# Post-Transplant Skin Cancer: The Influence of Organ and Pre-Transplant Disease

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Post-transplant skin malignancies have been extensively studied [1–6], but the role of the transplanted organ in the occurrence of tumours is still discussed. This chapter reviews the epidemiological, clinical, and therapeutic aspects of skin cancers in populations of kidney (KTR), heart (HTR), and liver transplant recipients (LTR). Furthermore, some data on the impact of the pre-existing disease leading to organ failure are now available [7–10], and we consider here whether certain disorders warrant more intensive dermatological surveillance.

This update takes into account mainly keratinocyte skin cancers (KSC), which represent 95% of all post-transplant skin cancers, and Kaposi's sarcoma (KS). Data on the other types of skin cancers are not sufficient to allow any comparison. Kidney transplant recipients will be considered as the reference population as they have the longest follow-up, currently reaching more than 40 years.

## Influence of Organ

### *Keratinocyte Skin Cancer*

Many authors have reported the incidence of skin cancers in KTR in various countries including Europe, North America, and Australia (Table 1). Selected relevant series that have been published these past 10 years have shown that the incidence always increases with time after transplantation and varies in large groups from 0.2% to 2.25% [2, 7] at 1 year to 10% to 17% at 10 years and 40% to 60% at 20 years in the United States and Western Europe [2, 11]. Higher figures are reached sooner in Australia: 7% at 1 year, and 25% to 30% at 5 years [2, 12], the long-term incidence at 20 years (70%–82%) being still higher than in Europe (40%–60%). However, some differences may be observed in countries with similar sun exposure: At 10 years post transplant the incidence was 10.8% to 17% in Italy [3, 13] and 48%

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**Table 1** Incidence of skin cancer in series of kidney, heart, and liver transplant recipients according to the length of immunosuppression

| Author | Numbers of patients | Country | Year 1 | Year 2 | Year 3 | Year 5 | Year 6 | Year 7 | Year 10 | Years 12–15 | Year 15 | ≥20 years |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Kidney** | | | | | | | | | | | | |
| Bouwes Bavinck 1996 | 1098 | Australia | 7% | | 16% | 25% | | 33% | | 45% year 11 | 59% | 70% |
| | | The Netherlands | 0.2% | | 0.7% | 3% | | 6% | | 16% year 11 | 24% | 41% |
| Fortina 2000 | 228 | Italy | | | | 6% | | | 17% | | | |
| Naldi 2000 | 1062 | Italy | | | | | | | 9.7% | | | |
| Harden 2001 | 211 | UK | | | | 3.2% (<5) | | 8.4% (5–10) | 9.3% (>10) | | | |
| Ramsay 2002 | 398 | Australia | | | | 29.1% (<5) | | 52.2% (5–10) | 72.4% (10–20) | | | 82.1% (>20) |
| Fuente 2003 | 174 | Spain | | | 13% | | 27.5% | | 48% | | | |
| Bordea 2004 | 979 | UK | | | | | | | | | | 61% |
| Kasiske 2004 | 35, 765 | US | 2.25 | 4.95 | 7.43 | | | | | | | |
| Otley 2006 | 46, 355 | US | | | 1.12% | | | | | | | |
| **Heart** | | | | | | | | | | | | |
| Espana 1995 | 92 | Spain | 4.3% | | | | | 43.8% | | | | |
| Lampros 1998 | 248 | USA (Oregon) | 3% | | | 21% | | | 35% | | | |
| Ong 1999 | 455 | Australia | | | | 31% | | | 43% | | | |
| Naldi 2000 | 267 | Italy | | | | | | | 11.4% | | | |
| Caforio 2000 | 300 | Italy | | | | 15% | | | 35% | | | |
| Fortina 2000 | 252 | Italy | | | | 16% | | | 33% | | | |
| Otley 2006 | 8594 | US | | | 5.18% | | | | | | | |
| **Liver** | | | | | | | | | | | | |
| Haagsma 2001 | 174 | The Netherlands | | | | 4% | | | 13% | | | |
| Otley 2006 | 8075 | US | | | 1.08% | | | | | | | |

in Spain [14], but this could be explained by the older age of the Spanish population at transplantation (45 vs. less than 37 years).

