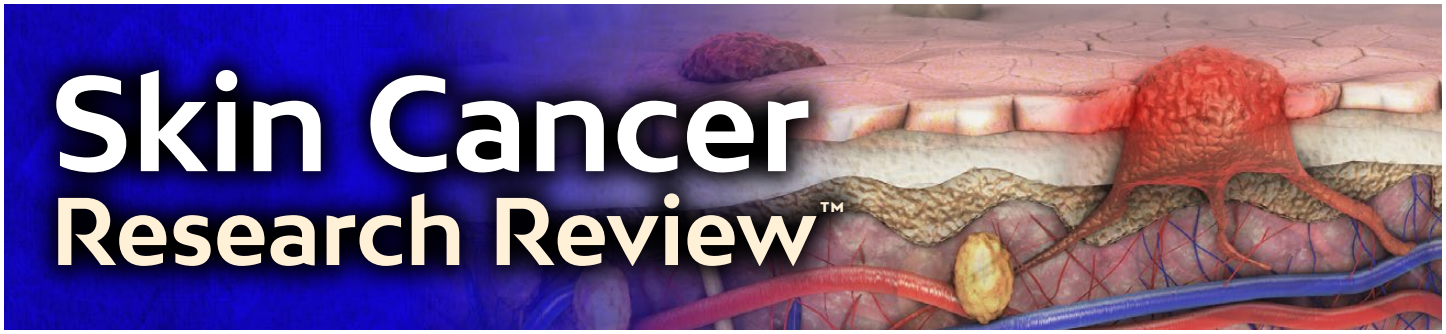
Skin Cancer Research Review™



Making Education Easy

Issue 6 - 2021

In this issue:

Abbreviations used in this issue:

BCC = basal cell carcinoma; **cSCC** = cutaneous squamous cell carcinoma; **CT** = computed tomography; **HR** = hazard ratio; **KA** = keratoacanthoma; **MCC** = Merkel cell carcinoma; **PET** = positron emission tomography; **PY** = patient years; **WHO** = World Health Organisation.

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Welcome to the latest issue of Skin Cancer Research Review.

We begin this review with a cross-sectional analysis of the Surveillance, Epidemiology, and End Results Program published in *JAMA Dermatology* that examined trends in Merkel cell carcinoma (MCC) incidence in the United States. There was a 3.5-times increase in incidence rates between 1987-1991 and 2012-2016 and rates are projected to continue to rise with an estimated 5,130 new cases in 2030. Males had a higher incidence than females and increasing age was also a risk factor. Continuing on with research on MCC, we discuss a retrospective study published in *Journal of the American Academy of Dermatology* that found that baseline imaging in patients with clinically node-negative MCC resulted in disease upstaging in 13% of cases, suggesting that guidelines should be updated to recommend baseline imaging in order to optimise treatments in this population and a study by Tarabadkar et al reveals excellent local control rates with the addition of adjuvant radiotherapy to a surgical management plan, even in high-risk tumours, that negates the need to increase surgical margins. An analysis of the World Health Organization (WHO) Mortality Database reveals that worldwide malignant melanoma mortality has increased over the last 30 years but rates vary between countries with Australia having one of the highest melanoma mortality rates in the world. We conclude this edition of Skin Cancer with a study that aims to characterise the aggressive sclerodermiform variant of basal cell carcinoma in order to enable differentiation from the less aggressive nodular and superficial variants.

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind Regards,

Dr David Simpson

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Assessment of age, period, and birth cohort effects and trends in Merkel cell carcinoma incidence in the United States

Authors: Jacobs D et al.

Summary: This cross-sectional retrospective analysis of data for 3,720 patients (median age 77 years) with Merkel cell carcinoma (MCC) between 1987 and 2016 from the Surveillance, Epidemiology, and End Results Program was published in *JAMA Dermatology* by a group from Yale School of Medicine, Connecticut, USA. The age-adjusted incidence rate increased 3.5-fold from 1987-1991 to 0.66 per 100,000 persons in 2012-2016 with the increased rate attributed mostly to a period-affect due to improved diagnostics (notably CK-20 staining for MCC in 1999) and awareness. A positive correlation was observed between patient age and MCC incidence with patients over the age of 85 years having age-adjusted rates in 2012-2016 of 14.6 and 5.5 per 10,000 persons for men and women, respectively. The authors projected an ongoing increase in incidence rates driven mostly by the aging population, with an estimated 3,023 new cases of MCC in 2020 and 5,130 in 2030.

