

# Management of Skin Cancer in Organ Transplant Recipients

by  
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**S**KIN CANCERS are overwhelmingly the most common post-transplant malignancies and represent an important and escalating challenge in terms of their frequency, diversity, atypical, and often aggressive nature<sup>1,2</sup>. Although mortality may be relatively low, their associated morbidity is often considerable, representing a significant burden of disease for a subgroup of high-risk patients<sup>3</sup>. A robust evidence base to guide management is lacking in many key areas, and decision-making is often based upon expert consensus opinion. This review aims to summarise current clinical practice relating to diagnosis, treatment, prevention and surveillance strategies for post-transplant skin cancer. It will particularly focus on keratinocyte skin cancers (squamous and basal cell carcinoma), which account for more than 95% of skin cancers seen in European and North American transplant populations<sup>4</sup>.

## DIAGNOSIS

For most skin cancers, diagnosis is made clinically prior to primary excision. In some instances, particularly for larger lesions requiring more extensive surgery, in cases of diag-

nostic uncertainty, or for tumours in which non-surgical treatment is being considered, an initial incisional biopsy may be required to confirm the diagnosis before definitive therapy.

### **Squamous cell carcinoma (SCC)**

SCC in organ transplant recipients (OTRs) may have an atypical clinical appearance, and a high index of suspicion is required. Pain and tenderness are useful guides to possible malignancy, but diagnostic accuracy may be as low as 50%<sup>5</sup>. Important differential diagnoses include viral warts (which may be clinically and histologically atypical), squamous cell carcinoma-*in-situ* (Bowen's disease), actinic keratoses (AK, partial thickness keratinocyte intraepithelial dysplasia), other rare skin tumours such as appendageal malignancies and atypical infections (**Figure 1**).

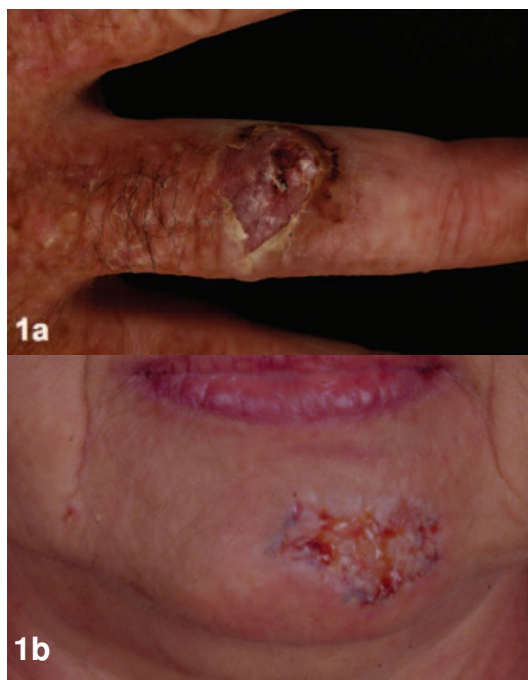
### **Basal cell carcinoma (BCC):**

Diagnosis of OTR BCC is usually straightforward, although superficial BCCs on the trunk are more common, usually asymptomatic and are often unnoticed by patients<sup>6</sup>. One common, benign post-transplant skin lesion often misdiagnosed as nodular BCC is sebaceous gland hyperplasia (**Figure 2**).

#### **Figure 1: Infective lesions simulating squamous cell carcinoma:**

**1a:** Ulcerated nodule on the dorsum of the left middle finger due to atypical mycobacterial infection.

**1b:** Chronic herpes simplex infection on the chin. Both lesions 1a and 1b were diagnosed clinically as possible SCC.



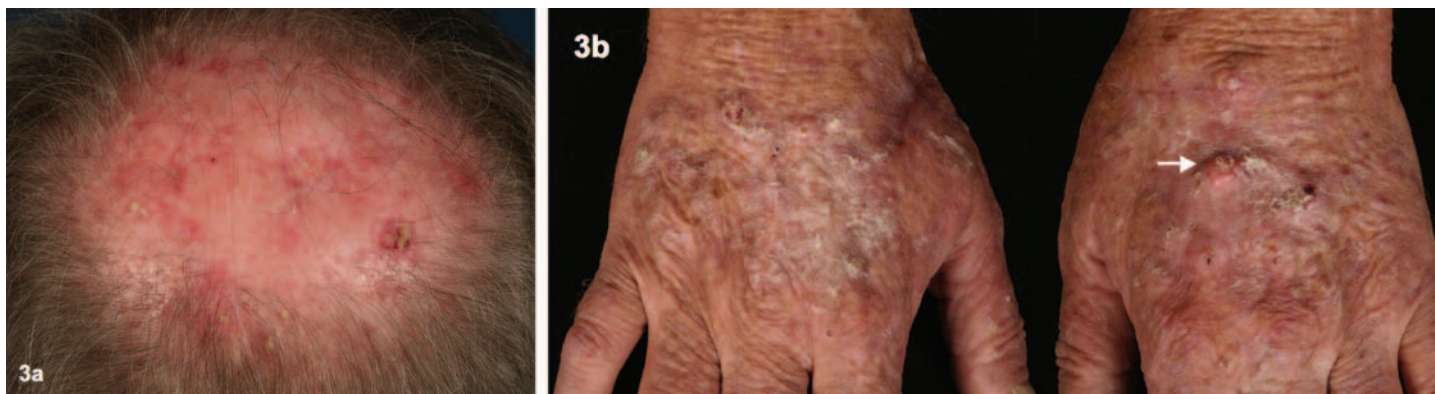
**Figure 2: Sebaceous gland hyperplasia may simulate BCC**  
Sebaceous gland hyperplasia is common in OTRs and is probably related to ciclosporin exposure. Individual lesions may be misdiagnosed as BCC or as molluscum contagiosum.

