Taipei Veterans General Hospital Practices Guidelines Oncology

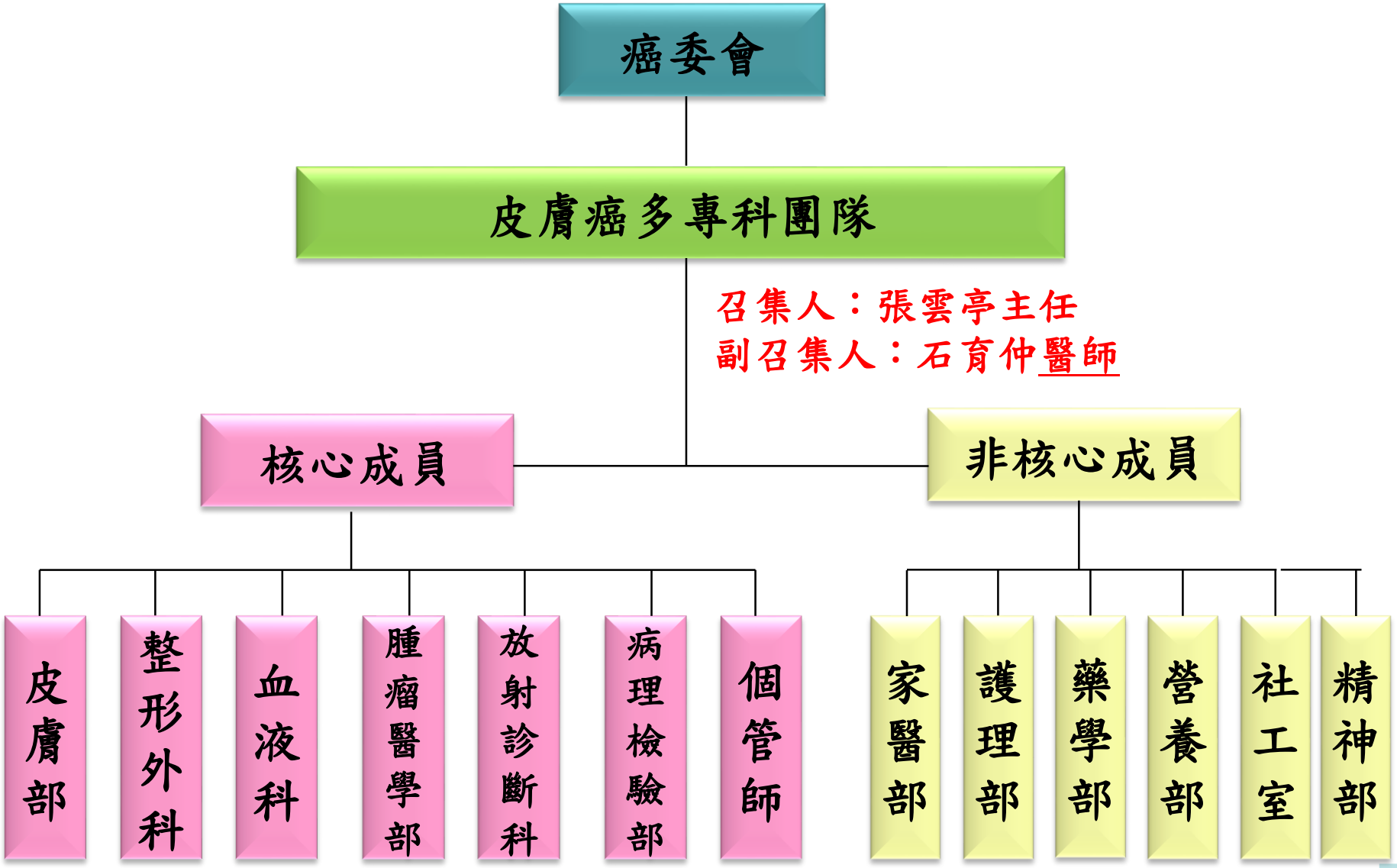
Skin Cancer

2021/12/21

台 北 榮 總 皮膚 癌 診 療 共 識

- Multidisciplinary Team
- Taipei VGH Skin Cancer Panel Members
- Squamous cell carcinoma
- Basal cell carcinoma
- Melanoma

臺北榮總皮膚癌多專科團隊組織架構



團隊成員名單

核心科別	成員名單	
皮膚部	張雲亭醫師	李政源醫師
	何翊芯醫師	
整形外科	石育仲醫師	
腫瘤醫學部	吳元宏醫師	
血液科	柯博伸醫師	鄧豪偉醫師
放射診斷科	吳慶蘭醫師	
病理檢驗部	許志怡醫師	
個案管理	簡伶怡護理師	

非核心科別	成員名單	
家醫部（安寧共照）	賴志冠醫師	陳慧芳護理師
精神部	劉英杰醫師	
藥學部	林欣怡藥師	
社工室	蕭美華社工師	
營養部	謝伊晴營養師	

Squamous cell carcinoma

PRINCIPLES OF PATHOLOGY REPORT

- **Principles of Biopsy reporting**
  - **Pathologic evaluation of skin biopsies is ideally performed by a dermatologist or pathologist who is experienced in interpreting cutaneous neoplasms.**
  - **Clinical information to be submitted on biopsy requisition includes:**
    - **Patient demographics**
    - **Anatomic location**
    - **Prior treatment of lesion**
    - **Clinical diameter of lesion**
    - **Patient risk factors: such as immunosuppression, radiation treatment, or organ transplant history.**
  - **The final pathology report should include:**
    - **Histologic subtype (if it is one of the specified high- or low-risk types[1])**
    - **Presence of any features that would classify the lesion as T2 or above (per AJCC, 8 th edition staging)**
      - **Tumor diameter > 2cm**
      - **Tumor depth >6 mm**
      - **Extension beyond subcutaneous fat**
      - **Bone erosion**
      - **Perineural invasion involving nerve below dermis or > 0.1mm in caliber[2]**
    - **Histologic grade (degree of cellular differentiation) if possible**
    - **Involvement of deep shave biopsy edge should be noted**

1 High-risk histologic subtypes include acantholytic, adenosquamous, desmoplastic or carcinosarcomatous; low-risk histologic subtypes include verrucous and keratoacanthomatous SCC.

2 Alam M, Armstrong A, Baum C, et al. Guidelines of care for the management of cutaneous squamous cell carcinoma. J Am Acad Dermatol 2018;78:560-578.

PRINCIPLES OF PATHOLOGY REPORT

- **Principles of excision reporting**
  - **Saucerization specimens intended for definitive surgical therapy should be labeled as such. They must be evaluated for margin status.**
  - **Clinical information to be submitted on biopsy requisition includes:**
    - **Patient demographics**
    - **Anatomic location**
    - **Clinical diameter of lesion**
    - **Additional clinical information listed above under biopsy if note previously reported**
  - **The final pathology report should include:**
    - **Histologic subtype (if it is one of the specified high- or low-risk types[1])**
    - **All features necessary for accurate staging per AJCC, 8 th edition staging, include:**
      - **Tumor diameter (clinical, gross, and/or microscopic)**
      - **Histologic grade (degree of cellular differentiation)**
      - **Depth of invasion: both**
        - **1. distance from the granular layer of adjacent normal epidermis to the base of the specimen (in mm)**
        - **2. anatomic level of invasion if beyond subcutaneous fat**
      - **Perineural invasion involving nerve below dermis or if largest nerve involed is > 0.1mm in caliber[2]**
      - **Margin status**

1 High-risk histologic subtypes include acantholytic, adenosquamous, desmoplastic or carcinosarcomatous; low-risk histologic subtypes include verrucous and keratoacanthomatous SCC.

3 Califano JA, Lydiatt WM, Nehal KS, et al. Cutaneous squamous cell carcinoma of the head and neck. In: Amin MB, Edge S, Greene F, et al., eds. AJCC Cancer Staging 4 Manual (ed Eighth). New York: Springer International Publishing; 2017:171-181

4 Karia PS, Jambusaria-Pahlajani A, Harrington DP, et al. Evaluation of American Joint Committee on Cancer, International Union Against Cancer, and Brigham and Women's Hospital tumor staging for cutaneous squamous cell carcinoma. J Clin Oncol 2014;32:327-334.

RISK FACTORS FOR LOCAL RECURRENCE OR METASTASES

H&P	Low Risk	High Risk
Location/size[1]	Area L <20 mm Area M <10 mm[4]	Area L ≥20 mm Area M ≥10 mm Area H[5]
Borders	Well-defined	Poorly defined
Primary vs. recurrent	Primary	Recurrent
Immunosuppression	(-)	(+)
Site of prior RT or chronic inflammatory process	(-)	(+)
Rapidly growing tumor	(-)	(+)
Neurologic symptoms	(-)	(+)
Pathology (See SCC-A)		
Degree of differentiation	Well or moderately differentiated	Poorly differentiated
Adenoid (acantholytic), adenosquamous (showing mucin production), desmoplastic, or metaplastic (carcinosarcomatous) subtypes	(-)	(+)
Depth[2,3]: Thickness or level of invasion	≤ 6 mm and no invasion beyond subcutaneous fat	> 6 mm or invasion beyond subcutaneous fat
Perineural, lymphatic, or vascular involvement	(-)	(+)

1 Must include peripheral rim of erythema.

2 If clinical evaluation of incisional biopsy suggests that microstaging is inadequate, consider narrow margin excisional biopsy.

3 Deep invasion is defined as invasion beyond the subcutaneous fat OR > 6mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor)

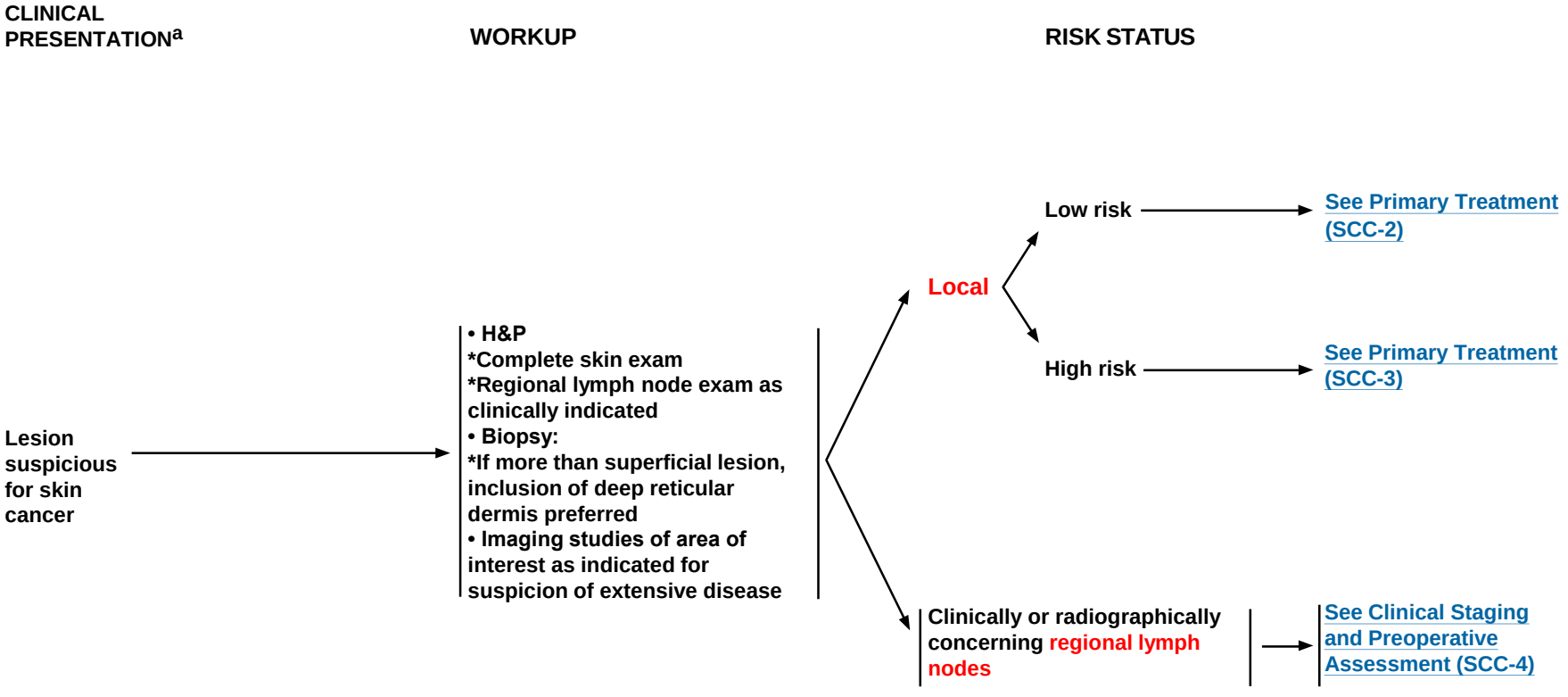
4 Location independent of size may constitute high risk.

5 Area H constitutes high risk based on location, independent of size. Narrow excision margins due to anatomic and functional constraints are associated with increased recurrence rates with standard histologic processing. Complete margin assessment such as with Mohs micrographic surgery is recommended for optimal tumor clearance and maximal tissue conservation. For tumors <6 mm in size, without other high risk features, other treatment modalities may be considered if at least 4-mm clinically tumor-free margins can be obtained without significant anatomic or functional distortions.

