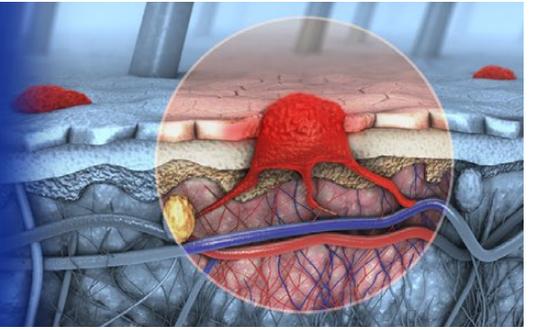


Melanoma Practice Review™



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Issue 5 - 2021

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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 5th 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 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

Melanoma and the gastrointestinal tract: Maintaining a high index of suspicion

This article discusses the symptomatology and management of metastatic melanoma of the gastrointestinal tract. A case report is described, highlighting the severity of melanoma and its negative impact on the gastrointestinal tract.

Metastatic melanoma of the gastrointestinal tract is often detected post-mortem; a clinical diagnosis is made in only 2% of living cases. Patients with metastatic melanoma to the gastrointestinal tract can present with nonspecific, generalised gastrointestinal symptoms such as abdominal pain or constipation. As such, gastrointestinal symptoms in a patient with cutaneous melanoma should prompt endoscopic investigation. The challenge lies in that most metastatic melanomas of the gastrointestinal tract occur in the jejunum and ileum, thus standard oesophagogastroduodenoscopy and colonoscopy may not reveal the cancer. Therefore, in symptomatic patients with negative endoscopy, capsule endoscopy should be considered to allow thorough examination of the gastrointestinal tract.

Treatment involves surgery, chemotherapy, immunotherapy, or participation in clinical trials. Surgery is almost never curative, but is considered palliative.

These authors describe the case of a 49-year-old female with superficial spreading melanoma of the back, who presented three years later with gastrointestinal symptoms including decreased oral intake, generalised abdominal pain, fatigue, a 13.6 kg weight loss, with nausea and vomiting for eight weeks.

The patient underwent percutaneous endoscopic gastrostomy which revealed metastasis to the stomach and duodenum; she had three mucosal polypoid nodules in the gastric body and several mucosal nodules in the duodenum. Biopsies detected S-100 and MART-1 positive metastatic melanoma. MRI of the brain showed a very subtle region of increased signal in the right pons.

The patient was started on enteral nutrition, along with antiemetics to control nausea and vomiting. She also underwent stereotactic radiosurgery and was started on nivolumab.

This case highlights the need for a high index of suspicion of gastrointestinal metastasis in melanoma patients with gastrointestinal symptoms.

[Cureus. 2021;13\(2\):e13408.](#)

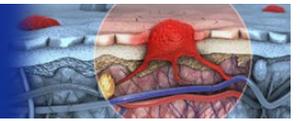
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Acral lentiginous melanoma in situ: dermoscopic features and management strategy

This paper described clinical and dermoscopic findings in patients with acral lentiginous melanoma in situ (ALMIS) and proposed a dermoscopic algorithm for the diagnosis of ALMIS.

Twenty-one patients with ALMIS and available dermoscopic images were retrospectively evaluated at a single institution between January 2013 and February 2020. Clinical and dermoscopic characteristics were examined and compared between small (< 15 mm) and large (≥ 15 mm) lesions.

Small lesions had significantly fewer parallel ridge patterns (54.5% vs 100%; $P=0.035$), irregular diffuse pigmentation (27.3% vs 100%; $P=0.001$) and grey colour (18.2% vs 90%; $P=0.002$), compared with large lesions.

Two patients with small ALMIS were also described. These patients initially had pigmented macules measuring 2.5 mm and 3.5 mm, respectively, with a non-typical pattern detected on initial dermoscopic examination. However, serial follow-up dermoscopic evaluation showed an increase in size and changing dermoscopic patterns. Histopathologic analysis confirmed ALMIS, of 4.5 mm and 5.0 mm, respectively. These cases highlight the importance of detecting small evolving pigmented macules for the early detection of malignant lesions.

