REVIEW

[Translated article] Update on the Diagnosis and Management of Desmoplastic Melanoma☆

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Abstract Desmoplastic melanoma (DM) accounts for 0.4% to 4% of all melanomas. These skin tumors are mainly formed by amelanotic spindled melanocytes immersed in an abundant collagen stroma and are classified as pure when the desmoplastic component accounts for at least 90% of the invasive tumor and as mixed or combined otherwise. DMs are more common in men (male to female ratio, 1.7 to 2:1), and the mean age at diagnosis is 66 to 69 years. The tumors tend to occur in chronically sun-exposed areas, often in association with lentigo maligna, and are difficult to recognize because they can resemble a scar, presenting as a firm, unpigmented papule or plaque with poorly defined borders. DMs also have a strong tendency to recur locally, and pure variants rarely spread to the lymph nodes. Nonetheless, recently published series suggest that patients with DM have a similar prognosis to those with nondesmoplastic melanoma of the same thickness. The clinical management of DM varies in certain aspects from that of other melanomas and is reviewed in this article.
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Actualización en el diagnóstico y manejo del melanoma desplásico

Resumen El melanoma desmoplásico (MD) representa entre el 0,4-4% de todos los melanomas. Se presenta como un tumor constituido predominantemente por melanocitos fusiformes amelanóticos inmersos en un estroma colágeno abundante. Se clasifica en MD puro o mixto, basándose en la proporción de melanoma desmoplásico frente a la del melanoma no desmoplásico presente en el tumor infiltrante. En el MD puro el componente desmoplásico representa más del 90% del melanoma infiltrante mientras que, en el MD combinado o mixto, el componente desmoplásico representa menos del 90%.

El MD es más frecuente en varones (ratio 1,7-2 :1); la edad media al diagnóstico oscila entre 66-69 años, y suele localizarse en áreas de fotoexposición crónica, a menudo asociado a un lentigo maligno. Su reconocimiento clínico es difícil ya que se presenta como una pápula o placa no pigmentada, indurada y de bordes mal definidos, que recuerda a una cicatriz.

El MD es un tumor con una alta tendencia a la recurrencia local y en el caso del MD puro, una baja tendencia a la diseminación ganglionar. Sin embargo, en las series más contemporáneas, su pronóstico global parece ser similar al de melanomas no desmoplásicos (MND) del mismo grosor. Su abordaje clínico posee algunos matices diferenciales, en comparación al resto de melanomas, que se revisan en el presente trabajo.

Introduction

Desmoplastic melanoma (DM) is a rare variant of melanoma that has distinct histologic features and biological behavior to conventional melanoma. It was described by Conley et al.[1] in 1971 as a paucicellular tumor composed of spindle cells with little atypia and abundant collagenous stroma.[1] In terms of prognosis, there is some controversy regarding the risk of lymph node spread and its impact on survival.[2–4] This review offers updated, practical information on how to manage DM.

Material and Methods

We conducted a literature search in PubMed, EMBASE, and Google Scholar databases using the search term ''desmoplastic melanoma'' and additional terms depending on the subsection studied. We also scanned the reference lists of selected articles to identify other potentially relevant articles.

Epidemiology

DM is rare and accounts for less than 4% of all melanomas.[5,6] According to a recent retrospective study, just 0.4% of all melanomas diagnosed in the Netherlands between 2000 and 2014 were DMs.[7] In another study using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, the authors estimated an annual incidence of 0.2 cases of DM per 100000 inhabitants, with an annual increase of 4.6%.[5] This increase was attributed to the relationship between DM and sun exposure, population aging, and improvements in diagnosis.

DM is more common in men, with a male to female ratio of approximately 1.7-2 to 1.[5,8,9] Mean age at diagnosis is 66 to 69 years, which is considerably older than that described for nondesmoplastic melanoma (NDM) (approximately 60 years).[5,8–10]

Similarly to lentigo maligna (LM) and lentigo maligna melanoma (LMM), DM tends to occur in areas of chronic sun exposure. The most common location is the head and neck (50% of cases), followed by the trunk (20%-25%) and extremities (20%-25%). DM can, however, arise in areas not chronically exposed to the sun, such as mucous membranes[11] and acral sites.[12]

Histopathology

DM is an invasive melanoma primarily composed of amelanotic spindle-shaped melanocytes immersed in a highly collagenous stroma.[1,8] Its characteristic morphologic appearance is that of a paucicellular dermal tumor with an irregular outline, a poorly defined contour, and a low to moderate density of melanocytes in a prominent collagenous stroma (Fig. 1A). Tumor cells are typically arranged in an isolated, disordered fashion among the collagen bundles.[13] Melanocytes are usually spindle shaped and nonpigmented (similar to fibroblasts) and have poorly defined cytoplasms and cytoplasmic membranes. Cytologic atypia ranges from minimal to moderate; mitotic figures are uncommon (Fig. 1B).

The overlying epidermis shows few or no alterations in almost 50% of cases[14] and the appearance is that of a fibrous or mesenchymal tumor. In the remaining cases, histology shows an atypical proliferation of melanocytes at the dermoepidermal junction or a melanoma in situ, usually LM[15] (Fig. 1C). In these cases, the appearance may be that of a melanoma in situ or a junctional melanocytic lesion with a prominent underlying scar.[16,17]

The histologic diagnosis of DM presents challenges. Because of its inoffensive, deceptive appearance and the superficial nature of some biopsies, DM can go unnoticed or be mistaken for other lesions. The differential diagno-
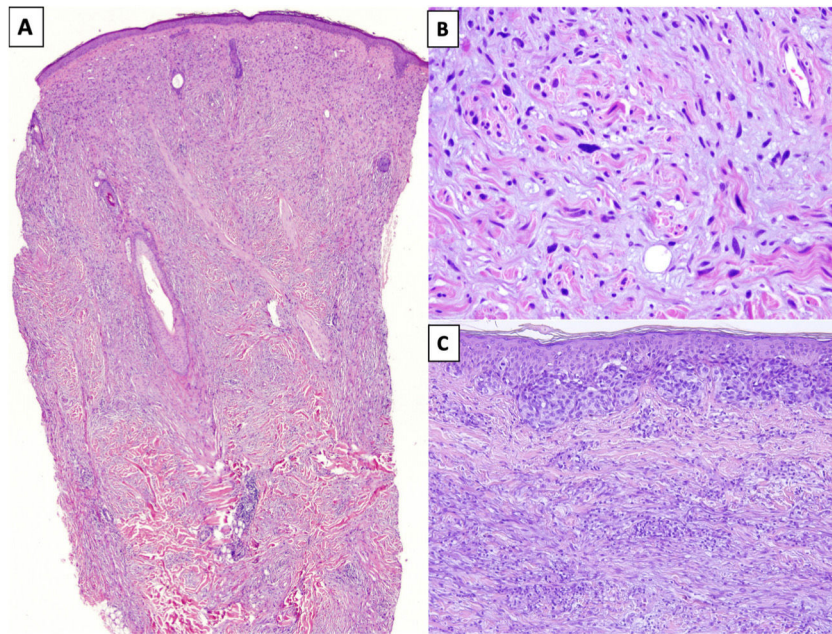
Figure 1 A, Invasive desmoplastic melanoma (DM) extending into the deep reticular dermis (hematoxylin-eosin, original magnification ×20). B, DM with spindle-shaped melanocytes with several, large hyperchromatic nuclei arranged in an isolated, disordered fashion among a slightly fibromyxoid stroma (hematoxylin-eosin, original magnification ×200). C, DM associated with a melanoma in situ (hematoxylin-eosin, original magnification ×200).

