Melanoma Research Review™

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Issue 36 - 2020

In this issue:

Abbreviations used in this issue:

CMM = cutaneous malignant melanoma; **MMS** = Mohs micrographic surgery; **NCDB** = National Cancer Database; **WLE** = wide local excision.

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Welcome to the 36th issue of Melanoma Research Review.

The lead article in this issue investigated the predictive value of FDG-PET imaging for relapse in metastatic melanoma patients treated with immunotherapy. The authors concluded FDG-PET imaging could play a crucial role in predicting long-term outcome and help to decide whether treatment should be discontinued. There are also several articles in this issue focusing on clinicoprognostic characteristics of cutaneous metastatic melanoma, primary dermal melanoma and bone metastases in melanoma.

The concluding articles report updated outcomes of the CheckMate 238 and CheckMate 066 trials. Four year follow-up of the CheckMate 238 trial found nivolumab demonstrated sustained recurrence-free survival benefit versus ipilimumab in resected stage IIIB-C or IV melanoma indicating a long-term treatment benefit with nivolumab. The CheckMate 066 trial investigated nivolumab monotherapy as first-line treatment for patients with previously untreated BRAF wild-type advanced melanoma. Results from the 5-year analysis confirm the long-term survival and durable benefits with nivolumab monotherapy.

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

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Predictive value of FDG-PET imaging for relapse in metastatic melanoma patients treated with immunotherapy

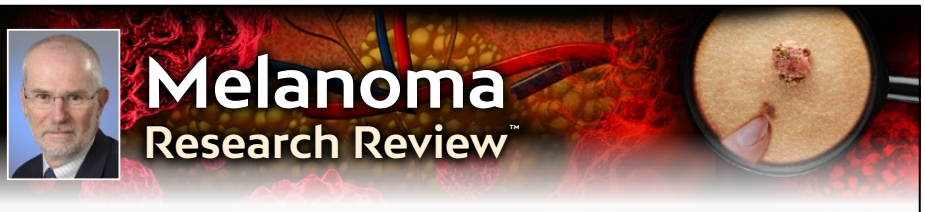
Authors: Mesnard C, et al

Summary: The objective of this retrospective study was to determine whether FDG-PET imaging could be superior to CT scan in distinguishing residual tumours versus the absence of tumour in patients (n =26) with metastatic melanoma treated with anti-PD1 immunotherapy considered to be in complete remission. CT scan and FDG-PET scan had to be performed within a maximum of 2 months of treatment discontinuation. The authors reported two patients had a stable disease on CT scan and a complete metabolic response on FDG-PET scan and none of them relapsed. Ten patients had a partial response on CT scan and a complete metabolic response on FDG-PET scan, and none of them relapsed. The mean treatment duration to achieve a complete remission was 7 months (3-23). They showed that a residual FDG avidity assessed on the FDG-PET scan was significantly associated with a relapse (P = 0.00231).

Comment: This is a small study of only 26 patients, which compared the predictive value of either PET or CT scanning in patients who had completed a course of anti-PD1 therapy for metastatic melanoma. Not surprisingly residual FDG activity at the end of treatment was associated with poorer progression free survival. A complete metabolic response on PET was a better predictor than complete morphological response seen on CT. The authors identified distinguishing pseudo-progression from true progression and granulomatous/sarcoid reactions from persistent disease as further advantages for PET scans. This was a small retrospective study but again highlights the superiority of PET scanning in patients receiving immune checkpoint inhibitor therapy.

Reference: J Eur Acad Dermatol Venereol. 2020 Oct;34(10):2261-2267

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).

Survival in patients with multiple primary melanomas: Systematic review and meta-analysis

Authors: Peek G, et al

Summary: The authors identified 14 eligible studies examining survival in patients with multiple melanomas. Four studies that accounted for survival bias were included in the quantitative review, with three of these reporting a survival disadvantage for multiple primary melanomas, whereas the fourth showed no difference in survival. The pooled hazard ratio was 1.39 (95% CI, 1.07-1.81) but with significant heterogeneity. They noted conclusions on survival varied markedly depending on the statistical method used.

