Automatic Diagnosis of Breast Cancer from Histopathological Images Using Deep Learning Technique

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Abstract. Breast cancer is the primary cause of women cancer death globally. Advancement in screening methods and early diagnosis can increase survival from breast cancer. Clinical breast examination, imaging, and pathological assessment are common techniques of a breast cancer screening. Biopsy test is the standard breast cancer screening method due to its ability to identify types and sub-types of cancer. However, current diagnosis using this method is generally made by visual inspection. The manual technique is time taking, dreary, and subjective, that can also lead to misdiagnosis. The current article proposes an automatic diagnosis system for breast cancer based on the deep learning neural network model. The model was trained and validated on histopathological images obtained from online data sets and local data obtained from Jimma University Medical Center using a digital camera mounted on a microscope. All images were pre-processed and enhanced before being fed into the previously trained ResNet 50 model. The developed technique is able to classify breast cancer into benign and malignant and to their subtypes. The results of our test showed that the proposed technique is 96.75%, 96.7% and 95.78% for the benign subtype and the malignant subtype classification, respectively. The developed technique has a potential to be used as a computer aided diagnosis system for clinicians, particularly in low resources setting, where both resources and experience are limited.

Keywords: Breast cancer · Cancer sub-type · Classification · Grading · ResNet · Transfer learning

1 Introduction

Breast cancer is the number one and most common cause of cancer in women, and it is still the main concern globally [1, 2]. It is an out-of-control growth of cells in breast. It includes both the benign and malignant cancer types. The benign cancer type includes Adenosis, fibro adenoma, phyllodes tumor and tubular adenoma tumor and the malignant cancer types incudes invasive ductal carcinoma, invasive lobular carcinoma, mucinous and papillary [3].

Clinical examination, imaging and pathological test are the methods that are usually used to identify breast cancer type and sub-types [4]. The histopathology is the gold standard for identifying breast cancer type and sub-types [5].

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Because histopathological analysis through biopsy test is done usually through visual inspection, the result is dependent on physician's expertise level and performance. Therefore, breast cancer multi-classification using biopsy test is a complex and the accuracy is dependent on the observer's knowledge and experience. Also, due to the lack of trained pathologists in many of low-income countries, a single pathology expert examines various types of biopsy specimens with different types of cases on a daily basis. The diversity and quantity of microscopic image analyzed by the expert and the intricacy of the histopathological images can lead to wrong diagnosis of the breast cancer. A misdiagnosis can be either an over or under-interpretation. Over-interpretation means that a woman free from cancer could face with potentially harmful treatments and needless expenses. Conversely, under-inaccurate interpretation of the biopsy result could prevent a woman from receiving treatment early, which can lead to the cancer growing in more invasive stages. Furthermore, the decision on the best therapeutic strategy for breast cancer is based on an advanced multi-class classification of cancer type. Precise identification of breast cancer subclasses could help control tumor cell metastasis at an early stage with therapeutic techniques.

Computer aided diagnosis (CAD) techniques has a potential to advance the breast screening method. Intelligent techniques have a potential to boost the screening accuracy of breast cancer, reduce misdiagnosis and decrease the work-load of pathologists [6–8]. However, developing efficient microscopic image analysis, and smart feature-extraction method is a complex task for computer-assisted screening of breast cancer [9].

2 Related Works

Artificial intelligence methods have the potential to enhance image processing and feature extraction techniques by detecting and extracting patterns in the image automatically. Deep learning techniques have been proposed in the literature for classification of breast cancer types from microscopic images [9–13]. To classify the breast tissue microscopic images into normal, benign, or malignant, a convolutional neural network (CNN) based deep patch level voting model and fusion model were proposed and reported to have an accuracy of 87.5% [10]. Similarly, the Deep CNN and Gradient Boosted Tree method have used to classify breast cancer types and an accuracy of $93.8 \pm 2.3\%$ and $87.2 \pm 2.6\%$ were reported [14]. Support vector machine (SVM) as a classifier and CNN as a feature-extractor were also proposed by Araújo et al. [15] and were implemented for retrieving information from images at various scales, including nuclei and total tissue organization, accuracy of 77.8% for all four classes and 83.3% for carcinoma (in situ and invasive) or non-carcinoma (healthy and benign) were claimed. Inceptionv3 CNN has also been fine-tuned and refined for patch classification and a majority vote was taken into account for the entire slide classification, resulting an accuracy of 85% for all four classes and 93% for non-cancerous type [16]. These studies achieved better precision in classifying breast cancer into 4 main sub-classes. However, precise classification of breast cancer into clinically relevant sub-types is also of particular importance for treatment decisions [17] and the need to classify histological images of breast tissue into more breast cancer subclasses has led many