The number of publications concerning non kidney transplant recipients is increasing, but longitudinal studies are limited, and there are no data beyond 10 years post transplant [15–18]. Several comparative studies show a 2- to 4-fold-higher risk in HTR as compared to KTR [8, 13, 19–21]. The incidence varies from 3% to 4% at 1 year [15, 17] to 11.4% to 35% at 10 years [3, 13, 18] in Europe and the United States and 43% in Australia [16]. Although the higher prevalence of KSC in HTR has been initially thought to be caused by deeper immunosuppression [19, 21], it seems this would be mainly related to their older age at transplantation as compared to KTR [3, 8, 13]. In a Spanish group of HTR, a high incidence of 43% at 7 years was reported [15]. Indeed, in a recent study, we found that at the occurrence of skin cancer, the dosages of immunosuppressive treatment according to the weight of patients were similar in HTR and KTR [20]. In both KTR and HTR, the risk ratio was reported to be 6-fold- and 12-fold-higher in patients grafted between 35 and 55 years, respectively, and in those beyond 55 years of age as compared to those grafted at less than 34 years [8]. These differences between HTR and KTR could be less pronounced in years to come as the mean age of transplantation in KTR increases.

Few studies have been specifically devoted to skin cancer in LTR [22–25], and most epidemiological data are briefly reported in series dealing with general complications after liver transplantation. The global incidence of skin cancer in various centres, independent of the time of transplantation, ranges from 1.1%–1.6% to 22.5% [22–28]. The two available studies providing time-related incidence show similar figures at 3, 4, and 10 years in LTR as compared to control KTR from the same area [8, 28]. The highest reported incidence per centre (22.5%) comes from a survey performed in Boston where data were collected using a questionnaire that was sent to patients with a median follow-up of 4 years. This study suggests that some KSC in LTR are treated by local physicians and could be under-reported in many series [23].

## *Kaposi's Sarcoma*

The incidence of KS varies from 0.14% to 0.5% in Western countries and the United States to 1.5% in Northern Italy and 4.1% in the Middle East [1, 7]. Several series from France, Italy, and Spain have reported a higher incidence of KS in LTR as compared with KTR [29–32]. In a study performed in Italy, LTR were at 2.7-fold-higher risk of KS than KTR [30], which could be caused by a higher risk of human herpesvirus 8 (HHV8) infection transmission from the graft, which was found to be 40% as compared with 33% for heart and less than 5% for kidney [33]. Although older age at transplantation increases the risk of KS, HTR seem to be involved less often, possibly because viral coinfections are less frequent in HTR as compared to LTR and older KTR, in whom hepatitis viruses are very common.

## Influence of End-Stage Disease

### *Kidney*

Data on the impact of the *dialysis period* are controversial. Cancer has been reported to be more common among dialysed patients compared with the general population because kidney failure is associated with abnormalities in the immune system, and the relative risk was found to be higher in younger patients [34]. The improvement in dialysis procedures is probably changing the current data, and a recent study has shown that a longer time on dialysis before transplantation was found to be associated with a lower risk of skin cancer [7].

Table 2 shows the percentage and the risk ratio of skin cancer and non-skin cancer according to the *underlying kidney disease* in several series [7–10]. The two disorders that deserve special mention are diabetes and polycystic kidney disease.

The lower incidence of skin cancer in patients with *diabetic nephropathy* as compared with the other renal diseases had been already mentioned in two series of more than 1,000 patients [35, 36]. Three recent multicentric American studies of patients who received a first kidney transplantation have assessed the impact of the underlying disease leading to end-stage kidney failure and the development of post-transplant skin and non-skin cancer [7–9]. Kasiske et al. [7] examined the 3-year incidence of most major post-transplant malignancies among recipients of both deceased or living donor kidney transplantations in 1995–2001 ($n = 35,765$) using Medicare billing claims. Taking glomerulonephritis as reference, diabetes was found to be protective for both skin and non-skin malignancies, but this was more pronounced for skin. Two other publications used the data from the Transplant Tumor Registry of the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS), which were collected in transplants performed between January 1996 and December 2001 [8, 9]. Data were censored at 963 days for all the patients studied by Kauffman et al. [9] to allow comparable