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### **Actinic keratoses, Bowen's disease and field carcinogenesis**

Usually presenting as red, hyperkeratotic papules and plaques, AK and Bowen's disease may arise as discrete lesions or may be multiple and confluent on locations such as the dorsa of the hands and scalp. These areas of 'field carcinogenesis' are sites at which SCC



preferentially develop and are a common problem in OTRs. They may be contiguous with multiple plane warts and it can be almost impossible to distinguish viral and dysplastic lesions from each other without diagnostic biopsy (**Figure 3**).

### Melanoma

Accounting for less than 1% of post-transplant skin cancer, melanoma is 2-8 times more common in OTRs<sup>7</sup>. In a recent multicentre study by the Skin Care in Organ transplant Patients, Europe (SCOPE) Network, there was no evidence that the clinical presentation of melanoma in OTRs differed substantially from that in the general population<sup>8</sup>. However, for melanomas >2mm Breslow thickness, outcome was significantly worse, underscoring the importance of early detection and treatment (**Figure 4**).

### Kaposi's sarcoma (KS)

Occurring mainly in OTRs from areas of high human herpes virus 8 (HHV8) seroprevalence (Africa, the Middle East, parts of the Mediterranean and Caribbean), this tumour is usually due to reactivation of latent virus<sup>9,10</sup>. In many cases, oedema of the legs (usually unilateral) precedes the appearance of typical purple/red papules, plaques and nodules on

the skin (**Figure 5**). Diagnosis is confirmed by skin biopsy; upper gastrointestinal endoscopy and lung imaging/bronchoscopy may be required to exclude visceral disease.

### Rare skin malignancies

Skin tumours of eccrine, apocrine, follicular and sebaceous appendages, particularly sebaceous carcinoma and eccrine porocarcinoma, are more common in OTRs, but are rarely diagnosed prior to surgery, as most present as rather non-specific, ulcerated, red nodules<sup>11</sup>. Merkel cell carcinoma, a highly aggressive cutaneous neuroendocrine tumour, is also more common in OTRs, is associated with significant mortality and presents as a rapidly growing, purple nodule on sun-exposed sites<sup>12</sup>.

## TREATMENT OF PRIMARY TUMOURS

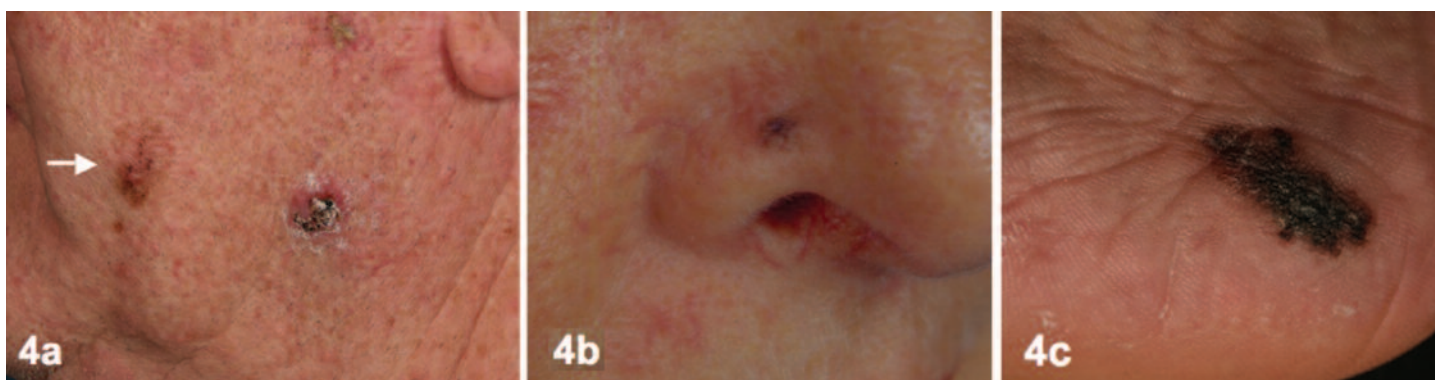
The available evidence informing appropriate treatment for OTR skin malignancies is far from complete. There are few prospective, randomised control trials and only limited numbers of retrospective and/or observational studies to guide decision-making. In the absence of systematic evidence, efforts have been made to obtain consensus expert opinion in particularly important management areas<sup>13,14,7</sup>. A multidisciplinary approach is

### Figure 3: Field carcinogenesis

**3a:** Multiple actinic keratoses, which are confluent in areas – 'field carcinogenesis'. The balding scalp in male OTRs is a common site for these changes.  
**3b:** Another common site for field carcinogenesis in OTRs is on the dorsa of the hands. AKs, Bowen's disease and viral warts are all present, but are almost impossible to distinguish clinically. SCC commonly arise in such areas: an early SCC on the dorsum of this patient's left hand is indicated by an arrow.

