Melanoma Research Review™

Making Education Easy

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Abbreviations used in this issue:

AI = artificial intelligence; **AJCC** = American Joint Committee on Cancer; **AUC** = area under the receiver-operating characteristic curve; **CI** = confidence interval; **HR** = hazard ratio; **OR** = odds ratio; **OS** = overall survival; **PD-1** = programmed cell death 1.

Welcome to the 54th issue of Melanoma Research Review

Findings from a Dutch study suggest that while frailty is unrelated to the occurrence of severe immune-related adverse events in older patients with melanoma receiving immune checkpoint inhibitor therapy, it is an indicator of immune-related adverse event-related adverse sequelae, such as hospital admission. The multinational CONCORD-3 study confirmed a disproportionately higher incidence of aggressive subtypes, acral lentiginous and nodular melanoma in darker skinned populations. Other topics covered in this issue include the prognosis of melanoma patients with positive sentinel node biopsy, predictors of germline status for hereditary melanoma, increasing Breslow thickness and decreasing survival, the validity of skin self-examination for detection of suspicious pigmented lesions, and convolutional neural network prediction of melanoma within 5 years.

I hope you find the research in this issue useful to you in your practice and I look forward to your comments and feedback.

Kind Regards,

Professor Michael Henderson
michael.henderson@researchreview.com.au

The role of sentinel node tumor burden in modeling the prognosis of melanoma patients with positive sentinel node biopsy: An Italian melanoma intergroup study (N = 2,086)

Authors: Tropea S et al

Summary: This Italian multicentre, retrospective cohort study assessed outcomes in 2086 patients treated with completion lymph node dissection (CLND) after a positive sentinel node biopsy. Overall survival (OS) rates were 79% at 3 years, 70% at 5 years and 54% at 10 years. Multivariate analysis suggested that older age ($p < 0.0001$), male gender ($p = 0.04$), increasing Breslow thickness ($p < 0.0001$), presence of ulceration ($p = 0.004$), sentinel node tumour burden (SNTB) size ($p < 0.0001$) and metastatic non-sentinel lymph nodes (NSN; $p < 0.0001$) independently predicted OS and were incorporated into a nomogram to improve treatment personalisation.

Comment: Although the issue of completion lymphadenectomy should have been settled by the results of the Multicenter Selective Lymphadenectomy Trial II (MSLT-II) and German Dermatologic Cooperative Oncology Group (DeCOG) study, some reservations remain. This study was a retrospective, multicentre review of 2086 patients from 13 Italian centres who underwent completion lymphadenectomy for a positive sentinel node in the era prior to routine adjuvant therapy, although some patients received interferon. 22% of patients had non-sentinel nodes identified in the completion lymphadenectomy. Tumour burden in the sentinel node stratified by size of the deposit (0.01-0.4, 0.41-0.96, 0.97-3, 3.1-35 mm) was strongly associated with outcome. The authors concede lymphadenectomy offers no survival advantage but argue it provides a greater chance of regional control (but presumably only in the 22% of patients with NSN) and may assist in identifying patients for adjuvant therapy. They created a nomogram to predict outcome based on the results of a multivariate analysis which identified older age, male sex, tumour thickness, ulceration, non-sentinel nodes and tumour burden. This is an interesting study that confirms the significance of SNTB but does not support a role for completion lymphadenectomy in patients with a positive sentinel node.

Reference: BMC Cancer 2022;22(1):610
Abstract

Predictors of germline status for hereditary melanoma: 5 years of multi-gene panel testing within the Italian Melanoma Intergroup

Authors: Bruno W et al.

Summary: Another Italian, multicentre, prospective cohort study was conducted to identify predictors of susceptibility variants for high-risk melanoma in 1044 family members with germline sequencing of 940 cutaneous melanoma index cases through a gene panel including *CDKN2A*, *CDK4*, *BAP1*, *POT1*, *ACD*, *TERF2IP*, *MITF* and *ATM* genes. Overall detection rate was 9.47% (5.53% for *CDKN2A*), with up to 13.9% in familial cases with at least 3 members. Germline status was predicted by ≥3 cutaneous melanomas in sporadic multiple melanoma cases (OR 3.23; $p < 0.05$), pancreatic cancer (OR 3.15; $p < 0.05$) and the region of origin (OR 2.43; $p < 0.05$); age >60 years was a negative predictor (OR 0.13; $p = 0.008$), and had the lowest detection rate, especially for *CDKN2A*. The detection rate was 19% for clustering of cutaneous melanoma and pancreatic cancer.