sis should include benign tumors and lesions such as scars, dermatofibroma, neurofibroma, and desmoplastic nevus, in addition to malignant tumors, such as desmoplastic sarcomatoid carcinoma, atypical fibroxanthoma, dermatofibrosarcoma protuberans, fibrosarcoma, leiomyosarcoma, and malignant peripheral nerve tumor.

Immunohistochemistry can be very useful in the differential diagnosis, but on occasions it is of no help. In such cases, it is important to check for morphologic features often seen in DM. While these features are not specific, they can help establish a diagnosis.

- DM often spreads to deep layers, in many cases occupying the entire dermis and extending into the subcutaneous tissue.[18]
- Fibromyxoid stroma is common.[19]
- Solar elastosis is observed in the superficial dermis in approximately 80% of tumors.[20] Observation of clumps of elastotic material trapped in the core of the tumor, even in its deeper regions, offers important diagnostic information as these clumps are not seen in other entities in the differential diagnosis (Fig. 2A).[16]
- The presence of small peripheral or perineural lymphoid aggregates can also help raise suspicion of DM in paucicellular tumors with minimal atypia (Fig. 2B).[21]
- Neurotropism (perineural or intraneural invasion) is observed in approximately 30% of DMs (Fig. 2C).[22] DM can sometimes exhibit neural transformation, which is currently considered to be a form of neurotropism.[23]
- Melanocytes with large, hyperchromatic nuclei are always present, even if focally.
- DM is a predominantly amelanotic tumor; diffuse pigmentation is very unusual.

In 2004, Busam et al.[13] proposed classifying DM as pure or mixed (combined) depending on the proportion of the invasive tumor occupied by the desmoplastic component. For a DM to be classified as pure, at least 90% of the invasive component had to be desmoplastic and be accompanied by a fibrous stroma. Mixed DM, by contrast, had a smaller desmoplastic component (<90%) and was accompanied by an NDM component comprising cohesive groups of epithelioid and/or spindle-shaped melanocytes without an intercellular fibrous stroma (Fig. 2D).

Histologic subtypes of DM also show other microscopic differences. Mixed DM tends to be more cellular and has greater cytologic atypia, a higher mitotic rate, and a higher proliferative index (KI67). Neurotropism and neural differentiation, by contrast, are more common in pure DM[13,24].

Busam et al.[13] also showed that the above histologic distinction might have prognostic and treatment implications, highlighting the importance of correct classification. In some cases, particularly in more cellular tumors, the desmoplastic component can be difficult to detect using hematoxylin-eosin staining, leading to staging errors.

The most common immunohistochemical profile for DM is positive staining with S100, SOX10, and nerve growth factor receptor (NGFR) (75%) and negative staining with the melanocytic differentiation markers human melanoma black 45 (HMB45), tyrosinase, microphthalmia-associated transcription factor (MITF), and melan antigen recognized by T cells 1 (Melan-A or MART-1) (Fig. 3).[25] It is important to correlate positive results with morphologic findings, especially in re-excision specimens, as S100[26] and SOX-10[27] may also be expressed in stromal and inflammatory cells, while NGFR is seen in myoepithelial cells, fibroblasts, reactive myofibroblasts, and nerve fibers.[28] Before ruling out DM,
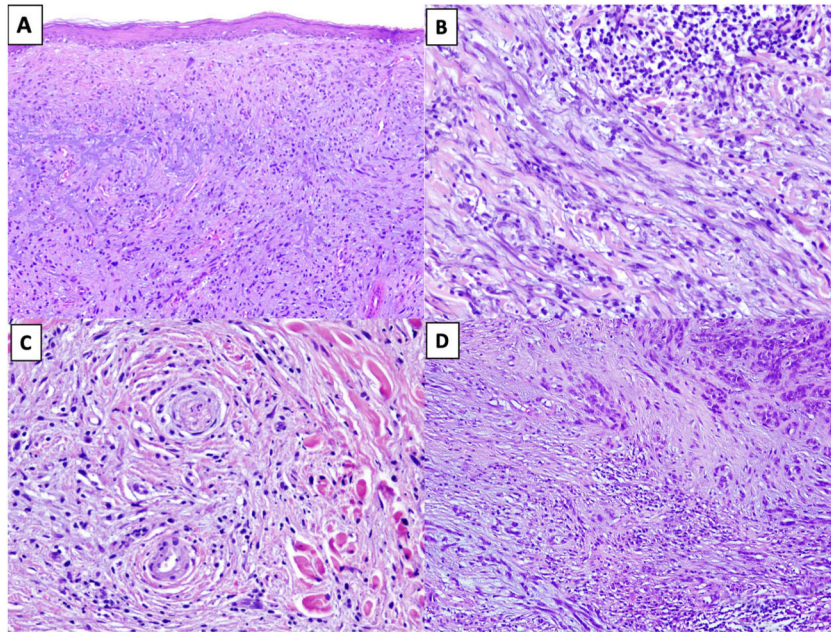
Figure 2 A, DM with actinic elastosis and trapped elastolytic material (hematoxylin-eosin, original magnification ×100). B) DM with a nodular aggregate of lymphocytes (hematoxylin-eosin, original magnification ×200). C, DM with perineural invasion (hematoxylin-eosin, original magnification ×200). D, Mixed DM. Note the nondesmoplastic component formed by compact nests of epithelioid melanocytes in the top right corner and the desmoplastic component occupying less than 90% of the invasive tumor in the lower part of the image (hematoxylin-eosin, original magnification ×100).
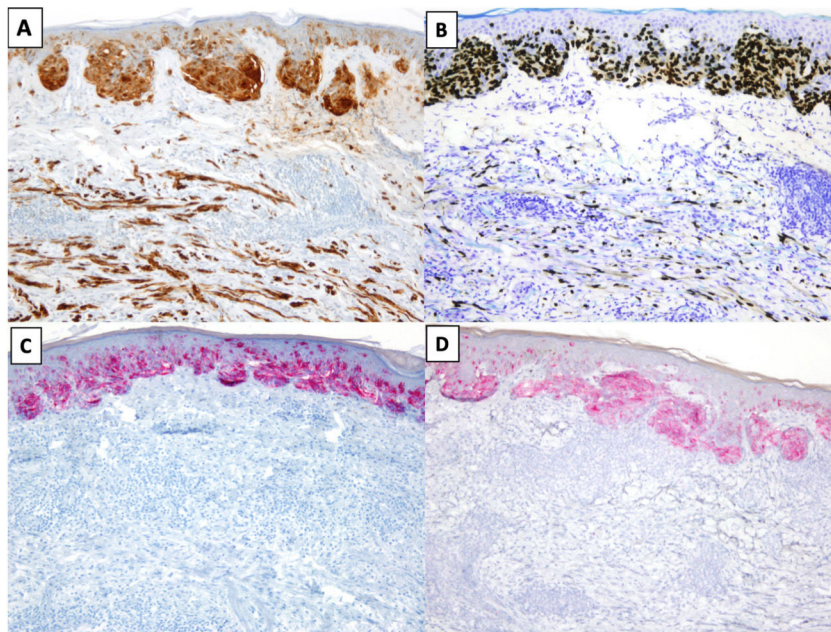
Figure 3 Desmoplastic melanoma (DM) associated with superficial spreading melanoma. A and B, Immunohistochemical staining with S100 (×100) and SOX10 (original magnification ×100). Both stains were positive for DM and melanoma in situ cells. C and D, Immunohistochemical staining with melanoma antigen (original magnification ×100) and human melanoma black 45 (original magnification ×100): Both stains were positive for melanoma in situ cells and negative for DM cells.