**Table 2** Influence of kidney diseases on the incidence of skin cancers

| Authors | Kauffman | Otley | Kasiske | Kasiske | Agraharkar | Agraharkar |
|---|---|---|---|---|---|---|
| Number of patients | 33,249 | 46,355 | 35,765 | 35,765 | 1,739 | 1,739 |
| Percent (%) or risk ratio (RR) | % of cancers | % and RR of skin cancers | RR non-skin | RR skin | RR all cancers | Without skin |
| Glomerular diseases | 1.29 | 0.99 (RR 1) | 1 | 1 | 1 | 1.3 |
| Tubular interstitial | 2.31 | 1.62 (RR 1.38) | NA | NA | NA | NA |
| Diabetes mellitus | 1.50 | 0.89 (RR 0.70) | 0.82 | 0.63 | 1 | 1 |
| Hypertensive nephro-sclerosis | 1.97 | 0.95 (RR 1.13) | 1.06 | 1.05 | 1.6 | 2.3 |
| Polycystic kidneys | 2.87 | 2.52 (RR 1.65) | 0.99 | 1.27 | NA | NA |
| Renovascular and vascular diseases | 1.71 | 1.05 (RR 1.38) | NA | NA | NA | NA |
| Other diseases | 1.37 | 0.82 (RR 0.97) | 1.49 | 0.89 | 1.1 | 1.5 |

follow-up time, while the follow-up varied from 18 to 90 months for those included in the series of Otley et al. [8]. In both studies, glomerular diseases were also taken as reference. Diabetic nephropathy was associated with the lowest incidence of skin cancer [8], but not for all cancers (including skin and nonskin cancer) where glomerular diseases had the lowest incidence [9]. Agraharkar et al. described a total of 1,979 transplants performed in 1,739 patients from 1967 to 2002 at a single centre in Texas with a mean follow-up of 6.1 years [10]. They classified the end-stage renal diseases into four groups comprising diabetes, hypertension, glomerulonephritis, and miscellaneous. The risk ratio for diabetes was found to be the lowest for all cancers with or without skin cancers. The lower risk of skin cancer in transplant patients with diabetes could be due to a lower absorption of immunosuppressive drugs because of gastroparesis, resulting in decreased blood levels of cyclosporine [37], tacrolimus [38], or mycophenolate mofetil [39]. It has been also speculated that a lower rate of cigarette smoking among diabetics could reduce the overall risk of cancer [7].

The higher trend of *polycystic kidney disease* to malignancy, which has been already suggested [40, 41], has been confirmed (see Table 2) [8, 9]. The results of Kauffman et al. analyse globally all types of "de novo" cancer, including skin cancer, but it seems that the increase would be mainly related to skin cancer [8]. Kasiske, who studied separately the impact of the disease on skin and non-skin cancer, found an increased risk only for skin cancer. A major limitation of these studies is the relatively short duration of follow-up (3 years) in which patients with skin cancer were the oldest patients. Mean age at transplant is significantly older for patients with polycystic kidney disease, and another explanation could be the "overrepresentation" of this disorder where graft and patient survival are better as compared to the other kidney diseases [42]. Thus, there are several confounders that could explain, at least in part, the apparent excess of skin cancer in allograft recipients with polycystic kidney disease.

## *Heart*

To our knowledge, the only work studying the impact of the initial heart disease is provided by the data of the registries of the OPTN/UNOS, where 8,594 HTR were included with a mean follow-up of 1,107 days [8]. Although the highest incidence of skin cancer was described in patients with coronary artery disease (6.72%) as compared with those grafted for cardiomyopathy, valvular diseases, and miscellaneous, multivariate analysis showed that underlying diseases had comparable risks.

## *Liver*

By contrast to the previous organs, it seems that a greater number of authors have endeavoured to assess the impact of the primary liver disease in LTR on the occurrence of cancers [8, 23–26, 28, 43, 44]. Several works have reported a higher global

incidence of cancer in alcoholic cirrhosis [26,44], and it has been shown that alcohol intake may be responsible for genetic alterations [45]. Furthermore, alcohol consumption is often associated with smoking, a well-known risk factor for several types of cancer. A Spanish study has recently reported a twofold-higher risk for skin cancer in a group of 276 patients grafted for alcoholic cirrhosis as compared to 425 grafted for nonalcoholic disease. In this work, the authors mentioned that 85% of the patients with skin cancer from the alcoholic group were smokers as compared to 30% in the nonalcoholic group [25]. However, this study reported a higher rate of basal cell carcinoma (BCC), although smoking is recognised to increase the risk of squamous cell carcinoma (SCC). Primary sclerosing cholangitis has been reported to increase the risk of skin cancer in a series of 151 patients [23], which could be due to the additional immunosuppression given before transplantation to treat occasionally associated inflammatory bowel disease or autoimmune hepatitis [28]. A larger study on 8,594 LTR recorded in the OPTN/UNOS data confirmed that patients with cholestatic liver diseases (including primary sclerosing cholangitis) and cirrhosis had an increased risk of skin cancer [8]. Patients with hepatocarcinoma would also have an increased risk, although this was not statistically significant [8, 43]. Hepatitis C virus, which was reported to play a role in internal neoplasms in LTR [44], was mentioned only in a univariate analysis in one study as a risk factor for skin cancers [23].