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### Figure 4: Post-transplant melanoma

**4a:** A 0.9mm Breslow thickness melanoma is arrowed on the face of this cardiac transplant recipient. The other visible hyperkeratotic lesions are all areas of AK or Bowen's disease.

**4b:** A small melanoma on the right side of this patient's nose was only 0.3mm Breslow thickness, but eventually metastasised.

**4c:** A 0.9 mm Breslow thickness acral melanoma on this patient's heel was detected at routine skin surveillance, highlighting the importance of full skin examination.



**Table 1: Factors associated with risk of local SCC recurrence and metastasis<sup>13,76,77</sup>.**

Low risk SCC:	High risk SCC:
Size <2cm diameter	Size >2cm diameter
Well differentiated	Poorly differentiated
Depth of invasion <2mm	Depth of invasion >4mm
No perineural/vascular invasion	Perineural/vascular invasion and satellite lesions
	High-risk location (forehead, temple, ear, lip)

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important<sup>1,2,15</sup> and close dialogue between dermatologists and transplant clinicians is crucial<sup>1,2,16</sup>.

### Low-risk primary tumours

Low-risk invasive skin tumours and premalignancies, e.g. superficial and nodular BCC, Bowen's disease, low-risk SCC (Table 1), are managed in a similar manner to the general population, using 'standard treatments with increased diligence'<sup>1</sup>.

**1. Surgery:** Surgical excision is often the most appropriate option for the majority of tumours. There are few data to indicate whether excision margins should differ in OTRs and, in the absence of such data, it is reasonable to excise lesions with narrow margins<sup>13</sup>. Curettage and electrocautery also offers satisfactory clearance rates for most selected low-risk tumours, including well-differentiated SCC, and may be the preferred option in certain clinical situations for reasons of cosmesis and convenience<sup>17</sup>.

**2. Non-surgical modalities:** In carefully selected cases, non-surgical approaches, including cryotherapy, photodynamic therapy, topical imiquimod and 5-fluorouracil (see below), may also have a therapeutic role. This is a particular consideration in OTRs with multiple malignancies and field carcinogenesis, in whom repeated surgery is otherwise required.<sup>1,13</sup>

### High-risk primary tumours

The characteristics of high-risk SCC, i.e. those at potentially increased risk of local recurrence and metastasis<sup>1,13,18</sup> are detailed in Table 1. Other skin tumours regarded as high-risk include infiltrative/morphoeic and baso-squamous BCC, melanoma, Merkel cell carcinoma, and certain appendageal tumours<sup>1,2,3,7,14</sup>.

**1. Surgery:** It is usually recommended that surgery for high-risk OTR tumours should be 'more aggressive'<sup>13</sup>, but in most cases the nature of the surgical approach required has not been clearly defined. For example, in high-risk SCC, optimal excision margins are not

established and, although Mohs' micrographic surgery with intra-operative margin control is often advised<sup>13</sup>, the circumstances in which it is preferable to standard surgical approaches in OTRs have not been rigorously evaluated<sup>18</sup>. In the case of melanoma, there is reasonably good evidence for recommended surgical excision margins in the general population, but there has been no specific validation of this in OTRs<sup>7</sup>. Sentinel node biopsy may be used as a staging procedure in selected melanomas<sup>7</sup> and it has also been proposed that it may provide prognostic information in other high-risk OTR skin cancers<sup>13</sup>, although there are currently few data to guide its use<sup>18</sup>.

**2. Radiotherapy:** Surgery with clear margins usually gives the best outcome in terms of recurrence<sup>18</sup>. In the general population, radiotherapy is indicated for selected primary BCCs, inoperable SCCs and cases of SCC in which there are positive excision margins not amenable to further surgery or as adjunctive therapy if extensive perineural invasion is present, although the evidence for this is limited<sup>19</sup>. Radiotherapy may have a similar role in OTRs<sup>13</sup>, but case selection is particularly important: given the increased long-term risk of second skin malignancies following radiotherapy and in view of the accelerated carcinogenesis seen in OTRs, there is at least a theoretical concern that they may be more susceptible to subsequent ionising radiation-induced skin tumours.

**3. Alteration of immunosuppression:** This important adjunctive management strategy is discussed further in the accompanying article in this *Supplement* by Mackintosh and Jardine. Reduction of immunosuppression or switch to mTOR inhibitors should be considered for high-risk and/or multiple tumours and is usually a first-line intervention for patients with Kaposi's sarcoma<sup>10,20</sup>.

