Skin Cancer Research Review

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In this issue:

- Review of topical treatments for seborrheic keratoses
- Post solid organ transplant skin cancer rates differ by organ type and patient age
- Increased melanoma incidence in the US mostly reflects diagnostic scrutiny
- Heterogenous survival outcomes in black patients with mycosis fungoides/Sézary syndrome
- Neoadjuvant cemiplimab elicits high response rates in cutaneous SCC
- Racial differences in development of post-kidney transplant skin malignancy
- Follow-up of patients with keratinocyte carcinoma
- Dermoscopic features of baby melanomas
- Diagnosis of linear BCC requires dermoscopic examination
- Handheld RCM more accurate than dermoscopy for delineating BCC margins

Abbreviations used in this issue:

 $\begin{array}{l} BCC = basal \ cell \ carcinoma; \ Cl = confidence \ interval; \\ HPV = human \ papilioma \ virus; \ HR = hazard \ ratio; \\ RCM = \ reflectance \ confocal \ microscopy; \ SCC = \ squamous \ cell \ carcinomas; \\ UV = \ ultraviolet. \end{array}$

Welcome to the latest issue of Skin Cancer Research Review.

In this issue we look at results from an international phase 2, confirmatory trial of neoadjuvant immunotherapy for locally advanced, resectable cutaneous squamous cell carcinoma (SCC) that may be practice changing. Data from the trial, published in *the New England Journal of Medicine*, reported that cemiplimab monotherapy elicited an almost complete decimation of cancer cells in almost two-thirds of patients with stage 2-4 disease. We have also included research from Vanderbilt University Medical Centre in Nashville that investigated differences in skin cancer rates after solid organ transplant in white patients according to organ type; a US ecological cross-sectional study suggests that changes in melanoma incidence are more reflective of diagnostic scrutiny than ultraviolet (UV) radiation exposure; and a retrospective cohort study evaluated the clinical presentation and survival outcomes between black and patients of other races with mycosis fungoides and Sézary syndrome. Finally, articles in *Dermatology Practical & Conceptual* characterise the dermoscopic features of baby melanomas and linear basal cell carcinoma (BCC).

We hope you find these and the other selected studies interesting, and wish you a safe and relaxing holiday period.

Kind Regards,

Dr David Simpson

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Efficacy and safety of topical treatments for seborrheic keratoses: a systematic review

Authors: Natarelli N et al.

Summary: Natarelli et al provide a systematic review of the efficacy and safety of topical treatments for seborrheic keratoses. A total of 26 studies published prior to November 2021 were identified from a search of four online databases - Embase, Scopus, PubMed and Cochrane. Meta-analysis was precluded by a high heterogeneity of outcome measures and there was a dearth of head-to-head clinical trial evidence, but a good or better response with only mild and transient localised adverse reactions was reported for treatment with hydrogen peroxide, maxacalcitol $25 \,\mu g/g$, tazarotene 0.1% cream twice-daily, 5% potassium dobesilate cream, 1% diclofenac sodium solution, urea-based solution and 65%-80% trichloroacetic acid. The authors commented on the need for a topical therapy with a comparable efficacy as cryotherapy or shave excision front-line treatments.

Comment: Seborrhoeic keratoses are a common finding in patients presenting for skin examinations and can mimic melanoma and so require a thorough dermatoscopic and clinical assessment prior to considering cosmetic removal. This review looked at various methods to deal with seborrhoeic keratoses and found that none have equivalent efficacy to cryotherapy of shave removal but there have been promising results with a range of topical solutions. Hydrogen peroxide solutions have shown clearance in 30%-90.2% of lesions and high concentration urea creams as well as acids may be useful. Retinoids, calcipotriol, 5-fluorouracil, imiquimod and ingenol mebumate have all been studied and had some benefit but cryotherapy or shave removal/curettage are still the most effective therapies.

