Melanoma Research Review™

Making Education Easy

Issue 43 - 2021

In this issue:

Abbreviations used in this issue:

CLND = completion lymph node dissection; **CR** = complete response; **DFS** = disease-free survival; **DMFS** = distant metastasis-free survival; **DSS** = disease-specific survival; **ICI** = immune checkpoint inhibition; **irAE** = immune related adverse effect; **MBM** = melanoma brain metastasis; **MSS** = melanoma-specific survival; **ORR** = objective response rate; **OS** = overall survival; **RFS** = recurrence-free survival; **RT** = radiotherapy; **SLN** = sentinel lymph node; **SN** = sentinel node; **SRS** = stereotactic radiosurgery.

Claim CPD/CME points Click here for more info.

Like us on Facebook
facebook.com/researchreviewau/

Kindly Supported by

AUSTRALIAN MELANOMA RESEARCH FOUNDATION

Welcome to the 43rd issue of Melanoma Research Review.

The lead article in this issue analysed Dutch registry data and found high discordance rate in assessing SN positivity in cutaneous melanoma. The authors advocate that when adjuvant treatment is considered in patients with stage III melanoma SN biopsies should be reassessed by an expert melanoma pathologist. Another study assessed international, real-world outcomes of active surveillance of patients who have SN positive melanoma. The researchers showed, compared with up-front surgery, ultrasound monitoring results in the same overall risk of melanoma coming back at any location or of dying from melanoma. A meta-analysis found there were no significant differences in patient outcomes between a short interval versus a long interval between the primary biopsy procedure and obtaining a SNL biopsy specimen.

A large, single-institution study demonstrated a significant increase in survival of patients with MBM in the era of immunotherapy and targeted medicines. Another study showed sustainable responses in metastatic melanoma patients with and without brain metastases after elective discontinuation of anti-PD1 therapy due to CR. A multicentre, retrospective, cohort study found in patients with metastatic melanoma who are resistant to anti-PD-(L)1, ipilimumab plus anti-PD-1 seemed to yield higher efficacy than ipilimumab alone. The authors suggest ipilimumab plus anti-PD-1 should be favoured over ipilimumab alone as a second-line immunotherapy for these patients.

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

High discordance rate in assessing sentinel node positivity in cutaneous melanoma: Expert review may reduce unjustified adjuvant treatment

Authors: El Sharouni M, et al

Summary: The researchers analysed Dutch pathology registry data from patients with melanoma who underwent sentinel node (SN) biopsy between 2003 and 2014. A random sample of 322 histopathological slides of SN-positive patients was retrieved and reassessed by an expert melanoma pathologist. A group of SN-negative patients was included for comparison. Diagnosis was downgraded from melanoma metastasis to nodal neavus in 38 of the 322 reviewed patients (11.8%). The researchers noted patients with a low SN tumour burden and subcapsular SN tumour location had a significantly higher chance of being misclassified. The five-year recurrence-free survival (RFS) of the 38 downgraded patients was 86.7%, similar to the 85.9% for 6,413 SN-negative patients and better than the 53.2% of 284 patients who were truly SN positive upon review.

Comment: Benign lymph node naevus cells can be difficult to distinguish from isolated tumour deposits. Pathologists rely on a combination of cellular morphological features, location within the node and immunohistochemistry to diagnose lymph node metastases but occasionally this can be difficult particularly when the tumour volume is tiny. Even microscopic deposits have prognostic significance and depending on primary tumour characteristics may be an indication for adjuvant targeted or immune checkpoint inhibitor therapy. Surprisingly 10% of patients initially labelled as SN-positive were downgraded to lymph node negative and nearly half of these patients would have been spared adjuvant therapy. The validity of the author's approach which depended heavily on an experienced melanoma pathologist was confirmed by the results which indicated survival in the reclassified node negative group as equivalent to patients previously diagnosed as node negative. These results are highly consistent with real-life experience and emphasise the importance of specialist pathology review in a multidisciplinary setting.

