REVIEW

Melanoma on chronically sun-damaged skin: Lentigo maligna and desmoplastic melanoma

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There are multiple, genetically distinct pathways that give rise to melanoma. Melanomas on sun-damaged skin (MSDS), including lentigo maligna and desmoplastic melanoma, have distinct genetic profiles and are uniquely linked to chronic ultraviolet exposure. In this article, we discuss the etiologies of lentigo maligna and desmoplastic melanoma, emerging diagnostic adjuncts that might be helpful for accurately identifying these lesions, and the clinical relevance of their frequent co-occurrence. We present unique and overlapping features of these entities and discuss challenges in MSDS management, including margin assessment, excision, and the potential role of nonsurgical therapy. Last, we address the role of immunotherapy in invasive disease. Understanding MSDS as distinct from melanoma arising on intermittently sun-exposed or sun-protected skin will ultimately help optimize patient outcomes. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2019.03.066.)

Key words: dermoscopy; desmoplastic melanoma; lentigo maligna melanoma; melanoma; reflectance confocal microscopy; sun-damaged skin.

Primary cutaneous melanoma is usually categorized as superficial spreading, lentigo maligna (LM), nodular, or acral lentiginous on the basis of histologic morphology and the belief that all melanomas arise from a common pathway.[1,2] However, since the divergent pathways model was described in 2003,[3,4] genomic studies have supported the hypothesis that melanomas associated with chronic sun damage are genetically distinct from those arising on intermittently sun-exposed parts of the body.[5-9] Current frameworks now divide melanomas on the basis of their genetic profile and ultraviolet (UV) association, with chronic sun-induced damage melanoma and desmoplastic melanoma (DM) representing distinct entities linked by their association with extensive UV exposure.[10]

Although LM and DM have differing genetic profiles, their frequent co-occurrence and shared relationship with UV exposure have significant clinical implications. With an aging population, the incidence of melanoma on sun-damaged skin (MSDS) is increasing. Early diagnosis and an understanding of how MSDS differs from melanoma arising on intermittently sun-exposed or sun-protected skin is important to optimize patient outcomes.

MORPHOLOGY

The melanoma morphology typically associated with chronic sun exposure is lentigo maligna melanoma (LMM). The in situ form, LM, has been referred to as an infective senile freckle[11] or Hutchinson melanotic freckle[12] and can resemble a solar lentigo, pigmented actinic keratosis, or lichen planus-like keratosis.[13] LM exhibits a long radial growth pattern[14,15] and represents 79%-83% of all melanoma in situ (MIS) cases.[16] Estimated rates of progression from LM to LMM vary widely; in a 1987 epidemiologic analysis, a 5% lifetime risk for invasion was estimated for a person given an LM diagnosis at age 45 years.[17] Once dermal involvement occurs, LMM has the same prognosis as other

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invasive melanomas when adjusted for Breslow thickness.[18]

While rare, DM, a variant characterized by spindled melanocytes and dense collagenous stroma, is also linked to sun exposure. DM is commonly identified on chronically sun-exposed areas of the body, including the head, neck, and extremities. DM is often reported in association with overlying LM and LMM.[19-21] In a 2013 study, 89% of DM lesions occurred on sun-exposed areas, and 83% were associated with MIS, most commonly LM.[22] DM tends to be thick when definitively identified, possibly because of delayed diagnosis.[19] It has a high local recurrence rate, is associated with neurotropism, and is less likely to metastasize to local lymph nodes despite its depth.[23] Prognosis for DM is controversial, even when adjusting for tumor thickness.[24-27]

CAPSULE SUMMARY

- Melanoma on sun-damaged skin is a unique entity that includes lentigo maligna, lentigo maligna melanoma, and desmoplastic melanoma.
- These melanomas often present subtly and can behave aggressively; thus, they require clinical acumen, the use of all available diagnostic tools, and appropriately aggressive treatment.

EPIDEMIOLOGY

The incidence of MSDS is difficult to estimate. Registry data on MIS might be incomplete, thus underestimating LM incidence.[28] In a 2014 study, LM occurred at an estimated rate of 13.7 cases/100,000 person-years.[29] Evidence suggests that rates of LM and LMM are steadily increasing, with the incidence of LMM increasing faster than any other melanoma subtype.[16,29,30] DM occurs in 2 per 1,000,000 individuals but is estimated to be increasing by 4.6% per year.[20] As the US population ages, it can be expected that variants of MSDS will continue to become more prevalent.[31]

PATHOGENESIS

Melanoma has one of the highest mutation rates of all human cancers,[32] and mutation rates are especially high in MSDS due to chronic UV exposure.[33-37] UV radiation (UVR) stimulates melanin production, drives melanocytes to enter the cell cycle, and induces oxidative damage, leading to the production of signature C>T and CC>TT photoproducts.[38,39] UVR can cause mutations in hair follicle stem cells, contributing to LM development.[40] Cellular changes induced by UVR are potentiated by the immunosuppressive effects of UV light, resulting in decreased immune surveillance.[41]

On the basis of recent genomic analyses, the Cancer Genome Atlas Network categorized cutaneous melanomas into 4 genomic subtypes: mutant *BRAF*, mutant *NRAS*, mutant *NF1*, and triple wild-type.[42] Each mutation involves the mitogen-activated protein kinase pathway,[10,43] a series of receptor tyrosine kinases that respond to growth factor stimulation and, when constitutively activated, promotes cellular proliferation and inhibition of apoptosis.[44] Although the Cancer Genome Atlas Network subtypes represent the most common mutations in melanoma overall, their roles in MSDS are poorly understood. *BRAF* mutations, for example, occur in 50%-81% of primary cutaneous melanomas[5,43,45] but are significantly less common in MSDS (11%-21%).[5,7,46] Similarly, *NF1* mutations occur in 14% of all melanomas, but in a 2015 analysis, 93% of DMs analyzed were found to harbor *NF1* mutations.[47] MSDS are also more likely to be associated with mutations in *KIT*, a tyrosine kinase involved in the mitogen-activated protein kinase, phosphoinositide 3-kinase, and signal transducer and activator of transcription 3 pathways.[48] *KIT* mutations occur in <2% of all melanomas[49] but are found in 25%-28% of MSDS.[6,50] Multiple gain- or loss-of-function mutations have also been implicated in MSDS, including *CCND1*, a cyclin involved in cell cycle regulation, *MITF*, a transcription regulator of cellular proliferation, and *TP53*, a tumor suppressor gene.[10] The genetic profile of MSDS has important implications for selecting targeted therapies.

