ORIGINAL ARTICLE

Initial skin cancer screening for solid organ transplant recipients in the United States: Delphi method development of expert consensus guidelines

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SUMMARY

Skin cancer is the most common malignancy affecting solid organ transplant recipients (SOTR), and SOTR experience increased skin cancer-associated morbidity and mortality. There are no formal multidisciplinary guidelines for skin cancer screening after transplant, and current practices are widely variable. We conducted three rounds of Delphi method surveys with a panel of 84 U.S. dermatologists and transplant physicians to establish skin cancer screening recommendations for SOTR. The transplant team should risk stratify SOTR for screening, and dermatologists should perform skin cancer screening by full-body skin examination. SOTR with a history of skin cancer should continue regular follow-up with dermatology for skin cancer surveillance. High-risk transplant patients include thoracic organ recipients, SOTR age 50 and above, and male SOTR. High-risk Caucasian patients should be screened within 2 years after transplant, all Caucasian, Asian, Hispanic, and high-risk African American patients should be screened within 5 years after transplant. No consensus was reached regarding screening for low-risk African American SOTR. We propose a standardized approach to skin cancer screening in SOTR based on multidisciplinary expert consensus. These guidelines prioritize and emphasize the need for screening for SOTR at greatest risk for skin cancer.

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Introduction

Skin cancer is the most common malignancy affecting solid organ transplant recipients (SOTR). SOTR have a significantly increased risk for developing both melanoma and nonmelanoma skin cancers as compared to the general population (Table 1) [1]. The risk of cutaneous squamous cell carcinoma (SCC) is 65 times higher than that of the general population, and malignant melanoma (MM) risk is three times higher [2]. Organ transplants performed in the United States reached a record high during 2016, with over 33 000 transplants performed [3]. This was an 8.5% increase over 2015 and an almost 20% increase since 2012. With the rapid increases in numbers of SOTR and the increasing life expectancy of these recipients, the incidence of skin cancer in the aging transplant population has also risen, to over 1.4 per 100 person-years. Moreover, the disease-specific mortality from skin cancer in transplant recipients was recently reported to be similar to that from colon or breast cancer [4].

Given that SOTR are at an increased risk for skin cancer and associated morbidity and mortality, this patient population warrants a standardized approach to post-transplant skin cancer screening. An optimal screening program should reduce morbidity and mortality from cancer. Although some experts recommend universal skin cancer screening after transplant, there are no U.S.-based studies to date investigating the utility of annual skin cancer screening in improving outcomes in SOTR, and there are no formal consensus guidelines for screening [5].

In current practice, skin cancer screening varies greatly from institution to institution. In 2004, the International Transplant Skin Cancer Collaborative (ITSCC) and the European Skin Care in Organ Transplant Patients (SCOPE) Network published an expert opinion recommending skin cancer screening prior to transplant if practical, and then at least annually depending on a number of risk factors [6]. A recent systematic review by Acuna *et al.* [5] found ten recommendations in the medical literature for skin cancer screening in SOTR, with nine out of ten recommending annual screening. These recommendations represent individual expert opinions, but none have employed a multidisciplinary consensus methodology for development. Furthermore, international survey data suggest that adherence to these recommendations remains low. In the United States, only 27% of renal transplant

Table 1. Skin cancer rates by transplant organ type.

Organ	Rate*	95% CI
Lung, heart-lung	3520.94	3014.07–4113.04
Heart	1633.79	1345.59–1983.71
Kidney	1280.02	1158.19–1414.67
Liver	1196.32	1041.86–1373.69
Pancreas, kidney-pancreas	639.25	385.38–1060.35

*Rates of skin cancer, including SCC, Merkel cell carcinoma, and melanoma, per 100 000 person-years, based on TSCN data [2,4].

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patients had been evaluated by a dermatologist following transplantation [7]. Similar studies in France, Canada, and Denmark have reported similarly low rates of adherence to universal screening [8–10]. There are no studies of skin cancer screening rates in thoracic organ transplants, the more high-risk subgroup of SOTR, within the United States. Despite evidence from a population-based, retrospective cohort study in Canada that annual dermatology assessment after transplant reduces skin cancer morbidity and mortality, rates of post-transplant skin cancer screening remain low [10].

