A Hair Past A Freckle

a review of current melanoma practices

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STAAB SYMPOSIUM

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No Disclosures

Let's Talk Numbers

Over 75k new cases in US in 2012

5th most common cancer in men and women in the US

APC of HNMM increased by 2.4% from 1987 to 2009

Life-time risk is 1 in 75

2% of cancer deaths in the US

Leading cause of death among cutaneous malignancies

- Number of deaths from CMM has increased 2% per year since 1960 in US

More Numbers

More common in men 2:1

Median age of diagnosis is 55 years

More common in Caucasians 10:1

Head and neck is 9% of body area but accounts for nearly a third of melanoma cases

Risk Factors

UV-A and UV-B lead to higher relative risks

-including tanning beds

Genetics

-familial atypical mole-melanoma syndrome

-xeroderma pigmentosum

Immunosuppression

Fair-complexion

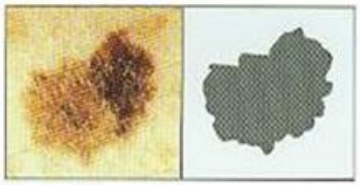
-blond and red hair

Presence of large number of melanocytic nevi

Viagra-lifestyle

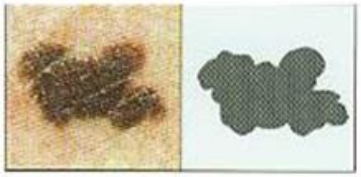
Physical Exam

A



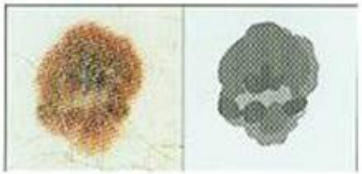
ASSYMETRY:
-If you were to fold it in half, the two sides wouldn't match up.

B



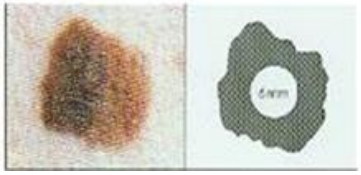
BORDER IRREGULARITY:
-Jagged or blurred edges rather than smooth, continuous line.

C



COLOR VARIATION or **C**HANGE:
-Two or more different colors are present.
-A mole has been changing in any way.

D



DIAMETER:
-Any sudden or continuing growth
-Any mole larger than 6mm (pencil-top eraser)

E Evolving = changing in shape, color, size

*Image from desertmap.org

Biopsy

If in doubt, cut it out!

Do not shave!

- 10% are amelanotic and resemble basal cell
- Involve some normal skin

Include subcutaneous fat for complete evaluation of depth

Consider photography

Ulceration

Up-stages melanoma

Prognosis

- Lowers over-all survival

Stains

S-100

HMB-45

H&E

Melan-A

Subtypes

Superficial spreading	• 75% • Typically from pre-existing nevus
Nodular	• 15%
Lentigo maligna	• 10%
Desmoplastic	• 1% • Associated with perineural invasion
Acral lentiginous	• 2%
Mucosal?	• 1%

Head & Neck Mucosal Melanoma

1 – 2% of all melanomas
- Over 50% in head and neck region

Differences compared with cutaneous melanoma
- Usually older patients (past 6th decade of life)
- Genetic mutations

More than 50% of HNMM within the nasal cavity
- Nasal obstruction and epistaxis are the most common presenting symptoms

Depth is not necessary
- Has little or no prognostic impact

HNMM, cont.

Kerr and Lewis showed 100% recurrence and / or mets within 25 months

- 5-year survival is less than 15%

Pharynx and larynx are endodermal in origin so less commonly affected

Must rule out ocular and cutaneous disease!

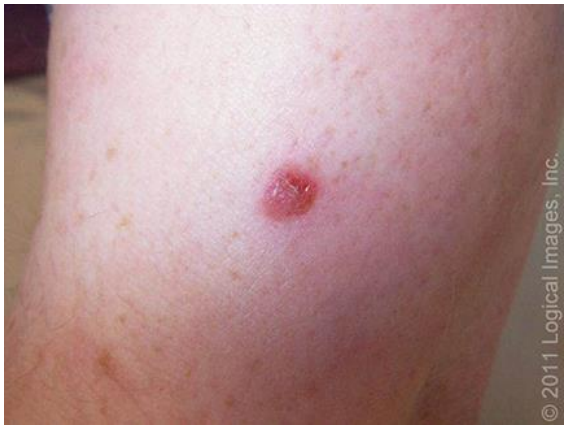
Amelanotic melanoma

Continue to express microphthalmia-associated transcription factor and tyrosinase

