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ORIGINAL PAPER

The risk of transmitting cutaneous malignancy through skin transplantation: a literature-based risk assessment

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Abstract According to the European Union Tissues and Cells Directives donation of tissue is contraindicated in the presence of or a previous history of malignant disease, with the exception of cutaneous basal cell carcinoma. Skin cancer is the most common cancer. Due to ultraviolet light exposure and increasing life expectancy an increasing prevalence of malignant or premalignant skin lesions is observed, which may result in a decline of the availability of skin for transplantation. A risk assessment based on published studies and expert opinion was performed in order to investigate the risk of transmitting malignant or premalignant skin lesions through tissue transplantation, and more particular through skin transplantation. The scarcity of data concerning cancer transmission in tissue transplantation was challenging. Circumstantial evidence, available for organ transplantation, was used to develop the following policy proposal for skin transplantation and cutaneous tumours. Malignant melanoma is an absolute contraindication for the donation of skin and also of other tissues, whereas, non-lesional skin and other tissues of a donor with non-melanoma skin cancer (basal cell and squamous cell carcinoma) or with a premalignant skin lesion can be considered for transplantation. The above mentioned protocol proposal might serve as a prototype for analogous protocols for non-cutaneous malignancies.

Keywords Tissue transplantation · Cutaneous malignancies · Transmission · Risk assessment · Guidelines

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Introduction

According to the European Union Tissues and Cells Directives (EU Directive 2006/17/EC; Directives 2006) donation of tissue, with the exception of corneas, is contraindicated in the presence, or with previous history, of malignant disease. Malignancies that can be allowed, are basal cell carcinoma, some types of primary brain tumours and carcinoma in situ of the uterine cervix, because of their low risk of metastasized disease. The Directives provide a common framework of minimum requirements, and stricter requirements in the national or local laws can be applied. The Directive also states that donors not

meeting the general acceptance criteria may be accepted on the basis of a documented risk assessment authorized by the responsible person of the tissue establishment (Cox and Brubaker 2012).

Due to ultraviolet light (UV) exposure and increasing life expectancy the prevalence of malignant or premalignant skin lesions, such as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) is increasing. With the increasing prevalence of these skin lesions and the ever-growing need for tissues for transplantation, the availability of skin for transplantation may become insufficient.

This raises the question as to how this will affect donor selection. Is a different approach necessary for SCC or melanoma as compared to BCC? What to do with premalignant skin lesions such as actinic keratosis, keratoacanthoma, dysplastic naevi? Is a change in policy necessary when a lesion has been adequately treated, compared to the situation where the tumour is still present? Does it make a difference whether skin or other tissues are recovered?

The current risk assessment was performed in order to investigate the risk of transmitting malignant or premalignant skin lesions through tissue transplantation and more particular skin transplantation. Risk assessment models, as described in annex 20 of the GMP guidelines, and frequently used in the pharmaceutical industry and in hospitals, are mostly quantitative and difficult to use for tissue transplantation because it is hard to incorporate all aspects of tissue transplantation into a single model and because reports with numbers of patients are scarce (van Wijk et al. 2011). Therefore, qualitative risk assessment is the best available instrument for this assessment (van Wijk et al. 2011). All factors that could be relevant for transmitting malignant and premalignant skin lesions through skin transplantation were analysed. These factors are the prevalence of cutaneous malignancy in the donor population, the chance to detect and identify the lesion correctly during physical examination, the presence of malignant or premalignant lesions in recovered tissue, inactivation of malignant cells during storage and processing, transmissibility and recipient susceptibility. For all factors evidence was searched in the scientific literature. The topic was also discussed in the Clinical Donor Case Workshop at the European Association of Tissue Banking meeting in 2012, based on the case of a donor with premalignant skin lesions (Beele et al. 2013). The common practices and expert opinions, that were expressed by the participants at the workshop, were used in the risk assessment. The aim of this risk assessment was to develop a protocol proposal that can be used to optimize the donor selection policy for tissue donors regarding malignant and premalignant skin lesions.

