Malignant Melanoma

Munich Re Life US

Overview

Malignant melanoma is the most serious form of skin cancer. The incidence of melanoma is rising in much of the world, and it is now the fifth most commonly diagnosed cancer in North America. Given also that it can occur at any age and that it is often found at early stages with a very good prognosis, it is one of the cancers most often encountered in underwriting. There are an estimated 1,300,000 melanoma survivors in U.S. currently, half of whom are under age 65.[1]

Because of its usually visible location, skin melanomas are often found at early stages without evidence of spread to elsewhere in the body, with 84% remaining localized at the time of diagnosis. The prognosis generally is therefore very good: the overall 5-year survival rate for melanoma in the U.S., based on results from the SEER database, is 92%. It varies significantly by stage, however, with a 5-year survival rate of 99% for localized skin melanomas, 65% when regional lymph nodes are involved, and just 25% if there are distant metastases.[2]

In addition, even localized melanomas have varying degrees of recurrence risk based on multiple other factors. Some of these are part of the staging criteria, such as the thickness of the lesion and the presence of ulceration. The risk increases with increasing thickness, and though staging guidelines require there to be set cut-off points (1, 2, and 4mm of thickness have been chosen), there is variable risk even within those ranges. This was recognized particularly with thin melanomas, those 1mm or less in thickness, such that a thickness of 0.8 to 1.0mm now places one into a higher stage unless a sentinel lymph node biopsy is without evidence of tumor spread. Similarly, the presence of ulceration leads to a prognosis similar to as if the thickness is one level greater.

Using the SEER database and other research sources allows us to identify other factors which affect the prognosis. The mitotic rate of the tumor was already part of the prior (AJCC 7th edition) staging criteria, and although no longer included to keep the staging more simplified, it remains an important prognostic factor for all stages of tumor thickness. In addition, a nodular growth pattern; the presence of lymphovascular invasion; regression of the tumor of greater than 50%; and a tumor location on the scalp, neck, lip, mucosal membrane, or eye, are all independent risk factors for recurrence and increased mortality. Men tend to have worse outcomes than women, and those diagnosed at older ages have higher recurrence rates in the first five years after discovery. For accurate underwriting risk assessment, it is helpful to take these factors into account.

The risk of recurrence, however, does not end at five years. Even for thin melanomas, one may go for many years without any evidence of disease only to present ultimately with a recurrence, and that risk persists for 15 to 20 years or more. This also needs to be factored into the underwriting risk assessment, especially for those with thicker tumors or with other higher risk features.

Melanoma Assessment – More Than Skin-Deep

Melanoma is a malignant tumor of melanocyte origin arising predominantly in the skin but also, less commonly, in the mucous membranes, eyes, or central nervous system. In the United States and Canada, melanoma is the fifth most frequently diagnosed cancer, with an estimated 100,350 new cases of invasive melanoma expected in the United States in 2020 (60 of those in men).[3]

The age-adjusted incidence of melanoma in the U.S. has increased notably in the past few decades to 22.9/100,000. Despite a dramatic increase in incidence, the overall mortality rate from melanoma rose more slowly, likely reflecting earlier detection and treatment, due to public education efforts. Mortality rates peaked at around 10,000 deaths in 2016, but since then, the rate has declined. Notably, in 2020, the estimated number of deaths falls to 6,850, which is felt to be due to major treatment breakthroughs for advanced disease. In recent years, the increase in melanoma incidence has been driven entirely by increases in those over the age of 40. Younger age groups have seen a stable to even declining rate, probably reflecting changes in sun-protection behaviors over the past few decades.[5]

In the U.S., the lifetime risk of developing melanoma was estimated to be about 1 in 28 for Caucasians in the year 2020. The incidence of melanoma is relatively low in dark-skinned populations. Overall, the lifetime risk of developing melanoma is greater for men than women; however, for those under age 50, the inverse is true. The incidence rate begins to rise after puberty, increases until the age of 65 to 70 years, and then decreases with the average age at diagnosis being around 65. Although about 84% of skin melanomas diagnosed in the United States are clinically localized, this number has been gradually rising over the past two decades, likely reflecting greater public awareness and earlier clinical assessment of suspicious lesions. Approximately 9% have regional spread at the time of diagnosis, 4% are metastatic, and the remainder unknown.[2,6]

Risk factors for developing melanoma

Numerous risk factors for the development of melanoma have been identified and these generally fall into two major categories: ultraviolet (UV) radiation exposure and genetic predisposition. Clinical and epidemiologic evidence has demonstrated higher rates of melanoma in people with intense exposure to solar UV radiation, and the majority of melanomas develop on areas of skin that are more susceptible to sunburn. Intermittent, intense exposure and blistering sunburn in adolescence or childhood are the factors most strongly associated with an increased risk. Adjusting for differences in skin type, the closer one resides to the equator, the higher the melanoma risk. In addition, indoor UV exposure from tanning beds appears to increase one's melanoma risk, particularly when the exposure begins before age 25 and lasts over 10 years. UV exposure also leads to higher numbers of nevi and to more atypical nevi, both associated with a higher risk of developing melanoma.[7-11]