Based on the authors data and limited evidence from the literature, they suggested the following stages for diagnosis of ALMIS:

- In a patient presenting with a melanocytic lesion on glabrous skin, evaluate for parallel ridge patterns.
- If parallel ridge patterns are present, differential diagnoses include acral subcorneal haemorrhage, exogenous pigmentation including para-phenylenediamine, chemotherapy-induced hyperpigmentation, hereditary syndromes such as Peutz-Jeghers syndrome or Laugier-Hunziker syndrome, acral Spitz nevus, and congenital melanocytic nevus. If benign causes of parallel ridge patterns can be ruled out, biopsy is recommended.
- If parallel ridge patterns are not present, evaluate the lesion for typical benign patterns (parallel furrow, lattice-like, regular fibrillar). If these patterns are present, the lesion is benign and no further treatment is necessary.
- If typical benign patterns are not present, the lesion has a non-typical pattern and should be evaluated for other malignant features.
- Malignant features include asymmetry, multicolour, irregular diffuse pigmentation, irregular dots and globules, blotches, irregular fibrillar pattern, regression, blue-white veil, or atypical vascular patterns; if present, consider histopathologic examination.
- If malignant features are absent, examine the lesion size. Excise lesions with a diameter > 7 mm for histopathologic examination. Closely monitor lesions with a diameter ≤ 7 mm, and, if the lesion shows any change in size, colour or pattern, consider biopsy.

[Sci Rep. 2020;10\(1\):20503.](https://doi.org/10.1038/s41598-020-20503-0)

Whole-body magnetic resonance imaging: technique, guidelines and key applications

Many international guidelines now recommend whole-body MRI in the management of patients with melanoma and other cancers including multiple myeloma and prostate cancer. Its use is also increasing for metastatic breast cancer, ovarian cancer and lymphoma, and cancer screening.

Whole-body MRI is an imaging technique devoid of ionising radiation that can provide essential imaging of the whole body in less than 40 minutes. Sequences to examine specific regions of the body may complement whole-body MRI if required. In many cases, whole-body MRI is more effective than bone scintigraphy and CT in detecting and characterising lesions, assessing their response to therapy and in screening of high-risk patients.

In the setting of melanoma, the German Dermatological Society and the Dermatologic Cooperative Oncology Group recommend the use of whole-body MRI as an effective substitute to contrast-enhanced CT or PET/CT for follow-up of advanced melanoma (stage III or greater) and this is also the recommendation in Swiss guidelines for the treatment and follow-up of cutaneous melanoma. Whole-brain MRI is also able to effectively detect extracranial metastases from melanoma and other tumours in a number of body regions.

The current Cancer Council Australia Guidelines For Cutaneous Melanoma ([cancer wiki melanoma](https://www.cancer.gov.au/clinical-trials/guidelines-and-research/research-reports/cancer-wiki-melanoma)) are an evidence based and updated guide to clinical practice in Australia. In summary, whole-body MRI is less accurate than standard PET-CT scans (level of evidence II). Furthermore it is limited by contraindications such as metal implants, long scan times and reduced diagnostic accuracy of lung nodules in addition to high inter-reader variability and cost. If surveillance imaging is to be performed PET-CT is the appropriate diagnostic approach.

[Ecancermedscience. 2021;15:1164.](https://doi.org/10.1186/s12916-021-01164-4)

Metastatic melanoma causing recurrent intussusception and perforation of small bowel: case reports and literature review

These authors presented cases of recurrent jejunum-jejunal intussusception and jejunal perforation due to metastatic melanoma.

Gastrointestinal tract metastases are detected in around 20% of patients with stage IV metastatic cutaneous melanoma. The most common sites of metastases are the small bowel, followed by the large bowel and the stomach. Intestinal intussusception and bowel perforation due to metastatic cutaneous melanoma are rare.

