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Cutaneous Melanoma

Kelley A. Sookraj, MD
Downstate Medical Center
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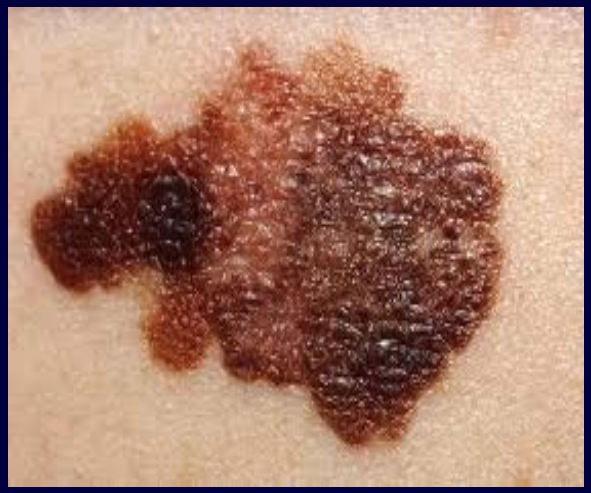
Case Presentation

- A xx year old male presents to your office with a complaint of a right upper extremity skin lesion that has changed in size, shape and color. He is afraid that it might be melanoma. How would you approach and evaluate this patient?



Case Presentation

- History

  race
  complexion
  sun exposure
  dysplastic nevi
  family history of melanoma
  (genetic predisposition)
  previous history of melanoma

- Physical Exam

  evaluate lesion (ABCDE)
  complete skin exam
  evaluate nodal basins

- What would be the next step?

punch biopsy

Results: 1.5mm thick, no ulceration, mitosis < 1/mm^2,
Clark level III

- The patient presents for a follow-up visit and inquires about his biopsy results.

Requires wide local excision of lesion

AND

Sentinel lymph node biopsy

- Prior to the OR, is there anything that you would do?

  lymphoscintigraphy

- Intra-operatively?

  inject isosulfan blue dye; resect SLN

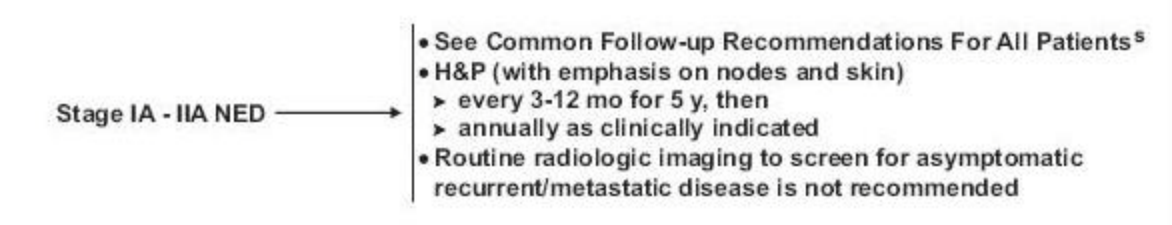
- What would be appropriate margins during resection?

  1-2cm

- SLN biopsy: negative for micrometastatic disease

T2a N0 M0 = Stage 1B

- The patient returns for a post-op check and inquires about results of biopsy.



Melanoma

- Melanocytes
  - originate from neural crest cells
  - found along basement membrane at the dermoepidermal junction
  - exposure to carcinogenic stimuli result in malignant transformation and melanoma

- Accounts for 4 – 5% of all skin cancers, but causes majority of deaths

- Eighth most common cancer in the United States

- 68,130 new cases; 8700 deaths in US (2010)

Melanoma

- Epidemiology

  - 20x more common in white individuals, especially those of Celtic ancestry; less in Asian and black population

  - anatomic distribution varies among gender
    - men: trunk, head and neck
    - women: lower extremities

  - median age at presentation: 45-55yrs

Melanoma

- Etiology

  - exposure to sunlight
    - UV radiation (UVA and UVB)
    - UVA: deeper level of penetration leading to dermal connective tissue damage
    - UVB: induces effects of sunburn, increases melanin production and is most carcinogenic part of UV spectrum

Melanoma

- Risk Factors

  - fair complexion, severe sunburns, intermittent doses of radiation (sun bathing, tanning beds)

  - xeroderma pigmentosum, family history of melanoma, history of non-melanoma skin cancer, dysplastic nevi syndrome

  - Aging: related to either exposure to carcinogens (UV radiation) or the decreasing ability of individual cells to repair DNA damage

  - Precursor Lesions: congenital nevi, dysplastic nevi, spitz nevi

Melanoma

- Xeroderma Pigmentosum
  - autosomal recessive
  - inability to repair DNA damage caused by UV radiation
  - incidence 1 in 250,000
  - increased risk for skin cancers; melanoma and SCC most common cause of death
  - symptoms: severe sun burn to minimal sun exposure, freckles, solar keratoses, painfully sensitive eyes to sun exposure
  - poor prognosis, less than 40% survive beyond 20 yrs of age

Melanoma

- Giant Congenital Nevi
  - rare, occurs in 1 in 20,000 newborns
  - increased risk of melanoma within nevi
  - lifetime risk 5-8%
  - require regular examination throughout life

- Dysplastic Nevi (DN)
  - large (6-15mm), flat pigmented lesion
  - indistinct margins, variable color
  - may occur sporadically or in a familial pattern