it is important to bear in mind that some tumors express minimal or no SOX10.[29] Unlike melanocytes in DM, those in melanoma in situ or in the NDM component of mixed DM show positive staining with HMB45, tyrosinase, MITF, and Melan-A and do not express NGFR. PReferentially expressed Antigen in MElanoma (PRAME) is more common in other variants of melanoma than in DM, where it is expressed in just 35% of cases.[30]

Figure 4 Clinical image of a desmoplastic melanoma (DM) in a 62-year-old man who presented with a progressively growing lesion on his cheek. The lesion was light brown and had a firm scar-like appearance. It was a pure DM with a thickness of 5 mm.

Figure 5 Clinical image of a desmoplastic melanoma (DM) in a 53-year-old woman who presented with a firm, pink interscapular tumor initially thought to be a keloid lesion. Biopsy showed a pure DM with a thickness of 8.5 mm.

Most DMs in severely sun-damaged skin have very high mutational burden with a strong UV radiation signature. Activating mutations in the MAPK signaling pathway (e.g., the *BRAF* V600E mutation), which are relatively common in other types of melanomas, are usually absent in DM. Mutations in *NF1* (55%)[31], *TP53* (48%), and *CDKN2A* (47%), however, are common. Other less common activating mutations in the MAPK pathway may also be seen, such as amplifications of the receptor tyrosine kinase gene (*EGFR*, *MET*, and *ERBB2*) and loss of *CBL*.[32] Some of these alterations could be potential therapeutic targets.

Clinical Presentation

DM usually presents as a firm, nonpigmented papule or plaque with poorly defined borders in sun-damaged skin (Fig. 4). Malignant melanoma is suspected initially in just 27% of cases.[20] Clinically, DM is often confused with a benign skin lesion, such as scar tissue, dermatofibroma, neurofibroma, and intradermal melanocytic nevus, or with a
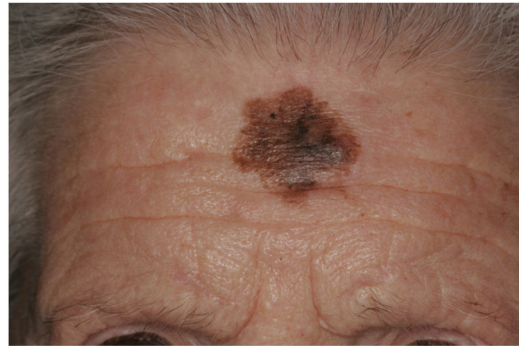

Figure 6 Clinical image of a desmoplastic melanoma (DM) associated with lentigo maligna (LM) in an 89-year-old woman who presented with a lesion on her forehead suggestive of LM. Excision showed a DM with a thickness of 2.95 mm.
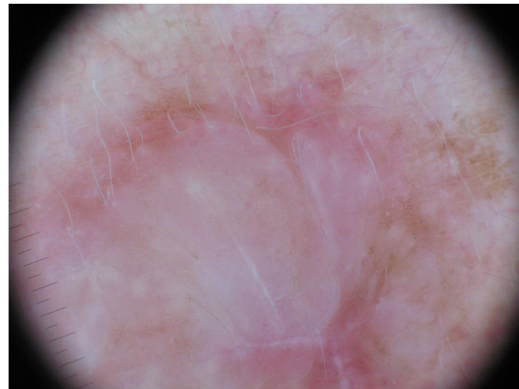

Figure 7 Dermoscopic image of the tumor with a palpable pink component shown in Fig. 4. Observation of a pigment network in several areas of the lesion indicated a melanocytic lesion.

malignant nonmelanocytic skin tumor such as basal cell carcinoma and squamous carcinoma (Fig. 5).

