

# Melanoma

---

**Consensus in Diagnosis and Management  
from Taiwanese Experts**

# 序言

曾經以為台灣的黑色素癌治療只要依據美國的治療準則執行即可，但是最近因為健保給付越來越無法跟上最新的治療準則，加上包括台灣的亞洲地區國家的黑色素癌與歐美地區的黑色素癌有明顯的不同，因此萌生台灣需要有自己的黑色素癌治療準則的想法。兩年前與許多黑色素癌治療的專家討論國內治療的現況，發現我們需要與多個黑色素癌診斷治療相關的學會合作，找出與歐美治療準則有差異的地方加以討論，並與相關領域的專家們共同提出診斷治療的共識，一方面讓經驗比較少的醫師們有所參考，另一方面也希望藉由準則的共識提供國家相關政策的制定參考。

經過了數次的討論開會文字修飾，終於完成了這一版的黑色素癌治療共識，我們也知道癌症治療日新月異，這一版完成的時候又有許多新的資料發表了，其中有些資料更會改變原先討論者的想法與治療順序。幾經思考，決定先把這一版先出刊，之後定期做修改，以及跟上歐美地區治療黑色素癌的腳步，讓包括台灣在內的亞洲人能夠得到最佳、最適合亞洲人的黑色素癌治療方案，並且能夠提供國家政策制定與健保給付的參考。感謝各個學會的支持與作者群的付出，讓這一本治療共識終於成真。

台灣免疫暨腫瘤學會

理事長 張文震

2022/11

# 序言

黑色素瘤屬皮膚癌中較為致命的惡性腫瘤，病灶不只侷限於皮膚，甚至出現於體腔或臟器內，惡性程度高且轉移能力強，是個相當棘手的癌症。

黑色素瘤的發生率及好發部位和人種有關，白種人的發生率遠高於黃種人和黑人。白種人好發於日曬部位，而黃種人以四肢末端居多，因此，針對台灣的病患，在肢體末端部分的黑色素腫瘤更需提高警覺。

由於惡性度及死亡率高，專家學者長久以來投入很多心力做了相關研究，值得注意的是，最新的治療已經邁入標靶藥物時代，而在癌症免疫治療方面更有突破性的進展和療效，不僅助於延長患者的存活期，更能降低復發率，為黑色素瘤患者帶來一線生機。

台灣免疫暨腫瘤學會邀請相關醫學會專家編撰本手冊，兼具理論及實務經驗而成，針對黑色素瘤的檢驗、診斷、和治療選項做統整性的介紹，有別於白種國家的需求，對台灣而言是創舉且實用的指引。期待未來醫師和病人共同努力配合之下，能早期診斷，早期治療以提高病患的治癒率，讓病患免於死亡的恐懼。

中華民國癌症醫學會  
理事長 楊志新

# 序言

惡性黑色素瘤是一種從黑色素細胞發展而來的癌症，屬於皮膚癌中嚴重的一種惡性腫瘤，若能早期診斷治療可以提高治癒率。

醫療現在是跨領域的團隊合作，此次由台灣免疫暨腫瘤學會、臺灣皮膚科醫學會、台灣病理學會、中華民國癌症醫學會及中華民國核醫學學會的專家們攜手合作訂定黑色素瘤的診斷及治療的共識，涵蓋了：疾病介紹、臺灣黑色素瘤的流行病學資料、切片及病理檢查（包含莫氏顯微手術、前哨淋巴結切片）、基因檢測（BRAF V600 突變）、整體評估及追蹤、全身治療（Target therapy 及 Immuno-Oncology），也對粘膜黑色素瘤和葡萄膜黑色素瘤提出治療建議。

此次共識手冊圖片精美、內容簡潔易懂，讓臨床醫師及病友更瞭解此一疾病。期待能讓黑色素細胞瘤患者接受最好的治療，以提升患者的存活率。

臺灣皮膚科醫學會

理事長 趙曉秋

2022/11/05

Melanoma is a cancer that develops from melanocytes and is a serious malignant tumor of skin cancer. Early diagnosis and treatment can improve the cure rate.

Medical care is now a cross-disciplinary teamwork. This time, experts from the Taiwan Society for Immunotherapy of Cancer, Taiwanese Dermatological Association, Taiwan Society of Pathology, Taiwanese Oncology Society, and Society of Nuclear Medicine, Taiwan worked together to define the diagnosis and treatment consensus of melanoma.

The consensus covers: disease introduction, epidemiological data of melanoma in Taiwan, biopsy and pathology ( include Mohs micrographic surgery and sentinel lymph node biopsy), molecular testing (BRAF V600 mutation), Baseline workup and follow-up, imaging, systemic treatment (Target therapy and Immuno-Oncology) and mucosal melanoma and uveal melanoma.

This consensus handbook has beautiful pictures, concise and easy-to-understand content, providing clinicians and patients with a better understanding of this disease. Looking forward to allowing melanoma patients to receive the best treatment and improve patient survival.

President, Taiwanese Dermatological Association

**Sheau-Chiou Chao**

# 序言

看到這份圖文並茂的黑色素瘤診斷治療準則指引終於完成，真是令人欣慰，也容我先向台灣免疫暨腫瘤學會張文震理事長及所有參與編纂的專家與醫師們致上崇高的敬意與謝意。這個艱鉅的工作緣起於張文震理事長的發想，張理事長希望透過集合台灣各相關領域專家學者豐富的診斷與治療經驗，集結成冊，提供黑色素瘤診斷與治療相關的醫師參考，給病人最高品質的診療，並將此台灣經驗分享國際，期對醫學領域有所貢獻。

此指引自 2021 年 4 月開始著手準備，歷經 1 年半，於 2022 年 10 月完成編寫，台灣病理學會有此榮幸被邀請共襄盛舉，協助此指引之病理醫師團隊包含有：林口長庚醫院黃彥霖醫師、陳冠樺醫師、臺中榮總陳志榮醫師、成大醫院巫政霖醫師。病理醫師們與全國各大醫學中心之皮膚科、血液腫瘤科等臨床醫師及其他相關專科別之醫師們進行跨科別討論，除各自編寫之外，另外舉行線上加實體討論會，修訂共識達 5 次以上，將各領域寶貴經驗相互串連，充分展現台灣的醫療實力，為黑色素瘤的診療立下嶄新的里程碑。