## Clinical Features

It seems that some clinical differences may be highlighted according to the type of grafted organ.

### *Keratinocyte Skin Cancers*

*Location.* Although most skin cancers are located on the uncovered areas, it seems that some differences may be observed between HTR and KTR [19]. Indeed, these differences are probably related to the younger age of KTR. Those transplanted before 40 years of age developed most of their lesions on the upper limbs, mainly the dorsum of the hand and the forearm, whereas patients transplanted at an older age have the greater number of lesions on the head. The reasons for these differences remain unclear [19, 46].

*Number of lesions.* Another difference between HTR and KTR could be the number of lesions, which seems greater in KTR. In one recent single-centre study, we found that the mean number of lesions per patient was increased by a factor of 2 in KTR [20] at 5 years (10 vs. 5). The comparative study performed by Fortina also showed a slightly higher number of tumours in KTR as compared to HTR for similar follow-up [13].

*Distribution of lesions.* The reversal of the ratio SCC/BCC observed in the transplant population as compared to the control groups seems variable according to the series and increases with sun exposure and the length of follow-up [1]. Although for similar age KTR and HTR show similar figures, several studies mentioned that LTR could have a higher rate of BCC [24, 25, 47–50], as we observed in our patients (unpublished data). This finding seems to be related neither to a higher age of LTR nor to a shorter follow-up.

A number of series reporting the occurrence of skin cancers do not mention keratoacanthoma (KA), probably because lesions of this type are included in the SCC group by several authors. However, KA that can be considered as a well-differentiated SCC has specific clinical and histological features and is regularly reported in many series [11, 12, 16, 19, 20]. In a former study, we noticed that KA were less frequent in HTR as compared to KTR [19]. From a total of 540 skin tumours, the rate of KA was found to be 6% in our KTR versus 1.5% in HTR. In two other studies on KTR performed in Queensland on 361 KTR who had developed 3,979 NMSC, and in UK on 187 KTR with 1065 lesions, KA represented, respectively, 5.7% and 6.6% of all the tumours [11, 12]. In the single other series of 148 Australian HTR who had developed 1,410 skin cancers, KA represented less than 2% of lesions [16].

*Course.* Reports of aggressive SCC seem more frequent in HTR [51, 52], but it is unclear if heart transplantation increases the risk of aggressive SCC, which is mainly associated with older age.

### *Kaposi's Sarcoma*

The prognosis of KS is related to the existence of visceral involvement, which seems more frequent after liver and heart transplantation [29]. As we mentioned earlier, HHV8 transmission from the graft is higher in nonkidney transplant recipients, while most cases result from reactivation of pre-existing HHV8 infection in KTR. Especially in LTR, this is supported by several reports of grafted liver involvement with a disseminated disease [53–55]; this raises the question of routine screening of liver and heart donors for HHV8 to clinically and biologically monitor patients who have received a graft from a positive donor. A lower rate of survivals in HTR as compared to KTR has been reported [56]. In our experience with 26 transplant patients with KS including 18 KTR, 6 LTR, and 2 HTR, only 2 patients died of disseminated KS, and they were both HTR [32].

## Therapeutical and Prophylactic Aspects

Minimisation of immunosuppression is increasingly popular in an attempt to reduce the rate of subsequent skin cancers in all types of organ transplantation [57]. In addition, new strategies with m-TOR inhibitors are emerging, especially in KTR [58, 59], while experience with HTR and LTR seems much more limited.

Prophylaxis of skin cancers is currently performed worldwide in most kidney transplantation centres, and a dermatological examination is proposed once a year for all patients. This procedure allows early detection and treatment of skin tumours and reinforces education about sun protection. Many publications about KTR have been devoted to the need for information on sun protection, and recent reports have shown the better results of a reinforced education using written advice [60, 61]. Dermatological referral has been more recently adopted by cardiologists, but LTR are not yet regularly screened in many centres.

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