There are also clinical differences between pure and mixed DMs.[13] An epidermal component in the form of LM, LMM, or superficial spreading melanoma appears to be present in 80% to 100% of mixed DMs. Lesions suspicious for LMM should therefore be palpated to check for a firm subcutaneous nodule indicative of DM (Fig. 6).[15]

Associated epidermal lesions are less common in pure DM (63%-80% of cases), which usually presents as a nodule or indurated subcutaneous plaque without superficial changes, explaining why its diagnosis is often delayed and why it is thicker at diagnosis than the mixed variant.[20,33] Both pure and mixed DMs are thicker at diagnosis than conventional melanomas, with a mean Breslow thickness of 2.5 to 6.5 mm and in most cases a Clark level of IV or V.[5,10,20,34]

Dermoscopy can be a useful tool for the diagnosis of DM. Absence of a pigment network and observation of regression structures with off-white scar areas, granules (peppering), and atypical vascular patterns should raise suspicion.[35] Jaimes et al.,[33] in a study of 37 DMs, reported that the most common dermoscopic characteristics were vascular blush, polymorphous vessels, peppering, and asymmetric perifollicular hyperpigmentation. Just 43% of the tumors had features specific to melanocytic lesions, such

as globules (44%), a pigment network (38%), a pseudonetwork (25%), and a negative network (6%) (Fig. 7). In other series, however, all the tumors analyzed showed at least 1 melanoma-specific characteristic.[15,33,36] As expected, mixed DMs, which more often have an epidermal component, show a greater number and variety of melanoma-specific characteristics and dermoscopic findings associated with LM, such as the annular-granular pattern and polygonal lines.[33]

There is still little evidence to support the usefulness of confocal reflectance microscopy (CRM) in the diagnosis of DM. In a study of 14 cases analyzed by CRM followed by histopathologic analysis, Maher et al.[36] found that CRM detected a similar frequency of melanoma-specific features (pagetoid cells, cells with atypia and nucleated cells in the dermis) to that observed in other subtypes of melanoma. By contrast, abundant spindle cells interspersed with collagen fibers in the superficial dermis appeared to be more specific to DM.

Prognosis

Current evidence suggests that DM behaves differently to conventional melanoma.[3,37] It appears to be associated with a higher risk of local recurrence and a lower rate of lymph node metastasis.[3,34,38] The risk of lymph node involvement seems to be lower than in NMDs of a similar thickness[3,37]; variable rates have been reported for sentinel lymph node involvement (0% to 18.2% depending on the series).[3] It is difficult to accurately predict the prognosis of DM, as conflicting data have been reported and many studies do not distinguish between pure and mixed variants. Most recent studies, however, have not found significant differences in survival between patients with DMs and NDMs of a similar thickness.[3,6,20,37,39,40] The impression that pure DM is less likely than mixed DM to spread to distant sites and therefore has better survival rates has not been consistently demonstrated. Maurichi et al.[39] observed significant differences in overall survival between patients with mixed and pure DM (61.3% vs. 79.5%), but their findings have not been corroborated by subsequent studies.[7,41] Distant metastases, which are mostly located in the lung, have been linked to previous recurrences and deep lesions.[34]

Most studies have shown that DM has a high risk of local recurrence (approximately 10%-14%)[37,39,42,43], particularly in the case of mixed DMs.[39] Some authors have attributed the more local aggressive nature of pure DM to its later diagnosis (it is a rare tumor with an atypical presentation) and to the high frequency of perineural invasion and inadequate surgical margins.[20,37]

A number of factors might explain the more aggressive behavior of DM. Shi et al.,[38] in a retrospective study of 3657 DM cases, found that male sex and an age of older than 68 years were independent predictors of worse overall and disease-free survival. Although these findings have some support in the literature,[31,36,40] other authors have not detected any differences in disease-free survival.[37,44,45] Perineural invasion has also been proposed as a poor prognostic factor in DM[6,46] and has been seen to significantly correlate with greater Breslow thickness.[20]

Treatment Strategies in DM

Surgery

Numerous studies have shown that wide excision (with margins of ≥ 2 cm) does not improve survival in primary cutaneous melanoma with a Breslow thickness ≤ 2 mm.[39,47] DMs, however, tend to be thicker than conventional melanoma at diagnosis and more often need excision with 2-cm margins. Wide excision is especially important considering the higher local recurrence rates described for DM.[6,34,42]

In one Australian series, an excision margin of ≥ 2 cm was associated with fewer recurrences than one of < 1 cm.[6] Maurichi et al.[39] also evaluated prognosis according to DM subtype and surgical margins and found that patients with pure DM and a Breslow thickness ≤ 2 mm had higher recurrence rates and worse overall 5-year survival when 1-cm rather than 2-cm margins were used. Prognosis, however, was similar when 2-cm margins were used to treat patients with pure DM and a Breslow thickness of ≤ 2 mm or > 2 mm. Margin size did not significantly influence prognosis in patients with mixed DM.

A surgical margin of 2 cm thus should be considered for the excision of pure DMs, even in tumors thinner than 2 mm. This recommendation is less clear for tumors thinner than 1 mm, as no studies have analyzed outcomes with 1-cm margins.[3] In conclusion, wide excision should be prioritized whenever possible in pure DMs to avoid local recurrence, although this may not always be possible as many lesions are located in anatomically complex areas, such as the head and neck.[15]

Sentinel Lymph Node Biopsy

The value of sentinel lymph node (SLN) biopsy in DM is controversial. In melanoma, this procedure is currently used to identify patients with a worse prognosis who could benefit from adjuvant therapy. Evidence of its usefulness in DM is based on data from retrospective case series, several of which have shown clear differences in melanoma-specific survival according to SLN status.[5,37,40,44]

A 5% probability of SLN positivity is the usual threshold for considering SLNB.[48] According to the most recent series of DM, SLN positivity rates range between 0% and 18.2%[7,37,39–43,49–58] (Table 1), and the 5 series that reported a rate of 0% all had fewer than 25 patients.[42,43,49,50,55] Dunne et al.[59] reported a rate of 6.5% in a systematic review published in 2017.

It could be helpful to distinguish between DM subtypes when evaluating the risk of SLN involvement and the value of SLN biopsy. SLN involvement is more likely in mixed DMs (8.5%-25%) than pure DMs (0-18.2%).[7,39,41,52,54–56,58,60] The respective rates reported by Dunne et al.[59] in their systematic review were 13.8% and 5.4%.[59] Just 1 study has reported a higher risk of SLN involvement in pure DMs.[41]

To sum up, the value of SLN biopsy is clearer in mixed DM than in pure DM. It is also important, however, to consider other factors such as age, comorbidities, and primary tumor location. Old age and a head and neck location have traditionally been considered to be associated with a lower risk of SLN involvement.[61]

Table 1 Case Series Evaluating SLN Biopsy in DM.