Prevalence in the donor population

Skin cancer is the most common cancer comprising at least a quarter of all new cancer diagnoses (Network 2010). There are three major types of skin cancer. BCC and SCC are both carcinomas derived from epithelial cells, whereas melanoma originates from the melanocytes of the skin (Lanssens and Ongenae 2011). Because BCC and SCC both originate from epithelial cells, they are often called the non-melanoma skin cancers (NMSCs). Each type has its own precursor skin lesions.

BCC is the most frequent form of skin cancer (in the Belgian population up to 70 % of all skin cancers) and has only a few precursors (e.g. naevus sebaceous; Lanssens and Ongenae 2011). SCC usually arises in precancerous lesions, such as actinic keratosis, morbus Bowen or keratoacanthoma (Fitzpatrick et al. 2001). Actinic keratosis lesions have an average risk of about 10 % of becoming an invasive SCC, whereas morbus Bowen is considered to be an in situ SCC, having a 3–5 % risk of becoming invasive. Most keratoacanthomas spontaneously regress. Dysplastic naevi are potential precursor lesions of melanoma. Their presence increases an individual's relative risk of melanoma by a factor fifteen (Lanssens and Ongenae 2011). Lentigo maligna can give rise to an invasive lentigo maligna melanoma, which represents approximately 15 % of all melanoma cases (Lanssens and Ongenae 2011).

Like most cancers, skin cancer and their precursors are more common with older age. With the aging of the population the prevalence of skin malignancies and their precursors is increasing. In the North Western European population between 50 and 60 years of age, the incidence of actinic keratosis lesions is 15.4 % in men and 5.9 % in women. At the age of 70, a rise to about 33 % in men and 20 % in women is seen (Lanssens and Ongenae 2011).

Malignant melanoma incidence rates have more than quadrupled over the last 30 years in the UK (UK

2010). In 2010, 12,818 new malignant melanomas of the skin and 99,549 NMSCs were registered on a population of 62.3 million UK inhabitants (UK 2010; England). Thus, NMSCs are about ten times more frequent than malignant melanomas. However, because of incomplete NMSC recording, their true number may be underestimated (UK 2010). In the UK in 2010 2,746 deaths due to skin cancer have been reported, of which are 2,203 due to malignant melanomas and 546 due to NMSC (UK 2010). These data show that while NMSC is a common type of cancer, relatively few deaths are caused by it. This is in contrast to malignant melanoma, which is significantly less prevalent, but has a higher fatality rate (17.2 % for melanoma skin cancer vs. 0.5 % for NMSC in the UK in 2010; UK 2010).

Detection during physical examination

According to the EU Directive 2006/17/EC European tissue banks are required to perform a physical examination on potential tissue donors (Directives 2006). The directive itself, however, does not specify the content of this examination. A previous survey among European tissue banks in 2007 showed that not all banks perform physical examination (Van Geyt et al. 2010). Those banks that do, usually look for signs suspect for malignancy (Beele et al. 2009). As a first step in physical examination, lesional skin must be differentiated from non-lesional, normal skin. Primary skin tumours, such as melanoma and SCC are lesions that can be detected. Next to these primary skin tumours one should also consider metastatic lesions of other tumours and pre-malignant lesions (Beele et al. 2009). During physical examination, all these malignant and pre-malignant skin manifestations will be recognized as lesional skin.