investigators to do more study with machine learning. With this regard, breast cancer classification into their sub-types has been proposed in many literatures [18–22]. However, in many cases, sporadic classes of breast cancers including mucinous-carcinoma were not considered. Moreover, other breast cancer areas, that are different from invasive cancers were wrongly detected as invasive breast cancer [22].

Hence, the techniques proposed in related works to classify breast cancer are either designed for single purpose or computationally expensive and magnification dependent. To determine the appropriate clinical course of treatment and surgical planning, it is essential to have an integrated system for classifying breast cancer using a deep learning technique. This will also help reduce the heavy workload of physicians and reduce errors in diagnosis.

This paper presents an integrated magnification-independent technique for breast cancer classification using a deep-learning technique.

3 Methods

3.1 Dataset

For model training, validation and testing. microscopic histopathological images were collected from Jimma University Medical Center (JUMC) and 'break-his' [23] and 'zenodo repository' [24] online datasets.

The images collected from JUMC were stained using H&E staining technique and were acquired using the Optika-vision camera attached with a simple light-microscope with four magnification powers (40X, 200X, and 400X) and resolution of 2592 $\times$ 1936.

Similarly, images collected from the break-his dataset were captured using different magnification factors (40X, 100X, 200X, and 400X) and Nikon digital camera attached to a microscope. The image frames collected were selected from regions aggrieved by tumor growth.

3.2 Image Pre-processing and Enhancement

In the pre-processing stage, image re-sizing and data augmentation were applied to all images. All images were adjusted to 224 $\times$ 224 size. To increase the training dataset, all images were also rotated by 90°, 180° and 270°.

For images enhancement contrast limited adaptive histogram equalization (CLAHE) technique was selected and applied to collected data for each RGB channels, separately. RGB to YCbCr color space conversion were also applied to all images to preserve detail information of luminance component [25].

Another enhancement technique applied in this study is histogram matching. Histogram helps reduce color variance in biopsy samples that occur because of variations in scanning conditions and staining protocol. For sample true-color RGB images, each color-channel of the histopathological image was separately matched to the corresponding color-channel of a selected template image. According to the staining protocol, the template image selected was the image where the cytoplasm is presented as pinkish and nuclei are presented as blue.

Data were split after pre-processing stage and images were divided into 80%, 10%, and 10% for training, validation and test, respectively.

3.3 Classification

The accuracy of the classification depends mainly on the properties of the data, difficulty of the problem to be analyzed, and the robustness of the classification algorithm. Accuracy, precision, computation time and memory usage can used to evaluate the robustness of a classification algorithm. Training deep neural networks is challenging due to since the gradient is unstable. Since the gradient propagates back to previous layers through iterative multiplication, the gradient could become extremely small. Due to this, the performance degrades rapidly as a network depth increase [26, 27].

In this paper, ResNet 50 model, initially presented by He et.al (2015) [28] has been used due to its flexibility and efficiency [14, 29–31]. The ResNet50 model uses an identity-shortcut connection to avoid the vanishing gradient problem [28, 32]. Due to this feature, deep neural networks can be trained without gradient instability problem.

The pre-trained ResNet50 model has 3 parts and 4 stages. The parts include the convolutional base, pooling layer (the feature generator) and a classifier that is composed of the fully-connected layers. After an input data is fed to the network, it starts with executing the initial convolution and max-pooling using 7×7 and 3×3 kernel sizes, respectively. First stage of the network has three residual-blocks containing three layers each. 64, 64 and 128 kernel sizes are used for convolution operation in the three layers. In addition, identity-shortcut-connection is used to avoid the vanishing gradient problem by addition the original input to the output of a series of operations [32]. The bottleneck design [28, 33] is also included to increase the efficiency of the ResNet50 model. A 1×1, 3×3 and 1×1 layers are added concurrently in each of the residual function. The network has also Pooling layer at the end, trailed by a fully-connected layer with neurons same as input class numbers.

