Large-scale Gastric Cancer Screening and Localization Using Multi-task Deep Neural Network

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Abstract

Gastric cancer is one of the most common cancers, which ranks third among the leading causes of cancer death. Biopsy of gastric mucosal is a standard procedure in gastric cancer screening test. However, manual pathological inspection is labor-intensive and time-consuming. Besides, it is challenging for an automated algorithm to locate the small lesion regions in the gigapixel whole-slide image and make the decision correctly. To tackle these issues, we collected large-scale whole-slide image dataset with detailed lesion region annotation and designed a whole-slide image analyzing framework consisting of 3 networks which could not only determine the screen result but also present the suspicious areas to the pathologist for reference. Experiments demonstrated that our proposed framework achieves sensitivity of 97.05% and specificity of 92.72% in screening task and Dice coefficient of 0.8331 in segmentation task. Furthermore, we tested our best model in real-world scenario on 10,316 whole-slide images collected from 4 medical centers.

Keywords: gastric cancer, deep neural network, semi-auto annotation, whole-slide image, large-scale dataset

1. Introduction

Gastric cancer remains important cancer worldwide and is responsible for over 1,000,000 new cases in 2018 and an estimated 783,000 deaths (equating to 1 in every 12 deaths globally), making it the fifth most frequently diagnosed cancer and the third leading cause of cancer death. Biopsy of the gastric mucosa is one of the most effective methods of early detection of gastric cancer [1]. It is estimated that there are hundreds of millions of gastric biopsy slides need to be examined in China each year, while the number of certified pathologists is only about 10 thousand, which causes excessive workloads on these pathologists.

To reduce the workload of the pathologists, there are extensive studies focus on pathology image analysis [2][3][4][5]. In recent years, deep neural network techniques have achieved remarkable performance on a wide range of computer vision tasks, such as image classification [6][7][8], object detection [9][10][11], semantic segmentation [12][13], etc. These techniques have been applied in automated pathology image analysis in the past few years. Unlike natural images, digital pathology images, named whole-slide images (WSIs), are extremely large.
whose width and height often exceed 100,000 pixels. On the other hand, histological diagnosis requires high accuracy since it is commonly considered as the gold standard. As a result, some of the studies focus on the selected regions of interest (ROIs) \[14, 15, 16, 17\], while there are several attempts on analyzing WSI \[18, 19, 20, 21\].

Besides the difficulties in applying the deep neural network on gigapixel resolution images, the main challenge in examining the WSIs is that the diagnostic results labeled by the pathologists are usually on the slide level in most of the publicly available datasets, while the lesion regions that draw the pathologists’ attention are extremely small compared with the size of the WSI. It is tough to train a deep neural network to locate those regions and make the correct decision only using slide level labels such “positive/negative”. Therefore, we collect a large dataset that not only has the slide level annotation but also carries the lesion region annotation and design a framework leveraging the detailed supervised information.

To our best knowledge, there have been no studies on automated pathology image analysis with lesion region annotation in clinical settings for gastric cancer. We propose an automated screening framework that could not only provide the screening results, i.e., positive/negative, but also show the suspicious areas to pathologists for further reference.

2. Related Works

2.1. Pathology Image Analysis for Gastric Cancer

Only a few existing works are focusing on analyzing the pathology image from the biopsy of the gastric mucosa for diagnosis.

Cosattoa et al. \[22\] designed a semi-supervised multiple instance learning framework that takes 230 × 230 microns at magnification of 20X and 460 × 460 microns at magnification of 10X ROIs segmented from tissue units as input and analyzes their color features.

Oikawa et al. \[23\] proposed a computerized analysis system which first analyzes color and texture features on the entire H&E-stained section at low resolution to search suspicious areas for cancer (except signet ring cell which is detected by CNN-based method), and then analyzes contour and pixel features at high resolution on selected area and uses a trained SVM to confirm the initial suspicion.

Li et al. \[24\] proposed GastricNet using different structures for shallow and deep layers, and applied it on 224 × 224 patches cropped from 600 2048 × 2048 ROIs with a magnification factor of 20X.

Yoshida et al. \[25\] compared the classification results of human pathologists and of the e-Pathologist. The e-Pathologist analyzes high-magnification features that characterized the nuclear morphology and texture as well as low-magnification features that characterized the global H&E stain distribution within an ROI and the appearance of blood cells and gland formation. The classification was modeled as a multi-instance learning problem and solved by training a multi-layer neural network.

