Skin Cancer Research Review™

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In this issue:

Abbreviations used in this issue:

MSM = melanoma-specific survival; **PD-1** = programmed cell death protein 1; **PDT** = photodynamic therapy; **SCC** = squamous cell carcinoma; **SLNB** = sentinel lymph node biopsy; **TPFM** = two-photon fluorescence microscopy.

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Welcome to the latest issue of Skin Cancer Research Review.

Clinical management of resectable stage 2-4 cutaneous squamous cell carcinoma (SCC) may be transformed by the findings from an international Regeneron Pharmaceuticals trial that neoadjuvant immunotherapy with the anti- programmed cell death protein 1 (PD-1) antibody cemiplimab elicits deep pathologic responses in a high proportion of patients. Data was published in a September issue of *The New England Journal of Medicine* and longer-term results, secondary outcome measures including overall survival and disease-free survival, as well as delineation of a patient population that will derive the most benefit and definition of those who can avoid surgery altogether are eagerly awaited. Research from the University of Rochester in the US may render the longstanding process for nonmelanoma skin cancer diagnosis, whereby biopsy samples undergo several steps of processing and are sent away for pathological examination, obsolete, reporting a high diagnostic accuracy for two-photon fluorescence microscopy (TPFM) examination of unprocessed, fresh tissue samples. The technology could potentially provide an almost instantaneous diagnosis and enable treatment commencement in the same visit. Finally, long-term results from the International Multicentre Selective Lymphadenectomy Trial II find a high rate of definitive lymph node basin disease clearance by sentinel lymph node biopsy (SLNB) without complete lymph node dissection in patients with cutaneous melanoma, confirming that it has therapeutic, as well as prognostic, value in this setting.

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

Kind Regards,

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Therapeutic value of sentinel lymph node biopsy in patients with melanoma. A randomised clinical trial

Authors: Multicentre Selective Lymphadenectomy Trials Study Group

Summary: The International Multicentre Selective Lymphadenectomy Trial II (MSLT-II; NCT00297895) established that melanoma-specific survival (MSS) was not improved by the addition of complete lymph node dissection after sentinel lymph node biopsy (SLNB; sentinel lymphadenectomy) in adult patients with cutaneous intermediate-thickness melanomas (Faries M et al. *N Engl J Med* 2017 8;376[23]:2211-22). In this *JAMA Surgery* report the group provides long-term 10-year results regarding regional lymph node basin control from the cohort who received nodal ultrasound observation (n=823; median age 52.8 years). Nodal recurrence at 10-years after a positive biopsy was observed in approximately one-fifth of this cohort, corresponding to a lymph node basin disease-free survival rate of 80.2%. Favourable factors associated with reduced risk of nodal basin disease recurrence included younger age, thinner primary melanoma, axillary basin and smaller sentinel lymph node metastasis (diameter < 1 mm and area < 5%), all of which conferred an approximate halved risk of nodal basin recurrence on multivariable analysis (hazard ratio [HR] range, 0.40-0.58). The high rate of long-term definitive basin disease clearance elicited by the less invasive sentinel biopsy procedure confirmed its therapeutic value in this setting.

Comment: Following the completion of the two Multicentre Selective Lymphadenectomy Trials, it was concluded that there was no survival benefit from complete lymph node dissection in patients found to have a positive SLNB. The main benefit of SLNB was that it acts as a prognostic marker which upstages positive patients from stage 2 to stage 3 and so can be used to select higher risk patients for targeted or immunotherapy. In this paper the authors looked at the long-term effect on disease control in the regional lymph node basin in patients who were found to have a positive SLNB but did not have complete lymph node dissection and were followed up instead with ultrasonography. The majority, over 80%, remained free of regional lymph node recurrence and several risk factors were identified that were linked to a higher risk of recurrence: age over 50 years, ulceration, Breslow thickness greater than 3.5mm, non-axillary node basin and larger lymph node metastasis size. The authors suggest that rather than being merely a prognostic marker, SLNB has a therapeutic role resulting in improved regional lymph node disease control.

Reference: JAMA Surg 2022;157(9):835-42
Abstract

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Real-time analysis of skin biopsy specimens with 2-photon fluorescence microscopy

Authors: Ching-Roa V et al.