The model used for this paper was adapted and fine-tuned for BC multiclassification. The model was used as a feature extractor and both its architecture and weight value were adapted. The top layers were frozen, and some parameters including the learning rate, optimizer type, loss function and decay rate, which are used to optimize the model were adjusted. At the end, a soft-max classifier [34] is used to classify each image in their corresponding class. To increase the performance of the system, a set of hyper-parameters such as optimizer, learning rate and activation function were fine-tuned. ADAM [35] optimizer was selected due to its speed convergence and accuracy. A total of 50 number of epochs, with learning rate 0.01–0.001 and Rectified Liner Unit (ReLu) activation function [36] were also set to increase the accuracy of the system. For binary classification a binary cross-entropy loss function and for multi class classification a categorical cross-entropy was selected. The technique used in this paper is demonstrated in Fig. 1.

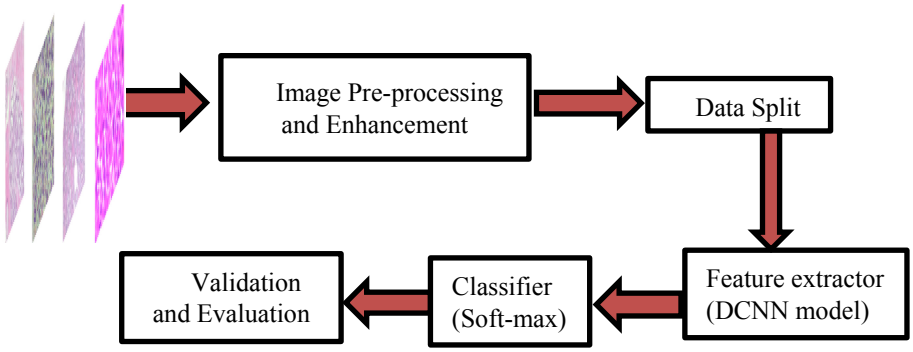


Fig. 1. Overall methodology used for BC classification

The proposed system first categorizes images into two classes: benign or malignant types. Then each of the binary classes are further classified into their sub-classes (benign: adenosis, fibro adenoma, phyllodes and tubular adenoma, Malignant: invasive ductal carcinoma, invasive lobular carcinoma, invasive mucinous carcinoma and papillary carcinoma).

3.4 Performance Evaluation Metrics

For performance evaluation precision, F1-score, recall or sensitivity, specificity and accuracy metrics were selected and calculated from confusion metrices (Eqs. 1–5). Proportions of actual negatives are identified mainly by F1-score and specificity. Accuracy was determined using true positive (TP), false positive (FP), false negative (FN), and true negative (TN) values.

$$\text{Precision} = \text{TP}/((\text{TP}+\text{FP})) \tag{1}$$

$$\text{Recall} = \text{TP}/((\text{TP}+\text{FN})) \tag{2}$$

$$\text{F1}-\text{Score} = ((2*\text{Precision}*\text{Recall}))/((\text{Precision} + \text{Recall})) \tag{3}$$

$$\text{Specificity} = \text{TN}/((\text{TN}+\text{FP})) \tag{4}$$

$$\text{Accuracy} = ((\text{TP}+\text{TN}))/((\text{TP}+\text{TN}+\text{FN}+\text{FP})) \tag{5}$$

4 Results

4.1 Image Pre-processing and Enhancement

After image resizing, data augmentation was applied using image transformation (rotation) technique to increase the training dataset. Figure 2 shows sample result of the data augmentation.

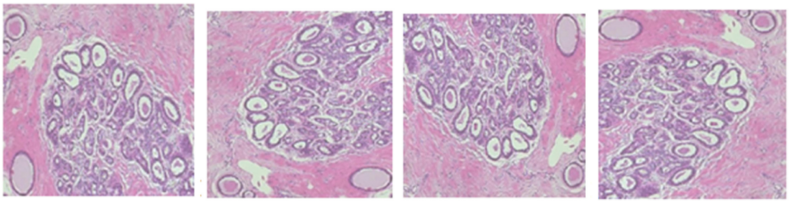


Fig. 2. Sample images augmented images by applying image transformation operation using 90°, 180° and 270° rotation, respectively

Figure 3 illustrates the original image and CLAHE applied image. The images contrast has been increased after CLAHE is applied. The histogram plots demonstrate an improved histogram distribution. The color differences of the histopathology images were adjusted by applying the histogram matching technique. Figure 4 shows sample result of the effect of histogram matching.

