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ORIGINAL ARTICLE

Sirolimus in renal transplant recipients with malignancies in Germany

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ABSTRACT

Background. Renal transplant recipients have an increased cancer risk. The mammalian target of rapamycin inhibitor sirolimus (SRL) has immunosuppressive and antitumour activities but knowledge about its use in recipients with cancer is limited.

Methods. We retrospectively analysed 726 renal allograft recipients converted to SRL from 10 German transplant centres. Patient and graft survival were analysed depending on malignancy status prior to conversion and tumour entity.

Results. Malignancy before conversion to SRL was reported in 230 patients, with 137 patients having skin cancers and 101 having solid cancers. Cancer occurred 4.6 ± 9.4 (median 3.0) years after transplantation. Basal cell carcinoma, squamous cell carcinoma and Bowen's disease were the most prevalent skin cancers, while carcinomas of the kidney, colon and breast were the most prevalent solid cancers before conversion. Patients with prior malignancy were older and had better renal function at conversion compared with patients without a history of cancer. After conversion to SRL, cancer incidence rates (IRs) of all tumours were lower compared with rates before conversion. Cancer IRs after conversion were higher in patients with malignancy before conversion compared with those without. Patient survival was worse in patients with solid cancers

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compared with patients with skin cancers or without malignancies. Biopsy-proven acute rejections in the first year after conversion were less frequent in patients with malignancy compared with those without. Graft survival and renal function in all cancer types were better than in patients converted to SRL without cancers.

Conclusions. Conversion to SRL in patients with a history of cancer is safe regarding renal function and graft survival, while patient survival is largely dependent on tumour entity.

Keywords: cancer, graft survival, immunosuppression, kidney transplantation, multicentre study, sirolimus, survival analysis

INTRODUCTION

Chronic immunosuppression plays a key role in cancer pathogenesis. Renal transplant recipients have a significantly higher cancer risk at a variety of sites, including non-melanoma skin cancer, lymphoma, Kaposi sarcoma, thyroid cancer and genitourinary cancer [1, 2]. Malignancies after transplantation (Tx) increased the economic burden on the health system [3].

Sirolimus (SRL) is a mammalian target of rapamycin (mTOR) inhibitor. It is an immunosuppressive substance with additional antimicrobial and antitumour activity. Guba *et al.* [4, 5] described how SRL treatment of mice inhibited tumour angiogenesis and subsequent tumour growth at concentrations comparable with long-term immunosuppression in human transplant recipients. Clinical observations and controlled clinical studies detected lower malignancy rates in renal transplant recipients treated with the mTOR inhibitors SRL and everolimus [6–8].

The optimal immunosuppression is unclear in renal transplant recipients developing *de novo* post-transplant malignancy. Given the documented antitumour effects of mTOR inhibitors, a conversion to SRL is considered and performed in patients with post-transplant malignancies in many transplant centres worldwide. Despite its frequent use, however, our current knowledge is still very limited regarding the efficacy and safety. A change in immunosuppression might be associated with an increase in rejection rates. Treatment with SRL can be associated with side effects (e.g. proteinuria and mucosal ulcers). Current knowledge is insufficient in renal transplant recipients who are converted to SRL because of a malignancy.

The German Sirolimus Study Group has established a retrospective, multicentre cohort of >700 renal transplant recipients converted to SRL at least 3 months after renal Tx [9]. This patient cohort represents clinical practice in 10 German renal transplant centres. Our study reports a detailed analysis of demographics, safety and efficacy in the largest documented cohort of renal transplant recipients converted to SRL.

Our investigation had the following aims: to compare patients with malignancy before conversion versus those without tumours regarding graft and patient survival, to describe most frequent tumours before and after conversion and to analyse graft and patient survival depending on the tumour entity (solid, skin, solid and skin and others) before TX.

MATERIALS AND METHODS

Demographic, clinical and laboratory data were entered into a customized database. Validation and completeness of the data were checked centrally after database closure. Discrepant data were resolved by inquiries to the contributing transplant centres. A total of 726 patients remained eligible for analysis [9].

This retrospective multicentre study included patients with kidney or combined kidney–pancreas Tx who received an SRL-containing maintenance immunosuppressive therapy between 1 January 2000 and 31 December 2008. We aimed to include all converted patients in each of the participating centres regardless of success, length of SRL therapy, age, type of donation, number of previous transplants and reason for conversion to SRL. All patients were >18 years of age. We excluded all patients treated with SRL within the first 3 months after Tx. Apart from that, no patients were excluded from this database to reduce the selection bias and include the full spectrum of therapeutic approaches across different centres. The local ethics committees approved the study and all patients provided informed consent for the scientific use of their data.

Data collection included four time points before SRL initiation and one at the beginning of SRL therapy to establish baseline values for allograft function, proteinuria, comorbidities and medical therapies. Data were collected in the first year of SRL therapy at 3, 6 and 12 months and in semi-annual intervals thereafter. Endpoints were patient's death, terminal allograft failure and termination of SRL therapy. Renal function was calculated by the abbreviated Modification of Diet in Renal Disease formula [10]. Urinary protein was assessed based on local practice and availability and included dipstick analysis, spot urine proteinuria concentrations or 24-h proteinuria determination.

Continuous data were described as mean ± standard deviation (SD) (normal distribution) or by median and range of values (uneven distribution). Univariate comparisons of continuous data among subgroups of the study population were performed by *t*-test and one-way analysis of variance or by Mann–Whitney U-test and Kruskal–Wallis test, depending on the results of the tests for normal distribution. Categorical data were analysed by Fisher's exact test or chi-squared test for more than two groups. Factors that were significant in univariate analysis were entered into a multivariate analysis using enter selection, with thresholds of 0.05 for entry and 0.20 for removal of covariates.

The type of tumour was analysed descriptively and categorized into the entities skin or solid cancers and haematological/lymphoma. Incidence ratios of tumours were calculated to compare patients with and without prior tumours. For calculation of the incidence rate (IR), the cumulative number of tumours was divided by the cumulative observation time. For comparison of the IR before conversion to SRL with the period after conversion, the incidence ratio was calculated dividing the IR before conversion by the IR after conversion. Survival analyses were performed using Kaplan–Meier for patient survival (event = death), graft survival including death (event = death and graft failure) and death-censored graft survival (event = graft failure). The time from conversion to the event or the maximal observation time was calculated. The analysis for termination of SRL therapy was censored for graft survival including death.

