CUTANEOUS MELANOMA
An Underwriting Primer

Hank George, FALU

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"*Melanomas are gram for gram the deadliest cancer in humans."*

Julie Anderson, MD
University of Connecticut Health Center
Clinics in Dermatology
30(2012):174

"The incidence of melanoma continues to increase dramatically… [and] *an individual loses an average of 20.4 years of potential life as a result of melanoma mortality, compared with 16.6 years for all malignancies."*

Samit Patrawala, MD
Emory University School of Medicine
Journal of the American Academy of Dermatology
74(2016):75

"The pathology report is critical to determining the management of patients with primary cutaneous melanoma… 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 of Australia
American Journal of Surgical Pathology
37(2013):1797

"Even after a period of 5 years free of disease, a patient cannot be considered cured, thus demonstrating the importance of continued follow-up".

Bernardo Balcalari, MD
Department of Dermatology
Valencia Institute of Oncology, Spain
European Journal of Dermatology
31(2021):192

"Although a few patients present with distant metastases at diagnosis, approximately one quarter to one third of all patients with melanoma will eventually experience recurrence and development of more advanced-stage disease"

Darshil J. Shah, MD
William Beaumont School of Medicine,
Royal Oak, Michigan
Mayo Clinic Proceedings
89(2014):504

This course is on cutaneous (skin) melanomas. Melanomas also arise on the mucous membranes, in the eyes and at other non-skin sites. Underwriters seldom see non-cutaneous primary melanomas.

How common is melanoma?

Overall, melanoma ranks as the 3rd most common cancer in America and Australia. [Scolyer-2, Welch]

- 95,800 in situ and 96,500 invasive melanomas are diagnosed each year in the US.
- The incidence increased from 7.9/100,00 to 25.4/100,000 since 1975.
- The incidence of in situ cases increased 50-fold over the same interval.
- The increase in incidence is due to heightened public awareness, greater scrutiny of high-risk individuals melanoma and better diagnostic tools such as dermoscopy.
- The median age at diagnosis is 60 and 20% are under age 45.

[Helvind, Scally, Schuchter, Siegel, Welch]

Are most melanomas detected while still localized?

Absolutely… 82% in the US are in situ or thin (1 mm or less in thickness). [Sperry]

In other recent studies, 31% to 48% were in situ, and 70% of invasive melanomas were thin.

This means most newly diagnosed melanomas in higher prevalence regions should be readily insurable.

[Geller, Han, Lott, Reed-2]

How significant is family history as a risk factor for melanoma?

There are rare highly melanoma-prone families with multiple melanoma cases over several generations.

Excluding these, 4 recent studies show that there is notably excess risk even if just one 1st-degree relative had melanoma:

Study	Relative Risk of Melanoma
Leeds	2.43
Swedish Women	2.13
Australian	1.91
Epigene-Qskin	1.61

[Kvaskoff-2, Newton-Bishop-2, Veierød, Vuong]

How are melanomas discovered?

Primarily by the patient or a family member, as well as during routine medical care, dermatologist visits for other skin problems and routine surveillance of high-risk individuals.

Are patient-detected melanomas worse risks?

Yes.

Dermatologists incidentally find 1/3rd of melanomas during non-referral patient visits. These lesions are more likely to be in situ or minimally invasive than those that motivate patients to see a dermatologist.

Bleeding, crusting, itching/pain, and/or progressive enlargement are more common in self-detected melanomas. These are all **RED FLAGS** for higher mortality risk melanoma.

Patient-discovered melanomas are more likely to be thicker, have less favorable pathologic features, and more apt to have already metastasized by the time they are diagnosed.

[Avilés-Isquierdo, Hanson, O'Shea, Shen, Watt]

Ideally, we should set a minimal interval in which medical records and pathology reports are required if an applicant went to a physician because of concern for these symptoms in a mole… even if he also says the mole was benign.

Are smartphones playing a larger role in melanoma detection?

Yes.

"While smartphones have been hailed as 'new clinical tools in oncology,' many experts remain cautious about the utility of the thousands of apps currently available, either free or at a small charge for the prevention, detection and management of cancer. It has also been suggested that apps for detecting cancers tend to lack scientific and specialty input."

A. P. Kassianos
Cambridge University
British Journal of Dermatology
172(2015):1507

Three studies have looked at this question with regard to melanoma:

- Wolf found that 3 of 4 apps identified 30% or more of melanomas as benign.
- Kassianos reported that none of the melanoma apps were validated for accuracy using established methods and discouraged colleagues from endorsing their use.

- Meier showed that 7 of 26 melanomas were identified to the patient as benign and concluded that smartphone apps were *"…insufficient to detect melanoma."*

It is likely that these apps will create a "false sense of security, delay diagnosis of a malignant lesion and ultimately harm the patient." [Zouridakis]

Does melanoma always arise from preexisting benign nevi (moles)?

No. In one study, only 30% did so. Even in a mole screening study, just 54% of melanomas were linked to a prior mole.

[Haenssle, Lin, Lipsker]

Melanomas arising from preexisting moles are more likely to be thin (≤ 1.00 mm in measured thickness).

[Argenziano, Haenssle]

Is it possible to accurately diagnose melanoma without a biopsy?

No – however, there are devices that enable dermatologists to distinguish between benign nevi and melanomas in many cases.

Dermoscopy amplifies a skin lesion such that dermatologists can detect 60%+ of probable melanomas while ruling out malignancy in the majority of benign moles. Dermoscopy is widely used in local dermatology practices, sometimes with computer-augmented image analysis. [Salerni]

Reflectance confocal microscopy (RCM) improves diagnostic sensitivity to the extent that only 4% of melanomas are missed. There are contexts wherein the incidences of false-positives and false-negatives are higher. Most of these patients are referred to experts in specialized melanoma centers.

[Carrera, Longo, Scope, Stanganelli]

There are also other ways in which moles are sometimes evaluated clinically before a decision is made about the need for a biopsy: [Rigel]

- Confocal scanning laser microscopy
- Optical coherence tomography
- Ultrasound
- Electrical bioimpedance

Bottom lines:

- Because of these devices, many benign nevi are no longer subjected to biopsy.

- Therefore, the % of mole biopsies revealing an situ or invasive melanoma is increasing.
- If a mole is said to be clinically benign on this basis, I am comfortable accepting the case in the absence of other **RED FLAGS** such as: prior melanoma; many dysplastic nevi; positive family history; mole on scalp, soles, under finger/toe nails; with mole-related symptoms; etc.
- However, if I have any concerns I postpone for 1 year and reconsider thereafter if the mole has been re-examined and still said to be benign or a biopsy has been done in the interim.

What methods are used to do a mole biopsy?

The ideal approach is to remove the entire lesion. This is called an excisional biopsy. In some cases where melanoma is present, further surgery is needed to assure complete removal of all tumor cells.

Partial (incisional) biopsy techniques extract part of the lesion. Nearly all of these procedures are either punch or shave biopsies, the latter of which may be superficial or more extensive (scoop/saucerization). If melanoma is diagnosed, further surgery must be done to excise any known or potential residual melanoma.

- Partial biopsies are often done when the likelihood of melanoma is lower or the mole is located in a cosmetically sensitive area.
- They may also result in misdiagnoses, most importantly false-negative results. This is far more common in punch biopsies than shave biopsies.

[Egnatios, Farberg, Marsch, Ng, Scolyer-2, Zager]

Why is delayed post-biopsy surgery a RED FLAG?

Most routine second (post-biopsy) procedures are done within weeks of the biopsy.

When additional surgical procedures are delayed, the reason is usually local recurrence or the finding of cutaneous metastases (called satellites or in-transit metastases - see further on for details).

Over half of local melanoma recurrences occur within 1 year of the biopsy diagnosis.

[Bolshinsky, Gilgren, Grotz-2, Ivan, Mills, Rockberg, Scally, Synder]

What is meant by WLE (wide local excision)?

This is the term for the surgical procedure done:

1. After a melanoma diagnosis is made using a partial biopsy
2. After an excisional biopsy is done to assure that there are adequate surgical margins of melanoma-free normal tissue surrounding the tumor

If there is no further treatment given or advised after a WLE, this favors a diagnosis of localized melanoma.

However, WLE is also often done palliatively in cases with regional and distant metastases. Therefore, any additional intervention besides WLE is a **RED FLAG**.

[Pasquali-1, Thompson-1]

Is residual melanoma ever still present after doing a proper WLE?

Yes – but rarely (< 4%).