CLINICAL PRESENTATION

The presentation of MSDS is variable, and LM, LMM, and DM might appear similar to benign lesions. Classically, LM and LMM occur on the face of older, male patients (Fig 1).[11,12,28,51] A history of chronic solar damage and other UV-associated neoplasms is frequently present.[5,12,52,53]

DM presents a clinical challenge as well (Fig 2).[10,19,54] DM might be misdiagnosed as a benign entity and treated with cryotherapy, steroids, or laser therapy before diagnosis is confirmed. In one 2013 retrospective study, 27% of DM cases analyzed had been treated as benign lesions before biopsy and definitive diagnosis.[22]

DERMOSCOPY

Dermoscopic characteristics of LM are well described in the literature and include asymmetric pigmented follicular openings, dark rhomboidal

Abbreviations used:

AAD:	American Academy of Dermatology
DM:	desmoplastic melanoma
LM:	lentigo maligna
LMM:	lentigo maligna melanoma
MIS:	melanoma in situ
MMS:	Mohs micrographic surgery
MSDS:	melanoma on sun-damaged skin
NCCN:	National Comprehensive Cancer Network
RCM:	reflectance confocal microscopy
UV:	ultraviolet
UVR:	ultraviolet radiation

structures (angulated lines), and gray dot granules (peppering).[54-60] Additional notable features include a follicular circle within a circle pattern, indicative of atypical melanocytes extending down adnexa,[57] and angulated lines. Gray pigmentation might be the most common finding in early LM and, in one 2015 analysis, was found in 88.6% of LM cases (Fig 3, *A*).[59,60]

The dermoscopic features of DM are less well described. Typical melanocytic structures, such as globules or a pigment network, are observed in 43%-60% of DMs. However, in 2 recent studies, ≥1 melanoma-specific structure was present on dermoscopic exam in 100% of DMs analyzed. These included atypical or polymorphous vascular structures (81%-87%), crystalline structures (shiny white lines, 80%), an annular-granular pattern (24%-40%), and scar-like areas (8%-67%).[23,54] Evidence of regression, such as gray dot granules, is also common in DM (Fig 3, *B*).[22]

REFLECTANCE CONFOCAL MICROSCOPY (RCM)

RCM is a noninvasive tool that can be helpful for identifying MSDS. RCM can be used to image skin to a depth of 250 μm (superficial dermis), and its utility for the diagnosis of melanocytic lesions is well established (Fig 4).[61-65] The RCM criteria for LM and LMM diagnosis (sensitivity 85%, specificity 76%) have been previously described.[66]

The use of RCM to identify DM has been studied, but unique features remain elusive. Cellular atypia and pagetoid spread are usually visible.[67] Dermal inflammation, spindle cells in the superficial dermis, and nucleated cells in the dermis can help distinguish DM from non-DM MIS, but these features are not present in all cases and might be seen in other lesions.[23]

The limitations of RCM include the equipment cost, training requirement, and inability to visualize deeper than 250-300 μm, which is particularly disadvantageous in identifying dermal entities, such as DM.[28] In addition, pagetoid melanocytes might be difficult to distinguish from dendritic Langerhans cells.[68]

HISTOLOGY

Despite the fact that MSDS tends to appear on cosmetically sensitive sites, excisional biopsy with narrow margins, incisional biopsy of the most concerning or thickest part of the lesion, or excisional broad shave biopsy below the anticipated plane of the lesion are the gold standard for diagnosis.[15,69] Because DM is associated with LM and LMM, site selection for a partial biopsy should be carefully considered to avoid missing a dermal component. The use of RCM to determine biopsy site has been used successfully in cases of facial LM and LMM,[70] and using RCM to determine the type and size of the biopsy required for proper sampling is recommended.

Both LM and DM present histopathologic challenges. LM is often subtle and might only show increased numbers of atypical melanocytes at the dermoepidermal junction, a finding also attributable to chronic sun damage.[52,71] Margins might be difficult to delineate because lesion edges can blend with background melanocytic hyperplasia, prompting the recommendation that a control biopsy be taken from a clinically unaffected area.[15] The most reproducible feature of LM is proliferation of atypical melanocytes at the dermoepidermal junction with underlying solar elastosis (Fig 5).[11,13,51,71-73]

DM is defined by desmoplasia, but the diagnostic requirements are controversial. DM may be classified as pure or mixed, with pure DM defined by prominent desmoplasia throughout the tumor and mixed DM having a higher cellular density (Fig 5).[73] DM presents without an obvious associated MIS up to 30% of the time,[19] and when it is paucicellular, it can be confused with a scar. There should be an increased index of suspicion and evaluation for DM in the biopsy specimen when LM and LMM has been excised.

Immunohistochemistry can be useful in both LM and DM. Staining patterns for LM are identical to those described for other types of cutaneous melanomas,[11-13,72] but nuclear stains (micropthalmia transcription factor, SOX-10, soluble adenyl cyclase) could play a larger role in defining margins.[74] For DM, staining patterns are variable and might be negative with standard melanocytic markers (human melanoma black 45 and melanoma antigen recognized by T cells 1).[75] As a result, S-100 is commonly used, although it might be positive in multiple types of dermal tumors. Wilms tumor 1, SOX-10, nestin, and p75 have all been proposed as equally sensitive to and much more specific than S-100.[76]

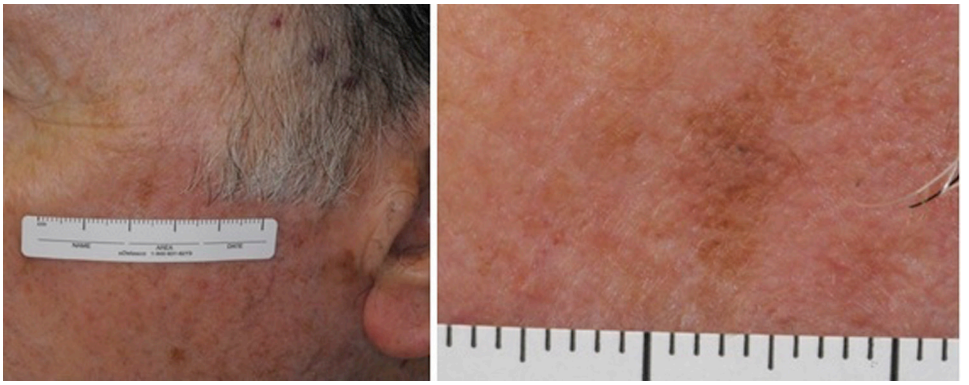

Fig 1. Lentigo maligna in 76-year-old man with history of multiple melanomas. On his follow-up exam, an irregular 5-mm pigmented macule on the left cheek was noted. Lentigo maligna and lentigo maligna melanoma are typically slow growing and present as flat, irregularly pigmented, brown-to-black macules with asymmetric borders. The edges might be obscured by other manifestations of chronic sun damage[11,28,51]; regression is common.[12]

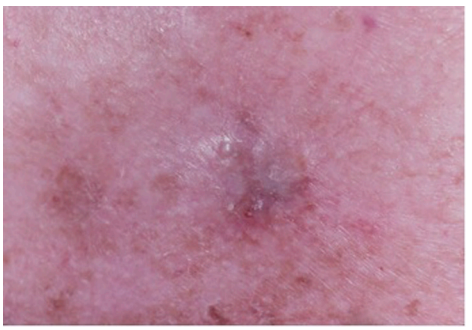

Fig 2. Desmoplastic melanoma appearing as a scar-like lesion. These lesions tend to arise on sun-damaged skin of the head and neck and are often hypopigmented or amelanotic.[10,54] Desmoplastic melanoma might appear as a nodule, plaque, or scar-like lesion or be identified as a palpable component within a pigmented lesion.[19]

EXCISION

The primary goal in treating MSDS is surgical excision with histologically negative margins to eliminate the risks of residual tumor and recurrence.[67] This is challenging for multiple reasons. LM, LMM, and DM tend to occur in cosmetically sensitive areas, particularly the head and neck. In addition, because it is often difficult to determine the clinical margins of LM and skip areas have been described, surgical margins might be equivocal.[77] LM notoriously extends beyond the clinically apparent lesion; a Wood's lamp,[67] dermoscopy,[78] and RCM have all been utilized as tools in surgical planning.[28,77,79-83] Last, nerve involvement in DM is common and, if extensive, can make surgical excision technically challenging.

