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Title: Differences between pure desmoplastic melanoma and superficial spreading melanoma in terms of survival, distribution and other clinicopathologic features.

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Abstract (287 words/300 words)

Background: Pure desmoplastic melanoma (pDM) is an uncommon subtype of malignant melanoma with comparative high rates of local recurrence and low rates of sentinel lymph node positivity. The melanoma specific survival (MSS) of pDM compared to other melanoma subtypes is unclear, with conflicting reports and lack of multivariable analyses.

Objectives: We aimed to describe clinicopathological characteristics of a cohort of patients with pDM and to compare the MSS of pDM with superficial spreading melanoma (SSM).

Methods: A prospective cohort study was performed of all primary invasive cutaneous pDM with known tumour location and thickness reviewed at a tertiary referral centre over 21 years.

Results: 119 primary cutaneous invasive pDMs from 3570 total invasive cutaneous melanomas were included. Compared to 2,272 SSMs, and due largely to their greater average thickness, patients with pDM had worse MSS (unadjusted hazard ratio, HR, 2.56, 95% confidence interval, CI, 1.56 to 4.22). After adjustment for clinicopathologic factors (including thickness, ulceration, mitotic rate, age and sex), there was evidence that patients with pDM had an improved MSS (adjusted HR, 0.49; 95% CI, 0.28 to 0.87). Median thickness of head and neck pDM was greater than non-head and neck pDM ($p < 0.001$). There was reduced univariable MSS in head and neck pDM compared to the rest of the body.

Conclusions: Decreased univariable MSS of patients with pDM compared to SSM was explained by the increased frequency of adverse clinicopathologic features at diagnosis, in particular the greater Breslow thickness of pDM. After adjustment, patients with pDM had half the chance of melanoma specific death compared to SSM. Head and neck pDM were thicker at diagnosis compared to the rest of the body, which may account for its poorer survival compared to the rest of the body.

Introduction

Desmoplastic melanoma (DM) is an uncommon subtype of cutaneous malignant melanoma characterised by the presence of malignant spindle cells encased in a prominent collagenous stroma¹. The atypical features of this melanoma (often presenting as a hypomelanotic plaque or nodule) has often caused DM to be mistaken for benign lesions such as scar tissue or a dermatofibroma². With these features hindering early clinical diagnosis, DM is often advanced when diagnosed (average Breslow thickness between 2.5-6mm in reports)²⁻⁶.

Desmoplastic melanoma has been subclassified into two groups: pure (predominant features of desmoplasia) and mixed (partial focus of desmoplasia) to delineate differing histology and behaviour^{2, 5, 7}. Patients with pure DM (pDM) appear to have relatively low rates of lymph node metastases/sentinel lymph node positivity^{2, 8-12}, high rates of neurotropism and local recurrence when compared to mixed DM (mDM)^{2, 13}. Some have attributed the poor MSS associated with DM to high median thickness, however there is

75 mixed evidence^{1, 14-18}. Early case series that included a small number of DM cases suggested
76 poorer survival outcomes^{1, 16, 19}. However, there was limited pathological information
77 provided for the cases with no subtype comparison^{1, 16, 19}. More recent and larger studies
78 have suggested that patients with DM have either improved survival^{3, 18} or similar survival to
79 all conventional melanoma^{2, 15, 17, 20} in unadjusted and matched case control analysis.
80 Patients with mDM appeared to have poorer adjusted survival compared to pDM in two
81 studies^{5, 21}. Heterogeneity of DM classification in studies (inclusion of both pDM and mDM)
82 comparing survival to conventional melanoma may have limited the ability to detect survival
83 differences along with unaccounted confounding due to different behaviour between pDM
84 and mDM^{7, 22}. The inclusion of multiple melanoma subtypes together in conventional
85 melanoma comparison groups further complicates survival analysis due to heterogenous
86 distribution of prognostic factors between subtypes.

87 No previous studies have compared multivariable pDM MSS against conventional melanoma
88 or against a single subtype. In addition, MSS of head and neck DM was found to be lower
89 than that of non-head and neck DM, however it is unknown whether this is due to mDM or
90 pDM, as there was no subclassification of DM in this data^{14, 23}.

91 The aims of this study were to compare survival associated with pDM with that associated
92 with the most common melanoma subtype, superficial spreading melanoma (SSM) and to
93 assess any impact on survival of anatomic tumour location of pDM.

94 **Materials and Methods**

95 Institutional ethics approval was obtained from the Alfred Hospital HREC and Monash
96 University for this study. All invasive cutaneous primary melanoma cases reviewed at the
97 Victorian Melanoma Service (VMS) from the commencement of the service in 1994 until
98 January 2016 with known Breslow thickness and tumour location were included. The VMS is
99 a multidisciplinary tertiary referral service located at the Alfred Hospital in Melbourne. It
100 reviews approximately one quarter of total new diagnoses of melanoma in the Australian
101 state of Victoria.