On those occasions when residual melanoma persists after a WLE, 5-year mortality is significantly worse (64%) as compared to when WLE totally removes all of the melanoma (88%). [Hocevar]

Should we see pathology reports on ALL surgical procedures, regardless of when they occur?

Yes.

I think we should see <u>every</u> path report in <u>every</u> cancer case, with the <u>sole</u> exception of (most) basal cell carcinomas.

However, if it is clearly stated in the physician's records that a 2nd surgery was done solely to assure complete tumor excision and that no residual melanoma was present, we can accept most of these, provided:

1. They are done <u>within</u> <u>close</u> <u>proximity</u> to the biopsy, which means they have inadequate margins (not enough tumor-free tissue between the melanoma and the edge of the biopsy.
2. Margins are adequate; inadequate margins is a **RED FLAG** for both recurrence and higher mortality
3. There are no suspicious extenuating circumstances such as further testing (X-ray, scanning procedures), intensive follow-up, any form of additional treatment or patient referral to melanoma specialists.

If scans or other additional tests are done, we must know the results – ideally, by reviewing the radiology report.

One compelling reason: in a 2016 study, 56% of patients said to be "clinically free of metastases" had positive CT/PET scans!

This high percentage of occult, clinically silent metastases is due to the fact that CT/PET scans are done mainly in cases with high-risk features.

[Danielsen, Gerschenwald]

What is a pseudomelanoma?

Partial biopsies may lead to regrowth of benign nevi. These so-called “regenerating nevi” often have one or more malignant-appearing pathological features and are therefore at risk for being misdiagnosed as melanoma by less-experienced pathologists. [Scolyer-2]

Melanoma Pathology Report Analysis

"For patients presenting with a primary cutaneous melanoma, an accurate and comprehensive histopathology report is essential for staging, to determine appropriate treatment and provide a reliable estimate of prognosis."

Maarten G. Niebling
Melanoma Institute, Sydney
Annals of Surgical Oncology
21(2014):2245

American, Australian and British pathologists have set official criteria for expected content of all melanoma pathology reports. There are some differences; however, they largely agree on the most key components.

One important exception is regression, which only matters to us in thin melanomas and will be covered separately further on.

What are the pathological factors on which there is a consensus that they must be addressed in all path reports?

- Breslow thickness
- Ulceration
- Mitotic rate
- Lymphovascular invasion
- Pathological stage
- Tumor location
- In-transit and satellite skin metastases
- Sentinel lymph node status

[Scolyer-2]

What can we say about the impact of age and gender?

- Melanoma can occur at any age.
- It is rare under age 18, and prevalence increases with age thereafter.
- In a 70,891-case American database, patients diagnosed under age 45 had 70% lower mortality risk than those discovered later in life.
- Men have a somewhat worse overall prognosis, due in part to females having tumors more commonly at lower risk sites.

[Yang]

What is measured (Breslow) thickness?

Tumor thickness is measured in millimeters and fractions thereof. It is a fairly easy determination for experienced pathologists.

It was introduced by Australian melanoma-ologist Arthur Breslow.

Thickness at the time of diagnosis is the #1 prognostic risk factor in localized, metastasis-free melanoma.

[Cockrell, Ivan]

How do mortality risk and survival rates correlate with thickness?

Using data from the abovementioned 70,891-patient American database study [Yang], these are rather typical 5-year mortality hazard ratios by subsets of thickness:

Thickness (mm)	Mortality HR
≤ 1.00 (thin)	1.00
1.00-2.00	1.65
2.01-4.00	2.35
> 4.00	2.96

A major Australian 10-year study reported these univariate survival rates using somewhat different thickness subsets: [Baade-1]

Thickness (mm)	10-Year Survival
≤ 0.50	99.0%
0.50-1.00	96.2%
1.01-1.50	88.3%
1.51-2.00	80.3%
2.01-4.00	70.8%
> 4.00	61.4%

As a rule of thumb: the thicker the melanoma, the lower the probability of disease-free survival.

What is level of invasion?

Level of invasion is the extent to which a melanoma invades the layers of the skin.

It was first identified by Wallace Clark at the University of Pennsylvania's Pigmented Lesion Clinic and is sometimes referred to as Clark Level.

Prior to the advent of widespread embrace of measured thickness, level of invasion was considered the #1 mortality predictor in localized melanoma.

What are the 5 levels of invasion?

Level I Confined to epidermis (melanoma in situ)
Level II Present in the papillary (upper) dermis
Level III Filling the papillary dermis
Level IV Present in the reticular (lower) dermis
Level V Extending into the subcutaneous fat

How do survival rates compare based on level of invasion?

These data are from the aforementioned Australian 10-year study. [Baade-1]

Level	10-Year Survival
II	98.5%
III	92.7%
IV	80.3%
V	60.7%

What else is important about level of invasion?

- Unlike thickness, there is a significant incidence of disagreement between expert dermatopathologists when assessing level of invasion.
- Level is seldom used by dermatopathologists in the assessment of prognosis because most studies show that it is insignificant after adjustment for measured thickness.
- If thickness is not cited (a rare occurrence), level is used as a surrogate for prognostic assessment.
- Level of invasion is an important insurability consideration in specific subsets of thin melanoma; this is covered further on.

[Cockrell, Ivan, Scolyer-2]

What is important about melanoma in situ (MIS)?

- Level I cutaneous melanoma and lentigo maligna (LM) are b both melanomas-in situ.
- MIS was once thought to be a precursor of invasive melanoma. Recent evidence suggests this not true.
- MIS is more likely to be detected by a physician than by a patient.
- A substantial (and increasing) portion of newly diagnosed melanomas are in situ.
- This increase is due in part to skittish dermatologists concerned about malpractice and thus doing biopsies on pigmented lesions with a low index of suspicion for malignancy.
- In situ melanoma may also be managed with topical imiquimod in lieu of excision.
- MIS is the only melanoma that does not “officially” require protracted follow-up. However, most patients are advised to have periodic skin examinations.

[Anderson, Jancin, Mooi, Reed-1, Tzellos, Walls]

Does a patient with a prior invasive melanoma have any increased mortality risk if he is subsequently diagnosed with melanoma in situ?

Not for mortality due to melanoma. [Youlden-2]

Does MIS confer any increased extra mortality?

Strictly speaking, it cannot.

However...in a 37,210-case study, 1.1% of patients “diagnosed” with MIS died of melanoma within 10 years. [Landow]

The explanation for this incongruity is a pathologist error.

Rarely, melanomas diagnosed as in situ by local pathologists have tiny clusters of tumor cells within the papillary dermis. These clusters may acquire the somatic gene changes needed to progress further and eventually metastasize. [Drabeni]

But the point is that they should not have been diagnosed as in situ!

Is there an increased risk of 2nd cancers in MIS patients?

Yes, revealed for the first time in a 2019 study.

Kimlin followed 39,872 Australian MIS patients. The risk of a 2nd neoplasm was only significant under age 50. After 10.6 years follow-up, there were elevated SIRs (standardized incidence ratios) for 4 malignancies in those age 50 or younger:

	SIR
Myeloma	1.87
Thyroid	1.82
Prostate	1.55
Colon/Rectum	1.30

These findings justify using a questionnaire in all MIS cases.

What is ulceration?

Ulceration is defined as full-thickness interruption of the epidermis by the melanoma without a history of prior surgery or trauma to the site, accompanied by reactive changes such as inflammation.

What are the implications of ulceration?

- Its presence directly impacts tumor staging adversely; in the T-N-M system, the tumor is in the “b” category (vs. “a” without ulceration).
- The measured extent of ulceration affects prognosis, but this is rarely noted on pathology reports.
- Ulceration is independently associated with excess mortality in nearly every study; most experts consider ulceration second only to thickness as a prognostic marker.

[Bønnelykke-Behrndtz-2, In’t Hout]

What is the magnitude of its impact on mortality?

In the aforementioned 70,891-case study, ulceration’s presence increased multivariate-adjusted mortality 59% overall. [Yang]

In the previously cited Australian 10-year mortality study, 71% of subjects with ulceration and 96% of those without it were alive at the end of the first decade. [Baade-1]

What is pseudo-ulceration?

What appears to be ulceration is sometimes due to epidermal trauma from surgery. This is most common in specimens from 2nd surgical procedures done after a partial or excisional biopsy. It has no mortality significance.

Pseudo-ulceration is sometimes attributed to the tumor by less-experienced pathologists. This harmless scenario can only be identified if a second 2nd expert opinion is procured.