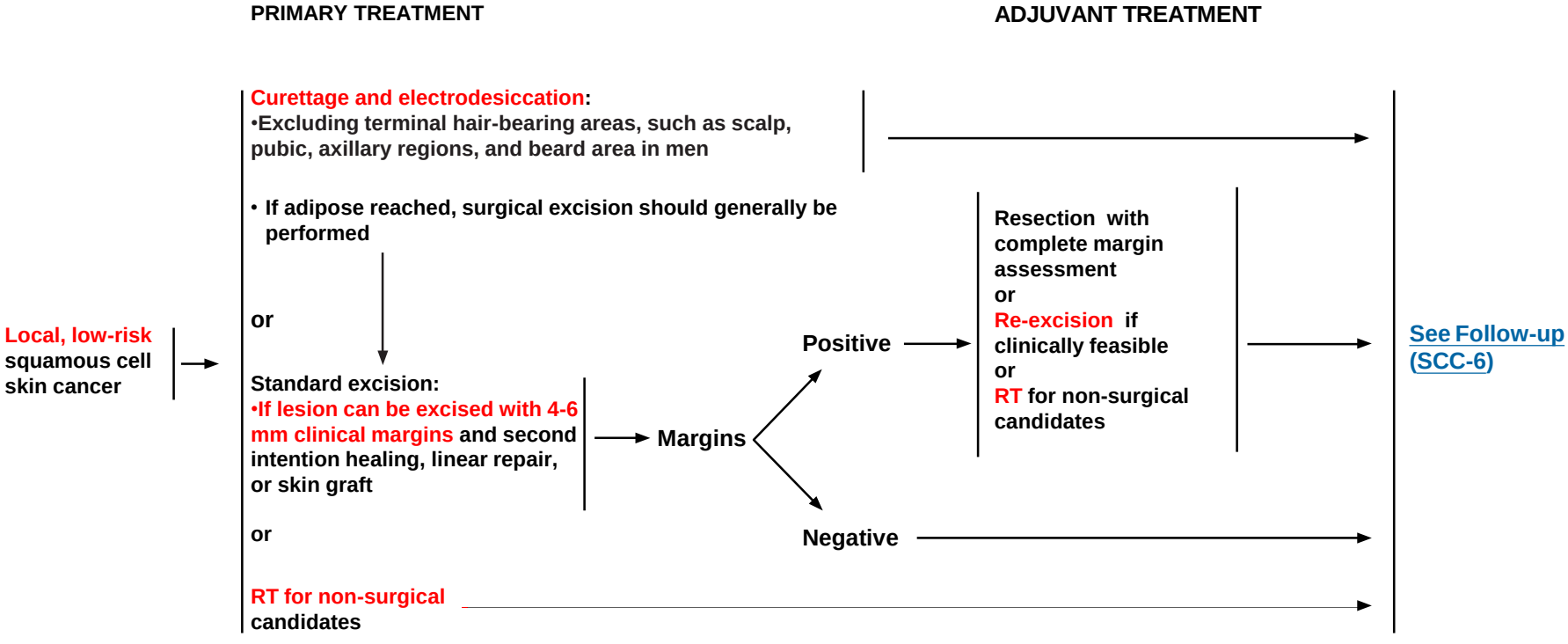
Area H = "mask areas" of face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, ear), genitalia, hands, and feet.

Area M = cheeks, forehead, scalp, neck, and pretibia.

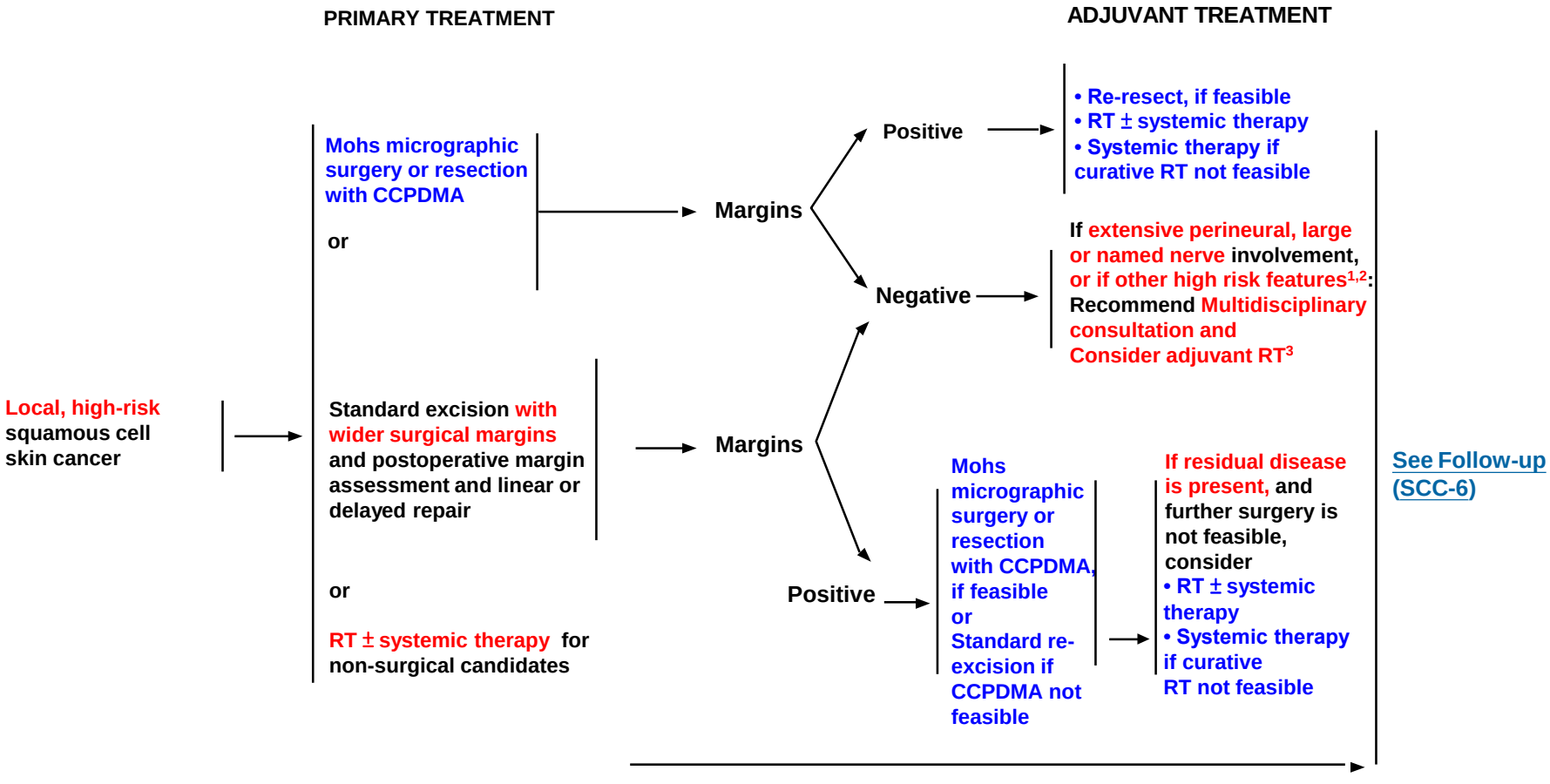
Area L = trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles).



1 See Principles of Pathology (SCC-A)


PRIMARY TREATMENT
ADJUVANT TREATMENT
Local, low-risk squamous cell skin cancer
Curettage and electrodesiccation:
•Excluding terminal hair-bearing areas, such as scalp, pubic, axillary regions, and beard area in men
• If adipose reached, surgical excision should generally be performed
or
Standard excision:
•If lesion can be excised with 4-6 mm clinical margins and second intention healing, linear repair, or skin graft
Margins
Positive
Resection with complete margin assessment
or
Re-excision if clinically feasible
or
RT for non-surgical candidates
Negative
or
RT for non-surgical candidates
See Follow-up (SCC-6)

Skin Cancer

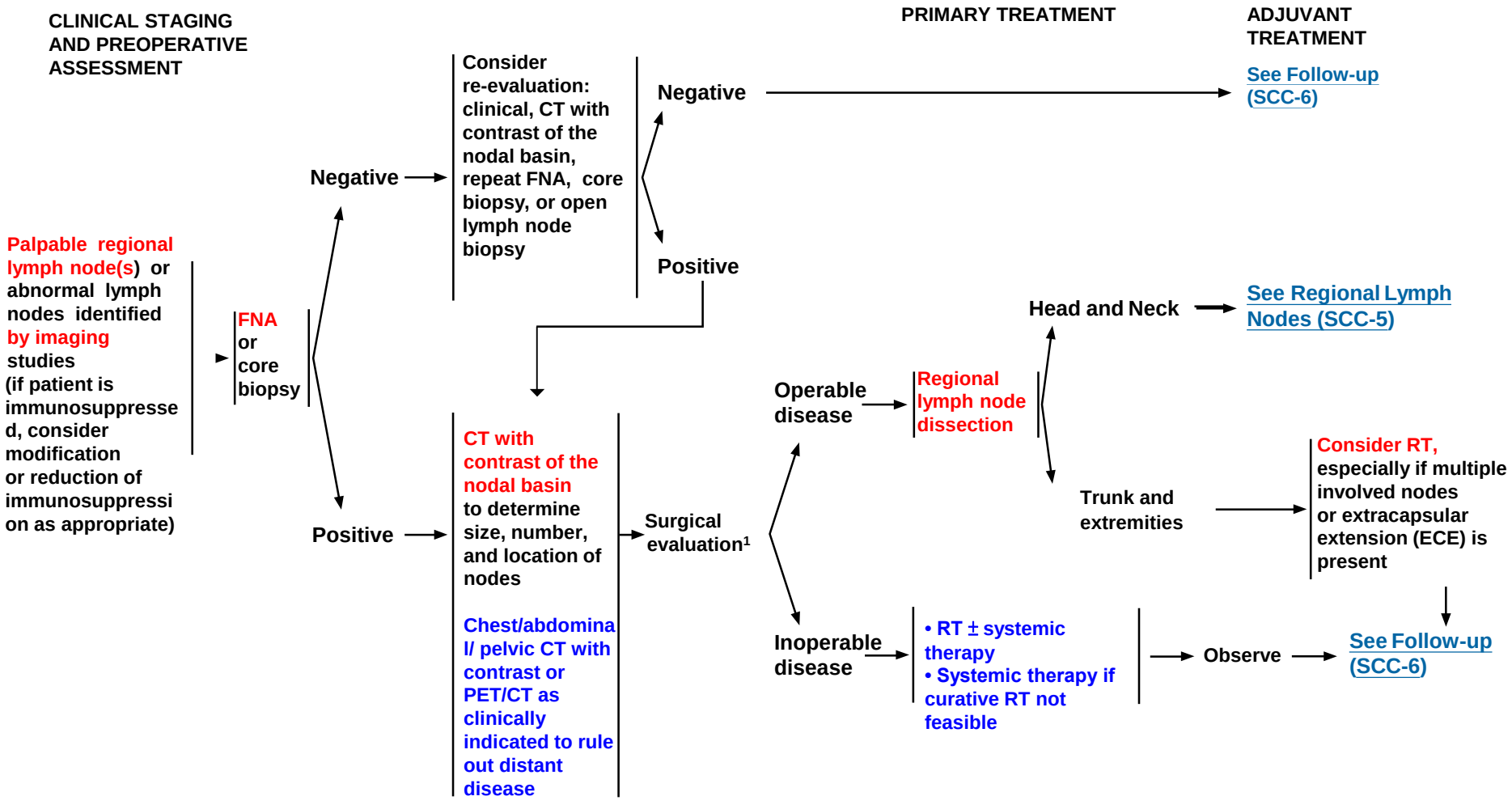


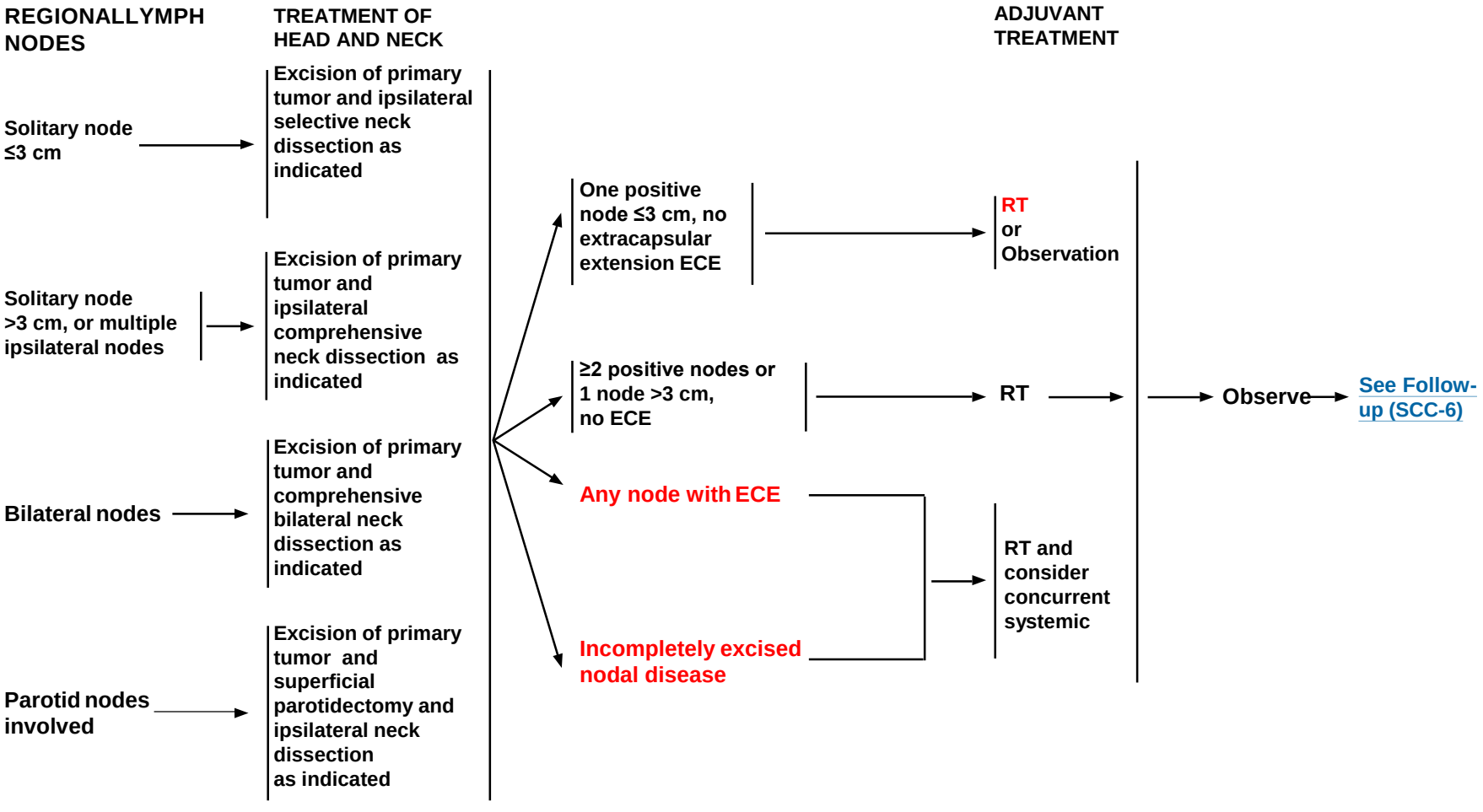
1 See Principles of Pathology (SCC-A)

2 Large nerve involvement is defined by AJCC 8th edition for cutaneous SCC of the head and neck as ≥ 0.1mm; most nerves deep to the dermis are > 0.1mm

