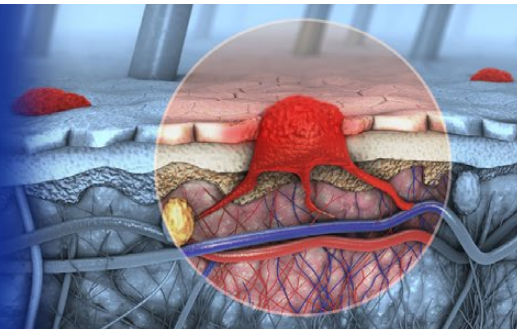


# Melanoma Practice Review™



Making Education Easy

Issue 9 - 2021

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## Abbreviations used in this issue:

FNA = fine needle aspiration; MBS = Medicare Benefits Schedule;  
SLNB = sentinel lymph node biopsy.

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## Welcome to the 9<sup>th</sup> issue of Melanoma Practice Review.

This 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 COVID-19 resources, and a summary of upcoming local and international educational opportunities including workshops, webinars and conferences.

We hope you enjoy this 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

### ESMO Congress 2021: COVID-19 vaccines in patients with cancer

A number of studies presented at the ESMO 2021 Congress showed that individuals with cancer have a suitable immune response to COVID-19 vaccination and experience a similar side effect profile to the general population. A third primary dose may be considered to increase levels of protection in some patients. The studies are welcome as patients with cancer were excluded from the clinical trials that supported the vaccines' authorisation for use.

### Impact of current oncology treatment

The VOICE study from the Netherlands examined the impact of chemotherapy and immunotherapy on the efficacy of the two-dose mRNA-1273 Moderna vaccine in 791 individuals. Four cohorts were enrolled: individuals without cancer; patients with cancer treated with immunotherapy; patients with cancer treated with chemotherapy; and patients with cancer treated with a chemo-immunotherapy combination.

Twenty-eight days after the second vaccine dose, adequate levels of antibodies were detected in 99.6% of individuals without cancer, 93% of patients on immunotherapy, 84% of patients receiving chemotherapy, and 89% of patients receiving chemo-immunotherapy.

Data also showed the importance of receiving two vaccine doses; only about one third of patients on chemotherapy or chemo-immunotherapy achieved a sufficient response after their first dose, compared with two thirds of individuals without cancer.

Similar results were observed in a study from Israel of the Pfizer-BioNTech mRNA vaccine. Among 232 patients with cancer and 261 control subjects, 29% of the cancer patients developed antibodies after one dose, compared with 84% of the control group. Two cases of COVID-19 occurred during the study, both of which occurred in patients who had only received one dose.

### Booster dose?

The UK CAPTURE study revealed that among 585 patients with cancer who received two doses of either the Pfizer-BioNTech mRNA vaccine or AstraZeneca's adenoviral vector vaccine, those with previous COVID-19 infection had higher levels of virus-neutralising antibodies, including against the Delta variant.

Another study showed that the antibody response to vaccination was significantly increased even after the first dose among patients with cancer who had recovered from previous COVID-19 infection.

Such data show that patients with cancer are able to respond to extra immune stimulation, supporting the possibility of a third dose for this patient population.

A study from Israel in individuals aged 60 years or older (comorbidities not defined) showed that a third booster dose of the Pfizer-BioNTech mRNA vaccine 5 months after their second dose reduced the incidence of COVID-19 and severe illness.

### Tolerability

In a phase III randomised controlled trial of 3813 patients with a history of past or active cancer who received the Pfizer-BioNTech mRNA vaccine, the most common adverse effects of vaccination were injection-site pain, fatigue, fever, chills, headache and muscle pain. These events were mostly mild and occurred at a similar rate as within the overall trial population (44,047 participants). Of note, the trial excluded patients on immune-function suppressing anticancer treatment such as chemotherapy.

Read more [here](#)

## Skin cancer and sun protective behaviours in water-based sports: A scoping review

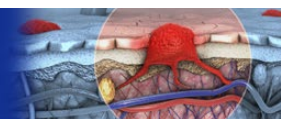
People who participate in outdoor sports have an increased risk of developing skin cancer. However, until now, there has been no review evaluating skin cancer and sun protective behaviours among people who participate in outdoor, water-based sports.

This scoping review by Australian researchers summarised the current evidence relating to outdoor water-based sports, skin cancer, and sun protective behaviours. Nine cross-sectional studies were identified, all defined as low-level evidence.

