2018

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HHS Public Access

Author manuscript

J Am Acad Dermatol. Author manuscript; available in PMC 2019 February 01.

Published in final edited form as:

J Am Acad Dermatol. 2018 February ; 78(2): 419–421. doi:10.1016/j.jaad.2017.07.059.

Predicting the incidence and timing of central nervous system disease in metastatic melanoma: Implications for surveillance and preventative therapy

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Effective systemic therapies have improved survival in advanced melanoma, resulting in a higher lifetime risk of brain metastases.[1] Male sex, truncal or head / neck location, and thick or ulcerated primary lesions are well-accepted risk factors.[2] Histologic subtype, however, has not been extensively studied. We report one of the largest series of MBM to better define clinicopathologic risk factors, guide management and surveillance decisions.

An institutional melanoma database review identified 3,756 patients diagnosed with metastatic melanoma between 1971 and 2013. Patients were divided into two groups based on whether or not they developed MBM. Primary endpoints were development of MBM and two-year melanoma brain metastases-free survival (MBMFS). The secondary endpoint was overall survival (OS).

Of 2,132 patients included in the final analysis, 397 (18.6%) of these patients developed brain metastases. Univariable analysis identified sex, primary location, ulceration, and histologic subtype as predictors of 2-year MBMFS in patients who developed stage IV disease (Figure 1). Multivariable analyses demonstrated that axial location ($p<0.01$), presence of ulceration ($p=0.04$), and desmoplastic ($p=0.02$) and nodular ($p=0.03$) histological variants were associated with a higher risk of developing MBM. The presence of ulceration ($p<0.01$), axial primary location ($p<0.01$), desmoplastic histologic subtype ($p=0.03$), and era of stage IV diagnosis (1990–1999 vs. 1970–1979 [$p<0.01$] and 2000–2009 vs. 1970–1979 [$p=0.01$]) were independent predictors of 2-year MBMFS (Table 1). Ipilimumab had no significant effect on the incidence or timing of MBM. An inferior 2-year

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Presented at the American Radium Society annual meeting, Kauai, HI, May 2–6, 2015.

Conflicts of Interest: The content of this report is solely the responsibility of the authors and does not necessarily represent the official view of the National Cancer Institute or the National Institutes of Health.

OS was seen with male sex (HR=1.15, p=0.02), older age (HR=1.01, p=0.01), axial location (HR=1.14, p=0.03), and ulceration (HR=1.19, p<0.01). Patients treated with ipilimumab (HR=0.16, p<0.01) demonstrated improved 2-year OS. Of the patients diagnosed with desmoplastic melanoma (n=25), 9 (36%) were found to have MBM, all within the first year after the diagnosis of other systemic disease. The primary lesion was greater than 4.0 mm deep in 7/9 (78%) and located in the head and neck region in 6/9 (67%).

Proposed mechanisms include travel along the external surface of vessels (angiotropism) and nerves (neurotropism). In a case series of 20 patients with MBM, 14 showed angiotropism in the primary lesion. The tumors with angiotropism had an average time to MBM of 33 months, compared to 57 months in the melanomas without angiotropism, although not statistically significant.[3] The largest series of desmoplastic melanoma described four patients with neurotropism involving named nerves of the head and neck.[4] Survival after diagnosis of stage IV disease has been shown to be significantly lower in patients with isolated MBM when compared to multiple metastatic sites.[5] Our results differed, perhaps as a result of newer treatment options (i.e. stereotactic radiosurgery). Although many of these patients are traditionally excluded from clinical trials, our findings suggest they should be given equal consideration.

This study identifies desmoplastic subtype as a strong predictor of MBM development and decreased 2-year MBMFS. In patients with desmoplastic subtype, particularly thick lesions involving the head and neck, serial screening for CNS metastases with brain magnetic-resonance imaging should be considered during the first year after Stage IV diagnosis.

Acknowledgments

This study was supported by grant (R01 CA189163) from the National Cancer Institute.

