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# A deep look into thin melanomas: What's new for the clinician and the impact on the patient☆,☆☆

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ABSTRACT

Melanoma incidence and mortality are on the rise and although most new cases of melanoma are thin, a significant percentage of these patients still experience disease progression. The American Joint Committee on Cancer publishes staging criteria for melanoma, which were recently updated to the 8th edition. The most significant revision from the 7th edition affects the T1b classification, which now includes melanomas with a Breslow depth of 0.8 mm to 1.0 mm. The second major revision eliminates mitoses as a criterion to upstage a thin melanoma to T1b. Although mitotic figures have been established as an independent prognostic factor, they do not have a significant correlation with sentinel lymph node (SLN) biopsy positivity. SLN status remains the most important independent prognostic factor in thin melanomas. Nonetheless, the identification of patients who are at the highest risk for having a positive SLN test result remains difficult. Importantly, a positive SLN test result has high positive predictive value, but a negative one has very low negative predictive value. Since there is no proven survival benefit in performing an SLN biopsy in T1 disease, dermatologists need to have a personalized discussion with patients with thin melanomas to review expected risks and benefits before undertaking this procedure.



## Introduction

Melanoma incidence is on the rise and has increasingly become a public health concern. Approximately 87,000 new cases of invasive melanoma were diagnosed in 2017 (Siegel et al., 2017). This rising incidence of melanoma has exponentially affected the expanding population of people over the age of 60 years compared with other age groups (Whiteman et al., 2016). Thin melanomas, which up until this point were defined as those with <1mm Breslow depth, account for approximately 70% of new cases and approximately 25% of melanoma deaths (Hieken et al., 2015) despite having an excellent prognosis with an observed 12-year survival of approximately 85% (Maurichi et al., 2014).

The American Joint Committee on Cancer (AJCC) recently published its 8th edition of staging criteria, which went into effect as of January 1, 2018 (Gershenwald et al., 2017). Herein, we summarize the staging changes and rationale for these changes most specifically for T1 tumors because these are the melanomas that dermatologists commonly manage alone.

## American Joint Committee on Cancer 8th edition tumor staging update

The impact of Breslow depth and mitoses has been adjusted in the new AJCC staging. The most significant change is that all tumors with a Breslow depth of 0.8 mm to 1.0 mm are now staged as T1b. Nonulcerated tumors with a Breslow depth of <0.7 mm are still classified as T1a. In addition, Breslow depth is now reported to the nearest tenth decimal place. Therefore, with rounding, T1b tumors encompass 0.75 mm to 1.04 mm or any ulcerated tumor of <0.7 mm (Gershenwald et al., 2017). Mitoses are no longer part of the criteria to upstage from T1a to T1b. There were no changes to T2-T4 staging (Gershenwald et al., 2017). The clinical stage groups were not altered; T1a is still stage 1A, and T1b is still stage 1B (Gershenwald et al., 2017).

### *Breslow depth*

Breslow depth is measured from the granular layer or base of an ulcer to the deepest invasive cell across the broad base of the tumor

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(Breslow, 1970). In a prospective study of 2243 patients in six European centers, the authors found that increasing depth was a statistically significant independent prognostic factor for thin melanomas (Maurichi et al., 2014). Patients with tumors >0.75 mm in depth had a positive sentinel lymph node biopsy (SLNB) test result in 11.7% of cases compared with 4.6% in tumors of 0.50 mm to 0.75 mm (Maurichi et al., 2014).

Another group compared 178 thin melanomas with and without distant metastases and found that the 0.76 to 1.00 mm Breslow depth group had a statistically worse cumulative survival rate (Murali et al., 2012). This prognostic concern for melanomas >0.75 mm in depth was further reinforced in a small retrospective study of 512 patients that showed that all deaths from thin melanomas were due to tumors ≥0.8 mm (Durham et al., 2017).

A recent, large meta-analysis of 10,928 patients with thin melanomas who underwent SLNB examined depth as a prognostic factor. The results showed that patients with tumors >0.75 mm had an increased risk of a positive SLNB compared with tumors <0.75 mm (Cordeiro et al., 2016). The association was even stronger when other high-risk features were present (Cordeiro et al., 2016). Due to the significant evidence demonstrating that melanomas >0.75 mm to 1.00 mm have a worse prognosis, the updated AJCC 8$^{th}$ edition criteria now categorize these tumors as T1b.