再次感謝張文震理事長及所有參與編纂的專家與醫師們，為各相關人員、指引使用者及病人所作的努力，也歡迎所有使用者不吝提出指教與意見，作為未來編修重要的參考。感恩！

台灣病理學會  
理事長 賴瓊如  
2022/11/4

# 序言

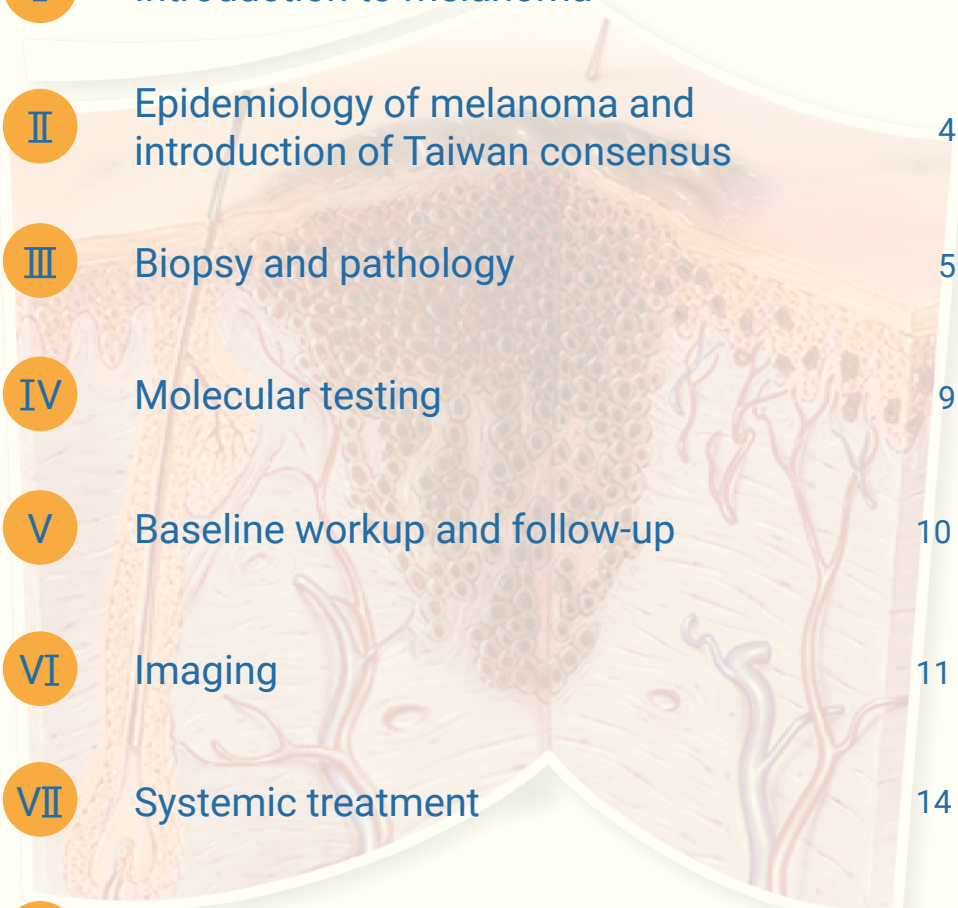
黑色素瘤是黑色素細胞的惡性腫瘤，不僅存在於皮膚，如腸道、眼睛或身體的任何部位皆可能發現，且值得注意的是黑色素癌之全球盛行率有上升之趨勢，根據我國癌症登記報告，台灣黑色素癌的盛行率也逐年上升。

雖然專家呼籲民眾自我篩檢的重要性，但要如何確切的早期診斷和治療是處理黑色素瘤的一大課題。所幸隨著醫學科技發達，黑色素癌的相關研究和治療更是有突破性的發展，例如標靶藥物和免疫治療藥物等治療方法，也大幅地改善患者的存活和預後。

本手冊由台灣免疫暨腫瘤學會發起，邀請各領域的專家醫師編稿及多次會議討論，將其專才和實務經驗攜手合作共同分享的成果。很高興本學會能在此手冊盡棉薄之力，提供核子醫學運用在診斷治療過程中的專業意見，讓本臨床上黑色素瘤實用手冊能提供醫療專業更便利與豐富的資訊，也讓我們朝向共同目標提升黑色素瘤診療醫學，以達到嘉惠病患的目的。

中華民國核醫學學會  
第九屆理事長 顏若芳

# Index



I	Introduction to melanoma	2
II	Epidemiology of melanoma and introduction of Taiwan consensus	4
III	Biopsy and pathology	5
IV	Molecular testing	9
V	Baseline workup and follow-up	10
VI	Imaging	11
VII	Systemic treatment	14
VIII	Mucosal melanoma and uveal melanoma	17



# Introduction to melanoma

## What is melanoma?

Melanoma is a skin cancer developed from pigment cells called melanocytes in the outermost layer of the skin (epidermis). It is a serious disease because the rate of metastasis is often high<sup>1</sup>.



Photo (left panel) credit: National Comprehensive Cancer Network® Guidelines for Patients. Melanoma. <https://www.nccn.org/patients/guidelines/content/PDF/melanoma-patient.pdf>. Accessed 5Aug2022.

Photo (right panel) credit: Dr. Yi-Hua Liao

Melanoma, skin cancer<sup>1</sup>

## What are the risk factors for melanoma?

- Environmental factors include exposure to ultraviolet light from tanning beds or sun exposure<sup>1,2</sup>.
- Genetic predispositions include presence of germline mutations or polymorphisms predisposing to melanoma and family history<sup>2</sup>.
- Male sex<sup>2</sup>.
- Age >60 years old<sup>2</sup>.
- Mechanical stress may be related to acral lentiginous melanoma<sup>3,4</sup>.

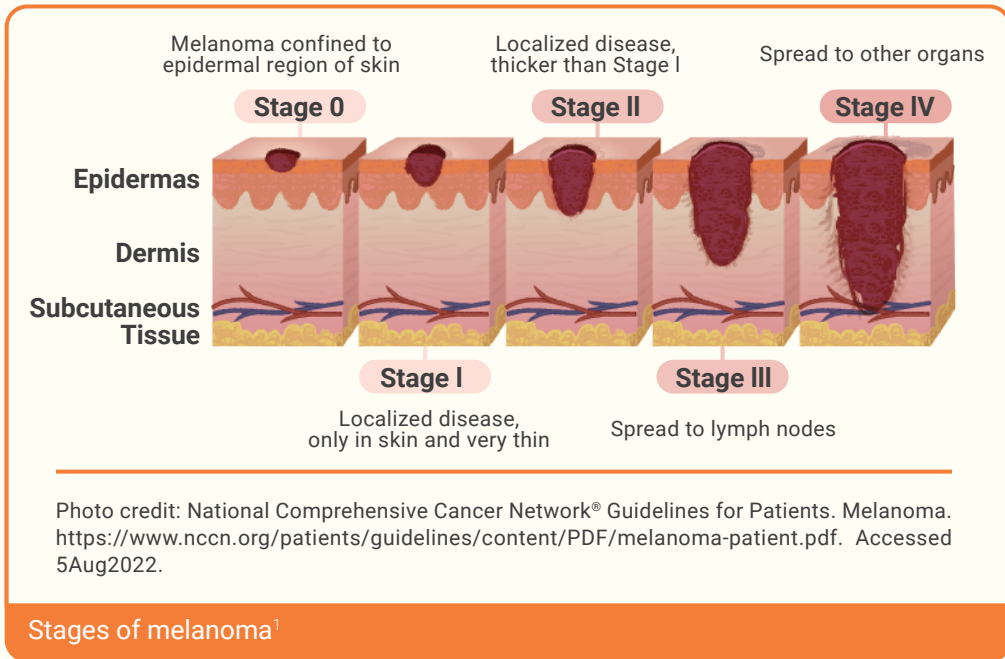
## What are the signs and symptoms of melanoma?

Melanoma can be found anywhere on the body, including areas with the most sun exposure and areas with little to no sun exposure. People should be attentive of changes in existing moles, new spots on the skin, or any spot that looks different from all the other spots on the skin<sup>1</sup>.