Comment: The primary purpose of this Italian study was to refine criteria for genetic testing in patients with a family history of melanoma (at least two affected family members). The commonest mutation, *CDKN2A* confers at least a 30-fold increase in the risk of developing melanoma. The significance of this study is that in addition to *CDKN2A*, other possible pathogenic variants including *CDK4*, *BAP1*, *POT1*, *ACD*, *TERF2IP*, *MITF* and *ATM* were also investigated. Mutations in the latter group accounted for approximately half of the pathogenic variants. Factors associated with development of melanoma included increasing number and age (lower) of affected family members and history of pancreatic cancer. A comparable large study in an Australian population did not identify a specific family history of pancreatic cancer as associated with a mutation in *CDKN2A*, rather a family history of any malignancy (Holland EA et al., 2021). These findings are included in the current Australian ACN guidelines (available here)

Reference: ESMO Open 2022;7(4):100525
Abstract

Frailty and checkpoint inhibitor toxicity in older patients with melanoma

Authors: Bruijnen CP et al.

Summary: This Dutch study assessed whether immune-related adverse events and sequelae were more common in 26 frail versus 66 fit patients (based on the Geriatric 8 assessment) with melanoma aged ≥70 years receiving immune checkpoint inhibitors (ICIs). Grade ≥3 immune-related adverse events (irAEs) were reported in 20% of patients, with no significant difference between fit and frail patients (17% vs 27%). More frail patients were admitted to hospital because of irAEs (54% vs 29%; $p = 0.02$), had a trend for increased length of hospitalisation (8 vs 5 days; $p = 0.06$), and more frequent immunosuppressant use or ICI discontinuation (58% vs 36%; $p = 0.06$), compared with fit patients.

Comment: This was a prospective study of patients aged over 70 years of age commencing anti-PD-1 therapy for AJCC stage 3 or 4 disease. Patients were evaluated using the Geriatric 8 tool, a validated geriatric assessment tool for assessing elderly patients with cancer. Most patients were regarded as fit (71%). 20% of patients developed grade ≥3 irAEs, which is similar to what has previously been described in cohorts treating younger patients. No difference in the frequency or severity of irAEs was found between the fit and frail patients nor was there any difference in the use of steroids or cessation of therapy. The frail patients were more likely to present to the hospital emergency department with symptomatic irAEs (not statistically significant). The problem with this study is selection bias, in that the unfit patients were considered fit for single-agent anti PD-1 therapy in the first place, but amongst that group this study confirms the safety and appropriateness of treating these patients.

Reference: Cancer 2022;128(14):2746-2752
Abstract

Does the morphology of cutaneous melanoma help explain the international differences in survival? Results from 1,578,482 adults diagnosed during 2000-2014 in 59 countries (CONCORD-3)

Authors: Di Carlo V et al.

Summary: This analysis of data from the multinational CONCORD-3 study assessed whether differences in morphology might explain wide disparities in 5-year net survival. Nodular melanoma rates ranged from 7-13% around the globe, while acral lentiginous melanoma accounted for <2% of cases but was more common in Asia (6%) and Central and South America (7%). Superficial spreading melanoma comprised 36% of tumours. Over the period 2010-14, age-standardised 5-year net survival for superficial spreading melanoma was ≥95% in Oceania, North America and European countries, but was only 71% in Taiwan. Acral lentiginous melanoma survival rates ranged from 66% to 95%, while nodular melanoma had poor outcomes everywhere. Multivariate analysis found that sex, age and stage at diagnosis partially explained the higher risk for nodular and acral lentiginous subtypes that are more common in Asia and Latin America.

Comment: The aim of the study was to investigate whether the histological subtype accounted for the international variation in outcome seen in patients with melanoma. The study sample was enormous (over 1.5 million) and was undertaken on a background that histological subtype is not regarded as a significant prognostic factor (e.g., AJCC staging system, 8th edition). This study confirmed a disproportionately higher incidence of aggressive subtypes, acral lentiginous and nodular melanoma in darker skinned populations. Even allowing for factors such as age, sex and primary tumour characteristics, these two subtypes were independently associated with poorer survival. One of the major limitations of the study probably reflecting the ambivalence about the prognostic significance of subtypes was the very high rate of diagnosis of malignant melanoma, not otherwise specified. Australian and New Zealand like most North American and European countries had high rates of superficial spreading melanoma, but the incidence of nodular melanoma appeared to be lower in Australia and New Zealand while the rates of lentigo maligna melanoma were slightly higher. The highest rates of nodular melanoma with the poorest survival were seen in Asia and Latin America.

