中 山 醫 學 大 學 附 設 醫 院

皮 膚 癌 診 療 指 引

本臨床指引參考美國NCCN版本

皮膚癌多專科醫療團隊編修

2018/01/18 Version2.0
2016/12/21 Version1.0

癌症委員會主任委員	癌症委員會執行長	癌症中心主任	團隊負責人

修訂內容

頁數	原文	修訂/增修
第 1 頁	前言 2016/12/21 Version1.0	前言 2018/01/18 Version2.0
第 4 頁	**(2) 鱗狀上皮細胞癌** **Tumor–node–metastasis(TNM) staging system for carcinoma of the breast(AJCC7th)** T0 No evidence of primary tumor T4 Tumor with invasion of skeleton(axial or appendicular) or perineural invasion of skull base Clinical N (cN) N3 Metastasis in a lymph node, more than 6cm in greatest dimension.	**Tumor–node–metastasis(TNM) staging system for carcinoma of the breast(AJCC8th)** 刪除 T0 No evidence of primary tumor 增訂 T4a Tumor with gross cortical bone/marrow invasion 增訂 T4b Tumor with skull base invasion and/or skull base foramen involvement. 增訂 N3a Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-). 增訂 N3b Metastasis in any node(s) and ENE(+).
第 5 頁	黑色素細胞癌(Melanoma) **Tumor–node–metastasis(TNM) staging system for carcinoma of the breast(AJCC7th)** T1 Melanomas 1.0 mm or less in thickness T2 Melanomas 1.01-2.0 mm T3 Melanomas 2.01-4.0 mm T4 Melanomas more than 4.0mm N1a Metastastic 1 Node;micrometastasis. N1b Metastastic 1 Node;macrometastasis. N3 4 or more metastastic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s) M0 No detectable evidence of distant metastases	**Tumor–node–metastasis(TNM) staging system for carcinoma of the breast(AJCC8th)** 增訂 T1a Thickness <0.8mm without ulceration 增訂 T1b Thickness <0.8mm with ulceration 增訂 T1b Thickness0.8-1.0mm with or without ulceration. 增訂 T2a Thickness >1.0-2.0mm without ulceration 增訂 T2b Thickness >1.0-2.0mm with ulceration 增訂 T3a Thickness >2.0-4.0mm without

	M1a Metastases to skin, subcutaneous, or distant lymph nodes M1b Metastases to lung M1c Metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH	ulceration 增訂 T3b Thickness >2.0-4.0mm with ulceration 增訂 T4a Thickness >4.0mm without ulceration 增訂 T4b Thickness >4.0mm with ulceration 增訂 N1c No regional lymph node disease; Presence of in-transit, satellite, and /or microsatellite metastases 增訂 N3a Four or more clinically occult (i.e., detected by SLN biopsy) 增訂 N3b Four or more, at least one of which was clinically detected, or presence of any number of matted nodes. 增訂 N3c Two or more clinically occult or clinically detected and/or presence of any number of matted nodes; Presence of in-transit, satellite, and /or microsatellite metastases 增訂 M1 Evidence of distant metastasis 增訂 M1d Distant metastasis to CNS with or without M1a, M1b, or M1c sites or disease.
第 32 頁	泰伏樂(Dabrafenib) 曲美替尼片(Trametinib) Dabrafenib+ Trametinib	刪除 泰伏樂(Dabrafenib) 刪除 曲美替尼片(Trametinib) 刪除 Dabrafenib+ Trametinib

目錄

一、前言

常見的皮膚癌有基底細胞癌(Basal Cell Carcinoma)、鱗狀細胞癌(Squamous Cell Carcinoma)、黑色素細胞癌(Melanoma)。基底細胞癌源自於皮膚表皮底層的柱狀基底細胞，是人類最常見的癌症，臨床可見 Pearly border 與微血管擴張，少數有 Rodent ulcer，基底細胞癌侵襲性與轉移性皆低，通常手術切除乾淨與定期追蹤，預後通常都不錯並且有極高的生存率。鱗狀細胞癌源自於皮膚表皮層的棘狀細胞，臨床常見有角化與色澤形狀不一的腫瘤，有時有 Marjolin's ulcer，預後與腫瘤大小、位置、是否有神經侵犯、是否有淋巴與遠端器官轉移有關。黑色素癌是轉移性高且死亡率也高的皮膚癌，在臺灣的發生率約為十萬分之零點八。東方人的黑色素癌好發在手指尖或是腳掌，稱為肢端型黑色素癌（acral lentiginous type of melanoma）。警覺心不足或忽略檢查腳底有無異常黑點，常會延誤診斷而耽誤治療。黑色素癌的厚度與是否有淋巴結或器官轉移，影響了患者的預後，早期黑色素癌，以手術與前哨淋巴結檢查切除，為最佳治療方式，然而，轉移型黑色素癌的治療則相當不容易，黑色素癌容易轉移到肺部，腦部，骨頭，肝臟等。傳統藥物化療藥物 Dacarbazine 對第四期轉移性黑色素癌的療效有限，平均存活時間大約只有 6 至 7 個月。而傳統免疫藥物 IFN　2b 與高劑量 IL-2 的副作用多，包括高燒、寒顫、低血壓、心跳過速等等不舒服的症狀，往往讓患者難以承受而放棄治療。

然而，自人類基因解序幫助科學家對疾病致病機轉更加地瞭解，轉移型黑色素癌治療在 2010 年有了新的突破。整個癌症治療指引也有了重大改變。發展中的新治療主要分成兩個部分，一個是標靶治療，另一個則是新型的免疫治療，並以合併治療為趨勢。標靶治療主要是針對黑色素癌細胞生長所需的訊息傳遞因子(標的)給予抑制，例如 BRAF 基因 V600E 的突變對黑色素癌細胞生長非常重要，標靶治療針對 BRAF 抑制的藥物有日沛樂/Zelboraf (Vemurafenib)以及泰伏樂/Tafinlar (Dabrafenib)，日沛樂於 2014 年在台灣上市，有健保給付，用於治療 BRAF V600E 突變陽性 WHO 體能狀態小於等於二，且罹患無法切除(第ⅢC 期)或轉移性(第Ⅳ期)黑色素癌之病人。在 BRAF 基因 V600E 突變陽性的轉移型黑色素癌病患，標靶治療可以讓腫瘤快速地縮小，但對生存率的延長沒有顯著幫忙。

在腫瘤微環境研究發現，癌細胞為了能逃避免疫細胞的追殺，會用各種方法去干擾身體的免疫系統。其中一種方式就是藉由活化免疫系統的控制因子(免疫檢查點蛋白)，進而讓免疫系統失能，無法攻擊黑色素癌細胞。新的免疫療法就是想辦法去抑制這些控制因子，減弱免疫檢查點蛋白的抑制能力，讓免疫系統能夠恢復原本的功能，去攻擊黑色素癌細胞。臺灣有抑制 CTLA-4 的益伏/Yervoy (ipilimumab)與抑制 PD-l 的吉舒達 Keytruda (Pembrolizumab)及抑制 PD-l 的保疾伏 Opdivo (Nivolumab)。對於轉移性黑色素癌的新進展，著實另人振奮，但仍有許多待解決的問題例如亞洲病

患標靶基因突變比率偏低、抗藥性、副作用、健保給付、昂貴藥費等等。如何結合目前所有的各種標靶治療，免疫治療，找出病人最適合的治療藥物組合，成了當前最大挑戰。

二、皮膚癌分期

(1) 基底細胞癌(Basal cell carcinoma)

Stage 0: Cancer involves only the epidermis and has not spread to the dermis
Stage I: Cancer is not large (ie, < 2 cm) and has not spread to the lymph nodes or other organs
Stage II: Cancer is large (ie, >2 cm) but has not spread to lymph nodes or other organs
Stage III: Cancer has spread to tissues beneath the skin (eg, muscle, bone, cartilage), and/or to regional lymph nodes but not to other organs.
Stage IV: Cancer can be any size and has spread to other organs

(2) 鱗狀上皮細胞癌(Cutaneous Squamous Cell Carcinoma)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor smaller than 2 cm in greatest dimension
T2	Tumor 2 cm or larger, but smaller than 4 cm in greatest dimension
T3	Tumor 4 cm or larger in maximum dimension or minor bone erosion or perineural invasion or deep invasion*
T4	Tumor with gross cortical bone/marrow, skull base invasion and/or skull base foramen invasion
T4a	Tumor with gross cortical bone/marrow invasion
T4b	Tumor with skull base invasion and/or skull base foramen involvement

*Deep invasion is defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor); perineural invasion for T3 classification is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.

Regional Lymph Node (N)

Clinical N (cN)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); or in metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); or metastasis in any node(s) and clinically overt ENE [ENE(+)]
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in any node(s) and ENE (+)
Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological extranodal extension (ENE) should be recorded as ENE(−) or ENE(+).	

Staging continued

American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Cutaneous Squamous Cell Carcinoma of the Head and Neck (cSCC) (8th ed., 2016)

Regional Lymph Node (N) continued

Pathological N (pN)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); or larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); or in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension, ENE(−)
N2a	Metastasis in single ipsilateral node 3 cm or smaller in greatest dimension and ENE(+); or a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastasis in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); or in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+); or a single contralateral node of any size and ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+); or a single contralateral node of any size and ENE(+)
Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological extranodal extension (ENE) should be recorded as ENE(−) or ENE(+).	