Summary: Two-photon fluorescence microscopy (TPFM) may transform nonmelanoma skin cancer diagnosis, enabling almost instant, same-visit examination and treatment and eliminating the need for, and delays associated with, conventional histologic processing as reported in *JAMA Dermatology* by a group from the University of Rochester in the US. In their pilot comparative effectiveness study, the researchers obtained shave, curettage or punch biopsy samples of residual nonmelanoma skin tumours from 27 patients scheduled to undergo Mohs micrographic surgery at the University of Rochester Medical Centre. Tumour samples were stained with acridine orange and sulforhodamine 101 and digital images of the en face cut surface acquired by automated strip imaging with a clinical TPF microscope with a 1040 nm laser employing 518-558 nm and 620-680 nm fluorescence bands to visualise the two stains. All tumour samples were subsequently formalin fixed, paraffinized, sectioned, haematoxylin-eosin stained and imaged as per usual histologic protocol to obtain matched sets of TPFM/histology images. A dermatopathologist was trained on one set of matched images (n=12) and performed a masked evaluation on 15 TPFM images to determine key histological characteristics and diagnosis. The authors noted that although depth of imaging is superior to other techniques it is still limited to roughly 100 µm but specimens can be further dissected to allow examination of internal tissue. Furthermore, sample integrity is maintained allowing subsequent histology or immunohistochemistry analysis, requires minimal operator training and can be done in a couple of minutes. A high accuracy for the diagnosis of both basal cell carcinoma and SCC was demonstrated by the TPFM technique with sensitivities of 100% and 89%, respectively and perfect specificity for both skin cancer type. This research group are further evaluating the diagnostic performance of TPFM for skin cancer in a real-world clinical setting (planned patient accrual 200) and as a real-time virtual video guide for surgical excision of both skin and other cancer types.

Comment: TPFM is an interesting new method for analysing fresh tissue. A DNA stain is used which rapidly permeates the tissue and then can be stimulated to emit fluorescence simulating haematoxylin/eosin staining. The advantage over other rapid alternatives to traditional paraffin slides is its ability to allow deeper examination into tissue without destruction or loss of accuracy. A series of shave and punch biopsy specimens were examined immediately after being taken with TPFM and the samples were then sent for histological examination. TPFM was able to diagnose both basal and SCC with similar accuracy to traditional testing but the preparation time was only two minutes and so offers a promising method for point-of-care diagnosis.

Reference: JAMA Dermatol 2022;7 Sept [Epub ahead of print]
Abstract

Does the morphology of cutaneous melanoma help to explain the international differences in survival? Results from 1578482 adults diagnosed during 2000–2014 in 59 countries (CONCORD-3)

Authors: Di Carlo V et al., on behalf of the CONCORD Working Group

Summary: In order to elucidate what proportion of disparity in global primary invasive cutaneous melanoma survival (>30% discrepancy between Australia/USA/New Zealand and Nordic nationals versus most Asian; five-year net survival ≥90% vs <60%) is attributable to disease subtypes Di Carlo et al analysed data up to 2014 from the third iteration of the CONCORD programme for the global surveillance of cancer survival (CONCORD-3). The relative prevalence and five-year age-adjusted mortality rates were assessed in almost 1.6 million adults from 59 countries (Central and South America, nine countries, North America, two countries; Asia, 13 countries; Oceania, two countries; Europe, 28 countries; Africa, four countries) according to seven melanoma morphological categories – malignant not otherwise specified superficial spreading, lentigo maligna, nodular, acral, desmoplastic and other. The most common histological subtypes globally were malignant not otherwise specified and superficial spreading, accounting for 42% and 36% of cases globally. Nodular morphology universally conferred the worst prognosis with age-standardised five-year net survival rates ranging from 58% to 80%. Acral lentiginous, also an aggressive subtype with a poor prognosis, had a more than five-fold increased prevalence in Asia and South/Central America compared to Oceanic, North American and European countries (>10% vs <2%) and a particularly poor five-year survival was noted in Taiwan (58% vs >95%). The excess mortality risk associated with nodal and acral lentiginous melanoma subtypes was only partly attributable to sex, age and stage at diagnosis with morphology alone conferring a between two- and 14-fold increased risk of death compared to superficial spreading subtype on multivariable analysis. These findings may have clinical implications for differential treatment strategies according to morphology.

Comment: Survival rates for invasive melanoma differ across the world and even between neighbouring countries. Factors affecting mortality include stage at diagnosis and access to healthcare but this study examined melanoma subtype as a risk factor. As has been seen before, nodular melanoma and acral lentiginous melanoma subtypes are found to have a worse prognosis, independent of stage at diagnosis. In Asian and African regions, the proportion of acral lentiginous melanomas is higher and this results in an overall poorer melanoma prognosis. Early diagnosis is still a major factor for survival and this can be seen in Australia and North America where the mortality for nodular and acral lentiginous melanoma is better than elsewhere in the world but still worse than other melanoma subtypes.