Table 1. Demographic and clinical data of the study population at Tx

At Tx	All patients ($N = 726$)	Tumours before conversion		P-value
		Yes ($n = 230$)	No ($n = 496$)	
Ethnicity, %	99.0	99.6	98.8	0.176
Recipient age at Tx (years)	43.3 ± 13.6	47.1 ± 13.2	41.5 ± 13.4	<0.001
Recipient sex (male), %	63.6	64.8	63.1	0.662
Cause of ESRD, %				
Diabetic nephropathy	12.4	4.4	16.1	0.002
Hypertensive nephropathy	3.6	3.5	3.7	–
Polycystic kidney disease	11.4	11.4	11.4	–
Glomerulonephritis	43.4	48.7	40.9	–
Tubulointerstitial disease	14.3	14.0	14.5	–
Other inherited diseases	3.6	5.3	2.9	–
Other diseases/unknown	11.3	12.7	10.6	–
Living donation, %	16.4	13.0	18.1	0.094
Kidney re-TX, %	25.5	17.6	29.2	0.001
Kidney–pancreas Tx, %	9.1	2.6	12.1	<0.001
Cold ischaemia time (h)	14.2 ± 8.0	15.8 ± 8.3	13.5 ± 7.8	0.001
HLA mismatches on locus A, B, DR, *n*	2.4 ± 1.6	2.2 ± 1.6	2.5 ± 1.6	0.123
Donor age (years)	44.3 ± 15.9	43.8 ± 17.1	44.5 ± 15.2	0.614
Donor sex (male), %	56.6	56.3	56.8	0.900
DGF, %	25.0	24.3	25.3	0.807
Immunosuppression at Tx, %				
Cytotoxic antibodies	15.6	13.7	16.5	0.335
Basiliximab	20.3	23.9	18.6	0.100
Cyclosporine	62.0	66.4	60.0	0.103
Tacrolimus	26.8	16.8	31.4	<0.001
Azathioprine	31.7	44.7	25.7	<0.001
Mycophenolate	53.5	41.6	59.0	<0.001
Corticosteroids	96.6	96.5	96.7	0.850
Others	5.7	4.9	6.1	0.502

Values are presented as mean ± SD unless stated otherwise. ESRD, end-stage renal disease; DGF, delayed graft function; HLA, human leucocyte antigen.

Table 2. Demographic and clinical data of the study population at and after conversion to SRL

At conversion	All patients ($N = 726$)	Tumours before conversion		P-value
		Yes ($n = 230$)	No ($n = 496$)	
Age at conversion (years)	49.8 ± 13.4	56.4 ± 11.6	46.8 ± 13.0	<0.001
Period since Tx (years)	6.1 ± 6.1	8.9 ± 7.4	4.8 ± 4.9	<0.001
Body weight (kg)	73.8 ± 15.5	73.6 ± 14.4	73.8 ± 16.0	0.914
BMI (kg/m^2)	24.9 ± 4.2	25.1 ± 3.9	24.9 ± 4.4	0.435
eGFR (mL/min)	39 ± 19	47 ± 21	35 ± 18	<0.001
eGFR 1 year after conversion (mL/min)	41 ± 20	49 ± 22	37 ± 18	<0.001
Proteinuria (mg/L)	348 ± 751	197 ± 291	419 ± 880	0.001
SRL dose (mg/day)	2.9 ± 1.6	2.6 ± 1.2	3.1 ± 1.8	<0.001
SRL dose at 3 months (mg/day)	2.7 ± 1.8	2.2 ± 1.4	2.9 ± 1.9	<0.001
SRL at 3 months (ng/mL)	8.1 ± 3.8	7.6 ± 3.4	8.4 ± 4.0	0.089
BPAR prior to SRL, %	38.1	35.9	39.3	0.615
BPAR after conversion, %	9.0	4.3	11.1	0.003
Reason for conversion, %				
Study related	11.0	15.2	9.1	0.014
Tumour	24.8	75.2	1.4	<0.001
Creeping creatinine	22.3	7.4	29.3	<0.001
Chronic allograft nephropathy	17.7	4.8	23.6	<0.001
Calcineurin inhibitor toxicity	26.1	11.7	32.7	<0.001
Side effect from other immuno suppressant	12.3	6.5	14.9	0.001
Acute rejection	12.0	5.2	15.2	<0.001
Others	15.7	8.7	19.0	<0.001
1 reason for conversion, %	64.3	68.3	62.4	0.127
≥2 reasons for conversion, %	35.7	31.7	37.6	
Follow-up (months)	27.0 ± 22.2	27.7 ± 20.8	26.8 ± 22.8	0.288
Outcome, %				
Death censored for graft failure	7.3	9.6	6.3	0.106
Graft failure censored for death	18.5	5.7	24.4	<0.001
Death including graft failure	24.4	28.6	15.2	<0.001
SRL treatment discontinuation	45.3	43.5	46.2	0.498

Values are presented as mean ± SD unless stated otherwise.

For comparison between groups, the log-rank test was used. To determine the influence of covariates on survival, we performed multivariate Cox regression analyses. As group sizes were small for certain cancer categories, four major groups were defined for comparison: skin cancers, solid cancers, skin and solid cancers and other combinations.

P-values <0.05 were considered statistically significant. For most statistical analysis we used SPSS versions 25 and 27 (IBM, Armonk, NY, USA). For calculation of IRs, we used R version 4.0.2 and epiR package version 1.0-15 with RStudio version 1.3.1073 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

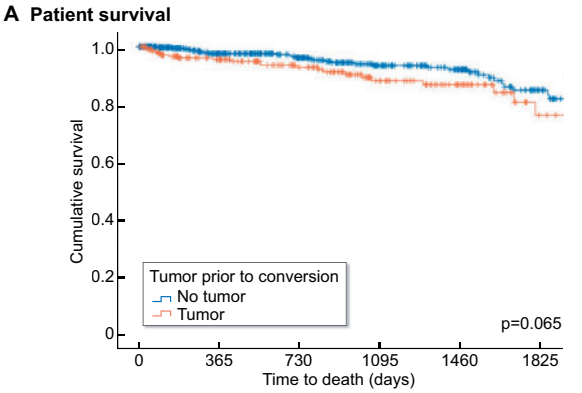
Study population

Altogether 726 patients were analysed from 10 transplant centres. Basic demographic and clinical data at Tx and at the time of conversion to SRL are shown in Tables 1 and 2, respectively.