Genetic factors play an important role in melanoma risk as well. Individuals with lighter skin pigmentation, red or blond hair, and blue or green eyes are most vulnerable. An increased propensity to freckle and an inability to tan are well recognized risks. Approximately 10% of melanomas are considered to be familial, and having a family history of melanoma, especially when manifesting at young ages or in multiple close relatives, is an important additional risk. Heredity certainly plays a role in one's skin, hair, and eye color, and families usually share environmental and behavioral factors, but specific genetic alterations predisposing one to melanoma and to dysplastic nevi have also been identified. Most notable is that of a mutation in the CDKN2A tumor suppressor gene. Mutations in BAP1, CDK4, MITF, and POT1 genes have also been associated with melanoma.[9,11-14]

Types of Melanoma

There are four major subtypes of malignant melanoma: superficial spreading, nodular, lentigo maligna, and acral lentiginous. Superficial spreading melanoma comprises 70% of all melanomas. These can be found on any skin location but are most commonly seen on the torso in men and the lower legs in women. They are most often diagnosed as a thin lesion that is highly curable and is often present for some years before developing its vertical invasive growth phase. Melanomas arising in dysplastic nevi are usually of this type, though most still arise de novo (as new lesions). Nodular melanoma is the second most common type, accounting for approximately 15% of all melanomas. These can also occur in any location but grow at a more rapid pace, entering the vertical invasive growth phase at an early stage making detection at an earlier and curable phase much more difficult. This is reflected by the fact that nodular melanomas contribute a greater proportion to melanoma mortality than do the other types.

Lentigo maligna melanoma tends to occur on sun-exposed regions such as the face and usually grow very slowly for many years in a superficial (radial) growth pattern before becoming deeply invasive. Lentigo maligna melanoma occurs, on average, at age 70 and appears to result from chronic solar damage. Acral lentiginous melanomas are located on palms, soles, nail beds, and mucous membranes. These represent less than 5% of melanomas but are the type most frequently encountered in dark-skinned individuals. Acral lentiginous melanomas are often more difficult to recognize, often present at more advanced stages, and, thus, generally carry a worse prognosis.[15-19]

Other less common melanoma variants include the following types. Amelanotic melanomas present clinically as amelanotic (lacking pigment) or hypomelanotic lesions, which, accordingly, poses diagnostic challenges. As such, they can often be confused clinically with benign lesions and, therefore, may not be properly diagnosed until more advanced stages. Desmoplastic melanomas are a histologically distinct variant that presents as a slowly growing, often amelanotic, plaque or nodule. Though typically quite thick when diagnosed, the prognosis is more favorable than other melanomas of similar thickness. Spitzoid melanoma refers to a subset of melanomas that have a morphologic resemblance to Spitz tumors, both clinically and histologically, from which the distinction may be difficult. These frequently have a red hue to them or can be amelanotic, brown, black, or blue in color. Spitzoid tumors are the most common type seen in children. Ocular melanomas are usually found in the uveal tract (choroid, iris, and ciliary body) or less often in the conjunctiva. About half the time, they are discovered asymptomatically on routine exam.[20-22]

Diagnosis

The presence of most melanomas on visible skin makes them easier to identify at early stages than most cancers; however, recognizing them clinically and distinguishing them from benign lesions can at times be challenging, even for experienced dermatologists. Characteristics of the lesion are useful, such as the so-called ABCDE criteria: Asymmetry, Border irregularities, Color variegation, Diameter >6mm, and Evolution (changes in size or shape). Dermoscopic examination is a recommended technique to improve both sensitivity and specificity for a clinical diagnosis of melanoma compared to the naked eye.

In addition, consideration should be given to the previously noted factors which increase one's risk for melanoma, such as the skin, hair and eye color; history of sun exposure; any family history of melanoma; a personal or family history of atypical nevi; and the total number of nevi.[23]

Suspicious lesions should undergo a full-thickness excisional biopsy whenever possible. No single pathologic feature is diagnostic of melanoma, but a definitive diagnosis can usually be made based upon the presence of atypical melanocytes and architectural disorder. Immunohistochemical stainings can also be helpful in difficult cases. Keep in mind that although the diagnosis is often straightforward, the interpretation is still largely subjective, and it is not always easy to distinguish between a dysplastic nevus, a melanoma-in-situ, and an early invasive melanoma, even for skilled dermatopathologists.[24]

Once a diagnosis has been established, additional evaluation is indicated to assess for spread of the melanoma beyond the biopsied site. This involves a thorough examination of the surrounding skin and the lymph nodes, and then, only based upon other signs or

symptoms, additional testing might be indicated, such as ultrasound of a lymph node bed if the exam is equivocal or a chest x-ray or CT if there are suspicious pulmonary symptoms. If there are no palpable nodes or other suggestions of metastases, then wide local excision of the biopsy site is generally advised as long as it is feasible. A sentinel lymph node (SLN) biopsy is typically then indicated, except in those at very low risk (usually taken to mean a <5% chance of finding a positive SLN).Given the excellent prognosis for tumors <1 mm in thickness, with a low rate of positive sentinel nodes, a SLN biopsy is usually recommended for thin melanomas only when additional risk factors are present. These factors are discussed under Staging for melanoma.[25,26]