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

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

AJCC Prognostic Stage Groups

Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1	N1	M0	III
T2	N1	M0	III
T3	N1	M0	III
T1	N2	M0	IV
T2	N2	M0	IV
T3	N2	M0	IV
Any T	N3	M0	IV
T4	Any N	M0	IV
Any T	Any N	M1	IV

HISTOLOGIC GRADE (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

(3) 黑色素細胞癌(Melanoma)

Definition of Primary Tumor (T)

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

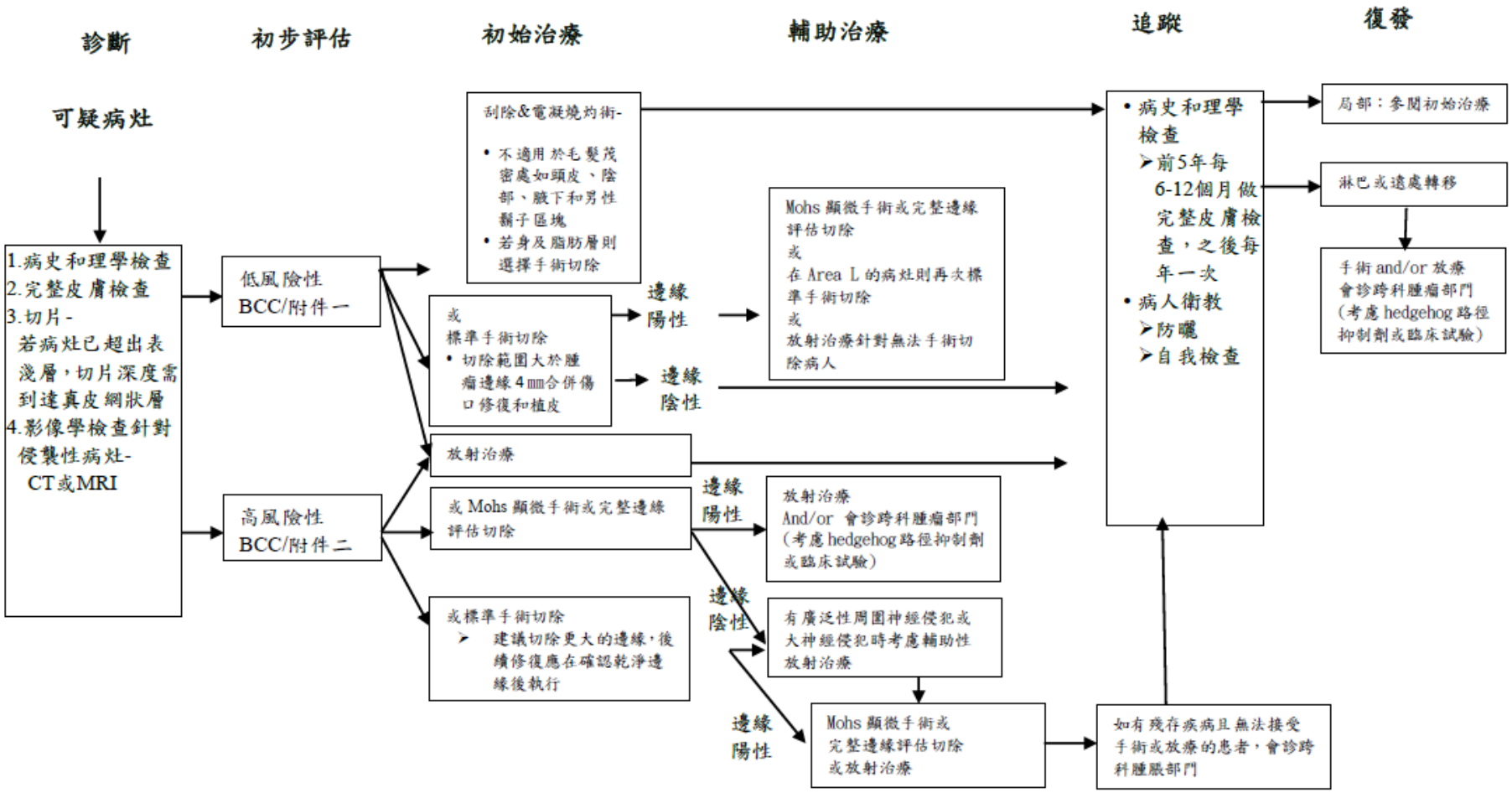
Definition of Reginal Lymph Node(N)

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(e.g., 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	No
N1a	One clinically occult (i.e.,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(i.e.,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 (i.e., 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

Definition of Distant Metastasis(M)

M Category	M Criteria	
	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

三、基底細胞癌



侵襲性病灶: 包含深部組織如骨頭、神經、深部軟組織。骨頭侵犯安排 CT；深部組織安排 MRI。

目前 FDA 核准的 Hedgehog 藥物: vismodegib/ sonidegib 懷疑大或深部神經侵犯：MRI with contrast

附件一、局部復發的危險因子

病史及理學檢查	低風險	高風險
位置/大小	Area L＜20 ㎜ Area M＜10 ㎜	Area L ≥20 ㎜ Area M ≥10 ㎜ Area H 任何大小
邊緣	界限分明	界線模糊
原發/續發	原發	續發
免疫抑制	無	有
病灶位置曾接受過放射治療	無	有
神經侵犯	無	有
病理分類	Nodular , superficial keratotic , infundibulocystic , fibroepithelioma of Pinkus ,	Morpheaform , basosquamous (metatypical) ,sclerosing , Mixed infiltrative , micronodular

Area H的腫瘤不論大小都屬於高風險。這些地方通常為了美觀，margin不夠大，易造成復發。建議使用Mohs micrographic surgery可達到邊緣乾淨，且最小切除範圍。對於<6mm的腫瘤，沒有其他危險因子，建議至少要切除4mm的margin。

附件二、PRINCIPLES OF TREATMENT FOR BASAL CELL SKIN CANCER

- The primary goal of treatment of basal cell skin cancer is the complete removal of the tumor and the maximal preservation of function and cosmesis. All treatment decisions should be customized to account for the particular factors present in the individual case and for the patient's preference.
- Surgical approaches often offer the most effective and efficient means for accomplishing cure, but considerations of function, cosmesis, and patient preference may lead to choosing radiation therapy as primary treatment in order to achieve optimal overall results.
- In certain patients at high risk for multiple primary tumors, increased surveillance and consideration of prophylactic measures may be indicated.
- In patients with low-risk, superficial basal cell skin cancer, where surgery and radiation are contraindicated or impractical, therapies such as topical 5-fluorouracil, topical imiquimod, photodynamic therapy (eg, aminolevulinic acid [ALA], porfimer sodium), or vigorous cryotherapy may be considered, even though the cure rates may be lower than with surgical treatment modalities.
- When Mohs micrographic surgery with marginal assessment is being performed and the preoperative biopsy is considered insufficient for providing all the staging information required to properly treat the tumor, submission of the central specimen for permanent vertical sections is recommended.
- Use of nicotinamide has been effective in reducing the development of basal cell skin cancers.

附件三、PRINCIPLES OF RADIATION THERAPY FOR BASAL CELL SKIN CANCER

Primary Tumor		**Dose Time Fractionation Schedule**
Tumor Diameter	Margins	Examples of Dose Fractionation and Treatment Duration
<2 cm	1 – 1.5 cm	64 Gy in 32 fractions over 6 – 6.4 weeks 55 Gy in 20 fractions over 4 weeks 50 Gy in 15 fractions over 3 weeks 35 Gy in 5 fractions over 5 days
≥2 cm	1.5 – 2 cm	66 Gy in 33 fractions over 6–6.6 weeks 55 Gy in 20 fractions over 4 weeks
Postoperative adjuvant		50 Gy in 20 fractions over 4 weeks 60 Gy in 30 fractions over 6 weeks

附件四、藥物治療

1.Inductions and Usage for Erivedge

Erivedge capsule is indicated for the treatment of adults with metastatic basal carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.

Erivedge Dosage nad Administration

The recommended dose of Erivedge is150mg taken orally once daily until disease progression or until unacceptable toxicity.

Erivedge may be taken with or without food.Swallow capsules wholes. Do not open or crush capsules.

If a dose of Erivedge is missed, do not make up that dose.

Dosage Forms and Strengths

Erivedge (vismodegib) capsules, 150mg. The capsule has a pink opaque body and a gery opaque cap, with "150mg"printed on the capsule body and "VISMO" printed on the capsule cap in black ink.

2. Clinical trial

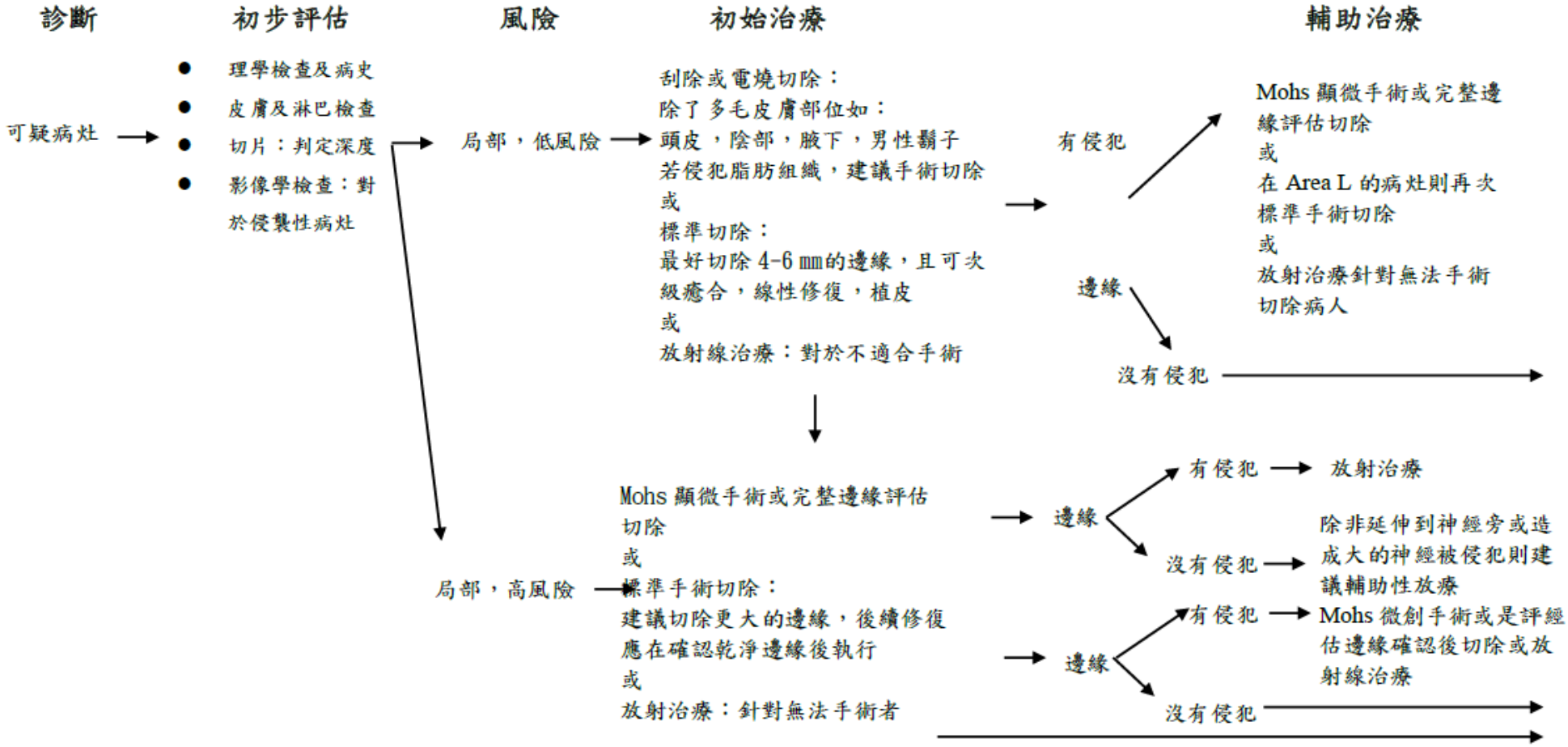
3. Cisplatin + paclitaxol (self pay)

cisplatin (75 mg/m2) and paclitaxel (135 mg/m2, 3 h infusion) every 3 weeks

Ref: Metastatic basal cell carcinoma: rapid symptomatic response to cisplatin and paclitaxel. ANZ J Surg. 2004 Aug;74(8):704-5.

