Comparison of different methods for Ki-67 quantification in breast cancer biopsies

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Abstract

Ki-67 is an important biomarker for the clinical management of patients with breast cancer. However, the evaluation of Ki-67 protein in breast cancer tissues is prone to inter-observer variability. Here, we compare different manual methods and image analysis tools for quantifying Ki-67 and determine whether results from a classifier compare to pathologists' scores. Breast cancer biopsies were immunostained for Ki-67 and digitized. A small test set of <30 cases was used to generate a tumor-stroma segmentation followed by a tumor cell Ki-67 detection classifier using QuPath. A second set of 100 cases was then prospectively included. A region of interest (ROI) was outlined on each image and tumor cell Ki-67 was quantified different ways: 1) two pathologists "eyeballing" the Ki-67 counts, 2) ground truth counts of individual positive tumor cells, 3) analysis using the QuPath classifier, 4) export of ROIs to a second software VMScope and analysis with the classifier and 5) using an algorithm with no user interaction which identifies the ROI and performs tumor cell Ki-67 counts automatically. Intraclass correlation coefficients (ICC) indicating intra-observer agreement between both pathologists' scores (ICC=0.94), pathologists' scores and ground truth (ICC=0.92), ground truth and QuPath classifier (ICC=0.95) as well as ground truth and VMscope classifier (ICC=0.95), were excellent. The fully automated algorithm with hotspot detection showed promising results when compared to the ground truth (ICC=0.7). These results suggest a machine learning classifier for Ki-67 with manual annotation of ROIs leads to reliable results. Areas for improvement of the fully automated one include optimization of the number and size of individual ROIs and removal of scan artefacts.