Reference: Br J Dermatol. 2022;Mar 29 [Epub ahead of print]
Abstract

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The progressive relationship between increasing Breslow thickness and decreasing survival is lost in patients with ultrathick melanomas (≥15 mm in thickness)

Authors: El Sharouni MA

Summary: This multinational retrospective (2000-14) study examined survival in 5595 patients with melanomas ≥4.0 mm in Breslow thickness, over a median follow-up of 3.4 years. Continuous HRs for OS and recurrence-free survival (RFS) increased with Breslow thickness up to 15 mm, stabilised up to 20 mm, and then decreased. Using melanomas 4-10 mm as a reference, the categoric OS HR increased for 10-15 mm (HR 1.46; 95% CI 1.29-1.66; $p < 0.0001$), and 15-20 mm (HR 1.97; 95% CI; 1.55-2.51; $p < 0.0001$) and then decreased at ≥20 mm (HR 1.36; 95% CI 1.07-1.84; $p = 0.045$ for). Similar results were observed for RFS.

Comment: Survival rates typically decrease with increasing thickness of the primary tumour. Approximately 5-7% of patients present with T4 (>4 mm) melanomas of whom the majority have lesions <10 mm. In this study the majority of the patients were male, had nodular melanomas that were commonly ulcerated with a sentinel node biopsy positive rate of 37%. Overall, there was only slightly poorer OS and RFS for melanomas 4-10, 10-15 and 15-20 mm thick. The small group of patients with melanomas thicker than 20 mm had OS equivalent to the 4-10 mm thick group of patients. This is the largest study to date of thick melanomas and supports previous reports. The reasons for this anomaly are not understood but the authors reported possibly more favourable histology and desmoplastic subtype, which tend to have a more favourable prognosis in patients with the thickest melanomas.

Reference: Am Acad Dermatol. 2022;87(2):298-305
Abstract

Defining the validity of skin self-examination as a screening test for the detection of suspicious pigmented lesions: A meta-analysis of diagnostic test accuracy

Authors: Jiyad Z et al.

Summary: This systematic review and meta-analysis analysed pooled estimates of skin self-examination diagnostic accuracy for detection of suspicious pigmented lesions based on 3 studies (all at risk of bias) including 553 participants. Pooled sensitivity was 59% and pooled specificity was 82%. Summary diagnostic odds ratio was 5.88 and the area under the curve (AUC) was 0.71.

Comment: While the general consensus that population-based screening is not justified (most likely due to over-diagnosis of clinically irrelevant lesions with no effect on population mortality) other strategies to reduce the burden of melanoma including targeted screening, social media, diagnostic apps and recommendations for skin self-examination are of considerable interest. This study was a meta-analysis based on only 3 studies (533 subjects) from 757 possible studies which evaluated the effectiveness of skin self-examination. The sensitivity and specificity (59% and 82%) are reasonable compared with other cancer screening tests e.g., mammography. On the face of it, this report would support adoption of skin self-examination to reduce mortality; however, as the authors point out, further evaluation is necessary. Apart from the stress of a potential diagnosis and the need for intervention, there remains the ongoing debate about over diagnosis and the significance of potentially clinically insignificant disease. They recommend additional studies in high- and low-risk groups as well as strategies for educating patients, thereby maximising the benefit of the intervention (and minimising harm).

Reference: Dermatology 2022;238(4):640-648
Abstract

Validation of a market-approved artificial intelligence mobile health app for skin cancer screening: A prospective multicenter diagnostic accuracy study

Authors: Sangers T et al.

Summary: This prospective multicentre study examined the diagnostic accuracy of a mobile health app (SkinVision) integrated with a convolutional neural network for identification of 785 premalignant and malignant skin lesions (including 418 suspicious and 367 benign control lesions; 372 patients; 50.8% women; median age 71 years). Overall sensitivity was 86.9% (95% CI 82.3-90.7) and specificity was 70.4% (95% CI 66.2-74.3). Specificity based on benign control lesions was higher than suspicious skin lesions (80.1 vs 45.5%; $p < 0.001$), while sensitivity was higher in skinfold areas versus smooth skin areas (92.9 vs. 84.2%; $p = 0.01$), and specificity was higher in smooth skin areas (72.0 vs 56.6%; $p = 0.02$). Sensitivity was higher when tested on iOS versus Android devices (91.0 vs 83.0%; $p = 0.02$).