2.2. Whole-Slide Image Analysis

As the gold standard for various cancer diagnosis, WSIs analysis related techniques have been well-studied in recent years.

Liu et al. \[26\] presented a CNN framework to aid breast cancer metastasis detection in lymph nodes. The model is based on Inception architecture with careful image patch sampling and data augmentations. Random forest classifier and feature engineering were used for whole-slide classification procedure.

Hou et al. \[27\] proposed to train a decision fusion model to aggregate patch-level predictions given by patch-level CNNs. In addition, authors formulated a Expectation-Maximization based method that automatically locates discriminative patches robustly by utilizing the spatial relationships of patches.

Zhu et al. \[28\] proposed a survival analysis framework which first extract hundreds of patches by adaptive sampling and then group these images into different clusters. An aggregation model was trained to make patient-level predictions based on cluster-level results.

Mercan et al. \[29\] developed a framework to analyze breast histopathology image. Candidate ROIs were extracted from the logs of pathologists image screenings based on different behaviors. Class labels were extracted from the pathology forms and slides were modeled as bags of instances which are represented by the candidate ROIs.
Localizing of lesion regions in WSIs by image segmentation related techniques is also a crucial direction for helping pathologists make the correct decision efficiently.

Qaiser et al. [30] proposed a tumor segmentation framework based on the concept of persistent homology profiles which models the atypical characteristics of tumor nuclei to localize the malignant tumor regions. Dong et al. [31] proposed a reinforcement learning based framework motivated by the zoom-in operation of a pathologist which learns a policy network to decide whether zooming is required in a given ROI.

Our main contributions:

- We collect a large-scale dataset for gastric cancer screening and develop a semi-automated annotation system to help obtain the detailed lesion region annotation.
- We take advantage of the region annotation by proposing a multi-task network structure which could provide the classification label (screening result) as well as the segmentation mask (suspicious region) simultaneously.
- We design a practical framework consisting of 3 networks to process the high-resolution WSIs, and employ the deformable convolution operation based on the observation of the characteristics of the pathology images.

3. Data Collection

3.1. Data Acquisition

All the annotated slides are automatically scanned using the digital pathology scanner Leica Aperio AT2 at 20X magnification (0.50um/pixel) and labeled by pathologists under the supervision of the experts in Shanghai General Hospital.

The slide-level annotation is either “positive” (refers to the malignant sample such as low-grade intraepithelial neoplasia, high-grade intraepithelial neoplasia, adenocarcinoma, signet ring cell carcinoma, and poorly cohesive carcinoma) or “negative” (refers to the benign sample such as chronic atrophic gastritis, chronic non-atrophic gastritis, intestinal metaplasia, gastric polyps, gastric mucosal erosion, etc). All the malignant regions are labeled along with their contours and converted to a mask. (Shown in Fig. 1)

3.2. Semi-automated Annotation System

The manual annotation procedures designed by the experts of Shanghai General Hospital are:

1) Coarse labeling. The pathologist finds the suspicious area in the high-resolution gigapixel image and selects them with bounding boxes.

2) Fine labeling. Within the selected bounding box, pathologist further confirms whether it is malignant, draws a closed curve along the contour of the malignant region and marks the lesion type of the region.
Figure 2: Our annotation pipeline. The pipeline consists of two parts, namely the initial annotation and the refinement. The initial annotation part (on the left) has two routes: manual annotation (blue overlay) and semi-auto annotation (pink denotes the output of the U-Net, blue denotes the annotation after pathologists’ editing). The refinement part (on the right) shows I) the annotation from pathologists (blue), II) output of color deconvolution, III) binary image after applying Otsu thresholding. IV) the final ground truth annotation (green) after refinement.

3) Double checking. Finally, the experts go through all the annotated WSIs and verify the correctness of the labels.

Figure 3: An enlarged part of WSI. Blue overlay in the right image denotes the manual annotation from the pathologist, which may cover many empty regions.

Manually labeling a WSI usually takes 1 – 3 hours and the contour may not align perfectly with the border due to the enormous image size and the highly unsmooth edge (shown in Fig. 3).