102 Clinical features of each patient collected by the reviewing clinician included: age, sex, date
103 of diagnosis (biopsy date) and tumour location coded utilising a body map of 232 areas
104 differentiating anterior from posterior, left from right and midline structures, as developed

by the Pigmented Lesion Study Group²⁴. Other clinical features recorded included: clinical hypomelanosis, Fitzpatrick skin type, hair colour, presence of actinic keratosis and previous history of non-melanoma skin cancer and family history of melanoma. Patients were subsequently examined by clinicians to determine total naevus count, number of dysplastic naevi, ephelides and lentigines. Independent pathology review of each melanoma was undertaken by VMS dermatopathologists. Histologic features that were assessed included tumour subtype according to World Health Organization guidelines²⁵, Breslow thickness, ulceration status, mitotic rate (mm²), neurotropism, lymphovascular invasion, satellite metastasis, regression and tumour invading lymphocytes. Pure desmoplastic melanoma was defined in our study as more than 80% involvement of the invasive tumour with stromal fibrosis, consistent with the definition used in other reports^{2, 4, 5, 7}. As mitotic rate was recorded in per 10 high powered field (HPF) prior to 2005, reporting pathologist's conversion factors were utilised to convert to per millimetre squared.

Survival information for all patients in the study was obtained by linkage with the Victorian Cancer Registry (VCR), a population-based cancer registry that collects data on all cancer diagnoses and mortality for residents in the state of Victoria, Australia. Patient vital status was current as of 31st December 2015. For patients diagnosed with more than one primary cutaneous melanoma, the melanoma with the greatest Breslow thickness was retained²⁶. 3570 invasive cutaneous melanomas were retrieved out of 5598 total melanoma records after exclusion of cases that were insitu (n=1329), non-registry linked (n= 317), of unknown Breslow thickness (n= 44), non cutaneous melanoma (n=4) and multiple melanomas (n= 334). 317 cases were not able to be linked to the VCR (the earliest diagnosis date of affected cases was October 2015) due to migration outside of Victoria, of which 17 were pDM.

Analysis of MSS for melanoma subtype, clinicopathologic characteristics and tumour location was performed using Kaplan-Meier survival estimates and Cox proportional hazards models. Difference between pDM and SSM clinicopathologic characteristics were compared using Wilcoxon Rank-sum test for continuous variables and chi-squared test for categorical variables. Significant difference between medians was assessed by the nonparametric equality of medians test. Given a skewed distribution for Breslow thickness, a log transformation was applied with the transformed variable included in models as a

continuous variable. Age at diagnosis was dichotomised for analysis at the median age of the total invasive melanoma cohort of 65 years. Mitotic rate was categorised into five strata to allow discrimination and create similar strata to observed survival differences in AJCC data²⁶.

Multiple imputation using chained equations (MICE) was used to impute values in place of missing data for all variables except thickness and tumour location (see Table 1 legend for the number of missing values for each variable)²⁷. There were no missing values for age, sex and previous history of melanoma. The calculated Nelson-Aalen estimate of cumulative hazard generated from univariable analysis and the censor indicator variable were included in the imputation model²⁸. Ten data sets (cycles) with imputed values were generated and results of analysis applied to all ten sets with results combined according to Rubin's rules²⁹. All statistical analyses were performed using Stata (Version 14.3, StataCorp, College Station, TX). Multivariable results were considered statistically significant if the P value was less than 0.05. Clinicopathologic variables were included in the multivariable analysis if the overall P-value from a univariable Cox proportional hazards model was less than 0.1³⁰. Age and sex were included in the multivariable model regardless of univariable results, due to previous research indicating their importance as prognostic factors in all melanoma survival³¹. Justification for the chosen approach to multivariable analysis came from there being at least 8 melanoma specific deaths per variable in the multivariable models³²⁻³⁴ and there being no evidence of violation of the proportional hazards assumption on the basis of Schoenfeld residuals.

Results

Cohort characteristics

Baseline clinical and pathologic characteristics of the patients with pDM and SSM are detailed in Table 1. Patients with pDM were older, a greater proportion were male, they had greater median Breslow thickness and mitotic rate, higher frequency of ulceration, neurotropism, microsatellites and hypomelanosis compared to SSM (Table 1). Patients with SSM had greater proportion of naevus associated melanoma, total naevus and dysplastic naevus counts whilst patients with pDM had more previous non-melanoma skin cancers and

lighter eye colour (Table 1). Within our melanoma cohort, there were 119 cases of pDM leading to 17 pDM specific deaths (3.3% of total included melanoma cases) and 2,272 superficial spreading melanomas with 187 melanoma specific deaths (SSM, 63.6% of total included melanoma cases). Cause of death could not be determined for one pDM case. Median follow-up was 3.6 years for patients with pDM (IQR= 1.7-6.6) and 8.0 years (IQR= 2.75-14.7) for the SSM cohort ($p<0.001$). Five clinicopathologic factors were associated with pDM specific survival on univariable analysis and were thus included in subsequent multivariable model analyses (Table 2, P values <0.10). Independent prognostic factors for pDM included Breslow thickness, ulceration, mitotic rate and presence of microsatellites (Table 2, P values <0.05). The majority of deaths occurred in the AJCC²⁶ tumour stage T4 patients (Table 3). Selected outcomes for the pDM cohort are also listed in Table 2. Thirteen percent of primary pDM cases had at least one local recurrence of persistent primary pDM (15/119 cases) and 3/17 pDM specific deaths had a local recurrence of primary pDM detected prior to developing metastatic disease.

