CLASSIFYING BREAST CANCER LYMPH NODE HISTOPATHOLOGY USING CONVOLUTIONAL NEURAL NETWORKS

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ABSTRACT

Breast cancer is the most prevalent cancer among women worldwide, and histopathological evaluation of patients' lymph nodes plays an indispensable role in tumor staging. However, this procedure is tedious and time-consuming. In this study, we processed the whole-slide histopathology images of lymph node biopsy from 200 breast cancer patients in the CAMELYON17 cohort. We built convolutional neural network models to distinguish lymph nodes with and without visible metastasis (AUC > 0.85) and recapitulated expert pathologists' staging with a kappa value approximately 0.7. Our approach does not rely on manual segmentation, and can discover novel clinically-relevant histopathology patterns objectively. The procedure can potentially reduce the workload of pathologists and provide decision support to clinicians encountering ambiguous lymph node histopathology patterns.

Index Terms— Convolutional neural networks, breast cancer, lymph node histopathology, machine learning, CAMELYON17

1. INTRODUCTION

Breast cancer is the most common type of cancer among women, with more than 1.67 million newly diagnosed patients per year worldwide[1, 2]. Histopathology analysis of the lymph nodes by trained pathologists is the gold standard of determining the pathological lymph node stages (pN) of breast cancer patients[3]. Patients with different tumor stages are prescribed different treatments. For instance, clinical guideline suggests that patients with stage I breast cancer (lymph node stage pN0 (stage IA) or pN1mi (stage IB)) are to be treated with breast-conserving surgery plus radiation therapy or mastectomy, while those with stage III disease (lymph node stage pN2 or higher) should be treated by a combination of chemotherapy, surgery, and radiation therapy.[4]. Therefore, accurate histopathology evaluation of the lymph nodes is crucial for formulating optimal treatment plans for breast cancer patients[4].

However, the current process of histopathology assessment is far from perfect. Erroneous diagnosis can lead to suboptimal treatment and loss of quality of life in numerous patients.

Computer vision algorithms, including convolutional neural networks, have shown exceptionally good performance for image classification[5]. Convolutional neural network is a type of artificial neural network inspired by neuron connections of the organisms. In this network, individual neurons were organized in layers: each neuron receives inputs from the neurons in the previous layer, integrates the inputs with mathematical functions, and generates an output to the neurons in the next layer. Convolutional neural networks learned data-specific convolution kernels to transform lower-level features, such as individual pixels, to higher-level features, such as edges or geometric shapes[6]. Researchers have utilized this framework to identify objects in images and videos[7] and have demonstrated its superior performance in many image recognition tasks compared with conventional machine learning methods with pre-defined features. However, it has been difficult to apply convolutional neural network in many medical studies as it generally requires thousands to millions of training cases to achieve satisfactory performance[8, 9].

With the recent availability of digital whole slide histopathology image in large cohorts[10], we can now profile millions of tumor cells from a patient simultaneously and quantify the morphological differences in tumor cells among patients. Leveraging terabytes of microscopic tissue image data, we can fine-tune the parameters in the neural networks to achieve optimal performance. As the diagnosis of breast cancer is established by the morphological features of tumor cells and diagnostic accuracy is positively associated with evaluator's experience, we hypothesize that convolutional neural networks trained on millions of histopathology image patterns can distinguish lymph nodes without tumor invasion, isolated tumor cells, as well as microscopic and macroscopic invasions. An accurate diagnostic system will benefit the patients by suggesting adequate treatment options and providing precise prognoses.

In this study, we built convolutional neural networks to distinguish the histopathology of different lymph node involvement in breast cancer patients. Through this fully

automated computational method, we can identify the morphological differences in an unbiased fashion. Our work can be applied to providing decision support to clinicians encountering ambiguous forms of pathology, increase the accuracy of breast cancer staging, and contribute to precision cancer medicine.

2. MATERIALS AND METHODS

Whole-slide histopathology images of breast cancer lymph nodes were obtained from the CAMELYON 17 challenge. In total, there are 100 patients in the training set and 100 patients in the test set, each with 5 lymph node histopathology slides. For the patients in the training set, the extent of lymph node involvement (no involvement, isolated tumor cells, microscopic invasion, macroscopic invasion) for each slide as well as their lymph node stages (N) were also obtained. The whole-slide images were broken into tiles with 256x256 pixels using the Automated Slide Analysis Platform (ASAP).

As many of the resulting tiles did not contain any lymph node tissue, a filtering method based on the RGB value distribution was used to select the image tiles with cells. Specifically, we defined intermediate RGB values as those darker than (R, G, B) = (200, 200, 200) but lighter than (R, G, B) = (10, 10, 10), calculated the percentage of pixels of intermediate RGB values, and selected the 200 tiles with the highest percentage of pixels with intermediate RGB value. The selected image tiles were used as our input to the convolutional neural networks.