In the literature, the primary barriers to skin cancer screening include access to dermatology, insurance coverage, and a perceived lack of medical evidence for screening [10,11]. The most significant barrier to skin cancer screening for SOTR reported was the perceived lack of medical evidence for skin cancer screening among transplant providers. To better address this perception, the Delphi consensus guideline aimed to identify evidence-based risk factors for skin cancer after transplant that are agreed upon by both the dermatology and transplant medical communities, as well as supported by epidemiologic data.

Additionally, with the increasing numbers of living SOTR, it is unlikely that the current dermatology workforce could perform skin cancer screening universally on an annual basis, particularly in a healthcare environment increasingly challenged for resources and by rising cost. For these reasons, it is important to identify those at greatest risk for developing skin cancer and create a more standardized approach to skin cancer screening in SOTR that is accepted by both practicing transplant providers and dermatologists.

An understanding of the risk factors and trends in post-transplant skin cancer is required to accurately risk stratify SOTR and create targeted screening guidelines. Recently, a multi-center population-based study led by the Transplant Skin Cancer Network (TSCN) identified specific risk factors for development of skin cancer: age >50 at time of transplant, white race, male sex, and thoracic organ transplantation [4]. Although many risk predictors for skin cancer have been characterized, few risk stratification tools have been developed to guide physicians in referral for skin cancer screening [12]. Additionally, the tools available have been based on small cohorts of Caucasian kidney transplant recipients, and may not be generalizable to the variable types of transplanted organs and multi-ethnic population in the U.S.

Until appropriate outcomes data to further inform guidelines becomes available, we have developed an expert consensus guideline using a multidisciplinary Delphi panel. The Delphi method is a structured communication technique, originally developed as a systematic, interactive forecasting method that relies on a panel of experts [13–15]. The Delphi method has become increasingly popular across a broad range of medical specialties to create consensus clinical practice guidelines in areas with a paucity of data. Recently, groups such as the American College of Radiology have employed Delphi panels to create evidence-based consensus guidelines for colorectal cancer screening and supplemental breast cancer screening for high-risk women [16,17]. Delphi method expert consensus guidelines such as these help to fill the gaps in high-quality evidence with an objective means to standardize and approach screening for at-risk populations such as SOTR. Goals of the panel were to develop a mutual understanding across transplant medicine and dermatology of the intricacies of post-transplant skin cancer, identify current barriers to skin cancer screening, and finally, to create a standardized approach to skin cancer screening in SOTR.

Methods

Panel selection

A panel of dermatologists and transplant physicians (medical dermatologists, Mohs micrographic surgeons, transplant pulmonologists, cardiologists, nephrologists, hepatologists, and surgeons) was formed from 42 different institutions around the United States. To recruit dermatologists, participants in the International Transplant Skin Cancer Collaborative 2016 Screening Guidelines Workgroup were identified and invited to participate via e-mail. Dermatology panelists were then asked to provide recommendations for interested transplant physicians from their respective institutions to participate in the panel. Eighty-nine physicians were identified and participated in the initial round of the Delphi surveys. This study was exempt from IRB review.

Survey methods

To complete the Delphi, experts answered questionnaires, and after each round of questions, the facilitator provided an anonymized summary of the experts' responses from the previous round, as well as the reasons provided for their judgments. Experts revised their responses in subsequent surveys in light of the replies of

other members of the panel. The goal of this process was to decrease the range of the answers until the group converged on a consensus answer. The process was stopped after a predefined stop criterion of three rounds.

Surveys were administered via Microsoft Word documents, which panelists completed according to instructions contained within the document. Completed surveys were emailed back to the Delphi mediator and results were compiled, analyzed, and de-identified prior to being released to participants. Participants could also submit comments to be incorporated into subsequent Delphi rounds. Descriptive data analysis was performed using STATA 14 and compiled into summary reports for every round. Consensus was set *a priori* at 80% agreement of experts. Prior to survey completion, panelists were asked to review current literature regarding skin cancer incidence, morbidity, and mortality.

First round

Panelists were asked to identify which physicians should be performing risk assessment, patient education, and full-body skin examinations (FBSE) for skin cancer screening. Participants were then asked to identify and define the specific risk factors to consider when assessing the appropriateness of referral to dermatology for screening in a transplant recipient based on clinical experience and current evidence in the literature (Table S1). For the provided variables, panelists were asked to rate the variable on a 5-point Likert scale in terms of clinical importance and to provide feedback about the definition and concept wording of the given variables. The top five most important risk factors identified by the panel included: a personal history of previous skin cancer, degree of post-transplant immunosuppression, race, age at transplantation, and Fitzpatrick skin type. There were also blank variables that were open for panelists to provide additional risk factors. The format of the first round was open-ended to encourage maximum participation and control of consensus formation by panelists. The demographics of the panelists were also obtained.

