高 雄 榮 民 總 醫 院

皮膚癌(melanoma)診療原則

2018年01月23日 第一版

皮膚癌醫療團隊擬定

注意事項：這個診療原則主要作為醫師和其他保健專家診療癌症病人參考之用。假如你是一個癌症病人，直接引用這個診療原則並不恰當，只有你的醫師才能決定給你最恰當的治療。

修訂指引

- 本共識依下列參考資料修改版本
  - NCCN 2018版 診療指引

melanoma診療指引審視修訂會議討論日期

- 上次會議：2017/03/21
- 本共識經審視後與上一版之差異

上一版:	新版:
1.使用NCCN 2017版 診療指引 2.修改輔助性治療藥物	▸ 更新 NCCN 2018版 診療指引 ▸ 修改輔助性治療藥物 ◆ 增加Target therapy藥物 ◆ 增加Immunotherapy藥物 ◆ 增加Metastasis藥物

黑色素細胞癌(melanoma)

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臨床診療指引 2018第一版

診斷	初步評估	分期(附件1)	評估

臨床診斷之可疑病灶，經皮膚切片及病理組織學證實。

1、病史
2、理學檢查
(1)完整皮膚檢查。
(2)淋巴結檢查。
3、黑色素細胞癌危險因子評估
4、實驗室檢查
(1)CBC/DC
(2)Biochemistry(包括LDH)
(3)HBV/HCV
5、初步影像學檢查§
(1)CXR
(2)Regional LNs, echo

1、影像學檢查△
(1)CT
(2)MRI
(3)Gallium scan
(4)Bone scan
(5)PET / CT
2、sentinel LNs biopsy

- Stage 0 (melanma in situ)
- Stage I
- Stage II
- Stage III
- Stage IV

§： 可選擇

△：建議 whole body PET / CT + brain MRI

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分期	初步治療(附件2)	輔助治療	再評估	追蹤

Stage 0
(melanma in situ) → **wide excision** → **negative** → **Monthly*III ↓ Quarterly Or Palliative care (安寧緩和)**

Stage I → **wide excision**
Stage II → **wide excision**

◎可選擇是否須使用輔助性化療

CVD regimen(附表4)
Interferon-α
Ipilmumab
Nivolumab
Vemurafenib⁺
Dabrafenib⁺
RT(附表3)
＋ **Restage：Brain MRI and PET**

If病程持續進展

Stage III → **wide excision + complete LNs dissection**
Stage IV → **wide excision + complete LNs dissection**

◎可選擇使用藥物

Dantmouth regimen(附表5)
Interferon-α
Ipilmumab
Nivolumab
Vemurafenib⁺
Dabrafenib⁺
Palliative symptom management,
Clinical trial、RT(附表3)
Temozolomide、Palliative surgery
＋ **Restage：Brain MRI and PET**

◎：可選擇

+：for BRAF mutation patient

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2、理學檢查
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(1)CT
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(4)Bone scan
(5)PET / CT
2、sentinel LNs biopsy

Stage 0 (melanma in situ) → wide excision

Stage I → wide excision

Stage II → wide excision

Stage III → wide excision + complete LNs dissection

Stage IV → wide excision + complete LNs dissection

◎可選擇使用藥物

CVD regimen(附表4)
Interferon-α
Ipilmumab
Nivolumab
Vemurafenib+
Dabrafenib+
RT(附表5)

＋ Restage：Brain MRI and PET

Nivolumab

negative → Monthly*III → Quarterly Or Palliative care (安寧緩和)

if 病程持續進展

◎可選擇使用藥物

Dantmouth regimen(附表5)
Interferon-α
Ipilmumab
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＋ Restage：Brain MRI and PET

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癌症藥物停藥準則

- 根據CTCAE (Common Terminology Criteria for Adverse Events, Version 4.0 Published: May 28, 2009 【v4.03: June 14, 2010】)，出現Grade 3 ~ Grade 4 adverse event。
- 停藥至adverse event回復至Grade 1或Baseline時可再次用藥，但有些患者必須調整用藥劑量。
- 使用BRAF inhibitor時可能產生cutaneous SCC。此現象雖被CTCAE列為Grade 3 toxic effect, 但此現象不必停藥或調整劑量。
- 特定藥物治療下疾病仍持續進展，根據追蹤及評估顯示疾病對此特定藥物治療無效(考慮停止投藥並選擇其他治療方法)。
- 病患要求 (Hospice care或其他因素)。
- 病患死亡。

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附件一-1:

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018 Staging Melanoma

NCCN Guidelines Index
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Discussion

Table 1

American Joint Committee on Cancer (AJCC)
Definitions of TNM for Melanoma (8th ed., 2016)

Definition of Primary Tumor (T)

T Category	Thickness	Ulceration Status
TX: primary tumor thickness cannot be assessed (eg, diagnosis by curettage)	Not applicable	Not applicable
T0: no evidence of primary tumor (eg, unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma *in situ*)	Not applicable	Not applicable
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm 0.8–1.0 mm	With ulceration With or without ulceration
T2	>1.0–2.0 mm	Unknown or unspecified
T2a	>1.0–2.0 mm	Without ulceration
T2b	>1.0–2.0 mm	With ulceration
T3	>2.0–4.0 mm	Unknown or unspecified
T3a	>2.0–4.0 mm	Without ulceration
T3b	>2.0–4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

The AJCC 8th Edition Cancer Staging System will be implemented on January 1, 2018.
For the AJCC 7th Edition Staging Manual, visit www.springer.com.