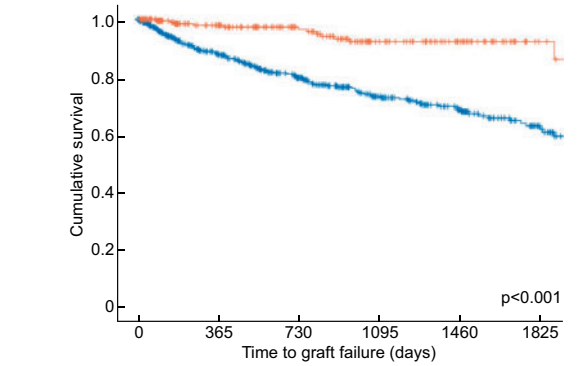
Observation times after conversion to SRL ranged from 4 days to 9 years (mean 27 ± 22 months), translating into an overall observation time of 19 630 patient-months or 1613 patient-years. Death occurred in 53/726 (7.3%) patients and allograft failure including death in 177/726 (24.3%) patients during the observation period. Reasons for death included tumours in 19/53 (35.8%), cardiovascular events in 13/53 (24.5%), infections in 9/53 (17.0%), other reasons in 5/53 (9.4%) and unknown reasons in 7/53 (13.2%). In patients without graft loss or death, SRL treatment was terminated for various reasons in 276/726 (38%) patients. Reasons for SRL discontinuation included renal reasons in 97/276 (35.5%), infections and pulmonary reasons in 47/276 (17.0%), patient's wish in 28/276 (10.1%), unknown reasons in 27/276 (9.8%), other reasons in 26/276 (9.4%), skin, muscle and joint problems in 23/276 (8.3%), gastrointestinal side effects in 14/276 (5.1%) and planned surgery in 11/276 (4.7%).

Patient survival in patients with malignancy before conversion versus those without. In 230/726 (31.7%), a malignancy prior to conversion to SRL was reported to have occurred 4.6 ± 9.4 (median 3.0) years after Tx. Patients with malignancy before conversion were ~5–6 years older and had ~4 years longer time after Tx and better estimated glomerular filtration rate (eGFR) at conversion compared with patients with no malignancy prior conversion; however, they were less frequently retransplanted or had combined pancreatic Tx (Tables 1 and 2). Patients with tumours were treated more often with a dual immunosuppressive regimen prior to conversion. Immunosuppressive therapy more frequently included azathioprine, while tacrolimus or mycophenolate were less frequent in patients with previous malignancy. Furthermore, patients with tumours before conversion had lower proteinuria at conversion and a lower SRL dose. Biopsy-proven acute rejections (BPARs) after conversion were less frequent in patients with tumours before conversion (4.3 versus 11.1%) compared with patients converted to SRL without prior malignancy.

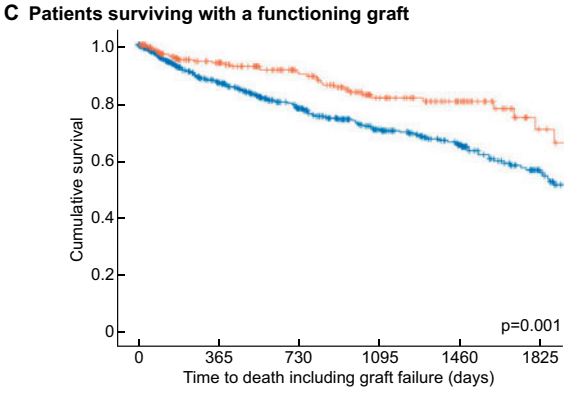
As expected, reasons for conversion to SRL were most frequently tumours (75.2%) in the group of patients with malignancy before conversion, whereas renal reasons (rejection, creeping creatinine and increasing proteinuria) were dominating in patients converted to SRL without prior tumour history. After conversion to SRL, death occurred more



No tumor (N)*	496	345	251	174	118	60
Survival (%)**	100	97.7±0.8	96.2±1.1	93.5±1.5	92.1±1.8	85.0±3.1
Tumor*	230	166	124	75	46	16
Survival (%)**	100	95.6±1.4	92.9±1.9	88.2±2.8	86.6±3.0	76.3±6.5
All*	726	511	375	249	164	76
Survival(%)**	100	97.1±0.7	95.2±0.9	91.9±1.3	90.5±1.5	82.8±2.8

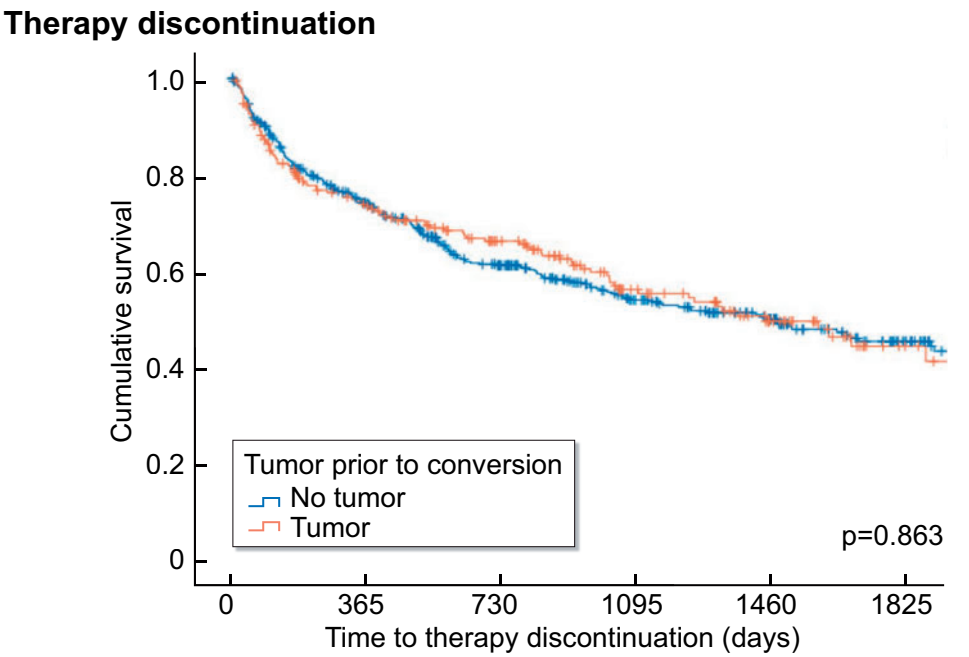


No tumor (N)*	496	335	237	168	111	56
Survival (%)**	100	87.8±1.6	79.7±2.0	73.2±2.4	68.8±2.7	61.9±3.4
Tumor (N)*	230	165	123	75	46	16
Survival (%)**	100	97.9±1.0	96.5±1.4	92.3±2.3	92.3±2.3	92.3±2.3
All (N)*	726	500	360	243	157	72
Survival (%)**	100	91.0±1.1	84.9±1.5	79.0±1.9	75.5±2.1	70.0±2.8