## How to stage melanoma?

Melanoma is staged according to the American Joint Committee on Cancer (AJCC) TNM staging system. T stands for the primary tumor depth; N stands for the number of tumor-involved lymph nodes (LNs); and M stands for the distant metastasis<sup>2</sup>. The following image depicts the different stages of melanoma<sup>1</sup>.



## References

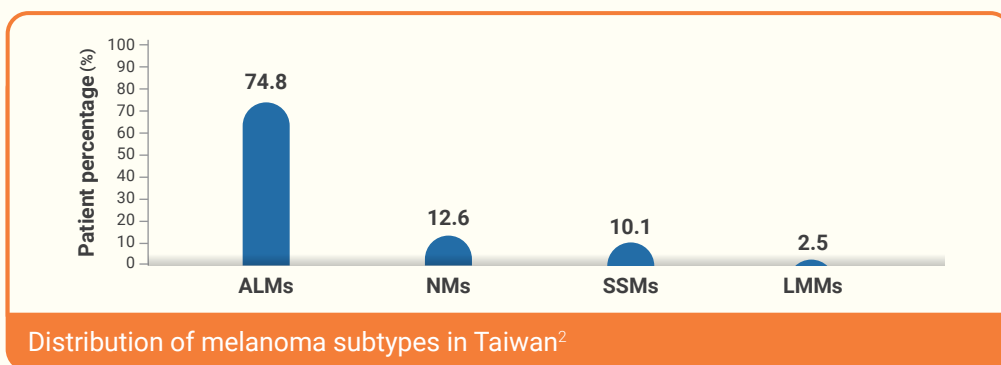
1. National Comprehensive Cancer Network® Guidelines for Patients. Melanoma. <https://www.nccn.org/patients/guidelines/content/PDF/melanoma-patient.pdf>. Accessed 5Aug2022.
2. National Comprehensive Cancer Network® Clinical Practice Guidelines. Melanoma: Cutaneous. Version 2.2021 – February 19, 2021. [https://www.nccn.org/professionals/physician\\_gls/pdf/cutaneous\\_melanoma.pdf](https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf). Accessed 5Aug2022.
3. Minagawa A, et al. N Engl J Med. 2016 Jun 16;374(24):2404-6.
4. Sheen YS, et al. Sci Rep. 2017 Jul 17;7(1):5564.



# Epidemiology of melanoma and introduction of Taiwan consensus

Melanoma is a rare disease in Taiwan with incidence rates of 0.82 per 100,000 in males and 0.68 per 100,000 in females in 2019. The number of patients who were diagnosed with melanoma accounted for 0.24% of all patients with malignant tumors, and the number of patients who died from melanoma accounted for 0.30% of all deaths due to malignant tumors in the same year<sup>1</sup>.

Cutaneous melanomas are categorized by the World Health Organization (WHO) into the following four subtypes: acral lentiginous melanomas (ALMs), superficial spreading melanomas (SSMs), lentigo maligna melanomas (LMMs), and nodular melanomas (NMs). The most common subtype of melanoma in Taiwan is ALM, while NMs, SSMs, and LMMs are less common<sup>2</sup>.



In order to enhance diagnosis and treatment of melanoma in Taiwan, experts from the Taiwan Society for Immunotherapy of Cancer, the Taiwanese Dermatological Association, the Society of Nuclear Medicine, the Taiwan Society of Pathology, and the Taiwan Oncology Society developed a consensus based on clinical guidelines from the National Comprehensive Cancer Network (NCCN)<sup>3</sup> and the European Society for Medical Oncology (ESMO).<sup>4</sup> The booklet will introduce the contents of said consensus to help healthcare professionals understand more about melanoma and provide the best care for melanoma patients in Taiwan.

## References

1. Health Promotion Administration, Ministry of Health and Welfare, Taiwan. Cancer registry annual report, 2019. [https://www.hpa.gov.tw/Pages/ashx/File.ashx?FilePath=~/File/Attach/14913/File\\_18302.pdf](https://www.hpa.gov.tw/Pages/ashx/File.ashx?FilePath=~/File/Attach/14913/File_18302.pdf). Accessed 5Aug2022.
2. Sheen YS, Liao YH, Liaw JY, et al. Prevalence of BRAF and NRAS mutations in cutaneous melanoma patients in Taiwan. *J Formos Med Assoc.* 2016 Feb;115(2):121-7.
3. National Comprehensive Cancer Network® Clinical Practice Guidelines. Melanoma: Cutaneous. Version 2.2021 – February 19, 2021. [https://www.nccn.org/professionals/physician\\_gls/pdf/cutaneous\\_melanoma.pdf](https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf). Accessed 5Aug2022.
4. Michielin O, van Akkooi ACJ, Ascierto PA, et al. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol.* 2019 Dec 1;30(12):1884-1901.



## Recommendations for biopsies

Patients presenting with a suspicious pigmented lesion are recommended to undergo an excisional biopsy (elliptical, punch, or saucerization), preferably with 1- to 3-mm negative margins<sup>1</sup>. Preoperative biopsies provide basic pathological information which serve as a reference to determine the scope and depth of operations. For incisional biopsies, it is recommended to obtain the most elevated and/or darkest lesion areas.

Nail matrix biopsy is recommended in patients presenting with melanonychia. Depending on clinical conditions, a number of different techniques can be used including a 3-4 mm punch biopsy, tangential (shave) biopsy, transverse elliptical biopsy, or lateral longitudinal biopsy for lateral part longitudinal melanonychia. The biopsy is better taken from the distal matrix to minimize nail plate deformity.

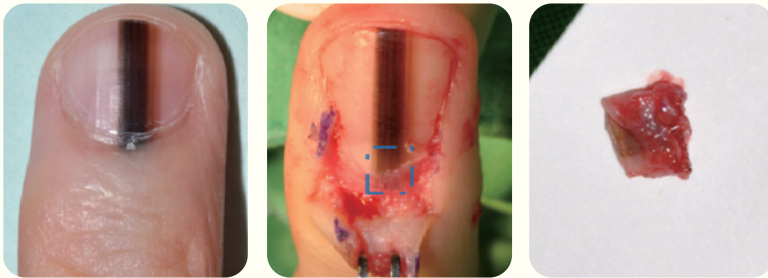


Photo credit: Dr. Yi-Hua Liao

Matrix incisional biopsy in a patient with melanonychia



Photo credit: Dr. Yi-Hua Liao

Lateral longitudinal biopsy in a patient with melanonychia

Scouting biopsies can be conducted for large and/or poorly defined melanoma in situ (MIS). It is recommended to conduct dermoscopy for real safety margins to identify haphazard pigmentation distributed in disorderly parallel ridge pattern as commonly seen in ALMs.

## Recommendations for Mohs micrographic surgery

Mohs micrographic surgery (MMS) is a tissue-sparing method of skin cancer removal which offers precise microscopic control of the entire tumor margin while maximizing conservation of healthy tissues<sup>2</sup>. At present, MMS is not part of routine practice in Taiwan due to limited manpower and equipment. MMS is not recommended for primary treatment of invasive cutaneous melanoma. Potential candidates for MMS are patients with MIS or minimally invasive melanomas in anatomically constrained areas, such as lentigo maligna (LM) on the face, or large and/or poorly defined MIS on the acral areas (ALM), as substantial subclinical spread may not be identifiable through standard histologic processing following wide excision in these patients<sup>3-5</sup>. Slow Mohs surgery can be performed through staged excision with permanent sections.