4. Treat as recurrent/metastatic head and neck squamous cell carcinoma

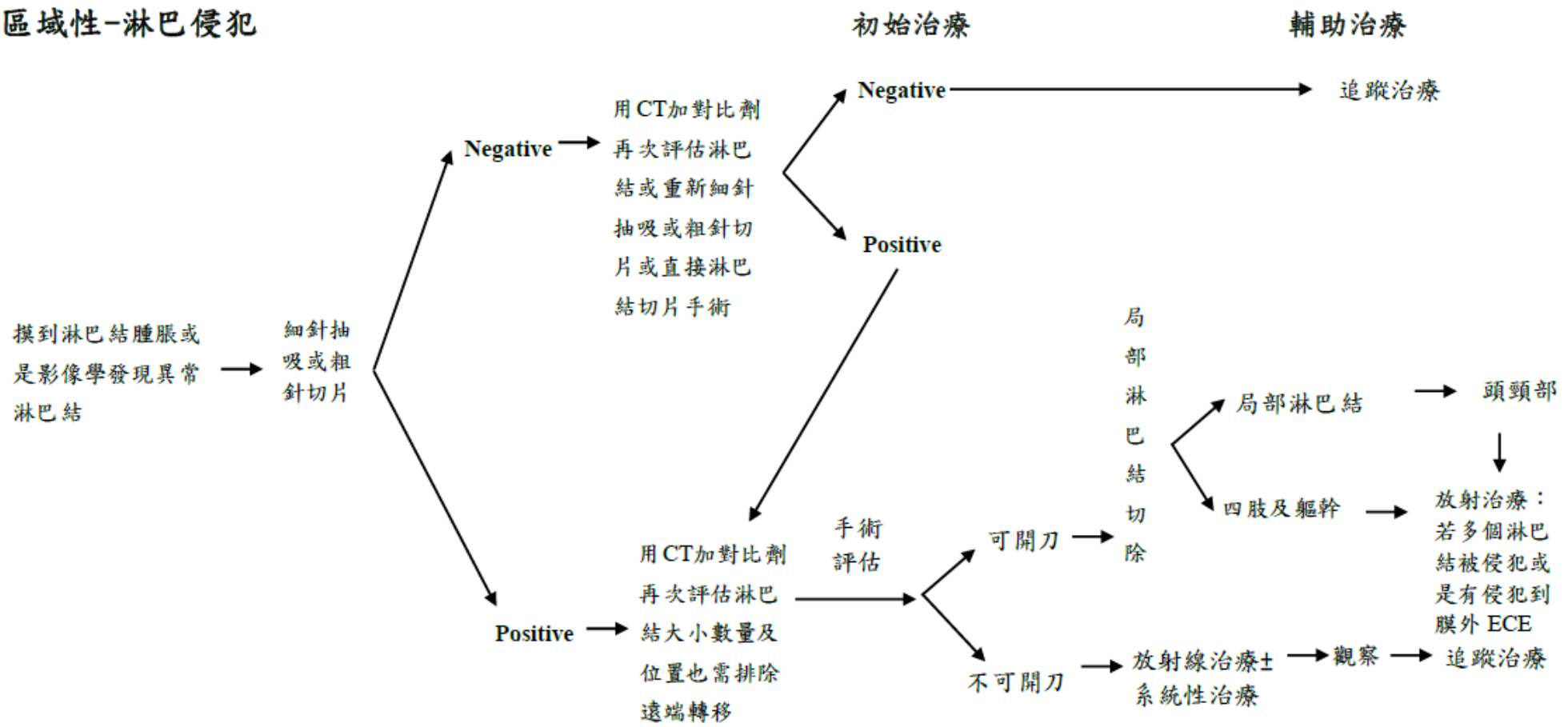
四、鱗狀上皮細胞癌

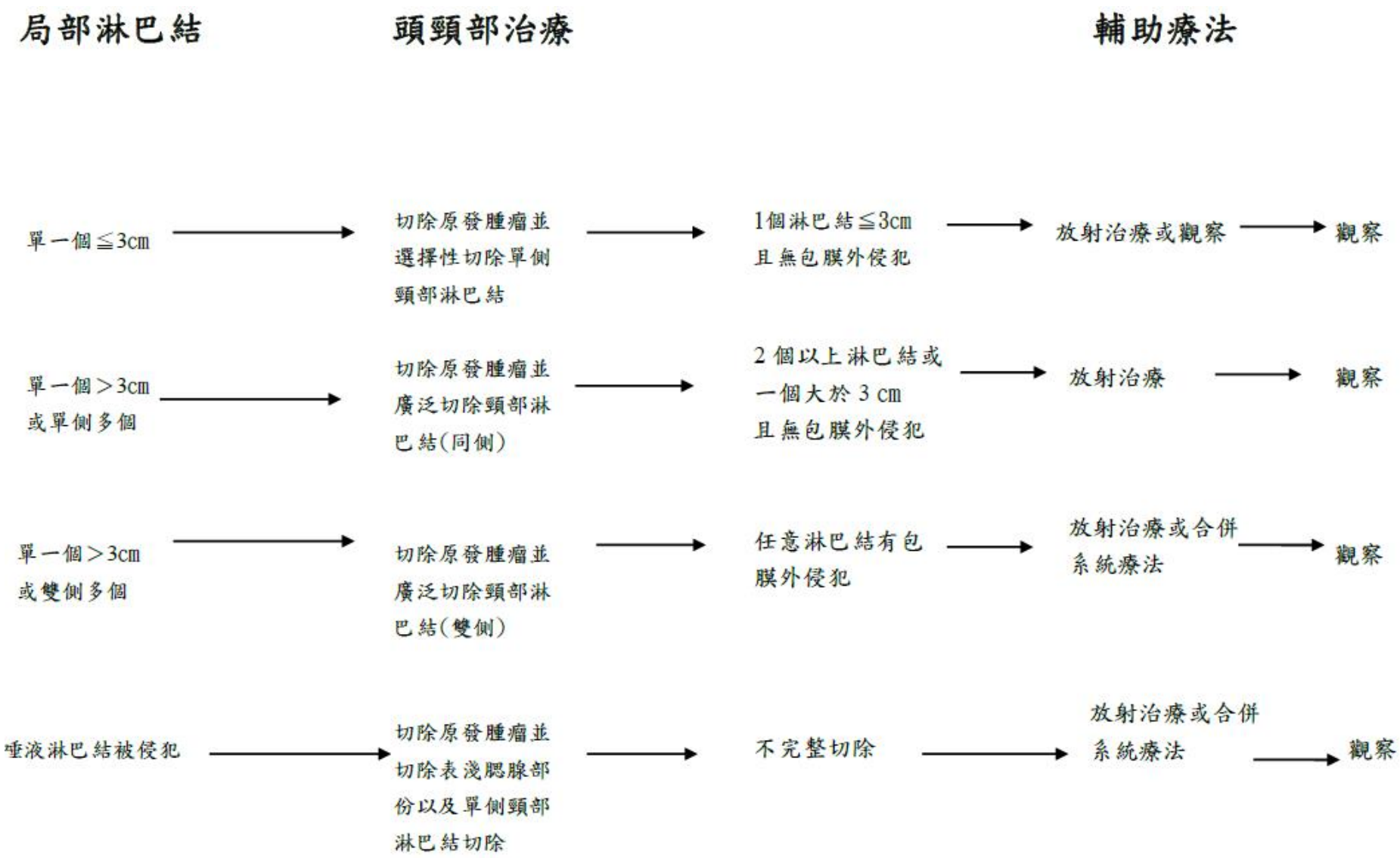


放射線治療：通常建議保留再 60 歲以上的病人。

Area L: 軀幹或四肢(不包含 hands,feet,pretibial area, nail unit, ankle)

懷疑大或深部神經侵犯：MRI with contrast


區域性-淋巴侵犯
初始治療
輔助治療
摸到淋巴結腫脹或是影像學發現異常淋巴結
細針抽吸或粗針切片
Negative
用CT加對比劑再次評估淋巴結或重新細針抽吸或粗針切片或直接淋巴結切片手術
Negative
追蹤治療
Positive
Positive
用CT加對比劑再次評估淋巴結大小數量及位置也需排除遠端轉移
手術評估
可開刀
局部淋巴結切除
局部淋巴結
頭頸部
四肢及軀幹
放射治療：若多個淋巴結被侵犯或是有侵犯到膜外 ECE
不可開刀
放射線治療±系統性治療
觀察
追蹤治療


局部淋巴結
頭頸部治療
輔助療法
單一個≦3cm
切除原發腫瘤並選擇性切除單側頸部淋巴結
1個淋巴結≦3cm且無包膜外侵犯
放射治療或觀察
觀察
單一個＞3cm或單側多個
切除原發腫瘤並廣泛切除頸部淋巴結(同側)
2個以上淋巴結或一個大於3 cm且無包膜外侵犯
放射治療
觀察
單一個＞3cm或雙側多個
切除原發腫瘤並廣泛切除頸部淋巴結(雙側)
任意淋巴結有包膜外侵犯
放射治療或合併系統療法
觀察
唾液淋巴結被侵犯
切除原發腫瘤並切除表淺腮腺部份以及單側頸部淋巴結切除
不完整切除
放射治療或合併系統療法
觀察