Skin cancer was reported in the majority of the papers. Among 4377 participants across six countries and five water-based sports, basal cell carcinoma was the most common skin cancer (71%), followed by melanoma (18%) and squamous cell carcinoma (10%). Due to difficulty adhering to sun protective behaviours, the most frequent locations of skin cancer were the head (41%) and upper limbs (27%). Older individuals participating in water-based sports and more experienced athletes had a higher incidence of skin cancer than their younger counterparts.

All participants had a history of sunburn. Participants had a tolerant attitude towards sun overexposure and used sunscreen more than other sun protective measures. Compared to older individuals, younger water-based athletes did not routinely comply with sun protective behaviours.

[Photodermatol Photoimmunol Photomed. 2021 Sep 28](#)



## Melanoma of the hands and feet

While only 4% of skin cancers are melanomas, 80% of skin cancer deaths are caused by melanoma. Melanomas of the hand and foot have a poorer prognosis compared to melanoma in other areas of the body. This is thought to be due to intrinsic biologic characteristics, late diagnosis, challenging surgical removal due to anatomical location, and lack of standard diagnostic and therapeutic guidelines.

Melanoma of the foot is most commonly located on the planar surface, followed by the dorsal surface, then subungual area. Melanoma of the hand is most often located on the subungual area, followed by the dorsal surface, then palmar surface.

Diagnosis of melanoma of the hand and foot is challenging because the standard "ABCDE" (asymmetric shape, border, colour, diameter, evolution) characteristics are not relevant. Newer acronyms have been proposed including "CUBED" (coloured, uncertain, bleeding, enlarged, delayed) and "ABCD" for subungual melanoma (age, brown bands in a brown background, colour in peringual skin, one digit). Standard treatment is surgical excision and reconstruction, with the goal of preserving function and anatomy.

[Clin Plast Surg. 2021;48\(4\):687-698](#)

## Metastatic acral melanoma treatment outcomes: A systematic review and meta-analysis

Acral melanoma is subtype of melanoma found on the palms, soles, and nails. Patients with acral melanoma have poor outcomes if treated with surgery alone. To date, there are no standard guidelines for the management of metastatic acral melanoma.

This systematic review and meta-analysis examined outcomes for patients with metastatic acral melanoma treated with systemic therapy. Nineteen nonrandomised studies were included in the analysis, including 646 patients with acral melanoma and 1609 patients with nonacral melanoma treated with chemotherapy, KIT-targeted drugs, and anti-CTLA-4 and anti-PD-1 checkpoint inhibitor therapy.

Median overall survival was shorter in patients with acral melanoma compared to patients with nonacral cutaneous melanoma (15 months vs 24 months, respectively;  $P < 0.001$ ). Among patients with acral melanoma, 12-month overall survival was greater in patients who received anti-PD-1 monotherapy (53%) compared with anti-CTLA-4 monotherapy (34%;  $P < 0.001$ ).

[Melanoma Res. 2021;31\(5\):482-486](#)

## Cytologic diagnosis of metastatic melanoma by fine needle aspiration: A practical review

This review described the cytomorphology, immunocytochemical tools, and molecular tools used for the diagnosis of malignant metastatic melanoma on fine needle aspiration (FNA).

The most common and initial sites of metastasis are regional lymph nodes and skin followed by distant visceral sites, including the lungs, liver, and central nervous system, and bone. In this scenario, FNA is often the first step to gain a rapid and accurate diagnosis, in combination with ancillary techniques and molecular analysis.

Clinical settings in which FNA may be considered useful include suspicious enlarged lymph nodes or visceral metastases in patients with a known previous malignant melanoma or metastases of unknown primary origin.

Diagnosis of malignant melanoma can be difficult due to the heterogeneity of cytomorphologic findings and architectural patterns seen on smears. Thus, a good understanding of morphology is required but attention also needs to be paid to collection and preparation of the specimen. Immunocytochemistry is also important for confirming the diagnosis and for determining the differential diagnosis, which can include a number of other cancers.

[Cancer Cytopathol. 2021 Jul 26](#)

## Regulatory News

### MBS – new item for sentinel lymph node biopsy for intermediate thickness melanoma

There is a revised structure for MBS items for sentinel lymph node biopsy for cutaneous melanoma with intermediate thickness ( $\geq 1.0$  mm Breslow thickness, or those  $\geq 0.8$  mm with high-risk features).