A significant proportion (16%-32.5%) of tumors classified as LM on biopsy are upstaged to invasive disease after definitive surgical excision and leveling of the specimen.[84-86] In many studies, the 5-mm margin accepted in a 1992 National Institutes of Health consensus statement[87] was found to be too narrow for LM and LMM,[78,84,88-91] and newer guidelines acknowledge that clinically measured surgical margins might need to be >5 mm.[69,92] A variety of staged surgical techniques to ensure adequate margins have been studied,[78,82,93-97] and Mohs micrographic surgery (MMS) currently shows the most promise.[88,98-101] In a 2017 retrospective analysis of MIS patients, no difference was found between MMS and excision with respect to local recurrence and survival.[101] Other studies have demonstrated improved outcomes with MMS for MIS of the head and neck.[88,102,103] Determining the extent of margin clearance and reading melanocytic lesions on frozen section can be challenging,[104] but Mohs surgeons often now use immunohistochemistry stains to accurately identify melanocytes.[105] Slow Mohs (in which the tumor is embedded in paraffin, sectioned en-face, and reviewed by a dermatopathologist) results in similar rates of margin clearance and recurrence.[106,107] Last, although time-consuming, RCM can be used intraoperatively to help determine lateral free margins and unexpected asymmetric extensions of the melanoma.[83] The recent American Association of Dermatology (AAD) guidelines suggests considering MMS for LM of the face, ears, or scalp, with the stipulation that if invasive disease is identified, complete excision and a formal pathology review should be performed.[108]

NONSURGICAL TREATMENT MODALITIES

Although surgical modalities offer the best chance of cure for local disease, there is a limited role for

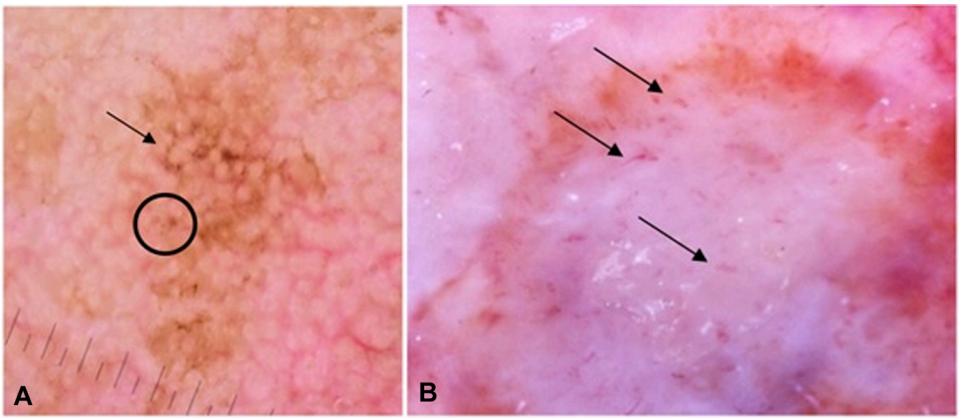

Fig 3. **A**, Dermoscopy of lentigo maligna demonstrating angulated lines (*arrow*) and gray dot granules (*circle*). **B**, Dermoscopy of desmoplastic melanoma revealing polymorphous blood vessels (*arrows*).

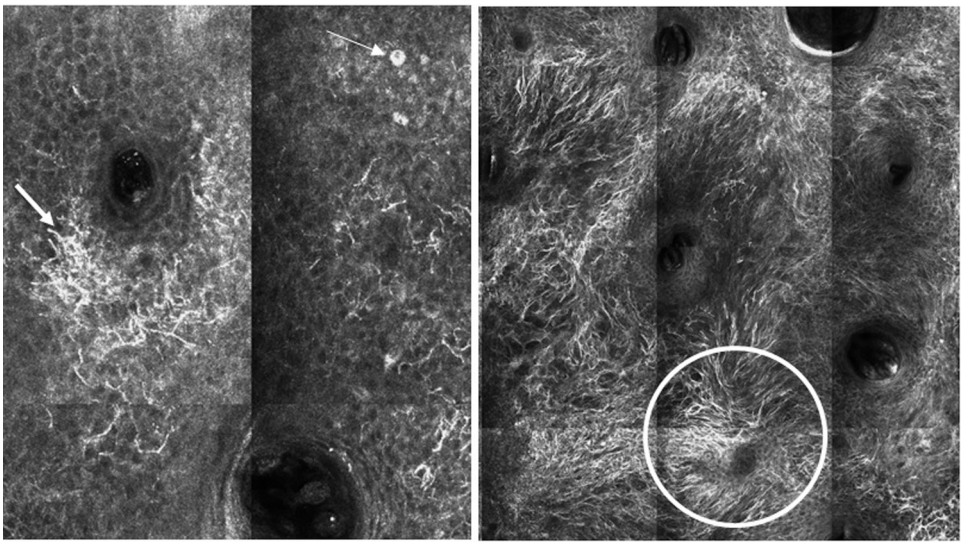

Fig 4. Reflectance confocal microscopy of lentigo maligna. Reflectance confocal microscopy images often demonstrate disrupted architecture or a honeycomb pattern of the epidermis and disruption of the dermoepidermal junction by atypical melanocytes. Extension of refractile dendritic cells down hair follicles might also be seen.[65] Our patient's lesion demonstrated at the spinous granular level bright pagetoid cells that are dendritic (*thick arrow*) and rounded (*thin arrow*) focally infiltrating the epidermis. At the dermoepidermal junction, there are sheets of dendritic cells in the pattern of tangled lines and around follicles (*circle*).

nonsurgical therapy in MSDS, especially for lesions in cosmetically sensitive areas or patients with comorbidities. Disadvantages of nonsurgical treatment include the risk of missing or undertreating invasive melanoma, higher local recurrence rates, the risk of subclinically positive margins, and the absence of long-term randomized clinical trial data.[69] When LM is treated nonsurgically, the possibility of an underlying DM should always be considered and ruled out. Imiquimod, a synthetic imidazoquinoline amine with inflammatory and antitumor effects, currently shows the most promise for topical treatment of LM.[109] Published histologic clearance rates range 59%-75%,[110-114] but protocols vary and follow-up periods are short.[110-115] National Comprehensive Cancer Network (NCCN) recommendations reserve imiquimod for MIS patients with positive margins after optimal surgery.[92] Cryotherapy,[116,117] laser,[118-120] curettage and electrodessication,[121,122] fluorouracil,[121-123] and photodynamic therapy[124] have also been studied.