追蹤

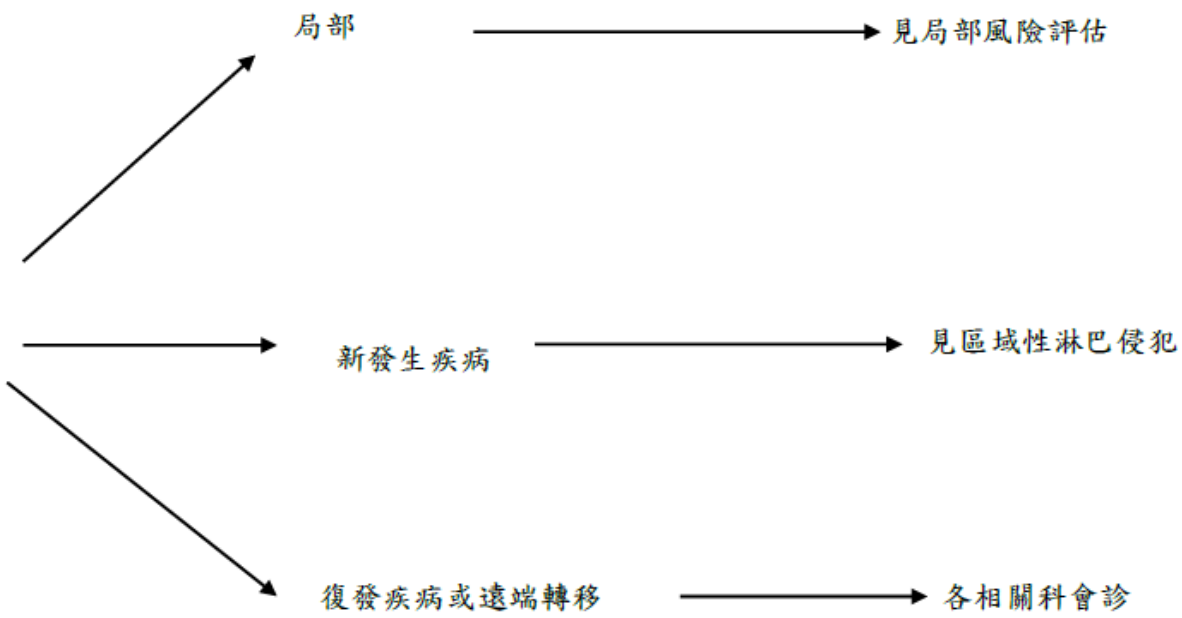
Local disease：

- 前2年：3-12個月追蹤
- 第3年：6-12個月追蹤
  之後每年追蹤一次
- 病人衛教
  - 防曬
  - 自我皮膚檢測

Regional disease：

- 第1年：1-3個月追蹤
- 第2年：2-4個月追蹤
- 第3年：4-6個月追蹤
  之後每年6-12個月追蹤一次
- 病人衛教
  - 防曬
  - 自我皮膚及淋巴結檢測

復發及病程進展



附件一、局部，高低風險判斷標準

病史及理學檢查	低風險	高風險
位置/大小	Area L < 20mm Area M < 10mm	Area L ≥ 20mm Area M ≥ 10mm Area H 任何大小
邊緣	界限分明	界線模糊
原發/續發	原發	續發
免疫抑制	無	有
病灶位置曾接受過放射線治療或慢性發炎狀態	無	有
生長快速	無	有
神經、血管、淋巴侵犯	無	有
神經學症狀	無	有
病理分類	分化良好	分化不良 (Adenoid-acantholytic, adenosquamous-mucin production, desmoplastic, metaplastic-carcinosarcomatous type)
深度	<2mm or Clark level I II III	≥2mm or Clark level IV V

Area Low risk: trunk and extremities(excluding hands, feet, pretibial area)

Area Medium risk: pretibial area, face other than mask area (cheek, forehead, scalp, neck)

Area High risk: face mask area+ hands+feet+genitalia (mask area: central face, eyelid, eyebrow, nose, lips-cutaneous and vermilion, chin, mandible, preauricular/postauricular skin sulci, temple, ear)

Area H 的腫瘤不論大小都屬於高風險。這些地方通常為了美觀，margin 不夠大，易造成復發。建議使用 Mohs micrographic surgery 可達到邊緣乾淨，且最小切除範圍。對於<6mm 的腫瘤，沒有其他危險因子，建議至少要切除 4mm 的 margin。

附件二、PRINCIPLES OF RADIATION THERAPY FOR SQUAMOUS CELL SKIN CANCER

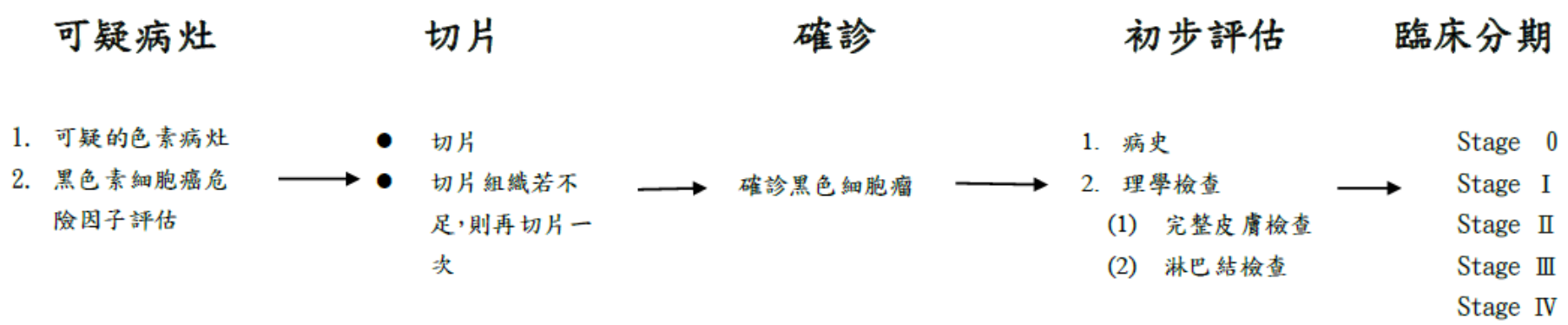
Primary Tumor		**Dose Time Fractionation Schedule**
Tumor Diameter	Margins	Examples of Dose Fractionation and Treatment Duration
<2 cm	1 – 1.5 cm	64 Gy in 32 fractions over 6–6.4 weeks 55 Gy in 20 fractions over 4 weeks 50 Gy in 15 fractions over 3 weeks 35 Gy in 5 fractions over 5 days
≥2 cm	1.5 – 2 cm	66 Gy in 33 fractions over 6–6.6 weeks 55 Gy in 20 fractions over 4 weeks
Postoperative adjuvant		50 Gy in 20 fractions over 4 weeks 60 Gy in 30 fractions over 6 weeks

- Protracted fractionation is associated with improved cosmetic results.
- Radiation therapy is contraindicated in genetic conditions predisposing to skin cancer (eg, basal cell nevus syndrome, xeroderma pigmentosum) and connective tissue diseases (eg, scleroderma).

附件三、藥物治療

Chemotherapy regimen & EGFRI	
Published C/T regimens	schedule
Cisplatin 100mg/m^2 IV D1	Q21 days *6cucles
5-FU 1g/m^2 IV D1-4	Q21 days *6cucles
Cetuximab,400mg/m2 IV Week1 , then 250mg/m2 QW	Till IV or unacceptable toxicity

五、黑色素細胞癌



切片病理組織學證實：

Breslow thickness +

Ulceration status (present or absent) +

Dermal mitotic rate(#/㎜^{2}) +

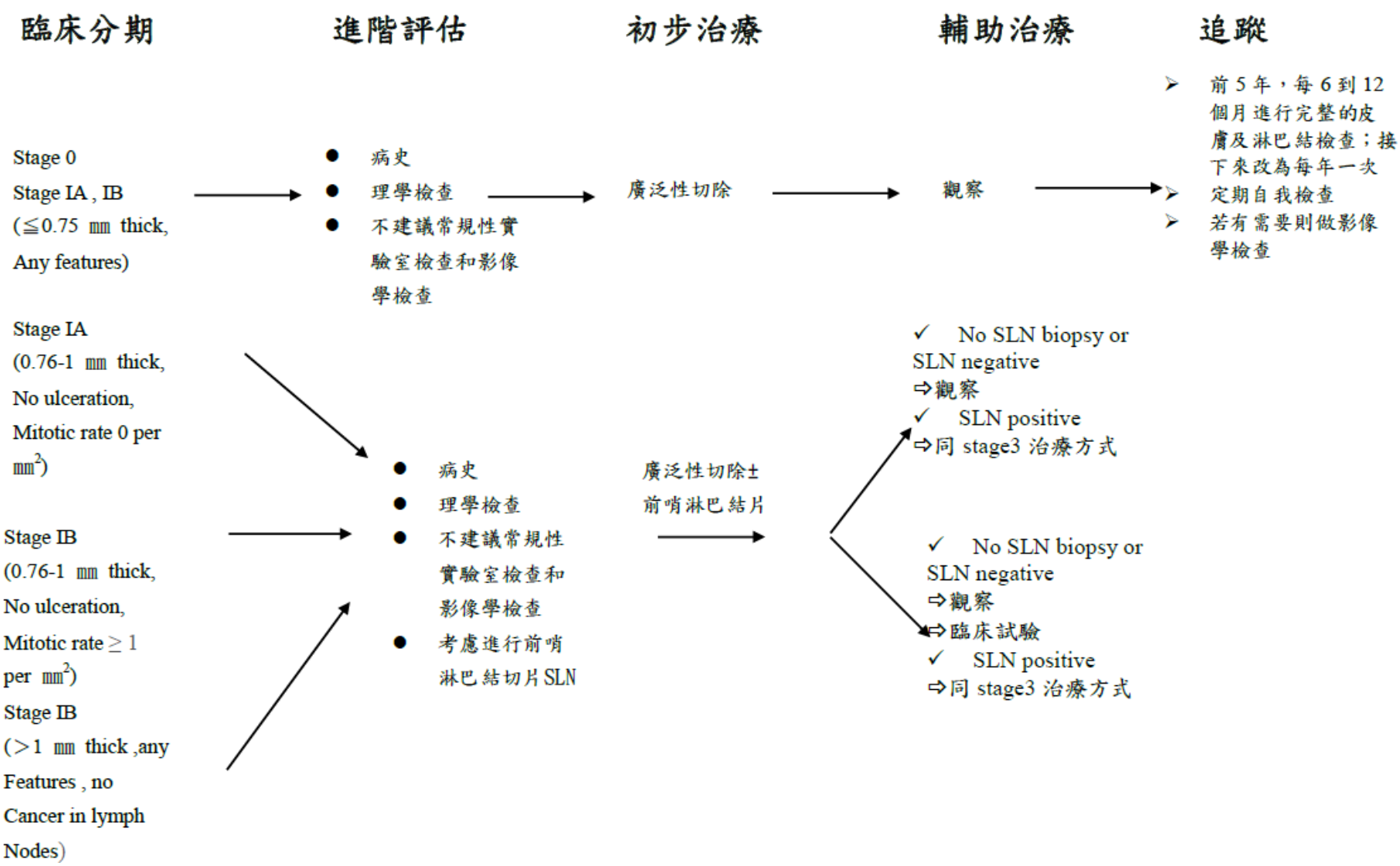
Assess deep and peripheral margin status +

