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Deep Learning Approach for Colorectal Cancer's Automatic Tumor Grading on Whole Slide Images

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Abstract : Tumor grading is an essential reference for colorectal cancer (CRC) staging and survival prognostication. The widely used World Health Organization (WHO) grading system defines histological grade of CRC adenocarcinoma based on the density of glandular formation on whole slide images (WSI). Tumors are classified as well-, moderately-, poorly- or un-differentiated depending on the percentage of the tumor that is gland forming; >95%, 50-95%, 5-50% and <5%, respectively. However, manually grading WSIs is a time-consuming process and can cause observer error due to subjective judgment and unnoticed regions. Furthermore, pathologists' grading is usually coarse while a finer and continuous differentiation grade may help to stratifying CRC patients better. In this study, a deep learning based automatic differentiation grading algorithm was developed and evaluated by survival analysis. Firstly, a gland segmentation model was developed for segmenting gland structures. Gland regions of WSIs were delineated and used for differentiation annotating. Tumor regions were annotated by experienced pathologists into high-, medium-, low-differentiation and normal tissue, which correspond to tumor with clear-, unclear-, no-gland structure and non-tumor, respectively. Then a differentiation prediction model was developed on these human annotations. Finally, all enrolled WSIs were processed by gland segmentation model and differentiation prediction model. The differentiation grade can be calculated by deep learning models' prediction of tumor regions and tumor differentiation status according to WHO's defines. If multiple WSIs were possessed by a patient, the highest differentiation grade was chosen. Additionally, the differentiation grade was normalized into scale between 0 to 1. The Cancer Genome Atlas, project COAD (TCGA-COAD) project was enrolled into this study. For the gland segmentation model, receiver operating characteristic (ROC) reached 0.981 and accuracy reached 0.932 in validation set. For the differentiation prediction model, ROC reached 0.983, 0.963, 0.963, 0.981 and accuracy reached 0.880, 0.923, 0.668, 0.881 for groups of low-, medium-, high-differentiation and normal tissue in validation set. Four hundred and one patients were selected after removing WSIs without gland regions and patients without follow up data. The concordance index reached to 0.609. Optimized cut off point of 51% was found by "Maxstat" method which was almost the same as WHO system's cut off point of 50%. Both WHO system's cut off point and optimized cut off point performed impressively in Kaplan-Meier curves and both p value of logrank test were below 0.005. In this study, gland structure of WSIs and differentiation status of tumor regions were proven to be predictable through deep leaning method. A finer and continuous differentiation grade can also be automatically calculated through above models. The differentiation grade was proven to stratify CAC patients well in survival analysis, whose optimized cut off point was almost the same as WHO tumor grading system. The tool of automatically calculating differentiation grade may show potential in field of therapy decision making and personalized treatment.

Keywords : colorectal cancer, differentiation, survival analysis, tumor grading
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