Second round

In the second round, participants were asked to provide screening recommendations for four clinical scenarios based on survey responses from the first round, and to report whether the addition of different individual risk features to the clinical scenarios would change their recommendations for screening. Panelists were also asked to identify potential forms and settings for risk assessment and cancer screening within the current transplant and dermatology workflows (Table S2).

Third round

For the final round of the Delphi surveys, final recommendations for screening were developed through further case-based clinical scenarios that examined combinations of risk factors, refined based on feedback from the first two rounds (Table S3). Risk assessment recommendations around which consensus had not yet been obtained, such as screening in African American SOTR, were explored in greater detail in an effort to reach consensus. In addition, panelists were asked to determine the cancer incidence threshold at which they would recommend screening patients. This was determined as the number needed to screen to find one skin cancer.

Results

Panelist participation

Eighty-nine panelists participated in the first round of the Delphi surveys. For the second and third rounds, 84 of the initial panelists completed the surveys, an overall completion rate of 94%. The panel was made up of 47

Table 2. Panelist demographics.*

	N
Specialty	
Dermatology	47
Medical dermatology	26
Mohs micrographic surgery	21
Transplant	37
Cardiology	6
Pulmonology	15
Nephrology	12
Hepatology	2
Surgery	2
Total	84
Years treating SOTR	
Mean (range)	13.2 (1–42)
Total among panelists	1105
Practice type	
Academic	81
Private	3

*Only panelists who completed all three rounds of Delphi surveys are included.

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dermatologists and 37 transplant physicians. A breakdown of panelist demographics can be found in Table 2.

Consensus

After three rounds of Delphi surveys, panelists achieved consensus around several recommendations for risk assessment and skin cancer screening (Tables 3 and 4). Panelists agreed that the transplant team should conduct skin cancer risk assessment, either at the time of listing or at the time of transplant. A consensus of panelists also agreed that there is a need for an evidence-based risk assessment or risk stratification tool. Panelists identified a need for a risk stratification tool that is both time-efficient (requiring less than five minutes to complete) and resource-efficient (can be completed by office staff using basic patient health information).

The Delphi panel also achieved consensus that dermatologists should perform FBSE for cancer screening. The panel recommended that SOTR with a history of skin cancer should continue with routine skin cancer surveillance as recommended by their dermatologist. Race was determined by panelists to be the most important risk factor for the development of post-transplant skin cancer. There was consensus agreement that Caucasian SOTR who are deemed high risk based on the cumulative effect of race and any of the following risk factors—age over 50, thoracic organ transplant, or male gender—should be screened within 2 years following organ transplant. Low-risk Caucasian SOTR with none of these risk factors should be screened within 5 years following organ transplant. The panel recommends that all Hispanic and Asian SOTR should receive skin cancer screening within 5 years following organ transplant. There was consensus agreement that high-risk African American SOTR (male, age over 50, thoracic organ) should also receive skin cancer screening within 5 years following organ transplant. No consensus was reached for lower-risk African American SOTR.

The panel also weighed in on the appropriate screening threshold for skin cancer, or the desired number needed to screen to detect one skin cancer. Transplant physicians recommended screening if the risk of skin cancer in a group of SOTR was 1%, and dermatologists recommended screening if the risk of skin cancer in a group of SOTR was 4%. Collectively, experts agreed that a screening threshold of one in fifty, or 2% incidence would be an ideal target for screening. Therefore, if there were 100 patients in a given group of SOTR, panelists felt it would be worthwhile to screen the entire group to detect two skin cancers. For reference, the breast cancer number needed to screen to prevent one breast cancer-related mortality is approximately 746 under the current USPSTF screening recommendations, and the disease-specific mortality for skin cancer is higher in SOTR than the disease-specific mortality of breast cancer [4,18].

Table 3. Screening recommendations for each SOTR patient demographic.

SOTR patient characteristics	Screening recommendation
Caucasian: high risk • Any one of the following additional risk factors: thoracic organ, age >50 years at time of transplant, or male gender	Within 2 years
Caucasian: low risk • None one of the following additional risk factors: thoracic organ, age >50 years at time of transplant, or male gender	Within 5 years
Hispanic	Within 5 years
Asian	Within 5 years
African American: high risk • Any one of the following additional risk factors: thoracic organ, age >50 years at time of transplant, or male gender	Within 5 years
African American: low risk • None one of the following additional risk factors: thoracic organ, age >50 years at time of transplant, or male gender	No consensus

Discussion

This report summarizes the first multidisciplinary expert consensus on screening recommendations for skin

Table 4. Risk assessment and skin cancer screening consensus statements by panel.