Reference: Eur J Cancer 2021 May;149:105-113

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).

Melanoma brain metastasis presentation, treatment, and outcomes in the age of targeted and immunotherapies

Authors: Bander ED, et al

Summary: This large, single-institution, retrospective study included a cohort of 425 melanoma patients with 2,488 brain metastases. The median overall survival (OS) after a melanoma brain metastasis (MBM) diagnosis was 8.9 months. Patients who were diagnosed with MBM between 2015 and 2019 experienced longer OS compared to those who were diagnosed between 2010 and 2014 (OS, 13 months vs 7 months; P = 0.0003). The authors found shortened OS was independently associated with leptomeningeal dissemination (P < 0.0001), increasing numbers of brain metastases at diagnosis (P < 0.0001), earlier MBM diagnosis year (P = 0.0008), higher serum levels of LDH (P < 0.0001), receipt of immunotherapy before MBM diagnosis (P = 0.003), and the presence of extracranial disease (P = 0.02). They also demonstrated the use of different CNS-directed treatment modalities was associated with presenting symptoms, diagnosis year, number and size of brain metastases, and the presence of extracranial disease. Furthermore, they demonstrated improved survival for patients who underwent craniotomy (P = 0.01).

Comment: This is a comprehensive review of 425 patients from a single centre. The major finding was a nearly doubling in survival (13 v 7 months) for patients treated in an era of established immunotherapy or targeted therapy (2015-2019) compared with a similar group treated in the previous five years most of whom did not receive these therapies. The results are consistent with the effect of therapy on both intra- and extra-cranial disease contributing to the improved survival. The latter time period also saw significant changes in the use of radiation with a considerable reduction in the use of whole brain radiotherapy (RT) and increasing use of stereotactic radiosurgery (SRS). It was not possible to determine whether the increasing use of SRS and ICI therapy improved survival through a potential abscopal effect. Another observation was the extremely poor prognosis for patients with leptomeningeal disease which was a rare event at first presentation (and excluded from this study) but developed in 15% of patients predominantly in the first two years after first presentation with brain metastases.

Reference: Cancer 2021 Jun 15;127(12):2062-2073
Abstract

Active surveillance of patients who have sentinel node positive melanoma: An international, multi-institution evaluation of adoption and early outcomes after the multicenter selective lymphadenectomy trial II (MSLT-2)

Authors: Broman KK, et al

Summary: The authors studied real-world outcomes in over 1,000 patients with sentinel lymph node (SLN)-positive cutaneous melanoma treated at 21 centres worldwide. They evaluated the impact of active surveillance with ultrasound monitoring and adjuvant therapy on all-site recurrence-free survival (RFS), isolated nodal RFS, distant metastasis-free survival (DMFS), and disease-specific survival (DSS). Among 6,347 SLN biopsies, 18% were positive and had initial negative distant staging. In total, 84% received active surveillance and 16% underwent completion lymph node dissection (CLND). Four hundred and thirty-nine patients received adjuvant therapy (surveillance, 38%; CLND, 39%), with the majority (83%) receiving anti-PD-1 immunotherapy. The authors reported after a median follow-up of 11 months, 220 patients developed recurrent disease (surveillance, 19%; CLND, 22%), and 24 died of melanoma (surveillance, 2%; CLND, 4%). Sixty-eight patients had an isolated nodal recurrence (surveillance, 6%; CLND, 4%). In patients who received adjuvant treatment without undergoing prior CLND, all isolated nodal recurrences were resectable. They also found CLND was associated with improved isolated nodal RFS (HR, 0.36), but not all-site RFS (HR, 0.68). Adjuvant therapy improved all-site RFS (HR, 0.52). It was noted DSS and DMFS did not differ by nodal management or adjuvant treatment.

