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Mixed versus pure variants of Desmoplastic Melanoma: The Cleveland Clinic Experience

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Abstract

Background—Desmoplastic melanoma (DM) is a sub-variant of spindle cell melanoma, accounting for less than 4 percent of all cutaneous melanomas. It occurs later in life and is associated with chronic sun exposure. DM prognosis is considered more favorable than other variants, with lower rates of metastasis and higher survival. Recently DM has been further sub-classified into pure and mixed, calling into question surgical management and patient outcomes as well as viability of current nationwide databases without this distinction.

Methods—We identified all patients with a histopathologic diagnosis of desmoplastic melanoma from the Cleveland Clinic electronic melanoma database (n=58) from 1997–2013. Clinical and histopathologic data were collected. Comparison in clinical variables was performed between patients who had pure (n=15) and mixed (n=43) variants of DM.

Results—There were no differences in age, gender, location of lesion, Breslow depth, ulceration, or regression. Patients with mixed desmoplastic melanoma were more likely to have lymphovascular invasion (p=0.03) compared to pure desmoplastic melanoma. There was no difference in performance of sentinel lymph node biopsy (p=0.25) or sentinel lymph node positivity (p=0.31) between the two groups. Recurrence was present in 13.3% of pure and 30.2% of mixed patients. Overall Kaplan Meier 3 year survival was 75% for pure and 80% for mixed desmoplastic melanoma (p=0.53).

Conclusion—Pure and mixed desmoplastic melanomas appear to have similar clinical characteristics and outcomes. This indicates that analysis of national datasets without this sub classification remains viable.

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Keywords

desmoplastic melanoma; pure desmoplastic melanoma; mixed desmoplastic melanoma; survival; recurrence

BACKGROUND

Desmoplastic melanoma (DM) is a sub-variant of spindle cell melanoma first described by Conley et al in 1971, accounting for less than 4 percent of all cutaneous melanomas.[1–3] DM occurs later in life compared to conventional melanoma, with mean age around 66, and predominantly affects males.[4] Etiology is uncertain however chronic sun exposure appears to be a risk factor. Clinical appearance varies with appearance of nodules, plaques to ill-defined scar-like lesions, which are most often amelanotic.[4] Histologically, DM is characterized by proliferation of malignant spindle cells associated with a dense collagenous stroma. There is often an overlying junctional component present.

Prognosis for patients with DM varies widely among studies. The first reports suggested that patients with DM may have poorer prognosis than patients with other types of melanomas.[5] Later reports suggested that survival was better among patients with DM than those with conventional melanoma.[6] However, estimated 5-year survival of conventional melanomas regardless of stage is 91%, while in DM studies survival ranges from 67–89%.[1,4,7,8] These survival differences have been further emphasized in recent histopathologic distinction between pure and mixed desmoplastic melanoma. Pure DM (pDM) lesions are characterized by at least 90% of desmoplasia, while mixed DM (mDM) contain less than 90 % desmoplasia and a high cellular density.[9]

Due to this variability we examined patients in a single tertiary-referral center in the Midwest. In this historical cohort study we compared recurrence rates and survival of patients diagnosed with pDM or mDM.

METHODS AND MATERIALS

Patient Sample

This study was approved by the Cleveland Clinic Institutional Board Review. We used the Cleveland Clinic melanoma database to identify all patients with histopathologic diagnosis of desmoplastic melanoma in the period from 1997 to 2013. Demographic and clinical data, including recurrence, metastasis and death, were collected using manual search of electronic medical records. Occurrence of death was rechecked using the Social Security Death Index. Histopathologic information analysis comprised of melanoma location, Breslow thickness, Clark level, ulceration, mitotic index, presence of micro- and macrosatellitosis, regression, lymphocytosis, lymphovascular and perineural invasion. Histopathologic slides were reviewed by a board certified dermatopathologist to establish whether melanomas were pure or mixed type. Pure desmoplastic melanoma was defined as at least 90% of desmoplasia with a pauci-cellularity whereas mixed desmoplastic melanoma contained less than 90 % desmoplasia and a high cellular density.[9]

Surgical and pathologic reports were also included for sentinel lymph node biopsy and lymphadenectomy data. Survival was measured using overall survival.