[Bønnelykke-Behrndtz-1, Ivan, Scolyer-2]

What is mitotic rate?

It is the preferred method for quantifying the extent of mitotic (cell division) activity, as seen by the pathologist. [Shen]

- The mitotic rate is reported as the number of mitoses per mm^2.
- If no mitoses are seen, this should be cited as a rate of 0/mm^2, but the comment “no mitoses/mitotic activity is present” is often made instead.
- In the most common subtype of melanoma – superficial-spreading – a mitotic rate ≥ 1/mm^2 is associated with twice the melanoma growth rate, which means that a high mitotic rate is a marker for a more aggressive tumor.
- Interobserver agreement is poor, which means the mitotic rate is prone to being changed on 2nd opinions.

Previously, mitotic activity was reported as number of mitoses seen per 10 high-powered microscopic fields (10 HPF).

The official conversion rate pathologists use when the old approach is cited on a path report is 4 mitoses per HPF = 1 mitosis per mm^2.

One recent study found that the ideal approach is 10/HPF = 1/mm^2. This has not been adequately vetted as yet, so we use the official criterion of 4/HPF.

My approach is:

1. If the pathologist reports at least 4 mitoses per HPF, we consider this equivalent to a rate ≥ 1/mm^2.
2. If the pathologist simply notes that mitoses are present without any quantifying language, consider this also equivalent to a rate ≥ 1/mm^2.
3. Ignore reference to “scattered” or “occasional” mitoses/mitotic figures.

[Balin, Betti, Burton-3, Garbe-2, Scolyer-2]

Are mitoses ever cited on benign nevus path reports?

Yes. The rate varies from 17% to 43% of path reports, depending on the immunohistochemical tests done by the pathologist.

There is no consensus on the implications of mitoses in benign lesions. From my perspective, mitoses in ostensibly benign nevi can be ignored if the lesion has no other features suggestive of malignancy.

[Glatz, Litzner]

How does the mitotic rate impact mortality?

A Swedish study of 4,237 stage 1 and 2 melanoma patients looked at the melanoma-specific mortality hazard ratio based on mitotic rate: [Eriksson-3]

Mitotic Rate	Mortality HR
0/mm^2	1.00
1-5/mm^2	2.25
6-10/mm^2	2.34
> 10/mm^2	2.64

Notice that all positive mitotic rates at least doubled the mortality risk.

In a smaller 2021 study, recurrence-free survival (RFS) decreased as mitotic rates increased: [Tas-2]

Mitotic Rate	RFS
0-1.0	85.2%
1.1-4.9	60.8%
5.0-9.9	49.6%
10.0+	40.0%

Which other prognostic factors are associated with a very high (≥ 10/mm^2) mitotic rate?

These are the comorbid findings encountered in this context. All are relative or absolute unfavorable prognostic factors. [Shen]

- Level of invasion IV or V
- Nodular melanoma (NM) subtype
- Amelanotic (no pigmentation present) melanoma
- Ulceration

What is lymphovascular Invasion (LVI)?

It is the presence of tumor cells within or adjacent to blood or lymphatic vessels. It should always be cited as either present or absent on path reports.

LVI is also a major risk factor in many other cancers. In melanoma, it is consistent with an aggressive tumor and a prerequisite for distant metastases.

[Donizy, Egger-6, Feldmeyer, Ivan]

How does it affect prognosis?

In one study, LVI was present in 43% of melanomas, and the risk of 1st metastases within 10 years doubled (65%) compared to those without LVI.

It is generally considered a “marker of poor prognosis” and independently predictive of lower disease-free survival in most studies.

[Maurichi, Xu, Yun]

What does “growth phase” signify?

The most common kind of melanoma is the superficial spreading melanoma (SSM). It starts growing horizontally in the upper portion of the dermis, which is level II. This is called the radial growth phase (RGP). Metastasis does not happen in the RGP.

The vertical growth phase (VPG) typically begins in level III but there are some at level II. Now the malignant melanocytes have acquired the capacity for deep dermal invasion (levels IV, V and the underlying fat) and metastasis.

[Ivan, Kosary, Xu]

Is growth phase used for determining insurability?

No.

It is not an independent risk predictor. Its impact is accounted for by thickness and tumor stage.

The exception would be VGP at level II. When this happens, the case should be underwritten as level III. [Eguchi]

Perineural Invasion (PNI)

Perineural invasion (PNI) is defined as the presence of tumor cells along the sides of nerves and/or inside the nerve sheath.

It makes curative resection with adequate margins difficult. And the residual melanoma cells in or around nerves may lead to recurrence, extensive local area invasion and metastasis. [Zhang].

When cited on the pathology report, the risk of metastases to regional and distant sites is significantly increased. [Wainstein]

The only good news is that it occurs in just 4% of cases.

Tumor-infiltrating Lymphocytes (TIL)

Tumor-infiltrating lymphocytes can slow and even block melanoma progression.

- They should be collectively characterized by the pathologist as brisk (dense), non-brisk or absent.
- Their volume may also cited as few, moderate or marked.
- In a 2015 study, patients with a marked TIL response had barely 1/3rd the mortality risk of those without TILs. This was after full adjustment for other risk factors.
- They are thought by many to be the catalyst for a process called regression, which we will discuss in depth further on.
- In most, but not all, other recent studies, the absence of TILs is predictive of increased odds of lymph node metastases and/or poorer survival.

5-year survival in 14,000+ melanoma cases was 85% with brisk TIs vs. 76.5% when TILs were non-brisk.

The assessment and grading of TILs is challenging and experts often disagree with how they are characterized by local pathologists.

[Azimi, Ivan, Scolyer-2, Yong]

Are TILs important in underwriting?

Their impact on mortality remains a debated subject.

In the original 1989 study by Clark, TIL response was an independent mortality predictor. Those with no TIL response had a substantially lower 8-year survival.

Another study reported brisk TIL responses in 3.2% of 1,865 cases.

All of those with a brisk response survived 5 years.

In a 2015 Italian study, patients with a marked TIL response had barely 1/3rd the mortality risk of those without TILs. This was after full adjustment for other risk factors.

In most, but not all, other recent studies, the TIL response was significant for increased risk of lymph node metastases and/or poorer survival.

[Azimi, Burton-1, Clark, Cockrell, Fortes, Grotz-1, Mandala-1]

Should TIL response be considered in underwriting?

In localized melanoma > 1.00 mm thick, the body of evidence supports giving credit for a brisk/marked TIL response and, conversely, adding a debit when no TILs are present.

The only caveat is that TILs are not frequently mentioned on path reports and may only be noted on a 2nd opinion.

What are satellites?

Satellites are nests of melanoma cells at least 0.5 mm in diameter, separated from the primary tumor by >0.05mm of normal dermis. They are one of 2 forms of skin metastasis. The other is in-transit metastases.

They may be characterized as satellites (satellitosis) or microsatellites (microsatellitosis). The former are visible and the latter require microscopic examination of a biopsy specimen for detection.

Their incidence is approximately 4%.

Regardless of size, they are a highly unfavorable finding. In one study, melanoma specific survival decreased 76% compared to otherwise similar cases that did not have either kind of satellite lesions present.

[Ivan, Kumar, Riquelme-McLoughlin, Scolyer-2]

What are in-transit metastases (ITMs)?

They are cutaneous or subcutaneous tumor deposits between the primary melanoma and regional lymph nodes.

- There may be anywhere from 1 or hundreds of ITMs.
- They vary widely in size from < 1 mm to several centimeters wide.
- They may not be detected until after excision of the melanoma.
- Small isolated ITMs may be easily excised or ablated.
- More extensive deposits are difficult to treat and may require systemic immunotherapy or **RED FLAG** interventions like isolated limb perfusion.

- 50% to 75% of patients with ITMs have or will develop distant metastases.

[Grotz-2, Holtkamp, Olino, Patel, Pawlik, Thompson]

How do satellites and in-transit metastases differ?

Satellites are within 2 cm of the primary tumor and ITCs are found between 2 cm and the nearest lymph nodes.

From my perspective nearly all cases with either type of cutaneous metastasis are uninsurable.

The Conundrum: Missing Information on Path Reports

"There is variability between different institutions and pathologists regarding the routine reporting of histologic parameters in melanomas. Some of the reports contain minimal information (such as tumor thickness or the presence or absence of ulceration) while others are very comprehensive."

