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Can Artificial Intelligence Help?

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Introduction

Papillary thyroid carcinoma (PTC) is the fifth most common malignant tumor in women worldwide and the most common cancer in women younger than 25 years [1]. Fortunately, the first is that the prognosis is excellent compared to other malignant tumors [2]. The second is that an invasive procedure is not required for its diagnosis, so early diagnosis is possible. After observing the thyroid gland under the thin skin in the front of the neck with ultrasound sonography, the cells are collected by piercing the area suspected of cancer with a thin needle, called a fine-needle aspiration (FNA). Third, the cytological diagnosis of PTC is relatively easy because it is cytologically very characteristic compared to other types of malignant cell diagnosis. When observed under a microscope, the nuclear membrane of PTC is wrinkled, the nucleolus is transparent, has a bubble, and a deep groove is formed that crosses the nucleus [1,3] (Figure 1). Thanks to the above three lucks, we tried to use artificial intelligence in the cytologic diagnosis of PTC. The Bethesda system used worldwide makes the cytologic diagnosis of PTC, which has six tired categories describing the almost cytologic features observed in thyroid disease in human beings.

Why Should Papillary Thyroid Carcinoma be Investigated?

The last luck we face is Liquid-based cytology (LBC). The LBC is a method in which cells obtained through FNA are centrifuged, treated with a solution of methanol or ethanol, and then placed on a slide as if stamping. The cells are evenly distributed in a circle with a diameter of 20 mm. These automated processes take a short time; the degree of staining and cell change has already been standardized worldwide [4]. We used Hologics' ThinPrep® System. Along with such methodological luck, we directly investigated the work intensity of actual pathologists through a questionnaire. Compared to the histologic diagnosis of biopsied or resected samples, the cytologic diagnosis was very difficult, requiring perfect observation of about 6,000 to 30,000 cells within a 20 mm circle in each slide produced by the LBC method. If even one cancer cell is missed, it will be a misdiagnosis inevitably, which will be the worst situation we can imagine for the patient or pathologist. Considering all the circumstances and possibilities mentioned above, we are compelled to undertake this study immediately.

What We Have Done

The cytological images required to develop and evaluate our method were collected from patients who underwent thyroid nodule FNA and thyroidectomy from January 1st, 2013, to December 31st, 2013. Before the FNA procedure, written informed consent was obtained from all patients. An FNA biopsy was performed with 22-gauge needles by an experienced sonographer under ultrasonographic guidance. Most of the FNA samples were transferred to a 10 ml syringe and then prepared with a natural sedimentation-type thin layer LBC system using a ThinPrep® System. A digital still camera (DP73, Olympus, Tokyo, Japan) with a 40× objective lens attached to a microscope (BX52, Olympus) was used to