The relevance of looking for signs that can indicate current or past malignancy in the skin is confirmed by a quantitative risk assessment performed by Van Wijk et al. (2012) to identify the critical elements of the physical examination. Their risk assessment indicated that signs of malignancies, such as suspect erythrosquamous lesions on sun-exposed skin, abnormal pigmented skin lesions or scars of excisions or major surgery, need to be investigated. However, without additional control measures, the distinction between suspicious and benign lesions can be very difficult, even with specific and continuous training (Beele et al. 2009). Malignant melanocytic lesions are highly suspected when they are large with irregular pigmentation and irregular borders. However, it can be difficult to distinguish between a melanoma and an atypical nevus (Fitzpatrick et al. 2001). Additional evaluation tools, such as photographs and biopsies, judged by experienced dermatologists and dermatopathologists, can be helpful in establishing the nature of the lesion (benign or malign) and the aggressiveness, and thereby improving the reliability of donor selection. However, although benign, pre-malignant, and malignant skin lesions will be recognized as lesional skin during physical examination, it may not be feasible to distinguish between benign and malignant lesions.

Presence of malignancy and risk factors in donated skin

Various mechanisms can increase the risk of donated skin transmitting cutaneous malignancy. Donated skin can contain a primary cutaneous malignancy or precursor lesion, metastatic cells from a distant malignancy or can contain a risk factor such as an oncogenic virus.

Regarding the risk of transmitting risk factors, i.e. the role of cutaneous human papilloma virus (HPV) has been studied. There are some arguments in favour of the idea that HPV plays an active role in the pathogenesis of NMSC and its precursors, and is therefore a possible risk factor which might be transmitted (Nindl et al. 2007). In a study by Iftner et al. (2003) 390 non-immunosuppressed patients with skin lesions as well as 106 control patients were analysed for infection with HPV and, if positive, HPV was typed by sequencing. HPV DNA was detected in only 4.7 % of controls, in 90.9 % of benign warts, in 60.4 % of precancerous lesions, in 59.7 % of SCC, and in 27.8 % of BCC, which demonstrates that viral infection is linked to skin disorders (Iftner 2003), but not absolutely. HPV has been found in a number of samples of normal control skin and not all SCC contain viral DNA.

The distribution of viral types found is distinctly different between warts and premalignant skin lesions, supporting an etiological role of specific HPV types (Iftner 2003). The HPV genus is divided into

cutaneous HPV (beta genus) that can result in lesions on the external skin and mucocutaneous HPV (alpha genus) Hthat can result in anogenital and oral lesions. The mucocutaneous HPV types can be subdivided into low risk (LR-HPV), mainly associated with benign (genital) warts, and high risk (HR-HPV), defined by their risk of progression to malignancy (Cubie 2013). Certain mucocutaneous HPV types (especially HR-HPV) have indeed been identified as risk factors for cervical cancer. In cervical carcinoma it has been shown that viral DNA can be detected in the majority of the carcinomas, viral genes are expressed in tumour cells, and the viral genome persists during metastatic spread of the tumour cells and during passage in vitro (Pfister and Ter Schegget 1997).

Analogous with these findings, it has been suggested that infections of the skin with certain cutaneous HPV types, may form a risk factor for NMSC (Iftner 2003; Reuschenbach 2011). However, the large majority of cutaneous HPV infections are controlled by intact cell-mediated and humoral immune mechanisms and thus remain latent or result in benign warts of which 90 % resolve spontaneously in 2 years (Cubie 2013). A case of a double forearm and hand transplant, published by Bonattie, not only shows CMV infection transmission but also development of warts on both thumbs, thereby suggesting HPV transmission. The growth of the warts was inversely related to the dose of immunosuppressive drugs (Bonatti et al. 2009). HPV persists in a small percent of those infected, particularly in patients with cell-mediated immunodeficiency. Persistent infection with HR-HPV types increases the risk of premalignant skin lesions progression to cancer (Cubie 2013). This suggests that immune suppression, and not infection with HPV itself, causes the malignant or premalignant skin lesions. Review of the published studies performed by the group of Bouwes Bavinck provides further arguments against a major role of HPV in the pathogenesis of malignant lesions (Bavinck et al. 2001). Besides the similar prevalence of HPV DNA in premalignant and malignant lesions (Berkhout et al. 2000; Iftner 2003), they mention the research by Boxman et al. (2000), who could not detect HPV DNA in the outgrowing cells on the margin of explant cultures, thereby suggesting that HPV is not associated with the proliferating cells. Cutaneous HPV DNA is not only found in premalignant and malignant skin lesions, but also in skin samples of patients with psoriasis and bullous disease, suggesting that other factors such as proliferation, genetic predisposition, and especially exposure to UV radiation play a major role and that cutaneous HPV infection does not have a direct causative role (Bavinck et al. 2001). This is further supported by findings of Akgül et al. (2006), who demonstrated in vitro that lesional skin contains active HPV virus. Active virus causes protein E5, E6 and E7 expression, which in turn can destabilise keratinocytes and lead to hyperproliferation. The E6 protein e.g., effectively inhibits apoptosis in response to UV-light damage (Bavinck et al. 2001).