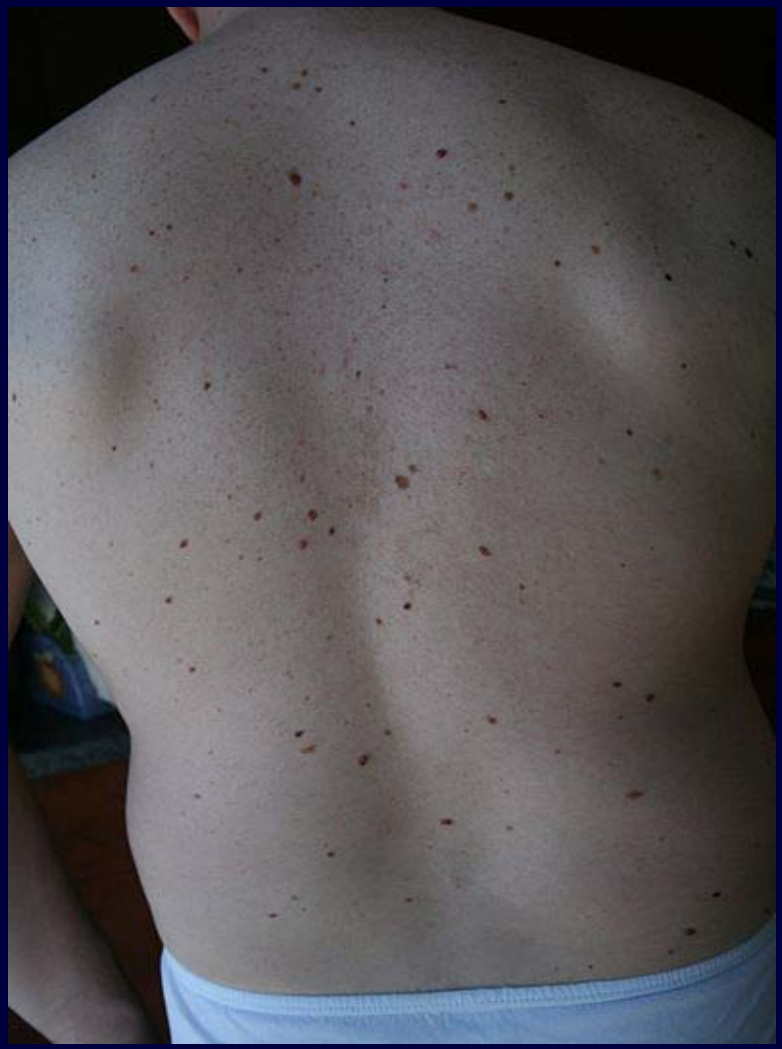
Melanoma

- Dysplastic Nevi (DN)

  - DN syndrome (BK mole syndrome, FAMMM syndrome): multiple nevi >100, mutation CDKN2A gene, chromosome 9, leads to unstable p53; penetrance for melanoma ranges 52-98%

  - unclear consensus in management; can excise all lesions

  - surveillance mandatory; complete skin examination every 3-6 months, monthly self-examination



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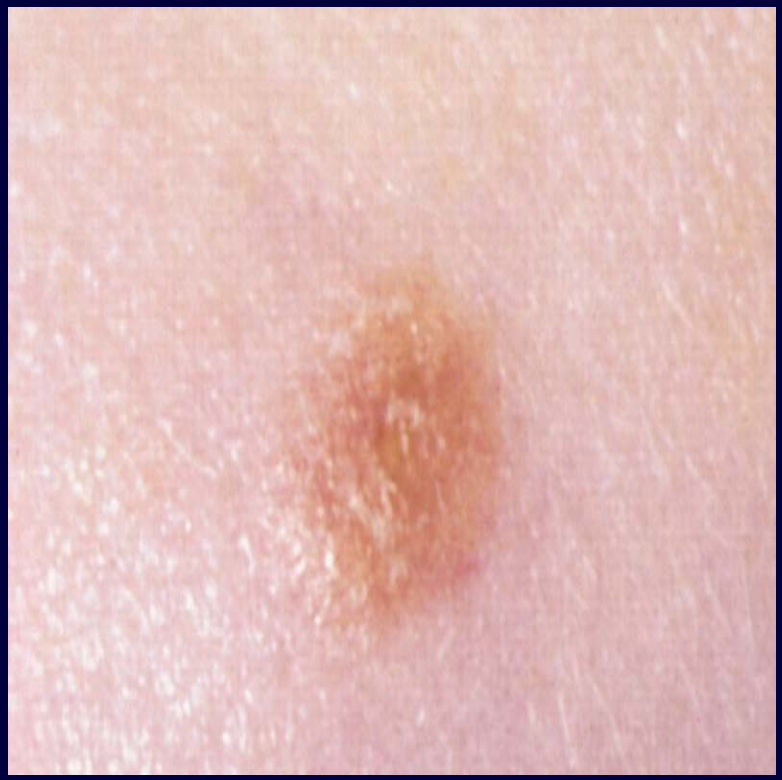
- Spitz Nevi

  - rapidly growing, pink, brown lesions

  - occurs in children and adolescents

  - difficult to distinguish from melanoma; requires an experienced pathologist

  - treatment: complete local excision



Melanoma

- Clinical Features

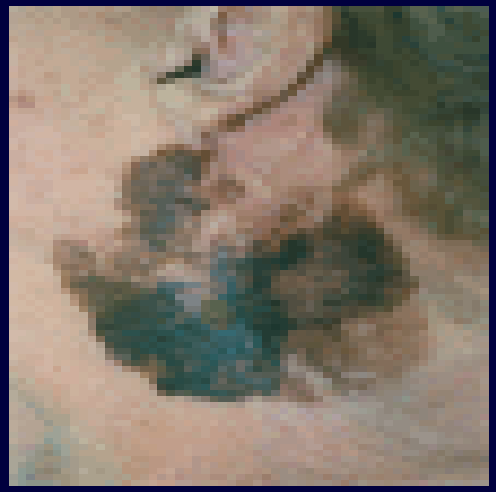
  - *changing*, pigmented skin lesion, that is initially flat and spreads over the skin but later becomes elevated

  - Asymmetric outline
  - irregular Borders
  - variation in Color
  - Diameter greater than 6mm
  - Elevation

Melanoma

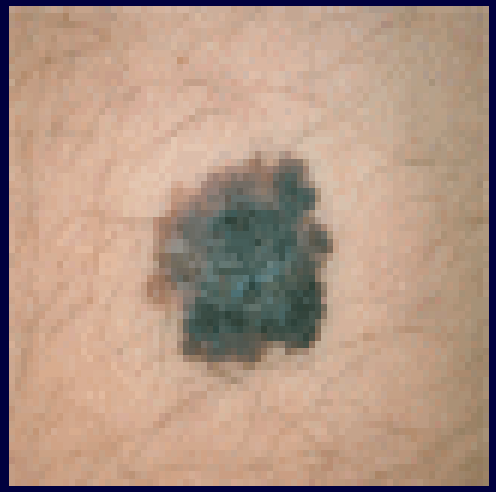
- Types of Melanoma
  - Lentigo Maligna Melanoma (10%)

    - occurs in older individuals with sun damaged skin
    - flat, dark pigmented lesion with irregular borders
    - slow progression; can be several centimeters in diameter
    - better prognosis due to superficial spread



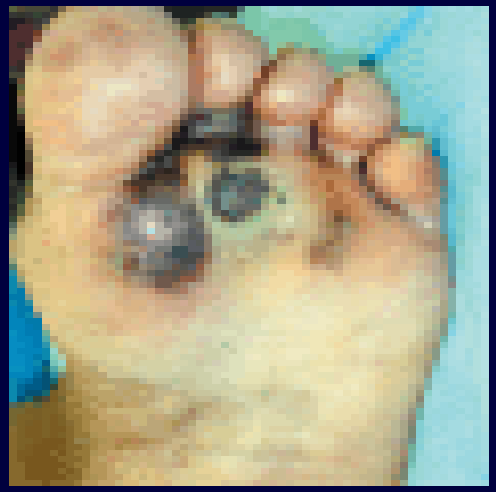
Melanoma

- Types of Melanoma
  - Superficial Spreading Melanoma (70%)
    - most common
    - flat, pigmented lesion with a radial growth pattern
    - may not be associated with sun exposure
    - if left in place will begin to thicken (increase vertical growth)