Comment: The role of artificial intelligence in diagnosis of skin lesions is a work under construction. Initial efforts were directed at clinicians but in recent years a number of mobile phone apps have become available. The first of these apps left much to be desired and generated considerable controversy. Nevertheless, advances in deep learning and a more rational approach to development has seen major improvements. This report, the first of a small prospective study of a phone-based app, found reasonable sensitivity and specificity (87% and 70%). The app performed better on iOS than Android operating systems and performed better for non-melanoma skin cancers than pigmented lesions. Unlike previous studies, the current one was more representative of the real-life situation, which may explain the poorer results than seen previously. Given the advances in artificial intelligence it is highly likely that significant improvements in this technology will occur in the near future that will require validation and integration into current practice.

Reference: Dermatology 2022;238(4):649-656
Abstract

Melanoma Research Review™

Independent commentary by Professor Michael Henderson

Michael A Henderson is Professor of surgery at the University of Melbourne and surgeon in the multidisciplinary Melanoma and Skin Service at the Peter MacCallum Cancer Centre in Melbourne. He is a graduate of the University of Melbourne and after obtaining a Fellowship of the Royal Australasian College of Surgeons, spent two and a half years undertaking a fellowship in surgical oncology at the University of Texas MD Anderson Cancer Centre. His clinical practice is confined to surgical oncology. His major clinical interests are in the management of patients with melanoma and maintains an active clinical and translational research interest in melanoma. He led a major international multicentre study of adjuvant radiotherapy after link for melanoma and is currently the principal investigator of a multicentre international trial of margins of excision of intermediate and thick melanoma (MELMART).

Landscape of mutations in early stage primary cutaneous melanoma: An InterMEL study

Authors: Luo L et al.

Summary: This multinational study examined the genomic landscape of early-stage melanomas diagnosed prior to immunological treatments based on stage II/III cutaneous melanomas. Preliminary mutation profiling and clinical pathologic results identified 4 driver mutation sub-types *BRAF* (31%), *NRAS* (18%), *NF1* (21%), and triple wild-type (26%). Patients with *BRAF*-mutant tumours were younger age at diagnosis, with more associated nevi, more tumour infiltrating lymphocytes, and fewer thick tumours that were generally more advanced. *NF1*-mutant tumours were frequently observed on the head and neck in older patients with severe solar elastosis, with thicker tumours in earlier stages. Triple wild-type tumours were predominantly observed in males, frequently on the legs, with more perineural invasion. Mutations in *TERT*, *TP53*, *CDKN2A* and *ARID2* were often observed, with *TP53* mutations particularly frequent in the *NF1* sub-type.

Comment: The Cancer Genome Atlas (TCGA) study of melanoma was the landmark study investigating the genomic landscape of melanoma, but given the need for large specimens it is predominantly based on metastatic and very thick primary tumours. The InterMEL study reported here represents collaborators from the US, Spain and Australia specifically charged with exploring the genomic landscape for early-stage melanoma (stage II-III). 518 patients were investigated using a multi-omic strategy. The 4 driver mutation subtypes were *BRAF*, *NRAS*, *NF1* and triple wild-type. Differences between InterMEL and the TCGA study include a lower proportion of the *BRAF*-mutated tumours and a reciprocal higher incidence in other subtypes. This interim report of this tool for investigating early-stage melanoma confirms its relevance and importance and will provide a platform for ongoing studies.

Reference: Pigment Cell Melanoma Res. 2022;Jul 25 [Epub ahead of print]
Abstract

Ability to predict melanoma within 5 years using registry data and a convolutional neural network: A proof of concept study

Authors: Gillstedt M & Polesie S

Summary: This pilot study examined how accurately a convolutional neural network, trained on data from patients in a Swedish registry, could predict cutaneous invasive and in situ melanoma (CMM) within 5 years. The algorithm was trained on 23,886 individuals, with 6000 patients included in a validation set, and evaluated on a test set of 1000 individuals with CMM occurring within 5 years and 5000 without CMM. The receiver-operating characteristic curve AUC was 0.59 (95% CI 0.57-0.61). The point where AUC sensitivity equalled specificity occurred at a value of 56% (sensitivity 95% CI 53-60; specificity 95% CI 55-58).

Comment: This intriguing study used Swedish population registry data to predict the development of melanoma in the next 5 years with at least moderate success (AUC 0.59). While the relevance of this study for the Australian population must be limited, it highlights the role of large observational studies and the increasing use of artificial intelligence. The significance of the artificial intelligence approach cannot be underestimated given the numbers of persons involved (24,000 controls and 5000 persons with melanoma) and the limited information available within the registry such as place of birth, income, prescribed medications. Further work including expansion of the training and validation sets using a much larger proportion of the Swedish population will be undertaken given the encouraging results seen at this early stage.

Reference: Acta Derm Venereol. 2022;102:adv00750
Abstract