Risk of Aggressive Skin Cancers After Kidney Retransplantation in Patients With Previous Posttransplant Cutaneous Squamous Cell Carcinomas: A Retrospective Study of 53 Cases

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Background. The course of skin cancer after retransplantation in organ-transplant recipients who have already developed posttransplant skin cancer has not been assessed. **Methods.** This retrospective multicentric study included 53 patients with a history of cutaneous squamous cell carcinoma (SCC) after a first kidney transplantation who received a second kidney transplantation. The primary endpoint was the occurrence of aggressive cutaneous SCC after the second transplantation. Secondary endpoints included the course of skin cancers over 3 periods (first transplantation, return to dialysis, second transplantation), the time to occurrence, and risk factors for aggressive SCC after retransplantation. **Results.** The first SCC developed in 47 patients with a functional graft and in 6 after return to dialysis. After the first transplantation, 17 (33.3%) patients developed SCC in dialysis and 39 (73.6%) after the second transplantation, respectively. Twenty aggressive SCC developed over the study period. They occurred in 14 (26.4%) patients after retransplantation vs 5 (9.4%) after the first transplantation with a median delay of 50 months and were responsible for 5 deaths. Fair skin type, multiple tumors before retransplantation, treatment with azathioprine, T cell-depleting antibodies, and delayed revision of immunosuppression were associated with an increased risk of aggressive cutaneous SCC after retransplantation. **Conclusions.** Candidates to retransplantation with a history of posttransplant SCC have a high risk of aggressive SCC. Our data suggest that the risk could be reduced by a tailored immunosuppression. A wait period may be required depending on the clinicopathological characteristics of the previous SCC and discussed on an individual patient basis.

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The course of skin cancers after retransplantation in kidney-transplant recipients (KTR) who have already developed at least 1 posttransplant cutaneous squamous cell carcinoma (SCC) has not been assessed. Guidelines about skin cancer as a contraindication to organ transplantation are rare and mostly extrapolated from findings concerning

nonimmunosuppressed patients rather than relying on evidence-based data.^{1–3} History of SCC is uncommon in candidates to a first kidney transplantation because the mean age of occurrence of this tumor lies within the seventh life decade in the general population. By contrast, as kidney transplantation has regularly been performed since 1966 and skin cancer affects more than half of organ-transplant recipients in the long term, an increasing number of candidates to

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retransplantation have already developed 1 or more post-transplant cutaneous SCC.⁴⁻⁷ After a first SCC, 60% to 80% of KTR develop new SCC within 3 years.^{8,9} Currently, SCC are considered as more aggressive in transplant recipients than in nonimmunosuppressed patients,^{4,10} as they recur locally in 13.4% of patients, generally during the first 6 months after excision, and metastasize in 5% to 8% of patients, usually within 2 years after excision.^{11,12} Factors of unfavorable prognosis of SCC in transplant patients are multiple. They include factors shared with nonimmunosuppressed patients, such as older age, location on the head/neck, tumor size, multiplicity of lesions, higher sun exposure, specific histological features,¹³ presence of extracutaneous tumors and transplantation-related factors, mainly the immunosuppressive treatment. Skin cancer in KTR is favored by a decrease in immunosurveillance and by drug-specific properties.¹⁴⁻²⁴ Changes in immunosuppression are frequently introduced in transplant patients to reduce the risk of subsequent skin cancers.²⁵⁻²⁸ Retransplantation entails a new load of immunosuppressive medications, including often a depleting induction treatment, and thereby increases the risk of new SCC. Due to the chronic shortage of organs, it is important to allocate them to patients who will obtain the greatest benefit. The occurrence of aggressive SCC in 5 of 15 patients after retransplantation in a pilot study carried out in 1 of our centers suggested that such patients could be at a higher risk of aggressive SCC than after the first kidney transplantation. The aim of this study was to assess, in a larger cohort, the risk of aggressive SCC after a second kidney transplantation in patients with previous posttransplant SCC, and to identify factors that could help in improving their management.

MATERIALS AND METHODS

Patients

KTR who developed at least 1 SCC after a first transplantation, and who received a second kidney transplantation, were included. The follow-up after the second transplantation was at least 3 years (shorter if the main endpoint occurred earlier). We excluded patients with nonkidney or multiorgan transplantation, those with *in situ* SCC (ie, Bowen disease or actinic/premalignant keratoses), those who developed the first SCC before the first kidney transplantation, and those who developed SCC after the second transplantation.