Most likely another subtype of melanoma instead of a de-differentiated melanoma

Lower OS if mucosal amelanotic lesion

Picture from UpToDate



Occult Disease

26% of unknowns involve parotid

Survival similar to primary with nodal mets

- 31 months compared with 37.9 months

Resembles cutaneous melanoma genetically

- 52.3% had mutated BRAF
- 28.6% had NRAS mutation
- No KIT mutations

Genetics

Cutaneous melanomas

- BRAF (serine / threonine kinase) mutations are frequent
- V600E codon is the most common

Mucosal melanomas

- BRAF mutations uncommon
- 15 – 39% have mutations / amplification of KIT (receptor tyrosine kinase)

Staging

Clark levels

Breslow thickness

TNM

Clark Levels

Level I = only the epidermis (in situ); not an invasive lesion

Level II = invasion into papillary dermis but does not reach papillary-reticular dermal interface

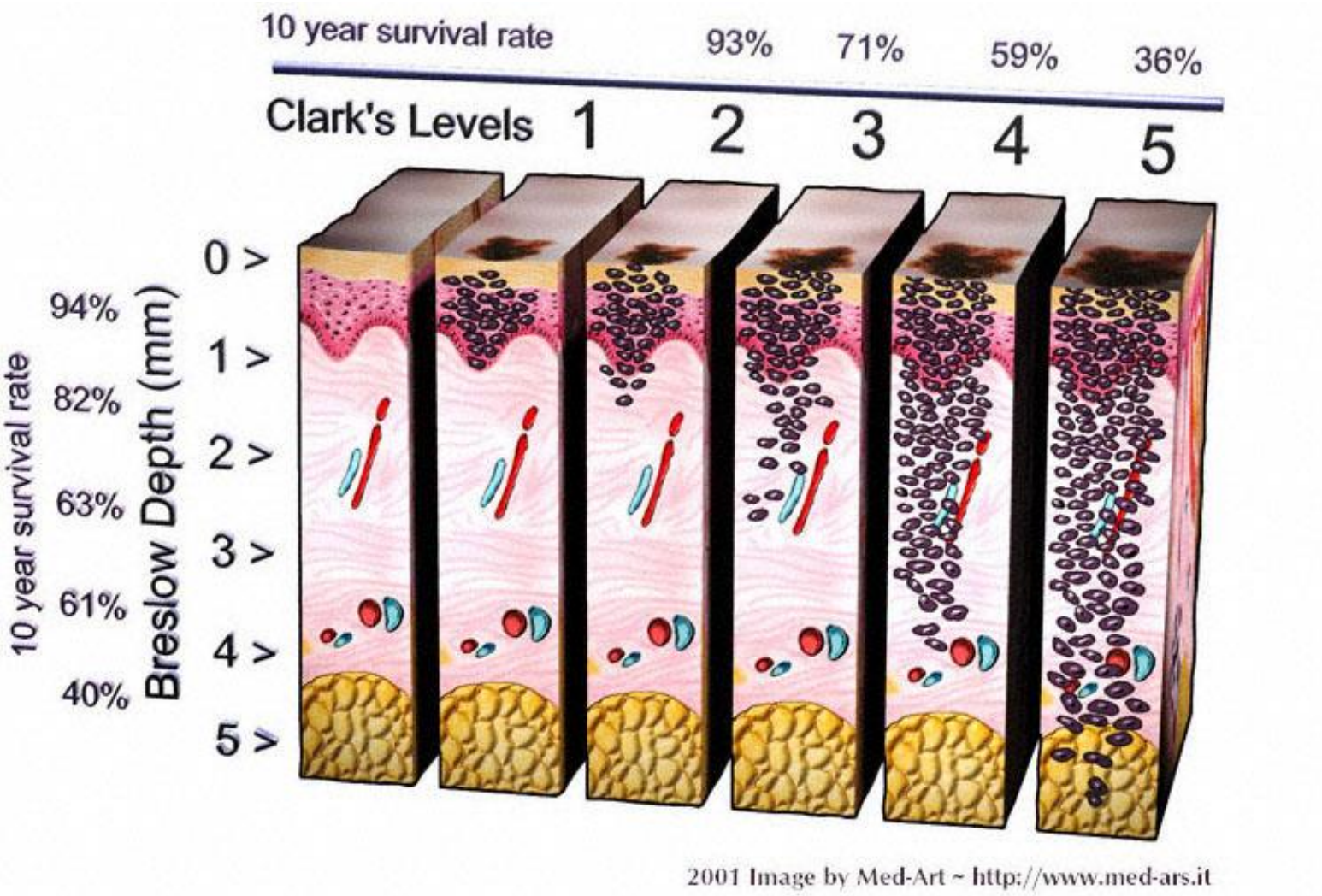
Level III = invasion fills and expands the papillary dermis but does not penetrate the reticular dermis