For those found to have a positive SLN, and in some cases with thick primary tumor even with a negative SLN, adjuvant checkpoint inhibitor immunotherapy has become the favored treatment. Targeted therapy with a BRAF inhibitor and a MEK inhibitor for those with a BRAF V600 driver mutation is also under study. These same agents are the preferred treatment for metastatic and relapsed disease. This is a rapidly evolving area with reports of excellent extended survival in some individuals.

For those not warranting SLN biopsy or with low to intermediate risk SLN negative disease, surveillance alone is sufficient. A history and physical exam every 6-12 months with attention to regional recurrences and new primary tumors is usually adequate in such situations.

Staging for Melanoma

A revised American Joint Committee on Cancer (AJCC) staging classification system for malignant melanoma was instituted in 2018. It is able to better guide patient treatment and further refine stratification of those patients entering clinical trials. As with most cancer staging systems, the goal is also to provide improved prognostic estimates based on the stage categories. For this 8th edition of staging, the Tumor, Node, Metastasis (TNM) foundation of assessing the anatomic extent of disease remains, including factors of melanoma thickness, the presence or absence of lesion ulceration, nodal involvement, and the degree or absence of metastases continue as the major prognostic indicators. However, some important changes have been instituted with this newest evidence-based revision. For lesions with a thickness of 1 millimeter or less, to differentiate between stage T1a and T1b disease, the new system uses, in addition to ulceration, a thickness at the high end of that range, 0.8 to 1.0mm, rather than the mitotic rate. Also, the T categories of melanoma thickness are now to be rounded to the nearest 0.1 millimeter, such that 0.75mm of thickness would now be read as 0.8mm. In addition, if the sentinel node biopsy is negative, the prognosis is better than if no SLN biopsy was undertaken. This is taken into account in the staging system whereby a clinical T1b lesion for which a SLN biopsy is then negative is accorded a Stage IA pathologic stage.[27]

AJCC 8th Edition Melanoma TNM Definitions

T T Category	Thickness and Ulceration
TX	Primary tumor thickness cannot be assessed
T0	No evidence of primary tumor (e.g., unknown primary or completely regressed)
Tis	Melanoma in situ
T1a	<0.8 mm and without ulceration
T1b	0.8 to 1 mm and without ulceration or <1mm and with ulceration
T2a	>1 to 2 mm and without ulceration
T2b	>1 to 2 mm and with ulceration
T3a	>2 to 4 mm and without ulceration
T3b	>2 to 4 mm and with ulceration
T4a	>4 mm and without ulceration
T4b	>4 mm and with ulceration
N Category	**Extent of Regional Lymph Node and/or Lymphatic Metastasis**
NX	Regional nodes not assessed
N0	No regional metastases detected
N1a	One clinically occult node (i.e., detected by SLN biopsy)
N1b	One clinically detected node
N1c	No regional lymph node disease but with in-transit or satellite metastases
N2a	Two or three clinically occult nodes
N2b	Two or three nodes, at least one of which was clinically detected
T2c	One node detected, plus in-transit or satellite metastases
T3a	Four or more clinically occult nodes
T3b	Four or more nodes, at least one of which was clinically detected, or presence of matted nodes
T3c	Two or more nodes detected and/or presence of any number of matted nodes, plus in-transit or satellite metastases
M Category	**Distant Metastases by Site. Suffixes: (0) LDH Not Elevated, (1) LDH Elevated.**
M0	No evidence of distant metastasis
M1a	Metastasis to skin, soft tissue, and/or nonregional lymph node
M1b	Metastasis to lung with or without M1a sites of disease
M1c	Metastasis to non-CNS visceral sites with or without M1a or M1b sites
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites

Source: Gershenwald, Scolyer, et al. Melanoma. In Amin, M.B., Edge, S.B. Greene, F.L. et al. (EDS.) AJCC Cancer Staging Manual. 8th Ed. New York: Springer, 2017.

Prognosis and Prognostic Factors

The prognosis for malignant melanoma is tied closely to staging (see below). As a whole, the prognosis is often quite favorable with an overall 5-year survival rate of 92%. It varies significantly by stage, however, with 5-year survival rates of 99% if localized, 65% with regional spread involved, and 25% if distant metastasis occurs.

Prognostic stage groups, based on the TMN criteria, correlate with these survival ranges. In summary:

- Stage I – low-risk primary skin melanomas, divided into IA (T1a tumors, and T1b with a negative SLN) and IB (T2a and T1b without a SLN study).
- Stage II – higher risk but localized primary tumors, divided into IIA (T2b, T3a), IIB (T3b, T4a), and IIC (T4b).
- Stage III – involvement of regional lymph nodes or the presence of in transit or satellite metastases, subclassified as IIIA if a T1a, T1b, or T2a with 1-3 nodes found only at SLN biopsy, and stages IIIB, IIIC, and IIID each with advancing T and/or N stage.
- Stage IV – the presence of distant metastases.