Study	Year	Design	Country	Period, y	No. of patients	Mean age, y	Male to female ratio	Mean Breslow thickness, mm	Location	SLN biopsy, No. of cases	SLN positivity	Mixed DM	SLN positivity in mixed DM	Pure DM	SLN positivity in pure DM
Jaroszewski	2001	Case series	United States	15	59	62.8	1.7:1	6.5	All	12	0				
Thelmo	2001	Case series	United States	6	16	57.5	2.2	3.9	All	16	0				
Gyorki	2003	Case series	United States	5	27	64	2.8:1	2.2	All	24	0				
Su	2004	Case series	United States	5	33	61	3.1:1	2.8	All	33	12.1%				
Livestro	2005	Case-control study	United States	32	89	63.9	1.7:1	2.6	All	25	8%				
Pawlik	2006	Case series	United States	11	65	61	1.3:1	2.9	All	65	6.2%	19	15.8%	46	2.2%
Posther	2006	Case series	United States	23	129	55.2	1.7:1	4.4	All	11	0				
Cummins	2007	Case series	United States	5	28	64	1:1	2.3	All	15	6.7%				
Maurichi	2009	Case series	Italy	25	242	64	1.3:1	2	All	100	9%	51	13.7%	49	4%
George	2009	Case series	United States	26	87	64	1.5:1	4.2	All	40	12.5%	23	22%	17	0%
Murali	2010	Case series	Australia	14	252	61	1.9:1	2	All	252	6.7%	129	8.5%	123	4.9%
Mohebati	2012	Case series	United States	24	47	71	1.4:1	6.1	Head and neck	23	0%	8	0	15	0%
Broer	2013	Case series	United States	12	22	64	3:1	3.9	All	22	18.2%	8	25%	14	14%
Egger	2013	Case series	United States	11	47	57	2.1:1	2.6	All	47	17%				
Han	2013	Case series	United States	18	205	66	2.2:1	3.7	All	205	13.7%	61	24.6%	67	9%
Conic	2018	Case series	United States	17	58			3.4	All	35	14.3%	24	12.5%	11	18.2
Laeijendecker	2020	Case series	Netherlands	15	239	67.2	1:1	4	All	62	9.7%	36	16.7%	26	0%

Abbreviations: DM, desmoplastic melanoma; SLN, sentinel lymph node.

Few studies have reported positivity rates for non-SLN lymph nodes in patients with DM who have undergone complete lymph node dissection after a positive SLN biopsy. Two studies with over 200 DM patients each reported non-SLN lymph node positivity rates of 16.7% and 23.5%,[37,58] which are similar to those reported for NDM.[62] Although the evidence is limited, it would seem sensible to apply the same algorithm as that used in conventional melanoma to manage DM patients with a positive SLN biopsy.[63]

Radiotherapy

Radiotherapy may be potentially useful in DM considering the high rates of local recurrence described.[37,64] Unlike in conventional melanoma, which is relatively resistant to radiotherapy, several studies have shown that this treatment may be a useful adjunct for achieving local control in DM.[3,34,65]

A number of studies have also shown the possible benefits of adjuvant radiotherapy in patients with DM and associated risk factors (perineural invasion, extensive desmoplasia, positive margins, and recurrent disease).[38,66,67] Two more recent studies confirmed that adjuvant radiotherapy improved local control in DM. Guadagnolo et al.,[68] in a study of 130 patients with DM, found that 24% of patients treated exclusively with surgery and 7% of those treated with surgery plus adjuvant radiotherapy developed local recurrence. They also detected a significant association between adjuvant radiotherapy and superior local control in the multivariate analysis. Strom et al.[69] also found that adjuvant radiotherapy was a significant predictor of better local control in their multivariate analysis. In particular, 14% of patients with positive resection margins treated with adjuvant radiotherapy developed recurrent disease compared with 54% of those who underwent excision only. The authors also described several prognostic factors that could be used to select DM patients with negative margins who might benefit from adjuvant radiotherapy: head and neck location, Breslow thickness > 4 mm, and Clark level V. Oliver et al.,[70] in a more recent retrospective study, evaluated 100 patients with DM treated with surgery, surgery plus adjuvant radiotherapy, or surgery plus salvage radiotherapy for postoperative recurrences. They found 100% local control rates in the 7 patients treated with salvage radiotherapy and the 10 treated with adjuvant radiotherapy.

The current evidence, however, is based on retrospective studies. Prospective randomized trials are needed. One trial currently underway (NCT00975520)[71] is comparing surgery alone versus surgery plus adjuvant radiotherapy in patients with DM excised with wide negative margins.

Systemic Therapy

Immunotherapy with anti-PD1 drugs has demonstrated efficacy in the treatment of metastatic DM. A recent retrospective multicenter study of 60 cases of metastatic DM treated with anti-PD1 drugs reported objective tumor responses in 70% of patients over a mean follow-up of 22 months, and 32% of the patients achieved complete response.[72] These rates, which are even higher than those observed in NDM, are probably due to the high mutational burden induced by UV radiation in DM. It has been proposed that immunotherapy might be more effective in tumors with a high mutational burden.[73] These promising results need to be confirmed in prospective clinical trials. A phase II trial (NCT02775851)[74] is currently recruiting patients to evaluate the efficacy of pembrolizumab in DM. BRAF inhibitors are not useful in DM as most patients do not have BRAF mutations.

Conclusions

DM is a rare variant of melanoma. It behaves differently to conventional melanoma and therefore requires different diagnostic and treatment strategies. Its diagnosis presents challenges for both clinicians and pathologists. Histologic classification of DM into pure and mixed variants appears to offer important information on tumor behavior and should be taken into account when taking treatment decisions. Pure DMs have a desmoplastic component that occupies at least 90% of the invasive tumor. Mixed DMs have a smaller desmoplastic component accompanied by a nondesmoplastic component.

Wide excision is essential for preventing recurrence and improving survival. SLN status appears to have prognostic value in DM, and SLN biopsy should be considered in mixed variants. Its usefulness in pure DM is less clear. Adjuvant radiotherapy to the tumor bed may be useful in patients with associated risk factors. Current evidence suggests that immune checkpoint inhibitors are associated with good response rates in metastatic DM.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ad.2021.06.013.

References

1. Conley J, Lattes R, Orr W. Desmoplastic malignant melanoma (a rare variant of spindle cell melanoma). Cancer. 1971;28:914–36, http://dx.doi.org/10.1002/1097-0142(1971)28:4<914::aid-cncr2820280415>3.0.co;2-e.
2. Hadfield MJ, Helsing R, Grant-Kels JM. Desmoplastic melanoma: an updated clinical review and the emerging role of genetic markers and immunotherapies. Melanoma Res. 2020;30:429–32, http://dx.doi.org/10.1097/CMR.0000000000000679.