No tumor (N)*	496	335	237	168	111	56
Survival (%)**	100	86.7±1.6	77.7±2.1	70.4±2.5	64.9±2.8	55.2±3.5
Tumor (N)*	230	165	123	75	46	16
Survival (%)**	100	93.7±1.7	89.7±2.3	81.4±3.3	80.2±3.4	70.4±6.2
All (N)*	726	500	360	243	157	72
Survival (%)**	100	88.9±1.3	81.5±1.6	73.8±2.0	69.5±2.2	59.8±3.0

FIGURE 1: Outcome analysis using Kaplan–Meier for (**A**) patient survival, (**B**) death-censored graft survival and (**C**) patients surviving with functioning graft is shown for patients with and without tumours prior to conversion. Censored observations are indicated by vertical lines. In the tables below, the number of patients at risk and Kaplan–Meier survival estimators are given for each outcome over 5 years.



No tumor (N)*	496	320	223	154	103	55
Survival (%)**	100	73.7±2.0	61.1±2.3	53.9±2.5	49.9±2.6	45.3±2.8
Tumor*	230	150	112	67	40	15
Survival (%)**	100	72.9±3.0	66.2±3.3	55.3±3.7	49.5±4.0	44.3±4.6
All*	726	470	335	221	143	70
Survival(%)**	100	73.4±1.7	62.7±1.9	54.3±2.1	49.8±2.2	45.1±2.4

FIGURE 2: Therapy discontinuation is shown for patients with and without tumours prior to conversion using Kaplan–Meier analysis. Censored observations are indicated by vertical lines. In the tables below, the number of patients at risk and Kaplan–Meier survival estimators are given over 5 years.

frequently in patients with a tumour history (9.1 versus 3.8%), whereas graft loss was less frequent (2.6 versus 20.2%) than in patients converted to SRL without a tumour history.

Five-year patient survival (Figure 1A) tended to be lower after conversion in patients with prior tumour history compared with patients without tumours (76.4 ± 6.5% versus 85.1 ± 3.0%, $P = 0.063$). Overall graft survival (including death) (70.4 ± 6.2% versus 55.2 ± 3.5% at 5 years, $P < 0.001$; Figure 1B) and death-censored graft survival (92.3 ± 2.3% versus 61.9 ± 3.4% at 5 years, $P < 0.001$; Figure 1C) were better in patients with tumours prior to conversion compared with patients without a tumour history. SRL was frequently discontinued (Figure 2) in patients with tumours prior to conversion and the discontinuation rate was similar to the overall cohort (44.3 ± 4.6% versus 45.2 ± 2.8%, $P = 0.863$) at 5 years.

The multivariate Cox regression analysis on graft failure including death (Table 3) shows a significant influence of eGFR, proteinuria, age at Tx and previous Txs. The model showed a 5% risk reduction per millilitre of eGFR, a 67% risk increase per gram per day of proteinuria at conversion, a 2% increase in risk per 1-year age increase at Tx and a 61% increase of risk if previous renal Tx had occurred.

Tumours before conversion. The different types of skin and solid tumours before and after conversion for patients with and without malignancy before conversion are shown in Table 4. As a given patient could have different tumours, the numbers do not match the group size. For a better comparison of tumours before and after conversion, IRs per 100 patient-years were calculated and are shown in Table 5 for skin and solid cancer.

There were 137 patients with skin tumours before conversion. The IRs per 100 patient-years for each tumour in the group of patients with a tumour before conversion are shown in Table 5. The most prevalent skin tumours showed an IR between 1.3 (actinic keratosis) and 3.0 (squamous cell carcinoma) and even 3.8 (basal cell carcinoma) per 100 patient-years before conversion.

There were 101 patients with solid tumours before conversion (Table 5). Most prevalent solid tumours were renal cell carcinoma, followed by breast carcinoma and colon carcinoma, with an IR between 0.7 (colon carcinoma) and 1.7 (renal cell carcinoma) per 100 patient-years at baseline. The IR was ∼50% lower after conversion in most tumours. This effect was less pronounced in skin tumours (Table 5).

Tumours before and after conversion. After conversion, skin cancers were detected in 52 patients. In 40/230 (17.4%) patients from the group of patients with tumours before conversion, a skin tumour after conversion was detected. In 12/496 (2.4%) patients from the group without tumours before conversion, a skin tumour was detected after conversion. Most skin cancers after conversion were basal cell carcinoma, actinic keratosis, Bowen's disease, keratoacanthoma and squamous cell carcinoma (Table 6).

The IRs for tumours after conversion (Table 7) were higher in patients with a tumour history before conversion. The overall IR in skin tumours after conversion was 8.3/100 patient-years in

Table 3. Cox regression for graft survival including death in patients after conversion to SRL with and without previous malignancy

Cox regression analysis for graft survival including death			
Parameters	P-value	Exp(B)95% confidence interval for Exp(B)	
Sex (male versus female)	0.755	0.940	0.637–1.387
eGFR at conversion (mL/min)	<0.001	0.947	0.931–0.963
Proteinuria at conversion (g/day)	<0.001	1.668	1.395–1.995
Age at Tx (years)	0.022	1.018	1.003–1.034
Tumours prior to conversion (yes/no)	0.373	1.241	0.772–1.995
Prior renal Tx (yes/no)	0.022	1.614	1.071–2.432
Time Tx to conversion (years)	0.173	1.026	0.989–1.064
BPAR after conversion (yes/no)	0.404	0.769	0.416–1.424

