not clear how the diagnosis of a malignancy may affect graft function as compared to patients without malignancy. Indeed, there are some studies reporting death-censored graft survival rates after the diagnosis of some specific malignancies (particularly after post-transplant lymphoprolipherative disorders – PTLD and renal cell carcinoma – RCC [16–18]), showing a worse renal prognosis for patients with a malignancy if compared to matched unaffected KTR [19]. However, it is difficult from these studies to quantify the increase in risk of graft failure associated with the development of a tumor.

Indeed, there could be at least two opposite situations: On the one side, immunosuppressive (IS) therapy is often reduced after a malignancy diagnosis [19–21] and exposure to chemotherapy and radiation therapy is common, which may trigger or favor chronic rejection, yielding eventually to a premature graft failure. On the other side, some patients may be particularly "susceptible" to IS and therefore develop some virus-associated malignancy (i.e., PTLD and Epstein–Barr virus (EBV), Kaposi sarcoma and Kaposi sarcoma herpesvirus (KSHV) [22]): These patients may be protected from chronic rejection as they might be adequately immunosuppressed even with a low-dose IS.

Given these premises, the aim of this cohort study was to evaluate the impact of NMSCs and NCMs on death-censored graft survival in a cohort of recipient of their first KTx from a deceased donor, taking into account other known prognostic variables and considering the onset of malignancies as a time-dependent factor.

Patients and methods

Patient selection and design

We retrospectively analyzed a prospective cohort of 672 patients who have been transplanted in a single KTx center between November 1998 and November 2013. Adult patients receiving their first kidney transplant from a deceased donor at our transplant center have been included if they had a minimum follow-up of 6 months after KTx. In the same period in our center, 44 transplants were performed from a living donor and 103 patients received a second or third transplant and were not included in this analysis. Patients with a known active malignancy at the time of transplantation do not receive a KTx, and therefore, none of the included patients were known to carry a malignant disease at the start of observation. However, ten patients developed a NCM within 6 months from transplantation and were excluded as they might have had an undiagnosed malignancy before surgery, even if all KTx candidates underwent a strict pretransplant screening for malignancy and premalignant lesions.

All procedures performed were in accordance with the ethical standards of our institution and with the 1964 Helsinki Declaration and its later amendments. As this is a retrospective analysis, for this type of study, formal consent is not required; however, all patients were informed at the time of transplantation that their clinical data would be used for research purposes and signed a written informed consent.

Data collection and variable definition

Data have been collected from patient records and entered in the local KTx database, which includes their major clinical, demographical, and transplant variables and complications.

Graft failure was defined as the need of chronic dialysis at any time after KTx. Chronic rejection was diagnosed with renal biopsy performed for a worsening renal function or clinically by the presence of a progressive renal function deterioration, increased urinary proteins, and the presence of donor-specific antibodies (DSA), after excluding other plausible causes of renal damage. No patient developed a graft failure due to a late-onset acute rejection. Graft failure due to other causes was usually diagnosed by renal biopsy and included relapse of underlying nephropathy, new onset ("*de novo*") nephropathies (including paraneoplastic nephropathies, like myeloma kidney), BK virus-associated nephropathy, chronic vascular nephropathy (including cardiorenal syndrome), chronic pyelonephritis, and chronic obstructive/reflux nephropathy: These cases have been included in the group of "graft failure not due to chronic rejection." All patients with a NCM were biopsied if they had a worsening renal function or increase in proteinuria and therefore their causes of graft failure are histologically defined.