Comment: Based on the MSLT-2 and DECOG studies, patients with SN involvement are recommended active surveillance rather than completion lymphadenectomy. This is a very large study of 1,154 patients with SLN spread of melanoma and their subsequent management. The median follow-up was only 11 months and there was significant variation in the use of ultrasound surveillance of the affected lymph node basin (an integral part of the MSLT-2 and DECOG surveillance regimes) and CT/PET scanning. Patients from Australian centres were far less likely to undergo complete lymphadenectomy then those in Europe or the US. CLND did not improve loco-regional RFS but was reduced by adjuvant therapy by approximately two thirds in both the surveillance and surgery groups. While this study demonstrates relatively high compliance with the findings from MSLT-2, it is likely that already there is increasing use of adjuvant therapy and reduced use of CLND in routine practice. This change in practice is supported by the data from this study.

Disclosure: the reviewers institution participated in this study.

Reference: Cancer 2021 Jul 1;127(13):2251-2261
Abstract

Ipilimumab alone or ipilimumab plus anti-PD-1 therapy in patients with metastatic melanoma resistant to anti-PD-(L)1 monotherapy: A multicentre, retrospective, cohort study

Authors: da Silva IP, et al

Summary: This multicentre, retrospective, cohort study included 355 patients with metastatic melanoma (unresectable stage III and IV), resistant to anti-PD-(L)1, who had been treated with ipilimumab monotherapy (n=162) or ipilimumab plus anti-PD-1 (n=193). The investigators reported the objective response rate (ORR) was higher with ipilimumab plus anti-PD-1 (31% of patients) than with ipilimumab monotherapy (13% of patients; p<0.0001) at a median follow-up of 22.1 months. OS was longer in the ipilimumab plus anti-PD-1 group (median OS 20.4 months) than with ipilimumab monotherapy (8.8 months, HR 0.50; p<0.0001). Furthermore, PFS was longer with ipilimumab plus anti-PD-1 (median 3.0 months) than with ipilimumab (2.6 months, HR 0.69; p=0.0019). They noted similar proportions of grade 3-5 adverse events in both groups (31% of patients in the ipilimumab plus anti-PD-1 group vs 33% of patients in the ipilimumab group). The most common grade 3-5 adverse events were diarrhoea or colitis (12% patients in the ipilimumab plus anti-PD-1 group vs 20% of 162 patients in the ipilimumab group) and increased alanine aminotransferase or aspartate aminotransferase (12% vs 9%).

Comment: This is an important study, although retrospective, which addresses a major problem - the management of patients who fail first-line anti-PD-1 monotherapy. In summary combination ipilimumab and anti-PD-1 therapy was superior to single-agent ipilimumab for this group of patients with acceptable toxicity. This study represents the most comprehensive evidence to date to support this approach. As would be anticipated there are a number of methodological issues inherent in retrospective and nonrandomised studies noted in this study and are discussed in an associated editorial (Wong and Gyorki). Reassuringly, however, on multivariate analysis combination therapy was independently associated with improved outcomes.

Disclosure: the reviewers institution participated in this study.

Reference: Lancet Oncol 2021 Jun;22(6):836-847
Abstract

Sustainable responses in metastatic melanoma patients with and without brain metastases after elective discontinuation of anti-PD1-based immunotherapy due to complete response

Authors: Dimitriou F, et al

Summary: The researchers evaluated the outcome of patients with advanced melanoma with and without MBM, treated either with anti-PD-1 monotherapy (n = 97) or combined with anti-CTLA4 (n = 28) after elective treatment discontinuation due to CR (n = 86) (group A), or treatment-limiting toxicity (n = 33) and investigator's decision (n = 6) (group B) with subsequent CR. For group A, median duration of treatment was 22 months and median time to CR 9 months. Median duration of treatment for group B was 3 months and median time to CR 7 months. Seven patients from group A and three from group B experienced disease recurrence. Off-treatment survival was not reached. Median off-treatment response time was 19 months and 25 months, respectively. For MBM, median off-treatment response time was 17 months and 28 months, respectively. After a median follow-up of 38 months, seven patients had died, one due to melanoma.