**4. Systemic retinoids:** In patients with high-risk and/or multiple primary SCC in whom immunosuppression cannot be altered, adjunctive use of systemic retinoids may be beneficial (see below).

## Treatment of locally advanced and metastatic disease

### Squamous cell carcinoma

There is an estimated 7% metastatic risk for SCC in OTRs, with an overall 5-year survival of 14-39% and median 3-year survival of 56%<sup>21</sup>. In transit metastases are more common in OTRs and often present as discrete dermal papules distinct from the primary SCC<sup>22</sup>. It has been suggested that



**Figure 5: Post-transplant Kaposi's sarcoma (KS)**

**5a:** KS may initially present with unilateral leg oedema, especially in OTRs of African origin.  
**5b:** Early macular skin lesions.  
**5c:** An ulcerated nodule of KS.  
**5d:** More extensive plaque KS.  
**5e:** Chronic lymphoedema due to KS may lead to secondary skin changes, as illustrated here.

advanced cutaneous OTR SCC resembles head and neck SCC in the general population<sup>23</sup>. Although this is likely to become an increasingly common scenario in the future, there are currently no standards of care for management of regionally advanced and metastatic SCC in OTRs. In the absence of specific clinical trials, the use of surgery and radiotherapy is currently broadly similar to that in the general population<sup>23,24</sup>. Chemotherapeutic approaches reported include use of systemic 5-fluorouracil (capecitabine), cisplatin, paclitaxel, interferon and retinoids, with transplant-directed dosage adjustment and close monitoring of graft function<sup>24</sup>. Epidermal growth factor receptor (EGFR) inhibitors are showing promise in metastatic head and neck SCC and there are case reports of benefit from cetuximab in cutaneous SCC<sup>25,26</sup>. Such targeted therapies for SCC have not specifically been evaluated in OTRs, but some ongoing clinical trials allow OTR recruitment, e.g. OTRs with aggressive and/or metastatic SCC are eligible for inclusion in phase II trial of erlotinib prior to surgery or radiation and a phase II study of dasatinib (www.clinicaltrials.gov). Systemic retinoids may

also play a role in the management of advanced SCC, as may reduction of immunosuppression and/or switch to mTOR inhibitors. However, there are few data to guide of when and how such approaches should be introduced<sup>1,14,18,21,24</sup>.

#### Other skin cancers

The prognosis for melanoma in OTRs is worse for tumours with a Breslow thickness greater than 2mm<sup>8</sup>. Current management for advanced melanoma and other skin tumours (e.g. metastatic Merkel cell or sebaceous carcinoma) is similar to that for the general population, in the absence of specific clinical studies, although with the additional strategy of possible immunosuppression reduction<sup>7,14,24</sup>.

### PREVENTION OF SKIN CANCER

In the face of the growing clinical problem of post-transplant skin cancer, what should be done to reduce or prevent this risk? Despite limited available evidence addressing this issue, OTRs present an accelerated model of skin carcinogenesis and may therefore be regarded as an ideal population in which to test interventions aimed at preventing skin cancer.

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Table 2: Suggested management and surveillance protocols based on current consensus guidelines and expert opinion.

Stage of disease	Therapeutic and preventive considerations	Surveillance
<b>Pre-transplant</b>	Risk assessment Education; Photoprotection Treatment of precancerous lesions	Whilst on transplant waiting list
<b>Post-transplant</b>	Baseline risk assessment Education; Photoprotection	Within 6 months of transplantation
<b>No skin cancer</b>	Low risk (e.g. <35y; low UV exposure; darker skin types e.g. Asian/black, unless at risk for KS) Moderate risk (e.g. >50y; fair skin; high UV exposure; chronic photodamage; from HHV8 endemic area) High risk (e.g. >50y; fair skin, high UV; AK/keratotic lesions; previous skin cancer)	2-5 years 12 months 6-12 months
<b>AK/Bowen's disease</b>	Strict photoprotection Lesion-directed therapy (e.g. cryotherapy, surgery) Field-directed therapy (e.g. topical 5-fluorouracil, imiquimod and diclofenac; photodynamic therapy)	6-12 months
<b>Early skin cancer</b> SCC (n=1)  BCC (n=1)	Low risk: Surgery (excision, curettage/cautery); treatment of AK/Bowen's disease and field carcinogenesis High risk: Surgery (excision, Mohs' micrographic surgery); may need to consider sentinel node biopsy, adjunctive radiotherapy, alteration of immunosuppression or systemic retinoids in appropriate circumstances Infiltrative, nodular: Surgery (excision, Mohs' micrographic surgery) Superficial: surgery (excision, curettage/cautery); non-surgical (cryotherapy; 5-fluorouracil; imiquimod)	6 months 4-6 months 6-12 months 6-12 months
<b>Moderate risk skin cancer</b> (>3-5 KSC; early KS)	Treatment of individual lesions as indicated above Rigorous treatment of AK/Bowen's/Field carcinogenesis Consider alteration of immunosuppression (reduction or switch to mTOR inhibitor) in consultation with transplant clinicians Systemic retinoids (for SCC)	3-4 months
<b>High risk skin cancer</b> (>10 SCC; melanoma; extensive KS; Merkel cell carcinoma; certain appendageal tumours)	Aggressive treatment of individual lesions as indicated above Strong indication to alter immunosuppression (reduction or switch to mTOR inhibitor) in consultation with transplant clinicians Strong indication for systemic retinoids (for SCC)	1-3 months

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Possible preventative strategies include: primary prevention of *de novo* pre-invasive and invasive malignancies; prevention of progression of pre-malignant lesions to invasive tumours; prevention of second primary tumours.