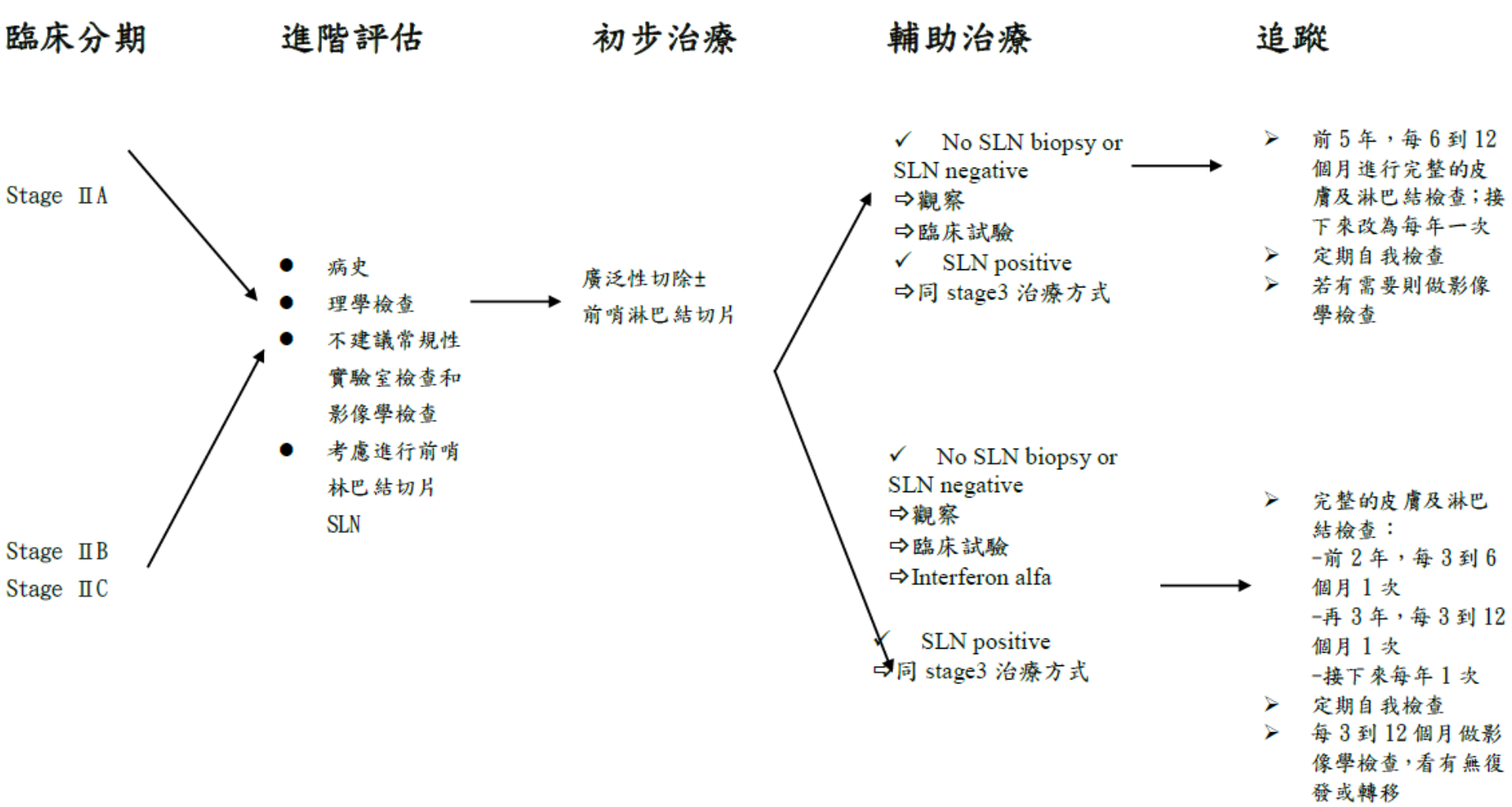
Microsatellitosise (present or absent) +

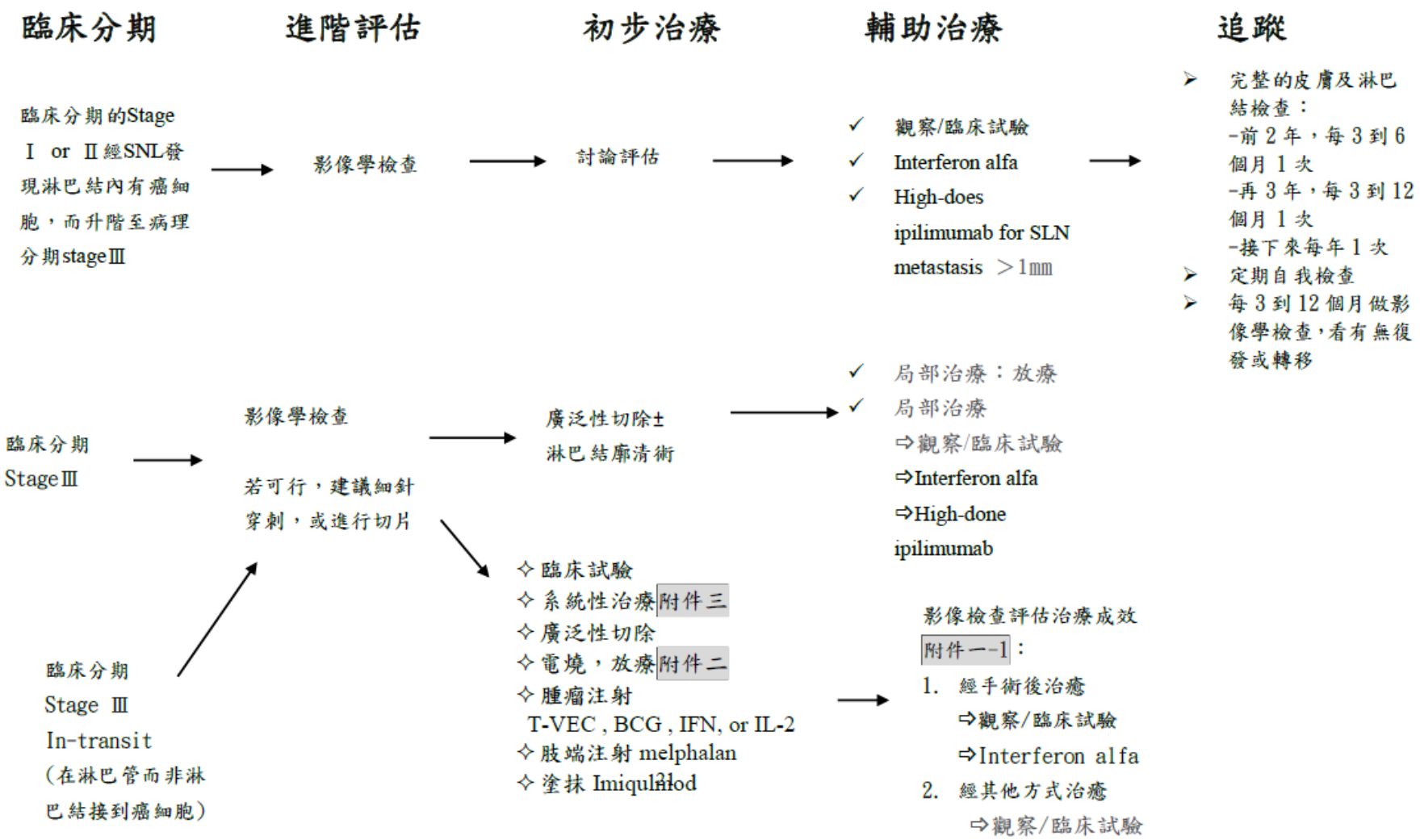
Clark level (for nonulcerated lesions where mitotic rate is not determined,