We can conclude that evidence to link cutaneous HPVs causally to skin carcinogenesis is limited by the prevalence of beta-HPV in the general population, and by common risk factors for activation (UV exposure, immunosuppression and hyperproliferation; Cubie 2013). Therefore, the risk of transmitting a potential oncogenic factor is not relevant when non-lesional skin is transplanted. Some caution should be taken when lesional skin is transplanted as it may contain active virus. As papilloma viruses are only infecting differentiating squamous epithelium (Bernard et al. 2010), transmission through transplantation of non-mucocutaneous tissue is not expected.

Concerning the chance of malignant degeneration of a premalignant lesion, data from published studies suggest a limited risk. For instance, the published risk of progression of actinic keratosis lesions to invasive SCC in individual lesions ranged from 0.025 to 16 % per year, with extrapolation studies suggesting a risk of progression of approximately 8 % (Glogau 2000; Fuchs 2007). Bowen's disease or SCC in situ have a 3–5 % risk of becoming invasive (Lanssens and Ongenae 2011).

Regarding the risk of metastasis in the donor, this is substantially higher in malignant melanoma compared to SCC with an overall metastatic rate of <5 % in the general population, and even less with BCC, which is known to almost never metastasize (Lanssens and Ongenae 2011). Metastatic melanoma occurs in 15–26 % of low-stage melanoma with no palpable nodes (Fitzpatrick et al. 2001). Late recurrence (>10 years) is seen in melanoma, with a median time of 14 years (Fitzpatrick et al. 2001). A number of donors, who were initially diagnosed to have had a intracranial bleeding or stroke or primary brain tumour as cause of death, have been found to have transmitted malignant melanoma. This indicates that metastasis

had occurred in these donors at the time of donation (Zwald 2010). In SCC on the contrary, metastases are directed to regional lymph nodes and appear 1–3 years after initial diagnosis (Fitzpatrick et al. 2001).

Inactivation during storage and processing

Human allograft skin can be preserved by several methods. In contrast to a number of other tissues such as cornea, in which the viability of the tissue is crucial, skin can be preserved viable or non-viable. The choice to preserve skin as viable or as non-viable tissue, critically affects the way of processing, but also the integrity and immunogenicity of the skin (Verbeken et al. 2012). Cryopreservation is the preferred method for long term storage of viable skin grafts. If viability is not required deep-freezing, freeze-drying or glycerol preservation may be used (Kearney 2005; Huang et al. 2004).

Skin tissue is inherently colonized by skin associated micro-organisms and thus non-sterile at the time of harvesting (Verbeken et al. 2012). Microbial contamination of skin allograft depends on the type of donor (living or deceased) and the type of processing (cryo- or glycerol preservation), with higher levels of contamination found in cryopreserved cadaveric donor skin (Pianigiani et al. 2010).

The risk of infectious disease transmission by allografts, including skin allografts, remains a concern, although only one case of HIV transmission from a skin donor to a recipient has been reported and although skin allografts are mostly used as a 'biological dressing' and only present on the wound for 7–10 days (Clarke 1987; Kearney 2005).

Further sterilisation techniques can be applied for non-viable grafts, including radiation, alkylating agents (e.g. alcohols) and oxygen-releasing compounds (e.g. hydrogen peroxide and peracetic acid; Kearney 2005). These techniques are not suitable for viable skin grafts, because of their tendency to inactivate human cells at an equal or even greater rate than bacteria.