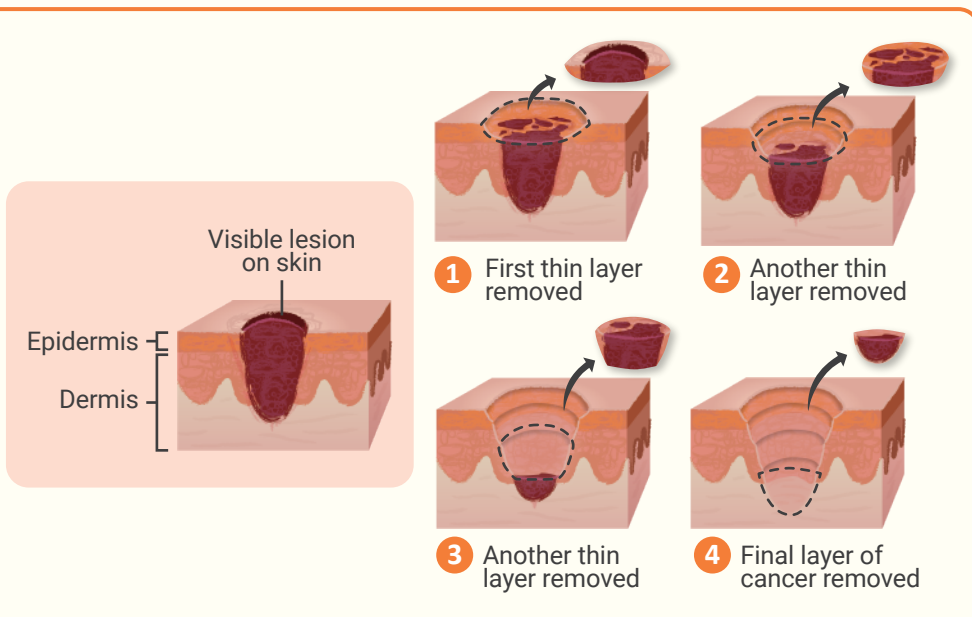
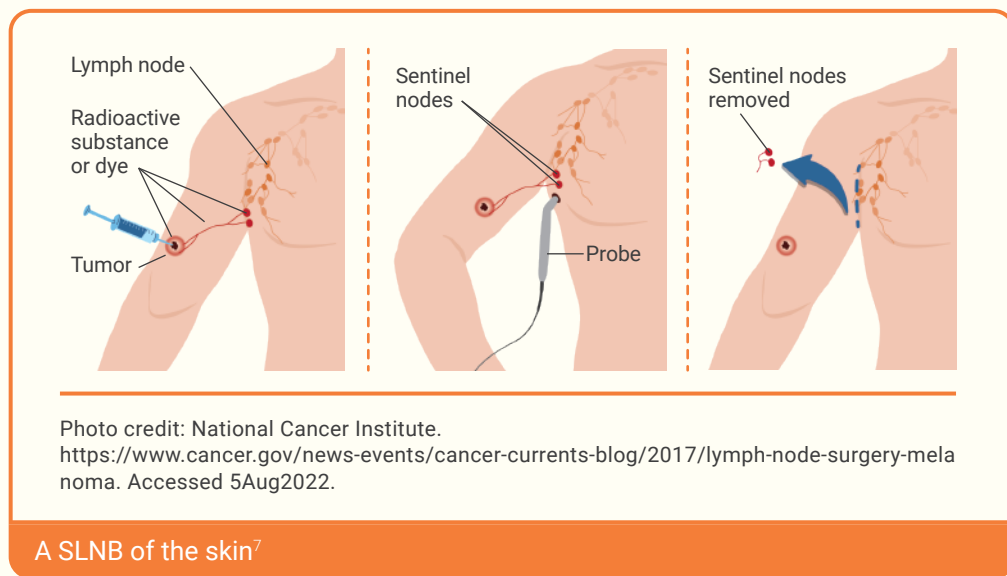


Photo credit: National Cancer Institute. Definition of Mohs micrographic surgery.  
<https://www.cancer.gov/publications/dictionaries/cancer-terms/def/mohs-micrographic-surgery>.  
Accessed 5Aug2022.

Mohs micrographic surgery<sup>6</sup>

## Recommendations for sentinel lymph node biopsy

Sentinel lymph node biopsy (SLNB) is a surgical procedure developed to accurately stage patients with cutaneous melanoma through pathologic assessment of regional nodal basins and to provide prognostic information for patients with clinical stage I/II melanoma<sup>1</sup>. SLNB should be recommended in patients with clinical stage IB, T1b melanoma (depth <0.8 mm with ulceration or depth 0.8–1 mm with or without ulceration), or T1a melanoma (depth <0.8 mm without ulceration) with adverse features (e.g. mitotic index >2/mm<sup>2</sup>, particularly in young patients or patients with lymphovascular invasion)<sup>1</sup>.



Clinical studies in Taiwan found SLNB to be beneficial for subsequent diagnosis and treatment in melanoma patients. SLNB was also associated with a lower 5-year distant metastasis rate in ALM patients<sup>8,9</sup>. Therefore, it is recommended that specimens be collected according to NCCN guidelines, then fixed in formaldehyde, and embedded in paraffin (instead of intraoperative frozen preparations) for better accuracy. Ancillary tests including morphology and/or immunohistochemistry (IHC) stains can also be utilized to ensure a comprehensive result.

It is recommended that SLNB be guided with radiolabeled tracers. All LNs with >10% of the highest sentinel LNs counts detected by gamma probe should be removed. Additional intra-operative interstitial injections of blue dyes or fluorescent dyes may be required if sentinel LNs cannot be detected by radiolabeled tracer, though dyes should be used cautiously due to the potential risks of anaphylactic shock.

Patient age, functional status, and life expectancy should be taken into account when considering SLNB.

For patients with a positive SLNB result, complete lymph node dissections (CLND) may be performed if expertise and equipment are available. Otherwise, patients should be followed up and ultrasounds should be performed by clinicians with relevant expertise.

## References

1. National Comprehensive Cancer Network® Clinical Practice Guidelines. Melanoma: Cutaneous. Version 2.2021 – February 19, 2021. [https://www.nccn.org/professionals/physician\\_gls/pdf/cutaneous\\_melanoma.pdf](https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf). Accessed 5Aug2022.
2. Prickett KA, Ramsey ML. Mohs Micrographic Surgery. [Updated 2022 May 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. <https://www.ncbi.nlm.nih.gov/books/NBK441833/>. Accessed 5Aug2022.
3. Miller CJ, Bichakjian CK. Mohs Micrographic Surgery for Melanoma-Do Outcomes Vary Among Treatment Facilities? *JAMA Dermatol*. 2021 May 1;157(5):513-515.
4. Shin TM, Shaikh WR, Etkorn JR, et al. Clinical and pathologic factors associated with subclinical spread of invasive melanoma. *J Am Acad Dermatol*. 2017 Apr;76(4):714-721.
5. Miller CJ, Shin TM, Sobanko JF, et al. Risk factors for positive or equivocal margins after wide local excision of 1345 cutaneous melanomas. *J Am Acad Dermatol*. 2017 Aug;77(2):333-340.e1.
6. National Cancer Institute. Definition of Mohs micrographic surgery. <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/mohs-micrographic-surgery>. Accessed 5Aug2022.
7. National Cancer Institute. Extensive Lymph Node Surgery Does Not Increase Survival in Melanoma. <https://www.cancer.gov/news-events/cancer-currents-blog/2017/lymph-node-surgery-melanoma>. Accessed 5Aug2022.
8. Chang JW, Huang YL, Chang YY, et al. Sentinel Lymph Node Biopsy Was Associated With Favorable Survival Outcomes For Patients With Clinically Node-Negative Asian Melanoma. *Cancer Manag Res*. 2019 Nov 14;11:9655-9664.
9. Lee TL, Liao YH, Liau JY, et al. Risk factors of recurrence and distant metastasis in primary cutaneous melanoma in Taiwan. *Sci Rep*. 2021 Oct 25;11(1):21012.