According to the AJCC database, the following 5- and 10-year survivals by stage group were seen:[28]

Stage Group	5-Year Survival	10-Year Survival
IA	99%	98%
IB	97%	94%
IIA	94%	88%
IIB	87%	82%
IIC	82%	75%
IIIA	93%	88%
IIIB	83%	77%
IIIC	69%	60%
IIID	32%	24%

However, even 10-year survival rates for melanoma can be misleading; recurrence of melanoma is not uncommon after 10 years, and late recurrences may occur at any stage, developing even 15 years or more after the date the original tumor was excised. This long tail of risk must be factored into the underwriting risk assessment.[29-31]

Despite the latest modification of the staging system, the mitotic rate remains an important additional independent prognostic factor. Besides an increased mitotic rate, there are a number of other features shown to have adverse prognostic significance that are also not included in the staging criteria: a nodular growth pattern, the presence of lymphovascular invasion, regression of the tumor of greater than 50%, and tumor location on the scalp, neck, lip, mucosal membrane, or eye. Age and sex also affect the prognosis.

Considering each of these in more detail:

- Mitotic rate – In a European multivariate analysis of 2,243 patients with T1 melanomas, a mitotic rate of 1 per mm2 was found to be an independent risk for mortality with a hazard ratio (HR) of 1.58, and among 17,204 patients in the National Cancer Database with thin melanomas with data on Breslow depth, ulceration, and mitotic rate who underwent a lymph node biopsy, there was a strong linear relationship between odds of having a positive lymph node and mitotic rate with the odds increased by 19% with each 1-point increase in mitotic rate.[32-35]
- Nodular growth pattern – Though strongly associated with thicker melanomas, a nodular histology subtype was also an independent risk factor for death in two separate melanoma cohorts (HR 1.47 and 1.55), controlling for thickness, ulceration, stage, and other variables. Another study found nodular subtype to be an independent risk for melanomas 2mm or less in thickness, but not for thicker lesions.[16,35, 36]
- Lymphovascular invasion (LVI) – The above noted analysis of 2,243 patients with melanoma found a HR of 1.81 with the presence of LVI vs absence of it. Another study found lymphatic invasion to be independent prognostic factor for metastasis in patients in clinical stages IB and IIA.[34,37]
- Tumor regression of >50% – Regression of a melanoma is a result of an immune response, which, when mild, is generally thought to be favorable. However, when extensive, it means the tumor thickness was at one time much greater, and thus a greater risk for having already spread beyond the local site. The above European data found melanoma regression of >50% to have a HR of 3.32 compared to regression of <50%.[34]
- Location on scalp, neck or lip – Anatomic location of the lesion has some prognostic impact with those on the extremities (except palms and soles) doing better than those on the trunk, which fare better than those on the head or neck.[38,39]
- Location on mucosal membranes – Melanomas arising on mucosal surfaces, including the oral cavity, nasal passages, anus and vulvovaginal regions, are uncommon. These are often amelanotic, multifocal, and have a relatively poor prognosis.[40,41]
- Ocular melanoma – Melanomas can be found in the uveal tract of the eye (choroid, iris, and ciliary body) or the conjunctiva. Because of the difficulty obtaining a biopsy, the diagnosis of a uveal melanoma is usually made clinically, though distinguishing a choroid nevus from a melanoma can be a challenge and close observation of such lesions is needed. Typical treatment includes irradiation or occasionally removal of the eye (enucleation). However, late recurrences are still common, frequently manifesting as liver metastases up to 20 or more years since diagnosis. Basal diameter of the tumor appears to be the most significant predictor of outcomes.[42-44]
- Age – Advancing age and male sex are both clearly associated with a worse prognosis. Much of that risk is related to a higher preponderance of adverse prognostic factors in older individuals and in men, but even after allowing for those factors, younger individuals and women overall have a better prognosis. Older men, in particular, have higher rates of recurrence in the first five years after diagnosis. Two studies showed an approximately 30% better survival rate in women than men, after adjusting for other factors.[32,45-47]

Though not consistently found to be independent of other factors, the lack of brisk tumor-infiltrating lymphocytes, an elevated serum S-100 protein following resection, and, for thin melanomas, a Clark's level of IV or V, have been found to be adverse features in some analyses.[38,48-50]

Cancers are increasingly being classified by their genetic signature, and melanoma is no exception. Though the impact of genetic markers on treatment options has been notable, the prognostic relevance of genetic patterns for melanoma has been limited, and longer-term data is needed. A 31-gene expression profile (DecisionDx-Melanoma) has been developed that has shown some ability to predict recurrences in stage I-III melanoma, independent of other factors. In addition, two biomarkers, AMBA1 and loricrin in combination (AMLo) were also found to be predictive of short-term recurrences with a HR of 3.89 for a high risk AMLo score.[51-52]