Statistical Methods

Continuous variables were expressed as mean (standard deviation, SD) and compared by using the t test. Categorical variables were expressed as percentages and compared using the Chi-Square or Fisher exact tests. The groups' survival rates were calculated by using the Kaplan-Meier method and compared by using log-rank test. A p-value < 0.05 was considered significant.

RESULTS

A total of 58 patients with desmoplastic melanoma were identified. Of these, 43 were considered mixed and 15 were pure DM. There were no significant differences in age, gender, family history of melanoma, immunosuppression and location of lesion between mixed and pure DM patients (Table 1). Mixed DM was most often located on head and neck area, followed by upper extremity while pure DM was located mostly on the trunk. Average follow up time was 3.46 years.

Breslow depth (3.51±3.51 mDM vs 3.36±2.63 pDM, p=0.88), Clark level, ulceration, mitotic index, presence of micro and macrosatellites, regression, and perineural invasion did not differ between the two groups (Table 2). Patients with mDM were more likely to have lymphovascular invasion (p=0.03, Figure 1) and tended to have less lymphocytic infiltrate (p=0.09).

Sentinel lymph node biopsy (SLNB) was performed in 55.8% of mixed, and 73.3% of pure DM patients, however this difference was not statistically significant (p=0.25, Figure 2). There was no difference in number of sentinel lymph nodes (SLN) removed (2.25±2.11 mDM vs 2.27±1.19 pDM, p=0.97) or in sentinel node positivity (0.12±0.34 mDM vs 0.33±0.89 pDM, p=0.31). Lymphadenectomy was performed in 23.3% of mDM patients and 20% of pDM patients (p=0.72). There was no difference in the number of nodes removed (p=0.77) or in node positivity (n=0.61) after lymphadenectomy between the two groups.

Recurrence occurred in 30% of patients with mDM and 13.3% of patients with pDM, but this difference was not significant (p=0.22). Average time to detection of recurrence was 3.09 years. Distant metastases developed in 18.6% of mDM and in 6.7% of pDM patients. Kaplan-Meier 3 year survival for pDM was 75% versus 80% for mDM while 5 year survival was 75% and 73% respectively (p=0.53, Figure 3). The majority of recurrences occurred within 1 year from diagnosis for pure type and 3 years for mixed type (p=0.88).

DISCUSSION

Recently, desmoplastic melanoma was separated into pure and mixed subtypes, and little information exists on how these histopathologic differences have influenced surgical management. In this single-center cohort study we found that there is no significant difference in the overall 3- and 5-year survival between pDM and mDM. Lympho-vascular

invasion was higher among mDM patients, while there was no difference in melanoma location, Breslow depth, Clark level, ulceration, mitotic index, presence of micro and macrosatellites, regression, lymphocytosis and perineural invasion. Interestingly, there was no difference between performance of sentinel lymph node biopsy and sentinel node positivity among the two groups. Additionally, the number of nodes removed during lymphadenectomy, and node positivity did not differ between the two groups. Distant metastases occurred in 18.6% of mixed and 6.6% of pure desmoplastic melanoma.

This study is in agreement with prior reports of male predominance in development of DM with 2.1:1 ratio, slightly lower than the SEER report of 2.3:1 for mixed type of melanoma and higher than the 1.7:1 in conventional melanoma.[1,10] This could be explained by our smaller numbers and an apparent increasing incidence trend.[1] Interestingly, among the patients with pure desmoplastic melanoma, the ratio was 1:1.14, indicating more women had pure DM. The mean age of patients was 64 for mixed, and 60 for pure, both of which are younger than the previously reported 66 and closer to the median age of conventional melanoma.[1,4,10] In contrast, a study comparing patients with pure and mixed DM showed that those with mixed DM are younger than patients with pure DM.[11]