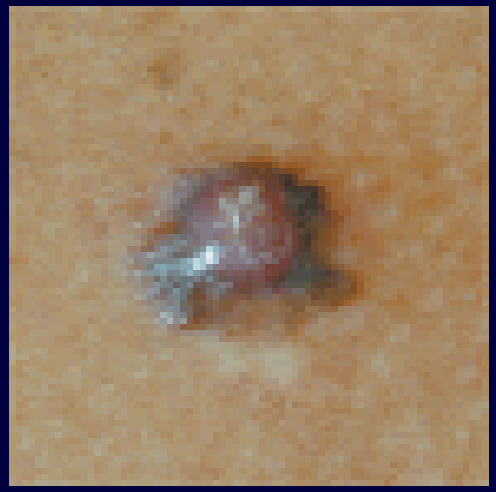
Melanoma

- Types of Melanoma
  - Acral Lentiginous Melanoma (5%)
    - classified by its anatomic site of origin
    - confined to subungual area, skin of palms and soles
    - most common in black individuals
    - poor prognosis due to delayed diagnosis



Melanoma

- Types of Melanoma
  - Nodular Melanoma (15%)
    - early development of vertical growth phase
    - worst prognosis due to tumor thickness



Melanoma

- Prognostic Factors: 1969 Clark's Classification
  - based on extent of tumor invasion relative to anatomic layers
  - level of invasion was related to survival
  - Clark level was difficult to determine and differed among pathologists with same slides

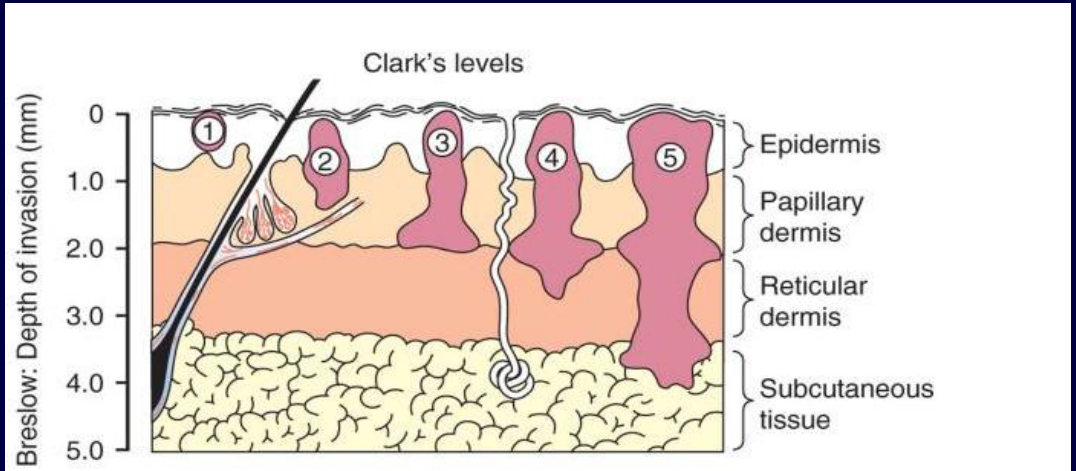


Figure 30-6 Schematic representation of Clark's levels of tumor penetration in relation to the normal layers of skin.

Melanoma

- Prognostic Factors: 1970 Breslow Classification
  - measured vertical thickness of tumor in millimeters
  - accurately reproducible among pathologists
  - prognosis worsens with increasing thickness
  - correlated with 5yr survival

Tumor Thickness

≤ 1 mm
1.01 - 2 mm
2.01 - 4 mm
> 4 mm

Melanoma

- Prognostic Factors: American Joint Committee on Cancer (AJCC) Melanoma Database

  - Balch and collaborators defined multiple prognostic factors

    Age, Gender, Level, Site, Thickness, Ulceration

  - Strongest predictor of outcome

  - Associated with local recurrence, regional and distant metastasis, survival

  - Same findings at other institutions in North America, Australia and Europe; confirmed in SEER database

Melanoma

- Management

  - begins with an accurate diagnosis
  - classic signs not only include ABCDE, but also bleeding, itching and/or ulceration
  - decision to perform biopsy
    - history and physical
    - clinical experience
    - high index of suspicion
  - method (excisional or punch) of biopsy is determined by size of lesion and anatomic location

Melanoma

- Management

- Biopsies must be full thickness with a margin of normal skin regardless of method

- *Tumor Thickness is the most important prognostic factor*

- Determines further management (WLE, SLN biopsy, adjuvant therapy) and therefore survival in patients with melanoma

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NCCN Guidelines Index
Melanoma Table of Contents
Discussion

PRINCIPLES OF BIOPSY

- Excisional biopsy (elliptical, punch, or saucerization) with 1-3 mm margins preferred. Avoid wider margins to permit accurate subsequent lymphatic mapping.
- The orientation of the biopsy should be planned with definitive wide excision in mind.
- Full thickness incisional or punch biopsy[1] of clinically thickest portion of lesion acceptable, in certain anatomic areas (eg, palm/sole, digit, face, ear) or for very large lesions.
- Shave biopsy[1,2] may compromise pathologic diagnosis and complete assessment of Breslow thickness, but is acceptable when the index of suspicion is low.

PRINCIPLES OF PATHOLOGY

- Biopsy to be read by a pathologist experienced in pigmented lesions.
- Minimal elements to be reported should include Breslow thickness (mm), histologic ulceration, dermal mitotic rate per mm[2,3] Clark level (encouraged for lesions ≤ 1 mm, optional for lesions > 1 mm), and peripheral and deep margin status of biopsy (positive or negative).
- Microsatellitosis, if present, should be reported.
- Encourage consistent reporting of these additional factors (compatible with American Academy of Dermatology recommendations):
  - Location
  - Regression
  - Tumor infiltrating lymphocytes (TIL)
  - Vertical growth phase (VGP)
  - Angiolymphatic invasion
  - Neurotropism
  - Histologic subtype
  - Pure desmoplasia, if present (specify pure vs. mixed desmoplastic with spindle cell and/or epithelioid cells)
- Consider use of comparative genomic hybridization (CGH) or fluorescent in situ hybridization (FISH) for histologically equivocal lesions.[4]

[1] If clinical evaluation of incisional biopsy suggests that microstaging is inadequate, consider narrow margin excisional biopsy.
[2] For lentigo maligna, melanoma in situ, a broad shave biopsy may help to optimize diagnostic sampling.
[3] Dermal mitotic rate should be determined using the "hot spot" technique and expressed as number of mitoses per square millimeter. (Sondak VK, Taylor JM, Sabel MS, et al. Mitotic rate and younger age are predictors of sentinel lymph node positivity; lessons learned from the generation of a probabilistic model. Annals of Surgical Oncology 2004;11:247-258 and Clark WH, Elder DE, Guerry D. Model Predicting survival in Stage I Melanoma Based on tumor Progression. Journal of the National Cancer Institute 1989;81:1893-1904.)
[4] CGH may be more accurate than FISH in identifying relevant genetic mutations (Raskin L, Ludgate M, Iyer RK,, et al. Copy number variations and clinical outcome in atypical spitz tumors. Am J Surg Pathol 2011;35:243-252).