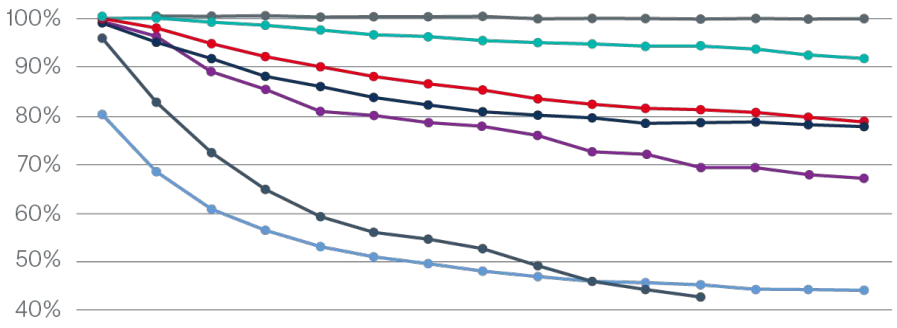
Munich Re Analysis

To understand better the anticipated survival patterns seen with melanoma, a comprehensive analysis of the Surveillance, Epidemiology, and End Results (SEER) database was undertaken, in addition to a thorough review of the clinical literature. The SEER registries have collected data on various cancers, including melanoma, since 1973, allowing one to access survival outcomes compared to a control population. The program expanded over time, incorporating more details of the cancer pathology and demographics, though alterations in the formatting of the data collected and changes in melanoma staging criteria limit the consistency of the search parameters used if extended too far into the past. Attempts were made to adjust for these limitations in order to achieve longer durations of follow-up data, noting that distant melanoma recurrences are not uncommon. Additional limitations of the data source to gaining completely accurate assessments of survival are the introduction of improved treatments over time and that the end result is mortality, not tumor recurrence.

Conclusions from this analysis include the following:

The general survival results by stage are fairly consistent with that identified in the AJCC database. Most notably, the prognosis for Stage IA melanoma is excellent with overall survival closely matching the expected rates out to 15 years, though with some late mortality was seen. Survival is then progressively worse with advancing stage, except that those with Stage IIIA disease – thinner tumors with occult nodal metastases only – fare notably better than thick, ulcerated melanomas, which do not have evidence of metastases (Stage IIC). There were limited numbers fitting into Stage IIC, which no doubt influences the accuracy of that survival curve.

Figure 1. Relative Cumulative Survival by Stage



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1A	100.0	100.0	100.0	99.9%	99.9%	99.8%	99.7%	99.7%	99.5%	99.5%	99.5%	99.5%	99.5%	99.5%	99.5%
1B	99.9%	99.6%	98.9%	97.9%	97.1%	96.3%	95.8%	95.1%	94.5%	94.3%	94.0%	93.8%	93.2%	91.9%	91.2%
2A	99.6%	97.4%	94.3%	91.6%	89.6%	87.5%	86.2%	84.5%	83.1%	81.9%	80.8%	80.4%	80.2%	79.2%	78.3%
2B	98.9%	95.1%	91.2%	87.5%	85.4%	83.0%	81.8%	80.5%	79.9%	79.1%	78.4%	78.3%	78.2%	77.8%	77.7%
2C	95.3%	82.5%	72.1%	64.6%	59.2%	55.9%	54.4%	52.2%	49.0%	45.8%	44.1%	42.5%			
3A	99.2%	95.7%	88.8%	85.1%	80.4%	79.7%	78.3%	77.5%	75.6%	72.3%	71.5%	69.2%	68.9%	67.6%	67.0%
3B-4	79.9%	68.4%	60.6%	56.2%	53.2%	51.0%	49.2%	47.9%	46.7%	45.8%	45.3%	44.8%	44.3%	44.0%	43.8%

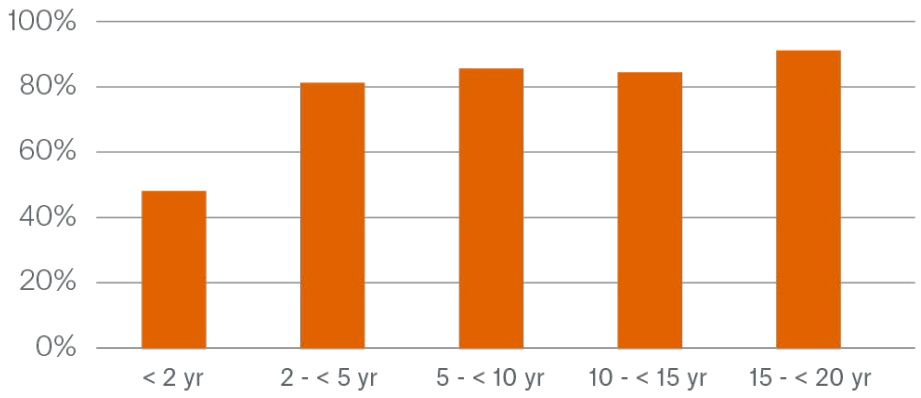
Figure 1 shows the relative cumulative survival rates in years since diagnosis for melanoma stages 1A through 4.[2]

It's useful to note that even though the prognosis is quite good for lower stage melanomas, there continues to be excess mortality beyond 10 years after diagnosis (the survival curves, relative to expected, do not flatten out). Some of these individuals certainly had recurrences years prior to succumbing to the melanoma, and many of these could probably be identified in underwriting; however, these findings do reinforce the evidence that late recurrences is not uncommon and remains a potential risk even after many years without apparent disease.