Malignancy was diagnosed histologically or – rarely – on clinical bases, the latter case being relevant only for NMSC, which were sometimes treated with cryotherapy. All KTRs referring to our center are proposed to cancer screening as for the general population (breast, prostate,

colon rectum, cervix uterus), and additionally, they undergo to a yearly dermatologic evaluation, abdomen ultrasonography, and chest X-ray. NMSC included skin lesions with the ICD-9 code 173, being basal cell carcinomas and squamous cell carcinomas; no Merkel cell carcinomas were diagnosed. NCM included all other invasive malignancies, including both solid and hematologic tumors and excluding precancerous lesions: The ICD-9 codes included 140–172 and 174–208 mostly being carcinomas of gastrointestinal tract, genito-urinary tract, and female breast and hematologic malignancies (Tables S1 and S2).

A strongly reduced IS therapy was defined as a one-drug therapy with very low daily drug exposure, defined as prednisone <10 mg/day, mycophenolate <500 mg/day, tacrolimus or sirolimus or everolimus trough level <4 ng/ml or cyclosporine 2-h blood level <300 ng/ml. No patient was in this group. A reduced immunosuppression (Red-IS) included any single-drug therapy with a daily drug dose or exposure greater than the above cutoffs or a therapy with steroids and either an mTOR-inhibitor or mycophenolate (CNI-free). All other IS drug combinations (i.e., CNI-steroids, CNI-MMF, CNI-mTORi, three-drug therapy) were considered as "standard dose" maintenance IS regardless of drug doses and levels.

Statistical methods

In time-to-event analyses, the primary event of interest was graft failure. Six months after, KTx was considered as the baseline time for all the analyses. Patient's death was considered as a competing event while patients alive without graft failure were censored at the date of last available visit (KTRs undergo at least four nephrology visits each year even if transplant function is stable). The cumulative incidences of graft failures and deaths were calculated using the method of Kalbfleisch and Prentice [23]. To illustrate the effect of tumor (NMSC or NCM) occurrence over time on the risk of graft failure, we used a modified Kaplan–Meier method [24] that estimated cumulative hazard rates of graft failure according to the presence or absence of tumor. All patients at the beginning of the observation were included in the tumor-free group, and the assignment to the tumor group was updated at the time of the tumor diagnosis. To quantify the tumor effect in terms of hazard ratio, we fitted both univariable and multivariable-adjusted Cox models in which patient's status (with or without tumor) was similarly updated. We considered, as adjusting factors in the multivariable models, the following variables evaluated at baseline (i.e., 6 months from KTx): gender, donor age, year of transplant, underlying nephropathy, acute rejection episodes, creatinine, and proteinuria levels. These variables were selected among known predictors of long-term graft failure that were significant risk factors at the univariate analysis in our cohort (Table S3). If two covariates were associated (e.g., donor and recipient age), we maintained in the model the variable with the strongest association or the one with the highest clinical significance.

The heterogeneity of the effect of tumor occurrence on the cause-specific graft failure (chronic rejection versus other causes) was assessed comparing the hazard ratios estimated from two time-dependent multivariable Cox models, using the methods described by Putter *et al.* [25]. In the two models, chronic rejection and failure from other causes were considered alternatively as the event of interest or as the censoring event.

Finally, to evaluate the joint effect of the reduction of the IS therapy and the occurrence of NCM on graft failure, a Poisson regression analysis was performed. For each patient the observation time was split into the following periods: (i) free from NCM and treated with full dose of IS therapy, (ii) free from NCM and treated with a reduced dose of IS therapy, (iii) with NCM and treated with full dose of IS therapy, and (iv) with NCM and treated with a reduced dose of IS therapy. In each time period, the graft failure rate was calculated. The Wald test was used to compare different rates.

All statistical analyses were performed with SAS (SAS institute, Cary, NC, USA) and R (R Foundation for Statistical Computing, Vienna, Austria) software.

Results

This cohort study includes 672 KTRs (61.9% male, median age 53 years), whose main characteristics are outlined in Table 1. Most patients received an induction therapy with basiliximab (75.7%) and were on tacrolimus, mycophenolate, and steroids (80%). A delayed graft function was observed in 21.4% of KTx, while acute rejections occurred in 5.5% of patients within 6 months from surgery.