Study Design

This is an international retrospective multicentric study, coordinated by the members of the French group "Peau et Greffe d'Organe" and the members of the European SCOPE group (Skin Care of Organ-Transplant Patients-Europe, <http://www.scopenetwork.org>) in collaboration with the participating transplantation departments. The study was approved by the "Commission Nationale de l'Informatique et des Libertés." Data were collected between January 2014 and March 2015 from 6 centers with dedicated transplant skin clinics, including 5 French centers: Nantes, Lyon, Paris (Necker, Saint-Louis, and Tenon hospitals), and 1 Dutch center (Leiden). Cases were selected from databases of patients with posttransplant SCC and 2 kidney transplantations and from databases of transplant dermatologists.

Data Collection

Clinical and histological data were retrieved from the files of the patients in the departments of Dermatology and Nephrology. A standardized questionnaire (available on request) was sent to the participating centers to collect the patients' characteristics: date of birth, gender, Fitzpatrick skin type (I, always burns/never tans; II, usually burns/sometimes tans; III, usually tans/sometimes burns; IV, always tans/rarely burns), eye and hair color, history of sun exposure (scored low, medium, or high according to indoor/outdoor occupation or residence in a sunny country for over 6 months, or rare/occasional/frequent sunny leisure or tanning bed use). The characteristics of each SCC were retrieved, including date of excision, location, pathological features, that is, degree of differentiation, histological subtype, invasion level (Clark), microscopic tumor thickness (Breslow index), perineural and/or intravascular invasion, excision margin status. The histological features considered as predictive of aggressive outcome, namely, low differentiation, desmoplastic subtype, Breslow thickness greater than 2 mm, subcutaneous fat involvement, perineural and/or intravascular invasion were recorded. SCC were considered clinically aggressive if they had developed either local recurrences (possibly followed by metastasis) and/or metastases (in transit, to the lymph-nodes and/or to viscera). For aggressive SCC, the dates of first excision, local recurrences, and/or metastases, as well as their treatment, were recorded. All histologically confirmed skin tumors (including premalignant/actinic keratoses, Bowen disease, keratoacanthoma, basal cell carcinoma, melanoma, and Kaposi sarcoma) and the occurrence of internal malignancies were also recorded. A count of all histologically-proven skin tumors was performed over 3 periods: the period of the first transplantation with a functional graft, the period during which the patient returned to dialysis, and the period after the second transplantation. Transplantation data included date of transplantation, return to dialysis, age at both transplantations, history of acute rejection, immunosuppressive treatment. The influence of immunosuppressive drugs on the occurrence of aggressive SCC was assessed. Patients in whom a revision of immunosuppression was introduced (either by minimization or by switch from calcineurin inhibitors to mammalian target of rapamycin [mTOR] inhibitors) were compared with those who had no treatment change. We considered that minimization was achieved if the dose of at least 1 drug was decreased by 30% or more, this cutoff being based on usual practices. The duration of immunosuppression was calculated by summing the number of months under immunosuppressants from the first transplantation and subtracting the duration of dialysis.

Endpoints

The primary endpoint was the number of patients with at least 1 aggressive SCC after the second transplantation. Secondary endpoints were the time of occurrence of aggressive SCC after retransplantation, the number of patients with aggressive SCC before, the number of skin tumors over the 3 periods, the number of patients with internal malignancies, survival after the second transplantation, and the analysis of possible risk factors favoring the development of an aggressive SCC after a second transplantation, namely, skin type, history of sun exposure, occurrence of SCC with aggressive histological features, number of previous SCC before,

wait period before the last SCC and the second transplantation, duration of dialysis period, occurrence (or not) of SCC during dialysis, immunosuppressive regimens.

Statistical Analysis

The characteristics of patients' grafts and skin tumors were expressed as absolute numbers and percentages (for qualitative data), and as mean ($\pm$ SD) and/or median (minimum-maximum) for quantitative data. Patients with and without aggressive SCC were compared by the χ^2 test for qualitative risk factors (or the Fisher test when appropriate), or by the Student *t* test for quantitatives (or the Mann-Whitney test for data with non-normal distribution). Time to first aggressive SCC was also compared using the Cox proportional hazard model. Overall survival was computed using the Kaplan-Meier method.

