Melanoma Underwriting

Presented at 2018 AHOU Conference

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MELANOMA EPIDEMIOLOGY

- 70-80,000 American cases annually
- Majority are in situ or thin
- > 20% are diagnosed ≤ age 45
- 8-9,000 melanoma deaths annually
- Melanoma mortality is rising
- 1,000,000 melanoma survivors craving coverage

Varieties of Invasive Melanoma

- **Superficial-spreading** (SSM) - 70-75%
- **Nodular** (NM) - 10-15%
- **Lentigo maligna melanoma** (LMM) - 10-15%,
- **Acral lentiginous** (ALM) - 3-5%, plantar (on soles) and subungual (under fingernails)
- **Desmoplastic, spitzoid, malignant Spitz nevus, malignant blue nevus, et al** - *be sure to research these rarer cases carefully before taking action!*

Acral vs. Acral Lentiginous

- Acral refers to the site of tumor
- Acral lentiginous is a pathological subtype
- 35% of foot melanomas are SSMs
- ALM is the #1 melanoma in non-Caucasians
- ALM has a worse prognosis solely (no pun) because of delayed diagnosis

Prognostic Considerations in Melanoma

“For clinically localized primary melanoma, sentinel lymph node biopsy remains the strongest predictor of recurrence and death”*

Georgina V. Long, MB, PhD
Melanoma Institute, Australia
NEJM. 378(2018):679[letter]

* No clinically evident (vs. pathologically determined) findings suggesting metastasis

Sentinel Lymph Node (SLN) Biopsy (Bx)

- SLN = 1st node to receive lymphatic drainage
- Pinpointed by lymphoscintigraphy
- If Bx negative, metastases to any LN are highly unlikely
- 15% are false-negative
- Non-thin SLN+ = 51% 10-yr DFS
- Thin SLN+ = 81% 10-yr DFS…but done in < 10%
- No SLN Bx in non-thin = **RED FLAG**

(Breslow) Thickness
(measured in millimeters)

#1 Prognostic factor in localized melanoma when SLN Bx is negative or not done

4 subsets:

T1	**≤ 1.00 = thin**
T2	**1.1-2.0**
T3	**2.1-4.0**
T4	**> 4.0**

(Clark) Level of Invasion

Levels	Depth of Invasion
I	Confined to epidermis (in situ)
II	Upper papillary dermis
III	Lower papillary dermis
IV	Reticular dermis
V	Subcutaneous fat

What Matters about Level?

- ✓ Distinguishes radial vs. vertical growth phases
- ✓ Seldom independent prognostic marker after adjusting for measured thickness
- ✓ Critical exception: level III/IV thin melanoma

Growth Phase

Radial

- Mainly in situ and Level II
- No metastatic potential
- Excellent overall prognosis

Vertical

- Levels III, IV and V
- Disposed to eventual metastasis
- Survival decreases as level increases

Ulceration

- Defined as “full thickness interruption of epidermis without history of prior surgery or trauma”
- Major prognostic factor in localized melanoma
- Ulcerated thin melanoma is stage T1b (vs. T1a if not ulcerated)
- Mortality risk in ulcerated thin melanoma is the same as in non-ulcerated 1.01-2.00 mm lesion

Mitotic Activity

Tumor Cells Having "Sex"

- Expressed as mitoses per mm^2
- Significant = ≥ 1 mitosis/mm^2
- Thin + ≥ 1mitosis/mm^2 is now stage T1b
- **RED FLAG** in localized melanoma
- Poor interobserver agreement means mitotic activity status is prone to change on 2nd opinions

Lymphovascular Invasion (LVI)

- A/K/A “vascular invasion”
- Tumor cells in/adjacent to vascular lumen
- Independent risk factor, found to be as important as ulceration in most studies
- **RED FLAG** in localized melanoma

Host Immune Response

- May be brisk, non-brisk or none present
- Brisk response = tumor-infiltrating lymphocytes (TILs) abundantly present across base of tumor
- Brisk TIL response may induce regression
- Brisk = favorable prognostic factor in non-thin tumors
- No TIL response predicts for lymph node metastasis
- SLN Bx essential in these cases

The Truth about REGRESSION in THIN Melanoma

“Regression in melanoma is an immunologic process characterized by lymphocytic infiltration [TIL] causing the spontaneous disappearance of tumor cells.”

Jill C. Rubinstein, MD
Melanoma Center
Yale University School of Medicine
Cancer Medicine
5(2016):2832

Regression Realities

- ✓ Due to lack of a standardized definition and consensus objective criteria, regression is often not mentioned and rarely quantified in pathology reports.
- ✓ Significance depends on extent and context.
- ✓ Regression is insignificant (even potentially favorable) in **non-thin** melanoma.
- ✓ In level III/IV **thin** melanoma, extensive/complete regression is a **RED FLAG**

Microscopic Satellites

Adjacent tumor nests separated by normal tissue

- A/K/A satellitosis
- This is one type of metastasis
- **RED FLAG** for unfavorable prognosis
- As are **in-transit metastases**, which are similar but not separated by non-tumor tissue

"Patients with suboptimal pathology reports may be staged inadequately, managed poorly and they may ultimately experience an adverse clinical outcome."*

Richard A. Scolyer, MD
Melanoma Institute, Australia
American Journal of Surgical Pathology
37(2013):1797

***** ***In other words, die!***

How often are major pathological factors NOT MENTIONED on pathology reports?