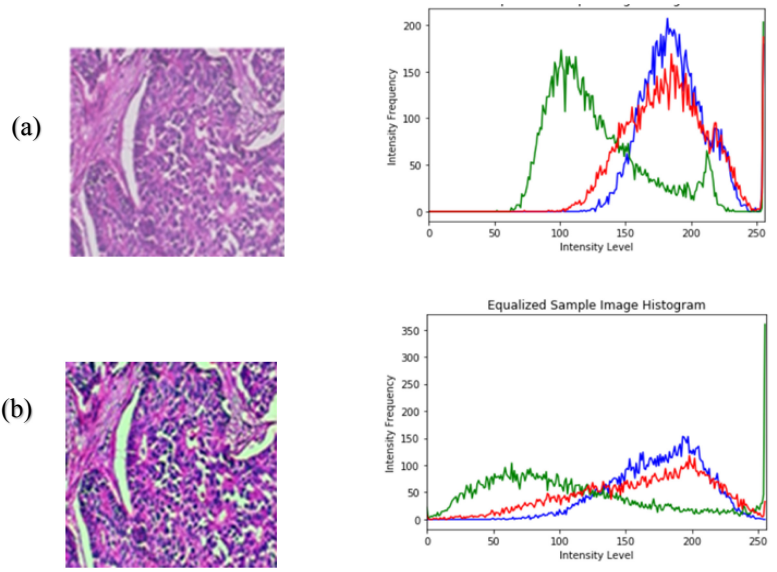


Fig. 3. Result of image enhancement using CLAHE. (a) Original image and its histogram (b) CLAHE applied image and its histogram (Left to Right)

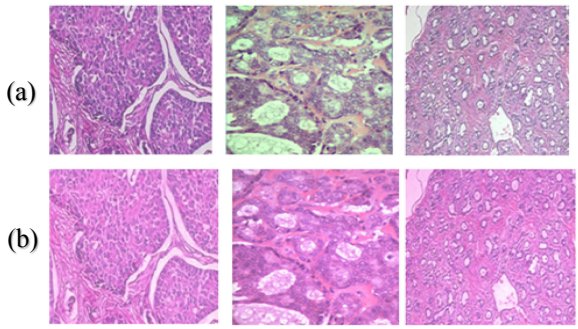


Fig. 4. Effect of histogram matching (a) Original image (b) Histogram matched image

4.2 Classification

Optimal result was achieved at the 37th epoch for the binary classification, yielding a validation loss of 0.1490, training accuracy of 98.58% and validation accuracy of 95.09%. Figure 5 shows the training and validation accuracy and loss plot on epoch versus accuracy and epoch versus loss graph for breast cancer type classification.

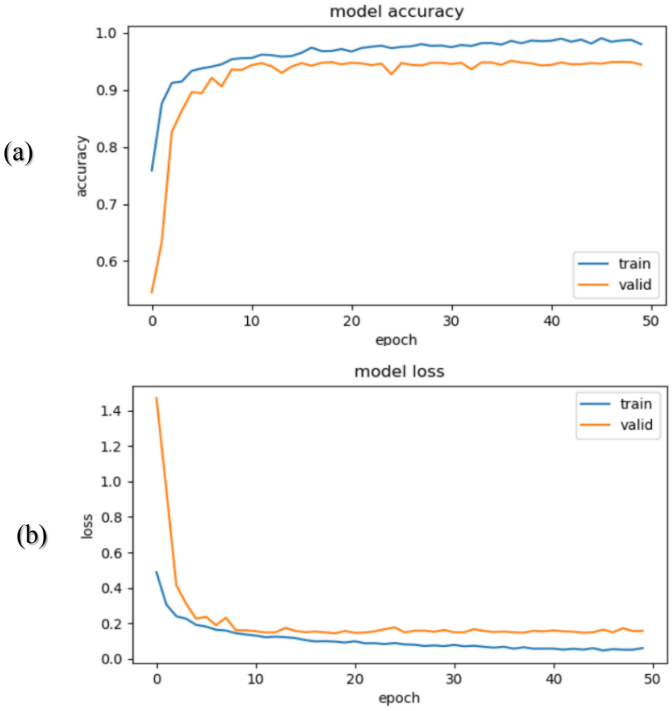


Fig. 5. (a) Training and validation accuracy curve with respect to the epoch (b) Training and validation loss curve with respect to the epoch for breast cancer type classification

Smallest validation loss of 0.1598 was obtained at the 27th epoch for benign sub-type classification resulting 99.14% training accuracy and 94.57% validation accuracy. This is demonstrated in Fig. 6. On the other hand, lowest validation loss of 0.1657 was achieved at the 49th epoch for malignant type classification resulting a 92.15% and 99.67% validation and training accuracy, respectively. Figure 7 shows the results obtained during the training phase for malignant sub-type classification.