The transplant team should perform risk assessment at either the time of listing or at the time of transplant
The panel recommends that the transplant team perform risk assessment with the aid of an evidence-based risk stratification tool
The panel would prefer a risk assessment tool that can be completed in less than five minutes
The panel would prefer a risk assessment tool that can be completed by nonphysician office staff
Skin cancer screening by full-body skin examination should be completed by a dermatologist
Solid organ transplant recipients with a history of skin cancer should continue standard skin cancer surveillance as recommended by their dermatologists

cancer after organ transplantation in the United States. The recommendations for initial skin cancer screening put forth by the panel represent a minimum recommendation taking into account the feasibility of dermatology access in a resource-limited healthcare environment. As such, the screening guidelines proposed by this Delphi panel aim to optimize the use of dermatology resources for screening the most high-risk individuals. Ideally, transplant providers should ask patients about new skin complaints at every visit and refer promptly for evaluation if necessary. Even in the absence of concerning lesions, patient-specific risk factors, such as extensive sun damage, may prompt an earlier screening referral than suggested by these guidelines.

The panel recommended that skin cancer risk assessment be performed by the transplant team, either at the time of listing or at the time of transplant. There was a unified desire for a simple risk prediction tool, which could be completed by office staff in less than five minutes. Our team has separately developed an evidence-based multivariate risk assessment tool meeting these criteria[19]. Panelists recommended screening based on race in combination with a variety of other risk factors defined by the panel.

A history of skin cancer was the first risk factor around which the panelists formed a strong consensus. By the end of the first round of surveys, a consensus majority of panelists agreed that SOTR with a history of skin cancer should follow-up regularly with a dermatologist in order to determine the appropriate intervals for continued skin cancer surveillance. Consensus regarding ongoing screening intervals was beyond the scope of this study, and remains an important topic within the field of transplant skin cancer. If SOTR have not been seen by a dermatologist in a number of years, it would be appropriate for that patient to reestablish dermatologic care for skin cancer screening as soon as possible, as a history of skin cancer is one of the strongest risk factors for the development of future skin cancer [4]. A survey study of 339 transplant patients found that the self-reporting of skin cancer history had a sensitivity of 0.92 and a specificity of 1.00, making patient report of skin cancer history a reliable predictive risk factor [20].

Other risk factors defined as "high-risk" by the panel included any of the following: thoracic organ transplant, age over 50 at time of transplant, or male gender. Therefore, possession of any one of these risk factors immediately categorizes a transplant patient as "high-risk" for his or her respective race. Low risk was defined by the panel as absence of all of these features. These risk factors that achieved consensus by the Delphi panel closely matched data from the TSCN study identifying the most important risk factors for skin cancer following SOTR [2,4]. SOTR who demonstrate any one of these risk factors is deemed to be in the "high-risk" subgroup of his or her race. While there were a number of other skin cancer risk factors discussed and surveyed by the group, none of these other variables reached the consensus threshold for inclusion in the final screening recommendations.

The panel recommended that screening by FBSE should be performed by a dermatologist. Initial screening should occur within 2 years of transplant for high-risk Caucasian recipients and within 5 years of transplant for low-risk Caucasian, Hispanic, Asian, and high-risk African American recipients. No consensus was achieved regarding screening for low-risk African American recipients. Ongoing skin cancer surveillance intervals following initial assessment should be determined by the screening dermatologist after the performance of a detailed history and FBSE.

Due to the incompletely understood variability in referral practices and adherence to screening, we asked panelists to answer survey questions related to the logistical workflow of implementing two different processes, risk assessment, and cancer screening, within the current healthcare environment. Distinguishing between these two separate and important processes allowed our panel to achieve consensus in defining a role for standardized risk assessment by the transplant team and cancer screening by the dermatology team. When creating a screening guideline, it was important to consider clinical feasibility such that the guideline would be more likely to be adopted into current practice. Some dermatology panelists commented that they would prefer that all patients see dermatology for skin cancer screening at one time point in the early post-transplant period, both for ease of referral, as well as to avoid loss to follow-up seen with deferred events. However, this practice would not be feasible in areas with a high volume of organ transplants but limited access to dermatology. Additionally, risk-based screening represents responsible financial stewardship of valuable healthcare resources. The proposed guideline addresses both of these issues by defining which patients need more urgent referral to dermatology, and which patients with a lower risk of post-transplant skin cancer may safely wait longer before screening. This improves on prior opinion recommendations calling for universal annual screening by increasing the likelihood that providers will correctly identify and refer high-risk patients for screening and by increasing access to dermatologists for the most at-risk SOTR through the triage of referrals.