## Molecular testing

---

Molecular testing detects gene expressions to help differentiate benign and malignant neoplasms, distinguish melanomas at low- versus high-risk for metastasis, or identify specific gene mutations such as BRAF or KIT that may impact potential future treatment options<sup>1</sup>.

BRAF mutations are present in 41–56% of malignant melanomas and BRAF inhibitors can be used to treat unresectable or metastatic melanoma. VE1 IHC only has good sensitivity and excellent specificity for detection of BRAF V600E mutations; therefore, a sequencing or polymerase chain reaction (PCR) test is still needed for other BRAF V600 mutations<sup>2</sup>. Regional and district hospitals that do not have molecular pathology laboratories currently use the IHC test. A Taiwanese study found KIT mutation or amplification in 24.4% of ALM patients<sup>3</sup>. Therefore, molecular testing for KIT can be considered in metastatic melanoma from ALM.

Experts in Taiwan agree with ESMO on the timing of molecular testing for BRAF mutation. Molecular testing for actionable BRAF mutations is mandatory in patients with resectable or unresectable stage III or stage IV and is also highly recommended in high-risk resected disease stage IIC<sup>4</sup>.

### References

1. National Comprehensive Cancer Network® Clinical Practice Guidelines. Melanoma: Cutaneous. Version 2.2021 – February 19, 2021. [https://www.nccn.org/professionals/physician\\_gls/pdf/cutaneous\\_melanoma.pdf](https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf). Accessed January 3, 2022.
2. Lo MC, Paterson A, Maraka J, et al. A UK feasibility and validation study of the VE1 monoclonal antibody immunohistochemistry stain for BRAF-V600E mutations in metastatic melanoma. *Br J Cancer*. 2016 Jul 12;115(2):223-7.
3. Sheen YS, Tan KT, Tse KP, et al. Genetic alterations in primary melanoma in Taiwan. *Br J Dermatol*. 2020 May;182(5):1205-1213.
4. Michielin O, van Akkooi ACJ, Ascierto PA, et al. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2019 Dec 1;30(12):1884-1901.



## Baseline workup and follow-up

After the diagnosis of cutaneous melanoma has been confirmed, detailed medical and family history should be obtained. A complete dermatologic examination is recommended for all patients with newly diagnosed melanoma. Baseline laboratory tests and imaging shall be established for future references, for detection of occult disease, or for potential inclusion into clinical trials<sup>1</sup>. In consideration of Taiwan-specific needs and reimbursement policies, the experts recommended the following baseline workups and follow-up frequencies:

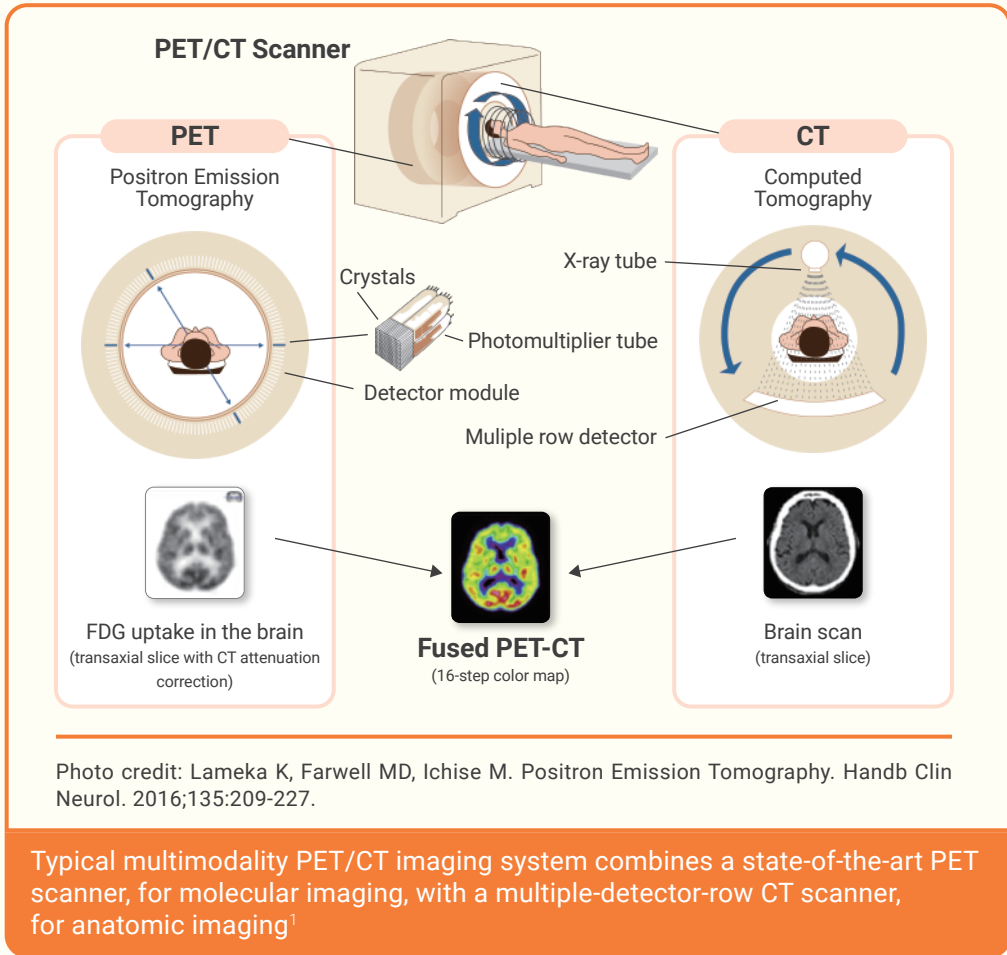
Timing	Recommendations
Baseline	<ul style="list-style-type: none"><li>• Check skin and LN and educate patients on self-examination.</li><li>• Computed tomography (CT) with contrast of the head, neck/chest/abdomen/pelvic areas, or extremities according to melanoma location, regardless of staging.</li></ul>
Stage 0 in situ	<ul style="list-style-type: none"><li>• Check skin and LN annually.</li><li>• Imaging screens should be performed for clinical symptoms or if clinically indicated.</li></ul>
Stage IA-IIA	<ul style="list-style-type: none"><li>• Check skin and LN every 6 months for 5 years, then annually for 5 years or more if clinically indicated.</li><li>• Routine imaging screens should be performed every 6-12 months for 5 years, then annually thereafter.</li></ul>
Stage IIB-IV	<ul style="list-style-type: none"><li>• Check skin and LN every 3 months for 2 years, then every 6 months for 3-5 years, then every 6-12 months for 6-10 years or more if clinically indicated.</li><li>• A routine imaging screen should be performed every 3-12 months for 5 years.</li><li>• Periodic magnetic resonance imaging (MRI) with contrast of the brain should be performed for up to 3 years for patients with stage IIIC or previous brain metastasis, or patients with symptoms or physical findings suggestive of central nervous system involvement.</li><li>• Positron emission tomography (PET)/CT scans can further characterize lesions found to be indeterminate on CT scans.</li><li>• Serum lactate dehydrogenase (LDH) should be obtained following diagnosis of stage IV disease.</li></ul>

## References

1. National Comprehensive Cancer Network® Clinical Practice Guidelines. Melanoma: Cutaneous. Version 2.2021 – February 19, 2021. [https://www.nccn.org/professionals/physician\\_gls/pdf/cutaneous\\_melanoma.pdf](https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf). Accessed 5Aug2022.



