Melanoma Research Review™

Making Education Easy

Issue 51 - 2022

In this issue:

Abbreviations used in this issue:

AE = adverse event; **ED** = emergency department; **GEP** = gene expression profile; **ICI** = immune checkpoint inhibitor; **ORR** = overall response rate; **OS** = overall survival; **PFS** = progression-free survival; **PPI** = proton pump inhibitor; **RFS** = recurrence free survival; **SLNB** = sentinel lymph node biopsy; **TMB** = tumour mutational burden.

Claim CPD/CME points Click here for more info.

Research Review Australia is now on Linked-in. Follow us to keep up to date.

Welcome to the 51st issue of Melanoma Research Review.

The lead article in this issue investigated gut microbiome associations with ICI response in advanced melanoma. The authors report within cohorts microbiome patterns were predictive of outcome however, there was limited reproducibility of microbiome-based signatures across cohorts. A meta-analysis reports radiotherapy combined with ICIs can improve the effective rate of treatment of patients with melanoma. Although there was no obvious OS advantage, the combination improved PFS without serious adverse effects. Another study found the majority of patients with melanoma brain metastases received anti-tumour treatment during the last 3 months of life. The authors highlight ED visits and hospitalisations occurred more often in patients on anti-tumour treatment.

A retrospective review investigating tumour mutational burden to predict disease recurrence reports classification into BRAFmut, NRASmut, and tumour mutational load groups may aid in identifying patients who are more likely to have disease recurrence in advanced melanoma. Researchers assessed a nomogram incorporating gene expression profiling and clinical factors for prediction of metastasis in patients with cutaneous melanoma. They found Integration of gene expression profiling and T stage can provide clinically useful prognostic information. Other research reviewed in this issue includes risk factors and patterns of recurrence after SLNB for thin melanoma and complications associated with Mohs micrographic surgery.

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

Cross-cohort gut microbiome associations with immune checkpoint inhibitor response in advanced melanoma

Authors: Lee KA, et al

Summary: The investigators performed shotgun metagenomic sequencing of stool samples collected from patients with advanced cutaneous melanoma before immune checkpoint inhibitor (ICI) initiation from five observational cohorts. This dataset was integrated with 147 metagenomic samples from previously published studies. The investigators found that the gut microbiome has a relevant, but cohort-dependent, association with the response to ICIs. A machine learning analysis confirmed the link between the microbiome and overall response rates (ORRs) and progression-free survival (PFS) with ICIs but also revealed limited reproducibility of microbiome-based signatures across cohorts. They identified species associated with responders but noted no single species could be regarded as a fully consistent biomarker across studies.

Comment: An array of pre-clinical and limited clinical studies has suggested a role for the microbiome as a biomarker of response in patients with advanced melanoma receiving ICI therapy. Given the importance of selecting patients likely to benefit from a potentially toxic therapy, this study accessed material from seven prospective cohorts of patients prior to commencing ICI. Within cohorts microbiome patterns were predictive of outcome however, across the cohorts there were few reproducible biomarkers of response. Clinical parameters such as use of proton pump inhibitors (PPIs) also appear to influence the microbiome and confound a potential relationship to outcome. The authors noted that there were differences in the clinical characteristics including BRAF status and previous use of targeted therapy between cohorts and acknowledge that the patient's malignancy may impact the response of the immune system both within and between cohorts. Not surprisingly the authors conclude with the comment that further studies are required.

Reference: Nat Med. 2022 Mar;28(3):535-544

Abstract

Independent commentary by Professor Michael Henderson.

Michael A Henderson is Professor of surgery in 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 2 1/2 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).

Utilization and evolving prescribing practice of opioid and non-opioid analgesics in patients undergoing lymphadenectomy for cutaneous malignancy

Authors: Witt RG, et al

Summary: This single-institution retrospective study assessed changes in prescribing practices following an opioid education initiative for patients undergoing lymphadenectomy for cutaneous malignancy. Indications for lymphadenectomy in the study cohort of 328 patients were metastatic melanoma (84%), squamous cell carcinoma (10%), and Merkel cell carcinoma (5%). The authors reported at discharge, non-opioid analgesics were increasingly utilised over the 4-year study period (3/2016-3/2020), with dramatic increases after education initiatives (32%, 42%, 59%, and 79% of pts, respectively each year; $p < 0.001$). They also noted oral morphine equivalents prescribed decreased dramatically, starting in year 3 (250, 238, 150, and 100 mg, respectively; $p < 0.001$). Patients discharged with 200 mg oral morphine equivalents were less likely to also be discharged with non-opioid analgesics (40% vs. 64%. respectively, $p < 0.001$).