RESULTS

Study Population

Fifty-three patients were included in the study (Figure 1). Forty-seven cases were provided by 3 centers where all cases were systematically recorded (Nantes, Leiden, Lyon). These centers totaled 1375 KTR with a second transplantation. 126 patients with SCC were excluded because the first SCC occurred after the second transplantation. Six additional cases were retrieved from the databases of transplant dermatologists working with several transplant centers in Paris.

The patient's characteristics are shown in Table 1. The median follow-up time was 24.9 years (range, 9.1-38.2) after the first transplantation, including 9.7 years (range, 2.1-25.8) before, and 14.5 years (range, 3.9-31.0) after the first SCC. The first transplantations were performed between 1970 and

2001, and the second ones between 1986 and 2012. The initial immunosuppressive regimens reflected the various protocols in each era, and included (after the first transplantation) mainly 2 combinations, that is, corticosteroids + azathioprine in bitherapy (*n* = 21), associated with cyclosporine in tritherapy (*n* = 21). After the second transplantation, 41 patients received a triple immunosuppressive treatment. Since 1996, the protocols replaced progressively azathioprine by mycophenolate mofetil and cyclosporine by tacrolimus. Sirolimus was given initially only in 2 patients. When the patients returned to dialysis, the immunosuppressive treatments were gradually decreased and totally discontinued within 6 to 12 months.

Endpoints

Primary Endpoint

Fourteen of the 53 (26.4%) patients developed 15 aggressive SCC after the second transplantation with a median delay of 50 months (range, 3-97) (Table 2). They included 4 patients who developed only local recurrences and 10 patients who developed metastases, preceded by local recurrences in 8 cases (in the latter group, 1 patient had 2 aggressive SCC). Local recurrences and metastases were diagnosed after a mean delay of 6 (range, 1-20) and 13 months (range, 1-23), respectively, after the diagnosis of SCC. Fourteen of the 15 aggressive SCC were new tumors. Among these patients, 3 had a history of metastatic SCC in another location after the first transplantation. One of the 15 aggressive SCC corresponded to a recurrence of a SCC, which developed 18 months before the second transplantation in a patient who did not return to dialysis. This patient died of metastasis of this SCC 18 months after retransplantation. All local recurrences were treated by wide surgical excision (along with adjuvant radiotherapy in 3 cases). Six patients with nodal or

FIGURE 1. Distribution of patients with SCC according to the 3 study periods.

TABLE 1.
Patients' characteristics and predictive factors for aggressive SCC after a second transplantation