Figure 1a shows the transitions between states (i.e., NMSC, NCM, graft failure, and death) observed in the cohort. During a total follow-up of 3523 person-years (median: 4.7 years, maximum: 13.6 years), 47 patients developed a NMSC as first-event and 35 a NCMs. In five

Table 1. Main clinical characteristics of the study cohort. Values are expressed as median (interquartile range) or *n*/tot (%).

Parameter	
Recipient age at KTx (years)	53 (43–61)
Male recipients	416/672 (61.9)
Underlying nephropathy	
Primary nephritis/nephropathy	393/672 (58.5)
Secondary nephropathy	121/672 (18.0)
Unknown	158/672 (23.5)
Donor age	55 (43–67)
Total HLA mismatches	3 (2–4)
Peak PRA > 0%	167/661 (25.3)
Missing	11 (1.6)
Cold ischemia time (hours) missing	19 (16–22)
	4 (0.6)
Delayed graft function	144/672 (21.4)
Induction therapy	
None	78/672 (11.6)
Anti-IL-2 receptor	509/672 (75.7)
ATG	85/672 (12.7)
Maintenance IS therapy	
Tacrolimus – MMF/AZA ± steroids	524/672 (78.0)
Cyclosporine - MMF/AZA ± steroids	43/672 (6.4)
Other	105/672 (15.6)
One or more acute rejection episodes within 6 months	37/672 (5.5)
Serum creatinine at 6 months (mg/dl)* missing	1.6 (1.3–2.0)
	3 (0.4)
Urinary proteins at 6 months (g/24 h) missing	0.20 (0.1–0.4)
	9 (1.3)
Pretransplant diabetes	42/672 (6.3)
BMI	23.9 (21.9–26.2)
CMV negative	98/664 (14.8)
missing	8 (1.2)
EBV negative	36/491 (7.3)
missing	181 (26.9)
HCV positive	43/672 (6.4)

KTx, kidney transplant; ATG, antithymocyte globulin; MMF, mycophenolate or mycophenolic acid; AZA, azathioprine; CMV, cytomegalovirus; EBV, Epstein–Barr virus.

*Conversion factors serum creatinine in mg/dl to μmol/l, ×88.4.

patients a transition from NMSC to NCM was observed, leading to a total of 40 NCM. The 5-year incidence of NMSC and NCM were, respectively, 6.5% (95% CI: 4.5–9.0) and 5.6% (95% CI: 3.8–7.9) (Fig. 1b).

A total of 59 graft failures were observed (39 due to chronic rejection and 20 for other causes) with a 5-year cumulative incidence of 7.5% (95% CI: 5.3–10.0). Death was defined as a competitive risk in the analysis of graft failure incidence, and therefore, only deaths occurring before graft failure were considered. Thirty-seven deaths with a functioning kidney were observed, with a 5-year cumulative incidence of 4.8% (95% CI: 3.2%–7.0%) (Fig. 1c).

Occurrence of malignancy and risk of graft failure

Among the 40 observed NCMs, 29 were solid tumors (including six breast carcinomas, five renal cell carcinomas and four prostate carcinomas) and 11 were hematologic tumors (including seven lymphomas). For solid and hematologic malignancies, the median age at diagnosis was, respectively, 59.4 and 58.3 years, the time from KTx to diagnosis 2.16 and 3.81 years and male recipients were 16 of 29 (55.2%) among solid NCM and 9 of 11 (81.8%) among hematologic NCM. Indeed, during a median follow-up after NCM of 3.5 years, 19 patients reduced their IS therapy after a median time of 0.8 months (Table S2). After a diagnosis of NCM, 10 patients died with a functioning graft (25.0%), of which eight were diagnosed with a solid malignancy and two with a hematologic malignancy.