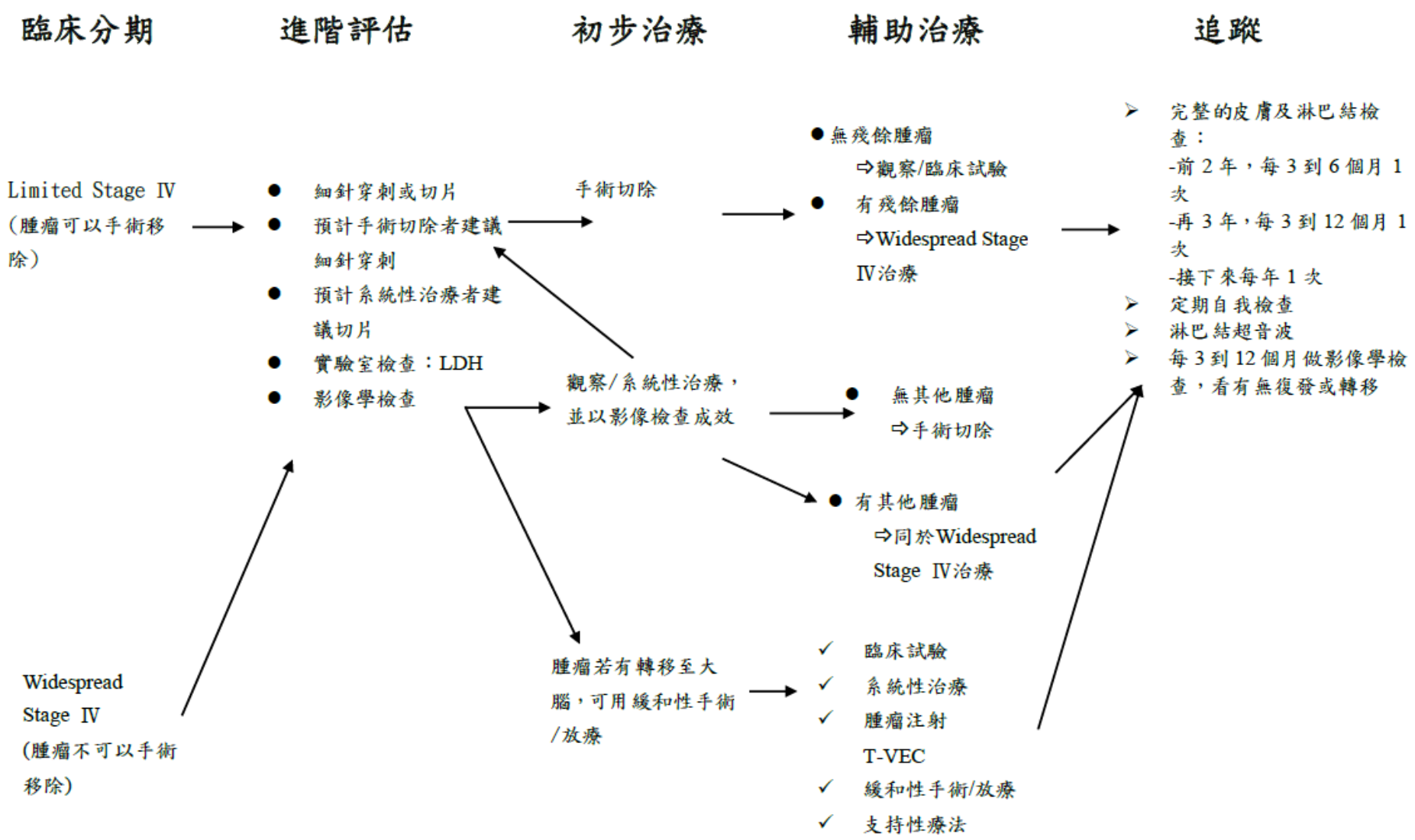
For lesions ≤1 ㎜) +

Pure desmoplasiaf if present

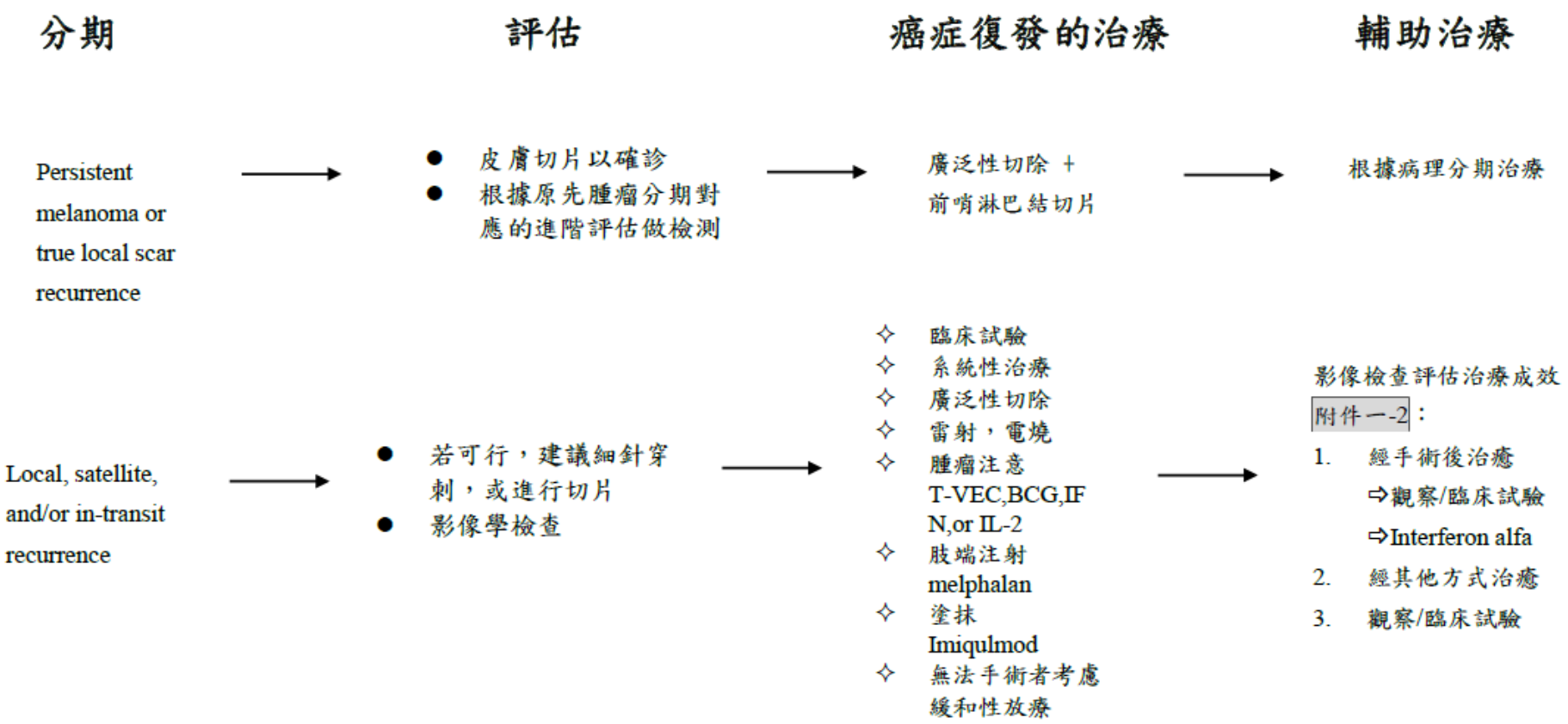

臨床分期
進階評估
初步治療
輔助治療
追蹤
Stage 0
Stage IA , IB
(≦0.75 ㎜ thick,
Any features)
病史
理學檢查
不建議常規性實驗室檢查和影像學檢查
廣泛性切除
觀察
前 5 年，每 6 到 12 個月進行完整的皮膚及淋巴結檢查；接下來改為每年一次
定期自我檢查
若有需要則做影像學檢查
Stage IA
(0.76-1 ㎜ thick,
No ulceration,
Mitotic rate 0 per ㎜²)
Stage IB
(0.76-1 ㎜ thick,
No ulceration,
Mitotic rate ≥ 1 per ㎜²)
Stage IB
(>1 ㎜ thick ,any Features , no Cancer in lymph Nodes)
病史
理學檢查
不建議常規性實驗室檢查和影像學檢查
考慮進行前哨淋巴結切片 SLN
廣泛性切除± 前哨淋巴結片
✓ No SLN biopsy or SLN negative
⇨觀察
✓ SLN positive
⇨同 stage3 治療方式
✓ No SLN biopsy or SLN negative
⇨觀察
⇨臨床試驗
✓ SLN positive
⇨同 stage3 治療方式


臨床分期
進階評估
初步治療
輔助治療
追蹤
Stage ⅡA
Stage ⅡB
Stage ⅡC
病史
理學檢查
不建議常規性實驗室檢查和影像學檢查
考慮進行前哨林巴結切片
SLN
廣泛性切除±
前哨淋巴結切片
✓ No SLN biopsy or SLN negative
⇨觀察
⇨臨床試驗
✓ SLN positive
⇨同 stage3 治療方式
➢ 前 5 年，每 6 到 12 個月進行完整的皮膚及淋巴結檢查；接下來改為每年一次
➢ 定期自我檢查
➢ 若有需要則做影像學檢查
✓ No SLN biopsy or SLN negative
⇨觀察
⇨臨床試驗
⇨Interferon alfa
✓ SLN positive
⇨同 stage3 治療方式
➢ 完整的皮膚及淋巴結檢查：
-前 2 年，每 3 到 6 個月 1 次
-再 3 年，每 3 到 12 個月 1 次
-接下來每年 1 次
➢ 定期自我檢查
➢ 每 3 到 12 個月做影像學檢查，看有無復發或轉移

