Skin Cancer RESEARCH REVIEW™

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Issue 1 – 2020

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Abbreviations used in this issue
CR = complete response
HR = hazard ratio
NMSC = nonmelanoma skin cancer
OS = overall survival
PD-1/PD-L1 = programmed cell death (ligand)-1
QOL = quality of life
RCT = randomised controlled trial

Welcome to the latest issue of Skin Cancer Research Review.

This winter issue begins with research describing patterns of recurrence and long-term outcomes of surgically managed NMSC among immunosuppressed cardiac and liver transplant recipients. NZ researchers have reported that an e-referral and teledermatoscopy service for suspected melanomas resulted in a reduction in unnecessary excisions of benign lesions. The association between immune-related adverse events and recurrence-free survival has been reported for participants from the EORTC 1325/KEYNOTE-054 trial, which compared pembrolizumab with placebo for high-risk stage III melanoma. This issue concludes with research reporting that CNS metastasis rates were similar between two large, geographically distinct cohorts of patients with stage III melanoma.

We hope you find this update in skin cancer research informative. We look forward to receiving your comments and feedback.

Kind regards,

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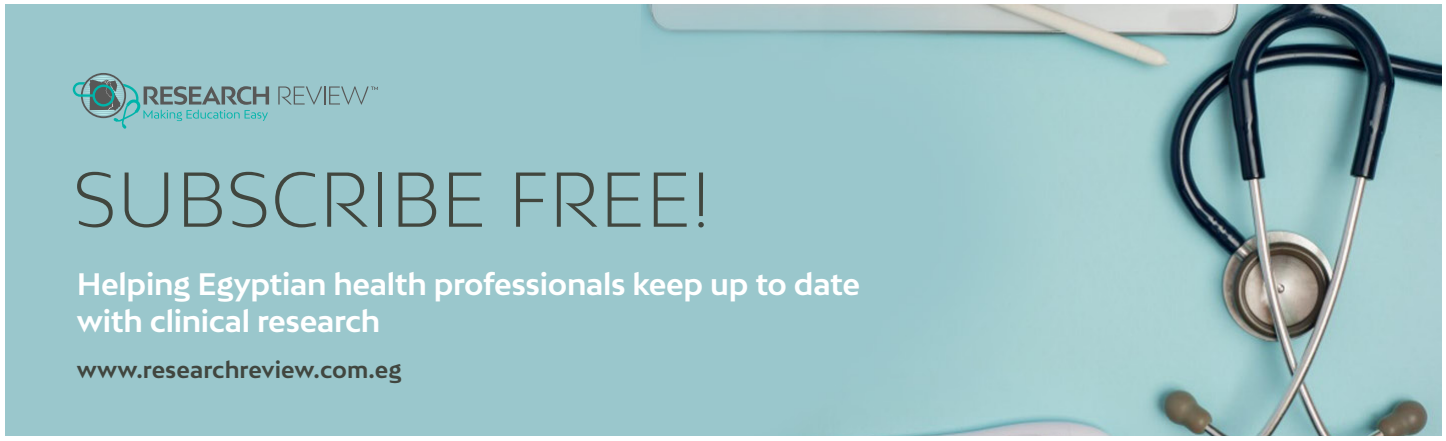
Risk of recurrence and 10-year outcomes in surgically treated nonmelanoma skin cancer in cardiac and liver transplant recipients

Authors: Yu NY et al.

Summary: These researchers reported on patients who had undergone immunosuppressed cardiac (n=138) or liver (n=609) transplantation, focussing on long-term outcomes for 97 who developed 382 invasive NMSCs. Median follow-up for survivors was 11 years, and surgery alone was the primary treatment for the NMSCs. The 10-year local recurrence rate was 20%, with 14% of patients experiencing multiple local recurrences and a higher rate for T3/T4 tumours than for T1/T2 tumours (32.5% vs. 20% [p=0.05]). The 10-year OS rate was 79%, with patients aged ≥61 years having significantly inferior OS (p<0.01).