Doina Ivan, MD
MD Anderson Cancer Center, Houston
Archives of Pathology and Laboratory Medicine
135(2011):825

Experienced underwriters can certainly confirm this statement! We have seen incredibly brief path reports containing little useful information, and many fail to comment on essential risk predictors.

Which risk factors are most often unreported?

A comprehensive review of 1,124 cases reported the incidences of failure to mention 3 key risk factors. [Bello-2]

I have cited those 3 and 3 more below, then added in parentheses additional percentages of their omission noted in numerous other recent studies. I did that to underscore the magnitude of this knotty problem:

- Ulceration – 25% (8%, 13%, 18%, 28%, 37%, 43%)
- Mitotic Rate – 42% (10%, 41%, 47%)
- Regression (thin cases only) – 42% (49%, 58%)
- LVI – (10%, 37%, 41%)
- TILs – (51%)
- Satellites – (20%, 79%)

To clarify: failure to comment on ulceration happens in anywhere from 8% to 43% of cases whereas the absence of mention of LVI ranged from 10% to 41%... and so on.

In one study, even thickness was left off of 9% of path reports, seriously questioning the competence of the pathologists involved!

Moreover, in 2 studies over 50% of path reports without comment on ulceration were found to have ulceration present by experts giving 2nd opinions!

[Busam-1, Kosary, Matheson-1, Monshizadeh, Murali-1, Santillan]

How does failure to mention ulceration impact insurability?

Take note of the profound impact in these cases:

In the aforementioned 70,891-case study with 10-year data: [Yang]

Ulceration Status	Mortality Hazard Ratio
Absent	1.00
Present	1.59
Not Mentioned	**2.28**

Karakousis looked at mortality impact on thin melanomas with lymph node metastases:

Absent	1.00
Present	1.92
Not Mentioned	**1.64**

A third report found the following multivariate hazard ratios for disease-specific survival (DSS): [Bello-1]

Absent	1.00
Present	3.50
Not Mentioned	**4.30**

In a 2021 study with almost 14,000 cases: [Yong]

Absent	1.00
Present	2.14
Not Mentioned	**2.09**

Clearly, there is substantial excess mortality when no mention is made of ulceration on the pathology report.

How does unknown lymphovascular invasion (LVI) status affect survival?

In a 2021 study: [Yong]

LVI Status	Mortality Hazard Ratio
Absent	1.00
Present	1.58
Not Mentioned	**1.59**

If we had data on cases where pathologists failed to comment on mitotic rate and other key risk markers, those affected cases would also manifest mortality risks at least as high as when the variable is properly cited as “absent” or “present.”

Bottom Lines:

- It is a huge **RED FLAG** when key factors are not commented on in the pathology report.
- We cannot assume that failure to mention them equates to their absence, unless we have the report of a recent 2nd (expert) opinion)
- Additional debits are indicated to account for failure to mention ulceration and mitotic activity.

Melanoma Staging

What is the T-N-M classification system used in melanoma staging?

Please see Table 1.

Table 1: T-N-M Classification System For Cutaneous Melanoma Pathology

TX – Primary tumor cannot be assessed for various reasons
T0 – No evidence of primary tumor
Tis – Melanoma in situ
T1a – < 0.8 mm; no ulceration
T1b – < 0.8 + ulceration; 0.8-1.00
T2 – 1.01-2.0 mm; "a" (no ulceration); "b" (with ulceration)
T3 – 2.01-4.0 mm; a + b same as T2
T4 - > 4.0 mm; a + b same as T2

NX – Regional nodes cannot be assessed
N0 – No regional node metastasis detected
N1-3 – Depends on number of nodes, in-transit, satellite or microsatellite metastases and matted nodes; and whether node was detected by SLN biopsy or clinically

M0 – No distant metastases detected
M1a-b-c-d – Location of distant metastases

How does the T-N-M system correlate with clinical staging of melanoma?

Please see Table 2.

Table 2: Clinical Staging Based On T-N-M System

Stage	T-N-M Status
Tis	Melanoma in situ
IA	T1a-N0-M0 + T1b-N0-M0
IB	T2a-N0-M0 + T2b-N0-M0
IIA	T3a-N0-M0 + T3b-N0-M0
IIB	T4a-N0-M0
IIC	T4b-N0-M0
III	Any T + N1, N2 or N3 +M0
IV	Any T + Any N + M1a-c

Bottom Line: We need to know the stage of an invasive melanoma in order to properly underwrite. Fortunately, we can usually determine the stage by using the information on the path report.

Additional Prognostic Factors

What are the major subtypes of melanoma?

- Superficial spreading melanoma (SSM)
- Nodular melanoma (NM)
- Acral lentiginous melanoma (ALM)
- Lentigo maligna (LM); lentigo maligna melanoma (LMM)
- Desmoplastic melanoma (DM)

There are also rare melanomas such as malignant Spitz nevus, malignant blue nevus, nevoid melanoma, etc.

These cannot be properly underwritten without sufficient research into their characteristics and prognoses because some are highly aggressive and others are more readily insurable. [Singh]

What is significant about superficial spreading melanoma?

- It accounts for 60% of melanomas among Caucasians.
- It tends to arise at sites prone to intense, sporadic sun exposure, especially the extremities and trunk.
- It accounts for 90% of all melanomas in the radial growth phase.
- It accounts for most level II cases

The substantial majority of the **BEST CASE** melanomas will be SSMs. This said, both prognosis and insurability status always depend on all of the aforementioned mortality risk factors.

What do we need to know about nodular melanomas?

- They rarely exhibit a radial growth phase; thus, they are more aggressive than SSMs.
- Their average thickness is > 2 mm, and their average growth rate is 0.5 mm/month.
- 80% are at least level IV.
- Many are amelanotic.
- Over 90% have a mitotic rate ≥ 1/mm^2, and nearly half are ulcerated.
- 22%-27% have metastatic disease at diagnosis, including 5% with distant metastases.
- NMs represent 14% of melanomas and 43% of melanoma-related deaths.
- Nevertheless, nodular status, per se, is an independent risk factor in only a minority of studies after adjusting for other key pathology findings.
- This is because of the high percentage of thick, ulcerated, mitoses- and LVI-positive nodular melanoma.

Bottom line: Nodular melanomas should be underwritten conservatively, with an adequate waiting interval following excision before coverage is issued… even if the impact of other major risk factors is favorable.

[Allais, Cockrell, Egger-2, Mar, Marghoob, Warycha]

What is meant by "amelanotic"?

Amelanotic melanomas are devoid of melanin pigmentation. For this reason, they are often overlooked and thus mostly diagnosed at an advanced stage.

Up to 20% of melanomas in some studies have been amelanotic. They occur in all subtypes, but are most common in NM and DM.

After adjusting for risk factors, there is no independent excess mortality based on a melanoma being amelanotic, per se. [McClain-2, Thomas-2]

What is acral lentiginous melanoma (ALM)?

ALM is a pathologically distinct subtype of melanoma.

They are most often found on the soles of the feet and under the fingernails. But they do not account for all melanomas at these sites.

ALMs are not innately more aggressive tumors. Their higher mortality is attributable to delayed diagnosis, which is common overall and especially in darker-skinned individuals for whom melanoma is a rare form of cancer.

What are the key things we need to know about ALMs?

- They are rare in <u>all</u> ethnicities; however, they represent the vast majority of melanomas diagnosed in non-Caucasians and are even more prevalent in Southern Europeans than Northern Europeans.
- ALMs account for 75% and 45% of melanomas in African Americans and Asians respectively.
- Only 18% are in situ.
- The majority of ALMs are diagnosed at level IV.
- Over 70% arise on the soles, and the majority of the rest occur in the fingernail/toenail beds. These are called subungual melanomas.
- Over 35% of foot melanomas are SSMs. Thus, knowing the applicant had a melanoma on the foot does not ensure that it was an ALM.
- There is no significant difference between ALM and SSM in terms of mortality in stages I and II in most Western studies.
- However, the risk of death in stage III tumors is significantly higher in ALM than in SSM.

[Bello-1, Bradford-1, Duarte, Egger-4, Fernandez-Flores, Lino-Silva, Lv, Palicka, Phan]

A new Chinese study underscores the higher mortality with ALM in Asian patients. [Lv]

In 172 subjects, the average interval from a patient first noticing the tumor to a clinical diagnosis and surgery was > 30 months. Mean thickness was > 4.0 mm, and most were at

least stage III.

In this Chinese study, disease-free survival was 53% at 5 years and 27% after 10 years.