### **Primary prevention of *de novo* pre-invasive and invasive malignancies**

Ultraviolet radiation (UVR) is the principle carcinogen responsible for most skin cancers. European, North American and other expert consensus guidelines all recommend strict UV photoprotection post-transplant to reduce skin cancer risk<sup>3,13,27,29</sup>. Advice usually includes avoidance of sunburn, intentional tanning and unnecessary UVR exposure, especially between 11am-3pm, April to October, in the UK. Sunscreens with broad-spectrum, high factor UVB and UVA protection are recommended, together with the use of broad-brimmed hats, sunglasses and protective clothing. But does sunscreen use post-transplantation translate into a reduction in skin (pre)-malignancy? There is convincing evidence that sunscreens

reduce AK and SCC in the general population<sup>29,30,31</sup>. More recently, a randomised controlled trial (RCT) of liposomal sunscreen use in Germany showed significant reduction in AK and SCC but not BCC after 24 months<sup>32</sup>. Strict photoprotection measures would therefore appear justified, at least in OTRs at high risk for developing SCC. Previous studies have shown that information regarding such photoprotective measures is best delivered in a specialist clinic setting<sup>33</sup> and compliance is improved by intensive educational reinforcement<sup>34,35</sup>.

One of the possible adverse effects of adhering to such photoprotective measures is a reduction in vitamin D levels, and this issue has received increasing attention in recent years. UVR is important for generation of adequate vitamin D, which may already be compromised in OTRs<sup>36</sup>. In the liposomal sunscreen study, 25-hydroxy vitamin D levels were lower in the sunscreen group<sup>32</sup>. Although there is no evidence that tanning or burning is required to achieve



**Figure 6: Advanced squamous cell carcinoma**

**6a,b:** A moderately differentiated SCC excised from this patient's right forehead recurred (**6a**) and then metastasised to local lymph nodes (**6b**), ultimately proving fatal. **6c:** This recurrent SCC overlying a haemodialysis fistula eventually metastasised to local lymph nodes, despite extensive surgery.

adequate vitamin D levels, this is clearly an area requiring further research. At present, monitoring of vitamin D levels in OTRs and oral supplementation, if necessary, is advisable when rigorous photoprotection is being advocated<sup>36</sup>.

## 2. Preventing progression of pre-malignant lesions to invasive tumours

It is assumed, although not proven, that AK and Bowen's disease are precursors of SCC. The presence of 7.7 AKs predicts a 10% risk of transformation to SCC within 10 years in the general population<sup>37</sup>; no equivalent data exist for OTRs. The rate of progression from an individual AK to SCC is controversial, ranging from 0.025% to 20% per year/per lesion in the general population, with up to 25% of AK regressing over one year and numbers of prevalent AK strongly influenced by ongoing UV exposure<sup>38</sup>. A recent prospective study showed that the risk of progression for a specific AK was 2.57% at 4 years, but that 65% of all primary SCC arose directly in AK<sup>39</sup>. The remainder of SCC are presumed to arise from sub-clinical AK, providing a rationale for treating the whole 'field' and not just individual lesions. However, there are no clinical trials in either the general population or in OTRs confirming that treating AK/Bowen's disease will prevent SCCs. In the absence of such proof, it would nonetheless seem prudent to treat AK/Bowen's disease, which may cause morbidity in their own right.

**Lesion-directed versus field-directed treatments:** Cryotherapy and surgery are used as 'lesion-directed' treatments for individual AKs/Bowen's lesions. Although surgery to prophylactically resurface areas of severe field carcinogenesis on the dorsa of the hands may be beneficial in reducing SCC<sup>40</sup>, such approaches generally tend to be less suitable for larger areas of multiple and confluent pre-malignancy (**Figure 3**). These are usually more amenable to 'field-directed' therapies. Those currently licensed in the UK include three topical agents

(5-fluorouracil cream, imiquimod 5% cream and diclofenac 3% gel), and photodynamic therapy. Sub-clinical lesions within the areas of field change are also likely to be treated with this approach, possibly increasing the benefit in terms of potential reduction in SCC. Field-directed treatments are often combined with lesion-directed therapies for more resistant lesions, and a low threshold for biopsy of any persistent lesions is indicated to exclude invasive malignancy.