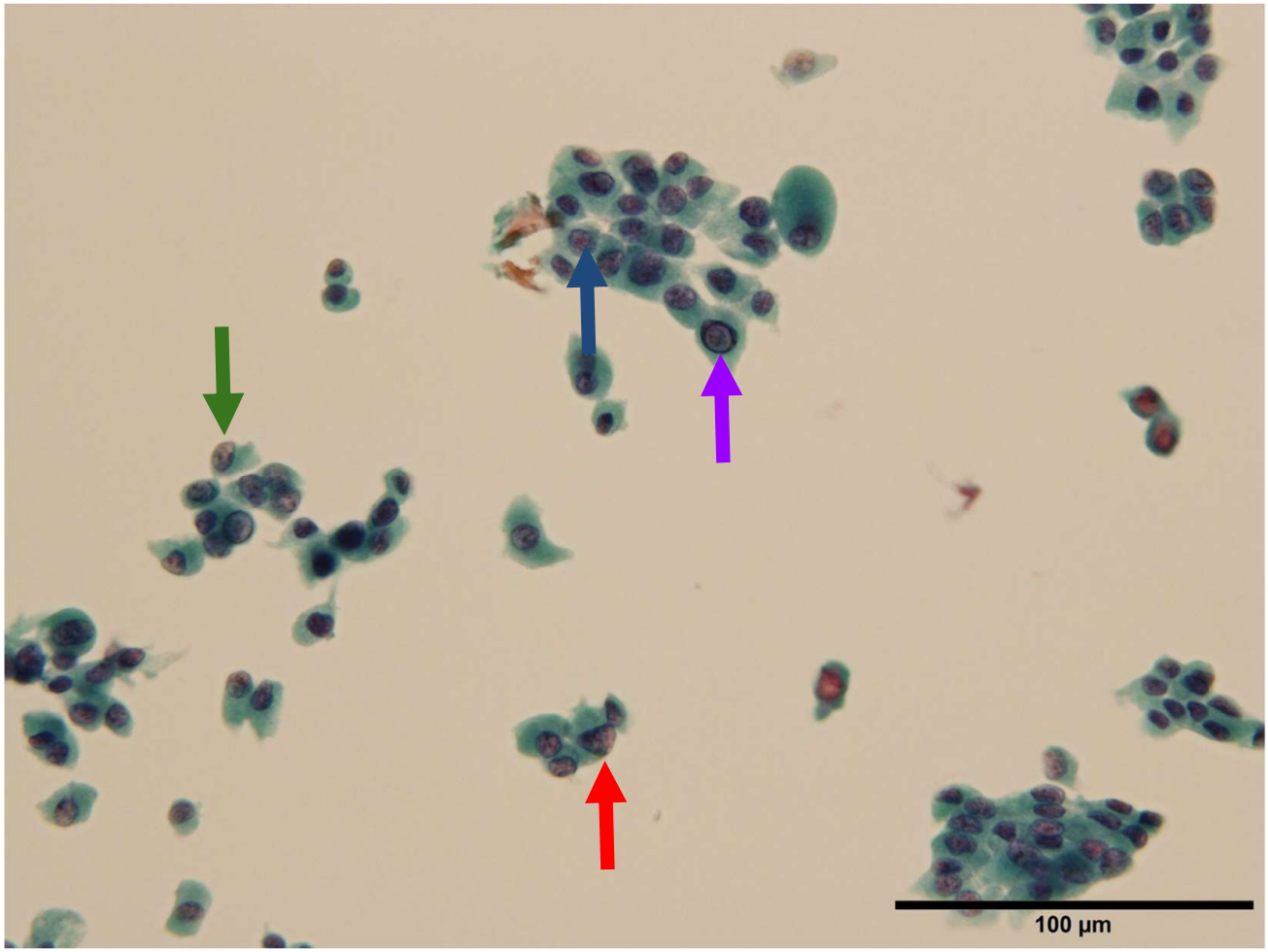

Figure 1: The characteristic nuclei of PTC demonstrate wrinkled (red arrow), transparent (green arrow), bubbled (purple arrow), and deep grooved (blue arrow).

take the pictures for the ThinPrep®. All photos were collected by experienced cytopathologists and saved in JEPG format. We introduced an automatic computer-aided diagnostic system for differentiating PTC tissues from the benign ones from FNA digital images processed by ThinPrep® using deep convolution neural network (CNN) frameworks.

We have selected to train the CNN models only with cytologically confirmed cases of PTC and not to include suspicious cases. We first proposed an automatic approach for preprocessing and stain normalization of high-resolution cytological digital images captured from the Olympus microscopy systems. Next, the fragments for training the deep CNN models are automatically generated using Canny edge detection and contours methods, which can be classified as unsupervised deep learning. We then employed a combination of transfer learning and data augmentation to retrain well-established CNN-based ResNet, DenseNet and Inception models. After being trained on a large-scale dataset, the CNN models are expected to perform better. We proposed a novel CNN deep learning framework that can be implemented in modern automatic Computer-aided diagnosis (CAD) systems for accurately identifying the PTC tissues from the normal ones using FNA digital images.

At last, we proposed an ensemble deep learning architecture, which combined multiple individual deep learning models to boost the predictive performances significantly. We performed an automatic smear extraction (fragments) from original cytology FNA images and implemented the Gradient-weighted Class Activation Mapping (GRAD-CAM) approach to highlight the essential regions that are highly dominant in the discrimination decisions. Our proposed ensemble deep learning model is superior to the existing models in current literature in the cytologic diagnosis of PTC [5].

In recent advances, deep Convolutional Neural Networks (CNN) have appeared as new angled approaches for analyzing multiple clinical pathologies listed in Table 1. The successful results achieved in these studies ensure promising performances for deep CNN networks in cytological diagnosis. However, the training of CNN models is learned using a stochastic algorithm which means that they are sensitive to the training data's specifics. Thus, a different set of weights each time they are trained can be achieved, which produces other predictions. In our previous work, to diminish the variances in predictions and increase predictive results, we proposed an ensemble deep learning approach, which trains multiple CNN deep learning models instead of a single model and combines these models' prediction results. After the training of CNN models reached convergences, we performed ensemble learning with bagging by considering each result of CNN models as a feature using a single machine learning algorithm at the end of inference.