3 The outcome benefit of adjuvant RT following resection of any cutaneous SCC with negative surgical margins is uncertain

Skin Cancer


CLINICAL STAGING AND PREOPERATIVE ASSESSMENT
PRIMARY TREATMENT
ADJUVANT TREATMENT
Palpable regional lymph node(s) or abnormal lymph nodes identified by imaging studies (if patient is immunosuppressed, consider modification or reduction of immunosuppression as appropriate)
FNA or core biopsy
Negative
Consider re-evaluation: clinical, CT with contrast of the nodal basin, repeat FNA, core biopsy, or open lymph node biopsy
Negative
See Follow-up (SCC-6)
Positive
Positive
CT with contrast of the nodal basin to determine size, number, and location of nodes
Chest/abdominal/ pelvic CT with contrast or PET/CT as clinically indicated to rule out distant disease
Surgical evaluation[1]
Operable disease
Regional lymph node dissection
Head and Neck
See Regional Lymph Nodes (SCC-5)
Trunk and extremities
Consider RT, especially if multiple involved nodes or extracapsular extension (ECE) is present
Inoperable disease
• RT ± systemic therapy
• Systemic therapy if curative RT not feasible
Observe
See Follow-up (SCC-6)


REGIONALLYMPH NODES
TREATMENT OF HEAD AND NECK
ADJUVANT TREATMENT
Solitary node ≤3 cm
Excision of primary tumor and ipsilateral selective neck dissection as indicated
Solitary node >3 cm, or multiple ipsilateral nodes
Excision of primary tumor and ipsilateral comprehensive neck dissection as indicated
Bilateral nodes
Excision of primary tumor and comprehensive bilateral neck dissection as indicated
Parotid nodes involved
Excision of primary tumor and superficial parotidectomy and ipsilateral neck dissection as indicated
One positive node ≤3 cm, no extracapsular extension ECE
RT or Observation
≥2 positive nodes or 1 node >3 cm, no ECE
RT
Any node with ECE
Incompletely excised nodal disease
RT and consider concurrent systemic
Observe
See Follow-up (SCC-6)

FOLLOW-UP

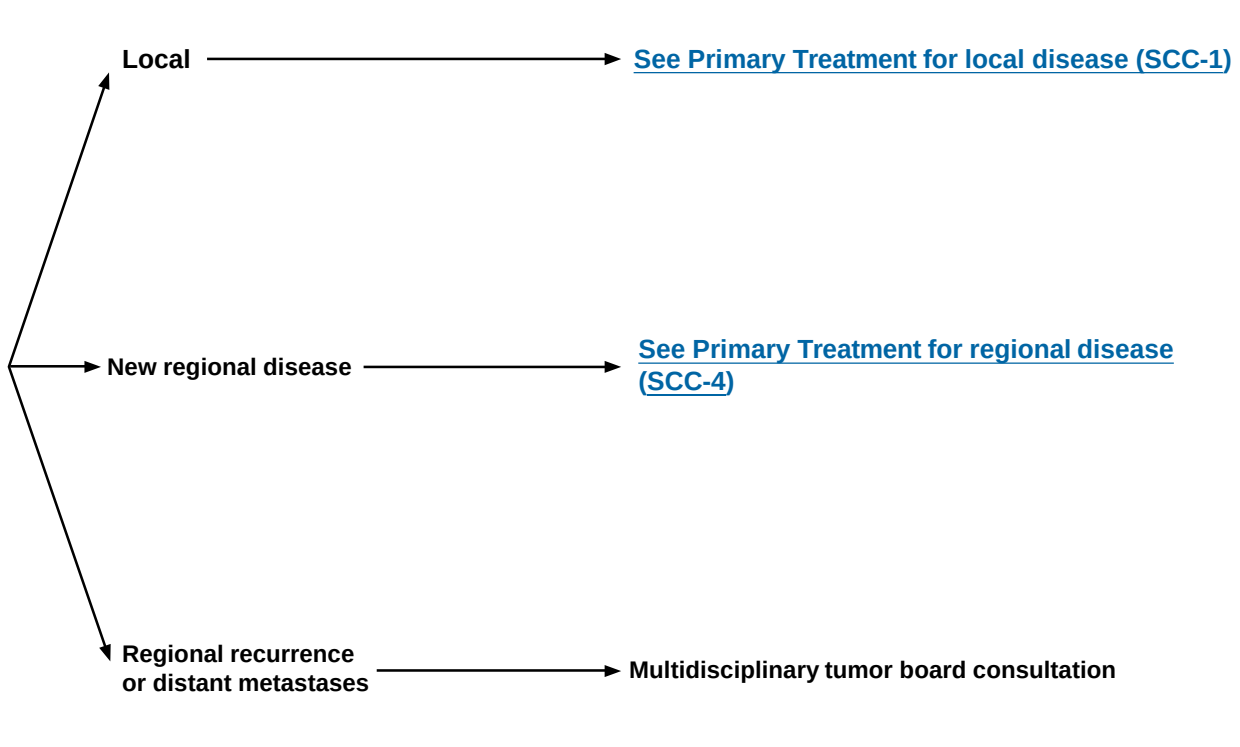
Local disease:

- **H&P**
  - ◆**Every 3–12 mo for 2 y, then every 6–12 mo for 3 y, then annually for life**
- **Patient education**
  - ◆**Sun protection**
  - ◆**Self examination of skin**

Regional disease:

- **H&P**
  - ◆**Every 1–3 mo for 1 y, then every 2–4 mo for 1 y, then every 4–6 mo for 3 y, then every 6–12 mo for life**
- **Patient education**
  - ◆**Sun protection**
  - ◆**Self examination of skin and lymph nodes**

RECURRENCE/DISEASE PROGRESSION



Staging

Table 1

American Joint Committee on Cancer (AJCC)

TNM Staging Classification for Cutaneous Squamous Cell Carcinoma (cSCC) (8th ed.)

Primary Tumor (T)

TX Primary tumor cannot be assessed

Tis Carcinoma in situ

T1 Tumor 2 cm or less in greatest dimension

T2 Tumor greater than 2 cm, but smaller than 4cm in greatest dimension

T3 Tumor greater than 4cm in maximun 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.

Clinical lymph Nodes (cN)

cN Regional lymph nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastases

N1 Metastasis in a single ipsilateral lymph node, 3 cm or less 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(+).

Table 1 Continued

Pathological lymph Nodes (pN)

pN Regional lymph nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastases

N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension and ENE(-)

N2.

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 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 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(+).

Distant Metastasis (M)

M0 No distant metastases

M1 Distant metastases

Histologic Grade (G)

GX Grade cannot be assessed

G1 Well differentiated

G2 Moderately differentiated

G3 Poorly differentiated

G4 Undifferentiated

Table 2. AJCC Prognostic Stage Group

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

Basal cell carcinoma

PRINCIPLES OF PATHOLOGY REPORT

- **Principles of Biopsy reporting**
  - **Pathologic evaluation of skin biopsies is ideally performed by a dermatologist or pathologist who is experienced in interpreting cutaneous neoplasms.**
  - **Clinical information to be submitted on biopsy requisition includes:**
    - **Patient demographics**
    - **Anatomic location**
    - **Prior treatment of lesion**
    - **Clinical diameter of lesion**
    - **Patient risk factors: such as immunosuppression, radiation treatment, or organ transplant history.**
  - **The final pathology report should include:**
    - **Histologic subtype [1]**
    - **Presence of any features that would increase the risk for local recurrence**
      - **invasion of tumor beyond reticular dermis**
      - **Perineural invasion involving nerve below dermis or > 0.1mm in caliber[2]**
    - **Histologic grade (degree of cellular differentiation) if possible**
    - **Involvement of deep shave biopsy edge should be noted**

1 High-risk histologic subtypes include basosquamous, infiltrative, sclerosing/morpheaform, micronodular and BCC with carcinosarcomatous differentiation; low-risk histologic subtypes include superficial, nodular, keratotic, infundibulocystic and fibroepithelial BCC

2 Alam M, Armstrong A, Baum C, et al. Guidelines of care for the management of cutaneous squamous cell carcinoma. J Am Acad Dermatol 2018;78:560-578.

PRINCIPLES OF PATHOLOGY REPORT

- **Principles of excision reporting**
  - **Saucerization specimens intended for definitive surgical therapy should be labeled as such. They must be evaluated for margin status.**
  - **Clinical information to be submitted on biopsy requisition includes:**
    - **Patient demographics**
    - **Anatomic location**
    - **Clinical diameter of lesion**
    - **Additional clinical information listed above under biopsy if note previously reported**
  - **The final pathology report should include:**
    - **Histologic subtype (if it is one of the specified high- or low-risk types[1])**
    - **Invasion of tumor beyond deep reticular dermis**
    - **Perineural invasion involving nerve below dermis or if largest nerve involved is > 0.1mm in caliber**
    - **Angiolymphatic invasion**
    - **Margin status**

1 High-risk histologic subtypes include basosquamous, infiltrative, sclerosing/morpheaform, micronodular and BCC with carcinosarcomatous differentiation; low-risk histologic subtypes include superficial, nodular, keratotic, infundibulocystic and fibroepithelial BCC

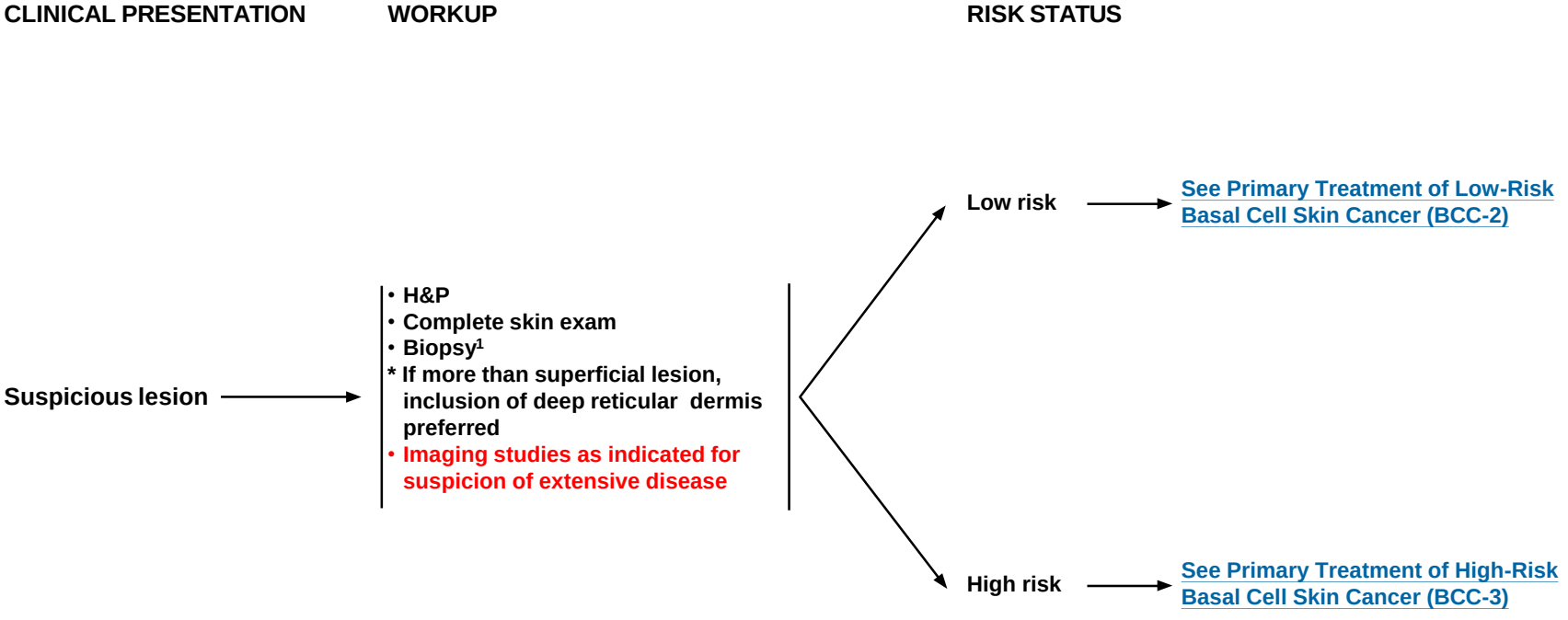
RISK FACTORS FOR RECURRENCE

H&P	Low Risk	High Risk
Location/size1	Area L <20 mm Area M <10 mm[1]	Area L ≥20 mm Area M ≥10 mm Area H[3]
Borders	Well-defined	Poorly defined
Primary vs. recurrent	Primary	Recurrent
Immunosuppression	(-)	(+)
Site of prior RT	(-)	(+)
Pathology[5]		
Subtype	Nodular, superficial[2]	Aggressive growth pattern[4]
Perineural involvement	(-)	(+)

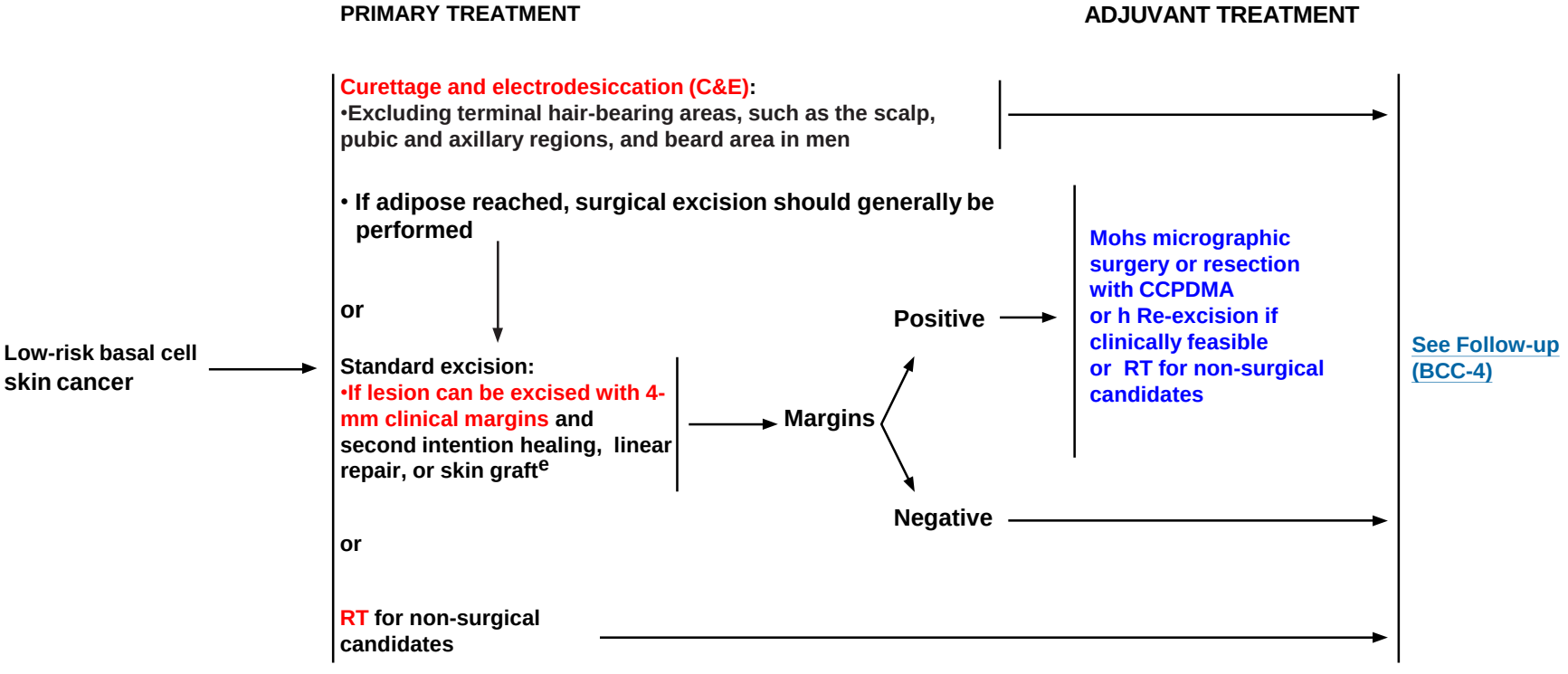
Area H = "mask areas" of face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, ear), genitalia, hands, and feet.
Area M = cheeks, forehead, scalp, neck, and pretibia.
Area L = trunk and extremities (excluding pretibia, hands, feet, nail units, and ankles).