Radiotherapy might play a role in the treatment of MSDS as primary therapy for in situ lesions when surgery is not an option or as adjuvant treatment after

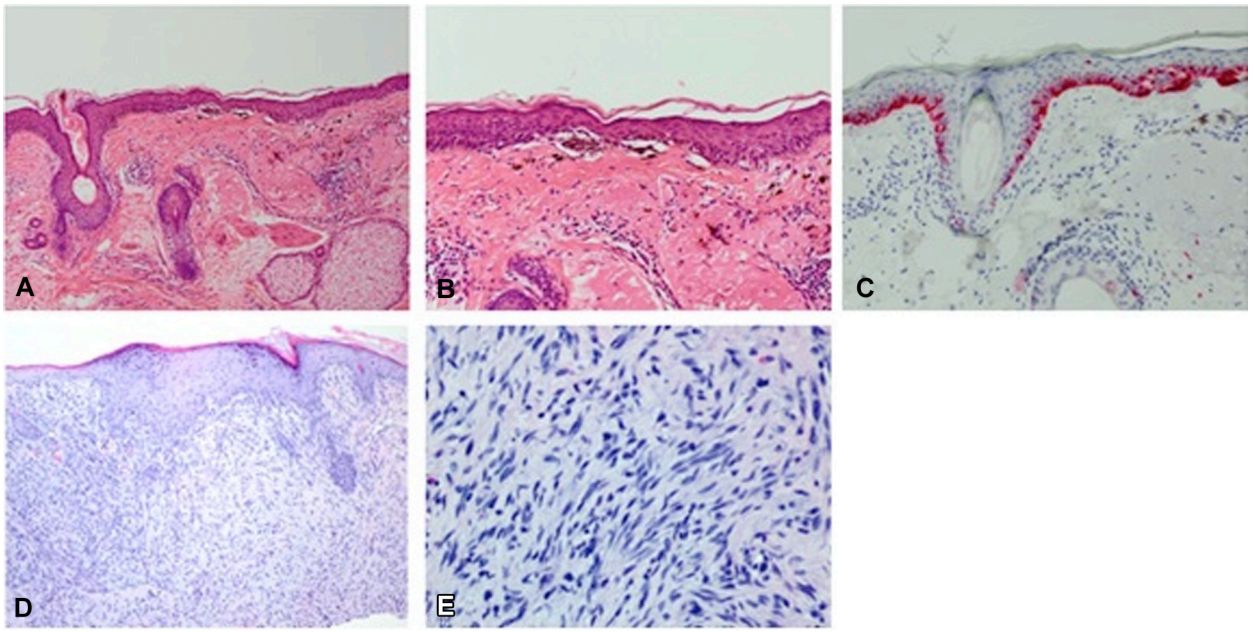

Fig 5. Histochemical characterization of lentigo maligna (**A-C**) and desmoplastic melanoma (**D** and **E**). **A-C**, There is no minimum number of melanocytes for diagnosis of lentigo maligna, but the presence of junctional nests (rather than single cells) has been suggested as a defining feature.[15] Descent of melanocytes along adnexal structures and pagetoid spread are also highly concerning features.[13,71,72] Our case demonstrated atypical single and nested melanocytic hyperplasia predominantly at the dermoepidermal junction and extending down adnexa, which is highlighted in **C**. **D** and **E**, Clusters of hyperchromatic spindle cells with elongated nuclei and lymphocytic aggregates are characteristic of desmoplastic melanoma and should raise suspicion and prompt the use of immunostaining.[73] (**A**, **B**, **D**, and **E**, Hematoxylin-eosin stain; **C**, S-100 immunostain: **A** and **D**, ×100; **B** and **C**, ×200 **E**, ×400.) (Images courtesy of Dr Katalin Ferenczi, UCONN Dermatopathology Lab.)

excision.[125-133] When used as primary treatment for LM, recurrence rates for radiotherapy can be as high as 14%, and there is little data on histologic clearance.[69] NCCN suggests that radiotherapy should be considered for patients who are not good candidates for surgery or who have positive margins after surgical resection. Adjuvant radiotherapy might also be appropriate for DM when there is extensive neurotropism limiting surgical options.[92]

INVASIVE DISEASE

Once MSDS is invasive, workup and staging are largely the same as for other cutaneous melanomas. Current clinical guidelines do not distinguish between MSDS and other types of melanoma in terms of treatment, including surgical options.[130]

The recommended margins for excision of invasive disease are based on high-level, randomized control trial data, although the 2019 AAD guidelines do acknowledge that many studies excluded head and neck sites.[108] Retrospective studies suggest that MMS might be used in the treatment of invasive melanoma,[99,102,105,134] but follow-up periods are short and prospective data are needed. Currently, both the NCCN and AAD caution against sub−1-cm margins, regardless of anatomic site or surgical technique.[92,108]

The NCCN does acknowledge uncertainty regarding the probability and prognostic significance of a positive sentinel lymph node biopsy in DM.[92] In a 2017 systematic review, rates of positive sentinel lymph node biopsy were found to be lower in DM than other types of melanoma, and nodal status was concluded to be an important predictor of survival. This is especially true for mixed DM, which has higher rates of micrometastases to regional lymph nodes.[135]

KIT mutations are more common in MSDS, suggesting that tyrosine kinase inhibitors might play a larger therapeutic role. Early studies of tyrosine kinase inhibitors failed to show improvement in patients with metastatic disease, but these trials enrolled patients with all forms of melanoma and might have been skewed toward non-MSDS disease.[136] More recent trials of imatinib and second generation tyrosine kinase inhibitors that have

selected patients with MSDS or known *KIT* mutations are more promising.[137-140] For DM, there is little data on effective immunotherapy because of its unique genetic profile and relative rarity. There has been minimal research to date on immunotherapy for *NF1*-associated tumors.[141] However, DM demonstrates increased programmed cell death ligand 1 expression compared with other melanoma subtypes,[142] and initial studies of programmed cell death 1 or programmed cell death ligand 1 blockade have shown promising results.

CONCLUSION

MSDS is a unique entity clinically, genetically, and therapeutically. Although LM and DM are genetically distinct, they are linked by their relationship to UV exposure and often co-occur. Their unique and overlapping features in the context of MSDS warrant additional study to improve patient outcomes.