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

Melanoma

- Surgery

  - fundamental principle: resection of primary tumor with minimal risk for recurrence

  - William S. Handley (1907) recommended wide local excision (WLE) with regional lymph node (LN) dissection

  - contributions from Clark and Breslow gave more insight into the natural history of melanoma:

  risk for local recurrence and overall survival rates were related to tumor thickness

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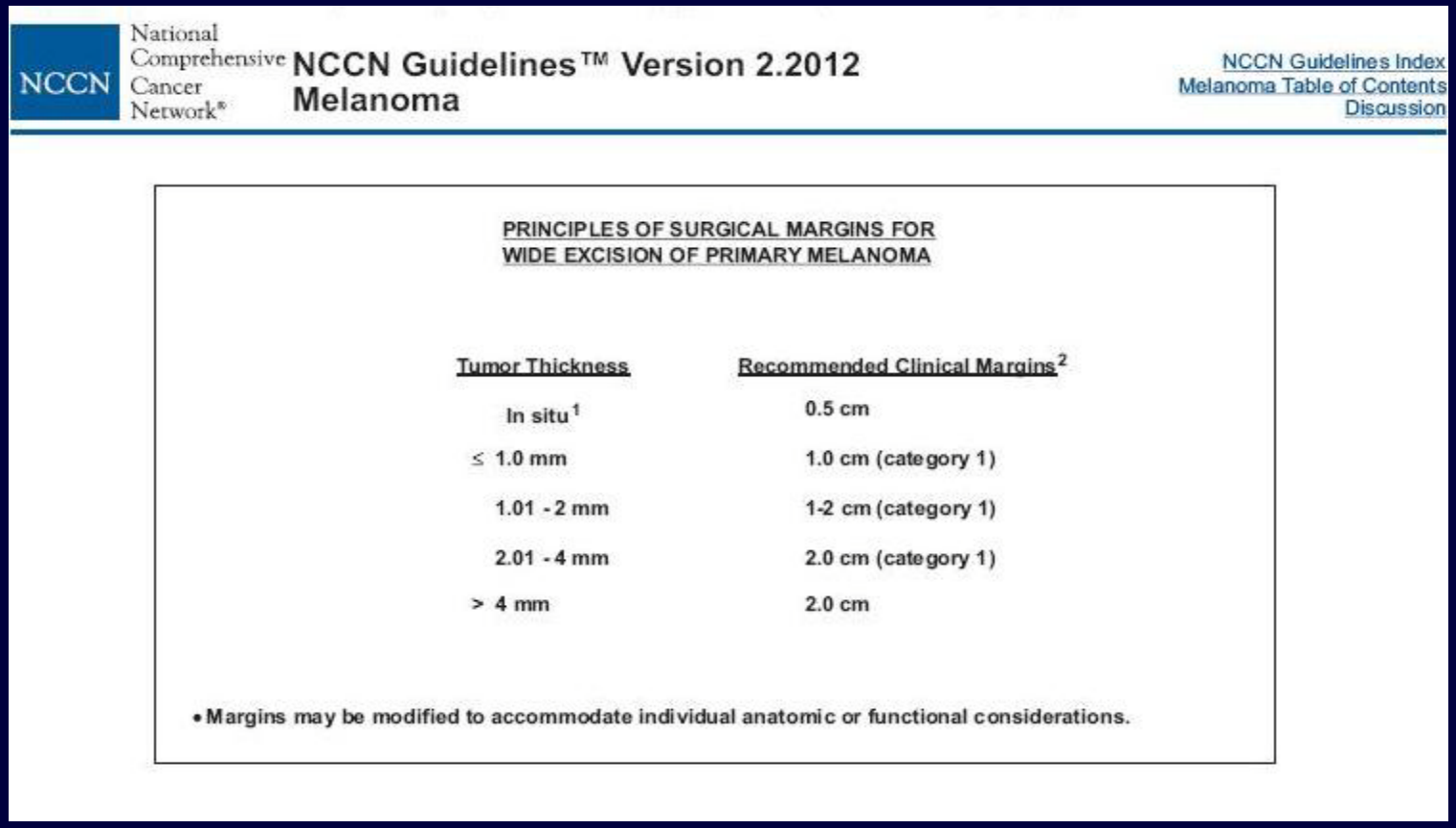
Melanoma

- What margins were necessary to achieve these results?
  - multiple randomized trials conducted



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NCCN Guidelines Index
Melanoma Table of Contents
Discussion

PRINCIPLES OF SURGICAL MARGINS FOR WIDE EXCISION OF PRIMARY MELANOMA

Tumor Thickness	Recommended Clinical Margins[2]
In situ[1]	0.5 cm
≤ 1.0 mm	1.0 cm (category 1)
1.01 - 2 mm	1-2 cm (category 1)
2.01 - 4 mm	2.0 cm (category 1)
> 4 mm	2.0 cm

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

Melanoma

- Surgery: Resection/Reconstruction

  - wide local excision, measured from biopsy scar

  - specimen oriented for pathologist

  - reconstruction: primary closure, advancement flaps, skin grafts, Z plasty, V-Y flaps

Melanoma

- Surgery

  - following WLE, many patients found to have recurrence within lymphatic basins draining the primary site

  - surgeons concluded that resection of the nodal basin containing occult metastasis would increase survival:

    elective lymph node dissection (ELND)

  - significant morbidity: lymphedema, muscle weakness, restricted range of motion

Melanoma

- Surgery

  - with better understanding of prognostic factors (tumor thickness):

< 1mm	low risk of metastasis
> 4mm	high risk of distant metastasis
1-4mm	*elevated risk for nodal metastasis* (may benefit from ELND)

  - Intergroup Melanoma Trial and WHO Melanoma Programme Trial: no benefit to ELND in intermediate thickness melanoma

Melanoma

- Surgery

  - 1970s Dr. Morton and colleagues described a radionuclide mapping technique to define lymphatic drainage from any primary site on skin

  - technetium-99m labeled colloid injected intradermally

  - flow through lymphatic vessels with up take in regional nodes

  - used by surgeons for ELND

Melanoma

- Surgery

  - 15 yrs later, Morton and group injected blue dye to show the first blue node in the regional lymphatic basin

  - this node would be the first node to contain metastasis if tumor were present, termed the *Sentinel Lymph Node (SLN)*

  - the concept of SLN biopsies put and end to ELND and changed clinical management

  - allowed for identification of the SLN in 95% groin and axilla; 85% head and neck regions

Melanoma

- Surgery

  - lymphoscintigraphy: performed the day before or on day of procedure

  - all regions of uptake are labeled on lymphoscintigram

  - intra-op blue dye (isosulfan blue) is injected and the first blue node in the basin of interest is resected

Melanoma

- Was there a benefit to Sentinel Lymph Node Biopsy?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 28, 2006 VOL. 355 NO. 13

Sentinel-Node Biopsy or Nodal Observation in Melanoma

Donald L. Morton, M.D., John F. Thompson, M.D., Alistair J. Cochran, M.D., Nicola Mozzillo, M.D., Robert Elashoff, Ph.D., Richard Essner, M.D., Omgo E. Nieweg, M.D., Ph.D., Daniel F. Roses, M.D., Harald J. Hoekstra, M.D., Ph.D., Constantine P. Karakousis, M.D., Ph.D., Douglas S. Reintgen, M.D., Brendon J. Coventry, M.D., Edwin C. Glass, M.D., and He-Jing Wang, M.D., for the MSLT Group*

ABSTRACT

BACKGROUND

We evaluated the contribution of sentinel-node biopsy to outcomes in patients with newly diagnosed melanoma.