These guidelines purposefully leave room for clinical judgment on the part of the provider. The timeline for

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referral for screening is an outer limit; patients may be referred sooner as determined by the transplant team. One of the most heavily debated risk factors for this panel was race vs. Fitzpatrick skin type (FST). The FST scale offers a useful method of classifying patients' skin phototype, and thus, the ability to burn and tan when challenged with UV radiation (UVR) [21]. This classification system has been validated in a number of studies since its inception in 1975 [22]. Many dermatologists cited evidence that FST is more strongly indicative of skin cancer risk than race [23]. However, the panel was divided when it came to including this measure in risk assessment and screening guidelines. Transplant physicians commented on their low level of comfort with assessing FST and noted that the variable is a patient-reported measure. This makes it less practical for risk assessment than race, which is generally available within the electronic medical record, is easily understood throughout the spectrum of providers, and has also been shown to correlate with FST [23]. Providers may apply additional information such as FST and sun exposure history to broaden risk assessment and refer for screening sooner if warranted.

This guideline focused on skin cancer screening for melanoma and keratinocyte carcinomas, and therefore does not specifically address Kaposi sarcoma, other types of cutaneous cancers, or genital carcinoma. Thus, the physician should keep patient-specific risks in mind when referring for screening or performing a FBSE. Genital lesions are often asymptomatic and are more prevalent in non-Caucasian recipients [24]. Due to the fact that our data for the epidemiology of genital lesions or other cutaneous cancers in SOTR are limited, we did not ask panelists to debate screening recommendations for these diagnoses. The panel was comprised of U.S. physicians and panelists reviewed data on post-transplant cancer incidence in the U.S. As such, these recommendations may not be applicable to post-transplant screening outside of the U.S.

Ultimately, the goal of this guideline is to reduce the burden of skin cancer morbidity and mortality in the transplant population and to increase access to healthcare resources. By utilizing dermatologic resources more efficiently, we can provide increased access to dermatologic care for all patients. In addition, this guideline aims to increase skin cancer awareness, education, and prevention for SOTR. The act of referring a patient early to dermatology increases awareness of risk and may encourage sun protective behaviors—helping to reduce future risk. The results of this Delphi panel are relevant to healthcare providers across the specialties of transplant medicine, primary care, and dermatology.

While this consensus guideline and the accompanying evidence-based risk prediction tool from Jambusaria *et al*. provide screening recommendations based on post-transplant skin cancer incidence, more data are needed to inform future evidence-based screening guidelines. The U.S. Preventive Services Task Force (USPSTF) bases screening recommendations on randomized trial data demonstrating reduction in morbidity or mortality from skin cancer. The 2013 USPSTF recommendation for skin cancer screening is that the current evidence is insufficient to assess the balance of benefits and harms of visual skin examination by a clinician to screen for skin cancer in adults in the general population [25]. However, it is currently unknown whether screening SOTR improves morbidity and mortality outcomes over patient-directed education and prompt evaluation of symptomatic or suspicious lesions. In accordance with the AGREE guideline reporting criteria, future evaluation of effective guideline implementation as well as assessment of the clinical impact that these screening practices make on skin cancer morbidity and mortality in SOTR should be performed [26]. Additionally, investigation of the resulting outcomes for healthcare resource utilization and the reduction of healthcare costs through skin cancer screening of SOTR should help to inform future updates to these screening guidelines.

Authorship

LDC, CLC, AJP, and STA: designed the study, collected study data, analyzed study data, created figures and tables, and wrote the manuscript. All of the other authors participated in the collection of study data as expert panelists and assisted in the development of the manuscript.

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Conflict of interest

The authors do not have any conflicts of interest relevant to this work to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Delphi round 1 survey responses of clinical importance for screening of skin cancer risk factors by panelist group.

Table S2. Delphi round 2 survey responses of clinical feasibility of skin cancer risk assessment and screening for SOTR by panelist group.

Table S3. Delphi survey round 3 case-based screening recommendations in total and cumulative percent panelists.

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