Reference: Br J Dermatol 2022;187(3):364-80
Abstract

Dermoscopic features of eyelid margin tumours: A single-centre retrospective study

Authors: Jaworska K et al.

Summary: Karolina Jaworska and colleagues from the Medical University of Gdańsk in Poland provide a characterisation of eyelid margin tumour appearance based on a retrospective evaluation of consecutive cases seen through their Department of Dermatology, Venereology and Allergology over a four-and-a-half-year period (June 2016 to Dec 2020). Malignant versus benign non-melanocytic, but not melanocytic, lesions were able to be differentiated by dermoscopic evaluation, with distinguishable features including eyelash growth changes, structureless pink areas, starry milia-like cysts and perpendicular vessels. Basal cell carcinoma tumours commonly had ulceration, and perpendicular vessels inter alia signs. The authors reported difficulty distinguishing between blue nevus, haemangioma or pigmented hidrocystoma when the sole dermoscopic feature was blue structureless areas.

Comment: Tumours at the eyelid margin represent a "special site" due to the junction from skin to mucosa and the very thin skin tissue. It is also a difficult area to assess with dermatoscopy and few studies have described clues to diagnosis here. The scarcity of good quality eyelid margin dermatoscopic images meant that in a database of 65,100 images there were 50 lesions suitable for assessment. The three main lesions found were hidrocystomas, dermal naevi and basal cell carcinomas. Most basal cell carcinomas, SCC and hidrocystomas – and all melanomas - were located on the lower eyelid. Features of basal cell carcinomas – distinguishing them from dermal naevi – were ulceration, alterations in eyelashes growth (loss of eyelashes), pink and white structureless areas and linear vessels arranged perpendicular to the eyelid margin – as opposed to next to the lesion in other diagnoses. There were only three melanomas to assess but rhomboidal structures were noted and no loss of eyelashes was seen.

Reference: J Dermatol 2022;49(9):851-61
Abstract

Randomised clinical trial of conventional versus indoor daylight photodynamic therapy for treatment of actinic cheilitis

Authors: Arisi M et al.

Summary: Indoor daylight photodynamic therapy (PDT) may be a more tolerable therapeutic alternative to conventional red-light PDT for actinic cheilitis of the lip vermilion, with results from a small Italian randomised trial reporting comparable efficacy. A total of 16 adult patients with histologically confirmed lip vermilion actinic cheilitis who had not received a recent medical or surgical treatment for that indication were enrolled through the Dermatologic Department of the University of Brescia. Sensitising 160 mg methyl aminolevulinate (MAL) cream was applied to all lesions followed by a single irradiation session comprised of either conventional red-light PDT (n=8; waveband, 630 nm; light dose 37 J/cm^2) or indoor daylight PDT with a polychromatic white LED lamp (n=8; waveband, 400-700 nm; light dose 152.3 J/cm^2). The study cohort had a median age of 64 years and was comprised predominantly of female, previously untreated patients. At three-month follow-up both treatments were efficacious, eliciting significant and comparable reductions in the extent and severity of actinic cheilitis lesions (median change in cumulative area, 2.2 vs 2.2 cm2; median improvement in severity, 3 vs 2.5 on a 24-point scale considering dyschromia, atrophy, erythema, dryness, scales/hyperkeratosis, crusts, erosions/fissures and infiltration). Indoor daylight PDT demonstrated non-inferiority to conventional PDT with respect to proportion of responding patients (defined as those achieving at least a 65% decrease in lesion area; 100% vs 87%), but almost ameliorated pain as a treatment side effect (mean patient-reported pain on a 10-point visual analogue scale, 0 vs 4; p<0.0001) and had a trend toward better cosmetic outcome (excellent outcome, 62.5% vs 25%).

Comment: Actinic cheilitis is a common finding on skin examinations in Australia and has a risk of progression to invasive SCC of 10%-30%. Unfortunately, none of our existing treatments - ranging from topical creams to vermilionectomy – are pleasant for the patient. PDT can be very effective and quick to perform but is often very uncomfortable. Daylight PDT has been shown to be better tolerated and equally efficacious as conventional PDT and, in this study, a polychromatic white LED lamp was used as an indoor daylight equivalent light source. As might be predicted from similar studies of actinic keratoses, the daylight/white light illumination was well tolerated and produced the same result. It will be interesting to see if long-term results show an equivalent reduction in invasive SCC since red light is known to penetrate deeper than daylight and I would like to see a study using "painless PDT" with no incubation and a long red-light illumination.