To address this issue, we introduce a semi-automated annotation system (shown in Fig. 2). An annotation refinement module with a series of image processing techniques is employed to eliminate the background areas in the manually labeled regions (shown in the right part of Fig. 2). Color deconvolution technique [32, 33] is used to extract Hematoxylin & Eosin-stained regions (image II). Based on the output of color deconvolution, we could obtain the foreground by applying Otsu thresholding [34] (image III). The final segmentation annotations are the intersection between the foregrounds and the pathologists annotated areas (image IV). These procedures could fix the empty regions and loose boundary without modifying the true malignant region.

As shown in the left part of Fig. 2, we further propose to initialize a preliminary annotation with the output of a segmentation network trained on a few labeled WSIs. Then, pathologists only need to modify the masked regions discovered by the segmentation network, which could effectively speed up the labeling procedure.

Basically, our semi-automated annotation system could generate more accurate region contour and reduce the labeling time to 20 minutes.

3.3. Large-scale Screening Dataset from Multiple Medical Centers

Moreover, in order to test our proposed framework in real-world scenario, we collected 10,316 WSIs from four hospitals in East China, i.e., Sijing Hospital of Shanghai Songjiang District (SHSSD), Songjiang District Center Hospital (SDCH), Zhejiang Provincial Peoples Hospital (ZPPH) and Shanghai General Hospital (SGH).

4. Methods

The main challenge in analyzing WSIs is that the images are extremely large, while only a small part of images contains the lesion region. Hence, we propose a gastric cancer screening and localization framework (shown
in Fig. 4, which consists of 1) a lite segmentation network for extracting the tissue region and eliminating the background area, 2) a multi-task network for generating classification and segmentation results for every cropped patch, and 3) a simple feedforward network for providing the slide-level screening result.

4.1. Network Structure

Multi-task Network. We employ deep layer aggregation (DLA) structure [35] as the backbone since it is designed to aggregate layers to fuse semantic and spatial information for better recognition and localization. In our case, we utilize the dense prediction network for lesion region segmentation and change it to a multi-task structure by adding a classification branch on the output of the encoder. In the training phase, we use the patches cropped from ROIs with their annotated malignant region masks as the positive inputs and the patches randomly cropped from the benign region with the background (all-zero) masks as the negative inputs, and train the network in an end-to-end manner by combining the classification loss and the segmentation loss (Eq. 1). In the inference phase, patches from each sliding window are sent to the network to generate the classification score and the segmentation heatmap.

\[ L = \lambda L_{cls} + L_{seg} \]  

where \( L_{cls} \) denotes the loss in classification branch, \( L_{seg} \) is the binary cross entropy loss in segmentation branch, and \( \lambda \) is a hyper-parameter to balance the weights of these two losses.

Feedforward Screening Network. The input of this network is a matrix \( X \in \mathbb{R}^{k \times d} \) which consists of the mid-layer features (i.e., the output of encoder) \( x \in \mathbb{R}^{1 \times d} \) in the dense prediction DLA structure from \( k \) patches with the highest probability of being malignant. The followings are a \( 1 \times 1 \) convolution layer with a ReLU layer, a max-pooling operation along the sample axis which generates...
a \( \mathbf{Y} \in \mathbb{R}^{1 \times d} \) tensor, and a fully connected layer followed by a sigmoid function. Ground truth label of this network is defined in a multi-instance learning (MIL) manner, i.e., whether the WSI contains at least one malignant region.

Since lesion regions only account for 20\% percent of the tissue or less, it is difficult for a network targeting at recognition task such as \([6, 7, 8]\) to find where to pay attention to. In this project, we could take advantage of the detailed lesion region annotation. The multi-task network is designed for producing patch-level results. The segmentation task could not only generate the lesion region mask but also help the whole network locate the regions that really need to focus, which could implicitly support the classification branch to achieve higher performance.

The feedforward screening network is proposed for generating the slide-level results. The basic idea in designing this simple feedforward network follows the concept of MIL.

Because the gastric WSIs usually carry many blank areas. We further design a foreground extraction network to extract all tissue region and reduce the running time in the inference phase. It is a segmentation network with 4 convolution layers and 1 upsampling layer. The input of this network are the resized WSIs from the lowest magnification level (i.e., \( \times 0.635 \)) and the masks generated by color deconvolution \([32, 33]\) and Otsu thresholding \([34]\) with manually modification. The output of this network is utilized in the inference stage for selecting the sliding window area.