Table 4. Distribution of tumours before conversion to SRL

Skin tumours	Percentage of skin tumours	Number of patients
Actinic keratosis	15.3	21
Basal cell carcinoma	43.1	59
Kaposi sarcoma	4.4	6
Keratoankanthoma	6.6	9
Melanoma	9.5	13
Bowen's disease	25.5	35
Squamous cell carcinoma	35.0	48
Warts	10.9	15
Other skin tumours	8.8	12
Total of skin tumours	100	137
Solid tumours	**Percentage of solid tumours**	**Number of patients**
Colon	12.7	13
Lung	4.9	5
Stomach	2.0	2
Breast	12.7	13
Prostate	7.8	8
Bladder	5.9	6
Others	15.7	16
Renal	30.4	31
Gynaecological	7.8	8
Thyroid	4.9	5
Central nervous system	2.0	2
Total of solid tumours	100	101

patients with tumours before conversion versus 1.1/100 patient-years in patients without a tumour history. The IR ratios (IRRs) in skin cancers comparing IRs in patients with and without tumours before conversion were highest in basal cell carcinoma and actinic keratosis. The overall IR in solid tumours after conversion was 3.7/100 patient-years in patients with a tumour history before conversion versus 0.4/100 patient-years in patients without a tumour before conversion. The IRRs in solid cancers could not be calculated due to low numbers in patients without a cancer history before conversion.

Graft and patient survival depending on the tumour entity. For a reasonable comparison of outcome events, we defined five groups of cancer types (Table 8). Prior to conversion, most patients [101/230 (43.9%)] had only skin tumours, followed by

Table 5. Comparison of IRs before and after conversion to SRL in 230 patients with tumours before conversion

Type	Patients, *n*	Time (patient-years)	IR	IRR (IQR)
Any tumour				
Before	230	1015	22.7	1.9 (1.4–2.6)
After	56	469	11.9	
All skin tumours				
Before	146	1154	12.7	1.5 (1.1–2.2)
After	40	480	8.3	
Basal cell carcinoma				
Before	59	1541	3.8	1.3 (0.7–2.4)
After	14	456	3.1	
Squamous cell carcinoma				
Before	47	1556	3.0	2.0 (0.9–5.3)
After	7	467	1.5	
Bowen's disease				
Before	37	1621	2.3	1.4 (0.6–3.4)
After	8	476	1.7	
Actinic keratosis				
Before	22	1661	1.3	0.5 (0.2–1.6)
After	12	468	2.6	
All solid tumours				
Before	101	1135	8.90	2.4 (1.5–4.1)
After	19	510	3.73	
Renal cell carcinoma				
Before	28	1635	1.71	4.0 (1.0–34.9)
After	2	471	0.43	
Colon carcinoma				
Before	12	1690	0.71	3.3 (0.5–141.8)
After	1	467	0.21	
Breast carcinoma				
Before	13	1690	0.77	1.8 (0.4–16.5)
After	2	470	0.43	

IR: occurrence of tumours divided by follow-up time, IRR and its 95% CI, i.e. IR before conversion divided by IR after conversion. Time: cumulative observation time in years.

only solid tumours in 63/230 (27.4%) patients. Skin and solid tumours were present in 32/230 patients (13.9%) and other combinations accounted for 14.8%. Among other combinations, lymphoma and haematological malignancies were included with or without the other classes.

The demographics of these tumour entity groups at Tx and at conversion are shown in Tables 9 and 10. Patients with skin tumours or with solid tumours were less frequently retransplanted. The eGFR was higher in patients with skin or solid tumours than in patients without tumours at the time of conversion. Patients with solid tumours were transplanted in a shorter time compared with patients with skin tumours.

Patient survival censored for graft failure (Figure 3A) was lowest in the tumour entities of patients with only solid tumour and other tumours, whereas in patients with skin tumours only or combined with solid tumours it was similar to patients without tumour. This finding was statistically significant ($P < 0.001$).

Graft survival including death (Figure 3B) after 5 years was highest in patients with skin tumours followed by the group of solid tumours and skin and solid tumours. In patients without tumours and other tumours, graft survival was lowest. This finding was statistically significant ($P < 0.001$).

Table 6. Distribution of tumours after conversion to SRL

Type	Patients with tumours before conversion ($n = 230$)	Patients without tumours before conversion ($n = 496$)
Skin tumours, *n*		
Actinic keratosis	12	3
Basal cell carcinoma	14	4
Kaposi sarcoma	1	0
Keratoankanthoma	9	0
Melanoma	0	1
Bowen's disease	8	3
Squamous cell carcinoma	7	0
Warts	4	2
Other skin tumours	5	3
Total number of skin tumours	40	12
Solid tumours, *n*		
Colon	1	0
Lung	3	2
Stomach	0	0
Breast	2	0
Prostate	1	1
Bladder	1	0
Others	7	1
Renal	2	0
Gynaecological	1	0
Thyroid	1	0
Central nervous system	0	1
Total of solid tumours	19	5

All tumours diagnosed after conversion are shown for the group of 230 patients with tumours before conversion and the group of 496 patients without tumours before conversion.

Death-censored graft survival (Figure 3C) after 5 years was lowest in patients without tumours. In patients with only skin, only solid and skin and solid, death-censored survival was higher than in patients with other tumours. This finding was statistically significant ($P < 0.001$).

Figure 4 shows the SRL discontinuation and the tumour entity. No statistically significant differences between groups were seen.

DISCUSSION

To our knowledge, this is the largest study of patients converted to SRL with tumours before conversion. Our data report the use of SRL in 10 different transplant centres across Germany, reflecting real-life use.

Patients with malignancy before conversion versus those without and their survival

As shown in a large registry analysis, the occurrence of a tumour disease after Tx was higher in patients with tumour pre-Tx [11]. We found a higher incidence of tumours after conversion in our cohort in patients with tumours before conversion. Current guidelines recommend Tx after a recurrence-free period in patients with malignancy [12]. However, recent studies have assessed the risk and benefit of early Tx in patients with malignancy to be beneficial due to better overall outcome [13, 14].