Comment (JW): Early skin cancer detection and management play a significant role in reducing organ transplant-related morbidity and mortality. This study serves as a reminder of the importance of regular skin surveillance in transplant patients, and highlights the need to treat patients promptly and appropriately. Mohs micrographic surgery and skin excision remain the gold standard in the treatment of T1/T2 tumours. Premalignant lesions such as Bowen's disease and actinic keratosis need to be aggressively treated in this high-risk patient group. Chemopreventive agents such as acitretin or nicotinamide should also be considered early for immunosuppressed transplant recipients with multiple skin cancers.

Reference: Am J Clin Oncol 2020;43:366–70
Abstract



Cutaneous melanoma associated with naevi prevalence

Authors: Scalvenzi M et al.

Summary: This cross-sectional retrospective study on the prevalence and features of naevus-associated melanoma included 1986 melanomas diagnosed and treated at a single skin cancer centre in Italy over 15 years. Histopathological examinations revealed that 8.4% of the melanomas were naevus-associated, with the remainder being *de novo*. Compared with *de novo* melanomas, naevus-associated melanomas were significantly more frequent in younger patients (mean age, 48 vs. 54.3 years [p<0.001]), more often involved the trunk (62.3% vs. 51.8% [p=0.01]) and had higher mean Breslow thickness (0.97 vs. 0.83mm [p<0.001]), but were less likely to be *in situ* melanomas (24.5% vs. 35.2% [p<0.01]) and more likely to be invasive (75.5% vs. 64.8% [p<0.01]).

Comment (JW): In my experience, patients more often present when they detect a change in an existing mole. Yet, as demonstrated in this study, melanomas are more likely to develop *de novo*, accounting for over 90% of melanomas in this study group. When counselling patients on self-monitoring, it is important to stress the need to identify new lesions, in addition to any change in existing lesions. I often advise my patients to take photographs of their own on their smartphone to aid self-monitoring in between skin checks.

Reference: Australas J Dermatol 2020;61:39–42
Abstract

The anatomic distribution of cutaneous melanoma

Authors: Wee E et al.

Summary: Using high-resolution anatomical site data, these researchers reported on the anatomical distribution of 5141 primary cutaneous melanomas (76.2% invasive) and their variation by patient characteristics, subtype and Breslow thickness. The median Breslow thickness of the invasive melanomas was 1.0mm. The most common histopathological subtypes were superficial spreading (57.2%), lentigo maligna (20.8%) and nodular (12.2%). The highest melanoma incidences per unit area were sun-exposed sites (the nose and cheeks for females, the ears for males and the upper back for both sexes). Compared with the posterior forearm, significantly thicker invasive melanomas were seen on the scalp, ear, preauricular, perioral, subungual and plantar sites. The highest incidences of nodular melanomas per unit area were seen in the peri-auricular area, ears and cheeks.

Comment (JW): This study helpfully highlights the areas most at risk of developing melanomas, by gender and age. Although melanomas most commonly affect the trunk in men and legs in women, melanoma incidence per unit area are highest in the sun-exposed facial sites, i.e. ears in men, and nose and cheeks in women. When conducting a skin check, one should not neglect the scalp, subungual and plantar sites, where melanomas can easily be missed unless specifically checked. These sites were associated with the highest Breslow thickness in this study.

Reference: Australas J Dermatol 2020;61:125–33
Abstract

E-referrals and teledermatoscopy grading for melanoma: a successful model of care

Authors: Sunderland M et al.

Summary: These NZ researchers reviewed the efficacy of 3470 skin cancer e-referrals for improving the diagnostic accuracy of melanoma. Of 809 that were categorised as confirmed, likely or suspected melanoma, 28.4% included a histopathology referral confirming melanoma or melanoma *in situ*. Of the remaining 579 referrals, 315 underwent diagnostic excision, of which 53 and 67 were confirmed as melanoma and melanoma *in situ* on histopathology, respectively (positive predictive value, 38.1%; number needed to excise, 2.6). Of 264 melanomas referred for teledermatoscopy, 24 were confirmed as melanoma. Overall, 45.6% of e-referrals were melanoma or melanoma *in situ*, with a melanoma-melanoma *in situ* ratio of 1:1.18.