Comment: This study evaluated approaches to pain management for patients undergoing lymphadenectomy for cutaneous malignancy at a single academic centre (MD Anderson Hospital). Well-established data confirm the role of post-operative narcotic prescribing in the development of the current US opioid epidemic and while this has not been anywhere near a major issue in Australia this study offers several observations surgeons in particular may wish to consider. Prompted by the epidemic, opioid use was reviewed from 2016-2020. At the start of the study 96% received narcotics on discharge (median length of stay one day) and this had fallen to 48% within four years which by Australian standards would be still much higher, although median length of stay in Australia is 2-3 days. The biggest driver of reduction in opioid use was an education program as the primary drivers of discharge prescribing were trainees. Patient expectations were also important and other initiatives included improved recognition of the patient's level of pain which was previously heavily overestimated, a standardised discharge analgesic protocol and a significant reduction in combined drugs which allowed baseline continuous maximum dosing with agents such as paracetamol.

Reference: J Surg Oncol. 2022 Mar;125(4):719-729
Abstract

Anti-tumor treatment and healthcare consumption near death in the era of novel treatment options for patients with melanoma brain metastases

Authors: Eggen AC, et al

Summary: The retrospective, single-centre study, included 100 patients with melanoma brain metastases diagnosed between June-2015 and June-2018 and died before November-2019. The researchers used medical records to assess patient and tumour characteristics, anti-tumour treatments, healthcare consumption, presence of neurological symptoms, and do-not-resuscitate status. A BRAF-mutation was present in 66 patients. Systemic anti-tumour therapy was given to 72% of patients during the last 3 months of life, 34% in the last month, and 6% in the last week. Patients with a BRAF-mutation more frequently received systemic treatment during the last 3 (85% vs 47%) and last month (42% vs 18%) of life than patients without a BRAF-mutation. Furthermore, patients receiving systemic treatment were more likely to visit the emergency department (ED, 75% vs 36%) and be hospitalised (75% vs 36%) than those who did not.

Comment: This was a small and thoughtful retrospective study of the use of specific anti-tumour therapy and healthcare intervention in the last three months of life in patients with brain metastasis in the era of new systemic therapies. In summary, they found that one third of patients received specific therapy in the last four weeks of life and this was associated with a much higher chance of presenting to the ED or requiring inpatient admission compared to patients receiving palliative or best supportive care (both 75% versus 36%). Most presentations to the ED or hospitalisation were associated with neurological symptoms suggesting the limited effect of systemic therapy on these symptoms prior to death. There are multiple reasons to explain these differences but the fact remains there is much to be done to improve the care of patients with brain metastases in the last weeks of their life.

Reference: BMC Cancer. 2022 Mar 5;22(1):247
Abstract

Risk factors and patterns of recurrence after sentinel lymph node biopsy for thin melanoma

Authors: Kim D, et al

Summary: The retrospective single centre review included 209 patients with thin melanomas (defined as AJCC 8 T1 stage tumour ≤ 1.0 mm) and negative sentinel lymph node biopsy (SLNB). Clinicopathologic characteristics of the primary melanoma were collected and patterns of recurrence for local/in-transit, nodal or distant recurrence and survival outcomes analysed. The authors reported 18 patients (8.6%) developed recurrence: 3 (1.9%) local/in-transit, 4 (2.9%) regional/nodal, and 11 (5.3%) distant recurrence during a median follow-up time of 62 months. They also showed that head and neck site (HR 3.52), ulceration (HR 10.8), and mitotic rate (HR 1.39) were significant risk factors for recurrence. Median time to first recurrence was 49 months. It was noted patients with recurrence had a significantly worse 5 year overall survival (OS) than those without recurrence (82.2 vs 99.2%).

Comment: Clinicians tasked with managing all the patients with thin melanomas (< 1 mm in thickness) must balance the excellent prognosis these patients have with the knowledge that these patients account for an increasing proportion of all patients who develop recurrent disease. This was a highly selected group of patients with thin melanomas as all had undergone a SLNB and the median tumour thickness was 0.75 mm (IQR 0.6-0.9). The majority of first recurrences were distant. Survivals were consistent with AJCC data, only 8.6% developed a recurrence. Ulcerated lesions and melanomas located in the head and neck were associated with poorer outcomes, although mitotic rate had a statistically significant but clinically insignificant impact. The authors include that patients with melanomas of the head and neck and/or ulceration should be considered for enhanced surveillance although the evidence for this is scant. What the authors do not comment on is the current lack of effective biomarkers and this is where any improvements in care are likely to come from.