Seven graft failures occurred after diagnosis of NCM, of which five after diagnosis of a solid malignancy and two after diagnosis of a hematologic malignancy. The absolute death-censored graft survival after NCM was 92%, 89% and 71% at, respectively, 1, 3, and 5 years after malignancy. The risk of graft failure increased significantly after the occurrence of NCM, when compared with NCM-free period (Fig. 2a).

The hazard ratio, derived from a univariable Cox regression model where NCM was treated as a time-dependent covariate, was 3.31 (95% CI: 1.48–7.42, $P = 0.004$). This association did not materially change after adjustment for creatinine and proteinuria levels, acute rejection episodes within 6 months after KTx, donor age, gender, year of transplant, and underlying nephropathy (Table 2).

The causes of graft failure in patients with a NCM were in 2 of 7 (29%) chronic rejection, in 2 of 7 (29%) a "*de novo*" nephropathy (1 myeloma kidney and 1 immunotactoid glomerulonephritis), in 1 of 7 (14%) chronic pyelonephritis, in 1 of 7 (14%) chronic pyelonephritis and reflux nephropathy following radical prostatectomy, and in 1 of 7 (14%) graft nephrectomy for a RCC of the transplanted kidney. Even if only seven graft failed after a NCM, we tried to investigated the effects of NCM on cause-specific graft failure, finding an apparently different effect of a NCM diagnosis

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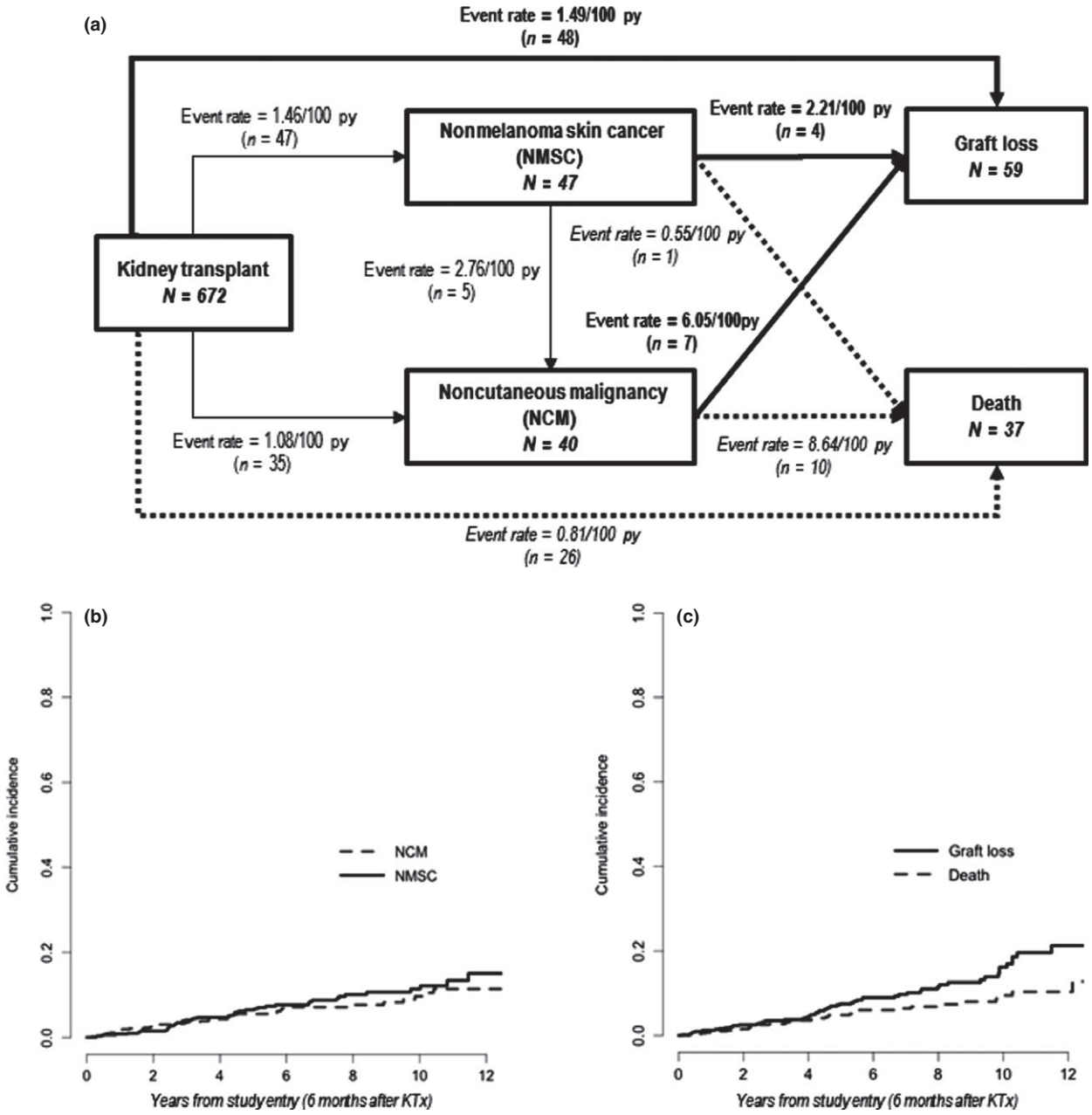