Desmoplastic melanoma tumour location analysis

Pure desmoplastic melanoma predominantly (66%) occurred on the head and neck (Fig. 1). In comparison, the proportion of head and neck SSM was substantially lower (11% compared to 65% of pDM cases respectively). Occurrence of pDM on the back, lower extremities, anterior trunk and upper extremities was proportionally less frequent than SSM (chi-squared $p<0.001$)

Compared to the rest of the body, there was reduced survival of head and neck pDM (Table 3). Adjusted analysis for variables in addition to Breslow thickness was not possible due to the low number of melanoma specific deaths among patients with pDM at non-head and neck sites. There was a significant difference in median Breslow thickness between pDM of the head and neck and the rest of body (medians 5.1mm and 3.5mm respectively, $p<0.01$).

Desmoplastic subtype specific survival

Unadjusted melanoma specific survival for pDM and SSM was similar at one year (99%), however, this diverged at 5 years, with pDM having the poorer survival (Fig. 2). In unadjusted analysis, pDM was associated with significantly decreased MSS (HR 2.56,

P<0.001, Table 4) compared to SSM. However, after adjustment for clinicopathologic variables, there was evidence for improved MSS for pDM compared to SSM (HR 0.49, P=0.01). Using complete case analysis, the difference between SSM and pDM multivariate survival was similar to that of the multiple imputation model (complete-case analysis HR 0.55, 95% CI 0.30-0.99, p=0.05). Increasing thickness and ulceration were strongly associated with reduced MSS for pDM.

Discussion

This study describes clinicopathologic and survival data of a prospectively collected Australian pDM cohort with respect to anatomical tumour location and compared to SSM. Patients with pDM had greater absolute risk of melanoma specific death than SSM. This poorer survival was more than explained by differences in the distribution of Breslow thickness, mitotic rate, ulceration, lymphovascular invasion and sex between pDM and SSM. Adjusted MSS of patients with pDM in our study was significantly better than those with SSM (HR 0.49, P=0.01). The only multivariable survival analyses involving pDM have found improved disease free survival⁵ and overall survival²¹ compared to mDM. While mDM contains significant desmoplasia, associated subtypes include lentigo maligna melanoma and superficial spreading melanoma and therefore were in agreement with our multivariable findings⁴. Distinct metastatic pathways and tumour biology between pDM and SSM may explain our suggested subtype survival differences. Although limited by low numbers of DM, systematic review of multiple DM studies has shown positivity of sentinel lymph node biopsy for pDM (5.4%) was less than half that of mDM (13.8%)⁸. The lower relative tumour volume of pDM compared to conventional melanoma subtypes due to high proportion of fibroblasts may explain the improved prognosis³⁵⁻³⁷.

A previous case control study found that thickness, age and sex matched survival of 89 DM cases was the same as control melanomas¹⁵. However, the subtype of controls was not known and mixed DM were included¹⁵. Several studies have compared unadjusted melanoma specific and overall survival of patients with DM, pDM and non-DM with varying findings. One found similar unadjusted MSS² but noted greater median thickness in pDM (4.5mm in compared with 2.1mm in non-DM)², another found overall survival of DM to be the same as non-DM¹⁷ and older series had higher five year disease free survival rate for DM than non DM¹⁸. Varying thickness of DM and non DM cases amongst other clinicopathologic

features complicate these univariable comparisons. None of these studies documented the full distribution of tumour subtype in the non DM cases. No published studies have compared survival with pDM to a single conventional melanoma subtype (eg, SSM) using a multivariable Cox proportional hazards model with adjustment for potential confounders.

Pure DM was most frequently diagnosed in the scalp and face similar to one other study⁵, with the majority of pDM related deaths occurring in the head and neck. While patients with head and neck pDM had a worse MSS than pDM on the rest of the body on univariable analysis, after adjustment for Breslow thickness this no longer held. The greater median Breslow thickness of pDM from the head and neck compared to the rest of body likely accounted for the reduced univariable survival of head and neck pDM patients. The increased thickness of head and neck melanoma has also been reported with all subtypes on the head and neck^{38, 39}. Our five year MSS estimate for pDM of head and neck was similar to a large registry study examining DM of head and neck (80.5%), however, this study cohort likely included mDM¹⁴. A separate multivariable analysis of the same large SEER registry data found that patients with DM of the scalp and neck had similar survival to those with DM of the face and ears but lower survival than those with DM of the trunk and extremities²³.

In our study, median Breslow thickness at diagnosis was also significantly higher for pDM (4.2mm) than SSM (0.8mm). A previous report has also demonstrated greater depth in pDM compared to all melanomas². The deep thickness of pDM compared to SSM is likely due to the subtle clinical presentation (rates of hypomelanosis between 40-90% in DM cohorts)^{9, 40-43} hindering earlier clinical diagnosis.