Given that the majority of melanomas encountered in underwriting are early stage tumors, a closer focus was made on Stage IA and IB melanomas and the impact, beyond the stage group, of additional prognostic factors. Important observations and some representative examples include:

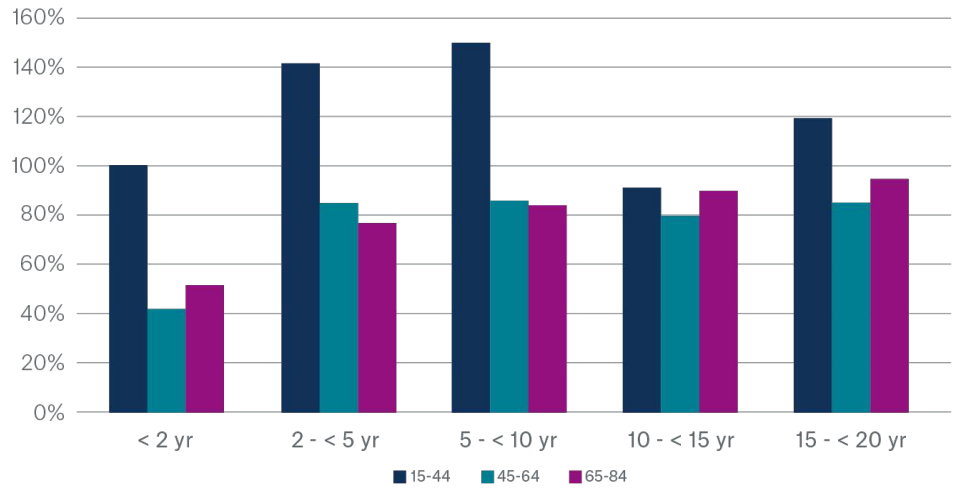
- Figure 2 demonstrates that mortality is low in the first two years following diagnosis and treatment of early stage melanomas. This likely reflects a selection effect, meaning those being diagnosed with melanoma had both enough health concern to pursue an evaluation and the health care access to receive care, along with a reasonably prolonged survival expected in such cases following any early recurrence.

Figure 2. T1a Mortality Ratio by Interval - All Ages



- The noted long tail of excess risk for thin melanomas appears to be more evident at younger ages on a relative risk basis, as shown in Figure 3.

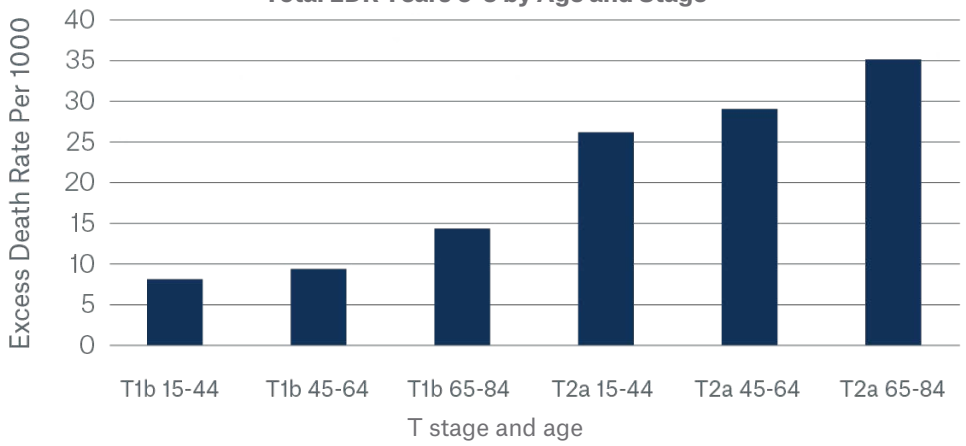
Figure 3. T1a Mortality Ratio by Age



- During the first five years, the absolute risk of dying, i.e., the excess death rate (EDR), is highest at older ages. However, the relative risk, compared to the expected mortality (SMR), is higher in the 15-44 age group, as shown in Figure 4.