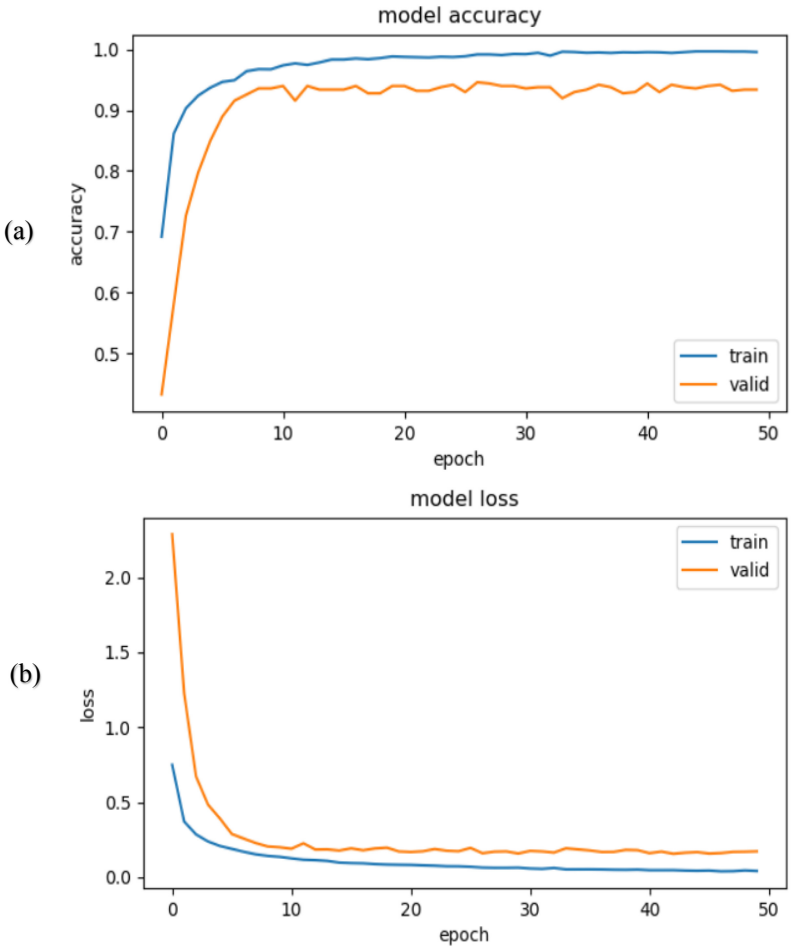


Fig. 6. (a) Training and validation accuracy curve with respect to the Epoch length. (b) Training and validation loss curve with respect to the epoch for benign type classification