Comment: There is great uncertainty whether multiple primary melanomas are associated with poorer outcomes. Possible reasons for the variation in results may be failure to account for survival bias (i.e. patients must live long enough to develop a second melanoma). Of 14 studies eligible for this meta-analysis only four were sufficiently statistically robust to evaluate the effects of multiple primary melanomas. Possible reasons for a protective or no effect on outcome include 'immunisation' by the first melanoma and closer follow-up by both patient and clinician leading to early diagnosis however this study indicates that outcomes are poorer when appropriate statistical methodology is employed.

Reference: J Am Acad Dermatol. 2020 Nov;83(5):1406-1414
Abstract

Methotrexate treatment for patients with psoriasis and risk of cutaneous melanoma: a nested case-control study

Authors: Polesie S, et al

Summary: This Swedish nested case-control study used registry data to investigate whether methotrexate increases the risk of cutaneous malignant melanoma (CMM) among patients with psoriasis. The study cohort included 395 previously cancer-free patients with psoriasis who had CMM and 3,950 matched cancer-free patients with psoriasis. Of 395 patients with psoriasis who had CMM, 97 (25%) had filled a prescription of methotrexate; of 3,950 controls, the corresponding number was 954 (24%). The authors concluded there was no association between methotrexate exposure and risk for CMM in patients with psoriasis.

Comment: The use of methotrexate and other immune suppressant agents in the general community is common. Previous reports have noted an increased risk of melanoma in patients with rheumatoid arthritis treated with methotrexate but in other studies not specifically confined to rheumatoid arthritis, no effect was noted. This study evaluated the risk in patients with psoriasis and found no evidence of an increased rate. Unfortunately the authors were not able to investigate the effects of cumulative UV dose, skin phenotype and most importantly exposure to PUVA, which is probably associated with an increased risk of melanoma. This study while providing some reassurance does not exclude the possibility of an increased risk of developing melanoma.

Reference: Br J Dermatol. 2020 Oct;183(4):684-691
Abstract

Association of Mohs micrographic surgery vs wide local excision with overall survival outcomes for patients with melanoma of the trunk and extremities

Authors: Demer AM, et al

Summary: This retrospective cohort study examined data from the National Cancer Database (NCDB). Inclusion criteria for the analysis included diagnosis of trunk, upper extremity, or lower extremity melanoma; known Breslow depth; removal by Mohs micrographic surgery (MMS) or wide local excision (WLE); and known last date of survival status. A total of 188,862 in situ and invasive melanomas were included in the analysis (MMS, 2.3%; WLE, 97.7%). The authors concluded there was no overall survival difference among trunk (WLE HR, 1.097; P = .21), upper extremity (WLE HR, 1.013; P = .87), lower extremity (WLE HR, 0.934; P = .49), or combined trunk and extremity (WLE HR, 1.031; P = .51) tumours. Factors associated with increased risk of all-cause mortality on multivariate analysis of all tumours included increasing age, no insurance or nonprivate insurance, positive surgical margins, a Charlson-Deyo comorbidity score greater than 0, tumour ulceration and increasing Breslow depth. Female sex and nonnodular subtype were associated with improved overall survival.

Comment: This was a retrospective study from data obtained from the US NCDB and included patients treated between 2004 and 2015 for melanomas of the trunk and extremity. In summary no difference in all-cause mortality was found between WLE and MMS. Quite extraordinarily this study does not mention the role of sentinel node biopsy, which for most of the study duration was accepted as standard of care (median thickness was 1.4 mm suggesting over half the patients should have had the procedure). It would not be anticipated that there would be a major difference in survival but unfortunately because of the structure of the NCDB, local and/or regional recurrence data was not available. This study does not provide any evidence or support for the widespread use of Mohs in melanomas of the trunk and extremity.

Reference: JAMA Dermatol. 2020 Oct 21;e203950. Online ahead of print.
Abstract

Primary dermal melanoma: clinical behaviour, prognosis and treatment

Authors: Harris CG, et al

Summary: The authors compared the overall, melanoma-specific and disease-free survival outcomes in a cohort of patients with primary dermal melanoma (n = 62) to those of similar cohorts of patients with stage I-II and stage IV M1a melanoma. Median follow-up of 6.3 years. Five-year survival was 87.1% and overall survival was 74.2%. Primary dermal melanoma had a significantly improved overall survival ($p = 0.0002$) and melanoma-specific survival ($p = 0.001$) compared to Stage I-II controls, however there was no difference in disease-free survival ($p = 0.08$). In addition primary dermal melanomas demonstrated improved overall survival ($p < 0.0001$), melanoma-specific survival ($p < 0.0001$) and disease-free survival ($p < 0.0001$) compared to Stage IV M1a controls.