Case 1

A 43-year-old male receiving treatment for malignant melanoma presented with abdominal pain and distention. A 10 cm intussuscepted jejunum was resected and the patient was discharged with good bowel sound and normal bowel motions. A second exploration was conducted due to failure to pass gas and stool 22 days after the first operation. Reintussusception was detected and resection of the affected jejunum was performed. The patient was discharged on the postoperative fifth day and transferred to an oncology unit for ongoing treatment.

Case 2

A 63-year-old male receiving treatment for malignant melanoma presented with abdominal pain and signs of peritonitis. Abdomen CT revealed free air in the abdomen suggesting intestinal perforations. A perforated area at 80 cm from the duodenal-jejunal flexure was closed. There were mesenteric oedema and pigmented lesions in the jejunal segment. The patient was discharged at the fifth day with a plan for further treatment.

Discussion

Surgeons should be aware of malignant intussusception in patients presenting with symptoms of bowel obstruction and abdominal pain and a past history of cutaneous melanoma.

The small intestine is well perfused, allowing for metastasis from cutaneous melanomas. Primary intestinal melanoma usually occurs in the ileum as a single intramural lesion, whereas metastasis to the gastrointestinal tract typically occurs in both the jejunum and ileum as polypoid submucosal lesions. Ulceration and amelanotic characteristics may be present.

Preoperative diagnosis of metastatic or small intestine melanoma is challenging.

Anastomotic site intussusception is a very rare complication post resection of the proximal jejunum. Risk factors include abnormal motility in proximity to the duodenojejunal flexure, larger diameter, and two-layer Albert-Lembert type anastomosis. High motility and a relatively large enteric diameter of the proximal small intestine may increase the risk of intussusception.

Otherwise asymptomatic patients with intussusception due to metastatic melanoma should be followed, with a low threshold for surgery particularly if they are receiving systemic therapy. Surgical resection is indicated in symptomatic patients with metastatic melanoma.

For patients with bowel obstruction due to intussusception, resection of the intussuscepted segment is recommended.

For patients with bowel perforation from metastatic melanoma, treatment decisions may be impacted by the patients's status, extent of disease and extent of any contamination. Laparotomy including intestinal resection possibly with lymph nodes is the treatment of choice. Surgical closure for small perforated areas may be considered for palliation.

[Melanoma Manag. 2021 Jan 18;8\(1\):MMT54.](https://doi.org/10.1186/1745-7581-18-1)

Clinical impact of COVID-19 on patients with cancer treated with immune checkpoint inhibition

New research, led by Melanoma Institute Australia, has shown that cancer patients treated with immunotherapy are not at a higher risk of developing severe COVID-19 infection compared to other cancer patients. This finding will have implications for clinical decision-making in patients being treated with immunotherapy for cancer, including melanoma.

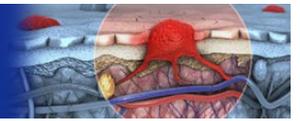
Previous studies have revealed that cancer patients with COVID-19 are more likely to develop severe and fatal COVID-19 compared to those without cancer. However, it was not known if patients with cancer treated with immunotherapy would have an increased or decreased risk of severe COVID-19, which led to the current study.

The study analysed data from 110 patients with SARS-CoV-2 while on treatment with immune checkpoint inhibitors without chemotherapy in 19 hospitals in Australia, Europe, and North America. The primary endpoint was clinical outcomes and factors associated with hospital and ICU admission and mortality.

Eighty-three (75%) patients had advanced cancer, including 64 (58%) with melanoma. Thirty-five (32%) patients were admitted to hospital and four patients were admitted to ICU. Eighteen (16%) patients died and all 18 had advanced cancer. COVID-19 was the primary cause of death in 8 (7%) patients. Factors independently associated with higher rates of hospital admission for COVID-19 management were ECOG performance status ≥2, treatment with combination immune checkpoint inhibitors and presence of COVID-19 symptoms. Immune checkpoint inhibitor therapy was interrupted due to SARS-CoV-2 infection in 76 (73%) patients, 43 (57%) of whom restarted treatment.