	Modalities	Overall	Nonaggressive SCC (n = 39)	Aggressive SCC (n = 14)	P ^a	HR (95% CI)	P ^b
Sex	Male	32 (60.4)	22 (56.4)	10 (71.4)	ns	2.23 (0.70-7.16)	ns
Age, y	First TR, mean (SD)	39.45 (10.78)	40.92 (10.79)	35.36 (10.02)	ns	0.97 (0.93-1.02)	ns
	Second TR, mean (SD)	57.58 (9.11)	58.33 (9.3)	55.5 (8.54)	ns	1.00 (0.94-1.05)	ns
Total length of follow-up with immunosuppression, mo	Mean (SD)	268.98 (77.89)	262.72 (82.47)	286.43 (62.78)	ns	1.00 (0.99-1.01)	ns
Skin type	I or II	17 (39.5)	11 (36.7)	6 (46.2)	ns	1.00	ns
	III or IV	26 (60.5)	19 (63.3)	7 (53.8)	ns	0.73 (0.24-2.18)	
Eye color	Unknown	10	9	1			
	Black or brown	17 (40.5)	15 (51.7)	2 (15.4)	0.0265	1.00	ns
	Hazel, green, blue, grey	25 (59.5)	14 (48.3)	11 (84.6)		3.67 (0.81-16.58)	
	Unknown	11	10	1			
At-risk skin type patients	No (skin type ≥ III and brown/black hair and eye color)	22 (52.4)	19 (65.5)	3 (23.1)	0.0109	1.00	0.0179
	Yes (skin type ≤ II or blond/red hair color or hazel green/blue/grey eye color)	20 (47.6)	10 (34.5)	10 (76.9)		4.88 (1.31-18.12)	
Sun exposure	Unknown	11	10	1			
	Low or moderate	26 (81.1)	16 (76.2)	10 (91)	ns	1.00	ns
	High	6 (18.8)	5 (23.8)	1 (9.1)		0.50 (0.06-3.93)	
Length of T1, mo	Unknown	21	18	3			
Length of immunosuppression after the first SCC in T1, mo	Mean (SD)	182.92 (72.79)	174.49 (74.95)	206.43 (62.97)	ns	1.01 (1-1.01)	ns
At least 1 acute rejection after the first transplantation	Mean (SD)	53.47 (49.73)	42.64 (40.23)	82.43 (61.98)	0.0208●	1.01 (1-1.02)	0.0044
	Yes	19 (36.5)	15 (38.5)	4 (30.8)	ns	0.96 (0.29-3.17)	ns
At least 1 acute rejection after the second transplantation	Unknown			1			
	Yes	8 (15.1%)	4 (10.3)	4 (28.6)	ns	2.37 (0.73-7.69)	ns
Azathioprine T1/T2	Yes	43 (81.13)	29 (74.4)	14 (10)	0.0470●	5.88 (0.31-109.93)	ns
Mycophenolate mofetil T1/T2	Yes	40 (75.5%)	29 (74.4%)	11 (78.6)	ns	1.76 (0.49-6.37)	ns
Cyclosporine T1/T2	Yes	37 (69.8)	27 (69.2)	10 (71.4)	ns	1.38 (0.43-4.43)	ns
Tacrolimus T1/T2	Yes	28 (52.83)	20 (51.3)	8 (57.1)	ns	1.64 (0.57-4.76)	ns
T cell-depleting induction T1	Yes	25 (52.1)	16 (44.4)	9 (75)	ns	4.71 (1.25-17.75)	0.0219
	Unknown	5	3	2			
T cell-depleting induction T2	Yes	36 (67.92)	24 (61.5)	12 (85.7)	ns	3.83 (0.85-17.22)	ns
T cell-depleting induction/rejection T2	Yes	37 (69.8)	24 (61.5)	13 (92.9)	0.0410●	7.8 (1.02-59.97)	0.0483
No. SCC/year during T1	Mean (SD)	0.18 (0.16)	0.16 (0.14)	0.26 (0.18)	0.0375●	20.61 (1.2-353.45)	0.0369
Aggressive SCC during T1	Yes	5 (9.4)	2 (5.1)	3 (21.4)	ns	2.27 (0.63-8.21)	ns
Occurrence of SCC during dialysis	Yes	17 (32.1)	13 (33.3)	4 (28.6)	ns	0.84 (0.26-2.68)	ns
No. SCC/years of D	Mean (SD)	0.26 (0.62)	0.22 (0.44)	0.38 (1.00)	ns	1.06 (0.54-2.07)	ns
Length of D, mo	Mean (SD)	32.59 (24.62)	30.63 (26.55)	38.31 (17.45)	ns	1.01 (0.99-1.02)	ns
Waiting period between the last SCC and second transplantation	Mean (SD)	46.17 (51.61)	41.82 (38.87)	58.29 (77.6)	ns	1.00 (1.00-1.01)	ns

^a P values are for χ^2 test or Student *t* test unless ● is specified (Fisher exact test or Mann-Whitney test).
^b P values are for Cox proportional hazard model.
Values are n (%) unless otherwise specified.
T1, period of first transplantation; T2, period of second transplantation; D, period of dialysis; ns, not significant.