Figure 1 The multistate process for graft failure. (Panel a) Diagram of the observed transitions: bold lines are transitions to graft failure and dotted lines are transitions to death with a functioning graft. (Panel b) Cumulative incidence of noncutaneous malignancy (NCM, dashed line) versus nonmelanoma skin cancer (NMSC, bold line); time is expressed in years after study entry (6 months after transplant). (Panel c) Cumulative incidence of graft failure (bold line) versus death (dashed line); time is expressed in years after study entry (6 months after transplant).

($P = 0.002$) when considering graft failed due to chronic rejection (HR 0.55, 95% CI: 0.07–4.08) or for other causes (HR 15.59, 95% CI 5.43–44.76).

The occurrence of a NMSC was, on the contrary, not associated with the graft failure risk, both in the univariable (HR = 1.24, 95% CI 0.49–3.18, $P = 0.70$) and multivariable analysis (HR = 0.80; 95% CI = 0.30–2.14, $P = 0.66$) (Fig. 2b).

Effect of the reduction of immunosuppression

We then evaluated the impact of reduced immunosuppression on graft failure risk in patients with NCM and without: None of the included patients was in the strongly reduced IS group (i.e., low-dose, single-drug IS); however, 54 patients had a small but significant reduction of their overall IS burden, of which 19 had