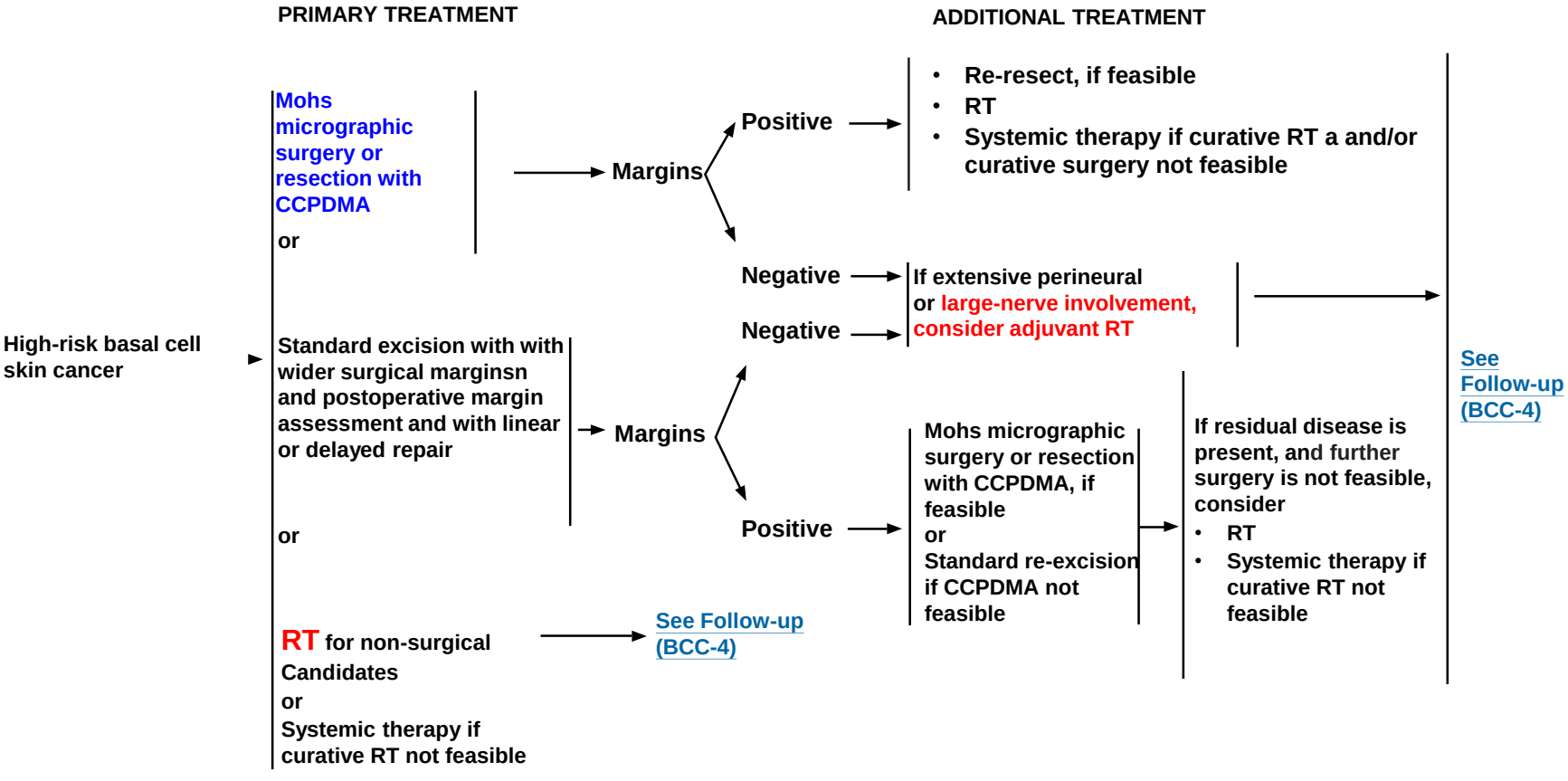
1 Location independent of size may constitute high risk.
2 Low-risk histologic subtypes include nodular, superficial, and other non-agressive growth patterns such as keratotic, infundibulocystic, and fibroepithelioma of Pinkus.
3 Area H constitutes high risk based on location, independent of size. Narrow excision margins due to anatomic and functional constraints are associated with increased recurrence rates with standard histologic processing. Complete margin assessment such as with Mohs micrographic surgery is recommended for optimal tumor clearance and maximal tissue conservation. For tumors <6 mm in size, without other high-risk features, other treatment modalities may be considered if at least 4-mm
4 clinically tumor-free margins can be obtained without significant anatomic or functional distortions.
Having (mixed) infiltrative, micronodular, morpheaform, basosquamous, sclerosing, or carcinosarcomatous differentiation features in any portion of the tumor. In some
5 cases basosquamous tumors may be prognostically similar to SCC; clinicopathologic correlation is recommended in these cases.
See Principles of Pathology (BCC-A).

Skin Cancer



[1] See Principles of Pathology (BCC-A)


PRIMARY TREATMENT
ADJUVANT TREATMENT
Low-risk basal cell skin cancer
Curettage and electrodesiccation (C&E):
•Excluding terminal hair-bearing areas, such as the scalp, pubic and axillary regions, and beard area in men
• If adipose reached, surgical excision should generally be performed
or
Standard excision:
•If lesion can be excised with 4-mm clinical margins and second intention healing, linear repair, or skin graft[e]
Margins
Positive
Negative
Mohs micrographic surgery or resection with CCPDMA
or h Re-excision if clinically feasible
or RT for non-surgical candidates
or
RT for non-surgical candidates
See Follow-up (BCC-4)


PRIMARY TREATMENT
ADDITIONAL TREATMENT
High-risk basal cell skin cancer
Mohs micrographic surgery or resection with CCPDMA
or
Margins
Positive
Re-resect, if feasible
RT
Systemic therapy if curative RT a and/or curative surgery not feasible
Negative
Negative
If extensive perineural or large-nerve involvement, consider adjuvant RT
Standard excision with with wider surgical marginsn and postoperative margin assessment and with linear or delayed repair
or
Margins
Positive
Mohs micrographic surgery or resection with CCPDMA, if feasible
or
Standard re-excision if CCPDMA not feasible
If residual disease is present, and further surgery is not feasible, consider
RT
Systemic therapy if curative RT not feasible
RT for non-surgical Candidates
or
Systemic therapy if curative RT not feasible
See Follow-up (BCC-4)
See Follow-up (BCC-4)

FOLLOW-UP

- H&P
  - ◆Including complete skin exam every 6–12 mo for first 5 years, and then at least annually for life
  - ◆Consider imaging if clinical exam insufficient for following disease
- •Patient education:
  - ◆Sun protection
  - ◆Self-examination

RECURRENCE

Local → Follow Primary Treatment Pathways (BCC-1)

Nodal or distant metastases →

Multidisciplinary consultation to consider one or more of the following options:

- Hedgehog pathway inhibitor
  - * Vismodegib
  - * Sonidegib (category 2B)
- Surgery
- RT
- Clinical trial

Melanoma

RISK FACTORS FOR DEVELOPMENT OF SINGLE OR MULTIPLE PRIMARY MELANOMAS[1]

- Male sex
- Age >60 years•
- Phenotypic predisposition
  - Atypical mole/dysplastic nevus pattern
  - Increased mole count (particularly large nevi)
  - Sun-phenotype/tendency to sunburn
  - Red hair-blue eyes/Fitzpatrick skin type I/pheomelanin predominant phenotype
- Personal medical history/comorbidities
  - Multiple and/or blistering sunburns
  - Precancer/cancers, especially:
    - Actinic keratosis/non-melanoma (keratinocyte) skin cancer (eg, basal cell and squamous cell carcinomas)
    - Childhood cancer
  - Immunosuppression/immune perturbation related to:
    - Solid organ transplantation
    - Hematopoietic cell transplantation (HCT)
    - Human immunodeficiency virus/ acquired immunodeficiency syndrome (HIV/AIDS)
  - Rare genodermatoses: xeroderma pigmentosum
- Genetic predisposition
  - Presence of germline mutations or polymorphisms predisposing to melanoma (including CDKN2a, CDK4, MC1R, BAP1, and potentially other genes)
  - Family history of cutaneous melanoma (especially if multiple), pancreatic cancer, astrocytoma, uveal melanoma, and/or mesothelioma.
- Environmental factors
  - Tanning bed use
  - Residence in sunnier climate/latitude nearer to equator
  - Intermittent, intense sun exposure (for truncal/extremity melanomas, often observed with associated increased nevus count)
  - Chronic sun exposure (for head/neck/arm melanomas, often associated with lower nevus count)

1 Risk factors for development of single or multiple primary melanomas, including subsequent primaries after index diagnosis. This list does not include risk factors for melanoma recurrence or progression, as those are covered elsewhere in the algorithm.

PRINCIPLES OF BIOPSY OF A SUSPIVIOUS PIGMENTED LESION

- Excisional biopsy (elliptical, punch, or saucerization/deep shave) with 1- to 3-mm margins preferred. Avoid wider margins to permit accurate subsequent lymphatic mapping.
- The orientation of an elliptical/fusiform excisional biopsy should be planned with definitive wide local excision in mind (eg, longitudinally [axially] and parallel to the underlying lymphatics on the extremities).
- Full-thickness incisional or punch biopsy of clinically thickest portion of lesion acceptable, in certain anatomic areas (eg, palm/sole, digit, face, ear) or for very large lesions.
- Superficial shave biopsy may compromise pathologic diagnosis and complete assessment of Breslow thickness, but is acceptable when the index of suspicion is low
- Repeat narrow-margin excisional biopsy is recommended if an initial partial biopsy is inadequate for diagnosis or microstaging but should not be performed if the initial specimen meets criteria for SLN staging.

1 High-risk histologic subtypes include acantholytic, adenosquamous, desmoplastic or carcinosarcomatous; low-risk histologic subtypes include verrucous and keratoacanthomatous SCC.

3 Califano JA, Lydiatt WM, Nehal KS, et al. Cutaneous squamous cell carcinoma of the head and neck. In: Amin MB, Edge S, Greene F, et al., eds. AJCC Cancer Staging 4 Manual (ed Eighth). New York: Springer International Publishing; 2017:171-181

4 Karia PS, Jambusaria-Pahlajani A, Harrington DP, et al. Evaluation of American Joint Committee on Cancer, International Union Against Cancer, and Brigham and Women's Hospital tumor staging for cutaneous squamous cell carcinoma. J Clin Oncol 2014;32:327-334.