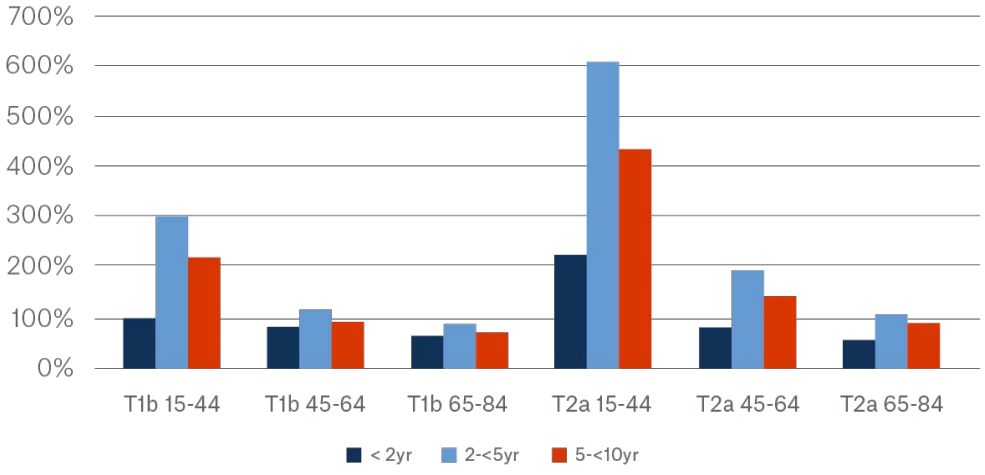
Figure 4. Stage IB:

Total EDR Years 0-5 by Age and Stage



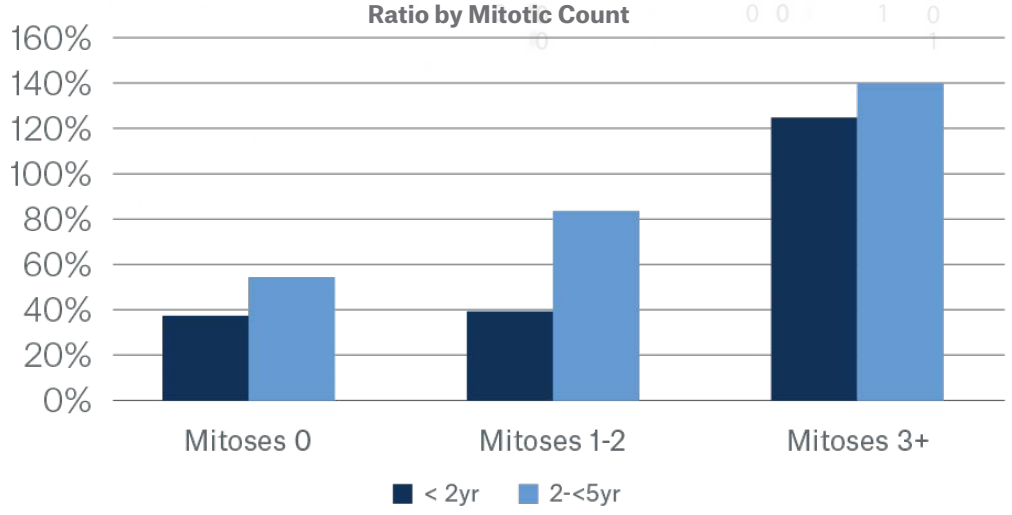
- Despite both being included in stage group IB, the risk with T2a lesions is clearly worse than for T1b lesions as demonstrated in Figure 5. This finding was also seen with the AJCC dataset.

Figure 5. Mortality ratio by T stage and Interval



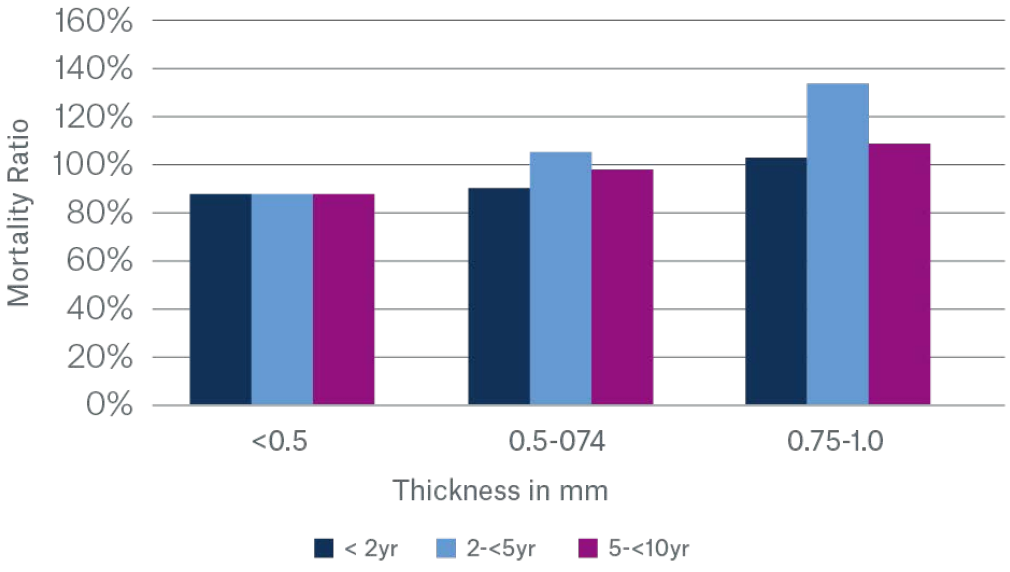
- Figure 6 shows mitotic rate remains an important prognostic factor for thin melanomas even when stratified by specific stage group.