3. Nicolson NG, Han D. Desmoplastic melanoma. J Surg Oncol. 2019;119:208–15, http://dx.doi.org/10.1002/jso.25317.

4. Hughes TM, Williams GJ, Gyorki DE, Kelly JW, Stretch JR, Varey AHR, et al. Desmoplastic melanoma: a review of its pathology and clinical behaviour, and of management recommendations in published guidelines. J Eur Acad Dermatol Venereol. 2021, http://dx.doi.org/10.1111/jdv.17154.

5. 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;38:616–24, http://dx.doi.org/10.1111/j.1600-0560.2011.01704.x.

6. Quinn MJ, Crotty KA, Thompson JF, Coates AS, O'Brien CJ, McCarthy WH. Desmoplastic and desmoplastic neurotropic melanoma: experience with 280 patients. Cancer. 1998, http://dx.doi.org/10.1002/(SICI)1097-0142(19980915)83:6<1128::AID-CNCR11>3.0.CO;2-7.

7. Laeijendecker AE, El Sharouni MA, Sigurdsson V, van Diest PJ. Desmoplastic melanoma: the role of pure and mixed subtype in sentinel lymph node biopsy and survival. Cancer Med. 2020;9:671–7, http://dx.doi.org/10.1002/cam4.2736.

8. Busam KJ. Desmoplastic melanoma. Clin Lab Med. 2011;31:321–30, http://dx.doi.org/10.1016/j.cll.2011.03.009.

9. Xu Z, Yibulayin F, Shi P, Feng L. Desmoplastic melanoma versus spindle cell melanoma. Medicine (Baltimore). 2018;97:e11563, http://dx.doi.org/10.1097/md.0000000000011563.

10. Wasif N, Gray RJ, Pockaj BA. Desmoplastic melanoma - the stepchild in the melanoma family? J Surg Oncol. 2011;103:158–62, http://dx.doi.org/10.1002/jso.21778.

11. Prasad ML, Patel SG, Busam KJ. Primary mucosal desmoplastic melanoma of the head and neck. Head Neck. 2004;26:373–7, http://dx.doi.org/10.1002/hed.10384.

12. Chung KC, Calkins ER, Crawford R, Rees RS. Desmoplastic melanoma of the hand: case reports and review of the literature. J Hand Surg Am. 1995;20:873–6, http://dx.doi.org/10.1016/S0363-5023(05)80447-2.

13. Busam KJ, Mujumdar U, Hummer AJ, Nobrega J, Hawkins WG, Coit DG, et al. Cutaneous desmoplastic melanoma: reappraisal of morphologic heterogeneity and prognostic factors. Am J Surg Pathol. 2004;28:1518–25, http://dx.doi.org/10.1097/01.pas.0000141391.91677.a4.

14. Massi D, Cree I, Elder D, Kazakov D, Scolyer R. WHO Classification of Skin tumours Tumours. 4th edition Lyon: International Agency for Research on Cancer; 2018.

15. Chen LL, Jaimes N, Barker CA, Busam KJ, Marghoob AA. Desmoplastic melanoma: a review. J Am Acad Dermatol. 2013;68:825–33, http://dx.doi.org/10.1016/j.jaad.2012.10.041.

16. Massi G, LeBoit PE. Histological Diagnosis of Nevi and Melanoma. second edition Berlin, Heidelberg: Springer Berlin Heidelberg; 2014.

17. Carlson JA, Dickersin GR, Sober AJ, Barnhill RL. Desmoplastic neurotropic melanoma. A clinicopathologic analysis of 28 cases. Cancer. 1995;75:478–94, http://dx.doi.org/10.1002/1097-0142(19950115)75:2<478::AID-CNCR2820750211>3.0.CO;2-O.

18. Busam KJ. Cutaneous desmoplastic melanoma. Adv Anat Pathol. 2005;12:92–102, http://dx.doi.org/10.1097/01.pap.0000155071.86944.a6.

19. McCarthy SW, Scolyer RA, Palmer AA. Desmoplastic melanoma: a diagnostic trap for the unwary. Pathology. 2004;36:445–51, http://dx.doi.org/10.1080/00313020412331285336.

20. De Almeida LS, Requena L, Rütten A, Kutzner H, Garbe C, Pestana D, et al. Desmoplastic malignant melanoma: a clinicopathologic analysis of 113 cases. Am J Dermatopathol. 2008;30:207–15, http://dx.doi.org/10.1097/DAD.0b013e3181716e6b.

21. Stowman AM, Hickman AW, Mauldin IS, Mahmutovic A, Gru AA, Slingluff CLJ. Lymphoid aggregates in desmoplastic melanoma have features of tertiary lymphoid structures. Melanoma Res. 2018;28:237–45, http://dx.doi.org/10.1097/CMR.0000000000000439.

22. Varey AHR, Goumas C, Hong AM, Mann GJ, Fogarty GB, Stretch JR, et al. Neurotropic melanoma: an analysis of the clinicopathological features, management strategies and survival outcomes for 671 patients treated at a tertiary referral center. Mod Pathol Off J United States Can Acad Pathol Inc. 2017;30:1538–50, http://dx.doi.org/10.1038/modpathol.2017.76.

23. Tejera-Vaquerizo A, Fernández-Figueras MT, Santos-Briz A, Ríos-Martín JJ, Monteagudo C, Fernández-Flores A, et al. Protocol for the histologic diagnosis of cutaneous melanoma: consensus statement of the Spanish Society of Pathology and the Spanish Academy of Dermatology and Venereology (AEDV) for the National Cutaneous Melanoma Registry. Actas Dermosifiliogr. 2021;112:32–43, http://dx.doi.org/10.1016/j.ad.2020.09.002.

24. Yang K, Mahalingam M. Differing biologic behaviors of desmoplastic melanoma subtypes: insights based on histopathologic, immunohistochemical, and genetic analyses. J Am Acad Dermatol. 2020;83:523–31, http://dx.doi.org/10.1016/j.jaad.2020.02.014.

25. Plaza JA, Bonneau P, Prieto V, Sangueza M, MacKinnon A, Suster D, 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;43:313–23, http://dx.doi.org/10.1111/cup.12654.

26. Chorny JA, Barr RJ. S100-positive spindle cells in scars: a diagnostic pitfall in the re-excision of desmoplastic melanoma. Am J Dermatopathol. 2002;24:309–12, http://dx.doi.org/10.1097/00000372-200208000-00004.

27. Behrens EL, Boothe W, D'Silva N, Walterscheid B, Watkins P, Tarbox M. SOX-10 staining in dermal scars. J Cutan Pathol. 2019;46:579–85, http://dx.doi.org/10.1111/cup.13468.