TABLE 2.**Distribution of SCC (including aggressive ones) during the 3 periods**

	First transplantation, n = 53	Dialysis, n = 51 (2 did not dialyze)	Second transplantation, n = 53
No. patients with SCC, n (%)	47 (88.6)	17 (33.3) including 6 patients with a first SCC	39 (73.6)
Median follow-up (range), mo	176 (50-376)	31 (5-103)	71 (18-244)
No. SCC	141	40	281
Median (range)	2 (1-13)	1 (1-17)	4 (1-40)
Mean no. SCC per year (SD)	0.18 (0.16)	0.26 (0.62)	0.91 (1.55)
	1.06 after the first SCC		
Location (452)	135	38	279
(10 unspecified)	(6 unspecified)	(2 unspecified)	(2 unspecified)
Head and neck (153)	58	8	87
Face (unspecified)	1	0	3 (3 AG)
Cheek	7	1	12
Eyelid/periorbital	0	1	3
Chin	0	0	5
Ear or preauricular	15	2	17 (1 AG)
Forehead	9	0	11 (2 AG)
Temple	10 (1AG)	1	7
Lip	8 (3 AG)	1	4
Nose	5	0	6
Scalp	3	2	7
Neck	5	0	12
Limbs and trunk (299)	77	30	192
Arm/forearm	24	2	44 (1 AG)
Hand	33	19	89 (4 AG)
Thigh/leg	11	6	26 (1 AG)
Foot	1 (1 AG)	0	9 (1 AG)
Trunk	5	3	24 (2 AG)
No. patients with aggressive SCC, n (%)	5 (9.4) ^a	0	14 (26.4) ^a (15 lesions)
No. patients with local recurrence only	1	0	4
No. patients with metastases without local recurrence	4	0	2
	Cutaneous: 1 Nodal: 3		Nodal: 2
No. patients with local recurrences and metastases	0	0	8 Cutaneous: 4 Nodal: 6 Visceral: 4 (lung, 3; bone, 1)

^a Three patients had 2 different aggressive SCC after the first and second transplantations.
AG, aggressive.

cutaneous metastases were treated with surgery (and adjuvant radiotherapy in 5 cases). Among patients with visceral metastases, 3 were treated with chemotherapy; one of them died before chemotherapy induction.

Secondary Endpoints

Five (9.4%) patients developed an aggressive SCC after the first transplantation. One patient who had only 1 local recurrence was treated with surgical excision and was re-transplanted 2.5 years later. Four patients had SCC with a metastatic course. One patient with in-transit cutaneous metastasis was treated with wide surgical excision. Three patients with nodal metastases underwent lymph-node dissection and adjuvant radiotherapy. The second transplantation in these 4 patients was performed 5, 6, 10, and 11 years after the occurrence of metastases. None of these patients developed further recurrence of the first aggressive SCC. In total,

20 aggressive SCC developed in 16 patients over the 2 periods of transplantation. During the study period, the 53 patients developed a total of 958 epithelial skin tumors including 462 SCC (Figure 2). The locations of aggressive and non-aggressive SCC are shown in Table 2. The percentage of aggressive SCC occurring on the head/neck and the limbs/trunk over both transplantation periods was 6.5% and 3.3%, respectively ($P = 0.12$).

Seventeen (33.3%) patients developed SCC after they returned to dialysis, including 8 patients who had lesions only during the first year, when the weaning of immunosuppressive treatment was still ongoing or only recently achieved. Six patients had their first SCC over this period. After the second transplantation, 39 (73.6%) patients had new SCC with a comparable mean number of SCC per year as compared with the period after the first transplantation (0.91 SSC/year vs 1.06 SCC/year, $P = 0.10$). The occurrence of aggressive and

FIGURE 2. Count of skin tumors in 53 patients during the 3 periods (T1, period of first transplantation; D, period of dialysis; T2, period of second transplantation).

nonaggressive SCC after the second transplantation according to the number of SCC before retransplantation is shown in Figure 3. The percentage of patients developing SCC with unfavorable histological characteristics reached 28.3%, 23.5%, and 46.2% during the periods of first transplantation, dialysis, and second transplantation, respectively. The histological features of the initial SCC responsible for local recurrence and/or metastasis were available only in 11 cases; 9 of them had at least 1 unfavorable histological feature. In the remaining cases, it was not possible to identify the initial location due to a high number of coexisting tumors, which were occasionally treated without histological examination. Three patients developed other skin malignancies, including 2 melanomas and 1 Kaposi sarcoma, after the second transplantation. Internal malignancies occurred in 9 patients, including 7 after

the second transplantation associated with aggressive SCC in 2 cases; they involved the prostate (n = 2), colon (n = 1), bladder (n = 1), kidney (n = 2), lung (n = 1), anus (n = 1) and one of unknown origin (the latter 5 cases had a fatal outcome). Twenty-six patients (49%) died during the follow-up after retransplantation. Among the 14 patients with aggressive SCC, 11 (78.5%) died (5 of SCC metastases and 6 from other causes). The median survival after the second transplantation was 111 months (95% confidence interval, 91-163), but significantly shorter in patients with aggressive SCC (Figure 4).

