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Computer-aided evaluation of neuroblastoma on whole-slide histology images: Classifying grade of neuroblastic differentiation

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ABSTRACT

Neuroblastoma (NB) is one of the most frequently occurring cancerous tumors in children. The current grading evaluations for patients with this disease require pathologists to identify certain morphological characteristics with microscopic examinations of tumor tissues. Thanks to the advent of modern digital scanners, it is now feasible to scan cross-section tissue specimens and acquire whole-slide digital images. As a result, computerized analysis of these images can generate key quantifiable parameters and assist pathologists with grading evaluations. In this study, image analysis techniques are applied to histological images of haematoxylin and eosin (H&E) stained slides for identifying image regions associated with different pathological components. Texture features derived from segmented components of tissues are extracted and processed by an automated classifier group trained with sample images with different grades of neuroblastic differentiation in a multi-resolution framework. The trained classification system is tested on 33 whole-slide tumor images. The resulting whole-slide classification accuracy produced by the computerized system is 87.88%. Therefore, the developed system is a promising tool to facilitate grading whole-slide images of NB biopsies with high throughput.

1. Introduction

Peripheral neuroblastic tumors (pNTs) are a group of embryonal tumors of the sympathetic nervous system, and include neuroblastoma (NB), ganglioneuroblastoma, and ganglioneuroma category [1]. Each year, more than 600 children and adolescents are diagnosed with pNTs in the United States, and it comprises about 8–10% of all childhood cancers [1,2]. Of all the cancer categories in pNTs, NB, composed of neoplastic neuroblasts in various maturation grades with no or limited Schwannian stromal development, is the most common tumor that affects children ranging from newly born infants to teenagers.

According to the International Neuroblastoma Pathology Classification System (the Shimada system), NB can be further classified into three categories, namely undifferentiated (UD), poorly differentiated (PD), and differentiating (D) subtype, based on the grade of differentiation [3]. A simplified classification tree diagram of this recommended classification system is shown in Fig. 1. NB, with different grades, usually has unique pathological characteristics and micro-texture features [4]. Representative tumors of the three differentiation grades are shown in Fig. 2. Typical features of these subtypes can be briefly summarized as follows:

(1) Tumors in the UD subtype often present such features as small to medium-sized NB cells, thin cytoplasm, none-to-few neurites, round to elongated nuclei, and the salt and pepper appearance of chromatin with or without prominent nucleoli.
(2) As for PD cases, the typical rosette formations and/or clearly recognizable neurites are observed in tumor tissues.
(3) Tumors in the D subtype contain > 5% of D neuroblasts characterized by nuclear and cytoplasmic enlargement; an eccentrically located nucleus containing a single prominent nucleolus in most cases; and the increased ratio of the diameter of the cell to that of the nucleus (typically > 2).

It is usually the case that the more differentiated tumors are, the less aggressively they behave. As a result, patients with tumors of higher grades of differentiation may have better chances to survive.

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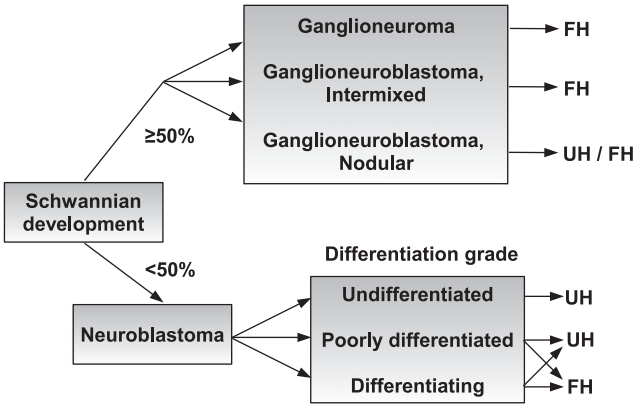

Fig. 1. A simplified tree diagram of the International Neuroblastoma Pathology Classification (the Shimada system), where UH represents "unfavorable histology" and FH stands for "favorable histology".

In clinical practice, treatments for cases with different neuroblastic grades are quite different. For this reason, an accurate grading of a NB sample is crucial to make an appropriate choice of treatment plans.

In current clinical practice, differentiation grading is made with visual examinations of tumors by pathologists under the microscope. There are several weaknesses associated with visual evaluations. First of all, it is often time-consuming and cumbersome for pathologists to review a large number of slides in practice. Secondly, visual evaluations can be subject to unacceptable inter- and even intra-reviewer variations. A recent study reports that there is a 20% discrepancy between central and institutional reviewers [5]. Thirdly, for practical reasons, pathologists often sample slide regions to be examined, making the whole process subject to sampling bias. However, this may lead to erroneous results for tumors exhibiting strong heterogeneity.