Reference: Arch Dermatol Res. 2022 Apr;314(3):285-292
Abstract

Complications associated with Mohs micrographic surgery: Data from the nationwide prospective cohort REGESMOHS

Authors: Ruis-Salas V, et al

Summary: The researchers explored Mohs micrographic surgery complications in a nationwide prospective cohort study across 22 specialised centres. All adverse events were collected in a cohort of 5,017 patients with 14,421 patient-years of follow-up. 7.0% had some perioperative morbidity and 6.5% had mid-term and scar-related complications. The researchers reported the overall risk of complications was mainly associated with use of antiaggregant/anticoagulant and larger tumours, affecting deeper structures, not reaching a tumour-free border, and requiring complex repair. Risk factors for haemorrhage (0.9%) were therapy with antiaggregant/anticoagulants, tumour size, duration of surgery, and unfinished surgery. Wound necrosis (1.9%) and dehiscence (1.0%) were associated with larger defects and complex closures. Immunosuppression was only associated with an increased risk of necrosis. Surgeries reaching deeper structures, larger tumours and previous surgical treatments were associated with wound infection (0.9%). Aesthetic scar alterations (5.4%) were more common in younger patients, with larger tumours, in H-area, and in flap and complex closures. Risk factors for functional scar alterations (1.7%) were the need for general anaesthesia, larger tumours that had received previous surgery, and flaps or complex closures.

Comment: This is another retrospective review advancing the role of Mohs micrographic surgery in the management of early-stage melanoma. The data was collected from 22 centres and included 5,017 patients, the median length of follow-up appears to be short but is not described. Not surprisingly morbidity (7%) was associated with larger tumours, requirement for a complex repair, and positive margins. These results are no different from what might be obtained using standard surgical procedures as undertaken by primary care practitioners, dermatologists and surgeons at a considerably reduced cost. Cosmetic deformity described as "aesthetic scar alterations" occurred in 5.4% and not surprisingly were associated with size of the tumour, location, et cetera. The fact that this study does not compare the results with standard of care simple wide excision nor provide a sufficient length of follow-up or outcome data is a major concern.

Reference: Dermatology. 2022;238(2):320-328
Abstract

Efficacy of radiotherapy combined with immune checkpoint inhibitors in patients with melanoma: A systemic review and meta-analysis

Authors: Yin G, et al

Summary: The meta-analysis, assessing the efficacy of radiotherapy combined with ICIs in patients with melanoma, included 624 patients from nine published studies and three clinical trials. The authors found radiotherapy combined with ICIs had a higher ORR compared with ICIs alone (35.00 vs 20.39%), however, there was no OS advantage. There was no statistically significant difference between 6-month and 12-month OS (P = 0.13; P = 0.69). There was no significant difference in PFS at 6 months (P = 0.08), but there was a significant difference in PFS at 12 months (P = 0.005). It was noted there were no serious adverse effects with the combination.

Comment: Two previous meta-analyses of combined radiotherapy and ICI therapy for cerebral metastases leave open the possibility of enhanced response to ICI. The current report was a meta-analysis of combined therapy in 624 patients from 12 studies with extracranial metastatic melanoma. Most studies were retrospective and there was considerable variation in clinical variables but this did not translate into improved overall survival (PFS was slightly improved at 12 months). Adverse events were inconsistently reported in the reports selected for review but appear to be consistent with the literature. The authors conclude that there may be a benefit to combined radiotherapy and ICI but further study is warranted.

Reference: Melanoma Res. 2022 Apr 1;32(2):71-78
Abstract

Development and validation of a nomogram incorporating gene expression profiling and clinical factors for accurate prediction of metastasis in patients with cutaneous melanoma following Mohs micrographic surgery

Authors: Thorpe RB, et al

Summary: The researchers developed a nomogram incorporating a 31-gene expression profile (31-GEP) test with clinical factors to improve prognostic accuracy. A cohort of 1,124 patients treated with Mohs micrographic surgery underwent 31-GEP testing. Data from 684 of those patients with at least 1-year follow-up or a metastatic event were included in nomogram development to predict metastatic risk. The researchers reported logistic regression modelling of 31-GEP results and T stage provided the simplest nomogram with the lowest Bayesian information criteria score. Validation in an archival cohort (n = 901) demonstrated a significant linear correlation between observed and nomogram-predicted risk of metastasis. The resulting nomogram more accurately predicted the risk for cutaneous melanoma metastasis than T stage or 31-GEP alone.