Comment: MCC is an aggressive neuroendocrine skin malignancy originally thought to be derived from Merkel cells but now thought to be from pluripotential stem cells in the dermis or neural crest cells. It was first described in 1972 and its incidence appears to be increasing. The two main initiating factors appear to from a combination of UV radiation-induced and viral-induced DNA damage. 80% of MCC's have Merkel cell polyoma virus present but the majority of cases are also found in white patients on sun exposed skin. This study examined the factors associated with the increasing incidence and showed that there is a definite increasing incidence with age, with patients over 85 years most at risk. The risk is also greater in men and white subjects. There was a period where the incidence rose at a faster rate but this has now plateaued and the authors proposed that this was due to the introduction of accurate diagnostic testing such as cytokeratin 20 in 1992 as well as increased physician awareness.

Reference: JAMA Dermatol 2021;157(1):59-65
Abstract

The Australasian College of Dermatologists has approved all **Dermatology Research Reviews** for accreditation as a **Category 1 Level 1 activity = 1 point per hour.**
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Incidence of multiple vs first cutaneous squamous cell carcinoma on a nationwide scale and estimation of future incidences of cutaneous squamous cell carcinoma

Authors: Tokez S et al.

Summary: This Dutch population-based epidemiologic cohort study concludes that incidence rates of cutaneous squamous cell carcinoma (cSCC) are still increasing and that the rate of increase is especially high in females. Analysis of the Netherlands Cancer Registry identified 145,619 patients with a first diagnosis of cSCC between 1989 and 2017. Age-standardized incidence rates for first cSCC (standardized to the European Standard Population 2013) increased in both males and female patients from 40 and 13.9 per patient per 100,000 patient years (PY), respectively to 107.6 and 68.7 per 100,000 PYs in 2017. The highest increase of 8.2% per year was seen in female patients between 2002 and 2017. When multiple cSCC were considered European Standardised Rates increased to 170.4 for males and 92.6 per 100,000 PYs for female patients. A regression model with positive slope estimated cSCC European Standardised incidence rates up to 2027 of 132.4 and 88.9 per 100,000 PY for male and female patients, respectively.

Comment: cSCC is becoming increasingly common and is related to chronic sun exposure. The incidence has been increasingly in Caucasian populations and this study examined the trends in the Netherlands which has the second highest incidence of cSCC in Europe, after the UK. The face was the most affected area in male and female subjects but in men the next most common region was the scalp and neck and in women the arms. Lesions on the sun protected trunk and limbs are becoming more common which is probably related to tanning and clothing. Whilst the incidence in males is greater than in females, the rate of increase was much higher in females, which may reflect increased outdoor recreational and occupational activity. One third of patients had multiple cSCCs and the overall incidence of cSCC was projected to rise dramatically which will require adequate health care resources and should prompt renewed Sun safety campaigns.

Reference: JAMA Dermatol 2020;156(12):1300-06
Abstract

Assessment of incidence rate and risk factors for keratoacanthoma among residents of Queensland, Australia

Authors: Claeson M et al.

Summary: This prospective cohort study from the QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia, quantifies the incidence rate and risk factors for keratoacanthoma (KA) in an Australian population. Analysis was based on data from 40,438 Queensland residents (mean age 56 years) who completed the QSkin Sun and Health study with data linkage to pathological records. With a median follow-up of three years 596 patients (1.5%) developed at least one KA (total of 776 KA tumours). Cox proportional hazards model analysis identified several statistically significant independent risk factors for KC with the highest risk found in older patients (≥ 60 years; hazard ratio [HR] 6.38), those with previous excision of keratinocyte cancers (HR 6.28) and patients with UV radiation-sensitive phenotypes (fair skin, HR 3.42. Inability to tan, HR 1.69). An increased risk was also found in smokers (HR 2.01), patients who consumed ≥ 14 alcoholic drinks per day (HR 1.42) and in males (HR 1.56).

Comment: KA is a rapidly growing tumour closely related to cSCC but which may spontaneously resolve. It can be difficult to distinguish from cSCC and there have been rare reports of metastases. The incidence in Queensland was found to be 409 per 100,000 PY which is 2.5 times higher than a study carried out in 1979. This study used data from the QSkin cohort study to examine risk factors for KA. As with cSCC, male sex and age over 60 years were highly associated with risk as well as fair skin phenotype and a history of sun burn before 10 years of age. Smoking was shown to increase risk which may be related to immunosuppression by nicotine as well as downregulation of the Notch tumour suppressor function due to toxic tobacco components. Alcohol intake was also associated in a dose dependant relationship and the authors postulated that this could be related to the immunosuppressive effect of ethanol as well as the ethanol metabolite acetaldehyde.

Reference: JAMA Dermatol 2020;156(12):1324-32
Abstract

Survival in 31 670 patients with thin melanomas: A Swedish population-based study

Authors: Isaksson K et al.

