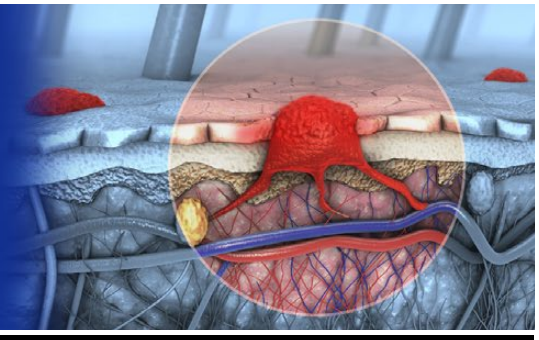
Melanoma Practice Review™



Making Education Easy

Issue 4 - 2020

In this issue:

Abbreviations used in this issue:

AMHN = amelanotic melanoma of the head and neck
NLR = neutrophil-to-lymphocyte ratio

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Welcome to the 4th issue of Melanoma Practice Review.

This new Review covers news and issues relevant to clinical practice in melanoma. It will bring you the latest updates, both locally and from around the globe, in relation to topics such as new and updated treatment guidelines, changes to medicines reimbursement and licensing, educational, professional body news and more. And finally, on the back cover you will find our **new COVID-19 resources**, and a summary of upcoming local and international educational opportunities including workshops, webinars and conferences.

We hope you enjoy this new Research Review publication and look forward to hearing your comments and feedback.

Kind Regards,

Dr Janette Tenne
Medical Research Advisor
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Clinical Practice

Melanomas of the scalp: is hair coverage preventing early diagnosis?

Melanomas of the scalp account for a disproportionately large number of melanoma-related deaths, which may, in part, be due to delayed diagnosis. While hair coverage may protect against UV damage and melanomagenesis, it may also delay diagnosis if and when melanomas do arise.

This retrospective, observational study was conducted at four dermatology referral centres in Australia and Italy to evaluate the characteristics of scalp melanoma as they relate to hair coverage.

Overall, 113 melanoma cases were identified, with most located on the easily visible areas of the hairless scalp (49%) and hairline (15%). The remaining 36% were located in hair-covered areas, but most of these melanomas were in areas with hair thinning (63%). Melanomas in hair-covered locations were usually invasive (81%) with a significantly higher median Breslow thickness (0.8 mm; P=0.004) compared to melanomas located on the bald scalp. However, no significant difference was noted in Breslow thickness when considering just the invasive melanoma cases in each location. Whereas melanomas detected by physicians had a significantly decreased Breslow thickness (P<0.001), hair-covered melanomas were detected more often by relatives, patients, or hairdressers (P=0.05).

Of note, these analyses were not adjusted for other potential prognostic factors (such as age, sex, and histologic subtype) nor was the study designed to assess potential survival differences among groups. Although hair-covered melanomas were less common in this study, the authors urge physicians to be proactive in screening the scalp area and to encourage patients to involve hairdressers in screening this area as well.

Int J Dermatol. 2020 Oct 31.

The challenge of primary gastric melanoma

The purpose of this review was to compare the 1-year survival in patients with primary gastric melanoma who underwent surgery with patients who did not receive treatment.

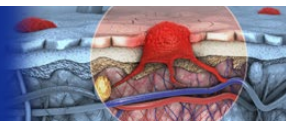
Primary gastric melanoma is a rare clinical presentation with fewer than 50 cases reported globally. Falling under the term of mucosal melanoma, it represents around 1.4% of melanomas and has a poor prognosis at diagnosis. Appearances can vary widely at endoscopy and lesions can appear without melanin. Immunohistochemistry is important at histological workup for identification of gastric melanoma, and is critical in amelanotic lesions. Full clinical and ophthalmological examination should be undertaken to rule out metastasis from a primary cutaneous lesion; PET/CT is the best tool for assessing metastatic spread.

A systematic search of databases for case reports and case series of primary gastric melanoma was undertaken. Forty-four case studies of primary gastric melanoma in the literature were identified. Due to the rarity of primary gastric melanoma, all relevant studies were single-case reports, with no case series published. Thirty-four cases had sufficient history, description and follow-up to be included in an analysis of 1-year survival rates post-diagnosis.

The median age of patients was 64.5 years and 24 patients were male. Seventeen patients were anaemic at presentation. Twenty-three of the 34 patients had surgical resection with curative intent. One-year survival was 56.5% with surgery, increasing to 66% with adjuvant therapy. Mean survival of the surgical group with treatment was 17.7 months versus 22.6 months in the non-adjuvant group. This difference was not statistically significant. Mean survival of the surgical group overall was 21.1 months versus 4.5 months in the nonsurgical group. Distal solid metastases at diagnosis significantly reduced 1-year survival whereas local lymph node metastases did not significantly impact survival.