REFERENCES

1. Clark W, From L, Bernardino E, Mihm MC. The histogenesis and biologic behavior of primary human malignant melanomas of the skin. *Cancer Res*. 1969;23.
2. McGovern VJ, Mihm MC, Bailly C, et al. The classification of malignant melanoma and its histologic reporting. *Cancer*. 1973;32(6):1446-1457.
3. Whiteman DC, Watt P, Purdie DM, Hughes MC, Hayward NK, Green AC. Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. *J Natl Cancer Inst*. 2003; 95(11):806-812.
4. Whiteman DC, Parsons PG, Green AC. p53 expression and risk factors for cutaneous melanoma: a case-control study. *Int J Cancer*. 1998;77(6):843-848.
5. Curtin JA, Fridlyand J, Kageshita T, et al. Distinct sets of genetic alterations in melanoma. *N Engl J Med*. 2005;353(20): 2135-2147.
6. Curtin JA, Busam K, Pinkel D, Bastian BC. Somatic activation of KIT in distinct subtypes of melanoma. *J Clin Oncol*. 2006; 24(26):4340-4346.
7. Kim SY, Kim SN, Hahn HJ, Lee YW, Choe YB, Ahn KJ. Metaanalysis of *BRAF* mutations and clinicopathologic characteristics in primary melanoma. *J Am Acad Dermatol*. 2015; 72(6):1036-1046.e2.
8. Bastian BC, Olshen AB, LeBoit PE, Pinkel D. Classifying melanocytic tumors based on DNA copy number changes. *Am J Pathol*. 2003;163(5):1765-1770.
9. Maldonado JL, Fridlyand J, Patel H, et al. Determinants of *BRAF* mutations in primary melanomas. *J Natl Cancer Inst*. 2003;95(24):1878-1890.
10. Bastian BC. The Molecular pathology of melanoma: an integrated taxonomy of melanocytic neoplasia. *Annu Rev Pathol Mech Dis*. 2014;9(1):239-271.
11. Kallini JR, Jain SK, Khachemoune A. Lentigo maligna: review of salient characteristics and management. *Am J Clin Dermatol*. 2013;14(6):473-480.
12. Juhász MLW, Marmur ES. Reviewing challenges in the diagnosis and treatment of lentigo maligna and lentigo-maligna melanoma. *Rare Cancers Ther*. 2015;3:133-145.
13. Reed JA, Shea CR. Lentigo maligna: melanoma in situ on chronically sun-damaged skin. *Arch Pathol Lab Med*. 2011; 135(7):838-841.
14. McKENNA JK, Florell SR, Goldman GD, Bowen GM. Lentigo maligna/lentigo maligna melanoma: current state of diagnosis and treatment. *Dermatol Surg*. 2006;32(4):493.
15. McGuire LK, Disa JJ, Lee EH, Busam KJ, Nehal KS. Melanoma of the lentigo maligna subtype: diagnostic challenges and current treatment paradigms. *Plast Reconstr Surg*. 2012; 129(2):288e-299e.
16. Swetter SM, Boldrick JC, Jung SY, Egbert BM, Harvell JD. Increasing incidence of lentigo maligna melanoma subtypes: northern California and national trends 1990−2000. *J Invest Dermatol*. 2005;125(4):685-691.
17. Weinstock MA, Sober AJ. The risk of progression of lentigo maligna to lentigo maligna melanoma. *Br J Dermatol*. 1987; 116(3):303-310.
18. Florell SR, Boucher KM, Leachman SA, et al. Histopathologic recognition of involved margins of lentigo maligna excised by staged excision: an interobserver comparison study. *Arch Dermatol*. 2003;139(5):595-604.
19. Chen LL, Jaimes N, Barker CA, Busam KJ, Marghoob AA. Desmoplastic melanoma: a review. *J Am Acad Dermatol*. 2013;68(5):825-833.
20. Feng Z, Wu X, Chen V, Velie E, Zhang Z. Incidence and survival of desmoplastic melanoma in the United States, 1992-2007. *J Cutan Pathol*. 2011;38(8):616-624.
21. Lens MD, et al. Desmoplastic malignant melanoma: a systematic review. *Br J Dermatol*. 2005;152(4):673-678.
22. Jaimes N, Chen L, Dusza SW, et al. Clinical and dermoscopic characteristics of desmoplastic melanomas. *JAMA Dermatol*. 2013;149(4):413-421.
23. Maher NG, Solinas A, Scolyer RA, Puig S, Pellacani G, Guitera P. Detection of desmoplastic melanoma with dermoscopy and reflectance confocal microscopy. *J Eur Acad Dermatol Venereol*. 2017;31(12):2016-2024.
24. Walsh NM, Roberts JT, Orr W, Simon GT. Desmoplastic malignant melanoma. A clinicopathologic study of 14 cases. *Arch Pathol Lab Med*. 1988;112(9):922-927.
25. Baer SC, Schultz D, Synnestvedt M, Elder DE. Desmoplasia and neurotropism. Prognostic variables in patients with stage I melanoma. *Cancer*. 1995;76(11):2242-2247.
26. Skelton HG, Smith KJ, Laskin WB, et al. Desmoplastic malignant melanoma. *J Am Acad Dermatol*. 1995;32(5, Part 1):717-725.
27. Quinn MJ, Crotty KA, Thompson JF, Coates AS, O'Brien CJ, McCarthy WH. Desmoplastic and desmoplastic neurotropic melanoma: experience with 280 patients. *Cancer*. 1998;83(6): 1128-1135.
28. Star P, Guitera P. Lentigo maligna, macules of the face, and lesions on sun-damaged skin: confocal makes the difference. *Dermatol Clin*. 2016;34(4):421-429.
29. Mirzoyev SA, Knudson RM, Reed KB, et al. Incidence of lentigo maligna in Olmsted County, Minnesota, 1970 to 2007. *J Am Acad Dermatol*. 2014;70(3):443-448.
30. Greveling K, Wakkee M, Nijsten T, van den Bos RR, Hollestein LM. Epidemiology of lentigo maligna and lentigo maligna melanoma in the Netherlands, 1989-2013. *J Invest Dermatol*. 2016;136(10):1955-1960.
31. US Census Bureau. Older people projected to outnumber children. https://www.census.gov/newsroom/press-releases/2018/cb18-41-population-projections.html. Accessed September 18, 2018.
32. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. *Nature*. 2013; 500(7463):415-421.