The  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) PET scan combining anatomic imaging information from CT<sup>1</sup> is the preferred modality to define the total body burden of metastases, and can provide additional information on specific metastasis sites such as the lung, mediastinum, and abdomen<sup>2-7</sup>. This section will address the appropriate indications for application of  $^{18}\text{F}$ -FDG PET in patients with melanoma.



## Recommendations for initial staging

Overall,  $^{18}\text{F}$ -FDG PET/CT does not provide significant additional information in the staging of AJCC Stage I or II melanoma and is inferior to lymphoscintigraphy (LS) and sentinel node (SN) biopsy for diagnosis of regional lymph node involvement<sup>3,5</sup>.

FDG PET metastatic detection sensitivity varies in different parts of the body due to the normal biodistribution of  $^{18}\text{F}$ -FDG.  $^{18}\text{F}$ -FDG PET scans may lead to altered disease staging in 12–34% of patients and lead to changes in management in 8–74% of patients. The different degrees of change depend on investigations already performed prior to  $^{18}\text{F}$ -FDG PET/CT, and such changes may include alteration or abandonment of planned surgeries and modifications of systemic therapies<sup>3, 5, 8-17</sup>.

The best diagnostic protocol for evaluation of most patients with suspected metastatic disease is a combination of imaging procedures such as whole-body  $^{18}\text{F}$ -FDG PET, high-resolution CT of the chest, and MRI of the brain<sup>3,5</sup>.

## Monitoring treatment effects from *BRAF*(/*MEK*)-targeted therapy using $^{18}\text{F}$ -FDG PET/CT

Although  $^{18}\text{F}$ -FDG PET/CT can detect early metabolic responses to BRAF and MEK inhibitors, this is not predictive of subsequent RECIST (Response Evaluation Criteria in Solid Tumors) responses on contrast-enhanced CT. Future prospective studies in patients treated with standard BRAF (/MEK) inhibitors are required to determine whether  $^{18}\text{F}$ -FDG PET can detect resistance to BRAF (/MEK) at an earlier time point than CT-based RECIST progression or clinical symptoms<sup>7</sup>.

## Monitoring treatment effects from immunotherapy using $^{18}\text{F}$ -FDG PET/CT

Interim  $^{18}\text{F}$ -FDG PET/CT scans obtained 3–4 weeks or 2 cycles (8–12 weeks) after treatment initiation have been studied to determine responses to immunotherapy<sup>18,19</sup>. However, these studies were based on small populations, usually did not contain other prognostic information such as LDH, or did not adhere to standard scan timing. Thus, the prognostic value of interim  $^{18}\text{F}$ -FDG PET/CT scans remains uncertain.

On the other hand, the “pseudoprogression” phenomenon caused by an influx of immune cells was observed in some studies<sup>18,20</sup>. Histological confirmation of metabolically active lesions to elucidate the phenomenon of pseudoprogression and incorporation of clinical information such as symptoms and biomarkers of progression is recommended.

## Detection of immune-related adverse events of systemic treatment on $^{18}\text{F}$ -FDG PET/CT

FDG PET/CT may be able to detect immune-related adverse events (irAEs) such as colitis, hepatitis, and hypophysitis in patients on immunotherapy<sup>2</sup>.

There have been some reports of cases where 18F-FDG PET/CT scans performed for treatment monitoring revealed irAEs such as hypophysitis, gastrointestinal inflammation, and inflammatory reactions of soft tissues such as myositis or fasciitis and sarcoid-like lymphadenopathy before clinical symptoms became apparent<sup>21-22</sup>.

Generally, clinical information and/or biopsies of newly detected lesions are still needed to differentiate between adverse events and melanoma progression. The current level of evidence does not justify the use of 18F-FDG PET/CT for mere detection or monitoring of adverse events.