Figure 6. StageT1N0M0 Mortality Ratio by Mitotic Count



- The increased risk associated with T1a melanomas at the higher thickness range (0.8-1.0mm) is apparent in SEER as well as in the AJCC dataset, as shown in Figure 7.

Figure 7. T1aN0M0 Mortality Ratio Compared to Thickness <0.5mm



These data are, of course, instrumental in guiding our underwriting decisions. It is important to note, however, that this survival data predates a number of significant treatment advances that are likely to have a big impact on the mortality outcomes. Research advancements made in understanding the molecular and immune biology of melanoma has led to the introduction of powerful new immunotherapies and targeted therapies, such as nivolumab, pembrolizumab, vemurafenib, and dabrafenib plus trametinib. Historically, most recurrences led to death at a median of 18-24 months, but with the utilization of these treatments, this has been markedly extended. Pooled data in a large study that implemented immunotherapies found half of those with metastatic disease were still alive at 5 years, including what may be some durable complete responses (possible cures?). Furthermore, population-based studies have found that the overall melanoma mortality rate (i.e., for all stages combined) dropped by 7% annually between 2013 and 2017. This approximately 25% decrease is attributed almost entirely to the broad use of these breakthrough treatments in those who present with metastatic disease and those with metastatic recurrence. Use is now being extended to adjuvant treatment for those at high risk of recurrence with favorable preliminary results. New treatments are on the horizon as well. For this reason, it is quite likely that we will already see a 25% or greater reduction in overall mortality compared to the results determined from SEER and the AJCC datasets.[3,53]

Underwriting of Melanoma For Life and DI Coverage

Recognizing that melanoma prognosis closely correlates with tumor stage, but that other factors are important as well, it is prudent to obtain pathology reports and to consider the following in an underwriting assessment when possible:

- Applicant's age
- Location of the primary tumor
- Tumor thickness
- Presence or absence of ulceration
- Mitotic rate
- A nodular "vertical" growth phase
- Clark's level
- Any lymphovascular invasion
- The extent of any tumor regression
- The degree of any tumor infiltrating lymphocytes.
- The recurrence score, if a tumor gene-expression profile was done

For thin melanomas, clinical follow-up alone is sufficient, assessing for spread to the skin around the excision site, to regional nodes, or to the region between these (in-transit metastases). Additional testing is done if suspicious signs or symptoms develop. Common sites for systemic metastasis of melanoma are the liver, lung, and brain, and though not routinely checked as part of follow-up, underwriters are advised to assess with caution if there is any indication of abnormal liver function test results (especially LDH), abnormal chest x-ray findings, neurologic findings, or respiratory symptoms, that are not explained by other causes. For more advanced melanomas, during the initial years of high recurrence rates, more extensive follow-up testing including PET-CT scanning is usually done.

For any melanoma, even years after its occurrence, follow-up examinations looking also for a second primary melanoma are generally warranted, given the significantly increased risk of additional tumors. It is worthwhile in underwriting to also consider other factors which increase this risk, such as any family history of melanoma, the presence of atypical or dysplastic nevi, and simply the overall number of nevi. The presence of a number of these factors, especially in those with a personal or family history of melanoma at a young age, also raises the specter of an underlying genetic predisposition, such as the Familial atypical multiple mole and melanoma (FAMMM) syndrome, often associated with a CDKN2A gene mutation. This has additional relevance in that it is a risk for other malignancies besides melanoma, particularly pancreatic adenocarcinoma.[54-56]

The morbidity risk related to localized melanomas is generally tied to the recurrence risk, given that the treatment itself in such cases is usually limited. There may be some long-term risk associated with the treatment of advanced melanomas, such as from lymph node dissection or chemotherapies, or if there are concerns of an underlying cancer syndrome, as discussed above. Increased psychological stress in cancer survivors has been found in some studies, but there is no reason to believe that this would be an important issue with melanoma.

Looking ahead

Melanoma is a commonly encountered cancer, and it is therefore necessary for an underwriter to understand well the factors that impact the overall prognosis for this malignancy. As more of these are being identified at early stages, the prognosis is often very good, but it is important to keep in mind that certain features put applicants at a higher risk of recurrence and that that recurrence risk persists for 15 years or more. At the same time, major advances in melanoma treatment have already had a major bearing on outcomes and are expected to have an even greater impact over the coming years. Many experts currently speak of metastatic melanoma as likely becoming more of a chronic, treatable disease in the future, rather than an ultimately terminal event. It will be exciting to follow those advances, and you can count on Munich Re to be attuned to these improvements as they develop.

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