33. Mar VJ, Wong SQ, Li J, et al. *BRAF/NRAS* Wild-type melanomas have a high mutation load correlating with histologic and molecular signatures of UV damage. *Clin Cancer Res*. 2013; 19(17):4589-4598.
34. Shain AH, Garrido M, Botton T, et al. Exome sequencing of desmoplastic melanoma identifies recurrent *NFKBIE* promoter mutations and diverse activating mutations in the MAPK pathway. *Nat Genet*. 2015;47(10):1194-1199.
35. Marks R. Epidemiology of melanoma. *Clin Exp Dermatol*. 2000;25(6):459-463.
36. Whiteman DC, Whiteman CA, Green AC. Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies. *Cancer Causes Control*. 2001;12(1): 69-82.
37. Davis EJ, Johnson DB, Sosman JA, Chandra S. Melanoma: what do all the mutations mean? *Cancer*. 2018;124(17):3490-3499.
38. Zaidi MR, Davis S, Noonan FP, et al. Interferon-γ links UV to melanocyte activation and promotes melanomagenesis. *Nature*. 2011;469(7331):548-553.
39. Noonan FP, Zaidi MR, Wolnicka-Glubisz A, et al. Melanoma induction by ultraviolet A but not ultraviolet B radiation requires melanin pigment. *Nat Commun*. 2012;3(1).
40. Bongiorno MR, Doukaki S, Malleo F, Aricò M. Identification of progenitor cancer stem cell in lentigo maligna melanoma. *Dermatol Ther*. 2008;21(s1):S1-S5.
41. Bruhs A, Schwarz T. Ultraviolet radiation-induced immunosuppression: induction of regulatory T cells. In: Clausen BE, Laman JD, eds. *Inflammation: Methods and Protocols. Methods in Molecular Biology*. New York, NY: Springer New York; 2017: 63-73.
42. Cancer Genome Atlas Network. Genomic classification of cutaneous melanoma. *Cell*. 2015;161(7):1681-1696.
43. Lee J-H, Choi J-W, Kim Y-S. Frequencies of *BRAF* and *NRAS* mutations are different in histological types and sites of origin of cutaneous melanoma: a meta-analysis. *Br J Dermatol*. 2011;164(4):776-784.
44. Amaral T, Sinnberg T, Meier F, et al. The mitogen-activated protein kinase pathway in melanoma part I — activation and primary resistance mechanisms to BRAF inhibition. *Eur J Cancer*. 2017;73:85-92.
45. Davies H, Bignell GR, Cox C, et al. Mutations of the *BRAF* gene in human cancer. *Nature*. 2002;417(6892):949-954.
46. Stadelmeyer E, Heitzer E, Resel M, Cerroni L, Wolf P, Dandachi N. The *BRAF* V600K mutation is more frequent than the *BRAF* V600E mutation in melanoma in situ of lentigo maligna type. *J Invest Dermatol*. 2014;134(2):548-550.
47. Wiesner T, Kiuru M, Scott SN, et al. *NF1* Mutations are common in desmoplastic melanoma. *Am J Surg Pathol*. 2015; 39(10):1357-1362.
48. Kunz M. Oncogenes in melanoma: an update. *Eur J Cell Biol*. 2014;93(1):1-10.
49. Beadling C, Jacobson-Dunlop E, Hodi FS, et al. *KIT* gene mutations and copy number in melanoma subtypes. *Clin Cancer Res*. 2008;14(21):6821-6828.
50. Jin SA, Chun SM, Choi YD, et al. *BRAF* mutations and *KIT* aberrations and their clinicopathological correlation in 202 Korean melanomas. *J Invest Dermatol*. 2013;133(2):579-582.
51. Tanaka M, Sawada M, Kobayashi K. Key points in dermoscopic differentiation between lentigo maligna and solar lentigo. *J Dermatol*. 2011;38(1):53-58.
52. Higgins HW, Lee KC, Galan A, Leffell DJ. Melanoma in situ: part I. Epidemiology, screening, and clinical features. *J Am Acad Dermatol*. 2015;73(2):181-190.
53. Kvaskoff M, Siskind V, Green A èle C. Risk Factors for lentigo maligna melanoma compared with superficial spreading melanoma: a case-control study in Australia. *Arch Dermatol*. 2012;148(2):164-170.
54. Jaimes N, Marghoob AA, Rabinovitz H, et al. Clinical and dermoscopic characteristics of melanomas on nonfacial chronically sun-damaged skin. *J Am Acad Dermatol*. 2015; 72(6):1027-1035.
55. Schiffner R, Schiffner-Rohe J, Vogt T, et al. Improvement of early recognition of lentigo maligna using dermatoscopy. *J Am Acad Dermatol*. 2000;42(1):25-32.
56. Stolz W, Schiffner R, Burgdorf WHC. Dermatoscopy for facial pigmented skin lesions. *Clin Dermatol*. 2002;20(3):276-278.
57. Pralong P, Bathelier E, Dalle S, Poulalhon N, Debarbieux S, Thomas L. Dermoscopy of lentigo maligna melanoma: report of 125 cases. *Br J Dermatol*. 2012;167(2):280-287.
58. Giacomel J, Lallas A, Zalaudek I, Argenziano G. Dermoscopic "signature" pattern of pigmented and nonpigmented lentigo maligna. *J Am Acad Dermatol*. 2014;70(2):e33-e35.
59. Tiodorovic-Zivkovic D, Argenziano G, Lallas A, et al. Age, gender, and topography influence the clinical and dermoscopic appearance of lentigo maligna. *J Am Acad Dermatol*. 2015;72(5):801-808.
60. Tiodorovic-Zivkovic D, Zalaudek I, Lallas A, Stratigos AJ, Piana S, Argenziano G. The importance of gray color as a dermoscopic clue in facial pigmented lesion evaluation: a case report. *Dermatol Pract Concept*. 2013;3(4):37-39.
61. Rajadhyaksha M, González S, Zavislan JM, Rox Anderson R, Webb RH. In vivo confocal scanning laser microscopy of human skin II: advances in instrumentation and comparison with histology. *J Invest Dermatol*. 1999; 113(3):293-303.
62. Rajadhyaksha M, Grossman M, Esterowitz D, Webb RH, Rox Anderson R. In vivo confocal scanning laser microscopy of human skin: melanin provides strong contrast. *J Invest Dermatol*. 1995;104(6):946-952.
63. Gerger A, Koller S, Kern T, et al. Diagnostic applicability of in vivo confocal laser scanning microscopy in melanocytic skin tumors. *J Invest Dermatol*. 2005;124(3):493-498.
64. Pellacani G, Cesinaro AM, Seidenari S. Reflectance-mode confocal microscopy of pigmented skin lesions—improvement in melanoma diagnostic specificity. *J Am Acad Dermatol*. 2005;53(6):979-985.
65. Langley RGB, Burton E, Walsh N, Propperova I, Murray SJ. In vivo confocal scanning laser microscopy of benign lentigines: comparison to conventional histology and in vivo characteristics of lentigo maligna. *J Am Acad Dermatol*. 2006;55(1):88-97.
66. Guitera P, Pellacani G, Crotty KA, et al. The Impact of in vivo reflectance confocal microscopy on the diagnostic accuracy of lentigo maligna and equivocal pigmented and nonpigmented macules of the face. *J Invest Dermatol*. 2010;130(8): 2080-2091.
67. Waddell A, Star P, Guitera P. Advances in the use of reflectance confocal microscopy in melanoma. *Melanoma Manag*. 2018;5(1).
68. Hashemi P, Pulitzer MP, Scope A, Kovalyshyn I, Halpern AC, Marghoob AA. Langerhans cells and melanocytes share similar morphologic features under in vivo reflectance confocal microscopy: a challenge for melanoma diagnosis. *J Am Acad Dermatol*. 2012;66(3):452-462.
69. Bichakjian CK, Halpern AC, Johnson TM, et al. Guidelines of care for the management of primary cutaneous melanoma. *J Am Acad Dermatol*. 2011;65(5):1032-1047.