METHODS

From the Departments of Surgical Oncology (D.L.M., R. Essner) and Biostatistics (R. Elashoff, H.-J.W.), John Wayne Cancer Institute at Saint John's Health Center,

Melanoma

- Multicenter Selective Lymphadenectomy Trial (MSLT I)

- evaluate contribution of SLN biopsy to outcomes in patients with melanoma

- patients were randomized to wide excision with observation of LN or sentinel LN biopsy

- if positive they would undergo immediate lymphadenectomy

Melanoma

- Multicenter Selective Lymphadenectomy Trial (MSLT I)

  - 1269 patients with intermediate thickness melanoma were enrolled from 1994 – 2002

    500 observation arm; 769 biopsy arm

  - demographics, clinical and pathologic characteristics of lesion were similar

  - primary endpoint was melanoma specific survival

  - secondary endpoint was disease-free survival before first recurrence

Melanoma

- Multicenter Selective Lymphadenectomy Trial (MSLT I)

  - follow-up was 5 years

  - melanoma-specific survival was similar in both arms
    86.6% (biopsy); 87.1% (observation)

  - disease-free survival significantly higher in biopsy arm
    78.3% vs. 73.1%

Melanoma

- Multicenter Selective Lymphadenectomy Trial (MSLT I)

  - biopsy arm: 122 SLN +, 642 SLN –

  - disease free survival in the biopsy arm
    + mets 53% vs. - mets 83%

  - melanoma specific survival in biopsy arm
    + mets 72.3% vs. - mets 90%

Melanoma

- Multicenter Selective Lymphadenectomy Trial (MSLT I)

  - 5 yr survival rate among node + group was significantly higher compared to observation group: 66% vs. 54%

  - biopsy arm with + mets: AJCC nodal stage I (39%)
    observational arm with clinical mets: nodal stage III (70%)

  - results confirmed: prolonged disease free survival and increased melanoma-specific survival rate when compared to observation and delayed lymphadenectomy: 72% vs. 52.4%

Melanoma

- Multicenter Selective Lymphadenectomy Trial (MSLT I)

  - provided evidence that occult disease can develop into aggressive regional and distant metastasis

  - SLN bx has staging and prognostic value in patients with intermediate-thickness melanoma and along with immediate lymphadenectomy improves survival

  - study results were confirmed with other trials conducted by WHO Melanoma Program

  - SLN biopsy is now standard of care for tumors >1mm thick; accurate staging and further treatment

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Melanoma

- Staging : TNM AJCC system

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NCCN Guidelines Index
Melanoma Table of Contents
Discussion

Table 1

American Joint Committee on Cancer (AJCC)
TNM Staging System for Melanoma (7th ed., 2010)

Primary Tumor (T)

TX	Primary tumor cannot be assessed (eg, curettaged or severely regressed melanoma)
T0	No evidence of primary tumor
Tis	Melanoma *in situ*
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 that 4.0 mm

Note: a and b sub categories of T are assigned based on ulceration and number of mitoses per mm^2 as shown below:

T classification	*Thickness (mm)*	*Ulceration Status/Mitoses*
T1	≤ 1.0	a: w/o ulceration and mitosis $<1/mm^2$ b: with ulceration or mitoses $\geq 1/mm^2$
T2	1.01-2.0	a: w/o ulceration b: with ulceration
T3	2.01-4.0	a: w/o ulceration b: with ulceration
T4	>4.0	a: w/o ulceration b: with ulceration

Regional Lymph Nodes (N)

NX	Patients in whom the regional lymph nodes cannot be assessed (eg, previously removed for another reason)
N0	No regional metastases detected
N1-3	Regional metastases based upon the number of metastatic nodes and presence or absence of intralymphatic metastases (in transit or satellite metastases)

Note: N1-3 and a-c sub categories are assigned as shown below:

N Classification Mass	*No. of Metastatic Nodes*	*Nodal Metastatic*
N1	1 node	a: micrometastasis* b: macrometastasis**
N2	2-3 nodes	a: micrometastasis* b: macrometastasis** c: in transit met(s)/ satellite(s) *without* metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) *with* metastatic node(s)	

*Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed).
**Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

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- Staging : TNM AJCC system

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NCCN Guidelines Index
Melanoma Table of Contents
Discussion

Distant Metastasis (M)

M0	No detectable evidence of distant metastases
M1a	Metastases to skin, subcutaneous, or distant lymph nodes
M1b	Metastases to lung
M1c any	Metastases to all other visceral sites or distant metastases to site combined with an elevated serum LDH

Note: Serum LDH is incorporated into the M category as shown below:

M Classification	*Site*	*Serum LDH*
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

Anatomic Stage/Prognostic Groups

Clinical Staging*

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	≥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**

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 IIIA	T(1–4)a	N1a	M0
	T(1–4)a	N2a	M0
Stage IIIB	T(1–4)b	N1a	M0
	T(1–4)b	N2a	M0
	T(1–4)a	N1b	M0
	T(1–4)a	N2b	M0
	T(1–4)a	N2c	M0
Stage IIIC	T(1–4)b	N1b	M0
	T(1–4)b	N2b	M0
	T(1–4)b	N2c	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

**Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 or Stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

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- Surgery: NCCN Algorithm

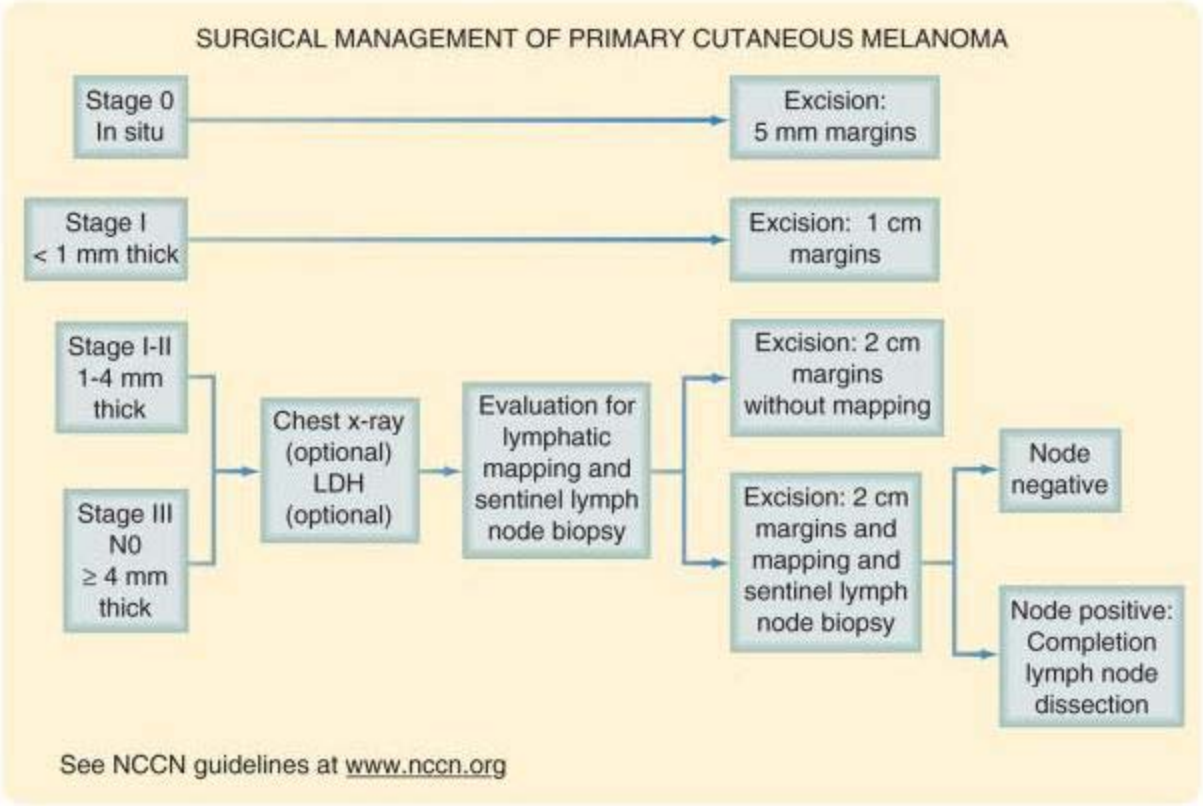

Figure 30-9 Management algorithm for primary cutaneous melanoma derived from the National Comprehensive Cancer Network (NCCN) guidelines (available at www.nccn.org). LDH, lactate dehydrogenase.

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- Surgery: AJCC; Survival

Stage IA: The 5-year survival rate is around 97%. The 10-year survival is around 95%.

Stage IB: The 5-year survival rate is around 92%. The 10-year survival is around 86%.

Stage IIA: The 5-year survival rate is around 81%. The 10-year survival is around 67%.

Stage IIB: The 5-year survival rate is around 70%. The 10-year survival is around 57%.

Stage IIC: The 5-year survival rate is around 53%. The 10-year survival is around 40%.

Stage IIIA: The 5-year survival rate is around 78%. The 10-year survival is around 68%

Stage IIIB: The 5-year survival rate is around 59%. The 10-year survival is around 43%

Stage IIIC: The 5-year survival rate is around 40%. The 10-year survival is around 24%

Stage IV: The 5-year survival rate for stage IV melanoma is about 15% to 20%. The 10-year survival is about 10% to 15%. The outlook is better if the spread is only to distant parts of the skin or distant lymph nodes rather than to other organs, or if the blood level of lactate dehydrogenase (LDH) is normal.

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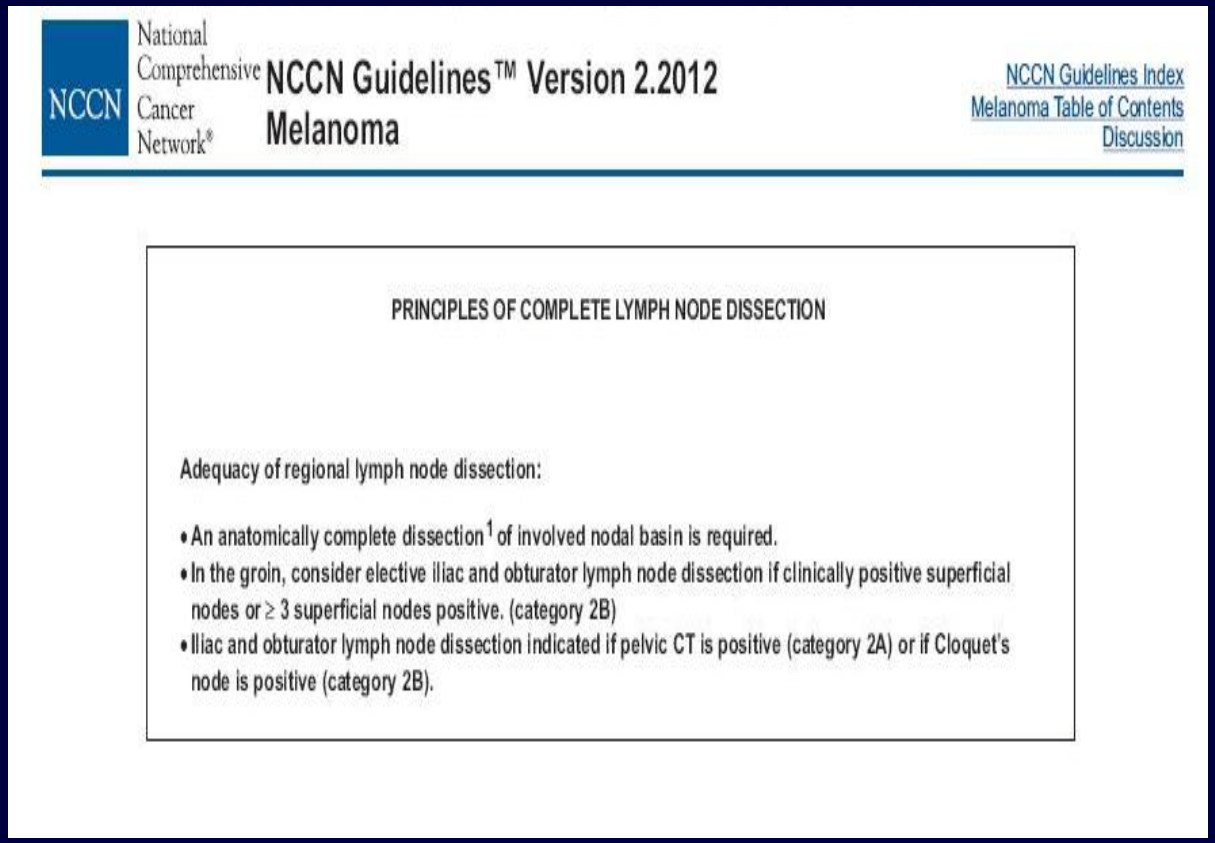
- Surgery: Complete Lymph Node Dissection (CLND)



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NCCN Guidelines Index
Melanoma Table of Contents
Discussion

PRINCIPLES OF COMPLETE LYMPH NODE DISSECTION

Adequacy of regional lymph node dissection:

- An anatomically complete dissection[1] of involved nodal basin is required.
- In the groin, consider elective iliac and obturator lymph node dissection if clinically positive superficial nodes or ≥ 3 superficial nodes positive. (category 2B)
- Iliac and obturator lymph node dissection indicated if pelvic CT is positive (category 2A) or if Cloquet's node is positive (category 2B).

