Bioinformatics Analysis Of Histopathological Variables In Melanoma Patients To Determine Prognostic Significance

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Introduction

Currently, melanoma has a high mortality rate in the UK with 2,400 deaths every year [1]. Evidence-based melanoma staging systems are key to improving survival rates, however there is conflicting data surrounding the prognostic significance of some histopathological variables. Therefore, analysis of these variables is key to improve staging systems.

The aim of this research is to identify significant melanoma prognostic markers using statistical methods. It is hypothesised that univariate and multivariate analysis of pathological variables will help determine clinically significant prognostic markers for melanoma.

Methods

A retrospective cohort study was conducted on a melanoma patients (n=966) who presented to Queen's Medical Centre (QMC), Nottingham. Histopathological, clinical data and long term clinical follow up data was collected from the hospital electronic clinical notes system (Notis).

The Kaplan-Meier method and log-rank test was used to assess survival and determine key prognostic variables. Variables identified as significant through univariate analysis were incorporated into multivariate analysis via a Cox proportional hazard regression model.

Results

Univariate Analysis

Kaplan-Meier curve and log rank tests using overall survival data, allowed determination of significant univariate prognostic indicators. There were a number of significant prognostic markers identified. Kaplan-Meier curves for mitotic rate and local recurrence, is presented (figure 1 and 2).

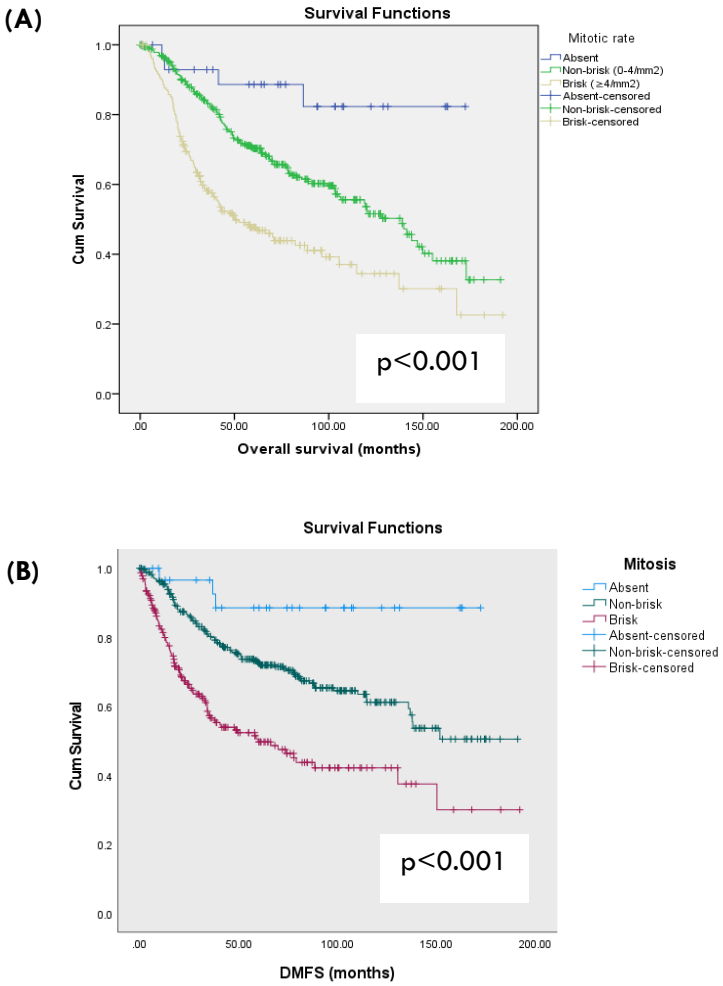

Figure 1. Kaplan-Meier curves for mitotic rate categorise into absent, brisk (0-4/mm²) and non brisk (≥4/mm²) (A) Overall survival Kaplan-Meier curve (B) Distant metastasis free survival Kaplan-Meier curve.

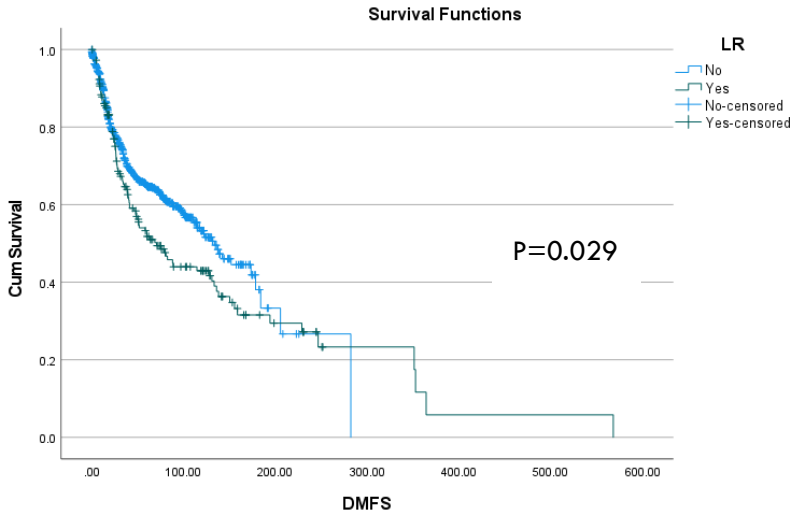

Figure 2. Kaplan-Meier curve for local recurrence, a significant variable for distant metastasis free survival (DMFS).

Multivariate analysis

Key variables that were significant as a prognostic marker for overall survival from multivariate analysis included age (p=<0.001), mitotic rate (0=0.011), Breslow thickness (p<0.001), vascular invasion (p<0.001) and distant metastasis p<0.001). For distant metastasis free survival, key variables that were significant from multivariate analysis included age (p=0.022), local recurrence (p=0.004), mitotic rate (p=0.002) and Breslow thickness (p=0.002).

Discussion

The most important findings from this research project, was that mitotic rate was a significant variable through from univariate and multivariate methods as a prognostic marker for both Overall Survival and Distant metastasis free survival. Furthermore, although ulceration and microsatellites are variables used in the AJCC8 staging system, these were not significant variables in multivariate analysis for both overall survival and distant metastasis free survival. Several other studies have also shown the prognostic significance of mitotic rate in predicting melanoma specific survival (MSS) [2-5]. A number of studies have also found that mitotic rate is a more reliable prognostic indicator of melanoma survival, with a higher prognostic impact than ulceration [3, 6, 7, 8]. Some studies have suggested that when mitotic rate is included in multivariate analysis, that ulceration is no longer an independent prognostic factor [3, 6, 8, 9, 10]. Mitotic rate was included in the AJCC 7th Edition staging system, however was consequently excluded due to difficulty determining optimum mitotic rate categories. In addition, since local recurrence is shown from this research to be a potential prognostic marker of distant metastasis free survival – this prognostic marker should be explored further.

Conclusion

This research was successful in identifying important prognostic markers for melanoma. It is proposed from this research that mitotic rate should be studied further for incorporation for use in future staging systems to improve prediction of melanoma survival rates in future. Future directions also involve developing a prognostic model using these variables via algorithms that will help improve survival rates for melanoma.

References

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