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Significance of Breslow Density as a New Prognostic Feature in Cutaneous Melanoma

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Abstract

Breslow density is a novel biomarker for the assessment of tumor load in cutaneous melanoma cases. Breslow density is measured in the deepest invasive area that Breslow thickness was measured in the formalin-fixed paraffin-embedded sections. The determination of Breslow density is a simple, low-cost, and reproducible method. Interobserver compliance and accuracy rates are very high. Studies in the literature have reported that high Breslow density is associated with poor prognosis and is a predictive biomarker of short survival. Considering the prognostic and predictive value of Breslow density and the strong interobserver agreement, documentation of Breslow density in the pathology report would contribute to the prediction of the prognosis.

Keywords Breslow density; Biomarker; Melanoma; Prognosis

Abbreviations MM: Malignant Melanoma; BD: Breslow Density; BT: Breslow Thickness; OS: Overall Survival; MSS: Melanoma-Specific Survival; MFS: Metastasis-Free Survival; HR: Hazard Ratio; ICC: Intra-Class Correlation Coefficient; CSD: Cumulative Sun Damage

Introduction

Malignant Melanoma (MM) is one of the malignancies that present a rapidly increasing global incidence due to approximately 160,000 new cases every year and high mortality rates [1]. There are various newly developed molecular tests to predict the prognosis of melanoma, and the role of these molecular tests in the selection of patients for targeted therapy is undeniable, but the use of molecular tests is limited due to their high cost. Therefore, the invention of novel biomarkers is still needed. An accurate estimate of the prognosis is very important for the selection of the most appropriate treatment option. Histology still maintains its primary priority in prognostic evaluation. Tumor thickness defined by Breslow [2] and termed in the literature as Breslow Thickness (BT) is one of the main prognostic determinants. BT and ulceration constitute the basis of the T category in the TNM staging system of the American Joint Committee on Cancer [3]. Since the years of 1970s when Breslow demonstrated the prognostic importance of tumor thickness, it has been suggested that tumor volume may have a higher prognostic value than BT and it was been aimed to design a model for tumor volume assessment in melanoma [4,5]. The essential purpose for the calculation of tumor volume is to find out the total tumor load. However, most methods could not have been introduced to routine pathology practice because of their high costs and uneasy application. Breslow Density (BD) has been defined by Rashed as a novel biomarker for the assessment of tumor load in their retrospective study involving 100 cutaneous melanoma cases [6].

The Measurement Method of Breslow Density and Targeted Burden Score (TBS)

BD is measured in the deepest invasive area that BT was measured in the formalin-fixed paraffin-embedded sections. It is required to determine the location where the deepest melanoma cell, in another saying, BT is measured. The vertical axis of the virtual window created for the measurement is bounded by the epidermal basement membrane and the deepest melanoma cell in the upper and lower sections of the examination frame, respectively. The horizontal axis of the window is X10 magnification objective field (approximately 2 mm) of the microscope. At low magnification power, the predicted virtual window is horizontally shifted to the area with the highest density of cutaneous melanoma cells containing the deepest melanoma cell. The rate of melanoma cells invading the cutaneous stroma in the created windows represents BD. The structures such as hair follicles and sebaceous glands are not included in the cutaneous stroma. BD is recorded as to the nearest 5%, however, with sensitivity to the nearest 1% for the scores under 5% and over 95% [6]. The evaluation of BD can be performed adequately using only Haematoxylin-Eosin stained sections while melanoma-specific immunohistochemical stains can be utilized only in the conditions where inflammation is very intense and melanoma cells cannot be distinguished. TBS is the combination of BD and BT and is formulated as BT × BD/100.

Interobserver Compliance of Breslow Density

The measurement of BD is an easily understandable and calculable method without the need for complicated formulas; it can be evaluated in a short additional time and requires no additional cost [6-9]. Interobserver compliance is very high [6-8]. Rashed and Secinti have detected precise compliance between the two pathologists in their studies on 20 and 19 cases, respectively (Intra-class correlation coefficient (ICC):0.96 and 0.99, respectively) [6,8]. In the study of Saldanha in 24 cases, the interobserver compliance of 3 pathologists was shown to be perfect compliance (ICC:0.93) [7]. In addition, a fourth pathologist not included in the study measured BD in the same

24 cases using written instructions and was blinded to previous scores. The BD scores of the fourth pathologist were in excellent compliance with the mean score of the 3 pathologists (ICC:0.93). The fact that raters can only score with written instructions indicates that BD scoring can be generalized.

The Accuracy of Breslow Density Measurement

BD measurement is a semi-quantitative assessment. The disadvantage of the semi quantitative assessments is their subjectivity involving interobserver compliance and accuracy rate. Saldanha compared the BD scores with a computer-assisted image analysis program and a precise accuracy was determined (ICC:0.84). However, this accuracy rate could be confirmed in a low number of cases while it was not assessed in the other studies [6,8,9]. The confirmation of measurement accuracy with a further number of studies will increase its reliability. The evaluation of BD measurement using digital image analysis systems will make it a more quantitative measurement and elevate its accuracy rate. However, since digital pathology is not widely used in all laboratories, recommending performing BD measurement using image analysis systems under today's conditions may constitute an obstacle to its widespread use.

