

47. Melanoma of the Skin

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Emerging Prognostic Factors for Clinical Care

Melanoma Subtype

The major melanoma subtypes defined by the World Health Organization (WHO)¹ are superficial spreading, nodular, lentigo maligna, acral lentiginous, and desmoplastic. This classification correlates with the epidemiologic characteristics of the patient populations and with the genomic status of the tumors. The data used to derive the TNM categories were based largely on melanomas of superficial spreading and nodular subtypes. There is evidence that melanomas of other subtypes, especially desmoplastic melanomas, but perhaps also lentigo maligna and acral lentiginous melanomas, have a different etiology and/or pathogenesis and natural history.²⁻⁶ At present, the same staging criteria should be used for melanomas with any growth pattern.

Desmoplastic melanoma is a rare subtype of melanoma characterized by malignant spindle cells separated by prominent fibrocollagenous or fibromyxoid stroma. Primary melanomas may be entirely or almost entirely (>90% of dermal invasive tumor) desmoplastic (“pure” desmoplastic melanoma) or exhibit a desmoplastic component admixed with a nondesmoplastic component (“mixed” desmoplastic melanoma: 10–90% desmoplastic).⁷ Improved disease-specific survival is observed in patients with pure desmoplastic melanoma, compared with patients with mixed desmoplastic melanoma and those with melanomas lacking a desmoplastic component.⁸⁻¹⁰ Furthermore, regional nodal metastasis (including metastasis detected by SLN biopsy) is less common in patients presenting with clinically localized pure desmoplastic melanoma compared with those with mixed desmoplastic melanomas or conventional (nondesmoplastic) melanomas.¹¹⁻¹⁴ AJCC Level of Evidence: III

Regression

Regression occurs when a host immunologic response is directed against melanoma cells and results in elimination of part or all of the melanoma. It is characterized by immature or mature superficial dermal fibrosis, often accompanied by the presence of melanophages, lymphocytes, and effacement of the rete architecture, with absence of melanoma in the region of regression. Although a different pattern of

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regression may be demonstrated in the tumorigenic compartment of melanomas and in metastases, this term in practice generally refers to the *in situ* or superficially invasive primary melanomas. Regression is often patchy within a tumor, and if regression is present at a resection margin, the margin should be considered positive, or at least questionable. It is scored as present or absent.

The prognostic significance of regression is controversial. Some studies report that it portends a worse prognosis (particularly in thin melanomas), whereas others report that it is associated with a more favorable outcome.¹⁵ Difficulties in interpreting such studies include lack of a standardized definition or criteria for its diagnosis, selection bias, and poor interobserver reproducibility. AJCC Level of Evidence: III

Extent of Primary Tumor Ulceration

The maximum extent of ulceration is measured in millimeters. Percentage ulceration is defined as the ratio of the greatest diameter of the ulceration (in millimeters) to the greatest diameter (in millimeters) of the dermal-invasive component of the melanoma. All measurements should be made by using an ocular micrometer. In one recent study of 4,661 patients, 5-year melanoma-specific survival was 91.3% for nonulcerated melanomas, 82.7% for tumors with an ulcer diameter ≤ 5 mm, and 59.3% for melanomas with an ulcer diameter > 5 mm.¹⁶ AJCC Level of Evidence: III

Risk Assessment Models

The AJCC recently established guidelines that will be used to evaluate published statistical prediction models for the purpose of granting endorsement for clinical use.¹⁷ Although this is a monumental step toward the goal of precision medicine, this work was published only very recently. Four models¹⁸⁻²¹ were evaluated for this cancer site by the Precision Medicine Core, but thus far, no existing melanoma model appears to have met the agreed-upon criteria.²² A full list of the evaluated models and their adherence to the quality criteria is available on www.cancerstaging.org.

In the future, the statistical prediction models for this cancer site will be reevaluated, and those that meet all criteria will be endorsed.¹⁷⁻²¹

Recommendations for Clinical Trial Stratification - DRAFT

The following stratification criteria stem from the prognostic factor analyses that are suggested for use in melanoma trials, depending on the specific objectives of the study, the cancer stage(s), and the population under study, including sample size. These recommended criteria for clinical trials are listed in approximate order of their clinical impact by stage, although ongoing and expanded analyses likely will continue to inform these recommendations over time.

Stages I and II

Primary tumor thickness

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Primary tumor ulceration
Primary tumor mitotic rate
Patient age (<65 vs >65 years)
Patient gender ????

Stage III

Number of tumor-involved regional nodes
 One versus two or three versus four or more metastatic nodes
Regional lymph node method of detection: clinically evident or clinically occult (i.e., SLN positive)
Presence of in-transit/satellite/microsatellite disease?
Tumor thickness of the primary melanoma
Ulceration of the primary melanoma
Sentinel node tumor burden
Patient age (<65 vs >65 years)????
?Resectability?

Stage IV

Anatomic site of distant metastasis(es)
Serum LDH
Mutation status?
?Resectability?

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