Table 7. Comparison of tumour IRs after conversion to SRL in patients with and without tumours before conversion

	n	Time (patient-years)	IR	IRR (IQR)
Any tumour				
Tumour before conversion	56	469	11.94	8.0 (4.6–14.7)
No tumour before conversion	17	1139	1.49	
All skin tumours				
Tumour before conversion	40	480	8.33	7.97 (4.1–16.7)
No tumour before conversion	12	1148	1.10	
Basal cell carcinoma				
Tumour before conversion	16	456	3.51	10.9 (3.5–44.9)
No tumour before conversion	4	1245	0.32	
Squamous cell carcinoma				
Tumour before conversion	6	467	1.29	–
No tumour before conversion	0	1239	0	
Bowen's disease				
Tumour before conversion	8	476	1.68	7.0 (1.7–40.7)
No tumour before conversion	3	1240	0.24	
Actinic keratosis				
Tumour before conversion	10	468	2.14	8.9 (2.3–50.1)
No tumour before conversion	3	1245	0.24	
All solid tumours				
Tumour before conversion	19	510	3.73	9.0 (3.3–30.7)
No tumour before conversion	5	1203	0.42	
Renal cell carcinoma				
Tumour before conversion	2	471	0.43	–
No tumour before conversion	0	1239	0	
Colon carcinoma				
Tumour before conversion	1	467	0.21	–
No tumour before conversion	0	1239	0	
Breast carcinoma				
Tumour before conversion	2	470	0.43	–
No tumour before conversion	0	1239	0	

IR: occurrence of tumours divided by follow-up time, IRR and its 95% CI, i.e. IR of patients with tumour before conversion divided by IR of patients without tumours. Time: cumulative observation time after conversion in years. IR in 100 patient-years.

The eGFR at conversion was better in patients with tumours and remained better. Conversion to SRL with eGFR >40 mL/min was reported as favourable [15]. In our study

cohort, graft survival was better with tumours, showing a good immunosuppressive efficacy with an SRL-based regimen with fewer BPARs. The patient survival with tumours was worse, mainly due to the impact from solid tumours like renal cell carcinoma, colon carcinoma and breast cancer. Skin tumours showed a comparable patient survival to the patients without tumours.

Table 8. Tumour entities before conversion to SRL

Tumour entity	*n*	All tumours, %
All	230	100
Skin	101	43.9
Solid	63	27.4
Skin and solid	32	13.9
Others	34	14.8
Lymphoma	8	3.5
Solid and lymphoma	4	1.7
Lymphoma and skin	2	0.9
Skin, solid and haematological	1	0.4
Lymphoma, solid and skin	1	0.4
Haematological	1	0.4
Solid and haematological	1	0.4
Not specified	16	7.0

Tumours before and after conversion

Malignancy after Tx is frequently reflected in a higher standardized incidence ratio in transplanted patients than the general population [2, 16, 17]. Consistent with others, we have many patients with renal cell carcinoma and skin cancers in our cohort. As shown previously, skin tumours are very frequent [2]. An increased risk of squamous cell carcinoma in patients on azathioprine was shown earlier [18]. Our data are consistent with the association of azathioprine and skin tumours. In fact, conversion from azathioprine to mycophenolate was proven to reduce the incidence of squamous cell carcinoma [19]. That is also reflected in our data. A benefit for non-melanoma skin cancers has been shown for mTOR inhibitors [20]. Survival was excellent in patients with skin cancers and showed no difference from patients without tumours. Graft survival was statistically better.

In skin tumours, the proportion with more than one skin tumour was higher than in patients with solid tumours, indicating the importance of regular dermatological check-ups after Tx. Within the entity of skin tumours there were a large number of patients with basal cell carcinoma, squamous cell carcinoma or Bowen's disease. As shown in an earlier study, the risk of subsequent squamous cell carcinoma could be reduced in an SRL-based regimen compared with a calcineurin inhibitor (CNI)-based regimen [6, 7]. The development of new tumours after conversion was reduced in patients on SRL compared with IRs before conversion. The finding that patients

Table 9. Characteristics of patient groups with different tumour entities at time of Tx

	Tumours					
At Tx	None ($n=496$)	Skin ($n=101$)	Skin and solid ($n=32$)	Solid ($n=63$)	Other ($n=34$)	P-value
Caucasian ethnicity, %	98.8	100	100	100	97.0	0.024
Age at Tx (years)	41.5 ± 13.4	47.4 ± 12.5	47.1 ± 14.0	48.4 ± 13.0	43.4 ± 14.6	<0.001
Sex (male), %	63.1	68.3	81.3	52.4	61.8	0.066
Cause of ESRD, %						
Diabetic	16.1	3.0	0	8.1	5.9	0.029
Hypertensive	3.7	3.0	3.1	3.2	5.9	–
Polycystic kidney disease	11.4	17.0	3.1	9.7	5.9	–
Glomerulonephritis	40.9	50.0	59.4	43.5	44.1	–
Tubulointerstitial disease	14.5	15.0	9.4	12.9	17.6	–
Other inherited diseases	2.9	4.0	3.1	4.8	11.8	–
Other diseases/unknown	10.6	8.0	21.9	17.7	8.8	
Living donation, %	18.1	13.8	9.7	15.0	9.7	0.473
Kidney re-Tx, %	29.2	16.2	25.0	11.1	27.3	0.005
Kidney–pancreas Tx, %	12.1	2.0	0	4.8	2.9	0.012
Cold ischaemia time (h)	13.5 ± 7.8	16.1 ± 8.6	18.7 ± 8.7	13.1 ± 7.3	17.3 ± 7.7	<0.001
HLA mismatches on locus A, B, DR, *n*	2.5 ± 1.6	2.1 ± 1.6	1.8 ± 1.3	2.6 ± 1.8	2.1 ± 1.5	0.085
Donor age (years)	44.5 ± 15.2	42.9 ± 16.8	38.7 ± 15.4	48.1 ± 17.6	43.2 ± 17.8	0.099
Donor sex (male), %	56.8	58.7	57.1	51.8	56.3	0.951
DGF, %	25.3	29.5	23.1	15.4	28.0	0.464
Immunosuppression, %						
Cytotoxic antibodies	16.5	9.2	28.1	17.7	5.9	0.043
Basiliximab	18.6	20.4	3.1	35.5	32.4	0.001
Cyclosporine	60.0	61.2	68.8	71.0	70.6	0.324
Tacrolimus	31.4	15.3	6.3	25.8	14.7	<0.001
Azathioprine	25.7	55.1	59.4	22.6	41.2	<0.001
Mycophenolate	59.0	29.6	21.9	66.1	50.0	<0.001
Corticosteroids	96.7	95.9	96.9	98.4	94.1	0.839
Others	6.1	4.1	6.3	4.8	5.9	0.946

Values are presented as mean ± SD unless stated otherwise.