The changes were made because there was no melanoma specific sentinel lymph node biopsy items in the MBS. The introduction of this item (30311) will allow practitioners to undertake a biopsy of nearby sentinel lymph nodes to determine if the cancer has spread into lymph nodes.

Read more [here](#)

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## News in Brief

### Effects of COVID-19 lockdown on tumour burden of melanoma and cutaneous squamous cell carcinoma

Tumour burdens were compared in patients who underwent surgery for skin cancer during the nationwide lockdown in Spain due to COVID-19 and during the same dates in 2019 before the pandemic. Results showed that the lockdown resulted in a reduction in skin cancer treatment; during the 3-month lockdown, melanoma surgeries decreased by 41% and cutaneous squamous cell carcinoma surgeries decreased by 44%, compared with the previous year. For patients who did get referred, their skin cancer was at a higher stage. Fear of SARS-CoV-2 infection and lesion detection by either the patient or doctor were associated with thicker melanomas. Therefore, health education programs targeting the general population are required to ensure the prompt treatment of patients with skin cancer during lockdowns.

[Acta Derm Venereol. 2021;101\(8\):adv00525](#)

### Dermatologic follow-up and assessment of suspicious lesions

This was a review of follow-up and evaluation of melanoma patients after definitive treatment. To date, there is no consensus across global guidelines regarding the follow-up of melanoma. However, more thorough surveillance is recommended for patients with advanced disease. A systematic approach to surveillance is recommended, with consideration of non-invasive imaging techniques, liquid biopsies and artificial intelligence to improve melanoma detection.

[Clin Plast Surg. 2021;48\(4\):617-629](#)

### Assessment of diagnostic accuracy of dermoscopic structures and patterns used in melanoma detection

This systematic review and meta-analysis assessed the diagnostic accuracy of dermoscopic structures and patterns used in melanoma detection. A search of Ovid Medline, Embase, Cochrane CENTRAL, Scopus, and Web of Science databases identified 40 studies evaluating dermoscopic structures and patterns in melanoma versus nonmelanoma lesions that were suitable for inclusion. A total of 22,796 skin lesions and 5736 melanomas were evaluated. The structures and patterns with the highest risk for melanoma were shiny white structures, pseudopods, irregular pigmentation, blue-white veil, and peppering. With regard to diagnostic accuracy, structures with the highest specificity were pseudopods, shiny white structures, peppering, and streaks, while those with the highest sensitivity were irregular pigmentation, blue-white veil, atypical network, and a multicomponent pattern.

[JAMA Dermatol 2021;157\(9\):1078-88](#)

### Immune checkpoint inhibitors in melanoma

This review discusses the role of immune checkpoint inhibitor therapy in melanoma management. The efficacy of these inhibitors in advanced melanoma and brain metastases was highlighted, along with the effects of combining checkpoint inhibitors or combining immune checkpoint inhibition with antibody therapy. The use of checkpoint inhibitors as adjuvant therapy in high-risk stage III or completely resected stage IV melanoma was also reviewed. In addition, potential biomarkers were described, as well as a thorough discussion of the toxicities associated with immune checkpoint inhibition.

[Lancet 2021;398\(10304\):1002-1014](#)

### Sentinel lymph node biopsy, lymph node dissection, and lymphoedema management

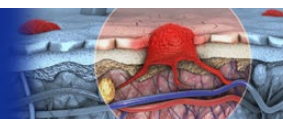
This paper is a review of sentinel lymph node biopsy (SLNB), lymph node dissection, and lymphoedema management options in melanoma. Nodal spread is predicted by melanoma tumour thickness and ulceration. US guidelines for SLNB have recently been updated to include tumour thickness  $\geq 0.8$  mm or any ulcerated melanoma. Mitotic rate is no longer recommended as a characteristic for determining T category. Furthermore, the role for completion lymph node dissection has changed to less surgery in light of the Multicenter Selective Lymphadenectomy Trial (MSLT) II and Dermatologic Cooperative Oncology Group Selective Lymphadenectomy Trial (DeCOG-SLT) data showing improved melanoma-specific survival. Regarding prevention of lymphoedema, modern treatments include immediate lymphatic reconstruction, lymphovenous anastomosis, and vascularised lymph node transfer.