- **Ulceration** – 8% to 43%
- **Mitotic Rate** – 10% to 47%
- **LVI** – 10% to 41%
- **Satellites** – 20% to 79%
- **Regression (thin only)** – 42% to 58%

In 2 studies, > 50% of path reports without mention of ulceration were found to have ulceration present based on 2nd opinions by experts!

It gets worse…

Ulceration Status	DSS* Hazard Ratio
Absent	1.0
Present	3.5
No mention	4.3

Take Home Message: when any key pathology factor is not specifically said to be either present or absent, never assume it was absent!

* disease-specific survival

Adjuvant Melanoma Therapy

"Head-Spinning Progress"

- Ipilimumab and nivolumab have robust antitumor effects in subsets of advanced and otherwise incurable melanoma
- With nivolumab, almost 50% alive at 48 months and there are 10-year (apparent) disease-free survivors
- This drug is now the standard of care in node-positive melanoma
- Way too soon to consider these cases in underwriting

Wolchok. NEJM. 377(2017):1345
Schuchter, NEJM. 377(2017):1888[editorial]

Thin Melanoma Realities

- ✓ Median time to recurrence overall is 6.5 years
- ✓ Median time to distant recurrence is 8.9 years
- ✓ ≤ 0.76 mm = 2/3rd of metastases first detected after 8 years
- ✓ Over 60% of thin melanoma deaths occur after 5 years
- ✓ 30% of brain metastases cases involve thin melanomas!

Is your current approach to thin melanoma consistent with these realities?

Latest major study on thin melanoma long-term survival…

Melanoma-Specific Survival (MSS)

6263 localized thin lesions; 17% died from melanoma

MSS (years)	Thickness (mm)		Difference
	≤ 0.8	0.9-1.0	
3	97.9%	94.9%	**3%**
5	96.2%	91.6%	**5%**
10	93.4%	81.1%	**12%**
20	85.7%	71.4%	**14%**

✓ Adjusted HR in ≥ 0.9-1.0 vs. ≤ 0.8 = 2.22 (1.63-3.04) p <.0001

✓ This is a bigger difference than in T1b vs. T1a

Lo. Annals of Surgical Oncology. E-published 1/12/18

Smartphones and Melanoma

- Smartphone apps to identify/monitor moles are widely used and heavily promoted as accurate (but most aren't).
- They create a *"false sense of security, delay diagnosis of a malignant lesion and ultimately harm the patient."*
- If you encounter this scenario, get the details and defer if the applicant is self-monitoring without involving an MD.

Zouridakis. "Mobile Health Technologies: Methods and Protocols." Chapter 30. Springer; New York, 2015:459-92

Maier. Journal of the European Academy of Dermatology and Venereology. 29(2015):663

Wolf. JAMA Dermatology. 149(2013):422

Why is 2nd opinion-seeking re: melanoma pathology reports rising?

Because of a common syndrome called CYA.

Melanoma misdiagnosis is a leading cause of cancer malpractice claims.

#1 nightmare scenario: a community pathologist diagnosing a melanoma as a benign mole.

Expert 2nd Opinions

Findings from various studies:

✓ 14%-27% had impactful differences in pathology analysis

✓ 8% changed diagnosis from in situ to invasive

✓ 22% to 24% had significant staging changes

✓ 5%-20% changed from melanoma to benign…or vice versa

✓ In the latest study, in situ and thin melanoma diagnoses are described as *"neither reproducible nor accurate"*

We must account for the results of all 2nd opinions, which may not be cited in the APS from the attending physician

Elmore. British Medical Journal. 357(2017):i2813

From the 2018 NB Critical Issues Survey, based on responses from 93 US insurers:

Do cancer calculators increase the risk of missing key factors on cancer cases?

Yes = 79%

Do cancer calculators promote the concept of machine-based underwriting?

Yes = 62%

BOTTOM LINE: Melanoma calculators are detrimental to the risk appraisal process and the best interests of our profession

10 reasons to get the pathology report when the applicant reports having a mole removed, in the not-too- distant past

1. Applicant does not specifically say it was benign
2. Applicant is ≥ age 60
3. Removed at the advice of a physician
4. Removed because of enlargement or color change
5. Symptomatic (itching, crusting, bleeding) lesion
6. Site was scalp, back, fingernail bed or foot
7. > 1 surgical procedure to excise mole
8. > 1 post-excision MD visit specifically regarding mole
9. Any treatment other than/in addition to excision
10. Excised within ± 60 days of application