As in prior studies, most common location of DM was on head and neck area, while second most common location was upper extremity for mixed, and trunk for pure DM.[2,6,12,13] Similar to George et al, there was no difference between the pure and mixed DM subtypes.[9] The severity of DM and predominantly sun exposed locations are in line with prior statements of increasing occurrence with sun exposure.[1]

In our patient population, Breslow thickness did not differ between the two groups. Similarly, in another study, there was no difference in Breslow thickness among pure or mixed DM patients.[11] The majority of our patients were Clark level 4 or 5, with no difference between pure and mixed DM. This was supported by George et al.[11]

Unlike George et al. we found no statistically significant difference in mitotic index between the two groups. Interestingly, we also found that mixed DM patients were more likely to have lymphovascular invasion, which conflicts with the findings of George et al.[11]

Sentinel lymph node biopsy use in desmoplastic melanoma has been evaluated in several studies. Reported SLN positivity for DM ranges from 0–12.1%, which was similar to mixed DM in our study; however 18.2% of pure desmoplastic were positive.[3] In contrast, several studies found that rates of node positivity ranged between 0% and 2% among patients with pure DM and between 16% and 22% for mDM.[11,14–16] Dunne et al recommended SLNB for mDM but not for pDM due to previously reported low rates of SLN positivity, given the procedural complications and cost; however we recommend considering SLNB in both types based on our results.[16]

Rates of distant metastases among studies vary from 0 to 19% with the older studies presenting higher numbers of distant metastasis, while approximately 4% of conventional melanomas have distant metastases.[1,7,10] The largest study examining desmoplastic melanomas, using SEER data, demonstrates a 5% distant metastasis rate.[1] A study of 280 patients in the Melanoma Unit of Australia found that there was no difference between rates

of metastasis of desmoplastic and non-desmoplastic melanomas.[2] In our study, rate of distant metastasis was 18.6% for mixed and 6.7% for pure DM, but this difference was not statistically significant.

Our survival rates are similar to the 75% 5-year survival reported by Quinn et al.[2] Interestingly, a recent paper by Han et al. also showed a similar five-year OS of 74.5% with lower limit of 95% CI: 69.2%.[17] It is possible that the lack of a difference in survival between the two groups could be attributed to no difference in age, Breslow thickness, ulceration, mitotic index and perineural invasion.[1]

Due to the varied behavior of desmoplastic melanoma, certain treatment modalities have also shown different effects on recurrence and survival. For example, performing sentinel lymph node biopsy has been highly questioned, with lower node positivity, and, according to a recent systematic review, sentinel node biopsy should be considered only in mDM.[16] Furthermore treatment of desmoplastic melanomas with wide local excision and postoperative radiation therapy had improved outcomes compared to wide local excision only and is suggested for superior local recurrence control.[18] Finally, recent reports on anti-PD/PD-L1 therapy have shown a better response of metastatic desmoplastic melanoma, indicating that these patients could be better candidates for therapy.[19] Future treatment modalities may highlight additional differences in the behavior of desmoplastic melanoma.

CONCLUSION

Despite the histopathologic distinction in pDM and mDM, in our experience, these are biologically too similar to recommend any change in management. As such, and given the limited numbers available for study, mDM and pDM can be grouped together to assess best practices. Although distant metastases occurred in 18.6 % in mDM and 6.7% in pDM, 5-year survival for both was approximately 75%. Mixed DM patients were predominantly male, while there was no gender difference in pure patients. There was no difference in immunosuppression and family history between pure and mixed DM patients. It is interesting to note that while histopathologic differences exist, there is no difference in surgical management and overall patient survival in the desmoplastic melanoma subtypes.