Now We are Going to Do

We started analyzing image files through a whole slide image (WSI) scan similar to a pathologist observes with their eyes in the real world, and we expect more practical and innovative results than previous microscopic images.

The Future We Dream

Digital pathology refers to acquiring digital images using a digital scanner on a glass slide and diagnosing, managing, sharing and analyzing them. In the past, a glass slide was viewed through a microscope, but WSI is used to diagnose digital images in front of a monitor in a digital pathology environment. Digital files are shared without exchanging glass slides as in the past when cooperating, including secondary diagnosis for consultation. In the era of analogue pathology, glass slide-based pathology, diagnosis flow goes through the flow of glass slide, microscope, consultation, diagnosis, storage, re-staining when needed occasionally, transportation, and microscope reading. In addition, the diagnosis can be made using a computer, and the process becomes straightforward as the intermediate process is omitted. With the commercialization of high-speed, high-capacity digital scanners, the world's leading university hospitals have actively introduced digital scanners to digitize pathological slides [6]. It is expected that digital scanners with more diverse

Types	Dataset	Classifier	ACC(%)
PTC	FNAC smears	ANN	85.06
Breast carcinoma	Histology images	CNN + SVM	88.90
Lung Carcinoma	Cytological images	CNN	89.30
Thyroid carcinoma	FNAC images	DT + KNN	90.00
Thyroid carcinoma	FNAC images	ENN	93.33
Thyroid carcinoma	FNAC images	SVM	96.70
PTC	Cytological images	VGG-16	97.66
Lung Carcinoma	Whole-Slide Image	EfficientNet-B3 CNN	98.10
PTC	**Cytological images**	**Ensemble deep learning**	**99.71**

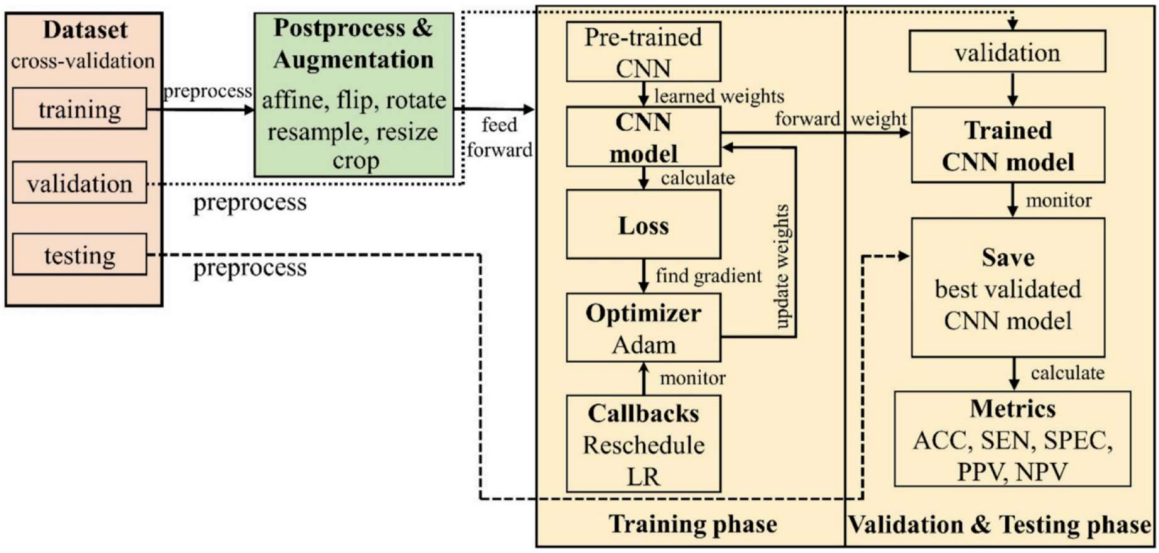

Table 1: The comparison of the accuracy (ACC) between recent CNN based pathology studies and ours (up) using the Ensemble deep learning model (down) [5].