4.2. Deformable Convolution

Another issue in WSIs is that the lesion regions often come with irregular shapes and various sizes while standard convolution operation always fails to handle large geometric transformations due to the fixed geometric structures. Therefore, instead of using standard convolution operation, we employ the deformable convolution layer \([36]\) in the decoder.

Deformable convolution is proposed based on the idea of augmenting the spatial sampling locations in the modules with additional offsets:

\[
y(p_0) = w(p_n) \cdot x(p_0 + p_n + \Delta p_n)
\]

where \( x \) denotes the input feature map, \( y \) denotes the output feature map, \( p_0 \) is a location on input feature map, \( p_n \in \mathcal{R} \) and \( \mathcal{R} \) is a regular grid \( (1, 1), (1, 0), \ldots, (0, 1), (1, 1) \). This type of convolution operation allows adding 2D offsets \( \Delta p_n \) to the regular grid sampling locations \( p_0 + p_n \) in the standard convolution.

As demonstrated in Fig. 5, we could easily benefit from the adaptive receptive field when handling the lesion regions with irregular shapes. The deformable convolution operation enables free form deformation of the sampling grid by adding additional offsets (the arrows in the right image of Fig. 5). The offsets are learned from the segmentation task simultaneously with convolutional kernels during training. Hence, the deformation is conditioned on the input features in a local, dense, and adaptive way.

As a consequence, we could capture the feature of the tissue regions with various shapes by utilizing deformable convolution operation, which leads to better performance on the segmentation task.

5. Evaluation

5.1. Implementation Details

We choose the basic DLA-34 with dense prediction part as the backbone of the multi-task network, replace the first 7 \( \times 7 \) convolution layer with three 3 \( \times 3 \) convolution layers, and several standard convolution in decoder with 3 \( \times 3 \) deformable convolution. The output of classification branch of this network is a 512 feature vector. We pick \( k = 64 \) to form a 64 \( \times \) 512 matrix as the input of the feedforward screening network. The \( \lambda \) in Eq. 1 used for balancing the classification loss and segmentation loss is set to 0.01. Besides, in-place activated batch normalization \([37]\) is employed to reduce the memory requirement in training deep networks.
We use Adam optimizer to train the mentioned networks separately. The initial learning rate is set to $10^{-3}$ and reduced by a factor 0.5 when the validation loss stagnates for 3 epochs. The multi-task network is trained for 100 epochs with the batch size of 16 on 4 Nvidia GTX 1080 Ti with 12GB RAM GPUs. And the feedforward screening network is trained for 20 epochs with the batch size 32 on a single GPU.

5.2. Evaluation of Segmentation

21,507 positive patches are cropped from the annotated 400 ROIs, and 168,485 negative patches are collected from the WSIs that are diagnosed as benign. Data augmentation techniques such as horizontal/vertical flip, rotation, random cropping and resizing, changing the aspect ratio and image contrast, and adding Gaussian noise are applied during training. We use repeated random subsampling strategy in evaluation. Patches from about 30% WSIs are selected as the testing set by the patient ID, and the whole procedures are repeated 4 times for stable results.

For the evaluation metric, we use the Dice coefficient (DSC) defined over image pixels.

$$DSC = \frac{2TP}{2TP + FP + FN}$$  \hspace{1cm} (3)

We compare our proposed method with commonly used segmentation networks, i.e., FCN [12], U-Net [38], and the standard DLA [35] structure without any modification.

FCN and U-Net serve as the baselines, which give us a sense about the performance of commonly used methods on our dataset. Dice coefficient of these two methods is 0.8109 and 0.7847, respectively. The possible reason for FCN performing better could be it benefits more from classification branch without the skip connections like U-Net. DLA performs better, i.e., 0.8248, because it benefits from fusing information by aggregating layers. Our proposed model achieves the highest DSC of 0.8331 as we adjust the standard DLA structure according to our problem settings by replacing the standard convolution with deformable convolution operator, adding classification branch, etc.