By contrast, in an Italian study of 244 Caucasian patients, median thickness was 0.8 mm, the recurrence rate was 20%, and the only significant mortality determinant was thickness. Survival rates were the same as those in SSM, after adjusting for thickness, etc. [Paolino]

Tan reported on a large cohort of patients with subungual melanomas.

- 66% were ALM and 25% were nodular.
- The most common site was the nail bed of the great toe.
- 9% were in situ, 78% were level IV/V, and median thickness was 3.2 mm.
- #1 prognostic factor was stage at diagnosis.
- Another subungual ALM study reported melanoma-specific survival rates of 56% and 48% after 5 and 10 years respectively.
- ALM is underwritten essentially the same as SSM for Caucasian patients.
- Underwriting non-Caucasians is tricky because a larger portion of cases will be uninsurable.
- Also, pathologists in Asia and other countries with predominantly non-Caucasian populations have little experience in analyzing melanoma biopsy specimens.

[Bello-1, Bradford-1, Duarte, Egger-4, Fernandez-Flores, Lino-Silva, Lv, Mejbel, Palicka, Phan]

What are lentigo maligna (LM) and lentigo maligna melanoma (LMM)?

Lentigo maligna (LM) is a in situ tumor. The word “melanoma” is added after lentigo maligna (LMM) when the tumor is invasive.

What are the risk factors for LM?

- Age > 60.
- Large number of actinic keratoses.
- Many small dark patches called lentigines.
- Prior basal and squamous cell carcinomas.
- Rare genetic conditions such as xeroderma pigmentosum.

What else do we need to know about LM?

- Almost 70% arise in the head/neck region, and 16% on the upper limbs.
- Mean age at diagnosis is 61; LM is rare under age 45.
- Delays in diagnosis are common; nearly half are > 1 centimeter in diameter (not thickness!) when first seen by a physician.
- It presents as a slowly enlarging pigmented patch.
- LM is a precursor of LMM. In fact the #1 risk factor for progression to invasive LMM is size

of LM precursor.

Surgical excision with Mohs surgery is the most common intervention. However, because of adverse cosmetic implications, many are treated in other ways, including radiation, laser ablation, cryotherapy, electro-destruction curettage and topical drugs.

Imiquimod is a topical drug used in LM and other skin cancers. In one 2016 study, there were no recurrences as long as 5 years after treatment. However, recurrences do occur as late as 15 years after some forms of treatment.

Radiation Treatment is a **YELLOW FLAG** because it is mainly used for recurrent disease.

"Wait-and see" is a **RED FLAG** because it is mainly resorted to when potentially life-threatening comorbidities are present.

10-year survival is 96%. The few deaths are due to pathologists missing a focus (tiny area) of invasive disease, as noted earlier with level I melanoma.

What is significant about LMM?

- Radiation and other nonsurgical procedures are **RED FLAGS** because they are often used in unresectable tumors.
- Recurrence rate is 5%, and most that have not metastasized are readily curable with additional local treatment.
- In a large study, mortality in LMM was 47% higher than in SSM, and it was almost the same as in nodular tumors (48% increased death risk). Most of this is due to delayed diagnosis in elderly patients.

Bottom Lines:

We are not concerned with adequately treated, nonrecurrent lentigo maligna any more than we are about typical level I melanoma in situ.

On the other hand, new and especially recurrent LMs are best deferred until biopsied/excised and invasive disease is ruled out.

[Erikson, Fogarty, Gamblicher, Kai, Kvaskoff-1, Mirzoyev, Reed-1, Tzellos, Yang]

What is desmoplastic melanoma (DM)?

DM is a rare and distinctive melanoma.

- It arises mainly on the trunk.
- Median age at diagnosis is 60.
- It is usually amelanotic and thus is often diagnosed late.
- It is frequently difficult, if not impossible, to fully remove surgically.
- Lymph node metastases are uncommon, occurring in just 8%.

- Only 29% are stage 1 when diagnosed.
- Radiation therapy is often used palliatively.
- After 5 years, 50% have distant metastases.
- Thus, DM is most often a chronic, slowly progressive and ultimately fatal disease wherein patients enjoy protracted survival despite being deemed incurable

[Busam-2, Cheng, Egger-3, Feng, Guandagnolo, Moloney]

Does mortality differ significantly between upper vs. lower limb melanoma?

No. While it is somewhat lower overall for the upper extremities overall, the difference is statistically insignificant in most studies.

In some studies, mortality is higher for trunk vs. extremity melanomas. But, once again, this difference is usually insignificant adjustment for the major risk factors we have discussed.

[Callendar, Egger-1, Egger-6, Yang]

Do head and neck melanomas have a significantly worse prognosis overall?

Yes, when considered collectively at all head/neck sites.

[Fadaki, Murali-3, Patuzzo]

In a 1,548-patient study, subjects with head and neck melanomas had these notable disadvantages compared to those arising on the trunk and extremities: [Dabouz]

- Older average patient age, due in part to association with protracted sun exposure over decades.
- Significantly thicker on average.
- Higher percentage of cases are nodular melanoma.
- 22% recur within 20 months.

The risk of recurrence is also somewhat higher for head/neck lesions. This is said to be due, at least in part, to surgeons limiting the extent of wide local excisions for cosmetic reasons. The result is more cases with insufficient margins and residual melanoma. [Ettl]

5-year survival in recurring head/neck melanoma is 57%, compared to 91.8% in localized nonrecurrent cases. [Davis-Malesevich]

Why are scalp melanomas of special concern in underwriting?

- The average delay in diagnosis is 17 months.
- They tend to be thicker (mean 2.4 mm).
- They are twice as prone to ulceration, significant mitotic activity and perineural invasion.
- They are twice as likely to have positive sentinel lymph node biopsies (see below).

- Their recurrence rate is higher than at most other sites.
- They are 3 times more likely to have brain metastases (12.7%) as other head and neck melanomas (4.7%).
- In an Australian 10-year disease-specific mortality study, only 69.3% of patients with scalp lesions lived for a decade, as compared to 92.6% of all study subjects.

[Baade-1, Cappello, Gadja, Huisman, Patuzzo, Perto, Sperry]

Bottom Lines:

For the most part, I do not consider head/neck melanomas differently from those at other sites, with some exceptions for those arising on the ears, back of the neck, etc., although there is not much literature available on prognosis at these more "exotic" sites.

For scalp tumors, a longer waiting interval plus evidence of both follow-up (including CT/PET scans) and patient compliance with physician advice regarding follow-up intervals are ideal.

What is a sentinel lymph node (SLN)?

"The integration of sentinel-node biopsy into the management of intermediate-risk and high-risk primary melanomas has significantly changed the landscape of melanoma treatment."

Charles M. Balch, MD
University of Texas
New England Journal of Medicine
370(2014):663[editorial]

The SLN is the lymph node in which metastatic melanoma is most likely to be detected first.

The SLN is pinpointed by a noninvasive procedure called lymphatic mapping or lymphoscintigraphy.

[Gerschenwald, Morton, Quaglino, Rhodes, Sakowska, Torjesen]

Does the extent of the metastatic disease found in the sentinel lymph node have any implications?

Yes. If the melanoma cells are present deep within the central portion of the SLN or occupy a large portion of the node, the odds of further spread are substantially higher.

If we have sufficient pathology report details, evidence of extensive vs. minimal metastatic tumor deposits in the sentinel lymph node is significant to insurability, especially when a more extensive lymphadenectomy was not done. Unfortunately, pathologists seldom report such detailed information about SLNs.

[Cadili, Murali-3, Murali-5]

What are the 4 possible outcomes for melanoma cells once they have metastasized to a sentinel lymph node? [di Giorgi]

1. They are destroyed by the host's immune response.
2. They are totally eradicated by excising the node.
3. They continue to spread to other nodes and beyond.
4. They become dormant (but can reactivate later).

When is an SLN biopsy (Bx) done?

In the US, it is advised for all non-thin (> 1.00 mm) melanomas in the absence of clinically evident node metastases.

Some melanoma treatment centers also do an SLN Bx in thin melanoma cases, primarily when the tumor is at least 0.5 mm thick and/or when high risk findings such as ulceration, mitoses, extensive regression, involvement of levels IV or V, etc., are present. [Gerschenwald].

Are there false-negative SLN biopsies?

Yes, up to 15% in some studies. In most cases the pathologist missed a very small melanoma cell deposit.