The Relationship of Breslow Density With Prognostic Parameters

The median value of BD ranges between 60%-80% in cutaneous melanomas [6-8]. No consensus could have been achieved on the relationship of BD with age and gender; Saldanha and Secinti have reported in their studies that the patients with high BD had more advanced ages whereas no relationship has been found between BD and age in the study of Figuera [7-9]. Concerning gender, Saldanha determined no relationship with BD whereas it has been reported in the other studies that females had lower BD rates than males. This result suggests that hormonal effects may be effective on BD in females. It has been reported that similar BD scores were detected in different tumor localizations [7-9].

All the studies on BD reported in the literature have manifested that BD was correlated with BT [6-9]. It has been shown that melanoma cases with high BD rates had higher frequencies of ulcerations and microsatellites, higher mitotic count and advanced AJCC stages [7,9]. It has been noted in the study of Saldanha that 85% of the melanomas with BD<25% were Stage 1A whereas only 4.4% of the melanomas with BD>80% were Stage 1A. The relationship between BD and pT category could not be demonstrated in the study of Secinti however, this result was attributed to the limited number of the cases and the fact that all the cases were in the pT3 and pT4 categories [7-9]. Differently from other studies, Secinti evaluated the relationship of BD with neurotropism and LVI in their study. The melanomas with LVI were found to have higher BD (70% vs. 87.5%; p=0.035, respectively), however, the relationship between neurotropism and BD could not be exhibited [8].

The Relationship of Breslow Density with Molecular Biomarkers

MM usually occurs due to various molecular changes caused by UV radiation. According to the latest classification of the World Health Organization, specific genetic drivers leading to melanoma have been accepted and melanocytic lesions were classified according to the Cumulative Sun Damage (Ultraviolet damage/CSD) associated with molecular changes in the tumor. BRAF V600 mutation is the most commonly seen mutation and is usually associated with low CSD and superficial spreading tumors. Lentigo maligna type and desmoplastic melanomas are the high CSD melanomas and these subtype melanomas usually involve NRAS, BRAF non-V600E, or NF1 mutations. Non-CSD melanomas are acral and mucosal melanomas and usually do not present the BRAF, NRAS, or NF1 mutations (triple wild type) [10]. In the literature, no study has been reported yet that addressed the relationship between BD and molecular markers in the melanoma cases except the study of Figuera-Silva. Figuera-Silva has detected V600E BRAF mutation in 28 (26.4%) melanomas whereas no mutation was found in 78 (73.6%) melanomas (wild-type). It has been reported that mean BD was higher (58.6% vs. 40.5%; p=0.032) in the melanomas detected with BRAF mutation [9]. This result may help answer the question that why melanomas with BRAF mutation have worse prognoses.

Survival Predictive Value of Breslow Density

BD is correlated with but independent parameter from BT. BT is a unidimensional quantitative measurement whereas BD is a two-dimensional semi-quantitative measurement. Although, BD has been noted to be more determinant in the prediction of melanoma-specific survival, however, it is not solely likely to take the place of BT. The tumor load of a tumor with 65% BD and BT<1 mm is expected to be significantly different compared with a tumor with 65% BD and BT>4 mm. Therefore, BD and BT are more valuable in measuring total tumor load when evaluated together than evaluated solely.

Saldanha have shown in their study that BD is a significant predictive in the multivariate analysis for Overall Survival (OS), Melanoma-Specific Survival (MSS), and Metastasis-Free Survival (MFS) and noted that it explained MSS better than BT, however, BT and BD exhibited the highest explanatory ability [7]. In the study of Secinti BD was found to be a significant predictor by the multivariate analysis for Disease-Free Survival (DFS) (HR:1.100 (95% Cl: 1.002-1.207), p=0. 046) [8].

Saldanha have shown that the cut-off value for BD was 65% in 907 melanoma cases with a mean BT value of 0.9 mm (HR:2.03 (95% Cl: 1.04-3.94), p=0.037) and confirmed that the result in 359 melanoma cases with different mean values of BT. Accordingly, they have recommended accepting melanomas with BD>65% as high-risk melanoma [7]. Also, Figuera-Silva have divided melanoma cases into two groups BD>65% and BD<65%, and reported that 5–year survival rate of the patient group with BD>65% was worse than the patient group with BD<65% (OS:70.3 vs. 93.4; DFS:59.9 vs. 98.3, MSS:81.7 vs. 98.3; MFS 74.1 vs. 98.3, respectively) [9].

Conclusion

In a conclusion, the determination of Breslow density is worthy since it is a simple, low-cost, and reproducible method. Since BD is a semi-quantitative and subjective measurement, it cannot represent the invasive tumor load directly BD. However, the detection of very high inter-observer compliance shows that subjectivity is not an important issue regarding the accuracy of the measurement. The measurement of BD will be a more quantitative and simpler assessment with a proliferation of digital pathology. Although all these studies have suggested that BD can be involved in the TNM staging system together with BT, a further number of studies are needed for the

inclusion of these measurements in the staging system. Considering the prognostic and predictive value of BD and the strong interobserver agreement, documentation of BD in the pathology report would contribute to the prediction of the prognosis.

Declarations

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

IES designed the article, read and commented on the references, wrote the article. DG searched the references. All authors read and approved the final article.

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