In order to study the possible reduction of tumour transmission and transmission of oncogenic risk factors by preservation or sterilisation techniques, a search in published studies of the methods mentioned above was performed to assess the effects on cell viability and virus inactivation. The results are listed in Table 1. In general there are no remaining viable cells reported except after the freezing process. The absence of living cells not only lowers the risk of immediate rejection significantly (Kearney 1996; Richters 1996), but also indicates that tumour cells are probably also inactivated, although no studies have investigated this aspect specifically. Furthermore, virus inactivation is reported for most methods except for freezing and freeze-drying and it has even been validated for peracetic acid (Huang et al. 2004). Moreover, a major advantage of peracetic acid is its non-toxic breakdown products, which makes it a suitable sterilization method (Huang et al. 2004). This is in contrast with radiation, of which the effectiveness has been questioned because of its dose dependent inactivation of viruses (Smolko and Lombardo 2005). Many small viruses are fairly resistant and the high doses required to effectively inactivate viruses cause extensive damage to the graft (Kearney 2005). Even though virus inactivation has been reported for glycerol, it is not recognized as a sterilising agent, since even after preservation for several months infectious viruses can still be recovered (Huang et al. 2004).

It can be concluded that application of processing and sterilization methods, as described above and frequently used in tissue banking, reduces the risk of transmitting infectious disease, and more particular viral transmission, even if they only play a minor role in the development of skin cancer. Furthermore, these techniques have a major effect on cell viability, thereby reducing the risk of transmission of skin cancer.

Transmissibility

The frequency of detection of unexpected cancer at autopsy, raises concern for the prevalence of malignancies in otherwise eligible prospective donors (Sens et al. 2009). In their detailed review of the scientific literature, Eastlund and Warwick (2012) state that there have been no reports of malignancies transmitted by skin allograft transplantation despite wide use of skin allografts and despite most recipients having burn-related immune suppression. In contrast, the risk of transmitting malignancies is well described in the scientific literature of organ transplantation. Transmitting malignancies through organ transplantation

Table 1 The effects of different preserving/storage methods on cell viability and virus inactivation (26–33)

Processing methods	Reduce cell viability	Virus inactivation
Freezing	Not expected	Not expected
Freeze drying	Reported	Not expected
Peracetic acid	Reported	Reported
Peroxides	Reported	Reported
Alcohols	Reported	Reported
Radiation	Reported	Reported
Glycerol	Reported	Reported

may serve as a worst case model for tissue transplantation as organ transplantation requires optimal cell viability and as recipients are usually immunocompromised, thereby rendering them more susceptible for transmittable disease and tumour development. The Cincinnati Transplant Tumour Registry (CTTR) and the Israel Penn Transplant Tumour Registry (IPTTR) data showed an overall tumour transmission rate of approximately 45 % through organ transplantation of donors with any malignancy (Penn 1997; Buell et al. 2001). Malignant melanoma has demonstrated a very high chance of fatal tumour transmission in organ donor recipients. Based on the IPTTR data a malignant melanoma transmission rate of 74 % was seen, which resulted in a mortality of 58 % (Buell et al. 2004). There are many case reports that substantiate this claim of high risk of transmitting melanoma through organ transplantation with a high fatality rate (Bajaj et al. 2010; Milton et al. 2006; Morris-Stiff et al. 2004; Penn 1996; Stephens et al. 2000; Strauss and Thomas 2010; Sullivan et al. 2012; Michael et al. 1998; MacKie et al. 2003; Cankovic et al. 2006; Kim et al. 2009). Moreover, recurrences have been reported to occur up to 15 years after spontaneous resolution or surgical excision of superficial lesion in non-immunosuppressed patients (Buell et al. 2004). These late recurrences are seen in both the general population and in organ transplant recipients. This makes it difficult to set up a time limit, after which the donor is considered to be cured. Because of its aggressiveness, any history of malignant melanoma, regardless of the stage and disease free interval, is considered an unacceptable risk in the Council of Europe Guide (NOTIFY Exploring vigilance notification for organs 2011). The United Network of Organ Sharing (UNOS) data found no tumour transmission through 1,276 organs from 488 donors with a history of skin or solid tumour malignancy (Myron Kauffman et al. 2002). However, most of these individuals had a history of NMSC or a low-grade malignancy (Gandhi and Strong 2007; Myron Kauffman et al. 2002). This result reflects the finding that there are no published reports of BCC or SCC or carcinoma in situ transmission in organ transplant recipients.