Our clinicopathologic findings further emphasised differences in patient characteristics between pDM and SSM. The 3.3% proportion of pDM in our total cohort of 3570 cutaneous melanoma was similar to one other of 2.5%¹¹. Our rates of ulceration, neurotropism and median Breslow thickness were similar to other published DM studies⁸⁻¹². A male predominance among cases of pDM compared to other melanomas (male : female ratio of 2:1) was demonstrated in a systematic review, consistent with our findings^{10, 17, 41}. However, altered distribution of sex in the pDM cohort compared to SSM was not associated with a sex dependent difference in pDM specific survival in our data on univariable analysis or on

multivariable analysis, unlike univariable findings in other studies^{5, 6, 44, 45}. The majority of our cohort of pDMs were associated with lower total naevus counts and a lower proportion of pre-existing naevus than SSM. This may point to an alternate melanoma pathway of causation for DM with fewer associated naevi and a higher accumulation of mutations in DM compared to other subtypes⁴⁶⁻⁴⁸. pDMs in our cohort were associated with markers of chronic sun-exposure such as history of previous severe sunburns, prior NMSC and solar keratosis, in keeping with accumulated UVR mutations. Another study showed that 93 of 113 cases of DM were associated with histological features of solar elastosis⁴. Further evidence for the role of chronic UV damage is the strong head and neck predominance of pDM, and the higher proportion of extremity pDM compared to the trunk in our cohort and others^{2, 4-6, 9, 10, 13, 41}.

There were limitations to our study. Molecular testing was introduced relatively recently and therefore the impact of mutational status could not be assessed due to a lack of data. Larger and longer follow-up studies are needed to validate our findings.

Conclusion

This study suggests that pDM may have a better multivariable survival than SSM when the influence of other prognostic factors is considered. The comparatively deep median thickness and poorer univariable survival likely result from difficulties in early detection contributed to by a higher proportion of hypopigmented melanoma. Pure desmoplastic melanoma also has a distinctive distribution on the head and neck where all subtypes tend to be thicker. The higher Breslow thickness of pDM of the head and neck explained the poorer survival observed for patients compared to pDM from the rest of the body. Other important and distinct clinicopathological features of pDM compared to SSM included higher rates of ulceration, hypomelanosis and mitotic rate. An association of pDM with markers of chronic solar damage support an alternate pathway of causation.

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289 **Abbreviations:**

290 pDM- pure desmoplastic melanoma

291 mDM- mixed desmoplastic melanoma

292 MSS- melanoma specific survival

293 SSM- superficial spreading melanoma

294 HR- Hazard ratio

295 CI- Confidence interval

296 AJCC- American joint committee on cancer

297 VMS- Victorian Melanoma Service

298 NMSC- non-melanoma skin cancer

299 HPF-high powered field

300 VCR- Victorian Cancer Registry

301 MICE- Multiple imputation using chained equations

302

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Conflict of interest:

None to declare

References

1. Conley J, Lattes R, Orr W. Desmoplastic malignant melanoma (a rare variant of spindle cell melanoma). *Cancer*. 1971;28(4):914-36. .
2. Hawkins WG, Busam KJ, Ben-Porat L, Panageas KS, Coit DG, Gyorki DE, et al. Desmoplastic Melanoma: A Pathologically and Clinically Distinct Form of Cutaneous Melanoma. *Ann Surg Oncol*. 2005;12(3):207-13.
3. Carlson JA, Dickersin GR, Sober AJ, Barnhill RL. Desmoplastic neurotropic melanoma: a clinicopathologic analysis of 28 cases. *Cancer*. 1995;75(2):478-94.
4. de Almeida LS, Requena L, Rutten A, Kutzner H, Garbe C, Pestana D, et al. Desmoplastic Malignant Melanoma: A Clinicopathologic Analysis of 113 Cases. *Am J Dermatopathol*. 2008;30(3):207-15.
5. 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(11):1518-25.
6. Murali R, Shaw H, Lai K, McCarthy S, Quinn M, Stretch J, et al. Prognostic factors in cutaneous desmoplastic melanoma: a study of 252 patients. *Cancer*. 2010;116(17):4130-8.
7. Scolyer RA, Thompson JF. Desmoplastic melanoma: a heterogeneous entity in which subclassification as "pure" or "mixed" may have important prognostic significance. *Ann Surg Oncol*. 2005;12(3):197-9.