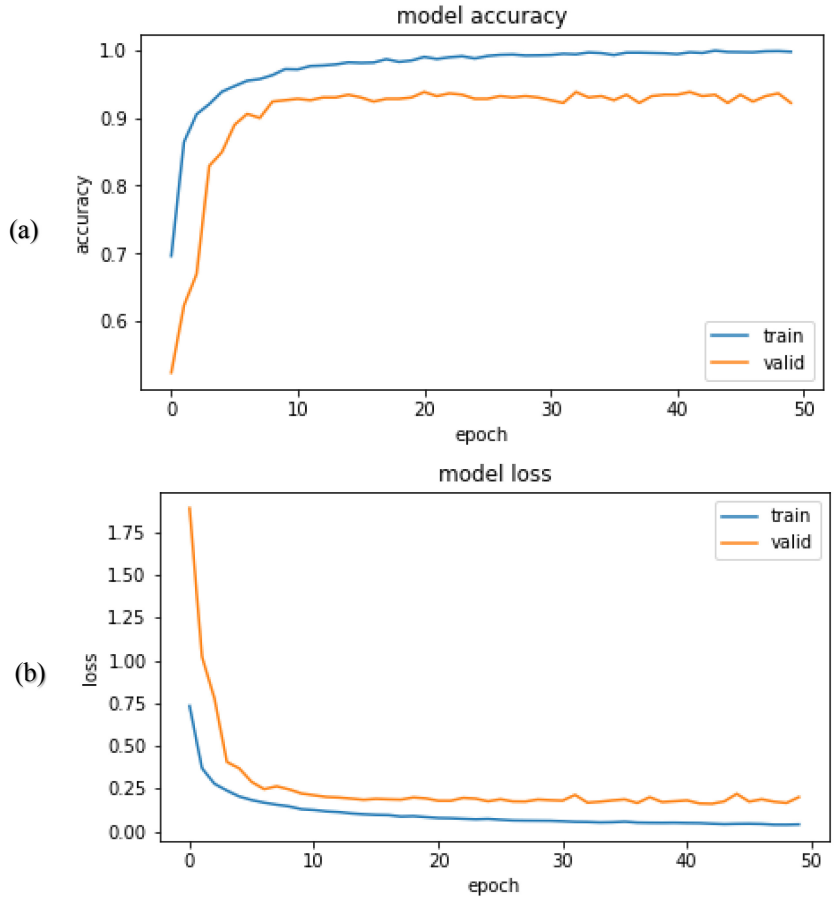
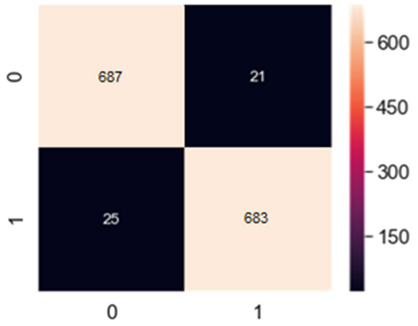


Fig. 7. (a) Training and validation accuracy curve with respect to the epoch for malignant type classification. (b) training and validation loss curve with respect to the epoch for malignant type classification

4.3 Test Results

A total of 708 test images were used for binary classification per class. Table 1 demonstrates the confusion matrix showing the test result of the binary classifier. Among all the malignant class images, a total of 687 images were correctly classified as malignant types, while the rest 21 images were predicted as benign. For the benign class, 683 images were correctly classified as benign tumors, and 25 of the images were wrongly classified in the malignant class.

Table 1. Test result of the binary classifier: malignant (‘0’) and benign (‘1’)



Accordingly, for the test result, an accuracy of 96.75%, precision of 96.755%, recall of 96.75% and specificity of 96.75% were achieved for the benign and malignant type classification as demonstrated in Fig. 8.

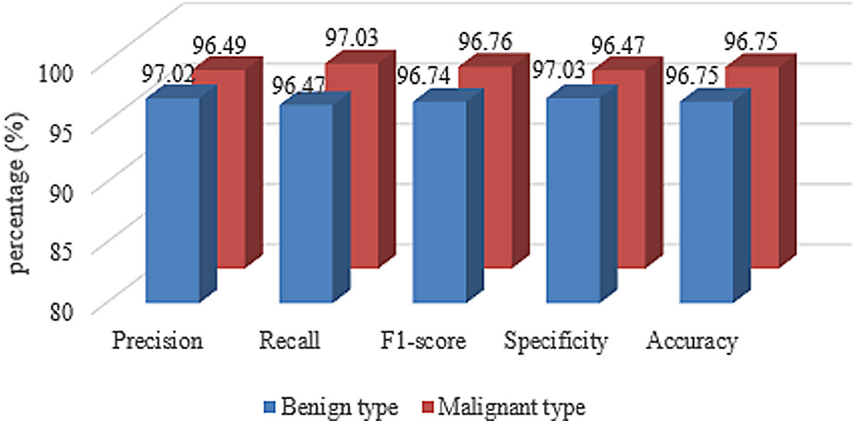
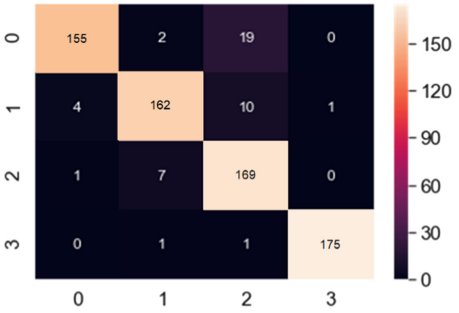


Fig. 8. Result of binary classification

For performance testing of the benign sub-type, 177 images were used per class. The confusion matrix for benign sub-type classification test result is demonstrated in Table 2.