Reference: Dermatol Ther (Heidelb) 2022;12(9):2049-61
Abstract

Sentinel lymph node biopsy in patients with clinical stage IIB/C cutaneous melanoma: A national cohort study

Authors: Straker 3rd R et al.

Summary: The presence of lymph node metastasis from primary cutaneous melanoma significantly reduces disease-specific survival, highlighting how essential SLNB is for risk stratification, as reported in this analysis of the US Surveillance, Epidemiology, and End Results database. Of 8,562 patients with pathologic stage 2B/C melanoma registered in the database over an eight-year period from 2004 to 2011 (representing an era prior to the introduction of adjuvant immunotherapy), 70.3% underwent SLNB. Five-year disease-specific survival overall was almost 30% lower in patients with a positive versus negative SLNB, reducing the survival from almost three-quarters to less than half (47.1% vs 75.5%; p<0.001). This trend of inferior survival with SLNB-positivity was consistent across clinical stages of disease (T3b; 54.2% vs 64.8%; T4a; 55.5% vs 71.6%; T4b; 38.6% vs 60.9%; all p<0.005).

Comment: Thicker primary melanomas and the presence of ulceration are poor prognostic features and with the advent of effective immunotherapies an argument could be made to omit sentinel lymph node biopsy and treat based on these features. In this review of prognosis of thicker and/or ulcerated melanomas without clinical evidence of lymph node or distant spread in the pre-immunotherapy era, SLNB positivity was still shown to offer important prognostic information. SLNB positivity resulted in a 30% reduction in five-year disease-specific survival and this information might help patients decide whether they wish to embark on potentially toxic immunotherapy.

Reference: J Am Acad Dermatol 2022;87(4):754-60
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.

Delays in the surgical treatment of melanoma are associated with worsened overall and melanoma-specific mortality

Authors: Xiong D et al.

Summary: A population-based analysis from the US in *Journal of the American Academy of Dermatology* interrogated the Surveillance, Epidemiology, and End Results database to explicate the impact of surgical delays on survival in patients with stage 1-3 cutaneous melanoma. Cox proportional hazards and Fine-Gray competing risks analyses including over 108 thousand patients revealed that overall delays in surgery exceeding one month deleteriously impacted overall mortality while an adverse impact on melanoma-specific survival (MSM) was not observed until at least a three-month surgical delay. Subgroup analysis according to disease stage found that mortality (both overall and melanoma-specific) was reduced in early-stage (stage 1/2) disease with even relatively short surgical delays (stage 1; overall mortality reduced with delays of one month and MSM by delays of three or more months) whereas no consequence of delayed surgical intervention was found in patients with advanced (stage 3) disease. The authors acknowledged that analysis was limited by lack of adjuvant treatment, disease recurrence or treatment failure data.

Comment: Previous studies have suggested that delays from diagnostic biopsy to definitive excision of melanomas does not lead to increased mortality but this study looked at both overall mortality and MSM and found a strong association between delayed wide excision and mortality. This was most marked in stage 1 melanoma and the effect decreased at higher stages. It is unclear why there was a difference with more advanced disease but it may be that stage 3 and higher disease was treated promptly with immunotherapy, which reduced mortality in this group. The take home message was that stage 1 melanoma should be excised with appropriate margins within a month of biopsy and that factors suggesting a more aggressive lesion such as increased Breslow thickness and ulceration should prompt early definitive treatment.

Reference: J Am Acad Dermatol 2022;87(4):807-14
Abstract

Neoadjuvant cemiplimab for stage II to IV cutaneous squamous cell carcinoma

Authors: Gross N et al.

Summary: Neoadjuvant cemiplimab treatment elicits deep pathologic responses with complete or almost complete eradication of tumour cells in almost two-thirds of patients with resectable stage 2-4 cutaneous SCC, according to data from this phase 2 Regeneron Pharmaceuticals/Sanofi sponsored trial (NCT04154943) in *The New England Journal of Medicine*. Adult patients (n=79; median age 73 years; male predominance), mostly with tumours located on the head and neck, with no evidence of metastasis were accrued from sites in the US, Australia and Germany and administered up to four doses of open-label cemiplimab at a dosage of 350 mg every three weeks, followed by curative-intent surgery. With an independently reviewed pathological complete response rate of 51% (n=40/79) the null hypothesis was more than doubled to meet the primary outcome measure and demonstrate efficacy. An additional 10 patients attained a major pathological response for a combined pathologic response rate of 63%. The objective response by radiological assessment was 68%. Serious adverse events of any aetiology were experienced by 18% of patients. The study did not report any novel safety concerns for the anti-PD-1 immunotherapeutic.