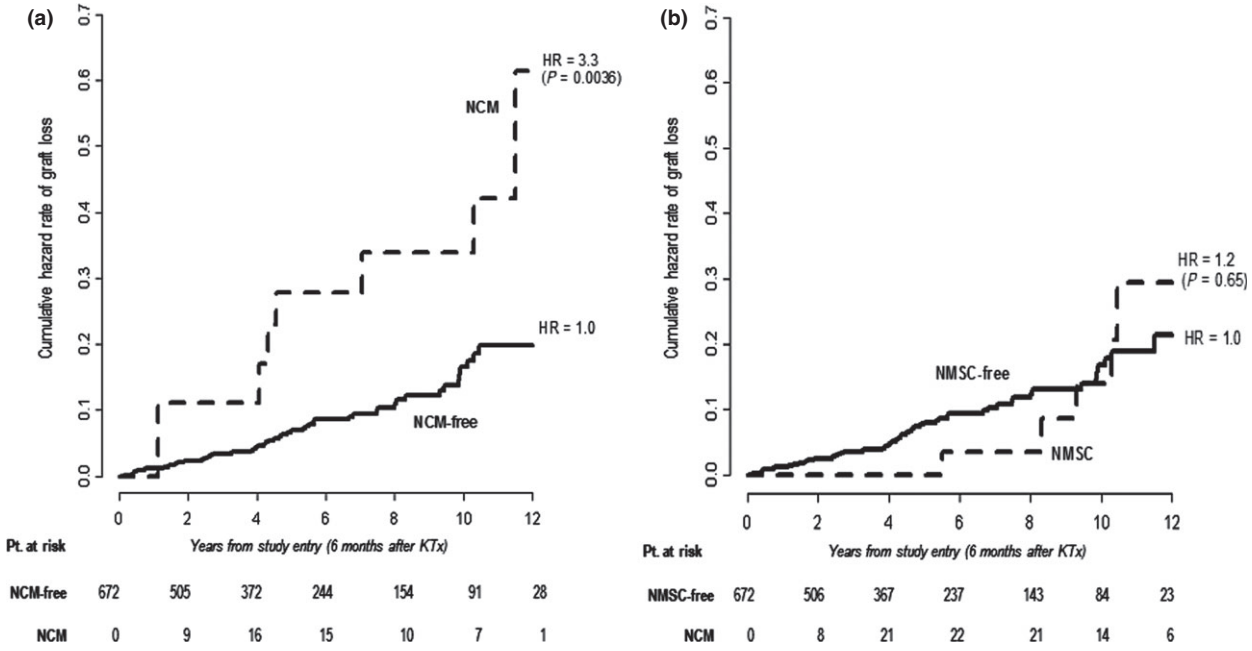

Figure 2 (Panel a) Cumulative hazard rates of death-censored graft failure stratified by a time-varying indicator of diagnosis of a noncutaneous malignancy (NCM). The hazard ratio (HR) from a univariate Cox regression model, in which the diagnosis of a NCM malignancy was represented as a time-dependent covariate, is reported. (Panel b) Cumulative hazard rates of death-censored graft failure stratified by a time-varying indicator of diagnosis of a nonmelanoma skin cancer (NMSC). The hazard ratio (HR) from a univariate Cox regression model, in which the diagnosis of a NMSC was represented as a time-dependent covariate, is reported. Time is expressed in years and observation (time = 0) starts at 6 months after transplant.

Table 2. Multivariable Cox regression analysis for death-censored graft failure.

Factor	Level	HR (IC 95%)	*P*-value
Noncutaneous malignancy (time dependent)	Yes versus No	3.27 (1.44–7.44)	0.005
Creatinine (mg/dl)	≥2.0 versus <2.0	2.95 (1.59–5.47)	<0.001
Proteinuria (g/24 h)	≥0.5 versus <0.5	2.28 (1.28–4.06)	0.005
Acute rejection episode	Yes versus No	3.14 (1.61–6.14)	<0.001
Donor age	10 years increase	1.34 (1.10–1.64)	0.004
Gender	Female versus male	2.21 (1.28–3.81)	0.004
Year of transplant	5 years increase	1.34 (0.80–2.25)	0.3
Underlying nephropathy	Secondary versus Primary	1.80 (0.94–3.43)	0.07
	Unknown versus Primary	1.79 (0.94–3.40)	0.07

The diagnosis of a noncutaneous malignancy was included as a time-dependent covariate in the Cox model. The other variables, measured at 6 months after the transplantation, were considered as time-fixed.

a NCM (47.5% of patients with an NCM) and 35 did not (5.5% of patients without an NCM). The yearly incidence rate of graft failure after NCM was not affected by a reduced IS, being 5.3% (95% CI 1.2–22.9) in patients with a reduced IS and 6.8% (95% CI 1.8–25.3; ratio = 0.78) in patients maintained on standard IS. However, an IS reduction seemed to be associated with a higher rate of graft failure in patients without a NCM: In patients with a reduced IS, it was 4.3% (95% CI 1.45–12.84) and in patients on standard IS, it was 1.4% (95% CI 1.0–1.9; ratio = 3.12) (Fig. 3). The test for interaction between IS reduction and NCM diagnosis on the risk of graft failure, calculated from a Poisson regression model, gave a *P*-value of 0.11.