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附件一-2:

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018 Staging Melanoma

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Definition of Regional Lymph Node (N)

Extent of regional lymph node and/or lymphatic metastasis		
N Category	**Number of tumor-involved regional lymph node**	**Presence of in-transit, satellite, and/or microsatellite metastases**
NX	Regional nodes not assessed (eg, SLN biopsy not performed, regional nodes previously removed for another reason) **Exception**: pathological N category is not required for T1 melanomas, use cN.	No
N0	No regional metastases detected	No
N1	One tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (ie, detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	
N2a	Two or three clinically occult (ie, detected by SLN biopsy)	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (ie, detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018 Staging Melanoma

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Definition of Distant Metastasis (M)

	M Criteria	
M Category	**Anatomic site**	**LDH level**
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Normal
M1d(1)		Elevated

- **Serum lactate dehydrogenase (LDH)**
- **Suffixes for M category: (0) LDH not elevated, (1) LDH elevated.**
- **No suffix is used if LDH is not recorded or is unspecified.**

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附件一-4:

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018 Staging Melanoma

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AJCC PROGNOSTIC STAGE GROUPS

Clinical Staging (cTNM)*

	T	N	M
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage III	AnyT, Tis	≥N1	M0
Stage IV	Any T	Any N	M1

*Clinical staging includes microstaging of the primary melanoma and clinical/radiologic/biopsy evaluation for metastases. By convention, clinical staging should be used after biopsy of the primary melanoma, with clinical assessment for regional and distant metastases. Note that pathological assessment of the primary melanoma is used for both clinical and pathological classification. Diagnostic biopsies to evaluate possible regional and/or distant metastasis also are included. Note there is only one stage group for clinical Stage III melanoma.

Pathological Staging (pTNM)†

	T	N	M
Stage 0††	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1a/b,T2a	N1a, N2a	M0
Stage IIIB	T0	N1b, N1c	M0
	T1a/b, T2a	N1b/c, N2b	M0
	T2b, T3a	N1a/b/c, N2a/b	M0
Stage IIIC	T0	N2b/c, N3b/c	M0
	T1a/b, T2a/b, T3a	N2c, N3a/b/c	M0
	T3b, T4a	Any N ≥N1	M0
	T4b	N1a/b/c, N2a/b/c	M0
Stage IIID	T4b	N3a/b/c	M0
Stage IV	Any T, Tis	Any N	M1

†Pathological staging includes microstaging of the primary melanoma, including any additional staging information from the wide-excision (surgical) specimen that constitutes primary tumor surgical treatment and pathological information about the regional lymph nodes after SLN biopsy or therapeutic lymph node dissection for clinically evident regional lymph node disease.

††Pathological Stage 0 (melanoma *in situ*) and T1 do not require pathological evaluation of lymph nodes to complete pathological staging; use cN information to assign their pathological stage.

The AJCC 8th Edition Cancer Staging System will be implemented on January 1, 2018. For the AJCC 7th Edition Staging Manual, visit www.springer.com.

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附件二:

PRINCIPLES OF SURGICAL MARGINS FOR WIDE EXCISION OF PRIMARY MELANOMA

Tumor Thickness	Recommended Clinical Margins[2]
In situ[1]	0.5–1.0 cm
≤1.0 mm	1.0 cm (category 1)
>1.0–2 mm	1–2 cm (category 1)
>2.0–4 mm	2.0 cm (category 1)
>4 mm	2.0 cm (category 1)

• Margins may be modified to accommodate individual anatomic or functional considerations.

[1]For large melanoma in situ (MIS), lentigo maligna type, surgical margins >0.5 cm may be necessary to achieve histologically negative margins; techniques for more exhaustive histologic assessment of margins should be considered. For selected patients with positive margins after optimal surgery, consider topical imiquimod (for patients with MIS) or RT (category 2B).
[2]Excision recommendations are based on measured clinical margins taken at the time of surgery and not gross or histologic margins, as measured by the pathologist (category 1).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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附件三：

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Melanoma

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PRINCIPLES OF RADIATION THERAPY FOR MELANOMA

Consider RT in the following situations:[1]

PRIMARY DISEASE
- Adjuvant treatment in selected patients with factors including, but not limited to deep desmoplastic melanoma with narrow margins, extensive neurotropism, or locally recurrent disease.