To distinguish image tiles with and without tumor cells, convolutional neural networks were built using the Caffe platform[11]. AlexNet[12], GoogLeNet[13], VGGNet[14], and the Residual Network (ResNet)[15] were chosen as our baseline networks architecture due to their superior performance in the ImageNet challenges. AlexNet has a very efficient network design and employed non-saturating neurons to reduce training time[12]. The design of the GoogLeNet architecture is largely based on the Hebbian principle and has increased depth and width of the network with a budgeted computational cost[13]. VGGNet possesses a deep and homogeneous convolution structure and demonstrates that the depth of a neural network is a crucial factor of its performance[14]. ResNet is significantly deeper than VGGNet but lowered its model complexity by residual learning[15]. Classification models for histopathology images were built based on these frameworks.

The convolutional neural network models described above were used to determine the probability each image tile contains tumor cells. After the tile-level probability was calculated, these statistics were aggregated to give a summary probability of the slide containing isolated tumor cells (ITC) ($0.6 \leq$ malignancy probability < 0.7), micro-metastasis ($0.7 \leq$ malignancy probability < 0.8), or macro-metastasis (malignancy probability ≥ 0.8). The slide-level summary is translated into lymph node stage using the pathologic lymph node classification rule defined by CAMELYON17. Specifically, no micro-metastases or macro-metastases or ITCs found is defined as pN0, only ITCs found is pN0(i+), micro-metastases but no macro-metastasis is pN1mi, metastases found in 1–3 lymph nodes (of which at least one is a macro-metastasis) is pN1, metastases found in 4–9 lymph nodes (of which at least one is a macro-metastasis) is pN2.

To evaluate the performance of the classifier, the CAMELYON 17 training set was divided into distinct training and validation sets using a 4:1 partition. The convolutional neural network model was trained and all hyper-parameters were finalized through cross-validation on the training set. The finalized model was applied to the validation set and the predicted classification for each image was compared to pathologists' label. Receiver operating characteristics (ROC) curves for the predictions on the validation set were plotted and the areas under ROC curves (AUCs) were calculated. The AUCs of different classification tasks were compared. As the test set labels were unknown at the time of submission, all the model performance results described below were those evaluated on the validation set. All statistical analyses were performed in R version 3.3.

The model trained by the whole CAMELYON 17 training set was used to predict lymph node stages for patients in the test set following the same procedure.

3. PATIENT CHARACTERISTICS

We obtained the whole-slide histopathology images from 100 breast cancer patients in the CAMELYON17 database. Additional 100 patients were identified from the same database as test cases. The lymph node involvement level as well as lymph node stages annotated by pathologists were also obtained. Table 1 summarizes the patient characteristics of the CAMELYON17 training set.

4. METASTASIS VERSUS BENIGN CLASSIFICATION

In order to distinguish tumor from benign tissue, we first built a convolutional neural network to classify lymph nodes with breast cancer metastases from the unaffected ones. Results showed that our convolutional neural network successfully distinguished breast cancer metastasis from benign tissue at the patch level, with areas under receiver operating characteristic curves (AUC) approximately 0.78-

0.85 in classifiers built on the four different architectures. Specifically, AlexNet and VGGNet performed slightly better than GoogLeNet, while GoogLeNet performed significantly better than ResNet. We investigated the excitation patterns of neurons in the convolution layers, and demonstrated that different neurons complemented one another in their ability to detect cell alignment patterns, and subcellular structures.

Table 1. The distribution of pathological lymph node stage (N) and invasion status of each microscopic slide in the training set.

Patient Characteristics	Summary
Number of patients in the training set	100
Pathological Lymph Node stage (pN)	
pN0	24 (24%)
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pN1	25 (25%)
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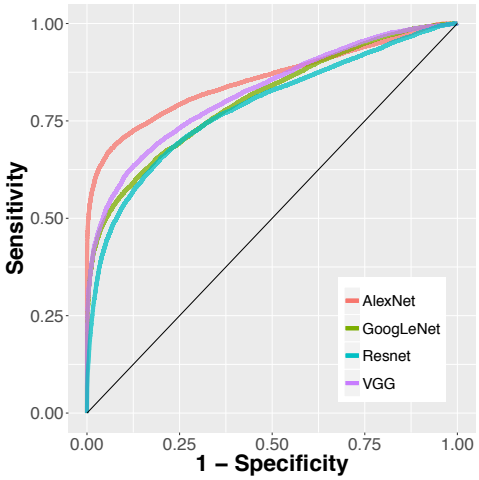
Number of whole slide lymph node pathology per patient	5
The invasion status shown in each microscopic slide	
Negative	313 (62.6%)
Isolated tumor cells	35 (7.0%)
Microscopic invasion	64 (12.8%)
Macroscopic invasion	88 (17.6%)

Figure 1. Convolutional neural networks distinguished lymph node histopathology slides with breast cancer metastases from those without. The areas under receiver operating characteristic curves in the held-out validation set were 0.78-0.85 for classifiers based on the AlexNet, GoogLeNet, VGGNet, and ResNet architectures.