Comment: Unlike other malignancies such as breast cancer, gene expression profiling to guide treatment by providing enhanced information over standard (AJCC) staging has yet to become the standard of care for patients with stage I-III melanoma. The most recent version of the NCCN guidelines suggest GEP may have a role as an adjunct to standard staging but is otherwise not recommended. In order to get around this issue, this study as have others, combined standard prognostic information with a GEP score. The current report is one of an increasing number, relatively small in size, usually retrospective studies which claim clinical utility for a GEP clinico-pathologic nomogram. This study as with previous reports identifies a clinical benefit. The novelty of this study is the claimed benefit for patients with stage I melanoma which was the group identified in a recent meta-analysis of GEP scoring in melanoma as least likely to benefit. At the present time GEP scoring has limited applicability and is not currently recommended in Australia.

Reference: J Am Acad Dermatol. 2022 Apr;86(4):846-853
Abstract

Tumor mutational burden and somatic mutation status to predict disease recurrence in advanced melanoma

Authors: Hotz MJ, et al

Summary: The objective of this retrospective review was to evaluate the potential for tumour mutational burden (TMB) and somatic mutations to predict the recurrence of disease in advanced melanoma. Tumours from 85 patients with stage III or IV melanoma were analysed by next-generation sequencing. The authors reported the most frequently detected mutations were TERT (32.9%), CDKN2A (28.2%), KMT2 (25.9%), BRAF V600E (24.7%), and NRAS (24.7%). Patients with TMB-L + BRAFWT status were more likely to have a recurrence (HR 3.43; P = 0.01) compared to TMB-H + BRAF WT. Patients with TMB-L + NRASmut were more likely to have a recurrence (HR 5.29; P = 0.01) compared to TMB-H + NRAS WT. TMB-L tumours were associated with local (P = 0.029) and in-transit (P = 0.004) recurrences.

Comment: Tumour mutational burden is an established biomarker of response to anti-PD-1 therapy for a variety of tumours but the significance for melanoma is far from clear. This study sought to investigate the impact of TMB on outcome investigating the role of other putative biomarkers in a retrospective study of patients with advanced melanoma receiving anti-PD-1 therapy. Patients with a high TMB had improved relapse free survival compared to those with low TMB. Further evaluation identified patients with a high TMB and an NRAS mutation had improved recurrence free survival (RFS) while patients with a BRAF V600 E mutation and low TMB had a more favourable RFS than those with a high TMB. TERT, CDKN2A and KMT2 mutations did not impact RFS by TMB status. The authors conclude that in the case of melanoma TMB by itself is not a reliable predictor of response to anti-PD-1 therapy or outcome but further investigation of the relationships with the tumour molecular profile may be a more productive approach.

Reference: Melanoma Res. 2022 Apr 1;32(2):112-119
Abstract

Immune-related adverse events after immune checkpoint inhibitors for melanoma among older adults

Authors: Schonfelf SJ, et al

Summary: The researchers evaluated the association between use of ICIs and immune-related adverse events (AEs) among older patients with cutaneous melanoma. Medicare claims and population-based cancer registries were used to identify 4,489 patients of White race diagnosed with stages II-IV or unknown first primary cutaneous melanoma (66.9% men, median age 74.9 [range, 66.0-84.9] years). During follow-up (median, 1.4 [range, 0-5.0] years), 1,576 patients (35.1%) had an immune-related AE on a Medicare claim. The researchers found use of ICIs (reported for 418 patients) was associated with autoimmune-related AEs (HR 2.5), including primary adrenal insufficiency (HR 9.9) and ulcerative colitis (HR 8.6). Other immune-related AEs (HR 2.2), included Cushing syndrome (HR 11.8), hyperthyroidism (HR 6.3), hypothyroidism (HR 3.8), hypopituitarism (HR 19.8), other pituitary gland disorders (HR 6.0), diarrhoea (HR 3.5), and sepsis or septicaemia (HR 2.2). They noted the cumulative incidence at 6 months following the first ICI claim was 13.7% for autoimmune-related AEs and 46.8% for other immune-related AEs.

Comment: This is a relatively small study of AEs occurring in elderly patients (aged 65-85 years) who were treated for stage II-IV melanoma identified through the US SEER database. The commonest autoimmune related AEs were primary adrenal insufficiency and ulcerative colitis (14%). This is an unusual spectrum of AEs and the incidence was higher than it is generally reported in younger patients. Possibly it was due to miscoding of the more common AE of immune colitis. Given the limitations imposed by the data source, these results require further validation given the concerns about treatment of older patients with ICI therapy.

Reference: JAMA Netw Open. 2022 Mar 1;5(3):e223461
Asbtract