## References

1. Lameka K, Farwell MD, Ichise M. Positron Emission Tomography. *Handb Clin Neurol*. 2016;135:209-227.
2. UpToDate. Imaging studies in melanoma. Published 2021. [https://www.uptodate.com/contents/imaging-studies-in-melanoma?search=melanoma%20FDG%20PET&source=search\\_result&selectedTitle=2~150&usage\\_type=default&display\\_rank=2#H1956366](https://www.uptodate.com/contents/imaging-studies-in-melanoma?search=melanoma%20FDG%20PET&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2#H1956366). Accessed 5Aug2022.
3. Uren RF, Howman-Giles R, Chung D, et al. Guidelines for lymphoscintigraphy and F18 FDG PET scans in melanoma. *J Surg Oncol*. 2011 Sep;104(4):405-19.
4. Etchebehere EC, Romanato JS, Santos AO, et al. Impact of [F-18] FDG-PET/CT in the restaging and management of patients with malignant melanoma. *Nucl Med Commun*. 2010 Nov;31(11):925-30.
5. Perng P, Marcus C, Subramaniam RM. (18)F-FDG PET/CT and Melanoma: Staging, Immune Modulation and Mutation-Targeted Therapy Assessment, and Prognosis. *AJR Am J Roentgenol*. 2015 Aug;205(2):259-70.
6. Perissinotti A, Rietbergen DD, Vidal-Sicart S, et al. Melanoma & nuclear medicine: new insights & advances. *Melanoma Management*. 2018;5(1):MMT06.
7. Bisschop C, de Heer EC, Brouwers AH, et al. Rational use of 18F-FDG PET/CT in patients with advanced cutaneous melanoma: A systematic review. *Crit Rev Oncol Hematol*. 2020 Sep;153:103044.
8. Pfannenber C, Aschoff P, Schanz S, et al. Prospective comparison of 18F-fluorodeoxyglucose positron emission tomography/computed tomography and whole-body magnetic resonance imaging in staging of advanced malignant melanoma. *Eur J Cancer*. 2007 Feb;43(3):557-64.
9. Reinhardt MJ, Joe AY, Jaeger U, et al. Diagnostic performance of whole body dual modality 18F-FDG PET/CT imaging for N- and M-staging of malignant melanoma: experience with 250 consecutive patients. *J Clin Oncol*. 2006 Mar 1;24(7):1178-87.
10. Bronstein Y, Ng CS, Rohren E, et al. PET/CT in the management of patients with stage IIIC and IV metastatic melanoma considered candidates for surgery: evaluation of the additive value after conventional imaging. *AJR Am J Roentgenol*. 2012 Apr;198(4):902-8.
11. Schüle SC, Eigentler TK, Garbe C, et al. Influence of (18)F-FDG PET/CT on therapy management in patients with stage III/IV malignant melanoma. *Eur J Nucl Med Mol Imaging*. 2016 Mar;43(3):482-8.
12. Subesinghe M, Marples M, Scarsbrook AF, et al. Clinical impact of (18)F-FDG PET-CT in recurrent stage III/IV melanoma: a tertiary centre Specialist Skin Cancer Multidisciplinary Team (SSMDT) experience. *Insights Imaging*. 2013 Oct;4(5):701-9.
13. Forschner A, Olthof SC, Gückel B, et al. Impact of 18F-FDG-PET/CT on surgical management in patients with advanced melanoma: an outcome based analysis. *Eur J Nucl Med Mol Imaging*. 2017 Aug;44(8):1312-1318.
14. Bastiaannet E, Wobbes T, Hoekstra OS, et al. Prospective comparison of [18F]fluorodeoxyglucose positron emission tomography and computed tomography in patients with melanoma with palpable lymph node metastases: diagnostic accuracy and impact on treatment. *J Clin Oncol*. 2009 Oct 1;27(28):4774-80.
15. Singnurkar A, Wang J, Joshua AM, et al. 18F-FDG-PET/CT in the Staging and Management of Melanoma: A Prospective Multicenter Ontario PET Registry Study. *Clin Nucl Med*. 2016 Mar;41(3):189-93.
16. Falk MS, Truitt AK, Coakley FV, et al. Interpretation, accuracy and management implications of FDG PET/CT in cutaneous malignant melanoma. *Nucl Med Commun*. 2007 Apr;28(4):273-80.
17. Taghipour M, Marcus C, Sheikhbahaei S, et al. Clinical Indications and Impact on Management: Fourth and Subsequent Posttherapy Follow-up 18F-FDG PET/CT Scans in Oncology Patients. *J Nucl Med*. 2017 May;58(5):737-743.
18. Cho SY, Lipson EJ, Im HJ, et al. Prediction of Response to Immune Checkpoint Inhibitor Therapy Using Early-Time-Point 18F-FDG PET/CT Imaging in Patients with Advanced Melanoma. *J Nucl Med*. 2017 Sep;58(9):1421-1428.
19. Sachpekidis C, Larrubere L, Pan L, et al. Predictive value of early 18F-FDG PET/CT studies for treatment response evaluation to ipilimumab in metastatic melanoma: preliminary results of an ongoing study. *Eur J Nucl Med Mol Imaging*. 2015 Mar;42(3):386-96.
20. Kong BY, Menzies AM, Saunders CA, et al. Residual FDG-PET metabolic activity in metastatic melanoma patients with prolonged response to anti-PD-1 therapy. *Pigment Cell Melanoma Res*. 2016 Sep;29(5):572-7.
21. Tirumani SH, Ramaiya NH, Keraliya A, et al. Radiographic Profiling of Immune-Related Adverse Events in Advanced Melanoma Patients Treated with Ipilimumab. *Cancer Immunol Res*. 2015 Oct;3(10):1185-92.
22. Bronstein Y, Ng CS, Hwu P, et al. Radiologic manifestations of immune-related adverse events in patients with metastatic melanoma undergoing anti-CTLA-4 antibody therapy. *AJR Am J Roentgenol*. 2011 Dec;197(6):W992-W1000.

The section is focused on adjuvant treatment for resectable melanoma and systemic treatment for unresectable/metastatic melanoma, as neoadjuvant treatment is not the standard of care and most studies are still ongoing.

## Current medications used for treating melanoma<sup>1</sup>

Category	Mechanism of action	Medications
Target therapy (TT)		<p><b>BRAF inhibitors</b></p> <ul style="list-style-type: none"> <li>Dabrafenib</li> <li>Vemurafenib</li> </ul> <p><b>MEK inhibitors</b></p> <ul style="list-style-type: none"> <li>Cobimetinib</li> <li>Trametinib</li> </ul> <p><b>BRAF/MEK combinations</b></p> <ul style="list-style-type: none"> <li>Dabrafenib/Trametinib</li> <li>Vemurafenib/Cobimetinib</li> </ul>
Immuno-Oncology (IO)		<p><b>Anti-CTLA-4</b></p> <ul style="list-style-type: none"> <li>Ipilimumab</li> </ul> <p><b>Anti-PD-1</b></p> <ul style="list-style-type: none"> <li>Nivolumab</li> <li>Pembrolizumab</li> </ul>

Photo credit: Terheyden P, Krackhardt A, Eigentler T. The Systemic Treatment of Melanoma. Dtsch Arztebl Int. 2019 Jul 22;116(29-30):497-504.

CTLA, cytotoxic lymphocyte antigen; ERK, extracellular signal-regulated kinases; MAPK, mitogen-activated protein kinase; PD, programmed death; RTK, receptor-tyrosine-kinase

## Recommendations regarding timing and choices of systemic treatments

Although high-risk stage II melanoma (IIB/C) patients experience a similar-to-higher recurrence rate compared with stage III melanoma patients, adjuvant treatment is not recommended in patients with high-risk stage II due to lack of sound evidence. Despite KEYNOTE-716 demonstrating that pembrolizumab resulted in better disease-free survival for patients with high-risk stage II melanoma<sup>2</sup>, the data was considered too preliminary and has not been included in the NCCN at the current time.

### **BRAF-mutated stage III/IV resectable melanoma**

- TT is favored over IO as adjuvant therapy for treating patients with stage III/IV BRAF-mutated melanoma.

### **BRAF-wild-type stage III/IV resectable melanoma**

- IO should be the adjuvant therapy for treating patients with stage III/IV BRAF-wild-type melanoma.

### **BRAF-mutated unresectable/metastatic melanoma**

- TT is preferred over IO treatment.
- In terms of TT, combination of BRAF/MEK inhibitors should be used before BRAF inhibitor monotherapy.
- For IO, monotherapy is preferred over combination therapy due to cost-effectiveness and tolerability.
- Although data from a clinical study demonstrated efficacy in IO and TT combination therapy<sup>3</sup>, a treatment which has since been approved by the Food and Drug Administration, not all experts recommended this regimen as frontline treatment because overall survival data is not yet available.
- Chemotherapy is preferable to cytokines as a later treatment option.

### **BRAF-wild-type unresectable/metastatic melanoma**

- IO should be the first treatment of choice, following which chemotherapy is preferred over cytokines.
- Half the experts recommended that dual IO combination therapy (anti-programmed cell death protein-1 [anti-PD-1] and anti-cytotoxic T-lymphocyte-associated protein 4 [anti-CTLA-4]) should be used; the remaining half recommended anti-PD-1 monotherapy.

Most experts recommended the oncolytic virus as a later-line treatment when all other treatment options have been exhausted. The Taiwan Food and Drug Administration has yet to approve any relevant agents.

Radiation therapy is mostly used for palliative care in the terminal stages of bone or brain metastases and is rarely used in the primary treatment of melanoma. Radiation therapy as adjuvant therapy to enhance nodal regional control can be considered for primary treatment of patients with high recurrence risks, though progression-free survival or overall survival may not be prolonged. An expert in radiation oncology from a medical center recommended the administration of radiation therapy as per the ME-H section of NCCN guidelines<sup>4</sup>.