Table 10. Characteristics of patient groups with different major tumour entities at and after conversion to SRL

	Tumours					
At conversion	None ($n = 496$)	Skin ($n = 101$)	Skin and solid ($n = 32$)	Solid ($n = 63$)	Other ($n = 34$)	P-value
Age at conversion (years)	46.8 ± 13.0	58.2 ± 10.2	60.1 ± 11.6	54.4 ± 11.4	51.5 ± 13.7	<0.001
Time since Tx (years)	4.8 ± 4.9	10.4 ± 7.8	12.4 ± 6.9	5.4 ± 5.7	7.5 ± 6.9	<0.001
Body weight (kg)	73.8 ± 16.0	76.4 ± 13.8	74.8 ± 14.7	69.9 ± 16.3	70.3 ± 11.1	0.105
BMI (kg/m^2)	24.9 ± 4.4	25.6 ± 3.9	25.2 ± 3.4	24.6 ± 4.5	24.8 ± 3.5	0.594
eGFR (mL/min)	35 ± 18	49 ± 20	50 ± 28	47 ± 17	42 ± 24	<0.001
eGFR at 1 year (mL/min)	37 ± 18	51 ± 21	48 ± 23	51 ± 23	41 ± 24	<0.001
Proteinuria (mg/L)	419 ± 880	171 ± 275	211 ± 259	163 ± 173	322 ± 466	0.011
SRL dose (mg/day)	3.1 ± 1.8	2.5 ± 1.0	2.3 ± 1.6	2.7 ± 1.3	2.9 ± 1.0	0.001
SRL dose at 3 months (mg/day)	2.9 ± 1.9	2.0 ± 1.2	2.2 ± 1.4	2.7 ± 1.6	2.3 ± 1.6	<0.001
SRL TL at 3 months (ng/mL)	8.4 ± 4.0	8.1 ± 3.2	7.2 ± 3.7	7.2 ± 2.8	7.6 ± 4.5	0.281
BPAR prior to SRL, %	39.3	36.3	28.6	34.5	43.8	0.600
BPAR after conversion, %	11.1	3.0	3.1	6.3	5.9	0.051

Values presented as mean ± SD unless stated otherwise.
BMI: body mass index; TL: trough level.

with previous tumours have an increased risk for tumours after Tx was shown in a large study [11].

Graft and patient survival depending on the tumour entity

Smaller studies using SRL in transplanted patients with lymphoma showed an equal safety in terms of acute rejection or graft loss as our study [7, 8, 21]. Our data show a higher incidence of cancer recurrence in patients with skin as well as solid tumours. That finding is consistent with earlier studies showing a higher risk of cancer recurrence after Tx in transplanted patients with previous malignancies [11, 20, 22, 23]. Due to the lack of a non-mTOR-inhibitor control group, we cannot compare our findings with a non-mTOR-inhibitor-based regimen. That is one major limitation of our study. CNI withdrawal and conversion to mTOR inhibitors showed an increase in renal function in many other trials [24–28]. Our data show that patients with skin, solid or skin and solid tumours had better graft survival than patients without tumours. However, patients with tumours experienced a worse survival, especially for tumours other than skin tumours. Patients with skin tumours showed a survival similar to patients without tumours. In a multivariate analysis, creatinine at conversion and proteinuria at conversion appeared to be the most influential factors for survival.

Limitations

One major limitation of our retrospective registry study is the lack of an adequate control group, which was not treated with an mTOR inhibitor and ideally would be matched for important clinical characteristics such as age and immunosuppression. In most tumour patients, the reason for conversion to SRL was the underlying malignancy, while patients without a history of malignancy were converted mainly due to renal reasons, which might explain the differences in patient and graft survival, as well as some important clinical differences at the time of conversion. Another weakness of our study is the fact that the differentiation into tumour entities only provides a rough estimate of outcome, but the number of different cancer types was small. Ideally the grading and treatment of the tumour should be captured in more detail, which was beyond the scope of our registry. While those data on grading and adjunct tumour treatment were not captured in our retrospective registry, our large study provides at least some key outcome parameters after conversion to SRL under real-life conditions. Due to the antiproliferative properties of mTOR inhibitors, such a conversion is frequently done in patients with malignancy, however, outcome data of such conversions are surprisingly sparse.

CONCLUSION

The conversion to SRL is safe regarding renal function, risk of rejection and graft survival in patients with malignancy before conversion, while patient survival was mainly dependent on the tumour entity. Importantly, patients experienced a low cancer IR after conversion to SRL.

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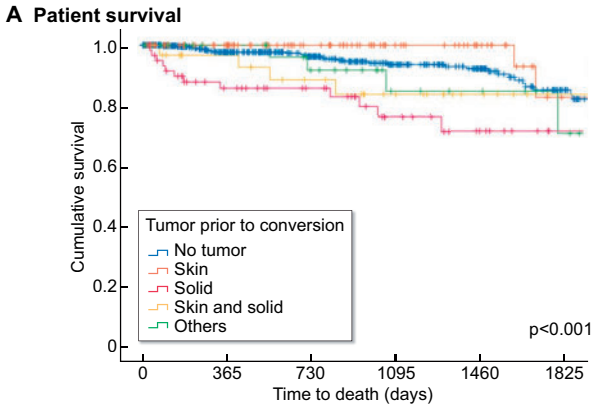
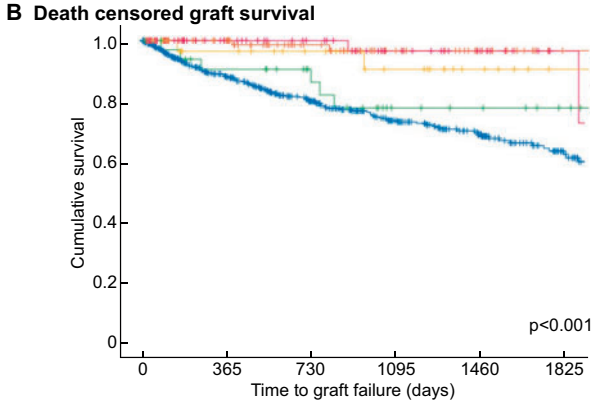
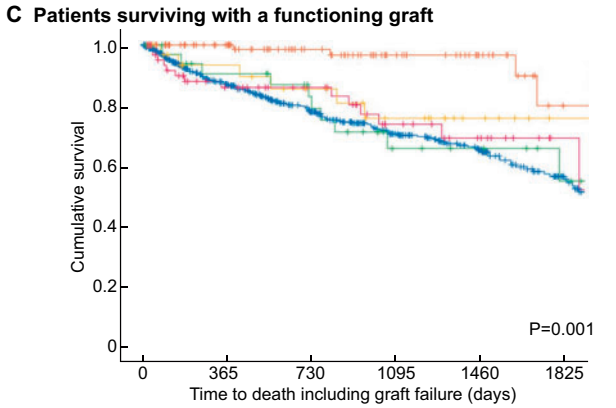