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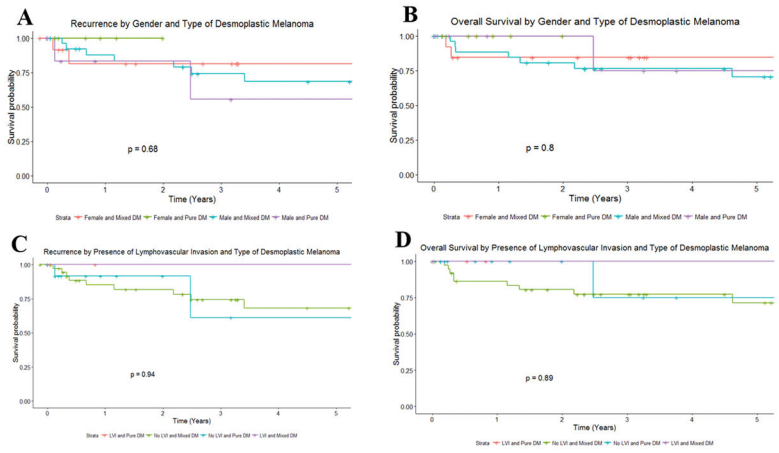

Figure 1.

Recurrence and Overall Survival by demographic and histopathologic characteristics. Figure 1A. Recurrence Status by Gender and Type of Desmoplastic Melanoma; Figure 1B. Overall Survival by Gender and Type of Desmoplastic Melanoma; Figure 1C. Recurrence Status by Presence of Lymphovascular Invasion and Type of Desmoplastic Melanoma; Figure 1D. Overall Survival by Presence of Lymphovascular Invasion and Type of Desmoplastic Melanoma.

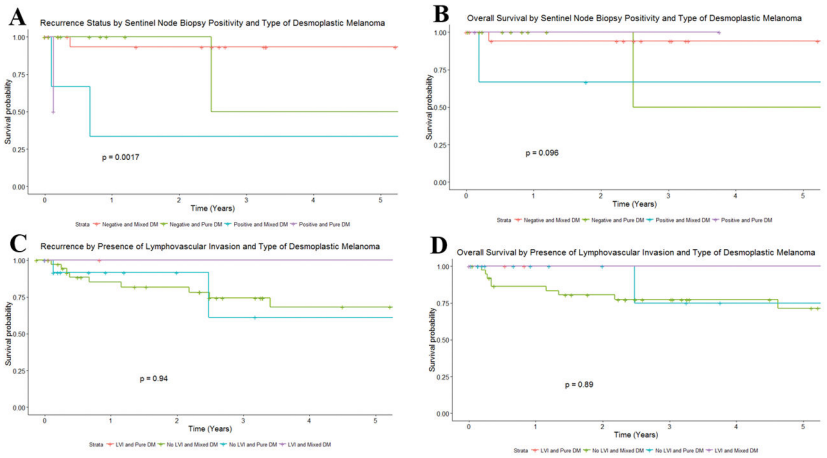

Figure 2.

Recurrence and Overall Survival by Surgical Management. Figure 2A. Recurrence Status by Sentinel Node Biopsy Positivity and Type of Desmoplastic Melanoma; Figure 2B. Overall Survival by Sentinel Node Biopsy Positivity and Type of Desmoplastic Melanoma; Figure 2C. Recurrence Status by Lymphadenectomy Positivity and Type of Desmoplastic Melanoma; Figure 2D. Overall Survival by Lymphadenectomy Positivity and Type of Desmoplastic Melanoma.

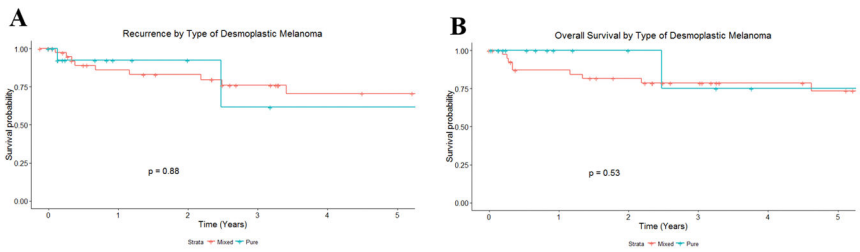

Figure 3.