Comment: Cemiplimab, an anti-PD-1 monoclonal antibody has been shown to be effective in treating locally advanced and unresectable cutaneous SCC. In this study, neoadjuvant therapy patients with resectable stage 3 and 4 cutaneous SCC were treated with four doses of cemiplimab over a 12-week period prior to surgery. Histology of the resected specimens showed 51% with complete response and a further 11% with a major response to immunotherapy. In melanoma studies a major histopathological response to immunotherapy is associated with a high incidence of disease-free survival after surgery and hopefully this will be the case for cutaneous SCC too. There were four deaths out of 79 patients, one of which appeared linked to therapy, all of them due to cardiac disease in very elderly patients suggesting that pre-treatment screening is important.

Reference: N Engl J Med 2022; Sep 12 [Epub ahead of print]
Abstract

Microbiology of surgical site infections (SSIs) following skin cancer surgery

Authors: Goh M et al.

Summary: This report from the Auckland Regional Plastic & Reconstructive Surgery Unit in New Zealand identified the bacterial cause of infection after skin cancer surgery over a six-month period at a regional skin cancer treatment centre to delineate whether empiric treatment guidelines are reasonable in this setting. Approximately one-third of lesions included in the study (n=104/333) had a clinically significant infection within three weeks of surgery of which 27% were cultured. Although methicillin-susceptible *Staphylococcus aureus* was the principal cause of post-operative surgical site infections, cultured in 79% of samples, methicillin-resistant *Staphylococcus aureus* was found in 14% of cases and was not considered in guideline treatment. The authors stated that guidelines may need to be amended to included treatment suited to methicillin-resistant organisms.

Comment: Information on surgical site infections is based on a wide range of surgery including major abdominal, cardiac, orthopaedic and gynaecological. In this paper in a major skin cancer surgical centre in New Zealand the vast majority of wound infections were caused by non-methicillin-resistant *Staphylococcus aureus* with a small percentage of methicillin-resistant. Most of the infected cases were in head and neck surgery which probably reflects the higher burden of skin cancer in this anatomical region rather than a propensity for infection and current antibiotic treatment guidelines appear appropriate for the flora detected. All methicillin-susceptible infections were sensitive to co-trimoxazole.

Reference: ANZ J Surg 2022;92(9):2269-73
Abstract

Reporting of melanoma cell densities in the sentinel node refines outcome prediction

Authors: Ulmer A et al

Summary: This prospective study from a group at the University of Tübingen in Germany examined whether quantification of melanoma cell densities in the sentinel node of patients with cutaneous melanoma improves prognostication granularity. In a sample of 900 sentinel nodes examined by immunocytology to gauge melanoma cell density (number of HMB45 positive cells per million lymphocytes with at least one cell showing morphological features of a melanoma cell) and by semiquantitative histopathology, the rate of sentinel lymph node positivity was doubled with immunocytology (24% vs 12%). Approximately one-quarter of samples with discordant immunocytology/histopathology results were subsequently confirmed as positive. Multivariable analysis and random forest modelling with a median follow-up of three years confirmed melanoma cell density in sentinel nodes as independently associated with inferior MSS. Thickness of primary tumour and ulceration status were also identified as impacting MSS. It was concluded that melanoma cell density in sentinel lymph nodes predicts melanoma outcome with greater accuracy than semiquantitative histopathology.

Comment: Sentinel lymph node biopsies are used to provide optimal staging and prognostic information and guide the necessity for further potentially toxic therapy. The size of the melanoma deposit has been shown to be useful as an indicator of the likelihood of involvement of non-sentinel nodes. An alternative method for assessing node positivity is to create a suspension of lymph node cells, stain them with a melanoma-specific immunostain (HMB45) and create slides of the cell suspension. Using this second technique the disseminated cancer cell density (DCCD) in the sentinel node can be calculated. The ability to detect melanoma node metastases was greatly increased using this quantitative cell suspension immunocytology method. The main independent prognostic indicators were found to be melanoma cell density, primary tumour ulceration and Breslow thickness.

Reference: Eur J Cancer 2022;174:121-30
Abstract