*Ulceration*

Although common in thick melanomas, ulceration is rare in T1 disease (Garbe et al., 2002). One study found that ulceration was present in only 1.7% of T1 disease but rates of 34.0% and 53.2% were noted in T3 and T4 disease, respectively (Garbe et al., 2002). The presence of ulceration is an independent adverse prognostic parameter in thick melanomas but its predictive value has been inconsistent in thin melanomas (Garbe et al., 2002). One study from the German Central Malignant Melanoma Registry and another that examined 1563 patients over 30 years noted no difference in prognosis for T1 melanomas with and without ulceration (Garbe et al., 2002; Kalady et al., 2003). It was suggested that the statistical power needed to demonstrate a subtle survival difference with ulceration was not achieved due to insufficient patient numbers (Kalady et al., 2003).

One small study previously discussed did show a statistical difference in distant metastasis-free survival between ulcerated and nonulcerated thin melanomas (Murali et al., 2012). However, these results were questionable since the ulceration rate was much higher than that of other studies at 9.5% (Garbe et al., 2002; Murali et al., 2012). Another review demonstrated that ulcerated thin melanomas had a higher association of positive SLNB compared with nonulcerated tumors (Maurichi et al., 2014), but few other investigations reached this same conclusion (Cooper et al., 2013; Warycha et al., 2009). A recent Surveillance, Epidemiology and End Results registry study showed that 16.1% of patients with ulcerated thin melanomas died at 10 years compared with only 2.8% of patients with nonulcerated tumors (Landow et al., 2017). However, this paper did not analyze other secondary factors that may have affected prognosis, specifically mitoses (Landow et al., 2017). Therefore, at this time, there are conflicting reports documenting the prognostic importance of ulceration in thin melanomas, and there is mixed support for the AJCC 8$^{th}$ edition upstaging T1 disease.

*Mitoses*

The prognostic significance of mitoses has long been debated in the literature. In the 7$^{th}$ edition of the AJCC staging criteria, mitotic rate was included as a criterion for upstaging a thin melanoma to T1b, replacing Clark level of invasion. The first large study to examine the mitotic rate studied 3661 patients with stage 1 and 2 melanomas (Azzola et al., 2003). The study showed that mitotic rate was an independent prognostic factor, was more significant than ulceration, and that even the presence of one mitotic figure conferred a statistically worse prognosis than no mitoses (Azzola et al., 2003). These conclusions were confirmed with a larger multicenter study that studied 13,296 stage 1 and 2 melanomas and found that the mitotic rate was the strongest prognostic factor after depth (Thompson et al., 2011). Another group revealed that the presence of mitoses had a worse cumulative survival, specifically in T1 melanomas (Murali et al., 2012).

Today, there is little debate about the prognostic significance of mitoses but a debate persists with regard to what number of mitoses per mm$^2$ is required to affect staging. There is also a debate concerning the ability to predict SLNB positivity. These studies have all been complicated by the variability in observing and documenting mitotic figures, which supports the need to adhere to a standardized detection method when studying this characteristic (Knezevich et al., 2014).

A large meta-analysis studied the factors predicting a positive SLNB in 3651 thin melanomas and showed that mitotic rate did not correlate with a positive SLNB (Warycha et al., 2009). However, another study revealed conflicting results by demonstrating that the presence of one mitosis was significant in predicting a positive SLNB compared with no mitoses (Maurichi et al., 2014). A large Dutch study retrospectively reviewed the impact of the transition from the AJCC 6$^{th}$ to 7$^{th}$ edition with the addition of mitoses to the criteria (Oude Ophuis et al., 2017). During the study period, the T1b cohort doubled with the AJCC 7$^{th}$ edition criteria, and there was an almost 400% increase in performed SLNBs (Oude Ophuis et al., 2017). They found no difference in SLNB positivity rates or survival at 5 years between the two groups. The conclusion of the study was to reconsider the incorporation of mitotic rate in the staging criteria (Oude Ophuis et al., 2017). Another extensive review concluded that one mitotic figure did not predict a positive SLNB and should not be the sole criteria to encourage an SLNB (Kirkland and Zitelli, 2014).

