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Automatic measurement of melanoma depth of invasion in skin histopathological images

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ABSTRACT

Measurement of melanoma depth of invasion (DoI) in skin tissues is of great significance in grading the severity of skin disease and planning patient's treatment. However, accurate and automatic measurement of melanocytic tumor depth is a challenging problem mainly due to the difficulty of skin granular identification and melanoma detection. In this paper, we propose a technique for measuring melanoma DoI in microscopic images digitized from MART1 (i.e., meleanoma-associated antigen recognized by T cells) stained skin histopathological sections. The technique consists of four modules. First, skin melanoma areas are detected by combining color features with the Mahalanobis distance measure. Next, skin epidermis is segmented by a multi-thresholding method. The skin granular layer is then identified based on Bayesian classification of segmented skin epidermis pixels. Finally, the melanoma DoI is computed using a multi-resolution approach with Hausdorff distance measurement. Experimental results show that the proposed technique provides a superior performance in measuring the melanoma DoI than two closely related techniques.

1. Introduction

Skin cancer is a public health problem around the world (Maglogiannis and Doukas, 2009), and melanoma is the most aggressive type of skin cancer, which causes a majority of skin cancer deaths. The early identification of melanoma can greatly reduce the mortality from this cancer, as the melanoma in early stages can often be cured with a simple excision. In order to determine the stage of melanoma, pathologists generally examine the biopsy slide to measure the tumor depth of invasion (e.g., Breslow depth). The deeper the tumor DoI, the greater is the possibility of metastases, and the worse is the prognosis for the patient. A study (Roberts et al., 2002) has indicated that the 5-year survival rate decreases continuously with the increase of tumor depth. Traditionally, pathologists measure the tumor DoI by observing the histological slides under the microscope. However, the manual measurement is subject to intra- and inter- observer variability, and also is labor-intensive due to the large volume of data to be analyzed. Therefore, computer-aided tools which can provide reliable and reproducible results for measurement of melanoma DoI are desirable.

The digitized skin histological images used in this work have been obtained using the MART1 (Melanoma-Associated Antigen Recognized by T cells) stain. Note that MART1 antibody is a type of immunohistochemical stain specific and sensitive to the melanoma, which has been shown to be a superior immunohistochemical marker for the diagnosis of malignant melanoma than HMB-45 and S100 (Fetsch et al., 1999). Fig. 1 shows a typical skin image in our database, which mainly includes image background, skin epidermis and dermis regions. As shown in Fig. 1, the epidermis can be divided into three layers: cornified layer (L1), granular layer (L2) and malpighian layer (L3). The dermis is located below the dermis-epidermis (DE) junction (indicated by the cyan curve). In the skin dermis, the regions with dark brown colors represent MART1-verified skin melanoma areas. In clinical setting, the melanoma DoI is measured as the maximum distance between the malignant cells and the top of skin granular layer (Noroozi and Zakerolhosseini, 2015). In Fig. 1, the manually identified skin granular layer is indicated by the red curve and the melanoma invasion depth is measured as 0.46 mm. Note that since skin granular layer is a middle (thin) layer of skin epidermis and looks similar to other skin epidermis layers, the accurate detection of skin granular layer is critical in achieving accurate melanoma DoI measurement.

Several works have been reported on histopathological image analysis of skin cancers in the past decade. Smolle (2000) proposed a tissue counter analysis technique that recognizes skin structures

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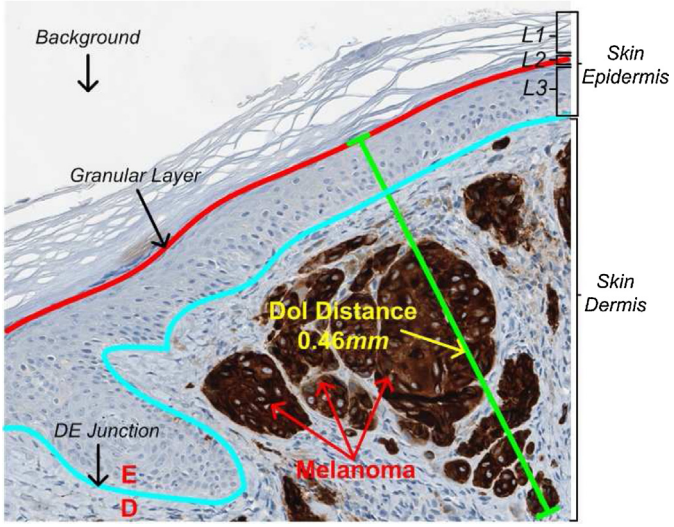