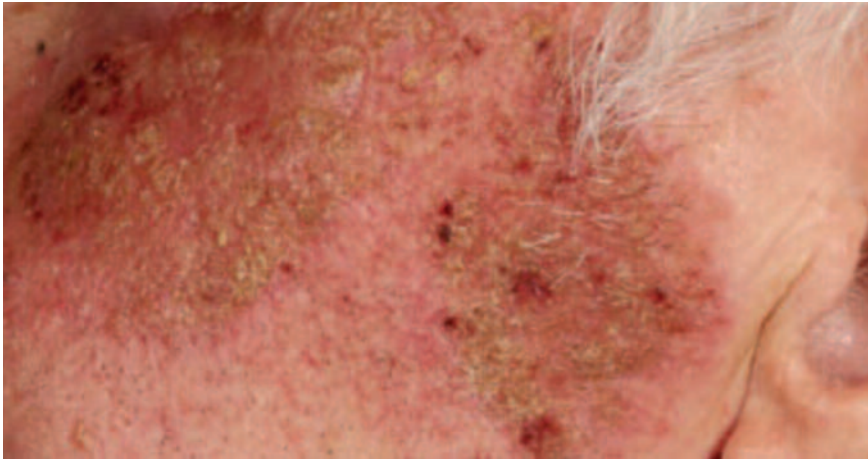
(i) *5-Fluorouracil cream*, an inhibitor of thymidylate synthetase, is cytostatic to proliferating cells. As a 5% cream, it has been used widely for over 35 years as a treatment for AK, although few controlled studies of its efficacy in either the general population or OTRs have been published<sup>40,41</sup>. It is usually applied once or twice daily for 3-4 weeks. In two studies in the general population, it achieved 70% clearance of AK at 6 months<sup>42</sup> and 78% clearance sustained for 12 months<sup>43</sup>. Lower clearance rates have been reported in OTRs<sup>44</sup>. Both 5-fluorouracil (5-FU) and 5% imiquimod have similar local side-effects with erythema (often severe) with crusting, erosions or even ulceration (**Figure 7**). The clinical response is largely in proportion to these side-effects.

(ii) *5% Imiquimod cream* is an immune response modifier and agonist for toll-like receptors 7 and 8, activating the innate immune system and generating a Th1 cytotoxic response. It has been more rigorously studied in clinical trials compared to 5-FU<sup>41</sup>. Several randomised controlled trials in the general population, using 5% imiquimod 3 times per week for 4-16 weeks demonstrated 64-84% clearance of AK, with limited long-term data<sup>45,46</sup>. In an RCT in 20 OTRs, 50% clinical and 37% histological improvement were obtained and there were fewer SCC in treated skin over 12 months, although this did not reach statistical significance<sup>47</sup>. In a larger, multicentre RCT including 43 OTRs in 6

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**Figure 7: Topical treatments for AK/field carcinogenesis**

Both 5-fluorouracil and 5% imiquimod creams usually cause erythema with crusting, erosions and even ulceration. Areas of subclinical disease are often highlighted by the application of these agents, as illustrated here. The reaction to topical diclofenac gel tends to be milder.

general population is well established<sup>41</sup>, and there have been a number of studies in OTRs. In an RCT of ALA-PDT with red light, 88% of OTRs responded at 4 weeks, reducing to 48% at 48 weeks, compared with 94% response reducing to 72% in immunocompetent patients ( $p < 0.05$ ). This difference possibly reflects either more persistent lesions in OTRs or increased recurrence rates. Response was lowest on hands/arms, a feature also noted in use of topical agents<sup>50</sup>. In a separate RCT in 17 OTR using MAL-PDT, 76% complete clearance was observed at 16 weeks<sup>51</sup>. In a small, within-patient RCT comparing MAL-PDT with topical 5-fluorouracil, PDT was found to be significantly more effective, with superior cosmesis and patient satisfaction, but was also associated with more pain<sup>44</sup>. Several RCTs have directly investigated PDT in SCC prevention<sup>52,53,54,55</sup>. Although all have shown significant reductions in AK, this is not always sustained and only one has shown a possible prophylactic effect<sup>55</sup>.

### 3. Prevention of second primary tumours

Over 60% of OTRs will develop more than one skin malignancy and, after a first KSC, 75% will have a second within 5 years<sup>56,57</sup>. The time interval between subsequent KSC shortens progressively. What additional preventative strategies are available for such high-risk individuals?

#### 1. Alteration of immunosuppressive drug regimens

Alteration of immunosuppression as an approach to reducing SCC risk has been discussed in detail in the accompanying review by Mackintosh and Jardine. Reduction of immunosuppression is probably the most frequently considered approach in current practice, but there is limited evidence on which to base the decision of when to consider it and to what extent immunosuppression should be reduced<sup>14</sup>. Increasing evidence also supports conversion from calcineurin inhibitors to mTOR inhibitors as an additional strategy; Salgo *et al*<sup>58</sup> have recently shown that conversion from CNIs to sirolimus significantly reduces incidence of SCC at 12 months and there are a number of other ongoing RCTs (TUMORAPA, RESCUE, PROSKIN, CERTICOEUR; [www.clinicaltrials.gov](http://www.clinicaltrials.gov)), which should inform development of clear guidelines in the near future.