- 333 8. Dunne JA, Wormald JCR, Steele J, Woods E, Odili J, Powell BWEM. Is sentinel lymph
334 node biopsy warranted for desmoplastic melanoma? A systematic review. *J Plast Reconstr*
335 *Aesthet Surg.* 2017;70(2):274-80.
- 336 9. George E, McClain S, Slingluff C, Polissar N, Patterson J. Subclassification of
337 desmoplastic melanoma: pure and mixed variants have significantly different capacities for
338 lymph node metastasis. *J Cutan Pathol.* 2009;36(4):425-32.
- 339 10. Han D, Zager JS, Yu D, Zhao X, Walls B, Marzban SS, et al. Desmoplastic melanoma: is
340 there a role for sentinel lymph node biopsy? *Ann Surg Oncol.* 2013;20(7):2345-51.
- 341 11. Pawlik TM, Ross MI, Prieto VG, Ballo MT, Johnson MM, Mansfield PF, et al.
342 Assessment of the role of sentinel lymph node biopsy for primary cutaneous desmoplastic
343 melanoma. *Cancer.* 2006;106(4):900-6.
- 344 12. Murali R, Shaw HM, Lai K, McCarthy SW, Quinn MJ, Stretch JR, et al. Prognostic
345 factors in cutaneous desmoplastic melanoma: a study of 252 patients. *Cancer.*
346 2010;116(17):4130-8.
- 347 13. Maurichi A, Miceli R, Camerini T, Contiero P, Patuzzo R, Tragni G, et al. Pure
348 desmoplastic melanoma: a melanoma with distinctive clinical behavior. *Ann Surg.*
349 2010;252(6):1052-7.
- 350 14. Khan F, Strohl A, Allen PD, Doerr TD. Desmoplastic Melanoma of the Head and Neck:
351 Incidence and Survival, 1992-2013. *Otolaryngol Head Neck Surg.* 2017;157(4):648-56.
- 352 15. Livestro DP, Muzikansky A, Kaine EM, Flotte TJ, Sober AJ, Mihm MC, et al. Biology of
353 Desmoplastic Melanoma: A Case-Control Comparison With Other Melanomas. *J Clin Oncol.*
354 2005;23(27):6739-46.
- 355 16. Egbert B, Kempson R, Sagebiel R. Desmoplastic malignant melanoma. A
356 clinicohistopathologic study of 25 cases. *Cancer.* 1988;62(9):2033-41.
- 357 17. Quinn MJ, Crotty KA, Thompson JF, Coates AS, O'Brien CJ, McCarthy WH.
358 Desmoplastic and Desmoplastic Neurotropic Melanoma: Experience with 280 Patients.
359 *Cancer.* 1998;83(6):1128-35.

- 360 18. Skelton H, Smith K, Laskin W, McCarthy W, Gagnier J, Graham J, et al. Desmoplastic
361 malignant melanoma. *J Am Acad Dermatol*. 1995;32(5):717-25.
- 362 19. Reiman H, Goellner J, Woods J, Mixer R. Desmoplastic melanoma of the head and
363 neck. *Cancer*. 1987;60(9):2269-74.
- 364 20. Baer SC, Schultz D, Synnestvedt M, Elder DE. Desmoplasia and neurotropism:
365 prognostic variables in patients with Stage I melanoma. *Cancer*. 1995;76(11):2242-7.
- 366 21. Murali R, Zannino D, Synnott M, McCarthy SW, Thompson JF, Scolyer RA. Clinical and
367 pathological features of metastases of primary cutaneous desmoplastic melanoma.
368 *Histopathology*. 2011;58(6):886-95.
- 369 22. Chen LL, Jaimes N, Barker CA, Busam KJ, Marghoob AA. Desmoplastic melanoma: a
370 review. *J Am Acad Dermatol*. 2013;68(5):825-33.
- 371 23. Feng Z, Wu X, Chen V, Velie E, Zhang Z. Incidence and survival of desmoplastic
372 melanoma in the United States, 1992–2007. *J Cutan Pathol*. 2011;38(8):616-24.
- 373 24. Clark WH, Jr., Elder DE, Van Horn M. The biologic forms of malignant melanoma.
374 *Hum Pathol*. 1986;17(5):443-50.
- 375 25. Smoller BR. Histologic criteria for diagnosing primary cutaneous malignant
376 melanoma. *Mod Pathol*. 2006;19(S2):S34-40.
- 377 26. Gershenwald JE, Scolyer RA, Thompson JF, Hess KR, Sondak VK, Long GV, et al.
378 Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer
379 eighth edition cancer staging manual. *CA Cancer J Clin*. 2017;67(6):472-92.
- 380 27. Lee KJ, Simpson JA. Introduction to multiple imputation for dealing with missing
381 data. *Respirology*. 2014;19(2):162-7.
- 382 28. White IR, Royston P. Imputing missing covariate values for the Cox model. *Stat Med*.
383 2009;28(15):1982-98.
- 384 29. Rubin DB. Multiple imputation for nonresponse in surveys. New York: Wiley & Sons
385 Inc; 1987.

30. Mickey R, Greenland S. The Impact of Confounder Selection Criteria on Effect Estimation. *Am J Epidemiol*. 1989;129(1):125-37.
31. Lasithiotakis K, Leiter U, Meier F, Eigentler T, Metzler G, Moehrle M, et al. Age and gender are significant independent predictors of survival in primary cutaneous melanoma. *Cancer*. 2008;112(8):1795-804.
32. Harrell FE, Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modelling strategies for improved prognostic prediction. *Stat Med*. 1984;3(2):143-52.
33. Peduzzi P, Concato J, Kemper E, Holford T, Feinstein A. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol*. 1996;49(12):1373-9.
34. Vittinghoff E, McCulloch CE. Relaxing the Rule of Ten Events per Variable in Logistic and Cox Regression. *Am J Epidemiol*. 2007;165(6):710–8.
35. Smolle J, Okcu A, Hofmann-Wellenhof R, Pfaffenthaler E, Fink-Puches R, Richtig E, et al. Automated measurement of melanoma cross-sectional area. *Am J Dermatopathol*. 1998;20(2):155-9.
36. Temple C, Huchcroft S, Hurlbut D, Davidson J. Histologic staging in malignant melanoma: cross-sectional area revisited. *J Surg Oncol*. 1998;69(2):83-7.
37. Friedman R, Rigel D, Kopf A, Grin C, Heilman E, Bart R, et al. Volume of malignant melanoma is superior to thickness as a prognostic indicator. Preliminary observation. *Dermatol Clin*. 1991;9(4):643-8.
38. Dabouz F, Barbe C, Lesage C, Le Clainche A, Arnoult G, Hibon E, et al. Clinical and histological features of head and neck melanoma: a population-based study in France. *Br J Dermatol*. 2015;172(3):707-15.
39. Golger A, Young D, Ghazarian D, Neligan P. Epidemiological features and prognostic factors of cutaneous head and neck melanoma: a population-based study. *Arch Otolaryngol Head Neck Surg*. 2007;133(5):442-7.