Reference: J Dermatolog Treat 2022; Nov 13 [Epub ahead of print] Abstract

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Single-Session²⁻⁴ Complete tumour regression n 98.5% of lesions treated. References: 1. Cipriani C, et al. International J Nucl Med. 2017; July:114-112. 2. Cipriani C, et al. J Dermatol Treat. 2020; DOI: 10.1080/09546634.2020.1793890. 3. Castellucci P, et al. Eur J Nucl Med Mol Imaging. 2021; 48(5):1511-1521. 4. Cipriani C, et al. In Therapeutic Nuclear Medicine. 2014. RP Baum (Ed), New York: Springer. 5. Therapeutic Goods Administration. ARTG Public summary 351390. OncoBeta Therapeutics Pty Ltd – Radionuclide system, therapeutic, brachytherapy, manual (9/12/2020). https://compliance. health.gov.au/artg/ (accessed September 2022).

Please review the Product and User information before use. This can be accessed at www.oncobeta.com. Indication: Rhenium-188 paste for the treatment of skin cancer lesions and skin tumours. OncoBeta® GmbH, Scheißheimer Str. 91, 85748 Garching near Munich, GERMANY. SHOW3872.19. Date of preparation: October 2022

Differences in skin cancer rates by transplanted organ type and patient age after organ transplant in white patients

Authors: Wheless L et al.

Summary: Dr Lee Wheless and colleagues from the Vanderbilt University Medical Centre in Nashville. Tennessee analysed rates of skin cancer development in recipients of solid organ transplants to elucidate factors associated with risk of multiple skin malignancies. Data on 5,129 adult Caucasian patients, predominantly male (64%; mean age 51.3 years), who received a solid organ transplant over a 25-year period spanning 1992 onwards were extracted from the centre's electronic health record database. At a mean follow-up of 6.6 years, 13.6% (n=695) of patients had developed at least one skin cancer with a total of almost seven thousand cutaneous cancers (n=6,842). With a first skin cancer prevalence approaching 20% in recipients of a lung, kidney or heart, more than double that of liver recipients, these patients were significantly more likely to develop a post-transplant skin malignancy (17.7%, 16.5% and 16.1% vs 6.8%; x2 test, 25.6; df, 4; p< 0.001). The total burden of skin cancer varied by transplanted organ, with the greatest number of skin cancers seen in kidney transplant recipients and the lowest in lung recipients (mean skin cancer total per patient, 11.9 vs 4.6; p<0.001). Time to second and third cancer development was comparable across transplanted organ types but older age at transplant associated with greater risk for more than one skin cancer (time to second skin cancer, x2 test, 20.4; df, 4; p<0.001).

Comment: Post-transplant immunosuppression in solid organ transplant recipients is known to increase the risk of skin cancers, particularly cutaneous SCC. This study of over 5,000 white solid organ transplant recipients found that whilst all groups had an increased risk of skin cancer, liver transplant recipients were less likely to develop a first skin cancer but once they had developed a first lesion the rate of further lesions was the same across all solid OTRs. Those patients who had a pre-transplant skin cancer had a 100% risk of post-transplant skin cancers and the 10% of organ transplant recipients contributed nearly 50% of the total skin cancers found in the study, indicating that patients developing multiple lesions needs more intensive follow-up and management.

Reference: JAMA Dermatol 2022;158(11):1287-92 Abstract

Association of UV radiation exposure, diagnostic scrutiny, and melanoma incidence in US counties

Authors: Adamson A et al.