PRINCIPLES OF PATHOLOGY FOR PRIMARY MELANOMA

• The biopsy should be reported by a pathologist experienced in melanocytic neoplasms.
• Minimal elements to be reported should include factors that inform pathologic T-stage: Breslow thickness (reported to the nearest 0.1 mm), ulceration (present or absent). c,d
•Microsatellites should be reported if observed on either initial biopsy or subsequent wide excision.
•Margin status should be reported on all biopsies and excisions.e 1 • Encourage consistent synoptic reporting of additional prognostic criteria, including:
Presence of macroscopic satellite lesions in the gross tumor specimen.
Dermal mitotic rate per mm^2 f d
Lymphovascular/angiolymphatic invasion g
Histologic subtype (if desmoplastic, specify pure or mixed)
Regression (if extensive [>75%] or extending beneath measured Breslow thickness) Neurotropism/perineural invasion
• If there is a residual invasive melanoma in the wide excision specimen, the pathologist should incorporate elements of the initial biopsy and wide excision (thickest tumor depth, ulceration) to arrive at a final pathologic T-stage.
• Consider the use of molecular testing for histologically equivocal lesions.h

PRINCIPLES OF IMAGING

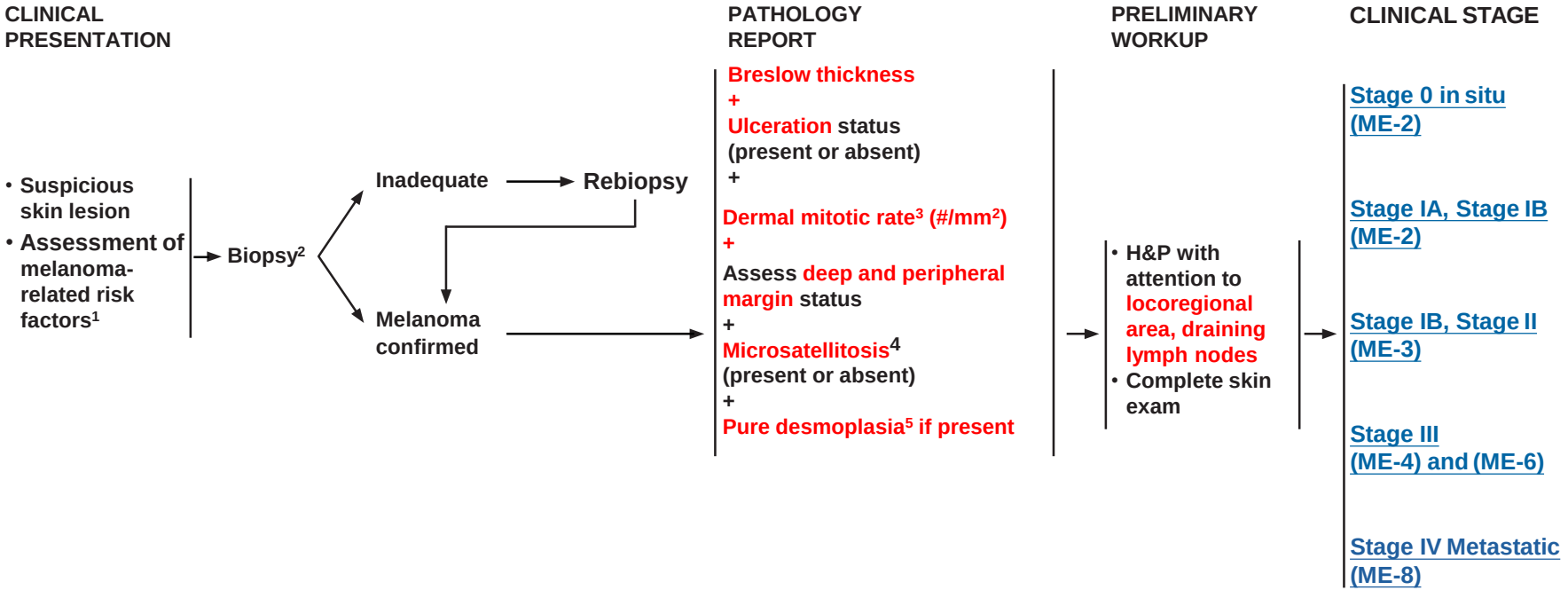
Follow-up (surveillance for recurrence in patients with no evidence of disease)•

- **Surveillance duration and interval should be tailored to stage and based on assessment of risk factors for recurrence. The intensity and interpretation of cross-sectional imaging should also be influenced by the potential for false positives, the desire to avoid unnecessary invasive tests or treatment, patient anxiety, the potential adverse effects of cumulative radiation exposure, and medical costs, as well as treatment options available in the event that asymptomatic recurrence is detected.**
  - **Regional lymph node US should be performed in patients with an equivocal lymph node exam. For patients who were offered but did not undergo SLNB, patients in whom SLNB was not possible (or not successful), or patients with a positive SLNB who did not undergo CLND, consider regional lymph node US every 3−12 months for the first 2−3 years from diagnosis, depending on the conditional risk of nodal recurrence.**
- **For patients with a positive SLNB who do not undergo CLND, it would be appropriate for the frequency of clinical exam and US surveillance to be consistent with the two prospective randomized trials (MSLT-II and DeCOG): at least every 4 months during the first 2 years, then every 6 months during years 3 through 5.**

Stage	Recommendation
Stage 0	• Routine imaging to screen for asymptomatic recurrence or metastatic disease is not recommended.
Stage IA Stage IB Stage IIA	• Imaging as indicated to evaluate specific signs or symptoms. • Routine imaging to screen for asymptomatic recurrence or metastatic disease is not recommended.

Stage IIB
Stage IIIA
Stage IIIB
Stage IIIC
Stage IIID
Stage IV
	• Imaging as indicated to evaluate specific signs or symptoms.
	• Consider imaging every 3−12 months (unless otherwise mandated by clinical trial participation) to screen for recurrence or metastatic disease (category 2B)
	  • In addition to the global imaging modality options (see ME-C-1), consider chest x-ray for surveillance of lung metastases.
	  • More frequent surveillance with brain MRI is recommended for patients with prior brain metastases.
	  • Periodic brain MRI for up to 3 years may be appropriate to screen for asymptomatic brain metastases in high-risk patients who had stage IIIC or higher without prior CNS metastases.
	• Routine imaging to screen for asymptomatic recurrence or metastatic disease is not recommended after 3−5 years.

Skin Cancer



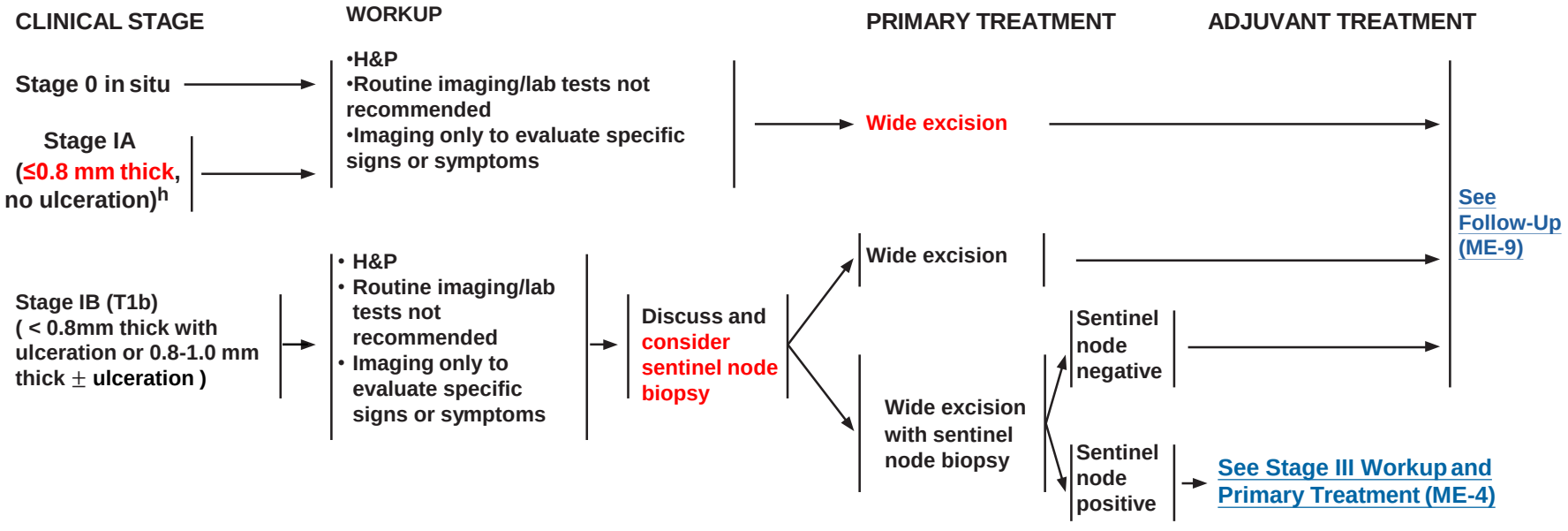
[1] See Risk Factors for Melanoma Development (ME-A)

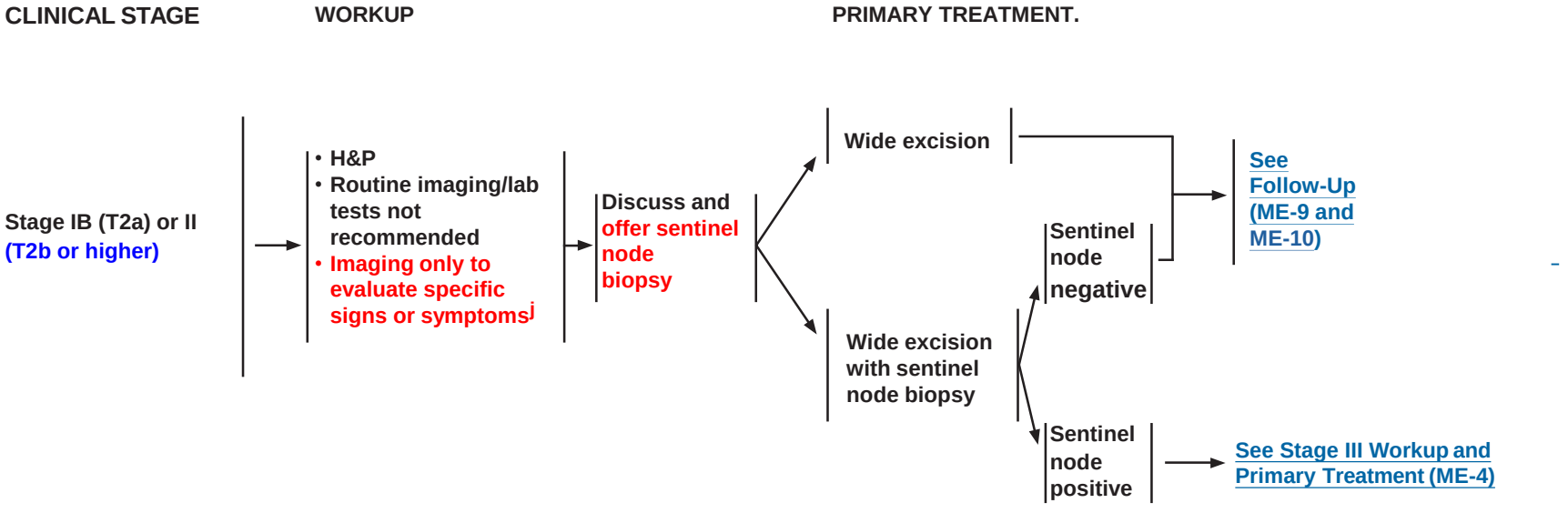
2 See Principles of Biopsy and Pathology (ME-B)

3 Although dermal mitotic rate is no longer included in the determination of T1 staging in the AJCC Cancer Staging Manual, Eighth Edition (2017), it remains an importantg prognostic factor across all thickness categories and should be included in the pathology assessment of melanoma biopsies and surgical excisions.

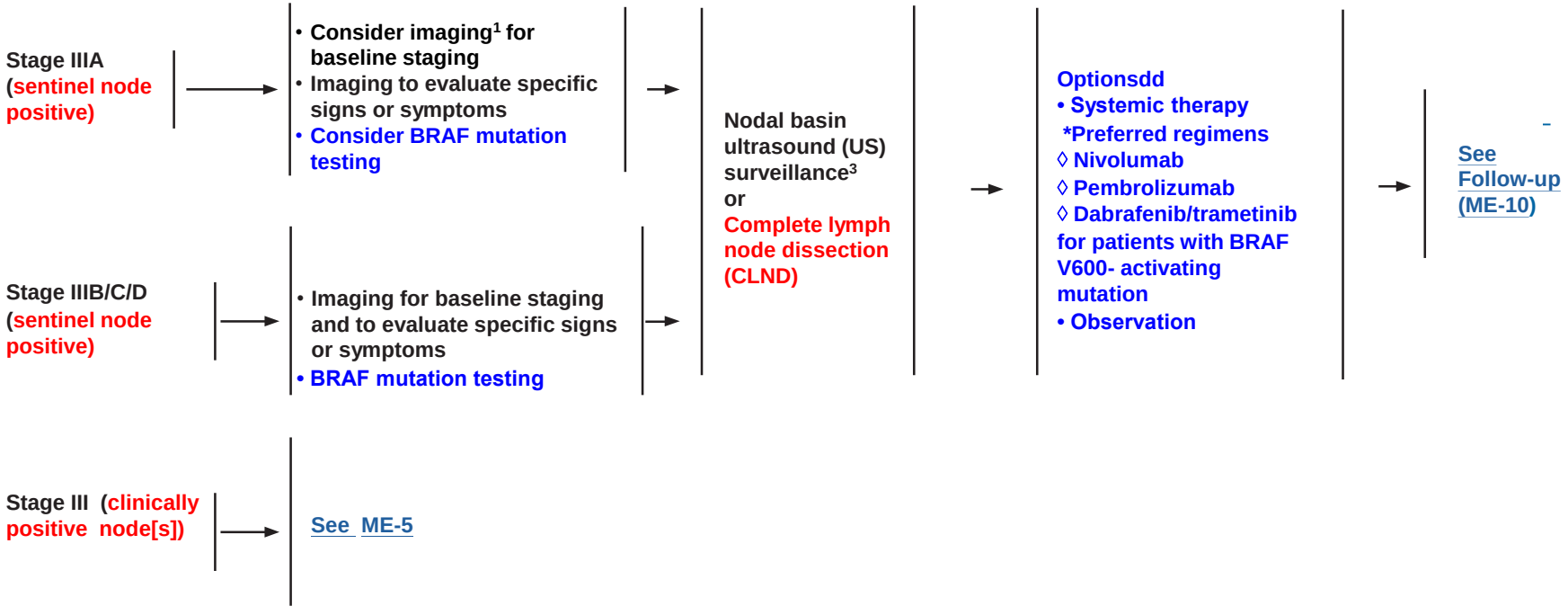
4 Microsatellitosis is defined in the CAP 2016 melanoma protocol (version 3.4.0.0) as "the presence of tumor nests greater than 0.05 mm in diameter, in the reticular dermis, panniculus, or vessels beneath the principal invasive tumor, but separated from it by at least 0.3 mm of normal tissue on the section in which the Breslow measurement was taken." The presence of microsatellitosis is associated with higher risk of recurrence. The AJCC Cancer Staging Manual, Eighth Edition (2017) no longer defines microsatellitosis according to tumor nest dimension or distance from the primary tumor. It classifies cases with microsatellitosis, clinical satellites, or in-transit metastases as N1c, N2c, or N3c based on the number of tumor-involved regional lymph nodes (0, 1, or ≥2, respectively). Consider SLNB in patients with microscopic satellitosis for risk assessment, especially if it will alter subsequent management. Their follow-up should be more frequent, commensurate with their increased risk of recurrence.