- 412 40. Wee E, Wolfe R, McLean C, Kelly J, Pan Y. Clinically amelanotic or hypomelanotic
413 melanoma: Anatomic distribution, risk factors, and survival. *J Am Acad Dermatol*.
414 2018;79(4):645-51.
- 415 41. Lens M, Newton-Bishop J, Boon A. Desmoplastic malignant melanoma: a systematic
416 review. *Br J Dermatol*. 2005;152(4):673-8.
- 417 42. Thomas N, Krickler A, Waxweiler W, Dillon P, Busman K, From L, et al. Comparison of
418 clinicopathologic features and survival of histopathologically amelanotic and pigmented
419 melanomas: a population-based study. *JAMA Dermatol*. 2014;150(12):1306-314.
- 420 43. Moreau J, Weissfeld J, Ferris L. Characteristics and survival of patients with invasive
421 amelanotic melanoma in the USA. *Melanoma Res*. 2013;23(5):408-13.
- 422 44. Han D, Han G, Zhao X, Rao NG, Messina JL, Marzban SS, et al. Clinicopathologic
423 Predictors of Survival in Patients with Desmoplastic Melanoma. *PLoS ONE*. 2015(3).
- 424 45. Posther KE, Selim MA, Mosca PJ, Stanley WE, Johnson JL, Tyler DS, et al.
425 Histopathologic Characteristics, Recurrence Patterns, and Survival of 129 Patients With
426 Desmoplastic Melanoma. *Ann Surg Oncol*. 2006;13(5):728-39.
- 427 46. Jaimes N, Chen L, Dusza SW, Carrera C, Puig S, Thomas L, et al. Clinical and
428 dermoscopic characteristics of desmoplastic melanomas. *JAMA Dermatol*. 2013;149(4):413-
429 21.
- 430 47. Shain AH, Garrido M, Botton T, Talevich E, Yeh I, Sanborn JZ, et al. Exome sequencing
431 of desmoplastic melanoma identifies recurrent NFKBIE promoter mutations and diverse
432 activating mutations in the MAPK pathway. *Nat Genet*. 2015;47(10):1194-99.
- 433 48. Whiteman DC, Watt P, Purdie DM, Hughes MC, Hayward NK, Green AC. Melanocytic
434 Nevi, Solar Keratoses, and Divergent Pathways to Cutaneous Melanoma. *J Natl Cancer Inst*.
435 2003;95(11):806-12.
- 436 49. Howard M, Wee E, Wolfe R, McLean C, Kelly J, Pan Y. Anatomical location of primary
437 melanoma: survival differences and sun exposure. *J Am Acad Dermatol [Internet]*. 2019.

Figure legends

Figure 1: Detailed body map of anatomical subsites diagnosed with pure desmoplastic melanoma during follow-up, laterality was not assessed with these areas shaded in blue, Adapted from Howard et al⁴⁹.

Figure 2: Kaplan-Meier estimates of melanoma-specific survival probabilities by melanoma subtype

Figure 3: Kaplan-Meier estimates of melanoma-specific survival probabilities in pure desmoplastic melanoma by tumour location

Table 1: Baseline clinicopathologic characteristics of 119 individuals with invasive pure desmoplastic melanomas and 2272 with superficial spreading melanomas, with P values for difference between these two subtypes.

Clinicopathologic factor	pDM	SSM	P value [#]
Female Sex, n (%)	39 (33%)	1158 (51%)	<0.001
Age, y, median (IQR)	74 (62-85)	61 (50-71)	<0.001
Breslow thickness*, mm, median (IQR)	4.2 (2.5-6.5)	0.8 (0.5-1.4)	<0.001
Ulceration, n (%)	23 (20%)	244 (12%)	0.01
Mitotic rate, per mm ² , n (%)	1 (0-6)	0.5 (0-2)	<0.001
<1	39 (34%)	959 (51%)	
1-4	43 (38%)	691 (37%)	
5-9	16 (14%)	142 (8%)	
10-19	12 (10%)	57 (3%)	
>20	4 (3%)	26 (1%)	
Regression, n (%)	5 (4%)	426 (23%)	<0.001
Lymphovascular invasion, n (%)	6 (5%)	50 (3%)	0.11
Neurotropism, n (%)	59 (51%)	24 (1%)	<0.001
Satellite metastases, n (%)	5 (4%)	16 (1%)	<0.001
Previous melanoma, n (%)			0.05
0	97 (81%)	2017 (89%)	
1	17 (14%)	188 (8%)	
≥2	5 (4%)	67 (3%)	
Previous history NMSC, n (%)			<0.001
0	52 (45%)	1571 (76%)	
1	24 (21%)	242 (12%)	
2-5	23 (20%)	173 (8%)	
6-10	9 (8%)	31 (2%)	