Summary: Findings from this US cross-sectional ecological study in *JAMA Internal Medicine* indicate that changes in melanoma incidence are more reflective of diagnostic scrutiny than UV radiation exposure. A total of almost one-quarter of a million (n=235,333) cases of in situ or invasive melanoma in non-Hispanic White patients, diagnosed between 2013 and 2016 in 727 continental US counties, were extracted from the Surveillance, Epidemiology, and End Results (SEER) database and included in the analysis. Correlations were examined to proxies of UV radiation including daily UV dose, cloud and temperature variability and proxies of diagnostic scrutiny including household income and supply of dermatologists and primary care physicians. The study found no relationship between melanoma incidence and measures of UV radiation exposure (r=0.03; p=0.42) but a positive correlation with median household income and plentiful physician supply. A tenuous association bordering on statistical significance between melanoma incidence and melanoma-specific mortality was noted (r=0.09; p=0.05). The study authors noted that the findings were in contrast to those in lung cancer where a strong correlation was found between incidence and both smoking and cancer-specific mortality (r=0.81; p<0.001 and r=0.96; p<0.001, respectively).

Comment: Melanoma incidence has dramatically increased but there has not been a corresponding increase in mortality, raising the question of whether many of these melanomas were either incorrectly classified as cancer or their behaviour was likely to be benign. The researchers looked at proxies for UV light exposure as well as physician supply, household income proxies across the USA and found that there was a link between the number of dermatologists and family physicians per capita and the incidence of melanoma as well as links to increased wealth but not UV radiation exposure. There were also similar findings for other cancers with screening programs such as breast and prostate cancers. The problems arising from screening populations for early cancers are yet to be solved but questions remain as to how to separate lesions which will result in the patient's death from those which are unlikely to progress.

Reference: JAMA Intern Med 2022;182(11):1181-89 Abstract

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Clinical presentation and outcome differences between black patients and patients of other races and ethnicities with mycosis fungoides and Sézary syndrome

Authors: Allen P et al.

Summary: This retrospective cohort study examined data on patients with two types of cutaneous T-cell lymphoma - mycosis fungoides and Sézary syndrome - to assess race-specific clinical presentation and disease progression. The study cohort consisted of 566 patients (mean age 55 years; 47.7% female) diagnosed in the ten-years preceding 2020 at the Winship Cancer Institute of Emory University or the Grady Memorial Hospital, both in Atlanta, USA. Slightly less than half of the cohort (45.4%; n=257) were Black patients with the other half comprised of all other races including Asian, Hispanic, Caucasian (non-Black). A hypopigmented phenotype disease was found in 11% of the entire cohort but was restricted almost exclusively to black patients, found in almost one-quarter of black patients but less than 1% of non-Black patients. Black patients with mycosis fungoides/ Sézary syndrome were characterised by younger age, higher TNMB and tumour stage, nodal metastasis and higher lactate dehvdrogenase level versus non-Black patients. Clinical outcomes in Black patients were heterogenous with a favourable survival in those with hypopigmented mycosis fungoides (10-year survival, 100% vs 51.8% in patients without hypopigmented disease) but significantly worse outcomes in patients younger than 60 years compared to non-Black patients (hazard ratio [HR] 1.27: 95% confidence interval [CI], 1.08-2.87; p=0.43).

Comment: Mycosis fungoides is a T cell lymphoma affecting the skin whilst in Sézary syndrome large numbers of malignant lymphocytes are also found in the blood. Black patients are at higher risk of developing these diseases and do so a decade before white patients. There were differences between the presentation in black patients including a higher lactate dehydrogenase, greater incidence of hypopigmented mycosis fungoides and higher tumour and nodal stages at diagnosis but the mortality and treatment course was similar to non-black patients. Younger black patients without the hypopigmented variant were the only group with a worse prognosis compared to non-white patients.

Reference: JAMA Dermatol 2022;158(11):1293-99 Abstract



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Neoadjuvant cemiplimab for stage II to IV cutaneous squamous-cell carcinoma

Authors: Gross N et al.