The take-home message = we cannot assume that because the SLN Bx was negative the applicant was definitely cured by complete local excision of the melanoma.

[Bañuelos-Andrio, Jones, Manca, Tardelli]

What factors are associated with an increased likelihood of a positive SLN Bx in thicker (> 1.00 mm) melanomas?

- Ulceration
- Lymphovascular invasion (LVI)
- Mitotic index ≥ 1/mm^2
- Level IV/V
- Trunk and lower extremity sites

Treatment with interferon alfa-2 is a RED FLAG for a positive SLN Bx.

[Balch, Bartlett-2, Callendar, Han, Mandala-2, White-1]

How does a positive sentinel lymph node correlated with prognosis in thicker melanomas?

In a 2013 analysis, a positive SLN was less significant than thickness, except in melanomas thicker than 4 mm. [Freeman]

However, more recent major studies have found that a positive sentinel lymph node is a powerful independent predictor of recurrence as well as 2 to 3 times higher mortality in all melanomas > 1.00 mm thick.

[Erman, Kachare, Kyrgidis, Kunte, Mandala-1, Morton, Oudeophuis, Sabel, Seyed]

How common are positive SLN biopsies in thin cases?

Between 4.1% and 7.8%, and it increases with age.

[Green, Han, Hieken, Shannon, Walker]

What are the risk factors for a positive SLN Bx in thin cases?

In a review of 60 studies involving over 10,000 thin cases, Cordeiro reported 3 significant predictors:

	Positive SLN
Level IV/V	7.3%
Thickness ≥ 0.75 mm	8.8%
Mitotic index ≥ 1/mm^2	8.8%

If 2 of these are present, at least 16% of patients will have a positive SLN biopsy.

Other reports cite both corroborative and additional findings:

- Head and neck tumors have twice the positive SLN risk, as compared to those at other sites.
- Lymphovascular invasion (LVI) is also a significant risk factor in some studies.

[Bartlett-1, Lee-2, Murali-4, Rubinstein, Sperry, Walker]

How does a positive SLN impact survival in thin melanoma?

These are 5-year survival results from 4 major studies of thin melanomas:

	% Surviving 5 Years		
	SLN-neg	SLN-pos	Difference
Han	98%	91%	- 7%
Mozillo	93%	81%	-12%
Venna	97%	92%	- 5%

	% Surviving 5 Years		
	SLN-neg	SLN-pos	Difference
Wright	98%	83%	- 15%

Bottom lines:

- It is a **RED FLAG** when SLN Bx is not done in melanomas > 1.00 mm.
- It is also a **RED FLAG** if it is not done in higher risk thin melanoma.

Should a completion lymph node dissection (CLND) be done if the SLN Bx is positive?

Historically most experts say YES.

Now some favor observation and do further surgery only when interim developments increase the odds of lymphatic spread beyond the sentinel node.

In a 2022 study, there was no difference in terms of 2.2-year recurrence or mortality between those having CLND and those managed with observation only. [Parvez]

but there are reasons why it may intentionally not be done...in some cases despite the presence of suspicious palpable lymph nodes! [Wasif]

This is the ultimate RED FLAG scenario from my perspective, making the applicant uninsurable until the question of whether those nodes contain metastases is fully resolved.

Bottom line: Expect to see a path report from a CLND in cases with either a positive SLN Bx or clinically detected evidence of lymph node spread.

If it is not provided, make sure you determine whether this procedure was done and, if so, get the path report.

What is the significance of positive non-sentinel nodes found during CLND?

In these cases, the risk of a local recurrence ranges from 11% to 50%, and the likelihood of recurrence at any site is greatly increased. [Bañuelos-Andrio]

If at least 2 nodes contain metastatic disease, mortality due to melanoma increases 60%, independent of all other risk considerations. [Pasquali-2]

Applicants with positive non-sentinel lymph nodes should be postponed for a substantial waiting interval.

What is regression?

"Regression in melanoma is an immunologic process characterized by lymphocytic infiltration causing the spontaneous disappearance of tumor cells."

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

Why are we covering regression separately and in considerable depth?

Many melanoma studies either ignore regression or dismiss it as insignificant. This creates the misperception that regression is never important and probably explains why it is often not adequately addressed in underwriting guidelines.

How common is regression?

It is present in anywhere from 10% to 70% of melanomas, based on countless studies over the past 40 years. This broad range is a reflection of a lack of attention to evidence of regression by many pathologists

It is most often reported in thin melanomas (10% of T1a cases and 18% of T1b cases).

[Botella-Estrada, McClain-1, Maurichi, Ribero-1]

Regression can be partial, extensive or complete. Extensive regression has been variously defined as the absence of anywhere from 50% to > 80% of tumor cells.

[Ivan, McClain-1, Tas, Yun]

What are the issues plaguing regression?

- Pathologists have no guidelines because there is no standardized definition or even consensus criteria to establish its presence.
- There is often disagreement in this regard, even among experts.
- It is only useful if we know the extent of its presence.
- Simply saying "regression present" is worthless, and this is usually what we find when it is mentioned at all.
- Extensive regression in thin melanoma creates the mistaken impression that there is little risk of metastasis or tumor-related mortality.

[Brauer, Elder, Han, Ivan, Murali-4, Ribero-2, Scolyer-2, White-1]

When is regression important in underwriting?

When there is extensive or complete regression present in vertical growth phase (mainly levels III and IV) thin melanoma. [Murali-3]

This is the only context in which regression is a huge – but widely unappreciated – mortality **RED FLAG**.

By causing increased lymphatic vessel density, regression facilitates metastasis in thin melanomas. [da Costa, Yun]

In one study, 51% of thin melanoma patients having both extensive regression and lymphovascular invasion (LVI) died within 5 years after diagnosis! [Egger-1]

Regression is associated with a high risk of false-negative sentinel lymph node biopsies. Intensive follow-up surveillance is essential in extensively regressed thin melanoma, even when an SLN Bx is negative. [Mitteldorf, Rubinstein]

The Italian National Tumor Institute has recommended that regression be added to the staging system, akin to ulceration and mitotic activity. [Maurichi]

Does regression matter in melanomas > 1.00 mm?

Ironically, some studies show a better prognosis when regression is present in melanomas > 1.00 mm!

In a 2021 study, patients with non-thin melanomas had 1/3rd less mortality when regression was credibly cited on the path report!.

I do not use regression as an insurability risk factor in non-thin melanoma. And even if I was so inclined, most regression is not reported in non-thin melanoma.

[Burton-2, Botella-Estrada, Ribero-1, Subramanian, Tas-1, Yun]

How do we explain this paradox: *extensive regression is a major unfavorable factor in some thin melanomas, but is either irrelevant or even potentially favorable in thicker tumors?*

"…early and late regression may be biologically distinct entities with distinct prognostic values. Combining the two phases into a single category may account for the disparity between studies."

Susannah E. McClain, MD
University of Maryland Medical School
Melanoma Research
22(2012):302

How is thin melanoma defined?

Thin melanomas are those ≤ 1.00 mm in measured thickness. They are all stage T1 tumors, with T1b distinguished from T1a by the presence of ulceration.

[Bartlett-1, Caldarella, de Waal, Lee-2, Murali-4, Sperry]

When do recurrences occur in thin melanoma?

…some patients with thin melanoma have poor outcomes and develop recurrent disease, sometimes 10 years after the initial diagnosis, which can result in melanoma-related death.

Dale Han, MD
Moffitt Cancer Center, Tampa
Journal of Clinical Oncology
31(2013):4387

The 5-year recurrence rate was 11% in a 2,243-patient study. However, the median interval from diagnosis to recurrence was 6.5 years overall, and 8.9 years for distant recurrence.

That is significantly longer than in thicker melanomas!

Melanomas with very long (10+-year) intervals between diagnosis and distant recurrence are most likely to be thin tumors without node metastases.

Metastatic recurrences in thin melanomas are 5 times more likely to occur 8 years after surgery than within 3 years!

[Brauer, El Sharouni, Maurichi, Murali-3, Scally]

Despite these critical revelations, we often offer coverage in thin melanoma cases with shorter waiting intervals and shorter duration flat extras than we use in thicker melanomas!

What are the main risk factors for recurrence, metastases and mortality in thin melanoma?

- Thickness - those < 0.8 have lower risks compared to 0.8-1.0 and those < 0.5 rarely metastasize or prove fatal.
- Ulceration
- Mitotic index ≥ 1/mm^2
- Level IV/V
- Extensive/complete regression
- Lymphovascular invasion
- Positive SLN Bx
- Site: trunk, head/neck (especially scalp)
- Acral lentiginous and nodular subtypes, both of which are seldom thin.