Comment (JW): With the high and rising incidence of skin cancers, more efficient and effective pathways to triage and manage skin cancer referrals are vital. The e-referral system in this NZ study has demonstrated the value of multidisciplinary teams in the management of skin cancers, with the involvement of general practitioners, oncologists, dermatologists and qualified nurses working as melanographers. Furthermore, it has highlighted the role of public-private partnerships in augmenting NZ's health infrastructure. The positive predictive value of 38.1% and the low number needed to excise of 2.6 are impressive. However, it is important that melanomas are not missed, and it would have been useful if the negative predictive value was studied and reported. The authors have acknowledged this in the paper and are currently working to review a cohort of lesions referred to their service to detect the false-negative or missed melanoma rate.

Reference: Australas J Dermatol 2020;61:147–51
Abstract

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A risk prediction model for the development of subsequent primary melanoma in a population-based cohort

Authors: Cust AE et al.

Summary: A risk prediction model for subsequent primary melanomas was developed using Cox regression frailty models applied to data from 1266 participants from the Australian Genes, Environment and Melanoma study who had 2613 primary melanomas and a median 14 years of follow-up. The median time to a subsequent primary melanoma diagnosis decreased with each new primary melanoma. Twelve risk factors were included in the final model, for which the respective Harrell's C-statistic values for predicting second, third and fourth melanomas were 0.73 (95% CI 0.68, 0.77), 0.65 (0.62, 0.68) and 0.65 (0.61, 0.69). Compared with the lowest risk score quintile, scores in the highest quintile were associated with a 4.75-fold risk of a subsequent primary melanoma. The respective mean absolute 5-year risks of a subsequent primary melanoma after first and second primary melanomas were 8.0% and 46.8%, but there was considerable variability by risk score.

Comment (JW): In the current study, a risk prediction model was developed based on the following risk factors: age at first melanoma, sex, history of keratinocyte cancer, family history of melanoma, skin colour, ability to tan, numbers of naevi, polygenic risk score, presence of CDKN2A mutation, level of outdoor recreation activities, site of melanoma and histological subtype. The model demonstrated good discrimination for predicting a second primary melanoma, and a moderate discrimination for predicting a third or fourth primary melanoma. The diagnosis of a melanoma can be associated with significant psychological stress and anxiety among patients, mostly driven by feelings of uncertainty. Studies such as these, by providing information on prognosis and future risks, can be helpful in patient education and managing their fear of recurrence and new melanoma. In addition, current guidelines on follow-up intervals are based on melanoma staging, as opposed to patient risk factors. The development and use of risk prediction models will allow physicians to better manage individual patients based on their risk factors and tailor surveillance intensity accordingly.

Reference: Br J Dermatol 2020;182:1148–57
Abstract

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Characterization of risk factors and efficacy of medical management of immune-related hepatotoxicity in real-world patients with metastatic melanoma treated with immune checkpoint inhibitors

Authors: Romanski NA et al.

Summary: This retrospective study included a cohort of 521 patients from the Danish Metastatic Melanoma Database who received checkpoint inhibitor therapy, 6.8% of whom had immune-related hepatitis. The risk of immune-related hepatitis was significantly greater among combination therapy recipients than monotherapy recipients. Different hepatitis grading was seen for 34.9% of patients with hepatitis according to either aminotransferase alanine aminotransferase or aspartate aminotransferase level. Steroids were administered to 72.1% of patients with hepatitis; two received additional second-line immunosuppressants. The overall relapse rate for hepatitis during steroid tapering was 35.5%. Hepatitis emerged within 7 days of finishing antibiotic treatment for infection in 18.6% and 25% of patients with grades ≥2 and ≥3, respectively. The cancer progression rate was greater for patients who received a cumulative steroid dose of >4000mg compared with those who received a lower cumulative dose (62.5% vs. 22.7%).