Summary: This phase 2, confirmatory, single-arm trial of neoadjuvant immunotherapy for advanced cutaneous SCC (NCT04154943), sponsored by Regeneron Pharmaceuticals in conjunction with Sanofi, met its primary outcome measure to demonstrate efficacy of cerniplimab for resectable disease. A total of 79 patients with stage 2-4 disease without evidence of distant metastasis were enrolled from sites in the US, Australia and Germany and administered up to four doses of 350 mg cerniplimab monotherapy prior to curative-intent resection. The pathological complete response rate (the absence of viable tumour cells in the surgical specimen) per independent central pathology review was 51%, exceeding the null hypothesis of 25% to demonstrate efficacy. An additional 13% of patients attained a pathological major response with ≤10% tumour cells in the surgical specimen and more than two-thirds of patients (68%) achieved an objective radiological response. Severe adverse events (grade ≥3) were experienced by 18% of patients.

Comment: Cemiplimab, an anti-programmed cell death 1 monoclonal antibody, has previously been shown to be useful in treating unresectable locally advanced cutaneous SCC. In this study it was used as neoadjuvant therapy prior to resecting tumours which were considered resectable but were stage 2, 3 or 4 without metastases. Imaging was performed at baseline and pre- and post-surgery using computed tomography or magnetic resonance imaging scans and it was interesting that although imaging showed a similar rate of response as histopathology the degree of response was different. The majority of patients that had a partial response on imaging had a complete response found when the lesion was resected and overall, 51% of patients had a complete pathological response after cemiplimab neoadjuvant therapy. One elderly patient had a fatal exacerbation of cardiac failure and this reinforces the need for pre-treatment screening. The discordance between response on imaging and actual complete response on pathology indicates that superior methods to assess effectiveness of neoadjuvant therapy are needed.

Reference: N Engl J Med 2022;387(17):1557-68 Abstract

Post-kidney transplant cancers: Racial and ethnic differences in sun-exposed skin versus non-sun-exposed anogenital skin Authors: Takeda K et al.

Summary: In order to guide post-kidney transplant cancer screening recommendations Takeda et al retrospectively examined rates and characteristics of first subsequent malignancy in a cohort of kidney recipients treated through the East Carolina University Vidant Medical Centre in North Carolina, USA. The study cohort included 439 adult patients (median age at transplant, 58.50 years; age range, 17-82 years) who received a kidney between 2009 and 2015. Almost three-quarters of patients were black (71.1%). With a follow-up to February 2020 the rate of posttransplant malignancy was 13.4% (n=59) of which over half (54%) were skin or mucosal cancers. Kidney, prostate, lung and blood were the next most common sites of malignancy. Skin/mucosal cancers were predominantly found in sun-exposed areas including the head, cheek, ear, neck, forearm and hand and were entirely restricted to white patients while skin/mucosal cancers in non-sun exposed anogenital areas such as the perianal, anal or vulvar regions were almost exclusively found in black patients (n=7/8). The authors concluded that white versus black patients are at a significantly higher risk of skin cancer after kidney transplant, with risk potentially attributable to the presence of undetectable precancerous precursor lesions that develop in the setting of immunosuppression.

Comment: Immunosuppression after solid organ transplant is well known to increase the risk of developing skin cancers. In white patients the majority of skin cancers were in sun-exposed skin with the majority being cutaneous SCCs. In black patients there was also an increased incidence in SCC but these were mostly found in anogenital skin and had p16 positivity which is a biomarker for human papilloma virus (HPV) infection. One patient, a black woman, developed and died from anal SCC during the study and it was found that a high proportion of genital cancers in black patients were related to HPV infection and this is likely to be re-activated by immunosuppression. HPV can also be found in non-genital cutaneous SCCs but it appears less likely that the infection is causal and high-risk subtypes are generally not seen in non-genital sun exposed sites. Whether beta HPV - which are part of the normal skin flora and are acquired soon after birth – are involved in the development of cutaneous SCC is still under investigation.

Reference: Cancer Med 2022; Nov 14 [Epub ahead of print] Abstract Rhenium-SCT®

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Follow-up of patients with keratinocyte carcinoma: A systematic review of clinical practice guidelines

Authors: Mirali S et al.