Comment: This is a very comprehensive and detailed review of 125 patients with advanced melanoma with or without brain metastases who ceased anti-PD-1 single agent or combination therapy. Although this is a collected series from a number of institutions with the usual caveats, including considerable heterogeneity in the patient population, the results are consistent with previous data. It is worth reiterating this study includes patients who completed planned treatment with a CR (based on PET scan) but also patients who ceased therapy with less than a CR consequent to treatment limiting immune-related adverse events. 92% were alive without additional therapy three years after discontinuation and it appeared that it was safe to do so even for patients with brain metastases. Patients who recurred fared acceptably with anti-PD-1 on rechallenge. The unresolved issue is what are safe criteria for ceasing treatment.

Reference: Eur J Cancer 2021 May;149:37-48
Abstract

Risk factors for melanoma by anatomical site: an evaluation of aetiological heterogeneity

Authors: Laskar R, et al

Summary: The associations with melanoma by anatomical site for a comprehensive set of risk factors was examined using data from 2,617 people with incident first invasive melanoma and 975 healthy controls. Participants completed questionnaires and polygenic risk scores were derived from DNA samples. When cases were compared with control participants, there were stronger associations for many naevi versus no naevi for melanomas on the trunk, and upper and lower limbs than on the head and neck (P-heterogeneity < 0.001). Very fair skin (versus olive/brown skin) was more weakly related to melanoma on the trunk than to melanomas at other sites (P-heterogeneity = 0.04). It was noted there was no significant difference by anatomical site for polygenic risk. Increased weekday sun exposure was positively associated with melanoma on the head and neck but not on other sites.

Comment: This large Australian-UK study sought to unravel the aetiology of melanoma by site. The current paradigm is a dual pathway model characterised by the naevus pathway, sun exposure at an early age with repeated intermittent exposure leading to early onset melanomas predominantly on the trunk. The alternative sun exposure pathway reflects progressive cumulative sun exposure leading to melanomas in sun affected areas e.g., head and neck in older persons. This study found an association between number of naevi and trunk melanoma and chronic exposure with head and neck melanoma as would be anticipated. Pigmentary phenotype, sun exposure and genetically assessed risk factors had much less of an impact than naevus phenotype on the distribution of melanomas. Apart from the insights into melanoma biology this study potentially provides information to guide clinicians performing melanoma surveillance.

Reference: Br J Dermatol 2021 Jun;184(6):1085-1093
Abstract

Delayed immune-related adverse events with anti-PD-1-based immunotherapy in melanoma

Authors: Owen CN, et al

Summary: This article describes the incidence, nature and management of delayed immune-related adverse events (irAEs) in patients receiving anti-PD-1-based immunotherapy from 20 centres. 118 patients developed a total of 140 delayed irAEs (20 after initial combination with anti-CTLA4), with an estimated incidence of 5.3%. The median onset of delayed irAE was 16 months. The investigators reported 74% of patients were on anti-PD-1 at irAE onset, 12% were <3 months from the last dose and 14% were >3 months from the last dose of anti-PD-1. The most common delayed irAEs were colitis, rash and pneumonitis with 39% of all irAEs being ≥grade 3. Steroids were required in 68% of patients. There were two irAE-related deaths: encephalitis with onset during anti-PD-1 and a multiple-organ irAE with onset 11 months after ceasing anti-PD-1. Early irAEs (<12 months) had also occurred in 58% of patients affecting a different organ from the delayed irAE in 86% of patients.