Fig. 1. Melanoma DoI measurement in a MART1 stained skin image. L1: Cornified layer, L2: Granular layer, L3: Malpighian (squamous and basal) layer, E: Epidermis, D: Dermis. Note that the measured DoI distance (green line segment) is 0.46 mm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

like epidermis and dermis by using color features and Haralick texture features of each tissue element. Wiltgen et al. (2003) further applied the tissue counter analysis technique on skin tissue classification, which classifies skin histological images as benign nevi or malignant melanoma using features from histogram and co-occurrence matrix. Miedema et al. (2012) reported an image and statistical analysis system for melanocytic histology classification, which distinguishes melanoma from nevus by using cytological and textural features in DE junction areas. Zhang et al. (2013) proposed a technique for automatic annotation of skin histopathological images. This technique first segments skin image into different regions by a normalized graph cut algorithm, and then extracts features by using 2-D wavelet transform and scale-invariant feature transform. The multi-instance learning algorithms are finally applied to annotate the segmented regions based on extracted features. A few works, which aims at assisting automatic skin histopathological image analysis, have been developed by Lu and Mandal (2012), Lu et al. (2012, 2013, 2013). These works include epidermis segmentation (Lu and Mandal, 2012), nuclear segmentation (Lu et al., 2012) and melanocytes detection (Lu et al., 2013, 2013). In Lu and Mandal (2015), an automatic system that combines morphological features and spatial distributions of melanocytes is proposed for skin whole slide image classification. Xu et al. (2014) proposed a technique that segments nuclear clumps in skin histopathological images based on ellipse descriptor analysis and improved voting algorithm. Note that all these techniques are concerned with segmentation of biological components in skin images or skin tissue classification.

Recently, there have been two closely related works in the literature, where the melanocytic tumor DoI in H&E stained skin images is measured. Mokhtari et al. (2014) proposed a technique to measure the melanoma DoI in skin microscopic images. The technique first segments skin epidermis based on morphological closing and thresholding. The melanocytes containing melanin are then detected based on color features by the support vector machine (SVM). Finally, the epidermis orientation is estimated by using Hough transform. The distance between the outermost pixel of epidermis and the farthest melanocyte along a direction perpendicular to epidermis orientation is calculated as the invasion depth. This technique has the advantages of simplicity and efficiency, but it may result in incorrect DoI measurements due to the inclusion of skin cornified layer within segmented epidermis or inaccurate epidermis orientation estimation by Hough transform. Noroozi and Zakerolhosseini (2015) proposed an improved technique that segments the cornified layer from epidermis based on entropy analysis. The cell nuclei in skin dermis are segmented by using color features and active contour model. The segmented melanocytes are distinguished from lymphocytes based on shape analysis. The maximum distance between the detected melanocyte and the outer boundary of skin epidermis is finally measured as the invasion depth. The technique provides a good performance in melanocytes detection. However, since both cornified and granular layers in skin biopsy images have ridged shapes, the entropy analysis tends to segment out these two layers together which makes the automatically measured DoI less than the manually identified depth. Therefore, the DoI measurement may not be very accurate.

In this work, we propose an automated technique for measuring the melanoma DoI in MART1 stained skin microscopic images, which tries to address the limitations of existing techniques and achieves more accurate tumor invasion measurements. The main contributions of this work includes: (1) a Bayesian classification based framework is proposed to identify skin granular layer, (2) a multi-resolution approach with Hausdorff distance measure is proposed to measure melanoma invasion depth. Because of accurate detection of melanoma areas and skin granular layer, the proposed technique provides a superior performance compared to existing techniques for measuring melanoma DoI.

The organization of this paper is as follows. Section 2 describes the database used in this work. Section 3 describes the proposed technique in detail, followed by results and discussion in Section 4. The conclusion is presented in Section 5.

2. Dataset description

In this study, all skin histopathological images are collected from the Cross Cancer Institute, University of Alberta in accordance with the protocol for the examination of specimens with skin melanoma. The histological sections of skin tissues are about 4 μm thick each and are stained with anti-MART1 clone A103, 1:25 dilution using a avidin-biotin procedure with 3,3′-Diaminobenzidine (DAB) as the chromogen. The skin images were captured under 40× magnification on Aperio Scanscope CS scanning system (0.25 μm/pixel) with default calibration and illuminance settings (based on Aperio service notes). The dataset used in this work consists of 29 MART1