Summary: In this Swedish Melanoma Registry study Isaksson et al report excellent melanoma-specific survival (MSS) rates for patients with thin tumours (≤ 1 mm). Analysis of a total of 31,670 patients with thin melanomas diagnosed between 1990 and 2017 revealed a 10-year MSS rate of 97% and 20-year rate of 95%. Cox regression analyses showed that above a 0.7 mm tumour depth threshold, survival was inversely related to tumour depth but long-term survival was still favourable. Women had better MSS than men.

Comment: Thin melanomas – those with a Breslow thickness of 1mm or less – have been shown to have an excellent prognosis in previous studies. This examination of the records of over 30,000 thin melanoma cases in Sweden is reassuring. Whilst a similar study at the Melanoma Institute Australia demonstrated a worse prognosis for melanomas greater than or equal to 0.8mm thick this Swedish study found that the prognosis declined above 0.6 mm thickness but was still excellent. The standard follow-up in Sweden is much shorter than here in Australia and the authors suggest that this might be more appropriate and cost-effective.

Reference: Br J Dermatol 2021;184(1):60-7
Abstract

Trends in malignant melanoma mortality in 31 countries from 1985 to 2015

Authors: Yang D et al.

Summary: This report presents melanoma mortality trends between 1985 and 2015 from 31 countries with high usability death registration data in the WHO Mortality Database. Over this 30-year period melanoma mortality increased overall with most of the increase attributed to an increase in the death rate in males. Male patients had an increased mortality rate compared to females in all countries with the exception of the Czech Republic (median for 2013-2015; 2.57 vs 1.55 deaths per 100,000, respectively) with the disparity between sexes increasing over time. The world's highest death rate for males was found in Australia (5.72 per 100,000) and the highest for females was Norway (3.02 per 100,000).

Comment: Melanoma mortality has increased worldwide over the past 30 years but rates differ between countries in the same region as well as between geographical regions. Australia has the highest figures, most likely due to the combination of high ambient UV light levels with a predominantly fair skinned population. Norway and Slovenia have surprisingly high melanoma incidence and mortality. South East Asian countries have the lowest melanoma mortality rates. Males continue to be affected more than females and whilst melanoma mortality is continuing to increase in older age groups there are signs that it is declining in younger cohorts. Countries that have implemented sun safety campaigns have seen a decline in melanoma mortality and in Australia there has been a decline in mortality in females and a flattening in males. Recent mortality would be expected to be improved due to the use of new immunotherapy and targeted therapies but these are still not subsidised in many countries which may cause further disparities between countries and regions.

Reference: Br J Dermatol 2020;183(6):1056-64
Abstract

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.

LIBTAYO® (cemiplimab)

NEW treatment option for advanced cutaneous squamous cell carcinoma (CSCC)[1]

Candidates for LIBTAYO[1]

Metastatic CSCC[1]

- Nodal metastasis
- Distant metastasis

Locally advanced CSCC[1]

- Locally advanced CSCC patients who are not candidates for curative surgery or curative radiation

In a Phase II study, LIBTAYO demonstrated substantial clinical activity in patients with advanced CSCC[1]

Response rates[*†]
Primary end point ORR, with an ORR of 49.2% for the group with the longest duration of follow up (Group 1)[1]

Time to response
Median time to response was at the first assessment for Groups 1-3 (time of first assessment was 8 or 9 weeks, depending on dosing group)[1]

Duration of response[*]
Median duration of response was not reached for Groups 1-3[1]

*Data cut-off was Sep 20, 2018 for Groups 1 and 3 patients, and Oct 10, 2018 for Group 2 patients.[1]

†Median duration of follow up for Group 1: 16.8 months (mCSCC), Group 2: 9.3 months (laCSCC), Group 3: 8.1 months (mCSCC)[1]

Demonstrated acceptable risk/benefit profile with LIBTAYO[1]

LIBTAYO demonstrated an acceptable risk/benefit profile in clinical studies of 591 patients with advanced solid malignancies, including 219 advanced CSCC patients who received LIBTAYO monotherapy.[1]

Contact the oncology team at Sanofi Genzyme to find out more: LibtayoCSCC.AU@sanofi.com

PBS Information: This product is not listed on the PBS

Please review full Product Information before prescribing. Full Product Information is available here, or by contacting Sanofi Medical Information on 1800 818 806.

▼This medicinal product is subject to additional monitoring in Australia due to provisional approval. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

Abbreviations: CSCC, Cutaneous Squamous Cell Carcinoma; **ORR,** overall response rate.

References: 1. LIBTAYO® (cemiplimab) Approved Product Information. July 2020.

Sanofi and Regeneron are collaborating in the global development and commercialisation for LIBTAYO (cemiplimab).

SANOFI GENZYME

Clinical benefit of baseline imaging in Merkel cell carcinoma: Analysis of 584 patients

Authors: Singh N et al.