Early surgical intervention should be offered to patients where suitable. Due to lack of guidelines, treatment regimens are extrapolated from cutaneous melanoma. Genotyping of lesions may help better direct future treatments.

Melanoma Management 2020 7:4



Pandemic medicine: the management of advanced melanoma during COVID-19

This editorial was a report of two US authors' experience and recommendations for management of advanced melanoma patients during the COVID-19 pandemic, highlighting the importance of patient-centred planning based on tumour characteristics, resource availability and the local state of COVID-19 control.

Cancer patients present a unique challenge during the COVID-19 pandemic, as they may be immunosuppressed or at risk of treatment-related toxicities that may cause severe COVID-19 disease manifestations. In the US, restrictions on the healthcare system to reduce COVID-19 transmission have considerably changed melanoma management practices from the initial diagnosis of primary cutaneous disease to systemic treatment for advanced and metastatic melanoma.

Management of primary disease

Because melanoma is usually identified via routine skin exams or in response to a changing mole, restrictions or reluctance to attend initial appointments may result in delayed diagnosis and possibly upstaging. Telehealth initiatives and digital solutions have been utlised for initial melanoma screening and evaluation, although challenges remain. Furthermore, patients with confirmed melanoma may undergo delays in surgical resection and lymph node staging. Fortunately in the US, most surgeries for active cancer management have not suffered stringent restrictions on elective surgery.

Management of advanced disease

Metastatic or unresectable melanoma necessitates urgent treatment with systemic therapy. Before making decisions regarding systemic therapies during the COVID-19 pandemic, there are a number of considerations to be made on a case-by-case basis, such as the aggressiveness of the patient's disease, the dosing schedule and ability to receive treatment at home or in outpatient units, the risk and toxicity profile of each treatment, and the state of COVID-19 in the local hospital and availability of resources for protection and management. Thus far, there is no robust evidence that immune stimulating or cytotoxic drugs worsen outcomes with COVID-19 although this remains the subject of ongoing research.

In patients with advanced melanoma, immune checkpoint inhibitors have become the standard of care, with 5-year overall survival rates of 40–50%. However, immune checkpoint inhibitors are associated with immune-related adverse events caused by aberrant immune cell activation targeting host tissues, which often necessitates immunosuppressive therapies and management in hospital. Patients requiring extended or high-dose immunosuppressants may be at increased risk for COVID-19 infection and severe disease, as well as complications from hospitalisation. An immune-related adverse event of particular concern is pneumonitis. With the substantial pulmonary involvement of COVID-19 and often severe manifestations of pneumonitis, a combination of the two may be potentially life-threatening. Other clinical presentations that overlap with immune-related adverse events and COVID-19 include hepatitis and myocarditis. Due to these concerns, therapy selection and dosing regimens should be managed carefully. For example, anti-PD-1 inhibitors are often combined with CTLA-4 inhibitors due to the benefits of improved response and progression-free survival rates. However, such a combination significantly increases the risk of severe immune-related adverse events from 15–20% with anti-PD-1 monotherapy to 50–60%. These authors therefore suggest that the use of the CTLA-4 inhibitor ipilimumab should be carefully considered, in order to reduce the need for immunosuppressive therapy, the risk of COVID-19 transmission from hospitalisation, and the rate of severe auto-inflammation. Most patients, in the absence of bulky, symptomatic disease, active brain metastases or other adverse prognostic features, should preferentially receive anti-PD-1 monotherapy during the pandemic. Furthermore, patients with advanced melanoma receiving immune checkpoint inhibitors who test positive for COVID-19 should have therapy held for at least one week after symptom resolution to avoid the risk of developing pneumonitis.

Another consideration during the pandemic is the immune checkpoint inhibitor dosing schedule. Although the risk of COVID-19 transmission is reduced by utilising strict screening procedures and social distancing, any contact with the healthcare system can present a possibility of COVID-19 transmission. The US FDA has approved a 6-weekly dosing schedule for pembrolizumab, as has Australia. Nivolumab may also be dosed every 4 weeks. Home-care infusion is a possibility, and discontinuing therapy following a prolonged duration may be considered (e.g., complete response following 1–2 years of therapy) or pausing therapy in areas of high COVID-19 case numbers.

Targeted therapy with BRAF and MEK inhibitors may be considered for patients with metastatic melanoma with BRAF V600 mutations. There is no current evidence that BRAF and MEK inhibitors dampen the antiviral immune response or increase adverse inflammation if an infection occurs.

Once metastatic melanoma is well controlled, other considerations include surgical resection and radiotherapy in patients with isolated areas of metastatic disease, the risk and benefit of delaying therapy, the ICU capacity if surgery necessitates extended observation and the availability of isolation rooms and equipment for the patient.