28. Otaibi S, Jukic DM, Drogowski L, Bhawan J, Radfar A. NGFR (p75) expression in cutaneous scars; further evidence for a potential pitfall in evaluation of reexcision scars of cutaneous neoplasms, in particular desmoplastic melanoma. Am J Dermatopathol. 2011;33:65–71, http://dx.doi.org/10.1097/DAD.0b013e3181dfcb9f.

29. Kossard S, Doherty E, Murray E. Neurotropic melanoma. A variant of desmoplastic melanoma. Arch Dermatol. 1987;123:907–12.

30. Lezcano C, Jungbluth AA, Nehal KS, Hollmann TJ, Busam KJ. PRAME expression in melanocytic tumors. Am J Surg Pathol. 2018;42:1456–65, http://dx.doi.org/10.1097/PAS.0000000000001134.

31. Wiesner T, Kiuru M, Scott SN, Arcila M, Halpern AC, Hollmann T, et al. NF1 mutations are common in desmoplastic melanoma. Am J Surg Pathol. 2015;39:1357–62, http://dx.doi.org/10.1097/PAS.0000000000000451.

32. Shain AH, Garrido M, Botton T, Talevich E, Yeh I, Sanborn JZ, et al. Exome sequencing of desmoplastic melanoma identifies recurrent NFKBIE promoter mutations and diverse activating mutations in the MAPK pathway. Nat Genet. 2015;47:1194–9, http://dx.doi.org/10.1038/ng.3382.

33. Jaimes N, Chen L, Dusza SW, Carrera C, Puig S, Thomas L, et al. Clinical and dermoscopic characteristics of desmoplastic melanomas. JAMA Dermatol. 2013;149:413–21, http://dx.doi.org/10.1001/jamadermatol.2013.2248.

34. Lens MB, Newton-Bishop JA, Boon AP. Desmoplastic malignant melanoma: a systematic review. Br J Dermatol. 2005;152:673–8, http://dx.doi.org/10.1111/j.1365-2133.2005.06462.x.

35. Debarbieux S, Ronger-Salve S, Dalle S, Balme B, Thomas L. Dermoscopy of desmoplastic melanoma: report of six cases. Br J Dermatol. 2008;159:360–3, http://dx.doi.org/10.1111/j.1365-2133.2008.08687.x.

36. 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 Dermatology Venereol. 2017;31:2016–24, http://dx.doi.org/10.1111/jdv.14381.

37. Murali R, Shaw HM, Lai K, McCarthy SW, Quinn MJ, Stretch JR, et al. Prognostic factors in cutaneous desmoplastic melanoma: a study of 252 patients. Cancer. 2010;116:4130–8, http://dx.doi.org/10.1002/cncr.25148.

38. Shi P, Xu Z, Lei X, Yibulayin F, Wushou A. Desmoplastic melanoma: demographic and clinicopathological features and disease-specific prognostic factors. Oncol Lett. 2019;17:5619–27, http://dx.doi.org/10.3892/ol.2019.10259.

39. Maurichi A, Miceli R, Camerini T, Contiero P, Patuzzo R, Tragni G, et al. Pure desmoplastic melanoma: a melanoma with distinctive clinical behavior. Ann Surg. 2010;252:1052–7, http://dx.doi.org/10.1097/SLA.0b013e3181efc23c.

40. Livestro DP, Muzikansky A, Kaine EM, Flotte TJ, Sober AJ, Mihm MC, et al. Biology of desmoplastic melanoma: a case-control comparison with other melanomas. J Clin Oncol. 2005;23:6739–46, http://dx.doi.org/10.1200/JCO.2005.04.515.

41. Conic RZ, Ko J, Allam SH, Atanaskova-Mesinkovska N, Kovalyshyn I, Bergfeld W, et al. Mixed versus pure variants of desmoplastic melanoma: the Cleveland clinic experience. Ann Plast Surg. 2018;80:277–81, http://dx.doi.org/10.1097/SAP.0000000000001225.

42. Jaroszewski DE, Pockaj BA, DiCaudo DJ, Bite U. The clinical behavior of desmoplastic melanoma. Am J Surg. 2001;182:590–5, http://dx.doi.org/10.1016/S0002-9610(01)00819-4.

43. Posther KE, Selim MA, Mosca PJ, Stanley WE, Johnson JL, Tyler DS, et al. Histopathologic characteristics, recurrence patterns, and survival of 129 patients with desmoplastic melanoma. Ann Surg Oncol. 2006;13:728–39, http://dx.doi.org/10.1245/ASO.2006.03.091.

44. Han D, Han G, Zhao X, Rao NG, Messina JL, Marzban SS, et al. Clinicopathologic predictors of survival in patients with desmoplastic melanoma. PLoS One. 2015;10, http://dx.doi.org/10.1371/journal.pone.0119716.

45. Khan F, Strohl A, Allen PD, Doerr TD. Desmoplastic melanoma of the head and neck: incidence and survival, 1992-2013. Otolaryngol - Head Neck Surg (United States). 2017;157:648–56, http://dx.doi.org/10.1177/0194599817725696.

46. Baer SC, Schultz D, Synnestvedt M, Elder DE. Desmoplasia and neurotropism. Prognostic variables in patients with stage I melanoma. Cancer. 1995;76:2242–7, http://dx.doi.org/10.1002/1097-0142(19951201)76:11<2242::AID-CNCR2820761110>3.0.CO;2-I.

47. Thomas JM, Newton-Bishop J, A'Hern R, Coombes G, Timmons M, Evans J, et al. Excision margins in high-risk malignant melanoma. N Engl J Med. 2004;350:757–66, http://dx.doi.org/10.1056/nejmoa030681.

48. Morton DL, Cochran AJ, Thompson JF, Elashoff R, Essner R, Glass EC, et al. Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial. Ann Surg. 2005;242:302–11, discussion 311-313.

49. Thelmo MC, Sagebiel RW, Treseler PA, Morita ET, Nguyen LH, Kashani-Sabet M, et al. Evaluation of sentinel lymph node status in spindle cell melanomas. J Am Acad Dermatol. 2001;44:451–5, http://dx.doi.org/10.1067/mjd.2001.110881.

50. Gyorki DE, Busam K, Panageas K, Brady MS, Coit DG. Sentinel lymph node biopsy for patients with cutaneous desmoplastic melanoma. Ann Surg Oncol. 2003;10:403–7, http://dx.doi.org/10.1245/ASO.2003.04.003.