Summary: This retrospective study found that baseline imaging in patients with clinically node-negative MCC resulted in upstaging in 13% of cases, suggesting that guidelines should be updated to recommend baseline imaging, preferably positron emission tomography–computed tomography (PET-CT) in this population. A total of 584 patients with newly diagnosed disease ± palpable nodal involvement underwent baseline combined PET-CT or PET imaging. Disease was upstaged following imaging in 13.2% of patients whose clinical signs indicated no regional node involvement and 10.8% of patients with clinically involved regional nodes. Primary tumours of any size were upstaged by imaging (>4 cm, 29.4% upstaged after imaging. < 1cm, 7.8%). Baseline PET-CT imaging performed significantly better than CT imaging for upstaging identification (16.8% vs 6.9%; p=0.0006). The estimated positive predictive value of imaging was 88.6%.

Comment: MCC is known to be an aggressive tumour but recommendations on baseline imaging have been mostly based on those for melanoma. Melanoma imaging in clinically localised disease reveals spread in less than 1% of cases and the risk of harm due to further management of false positives outweighs any benefit. In this study, 13.2% of patients with clinically localised MCC were upstaged after imaging. Tumours on the trunk and larger tumours were more likely to be associated with radiological evidence of spread but this was also seen in small tumours. In patients with clinically palpable lymph nodes imaging detected distant spread in 10.8% of patients. The optimum imaging was PET-CT scanning. Patients without clinical evidence of spread who underwent Sentinel lymph node biopsy had a positive result in 30.6% of cases which would appear to support the current practice of early wide-field radiotherapy to the site of the lesion, in-transit sites and the draining nodes.

Reference: J Am Acad Dermatol 2021;84(2):330-9
Abstract

Narrow excision margins are appropriate for Merkel cell carcinoma when combined with adjuvant radiation: Analysis of 188 cases of localized disease and proposed management algorithm

Authors: Tarabadkar E et al.

Summary: Tarabadkar et al conducted a retrospective analysis of the impact of margin size in patients with MCC without clinical nodal involvement. Rates of local recurrence were compared in a cohort of patients who received either surgery plus adjuvant radiotherapy (n=140) or surgery alone. Patients who underwent adjuvant radiotherapy had excellent local control regardless of surgical excision margin (≤ 1 cm vs > 1 cm margins; each 1% local recurrence) despite having higher risk tumours compared to the patient group undergoing surgery alone (15% vs 1%; p=0.001). In the surgery only group, surgical margins of > 1 cm resulted in significantly lower incidence of local recurrence (0% vs 20%; p=0.049). The authors suggest an algorithm to balance local control and morbidity in this population.

Comment: MCC is a highly radiosensitive malignancy and adjuvant radiotherapy is often recommended. Wide margins are recommended but the latest National Comprehensive Cancer Network guidelines recommend excision with smaller margins if flap/graft surgery would delay planned adjuvant radiotherapy treatment. Head and neck tumours are often excised with smaller margins due to their location but if adjuvant radiotherapy is used a local recurrence rate of 25% can be reduced to 5% in tumours where the initial excision margin was less than 1 cm. Since in this study 89% of local recurrences were on the head and neck, it is vital to consider adjuvant radiotherapy in this patient group. Margin size does not appear to be important when adjuvant radiotherapy is used. This should reduce the need for potentially disfiguring surgery in head and neck sites.

Reference: J Am Acad Dermatol 2021;84(2):340-7
Abstract

Sclerodermiform basal cell carcinomas vs. other histotypes: Analysis of specific demographic, clinical and dermatoscopic features

Authors: Conforti C et al.

Summary: This study characterises the sclerodermiform variant of basal cell carcinoma (BCC) to allow differentiation from the less aggressive superficial and nodular clinical variants. Analysis was based on clinical and dermoscopic images of a total of 291 histopathologically proven BCCs. Nodular BCCs were more commonly located on the trunk and limbs than the head and neck and were defined by the presence of three dermoscopic features: classical arborising vessels, multiple blue-grey dots and globules. Sclerodermiform BCCs were characterised by amelanotic hypopigmented plaques and the presence of arborizing and fine superficial telangiectasia.

Comment: Sclerodermiform (morpheiform) BCCs present a challenge due to their increased risk of recurrence and their subtle features which often leads to delayed diagnosis. It is a slow-growing skin-coloured plaque and only shows vascular patterns when advanced. This study from Austria, Italy and Australia (Perth and Brisbane) examined the clinical and dermatoscopic features of sclerodermiform BCC. The most frequently affected area was the nose, followed by the cheek and periauricular zones – the H and M zones - which are known to be more prone to recurrence. The edges of sclerodermiform BCCs were poorly defined which is another risk factor for local recurrence. Dermatoscopy shows short fine arborizing vessels, white/pink areas representing dermal fibrosis and ulceration may be seen especially with head/neck lesions.

Reference: J Eur Acad Dermatol Venereol 2021;35(1):79-87
Abstract

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