Table 2. Test result of the benign classifier. The benign classes adenosis tumor, fibro adenoma, phyllodes and tubular are labeled as 0, 1, 2 and 3 respectively.



For the malignant sub-type classifier performance testing, a total of 177 images were used per class. The test results are demonstrated in Table 3.

Table 3. Test result of the malignant sub-type classifier with classes of ductal carcinoma, lobular carcinoma cancer, papillary carcinoma cancer and mucinous carcinoma cancer labeled as 0, 1, 2 and 3 respectively

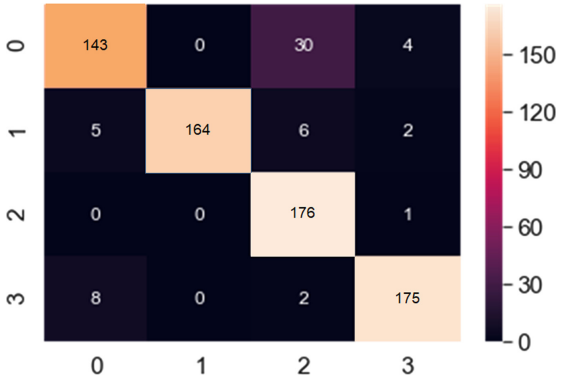


Figure 9 demonstrates the calculated performance metrics for binary, malignant and benign sub-type classifiers. An average accuracy of 96.7%, precision of 93.87%, recall/sensitivity of 93.51% and specificity of 97.8% were achieved for the benign classification. Whereas, an average test accuracy of 95.78%, average precision of 92.49%, an average recall/sensitivity of 91.85% and specificity of 97.17% were obtained for malignant sub-type classification. Figure 10 demonstrates the summary of the model's performance.