[Baade-2, Claeson, El Sharouni, Elder, Gimotty, Green, Han, Maurichi, Murali-3, Sacchetto, Xu]

How does ulceration impact 10-year mortality?

- It increases 10-year mortality between 3 and 8 times, depending on thickness.
- The combination of level IV or V plus ulceration has a 10-year survival of just 69.8%.

[Elder, Landow]

Is the overall prognosis more favorable in thin vs. thicker melanoma?

Absolutely, because the substantial majority of thin melanomas lack the high-risk considerations cited.

In various studies of T1a thin melanoma, 5-year survival ranges from 95% to 98%, and 15-year survival up to 95% has been reported in major studies.

However:

- Survival rates are much lower in T1b cases (ulceration present).
- Over 60% of deaths occur after 5 years, and there are deaths due to thin melanoma as late as 20 years.
- In a Mayo Clinic study of 40- to 60-year-olds, 25% of melanoma-related deaths occurred in thin cases.
- Melanoma accounted for 25% and 28% of melanoma deaths, respectively, in 2 other studies.
- 30% with brain metastases have thin melanomas!

[Green, Elias, Hamilton, Han, Hieken, Gimotty, Lowe, Murali-6, Swetter, Whiteman]

Bottom line: we have to identify thin cases with uncommon but highly significant features based on the criteria set forth in this course…or we will incur substantial <u>avoidable</u> excess mortality.

What is the risk of recurrence in thick (> 1.00 mm) melanoma?

It is steeply associated with disease stage, as shown in this study of 33,384 German patients:

Stage	Recurrence Rate
I	7.1%
II	32.5%
III	51.0%

23% first recurred at distant sites. [Leiter]

It is also important that in thicker melanomas, 80% of the recurrences are detected within 3 years of original melanoma diagnosis, which is far earlier than in thin tumors. [Anderson]

Furthermore, recurrences in 1.0-4.0 mm tumors are detected on average 19 months after diagnosis vs. just 9 months after diagnosis when melanoma is > 4.0. [Morton]

Bottom line: the thicker the melanoma, the greater the recurrence risk, and the earlier it occurs.

What are the major risk factors for recurrence?

- Older age (mainly age 65+)
- Thicker – especially >4.0 mm
- Level of invasion
- Mitotic rate ≥ 1/mm^2 – 2.2-5 times higher
- Ulceration – 2-5 times greater
- Lymphovascular invasion – 2 times increased
- SLN Bx positive – 3 times higher
- Nodular – 1.5-2.5 times greater
- Satellitosis – 6.6 times higher
- History of an autoimmune disease
- History of nonmelanoma skin cancer
- LDH enzyme elevated

[Baker-2, Brauer, Faut, Jones, Matheson, Murali-2]

How common are very late recurrences?

7-13% of melanoma patients die from the disease between 5-10 years after diagnosis and treatment. [Bancalari]

5.6% of stage I/II melanomas recur either regionally or at distant sites after 10 years. [Osella-Abate]

Melanoma cells can lie dormant in lymph nodes or distant organs for an extended period, then reactivate when immune function decreases for whatever reason.

Does mortality increase with tumor stage?

Yes.

For example, 10-year survival is 83% in stage 2a, as compared to 66% in stage 3a and 39% in stage 4b.

[Egger-6, Elias, Madu, Van der Ploeg]

These are 10-year survival rates in 40,520 cases [Xing]:

Stage	% Surviving
I	94.3%
II	61.5%
III	44.1%
IV	16.1%

In another study, 15% of patients with stage IV disease survived at least 10 years. However, nearly all had persistent disease and experienced an eventual fatal recurrence. [Murali-2]

Is melanoma-related death more likely to occur earlier in higher vs. lower stage cases?

Yes. [Xing]

For example, 10-year stage I survival is the same whether measured from diagnosis or in patients that have already survived for 5 years.

By contrast, 10-year stage IV survival is just 16% at diagnosis, whereas 80% that have already survived 5 years will be alive at least 10 more years. In other words, most mortality in higher stage cases is clustered within the first 5 years.

What are the main adverse outcome markers in > 1.00 mm melanoma?

They are quite similar to those for recurrence, mainly because most patients with recurrent melanoma eventually succumb to the disease.

- Age 65 and older, with twice the risk for those < age 46
- Thickness – the thicker, the higher the mortality
- Positive SLN Bx – roughly 2 times greater mortality
- Positive non-sentinel lymph node – 3 times higher risk
- Ulceration – 1.7 to 4 times greater mortality
- Mitotic rate ≥1/mm^2 – 1.6 times higher death risk overall
- Lymphovascular invasion (LVI) – 2.3 times higher risk
- Scalp – over 2 times greater mortality
- Satellite and in-transit skin metastases

In addition, 3 test-related risk factors have recently been identified. I am citing them for reference purposes, but would not use them in underwriting at this time:

- Elevated CRP marker – up to 3 times higher mortality
- Low vitamin D level – 1.5 times higher mortality
- D-Dimer test > 0.6 mg/L – 3 times greater mortality

[Allin, Bello-2, Callendar, Desch, Egger-6, Fang-1, Fang-2, Kricker, Lamboo, Madu, Mays, Morton, Newton-Bishop-1, Seyed, Sosman, Weiss-2, Yamamoto]

In a new study, mortality was 50% lower in patients having over 50 nevi (moles). [Ribero-3]

We found contradictory evidence on the impact of pregnancy, but the overall evidence seems to favor no significantly increased risk. [Driscoll, Tellez]

Lastly, as cited earlier, the absence of a sentinel lymph node biopsy in melanoma > 1.00 mm thick is a highly unfavorable factor and justifies adding debits within (at least) the first 5 years after diagnosis.

What is oligometastatic disease?

"Oligo-" is a medical prefix meaning "few" or "little."

The term "oligometastatic" is used when the volume and extent of tumor metastases is minimal. In these cases, it may be possible to completely eradicate detectable metastatic disease, sometimes leading to prolonged survival and, on occasion, resulting in a cure.

Metastasectomy is the term for surgery to excise oligometastatic tumor deposits.

Unfortunately the recurrence rate after surgery for oligometastatic disease is 90%+ within 2 years. [White-2]

Do any patients with brain metastases survive for an extended period of time?

Yes.

While the median survival is only 4-6 months, 21% survive 3 years, 15% survive 5 years, and 2-3% are still alive after 12+ years. [Davies, Zakrzewski]

Just a thought: if an applicant with minimal brain metastases purchased life insurance by not disclosing his melanoma history, he would have a reasonably good chance of outliving the 2 year contestable period in the USA.

What follow-up is recommended after initial treatment?

There are no consensus surveillance guidelines.

No follow-up is officially advised for in situ melanoma.

For invasive cases:

- In the US, stages 1a and 2a should be seen every 6 months for up to 3 years, then annually thereafter.
- In Europe, stage 1a cases are seen 2-4 times in 1st year, then no longer.
- For stages 1b and 2b every 3-6 months and lymph node sonography every 6 months for 3 years and annually thereafter.

- In high-risk cases, exam and sonography every 6 months and CT/PET scans at various intervals.

Most experts advocate lifelong surveillance for the risk of additional melanomas, and some argue that high-risk cases should follow-up done at melanoma specialty centers.

[Iznardo, Moscarella, Salerni, Scally]

What are the follow-up RED FLAGS?

All of the following 7 clues are subtle but critical **RED FLAGS** we need to be attentive to in invasive melanoma cases:

- Imaging studies done or recommended at any interval. This is because CT scanning is the #1 way in which melanoma recurrences are found.
- Out of pattern appointment made by applicant suggesting he detected a recurrence.
- Referral to any specialist at any time.
- Failure to make/keep follow-up visit appointments, (especially the one nearest to applying for coverage).
- After a routine follow-up, applicant is asked to set his next follow-up appointment after a significantly shorter interval than used previously.
- Applying within short interval after last follow-up visit.
- Applicant does not do home skin self-examinations as advised.

[Coups, Podlipnik, Scally]

Does a history of 2 or more melanomas portend less favorable outcomes than having 1 melanoma?

Yes.

For example, a 2022 University of Pittsburgh Hillman Cancer Center study reported higher recurrence and mortality hazard ratios (2.17 and 4.52, respectively) in patients with 2 vs. 1 melanoma. [Karapetyan]

What is the most widely used melanoma biomarker?