5. LYMPH NODE STAGE CLASSIFICATION

We further aggregated the slide-level classification results to determine the lymph node stage of each patient. Since AlexNet has good performance at the patch level, we used the patch-level prediction results from AlexNet. We followed the CAMELYON 17 definition of lymph node stage to map the slide-level predictions into the stage of each patient, and compared our predicted lymph node stage with pathologists' annotations. Results showed that our methods successfully classified lymph node stages of patients in the validation set, with kappa value approximately 0.75 in models built on AlexNet.

6. DISCUSSION

This is the first study using convolutional neural networks to study the histopathology of breast malignancy. Results demonstrated that the deep learning framework captured the cell morphologies related to breast cancer staging and identified histopathology slides with tumor cells. Our analysis framework requires no human intervention and the results are useful for building a decision support system for tumor pathology analysis.

The general structures of our convolutional neural networks were trained on the ImageNet data, which bears no resemblance to histopathology images. However, we showed that these frameworks generated good classification performance when refined with adequate amount of training data. This indicates the generalizability of pre-trained convolutional neural networks plus parameter fine-tuning through thousands of pathology training images.

As expected, convolutional neural networks work best when the number of training cases is large. Whole-slide histopathology of cancers provides a timely opportunity for convolutional neural network applications, as one slide generally shows thousands of tumor cells. In addition, several types of tumor cell variations were represented in different parts of the same whole-slide image. The abundance of tumor cells and their variations per slide provided sufficient data for training the network for identifying the lymph node with breast cancer metastasis. Further studies can explore the utility of computer vision methods in the histopathology diagnosis of primary breast cancer and the classification of other clinically important phenotypes.

One limitation of the study is that all of the histopathology slides in this study were gathered retrospectively. Future studies are needed to investigate the utility of implementing an automated image classification system in the clinical setting. In addition, the methods

described here need to be further validated in different cohorts with larger sample sizes.

Overall our study demonstrated the utility of convolutional neural networks in classifying lymph node histopathology images. The machine learning system presented here can provide decision support to pathologists and reclassify patients with ambiguous histopathology presentations. This bioinformatics workflow is generalizable to other tumor types or diseases.

7. ACKNOWLEDGEMENTS

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8. REFERENCES

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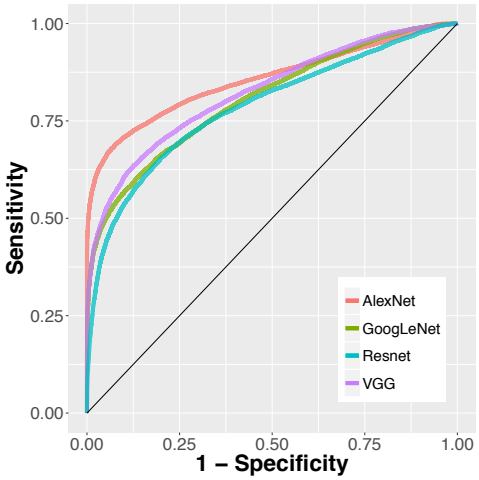

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A Short Description of the Difference of the Method from the Previous Submissions:

This submission used the VGGNet architecture as the patch-level classifier, instead of AlexNet. VGGNet architecture contains 16 convolutional and fully-connected layers in its neural network, which is deeper than AlexNet (five convolutional layers). VGGNet has approximately 140 million parameters, and we fined tuned these parameters by the CAMELYON17 training set. The probability aggregation algorithm is described in the previous submission.

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A Short Description of the Difference of the Method from the Previous Submissions:

This submission used a machine learning approach to aggregate tile-level probability into slide-level classes. We used the AlexNet architecture for the patch-level classification as described in submission 1. However, instead of using a rule-based approach, we built a support vector machine classifier to map the patch-level probabilities into slide-level classifications. Specifically, the mean, standard deviation, as well as each of the 10^{th} quantiles of the tile-level probability were used as the input features. The tile-level predictions of the whole training set were used to train the support vector machine model.