Finally, we were not able to identify any significant association between post-NCM variables and graft failure risk among patients with a NCM, including

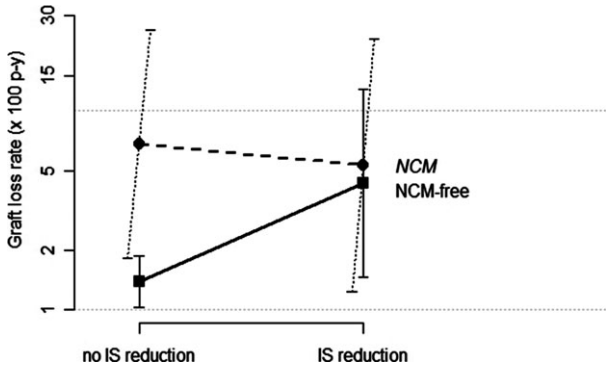

Figure 3 Interaction between the reduction of the immunosuppressive (IS) therapy and NCM diagnosis on the risk of graft failure.

chemotherapy, radiation therapy, and oncological surgery (data not shown).

Discussion

The aim of this study was to evaluate the impact of NMSCs and NCMs on death-censored graft survival of KTRs, being able to define the HR associated with the development of the first NMSC (HR = 0.79, $P = 0.66$) or the first NCM (HR = 3.27; $P = 0.005$).

Some of our results confirm what is known about post-transplant malignancies: For instance, their incidence at 5 years is 5.6% in our cohort, similar to other Italian and international cohorts that reported 3.8–6.6% [4,13,26]. Besides, the lack of association between NMSC and graft failure could be expected from previous epidemiological and laboratory studies. NMSC have been associated with a chronic replication of beta-HPV in KTRs [27]: Probably, these patients are particularly susceptible to chronic IS and therefore have a reduced risk of chronic rejection. Indeed, Christenson *et al.* [28] showed on 46 216 KTRs that NMSC had a protective effect on graft failure (HR = 0.55; 95% CI 0.44–0.68); however, in their study, only 1.6% of KTRs developed a NMSC at 5 years (versus 6.5% in our cohort), reflecting probably different diagnostic and inclusion criteria and yielding eventually to slightly different results.

Nevertheless, the association of post-transplant NCM with graft failure has not yet been investigated considering NCM occurrence as a time-dependent variable and its HR has not yet been defined. Indeed, many different studies investigated graft survival since the diagnosis of a NCM, but they usually included both patients with early diagnoses – who likely have a good graft function – and patients with late diagnoses, who might have a failing graft independently from malignancy [20,29,30]. Therefore, such studies are not able to compare directly patients with a NCM with those without a NCM and may not be able to adjust for all known malignancy-independent risk factors.

Yet our result is not completely unexpected as most studies on post-transplant malignancies presented a relatively low graft survival after NCM diagnosis. For example, the case-cohort study published by Rabot *et al.* [19] showed a 5-year graft survival of 63% after a diagnosis of PTLD, which was much less than the one of matched patients from the DIVAT cohort. Other studies included different types of malignancy with more favorable results (i.e., 11.5% graft failures at almost 5 years after a RCC of native kidneys [17]). Recently, Salesi *et al.* [20] investigated the incidence of graft failure after any post-transplant malignancy in recipients of living donor kidney grafts: Even if they did not compare this result with similar recipients without any NCM, the incidence of graft loss was relatively high (4.4 of 100 patient-year) if compared with other cohorts of KTRs from living donors, in which the graft failure rate is about 2–3 of 100 patient-year in the first 5–10 years after KTx [31].