Based on these findings in organ transplantation, the risk of transmitting malignant melanoma must be considered substantial. Considering the lack of cases of transmitted malignancies through skin and bone allograft transplantation, the risk in skin transplantation is probably much lower than in organ transplantation, but not negligible. On the other hand, in BCC, SCC and premalignant skin lesions, transmission in tissue transplant recipients seems highly unlikely, especially since no transmissions of these lesions have been reported in organ transplantation.

Recipient susceptibility

Immunosuppression increases the susceptibility for development of skin malignancies (Fitzpatrick et al. 2001). In general, tissue graft recipients are immunocompetent. However, immunocompromised tissue recipients do exist, i.e. patients with extensive burns (receiving skin grafts) or patients with malignancies (e.g. patients with osseous malignancies receiving a bone graft). No graft-related malignancy transmissions were reported in immunocompromised tissue recipients. As organ recipients usually are immunocompromised due to the use of immunosuppressive drugs, malignancy transmission was also investigated in this group, as these patients can be seen as worst case scenario group. In organ transplant recipients, skin cancer is the most frequent malignancy post-

transplantation (Zwald and Brown 2011), affecting up to 50 % of these patients (Zwald 2010). An increased incidence of not only skin tumours, 95 % of which are NMSC, but also their precursors is seen (Zwald and Brown 2011).

Published studies suggest that the increased risk of skin cancer following organ transplantation is not caused by the organ transplant itself but rather by the immune status and characteristics of the recipient. Risk predictors are the type of immune suppression, the overall duration and the dosage of immunosuppression (Ulrich et al. 2004), the post-transplantation interval (Harwood et al. 2013), recipient age (Zwald and Brown 2011), recipient skin color and UV exposure (Gogia et al. 2012; Harwood et al. 2013). A higher skin cancer risk is seen with Cyclosporin A as compared to other immunosuppressants such as azathioprine and even more as compared to sirolimus and everolimus (Kuschal et al. 2012). However, the underlying molecular mechanisms remain unclear (Kuschal et al. 2012). Furthermore, the risk of skin cancer development rises steadily with time post-transplant (Harwood et al. 2013). The incidence in Western Europe increases from 10 to 27 % at 10 years and 40 to 60 % at 20 years post-transplant (Zwald and Brown 2011), thus providing evidence that the risk is recipient-related rather than transplant-related. Another argument for the risk being recipient- rather than transplant-related is the importance of age at the time of transplantation. A higher risk of skin cancer is seen in heart and lung transplant-recipients compared to renal transplant-recipients, probably because of more intensive immunosuppression regimens and older age at time of transplant (Zwald and Brown 2011).

Malignant melanoma is a frequent cause of donor-derived post-organ transplantation malignancies (Morris-Stiff et al. 2004). A very high chance of transmission has been demonstrated in organ recipients, combined with a substantial mortality rate (Buell et al. 2004). Besides the presence of a malignant melanoma, no donor-related characteristics or risk predictors were found.

Thus, in tissue transplantation in immunocompromised recipients, which is a worst case scenario, the immune suppression regimen and characteristics of the recipient may be important factors. The only important donor-related risk predictor may be the presence of malignant melanoma in the donor.

Risk management proposal

No guidelines on management of skin cancer related risk in tissue donation have been found in published studies.