Summary: There is a high heterogeneity in global national and international guidelines regarding follow-up frequency after primary treatment for localised cutaneous keratinocyte carcinoma according to results from this systematic review in *JAMA Dermatology*. The study authors identified 14 guidelines published in the 12-year period up to 2022 from a search of three online databases. There was a wide range in proposals for the optimal follow-up schedule after SCC or basal cell carcinoma (BCC) treatment ranging from a sole follow-up appointment to ongoing continual regular check-ups. Follow-up duration was generally stratified by recurrence risk with most guidelines advocating for follow-up in patients with low-risk disease bi-annually or annually and from anywhere from three-monthly to annually for high-risk

Comment: Keratinocyte carcinomas - SCC and BCC - are increasingly common and can cause substantial morbidity and even mortality, particularly in SCC. On the other hand, the majority of lesions can be treated with simple surgical and non-surgical methods if they are detected at an early stage. With rising costs in managing keratinocyte carcinomas, it is important that safe but efficient follow-up arrangements are made and that resources are spent appropriately. It appears from this paper that in the USA, Canada and the UK there are no standard protocols for follow-up and the lack of dermatologists leads to long delays in being treated. Strategies need to be implemented to prioritise high-risk patients such as organ transplant recipients and perhaps concentrate follow-up visits to the first few years after diagnosis when the likelihood of recurrence or metastasis is highest.

Reference: JAMA Dermatol 2022; Nov 2 [Epub ahead of print] Abstract

The hunt for baby melanomas: A prospective study of the dermoscopy features on 100 small melanoma cases with *in vivo* surface diameters up to a maximum of 6 mm

Authors: Pyne J et al.

Summary: This study of micromelanoma cases from two Australian centres characterised dermoscopic structures to aid in early diagnosis. The study cohort consisted of 100 consecutive patients with a histopathologic diagnostic confirmation of small, previously untreated melanoma with an in vivo maximum horizontal diameter of six mm or less fully excised at two Sydney medical practises between 2019 and 2021. Lesions presented as a non-elevated, distinct discoloured area of skin, were most frequently (60%) located on the back or leg and were predominantly in situ (n=96) with an average surface diameter of 3.9 mm and the smallest lesion measuring 1.2 mm. Invasive (n=4) melanomas had a Breslow invasion depth ranging from 0.4 mm to 0.5 mm, an average surface diameter of 3.6 mm and the smallest lesion measured 2.5 mm in diameter. Melanomas were most commonly characterised by light/dark brown or grey colouring, asymmetric shape. Lesions with edge angulation were more common than pigmented circles or polygons overall. Analysis of dermoscopy features by surface diameter revealed an increasing prevalence of most features with increased diameter including brown and grey colour, asymmetric shape, atypical network, grey circles and polygons. The authors noted an almost nine-fold increased likelihood of focal pseudopods in smaller melanomas (< 4 mm vs > 4 mm; odds ratio 8.81; p=0.004), a significantly higher odds of brown hair follicle pigment in legs versus other anatomic sites (odds ratio 14.6; p=0.03) and an elevated proportion of grey in cases with structureless area (odds ratio 7.08; p=0.01).

Comment: Whilst there has been a lot of questioning recently of the benefits or validity of identifying early borderline melanocytic lesions there is no doubt that early detection and treatment is a vital aspect of melanoma management. In the past the ABCD method for detecting melanoma was used extensively and the diameter in that algorithm where melanoma should be considered was 6 mm or greater. This study of over 100 melanomas less than 6 mm diameter found that although 96% were in situ there were a small number of lesions which were already invasive. Focal pseudopods were a strong clue for melanoma and black colour was seen frequently even in very small lesions. In situ and invasive melanomas had similar mean surface diameters (3.9 mm vs 3.6 mm), highlighting the need for examining all pigmented lesions during skin examinations with dermatoscopy.