Risk Factors

Several risk factors were found to be associated with an increased risk of aggressive SCC after the second transplantation (Table 1). They include classical phenotype characteristics

FIGURE 3. Occurrence of aggressive and nonaggressive SCC after retransplantation according to the cumulative number of SCC before retransplantation.

FIGURE 4. Survival of the 53 patients according to the occurrence of aggressive SCC after the second transplantation (Log-rank *P* value = 0.0253).

(fair skin type and eye color) and a higher number of SCC per year before retransplantation. A history of aggressive SCC after the first transplantation was more frequent, but this difference did not reach statistical significance (hazard ratio [HR], 2.27). The impact of the various immunosuppressive drugs is presented in Table 1. Use of azathioprine over the 2 transplantation periods and T cell–depleting treatments after the second transplantation were found to be significantly associated with the occurrence of aggressive SCC after the second transplantation. Revision of the immunosuppressive treatment was introduced in 45 patients during the first transplantation after one or several SCC and in 28 patients after the second transplantation after the occurrence of new SCC. The delay of the first change after SCC diagnosis in the first transplantation period was 15.83 ± 28.01 months for patients who had aggressive SCC after the second transplantation, as compared with 6.58 ± 13.36 months for patients without aggressive SCC (aggressive SCC-free survival, $P = 0.0241$). mTOR inhibitors were prescribed to 18 (34%) patients after the second transplantation, on average 54.67 ± 43.98 months after SCC diagnosis in patients with aggressive SCC versus 25.33 ± 32.33 in patients without (HR, 1.01; NS).

DISCUSSION

Our study is the first one to assess the course of skin cancers after a second kidney transplantation in patients who had developed SCC after a first transplantation and highlights the high risk of aggressive SCC and the high mortality they entail in these patients. The rate of patients who developed aggressive SCC after the second transplantation reached 26.4% versus 9.4% of the same cohort after their first

transplantation, this latter figure being in keeping with data from the literature.⁴ We believe that our population is representative of the population with a second transplant, even though the rate of aggressive SCC could be slightly overrepresented due to the method of inclusion. On the other hand, this bias could be balanced by the inclusion criteria we adopted, because the follow-up in some of our patients after the second transplantation did not exceed 36 months. An older age and an increased duration of immunosuppression, which are risk factors for aggressive SCC, probably play a role. Although the burden of skin cancer and the distribution of the other nonmelanoma skin cancers remained similar after the second, compared with the first, kidney transplantation, there was a higher proportion of patients developing SCC with aggressive histological features; furthermore, most (albeit not all) aggressive SCC whose histology was available showed at least 1 histological feature of unfavorable prognosis. Remarkably, although aggressive SCCs are usually located on the head, a higher proportion of aggressive SCC developed on the limbs or the trunk, reflecting the localization of all SCC in the study population. Furthermore, 10 additional malignancies (including 2 melanomas, 1 Kaposi sarcoma, and 7 nonskin cancers) developed among the 53 (18.9%) patients. This percentage is comparable to the one previously reported in transplant patients with SCC^{8,9,29} and reflects the long-term immunosuppression.³⁰ However, the number of cases in our study was too limited to assess an association with aggressive SCC.

Several factors were found to be associated with an increased risk of aggressive SCC after retransplantation. Factors before retransplantation comprise classical phenotypic characteristics (fair skin type and eye color), a high number of

SCC and probably a past history of aggressive SCC, although the relatively low number of patients of our series did not allow the differences to reach statistical significance. Noteworthy, our finding of a longer wait period between the last SCC and retransplantation in patients with aggressive SCC after the second transplantation is probably biased by a profile of patients with multiple tumors who were at-risk. Although the rate of SCC globally decreased after return to dialysis, one-third of patients developed SCC during this period, this rate being similar to that reported in a small case series.³¹ Furthermore, patients under dialysis also have a higher rate of cancer.³² Indeed, the occurrence of SCC after the first transplantation alone does not necessarily predict the development of aggressive SCC after the second transplantation, if the histological features of the SCC are not considered, even though not all clinically aggressive SCC have aggressive histological features. In our series, 5 patients were retransplanted after having developed an aggressive SCC, which did not recur after the second transplantation; even though 3 of these patients developed new aggressive SCC, this finding suggests that a history of aggressive SCC should not preclude retransplantation. The wait period before the second transplantation invariably exceeded 5 years for the patients with metastases. These findings are in keeping with the general recommendation for internal malignancies^{3,6,24} and with older guidelines concerning SCC.^{1,2} The length of immunosuppression during the first transplantation period after the first SCC was found significantly longer, possibly because of a long-term deeper immunosuppression, which was related to a delay in immunosuppression revision in patients with aggressive SCC after the second transplantation.