51. Su LD, Fullen DR, Lowe L, Wang TS, Schwartz JL, Cimmino VM, et al. Desmoplastic and neurotropic melanoma: analysis of 33 patients with lymphatic mapping and sentinel lymph node biopsy. Cancer. 2004;100:598–604, http://dx.doi.org/10.1002/cncr.11947.

52. Pawlik TM, Ross MI, Prieto VG, Ballo MT, Johnson MM, Mansfield PF, et al. Assessment of the role of sentinel lymph node biopsy for primary cutaneous desmoplastic melanoma. Cancer. 2006;106:900–6, http://dx.doi.org/10.1002/cncr.21635.

53. Cummins DL, Esche C, Barrett TL, Balch CM, Mofid M. Lymph node biopsy results for desmoplastic malignant melanoma. Cutis. 2007;79:390–4.

54. George E, McClain SE, Slingluff CL, Polissar NL, Patterson JW. Subclassification of desmoplastic melanoma: pure and mixed variants have significantly different capacities for lymph node metastasis. J Cutan Pathol. 2009;36:425–32, http://dx.doi.org/10.1111/j.1600-0560.2008.01058.x.

55. Mohebati A, Ganly I, Busam KJ, Coit D, Kraus DH, Shah JP, et al. The role of sentinel lymph node biopsy in the management of head and neck desmoplastic melanoma. Ann Surg Oncol. 2012;19:4307–13, http://dx.doi.org/10.1245/s10434-012-2468-2.

56. Broer PN, Walker ME, Goldberg C, Buonocore S, Braddock DT, Lazova R, et al. Desmoplastic melanoma: a 12-year experience with sentinel lymph node biopsy. Eur J Surg Oncol. 2013;39:681–5, http://dx.doi.org/10.1016/j.ejso.2013.02.025.

57. Egger ME, Huber KM, Dunki-Jacobs EM, Quillo AR, Scoggins CR, Martin RCG 2nd, et al. Incidence of sentinel lymph node involvement in a modern, large series of desmoplastic melanoma. J Am Coll Surg. 2013;217:35–7, http://dx.doi.org/10.1016/j.jamcollsurg.2013.05.006.

58. Han D, Zager JS, Yu D, Zhao X, Walls B, Marzban SS, et al. Desmoplastic melanoma: is there a role for sentinel lymph node biopsy? Ann Surg Oncol. 2013;20:2345–51, http://dx.doi.org/10.1245/s10434-013-2883-z.

59. 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;70:274–80, http://dx.doi.org/10.1016/j.bjps.2016.11.003.

60. Murali R, Zannino D, Synnott M, Mccarthy SW, Thompson JF, Scolyer RA. Clinical and pathological features of metastases of primary cutaneous desmoplastic melanoma. Histopathology. 2011;58:886–95, http://dx.doi.org/10.1111/j.1365-2559.2011.03808.x.

61. Tejera-Vaquerizo A, Martín-Cuevas P, Gallego E, Herrera-Acosta E, Traves V, Herrera-Ceballos E, et al. Predictors of sentinel lymph node status in cutaneous melanoma: a classification and regression tree analysis. Actas Dermosifiliogr. 2015;106, http://dx.doi.org/10.1016/j.ad.2014.10.012.

62. Faries MB, Thompson JF, Cochran AJ, Andtbacka RH, Mozzillo N, Zager JS, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. N Engl J Med. 2017;376:2211–22, http://dx.doi.org/10.1056/NEJMoa1613210.

63. Moreno-Ramírez D, Boada A, Ferrándiz L, Samaniego E, Carretero G, Nagore E, et al. Disección ganglionar en el paciente con melanoma y metástasis en el ganglio centinela: propuesta de decisión basada en la evidencia actual. Actas Dermosifiliogr. 2018;109:390–8, http://dx.doi.org/10.1016/j.ad.2018.02.008.

64. Pace CS, Kapil JP, Wolfe LG, Kaplan BJ, Neifeld JP. Desmoplastic melanoma: clinical behavior and management implications. Eplasty. 2016;16:e3.

65. Vongtama R, Safa A, Gallardo D, Calcaterra T, Juillard G. Efficacy of radiation therapy in the local control of desmoplastic malignant melanoma. Head Neck. 2003;25:423–8, http://dx.doi.org/10.1002/hed.10263.

66. Arora A, Lowe L, Su L, Rees R, Bradford C, Cimmino VC, et al. Wide excision without radiation for desmoplastic melanoma. Cancer. 2005;104:1462–7, http://dx.doi.org/10.1002/cncr.21311.

67. Foote MC, Burmeister B, Burmeister E, Bayley G, Smithers BM. Desmoplastic melanoma: the role of radiotherapy in improving local control. ANZ J Surg. 2008;78:273–6, http://dx.doi.org/10.1111/j.1445-2197.2008.04436.x.

68. Guadagnolo BA, Prieto V, Weber R, Ross MI, Zagars GK. The role of adjuvant radiotherapy in the local management of desmoplastic melanoma. Cancer. 2014;120:1361–8, http://dx.doi.org/10.1002/cncr.28415.

69. Strom T, Caudell JJ, Han D, Zager JS, Yu D, Cruse CW, et al. Radiotherapy influences local control in patients with desmoplastic melanoma. Cancer. 2014;120:1369–78, http://dx.doi.org/10.1002/cncr.28412.

70. Oliver DE, Patel KR, Switchenko J, Parker D, Lawson DH, Delman KA, et al. Roles of adjuvant and salvage radiotherapy for desmoplastic melanoma. Melanoma Res. 2016;26:35–41, http://dx.doi.org/10.1097/CMR.0000000000000201.

71. Neurotropic Melanoma of the Head and Neck - Full Text View - ClinicalTrials.gov n.d. [accessed 8 Dec 2020]. Available from: https://clinicaltrials.gov/ct2/show/NTC00975520.

72. Eroglu Z, Zaretsky JM, Hu-lieskovan S, Kim DW, Johnson DB, Liniker E, et al. High response rate to PD-1 blockade in desmoplastic melanomas. Nature. 2018;553:347–50, http://dx.doi.org/10.1038/nature25187.High.

73. Ochoa CE, Joseph RW. Desmoplastic melanoma: a brief review and the efficacy of immunotherapy. Expert Rev Anticancer Ther. 2019;19:205–7, http://dx.doi.org/10.1080/14737140.2019.1574573.

74. Pembrolizumab in Treating Patients With Desmoplastic Melanoma That Can or Cannot Be Removed by Surgery. ClinicalTrials.gov n.d. [accessed 8 Dec 2020]. Available from: https://clinicaltrials.gov/ct2/show/NCT02775851.