REGIONAL DISEASE[2]
- Adjuvant treatment in selected patients following resection of clinically appreciable nodes (category 2B)[3] if
  - Extranodal tumor extension AND/OR
    - Parotid: ≥1 involved node, any size of involvement
    - Cervical: ≥2 involved nodes and/or ≥3 cm tumor within a node
    - Axillary: ≥2 involved nodes and/or ≥4 cm tumor within a node
    - Inguinal: ≥3 involved nodes and/or ≥4 cm tumor within a node
- Palliative
  - Unresectable nodal, satellite, or in-transit disease

METASTATIC DISEASE
- Brain metastases
  (See NCCN Guidelines for Central Nervous System Cancers)
  - Stereotactic radiosurgery as primary treatment
  - Stereotactic radiosurgery as adjuvant treatment
  - Whole brain radiation therapy as primary treatment
  - Whole brain radiation therapy as adjuvant treatment (category 3)[4]
- Other symptomatic or potentially symptomatic soft tissue and/or bone metastases[2]

[1]Interactions between radiation therapy and systemic therapies (eg, *BRAF* inhibitors, interferon alfa-2b, immunotherapies, checkpoint inhibitors) need to be very carefully considered as there is potential for increased toxicity.
[2]A wide range of radiation dose/fractionation schedules is effective. Hypofractionated regimens may increase the risk for long-term complications.
[3]Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has shown no improvement in relapse-free or overall survival. Its benefits must be weighed against potential toxicities. The impact of these potential toxicities should be considered in the context of other adjuvant treatment options.
[4]Adjuvant whole brain radiation following resected melanoma brain metastasis is controversial and should be considered on an individual patient basis.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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附件四-1:CVD regimen

化學治療處方	
CVD regimen	
published C/T regimens	**schedule**
Dacarbazine 800mg/m2, IV, D1	**Q28d * 6 cycles**
Cisplatin 20mg/m2, IV, D2-5	**Q28d * 6 cycles**
Vinblastine 1.6mg/m2, IV, D1-5	**Q28d * 6 cycles**

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附件四-2:CVD regimen, CCr < 60

化學治療處方	
CVD regimen, CCr < 60	
published C/T regimens	**schedule**
Dacarbazine 800mg/m2, IV, D1	**Q28d * 6 cycles**
Vinblastine 1.6mg/m2, IV, D1-5	**Q28d * 6 cycles**
Paraplatin auc*1.25mg, IV, D2-5	**Q28d * 6 cycles**

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附件五-1：Dartmouth regimen (Odd) (or metastasis)

化學治療處方	

Dartmouth regimen (Odd)	
published C/T regimens	**schedule**
Carmustine 150mg/m2, IV, D1	**Q28d * 6 cycles**
Dacarbazine 220mg/m2, IV, D1-3	**Q28d * 6 cycles**
Cisplatin 25mg/m2, IV, D1-3	**Q28d * 6 cycles**
Nolvadex 10mg, PO, D1-3	**Q28d * 6 cycles**

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附件五-2：Dartmouth regimen (Even) (or metastasis)

化學治療處方

Dartmouth regimen (Even)	
published C/T regimens	**schedule**
Dacarbazine 220mg/m2, IV, D1-3	**Q28d * 6 cycles**
Cisplatin 25mg/m2, IV, D1-3	**Q28d * 6 cycles**
Nolvadex 10mg, PO, D1-3	**Q28d * 6 cycles**

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附件五-3：Dartmouth regimen (Odd), CCr < 60 (or metastasis)

化學治療處方

Dartmouth regimen (Odd), CCr < 60	
published C/T regimens	**schedule**
Carmustine 150mg/m2, IV, D1-3	**Q28d * 6 cycles**
Dacarbazine 220mg/m2, IV, D1-3	**Q28d * 6 cycles**
Paraplatin auc*1.6mg, IV, D1-3	**Q28d * 6 cycles**
Nolvadex 10mg, PO, D1-3	**Q28d * 6 cycles**

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附件五-4：Dartmouth regimen (Even),CCr < 60 (or metastasis)

化學治療處方

Dartmouth regimen (Even),CCr < 60	
published C/T regimens	**schedule**
Dacarbazine 220mg/m2, IV, D1-3	**Q28d * 6 cycles**
Paraplatin auc*1.6mg, IV, D1-3	**Q28d * 6 cycles**
Nolvadex 10mg, PO, D1-3	**Q28d * 6 cycles**

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附件六：melanoma with brain metastasis

化學治療處方

melanoma with brain metastasis	
published C/T regimens	**schedule**
Temodal 150mg/m2/, IV, D1-5	**Q28d * 6 cycles**

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附件七：melanoma with Target therapy (or metastasis)

標靶治療處方	

melanoma with Target therapy	
Target therapy	**schedule**
Vemurafenib 960mg, oral	**Twice daily, continued**

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附件八：melanoma with Immunotherapy (or metastasis)

免疫治療處方

melanoma with Immunotherapy	
Immunotherapy	**schedule**
Ipilmumab 3mg/kg, IV	**Every 3wks, 4 sessions**
Nivolumab 3mg/kg, IV	**Every 2 wks, at least 2 yaers**

Reference

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