Comment: An uncommon scenario is the patient who presents ab initio with a dermal deposit. Possibilities include a regressed or previously treated primary, an in transit deposit from an unknown primary or a subcutaneous metastasis (stage IV). This report was a retrospective review from the Melanoma Institute of Australia which found improved overall survival and melanoma specific survival for these lesions compared to metastatic disease and stage I-II disease indicating that these lesions most likely represent a form of early stage cutaneous melanoma. Although sentinel biopsy was performed in a number of these cases, none were positive. The limitations of this study include the small numbers (64) and the retrospective nature, although the follow-up was prolonged (6.3 years). Patients should be reassured, outcomes are good but the issue of the margins of excision and sentinel node biopsy are yet to be resolved.

Reference: Eur J Surg Oncol. 2020 Nov;46(11):2131-2139
Abstract

Preliminary analysis of distinct clinical and biologic features of bone metastases in melanoma

Authors: Wilson MA, et al

Summary: The study cohort comprised of patients with cutaneous melanoma. The investigators compared patients with metastatic melanoma and bone metastases to those with metastatic disease but no bone metastases. Of the 463 (42.7%) patients, 198 with unresectable metastatic melanoma had bone metastases and 98 developed bone metastases as first site. The investigators found progression-free survival and overall survival were significantly worse in patients with bone metastases compared to those without bone metastases ($P < 0.001$) independent of treatment modalities, and in patients whose melanoma spread to bone first, compared to those who developed first metastases elsewhere ($P < 0.001$). They noted, patients with bone metastases presented with primary tumours that had more tumour infiltrating lymphocytes ($P < 0.001$) and less often a nodular histologic subtype compared to patients without bone metastases ($P < 0.001$).

Comment: This is an intriguing retrospective study of bone metastases in melanoma. In this report 43% of patients with metastatic melanoma developed bone metastases at some stage, somewhat higher than previously reported. Metastases tended to be axial in location. Patients with bone metastases at any time fared significantly worse than patients without bone metastases. Median survival after diagnosis of bone metastasis was nine months. Paradoxically patients with bone metastases tended to have more favourable primary lesions (less likely to be nodular melanomas and reduced TILs) than those without bone metastasis.

Reference: Melanoma Res. 2020 Oct;30(5):492-499
Abstract

Clinicoprognostic characteristics of cutaneous metastatic melanoma: A retrospective comparative study between acral and nonacral melanoma

Authors: Kang HJ, et al

Summary: Medical database review identified 492 cases of cutaneous metastatic melanoma that had been confirmed by skin biopsy. Cutaneous metastasis occurred in 12.4% of our cohort. The authors noted the frequency of cutaneous metastasis was higher in nonacral melanoma than that in acral melanoma. The mean duration between the initial diagnosis of a primary tumour and cutaneous dissemination was 19.8 months. Cutaneous metastasis developed earlier during the disease course in acral melanoma than that in nonacral melanoma. In addition, cutaneous metastasis was more disseminated, involving multiple anatomy sites in nonacral melanoma than that in acral melanoma. The disease stage at the time of cutaneous metastasis was not significantly different between acral and nonaral melanoma. In-transit metastasis was significantly more common in acral melanoma than that in nonacral melanoma and were commonly associated with visceral involvement in acral melanoma but not in nonacral melanoma. No significant difference in survival during the cutaneous metastasis was observed between acral and nonacral melanoma.

Comment: This study was a retrospective review evaluating the differences in recurrence patterns between acral and cutaneous/non-acral melanoma. Cutaneous metastases (stage 4) were more commonly seen in patients with cutaneous melanoma compared to acral melanoma but in-transit recurrence was far more common with acral melanoma. Visceral metastases were more commonly seen with cutaneous metastasis but for patients with in-transit melanoma, patients with acral primaries had a higher risk of visceral involvement as well. While small, this study points to differences in the natural history of acral melanoma, specifically the much greater incidence of in transit metastases, which indicate a poor prognosis. Patients with acral melanoma tend to be older and present with more advanced disease.