[Clin Plast Surg. 2021;48\(4\):607-616](#)

### Surgical excision margins in primary cutaneous melanoma: A systematic review and meta-analysis

This review evaluated the optimal width of excision margin that lessens the risk of poor surgical outcomes, locoregional recurrence, distant recurrence, and death in patients with primary cutaneous melanoma. Seven randomised controlled trials that enrolled 4579 patients were included in the review. Narrow (1-2 cm) and wide (3-5 cm) excision margins were compared. No statistically significant difference was found in wound infection, wound dehiscence, locoregional recurrence, local recurrence, in-transit metastasis, regional nodal metastasis, distant metastasis, overall death, or death from melanoma, when narrow versus wide excision margins were compared. However, patients who underwent narrow excision had a significant reduction in complex surgical reconstruction (RR 0.30; 95% CI 0.19-0.49;  $P < 0.0001$ ) compared to those who underwent wide excision.

[Eur J Surg Oncol. 2021;47\(7\):1558-1574](#)



**KEYTRUDA®**  
(pembrolizumab)

## KEYTRUDA AS AN ADJUVANT TREATMENT: HELPING PATIENTS WITH RESECTED MELANOMA LIVE THEIR LIVES WITHOUT RECURRENCE\*<sup>1,2</sup>

\*RECURRENCE-FREE SURVIVAL was significantly improved for KEYTRUDA vs placebo in KEYNOTE-054 in patients with melanoma with involvement of lymph node(s) following complete resection, number of events 135/514 (26%) vs 216/505 (43%), HR 0.57 (98.4% CI: 0.43–0.74),  $p < 0.001$ , overall median follow-up of 15.1 months.



**PSB LISTED<sup>3</sup>**

Criteria apply, see [www.pbs.gov.au](http://www.pbs.gov.au)

### SELECTED SAFETY INFORMATION

- Immune-mediated adverse reactions (ImAEs), 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.<sup>1</sup>
- The safety of KEYTRUDA was evaluated in 2799 patients with unresectable or metastatic melanoma or metastatic NSCLC. The most common treatment-related serious AEs 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. The overall safety profile of pembrolizumab for the adjuvant treatment of melanoma was generally similar, with ImAEs the predominant significant toxicity.<sup>1</sup>
- In KEYNOTE-054, the most common adverse reactions (occurring in ≥15% of patients who received KEYTRUDA) were fatigue/asthenia, diarrhoea, pruritus and rash.<sup>2</sup>

The Product Information is available at [www.msinfo.com.au/keytrudapi](http://www.msinfo.com.au/keytrudapi)

**Study design:** KEYNOTE-054 was a multicentre, randomised, double-blind, placebo-controlled trial in patients aged >18 years of age with completely resected stage IIIA (>1 mm lymph node metastasis), IIIB or IIIC melanoma with no in-transit metastases as defined by AJCC 2009 (7th edition). Exclusion criteria included active autoimmune disease, a medical condition that required immunosuppression, mucosal melanoma, ocular melanoma, ECOG PS >1, uncontrolled infections, use of systemic glucocorticoids, and previous systemic therapy for melanoma. In part 1 of the trial (adjuvant), patients were randomised to receive KEYTRUDA 200 mg Q3W (n=514) or placebo IV Q3W (n=505). Patients were treated for 18 doses or until disease recurrence, unacceptable toxicity, protocol violation or withdrawal of consent. The primary efficacy endpoints were RFS in the whole population and RFS in the subgroup with PD-L1 positive tumours.<sup>1,2</sup>

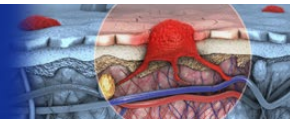
**References:** **1.** KEYTRUDA Approved Product Information, <http://msinfo.com.au/keytrudapi>. **2.** Eggermont AMM *et al*. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. *N Engl J Med* 2018; 378(19): 1789–801. **3.** Australian Government Department of Health. Pharmaceutical Benefits Scheme (PBS). Available at: [www.pbs.gov.au](http://www.pbs.gov.au) Accessed 1 January 2021.

**AEs:** adverse events. **AJCC:** American Joint Committee on Cancer. **ECOG PS:** Eastern Cooperative Oncology Group performance status. **NSCLC:** non-small-cell lung cancer. **PD-L1:** programmed death-ligand.

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## 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](#)

## Research Review Publications

**Melanoma Research Review**  
with Professor Michael Henderson and Peter Hersey  
<https://tinyurl.com/y950loy7>

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

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



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