**2. Systemic retinoids** Retinoids (acitretin, isotretinoin and previously etretinate) alter gene transcription through action on cellular retinoid receptors. They are antiproliferative, antiapoptotic, immunomodulatory, modulate keratinocyte differentiation and arrest growth and replication of HPV<sup>59</sup>, all of which may be relevant to skin cancer prophylaxis. Three RCTs have examined

countries, complete response was observed in 62.1% and partial response in 80%<sup>48</sup>.

(iii) *Diclofenac 3% gel* inhibits cyclo-oxygenase-2 pathways and tends to be used for less severe disease, as it generally causes less inflammatory response compared with 5-fU and 5% imiquimod. In an RCT of 32 OTR with multiple AK treated twice daily for 16 weeks with 3% diclofenac gel, complete clearance was obtained in 41% but recurrent disease was noted at 24 months in 55%<sup>49</sup>.

A problem with many previous clinical trials has been that rates of recurrence and/or development of new lesions within the field after a course of treatment with these topical agents have not been well characterised, as follow-up is often insufficiently prolonged. It is therefore not clear how frequently such field treatments should be used to maintain clearance and thereby, it is assumed, to reduce SCC development. This is particularly important in OTRs in whom the rate of recurrence and/or development of new lesions within a field is likely to be accelerated compared with the general population.

**Photodynamic Therapy (PDT)** PDT is an alternative non-surgical option for treating individual AKs or larger fields of thin, non-hyperkeratotic AK. Topical aminolaevulinic acid (ALA) or methylaminolaevulinic acid (MAL) is applied to the target lesions (after removal of hyperkeratosis if necessary). The drug preferentially accumulates in dysplastic keratinocytes and is converted into protoporphyrin IX. This is a potent photosensitiser and, upon exposure to a light source, generates reactive oxygen species, which leads to destruction of dysplastic cells. The use of PDT for treatment of AK in the

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the chemopreventive effects of systemic retinoids in reducing in AK and/or SCC in OTRs<sup>60,61,62</sup>. All studies except one were for 2 years or less, but all confirmed a reduction in AK and, to a variable extent, SCC. In a retrospective analysis of low-dose systemic retinoids over 16 years at our institution, retinoids resulted in a significant reduction in SCC, particularly in the first 3-4 years of treatment, but probably sustained for much longer. They were generally well tolerated, the main adverse effects being cheilitis, xerosis and hyperlipidaemia. Although adverse effects limited dosing in some patients, in only a small minority was the drug discontinued because of these adverse effects. If withdrawn, either intentionally or inadvertently, a rebound phenomenon with a sharp increase in SCC development was common approximately 3-4 months after stopping systemic retinoids<sup>63</sup>. Consensus opinion recommends that retinoids should be started at low dose and increased as tolerated to minimally effective dose<sup>64</sup>. However, further research is needed to clarify the indications for their initiation, as well as the tolerability and efficacy of optimal dosing regimens.

### Future prospects for prevention

A number of topical and systemic approaches are currently in clinical trials in OTRs or have shown promise in the immunocompetent population and may have potential prophylactic properties. For most, clinical evidence remains relatively limited.

*T4 endonuclease V (T4N5)* is an enzyme involved in repair of DNA damage after exposure to UVR, specifically cyclobutane pyrimidine dimers. Clinical efficacy of a topical liposomal formulation in reducing AKs has been demonstrated in patients with the xeroderma pigmentosum, a disorder of nucleotide excision repair<sup>65</sup>. A Phase II study of T4N5 lotion looking at safety and efficacy in preventing keratinocyte skin cancer in OTRs is currently underway in OTRs (www.clinicaltrials.gov; identifier, NCT00089180).

*New topical agents for treatment of AK* are in development and include, for example, alpha-difluoromethylornithine (an irreversible inhibitor of ornithine decarboxylase), resiquimod (a more potent toll-like receptor 7/8 agonist than imiquimod), ingenol mebutate (an extract from the plant *Euphorbia peplus*) and betulinic acid (a pentacyclic triterpene from the outer bark of birch). These agents have various antitumoural effects and are currently in phase II and III clinical trials in the general population<sup>41</sup>.

*Laser* induction of coagulative necrosis and tissue destruction has been used in the general

population to treat skin cancer; CO<sub>2</sub> lasers have been used to treat superficial BCCs and Bowen's disease<sup>66</sup> and neodymium (Nd) and Nd:YAG lasers have also been used to treat BCC and SCC<sup>67</sup>. Their use in field carcinogenesis in OTRs has not yet been specifically reported, but lasers and other resurfacing techniques such as dermabrasion and chemical peels may be predicted to be a potentially useful adjunct to treatment of field change<sup>1</sup>.

*Capecitabine* is an oral prodrug of 5-fluorouracil. Its use in prevention of SCC was reported recently in a retrospective series of 15 OTRs with recurrent KSC in whom it was used at low dose over 12 months. It significantly reduced the incidence rates of SCC, BCC and AK and associated toxicity was deemed to be manageable, although one-third of patients had discontinued use by 12 months<sup>68</sup>.