No tumor (N)*	496	345	251	174	118	60
Survival (%)**	100	97.7±0.8	96.2±1.1	93.5±1.5	92.1±1.8	85.0±3.1
Skin (N)*	101	73	52	32	20	6
Survival (%)**	100	100	100	100	100	82.5±11.0
Solid (N)*	63	41	32	19	11	4
Survival (%)**	100	85.6±4.7	85.6±4.7	76.0±6.7	71.2±7.8	71.2±7.8
Skin and solid*	32	25	20	13	6	1
Survival (%)**	100	96.7±3.3	88.4±6.3	83.5±7.7	83.5±7.7	83.5±7.7
Others (N)*	34	27	20	11	9	5
Survival (%)**	100	100	91.6±3.9	84.6±8.6	84.6±8.6	70.5±14.7

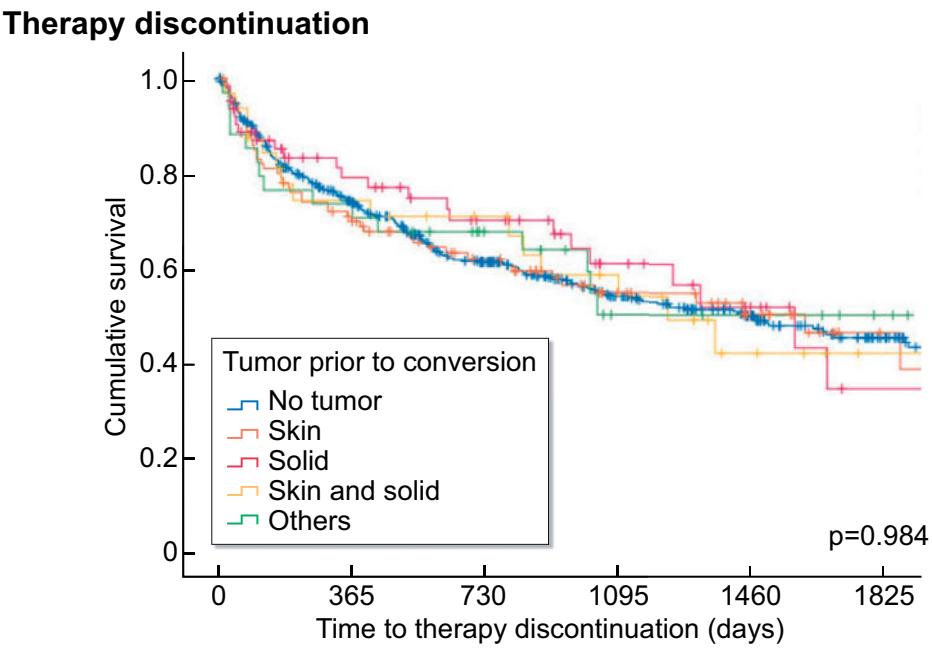


No tumor (N)*	496	335	237	168	111	56
Survival (%)**	100	87.8±1.6	79.7±2.0	73.2±2.4	68.6±2.7	61.9±3.4
Skin (N)*	101	73	52	32	20	6
Survival (%)**	100	100	98.6±1.4	96.6±2.4	96.6±2.4	96.6±2.4
Solid (N)*	63	41	32	19	11	4
Survival (%)**	100	100	100	96.6±3.4	96.6±3.4	96.6±3.4
Skin and solid*	32	24	19	13	6	1
Survival (%)**	100	96.4±3.5	96.4±3.5	90.4±6.7	90.4±6.7	90.4±6.7
Others (N)*	34	27	20	11	9	5
Survival (%)**	100	90.4±5.3	86.1±6.5	77.5±8.3	77.5±8.3	77.5±8.3



No tumor (N)*	496	335	237	168	111	56
Survival (%)**	100	86.7±1.6	77.7±2.1	70.4±2.5	64.9±2.8	55.2±3.5
Skin (N)*	101	73	52	32	20	6
Survival (%)**	100	100	98.6±1.4	96.6±2.4	96.6±2.4	79.8±11.3
Solid (N)*	63	41	32	19	11	4
Survival (%)**	100	85.8±4.7	85.8±4.7	73.6±7.0	69.0±7.9	69.0±7.9
Skin and solid*	32	24	19	13	6	1
Survival (%)**	100	93.3±4.6	85.4±6.8	75.6±8.9	75.6±8.9	75.6±8.9
Others (N)*	34	27	20	11	9	5
Survival (%)**	100	93.8±4.3	78.9±7.7	65.5±9.6	65.5±9.6	54.6±12.8

FIGURE 3: Outcome analysis using Kaplan–Meier for (**A**) patient survival, (**B**) death-censored graft survival and (**C**) patients surviving with functioning graft for patients with different tumour entities prior to conversion. Censored observations are indicated by vertical lines. In the tables below, the number of patients at risk and Kaplan–Meier survival estimators are given for each outcome over 5 years.



No tumor (N)*	496	335	237	168	111	56
Survival (%)**	100	73.7±2.0	61.1±2.3	53.9±2.5	49.9±2.6	45.3±2.8
Skin (N)*	101	73	52	32	20	6
Survival (%)**	100	69.9±4.6	61.1±5.0	54.6±5.4	50.2±5.8	46.3±6.5
Solid (N)*	63	41	32	19	11	4
Survival (%)**	100	79.1±5.4	70.1±6.4	60.8±7.5	51.7±8.7	34.5±11.5
Skin and solid*	32	24	19	13	6	1
Survival (%)**	100	74.3±7.9	70.9±8.2	53.9±9.7	53.9±9.7	42.0±10.7
Others (N)*	34	27	20	11	9	5
Survival (%)**	100	70.6±7.8	67.6±8.0	50.0±9.7	50.0±9.7	50.0±9.7

FIGURE 4: Therapy discontinuation for patients with different tumour entities prior to conversion. Censored observations are indicated by vertical lines. In the tables below, the number of patients at risk and Kaplan–Meier survival estimators are given for each year, e.g. 61.1±2.3% at 1 year in patients without tumor or 34.5±11.5% in patients with solid tumors at 5 years.

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