Comment: Reportedly this is the largest study of delayed irAEs, defined as occurring after 12 months since treatment initiation (n = 118). irAEs were uncommon (5.3%) and did not appear to be related to early onset irAEs and the type was usually different. Most occurred within the first 12 months (i.e., during the second year of treatment) but a small proportion occurred in subsequent years after finishing anti-PD-1 treatment. Most of the irAEs were grade 3 or higher but given the retrospective nature of the study less severe toxicity may have been missed. The need for steroids and immunosuppressive agents was common and two patients died with irAE toxicity. The importance of this study is to highlight the relative infrequency of delayed irAEs which may be severe but nevertheless need to be communicated to patients and considered when deciding on length of treatment with anti-PD-1 therapy.

Reference: Ann Oncol 2021 Jul;32(7):917-925
Abstract

Impact of the time interval between primary melanoma excision and sentinel node biopsy: A systematic review and meta-analysis

Authors: Vargas-Mora P, et al

Summary: This meta-analysis included 6 retrospective studies. Of the 9,705 patients identified 4,383 underwent a SNL biopsy procedure at a time interval defined as early and 4,574 at an interval defined as late. A combined hazard ratio of 1.25 was determined, and there was high heterogeneity (I2 = 83%; P = .002) of the SLN biopsy time interval on melanoma-specific survival (MSS). The combined HR for disease-free survival (DFS) was 1.05, with low heterogeneity (I2 = 9%; P = .36) and the combined HR for OS was 1.25, with low heterogeneity (I2 = 37%; P = .2).

Comment: The original MSLT-1 study allowed a considerable period from excision biopsy to sentinel biopsy but in routine practice, most patients would wait less than 28 days. There is only limited retrospective data which addresses the time interval between melanoma excision and sentinel biopsy and this meta-analysis is based on nearly 9,000 patients from six studies. A variety of cutpoints defining early versus late were used to evaluate effects on MSS, OS and DFS varying from 28 to 43 days (not all cutpoints were used for all of these survival times). No effect on any of these outcome variables and others such as tumour characteristics was noted when comparing short versus delayed time interval. What this study does not address is the effect of any delay on institution of adjuvant therapy following sentinel biopsy which is increasingly becoming standard of care certainly for patients with stage III B and C disease.

Reference: J Am Acad Dermatol 2021 Jul;85(1):128-134
Abstract

Validation of CP-GEP (Merlin Assay) for predicting sentinel lymph node metastasis in primary cutaneous melanoma patients: A U.S. cohort study

Authors: Yousaf A, et al

Summary: The CP-GEP assay combines clinicopathologic and gene expression variables to identify primary cutaneous melanoma patients who may safely forgo SLNB due to their low risk for nodal metastasis. This study aimed to validate the assay in a US cohort of 208 patients with primary cutaneous melanoma. SLNB positivity rate for the entire cohort was 21%. Most patients had a T1b (34%) or T2a (31%) melanoma. In the T1-T2 group (153 patients), CP-GEP achieved an SLNB reduction rate of 41.8% at a negative predictive value of 93.8%. Subgroup analysis showed similar performance in T1-T2 patients ≥65 years of age (51 patients; SLNB positivity rate, 9.8%): SLNB reduction rate of 43.1% (95% CI: 29.3-57.8) at a negative predictive value of 95.5% (95% CI: 77.2-99.9).

Comment: This study reports a previously described clinicopathological gene expression profile assay which classifies patients at high risk or low risk for SLN involvement. This assay has previously been validated in a European study and essentially the results from this report mirror the previous. The Merlin assay is one of several commercially available gene expression profile tests which are increasingly commonly used in the USA. This study was particularly interested in the patients in whom it may be worthwhile considering avoiding a SLN biopsy particularly those with thin tumours or the elderly. This particular assay had a very high negative predictive value for thin, T1 and T2 melanomas but reduced with increasing tumour thickness. The assay was just as effective in the elderly as younger persons. Currently in Australia and New Zealand, these expression profile assays are rarely used and whilst an interesting study of what the future is likely to hold, this report which is small does not provide sufficient justification for routine use at the present time.

Reference: Int J Dermatol 2021 Jul;60(7):851-856
Abstract