Comment (DO): Pembrolizumab, nivolumab and ipilimumab are monoclonal antibodies directed against immune checkpoints. In metastatic melanoma, their use as first-line monotherapy since about 2012 has increased 5-year OS from 5–10% without treatment to 30–45% (Lancet Oncol 2019;20:1239–51, N Engl J Med 2019;381:1535–46). With increasing immunotherapy use, and better survival, oncologists are beginning to see more immunotherapy-related adverse events. Not to be missed in this paper is the importance of having (pragmatically utilising) nationalised databases; the Danish Metastatic Melanoma Database (DAMMED), accounts for 95% of patients with metastatic melanoma diagnosed in Denmark. It has enabled the publication of this large retrospective cohort, thus providing valuable insight into real-world rates of one type of otherwise infrequently documented immunotherapy-related adverse events, immune-related hepatitis. Whereas, randomised trial data report grade≥ 3 immunotherapy-related hepatitis of up to 10.9% (Nat Rev Clin Oncol 2019;16:563–80), it was 4.4% in this study, albeit with similar time to onset of approximately 6 weeks. Those with grade ≥3 immunotherapy-related hepatitis were more than twice as likely to relapse after high-dose steroid treatment compared with those with grade 2 immunotherapy-related hepatitis, with no clear association between relapse and steroid dosing or tapering rate. Progression-free survival did not differ between those who developed immunotherapy-related hepatitis and those who did not, which suggests that unlike, say, immunotherapy-associated vitiligo, which is thought of as a favourable prognostic factor associated with survival (JAMA Dermatol 2016;152:45–51), not all immune-mediated adverse events are associated with better OS.

Reference: Eur J Cancer 2020;130:211–8
Abstract

Association between immune-related adverse events and recurrence-free survival among patients with stage III melanoma randomized to receive pembrolizumab or placebo

Authors: Eggermont AMM et al.

Summary: This was a secondary analysis of a trial that randomised adults with stage III melanoma to receive pembrolizumab 200mg (n=509) or placebo (n=502) every 3 weeks for a total of 18 doses or until disease recurrence, unacceptable toxic effects, major protocol violation or consent withdrawal. Compared with placebo, pembrolizumab recipients had longer relapse-free survival among treatment initiators (HR 0.56 [98.4% CI 0.43, 0.74]), but a higher incidence of immune-related adverse events (37.4% vs. 9.0%). The occurrence of an immune-related adverse event was associated with longer relapse-free survival among pembrolizumab recipients (HR 0.61 [95% CI 0.39, 0.95]); this association was not significant in the placebo arm. Compared with placebo, pembrolizumab was associated with a greater reduction in the hazard of recurrence or death after the onset of an immune-related adverse event than without or before an immune-related adverse event (HR 0.37 vs. 0.61 [p=0.03]).

Comment (DO): The principle objective of adjuvant systemic therapy of any type in oncology is to improve OS; although were are currently unable to reliably identify them, there is a proportion of patients with completely resected stage III high-risk metastatic melanoma who may well have been cured after surgery. These patients are unlikely to benefit from adjuvant systemic therapy and may potentially be put in harm's way. On a separate but related note, it is difficult to determine whether (and by how much) those who may have residual micrometastatic disease after complete resection of the primary actually benefit from adjuvant immunotherapy. It is in this context of uncertainty that this secondary analysis of the randomised KEYNOTE-054 trial hopes to shed some light. The study provides a tantalising insight into using immune-related adverse events as a potential clinical prognostic marker of benefit from adjuvant immunotherapy for completely resected stage III melanoma. Thus the following key points from this paper may potentially be utilised in a clinical setting to counsel patients: i) in those receiving adjuvant pembrolizumab, the appearance of immune-related adverse events after initiating adjuvant pembrolizumab is associated with improved outcomes compared with those who do not develop them; and ii) the time to onset for immune-related adverse events for the majority was 6 months, the most common being endocrinopathies (~23%) and vitiligo (~4%). However, unfortunately the study is unable to inform whether specific types of immune-related adverse events are more likely to improve survival over others, or if the degree or duration of the symptoms of the immune-related adverse event plays a part in conferring benefit.

Reference: JAMA Oncol 2020;6:519–27
Abstract

Long-term outcomes and responses to retreatment in patients with melanoma treated with PD-1 blockade

Authors: Betof Warner A et al.