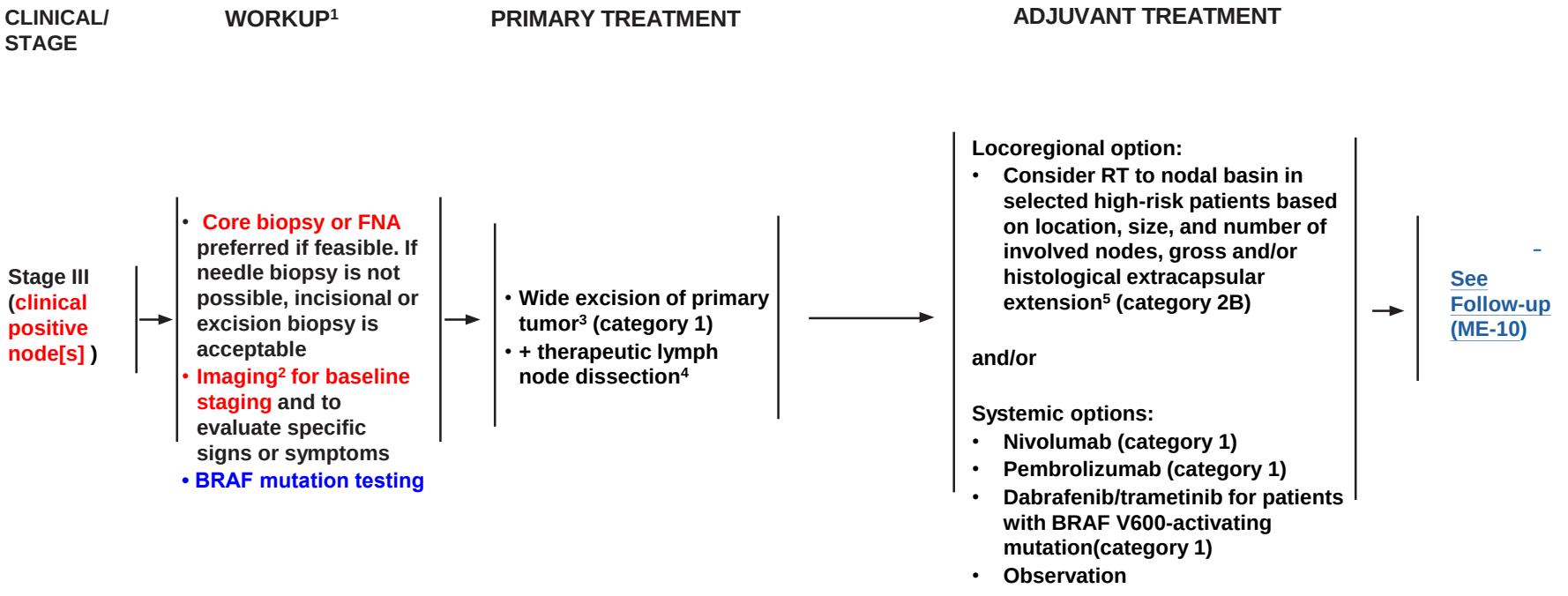
5 In patients with pure desmoplastic melanoma, there is uncertainty regarding the probability of finding a positive sentinel node and the prognostic significance of sentinel node status is unclear. Variability across studies may be due to lack of standardized criteria for defining pure desmoplastic melanoma. In the setting of these conflicting reports, the role of SLNB in patients with pure desmoplastic melanoma remains controversial.


CLINICAL STAGE
WORKUP
PRIMARY TREATMENT
ADJUVANT TREATMENT
Stage 0 in situ
Stage IA (≤0.8 mm thick, no ulceration)h
•H&P
•Routine imaging/lab tests not recommended
•Imaging only to evaluate specific signs or symptoms
Wide excision
See Follow-Up (ME-9)
Stage IB (T1b) (< 0.8mm thick with ulceration or 0.8-1.0 mm thick ± ulceration)
• H&P
• Routine imaging/lab tests not recommended
• Imaging only to evaluate specific signs or symptoms
Discuss and consider sentinel node biopsy
Wide excision
Wide excision with sentinel node biopsy
Sentinel node negative
Sentinel node positive
See Stage III Workup and Primary Treatment (ME-4)

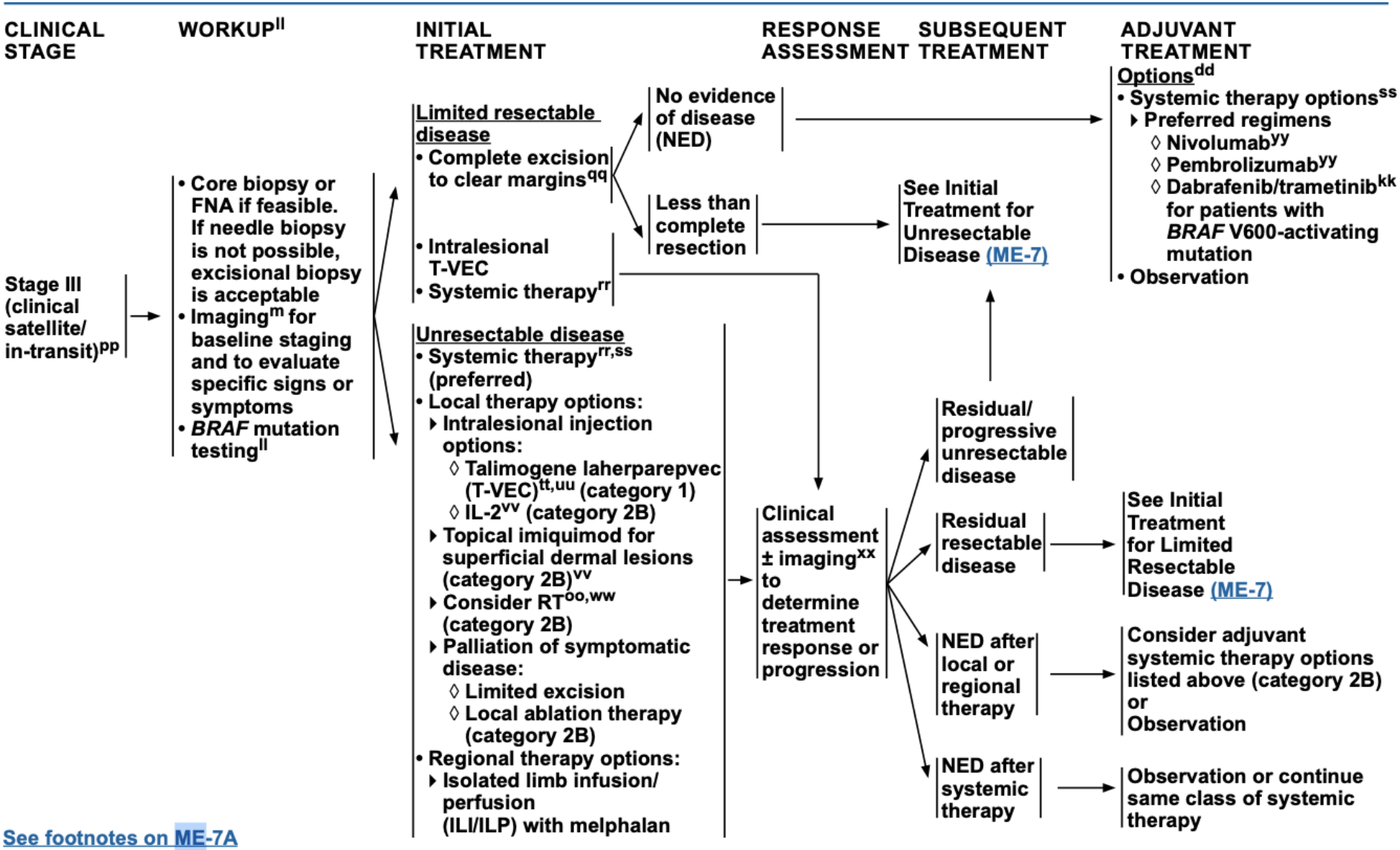

CLINICAL STAGE
WORKUP
PRIMARY TREATMENT.
Stage IB (T2a) or II
(T2b or higher)
• H&P
• Routine imaging/lab tests not recommended
• Imaging only to evaluate specific signs or symptoms[j]
Discuss and offer sentinel node biopsy
Wide excision
Wide excision with sentinel node biopsy
Sentinel node negative
Sentinel node positive
See Follow-Up (ME-9 and ME-10)
See Stage III Workup and Primary Treatment (ME-4)

Skin Cancer


CLINICAL/ PATHOLOGIC STAGE
WORKUP[2]
PRIMARY TREATMENT
ADJUVANT TREATMENT
Stage IIIA (sentinel node positive)
• Consider imaging[1] for baseline staging
• Imaging to evaluate specific signs or symptoms
• Consider BRAF mutation testing
Nodal basin ultrasound (US) surveillance[3] or Complete lymph node dissection (CLND)
Optionsdd
• Systemic therapy
*Preferred regimens
◊ Nivolumab
◊ Pembrolizumab
◊ Dabrafenib/trametinib for patients with BRAF V600- activating mutation
• Observation
See Follow-up (ME-10)
Stage IIIB/C/D (sentinel node positive)
• Imaging for baseline staging and to evaluate specific signs or symptoms
• BRAF mutation testing
Stage III (clinically positive node[s])
See ME-5



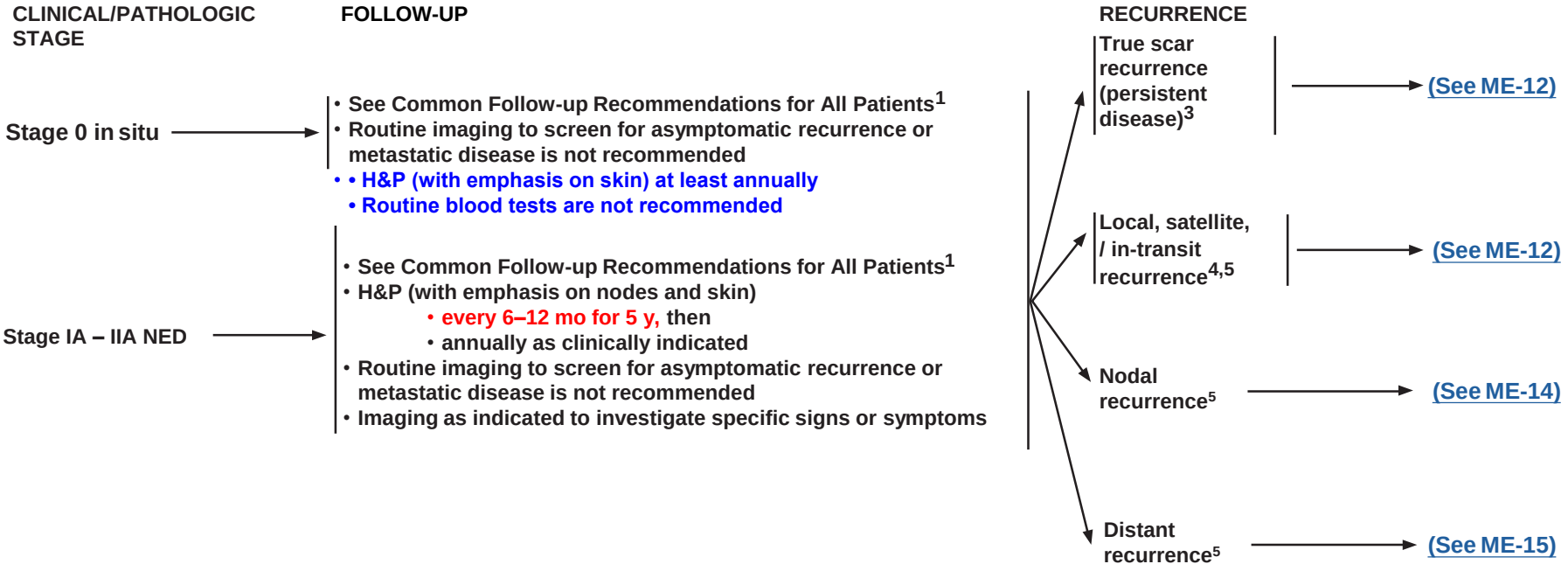
1 BRAF mutation testing is recommended for patients with stage III at high risk for recurrence for whom future BRAF-directed therapy may be an option.
2 See Principles of Imaging–Workup (ME-C).
3 See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-D).
4 In patients with borderline resectable lymphadenopathy or very high risk of recurrence after lymphadenectomy, consider a clinical trial of neoadjuvant systemic therapy.
5 Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has shown no improvement in RFS or OS. Its benefits must be weighed against potential toxicities such as lymphedema (limb) or oropharyngeal complications. The impact of these potential toxicities should be considered in the context of other adjuvant treatment options.



See footnotes on ME-7A

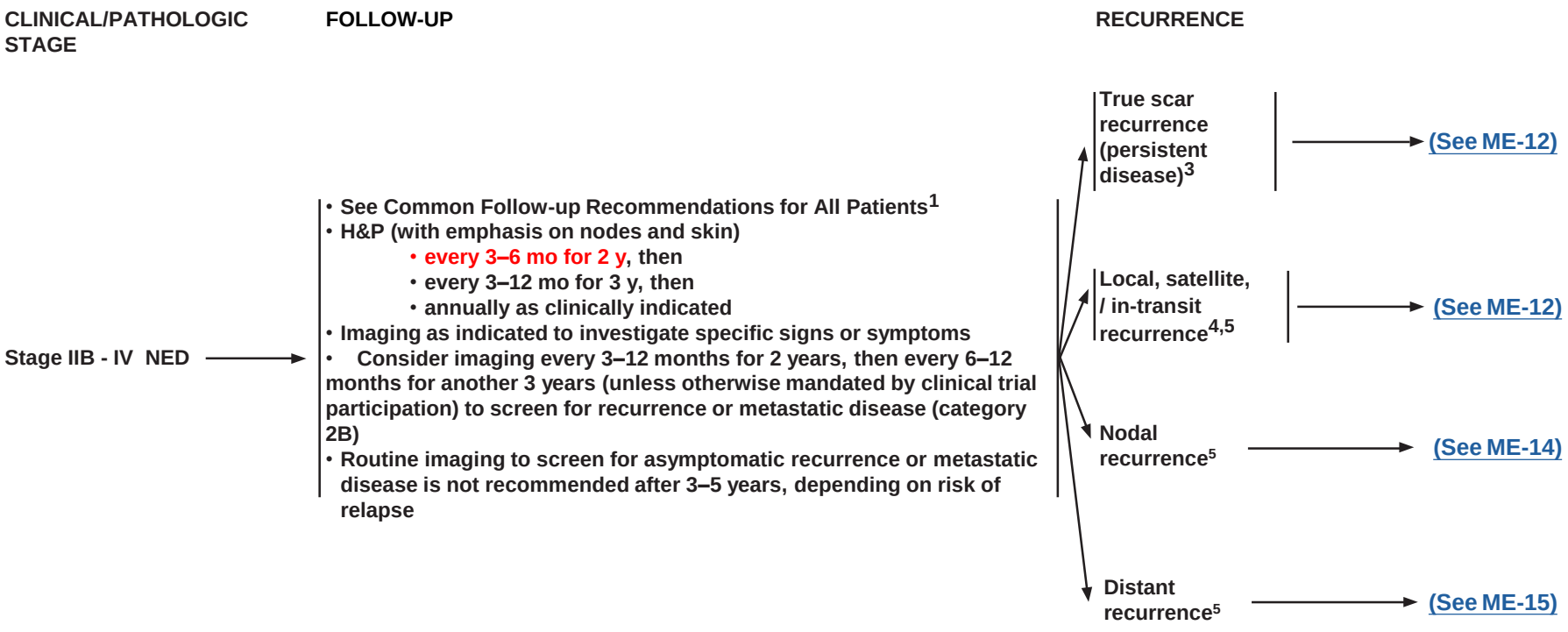
CLINICAL/ PATHOLOGIC STAGE	WORKUP	
Stage IV Metastatic	• Biopsy to confirm[1] • LDH • Imaging[2] for baseline staging and to evaluate specific signs and symptoms	See Treatment for Limited (Resectable) or Disseminated (Unresectable) Disease (ME-15)

1 Initial presentation with stage IV disease or clinical recurrence should be confirmed pathologically whenever possible or if clinically indicated. Biopsy techniques may include FNA, core, incisional, or excisional. Tissue is always preferred over cytology for mutational analysis. Obtain tissue to ascertain alterations in BRAF, and in the appropriate clinical setting, KIT from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy. Consider broader genomic profiling if the test results might guide future treatment decisions or eligibility for participation in a clinical trial. See Principles of Biopsy and Pathology (ME-B).
2 See Principles of Imaging–Workup (ME-C).