Level IV = invasion into reticular dermis but not the subcutaneous tissue

Level V = invasion through the reticular dermis into the subcutaneous tissue

Breslow Thickness

Stage	Depth
Stage I	0 – 0.75 mm
Stage II	0.76 – 1.5 mm
Stage III	1.51 – 2.25 mm
Stage IV	2.26 – 3 mm
Stage V	3 mm and larger


10 year survival rate
93%
71%
59%
36%
Clark's Levels
1
2
3
4
5
10 year survival rate
94%
82%
63%
61%
40%
Breslow Depth (mm)
0 >
1 >
2 >
3 >
4 >
5 >
2001 Image by Med-Art ~ http://www.med-ars.it

T N M, AJCC 2010

Stage	Depth
Stage I	0 – 0.75 mm
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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

TNM Staging, AJCC 7th ed,

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	> N1	M0
Stage IV	Any T	Any N	M1

American Joint Committee on Cancer (AJCC)
TNM Staging System for Mucosal Melanoma of the Head and Neck
(7th ed., 2010)

Primary Tumor (T)

T3	Mucosal disease
T4a	Moderately advanced disease Tumor involving deep soft tissue, cartilage, bone, or overlying skin
T4b	Very advanced disease Tumor involving brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases present

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Anatomic Stage/Prognostic Groups

Stage III	T3	N0	M0
Stage IVA	T4a	N0	M0
	T3-T4a	N1	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Histologic Grade (G)

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

PET Scan in Staging

University of Nebraska study in 2013

- No benefit in staging if clinically node negative neck!
- 165 patients: 8 false positives, 2 false negatives

Study from Germany 2012

- 59 patients
- 50% of patients had more lymph nodes involved than suspected
- Suspicious nodes often proved to be benign

Treatment, surgery

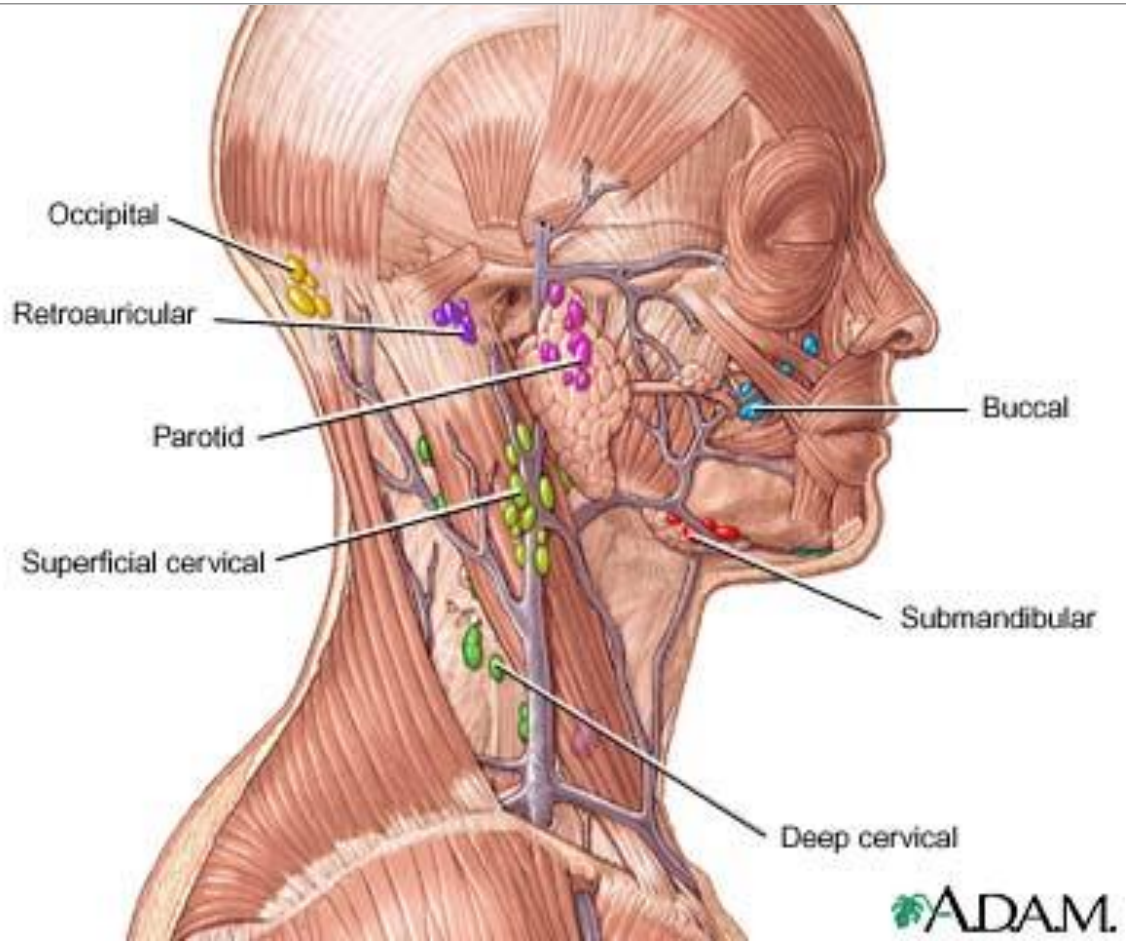
Wide margins
- In situ, 0.5 cm
- < 1 mm, 1 cm
- 1.01 – 2 mm, 1 – 2 cm
- 2.01 – 4 mm, 2 cm
- > 4 mm, > 2 cm