This risk assessment, based on scientific literature data and expert consultation, shows that skin cancer, as the most common type of cancer, is frequently seen in the donor population. NMSCs are extremely common with relatively few deaths, while malignant melanoma is less prevalent, but more often fatal. Performing a physical examination is necessary to identify suspicious lesions. Biopsies, with pathology and staging report, are needed to establish the precise nature and aggressiveness of the lesion, but not always available. There is a limited risk that a malignancy or risk factor, such as HPV, is found in donated skin. On the other hand, the presence of malignant melanoma in the donor is dangerous, because of the high risk of metastasis. The storage and processing techniques have a major effect on cell viability and virus transmission, thereby reducing the risk of transmitting skin cancer and its precursors. This risk of tumour transmission on its own is considered low, since no cases on transmission via skin transplantation are reported. However, vigilance is needed for malignant melanoma, because of multiple fatal reports of transmission in organ transplantation. In general, recipient susceptibility is low, because most tissue graft recipients are immunocompetent. In the exceptional case of an immunocompromised recipient, the only important donor-related risk predictor may be the presence of malignant melanoma.

Protocols for organ donation, that address the issue of potential or proven skin malignancies in donors, have been published (Fiorentino et al. 2003; Nalesnik et al. 2011). These protocols were analysed in order to be able to identify aspects that may be relevant for a tissue donation protocol.

A protocol developed by Fiorentino et al. (2003) describes a classification system for donors with malignancies and premalignant lesions, that can be used to optimize donation safety while rationalizing the use of marginal donors. Donor candidates are divided in three categories: a standard risk category, where no evident risk factor for cancer transmission is found, e.g. BCC or non-metastatic SCC of the skin, a non-standard risk category, where a potentially low risk of transmission is seen and an unacceptable risk

category, where an absolute contraindication is identified, such as history of melanoma and any other tumour (past or present) with a high potential of metastasis. Donors with a non-standard risk may only be used in case of certified clinical emergency and with informed consent. Implementation of this protocol for 3 years on 7,608 donor candidates resulted in 241 extra organs from organ donors of the standard and the non-standard risk group, without reported transmission of malignancies (Zucchini et al. 2008).

Starting from this example in published studies of a risk management protocol in organ donation, and taking into account the findings of this risk assessment, the following protocol can be proposed for the management of skin cancer related risk in tissue donation:

1. Malignant melanoma, present at the moment of procurement:
   - Absolute contraindication for donation of lesional skin, non-lesional skin and for donation of other types of tissue.
2. Non-melanoma skin cancer (BCC and SCC) and premalignant skin lesions, present at the moment of procurement:
   - Absolute contraindication for donation of lesional skin (that may contain viable malignant cells or oncogenic risk factors (e.g. active HPV virus) that could be transferred to a recipient).
   - No contraindication for donation of non-lesional skin.
   - No contraindication for donation of other types of tissue (except in the case of proven metastasized SCC).

Conclusion

Confronted with an increasing number of elderly potential donors and the current directive and subsequent legislations prescribes to reject donors with cutaneous malignancies, except for basal cell carcinoma, the decision was made to set up a risk assessment to evaluate the risk of transmitting malignancy through skin transplantation. Throughout the risk assessment, the scarcity of data concerning tissue donation was challenging. Skin cancer following organ transplantation, expert opinion, risk factors in tissue donors, behaviour of NMSC, effect of skin processing and storage, and skin recipient susceptibility were used as a basis to develop a proposal for tissue banks to determine the use of donated skin containing cutaneous malignancies. The proposed protocol recommends that malignant melanoma is an absolute contraindication for the donation of skin and also of other tissues, whereas non-lesional skin or other tissues of a donor with NMSC or with a premalignant skin lesion can be transplanted. The above mentioned risk-analysis and protocol may also serve as an example for analogous protocols for non-cutaneous malignancies and may form a reason to modify the contraindications concerning malignancies in the current EU directive.

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