Recurrence free survival and Overall Survival by type of desmoplastic melanoma. Figure 3A. Recurrence Status by Type of Desmoplastic Melanoma; Figure 3B. Overall Survival by Type of Desmoplastic Melanoma

Table 1

Demographic, histopathologic and surgical characteristics of pure and mixed desmoplastic melanoma

	Mixed (n=43)	Pure (n=15)	p-value
Age at Diagnosis	64.00±15.29	60.07±12.58	0.38
Gender (%)			0.26
Male	29 (67.4)	7 (46.7)	
Female	14 (32.6)	8 (53.3)	
Location (%)			0.26
Head and Neck	22 (51.2)	11 (73.3)	
Upper Extremity	11 (25.6)	1 (6.7)	
Trunk	7 (16.3)	3 (20.0)	
Lower Extremity	3 (7.0)	0 (0.0)	
Breslow	3.51±3.51	3.36±2.63	0.88
Clark (%)			0.69
III	1 (2.3)	0 (0.0)	
IV	25 (58.1)	11 (73.3)	
V	16 (37.2)	4 (26.7)	
Unknown	1 (2.3)	0 (0.0)	
Ulceration (%)			0.35
Yes	13 (30.2)	2 (13.3)	
No	29 (67.4)	12 (80.0)	
Unknown	1 (2.3)	1 (6.7)	
Mitotic Index	3.26±4.83	1.85±4.12	0.35
Regression (%)			0.27
Yes	1 (2.3)	0 (0.0)	
No	40 (93.0)	14 (93.3)	
Unknown	2 (4.7)	1 (6.7)	
Lymphocytes (%)			0.09
Present	24 (55.8)	13 (86.7)	
Brisk	4 (9.3)	0 (0.0)	
Absent	14 (32.6)	1 (6.7)	
Unknown	1 (2.3)	1 (6.7)	
Macrosatellites (%)			0.31
No	42 (97.6)	14 (93.3)	
Unknown	1 (2.3)	1 (6.7)	
Microsatellites (%)			0.31
Yes	1 (2.3)	0 (0.0)	
No	41 (95.3)	14 (93.3)	
Unknown	1 (2.3)	1 (6.7)	
Lymphovascular Invasion (%)			0.03
Present	3 (7.0)	0 (0.0)	
Not Present	40 (93.0)	13 (86.7)	

	Mixed (n=43)	Pure (n=15)	p-value
Unknown	0 (0.0)	2 (13.3)	
Presence of perineural invasion			0.66
Yes	18 (41.9)	6 (40)	
No	25 (58.1)	9 (60)	
Sentinel Node Biopsy Performed			0.25
Yes	24 (55.8)	11 (73.3)	
No	19((44.2)	4 (26.7)	
Sentinel nodes removed	2.25±2.11	2.27±1.19	0.97
Sentinel node positivity			0.66
Yes	3 (12.5)	2 (18.2)	
No	21 (87.5)	9 (81.8)	
Sentinel nodes positive	0.12±0.34	0.33±0.89	0.31
Lymphadenectomy performed (%)			0.72
Yes	10 (23.3)	3 (20)	
No	33 (76.7)	12 (80)	
Nodes removed in lymphadenectomy	32.09±20.27	28.00±22.11	0.77
Lymphadenectomy positivity			0.22
Yes	2 (20)	2 (66.7)	
No	8 (80)	1 (33.3)	
Nodes positive in lymphadenectomy	1.11±2.67	2.00±2.00	0.61
Recurrence			0.22
Yes	13 (30.2)	2 (13.3)	
No	30 (69.8)	13 (86.7)	
Alive			0.07
Yes	30 (69.8)	14 (93.3)	
No	13 (30.2)	1 (6.7)	
Immunosuppression			0.69
Yes	8 (18.6)	2 (13.3)	
No	35 (81.4)	13 (86.7)	
Family History			0.64
Yes	5 (11.6)	1 (6.7)	
No	38 (88.4)	14 (93.3)	
Distant Metastases			0.31
Yes	8 (18.6)	1 (6.7)	
No	35 (81.4)	14 (93.3)	