Abstract of Dissertation submitted by（PHAM HOANG NGOC HOA）

Title: Detection of Lung Cancer Lymph Node Metastases from Whole-Slide Histopathological Images Using a Two-Step Deep Learning Approach

Japanese title: 病理組織学標本におけるディープラーニングを用いた 2 ステップアプローチによる肺癌リンパ節転移の検出

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Introduction:

Lymph node metastasis plays an important role to evaluate stages, treatment and prognosis of lung cancer. The application of deep learning for the detection of lymph node metastases on histological slides has attracted worldwide attention, although false positive predictions remain problematic, particularly in the case of reactive lymphoid follicles. In this study, we hypothesized that lymphoid follicles are the most error-causing factor, therefore, a novel two-step deep learning algorithm including one step to exclude lymphoid follicles and the following step to detect tumor was developed to address the issue of false-positive prediction while maintaining accurate cancer detection.

Materials and Methods:

Total of 349 glass slides of lymph nodes of lung cancer patients were collected from 2014 to 2018 in Nagasaki University Hospital and from 2007 to 2018 in Kameda hospital, were then scanned by 40x objective by Aperio Scanscope CS2 scanner. 233 digital slides were used for training the algorithm, 10 slides for validation, and 106 digital slides were for testing the algorithm acquired by Halo ® AI 2.2 software. The task of the first step was to exclude lymphoid follicles, and the second step was to detect cancer cells. In the first step, two models (one random forest model (LFRFM) and one deep learning CNN algorithm (LFCNN)) were created for competition and the best one was chosen. The task of the second step was to detect cancer cells by a different deep learning CNN model (TDCNN). After all, the two steps would be combined by applying the TDCNN model on top of analyzed layer (after excluding lymphoid follicles) of the best model choosing from the first step. In the end, we compared the results of metastasis detection between two-step and one-step deep learning algorithm.

Results:

In the first step, the accuracy of model 1 (LFRFM) and model 2 (LFCNN) was 51.7% and 94.5%, respectively. The LFCNN model showed a well-fitting shape with the original

lymphoid follicles seen in hematoxylin and eosin images, while the LFRFM showed many false positives in which tumor cells were misclassified as lymphoid follicles. Based on these results, the LFCNN model was chosen to eliminate all lymphoid follicles from the slides prior to the second step.

In the second step, the result showed 36.5% and 5.4% in average of reduction of error in all cases between groups with lymphoid follicles and without lymphoid follicles, respectively. In group that contained prominent reactive lymphoid follicles, an 89% reduction in false-positive area was reached by lymphoid follicle exclusion and remained true detection of tumor areas in metastatic cases.

For the task of metastasis detection, the two-step deep learning algorithm performed well in identifying positive slides, including all macro-metastases, micro-metastases, and ITC with 100% accuracy. In case of negative slides (no metastases), some small false-positive foci that were unrelated to lymphoid follicles remained, causing a 0% specificity which were considered by the algorithm as either ITC (31.6%) or micro-metastasis (68.4%). Applying the solution of removing positive detection area by size, different levels of specificity and sensitivity were obtained. An ROC curve was plotted based on the largest diameter of the deleted positive area, in order to evaluate metastasis classification, which reached an area under the curve (AUC) of 0.922. The two best filters were 0.6 mm, which achieved a sensitivity and specificity of 79.6% and 96.5%, respectively, and 0.7 mm, which achieved a sensitivity and specificity of 75.5% and 98.2%, respectively.

Discussion:

A strong point of this study is the development of a unique novel two-step approach to remove false positive errors in metastatic tumor cell detection. The effective exclusion step (first step) in this study was based on the better LFCNN algorithm chosen between two models – LFCNN and LFRFM. Slides with reactive lymphoid follicles have the potential to have larger false positive areas due to cancer-mimicking germinal center areas, and in our study, up to 89% reduction of error can be reached in this group of slides.

This study describes the successful detection of lymph node metastases, especially the sensitivity for detection of micro-metastases and ITC (100% for both) was significantly higher than those of previous studies. For non-metastasis slides, the low percentage of error reduction was due to the accumulation of multiple small pseudo-positive areas on the whole-slide images. In this study, to deal with the low original specificity, an ROC curve was created using different sizes of false positive foci as the filter and by comparing the sensitivity and specificity of metastasis detection, showing the two best size filters were 0.6 mm and 0.7 mm. These filters can be integrated with the two-step deep learning approach for lymph node metastases detection. Although these filters excluded some foci of true micro-metastases, it is notable that the role of small metastases and ITCs in the prognosis of lung cancer is less certain when compared to macro-metastases.

In summary, the two-step approach can be a useful protocol, which can serve as a tool to assist with the work of the pathologist to detect metastases in lung cancer lymph nodes.

(831 words)