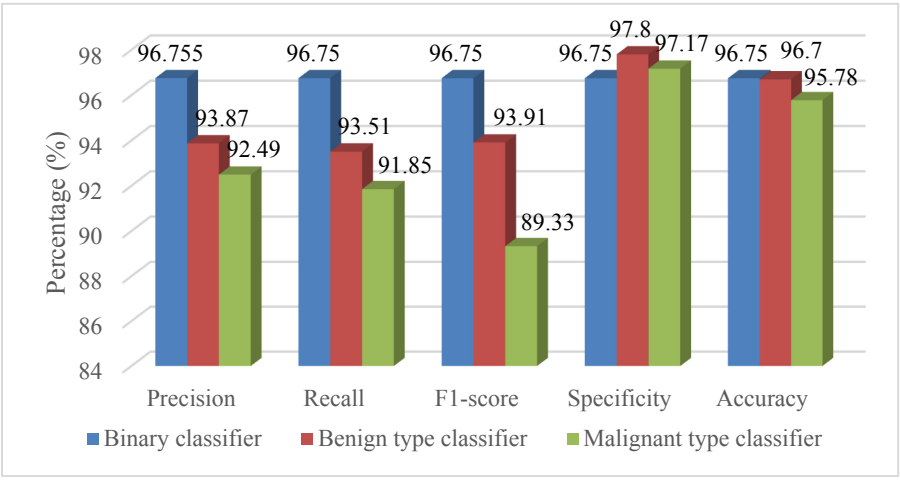


Fig. 9. Result of multi-class classifying model

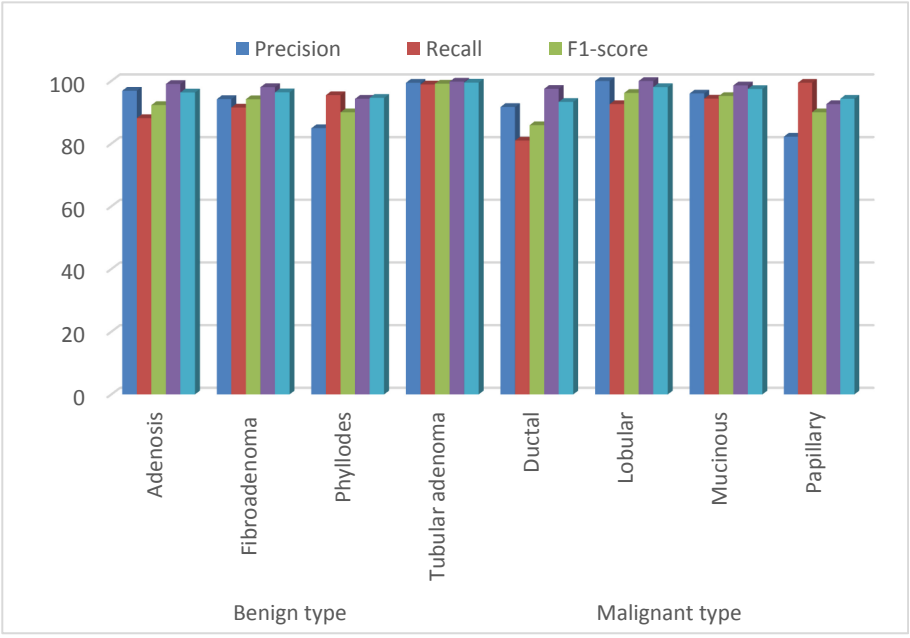


Fig. 10. Performance result summary of the proposed classification technique

5 Discussion

Among the triple assessment techniques, histopathology test is usually assumed as gold standard to identify breast cancer type and subtype prior to conducting a treatment [4]. The lack of trained pathologists and the manual diagnostic process prevent many breast cancer women in most developing countries from being diagnosed at an early stage. Furthermore, due to the subjectivity of the experts and complexity nature of the cancer cells, the manual diagnosis technique may lead to a misdiagnosis [37]. Computer diagnostic systems have a promising potential for early diagnosis of breast cancer by decreasing the rate of misdiagnosis.

This paper presents an automatic classification technique for breast cancer biopsy images using a deep learning technique. For deep model training, validation and testing, histopathological images were obtained from BreakHis online dataset and locally acquired from Jimma University Medical Center. All histopathological images were pre-processed by applying data augmentation, image resizing and normalization and enhancement using contrast limited adaptive histogram equalization and histogram matching techniques prior to model training.

Three ResNet50 model was trained, validated and finetuned. Good results were achieved after model fine-tuning with an ADAM optimizer, a 0.01–0.001 learning rate, 50 number of epochs, ReLu Activation function, 100 batch size, binary cross-entropy loss function (for the binary class classification) categorical cross-entropy (for multi-class classification).

The training evaluation of the model for 50 epochs is demonstrated in learning curves of Figs. 5, 6, 7. The training accuracy and training loss curves were used to observe the model performance and evaluate its classification accuracy. Better results were obtained during accuracy curve increment, loss curve decrement and large epoch size.

For sub-type classification, first a given image has to classified in to its type, either benign or malignant and then its sub-type will be identified. The model's performance for the first classification (binary) was tested using an unseen dataset and promising results were achieved as indicated in Fig. 9. Accordingly, 96.75%, 96.75%, 96.75%, 96.75% and 96.75% average accuracy, precision, Fl-score, recall/sensitivity, and specificity were achieved, respectively. On the other hand, an average accuracy, precision, recall/sensitivity and specify of 96.7%, 93.87%, 93.51% and 97.8% were achieved for the benign type classification. Similarly, for the malignant sub-type classification, an average test accuracy, precision rate, sensitivity/recall, and specificity of 95.78, 92.49%, 91.85% and 97.17% were obtained. The results of these tests show that the proposed method outperforms the recent related studies [21, 23].

In summary, comparing to the results found in related literatures with similar dataset [9, 16, 22, 23, 38], the developed system has a potential of classifying whole slide breast cancer histopathology images with promising classification accuracy. Moreover, the developed system has overcome the gap of further classification of histopathology images in to their sub-types.

6 Conclusion

A transfer learning method has been used to classify histopathological images of breast cancer into cancerous and non-cancerous and further classifies benign class into sub-types (Adenosis, fibro adenoma, phyllodes and tubular adenoma) and malignant in to ductal carcinoma, lobular carcinoma, mucinous carcinoma and papillary carcinoma sub-types. The Resnet50 model was used as a feature extractor and the extracted features were given to a soft-max classifier for classification. As a result, an average accuracy of 96.75%, 96.7%, and 95.78% were obtained for breast cancer type, benign sub-type and malignant sub-type classification, respectively. This developed system can be used as a decision support in the diagnosis of breast cancer and can help pathologists, especially in those resource limited settings.

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