**Table II.** Considerations for treatment of metastatic melanoma in organ transplant recipients

- Targeted therapy with single agent B-raf inhibitor or dual kinase inhibitor agents may be used in *BRAF* V600E–mutated tumors.
- Checkpoint inhibitors may be used with caution and frequent monitoring for patients with *BRAF* WT tumors.
- Caution should be exercised with the use of checkpoint inhibitors in liver, lung, and heart transplant patients.

*WT*, Wild type.

therapy in a patient with metastatic cutaneous squamous cell carcinoma.[6] Blockade of CTLA-4 and PD-1 increases the activation of T cells, not only against malignant cells, but also other cells expressing foreign antigens such as kidney allograft donor antigens. One renal OTR with *BRAF* V600E–mutated melanoma progressed on dual kinase treatment and single agent anti–PD-1 (pembrolizumab) and is currently being treated with nivolumab and talimogene laherparepvec (a herpes simplex type 1–derived oncolytic intralesional immunotherapy) to subcutaneous metastases. Talimogene laherparepvec has not previously been reported among OTRs as a single agent therapy or in conjunction with checkpoint inhibitors.

In summary, the use of checkpoint inhibitors in OTRs with metastatic melanoma should be considered (Table II). However, special considerations should be given for the use of checkpoint inhibitors in patients with certain types of transplanted organs (such as liver) because of the potential for graft rejection. We also propose that multiple institutions report the use of these agents; this practice would be more effective at determining the drug efficacy and risk among OTRs.

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*Funding sources: None.*

*Conflicts of interest: None declared.*

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http://dx.doi.org/10.1016/j.jaad.2017.06.031

## Interrater reliability for histopathologic diagnosis of keratinocyte carcinomas

*To the Editor:* Treatment of keratinocyte carcinomas (KCs, ie, basal cell carcinoma [BCC] and squamous cell carcinoma [SCC]) often depends on histopathologic diagnosis, which might be unreliable. We sought to achieve high diagnostic reliability among dermatopathologists through measures such as meeting quarterly to review cases and discuss diagnostic criteria.

Participants were enrolled in the Veterans Affairs (VA) Keratinocyte Carcinoma Chemoprevention Trial.[1] Biopsied lesions were read by local pathologists, and biopsies acquired from the face and ears were sent for central review by up to 3 board-certified dermatopathologists. Diagnostic categories included BCC (including histologic subtype), SCC (including invasive SCC and SCC in situ), actinic keratosis (AK), and other (Table I).

We used kappa ($\kappa$) and percent agreement to calculate the interrater reliability of diagnoses. The standardized values of kappa typically range from 0 to 1, with 0 depicting agreement expected by random chance and 1 representing perfect agreement.[2,3]

**Table I.** Diagnostic criteria for AK and the BCC and SCC subtypes used by all 3 dermatopathologists

| AK and KC subtype | Dermatopathologist diagnostic criteria |
|---|---|
| Actinic keratosis | Atypical keratinocytes arising in the basilar and lower layers of the epidermis with or without overlying parakeratosis |
| BCC with squamous differentiation* | Aggregates of atypical basaloid cells within the dermis with focal keratinization, dyskeratosis, with or without keratin pearl formation |
| BCC, infiltrative and morpheaform* | Variably sized strands and cords of atypical basaloid cells infiltrating between collagen bundles within the dermis with a sclerotic stroma |
| BCC, nodular and infiltrative* | Nodular aggregates of atypical basal cells and variably sized strands and cords of basal cell carcinoma infiltrating between collagen bundles |
| BCC, nodular (including nodulocystic adenoid) | Nodular aggregates of atypical basaloid cells within the dermis, might be nodulocystic |
| BCC, superficial | Aggregates of atypical basaloid cells arising in several foci but limited to the undersurface of the epidermis |
| SCC, in situ | Keratinocyte atypia involving all layers of the epidermis without sparing of adnexae |
| SCC, invasive | Malignant neoplasm arising from the epidermis penetrating the dermis and composed of variably sized islands and aggregates of atypical keratinocytes often with dyskeratosis and keratin pearl formation |

*AK*, Actinic keratosis; *BCC*, basal cell carcinoma; *KC*, keratinocyte carcinomas; *SCC*, squamous cell carcinoma.
*Included in the aggressive BCC category.

Statistical analysis was performed with Stata statistical software (release 8.0, StataCorp, College Station, TX). The study was approved by the VA Central Institutional Review Board.

A total of 2701 lesions were biopsied from 672 participants, and 1,204 of these specimens were acquired from the face or ears. All biopsied lesions were initially read by a local pathologist. We excluded 30 of the specimens acquired from the face and ears because the slides were not received for central review, resulting in 1174 specimens being read by at least 1 of the 3 board-certified dermatopathologists.

The first 176 (15%) biopsied lesions were read independently by all 3 dermatopathologists. The agreement for all diagnoses was high (Table II). For the diagnosis of KC, $\kappa$ (or interobserver agreement) was 0.91. For the diagnosis of BCC, $\kappa$ was 0.96, and for SCC, $\kappa$ was 0.90. Aggressive BCC had less interobserver agreement ($\kappa = 0.57$). The diagnosis of invasive SCC had a higher reliability than the diagnosis of SCC in situ.