1 See Common Follow-up Recommendations for All Patients (ME-11)
2 See Principles of Imaging–Follow-up (ME-C).
3 True scar recurrence (persistent disease) is defined by the presence of in situ and/or radial growth phase.
4 Local satellite/in-transit recurrence without in situ or radial growth phase, with intralymphatic deep dermal or subcutaneous fat recurrence within the melanoma scar or satellite metastasis adjacent to the melanoma scar. Satellite and in-transit metastases are prognostically equivalent, with no distance measurement from the primary tumor necessary to distinguish between these intracutaneous or subcutaneous lymphatic metastases.
5 Initial presentation with stage IV disease or clinical recurrence should be confirmed pathologically whenever possible or if clinically indicated. Biopsy techniques may include FNA, core, incisional, or excisional. Tissue is always preferred over cytology for mutational analysis. Obtain tissue to ascertain alterations in BRAF, and in the appropriate clinical setting, KIT from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy. Consider broader genomic profiling if the test results might guide future treatment decisions or eligibility for participation in a clinical trial. See Principles of Biopsy and Pathology (ME-B).

Skin Cancer



1 See Common Follow-up Recommendations for All Patients (ME-11)
2 The duration and frequency of follow-up and intensity of cross-sectional imaging should be based on the conditional probability of recurrence at any point in time after initial treatment. Follow-up recommendations listed here are for surveillance for recurrence in patients with no evidence of disease.
3 True scar recurrence (persistent disease) is defined by the presence of in situ and/or radial growth phase.
4 Local satellite/in-transit recurrence without in situ or radial growth phase, with intralymphatic deep dermal or subcutaneous fat recurrence within the melanoma scar or satellite metastasis adjacent to the melanoma scar. Satellite and in-transit metastases are prognostically equivalent, with no distance measurement from the primary tumor necessary to distinguish between these intracutaneous or subcutaneous lymphatic metastases.
5 Initial presentation with stage IV disease or clinical recurrence should be confirmed pathologically whenever possible or if clinically indicated. Biopsy techniques may include FNA, core, incisional, or excisional. Tissue is always preferred over cytology for mutational analysis. Obtain tissue to ascertain alterations in BRAF, and in the appropriate clinical setting, KIT from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy. Consider broader genomic profiling if the test results might guide future treatment decisions or eligibility for participation in a clinical trial. See Principles of Biopsy and Pathology (ME-B).

COMMON FOLLOW-UP RECOMMENDATIONS FOR ALL PATIENTS

- **H&P (with emphasis on nodes and skin) at least annually.**
- **Available, noninvasive pre-biopsy imaging and molecular technologies have not been prospectively compared for diagnostic accuracy.**

Pre-diagnostic clinical modalities (ie, total-body photography and sequential digital dermoscopy), and other imaging technologies (eg, reflectance confocal microscopy, electrical impedance spectroscopy) may enhance early detection of new primary melanoma in patients with high mole count and/or presence of clinically atypical nevi. Pre-diagnostic noninvasive genomic patch testing be may also be helpful to guide biopsy decisions.

- **Patient education in regular skin and lymph node self-examination.**
- **Patient education in principles of sun safety, including sun avoidance during peak hours, use of sun-protective clothing/hat/eyewear,**

and regular application of broad-spectrum sunscreen to exposed skin when outdoors, particularly in individuals with sun sensitivity/light
complexion.

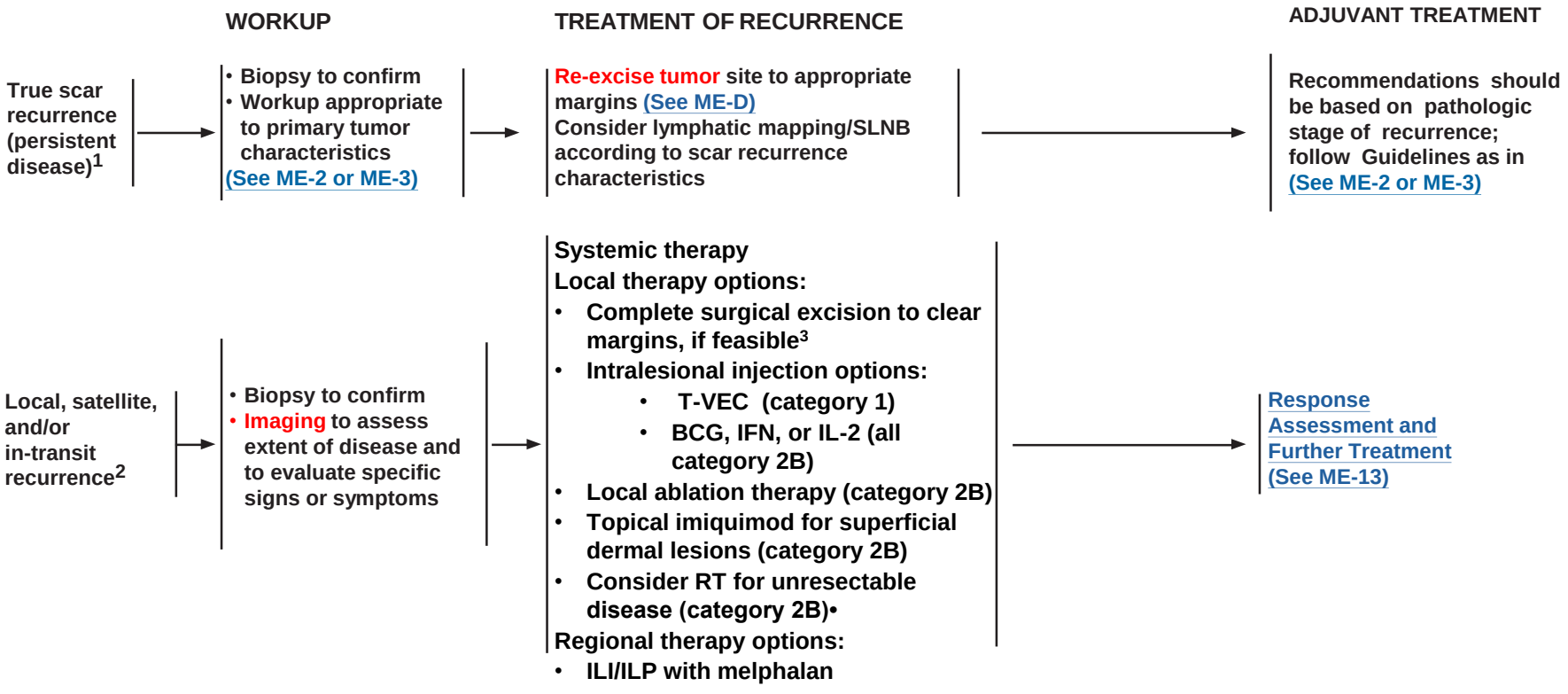
- **In patients with an equivocal lymph node exam, short-term follow-up and/or additional imaging (US [preferred] or CT) should be considered, with imaging-directed biopsy as warranted.**
- **Regional lymph node US in patients with a positive SLNB who did not undergo CLND should be considered where expertise is available. It would be appropriate for the frequency of clinical exam and US surveillance to be consistent with the two prospective randomized trials**

(MSLT-II and DeCOG):
every 4 months during the first 2 years,
then every 6 months during years 3 through 5.

• Follow-up schedule is influenced by risk of recurrence and new primary melanoma, which depends on patient/family history of melanoma, mole count, and/or presence of atypical moles/dysplastic nevi.

• Clinical and family history can identify patients in whom multigene testing might indicate an increased genetic risk for cutaneous and uveal melanoma, astrocytoma, mesothelioma, and cancers of the breast, pancreas, and kidney. This information can guide recommendations for surveillance and early detection in the patient and his/her relatives.

1 Risk factors for development of single or multiple primary melanomas, including subsequent primaries after index diagnosis. This list does not include risk factors for melanoma recurrence or progression, as those are covered elsewhere in the algorithm.