To better demonstrate the effectiveness of our proposed method, we show some examples in Fig. 7. FCN and U-Net often generate unclear and unsmooth boundaries (1st and 2nd row). As we could see from the 3rd to the 5th column, the 3 comparison methods make a lot of false positives compared to our method. In the 2nd row, U-Net even includes red blood cell area in the result. In the 5th row, our model is the only one that successfully identifies the tissue on the bottom to be negative.

5.3. Evaluation of Screening

Compare with the segmentation evaluation that requires a testing set with lesion region annotation, evaluating the screening results of our proposed model could be done on a larger testing set with screening annotation only, i.e., 102 positive samples and 838 negative samples.

In Table 1 we report the screening results of our proposed framework and comparison methods on multiple evaluation metrics, i.e., sensitivity, specificity, and Area Under ROC Curve (AUC). The comparison methods are a single task classification network with the same backbone as our proposed network structure (W/O seg) and multi-task network structure with different backbones (FCN and U-Net).

The primary goal of our proposed framework is gastric cancer screening. In other words, the number of negative samples is much larger than the positive ones (about 9 : 1 in this testing set). In this case, sensitivity is the most critical evaluation metric when we take clinical background
knowledge into consideration since we would not like to miss any of the malignant cases. Besides, specificity is the second priority because we do not want too many false alarms, either. AUC is a metric that expresses both sensitivity and specificity. Although the single task classification network (W/O seg) achieves the highest specificity of 95.82%, it is not a suitable choice as it generates too many false negative. The proposed method shows the highest sensitivity of 97.05%(95%CI, 91.02% – 99.24%), the second-best specificity of 92.72%(95%CI, 90.69% – 94.34%), and the leading AUC of 0.9872, which outperforms others methods by a large margin.

5.4. Evaluation in Real-world Scenario

Also, we test our best model on our large-scale real-world set collected from 4 medical centers. Table 2 shows the numbers of images of the collected data.
| Year | Total | Positive | Negative |
|------|-------|----------|----------|
| 2015 | 2083  | 85       | 1998     |
| 2018 | 3207  | 299      | 2908     |
| 2019 | 3670  | 50       | 3620     |
| SHSSD| 495   | 8        | 487      |
| SDCH | 391   | 6        | 385      |
| ZPPH | 469   | 8        | 461      |

Table 2: Number of WSIs collected from the four institutes in different years.

All the training images with lesion region annotation are from SGH in the year 2018. Besides those training images, we further collect 3,207 images in that year, 3,670 images in 2019 as the most recent samples, and 2,083 images in 2015 as the old samples since they did not use too many automated devices for fixation, sectioning, and staining at that time. Moreover, to test the generalization ability of our proposed model, we collect 1,356 images from 3 other hospitals, i.e., SHSSD, SDCH, and ZPPH. The devices and procedures in making histology slides are different in these hospitals which may affect the final WSIs. Overall, we have 10,316 WSIs from 4 hospitals and years, and the positive ratio is less than 5%.

| Year | Sensitivity | Specificity |
|------|-------------|-------------|
| 2015 | 1.0000      | 0.7753      |
| 2018 | 0.9967      | 0.7995      |
| 2019 | 1.0000      | 0.7829      |
| SHSSD| 1.0000      | 0.7371      |
| SDCH | 1.0000      | 0.6571      |
| ZPPH | 1.0000      | 0.7527      |

Table 3: Screening results in real-world scenario.

6. Conclusion and Future Work

In conclusion, with the assumption that detailed lesion region annotation is necessary for the network to locate the crucial part in the gigapixel resolution WSIs and achieve the better performance, we designed a semi-automated annotation system and collected a large dataset consisting of 518 WSIs with lesion region masks and over 10,000 samples with screening results. To exploit our dataset, we propose a gastric slides screening framework to reduce the workload of pathologists and lower the inter-observer variability. The whole framework consists of three networks, a multi-task network for patch-level classification and segmentation, a 3-layer feed-forward network for slide-level screening result, and a simple segmentation network for foreground extraction.

One of the possible future direction of this project is cancer subtype diagnosis. Instead of just providing the “positive/negative” screening result, an automated lesion type diagnosis system could present the result like “adenocarcinoma”, “signet ring cell carcinoma”, “chronic atrophic gastritis”, etc. Furthermore, since a single WSI may contain multiple lesion types, displaying the labels on each segmented region/ROI could be more helpful, which requires an instance-level segmentation structure.

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