70. Alarcón I, Carrera C, Puig S, Malvehy J. Clinical usefulness of reflectance confocal microscopy in the management of facial lentigo maligna melanoma. *Actas Dermosifiliogr*. 2014;105(3):e13-e17.
71. Weyers W, Bonczkowitz M, Weyers I, Bittinger A, Schill W-B. Melanoma in situ versus melanocytic hyperplasia in sun-damaged skin: assessment of the significance of histopathologic criteria for differential diagnosis. *Am J Dermatopathol*. 1996;18(6):560.
72. Higgins HW, Lee KC, Galan A, Leffell DJ. Melanoma in situ: part II. Histopathology, treatment, and clinical management. *J Am Acad Dermatol*. 2015;73(2):193-203.
73. Busam KJ, Mujumdar U, Hummer AJ, et al. Cutaneous desmoplastic melanoma: reappraisal of morphologic heterogeneity and prognostic factors. *Am J Surg Pathol*. 2004;28(11):1518-1525.
74. Kasprzak J, Xu Y. Diagnosis and management of lentigo maligna: a review. *Drugs Context*. 2015;4:1-16.
75. Bastos Junior Cde S, Piñeiro-Maceira JM, de Moraes FMB. Desmoplastic melanoma associated with an intraepidermal lentiginous lesion: case report and literature review. *An Bras Dermatol*. 2013;88(3):408-412.
76. Plaza JA, Bonneau P, Prieto V, et al. Desmoplastic melanoma: an updated immunohistochemical analysis of 40 cases with a proposal for an additional panel of stains for diagnosis. *J Cutan Pathol*. 2016;43(4):313-323.
77. Guitera P, Moloney FJ, Menzies SW, et al. Improving management and patient care in lentigo maligna by mapping with in vivo confocal microscopy. *JAMA Dermatol*. 2013;149(6):692-698.
78. Kassi K, Vanwijck R, Kanga J-M. The ''collerette'' technique for skin excision and biopsy: an efficient method for managing lentigo maligna of the head and neck. *Int J Dermatol*. 2014;53(7):899-903.
79. Curiel-Lewandrowski C, Williams CM, Swindells KJ, et al. Use of in vivo confocal microscopy in malignant melanoma: an aid in diagnosis and assessment of surgical and nonsurgical therapeutic approaches. *Arch Dermatol*. 2004;140(9):1127-1132.
80. Chen C-SJ, Elias M, Busam K, Rajadhyaksha M, Marghoob AA. Multimodal in vivo optical imaging, including confocal microscopy, facilitates presurgical margin mapping for clinically complex lentigo maligna melanoma. *Br J Dermatol*. 2005;153(5):1031-1036.
81. Yélamos O, Cordova M, Blank N, et al. Correlation of handheld reflectance confocal microscopy with radial video mosaicing for margin mapping of lentigo maligna and lentigo maligna melanoma. *JAMA Dermatol*. 2017;153(12):1278-1284.
82. Champin J, Perrot J-L, Cinotti E, et al. In vivo reflectance confocal microscopy to optimize the spaghetti technique for defining surgical margins of lentigo maligna. *Dermatol Surg*. 2014;40(3):247-256.
83. Hibler BP, Cordova M, Wong RJ, Rossi AM. Intraoperative real-time reflectance confocal microscopy for guiding surgical margins of lentigo maligna melanoma. *Dermatol Surg*. 2015;41(8):980-983.
84. Agarwal-Antal N, Bowen GM, Gerwels JW. Histologic evaluation of lentigo maligna with permanent sections: implications regarding current guidelines. *J Am Acad Dermatol*. 2002;47(5):743-748.
85. Erickson C, Miller SJ. Treatment options in melanoma in situ: topical and radiation therapy, excision and Mohs surgery. *Int J Dermatol*. 2010;49(5):482-491.
86. Etzkorn JR, Sobanko JF, Shin TM, et al. Correlation between appropriate use criteria and the frequency of subclinical spread or reconstruction with a flap or graft for melanomas treated with Mohs surgery with melanoma antigen recognized by T cells 1 (MART-1) immunostaining. *Dermatol Surg*. 2016;42(4):471-476.
87. National Institutes of Health. NIH Consensus Development Program: diagnosis and treatment of early melanoma. https://consensus.nih.gov/1992/1992Melanoma088html.htm. Accessed August 15, 2018.
88. Bricca GM, Brodland DG, Ren D, Zitelli JA. Cutaneous head and neck melanoma treated with Mohs micrographic surgery. *J Am Acad Dermatol*. 2005;52(1):92-100.
89. Hazan C, Dusza SW, Delgado R, Busam KJ, Halpern AC, Nehal KS. Staged excision for lentigo maligna and lentigo maligna melanoma: a retrospective analysis of 117 cases. *J Am Acad Dermatol*. 2008;58(1):142-148.
90. Kunishige JH, Brodland DG, Zitelli JA. Surgical margins for melanoma in situ. *J Am Acad Dermatol*. 2012;66(3):438-444.
91. Miller CJ, Shin TM, Sobanko JF, et al. Risk factors for positive or equivocal margins after wide local excision of 1345 cutaneous melanomas. *J Am Acad Dermatol*. 2017;77(2):333-340.e1.
92. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Melanoma. Version 3. 2018.
93. Wilson JB, Walling HW, Scupham RK, Bean AK, Ceilley RI, Goetz KE. Staged excision for lentigo maligna and lentigo maligna melanoma. *J Clin Aesthetic Dermatol*. 2016;9(6):25-30.
94. Bosbous MW, Dzwierzynski WW, Neuburg M. Staged excision of lentigo maligna and lentigo maligna melanoma: a 10-year experience. *Plast Reconstr Surg*. 2009;124(6):1947-1955.
95. Abdelmalek M, Loosemore MP, Hurt MA, Hruza G. Geometric staged excision for the treatment of lentigo maligna and lentigo maligna melanoma: a long-term experience with literature review. *Arch Dermatol*. 2012;148(5):599-604.
96. Johnson TM, Headington JT, Baker SR, Lowe L. Usefulness of the staged excision for lentigo maligna and lentigo maligna melanoma: the ''square'' procedure. *J Am Acad Dermatol*. 1997;37(5, Part 1):758-764.
97. Gaudy-Marqueste C, Perchenet A-S, Taséi A-M, et al. The ''spaghetti technique'': an alternative to Mohs surgery or staged surgery for problematic lentiginous melanoma (lentigo maligna and acral lentiginous melanoma). *J Am Acad Dermatol*. 2011;64(1):113-118.
98. Walling HW, Scupham RK, Bean AK, Ceilley RI. Staged excision versus Mohs micrographic surgery for lentigo maligna and lentigo maligna melanoma. *J Am Acad Dermatol*. 2007;57(4):659-664.
99. Newman J, Beal M, Schram SE, Lee PK. Mohs Micrographic surgery for lentigo maligna and lentigo maligna melanoma using mel-5 immunostaining: an update from the University of Minnesota. *Dermatol Surg*. 2013;39(12):1794-1799.
100. Stigall LE, Brodland DG, Zitelli JA. The use of Mohs micrographic surgery (MMS) for melanoma in situ (MIS) of the trunk and proximal extremities. *J Am Acad Dermatol*. 2016;75(5):1015-1021.
101. Nosrati A, Berliner JG, Goel S, et al. Outcomes of melanoma in situ treated with Mohs micrographic surgery compared with wide local excision. *JAMA Dermatol*. 2017;153(5):436-441.
102. Etzkorn JR, Sobanko JF, Elenitsas R, et al. Low recurrence rates for in situ and invasive melanomas using Mohs micrographic surgery with melanoma antigen recognized by T cells 1 (MART-1) immunostaining: tissue processing