Melanoma Management 2020 7:3

Is the neutrophil-to-lymphocyte ratio a useful prognostic indicator in melanoma patients?

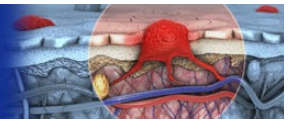
The neutrophil-to-lymphocyte ratio (NLR) is increasing in importance as a biomarker in a number of malignancies including melanoma. Lymphocytes, including natural killer cells and $CD8^+$ cytotoxic T cells, are important for tumour surveillance and destruction. In contrast, neutrophils help suppress lymphocyte proliferation and play a role in the induction of lymphocyte apoptosis.

Emerging data indicates that in high-risk nonmetastatic melanoma, a high NLR is predictive of worse overall and disease-free survival. At this point, however, the optimal cut-off for NLR is unknown, with studies reporting values between 2 and 5. Paradoxically, there are limited data to suggest that in early-stage localised melanoma a high NLR may be protective.

In metastatic melanoma treated with both metastasectomy and immunotherapies, an elevated NLR is also predictive of shortened overall and progression-free survival. The studies utilised an NLR cut-off of 4 or 5.

Future studies should aim to standardise the patient population and NLR cut-offs to improve external study validity. It will also be important to focus on practical management changes such as predicting sentinel or nonsentinel lymph node positivity, the need for adjuvant therapy and the response to immunotherapy.

Melanoma Management 2020 7:3



PBS CHANGES FROM 1 SEPT 2020

Criteria apply, see www.pbs.gov.au

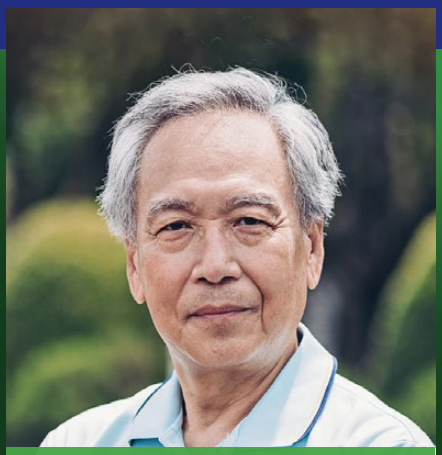
KEYTRUDA®
(pembrolizumab)

ADJUVANT TREATMENT OF MELANOMA

NEW PBS LISTING

Resected Stage IIIB, IIIC, and IIID malignant melanoma
(Regardless of *BRAF* mutation status)[1]

Authority required.



ADVANCED MELANOMA

UPDATED STREAMLINED AUTHORITY PBS LISTING: FIRST-LINE REGARDLESS OF *BRAF* MUTATION STATUS[1]

Unresectable Stage III or Stage IV malignant melanoma

ADVANCED MELANOMA

NEW STREAMLINED AUTHORITY FOR Q6W (400 MG) DOSING[1]

CONSIDER INITIATING IN YOUR ELIGIBLE PATIENTS TODAY[1,2]

KEYTRUDA Q3W (200 mg) and Q6W (400 mg) dosing available[1,2]

SELECTED SAFETY INFORMATION

- Immune-mediated adverse reactions (ImAE), including severe and fatal cases, have occurred in patients receiving KEYTRUDA. These have included but are not limited to: pneumonitis, colitis, hepatitis, nephritis, endocrinopathies, severe skin reactions and severe infusion reactions. ImAEs have occurred after discontinuation of KEYTRUDA, may affect more than one body system and can occur simultaneously.[2]
- The safety of KEYTRUDA was evaluated in 2799 patients with unresectable or metastatic melanoma or metastatic NSCLC. The most common treatment-related serious adverse events were: pneumonitis, colitis, diarrhoea, and pyrexia. The most common treatment related adverse reactions (reported in >10% of patients) were: fatigue, pruritus, rash, diarrhoea, and nausea.[2]
- In the adjuvant melanoma study, the most common treatment-related adverse events observed in the KEYTRUDA arm (reported in >10% patients) were: fatigue or asthenia (37.1%), diarrhea (19.1%), pruritis (17.7%), rash (16.1%), hypothyroidism (14.3%), arthralgia (12.0%), nausea (11.4%) and hyperthyroidism (10.2%).[3]

The Product Information is available at www.msdinfo.com.au/keytrudapi.

References: 1. Australian Government Department of Health. Pharmaceutical Benefits Scheme (PBS). Available at: www.pbs.gov.au Accessed 1 September 2020. **2.** KEYTRUDA Approved Product Information, http://msdinfo.com.au/keytrudapi. **3.** Eggermont AMM *et al.* Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. *N Engl J Med* 2018; 378(19): 1789–801.

Q3W: every 3 weeks. Q6W: every 6 weeks.