Mitotic rate has been shown to be an independent prognostic factor and is likely more important than ulceration in T1 disease. However, there is no good evidence that mitotic rate correlates with a positive SLNB, and too many patients were undergoing SLNB solely due to a mitotic figure from the AJCC 7$^{th}$ edition. Some have recommended that the cutoff of one mitosis be elevated to increase correlation, but to date this has not been validated (Cooper et al., 2013). Therefore, the evidence supported removing mitotic rate from the AJCC 8$^{th}$ edition staging criteria.

Future studies need to reproduce the prognostic and SLNB impact in large prospective studies, paying close attention to standardized reporting of mitotic figures. Meanwhile, mitotic rate should remain a part of the pathology report for all melanomas and, although not a criteria for SLNB, should remain part of the discussion with the patient with regard to work up and prognosis.

## Sentinel lymph node biopsy

One of the most difficult decisions dermatologists face when treating thin melanomas is when to refer for SLNB. There is some guidance, but strict guidelines do not exist. The National Comprehensive Cancer Network recommends “discussion and consideration” of SLNB for melanomas that are 0.76 mm to 1.00 mm, especially if other high-risk features of ulceration, lymphovascular invasion, regression, or a high mitotic rate are identified (Coit et al., 2016). A recent review took a stricter stance and recommended that patients with melanomas of 0.76 mm to 1.0 mm without other high-risk features should not consider an SLNB (Rosko et al., 2017).

In 2014, the 10-year results of the Multicenter Selective Lymphadenectomy Trial that compared patients who underwent SLNB with those who underwent nodal observation were published (Morton et al., 2014). This was the first randomized controlled trial that conclusively showed that management with an SLNB improves melanoma-specific survival (Morton et al., 2014). The results also showed that sentinel node status was the most important independent prognostic indicator. The issue for dermatologists was that these results were for melanomas of an intermediate thickness (1.20-3.50 mm; Morton et al., 2014). The thin melanomas that dermatologists primarily manage were not included in this trial; therefore, the results cannot be extrapolated to tumors <1.0 mm.

Fortunately, other studies have specifically examined SLNBs in thin melanomas. A large review of the Surveillance, Epidemiology and End Results registry examined 32,527 T1 melanomas (Hieken et al., 2015). This analysis showed that a positive sentinel lymph node confers a worse cancer-specific survival for all T1a tumors, T1b tumors, and the combination of T1a and T1b tumors. The study also recommended consideration of SLNB for T1b melanomas SLNB was the most important prognostic factor in the review (Hieken et al., 2015). The Dutch registry study found that a positive SLNB correlated with depth, but the authors cited the financial burden and associated morbidity with SLNB as the reason why the risk may outweigh the benefits for T1b disease (Oude Ophuis et al., 2017).

SLN positivity rates varied from 3.2% to 9.5% with most studies around 5% for thin melanomas (Coit et al., 2016; Hieken et al., 2015; Morton et al., 2014; Murali et al., 2012; Oude Ophuis et al., 2017; Rosko et al., 2017). The predicament in T1 disease is that a positive SLN has high positive predictive value but a negative node has very low negative predictive value (Hieken et al., 2015). This conundrum must be explained to patients, and they must be informed that close clinical follow-up is necessary even with a negative SLNB.

The other important fact is that there is no proven survival benefit to performing an SLNB in T1 disease, as shown in a randomized controlled trial (Morton et al., 2014). Therefore, evidence supports discussing and considering an SLNB for patients with T1b melanomas but SLNB should not be routinely recommended. Future large multicenter prospective studies are needed to further characterize the impact of SLNBs.

## Conclusions

Dermatologists are the primary physicians managing patients with thin melanomas. There are significant changes to the T1 staging system in the 8th edition from the AJCC with regard to the Breslow depth and mitotic figures. The evidence supports these changes. The most difficult decision for dermatologists is which patients with T1b melanomas should receive an SLNB. The transition to the 8th edition will likely reduce the number of SLNBs due to the absence of mitotic figures as a criterion.

The change in depth will not likely change the way we practice given that we already approach tumors >0.75mm with greater caution. Dermatologists will need to continue to discuss SLNBs with patients with T1b melanomas who have additional high-risk features. However, SLNB for patients with T1b melanomas will not be automatically recommended because the test is expensive, has associated morbidity, and does not have a proven survival benefit for thin melanomas. Regardless of whether an SLNB is performed, patients with T1 melanomas are at risk for disease progression, so vigilant, long-term clinical follow up is essential for these patients.

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