Reference: Int J Dermatol. 2020 Jul 27. Online ahead of print.
Abstract

Adjuvant nivolumab versus ipilimumab in resected stage IIIB-C and stage IV melanoma (CheckMate 238): 4-year results from a multicentre, double-blind, randomised, controlled, phase 3 trial

Authors: Ascierto PA, et al

Summary: CheckMate 238 was a double-blind, phase 3 trial of adjuvant nivolumab (n=453) versus ipilimumab (n=453) in patients with resected stage IIIB-C or stage IV melanoma. This report provides updated 4-year efficacy, initial overall survival, and late-emergent safety results. Median follow-up was 51.1 months with nivolumab and 50.9 months with ipilimumab. The authors reported 4-year recurrence-free survival was 51.7% (95% CI 46.8-56.3) in the nivolumab group and 41.2% (36.4-45.9) in the ipilimumab group (HR 0.71 [95% CI 0.60-0.86]; p=0.0003). With 211 (122% in the nivolumab group and 25% of patients in the ipilimumab group) of 302 anticipated deaths observed, 4-year overall survival was 77.9% (95% CI 73.7-81.5) with nivolumab and 76.6% (72.2-80.3) with ipilimumab (HR 0.87 [95% CI 0.66-1.14]; p=0.31). Late-emergent grade 3-4 treatment-related adverse events were observed in three (1%) of 452 and seven (2%) of 453 patients. It was noted the most common late-emergent treatment-related grade 3 or 4 adverse events reported were diarrhoea, diabetic ketoacidosis, and pneumonitis in the nivolumab group, and colitis in the ipilimumab group.

Comment: This report describes longer-term follow-up (median 51 months) of the CheckMate 238 study, which randomised patients with resected stage III B-C, and IV melanoma to adjuvant nivolumab or ipilimumab. Improved metastasis free survival and recurrence free survival were seen in the nivolumab arm but there was no difference in overall survival. The rate of recurrence after four years of follow-up has slowed with plateauing of the survival curves. The implications of this are as yet unclear but hopefully indicate ongoing long-term control. Nearly half the patients in the ipilimumab arm received immune checkpoint inhibitor therapy on recurrence. There was no significant change in the adverse event profile with ongoing follow-up. This study confirms the superiority of anti-PD-1 over ipilimumab with extended follow-up in this group of patients.

Reference: Clinical Trial Lancet Oncol. 2020 Nov;21(11):1465-1477
Abstract

Five-Year Outcomes With Nivolumab in Patients With Wild-Type BRAF Advanced Melanoma

Authors: Robert C, et al

Summary: CheckMate 066 was a double-blind, phase III trial, investigating nivolumab monotherapy as first-line treatment for patients with previously untreated BRAF wild-type advanced melanoma. The cohort of 418 patients was randomly assigned 1:1 to receive nivolumab or dacarbazine. This report provides the updated five-year analysis. Patients were followed for a minimum of 60 months from the last patient randomly assigned (median follow-up, 32.0 months for nivolumab and 10.9 months for dacarbazine). The authors reported five-year overall survival rates were 39% with nivolumab and 17% with dacarbazine; progression-free survival rates were 28% and 3%, respectively. Five-year overall survival was 38% in patients assigned to dacarbazine who had subsequent therapy, including nivolumab (n = 37). Objective response rate was 42% with nivolumab and 14% with dacarbazine; among patients alive at 5 years, objective response rate was 81% and 39%, respectively. Of 42 patients treated with nivolumab who had a complete response (20%), 88% (37 of 42) were alive as of the 5-year analysis. Among 75 nivolumab-treated patients alive and evaluable at the 5-year analysis, 83% had not received subsequent therapy; 23% were still on study treatment, and 60% were treatment free. The authors noted safety analyses were similar to the 3-year report.

Comment: This report details the results of the CheckMate 066 trial of nivolumab in patients with advanced melanoma after five years minimum follow-up. The hazard ratio reduction of approximately 0.5 is maintained from previous analyses. Outcomes were poorer in patients with elevated LDH but improved in patients whose tumours expressed PDL-1. The depth of the initial response was associated with improved long-term survival. This study confirms the long-term and durable benefits of anti-PD1 therapy. Relatively few patients stopped treatment because of toxicity during prolonged follow up.

Reference: J Clin Oncol. 2020 Nov 20;38(33):3937-3946
Abstract