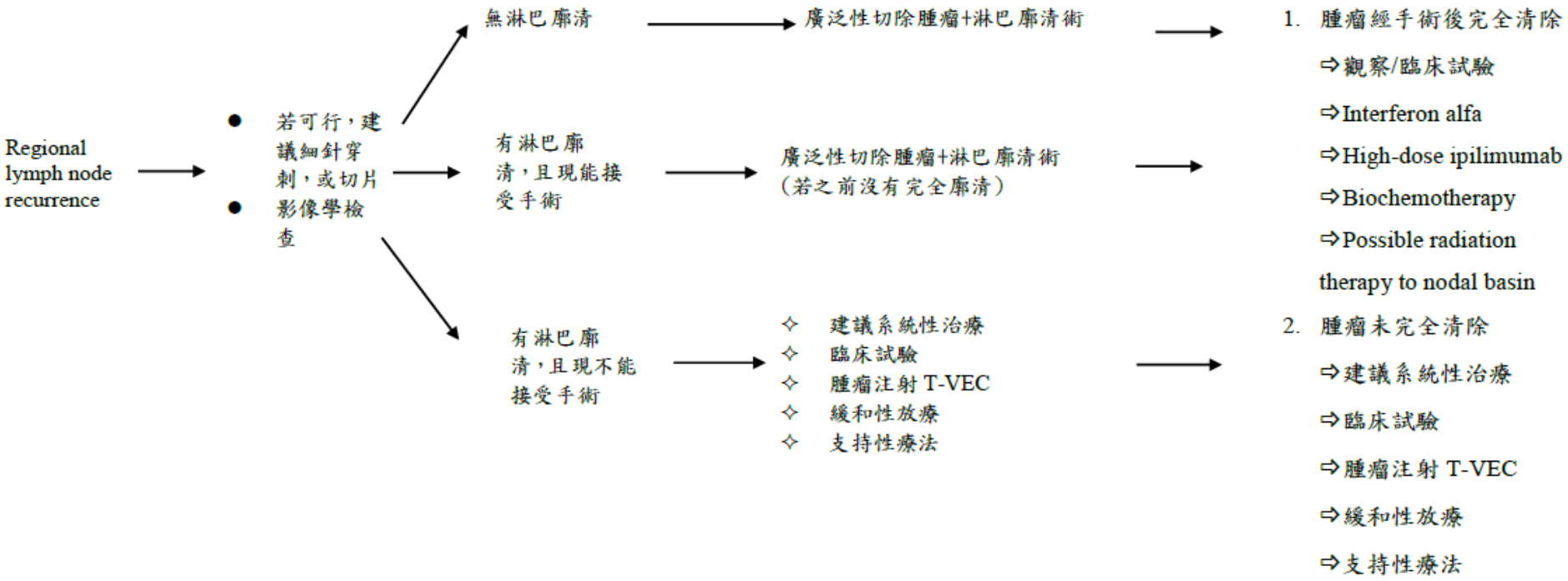

臨床分期
進階評估
初步治療
輔助治療
追蹤
臨床分期的Stage Ⅰ or Ⅱ經SNL發現淋巴結內有癌細胞，而升階至病理分期stageⅢ
影像學檢查
討論評估
✓ 觀察/臨床試驗
✓ Interferon alfa
✓ High-does ipilimumab for SLN metastasis ＞1㎜
➢ 完整的皮膚及淋巴結檢查：
-前 2 年，每 3 到 6 個月 1 次
-再 3 年，每 3 到 12 個月 1 次
-接下來每年 1 次
➢ 定期自我檢查
➢ 每 3 到 12 個月做影像學檢查，看有無復發或轉移
臨床分期 StageⅢ
影像學檢查
若可行，建議細針穿刺，或進行切片
廣泛性切除±淋巴結廓清術
✓ 局部治療：放療
✓ 局部治療
⇨觀察/臨床試驗
⇨Interferon alfa
⇨High-done ipilimumab
臨床分期 Stage Ⅲ In-transit（在淋巴管而非淋巴結接到癌細胞）
✧ 臨床試驗
✧ 系統性治療附件三
✧ 廣泛性切除
✧ 電燒，放療附件二
✧ 腫瘤注射 T-VEC , BCG , IFN, or IL-2
✧ 肢端注射 melphalan
✧ 塗抹 Imiquimod
影像檢查評估治療成效附件一-1：
1. 經手術後治癒
⇨觀察/臨床試驗
⇨Interferon alfa
2. 經其他方式治癒
⇨觀察/臨床試驗


臨床分期
進階評估
初步治療
輔助治療
追蹤
Limited Stage Ⅳ
(腫瘤可以手術移除)
細針穿刺或切片
預計手術切除者建議細針穿刺
預計系統性治療者建議切片
實驗室檢查：LDH
影像學檢查
手術切除
無殘餘腫瘤
⇨觀察/臨床試驗
有殘餘腫瘤
⇨Widespread Stage Ⅳ治療
觀察/系統性治療，並以影像檢查成效
無其他腫瘤
⇨手術切除
有其他腫瘤
⇨同於Widespread Stage Ⅳ治療
Widespread Stage Ⅳ
(腫瘤不可以手術移除)
腫瘤若有轉移至大腦，可用緩和性手術/放療
✓ 臨床試驗
✓ 系統性治療
✓ 腫瘤注射 T-VEC
✓ 緩和性手術/放療
✓ 支持性療法
➢ 完整的皮膚及淋巴結檢查：
-前 2 年，每 3 到 6 個月 1 次
-再 3 年，每 3 到 12 個月 1 次
-接下來每年 1 次
➢ 定期自我檢查
➢ 淋巴結超音波
➢ 每 3 到 12 個月做影像學檢查，看有無復發或轉移

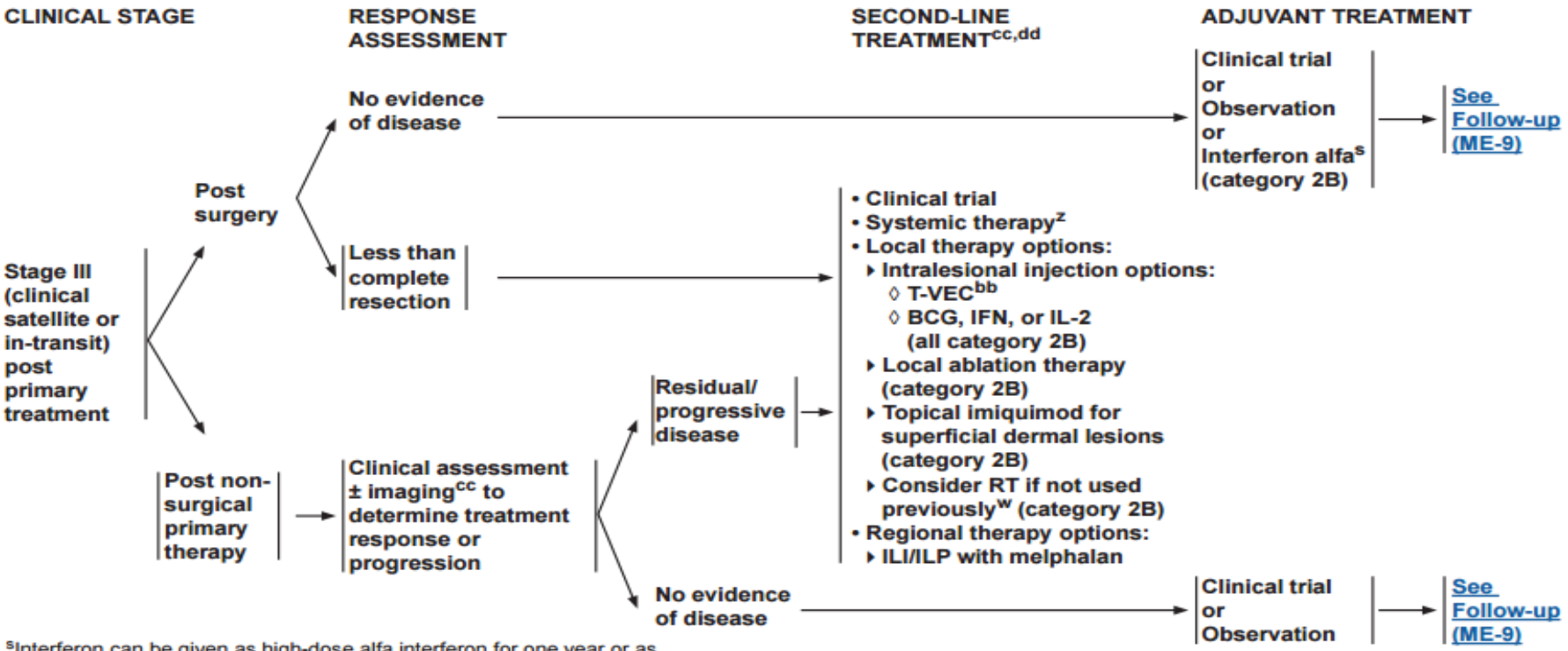
Node-negative recurrence treatment



Regional lymph node recurrence treatment



附件一、影像檢查評估治療成效 1



[s]Interferon can be given as high-dose alfa interferon for one year or as peginterferon alfa-2b for up to 5 years. Adjuvant interferon has been shown to improve DFS (category 1); but there is no impact on overall survival.

[w]See Principles of Radiation Therapy for Melanoma (ME-F).

[z]See Systemic Therapy for Metastatic or Unresectable Disease (ME-G 1 of 6)

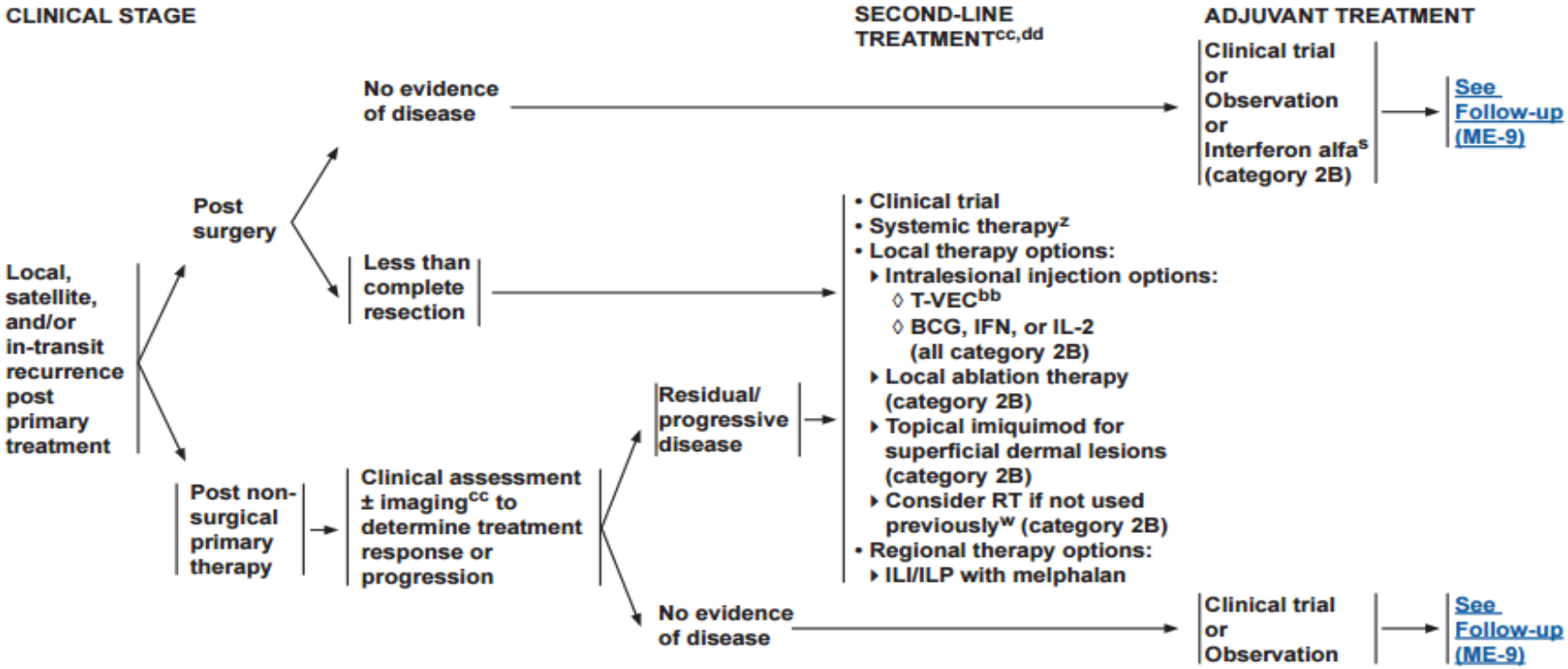
[bb]T-VEC was associated with a response rate (lasting ≥6 months) of 16% in highly selected patients with unresectable metastatic melanoma. Efficacy was noted in Stage IIIB and IIIC disease, and was more likely in patients who were treatment naive.