Basin	No. of Nodes
Axillary	15
Inguinal, superficial	8
Inguinal, deep	6
Cervical, anterior	15
Cervical, posterior	15
Supraclavicular	6
Suprahyoid	4
Parotid	3
Popliteal	2–3

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- Surgery: Adjuvant Therapy

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Melanoma Table of Contents
Discussion

SYSTEMIC THERAPY OPTIONS FOR ADVANCED OR METASTATIC MELANOMA[1]

- Clinical trial (preferred)
- Ipilimumab (category 1)[2,3]
- Vemurafenib (category 1)[4,5]
- Dacarbazine
- Temozolomide
- High-dose Interleukin-2[6,7]
- Dacarbazine-or temozolomide-based combination chemotherapy/biochemotherapy, (including cisplatin and vinblastine with or without IL-2, interferon alfa) (category 2B)[7]
- Paclitaxel (category 2B)
- Paclitaxel/cisplatin (category 2B)
- Paclitaxel/carboplatin (category 2B)

[1] Patients who progress after initial therapy may be offered subsequent therapy if they maintain a performance status of ECOG 0-2 or Karnofsky score ≥ 60.
[2] Ipilimumab has the potential for significant immune-mediated complications. Participation in the risk evaluation and mitigation strategy (REMS) program and/or experience in use of the drug as well as resources to follow the patient closely are essential. Ipilimumab should be used with extreme caution, if at all, in patients with serious underlying autoimmune disorders.
[3] Re-induction with ipilimumab may be considered for select patients who experienced no significant systemic toxicity during prior ipilimumab therapy and who relapse after initial clinical response or progress after stable disease > 3 months.
[4] Vemurafenib is recommended for patients with V600 mutation of the BRAF gene documented by an FDA-approved or Clinical Laboratory Improvement Amendments (CLIA)-approved facility.
[5] Vemurafenib has the potential for significant dermatologic complications including cutaneous squamous cell carcinoma and extreme photosensitivity. Regular dermatologic evaluation with referral to a dermatologist as clinically indicated. Patients should also be carefully monitored for the development of other adverse reactions such as joint pain and swelling.
[6] High-dose interleukin-2 should not be used for patients with inadequate organ reserve, poor performance status, or untreated or active brain metastases. For patients with small brain metastases and without significant peritumoral edema, IL-2 therapy may be considered (category 2B).
[7] Administration of multiagent regimens and high-dose interleukin-2 is complex and associated with significant toxicities. Therapy should be restricted to an institution with medical staff experienced in the administration and management of regimens.

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

References on next page

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Melanoma

- Surgery: Radiation Therapy

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NCCN Guidelines™ Version 2.2012
Melanoma

NCCN Guidelines Index
Melanoma Table of Contents
Discussion

PRINCIPLES OF RADIATION THERAPY FOR MELANOMA

Consider radiation therapy in the following situations:[1]

PRIMARY DISEASE
- Adjuvant treatment for selected patients with desmoplastic melanoma with extensive neurotrophism.

REGIONAL DISEASE
- Extracapsular extension
- ≥ 4 involved nodes
- Size ≥ 3 cm
- Cervical[2] > Axillary > Inguinal Location
- Recurrent disease after prior complete nodal dissection[3]

METASTATIC DISEASE
- Brain metastases (see NCCN Central Nervous System Cancers Guidelines)
  - Definitive or palliative stereotactic radiosurgery and/or whole brain radiation therapy
  - Adjuvant radiation following resection of brain metastases.
- Other symptomatic or potentially symptomatic soft tissue and/or bone metastases

[1] Most systemic treatments should be held during radiation.
[2] In the cervical location, consider adjuvant radiation if ≥ 2 lymph nodes are involved and for lymph nodes ≥ 2 cm.
[3] A wide range of radiation dose/fractionation schedules is effective. Hypofractionated regimens may increase the risk for long term complications such as lymphedema and small bowel obstruction.

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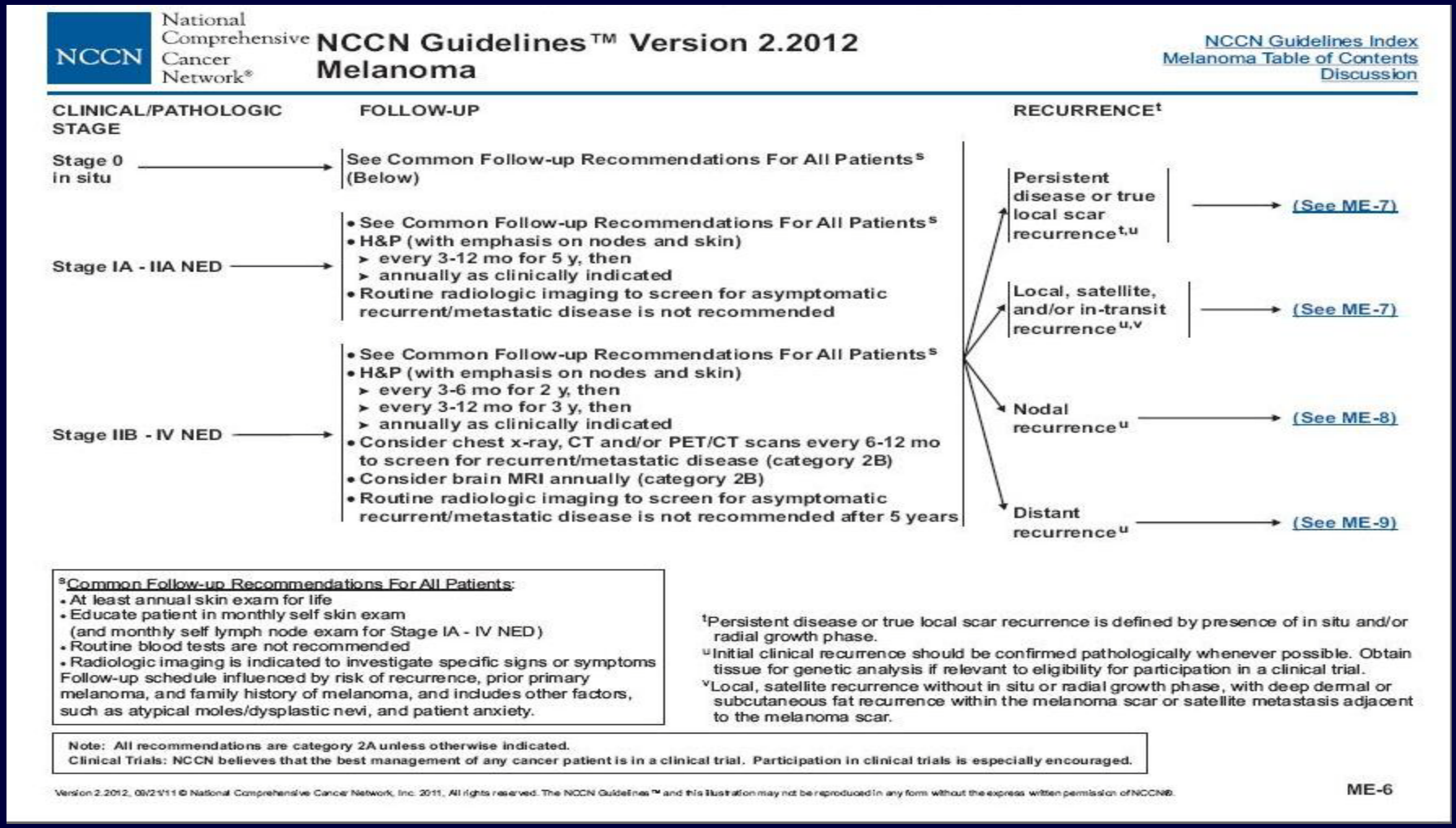
- Surgery: Follow-Up