Interestingly, in our cohort, only a minority of grafts failed because of chronic rejection (28.6%), probably because the follow-up time after NCM and IS reduction was relatively short to be able to see an increased risk of graft failure due to chronic rejection. However, a reduced IS was associated in our cohort with a higher rate of graft failure in patients without malignancy (graft failure rate ratio of 3.12), but not for patients with a NCM (graft failure rate ratio of 0.78), despite the fact that almost half of the patients with a NCM reduced their IS burden. This finding could be due to a relatively aggressive policy of our center, in which, for example, no patient had a severe reduction of their maintenance IS and even the Red-IS group included patients on a one-drug IS regimen at full dose. However, in our cohort, NCMs seem to act as an effect modifier of the relationship between IS reduction and graft failure. This observation might be consistent with the hypothesis speculating that patients who develop a malignancy are particularly susceptible to chronic IS at "standard doses". However, given the very limited event rate in patients with a NCM, we could not exclude a random effect: Still, the interactions between NCM, IS, and graft failure could be investigated in larger cohorts, possibly investigating more accurate biomarkers of "excessive" IS than drug through levels [32].

Lastly, we tried to investigate which "malignancy-associated" variable could explain the increased risk of graft failure, but we were not able to find any significant association, due to the low event rate in this subgroup.

However, our results may stimulate further analyses on the relationship between malignancies and kidney function in the general population [33], particularly in patients with a reduced renal function at the time of diagnosis (i.e., eGFR < 45 ml/min/1.73 m^2), like KTRs commonly are.

Even if this study has a relatively novel methodological approach and shows interesting results, we were limited by two main factors: the cohort size and event rate, which are too small to perform further analyses, particularly on single tumor types, and the relatively short follow-up time, particularly after malignancies. Cohort studies on malignancies in KTRs are usually much wider than ours [4,13,26], and we only had 40 patients with a NCM. Therefore, each single tumor site has only few cases (no malignancy with more than six affected patients) and the specific impact of high-risk localizations (like cancer of the lower urinary tract) or paraneoplastic nephritides (like myeloma kidney) could not be estimated. Moreover, our mean follow-up after the sixth post-transplant month was 5.24 years per patient, which is relatively short for studies on long-term graft failure, which is expected to happen about 10 years after KTx. This issue is particularly relevant for patients with a NCM: Their median follow-up time after NCM diagnosis was 3.5 years, which is relatively short to be able to observe graft failure due to a chronic rejection arising after IS reduction. Indeed, of seven grafts failed after an NCM, two were due to paraneoplastic kidney diseases diagnosed early after the malignancy and one was a transplant nephrectomy for a RCC of the graft. Lastly, as we could not find any significant association with potentially biologically relevant causes of graft failure in our cohort due to the low event rate, the association between NCM and graft failure may not be considered a causal relationship at this point. We have adjusted our estimates for the known potential confounders (age, renal function, year of transplant), but we cannot exclude "*a priori*" that other still-unknown confounders might play a role.

In conclusion, this study shows that in our cohort NCM are associated with a higher graft failure risk and might suggest that early after a NCM diagnosis the causes of graft failure may include chronic rejection, paraneoplastic nephropathies and other "uncommon" nephropathies, such as chronic pyelonephritis and reflux nephropathy. Therefore, transplant physicians should be aware of these associations and should be careful in kidney function monitoring of KTRs with a NCM, which should include specific evaluations depending on the malignancy itself. Further studies are warranted to better define the post-NCM risk factor of graft failure and to develop strategies to preserve kidney function after each tumor type.

Authorship

TC, CMa and VB: performed the analysis. CMu and MQ: collected the data. CMu, VC and PS: designed the study. TC, CMu, VB and VC: wrote the manuscript.

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Conflict of interest

The authors have declared no conflicts of interest.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. ICD-9 classification of malignancies (by site) and number of observed cases and outcome.

Table S2. Clinical characteristics of patients with a non-cutaneous malignancy (NCM), divided by solid versus hematologic malignancies.

Table S3. Main clinical characteristics of the study cohort evaluated at baseline and univariate Cox regression analysis.

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