methodology to optimize pathologic staging and margin assessment. *J Am Acad Dermatol*. 2015;72(5):840-850.
103. Bene NI, Healy C, Coldiron BM. Mohs micrographic surgery is accurate 95.1% of the time for melanoma in situ: a prospective study of 167 cases. *Dermatol Surg*. 2008;34(5):660-664.
104. Beaulieu D, Fathi R, Srivastava D, Nijhawan RI. Current perspectives on Mohs micrographic surgery for melanoma. *Clin Cosmet Investig Dermatol*. 2018;11:309-320.
105. Valentín-Nogueras SM, Brodland DG, Zitelli JA, González-Sepúlveda L, Nazario CM. Mohs micrographic surgery using MART-1 immunostain in the treatment of invasive melanoma and melanoma in situ. *Dermatol Surg*. 2016;42(6):733-744.
106. Mahoney EJ, Dolan RW, Choi EE, Olbricht SM. Surgical reconstruction of lentigo maligna defects. *Arch Facial Plast Surg*. 2005;7(5):342-346.
107. Lawrence CM, Rahim R, Charlton F, Husain A. Prospective study of formalin-fixed Mohs surgery and haematoxylin and eosin stains with control contralateral biopsies for lentigo maligna: 5-year follow-up results. *Br J Dermatol*. 2014;171(2):298-303.
108. Swetter SM, Tsao H, Bichakjian CK, et al. Guidelines of care for the management of primary cutaneous melanoma. *J Am Acad Dermatol*. 2019;80(1):208-250.
109. Hemmi H, Kaisho T, Takeuchi O, et al. Small-antiviral compounds activate immune cells via the TLR7 MyD88-dependent signaling pathway. *Nat Immunol*. 2002;3(2):196-200.
110. Cotter MA, McKENNA JK, Bowen GM. Treatment of lentigo maligna with imiquimod before staged excision. *Dermatol Surg*. 2008;34(2):147.
111. Alarcon I, Carrera C, Alos L, Palou J, Malvehy J, Puig S. In vivo reflectance confocal microscopy to monitor the response of lentigo maligna to imiquimod. *J Am Acad Dermatol*. 2014;71(1):49-55.
112. Mora AN, Karia PS, Nguyen BM. A quantitative systematic review of the efficacy of imiquimod monotherapy for lentigo maligna and an analysis of factors that affect tumor clearance. *J Am Acad Dermatol*. 2015;73(2):205-212.
113. Kirtschig G, van Meurs T, van Doorn R. Twelve-week treatment of lentigo maligna with imiquimod results in a high and sustained clearance rate. *Acta Derm Venereol*. 2015;95(1):83-85.
114. Tzellos T, Kyrgidis A, Mocellin S, Chan A-W, Pilati P, Apalla Z. Interventions for melanoma in situ, including lentigo maligna. *Cochrane Database Syst Rev*. 2014;12.
115. Donigan JM, Hyde MA, Goldgar DE, Hadley ML, Bowling M, Bowen GM. Rate of recurrence of lentigo maligna treated with off-label neoadjuvant topical imiquimod, 5%, cream prior to conservatively staged excision. *JAMA Dermatol*. 2018;154(8):885-889.
116. Kuflik EG, Gage AA. Cryosurgery for lentigo maligna. *J Am Acad Dermatol*. 1994;31(1):75-78.
117. Moraes AMD, Pavarin LB, Herreros F, Michelman FDA, Velho PENF, Souza EMD. Cryosurgical treatment of lentigo maligna. *J Dtsch Dermatol Ges*. 2007;5(6):477-480.
118. Madan V, August PJ. Lentigo maligna—outcomes of treatment with Q-switched Nd:YAG and alexandrite lasers. *Dermatol Surg*. 2009;35(4):607-612.
119. Lee H, Sowerby LJ, Temple CL, Yu E, Moore CC. Carbon dioxide laser treatment for lentigo maligna: a retrospective review comparing 3 different treatment modalities. *Arch Facial Plast Surg*. 2011;13(6):398-403.
120. de Vries K, Rellum R, Habets JMW, Prens EP. A novel two-stage treatment of lentigo maligna using ablative laser therapy followed by imiquimod. *Br J Dermatol*. 2013;168(6):1362-1364.
121. Coleman WPIMD, Davis RSMD, Reed RJMD, Krementz ETMD. Treatment of lentigo maligna and lentigo maligna melanoma. *J Dermatol Surg Oncol*. 1980;6(6):476-479.
122. Gaspar ZS, Dawber RP. Treatment of lentigo maligna. *Australas J Dermatol*. 1997;38(1):1-8.
123. Ryan RF, Krementz ET, Litwin MS. A role for topical 5-fluorouracil therapy in melanoma. *J Surg Oncol*. 1988;38(4):250-256.
124. Karam A, Simon M, Lemasson G, Misery L. The use of photodynamic therapy in the treatment of lentigo maligna. *Pigment Cell Melanoma Res*. 2013;26(2):275-277.
125. Tsang RW, Liu F-F, Wells W, Payne DG. Lentigo maligna of the head and neck: results of treatment by radiotherapy. *Arch Dermatol*. 1994;130(8):1008-1012.
126. Schmid-Wendtner MH, Brunner B, Konz B, et al. Fractionated radiotherapy of lentigo maligna and lentigo maligna melanoma in 64 patients. *J Am Acad Dermatol*. 2000;43(3):477-482.
127. Farshad A, Burg G, Panizzon R, Dummer R. A retrospective study of 150 patients with lentigo maligna and lentigo maligna melanoma and the efficacy of radiotherapy using Grenz or soft X-rays. *Br J Dermatol*. 2002;146(6):1042-1046.
128. Hedblad M-A, Mallbris L. Grenz ray treatment of lentigo maligna and early lentigo maligna melanoma. *J Am Acad Dermatol*. 2012;67(1):60-68.
129. Fogarty GB, Hong A, Scolyer RA, et al. Radiotherapy for lentigo maligna: a literature review and recommendations for treatment. *Br J Dermatol*. 2014;170(1):52-58.
130. Rule WG, Allred JB, Pockaj BA, et al. Results of NCCTG N0275 (Alliance) - a phase II trial evaluating resection followed by adjuvant radiation therapy for patients with desmoplastic melanoma. *Cancer Med*. 2016;5(8):1890-1896.
131. Guadagnolo BA, Prieto V, Weber R, Ross MI, Zagars GK. The role of adjuvant radiotherapy in the local management of desmoplastic melanoma. *Cancer*. 2014;120(9):1361-1368.
132. Oliver DE, Patel KR, Switchenko J, et al. Roles of adjuvant and salvage radiotherapy for desmoplastic melanoma. *Melanoma Res*. 2016;26(1):35-41.
133. Strom T, Caudell JJ, Han D, et al. Radiotherapy influences local control in patients with desmoplastic melanoma. *Cancer*. 2014;120(9):1369-1378.
134. Degesys CA, Powell HB, Hsia L-LB, Merritt BG. Outcomes for invasive melanomas treated with Mohs micrographic surgery: a retrospective cohort study. *Dermatol Surg*. 2018;45(2):223-228.
135. Dunne JA, Wormald JCR, Steele J, Woods E, Odili J, Powell BWEM. Is sentinel lymph node biopsy warranted for desmoplastic melanoma? A systematic review. *J Plast Reconstr Aesthetic Surg*. 2017;70(2):274-280.
136. Woodman SE, Davies MA. Targeting KIT in melanoma: a paradigm of molecular medicine and targeted therapeutics. *Biochem Pharmacol*. 2010;80(5):568-574.
137. Carvajal RD, Antonescu CR, Wolchok JD, et al. KIT as a therapeutic target in metastatic melanoma. *JAMA*. 2011;305(22):2327-2334.
138. Guo J, Si L, Kong Y, et al. Phase II, open-label, single-arm trial of imatinib mesylate in patients with metastatic melanoma harboring *c-Kit* mutation or amplification. *J Clin Oncol*. 2011;29(21):2904-2909.
139. Hodi FS, Corless CL, Giobbie-Hurder A, et al. Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. *J Clin Oncol*. 2013;31(26):3182-3190.

140. Minor DR, Kashani-Sabet M, Garrido M, O'Day SJ, Hamid O, Bastian BC. Sunitinib therapy for melanoma patients with *KIT* mutations. *Clin Cancer Res*. 2012;18(5):1457-1463.
141. Haworth KB, Arnold MA, Pierson CR, et al. Immune profiling of NF1-associated tumors reveals histologic subtype distinctions and heterogeneity: implications for immunotherapy. *Oncotarget*. 2017;8(47):82037-82048.
142. Kraft S, Fernandez-Figueras M-T, Richarz NA, Flaherty KT, Hoang MP. PDL1 expression in desmoplastic melanoma is associated with tumor aggressiveness and progression. *J Am Acad Dermatol*. 2017;77(3):534-542.