[cc]See Principles of Imaging--Treatment Response Assessment (ME-C).

[dd]For patients who experience progression of melanoma during or shortly after first-line therapy, consider second-line agents if not used first line and not of same class. For patients who experience disease control (CR, PR, or SD) and have no residual toxicity, but subsequently experience disease progression/relapse >3 months after treatment discontinuation, re-induction with the same agent or same class of agents may be considered.

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.

附件一、影像檢查評估治療成效 2



[s]Interferon can be given as high-dose alfa interferon for one year or as peginterferon alfa-2b for up to 5 years. Adjuvant interferon has been shown to improve DFS (category 1); but there is no impact on overall survival.
[w]See Principles of Radiation Therapy for Melanoma (ME-F).
[z]See Systemic Therapy for Metastatic or Unresectable Disease (ME-G 1 of 6).
[bb]T-VEC was associated with a response rate (lasting ≥6 months) of 16% in highly selected patients with unresectable metastatic melanoma. Efficacy was noted in Stage IIIB and IIIC disease, and was more likely in patients who were treatment naive.
[cc]See Principles of Imaging--Treatment Response Assessment (ME-C).
[dd]For patients who experience progression of melanoma during or shortly after first-line therapy, consider second-line agents if not used first line and not of same class. For patients who experience disease control (CR, PR, or SD) and have no residual toxicity, but subsequently experience disease progression/relapse >3 months after treatment discontinuation, re-induction with the same agent or same class of agents may be considered.

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.

ME-11

附件二、PRINCIPLES OF RADIATION THERAPY FOR MELANOMA

- Consider RT in the following situations:
  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
- 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
  - Adjuvant treatment in selected patients following resection of clinically appreciable nodes (category 2B) 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
    - 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)
  - Other symptomatic or potentially symptomatic soft tissue and/or bone metastases

附件三、系統性治療

OTHER SYSTEMIC THERAPIES

Cytotoxic Regimens for Metastatic Disease[1]

- Dacarbazine
- Temozolomide
- Paclitaxel
- Albumin-bound paclitaxel
- Carboplatin/paclitaxel

Biochemotherapy for Metastatic Disease[1]

- Dacarbazine or temozolomide, and cisplatin or carboplatin, with or without vinblastine or nitrosourea, and IL-2 and interferon alfa-2b

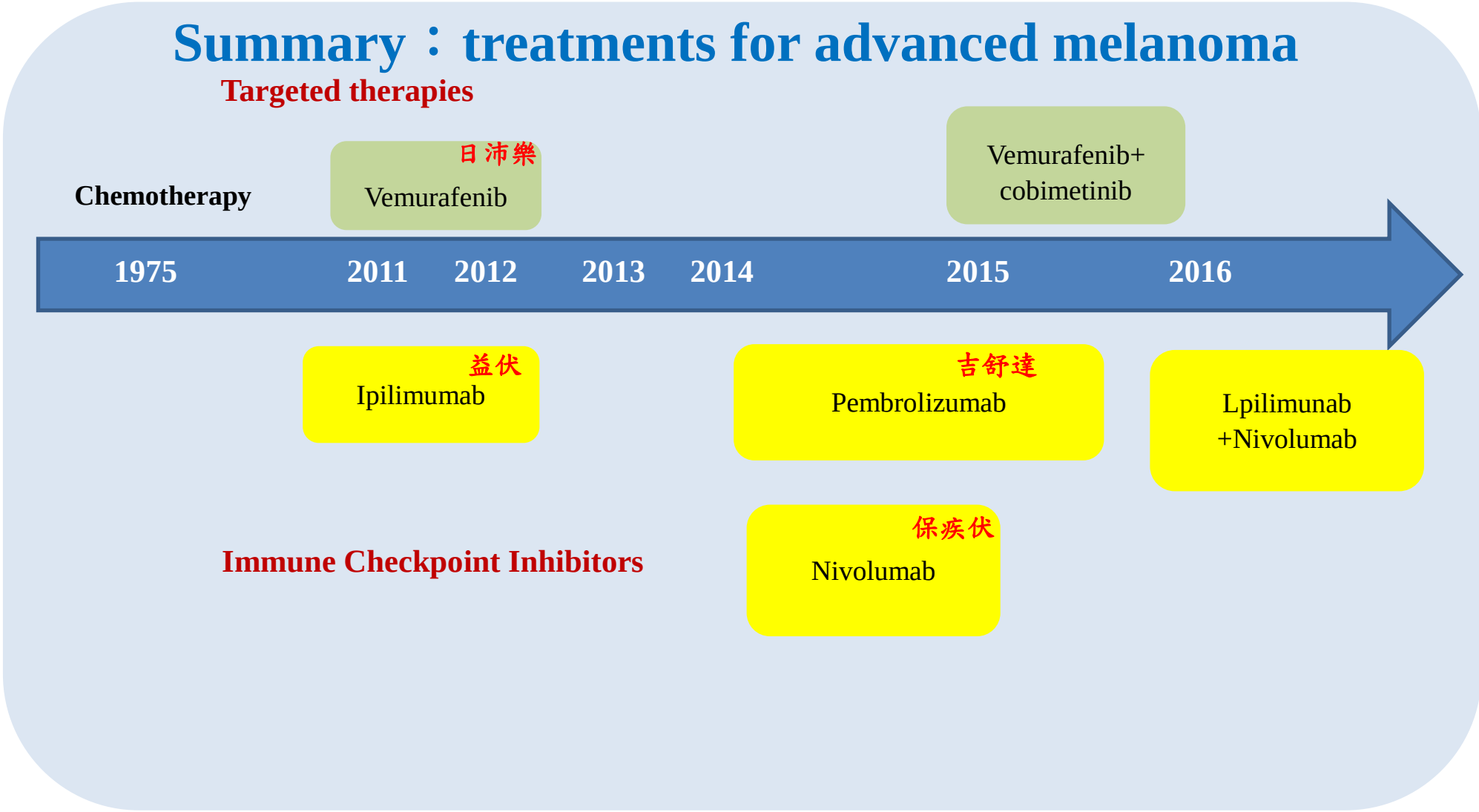
Biochemotherapy for Adjuvant Treatment of High-Risk Disease

- Dacarbazine, cisplatin, vinblastine, IL-2, and interferon alfa-2b (category 2B)

附件四、藥物治療

1. Anti PD-1 montherapy
   (1)Pembrolizumab: intravenous pembrolizumab 2 mg/kg or 10 mg/kg every 3 weeks,
   Lancet Oncol. 2015 Aug;16(8):908-18
   (2)Nivolumab: intravenous infusion of nivolumab 3 mg/kg every 2 weeks,
   Lancet Oncol. 2015 Apr;16(4):375-84
2. Vemurafenib
   (1)Vemurafenib at a dose of 960 mg orally twice daily, N Engl J Med. 2012 Feb 23;366(8):707-14
3. Imatinib for tumor with activating mutation of c-Kit
   (1)Imatinib 400 mg once per day or 400 mg twice per day if there was no initial response,
   J Clin Oncol. 2013 Sep 10;31(26):3182-90
4. Carboplatin + paclitaxel
   (1)intravenous paclitaxel 225 mg/m2 plus intravenous carboplatin at area under curve 6 (AUC 6) on day 1 of a 21-day cycle,
   J Clin Oncol. 2009 Jun 10;27(17):2823-30
5. Clinical trial

附件五、藥物整理


Summary：treatments for advanced melanoma
Targeted therapies
Chemotherapy
日沛樂
Vemurafenib
Vemurafenib+
cobimetinib
1975
2011
2012
2013
2014
2015
2016
益伏
Ipilimumab
吉舒達
Pembrolizumab
Lpilimunab
+Nivolumab
保疾伏
Nivolumab
Immune Checkpoint Inhibitors

六、安寧緩和照護原則

若預期疾病難以治癒時，病人存活期小於 6 個月便適合安寧療護(Pomeranz & Brustman, 2005；Waldrop & Rinfrette, 2009) 。

若藉由症狀、檢驗數據、及確切的腫瘤診斷，證實臨床上該惡性腫瘤已經廣泛侵犯、或進展快速；功能分數（Palliative Performance Scale）低於 70%；拒絕進一步腫瘤治癒性治療，或者在治療之下仍持續惡化者，即可轉介緩和醫療團隊（彭等，2006）。

七、參考文獻

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4. Mudigonda T, Pearce DJ, Yentzer BA, et al. The economic impact of non-melanoma skin cancer: a review. J Natl Compr Canc Netw 2010;8:888-896. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20870635.
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7. Brewster DH, Bhatti LA, Inglis JH, et al. Recent trends in incidence of nonmelanoma skin cancers in the East of Scotland, 1992-2003. Br J Dermatol 2007;156:1295-1300. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17535229.
8. Hayes RC, Leonfellner S, Pilgrim W, et al. Incidence of nonmelanoma skin cancer in New Brunswick, Canada, 1992 to 2001. J Cutan Med Surg 2007;11:45-52.
   Available at: http://www.ncbi.nlm.nih.gov/pubmed/17374314.

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