To overcome these weaknesses rooted in the visual evaluation process, several computerized methods that automate the image analysis procedures are being developed with promising initial results [6–8]. However, to the best of our knowledge, no research work, so far, has been devoted to developing a computer-aided classification methodology that automates the process of classifying NB whole-slide images in accordance with the grade of differentiation. In this study, we propose an image analysis framework that integrates intensive computer vision and machine learning techniques for the purpose of grading NB images. Within this system, an image hierarchy consisting of multiple image resolution levels is established for each given tumor image. Furthermore, the system dynamically changes the image resolution level at which it proceeds with sequential image analysis steps. At each image resolution level, every image is first segmented into four cytological components using an automated image segmentation method. Discriminating features extracted from segmented image regions are then used to classify each image into one of the three grading classes by a family of classifiers. The resulting decisions are next combined using a two-step classifier combining mechanism. Each classification decision is first evaluated with a confidence measure that indicates the degree of agreements across different classifiers. Based on the evaluation results, the proposed system either stops its analysis process or continues with further investigations by including more image details.

2. Methods

2.1. Image acquisition

In this study, all NB tumor slides are collected from Nationwide Children's Hospital in accordance with an Institutional Review Board (IRB) protocol. According to the protocols commonly used in the Children's Oncology Group, these tissue slides are cut at a thickness of 5 μm and soaked in paraffin at the preparation stage. Each NB slide in the dataset is prepared using a dual staining procedure in which haematoxylin and eosin (H&E) are used to increase the visual contrasts among different cytological components. After being stained with H&E, each thin tissue slide is then fixed on a scanning bed and digitized using ScanScope T2 digitizer (Aperio, San Diego, CA) at 40× magnification, allowing for clear visualization of tumor architectures. The resulting whole-slide images are quite large with their sizes up to 40 GB. Due to the limited hardware storage capability, the resulting digital images are compressed following the JPEG compression standards at approximately a 1:40 compression ratio. After the compression, the typical image sizes can vary from 1 to 4 GB. To make the image analysis more tractable, we partition each histology slide image into multiple non-overlapping image tiles of the size 512 × 512 in pixels, rather than requiring our classification system to work on the whole-slide image. Another benefit of breaking down whole-slide images into tiles is that we can make full use of the distributed computational infrastructure. The parallel implementation details will be discussed in Section 2.3.

2.2. Image dataset

The image dataset used in this study consists of 36 NB cases, covering all three subtypes of neuroblastic grading. All tumor slides are selected in such a way that they are good representatives of different grade subtypes and contain a sufficiently large number of cytological components of interest in the tissue regions. In our study, the training dataset consists of 389 image tiles of the size 512 × 512 in pixels, equally selected at random from three representative cases (one from each subtype). The remaining 33 case images from the dataset are used for the testing purpose. The images in our database are evaluated by an experienced pathologist who visually categorized them into three distinctive differentiation grades. The average storage size of testing slides is about 20 GB before compression, which approximately corresponds to 27,400 image tiles of 512 × 512 pixels in size.

2.3. Software and hardware

The developed classification algorithm and the graphical user interface are designed using MATLAB (The MathWorks, Inc., Natick, MA). All experimental evaluations of our work are carried out on a 64-node cluster with Linux OS owned by the Department of Biomedical Informatics at The Ohio State University. Each node of the cluster is equipped with dual 2.4 GHz Opteron 250 processors, 8 GB of DDR400 RAM with 1 GB dimms and a 250 GB SATA hard disk. The computation infrastructure is designed with a master–client architecture in which a master application and multiple client applications work in a collaborative pattern [9]. For each computation task, one master node is responsible for partitioning the tumor slide images into image tiles with a fixed size and distributing data to clients for further processing in a round-robin fashion. Each client keeps local copies of the assigned image tiles and initiates a local MATLAB application to analyze the cached image tiles with the developed classification algorithm. Once the automated image analysis process ends, the master node is, again, in charge of collecting classification results from client nodes and re-assembles them in order before it produces the grading classification results over the whole-slide images.

2.4. Multi-resolution paradigm

Multi-resolution analysis has shown its power in many computer-aided diagnosis (CAD) systems, as CAD systems usually involve