Sentinel lymph nodes

Neck dissection

Reconstruction

SLN Biopsies



SLN Biopsies

Indicated if melanoma $\geq$ 1 mm (T2)

Consider if 0.75 – 1 mm but adverse histology

- Ulceration, high mitotic rate, lymphovascular invasion

False negative rate ranges from 2 – 6%

- Regional recurrences within 6 months
- OS and RFS not significantly different than SLN + patients.

Over-all survival is significantly impacted if SLN +

- 5-year survival drops from 91.2% to 48.7%

Sunbelt Melanoma Trial (405 patients, 79 centers) showed that SLN + important in scalp lesions but not as much in non-scalp lesions

SPECT/CT may be beneficial just prior to SLN biopsy

Neck Dissections

Even with ND, nearly a third have locoregional recurrence and 60% eventually develop distant mets

No lymphadenectomy indicated for nasal / paranasal melanoma for N0 disease

END indicated if non-nasal / paranasal MM

- Oral cavity much more likely to involve lymph nodes

Reconstruction

Use permanent sectioning

Delay reconstruction until pathology margins clear

Consider skin graft as does not distort previous margins.

Treatment, radiation

RT can be done but not real effective

- OS after radiation to tumor bed rose to 56% from 43%
- No associated regional control even after neck dissection

With mucosal melanomas, higher local recurrence if no post-operative RT given

- But even with RT, approximately 25% recur regionally or distantly

Can be photons, protons, carbon ions, or neutrons

Treatment, medicines

Systemic therapy for adjuvant tx (after locoregional therapy) or distant mets

Single agent

Multiple agents

Consider surgery if partial or complete response of mets

NCCN Preferred Regimens

Ipilimumab

Vemurafenib

Dabrafenib

Clinical trial

High-dose IL-2

Chemotherapy (other regimens)

Dacarbazine

Temozolomide

Paclitaxel

Combo

- Dacarbazine or Temozolomide + cisplatin or vinblastine
- With or without IL-2 or interferon
- Paclitaxel + carboplatin

Biotherapy

Interferon-a-2b

- Both immunostimulatory and anti-angiogenic
- Enhances phagocytosis and free radical production in macropharges; increases activity of natural killer cells

Interleukin-2

- Both immunostimulatory and anti-tumor

Bacillus Calmette-Guerin (BCG)

- Given intra-lesional

Immunotherapeutic agents

c-KIT mutation or amplification

- Exon 9, 11, 13, 17
- Imatinib and other tyrosine kinase inhibitors
- Usually mucosal lesions

BRAF V600E mutation

- Vemurafenib
- Usually cutaneous lesions

Follow-up

Stage IA – IIA: every 6-12 months for 5 years then annually; no radiologic imaging recommended

Stage IIB – IV: every 3 – 6 months for 2 years then every 3 – 12 months for 3 years then annually

- CXR, CT, PET every 4 – 12 months
- Consider brain MRI annually
- No imaging if NED after 5 years

Routine blood tests not recommended

Thank you

Questions?