Funding: None

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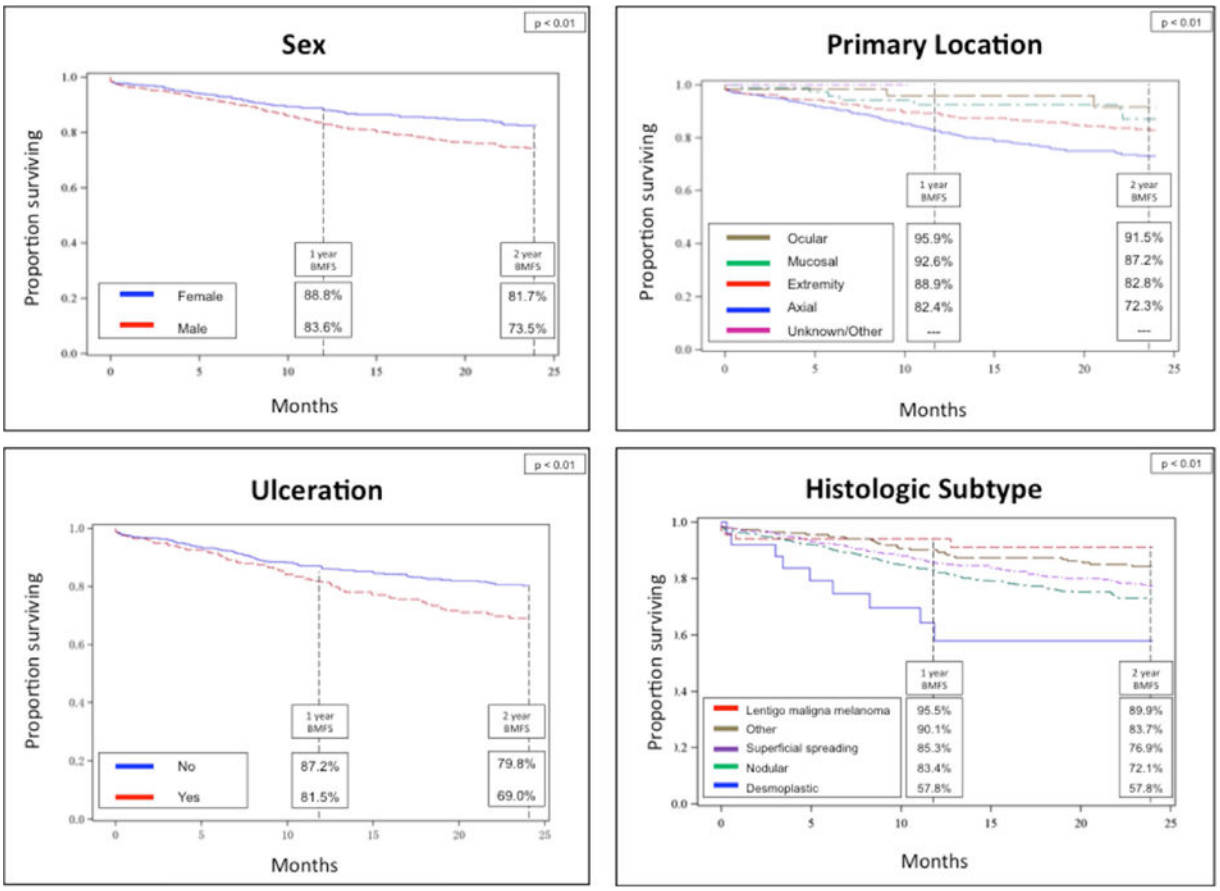

Figure 1.

Univariate predictors of 2-year melanoma brain metastases-free survival of patients with eventual stage IV disease. A: patient sex – female 81.7%, male 73.5% ($p<0.01$); B: primary location – ocular 91.5%, mucosal 87.2%, extremity 82.8%, and axial 72.3% ($p<0.01$); C: ulceration – yes 69.0%, no 79.8% ($p<0.01$); D: histologic subtype – lentigo maligna 89.9%, other 83.7%, superficial spreading 76.9%, nodular 72.1%, and desmoplastic 57.8% ($p<0.01$)

Table 1

Multivariable predictors of developing MBM among patients that develop stage IV disease

Variables	HR	P value
Male sex	1.30	0.04
Histology (ref → superficial spreading)		
Nodular	1.14	NS
Lentigo maligna	0.42	NS
Desmoplastic	2.27	0.02
Other	0.84	NS
Primary site (ref → head and neck)		
Lower extremity	0.68	0.04
Upper extremity	0.59	0.02
Trunk	0.95	NS
Mucosal	0.46	NS
Other/Unknown primary	0.97	<0.01
Ulceration (ref → No)		
Yes	1.49	<0.01
Unknown	1.14	0.33