Summary: This retrospective study included 396 patients from the Memorial Sloan Kettering Cancer Center with nonuveal, unresectable stage III/IV melanoma treated with single-agent anti-PD-1 therapy who had discontinued treatment and had ≥3 months of follow-up after discontinuation. The CR rate was 25.8%. Over median follow-up of 21.1 months from time of CR in patients who did not relapse, the probability of being alive and not needing additional melanoma therapy at 3 years was 72.1%. CR was associated with M1b disease and cutaneous versus mucosal or acral primaries. Among patients retreated after disease progression (n=78), responses were seen in 5/34 retreated with single-agent anti-PD-1 therapy and 11/44 escalated to anti-PD-1 plus ipilimumab.

Comment (DO): Since June 2018, there have been approximately 25–30 patients per month commencing pembrolizumab or nivolumab as first-line therapy for metastatic melanoma in NZ after special authority initiation. Furthermore, since becoming available in 2016, the number of patients on a PD-1 inhibitor has increased by 20–25% per year ('Pembrolizumab and nivolumab', PHARMAC, December 19, 2019). As such, it is not surprising that PHARMAC updated their special authority criteria in February 2020; this now allows patients to discontinue immunotherapy and subsequently restart it at disease progression, provided they had not progressed or developed severe toxicity while on treatment in the first place. This pragmatic, potentially cost-saving approach has been adopted by most jurisdictions worldwide where immunotherapy for metastatic melanoma is accessible; however, there are limited prospective data supporting it. This large, single-centre, retrospective cohort study boasting the longest published follow-up to date provides much valued clinical information around whether one can safely stop immunotherapy after achieving a CR. Unlike previous prospective trials (KENOTE 001 and KEYNOTE 006) and contemporary clinical practice in NZ, most patients in this study did not receive any further immunotherapy after achieving a CR; nevertheless, their 3-year time to treatment failure was 72%. However, in those retreated at relapse, the median OS was only 9.9 months. What's more, the likelihood of response was low if retreated with mono-immunotherapy and only modest with combination immunotherapy. Furthermore, there was no association between how long it took to get to CR from the get go and the likelihood of response at retreatment. So how can one best apply these data to NZ patients? In the first instance, those obtaining a CR and who are experiencing significant toxicities may consider stopping provided they understand that there is ~30% treatment failure in 3 years. However, in the absence of unfunded and limited effective second-line therapy options in this space, those with a partial response or stable disease should continue maintenance immunotherapy if tolerated, especially on account of 3-year OS rates of 57.3% and 39%, respectively, as reported in this paper.

Reference: J Clin Oncol 2020;38:1655–63
Abstract

Use of immunotherapy and surgery for stage IV melanoma

Authors: Molina G et al.

Summary: The impact of changes in systemic immunotherapy options on surgical resection rates was investigated in this research involving 14,433 patients with stage IV melanoma from the US NCDB (National Cancer Database); among patients treated during the era of checkpoint inhibitors (n=7524), 25% received immunotherapy. Compared with patients treated during the era of checkpoint inhibitors who did not receive immunotherapy, those who did were younger, healthier and more likely to have private insurance, come from upper income quartiles and be treated in academic programmes. Surgical resection rates for metastatic disease with immunotherapy use were similar before and after checkpoint inhibitors became available, irrespective of facility type.

Comment (DO): The authors of this study are to be commended for their herculean effort in sifting through data of over half a million patients from the US NCDB in an attempt to evaluate whether there was a difference between surgical resection rates for metastatic disease in stage IV melanoma, contrasting the pre-immunotherapy (2004–2010) and post-immunotherapy (2011–2015) eras. The final data analysis included a total of just over 14,000 patients. Although they did not find any differences in surgical resection rates or survival between the two eras, this large retrospective cohort study was beset by several limitations that might explain the apparent lack of difference: firstly, the data do not distinguish between those with relapsed versus those with *de novo* stage IV metastatic disease; secondly, the intent of the metastasectomy was not known (palliative versus complete resection of all metastatic disease); and thirdly, the time between diagnosis and surgical resection was not known. These are all factors that influence prognosis and therefore possibly survival. Additionally, although not expressively discussed in this paper, it is likely that patients in either era received ipilimumab rather than the better tolerated pembrolizumab or nivolumab (both US FDA approved in September and December 2014, respectively, on account of survival benefit). As such these outcomes may not reflect contemporary clinical practice where PD-1 inhibitors are favoured over CTLA4- antagonists in the first-line treatment of metastatic melanoma. Furthermore, no account is given of those who may have received BRAF monotherapy or in combination with an MEK inhibitor (FDA approved in 2011 and 2014, respectively), both of which have been shown to provide a nondurable but a survival benefit all the same. Finally, as of December 2017, nivolumab received FDA approval as adjuvant systemic therapy for fully resected stages III and IV melanoma. This not only brings sharply into focus the importance of subcategorising M-stage (i.e., M1a, M1b, M1c and M1d) when considering metastasectomy with a view to curative intent, but also demonstrates how information such as described in this paper can suddenly become redundant in the rapidly evolving therapeutic field of metastatic melanoma.