Reference: Dermatol Pract Concept 2022;12(4):e2022197 Abstract



Skin Cancer Research Review[®]

Independent commentary by Dr David Simpson

Dr David Simpson is a skin cancer doctor on the Sunshine Coast in Queensland. He has a masters degree in Skin Cancer Medicine from the University of Queensland and is a teaching assistant on the MMed program.



Dermoscopy of linear basal cell carcinomas. A potential mimicker of linear lesions

Authors: Navarrete-Dechent C et al.

Summary: A descriptive case series in Dermatology Practical & Conceptual retrospectively analysed the clinical and dermoscopic features of linear BCC, a rare variant of BCC. A total of 18 cases of biopsy-proven primary linear BCC with a length-to-width ratio of at least 3:1, diagnosed between 2016 and 2021 on 17 patients at one of six centres in Chile, Brazil and the US were included in the case series. The median age at diagnosis was 86 years and patients were predominantly male (60%). The most common anatomic locations were the head/neck followed by the trunk and the lower extremities (61%, 27.7% and 11.1%, respectively). Just over half of lesions were excised, one-third removed via Mohs micrographic surgery and one case was treated with electrodessication and curettage. Dermoscopic examination identified BCC-specific criteria in all linear BCCs the most common being blue-grey globules, in-focus dots, short-fine telangiectasia and leaf-like areas. Less frequently observed features such as milky-red background, ovoid nests, ulceration/erosions, shiny white blotches and strands, arborizing vessels and concentric structures were found in between 20% to 40% of cases. The authors commented that dermoscopy was required for definitive diagnosis of linear BCC as without it cases can be confused with scars or scratches.

Comment: Many of us will have seen BCC which appear to be growing along skin wrinkles, particularly around the neck. Factors which may be involved are skin fragility allowing easier extension of the skin cancer as well as the Koebner phenomenon in sites of trauma. The majority of lesions were found to be nodular subtype and, in this series, most were pigmented, although this may reflect the mostly Hispanic population. Dermatoscopy was useful for identifying features of BCCs and the clues were the same as for BCCs that were non-linear.

Reference: Dermatol Pract Concept 2022;12(4):e2022195 Abstract

Challenges for new adopters in pre-surgical margin assessment by handheld reflectance confocal microscope of basal cell carcinoma

Authors: Richarz N et al.

Summary: A prospective single-centre study from the Spanish Institut d'investigació Germans Trias Badalona reports that the use of a handheld *in vivo* reflectance confocal microscopy (RCM) device significantly improves delineation of lateral BCC margins presurgery versus dermoscopy, even when used by a novel user. Tumour margins of 17 consecutive patients with H zone high-risk BCC lesions on the face planned for Mohs micrographic surgery were calculated by RCM and dermoscopy. Margins were more accurately outlined by RCM compared to dermoscopy with comparable predicted and observed surgical defect areas by RCM but not dermoscopy (2.95 cm² vs 2.52 cm²; *p*=0.586 and 1.34 cm² vs 2.52 cm²; *p*<0.001). A purely invasive subtype, previous treatment and plentiful sebaceous hyperplasia were factors associated with poor prediction of surgical defect areas.

Comment: Handheld RCM offers a new portable method for assessing BCC margins prior to surgery. It also allows assessment of difficult areas such as skin folds and uneven facial structures such as around the nose. Most of the existing confocal microscopy studies involved very experienced physicians with several years practice but this study looked at real-world results using the newer handheld device and a physician with only 12 months experience following a short training course. When compared to margins determined using dermatoscopy, RCM performed better and resulted in more accurate estimates of the final Mohs surgery defect. Factors that made RCM less accurate were deep lesions, scarring from previous surgery or radiotherapy and there were some benign lesions incorrectly identified as part of the BCC. This final issue should become less problematic with increased operator experience.

Reference: Dermatol Pract Concept 2022;12(4):e2022162 Abstract



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