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Melanoma

NCCN Guidelines Index
Melanoma Table of Contents
Discussion

CLINICAL/PATHOLOGIC STAGE	FOLLOW-UP	RECURRENCE[t]
Stage 0 in situ	See Common Follow-up Recommendations For All Patients[s] (Below)	
Stage IA - IIA NED	• See Common Follow-up Recommendations For All Patients[s] • H&P (with emphasis on nodes and skin) ➤ every 3-12 mo for 5 y, then ➤ annually as clinically indicated • Routine radiologic imaging to screen for asymptomatic recurrent/metastatic disease is not recommended	Persistent disease or true local scar recurrence[t,u] → (See ME-7) Local, satellite, and/or in-transit recurrence[u,v] → (See ME-7)
Stage IIB - IV NED	• See Common Follow-up Recommendations For All Patients[s] • H&P (with emphasis on nodes and skin) ➤ every 3-6 mo for 2 y, then ➤ every 3-12 mo for 3 y, then ➤ annually as clinically indicated • Consider chest x-ray, CT and/or PET/CT scans every 6-12 mo to screen for recurrent/metastatic disease (category 2B) • Consider brain MRI annually (category 2B) • Routine radiologic imaging to screen for asymptomatic recurrent/metastatic disease is not recommended after 5 years	Nodal recurrence[u] → (See ME-8) Distant recurrence[u] → (See ME-9)

[s]Common Follow-up Recommendations For All Patients:
- At least annual skin exam for life
- Educate patient in monthly self skin exam (and monthly self lymph node exam for Stage IA - IV NED)
- Routine blood tests are not recommended
- Radiologic imaging is indicated to investigate specific signs or symptoms

Follow-up schedule influenced by risk of recurrence, prior primary melanoma, and family history of melanoma, and includes other factors, such as atypical moles/dysplastic nevi, and patient anxiety.

[t]Persistent disease or true local scar recurrence is defined by presence of in situ and/or radial growth phase.
[u]Initial clinical recurrence should be confirmed pathologically whenever possible. Obtain tissue for genetic analysis if relevant to eligibility for participation in a clinical trial.
[v]Local, satellite recurrence without in situ or radial growth phase, with deep dermal or subcutaneous fat recurrence within the melanoma scar or satellite metastasis adjacent to the melanoma scar.

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- Recurrence

  - signs and symptoms: local swelling, itching, new lesions, enlarged LN, GI, CNS and pulmonary symptoms

  - nodal: FNA; if + requires metastatic work-up and CLND

  - local and regional:

    tumor appears within 5cm radius of primary excision site

    surgical resection with histologically clear margins

    high risk of having distant mets; resection does not always achieve long-term disease free survival

Melanoma

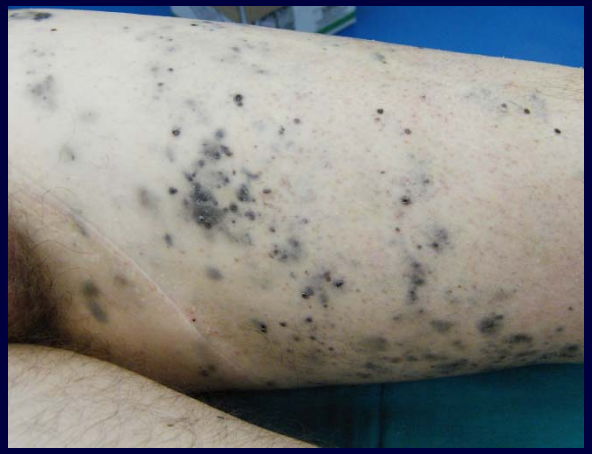
- Recurrence

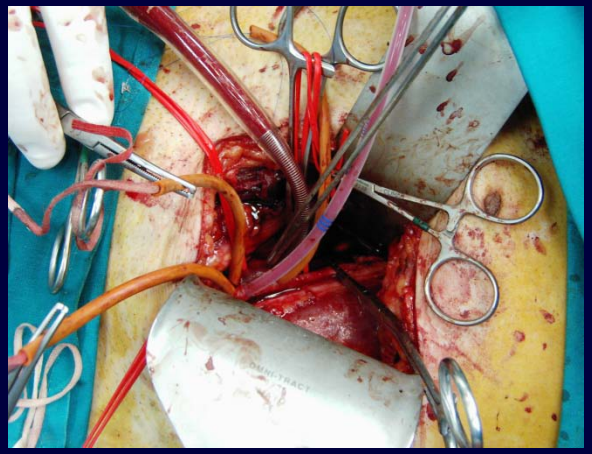
  - multiple recurrences on limb: isolated hyperthermic limb perfusion (IHLP)

    - isolate vein and artery; apply tourniquet; infuse chemotherapeutic agents (L-phenylalanine mustard, IL-2)

    - complete response in approx. 10-15%

    - recommended for patients with established in-transit metastasis





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- In-Transit Metastasis:

- foci of tumor cells that have spread via lymphatics but has not reached LNs and present as lesions on skin and subcutaneous tissue

- can be extensive metastasis; some lesions maybe excised; recurrence is common

- treatment:

IHLP

radiation - difficult to define field, but maybe effective in combination with other therapy

laser ablation - effective for dermal disease

immunotherapy – BCG, interferon-α, imiquimod (Aldara)

- 80% regress after injection

- erythema, edema, ulceration

Melanoma

- Distant Metastasis:

  - MC sites included brain, lung, liver, bone

  - may appear at multiple sites simultaneously; palliative systemic therapy

  - single metastasis; evaluate for resection; estimated long-term disease free survival 10-20%
    - complete staging: CT, PET
    - prognosis related to number of metastatic lesions and interval between primary therapy and recurrence

Melanoma

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