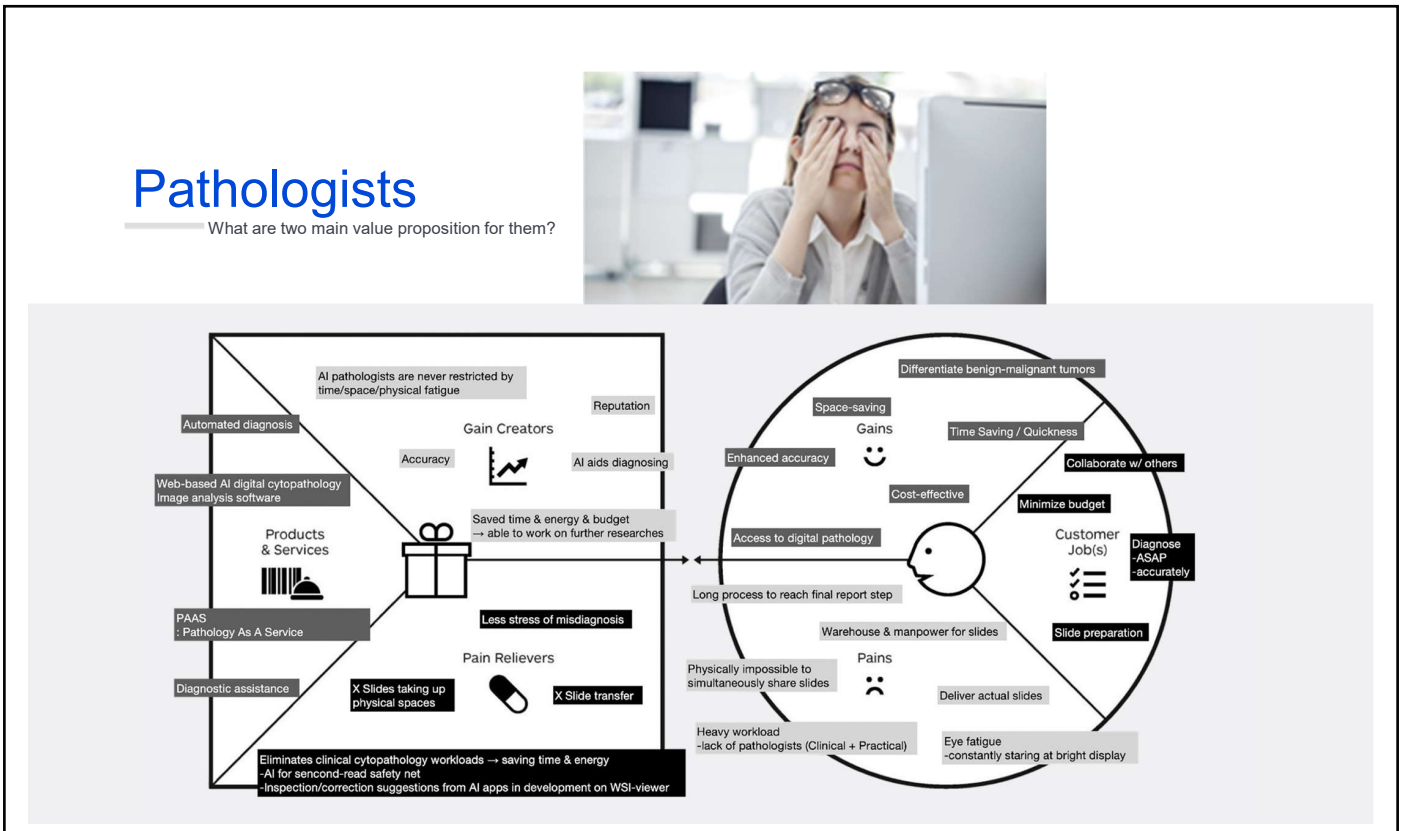

Figure 2: Digital pathology can help you in numerous ways.

functions will be developed in the future, and as a result, the price of scanners is expected to be levelled down due to competition. This will enable university hospitals and smaller hospitals to purchase digital scanners, and the significant dramatization of multiple digitized pathological slide images is a reality that will soon be realized. The artificial intelligence assistant cytologic diagnosis platform dramatically reduces the workload of pathologists, who are gradually decreasing worldwide in numbers (Figure 2), provides accurate diagnosis to primary medical staff prescribing cytopathology tests, and enables early surgery through rapid diagnosis. It is expected to improve the prognosis and quality of life and reduce national medical expenses. It is also the future that we earnestly dream of as pathologists who are tired of overloaded daily diagnosis.

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