>10	7 (6%)	42 (2%)	
Pre-existing naevus, n (%)		10 (9%)	703 (35%)
Clinically hypomelanotic, n (%)		47 (39%)	110 (5%)
Number of family members with history of melanoma, n (%)			0.17
0	101 (86%)	1783 (79%)	
1	14 (12%)	368 (16%)	
≥2	3 (2%)	117 (5%)	
Tumour invading lymphocytes, n (%)			0.02
Absent	59 (43%)	745 (40%)	
Minimal/mild	29 (36%)	681 (37%)	
Moderate	22 (15%)	310 (17%)	
Severe	3 (6%)	121 (6%)	
Previous severe sunburns, n (%)			0.64
0	36 (32%)	788 (35%)	
1-5	48 (43%)	992 (45%)	
6-10	11 (10%)	215 (10%)	
10-20	9 (8%)	135 (6%)	
>20	7 (6%)	87 (4%)	
Total naevus count, n (%)			<0.001
<50	64 (63%)	856 (42%)	
50-100	20 (20%)	487 (24%)	
100-200	10 (10%)	466 (23%)	
>200	8 (8%)	250 (12%)	
Clinical dysplastic naevus count, n (%)			<0.01
0	84 (84%)	1354 (67%)	
1	6 (6%)	175 (9%)	
2	4 (4%)	111 (5%)	
3	1 (1%)	80 (4%)	
≥4	6 (5%)	299 (15%)	

Fitzpatrick skin type, n (%)			0.42
1	40 (35%)	618 (28%)	
2	39 (34%)	912 (41%)	
3	30 (27%)	554 (25%)	
4	4 (3%)	125 (6%)	
Previous solar keratosis, n (%)	72 (60%)	667 (29%)	<0.001
Eye colour, n (%)[#]			0.02
Blue	74 (66%)	1172 (53%)	
Green	10 (9%)	267 (12%)	
Light brown/hazel	22 (20%)	441 (20%)	
Brown	6 (5%)	310 (14%)	
Hair colour, n (%)			0.95
Blonde	25 (22%)	509 (23%)	
Red	12 (10%)	256 (12%)	
Light brown	33 (29%)	640 (29%)	
Brown	38 (33%)	699 (32%)	
Black	6 (5%)	87 (4%)	
Ephelides count, n (%)			0.30
Few	39 (41%)	934 (49%)	
Moderate	31 (33%)	606 (31%)	
Many	24 (25%)	383 (20%)	
Lentigo count, n (%)			0.43
Few	37 (41%)	842 (44%)	
Moderate	30 (33%)	678 (35%)	
Many	24 (26%)	397 (21%)	

IQR= interquartile range,

P-value for difference between pDM and SSM from Wilcoxon Rank-sum test for continuous variables, chi-squared test for categorical variables and nonparametric equality of medians test for median values.

Number of missing values, n (% of observed) for pDM: ulceration status 2 (2%), mitotic rate (4%), previous history of NMSC 4 (4%), previous severe sunburns 8 (7%), family history of melanoma 1 (1%), Fitzpatrick skin type 6 (5%), eye colour 7 (6%), hair colour 5 (4%), total naevus count 17 (17%), dysplastic naevus count 19 (19%), ephelides 25 (21%), lentigo 28 (24%),

satellite metastasis 4 (4%), lymphovascular invasion 3 (3%), tumour invading lymphocytes 6 (5%), regression 4 (4%), pre-existing naevus 3 (3%), neurotropism 4 (4%),.

Number of missing values, n (% of observed) imputed for SSM: ulceration status 196 (9.4%), mitotic rate 397 (21.2%), previous history of NMSC 213 (10.3%), previous severe sunburns 55 (2.5%), family history of melanoma 4 (0.2%), Fitzpatrick skin type 49 (2.2%), eye colour 82 (3.7%), hair colour 81 (3.7%), total naevus count 213 (10.3%), dysplastic naevus count 253 (12.5%), ephelides 349 (18.1%), satellite metastasis 389 (20.7%), lymphovascular invasion 381 (20.1%), tumour invading lymphocytes 415 (22.3%), regression 388 (20.6%), pre-existing naevus 238 (11.7%), neurotropism 384 (20.3%)

Table 2: Univariable and multivariable melanoma-specific survival associations of 119 individuals with invasive pure desmoplastic melanomas