## References

1. Terheyden P, Krackhardt A, Eigentler T. The Systemic Treatment of Melanoma. *Dtsch Arztebl Int.* 2019 Jul 22;116(29-30):497-504.
2. Luke JJ, et al. Pembrolizumab versus placebo after complete resection of high-risk stage II melanoma: Efficacy and safety results from the KEYNOTE-716 double-blind phase III trial. Presented by during Presidential Symposium 1 on Saturday, 18 September, 15:05 to 16:35 (CEST) on Channel 1. *Annals of Oncology*, Volume 32, 2021 Supplement 5. LBA3\_PR.
3. Gutzmer R, Stroyakovskiy D, Gogas H, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAFV600 mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2020 Jun 13;395(10240):1835-1844.
4. National Comprehensive Cancer Network® Clinical Practice Guidelines. Melanoma: Cutaneous. Version 2.2021 – February 19, 2021. [https://www.nccn.org/professionals/physician\\_gls/pdf/cutaneous\\_melanoma.pdf](https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf). Accessed 5Aug2022.



# Mucosal melanoma and uveal melanoma

## Treatment of mucosal melanoma

- The prevalence rate of mucosal melanoma in Taiwan is high.
- Although no trial data specifically targeting adjuvant treatment in mucosal melanoma is available, over 70% of experts suggested treating mucosal melanoma in a manner similar to cutaneous melanoma in the adjuvant setting.
- Although no trial data is currently available for unresectable/metastatic mucosal melanoma, 90% of experts recommended treating mucosal melanoma similar to cutaneous melanoma in the unresectable/metastatic setting.

## Treatment of uveal melanoma

- Though there is currently no approved treatment for uveal melanoma, IO is recommended for the treatment of uveal melanoma in both adjuvant and metastatic settings based on phase II studies<sup>1-4</sup>. As a result, it is recommended that uveal melanoma be treated in a similar manner to cutaneous melanoma.
- Unless BRAF mutation is detected, BRAF-directed treatments are not considered in uveal melanoma.

## References

1. Fountain E, Bassett RL, Cain S, et al. Adjuvant Ipilimumab in High-Risk Uveal Melanoma. *Cancers (Basel)*. 2019 Jan 29;11(2):152.
2. Piulats JM, Espinosa E, de la Cruz Merino L, et al. Nivolumab Plus Ipilimumab for Treatment-Naïve Metastatic Uveal Melanoma: An Open-Label, Multicenter, Phase II Trial by the Spanish Multidisciplinary Melanoma Group (GEM-1402). *J Clin Oncol*. 2021 Feb 20;39(6):586-598.
3. Pelster MS, Gruschkus SK, Bassett R, et al. Nivolumab and Ipilimumab in Metastatic Uveal Melanoma: Results From a Single-Arm Phase II Study. *J Clin Oncol*. 2021 Feb 20;39(6):599-607.
4. Ny L, Jespersen H, Karlsson J, et al. The PEMDAC phase 2 study of pembrolizumab and entinostat in patients with metastatic uveal melanoma. *Nat Commun*. 2021 Aug 27;12(1):5155.









# Melanoma

Consensus in diagnosis and management from Taiwanese experts

## 發行單位及代表人

張文震	台灣免疫暨腫瘤學會理事長	林口長庚醫院	免疫腫瘤學卓越中心主任
楊志新	中華民國癌症醫學會理事長	台大醫院	癌醫中心分院院長
趙曉秋	台灣皮膚科醫學會理事長	成大醫院	皮膚科主任
賴瓊如	台灣病理學會理事長	台北榮民總醫院	病理部一般病理科主任
顏若芳	中華民國核醫學學會理事長	台大醫院	核子醫學部主任

## 執行編輯

吳教恩 林口長庚紀念醫院 腫瘤科

## 共同作者 (依姓氏筆劃排序)

朱家瑜	台大醫院	皮膚部	廖怡華	台大醫院	皮膚部
巫政霖	成大醫院	病理部	顏若芳	台大醫院	核子醫學部
吳教恩	林口長庚紀念醫院	腫瘤科			

## 編審委員 (依姓氏筆劃排序)

王慧晶	高醫附設醫院	血液腫瘤內科	莊佩儒	台大醫院雲林分院	核子醫學部
吳銘芳	中山附設醫院	腫瘤內科	黃彥霖	林口長庚紀念醫院	解剖病理科
吳介山	高雄榮民總醫院	皮膚科	黃玉儀	和信治癌中心醫院	核子醫學科
李政源	台北榮民總醫院	皮膚部	黃意婷	林口長庚紀念醫院	放射腫瘤科
何英右	成大醫院	皮膚部	曾能泉	童綜合醫院	核子醫學科
林家齊	台大醫院	腫瘤醫學部	楊慕華	台北榮民總醫院	腫瘤醫學部
林振源	中國醫藥附設醫院	血液腫瘤科	楊陽生	台中榮民總醫院	血液腫瘤科
張義芳	馬偕紀念醫院	血液腫瘤科	楊文祺	屏東基督教醫院	血液腫瘤科
張曜宇	林口長庚紀念醫院	皮膚外科	賴勇祈	中國醫藥附設醫院	核子醫學科
張文震	林口長庚紀念醫院	免疫腫瘤學卓越中心	顏厥全	台北榮民總醫院	腫瘤醫學部
許修誠	彰化基督教醫院	皮膚部	顏家瑞	成大醫院	腫瘤醫學部
陳冠樺	林口長庚紀念醫院	解剖病理科	蘇五洲	成大醫院	腫瘤醫學部
陳志榮	台中榮民總醫院	病理檢驗部			

出版單位 台灣免疫暨腫瘤學會

版權所有 台灣免疫暨腫瘤學會、中華民國癌症醫學會、台灣皮膚科醫學會、台灣病理學會、中華民國核醫學學會

版次 初版一刷 西元 2023 年 3 月

ISBN 978-986-98100-4-3 (平裝)

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means including but not limited to electronic, mechanical, photocopying, or recording without written permission of the publisher.



### 台灣免疫暨腫瘤學會 / Taiwan Society for Immunotherapy of Cancer

地址：33305 桃園市龜山區復興街 5 號  
信箱：taiwanimmunotherapy@gmail.com  
官網：https://www.tsitc.org.tw/



### 中華民國癌症學會 / Taiwanese Oncology Society

地址：100229 台北市常德街一號台大景福館二樓 204 室  
信箱：coste@ms16.hinet.net  
官網：http://www.taiwanoncologysociety.org.tw/



### 臺灣皮膚科醫學會 / Taiwanese Dermatological Association

地址：10046 台北市中正區武昌街一段 1-2 號 4 樓  
信箱：derma.email@msa.hinet.net  
官網：http://www.derma.org.tw/



### 台灣病理學會 / Taiwan Society of Pathology

地址：112 台北市北投區明德路 271 之 2 號一樓  
信箱：tspathol@yahoo.com.tw  
官網：https://www.twiap.org.tw/



### 中華民國核醫學學會 / Society of Nuclear Medicine, Taiwan

地址：100 台北市中正區中山南路 7 號核醫部轉核醫學學會  
信箱：tsnm.tw@gmail.com  
官網：http://www.snm.org.tw/