The main risk factor for the development of aggressive SCC after the second transplantation seems to be the immunosuppressive regimen. Our study suggests that treatment with T cell-depleting antibodies, used either in induction treatment or to reverse acute rejection, favors the occurrence of aggressive SCC after retransplantation. Although T cell-depleting antibodies reportedly increase the risk of melanoma²¹ and of cancer in patients treated for acute rejection,^{22,23} their role in nonmelanoma skin carcinomas has never been studied. As skin carcinomas are a rather long-term complication of immunosuppression, most studies addressing the role of immunosuppressive treatments have considered the maintenance (not induction) treatments. We found treatment with azathioprine to be associated with the risk of aggressive SCC after retransplantation. However, although large recent studies underlined the increased risk of skin cancer in patients under azathioprine,^{19,20} this finding could arguably be biased by other factors. Azathioprine was used in the early periods of transplantation when neither dermatological prevention with skin regular screening, nor sun protection advices were provided to the patients. In our patient cohort (that included patients transplanted since 1970), the management of immunosuppression has been heterogeneous, as the switch to mTOR inhibitors was introduced only over the last 10 years. Noteworthy, patients with aggressive SCC after retransplantation were switched later than those without aggressive SCC. Indeed, several studies have shown a decrease of skin cancers in KTR under sirolimus as compared with those receiving calcineurin inhibitors.^{29,33-35} This decrease is more pronounced if sirolimus is given early. Consequently, switch of KTR with skin cancer to mTOR inhibitors is increasingly performed in

order to reduce the occurrence of new skin tumors and speculatively of other cancers, although the preventive effect of these immunosuppressants on nonskin cancers has not yet been proven.³⁶ However, this strategy was more or less hampered by reports of poor tolerance and poorer survival, based on initial practices with abrupt conversion and high drug dosages.³⁷ Subsequent studies showed that a progressive switch to sirolimus and adequate dosages can be safe.^{29,35} Nevertheless, the impact of mTOR inhibitors in patients with retransplantation has not been specifically assessed, even though some studies included such patients.²⁹

In our study, retransplantation was associated with a 20% risk of mortality at 5 years, in relation (or not) with aggressive SCC; however, patients were on average 20 years older after the second, as compared with the first, kidney transplantation. Admittedly, immunosuppression in the long-term is associated with substantial comorbidities including not only malignancies but also cardiovascular disorders.

In conclusion, although our findings do not allow validation of firm guidelines, we believe they are helpful in making a decision of a second transplantation in patients with a history of posttransplant SCC. It seems that no wait period is warranted after a single SCC devoid of histological features of aggressiveness. By contrast, we recommend a waiting period of 2 years in case of SCC with histological features of aggressiveness (considering the median delay to the occurrence of metastasis), and of 5 years in case of history of metastatic SCC. Nevertheless, the length of the wait period should be discussed on an individual patient basis, according to the background and the tolerance of dialysis.

Furthermore, stronger prevention measures should be applied, especially in patients who accumulate several risk factors of aggressive SCC. These measures include adequate education about strict sun protection and regular dermatologic monitoring for early ablation of (pre)malignant lesions with adequate safety margins.³⁸⁻⁴²

The main issue is the management of immunosuppression. The availability of a well-matched donor should decrease the immunologic risk, allowing avoidance of a T cell-depleting induction treatment. We also advocate that azathioprine be avoided as much as possible. Patients who were heavily immunosuppressed after the first transplantation seem to be at higher risk of aggressive SCC after a second transplantation. This could be partly due to an individual higher susceptibility to immunosuppression. An early tailored immunosuppression, including mTOR inhibitors, should be the best prevention of aggressive SCC.

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