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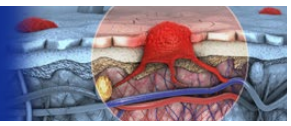
MSD



News in Brief

New systematic therapies and trends in cutaneous melanoma deaths

This US study was a retrospective review of melanoma incidence and mortality among whites (the group most affected by melanoma) in nine US SEER registry areas between 1986 and 2016. Until 2013, overall mortality rates increased by 7.5%. In 2011, the US FDA approved 10 new treatments for metastatic melanoma. From 2013 to 2016, overall mortality decreased by 17.9%. A significant reduction in population-level mortality was associated with the introduction of new therapies for metastatic melanoma. This multiyear decline is the largest and most sustained improvement in melanoma mortality ever observed and is unprecedented in cancer medicine.

Am J Public Health. 2020;110(5):731-733.

Melanoma risk in patients treated with biologic therapy for common inflammatory diseases

This systematic review and meta-analysis quantified the risk of melanoma in biologic-treated patients with inflammatory bowel disease, rheumatoid arthritis and psoriasis, compared with patients treated with conventional systemic therapies. Seven cohort studies comprising 34,029 biologic-treated patients and 135,370 biologic-naive patients treated with conventional systemic therapies were included. The positive associations of melanoma with biologic versus conventional treatment that were reported for patients with inflammatory bowel disease (pooled relative risk 1.20 [95% CI 0.60, 2.40]), rheumatoid arthritis (1.20 [0.83, 1.74]) and psoriasis (HR 1.57 [0.61, 4.09]) were not statistically significant.

JAMA Dermatol. 2020;156:787–94.

E-referrals and teledermatoscopy grading for melanoma

These New Zealand 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 /melanoma in situ. Overall, 45.6% of e-referrals were melanoma or melanoma in situ, with a melanoma/melanoma in situ ratio of 1:1.18.

Australas J Dermatol. 2020;61:147–51.

Amelanotic melanoma of the head and neck

This was a retrospective analysis of the US National Cancer Database comparing the characteristics between patients with a diagnosis of amelanotic melanoma of the head and neck (AMHN; n=368) and those with common malignant melanoma of the head and neck (CMMHN; n=69,267) in order to identify potential risk factors for AMHN. Patients with AMHN had a significantly increased risk of diagnosis after the age of 80 years (OR 3.28; P=0.03), a Breslow depth between 2.01 and 4.00 mm (OR 1.92; P=0.01), ulceration (OR 1.99; P=0.001), and a mitotic count ≥1/mm^2 (OR 2.53; P=0.03). There was no significant variation between groups in terms of gender, specific location on the head and neck, stage, or lymph node involvement.

Int J Dermatol. 2020 Oct 11.

Gamma knife radiosurgery for uveal melanomas and metastases

Gamma knife radiosurgery is the gold standard stereotactic radiosurgery method for the treatment of intracranial malignancies. It is now also used for the treatment of intraocular tumours. This systematic review and meta-analysis examined the efficacy, outcomes, and complications of gamma knife radiosurgery for the treatment of uveal melanomas and metastases. Studies of more than 1000 patients with uveal melanoma and 34 patients with intraocular metastasis treated with gamma knife radiosurgery were eligible for the analysis. In the meta-analysis component of this study, the rate of local control was 96% and rate of tumour regression was 81%.

Lancet Oncol. 2020;21(11):1526-1536.

COVID-19 Resources

The Australasian College of Dermatologists
Clinical Oncology Society of Australia
Cancer Australia
European Academy of Dermatology and Venereology
American Academy of Dermatology
European Society of Medical Oncology
American Society of Clinical Oncology

Conferences, Workshops and CPD

Please click on the links below for upcoming local and international melanoma meetings, workshops and CPD.

The Australasian College of Dermatologists - Events
DermNet New Zealand - Conferences
COSA - Events
MOGA - Events
COMS - Conferences and Meetings on Dermatology
The Conference Website - Dermatology Conferences
The Conference Website - Oncology Conferences

Research Review Publications

Melanoma Research Review
with Professor Michael Henderson
https://tinyurl.com/y95oloy7

Skin Cancer Research Review
with Dr David Simpson
https://tinyurl.com/y9v4htzj

Oncology Research Review
with Dr Genni Newnham
https://tinyurl.com/y8vytjzh

Dermatology Research Review
with Dr Warren Weightman and Clinical Assoc Prof Saxon D Smith
https://tinyurl.com/y7b6m4e3

Product Review – Encorafenib plus binimetinib in unresectable/ metastatic melanoma
https://tinyurl.com/y2xcoxq8

The Australasian College of Dermatologists
has approved all **Dermatology Research Reviews** for accreditation as a **Category 1 Level 1 activity = 1 point per hour.**
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