The authors concluded that COVID-19-related mortality in patients treated with immune checkpoint inhibitors does not appear to be higher than previously published mortality rates for patients with cancer. Mortality for patients treated with immune checkpoint inhibitors was high compared to previously reported rates for hospitalised patients with cancer and was due to COVID-19 in almost half of patients.

[J Immunother Cancer. 2021;9\(1\):e001931.](https://doi.org/10.1186/s12916-021-01931-4)



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*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.



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- 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.¹
- 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.¹
- In KEYNOTE-054, the most common adverse reactions (occurring in ≥15% of patients who received KEYTRUDA) were fatigue/asthenia, diarrhoea, pruritus and rash.²

The Product Information is available at www.msdsinfo.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.^{1,2}

References: **1.** KEYTRUDA Approved Product Information, <http://msdsinfo.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 Accessed 1 January 2021.

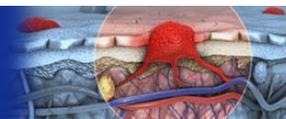
AEs: adverse events. **AJCC:** American Joint Committee on Cancer. **ECOG PS:** Eastern Cooperative Oncology Group performance status. **NSCLC:** non-small-cell lung cancer.

PD-L1: programmed death-ligand.

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News in Brief

Cancer Council Australia: Diagnosis and management of cutaneous melanoma

This article describes key evidence that has informed new Cancer Council Australia melanoma management guidelines. Clinical trials examining sentinel node biopsy, completion lymph node dissection and adjuvant medical therapies have provided evidence that has substantially changed practice. Complete excisional biopsy to achieve accurate tumour microstaging is essential. For patients with stage III disease, surgery is now recommended less often, and systemic therapies are potentially life-extending.

[Aust J Gen Pract. 2020;49\(11\):733-9](#)

Cancer Council Australia: Management of melanoma brain metastases

Cancer Council Australia established a multidisciplinary working party to produce guidelines for the management of melanoma brain metastases. It is recommended that such patients should be managed within a multidisciplinary team of melanoma specialists. Surgery is recommended for the treatment of symptomatic brain metastases. Stereotactic radiotherapy is recommended for single or a small number of asymptomatic brain metastases. Drug therapy may be considered for initial treatment of asymptomatic metastases if patients have not received previous systemic therapy. Palliative benefits may be provided by whole brain radiotherapy in patients with multiple lesions..

[Eur J Cancer. 2021;142:10-17.](#)

Sun protective clothing and sun avoidance practices in patients with melanoma

This paper compared photoprotective practices of patients with a personal history of melanoma versus those without skin cancer. Those with a melanoma history were more likely to report increased use of sun avoidance, shade, sunscreen, and wearing long sleeves and hats. However, the rates of recent sunburn between the groups did not differ. Only sun avoidance and long sleeves were associated with a decreased rate of sunburn. Melanoma patients also had decreased vitamin D supplementation. Dermatologists should recommend sun avoidance and use of photoprotective clothing as more reliable sun protective methods.

[Dermatol Surg. 2020 Sep 24.](#)

A review of desmoplastic melanoma

Desmoplastic melanoma is an uncommon melanoma subtype with biology that differs from that of other melanomas. It requires specific management strategies but few current guidelines address these. Patients with desmoplastic melanoma have substantially lower rates of sentinel node positivity and distant metastasis compared to patients with other melanomas. While local recurrence of desmoplastic melanoma is higher, resection margins wider than those recommended for non-desmoplastic melanomas have not led to better outcomes. When histological clearance ≥ 8 mm is not possible, adjuvant radiotherapy can decrease the risk of local recurrence.

[J Eur Acad Dermatol Venereol. 2021 Feb 5.](#)

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[MOGA - Events](#)

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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>

Dermatology Research Review

with Dr Warren Weightman and Clinical Assoc Prof Saxon D Smith

<https://tinyurl.com/y7b6m4e3>

SMR Virtual Congress 2020 Conference Review

<https://tinyurl.com/4lpvm98c>



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