*Afamelanotide (CUV1647)* is a chemical analogue of alpha-melanocyte stimulating hormone (α-MSH). Alpha-MSH is produced by keratinocytes and melanocytes in response UVB and induces synthesis of melanin in melanocytes as part of the tanning response. Afamelanotide is more potent and longer acting than natural alpha-MSH. It may be administered by subcutaneous pellet. It is currently in phase II trials to investigate its efficacy in reducing AKs and SCC in OTRs (www.clinicaltrials.gov; identifier NCT00829192).

## SCREENING, SURVEILLANCE AND FOLLOW-UP

Given the greatly increased incidence of skin cancer in the OTR population, it would seem appropriate to offer routine screening and surveillance for this high-risk group. However, the effectiveness and cost-benefit of screening for skin cancer has not been established in either the general population or in OTRs<sup>69</sup>. In the absence of such data, and based upon expert consensus opinion<sup>1,3,13,27,28,69,70,71</sup>, the following OTR surveillance strategies have been proposed:

### Baseline post-transplant assessment

Following transplantation, OTRs should be offered baseline assessment in which education regarding individual skin cancer risk, photoprotection, regular self-skin examination and early detection of suspicious lesions is provided. There is evidence that such health education advice is better recalled and implemented and skin cancer awareness is improved if information is provided in the setting of a specialist skin clinic<sup>33</sup>.

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### Subsequent post-transplant skin cancer surveillance

Individual risk stratification at baseline should determine the appropriateness and frequency of long-term surveillance. It is widely recommended that all OTRs should perform monthly self-skin examination and should have a full skin examination by a specialist every 6-12 months<sup>3,13,27,28,70,71</sup>, but the data to support these recommendations are limited. It might be argued, for example, that younger OTRs with darker skin types do not require such frequent surveillance, at least in the first 5-10 years post-transplant.

Once skin cancers and pre-cancerous lesions develop, routine surveillance is justifiable based upon the known epidemiology of skin cancer in this group; tumours are multiple in two-thirds of OTRs, the time interval between consecutive KSCs steadily decreases and over 75-80% of OTRs develop further tumours within 5 years of the first<sup>56,57,72</sup>. The increasing clinical need was highlighted in England and Wales in the 2006 National Institute for Health and Clinical Excellence (NICE) document 'Guidance on Improving Outcomes in People with Melanoma and Other Skin Cancers'<sup>73</sup>. This has recommended that OTRs (and other immunosuppressed individuals) who have pre-cancerous skin lesions or who have developed a skin cancer should be seen in dedicated clinics. Based upon OTR skin cancer epidemiology, those with low risk lesions, e.g. AK, Bowen's disease, BCC, are likely to benefit from at least annual review. Once SCC develop, surveillance should be more frequent – at least 6 monthly, reducing to 3-4 monthly for patients with multiple tumours and even more frequently in those with very high risk tumours<sup>1,2,7,13,18,27,28,70,71,72,73</sup>.

### Pre-transplantation screening

In order to make the greatest impact upon post-transplant skin cancer incidence, it is plausible that potential risk reduction strategies such as photoprotection and treatment of AK are best initiated in the pre-transplant period, although this has yet to be confirmed<sup>1,3,13,69,71,74</sup>. Risk stratification including, for example, determination of HHV 8 status, may inform appropriate tailoring of transplant immunosuppressive drug regimens. It is also becoming

increasingly common for patients with a history of skin cancer to present for organ transplantation<sup>74,75</sup>. For most, the benefits will outweigh the risks associated with further skin cancer development or possible recurrence and metastasis. In cases of metastatic KSC and in more advanced primary melanoma, transplantation is almost always contraindicated. In all other cases, it is advisable that decisions should be made in consultation with a transplant dermatologist<sup>74,75</sup>.

### ORGANISATIONS FOR PATIENTS AND HEALTH CARE PROFESSIONALS

Several special interest groups focusing on education for patients and health care providers, prevention, treatment and research have been launched in recent years, the most active being SCOPE and ITSCC. In Europe, SCOPE (Skin Care in organ transplant patients – Europe; www.sopenetwork.org) has coordinated a number of research initiatives and, in collaboration with ITSCC (International Transplant Skin Cancer Collaborative; www.itsc.org), has produced several expert consensus guideline documents for management of post-transplant skin cancer<sup>7,13,14</sup>. The AT-RISC Alliance (After Transplant-Reduce the incidence of Skin Cancer; www.at-risc.org) is linked to ITSCC and has developed very helpful educational resources for both patients and healthcare providers.

### CONCLUSIONS

The growing clinical problem of skin cancer in OTRs represents a significant burden for patients and poses a challenge for health care providers and resources. Recognition and assessment of the potential risk, together with appropriate counselling, surveillance, preventative strategies and, when suspicious skin lesions arise, rapid treatment, should help reduce the incidence and impact of these skin cancers in the future. However, the evidence base for their treatment and prevention is lacking in many areas and further research is urgently required. These high-risk patients present a model of accelerated skin carcinogenesis and are an ideal population for such clinical studies examining established and novel therapeutic and preventative approaches. Indeed, it is likely that many future advances in management of skin cancer, particularly KSC, will come from research in the transplant population.

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