The local pathologists generally had a lower agreement with the central dermatopathologists compared with the agreement that the central reviewers had with each other. After the initial 176 lesions, only central dermatopathologist 1 interpreted the remaining biopsies (n = 1160 specimens). Overall, we found less agreement between dermatopathologist 1 and the local pathologists in every category compared with the agreement among all 3 dermatopathologists.

Dermatopathologist 1 also reread 168 of the 1160 lesions (14.4%) at a later time (mean 1.27 years). Intrarater agreement values were similar to those found for all 3 dermatopathologists (Table II).

High interobserver agreement was achievable in almost every diagnostic category in the VA Keratinocyte Carcinoma Chemoprevention Trial. A similar study yielded lower interrater reliability when compared with our results.[4] Unlike our study, these dermatopathologists did not meet regularly to discuss the diagnostic criteria. The differences in the results between these 2 studies suggest that agreement, and therefore diagnostic outcomes, can be improved when dermatopathologists meet regularly for quality control discussion before slide review.

Clinical dermatologists rely on accurate, reliable histopathologic diagnoses for determining the most appropriate treatment for their patients' skin cancers. Measures to increase reliability of both clinical and research endeavors should be of high concern given the implications of what might result if agreement is poor.[5] We found that high reliability of histopathologic diagnosis of KCs can be achieved through collaborative work among dermatopathologists.

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**Table II.** Interrater and intrarater agreement for diagnoses among dermatopathologists and local pathologists

| Groups | Diagnosis | $\kappa$ | 95% CI | Agreement, %* |
|---|---|---|---|---|
| Among the 3 central dermatopathologists | All diagnoses† | 0.91 | 0.86-0.95 | 92 |
| | KC | 0.91 | 0.83-0.97 | 95 |
| | BCC | 0.96 | 0.92-0.99 | 97 |
| | BCC, aggressive‡ | 0.57 | 0.45-0.70 | 83 |
| | BCC, all subtypes | 0.78 | 0.72-0.84 | 80 |
| | SCC | 0.90 | 0.82-0.96 | 95 |
| | SCC, invasive | 0.79 | 0.67-0.88 | 92 |
| | SCC, in situ | 0.52 | 0.29-0.72 | 92 |
| | AK | 0.77 | 0.63-0.90 | 94 |
| Between local pathologists and central dermatopathologists | All diagnoses§ | 0.83 | 0.76-0.90 | 90 |
| | KC | 0.78 | 0.66-0.90 | 93 |
| | BCC | 0.93 | 0.87-0.99 | 97 |
| | SCC | 0.83 | 0.73-0.93 | 94 |
| | SCC, invasive | 0.82 | 0.70-0.94 | 95 |
| | SCC, in situ | 0.48 | 0.20-0.75 | 94 |
| | AK | 0.56 | 0.34-0.78 | 93 |
| Between dermatopathologist 1 and local pathologists | All diagnoses‖ | 0.79 | 0.77-0.82 | 86 |
| | KC | 0.83 | 0.80-0.87 | 93 |
| | BCC | 0.92 | 0.90-0.95 | 96 |
| | SCC | 0.78 | 0.73-0.83 | 94 |
| | SCC, invasive | 0.75 | 0.68-0.81 | 95 |
| | AK | 0.59 | 0.52-0.66 | 91 |
| Intrarater (test-retest) reliability of dermatopathologist 1 | All diagnoses¶ | 0.83 | 0.76-0.90 | 89 |
| | KC | 0.91 | 0.83-0.98 | 96 |
| | BCC | 0.92 | 0.86-0.98 | 96 |
| | SCC | 0.92 | 0.84-1.0 | 97 |
| | AK | 0.56 | 0.36-0.77 | 91 |

*AK*, Actinic keratosis; *BCC*, basal cell carcinoma; *KC*, keratinocyte carcinomas; *SCC*, squamous cell carcinoma.
*At least 2 of 3 dermatopathologists agreed with each other 100% of the time except for the category BCC, all subtypes, in which they agreed with each other 97% of the time.
†All diagnoses included categories AK, BCC, SCC in situ, invasive SCC, and other.
‡Aggressive BCC included BCC with squamous differentiation, infiltrative and morpheaform BCC, and nodular and infiltrative BCC.
§All diagnoses included categories AK, BCC, SCC, and other.
‖All diagnoses included categories AK, BCC, SCC, and other (n = 1160).
¶All diagnoses included categories AK, BCC, SCC, and other (n = 156). Average time between reads was 1.27 years.

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*Funding sources: None.*

*Conflicts of interest: None declared.*

*Reprints not available from the authors.*

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http://dx.doi.org/10.1016/j.jaad.2017.07.024

## Trends in US sunscreen formulations: Impact of increasing spray usage

*To the Editor:* Sunscreen is an important component of sun protection. Almost all dermatologists believe that sunscreen is safe, effective, and can reduce the risk of skin cancer.[1] In the United States, many different