	Univariable		Multivariable	
Clinicopathologic factor	HR (95% CI)	P value [^]	HR (95% CI)	P value ⁺
Female sex	0.53 (0.17-1.62)	0.26	0.58 (0.16-2.16)	0.42
Age >65 years	1.28 (0.45-3.62)	0.65	2.20 (0.64-7.58)	0.21
Breslow thickness*	2.93 (1.22-7.06)	0.02	3.66 (1.13-11.81)	0.03
Ulceration [@]	7.60 (2.85-20.23)	<0.001	7.81 (2.33-26.20)	0.001
Mitotic rate [@] , mm ²		0.04		0.02
1-4	2.10 (0.61-7.22)		1.47 (0.40-5.44)	
5-9	1.12 (0.12-10.19)		0.62 (0.06-6.08)	
10-19	9.15 (2.12-39.50)		3.32 (0.52-21.23)	
>20	3.95 (0.42-37.40)		0.69 (0.04-10.69)	

Lymphovascular invasion[@]	6.35 (1.40-29.04)	0.02	5.78 (0.55-60.92)	0.14
Neurotropism[@]	1.04 (0.40-2.70)	0.94		
Satellite metastases[@]	9.03 (2.24-36.49)	<0.01	16.80 (1.20-234.43)	0.04
Previous melanoma[@]	1.59 (0.45-5.58)	0.47		
Pre-existing naevus[@]	2.02 (0.58-7.13)	0.27		
Clinically hypomelanotic[@]	0.49 (0.17-1.40)	0.18		
Tumour invading lymphocytes[@]		0.28		
Mild/focal	2.55 (0.74-8.82)			
Moderate	2.32 (0.63-8.52)			

*logarithmic transformed continuous variable, HR is per log(mm)

HR: Hazard ratio derived from univariable/multivariable Cox proportional hazards regression models, CI: confidence interval

^ P-value obtained from univariable Cox proportional hazards model for the row variable and association pure desmoplastic melanoma specific survival

† P-value obtained from multivariable Cox proportional hazards model for the row variable and association pure desmoplastic melanoma specific survival, adjusted for clinicopathologic factors with a univariable P-value <0.1

@ P-values are from post processing of analysis applied to ten multiple imputed datasets

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Table 3: Selected outcomes and management of 119 individuals with invasive pure desmoplastic melanoma

Pure desmoplastic melanoma outcomes			
	Pure desmoplastic melanoma specific deaths per AJCC thickness category	Total pDM cases in thickness category	Percentage of total pDM deaths in selected thickness category
T1 (≤1mm thickness)	1	5	6%
T2 (1.01-2mm thickness)	1	16	6%
T3 (2.01-4mm thickness)	2	36	12%
T4 (>4mm thickness)	13	62	76%
Local recurrence			
pDM cases with local recurrence within follow-up, n (% of total pDM)	15 (13%)		
Mean time to recurrence, months	18 months		
pDM specific deaths with local recurrence prior to development of metastatic disease, n (% cases with metastatic disease during followup)	3 (18%)		
Excision margins in cases that had local recurrence, n (% of cases with local recurrence)	0-0.5cm	2 (13%)	
	0.51-1cm	3 (20%)	
	>1cm	10 (67%)	
Local recurrence cases	7 (47%)		

that received radiotherapy, n (% of cases with local recurrence)			
Local recurrence cases with neurotropism on primary melanoma sample, n (% of cases with local recurrence)	7 (47%)		
Pure desmoplastic melanoma management			
Radiotherapy, n (% of total pDM cases)			
Adjuvant	23 (19%)		
Palliative intent	8 (7%)		
Final pathological excision margins (% of total pDM cases)			
0-0.5cm	5 (4%)		
0.51-1cm	20 (17%)		
1.1-2cm	58 (50%)		
>2cm	34 (29%)		
Melanoma specific survival according to location: univariable results			
Region	Univariable, HR, 95% CI	P-value	Melanoma specific deaths / total pDM cases
pDM of the head and neck	5.19, 1.18-22.78	0.03	14/78
pDM of the body	Reference		3/41
Melanoma specific survival according to location: adjusted for Breslow thickness			
Region	Multivariable, HR, 95% CI	P-value	
pDM of head and	4.27, 0.96-18.90	0.06	

neck		
pDM of the body	Reference	

HR: Hazard ratio derived from univariable/multivariable Cox proportional hazards regression models,
CI: confidence interval, pDM: pure desmoplastic melanoma, AJCC: American Joint Committee on
Cancer

Table 4: Univariable and multivariable melanoma-specific survival associations for pure desmoplastic melanoma compared to superficial spreading melanoma

Subtype	Univariable		Multivariable†		
	HR (95% CI)	P-value	HR (95% CI)	P-value	Melanoma specific deaths / total melanoma
Superficial spreading	Reference		Reference		187/2272
Pure desmoplastic	2.56 (1.56-4.22)	<0.001	0.49 (0.28-0.87)	0.01	17/119

CI: confidence interval, HR: Hazard ratio

†Multivariable melanoma-specific survival for subtype, HRs estimated from a Cox proportional hazards regression model adjusted for: age>65 years, sex, log-transformed Breslow thickness, mitotic rate, ulceration, microsatellites, lymphovascular invasion using multiple imputation, i.e. results are from application of Rubin's rules to analyses in 10 imputed datasets

Legend	
Colour	Number of cases
White	0
Green	1-4
Pink	5-9
Orange	10-19
Red	>20

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