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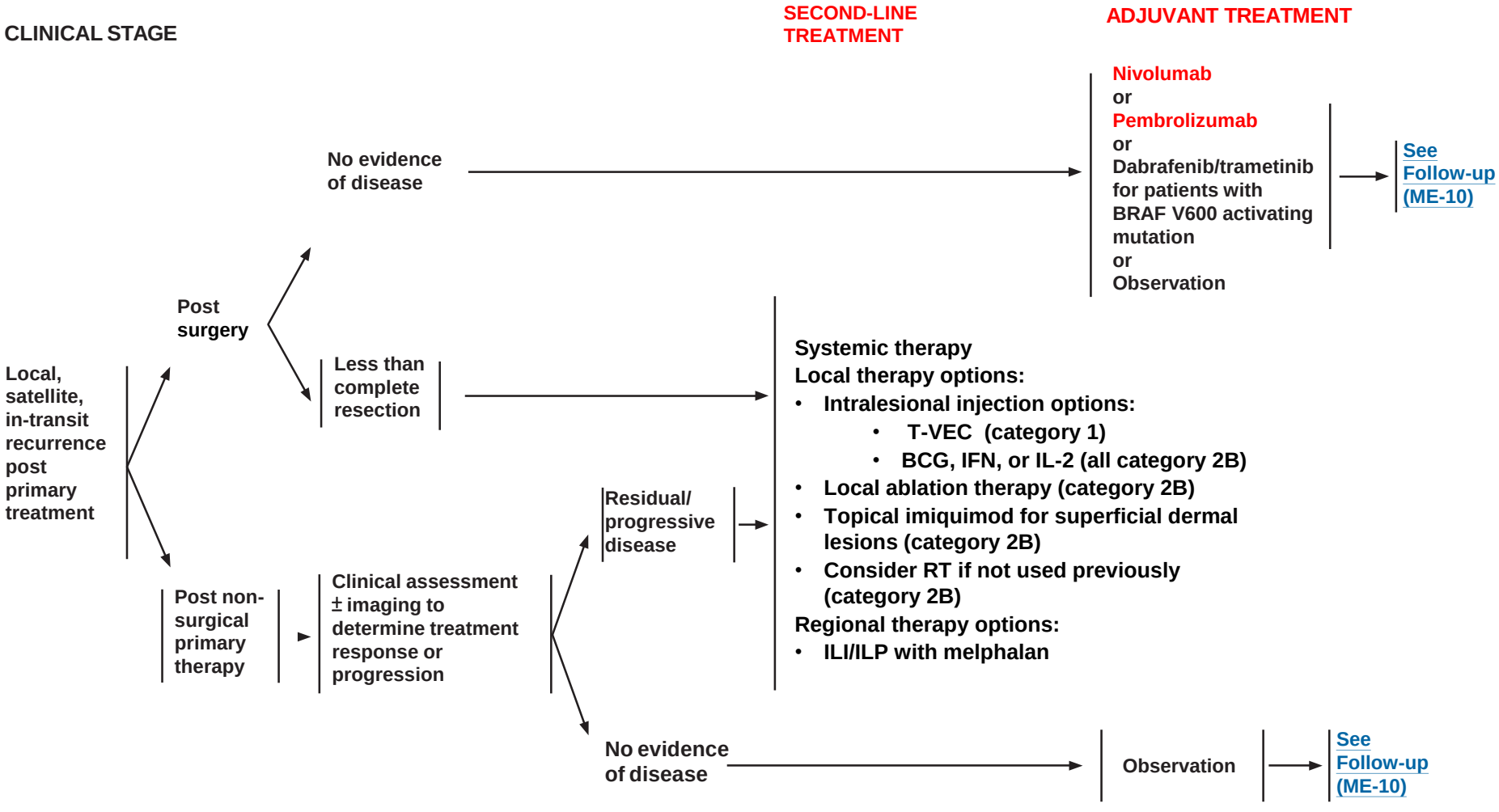
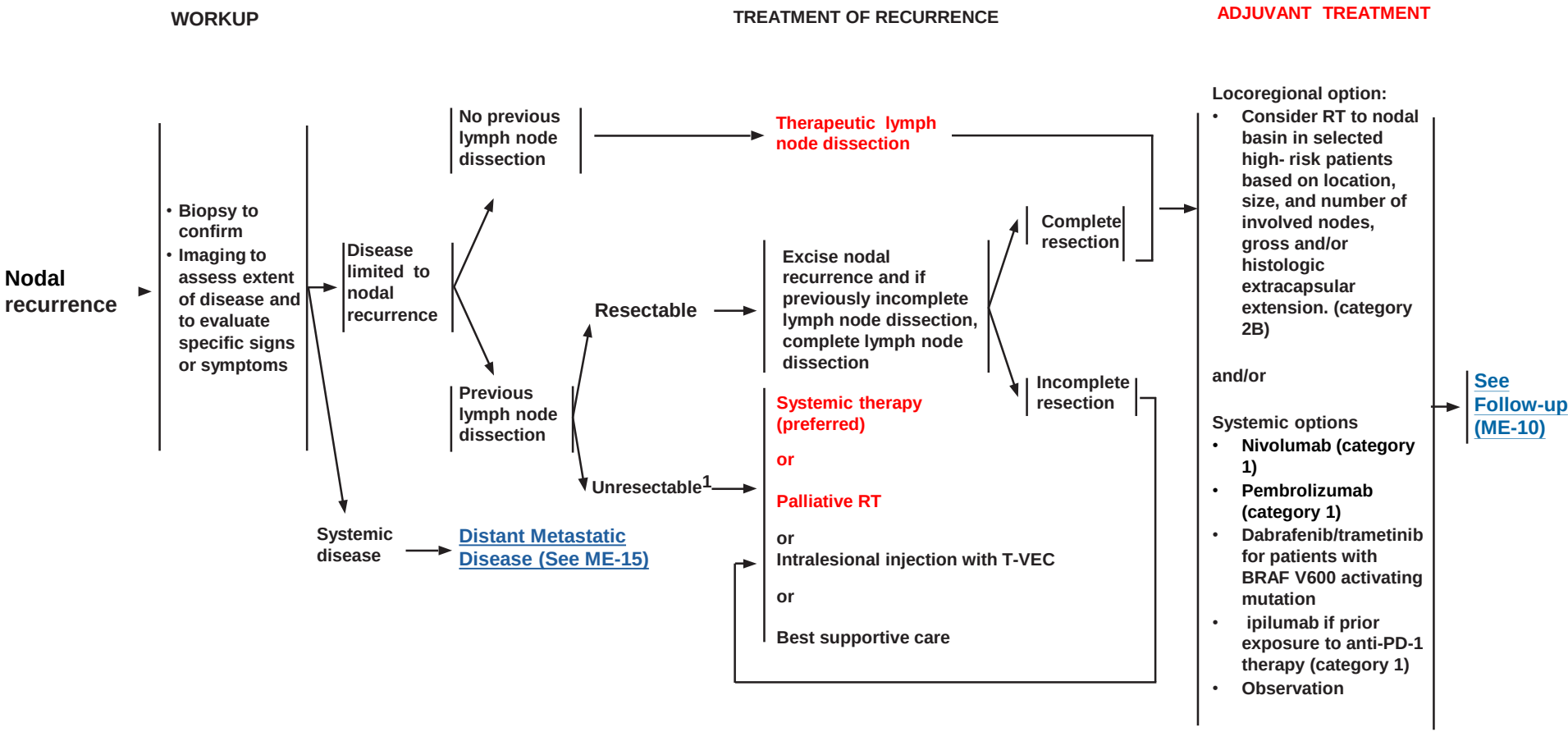
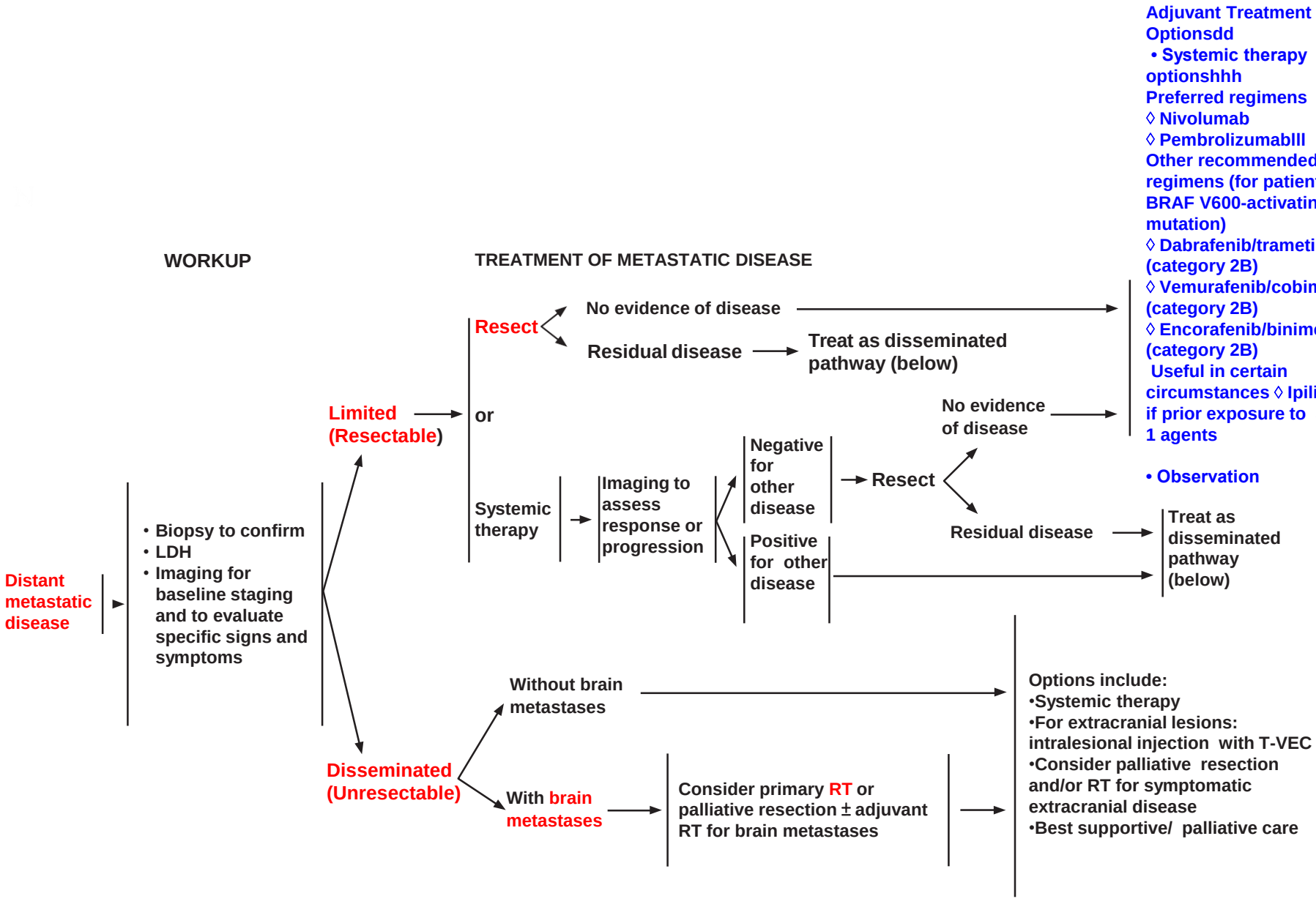
[1]True scar recurrence (persistent disease) is defined by the presence of in situ and/or radial growth phase.
[2] Local satellite/in-transit recurrence without in situ or radial growth phase, with intralymphatic deep dermal or subcutaneous fat recurrence within the melanoma scar or satellite metastasis adjacent to the melanoma scar. Satellite and in-transit metastases are prognostically equivalent, with no distance measurement from the primary tumor necessary to distinguish between these intracutaneous or subcutaneous lymphatic metastases.
3 Consider sentinel node biopsy for microscopic satellitosis or resectable clinicalsatellite/in-transit disease if it will change treatment options (category 2B)


CLINICAL STAGE
SECOND-LINE TREATMENT
ADJUVANT TREATMENT
No evidence of disease
Nivolumab
or
Pembrolizumab
or
Dabrafenib/trametinib for patients with BRAF V600 activating mutation
or
Observation
See Follow-up (ME-10)
Post surgery
Local, satellite, in-transit recurrence post primary treatment
Less than complete resection
Systemic therapy
Local therapy options:
• Intralesional injection options:
• T-VEC (category 1)
• BCG, IFN, or IL-2 (all category 2B)
• Local ablation therapy (category 2B)
• Topical imiquimod for superficial dermal lesions (category 2B)
• Consider RT if not used previously (category 2B)
Regional therapy options:
• ILI/ILP with melphalan
Residual/ progressive disease
Post non-surgical primary therapy
Clinical assessment ± imaging to determine treatment response or progression
No evidence of disease
Observation
See Follow-up (ME-10)

Skin Cancer



[1] Disease is defined as technically unresectable (ie, involvement of a major neurovascular structure) or clinically unresectable (ie, remote nodal disease), where surgery alone would have minimal clinical benefit.


WORKUP
TREATMENT OF METASTATIC DISEASE
Distant metastatic disease
• Biopsy to confirm
• LDH
• Imaging for baseline staging and to evaluate specific signs and symptoms
Limited (Resectable)
Resect
No evidence of disease
Residual disease
Treat as disseminated pathway (below)
or
Systemic therapy
Imaging to assess response or progression
Negative for other disease
Resect
No evidence of disease
Residual disease
Positive for other disease
Treat as disseminated pathway (below)
Disseminated (Unresectable)
Without brain metastases
With brain metastases
Consider primary RT or palliative resection ± adjuvant RT for brain metastases
Options include:
•Systemic therapy
•For extracranial lesions: intralesional injection with T-VEC
•Consider palliative resection and/or RT for symptomatic extracranial disease
•Best supportive/ palliative care
Adjuvant Treatment Optionsdd
• Systemic therapy optionshhh
Preferred regimens
◊ Nivolumab
◊ Pembrolizumablll
Other recommended regimens (for patients with BRAF V600-activating mutation)
◊ Dabrafenib/trametinib (category 2B)
◊ Vemurafenib/cobimetinib (category 2B)
◊ Encorafenib/binimetinib (category 2B)
Useful in certain circumstances ◊ Ipilimumab if prior exposure to anti PD-1 agents
• Observation

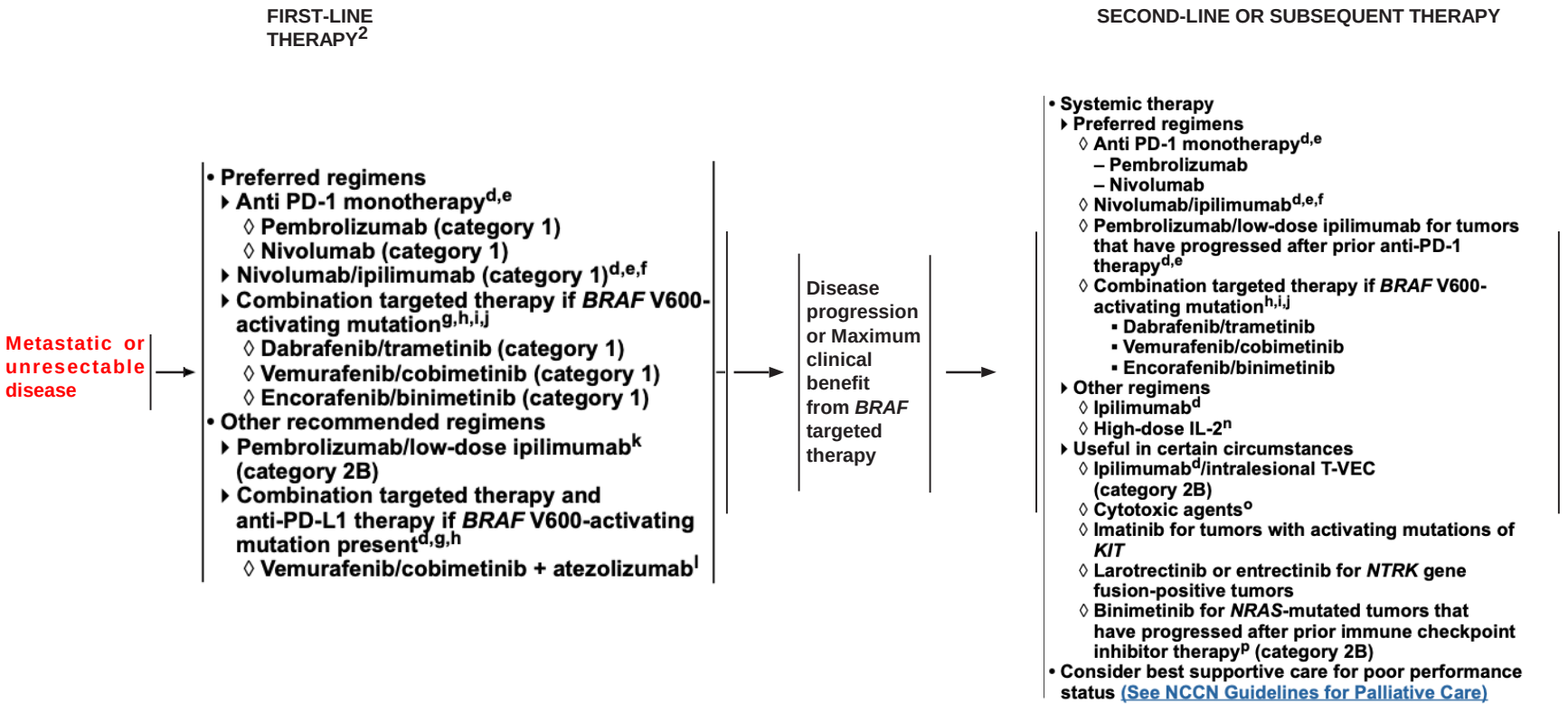
PRINCIPLES OF SURGICAL MARGINS FOR WIDE EXCISION OF PRIMARY MELANOMA

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.
[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.

SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE



1Cytotoxic Regimens for Metastatic Disease:

Dacarbazine
Temozolomide
Paclitaxel
Albumin-bound paclitaxel
Carboplatin/paclitaxel

Table 1

American Joint Committee on Cancer (AJCC) TNM Staging System for Melanoma (8th ed., 2017)

Primary Tumor (T)

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

Skin Cancer

Extent of regional lymph node and/or lymphatic metastasis

N Category		Number of tumor-involved lymph node and/or lymphatic metastasis	Presence of In-Transit, Satellite, and/or Microsatellite Metastasis
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.)		Not applicable	No
N0: No regional metastases detected			
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 to three clinically occult (ie, detected by SLN biopsy)	No
	N2b	Two to three clinically	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 leaset 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

M Category			Anatomic site	LDH level
M0			No evidence of distant metastasis	Not applicable
M1	• Evidence of distant metastasis			
	M1a	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	M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
		M1b(0)		Not elevated
		M1b(1)		Elevated
	M1c	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	M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
		M1d(0)		Not elevated
		M1d(1)		Elevated

Anatomic Stage/Prognostic Groups

Clinical Staging*

	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	Any T, Tis	≥ N1	M0
Stage IV	Any T	Any N	M1

*Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

Pathologic staging **

	T	N	M
Stage 0 [1]	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	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.

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