S100B.

The original S100 test distinguishes between melanoma vs. benign nevi. S100B is an enhancement because it is a prognostic indicator.

- S100B is rarely elevated in early melanoma, but commonly is increased in stage III and IV cases.
- In a 22-case analysis, elevated S100B doubled the mortality risk, but the impact was largely in high stage cases seldom insured until after long waiting intervals.
- It is also useful as a clue to a false-positive SLN Bx.

- A positive (elevated) S100B is a **RED FLAG** on any case.

[Damude, Gebhardt, Hill, Palmer, Weinstein]

Which other biomarkers have shown at least some potential?

- Elevated LDH has been recognized as a **RED FLAG** in advanced melanoma for many years.
- Higher KI-67 levels are linked to poorer all-cause survival in several studies, with greatest impact in thick (> 4.00 mm) tumors.
- MCAM (melanoma cell adhesion marker) may be an independent prognostic marker in advanced melanoma.
- Melanoma-inhibitory activity protein (MIA) is linked to greater recurrence risk and reduced disease-free survival in early stage melanoma.
- Tribbles 1 protein (TRIB1) may evolve as a blood marker for metastases in regional nodes. More studies are needed
- Circulating melanoma cells in the bloodstream...which may well be the best of the lot.

Most biomarker tests are not yet standardized for routine use.

When results of a biomarker test are reported, we need to determine its implications and consider a positive test to be a RED FLAG.

[Abbas, Chiu, Elder, Hill, Lade-Keller, Sandru, Weinstein, Weiss-1]

"We found that melanocytic neoplasms transitioned from linear to branched evolution at later stage of progression, leading to tumor heterogeneity."

A. Hunter Shain, MD
University of California-San Francisco Cancer Center
New England Journal of Medicine
373(2015):1926

All tumors have gene markers, which are either inherited or are due to tumor mutations as suggested above. Several are associated with higher mortality in melanoma.

What is important about the *BRAF* mutation?

- 50% of melanomas have an activated *BRAF* mutation. 80-90% are specifically called $BRAF^{v600E}$.
- This mutation appears to accelerate melanoma growth, resulting in a more aggressive neoplasm.
- A 2012 meta-analysis shows that this is a prognostic marker, and higher expression is associated with at least 2 times greater mortality.

The evidence suggests that when localized melanoma has a strongly positive level of

BRAF^{v600E}, this should be considered an unfavorable finding in context with other risk factors.

[Eriksson-2, Flaherty, Jarkowski, Nagore-1, Safaee, Shah, Tschandi, Weiss-1]

What are the other gene mutation markers that have been shown to potentially play a role in the management and outcome of melanoma?

NRAS, TERT and (possibly) *PHEN*.

- 16% of melanoma patients have the *NRAS* gene mutation.
- *NRAS*-mutated melanomas tend to have unfavorable risk factors (nodular, thicker, more mitotic activity).
- They may confer up to 3 times excess mortality risk, but not many studies have been done.
- They may also be used together with *BRAF* mutations, where they only have a significant value in more advanced cases.
- There are 2 *TERT* promotor gene mutations affecting 43% and 22% of melanoma patients, respectively. They are markers for higher risk cases.
- 10% have *PHEN* mutations, and these may play a prognostic role as well.

[Bressac-de Paillerets, Devitt, Lahtz, Nagore-2, Populo, Sivendran, Thomas-3, Weiss-1, Wisco]

What do we need to know about the management of metastatic melanoma?

Most metastatic melanoma cases are uninsurable.

The ones most apt to be acceptable involve positive sentinel lymph node biopsies with no further evidence of metastases or recurrence after a sufficient waiting interval = 5 years if not thin; arguably a bit longer if thin.

What are the main drugs currently used in metastatic melanoma?

Conventional cytotoxic chemotherapy is of little value in melanoma because it seldom results in prolonged survival and has no potential for curing these patients.

Therefore, several newer drug classes now account for most medical management of metastatic melanoma.

[Carlino, Kim, Kottschade]

What are these drugs?

Immune Checkpoint Inhibitors

- Ipilimumab

- Nivolumab
- Pembrolizumab
- Atezolizumab

Kinase Inhibitors
- Cobimetinib
- Vemurafenib

Other New Drugs
- Oncolytic viruses
- Trametinib
- Relatlimab

[Amaria, Niezgoda, Reed-1]

In a recent series of 839 patients treated with ICIs, 162 survived at least 2 years. Nearly all of them would have died over that interval prior to use of these drugs.

There have been some long-term (5+ year) survivors and cures may be possible. That said it is too soon to insure applicants treated with ICIs even if they are currently free of detectable disease. [Park]

What do we know about the kinase inhibitors?

- They extend survival in many metastatic cases with the *BRAF*^{v600E} mutation; 72% of patients given this treatment are alive in 12 months, and 15% survive up to 5 years.
- Stopping treatment leads to disease progression.
- In one study over 50% patients treated with these drugs developed <u>new</u> melanomas within 27 weeks of starting treatment.

[Fedorenko, Menzies, Robert-2, Salama, Scholtens, Zimmer]

What other treatments may be used in advanced, metastatic or recurrent melanoma?

- Radiation [Makre-1]
- CyberKnife surgery [Elias]
- Electrochemotherapy as palliative treatment of cutaneous and subcutaneous metastases [Caraco, Kis, Testori]
- Cryotherapy and CO^2 laser therapy [John]

Melanoma is notorious for *very* late recurrence.

In one case, a patient relapsed 21 years after a diagnosis of localized melanoma and by taking pembrolizumab, she has remained disease-free for 2 years.

In 2022 Sax reported on a melanoma that recurred 49 years after surgical excision!

Late recurrence is why medical records should be obtained as often as possible on all applicants with a history of invasive melanoma.

[Eggermont, Hodi, Larkin, Prieto, Ribas, Robert-1, Schadendorf, Shoushtari, Topalian]

What effects has the COVID-19 pandemic had on melanoma? [Lalles]

- In 2020 39% decrease in new diagnoses. This adverse effect disappeared in 2022.
- % of in situ and 1a decreased from 40% to 29%; more cases diagnosed at higher stages.
- Average thickness increased 20%.
- Mean interval from diagnosis to excision was longer.

Why are second opinions such a critical issue in underwriting?

Misdiagnosis in melanoma is the most common cause of malpractice claims involving pathology reports.

The leading misdiagnosis scenario is diagnosing a mole is benign…despite the fact that it is actually malignant!

[Carney, Rayess]

In one series of 80 litigation cases, 38% of cases misdiagnosed as benign resulted in death due to melanoma. [Rayess]

How often is there disagreement between the local pathologist and a 2nd opinion by an expert melanoma dermatopathologist?

In a large series from one US melanoma center, there were significant disagreements on pathological stage in 19% of 588 cases. The most frequent pathological criteria where disagreement occurred were thickness, mitotic rate and regression. [Patrawala]

In an Australian series, experts made changes in thickness and Clark level on 38% and 25% of cases, respectively. [Murali-1]

What else do we need to know about significant differences in melanoma pathology findings between local pathologists and melanoma experts?

Benign mole vs. melanoma

- This distinction can be quite challenging in certain kinds of moles, with disagreement occurring even among experts! [Marsch]
- In one series, the overall disagreement rate on benign vs. malignant was 14.3%; in 80% of these, the expert changed the diagnosis from malignant to benign. [Shoo]

- In a Dutch study, 35% had diagnosis changes split equally between benign to malignant and vice versa. [Hawryluk]

In situ vs. invasive

- In one study, 8% of melanomas initially diagnosed as in situ were changed to invasive. [Iorizzo]
- In another, experts found that 20% of 529 melanomas diagnosed initially as in situ were actually invasive. [Niebling]
- In a 3rd study, 15.5% were changed from invasive to in situ or vice versa. [Eriksson-1]

Stage of invasive melanoma

- German experts changed 24% initially diagnosed as T2b to T2a and made similar changes in 12% first diagnosed as T3 or T1. [Niebling]
- Experts at the University of Michigan Melanoma Center changed 8% of SLN biopsy pathology assessments. [Dandekar]

Are 3rd opinions ever needed?

Yes, although the frequency is far lower than with 2nd opinions. [Patrawala]

Bottom lines:

- **Underwriters need to identify all cases with 2nd opinions because they are mega RED FLAGS.**
- **We must have the findings of these experts opinions before making a decision because they could change the insurability status**

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