Reference: Cancer 2020;126:2614–24
Abstract

Cumulative incidence and predictors of CNS metastasis for patients with American Joint Committee on Cancer 8th edition stage III melanoma

Authors: Haydu LE et al.

Summary: These researchers extracted clinical data for 1918 patients with American Joint Committee on Cancer 8th edition stage III melanoma who had negative baseline CNS imaging within 4 months of diagnosis. At median follow-up of 70.2 months, distant recurrence had occurred in 37.1% of the patients. The first site of distant metastasis was CNS only for 3.9% of the patients, CNS and extracranial for 1.8% and extracranial only for 31.4%. Overall, 16.7% of the patients were diagnosed with CNS metastases during follow-up. The respective cumulative 1-, 2- and 5-year incidences of CNS metastases were 3.6%, 9.6% and 15.8%.

Comment (DO): Although patients with completely resected stage III metastatic melanoma are not without risk of CNS relapse, regular-interval screening with CT/MRI of the head is not routinely included as part of the standard practice body CT follow-up surveillance scanning in these patients in NZ. This large melanoma registry study is a testament to the power of collaborative research and the pragmatic utilisation of clinical and pathological patient characteristics to determine the risk of CNS metastases in this patient group. By incorporating patient data from two of the largest melanoma centres in the world, the authors of this paper demonstrate that their combined cohort with completely resected stage III melanoma, who were naïve to adjuvant immunotherapy, had an increasing cumulative incidence of CNS metastases at years 1, 2 and 5 of follow-up. The strongest of the clinicopathological factors identified by covariate analysis predicting CNS relapse were stage (IIIa vs. IIIb vs. IIIc, and so on) and (surprisingly) a high mitotic rate in the primary tumour specimen. What's fascinating is that mitotic rate not only remains but is also the only significant predictor of late relapse after 5 years of surviving without CNS metastases. So how can we make such data relevant to clinical practice? The next logical step would appear to be the development and validation of a clinical tool incorporating the most powerful clinicopathological factors for CNS relapse as characterised by this study. In time, such a tool may subsequently be utilised to identify a subset of patients with completely resected stage III melanoma in whom interval surveillance CT/MRI head imaging may be indicated to monitor for relapse.

Reference: J Clin Oncol 2020;38:1429–41
Abstract

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Independent commentary by Dr David Okonji, MB BCh (UK) MRCP(UK) MRCPS(Glas) FRACP

David Okonji specialises in treating breast and urogenital cancers, as well as melanoma. He has a particular focus on cancer care in the elderly. David currently practises at Wellington Regional Hospital and also undertakes private practice at Bowen Hospital, Wellington. David is a Clinical Senior Lecturer at the University of Otago School of Medicine. He is actively involved in research as an investigator in clinical trials at Wellington Hospital. He is also an active member of the American Society of Clinical Oncology, the European Society of Medical Oncology and the Society of Geriatric Oncology.

Independent commentary by Dr Junie Wong

Dr Junie Wong is a consultant dermatologist and Mohs micrographic surgeon. She runs general dermatology and skin surgery clinics at Skin Centre (Albany and Nelson) and at Auckland Dermatology. She graduated from the University of Edinburgh Medical School in 2008, and achieved membership of the Royal College of Physicians, UK in 2011. Junie completed her 4 years of postgraduate dermatology training in Liverpool, UK and worked there as a Locum Consultant Dermatologist before moving to NZ, where she completed the American College of Mohs Surgery (ACMS) approved fellowship in Mohs micrographic surgery. She has an interest in skin cancer diagnosis and management.

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